



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07F 9/38, C07H 19/06, 19/16, C07D 473/32	A1	(11) International Publication Number: WO 99/51613 (43) International Publication Date: 14 October 1999 (14.10.99)															
(21) International Application Number: PCT/SE99/00528 (22) International Filing Date: 30 March 1999 (30.03.99) (30) Priority Data: <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">9801216-4</td> <td style="width: 30%;">3 April 1998 (03.04.98)</td> <td style="width: 40%;">SE</td> </tr> <tr> <td>98/7267</td> <td>13 August 1998 (13.08.98)</td> <td>ZA</td> </tr> <tr> <td>PCT/SE98/01467</td> <td>14 August 1998 (14.08.98)</td> <td>SE</td> </tr> <tr> <td>09/249,317</td> <td>12 February 1999 (12.02.99)</td> <td>US</td> </tr> <tr> <td>PCT/SE99/00194</td> <td>15 February 1999 (15.02.99)</td> <td>SE</td> </tr> </table> (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/249,317 (CIP) Filed on 12 February 1999 (12.02.99)	9801216-4	3 April 1998 (03.04.98)	SE	98/7267	13 August 1998 (13.08.98)	ZA	PCT/SE98/01467	14 August 1998 (14.08.98)	SE	09/249,317	12 February 1999 (12.02.99)	US	PCT/SE99/00194	15 February 1999 (15.02.99)	SE	Christian [FI/SE]; Bäckgårdsvägen 16, 2 tr, S-143 42 Vårby (SE). WALLBERG, Hans [SE/SE]; Mangårdsvägen 10, S-141 51 Huddinge (SE). SALVADOR, Lourdes [PH/SE]; Saltängsgatan 1 B, S-602 22 Norrköping (SE). LINDSTRÖM, Stefan [SE/SE]; Marmorvägen 8 B, S-752 44 Uppsala (SE). (74) Agent: MORRISON, Iain; Medivir AB, Patentavdelningen, Lunastigen 7, S-141 44 Huddinge (SE). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
9801216-4	3 April 1998 (03.04.98)	SE															
98/7267	13 August 1998 (13.08.98)	ZA															
PCT/SE98/01467	14 August 1998 (14.08.98)	SE															
09/249,317	12 February 1999 (12.02.99)	US															
PCT/SE99/00194	15 February 1999 (15.02.99)	SE															
(71) Applicant (for all designated States except US): MEDIVIR AB [SE/SE]; Lunastigen 7, S-141 44 Huddinge (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): ZHOU, Xiao-Xiong [SE/SE]; Kallkärrsvägen 12, S-141 41 Huddinge (SE). JOHANSSON, Nils, Gunnar [SE/SE]; Bäverstigen 19, S-150 23 Enhörna (SE). WÄHLING, Horst [DE/SE]; Tempelriddarevägen 3, S-127 61 Skärholmen (SE). SUND,	Published With international search report.																
(54) Title: PRODRUGS OF PHOSPHOROUS-CONTAINING PHARMACEUTICALS																	
(57) Abstract Pharmaceutical compounds with the formula: Drug-P(=O)-O-Linker(-R ₂ ') _k -R ₂ where Drug-P(=O)-O- is the residue of a drug comprising a phosphonate, phosphinate or phosphoryl function, such as alendronate or foscarnet, R ₂ and R ₂ ' (if present) are independently the acyl residue of an aliphatic amino acid; Linker is an at least difunctional moiety comprising a first function ester-bonded to the phosphonate, phosphinate or phosphoryl function spaced from a second function ester-bonded to R ₂ ; and k is 1 or zero; have enhanced bioavailability or other pharmacokinetic performance relative to the parent drug.																	

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PRODRUGS OF PHOSPHOROUS-CONTAINING PHARMACEUTICALS

Technical Field

This invention relates to the field of phosphorous-containing pharmaceuticals,
5 including phosphonates, phosphinates and phosphates and in particular to prodrugs
of such pharmaceuticals. The invention provides novel pharmaceutical compounds
and compositions, methods for their preparation and pharmaceutical methods
employing them.

10 Background Art

Many phosphorous-containing pharmaceuticals have not reached their full clinical
potential due to difficulties in administering them, particularly via the oral route. Bis-
phosphonate bone resorption agents such as alendronate, for example, have oral
bioavailabilities of just a few percent and adsorption is diminished by food fruit juice
15 coffee, dairy products etc. This poor bioavailability is exacerbated by the caustic
nature of the drug which leads to irritation of the gastric walls, resulting in an
administration regime calling for a fasted stomach and the patient standing for half an
hour after ingestion to ensure transport of the drug past the gastric region.

20 A significant amount of work has been done to attempt to solve the administration
difficulties by optimising the formulation of phosphorous-containing drugs. Merck
for example describe various formulations of the bis-phosphonate alendronate, such
as a pH buffered formulation in WO98 14196, an effervescent formulation in WO97
44017, the monohydrate and disodium in WO96 39410, the anhydrate in WO96
25 39149, a liquid formulation with complexing agent in WO95 33755 and calcium salts
in EP 449 405. To our knowledge, however, none of these conventional formulation
approaches has produced a clinically succesful administration form.

Merck and others have also explored prodrugs of bis-phosphonate bone resorption
30 agents in an attempt to improve the clinical utility of these drugs. For example,
Leiras OY's US 5,376,649 describes esters of halogenated bis-phosphonates of the
clodronate type, wherein the prodrug moiety comprises an alkyl, alkenyl, alkynyl,
aryl, aralkyl and silyl. No improvements in bioavailability are reported. Leo's US

4,732,998, US 4,870,063 and WO86 00902 describe prodrugs of certain non-hydroxylated bis-phosphonates. In particular the pivaloyloxymethyl and acetoxymethyl tetraesters are prepared (although no improvements in bioavailability are reported) and certain other esters postulated, such as the C₃-C₆ alkanoyloxymethyl, C₄-C₇ 1-(alkanoyloxy)ethyl, C₅-C₈ 1-methyl-1-(alkanoyloxy)ethyl, C₄-C₇ 1-(alkoxycarbonyloxy)ethyl, C₃-C₆ alkoxycarbonyloxymethyl, C₄-C₇ 1-alkoxycarbonyloxyethyl, C₅-C₈ 1-methyl-1-(alkoxycarbonyloxy)ethyl, 3-phthalidyl, 4-crotonolactonyl, γ-butyrolacton-4-yl, (2-oxo-1,3-dioxolen-4-yl)methyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl, dialkylaminoalkyl, acetonyl and methoxymethyl.

Merck's US 5,227,506 describes acyloxymethyl esters of a number of bis-phosphonates, notable alendronate, wherein the acyl component is C₁-C₁₂ alkanoyl. As with the Leo patents above the preferred prodrug is pivaloyloxymethyl, although no bioavailability data is provided.

Other phosphorous-containing drugs where attempts to improve bioavailability shortcomings have employed prodrugs include the antiviral agent foscarnet (phosphonoformate). Astra's WO98 16537 and WO9825938 describe monosaccharide and cyclic esters of foscarnet. Boehringer's WO9722368, Hostetler's US 5,696,277 and WO94/13682, UC's WO96 15132 (inter alia) describe lipid or glycerol esters of foscarnet. Iyer et al, Tett. Letters 30 No 51, 7141-7144 (1989) describe acyloxyalkyl esters, wherein the acyl component is C₁-C₄ alkanoyl. Glazier's WO91/19721 describes acyloxybenzyloxy esters. Walker et al, Int J Pharmaceutics 104 (1994) 157-167 describes foscarnet-tyrosine conjugates wherein the hydroxy group on the amino acid side chain is esterified to the phosphonate. These compounds are not however orally administered prodrugs, but rather are designed to penetrate the blood brain barrier following iv administration.

A still further group of pharmaceuticals where prodrugs have been proposed to attempt to overcome bioavailability shortcomings are the phosphonate nucleoside analogues, such as those disclosed in Gilead's WO98 04569 and an extensive series of patents in the name Rega Stichting/Institute of Organic Chemistry & Biochemistry

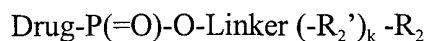
of the Academy of Sciences of the Czech Republic including EP 481214. However,
to our knowledge, the only such phosphonates to show clinical practicality are the
now marketed *bis*-POM and *bis*-POC adefovir (bis-pivoxil and bis-
isopropylloxycarbonyloxymethyl esters, respectively). WO 95/01363 also shows a
5 form of phosphonate nucleoside analogue.

Monophosphate esters of monophosphorylated nucleoside analogues are disclosed in
EP 763049 (glyceryl diethers), WO 95 32984 (lipid esters), US 5484911 (ether
lipids) WO 98 51692 (substituted benzyl esters) WO 96 33201 (alkylthioacyl esters)
10 Glazier's WO 91/19721 (above) and US 5 627 165 and Texas Uni's WO 90/08155
purport to provide prodrugs of diverse phosphorous-containing pharmaceuticals.
Bodor's WO 92/00988 employs a phosphonate prodrug of non-phosphorous
pharmaceuticals to target compounds to the brain.

15

Brief Description of the Invention

A first aspect of the invention provides pharmaceutical compound with the formula:



20

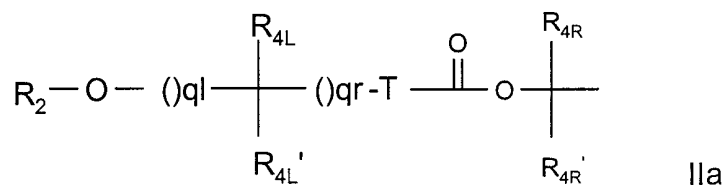
where Drug-P(=O)-O- is the residue of a drug comprising a phosphonate,
phosphinate or phosphoryl function,
R₂ and R₂' (if present) are independently the acyl residue of an aliphatic amino acid;
Linker is an at least difunctional moiety comprising a first function ester-bonded to
25 the phosphonate, phosphinate or phosphoryl function spaced from a second function
ester-bonded to R₂; and
k is 1 or zero.

The enzymatic and/or chemical cleavage of the compounds of the present invention
30 occurs in such a manner that the parent drug is released and the moiety or moieties
split off remain non-toxic or are metabolized so that non-toxic or acceptable amounts
of metabolic products are produced. The present compounds thus modify the in vivo
availability of the parent compound compared to what would be the case if the parent

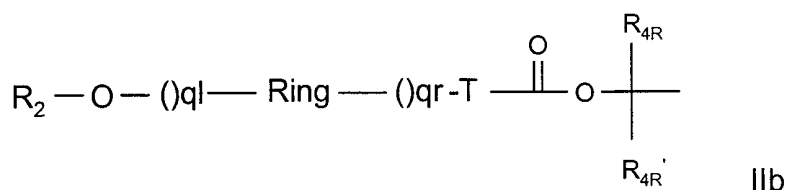
compound was to be administered itself. For instance the prodrugs of the invention may give higher bioavailabilities, varied bioavailability kinetics or bioavailabilities with a decreased interpersonal spread.

- 5 Representative phosphorous-containing drugs amenable to the prodrugs of the present invention include phosfestrol, (E)-(α,β-diethyl-4,4'-stilbenylen)bis(dihydrogenphosphate), nucleoside analogue phosphonates, nucleotide analogue mono-, di or triphosphates, phosphonoformic acid, phosphonoacetic acid, *bis* phosphonate bone metabolism agents, fosinoprilate, β-phosphonocarboxylic acid
- 10 farnesyl protein transferase inhibitors, α-phosphonosulfonate squalene synthase inhibitors, phosphonomethylamine neutral endopeptidase (24.11) inhibitors.

Favoured -linker $(-R_2')_k - R_2$ structures include those of the formulae:



or



15

where

R_2 is the acyl residue of an aliphatic amino acid,

R_{4L} and R_{4L}' are independently H, hydroxymethyl, C_{1-3} alkyl, C_3 - C_6 cycloalkyl, C_1 -

20 C_3 alkyl- C_1 - C_6 cycloalkyl, phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl,

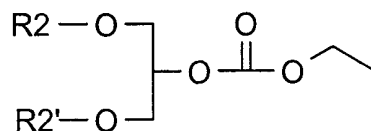
ql is 0-3, qr is 0-3,

T is a bond, $-NR_4-$ or $-O-$

R_4 is H or C_{1-3} alkyl;

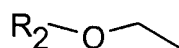
ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle.

Additional -linker $(-R_2')_k - R_2$ structures and intermediates for their application, such
 5 as those of the formula:



where R_2 and R_2' are as described above are disclosed and claimed in our co-pending
 application PCT/SE99/00194, the contents of which are hereby incorporated by
 10 reference.

Further linker- R_2 structures include:



such as alanyloxymethyl-, valyloxymethyl-, leucyloxymethyl- t-leucyloxymethyl-
 15 or isoleucyloxymethyl, especially valyloxymethyl-.

Where the Drug comprises a phosphonate or phosphoryl function, or a plurality of
 such functions, the compound of the invention may comprise a plurality of
 -linker $(-R_2')_k - R_2$ structures, preferably identical to each other for ease of synthesis.
 20

Preferred values for R_{4R} and R_{4R}' are hydrogen for ease of synthesis, although
 compounds wherein one of R_{4R} and R_{4R}' is hydrogen and the other methyl have the
 advantage of releasing the innocuous biproduct ethanol upon degradation.
 25 Representative values for R_{4L} and R_{4L}' include methyl, hydrogen; hydroxymethyl,
 methyl; or ethyl, ethyl, respectively. A particularly preferred value is methyl, methyl.

Favoured values for q_l and q_r , respectively, include

1,0;

30

2,0;

3,0; or

4,0;

particularly 1,0 when the -linker $(-R_2')_k - R_2$ structure has the formula IIa.

5 Alternative convenient values for ql and qr, respectively, include

1,1;

2,1;

3,1;

4,1; or

10 2,2.

Where the -linker $(-R_2')_k - R_2$ structure has the formula IIb, that is includes a -ring-moiety an alternative convenient configuration has ql and qr both 0.

The -ring- moiety in the above depicted -linker $(-R_2')_k - R_2$ structure may comprise
 15 furyl, thienyl, pyranal, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, and the like or bicyclic rings especially of the above fused to a phenyl ring such as
 20 indolyl, quinolyl, isoquinolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzothienyl etc. The carbo or heterocyclic ring may be bonded via a carbon or via a hetero atom, for instance a nitrogen atom, such as N-piperidyl, N-morpholinyl etc. The -ring- moiety is conveniently phenyl, furyl, pyridyl, cyclobutyl, cyclopentyl or cyclohexyl.

25

The -ring- moiety can be optionally substituted with one to three substituents such as halo, amino, mercapto, oxo, nitro, NHC_1-C_6 alkyl, $N(C_1-C_6 \text{ alkyl})_2$, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxy, thio C_1-C_6 alkyl, thio C_1-C_6 alkoxy, hydroxy, hydroxy C_1-C_6 alkyl, halo C_1-C_6 alkyl, amino C_1-C_6 alkyl, C_1-C_6 alkyl,
 30 cyano, carboxyl, carbalkoxy, carboxamide, carbamoyl, sulfonylamide, benzyloxy,

morpholyl-C₁-C₆ alkyloxy, a monocyclic carbo- or heterocycle, as defined above, a carbo- or heterocyclic group spaced by alkyl, such as C₁₋₃ alkylaryl, etc. A favoured optional substituent comprises an additional group R₂-()_{q1}.

5

The aliphatic amino acid R₂ is derived from D- or L- glycine, alanine, valine, leucine, tert-leucine and isoleucine. Preferably the or each R₂ is derived from L-valine to ensure nature identical breakdown products.

10 The currently preferred value for T is a bond.

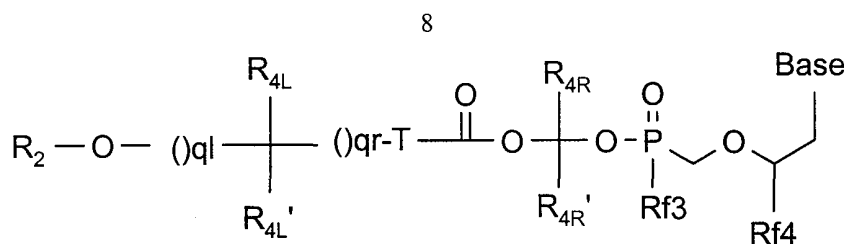
Representative phosphorous-containing drugs include phosfestrol, (E)-(α,β-diethyl-4,4'-stilbenylen)bis(dihydrogenphosphate) and cytostatic metabolites such as phosphorylated nucleoside analogues such as FLG, cytarabin or gemcitabin.

15

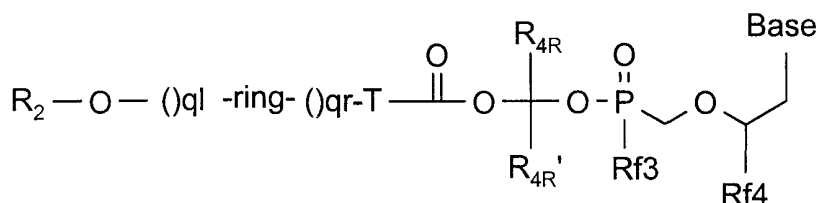
Representative drugs comprising a phosphonate function include antiviral nucleoside or nucleotide analogues such as PME₃, HPMP, PMPA and the like or phosphates such as the monophosphates, diphosphate or triphosphates of those nucleoside analogues which require phosphorylation for activity, such as gemcitabine, ACV, AZT, ddI, ddC, PCV, GCV, H2G, BV₂DU, FMAU, 3TC, FTC etc. Certain mixed amino acid/fatty acid acyloxyalkylphosphonates are proposed in our copending application PCT SE97 001903 and it should be thus appreciated that the prodrugs of the present invention are fatty acyl-free and/or apply the novel linkers defined herein in the phosphonate nucleotide field.

25

Taking the phosphonate antivirals adefovir and cidofovir as examples, prodrugs of the invention can be applied as shown in Formula PF2:



or



where

R_2 is the acyl residue of an aliphatic amino acid,

5 R_{4L} and R_{4L}' are independently H, C_{1-3} alkyl, hydroxymethyl, C_{3-6} cycloalkyl, C_1 - $_3$ alkyl- C_1C_6 cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl

ql is 0-3, qr is 0-3,

T is a bond, $-NR_4-$ or $-O-$

10 R_4 is H or C_{1-3} alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero- or carbocycle;

base is a natural or unnatural nucleotide base, especially guanine, adenine or cytosine,

Rf3 is H or a further structure of the formula IIa or IIb and Rf4 is H or CH_2OH .

15

Currently favoured values in formula PF2 include: R_{3R} and R_{3R}' are preferably H and/or R_{3L} and R_{3L}' are preferably ethyl or especially methyl. T is preferably $-O-$ or more preferably a bond. Preferably qr is 1 or more preferably 0 and ql is 0 or more preferably 1.

20

Thus a preferred group of phosphonate antivirals within the scope of the invention include:

- 9-[2-phosphonomethoxy]ethyl]adenine, mono(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
- 9-[2-phosphonomethoxy]ethyl]adenine, mono(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
- 5 9-[2-phosphonomethoxy]ethyl]adenine, mono(2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester,
- 9-[2-phosphonomethoxy]ethyl]adenine, mono(2-(L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester,
- 9-[2-phosphonomethoxy]ethyl]adenine, mono((1,3-di-valyloxy)propyl-2-oxycarbonyloxy methyl) ester,
- 10 9-[2-phosphonomethoxy]ethyl]adenine, mono(2-L-valyloxy)-DL-propionyloxymethyl) ester,
- 9-[2-phosphonomethoxy]ethyl]adenine, mono-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester,
- 15 9-[2-phosphonomethoxy]ethyl]adenine, mono-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester,
- 9-[2-phosphonomethoxy]ethyl]adenine, mono [4-(L-valyloxy)-butanoyloxymethyl] ester,
- 9-[2-phosphonomethoxy]ethyl]adenine, mono-(4-(L-valyloxy) benzoyloxymethyl) ester,
- 20 ester,
- 9-[2-phosphonomethoxy]ethyl]adenine, mono-(3-(3,4-di-(L-valyloxy) phenyl) propionyloxymethyl) ester,
- 9-[2-phosphonomethoxy]ethyl]adenine, mono-(2-methyl-1-(L-valyloxy)-2-propoxycarbonyloxymethyl) ester,
- 25 9-[2-phosphonomethoxy]ethyl]adenine, mono-(4-N-valyloxy)cyclohexanoyloxymethyl) ester
- 9-[2-phosphonomethoxy]ethyl]adenine, mono-(1-valyloxy-2-methylpropane-2-aminocarbonyloxymethyl) ester
- 9-[2-phosphonomethoxy]ethyl]adenine, mono-(1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester
- 30 9-[2-phosphonomethoxy]ethyl]adenine, mono-((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl) ester

9-[2-phosphonomethoxy)ethyl]adenine, mono-(2-hydroxymethyl-2-methylpropionyloxymethyl) ester

9-[2-phosphonomethoxy)ethyl]adenine, mono-(2-(L-valyloxymethyl)-2-ethyl butyroyloxymethyl) ester

5 9-[2-phosphonomethoxy)ethyl]adenine, mono-(3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester

9-[2-phosphonomethoxy)ethyl]adenine, mono-(3-(L-valyloxy)-2-methyl, 2-hydroxymethylpropionyloxymethyl) ester

the corresponding *bis* esters and pharmaceutically acceptable salts thereof. A further
10 preferred group comprises the corresponding derivatives of PMPA and HPMPC.

A particularly preferred group comprises.

9-[2-phosphonomethoxy)ethyl]adenine di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester

15 9-[2-phosphonomethoxy)ethyl]adenine mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester

9-[2-phosphonomethoxy)ethyl]adenine di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,

9-[2-phosphonomethoxy)ethyl]adenine mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
20

9-[2-phosphonomethoxy)ethyl]adenine di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,

9-[2-phosphonomethoxy)ethyl]adenine mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester and especially

25 9-[2-phosphonomethoxy)ethyl]adenine di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester and

9-[2-phosphonomethoxy)ethyl]adenine mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester;

and the corresponding derivatives of PMPA and HPMPC.

30

A further convenient group comprises

- 9-[2-phosphonomethoxy)ethyl]adenine mono -(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
- 9-[2-phosphonomethoxy)ethyl]adenine mono -(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
- 5 9-[2-phosphonomethoxy)ethyl]adenine mono -(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
- 9-[2-phosphonomethoxy)ethyl]adenine mono -(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
- 9-[2-phosphonomethoxy)ethyl]adenine mono (2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
- 10 the corresponding bis esters and the corresponding derivatives of PMPA and HPMPC.

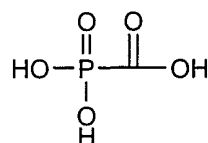
A further group of useful compounds comprises:

- 15 9-[2-phosphonomethoxy)ethyl]adenine mono-L-valyloxymethyl ester,
- 9-[2-phosphonomethoxy)ethyl]adenine di-L-valyloxymethyl ester,
- 9-[2-phosphonomethoxy)ethyl]adenine mono-L-leucyloxymethyl ester,
- 9-[2-phosphonomethoxy)ethyl]adenine di-L-leucyloxymethyl ester,
- 9-[2-phosphonomethoxy)ethyl]adenine mono-L-isoleucyloxymethyl ester,
- 20 9-[2-phosphonomethoxy)ethyl]adenine di-L-isoleucyloxymethyl ester,
- 9-[2-phosphonomethoxy)ethyl]adenine mono-L-t-leucyloxymethyl ester,
- 9-[2-phosphonomethoxy)ethyl]adenine di-L-t-leucyloxymethyl ester,
- 9-[2-phosphonomethoxy)ethyl]adenine mono-L-alanyloxymethyl ester,
- 9-[2-phosphonomethoxy)ethyl]adenine di-L-alanyloxymethyl ester,
- 25 and the corresponding derivatives of HPMPC and PMPA.

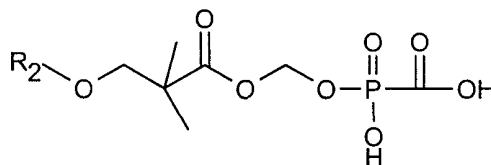
This aspect of the invention further provides a method for the treatment or prophylaxis of virus infections comprising the oral administration of an effective amount of a compound of the invention to a mammal (including humans) in need thereof. Viral infections include herpesvirus infections such as HSV-1, HSV-2, VZV, 30 CMV, HHV6, HHV8 and retroviruses such as HIV-1 and HIV-2. The invention further provides the use of the compounds defined above in medicine and the use of

these compounds in the preparation of a medicament for the prophylaxis or treatment of viral infections.

- A further group of phosphorous containing antivirals amenable to the invention include foscarnet (phosphonoformate) and PAA (phosphonoacetate). Taking foscarnet as an example:

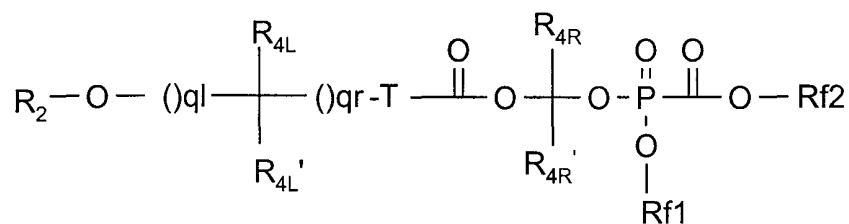


- it will be apparent that aside from conventional pharmaceutically acceptable esters applied to the carboxy function, one or two -linker(-R₂')_k-R₂ structures, preferably those of formula IIa or IIb can be applied to the phosphonate function to define compounds such as :

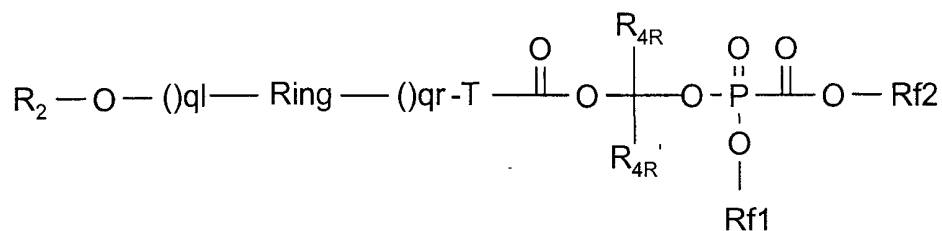


15

Thus a preferred group of compounds comprises foscarnet derivatives of the formula PF1:



or



where

R_2 is the acyl residue of an aliphatic amino acid,

5 R_{4L} and R_{4L}' are independently H, C_{1-3} alkyl, hydroxymethyl, C_3-6 cycloalkyl, C_1-3 alkyl- C_1C_6 cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl

ql is 0-3, qr is 0-3,

T is a bond, $-NR_4-$ or $-O-$

10 R_4 is H or C_{1-3} alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero- or carbocycle;

and Rf1 is H, a further ester of formula IIa or IIb and Rf2 is H, a further linker($-R_2'$) $_k$ - R_2 ester or a conventional pharmaceutically acceptable ester, including acyloxyalkyl esters.

15

Currently favoured values in Formula PF1 include: R_{4R} and R_{4R}' are preferably H and/or R_{4L} and R_{4L}' are preferably ethyl or especially methyl. T is preferably $-O-$ or more preferably a bond. Preferably qr is 1 or more preferably 0 and ql is 0 or preferably 1. If Rf1 is a further ester it is convenient if it is identical to the other
20 linker($-R_2'$) $_k$ - R_2 moiety. Conventional pharmaceutically acceptable esters for Rf2 include the methyl, ethyl and isopropyl esters or alternatively a similar structure to the linker($-R_2'$) $_k$ - R_2 moiety as envisaged in our copending PCT/SE99/00194.

A favoured group of compounds within formula PF1 include:

25 phosphonoformic acid, mono(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,

phosphonoformic acid, mono(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,

phosphonoformic acid, mono(2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester,

30 phosphonoformic acid, mono(2-(L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester,

phosphonoformic acid, mono((1,3-di-valyloxy)propyl-2-oxycarbonyloxy methyl) ester,

phosphonoformic acid, mono(2-L-valyloxy)-DL-propionyloxymethyl) ester,

- phosphonoformic acid, mono-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester,
 phosphonoformic acid, mono-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester,
 phosphonoformic acid, mono [4-(L-valyloxy)-butanoyloxymethyl] ester,
 phosphonoformic acid, mono-(4-(L-valyloxy) benzoyloxymethyl) ester,
 5 phosphonoformic acid, mono-(3-(3,4-di-(L-valyloxy) phenyl) propionyloxymethyl)
 ester,
 phosphonoformic acid, mono- (2-methyl-1-(L-valyloxy)-2-
 propoxycarbonyloxymethyl) ester,
 phosphonoformic acid, mono-(4-N-valyloxy)cyclohexanoyloxymethyl) ester
 10 phosphonoformic acid, mono-(1-valyloxy-2-methylpropane-2-
 aminocarbonyloxymethyl) ester
 phosphonoformic acid, mono-(1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-
 carbonyloxymethyl) ester
 phosphonoformic acid, mono-((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl)
 15 ester
 phosphonoformic acid, mono-(2-hydroxymethyl-2-methylpropionyloxymethyl) ester
 phosphonoformic acid, mono-(2-(L-valyloxymethyl)-2-ethyl butyroyloxymethyl)
 ester
 phosphonoformic acid, mono-(3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester
 20 phosphonoformic acid, mono-(3-(L-valyloxy)-2-methyl, 2-hydroxymethyl-
 propionyloxymethyl) ester
 the corresponding *bis* esters, the corresponding compounds additionally bearing a
 conventional carboxyl ester, and pharmaceutically acceptable salts thereof.
- 25 An especially favoured group comprises:
 phosponoformic acid di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester
 phosponoformic acid mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl)
 ester
 phosponoformic acid di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
 30 phosponoformic acid mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
 phosponoformic acid di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
 phosponoformic acid mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester and
 especially

phosponoformic acid di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester
phosponoformic acid mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl)
ester;
and pharmaceutically acceptable salts and conventional pharmaceutical carboxy-
5 esters thereof.

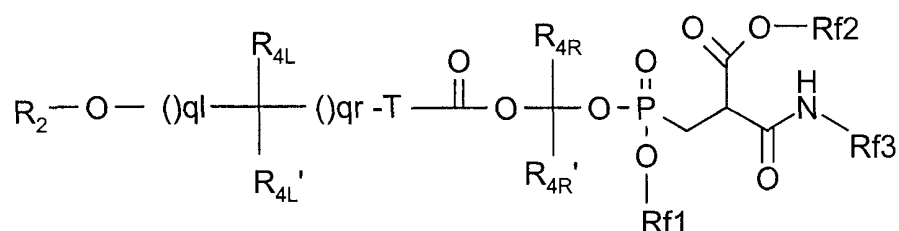
A further useful group of compounds comprises:
phosponoformic acid mono-(2-methyl-2-(L-isoleucyloxymethyl)
propionyloxymethyl) ester,
10 phosponoformic acid mono-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl)
ester,
phosponoformic acid mono-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl)
ester,
phosponoformic acid mono-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl)
15 ester,
phosponoformic acid mono-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl)
ester,
and the corresponding *bis* esters, conventional pharmaceutically acceptable carboxy
esters and pharmaceutically acceptable salts thereof.

20

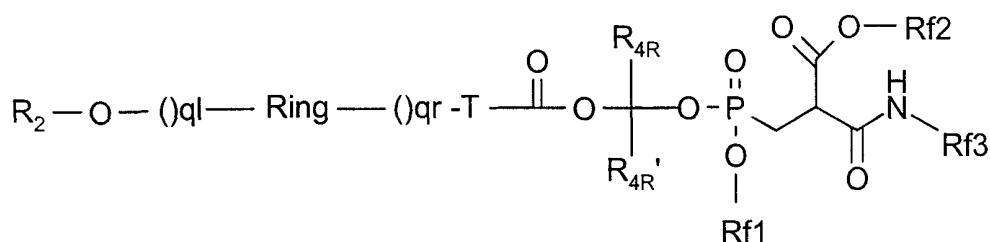
A further group of useful compounds comprises:
phosponoformic acid mono-L-valyloxymethyl ester,
phosponoformic acid di-L-valyloxymethyl ester,
phosponoformic acid mono-L-leucyloxymethyl ester,
25 phosponoformic acid di-L-leucyloxymethyl ester,
phosponoformic acid mono-L-isoleucyloxymethyl ester,
phosponoformic acid di-L-isoleucyloxymethyl ester,
phosponoformic acid mono-L-t-leucyloxymethyl ester,
phosponoformic acid di-L-t-leucyloxymethyl ester,
30 phosponoformic acid mono-L-alanyloxymethyl ester,
phosponoformic acid di-L-alanyloxymethyl ester,
conventional pharmaceutically acceptable carboxy esters and pharmaceutically
acceptable salts thereof.

This aspect of the invention further provides a method for the treatment or prophylaxis of virus infections comprising the oral administration of an effective amount of a compound of the invention to a mammal (including humans) in need thereof. Viral infections include herpesvirus infections such as HSV-1, HSV-2, VZV, CMV, HHV6, HHV8 and retroviruses such as HIV-1 and HIV-2. The invention further provides the use of the compounds defined above in medicine and the use of these compounds in the preparation of a medicament for the prophylaxis or treatment of viral infections.

A further class of phosphonates which are amenable to the invention and which share a structural similarity with phosphonoformic acid are the β -phosphonocarboxylic acid farnesyl protein transferase inhibitors, especially those of the formula PF4:



or



where RF1 is H or a further structure of formula IIa or IIb
 RF2 is H or a conventional pharmaceutically acceptable ester,
 RF3 is a polyunsaturated, branched C₆₋₂₂ alkyl,
 R₂ is the acyl residue of an aliphatic amino acid,

17

R_{4L} and R_{4L}' are independently H, C_{1-3} alkyl, hydroxymethyl, C_3-6 cycloalkyl, C_1-3 alkyl- C_1C_6 cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl

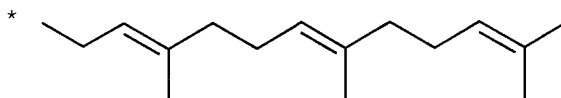
ql is 0-3, qr is 0-3,

5 T is a bond, $-NR_4-$ or $-O-$

R_4 is H or C_{1-3} alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle.

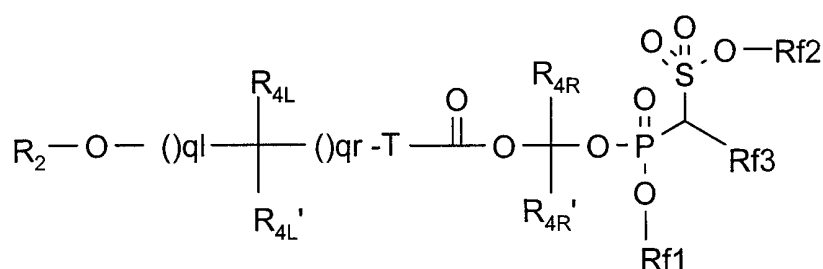
Currently favoured values in Formula PF4 include: R_{4R} and R_{4R}' are preferably H
 10 and/or R_{4L} and R_{4L}' are preferably ethyl or especially methyl. T is preferably $-O-$ or
 more preferably a bond. Preferably qr is 1 or more preferably 0 and ql is 0 or
 preferably 1. If Rf1 is a further ester it is convenient if it is identical to other linker-
 R_2 moiety. Conventional pharmaceutically acceptable esters for Rf2 include the
 methyl, ethyl and isopropyl esters or alternatively a similar structure to the linker- R_2
 15 moiety as envisaged in our copending PCT/SE99/00194. A convenient
 polyunsaturated alkyl Rf3 has the formula:



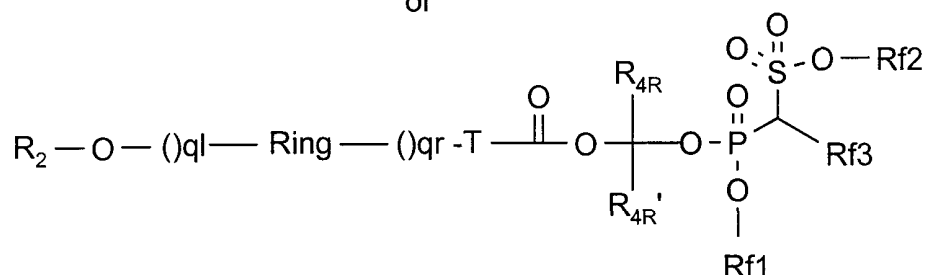
where the asterisk shows the point of attachment.

20

Other structurally similar phosphonates include α -phosphonosulphonates such as
 squalene synthase inhibitors of the formula PF5:



or



where RF1 is H or a further structure of formula IIa or IIb

RF2 is H or a conventional pharmaceutically acceptable ester a further structure of formula IIa or IIb

5

Rf3 is a polyunsaturated, branched C₆₋₂₂ alkyl,

R₂ is the acyl residue of an aliphatic amino acid,

R_{4L} and R_{4L}' are independently H, C₁₋₃ alkyl, hydroxymethyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-C₁C₆cycloalkyl phenyl or benzyl,

10 R_{4R} and R_{4R}' are independently H, C₁₋₃ alkyl or phenyl

ql is 0-3, qr is 0-3,

T is a bond, -NR₄- or -O-

R₄ is H or C₁₋₃alkyl;

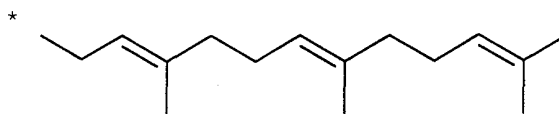
ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle.

15

Currently favoured values in Formula PF5 include: R_{4R} and R_{4R}' are preferably H and/or R_{4L} and R_{4L}' are preferably ethyl or especially methyl. T is preferably -O- or more preferably a bond. Preferably qr is 1 or more preferably 0 and ql is 0 or preferably 1. If Rf1 is a further ester it is convenient if it is identical to other linker-

20

R₂ moiety. Conventional pharmaceutically acceptable esters for Rf2 include the methyl, ethyl and isopropyl esters, or alternatively a similar structure to the linker-R₂ moiety. A convenient polyunsaturated alkyl Rf3 has the formula:

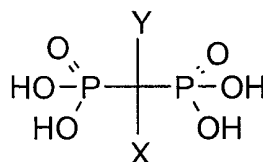


where the asterisk denotes the point of attachment.

- 5 The aspects of the invention immediately above further provide respective methods for the treatment or prophylaxis of neoplasma or cholesterol disorders comprising the oral administration of an effective amount of a compound of the invention to a mammal (including humans) in need thereof. The invention further provides the use of the compounds defined above in medicine and the use of these compounds in the
- 10 preparation of a medicament for the prophylaxis or treatment of neoplasma or cholesterol disorders.

A particularly preferred group of phosphorous containing drugs are the bisphosphonates active in bone and calcium metabolism. Favoured bis-phosphonates

15 drugs have the formula:



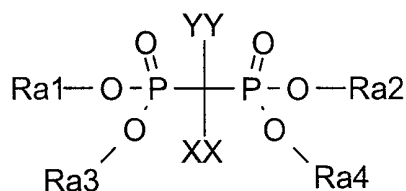
where

X is H, halo, hydroxy; and Y is

- a) C₁₋₁₀ alkyl, optionally substituted with
- 20 heterocycle,
- NR_aR_b, where R_a and R_b are independently hydrogen, C₁₋₆ alkyl or join together to form a 5 to 7 membered ring, optionally containing a further hetero atom,
- 25 OH, halo, -S(C₁₋₆ alkyl), phenyl, -C₁₋₇ cycloalkyl, (optionally substituted with -NR_aR_b or OH);
- b) C₃₋₇ cycloalkyl, optionally substituted with
- NR_aR_b, OH, halo, -S(C₁₋₆ alkyl), phenyl, morpholino or pyridyl;

- c) halo;
 d) piperidinyl;
 e) pyrrolidinyl;
 f) -S(C₁₋₆ alkyl), optionally substituted with
 5 -NR_aR_b, OH, halo or phenyl;
 g) -S-phenyl, optionally substituted with
 halo, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, trifluormethyl, -CONRaR_b or
 -COOH.
- 10 Preferred bis-phosphonates include alendronate (X is hydroxy, Y is
 NH₂CH₂CH₂CH₂-), clodronate (X is chloro, Y is chloro), etidronate (X is hydroxy, Y
 is CH₃-), pamidronate (X is hydroxy, Y is NH₂CH₂CH₂-), ibandronate (X is hydroxy,
 Y is N (CH₂CH₂CH₂CH₂CH₃)(CH₃)CH₂CH₂-), tiludronate (X is H, Y is
 4-chlorophenylthio-), risedronate (X is hydroxy, Y is 3-pyridinylmethylene-) and
 15 zoledronate (X is hydroxy, Y is (2-(1H-imidazol-1-yl)methylene-))

Preferred compounds within this bis-phosphonate aspect of the invention thus
 include those of the formula A1:



20

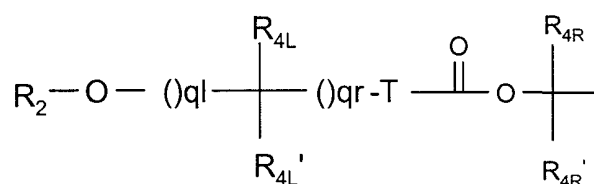
A-1

wherein YY and XX have the following values:

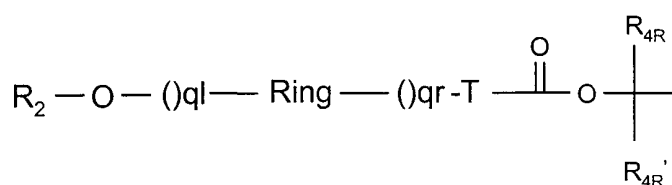
	NH ₂ (CH ₂) ₃ -	OH	(alendronate)
	NH ₂ (CH ₂) ₂ -	OH	(pamidronate)
25	cycloheptylamino-	H	(cimadronate)
	chloro-	chloro	(clodronate)
	pyrrolidin-1-ylCH ₂ CH ₂ -	OH	(EB 1053)
	CH ₃ -	OH	(etidronate)

	21	
methylopentylaminoCH ₂ CH ₂ -	OH	(ibandronate)
dimethylaminoCH ₂ CH ₂ -	OH	(olpadronate)
pyridin-3-ylCH ₂ -	OH	(risedronate)
(4-chlorophenyl)-thio-	H	(tiludronate)
5 imidazo-(1,2-a)pyridin-3-ylCH ₂ -	OH	(YH 529)
1H-imidazol-1-ylCH ₂ -	OH	(zoledronate)

wherein amino groups on YY can be optionally substituted with conventional
 pharmaceutically acceptable amide groups such as -C(=O)C₁₋₆alkyl or an aminoacyl
 10 or peptidyl derivative, as described in WO 96/31227;
 and wherein at least one of Ra1-Ra4 is a structure of the formula



or



where

- 15 R₂ is the acyl residue of an aliphatic amino acid,
 R_{4L} and R_{4L}' are independently H, C₁₋₃ alkyl, hydroxymethyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-C₁C₆cycloalkyl, phenyl or benzyl,
 R_{4R} and R_{4R}' are independently H or C₁₋₃ alkyl
 ql is 0-3, qr is 0-3,
 20 T is a bond, -NR₄- or -O-
 R₄ is H or C₁₋₃alkyl;
 ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;

and the remainder of Ra1-4 are hydrogen or conventional pharmaceutically acceptable esters. Preferably Ra1 and Ra2 comprise the same structure of formula IIa or IIb and Ra3 and Ra4 are H. A free amine group on YY could also be protected with the same linker $(R_2')_k-R_2$ structure, as envisaged in our copending application no
 5 PCT/SE99/00194.

In formula A-1, R_{4R} and R_{4R}' are preferably H and/or R_{4L} and R_{4L}' are preferably ethyl or especially methyl. T is preferably -O- or more preferably a bond. Preferably qr is 1 or more preferably 0 and ql is 0 or more preferably 1.

10

Representative compounds within formula A-1 thus include;
 (4-amino-1-hydroxybutylidene)-bisphosphonate, di(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, di(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
 15 (4-amino-1-hydroxybutylidene)-bisphosphonate, di (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, di (2-(L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester,
 20 (4-amino-1-hydroxybutylidene)-bisphosphonate, di ((1,3-di-valyloxy)propyl-2-oxycarbonyloxy methyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, di (2-L-valyloxy)-DL-propionyloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, di-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester,
 25 (4-amino-1-hydroxybutylidene)-bisphosphonate, di-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, bis [4-(L-valyloxy)-butanoyloxymethyl] ester,
 30 (4-amino-1-hydroxybutylidene)-bisphosphonate, di-(4-(L-valyloxy)benzoyloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, di-(3-(3,4-di-(L-valyloxy) phenyl) propionyloxymethyl) ester,

- (4-amino-1-hydroxybutylidene)-bisphosphonate, di- (2-methyl-1-(L-valyloxy)-2-propoxycarbonyloxymethyl) ester,
- (4-amino-1-hydroxybutylidene)-bisphosphonate, di-(4-valyloxy)cyclohexanoyloxymethyl) ester
- 5 (4-amino-1-hydroxybutylidene)-bisphosphonate, di-[N-(2-L-valyloxy-1,1-dimethylethyl) aminocarbonyloxymethyl] ester
- (4-amino-1-hydroxybutylidene)-bisphosphonate, di- (1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl)
- (4-amino-1-hydroxybutylidene)-bisphosphonate, di-((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl) ester
- 10 (4-amino-1-hydroxybutylidene)-bisphosphonate, di-(2-hydroxymethyl-2-methylpropionyloxymethyl) ester
- (4-amino-1-hydroxybutylidene)-bisphosphonate, di-(2-(L-valyloxymethyl)-2-ethyl butyryloxymethyl) ester
- 15 (4-amino-1-hydroxybutylidene)-bisphosphonate, di (3-(L-valyloxy)-2-methylpropionyloxymethyl) ester
- (4-amino-1-hydroxybutylidene)-bisphosphonate, di (3-(L-valyloxy)-2-methyl,2-hydroxymethyl-propionyloxymethyl) ester
- 20 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester,
- 25 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di (2-(L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di ((1,3-di-valyloxy)propyl-2-oxycarbonyloxy methyl) ester,
- 30 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di (2-L-valyloxy)-DL-propionyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester,

- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, bis [4-(L-valyloxy)-butanoyloxymethyl] ester,
- 5 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-(4-(L-valyloxy)benzoyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-(3-(3,4-di-(L-valyloxy) phenyl) propionyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di- (2-methyl-1-(L-valyloxy)-2-propoxycarbonyloxymethyl) ester,
- 10 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-(4-valyloxy)cyclohexanoyloxymethyl) ester
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-[N-(2-L-valyloxy-1,1-dimethyl-ethyl) aminocarbonyloxymethyl]ester
- 15 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di- (1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl) ester
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-(2-hydroxymethyl-20 2-methylpropionyloxymethyl) ester
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-(2-(L-valyloxymethyl)-2-ethyl butyroyloxymethyl) ester
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-(3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester
- 25 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, di-(3-(L-valyloxy)-2-methyl,2-hydroxymethyl-propionyloxymethyl) ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate di(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
- 30 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester,

- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di (2-(-L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di ((1,3-di-valyloxy)propyl-2-oxycarbonyloxy methyl) ester,
- 5 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di (2-L-valyloxy)-DL-propionyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester,
- 10 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, bis [4-(L-valyloxy)-butanoyloxymethyl] ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-(4-(L-valyloxy)benzoyloxymethyl) ester,
- 15 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-(3-(3,4-di-(L-valyloxy)phenyl) propionyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di- (2-methyl-1-(L-valyloxy)-2-propoxycarbonyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-(4-
- 20 valyloxy)cyclohexanoyloxymethyl) ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-[N-(2-L-valyloxy-1,1-dimethyl-ethyl) aminocarbonyloxymethyl] ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di- (1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester
- 25 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl) ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-(2-hydroxymethyl-2-methylpropionyloxymethyl) ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-(2-(L-valyloxymethyl)-2-
- 30 ethyl butyroyloxymethyl) ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-(3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester

1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, di-(3-(L-valyloxy)-2-methyl, 2-hydroxymethylpropionyloxymethyl) ester
and pharmaceutically acceptable salts thereof.

- 5 A further group of representative compounds include:
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
- 10 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono(2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono(2-(L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono((1,3-di-valyloxy)propyl-2-
- 15 oxycarbonyloxy methyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono(2-L-valyloxy)-DL-propionyloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester,
- 20 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono [4-(L-valyloxy)-butanoyloxymethyl] ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-(4-(L-valyloxy)
- 25 benzoyloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-(3-(3,4-di-(L-valyloxy) phenyl) propionyloxymethyl) ester,
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono- (2-methyl-1-(L-valyloxy)-2-propoxycarbonyloxymethyl) ester,
- 30 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-(4-valyloxy)cyclohexanoyloxymethyl) ester
 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-[N-(2-L-valyloxy-1,1-dimethyl-ethyl) aminocarbonyloxymethyl] ester

- (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-(1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester
- (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl) ester
- 5 (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-(2-hydroxymethyl-2-methylpropionyloxymethyl) ester
- (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-(2-(L-valyloxymethyl)-2-ethyl butyryloxymethyl) ester
- (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-(3-(L-valyloxy)-2-methyl-
- 10 propionyloxymethyl) ester
- (4-amino-1-hydroxybutylidene)-bisphosphonate, mono-(3-(L-valyloxy)-2-methyl,2-hydroxymethylpropionyloxymethyl) ester
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono(2-methyl-2-(L-
- 15 valyloxymethyl) propionyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester,
- 20 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono (2-(L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono ((1,3-di-valyloxy)propyl-2-oxycarbonyloxy methyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono (2-L-valyloxy)-
- 25 DL-propionyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono- ((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester,
- 30 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono [4-(L-valyloxy)-butanoyloxymethyl] ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-(4-(L-valyloxy) benzoyloxymethyl) ester,

- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-(3-(3,4-di-(L-valyloxy) phenyl) propionyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono- (2-methyl-1-(L-valyloxy)-2-propoxycarbonylmethyl) ester,
- 5 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-(4-N-valyloxy)cyclohexanoyloxymethyl) ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-[N-(2-L-valyloxy-1,1-dimethyl-ethyl) aminocarbonyloxymethyl] ester,
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-(1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester
- 10 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl) ester
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-(2-hydroxymethyl-2-methylpropionyloxymethyl) ester
- 15 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-(2-(L-valyloxymethyl)-2-ethyl butyroyloxymethyl) ester
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-(3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester
- 1-hydroxy-2-(1H-imidazolyl-1-yl)ethylidene-*bis* phosphonate, mono-(3-(L-valyloxy)-2-methyl,2-hydroxymethyl-propionyloxymethyl) ester
- 20 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate mono(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
- 25 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono (2-(L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono((1,3-di-valyloxy)propyl-2-oxycarbonyloxy methyl) ester,
- 30 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono(2-L-valyloxy)-DL-propionyloxymethyl) ester,

- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester,
- 5 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono [4-(L-valyloxy)-butanoyloxymethyl] ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-(4-(L-valyloxy) benzoyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-(3-(3,4-di-(L-valyloxy)
- 10 phenyl) propionyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono- (2-methyl-1-(L-valyloxy)-2-propoxycarbonyloxymethyl) ester,
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-(4 - valyloxy)cyclohexanoyloxymethyl) ester
- 15 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-[N-(2-L-valyloxy-1,1-dimethyl-ethyl) aminocarbonyloxymethyl] ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-(1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-((1,3-di-
- 20 (valyloxy)propyl-2-oxycarbonyloxy methyl) ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-(2-hydroxymethyl-2-methylpropionyloxymethyl) ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-(2-(L-valyloxymethyl)-2-ethyl butyroyloxymethyl) ester
- 25 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-(3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester
- 1-hydroxy-2-(pyrid-3-yl)ethylidene *bis*-phosphonate, mono-(3-(L-valyloxy)-2-methyl, 2-hydroxymethyl-propionyloxymethyl) ester
- and pharmaceutically acceptable salts thereof.

30

A favoured group of compounds within formula A-1 include:

alendronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,

- alendronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
alendronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
alendronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
alendronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
5 alendronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
alendronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
risedronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
risedronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
risedronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
10 risedronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
risedronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
risedronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
risedronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
zoledronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
15 zoledronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
zoledronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
zoledronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
zoledronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
zoledronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
20 zoledronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
pamidronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
pamidronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
pamidronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
pamidronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
25 pamidronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
pamidronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
pamidronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
cimadronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
cimadronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
30 cimadronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
cimadronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
cimadronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
cimadronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,

- cimadronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
clodronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
clodronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
clodronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
5 clodronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
clodronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
clodronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
clodronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
[1-hydroxy-3-(1-pyrrolidiny)-propylidene]-bis-phosphonate mono-(2-methyl-2-(L-
10 valyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-3-(1-pyrrolidiny)-propylidene]-bis-phosphonate di-(2-methyl-2-(D-
valyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-3-(1-pyrrolidiny)-propylidene]-bis-phosphonate mono-(2-methyl-2-(D-
valyloxymethyl) propionyloxymethyl) ester,
15 [1-hydroxy-3-(1-pyrrolidiny)-propylidene]-bis-phosphonate di-(2-methyl-2-(L-
valyloxy) propionyloxymethyl) ester,
[1-hydroxy-3-(1-pyrrolidiny)-propylidene]-bis-phosphonate mono-(2-methyl-2-(L-
valyloxy) propionyloxymethyl) ester,
[1-hydroxy-3-(1-pyrrolidiny)-propylidene]-bis-phosphonate di-(2-methyl-2-(D-
20 valyloxy) propionyloxymethyl) ester,
[1-hydroxy-3-(1-pyrrolidiny)-propylidene]-bis-phosphonate mono-(2-methyl-2-(D-
valyloxy) propionyloxymethyl) ester,
etidronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
etidronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
25 etidronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
etidronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
etidronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
etidronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
etidronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
30 olpadronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
olpadronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
olpadronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,

- olpadronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
olpadronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
olpadronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
olpadronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
5 ibandronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
ibandronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
ibandronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
ibandronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
ibandronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
10 ibandronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
ibandronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
[1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-
15 (D-valyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
20 [1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
[1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
[1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate mono-(2-
25 methyl-2-(D-valyloxy) propionyloxymethyl) ester,
tiludronate mono-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
tiludronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
tiludronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
tiludronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
30 tiludronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
tiludronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
tiludronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,

and pharmaceutically acceptable salts thereof.

A particularly favoured group of compounds of the invention comprises:

- alendronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
5 risedronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
zoledronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
pamidronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
cimadronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
clodronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
10 [1-hydroxy-3-(1-pyrrolidinyl)-propylidene]-bis-phosphonate di-(2-methyl-2-(L-
valyloxymethyl) propionyloxymethyl) ester,
etidronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
ibandronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
olpadronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
15 tiludronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-
(L-valyloxymethyl) propionyloxymethyl) ester,
and pharmaceutically acceptable salts thereof, especially the alendronate, zoledronate
and risedronate derivatives.

20

A further useful group of compounds within formula A-1 include:

- alendronate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
alendronate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
alendronate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
25 alendronate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
alendronate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
risedronate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
risedronate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
risedronate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
30 risedronate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
risedronate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
zoledronate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,

- zoledronate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
zoledronate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
zoledronate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
zoledronate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
5 pamidronate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
pamidronate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
pamidronate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
pamidronate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
pamidronate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
10 cimidronate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
cimadronate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
cimadronate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
cimadronate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
cimadronate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
15 clodronate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
clodronate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
clodronate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
clodronate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
clodronate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
20 [1-hydroxy-3-(1-pyrrolidinyl)-propylidene]-bis-phosphonate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-3-(1-pyrrolidinyl)-propylidene]-bis-phosphonate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-3-(1-pyrrolidinyl)-propylidene]-bis-phosphonate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
25 [1-hydroxy-3-(1-pyrrolidinyl)-propylidene]-bis-phosphonate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-3-(1-pyrrolidinyl)-propylidene]-bis-phosphonate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
30 etidronate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
etidronate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
etidronate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,

etidronate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
 etidronate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
 olpadronate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
 olpadronate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
 5 olpadronate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
 olpadronate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
 olpadronate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
 ibandronate di-(2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
 ibandronate di-(2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
 10 ibandronate di-(2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
 ibandronate di-(2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
 ibandronate di-(2-methyl-2-(L-glycyloxymethyl) propionyloxymethyl) ester,
 [1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-
 (L-isoleucyloxymethyl) propionyloxymethyl) ester,
 15 [1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-
 (L-leucyloxymethyl) propionyloxymethyl) ester,
 [1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-
 (L-t-leucyloxymethyl) propionyloxymethyl) ester,
 [1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-
 20 (L-alanyloxymethyl) propionyloxymethyl) ester,
 [1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-
 (L-glycyloxymethyl) propionyloxymethyl) ester,
 and pharmaceutically acceptable salts thereof, especially the alendronate, zoledronate
 and risedronate derivatives.

25

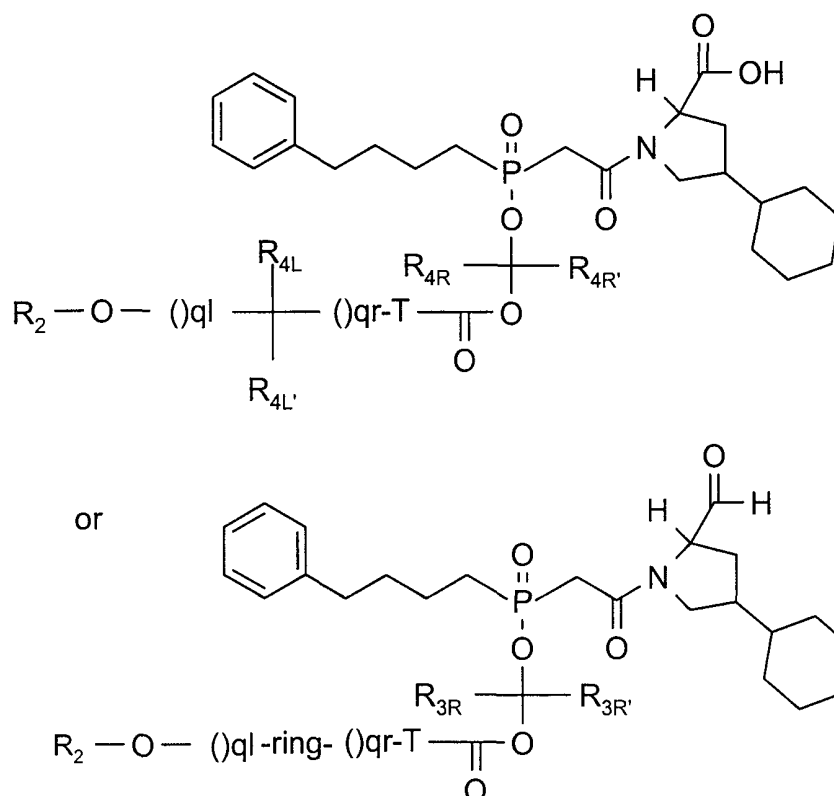
A further group of representative compounds comprises
 alendronate mono-L-valyloxymethyl ester,
 alendronate di-L-valyloxymethyl ester,
 alendronate mono-L-leucyloxymethyl ester,
 30 alendronate di-L-leucyloxymethyl ester,
 alendronate mono-L-isoleucyloxymethyl ester,
 alendronate di-L-isoleucyloxymethyl ester,

- alendronate mono-L-t-leucyloxymethyl ester,
alendronate di-L-t-leucyloxymethyl ester,
alendronate mono-L-alanyloxymethyl ester,
alendronate di-L-alanyloxymethyl ester,
5 risedronate mono-L-valyloxymethyl ester,
risedronate di-L-valyloxymethyl ester,
risedronate mono-L-leucyloxymethyl ester,
risedronate di-L-leucyloxymethyl ester,
risedronate mono-L-isoleucyloxymethyl ester,
10 risedronate di-L-isoleucyloxymethyl ester,
risedronate mono-L-t-leucyloxymethyl ester,
risedronate di-L-t-leucyloxymethyl ester,
risedronate mono-L-alanyloxymethyl ester,
risedronate di-L-alanyloxymethyl ester,
15 zoledronate mono-L-valyloxymethyl ester,
zoledronate di-L-valyloxymethyl ester,
zoledronate mono-L-leucyloxymethyl ester,
zoledronate di-L-leucyloxymethyl ester,
zoledronate mono-L-isoleucyloxymethyl ester,
20 zoledronate di-L-isoleucyloxymethyl ester,
zoledronate mono-L-t-leucyloxymethyl ester,
zoledronate di-L-t-leucyloxymethyl ester,
zoledronate mono-L-alanyloxymethyl ester,
zoledronate di-L-alanyloxymethyl ester,
25 and pharmaceutically acceptable salts thereof.

This aspect of the invention further provides a method for the treatment or prophylaxis of bone and calcium disorders comprising the oral administration of an effective amount of a compound of the invention to a mammal (including humans) in
30 need thereof. Bone and calcium disorders include osteoporosis, Paget's disease, hypercalcaemia of malignancy, tooth loss, bone loss in immunotherapy and rheumatoid arthritis, decreasing fracture, post orthopedic prosthesis and inhibiting ossification. The invention further provides the use of the compounds defined above

in medicine and the use of these compounds in the preparation of a medicament for the prophylaxis or treatment of bone and calcium disorders.

A still further preferred group of prodrugs of the invention are those based on
 5 fosinoprilate having the formula PF3:



where

R_2 is the acyl residue of an aliphatic amino acid,

10 R_{4L} and $R_{4L'}$ are independently H, C_{1-3} alkyl, hydroxymethyl, C_{3-6} cycloalkyl, C_1 - $_3$ alkyl- C_1C_6 cycloalkyl phenyl or benzyl,

R_{4R} and $R_{4R'}$ are independently H or C_{1-3} alkyl

ql is 0-3, qr is 0-3,

T is a bond, $-NR_3-$ or $-O-$

15 R_3 is H or C_{1-3} alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero- or carbocycle;
 and pharmaceutically acceptable salts thereof.

In formula PF3, R_{4R} and R_{4R}' are preferably H and/or R_{4L} and R_{4L}' are preferably ethyl or especially methyl. T is preferably -O- or more preferably a bond. Preferably qr is 1 or more preferably 0 and ql is 0 or preferably 1.

5 Representative compounds within formula PF3 thus include

- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (2-methyl-2-
10 (L-valyloxy) propionyloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (2-(-L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester,
- 15 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, ((1,3-di-valyloxy)propyl-2-oxycarbonyloxy methyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (2-L-valyloxy)-DL-propionyloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (5-(L-
20 valyloxy)-2,2-dimethylvaleryloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, ((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, [4-(L-valyloxy)-butanoyloxymethyl] ester,
- 25 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (4-(L-valyloxy) benzoyloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (3-(3,4-di-(L-valyloxy) phenyl) propionyloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (2-methyl-1-
30 (L-valyloxy)-2-propoxycarbonyloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (4-N-valyloxy)cyclohexanoyloxymethyl) ester

- (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, [N-(2-L-valyloxy-1,1-dimethyl-ethyl) aminocarbonyloxymethyl] ester
- (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, (1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester
- 5 (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline, ((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl) ester
- (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline(2-hydroxymethyl-2-methylpropionyloxymethyl) ester
- (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline(2-(L-valyloxymethyl)-2-ethyl butyroyloxymethyl) ester
- 10 (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester
- (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (3-(L-valyloxy)-2-methyl,2-hydroxymethyl-propionyloxymethyl) ester
- 15 and pharmaceutically acceptable salts thereof.

A favoured group of compounds within formula PF3 comprises:

- (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
- 20 (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
- (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
- 25 and especially;
- (4S)-4-cyclohexyl-1-[[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester:
- and pharmaceutically acceptable salts thereof

A further group of convenient compounds comprises

- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (2-methyl-2-(L-isoleucyloxymethyl) propionyloxymethyl) ester,
 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (2-methyl-2-(L-leucyloxymethyl) propionyloxymethyl) ester,
 5 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (2-methyl-2-(L-t-leucyloxymethyl) propionyloxymethyl) ester,
 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (2-methyl-2-(L-alanyloxymethyl) propionyloxymethyl) ester,
 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline (2-methyl-2-
 10 (L-glycyloxymethyl) propionyloxymethyl) ester,
 and pharmaceutically acceptable salts thereof.

A further group of useful compounds comprises:

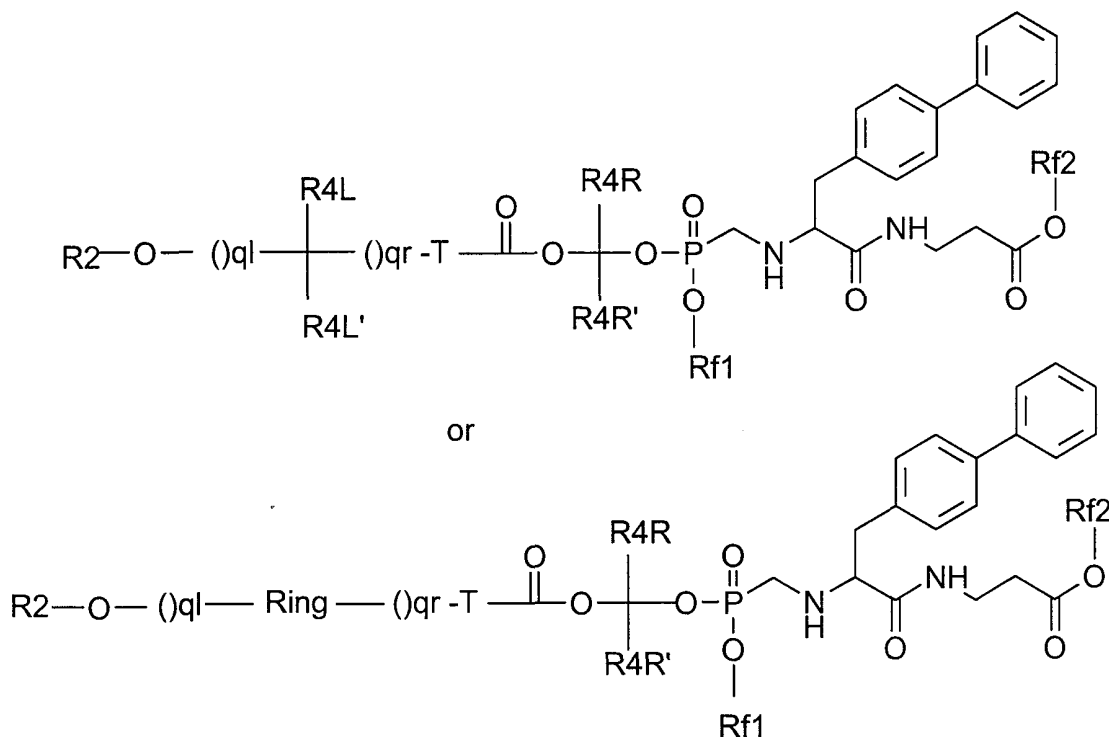
- (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline L-
 15 valyloxymethyl ester,
 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline L-leucyloxymethyl ester,
 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline L-isoleucyloxymethyl ester,
 20 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline L-t-leucyloxymethyl ester,
 (4S)-4-cyclohexyl-1-[[R](4-phenylbutyl)phosphinyl]acetyl]-L-proline L-alanyloxymethyl ester,
 and pharmaceutically acceptable salts thereof.

25

- This aspect of the invention further provides a method for the treatment or prophylaxis of hypertension comprising the oral administration of an effective amount of a compound defined above to a mammal (including humans) in need
 30 thereof. The invention further provides the use of these compounds in medicine and their use in the preparation of a medicament for the treatment or prophylaxis of hypertension

A further phosphonate compound amenable to the prodrugs of the invention are the neutral endopeptidase inhibitors such as CGS-24592 (Novartis), preferably those of the formula PF6:

5

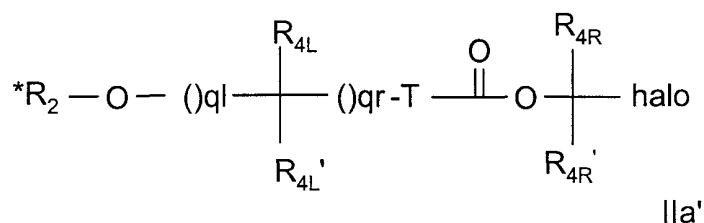


where RF1 is H or a further structure of formula IIa or IIb
 10 RF2 is H or a conventional pharmaceutically acceptable ester,

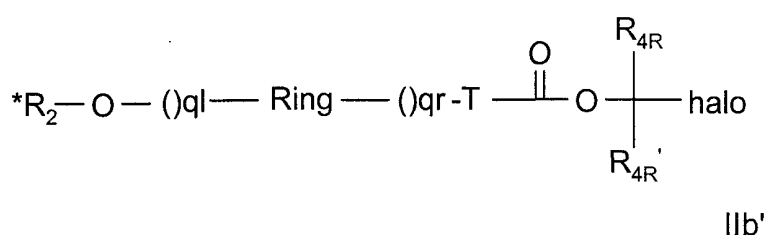
R_2 is the acyl residue of an aliphatic amino acid,
 R_{4L} and R_{4L}' are independently H, C_{1-3} alkyl, hydroxymethyl, C_{3-6} cycloalkyl, C_1 -
 C_3 alkyl- C_1C_6 cycloalkyl phenyl or benzyl,
 15 R_{4R} and R_{4R}' are independently H or C_{1-3} alkyl
 ql is 0-3, qr is 0-3,
 T is a bond, $-NR_4-$ or $-O-$
 R_4 is H or C_{1-3} alkyl;
 ring is an optionally substituted aromatic or non-aromatic, hetero- or carbocycle;
 20 and pharmaceutically acceptable salts thereof.

Currently favoured values in Formula PF6 include: R_{4R} and R_{4R}' are preferably H and/or R_{4L} and R_{4L}' are preferably ethyl or especially methyl. T is preferably -O- or more preferably a bond. Preferably qr is 1 or more preferably 0 and ql is 0 or
 5 preferably 1. If Rf1 is a further ester it is convenient if it is identical to other linker- R_2 moiety. Conventional pharmaceutically acceptable esters for Rf2 include the methyl, ethyl and isopropyl esters.

Compounds of the invention are typically prepared by esterifying the mother
 10 compound in which exposed functions such as the 4-amino group of alendronate or the carboxy group of foscarnet are protected with conventional amine and carboxy etc protecting groups respectively, with a structure of the formula IIa or IIb, the preparation of which are described in the abovementioned PCT/SE99/00194:



or



15

$*R_2$ is the acyl residue of an aliphatic amino acid, N-protected with a conventional N-protecting group such as CBz, Fmoc or Boc

R_{4L} and R_{4L}' are independently H, C_{1-3} alkyl, hydroxymethyl, C_3-6 cycloalkyl, C_1-3 alkyl- C_1C_6 cycloalkyl phenyl or benzyl,

20 R_{4R} and R_{4R}' are independently H or C_{1-3} alkyl

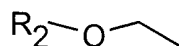
ql is 0-3, qr is 0-3,

T is a bond, -NR₃- or -O-

R₃ is H or C₁₋₃alkyl;

“ring” is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;

and halo is bromo, chloro and especially iodo. Alternatively, iodomethyl N-protected aminoacid esters are employed for linker-R₂ structures of the formula:



5

Hydroxymethyl bearing linkers such as those within formula IIa are prepared by methoxybenzylation of the free carboxy group of a bis hydroxy compound such as glycerol or bis 2,2 hydroxymethyl propionic acid, CBz monoprotection of one of the hydroxy groups, esterification with the N-protected R₂ group, debenzylation, reaction with chloriodomethyl and iodination as shown below prior to esterification to a phosphorous-containing pharmaceutical.

The mother compounds, that is the phosphorous containing drug, are all well known and readily accessible to those in the art.

In drugs comprising multiple phosphoryl/phosphonate/phosphinate functions, it is generally advantageous that an hydroxy group on each phosphorous moiety is esterified with a linker (-R₂')_k-R₂ structure such as those of formula IIa or IIb etc. Regioselective protecting groups which bridge the phosphate groups of bis phosphonates and thus assist mono and diacylation include Si compounds such as dichlorotetraisopropyldisiloxane or cresols.

Methodology for the derivatisation of phosphorous-containing compounds with acyloxyalkyl groups and which can be used analogously for the coupling of the -linker (-R₂')_k-R₂ structure is described in US patent 5 227 506, WO 94/13682, WO 94/13324, WO 98/04569, Starret et al J Med Chem 37 1857-1864 (1994) and Iyer et al Tetrahedron Lett 30 7141-7144 (1989). A number of approaches are also illustrated in the examples below. The N-protecting group on group R₂ is removed by conventional methodology.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino

- group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York, 1981), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl, and the like, carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butoxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl, and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Favoured N-protecting groups include formyl, acetyl, allyl, F-moc, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butoxycarbonyl (BOC) and benzyloxycarbonyl (Cbz).
- Hydroxy and/or carboxy protecting groups are also extensively reviewed in Greene *ibid* and include ethers such as methyl, substituted methyl ethers such as methoxymethyl, methylthiomethyl, benzyloxymethyl, t-butoxymethyl, 2-methoxyethoxymethyl and the like, silyl ethers such as trimethylsilyl (TMS), t-butyldimethylsilyl (TBDMS) tribenzylsilyl, triphenylsilyl, t-butyldiphenylsilyl triisopropyl silyl and the like, substituted ethyl ethers such as 1-ethoxymethyl, 1-methyl-1-methoxyethyl, t-butyl, allyl, benzyl, p-methoxybenzyl, diphenylmethyl, triphenylmethyl and the like, aralkyl groups such as trityl, and pixyl (9-hydroxy-9-phenylxanthene derivatives, especially the chloride). Ester hydroxy protecting groups

include esters such as formate, benzylformate, chloroacetate, methoxyacetate, phenoxyacetate, pivaloate, adamantate, mesitoate, benzoate and the like. Carbonate hydroxy protecting groups include methyl vinyl, allyl, cinnamyl, benzyl and the like.

- 5 The compounds of the invention can form salts which form an additional aspect of the invention. Appropriate pharmaceutically acceptable salts of the compounds of the invention include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, isethionate, adipate, alginate, aspartate, benzoate, butyrate, 10 digluconate, cyclopentenate, glucoheptenate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, propionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-naphthalenesulphonate, 15 benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, phosphoric and sulphonic acids. The compounds of the invention may in some cases be isolated as the hydrate.

- 20 While it is possible for the active agent to be administered alone, it is preferable to present it as part of a pharmaceutical formulation. Such a formulation will comprise the above defined active agent together with one or more acceptable carriers/excipients and optionally other therapeutic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the 25 formulation and not deleterious to the recipient.

The formulations include those suitable for rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration, but preferably the formulation is an 30 orally administered formulation. The formulations may conveniently be presented in

unit dosage form, e.g. tablets and sustained release capsules, and may be prepared by any methods well known in the art of pharmacy.

Such methods include the step of bringing into association the above defined active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a compound of the invention or its pharmaceutically acceptable salt in conjunction or association with a pharmaceutically acceptable carrier or vehicle. If the manufacture of pharmaceutical formulations involves intimate mixing of pharmaceutical excipients and the active ingredient in salt form, then it is often preferred to use excipients which are non-basic in nature, i.e. either acidic or neutral.

Formulations for oral administration in the present invention may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion and as a bolus etc.

20

With regard to compositions for oral administration (e.g. tablets and capsules), the term suitable carrier includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate

stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring or the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

5

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

15 Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

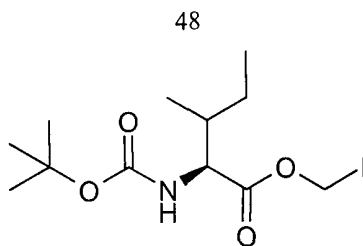
20 Detailed Description of the Invention

Various aspects of the invention will now be illustrated by way of example only with reference to the following non-limiting synthesis and biological examples:

25 Preparation of intermediates

Example P-I-1

N-BOC-L-isoleucine iodomethyl ester



a) N-BOC-L-isoleucine chloromethyl ester

To a solution of N-BOC-L-isoleucine (23.1 g, 0.1 mol) in dioxane (500 mL), was
5 added dropwise a 40% aqueous solution of tetrabutylammonium hydroxide (65.6
mL, 0.1 mol). After stirring for 15 min, the solution was evaporated to dryness
through co-evaporation with dioxane and toluene. The residue was dissolved in
dichloromethane (500 mL) and then chloriodomethane (72.8 mL, 1 mol) was added
and the solution was stirred for 6h at room temperature. The solution was
10 concentrated under reduced pressure and the residue was shaken with hexane / ethyl
acetate (1:1 v/v, 400 mL). The yellow crystalline solid was filtered off and the filtrate
was washed with aqueous solution of sodium thiosulfate (0.1 M) and then filtered
through anhydrous sodium sulfate and evaporated to dryness. The residue was
column chromatographed (silica gel, 1-2% MeOH in CH₂Cl₂), to give 20.8 g of N-
15 BOC-L-isoleucine chloromethyl ester.

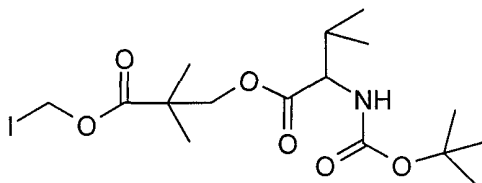
b) N-BOC-L-isoleucine iodomethyl ester.

To a solution of N-BOC-L-isoleucine chloromethyl ester (19.6 g, 70 mmol) in
acetonitrile (300 mL), was added sodium iodide (31.5 g, 210 mmol). The solution
20 was stirred for 4 h at 60 °C. The resulting suspension was filtered and the filtrate was
evaporated. The residue was dissolved in CH₂Cl₂ and washed with aqueous sodium
thiosulfate (0.1 M). The organic phase was dried (Na₂SO₄) and concentrated under
reduced pressure. The crude product was column chromatographed (silica gel, 2%
MeOH in CH₂Cl₂), to give 22.6 g of N-BOC-L-isoleucine iodomethyl ester.

25

¹H-NMR (CDCl₃): 6.04 (d, 1H), 5.82 (d, 1H), 4.97 (d, 1H), 4.25 (dd, 1H), 1.98-1.80
(m, 1H), 1.43 (s, 9H), 1.50-1.05 (m, 2H), 0.97-0.88 (m, 6H).

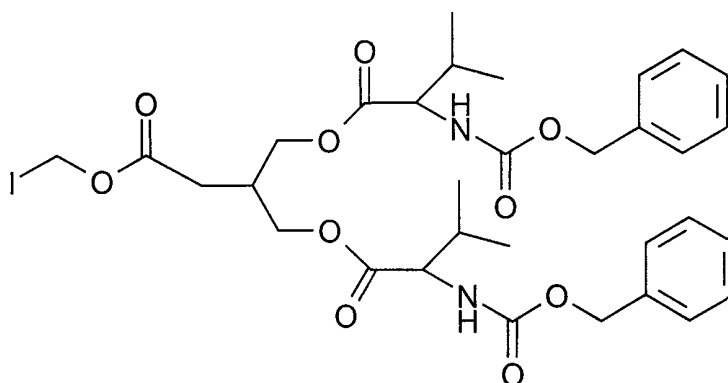
Example PI-2

2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid iodomethyl ester

- a) 2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid.
N-Boc-L-valine (10.8g, 50 mmole), 4-dimethylaminopyridine (610 mg, 5 mmole)
5 and DCC (6.18 g, 30 mmole) were dissolved in methylene chloride (100 ml). After stirring for 2 hour the mixture was filtered. To the filtrate were added 2,2-dimethyl-3-hydroxy-propionic acid (3.54g, 30 mmole) and pyridine (10 ml). After 18 hr, the reaction mixture was filtered, and the filtrate was poured into sodium hydrogen carbonate aqueous solution, the organic phase was then washed with citric acid
10 aqueous solution and water succesively. After evaporation the product was isolated with silica gel column chromatography to yield 4.4g.
- b) 2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid chloromethyl ester.
2,2-Dimethyl-3-(N-Boc-L-valyloxy)propionic acid (3.9 g, 12.3 mmole) was
15 dissolved in dioxane (60 ml). To the solution was added tetrabutylammonium hydroxide aqueous solution (40 %, 7.78 ml, 12 mmole). The solution was dried in vacuo, and it was coevaporated with toluene for several times. The residue was dissolved in methylene chloride and then chloriodomethane (18.9 ml, 260 mmole) was added to the solution. After 18 hr, the reaction solution was evaporated and the
20 product was isolated with silica gel column chromatography to yield 3.7 g.
- c) 2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid iodomethyl ester.
2,2-Dimethyl-3-(N-Boc-L-valyloxy)propionic acid chloromethyl ester (3.6 g, 10 mmole) was dissolved in acetonitrile (50 ml). Sodium iodide (2.1 g, 14 mmole) was
25 added to the solution. After reaction at 70° C for 2 hr, the reaction mixture was filtered and the residue was dissolved in methylene chloride (20 ml) and refiltered. The solution was dried and gave 4.34g of the titled product..

¹H-NMR (CDCl₃): 5.92 (dd, 2H) 5.10 (d, 1H) 4.24 (m, 1H) 4.15 (dd, 2H) 2.01
30 (m, 1H) 1.44 (s, 9H) 1.25 (d, 6H) 0.91 (m, 6H)

Example P-I-3

3,3- bis (N-CBz-L-valyloxymethyl)-propionic acid iodomethyl ester

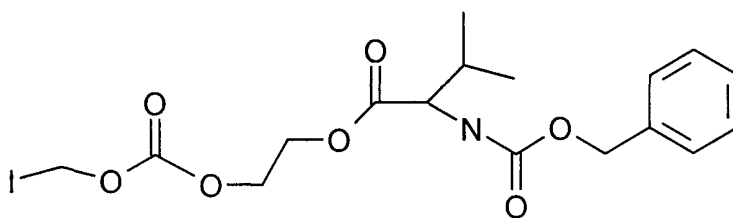
- 5 a) 3,3-Bis (N-CBz-L-valyloxymethyl)-propionic acid chloromethyl ester.
 3,3- bis (N-CBz-L-valyloxymethyl)-propionic acid (3 g, 5 mmole) prepared
 according to PCT/SE99/00194) was dissolved in dioxane (20 ml). To the solution
 was added tetrabutylammonium hydroxide aqueous solution (40 %, 3.11 ml, 4.8
 10 mmole). The solution was dried in vacuo, and it was coevaporated with toluene
 several times. The residue was dissolved in methylene chloride (15 ml) and then
 chloriodomethane (7.3 ml, 100 mmole) was added to the solution. The reaction
 solution was refluxed for 18 hr and then evaporated and the product was isolated
 with silica gel column chromatography. 900 mg.
- 15 b) 3,3-bis-(N-CBz-L-valyloxymethyl)propionic acid iodomethyl ester .
 3,3-Bis (N-CBz-L-valyloxymethyl)-propionic acid chloromethyl ester (900 mg, 1.38
 mmole) was dissolved in acetonitrile (5 ml). Sodium iodide (289 mg, 1.93 mmole)
 was added to the solution. After reaction at 70° C for 3 hr, the reaction mixture was
 20 filtered and the residue was dissolved in methylene chloride (5 ml) and refiltered.
 The solution was dried and gave the titled product. 800 mg.

¹H-NMR (CDCl₃): 7.35 (m, 10 H) 5.88 (dd, 2H) 5.25 (d, 2H) 4.29 (m, 2H) 4.18 (m,
 4H) 2.56 (m, 1H) 2.42 (d, 2H) 2.16 (m, 2H) 0.93 (m 12 H)

25

Example P-I-4

2-(N-CBz-L-valyloxy)ethoxycarbonyloxymethyl iodide

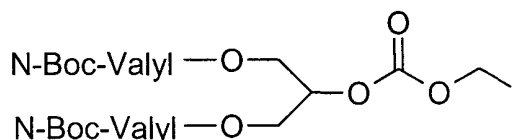


2-(N-CBz-L-valyloxy)ethoxycarbonyloxymethyl chloride (1.16 g, 3 mmole) was dissolved in acetonitrile (10 ml). Sodium iodide (630 g, 4.2 mmole) was added to the solution. After reaction at 65° C for 2.5 hr, the reaction mixture was cooled down to room temperature and filtered and the residue was dissolved in methylene chloride (5 ml) and refiltered. The solution was dried and gave the titled product. 1.2 g.

¹H-NMR (CDCl₃): 7.35 (m, 5H) 5.93 (dd, 2H) 5.26 (d, 1H) 5.11 (s, 2H) 4.39 (m, 5H) 2.18 (m, 1H) 0.94 (m, 6 H).

Example P-I-5

1,3-bis(N-tert-butoxycarbonyl-L-valyloxy)-2-propyl iodomethyl carbonate)



a) 1-*O*-(N-tert-butoxycarbonyl-L-valyl)glycerol.

N-tert-Butoxycarbonyl-L-valine (32.53 g, 0.150 mol), *N,N'*-dicyclohexylcarbodiimide (37.85 g, 0.183 mol, and 4-dimethylaminopyridine (1.83 g, 0.015 mol) were added to glycerol (138.12 g., 1.5 mol) in 500 mL dry DMF and the mixture was stirred at rt under N₂ for 3 days. The reaction mixture was filtered, concentrated under vacuum, and then partitioned between 300 mL EtOAc and 150 mL H₂O. The aqueous phase was reextracted with 150 mL EtOAc. The organic phases were combined and washed successively with 100 mL each of saturated aqueous NaHCO₃, saturated NH₄Cl, and brine. Drying over anhydrous Na₂SO₄, and concentration under vacuum gave a viscous light yellow oil as crude product. Flash column chromatography on silica gel with 4/1 EtOAc - petroleum ether (BP 40-60 °C) gave 18.27 g (42%) of product (alternative nomenclature: 3-(N-tert-

butoxycarbonyl-L-valyloxy)-1,2-propanediol). Reactions done overnight gave similar yields.

b) 1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol.

5 1-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol (17.95 g, 61.6 mmol), Boc-L-valine (6.69 g, 30.8 mmol), DMAP (0.38 g, 3.1 mmol), and DCC (7.10 g, 34.4 mmol) in 240 mL CH₂Cl₂ and 60 mL DMF were stirred at rt under N₂ for 18 h. The reaction mixture was filtered, concentrated under vacuum, and redissolved in 200 mL EtOAc. The organic solution was washed with 50 mL saturated NH₄Cl. The aqueous phase
10 was reextracted with 50 mL EtOAc. The organic phases were combined, washed successively with 50 mL saturated NaHCO₃ and 50 mL brine, dried over Na₂SO₄, and concentrated under vacuum. Flash column chromatography of the crude material on silica gel (eluent 2/1 petroleum ether – EtOAc, and then EtOAc) gave 7.41 g (49%) of the title compound (alternative nomenclature: 1,3-bis(*N*-tert-butoxycarbonyl-L-
15 valyloxy)-2-propanol).

c) 2-*O*-chloromethoxycarbonyl-1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol
Chloromethyl chloroformate (2.70 mL, 30 mmol) was added to a solution of 1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol (7.27 g, 14.8 mmol) and pyridine (7.2 mL, 89 mmol) in 60 mL dry CH₂Cl₂, in an ice bath, under N₂. After stirring for 1 h
20 45 min, the reaction mixture was diluted with 100 mL CH₂Cl₂ and washed with 40 mL water. The aqueous phase was reextracted with 20 mL H₂O. The organic phases were combined, washed with 40 mL saturated NaHCO₃, followed by 2 x 50 mL brine, dried over Na₂SO₄, and concentrated under vacuum. Flash column chromatography on silica gel with 2/1 hexane- EtOAc gave 8.03 g (93%) of the title
25 compound (alternative nomenclature: 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl chloromethyl carbonate).

d) 2-*O*-iodomethoxycarbonyl-1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol.

30 A solution of 2-*O*-chloromethoxycarbonyl-1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)propane-1,2,3-triol (7.86 g, 13.5 mmol) and NaI (8.09 g, 54.0 mmol) in 135 mL dry acetonitrile was refluxed at 80 °C for 4 h under N₂. The reaction mixture was

- concentrated under vacuum, and then partitioned between 150 mL diethyl ether and 50 mL H₂O. The aqueous layer was reextracted with 2 x 25 mL ether. The combined organic phases were washed successively with 25 mL aqueous Na₂S₂O₃ and 50 mL brine, dried over Na₂SO₄, and concentrated. Flash column chromatography (silica gel, 2/1 hexane-ethyl acetate gave 8.38 g (92%) title product (alternative name: 2-iodomethoxycarbonyloxy-1,3-bis-(*N*-tert-butoxycarbonyl-L-valyloxy)propane or 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl iodomethyl carbonate) as a white solid.
- ¹H NMR (250 MHz, CDCl₃) δ 0.81 (d, 6H), 0.88 (m, 6H), 1.36 (s, 18H), 2.06 (m, 2H), 4.11-4.46 (m, 6H), 5.0 (br d, 2H), 5.12 (m, 1H), 5.88 (s, 2H).

Example P-1-6

3-benzyloxycarbonylpropionic acid iodomethyl ester

- a) Succinic acid monobenzyl ester .
- Succinic anhydride (30 g, 300 mmole) was dissolved in methylene chloride (300 ml). To the solution were added benzyl alcohol (10.2 ml, 100 mmole), 4-dimethylaminopyridine (1.22 g, 10 mmole) and pyridine (48 ml). After 3 hours the reaction mixture was poured in to citric acid aqueous solution. The organic phase was concentrated to small volume and sodium hydrogen carbonate and water were added. Then mixture was stirred for 30 min. The aqueous phase was collected, and to it was added citric acid aqueous solution. The product precipitated out, was collected and dried. 15.3 g.
- b) 3-benzyloxycarbonylpropionic acid chloromethyl ester.
- Succinic acid monobenzyl ester (4.16 g, 20 mmole) was dissolved in dioxane (20 ml). To the solution was added tetrabutylammonium hydroxide aqueous solution (40 %, 11.6 ml, 18 mmole). The solution was dried in vacuo and coevaporated with toluene several times. The residue was dissolved in methylene chloride (60 ml) and then chloriodomethane (14.5 ml, 200 mmole) was added to the solution. The reaction solution was stirred for 18 hr and then evaporated and the product was isolated with silica gel column chromatography. 3.64 g

¹H-NMR (CDCl₃): 7.35 (m, 5H), 5.67 (s, 2H), 5.13 (s, 2H), 2.72 (s, 4H).

c) 3-Benzyloxycarbonylpropionic acid iodomethyl ester.

- 5 3-Benzyloxycarbonylpropionic acid chloromethyl ester (2 g, 1.38 mmole) was dissolved in acetonitrile (30 ml). Sodium iodide (1.6 g, 10.9 mmole) was added to the solution. After reaction at 70° C for 3 hr, the reaction mixture was filtered and the residue was dissolved in methylene chloride (20 ml) and refiltered. The solution was dried and gave intermediate 3-benzyloxycarbonylpropionic acid iodomethyl ester in
- 10 quantitative yield. This intermediate is bonded to an accessible function of a drug, such as a ring hydroxy or carboxy function using conventional alkylation/acylation conditions as described generally herein. Following deprotection of the terminal carboxy, a di/trifunctional linker bearing R₂, such as 1,3-bis- O-(L-valyl)glycerol or iodomethyloxy-L-valyl is acylated/alkylated thereon or R₂ amide bonded thereon by
- 15 conventional techniques as described herein, such as with DCC coupling agent.

A-I-1

Iodomethyl 2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionate

- 20 a) 4-Methoxybenzyl 2-(hydroxymethyl)-2-methyl propionate.
2-(Hydroxymethyl)-2-methyl propionic acid was esterified by alkylation with 4-methoxybenzyl chloride by conventional means, namely treatment with aqueous NaOH, followed by evaporation and dissolution in an organic solvent such as DMF to which the 4-methoxybenzyl chloride is added and the reaction warmed and
- 25 agitated, such as stirring at 60 C for one hour. The reaction mixture is cooled, concentrated by rotavapor and the resulting concentrated suspension partitioned between water and dichloromethane. The organic phase is evaporated and the residue subjected to silica gel column chromatography, for example with 0, 2, 4% EtOH in dichloromethane to yield the title compound (7.10 g). R_f (2%MeOH/CHCl₃) 0.40.
- 30 b) 4-Methoxybenzyl 2-(N- benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate.

4-Methoxybenzyl 2-(hydroxymethyl)-2-methyl propionate (2.50 g, 10.5 mmol), N-benzyloxy carbonyl-L-valine (2.51 g, 10 mmole), 4-dimethylaminopyridine (183 mg) and 1-hydroxybenzotriazole (1.35g, 10 mmole) were mixed and dissolved in N,N-dimethylformamide (90 ml). Then dicyclohexyl-carbodiimide (2.47 g 12 mmol) was added. After stirring for 3 days at room temperature the suspension was filtered and the filtrate evaporated in vacuo. The residue was partitioned between 0.1M citric acid and dichloromethane. The organic phase was then extracted with aqueous saturated NaHCO₃ and evaporated in vacuo. The residue was silica gel column chromatographed (0, 1, 2, 3% ethanol in dichloromethane). The appropriate fractions were pooled and evaporated in vacuo to give the title compound (2.72 g). R_f (2%MeOH/CHCl₃) 0.75.

d) 2-(N- benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionic acid. To a solution of 4-methoxybenzyl 2-(N- benzyloxycarbonyl -L-valyloxymethyl)-2-methyl propionate (2.72 g, 5.76 mmole), was added trifluoroacetic acid (11.5 ml) and the emerging dark red solution was stirred for 30 min at room temperature. The solution was evaporated to dryness with dioxane and toluene. The residue was silica gel column chromatographed (2, 3, 4% ethanol in dichloromethane). The appropriate fractions were pooled and evaporated in vacuo to give the title compound (1.86 g). R_f (2%MeOH/CHCl₃) 0.30.

¹H-NMR (CDCl₃): 7.32 (s, 5H), 5.32 (d, 1H), 5.10 (s, 2H), 4.32 (d,d, 1H), 4.21 (d,d, 2H), 2.13 (m, 1H), 1.26 (s, 3H), 1.25 (s, 3H), 0.95 (d, 3H), 0.86 (d, 3H).

c) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate. 2-(N- benzyloxycarbonyl -L-valyloxymethyl)-2-methyl propionic acid was esterified by conventional techniques, namely dissolution in an organic solvent such as dioxane and dropwise addition of aqueous tetrabutylammonium hydroxide, followed by evaporation. The residue is dissolved in dichloromethane and then chloriodomethane and the mixture stirred for 6 hours at room temperature, followed by partition, shaking the filtrate with aqueous sodium thiosulphate. 0.1M, filtration and evaporation. The title compound (1.40 g) was obtained after silica gel

column chromatography (0, 1, 2, 3% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.80.

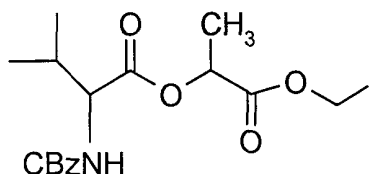
c) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate.

Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate was converted to iodide by conventional techniques, namely addition to NaI in acetonitrile, stirring and heating, for instance to 75 C for four hours. The resulting suspension is filtered and the filtrate evaporated, dissolved in organic solvent such as toluene and shaken with aqueous sodium thiosulphate (0.1M) and evaporation to give the title compound (1.25 g) practically pure. R_f (2%MeOH/ CHCl_3) 0.80.

$^1\text{H-NMR}$ (CDCl_3): 7.35 (s, 5H), 5.90 (d,d, 2H), 5.24 (d, 1H), 5.10 (s, 2H), 4.31 (d,d, 1H), 4.14 (d,d, 2H), 2.16 (m, 1H), 1.22 (s, 6H), 0.96 (d, 3H), 0.87 (d, 3H).

Example A-I-2

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-DL-propionate.



a) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-DL-propionate.

2-(N-benzyloxycarbonyl-L-valyloxy) propionic acid (1 g) was esterified by the method described in Example A-I-I, step d. The title compound (0.76 g) was obtained after silica gel column chromatography (0, 1% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.75.

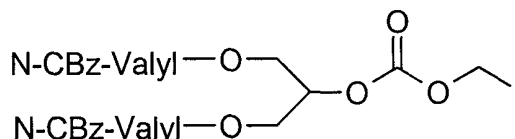
b) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-DL-propionate.

Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (0.95 g) practically pure. R_f (2%MeOH/ CHCl_3) 0.75.

¹H-NMR (CDCl₃): 7.33 (s, 5H), 5.98 (d, 1H), 5.86 (d, 1H), 5.26 (d, 1H), 5.10 (s, 2H), 5.07 (q, 1H), 4.38 (d,d, 1H), 2.30 (m, 1H), 1.49 (d, 3H), 1.03 (d, 3H), 0.95 (d, 3H).

5 Example A-I-3

Iodomethyl (1,3-di-(N-benzyloxycarbonyl)-L-valyloxy)-2-propyl carbonate.



a) Chloromethyl (1,3-di-(N-benzyloxycarbonyl)-L-valyloxy)-2-propyl carbonate.

- 10 To a solution of 1,3-di-((N-benzyloxycarbonyl)-L-valyloxy)propan-2-ol (1.34 g, 2.4 mmole) in dichloromethane (10 ml) was added dry pyridine (1.15 ml, 14.4 mmol) and chloromethyl chloroformate (0.43 ml, 4.8 mmole) at 0°C. The reaction was then stirred for 30 min and then poured into aqueous 50% saturated sodium chloride / 0.1M citric acid solution and extracted with dichloromethane. The organic phase was
- 15 evaporated and the residue silica gel column chromatographed (0, 1, 1.5% ethanol in dichloromethane). The appropriate fractions were pooled and evaporated in vacuo to give the title compound (1.26g). R_f (2%MeOH/ CHCl₃) 0.85.

- 20 b) Preparation of iodomethyl (1,3-di-(N-benzyloxycarbonyl)-L-valyloxy)-2-propyl carbonate.

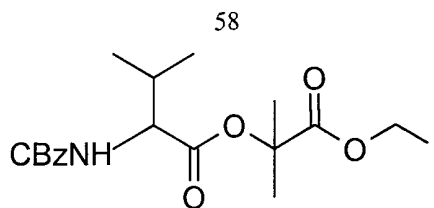
Chloromethyl (1,3-di-(N-benzyloxycarbonyl)valyloxy)-2-propyl carbonate was converted to iodide by the method described in Example A-I-1, step e) to give the title compound (1.37 g) practically pure. R_f (2%MeOH/CHCl₃) 0.85.

25

¹H-NMR (CDCl₃): 7.34 (s, 10H), 5.93 (d, 1H), 5.89 (d, 1H), 5.21 (m, 3H), 5.11 (s, 4H), 4.50-4.17 (m, 6H), 2.12 (m, 2H), 0.97 (d, 6H), 0.88 (d, 6H).

Example A-I-4

- 30 Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)isobutyrate.



a) 4-Methoxybenzyl 2-hydroxyisobutyrate.

2-hydroxy isobutyric acid (1.56 g) was esterified by alkylation with 4-methoxybenzyl chloride by the method described in Example A-I-1, step a). The title compound (2.65 g) was obtained after silica gel column chromatography (0, 1, 2% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.45.

b) 4-Methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate.

4-methoxybenzyl 2-hydroxyisobutyrate was acylated with N-benzyloxycarbonyl-L-valine by the method described in Example A-I-1, step b). The title compound (3.21 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.70.

c) 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyric acid.

4-methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate was de-esterified by the method described in Example A-I-1 step c). The title compound (2.01 g) was obtained after silica gel column chromatography (2, 10, 20% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.30.

$^1\text{H-NMR}$ (CDCl_3): 7.32 (s, 5H), 5.33 (d, 1H), 5.10 (s, 2H), 4.31 (d,d, 1H), 2.22 (m, 1H), 1.57 (s, 6H), 0.98 (d, 3H), 0.89 (d, 3H).

d) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate.

2-(N-benzyloxycarbonyl-L-valyloxy) isobutyric acid was esterified by the method described in Example A-I-1, step d). The title compound (1.90 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.80.

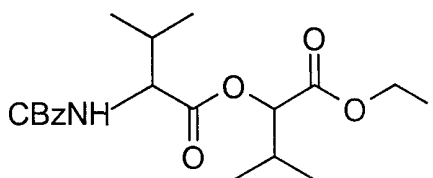
e) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate.

Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (2.32 g) practically pure. R_f (2%MeOH/ CHCl_3) 0.80.

- 5 $^1\text{H-NMR}$ (CDCl_3): 7.33 (s, 5H), 5.89 (s, 2H), 5.22 (d, 1H), 5.11 (s, 2H), 4.29 (d,d, 1H), 2.21 (m, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.00 (d, 3H), 0.93 (d, 3H).

EXAMPLE A-I-5

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate.



10

- a) 4-Methoxybenzyl 2-hydroxy-3-methyl-(S)-(+)-butyrate.

2-hydroxy-3-methyl-(S)-(+)-butyric acid (1.77 g) was esterified by alkylation with 4-methoxybenzyl chloride by the method described in Example A-I-1, step a. The title compound (3.10 g) was obtained after silica gel column chromatography (0, 1, 2% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.50.

15

- b) 4-Methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

- 20 4-Methoxybenzyl 2-hydroxy-3-methyl-(S)-(+)-butyrate was acylated with N-benzyloxycarbonyl-L-valine by the method described in Example A-I-1, step b. The title compound (5.74 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.70.

- 25 c) 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyric acid. 4-methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate was de-esterified by the method described in Example A-I-1, step c. The title compound (3.41 g) was obtained after silica gel column chromatography (2, 10, 20% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.45.

30

¹H-NMR (CDCl₃): 7.36 (s, 5H), 5.38 (d, 1H), 5.11 (s, 4H), 4.90 (d, 1H), 4.41 (d,d, 1H), 2.28 (m, 2H), 1.04-0.89 (m, 12H).

d) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyric acid was esterified by the method described in Example A-I-1, step d. The title compound (2.96 g) was obtained after silica gel column chromatography (0, 1, 2% ethanol in dichloromethane). R_f (2%MeOH/CHCl₃) 0.85.

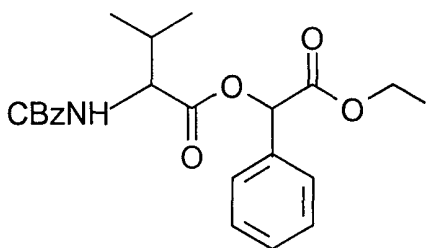
e) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (3.64 g) practically pure. R_f (2%MeOH/CHCl₃) 0.85.

¹H-NMR (CDCl₃): 7.36 (s, 5H), 6.00 (d, 1H), 5.83 (d, 1H), 5.28 (d, 1H), 5.11 (s, 4H), 4.83 (d, 1H), 4.41 (d,d, 1H), 2.29 (m, 2H), 1.05-0.90 (m, 12H).

20 EXAMPLE A-I-6

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate.



a) 4-Methoxybenzyl 2-hydroxy-2-phenyl-DL-acetate.

DL-mandelic acid (2.28 g) was esterified by alkylation with 4-methoxybenzyl

chloride by the method described in Example A-I-1, step a. The title compound (3.69 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/CHCl₃) 0.55.

b) 4-Methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate.

4-Methoxybenzyl 2-hydroxy-2-phenyl-DL-acetate was acylated with N-benzyloxycarbonyl-L-valine by the method described in Example A-I-1, step b. The title compound (6.50 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.75.

c) 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetic acid.

4-Methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate was de-esterified by the method described in Example A-I-1, step c. The title compound (4.75 g) was obtained after silica gel column chromatography (2, 10, 20% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.40.

$^1\text{H-NMR}$ (CDCl_3): 7.36 (m, 10H), 5.91 (d, 1H), 5.27 (m, 1H), 5.04 (s, 2H), 4.57-4.40 (2xd,d, 1H), 2.30 (m, 1H), 1.01-0.82 (m, 6H).

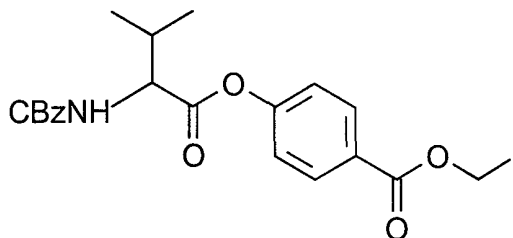
d) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate.

2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetic acid was esterified by the method described in Example A-I-1, step d. The title compound (1.69 g) was obtained after silica gel column chromatography (0, 1, 2% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.80.

e) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate. Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (1.89 g) practically pure. R_f (2%MeOH/ CHCl_3) 0.80.

$^1\text{H-NMR}$ (CDCl_3): 7.36 (m, 10H), 5.94-5.82 (m, 3H), 5.28 (m, 1H), 5.10 (s, 2H), 4.46 (m, 1H), 2.21 (m, 1H), 1.08-0.85 (m, 6H).

Example A-I-7

Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate.

a) 4-Methoxybenzyl 4-hydroxybenzoate.

4-Hydroxybenzoic acid (1.38 g) was esterified by alkylation with 4-methoxybenzyl chloride by the method described in Example A-I-1, step a. The title compound (2.06 g) was obtained after silica gel column chromatography (0, 1, 2, 3% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.40.

b) 4-Methoxybenzyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate.

4-Methoxybenzyl 4-hydroxybenzoate was acylated with N-benzyloxycarbonyl-L-valine by the method described in Example A-I-1, step b. The title compound (2.71 g) was obtained after silica gel column chromatography (0, 1% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.70.

c) 4-(N-benzyloxycarbonyl-L-valyloxy) benzoic acid.

4-Methoxybenzyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate was de-esterified by the method described in Example A-I-1, step c. The title compound (1.86 g) was obtained after silica gel column chromatography (2, 10, 20% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.20.

$^1\text{H-NMR}$ (CDCl_3): 8.15 (d, 2H), 7.34 (m, 5H), 7.22 (d, 2H), 5.38 (d, 1H), 5.17 (s, 2H), 4.58 (d,d, 1H), 2.34 (m, 1H), 1.12 (s, 3H), 0.96 (d, 3H).

d) Chloromethyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate.

4-(N-benzyloxycarbonyl-L-valyloxy) benzoic acid was esterified by the method described in Example A-I-1, step d. The title compound (0.95 g) was obtained after silica gel column chromatography (0, 1% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.80.

e) Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate.

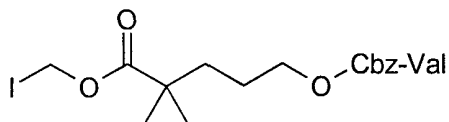
Chloromethyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (1.16 g) practically pure. R_f (2%MeOH/ CHCl_3) 0.80.

5

$^1\text{H-NMR}$ (CDCl_3): 8.11 (d, 2H), 7.35 (m, 5H), 7.21 (d, 2H), 6.15 (s, 2H), 5.32 (d, 1H), 5.14 (s, 2H), 4.55 (d,d, 1H), 2.34 (m, 1H), 1.10 (s, 3H), 1.03 (d, 3H).

Example A-1-8

10 Iodomethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate



a) 4-Methoxybenzyl 2,2-dimethyl-4-pentenoate

To a solution of 2,2-dimethyl-4-pentenoic acid (11.5 g, 90 mmol) in DMF (250 mL) at room temperature, was added potassium tert-butoxide (11.1 g, 99 mmol). The reaction mixture was stirred at 60 °C for 1h. 4-Methoxybenzyl chloride (16.9 g, 108 mmol) was added and the reaction mixture was stirred at 60 °C for 4h. The DMF was evaporated under vacuum, the residue was dissolved in ether (500 mL) and washed with water (3 x 200 mL). The organic phase was dried with Na_2SO_4 and evaporated to give 21.4 g of 4-methoxybenzyl 2,2-dimethyl-4-pentenoate.

20

b) 4-Methoxybenzyl 5-hydroxy-2,2-dimethylvalerate.

A mixture of 4-methoxybenzyl 2,2-dimethyl-4-pentenoate (9.50 g, 38 mmol) and 9-BBN (115 mL, 57 mmol, 0.5 M in THF) was stirred at 60 °C for 60 min, whereupon the reaction mixture was cooled to -5 °C. H_2O (35 mL) was added, the reaction mixture was stirred for 5 min at -5 °C, an aqueous solution of NaOH (35 mL, 3M) was added and the reaction mixture was stirred for a further 10 min at -5 °C. An aqueous solution of H_2O_2 (35 mL, 30%) was added dropwise and the temperature of the reaction mixture was allowed to assume room temperature, whereupon the reaction mixture was stirred for 30 min at room temperature. After evaporation, water (200 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (5 x 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under

30

reduced pressure. The crude product was column chromatographed (silica gel, 1→8% MeOH in CH₂Cl₂), to give 6.32 g of 4-methoxybenzyl 5-hydroxy-2,2-dimethylvalerate.

5 c) 4-Methoxybenzyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate.

To a mixture of DCC (9.41 g, 46 mmol), DMAP (0.586 g, 4.8 mmol) and N-CBz-L-valine (12.1 g, 48 mmol) in CH₂Cl₂ (200 mL) at 0 °C, was added dropwise a solution of 4-methoxybenzyl 5-hydroxy-2,2-dimethyl-valerate (6.40 g, 24 mmol) in CH₂Cl₂ (50 mL). After 1h at 0 °C, the temperature of the reaction mixture was allowed to
10 assume room temperature and then the mixture was stirred for 5h at room temperature. The mixture was filtered through a glass filter and the solvent was removed under reduced pressure. The crude product was column chromatographed (silica gel, 1→4% MeOH in CH₂Cl₂), to give 8.61 g 4-methoxybenzyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate.

15

d) 5-(N-CBz-L-valyloxy)-2,2-dimethylvaleric acid.

To a solution of 4-methoxybenzyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate (8.24 g, 16.5 mmol) in CH₂Cl₂ (100 mL) at room temperature, was added trifluoroacetic acid (5 mL). After 1h at room temperature, the reaction mixture was concentrated
20 under reduced pressure. The crude product was column chromatographed (silica gel, 3→5% MeOH in CH₂Cl₂), to give 6.00 g of 5-(N-CBz-L-valyloxy)-2,2-dimethylvaleric acid.

¹H-NMR (CDCl₃): 10.94 (br s, 1H), 7.35 (s, 5H), 5.45 (d, 1H), 5.11 (s, 2H), 4.30
25 (dd, 1H), 4.21-4.00 (m, 2H), 2.28-2.07 (m, 1H), 1.68-1.51 (m, 4H), 1.21 (s, 6H), 0.97 (d, 3H), 0.89 (d, 3H).

e) Chloromethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate.

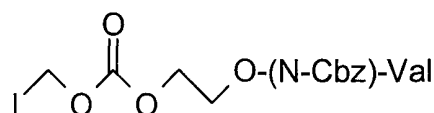
To a solution of 5-(N-CBz-L-valyloxy)-2,2-dimethylvaleric acid (5.88 g, 15.5 mmol)
30 in dioxane (100 mL), was added dropwise a 40% aqueous solution of tetrabutylammonium hydroxide (10.1 g). After stirring for 5 min, the solution was evaporated to dryness through co-evaporation with dioxane and toluene. The residue

was dissolved in dichloromethane (100 mL) and then chloriodomethane (11.3 mL, 155 mmol) was added and the solution was stirred for 6h at room temperature. The solution was concentrated under reduced pressure and the residue was shaken with hexane / ethyl acetate (1:1 v/v, 200 mL). The yellow crystalline solid was filtered off and the filtrate was washed with aqueous solution of sodium thiosulfate (0.1 M) and the filtered through anhydrous sodium sulfate and evaporated to dryness. The residue was column chromatographed (silica gel, 1-4% MeOH in CH₂Cl₂), to give 3.95 g of chloromethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate.

- 10 f) Iodomethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate.
To a solution of chloromethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate (3.85 g, 9 mmol) in acetonitrile (50 mL), was added sodium iodide (5.40 g, 36 mmol). The solution was stirred for 4 h at 60 °C. The resulting suspension was filtered and the filtrate was evaporated. The residue was dissolved in CH₂Cl₂ and washed with
15 aqueous sodium thiosulfate (0.1 M). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 1% MeOH in CH₂Cl₂), to give 4.26 g of iodomethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate
- 20 ¹H-NMR (CDCl₃): 7.34 (s, 5H), 5.90 (s, 2H), 5.32 (d, 1H), 5.10 (s, 2H), 4.29 (dd, 1H), 4.18-4.02 (m, 2H), 2.26-2.08 (m, 1H), 1.65-1.50 (m, 4H), 1.17 (s, 6H), 0.97 (d, 3H), 0.89 (d, 3H).

Example A-1-9

25 2-(N-CBz-L-valyloxy)-ethyl iodomethyl carbonate



a) 2-(N-CBz-L-valyloxy)-ethanol

- To a mixture of DCC (11.4 g, 55 mmol), DMAP (0.611 g, 5 mmol) and ethyleneglycol (55.8 mL, 1 mol) in CH₂Cl₂ (300 mL) at 0 °C, was added dropwise a
30 solution of N-CBz-L-valine (12.6 g, 50 mmol) in CH₂Cl₂ (100 mL). After 1h at 0 °C, the temperature of the reaction mixture was allowed to assume room temperature and

then the mixture was stirred for 5h at room temperature. The mixture was filtered through a glass filter and the solvent was removed under reduced pressure. The crude product was column chromatographed (silica gel, 5→10% MeOH in CH₂Cl₂), to give 12.0 g 2-(N-CBz-L-valyloxy)-ethanol.

5

b) 2-(N-CBz-L-valyloxy)-ethyl chloromethyl carbonate.

To a mixture of 2-(N-CBz-L-valyloxy)-ethanol (12.0 g, 40.6 mmol) and pyridine (19.7 mL, 0.24 mmol) in CH₂Cl₂ (300 mL) at 0 °C, was added dropwise chloromethyl chloroformate (10.5 g, 81.2 mmol). After 30 min at 0 °C, the reaction mixture was washed with H₂O (200 mL). The H₂O phase was washed with CH₂Cl₂ (100 mL) and the solvent of the combined organic phases was removed under reduced pressure. The crude product was column chromatographed (silica gel, 0.5→1% MeOH in CH₂Cl₂), to give 8.26 g 2-(N-CBz-L-valyloxy)-ethyl chloromethyl carbonate.

15

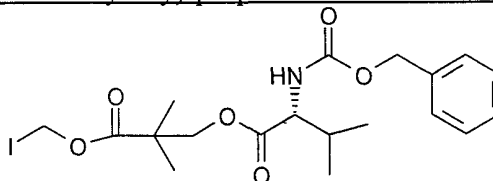
c) 2-(N-CBz-L-valyloxy)-ethyl iodomethyl carbonate.

To a solution of 2-(N-CBz-L-valyloxy)-ethyl chloromethyl carbonate (3.88 g, 10 mmol) in acetonitrile (50 mL), was added sodium iodide (7.50 g, 50 mmol). The solution was stirred for 4 h at 60 °C. The resulting suspension was filtered and the filtrate was evaporated. The residue was dissolved in CH₂Cl₂ and washed with aqueous sodium thiosulfate (0.1 M). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure, to give 4.51 g 2-(N-CBz-L-valyloxy)-ethyl iodomethyl carbonate.

25 ¹H-NMR (CDCl₃): 7.34 (s, 5H), 5.93 (s, 2H), 5.26 (d, 1H), 5.11 (s, 2H), 4.48-4.26 (m, 5H) 2.28-2.10 (m, 1H), 0.97 (d, 3H), 0.90 (d, 3H).

Example A-I-10

2,2-dimethyl-3-(N-CBz-D-valyloxy)-propionic acid iodomethyl ester



30

a) 2,2-dimethyl-3-(N-CBz-D-valyloxy)-propionic acid.

To a solution of 2,2-dimethyl propionic acid 4-methoxybenzyl ester (4.7 g, 20 mmole) and N-CBz-D-valine (5.5 g, 22 mmole) in dichloromethane (100 ml) were added 4-dimethylaminopyridine (305 mg, 2.5 mmole) and DCC (5.15 g, 25 mmole). After 18 hr, the solution was washed successively with sodium bicarbonate aqueous solution, citric acid solution and water. The organic phase was dried and the residue was dissolved in dichloromethane (100 ml). To the solution was added trifluoroacetic acid (10 ml). After 3 hr, it was evaporated and the product was isolated with silica gel column chromatography. 4.5 g.

¹H-NMR (CDCl₃): 7.36 (m, 5 H) 5.11 (s, 2H) 4.30 (m, 1H) 4.18 (dd, 2H) 2.17 (m, 1H), 1.23 (d, 6 H) 0.93 (m, 6H).

b) 2,2-dimethyl-3- (N-CBz-D-Valyloxy)-propionic acid chloromethyl ester.

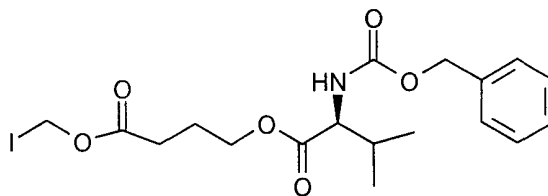
(2,2-dimethyl-3-(N-CBz-D-valyloxy)-propionic acid (4.5 g, 12.8 mmole) was dissolved in dioxane (20 ml). To the solution was added tetrabutylammonium hydroxide aqueous solution (40 %, 8.3 ml, 12.8 mmole). The solution was dried in vacuo, and it was coevaporated with toluene several times. The residue was dissolved in methylene chloride and then chloriodomethane (18 ml, 260 mmole) was added to the solution. After 18 hr, the reaction solution was evaporated and the product was isolated with silica gel column chromatography. 3.5 g.

c) 2,2-dimethyl-3-(N-CBz-D-valyloxy)-propionic acid iodomethyl ester.

2,2-Dimethyl-3-(N-CBz-D-valyloxy)-propionic acid chloromethyl ester (2.4 g, 6 mmole) was dissolved in acetonitrile (30 ml). Sodium iodide (1.26 g, 8.4 mmole) was added to the solution. After reaction at 70° C for 2 hr, the reaction mixture was filtered and the residue was dissolved in methylene chloride (20 ml) and refiltered. The solution was dried and gave the titled product. 2.68g.

¹H-NMR (CDCl₃): 7.36 (m, 5 H) 5.90 (dd, 2H) 5.26 (d, 1H) 5.11 (s, 2H) 4.31 (m, 1H) 4.15 (dd, 2H) 2.18 (m, 1H) 1.22 (d, 6H) 0.92 (m, 6H).

Example A-1-11

4-(N-CBz-L-valyloxy) butyric acid iodomethyl ester

5 a) 4-(N-CBz-L-valyloxy) butyric acid t-butyl ester.

N-CBz-L-valine (16.25 g, 65 mmole) was dissolved in DMF (40 ml). To the solution was added potassium t-butoxide (7.24 g, 65 mmole). After 10 min, 4-bromobutyric acid t-butyl ester (12 g, 53 mmole) was added. The reaction mixture was kept at 65° C for 2.5 hr and then poured into sodium bicarbonate aqueous solution and extracted
10 with dichloromethane. The organic phase was dried and the product was isolated with silica gel column chromatography. 20.1 g.

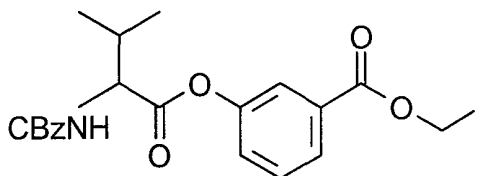
b) 4-(N-CBz-L-valyloxy)butyric acid chloromethyl ester.
4-(N-CBz-L-valyloxy) butyric acid t-butyl ester (20 g, 50.8 mmole) was treated with
15 trifluoroacetic acid (30 ml) at 0° C for 3 h and then evaporated. The residue was coevaporated with toluene several time. The intermediate acid (2.56 g, 7.6 mmole) was dissolved in dioxane (10 ml) and to the solution was added tetrabutylammonium hydroxide (40 %, 4.66 ml, 7.2 mmole). The solution was dried and dissolved in dichloromethane (20 ml) and then chloriodomethane (10 ml, 144 mmole) was added
20 to the solution. After 18 hr, the reaction solution was evaporated and the product was isolated with silica gel column chromatography. Yield 2.1 g.

c) 4-(N-CBz-L-valyloxy)butyric acid iodomethyl ester.
4-(N-CBz-L-valyloxy) butyric acid chloromethyl ester (1.54 g, 4 mmole) was
25 dissolved in acetonitrile (15 ml). Sodium iodide (840 mg, 5.6 mmole) was added to the solution. After reaction at 55° C for 3 hr, the reaction mixture was filtered and the residue was dissolved in methylene chloride (20 ml) and refiltered. The solution was dried and gave the titled product. Yield 1.9 g.

¹H-NMR (CDCl₃): 7.36 (m, 5H) 5.90 (dd, 2 H) 5.25 (d, 1H) 5.11 (s, 2H) 4.29 (dd, 1H) 4.18 (t, 2H) 2.43 (t, 2H) 2.20 (m, 1H) 2.00 (m, 2H) 0.93 (dd, 6 H).

Example A-I-12

5 Iodomethyl 3-(N-benzyloxycarbonyl-L-valyloxy)-benzoate



a) 4-Methoxybenzyl 3-hydroxybenzoate.

To a solution of 3-hydroxybenzoic acid (6.9g, 50 mmole) in DMF (100 ml) was added potassium-tert.-butoxide (6.17 g, 55 mmole) and the mixture was stirred at room temperature for one hour. 4-Methoxybenzyl chloride (9.4g, 60 mmole) was added and the mixture was stirred for 16 hours at 60°C. The mixture was evaporated under reduced pressure and ethyl acetate (250 ml) were added. The organic phase was washed five times with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone. Yield: 10.5g = 81%

b) 4-Methoxybenzyl 3-(N-benzyloxycarbonyl-L-valyloxy) benzoate.

To a cooled solution of 4-methoxybenzyl 3-hydroxybenzoate (7.7g, 29.8 mmole), 4-dimethylaminopyridine (0.73g, 6 mmole) and N-benzyloxycarbonyl-L-valine (8.3g, 33 mmole) in 100 ml dichloromethane was added dicyclohexyl-carbodiimide (7.22g, 35 mmole) and the mixture was stirred for 2 days at room temperature. The mixture was cooled and the urethane was filtered. The solution was evaporated and ethyl acetate (250 ml) was added. The organic phase was washed twice with 5% acetic acid; 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 13.9g = 94%

c) 3-(N-benzyloxycarbonyl-L-valyloxy) benzoic acid.

To a solution of 4-methoxybenzyl-3-(N-benzyloxycarbonyl-L-valyloxy)-benzoate (13.7g, 27.8 mmole) in dichloromethane (150 ml) was added trifluoroacetic acid (20 ml) and the mixture was stirred for 2 hours at room temperature. The solution was evaporated under reduced pressure and the product crystallized from toluene. Yield:

5 10.1g = 87%.

¹H-NMR (DMSO d-6) 1.01 (m, 6H) 2.21 (m, 1H) 4.17 (d, d, 1H) 5.08 (s, 2H)
7.28-7.96 (m, 10H)

10 d) Chloromethyl 3-(N-benzyloxycarbonyl-L-valyloxy)-benzoate.

To a solution of 3-(N-benzyloxycarbonyl-valyloxy)benzoic acid (7.42g, 20 mmole) in 1,4-dioxane (100 ml) was added a 40% solution of tetrabutylammonium hydroxide (12.97g, 20 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated
15 two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in dichloromethane (50 ml) and chloriodomethane (35.3g, 200 mmole) was added. The solution was stirred for two days at room temperature and evaporated under reduced pressure. Ethyl acetate (100 ml) was added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced
20 pressure: The product was isolated by silica gel column chromatography. Yield: 3.8g = 45%.

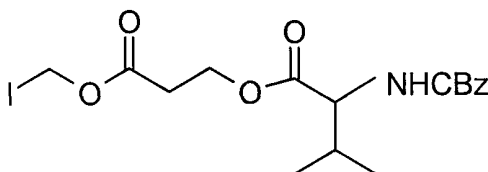
e) Iodomethyl 3-(N-benzyloxycarbonyl-L-valyloxy)-benzoate.

To a solution of chloromethyl 3-(N-benzyloxycarbonyl-L-valyloxy)-benzoate (2.0g, 4.76 mmole) in dry acetone (30 ml) was added sodium iodide (3.15g, 21 mmole) and
25 the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl acetate/water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield: 2.3g = 94%.

30

¹H-NMR (CDCl₃) 1.02 (m, 6H) 2.38 (m, 1H) 4.56 (d, d, 1H) 5.14 (s, 2H) 5.30 (d, 1H) 6.14 (s, 2H) 7.26-7.50 (m, 7H) 7.80(s, 1H) 7.96 (d, 1H)

Example A-I-13

Iodomethyl 3-(N-benzyloxycarbonyl-L-valyloxy)-propionate

a) 3-buten-1-yl-3-(N-benzyloxycarbonyl)-propionate.

- 5 To a solution of 3-buten-1-ol (2.16g, 30 mmole), N-benzyloxycarbonyl-L-valine (8.29g, 33 mmole) and 4-dimethylaminopyridine (0.37g, 3 mmole) in dichloromethane (80 ml) was added dicyclohexyl-carbodiimide (7.22g, 35 mmole) and the mixture was stirred overnight at room temperature. The mixture was cooled and the urethane was filtered. The solution was evaporated under reduced
- 10 pressure and ethyl acetate (200 ml) was added. The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 8.3g = 90%.

15

b) 3-(N-benzyloxycarbonyl-L-valyloxy)-propanoic acid.

- To a solution of 3-buten-1-yl-3-(N-benzyloxycarbonyl-L-valyloxy)-propionate (9.2g, 30 mmole) in 150 ml benzene was added tetrabutylammonium bromide
- 20 (1.62g, 5 mmole) and 100 ml water. The mixture was cooled to about 5°C and potassium permanganate (14.82g, 90 mmole) was added in portions. The mixture was stirred 2 hours at room temperature, diluted with water and decolorized by the addition of sodium bisulfite. The mixture was acidified with 2M hydrogen chloride and extracted 3 times with ethyl acetate. The combined organic phases were
- 25 washed with water and dried with sodium sulfate. The solution was evaporated under reduced pressure and the product isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 5.4g = 55%.

- ¹H-NMR (DMSO d-6) 0.90 (m, 6H) 2.5 (m, 2H) 3.88 (d, d, 1H) 4.32 (m, 2H) 5.03
- 30 (s, 2H) 7.36 (m, 5H) 7.68 (d, 1H)

c) Chloromethyl 3-(N-benzyloxycarbonyl-L-valyloxy)-propionate.

To a solution of 3-(N-benzyloxycarbonyl-L-valyloxy)propanoic acid (5.2g, 16.08 mmole) in 1,4-dioxane (50 ml) was added a 40% solution of tetrabutylammonium hydroxide (10.43g, 16.08 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in 40 ml dichloromethane and chloriodomethane (28.4g, 160 mmole) was added. The solution was stirred for two days at room temperature and evaporated under reduced pressure. Ethyl acetate (100 ml) was added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 2.2g = 35%

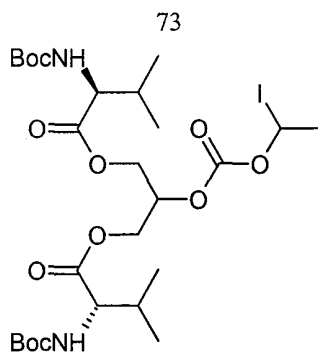
d) Iodomethyl 3-(N-benzyloxycarbonyl-L-valyloxy)-propionate.

To a solution of chloromethyl 3-(N-benzyloxycarbonyl-L-valyloxy)-propionate (2.05g, 5.51 mmole) in dry acetone (50 ml) was added sodium iodide (4.12g, 27.5 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl acetate water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield: 2.35g = 92%.

¹H-NMR (CDCl₃) 0.94 (m, 6H) 2.17 (m, 1H) 2.68 (t, 2H) 4.40 (m, 3H) 5.12 (s, 2H) 5.91 (s, 2H) 7.26 (m, 5H).

Example A-I-13A

1,3-bis(N-tert-butoxycarbonyl-L-valyloxy)-2-propyl 1-iodoethyl carbonate

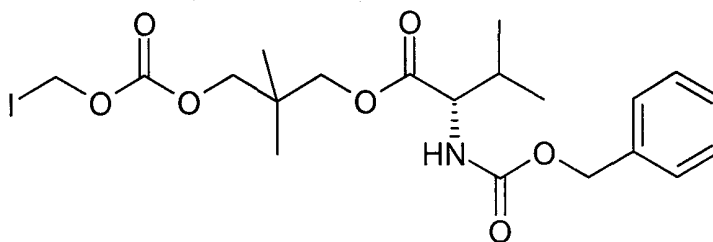


a) 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl 1-chloroethyl carbonate.
 To a solution of 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propanol (0.545 g,
 1.11 mmol) in 5 mL dry CH₂Cl₂ were added pyridine (540 μL, 6.68 mmol), with
 5 cooling and stirring in an ice bath, followed by 1-chloroethyl chloroformate (242 μL,
 2.22 mmol). After 1 h, the reaction mixture was diluted with 5 mL CH₂Cl₂ and
 washed with water (5 mL) and brine (5 mL). The organic phase was dried over
 anhydrous Na₂SO₄ and concentrated on a rotavapor, coevapoating several times with
 toluene. Column chromatography (silica, 4/1 petroleum ether - ethyl acetate) gave the
 10 chloride (596 mg, 90%) as a white solid.

b) 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl 1-iodoethyl
 carbonate.
 A mixture of the chloride (596 mg, 1.0 mmol) from step (a) and NaI (684 mg, 4.57
 15 mmol) in 10 ml dry MeCN was refluxed at 80 °C for 4 h. The reaction mixture was
 concentrated under vacuum and then partitioned between 30 mL diethyl ether and 10
 mL water. The organic phase was washed with 5% aqueous sodium thiosulfate (2 x 5
 mL), and the last aqueous layer was reextracted with ether (5 mL). The organic
 phases were combined, washed with brine, dried over Na₂SO₄, and concentrated.
 20 Flash column chromatography (silica, 4/1 petroleum ether – ethyl acetate) gave a
 fraction (275 mg) containing 80% iodide, as determined from ¹H NMR, and small
 amounts of the starting chloride and alkene from the elimination side reaction.

¹H NMR (250 MHz, CDCl₃) δ 0.81-0.85 (m, 6H), 0.88-0.92 (m, 6H), 1.37 (s, 18H),
 25 2.05 (m, 2H), 2.17 (d, 3H, *J* = 6.1 Hz), 4.12-4.46 (m, 6H), 5.00 (d, 2H, *J* = 8.8 Hz),
 5.11 (m, 1H), 6.68 and 6.69 (2 sets of q, 1H, *J* = 6.1 Hz).

Example A-I-14

3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethylpropyl iodomethyl carbonate(a) 3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethyl-1-propanol.

- 5 A mixture of *N*-benzyloxycarbonyl-L-valine (2.50 g, 10.0 mmol), 2,2-dimethyl-1,3-propanediol (5.30 g, 50.9 mmol), dicyclohexylcarbodiimide (2.60 g, 12.6 mmol), and 4-dimethylaminopyridine (125 mg, 1.0 mmol) in 100 mL dry CH₂Cl₂ was stirred for 23 h. The reaction mixture was filtered and washed successively with 50 mL each of water, saturated aqueous NH₄Cl, saturated aqueous NaHCO₃, and water. The organic
10 phase was dried over anhydrous Na₂SO₄ and concentrated. The title compound (2.99 g, 87%) was isolated by flash column chromatography (silica, 2/1 petroleum ether – ethyl acetate) as a white waxy solid.

(b) 3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethylpropyl chloromethyl carbonate.

- 15 Chloromethyl chloroformate (1.50 mL, 16.6 mmol) was added to a solution of the alcohol (2.74 g, 8.12 mmol) from step (a) and pyridine (4.9 mL, 61 mmol) in 40 mL dry CH₂Cl₂, in an ice bath. After stirring for 1 h, the mixture was diluted with CH₂Cl₂ and washed successively with water, saturated NaHCO₃, and brine. The organic
20 phase was dried over anhydrous Na₂SO₄ and concentrated, coevaporating several times with toluene on a rotavapor. Flash column chromatography (silica, 2/1 petroleum ether – ethyl acetate) gave 3.31 g (95%) of the title compound.

(c) 3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethylpropyl iodomethyl carbonate.

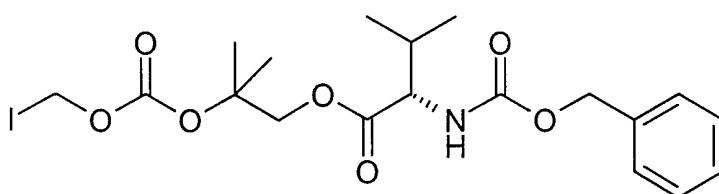
- 25 A mixture of the chloride (3.14 g, 7.30 mmol) from step (b) and NaI (4.37 g, 29.2 mmol) in 73 mL dry MeCN was refluxed at 80 °C for 3 h. After removal of solvent under vacuum, the mixture was partitioned between 80 mL ethyl acetate and 40 mL water. The organic phase was washed with 5% Na₂S₂O₃, and then brine, dried over

anhydrous Na_2SO_4 , and concentrated. Flash column chromatography (silica, petroleum ether – ethyl acetate) gave 3.68 g (97%) of the title compound.

^1H NMR (250 MHz, CDCl_3) δ 0.88 and 0.96 (2d, 3H each), 0.98 (s, 6H), 2.18 (m, 1H), 3.94 and 4.02 (2s, 2H each), 4.32 (dd, 1H, $J = 9.0, 4.7$ Hz), 5.11 (s, 2H), 5.26 (d, 1H), 5.92 and 5.93 (ABq, 2H, $J_{AB} = 5.1$ Hz), 7.35 (s, 5H).

Example A-I-15

1-(*N*-benzyloxycarbonyl-L-valyloxy)-2-methyl-2-propyl iodomethyl carbonate



10

(a) 1-(*N*-benzyloxycarbonyl-L-valyloxy)-2-methyl-2-propanol

N-Benzyloxycarbonyl-L-valine (2.02 g, 8.0 mmol), 4-dimethylaminopyridine (100 mg, 0.8 mmol), and), and dicyclohexylcarbodiimide (2.04 g, 9.9 mmol, in 20 mL CH_2Cl_2) were added to 2-methyl-1,2-propanediol (12.2 mmol) in 30 mL dry CH_2Cl_2 , with cooling in an ice bath. DMF (5 mL) was added. After stirring for 5 h at 10 °C , the reaction mixture was filtered, concentrated, and then redissolved in ethyl acetate. The organic solution was washed with saturated NaCl, dried over anhydrous Na_2SO_4 , and concentrated. Flash column chromatography (silica, 2/1 petroleum ether – ethyl acetate) gave 2.3 g of the title compound.

20

(b) 1-(*N*-benzyloxycarbonyl-L-valyloxy)-2-methyl-2-propyl chloromethyl carbonate.

All of the alcohol from above was dissolved in 35 mL dry CH_2Cl_2 and cooled in an ice bath. Pyridine (3.50 mL, 43.4 mmol) was added, followed by chloromethyl chloroformate (1.30 mL, 14.4 mmol). After 1 h, the ice bath was removed and stirring was continued for 2 h at ambient temperature. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (50 mL), and then brine (2 x 25 mL). Drying over anhydrous Na_2SO_4 of the combined organic phases and concentration under vacuum, coevaporating several times with toluene, gave a yellow-brown oil that was subjected to flash column chromatography (silica, 2/1 petroleum ether – ethyl

30

acetate) to yield 2.86 g (86% from *N*-benzyloxycarbonyl-L-valine) of the title compound.

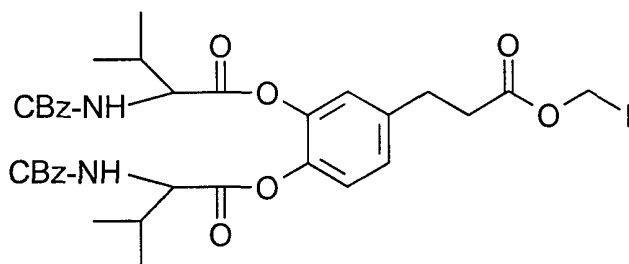
- (c) 1-(*N*-benzyloxycarbonyl-L-valyloxy)-2-methyl-2-propyl iodomethyl carbonate.

A mixture of the chloride (2.84 g, 6.84 mmol) from step (b) and NaI (4.15 g, 27.2 mmol) in 68 mL dry acetonitrile was refluxed at 75 °C for 4 h. After evaporation of solvent under vacuum, the residue was partitioned between ethyl acetate (80 mL) and water (40 mL), and the organic layer was washed with 5% Na₂S₂O₃ (15 mL) and brine (25 mL). Drying the organic phase over anhydrous Na₂SO₄ and concentration gave a yellow oil that was subjected to flash column chromatography (silica, 2/1 petroleum ether - ethyl acetate) to furnish 3.29 g (95%) of the title compound.

¹H NMR (250 MHz, CDCl₃) δ 0.90 and 0.94 (2d, 3H each, *J* = 6.8 Hz), 1.52 (s, 6H), 2.17 (m, 1H), 4.35 (m, 1H), 4.22 and 4.39 (ABq, 2H, *J*_{AB} = 11.7 Hz), 5.10 (s, 2H), 5.30 (d, 1H), 5.86 (s, 2H), 7.34 (s, 5H)

Example A-I-16

Iodomethyl 3,4-di-(*N*-CBZ-L-valyloxy)hydrocinnamate



20

- a) 4-Methoxybenzyl-3,4-dihydroxyhydrocinnamate.

3,4-Dihydroxycinnamic acid (6.5 g, 35.7 mmol) was dissolved in DMF (50 ml) and cooled to 0°C on an ice-bath. 4-Potassium tert-butoxide (35.7 mmol), was then added and the mixture was left for approximately 30 min at 0°C, followed by dropwise addition of 4-methoxy-benzylchloride (39 mmol) in DMF (25 ml). The mixture was allowed to reach room temperature and left over-night. The solvent was then evaporated and the crude product was purified by chromatography (ethyl acetate-hexane, 1:1) to give 6 g of the title compound (55%).

25

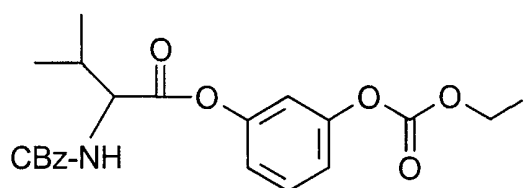
- b) 4-Methoxybenzyl-3,4-di-(N-CBZ-L-valyloxy)hydrocinnamate.
4-Methoxybenzyl-3,4-dihydroxyhydrocinnamate (5 g, 16.5 mmol), *N,N*-dimethylaminopyridine (2g, 16.5 mmol), *N,N'*-dicyclohexyl carbodiimide (8.5 g, 41.3 mmol) and Cbz-L-valine (10.4 g, 41.3 mmol) were dissolved in
5 dichloromethane (50 ml). After 4 h, the mixture was filtered and evaporated onto silica gel and purified by chromatography (hexane-EtOAc, 5:2 → 3:2) to give pure title product (10.1 g, 79 %).
- c) 3,4-Di-(N-CBZ-L-valyloxy)hydrocinnamic acid.
10 4-Methoxybenzyl-3,4-di-(N-CBZ-L-valyloxy)hydrocinnamate (10 g, 13 mmol) was dissolved in dichloromethane and 1,1,1 trifluoroacetic acid (30 ml) and left at ambient temperature for 3.5 h. Evaporation under reduced pressure and purification by chromatography (chloroform-methanol, 10:1) yielded 6.7 g (80%) pure title product.
15 ¹H NMR (CDCl₃, 45 °C): 7.24-7.0 (m, 13H), 5.65 (br s, 1H), 5.55 (br s, 1H), 5.1 (m, 4H), 4.46 (m, 2H), 2.95 (t, 2H), 2.66 (t, 2H), 2.35 (m, 2H).
- d) Chloromethyl 3,4-di-(N-CBZ-L-valyloxy)hydrocinnamate.
3,4-Di-(N-CBZ-L-valyloxy)hydrocinnamic acid (4.2 g, 6.47 mmol) was dissolved in
20 dioxane (70 ml). Tetrabutylammonium hydroxide was added dropwise until pH=8. The solvent was then removed under reduced pressure. The solid was redissolved in dioxane (30 ml) and toluene (30 ml) and evaporated. The procedure was repeated twice (for removal of water). Dichloromethane (60 ml) and chloro-iodomethane was added in one portion and the mixture was left at ambient temperature for 6 h.
25 Evaporation of the solvent and purification by chromatography yielded 1.7 g title product (38%).
- e) Iodomethyl 3,4-di-(N-CBZ-L-valyloxy)hydrocinnamate.
Chloromethyl 3,4-di-(N-CBZ-L-valyloxy)hydrocinnamate (1.9 g, 2.7 mmol) and
30 sodium iodide (2 g, 13.3 mmol) were dissolved in acetonitrile (50 ml) and heated to 65° C for 60 min. The solvent was removed under reduced pressure and the residue was taken up in dichloromethane and filtrated. Removal of the solvent and

purification by chromatography (ethyl acetate-hexane, 2:5) gave pure title product (1.9 g, 90 %)

¹H NMR (CDCl₃, 45 °C): 7.34-7.02 (m, 13H), 5.89 (s, 2H), 5.64 (br s, 2H), 5.14-5.02 (m, 4H), 4.47 (m, 2H), 2.96 (t, 2H), 2.64 (t, 2H), 2.33 (m, 2H), 1.08-0.99 (m, 12H)

Example A-I-17

3-(N-CBZ-L-valyloxy)phenyl iodomethyl carbonate



10 a) 3-(N-CBZ-L-valyloxy)phenol.

CBZ-L-valine (10 g, 40 mmol), 1,3-dihydroxybenzene (8.7g, 79 mmol)

N,N'-dicyclohexylcarbodiimide (10.2g, 44 mmol) and 4-dimethylaminopyridine (2.4 g, 20 mmol) were dissolved in DMF (50 ml) and left at ambient temperature overnight. The reaction mixture was filtered, the solvent removed under reduced

15 pressure and the crude product was taken up in dichloromethane and filtered.

Removal of the solvent followed by purification by chromatography (chloroform-methanol, 10:1) yielded pure title product (10.9 g, 79%).

b) (N-CBZ-L-valyloxy)phenyl chloromethyl carbonate.

20 3-(N-CBZ-L-valyloxy)phenol (5.4 g, 15.7 mmol) was dissolved in dichloromethane (70 ml) and cooled in an ice-bath. Pyridine (1.2 g, 23.5 mmol) was added followed by dropwise addition of 1-chloro-methylchloroformate (2.3 g, 18.8 mmol) in dichloromethane (10 ml). The mixture was left at room temperature for 4 h. Water (25 ml) was then added and the phases were separated. The organic layer was washed

25 with 0.01 M aqueous hydrochloric acid (25 ml). Purification by chromatography (ethyl acetate-hexane, 1:1) gave the title compound (4.5 g, 65 %)

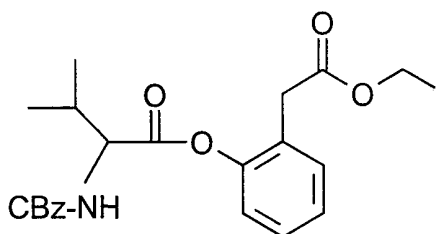
c) 3-(N-CBZ-L-valyloxy)phenyl iodomethyl carbonate.

(N-CBZ-L-valyloxy)phenyl chloromethyl carbonate (1.5g, 3.44 mmol) and sodium iodide (2 g, 13.3 mmol) were stirred at 60°C in acetonitrile (50 ml) for 4.5 h. The mixture was filtered, the solvent removed and the crude product was taken up in 100 ml hexane-ethyl acetate, 1:1, and filtered through a sintered glass funnel, packed with
 5 2 cm silica gel. Removal of the solvent yielded pure title product (1.68 g, 92%)

¹H NMR (CDCl₃, 45 °C): 7.38-7.02 (m, 9H), 6.03 (s, 2H), 5.2 (br s, 1H), 5.14 (s, 2H), 4.48 (m, 1H), 2.30 (m, 1H), 1.09-1.01 (m, 6H)

Example A-I-18

10 Iodomethyl 2-(N-CBZ-L-valyloxy)phenylacetate



a) 4-Methoxybenzyl 2-hydroxyphenylacetate.

2-hydroxyphenylacetic acid (10 g, 66 mmol) was dissolved in *N,N*-dimethylformamide (100 ml) and cooled on ice-bath. Potassium *tert*-butoxide (8.85 g, 78
 15 mmol) was added. The mixture was left for 30 min and allowed to reach room temperature. 4-Methoxy-benzylchloride (11.7 g, 72 mmol) in *N,N*-dimethylformamide (30 ml) was then added dropwise, under nitrogen atmosphere and left over-night. The solvent was evaporated under reduced pressure and the crude mixture was dissolved in ether (100 ml) and washed with water (25 ml), brine and dried over
 20 sodium sulphate. Chromatography (hexane-ethyl acetate, 2:1) followed by recrystallization (hexane-ethyl acetate) gave the title compound (7.6 g, 42%).

b) 4-Methoxybenzyl 2-(N-CBz-L-valyloxy)phenylacetate.

4-Methoxybenzyl 2-hydroxyphenylacetate 3g, 11 mmol), *N,N*-dichlorohexylcarbodiimide (2.7 g, 13.2 mmol), dimethylaminopyridine (0.134 g, 1.1 mmol) and
 25 CBz-L-valine (3.3 g, 13.2 mmol) were dissolved in dichloromethane (50 ml). After the weekend the solid was filtered off, the solvent removed under reduced pressure

and the crude product purified by chromatography (ethyl acetate, hexane, 1:2) to give the title compound (5.2 g, 93%).

c) 2-(N-CBz-L-valyloxy)phenylacetic acid.

- 5 4-Methoxybenzyl 2-(N-CBz-L-valyloxy)phenylacetate (4.25 g, 8.4 mmol), was dissolved in dichloromethane (40 ml). Trifluoroacetic acid (8 ml) was added with cooling on ice. The mixture was allowed to reach room temperature and stirred for 40 min. The solvent was removed under reduced pressure and the crude product was recrystallized twice (hexan-ethyl acetate + a small amount of dichloromethane) to
10 give the title compound (2.6 g, 80 %).

^1H NMR (CDCl_3 , 45 °C): 7.35-7.08 (m, 9H), 5.35 (br s, 1H), 5.13 (s, 2H), 4.48 (m, 1H), 3.57 (s, 2H), 2.33 (m, 1H), 1.08 (d, 3H), 1.02 (d, 3H).

- 15 d) Chloromethyl 2-(N-CBZ-L-valyloxy)phenylacetate.

This compound was prepared in poor yield from 2-(N-CBz-L-valyloxy)phenylacetic acid (5.5 g, 14.3 mmol) by an unoptimized procedure essentially as described in Example A-I-16 d). Yield: 0.265 g

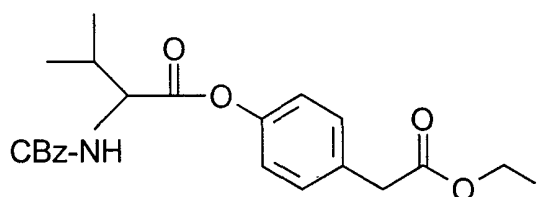
- 20 ^1H NMR (CDCl_3 , 45 °C): 7.28-7.01 (m, 9H), 5.55 (s, 2H), 5.2 (br s, 1H), 5.07 (s, 2H), 4.43 (m, 1H), 3.53 (s, 2H), 2.26 (m, 1H), 1.02 (d, 3H), 0.95 (d, 3H).

e) Iodomethyl 2-(N-CBZ-L-valyloxy)phenylacetate.

- Chloromethyl 2-(N-CBZ-L-valyloxy)phenylacetate is treated with NaI and purified
25 as described in the Examples above to yield the title compound.

Example A-I-19

Iodomethyl 4-(N-CBZ-L-valyloxyxy)phenylacetate



a) 4-Methoxybenzyl 4-hydroxyphenylacetate.

Prepared from 4-hydroxyphenylacetic acid (10 g, 65.7 mmol) in 70 % yield by the same procedure as for Example A-I-18 a) above, but wherein the solvent for the recrystallization was changed to hexane-ether.

5

b) 4-Methoxybenzyl 4-(N-CBz-L-valyloxy)phenylacetate.

Prepared from 4-methoxybenzyl 4-hydroxyphenylacetate (3 g, 11 mmol) by the same procedure as for Example A-I-18 b) in 87 % yield. Solvent for chromatography: ethyl acetate-hexane, 1:2.

10

c) 4-(N-CBZ-L-valyloxy)phenylacetic acid.

Prepared in 82 % yield from 4-methoxybenzyl 4-(N-CBz-L-valyloxy)phenylacetate (1.6 g, 288 mmol) by the procedure described for Example A-I-18 c). Solvent for recrystallization: hexane-ether and a small amount of dichloromethane.

15 ¹H NMR (CDCl₃, 45 °C): 7.36-7.27 (m, 7H), 7.02 (d, 2H), 5.25 (d, 1H), 5.14 (s, 2H), 4.52 (m, 1H), 3.64 (s, 2H), 2.3 (m, 1H), 1.08 (d, 3H), 1.02 (d, 3H).

d) Chloromethyl 4-(N-CBZ-L-valyloxy)phenylacetate.

Prepared from 4-(N-CBZ-L-valyloxy)phenylacetic acid (3 g, 7.8 mmol) in 26 %
20 yield by the same procedure as described for Example A-I-18 d). Solvent for chromatography: hexane-ether, 3:2.

e) Iodomethyl 4-(N-CBZ-L-valyloxy)phenylacetate.

Chloromethyl 4-(N-CBZ-L-valyloxy)phenylacetate (0.83 g, 1.9 mmol) and sodium
25 iodide (1.15 g, 7.6 mmol) were heated in acetonitril (45 ml) for 5 h. The mixture was filtrated, the solvent removed, taken up in dichloromethane and filtrated again. Evaporation and purification by chromatography (ether-hexane, 2:3) yielded the title product (0.8 g, 80 %).

30 ¹H NMR (CDCl₃, 45 °C): 7.38-7.09 (m, 4H), 5.84 (s, 1H), 5.30 (br s, 1H), 5.15 (s, 2H), 4.5 (m, 1H), 3.56 (s, 2H), 2.36 (m, 1H), 1.10 (d, 3H), 1.00 (d, 3H).

Example A-I-20

Iodomethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl) benzoate

a) 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)-toluene.

- 5 To a cooled solution of 4-methylphenylethanol-2 (5.0g, 36.7 mmole), 4-dimethylaminopyridine (0.98g, 8 mmole) and N-benzyloxycarbonyl-L-valine (10.05g, 40 mmole) in dichloromethane (120 ml) was added dicyclohexylcarbodiimide (9.1g, 44 mmole) and the mixture was stirred overnight at room temperature. The mixture was cooled and the urethane was filtered. The solution was
- 10 evaporated under reduced pressure and ethyl acetate (250 ml) was added. The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone. Yield: 13.3g = 97%

- 15 b) 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)- benzoic acid.

To a cooled mixture of chromic anhydride (7.55g, 75 mmole) in acetic acid (100 ml) was added dropwise a solution of 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)-toluene (9.3g, 25.1 mmole) in acetone (50 ml). The mixture was stirred at room temperature for 3 days and reduced to about 100 ml. 600ml 10% sodium chloride

20 solution was added and the mixture was extracted four times with ethyl acetate. The organic phase was washed with brine and dried with sodium sulfate. The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography with dichloromethane/methanol. Yield : 2,1g = 21%.

- 25 ¹H-NMR (CDCl₃) 0.79 (d, 3H) 0.90 (d, 3H) 2.08 (m, 1H) 3.04 (t, 2H) 4.28 (d, 1H) 4.39 (m, 2H) 5.11 (s, 2H) 5.26 (d, 1H) 7.34 (m, 7H) 8.04 (d, 2H)

c) Chloromethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)benzoate.

- To a solution of 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)benzoic acid (2.0g, 5.0
- 30 mmole) in 1,4-dioxane (20 ml) was added a 40% solution of tetrabutylammonium hydroxide (3.1g, 4.75 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and coevaporated

two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in dichloromethane (10 ml) and iodochloromethane (13.2g, 75 mmole) was added. The solution was stirred overnight at room temperature and evaporated under reduced pressure. About 50 ml ethyl acetate were added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 0.5g = 23%

d) Iodomethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl) benzoate.

To a solution of chloromethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl) benzoate (0.5g, 1.11 mmole). In dry acetone (10 ml) was added sodium iodide (0.75g, 5.0 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl acetate/water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield: 0.53g = 88%.

¹H-NMR (CDCl₃) 0.88 (d, 3H) 0.90 (d, 3H) 2.08 (m, 1H) 3.02 (t, 2H) 4.28 (d, d, 1H) 4.38 (m, 2H) 5.10 (s, 2H) 5.22 (d, 1H) 6.15 (s, 2H) 7.35(m, 7H) 7.98 (d, 2H)

Example A-I-21

Iodomethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)
2-methyl propionate.

a) 4-methoxybenzyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-
2-methyl propionate.

To a cooled solution of 4-methoxybenzyl 2-(hydroxymethyl)-2-methyl propionate (6.0g, 25 mmole), 4-dimethylaminopyridine (0.61g, 5 mmole) and N-benzyloxycarbonyl-L-isoleucine (6.90g, 26 mmole) in dichloromethane (100 ml) was added dicyclohexyl-carbodiimide (6.2g, 30 mmole) and the mixture was stirred overnight at room temperature. The mixture was cooled and the urethane was filtered. The solution was evaporated and 200 ml ethyl acetate was added, The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced

pressure. The product was isolated by silica gel column chromatography with toluene/acetone. Yield: 11.7g = 96%.

2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl propionic acid.

- 5 To a solution of 4-methoxybenzyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl propionate (11.0g, 22.6 mmole) in 100 ml dichloromethane was added trifluoroacetic acid (15 ml) and the mixture was stirred overnight at room temperature. The solution was evaporated under reduced pressure and coevaporated two times with toluene. The residue was stirred 1 hour with 100 ml ethanol and the
- 10 white solid was filtered (byproduct). The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 7.4g = 89%.

- ¹H-NMR (CDCl₃) 0.90 (m, 6H) 1.26 (m, 8H) 1.88 (m, 1H) 4.12 (d, d, 2H) 4.38
- 15 (d, d, 1H) 5.10 (s, 2H) 5.32 (d, 1H) 7.28 (m, 5H)

c) Chloromethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxy)-2-methyl propionate.

- To a solution of 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl
- 20 propionic acid (7.0g, 19 mmole) in 80 ml 1,4-dioxane was added a 40% solution of tetrabutylammonium hydroxide (12.4g, 19 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in 25 ml dichloromethane and iodochloromethane (33.7g, 190
- 25 mmole) was added. The solution was stirred overnight at room temperature and evaporated under reduced pressure. About 100 ml ethyl acetate was added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone. Yield: 4.2 = 54%

30

d) Iodomethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl propionate.

To a solution of chloromethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl propionate (3.0g, 7.2 mmole) in 50 ml dry acetone was added sodium iodide (4.8g, 32 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl acetate
5 water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield: 3.3g = 90%.

¹H-NMR (CDCl₃) 0.93 (m, 6H) 1.23 (m, 8H) 4.12 (m, 2H) 4.38 (d, d, 1H) 5.10 (s, 2H) 5.26 (d, 1H) 5.92 (m, 2H) 5.35 (m, 5H)

10

Example A-I-22

Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy)cyclohexanoate.

a) 4-Methoxybenzyl 4-hydroxycyclohexanoate.

15 To a solution of ethyl 4-hydroxycyclohexanoate (8.61g, 50 mmole) in 50 ml ethanol was added a solution of potassium hydroxide 85% (3.63g, 55 mmole) and the mixture was stirred for 6 hours at 70°C. The mixture was evaporated under reduced pressure, coevaporated two times with N,N-dimethylformamide and reduced to about 100 ml. 4-Methoxybenzyl chloride (9.4g, 60 mmole) was added and the mixture was
20 stirred for 18 hours at 60°C. The mixture was evaporated under reduced pressure and 250 ml ethyl acetate was added. The organic phase was washed five times with water, dried with sodium sulfate and evaporated under reduced pressure. Yield: 13.2g =100% (crude)

25 b) 4-methoxybenzyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate.

To a cooled solution of 4-methoxybenzyl 4-hydroxycyclohexanoate (7.5g, 28 mmole), 4-dimethylaminopyridine (0.73g, 6 mmole) and N-benzyloxycarbonyl-L-valine (7.54g, 30 mmole) in dichloromethane (90 ml) was added dicyclohexylcarbodiimide (6.8g, 33 mmole) and the mixture was stirred for 2 days at room
30 temperature. The mixture was cooled and the urethane was filtered. The solution was evaporated and 250 ml ethyl acetate was added. The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase

was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone. Yield : 13g = 93%

5 c) 4-(N-benzyloxycarbonyl-L-valyloxy) cyclohexanoic acid.

To a solution of 4-methoxybenzyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate (12g, 24.1 mmole) in dichloromethane (100 ml) was added trifluoroacetic acid (20 ml) and the mixture was stirred for 3 hours at room temperature. The solution was evaporated under reduced pressure and coevaporated
10 two times with toluene. The residue was stirred 1 hour with about 100 ml ethanol and the white solid was filtered (byproduct). The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography with toluene/acetone. Yield: 6.8g = 74%.

15 ¹H-NMR (CDCl₃) 0.91 (m, 6H) 1.52-2.54 (m, 10H) 4.28 (m, 1H) 4.82-5.08 (m, 1H) 5.11 (s, 2H) 5.28 (d, 1H) 7.36 (m, 5H)

d) Chloromethyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate.

To a solution of 4-(N-benzyloxycarbonyl-L-valyloxy) cyclohexanoic acid (6.6g, 20
20 mmole) in 1,4-dioxane (70 ml) was added a 40% solution of tetrabutylammonium hydroxide (11.34g, 17.5 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in 60 ml dichloromethane and iodochloromethane (30.9g, 175 mmole) was
25 added. The solution was stirred for two days at room temperature and evaporated under reduced pressure. About 100 ml ethyl acetate was added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone. Yield: 4.1g = 55%.

30

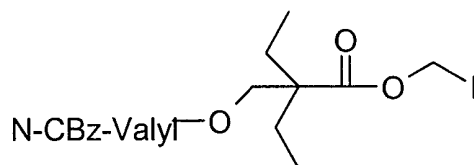
e) Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate.

To a solution of chloromethyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate (4.0g, 9.4 mmole) in dry acetone (50 ml) was added sodium iodide (6.3g, 42 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl acetate water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield 4.5g = 93%.

¹H-NMR (CDCl₃) 0.90 (m, 6H) 1.52-2.02 (m, 8H) 2.18 (m, 1H) 2.43 (m, 1H) 4.30 (m, 1H) 4.76-5.08 (m, 1H) 5.11 (s, 2H) 5.26 (d, 1H) 5.91 (d, 2H) 7.34 (m, 5H)

Example A-I-23

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyrate



a) 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethylbutan-1-ol.

To a cooled solution of 2-ethyl-2-hydroxymethyl-butan-1-ol (33.1g, 250 mmole), 4-dimethylaminopyridine (1.22g, 10 mmole) and N-benzyloxycarbonyl-L-valine (12.6g, 50 mmole) in 350 ml dichloromethane was added dropwise a solution of dicyclohexyl-carbodiimide (12.4g, 60 mmole) in 50 ml dichloromethane. The mixture was stirred 2 days at room temperature and cooled. The urethane was filtered and the solution evaporated under reduced pressure. 350 ml ethyl acetate was added and the organic phase was washed twice with 5% acetic acid, 5% sodium-hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with dichloromethane/methanol. Yield: 16.4g = 90%.

c) 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl-butyric acid.

To a cooled mixture of chromic anhydride (8.5g, 85.2 mmole) in 100 ml acetic acid was added dropwise a solution of 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl-butan-1-ol (10.4g, 28.4 mmole) in 50 ml acetone and the mixture was stirred 24 hours at room temperature. The mixture was added to 1000 ml 10% sodium chloride

solution and extracted four times with ethyl acetate. The organic phase was washed twice with brine, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 7g = 65%.

5

¹H-NMR (CDCl₃) 0.88 (m, 12H) 1.67 (m, 4H) 2.14 (m, 1H) 4.26 (m, 3H) 5.10 (s, 2H) 5.30 (d, 2H) 7.34 (m, 5H)

d) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyrate.

To a solution of 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl-butyric acid (7.2g, 18.9 mmole) in 1,4-dioxane (80 ml) was added a 40% solution of tetrabutylammonium hydroxide (12.26g, 18.9 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated once with 1,4-dioxane and two times with toluene. The dried product was dissolved in 30 ml dichloromethane and iodochloromethane (49.4g, 280 mmole) was added. The solution was stirred for two days at room temperature and evaporated under reduced pressure. About 100 ml ethyl acetate were added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 5.2g = 63%.

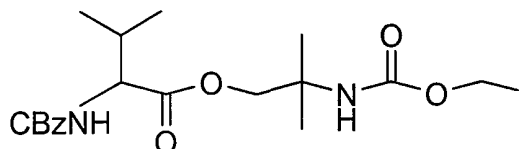
e) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyrate.

To a solution of chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyrate (5.0g, 11.7 mmole) in dry acetone (60 ml) was added sodium iodide (7.5g, 50 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl acetate water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield: 5.4g = 90%.

30

¹H-NMR (CDCl₃) 0.92 (m, 12H) 1.65 (m, 4H) 2.18 (m, 1H) 4.28 (m, 3H) 5.10 (s, 2H) 5.22 (d, 1H) 5.92 (s, 2H) 7.36 (m, 5H)

Example A-I-24

2-(N-(iodomethoxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane

5

a) 2-(N-tert.-butyloxycarbonylamino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane.

To a cooled solution of 2-(N-(tert.-butyloxycarbonyl)-amino)-2-methylpropan-1-ol (J. Am. Chem. Soc 113 (1991) p 8883) (4.73g, 25 mmole), 4-dimethylamino-
 10 pyridine (0.61g, 5 mmole) and N-benzyloxycarbonyl-L-valine (6.28g, 25 mmole) in dichloromethane (70 ml) was added dicyclohexyl-carbodiimide (6.19g, 30 mmole) and the mixture was stirred 2 days at room temperature. The mixture was cooled, the urethane was filtered and the solution evaporated under reduced pressure. Ethyl acetate (200 ml) was added and the organic phase was washed twice with 5% acetic
 15 acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 10.2g = 96%.

b) 2-amino-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane.

20 To a solution of 2-(N-(tert.-butyloxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane (10g, 23 mmole) in dichloromethane (150 ml) was added trifluoroacetic acid (30 ml) and the mixture was stirred for 1 hour at room temperature. The solution was evaporated under reduced pressure and 10% sodium carbonate solution was added. The product was extracted four times with
 25 dichloromethane, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with dichloromethane/methanol. Yield: 3.0g = 40% (crude)

c) 2-(N-(chloromethoxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane.

To a solution of 2-amino-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane (2.9g, 9 mmole) and pyridine (2 ml) in dichloromethane (50 ml) was added
5 chloromethyl chloroformate (1.55g, 12 mmole) and the mixture was stirred for 3 hours at room temperature. The mixture was evaporated under reduced pressure and ethyl acetate was added. The organic phase was washed with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 1.1g = 29%.

10

d) 2-(N-(iodomethoxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane.

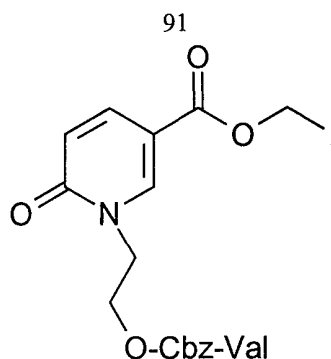
To a solution of 2-(N-(chloromethoxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)propane (1.05g, 2.53 mmole) in dry acetone (20 ml)
15 was added sodium iodide (1.8g, 12 mmole) and the mixture was stirred for 36 hours at room temperature. The mixture was evaporated under reduced pressure and ethyl acetate and water were added. The organic phase was washed with 10% sodium thiosulfate solution and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. Yield: 1.04g = 81%.

20

¹H-NMR (CDCl₃) 0.92 (m, 6H) 1.35 (s, 6H) 2.10 (m, 1H) 3.88 (m, 1H) 4.35 (m, 2H) 5.11 (s, 2H) 5.32 (d, 1H) 5.82 (s, 1H) 5.91 (s, 2H) 7.35 (m, 5H)

Example A-I-25

25 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester



a) 6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

To a solution of 6-hydroxynicotinic acid (4.87 g, 35 mmol) in DMF (100 mL) at room temperature, was added potassium tert-butoxide (3.93 g, 35 mmol). The reaction mixture was stirred at 60 °C for 1h. 4-Methoxybenzylchloride (8.30 g, 53 mmol) was added and the reaction mixture was stirred at 60 °C for 4h. The DMF was evaporated under vacuum, the residue was dissolved in ether (200 mL) and washed with water (3 x 100 mL). The organic phase was dried with Na₂SO₄ and evaporated to give 4.41 g of 6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

b) 1-(2-Hydroxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

To a solution of 6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester (4.41 g, 17 mmol) and K₂CO₃ (2.58 g, 18.7 mmol) in DMF (100 mL) at room temperature, was added 2-bromoethanol (2.02 g, 16.2 mmol). The reaction mixture was stirred at 80 °C for 30h, whereupon the DMF was evaporated under vacuum. The crude product was column chromatographed (silica gel, 2→5% MeOH in CH₂Cl₂), to give 3.91 g of 1-(2-hydroxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

c) 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

To a mixture of DCC (5.06 g, 24.5 mmol), DMAP (318 mg, 2.6 mmol) and N-CBz-L-valine (6.48 g, 25.8 mmol) in CH₂Cl₂ (200 mL) at 0 °C, was added dropwise a solution of 1-(2-hydroxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester (6.40 g, 24 mmol) in CH₂Cl₂ (200 mL). After 1h at 0 °C, the

temperature of the reaction mixture was allowed to assume room temperature and then the mixture was stirred for 5h at room temperature. The mixture was filtered through a glass filter and the solvent was removed under reduced pressure. The crude product was column chromatographed (silica gel, 2→5% MeOH in CH₂Cl₂), to give
5 6.81 g 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

d) 1-(2-N-CBz-L-valyloxyethyl)-2-pyridone-5-carboxylic acid.

To a solution of 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-
10 carboxylic acid 4-methoxybenzyl ester (6.46 g, 12 mmol) in CH₂Cl₂ (85 mL) at room temperature, was added trifluoroacetic acid (15 mL). After 1h at room temperature, the reaction mixture was concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 3→6% MeOH in CH₂Cl₂), to give 4.91 g 1-
(2-N-CBz-L-valyloxyethyl)-2-pyridone-5-carboxylic acid.

15

¹H-NMR (CDCl₃): 12.15 (br s, 1H), 8.29 (d, *J* = 2.2 Hz, 1H), 7.93 (dd, *J* = 9.5, 2.2 Hz, 1H), 7.31 (m, 5H), 6.69 (d, *J* = 9.5 Hz, 1H), 5.53 (d, 1H), 5.07 (s, 2H), 4.52-4.05 (m, 5H), 2.20-2.00 (m, 1H), 0.90 (d, 3H), 0.81 (d, 3H).

20 e) 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid chloromethyl ester.

To a solution of 1-(2-N-CBz-L-valyloxyethyl)-2-pyridone-5-carboxylic acid (4.91 g, 11.8 mmol) in dioxane (200 mL), was added dropwise a 40% aqueous solution of tetrabutylammonium hydroxide (7.65 g). After stirring for 5 min, the solution was
25 evaporated to dryness through co-evaporation with dioxane and toluene. The residue was dissolved in dichloromethane (200 mL) and then chloriodomethane (8.74 mL, 120 mmol) was added and the solution was stirred for 12h at room temperature. The solution was concentrated under reduced pressure and the residue was shaken with hexane / ethyl acetate (1:1 v/v, 200 mL). The yellow crystalline solid was filtered off
30 and the filtrate was washed with aqueous solution of sodium thiosulfate (0.1 M) and the filtered through anhydrous sodium sulfate and evaporated to dryness. The residue was column chromatographed (silica gel, 2-4% MeOH in CH₂Cl₂), to give 1.80 g of

1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid chloromethyl ester.

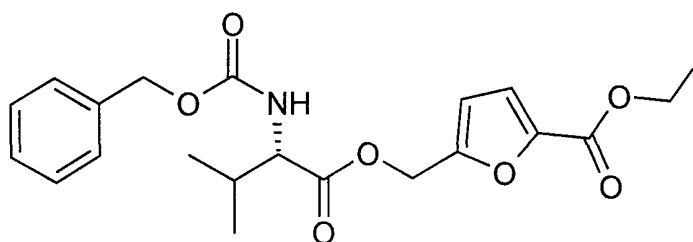
- f) 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester

To a solution of 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid chloromethyl ester (1.80 g, 3.87 mmol) in acetonitrile (30 mL), was added sodium iodide (2.32 g, 15.5 mmol). The solution was stirred for 4 h at 60 °C. The resulting suspension was filtered and the filtrate was evaporated. The residue was dissolved in CH₂Cl₂ and washed with aqueous sodium thiosulfate (0.1 M). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 1% MeOH in CH₂Cl₂), to give 2.04 g 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester.

¹H-NMR (CDCl₃): 8.19 (d, *J* = 2.5 Hz, 1H), 7.79 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.32 (m, 5H), 6.52 (d, *J* = 9.6 Hz, 1H), 6.04 (s, 2H), 5.38 (d, 1H), 5.07 (s, 2H), 4.54-4.06 (m, 5H), 2.20-2.00 (m, 1H), 0.91 (d, 3H), 0.81 (d, 3H).

Example A-I-26

Iodomethyl 5-[(*N*-benzyloxycarbonyl-L-valyloxy)methyl]-2-furoate



- (a) 5-[(*N*-Benzyloxycarbonyl-L-valyloxy)methyl]-2-furaldehyde.

A solution of 5-(hydroxymethyl)-2-furaldehyde (1.00 g, 7.69 mmol) in 5 mL dry CH₂Cl₂ was added to a mixture of *N*-benzyloxycarbonyl-L-valine (2.40 g, 9.57 mmol), *N,N'*-dicyclohexylcarbodiimide (2.00 g, 9.69 mmol), and 4-dimethylaminopyridine (117 mg, 0.96 mmol) in 45 mL CH₂Cl₂. After stirring overnight, the reaction slurry was filtered, concentrated under vacuum, and subjected to flash

column chromatography (silica, 2/1 petroleum ether - ethyl acetate to give the valine ester (quantitative yield).

(b) 5-[(*N*-Benzyloxycarbonyl-L-valyloxy)methyl]-2-furoic acid

- 5 A solution of NaClO₂ (2.8 mmol) in 3 mL water was added dropwise to a stirred solution of 5-[(*N*-benzyloxycarbonyl-L-valyloxy)methyl]-2-furaldehyde (798 mg, 2.22 mmol) from step (a) in 3 mL MeCN, with cooling in an ice bath. After 2.5 h, the ice bath was removed, 2 mL more MeCN was added, and the two-phase liquid reaction mixture was stirred at room temperature for 25 h. The reaction mixture was
- 10 diluted with water, made basic with saturated NaHCO₃, and extracted with ethyl acetate (3 x 50 mL). The separated aqueous solution was acidified to pH 2 with 5% aqueous HCl and extracted with ethyl acetate (3 x 50 mL). This second ethyl acetate solution was washed with brine, dried over anhydrous Na₂SO₄, and evaporated to dryness under vacuum to give the carboxylic acid (287 mg, 34%) which was used in
- 15 the next step without further purification.

(c) Chloromethyl 5-[(*N*-benzyloxycarbonyl-L-valyloxy)methyl]-2-furoate.

- Tetrabutylammonium hydroxide (40 wt. % solution in water, 0.55 mL, 0.84 mmol) was added to the carboxylic acid (286 mg, 0.76 mmol) from step (b) in 5 mL
- 20 dioxane. The yellow solution was concentrated under vacuum, coevaporating several times with dioxane, toluene, and, lastly, CH₂Cl₂. The residue was charged with 10 mL dry CH₂Cl₂ and chloriodomethane (0.55 mL, 7.55 mmol) was added. After stirring for 20.5 h, the reaction mixture was concentrated and subjected to flash column chromatography (silica, 2/1 petroleum ether - ethyl acetate) to give the
- 25 chloromethyl ester (137 mg, 42%).

(d) Iodomethyl 5-[(*N*-benzyloxycarbonyl-L-valyloxy)methyl]-2-furoate.

- All of the chloromethyl ester (137 mg, 0.32 mmol) from step (c) was refluxed with NaI (195 mg, 1.3 mmol) in 3.2 mL dry MeCN at 70 °C for 4 h. The solvent was
- 30 removed under vacuum and the residue was subjected to flash column chromatography (silica, 3/1 petroleum ether - ethyl acetate) to give the iodomethyl ester (152 mg, 92%).

¹H NMR (250 MHz, CDCl₃) δ 0.84 and 0.93 (2d, 3H each, *J* = 6.8 Hz), 2.16 (m, 1H), 4.33 (dd, 1H, *J* = 9.1, 4.7 Hz), 5.09-5.21 (m, 4H), 5.36 (d, 1H, *J* = 9.1 Hz), 6.08 (s, 2H), 6.52 (d, 1H, *J* = 3.4 Hz), 7.19 (d, 1H, *J* = 3.5 Hz), 7.33 (s, 5H).

5 Example A-I-27

Iodomethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy) benzoate

a) 4-Methoxybenzyl 4-(2-hydroxyethoxy)benzoate.

To a solution of 4-methoxybenzyl 4-hydroxybenzoate (7.0g, 27 mmole) in dry N,N-dimethylformamide (50 ml) was added potassium carbonate (4.15g, 30 mmole) and 2-bromoethanol. The mixture was stirred 48 hours at 80°C, evaporated under reduced pressure and ethyl acetate and water were added. The organic phase was washed five times with water and dried with sodium sulfate. The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 6.8g = 83%.

b) 4-methoxybenzyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy)benzoate.

To a solution of 4-methoxybenzyl 4-(2-hydroxyethoxy) benzoate (6.6g, 21.8 mmole), 4-dimethylaminopyridine (0.61g, 5 mmole) and N-benzyloxycarbonyl-L-valine (6.3g, 25 mmole) in dichloromethane (80 ml) was added dicyclohexylcarbodiimide (5.2g, 25 mmole) and the mixture was stirred overnight at room temperature. The mixture was cooled and the urethane was filtered. The solution was evaporated and ethyl acetate (200 ml) was added. The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with dichloromethane/methanol. Yield: 10.6g = 90 %.

c) 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy)-benzoic acid.

To a solution of 4-methoxybenzyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy) benzoate (10.2g, 19.04 mmole) in dichloromethane (100 ml) was added trifluoroacetic acid (20 ml) and the mixture was stirred 3 hours at room temperature.

The solution was evaporated under reduced pressure and co-evaporated two times with toluene. The product was isolated by silica gel column chromatography. Yield: 6.9g = 87%.

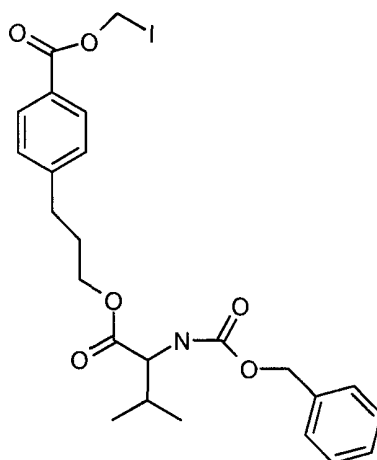
- 5 ¹H-NMR (CDCl₃) 0.94 (m, 6H) 2.18 (m, 1H) 4.22- 4.68 (m, 5H) 5.10 (s, 2H)
6.94 (d, 2H) 7.35 (m, 5H) 8.05 (d, 2H)

- d) Chloromethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy)
10 benzoate.
To a solution of 4-(2- N-benzyloxycarbonyl-L-valyloxyethoxy) benzoic acid (6.7g, 16.1 mmole) in 1,4-dioxane (80 ml) was added a 40% solution of tetrabutylammonium hydroxide (9.74g, 15 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and
15 coevaporated two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in dichloromethane (30 ml) and iodochloromethane (42.5g, 241 mmole) was added. The solution was stirred overnight at room temperature and evaporated under reduced pressure. About 150 ml ethyl acetate were added and the organic phase washed twice with water, dried with sodium sulfate and
20 evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 1.2g = 17%

- e) Iodomethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy) benzoate.
To a solution of chloromethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy)
25 benzoate (1.1g, 2.37 mmole) in dry acetone (40 ml) was added sodium iodide (1.5g, 10.0 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl acetate water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield: 1.3g = 98%.

- 30 ¹H-NMR (CDCl₃) 0.88 (d, 3H) 0.95 (d, 3H) 2.18 (m, 1H) 4.22 (m, 2H) 4.32 (d, d, 1H) 4.50 (m, 2H) 5.10 (s, 2H) 5.22 (d, 1H) 6.14 (s, 2H) 6.90 (d, 2H) 7.35(m, 7H) 7.98 (d, 2H)

Example A-I-28

Iodomethyl 4-[3-(Cbz-L-valyloxy)-1-propyl]benzoate

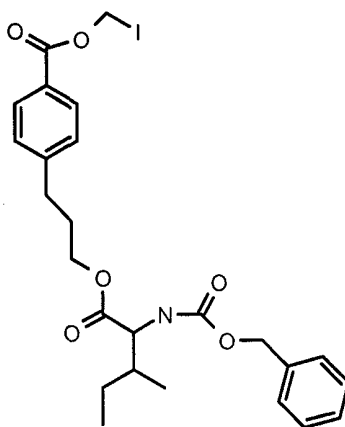
- 5 a) t-Butyl 4-[3-(Cbz-L-valyloxy)-1-propyl]benzoate.
t-Butyl 4-(3-hydroxy-1-propyl)benzoate (Taylor et al *J. Org. Chem.* 1995, 60, 7947) (3.3 g, 14 mmol), *N,N'*-dicyclohexyl carbodiimide (3.3 g, 16.8 mmol), CBZ-L-valine (4.2 g, 16.8 mmol) and *N,N*-dimethylaminopyridine (0.85 g, 7 mmol) were
10 dissolved in a minimum amount of dichloromethane and left at ambient temperature over-night. The slurry was then filtrated and the solvent evaporated. Purification by chromatography (dichloromethane-ether, 20:1) gave pure title compound (7 g, 100 %).
- 15 b) Chloromethyl 4-[3-(Cbz-L-valyloxy)-1-propyl]benzoate
t-Butyl 4-[3-(Cbz-L-valyloxy)-1-propyl]benzoate (6.5 g, 13.8 mmol) was dissolved in dichloromethane (50 ml). Trifluoroacetic acid (10 ml) was added and the mixture was left over-night. The solvent was then removed and the crude residue co-
evaporated with toluene and 1,4-dioxan and dried in vacuum over-night. The dried
20 product was dissolved in 1,4-dioxane (100 ml) and tetrabutyl ammoniumhydroxide (40 w/w % in water) was added dropwise until the pH = 7-8. The solvent was co-
evaporated with toluene four times, and then dissolved in dichloromethane (100 ml) followed by addition of 100 g of molecular sieve (4Å) and the mixture was stirred for 30 minutes. Chloriodomethane (15 ml) was added and the reaction mixture was
25 left for five hours. Filtration and purification by chromatography (hexane-ethyl acetate, 3:1) gave pure title product (3.3 g, 52 %).

c) Iodomethyl 4-[3-(cbz-L-valyloxy)-1-propyl]benzoate

Chloromethyl 4-[3-(Cbz-L-valyloxy)-1-propyl]benzoate (3 g, 6.5 mmol) and sodium iodide (4.9 g, 32 mmol) were dissolved in acetonitril (50 ml) and heated to 65 C for 4 hours. The solvent was removed under reduced pressure and the residue was taken up in dichloromethane and filtrated. Removal of the solvent and purification by chromatography (dichloromethane-ether, 20:1) gave pure title product (2.4 g, 67 %).

¹H NMR (CDCl₃, 45 °C): 7.95 (d, 2H), 7.36-7.24 (m, 7H), 6.15 (s, 2H), 5.2 (br s, 1H), 5.12 (s, 2H), 4.330-4.20 (m, 1H), 4.15 (t, 2H), 2.74 (t, 2H), 2.2-2.1 (m, 1H), 1.99 (m, t 2H), 0.98 (d, 3H), 0.91 (d, 3H)

Example A-I-29

Iodomethyl 4-[3-(Cbz-L-isoleucyloxy)-1-propyl]benzoate

a) t-Butyl 4-[3-(Cbz-L-isoleucyloxy)-1-propyl]benzoate.

Prepared from t-butyl 4-(3-hydroxy-1-propyl)benzoate (3.5 g, 14.8 mmol) by the same procedure as described for Example A-I-28 to give the title compound (7 g, 97%).

b) Chloromethyl 4-[3-(Cbz-L-isoleucyloxy)-1-propyl]benzoate.

Prepared from the material of step a) (6.9 g, 14.4 mmol) by the procedure described in Example A-I-28 to give the title compound (3.8 g, 55%) as a colourless oil.

c) Iodomethyl 4-[3-(Cbz-L-isoleucyloxy)-1-propyl]benzoate.

Prepared from the product of step b (3.26 g, 6.8 mmol) by the same procedure as for Example A-I-28 to give pure title compound. (3.46 g, 90 %).

¹H NMR (CDCl₃, 45 °C): 7.98-7.93 (m, 2H), 7.35-7.23 (m, 7H), 6.15 (s, 2H), 5.25-5.15 (br s, 1H), 5.13 (s, 2H), 4.32 (m, 1H), 4.12 (t, 2H), 2.74 (t, 2H), 1.94 (m, 2H), 1.86 (m, 1H), 1.5-1.4 (m, 1H), 1.25-1.15 (m, 1H), 0.95-0.86 (m, 6H).

Example A-I-30

Iodomethyl 2-(N-benzyloxycarbonylamino-2-methylpropionyloxy-methyl)-2-methyl propionate

a) 2-benzyloxycarbonylamino-2-methyl propionic acid.

To a solution of sodium carbonate (13.3g, 125 mmole) in water (100 ml) was added 2-amino-2-methylpropionic acid (5.0g, 50 mmole) and the mixture was stirred for 30 minutes. The solution was cooled to about 10°C and a 50% solution of benzyl chloroformate (20.5g, 60 mmole) was added dropwise. The mixture was stirred at roomtemperature overnight and acidified with 2M hydrochloric acid. The mixture was extracted two times with ethyl acetate. The organic phase was washed with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 7.7g = 64%

b) 4-methoxybenzyl 2-(2-benzyloxycarbonylamino-2-methylpropionyloxymethyl)-2-methyl propionate.

To a cooled solution of 4-methoxybenzyl 2-(hydroxymethyl)-2-methyl propionate (3.6g, 15 mmol), 4-dimethylaminopyridine (0.37g, 3 mmole) and 2-benzyloxycarbonylamino-2-methylpropionic acid (3.8g, 16 m-mole) in dichloromethane (60 ml) was added dicyclohexyl-carbodiimide (3.7g, 18 mmole) and the mixture was stirred overnight at room temperature. The mixture was cooled and the urethane was filtered. The solution was evaporated and 150 ml ethyl acetate were added, The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and

evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene / acetone. Yield: 6,2g =91%

- c) 2-(benzyloxycarbonylamino-2-methylpropionyloxymethyl)-2-methylpropionic acid.

To a solution of 4-methoxybenzyl 2-(2-benzyloxycarbonylamino-2-methylpropionyloxymethyl)-2-methyl propionate (6,1g, 13,3 mmole) dichloromethane (50 ml) was added trifluoro acetic acid (10 ml) and the mixture was stirred 3 hours at room temperature. The solution was evaporated under reduced pressure and coevaporated two times with toluene. The product was isolated by silica gel column chromatography with dichloromethane/methanol. Yield: 4.1g = 91%

¹H-NMR (CDCl₃) 1.22 (s, 6H) 1.52 (s, 6H) 4.13 (m, 2H) 5.07 (s, 2H) 5.44 (s, 1H) 7.33 (m, 5H)

- d) Chloromethyl 2-(2-benzyloxycarbonylamino-2-methylpropionyloxymethyl)-2-methyl propionate.

To a solution of 2-(2-benzyloxycarbonylamino-2-methylpropionyloxymethyl)-2-methyl propionic acid (4.0g, 11.8 mmole) in 80 ml 1,4-dioxane was added a 40% solution of tetrabutylammonium hydroxide (7.5g, 11.5 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in 20 ml dichloromethane and iodochloromethane (31.7g, 180 mmole) was added. The solution was stirred overnight at room temperature and evaporated under reduced pressure. About 100 ml ethyl acetate were added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone. Yield: 2.0g = 45%.

- e) Iodomethyl 2-(N-benzyloxycarbonylamino-2-methylpropionyloxymethyl)-2-methyl propionate.

To a solution of chloromethyl 2-(N-benzyloxycarbonylamino-2-methylpropionyloxymethyl)-2-methyl propionate (1.9g, 4.92 mmole) in 50 ml dry acetone was added sodium iodide (3.0g, 20 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl acetate water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure.

Yield: 2,1g.

¹H-NMR (CDCl₃) 1.20 (s, 6H) 1.53 (s, 6H) 4.13 (s, 2H) 5.07 (s, 2H) 5.30 (s, 1H) 5.90 (s, 2H) 7.35 (m, 5H)

Example A-I-31

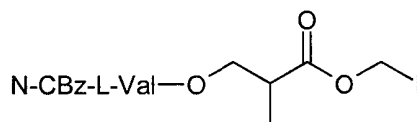
Iodomethyl 2-methyl-2-(N-benzyloxycarbonyl-L-alanyloxymethyl)propionate

The title compound (alternative nomenclature 2,2-dimethyl-3-(CBz-alanyloxy)-propionic acid iodomethyl ester) is prepared in a similar manner as described in Example A-I-10 using N-CBz protected L-alanine in place of N-CBz-D-valine.

¹H-NMR (CDCl₃): 7.33 (m, 5H), 5.91 (m, 2H), 5.11 (s, 2H), 4.38 (m, 1H), 4.14 (m, 2H), 1.40 (d, 3H), 1.21 (d, 6H).

Example A-I-32

Iodomethyl 3-(N-CBz-L-valyloxy)-2-methyl-propionate



a) 3-(N-CBz-L-valyloxy)-2-methyl-1-propanol.

To a mixture of DCC (16.5 g, 80 mmol), DMAP (0.977 g, 8 mmol) and N-CBz-L-valine (20.1 g, 80 mmol) in CH₂Cl₂ (400 mL) at 0 °C, was added dropwise a solution of 2-methyl-1,3-propanediol (72.1 g, 800 mmol) in CH₂Cl₂ (100 mL). After 1h at 0

°C, the temperature of the reaction mixture was allowed to assume room temperature and then the mixture was stirred for 16h at room temperature. The mixture was filtered through a glass filter and the solvent was removed under reduced pressure. The crude product was column chromatographed (silica gel, 5% MeOH in CH₂Cl₂),
5 to give 20.3 g 3-(N-CBz-L-valyloxy)-2-methyl-1-propanol.

b) 3-(N-CBz-L-valyloxy)-2-methyl-propionic acid.

To a solution of CrO₃ (4.29 g, 42.9 mmol) in HOAc (50 mL) at 20 °C, was added dropwise a solution of 3-(N-CBz-L-valyloxy)-2-methyl-1-propanol (4.61 g, 14.3
10 mmol) in aceton (25 mL). After stirring for 24h, water (300 mL) was added and the reaction mixture was extracted with CH₂Cl₂ (4x200 mL) . The combined organic layers was concentrated under reduced pressure. The residue was column chromatographed (silica gel, 5-10% MeOH in CH₂Cl₂), to give 3.10 g of 3-(N-CBz-L-valyloxy)-2-methyl-propionic acid.

15

¹H-NMR (CDCl₃): 11.54 (br s, 1H), 7.33 (s, 5H), 5.48 (d, 1H), 5.11 (s, 2H), 4.40-4.00 (m, 3H), 2.95-2.70 (m, 1H), 2.25-2.05 (m, 1H), 1.30-1.12 (m, 3H), 0.95 (d, 3H), 0.87 (d, 3H).

20 c) Chloromethyl 3-(N-CBz-L-valyloxy)-2-methyl-propionate.

To a solution of 3-(N-CBz-L-valyloxy)-2-methyl-propionic acid (3.10 g, 9.2 mmol) in dioxane (100 mL), was added dropwise a 40% aqueous solution of tetrabutylammonium hydroxide (5.97 g). After stirring for 5 min, the solution was evaporated to dryness through co-evaporation with dioxane and toluene. The residue
25 was dissolved in dichloromethane (100 mL) and then chloriodomethane (6.70 mL, 92 mmol) was added and the solution was stirred for 6h at room temperature. The solution was concentrated under reduced pressure and the residue was shaken with hexane / ethyl acetate (1:1 v/v, 200 mL). The yellow crystalline solid was filtered off and the filtrate was washed with aqueous solution of sodium thiosulfate (0.1 M) and
30 the filtered through anhydrous sodium sulfate and evaporated to dryness. The residue was column chromatographed (silica gel, 0.5-2% MeOH in CH₂Cl₂), to give 1.90 g of chloromethyl 3-(N-CBz-L-valyloxy)-2-methyl-propionate.

d) Iodomethyl 3-(N-CBz-L-valyloxy)-2-methyl-propionate.

To a solution of chloromethyl 3-(N-CBz-L-valyloxy)-2-methyl-propionate (1.84 g, 4.77 mmol) in acetonitrile (50 mL), was added sodium iodide (2.86 g, 19.0 mmol).

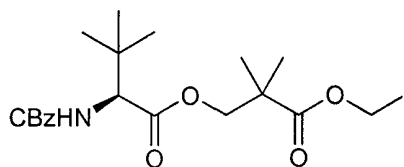
- 5 The solution was stirred for 3.5 h at 60 °C. The resulting suspension was filtered and the filtrate was evaporated. The residue was dissolved in CH₂Cl₂ and washed with aqueous sodium thiosulfate (0.1 M). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 1% MeOH in CH₂Cl₂), to give 1.78 g of iodomethyl 3-(N-CBz-L-valyloxy)-2-methyl-propionate.

¹H-NMR (CDCl₃): 7.35 (s, 5H), 5.90 (s, 2H), 5.25 (d, 1H), 5.10 (s, 2H), 4.36-4.18 (m, 3H), 2.94-2.73 (m, 1H), 2.26-2.08 (m, 1H), 1.28-1.18 (m, 3H), 0.96 (d, 3H), 0.87 (d, 3H).

15

Example A-I-33

Iodomethyl 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionate



- a) 4-Methoxybenzyl 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionate.

- 20 To a mixture of DCC (4.95 g, 24 mmol), DMAP (293 mg, 2.4 mmol) and N-CBz-L-t-butylglycine (6.37 g, 24 mmol) in CH₂Cl₂ (100 mL) at 0 °C, was added dropwise a solution of 4-methoxybenzyl 2,2-dimethyl-3-hydroxypropionate (2.86 g, 12 mmol) in CH₂Cl₂ (50 mL). After 1h at 0 °C, the temperature of the reaction mixture was
- 25 allowed to assume room temperature and then the mixture was stirred for 48h at room temperature. The mixture was filtered through a glass filter and the solvent was removed under reduced pressure. The crude product was column chromatographed (silica gel, 1-2% MeOH in CH₂Cl₂), to give 5.60 g 4-methoxybenzyl 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionate.

30

b) 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionic acid

To a solution of 4-methoxybenzyl 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionate (5.60 g, 11.5 mmol) in CH_2Cl_2 (90 mL) at room temperature, was added trifluoroacetic acid (10 mL). After 1h at room temperature, the reaction mixture was concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 3→5% MeOH in CH_2Cl_2), to give 2.70 g of 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionic acid.

$^1\text{H-NMR}$ (CDCl_3): 11.2 (br s, 1H), 7.34 (s, 5H), 5.44 (d, 1H), 5.11 (s, 2H), 4.25-4.03 (m, 3H), 1.32-1.22 (m, 6H), 0.97 (s, 9H).

c) Chloromethyl 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionate.

To a solution of 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionic acid (2.70 g, 7.38 mmol) in dioxane (100 mL), was added dropwise a 40% aqueous solution of tetrabutylammonium hydroxide (4.79 g). After stirring for 5 min, the solution was evaporated to dryness through co-evaporation with dioxane and toluene. The residue was dissolved in dichloromethane (100 mL) and then chloriodomethane (5.37 mL, 73.8 mmol) was added and the solution was stirred for 6h at room temperature. The solution was concentrated under reduced pressure and the residue was shaken with hexane / ethyl acetate (1:1 v/v, 200 mL). The yellow crystalline solid was filtered off and the filtrate was washed with aqueous solution of sodium thiosulfate (0.1 M) and the filtered through anhydrous sodium sulfate and evaporated to dryness. The residue was column chromatographed (silica gel, 0.5-1% MeOH in CH_2Cl_2), to give 2.44 g of chloromethyl 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionate.

d) Iodomethyl 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionate.

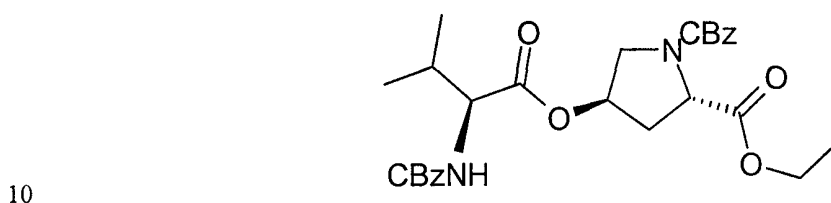
To a solution of chloromethyl 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionate (2.44 g, 5.90 mmol) in acetonitrile (50 mL), was added sodium iodide (3.54 g, 23.6 mmol). The solution was stirred for 3.5 h at 60 °C. The resulting suspension was filtered and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and washed with aqueous sodium thiosulfate (0.1 M). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was column

chromatographed (silica gel, 1% MeOH in CH₂Cl₂), to give 2.61 g of iodomethyl 3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionate.

¹H-NMR (CDCl₃): 7.32 (s, 5H), 5.89-5.82 (m, 2H), 5.40 (d, 1H), 5.07 (s, 2H), 4.17 (d, 1H), 4.11 (s, 2H), 1.22-1.19 (m, 6H), 0.95 (s, 9H).

Example A-I-34

N-benzyloxycarbonyl-*trans*-4-(*N*-benzyloxycarbonyl-L-valyloxy)-L-proline iodomethyl ester.



(a) *N*-benzyloxycarbonyl-*trans*-4-hydroxy-L-proline *p*-methoxybenzyl ester.

Cesium carbonate (1.23 g, 3.78 mmol) was added to a stirred solution of *N*-benzyloxycarbonyl-*trans*-4-hydroxy-L-proline (2.00 g, 7.54 mmol) in 20 mL dry DMF. After 15 min, *p*-methoxybenzyl chloride (1.25 mL, 9.21 mmol) was added and the mixture was stirred for 17 h. The solvent was evaporated under vacuum, and the residue was partitioned between EtOAc (100 mL) and water (50 mL). The organic phase was washed with water (2 x 25 mL), dried over anhydrous Na₂SO₄, and concentrated. Flash column chromatography (silica gel, 2/1 EtOAc - petroleum ether) gave 2.69 g (92%) of the *p*-methoxybenzyl ester.

(b) *N*-benzyloxycarbonyl-*trans*-4-(*N*-benzyloxycarbonyl-L-valyloxy)-L-proline *p*-methoxybenzyl ester.

A mixture of *N*-benzyloxycarbonyl-*trans*-4-hydroxy-L-proline *p*-methoxybenzyl ester (2.54 g, 6.59 mmol), *N*-benzyloxycarbonyl-L-valine (1.82 g, 7.24 mmol), 4-dimethylaminopyridine (90 mg, 0.7 mmol), and dicyclohexylcarbodiimide (1.64 g, 7.95 mmol) in 26 mL dry CH₂Cl₂ was stirred overnight. The slurry was filtered, and the filtrate was concentrated under vacuum to give an oil that was subjected to flash column chromatography (silica gel, 3/1 and then 2/1 petroleum ether - EtOAc) to yield 3.70 g (91%) of the title compound.

(c) *N*-benzyloxycarbonyl-*trans*-4-(*N*-benzyloxycarbonyl-L-valyloxy)-L-proline chloromethyl ester.

The *p*-methoxybenzyl group was removed by stirring a solution of the compound
5 (2.47 g, 4.0 mmol) from step (b) and 8 mL CF₃COOH in 40 mL CH₂Cl₂ for 30 min. The reaction mixture was concentrated under vacuum, coevaporating several times with more CH₂Cl₂ and toluene. A second sample (1.14 g, 1.84 mmol) was treated similarly. The crude products obtained from both samples were combined and subjected to flash column chromatography (silica gel, 15% methanol in CH₂Cl₂ to
10 give 2.58 g of cream-colored solids containing *N*-benzyloxycarbonyl-*trans*-4-(*N*-benzyloxycarbonyl-L-valyloxy)-L-proline (TLC 15/85 MeOH/CH₂Cl₂ R_f = 0.25). This material (1.14 g) was dissolved in 10 mL dioxane. Tetrabutylammonium hydroxide (1.15 mL of a 40 wt % solution in H₂O, 1.76 mmol) was added, the mixture was evaporated to dryness, and the residue was coevaporated several times
15 with toluene and, lastly, CH₂Cl₂. The resulting Q salt was stirred with chloriodomethane (1.30 mL, 17.8 mmol) in dry CH₂Cl₂ (20 mL) for 20 h. The solvent was removed under vacuum, 25 mL of 2/1 petroleum ether – EtOAc was added, and the precipitates which formed were filtered. Concentration of the filtrate, followed by flash column chromatography (silica gel, 4/1 and then 2/1 petroleum
20 ether – EtOAc) gave the chloromethyl ester (580 mg) as white solids.

(d) *N*-benzyloxycarbonyl-*trans*-4-(*N*-benzyloxycarbonyl-L-valyloxy)-L-proline iodomethyl ester.

The chloromethyl ester (533 mg, 0.974 mmol) from step (c) and NaI (594 mg, 3.96
25 mmol) were refluxed in dry MeCN (10 mL) at 75 °C for 4 h. After removal of solvent under vacuum, the mixture was partitioned between 20 mL EtOAc and 10 mL water. The organic phase was washed with 5% Na₂S₂O₃ and then brine, dried over anhydrous Na₂SO₄, and concentrated. Flash column chromatography (silica gel, 3/1 petroleum ether – EtOAc) gave the iodomethyl ester (526 mg, 84%) as white solids.

30

¹H NMR (250 MHz, CDCl₃) δ 0.86 and 0.94 (2d, 3H each, *J* = 6.8 Hz), 2.13 (m, 2H), 2.31 (m, 1H), 3.65-3.80 (m, 2H), 4.24 (m, 1H), 4.43 (m, 1H), 5.03-5.19 (m, 4H), 5.30

(br s, 1H), 5.54 (br d, 1H), 5.70 and 5.83-5.97 (s and ABq, 2H total), 7.30-7.32 (m, 10H).

Prodrugs of the invention

5

EXAMPLE A-1

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, tri(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester.

- 10 a) 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, tri(2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionyloxymethyl) ester and 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di(2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionyloxymethyl) ester.
- 15 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid is prepared by the methodology in Kieczkowski et al, J Org Chem 1995, 60, 8310-8312, and the 4-amino group CBz protected as shown in US 5 227 506. To a solution thereof (195 mg, 0.51 mmole) in dry N,N-dimethylformamide (2 ml), was added diisopropylethylamine (0.27 ml, 1.53 mmole), followed by an injection of a solution of iodomethyl 2-
- 20 methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionate (626 mg, 1.27 mmole) in N,N-dimethylformamide (2 ml). After stirring under argon for 2,5 h at room temperature, the solution was concentrated on rotavapor and treated with ethyl acetate (10 ml). Crystals were filtered off and the filtrate was extracted with brine containing a small amount of sodium thiosulfate. The organic phase was filtered
- 25 through anhydrous sodium sulfate and evaporated. The title compounds were isolated by silica gel column chromatography (0-4, 7-8, 20-30% ethanol in dichloromethane).

Triester (70 mg). R_f (10%MeOH/ CHCl_3) 0.45. $^1\text{H-NMR}$ (CDCl_3): 7.30 (m, 20H), 5.85-5.43 (m, 9H), 5.08 (m, 8H), 4.36-3.95 (m, 9H), 3.10 (m, 2H), 2.15-1.75 (m, 7H), 1.19 (s, 18H), 0.86 (m, 18H). $^{31}\text{P-NMR}$ ($\text{CDCl}_3+1\%\text{CD}_3\text{OD}$) (H_3PO_4 reference):

30 δ 23.8 (d), 11.8(d);

Diester (185 mg), R_f (10%MeOH/ CHCl_3) 0.10 (at the center of oval spot from baseline). $^1\text{H-NMR}$ ($\text{CDCl}_3+1\%\text{CD}_3\text{OD}$): 7.31 (m, 15H), 5.79-5.63 (m, 4H), 5.08 (m, 6H), 4.35-4.10 (m, 6H), 3.10 (m, 2H), 2.18-1.70 (m, 6H), 1.19 (m, 12H), 0.87 (m, 12H). $^{31}\text{P-NMR}$ ($\text{CDCl}_3+1\%\text{CD}_3\text{OD}$)(H_3PO_4 reference): δ 16.6 (s).

5

b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, tri(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester.

A solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid tri(2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionyloxymethyl)

10 Ester (203 mg, 0.136 mmol) in methanol / ethyl acetate / acetic acid (2:1:1 v/v/v) (8.7 ml) was hydrogenated over a Pd-black catalyst (93 mg) at 40 psi of hydrogen for 16 h. The suspension was filtered through Celite on a fine pore sized glassinter and washed with methanol/ethyl acetate (2:1). The filtrate was evaporated to dryness in vacuo and the title compound as the tetra acetate was obtained as a white solid after a
15 few co-evaporations with dioxane and hexane.

$^{31}\text{P-NMR}$ ($\text{CDCl}_3+5\%\text{CD}_3\text{OD}$)(H_3PO_4 reference): δ 23.1 (m), 11.1 (m).

Example A-2

20 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di(2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionyloxymethyl) ester (130

25 mg, 0.112 mmol) was hydrogenated over Pd-black (48 mg) by the method of Example A-1 b), to give the title compound as the triacetate as a white solid (90 mg).

$^{31}\text{P-NMR}$ ($\text{CDCl}_3+5\%\text{CD}_3\text{OD}$)(H_3PO_4 reference): δ 16.2 (br, s).

30 Example A-3

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester

a) 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di(2-methyl-2-(N-benzyloxycarbonyl-L-valyloxy) propionyloxymethyl) ester.

5 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (306 mg, 0.80 mmole) was esterified by the method described in Example A-1-a. After silica gel column chromatography (2-4, 6-12, 15-20% ethanol in dichloromethane), the pure fractions containing the title compound were pooled together and evaporated. The residue was then dissolved in ethyl acetate and the solution extracted twice with
10 aqueous saturated sodium bicarbonate and then twice with 5% aqueous EDTA-disodium salt. (116 mg of title compound). R_f (20%MeOH/ CHCl_3) 0.20 (at the center of oval spot from baseline).

$^1\text{H-NMR}$ ($\text{CDCl}_3+1\%\text{CD}_3\text{OD}$): 7.28 (m, 15H), 5.60 (m, 4H), 5.05 (m, 6H), 4.13 (m,
15 2H), 3.09 (m, 2H), 2.19-1.72 (m, 6H), 1.49 (m, 12H), 0.89 (m, 12H). $^{31}\text{P-NMR}$ ($\text{CDCl}_3+1\%\text{CD}_3\text{OD}$)(H_3PO_4 reference): δ 15.3 (s).

b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester.

20 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di(2-methyl-2-(N-benzyloxycarbonyl-L-valyloxy) propionyloxymethyl) ester (116 mg, 0.107 mmol) was hydrogenated over Pd-black (46 mg) by the method of Example A-1-b, to give the title compound as the triacetate as a white solid (71 mg).

25 $^{31}\text{P-NMR}$ ($\text{CDCl}_3+5\%\text{CD}_3\text{OD}$)(H_3PO_4 reference): δ 14.9 (s).

Example A-4

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester.

30

a) 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (383 mg, 1 mmole) was esterified by the method described in Example A-3-a to yield 184 mg of title compound. R_f (20%MeOH/ CHCl_3) 0.20 (at the center of oval spot from baseline).

5

$^1\text{H-NMR}$ ($\text{CDCl}_3 + 1\%\text{CD}_3\text{OD}$): 7.27 (m, 15H), 5.62 (m, 4H), 5.15-4.72 (m, 8H), 4.32 (m, 2H), 3.08 (m, 2H), 2.16-1.73 (m, 6H), 0.88 (m, 24H). $^{31}\text{P-NMR}$ ($\text{CDCl}_3 + 1\%\text{CD}_3\text{OD}$) (H_3PO_4 reference): δ 15.5 (s).

10 b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester (184 mg, 0.166 mmol) was hydrogenated over Pd-black (71 mg) by the method of Example A-
15 1-b, to give the title compound as the triacetate as a white solid (95 mg).

$^{31}\text{P-NMR}$ ($\text{CDCl}_3 + 5\%\text{CD}_3\text{OD}$) (H_3PO_4 reference): δ 14.6 (s).

Example A-5

20 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, mono (2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester.

a) 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, tribenzyl mono (2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionyloxymethyl) ester.
25

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (1.54 g, 4 mmole) in dry N,N-dimethylformamide (24 ml), heated at 50 °C, was added diisopropylethylamine (2.78 ml, 16 mmole), followed by dropwise addition of benzylbromide (1.9 ml, 16 mmole). After stirring under argon for 4 h, the solution
30 was concentrated on rotavapor and treated with ethyl acetate (20 ml). Crystals were filtered off and the filtrate was extracted with brine. The organic phase was filtered through anhydrous sodium sulfate and evaporated. The 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, tribenzylester was isolated by silica gel

column chromatography (2-4, 7-10, 15-20% ethanol in dichloromethane). The pure fractions containing the pure triester were pooled together and evaporated. The residue was then dissolved in ethyl acetate and the solution extracted three times with 2M aqueous solution of citric acid. Triester (990 mg); R_f (20%MeOH/ CHCl_3) 0.15 (at the center of oval spot from baseline);

^{31}P -NMR (CDCl_3) (H_3PO_4 reference): δ 20.4(d), 13.3 (d); ^1H -NMR (CDCl_3): 7.35-7.10 (m, 20H), 5.20-4.91 (m, 8H), 4.60 (br, 1H), 3.00 (m, 2H), 2.12-1.75 (m, 4H).

b) Dried tribenzyl ester (395 mg) was dissolved in dry N,N-dimethylformamide (3 ml), followed by addition of diisopropylethylamine (99 ml) and a solution of iodomethyl 2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionate (737 mg) in N,N-dimethylformamide (1 ml). After stirring under argon for 4 h at 30 °C, the solution was concentrated to dryness on rotavapor and treated with ethyl acetate (10 ml). Crystals were filtered off and the filtrate was extracted with brine containing a small amount of sodium thiosulfate. The organic phase was filtered through anhydrous sodium sulfate and evaporated. The title compound (84 mg) was isolated by silica gel column chromatography (1, 2, 3% ethanol in dichloromethane). R_f (2%MeOH/ CHCl_3) 0.60;

^{31}P -NMR (CDCl_3) (H_3PO_4 reference): δ 16.4(m). ^1H -NMR (CDCl_3): 7.28 (m, 25H), 5.22 (d, 1H), 5.62-5.53 (m, 3H), 5.07, 5.04 (2xs, 10H), 4.93 (br, 1H), 4.27 (d,d, 1H), 4.15 (d,d, 2H), 3.11 (m, 2H), 2.13-1.77 (m, 5H), 1.17 (s, 6H), 0.92 (d, 3H), 0.83 (d, 3H).

c) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, mono (2-methyl-2-(L -valyloxymethyl) propionyloxymethyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid tribenzyl mono (2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionyloxymethyl) ester (84 mg, 0.083 mmol) was hydrogenated over Pd-black (60 mg) by the method of Example A-1-b, to give the title compound as a white solid (35 mg).

^{31}P -NMR ($\text{CDCl}_3 + 5\% \text{CD}_3\text{OD}$) (H_3PO_4 reference): δ 14.5 (m).

Example A-6

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-(-L-valyloxy)-2-phenyl-DL-acetyloxymethyl) ester.

4-Benzylloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (192 mg, 0.5 mmole) was esterified with the corresponding iodomethyl ester by the method described in Example A-3-a to yield 72 mg of the title compound as the tri-N-CBz protected form, ready for deprotection. R_f (20%MeOH/ CHCl_3) 0.20 (at the center of oval spot from baseline).

^1H -NMR ($\text{CDCl}_3 + 1\% \text{CD}_3\text{OD}$): 7.44-7.10 (m, 25H), 5.94 (m, 2H), 5.59 (m, 2H), 5.18-4.85 (m, 6H), 4.36 (m, 2H), 3.00 (m, 2H), 2.12-1.63 (m, 6H), 0.95 (m, 12H).

^{31}P -NMR ($\text{CDCl}_3 + 1\% \text{CD}_3\text{OD}$) (H_3PO_4 reference): δ 15.5 (s).

Example A-7

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di ((1,3-di-valyloxy)propyl-2-oxycarbonyloxy methyl) ester.

4-Benzylloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (141 mg, 0.37 mmole) was esterified from the corresponding iodomethyl ester by the method described in Example A-1-a to yield 90 mg of title compound as the tri CBz protected form, ready for deprotection. R_f (10%MeOH/ CHCl_3) 0.20 (at the center of oval spot from baseline). (153 mg of mixture of the diester and triester).

^1H -NMR ($\text{CDCl}_3 + 1\% \text{CD}_3\text{OD}$) of title compound: 7.29 (m, 25H), 5.65 (m, 4H), 5.14-4.85 (m, 12H), 4.45-4.05 (m, 12H), 3.11 (m, 2H), 2.14-1.76 (m, 8H), 0.87 (m, 24H).

^{31}P -NMR ($\text{CDCl}_3 + 1\% \text{CD}_3\text{OD}$) (H_3PO_4 reference): δ 16.7 (s).

Example A-8

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-L-valyloxy)-DL-propionyloxymethyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (158 mg, 0.41 mmole) was esterified from the corresponding iodomethyl ester by the method described in Example A-3-a to yield 110 mg of the title compound as the tri N-Boc protected from, ready for deprotection. R_f (20%MeOH/ CHCl_3) 0.15 (at the center of oval spot from baseline).

$^1\text{H-NMR}$ ($\text{CDCl}_3+1\%\text{CD}_3\text{OD}$): 7.29 (m, 15H), 5.65 (m, 4H), 5.15-4.95 (m, 8H), 4.33 (m, 2H), 3.09 (m, 2H), 2.22-1.74 (m, 6H), 1.52 (m, 6H), 0.92 (m, 12H). $^{31}\text{P-NMR}$ ($\text{CDCl}_3+1\%\text{CD}_3\text{OD}$)(H_3PO_4 reference): δ 16.8 (s).

Example A-9

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester

15

a) 4-Benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(5-(N-CBz-L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (575 mg, 1.50 mmol) in DMF (10 mL), was added diisopropylamine (0.78 mL, 4.5 mmol), followed by an injection of a solution of give iodomethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate (1.95 g, 3.75 mmol) in DMF (5 mL). After stirring under argon for 1.5 h at room temperature, the solution was concentrated on rotavapor and treated with ethyl acetate (100 mL). Crystals were filtered off and the filtrate was extracted with brine containing a small amount of sodium thiosulfate.

The organic phase was filtered through anhydrous sodium sulfate and evaporated. After silica gel column (silica gel, 4 $\rightarrow$ 20% MeOH in CH_2Cl_2), the pure fractions containing the title compound were combined and evaporated. The residue was then dissolved in ethyl acetate and the solution extracted twice with aqueous saturated sodium bicarbonate and then twice with 5% aqueous EDTA-disodium salt. The ethyl acetate phase was evaporated, to give 171 mg of 4-benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(5-(N-CBz-L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester.

$^1\text{H-NMR}$ (CDCl_3): 7.30 (br s, 15H), 5.85-5.25 (m, 4H), 5.20-4.95 (m, 6H), 4.30-3.95 (m, 6H), 3.18-3.00 (m, 2H), 2.20-1.75 (m, 6H), 1.7-1.4 (m, 8H), 1.3-1.0 (s, 12H), 1.0-0.8 (m, 12H).

5 $^{31}\text{P-NMR}$ (CDCl_3)(H_3PO_4 reference): 16.0 (s).

b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester.

10 A solution of 4-benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(5-(N-CBz-L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester (171 mg, 0.147 mmol) in methanol / ethyl acetate / acetic acid (2:1:1 v/v/v) (20 mL) was hydrogenated over a Pd-black catalyst (30 mg) at 40 psi of hydrogen for 6 h. The suspension was filtered through celite and the filtrate was evaporated to dryness
15 under reduced pressure, to give 95 mg of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(5-(L-valyloxy)-2,2-dimethylvaleryloxymethyl) ester was obtained as a white solid.

$^1\text{H-NMR}$ (CDCl_3): 5.75-5.30 (m, 4H), 5.20-4.95 (m, 6H), 4.20-3.80 (m, 6H), 3.00-2.80 (m, 2H), 2.20-1.40 (m, 14H), 1.3-1.0 (m, 12H), 1.0-0.8 (m, 12H).

20 $^{31}\text{P-NMR}$ ($\text{CDCl}_3+\text{CD}_3\text{OD}$)(H_3PO_4 reference): δ 17.3 (br s)

Example A-10

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid di-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester
25

a) 4-benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-((2-(N-CBz-L-valyloxy)-ethoxycarbonyloxy) methyl) ester

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (550 mg, 1.44 mmol) in DMF (10 mL), was added diisopropylamine (0.75 mL, 4.32 mmol), followed by an injection of a solution of 2-(N-CBz-L-valyloxy)-ethyl iodomethyl carbonate (1.40 g, 3.60 mmol) in DMF (5 mL). After stirring under
30 argon for 1.5 h at room temperature, the solution was concentrated on rotavapor and

treated with ethyl acetate (100 mL). Crystals were filtered off and the filtrate was extracted with brine containing a small amount of sodium thiosulfate. The organic phase was filtered through anhydrous sodium sulfate and evaporated. After silica gel column (silica gel, 4→20% MeOH in CH₂Cl₂), the pure fractions containing the title compound were combined and evaporated. The residue was then dissolved in ethyl acetate and the solution extracted twice with aqueous saturated sodium bicarbonate and then twice with 5% aqueous EDTA-disodium salt. The ethyl acetate phase was evaporated, to give 160 mg of 4-benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-((2-(N-CBz-L-valyloxy)-ethoxycarbonyloxy) methyl) ester.

¹H-NMR (CDCl₃): 7.29 (br s, 15H), 5.90-5.30 (m, 4H), 5.15-4.90 (m, 6H), 4.50-4.00 (m, 10H), 3.18-3.00 (m, 2H), 2.20-1.50 (m, 6H), 1.05-0.80 (m, 12H).

³¹P-NMR (CDCl₃)(H₃PO₄ reference): 16.5 (s).

b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid di-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester.

A solution of 4-benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-((2-(N-CBz-L-valyloxy)-ethoxycarbonyloxy) methyl) ester (160 mg, 0.147 mmol) in methanol / ethyl acetate / acetic acid (2:1:1 v/v/v) (20 mL) was

hydrogenated over a Pd-black catalyst (30 mg) at 40 psi of hydrogen for 7 h. The suspension was filtered through celite and the filtrate was evaporated to dryness under reduced pressure, to give 100 mg of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di-((2-(L-valyloxy)-ethoxycarbonyloxy) methyl) ester was obtained as a white solid.

¹H-NMR (CDCl₃): 5.80-5.40 (m, 4H), 4.70-4.05 (m, 10H), 4.4-4.2 (m, 4H), 3.00-2.80 (m, 2H), 2.20-1.50 (m, 6H), 1.05-0.80 (m, 12H).

³¹P-NMR (CDCl₃+CD₃OD)(H₃PO₄ reference): δ 17.5 (br s).

Example A-11

4-Amino-1-hydroxybutyliden-1,1-bisphosphonic acid bis [2,2-dimethyl-3-(D-valyloxy)-propionyloxymethyl] ester

a) 4-Benzyloxycarbonylamino-1-hydroxybutyliden-1,1-bisphosphonic acid bis [2,2-dimethyl-3-(N-CBZ-D-valyloxy)-propionyloxymethyl] ester

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutyliden-1,1-bisphosphonic acid (382 mg, 1 mmole) and diisopropylethyl (0.43 ml, 2.5 mmole) in DMF (3 ml) at
5 -40° C was added 2,2-dimethyl-3-(N-CBz-D-valyloxy)-propionic acid iodomethyl ester (1.23 g, 2.5 mmole) in DMF (4 ml). The reaction was kept at 0° C for 2.5 hr and then at 4° C for 18 hr. The reaction mixture was evaporated in vacuo and ethyl acetate (20 ml) was added. The precipitate was filtered off and the organic phase was
10 washed with sodium bicarbonate aqueous solution and dried. The product was isolated with silica gel column chromatography. 125 mg.

¹H-NMR (CDCl₃): 7.31 (m, 15 H) 5.71 (m, 4 H) 5.58 (d, 2 H) 5.12 (s, 4H) 5.05 (s, 2H) 4.30 (dd, 2H) 4.12 (m, 4 H) 3.18 (m, 2H) 2.05 (m, 6 H) 0.92 (dd, 12 H).

15 ³¹P-NMR (CDCl₃): 15.1

b) 4-Amino-1-hydroxybutyliden-1,1-bisphosphonic acid bis [2,2-dimethyl-3-(D-valyloxy)-propionyloxymethyl] ester.

4-Benzyloxycarbonylamino-1-hydroxybutyliden-1,1-bisphosphonic acid bis [2,2-
20 dimethyl-3-(N-CBZ-D-valyloxy)-propionyloxymethyl] ester (130 mg) was dissolved in a mixed solvent of EtOAc/MeOH/AcOH (6 ml/3 ml/1.5 ml). To the solution was added palladium black (60 mg). The reaction was kept under hydrogen atmosphere (40 psi) until sampling showed the complete deprotection of the benzyloxycarbonyl groups. The reaction mixture was filtered, and then dried and coevaporated with
25 toluene and methanol, giving the titled product. 102 mg.

³¹P-NMR (CDCl₃ + CD₃OD) : 14.1

Example A-12

30 4-Amino-1-hydroxybutyliden-1,1-bisphosphonic acid bis [4-(N-CBz-L-valyloxy)-butanoyloxymethyl] ester

a) 4-Benzyloxycarbonylamino-1-hydroxybutyliden-1,1-bisphosphonic acid bis [4-(N-CBz-L-valyloxy)-butanoyloxymethyl] ester.

4-Benzyloxycarbonylamino-1-hydroxybutyliden-1,1-bisphosphonic acid (573 mg, 1.5 mmole) was dissolved in dioxane (10 ml). To the solution was added
 5 tetrabutylammonium hydroxide (40 %, 2.43 ml, 3.75 mmole). The solution was evaporated and coevaporated with DMF several times. The residue was dissolved in DMF (5 ml). To the solution was added 4-(N-CBz-L-valyloxy) butyric acid iodomethyl ester (1.79 g, 3.75 mmole) in DMF (5 ml) portionwise in one hour. The reaction was kept at room temperature for 3 hr and then evaporated in vacuo. Later,
 10 ethyl acetate (20 ml) was added. The precipitate was filtered off and the organic phase was washed with sodium bicarbonate aqueous solution and dried. The product was isolated with silica gel column chromatography. 135 mg.

¹H-NMR (CDCl₃): 7.25 (m, 15 H) 5.60 (m, 6 H) 5.05 (m, 8H) 4.30-3.90 (m, 6 H)
 15 3.10 (m, 2 H) 2.50-1.80 (m, 14 H) 0.85 (m, 12 H).

³¹P-NMR (CDCl₃): 13.7.

b) 4-amino-1-hydroxybutyliden-1,1-bisphosphonic acid bis 4-(L-valyloxy)-butanoyloxymethyl] ester.

20 4-Benzyloxycarbonylamino-1-hydroxybutyliden-1,1-bisphosphonic acid bis [4-(N-CBz-L-valyloxy)-butanoyloxymethyl] ester (100 mg) was dissolved in a mixed solvent of EtOAc/MeOH/AcOH (6 ml/3 ml/1.5 ml). To the solution was added palladium black (80 mg). The reaction was kept under hydrogen atmosphere (40 psi) until sampling showed the complete deprotection of the benzyloxycarbonyl groups.
 25 The reaction mixture was filtered, and then dried and coevaporated with toluene and methanol, giving the titled product. 70 mg.

³¹P-NMR (CD₃OD): 17.7

30 Example A-13

4-amino-1-hydroxybutyliden-1,1-bisphosphonic acid, di-(3-(L-valyloxy)benzoyloxymethyl) ester

a) 4-Benzoyloxycarbonylamino-1-hydroxybutyriden-1,1-bisphosphonic acid, di-(3-(N-benzoyloxycarbonyl-L-valyloxy) benzoyloxymethyl) ester.

To a solution of 4-benzoyloxycarbonylamino-1-hydroxybutyriden-1,1-bisphosphonic acid (0.59g, 1.5 mmole) and diisopropylethyl-amine (0.64g, 5 mmole) in N,N-dimethylformamide (40 ml) was added dropwise a solution of iodomethyl-3-(N-benzoyloxycarbonyl-L-valyloxy)-benzoate (2.2g, 4.3 mmole) in N,N-dimethylformamide (5 ml). The mixture was stirred 2 hours at room temperature under argon. The mixture was evaporated under reduced pressure. Ethyl acetate (50 ml) was added and the mixture was filtered after 2 hours. The organic phase was washed twice with 5% sodium hydrogencarbonate solution and dried with sodium sulfate. The product was isolated by silica gel column chromatography.

Yield: 0.23g = 15%

¹H-NMR (CDCl₃ + 5% CD₃OD) 0.89 (m, 12H) 1.58-2.28 (m, 6H) 2.92 (m, 2H) 4.26 (m, 2H) 5.00 (m, 6H) 5.46-6.02 (m, 4H) 6.78- 7.86 (8m, 23H)
³¹P-NMR (CDCl₃ + 5% CD₃OD) 16.5 (s)

b) 4-amino-1-hydroxybutyriden-1,1-bisphosphonic acid, di-(3-(L-valyloxy) benzoyloxymethyl) ester.

Deprotection of the CBz groups of 4-benzoyloxycarbonylamino-1-hydroxybutyriden-1,1-bisphosphonic acid, di-(3-(N-benzoyloxycarbonyl-L-valyloxy) benzoyloxymethyl) ester using mild conditions as specified in Greene, "Protecting Groups in Organic Synthesis, (John Wiley & Sons, New York, 1981) yields the title compound.

Example A-14

4-Amino-1-hydroxybutyriden-1,1-bisphosphonic acid, di-(3-(L-valyloxy)-propionyloxymethyl) ester

a) 4-Benzoyloxycarbonylamino-1-hydroxybutyriden-1,1-bisphosphonic acid, di-(3-(N-benzoyloxycarbonyl-L-valyloxy)-propionyloxymethyl) ester.

To a solution of 4-benzoyloxycarbonylamino-1-hydroxybutyriden-1,1-bisphosphonic acid (0.88g, 2,5 mmole) and diisopropylethyl-amine (0.78g, 6 mmole) in N,N-dimethylformamide (40 ml) was added dropwise a solution of iodomethyl-3-(N-

benzyloxycarbonyl-L-valyloxy)-propionate (2.3g, 4.95 mmole) in N,N-dimethylformamide (5 ml). The mixture was stirred 2 hours at room temperature under argon and evaporated under reduced pressure. Ethyl acetate (50 ml) was added and the mixture was filtered after 2 hours. The organic phase was washed twice with 5% sodium hydrogencarbonate solution and dried with sodium sulfate. The product was isolated by silica gel column chromatography. Yield: 0.19g = 8%

¹H-NMR (CDCl₃ + 5% CD₃OD) 0.89 (m, 12H) 1.62-2.16 (m, 6H) 2.60 (m, 4H) 3.08 (m, 2H) 4.12 (m, 2H) 4.30 (m, 4H) 5.02 (m, 6H) 5.42-5.64 (m, 4H) 7.24 (m, 15H)
³¹P-NMR (CDCl₃ + 5% CD₃OD) 16,9 (s)

b) 4-Amino-1-hydroxybutyliden-1,1-bisphosphonic acid, di-(3-(L-valyloxy)-propionyloxymethyl) ester.

Deprotection of the CBz groups of 4-benzyloxycarbonylamino-1-hydroxybutyliden-1,1-bisphosphonic acid, di-(3-(N-benzyloxycarbonyl-L-valyloxy)-propionyloxymethyl) ester using mild conditions as specified in Greene, "Protecting Groups in Organic Synthesis, (John Wiley & Sons, New York, 1981) yields the title compound.

Example A-15

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di-(4-(L-valyloxy)benzoyloxymethyl) ester.

a) 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di-(4-(N-benzyloxycarbonyl-L-valyloxy) benzoyloxymethyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (141 mg, 0.37 mmole) was esterified from the corresponding iodomethyl ester by the method described in Example A-3-a) to yield 55 mg of title compound. R_f (20%MeOH/CHCl₃) 0.15 (at the center of oval spot from baseline).

¹H-NMR (CDCl₃+ 1%CD₃OD): 7.82 (m, 4H), 7.29 (m, 15H), 6.97 (m, 4H), 5.85 (m, 4H), 5.11 (m, 6H), 4.46 (m, 2H), 3.10 (m, 2H), 2.30-1.77 (m, 6H), 1.52 (m, 6H), 0.99 (m, 12H).

^{31}P -NMR ($\text{CDCl}_3 + 1\% \text{CD}_3\text{OD}$) (H_3PO_4 reference): δ 15.6(s).

b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di-(4-(L-valyloxy) benzoyloxymethyl) ester.

5 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di-(4-(N-benzyloxycarbonyl-L-valyloxy) benzoyloxymethyl) ester is CBz deprotected using mild conditions as prescribed in Greene, "Protecting Groups in Organic Synthesis, (John Wiley & Sons, New York, 1981) to yield the title compound.

10 Example A-16

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di-(3-(3,4-di-(L-valyloxy) phenyl) propionyloxymethyl) ester.

a) 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic
15 acid, di-(3-(3,4-di(N-benzyloxycarbonyl-L-valyloxy) phenyl) propionyloxy- methyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (143 mg, 0.37 mmole) was esterified from the corresponding iodoemthyl ester by the method described in Example A-3-a) to yield 169 mg of the title compound. R_f
20 (20%MeOH/ CHCl_3) 0.15 (at the center of oval spot from baseline).

^1H -NMR ($\text{CDCl}_3 + 1\% \text{CD}_3\text{OD}$): 7.40-6.85 (m, 31H), 5.62 (m, 4H), 5.02 (m, 10H), 4.43 (m, 4H), 3.10 (m, 2H), 2.84 (m, 4H), 2.61 (m, 4H), 2.35-1.73 (m, 8H), 1.52 (m, 6H), 0.99 (m, 24H). ^{31}P -NMR ($\text{CDCl}_3 + 1\% \text{CD}_3\text{OD}$) (H_3PO_4 reference): δ 14.3 (s).

25

b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di-(3-(3,4-di-(L-valyloxy) phenyl) propionyloxymethyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di-(3-(3,4-di(N-benzyloxycarbonyl-L-valyloxy) phenyl) propionyloxy- methyl) ester
30 is CBz deprotected using mild conditions as prescribed in Greene, "Protecting Groups in Organic Synthesis, (John Wiley & Sons, New York, 1981) to yield the title compound.

Example A-17

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, tri(3-(L-valyloxy)-2,2-dimethylpropoxycarbonyloxymethyl) ester

- a) 4-Benzylloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic
5 acid tri(3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethylpropoxycarbonyl
oxymethyl) ester.

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic
acid (174 mg, 0.45 mmol) in dry DMF (1 mL) were added diisopropylethylamine
(240 μ L, 1.38 mmol), followed by 3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-
10 dimethylpropyl iodomethyl carbonate (592 mg, 1.14 mmol). After stirring for 5 h at
ambient temperature, under nitrogen, the reaction mixture was concentrated on a
rotavapor, treated with ethyl acetate (15 mL), and filtered. The organic solution was
washed with 5% Na₂S₂O₃, followed by brine. Drying over anhydrous Na₂SO₄ and
concentration gave a yellow oil that was subjected to column chromatography (silica,
15 2/1 petroleum ether – ethyl acetate, 2.5 – 20% methanol in CH₂Cl₂) to give fine,
white solids (147 mg) enriched in the triester. The solids were dissolved in ethyl
acetate, washed twice with 5% aqueous EDTA-disodium salt, dried over anhydrous
Na₂SO₄, and evaporated to dryness under vacuum.

R_f (10% methanol in CH₂Cl₂) 0.30; ¹H NMR (250 MHz, CDCl₃ + 1% CD₃OD) δ
20 0.85-0.95 (m, 36 H), 1.70-2.20 (m, 7H), 3.10 (br s, 2H), 3.85-3.95 (br, 12 H), 4.25
(m, 3H), 5.05 (s, 8H), 5.52-6.0 (m, 10H), 7.30 (s, 20H); ³¹P NMR (101 MHz, CDCl₃
+ 1% CD₃OD) δ 13.6 and 24.6 (2d, *J* = 47 Hz). The diester was a minor component:
³¹P NMR δ 18.6 (s).

- b) Removal of benzyloxycarbonyl protecting groups.
25 The triester (110 mg) from step (a) was hydrogenated at 40 psi over Pd black (14 mg)
in 4.2 mL solvent (2/1/1 ethyl acetate - methanol - acetic acid) for 18.5 h. The
suspension was filtered through a small column of celite and washed with ethyl
acetate - methanol. The filtrate was evaporated to dryness under vacuum to give

white solids (97 mg). Because proton NMR showed incomplete deprotection, the material was resubmitted for hydrogenation (14 mg Pd, 10 mL solvent) overnight to give the deprotected triester (as the acetate salt, 79 mg) as shown by the disappearance of peaks for the benzyloxy group at δ 5.05 and 7.30.

5 ^{31}P NMR (101 MHz, CDCl_3) δ 12.5 and 24.0.

Example A-18

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di-(2-methyl-1-(L-valyloxy)-2-propoxycarbonyloxymethyl) ester

a) 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid
10 di(1-(*N*-benzyloxycarbonyl-L-valyloxy)-2-methyl-2-propoxycarbonyloxymethyl)
ester.
4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (460 mg,
1.2 mmol) was esterified by the method described in Example A-17 a) with 1-(*N*-
benzyloxycarbonyl-L-valyloxy)-2-methyl-2-propyl iodomethyl carbonate (1.54 g, 3.0
15 mmol) for 2h. After column chromatography (silica, 4-20% methanol in CH_2Cl_2), the
pure fractions containing the title compound were pooled together and concentrated.
The residue was dissolved in ethyl acetate, washed twice with 5% aqueous EDTA-
disodium salt, and then, water, dried over Na_2SO_4 , and evaporated to dryness under
vacuum to give the diester as off-white solids (92 mg).

20 ^{31}P NMR (101 MHz, CDCl_3 + 1% CD_3OD) δ 19.5 (s); ^1H NMR (250 MHz, CDCl_3 +
1% CD_3OD) δ 0.76-1.41 (m, 24H), 1.74 (br s, 4H), 2.05 (m, 2H), 3.02 (br s, CH_2N),
3.90-4.30 (m, $\text{CH}_2\text{OC}=\text{O}$ and $\text{CH}\alpha$ valine), 4.93-5.01 (m, 6H), 5.30-5.90 (m, OCH_2O
and $\text{NHC}=\text{O}$), 7.22 (s, 15H).

(b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di(2-methyl-1-
25 (L-valyloxy)-2-propoxycarbonyloxymethyl) ester.

The benzyloxycarbonyl-protected diester (86 mg) from step (a) was hydrogenated by the method described in Example A-17 b) to give the title compound (as the acetate salt) as a white powder (72 mg).

^{31}P NMR (101 MHz, CDCl_3) δ 19.2 (s).

5 Example A-19

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di (2-methyl-2-(L-isoleucyloxymethyl)propionyloxymethyl) ester.

a) 4-N-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic
10 acid di (2-methyl-2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)propionyl-oxymethyl) ester.

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (824mg, 2.1 mmole) and diisopropylethylamine (0.8g, 6.3 mmole) in dry N,N-dimethylformamide (15 ml) was added dropwise a solution of iodomethyl 2-methyl-
15 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl) propionate (3.1g, 5.21 mmole) in N,N-dimethylformamide (6 ml). The mixture was stirred 2 hours at room temperature and evaporated under reduced pressure. Ethyl acetate (70 ml) was added and after 1 hour the crystals were filtered. The organic phase was washed two times with
20 evaporated under reduced pressure. The product was isolated by silica gel column chromatography with dichloromethane/methanol. Yield: 0.36g

^1H -NMR (CDCl_3) 0.86(m, 12H) 1.20 (m, 16H) 1.60-2.20 (m, 6H) 3.10 (m, 2H) 3.80-4.40 (m, 6H) 5.08 (m, 6H) 5.45 (m, 4H) 7.29 (m, 15H)
25 ^{31}P -NMR (CDCl_3 +5% CD_3OD) 14.2 (s)

b) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di (2-methyl-2-(isoleucyloxymethyl)propionyloxymethyl) ester.

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di (2-methyl-2-(N-benzyloxycarbonylamino-L-isoleucyloxymethyl)propionyl-
30 oxymethyl) ester (0.195g, 0.171 mmole) in ethyl acetate (10 ml), methanol (10 ml)

and acetic acid (5 ml) was added palladium black (100mg). The mixture was hydrogenated overnight at 45 psi. The catalyst was filtered and washed with ethyl acetate, methanol and acetic acid. The solution was evaporated under reduced pressure and the product was dried in vacuo to yield the title compound as the triacetate salt. Yield: 150mg.

^{31}P -NMR (CDCl_3 +5% CD_3OD) 18.1 (s)

Example A-20

10 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di (4-(L-valyloxy)-cyclohexanoyloxymethyl) ester

a) 4-N-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di (4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoyloxymethyl) ester.

15 To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (0.706g, 1.8 mmole) and diisopropylethylamine (07g, 5.4 mmole) in N,N-dimethylformamide (15 ml) was added dropwise a solution of iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate (2.35g, 4.5 mmole) in N,N-dimethylformamide (5 ml). The mixture was stirred 2 hours at room temperature under argon. The mixture was evaporated under reduced pressure. Ethyl acetate (60 ml) was added and the solid was filtered after 2 hours. The organic phase was washed twice with saturated sodium hydrogencarbonate and brine. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The products were isolated by silica gel column chromatography with dichloromethane/
25 methanol. After silica gel column chromatography the fractions were dissolved in ethyl acetate and washed three times with 5% aqueous EDTA-disodium salt solution, dried with sodium sulfate, evaporated under reduced pressure and dried in vacuo to yield 298mg

30 ^1H -NMR (CDCl_3) 0.84 (m, 12H) 1.35-2.35 (m, 24H) 3.10 (m, 2H) 4.08 (m, 2H) 5.02 (m, 8H) 5.55 (m, 4H) 7.24 (m, 15H)

^{31}P -NMR (CDCl_3 + 5% CD_3OD) 15.2 (s)

b) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di (4-(L-valyloxy)-cyclohexanoyloxymethyl) ester.

4-N-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di (4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoyloxymethyl) ester is de-
 5 CBz protected using conventional conditions as exemplified above to yield the title compound.

Example A-21

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid tri (4-(L-valyloxy)-
 10 cyclohexanoyloxymethyl) ester

The appropriate fraction of Example A-20, step a) was dissolved in ethyl acetate and washed three times with 5% aqueous EDTA-disodium salt solution, dried with sodium sulfate, evaporated under reduced pressure and dried in vacuo to yield 320
 15 mg which is deprotected using conventional conditions as exemplified above to yield the title compound.

¹H-NMR (protected form) (CDCl₃) 0.86 (m, 18H) 1.3-2.5 (m, 34H) 3.10 (m, 2H)
 4.22 (m, 3H) 4.55-5.10 (m, 11H) 5.50 (m, 6H) 7.28 (m, 20H)
 20 ³¹P-NMR (CDCl₃ + 5% CD₃OD) 20.8 (d) 10.0 (d)

Example A-22

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di [N-(2-L-valyloxy-1,1-
dimethyl-ethyl)aminocarbonyloxymethyl]ester.

25

a) 4-N-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di [N-(2-L-valyloxy-1,1-dimethyl-ethyl)aminocarbonyloxymethyl]ester.

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (0.1 g, 0. mmole) and diisopropylethylamine (0.31 g, 2.4 mmole) in N,N-dimethylformamide (5 ml) was added dropwise a solution of 2-(N-(iodomethoxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane in N,N-dimethylformamide (2.5 ml). The mixture was stirred 2 hours at room temperature under argon. The mixture was evaporated under reduced pressure. Ethyl acetate (40
 30

ml) was added and the solid was filtered after 2 hours. The organic phase was washed twice with saturated sodium hydrogencarbonate and brine. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with dichloromethane/methanol acetic acid. After silica gel column chromatography the fractions were dissolved in ethyl acetate and washed three times with 5% aqueous EDTA-disodium salt solution, dried with sodium sulfate, evaporated under reduced pressure and dried in vacuo. Yield: 165mg.

¹H-NMR (CDCl₃) 0.80 (m, 12H) 1.20 (m, 12H) 1.88 (m, 6H) 3.00 (m, 2H) 3.64 (m, 4H) 4.20 (m, 2H) 5.00 (m, 6H) 5.50 (m, 4H) 7.26 (m, 15H)
³¹P-NMR (CDCl₃ + 5% CD₃OD) 14.8 (s)

b) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di [N-(2-L-valyloxy-1,1-dimethyl-ethyl)aminocarbonyloxymethyl] ester.

A solution of 4-N-benzyloxycarbonylamino-1-hydroxybutyliden-1,1-bisphosphonic acid di[N-(2-L-valyloxy-1,1-dimethyl-ethyl)aminocarbonyloxymethyl] ester (0.16g 0.14mmole) in ethyl acetate (5ml), methanol (10 ml) and acetic acid (5 ml) was hydrogenated with palladium black 0.1g at room temperature and 45 psi overnight. The catalyst was filtered and washed with ethyl acetate and methanol. The solution was evaporated under reduced pressure and the product was dried in vacuo to yield the triacetate salt. Yield: 100mg

³¹P-NMR (CDCl₃ + 5% CD₃OD) 14.7 (s)

Example A-23

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester

a) 4-Benzoyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester.

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (565 mg, 1.44 mmol) in DMF (10 mL), was added diisopropylamine (0.75 mL, 4.32 mmol), followed by an injection of a solution of give 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester (2.00 g, 3.60 mmol) in DMF (5 mL). After stirring under argon for 1.5 h at room temperature, the solution was concentrated and treated with ethyl acetate (100 mL). Crystals were filtered off and the filtrate was extracted with brine containing a small amount of sodium thiosulfate. The organic phase was filtered through anhydrous sodium sulfate and evaporated. After silica gel column (silica gel, 4→20% MeOH in CH₂Cl₂), the pure fractions containing the title compound were combined and evaporated. The residue was then dissolved in ethyl acetate and the solution extracted twice with aqueous saturated sodium bicarbonate and then twice with 5% aqueous EDTA-disodium salt. The ethyl acetate phase was evaporated, to give 205 mg of 4-benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester.

¹H-NMR (CDCl₃): 8.35-7.95 (m, 2H), 7.85-7.50 (m, 2H), 7.26 (br s, 15H), 6.60-6.20 (m, 2H), 5.90-5.35 (m, 4H), 5.15-4.80 (m, 6H), 4.50-4.00 (m, 10H), 3.18-3.00 (m, 2H), 2.45-1.55 (m, 6H), 1.00-0.80 (m, 12H).
³¹P-NMR (CDCl₃)(H₃PO₄ reference): 16.8 (s).

b) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester.
A solution of 4-benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester (180 mg, 0.145 mmol) in methanol / ethyl acetate / acetic acid (2:1:1 v/v/v) (20 mL) was hydrogenated over a Pd-black catalyst (30 mg) at 40 psi of hydrogen for 10 h. The suspension was filtered through celite and the filtrate was evaporated to dryness under reduced pressure, to give 85 mg of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(1-(2-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyloxymethyl) ester was obtained as a white solid.

128

¹H-NMR (CDCl₃): 8.65-8.20 (m, 2H), 7.95-7.65 (m, 2H), 6.65-6.30 (m, 2H), 5.90-5.35 (m, 4H), 4.70-4.00 (m, 10H), 3.18-3.00 (m, 2H), 2.45-1.55 (m, 6H), 1.00-0.80 (m, 12H).

³¹P-NMR (CDCl₃)(H₃PO₄ reference): 13.9 (s).

5

Example A 24

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid di ((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl) ester

10 a) 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di ((1,3-di-(N-benzyloxycarbonyl)valyloxy)propyl-2-oxycarbonyloxy methyl) ester.

4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (141 mg, 0.37 mmole) was esterified by the method described in Example A-1 a using the
15 corresponding iodomethyl ester to give 90 mg of the title compound.
R_f (10%MeOH/CHCl₃) 0.20 (at the center of oval spot from baseline).

¹H-NMR (CDCl₃+ 1%CD₃OD): 7.29 (m, 25H), 5.65 (m, 4H), 5.14-4.85 (m, 12H), 4.45-4.05 (m, 12H), 3.11 (m, 2H), 2.14-1.76 (m, 8H), 0.87 (m, 24H). ³¹P-NMR
20 (CDCl₃+1%CD₃OD)(H₃PO₄ reference): δ 16.7 (s).

b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid di ((1,3-di-(valyloxy)propyl-2-oxycarbonyloxy methyl) ester.

A solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic
25 acid di ((1,3-di-(N-benzyloxycarbonyl)valyloxy)propyl-2-oxycarbonyloxy methyl) ester (162 mg, 0.1 mmol) in methanol / ethyl acetate / acetic acid (2:1:1 v/v/v) (6 ml) was hydrogenated over a Pd-black catalyst (70 mg) at 40 psi of hydrogen for 16 h. The suspension was filtered through Celite on a fine pore sized glass sinter and washed with methanol/ethyl acetate (2:1). The filtrate was evaporated to dryness in
30 vacuo and the title compound was obtained as the pentacetate, a white solid after a few co-evaporations with dioxane and hexane.

³¹P-NMR (CDCl₃+ 5%CD₃OD)(H₃PO₄ reference): δ 13.5 (br).

Example A 25

4-Amino-1-hydroxybutyliden-1,1-bisphosphonic acid di-(2-(L-valyloxymethyl)-2-ethyl butyroyloxymethyl) ester

- 5 a) 4-N-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di-(2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl)-butyroyloxymethyl) ester.

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutyliden-1,1-biphosphonic acid (0.777g, 2.0 mmole) and diisopropylethylamine (0.78g, 6.0 mmole) in N,N-
 10 dimethylformamide (15 ml) was added dropwise a solution of iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyrate (2.6g, 5 mmole) in N,N-dimethylformamide (5 ml). The mixture was stirred 2 hours at room temperature under argon. The mixture was evaporated under reduced pressure. Ethyl acetate (60 ml) was added and the solid was filtered after 2 hours. The organic phase was washed
 15 twice with saturated sodium hydrogencarbonate and brine. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The products were isolated by silica gel column chromatography with dichloromethane/methanol. After silica gel column chromatography the pure fractions were dissolved in ethyl acetate and washed three times with 5% aqueous EDTA-disodium salt solution, dried with
 20 sodium sulfate, evaporated under reduced pressure and dried in vacuo. Yield: 320mg

¹H-NMR (CDCl₃) 0.84 (m, 24H) 1.5-2.2 (m, 14H) 3.10 (m, 2H) 4.20 (m, 2H) 5.0 (m, 6H) 5.50 (m, 4H) 7.26 (m, 15H) ³¹P-NMR (CDCl₃ + 5% CD₃OD) 14.5 (s)

- 25 b) 4-amino-1-hydroxybutyliden-1,1-bisphosphonic acid di-(2-(L-valyloxymethyl)-2-ethyl butyroyloxymethyl) ester.

A solution of 4-benzyloxycarbonylamino-1-butylidene-1,1-bisphosphonic acid di-(2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyroyloxymethyl) ester (0.195g, 0.167 mmole) in methanol (15 ml), ethyl acetate (5 ml) and acetic acid (10
 30 ml) was hydrogenated with palladium black (120mg) at room temperature overnight with 45 psi. The catalyst was filtered and washed with ethyl acetate, methanol and acetic acid. The solution was evaporated under reduced pressure and solidified with ether. The product was filtered and dried in vacuo to yield the tri acetate salt.

Yield: 0.125g. ^{31}P -NMR ($\text{CDCl}_3 + 5\% \text{CD}_3\text{OD}$) 14.9 (s)

Example A 26

5 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester

a) 4-Benzoyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(N-CBz-L-valyloxy)-2-methyl-propionyloxymethyl) ester.

10 To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (580 mg, 1.48 mmol) in DMF (10 mL), was added diisopropylamine (0.773 mL, 4.44 mmol), followed by an injection of a solution of iodomethyl 3-(N-CBz-L-valyloxy)-2-methyl-propionate (1.77 g, 3.70 mmol) in DMF (5 mL). After stirring under argon for 1.5 h at room temperature, the solution was concentrated on
15 rotavapor and treated with ethyl acetate (100 mL). Crystals were filtered off and the filtrate was extracted with brine containing a small amount of sodium thiosulfate. The organic phase was filtered through anhydrous sodium sulfate and evaporated. After silica gel column (silica gel, 4→20% MeOH in CH_2Cl_2), the pure fractions containing the title compound were combined and evaporated. The residue was then
20 dissolved in ethyl acetate and the solution extracted twice with aqueous saturated sodium bicarbonate and then twice with 5% aqueous EDTA-disodium salt. The ethyl acetate phase was evaporated, to give 189 mg of 4-benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(N-CBz-L-valyloxy)-2-methyl-propionyloxymethyl) ester.

25

^1H -NMR ($\text{CDCl}_3 + 1\% \text{CD}_3\text{OD}$): 7.32 (br s, 15H), 5.85-5.30 (m, 4H), 5.18-4.93 (m, 6H), 4.30-3.95 (m, 6H), 3.22-3.00 (m, 2H), 2.93-2.70 (m, 2H), 2.20-1.65 (m, 6H), 1.35-1.05 (m, 6H), 1.00-0.75 (m, 12H).

^{31}P -NMR (CDCl_3)(H_3PO_4 reference): 15.1 (s).

30

b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester.

131

A solution of 4-benzyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(N-CBz-L-valyloxy)-2-methyl-propionyloxymethyl) ester (189 mg, 0.175 mmol) in methanol / ethyl acetate / acetic acid (2:1:1 v/v/v) (20 mL) was hydrogenated over a Pd-black catalyst (35 mg) at 50 psi of hydrogen for 7h. The suspension was filtered through celite and the filtrate was evaporated to dryness under reduced pressure, to give 110 mg of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(L-valyloxy)-2-methyl-propionyloxymethyl) ester as the acetate salt, a white solid.

³¹P-NMR (CDCl₃+CD₃OD)(H₃PO₄ reference): δ 14.7 (br s)

Example A 27

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(L-t-butylglycyloxy)-2,2-dimethylpropionyloxymethyl) ester

- 5 a) 4-Benzoyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionyloxymethyl) ester. To a solution of 4-benzoyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (588 mg, 1.50 mmol) in DMF (10 mL), was added diisopropylamine (0.783 mL, 4.50 mmol), followed by an injection of a solution of iodomethyl 3-(N-CBz-L-t-
- 10 butylglycyloxy)-2,2-dimethylpropionate (1.90 g, 3.75 mmol) in DMF (5 mL). After stirring under argon for 1.5 h at room temperature, the solution was concentrated on rotavapor and treated with ethyl acetate (100 mL). Crystals were filtered off and the filtrate was extracted with brine containing a small amount of sodium thiosulfate. The organic phase was filtered through anhydrous sodium sulfate and evaporated.
- 15 After silica gel column (silica gel, 5→20% MeOH in CH₂Cl₂), the pure fractions containing the title compound were combined and evaporated. The residue was then dissolved in ethyl acetate and the solution extracted twice with aqueous saturated sodium bicarbonate and then twice with 5% aqueous EDTA-disodium salt. The ethyl acetate phase was evaporated, to give 158 mg of 4-benzoyloxy carbonylamino-1-
- 20 hydroxybutylidene-1,1-bisphosphonic acid bis (3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionyloxymethyl) ester.

¹H-NMR (CDCl₃+1%CD₃OD): 7.26 (br s, 15H), 5.85-5.40 (m, 4H), 5.15-4.88 (m, 6H), 4.20-3.95 (m, 6H), 3.20-3.00 (m, 2H), 2.10-1.65 (m, 4H), 1.22-1.05 (m, 12H),

25 1.00-0.75 (m, 18H).

³¹P-NMR (CDCl₃)(H₃PO₄ reference): 15.1 (s).

- b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(L-t-butylglycyloxy)-2,2-dimethylpropionyloxymethyl) ester.
- 30 A solution of 4-benzoyloxy carbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(N-CBz-L-t-butylglycyloxy)-2,2-dimethylpropionyloxymethyl) ester (158 mg, 0.139 mmol) in methanol / ethyl acetate / acetic acid (2:1:1 v/v/v) (20 mL) was hydrogenated over a Pd-black catalyst (40 mg) at 50 psi of hydrogen for 16h.

The suspension was filtered through celite and the filtrate was evaporated to dryness under reduced pressure, to give 100 mg of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid bis (3-(L-t-butylglycyloxy)-2,2-dimethylpropionyloxymethyl) ester as a white solid.

5

^{31}P -NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) (H_3PO_4 reference): δ 14.6 (br s)

Example A 28

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di[*trans*-4-(L-valyloxy)-L-prolyloxymethyl] ester

10

a) 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid di[*N*-benzyloxycarbonyl-*trans*-4-(*N*-benzyloxycarbonyl-L-valyloxy)-L-prolyloxymethyl] ester.

15 Diisopropylethylamine (195 μL , 1.12 mmol) was added to a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (144 mg, 0.38 mmol) in 1 mL dry DMF, followed by the dropwise addition of a solution of the iodomethyl ester (520 mg, 0.814 mmol) from step (d) in 3 mL DMF. After stirring at ambient temperature for 5.5 h, the reaction mixture was concentrated on a rotavapor, treated with EtOAc (20 mL), and filtered. The precipitates were washed with 10 mL more EtOAc. The organic solution was washed with 10 mL saturated aqueous NaHCO_3 containing a small amount of $\text{Na}_2\text{S}_2\text{O}_3$, followed by reextraction of the aqueous phase with 10 mL EtOAc. The organic phases were combined, washed with 10 mL brine, dried over anhydrous Na_2SO_4 , and concentrated. Flash column chromatography (silica gel, 5 – 25 % MeOH in CH_2Cl_2 (20 mL) yielded a fraction that gave light yellow solids (59 mg) enriched in the diester. The solids were dissolved in 25 mL EtOAc, washed with 5% aqueous EDTA-disodium salt (2 x 2 mL), dried over anhydrous Na_2SO_4 , and evaporated to dryness under vacuum.

20

25

30 ^1H NMR (250 MHz, $\text{CDCl}_3 + 1\% \text{CD}_3\text{OD}$) δ 0.81-0.97 (m, 12H), 1.60-2.50 (br, 10H), 3.09 (br s, 2H), 3.55-3.77 (m, 4H), 4.20 (br s, 2H), 4.43 (m, 2H), 4.80-5.40 (m, 12H), 5.64 (br, 4H), 7.28-7.35 (m, 25H);

134

^{31}P NMR (101 MHz, CDCl_3 + 1% CD_3OD) δ 18.3.

b) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid di[*trans*-4-(*N*-benzyloxycarbonyl-L-valyloxy)-L-prolyoxymethyl] ester.

- 5 The product of step a) is deCBz protected by gentle conditions as described in Greene supra to yield the title compound.

Biological Example 1

The bioavailability of prodrugs of the invention built on the *bis*-phosphonate alendronate was assayed in rats. The prodrugs of the invention were orally
5 administered at a dose corresponding to 0.1 mmol/kg to triplicate rats in a propylene glycol vehicle. The mother compound was also administered IV at 1/10 of that does for the calculation of absolute oral bioavailability.

Urine was collected over 24 hours in a metabolic cage and analysed as shown in
10 Kline et al J Chromat. 534 (1990) 139-149, but modified as follows: 1 ml of urine is mixed with 50 µl of 1.25 M calcium chloride and 100 µl of 1M sodium hydroxide. After centrifugation, the urine was aspirated off and the pellet redissolved in 0.8 ml 0.2 M acetic acid, 0.4 ml of 0.01 M EDTA and 0.4 ml of 0.2 M sodium acetate. 1 ml of water was added and the solution loaded onto a preconditioned DEA cartridge.
15 The cartridge was washed with 1 ml of water and alendronate eluted with 1 ml of 1M carbonate buffer, pH 10.4. A part of the eluent, 150 µl was mixed with 5 µl of 0.05 M potassium cyanide and 5 µl of NDA solution (1 mg/ml) in methanol. 50 µl was injected into the chromatograph.

20 Absolute bioavailability is determined as the ratio between the AUC for the mother compound administered IV against the AUC for the prodrug administered orally. Results are presented in table 1 below:

Table 1

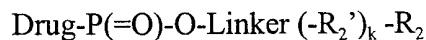
compound	absolute bioavailability (%)
alendronate	2.2
Example A-2	42
Example A-11	34
Example A-3	25
Example A-5	14
Example A-4	12
Example A-18	10
Example A-10	5
Example A-19	8
Example A-24	11
Example A-22	8
Example A-23	10
Example A-12	9

The compounds of the invention exhibit substantially enhanced oral bioavailability
5 relative to the alendronate. The pivaloyloxymethyl alendronate ester presented as the preferred prodrug in US 5 227 506 provided no better bioavailability than the mother compound in this assay (results not shown).

Although the invention has been illustrated by reference to a number of examples
10 built on the phosphorous-containing drug alendronate and employing various linkers and amino acids, it will be appreciated that the invention is not so limited to these values but extends throughout the spirit and scope of the accompanying claims.

Claims

1 A pharmaceutical compound with the formula:



5

where Drug-P(=O)-O- is the residue of a drug comprising a phosphonate, phosphinate or phosphoryl function,

R_2 and R_2' (if present) are independently the acyl residue of an aliphatic amino acid;

10 Linker is an at least difunctional moiety comprising a first function ester-bonded to the phosphonate, phosphinate or phosphoryl function spaced from a second function ester-bonded to R_2 ; and

k is 1 or zero.

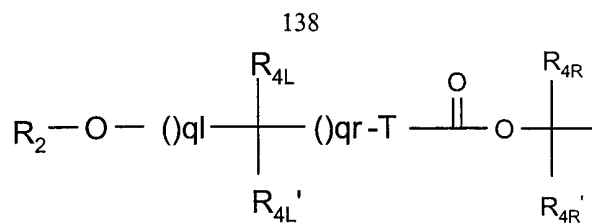
2 A compound according to claim 1, wherein Drug-P(=O)-O- is derived

15 from the group consisting of phosfestrol, (E)-(α,β -diethyl-4,4'-stilbenylen)bis(dihydrogenphosphate), nucleoside analogue phosphonates, nucleotide analogue mono-, di or triphosphates, phosphonoformic acid, phosphonoacetic acid, *bis* phosphonate bone metabolism agents, fosinoprilate, β -phosphonocarboxylic acid farnesyl protein transferase inhibitors, α -phosphonosulfonate squalene synthase

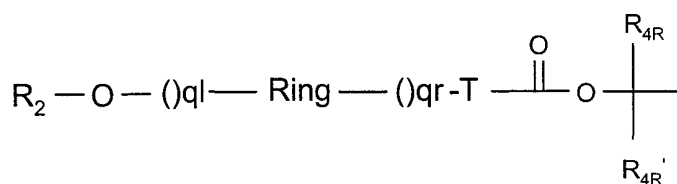
20 inhibitors, phosphonomethylamine neutral endopeptidase (24.11) inhibitors.

3 A compound according to claim 1, wherein the structure of the formula -linker $(-R_2')_k - R_2$ has one of the formulae:

25



or



where

 R_2 is the acyl residue of an aliphatic amino acid,

- 5 $\text{R}_{4\text{L}}$ and $\text{R}_{4\text{L}}'$ are independently H, C_{1-3} alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkyl- $\text{C}_1\text{-C}_6$ cycloalkyl, phenyl or benzyl,

 $\text{R}_{4\text{R}}$ and $\text{R}_{4\text{R}}'$ are independently H, C_{1-3} alkyl or phenyl,

ql is 0-3, qr is 0-3,

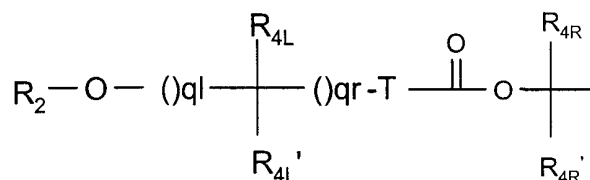
T is a bond, $-\text{NR}_4-$ or $-\text{O}-$

- 10 R_4 is H or C_{1-3} alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle.

- 4 A compound according to claim 3, wherein $\text{R}_{4\text{R}}$ and $\text{R}_{4\text{R}}'$ are hydrogen.

- 15 5 A compound according to claim 3, with the structure:



6. A compound according to claim 5, wherein $\text{R}_{4\text{L}}$ and $\text{R}_{4\text{L}}'$ are respectively: methyl, methyl;

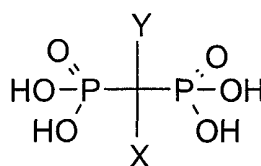
7. A compound according to claim 5, wherein R_{4L} and R_{4L}' are respectively methyl, hydrogen; or ethyl, ethyl.
- 8 A compound according to claim 3, wherein ql and qr are respectively
5 1,0;
2,0;
3,0; or
4,0;
- 10 9 A compound according to claim 8, wherein ql and qr are respectively
1,0.
- 10 A compound according to claim 3, wherein ql and qr are respectively
15 1,1;
2,1;
3,1;
4,1; or
2,2.
- 20 11 A compound according to claim 3 wherein -ring- is phenyl, furyl,
pyridyl, cyclobutyl cyclopentyl or cyclohexyl.
- 12 A compound according to claim 3, wherein the optional substituent to
25 -ring- comprises a structure of the formula: $R_2-()_{ql}$.
- 13 A compound according to claim 3, wherein R_2 is derived from valyl.
14. A compound according to claim 13, wherein R_2 is derived from
30 L-valine.
- 15 A compound according to claim 3, wherein T is a bond.

140

16 A compound according to claim 3, wherein T is -NH-.

17 A compound according to claim 3, wherein T is -O-.

5 18 A compound according to claim 2, wherein the *bis*-phosphonate is derived from a compound of the formula:



where

10 X is H, halo, hydroxy; and Y is

a) C₁₋₁₀ alkyl, optionally substituted with

heterocycle,

-NR_aR_b, where R_a and R_b are independently

hydrogen, C₁₋₆ alkyl or join together to form a 5 to 7

15 membered ring, optionally containing a further hetero atom,

OH, halo, -S(C₁₋₆ alkyl), phenyl, -C₁₋₇ cycloalkyl, (optionally substituted with -NR_aR_b or OH);

b) C₃₋₇ cycloalkyl, optionally substituted with

20 -NR_aR_b, OH, halo, -S(C₁₋₆ alkyl), phenyl, morpholino or pyridyl;

c) halo;

d) piperidinyl;

e) pyrrolidinyl;

f) -S(C₁₋₆ alkyl), optionally substituted with

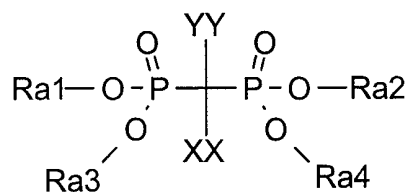
25 -NR_aR_b, OH, halo or phenyl;

g) -S-phenyl, optionally substituted with

halo, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, trifluormethyl, -CONRaR_b or

-COOH.

19 A compound according to claim 18 wherein the bisphosphonate has the formula A-1.



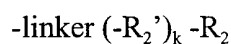
A-1

5

wherein YY and XX have the following values:

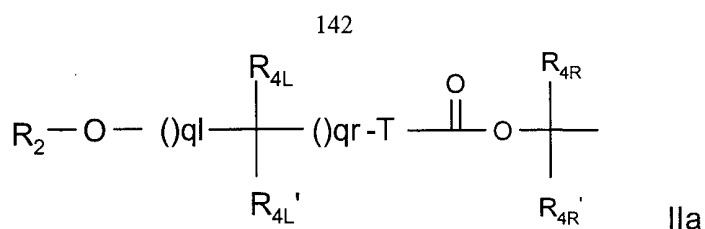
	NH ₂ (CH ₂) ₃ -	OH	(alendronate)
	NH ₂ (CH ₂) ₂ -	OH	(pamidronate)
	cycloheptylamino-	H	(cimadronate)
10	chloro-	chloro	(clodronate)
	pyrrolidin-1-ylCH ₂ CH ₂ -	OH	(EB 1053)
	CH ₃ -	OH	(etidronate)
	methylpentylaminoCH ₂ CH ₂ -	OH	(ibandronate)
	dimethylaminoCH ₂ CH ₂ -	OH	(olpadronate)
15	pyridin-3-ylCH ₂ -	OH	(risedronate)
	(4-chlorophenyl)-thio-	H	(tiludronate)
	imidazo-(1,2-a)pyridin-3-ylCH ₂ -	OH	(YH 529)
	1H-imidazol-1ylCH ₂ -	OH	(zoledronate);

20 at least one of Ra1-Ra4 is a structure of the formula

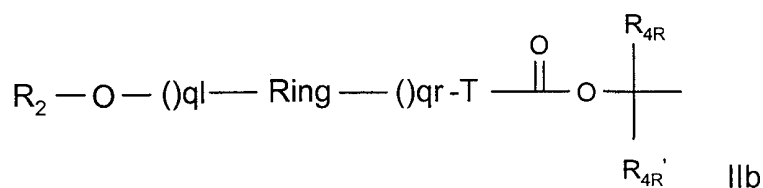


and the remainder are H.

25 20 A compound according to claim 19, wherein at least one of Ra1-Ra4 is a structure of the formula



or



where

R_2 is the acyl residue of an aliphatic amino acid,

R_{4L} and R_{4L}' are independently H, C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkyl- C_1C_6 cycloalkyl
 5 phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl

ql is 0-3, qr is 0-3,

T is a bond, $-NR_4-$ or $-O-$

R_4 is H or C_{1-3} alkyl;

10 -ring- is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;
 and the remainder of $Ra1$ - $Ra4$ are hydrogen or conventional pharmaceutically
 acceptable esters.

21 A compound according to claim 20, wherein $Ra1$ and $Ra2$ are each a
 15 structure IIa or IIb as defined in claim 20 and $Ra3$ and $Ra4$ are H.

22 A compound according to claim 19, derived from alendronate,
 zoledronate or risedronate.

20 23 A compound according to claim 22, selected from:
 alendronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester
 alendronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester
 alendronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,

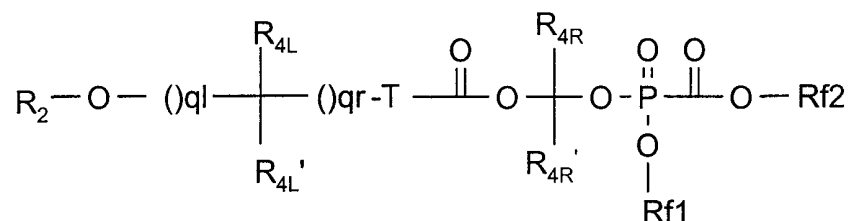
- alendronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester
alendronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
alendronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester
risedronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester,
5 risedronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester
risedronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester
risedronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
risedronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester
risedronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
10 zoledronate di-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester
zoledronate mono-(2-methyl-2-(D-valyloxymethyl) propionyloxymethyl) ester
zoledronate di-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
zoledronate mono-(2-methyl-2-(L-valyloxy) propionyloxymethyl) ester,
zoledronate di-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,
15 zoledronate mono-(2-methyl-2-(D-valyloxy) propionyloxymethyl) ester,

24 A compound according to claim 19, selected from:

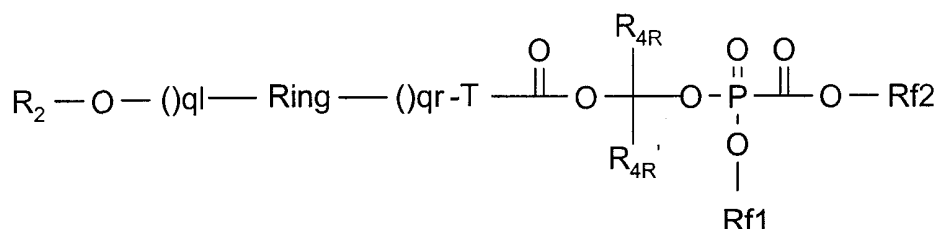
- alendronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
20 risedronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
zoledronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
pamidronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
cimadronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
clodronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
25 [1-hydroxy-3-(1-pyrrolidiny)-propylidene]-bis-phosphonate di-(2-methyl-2-(L-
valyloxymethyl) propionyloxymethyl) ester,
etidronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
ibandronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
olpadronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
30 tiludronate di-(2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester,
[1-hydroxy-2imidazo-(1,2-a)pyridin-3-ylethylidene]-bis-phosphonate di-(2-methyl-2-
(L-valyloxymethyl) propionyloxymethyl) ester,

and pharmaceutically acceptable salts thereof.

25 A compound according to claim 2 with the formula:



or



5

where

R_2 is the acyl residue of an aliphatic amino acid,

R_{4L} and R_{4L}' are independently H, C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkyl- C_1C_6 cycloalkyl,
10 phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl,

ql is 0-3, qr is 0-3,

T is a bond, $-NR_4-$ or $-O-$

R_4 is H or C_{1-3} alkyl;

15 ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;

Rf1 is H or a further -linker- (R_2') - R_2 structure as defined in claim 3,

and Rf2 is H, a conventional pharmaceutically acceptable ester or a further -linker-
 (R_2') - R_2 structure as defined in claim 3,

and pharmaceutically acceptable salts thereof.

20

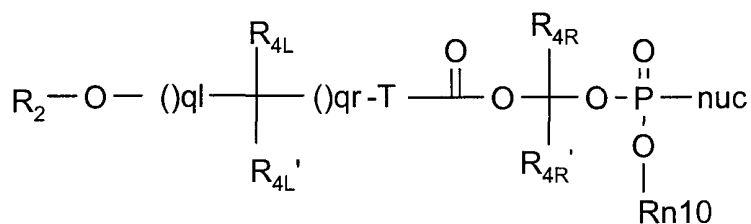
26 A compound according to claim 25, wherein Rf1 is H

27 A compound according to claim 25, wherein Rf1 is the same - linker $(-R_2')_k-R_2$ structure as depicted in claim 25.

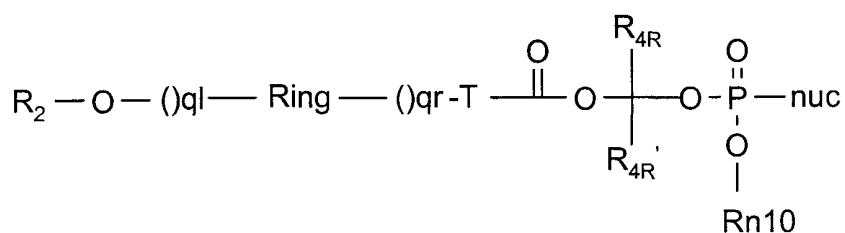
28 A compound according to claim 25, wherein Rf2 is H, methyl or ethyl.

5

29 A compound according to claim 2 of the formula:



or



- 10 wherein nuc is a cyclic or acyclic nucleoside analogue phosphonate;
 Rn10 is H or a further $(-R_2')_k-R_2$ structure as defined in claim 3;
 R₂ is the acyl residue of an aliphatic amino acid,
 R_{4L} and R_{4L}' are independently H, C₁₋₃ alkyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-C₁C₆cycloalkyl phenyl or benzyl,
 15 R_{4R} and R_{4R}' are independently H, C₁₋₃ alkyl or phenyl
 ql is 0-3, qr is 0-3,
 T is a bond, -NR₄- or -O-
 R₄ is H or C₁₋₃alkyl;
 ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;
 20 and pharmaceutically acceptable salts thereof.

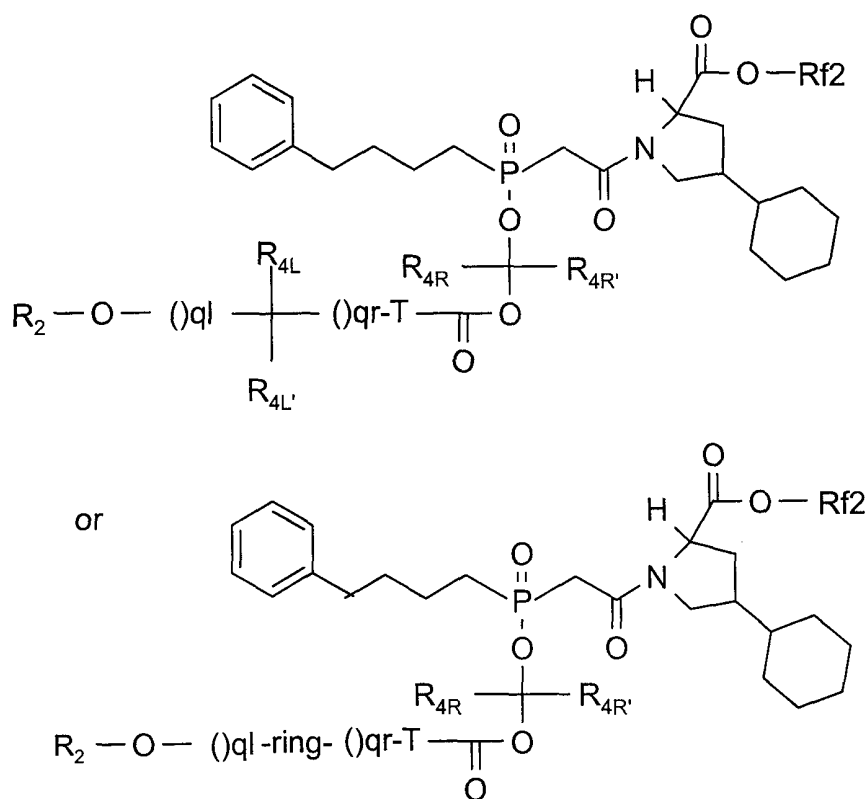
30 A compound according to claim 29, wherein Rn10 is identical to the - linker-(R₂')_k-R₂ structure in the depicted formula.

31 A compound according to claim 29, wherein Rn10 is H.

5

32 A compound according to claim 29, wherein the nucleoside analogue is derived from adefovir, cidefovir, PMPA, HPMP, HMPMPA, HPMPG or HPMPDAP.

33 A compound according to claim 2 of the formula PF3:



10

where

R₂ is the acyl residue of an aliphatic amino acid,

Rf2 is H, a pharmaceutically acceptable ester or a further linker(R₂')-R₂ structure as

15

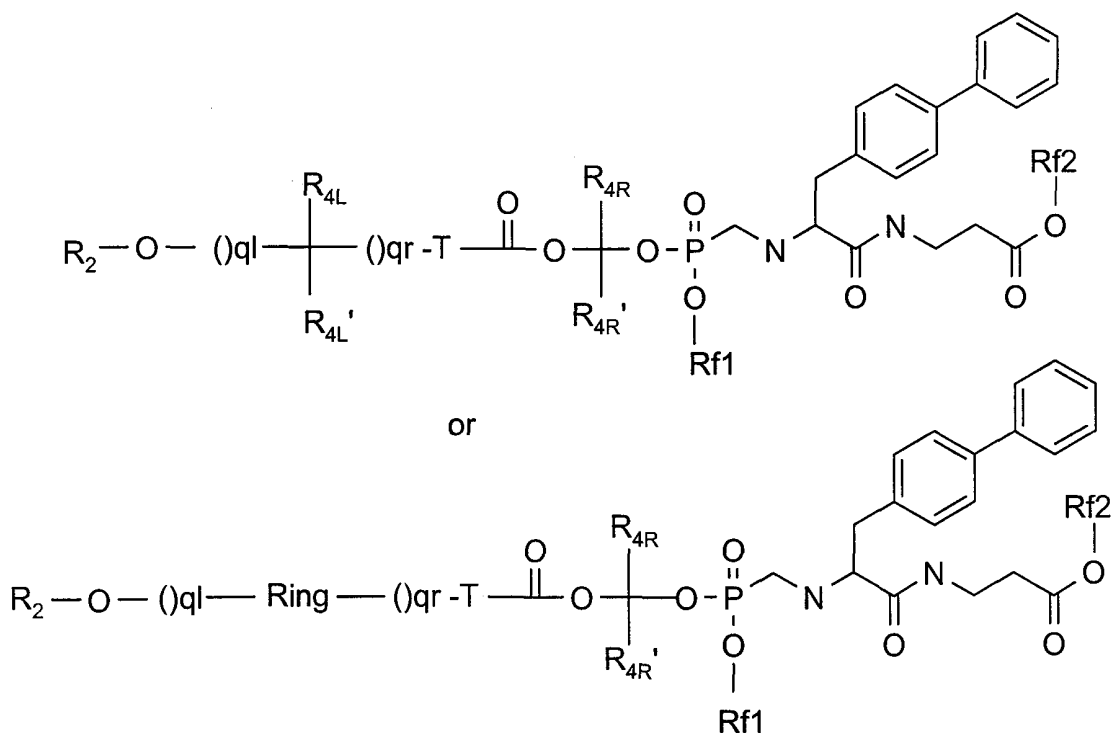
defined in claim 3,
R_{4L} and R_{4L'} are independently H, C₁₋₃ alkyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-C₁C₆cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R'} are independently H, C₁₋₃ alkyl or phenyl,

147

- ql is 0-3, qr is 0-3,
 T is a bond, -NR₄- or -O-
 R₄ is H or C₁₋₃alkyl;
 ring is an optionally substituted aromatic or non-aromatic, hetero- or carbocycle,
 5 and pharmaceutically acceptable salts thereof.

- 34 A compound according to claim 33, wherein Rf2 is H, methyl or ethyl.
- 35 A compound according to claim 2 wherein the neutral endopeptidase
 10 inhibitor has the structure:



- where
- Rf1 is H or a further structure as depicted in claim 3
- 15 Rf2 is H or a pharmaceutically acceptable ester,
- R₂ is the acyl residue of an aliphatic amino acid,
- R_{4L} and R_{4L}' are independently H, C₁₋₃ alkyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-C₁C₆cycloalkyl
 phenyl or benzyl,
- R_{4R} and R_{4R}' are independently H, C₁₋₃ alkyl or phenyl,
- 20 ql is 0-3, qr is 0-3,

T is a bond, -NR₄- or -O-

R₄ is H or C₁₋₃alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle, and pharmaceutically acceptable salts thereof.

5

36 A compound according to claim 35, wherein Rf1 is H.

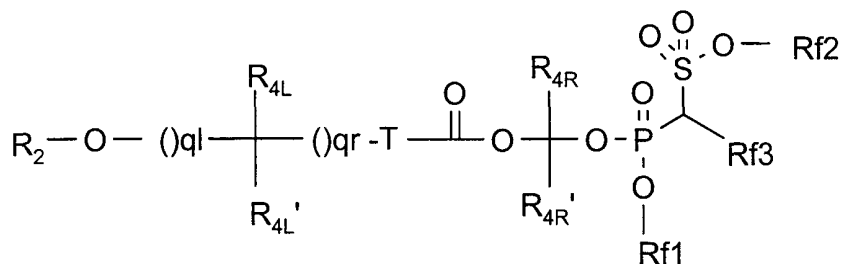
37 A compound according to claim 35, wherein Rf1 is the same
-Linker (-R₂')_x R₂ structure as depicted in claim 35.

10

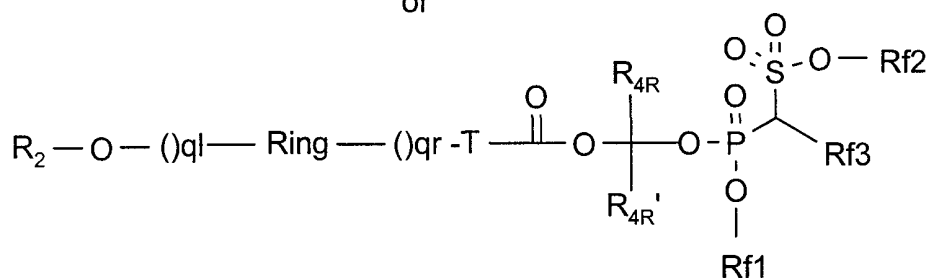
38 A compound according to claim 35, wherein Rf2 is hydrogen, methyl
or ethyl.

39 A compound according to claim 2, wherein the

15 α -phosphonosulphonate has the formula PF5:



or



where Rf1 is H or a further -linker(R₂')_k-R₂ structure as depicted in claim 3,

Rf2 is H or a pharmaceutically acceptable ester,

20 Rf3 is a polyunsaturated, branched C₆₋₂₂ alkyl,

R₂ is the acyl residue of an aliphatic amino acid,

149

R_{4L} and R_{4L}' are independently H, C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkyl- C_1C_6 cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H or C_{1-3} alkyl

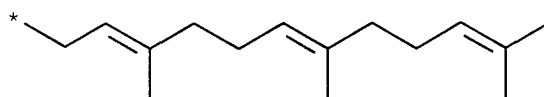
ql is 0-3, qr is 0-3,

5 T is a bond, $-NR_4-$ or $-O-$

R_4 is H or C_{1-3} alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle, and pharmaceutically acceptable salts thereof.

10 40 A compound according to claim 39, wherein the polyunsaturated alkyl Rf3 has the formula:



wherein the asterisk denotes the point of attachment.

15

41 A compound according to claim 39, wherein Rf1 is H.

42 A compound according to claim 39, wherein Rf1 is the same -Linker $(-R_2')$ R_2 structure as depicted in claim 39.

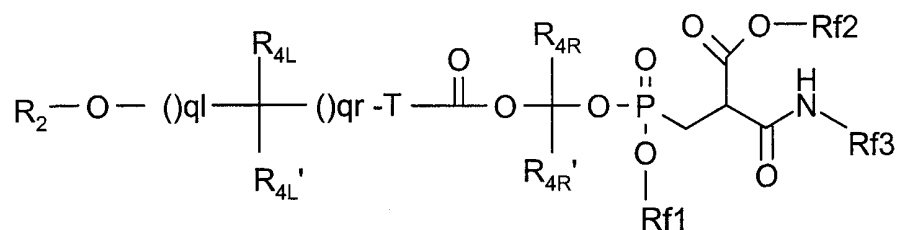
20

43 A compound according to claim 39, wherein Rf2 is H, methyl or ethyl.

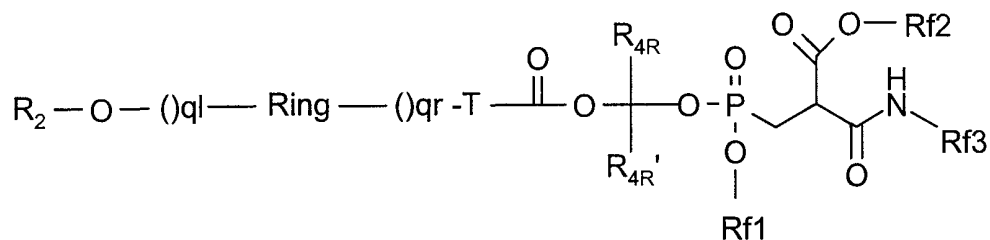
44 A compound according to claim 2 wherein the β -phosphonocarboxylic acid has the formula PF4:

25

150



or



Rf1 is H or a further -linker $(-R_2')_k$ R_2 structure as depicted in claim 3,

Rf2 is H or a pharmaceutically acceptable ester ,

5 Rf3 is a polyunsaturated, branched C_{6-22} alkyl,

R_2 is the acyl residue of an aliphatic amino acid,

R_{4L} and R_{4L}' are independently H, C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkyl- C_1C_6 cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl,

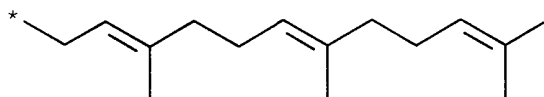
10 ql is 0-3, qr is 0-3,

T is a bond, $-NR_4-$ or $-O-$

R_4 is H or C_{1-3} alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle.

15 45 A compound according to claim 44, wherein the polyunsaturated alkyl Rf3 has the formula:



wherein the asterisk denotes the point of attachment.

20

46 A compound according to claim 44, wherein Rf1 is H.

- 47 A compound according to claim 44, wherein Rf1 is a further
-Linker(R₂')_k-R₂ structure.
- 5 48 A compound according to claim 44, wherein Rf2 is H, methyl or ethyl.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00528

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07F 9/38, C07H 19/06, C07H 19/16, C07D 473/32
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07F, C07H, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0375329 A2 (THE WELLCOME FOUNDATION LIMITED), 27 June 1990 (27.06.90) --	1-17,25-32
A	EP 0694547 A2 (F. HOFFMANN-LA ROCHE AG), 31 January 1996 (31.01.96) --	1-17,25-32
A	US 5484911 A (CHUNG I. HONG ET AL), 16 January 1996 (16.01.96) --	1-17,25-32
A	WO 9213561 A1 (PRO-NEURON, INC.), 20 August 1992 (20.08.92) --	1-17,25-32

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
 - "E" earlier document but published on or after the international filing date
 - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 - "O" document referring to an oral disclosure, use, exhibition or other means
 - "P" document published prior to the international filing date but later than the priority date claimed
 - "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 - "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 - "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 - "&" document member of the same patent family

Date of the actual completion of the international search

15 July 1999

Date of mailing of the international search report

28-07-1999

Name and mailing address of the ISA.

Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Eva Johansson/Elis
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00528

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9532984 A1 (BOEHRINGER MANNHEIM GMBH), 7 December 1995 (07.12.95) --	1-17,25-32
A	WO 9633201 A1 (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE), 24 October 1996 (24.10.96) --	1-17,25-32
A	WO 9200988 A1 (BODOR, NICHOLAS, S.), 23 January 1992 (23.01.92) --	1-28,33-48
A	WO 9413324 A1 (VESTAR, INC.), 23 June 1994 (23.06.94) --	1-28,33-48
A	WO 9615132 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA), 23 May 1996 (23.05.96) --	1-28,33-48
A	US 5227506 A (WALFRED S. SAARI ET AL), 13 July 1993 (13.07.93) --	1-28,33-48
P,A	WO 9821223 A1 (MEDIVIR AB), 22 May 1998 (22.05.98) -- -----	1-48

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00528

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00528

The formulation of the claims is so complicated, owing to the very wide range of combinations of variable parts, that PCT Article 6 is no longer complied with. This Article specifies that the claims must be formulated in a clear and concise manner. The search has therefore been limited to compounds with the same or similar structure as claimed having the same or similar effects as mentioned in the discription.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/06/99

International application No.

PCT/SE 99/00528

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
EP	0375329	A2	27/06/90	AT 123285 T	15/06/95
				AU 618436 B	19/12/91
				AU 4690989 A	21/06/90
				CA 2005815 A	19/06/90
				CY 2058 A	30/04/98
				DE 68922903 D,T	23/11/95
				HK 1000142 A	00/00/00
				JP 2218667 A	31/08/90
				JP 2788084 B	20/08/98
				US 5043339 A	27/08/91
				US 5318974 A	07/06/94
EP	0694547	A2	31/01/96	AT 179173 T	15/05/99
				AU 697107 B	24/09/98
				AU 2719595 A	08/02/96
				BR 9503468 A	27/02/96
				CA 2154721 A	29/01/96
				CN 1122804 A	22/05/96
				CZ 9501939 A	14/02/96
				DE 694547 T	24/10/96
				DE 69509173 D	00/00/00
				ES 2083348 T	16/04/96
				FI 953592 A	29/01/96
				GR 96300021 T	30/04/96
				HU 73246 A	29/07/96
				HU 9502238 D	00/00/00
				IL 114735 A	15/06/98
				JP 8041061 A	13/02/96
				NO 952977 A	29/01/96
				NZ 272652 A	20/12/96
				PL 309812 A	05/02/96
				SG 32424 A	13/08/95
				TR 960086 A	00/00/00
				US 5840891 A	24/11/98
				US 5856481 A	05/01/99
				ZA 9506228 A	22/02/96
US	5484911	A	16/01/96	NONE	
WO	9213561	A1	20/08/92	AT 179615 T	15/05/99
				AU 663309 B	05/10/95
				AU 1417792 A	07/09/92
				CA 2100655 A	09/08/92
				DE 69229108 D	00/00/00
				EP 0570519 A,B	24/11/93
				IL 100874 A	19/01/96
				JP 6511473 T	22/12/94
				ZA 9200914 A	09/08/93

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/06/99

International application No.

PCT/SE 99/00528

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9532984 A1	07/12/95	AU 688516 B	12/03/98
		AU 2615495 A	21/12/95
		BR 9507785 A	23/09/97
		CA 2190983 A	07/12/95
		CZ 9603477 A	16/04/97
		DE 4418690 A	11/01/96
		EP 0763049 A	19/03/97
		FI 964727 A	27/11/96
		HU 75340 A	28/05/97
		HU 9603269 D	00/00/00
		IL 113865 D	00/00/00
		JP 10500964 T	27/01/98
		NO 965054 A	28/01/97
		NZ 287434 A	26/01/98
		PL 317380 A	01/04/97
		SK 151896 A	04/06/97
		ZA 9504374 A	29/11/96
WO 9633201 A1	24/10/96	AU 5511196 A	07/11/96
		FR 2733234 A,B	25/10/96
		US 5627185 A	06/05/97
WO 9200988 A1	23/01/92	AT 150759 T	15/04/97
		AU 649466 B	26/05/94
		AU 8300091 A	04/02/92
		CA 2087194 A	14/01/92
		DE 69125377 D,T	09/10/97
		EP 0539493 A,B	05/05/93
		JP 5509313 T	22/12/93
		US 5177064 A	05/01/93
		US 5413996 A	09/05/95
WO 9413324 A1	23/06/94	US 5618803 A	08/04/97
		AU 681619 B	04/09/97
		AU 5803194 A	04/07/94
		CA 2149754 A	23/06/94
		EP 0674529 A	04/10/95
		JP 8504768 T	21/05/96
		US 5411947 A	02/05/95
		US 5484809 A	16/01/96
		US 5744592 A	28/04/98
WO 9615132 A1	23/05/96	US 5827831 A	27/10/98
		AU 700651 B	14/01/99
		AU 4163596 A	06/06/96
		CA 2205136 A	23/05/96
		EP 0792275 A	03/09/97
		JP 10508858 T	02/09/98
		US 5696277 A	09/12/97

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

01/06/99

PCT/SE 99/00528

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5227506 A	13/07/93	CA 2024694 A DE 69023844 D,T EP 0416689 A,B JP 2083796 C JP 3106893 A JP 7119230 B LV 11473 A,B	07/03/91 20/06/96 13/03/91 23/08/96 07/05/91 20/12/95 20/08/96
WO 9821223 A1	22/05/98	AU 5075998 A SE 9604165 D SE 9604154 D AU 8754898 A SE 9702957 D WO 9909031 A	03/06/98 00/00/00 00/00/00 08/03/99 00/00/00 25/02/99