Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2604165 A1 2006/11/30

(21) 2 604 165

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2006/05/24
(87) Date publication PCT/PCT Publication Date: 2006/11/30
(85) Entrée phase nationale/National Entry: 2007/10/05
(86) N° demande PCT/PCT Application No.: EP 2006/062612
(87) N° publication PCT/PCT Publication No.: 2006/125812
(30) Priorité/Priority: 2005/05/26 (EP05104511.0)

(51) Cl.Int./Int.Cl. *C07D 487/04* (2006.01), *A61K 31/403* (2006.01), *A61K 31/407* (2006.01), *A61P 25/00* (2006.01), *C07D 209/94* (2006.01), *C07D 221/18* (2006.01), *C07D 307/93* (2006.01), *C07D 311/94* (2006.01), *C07D 333/80* (2006.01), *C07D 491/04* (2006.01)

(71) Demandeur/Applicant:
JANSSEN PHARMACEUTICA N.V., BE

(72) Inventeurs/Inventors:
MEGENS, ANTONIUS ADRIANUS HENDRIKUS PETRUS, BE;
TRABANCO-SUAREZ, ANDRES AVELINO, ES;
KOUKNI, MOHAMED, BE; ...

(54) Titre : NOUVEAUX DERIVES DE TETRAHYDROTHIOPHENE, PYROLIDINE ET TETRAHYDROFURANE TETRACYCLIQUE SUBSTITUES ET LEUR UTILISATION EN TANT QUE MEDICAMENT

(54) Title: NOVEL SUBSTITUTED TETRACYCLIC TETRAHYDROFURAN, PYRROLIDINE AND TETRAHYDROTHIOPHENE DERIVATIVES AND THEIR USE AS A MEDICAMENT

(57) Abrégé/Abstract:
This invention concerns novel substituted tetracyclic tetrahydrofuran, pyrrolidine and tetrahydrothiophene derivatives with binding affinities towards serotonin receptors, in particular 5-HT_{2A} and 5-HT_{2C} receptors, and towards dopamine receptors, in particular dopamine D2 receptors and with norepinephrine reuptake inhibition properties, pharmaceutical compositions comprising the compounds according to the invention, the use thereof as a medicine, in particular for the prevention and/or treatment of a range of psychiatric and neurological disorders, in particular certain psychotic, cardiovascular and gastrokinetic disorders and processes for their production. The compounds according to the invention can be represented by general Formula (I), and comprises also the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form thereof and prodrugs thereof, wherein all substituents are defined as in Claim 1.

CA 2604165 A1 2006/11/30

(21) 2 604 165

(13) A1

(72) **Inventeurs(suite)/Inventors(continued)**: HOORNAERT, GEORGES JOSEPH CORNELIUS, BE; COMPERNOLLE, FRANS JOSEF CORNELIUS, BE; KOZLECKI, TOMASZ, PL; CID-NUNEZ, JOSE MARIA, ES; MAO, HUA, US; JHA, SUSHIL CHANDRA, IN; FERNANDEZ-GADEA, FRANCISCO JAVIER, ES

(74) **Agent**: GOWLING LAFLEUR HENDERSON LLP

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 November 2006 (30.11.2006)

PCT

(10) International Publication Number
WO 2006/125812 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *C07D 221/18* (2006.01)
C07D 209/94 (2006.01) *C07D 307/93* (2006.01)
C07D 491/04 (2006.01) *A61K 31/403* (2006.01)
C07D 333/80 (2006.01) *A61K 31/407* (2006.01)
C07D 311/94 (2006.01) *A61P 25/00* (2006.01)

(21) International Application Number:
PCT/EP2006/062612

(22) International Filing Date: 24 May 2006 (24.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
05104511.0 26 May 2005 (26.05.2005) EP

(71) Applicant *(for all designated States except US)*: **JANSSEN PHARMACEUTICA N.V.** [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MEGENS, Antonius, Adrianus, Hendrikus, Petrus** [BE/BE]; c/o: Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **TRABANCO-SUÁREZ, Andrés, Avelino** [ES/ES]; c/o: Johnson & Johnson Pharmaceutical Research and Development, Division of Janssen-Cilag, S.A., Calle Jarama, 75, Poligono Industrial (ES). **KOUKNI, Mohamed** [BE/BE]; c/o: K.U.Leuven Research & Development, Groot Begijnhof, Benedenstraat 59, B-3000 Leuven (BE). **HOORNAERT, Georges, Joseph, Cornelius** [BE/BE]; c/o: K.U.Leuven Research & Development, Groot Begijnhof, Benedenstraat 59, B-3000 Leuven (BE). **COMPERNOLLE, Frans, Josef, Cornelius** [BE/BE]; c/o: K.U.Leuven Research & Development, Groot Begijnhof, Benedenstraat 59, B-3000 Leuven (BE). **KOZLECKI, Tomasz** [PL/PL]; Gornickiego 33/3, PL-WROCLAW 50-337 (PL). **CID-NÚÑEZ, José, Maria** [ES/ES]; c/o: Johnson & Johnson Pharmaceutical Research and Development, Division of Janssen-Cilag, S.A., Calle Jarama, 75, Poligono Industrial (ES). **MAO, Hua** [CN/US]; 900n Leverett Avenue, Apt. 362, Fayetteville, Arkansas AR72701 (US). **JHA, Sushil, Chandra** [IN/IN]; A1/202, Nikash Lawns, Maharashtra, Sus Road, Pashan, Pune 411021 (IN). **FERNÁNDEZ-GADEA, Francisco, Javier** [ES/ES]; c/o: Johnson & Johnson Pharmaceutical Research and Development, Division of Janssen-Cilag, S.A., Calle Jarama, 75, Poligono Industrial (ES).

(74) Common Representative: **JANSSEN PHARMACEUTICA N.V.**; Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL SUBSTITUTED TETRACYCLIC TETRAHYDROFURAN, PYRROLIDINE AND TETRAHYDROTHIOPHENE DERIVATIVES AND THEIR USE AS A MEDICAMENT

(57) Abstract: This invention concerns novel substituted tetracyclic tetrahydrofuran, pyrrolidine and tetrahydrothiophene derivatives with binding affinities towards serotonin receptors, in particular 5-HT_{2A} and 5-HT_{2C} receptors, and towards dopamine receptors, in particular dopamine D2 receptors and with norepinephrine reuptake inhibition properties, pharmaceutical compositions comprising the compounds according to the invention, the use thereof as a medicine, in particular for the prevention and/or treatment of a range of psychiatric and neurological disorders, in particular certain psychotic, cardiovascular and gastrokinetic disorders and processes for their production. The compounds according to the invention can be represented by general Formula (I), and comprises also the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N-oxide* form thereof and prodrugs thereof, wherein all substituents are defined as in Claim 1.

WO 2006/125812 A1

NOVEL SUBSTITUTED TETRACYCLIC TETRAHYDROFURAN, PYRROLIDINE AND TETRAHYDROTHIOPHENE DERIVATIVES AND THEIR USE AS A MEDICAMENT

Field of the Invention

This invention concerns novel substituted tetracyclic tetrahydrofuran, pyrrolidine and tetrahydrothiophene derivatives with binding affinities towards serotonin receptors, in particular 5-HT_{2A} and 5-HT_{2C} receptors, and towards dopamine receptors, in particular dopamine D2 receptors and with norepinephrine reuptake inhibition properties, pharmaceutical compositions comprising the compounds according to the invention, the use thereof as a medicine, in particular for the prevention and/or treatment of a range of psychiatric and neurological disorders, in particular certain psychotic, cardiovascular and gastrokinetic disorders and processes for their production.

Background prior art

WO 97/38991, published October 23, 1997 (Janssen Pharmaceutica N.V.) discloses substituted tetracyclic tetrahydrofuran derivatives that may be used as therapeutic agents in the treatment or prevention of CNS disorders, cardiovascular disorders or gastrointestinal disorders. In particular, the compounds show affinity for the serotonin 5-HT_2 receptors, particularly for the 5-HT_{2A} and 5-HT_{2C}-receptors.

WO 99/19317, published April 22, 1999 (Janssen Pharmaceutica N.V.) discloses substituted tetracyclic tetrahydrofuran derivatives with a specific halogen substitution pattern on the dibenzoazepine, dibenzooxepine, dibenzothiepine or dibenzosuberane ring. The compounds are useful in the treatment or prevention of CNS disorders, cardiovascular disorders or gastrointestinal disorders and show a faster onset of action over the compounds as disclosed in WO 97/38991.

Both WO 03/048146, published June 12, 2003 (Janssen Pharmaceutica N.V.) and WO 03/048147, published June 12, 2003 (Janssen Pharmaceutica N.V.) disclose processes for the preparation of each of the four diastereomers of trans-, respectively cis-fused 3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-b]furan derivatives in a stereochemically pure form from a single enantiomerically pure precursor. The compounds of WO 03/048146 show affinity for 5-HT_2 receptors, particularly for

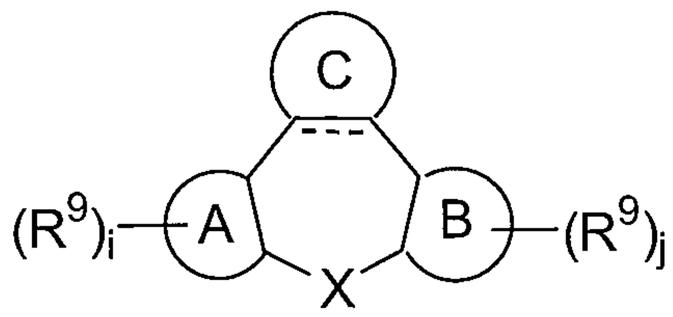
5-HT_{2A} and 5-HT_{2C} receptors. The compounds of WO 03/048147 show affinity for the serotonin 5-HT_{2A}, 5-HT_{2C} and 5-HT_7 receptors , the H_1-receptors (pIC_{50}=7.15-7.89), D2 and/or D3 receptors and for the norepinephrine reuptake transporters (pIC_{50} = 6.03-7.34). The compounds disclosed in the latter two publications do not contain a cyclic amine side chain.

WO 03/040122, published May 15, 2003 (Janssen Pharmaceutica N.V.) discloses mandelate salts of the compounds according to WO 97/38991 and WO 99/19317. Said salts were surprisingly found to be more stable at enhanced temperature and relative humidity than the compounds disclosed in WO 97/38991 and WO 99/19317.

Description of the Invention

It is the object of the present invention to provide novel analogues of the tetracyclic tetrahydrofuran derivatives of WO 97/38991 and WO 99/19317, which differ from such derivatives in that they demonstrate in general more selectivity for the norepinephrine reuptake transporter than the 5-HT_{2A}, 5-HT_{2C} and dopamine D_2 receptors, resulting in compounds which have a more pronounced antidepressant effect in relation to their antipsychotic properties. The compounds of formula (I) below where the basic nitrogen atom at the C-2 position is embedded in a cyclic system demonstrate a potent antagonistic effect against the 5-HT_{2A}, 5-HT_{2C} and dopamine D_2 receptors.

This goal is achieved by the present novel compounds according to Formula (I):



(I)

an *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

the dotted line represents an optional bond ;

i and j are integers, independently from each other, equal to zero, 1, 2, 3 or 4 ;

A and B are, each independently from each other, aryl or an heteroaryl radical selected from the group of furyl ; thienyl ; pyrrolyl ; oxazolyl ; thiazolyl ; imidazolyl ; isoxazolyl ; isothiazolyl ; oxadiazolyl ; triazolyl ; pyridinyl ;

pyridazinyl ; pyrimidinyl ; pyrazinyl ; indolyl ; indolizinyl ; isoindolyl ; benzofuryl ; isobenzofuryl ; benzothienyl ; indazolyl ; benzimidazolyl ; benzthiazolyl ; quinolizinyl ; quinolinyl ; isoquinolinyl ; phthalazinyl ; quinazolinyl ; quinoxalinyl ; chromenyl ; naphthyridinyl and naphthalenyl ;

each R^9 is, independently from each other, selected from the group of hydrogen ; halo ; cyano ; hydroxy ; carboxyl ; nitro ; amino ; mono- or di(alkyl)amino; alkylcarbonylamino ; aminosulfonyl ; mono- or di(alkyl)aminosulfonyl ; alkyl ; alkyloxy ; alkylcarbonyl and alkyloxycarbonyl ;

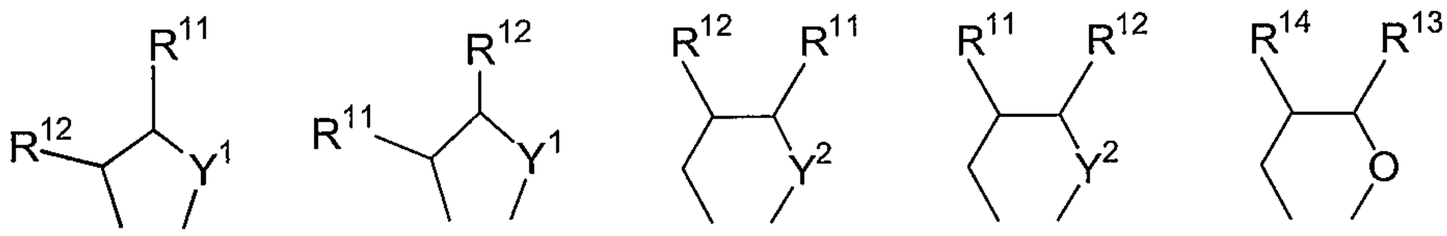
X represents CR^6R^7, O, S, S(=O), $S(=O)_2$ or NR^8 ; wherein :

R^6 and R^7 each independently are selected from the group of hydrogen, hydroxy, alkyl and alkyloxy; or

R^6 and R^7 taken together may form a radical selected from the group of methylene ($=CH_2$) ; mono- or di(cyano)methylene ; a bivalent radical of formula $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$; or together with the carbon atom to which they are attached, a carbonyl ;

R^8 is selected from the group of hydrogen ; alkyl ; alkylcarbonyl ; arylcarbonyl ; arylalkyl ; arylalkylcarbonyl ; alkylsulfonyl ; arylsulfonyl and arylalkylsulfonyl ;

C is a group of formula (c-1), (c-2), (c-3), (c-4) or (c-5) ;



(c-1) (c-2) (c-3) (c-4) (c-5)

wherein :

Y^1 and Y^2 each independently are S ; O ; S(=O) ; $S(=O)_2$ or NR^{10}; wherein R^{10} is selected from the group of hydrogen, cyano, alkyl, alkyloxyalkyl, formyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkylcarbonyl, arylcarbonyl, arylalkyl, arylalkylcarbonyl, alkylsulfonyl, arylsulfonyl and arylalkylsulfonyl ;

R^{10} and R^{11} may form together a bivalent radical (e-1) to (e-5);

$-CH_2-NH-CH_2-$ (e-1)

$-CH_2-NH-CH_2-CH_2-$ (e-2)

$-CH_2CH_2-NH-CH_2-$ (e-3)

-CH=N-CH_2- (e-4)

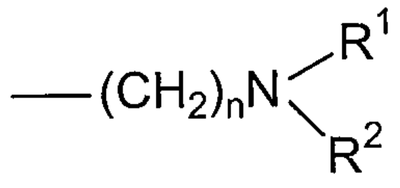
-CH_2-N=CH_2- (e-5)

wherein optionally in each radical (e-1) to (e-5) one or more hydrogens are replaced by one or more substituents selected from alkyl, -O-alkyl, -S-alkyl =O, =S, =S(=O) and =$S(=O)_2$;

R^{12} is hydrogen or alkyl ;

R^{13}, R^{14} each independently are hydrogen, hydroxy or oxo ;

R^{11} is a group of formula (d-1) ;



(d-1)

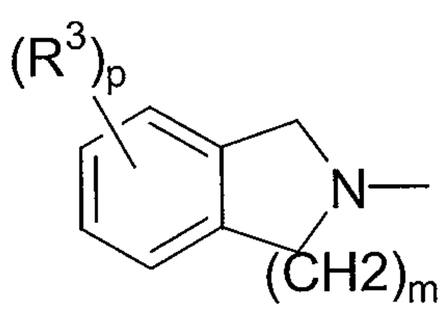
wherein :

n is zero, 1, 2, 3, 4, 5 or 6 ;

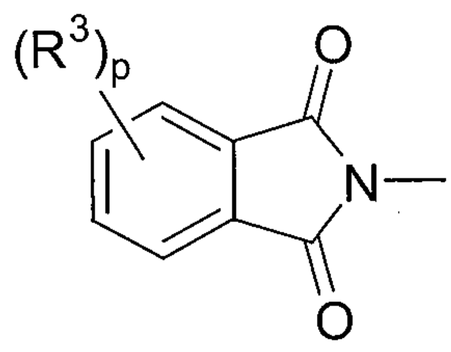
R^1 and R^2 each independently are hydrogen ; alkyl ; alkylcarbonyl ; alkyloxyalkyl ; alkylcarbonyloxyalkyl ; alkyloxycarbonylalkyl; arylalkyl ; arylcarbonyl ; alkyloxycarbonyl ; aryloxycarbonyl ; arylalkylcarbonyl ; alkyloxycarbonylalkylcarbonyl ; mono- or di(alkyl)aminocarbonyl ; mono- or di(aryl)aminocarbonyl ; mono- or di(arylalkyl)aminocarbonyl ; mono- or di(alkyloxycarbonylalkyl)aminocarbonyl ; alkylsulphonyl ; arylsulphonyl; arylalkylsulphonyl ; mono- or di(alkyl)aminothiocarbonyl ; mono- or di(aryl)aminothiocarbonyl ; mono- or di(arylalkyl)aminothiocarbonyl ; mono-, di- or tri(alkyl)amidino ; mono-, di- or tri(aryl)amidino and mono-, di- or tri(arylalkyl)amidino ;

or

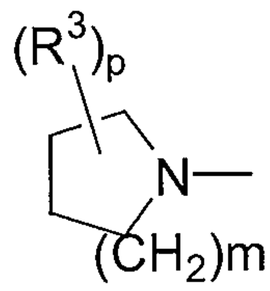
R^1 and R^2 taken together with the nitrogen atom to which they are attached may form a radical of formula (a-1), (a-2), (a-3), (a-4), (a-5) or (a-6) ;



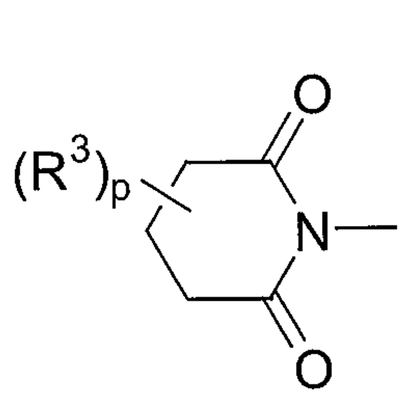
(a-1)



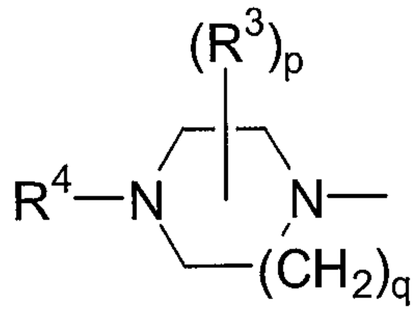
(a-2)



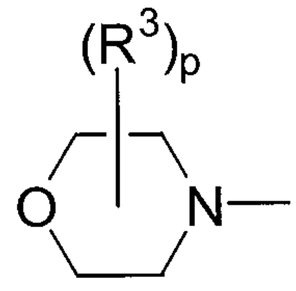
(a-3)



(a-4)



(a-5)



(a-6)

wherein :

p is zero, 1, 2, 3 or 4 ;

q is 1 or 2 ;

m is zero, 1, 2, or 3 ;

each R^3 independently is selected from the group of hydrogen ; halo ; hydroxy ; cyano ; alkyl ; alkyloxyalkyl ; aryloxyalkyl ; mono- or di-(alkyl)aminoalkyl ; hydroxycarbonylalkyl ; alkyloxycarbonylalkyl; mono- or di(alkyl)aminocarbonylalkyl ; mono- or di(aryl)aminocarbonylalkyl ; mono- or di(alkyl)aminocarbonyloxyalkyl ; alkyloxycarbonyloxyalkyl ; arylaminocarbonyloxyalkyl ; arylalkylaminocarbonyloxyalkyl ; aryl ; alkyloxy ; aryloxy ; alkylcarbonyloxy ; arylcarbonyloxy ; arylalkylcarbonyloxy ; alkylcarbonyl ; arylcarbonyl ; aryloxycarbonyl ; hydroxycarbonyl ; alkyloxycarbonyl ; alkylcarbonylamino ; arylalkylcarbonylamino ; arylcarbonylamino; alkyloxycarbonylamino ; aminocarbonylamino ; mono- or di(arylalkyl)aminocarbonylamino ; alkylsulphonylalkylaminocarbonylamino ; or two R^3-radicals may form together a bivalent radical

$-CR^5R^5-CR^5R^5-O-$ (b-1)

$-O-CR^5R^5-CR^5R^5-$ (b-2)

$-O-CR^5R^5-CR^5R^5-O-$ (b-3)

$-O-CR^5R^5-CR^5R^5-CR^5R^5-$ (b-4)

$-CR^5R^5-CR^5R^5-CR^5R^5-O-$ (b-5)

$-O-CR^5R^5-CR^5R^5-CR^5R^5-O-$ (b-6)

$-O-CR^5R^5-CR^5R^5-CR^5R^5-CR^5R^5-$ (b-7)

$-CR^5R^5-CR^5R^5-CR^5R^5-CR^5R^5-O-$ (b-8)

$-O-CR^5R^5-CR^5R^5-CR^5R^5-O-$ (b-9)

wherein R^5 is selected from the group of hydrogen, halo, hydroxy, alkyloxy and alkyl ;

R^4 is selected from the group of hydrogen ; alkyl ; arylalkyl ; alkyloxyalkyl ; alkylcarbonyloxyalkyl ; alkyloxycarbonylalkyl ; arylcarbonylalkyl ; alkylsulphonyloxyalkyl ; aryloxyaryl ; alkyloxycarbonylaryl ; alkylcarbonyl ; arylalkylcarbonyl ; alkyloxycarbonylalkylcarbonyl ; arylcarbonyl ; alkyloxycarbonyl ; aryloxycarbonyl ; arylalkyloxycarbonyl ; mono- or di(alkyl)aminocarbonyl ; mono- or di(aryl)aminocarbonyl ; mono- or di(arylalkyl)aminocarbonyl ; mono- or di(alkyloxycarbonylalkyl)aminocarbonyl ; alkyloxyalkylaminocarbonyl ; mono-, di- or tri(alkyl)amidino ; mono-, di- or tri(aryl)amidino ; mono-, di- or tri(arylalkyl)-amidino ; alkylsulphonyl ; arylalkylsulphonyl or arylsulphonyl ;

aryl is phenyl or naphthyl ; each radical optionally substituted with 1, 2 or 3 substituents selected from the group of halo, nitro, cyano, hydroxy, alkyloxy or alkyl ;

alkyl represents a straight or branched saturated hydrocarbon radical having from 1 to 10 carbon atoms, a cyclic saturated hydrocarbon radical having from 3 to 8 carbon atoms or a saturated hydrocarbon radical containing a straight or branched moiety having from 1 to 10 carbon atoms and a cyclic moiety having from 3 to 8 carbon atoms, optionally substituted with one or more halo, cyano, oxo, hydroxy, formyl, carboxyl or amino radicals ; and

halo represents fluoro, chloro, bromo and iodo.

More in particular, the invention relates to a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein A and B are each phenyl, optionally substituted with fluorine. Preferably, A is unsubstituted and B is substituted with fluor at the 11-position.

More in particular, the invention relates to a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein X is CH_2 or O.

More in particular, the invention relates to a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein C is a group of formula (c-1) or (c-2) ; wherein :

Y^1 is S ; S(=O) ; $S(=O)_2$ or NR^{10}; wherein R^{10} is selected from the group of hydrogen, cyano, alkyl, alkyloxyalkyl, formyl, alkylcarbonyl, alkyloxycarbonyl and alkyloxyalkylcarbonyl ; or adjacent R^{10} and R^{11} may form together a bivalent radical (e-1), (e-2) or (e-5) ; wherein optionally in each radical one or more hydrogens are replaced by one or more substituents selected from =O, =S, =S(=O), alkyl and alkylthio ; and

R^{12} is hydrogen.

More in particular, the invention relates to a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein C is a group of formula (c-3) or (c-4) ; wherein :

Y^2 is O or NH ; and

R^{12} is hydrogen.

More in particular, the invention relates to a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein C is a group of formula (c-5) ; wherein :

R^{13} is hydrogen ; and

R^{14} is hydroxy or oxo.

More in particular, the invention relates to a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein (d-1) is defined as wherein :

n is zero or 1 ;

R^1 and R^2 each independently are hydrogen ; alkyl or alkyloxycarbonylalkyl ; or R^1 and R^2 taken together with the nitrogen atom to which they are attached may form a radical of formula (a-3), (a-5) or (a-6) ; wherein :

p is zero or 1 ;

q is 1 ;

m is 1 ;

each R^3 independently is selected from the group of hydrogen and hydroxy ; and

R^4 is alkyl.

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein :

i and j are integers, independently from each other, equal to zero or 1 ;

A and B are, each independently from each other, phenyl, optionally substituted with fluor ;

each R^9 is, independently from each other, selected from the group of hydrogen and halo ;

X is CH_2 and O ;

C is a group of formula (c-1) or (c-2) ; wherein

Y^1 is S ; S(=O) ; $S(=O)_2$ or NR^{10}; wherein R^{10} is selected from the group of hydrogen, cyano, alkyl, alkyloxyalkyl, formyl, alkylcarbonyl, alkyloxycarbonyl and alkyloxyalkylcarbonyl ; or adjacent R^{10} and R^{11} may form together a bivalent radical (e-1), (e-2) or (e-5) ; wherein optionally in each radicalone or more hydrogens are replaced by one or more substituents selected from =O, =S, =S(=O), alkyl and alkylthio ; and

R^{12} is hydrogen ; or

C is a group of formula (c-3) or (c-4) ; wherein

Y^2 is O or NH ; and

R^{12} is hydrogen ; or

C is a group of formula (c-5) ; wherein

R^{13} is hydrogen ; and

R^{14} is hydroxy or oxo ;

R^{11} is a group of formula (d-1) ; wherein :

n is zero or 1 ;

R^1 and R^2 each independently are hydrogen ; alkyl or alkyloxycarbonylalkyl ; or R^1 and R^2 taken together with the nitrogen atom to which they are attached may form a radical of formula (a-3), (a-5) or (a-6) ; wherein:

p is zero or 1 ;

q is 1 ;

m is 1 ;

each R^3 independently is selected from the group of hydrogen and hydroxy ; and

R^4 is alkyl.

Preferably, alkyl is methyl, ethyl or propyl, optionally substituted with one or more halo, cyano, oxo, hydroxy, formyl, carboxyl or amino radicals. Preferably, alkyl is optionally substituted with hydroxy.

Preferably, aryl is phenyl, optionally substituted with 1, 2 or 3 substituents selected from the group of halo, nitro, cyano, hydroxy, alkyloxy or alkyl. Preferably, aryl is unsubstituted.

Preferably, halo is fluoro.

Preferred compounds are also those particular compounds according to the invention wherein the hydrogen atoms on carbon atoms 3a and 12b have a trans configuration and those having the(2α, 3aα, 12bβ) stereochemical configuration.

Preferred compounds are also those compounds according to the invention where the compounds are selected from the group of compounds :

Most preferred compounds are also those compounds according to the invention where the compounds are selected from the group of compounds defined by the compound numbers given in Tables 1 to 4.

Detailed description of the invention

In the framework of this application, alkyl is defined as a monovalent straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms, for example methyl, ethyl, propyl, butyl, 1-methylpropyl, 1,1-dimethylethyl, pentyl and hexyl ; alkyl further defines a monovalent cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, for example cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The definition of alkyl also comprises an alkyl radical that is optionally substituted on one or more carbon atoms with one or more phenyl, halo, cyano, oxo, hydroxy, formyl and amino radicals, for example hydroxyalkyl, in particular hydroxymethyl and hydroxyethyl and polyhaloalkyl, in particular difluoromethyl and trifluoromethyl.

In the framework of this application, halo is generic to fluoro, chloro, bromo and iodo.

In the framework of this application, with "compounds according to the invention" is meant a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof.

The pharmaceutically acceptable salts are defined to comprise the therapeutically active non-toxic acid addition salt forms that the compounds according to Formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, mandelic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclamic acid, salicylic acid, *p*-aminosalicylic acid and pamoic acid.

The compounds according to Formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salts forms by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said salts forms can be converted into the free forms by treatment with an appropriate base or acid.

The term addition salt as used in the framework of this application also comprises the solvates that the compounds according to Formula (I) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

The *N*-oxide forms of the compounds according to Formula (I) are meant to comprise those compounds of Formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more tertiary nitrogens (e.g of the piperazinyl or piperidinyl radical) are *N*-oxidized. Such *N*-oxides can easily be obtained by a skilled person without any inventive skills and they are obvious alternatives for the compounds according to Formula (I) since these

compounds are metabolites, which are formed by oxidation in the human body upon uptake . As is generally known, oxidation is normally the first step involved in drug metabolism (Textbook of Organic Medicinal and Pharmaceutical Chemistry, 1977, pages 70- 75). As is also generally known, the metabolite form of a compound can also be administered to a human instead of the compound per se, with much the same effects.

The compounds according to the invention possess at least 1 oxydizable nitrogen (tertiary amines moiety). It is therefore highly likely that *N*-oxides are to form in the human metabolism.

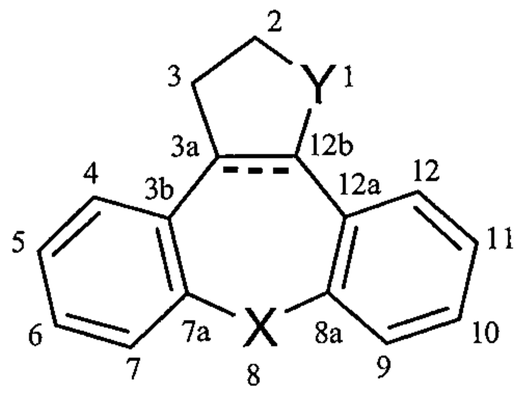
The compounds of Formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of Formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the *R*- or *S*-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of Formula (I) are obviously intended to be embraced within the scope of this invention.

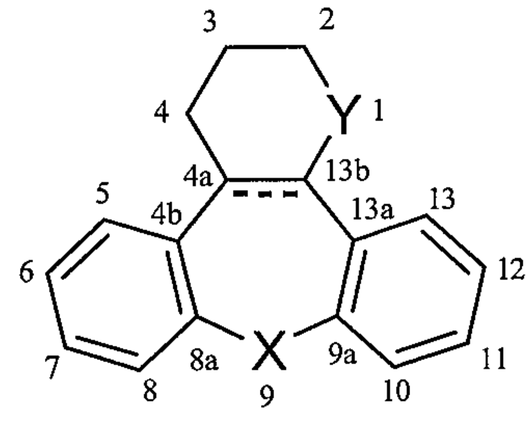
Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is as-

signed (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. *R** and *S** each indicate optically pure stereogenic centers with undetermined absolute configuration. If "α" and "β" are used: the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the "α" position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system (hydrogen atom in compounds according to Formula (I)) relative to the position of the highest priority substituent on the reference atom is denominated "α", if it is on the same side of the mean plane determined by the ring system, or "β", if it is on the other side of the mean plane determined by the ring system.

The numbering of the tetracyclic ring-systems present in the compounds of Formula (I-a) and (I-b) when A and B are phenyl, as defined by Chemical Abstracts nomenclature is shown below.



I-a



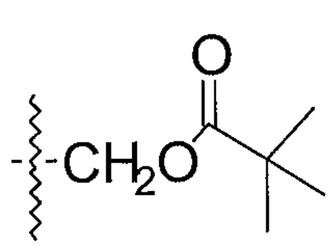
I-b

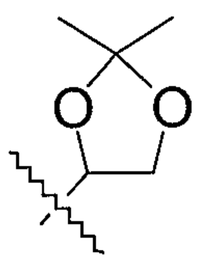
The compounds of Formula (I-a) and (I-b) have at least two asymmetric centers at respectively carbon atom 2 and 3. Said asymmetric center and any other asymmetric center, which may be present (e.g. at atom 8 in (I-a) or 9 in (I-b)), are indicated by the descriptors R and S. When e.g. a monocyanomethylene moiety is present in the compounds of Formula (I-a) at position 8, said moiety may have the E- or Z-configuration.

The invention also comprises derivative compounds (usually called "pro-drugs") of the pharmacologically active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly

transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs,* 1985, 29, pp. 455-473.

Prodrugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the *N*-oxide form thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the Formula $-COOR^x$, where R^x is a C_{1-6}alkyl, phenyl, benzyl or one of the following groups:





Amidated groups include groups of the Formula $-CONR^yR^z$, wherein R^y is H, C_{1-6}alkyl, phenyl or benzyl and R^z is –OH, H, C_{1-6}alkyl, phenyl or benzyl. Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

The compounds of Formula (I) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers that can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

Pharmacology

The compounds of the present invention show affinity for 5-HT_2 receptors, particularly for 5-HT_{2A} and 5-HT_{2C} receptors (nomenclature as described by D. Hoyer in "Serotonin (5-HT) in neurologic and psychiatric disorders" edited by M.D. Ferrari and published in 1994 by the Boerhaave Commission of the University of Leiden) and affinity for the D2 receptor as well as norepinephrine reuptake inhibition activity. The serotonin antagonistic properties of the present compounds may be demonstrated by their inhibitory effect in the "5-hydroxytryptophan Test on Rats" which is described in Drug Dev. Res., 13, 237-244 (1988).

In view of their capability to block 5-HT_2 receptors, and in particular to block 5-HT_{2A} and 5-HT_{2C} receptors, as well as the D2 receptor and by also effecting the norepinephrine reuptake inhibition activity, the compounds according to the invention are useful as a medicine, in particular in the prophylactic and therapeutic treatment of conditions mediated through either of these receptors.

The invention therefore relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, for use as a medicine.

The invention also relates to the use of a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof for the manufacture of a medicament for treating, either prophylactic or therapeutic or both, conditions mediated through the 5-HT_2, and D2 receptor, as well as the through norepinephrine reuptake inhibition.

In view of these pharmacological and physicochemical properties, the compounds of Formula (I) are useful as therapeutic agents in the treatment or the prevention of central nervous system disorders like anxiety, depression and mild depression, bipolar disorders, sleep- and sexual disorders, psychosis, borderline psychosis, schizophrenia, migraine, personality disorders or obsessive-compulsive disorders, social phobias or panic attacks, organic mental disorders, mental disorders in children such as ADHD, aggression, memory disorders and attitude disorders in older people, addiction, obesity, bulimia and similar disorders. In particular, the present compounds may be used as anxio-

lytics, antidepressants, antipsychotics, anti-schizophrenia agents, anti-migraine agents and as agents having the potential to overrule the addictive properties of drugs of abuse.

The compounds of Formula (I) may also be used as therapeutic agents in the treatment of motoric disorders. It may be advantageous to use the present compounds in combination with classical therapeutic agents for such disorders.

The compounds of Formula (I) may also serve in the treatment or the prevention of damage to the nervous system caused by trauma, stroke, neurodegenerative illnesses and the like; cardiovascular disorders like high blood pressure, thrombosis, stroke, and the like; and gastrointestinal disorders like dysfunction of the motility of the gastrointestinal system and the like.

In view of the above uses of the compounds of Formula (I), it follows that the present invention also provides a method of treating warm-blooded animals suffering from such diseases, said method comprising the systemic administration of a therapeutic amount of a compound of Formula (I) effective in treating the above described disorders, in particular, in treating anxiety, psychosis, depression, migraine and addictive properties of drugs of abuse.

The present invention thus also relates to compounds of Formula (I) as defined hereinabove for use as a medicine, in particular, the compounds of Formula (I) may be used for the manufacture of a medicament for treating anxiety, psychosis, depression, migraine and addictive properties of drugs of abuse.

Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic daily amount would be from about 0.01 mg/kg to about 10 mg/kg body weight, more preferably from about 0.05 mg/kg to about 1 mg/kg body weight.

The invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention, in particular a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof.

The compounds according to the invention, in particular the compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and the prodrugs thereof, or any subgroup or combination thereof may be Formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to Formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage.

Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Since the compounds according to the invention are potent orally administrable compounds, pharmaceutical compositions comprising said compounds for administration orally are especially advantageous.

In order to enhance the solubility and/or the stability of the compounds of Formula (I) in pharmaceutical compositions, it can be advantageous to employ α–, β– or γ-cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl-β-cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds according to the invention in pharmaceutical compositions.

Preparation

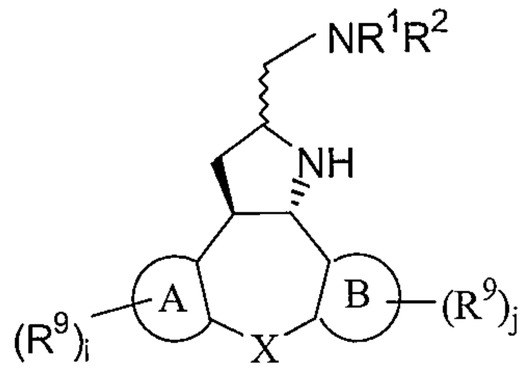
Suitable preparation methods for the compounds of the invention are described below:

The following abbreviations are used thoughout the text :

APCI	Atmospheric Pressure Chemical Ionization
AcOH	acetic acid
Ac_2O	Acetic anhydride
AcSH	thioacetic acid
Bu	*n*-butyl
Boc	tert-butyloxycarbonyl
Cbz-	4-carboxybenzoyl (e.g. CbzCl)
Celite®	diatomaceous earth from Celite Corporation
CI	Chemical Ionization
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DIAD	diisopropyl azodicarboxylate
DHP	2,3-dihydropirane
DMAP	*N*,*N*-4-dimethylaminopyridine

DMF	*N,N*-dimethylformamide
DOWEX®	ion exchange resin from the company DOW
DPPA	diphenyl phosphoryl azide
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EI	Electron Ionization
Et	ethyl
Et_3N	triethylamine
EtOH	ethanol
Et_2O	diethylether
EtOAc	ethyl acetate
HFIP	hexafluoroisopropanol
i-PrOH	isopropanol
IPy_2BF_4	bis(pyridine)iodonium tetrafluoroborate
t-BuOK	potassium salt of 2-methyl-2-propanol
mCPBA	*m*-chloroperoxybenzoic acid
Ns	Nosyl (e.g. *o*-nitrophenylsulfonyl chloride: NsCl)
Me	methyl
MeOH	methanol
Ms	mesyl (e.g. mesyl chloride : MsCl)
PCC	pyridinium chlorochromate
PPh_3	triphenylphosphine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
Tr	trityl (e.g. triphenylmethyl chloride : TrCl)
Ts	tosyl (e.g. 4-toluenesulfonyl chloride : TsCl)

The following reaction methods A to D illustrate the preparation of compounds of formula (I) in which C is a group of formula (c-1) in which Y^1 is NH, R^{11} is a group of formula (d-1) and R^{12} is hydrogen, represented by formulae (I-a) and (I-b) below:



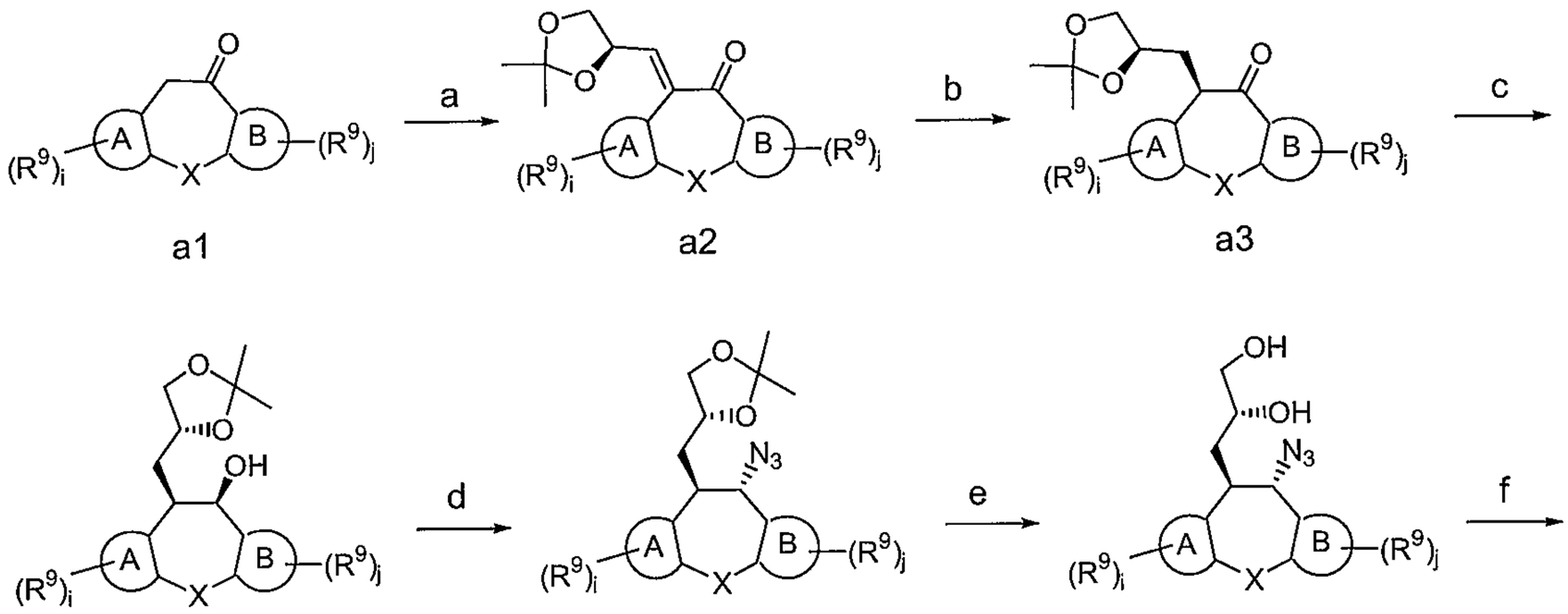
(I-a): 2*R*,3a*R*,x*S*

(I-b): 2*S*,3a*R*,x*S*

wherein x is 12b if A and B are each six-membered rings, such as phenyl

Method A : Preparation of pyrrolidine derivatives.

Method A1 : Synthesis of (2*R*,3a*R*,x*S*)-intermediate compounds.



Step a): treatment of an intermediate compound a1 with a ketal-protected (*S*)-glyceraldehyde (protected with e.g. acetone), a Lewis acid such as a magnesium halide, in particular magnesium bromide and a base catalyst such as t-BuOK , in a reaction-inert solvent such as toluene or THF, for example at room temperature;

Step b): hydrogenation of an intermediate compound a2 with a palladium-carbon catalyst (1 atm), in a reaction-inert solvent such as *i*-PrOH, in the presence of a base such

as a tertiary amine, in particular Et_3N, for example at room temperature for about 4 hours;

Step c); reduction of an intermediate compound a3, for example with an alkalimetal borohydride such as sodium borohydride, in a phosphate buffer at a maximum pH of 7 (preferably at a slightly acidic pH) and in a reaction-inert solvent such as *i*-PrOH or EtOH, for example at 0 °C for 15 min to form intermediate compound a4 in the *cis* configuration ;

Step d): nucleophilic substitution reaction of an intermediate compound a4 with DPPA in the presence $DIAD/PPh_3$ and a base such as or DBU, in a reaction-inert solvent such as THF, for example at about -15 °C to room temperature for about 24 hours;

Step e): deprotection of an intermediate compound a5 with an acid such as hydrochloric acid, in a reaction-inert solvent such as THF, for example at room temperature for about 16 hours;

Step f): tritylation of an intermediate compound a6 with a Tr-halide, in particular TrCl or TrBr, and a catalyst such as DMAP, in the presence of a base such as Et_3N, in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature for about 24 hours;

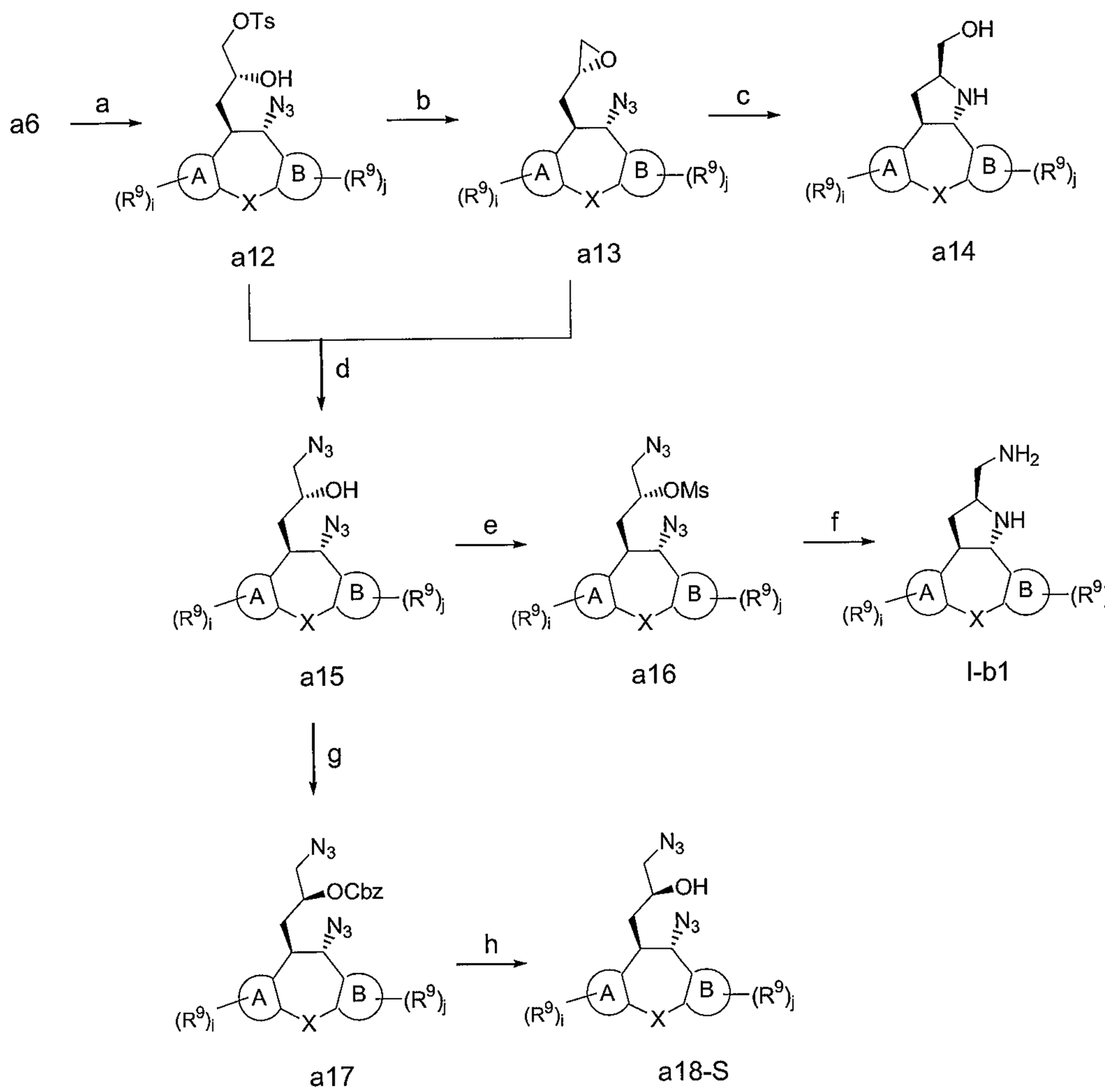
Step g): treatment of an intermediate compound a7 with MsCl or Ms-anhydride, in the presence of a base such as Et_3N, in a reaction-inert solvent such as CH_2Cl_2, for example at about -40 °C to room temperature for about 4 hours;

Step h): detritylation of an intermediate compound a8 with a strong acid in a non-aqueous medium such as Amberlyst-15 (macroreticular sulphonated polystyrene), in a reaction-inert solvent such as methanol, for example at about 45 °C for about 2-3 hours;

Step i): treatment of an intermediate compound a9 with a base such as K_2CO_3, in a reaction-inert solvent such as MeOH or EtOH, for example at room temperature for about 2 hours;

Step j): hydrogenation of an intermediate compound a10 with a palladium-carbon catalyst (1 atm) in a reaction-inert solvent such as MeOH, in the presence of a base such as Et_3N, for example at room temperature for about 3 hours. The resulting intermediate compound a11 may be used as a starting material as described in Method A3.

Method A2 : Synthesis of (2*S*,3a*R*,x*S*)-intermediate and final compounds.



Step a): tosylation of an intermediate compound a6 with TsCl in the presence of a base such as Et_3N and a catalyst such as Bu_2SnO, in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature for about 16 hours;

Step b): treatment of an intermediate compound a12 with a base such as K_2CO_3, in a reaction-inert solvent such as MeOH, for example at room temperature for about 10 minutes;

Step c): hydrogenation of an intermediate compound a13 with a palladium-carbon catalyst (1 atm), in a reaction-inert solvent such as MeOH, for example at room temperature for about 16 hours yielding the (2*S*,3a*R*,x*S*)-intermediate compound a14, which can be used as a starting material as described in Method A3.

Step d): nucleophilic substitution of an intermediate compound a12 or a13 with an alkalimetal azide such sodium azide, in a reaction-inert solvent such as DMF, for example at about 90 °C;

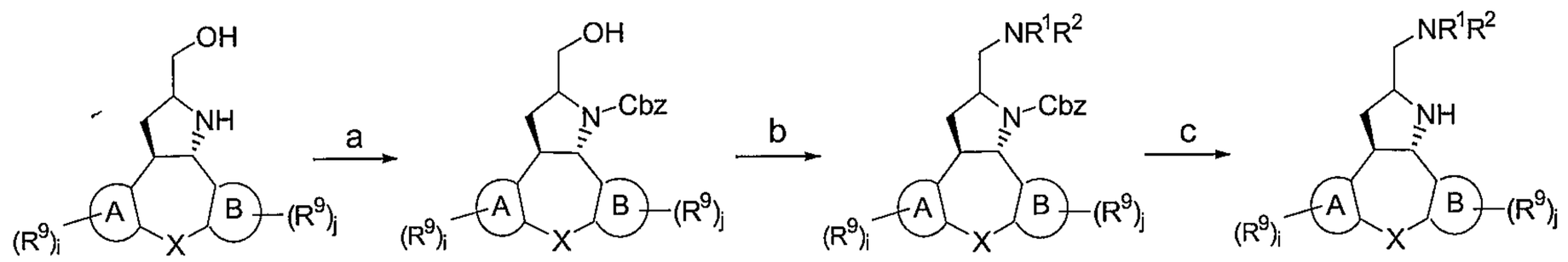
Step e): mesylation of an intermediate compound a15 with MsCl and optionally DMAP, with a tertiary amine base such as Et_3N in a reaction-inert solvent such as CH_2Cl_2, for example at about -40 °C to room temperature for about 4 hours;

Step f): hydrogenation of an intermediate compound a16 with a palladium-carbon catalyst (1 atm) with a base such as Et_3N, in a reaction-inert solvent such as MeOH, for example at room temperature for about 3 hours leads to a final compound of formula (I-b1), i.e. a compound of Formula (I-b) wherein R^1 and R^2 are both hydrogen.

Step g): Mitsonobu inversion of an intermediate compound a15 using DIAD/PPh_3 and CbzOH in THF at about 0 °C to room temperature for about 2 hours ;

Step h) hydrolysis of the intermediate compound a17 using for example K_2CO_3 in methanol, yielding intermediate compound a18 with S-configuration., which can be used as a starting material as described in Method B.

Method A3 : Synthesis of (2*R*,3a*R*,x*S*)- and (2*S*,3a*R*,x*S*)-final compounds



a11 and a14	a19	a20	(I-a): 2*R*,3a*R*,x*S* (I-b): 2*S*,3a*R*,x*S*

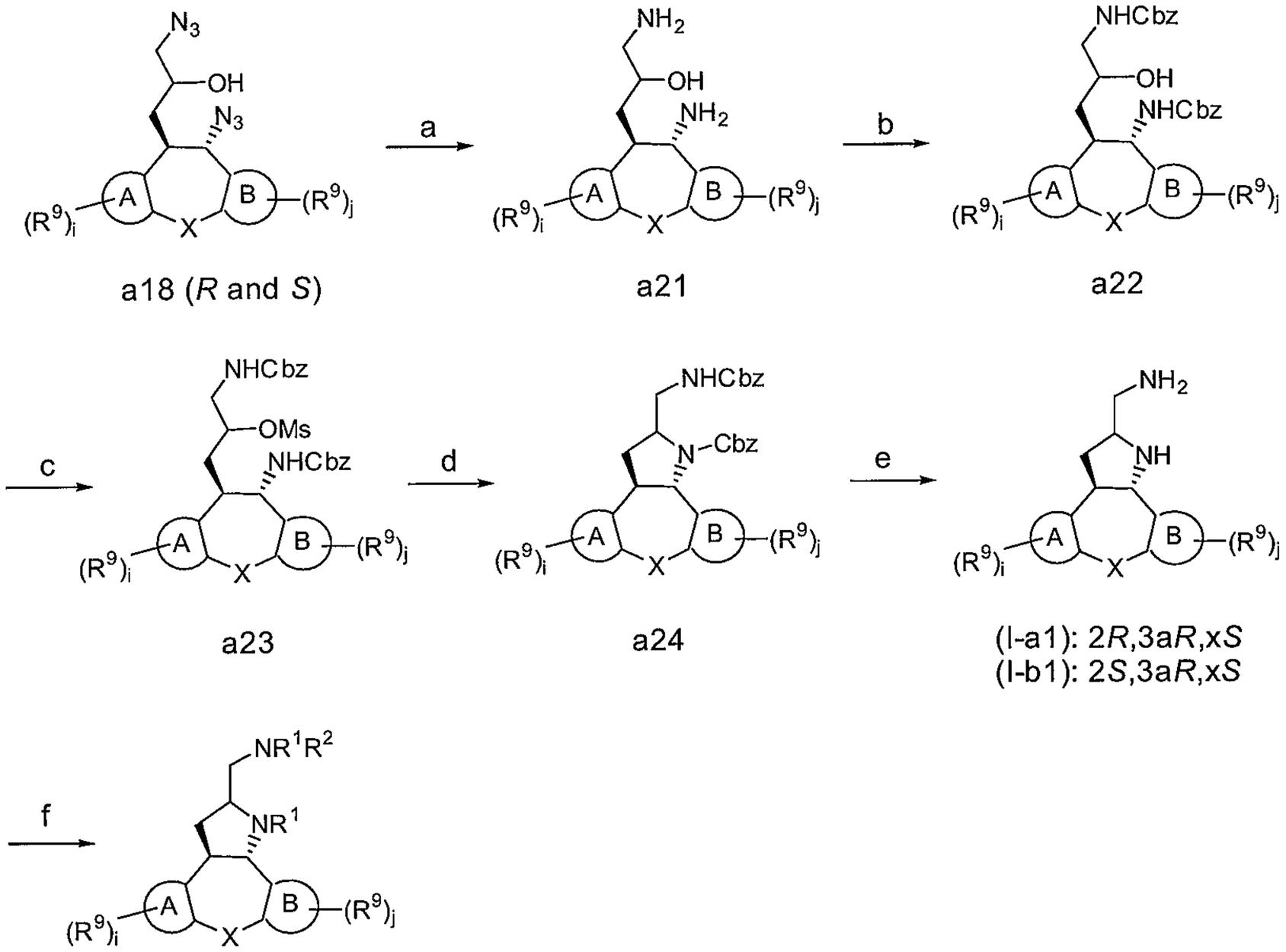
Step a): treatment of an intermediate compound a11 or a14 with CbzCl, with an aqueous solution of a base, such as K_2CO_3, in a reaction-inert solvent such as THF, for example at room temperature for 15 minutes;

Step b): Method 1: oxidation of an intermediate compound a19 with PCC ; then, reductive amination with HNR^1R^2 using a reducting agent such as $NaBH_4$; or Method 2: mesylation of an intermediate compound a19 with MsCl and DMAP, a base such as Et_3N, in a reaction-inert solvent such as CH_2Cl_2; then nucleophilic substitution with an excess of HNR^1R^2, optionally in the presence of a base such as K_2CO_3;

Step c): removal of the Cbz-protecting group by hydrogenation of an intermediate compound a20 with a palladium-carbon catalyst (1 atm) in a reaction-inert solvent such as MeOH, and in the presence of a base such as Et_3N, for example at room temperature for about 3 hours. An intermediate compound a11 leads to a final compound of formula (I-a); an intermediate compound a14 leads to a final compound of formula (I-b), wherein x is 12b if A and B are each a six-membered ring, such as phenyl.

Methods B-D below represent alternative routes to the preparation of the above final compounds of formula (I-a) and (I-b):

Method B : Synthesis of (2*R*,3a*R*,x*S*)- and (2*S*,3a*R*,x*S*)-final compounds



Step a): hydrogenation of an intermediate compound a18 (*R* or *S*) with a palladium-carbon catalyst (1 atm), in a reaction-inert solvent such as MeOH and in the presence of a base such as Et_3N, for example at room temperature for about 3 hours;

Step b): treatment of an intermediate compound a21 with CbzCl, with base such as K_2CO_3, in a reaction-inert solvent mixture such as THF-H_2O;

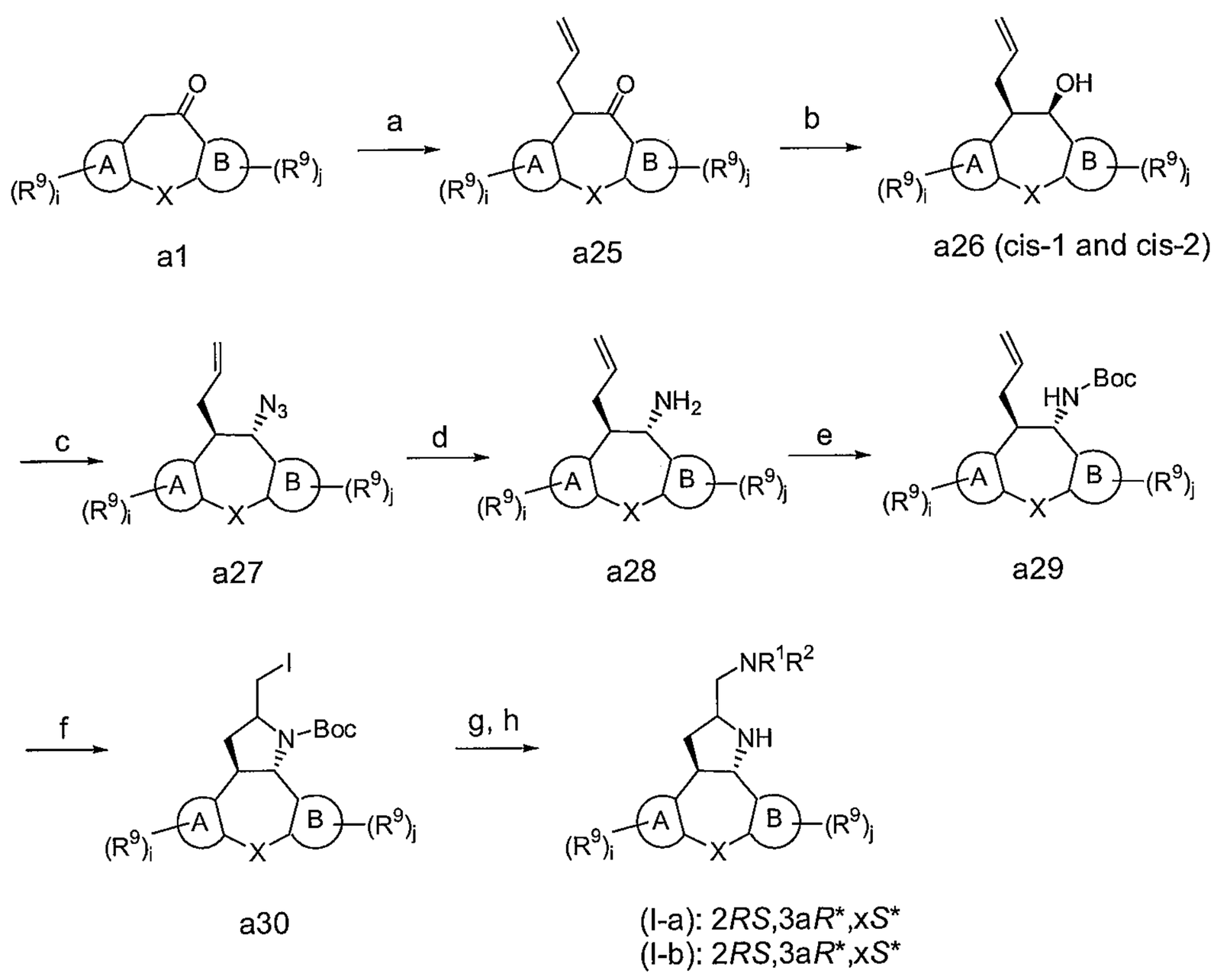
Step c): mesylation of an intermediate compound a22 with MsCl and DMAP, with a base such as Et_3N, in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature for about 16 hours;

Step d): treatment of an intermediate compound a23 with a base such as *t*-BuOK, in a reaction-inert polar aprotic solvent such as THF;

Step e): hydrogenation of an intermediate compound a24 with a palladium-carbon catalyst (1 atm), in a reaction-inert solvent such as MeOH, for example at room temperature for about 3 hours;

Step f) treatment of an final compound (I-a1) (having the 2*R*-configuration), or a final compound (I-b1) (having the 2*S*-configuration) with an aldehyde such formaldehyde or ketone, in an alcoholic solvent in the presence of AcOH and a reducing agent such as hydrogen/palladium on carbon or $NaCNBH_3$ leads to a trisubsituted final compound (I-a2) or (I-b2), respectively.

Method C : Synthesis of (2*RS*,3a*R**,x*S**)-final compounds



Step a): allylation of an intermediate compound a1 with a base such as NaH and allyl bromide, in a reaction-inert solvent such as THF, for example at about 65 °C for about 2-3 hours;

Step b): reduction of an intermediate compound a25 with a reducing agent such as $NaBH_4$ (in a phosphate buffer at pH 7), in a reaction-inert solvent such as *i*-PrOH, for example at room temperature, leads to intermediate compound a26 comprising a enantiomeric mixture of compounds with both substituents in either the up or down configuration (cis-1 and cis-2 configuration);

Step c): treatment of an intermediate compound a26 with DPPA, DIAD/PPh_3, in a reaction-inert solvent such as THF, for example at about -15 °C to room temperature for about 24 hours;

Step d): reduction of an intermediate compound a27 with a reducting agent, most preferably $LiAlH_4$, in a reaction-inert solvent such as THF, for example between about 0 °C and room temperature;

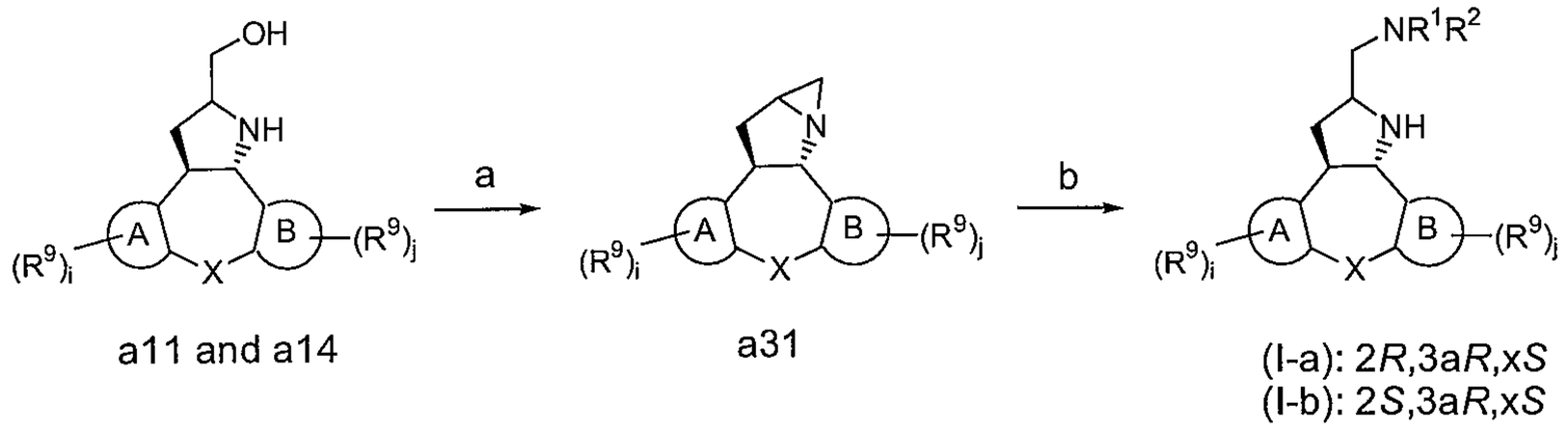
Step e): protection of an intermediate compound a28 with Boc_2O with an aqueous base such as K_2CO_3, in a reaction-inert solvent such as THF, for example at room temperature;

Step f): iodocyclization of an intermediate compound a29 with IPy_2BF_4 in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature;

Step g): amination of an intermediate compound a30 with excess HNR^1R^2 in aqueous THF, at about 135 °C in a pressurized vessel (for example a steel bomb) for about 3-6 hours ; or alternatively for example with $HNMe_2$ in anhydrous THF and calcium oxide to remove the leaving group.

Step h): deprotection with an acid such as HBr in AcOH, or HCl in MeOH, for about 1-2 hours under reflux or at room temperature, leading to a compound (I-a) or (I-b), wherein x is 12b if A and B are each a six-membered ring, such as phenyl.

<u>Method D : Synthesis of (2*RS*,3a*R*,x*S*)-final compounds</u>

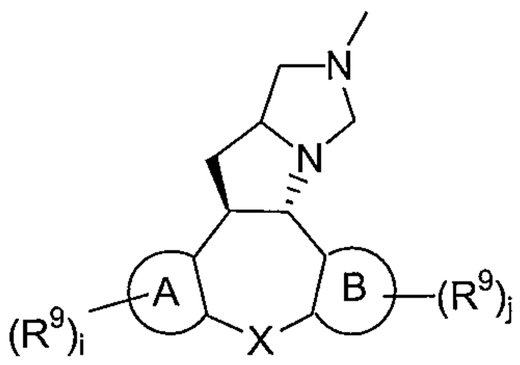


Step a): Mitsunobu-reaction of an intermediate compound a11 or a14 with DIAD/PPh_3, in a reaction-inert solvent such as THF, for example at about -15 °C to room temperature for about 24 hours;

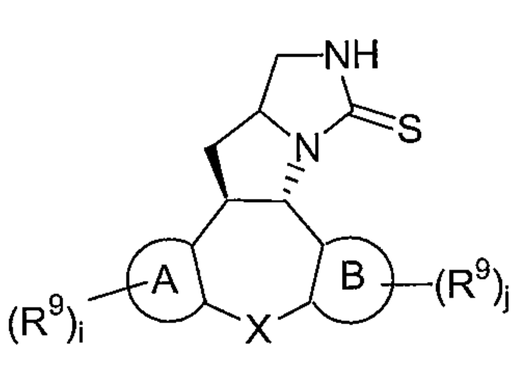
Step b): iodotrimethylsilane-mediated opening of the aziridine ring of an intermediate compound a31, followed by an in-situ reaction with an appropriate amine HNR^1R^2 in boiling acetonitrile. An intermediate compound a11 leads to a final compound of formula (I-a) ; an intermediate compound a14 leads to a final compound of formula (I-b), wherein x is 12b if A and B are each a six-membered ring, such as phenyl.

Method E : Preparation of pyrroloimidazole derivatives

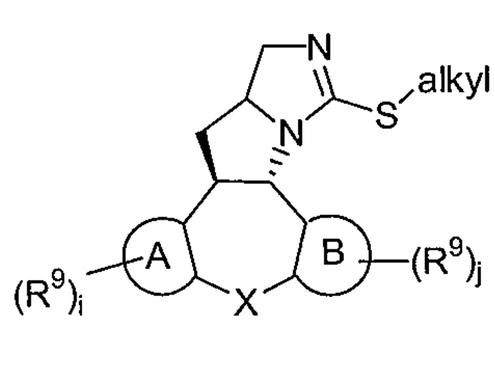
The following method illustrates the preparation of compounds of formula (I) in which C is a group of formula (c-1) in which R^{11} and R^{10} form a bivalent radical, represented by formulae (II-a), (II-b) and (II-c) below.



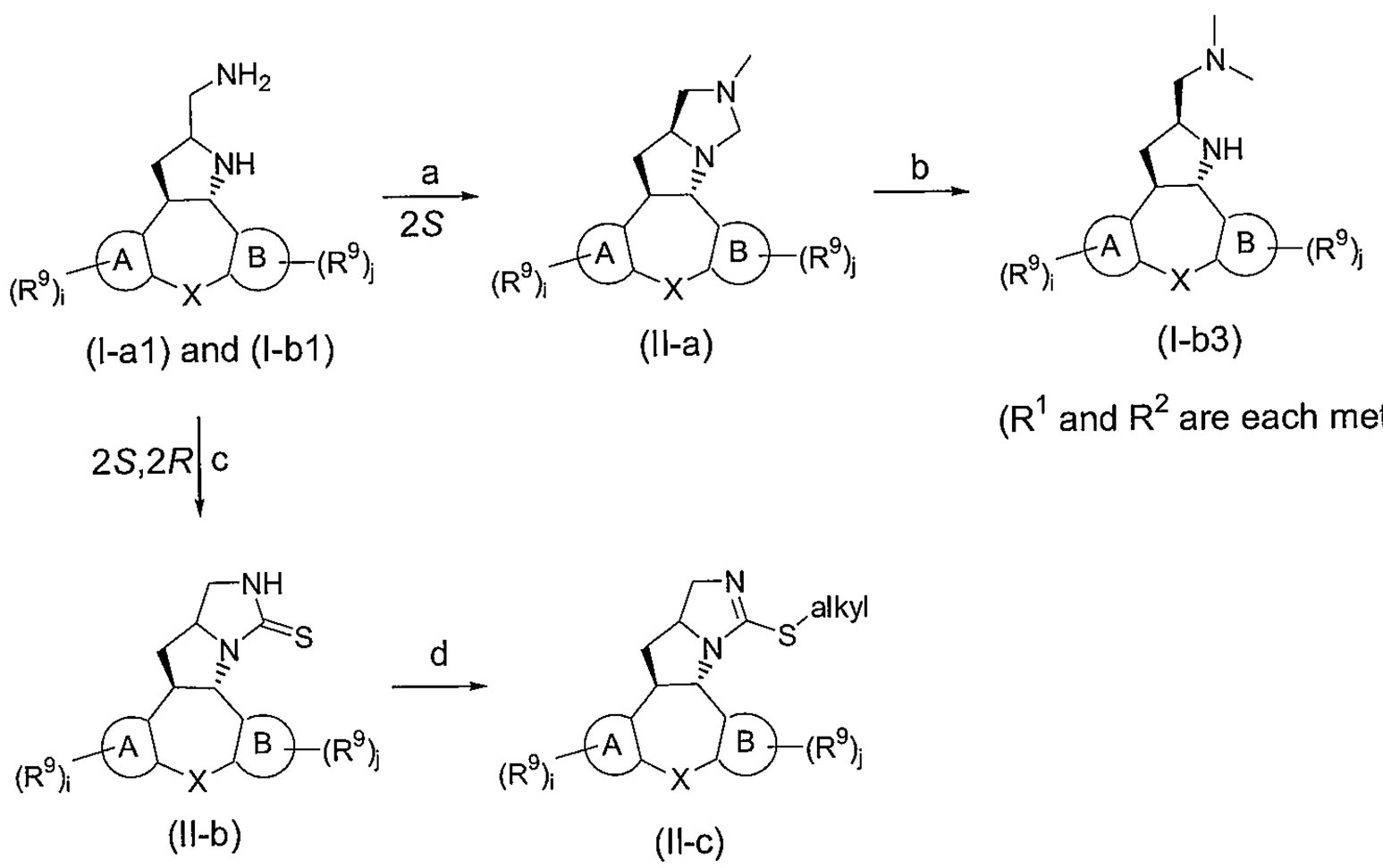
(II-a)



(II-b)



(II-c)



Step a): hydrogenation of a final compound (I-a1) or (I-b1) with a palladium-carbon catalyst (1 atm) with formaldehyde, in a reaction-inert solvent such as MeOH, for example at room temperature for about 3 hours, resulting in a final compound (II-a);

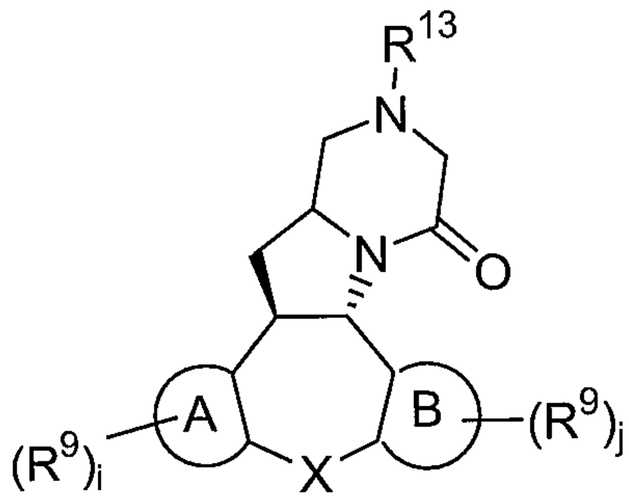
Step b): treatment of a final compound (II-a) with $NaCNBH_3$/TFA, in a solvent such as MeOH, resulting in a final compound (I-b3);

Step c): treatment of a final compound (I-a1) or (I-b1) (having respectively the 2*R* (down) or 2*S* (up) configuration) with CS_2 in a reaction-inert solvent such as DMF, for example at about 50 - 60 °C for about 30 minutes, resulting in a final compound (II-b);

Step d): alkylation of a final compound (II-b) with for example an alkyl halide, in a reaction-inert solvent such as MeOH or Et_3N, for example under reflux resulting in a final compound (II-c).

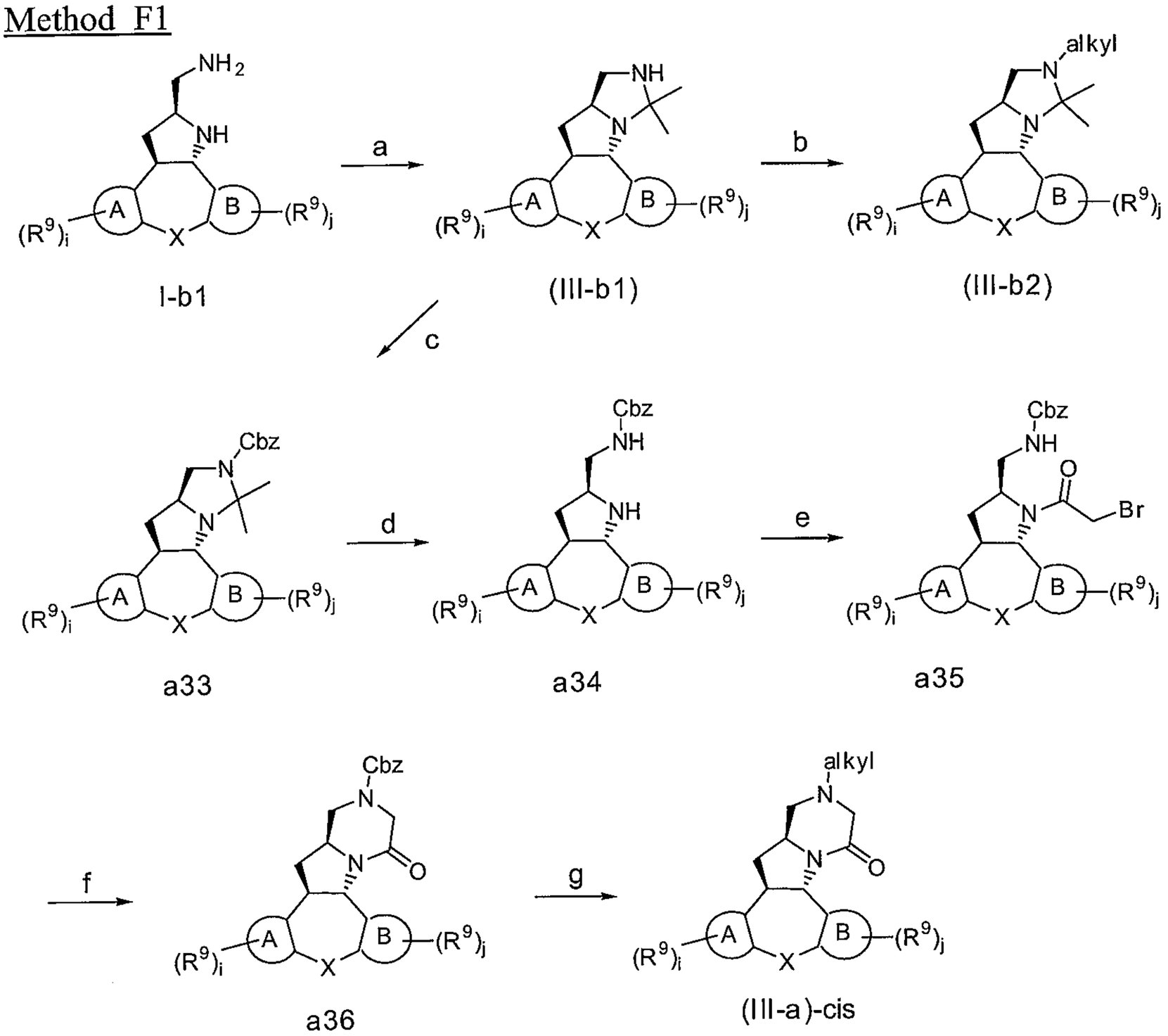
Method F : Preparation of pyrrolopiperazine derivatives

The following methods illustrate the preparation of compounds of formula (I) in which C is a group of formula (c-1) in which R^{11} and R^{10} form a condensed piperazine residue, represented by formula (III) below in which R^{13} is hydrogen or alkyl and the piperazine ring has the *S* configuration (Method F1) or the *R* configuration (Method F2).



(III)

Method F1



Step a): aminal formation from a final compound (I-b1) with acetone in a reaction-inert solvent such as MeOH, for example at about 60 °C for about 4 hours;

Step b): trans-aminalisation and reductive amination of a final compound(III-b1) with an appropriate aldehyde or ketone. for example formaldehyde, and hydrogenation with a palladium-carbon catalyst (1 atm), yielding final compound (III-b2);

Step c): protection of a final compound (III-b1) with CbzCl, with base such as K_2CO_3, in a reaction-inert solvent mixture such as THF-H_2O ;

Step d): hydrolysis of intermediate compound a33 with an acid such as hydrochloric acid, in aqueous THF, for example at room temperature for about 12 hours;

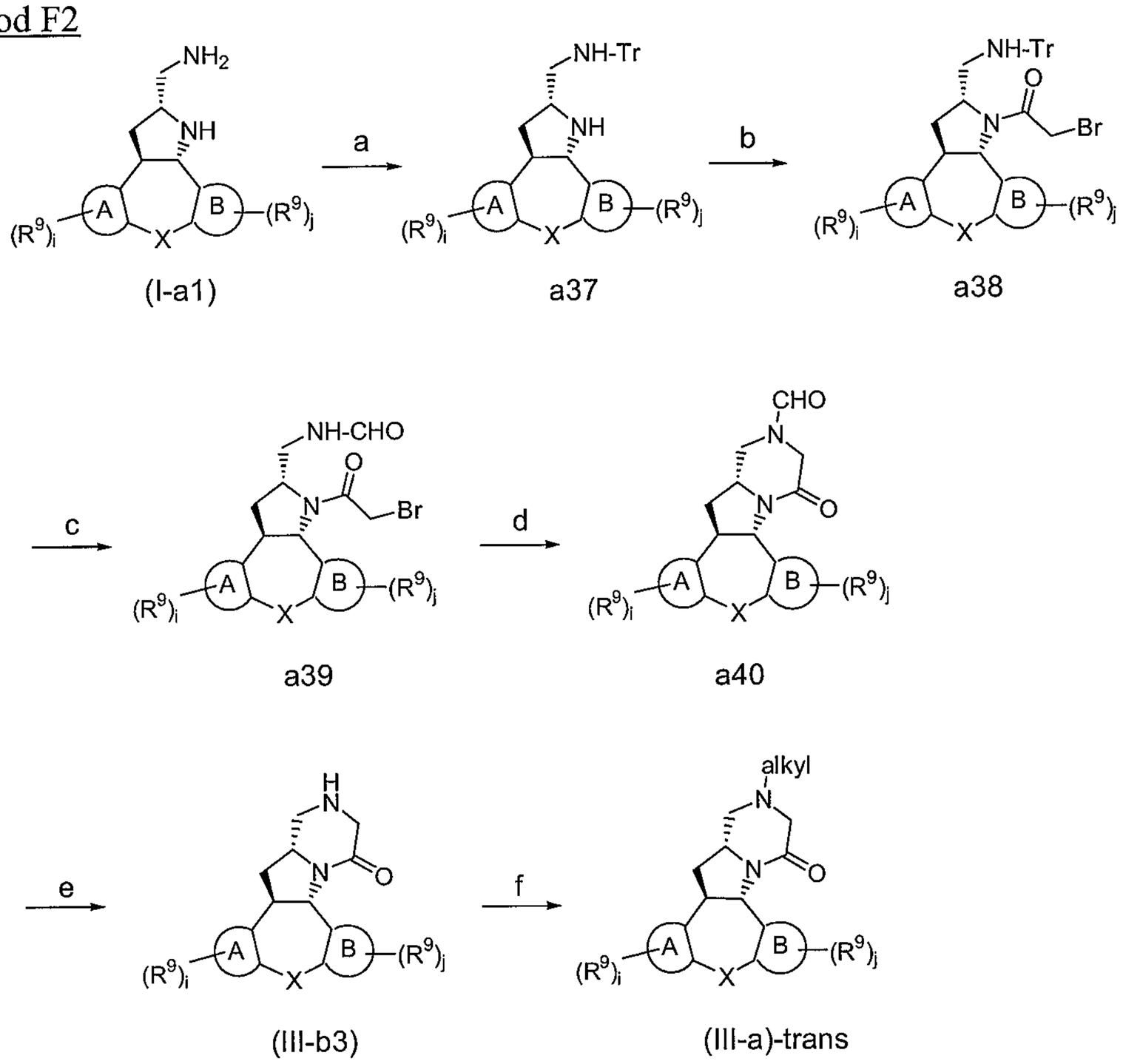
Step e): acylation of an intermediate compound a34 with an acid halide, in particular $BrCH_2COBr$, in EtOAc in the presence of aqueous sodium hydroxide ;

Step f): intramolecular cyclization of an intermediate compound a35 with a base such as K_2CO_3 in a reaction-inert solvent such as DMF;

Step g): removal of the Cbz-moiety by hydrogenation of an intermediate compound a36 with a palladium-carbon catalyst (1 atm) and in-situ treatment with an aldehyde or ketone, for example formaldehyde, in a reaction-inert solvent such as MeOH, for ex-

ample at room temperature for about 3 hours, yielding final compound (III-a), cis-configuration.

Method F2



Step a): tritylation of an intermediate compound (I-a1) with for example tritylchloride and DMAP generally in the presence of a base such as Et_3N and in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature for about 2 hours;

Step b): reaction of an intermediate compound a37 with $BrCH_2COBr$ in the presence of a base such as sodium hydrogen carbonate and in a reaction-inert solvent such as CH_2Cl_2;

Step c): reaction of an intermediate compound a38 with formic acid, for example for about 3 hours, and subsequently with EEDQ, in a reaction-inert solvent such as $CHCl_3$, for example at room temperature for 30 minutes;

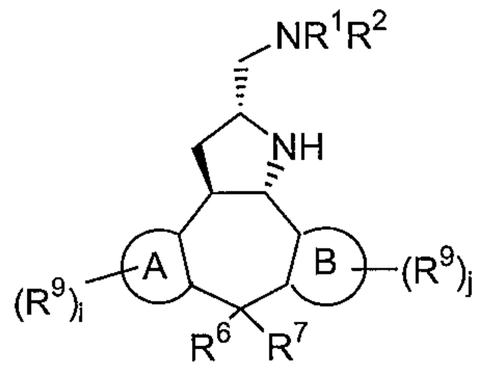
Step d): cyclisation of an intermediate compound a39 with a base such as *t*-BuOK, in a reaction-inert solvent such as THF;

Step e): removal of the aldehyde group from an intermediate compound a40, for example by treatment with an acid such as hydrochloric acid, for example in methanol;

Step f): reductive amination of a final compound (III-b3) with an appropriate aldehyde or ketone and hydrogenation with a palladium-carbon catalyst (1 atm), yielding the final compound (III-a), trans-configuration.

Method G : Preparation of 8,8-substituted pyrrolidinederivatives

The following method illustrates the preparation of compounds of formula (I) in which C is a group of formula (c-1) wherein Y^1 is NH, R^{11} is a group of formula (d-1) and R^{12} is hydrogen and X is a CR^6R^7 group with R^6 and R^7 other than a hydrogen group, represented by formula (IV) below.



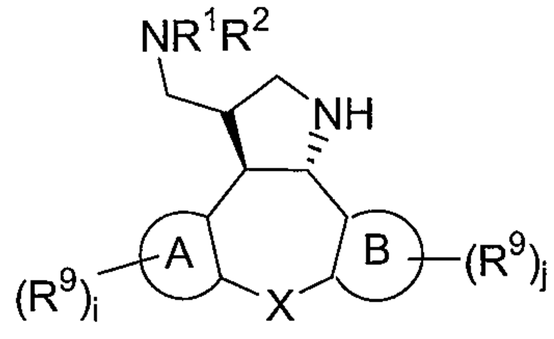
(IV)

Step a): treatment of an intermediate compound a11 or a14 with $(Boc)_2O$ and with a base such as aqueous KOH or NaOH, in a solvent such as THF or dioxane, for example at room temperature for about 6 hours;
Step b): treatment of an intermediate compound a37 with DIAD/PPh_3, in a solvent such as THF, for example at about -15 °C to room temperature;
Step c): oxidation of an intermediate compound a38 with $KMnO_4$, in the presence of a phase-transfer catalyst such as n-Bu_4NHSO_4, in a solvent system such as CH_2Cl_2-H_2O, for example at room temperature for about 16 hours;
Step d): hydrogenation of an intermediate compound a39 with a palladium-carbon catalyst (1 atm), in a reaction-inert solvent such as MeOH, for example at room temperature; followed by treatment with an aldehyde or ketone, such as formaldehyde, in the presence of AcOH to form an intermediate compound in which R^1 and R^2 are each alkyl;
Step e): treatment of intermediate compound a40 with 50 % sulfuric acid in dioxane, for example at room temperature for 3 hours to remove the Boc-protecting group to form a final compound (IV-a);
Step f): subjecting a final compound (IV-a) to a Grignard reaction with methyl magnesium bromide, in a solvent such as THF, for example at room temperature to form a final compound IV-b;
Step g): treatment of a final compound (IV-b) with sulfonylchloride and pyridine, for example at room temperature for 16 hours, to form a final compound (IV-c);
Step h): hydrogenation of a final compound (IV-c) with a palladium-carbon catalyst (1 atm), in a solvent such as MeOH, for example at room temperature to form a final compound (IV-d).

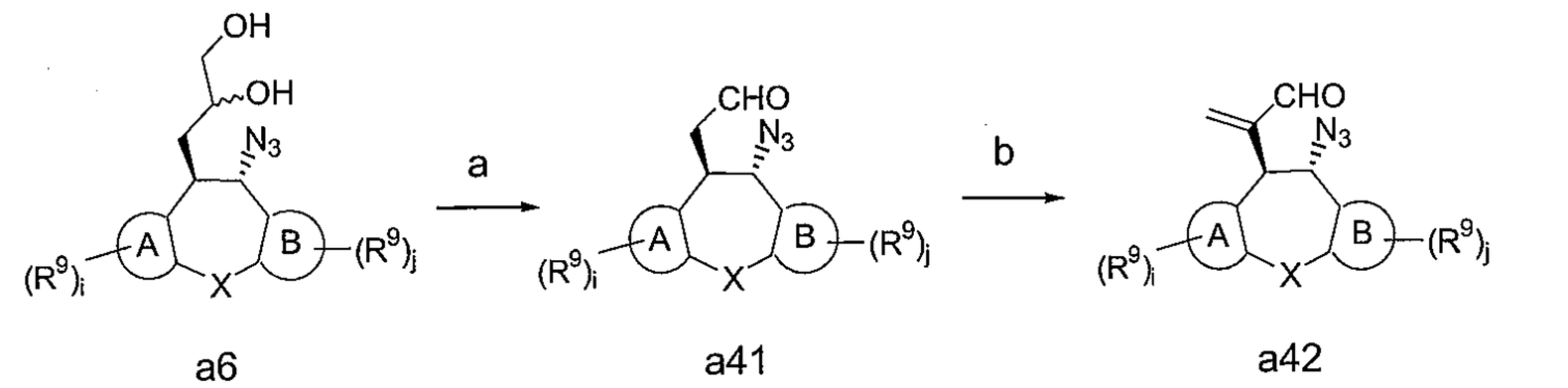
All compounds of formula (IV) have either the 2*R*- or 2*S*-configuration, depending on the starting compound a11 or a14.

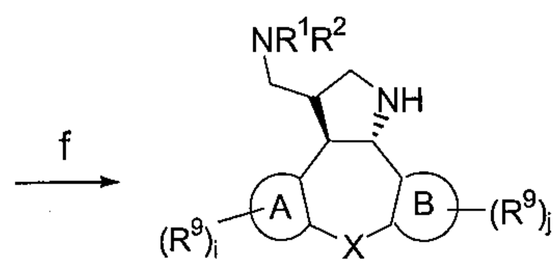
<u>Method H : Preparation of 3-substituted pyrrolidine derivatives</u>

The following method illustrates the preparation of compounds of formula (I) in which C is a group of formula (c-2), wherein Y^1 is NH and R^{11} is a group of formula (d-1) and R^{12} is hydrogen, represented by formula (V) below.



(V)





(V)

Step a): oxidative cleavage of an intermediate compound a6 (both R and S) with $NaIO_4$ in a phosphate buffer (at pH 7), in a reaction-inert solvent such as THF, for example at about 0 °C to room temperature for about 4 hours;

Step b): treatment of a intermediate compound a41 with $CH_2(NMe_2)_2$ and optionally AcOH, in a reaction-inert solvent such as THF, for example at room temperature for about 3 hours ;

Step c): (i) intramolecular cyclization of an intermediate compound a42 with polymer-bound PPh_3 in a reaction-inert solvent such as THF containing traces of water, for example at about 40 °C for about 1 hour ; followed by (ii) reduction of the resulting intermediate compound with $NaCNBH_3$ and AcOH in a reaction-inert solvent such as an alcohol, in particular MeOH, for example at room temperature for about 3 hours;

Step d): (i) treatment of an intermediate compound a43 with $ClCO_2Me$ and aqueous sodium hydrogen carbonate in a reaction-inert solvent such as CH_2Cl_2; (ii) followed by the treatment of the resulting intermediate compound with $NaBH_4$, $BF_3{\cdot}Et_2O$ in a reac-

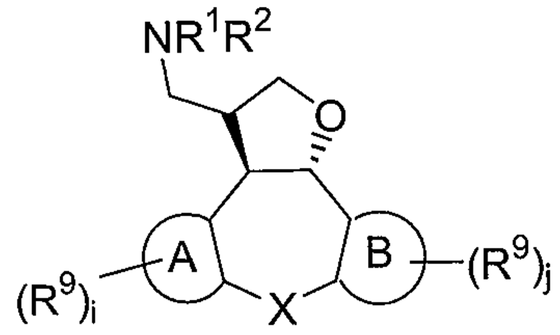
tion-inert solvent such as THF, for example at room temperature for about 24 h; and (iii) followed by the treatment of the resulting intermediate compound with H_2O_2 and aqueous KOH, for example at room temperature for about 3 hours ;

Step e): treatment of an intermediate compound a44 with DIAD/PPh_3 and DPPA in a reaction-inert solvent such as THF, for example at about -15 °C to room temperature;

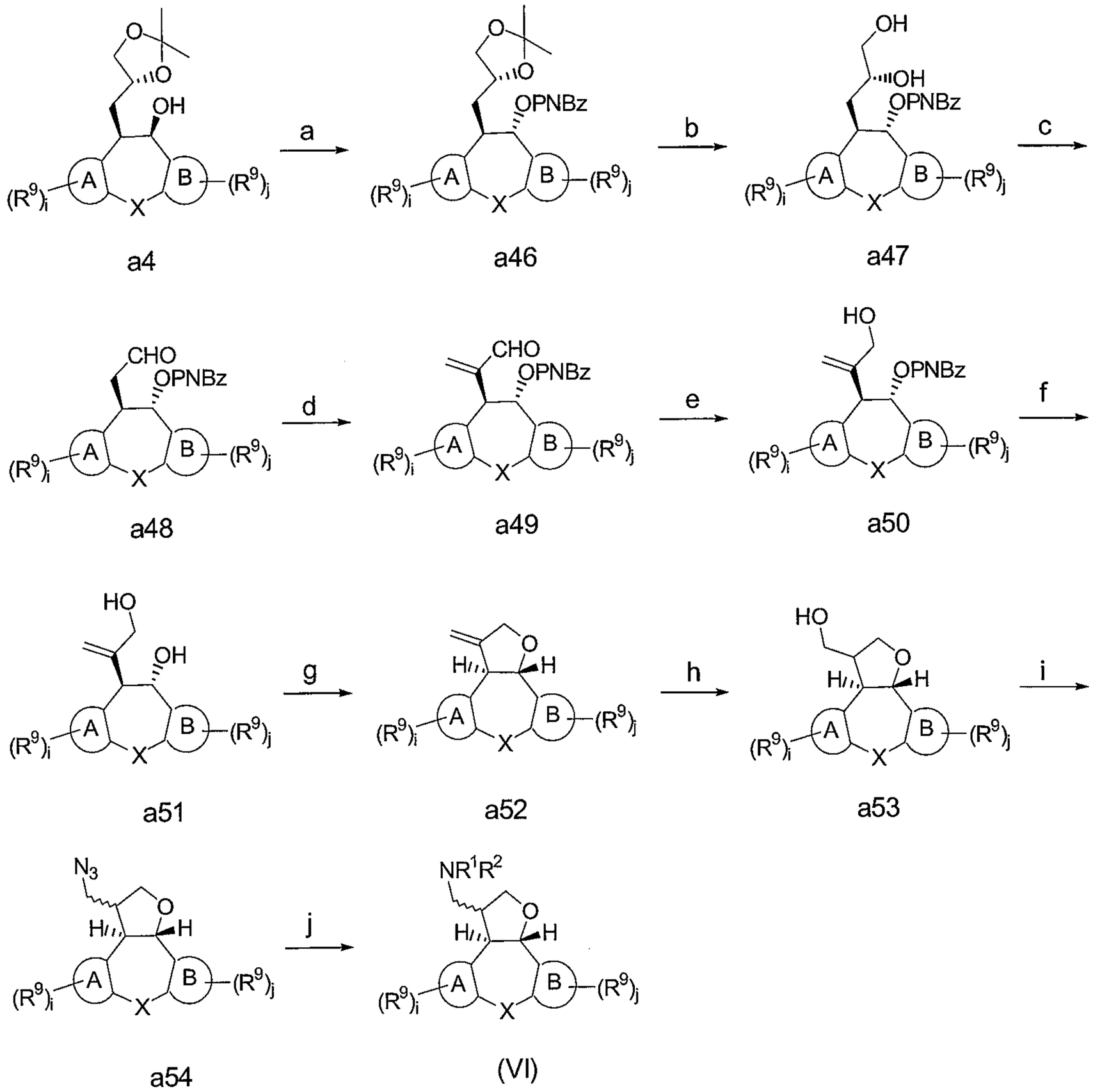
Step f): (i) subjecting an intermediate compound a45 to a Staudinger reaction or hydrogenating with a palladium-carbon catalyst (1 atm) in a reaction-inert solvent such as MeOH, for example at room temperature; and then (ii) followed by a reductive amination with an aldehydeor ketone, for example formaldehyde, yielding a final compound of formula (V).

Method I : Preparation of tetrahydrofurane-3-substituted derivatives

The following method illustrates the preparation of compounds of formula (I) in which C is a group of formula (c-3), R^{11} is a group of formula (d-1) and R^{12} is hydrogen, represented by formula (VI) below.



(VI)



Step a): protection of the alcohol function of an intermediate compound a4 with DIAD/PPh_3 and 4-nitrobenzoic acid (PNBzOH) in a reaction-inert solvent such as THF, for example at about -15 °C to room temperature, for a suitable time, for example about 15 hours ;

Step b): treatment of an intermediate compound a46 with hydrochloric acid in THF (for example as a 1:1 mixture using hydrochloric acid), for example at room temperature for about 5 hours;

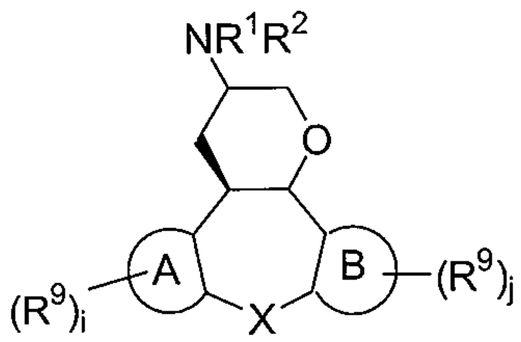
Step c): treatment of an intermediate compound a47 with $NaIO_4$ at pH 7 using a phosphate buffer, in a reaction-inert solvent such as THF, for example at about 0 °C to room temperature for about 4 hours;

Step d): treatment of an intermediate compound a48 with $CH_2(NMe_2)_2$ and AcOH in a reaction-inert solvent such as THF, for example at room temperature for about 3 hours;

Step e): reduction of an intermediate compound a49 with a reducting agent such as sodium borohydride, in a reaction-inert solvent such as methanol, EtOH or *i*-PrOH, for example at room temperature for about 4 hours;
Step f): treatment of an intermediate compound a50 with sodium methoxide in a reaction-inert solvent such as methanol, for example at room temperature for about 4 hours;
Step g): treatment of an intermediate compound a51 with DIAD/tributylphosphine in a reaction-inert solvent such as toluene, for example at room temperature for about 3 hours ;
Step h): (i) hydroboration of an intermediate compound a52 with sodium borohydride and BF_3-Et_2O, in a reaction-inert solvent such as THF, for example at room temperature for about 24 hours; and (ii) treatment with H_2O_2, aqueous sodium hydroxide , in a reaction-inert solvent such as THF, for example at room temperature for about 4 hours;
Step i): treatment of an intermediate compound a53 with DIAD/PPh_3, DPPA, in a reaction-inert solvent such as THF, for example at about –15 °C to room temperature for about 15 hours;
Step j): (i) subjecting an intermediate compound a54 to a Staudinger reaction, or hydrogenation with a palladium-carbon catalyst (1 atm), in a reaction-inert solvent such as MeOH, for example at room temperature for about 1.5 hours; and (ii) reductive amination with an aldehyde or ketone, for example aqueous formaldehyde in AcOH and methanol, yielding a final compound of formula (VI).

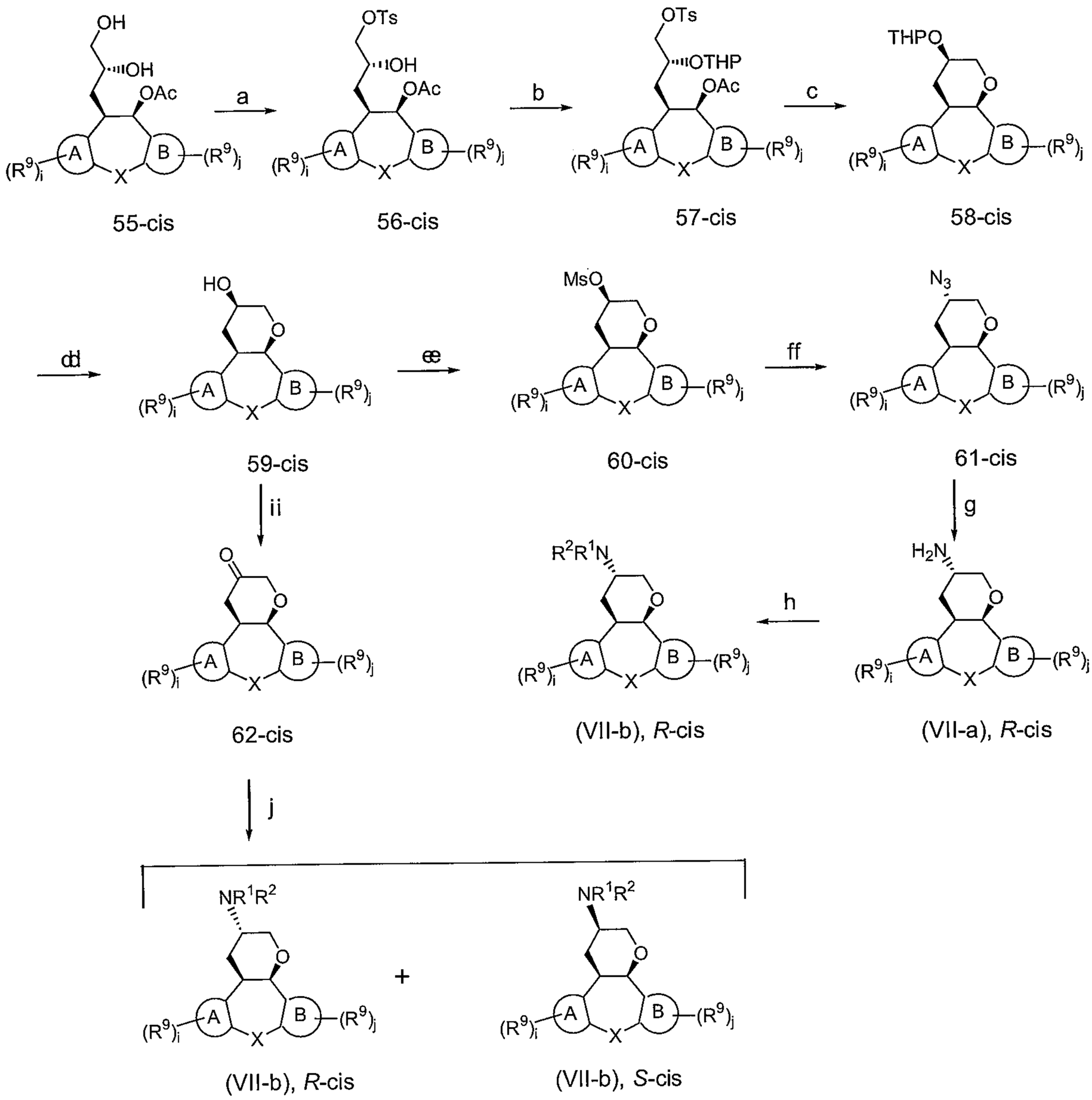
Method J : Preparation of 3-substituted tetrahydropyran derivatives

The following method illustrates the preparation of compounds of formula (I) in which C is a group of formula (c-5), Y^2 is O, R^{12} is hydrogen and R^{14} is a group of formula (d-1), represented by formula (VII) below. The compound can be either *cis* (Method J1) or *trans* (Method J2) with respect to the oxygen.



(VII)

Method J1 (*cis*)



Step a): monotosylation of an intermediate compound a55 with TsCl, Et_3N and Bu_2SnO, for example at room temperature, for example for about 16 hours, in a reaction-inert solvent such as toluene or CH_2Cl_2 ;

Step b): treatment of an intermediate compound a56 with DHP and CSA, in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature for about 3 hours ;

Step c): deacetylation of an intermediate compound a57 with a base such as K_2CO_3, in a reaction-inert solvent such as MeOH, for example at room temperature for about 3

hours, followed by intramolecular cyclization with NaH, in a reaction-inert solvent such as THF, for example at about 0 °C to room temperature for about 4 hours ;

Step d): deprotection of an intermediate compound a58 with Dowex, in a reaction-inert solvent such as MeOH/H_2O, for example at room temperature for about 2 days;

Step e): mesylation of an intermediate compound a59 with MsCl, DMAP and Et_3N, in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature for about 4 hours ;

Step f): treatment of an intermediate compound a60 with NaN_3, in a reaction-inert solvent such as DMF, for example at about 90 °C for about 2 hours;

Step g): hydrogenation of an intermediate compound a61 with a palladium-carbon catalyst (1 atm), in a reaction-inert solvent mixture such as *i*-PrOH/THF, for example at room temperature for about 3 hours ; yielding a final compund (VII-a).

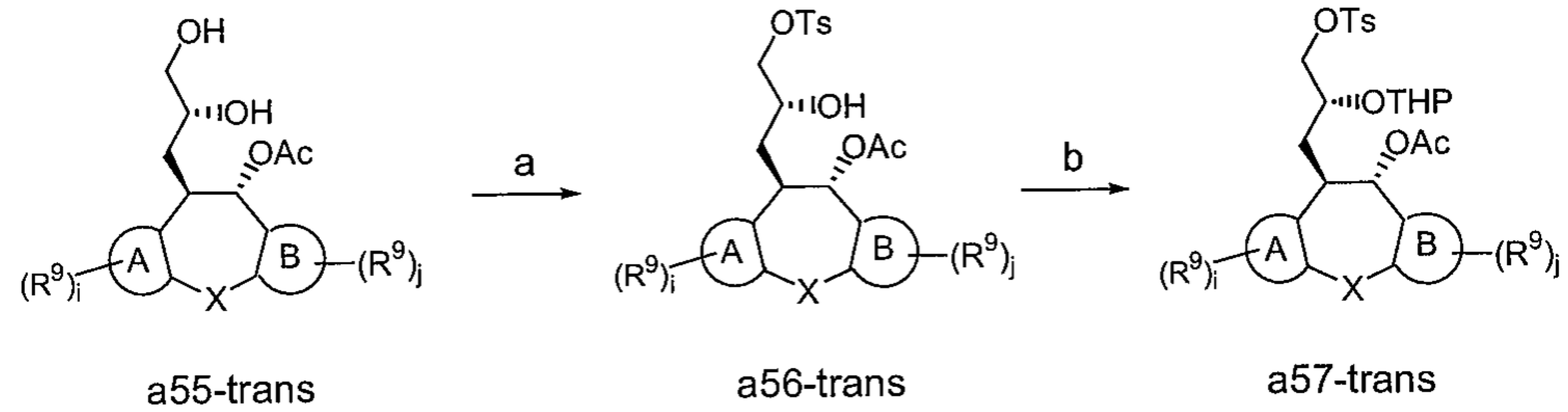
Step h): hydrogenation of final compound (VII-a) with a palladium-carbon catalyst (1 atm), in a reaction-inert solvent mixture such as *i*-PrOH/THF, and reductive amination with an aldehyde or ketone; yielding a final compound (VII-b), wherein at least one of R^1 and R^2 is alkyl.

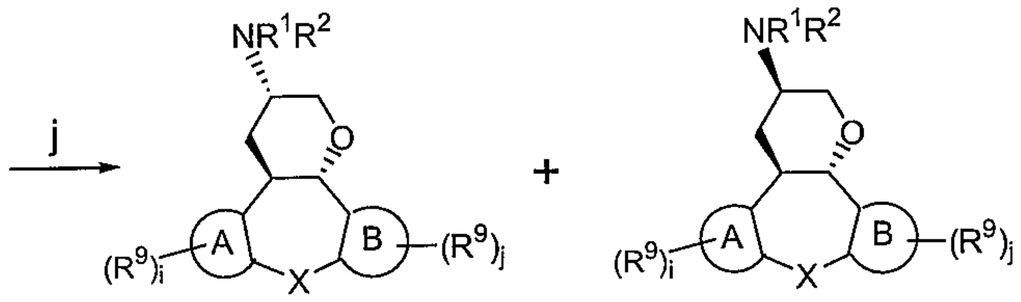
Step i): oxidation of an intermediate compound a59 with a PCC catalyst, in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature for about 24 hours;

Step j): reductive amination of an intermediate compound a62 with an appropriate R^1R^2NH compound and hydrogenation with a palladium-carbon catalyst (1 atm) in the presence of a base such as Et_3N, in a reaction-inert solvent such as MeOH, for example at room temperature for about 24 hours, yielding an enantiomeric mixture of final cis-compounds (VII-b).

Method J2 (*trans*)

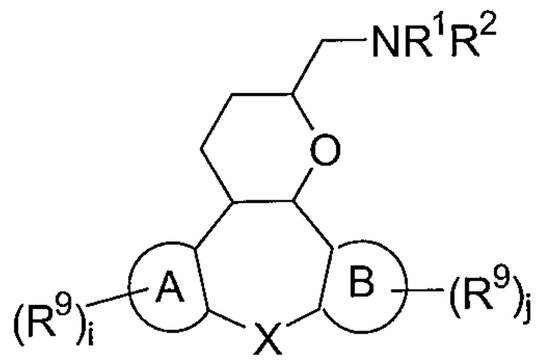
The method J1 can also be applied to the trans-epimer of intermediate compound a55, leading to trans-final compounds of formulae (VII-a) and (VII-b) below.



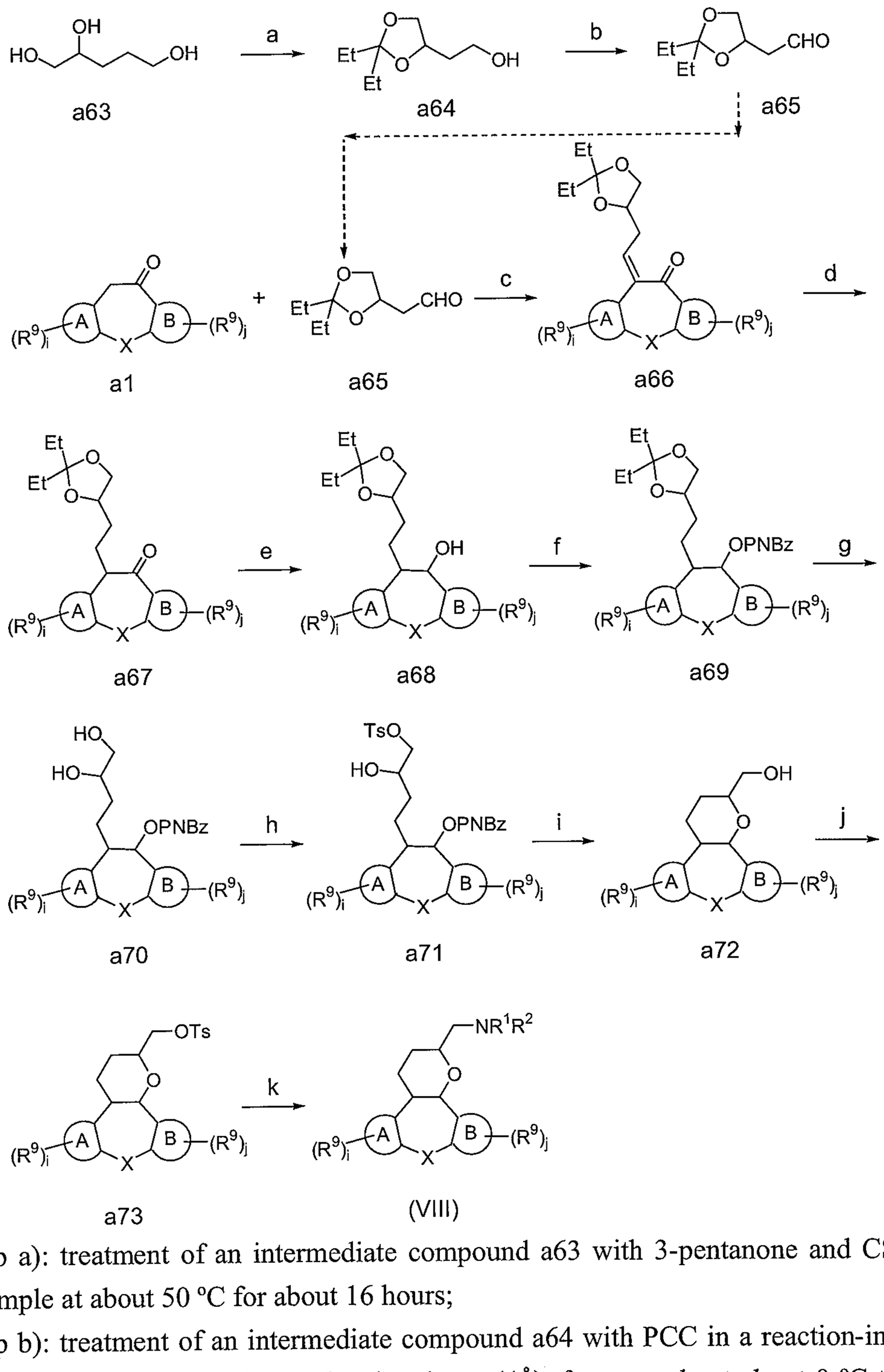


Method K : Preparation of 4-substituted tetrahydropyran-derivatives

The following method illustrates the preparation of compounds of formula (I) in which C is a group of formula (c-4), Y^2 is O, R^{11} is a group of formula (d-1) and R^{12} is hydrogen, represented by formula (VIII) below.



(VIII)



Step a): treatment of an intermediate compound a63 with 3-pentanone and CSA, for example at about 50 °C for about 16 hours;

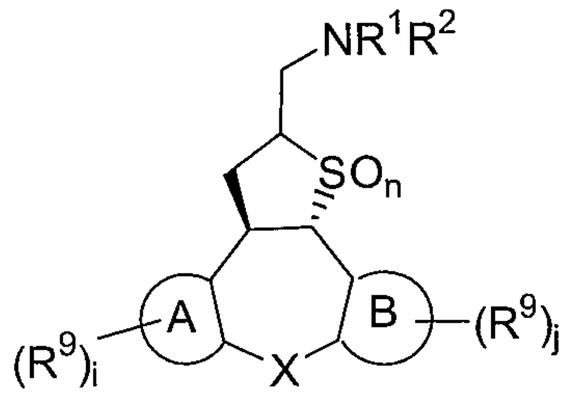
Step b): treatment of an intermediate compound a64 with PCC in a reaction-inert solvent such as CH_2Cl_2, using molecular sieves (4Å), for example at about 0 °C to room temperature for about 75 minutes;

Step c): reaction of an intermediate compound a1 with the intermediate compound a65, with $MgBr_2$, using t-BuOK as a catalyst, in a reaction-inert solvent such as toluene/THF, for example at room temperature for about 23 hours; this reaction must be carried out in the absence of oxygen, preferably under argon atmosphere;

Step d): hydrogenation of an intermediate compound a66 with hydrogen over a palladium-carbon catalyst (10 %) in a reaction-inert solvent such as Et_3N, *i*-PrOH or toluene, or a mixture of them, for example at room temperature for about 15 hours;
Step e): reduction of an intermediate compound a67 with a reducting agent such as sodium borohydride, in a phosphate buffer at pH 7, in a reaction-inert solvent such as *i*-PrOH, for example at about 0 °C to room temperature for about 1 hour;
Step f): treatment of an intermediate compound a68 with DIAD/PPh_3, 4-nitrobenzoic acid (PNBzOH), in a reaction-inert solvent such as THF, for example at about -15 °C to room temperature for about 15 hours ;
Step g): treatment of an intermediate compound a69 with hydrochloric acid (1 N) in THF (1:1), for example at room temperature for about 5 hours;
Step h): tosylation of an intermediate compound a70 with TsCl, Et_3N, dibutyl(oxo)stannane (Bu_2SnO), in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature for about 12 hours ;
Step i): cyclization of intermediate compound a71 with sodium methoxide in a reaction-inert solvent such as methanol, for example at room temperature for about 3 hours;
Step j): tosylation of an intermediate compound a72 with TsCl, Et_3N and DMAP, in a reaction-inert solvent such as CH_2Cl_2, for example at room temperature for about 16 hours;
Step k): treatment of an intermediate compound a73 with a compound of formula HNR^1R^2 in a reaction-inert solvent such as THF, in a steel bomb at about 135 °C for about 15 hours, yielding a compound of formula (VIII).

<u>Method L : Preparation of tetrahydrothiophene-2-substituted derivatives</u>

The following methods illustrates the preparation of compounds of formula (I) in which C is a group of formula (c-1) wherein Y^1 is SO_n and R^{11} is a group of formula (d-1) and R^{12} is hydrogen, represented by formulae (IX), (X) and (XI) below.



(2*R*,3a*R*,x*S*)

2*R*-IX (n=0)

2*R*-X (n=1)

2*R*-XI (n=2)

(2*S*,3a*R*,x*S*)

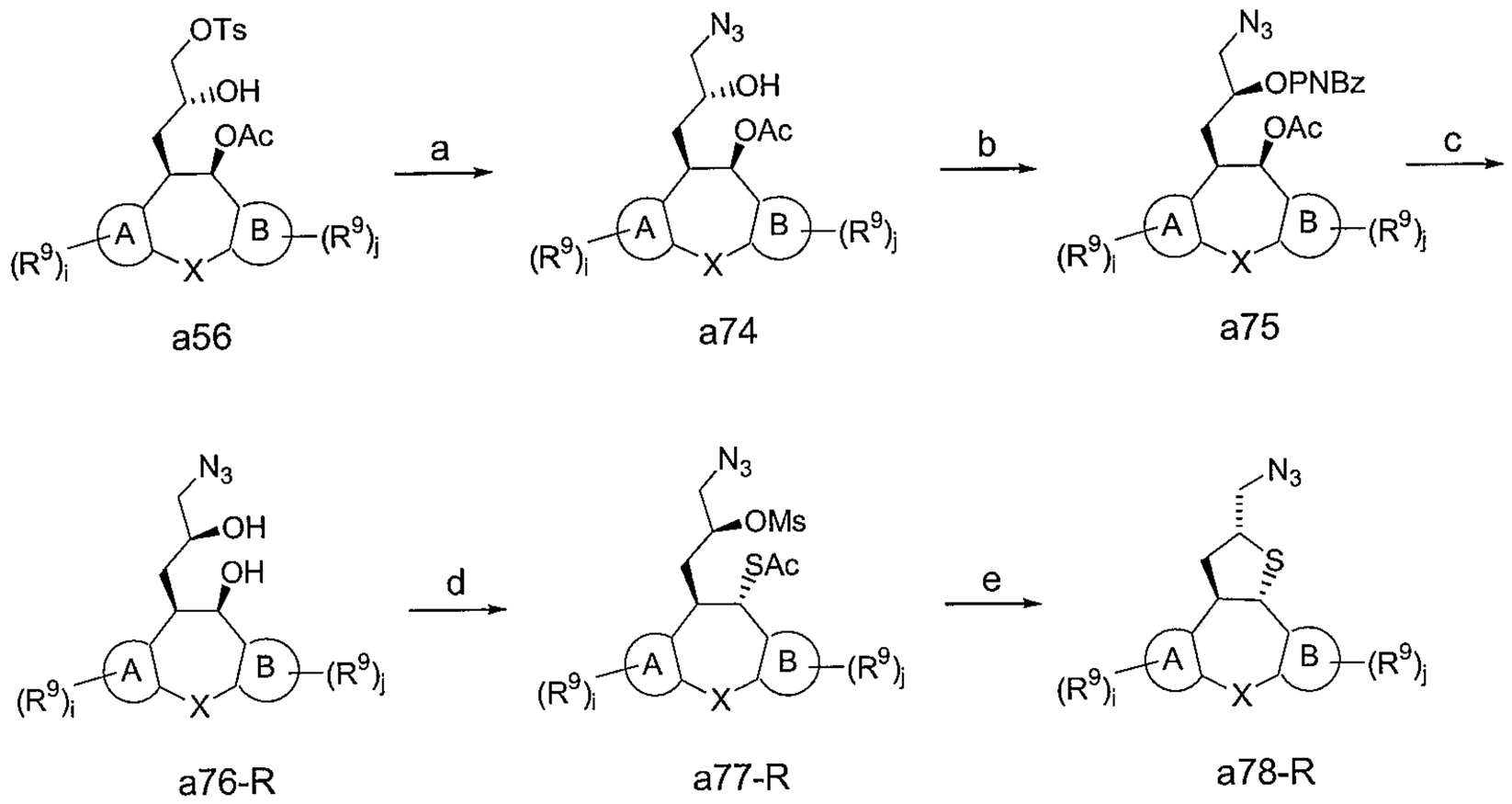
2*S*-IX (n=0)

2*S*-X (n=1)

2*S*-XI (n=2)

where x is 12b if A and B is a six-membered ring, such as phenyl

Method L1 : Synthesis of (2*R*,3a*R*,x*S*)-tetrahydrothiophene intermediate compounds



a56 a74 a75

a76-R a77-R a78-R

Step a): treatment of an intermediate compound a56 with sodium azide and ammonium chloride, in a reaction-inert solvent such as DMF, for example at about 90 °C;

Step b): subjecting an intermediate compound a74 to a Mitsunobu reaction (giving a supplementary inversion at the carbon atom) with DIAD/PPh_3 and *p*-nitrobenzoic acid (PNBzOH), in a reaction-inert solvent such as THF, for example at 0 °C to room temperature for about 2 hours ;

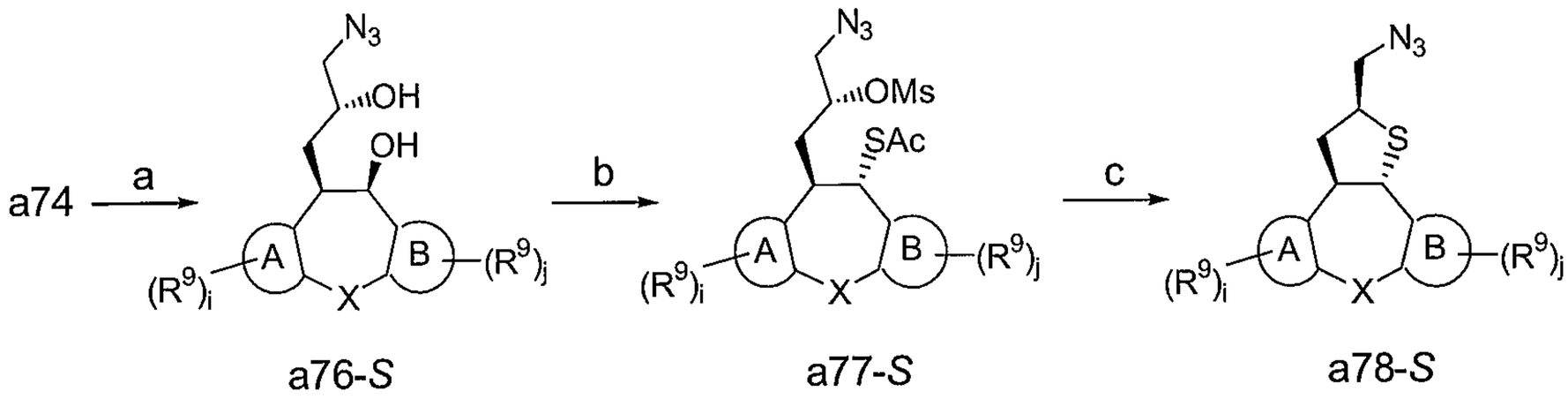
Step c): deprotection of an intermediate compound a75 with a base solution such as K_2CO_3/MeOH, for example at room temperature for about 2 hours ;

Step d): mesylation of an intermediate compound a76-R with MsCl and DMAP, using a base such as Et_3N, in a reaction-inert solvent such as CH_2Cl_2, for example at 0 °C to

room temperature for about 30 minutes, followed by *in situ* treatment with AcSH at 0 °C to room temperature for about 5 hours;

Step e): deacylation and concomitant cyclization of an intermediate compound a77-*R* with a base solution such as K_2CO_3/MeOH, for example at room temperature for about 2 hours;

Method L2 : Synthesis of (2*S*,3a*R*,x*S*)-tetrahydrothiophene intermediate compounds

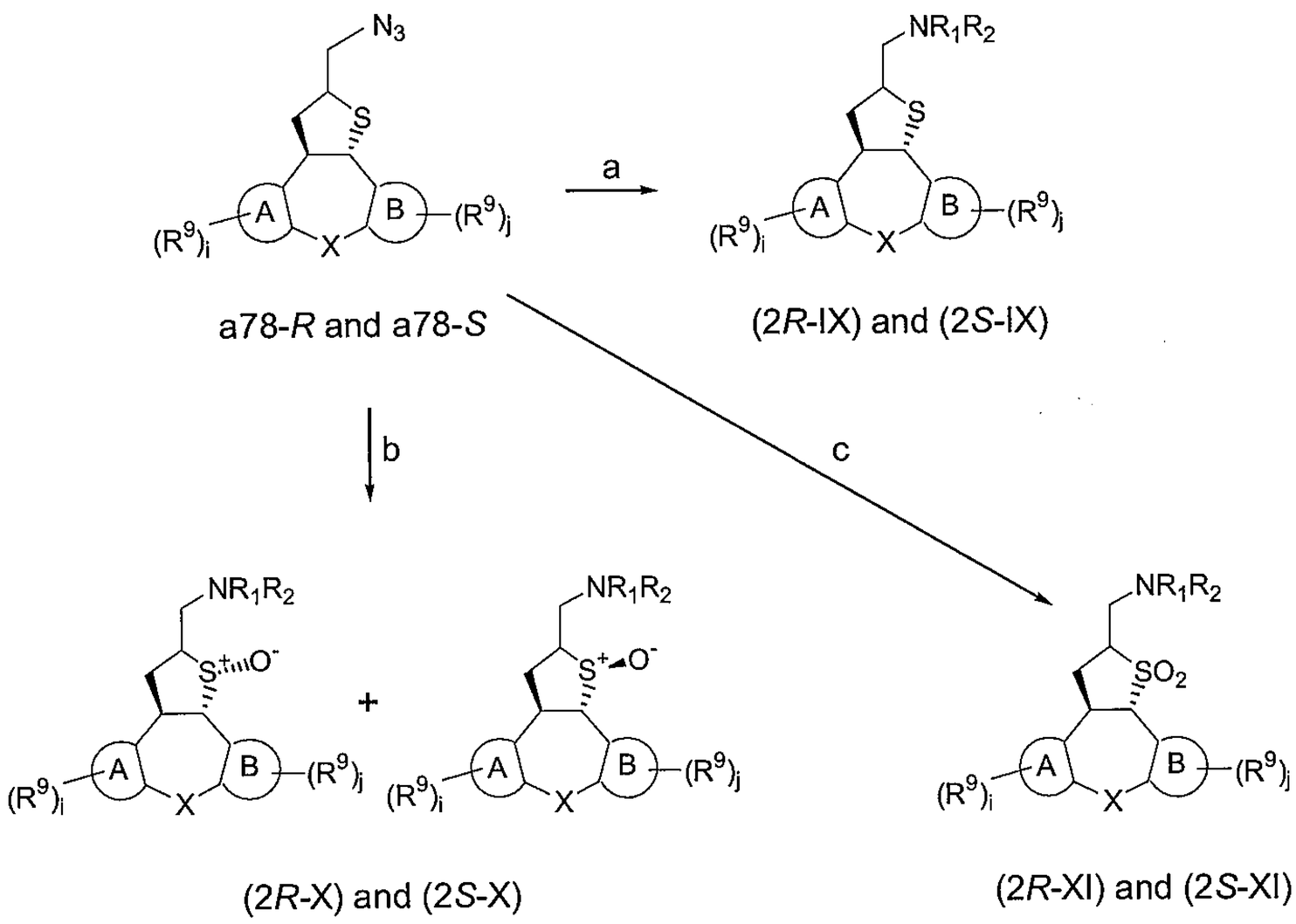


Step a): treatment of an intermediate compound a74 with a base solution such as K_2CO_3/MeOH, for example at room temperature for about 2 hours;

Step b): (i) treatment of an intermediate compound a76-*S* with $(CH_3SO_2)_2O$, Et_3N, DMAP, in a reaction-inert solvent such as CH_2Cl_2, for example at about 0 °C; or (ii) treatment of an intermediate compound 76-*S* with MsCl, DMAP and Et_3N, in a reaction-inert solvent such as CH_2Cl_2 at about 0 °C, followed by in situ treatment with AcSH at about 0 °C for about 5 hours;

Step c): deacylation and concommitant cyclization of an intermediate compound a77-S with a base such as K_2CO_3/MeOH, for example at room temperature for about 30 minutes.

Method L3 : Synthesis of (2*RS*,3a*R*,x*S*)-tetrahydrothiophene derivatives



Step a): (i) treatment of an intermediate compound a78-*R* or a78-*S* using a Staudinger reaction or hydrogenation with a palladium-carbon catalyst (1 atm) in a reaction-inert solvent such as MeOH, for example at room temperature; and (ii) reductive amination of the resulting intermediate compound with an aldehyde or ketone;

Step b): (i) treatment of an intermediate compound a78-*R* or a78-*S* with an aqueous hydrogen peroxide, in a reaction-inert solvent such as HFIP, for example at room temperature for about 15 minutes ; (ii) treatment of the resulting intermediate compound using a Staudinger reaction or hydrogenation with a palladium-carbon catalyst (1 atm) in a reaction-inert solvent such as MeOH, for example at room temperature; (iii) reductive amination of the resulting intermediate compound with an aldehyde or ketone ;

Step c): (i) treatment of an intermediate compound a78-*R* or a78-*S* with mCPBA in a reaction-inert solvent such as CH_2Cl_2; (ii) treatment of the resulting intermediate compound using a Staudinger reaction or hydrogenating with a palladium-carbon catalyst (1 atm), in a reaction-inert solvent such as MeOH, for example at room temperature; and (iii) reductive amination of the resulting intermediate compound with an aldehyde or ketone.

The compounds of Formula (I) may also be converted into each other following art-known transformation reactions. For instance,

a) a compound of Formula (I), wherein R^1 and R^2 taken together with the nitrogen atom to which they are attached form a radical of Formula (a-2), may be converted into the corresponding primary amine by treatment with hydrazine or aqueous alkali;

b) a compound of Formula (I), wherein R^1 or R^2 is trifluoromethylcarbonyl, may be converted into the corresponding primary or secondary amine by hydrolysis with aqueous alkali;

c) a compound of Formula (I), wherein R^1 or R^2 is C_{1-6} alkyl substituted with C_{1-6} alkylcarbonyloxy may be hydrolyzed into a compound of Formula (I) wherein R^1 or R^2 is C_{1-6} alkyl substituted with hydroxy;

d) a compound of Formula (I), wherein R^1 and R^2 are both hydrogen may be mono- or di-*N*-alkylated to the corresponding amine form;

e) a compound of Formula (I), wherein R^1 and R^2 are both hydrogen, or R^1 or R^2 is hydrogen, may be *N*-acylated to the corresponding amide;

f) a compound of Formula (I) containing a C_{1-6}alkyloxycarbonyl group may be hydrolyzed to the corresponding carboxylic acid;

g) a compound of Formula (I) in which R^9 is hydrogen, i.e. i and/or j is zero, can be converted to a corresponding alkyloxycarbonyl compound by treatment with an appropriate acylating agent, e.g. the appropriate alkyloxycarbonyl chloride in the presence of butyllithium in hexane using an organic solvent such as tetrahydrofuran; or

h) a compound of Formula (I) in which R^9 is alkyloxycarbonyl can be converted to a corresponding hydroxymethyl compound by reduction for example with $LiAlH_4$ for example in an organic solvent such as tetrahydrofuran.

The procedures described above can be modified by the use of conventional procedures which will be known to those skilled in the art to provide analogous processes for the preparation of compounds of Formula (I).

The starting materials mentioned hereinabove are either commercially available or may be made following art-known procedures. For instance, intermediate compound 1 may be prepared in accordance with the techniques described in patent specifications W0 03/048146 and WO03/048147 referred to above or by techniques analogous thereto.

Pure stereochemically isomeric forms of the compounds of Formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated

by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

The compounds of Formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid respectively with a suitable chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

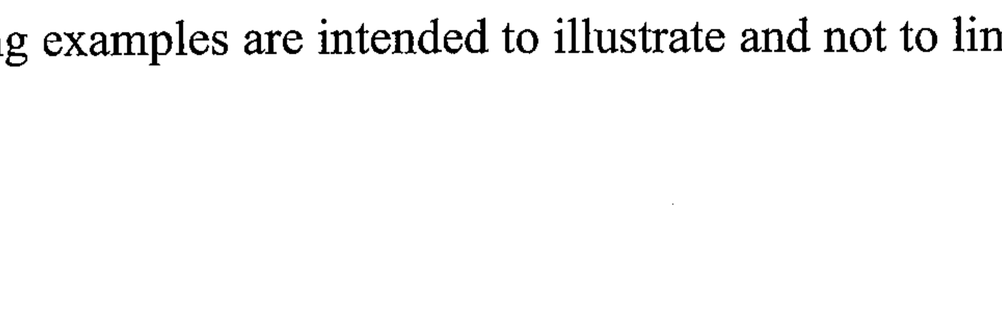
The following examples are intended to illustrate and not to limit the scope of the present invention.

Experimental part

A. Preparation of the intermediate compounds

Example A1

(11*R*)-11-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-8-fluoro-5,11-dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one (intermediate compound 2)



intermediate 1 intermediate 2

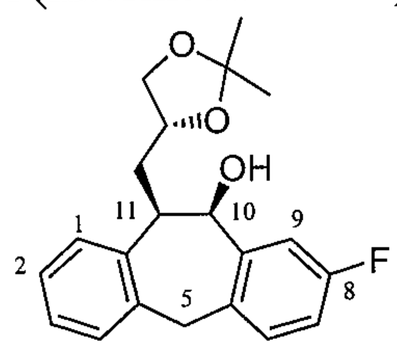
A solution of α,β-unsaturated ketone intermediate compound 1 (1.00 g, 2.96 mmol) and Et_3N (0.63 mL, 4.50 mmol) in *i*-PrOH (30 mL) was hydrogenated with 10 % Pd/C

at atmospheric pressure for 6 hours. Then the mixture was filtered through a pad of celite and the solids were washed with CH_2Cl_2 (4 × 20 mL). After evaporation, *i*-PrOH (5 mL) and Et_3N (1.20 mL) was added and the reaction mixture was stirred at 40 °C for 1 hour. The reaction mixture was cooled to room temperature and allowed to crystallize. The crystals were filtered off and dried under vacuum to afford pure intermediate compound 2 as a white crystalline powder (0.86 g, 86 %); mp: 144-146 °C.

Mass spectrum: CI m/z (assignment, relative intensity) 341 (MH^+, 2 %), 283 (MH^+ -acetone, 100 %); EI: m/z (assignment, relative intensity) 340 ($M^{+\cdot}$, 1 %), 282 ($M^{+\cdot}$ –acetone, 79 %), 226 ($M^{+\cdot}$–sidechain + H, 100 %); High resolution EI, Calculated $C_{21}H_{21}FO_3$ ($M^{+\cdot}$): 340.1475, Found: 340.1479 (1 %).

Example A2

(10*R*,11*R*)-11-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-8-fluoro-10,11 -dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-ol (intermediate compound 3)



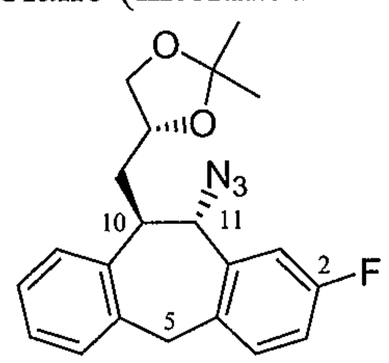
intermediate 3

To an ice-cooled solution of intermediate compound 2 (0.42 g, 1.23 mmol) in *i*-PrOH (15 mL) was added phosphate buffer solution (pH=7, 5 mL) and then portionwise $NaBH_4$ (0.23 g, 6.16 mmol). The reaction mixture was stirred at room temperature for 1 hour. Then 10 mL NH_4Cl (sat. aq. solution) was added, the mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the organic phases were dried with $MgSO_4$. After removal of the solvent, the residue was purified on a silica gel column by using ether/hexane (40:60), yielding intermediate compound 3 as a colorless oil (0.42 g, 99 %).

Mass spectrum: CI m/z (assignment, relative intensity) 325 (MH^+ -H_2O, 53 %), 267 (MH^+ -H_2O-acetone, 100 %), 249 (MH^+ -$2H_2O$-acetone, 97 %); EI: m/z (assignment, relative intensity) 342 ($M^{+\cdot}$, 3 %), 324 ($M^{+\cdot}$ -H_2O, 48 %), 266 ($M^{+\cdot}$ -H_2O-acetone, 35 %), 209 (100 %); High resolution EI Calculated $C_{21}H_{23}FO_3$ ($M^{+\cdot}$): 342.1631, Found: 342.1627 (5 %).

Example A3

(4*R*)-4-{[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]methyl}-2,2-dimethyl-1,3-dioxolane (intermediate compound 4)



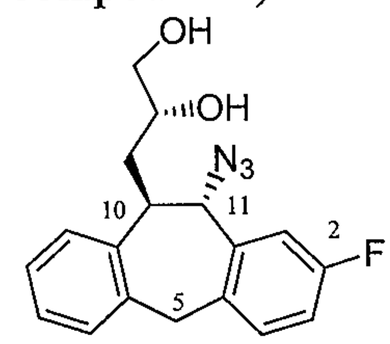
intermediate 4

To a cooled (-30 °C) solution of DIAD (2.43 mL, 33.47 mmol) in THF (10 mL) were added intermediate compound 3 (2.30 g, 6.73 mmol) in THF (18 mL) and PPh_3 (3.71 g, 14.07 mmol). After 20 minutes, DPPA (3.62 mL, 16.83 mmol) was added and the reaction mixture was allowed to warm up to room temperature. After stirring overnight, the solvent was removed in vacuo to give a red oil. The crude material was purified by column chromatography using ether/hexane (10/90) to give an unseparated mixture of intermediate compound 4, as an oil, and Ph_3PO (3.46 g).

Mass spectrum: CI m/z (assignment, relative intensity) 368 (MH^+, 1 %), 325 (MH^+ -HN_3, 9 %), 304 (13 %), 276 (MH^+ -HN_3-acetone, 100 %), 248 (20 %).

Example A4

(2*R*)-3-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-1,2-propanediol (intermediate compound 5)



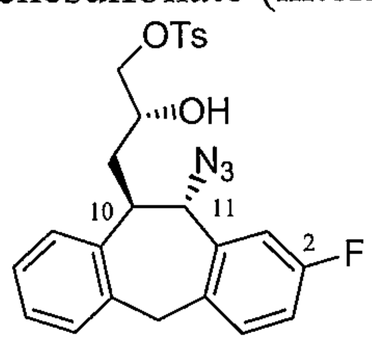
intermediate 5

To solution of intermediate compound 4 (3.68 g, 10.02 mmol) in THF (30 mL) was added 1N HCl (30 mL) and the mixture was stirred at room temperature for 8 hours. Add K_2CO_3 (sat. aq. sol.) at 0 °C, extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. The residue obtained upon evaporation was purified by column chromatography on silica gel using Et_2O/heptane (30/70) to give an oily intermediate compound 5 (3.19 g, 91 % for 2 steps from 3).

Mass spectrum: CI m/z (assignment, relative intensity) 328 (MH^+, 2 %), 310 (MH^+ -H_2O, 2 %), 300 (MH^+ -N_2, 5 %), 285 (MH^+ -HN_3, 11 %), 267 (MH^+ -HN_3-H_2O, 100 %), 249 (MH^+ -HN_3-$2H_2O$, 33 %), 225 (MH^+ -HN_3– CH_2OHCHO, 20 %).

Example A5

(2*R*)-3-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-10-yl]-2-hydroxypropyl4-methylbenzenesulfonate (intermediate compound 6)



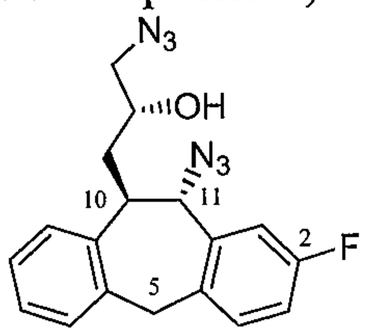
intermediate 6

To solution of intermediate compound 5 (1.11 g, 3.39 mmol) in dry toluene (10 mL) was added Bu_2SnO (97.6 mg, 0.39 mmol), Et_3N (1.07 mL, 7.74 mmol) and TsCl (0.739 g, 3.87 mmol). The mixture was stirred at room temperature overnight. Add NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. The residue was purified by column chromatography on silica gel using EtOAc/heptane (20/80) to give intermediate compound 6 as an oil (1.55 g, 95 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 454 (MH^+ -N_2, 1 %), 421 (MH^+ -HN_3-H_2O, 1 %), 282 (MH^+ -TsOH-HN_3, 20 %), 264 (MH^+ -TsOH-HN_3-H_2O, 15 %), 173 ($TsOH_2^+$, 100 %).

Example A6

(2*R*)-1-azido-3-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten- 10-yl]-2-propanol (intermediate compound 7)



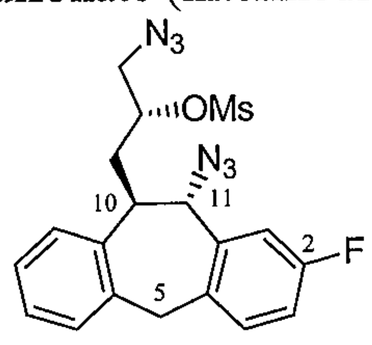
intermediate 7

A solution of intermediate compound 6 (2.00 g, 4.15 mmol) in DMF (30 mL) was treated with sodium azide (810.8 mg, 12.47 mmol) and the mixture was stirred at 90 °C in the dark for 2 hours. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with brine. Following concentration of the dried organic phases the residue was purified by column chromatography on silica gel using heptane/EtOAc (80/20) affording diazide intermediate compound 7 (1.22 g, 88 %) as an oil.

Mass spectrum: -CI m/z (assignment, relative intensity) 325 (MH^+ -N_2, 2 %), 310 (MH^+ -HN_3, 3 %), 297 (MH^+ - N_2- N_2, 1 %), 282 (MH^+ - HN_3 –N_2, 52 %), 268 (MH^+ - HN_3- HN_3, 3 %).

Example A7

(1*R*)-2-azido-1-{[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]methyl}ethyl methanesulfonate (intermediate compound 8)



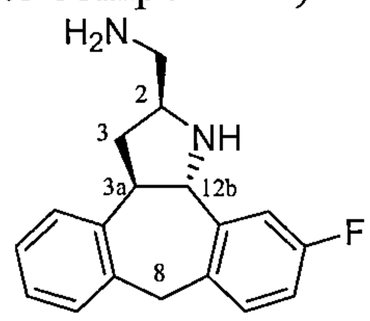
intermediate 8

To solution of intermediate compound 7 (65 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) was added DMAP (18.5 mg, 0.09 mmol), Et_3N (0.13 mL, 0.63 mmol) and MsCl (44.5 µL, 0.40 mmol). After stirring at room temperature for 10 minutes, 10 mL NH_4Cl (sat. aq. solution) was added. Extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column chromatography purification on silica gel using EtOAc/heptane (20:80) as eluent yielded intermediate compound 8 as an oil (78.2 mg, 98 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 403 (MH^+ -N_2, 3 %), 360 (MH^+ - N_2 – HN_3, 43 %), 307 (MH^+ - $MeSO_3H$ – N_2, 50 %), 264 (MH^+ -$MeSO_3H$ – HN_3 – N_2, 58 %), 250 (MH^+ - $MeSO_3H$ –HN_3, – N_3, 2 %), 197 (100 %).

Example A8

[(2*S*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]-pyrrol-2-yl]methanamine (intermediate compound 9)

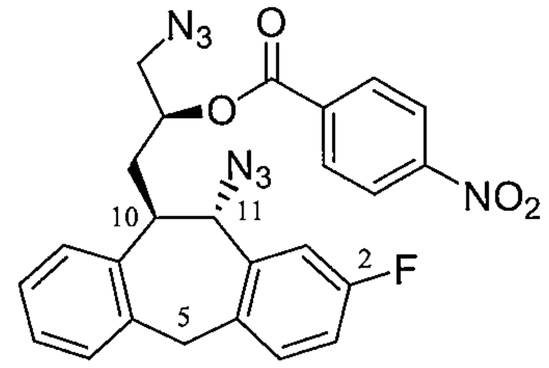


intermediate 9

A solution of intermediate compound 8 (98.2 mg, 0.23 mmol) in MeOH (10 mL) was hydrogenated at atmospheric pressure with 10 % Pd/C for 1 night. Then the mixture was filtered through a pad of celite and the solids were washed 4 times with CH_2Cl_2. After evaporation of the filtrate, the crude product was purified by column chromatography on silica gel using $CHCl_3$/MeOH/NH_4OH (90/9/1) as eluent. This afforded intermediate compound 9 as an oil (36.4 mg, 56 %).

Example A9

(1*S*)-2-azido-1-{[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]methyl}ethyl 4-nitrobenzoate (intermediate compound 10)



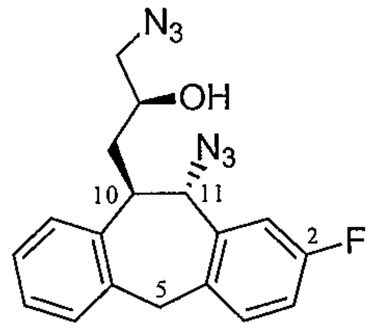
intermediate 10

To a cooled (0 °C) solution of DIAD (4.2 mL, 21.18 mmol) in THF (50 mL) was added PPh_3 (5.55 g, 21.18 mmol). Stir at 0 °C for 30 minutes (precipitation of white solid). Then, a mixture of intermediate compound 7 (3.727 g, 10.59 mmol) and 4-nitrobenzoic acid (3.54 g, 21.18 mmol) in THF (50 mL) was added. The reaction mixture was allowed to warm up to room temperature and after stirring for 2 hours, MeOH was added and the stirring continued for an additional 30 minutes. After removal of the solvent, the crude material was purified by column chromatography on silica gel using EtOAc/heptane (20/80) to give the ester intermediate compound 10 as an oil (4.85 g, 91 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 431 (MH^+ -N_2 – HN_3, 36 %), 307 (MH^+ - N_2 – p-NO_2PHCO_2H, 2 %), 264 (MH^+ – p-NO_2PHCO_2H– HN_3 – N_2, 58 %), 197 (100 %), 182 (72 %).

Example A10

(2*S*)-1-azido-3-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-2-propanol (intermediate compound 11)



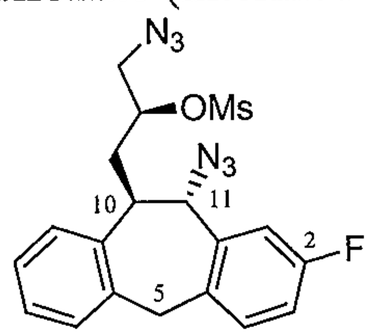
intermediate 11

A solution of intermediate compound 10 (78.0 mg, 0.15 mmol) in MeOH (2 mL) was treated with K_2CO_3 (76.9 mg, 0.47 mmol) and the mixture was stirred for 1 hour. Add NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. The residue was purified by column chromatography on silica gel using EtOAc/heptane (20/80) as eluent to give alcohol intermediate compound 11 as an oil (42.6 mg, 78 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 325 (MH^+ -N_2, 2 %), 310 (MH^+ -HN_3, 3 %), 297 (MH^+ - N_2- N_2, 1 %), 282 (MH^+ - HN_3 –N_2, 52 %), 268 (MH^+ - HN_3- N_3, 3 %).

Example A11

(1*S*)-2-azido-1-{[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]methyl}ethyl methanesulfonate (intermediate compound 12)



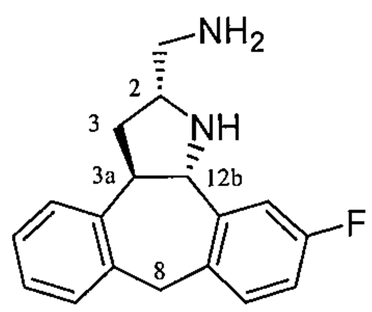
intermediate 12

To a solution of intermediate compound 11 (42.6 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) was added DMAP (12.7 mg, 0.06 mmol), Et_3N (0.047 mL, 0.42 mmol) and MsCl (33.9 µL, 0.30 mmol). Stir at room temperature for 10 minutes. Add 10 mL NH_4Cl (sat. aq. solution), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$; upon evaporation of the solvent intermediate compound 12 was obtained as an oil (53.0 mg, 100 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 403 (MH^+ -N_2, 3 %), 360 (MH^+ - N_2 – HN_3, 43 %), 307 (MH^+ - $MeSO_3H$ – N_2, 50 %), 264 (MH^+ -$MeSO_3H$ – HN_3 – N_2, 58 %), 250 (MH^+ - $MeSO_3H$ –HN_3 – N_3, 21 %), 197 (100 %).

Example A12

[(2*R*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]methanamine (intermediate compound 13)



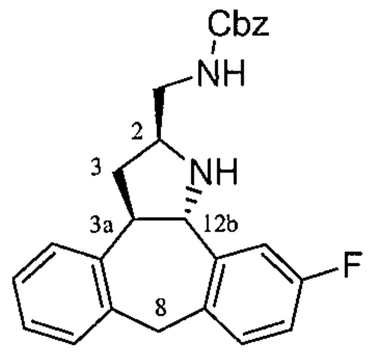
intermediate 13

A solution of intermediate compound 12 (501.0 mg, 1.16 mmol) in MeOH (10 mL) was hydrogenated under 1 atmospheric pressure with 10 % palladium-on-charcoal under vigorous stirring at room temperature for 1 night. Then the mixture was filtered through a pad of celite and the solids were washed 4 times with CH_2Cl_2. After evaporation, the crude product was purified by column chromatograhy on silica gel using

$CHCl_3$/MeOH/NH_4OH (90/9/1). This yielded intermediate compound 13 as an oil (270.0 mg, 82 %).

Example A13

Benzyl [(2*S*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]methylcarbamate (intermediate compound 14)



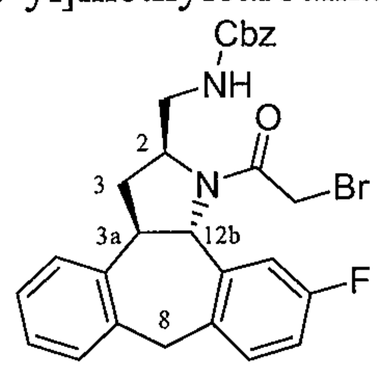
intermediate 14

To a solution of intermediate compound 9 (220.0 mg, 0.78 mmol) in CH_2Cl_2 (5 mL) at -20 °C was added Et_3N (0.109 mL, 0.78 mmol) and benzyl chloroformate (0.112 mL, 0.78 mmol). The mixture was then stirred for 1 hour. Add 10 mL of NH_4Cl (sat. aq. solution), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. The residue was purified by column chromatography on silica gel using EtOAc/heptane (20/80) to give a mono-Cbz intermediate compound 14 (128.9 mg, 40 %) and di-Cbz derivative (84.5 mg).

Mass spectrum: -CI m/z (assignment, relative intensity) 417 (MH^+, 100 %), 397 (MH^+ -HF, 8 %), 311 (MH^+ -PhCHO, 7 %), 309 (MH^+ - $PHCH_2OH$, 32 %), 283 (16 %), 252 (MH^+ - $PhCH_2OCONHCH_3$, 24 %).

Example A14

Benzyl [(2*S*,3a*R*,12b*S*)-1-(bromoacetyl)-11-fluoro-1,2,3,3a,8,12b-hexahydro dibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]methylcarbamate (intermediate compound 15)



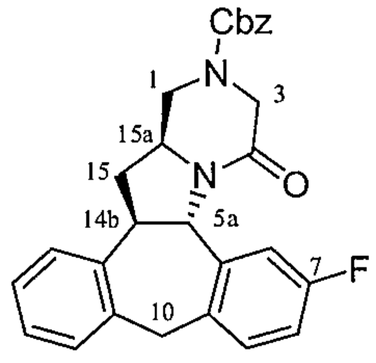
intermediate 15

To a solution of intermediate compound 14 (32.5 mg, 0.078 mmol) in EtOAc (3 mL) was added 1 mL of NaOH (sat. aq. solution) and bromoacetyl bromide (6.8 µL, 0.078 mmol). The two phases were stirred vigorously for 1 night. Add 10 mL of NH_4Cl (sat. aq. solution), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column

chromatography purification on silica gel using EtOAc/heptane (20/80) gave intermediate compound 15 as an oil (31.4 mg, 62 %).
Mass spectrum: -CI m/z (assignment, relative intensity) 457 (MH^+ - HBr, 3 %), 413 (MH^+ -HBr – CO_2, 1 %), 365 (MH^+ - HBr –$PhCH_3$ 1 %), 351 (MH^+ -PhCHO - HBr, 2 %), 323 (MH^+ - HBr –PhCHO - CO, 5 %), 119 (8 %), 91 (100 %).

Example A15

Benzyl (5a*S*,14b*R*,15a*S*)-7-fluoro-4-oxo-1,3,4,5a,10,14b,15,15a-octahydro-2*H*-dibenzo[3',4':6',7']cyclohepta[1',2':4,5]pyrrolo[1,2-*a*]pyrazine-2-carboxylate (intermediate compound 16)

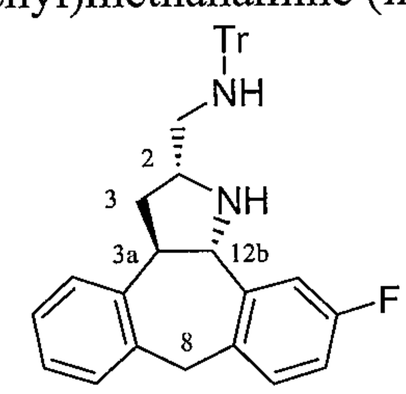


intermediate 16

To a solution of intermediate compound 15 (91.7 mg, 0.17 mmol) in DMF (5 mL) was added K_2CO_3 (103.0 mg, 0.75 mmol) and the mixture was stirred at room temperature for 36 hours. Add 10 mL of NH_4Cl (sat. aq. solution), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column chromatography purification on silica gel using EtOAc/heptane (30/70) gave polycyclic intermediate compound 16 (86.2 mg, 92 %) as an oil.
Mass spectrum: -CI m/z (assignment, relative intensity) 457 (MH^+, 1 %), 323 (MH^+ – PhCHO – CO, 5 %), 279 (MH^+ –Cbz – CH_2CO, 1 %), 91 (10 %).

Example A16

N-{[(2*R*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7] cyclohepta-[1,2-*b*]pyrrol-2-yl]methyl}(triphenyl)methanamine (intermediate compound 17)



intermediate 17

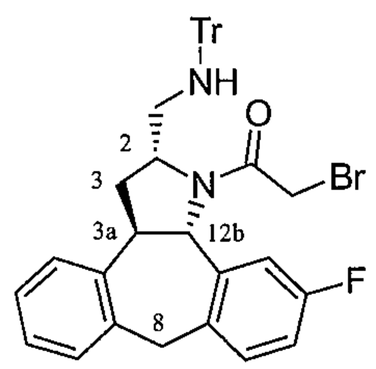
To an ice cooled solution of intermediate 13 (41.6 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (42.5 µL, 0.3 mmol), DMAP (9.4 mg, 0.07 mmol) and TrCl (46.1 mg, 0.16 mmol). The mixture was then stirred at 0 °C for 2 hours. Add 10 mL of NH_4Cl

(sat. aq. solution), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column chromatography purification on silica gel using EtOAc/heptane (20/80) gave a crystalline intermediate compound 17 (52.6 mg, 68 %) ; mp: 58-60°C.

Mass spectrum: -APCI m/z (assignment, relative intensity) 525 (MH^+, 38 %), 390 (4 %), 283 (MH^+ – (Tr–H), 15 %), 252 (MH^+ - CH_3NHTr, 27 %), 243 (Tr^+, 100 %), 228 (7 %), 165 (29 %).

Example A17

N-{[(2*R*,3a*R*,12b*S*)-1-(bromoacetyl)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]methyl}(triphenyl)methanamine (intermediate compound 18)



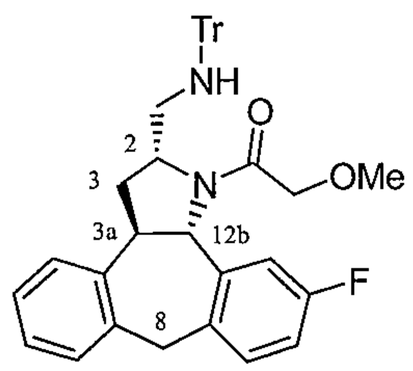
intermediate 18

The intermediate compound 17 (26.7 mg, 0.05 mmol) was added to a two-phase system consisting of 2 mL CH_2Cl_2 and 0.5 mL Na_2CO_3 (aq. sat. solution), and the mixture was stirred for 10 minutes. After adding bromoacetyl bromide (6.8 µL, 0.08 mmol) the two phases were stirred vigorously for 3 hours. Extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column chromatography purification on silica gel using EtOAc/heptane (20/80) gave intermediate compound 18 as an oil (27.9 mg, 85 %) characterised as a mixture of two conformers.

Mass spectrum: -APCI m/z (assignment, relative intensity) 645 (MH^+, 39 %), 601 (3 %), 403 (MH^+ – (Tr–H), 7 %), 321 (MH^+ – TrH – HBr, 21 %), 243 (Tr^+, 100 %), 228 (3 %), 165 (15 %).

Example A18

N-{[(2*R*,3a*R*,12b*S*)-11-fluoro-1-(methoxyacetyl)-1,2,3,3a,8,12b-hexahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]methyl}(triphenyl)methanamine (intermediate compound 19)



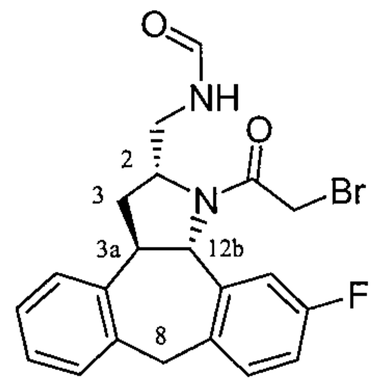
intermediate 19

To a solution of intermediate compound 18 (530 mg, 0.82 mmol) in MeOH (15 mL) was added $MeSO_3H$ (3 mL) and the mixture was stirred at 60 °C for 30 minutes. After complete evaporation of the solvent, the residue was dissolved in CH_2Cl_2/K_2CO_3 (sat. aq. solution) (15/15 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were then dried with $MgSO_4$. Column purification on silica gel using EtOAc/heptane (20/80) gave intermediate compound 19 as an oil (231.3 mg, 47 %), characterised as a mixture of two conformers.

Mass spectrum: -APCI m/z (assignment, relative intensity) 598 (MH^+, 1 %), 519 (2 %), 355 (MH^+ – Tr, 13 %), 283 (MH^+ -Tr –CO=CHOMe, 2 %), 271 (10 %), 243 (Tr^+, 100 %), 167 (21 %).

Example A19

[(2*R*,3a*R*,12b*S*)-1-(bromoacetyl)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo [3,4:6,7]-cyclohepta[1,2-*b*]pyrrol-2-yl]methylformamide (intermediate compound 20)



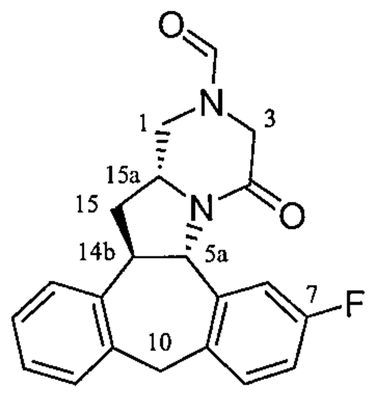
intermediate 20

The intermediate compound 18 (100 mg, 0.15 mmol) was dissolved in 98 % formic acid (2 mL) and the mixture was stirred at room temperature for 24 hours. After removal of excess of formic acid in vacuo, the residue was dissolved in $CHCl_3$ (2 mL) and EEDQ (47 mg, 0.19 mmol) was added. The solution was stirred at room temperature for 5 hours. Following evaporation of the solvent, the residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (98/2) as eluent. The intermediate compound 20 (54.7 mg, 82 %) was obtained as an oil.

Mass spectrum: -CI m/z (assignment, relative intensity) 431, 433 (MH^+, 42 %), 353 (MH^+ – HBr, 100 %), 294 (MH^+ – HBr – CH_3NHCHO, 9 %), 249 (4 %), 158 (2 %), 130 (7 %).

Example A20

(5a*S*,14b*R*,15a*R*)-7-fluoro-4-oxo-1,3,4,5a,10,14b,15,15a-octahydro-2*H*-dibenzo-[3',4':6',7']cyclohepta[1',2':4,5]pyrrolo[1,2-*a*]pyrazine-2-carbaldehyde (intermediate compound 21)



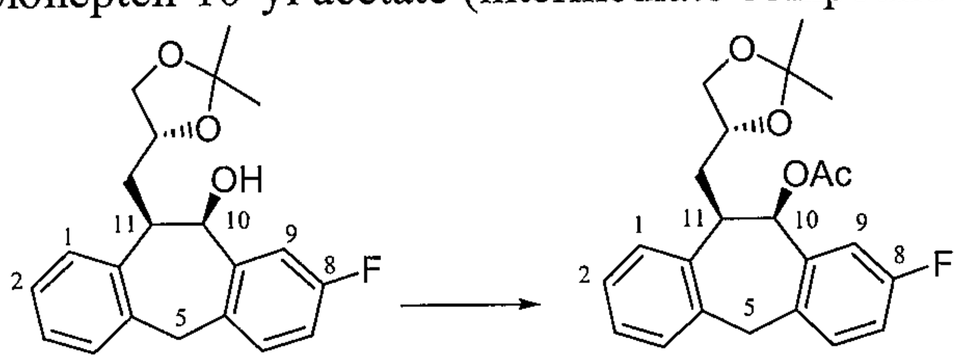
intermediate 21

To a solution of intermediate compound 20 (91 mg, 0.21 mmol) in dry THF (10 mL) was added a solution of *t*-BuOK (30.3 mg, 0.24 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 30 minutes. Water (10 mL) was then added and the mixture extracted with CH_2Cl_2 (10 mL). Column chromatography purification on silica gel using CH_2Cl_2/MeOH (97/3) gave the cyclic intermediate compound 21 (47.4 mg, 64 %) as an oil.

Mass spectrum: -CI m/z (assignment, relative intensity) 351 (MH^+, 100 %), 331 (MH^+ -HF, 5 %), 323 (MH^+ - CO, 6 %), 319 (8 %), 219 (2 %), 130 (4 %).

Example A21

(10*R*,11*R*)-11-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl acetate (intermediate compound 22)



intermediate 3 intermediate 22

To a solution of intermediate compound 3 (0.42 g, 1.23 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (0.43 mL, 3.07 mmol), DMAP (0.15 g, 1.23 mmol) and AcOH anhydride (0.29 mL, 3.07 mmol). Stir at room temperature for 1 hour, add NH_4Cl (sat. aq. solution, 20 mL), extract with CH_2Cl_2 (3 × 15 mL) and dry with $MgSO_4$. Column chroma-

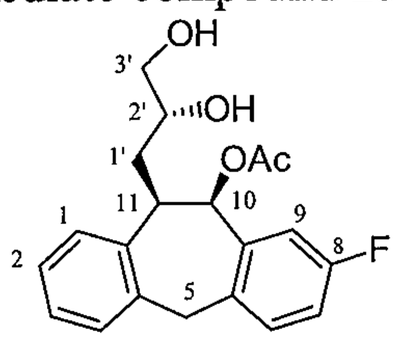
tography purification on silica gel using ether/hexane (30:70) gave a white crystalline intermediate compound 22 (0.45 g, 95 %) ; mp:147-149 °C.

Mass spectrum: -CI m/z (assignment, relative intensity) 385 (MH^+, 1 %), 325 (MH^+ – AcOH, 100 %), 267 (MH^+ – AcOH – acetone, 43 %), 249 (MH^+ – AcOH – acetone – H_2O, 47 %);

EI: m/z (assignment, relative intensity) 324 ($M^{+\cdot}$ – AcOH, 46 %), 266 ($M^{+\cdot}$ – AcOH – acetone, 20 %), 209 ($M^{+\cdot}$ – AcOH – sidechain, 100 %); High resolution EI Calculated $C_{22}H_{21}FO_2$ ($M^{+\cdot}$ – AcOH): 324.1526, Found: 324.1521 ($M^{+\cdot}$, 72 %).

Example A22

(10*R*,11*R*)-11-[(2*R*)-2,3-dihydroxypropyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-10-yl acetate (intermediate compound 23)



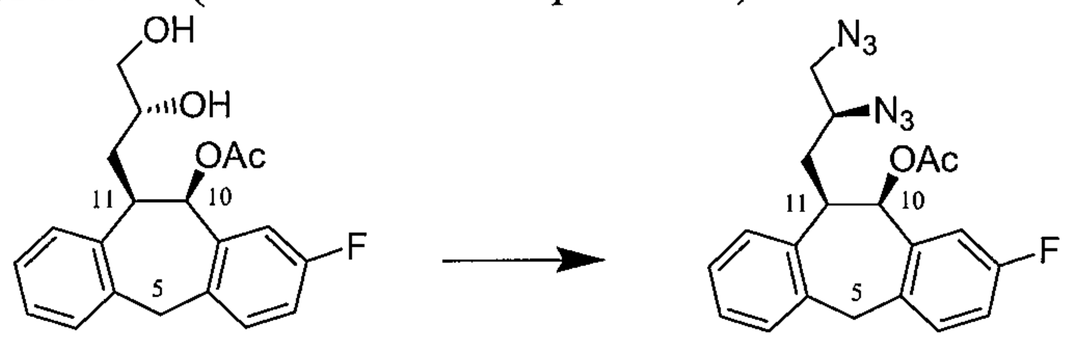
intermediate 23

To a solution of intermediate compound 22 (0.45 g, 1.17 mmol) in THF (10 mL) was added 1N HCl (10 mL). After stirring at room temperature for 8 hours, 10 mL Na_2CO_3 (sat. aq. solution) was added at 0 °C. Extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column chromatography purification on silica gel using EtOAc/hexane (70:30) gave diol intermediate compound 23 as a colorless oil (0.39 g, 96 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 345 (MH^+, 1 %), 327 (MH^+ – H_2O, 3 %), 309 (MH^+ – 2 H_2O, 3 %), 285 (MH^+ – AcOH, 17 %), 267 (MH^+ – AcOH-H_2O, 100 %), 249 (MH^+ – AcOH – 2 H_2O, 3 %);EI: m/z (assignment, relative intensity) 326 ($M^{+\cdot}$ – H_2O, 10 %), 284 ($M^{+\cdot}$ – AcOH, 13 %), 209 ($M^{+\cdot}$ – AcOH – sidechain, 100 %)) ; High resolution EI Calculated $C_{20}H_{19}FO_3$ ($M^{+\cdot}$ -H_2O): 326.1318, Found: 326.1316 (31 %).

Example A23

(10*R*,11*R*)-11-[(2*S*)-2,3-diazidopropyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-10-yl acetate (intermediate compound 24)

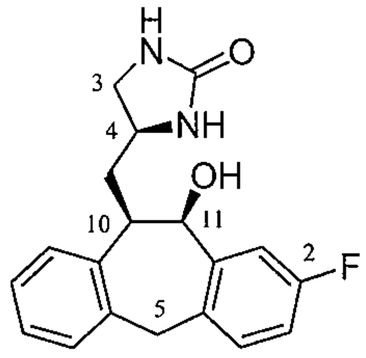


intermediate 23 intermediate 24

To the intermediate compound 23 (0.59 g, 1.72 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (0.96 mL, 6.86 mmol), DMAP (209 mg, 1.72 mmol) and MsCl (0.53 mL, 6.86 mmol) at 0 °C. Stir at room temperature for 1 hour. Work it up by adding NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. Column purification on silica gel using EtOAc/heptane (50/50) afforded dimesyl compound as an oil (0.84 g, 98 %). To this intermediate compound (182.5 mg, 0.36 mmol) in DMF (10 mL) was added NaN_3 (95 mg, 1.46 mmol). The reaction mixture was heated at 80 °C for 3 hours. After cooling, add NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. After evaporation the residue was purified on silica gel using EtOAc/heptane (20/80) to give intermediate compound 24 as an oily product (122.3 mg, 85 %).

Example A24

(4*S*)-4-{[(10*R*,11*R*)-2-fluoro-11-hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]methyl}-2-imidazolidinone (intermediate compound 25)



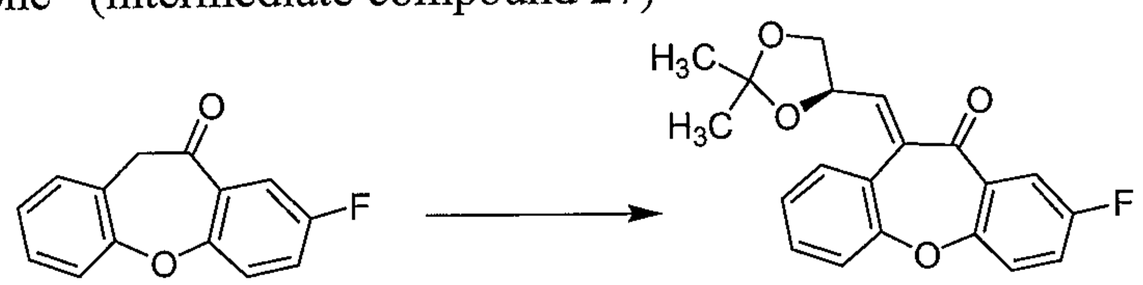
intermediate 25

Intermediate compound 24 was converted via diazido alcohol intermediate compound 24a into a diamine which was further converted into intermediate compound 25. To a solution of intermediate compound 24 (120.1 mg, 0.30 mmol) in MeOH (10 mL) was added K_2CO_3 (126.4 mg, 0.91 mmol). The reaction mixture was stirred at room temperature for 1 hour. Add NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column purification on silica gel using Et_2O/heptane (40/60) gave the diazido alcohol intermediate compound 24a as an oily product (77.5 mg, 72 %). This compound (75 mg, 0.21

mmol) in MeOH (5 mL) was hydrogenated at 1 atmospheric pressure with 10 % palladium-on-charcoal under vigorous stirring at room temperature for 1 night. Then the mixture was filtered through a pad of celite and the solids were washed 4 times with CH_2Cl_2. After evaporation of the solvent, the crude product was dissolved in 5 mL of CH_3CN and Et_3N (34 µL, 0.24 mmol) was added. The reaction mixture was heated under argon at 70 °C. After 1 hour, a solution of diphenyl carbonate (23 mg, 0.11 mmol) in CH_3CN was added dropwise and the mixture was stirred at 70 °C for 1 day. After evaporation, the crude product was purified by column chromatography on silica gel using $CHCl_3$/MeOH (90/10) to give the imidazolidinone intermediate compound 25 as an oil (34.4 mg, 48 %).

Example A25

(11*E*)-11-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methylene}-8-fluorodibenzo[*b*,*f*]-oxepin-10(11*H*)-one (intermediate compound 27)



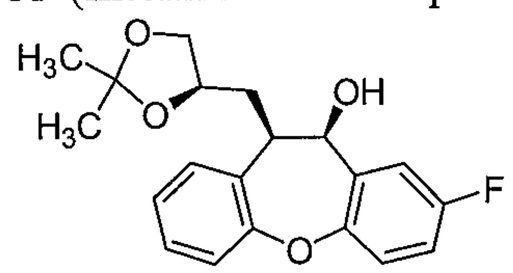
intermediate 26 intermediate 27

To a suspension of intermediate compound 26 (0.228g, 1 mmol) and $MgBr_2$ (0.202 g, 1.1 mmol) in dry toluene (5 mL), (*S*)-glyceraldehyde acetonide (4 mmol, 1.5 M solution in THF) and *t*-BuOK (22.4 mg, 0.2 mmol) was added and stirred for 3 hours at room temperature. A saturated aq. NH_4Cl solution (5 mL) was added, the organic layer was separated and kept over anhydrous $MgSO_4$. The solvent was removed under reduced pressure followed by the separation of α,β-unsaturated product by flash column chromatography using EtOAc:heptane (1:9)eluent to obtain intermediate compound 27 as a yellow liquid in a ratio of 85/15 *E* and *Z* isomer (85 %, 0.289 g).

HRMS: Calculated 340.1111; found 340.1122

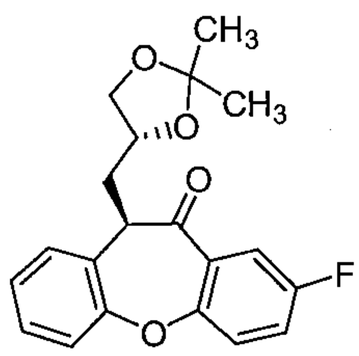
Example A26

a)(10*R*,11*R*)-11-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-8-fluoro-10,11-dihydrodibenzo[*b*,*f*]oxepin-10-ol (intermediate compound 29)



intermediate 29

To a solution of intermediate compound 27 (0.340 g, 1 mmol) in *i*-PrOH (5 mL) was added Et_3N (0.21 mL, 1.5 mmol) and the reaction mixture was hydrogenated under atmospheric pressure using 10 % Pd/C (40 mg) as a catalyst. After completion of the reaction (4 hours) the reaction mixture was passed through a small pad of celite and further washed with CH_2Cl_2 (2 × 5 mL) followed by the evaporation of the solvent to obtain crude ketone intermediate compound 28.



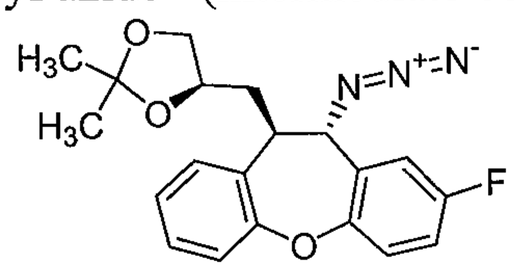
intermediate 28

b) The crude intermediate compound 28 thus obtained was dissolved in *i*-PrOH (10 mL) and aqeous phosphate buffer solution (3 mL, pH 7) was added to it. The temperature was lowered to 0 °C and $NaBH_4$ (0.152 g, 4 mmol) was added to it in several lots and then allowed to stir further for 15 minutes at the same temperature. Aq. NH_4Cl solution (5 mL) was added and the reaction mixture was extracted using Et_2O (3 × 5 mL). After drying over anhydrous $MgSO_4$ the solvent was removed under reduced pressure and the two diastereomeric alcohols (1:1) with slightly different polarity were separated by flash column chromatography using EtOAc:heptane (20:80) as an eluent to obtain the more polar cis-alcohol intermediate compound 29 as a white solid (mp: 59-61°C; 49 %, 0.16 g).

HRMS: Calculated 344.1424; found 344.1435

Example A27

(10*S*,11*R*)-11-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-8-fluoro-10,11-dihydrodibenzo[*b*,*f*]oxepin-10-yl azide (intermediate compound 30)



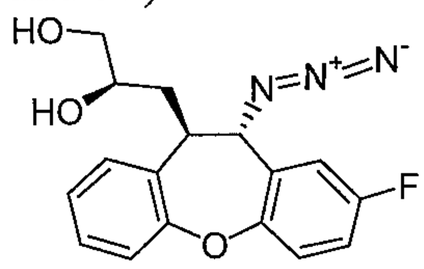
intermediate 30

To a solution of PPh_3 (0.524 g, 2 mmol) in dry THF (5 mL) at -15 °C, a solution of DIAD (0.424 g, 2.1 mmol) in THF (2 mL) was added and the resulting complex was stirred for 20 minutes followed by the addition of intermediate compound 29 (0.329 g, 1 mmol) dissolved in THF (2 mL) and a solution of DPPA (0.330 g, 1.2 mmol) in THF (1 mL). The reaction mixture was warmed to room temperature and stirred for 18 hours. After addition of MeOH the reaction mixture was dried under vaccum followed by separation of the azide using flash columnchromatography using EtOAc:heptane (1:9) as an eluent to obtain intermediate compound 30 as a colourless liquid (91 %, 0.335 g).

HRMS: Calculated 369.1489; found 369.1483.

Example A28

(2*R*)-3-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydrodibenzo[*b*,*f*]oxepin-10-yl]-1,2-propanediol (intermediate compound 31)



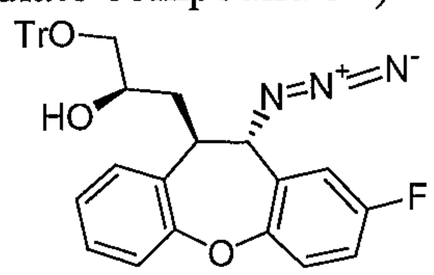
intermediate 31

To a solution of intermediate compound 30 (0.369 g, 1 mmol) in THF (5 mL) 1M aq. HCl solution (1 mL) was added and stirred for 18 hours. THF was removed under reduced pressure and the diol was extracted using Et_2O (3 × 10 mL). The organic layer was treated with aq. $NaHCO_3$ (5 mL) followed by a brine wash (5 mL). After drying over anhydrous $MgSO_4$ the solvent was removed under vacuum to obtain intermediate compound 31 as a thick viscous liquid (95 %, 0.313 g).

HRMS: Calculated 329.1176; found 329.1184.

Example A29

(2*R*)-1-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydrodibenzo[*b*,*f*]oxepin-10-yl]-3-(trityloxy)-2-propanol (intermediate compound 32)



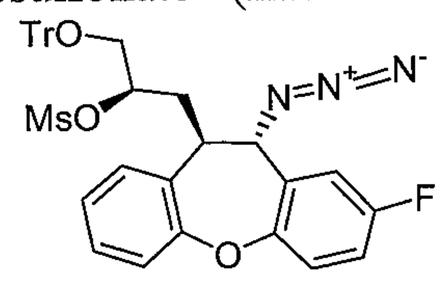
intermediate 32

To a solution of intermediate compound 31 (0.329 g, 1 mmol) in CH_2Cl_2 (10 mL) Et_3N (0.28 mL, 2 mmol), DMAP (0.1 mmol, 12.2 mg) and TrCl (0.307g, 1.1 mmol) were added and stirred for 24 hours. The solvent was removed under reduced pressure and the crude reaction mixture was subjected to flash column chromatography using EtOAc:heptane (1:9) as an eluent to obtain intermediate compound 32 as a white solid (mp: 58-59 °C; 80 %, 0.456 g).

HRMS: Calculated 571.2271; found 571.2286.

Example A30

(1*R*)-2-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydrodibenzo[*b*,*f*]oxepin-10-yl]-1-[(trityloxy)methyl]ethyl methanesulfonate (intermediate compound 33)



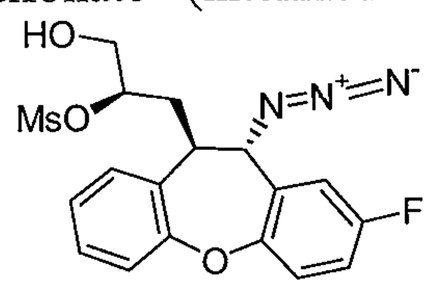
intermediate 33

To a solution of intermediate compound 32 (0.571 g, 1 mmol) in CH_2Cl_2 at -10 °C, Et_3N (0.28 mL, 2 mmol), DMAP (12.2 mg, 0.1 mmol) and MsCl (0.126 g, 1.1 mmol) were added. The reaction mixture was warmed up to room temperature and stirred for 4 hours. Water (3 mL) was added and the organic layer was separated and dried over anhydrous $MgSO_4$ followed by the purification by flash chromatography using EtOAc:heptane (1:9) as an eluent to obtain intermediate compound 33 as a white solid (mp:55-56 °C; 85 %, 0.515 g).

HRMS: Calculated 649.2047; found 649.2064

Example A31

(1*R*)-2-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydrodibenzo[*b*,*f*]oxepin-10-yl]-1-(hydroxymethyl)ethyl methanesulfonate (intermediate compound 34)



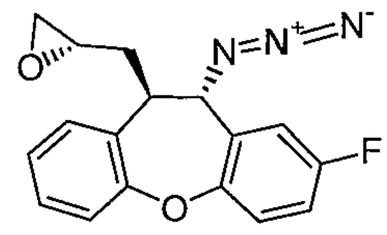
intermediate 34

To a solution of intermediate compound 33 (0.649 g, 1 mmol) in MeOH (5 mL) amberlyst-15 (0.1 g) was added and the reaction mixture was stirred at 40 °C for 3 hours, then filtered to remove the catalyst. The solvent was removed under reduced pressure and the product purified by flash column chromatography using EtOAc:heptane (2:8) as an eluent to obtain intermediate compound 34 as a thick viscous liquid (90 %, 0.366 g).

HRMS: Calculated 407.0951; found 407.0975.

Example A32

(10*R*,11*S*)-11-azido-2-fluoro-10-[(2*S*)-oxiranylmethyl]-10,11-dihydrodibenzo[*b*,*f*]-oxepine (intermediate compound 35)



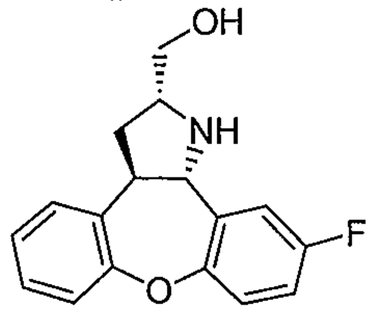
intermediate 35

A mixture of intermediate compound 34 (0.407 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) was stirred in *i*-PrOH (10 mL) for 8 hours, filtered to remove K_2CO_3 and the solvent was removed under reduced pressure. The product was purified by flash chromatograpy using EtOAc: heptane (2:8) as an eluent to obtain intermediate compound 35 as a colourless liquid (78 %, 0.242 g).

HRMS: Calculated 311.1070; found 311.1089.

Example A33

[(2*R*,3a*R*,12b*S*)-11-fluoro-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]-pyrrol-2-yl]methanol (intermediate compound 36)



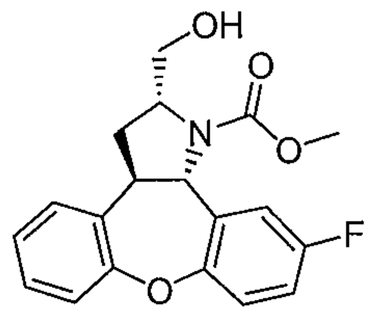
intermediate 36

To a solution of intermediate compound 35 (0.311 g, 1 mmol) in *i*-PrOH (10 mL), Et_3N (0.140 mL, 1 mmol) was added. The mixture was hydrogenated under atmospheric pressure using 10 % Pd/C (50 mg) as a catalyst. After completion of the reaction (3 hours), it was passed through a small pad of celite and the catalyst was washed with CH_2Cl_2 (2 × 5 mL). The combined organic layers were evaporated under reduced pressure and purified by flash column chromatography using EtOAC:heptane (1:1) as an eluent to obtain intermediate compound 36 as a white solid (mp: 108-109 °C; 83 %, 0.236 g).

HRMS: Calculated 285.1165; found 285.1172.

Example A34

Methyl (2*R*,3a*R*,12b*S*)-11-fluoro-2-(hydroxymethyl)-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]pyrrole-1-carboxylate (intermediate compound 37).



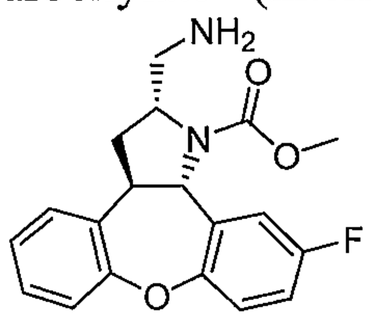
intermediate 37

To a solution of intermediate compound 36 (0.14 g, 0.5 mmol) in CH_2Cl_2 (4 mL) at 0 °C a saturated solution (aq.) of $NaHCO_3$ (2 mL) was added. After the addition of methylchloroformate (1.5 eq.), the reaction mixture was stirred vigorously at 0 °C for 20 minutes, warmed up to room temperature and allowed to stir further for 0.5 hour. The organic layer was separated, dried over $MgSO_4$ and purified by flash column chromatography using EtOAc:heptane (4:6) as an eluent to obtain intermediate compound 37 as a thick viscous liquid (83 %, 0.14 g).

HRMS: Calculated 343.1220; found 343.1218.

Example A35

Methyl (2*R*,3a*R*,12b*S*)-2-(aminomethyl)-11-fluoro-2,3,3a,12b-tetrahydro-1*H*-dibenzo-[2,3:6,7]oxepino[4,5-*b*]pyrrole-1-carboxylate (intermediate compound 38)



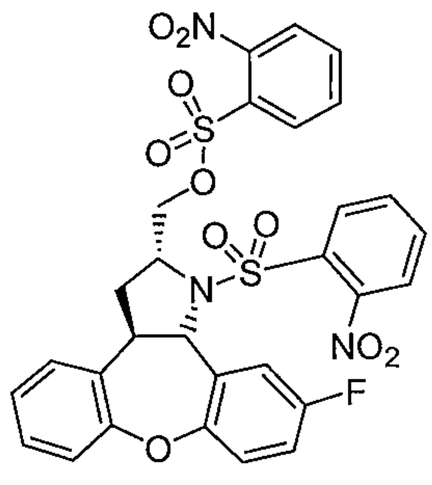
intermediate 38

To a solution of PPh_3 (0.26g, 1 mmol) in dry THF (4 mL) at –15 °C a solution of DIAD (0.22g, 1.1 mmol) in THF (1 mL) was added and the resulting complex was stirred for 20 minutes. After the addition of intermediate compound 37 (0.17g, 0.5 mmol) dissolved in THF (1 mL) and DPPA (0.14g, 0.5 mmol) in THF (1 mL), the reaction was warmed to up room temperature and stirred for 18 hours. An excess of PPh_3 (5 eq) and water (0.5 mL) was added to the reaction mixture and then heated at 40 °C for 3 hours to reduce the azide to amine functionality. Silica gel was added to the reaction mixture and the solvent was removed under reduced pressure followed by purification of the product by flash column chromatography using CH_2Cl_2:MeOH (9:1) as an eluent to obtain intermediate compound 38 as a thick viscous liquid (80 %, 0.14 g).

HRMS: Calculated 342.1380; found 342.1376.

Example A36

{(2*R*,3a*R*,12b*S*)-11-fluoro-1-[(2-nitrophenyl)sulfonyl]-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]pyrrol-2-yl}methyl 2-nitrobenzenesulfonate (intermediate compound 39)



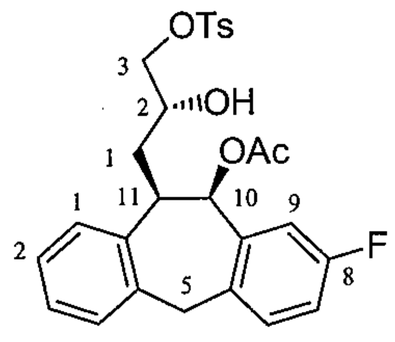
intermediate 39

To a solution of intermediate compound 36 (0.5 mmol, 0.14g), Et_3N (5 eq.) and DMAP (20 mol %) in CH_2Cl_2 at –20 °C, NsCl (3 eq.) was added. Reaction mixture was warmed up to room temperature and left for overnight stirring. Aqueous $NaHCO_3$ (2 mL) was added to the reaction mixture and the organic layer was separated and dried over $MgSO_4$. Following column chromatography (SiO_2) using EtOAc:heptane (1:1) as

an eluent yielded intermediate compound 39 as a yellow crystalline solid (mp: 88-90 °C, 71 %, 0.23 g).

Example A37

a) (10*R*,11*R*)-8-fluoro-11-((2*R*)-2-hydroxy-3-{[(4-methylphenyl)sulfonyl]oxy}propyl)-10, 11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl acetate (intermediate compound 23a)

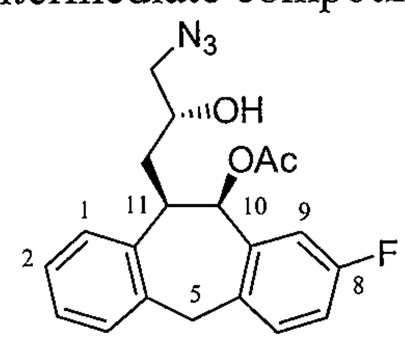


intermediate 23a

To a solution of intermediate compound 23 (0.12 g, 0.355 mmol) in dry toluene (10 mL) was added n-Bu_2SnO (9 mg, 0.036 mmol), Et_3N (0.13 mL, 0.888 mmol) and TsCl (0.10 g, 0.533 mmol). Stir at room temperature for 24 hours, add NH_4Cl (sat. aq. solution, 10 mL), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column chromatography purification on silica gel using EtOAc/hexane (30:70) yielded intermediate compound 23a as a colorless oil (0.15 g, 84 %).

Mass spectrum: CI m/z (assignment, relative intensity) 481 ($MH^+ - H_2O$, 1 %), 439 ($MH^+ - AcOH$, 4 %), 421 ($MH^+ - AcOH - H_2O$, 1 %), 267 ($MH^+ - AcOH - TsOH$, 18 %), 249 ($MH^+ - AcOH - TsOH - H_2O$, 100 %); EI: m/z (assignment, relative intensity) 480 ($M^{+\cdot} - H_2O$, 1 %), 438 ($M^{+\cdot} - AcOH$, 36 %), 266 ($M^{+\cdot} - AcOH - TsOH$, 15 %), 248 ($M^{+\cdot} - AcOH - TsOH - H_2O$, 18 %); High resolution EI Calculated $C_{25}H_{23}FO_4S$ ($M^{+\cdot} - AcOH$): 438.1301, Found: 438.1300 (51 %).

b) (10*R*,11*R*)-11-[(2*R*)-3-azido-2-hydroxypropyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cyclohepten-10-yl acetate (intermediate compound 40)



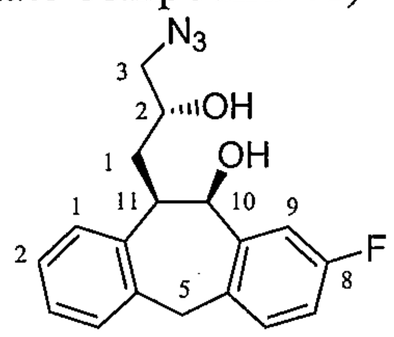
intermediate 40

To a solution of intermediate compound 23a (1.30 g, 2.61 mmol) in DMF (25 mL) was added NaN_3 (0.51 g, 7.83 mmol). The reaction mixture was heated at 100 °C for 1 night. After cooling, add NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. After evaporation the residue was purified by column chromatography on

silica gel using EtOAc/heptane (20/80) to give intermediate compound 40 as an oily product (0.79 g, 82 %).

Example A38

(10*R*,11*R*)-11-[(2*R*)-3-azido-2-hydroxypropyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cyclohepten-10-ol (intermediate compound 41)

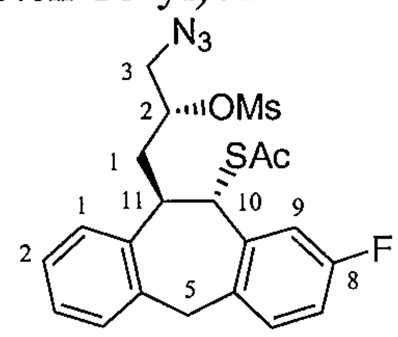


intermediate 41

A solution of intermediate compound 40 (454.9 mg, 1.23 mmol) in MeOH (10 mL) was treated with K_2CO_3 (340.1 mg, 2.46 mmol) and the mixture was stirred at room temperature for 1 hour. Add NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. The solution was filtered and evaporated and the residue was purified by column chromatography on silica gel using EtOAc/heptane (30/70) to give diol intermediate compound 41 (370.9 mg, 92 %).

Example A39

S-((10*S*,11*R*)-11-{(2*R*)-3-azido-2-[(methylsulfonyl)oxy]propyl}-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl)ethanethioate (intermediate compound 42)

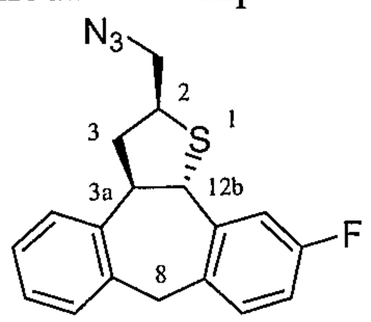


intermediate 42

To intermediate compound 41 (670 mg, 2.05 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (2.30 mL, 16.4 mmol), DMAP (0.13 mg, 1.02 mmol) and $(CH_3SO_2)_2O$ (1.07 g, 6.15 mmol) at 0 °C. Stir at room temperature for 1 hour, cool to 0 °C again, add AcSH (0.44 ml, 6.15 mmol) and stir at room temperature for 4 hours. Work up by adding NH_4Cl (sat. aq. sol.). Extract 3 times with CH_2Cl_2. Column chromatography on silica gel using CH_2Cl_2 (100 %) afforded intermediate compound 42 as an oil (0.68 g, 72 %).

Example A40

(2*S*,3a*R*,12b*S*)-2-(azidomethyl)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo [3,4:6,7]-cyclohepta[1,2-*b*]thiophene (intermediate compound 43)



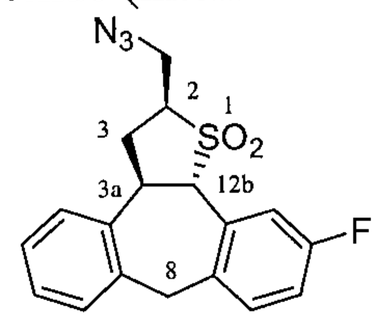
intermediate 43

To intermediate compound 42 (0.15 g, 0.33 mmol) in MeOH (5 mL) was added K_2CO_3 (92 mg, 0.67 mmol). After stiring at room temperature for 1 night, the mixture was worked up by adding NH_4Cl (sat. aq. sol.). Extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. Column chromatography purification on silica gel using CH_2Cl_2/heptane (40/60) gave intermediate compound 43 as an oily product (76 mg, 70 %).

Mass spectrum: CI m/z (assignment, relative intensity) 326 (MH^+, 25 %), 298 ($MH^+ - N_2$, 60 %), 283 ($MH^+ - HN_3$, 100 %), 269 ($MH^+ - N_2 - CH_2NH$, 12 %), 249 ($MH^+ - HN_3 - H_2S$, 25 %), 235 ($MH^+ - N_2 - CH_2NH - H_2S$, 21 %), 197 (61 %).

Example A41

(2*S*,3a*R*,12b*S*)-2-(azidomethyl)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo [3,4:6,7]-cyclohepta[1,2-*b*]thiophene 1,1-dioxide (intermediate compound 44)



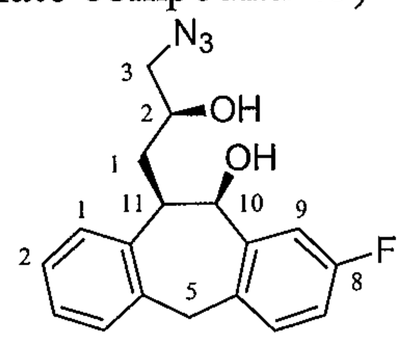
intermediate 44

To a solution of intermediate compound 43 (76.1 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) was added mCPBA (173.2 mg, 0.70 mmol). The mixture was stirred at room temperature for 15 min. Add $NaHCO_3$ (sat. aq. solution), extract 3 times with CH_2Cl_2. Column purification on silica gel using EtOAc/heptane (50/50) gave sulfone intermediate compound 44 (73.2 mg, 88 %) as an oil.

Mass spectrum: -CI m/z (assignment, relative intensity) 358 (MH^+, 21 %), 340 ($MH^+ - H_2O$, 9 %), 330 ($MH^+ - N_2$, 9 %), 303 (8 %), 265 (24 %), 264 ($MH^+ - N_2 - H_2SO_2$, 25 %), 237 ($MH^+ - N_2 - H_2SO_2 -$ HCN, 11 %), 211 (15 %), 197 (66 %).

Example A42

(10*R*,11*R*)-11-[(2*S*)-3-azido-2-hydroxypropyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cyclohepten-10-ol (intermediate compound 45)

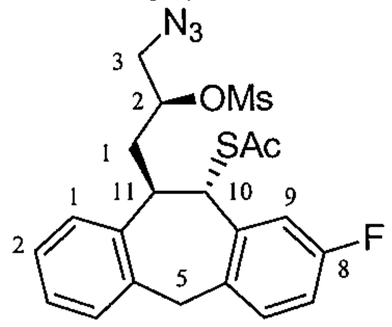


intermediate 45

To a solution of intermediate compound 40 (0.85 g, 2.32 mmol) in THF (10 mL) was added PPh_3 (1.22 g, 4.63 mmol) and DIAD (1.92 mL, 4.63 mmol). Then, a solution of *p*-nitrobenzoic acid (0.77 g, 4.63 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at room temperature for 2 hours. Work up by adding NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using CH_2Cl_2/heptane (70/30) gave the *p*-nitrobenzoate (inverted secondary OH group) as an oil (1.19 g, 99 %). To a solution of this compound (2.01 g, 4.05 mmol) in MeOH (50 mL) was added K_2CO_3 (1.12 g, 8.10 mmol). The reaction mixture was stirred at room temperature for 3 hours. Add NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column purification on silica gel using EtOAc/heptane (30/70) gave an oily intermediate compound 45 (0.71 g, 98 %).

Example A43

S-((10*S*,11*R*)-11-{(2*S*)-3-azido-2-[(methylsulfonyl)oxy]propyl}-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl) ethanethioate (intermediate compound 46)

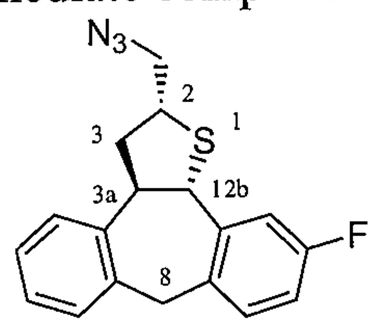


intermediate 46

To a solution of intermediate compound 45 (1.20 g, 3.66 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (4.10 mL, 29.3 mmol), DMAP (0.22 mg, 1.83 mmol) and $(CH_3SO_2)_2O$ (1.92 g, 11.0 mmol) at 0 °C. Stir at room temperature for 1 hour. Cool to 0 °C again and add AcSH (0.52 mL, 7.33 mmol) and stir at room temperature for 5 hours. Work up by adding NH_4Cl (sat. aq. sol.), extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. Column chromatography purification on silica gel using EtOAc/heptane (30/70) afforded intermediate compound 46 as an oil (1.32 g, 78 %).

Example A44

(2*R*,3a*R*,12b*S*)-2-(azidomethyl)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*b*]thiophene (intermediate compound 47)



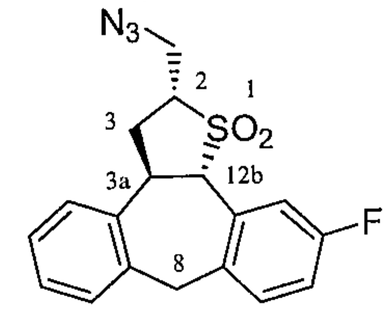
intermediate 47

To a solution of intermediate compound 46 (1.32 g, 2.86 mmol) in MeOH (30 mL) was added K_2CO_3 (0.79 g, 5.72 mmol). After stirring at room temperature for 2 hours, NH_4Cl (sat. aq. sol.) was added. Extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. Column chromatography purification on silica gel using CH_2Cl_2/heptane (40/60) gave intermediate compound 47 as an oily product (0.82 g, 89 %).

Mass spectrum: -CI m/z (assignment, relative intensity)326 (MH^+, 25 %), 298 ($MH^+ - N_2$, 60 %), 283 ($MH^+ - HN_3$, 100 %), 269 ($MH^+ - N_2 - CH_2NH$, 12 %), 269 ($MH^+ - HN_3 - H_2S$, 25 %), 235 ($MH^+ - N_2 - CH_2NH - H_2S$, 21 %), 197 (61 %).

Example A45

(2*R*,3a*R*,12b*S*)-2-(azidomethyl)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*b*]thiophene 1,1-dioxide (intermediate compound 48)



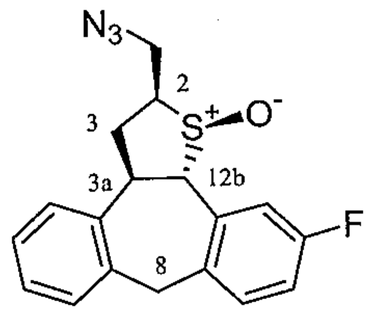
intermediate 48

To a solution of intermediate compound 47 (136.1 mg, 0.41 mmol) in CH_2Cl_2 (10 mL) was added mCPBA (310.0 mg, 1.26 mmol). The mixture was stirred at room temperature for 30 minutes. Add $NaHCO_3$ (sat. aq. solution), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using EtOAc/heptane (50/50) gave intermediate compound 48 (146.5 mg, 98 %) as an oil.

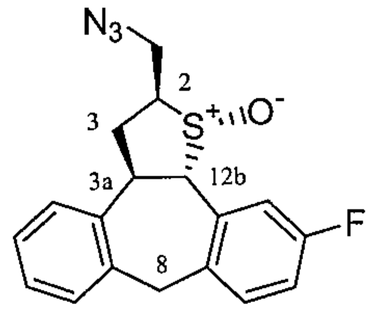
Mass spectrum: -CI m/z (assignment, relative intensity)358 (MH^+, 21 %), 340 ($MH^+ - H_2O$, 9 %), 330 ($MH^+ - N_2$, 9 %), 303 (8 %), 265 (24 %), 264 ($MH^+ - N_2 - H_2SO_2$, 25 %), 237 ($MH^+ - N_2 - H_2SO_2 - HCN$, 11 %), 211 (15 %), 197 (66 %).

Example A46

(2*S*,3a*R*,12b*S*)-2-(azidomethyl)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*b*]thiophene 1-oxides (intermediate compounds 49, 50)



intermediate 49



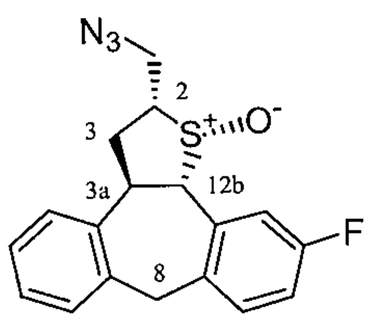
intermediate 50

To a solution of intermediate compound 43 (0.34 g, 1.05 mmol) in HFIP (5 mL) was added H_2O_2 (30 %, 0.24 mL, 2.10 mmol). The mixture was stirred at room temperature for 30 minutes. Add Na_2CO_3 (sat. aq. solution), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using Et_2O (100 %) afforded intermediate compounds 49 (110 mg) and 50 (130 mg) with a total yield of 78 %.

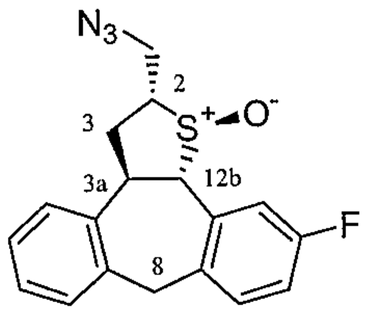
Mass spectrum: - CI m/z (assignment, relative intensity) 342 (MH^+, 100 %), 314 ($MH^+ - N_2$, 49 %), 299 ($MH^+ - HN_3$, 47 %), 264 (17 %), 197 (96 %).

Example A47

(2*R*,3a*R*,12b*S*)-2-(azidomethyl)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*b*]thiophene 1-oxides (intermediate compounds 51, 52)



intermediate 51



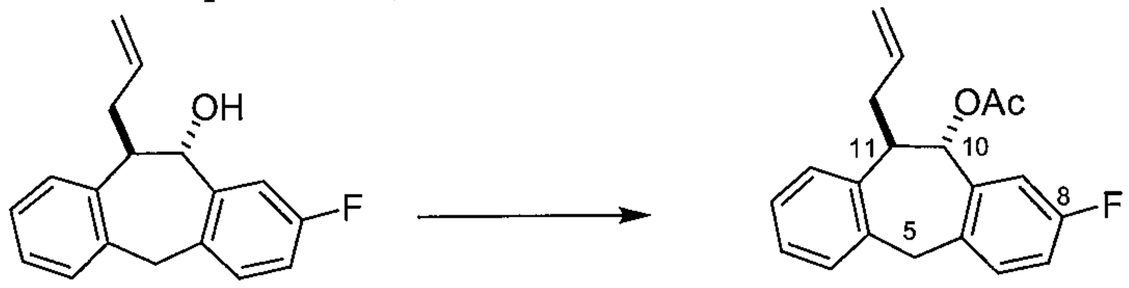
intermediate 52

To a solution of intermediate compound 47 (0.21 g, 0.64 mmol) in HFIP (3 mL) was added H_2O_2 (30 %, 0.15 mL, 1.27 mmol). The mixture was stirred at room temperature for 30 minutes. Add Na_2CO_3 (sat. aq. solution), extract 3 times with CH_2Cl_2. Column purification on silica gel using Et_2O (100 %) gave intermediate compound 51 (120 mg) and 52 (86 mg) with a total yield of 95 %.

Mass spectrum: - CI m/z (assignment, relative intensity) 342 (MH^+, 100 %), 314 ($MH^+ - N_2$, 49 %), 299 ($MH^+ - HN_3$, 47 %), 264 (17 %), 197 (96 %).

Example A48

(10*S**,11*R**)-11-allyl-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl acetate (intermediate compound 56)



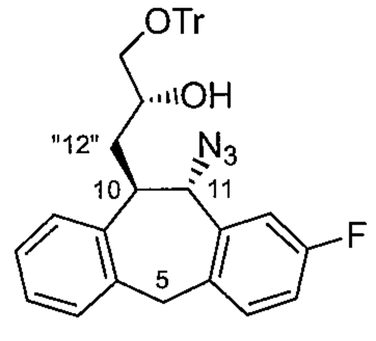
intermediate 55 intermediate 56

Dissolve intermediate compound 55 (1.72 g, 6.42 mmol) in CH_2Cl_2 (30 mL). Add Et_3N (1.79 mL, 12.8 mmol), DMAP (0.78 g, 6.42 mmol) and Ac_2O (1.21 mL, 12.8 mmol). Stir at room temperature for 1 hour and add sat. aq. NH_4Cl (15 mL). Extract 3 times with CH_2Cl_2 (3 × 20 mL) and dry with $MgSO_4$. Column chromatography purification on silica gel using CH_2Cl_2/hexane (60:40) yielded intermediate compound 56 as an oil (1.77 g, 89 %).

Mass spectrum: -CI m/z (assignment, relative intensity)311 (MH^+, 5 %), 251 (MH^+ – AcOH, 100 %); EI: m/z (assignment, relative intensity) 250 ($M^{+\cdot}$ – AcOH, 16 %), 209 ($M^{+\cdot}$ – AcOH – CH_2CH_2=CH_2, 100 %); High resolution EI Calculated $C_{18}H_{15}F$ ($M^{+\cdot}$ – AcOH): 250.1158, Found: 250.1162 (26 %).

Example A49

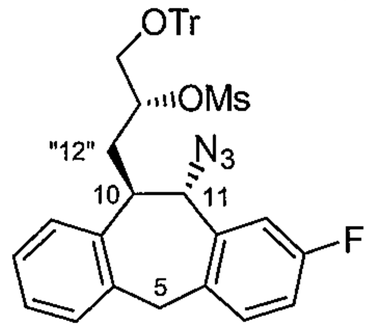
a) (2*R*)-1-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-3-(trityloxy)-2-propanol (intermediate compound 57)



intermediate 57

A mixture of intermediate compound 5 (6.022 g, 18.40 mmol), Et_3N (5.586 g, 55.2 mmol), DMAP (138 mg, 1.13 mmol), TrBr (9.444 g, 27.6 mmol) in CH_2Cl_2 (180 mL) was stirred at room temperature under nitrogen atmosphere for 2 hours, then quenched with sat. aq. NH_4Cl (50 mL). The organic phase was separated, aqueous layer extracted with CH_2Cl_2 (2 × 50 mL), combined organics washed with water (3 × 40 mL), brine (40 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash column chromatography (Kieselgel 60, 230-400 mesh, EtOAc-heptane, 5/95 to 10/90) gave intermediate compound 57 (8.595 g, 15.09 mmol, 82 %) as a brown semisolid.

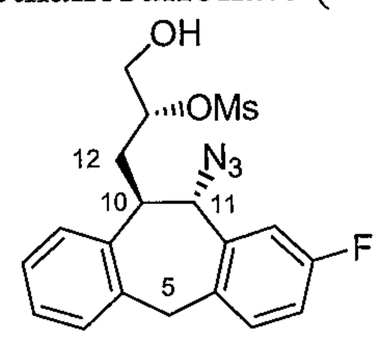
b)(1*R*)-2-[(10*R*,11*S*)-11-Azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-1-[(trityloxy)methyl]ethylmethanesulfonate (intermediate compound 58)



intermediate 58

A mixture of intermediate compound 57 (8.5 g, 14.92 mmol), Et_3N (4.529 g, 44.76 mmol) and DMAP (84 mg, 0.689 mmol) in CH_2Cl_2 (200 mL) was cooled down to –78 °C under N_2 atmosphere. MsCl (2.264 g, 22.38 mmol) was added in one portion, resulting solution slowly warmed up to room temperature (*ca.* 40 min) and quenched with sat. aq. NH_4Cl (50 mL). The organic phase was separated, aqueous layer extracted with CH_2Cl_2 (3 × 45 mL), combined organics washed with water (3 × 45 mL) and brine (40 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Due to the instability of intermediate compound 58 it was used immediately without further purification.

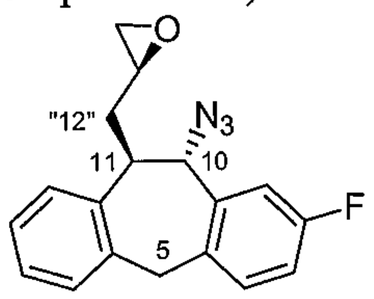
c) (1*R*)-2-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-1-(hydroxymethyl)ethyl methanesulfonate (intermediate compound 59)



intermediate 59

Crude intermediate compound 58 (unknown amount, assumed 14.92 mmol), was dissolved in MeOH (200 mL), dry Amberlyst-15 (15 g) added and the mixture was stirred at 45 °C for 4 hours; progress of reaction followed by TLC (Kieselgel on glass; EtOAc-heptane 30/70). The resin was filtered off and washed with MeOH (2 × 40 mL), methanolic solution concetrated *in vacuo* to 100 mL, and intermediate compound 59 used immediately for the next step.

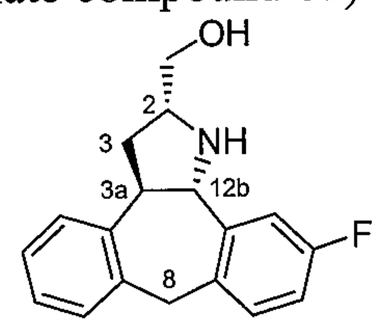
d) (10*S*,11*R*)-8-fluoro-11-[(2*S*)-oxiranylmethyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl azide (intermediate compound 60)



intermediate 60

Methanolic solution of intermediate compound 59, obtained as above, was treated with anhydrous K_2CO_3 (4.146 g, 30 mmol) and stirred at room temperature for 3 hours. After treatment with water (100 mL), MeOH was removed *in vacuo*, product extracted with Et_2O (3 × 75 mL). The combined organics were washed with water (3 × 75 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatographic purification (Kielselgel 60, 70-230 mesh, EtOAc-heptane 10/90) gave intermediate compound 60 (3.185 g, 10.29 mmol, 69 % from intermediate compound 57) as a colorless oil.
HRMS: Calcd. for $C_{18}H_{16}FN_3O$: 309.1277; Found: 309.1279.

e) [(2*R*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]methanol (intermediate compound 61)

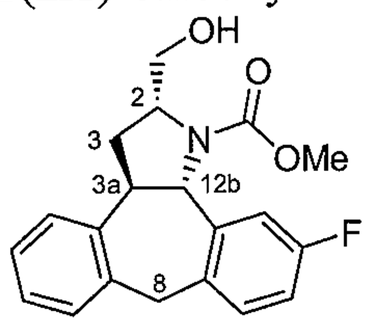


intermediate 61

Intermediate compound 60 (3.108 g, 10.04 mmol) was dissolved in MeOH (50 mL), Et_3N (1.012 g, 10 mmol) and 10 % Pd-C (150 mg) added, and resulting mixture hydrogenated under atmospheric pressure for 5 hours. Catalyst was removed by filtration through a short pad of Kieselguhr, MeOH and Et_3N removed *in vacuo*, and residue purified by column chromatography (Kieselgel 60, 70-230 mesh, EtOH-CH_2Cl_2 5/95) to yield intermediate compound 61 (2.333 g, 8.23 mmol, 82 %) as a yellowish oil, slowly solidifying on standing.

HRMS: Calcd. for $C_{18}H_{18}FNO$: 283.1372; Found: 283.1380.

f) Methyl (2*R*,3a*R*,12b*S*)-11-Fluoro-2-(hydroxymethyl)-3,3a,8,12b-tetrahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrole-1(2*H*)-carboxylate (intermediate compound 62)

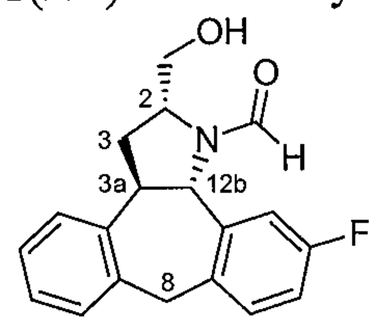


intermediate 62

Intermediate compound 61 (567 mg, 2.00 mmol) was dissolved at 0 °C in a mixture of CH_2Cl_2 (20 mL) and sat. aq. $NaHCO_3$ (20 mL), then methyl chloroformate (0.23 mL, 281 mg, 2.98 mmol) was added, ice bath removed, and resulting mixture stirred for 5 hours. The organic layer was separated, aqueous phase extracted with CH_2Cl_2 (40 mL) then the combined organics washed with water (2 × 40 mL), brine (20 mL), dried ($MgSO_4$) and vaporated. The residue was purified by column chromatography on silica (CH_2Cl_2-EtOH, 95/5) to give carbamate intermediate compound 62 (669 mg, 1.96 mmol, 98 %) as tan oil, solidifying on standing.

HRMS: Calcd. for $C_{20}H_{20}FNO_3$: 341.1427; Found: 341.1435.

g) (2*R*,3a*R*,12b*S*)-11-Fluoro-2-(hydroxymethyl)-3,3a,8,12b-tetrahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrole-1(2*H*)-carbaldehyde (intermediate compound 62a)



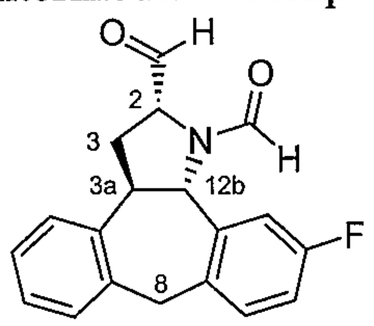
intermediate 62a

A mixture of intermediate compound 61 (283 mg, 1 mmol), ethyl formate (741 mg, 10 mmol) and acetonitrile (10 mL) was refluxed for 18 hours, then evaporated *in vacuo*. The residue was purified by chromatography (Kieselgel 60, 70-230 mesh, EtOH-CH_2Cl_2 5/95) to yield 62a (283 mg, 0.91 mmol, 91 %) as a tan solid.Product is mixture of 2 rotamers (3:2 ratio).

CI-MS (CH_4) 312 (MH^+, 100 %); 292 (MH^+ -HF, 13 %).

Example A50

(2*R*,3a*R*,12b*S*)-11-Fluoro-3,3a,8,12b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]-pyrrole-1,2(2*H*)-dicarbaldehyde (intermediate compound 63)



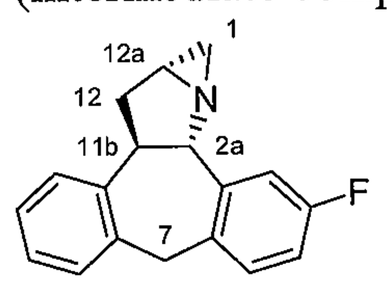
intermediate 63

PCC (104 mg, 0.48 mmol) was added to the solution of intermediate compound 62a (100 mg, 0.32 mmol) in CH_2Cl_2 (10 mL), and the resulting slurry was stirred under N_2 atmosphere for 3 hours. After addition of Et_2O (20 mL), the mixture was filtered through silica gel, the tar residue in flask washed with Et_2O (40mL), filtered again, the filtrates were evaporated to dryness *in vacuo*. Crude intermediate compound 63 (77 mg, 0.25 mmol, 78 %) was obtained as reddish oil, containing traces of chromium. Product was used immediately without purification.

CI-MS (CH_4) 310 (100 %, MH^+), 290 (11 %, MH^+ -HF); 282 (7 %, MH^+ -CO).

Example A51

(2a*S*,11b*R*,12a*R*)-4-Fluoro-1,2a,7,11b,12,12a-hexahydroazireno[1,2-*a*]dibenzo-[3,4:6,7]cyclo-hepta[1,2-*d*]pyrrole (intermediate compound 64)



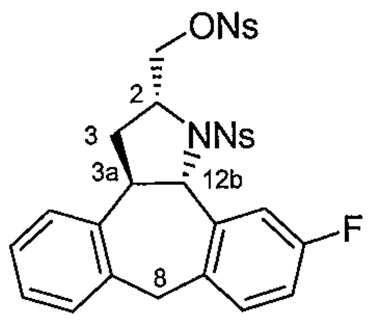
intermediate 64

Polymer supported triphenylphosphine (0.33 g, *ca.* 1 mmol of PPh_3) was swollen under argon atmosphere in dry CH_2Cl_2 (10 mL), then DIAD (222 mg, 1.1 mmol) in THF (3 mL) was added through septum at 0 °C. The suspension was stirred for 30 minutes at 0 °C, followed by addition of intermediate compound 61 (104 mg, 0.366 mmol) in THF (4 mL). The cooling bath was removed and reaction mixture was stirred at room temperature for 12 hours, then water (0.1 mL) was added, resin filtered off and washed with THF (15 mL), combined organics evaporated and purified by column chromatography (Kieselgel 60, 230-400 mesh, CH_2Cl_2-EtOH 100/0 to 96/4) to give intermediate compound 64 (63 mg, 0.238 mmol, 65 %) as yellowish oil.

HRMS Calcd. for $C_{18}H_{16}FN$: 265.1267; Found: 265.1270.

Example A52

a) {(2*R*,3a*R*,12b*S*)-11-Fluoro-1-[(2-nitrophenyl)sulfonyl]-1,2,3,3a,8,12b-hexahydro-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl}methyl 2-nitrobenzenesulfonate (intermediate compound 65)

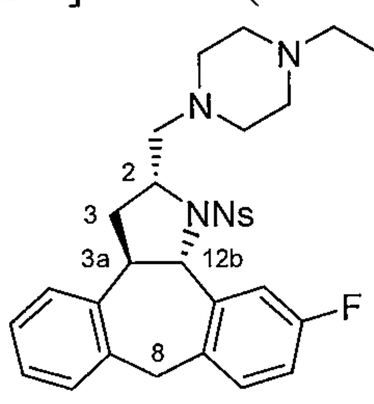


intermediate 65

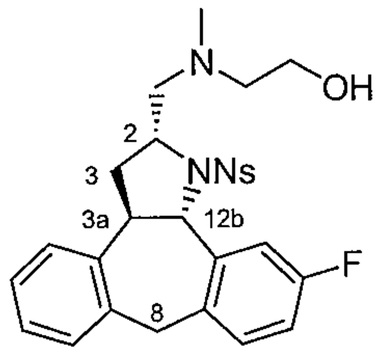
A solution of intermediate compound 61 (567 mg, 2.00 mmol), Et_3N (1.012 mmol, 10.00 mmol), DMAP (40 mg, 0.33 mmol) in CH_2Cl_2 (30 mL) was treated with NsCl (1.330 g, 6.00 mmol), and resulting mixture was stirred at room temperature for 3 hours, then quenched with sat. aq. NH_4Cl (30 mL). After extraction with CH_2Cl_2 (3 × 30 mL) the combined organics were washed with 1N HCl (15 mL), sat. aq. K_2CO_3 (40 mL), water (3 × 40 mL), brine, dried ($MgSO_4$), evaporated and purified by column chromatography on silica (heptane-EtOAc, 95/5 → 85/15) to give intermediate compound 65 (1.203 g, 1.84 mmol, 92 %) as yellow crystals, rapidly decomposing on standing.

^1H NMR (300 MHz, $CDCl_3$) δ 8.26-7.50 (m, 8H, Ar-H, 2-nosyl moieties); 7.20-7.03 (m, 6H, Ar-H, dibenzosuberone part); 6.81 (td, J = 8.3, 2.7 Hz, 1H, Ar-H); 5.40 (d, J = 11.0 Hz, 1H, CH-12b); 4.69 (d, J =16.7 Hz, 1H, CH_2-8); 4.60 (m, 2H, CH_2ONs); 4.40 (m, 1H, CH-2); 3.73 d, J =16.7 Hz, 1H, CH_2'-8); 3.55-3.40 (m, 1H, CH-3a); 2.80 (dd, J = 13.0, 6.2 Hz, CH_2-3); 2.33-2.18 (m, 1H, CH_2'-3).

b) 2-[4-({(2*R*,3a*R*,12b*S*)-11-Fluoro-1-[(2-nitrophenyl)sulfonyl]-1,2,3,3a,8,12b-hexahydro-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl}methyl)-1-piperazinyl]ethanol intermediate compound 66a) and 2-[({(2*R*,3a*R*,12b*S*)-11-Fluoro-1-[(2-nitrophenyl)-sulfonyl]-1,2,3,3a,8,12b-hexahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl}-methyl)(methyl)amino]ethanol (intermediate compound 66b)



intermediate 66a

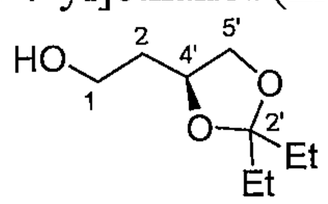


intermediate 66b

A mixture of intermediate compound 65 (0.35 g, 0.54 mmol) and the appropriate amine (3 mmol) in dioxane (10 mL) was refluxed for 4 hours, cooled down to ambient temperature, diluted with water (100 mL), precipitated product filtered off, washed with water (100 mL), dissolved in EtOAc, solution washed with brine, dried (K_2CO_3), evaporated, and used for next step without purification.

Example A53

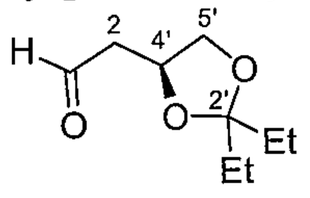
a) 2-[(4*S*)-2,2-Diethyl-1,3-dioxolan-4-yl]ethanol (intermediate compound 67b)



intermediate 67b

To a solution of (*S*)-1,2,4-butanetriol intermediate compound 67a (6.76 g, 63.68 mmol) in freshly distilled pentan-3-one (320 mL) was added *p*-toluenesulfonic acid (*p*-TSA) (6.06 g, 31.84 mmol). The reaction mixture was stirred at 53 °C for 16 hours, then Et_3N (10 mL) was added and the reaction mixture stirred at ambient temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure. Gradient flash chromatography (CH_2Cl_2/MeOH, 100:0 to 97:3 to 95:5) afforded the protected alcohol intermediate compound 67b (9.84 g, 89 %) as a colorless oil.

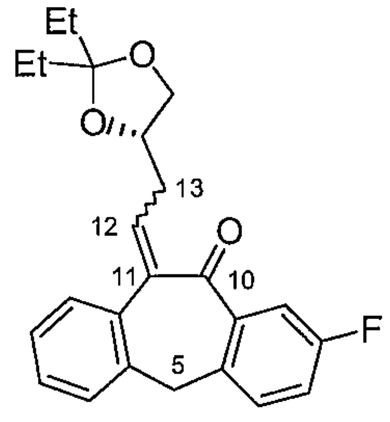
b) [(4'*S*)-2,2-Diethyl-1,3-dioxolan-4-yl]acetaldehyde (intermediate compound 67c)



intermediate 67c

To a solution of 2 intermediate compound 67b (4.00 g, 22.96 mmol) and 4Å molecular sieves (11.50 g) in CH_2Cl_2 (200 mL) stirred at 0 °C for 5 minutes was added PCC (9.90 g, 45.92 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. The crude reaction mixture was filtered through a pad of silica gel, washed with Et_2O (50 mL) and concentrated under reduced pressure to afford the intermediate compound 67c (3.56 g, 90 %) as a colorless oil.

c) 11-{2-[(4*S*)-2,2-diethyl-1,3-dioxolan-4-yl]ethylidene}-8-fluoro-5,11-dihydro-10*H*-dibenzo-[*a*,*d*]cyclohepten-10-one (intermediate compound 67d)

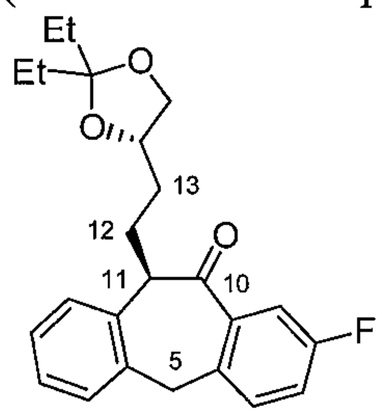


intermediate 67d

$MgBr_2$ (0.733 g, 3.98 mmol) was added to 8-fluoro-5,11-dihydro-10*H*-dibenzo[*a*,*d*]-cyclohepten-10-one (0.75 g, 3.32 mmol) in toluene (15 mL) and the reaction mixture stirred at room temperature for 30 minutes. Intermediate compound 67c (2.05 g, 11.92 mmol) in THF (10 mL) was added and in one time *t*-BuOK (0.074 g, 0.66 mmol). The reaction mixture was stirred for 22 hours at ambient temperature, then sat. aq. NH_4Cl (15 mL) was added. The product was extracted three times with Et_2O (3 × 30 mL), combined organics washed with water (2 × 35 mL), brine (25 mL) dried over $MgSO_4$. After evaporation of the toluene, the residue was purified on silica gel column using Et_2O/heptane (10/90) to obtain intermediate compound 67d (1.079 g, 86 %) as a yellowish oil.

HRMS (EI) Calcd. for $C_{24}H_{25}FO_3$: 380.1800; Found: 380.1785.

d) (11*R*)-11-{2-[(4*S*)-2,2-diethyl-1,3-dioxolan-4-yl]ethyl}-8-fluoro-5,11-dihydro-10*H*-dibenzo-[*a*,*d*]cyclohepten-10-one (intermediate compound 67e)

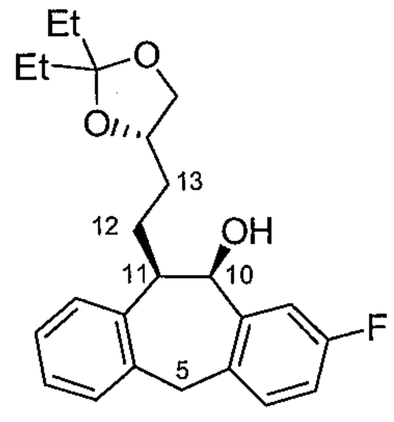


intermediate 67e

10 % Pd-C (200 mg) and Et_3N (0.135 mL, 0.97 mmol) were added to intermediate compound 67d (0.246 g, 0.647 mmol) in *i*-PrOH (25 mL) and toluene (15 mL) and subjected to hydrogenation overnight at room temperature. The reaction mixture was dissolved in CH_2Cl_2, filtered through celite and solvent evaporated. The residue was purified by column chromatography on silica gel using Et_2O/heptane (30/70) to give intermediate compound 67e (151 mg, 61 %) as a yellowish oil.

HRMS $C_{24}H_{27}FO_3$: 382.1944; Found: 382.1951.

e) (10*R*,11*R*)-11-{2-[(4*S*)-2,2-diethyl-1,3-dioxolan-4-yl]ethyl}-8-fluoro-10,11-dihydro-5*H*-di-benzo[*a*,*d*]cyclohepten-10-ol (intermediate compound 67f)

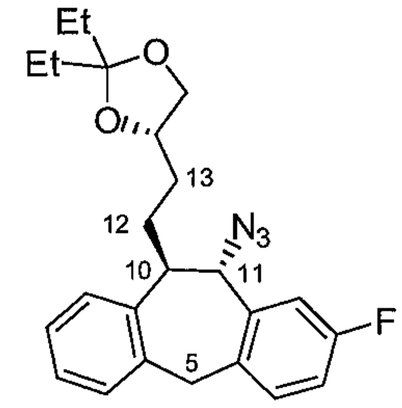


intermediate 67f

$NaBH_4$ (1.78 g, 46.84 mmol) was added to intermediate compound 35 (2.0 g, 5.88 mmol) dissolved in *i*-PrOH (80 mL)/pH 7 phosphate buffer (30mL) at 0 °C. After 1 hour of reaction at room temperature, NH_4Cl (sat. aq. solution) was added and the mixture was extracted three times with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and the solvent evaporated. The product was purified by column chromatography on silica gel using Et_2O/heptane (30/70) which gave intermediate compound 67f (1.96 g, 97 %) as colorless oil.

HRMS Calcd. for $C_{21}H_{23}FO_3$: 342.1631; Found: 342.1627.

f) (4*S*)-4-{2-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-ethyl}-2,2-diethyl-1,3-dioxolane (intermediate compound 67g)



intermediate 67g

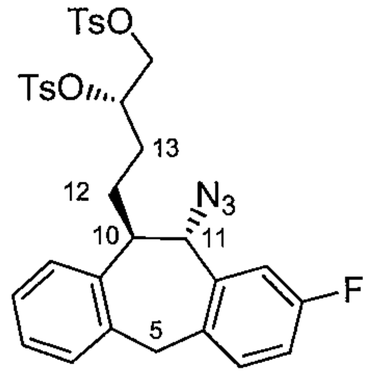
Intermediate compound 67g was obtained in the same way as described for intermediate compound 30.

g) (2*S*)-4-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-1,2-butanediol (intermediate compound 67h)

intermediate 67h

Intermediate compound 67h was obtained in the same way as described for intermediate compound 31.

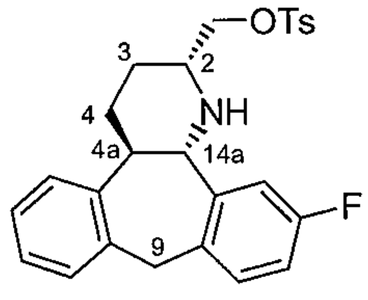
h) (2*S*)-4-[(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-2-{[(4-methylphenyl)sulfonyl]oxy}butyl 4-methylbenzenesulfonate (intermediate compound 67i)



intermediate 67i

A mixture of intermediate compound 67h (225 mg, 0.66 mmol), Et_3N (506 mg, 5.0 mmol), DMAP (12 mg, 0.1 mmol) and TsCl (503 mg, 2.64 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature under nitrogen atmosphere for 15 hours. After quenching with sat. aq. NH_4Cl (15 mL), the organic phase was separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with water (3 × 30 mL), brine (25 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography (Kieselgel 60, 70-230 mesh, heptane-EtOAc 90/10) to afford intermediate compound 67i (352 mg, 0.54 mmol, 82 %) as colorless semi-solid.

i) [(2*R*,4a*R*,13b*S*)-12-Fluoro-2,3,4,4a,9,13b-hexahydro-1*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyridin-2-yl]methyl 4-methylbenzenesulfonate (intermediate compound 67k)



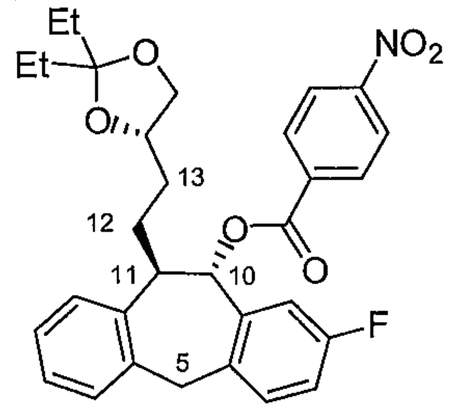
intermediate 67k

Intermediate compound 67i (340 mg, 0.52 mmol) was dissolved in MeOH (15 mL), Et_3N (1.012 g, 10 mmol) and 10 % Pd-C (150 mg) added, and resulting mixture hydrogenated under atmospheric pressure for 5 hours. Catalyst was removed by filtration through short pad of Kieselguhr, anhydrous K_2CO_3 (138 mg, 1 mmol) added and resulting slurry stirred at room temperature for 5 hours. After filtration of solids, MeOH and Et_3N were removed *in vacuo*, and residue purified by flash chromatography (Kieselgel 60, 230-400 mesh, EtOH-CH_2Cl_2 5/95 to 12/88) to yield intermdiate 67k (153 mg, 0.338 mmol, 65 %) as yellowish oil.

CI-MS (CH_4) 452 (MH^+, 1 %); 280 (MH^+ -TsOH, 100 %).

Example A54

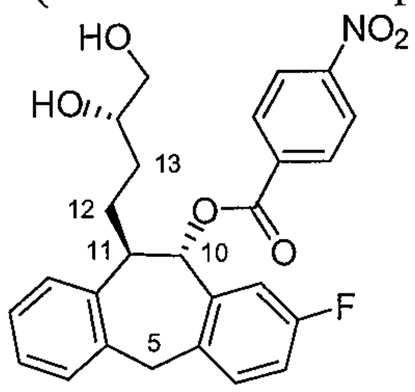
a) (10*S*,11*R*)-11-{2-[(4*S*)-2,2-diethyl-1,3-dioxolan-4-yl]ethyl}-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl 4-nitrobenzoate (intermediate compound 68a)



intermediate 68a

A solution of PPh_3 (910 mg, 3.5 mmol) in dry THF (25 mL) was placed in a two-necked 100 mL flask, equipped with septum, argon inlet and magnetic stirrer. After cooling down to –15 °C neat DIAD (708 mg, 3.5 mmol) was added through a septum with intensive stirring. Resulting yellow suspension was stirred at above temperature for 30 minutes, then a solution of 4-nitrobenzoic acid (585 mg, 3.50 mmol) and alcohol intermediate compound 67f (673 mg, 1.75 mmol) in THF (25 mL) was added within 10 minutes. The resulting yellow suspension was allowed to warm up to room temperature and stirred then for 12 hours. Water (0.3 mL) was added, followed by silica gel (Kieselgel 60, 70-230 mesh, 4 g), THF removed *in vacuo*, and the remaining silica powder was purified by flash column chromatography (Kieselgel 60, 230-400 mesh, EtOAc-heptane, 5/95 to 15/85) to give nitrobenzoate intermediate compound 68a (795 mg, 1.49 mmol, 85 %) as an orange semisolid.

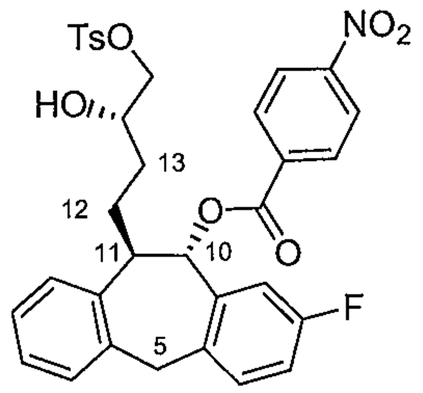
b) (10*S*,11*R*)-11-[(3*S*)-3,4-dihydroxybutyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-10-yl 4-nitrobenzoate (intermediate compound 68b)



intermediate 68b

Intermediate compound 68a (795 mg, 1.49 mmol) was carried out in the same was as described in Example A28 to give diol intermediate compound 68b (695 mg, 1.49 mmol, 100 %) as orange semisolid. Product intermediate 68b was used without purification.

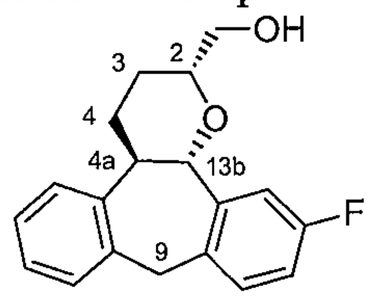
c) (10*S*,11*R*)-8-fluoro-11-((3*S*)-3-hydroxy-4-{[(4-methylphenyl)sulfonyl]oxy}butyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl 4-nitrobenzoate (intermediate compound 68c)



intermediate 68c

Intermediate compound 68b (695 mg, 1.49 mmol), Et_3N (607 mg, 6 mmol), dibutyl-(oxo)stannane (141 mg, 0.566 mmol), and TsCl (431 mg, 2.26 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature under N_2 for 12 hours. After quenching with sat. aq. NH_4Cl (15 mL) the organic phase was separated and the aqueous solution extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with water (3 × 20 mL), filtered through 5 cm layer of $MgSO_4$, and evaporated *in vacuo* to furnish crude intermediate compound 68c (601 mg, 0.97 mmol, 65 %) as a yellowish semisolid mass, which was used without further purification.

d) [(2*R*,4a*R*,13b*S*)-12-fluoro-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]cyclohepta-[1,2-*b*]pyran-2-yl]methanol (intermediate compound 68d)

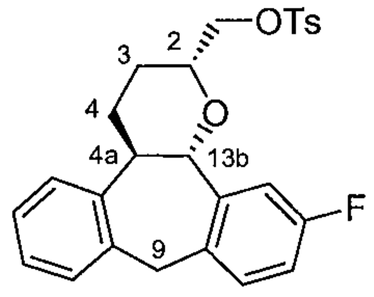


intermediate 68d

A mixture of intermediate compound 68c (601 mg, 0.97 mmol), sodium methoxide (162 mg, 3.0 mmol) and MeOH (10 mL) was stirred at room temperature for 3 hours. After treatment with water (100 mL) product was extracted with Et_2O (3 × 30 mL). The combined organics were washed with water (3 × 40 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatographic purification (Kielselgel 60, 70-230 mesh, EtOAc-heptane 10/90 to 25/75) gave intermediate compound 68d (211 mg, 0.71 mmol, 73 %) as a colorless oil.

HRMS Calcd. for $C_{19}H_{19}FO_2$: 298.1369; Found 298.1350.

d) [(2*R*,4a*R*,13b*S*)-12-fluoro-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]cyclohepta-[1,2-*b*]pyran-2-yl]methyl 4-methylbenzenesulfonate (intermediate compound 68e)

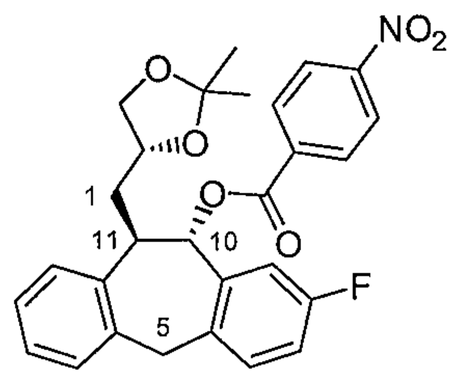


intermediate 68e

A mixture of intermediate compound 68d (211 mg, 0.708 mmol), Et_3N (209 µL, 287 mg, 2.83 mmol), DMAP (86.5 mg, 0.708 mmol), and TsCl (270 mg, 1.42 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature under N_2 for 16 hours. After quenching with sat. aq. NH_4Cl (10 mL) the organic phase was separated and the aqueous solution extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were washed with water (3 × 15 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give crude intermediate compound 68e (282 mg, 0.62 mmol, 88 %) as a yellowish oil, which was used without further purification.

Example A55

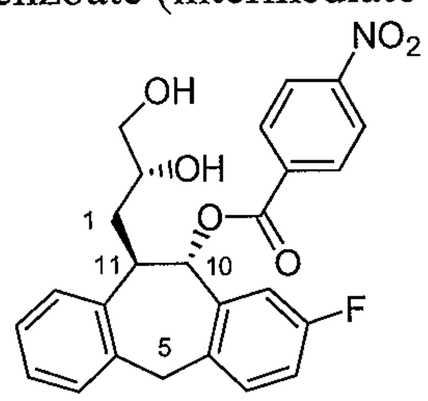
a) (10*S*,11*R*)-11-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl 4-nitrobenzoate (intermediate compound 69a)



intermediate 69a

A solution of PPh_3 (1049 mg, 4.0 mmol) in dry THF (20 mL) was placed in a two-necked 100 mL flask, equipped with septum, argon inlet and magnetic stirrer. After cooling down to −15 °C neat DIAD (809 mg, 4.0 mmol) was added through a septum with intensive stirring. Resulting yellow suspension was stirred at above temperature for 30 minutes, then a solution of 4-nitrobenzoic acid (4.0 mmol) and intermediate compound 3 (685. mg, 2.0 mmol) in THF (25 mL) was added within 10 minutes. The resulting yellow suspension was allowed to warm up to room temperature and stirred then for 12 hours. Water (0.3 mL) was added, followed by silica gel (Kieselgel 60, 70-230 mesh, 4 g), THF removed *in vacuo*, and the silica powder was submitted to the flash chromatography (Kieselgel 60, 230-400 mesh, EtOAc-heptane, 5/95 to 10/90) to give intermediate compound 69a (875 mg, 1.78 mmol, 89 %) as an orange semisolid.

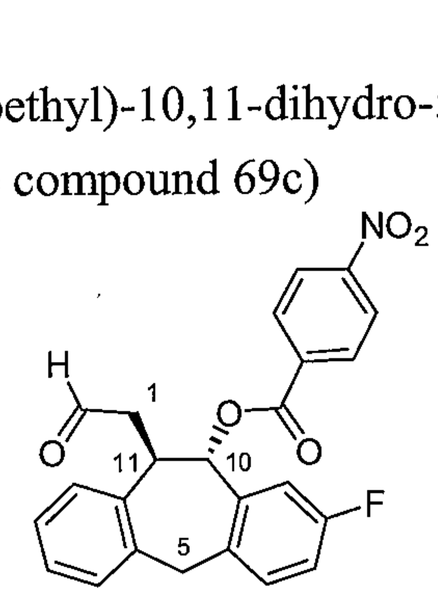
b) (10*S*,11*R*)-11-[(2*R*)-2,3-dihydroxypropyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cyclo-hepten-10-yl 4-nitrobenzoate (intermediate compound 69b)



intermediate 69b

Intermediate compound 69b has been obtained from acetal intermediate compound 69a (860 mg, 1.75 mmol) in the same way as described for intermediate compound 5. Column chromatography (Kieselgel 60, 70-230 mesh, EtOAc-heptane, 35/65 to 50/50) afforded intermediate compound 69b (774 mg, 1.715 mmol, 98 %) as a yellow semi-solid.

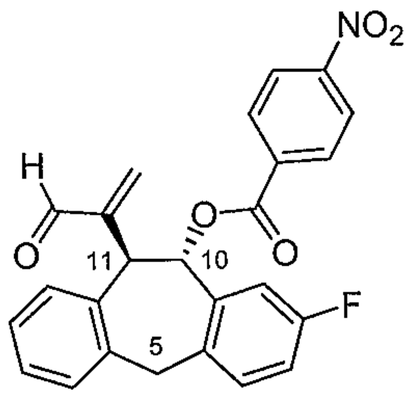
c) (10*S*,11*R*)-8-fluoro-11-(2-oxoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl 4-nitrobenzoate (intermediate compound 69c)



intermediate 69c

Intermediate compound 69b (774 mg, 1.715 mmol) was dissolved at 0 °C in a mixture of THF (25 mL) and pH 7 phosphate buffer (5 mL), then sodium periodate (642 mg, 3 mmol) was added in one portion at 0 °C, cooling bath removed, and resulting mixture was stirred at room temperature for 4 hours. Water (50 mL) was added, product extracted with Et_2O (3 × 30 mL). The combined organics were washed with sat. aq. sodium metabisulfite (50 mL), water (2 × 50 mL), brine (30 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give intermediate compound 69c (680 mg, 1.66 mmol, 97 %) as a yellow foam. Product was used immediately without purification.

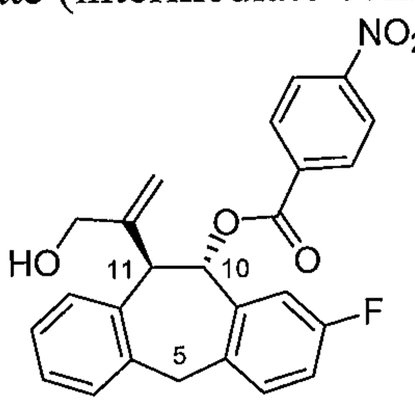
d) (10*S*,11*S*)-8-fluoro-11-(1-formylvinyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl 4-nitrobenzoate (intermediate compound 69d)



intermediate 69d

A mixture of intermediate compound 69c (680 mg, 1.66 mmol), AcOH (240 mg, 4.0 mmol), bis(dimethylamino)methane (719 mg, 7.0 mmol) and THF (30 mL) was stirred at room temperature for 3 hours. Water (50 mL) was added, product extracted with Et_2O (3 × 30 mL). The combined organics ware washed with sat. aq. $NaHCO_3$ (25 mL), water (2 × 50 mL), brine (30 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give intermediate compound 69d (680 mg, 1.58 mmol, 95 %) as a yellow oil.

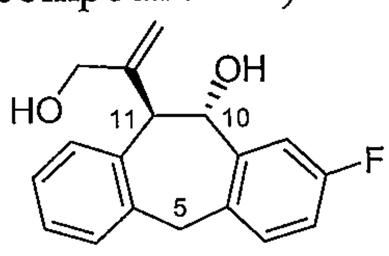
e) (10*S*,11*S*)-8-fluoro-11-[1-(hydroxymethyl)vinyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclo-hepten-10-yl 4-nitrobenzoate (intermediate compound 69e)



intermediate 69e

$NaBH_4$ (190 mg, 5.00 mmol) was added at room temperature within 10 minutes to the solution of intermediate compound 69d (680 mg, 1.58 mmol) in MeOH (30 mL). The reaction mixture was stirred at room temperature for 4 hours, quenched with sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organics ware washed with water (2 × 50 mL), brine (30 mL), dried over magnesium sulfate and evaporated *in vacuo* to give intermediate compound 69e (582 mg, 1.34 mmol, 85 %) as an orange oil.

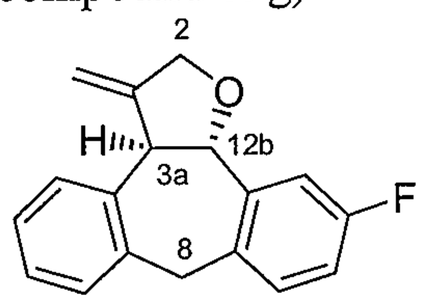
f) (10*S*,11*S*)-8-fluoro-11-[1-(hydroxymethyl)vinyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclo-hepten-10-ol (intermediate compound 69f)



intermediate 69f

A mixture of intermediate compound 69e (582 mg, 1.34 mmol), sodium methoxide (162 mg, 3.0 mmol) and MeOH was stirred at room temperature for 4 hours. Water (70 mL) was added, product extracted with EtOAc (3 × 30 mL). The combined organics were washed with water (2 × 50 mL), brine (30 mL), dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by flash column chromatography (Kieselgel 60, 230-400 mesh, EtOAc-heptane, 35/65 to 60/40) to give intermediate compound 69f (286 mg, 1.005 mmol, 75 %) as colorless oil.

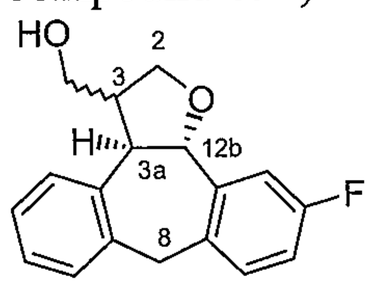
g) (3a*S*,12b*S*)-11-fluoro-3-methylene-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta-[1,2-*b*]furan (intermediate compound 69g)



intermediate 69g

PBu_3 (405 mg, 2.0 mmol) was dissolved in toluene (25 mL) under argon atmosphere. DIAD (405 mg, 2.0 mmol) in toluene (3 mL) was added dropwise, followed by solution of intermediate compound 69f (270 mg, 0.95 mmol). The resulting mixture was stirred at room temperature for 3 hours, then reaction was quenched water (1 mL). Silica gel (Kieselgel 60, 70-230 mesh, 1.3 g) was added, toluene removed *in vacuo*, and silica powder submitted to the flash chromatography (Kieselgel 60, 230-400 mesh, EtOAc-heptane, 5/95 to 12/88) to give intermediate compound 69g (205 mg, 0.77 mmol, 81 %) as colorless foam.

h) [(3a*R*,12b*S*)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]-furan-3-yl]methanol (intermediate compound 69h)

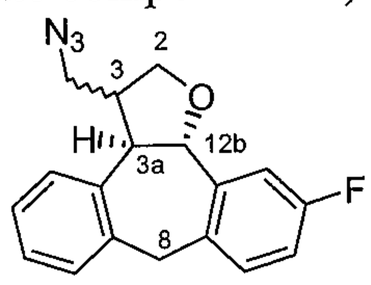


intermediate 69h

Boron trifloride etherate (0.43 mL, 3.54 mmol) in THF (1 mL) was added at room temperature under argon atmosphere to the solution of intermediate compound 69g (188 mg, 0.66 mmol), $NaBH_4$ (496 mg, 2.64 mmol) in dry THF (2 mL). The resulting solution was stirred under argon for 24 hours, excess of borohydrided decomposed carefully with water (3.8 mL), MeOH(1.5 mL) added, followed by 3M NaOH (3.8 mL) and 30 % hydrogen peroxide (0.55 mL). Reaction mixture was allowed to stir for 4

hours at room temperature, then the product was extracted with Et_2O (3 × 30 mL). The combined organics ware washed with water (2 × 50 mL), brine (30 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography (Kieselgel 60, 230-400 mesh, EtOAc-heptane, 5/95 to 20/80) to give THF derivative intermediate compound 69h (139 mg, 0.49 mmol, 74 %) as colorless oil.

i) (3a*R*,12b*S*)-3-(azidomethyl)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*b*]furan (intermediate compound 69i)

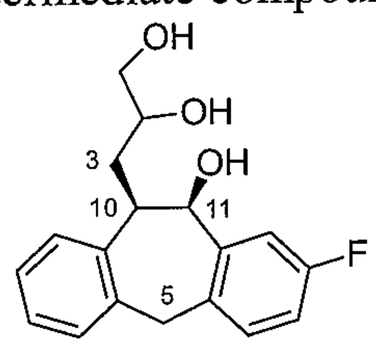


intermediate 69i

Polymer supported triphenylphosphine (0.33 g, *ca.* 1 mmol of PPh_3) was swollen at room temperature under argon atmosphere in dry THF (10 mL), then DIAD (222 mg, 1.1 mmol) in THF (3 mL) was added through septum at -15 °C. The suspension was stirred for 30 minutes at -15 °C, then alcohol intermediate compound 69h (139 mg, 0.49 mmol) in dry THF (2.5 mL) was added in one portion, followed by dropwise addition of DPPA (160 mg, 0.58 mmol) in THF (3 mL). Resulting suspension was stirred under argon for 12 hours. After quenching with water (0.3 mL), resin was filtered off and solvent removed *in vacuo*. The residue was purified by flash column chromatography (Kieselgel 60, 230-400 mesh, EtOAc-heptane, 15/85) to give intermediate compound 69i (136 mg, 0.44 mmol, 90 %) as colorless foam.

Example A56

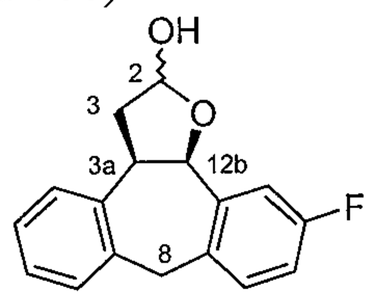
a) (2*R*)-3-[(10*R*,11*R*)-2-fluoro-11-hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-1,2-propanediol (intermediate compound 70a)



intermediate 70a

Triol intermediate compound 70a was obtained from intermediate compound 3 (514 mg, 1.50 mmol) in the same way as described in Example A4. Crude intermediate compound 70a (449 mg, 1.485 mmol, 99 %) was obtained as colorless oil and used without purification.

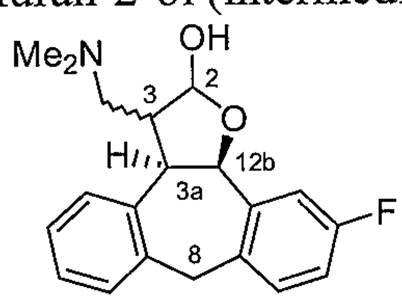
b) (3a*R*,12b*R*)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]-furan-2-ol (intermediate compound 70b)



intermediate 70b

Intermediate compound 70b was obtained from intermediate compound 70a (449 mg, 1.485 mmol) in the same way as described for intermediate compound 44. Flash column chromatography (Kieselgel 60, 230-400 mesh, EtOAc-heptane, 10/90 to 33/67) afforded intermediate compound 70c (357 mg, 1.32 mmol, 89 %) as a solid.

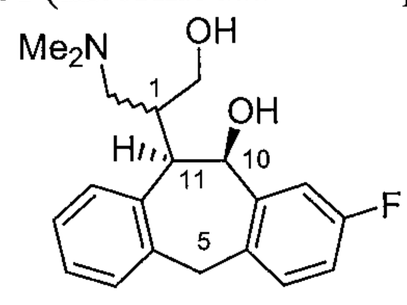
c) (3a*R*,12b*R*)-3-[(dimethylamino)methyl]-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo-[3,4:6,7]cyclohepta[1,2-*b*]furan-2-ol (intermediate compound 70c)



intermediate 70c

Reaction of intermediate compound 70c (335 mg, 1.24 mmol) was carried out in the same way as described for intermediate compound 45. Complex, unseparable mixture of products has been formed and used for the next step without purification.

d) (10*R*,11*R*)-11-[2-(dimethylamino)-1-(hydroxymethyl)ethyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-ol (intermediate compound 70d)

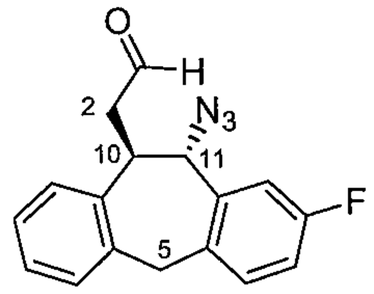


intermediate 70d

Reaction of the mixture containing intermediate compound 70c was was carried out in the same way as described for intermediate compound 46. Purification by RP-HPLC (Waters Xterra® C_{18}, 19 × 50 mm, MeOH-water 50/50, then pure MeOH, 4 mL/min) afforded intermediate compound 70d (135 mg, 0.41 mmol, 33 % from intermediate compound 70b) as yellow oil.

Example A57

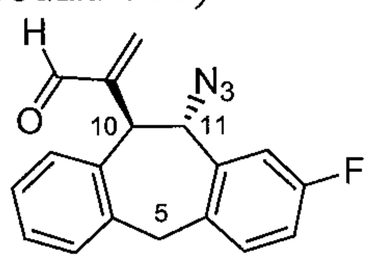
a) [(10*R*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-acetaldehyde (intermediate compound 71a)



intermediate 71a

Reaction of diol intermediate compound 5 (0.99 g mg, 3.02 mmol) was carried out in the same way as described for intermediate compound 44. Purification by column chromatography (Kieselgel 60, 230-400 mesh, Et_2O-heptane, 50/50) gave intermediate compound 71a (778 mg, 2.63 mmol, 87 %) as colorless oil.

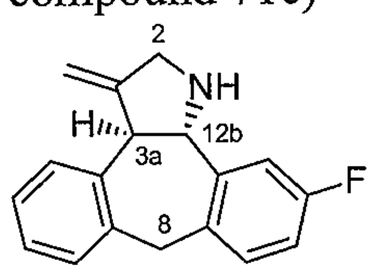
b) 2-[(10*S*,11*S*)-11-azido-2-fluoro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl]-acryl-aldehyde (intermediate compound 71b)



intermediate 71b

Reaction of intermediate compound 71a (618 mg, 2.09 mmol) was carried out in the same way as described for intermediate compound 45. Crude intermediate compound 71b (605 mg, 1.97 mmol, 94 %) was obtained as colorless oil and was used without further purification.

c) (3a*S*,12b*S*)-11-fluoro-3-methylene-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclo-hepta[1,2-*b*]-pyrrole (intermediate compound 71c)

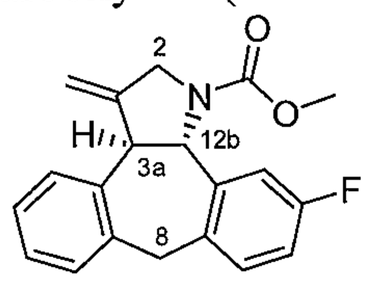


intermediate 71c

Polymer supported PPh_3 (1.40 g, *ca.* 4.2 mmol of PPh_3) was swollen at room temperature under argon atmosphere in THF (30 mL), then intermediate compound 71b (405 mg, 1.32 mmol) in THF (10 mL) and water (0.19 g) were added. The resulting mixture was stirred under argon at 50 °C for 1 hour. After this time resin was filtered off, THF remove *in vacuo*. The residue was dissolved in MeOH (10 mL), AcOH (1 mL) and $NaCNBH_4$ (200 mg, 3.2 mmol) added and resulting mixture stirred at room tempera-

ture for 2 hours, then quenched with concentrated HCl (1 mL), treated with sat. aq. $NaHCO_3$ (15 mL) and basified with 1N NaOH (3 mL). Product was extracted with CH_2Cl_2 (3 × 50 mL), combined organics washed with water (2 × 30 mL), brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo* to afford pyrrolidine intermediate compound 71c (258 mg, 0.97 mmol, 74 %) as yellow foam, used without further purification.

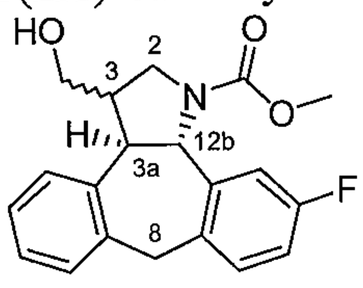
d) Methyl (3a*S*,12b*S*)-11-fluoro-3-methylene-3,3a,8,12b-tetrahydrodibenzo[3,4:6,7]-cyclo-hepta[1,2-*b*]pyrrole-1(2*H*)-carboxylate (intermediate compound 71d)



intermediate 71d

Reaction of intermediate compound 71c (258 mg, 0.97 mmol) was carried out in the same way as described for intermediate compound 9. Flash chromatography (Kieselgel 60, 230-400 mesh, heptane-EtOAc 50/50 to 0/100) afforded intermediate compound 71d (282 mg, 0.87 mmol, 90 %) as yellow oil.

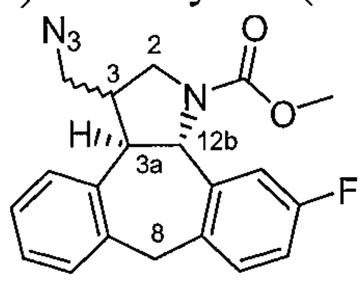
e) Methyl (3a*R*,12b*S*)-11-fluoro-3-(hydroxymethyl)-3,3a,8,12b-tetrahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrole-1(2*H*)-carboxylate (intermediate compound 71e)



intermediate 71e

Reaction of 71d (255 mg, 0.79 mmol) was carried out obtained in the same way as described for intermediate compound 49. Flash chromatography (Kieselgel 60, 230-400 mesh, EtOH-CH_2Cl_2 1/99 to 3/97) afforded 71e (215 mg, 0.63 mmol, 80 %) as colorless oil.

f) Methyl (3a*R*,12b*S*)-3-(azidomethyl)-11-fluoro-3,3a,8,12b-tetrahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrole-1(2*H*)-carboxylate (intermediate compound 71f)



intermediate 71f

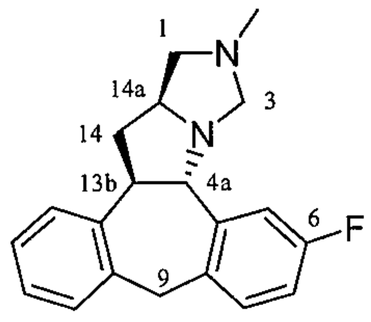
Reaction of intermediate compound 71f (215 mg, 0.63 mmol) was carried out obtained in the same way as described for intermediate compound 50. Flash chromatography (Kieselgel 60, 230-400 mesh, EtOAc) afforded intermediate compound 71f (194 mg, 0.53 mmol, 84 %) as colorless oil.

B. Preparation of the final compounds.

The compounds prepared hereinunder all are mixtures of isomeric forms, unless otherwise specified.

Example B1

(4a*S*,13b*R*,14a*S*)-6-fluoro-2-methyl-1,2,3,4a,9,13b,14,14a-octahydrodibenzo-[3',4':6',7']cyclohepta[1',2':4,5]pyrrolo[1,2-*c*]imidazole (final compound 1)



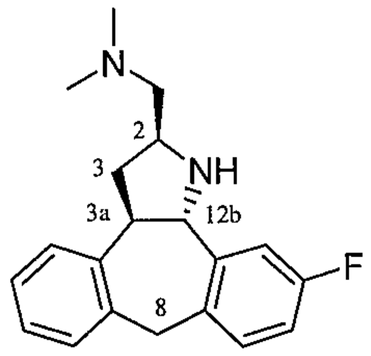
final compound 1

To a solution of intermediate compound 9 (130 mg, 0.3 mmol) in MeOH (5 mL) was added Et_3N (126.5 µL, 0.91 mmol) and the mixture was hydrogenated at 1 atmospheric pressure with 10 % palladium-on-charcoal under vigorous stirring at room temperature. After 1 hour, formaldehyde (112.8 µL, 1.5 mmol) was added and the mixture was hydrogenated for an additional hour. The suspension was then filtered through a pad of celite and the solids were washed 4 times with CH_2Cl_2. After evaporation, the crude product was purified by column chromatography on silica gel using $CHCl_3$/MeOH (95/5). This yielded final compound 1 as an oil (50.5 mg, 54 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 309 (MH^+, 100 %), 289 (MH^+ -HF, 26 %); EI: m/z (assignment, relative intensity) 308 ($M^{+\cdot}$, 68 %), 279 ($M^{+\cdot}$ - CH_2NH, 4 %), 265 ($M^{+\cdot}$ – CH_3NCH_2, 100 %), 197 (23 %); High resolution EI Calculated $C_{20}H_{21}FN_2$ ($M^{+\cdot}$): 308.1689, Found: 308.1684 (35 %).

Example B2

[(2*S*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]-pyrrol-2-yl]-*N*,*N*-dimethylmethanamine (final compound 2)



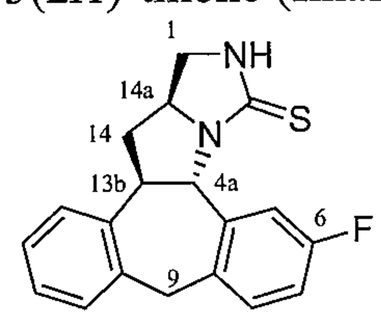
final compound 2

Dissolve final compound 1 (0.114 g, 0.37 mmol) in MeOH (10 mL) and add TFA (0.071 mL, 0.93 mmol), $NaCNBH_3$ (0.058 g, 0.93 mmol) and stir at room temperature for 1 hour. Add 10 mL K_2CO_3 (sat. aq. solution), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column purification on silica gel using CH_2Cl_2/MeOH (10 %) gave final compound 2 as an oil (0.067 g, 59 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 311 (MH^+, 100 %), 291 (MH^+ -HF, 25 %), 282 (MH^+ -CH_2NH), 266 (MH^+ - $HN(CH_3)_2$, 13 %), 252 (8 %);EI: m/z (assignment, relative intensity) 310 ($M^{+\cdot}$, 26 %), 266 ($M^{+\cdot}$ – $(CH_3)_2N$, 76 %), 252 ($M^{+\cdot}$ – $(CH_3)_2NCH_2$, 70 %), 235 (100 %), 209 (61 %); High resolution EI Calculated $C_{20}H_{23}FN_2$ ($M^{+\cdot}$): 310.1845, Found: 310.1820 (5 %).

Example B3

(4a*S*,13b*R*,14a*S*)-6-fluoro-1,4a,9,13b,14,14a-hexahydrodibenzo-[3',4':6',7']cyclohepta-[1',2':4,5]pyrrolo[1,2-c]imidazole-3(2*H*)-thione (final compound 3)



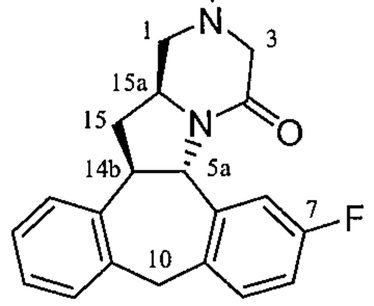
final compound 3

To solution of intermediate compound 9 (238.6 mg, 0.85 mmol) in DMF (3 mL) was added CS_2 (0.076 mL, 1.28 mmol). Stir at 60 °C for 20 minutes. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using EtOAc/heptane (50/50) to give final compound 3 as a semisolid final compound (124.6 mg, 45 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 325 (MH^+, 100 %), 252 (1 %), 224 (2 %).

Example B4

(5a*S*,14b*R*,15a*S*)-7-fluoro-2-methyl-1,2,3,5a,10,14b,15,15a-octahydro-4*H*-dibenzo [3',4':6',7']cyclohepta[1',2':4,5]pyrrolo[1,2-*a*]pyrazin-4-one (final compound 4)



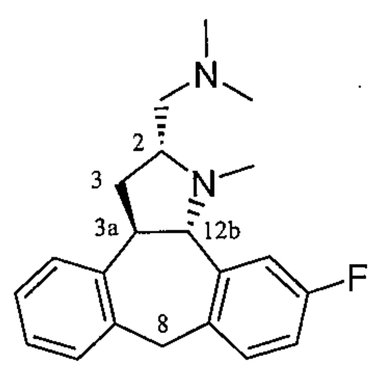
final compound 4

A solution of intermediate compound 16 (86.2 mg, 0.19 mmol) in MeOH (3 mL) was hydrogenated at 1 atmospheric pressure with 10 % palladium-on-charcoal under vigorous stirring at room temperature. After reaction for 1 hour, formaldehyde (70.7 µL, 0.94 mmol) was added and the mixture was hydrogenated for an additional hour. The suspension was filtered through a pad of celite and the solids were washed 4 times with CH_2Cl_2. After evaporation of the solvent, the crude product was purified by column chromatograhy on silica gel using $CHCl_3$ to yield final compound 4 (18.6 mg, 29 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 337 (MH^+, 100 %), 317 (MH^+ -HF, 18 %), 309 (MH^+ -CO, 9 %), 161 (9 %), 133 (75 %), 93 (72 %).

Example B5

[(2*R*,3a*R*,12b*S*)-11-fluoro-1-methyl-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]-*N*,*N*-dimethylmethanamine (final compound 5)



final compound 5

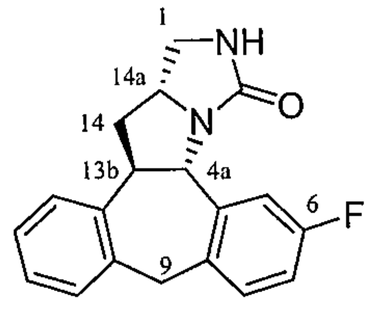
To a solution of intermediate compound 13 (28.7 mg, 0.05 mmol) in MeOH (2 mL) was added Et_3N (21.4 µL, 0.15 mmol) and formaldehyde (18.8 µL, 0.25 mmol) and the mixture was treated with hydrogen under 1 atmospheric pressure and 10 % palladium-on-charcoal under vigorous stirring at room temperature. After reaction for 1 hour, the suspension was filtered through a pad of celite and the solids were washed 4 times with

CH_2Cl_2. After evaporation, the crude product was purified by column chromatograhy on silica gel using $CHCl_3$/MeOH (90/10). This afforded final compound 5 as an oil (16.7 mg, 98 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 325 (MH^+, 100 %), 323 (25 %), 305 (MH^+ – HF, 19 %), 280 (MH^+ – $HN(CH_3)_2$, 12 %), 266 (MH^+ – $CH_3N(CH_3)_2$, 36 %).

Example B6

(4a*S*,13b*R*,14a*R*)-6-fluoro-1,4a,9,13b,14,14a-hexahydrodibenzo[3',4':6',7']cyclohepta-[1',2':4,5]pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (final compound 6)



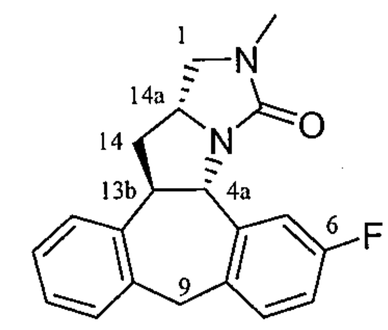
final compound 6

To a solution of intermediate compound 13 (40.4 mg, 0.14 mmol) in CH_3CN (2 mL) was added Et_3N (50 µL, 0.36 mmol) and the mixture was heated under argon at 70 °C. After 1 hour, a solution of diphenyl carbonate (36.6 mg, 0.17 mmol) in CH_3CN was added dropwise and the mixture was stirred at 70 °C for 2 days. After evaporation, the crude product was purified by column chromatography on silica gel using EtOAc/heptane (20/80) to yield final compound 6 as an oil (23 mg, 52 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 309 (MH^+, 100 %), 308 (12 %), 289 (MH^+ -HF, 20 %), 279 (3 %), 113 (8 %).

Example B7

(4a*S*,13b*R*,14a*R*)-6-fluoro-2-methyl-1,4a,9,13b,14,14a-hexahydrodibenzo[3',4':6',7']-cyclohepta[1',2':4,5]pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (final compound 7)



final compound 7

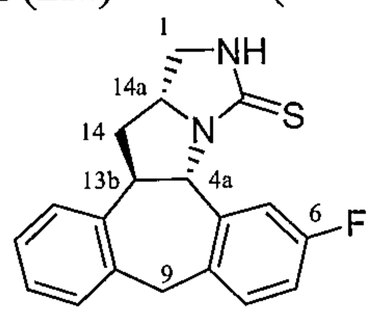
To a solution of final compound 6 (29 mg, 0.10 mmol) in THF (3 mL) was added NaH (15.9 mg, 0.31 mmol) and the mixture was stirred at room temperature for 20 minutes.

Then Me_2SO_4 (25.4 mg, 0.26 mmol) was added and the mixture was stirred for an additional 30 minutes. Add 10 mL of NH_4Cl (sat. aq. solution), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column purification on silica gel using EtOAc/heptane (40/60) gave the final compound 7 as an oil (19 mg, 63 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 323 (MH^+, 100 %), 303 (MH^+ -HF, 26 %), 209 (2 %), 127 (3 %).

Example B8

(4a*S*,13b*R*,14a*R*)-6-fluoro-1,4a,9,13b,14,14a-hexahydrodibenzo[3',4':6',7']cyclohepta-[1',2':4,5]pyrrolo[1,2-*c*]imidazole-3(2*H*)-thione (final compound 8)



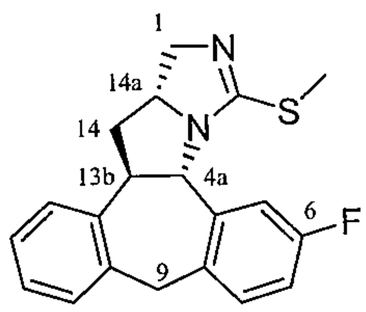
final compound 8

To a solution of intermediate compound 13 (54 mg, 0.19 mmol) in DMF (3 mL) was added CS_2 (17.3 µL, 0.29 mmol). After stirring at 60 °C for 20 minutes, followed by evaporation of the solvent, column chromatography purification on silica gel (eluent: EtOAc/heptane (50/50)) gave a crystalline final compound 8 (27.3 mg, 44 %); mp: 150-151 °C.

Mass spectrum: -CI m/z (assignment, relative intensity) 325 (MH^+, 100 %), 252 (1 %), 224 (2 %).

Example B9

(4a*S*,13b*R*,14a*R*)-6-fluoro-3-(methylsulfanyl)-1,4a,9,13b,14,14a-hexahydrodibenzo-[3',4':6',7']cyclohepta[1',2':4,5]pyrrolo[1,2-*c*]imidazole (final compound 9)



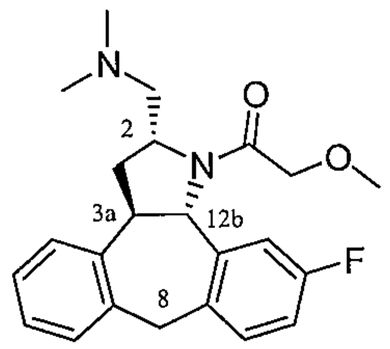
final compound 9

To a solution of final compound 8 (140.6 mg, 0.43 mmol) in MeOH (10 mL) was added methyl iodide (53.5 µL, 0.86 mmol) and Et_3N (129 µl, 0.86 mmol). After stirring at 80 °C for 2 days, solvent and reagents were evaporated. Column purification on

silica gel (eluent: EtOAc/heptane (40/60)) gave the final compound 9 as an oil (72.7 mg, 49 %).
Mass spectrum: -CI m/z (assignment, relative intensity) 339 (MH^+, 100 %), 319 (MH^+ -HF, 4 %), 268 (8 %), 266 (3 %).

Example B10

[(2*R*,3a*R*,12b*S*)-11-fluoro-1-(methoxyacetyl)-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]-*N*,*N*-dimethylmethanamine (final compound 10)

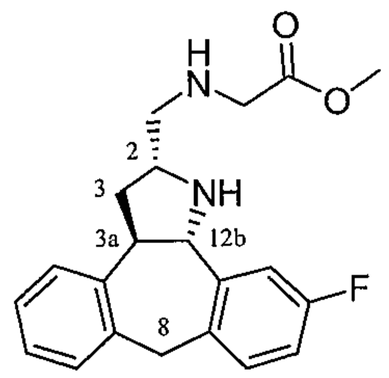


final compound 10

To a solution of intermediate compound 19 (265.3 mg, 0.44 mmol) in MeOH (20 mL) was added $MeSO_3H$ (2 mL) and the mixture was stirred at 60 °C for 30 minutes. After evaporation of the solvent, $NaHCO_3$ (sat. aq. solution) (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $MgSO_4$. Column chromatography purification on silica gel using CH_2Cl_2/MeOH (5 %) gave the amino compound (125 mg, 79 %). The latter was then dissolved in MeOH (30 mL). Following addition of formaldehyde (80 µL, 1.06 mmol) the mixture was hydrogenated (1 atmospheric pressure) with 10 % palladium-on-charcoal under vigorous stirring at room temperature for 6 hours. The suspension was then filtered through a pad of celite and the solids were washed 4 times with CH_2Cl_2. After evaporation of the solvent, the crude product was purified by column chromatograhy on silica gel using $CHCl_3$/MeOH (95/5). Final compound 10 (90.1 mg, 67 %) was obtained as an oil (mixture of conformers).
Mass spectrum: -APCI m/z (assignment, relative intensity) 383 (MH^+, 100 %), 369 (4 %), 367 (4 %), 363 (MH^+ -HF, 5 %), 354 (2 %), 351 (2 %).

Example B11

Methyl ({[(2*R*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]methyl}amino)acetate (final compound 11)



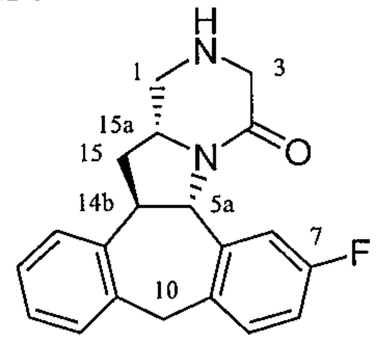
final compound 11

Intermediate compound 21 (53.4 mg, 0.15 mmol) was dissolved in a sat. solution of HCl in MeOH (10 mL) and the mixture was stirred at 60 °C overnight. After removal of solvent, 10 mL of K_2CO_3 (sat. aq. solution) was added and the mixture extracted with CH_2Cl_2 (3×10 mL). Column chromatography purification on silica gel using $CHCl_3$/MeOH (97/3) as eluent gave the final compound 11 (20 mg, 37 %) as an oil.

Mass spectrum: -CI m/z (assignment, relative intensity) 355 (MH^+, 100 %), 335 (MH^+ -HF, 14 %), 295 (MH^+ –CH_3OH – CO, 4 %), 252 (MH^+ –CH_3OH – CH_2CO – $NHCH_2$, 8 %), 169 (5 %), 141 (46 %); EI m/z (assignment, relative intensity) 354 (M^+, 3 %), 295 (M^+ – CH_3OCO, 4 %), 252 (M^+ –$CH_3OCOCH_2NHCH_2$, 100 %), 235 (M^+ - $CH_3OCOCH_2NHCH_2$ – NH_3, 68 %), 223 (8 %), 209 (22 %); High resolution EI Calculated $C_{21}H_{23}N_2O_2F$ ($M^{+\cdot}$): 354.1744,Found: 354.1751 (9 %).

Example B12

(5a*S*,14b*R*,15a*R*)-7-fluoro-1,2,3,5a,10,14b,15,15a-octahydro-4H-dibenzo[3',4':6',7']-cyclohepta[1',2':4,5]pyrrolo[1,2-*a*]pyrazin-4-one (final compound 12)



final compound 12

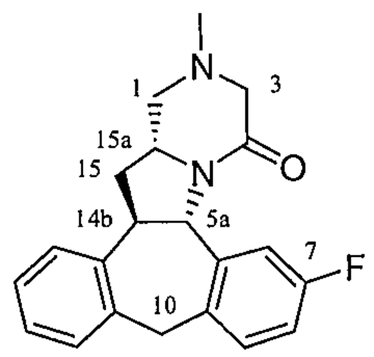
Intermediate compound 21 (250 mg, 0.71 mmol) was dissolved in 10 mL of HCl in MeOH (sat. solution) and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of 10 mL of K_2CO_3 (sat. aq. solution). The mixture was then extracted 3 times with 10 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. Column chromatography purification on silica gel using $CHCl_3$/MeOH (95/5) as eluent gave final compound 12 (67.6 mg, 29 %) as an oil.

Mass spectrum: -CI m/z (assignment, relative intensity) 323 (MH^+, 100 %), 303 (MH^+ -HF, 20 %), 295 (MH^+ -CO, 2 %), 252 (MH^+ – $COCH_2$ – $NHCH_2$, 1 %), 188 (2 %), 160 (5 %); EI m/z (assignment, relative intensity) 322 (M^+, 100 %), 252 (M^+ –

$COCH_2N{=}CH_2$, 40 %), 235 (68 %), 223 ($M^+ - COCH_2N{=}CH_2 - CH_2NH$, 44 %), 207 (13 %), 209 (88 %), 209 (22 %); High resolution EI Calculated $C_{20}H_{19}N_2OF$ ($M^{+\cdot}$): 322.1481, Found: 322.1484 (100 %).

Example B13

(5a*S*,14b*R*,15a*R*)-7-fluoro-2-methyl-1,2,3,5a,10,14b,15,15a-octahydro-4*H*-dibenzo-[3',4':6',7']cyclohepta[1',2':4,5]pyrrolo[1,2-*a*]pyrazin-4-one (final compound 13)



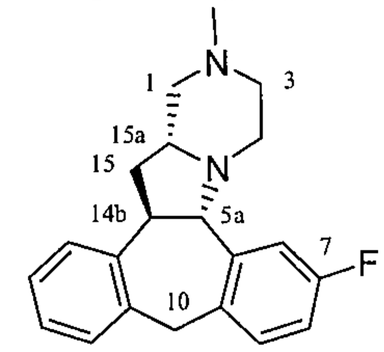
final compound 13

To a solution of final compound 12 (82.3 mg, 0.25 mmol) in MeOH (10 mL) was added formaldehyde (96 µL, 1.22 mmol) and the mixture was hydrogenated (1 atmospheric pressure) with 10 % palladium-on-charcoal under vigorous stirring at room temperature for 1 hour. Then the mixture was filtered through a pad of celite and the solids were washed 4 times with CH_2Cl_2. After evaporation, the crude product was purified by column chromatograhy on silica gel using $CHCl_3$/MeOH (3 %) as eluent. Final compound 13 (43.4 mg, 50 %) was obtained as a solid; mp: 139-141 °C.

Mass spectrum: -CI m/z (assignment, relative intensity) 337 (MH^+, 100 %), 317 (MH^+ -HF, 30 %), 279 (1 %), 251 (1 %), 209 (1 %); EI m/z (assignment, relative intensity) 336 (M^+, 74 %), 293 ($M^+ - COCH_3$, 13 %), 265 ($M^+ - CO{=}CHNHCH_3$, 9 %), 233 (18 %), 209 (42 %), 196 (26 %), 57 (100 %);High resolution EICalculated $C_{21}H_{21}N_2OF$ ($M^{+\cdot}$): 336.1638, Found: 336.1641 (100 %).

Example B14

(5a*S*,14b*R*,15a*R*)-7-fluoro-2-methyl-1,3,4,5a,10,14b,15,15a-octahydro-2*H*-dibenzo-[3',4':6',7']cyclohepta[1',2':4,5]pyrrolo[1,2-*a*]pyrazine (final compound 14)



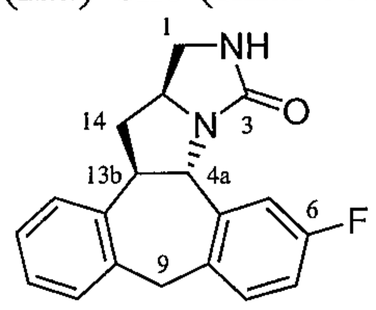
final compound 14

To a solution of final compound 13 (34.3 mg, 0.1 mmol) in THF (10 mL) was added $BH_3.Me_2S$ (100 µL, 0.2 mmol) and the mixture was heated at 85 °C overnight. Following evaporation of the solvent the residue was dissolved in 10 mL of HCl in MeOH (sat. solution) and the mixture was refluxed for 30 minutes. After removal of the solvent 10 mL of K_2CO_3 (sat. aq. solution) was added and the solution extracted 4 times with CH_2Cl_2. Then, the combined organic layers were evaporated and the crude product was purified by column chromatograhy on silica gel using $CHCl_3$/MeOH (3 %) as eluent. Final compound 14 (15.9 mg, 50 %) was obtained as an oil.

Mass spectrum: -CI m/z (assignment, relative intensity)323 (MH^+, 73 %), 303 (MH^+ - HF, 18 %), 247 (4 %), 219 (3 %), 43 (100 %); EI m/z (assignment, relative intensity) 322 (M^+, 73 %), 278 (M^+ -$N(CH_3)_2$, 44 %), 266 (M^+ – $N(CH_2)_3$, 85 %), 264 (M^+ – $CH_2CH_2NHCH_3$, 94 %), 251 (M^+ – CH_2CH_2 – $CH_2N(CH_3)$, 100 %), 209 (68 %), 196 (38 %); High resolution EI Calculated $C_{21}H_{23}N_2F$ ($M^{+\cdot}$): 322.1845, Found: 322.1849 (100 %).

Example B15

(4a*S*,13b*R*,14a*S*)-6-fluoro-1,4a,9,13b,14,14a-hexahydrodibenzo[3',4':6',7']cyclohepta-[1',2':4,5]pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (final compound 15)



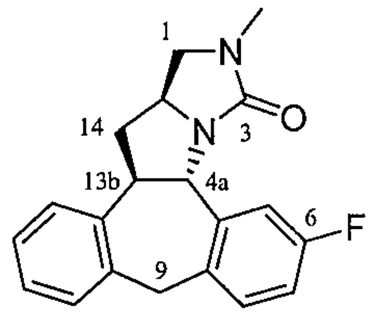
final compound 15

To the intermediate compound 25 (13.5 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) was added CH_3SO_3H (1.3 µL, 0.02 mmol). After stiring at room temperature for 1 minute, the mixture was worked up by adding Na_2CO_3 (sat. aq. sol.). Extract 3 times with CH_2Cl_2 and dry with $MgSO_4$. Column chromatography purification on silica gel using $CHCl_3$/MeOH (95/05) gave final compound 15 as an oily product (10.5 mg, 82 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 309 (MH^+, 100 %), 289 (MH^+ -HF, 17 %), 257 (1 %).

Example B16

(4a*S*,13b*R*,14a*S*)-6-fluoro-2-methyl-1,4a,9,13b,14,14a-hexahydrodibenzo[3',4':6',7']-cyclohepta[1',2':4,5]pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (final compound 16)

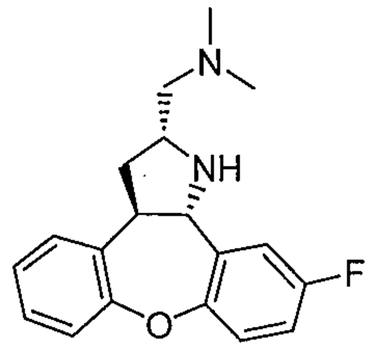


compound 16

To a solution of final compound 15 (10 mg, 0.03 mmol) in THF (1 mL) was added NaH (5 mg, 0.1 mmol) and the mixture was stirred at room temperature for 20 minutes. Then Me_2SO_4 (8 µL, 0.08 mmol) was added and the mixture was stirred for additional 30 min. Add 10 mL of NH_4Cl (sat. aq. solution), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column chromatrography purification on silica gel using EtOAc/heptane (50/50) as eluent gave the final compound 16 (8.4 mg, 80 %) as an oil.
Mass spectrum: -CI m/z (assignment, relative intensity) 323 (MH^+, 100 %), 303 (MH^+ -HF, 6 %), 257 (11 %), 252 ($MH^+ - CH_2N(CH_3)CO$, 9 %), 229 (9 %).

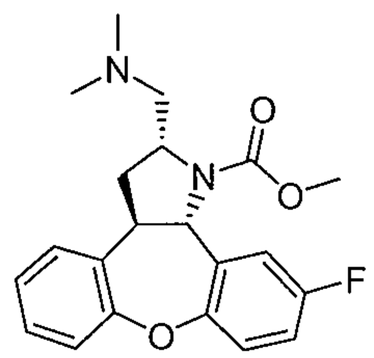
Example B17

[(2*R*,3a*R*,12b*S*)-11-fluoro-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]pyrrol-2-yl]-*N*,*N*-dimethylmethanamine (final compound 17)



compound 17

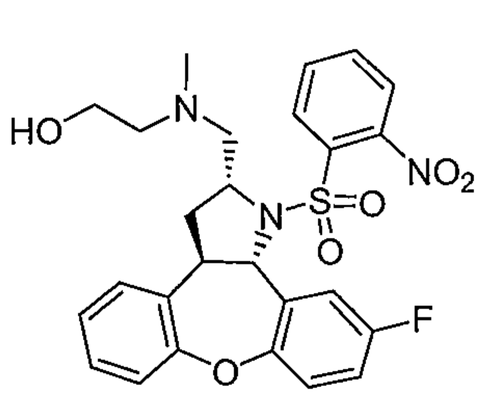
To a solution of intermediate compound 38 (0.17 g, 0.5 mmol), CH_2O (3 eq.) and AcOH (3 eq.) in MeOH (5 mL) at 0 °C, $NaCNBH_3$ (4 eq.) was added in several lots. The reaction mixture was warmed to room temperature and stirred for 6 hours. Solid $NaHCO_3$ (0.5 g) was added to the reaction mixture and stirred for 0.5 hour. To remove inorganic complexes the reaction mixture was put on sort filtration column and diluted with CH_2Cl_2:MeOH (9.5:0.5). The crude intermediate compound



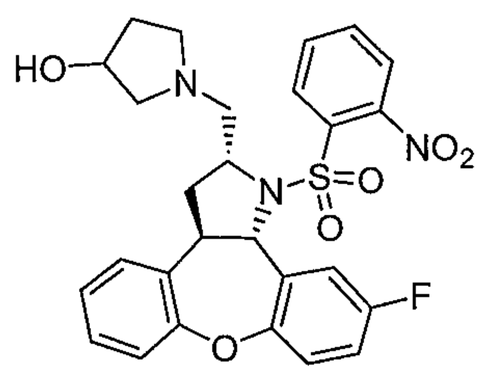
thus obtained was dissolved in *i*-PrOH (4 mL) and a solution of KOH (56 mg) in water (0.5 mL) was added to it and then refluxed for 3 hours. Silica gel was added to the reaction mixture and the solvent was removed under reduced pressure followed by purification of compound by flash column chromatography using CH_2Cl_2:MeOH (9:1) as an eluent to obtain final compound 17 as a thick viscous liquid (60 %, 93 mg).
HRMS: Calculated 312.1638; found 312.1633.

Examples B18-20

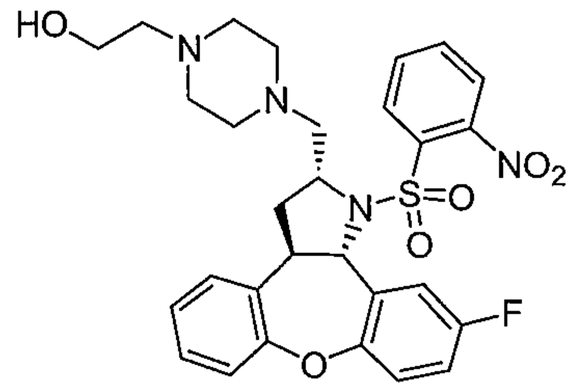
a) To a solution of intermediate compound 39 (0.5 mmol, 0.33 g) in dioxane (5 mL) the corresponding amino alcohol (5 eq.) was added and then refluxed for 6 hours. The solvent was removed under reduced pressure followed by column chromatography (silica gel) using CH_2Cl_2:MeOH (9:1) as an eluent to obtain intermediate compounds 39a, 39b and 39c as a thick viscous liquids in 40-50 % overall yield.



intermediate 39a



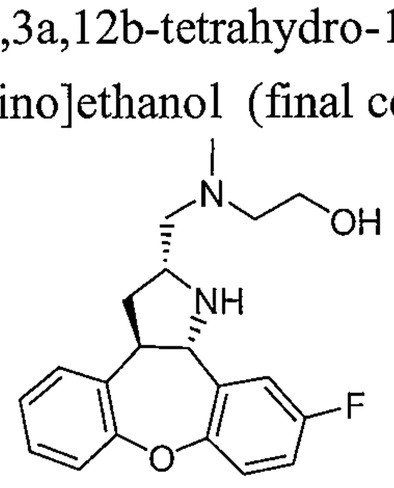
intermediate 39b



intermediate 39c

b) A mixture of appropriate intermediate compounds 39a, 39b and 39c (ca. 0.4 mmol), thiophenol (110 mg, 1.0 mmol), anhydrous K_2CO_3 (138 mg, 1 mmol) and DMF (20 mL) was stirred at 80 °C for 4 hours, cooled to ambient temperature, diluted with water, product extracted with EtOAc (3 × 50 mL), combined organics washed with water (4 × 50 mL), brine (35 mL), dried (K_2CO_3), evaporated and purified by solid phase extraction on basic alumina (Brockmann II, heptane-ethyl acetate 50/50, then ethyl acetate-MeOH 100/0 to 96/4 to 90/10) to obtain final compounds 18, 19 and 20.

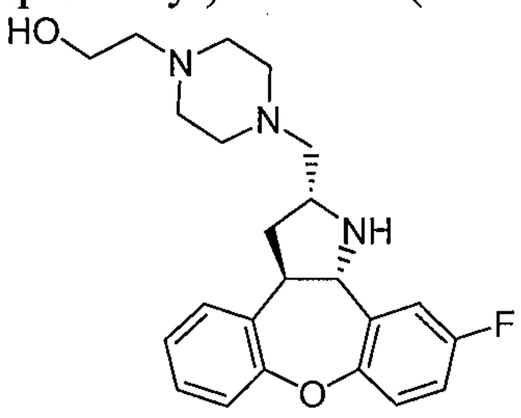
2-[{[(2*R*,3a*R*,12b*S*)-11-fluoro-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]pyrrol-2-yl]methyl}(methyl)amino]ethanol (final compound 18)



final compound 18

HRMS: Calculated 342.1744; found 342.1750

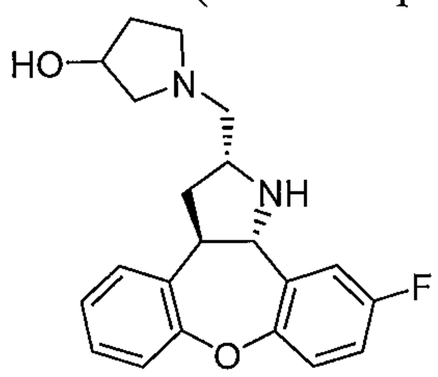
2-(4-{[(2*R*,3a*R*,12b*S*)-11-fluoro-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino-[4,5-*b*]pyrrol-2-yl]methyl}-1-piperazinyl)ethanol (final compound 19)



final compound 19

HRMS: Calculated 397.2166; found 397.2158

1-{[(2*R*,3a*R*,12b*S*)-11-fluoro-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino [4,5-*b*]pyrrol-2-yl]methyl}-3-pyrrolidinol (final compound 20)

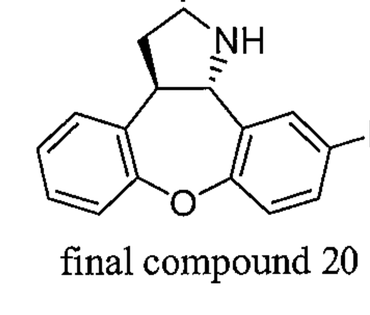


final compound 20

HRMS: Calculated 354.1744; found 354.1755

Example B21

[(2*S*,3a*R*,12b*S*)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7] cyclohepta [1,2-*b*]thien-2-yl]-*N*,*N*-dimethylmethanamine (final compound 21)



final compound 21

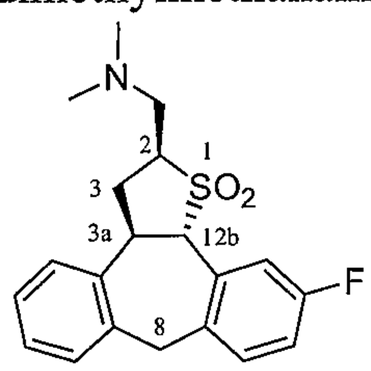
To a solution of intermediate compound 43 (81 mg, 0.25 mmol) in THF and water (3 mL/1 mL) was added PPh_3 (0.13 g, 0.50 mmol). The reaction mixture was stirred at room temperature for 1 night. After evaporation of the solvent, MeOH (5 mL), HCHO

(37 wt % aq. solution, 0.20 mL, 2.5 mmol), AcOH (1 mL) and $NaCNBH_3$ (75 mg, 1.20 mmol) were added. Stirring was continued at room temperature for 1 day. Add Na_2CO_3 (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using EtOAc as eluent gave final compound 21 as an oily product (70 mg, 86 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 328 (MH^+, 100 %), 308 (MH^+ – HF, 20 %), 283 (MH^+ – Me_2NH, 40 %), 249 (MH^+ – Me_2NH – H_2S, 12 %).

Example B22

[(2*S*,3a*R*,12b*S*)-11-fluoro-1,1-dioxido-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*b*]thien-2-yl]-*N*,*N*-dimethylmethanamine (final compound 22)



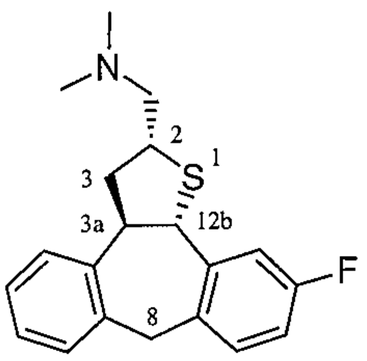
final compound 22

To a solution of intermediate compound 44 (133.5 mg, 0.37 mmol) in THF (8 mL) was added water (67.0 µL, 3.74 mmol) and PPh_3 (0.13 g, 0.50 mmol). The reaction mixture was stirred at room temperature for 1 night. After evaporation of the solvent, 5 mL of MeOH, HCHO (37 wt % aq. solution, 0.24 mL, 2.98 mmol), AcOH (0.5 mL) and $NaCNBH_3$ (94 mg, 1.49 mmol) were added. Stirring was continued at room temperature for 1 day. Add Na_2CO_3 (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using CH_2Cl_2/MeOH (95/05) as eluent gave final compound 22 as an oil product (60.7 mg, 45 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 360 (MH^+, 100 %), 358 (6 %), 340 (MH^+ – HF, 12 %), 303 (8 %), 294 (MH^+ – H_2SO_2, 4 %), 250 (1 %).

Example B23

[(2*R*,3a*R*,12b*S*)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7] cyclohepta[1,2-*b*]thien-2-yl]-*N*,*N*-dimethylmethanamine (final compound 23)



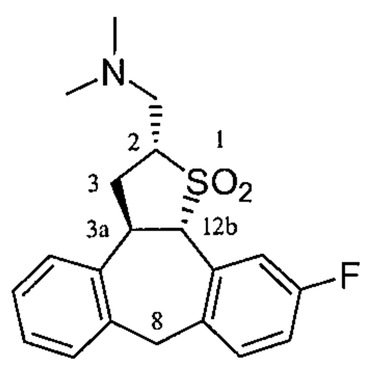
final compound 23

To a solution of intermediate compound 47 (0.15 g, 0.46 mmol) in THF and water (5 mL/1 mL) was added PPh_3 (0.13 g, 0.50 mmol). After stirring at room temperature for 1 night and evaporation of the solvent, 5 mL of MeOH, HCHO (37 wt % aq. solution, 0.20 mL, 2.5 mmol), AcOH (1 mL) and $NaCNBH_3$ (75 mg, 1.20 mmol) were added. Stirring was continued at room temperature for 1 day. Add Na_2CO_3 (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using EtOAc as eluent gave final compound 23 as an oily product (70 mg, 86 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 328 (MH^+, 100 %), 308 (MH^+ – HF, 20 %), 283 (MH^+ – Me_2NH, 40 %), 249 (MH^+ – Me_2NH – H_2S, 12 %).

Example B24

[(2*R*,3a*R*,12b*S*)-11-fluoro-1,1-dioxido-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*b*]thien-2-yl]-*N*,*N*-dimethylmethanamine (final compound 24)



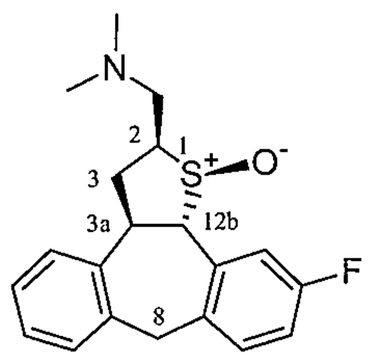
final compound 24

To a solution of intermediate compound 48 (146.5 mg, 0.41 mmol) in THF (8 mL) was added water (74.0 µL, 4.10 mmol) and PPh_3 (0.215 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 1 night. After evaporation of the solvent, 5 mL of MeOH, HCHO (37 wt % aq. solution, 0.28 mL, 3.51 mmol), AcOH (0.5 mL) and $NaCNBH_3$ (110.0 mg, 1.75 mmol) were added. Stirring was continued at room temperature for 1 day. Add Na_2CO_3 (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column

chromatography purification on silica gel using CH_2Cl_2/MeOH (90/10) gave final compound 24 as an oily product (105.0 mg, 71 %).
Mass spectrum: -CI m/z (assignment, relative intensity) 360 (MH^+, 100 %), 358 (6 %), 340 ($MH^+ - HF$, 12 %), 303 (8 %), 294 ($MH^+ - H_2SO_2$, 4 %), 250 (1 %).

Example B25

[(2*S*,3a*R*,12b*S*)-11-fluoro-1-oxido-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]thien-2-yl]-*N*,*N*-dimethylmethanamine (final compound 25)

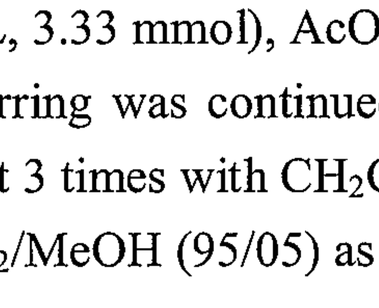


final compound 25

To a solution of intermediate compound 49 (107.9 mg, 0.32 mmol) in THF (5 mL) was added water (57 µL, 3.16 mmol) and PPh_3 (166.0 mg, 0.63 mmol). The reaction mixture was stirred at room temperature for 1 night. After evaporation of the solvent 5 mL of MeOH, HCHO (37 %, 0.26 mL, 3.33 mmol), AcOH (0.5 mL) and $NaCNBH_3$ (104.7 mg, 1.67 mmol) were added. Stirring was continued at room temperature for 1 day. Add Na_2CO_3 (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using CH_2Cl_2/MeOH (95/05) as eluent gave final compound 25 as an oily product (80.4 mg, 74 %).
Mass spectrum: -CI m/z (assignment, relative intensity) 344 (MH^+, 100 %), 328 ($MH^+ - O$, 13 %), 326 ($MH^+ - H_2O$, 15 %), 324 ($MH^+ - HF$, 15 %), 182 (14 %), 100 (27 %).

Example B26

[(2*S*,3a*R*,12b*S*)-11-fluoro-1-oxido-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*b*]thien-2-yl]-*N*,*N*-dimethylmethanamine (final compound 26)



final compound 26

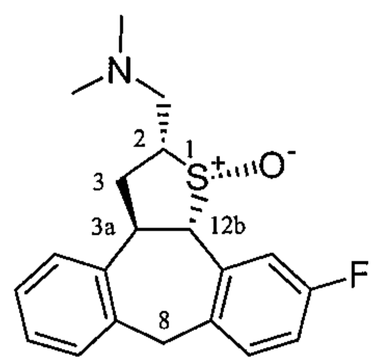
To a solution of intermediate compound 50 (133.4 mg, 0.39 mmol) in THF (5 mL) was added water (70 µL, 3.91 mmol) and PPh_3 (205.2 mg, 0.78 mmol). The reaction mix-

ture was stirred at room temperature for 1 night. After evaporation of the solvent, 5 mL of MeOH, HCHO (37 %, 0.24 mL, 2.99 mmol), AcOH (0.4 mL) and $NaCNBH_3$ (94.0 mg, 1.50 mmol) were added. Stirring was continued at room temperature for 1 day. Add Na_2CO_3 (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using CH_2Cl_2/MeOH (95/05) as eluent gave final compound 26 as an oily product (85.2 mg, 63 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 344 (MH^+, 100 %), 328 (MH^+ – O, 10 %), 327 (12 %), 326 ($MH^+ – H_2O$, 46 %), 324 (MH^+ – HF, 22 %), 283 (12 %).

Example B27

[(2*R*,3a*R*,12b*S*)-11-fluoro-1-oxido-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-b]thien-2-yl]-*N*,*N*-dimethylmethanamine (final compound 27)



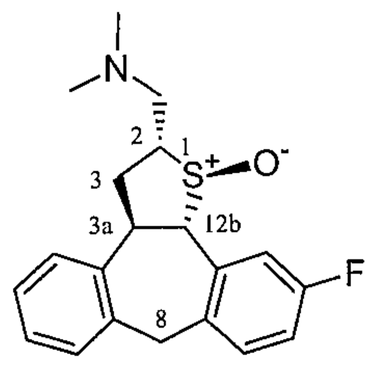
final compound 27

To a solution of intermediate compound 51 (85 mg, 0.25 mmol) in THF (5 mL) was added water (45 µL, 2.49 mmol) and PPh_3 (130.8 mg, 0.50 mmol). The reaction mixture was stirred at room temperature for 1 night. After evaporation of the solvent, 5 mL of MeOH, HCHO (37 %, 0.08 mL, 1.03 mmol), AcOH (0.3 mL) and $NaCNBH_3$ (32 mg, 0.52 mmol) were added. Stirring was continued at room temperature for 1 day. Add Na_2CO_3 (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using CH_2Cl_2/MeOH (95/05) as eluent gave final compound 27 as an oily product (35 mg, 41 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 344 (MH^+, 100 %), 328 (MH^+ – O, 4 %), 327 (3 %), 326 ($MH^+ – H_2O$, 10 %), 324 (MH^+ – HF, 8 %), 281 (6 %).

Example B28

[(2*R*,3a*R*,12b*S*)-11-fluoro-1-oxido-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]thien-2-yl]-*N*,*N*-dimethylmethanamine (final compound 28)



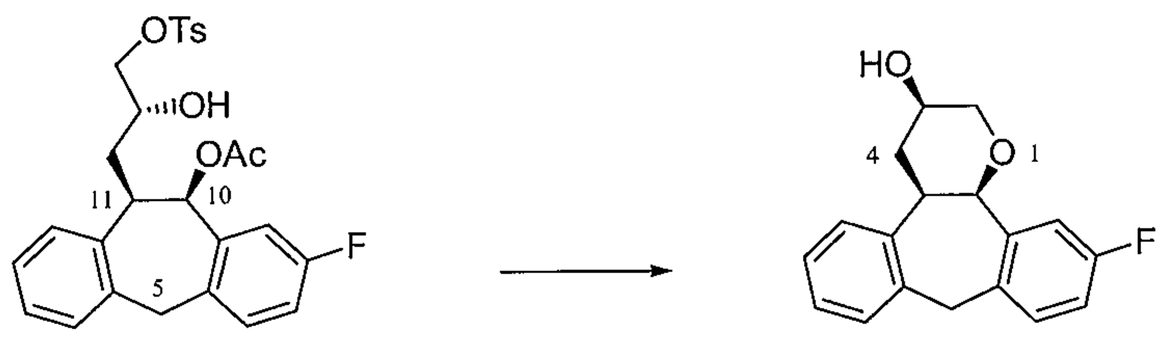
final compound 28

To a solution of intermediate compound 52 (158.5 mg, 0.46 mmol) in THF (5 mL) was added water (84 µL, 4.65 mmol) and PPh_3 (243.8 mg, 0.93 mmol). The reaction mixture was stirred at room temperature for 1 night. After evaporation of the solvent, 5 mL of MeOH, HCHO (37 %, 0.32 mL, 4.05 mmol), AcOH (0.5 mL) and $NaCNBH_3$ (130 mg, 2.03 mmol) were added. Stirring was continued at room temperature for 1 day. Add Na_2CO_3 (sat. aq. sol.), extract 3 times with CH_2Cl_2. Column chromatography purification on silica gel using CH_2Cl_2/MeOH (95/05) as eluent gave final compound 28 as an oily product (115.7 mg, 72 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 344 (MH^+, 100 %), 328 (MH^+ – O, 3 %), 327 (3 %), 326 (MH^+ –H_2O, 13 %), 324 (MH^+ – HF, 14 %), 281 (6 %).

Example B29

(3*R*,4a*R*,13b*R*)-12-fluoro-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]-pyran-3-ol (final compound 29)



intermediate 23a final compound 29

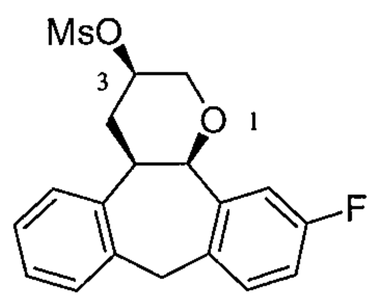
Dissolve intermediate compound 23a (1.31 g, 2.63 mmol) in CH_2Cl_2 (50 mL). Add DHP (1.20 mL, 13.2 mmol) and CSA (6 mg, 0.026 mmol). Stir at room temperature for 5 hours. Evaporate the solvent and dissolve the residue in 50 mL MeOH. Add K_2CO_3 (0.73 g, 5.26 mmol) and stir at room temperature for 1 night. Work up by adding sat. aq. NH_4Cl (30 mL), extract with CH_2Cl_2 (3 × 15 mL) and dry with $MgSO_4$. Evaporate the solvent and dissolve the residue in dry THF (50 mL). Add NaH (0.24 g, 7.78 mmol) and stir at room temperature for 1 day. Add 30 mL sat. aq. NH_4Cl, extract with CH_2Cl_2 (3 × 20 mL) and dry the organic phases with $MgSO_4$. Column purification on silica gel using Et_2O/hexane (35/65) gave an oil (0.86 g, 90 % from 2). Dissolve this oil (0.86 g, 2.34 mmol) in 20 mL MeOH/H_2O (9/1) and add Dowex 50WX8-100 (1.00 g).

Heat the mixture at 50 °C for 1 night. Filter through a P3 filter, wash the solids with CH_2Cl_2 (5 × 15 mL) and evaporate the solvent. Column chromatography purification on silica gel using ether/hexane (70:30) as eluent yielded final compound 29 as an oil (0.61 g, 93 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 285 (MH^+, 25 %), 267 (MH^+ - H_2O, 100 %), 249 (MH^+ – 2 H_2O, 36 %); EI: m/z (assignment, relative intensity) 284 ($M^{+\cdot}$, 1 %), 209 ($M^{+\cdot}$– $CH_2CHOHCH_2OH$, 100 %); High resolution EI Calculated $C_{18}H_{17}FO_2$ ($M^{+\cdot}$): 284.1213, Found: 284.1204 (2 %).

Example B30

a) (3*R*,4a*R*,13b*R*)-12-fluoro-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]cyclohepta [1,2-*b*]pyran-3-yl methanesulfonate (intermediate compound 53)

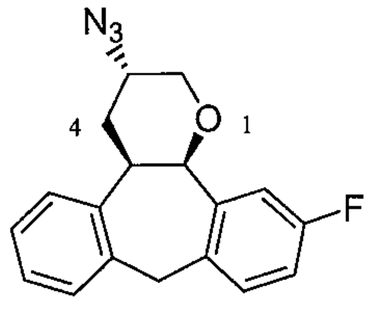


intermediate 53

Dissolve final compound 29 (0.61 g, 2.16 mmol) in CH_2Cl_2 (50 mL). Add Et_3N (0.60 mL, 4.32 mmol), DMAP (0.13 g, 1.08 mmol) and MsCl (0.25 mL, 3.24 mmol). Stir at room temperature for 4 hours. Work up by adding sat. aq. NH_4Cl (20 mL), extract with CH_2Cl_2 (3 × 20 mL) and dry with $MgSO_4$. Column chromatography purification on silica gel using CH_2Cl_2 as eluent yielded intermediate compound 53 as an oil (0.76 g, 97 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 363 (MH^+, 1 %), 267 (MH^+ – MsOH, 100 %), 249 (MH^+ – MsOH – H_2O, 33 %); EI: m/z (assignment, relative intensity) 362 ($M^{+\cdot}$, 5 %), 266 ($M^{+\cdot}$ – MsOH, 3 %), 248 ($M^{+\cdot}$ – MsOH – H_2O, 4 %), 209 ($M^{+\cdot}$– $CH_2CHOMsCH_2OH$, 100 %); High resolution EI Calculated $C_{19}H_{19}FO_4S$ ($M^{+\cdot}$): 362.0988, Found: 362.0984 (12 %).

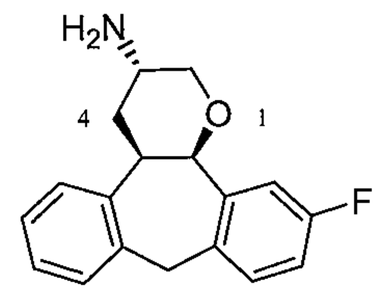
b) (3*S*,4a*R*,13b*R*)-3-azido-12-fluoro-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyran (intermediate compound 54)



intermediate 54

Dissolve intermediate compound 53 (0.29 g, 0.79 mmol) in DMF (10 mL), add NaN_3 (0.10 g, 1.58 mmol) and heat the mixture at 90 °C for 2 hours. Add sat. aq. NH_4Cl (10 mL), extract with CH_2Cl_2 (3 × 10 mL) and dry with $MgSO_4$. Column chromatography purification on silica gel using CH_2Cl_2/heptane (40:60) as eluent yielded intermediate compound 54 as a crystalline product (0.22 g, 88 %); mp: 91-93 °C.
Mass spectrum: -CI m/z (assignment, relative intensity) 310 (MH^+, 13 %), 282 ($MH^+ - N_2$, 100 %); EI: m/z (assignment, relative intensity) 281 ($M^{+\cdot} - N_2$, 28 %), 208 (100 %); High resolution EI Calculated $C_{18}H_{16}FNO$ ($M^{+\cdot} - N_2$): 309.1216, Found: 309.1223 (40 %).

c) (3*S*,4a*R*,13b*R*)-12-fluoro-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyran-3-amine (final compound 30)

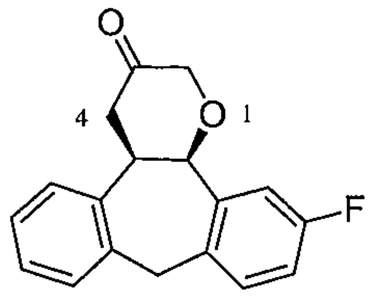


final compound 30

Dissolve intermediate compound 54 (0.16 g, 0.52 mmol) in *i*-PrOH/THF (2:1, 15 mL). Add 10 % Pd-C (ca. 100 mg) and subject to hydrogenation (1 atmospheric pressure) for 1 night. Filter through a pad of celite, wash the solids with CH_2Cl_2 (5 × 10 mL) and evaporate the filtrate. The residue is purified by column chromatography on silica gel using $CHCl_3$/MeOH (75:25) as eluent to give final compound 30 as a crystalline product (0.14 g, 94 %); mp:74-76 °C.
Mass spectrum: -CI m/z (assignment, relative intensity) 284 (MH^+, 100 %); EI: m/z (assignment, relative intensity) 283 ($M^{+\cdot}$, 5 %), 209 ($M^{+\cdot} - CH_2CHNH_2CH_2OH$, 100 %); High resolution EI Calculated $C_{18}H_{18}FNO$ ($M^{+\cdot}$): 283.1372, Found: 283.1370 (43 %).

Example B31

(4a*R*,13b*R*)-12-fluoro-4,4a,9,13b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyran-3(2*H*)-one (final compound 31)



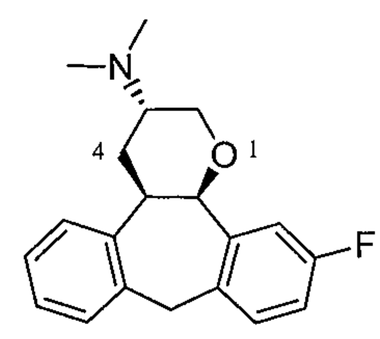
final compound 31

Dissolve final compound 29 (77 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) and add PCC (131 mg, 0.54 mmol). Stir at room temperature for 20 hours. Filter through a pad of celite, wash the solids with CH_2Cl_2 (5 × 20 mL) and evaporate the filtrates. Column chromatography purification on silica gel using Et_2O/hexane (50:50) as eluent yielded final compound 31 as a white crystalline product (61 mg, 80 %); mp: 146-148 °C.

Mass spectrum: -CI m/z (assignment, relative intensity) 283 (MH^+, 11 %), 265 ($MH^+ - H_2O$, 100 %), 237 ($MH^+ - H_2O - CO$, 22 %); EI: m/z (assignment, relative intensity) 282 ($M^{+\cdot}$, 26 %), 209 ($M^{+\cdot} - CH_2COCH_2OH$, 100 %); High resolution EI Calculated $C_{18}H_{15}FO_2$ ($M^{+\cdot}$): 282.1056, Found: 282.1057 (40 %).

Example B32

(3*S*,4a*R*,13b*R*)-12-fluoro-*N*,*N*-dimethyl-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]-cyclohepta[1,2-*b*]pyran-3-amine (final compound 32)



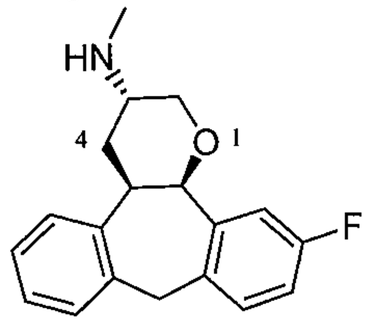
final compound 32

Intermediate compound 54 (0.24 g, 0.76 mmol) was dissolved in *i*-PrOH/THF (2:1, 15 mL). Add 10 % Pd-C (ca. 150 mg) and subject the mixture to hydrogenation (1 atmospheric pressure) for 1 night. Add 35 % aq. CH_2O (0.60 mL, 7.6 mmol) and continue hydrogenation for 2 days. Filter through celite and wash with CH_2Cl_2 (5 × 15 mL). Combine the organic phases and dry with $MgSO_4$. The solution was filtered and evaporated, and the residue was purified by column chromatography on silica gel using $CHCl_3$/MeOH (90:10) to yield final compound 32 as an oil (0.22 g, 93 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 312 (MH^+, 100 %); EI: m/z (assignment, relative intensity) 311 ($M^{+\cdot}$, 7 %).

Example B33

(3*R*,4a*R*,13b*R*)-12-fluoro-*N*-methyl-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyran-3-amine (final compound 33).



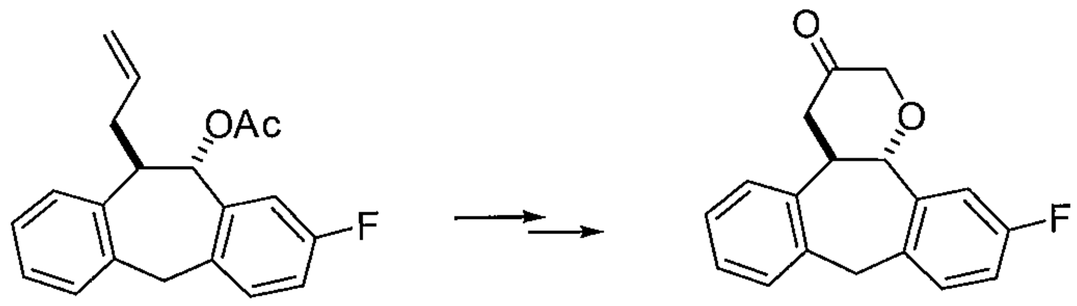
final compound 33

Dissolve final compound 31 (0.18 g, 0.63 mmol) in *i*-PrOH/THF (2:1, 10 mL). Add 10 % Pd-C (ca. 100 mg), Et_3N (0.87 mL, 6.3 mmol) and $MeNH_2 \cdot HCl$ (0.42 g, 6.3 mmol). Subject the mixture to hydrogenation (1 atmospheric pressure) for 1 night. Filter through a pad of celite and wash the solids with CH_2Cl_2 (5 × 15 mL). The solution was filtered and evaporated and the residue was purified by column chromatography on silica gel using $CHCl_3$/MeOH (90:10) to yield two diastereoisomers (0.18 g, 95 %) with a ratio of 5:1, from which the major (3*R*)-isomer (final compound 33) can be partly separated.

Mass spectrum: -CI m/z (assignment, relative intensity) 298 (MH^+, 100 %); EI: m/z (assignment, relative intensity) 297 ($M^{+\cdot}$, 5 %), 266 ($M^{+\cdot}$ -CH_3NH_2, 19 %); High resolution EI Calculated $C_{19}H_{20}FNO$ ($M^{+\cdot}$): 297.1529, Found: 297.1528 (3.5 %).

Example B34

(4a*R**,13b*S**)-12-fluoro-4,4a,9,13b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyran-3(2*H*)-one (final compound 34)



intermediate 56 final compound 34

a) Conversion of alkene into diastereoisomeric diols. Dissolve intermediate compound 56 (1.40 g, 4.52 mmol) in acetone (30 mL). Add a small crystal of OsO_4 (catalytic amount) and *N*-methylmorpholine *N*-oxide (0.63 g, 5.42 mmol). Stir at room temperature for 1 day. The solvent was removed under reduced pressure, and the residue was

purified by column chromatography on silica gel using EtOAc/hexane (80:20) to yield a mixture of two diastereoisomeric diols (oil, 1.45 g, 93 %).

b) Selective mono-tosylation of primary alcohol group. Dissolve the above diols (1.45 g, 4.22 mmol) in toluene (50 mL). Add Et_3N (1.76 mL, 12.6 mmol), TsCl (1.05 g, 5.48 mmol) and Bu_2SnO (0.10 g, 0.42 mmol). Stir at room temperature for 1 day. Add sat. aq. NH_4Cl (30 mL), extract with CH_2Cl_2 (3 × 20 mL) and dry with $MgSO_4$. The solution was filtered and evaporated and the residue was purified by column chromatography using EtOAc/hexane (40:60) to yield the diastereoisomeric monotosylate derivatives corresponding to selective sulfonylation of the primary OH group (oil, 1.74 g, 83 %).

c) Protection of secondary alcohol group. Dissolve the monotosylates (1.74 g, 3.49 mmol) in CH_2Cl_2 (60 mL) and add DHP (1.59 mL, 17.5 mmol), CSA (10 mg, 0.035 mmol). Stir at room temperature for 1 h and remove the solvent under reduced pressure.

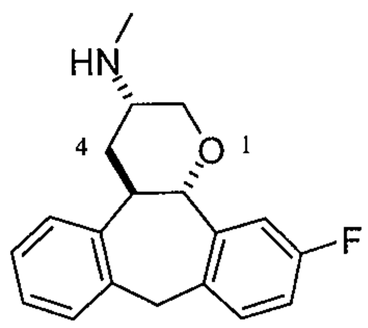
d) Deprotection and cyclisation of benzylic alcohol. The residue was dissolved in MeOH (50 mL). Add K_2CO_3 (0.79 g, 6.99 mmol) and stir at room temperature for 1 night. Work up by adding sat. aq. NH_4Cl (30 mL), extract 3 times with CH_2Cl_2 (3 × 20 mL) and dry with $MgSO_4$. The solvent was evaporated and the residue containing the benzylic alcohol was dissolved in dry THF (50 mL). Add NaH (0.21 g, 6.99 mmol) and stir at room temperature for 3 days to effect cyclisation. Work it up by adding sat. aq NH_4Cl (30 mL) and extract with CH_2Cl_2 (3 × 20 mL). Dry with $MgSO_4$ and evaporate the solvent.

e) Deprotection and oxidation of secondary alcohol group. Dissolve the residue (1.70 g) in 20 mL MeOH/H_2O (9:1) and add Dowex 50WX8-100 (1.00 g). Heat the mixture at 50 °C for 2 hours. Filter through P3 filter, wash the solids with CH_2Cl_2 (5 × 15 mL) and evaporate. Column purification on silica gel using Et_2O/hexane (70:30) yielded an oil (two diastereoisomeric alcohols) (0.87 g, 88 %). Dissolve the above oil (0.87 g, 3.06 mmol) in CH_2Cl_2 (40 mL). Add PCC (1.32 g, 6.13 mmol) and stir at room temperature for 1 night. Filter through a pad of celite, wash the solids with CH_2Cl_2 (5 × 20 mL) and evaporate. Column purification on silica gel using CH_2Cl_2/hexane (80:20) yielded final compound 34 as an oil (0.66 g, 76 %).

Mass spectrum: -CI m/z (assignment, relative intensity) 283 (MH^+, 25 %), 265 (MH^+ - H_2O, 100 %); EI: m/z (assignment, relative intensity) 282 ($M^{+\cdot}$, 39 %), 209 ($M^{+\cdot}$ – CH_2COCH_2OH, 100 %).

Example B35

(3*S**,4a*R**,13b*S**)-12-fluoro-*N*-methyl-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]-cyclohepta[1,2-*b*]pyran-3-amine (final compound 35)



final compound 35

Dissolve final compound 34 (0.23 g, 0.83 mmol) in *i*-PrOH (15 mL). Add Et_3N (1.15 mL, 8.25 mmol), $MeNH_2 \cdot HCl$ (0.56 g, 8.25 mmol) and 10 % Pd/C (ca. 150 mg). Subject to hydrogenation (1 atmospheric pressure) for 1 night. Filter through a pad of celite and wash the solids with CH_2Cl_2 (5 × 10 mL). The solution was filtered and evaporated, and the residue was purified by column chromatography on silica gel using $CHCl_3$/MeOH (90:10) to yield final compound 35 as the nearly exclusive diastereoisomer (0.23 g, 95 %).

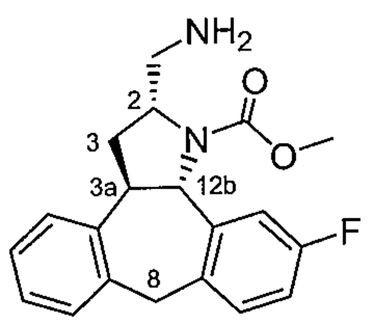
Mass spectrum: -CI m/z (assignment, relative intensity) 298 (MH^+, 100 %); EI: m/z (assignment, relative intensity) 209 ($M^{+\cdot}$ – $CH_2CH(NHMe)CH_2OH$, 100 %).

Example B36

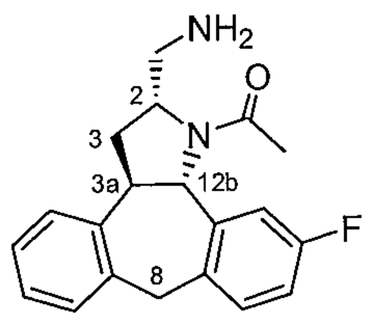
a1) Methyl (2*R*,3a*R*,12b*S*)-2-(aminomethyl)-11-fluoro-3,3a,8,12b-tetrahydrodibenzo-[3,4:6,7]-cyclohepta[1,2-*b*]pyrrole-1(2*H*)-carboxylate (intermediate compound 62b),

b1) [(2*R*,3a*R*,12b*S*)-1-acetyl-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]-cyclohepta[1,2-*b*]pyrrol-2-yl]methanamine (intermediate compound 62c), and

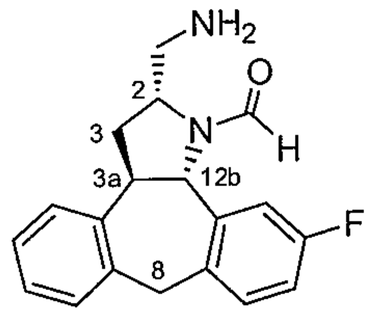
c1) (2*R*,3a*R*,12b*S*)-2-(aminomethyl)-11-fluoro-3,3a,8,12b-tetrahydrodibenzo[3,4:6,7]-cyclohepta-[1,2-*b*]pyrrole-1(2*H*)-carbaldehyde (intermediate compound 62d)



intermediate 62b



intermediate 62c



intermediate 62d

Representative Procedure – Synthesis of Methyl (2*R*,3a*R*,12b*S*)-2-(aminomethyl)-11-fluoro-3,3a,8,12b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrole-1(2H)-carboxylate (intermediate compound 62b) : A solution of PPh_3 (996 mg, 3.8 mmol) in

dry THF (20 mL) was placed in two-necked 100 mL flask, equipped with septum, argon inlet and magnetic stirrer; cooled down to –15 °C. Neat DIAD (768 mg, 3.8 mmol) was added through a septum with intensive stirring. Resulting yellow suspension was stirred at above temperature for 30 minutes, then carbamate intermediate compound 62 (650 mg, 1.9 mmol) in THF (5 mL) was added in one portion. After 5 minutes of stirring, DPPA (606 mg, 2.2 mmol) in THF (3 mL) was added dropwise for 3 minutes, resulting turbid mixture allowed to warm up to room temperature and stirred then for 12 hours. After this time water (0.2 mL) and PPh_3 (996 mg, 3.8 mmol) was added, and solution stirred at 45 °C for 2 hours. After cooling down to room temperature, silica gel (Kieselgel 60, 70-230 mesh, 4 g) was added, THF removed in vacuo, and silica powder submitted to the flash column chromatography (Kieselgel 60, 230-400 mesh, CH_2Cl_2-MeOH, 100/0, gradually to 85/15) to give desired intermediate compound 62b (401 mg, 1.18 mmol, 62 %) as colorless oil, darkening on standing.

Intermediate compound 62b

HRMS Calcd. for $C_{20}H_{21}FN_2O_2$: 340.1587; Found: 340.1588.

Intermediate compound 62c: two rotamers present (ca. 2:1 ratio)

CI-MS (CH_4) 325 (MH^+, 100 %); 305 (MH^+ -HF, 10 %).HRMS Calcd. for $C_{20}H_{21}FN_2O$: 324.1638; Found: 324.1644.

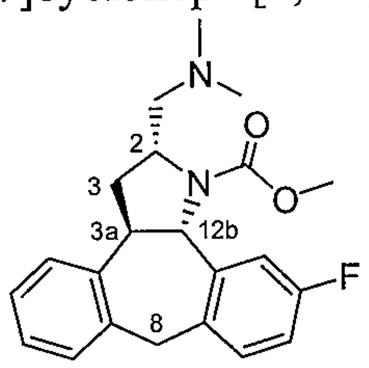
Intermediate compound 62d: two rotamers present (ca. 5:2 ratio)

HRMS Calcd. for $C_{19}H_{19}FN_2O$: 310.1481; Found: 310.1480.

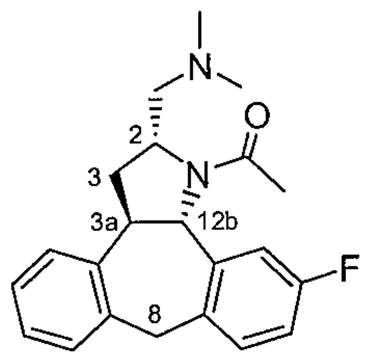
a2) Methyl (2*R*,3a*R*,12b*S*)-2-[(dimethylamino)methyl]-11-fluoro-3,3a,8,12b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrole-1(2*H*)-carboxylate (final compound 36a) ,

b2) [(2*R*,3a*R*,12b*S*)-1-acetyl-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-*2*-yl]-*N*,*N*-dimethylmethanamine (final compound 36b) and

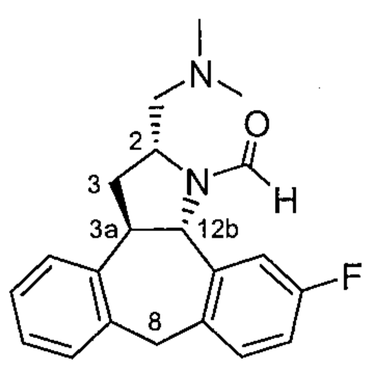
c2) (2*R*,3a*R*,12b*S*)-2-[(dimethylamino)methyl]-11-fluoro-3,3a,8,12b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrole-1(2*H*)-carbaldehyde (final compound 36c)



final compound 36a



final compound 36b



final compound 36c

Representative procedure – Synthesis of Methyl (2*R*,3a*R*,12b*S*)-2-[(dimethylamino)methyl]-11-fluoro-3,3a,8,12b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrole-1(2*H*)-carboxylate (final compound 36a) : Intermediate compound 62b (401 mg, 1.18

mmol) was dissolved in MeOH (30 mL), AcOH (1 mL) and 35 % aqueous formaldehyde (1 g, 11.7 mmol) added, followed by $NaCNBH_4$ (628 mg, 10 mmol). The resulting mixture was stirred at room temperature for 4 hours, quenched with concentrated HCl (5 mL), treated with solid $NaHCO_3$ (8.4 g, 100 mmol), 1N NaOH (15 mL). The precipitated product was filtered off, washed with water (5 × 25 mL), dissolved in EtOAc, washed with brine (30 mL), dried (K_2CO_3), evaporated *in vacuo* and purified by column chromatography (Kieselgel 60 , 230-400 mesh, CH_2Cl_2-MeOH 95/5 to 90/10 to 85/15) to give final compound 36a (313 mg, 0.85 mmol, 72 %) as yellowish oil.

Final compound 36a :

HRMS Calcd. for $C_{22}H_{25}FN_2O_2$: 368.1900; Found: 368.1895.

Final compound 36b: Two rotamers, ca. 3:2 ratio.

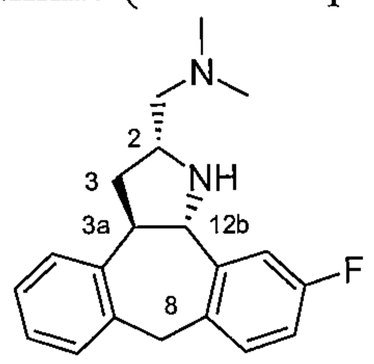
HRMS Calcd. for $C_{22}H_{25}FN_2O$: 352.1951; Found: 352.1955.

Final compound 36c: Two rotamers, ca. 5:3 ratio.

HRMS Calcd. for $C_{21}H_{23}FN_2O$ 338.1794; Found: 338.1790.

Example 37

[(2*R*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]-pyrrol-2-yl]-*N*,*N*-dimethylmethanamine (final compound 37)



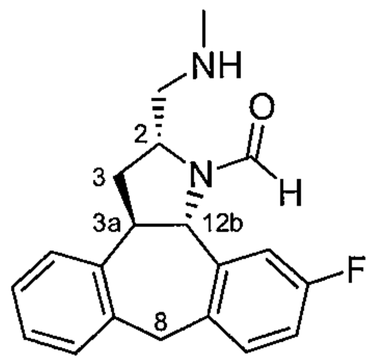
final compound 37

A mixture of final compound 36a (100 mg, 0.27 mmol), *i*-PrOH (10 mL), KOH (560 mg, 10 mmol) and water (0.1 mL) was refluxed under N_2 atmosphere for 12 hours (oil bath temperature 135 °C), then cooled to room temperature. After dilution with water (50 mL), extraction with EtOAc (3 × 40 mL), the combined organics were washed with water (3 × 40 mL), brine (40 mL), dried over K_2CO_3 and evaporated to give pure final compound 37 (84 mg, 100 %) as yellowish semisolid, which was converted to the hydrochloride salt (final compound 37a).

HRMS Calcd. for $C_{20}H_{23}FN_2$: 310.1845; Found: 310.1851.

Example B38

(2*R*,3a*R*,12b*S*)-11-fluoro-2-[(methylamino)methyll]-3,3a,8,12b-tetrahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrole-1(2*H*)-carbaldehyde (final compound 38)



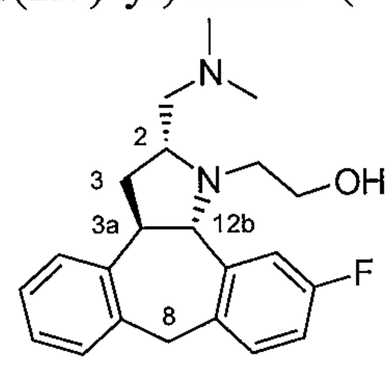
final compound 38

A mixture of intermediate compound 63 (50 mg, 0.162 mmol), methylamine hydrochloride (218 mg, 3.24 mmol), Et_3N (405 mg, 4.0 mmol), 10 % Pd-C (30 mg) and MeOH (12 mL) was hydrogenated for 2 hours at atmospheric pressure. The reaction mixture was filtered through Kieselguhr, which was subsequently washed with EtOAc (2 × 10 mL). The combined solutions were evaporated *in vacuo* and residue was purified by column chromatography (Kieselgel 60, 70-230 mesh, CH_2Cl_2/MeOH 100/0 to 85/15) to give final compound 38 (21 mg, 0.065 mmol, 40 %) as brown oil;Four rotamers present (10:6:4:1 ratio).

CI-MS (CH_4): 325 (100 %, $M+H^+$), 305 (12 %, -HF). HRMS Calcd. for $C_{20}H_{21}FN_2O$: 324.1638; Found: 324.1650.

Example B39

2-((2*R*,3a*R*,12b*S*)-2-[(dimethylamino)methyl]-11-fluoro-3,3a,8,12b-tetrahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-1(2*H*)-yl)ethanol (final compound 39)



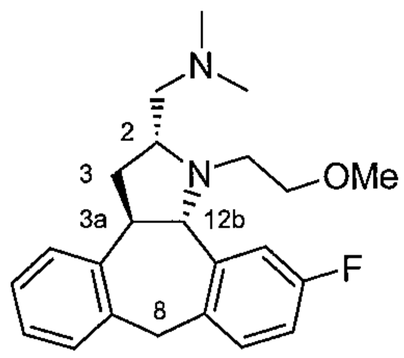
final compound 39

Hydroxyacetaldehyde dimer (2,5-dihydroxy-1,4-dioxane) (240 mg, 2.0 mmol) was dissolved in MeOH (25 mL) and stirred at 40 °C for 30 minutes, then final compound 37 (124 mg, 0.40 mmol) was added and stirring at 40 °C continued for another 30 minutes. After cooling down to room temperature, AcOH (120 mg, 2.0 mmol) was added, followed by sodium cyanoborohydride (188 mg, 3.0 mmol) and the resulting mixture was stirred for 2 hours. After this time it was quenched with concentrated HCl (2 mL), treated with solid $NaHCO_3$ (2.94 g, 35 mmol), 1N NaOH (3 mL). About 20 mL of MeOH was removed *in vacuo*, the residue diluted with water (30 mL), and extracted with EtOAc (3 × 30 mL). The combined organics were washed with water (5 × 25 mL), brine (30 mL), dried (K_2CO_3), evaporated *in vacuo* and purified by column chro-

matography (Kieselgel 60, 230-400 mesh, CH_2Cl_2-MeOH 95/5 to 90/10 to 85/15) to give the final compound 39 (80 mg, 0.244 mmol, 61 %) as colorless oil.
HRMS Calcd. for $C_{22}H_{27}FN_2O$: 354.2107; Found: 354.2107.

Example B40

[(2*R*,3a*R*,12b*S*)-11-Fluoro-1-(2-methoxyethyl)-1,2,3,3a,8,12b-hexahydrodibenzo-[3,4:6,7]-cyclohepta[1,2-*b*]pyrrol-2-yl]-*N*,*N*-dimethylmethanamine (final compound 40)

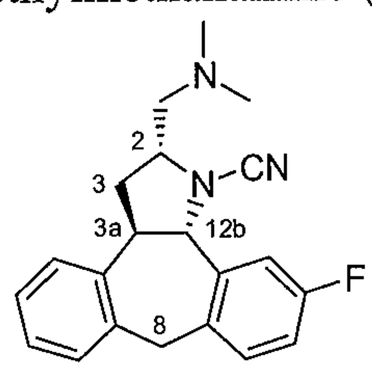


final compound 40

Final compound 39 (50 mg, 0.153 mmol) was dissolved in dry THF (10 mL), then 60 % NaH dispersion (8 mg, 0.2 mmol) was added, followed by dimethyl sulfate (25 mg, 0.2 mmol). The resulting mixture was stirred under argon atmosphere at 60 °C for 5 hours, then cooled, quenched with concentrated NH_4OH (2 mL), diluted with water (40 mL). After extraction of product with EtOAc (3 × 25 mL) the combined organics were washed with water (3 × 25 mL), brine (25 mL), dried over K_2CO_3, evaporated *in vacuo*, and the residue purified by column chromatography (Kieselgel 60, 230-400 mesh, CH_2Cl_2-MeOH 95/5 to 90/10 to 85/15) to give final compound 40 (39 mg, 0.107 mmol, 70 %) as yellowish oil.
HRMS Calcd. for $C_{23}H_{29}FN_2O$: 368.2264; Found: 368.2270.

Example B41

[(2*R*,3a*R*,12b*S*)-1-cyano-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclo-hepta[1,2-*b*]pyrrol-2-yl]-*N*,*N*-dimethylmethanamine (final compound 41)



final compound 41

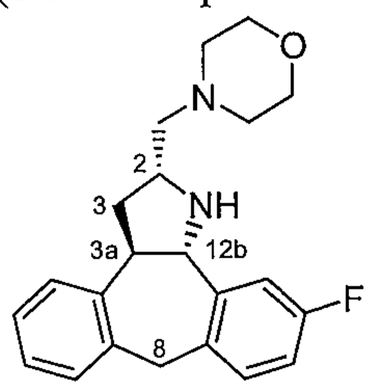
Poly(4-vinylpyridine) crosslinked with 2 % divinylbenzene (0.5 g) was swollen for 1 hour with CH_2Cl_2 (10 mL), then final compound 37 (57 mg, 0.184 mmol) in CH_2Cl_2 (2 mL) was added in one portion, followed by cyanogen bromide (39 mg, 0.367

mmol), then suspension stirred at room temperature for 30 minutes. The resin was filtered off, filtrate treated with sat. aq. K_2CO_3 (10 mL), organic phase was separated, evaporated *in vacuo*, and the residue purified by column chromatography (Kieselgel 60, 230-400 mesh, CH_2Cl_2-MeOH 95/5 to 90/10 → 87/13) to give final compound 41 (24 mg, 0.077 mmol, 42 %) as brownish oil.

CI-MS (CH_4): 308 (100 %, $M+H^+$), 288 (8 %, -HF). HRMS Calcd. for $C_{19}H_{18}FN_3$: 307.1485; Found: 307.1499.

Example B42

(2*R*,3a*R*,12b*S*)-11-fluoro-2-(4-morpholinylmethyl)-1,2,3,3a,8,12b-hexahydrodibenzo-[3,4:6,7]cyclohepta[1,2-*b*]pyrrole (final compound 42)



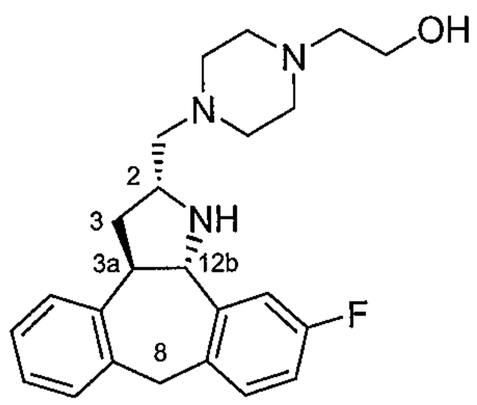
final compound 42

To a solution of intermediate compound 64 (63 mg, 0.237 mmol) in acetonitrile (1 mL) was added NaI (107 mg, 0.711 mmol) and trimethylsilyl chloride (90 µL, 0.711 mmol) at room temperature. After the solution was stirred for 2 hours, morpholine (44 mg, 0.5 mmol) in acetonitrile (0.5 mL) was added dropwise to the mixture. The solution was heated to the boiling point of the solvent for 2 hours. The dark brown reaction mixture was quenched with aqueous 1.2 N HCl solution and then was treated with sat. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with 20 mL of brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on basic alumina (Brockmann III, EtOAc-MeOH, 100/0 to 98/2 to 95/5) gave final compound 42 (38 mg, 0.11 mmol, 45 %) as brownish oil.

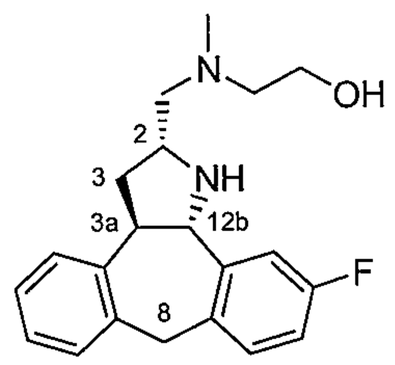
CI-MS (CH_4): 353 (100 %, $M+H^+$); 333 (-HF, 7 %). HRMS Calcd. for $C_{22}H_{25}FN_2O$: 352.1951; Found: 352.1966.

Example B43

2-(4-{[(2*R*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta-[1,2-*b*]pyrrol-2-yl]methyl}-1-piperazinyl)ethanol (final compound 43a) and 2-[{[(2*R*,3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-exahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrrol-2-yl]methyl}(methyl)amino]-ethanol (final compound 43b)



final compound 43a



final compound 43b

A mixture of appropriate intermediate compound 66a or 66b (*ca.* 0.4 mmol), thiophenol (110 mg, 1.0 mmol), anhydrous K_2CO_3 (138 mg, 1 mmol) and DMF (20 mL) was stirred at 80 °C for 4 hours, cooled to ambient temperature, diluted with water, product extracted with EtOAc (3 × 50 mL), combined organics washed with water (4 × 50 mL), brine (35 mL), dried (K_2CO_3), evaporated and purified by solid phase extraction on basic alumina (Brockmann II, heptane-ethyl acetate 50/50, then EtOAc-MeOH 100/0 to 96/4 to 90/10) to give final compound 43a (111 mg, 0.28 mmol, 52 % from intermediate compound 65) or final compound 43b (80 mg, 0.24 mmol, 44 % from intermediate compound 65), both as brownish oils.

Final compound 43a (TK-895):

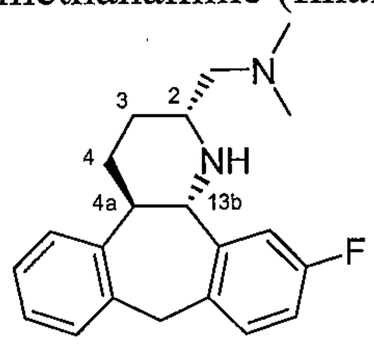
HRMS: Calcd. for $C_{24}H_{30}FN_3O$: 395.2373; Found: 395.2374.

Final compound 43b (TK-1013):

HRMS Calcd. for $C_{21}H_{25}FN_2O$: 340.1951; 340.1943.

Example B44

[(2*R*,4a*R*,13b*S*)-12-fluoro-2,3,4,4a,9,13b-hexahydro-1*H*-dibenzo[3,4:6,7]cyclohepta-[1,2-*b*]pyridin-2-yl]-*N*,*N*-dimethylmethanamine (final compound 44)



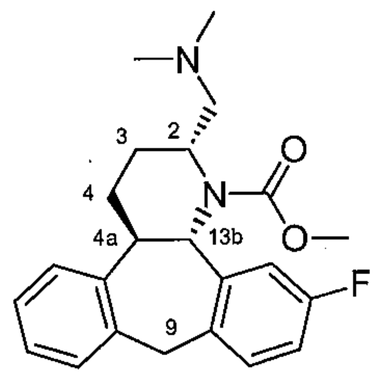
final compound 44

Intermediate compound 67k (153 mg, 0.338 mmol), 40 % aqueous methylamine (15 mL), and THF (35 mL) were heated in stainless-steel bomb at 135°C for 15 hours. After cooling, the bomb was opened, THF and methylamine evaporated *in vacuo*, residue extracted with CH_2Cl_2 (4 × 20 mL). The combined organics were washed with water (3 × 20 mL), dried (K_2CO_3), evaporated and purified by column chromatography (Kieselgel 60, 230-400 mesh, CH_2Cl_2-MeOH 98/2 to 85/15) to afford final compound 44 (32

mg, 0.098 mmol, 29 %) as a brown oil, which was converted to the oxalate salt (final compound 44a).
HRMS Calcd. for $C_{21}H_{25}FN_2$: 324.2002; Found: 324.1995.

Example B45

Methyl (2*R*,4a*R*,13b*S*)-2-[(dimethylamino)methyl]-12-fluoro-2,3,4,4a,9,13b-hexahydro-1*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyridine-1-carboxylate (final compound 45)

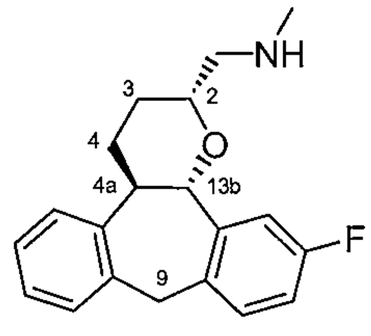


final compound 45

Conversion of final compound 44 (48 mg, 0.15 mmol) with methyl chloroformate was carried out in the same way as described for the preparation of intermediate compound 62. Column chromatography (Kieselgel 60, 70-230 mesh, MeOH-CH_2Cl_2 3/97 to 15/85) afforded final compound 45 (45 mg, 0.118 mmol, 79 %) as colorless oil.
HRMS Calcd. for $C_{23}H_{27}FN_2O_2$: 382.2057; Found: 382.2064.

Example B46

[(2*R*,4a*R*,13b*S*)-12-fluoro-2,3,4,4a,9,13b-hexahydrodibenzo[3,4:6,7]cyclohepta-[1,2-*b*]pyran-2-yl]-*N*-methylmethanamine (final compound 46)

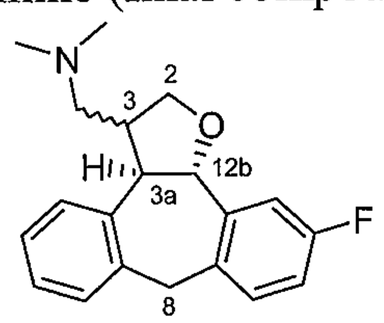


final compound 46

Intermediate compound 68e (282 mg, 0.62 mmol), 40 % aqueous methylamine (25 mL), and THF (35 mL) were heated in a steel bomb at 135 °C for 15 hours. After cooling, bomb was opened, THF and methylamine evaporated *in vacuo*. The residue was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organics were washed with water (3 × 20 mL), dried (K_2CO_3) and evaporated. Crystallization from CH_2Cl_2/hexane gave final compound 46 (70 mg, 0.225 mmol, 36 %) as beige powder.
HRMS Calcd. for $C_{20}H_{22}FNO$: 311.1685; Found: 311.1700.

Example B47

[(3a*R*,12b*S*)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]-furan-3-yl]-*N*,*N*-dimethylmethanamine (final compound 47)



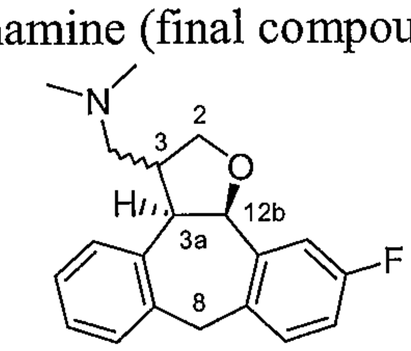
final compound 47

Intermediate compound 69i (122 mg, 0.39 mmol) was dissolved in MeOH (10 mL), 10 % palladium on carbon (40 mg) was added and the mixture submitted to the hydrogenation under atmospheric pressure for 1.5 hour, then 35 % aqueous formaldehyde (1 g) and AcOH (120 mg, 2 mmol) were added, and hydrogenation continued for 2 hours. After filtration through short pad of Celite, and addition of EtOAc (45 mL), the reaction mixture was washed with sat. aq. $NaHCO_3$ (25 mL), water (2 × 50 mL), brine (30 mL), dried over K_2CO_3 and evaporated *in vacuo*. The residue was purified by column chromatography (Kieselgel 60, 70-230 mesh, ethyl acetate-MeOH, 100/0 to 95/5 to 92/8 to 87/13) to afford final compound 47 (77 mg, 0.248 mmol, 63 %) as yellow oil. Product is a mixture of 2 epimers (12.8:1 ratio).

CI-MS (CH_4) 312 (MH^+, 100 %); 292 (MH^+ - HF, 9 %). HRMS Calcd. for $C_{20}H_{22}FNO$: 311.1685; Found: 311.1680.

Example B48

[(3a*R*,12b*R*)-11-fluoro-3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]-furan-3-yl]-*N*,*N*-dimethylmethanamine (final compound 48)



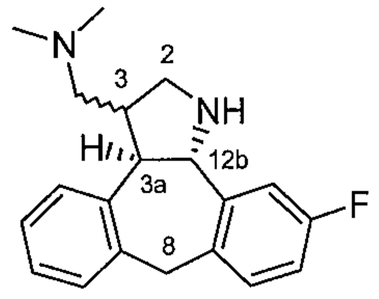
final compound 48

Reaction of intermediate compound 70d (100 mg, 0.304 mmol) was carried out was carried out in the same way as described for final compound 47. Purification by solid phase extraction (Alltech C_{18} 2g cartridge, wter-MeOH, 100/0 to 50/50 to 0/100) furnished final compound 48 (57 mg, 0.18 mmol, 59 %). Product is a mixture of 2 epimers (2:1 ratio).

CI-MS (CH_4) 312 (MH^+, 100 %); 292 (MH^+ - HF, 12 %). HRMS Calcd. for $C_{20}H_{22}FNO$: 311.1685; Found: 311.1692.

Example B49

[(3a*R*,12b*S*)-11-fluoro-1,2,3,3a,8,12b-hexahydrodibenzo[3,4:6,7]cyclohepta [1,2-*b*]-pyrrol-3-yl]-*N*,*N*-dimethylmethanamine (final compound 49)



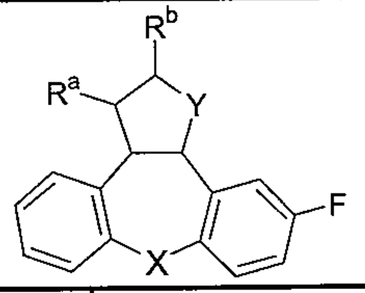
final compound 49

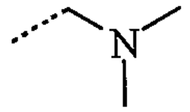
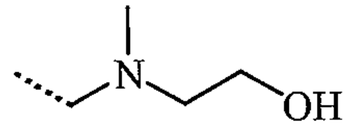
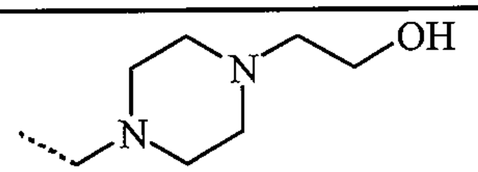
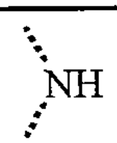
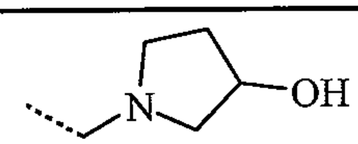
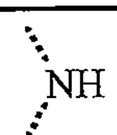
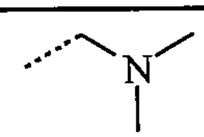
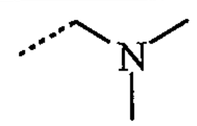
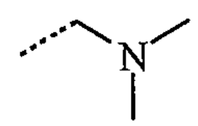
A mixture of intermediate compound 71f (194 mg, 0.53 mmol) and 10 % palladium on carbon (50 mg) in MeOH (35 mL) was hydrogenated at atmospheric pressure for 40 minutes, then 35 % aqueous formaldehyde (1 mL) was added and hydrogenation continued for another 40 minutes. After filtration through short pad of Celite, reaction mixture was evaporated *in vacuo*. The residue was dissolved *i*-PrOH (20 mL), KOH (560 mg, 10 mmol) and water (0.1 mL) were added and resulting solution was refluxed under nitrogen atmosphere for 12 hours (oil bath temperature 135 °C), then cooled to room temperature. After dilution with water (50 mL), extraction with EtOAc (3 × 40 mL), the combined organics were washed with water (3 × 40 mL), brine (40 mL), dried over K_2CO_3 and evaporated *in vacuo*. The residue was purified by column chromatography (basic alumina, Brockmann activity I, EtOAc-MeOH, 100/0 to 85/15) to give pure final compound 49 (102 mg, 0.33 mmol, 62 %) as brown oil. Product is a mixture of 2 epimers (1:1 ratio)

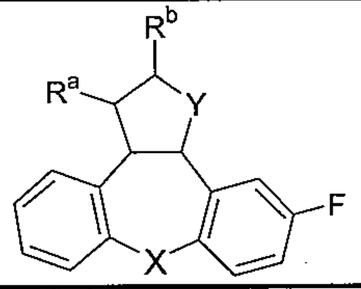
HRMS Calcd. for $C_{20}H_{23}FN_2$: 310.1845; Found: 310.1833.

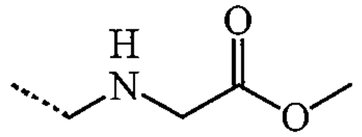
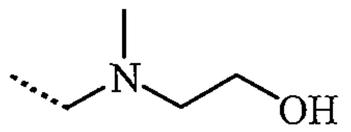
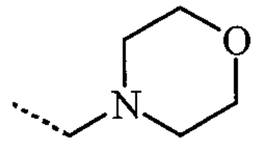
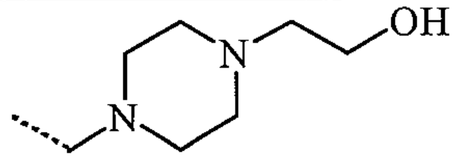
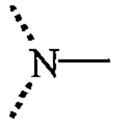
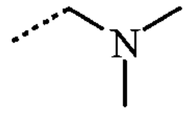
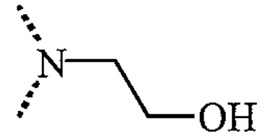
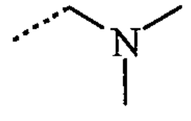
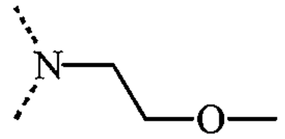
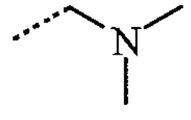
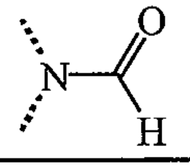
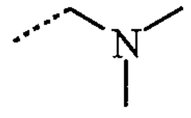
Tables 1-3 list compounds of Formula (I), which were prepared according to one of the above examples.

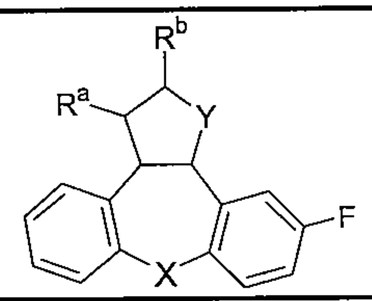
Table 1

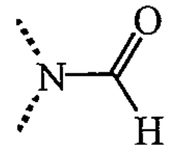
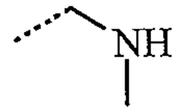
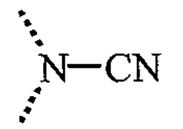
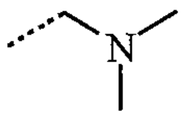
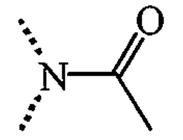
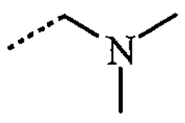
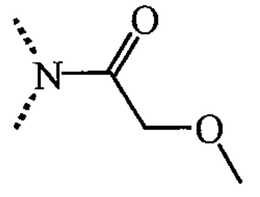
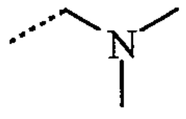
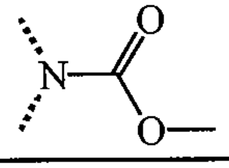
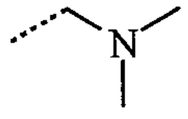
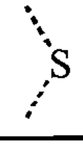
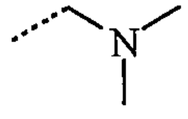
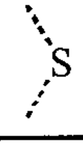
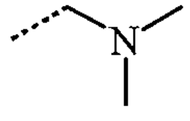
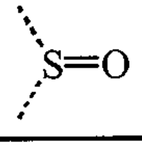
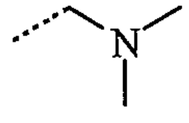


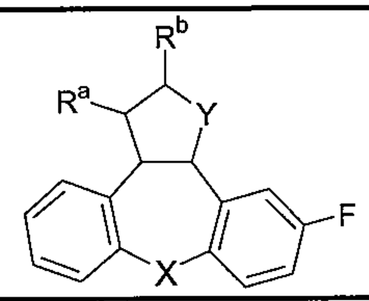
Co. No.	Ex. No.	X	Y	---R^a	---R^b	Stereochemical / salt data
17	B17	-O-		---H		2*R*,3a*R*,12b*S*
18	B18	-O-		---H		2*R*,3a*R*,12b*S*
19	B19	-O-		---H		2*R*,3a*R*,12b*S*
20	B20	-O-		---H		2*R*,3a*R*,12b*S*
2	B2	-CH_2-		---H		2*S*,3a*R*,12b*S*
37	B37	-CH_2-		---H		2*R*,3a*R*,12b*S*
37a	B37	-CH_2-		---H		.HCl 2*R*,3a*R*,12b*S*



Co. No.	Ex. No.	X	Y	---R^a	---R^b	Stereochemical / salt data
11	B11	-CH_2-		---H		2*R*,3a*R*,12b*S*
43b	B43	-CH_2-		---H		2*R*,3a*R*,12b*S*
42	B42	-CH_2-		---H		2*R*,3a*R*,12b*S*
43a	B43	-CH_2-		---H		2*R*,3a*R*,12b*S*
5	B5	-CH_2-		---H		2*R*,3a*R*,12b*S*
39	B39	-CH_2-		---H		2*R*,3a*R*,12b*S*
40	B40	-CH_2-		---H		2*R*,3a*R*,12b*S*
36c	B36c	-CH_2-		---H		2*R*,3a*R*,12b*S*



Co. No.	Ex. No.	X	Y	---R^a	---R^b	Stereochemical / salt data
38	B38	$-CH_2-$		---H		2*R*,3a*R*,12b*S*
41	B41	$-CH_2-$		---H		2*R*,3a*R*,12b*S*
36b	B36	$-CH_2-$		---H		2*R*,3a*R*,12b*S*
10	B10	$-CH_2-$		---H		2*R*,3a*R*,12b*S*
36a	B36	$-CH_2-$		---H		2*R*,3a*R*,12b*S*
21	B21	$-CH_2-$		---H		2*S*,3a*R*,12b*S*
23	B23	$-CH_2-$		---H		2*R*,3a*R*,12b*S*
25	B25	$-CH_2-$		---H		2*S*,3a*R*,12b*S*



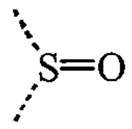
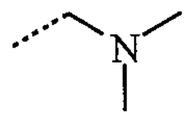
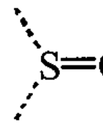
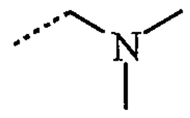
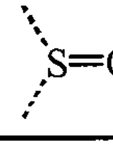
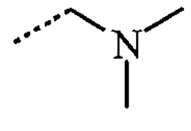
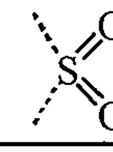
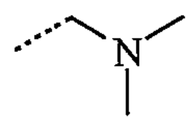
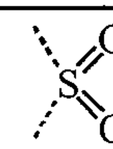
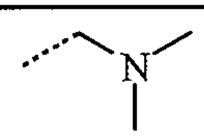
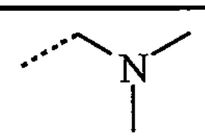
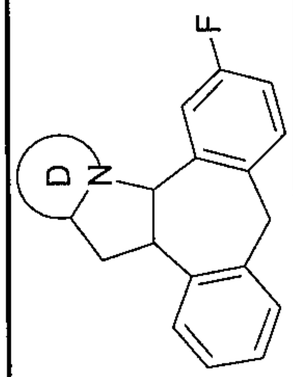
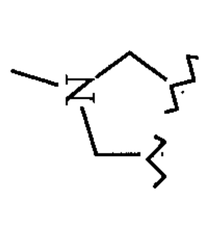
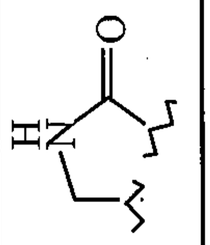
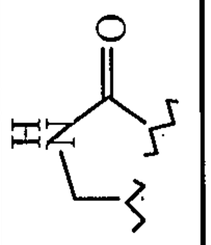
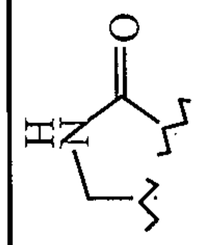
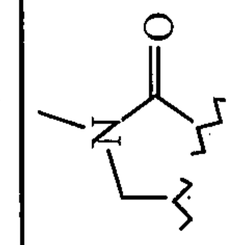
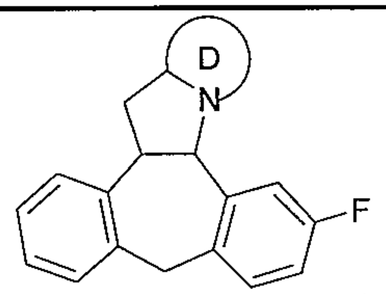
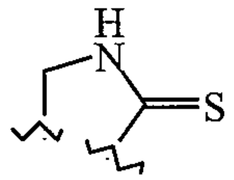
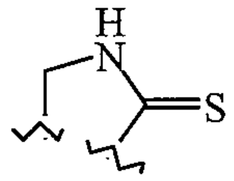
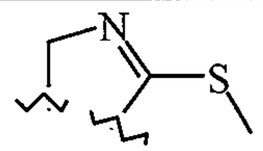
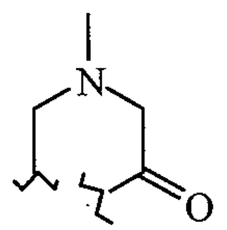
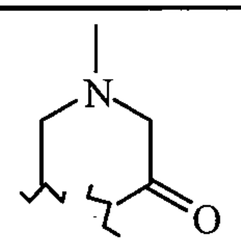
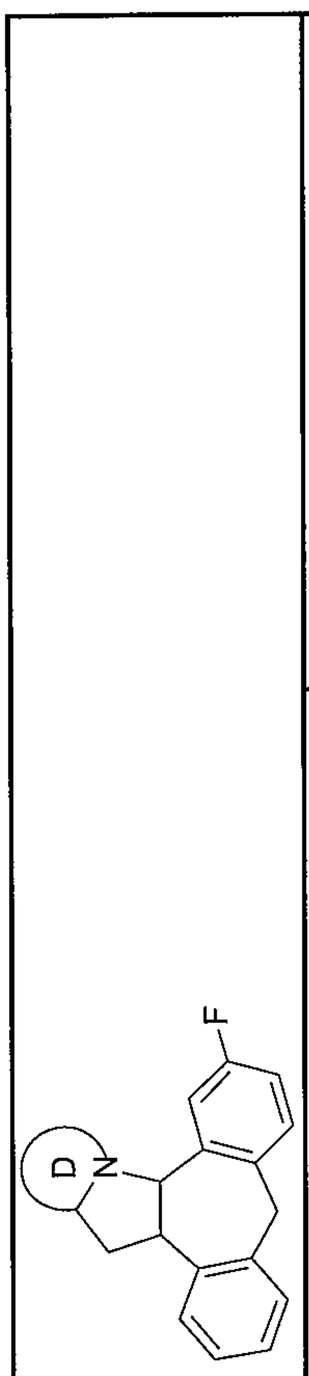
Co. No.	Ex. No.	X	Y	---R^a	---R^b	Stereochemical / salt data
26	B26	-CH_2-		---H		2*S*,3a*R*,12b*S*
27	B27	-CH_2-		---H		2*R*,3a*R*,12b*S*
28	B28	-CH_2-		---H		2*R*,3a*R*,12b*S*
22	B22	-CH_2-		---H		2*S*,3a*R*,12b*S*
24	B24	-CH_2-		---H		2*R*,3a*R*,12b*S*
49	B49	-CH_2-			--H	3a*R*,12b*S*

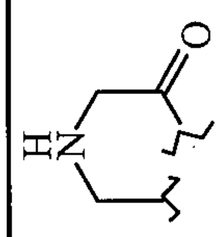
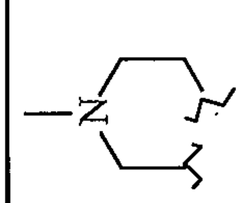
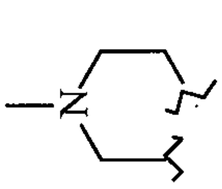
Table 2

	Ex. No.	Stereochemical / salt data	D
	B1	4a*S*,13b*R*,14a*S*	
	B6	4a*S*,13b*R*,14*R*	
	B15	4a*S*,13b*R*,14a*S*	
	B7	4a*S*,13b*R*,14*R*	
	B16	4a*S*,13b*R*,14*S*	
	Co. No.		
	1		
	6		
	15		
	7		
	16		



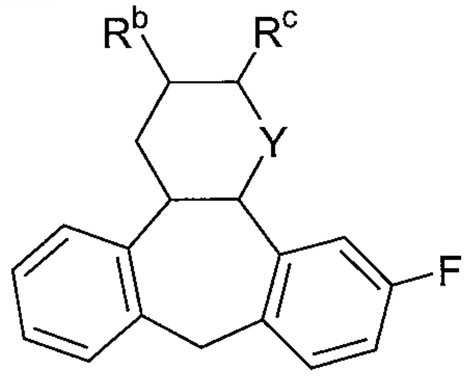
Co. No.	Ex. No.	D	Stereochemical / salt data
8	B8		4a*S*,13b*R*,14*R*
3	B3		4a*S*,13b*R*,14*S*
9	B9		4a*S*,13b*R*,14*R*
4	B4		5a*S*,14b*R*,15a*S*
13	B13		5a*S*,14b*R*,15a*R*

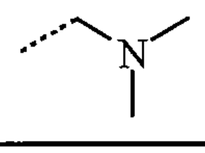


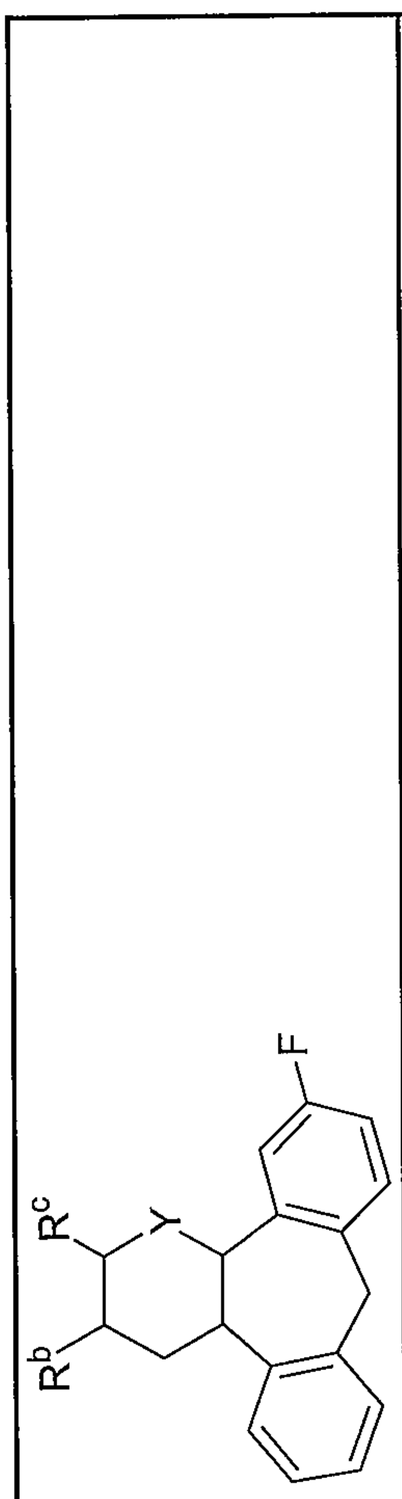
Co. No.	Ex. No.	D	Stereochemical / salt data
12	B12		5a*S*,14b*R*,15a*R*
14	B14		5a*S*,14b*R*,15a*R*
14a	B14		Oxalate (1:1) 5a*S*,14b*R*,15a*R*

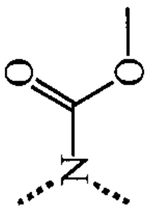
CA 02604165 2007-10-05

Table 3



Co. No.	Ex. No.	---Y---	---R^b	----R^c	Stereochemical / salt data
29	B29		---OH	---H	3*R*,4a*R*,13b*R*
31	B31		=O	---H	4a*R*,13b*R*
34	B34		=O	---H	4a*R**,13b*S**
30	B30		---NH_2	---H	3*S*,4a*R*,13b*R*
33	B33		----NH—CH_3	---H	3*R*,4a*R*,13b*R*
35	B35		----NH—CH_3	---H	3*S**,4a*R**,13b*S**
32	B32			---H	3*S*,4a*R*,13b*R*



Ex. No.	---Y---	---R^b	---R^c	Stereochemical / salt data	Co. No.
B46	---O---	---H		2*R*,4a*R*,13b*S*	46
B44	---NH---	---H		2*R*,4a*R*,13b*S*	44
B44	---NH---	---H		oxalate (1:2) 2*R*,4a*R*,13b*S*	44a
B45		---H		2*R*,4a*R*,13b*S*	45

C. Pharmacological Examples

Example C.1 : *In vitro* binding affinity for 5-HT_{2A} and 5-HT_{2C} receptors

The interaction of the compounds of Formula (I) with 5-HT_{2A} and 5-HT_{2C} receptors was assessed in *in vitro* radioligand binding experiments. In general, a low concentration of a radioligand with a high binding affinity for the receptor is incubated with a sample of a tissue preparation enriched in a particular receptor (1 to 5 mg tissue) in a buffered medium (0.2 to 5 ml). During the incubation, the radioligands bind to the receptor. When equilibrium of binding is reached, the receptor bound radioactivity is separated from the non-bound radioactivity, and the receptor bound activity is counted. The interaction of the test compounds with the receptors is assessed in competition binding experiments. Various concentrations of the test compound are added to the incubation mixture containing the tissue preparation and the radioligand. Binding of the radioligand will be inhibited by the test compound in proportion to its binding affinity and its concentration. The affinities of the compounds for the 5-HT_2 receptors were measured by means of radioligand binding studies conducted with: (a) human cloned 5-HT_{2A} receptor, expressed in L929 cells using [^{125}I]R91150 as radioligand and (b) human cloned 5-HT_{2C} receptor, expressed in CHO cells using [^{3}H]mesulergine as radioligand.

Example C.2 : *In vitro* determination of NET reuptake inhibition

Cortex from rat brain was collected and homogenised using an Ultra-Turrax T25 and a Dual homogeniser in ice-cold homogenising buffer containing Tris, NaCl and KCl (50 mM, 120 mM and 5 mM, respectively, pH 7.4) prior to dilution to an appropriate protein concentration optimised for specific and non-specific binding. Binding was performed with radioligand [^{3}H]Nixosetine (NEN, NET-1084, specific activity ~70 Ci/mmol) diluted in ice cold assay buffer containing Tris, NaCl and KCl (50 mM, 300 mM and 5 mM, respectively, pH 7.4). at a concentration of 20 nmol/L. Prepared radioligand (50 µl) was then incubated (60 min, 25 °C) with membrane preparations prediluted to an appropriate protein concentration (400 µl), and with 50 µl of either the 10 % DMSO control, Mazindol (10^{-6} mol/L final concentration), or compound of interest. Membrane-bound activity was detected by filtration through a Packard Filtermate harvester onto GF/B Unifilterplates, washed with ice-cold Tris-HCl buffer, containing NaCl and KCl (50 mM, 120 mM and 4 mM; pH 7.4; 6 × 0.5 ml). Filters were allowed to dry for 24 h before adding scintillation fluid. Scintillation fluid was allowed to saturate filters for 24 h before counting in a Topcount scintillation counter. Percentage specific bound and competition binding curves were calculated using S-Plus software (Insightful).

Example C.3 : *In vitro* binding affinity for human $D2_L$ receptor

Frozen membranes of human Dopamine $D2_L$ receptor-transfected CHO cells were thawed, briefly homogenised using an Ultra-Turrax T25 homogeniser and diluted in Tris-HCl assay buffer containing NaCl, $CaCl_2$, $MgCl_2$, KCl (50, 120, 2, 1, and 5 mM respectively, adjusted to pH 7.7 with HCl) to an appropriate protein concentration optimised for specific and non-specific binding. Radioligand [^{3}H]Spiperone (NEN, specific activity ~70 Ci/mmol) was diluted in assay buffer at a concentration of 2 nmol/L. Prepared radioligand (50 µl), along with 50 µl of either the 10 % DMSO control, Butaclamol (10^{-6} mol/l final concentration), or compound of interest, was then incubated (30 min, 37 °C) with 400 µl of the prepared membrane solution. Membrane-bound activity was filtered through a Packard Filtermate harvester onto GF/B Unifilterplates and washed with ice-cold Tris-HCl buffer (50 mM; pH 7.7; 6 × 0.5 ml). Filters were allowed to dry before adding scintillation fluid and counting in a Topcount scintillation counter. Percentage specific bound and competition binding curves were calculated using S-Plus software (Insightful).

Table 4 : Pharmacological data. n.d. = not determined

Co.No.	h-$5HT_{2A}$	h-$5HT_{2C}$	h-D2L	NET Reuptake Inhibition
17	6.24	6.30	5.63	8.13
37a	7.35	7.30	6.45	8.10
47	5.42	5.80	n.d.	7.96
43b	7.17	7.05	6.36	7.80
32	6.17	6.88	< 6	7.71
23	6.18	6.64	5.30	7.55
1	6.94	6.82	5.65	6.94
39	7.06	7.33	< 6	6.90
28	5.11	5.75	n.d.	6.84
48	5.21	5.52	n.d.	6.65
36c	6.26	7.11	5.31	6.65
5	7.56	8.27	6.88	6.54
30	6.57	6.84	< 6	6.52
46	7.86	8.23	5.20	6.40
20	n.d.	6.96	6.45	6.38
40	6.43	6.58	< 6	6.32

Co.No.	h-5HT$_{2A}$	h-5HT$_{2C}$	h-D2L	NET Reuptake Inhibition
38	6.20	6.73	5.15	6.31
36a	< 6	< 6	< 6	6.16
45	n.d.	5.65	< 5	6.10
7	< 6	< 6	< 6	6.05
8	7.07	6.60	< 5	5.66
15	5.08	5.63	<5	5.62
25	< 5	5.65	n.d.	5.54
14a	8.90	9.05	8.81	5.50
12	n.d.	7.23	6.08	5.46
36b	< 6	< 6	<6	5.41
9	< 6	< 6	<6	5.40
22	5.07	5.87	n.d.	5.32
10	6.16	6.37	< 6	5.32
42	6.20	6.26	n.d.	5.26
3	< 6	6.62	< 6	5.24
13	7.06	6.92	6.37	< 5
35	< 6	5.58	< 6	< 6
43a	6.37	6.39	n.d.	< 5
26	< 5	< 5	< 5	< 5
19	n.d.	5.37	6.95	< 5
16	< 5	< 5	< 5	< 5
4	< 6	< 6	< 6	< 5

D. Composition Examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of Formula (I), a pharmaceutically acceptable acid addition salt, a stereochemically isomeric form thereof or a *N*-oxide form thereof.

Example D.1 : ORAL SOLUTION

Methyl 4-hydroxybenzoate (9 g) and propyl 4-hydroxybenzoate (1 g) were dissolved in boiling purified water (4 l). In 3 l of this solution were dissolved first 2,3-dihydroxybutanedioic acid (10 g) and thereafter A.I (20 g). The latter solution was combined with the remaining part of the former solution and 1,2,3-propanetriol (12 l) and sorbitol 70 % solution (3 l) were added thereto. Sodium saccharin (40 g) were dis-

solved in water (500 ml) and raspberry (2 ml) and gooseberry essence (2 ml) were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example D.2 : FILM-COATED TABLETS

Preparation of tablet core

A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinylpyrrolidone (10 g) in water (200 ml). The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

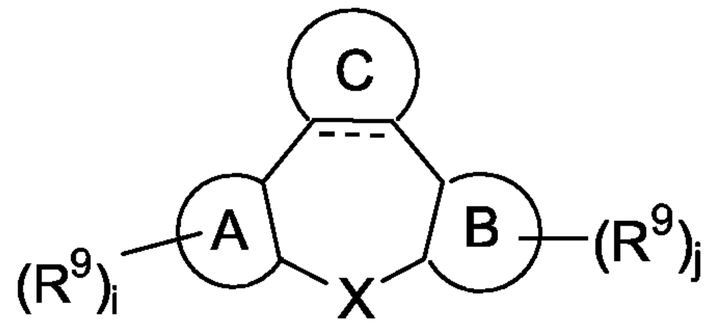
To a solution of methyl cellulose (10 g) in denaturated ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in dichloromethane (150 ml). Then there were added dichloromethane (75 ml) and 1,2,3-propanetriol (2.5 ml). Polyethylene glycol (10 g) was molten and dissolved in dichloromethane (75 ml). The latter solution was added to the former and then there were added magnesium octadecanoate (2.5 g), polyvinylpyrrolidone (5 g) and concentrated colour suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example D.3 : INJECTABLE SOLUTION

Methyl 4-hydroxybenzoate (1.8 g) and propyl 4-hydroxybenzoate (0.2 g) were dissolved in boiling water (500 ml) for injection. After cooling to about 50 °C there were added while stirring lactic acid (4 g), propylene glycol (0.05 g) and A.I. (4 g). The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1000 ml, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

Claims

1. A compound according to Formula (I)



(I)

an N-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

the dotted line represents an optional bond ;

i and j are integers, independently from each other, equal to zero, 1, 2, 3 or 4 ;

A and B are, each independently from each other, aryl or an heteroaryl radical selected from the group of furyl ; thienyl ; pyrrolyl ; oxazolyl ; thiazolyl ; imidazolyl ; isoxazolyl ; isothiazolyl ; oxadiazolyl ; triazolyl ; pyridinyl; pyridazinyl ; pyrimidinyl ; pyrazinyl ; indolyl ; indolizinyl ; isoindolyl ; benzofuryl ; isobenzofuryl ; benzothienyl ; indazolyl ; benzimidazolyl ; benzthiazolyl ; quinolizinyl ; quinolinyl ; isoquinolinyl ; phthalazinyl ; quinazolinyl ; quinoxalinyl ; chromenyl ; naphthyridinyl and naphthalenyl ;

each R^9 is, independently from each other, selected from the group of hydrogen ; halo ; cyano ; hydroxy ; carboxyl ; nitro ; amino ; mono- or di(alkyl)-amino; alkylcarbonylamino ; aminosulfonyl ; mono- or di(alkyl)-aminosulfonyl ; alkyl; alkyloxy ; alkylcarbonyl and alkyloxycarbonyl ;

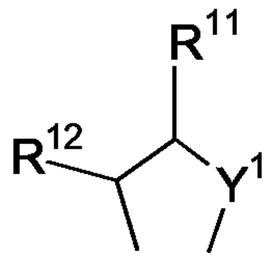
X represents CR^6R^7, O, S, S(=O), $S(=O)_2$ or NR^8 ; wherein :

R^6 and R^7 each independently are selected from the group of hydrogen, hydroxy, alkyl and alkyloxy; or

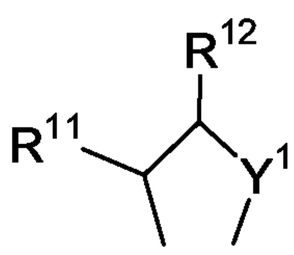
R^6 and R^7 taken together may form a radical selected from the group of methylene ($=CH_2$) ; mono- or di(cyano)methylene ; a bivalent radical of Formula $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$; or together with the carbon atom to which they are attached, a carbonyl ;

R^8 is selected from the group of hydrogen ; alkyl ; alkylcarbonyl ; arylcarbonyl ; arylalkyl ; arylalkylcarbonyl ; alkylsulfonyl ; arylsulfonyl and arylalkylsulfonyl ;

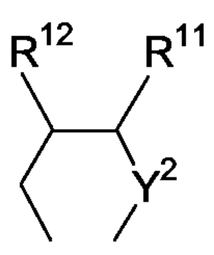
C is a group of formula (c-1), (c-2), (c-3), (c-4) or (c-5) ;



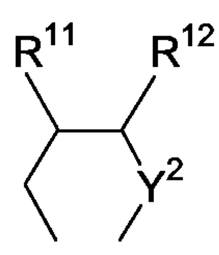
(c-1)



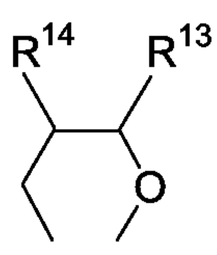
(c-2)



(c-3)



(c-4)



(c-5)

wherein :

Y^1 and Y^2 each independently are S ; O ; S(=O) ; $S(=O)_2$ or NR^{10}; wherein

R^{10} is selected from the group of hydrogen, cyano, alkyl, alkyloxyalkyl, formyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkylcarbonyl, arylcarbonyl, arylalkyl, arylalkylcarbonyl, alkylsulfonyl, arylsulfonyl and arylalkylsulfonyl ;

R^{10} and R^{11} may form together a bivalent radical (e-1) to (e-5);

$-CH_2-NH-CH_2-$ (e-1)

$-CH_2-NH-CH_2-CH_2-$ (e-2)

$-CH_2CH_2-NH-CH_2-$ (e-3)

$-CH=N-CH_2-$ (e-4)

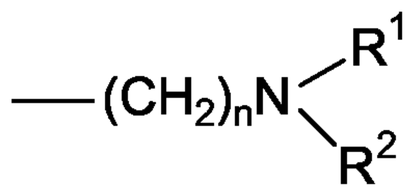
$-CH_2-N=CH_2-$ (e-5)

wherein optionally in each radical (e-1) to (e-5) one or more hydrogens are replaced by one or more substituents selected from alkyl, -O-alkyl, -S-alkyl =O, =S, =S(=O) and $=S(=O)_2$;

R^{12} is hydrogen or alkyl ;

R^{13}, R^{14} each independently are hydrogen, hydroxy or oxo ;

R^{11} is a group of formula (d-1) ;



(d-1)

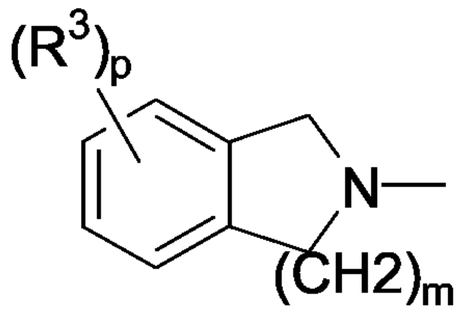
wherein :

n is zero, 1, 2, 3, 4, 5 or 6 ;

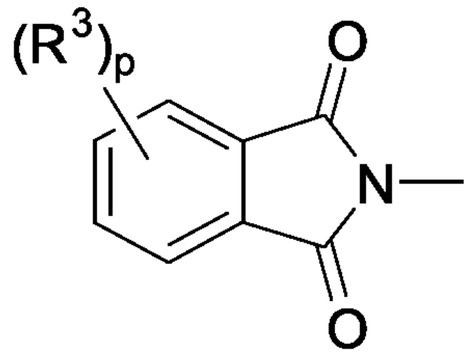
R^1 and R^2 each independently are hydrogen ; alkyl ; alkylcarbonyl ; alkyloxyalkyl ; alkylcarbonyloxyalkyl ; alkyloxycarbonylalkyl; arylalkyl ; arylcarbonyl ; alkyloxycarbonyl ; aryloxycarbonyl; arylalkylcarbonyl ; alkyloxycarbonylalkylcarbonyl ; mono- or di(alkyl)aminocarbonyl ; mono- or di(aryl)aminocarbonyl ; mono- or di(arylalkyl)aminocarbonyl ; mono- or di(alkyloxycarbonylalkyl)aminocarbonyl ; alkylsulphonyl ;

arylsulphonyl ; arylalkylsulphonyl ; mono- or di(alkyl)-aminothiocarbonyl ; mono-or di(aryl)aminothiocarbonyl ; mono- or di(arylalkyl)aminothiocarbonyl; mono-, di- or tri-(alkyl)amidino ; mono-, di- or tri(aryl)amidino and mono-, di- or tri(arylalkyl)amidino ; or

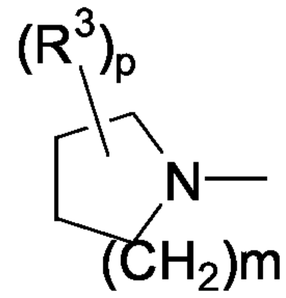
R^1 and R^2 taken together with the nitrogen atom to which they are attached may form a radical of formula (a-1), (a-2), (a-3), (a-4), (a-5) or (a-6) ;



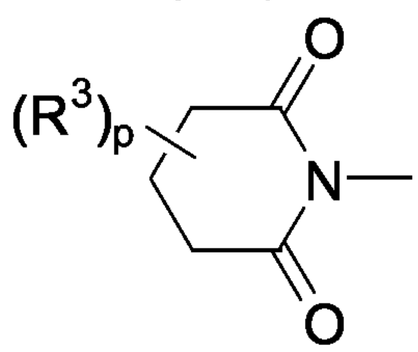
(a-1)



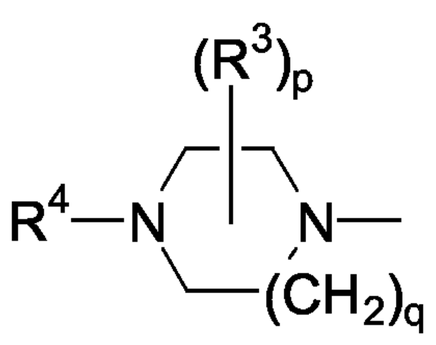
(a-2)



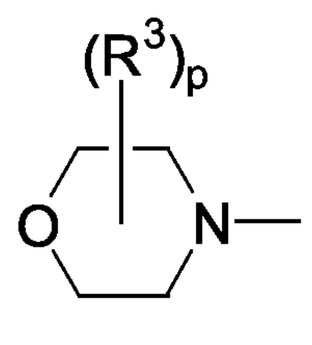
(a-3)



(a-4)



(a-5)



(a-6)

wherein :

p is zero, 1, 2, 3 or 4 ;

q is 1 or 2 ;

m is zero, 1, 2, or 3 ;

each R^3 independently is selected from the group of hydrogen ; halo ; hydroxy; cyano ; alkyl ; alkyloxyalkyl ; aryloxyalkyl ; mono- or di(alkyl)aminoalkyl ; hydroxycarbonylalkyl ; alkyloxycarbonylalkyl ; mono- or di(alkyl)aminocarbonylalkyl ; mono- or di(aryl)aminocarbonylalkyl ; mono- or di(alkyl)aminocarbonyloxyalkyl; alkyloxycarbonyloxyalkyl ; arylaminocarbonyloxyalkyl ; arylalkylaminocarbonyloxyalkyl ; aryl ; alkyloxy ; aryloxy ; alkylcarbonyloxy ; arylcarbonyloxy ; arylalkylcarbonyloxy ; alkylcarbonyl ; arylcarbonyl ; aryloxycarbonyl ; hydroxycarbonyl ; alkyloxycarbonyl ; alkylcarbonylamino ; arylalkylcarbonylamino ; arylcarbonylamino ; alkyloxycarbonylamino ; amino-

carbonylamino ; mono- or di(arylalkyl)aminocarbonylamino ; alkylsulphonylalkylaminocarbonylamino ; or two R^3-radicals may form together a bivalent radical

$-CR^5R^5-CR^5R^5-O-$ (b-1)

$-O-CR^5R^5-CR^5R^5-$ (b-2)

$-O-CR^5R^5-CR^5R^5-O-$ (b-3)

$-O-CR^5R^5-CR^5R^5-CR^5R^5-$ (b-4)

$-CR^5R^5-CR^5R^5-CR^5R^5-O-$ (b-5)

$-O-CR^5R^5-CR^5R^5-CR^5R^5-O-$ (b-6)

$-O-CR^5R^5-CR^5R^5-CR^5R^5-CR^5R^5-$ (b-7)

$-CR^5R^5-CR^5R^5-CR^5R^5-CR^5R^5-O-$ (b-8)

$-O-CR^5R^5-CR^5R^5-CR^5R^5-O-$ (b-9)

wherein R^5 is selected from the group of hydrogen, halo, hydroxy, alkyloxy and alkyl ;

R^4 is selected from the group of hydrogen ; alkyl ; arylalkyl ; alkyloxyalkyl ; alkylcarbonyloxyalkyl ; alkyloxycarbonylalkyl ; arylcarbonylalkyl ; alkylsulphonyloxyalkyl ; aryloxyaryl ; alkyloxycarbonylaryl ; alkylcarbonyl ; arylalkylcarbonyl ; alkyloxycarbonylalkylcarbonyl ; arylcarbonyl ; alkyloxycarbonyl ; aryloxycarbonyl ; arylalkyloxycarbonyl ; mono- or di(alkyl)aminocarbonyl ; mono- or di(aryl)aminocarbonyl ; mono-or di(arylalkyl)aminocarbonyl ; mono- or di(alkyloxycarbonylalkyl)aminocarbonyl ; alkyloxyalkylaminocarbonyl ; mono-, di- or tri(alkyl)amidino ; mono-, di- or tri(aryl)amidino ; mono-, di- or tri(arylalkyl)amidino ; alkylsulphonyl ; arylalkylsulphonyl or arylsulphonyl ;

aryl is phenyl or naphthyl ; each radical optionally substituted with 1, 2 or 3 substituents selected from the group of halo, nitro, cyano, hydroxy, alkyloxy or alkyl ;

alkyl represents a straight or branched saturated hydrocarbon radical having from 1 to 10 carbon atoms, a cyclic saturated hydrocarbon radical having from 3 to 8 carbon atoms or a saturated hydrocarbon radical containing a straight or branched moiety having from 1 to 10 carbon atoms and a cyclic moiety having from 3 to 8 carbon atoms, optionally substituted with one or more halo, cyano, oxo, hydroxy, formyl, carboxyl or amino radicals ; and

halo represents fluoro, chloro, bromo and iodo.

2. A compound according to claim 1, wherein A and B are each phenyl, optionally substituted with fluor.

3. A compound according to claim 1, wherein X is CH_2 or O.

4. A compound according to anyone of claims 1 to 3, wherein C is a group of formula (c-1) or (c-2) ; wherein

Y^1 is S ; S(=O) ; $S(=O)_2$ or NR^{10}; wherein R^{10} is selected from the group of hydrogen, cyano, alkyl, alkyloxyalkyl, formyl, alkylcarbonyl, alkyloxycarbonyl and alkyloxyalkylcarbonyl ; or adjacent R^{10} and R^{11} may form together a bivalent radical (e-1), (e-2) or (e-5) ; wherein optionally in each radicalone or more hydrogens are replaced by one or more substituents selected from =O, =S, =S(=O), alkyl and alkylthio ; and

R^{12} is hydrogen.

5. A compound according to anyone of claims 1 to 3, wherein C is a group of formula (c-3) or (c-4) ; wherein

Y^2 is O or NH ; and

R^{12} is hydrogen.

6. A compound according to anyone of claims 1 to 3, wherein C is a group of formula (c-5) ; wherein

R^{13} is hydrogen ; and

R^{14} is hydroxy or oxo.

7. A compound according to anyone of claims 1 to 6, wherein R^{11} is defined as a group of formula (d-1) wherein :

n is zero or 1 ;

R^1 and R^2 each independently are hydrogen ; alkyl or alkyloxycarbonylalkyl ; or R^1 and R^2 taken together with the nitrogen atom to which they are attached may form a radical of formula (a-3), (a-5) or (a-6) ; wherein :

p is zero or 1 ;

q is 1 ;

m is 1 ;

each R^3 independently is selected from the group of hydrogen and hydroxy; and

R^4 is alkyl.

8. A compound according to claim1, wherein :

i and j are integers, independently from each other, equal to zero or 1 ;

A and B are, each independently from each other, phenyl, optionally substituted with fluor ;

each R^9 is, independently from each other, selected from the group of hydrogen and halo ;

X is CH_2 and O ;

C is a group of formula (c-1) or (c-2) ; wherein

Y^1 is S ; S(=O) ; $S(=O)_2$ or NR^{10}; wherein R^{10} is selected from the group of hydrogen, cyano, alkyl, alkyloxyalkyl, formyl, alkylcarbonyl, alkyloxycarbonyl and alkyloxyalkylcarbonyl ; or adjacent R^{10} and R^{11} may form together a bivalent radical (e-1), (e-2) or (e-5) ; wherein optionally in each radicalone or more hydrogens are replaced by one or more substituents selected from =O, =S, =S(=O), alkyl and alkylthio ; and

R^{12} is hydrogen ; <u>or</u>

C is a group of formula (c-3) or (c-4) ; wherein

Y^2 is O or NH ; and

R^{12} is hydrogen ; <u>or</u>

C is a group of formula (c-5) ; wherein

R^{13} is hydrogen ; and

R^{14} is hydroxy or oxo ;

R^{11} is a group of formula (d-1) ; wherein :

n is zero or 1 ;

R^1 and R^2 each independently are hydrogen ; alkyl or alkyloxycarbonylalkyl ; or R^1 and R^2 taken together with the nitrogen atom to which they are attached may form a radical of formula (a-3), (a-5) or (a-6) ; wherein:

p is zero or 1 ;

q is 1 ;

m is 1 ;

each R^3 independently is selected from the group of hydrogen and hydroxy ; and

R^4 is alkyl.

9. A compound according to any one of claims 1 to 8 for use as a medicine.

10. The use of a compound according to any one of claims 1 to 8 for the manufacture of a medicament for the treatent of conditions, either prophylactic or therapeutic or both, mediated through the 5-HT_2, and D2 receptor, as well as the through norepinephrine reuptake inhibition.

11. The use of a compound according to any one of claims 1 to 8 for the manufacture of a medicament for the treatment and/or prevention of central nervous system disorders like anxiety, depression and mild depression, bipolar disorders, sleep- and sexual disorders, psychosis, borderline psychosis, schizophrenia, migraine, personality disorders or obsessive-compulsive disorders, social phobias or panic attacks, organic mental disorders, mental disorders in children, aggression, memory disorders and attitude disorders in older people, addiction, obesity, bulimia and similar disorders.

12. The use of a compound according to any one of claims 1 to 8 for the manufacture of a medicament for the treatment and/or prevention of anxiety, depression, psychosis, schizophrenia, migraine and addictive properties of drugs of abuse.

13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to any one of claims 1 to 8.

14. A process for the preparation of a composition as claimed in claim 13, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8.