

A&A Ref: 151939

PUBLICATION PARTICULARS AND ABSTRACT
(Section 32(3)(a) - Regulations 22(1)(g) and 31)

21	01	PATENT APPLICATION NO	22	LODGING DATE	43	ACCEPTANCE DATE
----	----	-----------------------	----	--------------	----	-----------------

io - 2005/01097

7 February 2005

13/09/06.

51	INTERNATIONAL CLASSIFICATION	NOT FOR PUBLICATION
----	------------------------------	---------------------

C07D

CLASSIFIED BY: ISA

71	FULL NAME(S) OF APPLICANT(S)
----	------------------------------

F. Hoffmann-La Roche AG

72	FULL NAME(S) OF INVENTOR(S)
----	-----------------------------

BINGGELI, Alfred
HILPERT, Hans
MAERKI, Hans-Peter
MOHR, Peter

GRETHER, Uwe
HIRTH, Georges
MEYER, Markus

EARLIEST PRIORITY CLAIMED	COUNTRY	NUMBER	DATE
	33 EP(CH)	31 02019146.6	32 30 August 2002

NOTE: The country must be indicated by its International Abbreviation - see schedule 4 of the Regulations

54	TITLE OF INVENTION
----	--------------------

Novel 2-arylthiazole compounds as PPARALPHA and PPARGAMA agonists

57	ABSTRACT (NOT MORE THAN 150 WORDS)
----	------------------------------------

NUMBER OF SHEETS	75
------------------	----

The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



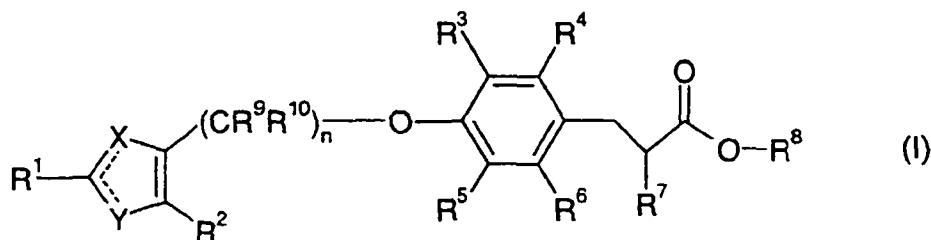
(43) International Publication Date
11 March 2004 (11.03.2004)

PCT

(10) International Publication Number
WO 2004/020420 A1

- (51) International Patent Classification⁷: **C07D 277/22**, 417/12 (74) Agent: **WITTE, Hubert**; Grenzacherstrasse 124, CH-4070 Basel (CH).
- (21) International Application Number: **PCT/EP2003/009281** (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 21 August 2003 (21.08.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 02019146.6 30 August 2002 (30.08.2002) EP (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant: **F.HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).
- (72) Inventors: **BINGGELI, Alfred**; Im Kugelfang 50, CH-4102 Binningen (CH). **GRETHER, Uwe**; Hugemattweg 10b, 79541 Loerrach (DE). **HILPERT, Hans**; Gustav Bay-Strasse 34, CH-4142 Munchenstein (CH). **HIRTH, Georges**; 7, rue de l'Ancre, F-68330 Huningue (FR). **MAERKI, Hans-Peter**; Seltisbergerstrasse 75, CH-4059 Basel (CH). **MEYER, Markus**; Maurenweg 6, 79395 Neuenburg (DE). **MOHR, Peter**; Benkenstrasse 26, CH-4054 Basel (CH).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL 2-ARYLTHIAZOLE COMPOUNDS AS PPARALPHA AND PPARGAMA AGONISTS



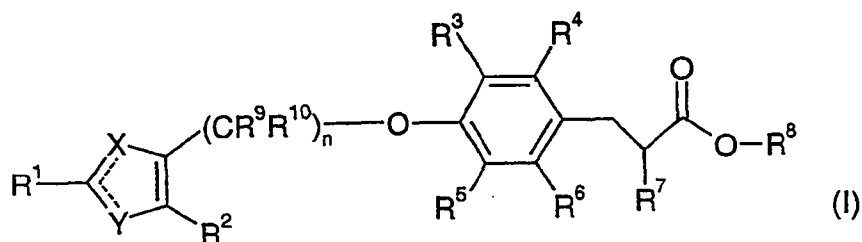
(57) Abstract: The present invention relates to compounds of formula (I) wherein R¹ to R¹⁰, X, Y and n are as defined in the description and claims, and pharmaceutically acceptable salts and esters thereof. The compounds are useful for the treatment of diseases such as diabetes.

WO 2004/020420 A1

- 1 -

NOVEL 2-ARYLTHIAZOLE COMPOUNDS AS PPAR α AND PPAR γ AGONISTS

The present invention is concerned with novel thiazole derivatives, their manufacture and their use as medicaments. In particular, the invention relates to compounds of the formula (I)



5 wherein

X is N and Y is S; or
X is S and Y is N;

R¹ is aryl or heteroaryl;

R² is hydrogen, lower-alkyl or fluoro-lower-alkyl;

10 R³, R⁴, R⁵ and R⁶ independently from each other are hydrogen, hydroxy, lower-alkenyl, halogen, lower-alkyl, fluoro-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, lower-alkoxy, fluoro-lower-alkoxy, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkoxy, wherein at least one of R³, R⁴, R⁵ and R⁶ is not hydrogen,
or

15 R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S-, -S-CH=CH-, -CH=CH-O-, -O-CH=CH-, -CH=CH-CH=CH-, -(CH₂)₃₋₅-, -O-(CH₂)₂₋₃- or - (CH₂)₂₋₃-O-, and R⁵ and R⁶ are as defined above;

R⁷ is lower-alkyl, lower-alkoxy, lower-alkenyloxy, aryloxy or aryl-lower-alkoxy;

20 R⁸ is hydrogen or lower-alkyl;

R⁹ and R¹⁰ independently from each other are hydrogen, lower-alkyl, lower-alkenyl, cycloalkyl, phenyl or [1,3]dioxan-2-ethyl;

n is 1, 2 or 3;

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Peroxisome Proliferator Activated Receptors (PPAR's) are members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. Various subtypes thereof have been identified and cloned. These include PPAR α , PPAR β (also known as PPAR δ), and PPAR γ . There exist at least two major isoforms of PPAR γ . While PPAR γ 1 is ubiquitously expressed in most tissues, the longer isoform PPAR γ 2 is almost exclusively found in adipocytes. In contrast, PPAR α is predominantly expressed in the liver, kidney and heart. PPAR's modulate a variety of body responses including glucose- and lipid- homeostasis, cell differentiation, inflammatory responses and cardiovascular events.

Diabetes is a disease in which a patient's ability to control glucose levels in blood is impaired, because he has partially lost the ability to respond properly to the action of insulin. In type II diabetes (T2D), often referred to as non-insulin dependent diabetes mellitus (NIDDM), which afflicts 80-90 % of all diabetic patients in developed countries, the Isles of Langerhans in the pancreas still produce insulin. However, the target organs, mainly muscle, liver and adipose tissue, exhibit a profound resistance to insulin stimulation, and the body compensates by producing unphysiologically high levels of insulin. In later stage of disease, however, insulin secretion decreases due to exhaustion of the pancreas. In addition to that T2D is a metabolic-cardiovascular disease syndrome. Among the comorbidities associated with T2D are for example insulin resistance, dyslipidemia, hypertension, endothelial dysfunction and inflammatory atherosclerosis.

Current first line treatment for diabetes generally involves low fat - and glucose - diet and exercise. However, compliance can be moderate and as the disease progresses, treatment with hypoglycemic drugs, e.g. sulfonylureas or metformin, becomes necessary. A promising new class of drugs has recently been introduced that resensitizes patients to their own insulin (insulin sensitizers), thereby reverting blood glucose and triglyceride levels to normal, and thus abolishing, or at least reducing, the requirement for exogenous insulin. Pioglitazone (ActosTM) and rosiglitazone (AvandiaTM) belong to the thiazolidinediones (TZD) class of PPAR γ -agonists and were the first representatives who had been approved for NIDDM in several countries. These compounds, however, suffer from side effects including rare but severe liver toxicity (as seen with troglitazone), and they increase body weight in humans. Therefore, new, better and more efficacious drugs for the treatment of NIDDM are urgently needed. Recent studies provide evidence that a coagonism on PPAR α and PPAR γ would result in compounds with enhanced therapeutic potential, i. e. such compounds should improve the lipid profile in addition to the normalization of glucose- and insulin-levels (Keller and Wahli: Trends Endocrin. Metab. 1993; 4:291-296, Macdonald and Lane: Current Biology Vol.5 pp.618-621 (1995)). Recent observations suggest furthermore that there is an independent PPAR α mediated effect on

insulin-sensitization that could result secondary to the reduction in lipids (Guerre-Millo et al; J Biol Chem 2000; 275: 16638-16642). Consequently, the incorporation of PPAR α activity into PPAR γ agonists is expected to give rise to more efficacious drugs for the treatment and/or prevention of diabetes.

5 The novel compounds of the present invention exceed the compounds known in the art, inasmuch as they bind to and activate both, PPAR α and PPAR γ , simultaneously and very efficiently. Therefore, these compounds combine the anti-glycemic effect of PPAR γ activation with the anti-dyslipidemic effect of PPAR α activation. Consequently, plasma glucose and insulin are reduced (=insulin sensitization), triglycerides lowered and HDL
10 cholesterol increased (=improved lipid profile). In addition, such compounds may also lower LDL cholesterol, decrease blood pressure and counteract inflammatory atherosclerosis. Since multiple facets of the T2D disease syndrome are addressed by PPAR α and γ coagonists, they are expected to have an enhanced therapeutic potential compared to the compounds already known in the art.

15 The compounds of the present invention further exhibit improved pharmacological properties compared to known compounds.

Unless otherwise indicated the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to
20 seven, preferably of one to four carbon atom(s).

The term "halogen" refers to fluorine, chlorine, bromine and iodine.

The term "protecting group" refers to groups such as e.g. acyl, alkoxy carbonyl, aryloxy carbonyl, silyl, or imine-derivatives, which are used to temporarily block the reactivity of functional groups. Well known protecting groups are e.g. t-butyloxy carbonyl,
25 benzyloxy carbonyl, fluorenylmethyloxy carbonyl or diphenylmethylen which can be used for the protection of amino groups, or lower-alkyl-, β -trimethylsilylethyl- and β -trichloroethyl-esters, which can be used for the protection of carboxy groups.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty
30 carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms.

The term "lower-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms,

preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like.

The term "cycloalkyl" refers to a monovalent carbocyclic radical of 3 to 10 carbon atom(s), preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or
5 cyclohexyl.

The term "fluoro-lower-alkyl" refers to lower-alkyl groups which are mono- or multiply substituted with fluorine. Examples of fluoro-lower-alkyl groups are e.g. CF_3 , CF_3CH_2 and $(\text{CF}_3)_2\text{CH}$.

The term "alkoxy" refers to the group $\text{R}'\text{-O-}$, wherein R' is alkyl. The term "lower-alkoxy" refers to the group $\text{R}'\text{-O-}$, wherein R' is lower-alkyl. Examples of lower-alkoxy
10 groups are e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and hexyloxy.

The term "fluoro-lower-alkoxy" refers to the group $\text{R}''\text{-O-}$, wherein R'' is fluoro-lower-alkyl. Examples of fluoro-lower-alkoxy groups are e.g. $\text{CF}_3\text{-O}$, $\text{CF}_3\text{CH}_2\text{-O}$ and $(\text{CF}_3)_2\text{CH-O}$.

The term "lower-alkenyl", alone or in combination signifies a straight-chain or
15 branched hydrocarbon residue comprising an olefinic bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms. Examples of alkenyl groups are ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and isobutenyl. A preferred example is 2-propenyl.

The term "lower-alkenyloxy" means a group $\text{R}''\text{-O-}$, wherein R'' is lower-alkenyl.
20 Examples of lower-alkenyloxy groups are butenyloxy, particularly but-3-enyloxy.

The term "aryl" relates to the phenyl or naphthyl group, preferably the phenyl group, which can optionally be mono- or multiply-substituted, particularly mono- or di-substituted by halogen, hydroxy, CN , CF_3 , NO_2 , NH_2 , N(H, lower-alkyl) , N(lower-alkyl)_2 ,
25 carboxy, aminocarbonyl, lower-alkyl, lower-alkoxy, aryl and/or aryloxy. Preferred substituents are halogen, CF_3 , lower-alkyl and/or lower-alkoxy.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur such as furyl, pyridyl, 1,2-, 1,3- and 1,4-diazinyl, thienyl, isoxazolyl, oxazolyl, imidazolyl, or pyrrolyl.
30 The term "heteroaryl" further refers to bicyclic aromatic groups comprising two 5- or 6-membered rings, in which one or both rings can contain 1, 2 or 3 atoms selected from nitrogen, oxygen or sulphur such as e.g. indole or quinoline, or partially hydrogenated bicyclic aromatic groups such as e.g. indolinyl. A heteroaryl group may have a substitution

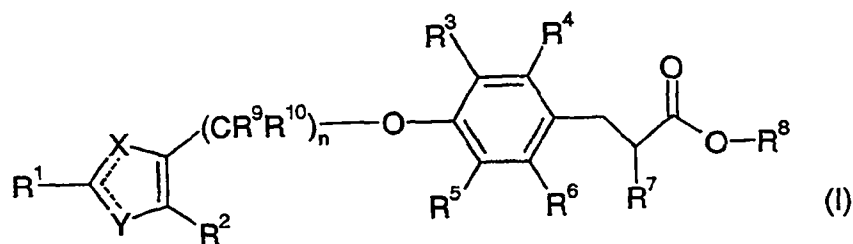
pattern as described earlier in connection with the term "aryl". Preferred heteroaryl groups are e.g. thienyl and furyl which can optionally be substituted as described above, preferably with halogen, CF₃, lower-alkyl and/or lower-alkoxy.

5 The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with pharmaceutically acceptable bases such as alkali salts, e.g. Na- and K-salts, alkaline earth salts, e.g. Ca- and Mg-salts, and ammonium or substituted ammonium salts, such as e.g. trimethylammonium salts. The term "pharmaceutically acceptable salts" also relates to such salts.

10 The compounds of formula (I) can also be solvated, e.g. hydrated. The solvation can be effected in the course of the manufacturing process or can take place e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of formula (I) (hydration). The term pharmaceutically acceptable salts also includes pharmaceutically acceptable solvates.

15 The term "pharmaceutically acceptable esters" embraces derivatives of the compounds of formula (I), in which a carboxy group has been converted to an ester. Lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, amino-lower-alkyl, mono- or di-lower-alkyl-amino-lower-alkyl, morpholino-lower-alkyl, pyrrolidino-lower-alkyl, piperidino-lower-alkyl, piperazino-lower-alkyl, lower-alkyl-piperazino-lower-alkyl and aralkyl esters are examples of suitable esters. The methyl, ethyl, propyl, butyl and benzyl
20 esters are preferred esters. The methyl and ethyl esters are especially preferred. The term "pharmaceutically acceptable esters" furthermore embraces compounds of formula (I) in which hydroxy groups have been converted to the corresponding esters with inorganic or organic acids such as, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-
25 toluenesulphonic acid and the like, which are non toxic to living organisms.

In detail, the present invention relates to compounds of formula (I)



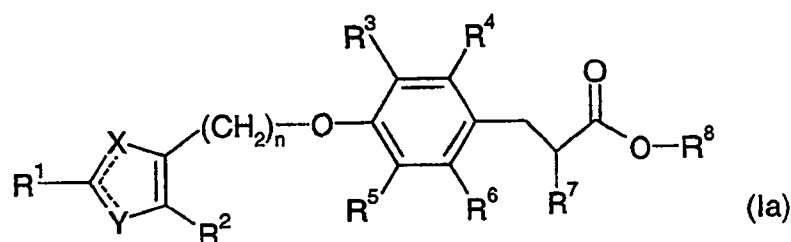
wherein

- X is N and Y is S; or
 5 X is S and Y is N;
- R¹ is aryl or heteroaryl;
- R² is hydrogen, lower-alkyl or fluoro-lower-alkyl;
- R³, R⁴, R⁵ and R⁶ independently from each other are hydrogen, hydroxy, lower-alkenyl,
 10 halogen, lower-alkyl, fluoro-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-
 lower-alkyl, lower-alkoxy, fluoro-lower-alkoxy, hydroxy-lower-alkoxy, lower-
 alkoxy-lower-alkoxy, wherein at least one of R³, R⁴, R⁵ and R⁶ is not hydrogen,
 or
- R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which
 they are attached, and R³ and R⁴ together are -CH=CH-S-, -S-CH=CH-, -
 15 CH=CH-O-, -O-CH=CH-, -CH=CH-CH=CH-, -(CH₂)₃₋₅-, -O-(CH₂)₂₋₃- or -
 (CH₂)₂₋₃-O-, and R⁵ and R⁶ are as defined above;
- R⁷ is lower-alkyl, lower-alkoxy, lower-alkenyloxy, aryloxy or aryl-lower-alkoxy;
- R⁸ is hydrogen or lower-alkyl;
- R⁹ and R¹⁰ independently from each other are hydrogen, lower-alkyl, lower-alkenyl,
 20 cycloalkyl, phenyl or [1,3]dioxan-2-ethyl;
- n is 1, 2 or 3;

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Preferably, R⁷ is lower-alkoxy, lower-alkenyloxy, aryloxy or aryl-lower-alkoxy, R⁹ is hydrogen and R¹⁰ is hydrogen. Such compounds are characterized by formula (Ia)

- 7 -



wherein

X is N and Y is S; or
X is S and Y is N;

5 R^1 is aryl or heteroaryl;

R^2 is hydrogen, lower-alkyl or fluoro-lower-alkyl;

R^3 , R^4 , R^5 and R^6 independently from each other are hydrogen, hydroxy, lower-alkenyl, halogen, lower-alkyl, fluoro-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, lower-alkoxy, fluoro-lower-alkoxy, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkoxy, wherein at least one of R^3 , R^4 , R^5 and R^6 is not hydrogen,
10 or

R^3 and R^4 are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R^3 and R^4 together are $-CH=CH-S-$, $-S-CH=CH-$, $-CH=CH-O-$, $-O-CH=CH-$, $-CH=CH-CH=CH-$, $-(CH_2)_{3-5}-$, $-O-(CH_2)_{2-3}-$ or $-(CH_2)_{2-3}-O-$, and R^5 and R^6 are as defined above;
15

R^7 is lower-alkoxy, lower-alkenyloxy, aryloxy or aryl-lower-alkoxy;

R^8 is hydrogen or lower-alkyl;

n is 1, 2 or 3;

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

20 Preferred compounds of the of the present invention are those, in which X is N and Y is S. Compounds, in which X is S and Y is N are also preferred. Compounds of formula (I) as defined above, in which R^1 is aryl are also preferred, with those compounds wherein R^1 is phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of lower-alkyl, lower-alkoxy, halogen and CF_3 being more preferred, and
25 with those compounds wherein R^1 is phenyl, 4-isopropyl-phenyl, 4-chloro-phenyl, 4-trifluoromethyl-phenyl or 3,5-dimethoxy-phenyl being particularly preferred. Compounds, wherein R^1 is phenyl, 4-isopropyl-phenyl, 4-chloro-phenyl or 4-trifluoromethyl-phenyl are also particularly preferred.

Furthermore, compounds as defined above in which R^2 is lower-alkyl or hydrogen are preferred, with methyl or hydrogen being particularly preferred. Methyl and hydrogen individually constitute separate preferred embodiments. Other preferred compounds are those, in which R^5 and R^6 are hydrogen.

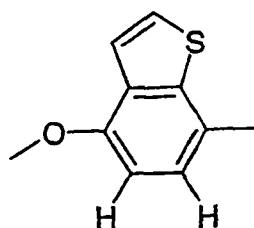
- 5 Compounds of formula (I), wherein R^3 , R^4 , R^5 and R^6 independently from each other are hydrogen, halogen, lower-alkyl or lower-alkoxy, wherein one or two of R^3 , R^4 , R^5 and R^6 are not hydrogen, or R^3 and R^4 are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R^3 and R^4 together are $-\text{CH}=\text{CH}-\text{S}-$, $-\text{S}-\text{CH}=\text{CH}-$, $-(\text{CH}_2)_{3-5}-$, $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{O}-\text{CH}=\text{CH}-$ or $-\text{O}-(\text{CH}_2)_{2-3}-$, and R^5 and R^6 are hydrogen are preferred. Furthermore, compounds as defined above, wherein one or two of R^3 , R^4 , R^5 and R^6 independently from each other are halogen, lower-alkyl or lower-alkoxy, and the others are hydrogen are also preferred. Compounds as defined above, wherein R^4 is methyl and R^3 , R^5 and R^6 are hydrogen are also preferred.

- 15 Compounds of formula (I), wherein R^3 and R^4 independently from each other are hydrogen, lower-alkyl, lower-alkoxy or halogen, wherein one of R^3 and R^4 is not hydrogen and R^5 and R^6 are hydrogen, or R^3 and R^4 are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R^3 and R^4 together are $-\text{CH}=\text{CH}-\text{S}-$, $-\text{S}-\text{CH}=\text{CH}-$, $-(\text{CH}_2)_{3-5}-$, and R^5 and R^6 are hydrogen also relate to a preferred embodiment of the present invention. Such compounds, wherein R^5 and R^6 are hydrogen; and R^3 is lower-alkyl or halogen and R^4 is hydrogen, or R^3 is hydrogen and R^4 is lower-alkyl or halogen are particularly preferred.

- 25 Further preferred compounds of formula (I) as described above are those, wherein R^5 and R^6 are hydrogen; and R^3 and R^4 are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R^3 and R^4 together are $-\text{CH}=\text{CH}-\text{S}-$, $-\text{S}-\text{CH}=\text{CH}-$, $-(\text{CH}_2)_{3-5}-$, $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{O}-\text{CH}=\text{CH}-$, or $-\text{O}-(\text{CH}_2)_{2-3}-$. Those compounds, wherein R^5 and R^6 are hydrogen; and R^3 and R^4 are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R^3 and R^4 together are $-\text{CH}=\text{CH}-\text{S}-$, $-(\text{CH}_2)_{3-5}-$, or $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, are particularly preferred.

- 30 Other preferred compounds of the present invention are those, wherein R^5 and R^6 are hydrogen; and R^3 and R^4 are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R^3 and R^4 together are $-\text{CH}=\text{CH}-\text{S}-$. Such compounds consequently comprise the following moiety

- 9 -



Further preferred compounds of formula (I) are those, wherein R^7 is lower-alkyl or lower-alkoxy, particularly lower-alkoxy, more particularly ethoxy. Compounds, in which R^7 is ethyl, ethoxy or isopropoxy are also preferred. Also preferred are compounds of
 5 formula (I), wherein R^8 is hydrogen.

Also preferred are compounds of formula (I), wherein n is 1. Further preferred are compounds of formula (I), wherein n is 2. Other preferred compounds are those, wherein n is 3.

In another preferred embodiment of the present invention, R^9 and R^{10}
 10 independently from each other are hydrogen, lower-alkyl or cycloalkyl. Preferably, R^9 and R^{10} are hydrogen.

The pharmaceutically acceptable salts of the compound of formula (I) and the pharmaceutically acceptable esters of the compounds of formula (I) individually constitute preferred embodiments of the present invention. Particularly preferred are compounds of
 15 formula (I).

Preferred compounds of general formula (I) are those selected from the group consisting of

- [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid,
- 20 [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-5,6,7,8-tetrahydronaphthalen-1-yl}-propionic acid,
- [rac]-2-Ethoxy-3-{7-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-4-yl}-propionic acid,
- [rac]-3-{4-[2-(4-tert-Butyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-2-ethoxy-
 25 propionic acid,
- [rac]-2-Ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-propionic acid,
- [rac]-2-Ethoxy-3-{3-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid,

- [rac]-3-{4-[2-(4-tert-Butyl-phenyl)-thiazol-4-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid,
[rac]-2-Ethoxy-3-{3-fluoro-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid,
5 [rac]-2-Ethoxy-3-{3-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid,
[rac]-2-Ethoxy-3-(2-methyl-4-[2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy]-phenyl)-propionic acid,
[rac]-2-Ethoxy-3-[2-methyl-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-
10 propionic acid,
[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid,
[rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid,
15 [rac]-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,
[rac]-3-{4-[2-(4-tert-Butyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,
[rac]-2-Ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-
20 propionic acid,
(2S)-3-{4-[2-(3-Chloro-4-fluoro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,
(2S)-2-Ethoxy-3-[2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl]-propionic acid,
25 (2S)-3-{4-[2-(3-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,
(2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,
(2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methoxy-phenyl}-2-ethoxy-
30 propionic acid,
(2S)-3-{2-Chloro-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-phenyl}-2-ethoxy-propionic acid,
(2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-ethyl-phenyl}-2-ethoxy-propionic acid,
35 [rac]-2-Ethoxy-3-{3-fluoro-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid,
[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-

- phenyl)-propionic acid,
[rac]-2-Ethoxy-3-{3-fluoro-4-[2-(2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid,
[rac]-2-Ethoxy-3-[3-fluoro-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-
propionic acid,
5 [rac]-2-Ethoxy-3-{3-fluoro-4-[3-(2-phenyl-thiazol-4-yl)-propoxy]-phenyl}-propionic
acid,
[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-
ethoxy}-phenyl)-propionic acid,
[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-thiazol-4-yl]-ethoxy}-3-fluoro-phenyl)-2-ethoxy-
10 propionic acid,
[rac]-2-Ethoxy-3-[2-methyl-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid,
[rac]-3-{4-[2-(2-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-
propionic acid,
[rac]-3-{4-[2-(4-tert-Butyl-phenyl)-4-methyl-thiazol-5-ylmethoxy]-3-fluoro-phenyl}-2-
15 ethoxy-propionic acid,
[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-
2-ethoxy-propionic acid,
[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-
propionic acid,
20 [rac]-3-{4-[2-(4-Chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-
ethoxy-propionic acid,
[rac]-2-Ethoxy-3-{2-methyl-4-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-
ylmethoxy]-phenyl}-propionic acid,
[rac]-3-{4-[2-(3-Chloro-4-fluoro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-
25 phenyl}-2-ethoxy-propionic acid,
[rac]-2-Ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-
phenyl)-propionic acid,
[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-
phenyl)-propionic acid,
30 [rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-
phenyl)-propionic acid,
[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-fluoro-phenyl)-
2-ethoxy-propionic acid,
[rac]-2-Ethoxy-3-(3-fluoro-4-{3-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-propoxy}-phenyl)-
35 propionic acid, and
[rac]-3-(4-{3-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-3-fluoro-

phenyl)-2-ethoxy-propionic acid,
and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Other preferred compounds of general formula (I) are those selected from the group consisting of

- 5 [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-dimethyl-phenyl)-2-ethoxy-propionic acid;
- [rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-dimethyl-phenyl)-propionic acid;
- [rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-
- 10 methyl-phenyl)-propionic acid;
- [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid;
- [rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid;
- 15 [rac]-2-Ethoxy-3-{3-fluoro-4-[2-(2-p-tolyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid;
- [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid;
- [rac]-3-{4-[2-(2-Benzo[1,3]dioxol-5-yl-5-methyl-thiazol-4-yl)-ethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid;
- 20 [rac]-2-Ethoxy-3-{3-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid;
- [rac]-3-{3-Fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-isopropoxy-propionic acid;
- [rac]-3-{4-[2-(3,5-Dimethoxy-phenyl)-thiazol-4-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-
- 25 propionic acid;
- [rac]-2-Ethoxy-3-[3-fluoro-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid;
- [rac]-2-Ethoxy-3-[3-fluoro-4-(2-p-tolyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid;
- [rac]-2-Ethoxy-3-[2-ethoxy-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-propionic acid;
- 30 [rac]-2-Ethoxy-3-(2-ethoxy-4-[2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy]-phenyl)-propionic acid;
- [rac]-2-Ethoxy-3-(3-methyl-4-[2-[5-methyl-2-(4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethoxy]-phenyl)-propionic acid;
- [rac]-2-Ethoxy-3-(3-fluoro-4-[2-[5-methyl-2-(4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethoxy]-phenyl)-propionic acid;
- 35 [rac]-2-Isopropoxy-3-{3-methoxy-4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-

- phenyl}-propionic acid;
[rac]-3-(3-Fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-2-isopropoxy-propionic acid;
[rac]-3-(4-{2-[2-(3,4-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid;
5 [rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-isopropoxy-propionic acid;
[rac]-3-(4-{2-[2-(3,5-Dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-isopropoxy-propionic acid;
10 [rac]-3-(4-{2-[2-(3,5-Dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid;
[rac]-2-Ethoxy-3-{5-ethoxy-2-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-yl]methoxy}-phenyl}-propionic acid;
[rac]-3-(4-{2-[2-(4-Chloro-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-5-ethoxy-2-fluoro-phenyl)-2-ethoxy-propionic acid;
15 [rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-difluoro-phenyl)-2-ethoxy-propionic acid;
[rac]-3-(4-{2-[2-(4-Chloro-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-difluoro-phenyl)-2-ethoxy-propionic acid;
20 [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid;
[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-2-ethoxy-propionic acid;
[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-25 7-yl)-2-ethoxy-propionic acid;
[rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-propionic acid;
[rac]-2-Isopropoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-propionic acid;
30 [rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-propionic acid;
[rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid;
[rac]-2-Isopropoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-35 7-yl}-propionic acid;
[rac]-3-{4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-2-propoxy-propionic acid;

- [rac]-2-Methoxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid;
- [rac]-3-{4-[2-(5-Methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-2-propoxy-propionic acid;
- 5 [rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-2-ethoxy-propionic acid;
- [rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-2-methoxy-propionic acid;
- [rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-
- 10 benzo[b]thiophen-7-yl)-2-isopropoxy-propionic acid;
- [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-2-isopropoxy-propionic acid;
- [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-2-propoxy-propionic acid;
- 15 [rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-2-ethoxy-propionic acid;
- [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid;
- [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-
- 20 yl}-propionic acid;
- [rac]-2-Ethoxy-3-[2-methyl-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid;
- [rac]-3-{4-[2-(2-Chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid;
- 25 (S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-fluoro-phenyl}-2-ethoxy-propionic acid;
- [rac]-3-{7-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2,3-dihydro-benzofuran-4-yl}-2-ethoxy-propionic acid;
- [rac]-3-{7-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-benzofuran-4-yl}-2-ethoxy-
- 30 propionic acid;
- [rac]-2-Ethoxy-3-[2-methyl-4-(5-methyl-2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid;
- [rac]-3-{4-[2-(4-Chloro-phenyl)-5-methyl-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid;
- 35 [rac]-2-Ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid;
- [rac]-2-Ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-

- propionic acid;
[rac]-2-Ethoxy-3-{4-[2-(3-methoxy-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-propionic acid;
[rac]-3-{4-[2-(2,4-Dichloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid;
5 [rac]-3-(4-{3-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid;
(S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2,6-dimethyl-phenyl}-2-ethoxy-propionic acid;
10 [rac]-3-(4-{2-[2-(4-Chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid;
[rac]-2-Ethoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid;
[rac]-3-(4-{2-[2-(2-Chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid;
15 (S)-2-Ethoxy-3-{2-ethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid;
(S)-3-{2,6-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-ethoxy-propionic acid;
20 [rac]-2-Ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid;
[rac]-2-Ethoxy-3-(2-methyl-4-{2-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid;
[rac]-2-Ethoxy-3-{2-methyl-4-[2-(4-methyl-2-phenyl-thiazol-5-yl)-ethoxy]-phenyl}-propionic acid;
25 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid, (mixture of two diastereomeric racemates);
[rac]-2-Ethoxy-3-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid;
30 2-Ethoxy-3-(2-methyl-4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-phenyl)-propionic acid, (mixture of two diastereomeric racemates);
[rac]-2-Ethoxy-3-(2-methyl-4-{1-methyl-1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid;
2-Ethoxy-3-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid, (mixture of two diastereomeric racemates);
35 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-but-3-enyloxy}-phenyl)-propionic acid, (mixture of two diastereomeric racemates);

- 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-butoxy}-phenyl)-propionic acid, (mixture of two diastereomeric racemates);
 (2S)-2-Ethoxy-3-(2-ethyl-4-((1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy)-phenyl)-propionic acid;
- 5 (2S)-2-Ethoxy-3-(2-methoxy-4-((1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy)-phenyl)-propionic acid;
- 3-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid, (mixture of two diastereomeric racemates);
 3-(4-{Cyclopentyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-
- 10 methyl-phenyl)-2-ethoxy-propionic acid, (mixture of two diastereomeric racemates);
 2-Ethoxy-3-(2-methyl-4-{[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-phenyl-methoxy}-phenyl)-propionic acid, (mixture of two diastereomeric racemates);
 3-(4-{3-[1,3]Dioxan-2-yl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid, (mixture of two diastereomeric
- 15 racemates);
 [rac]-2-{2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]methoxy}-benzyl}-butyric acid;
 [rac]-2-{2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]methoxy}-benzyl}-heptanoic acid;
- 20 2-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-heptanoic acid, (mixture of two diastereomeric racemates);
 2-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-butyric acid, (mixture of two diastereomeric racemates);
 [rac]-2-(2-Methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-
- 25 ethoxy}-benzyl)-butyric acid;
 [rac]-2-(2-Methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-heptanoic acid;
 [rac]-2-Butoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]methoxy}-phenyl}-propionic acid;
- 30 2-Butoxy-3-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-propionic acid, (mixture of two diastereomeric racemates);
 [rac]-2-Ethoxy-3-(4-{2-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-5,6,7,8-tetrahydro-naphthalen-1-yl)-propionic acid;
 [rac]-2-Ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]methoxy}-
- 35 5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid;
 [rac]-2-Ethoxy-3-{4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]methoxy}-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid;

- [rac]-2-Methoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalen-1-yl}-propionic acid;
[rac]-2-Ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalen-1-yl}-propionic acid;
5 [rac]-2-Methoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzo[b]thiophen-7-yl}-propionic acid;
[rac]-2-Ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzo[b]thiophen-7-yl}-propionic acid; and
2-Methoxy-3-(4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-benzo[b]thiophen-7-yl)-propionic acid, (mixture of two diastereomeric racemates);
10 and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Particularly preferred compounds of formula (I) are those selected from the group consisting of

- 15 [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid,
[rac]-2-Ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-propionic acid,
[rac]-2-Ethoxy-3-{3-fluoro-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid,
20 [rac]-2-Ethoxy-3-{2-methyl-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid,
[rac]-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,
25 (2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,
(2S)-3-{2-Chloro-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-phenyl}-2-ethoxy-propionic acid, and
[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid,
30 and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Other particularly preferred compounds of formula (I) are those selected from the group consisting of

- [rac]-2-Ethoxy-3-(3-fluoro-4-{3-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-propoxy}-phenyl)-
35 propionic acid;

- [rac]-2-Ethoxy-3-{5-ethoxy-2-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid;
- [rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-2-isopropoxy-propionic acid;
- 5 (S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-fluoro-phenyl}-2-ethoxy-propionic acid;
- 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid, (mixture of two diastereomeric racemates);
- 2-Ethoxy-3-(2-methyl-4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-phenyl)-propionic acid, (mixture of two diastereomeric racemates);
- 10 2-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-butyric acid, (mixture of two diastereomeric racemates);
- [rac]-2-Ethoxy-3-{4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid; and
- 15 [rac]-2-Ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalen-1-yl}-propionic acid;
- and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

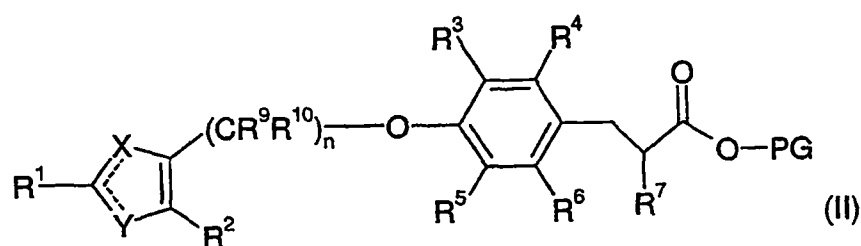
Compounds of formula (I) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for

20 example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or eluant). The invention embraces all of these forms.

25 It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo. Physiologically acceptable and metabolically labile derivatives, which are capable of producing the parent compounds of general formula (I) in vivo are also within the scope of this invention.

30 A further aspect of the present invention is the process for the manufacture of compounds of formula (I) as defined above, which process comprises removing a protecting group in a compound of formula (II)

- 19 -



wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁹, R¹⁰, X, Y and n are as defined as before and PG is a protecting group.

Possible protecting groups PG in compounds of formula (II) are e.g. lower-alkyl-, β -trimethylsilylethyl- and β -trichloroethyl-esters, which can be used for the protection of the corresponding carboxy group. Lower-alkyl-ester protecting groups can be removed in the presence of a base such as e.g. LiOH or NaOH in a solvent such as e.g. H₂O, ethanol, tetrahydrofuran, or dioxan, or in a mixture of such solvents, e.g. in a temperature range of 10 – 50°C. The β -trichloroethyl-ester protecting group can be removed in the presence of Zn in acetic acid, e.g. in a temperature range of 10 – 50°C. The β -trimethylsilylethyl-ester protecting group can be removed in the presence of tetrabutylammonium fluoride in tetrahydrofuran, e.g. in a temperature range of 20 – 65°C. Methods for converting a compound of formula (I) as defined above to a pharmaceutically acceptable salt are known in the art.

15 The invention further relates to compounds of formula (I) as defined above, when manufactured according to a process as defined above.

As described above, the compounds of formula (I) of the present invention can be used as medicaments for the treatment and/or prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists. Examples of such diseases are diabetes, particularly non-insulin dependent diabetes mellitus, elevated blood pressure, increased lipid and cholesterol levels, atherosclerotic diseases, metabolic syndrome, endothelial dysfunction, procoagulant state, dyslipidemia, polycystic ovary syndrome, inflammatory diseases (such as e.g. crown disease, inflammatory bowel disease, colitis, pancreatitis, cholestasis/fibrosis of the liver, and diseases that have an inflammatory component such as e.g. Alzheimer's disease or impaired/improvable cognitive function) and proliferative diseases (cancers such as e.g. liposarcoma, colon cancer, prostate cancer, pancreatic cancer and breast cancer). The use as medicament for the treatment and/or prevention of non-insulin dependent diabetes mellitus is preferred.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists. Examples of such diseases are diabetes, particularly non-insulin dependent diabetes mellitus, elevated blood pressure, increased lipid and cholesterol levels, atherosclerotic diseases, metabolic syndrome, endothelial dysfunction, procoagulant state, dyslipidemia, polycystic ovary syndrome, inflammatory diseases and proliferative diseases, preferably non-insulin dependent diabetes mellitus.

In another embodiment, the invention relates to a method for the treatment and/or prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists, which method comprises administering a compound of formula (I) to a human or animal. Preferred examples of such diseases are diabetes, particularly non-insulin dependent diabetes mellitus, elevated blood pressure, increased lipid and cholesterol levels, atherosclerotic diseases, metabolic syndrome, endothelial dysfunction, procoagulant state, dyslipidemia, polycystic ovary syndrome, inflammatory diseases and proliferative diseases, preferably for the treatment and/or prevention of non-insulin dependent diabetes mellitus.

The invention further relates to the use of compounds as defined above for the treatment and/or prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists. Preferred examples of such diseases are diabetes, particularly non-insulin dependent diabetes mellitus, elevated blood pressure, increased lipid and cholesterol levels, atherosclerotic diseases, metabolic syndrome, endothelial dysfunction, procoagulant state, dyslipidemia, polycystic ovary syndrome, inflammatory diseases and proliferative diseases,

preferably non-insulin dependent diabetes mellitus.

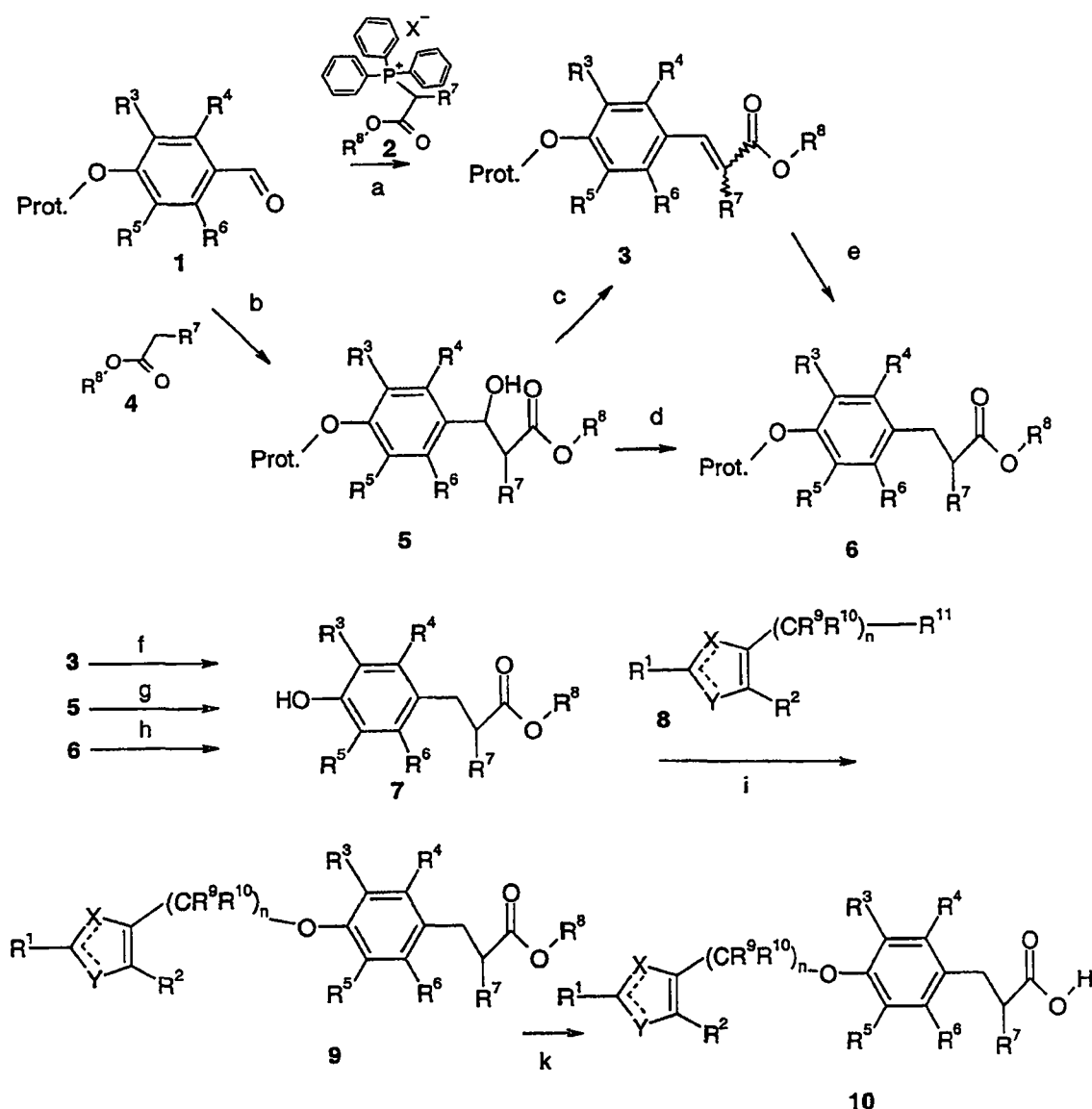
In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists. Preferred examples of such diseases are
5 diabetes, particularly non-insulin dependent diabetes mellitus, elevated blood pressure, increased lipid and cholesterol levels, atherosclerotic diseases, metabolic syndrome, endothelial dysfunction, procoagulant state, dyslipidemia, polycystic ovary syndrome, inflammatory diseases and proliferative diseases, preferably non-insulin dependent diabetes mellitus. Such medicaments comprise a compound as defined above.

The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. Starting materials are either commercially available or can be prepared by methods
5 analogous to the methods given below, by methods described in references cited in the text or in the examples, or by methods known in the art.

Racemates of compounds of formula (I) [compounds 9 and compounds 10 in scheme 1] can e. g. be synthesized according to the methods depicted in scheme 1 or by analogous methods.

10 Homochiral compounds of formula (I) (compounds 8 and 9 in scheme 2 and compounds 6 and 7 in scheme 3) can be prepared according to the methods depicted in scheme 2 and 3 or by analogous methods.

Scheme 1



Aldehydes **1** can be reacted with a *Wittig* salt **2** such as (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride or (1,2-dimethoxy-2-oxoethyl)triphenyl phosphonium bromide in solvents like isopropanol, dichloromethane or tetrahydrofuran or mixtures thereof in the presence of a base like potassium carbonate, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,1,3,3-tetramethyl-guanidine, preferably between 0°C and the reflux temperature of the solvents, giving acrylic esters **3** as E and/or Z isomers (step a). Hydrogenation of acrylic esters **3** using palladium on charcoal as catalyst, preferably at room temperature and 1 atm. pressure of hydrogen, in solvents like methanol, ethanol, tetrahydrofuran, acetic acid, dichloromethane and mixtures thereof, affords racemic esters **7**, provided that the protecting group can be cleaved reductively (step f). Hydrogenation of compounds in

which R^3 - R^4 together with the attached benzene ring form a benzofuran moiety can be performed using extended reaction times to provide the corresponding benzo-dihydrofuran analogues. In compounds, in which R^3 - R^4 together with the attached benzene ring form a benzothiophene or a benzofuran moiety, the reduction of the double
5 bond is preferably performed with a reducing metal like magnesium in solvent mixtures like tetrahydrofuran / methanol between room temperature and the reflux temperature of the solvents leading to saturated compounds 6 (step e). Subsequently, the protecting group like a benzyl ether is cleaved, e. g. by using dimethyl sulfide and boron trifluoride diethyl etherate in a solvent like dichloromethane between room temperature and the reflux
10 temperature of the solvent to give phenolic compounds 7 (step h).

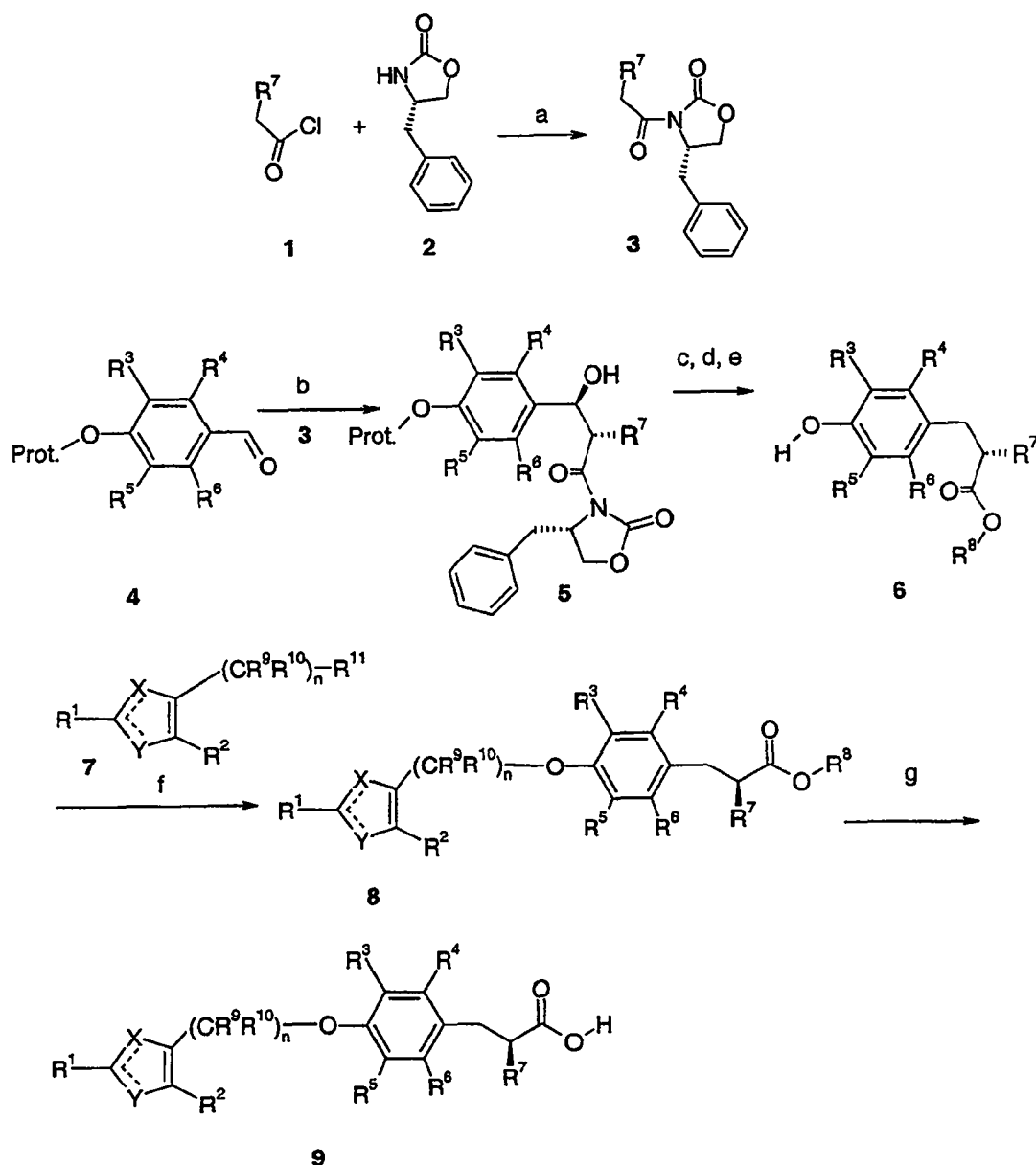
Alternatively, aldehydes 1 are reacted with the enolate of alkanolic acid esters or alkoxy- or aryloxy-acetic acid esters 4 (preferably the lithium-enolate, prepared at -78°C by treatment of 4 with a strong, non-nucleophilic base like lithium diisopropylamide in an inert solvent like tetrahydrofuran), preferably at temperatures around -78°C , in solvents like
15 tetrahydrofuran giving the aldol product 5 as a mixture of diastereomers (step b). Removal of the benzylic hydroxy group in 5 with a reducing agent like e. g. triethylsilane in the presence of a Lewis acid, like boron-trifluoride, or a protic acid, like trifluoroacetic acid, in a suitable solvent like trifluoroacetic acid itself or dichloromethane between 0°C and 60°C yields racemic esters 6 (step d); ensuing removal of the protecting group, e. g. a benzyloxy
20 function, can then be performed by standard technology, e. g. catalytic hydrogenation using hydrogen and a catalyst like palladium to give phenolic compounds 7 (step h). Catalytic hydrogenation can also be used to convert in one step benzyl protected hydroxy compounds 5 into phenolic compounds 7 (step g), preferably using palladium on charcoal as catalyst in the presence of an acid like oxalic acid in solvents like alcohols at
25 temperatures around room temperature and a hydrogen pressure up to 100 bar. The cleavage of the protective function can also be performed before the removal of the benzylic hydroxy group; in such a case, similar reaction conditions can be chosen for the removal of the benzylic hydroxy group as just described for the transformation of compounds 5.

30 As an alternative method, compounds 5 can be treated with catalytic amounts of an acid like para toluene sulfonic acid in a solvent like benzene or toluene, preferably under conditions allowing the removal of the water formed (e. g. with a Dean Stark trap or in the presence of molecular sieves) at temperatures between room temperature and the reflux temperature of the solvents to yield acrylic esters 3 (step c).

35 Aryl-thiazole compounds 8 (prepared as outlined in schemes 11-14) are condensed with phenols 7 according to well known procedures: if R^{11} represents a hydroxy group e. g. via *Mitsunobu*-reaction, with triphenylphosphine and di-tert-butyl-, diisopropyl- or diethyl-

- azodicarboxylate as reagents; this transformation is preferably carried out in a solvent like toluene, dichloromethane or tetrahydrofuran at ambient temperature. Alternatively, if R¹¹ represents a halide, mesylate or tosylate moiety, the aryl-thiazole compounds 8 can be reacted with phenols 7 in solvents like N,N-dimethylformamide, acetonitrile, acetone or methyl-ethyl ketone in the presence of a weak base like cesium or potassium carbonate at a temperature ranging from room temperature to 140°C, preferably around 50°C to yield ether compounds 9 (step i). Those can optionally be hydrolyzed according to standard procedures, e. g. by treatment with an alkali hydroxide like LiOH or NaOH in a polar solvent mixture like tetrahydrofuran/ethanol/water leading to carboxylic acids 10 (step k).
- 10 If the aryl-thiazole compounds 8 (prepared as described in schemes 11-14) contain chiral centers, ester compounds 9 and carboxylic acids 10 are obtained as mixtures of diastereomers, which can be separated by methods well known in the art, e. g. HPLC chromatography or crystallization.

Scheme 2

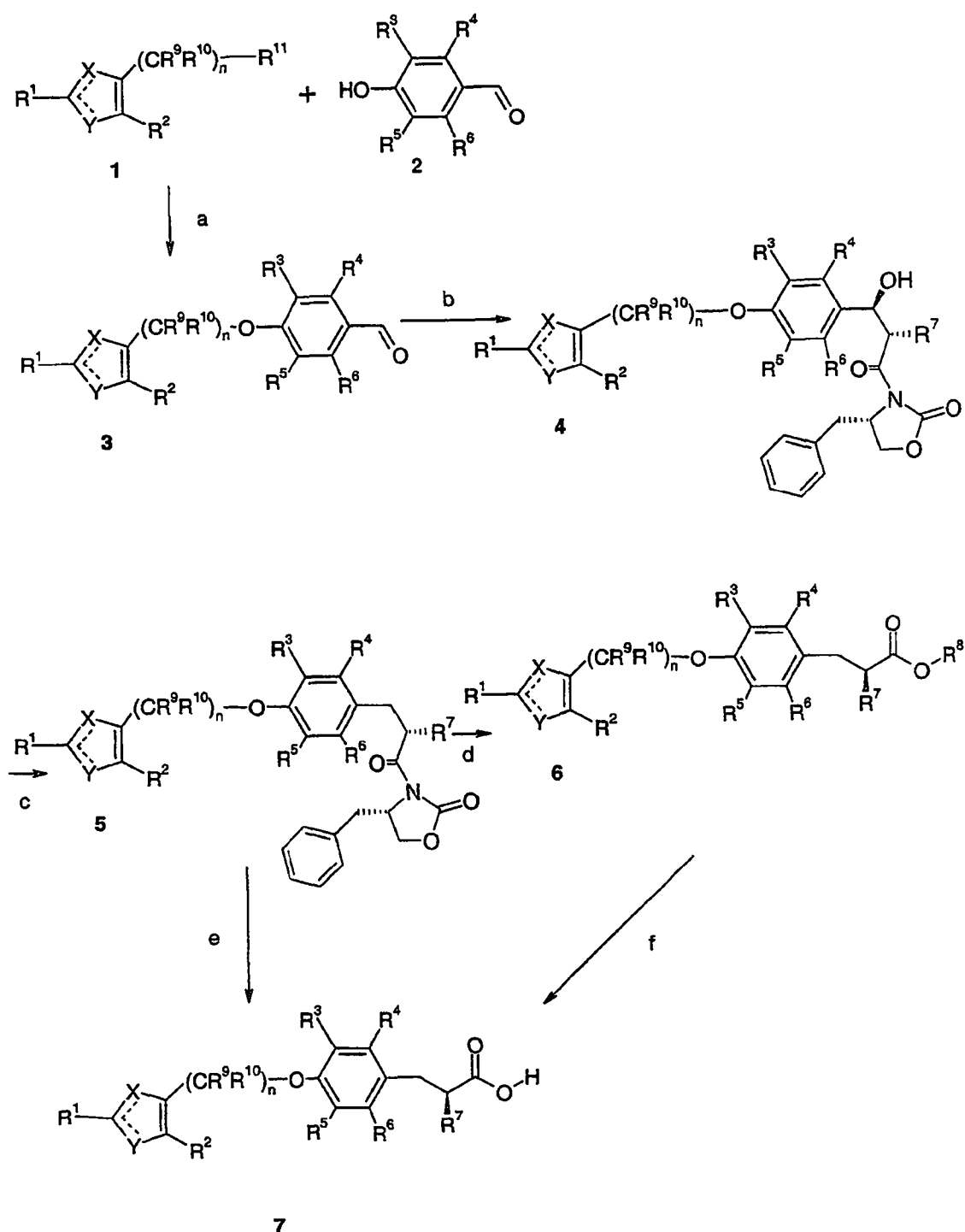


Homochiral α -substituted-phenyl-propionic acid esters of formula 8 and free acids of formula 9 can be prepared according to the method depicted in scheme 2 or by analogous methods known in the art.

The well known chiral auxiliary 2 [(S)-4-benzyl-oxazolidin-2-one] is condensed with an alkanoyl chloride or an alkoxy- or aryloxy-acetyl chloride 1 in the presence of a strong base like n-butyl lithium in an inert solvent like tetrahydrofuran at temperatures around -78°C to produce building block 3 (step a). The latter is then treated according to literature precedence [Tetrahedron Asymmetry (1999), 10, 1353-1367] with dibutylboron-triflate and a tertiary amine like triethylamine in dichloromethane to generate the corresponding

boron enolate, which is subsequently reacted at low temperatures with aldehydes 4 resulting in compounds 5 (step b). In compounds 5, one of all four possible stereoisomers is strongly predominating (stereochemistry as indicated without rigorous proof with respect to the benzylic position). Compounds 5 are converted into phenolic intermediates 6 via a three step sequence encompassing: i) carefully controlled ester formation using only a minimal excess of alcoholate in the corresponding alcohol as solvent or in solvents like tetrahydrofuran or dioxane at temperatures ranging from -20°C to room temperature (step c); ii) reductive removal of the benzylic hydroxy group as described above for the conversion of compounds 5 to compounds 6 in scheme 1 (step d); iii) removal of the protecting group by standard technology (step e); the order of the three reaction steps c, d, e is interchangeable, and the simultaneous removal of the benzylic hydroxy function and a benzyl protecting group as described for the conversion of compounds 5 to compounds 7 in scheme 1 is also possible. The transformation of phenolic intermediates 6 into ester 8 and / or acids 9 can be performed in perfect analogy as described for racemic phenolic intermediates 7 in scheme 1 (steps f and g). If carefully controlled reaction conditions are applied as detailed in the experimental part, hardly any racemisation occurs during this reaction sequence. The optical purity of compounds 8 and 9 can be determined by chiral HPLC or by ¹H-NMR-spectroscopy in the presence of a chiral solvent like 1-(9-anthryl)-2,2,2-trifluoro-ethanol. If the aryl-thiazole compounds 7 (prepared as described in schemes 11-14) contain chiral centers and are not optically pure, ester compounds 8 and carboxylic acids 9 are obtained as mixtures of diastereomers, which can be separated by methods well known in the art, e. g. HPLC chromatography or crystallization.

Scheme 3

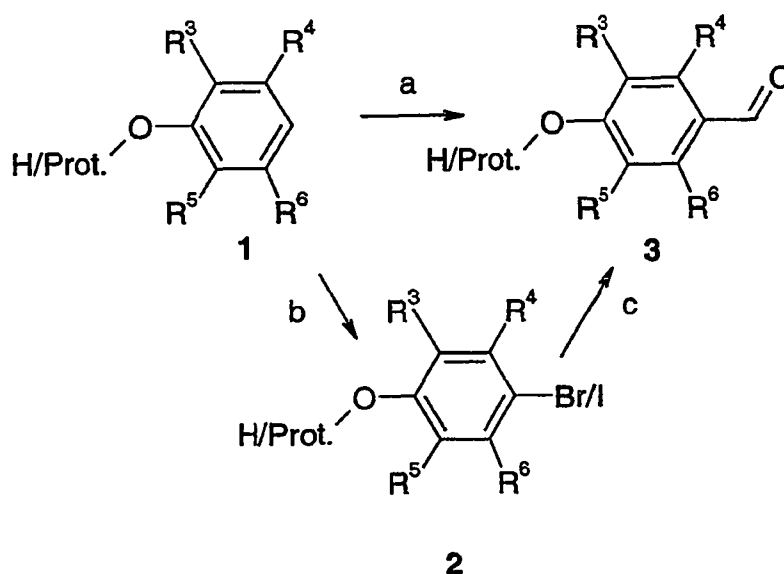


Homochiral α -substituted-phenyl-propionic acid esters of formula 6 and free acids of formula 7 can also be prepared according to a linear synthetic sequence depicted in scheme 3. Thus, reaction types already described in scheme 2 are used in a different order beginning with the condensation of aryl-thiazole synthons **1** with phenols **2** affording ether compounds **3** bearing an aldehyde moiety (step a). These ether compounds **3** are then

reacted with the chiral synthons (compounds 3 in scheme 2) to form aldol-adducts 4 (step b). Removal of the benzylic hydroxy function in compounds 4 leads to compounds 5 (step c), which can be converted into the corresponding esters 6 (step d) or acids 7 (step e) as described for the analogous reactions in scheme 1 and 2, respectively. Optionally, ester compounds 6 can be hydrolysed to acids 7 (step f). If the aryl-thiazole compounds 1 (prepared as described in schemes 11-14) contain chiral centers and are not optically pure, ester compounds 6 and carboxylic acids 7 are obtained as mixtures of diastereomers, which can be separated by methods well known in the art, e. g. HPLC chromatography or crystallization.

Aldehydes 1 (scheme 1), aldehydes 4 (scheme 2), aldehydes 2 (scheme 3), are known or can be synthesized by methods known in the art. Examples for possible syntheses of these key intermediates are given in schemes 4-10.

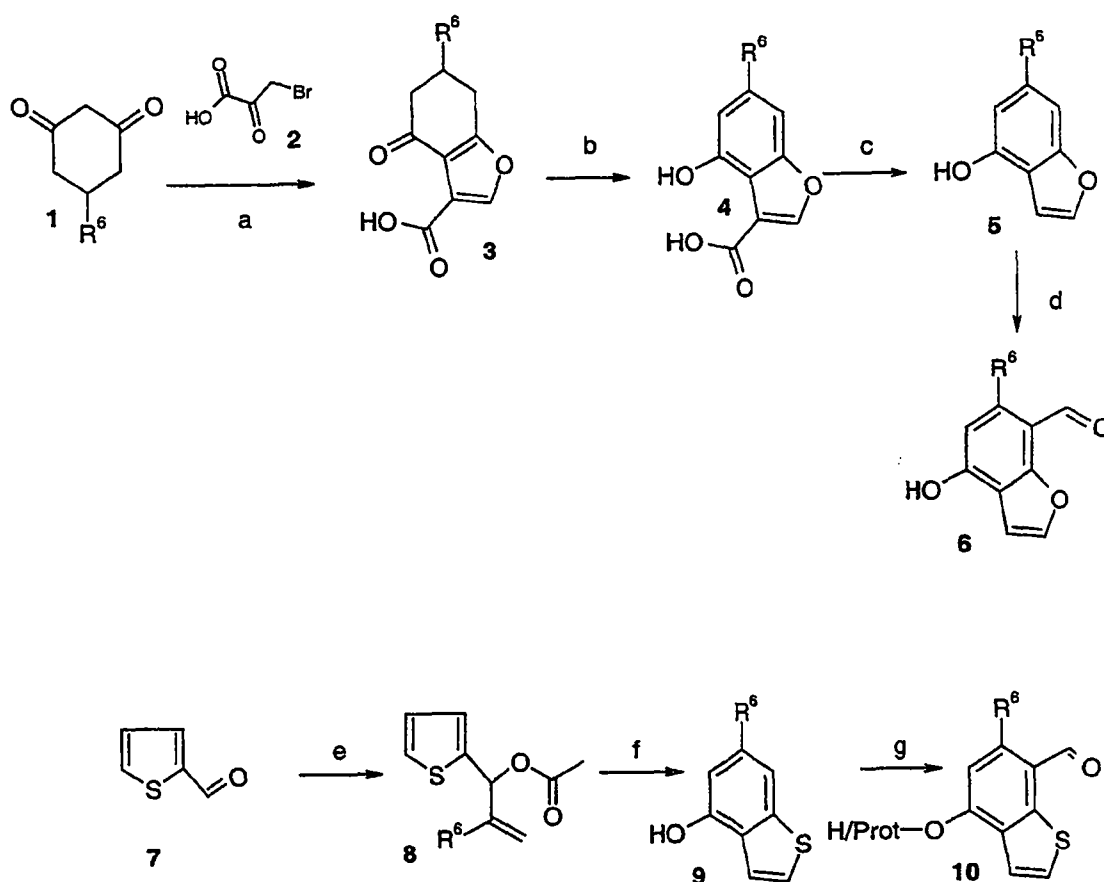
Scheme 4



Known phenols 1 can be transformed into aldehydes 3 either by known formylation reactions such as e. g. the *Vilsmeier* formylation, by treatment with hexamethylene tetramine under acidic conditions, e. g. in the presence of sulfuric acid or preferably with trifluoroacetic acid as solvent between 0°C and the reflux temperature of trifluoroacetic acid, or by formylation with dichloromethyl methyl ether in the presence of titanium tetrachloride, preferably in dichloromethane at temperatures between -78°C and the reflux temperature of the solvent (step a); alternatively, a two step procedure might be used: introduction of a halogen atom into the para position, e.g. by use of N-bromo- or N-iodo-succinimide, e. g. in a mixture of concentrated sulfuric acid and tetrahydrofuran preferably at ambient temperature, followed by a metal halogen exchange, realized by

treatment with an alkyl-lithium reagent like n-butyllithium, preferably at temperatures around -78°C , and quenching the resulting aryl-Li with a formyl transfer reagent like N,N-dimethylformamide or N-formyl-piperidine (steps b and c). Alternatively, a carbonylation reaction can be used for the introduction of the formyl group in step c, e. g. by use of sodium formate, bis(triphenylphosphine) palladium(II) dichloride and CO gas in a solvent like N,N-dimethylformamide, preferably at temperatures around 100°C .

Scheme 5

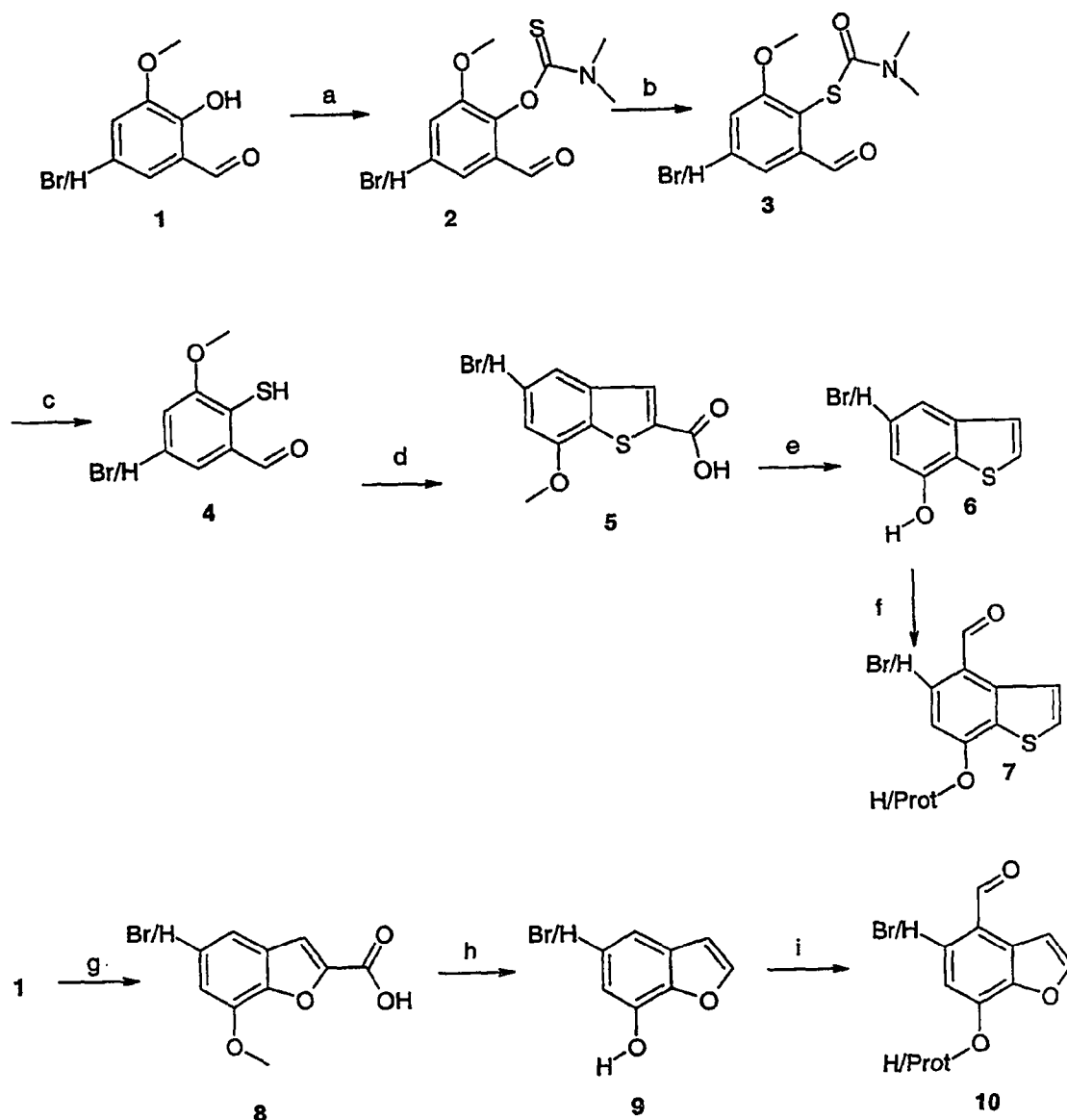


4-Hydroxy-benzofuran 5 ($\text{R}^6=\text{H}$) [Synthetic Communications (1986), 16(13), 1635-1640; Helvetica Chimica Acta (1933), 16, 121-129] and 4-hydroxy-benzothiophene 9 ($\text{R}^6=\text{H}$) [Jpn. Kokai Tokkyo Koho (2001), 2001048876A2] are known. Thus, cyclohexane-1,3-diones 1 carrying variable substituents R^6 at the 5-position can be reacted with bromo-pyruvic acid in methanol in the presence of a base like potassium hydroxide at temperatures between 0°C and the reflux temperature of methanol followed by treatment with hydrochloric acid at around 100°C to give furan-carboxylic acids 3 (step a). Treatment of these furan-carboxylic acids 3 in an inert solvent like decahydro-naphthalene in the presence of a hydrogen acceptor like dodecene and palladium on carbon, preferably at reflux, provides carboxy-benzofurans 4 (step b), which are decarboxylated to

benzofurans 5, e. g. by using copper powder in quinoline at temperatures between 200°C and 240°C (step c). Similar to the transformations described in scheme 4, benzofurans 5 can finally be converted into formylated benzofuran intermediates 6 (step d).

5 Treatment of 2-thiophenecarbaldehyde 7 with suitable vinyl-lithium- or vinyl-magnesium-derivatives in solvents like tetrahydrofuran or 1,2-dimethoxy-ethane, preferably in a temperature range between -78°C and room temperature, followed by in situ treatment with acetic anhydride yields thiophenes 8 with variable substitution R⁶ (step e). Treatment of thiophenes 8 with carbon monoxide, preferably at a pressure of 20 to 60 bar, a palladium catalyst like palladium acetate, a phosphine like triphenylphosphine, in
10 solvent mixtures which may typically contain acetic anhydride, triethylamine, toluene or tetrahydrofuran, preferably in a temperature range between 100°C to 160°C, affords after saponification of the acetate function benzothiophenes 9 (step f). Similar to the transformations described in scheme 4, benzothiophenes 9 can finally be converted into formylated benzothiophene intermediates 10 (step g).

Scheme 6



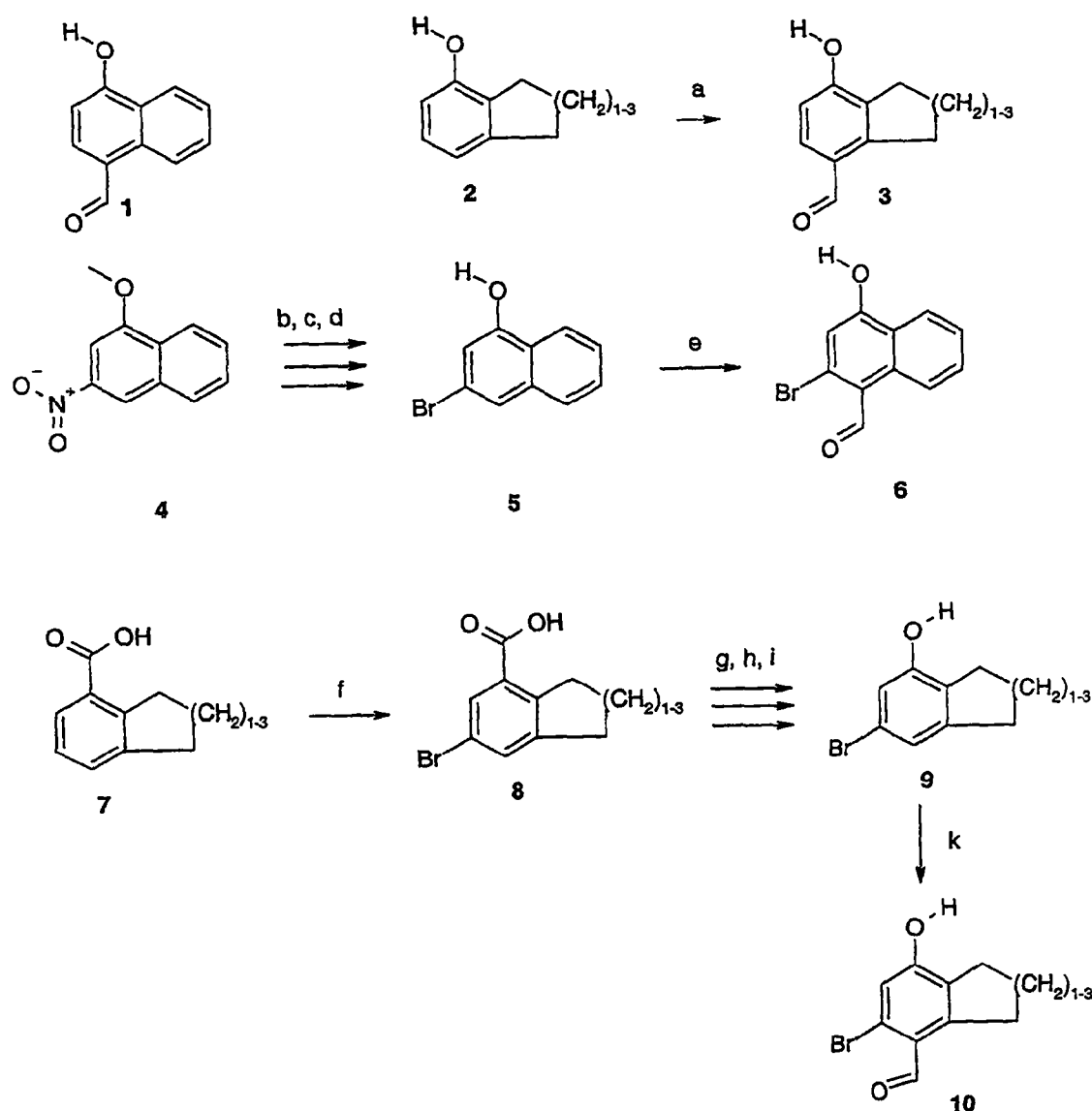
2-Hydroxy-3-methoxy-benzaldehyde 1, optionally substituted with bromine in position 5, can be transformed into benzo[b]thiophen-7-ol 6 or 5-bromo-benzo[b]thiophen-7-ol 6.

- 5 This sequence can be carried out in analogy to the method described in J. Chem. Soc., Perkin Trans. 1 1983(12), 2973-7; for the transformation of 2-hydroxy-3-methoxy-benzaldehyde into benzo[b]thiophen-7-ol. It involves the following steps: treatment with N,N-dimethylthiocarbamoyl chloride in a solvent like tetrahydrofuran in the presence of an aqueous base like potassium hydroxide in water or in the presence of an organic base
- 10 like diisopropyl-ethyl-amine, preferably at temperatures between 0°C and room temperature, generates thionocarbamates 2 (step a); thermal rearrangement of compounds 2 without solvent or preferably in an inert solvent like diphenyl ether at temperatures between 200°C and 280°C leads to arylthiocarbamates 3 (step b); saponification in a

solvent like an alcohol with a base like sodium or potassium hydroxide, preferably between room temperature and the reflux temperature of the solvents, leads then to thiophenols 4 (step c); reaction of these thiophenols 4 with sodium chloroacetate in water or a water / alcohol mixture in the presence of a base like sodium or potassium hydroxide in a temperature range between room temperature and the reflux temperature of the solvents produces then benzothiophene-carboxylic acids 5 (step d); decarboxylation, e. g. in quinoline in the presence of copper bronze at temperatures between 200°C and 240°C, followed by cleavage of the methyl ether function, e. g. by treatment with aqueous hydrobromic acid in acetic acid at reflux, then yields benzo[b]thiophen-7-ols 6 (step e).
10 Similar to the transformations described in scheme 4, benzo[b]thiophen-7-ols 6 can finally be converted into formylated benzo[b]thiophen-7-ol intermediates 7 (step f).

7-Hydroxy-benzofuran is known and commercially available [J. Med. Chem. (1987), 30(1), 62-7]. In a sequence similar to that described above, the 5-bromo-analogue can be prepared from 2-hydroxy-3-methoxy-benzaldehyde 1 by reaction with ethyl chloro-
15 acetate in a solvent like N,N-dimethylformamide in the presence of a base like potassium carbonate at temperatures between 60°C and 120°C yielding benzofuran carboxylic acid 8 (step g). Decarboxylation as described above and ensuing ether cleavage, preferably with pyridine hydrochloride at temperatures around 200°C, then leads to 5-bromo-7-hydroxy-benzofuran 9 (step h). Similar to the transformations described in scheme 4, 5-bromo-7-
20 hydroxy-benzofuran 9 can finally be converted into formylated 5-bromo-7-hydroxy-benzofuran intermediate 10 (step i).

Scheme 7



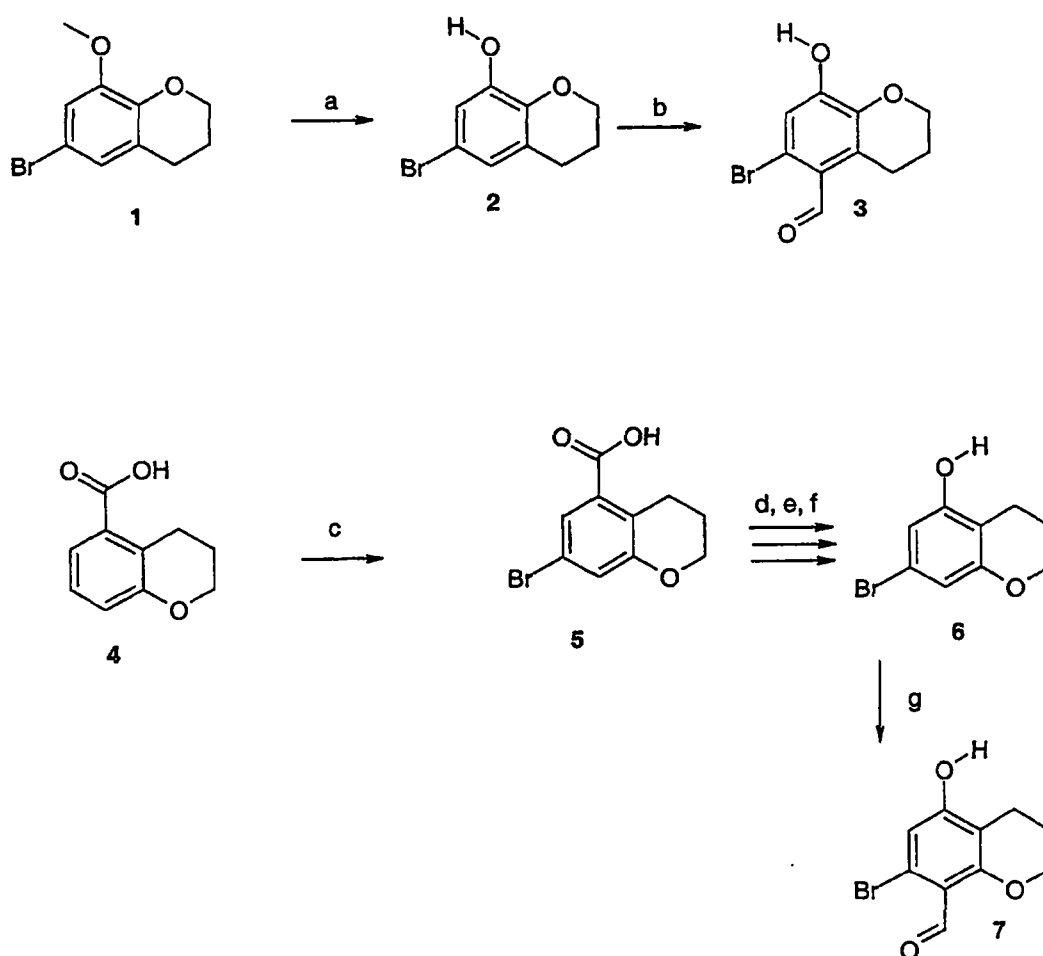
1-Hydroxy-4-formyl-naphthalene 1 and 2,3-annelated phenols 2 with a ring size of 5, 6 and 7 are commercially available or known [see J. Am. Chem. Soc. (1988), 110(19), 6471-6480; U.S. (2000) 6121397; PCT Int. Appl. (1999) WO99/10339]. Similar to the transformations described in scheme 4, 2,3-annelated phenols 2 can be converted into formylated 2,3-annelated phenols 3 (step a).

3-Bromo-1-hydroxy-naphthalene 5, an intermediate carrying a functionality, which allows synthetic modifications at a later stage, can be prepared from 3-nitro-1-methoxy-naphthalene 4 [Monatsh. Chem. (1992), 123(6-7), 637-645] by well established procedures, i. e. reduction of the nitro function, e. g. by hydrogenation in the presence of a palladium catalyst, followed by diazotisation, *Sandmeyer* reaction and cleavage of the

methyl ether function giving 3-bromo-1-hydroxy-naphthalene 5 (steps b, c, d). Similar to the transformations described in scheme 4, 3-bromo-1-hydroxy-naphthalene 5 can be converted into 3-bromo-4-formyl-1-hydroxy-naphthalene 6 (step e).

2,3-Annulated carboxylic acids 7 are known, their 3-bromo analogues 8 are known or can be prepared by established methods of bromination of aromatic nuclei [J. Org. Chem. (1978), 43(11), 2167-70; Ger. Offen. (1977), DE 2633905] (step f). Such 3-bromo-benzoic acids can then be converted into the corresponding phenols 9 by known methods such as e. g. exhaustive reduction with borane to the corresponding alcohol, oxidation, e. g. using Swern conditions (oxalyl chloride / dimethylsulfoxide / triethylamine in dichloromethane, -78°C to room temperature), to the corresponding aldehyde, followed by *Baeyer-Villiger* oxidation e. g. with peracetic acid (40%) in acetic acid (steps g, h, i). Similar to the transformations described in scheme 4, phenols 9 can be converted into intermediates 10 (step k).

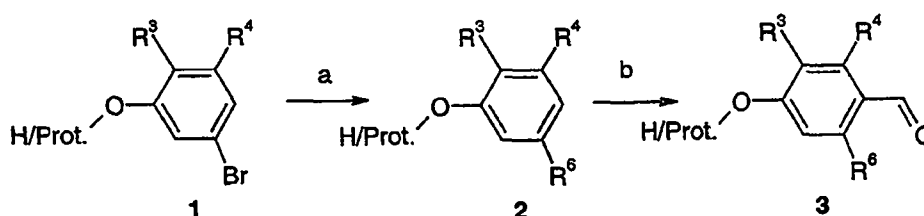
Scheme 8



Bromo-methoxy compound 1 characterized by an annelated dihydro-2H-pyran ring is known [Can. J. Chem. (1982), 60(16), 2093-8]. Cleavage of the methoxy ether function with pyridine hydrochloride at temperatures around 200°C leads to 3-bromo-phenol 2 (step a). Similar to the transformations described in scheme 4, compound 2 can be converted into intermediate 3 (step b).

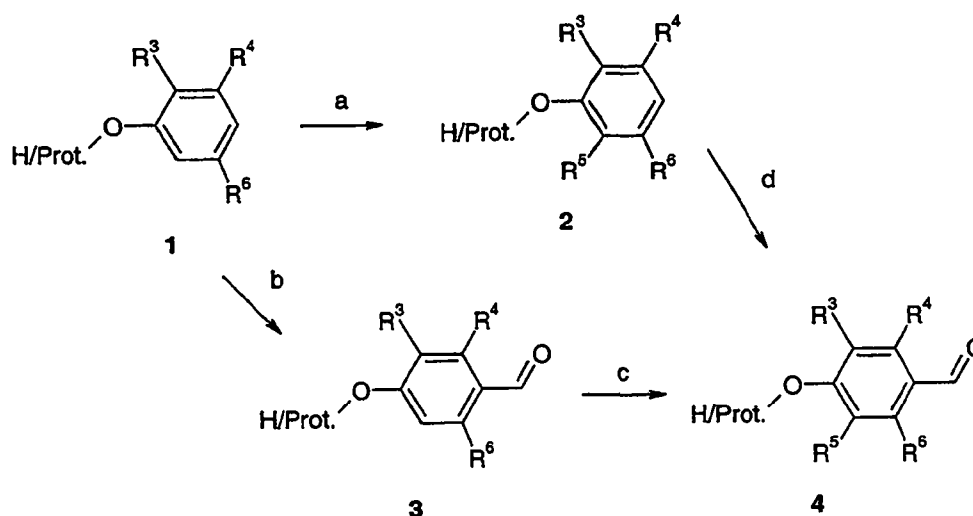
The isomeric building block can be obtained as follows: Carboxylic acid 4 [U.S. (1999), US 5856529 A] can be brominated to give the 3-bromo derivative 5 (step c), which can be transformed into phenol 6 by a sequence analogous to that described for the transformation of compounds 8 into compounds 9 in scheme 7 (steps d, e, f). Similar to the transformations described in scheme 4, phenol 6 can be converted into intermediate 7 (step g).

Scheme 9



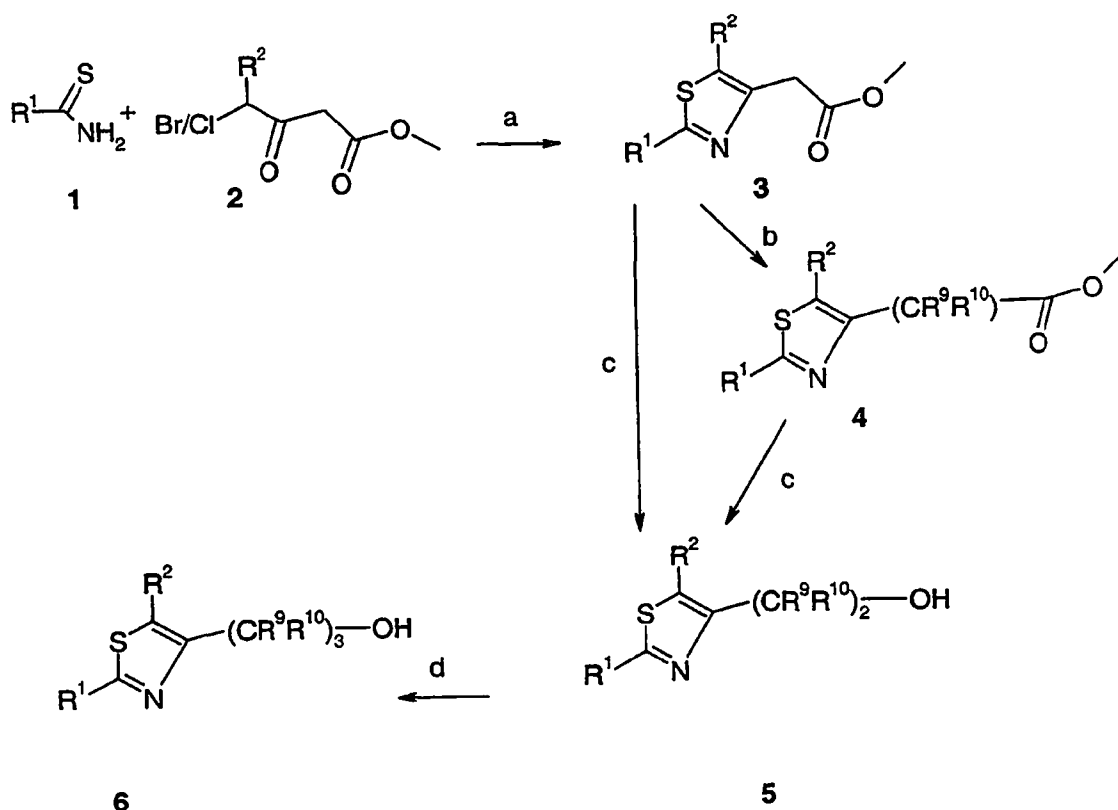
3-Bromo-phenols 1 (intermediates 6, scheme 6, intermediates 9, scheme 6, intermediates 5, scheme 7, intermediates 9, scheme 7, as well as intermediates 2 and 6, scheme 8), optionally carrying a protective function, can be converted into analogous phenols 2 carrying variable substituents R⁶ by first transforming the bromo-compound into the corresponding aryl-lithium derivative (e. g. by using an alkyl lithium reagent in a solvent like tetrahydrofuran, preferably at a temperature around -78°C) and then quenching the latter with a variety of electrophiles using methods well known in the art (step a). For the synthesis of phenols (R⁶=OH), the aryl lithium compounds are reacted with trimethylborate at temperatures between -78°C and the reflux temperature of tetrahydrofuran, followed by oxidation e. g. with N-methyl morpholine N-oxide or H₂O₂ / NaOH, preferably at the reflux temperature of tetrahydrofuran [compare Synlett 1995(09), 931-932]. These phenols 2 with R⁶ equal OH can then be transformed into the corresponding ether compounds by well known methods. Similar to the reaction sequence described in scheme 4, phenolic compounds 2 can finally be converted into phenolic aldehyde intermediates 3 (step b).

Scheme 10



- Phenols 1, optionally carrying a protecting group, can be further transformed into phenols 2 carrying additional substituents R⁵ by known methods of electrophilic aromatic substitution. In many cases, mixture of ortho / para - substitution-, and ortho / para - disubstitution-products will be formed in ratios depending on the precise reaction conditions. In such cases, the reaction conditions can be optimized in order to achieve the highest possible yield of mono-ortho product; optionally, product mixtures can also be separated into pure isomers by known methods such as silica gel chromatography (step a).
- 4-Formyl compounds 3 can be obtained from phenols 1, optionally carrying a protecting group, by transformations as described in scheme 4 (step b). 4-Formyl compounds 3 can then again be used as starting materials applying known methods of electrophilic aromatic substitutions leading to compounds 4 carrying an additional R⁵ substituent (step c). Alternatively, compounds 4 may be obtained from phenols 2 by transformations as described in scheme 4 (step d).

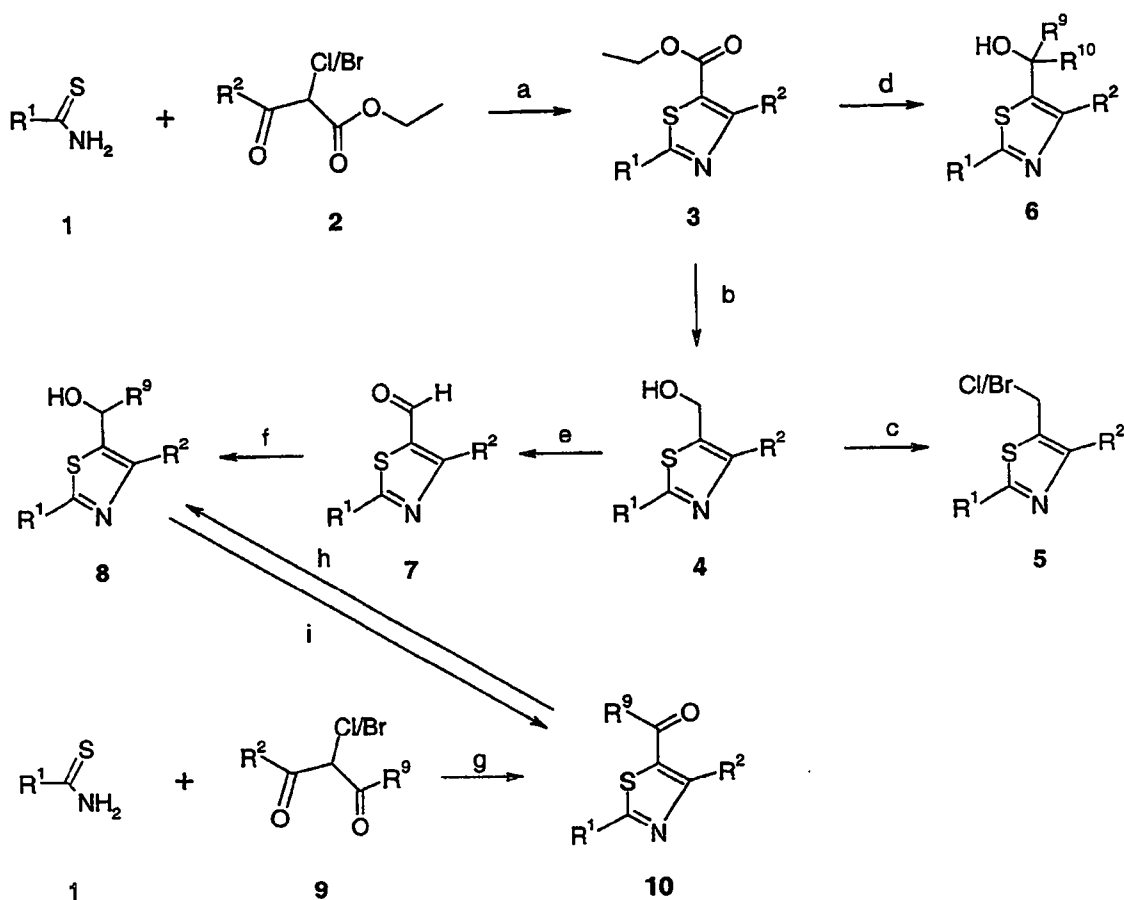
Scheme 11



Thioamides **1** are known or can be prepared by methods known in the art, e. g. by treatment of the corresponding carboxamide with phosphorus pentasulfide or with Lawesson's Reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] in a solvent like toluene at temperatures preferably between 60°C and the reflux temperature of the solvent. Condensation of thioamides **1** with a suitable bis-electrophile, e. g. methyl 4-bromo- or 4-chloro-3-oxo-alkanoates **2**, preferably in a solvent like toluene at elevated temperatures (e. g. at reflux temperature), gives thiazoles **3** carrying an acetic acid ester function at position 4 (step a) [compare PCT Int. Appl. (1997), WO97/31907 A1]. 4-Bromo-3-oxo-alkanoates **2** are known or can be prepared by methods known in the art [compare PCT Int. Appl. (2001), WO 01/79202 A1]. Thiazoles **3** can then be reduced, e. g. with lithium aluminum hydride in solvents like in ether or tetrahydrofuran, to thiazoles **5** with R⁹ = R¹⁰ = H (step c). Alternatively, alkyl groups R⁹ and/or R¹⁰ can be introduced into ester compounds **3** by treatment with a base like potassium tert-butoxide or sodium hydride in solvents like tetrahydrofuran or 1,2-dimethoxyethane followed by addition of one or sequentially two different alkyl halides, a reaction preferably performed between 0°C and 80°C (step b). Mono and/or dialkyl ester compounds **4** can be reduced to compounds **5** e. g. with lithium aluminium hydride in ether or tetrahydrofuran (step c). Alternatively, ester compounds **4** can be transformed into compounds **5** by i)

saponification to the corresponding acid; ii) treatment with R^9Li optionally in the presence of a Cu(I) salt in ether or tetrahydrofuran to yield the alkyl ketones $-COR^9$; iii) subsequent reaction with $R^{10}Li$ or lithium aluminium hydride in ether or tetrahydrofuran (step c). Optionally, an elongation of the side chain can then be performed by standard methods, such as transformation of the alcohol function into a leaving group, e. g. a mesylate, ensuing treatment with cyanide, saponification and reduction, affording thiazoles 6 with an optionally substituted hydroxy-propyl function attached to position 4 (step d). Alternatively, cyano intermediates of this elongation process can be reacted with alkyl Grignard reagents R^9MgX in solvents like ether or tetrahydrofuran between $0^\circ C$ and the reflux temperature of the solvent to form the corresponding R^9CO- alkyl ketones which upon treatment with an alkyllithium reagent $R^{10}Li$ or lithium aluminium hydride in solvents like ether or tetrahydrofuran give alcohols 6 (step d). The alcohol compounds 5 or 6 which contain one or more chiral centers can optionally be separated into optically pure antipodes by methods well known in the art, e. g. chromatography on a chiral HPLC column or by derivatization with an optically pure acid to form esters, which can be separated by conventional HPLC chromatography and then be converted back to the original alcohol. The alcohol compounds 5 or 6 correspond to or can be converted into compounds of general formula 8 (scheme 1), 7 (scheme 2) or 1 (scheme 3) e. g. by treatment with methanesulfonyl chloride in dichloromethane in the presence of a base like triethylamine preferably in a temperature range between $-20^\circ C$ and room temperature or e. g. by reaction with carbon tetrachloride or carbon tetrabromide and triphenylphosphine in solvents like tetrahydrofuran preferably in a temperature range between room temperature and the reflux temperature of the solvents.

Scheme 12



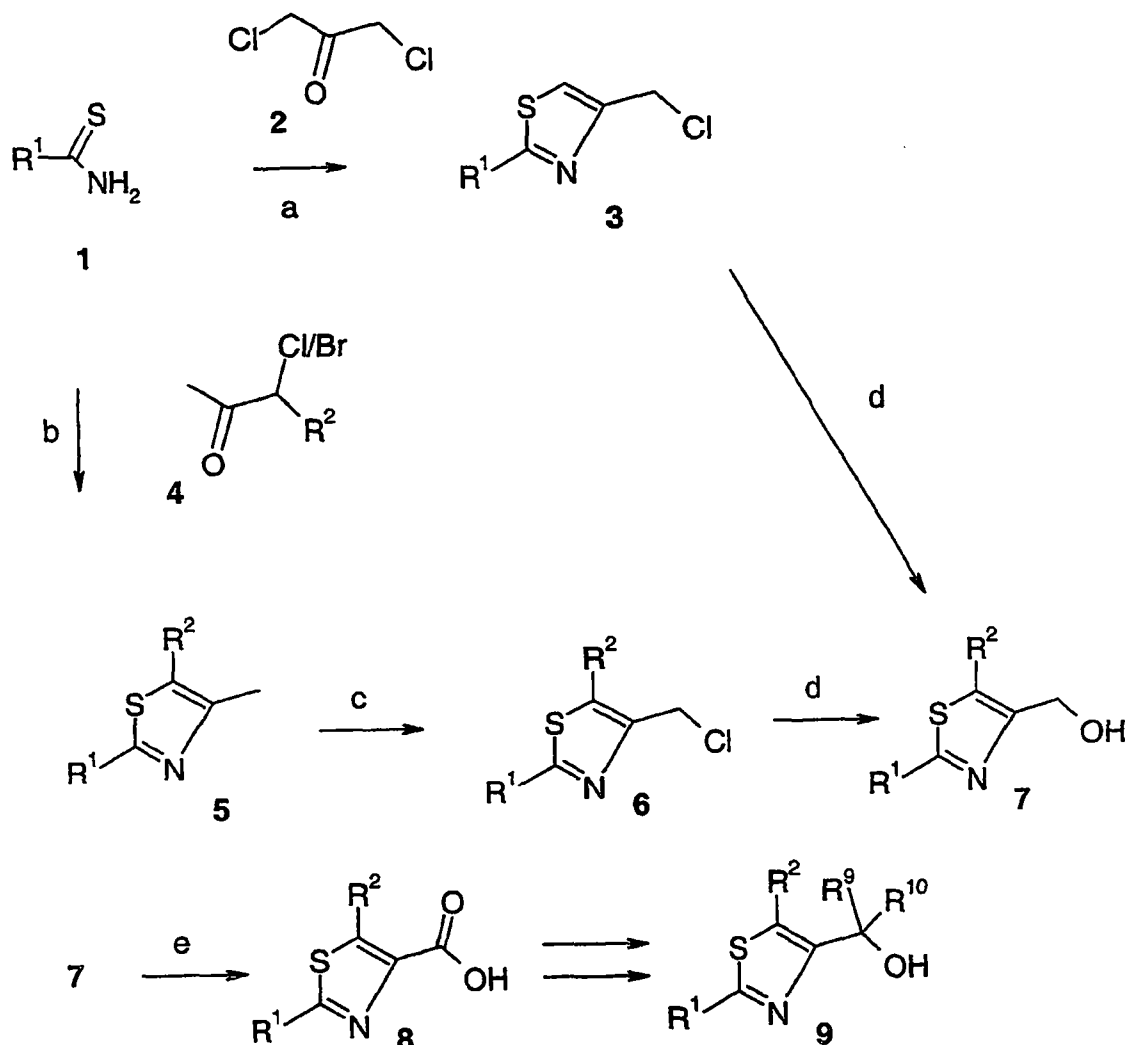
Thioamides **1** can be reacted with 2-halo acetoacetates **2** in solvents like ethanol, preferably at reflux temperature, to give thiazole-carboxylic esters **3** (step a). 2-Halo acetoacetates **2** are known or can be prepared by methods known in the art [compare PCT Int. Appl. (2002), WO 02/062774 A1]. Reduction of these esters **3**, preferably using lithium aluminium hydride in a solvent like ether or tetrahydrofuran, preferably between 0°C and room temperature, gives primary alcohols **4** (step b), which can be used as such or can be converted into the corresponding halides **5**, e. g. by treatment with methanesulfonyl chloride in dichloromethane in the presence of 2,6-lutidine, preferably between -20°C and the reflux temperature of dichloromethane [compare PCT Int. Appl. (2002), WO 02/28433], by treatment with thionyl chloride in a solvent like dichloromethane or chloroform preferably at temperatures between -20°C and +50°C or by treatment with tetrabromomethane, triphenylphosphine in solvents like tetrahydrofuran at temperatures between 0°C and the reflux temperature of the tetrahydrofuran (step c). Esters **3** can be further converted into tertiary alcohols **6** with R⁹ = R¹⁰ through reaction with alkyl organometallic reagents, preferably using alkyl Grignard compounds in a solvent like tetrahydrofuran or ether, preferably between -15 °C and the reflux temperature of the solvent [compare PCT Int. Appl. (2002), WO 02/062774 A1] (step d). Alcohols **6** with R⁹

not equal to R^{10} can be prepared by a sequential procedure: i) saponification to the acid; ii) treatment with R^9Li optionally in the presence of a Cu(I) salt in ether or tetrahydrofuran to yield the alkyl ketones $-COR^9$; iii) subsequent reaction with $R^{10}Li$ or lithium aluminium hydride in ether or tetrahydrofuran (step d). Primary alcohols 4 can be oxidized to aldehydes 7 by methods known in the art, e. g. by treatment with pyridinium chlorochromate in dichloromethane, preferably at temperatures between room temperature and the reflux temperature of dichloromethane or by treatment with manganese dioxide in solvents like dichloromethane, preferably at room temperature (step e). These aldehydes 7 can be converted to the corresponding secondary alcohols 8 through reaction with alkyl organometallic compounds, preferably under the conditions given for the transformation of esters 3 to tertiary alcohols 6 (step f).

Reaction of thioamides 1 with 2-halo 1,3-diketones 9 in solvents like ethanol, preferably at reflux temperature, gives thiazole ketones 10 (step g). Alternatively, ketones 10 can be obtained from secondary alcohols 8 by methods known in the art, e. g. by treatment with Cr(VI) reagents like the Jones reagent (Jones et al., *J. Chem. Soc.* 1953, 2548) (step i). These ketones 10 can be reduced to the corresponding secondary alcohols 8 by methods known in the art, e. g. by treatment with sodium borohydride in alcohol, preferably at temperatures between $-15\text{ }^{\circ}\text{C}$ and $40\text{ }^{\circ}\text{C}$ (step h). This reaction can also be carried out in stereoselective fashion leading to the (R)- or (S)-alcohols 8, e. g. by treatment with borane-dimethylsulfide complex and (S)- or (R)-2-methyl-CBS-oxazaborolidine as chiral catalyst in tetrahydrofuran, preferably at temperatures between $-78\text{ }^{\circ}\text{C}$ and ambient temperature according to Corey et al. (E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* 1987, 109, 5551-5553). If the alcohol compounds 4, 6, or 8 contains one or more chiral centers and are not optically pure, they can optionally be separated into optically pure antipodes by methods well known in the art, e. g. chromatography on a chiral HPLC column or by derivatization with an optically pure acid to form esters, which can be separated by conventional HPLC chromatography and then be converted back to the original alcohol.

The alcohol compounds 4, 6, and 8 and the halide compound 5 correspond to or can be converted into compounds of general formula 8 (scheme 1), 7 (scheme 2) or 1 (scheme 3) e. g. by treatment with methanesulfonyl chloride in dichloromethane in the presence of a base like triethylamine preferably in a temperature range between $-20\text{ }^{\circ}\text{C}$ and room temperature or e. g. by reaction with carbon tetrachloride or carbon tetrabromide and triphenylphosphine in solvents like tetrahydrofuran preferably in a temperature range between room temperature and the reflux temperature of the solvents.

Scheme 13

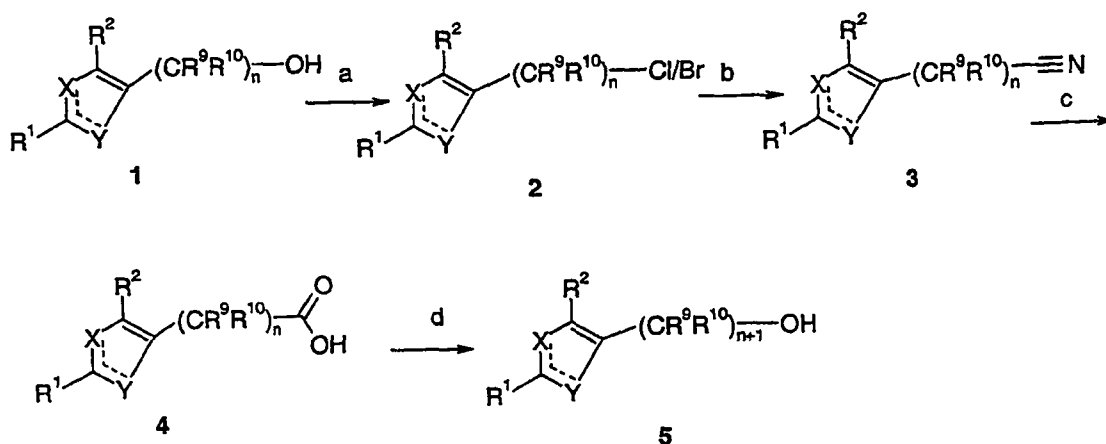


- Thioamides 1 may be condensed with 1,3-dichloroacetone in solvents like acetone or acetonitrile between room temperature and the reflux temperature of the solvents, followed by treatment with a strong acid, e. g. concentrated sulfuric acid, preferably at ambient temperature leading to chloromethyl compounds 3 (step a). Alternatively, thioamides 1 are condensed with α -bromo or α -chloro ketones 4 in a solvent like ethanol, preferably at reflux temperature, to give aryl-thiazoles 5 bearing a methyl function at position 4 (step b) [compare Eur. Pat. Appl. (1987), EP 207453 A2]. By treatment of these aryl-thiazoles 5 with N-chlorosuccinimide in solvents like acetonitrile, preferably at reflux temperature, chloromethyl compounds 6 are obtained (step c) [compare PCT Int. Appl. (2001), WO 0119805 A1]. Chloromethyl compounds 3 and 6 can be converted into hydroxymethyl compounds 7 e. g. by formation of the primary acetates (e. g. with acetic acid in the presence of sodium iodide, potassium carbonate at elevated temperature) and subsequent saponification (e. g. with lithium hydroxide in ethanol / water at room

temperature) (step d). Hydroxymethyl compounds 7 can be oxidized in one step to the corresponding acids 8, e. g. by use of oxidizing agents like chromic acid, permanganate or nitric acid; alternatively, a two step procedure can be used: i) oxidation of the hydroxymethyl compounds 7 to the corresponding aldehydes using e. g. Swern conditions
5 (oxalyl chloride / dimethylsulfoxide / triethylamine in dichloromethane, -78°C to room temperature); ii) subsequent oxidation to the acid compounds 8 by using e. g. sodium chlorite in an alcohol like tert-butanol and water in the presence of NaH_2PO_4 and 2-methyl-2-butene preferably at room temperature (step e). Acid compounds 8 or the
10 corresponding esters can be further transformed as described for esters 3 or the corresponding acids in scheme 12 to give the substituted alcohol compounds 9.

The alcohol compounds 7 and 9 and the halide compounds 3 and 6 correspond to or can be converted into compounds of general formula 8 (scheme 1), 7 (scheme 2) or 1 (scheme 3) e. g. by treatment with methanesulfonyl chloride in dichloromethane in the presence of a base like triethylamine preferably in a temperature range between -20°C and room
15 temperature or e. g. by reaction with carbon tetrachloride or carbon tetrabromide and triphenylphosphine in solvents like tetrahydrofuran preferably in a temperature range between room temperature and the reflux temperature of the solvents.

Scheme 14



Aryl-thiazole alkanols 1 with a chain length of n carbon atoms can be converted into analogues with a chain length of $n+1$ carbon atoms by methods well known in the art, e. g. by conversion of the primary alcohol function into a suitable leaving group, e. g. a halide (step a), reaction with cyanide ion (step b), saponification (step c) followed by reduction of the acid formed (compounds 4) to the primary alcohols 5, e. g. by using diborane in tetrahydrofuran (step d). In order to introduce substituents R^9 and/or R^{10} different from hydrogen, cyano intermediates 3 of this elongation process can be reacted with alkyl Grignard reagents $R^9\text{MgX}$ in solvents like ether or tetrahydrofuran between 0°C and the reflux temperature of the solvents to form the corresponding $R^9\text{CO-}$ alkyl ketones which upon treatment with an alkyllithium reagent $R^{10}\text{Li}$ or lithium aluminium hydride in solvents like ether or tetrahydrofuran give alcohols 5. $R^9\text{CO-}$ alkyl ketones can also be reduced e. g. by treatment with sodium borohydride in alcohol, preferably at temperatures between -15°C and 40°C . This reaction can also be carried out in stereoselective fashion leading to the (R)- or (S)-alcohols 5, e. g. by treatment with borane-dimethylsulfide complex and (S)- or (R)-2-methyl-CBS-oxazaborolidine as chiral catalyst in tetrahydrofuran, preferably at temperatures between -78°C and ambient temperature according to Corey et al. (E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* 1987, 109, 5551-5553). Alternatively, alcohol compounds 5 which contain one or more chiral centers can optionally be separated into optically pure antipodes by methods well known in the art, e. g. chromatography on a chiral HPLC column or by derivatization with an optically pure acid to form esters, which can be separated by conventional HPLC chromatography and then be converted back to the original alcohol. The alcohol compounds 5 correspond to or can be converted into compounds of general formula 8 (scheme 1), 7 (scheme 2) or 1 (scheme 3) e. g. by treatment with methanesulfonyl chloride in dichloromethane in the presence of a base like triethylamine preferably in a temperature range between -20°C and room temperature or e. g. by reaction with carbon tetrachloride or carbon tetrabromide

and triphenylphosphine in solvents like tetrahydrofuran preferably in a temperature range between room temperature and the reflux temperature of the solvents.

The following tests were carried out in order to determine the activity of the compounds of formula (I).

Background information on the performed assays can be found in: Nichols JS et al. "Development of a scintillation proximity assay for peroxisome proliferator-activated
5 receptor gamma ligand binding domain", (1998) Anal. Biochem. 257: 112-119.

Full-length cDNA clones for human PPAR α and mouse PPAR γ were obtained by RT-PCR from human adipose and mouse liver cRNA, respectively, cloned into plasmid vectors and verified by DNA sequencing. Bacterial and mammalian expression vectors were constructed to produce glutathione-s-transferase (GST) and Gal4 DNA binding
10 domain proteins fused to the ligand binding domains (LBD) of PPAR γ (aa 174 to 476) and PPAR α (aa 167 to 469). To accomplish this, the portions of the cloned sequences encoding the LBDs were amplified from the full-length clones by PCR and then subcloned into the plasmid vectors. Final clones were verified by DNA sequence analysis.

Induction, expression, and purification of GST-LBD fusion proteins were performed
15 in *E. coli* strain BL21(pLysS) cells by standard methods (Ref: Current Protocols in Molecular Biology, Wiley Press, edited by Ausubel et al.).

Radioligand Binding Assays

PPAR α receptor binding was assayed in TKE50 (50mM Tris-HCl, pH 8, 50 mM KCl, 2mM EDTA, 0.1 mg/ml fatty acid-free BSA and 10 mM DTT). For each 96 well reaction a
20 140 ng equivalent of GST-PPAR α -LBD fusion protein was bound to 10 ug SPA beads (PharmaciaAmersham) in a final volume of 50 ul by shaking. The resulting slurry was incubated for 1h at RT and centrifuged for 2 min at 1300g. The supernatant containing unbound protein was removed and the semidry pellet containing the receptor-coated beads was resolved in 50 ul of TKE. For radioligand binding e.g. 10000 dpm of 2(S)-(2-benzoyl-
25 phenylamino)-3-{4-[1,1-ditritio-2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid or 2,3-ditritio-2(S)-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid in 50 ul were added, the reaction incubated at RT for 1h and scintillation proximity counting performed. All binding assays were performed in 96 well plates and the amount of bound ligand measured on a Packard
30 TopCount using OptiPlates (Packard). Nonspecific binding was determined in the presence of 10^{-4} M unlabelled compound. Dose response curves were done in triplicates within a range of concentration from 10^{-10} M to 10^{-4} M.

PPAR γ receptor binding was assayed in TKE50 (50mM Tris-HCl, pH 8, 50 mM KCl, 2mM EDTA, 0.1 mg/ml fatty acid-free BSA and 10 mM DTT). For each 96 well reaction an
35 140 ng equivalent of GST-PPAR γ -LBD fusion protein was bound to 10 ug SPA beads

(PharmaciaAmersham) in a final volume of 50 ul by shaking. The resulting slurry was incubated for 1h at RT and centrifuged for 2 min at 1300g. The supernatant containing unbound protein was removed and the semidry pellet containing the recptor-coated beads was resolved in 50 ul of TKE. For radioligand binding e.g. 10000 dpm 2(S)-(2-benzoyl-phenylamino)-3-{4-[1,1-ditritio-2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid in 50 ul were added, the reaction incubated at RT for 1h and scintillation proximity counting performed. All binding assays were performed in 96 well plates and the amount of bound ligand measured on a Packard TopCount using OptiPlates (Packard). Nonspecific binding was determined in the presence of 10^{-4} M unlabelled compound. Dose response curves were done in triplicates within a range of concentration from 10^{-10} M to 10^{-4} M.

Luciferase Transcriptional Reporter Gene Assays

Baby hamster kidney cells (BHK21 ATCC CCL10) were grown in DMEM medium containing 10% FBS at 37°C in a 95%O₂:5%CO₂ atmosphere. Cells were seeded in 6 well plates at a density of 10^5 Cells/well and then batch-transfected with either the pFA-PPAR γ -LBD or pFA-PPAR α -LBD expression plasmids plus a reporter plasmid and an expression plasmid encoding the secretable form of alkaline phosphatase (SEAP) as a normalization control. Transfection was accomplished with the Fugene 6 reagent (Roche Molecular Biochemicals) according to the suggested protocol. Six hours following transfection, the cells were harvested by trypsinization and seeded in 96 well plates at a density of 10^4 cells/well. After 24 hours to allow attachment of cells, the medium was removed and replaced with 100 ul of phenol red-free medium containing the test substances or control ligands (final DMSO concentration: 0.1%). Following incubation of the cells for 24 hours with substances, 50 ul of the supernatant was recovered and analyzed for SEAP activity (Roche Molecular Biochemicals). The remainder of the supernatant was discarded, 50 ul PBS was added per well followed by one volume of Luciferase Constant-Light Reagent (Roche Molecular Biochemicals) to lyse the cells and initiate the luciferase reaction. Luminescence for both SEAP and luciferase was measured in a Packard TopCount. Luciferase activity was normalized to the SEAP control and transcriptional activation in the presence of a test substance was expressed as fold-activation over cells incubated in the absence of the substance. EC₅₀ values were calculated using the XLfit program (ID Business Solutions Ltd. UK).

The the free acids of the compounds of the present invention (R⁸ is hydrogen) exhibit IC₅₀ values of 0.1 nM to 50 μ M, preferably 1 nM to 10 μ M for PPAR α and PPAR γ . The compounds further exhibit EC₅₀ values of 0.1 nM to 50 μ M, preferably 1 nM to 10 μ M for PPAR α and PPAR γ . Compounds, in which R⁸ is not hydrogen are converted in vivo to

compounds in which R⁸ is hydrogen. The following table shows measured values for some selected compounds of the present invention and for a compound already known in the art (e.g.: Rosiglitazone, Drugs 1999, Vol 57(6), 921-930).

	PPAR α IC ₅₀	PPAR γ IC ₅₀	PPAR α EC ₅₀	PPAR γ EC ₅₀
Example 5	133 nmol/l	96 nmol/l	400 nmol/l	389 nmol/l
Example 14	109 nmol/l	457 nmol/l	77 nmol/l	608 nmol/l
Example 19	89 nmol/l	179 nmol/l	71 nmol/l	60 nmol/l
Example 20	24 nmol/l	738 nmol/l	27 nmol/l	209 nmol/l
Example 25	370 nmol/l	535 nmol/l	116 nmol/l	508 nmol/l
Example 43	50 nmol/l	52 nmol/l	2115 nmol/l	543 nmol/l
Example 60	37 nmol/l	42 nmol/l	748 nmol/l	411 nmol/l
Example 64	95 nmol/l	84 nmol/l	513 nmol/l	281 nmol/l
Example 95	114 nmol/l	925 nmol/l	54 nmol/l	1580 nmol/l
Example 102	15 nmol/l	20 nmol/l	215 nmol/l	42 nmol/l
Rosiglitazone	inactive	1090 nmol/l	inactive	405 nmol/l

The compounds of formula (I) and their pharmaceutically acceptable salts and esters can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and their pharmaceutically acceptable, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 1 mg to about 100 mg, comes into consideration. Depending on the dosage it is convenient to administer the daily dosage in several dosage units.

The pharmaceutical preparations conveniently contain about 0.1-500 mg, preferably 0.5-100 mg, of a compound of formula (I).

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

Abbreviations:

AcOEt = ethyl acetate, nBu₂BOTf = dibutylboron triflate, n-BuLi = n-butyllithium, DBAD = di-tert-butyl azodicarboxylate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DEAD = diethyl azodicarboxylate, DIAD = diisopropyl azodicarboxylate, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, eq. = equivalents, HPLC = high performance liquid chromatography, LDA = lithium diisopropylamide, POCl₃ = phosphorous oxychloride, THF = tetrahydrofuran, TMAD = N,N,N',N'-tetramethyl azodicarboxamide.

10

Example 1

a) 3-(4-Benzoyloxy-benzo[b]thiophen-7-yl)-2(Z,E)-ethoxy-acrylic acid ethyl ester

0.537 g (2.00 mmol) 4-Benzoyloxy-benzo[b]thiophene-7-carbaldehyde [Ger. Offen. (1998) DE 19711617 A1] were dissolved under an argon atmosphere in 15 ml of 2-propanol. After cooling to -20°C, 0.944 g (2.20 mmol) (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride [Tetrahedron 50(25), 7543-56(1994)], and 0.415 g (3.00 mmol) of dry potassium carbonate were added. The resulting suspension was stirred in an ice bath and allowed to reach room temperature and stirred overnight at ambient temperature. A second addition of the same amounts of Wittig-reagent and potassium carbonate at -20°C was performed as described above. After filtration and evaporation of the solvent, the residue was purified by flash chromatography (silica gel, hexane/AcOEt from 98:2 to 9:1) giving 0.586 g (77 % of theory) of 3-(4-benzoyloxy-benzo[b]thiophen-7-yl)-2(Z,E)-ethoxy-acrylic acid ethyl ester as a light yellow oil.

20

MS: 382.2 (M)⁺, 291.2, 189.1.

25

b) [rac]-3-(4-Benzoyloxy-benzo[b]thiophen-7-yl)-2-ethoxy-propionic acid methyl ester

0.383 g (1.00 mmol) 3-(4-Benzoyloxy-benzo[b]thiophen-7-yl)-2(Z,E)-ethoxy-acrylic ethyl ester were dissolved under an argon atmosphere in 20 ml THF/MeOH (1:1). 0.248 g (10.2 mmol) of magnesium were added and the reaction mixture then warmed up to 50°C. After 30 minutes, it was cooled down to room temperature and stirred overnight at ambient temperature. After addition of 5 ml HCl (25 % in water) at 25°C, the reaction mixture was stirred vigorously for one hour, then extracted with AcOEt (three times); the

30

organic phases were washed with brine, dried over MgSO_4 , filtered and evaporated. Purification of the yellow oil by flash chromatography (silica gel, hexane/ AcOEt from 9:1 to 4:1) afforded 0.366 g (99 % of theory) of [rac]-3-(4-benzyloxy-benzo[b]thiophen-7-yl)-2-ethoxy-propionic acid methyl ester as a yellowish oil.

5 MS: 370.1 (M^+), 311.2, 253.1.

c) [rac]-2-Ethoxy-3-(4-hydroxy-benzo[b]thiophen-7-yl)-propionic acid methyl ester

4.68 g (12.6 mmol) [rac]-3-(4-Benzyloxy-benzo[b]thiophen-7-yl)-2-ethoxy-propionic acid methyl ester were dissolved under an argon atmosphere in 150 ml dichloromethane at
10 room temperature. 23.9 ml Dimethyl sulfide and 16.03 ml boron trifluoride diethyl etherate were added drop by drop. After 5 hours stirring at room temperature, the reaction mixture was quenched by pouring it into crashed ice/water, then extracted three times with dichloromethane. The organic phases were washed with brine, dried over MgSO_4 , filtered and evaporated to afford 4.92 g of a yellow oil. Purification by flash
15 chromatography (silica gel, hexane, CH_2Cl_2 and MeOH) gave 3.51 g (99 % of theory) of [rac]-2-ethoxy-3-(4-hydroxy-benzo[b]thiophen-7-yl)-propionic acid methyl ester as light yellow solid.

MS: 279.1 (M-H^-).

20 d) [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid methyl ester

0.282 g (1.28 mmol) of 2-(5-methyl-2-phenyl-thiazol-4-yl)-ethanol [PCT Int. Appl. (2002), WO 02/18355 A1] were dissolved in 12 ml THF and treated successively at 0°C with 0.30 g (1.07 mmol) of [rac]-2-ethoxy-3-(4-hydroxy-benzo[b]thiophen-7-yl)-
25 propionic acid methyl ester, 0.397 g (1.50 mmol) of triphenylphosphine, and 0.32 g (1.39 mmol) of DIAD (diisopropyl azodicarboxylate). The cooling bath was then removed and stirring continued for 6 hours. Afterwards, the reaction mixture was evaporated to dryness in vacuo. Flash chromatography (SiO_2 , hexane/ AcOEt), followed by evaporation, delivered 0.474 g (92 % of theory) of [rac]-2-ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-
30 4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid methyl ester as colorless viscous oil.
MS: 482.4 (M+H^+).

e] [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid

0.465 g (0.97 mmol) of [rac]-2-ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid methyl ester were dissolved in 10 ml of dioxane;
5 1.65 ml of a 1N LiOH-solution in water (1.65 mmol) were then added slowly at room temperature. The resulting mixture was stirred for 5 hours at room temperature and then poured onto ice, neutralized to pH 4 with HCl (1N) and extracted 2 times with dichloromethane. The combined organic phases were washed with water, dried over magnesium sulfate and evaporated. Flash chromatography (SiO₂, MeCl₂/MeOH), followed
10 by evaporation, delivered 0.200 g (39 % of theory) of [rac]-2-ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid as colorless viscous oil.

MS: 466.2 (M-H)⁻.

15 **Example 2**

a] 4-Benzoyloxy-5,6,7,8-tetrahydro-naphthalene-1-carbaldehyde

1.00 g (4.20 mmol) of 5-benzoyloxy-1,2,3,4-tetrahydro-naphthalene [J. Org. Chem. (2001), 66(5), 1775-1780] and 0.765 ml (8.39 mmol) of dichloromethyl methyl ether were dissolved in 25 ml of dichloromethane. This solution was cooled down to 0°C, and 2.35 ml
20 (20.98 mmol) of titanium tetrachloride were added slowly. The resulting dark solution was stirred at 0°C for 30 minutes, and then 2.0 ml of HCl (25 % in water) were added slowly at <5°C. The mixture was stirred for 30 minutes at 0°C, the 2 phases were separated and the aqueous phase was extracted 3 times with dichloromethane. The combined organic phases were dried over MgSO₄ and evaporated to afford 1.40 g of a light red oil. Flash
25 chromatography (silica gel, cyclohexane/ethyl acetate = 95:5, then cyclohexane/ethyl acetate = 9:1) left finally 0.73 g (65 % of theory) of 4-benzoyloxy-5,6,7,8-tetrahydro-naphthalene-1-carbaldehyde as yellow solid.

MS: 266.2 (M⁺), 91.2.

30 b] 3-(4-Benzoyloxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-2(Z,E)-ethoxy-acrylic acid methyl ester and 3-(4-benzoyloxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-2(Z,E)-ethoxy-acrylic acid ethyl ester

In analogy to the procedure described in example 1 a), 4-benzyloxy-5,6,7,8-tetrahydro-naphthalene-1-carbaldehyde was reacted with (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride [Tetrahedron 50(25), 7543-56(1994)] to yield 3-(4-benzyloxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-2(Z,E)-ethoxy-acrylic acid methyl ester as colorless solid together with a minor amount of 3-(4-benzyloxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-2(Z,E)-ethoxy-acrylic acid ethyl ester as colorless solid (the use of methanol during the work-up process caused the transesterification observed).

MS (methyl ester): 367.3 (M+H)⁺.

MS (ethyl ester): 381.4 (M+H)⁺.

10

c) [rac]-2-Ethoxy-3-(4-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-propionic acid methyl ester

2.5 g of Pd/C (10 %) were added under argon to 12.5 g (34.1 mmol) of 3-(4-benzyloxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-2(Z,E)-ethoxy-acrylic acid methyl ester dissolved in 180 ml of methanol. The atmosphere was then replaced with H₂, and the suspension was rapidly stirred at room temperature for 2 hours. Filtration over dicalite and evaporation of the solvents left 9.25 g of a dark brown oil. Flash chromatography (silica gel, hexane/ethyl acetate = 9:1) finally gave 7.40 g (78 % of theory) of [rac]-2-ethoxy-3-(4-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-propionic acid methyl ester as yellow oil.

MS: 277.2 (M-H)⁻.

d) [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid methyl ester

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(4-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-propionic acid methyl ester was reacted with 2-(5-methyl-2-phenyl-thiazol-4-yl)-ethanol [PCT Int. Appl. (2002), WO 02/18355 A1] in tetrahydrofuran in the presence of triphenylphosphine and DIAD (diisopropyl azodicarboxylate) to yield [rac]-2-ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid methyl ester as colorless viscous oil.

MS: 480.5 (M+H)⁺.

e] [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid

In analogy to the procedure described in example 1 e], [rac]-2-ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid methyl ester was saponified to yield [rac]-2-ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid as colorless amorphous solid.

MS: 464.2 (M-H)⁻.

Example 3

10 a] [rac]-2-Ethoxy-3-(7-hydroxy-benzo[b]thiophen-4-yl)-propionic acid methyl ester

In analogy to the procedure described in example 2 a], 7-benzyloxy-benzo[b]thiophene (prepared from benzo[b]thiophen-7-ol [J. Chem. Soc., Perkin Trans. 1 (1983), (12), 2973-7] and benzylchloride by treatment with potassium carbonate in N,N-dimethylformamide at room temperature) was reacted with dichloromethyl methyl ether in dichloromethane at 0°C to give 7-benzyloxy-benzo[b]thiophene-4-carbaldehyde. Treatment of 7-benzyloxy-benzo[b]thiophene-4-carbaldehyde with (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride and potassium carbonate in 2-propanol in analogy to the procedure described in example 1 a] gave 3-(7-benzyloxy-benzo[b]thiophen-4-yl)-2(Z,E)-ethoxy-acrylic acid ethyl ester. Reduction of 3-(7-benzyloxy-benzo[b]thiophen-4-yl)-2(Z,E)-ethoxy-acrylic acid ethyl ester with magnesium in THF/MeOH (1:1) at 50°C in analogy to the procedure described in example 1 b], yielded [rac]-3-(7-benzyloxy-benzo[b]thiophen-4-yl)-2-ethoxy-propionic acid methyl ester; subsequent removal of the benzyl protective function with dimethyl sulfide and boron trifluoride diethyl etherate in dichloromethane at room temperature in analogy to the procedure described in example 1 c], gave [rac]-2-ethoxy-3-(7-hydroxy-benzo[b]thiophen-4-yl)-propionic acid methyl ester as light yellow oil.

MS: 279.0 (M-H)⁻.

30 b] [rac]-2-Ethoxy-3-{7-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-4-yl}-propionic acid methyl ester

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(7-hydroxy-benzo[b]thiophen-4-yl)-propionic acid methyl ester was reacted with 2-(5-methyl-2-

phenyl-thiazol-4-yl)-ethanol [PCT Int. Appl. (2002), WO 02/18355 A1] in tetrahydrofuran in the presence of triphenylphosphine and DIAD (diisopropyl azodicarboxylate) to yield [rac]-2-ethoxy-3-{7-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-4-yl}-propionic acid methyl ester as colorless viscous oil.

5 MS: 482.4 (M+H)⁺.

c) [rac]-2-Ethoxy-3-{7-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-4-yl}-propionic acid

In analogy to the procedure described in example 1 e), [rac]-2-ethoxy-3-{7-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-4-yl}-propionic acid methyl ester was
10 saponified to yield [rac]-2-ethoxy-3-{7-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-4-yl}-propionic acid as colorless amorphous solid.

MS: 466.2 (M-H)⁻.

15 **Example 4**

a) 2-(4-tert-Butyl-phenyl)-4-chloromethyl-thiazole

A mixture of 6.0 g of 4-tert-butyl-thiobenzamide (31 mmol) and 5.24 g of 1,3-dichloroacetone (41.3 mmol), dissolved in 20 ml of acetone, was stirred at room temperature for 5 hours and at reflux for 2 hours. After cooling to room temperature, the
20 solid compound formed was collected and dried. Afterwards, it was dissolved in 20 ml of concentrated sulfuric acid and the homogenous mixture was stirred for 15 minutes at ambient temperature. The reaction mixture was then poured onto crushed ice and the 2-(4-tert-butyl-phenyl)-4-chloromethyl-thiazole was extracted with two 50 ml portions of tert-butyl methyl ether. The combined organic phases were washed with water and with
25 brine, dried over anhydrous sodium sulfate and evaporated, leaving 6.65 g (60.5 % of theory) of a colorless viscous oil which solidified upon standing.

MS: 266.3 (M+H)⁺.

b) 3-(4-Benzyloxy-3-methyl-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester

30 In analogy to the procedure described in example 1 a), 4-benzyloxy-3-methyl-benzaldehyde [PCT Int. Appl. (2001), WO 0140172 A1] was reacted with (1,2-diethoxy-2-

oxoethyl)triphenyl phosphonium chloride [Tetrahedron 50 (25), 7543-56 (1994)] to yield 3-(4-benzyloxy-3-methyl-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester as light yellow oil.

MS: 340.2 (M^+).

5 c) [rac]-2-Ethoxy-3-(4-hydroxy-3-methyl-phenyl)-propionic acid ethyl ester

0.7 g of Pd/C were added under argon to a solution of 7.3 g of 3-(4-benzyloxy-3-methyl-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester (21.4 mmol) in 10 ml of tetrahydrofuran.

The atmosphere was then replaced with H_2 , and the suspension was rapidly stirred at room temperature for four hours. Filtration over dicalite and evaporation of the solvent left 4.3 g
10 (79.4 % of theory) of [rac]-2-ethoxy-3-(4-hydroxy-3-methyl-phenyl)-propionic acid ethyl ester as colorless viscous oil.

MS: 252.2 (M^+), 206.2 (M^+ -EtOH).

15 d) [rac]-3-{4-[2-(4-tert-Butyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester

A mixture of 150 mg of [rac]-2-ethoxy-3-(4-hydroxy-3-methyl-phenyl)-propionic acid ethyl ester (0.59 mmol), 190 mg of 2-(4-tert-butyl-phenyl)-4-chloromethyl-thiazole (0.71 mmol) and 325 mg of cesium carbonate (1 mmol) in 5 ml of acetonitrile was stirred at 60°C for 1 h. The solvent was then evaporated and the residue obtained was
20 chromatographed on silicagel using a 98:2 (v/v) mixture of dichloromethane and diethyl ether as the eluent. Thus, 150 mg (52 % of theory) of [rac]-3-{4-[2-(4-tert-butyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester was obtained as a colorless viscous oil.

MS: 482.4 ($M+H$)⁺.

25

e) [rac]-3-{4-[2-(4-tert-Butyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-2-ethoxy-propionic acid

140 mg of [rac]-3-{4-[2-(4-tert-butyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester (0.29 mmol) were dissolved in 5 ml of methanol; 1 ml of
30 a 2N aqueous lithium hydroxide solution was added and the reaction mixture was stirred at 55°C for 1 h. After cooling to room temperature, 1 ml of a 2N aqueous hydrochloric

acid solution and 0.5 ml of a saturated solution of potassium hydrogen sulfate were added. The reaction mixture was then extracted with two 10 ml portions of dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and evaporated, leaving 130 mg (98.6 % of theory) of [rac]-3-{4-[2-(4-tert-butyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-2-ethoxy-propionic acid as a colorless solid.

MS: 452.3 (M-H)⁺.

Example 5

[rac]-2-Ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-propionic acid

In analogy to the procedure described in example 4 d), [rac]-2-ethoxy-3-(4-hydroxy-3-methyl-phenyl)-propionic acid ethyl ester (example 4 c)) was reacted with 4-chloromethyl-2-(4-isopropyl-phenyl)-thiazole (prepared from 4-isopropyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) in acetonitrile in the presence of cesium carbonate to yield [rac]-2-ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-2-ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-propionic acid as colorless gum.

MS: 438.2 (M-H)⁺.

Example 6

[rac]-2-Ethoxy-3-{3-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 4 d), [rac]-2-ethoxy-3-(4-hydroxy-3-methyl-phenyl)-propionic acid ethyl ester (example 4 c)) was reacted with 4-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole (prepared from 4-trifluoromethyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) in acetonitrile in the presence of cesium carbonate to yield [rac]-2-ethoxy-3-{3-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example

4 e], to yield [rac]-2-ethoxy-3-{3-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid as colorless gum.

MS: 464.1 (M-H)⁺.

5 Example 7

a) [rac]-2-Ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester

In analogy to the procedure described in example 1 a), 4-benzyloxy-3-fluoro-benzaldehyde [prepared from 3-fluoro-4-hydroxy-benzaldehyde and benzyl bromide, cesium carbonate in acetonitrile] was reacted with (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium
10 chloride [Tetrahedron 50 (25), 7543-56 (1994)] to yield 3-(4-benzyloxy-3-fluoro-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester. Hydrogenation of 3-(4-benzyloxy-3-fluoro-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester as described in example 4 c) yielded [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester as colorless viscous oil.

MS: 255.0 (M-H)⁺.

15

b) [rac]-3-{4-[2-(4-tert-Butyl-phenyl)-thiazol-4-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 4 d), [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester was reacted with 2-(4-tert-butyl-phenyl)-4-
20 chloromethyl-thiazole (example 4 a)) in acetonitrile in the presence of cesium carbonate to yield [rac]-3-{4-[2-(4-tert-butyl-phenyl)-thiazol-4-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-3-{4-[2-(4-tert-butyl-phenyl)-thiazol-4-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid as colorless solid.

25 MS: 456.3 (M-H)⁺.

Example 8

[rac]-2-Ethoxy-3-{3-fluoro-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid

- In analogy to the procedure described in example 4 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 4-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole (prepared from 4-trifluoromethyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) in acetonitrile in the presence of cesium carbonate to yield [rac]-2-ethoxy-3-{3-fluoro-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-{3-fluoro-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid as colorless solid.
- MS: 468.1 (M-H)⁻.

Example 9

[rac]-2-Ethoxy-3-{3-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid

- In analogy to the procedure described in example 4 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 4-chloromethyl-2-(4-isopropyl-phenyl)-thiazole (prepared from 4-isopropyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) in acetonitrile in the presence of cesium carbonate to yield [rac]-2-ethoxy-3-{3-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-{3-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid as colorless solid.
- MS: 442.2 (M-H)⁻.

25

Example 10

a) 3-(4-Benzyloxy-2-methyl-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester

- A suspension of (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride [Tetrahedron 50(25), 7543-56(1994)] (35.5 g, 82.9 mmol) and DBU (13.6 ml, 91.2 mmol) in THF (60 ml) was stirred for 10 min at ambient temperature. 4-Benzyloxy-2-methyl-benzaldehyde (12.5 g, 55.2 mmol) was added and the reaction mixture was heated under reflux for 16 h. The solvent was concentrated at reduced pressure, the residue was taken up in AcOEt and washed with saturated aqueous NH₄Cl solution and brine. The organic layer

- 62 -

was dried over sodium sulfate, the solvent removed under reduced pressure and the residue purified by column chromatography (silica gel, hexane/AcOEt) to give 14.5 g (42.6 mmol, 77 %) of the title compound as yellow liquid.

MS: 340.2 (M)⁺, 249.2, 147.1, 91.1.

5

b) [rac]-2-Ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester

A solution of 3-(4-benzyloxy-2-methyl-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester (1 g, 2.9 mmol) in ethanol (50 ml) was hydrogenated over 10 % palladium on charcoal (250 mg) at ambient temperature for 2 h. The catalyst was filtered off and the solvent
10 evaporated under reduced pressure to give 600 mg (2.4 mmol, 81 %) of the title compound as yellow liquid which was used in the next step without further purification.

MS: 270.4 (M+NH₄)⁺, 253 (M)⁺, 207.2, 165.3.

c) [rac]-2-Ethoxy-3-(2-methyl-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester

15

To a ice cold solution of [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (50 mg, 0.2 mmol), 2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethanol (85 mg, 0.3 mmol) [PCT Int. Appl. (2001), WO 01/00603 A1] and triphenylphosphine (78 mg, 0.3 mmol) in dichloromethane (2 ml) was added diethyl
20 azodicarboxylate (46 µl, 0.3 mmol). The cooling bath was removed and stirring continued for 6 h. Evaporation of the solvent under reduced pressure gave an orange oil which was purified by column chromatography (silica gel, cyclohexane/AcOEt) to give 34 mg (70 µmol, 33 %) of the title compound as colorless oil.

MS: 522.2 (M+H)⁺, 476.2, 448.2, 270.2.

25

d) [rac]-2-Ethoxy-3-(2-methyl-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

To a solution of [rac]-2-ethoxy-3-(2-methyl-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester (34 mg, 70 µmol) in
30 THF/methanol 2/1 (750 µl) was added a 1 N aqueous LiOH solution (390 µl, 420 µmol).

The reaction mixture was stirred for 1.5 h at ambient temperature, neutralized with 1 N aqueous HCl solution under ice cooling and concentrated under reduced pressure. The residue was dissolved in 1 N HCl/ice water 1/1 and ethyl acetate, the layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were
5 washed with ice water/brine 1/1, dried over sodium sulfate and the solvent was evaporated in vacuo to give the title compound (30 mg, 6 μ mol, 93 %) as colorless solid.

MS: 494.1 (M+H)⁺, 448.2, 420.2, 288.2, 270.2.

Example 11

10 a) [rac]-2-Ethoxy-3-{2-methyl-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid ethyl ester

In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-(5-methyl-2-phenyl-thiazol-4-yl)-ethanol [PCT Int. Appl. (2002), WO 02/18355 A1] in the presence
15 of triphenylphosphine and diethyl azodicarboxylate to yield [rac]-2-ethoxy-3-{2-methyl-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid ethyl ester as colorless oil.

MS: 454.3 (M+H)⁺, 426.3, 370.2, 342.3, 279.2, 202.1.

20 b) [rac]-2-Ethoxy-3-{2-methyl-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 10 d), [rac]-2-ethoxy-3-{2-methyl-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-{2-methyl-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-
25 ethoxy]-phenyl}-propionic acid as colorless solid.

MS: 424.3 (M-H)⁻, 378.1, 329.1, 260.8.

Example 12

a) [2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-acetic acid methyl ester

30 6.75 g (32.3 mmol) of [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 5.0 g (25.9 mmol) of 4-tert-butyl-thiobenzamide were

dissolved in 10 ml of acetone and the mixture was heated at reflux for 1 h. The solvent was evaporated. In order to reesterificate the acid which was formed during the reaction, the residue was dissolved in 25 ml of methanol, 0.25 g of para-toluene sulfonic acid mono-hydrate and 5 ml of trimethyl orthoformate were added and the mixture was heated at
5 reflux for 2 hours. After cooling to room temperature, a solution of 3 g of potassium hydrogencarbonate in H₂O was added. Afterwards, most of the methanol was distilled off and the residue was extracted with tert-butyl methyl ether. After evaporation of the solvent, the residue was chromatographed on silicagel with dichloromethane as eluent. 6.2 g (79 % of theory) of 2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-acetic acid methyl
10 ester were obtained as yellow solid.

MS: 303.1 (M⁺).

b] 2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol

A solution of 6.2 g of 2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-acetic acid methyl
15 ester (20.4 mmol) in 20 ml of THF was added to a suspension of 0.93 g (24.5 mmol) of lithium aluminium hydride, under an argon atmosphere, at 0-5°C. Afterwards, the mixture was stirred at ambient temperature for 1 hour, treated cautiously with a small amount of H₂O followed by 50 ml of ethyl acetate and 20 g of anhydrous sodium sulfate and stirring was continued for 0.5 hours. Then, the reaction mixture was filtered, the
20 filtrate was evaporated, leaving 5.5 g (97 % of theory) of 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol as colorless solid.

MS: 276.2 (M+H)⁺.

c] [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester
25

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol in the presence of triphenylphosphine and diethyl azodicarboxylate to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-
30 4-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester as colorless oil.

MS: 510.4 (M+H)⁺, 464.2, 436.3, 258.2.

d) [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d), [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester was treated with LiOH to obtain [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid as colorless liquid.

MS: 482.3 (M+H)⁺, 430.3, 408.3, 371.3, 323.3, 276.2, 258.2.

Example 13

10 a) [2-(4-Isopropyl-phenyl)-thiazol-4-yl]-acetonitrile

14.5 g (57.6 mmol) of 4-chloromethyl-2-(4-isopropyl-phenyl)-thiazole (prepared from 4-isopropyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) and 4.08 g (83.4 mmol) of sodium cyanide in 50 ml of dimethyl sulfoxide were stirred at 40°C for 2 hours. Then, the reaction mixture was poured into a mixture of ice and water and was subsequently extracted with 3 portions of 75 ml of tert-butyl methyl ether. The combined organic phases were washed with water, then with brine and dried with anhydrous sodium sulfate. After evaporation of the solvent, 13.4 g (96 % of theory) of [2-(4-isopropyl-phenyl)-thiazol-4-yl]-acetonitrile were obtained as brown solid.

MS: 243.2 (M+H)⁺.

20

b) [2-(4-Isopropyl-phenyl)-thiazol-4-yl]-acetic acid

A mixture of 13 g (53.6 mmol) of [2-(4-isopropyl-phenyl)-thiazol-4-yl]-acetonitrile, 20 g of sodium hydroxide (500 mmol), 20 ml of water and 120 ml of propanol was stirred vigorously at 100°C. Hydrolysis was complete after 4 hours. The reaction mixture was then poured onto crushed ice and aqueous HCl, extracted three times with ethyl acetate, washed with water and brine, and dried with anhydrous sodium sulfate. Evaporation of the solvents left 13.8 g (98.5 % of theory) of [2-(4-isopropyl-phenyl)-thiazol-4-yl]-acetic acid as light brown solid.

MS: 260.0 (M-H)⁻.

30

c) [2-(4-Isopropyl-phenyl)-thiazol-4-yl]-acetic acid methyl ester

A solution of 6.9 g (26.4 mmol) of [2-(4-isopropyl-phenyl)-thiazol-4-yl]-acetic acid and 0.5 g of p-toluenesulfonic acid mono-hydrate (catalyst) in 70 ml of methanol and 5 ml of trimethyl orthoformate was heated at reflux for 5 hours. After neutralization with aqueous sodium bicarbonate solution, evaporation of the solvents, extraction of the residue with tert-butyl methyl ether, drying over anhydrous sodium sulfate and evaporation of the solvent, 6.4 g (88 % of theory) of [2-(4-isopropyl-phenyl)-thiazol-4-yl]-acetic acid methyl ester were obtained as light brown oil.

MS: 275.1 (M^+).

10 d) 2-[2-(4-Isopropyl-phenyl)-thiazol-4-yl]-ethanol

In analogy to the procedure described for example 12 b), 6.3 g (22.8 mmol) of [2-(4-isopropyl-phenyl)-thiazol-4-yl]-acetic acid methyl ester were reduced with lithium aluminium hydride to 2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethanol. 4.8 g of an orange, viscous oil were obtained (85 % of theory).

15 MS: 248.1 ($M+H$)⁺.

e) [rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester

In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethanol in the presence of triphenylphosphine and diethyl azodicarboxylate to yield [rac]-2-ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester as colorless oil.

MS: 482.3 ($M+H$)⁺, 436.2, 392.2, 364.2, 320.3, 256.2, 230.2.

25

f) [rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid

In analogy to the procedure described in example 10 d), [rac]-2-ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid as colorless liquid.

30

MS: 454.3 ($M+H$)⁺, 439.1, 371.3, 335.0, 258.3, 191.3.

Example 14**a) 4-Chloromethyl-2-(4-chloro-phenyl)-thiazole**

In analogy to the procedure described in example 4 a), 4-chlorothiobenzamide was reacted
5 with 1,3-dichloroacetone followed by treatment with concentrated sulfuric acid to obtain
4-chloromethyl-2-(4-chloro-phenyl)-thiazole as colorless crystals.

MS: 244.2 (M+H)⁺, 187.2.

**b) [rac]-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-
10 propionic acid ethyl ester**

A mixture of [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester
(37 mg, 0.15 mmol) (example 10 b)), 4-chloromethyl-2-(4-chloro-phenyl)-thiazole
(44 mg, 0.18 mmol), cesium carbonate (59 mg, 0.18 mmol) and a trace of potassium
iodide were suspended in acetone (3 ml). The suspension was heated under reflux for 5 h,
15 the solvent evaporated under reduced pressure and the residue dissolved in 2 N HCl/ice
water 1/1 and ethyl acetate. The layers were separated and the aqueous layer was extracted
two times with ethyl acetate. The combined organic layers were washed two times with
brine and dried over sodium sulfate. The solvent was removed under reduced pressure and
the residue purified by column chromatography (silica gel, cyclohexane/AcOEt) to give
20 46 mg (0.1 mmol, 68 %) of the title compound as colorless oil.

MS: 482.2 (M+Na)⁺, 460.2 (M+H)⁺, 432.3, 389.2, 317.2, 279.3, 211.3, 184.4.

**c) [rac]-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-
propionic acid**

25 In analogy to the procedure described in example 10 d), [rac]-3-{4-[2-(4-chloro-phenyl)-
thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester was treated
with LiOH to obtain [rac]-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-
phenyl}-2-ethoxy-propionic acid as light yellow liquid.

MS: 432.2 (M+H)⁺, 386.1, 249.2, 218.3, 176.2.

Example 15

a) [rac]-3-{4-[2-(4-tert-Butyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester

In analogy to the procedure described in example 14 b), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-(4-tert-butyl-phenyl)-4-chloromethyl-thiazole (example 4 a)) in the presence of cesium carbonate and potassium iodide to yield [rac]-3-{4-[2-(4-tert-butyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester as colorless liquid.

MS: 504.3 (M+Na)⁺, 482.3 (M+H)⁺, 438.3, 271.3, 230.2.

10

b) [rac]-3-{4-[2-(4-tert-Butyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d), [rac]-3-{4-[2-(4-tert-butyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester was treated with LiOH to obtain [rac]-3-{4-[2-(4-tert-butyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid as colorless foam.

MS: 454.3 (M+H)⁺, 383.1, 320.3, 266.8, 252.3, 234.3, 166.3.

Example 16

20 a) [rac]-2-Ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid ethyl ester

In analogy to the procedure described in example 14 b), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 4-chloromethyl-2-(4-isopropyl-phenyl)-thiazole (prepared from 4-isopropyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) in the presence of cesium carbonate and potassium iodide to yield [rac]-2-ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid ethyl ester as colorless liquid.

MS: 490.2 (M+Na)⁺, 468.2 (M+H)⁺, 424.4, 257.1, 216.3.

30

b) [rac]-2-Ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid

In analogy to the procedure described in example 10 d), [rac]-2-ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid ethyl ester was
5 treated with LiOH to obtain [rac]-2-ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid as colorless oil.

MS: 438.2 (M-H)⁻, 392.1, 348.3, 255.2.

Example 17

10 a) (S)-4-Benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-methyl-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one

(S)-4-Benzyl-3-ethoxyacetyl-oxazolidin-2-one (12.45 g, 47 mmol) (for the preparation of (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one see: D. Haigh, H. C. Birrell, B. C. C. Cantello, D. S. Eggleston, R. C. Haltiwanger, R. M. Hindley, A. Ramaswamy, N. C. Stevens,
15 *Tetrahedron: Asymmetry* 1999, 10, 1353-1367) was dissolved in dry dichloromethane (270 ml) under an argon atmosphere and the solution was cooled to -78 °C. Triethylamine (7.98 ml, 57 mmol) was added, followed by the slow addition, over approximately 20 min, of di-n-butylboron triflate (1 M solution in dichloromethane, 25 ml, 50 mmol) such that the reaction temperature was kept below -70 °C. The mixture was stirred at -78 °C for
20 50 min, the cooling bath was replaced with an ice bath and the mixture stirred at 0 °C for additional 50 min before being recooled to -78 °C. A solution of 4-benzyloxy-2-methyl-benzaldehyde (10.7 g, 47 mmol) in dry dichloromethane (130 ml) was added over ca. 45 min, such that the reaction temperature was maintained below -70 °C. The resulting mixture was stirred at -78 °C for 45 min, warmed from -78 °C to 0 °C and stirred at 0 °C
25 for a further 1.5 h. The reaction mixture was poured onto ice water/brine and extracted two times with dichloromethane. The combined extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, cyclohexane/AcOEt) to give 22.3 g (45.6 mmol, 96 %) of the title compound as colorless oil. According to ¹H-NMR
30 spectroscopy, one of the four isomers is strongly predominating. The configuration was tentatively assigned as 2S,3R according to D. Haigh et al., *Tetrahedron: Asymmetry* 1999, 10, 1353-1367.

MS: 512.3 (M+Na)⁺, 472.3, 447.2, 387.2, 327.2, 295.3, 267.3, 232.1, 175.1.

b) (2S,3R)-3-(4-Benzoyloxy-2-methyl-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester

A 5.4 M solution of sodium methoxide (7.3 ml, 39.5 mmol) was added to an ice-cooled and stirred suspension of (S)-4-benzyl-3-[(2S,3R)-3-(4-benzoyloxy-2-methyl-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one (17.6 g, 36 mmol) in dry methanol (87 ml). The mixture was stirred at 0 °C for 15 min, quenched and neutralized by the addition of dilute aqueous hydrochloric acid (1.0 M). The solution was concentrated under reduced pressure and the residue dissolved in ice water/ethyl acetate 1/1. The layers were separated and the aqueous layer was extracted two times with ethyl acetate. The combined organic layers were washed with ice water and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, cyclohexane/AcOEt) to give 8.6 g (25 mmol, 69 %) of the title compound as light yellow oil. According to ¹H-NMR spectroscopy, one single diastereomer was obtained.

MS: 367.2 (M+Na)⁺, 362.2 (M+NH₄)⁺, 327.3, 299.3, 239.3, 211.2.

c) (2S)-3-(4-Benzoyloxy-2-methyl-phenyl)-2-ethoxy-propionic acid methyl ester

Triethylsilane (23 ml, 145 mmol) was added to a vigorously stirred, ice-cooled solution of (2S,3R)-3-(4-benzoyloxy-2-methyl-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester (5 g, 14.5 mmol) in trifluoroacetic acid (84 ml) under an argon atmosphere. The mixture was stirred at 0 °C for 30 min and for additional 2 h at ambient temperature. The solution was poured onto crashed ice and extracted with ethyl acetate. The organic layer was washed two times with water and neutralized with saturated aqueous sodium bicarbonate solution. The ethyl acetate layer was washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure to give a colorless oil which was purified by column chromatography (silica gel, cyclohexane/AcOEt) to yield 2.15 g (6.5 mmol, 45 %) of the title compound as colorless oil.

MS: 351.2 (M+Na)⁺, 346.3 (M+NH₄)⁺, 283.2, 276.2, 223.2, 195.5.

d) (2S)-2-Ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester

A solution of (2S)-3-(4-benzoyloxy-2-methyl-phenyl)-2-ethoxy-propionic acid methyl ester (3.6 g, 11 mmol) in methanol (300 ml) was hydrogenated over 10 % palladium on charcoal (1 g) at ambient temperature for 2 h. The catalyst was filtered off and the solvent

evaporated under reduced pressure to give 2 g (8.4 mmol, 77 %) of the title compound as yellow liquid which was used in the next step without further purification.

MS: 261.2 (M+Na)⁺, 256.1 (M+NH₄)⁺, 239.3 (M+H)⁺, 193.2, 151.1.

5 e) (2S)-3-{4-[2-(3-Chloro-4-fluoro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid methyl ester

In analogy to the procedure described in example 14 b), (2S)-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester was reacted with 2-(3-chloro-4-fluoro-phenyl)-4-chloromethyl-thiazole (prepared from 3-chloro-4-fluoro-thiobenzamide and
10 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) in the presence of cesium carbonate and potassium iodide to yield (2S)-3-{4-[2-(3-chloro-4-fluoro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid methyl ester as yellow liquid.

15 f) (2S)-3-{4-[2-(3-Chloro-4-fluoro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d), (2S)-3-{4-[2-(3-chloro-4-fluoro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid methyl ester was treated with LiOH to obtain (2S)-3-{4-[2-(3-chloro-4-fluoro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid as colorless solid.
20

MS: 448.1 (M-H)⁻, 402.1, 357.9, 308.8, 283.5, 254.8, 222.8.

Example 18

25 a) (2S)-2-Ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid methyl ester

In analogy to the procedure described in example 14 b), (2S)-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (example 17 d)) was reacted with 4-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole (prepared from 4-trifluoromethyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example
30 4 a)) in the presence of cesium carbonate and potassium iodide to yield (2S)-2-ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid methyl ester as colorless liquid.

MS: 502.2 (M+Na)⁺, 480.3 (M+H)⁺, 434.2, 420.2, 392.0, 283.1, 242.1, 181.2.

b) (2S)-2-Ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid

- 5 In analogy to the procedure described in example 10 d), (2S)-2-ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid methyl ester was treated with LiOH to obtain (2S)-2-ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid as colorless solid.

MS: 488.2 (M+Na)⁺, 466.1 (M+H)⁺, 420.1, 371.3, 307.2, 269.2, 217.2, 187.2.

10

Example 19

a) (S)-4-Benzyl-3-[(2S)-3-(4-benzyloxy-2-methyl-phenyl)-2-ethoxy-propionyl]-oxazolidin-2-one

- 15 In analogy to the procedure described in example 17 c), (S)-4-benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-methyl-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one (example 17 a)) was treated with triethylsilane in trifluoroacetic acid to yield the title compound as colorless liquid.

MS: 496.2 (M+Na)⁺, 491.3 (M+NH₄)⁺, 474.2 (M+H)⁺, 428.3, 352.3, 251.2, 175.2.

- 20 b) (S)-4-Benzyl-3-[(2S)-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionyl]-oxazolidin-2-one

In analogy to the procedure described in example 17 d), (S)-4-benzyl-3-[(2S)-3-(4-benzyloxy-2-methyl-phenyl)-2-ethoxy-propionyl]-oxazolidin-2-one was hydrogenated over 10 % palladium on charcoal to give the title compound as yellow liquid.

- 25 MS: 382.1 (M-H)⁻, 324.9, 305.1, 282.9, 261.8, 255.2, 221.4, 175.6.

c) (S)-4-Benzyl-3-[(2S)-3-{4-[2-(3-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionyl]-oxazolidin-2-one

- 30 In analogy to the procedure described in example 10 c), (S)-4-benzyl-3-[(2S)-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionyl]-oxazolidin-2-one was reacted with [2-(3-

- chloro-phenyl)-thiazol-4-yl]-methanol (for the preparation of [2-(3-chloro-phenyl)-thiazol-4-yl]-methanol see: C. Lambert, R. Pepis, *International Patent Appl., Publication No.* WO 8900568 (A1), 1989) in the presence of triphenylphosphine and diethyl azodicarboxylate to yield (S)-4-benzyl-3-[(2S)-3-{4-[2-(3-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionyl]-oxazolidin-2-one as colorless solid.
- MS: 613.3 (M+Na)⁺, 591.2 (M+H)⁺, 561.4, 487.2, 465.2, 419.2, 368.1, 299.3, 211.3, 167.2.

d) (2S)-3-{4-[2-(3-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

- 10 (S)-4-Benzyl-3-[(2S)-3-{4-[2-(3-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionyl]-oxazolidin-2-one (80 mg, 140 µmol) was dissolved in ice-cooled THF (0.8 ml) and treated with 1 N NaOH (0.34 ml, 350 µmol) at 0 °C for 2 h. The reaction mixture was poured onto ice water/HCl and extracted two times with diethyl ether. The combined organic layers were washed with water and brine and dried over sodium sulfate.
- 15 Evaporation of the solvent gave 52 mg (120 µmol, 89 %) of the title compound as colorless solid.

MS: 454.2 (M+Na)⁺, 432.1 (M+H)⁺, 345.1, 269.2, 241.2, 187.2.

Example 20

- 20 a) (2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid methyl ester

- In analogy to the procedure described in example 14 b), (2S)-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (example 17 d)) was reacted with 4-chloromethyl-2-(4-chloro-phenyl)-thiazole (example 14 a)) in the presence of cesium carbonate and potassium iodide to yield (2S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid methyl ester as light yellow liquid.
- 25

MS: 446.1 (M+H)⁺, 342.2, 279.1, 242.2, 219.3.

- b) (2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid
- 30

- In analogy to the procedure described in example 10 d], (2S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid methyl ester was treated with LiOH to obtain (2S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid as colorless solid, which was crystalized from
5 hexane/AcOEt to afford colorless crystals. According to chiral HPLC of the corresponding methyl ester (Chiralcel-OJ), the enantiomeric excess amounts to 98.9 %.

MS: 430.2 (M-H)⁻, 384.1, 293.1, 255.2.

Example 21

- 10 a] (S)-4-Benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-methoxy-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one

- In analogy to the procedure described in example 17 a], (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one (for the preparation of (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one see: D. Haigh, H. C. Birrell, B. C. C. Cantello, D. S. Eggleston, R. C. Haltiwanger, R. M.
15 Hindley, A. Ramaswamy, N. C. Stevens, *Tetrahedron: Asymmetry* 1999, 10, 1353-1367) was reacted with 4-benzyloxy-2-methoxy-benzaldehyde in the presence of triethylamine and di-n-butylboron triflate to give (S)-4-benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-methoxy-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one as light yellow solid. According
20 to ¹H-NMR spectroscopy, one of the four isomers is strongly predominating. The configuration was tentatively assigned as 2S,3R according to D. Haigh et al., *Tetrahedron: Asymmetry* 1999, 10, 1353-1367.

MS: 528.3 (M+Na)⁺, 523.3 (M+NH₄)⁺, 488.3, 442.4, 311.2, 239.3.

- 25 b] (2S,3R)-3-(4-Benzyl-3-ethoxy-2-methoxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester

- In analogy to the procedure described in example 17 b], (S)-4-benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-methoxy-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one was treated with sodium methoxide in methanol to give (2S,3R)-3-(4-benzyloxy-2-methoxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester as colorless liquid. According to
30 ¹H-NMR spectroscopy, one single diastereomer was obtained.

MS: 383.2 (M+Na)⁺, 378.2 (M+NH₄)⁺, 343.2, 311.2, 283.2, 239.3, 163.2.

c] (2S)-2-Ethoxy-3-(4-hydroxy-2-methoxy-phenyl)-propionic acid methyl ester

A solution of (2S,3R)-3-(4-benzyloxy-2-methoxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester (100 mg, 200 μ mol) and oxalic acid dihydrate (150 mg, 1.2 mmol) in isopropanol (2 ml) was hydrogenated at a pressure of 50 atmospheres over 10 % palladium
5 on charcoal (20 mg) at ambient temperature for 6.5 h. The catalyst was filtered off and the solvent evaporated under reduced pressure. The residue was dissolved in ice water/aqueous sodium bicarbonate solution 1/1 and extracted two times with ethyl acetate. The combined extracts were washed two times with ice water/brine 1/1 and dried over sodium sulfate. The solvent was removed under reduced pressure to give a yellow liquid
10 which was purified by column chromatography (silica gel, cyclohexane/AcOEt) to yield 43 mg (170 μ mol, 85 %) of the title compound as light yellow liquid.

MS: 277.1 (M+Na)⁺, 209.2, 195.3, 181.2, 177.2, 167.2.

d] (2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methoxy-phenyl}-2-ethoxy-propionic acid methyl ester

In analogy to the procedure described in example 14 b], (2S)-2-ethoxy-3-(4-hydroxy-2-methoxy-phenyl)-propionic acid methyl ester was reacted with 4-chloromethyl-2-(4-chloro-phenyl)-thiazole (example 14 a]) in the presence of cesium carbonate and potassium iodide to yield (2S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methoxy-phenyl}-2-ethoxy-propionic acid methyl ester as light yellow liquid.
20

MS: 462.1 (M+H)⁺, 416.1, 305.4, 251.2, 174.3.

e] (2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methoxy-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d], (2S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methoxy-phenyl}-2-ethoxy-propionic acid methyl ester was treated with LiOH to obtain (2S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methoxy-phenyl}-2-ethoxy-propionic acid as colorless solid.
25

MS: 446.1 (M-H)⁻, 400.1, 356.0, 329.8, 281.0, 255.5, 227.0, 192.1.

Example 22

a) (S)-4-Benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-chloro-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one

In analogy to the procedure described in example 17 a), (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one (for the preparation of (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one see: D. Haigh, H. C. Birrell, B. C. C. Cantello, D. S. Eggleston, R. C. Haltiwanger, R. M. Hindley, A. Ramaswamy, N. C. Stevens, *Tetrahedron: Asymmetry* 1999, 10, 1353-1367) was reacted with 4-benzyloxy-2-chloro-benzaldehyde (for the preparation of 4-benzyloxy-2-chloro-benzaldehyde see: T. Kimachi, M. Kawase, S. Matsuki, K. Tanaka, F. Yoneda, *J. Chem. Soc., Perkin Trans. 1* 1990, 253-256) in the presence of triethylamine and di-n-butylboron triflate to give (S)-4-benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-chloro-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one as colorless liquid. According to ¹H-NMR spectroscopy, one of the four isomers is strongly predominating. The configuration was tentatively assigned as 2S,3R according to D. Haigh et al., *Tetrahedron: Asymmetry* 1999, 10, 1353-1367.

MS: 532.3 (M+Na)⁺, 527.2 (M+NH₄)⁺, 446.1, 381.2, 315.1, 287.2, 243.2, 178.2.

b) (2S,3R)-3-(4-Benzoyloxy-2-chloro-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester

In analogy to the procedure described in example 17 b), (S)-4-benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-chloro-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one was treated with sodium methoxide in methanol to give (2S,3R)-3-(4-benzyloxy-2-chloro-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester as colorless liquid. According to ¹H-NMR spectroscopy, one single diastereomer was obtained.

MS: 387.1 (M+Na)⁺, 382.2 (M+NH₄)⁺, 328.2, 319.2, 279.2, 203.2.

c) (2S)-3-(4-Benzoyloxy-2-chloro-phenyl)-2-ethoxy-propionic acid methyl ester

In analogy to the procedure described in example 17 c), (2S,3R)-3-(4-benzyloxy-2-chloro-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester was treated with triethylsilane in trifluoroacetic acid to yield (2S)-3-(4-benzyloxy-2-chloro-phenyl)-2-ethoxy-propionic acid methyl ester as colorless liquid.

MS: 371.4 (M+Na)⁺, 366.2 (M+NH₄)⁺, 303.2, 269.2, 222.2, 187.2.

d] (2S)-3-(2-Chloro-4-hydroxy-phenyl)-2-ethoxy-propionic acid methyl ester

Dimethyl sulfide (5.8 ml, 79 mmol) and boron trifluoride diethyl etherate (46 % purity, 4.3 ml, 16 mmol) were added to a ice cold solution of (2S)-3-(4-benzyloxy-2-chloro-phenyl)-2-ethoxy-propionic acid methyl ester (1.1 g, 3.2 mmol) in dichloromethane
5 (34 ml) under an argon atmosphere. The mixture was stirred for 5 h at ambient temperature, poured into ice water/brine 1/1 and extracted two times with dichloromethane. The combined extracts were washed with ice water/brine 1/1 and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a colorless oil
10 which was purified by column chromatography (silica gel, cyclohexane/AcOEt) to yield 0.6 g (2.3 mmol, 74 %) of the title compound as colorless oil.

MS: 281.0 (M+Na)⁺, 276.1 (M+NH₄)⁺, 251.3, 213.3, 187.2.

e] (2S)-3-{2-Chloro-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-phenyl}-2-ethoxy-propionic acid methyl ester
15

In analogy to the procedure described in example 14 b], (2S)-3-(2-chloro-4-hydroxy-phenyl)-2-ethoxy-propionic acid methyl ester was reacted with 4-chloromethyl-2-(4-chloro-phenyl)-thiazole (example 14 a]) in the presence of cesium carbonate and potassium iodide to yield (2S)-3-{2-chloro-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-phenyl}-2-ethoxy-propionic acid methyl ester as light yellow solid.
20

MS: 466.1 (M+H)⁺, 407.2, 371.4, 344.1, 300.2, 269.2, 187.2.

f] (2S)-3-{2-Chloro-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-phenyl}-2-ethoxy-propionic acid

25 In analogy to the procedure described in example 10 d], (2S)-3-{2-chloro-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-phenyl}-2-ethoxy-propionic acid methyl ester was treated with LiOH to obtain (2S)-3-{2-chloro-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-phenyl}-2-ethoxy-propionic acid as colorless solid.

MS: 452.1 (M+H)⁺, 420.9, 399.4, 371.4, 299.7, 265.3, 237.0, 190.2.

Example 23**a) 1-Ethyl-3-(phenylmethoxy)-benzene**

To a suspension of potassium carbonate (17 g, 123 mmol) in N,N-dimethylformamide (40 ml) was added a solution of 3-ethyl-phenol (14.8 ml, 123 mmol) in N,N-dimethylformamide (40 ml) at 2 °C under an argon atmosphere. After stirring for 50 min at 2 °C, benzyl bromide (14.6 ml, 123 mmol) was added over a period of 15 min at 2 °C. The suspension was stirred for additional 30 min at 2 °C and for 12 h at ambient temperature. After adding ice water (250 ml), the solution was extracted two times with diethyl ether. The combined extracts were washed two times with brine and dried over sodium sulfate. Evaporation of the solvent gave a yellow oil which was purified by column chromatography (silica gel, cyclohexane) to yield 24.3 g (114 mmol, 93 %) of the title compound as yellow liquid.

MS: 212.2 (M+H)⁺, 183.1, 91.2, 65.1.

b) 1-Bromo-2-ethyl-4-(phenylmethoxy)-benzene

To a solution of 1-ethyl-3-(phenylmethoxy)-benzene (15 g, 71 mmol) in THF (200 ml) were added N-bromosuccinimide (16.3 g, 92 mmol) and concentrated sulfuric acid (2.4 ml). The solution was stirred for 5 h at ambient temperature. Sodium bicarbonate (3.6 g) and 10 % aqueous NaHSO₃ solution (400 ml) were added under ice cooling. The resulting mixture was stirred for 10 min and then poured into ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were washed with ice water and brine and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a yellow oil which was purified by column chromatography (silica gel, cyclohexane) to yield 17.1 g (58.7 mmol, 83 %) of the title compound as colorless liquid.

MS: 292.0 (M)⁺, 290.0 (M)⁺, 212.2, 91.1, 65.2.

c) 4-Benzoyloxy-2-ethyl-benzaldehyde

A 1.6 M solution of n-BuLi in hexane (44.4 ml, 69.9 mmol) was added within 10 min to a stirred cooled (-85 °C) solution of 1-bromo-2-ethyl-4-(phenylmethoxy)-benzene (18.5 g, 63.5 mmol) in dry THF (22 ml). The mixture was stirred for 1 h at -85 °C under an argon atmosphere. N,N-Dimethylformamide (25.5 ml, 330.4 mmol) was added and the temperature was allowed to rise slowly to room temperature. An aqueous saturated NH₄Cl

solution (70 ml) was added under ice cooling. The mixture was extracted two times with dichloromethane, the combined extracts were washed with brine and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a yellow oil which was purified by column chromatography (silica gel, cyclohexane/AcOEt) to yield 11.9 g (49.5 mmol, 78 %) of the title compound as yellow oil.

MS: 240.1 (M+H)⁺, 91.1, 77.1, 65.2.

d] (S)-4-Benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-ethyl-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one

- 10 In analogy to the procedure described in example 17 a], (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one (for the preparation of (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one see: D. Haigh, H. C. Birrell, B. C. C. Cantello, D. S. Eggleston, R. C. Haltiwanger, R. M. Hindley, A. Ramaswamy, N. C. Stevens, *Tetrahedron: Asymmetry* 1999, 10, 1353-1367) was reacted with 4-benzyloxy-2-ethyl-benzaldehyde in the presence of triethylamine and di-n-
- 15 butylboron triflate to give (S)-4-benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-ethyl-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one as yellow foam. According to ¹H-NMR spectroscopy, one of the four isomers is strongly predominating. The configuration was tentatively assigned as 2S,3R according to D. Haigh et al., *Tetrahedron: Asymmetry* 1999, 10, 1353-1367.
- 20 MS: 526.3 (M+Na)⁺, 521.3 (M+NH₄)⁺, 486.2, 381.2, 309.2, 281.2, 253.3, 178.1.

e] (2S,3R)-3-(4-Benzyl-3-(4-benzyloxy-2-ethyl-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester

- In analogy to the procedure described in example 17 b], (S)-4-benzyl-3-[(2S,3R)-3-(4-benzyloxy-2-ethyl-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one was treated
- 25 with sodium methoxide in methanol to give (2S,3R)-3-(4-benzyloxy-2-ethyl-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester as colorless liquid. According to ¹H-NMR spectroscopy, one single diastereomer was obtained.

MS: 381.2 (M+Na)⁺, 376.3 (M+NH₄)⁺, 341.3, 295.3, 253.2, 225.3.

30

f] (2S)-3-(4-Benzyl-3-(4-benzyloxy-2-ethyl-phenyl)-2-ethoxy-propionic acid methyl ester

In analogy to the procedure described in example 17 c], (2S,3R)-3-(4-benzyloxy-2-ethyl-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester was treated with triethylsilane in trifluoroacetic acid to yield (2S)-3-(4-benzyloxy-2-ethyl-phenyl)-2-ethoxy-propionic acid methyl ester as colorless liquid.

5 MS: 365.2 (M+Na)⁺, 360.2 (M+NH₄)⁺, 297.3, 283.2, 237.2, 209.3, 181.2.

g] (2S)-2-Ethoxy-3-(2-ethyl-4-hydroxy-phenyl)-propionic acid methyl ester

In analogy to the procedure described in example 17 d], (2S)-3-(4-benzyloxy-2-ethyl-phenyl)-2-ethoxy-propionic acid methyl ester was hydrogenated over 10 % palladium on
10 charcoal to give (2S)-2-ethoxy-3-(2-ethyl-4-hydroxy-phenyl)-propionic acid methyl ester as colorless liquid.

MS: 275.2 (M+Na)⁺, 270.3 (M+NH₄)⁺, 253.3 (M+H)⁺, 207.2, 175.2, 165.3, 147.2.

h] (2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-ethyl-phenyl}-2-ethoxy-
15 propionic acid methyl ester

In analogy to the procedure described in example 14 b], (2S)-2-ethoxy-3-(2-ethyl-4-hydroxy-phenyl)-propionic acid methyl ester was reacted with 4-chloromethyl-2-(4-chloro-phenyl)-thiazole (example 14 a]) in the presence of cesium carbonate and
20 potassium iodide to yield (2S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-ethyl-phenyl}-2-ethoxy-propionic acid methyl ester as colorless liquid.

MS: 482.2 (M+Na)⁺, 460.2 (M+H)⁺, 414.1, 383.1, 354.1, 293.3, 249.2, 208.1.

i] (2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-ethyl-phenyl}-2-ethoxy-
propionic acid

25 In analogy to the procedure described in example 10 d], (2S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-ethyl-phenyl}-2-ethoxy-propionic acid methyl ester was treated with LiOH to obtain (2S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-ethyl-phenyl}-2-ethoxy-propionic acid as light yellow solid.

MS: 444.1 (M-H)⁻, 397.9, 353.7, 328.3, 232.7, 189.9.

Example 24

[rac]-2-Ethoxy-3-{3-fluoro-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 2-(5-methyl-2-phenyl-thiazol-4-yl)-ethanol [PCT Int. Appl. (2002), WO 02/18355 A1] in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-{3-fluoro-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-{3-fluoro-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid as an off-white solid.

MS: 428.2 (M-H)⁻.

Example 25

[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethanol (prepared from 4-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole (example 18 a] and 4 a]) in analogy to the sequence described in examples 13 a] to 13 d]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid as a colorless gum.

MS: 482.2 (M-H)⁻.

Example 26

[rac]-2-Ethoxy-3-{3-fluoro-4-[2-(2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 2-(2-phenyl-thiazol-4-yl)-ethanol (prepared from thiobenzamide and 1,3-dichloroacetone in analogy

to the procedure described in example 4 a] to give 4-chloromethyl-2-phenyl-thiazole followed by side chain elongation in analogy to the sequence described in examples 13 a] to 13 d]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-[3-fluoro-4-[2-(2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-[3-fluoro-4-[2-(2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-propionic acid as a light yellow gum.

MS: 414.2 (M-H)⁻.

10 Example 27

a] (4-Methyl-2-phenyl-thiazol-5-yl)-methanol

A solution of 5.9 g (23.85 mmol) of 4-methyl-2-phenyl-thiazole-5-carboxylic acid ethyl ester in 30 ml of absolute THF was added to a suspension of 1.1 g (29 mmol) of lithium aluminium hydride in 20 ml of THF, under an argon atmosphere at 0-5°C. Afterwards, the mixture was stirred at ambient temperature for 1 hour. Then, a small amount of water was added cautiously, followed by 50 ml of ethyl acetate and 20 g of anhydrous sodium sulfate and stirring was continued for 0.5 hours. Then, the reaction mixture was filtered, the filtrate was evaporated, leaving 3.85 g (78.6 % of theory) of (4-methyl-2-phenyl-thiazol-5-yl)-methanol as yellow solid.

20 MS: 206.1 (M+H)⁺.

b] [rac]-2-Ethoxy-3-[3-fluoro-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with (4-methyl-2-phenyl-thiazol-5-yl)-methanol in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-[3-fluoro-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-[3-fluoro-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid as a light yellow solid.

MS: 414.1 (M-H)⁻.

Example 28**a) 4-Iodomethyl-2-phenyl-thiazole**

2 g (13.35 mmol) of sodium iodide were added to a solution of 0.56 g (2.67 mmol) of 4-chloromethyl-2-phenyl-thiazole (prepared from thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) in 10 ml of acetone and the suspension was stirred at reflux for 2 hours. After cooling to ambient temperature, 30 ml of tert-butyl methyl ether and 10 ml of water were added and the mixture was transferred to a separatory funnel. The organic phase was washed with water and brine, dried with anhydrous sodium sulfate and finally evaporated, leaving 0.8 g of 4-iodomethyl-2-phenyl-thiazole as light yellow solid (99 % of theory).

MS: 300.9 (M)⁺.

b) 3-(2-Phenyl-thiazol-4-yl)-propionic acid ethyl ester

LDA was prepared by adding 4.7 ml of n-BuLi (1.6 M, hexane) to a solution of 0.76 g (7.5 mmol) of diisopropylamine in 3 ml of abs. THF at -5°C. Then, the mixture was cooled to -78°C, 0.77 g (8.74 mmol) of ethyl acetate were added and the mixture was kept for 15 minutes at that temperature to ensure complete deprotonation. Afterwards, 0.79 g (2.5 mmol) of 4-iodomethyl-2-phenyl-thiazole dissolved in 5 ml of abs. THF and 3 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon (DMPU) were added and stirring was continued for 0.5 hours at -78°C. Then, the reaction mixture was quenched with ammonium chloride solution, extracted twice with AcOEt, washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was chromatographed on silicagel with dichloromethane as eluent. 0.46 g of 3-(2-phenyl-thiazol-4-yl)-propionic acid ethyl ester were obtained as light yellow liquid (70 % of theory).

MS: 262.1 (M+H)⁺.

c) 3-(2-Phenyl-thiazol-4-yl)-propan-1-ol

In analogy of the procedure described in example 12 b), 0.44 g (1.68 mmol) of 3-(2-phenyl-thiazol-4-yl)-propionic acid ethyl ester was reacted with lithium aluminium hydride, yielding 0.28 g of 3-(2-phenyl-thiazol-4-yl)-propan-1-ol as colorless liquid (75.8 % of theory).

MS: 220.2 (M+H)⁺.

d] [rac]-2-Ethoxy-3-{3-fluoro-4-[3-(2-phenyl-thiazol-4-yl)-propoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 3-(2-phenyl-thiazol-4-yl)-propan-1-ol in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-{3-fluoro-4-[3-(2-phenyl-thiazol-4-yl)-propoxy]-phenyl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-{3-fluoro-4-[3-(2-phenyl-thiazol-4-yl)-propoxy]-phenyl}-propionic acid as a colorless gum.

MS: 428.3 (M-H)⁻.

Example 29

15 [rac]-2-Ethoxy-3-(3-fluoro-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethanol [PCT Int. Appl. (2001), WO 01/00603 A1] in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid as a light yellow solid.

25 MS: 496.1 (M-H)⁻.

Example 30

[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-thiazol-4-yl]-ethoxy}-3-fluoro-phenyl)-2-ethoxy-propionic acid

30 In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 2-[2-(4-tert-butyl-phenyl)-thiazol-4-yl]-ethanol (prepared from 2-(4-tert-butyl-phenyl)-4-chloromethyl-thiazole (example 4 a]) in analogy to the sequence described in examples

13 a] to 13 d]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-thiazol-4-yl]-ethoxy}-3-fluoro-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-thiazol-4-yl]-ethoxy}-3-fluoro-phenyl)-2-ethoxy-propionic acid as a light yellow solid.

MS: 470.2 (M-H)⁻.

Example 31

10 a] [rac]-2-Ethoxy-3-[2-methyl-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid ethyl ester

In analogy to the procedure described in example 14 b], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with 4-chloromethyl-2-phenyl-thiazole (prepared from thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a]) in the presence of cesium carbonate and potassium iodide to yield [rac]-2-ethoxy-3-[2-methyl-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid ethyl ester as colorless liquid.

MS: 448.2 (M+Na)⁺, 426.3 (M+H)⁺, 380.2, 347.4, 291.3, 248.3, 215.3, 174.2.

20 b] [rac]-2-Ethoxy-3-[2-methyl-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid

In analogy to the procedure described in example 10 d], [rac]-2-ethoxy-3-[2-methyl-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-[2-methyl-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid as colorless crystals.

25 MS: 396.2 (M-H)⁻, 350.2, 306.1, 255.0.

Example 32

a] [rac]-3-{4-[2-(2-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester

30 In analogy to the procedure described in example 14 b], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with 4-

chloromethyl-2-(2-chloro-phenyl)-thiazole (prepared from 2-chloro-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) in the presence of cesium carbonate and potassium iodide to yield [rac]-3-{4-[2-(2-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester as colorless liquid.

MS: 482.2 (M+Na)⁺, 460.2 (M+H)⁺, 426.2, 386.1, 347.4, 291.4, 248.3, 208.1.

b) [rac]-3-{4-[2-(2-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

10 In analogy to the procedure described in example 10 d), [rac]-3-{4-[2-(2-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester was treated with LiOH to obtain [rac]-3-{4-[2-(2-chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid as colorless solid.

MS: 430.2 (M-H)⁻, 384.0, 313.0, 255.2.

15

Example 33

a) 2-(4-tert-Butyl-phenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester

The solution of 3.87 g (20 mmol) of 4-tert-butyl-thiobenzamide and 3.45 g (21 mmol) of ethyl 2-chloro-acetoacetate in 15 ml of ethanol was heated at reflux for 3 hours.

20 Afterwards, the reaction mixture was cooled to ambient temperature and a solution of 3 g of potassium bicarbonate in 15 ml of water was added and the mixture was stirred until the gas evolution (CO₂) had ceased. The compound was then extracted with 3 portions of 50 ml of tert-butyl methyl ether, the combined organic phases were washed with water, then with brine, dried over anhydrous sodium sulfate and finally evaporated. 5.3 g of 2-(4-tert-butyl-phenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester (87.4 % of theory) were obtained as pale yellow viscous oil.

25

MS: 304.2 (M+H)⁺.

b) [2-(4-tert-Butyl-phenyl)-4-methyl-thiazol-5-yl]-methanol

In analogy to the procedure described for example 12 b], 5.3 g (17.4 mmol) of 2-(4-tert-butyl-phenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester were reduced to [2-(4-tert-butyl-phenyl)-4-methyl-thiazol-5-yl]-methanol with lithium aluminium hydride to give 4.3 g (94.1 % of theory) of [2-(4-tert-butyl-phenyl)-4-methyl-thiazol-5-yl]-methanol as a pale yellow solid.

MS: 262.1 (M+H)⁺.

c] [rac]-3-{4-[2-(4-tert-Butyl-phenyl)-4-methyl-thiazol-5-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with [2-(4-tert-butyl-phenyl)-4-methyl-thiazol-5-yl]-methanol in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-{4-[2-(4-tert-butyl-phenyl)-4-methyl-thiazol-5-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-{4-[2-(4-tert-butyl-phenyl)-4-methyl-thiazol-5-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid as a light yellow solid.

MS: 470.2 (M-H)⁻.

Example 34

[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(4-hydroxy-3-methyl-phenyl)-propionic acid ethyl ester (example 4 c]) was reacted with 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (example 12 b]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-2-ethoxy-propionic acid as colorless solid.

MS: 480.4 (M-H)⁻.

Example 35

[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethanol (prepared from 4-methoxy-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a) to yield 4-chloromethyl-2-(4-methoxy-phenyl)-thiazole, followed by side chain elongation in analogy to the sequence described in examples 13 a) to 13 d)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid as a light yellow solid.

MS: 444.2 (M-H)⁻.

Example 36

a) [rac]-3-{4-[2-(4-Chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester

In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with [2-(4-chloro-phenyl)-4-methyl-thiazol-5-yl]-methanol (prepared from 4-chloro-thiobenzamide and ethyl 2-chloro-acetoacetate in analogy to the procedures described in examples 33 a) and 33 b)) in the presence of triphenylphosphine and diethyl azodicarboxylate to yield [rac]-3-{4-[2-(4-chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester as colorless oil.

MS: 474.2 (M+H)⁺, 402.5, 350.1, 321.2, 257.2, 243.3, 222.1.

b) [rac]-3-{4-[2-(4-Chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d), [rac]-3-{4-[2-(4-chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester was

treated with LiOH to obtain [rac]-3-{4-[2-(4-chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid as colorless liquid.

MS: 444.1 (M-H)⁻, 398.0, 354.0, 285.9, 242.1.

5 Example 37

a) [rac]-2-Ethoxy-3-{2-methyl-4-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with [4-methyl-2-
10 (3-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol (prepared from 3-trifluoromethyl-thiobenzamide and ethyl 2-chloro-acetoacetate in analogy to the procedures described in examples 33 a) and 33 b)) in the presence of triphenylphosphine and diethyl azodicarboxylate to yield [rac]-2-ethoxy-3-{2-methyl-4-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester as colorless liquid.

15 MS: 530.3 (M+Na)⁺, 508.3 (M+H)⁺, 464.2, 391.2, 256.0, 207.2, 162.3.

b) [rac]-2-Ethoxy-3-{2-methyl-4-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 10 d], [rac]-2-ethoxy-3-{2-methyl-4-[4-
20 methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-{2-methyl-4-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid as colorless oil.

MS: 502.2 (M+Na)⁺, 480.3 (M+H)⁺, 391.2, 279.2, 256.1.

25 Example 38

a) [rac]-3-{4-[2-(3-Chloro-4-fluoro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with [2-(3-chloro-
30 4-fluoro-phenyl)-4-methyl-thiazol-5-yl]-methanol (prepared from 3-chloro-4-fluoro-

thiobenzamide and ethyl 2-chloro-acetoacetate in analogy to the procedures described in examples 33 a) and 33 b)) in the presence of triphenylphosphine and diethyl azodicarboxylate to yield [rac]-3-{4-[2-(3-chloro-4-fluoro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester as light yellow liquid.

5 MS: 493.2 (M+H)⁺, 454.4, 391.3, 279.2, 240.2.

b) [rac]-3-{4-[2-(3-Chloro-4-fluoro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d), [rac]-3-{4-[2-(3-chloro-4-fluoro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester was treated with LiOH to obtain [rac]-3-{4-[2-(3-chloro-4-fluoro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid as light yellow foam.

MS: 464.1 (M+H)⁺, 342.2, 310.1, 279.2, 274.1, 240.2.

15 **Example 39**

[rac]-2-Ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(4-hydroxy-3-methyl-phenyl)-propionic acid ethyl ester (example 4 c)) was reacted with 2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-methoxy-thiobenzamide in analogy to the procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-2-ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-propionic acid as light yellow gum.

MS: 454.3 (M-H)⁻.

Example 40

[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxopentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-methoxythiobenzamide in analogy to the procedures described in examples 12 a] and 12 b]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid as light yellow solid.

MS: 460.4 (M+H)⁺.

Example 41

[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxopentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-isopropylthiobenzamide in analogy to the procedures described in examples 12 a] and 12 b]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid as colorless gum.

MS: 470.2 (M-H)⁻.

Example 42

[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-fluoro-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (example 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-fluoro-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-fluoro-phenyl)-2-ethoxy-propionic acid as colorless solid.

MS: 484.3 (M-H)⁻.

Example 43

[rac]-2-Ethoxy-3-(3-fluoro-4-{3-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-propoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 3-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-propan-1-ol (prepared from 4-chloromethyl-2-(4-isopropyl-phenyl)-thiazole (obtained from 4-isopropyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) according to the sequence described in examples 28 a) to c)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(3-fluoro-4-{3-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-propoxy}-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-2-ethoxy-3-(3-fluoro-4-{3-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-propoxy}-phenyl)-propionic acid as light yellow gum.

MS: 470.2 (M-H)⁻.

Example 44

[rac]-3-(4-{3-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-3-fluoro-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 3-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-propan-1-ol (prepared from methanesulfonic acid 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethyl ester [obtained from 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (example 12 b)] and methanesulfonyl chloride in pyridine at 0°C] according to the sequence described in examples 13 a] to d]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{3-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-3-fluoro-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-(4-{3-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-3-fluoro-phenyl)-2-ethoxy-propionic acid as colorless solid.

MS: 500.3 (M+H)⁺.

Example 45

a) [rac]-2-Ethoxy-3-(4-hydroxy-3,5-dimethyl-phenyl)-propionic acid ethyl ester

In analogy to the procedure described in example 1 a], 4-benzyloxy-3,5-dimethyl-benzaldehyde was reacted with (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride [Tetrahedron 50 (25), 7543-56 (1994)] to yield 3-(4-benzyloxy-3,5-dimethyl-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester. Hydrogenation of 3-(4-benzyloxy-3,5-dimethyl-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester as described in example 4 c] yielded [rac]-2-ethoxy-3-(4-hydroxy-3,5-dimethyl-phenyl)-propionic acid ethyl ester as light yellow viscous oil.

MS: 265.2 (M-H)⁻.

b) [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-dimethyl-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(4-hydroxy-3,5-dimethyl-phenyl)-propionic acid ethyl ester was reacted with 2-[2-(4-tert-butyl-phenyl)-

5-methyl-thiazol-4-yl]-ethanol (example 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-dimethyl-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-dimethyl-phenyl)-2-ethoxy-propionic acid as colorless solid.

MS: 494.4 (M-H)⁺.

Example 46

10 [rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-dimethyl-phenyl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(4-hydroxy-3,5-dimethyl-phenyl)-propionic acid ethyl ester (example 45 a)) was reacted with 2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-isopropyl-thiobenzamide in analogy to the procedures described in examples 12 a] and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-dimethyl-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-dimethyl-phenyl)-propionic acid as yellow amorphous solid.

MS: 480.3 (M-H)⁺.

25 Example 47

[rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(4-hydroxy-3-methyl-phenyl)-propionic acid ethyl ester (example 4 c)) was reacted with 2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-isopropyl-thiobenzamide in analogy to the procedures described in examples 12 a] and 12 b)) in

- tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methyl-phenyl)-propionic acid as light yellow solid.

MS: 466.3 (M-H)⁻.

Example 48

- 10 a) [rac]-2-Ethoxy-3-(4-hydroxy-3-methoxy-phenyl)-propionic acid ethyl ester

- In analogy to the procedure described in example 1 a], 4-benzyloxy-3-methoxy-benzaldehyde was reacted with (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride [Tetrahedron 50 (25), 7543-56 (1994)] to yield 3-(4-benzyloxy-3-methoxy-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester. Hydrogenation of 3-(4-benzyloxy-3-methoxy-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester as described in example 4 c] yielded [rac]-2-ethoxy-3-(4-hydroxy-3-methoxy-phenyl)-propionic acid ethyl ester as colorless solid.

MS: 268.1 (M)⁺.

- 20 b) [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid

- In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(4-hydroxy-3-methoxy-phenyl)-propionic acid ethyl ester was reacted with 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (example 12 b]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-(4-{2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid as light yellow amorphous solid.

- 30 MS: 496.4 (M-H)⁻.

Example 49

[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethanol (prepared from 4-chloromethyl-2-(4-isopropyl-phenyl)-thiazole (example 5) according to the sequence described in examples 13 a] to d]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid as light yellow solid.

MS: 456.3 (M+H)⁺.

15

Example 50

[rac]-2-Ethoxy-3-{3-fluoro-4-[2-(2-p-tolyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a]) was reacted with 2-(2-p-tolyl-thiazol-4-yl)-ethanol (prepared from (2-p-tolyl-thiazol-4-yl)-acetic acid ethyl ester [Collection of Czechoslovak Chemical Communications (2001), 66(12), 1809-1830] with lithium aluminium hydride in analogy to the procedure described in example 12 b]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-{3-fluoro-4-[2-(2-p-tolyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-{3-fluoro-4-[2-(2-p-tolyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid as light yellow solid.

MS: 428.3 (M+H)⁺.

30 Example 51

a] [rac]-2-Ethoxy-3-(4-hydroxy-naphthalen-1-yl)-propionic acid ethyl ester

In analogy to the procedure described in example 1 a), 4-benzyloxy-naphthalene-1-carbaldehyde (prepared from 4-hydroxy-naphthalene-1-carbaldehyde, benzylchloride, potassium carbonate in N,N-dimethylformamide at room temperature) was reacted with (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride [Tetrahedron 50(25), 7543-56(1994)] to yield 3-(4-benzyloxy-naphthalen-1-yl)-2-ethoxy-(Z,E)-acrylic acid ethyl ester. Hydrogenation of 3-(4-benzyloxy-naphthalen-1-yl)-2-ethoxy-(Z,E)-acrylic acid ethyl ester as described in example 2 c) yielded [rac]-2-ethoxy-3-(4-hydroxy-naphthalen-1-yl)-propionic acid ethyl ester as light brown oil.

MS: 288.3 (M)⁺, 242.2, 215.3, 157.2.

10

b) [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(4-hydroxy-naphthalen-1-yl)-propionic acid ethyl ester was reacted with 2-(5-methyl-2-phenyl-thiazol-4-yl)-ethanol [PCT Int. Appl. (2002), WO 02/18355 A1] in tetrahydrofuran in the presence of triphenylphosphine and DIAD (diisopropyl azodicarboxylate) to yield [rac]-2-ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 1 e), to yield [rac]-2-ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid as colorless amorphous solid.

MS: 462.3 (M+H)⁺.

Example 52

[rac]-3-{4-[2-(2-Benzo[1,3]dioxol-5-yl-5-methyl-thiazol-4-yl)-ethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 2-(2-benzo[1,3]dioxol-5-yl-5-methyl-thiazol-4-yl)-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and benzo[1,3]dioxole-5-carbothioic acid amide in analogy to the procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-{4-[2-(2-benzo[1,3]dioxol-5-yl-5-methyl-thiazol-4-yl)-ethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid ethyl ester, which

was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-{4-[2-(2-benzo[1,3]dioxol-5-yl-5-methyl-thiazol-4-yl)-ethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid as colorless solid.

MS: 472.3 (M-H)⁺.

5

Example 53

[rac]-2-Ethoxy-3-{3-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(3-fluoro-4-
10 hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)] was reacted with [4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-{3-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure
15 described in example 4 e], to yield [rac]-2-ethoxy-3-{3-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid as light yellow solid.

MS: 482.2 (M-H)⁺.

20 Example 54

a] 3-(4-Benzoyloxy-3-fluoro-phenyl)-3-hydroxy-2-isopropoxy-propionic acid ethyl ester (mixture of diastereomers)

LDA was prepared under an Ar atmosphere by adding 18.75 ml (30 mmol) of n-butyllithium solution (1.6 M in hexane) to a stirred solution of 3.13 g (31 mmol) of
25 diisopropylamine in 20 ml of dry THF, at -5°C. After cooling to -78°C, 4.38 g of isopropoxy-acetic acid ethyl ester (Tetrahedron (1982), 38(17), 2733-9) (30 mmol) in 10 ml of THF was added and stirring was continued for 15 min. Then, 3.6 g of 4-benzoyloxy-3-fluoro-benzaldehyde (prepared from 3-fluoro-4-hydroxy-benzaldehyde, benzyl bromide and cesium carbonate in acetonitrile) (15.6 mmol) dissolved in a mixture
30 of 15 ml of THF and 20 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) were added and the reaction mixture was stirred at -78°C for 30 min, and then at 0°C for 30 min. Afterwards, it was quenched by addition of aqueous saturated ammonium

chloride solution and the compound was extracted twice with ethyl acetate. The combined organic phases were washed with water, then brine, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on silicagel (dichloromethane-diethyl ether 1/1 (v/v) as eluent). 4.9 g of 3-(4-benzyloxy-3-fluoro-phenyl)-3-hydroxy-2-isopropoxy-propionic acid ethyl ester (mixture of diastereomers) were obtained as colorless oil (83.3 % of theory).

MS : 376.0 (M)⁺.

b) [rac]-3-(4-Benzyloxy-3-fluoro-phenyl)-2-isopropoxy-propionic acid ethyl ester

To a cooled solution (ice bath) of 4.9 g of 3-(4-benzyloxy-3-fluoro-phenyl)-3-hydroxy-2-isopropoxy-propionic acid ethyl ester (mixture of diastereomers) (13 mmol) in 25 ml of trifluoroacetic acid, 23.8 ml of triethylsilane (26.5 mmol) and 15 ml of dichloromethane were added. The solution was stirred at 0°C for 1 hour and at ambient temperature for 2 hours. Then, the reaction mixture was poured onto a mixture of water, sodium bicarbonate and ice. The compound was extracted with tert-butyl methyl ether and after evaporation to dryness, the residue was chromatographed on silicagel with dichloromethane as eluent. 3.27 g of [rac]-3-(4-benzyloxy-3-fluoro-phenyl)-2-isopropoxy-propionic acid ethyl ester were obtained as colorless oil (69.7% of theory).

MS: 360.2 (M)⁺.

20

c) [rac]-3-(3-Fluoro-4-hydroxy-phenyl)-2-isopropoxy-propionic acid ethyl ester

0.5 g of 10% palladium on charcoal were added to a solution of 3.7 g of [rac]-3-(4-benzyloxy-3-fluoro-phenyl)-2-isopropoxy-propionic acid ethyl ester (10.26 mmol) in 30 ml of THF and the compound was stirred under an atmosphere of H₂, at normal pressure and ambient temperature, until the absorption of gas stopped. After filtration of the catalyst and evaporation of the filtrate, 2.7 g of [rac]-3-(3-fluoro-4-hydroxy-phenyl)-2-isopropoxy-propionic acid ethyl ester were obtained as colorless viscous oil (97.3% of theory).

MS: 269.2 (M-H)⁻.

30

d) [rac]-3-{3-Fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-isopropoxy-propionic acid

In analogy to the procedure described in example 1 d), [rac]-3-(3-fluoro-4-hydroxy-phenyl)-2-isopropoxy-propionic acid ethyl ester was reacted with [4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-{3-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-isopropoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-3-{3-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-isopropoxy-propionic acid as light yellow solid.

MS: 496.2 (M-H)⁺.

Example 55

15 [rac]-3-{4-[2-(3,5-Dimethoxy-phenyl)-thiazol-4-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 14 b), [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 4-chloromethyl-2-(3,5-dimethoxy-phenyl)-thiazole (prepared from 3,5-dimethoxy-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 20 4 a)) in the presence of cesium carbonate and potassium iodide to yield [rac]-3-{4-[2-(3,5-dimethoxy-phenyl)-thiazol-4-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-3-{4-[2-(3,5-dimethoxy-phenyl)-thiazol-4-ylmethoxy]-3-fluoro-phenyl}-2-ethoxy-propionic acid as light yellow solid.

25 MS: 460.1 (M-H)⁺.

Example 56

[rac]-2-Ethoxy-3-[3-fluoro-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid

In analogy to the procedure described in example 14 b), [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 4-chloromethyl-2-phenyl-thiazole (prepared from thiobenzamide and 1,3-dichloroacetone

in analogy to the procedure described in example 4 a)) in the presence of cesium carbonate and potassium iodide to yield [rac]-2-ethoxy-3-[3-fluoro-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-[3-fluoro-4-(2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid as light yellow solid.

MS: 400.1 (M-H)⁻.

Example 57

[rac]-2-Ethoxy-3-[3-fluoro-4-(2-p-tolyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid

In analogy to the procedure described in example 14 b), [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 4-chloromethyl-2-p-tolyl-thiazole (prepared from 4-methyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a)) in the presence of cesium carbonate and potassium iodide to yield [rac]-2-ethoxy-3-[3-fluoro-4-(2-p-tolyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-[3-fluoro-4-(2-p-tolyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid as as light yellow solid.

MS: 414.2 (M-H)⁻.

Example 58

a) [rac]-3-(4-Benzzyloxy-2-ethoxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid ethyl ester [mixture of diastereomers]

LDA was prepared by adding 13.3 ml n-BuLi (1.5 M, hexane) to a solution of 2.85 ml (20.0 mmol) of diisopropylamine in 90 ml of abs. THF at -5 °C. After cooling to -78 °C, 2.81 ml (20.0 mmol) of ethyl ethoxyacetate, dissolved in 10 ml of abs. THF, was added and the mixture kept for 15 minutes at that temperature to ensure complete deprotonation. 2.05 g (8.0 mmol) of 4-benzyloxy-2-ethoxy-benzaldehyde [prepared from 2-hydroxy-4-benzyloxy-benzaldehyde and ethyl iodide in analogy to the procedure described for 4-benzyloxy-2-isopropoxy-benzaldehyde in Chemical & Pharmaceutical Bulletin (1998), 46(2), 222-230: 2-hydroxy-4-benzyloxy-benzaldehyde, isopropyl bromide, potassium iodide, potassium carbonate, N,N-dimethylformamide, 100 °C], dissolved in 20 ml of abs. THF, were then added. After stirring for 30 minutes at dry ice temperature, the reaction

mixture was quenched with ammonium chloride solution, warmed up to 0 °C, then extracted twice with AcOEt, washed with water, dried over sodium sulfate, and evaporated to dryness. Flash chromatography (SiO₂, hexane/AcOEt = 9:1 to 1:1) yielded 3.09 g (99 % of theory) of [rac]-3-(4-benzyloxy-2-ethoxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid ethyl ester [mixture of diastereomers] as light yellow oil.

MS: 371.4 [(M+H)⁺ - H₂O].

b) 3-(4-Benzyloxy-2-ethoxy-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester

3.26 g (8.39 mmol) of [rac]-3-(4-benzyloxy-2-ethoxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid ethyl ester [mixture of diastereomers] and 0.15 g (0.84 mmol) 4-toluene sulfonic acid were stirred in 200 ml benzene at reflux for 30 minutes. Evaporation to dryness followed by flash chromatography (SiO₂, hexane/AcOEt = 95:5 to 4:1) yielded 2.12 g (68 % of theory) of 3-(4-benzyloxy-2-ethoxy-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester as light yellow oil.

MS: 370.1 (M)⁺.

c) [rac]-2-Ethoxy-3-(2-ethoxy-4-hydroxy-phenyl)-propionic acid ethyl ester

0.90 g of Pd/C (10%) were added under argon to 4.49 g (12.1 mmol) of 3-(4-benzyloxy-2-ethoxy-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester dissolved in 80 ml of ethanol. The atmosphere was then replaced with H₂, and the suspension was rapidly stirred at room temperature for two hours. Filtration over dicalite and evaporation of the solvents left 4.23 g of a light brown oil. Flash chromatography (SiO₂, hexane/AcOEt = 95:5 to 1:1) yielded 3.41 g (99 % of theory) of [rac]-2-ethoxy-3-(2-ethoxy-4-hydroxy-phenyl)-propionic acid ethyl ester as light yellow oil.

MS: 281.0 (M-H)⁻.

d) [rac]-2-Ethoxy-3-[2-ethoxy-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(2-ethoxy-4-hydroxy-phenyl)-propionic acid ethyl ester was reacted with 2-(5-methyl-2-phenyl-thiazol-4-yl)-ethanol [PCT Int. Appl. (2002), WO 02/18355 A1] in tetrahydrofuran in the presence of triphenylphosphine and DBAD (di-tert-butyl azodicarboxylate) to yield [rac]-2-ethoxy-3-[2-ethoxy-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-propionic

acid ethyl ester, which was further saponified in analogy to the procedure described in example 1 e], to yield [rac]-2-ethoxy-3-{2-ethoxy-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid as colorless oil.

MS: 454.3 (M-H)⁺.

5

Example 59

[rac]-2-Ethoxy-3-(2-ethoxy-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(2-ethoxy-4-
10 hydroxy-phenyl)-propionic acid ethyl ester (example 58 c]) was reacted with 2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethanol [PCT Int. Appl. (2001), WO 01/00603 A1] in tetrahydrofuran in the presence of triphenylphosphine and DBAD (di-tert-butyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(2-ethoxy-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester, which
15 was further saponified in analogy to the procedure described in example 1 e], to yield [rac]-2-ethoxy-3-(2-ethoxy-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid as colorless oil.

MS: 522.3 (M-H)⁺.

20 Example 60

[rac]-2-Ethoxy-3-(3-methyl-4-{2-[5-methyl-2-(4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(4-hydroxy-3-methyl-phenyl)-propionic acid ethyl ester (example 4 c]) was reacted with 2-[5-methyl-2-
25 (4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-trifluoromethoxy-thiobenzamide in analogy to the procedures described in examples 12 a] and 12 b]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(3-methyl-4-{2-[5-methyl-2-(4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester, which
30 was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-(3-methyl-4-{2-[5-methyl-2-(4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid as light yellow solid.

MS: 508.3 (M-H)⁻.

Example 61

5 [rac]-2-Ethoxy-3-(3-fluoro-4-{2-[5-methyl-2-(4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(3-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester (example 7 a)) was reacted with 2-[5-methyl-2-(4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-
10 trifluoromethoxy-thiobenzamide in analogy to the procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(3-fluoro-4-{2-[5-methyl-2-(4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield
15 [rac]-2-ethoxy-3-(3-fluoro-4-{2-[5-methyl-2-(4-trifluoromethoxy-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid as colorless solid.

MS: 514.2 (M+H)⁺.

Example 62

20 [rac]-2-Isopropoxy-3-{3-methoxy-4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 1 d), [rac]-3-(4-hydroxy-3-methoxy-phenyl)-2-isopropoxy-propionic acid ethyl ester [prepared from isopropoxy-acetic acid ethyl ester (Tetrahedron (1982), 38(17), 2733-9) and 4-benzyloxy-3-methoxy -
25 benzaldehyde in analogy to the procedures described in examples 54 a) to c)] was reacted with 2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-methyl-thiobenzamide in analogy to the procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl
30 azodicarboxylate) to yield [rac]-2-isopropoxy-3-{3-methoxy-4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-2-isopropoxy-3-{3-

methoxy-4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid as colorless amorphous solid.

MS: 470.2 (M+H)⁺.

5 Example 63

[rac]-3-(3-Fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-2-isopropoxy-propionic acid

In analogy to the procedure described in example 1 d), [rac]-3-(3-fluoro-4-hydroxy-phenyl)-2-isopropoxy-propionic acid ethyl ester [example 54 c)] was reacted with 2-[2-(4-
10 trifluoromethyl-phenyl)-thiazol-4-yl]-ethanol (prepared from 4-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole (example 18 a) and 4 a)) in analogy to the sequence described in examples 13 a) to 13 d)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(3-fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-2-isopropoxy-propionic acid
15 ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-3-(3-fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-2-isopropoxy-propionic acid as colorless solid.

MS: 498.2 (M+H)⁺.

20 Example 64

[rac]-3-(4-{2-[2-(3,4-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(4-hydroxy-3-methoxy-phenyl)-propionic acid ethyl ester [example 48 a)] was reacted with 2-[2-(3,5-
25 dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 3,5-dimethoxy-thiobenzamide (PCT Int. Appl. (1992), WO 92/09586 A1) in analogy to the procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(3,4-
30 dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure

described in example 4 e], to yield [rac]-3-(4-{2-[2-(3,4-dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid as light yellow solid.

MS: 500.3 (M-H)⁺.

5 Example 65

[rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-isopropoxy-propionic acid

In analogy to the procedure described in example 1 d], [rac]-3-(4-hydroxy-3-methoxy-phenyl)-2-isopropoxy-propionic acid ethyl ester [prepared from isopropoxy-acetic acid
10 ethyl ester (Tetrahedron (1982), 38(17), 2733-9) and 4-benzyloxy-3-methoxy-benzaldehyde in analogy to the procedures described in examples 54 a) to c)] was reacted with 2-[2-(3,5-dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 3,5-dimethoxy-thiobenzamide (PCT Int. Appl.(1992), WO 92/09586 A1) in analogy to the
15 procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(3,5-dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-isopropoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-(4-{2-[2-(3,5-dimethoxy-phenyl)-5-methyl-
20 thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-isopropoxy-propionic acid as colorless solid.

MS: 514.3 (M-H)⁺.

Example 66

[rac]-3-(4-{2-[2-(3,5-Dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-isopropoxy-propionic acid

In analogy to the procedure described in example 1 d], [rac]-3-(4-hydroxy-3-methoxy-phenyl)-2-isopropoxy-propionic acid ethyl ester [prepared from isopropoxy-acetic acid
ethyl ester (Tetrahedron (1982), 38(17), 2733-9) and 4-benzyloxy-3-methoxy-benzaldehyde in analogy to the procedures described in examples 54 a) to c)] was reacted
30 with 2-[2-(3,5-dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 3,5-dimethyl-thiobenzamide (from 3,5-dimethyl-benzonitrile and NaSH, NH₄Cl in N,N-

dimethylformamide) in analogy to the procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(3,5-dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-isopropoxy-propionic acid ethyl ester, which was further
5 saponified in analogy to the procedure described in example 4 e), to yield [rac]-3-(4-{2-[2-(3,5-dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-isopropoxy-propionic acid as light yellow solid.

MS: 482.3 (M-H)⁺.

10 Example 67

[rac]-3-(4-{2-[2-(3,5-Dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 1 d), [rac]-2-ethoxy-3-(4-hydroxy-3-methoxy-phenyl)-propionic acid ethyl ester [example 48 a)] was reacted with 2-[2-(3,5-dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-
15 pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 3,5-dimethyl-thiobenzamide (from 3,5-dimethyl-benzonitrile and NaSH, NH₄Cl in N,N-dimethylformamide) in analogy to the procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl
20 azodicarboxylate) to yield [rac]-3-(4-{2-[2-(3,5-dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e), to yield [rac]-3-(4-{2-[2-(3,5-dimethyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3-methoxy-phenyl)-2-ethoxy-propionic acid as colorless solid.

25 MS: 468.3 (M-H)⁺.

Example 68

a) [rac]-2-Ethoxy-3-(5-ethoxy-2-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester

In analogy to the procedure described in example 1 a), 4-benzyloxy-5-ethoxy-2-fluoro-benzaldehyde [prepared from 5-ethoxy-2-fluoro-4-hydroxy-benzaldehyde [PCT Int. Appl.
30 (2001), WO 01/90051 A1] and benzyl bromide, cesium carbonate in acetonitrile] was reacted with (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride [Tetrahedron 50

(25), 7543-56 (1994)] to yield 3-(4-benzyloxy-5-ethoxy-2-fluoro-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester. Hydrogenation of 3-(4-benzyloxy-5-ethoxy-2-fluoro-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester as described in example 4 c] yielded [rac]-2-ethoxy-3-(5-ethoxy-2-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester as colorless viscous oil.

5 MS: 299.2 (M-H)⁻.

b] [rac]-2-Ethoxy-3-{5-ethoxy-2-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 4 d], [rac]-2-ethoxy-3-(5-ethoxy-2-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester was reacted with 4-chloromethyl-2-(4-isopropyl-phenyl)-thiazole (prepared from 4-isopropyl-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a]) in acetonitrile in the presence of cesium carbonate to yield [rac]-2-ethoxy-3-{5-ethoxy-2-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid ethyl ester, which was
15 further saponified in analogy to the procedure described in example 4 e], to yield [rac]-2-ethoxy-3-{5-ethoxy-2-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid as light yellow solid.

MS: 486.3 (M-H)⁻.

20 **Example 69**

[rac]-3-(4-{2-[2-(4-Chloro-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-5-ethoxy-2-fluoro-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 4 d], [rac]-2-ethoxy-3-(5-ethoxy-2-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester [example 68 a)] was reacted with 2-[2-(4-chloro-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-chloro-thiobenzamide in analogy to the procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(4-chloro-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-5-ethoxy-2-fluoro-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further
30 saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-(4-{2-[2-(4-chloro-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-5-ethoxy-2-fluoro-phenyl)-2-ethoxy-propionic acid as light yellow solid.

MS: 508.1 (M+H)⁺.

Example 70

a) [rac]-3-(3,5-Difluoro-4-hydroxy-phenyl)-2-ethoxy-propionic acid ethyl ester

5 In analogy to the procedure described in example 1 a), 4-benzyloxy-3,5-difluoro-benzaldehyde [prepared from 3,5-difluoro-4-hydroxy-benzaldehyde [Journal of Medicinal Chemistry (1989), 32(2), 450-5] and benzyl bromide, cesium carbonate in acetonitrile] was reacted with (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride [Tetrahedron 50 (25), 7543-56 (1994)] to yield 3-(4-benzyloxy-3,5-difluoro-phenyl)-2(Z,E)-ethoxy-
10 acrylic acid ethyl ester. Hydrogenation of 3-(4-benzyloxy-3,5-difluoro-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester as described in example 4 c] yielded 3-(3,5-difluoro-4-hydroxy-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester. In order to hydrogenate the double bond in the acrylic acid part, 3-(3,5-difluoro-4-hydroxy-phenyl)-2(Z,E)-ethoxy-acrylic acid ethyl ester has been saponified to 3-(3,5-difluoro-4-hydroxy-phenyl)-2(Z,E)-
15 ethoxy-acrylic acid. 3-(3,5-Difluoro-4-hydroxy-phenyl)-2(Z,E)-ethoxy-acrylic acid was hydrogenated with palladium on charcoal in acetic acid giving [rac]-3-(3,5-difluoro-4-hydroxy-phenyl)-2-ethoxy-propionic acid which was subsequently re-esterified in ethanol in the presence of p-toluenesulfonic acid to give [rac]-3-(3,5-difluoro-4-hydroxy-phenyl)-2-ethoxy-propionic acid ethyl ester as light yellow viscous oil.

20 MS: 274 (M)⁺.

b) [rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-difluoro-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 1 d), [rac]-3-(3,5-difluoro-4-hydroxy-phenyl)-2-ethoxy-propionic acid ethyl ester was reacted with 2-[2-(3,5-dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 3,5-dimethoxy-thiobenzamide (PCT Int. Appl.(1992), WO 92/09586 A1) in analogy to the procedures described in examples 12 a) and 12 b)) in tetrahydrofuran in the presence of
25 triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(3,5-dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-difluoro-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure
30

described in example 4 e], to yield [rac]-3-(4-{2-[2-(3,5-dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-difluoro-phenyl)-2-ethoxy-propionic acid as colorless solid.

MS: 506.1 (M-H)⁺.

5 Example 71

[rac]-3-(4-{2-[2-(4-Chloro-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-difluoro-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 4 d], [rac]-3-(3,5-difluoro-4-hydroxy-phenyl)-2-ethoxy-propionic acid ethyl ester [example 70 a)] was reacted with 2-[2-(4-chloro-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-chloro-thiobenzamide in analogy to the procedures described in examples 12 a] and 12 b]) in tetrahydrofuran in the presence of triphenylphosphine and DEAD (diethyl azodicarboxylate) to yield [rac]-3-(4-{2-[2-(4-chloro-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-difluoro-phenyl)-2-ethoxy-propionic acid ethyl ester, which was further saponified in analogy to the procedure described in example 4 e], to yield [rac]-3-(4-{2-[2-(4-chloro-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-3,5-difluoro-phenyl)-2-ethoxy-propionic acid as light yellow amorphous solid.

MS: 480.1 (M-H)⁺.

20

Example 72

a] [rac]-4-[2-(5-Methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophene-7-carbaldehyde

0.275 g of the above prepared (example 62) 2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethanol (1.18 mmol) was dissolved in 6 ml of toluene and treated successively at 0° C with 0.210 g of 4-hydroxy-benzo[b]thiophene-7-carbaldehyde (1.18 mmol), 0.309 g of triphenylphosphine (1.18 mmol), and 0.238 g (1.18 mmol) of DIAD. The cooling bath was then removed and stirring continued for 6 h. Pouring onto crashed ice, twofold extraction with AcOEt, washing with dil. NaOH, water and NH₄Cl-solution, drying over magnesium sulfate, and evaporation of the solvents, followed by flash chromatography (SiO₂, hexane/AcOEt=8/2), produced finally 0.201 g of the title compound as colorless oil.

30

MS: 394.1 (M+H)⁺.

b) [rac]-2-Ethoxy-3-hydroxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid ethyl ester

- 5 LDA-solution in THF was prepared according to standard procedure from 0.102 g of diisopropylamine (1.0 mmol) and 0.61 ml of 1.5 M nBuLi (hexane) in 2 ml of abs. THF at -10° C. After cooling to -75° C, 0.121 g of ethyl ethoxyacetate (0.92 mmol), dissolved in 1 ml of THF, was added and stirring continued for 30 min. to complete enolate formation. 0.120 g of the above prepared [rac]-4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-
10 benzo[b]thiophene-7-carbaldehyde (0.305 mmol), dissolved in 2 ml of THF, was then added at -75° C and the mixture kept for another 30 min. at this temperature. Pouring onto crashed ice/NH₄Cl, twofold extraction with AcOEt, washing with water, drying over magnesium sulfate, and evaporation of the solvents, followed by flash chromatography (SiO₂, hexane/AcOEt=7/3) delivered 0.139 g of the title compound (syn/anti-isomers) as
15 yellowish oil.

MS: 526.3 (M+H)⁺.

c) [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid ethyl ester

- 20 0.138 g of the above prepared [rac]-2-ethoxy-3-hydroxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid ethyl ester (0.263 mmol) was dissolved in 1.3 ml of trifluoroacetic acid, treated at 0° C with 0.417 ml of triethylsilane (10 eq.) and then kept for 4 h at 0° C under vigorous stirring, when TLC indicated the disappearance of starting material. The reaction mixture was then poured onto crashed
25 ice/AcOEt/NaHCO₃, the organic layer washed with water (pH of aq. phase~8) and brine, dried over magnesium sulfate, and evaporated to dryness. Flash chromatography (SiO₂, hexane/AcOEt=82/18) yielded 0.090 g of the title compound as colorless oil.

MS: 510.4 (M+H)⁺.

- 30 d) [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid

0.089 g of the above prepared [rac]-2-ethoxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid ethyl ester (0.175 mmol) was dissolved in 1.1 ml of THF/EtOH=1/1, treated with 0.53 ml of 1N NaOH (3 eq.), and kept at ambient temperature for 1 h. The reaction mixture was then poured onto crashed ice/AcOEt/HCl
5 dil., the organic layer washed with water, dried over magnesium sulfate, and evaporated to dryness. Crystallization from hexane/AcOEt afforded finally 0.074 g of the title compound as white crystals of mp. 126-27° C.

MS: 480.3 (M-H)⁺.

10 Example 73

[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-2-ethoxy-propionic acid

was prepared in analogy to example 72, but using in step a) 4-hydroxy-naphthalene-1-carbaldehyde instead of 4-hydroxy-benzo[b]thiophene-7-carbaldehyde and 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (example 12 b)) instead of 2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethanol, respectively, as white solid of mp. 90-93° C.
15

MS: 516.4 (M-H)⁺.

Example 74

20 [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-2-ethoxy-propionic acid

was prepared in analogy to example 72, but using in step a) 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (example 12 b)) instead of 2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethanol, as white solid of mp. 152-54° C.

25 MS: 522.4 (M-H)⁺.

Example 75

[rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-propionic acid

was prepared in analogy to example 72, but using in step a) 2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (see example 41) instead of 2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethanol, and in step as white crystals of mp. 120-22° C.

MS: 508.3 (M-H)⁻.

5

Example 76

[rac]-2-Isopropoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-propionic acid

was prepared in analogy to example 73, but using in step a) 2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (see example 41) instead of 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol, and in step b) ethyl isopropoxyacetate instead of ethyl ethoxyacetate, as white foam.

MS: 516.4 (M-H)⁻.

15

Example 77

[rac]-2-Ethoxy-3-(4-{2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-propionic acid

was prepared in analogy to example 76, but using in step b) ethyl ethoxyacetate instead of ethyl isopropoxyacetate, as white crystals of mp. 111-13° C.

20

MS: 504.2 (M+H)⁺.

Example 78

[rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid

25

was prepared in analogy to example 72, but using in step a) 4-hydroxy-naphthalene-1-carbaldehyde instead of 4-hydroxy-benzo[b]thiophene-7-carbaldehyde, as white crystals of mp. 140-41° C.

MS: 474.3 (M-H)⁻.

Example 79

[rac]-2-Isopropoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid

- 5 was prepared in analogy to example 72, but using in step a] 2-(5-methyl-2-phenyl-thiazol-4-yl)-ethanol (see example 1) instead of 2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethanol, and in step b] ethyl isopropoxyacetate instead of ethyl ethoxyacetate, as off-white solid of mp. 73° C.

MS: 482.2 (M+H)⁺.

10

Example 80

[rac]-3-{4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-2-propoxy-propionic acid

- 15 was prepared in analogy to example 76, but using in step a] 2-(5-methyl-2-phenyl-thiazol-4-yl)-ethanol (see example 1) instead of 2-[2-(4-isopropyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol, and in step b] ethyl propoxyacetate instead of ethyl isopropoxyacetate, as white solid of mp. 95-99° C.

MS: 474.3 (M-H)⁻.

20 **Example 81**

[rac]-2-Methoxy-3-{4-[2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid

was prepared in analogy to example 78, but using in step b] ethyl methoxyacetate instead of ethyl ethoxyacetate, as white crystals of mp. 155-56° C.

- 25 MS: 462.2 (M+H)⁺.

Example 82

[rac]-3-(4-[2-(5-Methyl-2-p-tolyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl)-2-propoxy-propionic acid

was prepared in analogy to example 81, but using in step b) ethyl propoxyacetate instead
5 of ethyl methoxyacetate, as white crystals of mp. 123-24° C.

MS: 488.3 (M-H)⁺.

Example 83

[rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-2-ethoxy-propionic acid

was prepared in analogy to example 72, but using in step a) 2-[2-(3,5-dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethanol (see example 70 b)) instead of 2-(5-methyl-2-p-tolyl-thiazol-4-yl)-ethanol, as white crystals of mp. 148-50° C.

MS: 526.3 (M-H)⁺.

15

Example 84

[rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-2-methoxy-propionic acid

was prepared in analogy to example 83, but using in step b) ethyl methoxyacetate instead
20 of ethyl ethoxyacetate, as white crystals of mp. 156-57° C.

MS: 512.3 (M-H)⁺.

Example 85

[rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-2-isopropoxy-propionic acid

was prepared in analogy to example 83, but using in step b) ethyl isopropoxyacetate instead of ethyl ethoxyacetate, as white crystals of mp. 150-52° C.

MS: 540.3 (M-H)⁺.

Example 86

5 [rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-2-isopropoxy-propionic acid

was prepared in analogy to example 73, but using in step b) ethyl isopropoxyacetate instead of ethyl ethoxyacetate, as white solid of mp. 75-85° C.

MS: 530.3 (M-H)⁺.

10 Example 87

[rac]-3-(4-{2-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-benzo[b]thiophen-7-yl)-2-propoxy-propionic acid

was prepared in analogy to example 74, but using in step b) ethyl propoxyacetate instead of ethyl ethoxyacetate, as white solid of mp. 76° C.

15 MS: 536.3 (M-H)⁺.

Example 88

20 [rac]-3-(4-{2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-naphthalen-1-yl)-2-ethoxy-propionic acid

was prepared in analogy to example 83, but using in step a) 4-hydroxy-naphthalene-1-carbaldehyde instead of 4-hydroxy-benzo[b]thiophene-7-carbaldehyde, as white crystals of mp. 133-35° C.

MS: 520.3 (M-H)⁺.

Example 89

[rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid

was prepared in analogy to example 80, but using in step b) ethyl ethoxyacetate instead of
5 ethyl propoxyacetate, as white solid of mp. 140-43° C.

MS: 460.3 (M-H)⁻.

Example 90

[rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid

was prepared in analogy to example 89, but using in step a) 4-hydroxy-
benzo[b]thiophene-7-carbaldehyde instead of 4-hydroxy-naphthalene-1-carbaldehyde, as
white solid of mp. 146-48° C.

MS: 466.2 (M-H)⁻.

15

Example 91

a) [rac]-2-Ethoxy-3-[2-methyl-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid ethyl ester

In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-
20 methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with (4-methyl-2-phenyl-thiazol-5-yl)-methanol [PCT Int. Appl. (2002), WO 02/80899 A1] in the presence of triphenylphosphine and diethyl azodicarboxylate to yield [rac]-2-ethoxy-3-[2-methyl-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid ethyl ester as colorless oil.

25 MS: 440.2 (M+H)⁺, 396.3, 227.3.

b) [rac]-2-Ethoxy-3-[2-methyl-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid

In analogy to the procedure described in example 10 d], [rac]-2-ethoxy-3-[2-methyl-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-[2-methyl-4-(4-methyl-2-phenyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid as colorless oil.

5 MS: 434.4 (M+Na)⁺, 412.2 (M+H)⁺, 315.1, 228.3.

Example 92

a) [rac]-3-{4-[2-(2-Chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester

- 10 In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with [2-(2-chloro-phenyl)-4-methyl-thiazol-5-yl]-methanol (prepared from 2-chloro-thiobenzamide and ethyl 2-chloro-acetoacetate in analogy to the procedures described in examples 33 a) and 33 b)) in the presence of triphenylphosphine and diethyl azodicarboxylate to yield [rac]-3-
15 {4-[2-(2-chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester as colorless oil.

MS: 496.2 (M+Na)⁺, 474.1 (M+H)⁺.

b) [rac]-3-{4-[2-(2-Chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

20

In analogy to the procedure described in example 10 d], [rac]-3-{4-[2-(2-chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester was treated with LiOH to obtain [rac]-3-{4-[2-(2-chloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid as colorless oil.

25 MS: 468.1 (M+Na)⁺, 446.2 (M+H)⁺, 371.3.

Example 93

a) 1-Bromo-2-fluoro-4-(phenylmethoxy)-benzene

- In analogy to the procedure described in example 23 b), 1-fluoro-3-(phenylmethoxy)-
30 benzene (for the preparation of 1-fluoro-3-(phenylmethoxy)-benzene see: A. A. Durrani, J. H. P. Tyman, *J. Chem. Soc., Perkin Trans. 1* 1979, 8, 2079-2087) was treated with N-

bromosuccinimide in the presence of concentrated sulfuric acid to give 1-bromo-2-fluoro-4-(phenylmethoxy)-benzene as colorless oil.

b) 4-Benzoyloxy-2-fluoro-benzaldehyde

- 5 In analogy to the procedure described in example 23 c), 1-bromo-2-fluoro-4-(phenylmethoxy)-benzene was treated with n-BuLi and N,N-dimethylformamide in dry tetrahydrofuran to yield 4-benzoyloxy-2-fluoro-benzaldehyde as off-white crystals.

MS: 230.1 (M)⁺.

- 10 c) (S)-4-Benzyl-3-[(2S,3R)-3-(4-benzoyloxy-2-fluoro-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one

In analogy to the procedure described in example 17 a), (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one (for the preparation of (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one see: D. Haigh, H. C. Birrell, B. C. C. Cantello, D. S. Eggleston, R. C. Haltiwanger, R. M.

- 15 Hindley, A. Ramaswamy, N. C. Stevens, *Tetrahedron: Asymmetry* 1999, 10, 1353-1367) was reacted with 4-benzoyloxy-2-fluoro-benzaldehyde in the presence of triethylamine and di-n-butylboron triflate to give (S)-4-benzyl-3-[(2S,3R)-3-(4-benzoyloxy-2-fluoro-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one as colorless foam. According to ¹H-NMR spectroscopy, one of the four isomers is strongly predominating. The configuration was tentatively assigned as 2S,3R according to D. Haigh et al., *Tetrahedron: Asymmetry* 1999, 20 10, 1353-1367.

MS: 516.2 (M+Na)⁺, 476.2, 435.3, 419.3, 387.1, 330.2, 203.1.

- 25 d) (2S,3R)-3-(4-Benzoyloxy-2-fluoro-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester

In analogy to the procedure described in example 17 b), (S)-4-benzyl-3-[(2S,3R)-3-(4-benzoyloxy-2-fluoro-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one was treated with sodium methoxide in methanol to give (2S,3R)-3-(4-benzoyloxy-2-fluoro-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester as colorless liquid. According to ¹H-NMR spectroscopy, one single diastereomer was obtained.

30 MS: 371.3 (M+Na)⁺, 331.3, 303.2, 279.2, 242.2.

e] (2S)-3-(4-Benzoyloxy-2-fluoro-phenyl)-2-ethoxy-propionic acid methyl ester

In analogy to the procedure described in example 17 c], (2S,3R)-3-(4-benzoyloxy-2-fluoro-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester was treated with triethylsilane in trifluoroacetic acid to yield (2S)-3-(4-benzoyloxy-2-fluoro-phenyl)-2-ethoxy-propionic
5 acid methyl ester as colorless liquid.

MS: 355.2 (M+Na)⁺, 350.3 (M+NH₄)⁺, 333.3 (M+H)⁺, 245.3.

f] (2S)-2-Ethoxy-3-(2-fluoro-4-hydroxy-phenyl)-propionic acid methyl ester

In analogy to the procedure described in example 17 d], (2S)-3-(4-benzoyloxy-2-fluoro-phenyl)-2-ethoxy-propionic acid methyl ester was hydrogenated over 10 % palladium on
10 charcoal to give (2S)-2-ethoxy-3-(2-fluoro-4-hydroxy-phenyl)-propionic acid methyl ester as colorless liquid.

MS: 265.2 (M+Na)⁺, 260.2 (M+NH₄)⁺, 243.3 (M+H)⁺, 197.1, 155.3.

15 g] (S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-fluoro-phenyl}-2-ethoxy-propionic acid methyl ester

In analogy to the procedure described in example 14 b], (2S)-2-ethoxy-3-(2-fluoro-4-hydroxy-phenyl)-propionic acid methyl ester was reacted with 4-chloromethyl-2-(4-chloro-phenyl)-thiazole (example 14 a]) in the presence of cesium carbonate and
20 potassium iodide to yield (S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-fluoro-phenyl}-2-ethoxy-propionic acid methyl ester as light yellow oil.

MS: 472.0 (M+Na)⁺, 450.2 (M+H)⁺.

25 h] (S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-fluoro-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d], (S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-fluoro-phenyl}-2-ethoxy-propionic acid methyl ester was treated with LiOH to obtain (S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2-fluoro-phenyl}-2-ethoxy-propionic acid as light yellow solid.

30 MS: 436.1 (M+H)⁺, 390.9, 304.2, 261.7, 241.3.

Example 94**a) 4-Benzyloxy-benzofuran**

- To a suspension of potassium carbonate (2.68 g, 19.4 mmol) in N,N-dimethylformamide (8 ml) was added a solution of 4-hydroxy-benzofuran (2.6 g, 19.4 mmol) in N,N-dimethylformamide (8 ml) at 2 °C under an argon atmosphere (for the preparation of 4-hydroxy-benzofuran see: G. Kneen, P. J. Maddocks, *Syn. Commun.* 1986, 16, 1635-1640). After stirring for 50 min at 2 °C, benzyl bromide (3.3 ml, 19.4 mmol) was added over a period of 15 min at 2 °C. The suspension was stirred for additional 30 min at 2 °C and for 1.5 h at ambient temperature. After adding ice water (20 ml), the solution was extracted two times with diethyl ether. The combined extracts were washed three times with brine and dried over sodium sulfate. Evaporation of the solvent gave a yellow oil which was purified by column chromatography (silica gel, hexane) to give 4.3 g (19.2 mmol, 99 %) of the title compound as colorless oil.
- MS: 224.1 (M)⁺.

b) 4-Benzyloxy-benzofuran-7-carbaldehyde

- Dry N,N-dimethylformamide (12.1 g, 166 mmol) was added dropwise with stirring and cooling under an argon atmosphere to phosphorous oxychloride (11.4 g, 75 mmol) at such a rate that the temperature did not exceed 10 °C. After 30 min at 10 °C, a solution of 4-benzyloxy-benzofuran (9.3 g, 41 mmol) in N,N-dimethylformamide (9 ml) was added dropwise within 30 min. The reaction mixture was stirred 30 min at ambient temperature and then continuously heated to 100 °C. After 10 min at 100 °C the mixture was heated at 85 °C for 3 h, cooled to 10 °C, neutralized with 25 % aqueous sodium acetate, with cooling, and extracted with diethyl ether. The extract was washed with saturated aqueous sodium bicarbonate and water and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a brown oil which was purified by column chromatography (silica gel, hexane/AcOEt=19/1) to give 1.8 g (7 mmol, 17 %) of the title compound as yellow oil.
- MS: 252.1 (M)⁺.

c) 3-(4-Benzyloxy-benzofuran-7-yl)-2Z-ethoxy-acrylic acid ethyl ester

- A suspension of (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride (2.04 g, 4.8 mmol) and DBU (0.8 g, 5.2 mmol) in THF (40 ml) was stirred for 10 min at ambient temperature under an argon atmosphere [for the preparation of (1,2-diethoxy-2-oxoethyl)triphenyl phosphonium chloride see: K. K. Bach, H. R. El-Seedi, H. M. Jensen, H. B. Nielsen, I. Thomson, K. B. G. Torssell, *Tetrahedron* 1994, 50, 7543-7556]. 4-Benzyloxy-benzofuran-7-carbaldehyde (0.8 g, 3.2 mmol) was added and the mixture was heated under reflux for 12 h. The solvent was concentrated at reduced pressure, the residue taken up with ethyl acetate, washed with saturated aqueous NH_4Cl solution and two times with brine. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue purified by column chromatography (silica gel, hexane/AcOEt=9/1) to give 0.8 g (2.2 mmol, 69 %) of the title compound as colorless oil.
- MS: 366.1 (M)⁺, 275.1, 173.0.

d) [rac]-2-Ethoxy-3-(4-hydroxy-2,3-dihydro-benzofuran-7-yl)-propionic acid ethyl ester

- A solution of 3-(4-benzyloxy-benzofuran-7-yl)-2Z-ethoxy-acrylic acid ethyl ester (420 mg, 1.15 mmol) in methanol (17 ml) was hydrogenated over 10 % palladium on charcoal (100 mg) at ambient temperature for 20 h. The catalyst was filtered off, the solvent evaporated under reduced pressure and the residue chromatographed (silica gel, hexane/AcOEt=4/1) to give 240 mg (0.86 mmol, 75 %) of the title compound as colorless liquid.
- MS: 279.1 (M-H)⁺, 265.2, 141.0.

e) [rac]-3-{7-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2,3-dihydro-benzofuran-4-yl}-2-ethoxy-propionic acid ethyl ester

- In analogy to the procedure described in example 14 b), [rac]-2-ethoxy-3-(4-hydroxy-2,3-dihydro-benzofuran-7-yl)-propionic acid ethyl ester was reacted with 4-chloromethyl-2-(4-chloro-phenyl)-thiazole (example 14 a)) in the presence of cesium carbonate and potassium iodide to yield [rac]-3-{7-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2,3-dihydro-benzofuran-4-yl}-2-ethoxy-propionic acid ethyl ester as colorless oil.
- MS: 490.2 (M+H)⁺, 488.3 (M+H)⁺, 442.2, 414.2, 249.2.

f) [rac]-3-{7-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2,3-dihydro-benzofuran-4-yl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d), [rac]-3-{7-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2,3-dihydro-benzofuran-4-yl}-2-ethoxy-propionic acid ethyl ester
5 was treated with LiOH to obtain [rac]-3-{7-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2,3-dihydro-benzofuran-4-yl}-2-ethoxy-propionic acid as colorless oil.

MS: 458.3 (M-H)⁻, 340.2, 283.2, 255.4.

Example 95

10 a) [rac]-3-(4-Benzyloxy-benzofuran-7-yl)-2-ethoxy-propionic acid methyl ester

Magnesium turnings (0.5 g, 20.6 mmol) were added to a stirred solution of 3-(4-benzyloxy-benzofuran-7-yl)-2Z-ethoxy-acrylic acid ethyl ester (0.8 g, 2.18 mmol; example 94 c)) in methanol (26 ml) and THF (13 ml) at ambient temperature. The suspension was warmed to 40 °C until evolution of hydrogen commenced. Then, the heating bath was
15 replaced by a water bath, additional magnesium turnings (1 g, 41.2 mmol) were added and stirring of the reaction mixture was continued for 12 h. The suspension was cooled to 0 °C, then 25 % aqueous hydrochloric acid was added till all the solid had dissolved. The mixture was extracted twice with ethyl acetate and the combined ethyl acetate solutions were washed three times with water and dried over sodium sulfate. The solvent was
20 evaporated to afford the title compound (0.77 g, 2.16 mmol, 99 %) which was used in the next step without further purification.

MS: 354.2 (M)⁺, 237.2.

b) [rac]-2-Ethoxy-3-(4-hydroxy-benzofuran-7-yl)-propionic acid methyl ester

25 Dimethyl sulfide (4.4 ml, 60 mmol) and boron trifluoride diethyl etherate (46 % purity, 3.3 ml, 12 mmol) were added to an ice cold solution of [rac]-3-(4-benzyloxy-benzofuran-7-yl)-2-ethoxy-propionic acid methyl ester (0.85 g, 2.4 mmol) in dichloromethane (25 ml) under an argon atmosphere. The mixture was stirred for 6 h at ambient temperature, poured into ice water and extracted three times with dichloromethane. The combined
30 extract was washed with brine and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a brown oil which was purified by column chromatography (silica gel, hexane/AcOEt=4/1) to give 0.45 g (1.7 mmol, 71 %) of the title compound as light yellow oil.

MS: 263.0 (M-H)⁻.

c) [rac]-3-{7-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-benzofuran-4-yl}-2-ethoxy-propionic acid methyl ester

- 5 In analogy to the procedure described in example 14 b), [rac]-2-ethoxy-3-(4-hydroxy-benzofuran-7-yl)-propionic acid methyl ester was reacted with 4-chloromethyl-2-(4-chloro-phenyl)-thiazole (example 14 a)) in the presence of cesium carbonate and potassium iodide to yield [rac]-3-{7-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-benzofuran-4-yl}-2-ethoxy-propionic acid methyl ester as colorless oil.
- 10 MS: 489.3 (M+NH₄)⁺, 472.2 (M+H)⁺, 426.3, 325.3, 225.3.

d) [rac]-3-{7-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-benzofuran-4-yl}-2-ethoxy-propionic acid

- 15 In analogy to the procedure described in example 10 d), [rac]-3-{7-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-benzofuran-4-yl}-2-ethoxy-propionic acid methyl ester was treated with LiOH to obtain [rac]-3-{7-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-benzofuran-4-yl}-2-ethoxy-propionic acid as colorless solid.
- MS: 456.2 (M-H)⁻, 410.2, 340.1.

20 **Example 96**

a) [rac]-2-Ethoxy-3-[2-methyl-4-(5-methyl-2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid ethyl ester

- 25 In analogy to the procedure described in example 14 b), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 4-bromomethyl-5-methyl-2-phenyl-thiazole [PCT Int. Appl. (2001), WO 0119805 A1] in the presence of cesium carbonate and potassium iodide to yield [rac]-2-ethoxy-3-[2-methyl-4-(5-methyl-2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid ethyl ester as colorless liquid.

MS: 462.3 (M+Na)⁺, 440.4 (M+H)⁺, 394.3, 229.2.

b] [rac]-2-Ethoxy-3-[2-methyl-4-(5-methyl-2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid

In analogy to the procedure described in example 10 d], [rac]-2-ethoxy-3-[2-methyl-4-(5-methyl-2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid ethyl ester was treated with
5 LiOH to obtain [rac]-2-ethoxy-3-[2-methyl-4-(5-methyl-2-phenyl-thiazol-4-ylmethoxy)-phenyl]-propionic acid as colorless liquid.

MS: 434.2 (M+Na)⁺, 412.3 (M+H)⁺, 313.2, 229.2.

Example 97

10 a] [rac]-3-{4-[2-(4-Chloro-phenyl)-5-methyl-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester

In analogy to the procedure described in example 14 b], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with 4-bromomethyl-2-(4-chloro-phenyl)-5-methyl-thiazole (JP 62178590 A2) in the presence of
15 cesium carbonate and potassium iodide to yield [rac]-3-{4-[2-(4-chloro-phenyl)-5-methyl-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester as light yellow crystals.

MS: 496.1 (M+Na)⁺, 476.3 (M+H)⁺, 474.2 (M+H)⁺, 263.2.

20 b] [rac]-3-{4-[2-(4-Chloro-phenyl)-5-methyl-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d], [rac]-3-{4-[2-(4-chloro-phenyl)-5-methyl-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester was treated with LiOH to obtain [rac]-3-{4-[2-(4-chloro-phenyl)-5-methyl-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid as colorless solid.
25

MS: 468.3 (M+Na)⁺, 446.2 (M+H)⁺.

Example 98

30 a] [rac]-2-Ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with 2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethanol (prepared from [rac]-4-bromo-3-oxo-pentanoic acid methyl ester [PCT Int. Appl. (2001), WO 01/79202] and 4-methoxy-
5 thiobenzamide in analogy to the procedures described in examples 12 a] and 12 b]) in the presence of triphenylphosphine and di-tert-butyl azodicarboxylate to yield [rac]-2-ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester as yellow crystals.

10 b] [rac]-2-Ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid

In analogy to the procedure described in example 10 d], [rac]-2-ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-5-
15 methyl-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid as colorless oil.

MS: 478.5 (M+Na)⁺, 456.5 (M+H)⁺.

Example 99

a] [rac]-2-Ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-
20 phenyl)-propionic acid ethyl ester

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with 2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethanol (prepared from 4-methoxy-thiobenzamide and 1,3-dichloroacetone in analogy to the procedure described in example 4 a] to yield 4-
25 chloromethyl-2-(4-methoxy-phenyl)-thiazole, followed by side chain elongation in analogy to the sequence described in example 13 a] to 13 d]) in the presence of triphenylphosphine and di-tert-butyl azodicarboxylate to yield [rac]-2-ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester as light yellow solid.

30 MS: 492.3 (M+Na)⁺, 470.2 (M+H)⁺, 424.3, 396.3.

b) [rac]-2-Ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid

In analogy to the procedure described in example 10 d), [rac]-2-ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester was
5 treated with LiOH to obtain [rac]-2-ethoxy-3-(4-{2-[2-(4-methoxy-phenyl)-thiazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid as colorless liquid.

MS: 440.3 (M-H)⁻, 394.1.

Example 100

10 a) [rac]-2-Ethoxy-3-{4-[2-(3-methoxy-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-propionic acid ethyl ester

In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with [2-(3-methoxy-phenyl)-4-methyl-thiazol-5-yl]-methanol (prepared from 3-methoxy-
15 thiobenzamide [PCT Int. Appl. (2002), WO 0100433 A1] and ethyl 2-chloro-acetoacetate in analogy to the procedures described in example 33 a) and 33 b)) in the presence of triphenylphosphine and di-tert-butyl azodicarboxylate to yield [rac]-2-ethoxy-3-{4-[2-(3-methoxy-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-propionic acid ethyl ester as light yellow solid.

20 MS: 492.3 (M+Na)⁺, 470.2 (M+H)⁺, 426.4, 339.2, 255.2.

b) [rac]-2-Ethoxy-3-{4-[2-(3-methoxy-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-propionic acid

In analogy to the procedure described in example 10 d), [rac]-2-ethoxy-3-{4-[2-(3-methoxy-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-propionic acid ethyl
25 ester was treated with LiOH to obtain [rac]-2-ethoxy-3-{4-[2-(3-methoxy-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-propionic acid as colorless foam.

MS: 440.3 (M-H)⁻, 394.1, 255.3.

30 **Example 101**

a] [rac]-3-{4-[2-(2,4-Dichloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with 2-(2,4-dichloro-phenyl)-5-methoxymethyl-4-methyl-thiazole (prepared from 2,4-dichloro-thiobenzamide and ethyl 2-chloro-acetoacetate in analogy to the procedures described in examples 33 a] and 33 b]) in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield [rac]-3-{4-[2-(2,4-dichloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester as colorless liquid.

MS: 510.4 (M+H)⁺, 509.3 (M+H)⁺, 508.3 (M+H)⁺.

b] [rac]-3-{4-[2-(2,4-Dichloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d], [rac]-3-{4-[2-(2,4-dichloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester was treated with LiOH to obtain [rac]-3-{4-[2-(2,4-dichloro-phenyl)-4-methyl-thiazol-5-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid as colorless solid.

MS: 478.1 (M-H)⁻, 432.2.

Example 102

a] [rac]-3-(4-{3-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with 3-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-propan-1-ol (prepared from methanesulfonic acid 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethyl ester [obtained from 2-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-ethanol (example 12 b)] and methanesulfonyl chloride in pyridine at 0°C] according to the sequence described in examples 13 a] to d]) in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield [rac]-3-(4-{3-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester as colorless liquid.

MS: 546.4 (M+Na)⁺, 524.4 (M+H)⁺, 425.5.

b) [rac]-3-(4-{3-[2-(4-tert-Butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid

5 In analogy to the procedure described in example 10 d), [rac]-3-(4-{3-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester was treated with LiOH to obtain [rac]-3-(4-{3-[2-(4-tert-butyl-phenyl)-5-methyl-thiazol-4-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid as colorless liquid.

MS: 494.4 (M-H)⁻, 450.2.

10 **Example 103**

a) 4-Benzoyloxy-2,6-dimethyl-benzaldehyde

In analogy to the procedure described in example 23 a), 4-hydroxy-2,6-dimethyl-benzaldehyde was reacted with benzyl bromide in the presence of potassium carbonate to yield 4-benzoyloxy-2,6-dimethyl-benzaldehyde as orange liquid.

15 MS: 241.2 (M+H)⁺, 181.0.

b) (S)-4-Benzyl-3-[(2S,3R)-3-(4-benzoyloxy-2,6-dimethyl-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one

20 In analogy to the procedure described in example 17 a), (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one (for the preparation of (S)-4-benzyl-3-ethoxyacetyl-oxazolidin-2-one see: D. Haigh, H. C. Birrell, B. C. C. Cantello, D. S. Eggleston, R. C. Haltiwanger, R. M. Hindley, A. Ramaswamy, N. C. Stevens, *Tetrahedron: Asymmetry* 1999, 10, 1353-1367) was reacted with 4-benzoyloxy-2,6-dimethyl-benzaldehyde in the presence of triethylamine and di-n-butylboron triflate to give (S)-4-benzyl-3-[(2S,3R)-3-(4-benzoyloxy-2,6-dimethyl-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one as colorless liquid. According to ¹H-NMR spectroscopy, one of the four isomers is strongly predominating. The configuration was tentatively assigned as 2S,3R according to D. Haigh et al., *Tetrahedron: Asymmetry* 1999, 10, 1353-1367.

MS: 526.3 (M+Na)⁺, 486.3, 358.2, 309.1, 281.2, 237.2.

c] (2S,3R)-3-(4-Benzoyloxy-2,6-dimethyl-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester

In analogy to the procedure described in example 17 b], (S)-4-benzyl-3-[(2S,3R)-3-(4-benzoyloxy-2,6-dimethyl-phenyl)-2-ethoxy-3-hydroxy-propionyl]-oxazolidin-2-one was
5 treated with sodium methoxide in methanol to give (2S,3R)-3-(4-benzoyloxy-2,6-dimethyl-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester as colorless liquid. According to ¹H-NMR spectroscopy, one single diastereomer was obtained.

MS: 381.2 (M+Na)⁺, 376.3 (M+NH₄)⁺, 341.2, 313.2, 213.3.

10 d] (2S)-3-(4-Benzoyloxy-2,6-dimethyl-phenyl)-2-ethoxy-propionic acid methyl ester

In analogy to the procedure described in example 17 c], (2S,3R)-3-(4-benzoyloxy-2,6-dimethyl-phenyl)-2-ethoxy-3-hydroxy-propionic acid methyl ester was treated with triethylsilane in trifluoroacetic acid to yield (2S)-3-(4-benzoyloxy-2,6-dimethyl-phenyl)-2-ethoxy-propionic acid methyl ester as colorless liquid.

15 MS: 360.3 (M+NH₄)⁺, 284.1, 201.1.

e] (2S)-2-Ethoxy-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionic acid methyl ester

In analogy to the procedure described in example 17 d], (2S)-3-(4-benzoyloxy-2,6-dimethyl-phenyl)-2-ethoxy-propionic acid methyl ester was hydrogenated over 10 %
20 palladium on charcoal to give (2S)-2-ethoxy-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionic acid methyl ester as colorless liquid.

MS: 275.2 (M+Na)⁺, 270.3 (M+NH₄)⁺, 253.3 (M+H)⁺.

25 f] (S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2,6-dimethyl-phenyl}-2-ethoxy-propionic acid methyl ester

In analogy to the procedure described in example 14 b], (2S)-2-ethoxy-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionic acid methyl ester was reacted with 4-chloromethyl-2-(4-chloro-phenyl)-thiazole (example 14 a]) in the presence of cesium carbonate and potassium iodide to yield (S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2,6-
30 dimethyl-phenyl}-2-ethoxy-propionic acid methyl ester as off-white solid.

g] (S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2,6-dimethyl-phenyl}-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d], (S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2,6-dimethyl-phenyl}-2-ethoxy-propionic acid methyl ester was
5 treated with LiOH to obtain (S)-3-{4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-2,6-dimethyl-phenyl}-2-ethoxy-propionic acid as light yellow solid.

MS: 444.3 (M-H)⁻, 381.0, 309.2.

Example 104

10 a] 5-Chloromethyl-2-(4-chloro-phenyl)-4-methyl-thiazole

To a suspension of [2-(4-chloro-phenyl)-4-methyl-thiazol-5-yl]-methanol (643 mg, 2.7 mmol; obtained from 4-chloro-thiobenzamide and ethyl 2-chloro-acetoacetate in analogy to the procedures described in examples 33 a] and 33 b]) in chloroform (4 ml) was added thionyl chloride (390 µl, 5.4 mmol) at -10 °C under an argon atmosphere. The
15 reaction mixture was stirred for 30 min, saturated aqueous sodium bicarbonate solution/ice water 1/1 were added and the layers were separated. The aqueous layer was extracted two times with dichloromethane. The combined organic layers were washed with ice water/brine 1/1, dried over sodium sulfate and the solvent was evaporated in vacuo to give the title compound (595 mg, 2.3 mmol, 86 %) as colorless solid.

20 MS: 262.3 (M)⁺, 240.2.

b] [2-(4-Chloro-phenyl)-4-methyl-thiazol-5-yl]-acetonitrile

Tetrabutylammonium cyanide (804 mg, 3 mmol) was added to a solution of 5-chloromethyl-2-(4-chloro-phenyl)-4-methyl-thiazole (595 mg, 2.3 mmol) in acetonitrile
25 (25 ml). The solution was stirred at ambient temperature for 16 h, saturated aqueous sodium bicarbonate solution/ice water 1/1 and diethyl ether were added and the layers were separated. The aqueous layer was extracted one more time with diethyl ether, the combined organic layers were washed with ice water/brine 1/1, dried over sodium sulfate and the solvent was evaporated in vacuo to give orange crystals which were purified by
30 column chromatography (silica gel, cyclohexane/AcOEt) to yield 370 mg (1.5 mmol, 65 %) of the title compound as light yellow solid.

MS: 249.4 (M+H)⁺, 224.5, 217.5.

c) 2-[2-(4-Chloro-phenyl)-4-methyl-thiazol-5-yl]-ethanol

A solution of [2-(4-chloro-phenyl)-4-methyl-thiazol-5-yl]-acetic acid (300 mg, 1.1 mmol; prepared from [2-(4-chloro-phenyl)-4-methyl-thiazol-5-yl]-acetonitrile in analogy to the procedure described in example 13 b)) in tetrahydrofuran (4.5 ml) was treated at 0 °C with
5 borane-tetrahydrofuran complex (1 M solution in tetrahydrofuran; 2.8 ml, 2.8 mmol). The cooling bath was removed and the reaction mixture stirred at ambient temperature for 16 h. Careful quenching with MeOH and ice water, twofold extraction with AcOEt, washing with ice water/brine 1/1, drying over magnesium sulfate, and evaporation of the
10 solvent left a crude product which was refluxed for 30 min in MeOH to liberate quantitatively the free alcohol. The solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, heptane/AcOEt) to yield 240 mg (0.95 mmol, 84 %) of the title compound as colorless solid.

MS: 254.3 (M+H)⁺, 228.3.

15

d) [rac]-3-(4-{2-[2-(4-Chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester

In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-[2-(4-chloro-phenyl)-4-methyl-thiazol-5-yl]-ethanol in the presence of tributylphosphine and
20 N,N,N',N'-tetramethyl azodicarboxamide to yield [rac]-3-(4-{2-[2-(4-chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester as colorless liquid.

MS: 490.2 (M+H)⁺, 488.3 (M+H)⁺, 444.2, 356.3.

25

e) [rac]-3-(4-{2-[2-(4-Chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d), [rac]-3-(4-{2-[2-(4-chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl
30 ester was treated with LiOH to obtain [rac]-3-(4-{2-[2-(4-chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid as light yellow solid.

MS: 458.3 (M-H)⁻, 412.2.

Example 105

a) [rac]-2-Ethoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester

- 5 In analogy to the procedure described in example 14 b), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole [PCT Int. Appl. (2002), WO 0292590 A1] in the presence of cesium carbonate and potassium iodide to yield [rac]-2-ethoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester as colorless liquid.

MS: 530.3 (M+Na)⁺, 508.3 (M+H)⁺, 256.1.

b) [rac]-2-Ethoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid

- 15 In analogy to the procedure described in example 10 d), [rac]-2-ethoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid as light yellow solid.
- 20 MS: 478.2 (M-H)⁻, 434.3.

Example 106

a) [rac]-3-(4-{2-[2-(2-Chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester

- 25 In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-[2-(2-chloro-phenyl)-4-methyl-thiazol-5-yl]-ethanol (prepared from [2-(2-chloro-phenyl)-4-methyl-thiazol-5-yl]-methanol (obtained from 2-chloro-thiobenzamide and ethyl 2-chloro-acetoacetate in analogy to the procedures described in examples 33 a) and 33 b)) according to the sequence described in examples 104 a) to c)) in the presence of triphenylphosphine and di-tert-butyl azodicarboxylate to yield [rac]-3-(4-{2-[2-(2-chloro-

phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester as colorless liquid.

MS: 510.3 (M+Na)⁺, 490.4 (M+H)⁺, 488.2 (M+H)⁺, 350.3, 296.4, 250.3.

5 b) [rac]-3-(4-{2-[2-(2-Chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid

In analogy to the procedure described in example 10 d), [rac]-3-(4-{2-[2-(2-chloro-phenyl)-4-methyl-thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester was treated with LiOH to obtain [rac]-3-(4-{2-[2-(2-chloro-phenyl)-4-methyl-
10 thiazol-5-yl]-ethoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid as colorless liquid.

MS: 458.1 (M-H)⁻, 412.0, 255.2.

Example 107

15 a) (S)-2-Ethoxy-3-{2-ethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid methyl ester

In analogy to the procedure described in example 14 b), (2S)-2-ethoxy-3-(2-ethyl-4-hydroxy-phenyl)-propionic acid methyl ester (example 23 g)) was reacted with 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole [PCT Int. Appl. (2002), WO 0292590 A1] in the presence of cesium carbonate and potassium iodide to yield (S)-2-
20 ethoxy-3-{2-ethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid methyl ester as colorless oil.

MS: 530.3 (M+Na)⁺, 508.4 (M+H)⁺, 343.3, 300.3, 259.3.

25 b) (S)-2-Ethoxy-3-{2-ethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 10 d), (S)-2-ethoxy-3-{2-ethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid methyl ester was treated with LiOH to obtain (S)-2-ethoxy-3-{2-ethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid as yellow solid.

30 MS: 516.2 (M+Na)⁺, 494.2 (M+H)⁺, 429.0, 371.3, 256.1.

Example 108

a] (S)-3-{2,6-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-ethoxy-propionic acid methyl ester

- 5 In analogy to the procedure described in example 14 b], (2S)-2-ethoxy-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionic acid methyl ester (example 103 e]) was reacted with 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole [PCT Int. Appl. (2002), WO 0292590 A1] in the presence of cesium carbonate and potassium iodide to yield (S)-3-{2,6-dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-ethoxy-propionic acid methyl ester as yellow oil.

MS: 530.3 (M+Na)⁺, 508.3 (M+H)⁺, 443.5, 342.1, 269.2.

b] (S)-3-{2,6-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-ethoxy-propionic acid

- 15 In analogy to the procedure described in example 10 d], (S)-3-{2,6-dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-ethoxy-propionic acid methyl ester was treated with LiOH to obtain (S)-3-{2,6-dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-ethoxy-propionic acid as yellow solid.
- 20 MS: 494.2 (M+H)⁺, 388.3.

Example 109

a] [rac]-2-Ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester

- 25 In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with [2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield [rac]-2-ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester as yellow crystals.

- 136 -

MS: 516.2 (M+Na)⁺, 494.2 (M+H)⁺, 356.3, 242.4.

b] [rac]-2-Ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid

- 5 In analogy to the procedure described in example 10 d], [rac]-2-ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid as off-white solid.

MS: 488.1 (M+Na)⁺, 466.1 (M+H)⁺, 420.0, 300.1, 242.1.

10

Example 110

a] [rac]-2-Ethoxy-3-(2-methyl-4-{2-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester

- In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-yl]-ethanol (prepared from [4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol (obtained from 3-trifluoromethyl-thiobenzamide and ethyl 2-chloro-acetoacetate in analogy to the procedures described in example 33 a] and 33 b)) according to the reaction sequence described in example 104 a] to c)) in the presence of triphenylphosphine and di-tert-butyl azodicarboxylate to yield [rac]-2-ethoxy-3-(2-methyl-4-{2-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester as colorless oil.
- 20

MS: 522.3 (M+H)⁺, 478.4, 448.2.

- 25 b] [rac]-2-Ethoxy-3-(2-methyl-4-{2-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid

- In analogy to the procedure described in example 10 d], [rac]-2-ethoxy-3-(2-methyl-4-{2-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-(2-methyl-4-{2-[4-methyl-2-(3-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid as yellow oil.
- 30

MS: 492.2 (M-H)⁻, 446.1.

Example 111

a) [rac]-2-Ethoxy-3-{2-methyl-4-[2-(4-methyl-2-phenyl-thiazol-5-yl)-ethoxy]-phenyl}-propionic acid ethyl ester

- 5 In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-(4-methyl-2-phenyl-thiazol-5-yl)-ethanol (prepared from (4-methyl-2-phenyl-thiazol-5-yl)-methanol [PCT Int. Appl. (2002), WO 02/80899 A1] according to the reaction sequence described in example 104 a) to c)) in the presence of triphenylphosphine and di-tert-butyl
10 azodicarboxylate to yield [rac]-2-ethoxy-3-{2-methyl-4-[2-(4-methyl-2-phenyl-thiazol-5-yl)-ethoxy]-phenyl}-propionic acid ethyl ester as colorless liquid.

MS: 476.3 (M+Na)⁺, 454.4 (M+H)⁺, 380.3, 202.1.

- b) [rac]-2-Ethoxy-3-{2-methyl-4-[2-(4-methyl-2-phenyl-thiazol-5-yl)-ethoxy]-phenyl}-propionic acid
15

In analogy to the procedure described in example 10 d), [rac]-2-ethoxy-3-{2-methyl-4-[2-(4-methyl-2-phenyl-thiazol-5-yl)-ethoxy]-phenyl}-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-{2-methyl-4-[2-(4-methyl-2-phenyl-thiazol-5-yl)-ethoxy]-phenyl}-propionic acid as colorless liquid.

- 20 MS: 424.4 (M-H)⁻, 378.4.

Example 112

a) 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates)

- 25 In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with [rac]-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethanol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield 2-ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester as a mixture of two
30 diastereomeric racemates as colorless liquid.

MS: 544.2 (M+Na)⁺, 522.3 (M+H)⁺, 478.3, 298.4, 219.4.

b) 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid (mixture of two diastereomeric racemates)

- 5 In analogy to the procedure described in example 10 d), 2-ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 2-ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid as a mixture of two diastereomeric racemates as colorless foam.
- 10 MS: 516.1 (M+Na)⁺, 494.2 (M+H)⁺, 450.1, 371.3.

Example 113

a) [rac]-2-Ethoxy-3-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester

- 15 In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propan-2-ol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield [rac]-2-ethoxy-3-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester as light
- 20 yellow liquid.

MS: 558.4 (M+Na)⁺, 536.4 (M+H)⁺, 492.2, 284.1.

- b) [rac]-2-Ethoxy-3-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid
- 25

- In analogy to the procedure described in example 10 d), [rac]-2-ethoxy-3-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-
- 30 propionic acid as colorless liquid.

MS: 506.2 (M-H)⁻, 462.1.

Example 114

- 5 a] 2-Ethoxy-3-(2-methyl-4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with [rac]-2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propan-1-ol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield 2-ethoxy-3-(2-methyl-4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-phenyl)-propionic acid ethyl ester as a mixture of two diastereomeric racemates as light yellow liquid.

MS: 572.3 (M+Na)⁺, 550.3 (M+H)⁺, 508.4, 298.4.

- 15 b] 2-Ethoxy-3-(2-methyl-4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-phenyl)-propionic acid (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 d], 2-ethoxy-3-(2-methyl-4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates) was treated with
20 LiOH to obtain 2-ethoxy-3-(2-methyl-4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-phenyl)-propionic acid as a mixture of two diastereomeric racemates as colorless foam.

MS: 520.2 (M-H)⁻, 473.8, 255.2.

25 **Example 115**

- a] [rac]-2-Ethoxy-3-(2-methyl-4-{1-methyl-1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with 2-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propan-2-ol [PCT Int. Appl. (2002), WO 02/062774
30 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to

yield [rac]-2-ethoxy-3-(2-methyl-4-{1-methyl-1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester as yellow liquid.

MS: 544.3 (M+Na)⁺, 522.2 (M+H)⁺, 478.3.

5 b] [rac]-2-Ethoxy-3-(2-methyl-4-{1-methyl-1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 10 d], [rac]-2-ethoxy-3-(2-methyl-4-{1-methyl-1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester was treated with LiOH to obtain [rac]-2-ethoxy-3-(2-methyl-4-{1-methyl-1-[2-

10 (4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid as colorless oil.

MS: 516.2 (M+Na)⁺, 494.2 (M+H)⁺, 450.1.

Example 116

15 a] 2-Ethoxy-3-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with [rac]-1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethanol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to

20 yield 2-ethoxy-3-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester as a mixture of two diastereomeric racemates as colorless liquid.

25 b] 2-Ethoxy-3-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 d], 2-ethoxy-3-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 2-ethoxy-3-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid as a

30 mixture of two diastereomeric racemates as light yellow liquid.

MS: 478.1 (M-H)⁻, 432.2, 388.2.

Example 117

a] 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-but-3-enyloxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates)

- 5 In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with [rac]-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-but-3-en-1-ol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield 2-ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-but-3-enyloxy}-phenyl)-propionic acid ethyl ester as a mixture of
- 10 two diastereomeric racemates as yellow liquid.

MS: 570.3 (M+Na)⁺, 548.2 (M+H)⁺, 343.3, 296.3.

- b] 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-but-3-enyloxy}-phenyl)-propionic acid (mixture of two diastereomeric racemates)
- 15

- In analogy to the procedure described in example 10 d], 2-ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-but-3-enyloxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 2-ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-but-3-enyloxy}-phenyl)-propionic acid as a mixture of two diastereomeric racemates as colorless
- 20 solid.

MS: 518.2 (M-H)⁻, 474.2, 392.2.

Example 118

- a] 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-butoxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates)
- 25

- A solution of 2-ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-but-3-enyloxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates; 100 mg, 180 μmol; example 117 a]) in ethanol (5 ml) was treated with 10 %
- 30 palladium on charcoal (10 mg) under a hydrogen atmosphere at ambient temperature for 2 h. The mixture was filtered through a celite pad and rinsed with ethanol. The filtrate was

concentrated to dryness and the residue purified by column chromatography (silica gel, heptane/AcOEt) to give 60 mg (110 μ mol, 60 %) of the title compound as colorless oil.

MS: 573.3 (M+Na)⁺, 550.3 (M+H)⁺, 298.3, 256.1.

- 5 b) 2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-butoxy}-phenyl)-propionic acid (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 d), 2-ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-butoxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 2-ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-butoxy}-phenyl)-propionic acid as a mixture of two diastereomeric racemates as colorless foam.

MS: 520.3 (M-H)⁻, 476.2.

Example 119

- 15 a) (2S)-2-Ethoxy-3-(2-ethyl-4-{(1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid methyl ester

In analogy to the procedure described in example 10 c), (2S)-2-ethoxy-3-(2-ethyl-4-hydroxy-phenyl)-propionic acid methyl ester (example 23 g)) was reacted with [rac]-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethanol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield (2S)-2-ethoxy-3-(2-ethyl-4-{(1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid methyl ester as colorless oil.

MS: 544.2 (M+Na)⁺, 522.2 (M+H)⁺.

25

- b) (2S)-2-Ethoxy-3-(2-ethyl-4-{(1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 10 d), (2S)-2-ethoxy-3-(2-ethyl-4-{(1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid methyl ester was treated with LiOH to obtain (2S)-2-ethoxy-3-(2-ethyl-4-{(1R/S)-[4-

30

methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid as yellow oil.

MS: 530.3 (M+Na)⁺, 508.4 (M+H)⁺, 367.3.

5 Example 120

a) (2S)-2-Ethoxy-3-(2-methoxy-4-{(1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid methyl ester

In analogy to the procedure described in example 10 c], (2S)-2-ethoxy-3-(4-hydroxy-2-methoxy-phenyl)-propionic acid methyl ester (example 21 c]) was reacted with [rac]-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethanol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield (2S)-2-ethoxy-3-(2-methoxy-4-{(1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid methyl ester as colorless oil.

MS: 508.4 (M-15)⁺.

b) (2S)-2-Ethoxy-3-(2-methoxy-4-{(1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid

In analogy to the procedure described in example 10 d], (2S)-2-ethoxy-3-(2-methoxy-4-{(1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid methyl ester was treated with LiOH to obtain (2S)-2-ethoxy-3-(2-methoxy-4-{(1R/S)-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid as colorless oil.

MS: 530.3 (M-15)⁺.

25

Example 121

a) [rac]-Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol

To a solution of 4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carbaldehyde (500 mg, 1.8 mmol; PCT Int. Appl. (2002), WO 02/062774 A1) in tetrahydrofuran (25 ml) was slowly added a 0.5 M solution of cyclopropylmagnesium bromide in tetrahydrofuran

30

(4 ml, 2 mmol) under an argon atmosphere at -10°C . The mixture was naturally warmed to room temperature, stirred for 1.5 h, quenched with saturated NH_4Cl solution (50 ml) and extracted two times with ethyl acetate. The combined organic layers were washed with brine and water and dried over sodium sulfate. The filtrate was concentrated to dryness to
5 give 560 mg (1.79 mmol, 97 %) of the title compound as yellow solid.

b) 3-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester (mixture of two diastereomeric racemates)

10 In analogy to the procedure described in example 10 c), [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b)) was reacted with [rac]-cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol in the presence of tributylphosphine and N,N,N',N' -tetramethyl azodicarboxamide to yield 3-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-
15 phenyl)-2-ethoxy-propionic acid ethyl ester as a mixture of two diastereomeric racemates as yellow liquid.

MS: 570.3 ($\text{M}+\text{Na}$)⁺, 548.2 ($\text{M}+\text{H}$)⁺, 494.2, 416.3, 296.3.

c) 3-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 d), 3-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 3-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-
25 methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid as a mixture of two diastereomeric racemates as colorless solid.

MS: 542.2 ($\text{M}+\text{Na}$)⁺, 520.2 ($\text{M}+\text{H}$)⁺, 480.2, 392.2, 296.1.

Example 122

30 a) 3-(4-{Cyclopentyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester (mixture of two diastereomeric racemates)

- In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with [rac]-cyclopentyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield 3-(4-{cyclopentyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester as a mixture of two diastereomeric racemates as colorless liquid.

MS: 598.3 (M+Na)⁺, 576.3 (M+H)⁺, 340.3, 312.2, 247.1.

- 10 b] 3-(4-{Cyclopentyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid (mixture of two diastereomeric racemates)

- In analogy to the procedure described in example 10 d], 3-(4-{cyclopentyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 3-(4-{cyclopentyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid as a mixture of two diastereomeric racemates as colorless liquid.

MS: 546.3 (M-H)⁻, 424.4.

20 **Example 123**

a] 2-Ethoxy-3-(2-methyl-4-{[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-phenyl-methoxy}-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates)

- In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with [rac]-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-phenyl-methanol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield 2-ethoxy-3-(2-methyl-4-{[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-phenyl-methoxy}-phenyl)-propionic acid ethyl ester as a mixture of two diastereomeric racemates as colorless liquid.

MS: 606.2 (M+Na)⁺, 584.4 (M+H)⁺, 540.3, 508.3, 356.3.

b] 2-Ethoxy-3-(2-methyl-4-[[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-phenyl-methoxy]-phenyl)-propionic acid (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 d], 2-ethoxy-3-(2-methyl-4-[[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-phenyl-methoxy]-phenyl)-propionic acid ethyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 2-ethoxy-3-(2-methyl-4-[[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-phenyl-methoxy]-phenyl)-propionic acid as a mixture of two diastereomeric racemates as off-white gum.

MS: 578.2 (M+Na)⁺, 556.2 (M+H)⁺, 512.3, 493.2, 441.1, 332.1.

Example 124

a] [rac]-3-[1,3]Dioxan-2-yl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propan-1-ol

To a solution of 4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carbaldehyde (130 mg, 480 μmol; PCT Int. Appl. (2002), WO 02/062774 A1) in tetrahydrofuran (10 ml) was slowly added a 0.5 M solution of (1,3-dioxan-2-yl)magnesium bromide in tetrahydrofuran (1.3 ml, 679 μmol) under an argon atmosphere at ambient temperature. The mixture was stirred for 5 h at 30 °C, quenched with saturated NH₄Cl solution (10 ml) and extracted two times with ethyl acetate. The combined organic layers were washed with brine and water and dried over sodium sulfate. The filtrate was concentrated to dryness to give 185 mg (478 μmol, 99 %) of the title compound as yellow solid.

MS: 388.2 (M+H)⁺, 330.5, 275.4, 248.5.

b] 3-(4-{3-[1,3]Dioxan-2-yl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 c], [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 10 b]) was reacted with [rac]-3-[1,3]dioxan-2-yl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propan-1-ol in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield 3-(4-{3-[1,3]dioxan-2-yl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-

propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester as a mixture of two diastereomeric racemates as colorless oil.

MS: 644.4 (M+Na)⁺, 622.3 (M+H)⁺, 370.2, 268.4.

- 5 c) 3-(4-{3-[1,3]Dioxan-2-yl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 d), 3-(4-{3-[1,3]dioxan-2-yl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid ethyl ester (mixture of two diastereomeric racemates) was treated with
10 LiOH to obtain 3-(4-{3-[1,3]dioxan-2-yl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-2-methyl-phenyl)-2-ethoxy-propionic acid as a mixture of two diastereomeric racemates as colorless liquid.

MS: 592.4 (M-H)⁻, 548.3.

15

Example 125

a) 2-[(4-Benzyloxy-2-methyl-phenyl)-hydroxy-methyl]-butyric acid ethyl ester (mixture of two diastereomeric racemates)

To a solution of butyric acid ethyl ester (2.9 ml, 22.1 mmol) in tetrahydrofuran (125 ml)
20 was added a 2 M solution of lithium diisopropylamide in tetrahydrofuran (11.6 ml, 23.2 mmol) dropwise over 15 minutes at -78 °C under an argon atmosphere. After stirring for 10 minutes a solution of 4-benzyloxy-2-methyl-benzaldehyde (5 g, 22.1 mmol) in tetrahydrofuran (125 ml) was added dropwise over 30 minutes and stirring was continued for 20 h at -78 °C. Saturated aqueous ammonium chloride (60 ml) was added dropwise
25 and the mixture was warmed to ambient temperature. Ice water/brine 1/1 was added and the mixture was extracted two times with ethyl acetate. The combined organic layers were washed with ice water/brine 1/1 and dried over sodium sulfate. The filtrate was concentrated to dryness and the residue purified by column chromatography (silica gel, heptane/AcOEt) to give 3.4 g (9.9 mmol, 45 %) of the title compound as a mixture of two
30 diastereomeric racemates as light yellow oil.

MS: 365.3 (M+Na)⁺, 360.3 (M+NH₄)⁺, 325.4.

b) (E,Z)-3-(4-Benzoyloxy-2-methyl-phenyl)-2-ethyl-acrylic acid ethyl ester

To a solution of 2-[(4-benzoyloxy-2-methyl-phenyl)-hydroxy-methyl]-butyric acid ethyl ester (3.4 g, 9.9 mmol; mixture of two diastereomeric racemates) in dimethyl formamide (34 ml) was added concentrated sulfuric acid (1.4 ml) and the mixture was stirred for 1.5 h at 100 °C under an argon atmosphere. The reaction mixture was cooled to ambient temperature, ice water/saturated aqueous hydrogen carbonate 1/1 and ethyl acetate were added and the layers were separated. The aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with ice water/brine 1/1 and dried over sodium sulfate. The filtrate was concentrated to dryness and the residue purified by column chromatography (silica gel, heptane/AcOEt) to give 1.9 g (5.9 mmol, 59 %) of (E,Z)-3-(4-benzoyloxy-2-methyl-phenyl)-2-ethyl-acrylic acid ethyl ester as colorless oil.

MS: 342.3 (M+NH₄)⁺, 325.4 (M+H)⁺, 225.5.

c) [rac]-2-(4-Hydroxy-2-methyl-benzyl)-butyric acid ethyl ester

In analogy to the procedure described in example 118 a), (E,Z)-3-(4-benzoyloxy-2-methyl-phenyl)-2-ethyl-acrylic acid ethyl ester was hydrogenated in the presence of palladium on charcoal to obtain [rac]-2-(4-hydroxy-2-methyl-benzyl)-butyric acid ethyl ester as colorless liquid.

MS: 254.4 (M+NH₄)⁺.

d) [rac]-2-{2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-butyric acid ethyl ester

In analogy to the procedure described in example 14 b), [rac]-2-(4-hydroxy-2-methyl-benzyl)-butyric acid ethyl ester was reacted with 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole [PCT Int. Appl. (2002), WO 0292590 A1] in the presence of cesium carbonate and potassium iodide to yield [rac]-2-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-butyric acid ethyl ester as colorless oil.

e) [rac]-2-{2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-butyric acid

In analogy to the procedure described in example 10 d], [rac]-2-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-butyric acid ethyl ester was treated with 3 N NaOH to obtain [rac]-2-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-butyric acid as colorless solid.

5 MS: 462.2 (M-H)⁻, 311.2.

Example 126

a] 2-[(4-Benzyloxy-2-methyl-phenyl)-hydroxy-methyl]-heptanoic acid methyl ester (mixture of two diastereomeric racemates)

10 In analogy to the procedure described in example 125 a], methyl heptanoate was deprotonated with lithium diisopropylamide and reacted with 4-benzyloxy-2-methyl-benzaldehyde in tetrahydrofuran to obtain 2-[(4-benzyloxy-2-methyl-phenyl)-hydroxy-methyl]-heptanoic acid methyl ester as a mixture of two diastereomeric racemates as light yellow oil.

15 MS: 393.3 (M+Na)⁺, 388.3 (M+NH₄)⁺, 353.3.

b] (E,Z)-3-(4-Benzyloxy-2-methyl-phenyl)-2-pentyl-acrylic acid methyl ester

In analogy to the procedure described in example 125 b], 2-[(4-benzyloxy-2-methyl-phenyl)-hydroxy-methyl]-heptanoic acid methyl ester (mixture of two diastereomeric
20 racemates) was treated with concentrated sulfuric acid in dimethyl formamide to give (E,Z)-3-(4-benzyloxy-2-methyl-phenyl)-2-pentyl-acrylic acid methyl ester as yellow oil.

MS: 370.4 (M+NH₄)⁺.

c] [rac]-2-(4-Hydroxy-2-methyl-benzyl)-heptanoic acid methyl ester

25 In analogy to the procedure described in example 118 a], (E,Z)-3-(4-benzyloxy-2-methyl-phenyl)-2-pentyl-acrylic acid methyl ester was hydrogenated in the presence of palladium on charcoal to obtain [rac]-2-(4-hydroxy-2-methyl-benzyl)-heptanoic acid methyl ester as light brown oil.

MS: 282.4 (M+NH₄)⁺.

d) [rac]-2-{2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-heptanoic acid methyl ester

In analogy to the procedure described in example 14 b), [rac]-2-(4-hydroxy-2-methyl-benzyl)-heptanoic acid methyl ester was reacted with 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole [PCT Int. Appl. (2002), WO 0292590 A1] in the presence of cesium carbonate and potassium iodide to yield [rac]-2-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-heptanoic acid methyl ester as colorless oil.

MS: 520.4 (M+H)⁺.

10

e) [rac]-2-{2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-heptanoic acid

In analogy to the procedure described in example 10 d), [rac]-2-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-heptanoic acid methyl ester was treated with 3 N NaOH to obtain [rac]-2-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-heptanoic acid as yellow crystals.

15

MS: 504.3 (M-H)⁻.

Example 127

20 a) 2-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-heptanoic acid methyl ester (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 c), [rac]-2-(4-hydroxy-2-methyl-benzyl)-heptanoic acid methyl ester (example 126 c)) was reacted with [rac]-cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol (example 121 a)) in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield 2-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-heptanoic acid methyl ester as a mixture of two diastereomeric racemates as yellow oil.

25

MS: 560.5 (M+H)⁺, 421.5.

30

b] 2-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-heptanoic acid (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 d], 2-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-heptanoic acid
5 methyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 2-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-heptanoic acid as a mixture of two diastereomeric racemates as colorless oil.

MS: 568.3 (M+Na)⁺, 546.2 (M+H)⁺.

10

Example 128

a] 2-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-butyric acid ethyl ester (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 c], [rac]-2-(4-hydroxy-2-methyl-
15 benzyl)-butyric acid ethyl ester (example 125 c]) was reacted with [rac]-cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol (example 121 a]) in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield 2-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-butyric acid ethyl ester as a mixture of two diastereomeric racemates as light
20 yellow liquid.

MS: 532.5 (M+H)⁺, 345.4.

b] 2-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-butyric acid (mixture of two diastereomeric racemates)

25 In analogy to the procedure described in example 10 d], 2-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-butyric acid ethyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 2-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-butyric acid as a mixture of two diastereomeric racemates as colorless liquid.

30 MS: 504.4 (M+H)⁺.

Example 129

a) [rac]-2-(2-Methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-butyric acid ethyl ester

In analogy to the procedure described in example 10 c), [rac]-2-(4-hydroxy-2-methyl-benzyl)-butyric acid ethyl ester (example 125 c)) was reacted with 2-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propan-2-ol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield [rac]-2-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-butyric acid ethyl ester as colorless oil.

10 MS: 520.2 (M+H)⁺, 284.1.

b) [rac]-2-(2-Methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-butyric acid

In analogy to the procedure described in example 10 d), [rac]-2-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-butyric acid ethyl ester was treated with 3 N NaOH to obtain [rac]-2-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-butyric acid as colorless liquid.

MS: 492.3 (M+H)⁺.

20 **Example 130**

a) [rac]-2-(2-Methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-heptanoic acid methyl ester

In analogy to the procedure described in example 10 c), [rac]-2-(4-hydroxy-2-methyl-benzyl)-heptanoic acid methyl ester (example 126 c)) was reacted with 2-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propan-2-ol [PCT Int. Appl. (2002), WO 02/062774 A1] in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide to yield [rac]-2-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-heptanoic acid methyl ester as colorless oil.

MS: 548.4 (M+H)⁺.

b) [rac]-2-(2-Methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-heptanoic acid

In analogy to the procedure described in example 10 d), [rac]-2-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-heptanoic acid methyl ester was treated with LiOH to obtain [rac]-2-(2-methyl-4-{1-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-benzyl)-heptanoic acid as colorless liquid.

MS: 532.3 (M-H)⁻.

10 **Example 131**

a) 3-(4-Benzyloxy-2-methyl-phenyl)-2-butoxy-3-hydroxy-propionic acid methyl ester (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 125 a), butoxy-acetic acid methyl ester (V. Franzen, L. Fikentscher, *Ann.* 1958, 617, 1-10) was deprotonated with lithium diisopropylamide and treated with 4-benzyloxy-2-methyl-benzaldehyde in tetrahydrofuran at -78 °C for 3 h to obtain 3-(4-benzyloxy-2-methyl-phenyl)-2-butoxy-3-hydroxy-propionic acid methyl ester as a mixture of two diastereomeric racemates as yellow liquid.

MS: 395.4 (M+Na)⁺, 390.4 (M+NH₄)⁺, 336.5.

20

b) (E,Z)-3-(4-Benzyloxy-2-methyl-phenyl)-2-butoxy-acrylic acid methyl ester

In analogy to the procedure described in example 125 b), 3-(4-benzyloxy-2-methyl-phenyl)-2-butoxy-3-hydroxy-propionic acid methyl ester (mixture of two diastereomeric racemates) was treated with concentrated sulfuric acid in dimethyl formamide to give (E,Z)-3-(4-benzyloxy-2-methyl-phenyl)-2-butoxy-acrylic acid methyl ester as orange liquid.

MS: 372.5 (M+NH₄)⁺, 355.4 (M+H)⁺.

c) [rac]-2-Butoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester

30 In analogy to the procedure described in example 118 a), (E,Z)-3-(4-benzyloxy-2-methyl-phenyl)-2-butoxy-acrylic acid methyl ester was hydrogenated in the presence of palladium

on charcoal to obtain [rac]-2-butoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester as yellow liquid.

MS: 284.4 (M+NH₄)⁺.

5 d] [rac]-2-Butoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid methyl ester

In analogy to the procedure described in example 14 b], [rac]-2-butoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester was reacted with 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole [PCT Int. Appl. (2002), WO 0292590 A1] in the
10 presence of cesium carbonate and potassium iodide to yield [rac]-2-butoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid methyl ester as colorless liquid.

MS: 544.3 (M+Na)⁺, 522.2 (M+H)⁺.

15 e] [rac]-2-Butoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid

In analogy to the procedure described in example 10 d], [rac]-2-butoxy-3-{2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid methyl ester was treated with 1 N LiOH to obtain [rac]-2-butoxy-3-{2-methyl-4-[4-
20 methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-propionic acid as yellow solid.

MS: 506.2 (M-H)⁻.

Example 132

25 a] 2-Butoxy-3-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-propionic acid methyl ester (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 c], [rac]-2-butoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (example 131 c]) was reacted with [rac]-
30 cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol (example 121 a]) in the presence of tributylphosphine and N,N,N',N'-tetramethyl azodicarboxamide

to yield 2-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-butyric acid ethyl ester as a mixture of two diastereomeric racemates as yellow liquid.

MS: 584.5 (M+Na)⁺, 562.4 (M+H)⁺, 370.4.

5

b] 2-Butoxy-3-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-propionic acid (mixture of two diastereomeric racemates)

In analogy to the procedure described in example 10 d], 2-butoxy-3-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-propionic
10 acid methyl ester (mixture of two diastereomeric racemates) was treated with LiOH to obtain 2-butoxy-3-(4-{cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-phenyl)-propionic acid as a mixture of two diastereomeric racemates as yellow liquid.

MS: 546.3 (M-H)⁻.

15

Example 133

[rac]-2-Ethoxy-3-(4-{2-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-5,6,7,8-tetrahydro-naphthalen-1-yl)-propionic acid

In analogy to the procedure described in example 1 d], [rac]-2-ethoxy-3-(4-hydroxy-
20 5,6,7,8-tetrahydro-naphthalen-1-yl)-propionic acid methyl ester (example 2 c]) was reacted with 2-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethanol [PCT Int. Appl. (2001), WO 01/00603 A1] in tetrahydrofuran in the presence of triphenylphosphine and DBAD (di-tert-butyl azodicarboxylate) to yield [rac]-2-ethoxy-3-(4-{2-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-5,6,7,8-tetrahydro-naphthalen-1-yl)-
25 propionic acid methyl ester, which was further saponified in analogy to the procedure described in example 1 e], to yield [rac]-2-ethoxy-3-(4-{2-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-5,6,7,8-tetrahydro-naphthalen-1-yl)-propionic acid as colorless oil.

MS: 532.3 (M-H)⁻.

30

Example 134

[rac]-2-Ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid

In analogy to the procedure described in example 14 b], [rac]-2-ethoxy-3-(4-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-propionic acid methyl ester (example 2 c)) was reacted with 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole [PCT Int. Appl. (2001), WO 01/00603 A1] in N,N-dimethylformamide in the presence of cesium carbonate to give [rac]-2-ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid methyl ester, which was further saponified in analogy to the procedure described in example 1 e], to yield [rac]-2-ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid as colorless solid.

MS: 518.3 (M-H)⁻.

Example 135

[rac]-2-Ethoxy-3-{4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid

In analogy to the procedure described in 14 b], [rac]-2-ethoxy-3-(4-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-propionic acid methyl ester (example 2 c)) was reacted with 5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole (prepared from [2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol [PCT Int. Appl. (2002), WO 02/ 62774 A1] and methanesulfonyl chloride, triethylamine in dichloromethane) in N,N-dimethylformamide in the presence of cesium carbonate to give [rac]-2-ethoxy-3-{4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid methyl ester, which was further saponified in analogy to the procedure described in example 1 e], to yield [rac]-2-ethoxy-3-{4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid as light yellow solid.

MS: 504.2 (M-H)⁻.

Example 136

a) 4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalene-1-carbaldehyde

0.50 g of 4-hydroxy-naphthalene-1-carbaldehyde (2.90 mmol) was dissolved in 12 ml
5 acetone and treated at 0° C with 0.847 g of 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole (1.0 eq.) and 1.04 g of Cs₂CO₃ (1.1 eq.) and then kept for 4 h at ambient temperature and for 1 h at 35° C under stirring, when TLC indicated the disappearance of starting material. The bulk of the solvent was then removed i. V., the residue poured onto crashed ice/AcOEt, the organic layer washed with water, dried over sodium sulfate, and
10 evaporated to dryness. Flash chromatography (SiO₂, hexane/AcOEt=7/3) yielded 0.882 g of the title compound as colorless crystals.

MS: 427.3 (M)⁺.

b) 3-Hydroxy-2-methoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalen-1-yl}-propionic acid ethyl ester

LDA-solution in THF was prepared according to standard procedure from 0.391 g of diisopropylamine (3.86 mmol) and 2.19 ml of 1.6 M nBuLi (hexane) in 15 ml of abs. THF at -10° C. After cooling to -75° C, 0.415 g of ethyl methoxyacetate (3.51 mmol), dissolved in 1 ml of THF, was added and stirring continued for 30 min. to complete enolate
20 formation. 0.500 g of the above prepared 4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalene-1-carbaldehyde (1.17 mmol), dissolved in 8 ml of THF, was then added at -75° C and the mixture kept for another 30 min. at this temperature. Pouring onto crashed ice/NH₄Cl, twofold extraction with AcOEt, washing with water, drying over sodium sulfate, and evaporation of the solvents, followed by flash
25 chromatography (SiO₂, hexane/AcOEt=55/45) delivered 0.64 g of the title compound (syn/anti-isomers) as colorless oil.

MS: 546.3 (M+H)⁺.

c) 2-Methoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalen-1-yl}-propionic acid ethyl ester

0.64 g of the above 3-hydroxy-2-methoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalen-1-yl}-propionic acid ethyl ester (1.18 mmol) was

- dissolved in 5 ml of trifluoroacetic acid, treated at 0° C with 1.87 ml of triethylsilane (10 eq.) and then kept for 3 h at 0° C under vigorous stirring, when TLC indicated the disappearance of starting material. The reaction mixture was then poured onto crashed ice/AcOEt/Na₂CO₃, the organic layer washed with water (pH of aq. phase~8), dried over sodium sulfate, and evaporated to dryness. Flash chromatography (SiO₂, hexane/AcOEt=8/2) yielded 0.61 g of the title compound as colorless oil.

MS: 530.1 (M+H)⁺.

- 10 d) [rac]-2-Methoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalen-1-yl}-propionic acid

- 0.61 g of the above prepared 2-methoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalen-1-yl}-propionic acid ethyl ester (1.15 mmol) was dissolved in 5 ml of THF/EtOH=1/1, treated with 1.15 ml of 2N NaOH (2 eq.), and kept at ambient temperature for 1 h. The reaction mixture was then poured onto crashed ice/AcOEt/HCl dil., the organic layer washed with water, dried over sodium sulfate, and evaporated to dryness. Crystallization from hexane/AcOEt afforded finally 0.50 g of the title compound as white crystals of mp. 190-92° C.

MS: 500.2 (M-H)⁻.

20 **Example 137**

[rac]-2-Ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-naphthalen-1-yl}-propionic acid

was prepared in analogy to example 136, but using in step b) ethyl ethoxyacetate instead of ethyl methoxyacetate, as white crystals of mp. 186-88° C.

- 25 MS: 514.3 (M-H)⁻.

Example 138

[rac]-2-Methoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzo[b]thiophen-7-yl}-propionic acid

- 159 -

was prepared in analogy to example 136, but using in step a) 4-hydroxy-benzo[b]thiophene-7-carbaldehyde instead of 4-hydroxy-naphthalene-1-carbaldehyde, as white solid of mp. 140-42° dec.

MS: 506.2 (M-H)⁺.

5

Example 139

[rac]-2-Ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzo[b]thiophen-7-yl}-propionic acid

was prepared in analogy to example 137, but using in step a) 4-hydroxy-benzo[b]thiophene-7-carbaldehyde instead of 4-hydroxy-naphthalene-1-carbaldehyde, as white solid of mp. 178-79° C.

MS: 520.2 (M-H)⁺.

Example 140

15 [rac]-2-Methoxy-3-(4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-benzo[b]thiophen-7-yl)-propionic acid (1:1 diast. mixture)

was prepared in analogy to example 138, but using in step a) 5-(1-chloro-2-methyl-propyl)-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole (prepared from [rac]-2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propan-1-ol [PCT Int. Appl. 20 (2002), WO 02/062774 A1 in analogy to the procedure described in example 104 a]) instead of 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole, as colorless oil.

MS: 548.2 (M-H)⁺.

- 160 -

Example A

Tablets containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per tablet</u>
Compound of formula (I)	10.0 - 100.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

5

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per capsule</u>
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

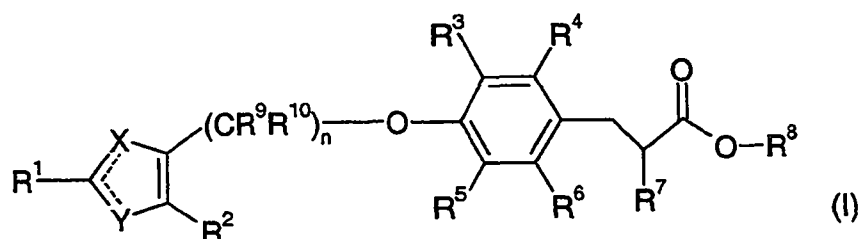
Example C

10 Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Sodium carbonate	to obtain a final pH of 7
Water for injection solutions	ad 1.0 ml

Claims

1. Compounds of formula (I)



wherein

5 X is N and Y is S; or
X is S and Y is N;

R¹ is aryl or heteroaryl;

R² is hydrogen, lower-alkyl or fluoro-lower-alkyl;

10 R³, R⁴, R⁵ and R⁶ independently from each other are hydrogen, hydroxy, lower-alkenyl, halogen, lower-alkyl, fluoro-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, lower-alkoxy, fluoro-lower-alkoxy, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkoxy, wherein at least one of R³, R⁴, R⁵ and R⁶ is not hydrogen,

or

15 R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S-, -S-CH=CH-, -CH=CH-O-, -O-CH=CH-, -CH=CH-CH=CH-, -(CH₂)₃₋₅-, -O-(CH₂)₂₋₃- or -(CH₂)₂₋₃-O-, and R⁵ and R⁶ are as defined above;

R⁷ is lower-alkyl, lower-alkoxy, lower-alkenyloxy, aryloxy or aryl-lower-alkoxy;

R⁸ is hydrogen or lower-alkyl;

20 R⁹ and R¹⁰ independently from each other are hydrogen, lower-alkyl, lower-alkenyl, cycloalkyl, phenyl or [1,3]dioxan-2-ethyl;

n is 1, 2 or 3;

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

25 2. Compounds according to claim 1, wherein R⁷ is lower-alkoxy, lower-alkenyloxy, aryloxy or aryl-lower-alkoxy, R⁹ is hydrogen and R¹⁰ is hydrogen.

3. Compounds according to claim 1 or 2, wherein X is N and Y is S.
4. Compounds according to any of claims 1 to 3, wherein R¹ aryl.
5. Compounds according to any one of claims 1 to 4, wherein R¹ is phenyl optionally substituted with 1 to 3 substituents independently selected from the group
5 consisting of lower-alkyl, lower-alkoxy, halogen and CF₃.
6. Compounds according to any one of claims 1 to 5, wherein R¹ is phenyl, 4-isopropyl-phenyl, 4-chloro-phenyl, 4-trifluoromethyl-phenyl or 3,5-dimethoxy-phenyl.
7. Compounds according to any one of claims 1 to 6, wherein R² is lower-alkyl or hydrogen.
- 10 8. Compounds according to any one of claims 1 to 7, wherein R² is methyl or hydrogen.
9. Compounds according to any one of claims 1 to 8, wherein R³, R⁴, R⁵ and R⁶ independently from each other are hydrogen, halogen, lower-alkyl or lower-alkoxy, wherein one or two of R³, R⁴, R⁵ and R⁶ are not hydrogen, or
15 R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S-, -S-CH=CH-, -(CH₂)₃₋₅-, -CH=CH-CH=CH-, -O-CH=CH- or -O-(CH₂)₂₋₃-, and R⁵ and R⁶ are hydrogen.
10. Compounds according to any one of claims 1 to 9, wherein one or two of R³, R⁴, R⁵ and R⁶ independently from each other are halogen, lower-alkyl or lower-alkoxy, and
20 the others are hydrogen.
11. Compounds according to any one of claims 1 to 10, wherein R⁴ is methyl and R³, R⁵ and R⁶ are hydrogen.
12. Compounds according to any one of claims 1 to 9, wherein R⁵ and R⁶ are hydrogen; and R³ and R⁴ are bonded to each other to form a ring together with the carbon
25 atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S-, -S-CH=CH-, -(CH₂)₃₋₅-, -CH=CH-CH=CH-, -O-CH=CH-, or -O-(CH₂)₂₋₃-.
13. Compounds according to any one of claims 1 to 9, wherein R⁵ and R⁶ are hydrogen; and R³ and R⁴ are bonded to each other to form a ring together with the carbon
30 atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S-, -(CH₂)₃₋₅-, or -CH=CH-CH=CH-.

14. Compounds according to any one of claims 1 to 13, wherein R⁷ is lower-alkyl or lower-alkoxy.
15. Compounds according to any one of claims 1 to 14, wherein R⁷ is ethyl, ethoxy or isopropoxy.
- 5 16. Compounds according to any one of claims 1 to 15, wherein R⁸ is hydrogen.
17. Compounds according to any one of claims 1 to 16, wherein n is 1.
18. Compounds according to any one of claims 1 to 16, wherein n is 2.
19. Compounds according to any one of claims 1 to 16, wherein n is 3.
20. Compounds according to any one of claims 1 to 19, wherein R⁹ and R¹⁰
10 independently from each other are hydrogen, lower-alkyl or cycloalkyl.
21. Compounds according to any one of claims 1 to 20, wherein R⁹ and R¹⁰ are hydrogen.
22. Compounds according to any one of claims 1 to 21 selected from the group consisting of
- 15 [rac]-2-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid,
[rac]-2-Ethoxy-3-{4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-3-methyl-phenyl}-propionic acid,
[rac]-2-Ethoxy-3-{3-fluoro-4-[2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid,
20 [rac]-2-Ethoxy-3-{2-methyl-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid,
[rac]-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,
25 (2S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,
(2S)-3-{2-Chloro-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethoxy]-phenyl}-2-ethoxy-propionic acid, and
[rac]-2-Ethoxy-3-(3-fluoro-4-{2-[2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-ethoxy}-phenyl)-propionic acid,
30 and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

23. Compounds according to any one of claims 1 to 21 selected from the group consisting of

[rac]-2-Ethoxy-3-(3-fluoro-4-{3-[2-(4-isopropyl-phenyl)-thiazol-4-yl]-propoxy}-phenyl)-propionic acid;

5 [rac]-2-Ethoxy-3-{5-ethoxy-2-fluoro-4-[2-(4-isopropyl-phenyl)-thiazol-4-ylmethoxy]-phenyl}-propionic acid;

[rac]-3-(4-[2-[2-(3,5-Dimethoxy-phenyl)-5-methyl-thiazol-4-yl]-ethoxy]-benzo[b]thiophen-7-yl)-2-isopropoxy-propionic acid;

(S)-3-{4-[2-(4-Chloro-phenyl)-thiazol-4-ylmethoxy]-2-fluoro-phenyl}-2-ethoxy-
10 propionic acid;

2-Ethoxy-3-(2-methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-ethoxy}-phenyl)-propionic acid;

2-Ethoxy-3-(2-methyl-4-{2-methyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-propoxy}-phenyl)-propionic acid;

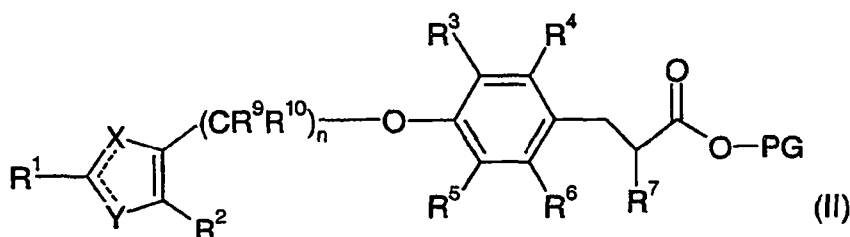
15 2-(4-{Cyclopropyl-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxy}-2-methyl-benzyl)-butyric acid;

[rac]-2-Ethoxy-3-{4-[2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl}-propionic acid; and

[rac]-2-Ethoxy-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-
20 naphthalen-1-yl}-propionic acid;

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

24. A process for the manufacture of compounds according to any one of claims 1 to 23, which process comprises removing a protecting group in a compound of formula (II)



25

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^9 , R^{10} , X, Y and n are as defined in any one of claims 1 to 23 and PG is a protecting group.

25. Compounds according to any of claims 1 to 23 when manufactured by a process according to claim 24.

26. Pharmaceutical compositions comprising a compound according to any of claims 1 to 23 and a pharmaceutically acceptable carrier and/or adjuvant.

27. Compound according to any of claims 1 to 23 for use as therapeutic active substances.

28. Compounds according to any of claims 1 to 23 for use as therapeutic active substances for the treatment and/or prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists.

29. A method for the prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists, which method comprises administering a compound according to any of claims 1 to 23 to a human being or animal.

30. The use of compounds according to any of claims 1 to 23 for the treatment and/or prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists.

31. The use of compounds according to any of claims 1 to 23 for the preparation of medicaments for the treatment and/or prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists.

32. The use and/or the method according to any one of claims 27 to 31 wherein the disease is diabetes, non-insulin dependent diabetes mellitus, elevated blood pressure, increased lipid and cholesterol levels, atherosclerotic diseases, metabolic syndrome, endothelial dysfunction, procoagulant state, dyslipidemia, polycystic ovary syndrome, inflammatory diseases or proliferative diseases.

33. A substance or composition for use in a method for treatment and/or prevention of diseases which are modulated by PPAR α and/or PPAR γ agonists, said substance or composition comprising a compound according to any of claims 1 to 23, and said method comprising administering said substance or composition to a human being or animal.

34. A substance or composition for use in a method of treatment or prevention according to claim 33 wherein the disease is diabetes, non-insulin dependent diabetes mellitus, elevated blood pressure, increased lipid and cholesterol

levels, atherosclerotic diseases, metabolic syndrome, endothelial dysfunction, procoagulant state, dyslipidemia, polycystic ovary syndrome, inflammatory diseases or proliferative diseases.

35. A compound according to any one of claims 1 to 23, 25, 27 or 28, substantially as herein described and illustrated.

36. A process according to claim 24, substantially as herein described and illustrated.

37. A composition according to claim 26, substantially as herein described and illustrated.

38. A method according to claim 29 or claim 32, substantially as herein described and illustrated.

39. Use according to any one of claims 30 to 32, substantially as herein described and illustrated.

40. A substance or composition for use in a method of treatment or prevention according to claim 33 or claim 34, substantially as herein described and illustrated.

41. A new compound, a new process for manufacturing a compound, a new composition, a new non-therapeutic method of treatment, a new use of a compound according to any one of claims 1 to 23, or a substance or composition for a new use in a method of treatment, substantially as herein described.

42. The novel compounds, processes and methods as well as the use of such compounds substantially as described herein before.