



(86) Date de dépôt PCT/PCT Filing Date: 2002/12/02

(87) Date publication PCT/PCT Publication Date: 2003/06/12

(85) Entrée phase nationale/National Entry: 2004/05/21

(86) N° demande PCT/PCT Application No.: EP 2002/013560

(87) N° publication PCT/PCT Publication No.: 2003/048146

(30) Priorité/Priority: 2001/12/07 (01204961.5) EP

(51) Cl.Int.⁷/Int.Cl.⁷ C07D 307/93, A61K 31/34

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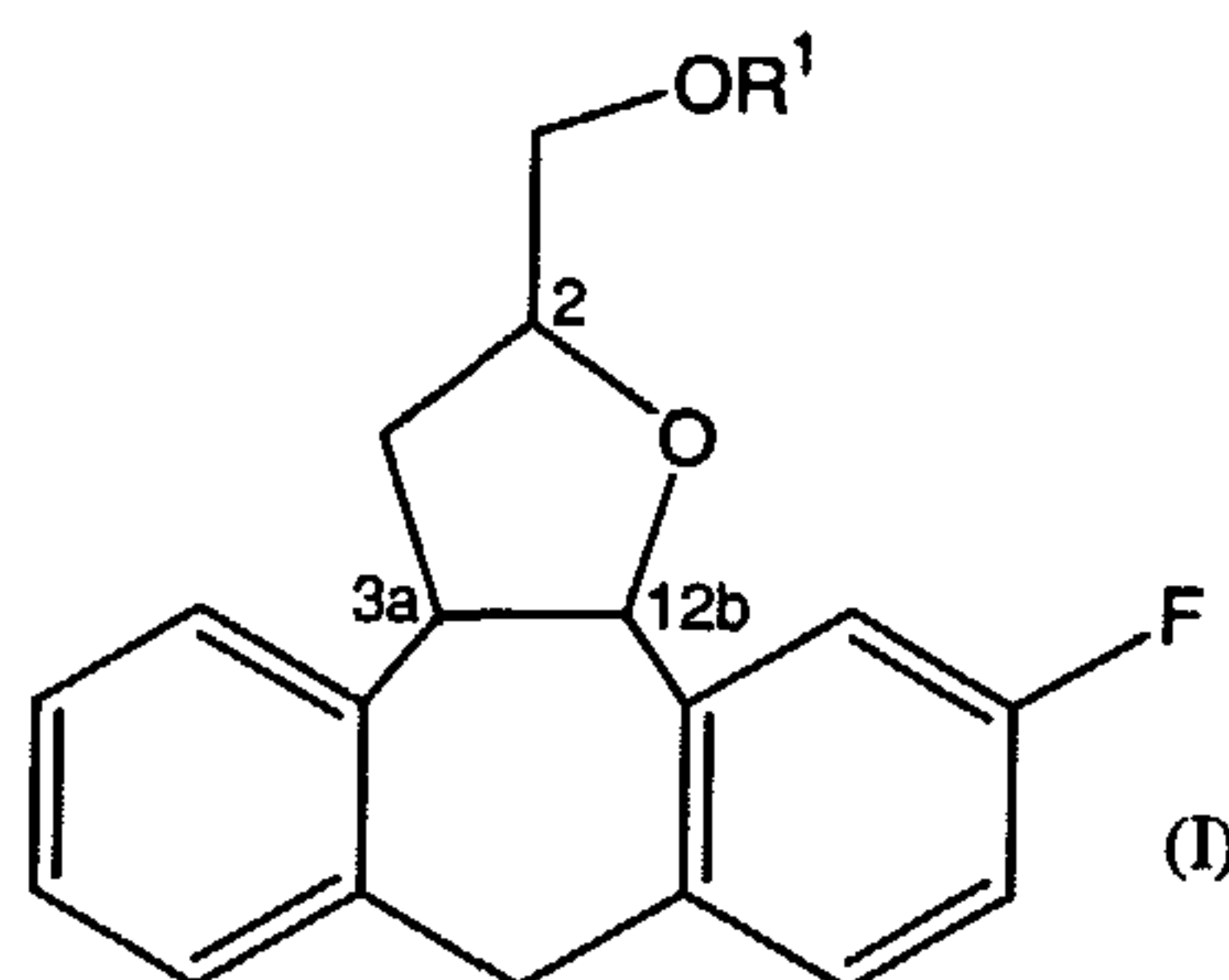
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(54) Titre : PREPARATION DE DERIVES DE 3,3a,b,12b-TETRAHYDRO-2H-DIBENZO[3,4:6,7]CYCLOHEPTA[1,2-b]FURANE A FUSION TRANS

(54) Title: PREPARATION OF TRANS-FUSED 3,3a,b,12b-TETRAHYDRO-2H-DIBENZO[3,4:6,7]CYCLOHEPTA[1,2-b]FURAN DERIVATIVES



(57) **Abrégé/Abstract:**

The present invention concerns processes for the preparation of each of the 4 diastereomers of formula (I): in stereochemically pure form from either of two enantiomerically pure precursors. The tetracyclic ringsystem having trans-fused five and seven membered rings is formed in an acid-catalysed cyclization reaction. The invention further relates to the thus obtained cis-fused tetracyclic alcohol intermediates, the methanamine end-products, the methanamine end-products for use as a medicine, in particular as CNS active medicines.



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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
12 June 2003 (12.06.2003)

PCT

(10) International Publication Number
WO 03/048146 A1(51) International Patent Classification⁷: **C07D 307/93**,
A61K 31/34Development, Groot Begijnhof, Benedenstraat 59, B-3000
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(21) International Application Number: PCT/EP02/13560

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(22) International Filing Date: 2 December 2002 (02.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01204961.5 7 December 2001 (07.12.2001) EP(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.(71) Applicant (*for all designated States except US*):
JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turn-
houtseweg 30, B-2340 Beerse (BE).(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

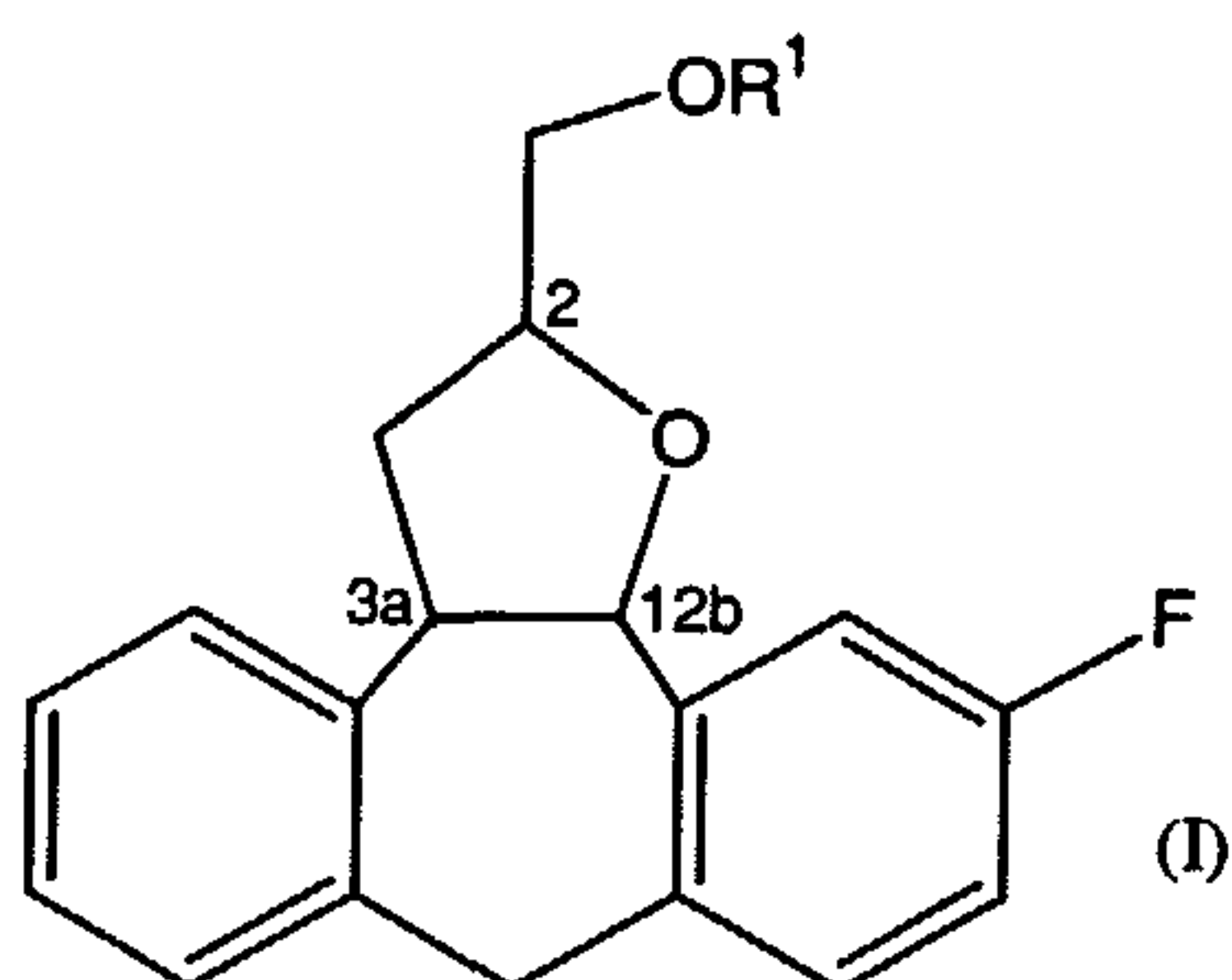
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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent
(GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR),
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG)*

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(54) Title: PREPARATION OF TRANS-FUSED 3,3a,8,12b-TETRAHYDRO-2H-DIBENZO[3,4:6,7]CYCLOHEPTA[1,2-b]FU-
RAN DERIVATIVES

(57) Abstract: The present invention concerns processes for the preparation of each of the 4 diastereomers of formula (I): in stereochemically pure form from either of two enantiomerically pure precursors. The tetracyclic ringsystem having trans-fused five and seven membered rings is formed in an acid-catalysed cyclization reaction. The invention further relates to the thus obtained cis-fused tetracyclic alcohol intermediates, the methanamine end-products, the methanamine end-products for use as a medicine, in particular as CNS active medicines.

WO 03/048146 A1



- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *of inventorship (Rule 4.17(iv)) for US only*

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.

Published:

- *with international search report*

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PREPARATION OF TRANS-FUSED 3,3a,8,12b-TETRAHYDRO-2H-DIBENZO[3,4:6,7]CYCLOHEPTA[1,2-b]FURAN DERIVATIVES.

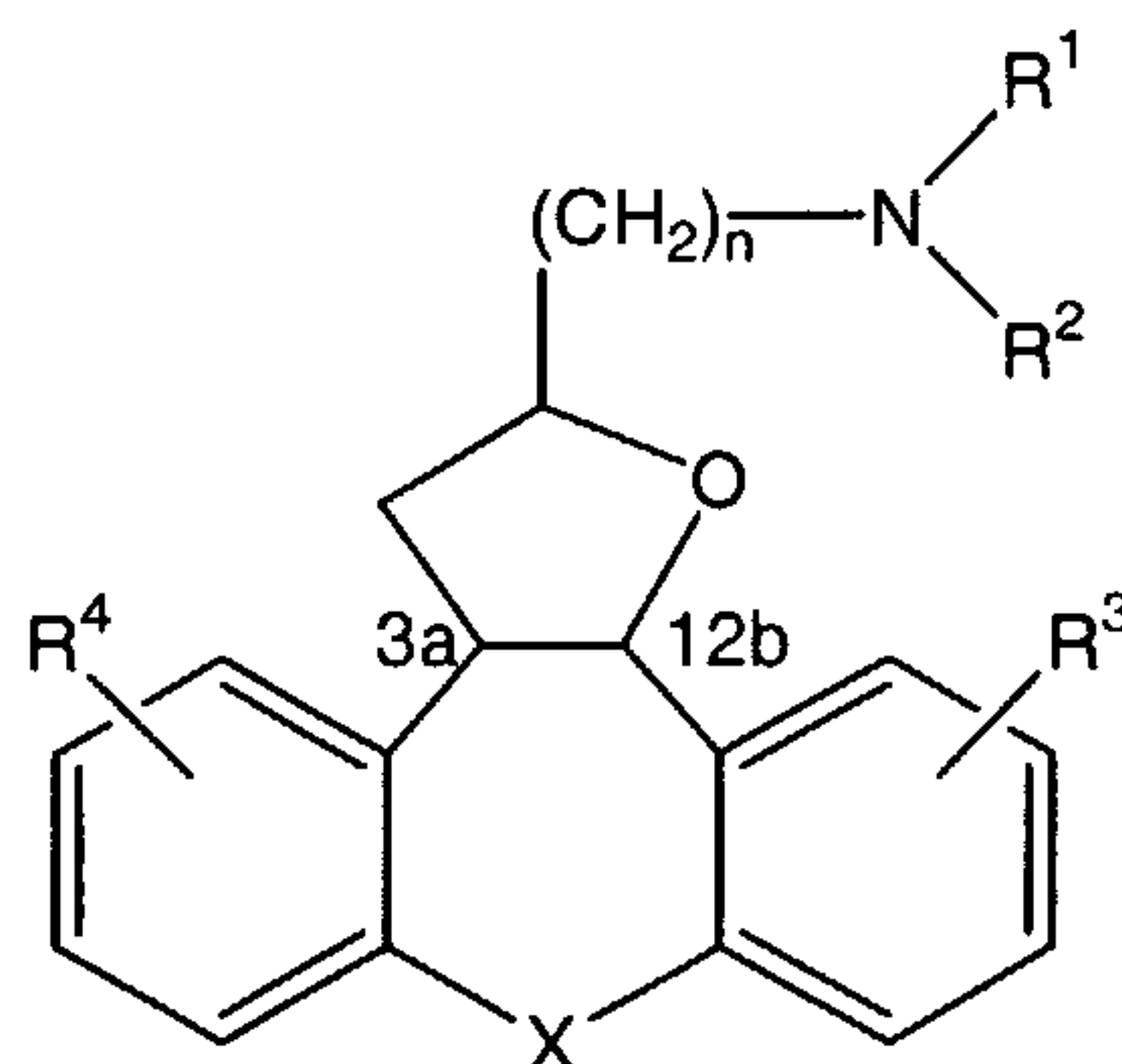
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The present invention concerns processes for the preparation of each of the 4 diastereomers of trans-fused 3,3a,8,12b-tetrahydro-2H-dibenzo[3,4:6,7]cyclohepta[1,2-b]furan derivatives in stereochemically pure form from either of two enantiomerically pure precursors. The tetracyclic ring system having trans-fused five and seven membered rings is formed in an acid-catalysed cyclization reaction. The invention further relates to the thus obtained cis-fused tetracyclic alcohol intermediates, the methanamine end-products, the methanamine end-products for use as a medicine, in particular as CNS active medicines.

15 An article by Monkovic et al. (J. Med. Chem. (1973), 16(4), p. 403-407) describes the synthesis of (±)-3,3a,8,12b-tetrahydro-N-methyl-2H-dibenzo[3,4:6,7]-cyclohepta[1,2-b]furan-2-methanamine oxalic acid. Said compound was synthesized as a potential antidepressant; however, it was found that this particular tetrahydrofurfurylamine derivative was inactive as an antidepressant at a dose of 300 mg/kg.

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WO 97/38991, published on 23 October 1997, discloses tetracyclic tetrahydrofuran derivatives of formula



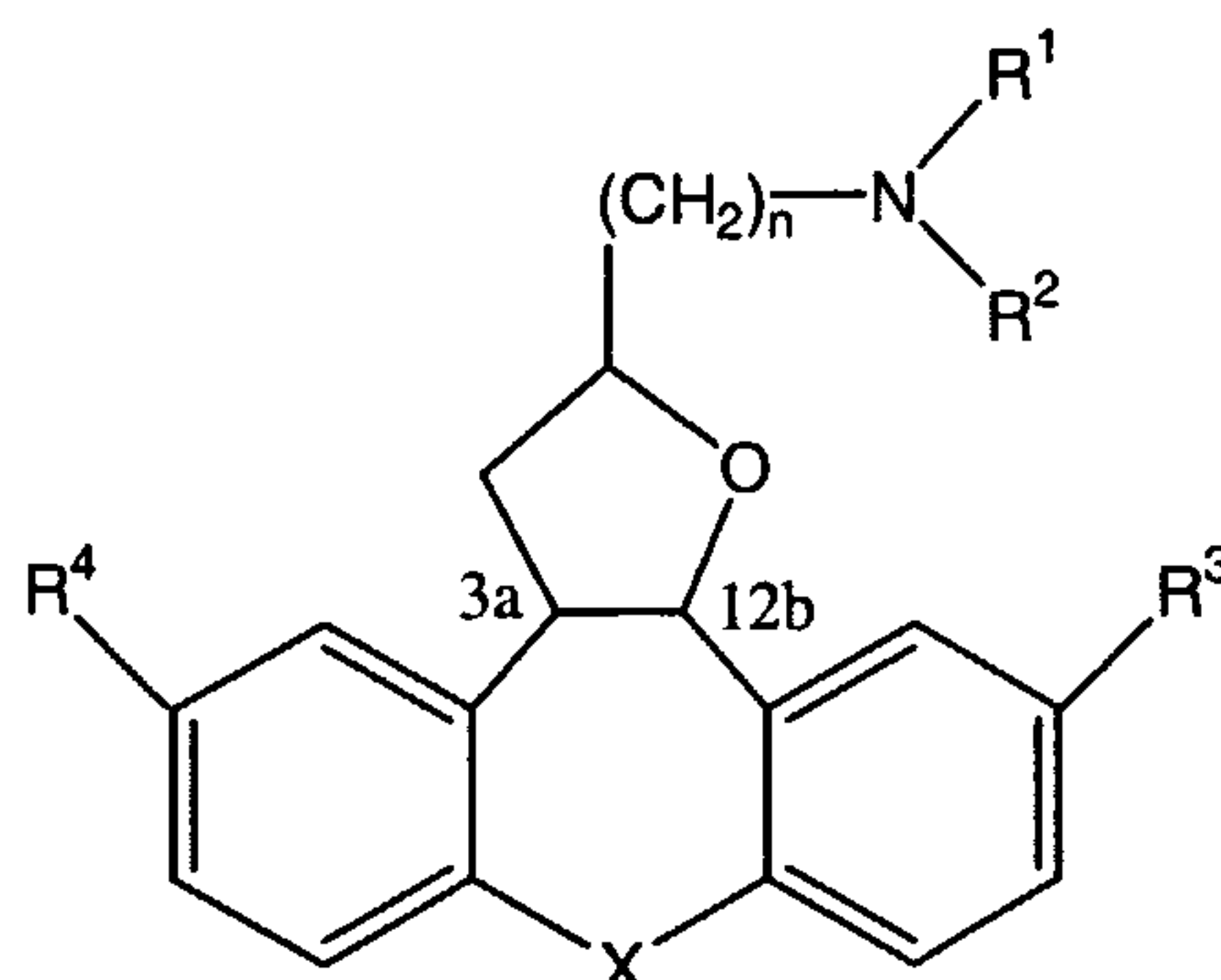
wherein the hydrogen atoms on carbon atoms 3a and 12b have the trans configuration.

25 The 4 possible trans products are obtained from a racemic intermediate in a non-selective cyclization reaction and can be separated from one another using HPLC techniques.

WO 99/19317, published on 22 April 1999, concerns halogen substituted tetracyclic tetrahydrofuran derivatives of formula

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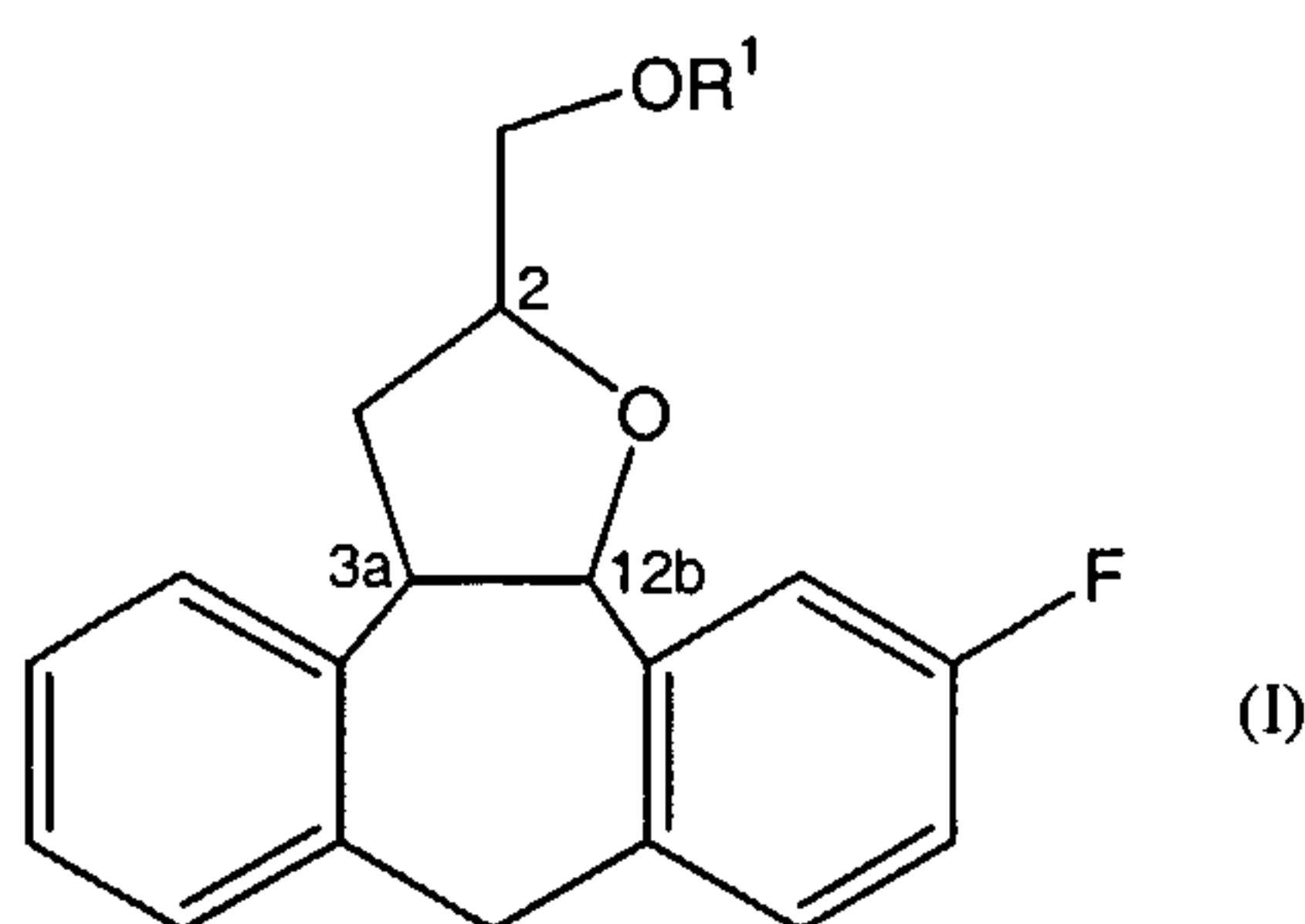
-2-



wherein the hydrogen atoms on carbon atoms 3a and 12b have the trans configuration. The 4 possible trans products are obtained from a racemic intermediate in a non-selective cyclization reaction and can be separated from one another using HPLC techniques.

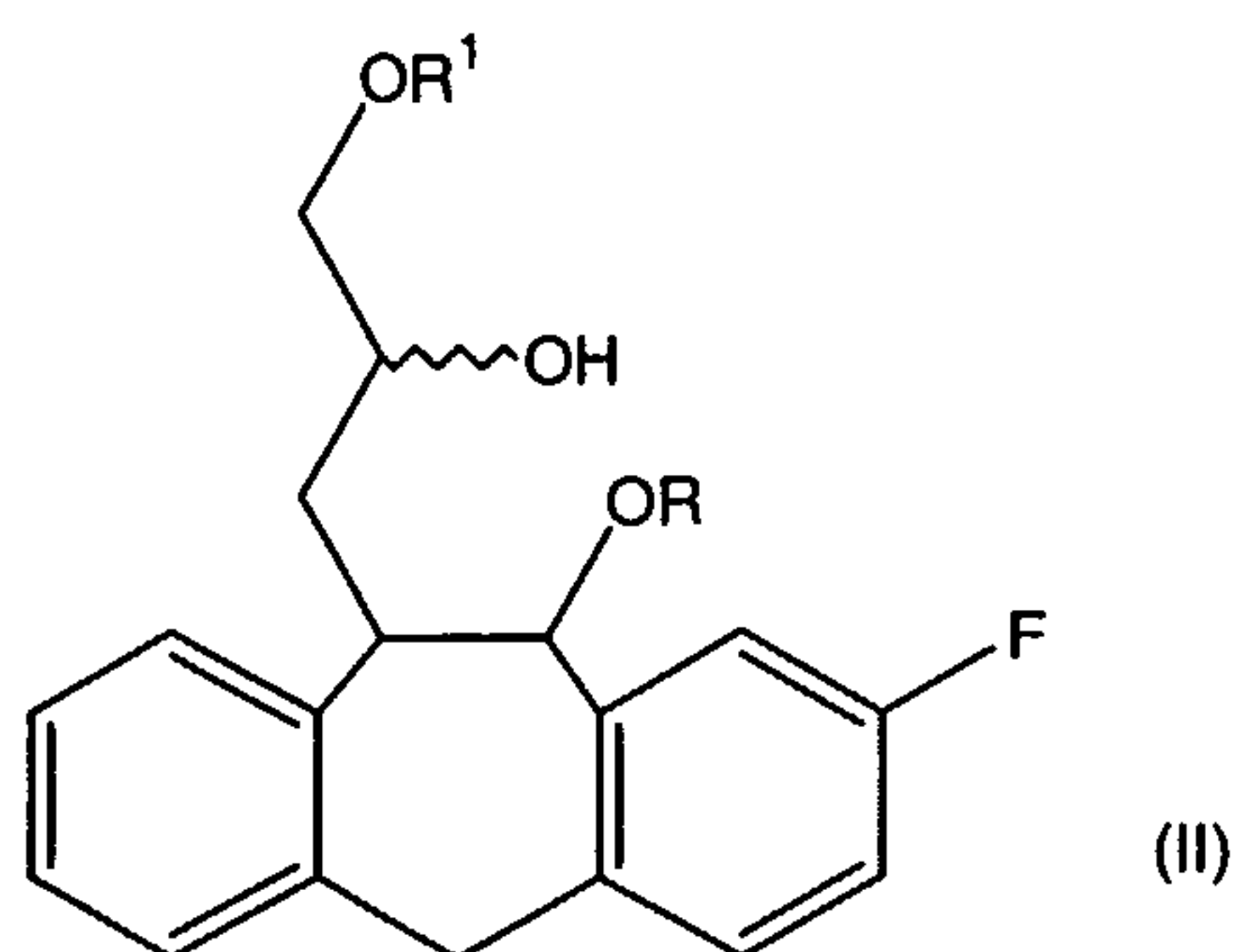
As the method for preparing the trans-fused compounds proved ill-suited for upscaling, alternative routes for synthesis of these trans-fused compounds were explored, one of which opened a pathway to each of the 4 diastereomers of the previously unknown cis-fused 3,3a,8,12b-tetrahydro-2H-dibenzo[3,4:6,7]cyclohepta[1,2-b]furan derivatives from a single enantiomeric precursor. This route allows for the synthesis of two of the four trans diastereomers; the enantiomers thereof can be prepared starting from the other enantiomer of the precursor.

The present invention concerns a process for preparing each of the 4 individual diastereomers of formula (I)



wherein the substituents on carbon atoms 3a and 12b have the trans configuration and the substituent on carbon atom 2 may have the R or the S configuration, comprising the step of cyclizing a compound of formula (II)

-3-

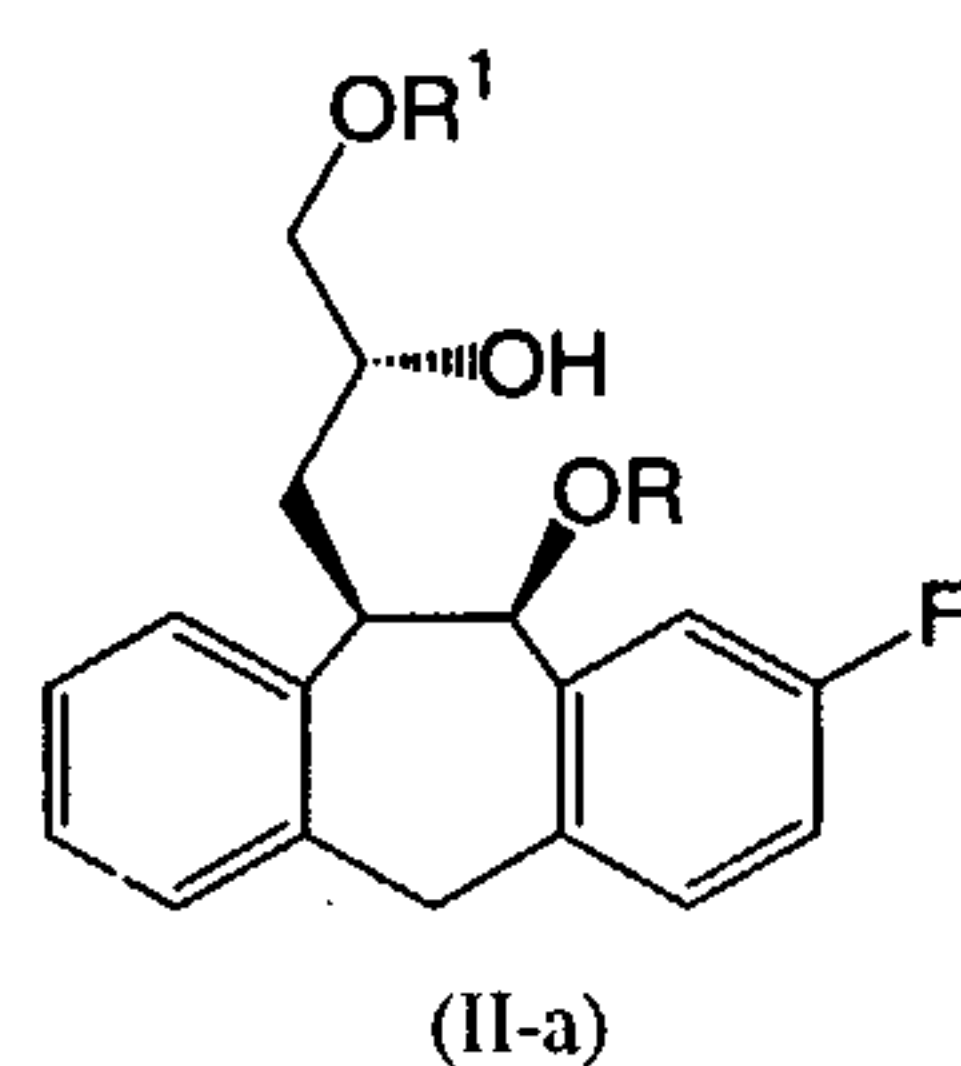


wherein R represents C₁₋₃alkylcarbonyl;

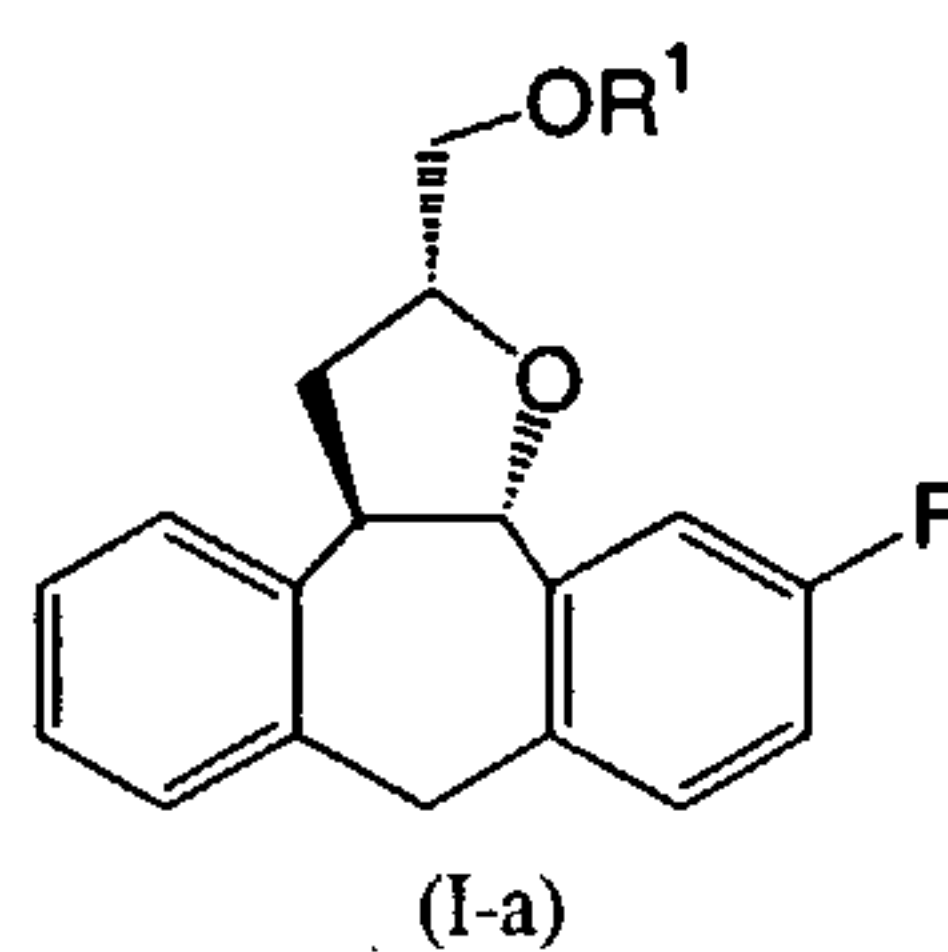
OR¹ is a leaving group; and

the substituents -OR and -CH₂-CHOH-CH₂OR¹ have the cis configuration,

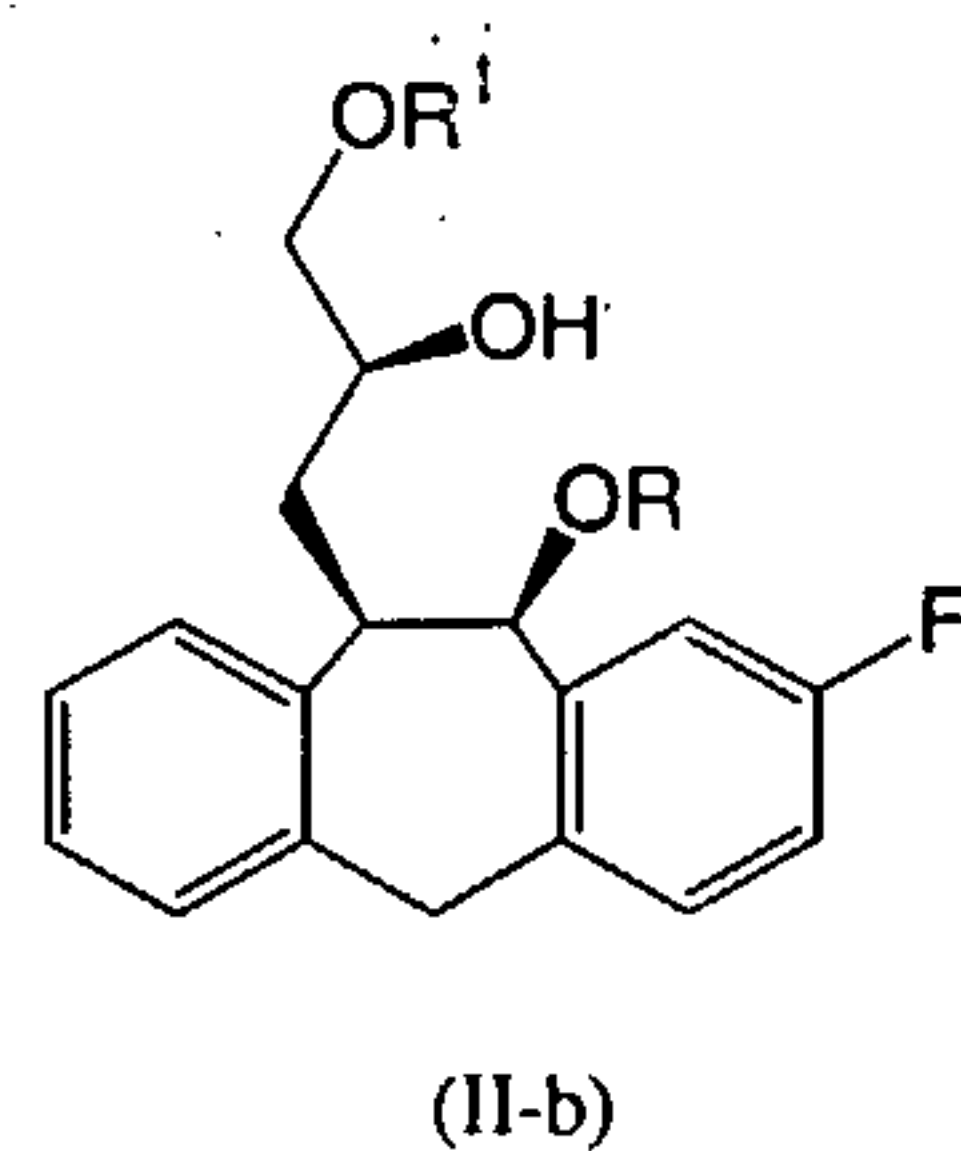
5 in a reaction inert solvent in the presence of a acid, whereby



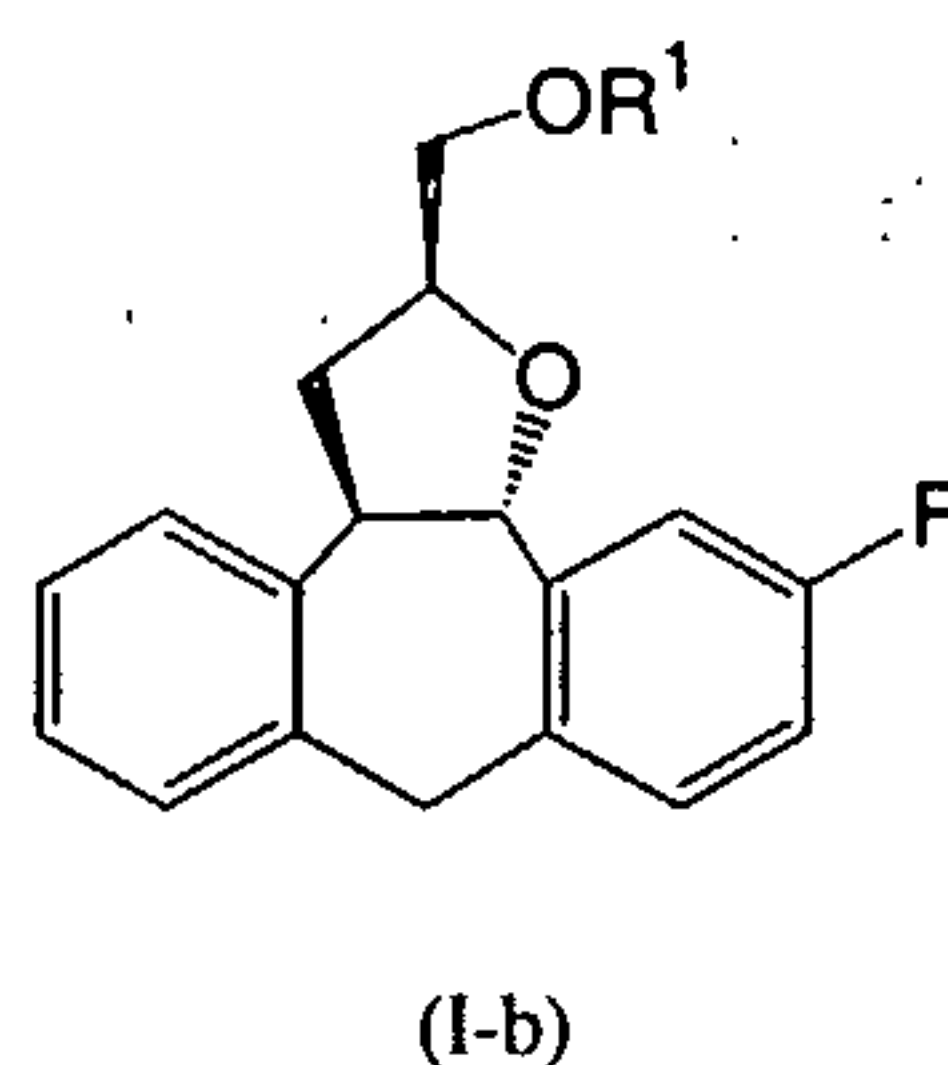
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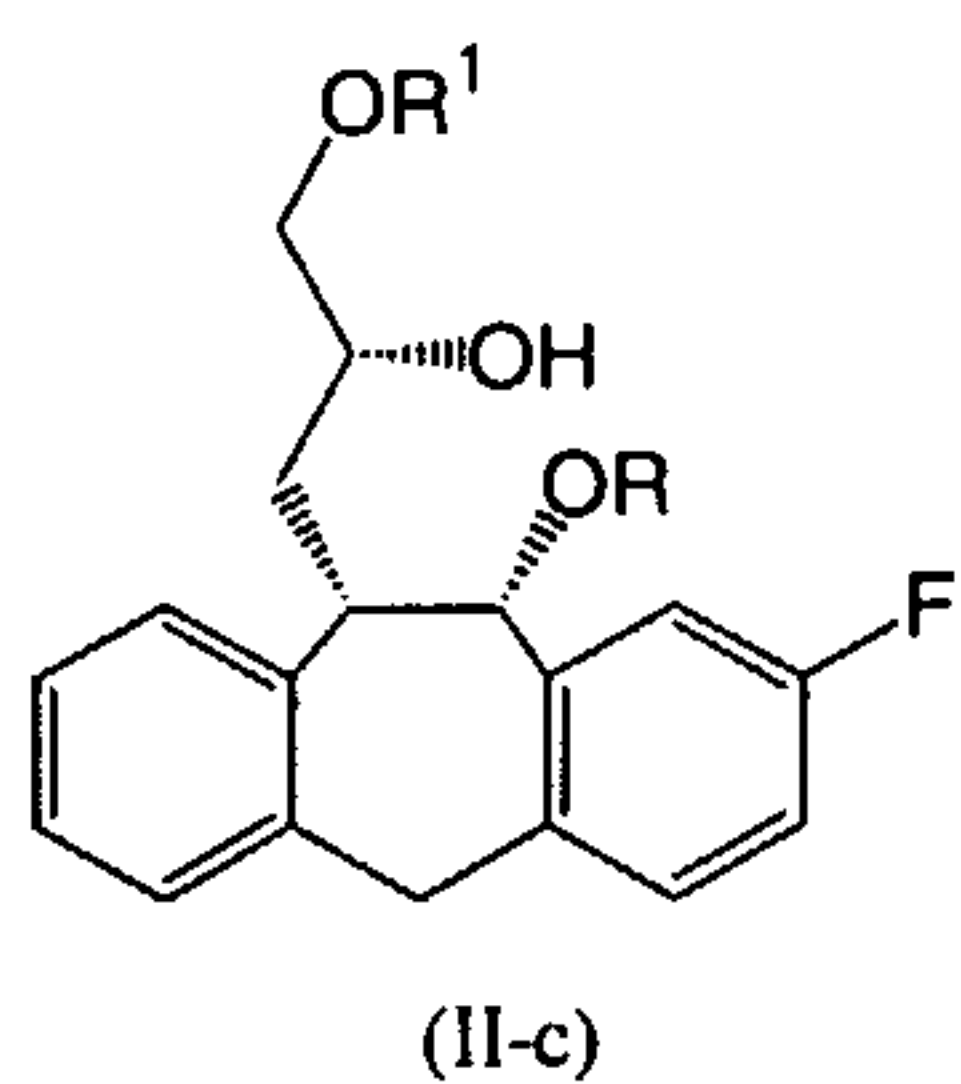
[2R, 3aR, 12bS] ,



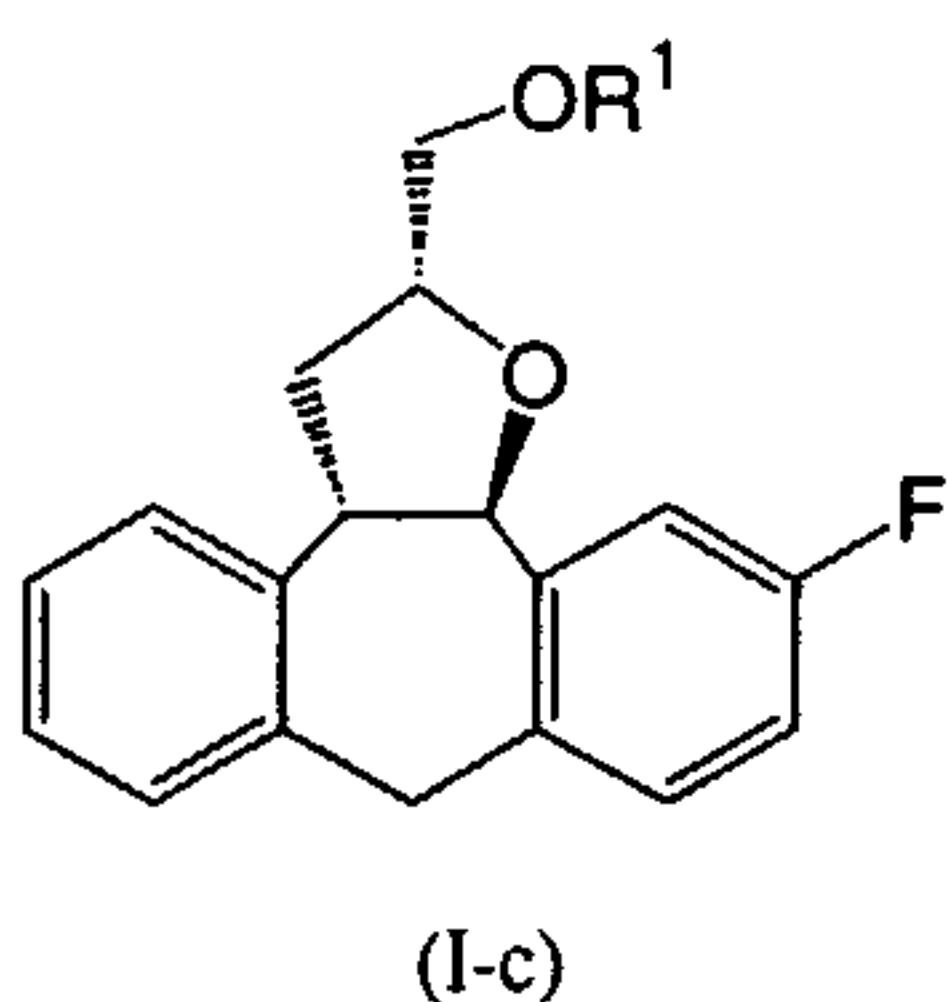
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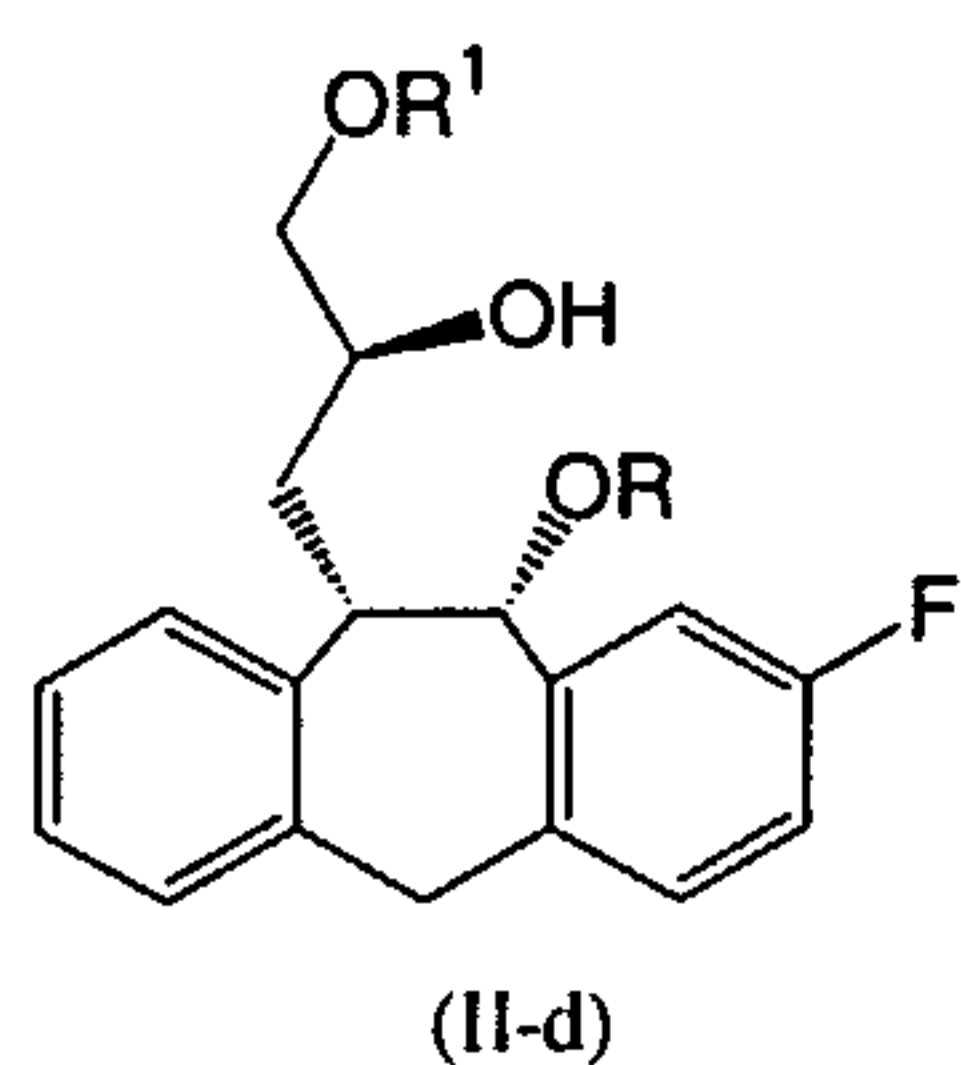
[2S, 3aR, 12bS] ,



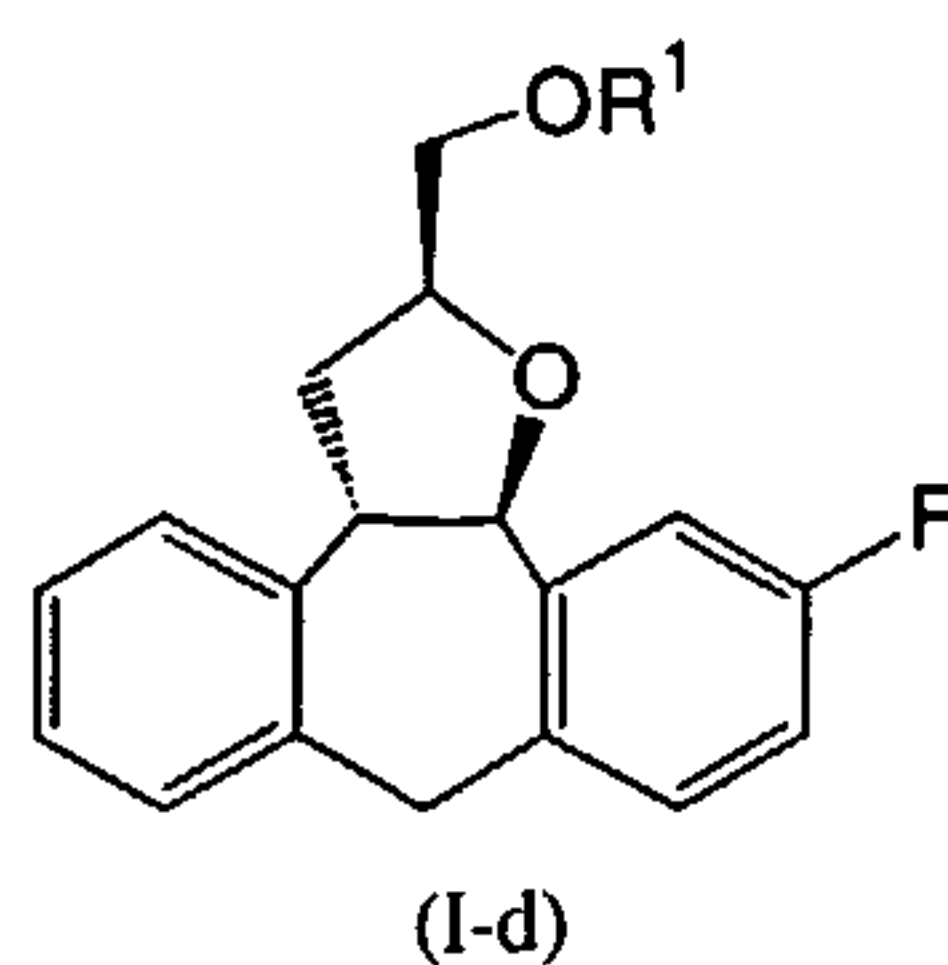
yields



[2R, 3aS, 12bR], and



yields



[2S, 3aS, 12bR].

C₁₋₃alkylcarbonyl represents methylcarbonyl, ethylcarbonyl and propylcarbonyl;

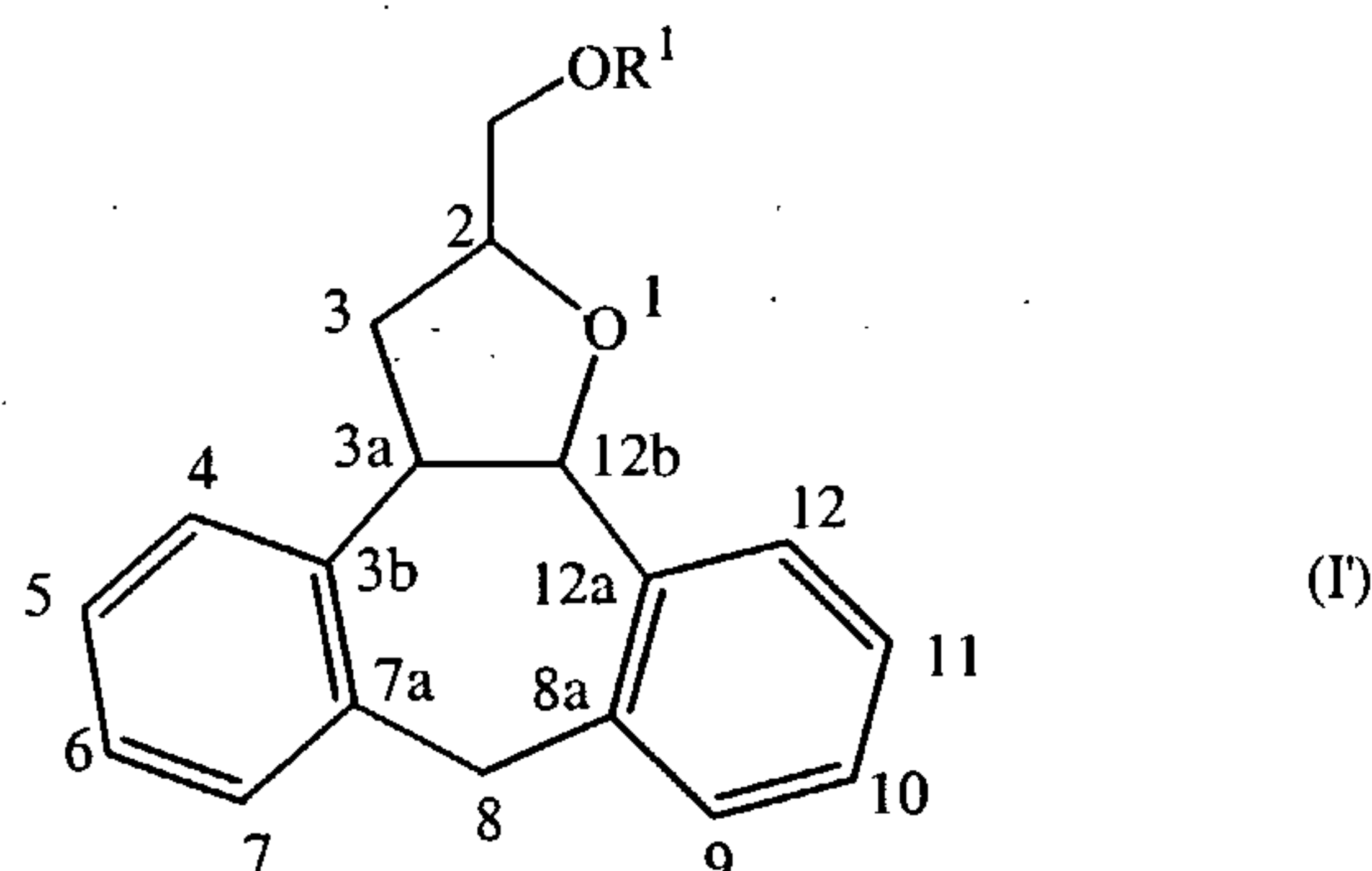
-4-

the term 'a leaving group' represents sulfonyloxy groups such as methanesulfonyloxy, trifluoromethanesulfonyloxy, benzenesulfonyloxy, 4-methylbenzenesulfonyloxy, 4-nitrobenzenesulfonyloxy and 4-bromobenzenesulfonyloxy.

- 5 Suitable solvents are, for example, aromatic hydrocarbons, e.g. benzene, toluene, chlorobenzene; halogenated hydrocarbons, e.g. dichloromethane, trichloromethane; acetonitrile. Suitable acids are, for example, sulfonic acids, e.g. methanesulfonic, trifluoromethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, camphorsulfonic acid; carboxylic acids, e.g. acetic or trifluoroacetic acid. The reaction can conveniently
10 be conducted by stirring the reagent, substrate and solvent at ambient temperature.

Under the reaction conditions, an internally solvated benzylic cation may form as an intermediate which cyclizes to a tetrahydrofuran ring with trans-fusion.

- 15 The numbering of the tetracyclic ring-system present in the compounds of formula (I), as defined by Chemical Abstracts nomenclature is shown in formula (I').



- The compounds of formula (I) have at least three asymmetric centers, namely carbon atom 2, carbon atom 3a and carbon atom 12b. Carbon atoms 3a and 12b are part of an
20 annelated ring system. In this case, where more than 2 asymmetric carbon atoms are present on a ring system, the substituent highest in priority (according to the Cahn-Ingold-Prelog sequence rules) on the reference carbon atom, which is defined as the asymmetric carbon atom 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
25 priority substituent on the other asymmetric carbon atoms relative to the position of the highest priority substituent on the reference atom is denominated by "α" or "β". "α" means that the highest priority substituent is on the same side of the mean plane determined by the ring system, and "β" means that the highest priority substituent is on the other side of the mean plane determined by the ring system.

-5-

Of some compounds of formula (I) and of intermediates used in their preparation, the absolute stereochemical configuration was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" isomeric forms can be unambiguously characterized by for instance their optical rotation in case "A" and "B" have an enantiomeric relationship. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction.

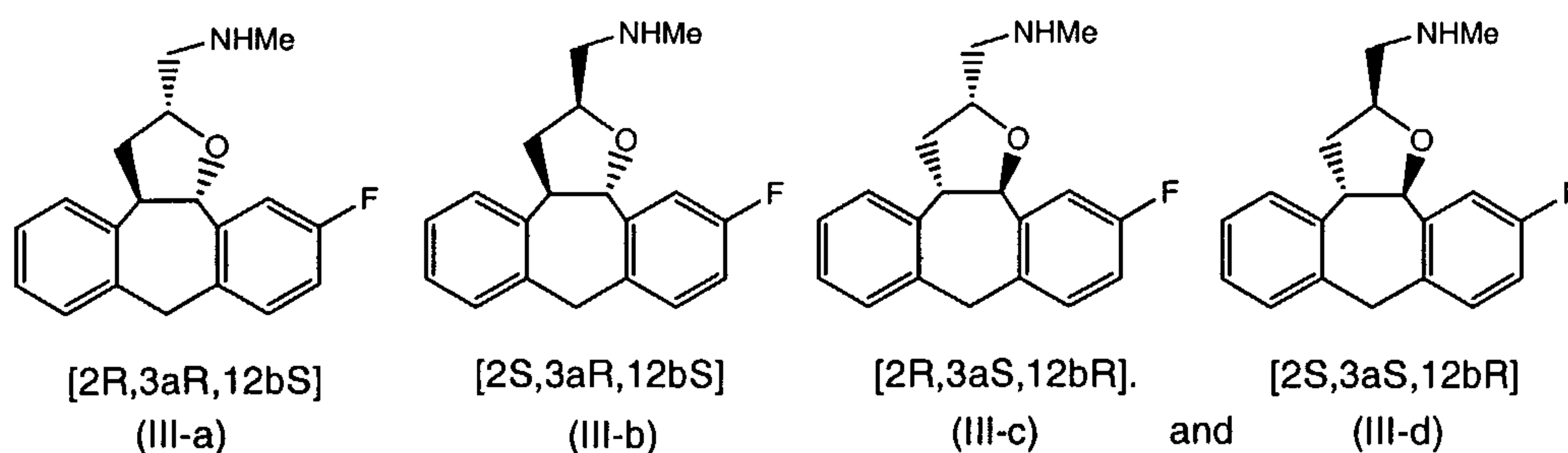
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The following table summarizes the nomenclatures using absolute and relative stereodescriptors of each of the four trans-stereoisomers of the compound of formula (I).

Absolute configuration			Relative configuration		
2	3a	12b	2	3a	12b
R	R	S	α	α	β
R	S	R	α	β	α
S	R	S	α	β	α
S	S	R	α	α	β

15

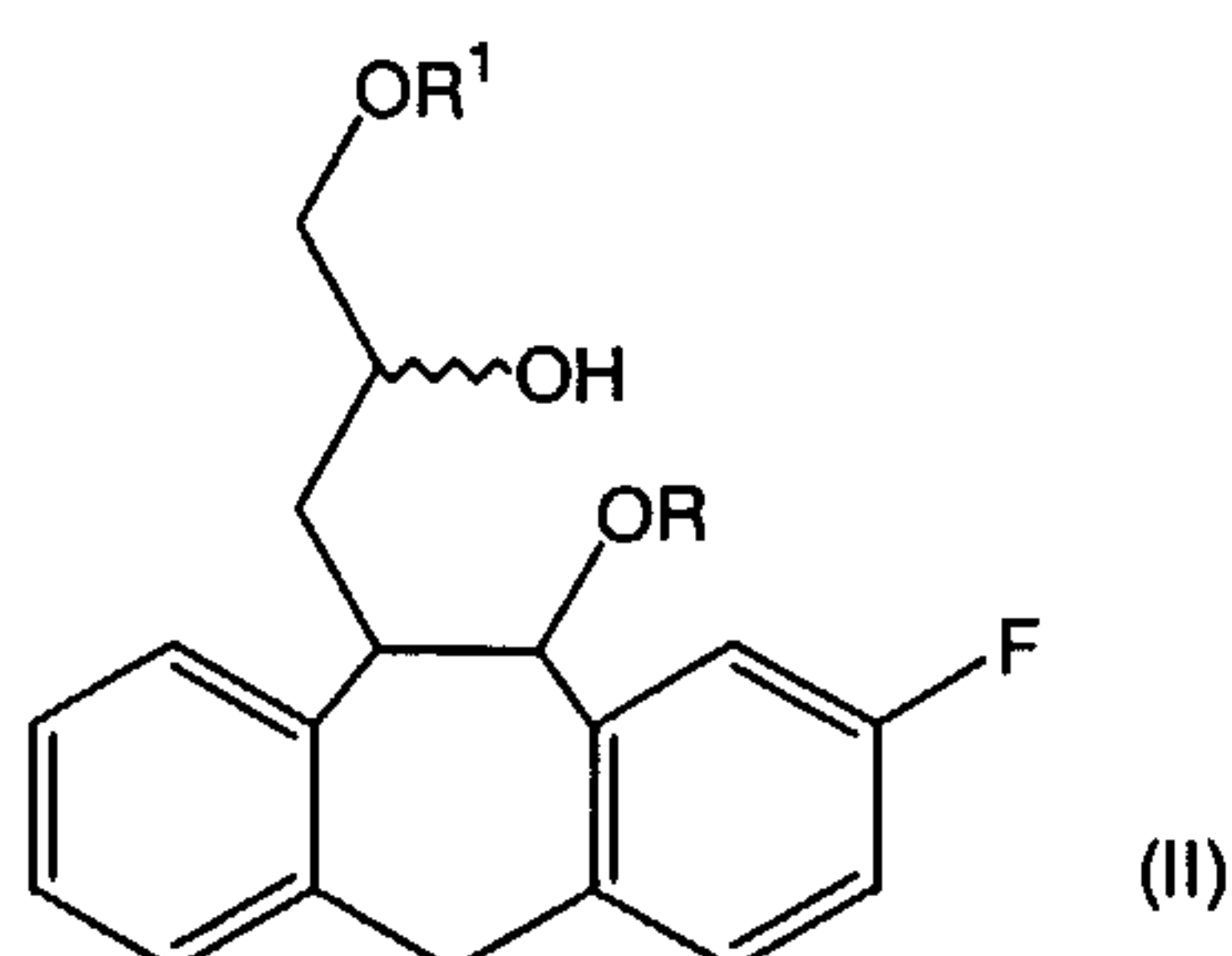
The tetracyclic sulfonates of formula (I) can be converted further into target compounds of pharmaceutical interest by further reaction with aqueous or gaseous methanamine in an organic solvent at an elevated temperature, thus yielding



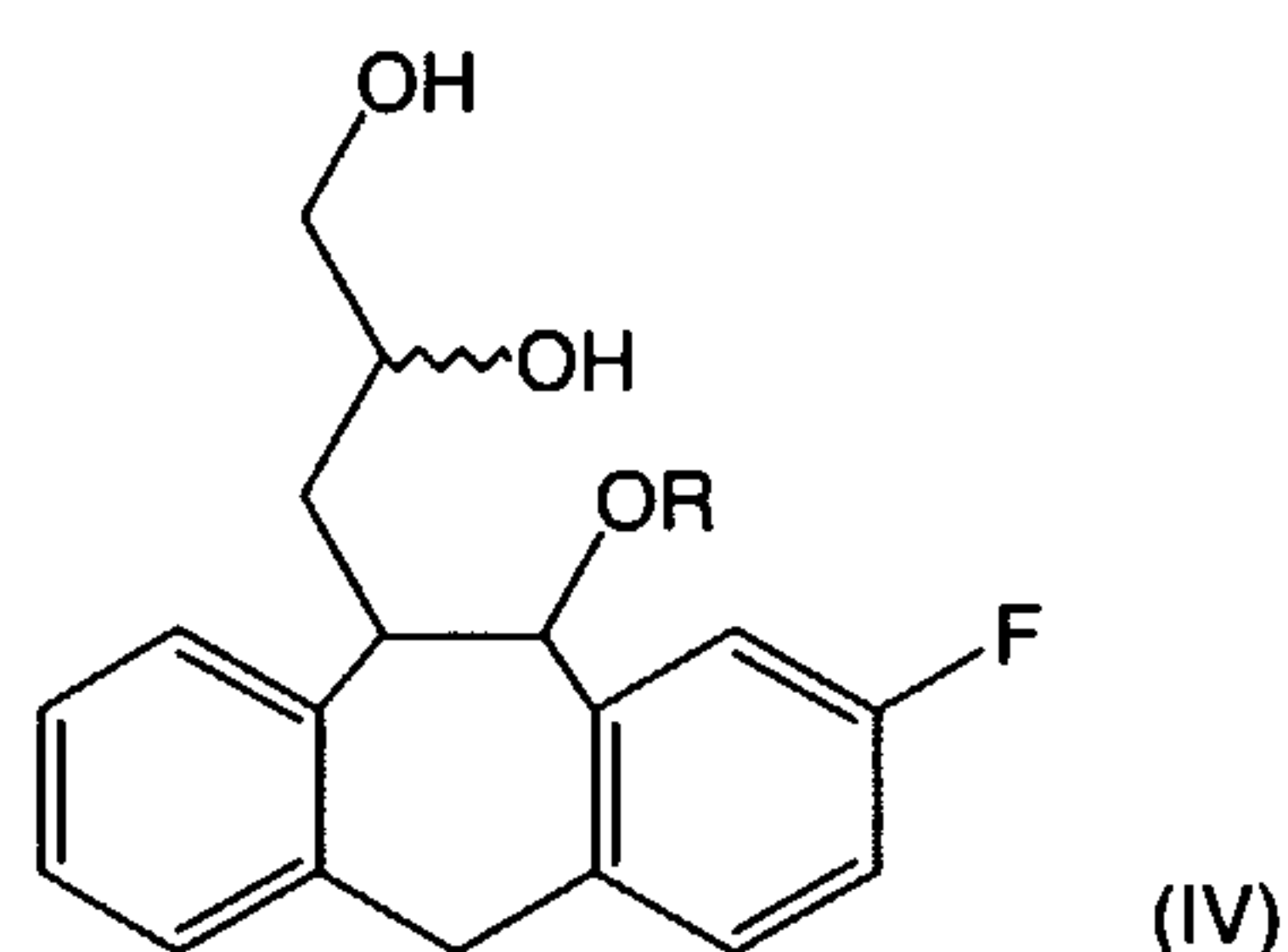
A suitable organic solvent is for example tetrahydrofuran. The reaction is preferably conducted in a pressure vessel at a temperature in the range of 120°C to 150°C.

Each of the intermediate compounds of formula

-6-

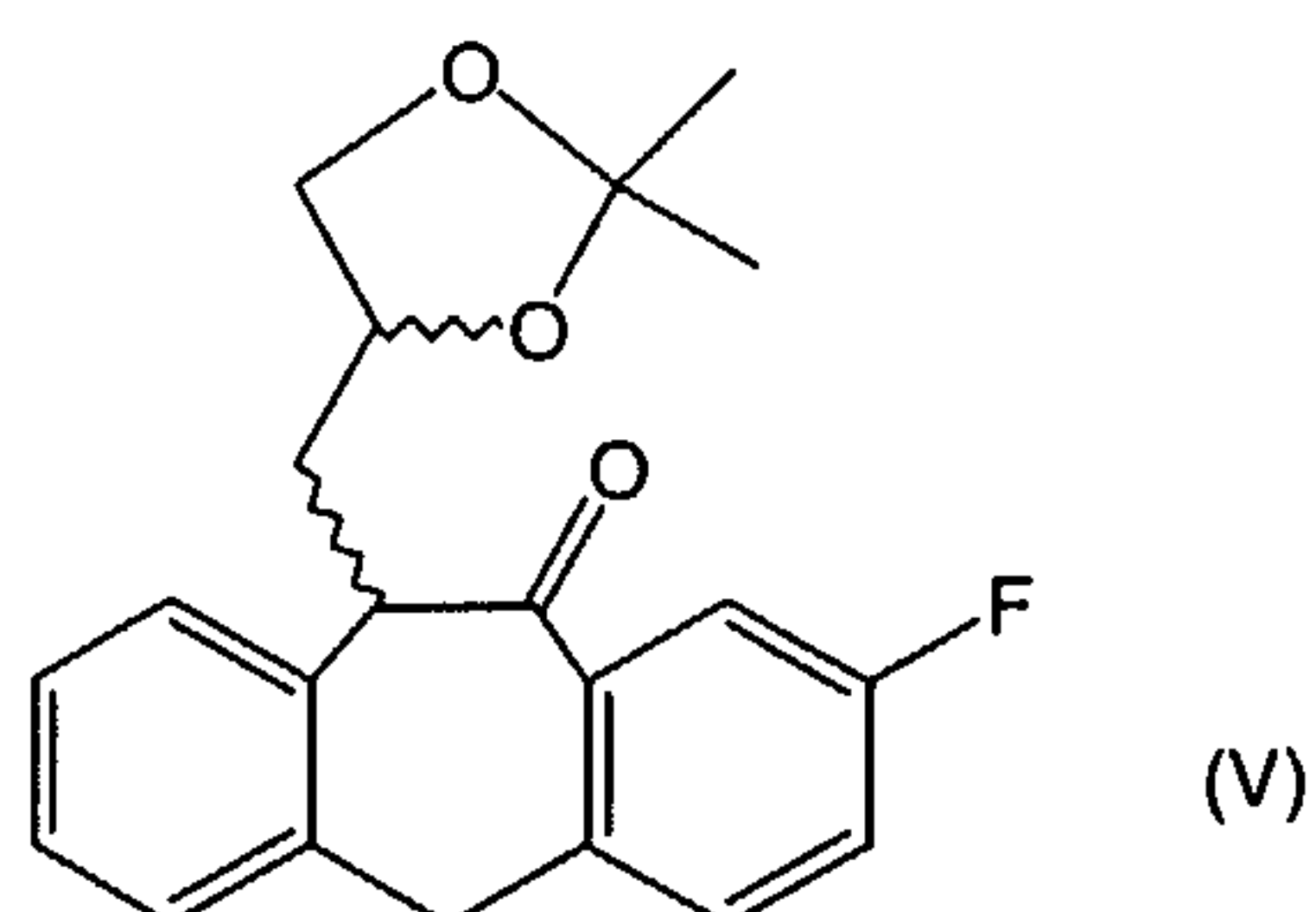


is prepared from a diol of formula



by chemoselective conversion of the primary hydroxyl group into a leaving group. One such method comprises stirring the diol of formula (IV) in a reaction inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, in the presence of an excess of a base such as triethylamine, an equivalent of dimethylaminopyridine and half an equivalent of dibutyl(oxo)stannane, and two equivalents of tosylchloride or a similar sulfonylchloride. The reaction may also be conducted in the absence of dibutyl(oxo)stannane and dimethylaminopyridine but typically will yield a mixture of substrate, mono- and disubstituted product from which the desired monosubstituted compound needs to be separated.

The intermediate diol of formula (IV) can be prepared from a ketone of formula (V)

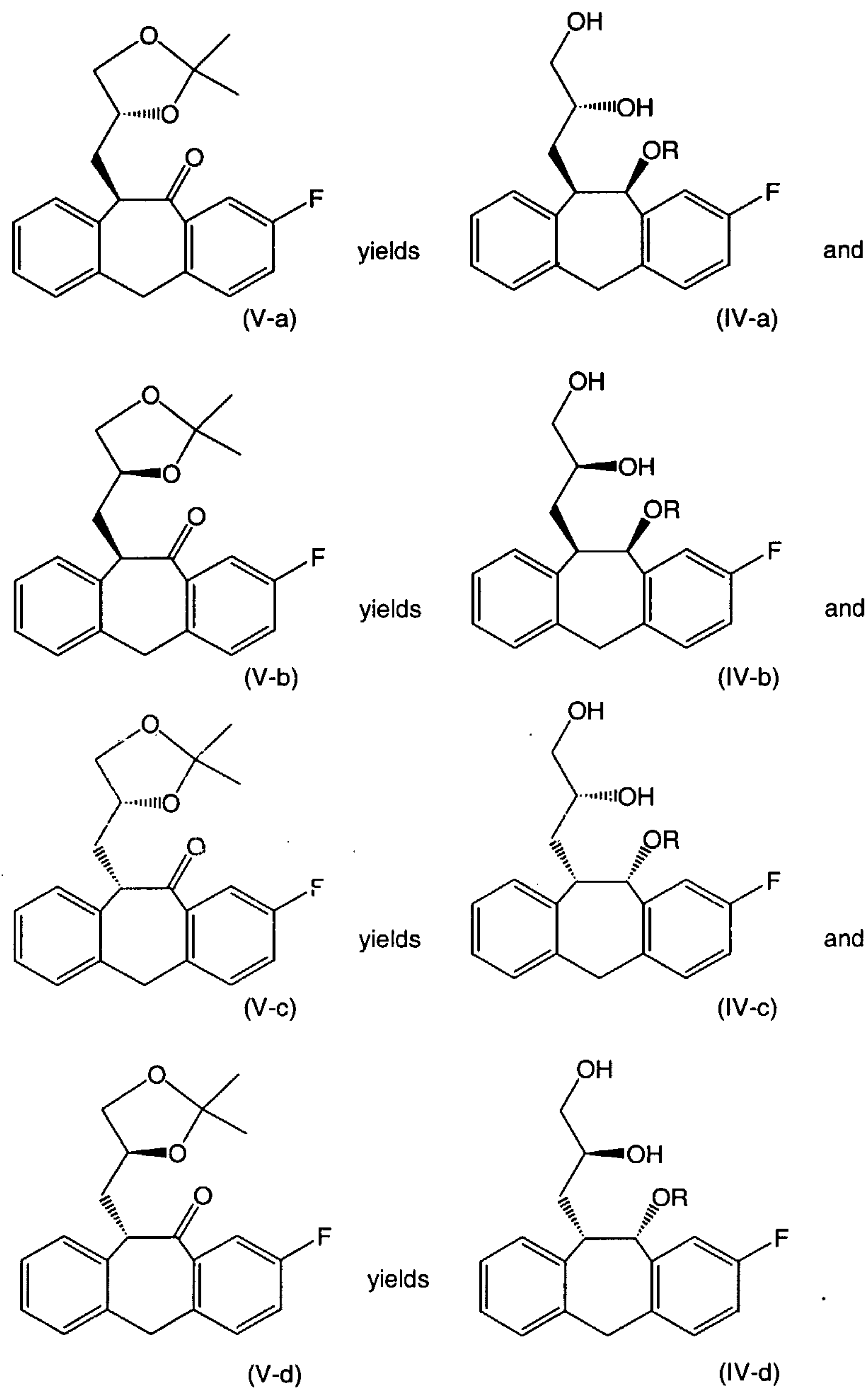


by the following series of reaction steps:

- (a) reducing the ketone of formula (V) to the cis-oriented hydroxyl group by reaction with lithium or sodium borohydride in a mixture of an organic solvent and an aqueous buffer having a pH of about 7 at a temperature below ambient temperature;
- 20 (b) acylating the hydroxyl group with an acylchloride or acyl anhydride following art-known procedures, and

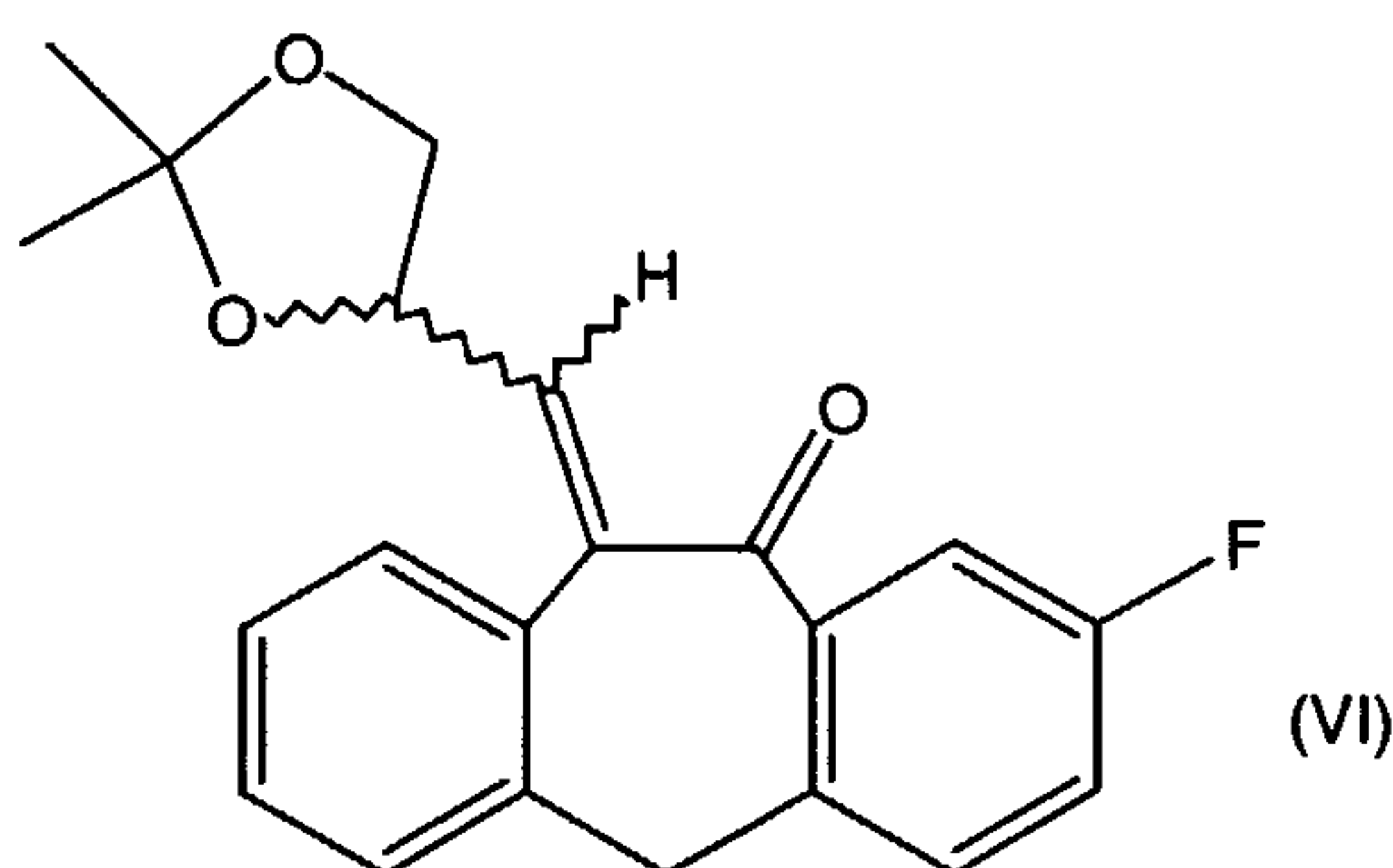
-7-

(c) unmasking the diol by a deacetalisation reaction in an organic solvent in the presence of an acid, whereby



The intermediate ketones of formula (V) are prepared from the α,β -unsaturated ketone
 5 (VI)

-8-



by either Pd/C catalyzed hydrogenation or a reduction procedure using sodiumcyanoborohydride, yielding a mixture of epimeric ketones (V-a) and (V-c), or (V-b) and (V-d), in a rather invariant ratio of about 3:2.

5

The hydrogenation reaction may conveniently be conducted in a variety of solvents such as alcohols, e.g. methanol, ethanol, isopropanol; esters, e.g. ethyl acetate; ethers, e.g. tetrahydrofuran; aromatic hydrocarbons, e.g. toluene; optionally in the presence of a tertiary amine such as triethylamine or quinine.

10

Reduction of (VI) can be accomplished with sodium cyanoborohydride under slightly acidic conditions.

15

The epimeric ketones (V-a) and (V-c), or (V-b) and (V-d), can be obtained separately by chromatographic separation (diethylether/hexane 60/40). Separation can also be effected on the epimeric alcohols obtained following reduction of (V) according to step (a).

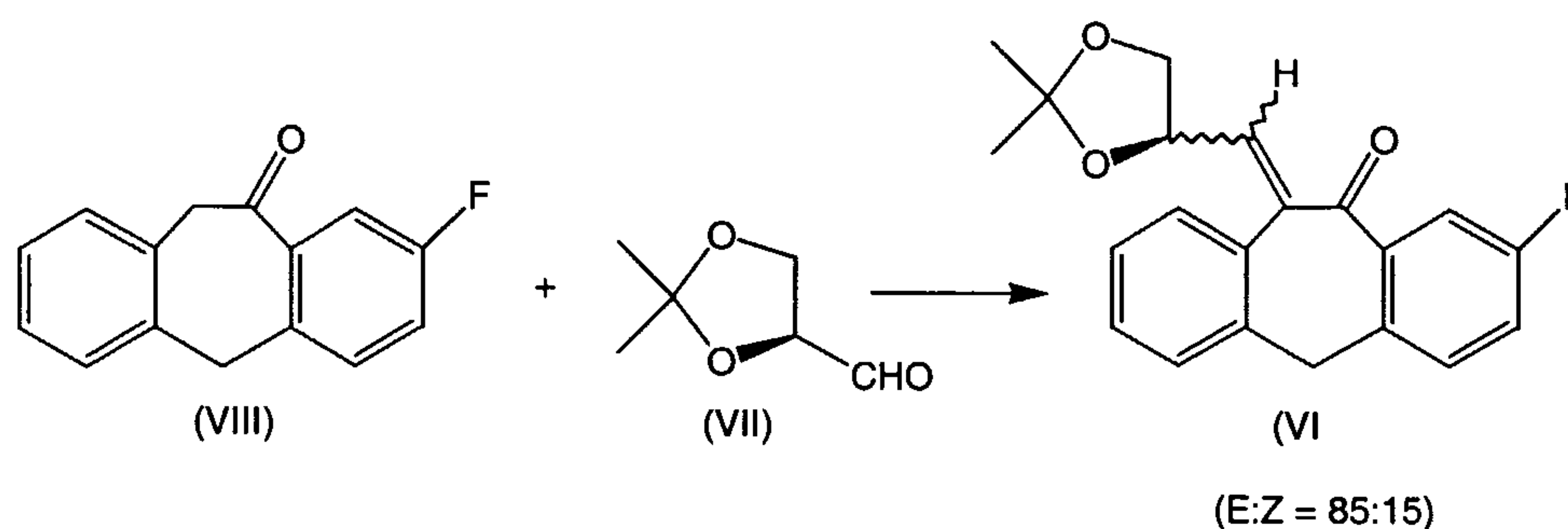
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The epimeric ketone of formula (V-c) may be converted into the epimeric ketone of formula (V-a) by treatment with a base such as triethylamine in a suitable solvent such as isopropanol at a slightly elevated temperature in the range of 35°C-45°C. The epimeric ketone (V-b) may likewise be converted into (V-d).

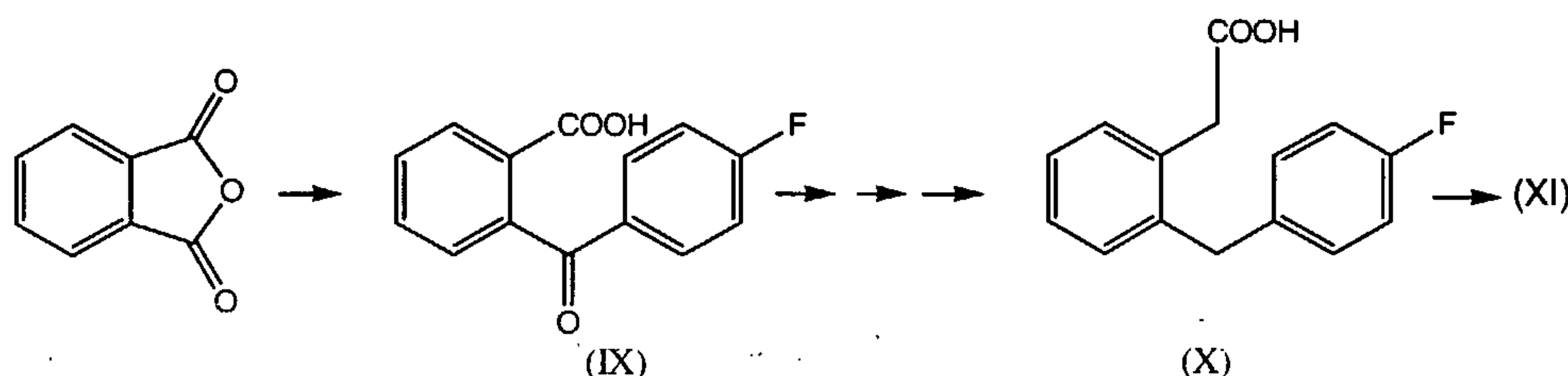
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To prepare intermediate (VI), (4S)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (VII) (or its enantiomer) and pro-chiral ketone (VIII) can be dissolved in a suitable solvent such as tetrahydrofuran and treated with a base such as tert.butyloxypotassium salt and a co-reagent such as magnesium chloride or bromide (aldol condensation).

-9-



The pro-chiral ketone (VIII) can be prepared by adaption of an art-known sequence (Can. J. Chem., 1971, 49, 746-754) starting with a Friedel-Crafts acylation reaction using fluorobenzene and phthalic anhydride to form keto-acid (IX), followed by
 5 reductive removal of the ketone group and homologation of the carboxylic acid function.



Cyclization of the homologous acid (X) in another Friedel-Crafts acylation affords ketone (VIII).

10

The process according to the present invention provides an enantioselective approach to the target molecule (III) in enantiopure form via the enantiopure sulfonates of formula (I). Both target and intermediate molecules of formulae (III) and (I) are novel.

15 The pharmaceutically active compounds of formula (III) may occur in their free form as a base or in a pharmaceutically acceptable salt form obtained by treatment of the free base with an appropriate non-toxic acid such as an inorganic acid, for example, hydrohalic acid, e.g. hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like acids; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic,
 20 lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The term addition salt as used hereinabove also comprises the solvates which the
 25 compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

-10-

The term 'enantiopure form' designates compounds and intermediates having a stereoisomeric excess of at least 80% (*i.e.* minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (*i.e.* 100% of one isomer and none of the other), more in particular, compounds or intermediates
5 having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%.

The compounds of the present invention show affinity for 5-HT₂ receptors, particularly
10 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). 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
15 Drug Dev. Res., 13, 237-244 (1988). Furthermore, the compounds of the present invention show interesting pharmacological activity in the "mCPP Test on Rats" which is described hereinafter, and in the "Combined Apomorphine, Tryptamine, Norepinephrine (ATN) Test on Rats" which is described in Arch. Int. Pharmacodyn., 227, 238-253 (1977).

20 In view of these pharmacological and physicochemical properties, the compounds of formula (III) 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
25 panic attacks, organic mental disorders, mental disorders in children, aggression, memory disorders and attitude disorders in older people, addiction, obesity, bulimia and similar disorders. In particular, the present compounds may be used as anxiolytics, antipsychotics, antidepressants, anti-migraine agents and as agents having the potential
30 to overrule the addictive properties of drugs of abuse.

The compounds of formula (III) 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.

35 The compounds of formula (III) may also serve in the treatment or the prevention of damage to the nervous system caused by trauma, stroke, neurodegenerative illnesses

-11-

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.

5 In view of the above uses of the compounds of formula (III), 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 (III) effective in treating the above described disorders, in particular, in treating anxiety, psychosis, schizophrenia, depression,
10 migraine, sleep disorders and addictive properties of drugs of abuse.

The present invention thus also relates to compounds of formula (III) as defined hereinabove for use as a medicine, in particular, the compounds of formula (III) may be used for the manufacture of a medicament for treating anxiety, psychosis,
15 schizophrenia, depression, migraine, sleep disorders 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
20 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.

For ease of administration, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical
25 compositions of this invention, a therapeutically 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 may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable,
30 preferably, for administration orally, rectally, percutaneously, or by parenteral injection. 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 and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules
35 and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers

-12-

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 solutions containing compounds of formula (III) may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects 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 or as an ointment. Acid or base addition salts of compounds of formula (III) due to their increased water solubility over the corresponding base or acid form, are more suitable in the preparation of aqueous compositions.

In order to enhance the solubility and/or the stability of the compounds of formula (III) 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 of formula (III) in pharmaceutical compositions.

Other convenient ways to enhance the solubility of the compounds of the present invention in pharmaceutical compositions are described in WO 97/44014.

More in particular, the present compounds may be formulated in a pharmaceutical composition comprising a therapeutically effective amount of particles consisting of a solid dispersion comprising a compound of formula (III), and one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is

-13-

dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid solutions
5 are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered.

The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically
10 uniform throughout or comprise more than one phase.

The water-soluble polymer in the particles is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.

15 Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxy-propyl
20 molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule.

The particles as defined hereinabove can be prepared by first preparing a solid dispersion of the components, and then optionally grinding or milling that dispersion.
25 Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation, melt-extrusion being preferred.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.
30 Dosage unit form as used in the specification and claims 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 dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers,
35 injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Experimental part

Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "THF" is defined as tetrahydrofuran, "DIPE" is defined as diisopropyl ether, "HCl_{cp}" is defined as
5 chemically pure hydrochloric acid (34.5% w/w).

A. Preparation of the intermediate compounds

Example A1a

10 Intermediate 1 : 2-(4-fluorobenzoyl)benzoic acid – CAS RN [7649-29-5]

(i) A solution of p-fluorobenzenemagnesium bromide (1.2M solution in THF, 1eq.) was added to a 0.4M solution of phthalic anhydride in THF, so that the temperature remained under 30°C. After 1h, half of the solvent was distilled off and the reaction mixture was stirred overnight at room temperature. The obtained precipitate was
15 filtered off and taken up in water (0.3L/mol). Toluene (1L/mol) and HCl_{cp} were added so that the temperature remained under 35°C. After stirring 1h, the organic layer was evaporated (50°C, vac.) and the obtained solid was dried at 50°C under vacuum.

Physical yield: 74%

Purity: 93% (LC abs%) ⇒ Active yield: 69% of intermediate 1

20 (ii) Alternatively, a Friedel-Crafts reaction can be performed:

Phthalic anhydride, fluorobenzene (1.2eq.) and CH₂Cl₂ (0.5L/mol) were mixed at room temperature. AlCl₃ (0.8eq.) was added over 60 min. (at 1 mol scale). After 5h at room temperature, the mixture was heated up to reflux during 18h, then cooled down to room temperature and poured very slowly in ice/water and stirred during 1h. The organic
25 layer was separated and the water layer was extracted with CH₂Cl₂ (0.25L/mol). The combined organic layers were washed with water (0.3L/mol), then extracted with 320 ml water (0.7L/mol)/NaOH 50% (0.07L/mol). The water layer was separated and washed with 60 ml CH₂Cl₂ (0.15L/mol). Norit-A-Supra (active charcoal) (10g/mol) was added and the mixture was stirred and filtered.

30 Water (0.7L/mol)/ HCl_{cp} (2.5eq.) solution was added dropwise, the mixture was stirred during 30min., the precipitate filtered off, washed with water (2x0.2L/mol) and dried. Yield: 92% of intermediate 1.

Example A1b

02 Intermediate 2 : 2-[(4-fluorophenyl)methyl]benzoic acid – CAS RN [346-47-4]

-15-

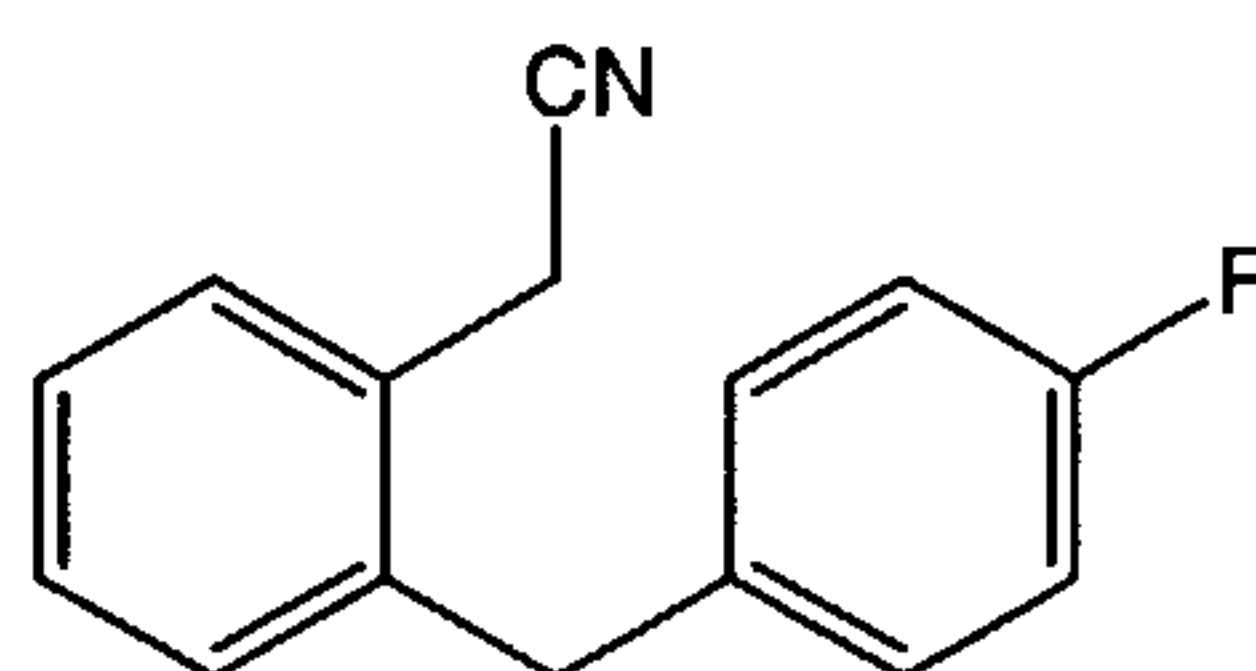
Intermediate 1 was dissolved in isopropanol (2L/mol) and Pd/C (10% dry) was added. The reaction mixture was heated up to 45°C and hydrogenated overnight at atmospheric pressure. After cooling the flask to room temperature, the catalyst was filtered off over diatomaceous earth and rinsed with 30ml isopropanol. The filtrate was
5 evaporated at 45°C under vacuum.

Physical yield: 98%

Purity: 96.4% (LC abs%) $\Rightarrow$ Active yield: 94% of intermediate 2

Example A1c

Preparation of intermediate 3



Intermediate 2 was dissolved in toluene (1.5L/mol) and DMF (1ml/mol) was added.
10 The reaction mixture was heated up to 40°C and thionyl chloride (1.1eq.) was added. During the addition the reaction mixture was further heated up to 50°C. The reaction mixture was stirred at 50°C during 2h30, then evaporated at 50°C under vacuum. THF (0.3L/mol) was added and that solution was dropped into a 2M NaBH₄ solution in THF (1.5eq.). The temperature rose to reflux (67°C) and the reaction mixture was stirred at
15 reflux during 2h. The reaction mixture was cooled down to room temperature. Aceton (350ml/mol) was added (temperature rose to 40°C), the reaction mixture was stirred during 30 minutes, followed by toluene (1L/mol) and water (1.5L/mol). The reaction mixture was heated up to 50°C and the organic layer evaporated at 50°C under vacuum. CH₂Cl₂ (3L/mol) was added, followed by triethylamine (1.1eq.). SOCl₂ (1.1eq.) was
20 added dropwise, the temperature rose to reflux. The reaction mixture was stirred during 45 min to room temperature. Water (1L/mol) was added and the reaction mixture was stirred vigorously during 15 min. The organic layer was washed a second time with water (1L/mol) and evaporated (40°C, vac.). The product was dissolved in toluene (2.5L/mol), tetrabutylammonium hydrogenosulfate (phase-transfer reagent) (0.1eq.)
25 was added at 70°C. NaCN 6M (1.6eq.) was added at 70°C under vigorous stirring. The reaction mixture was then heated up to reflux and stirred 3h. After cooling down to room temperature, water (0.5L/mol) was added, the reaction mixture was stirred during 30 minutes. After washing a second time with water (0.5L/mol), drying on MgSO₄ and evaporating the solvent, intermediate 3 was obtained.

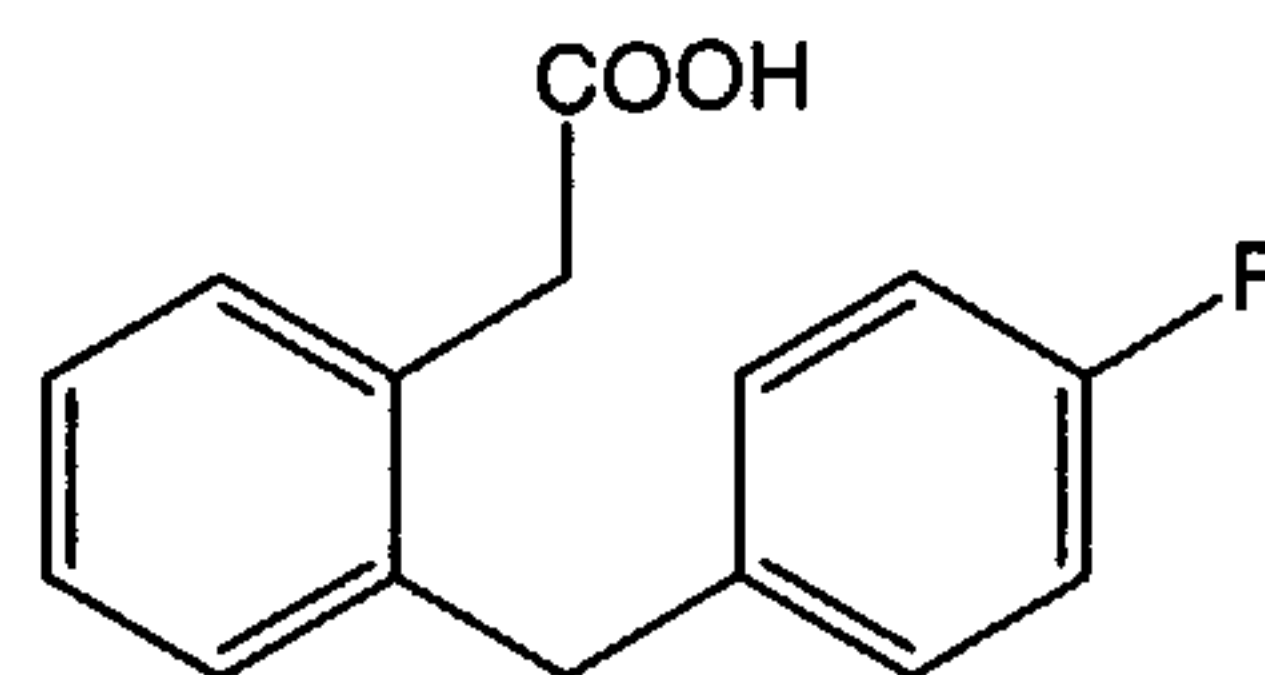
30 Physical yield: 98%

Purity: 96.4% (LC abs%) $\Rightarrow$ Active yield: 94% of intermediate 3

-16-

Example A1d

Preparation of intermediate 4

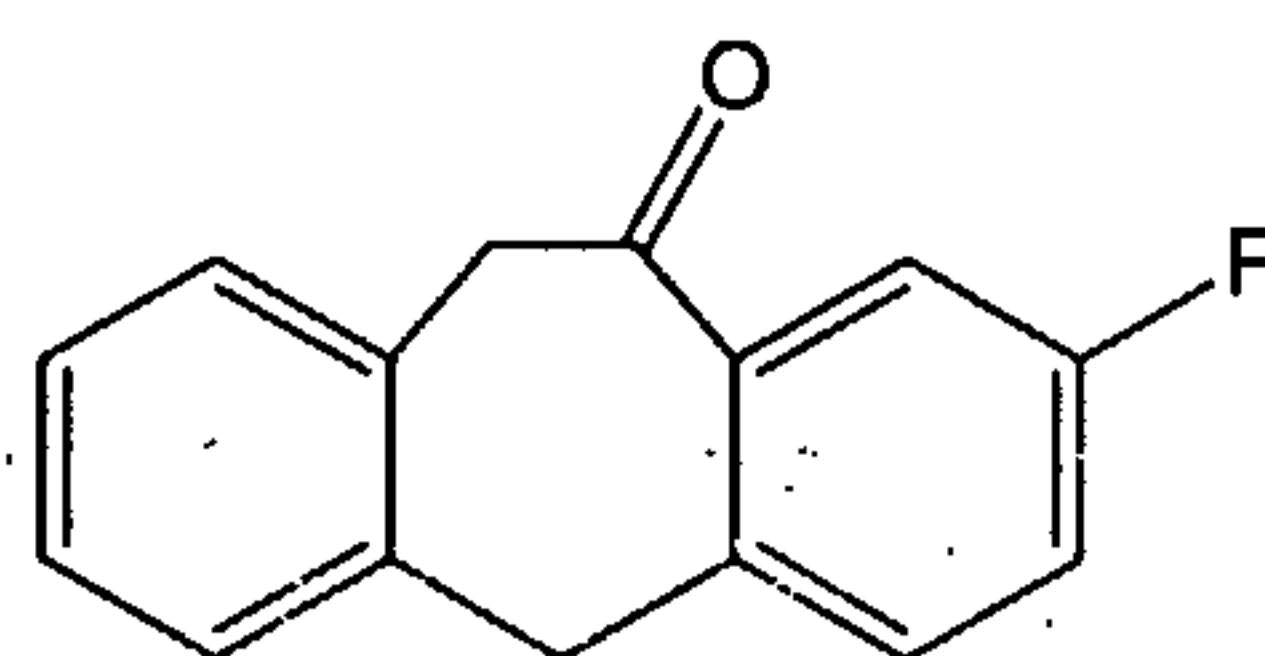


Intermediate 3 was suspended in acetic acid (0.5L/mol), water (0.3L/mol) and sulfuric acid (0.35L/mol). After 5h at reflux, the mixture was cooled down, water (1.2L/mol) and dichloromethane (0.3L/mol) were added. The organic extract was washed with water (1.3L/mol) and NaOH 50% (0.15L/mol). After stirring 20 min., the aqueous layer was separated and washed with CH₂Cl₂ (0.1L/mol), which was discarded. The aqueous layer was acidified with HCl_{cp} (2eq.). The mixture was stirred during 3h, the precipitate was then filtered off and washed with water (0.1L/mol).

Yield: 74% of intermediate 4

10 Example A1e

Preparation of intermediate 5



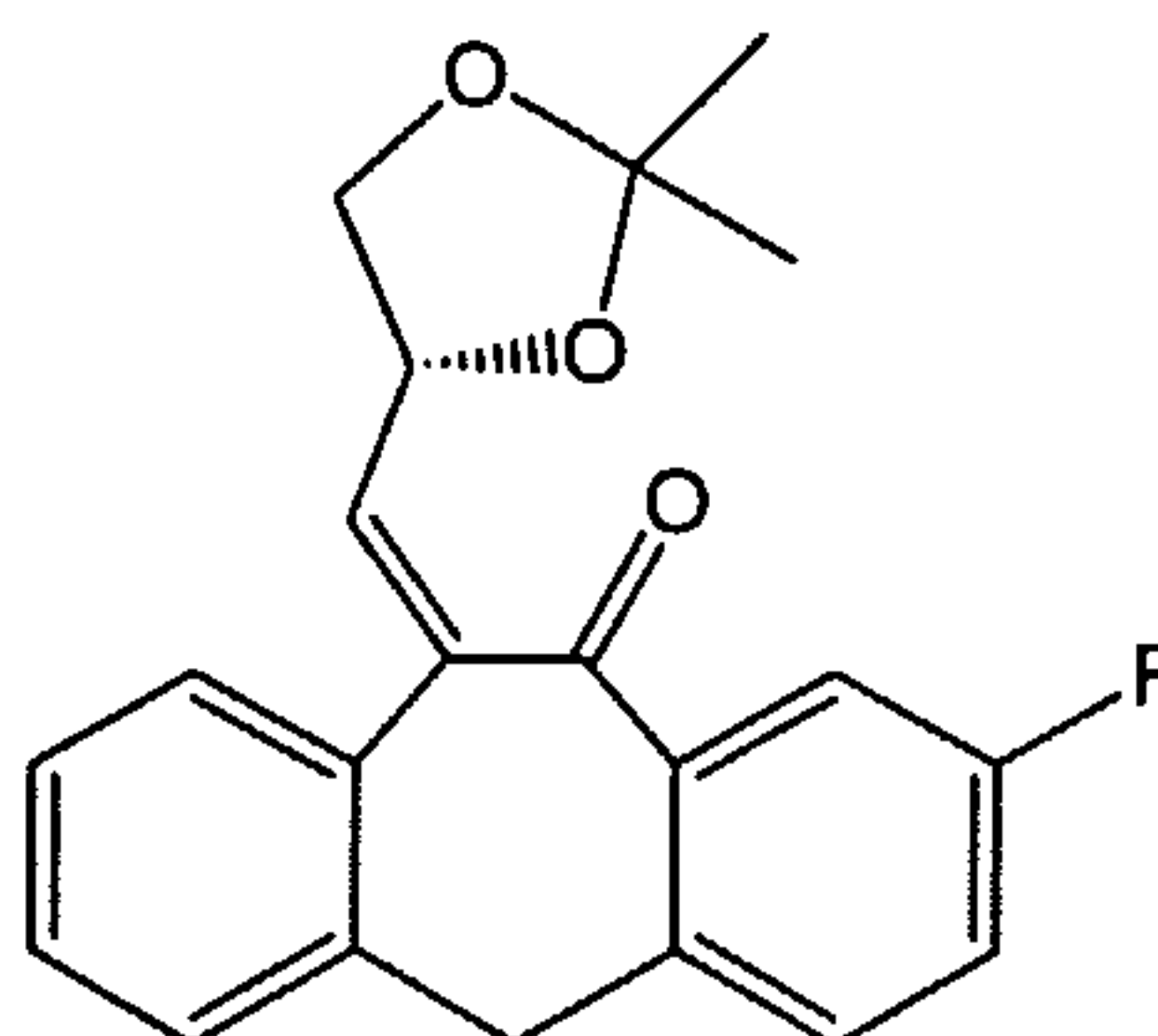
Intermediate 4 was dissolved in dichloromethane (0.6L/mol) and N,N-dimethyl acetamide, 15ml/mol). Thionyl chloride (1eq.) was added dropwise and the reaction mixture was refluxed during 1h30. After cooling down to 0°C, AlCl₃ (1eq.) was added and the mixture was stirred during 2h. HCl_{cp} (2eq.) and water (0.3L/mol) were added. The layers were separated, the organic layer was washed with 5% NaHCO₃ solution (0.6L/mol), then with water. The organic layer was evaporated, isopropanol (0.25L/mol) was added. The mixture was heated up to reflux (30 min.) and cooled down. Seeding occurred at 65°C. After cooling down further and stirring 2h at room temperature, the precipitate was filtered off, washed with isopropanol (0.05L/mol) and dried at 50°C under vacuum.

Yield: 40-80% of intermediate 5.

Typical purity between 77% and 93%

Example A1f

Preparation of intermediate 6



-17-

Intermediate 5 was dissolved in toluene (2L/mol). MgCl_2 anhydrous (1.2eq.) was added and the reaction mixture was stirred at room temperature during 30min. (S)-solketal aldehyde (from DSM, 1.7 eq., 20% solution in THF) was added and in one time 0.2eq. potassium tert-butoxide. Slight exothermicity was observed. The reaction mixture was stirred during 68h at room temperature. Water (0.5L/mol) was added, followed by 0.2eq. HCl_{cp} . The reaction mixture was stirred vigorously during 5min. The organic layer was washed again with 0.5L/mol water, then again with 1L/mol water. After adding Na_2SO_4 (125g/mol), active carbon (40g/mol), the mixture was filtered, the remaining solid was rinsed with toluene (0.2L/mol) and the filtrate was evaporated.

Isopropanol (1.5L/mol) was added, the reaction mixture was stirred at least 8h at 20-25°C, then cooled down to 0-5°C and stirred at that temperature for at least 2h. The precipitate was filtered off, washed with cold isopropanol (0.07L/mol) and air-dried at 40°C.

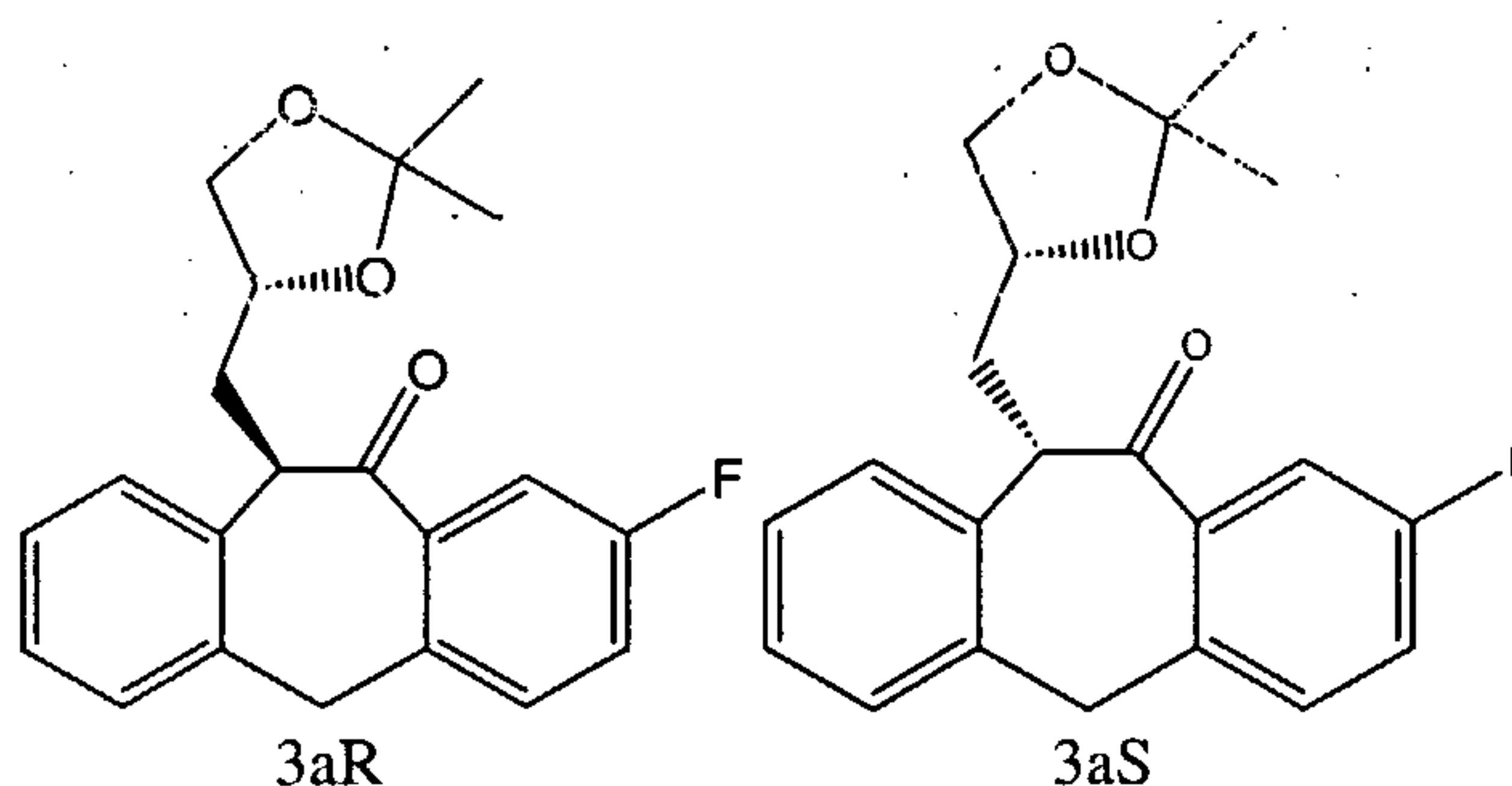
Physical yield: 58%

Purity: 93.1% (LC abs%) $\Rightarrow$ Active yield: 54% of intermediate 6.

The product could be recrystallized from iPrOH.

Example A2

a. Preparation of intermediate 7 and intermediate 8



Intermediate 6 was dissolved in acetone (2L/mol), triethylamine (1eq.) and thiophene (4% solution in EtOH, 0.007L/mol.) were added. After suspending Pd/C (60g/mol, 10% wet), the hydrogenation was performed. In case the conversion was low, another 60g/mol Pd/C was added and the hydrogenation was continued till complete conversion. Some exothermicity was observed (temperature rises to 35°C). When the reaction was completed, the catalyst was filtered off over diatomaceous earth and the solid was rinsed with acetone (0.07L/mol). The filtrate was evaporated (atm.) at 75-80°C. The residue was cooled down to 70-75°C. Isopropanol was added (0.84L/mol), then evaporated again. The reaction mixture was cooled down. The pure intermediate 7 and pure intermediate 8 could be obtained via chromatographic separation (HPLC: Waters 515 pump, Merck Hibar[®] 250x25 mm column filled with Lichrosorb[®] SI 60 7 μm ; Eluent: diether/hexane 60/40; flow rate: 11 mL/min). Yielding intermediate 7 and intermediate 8 in a ratio of 3:2.

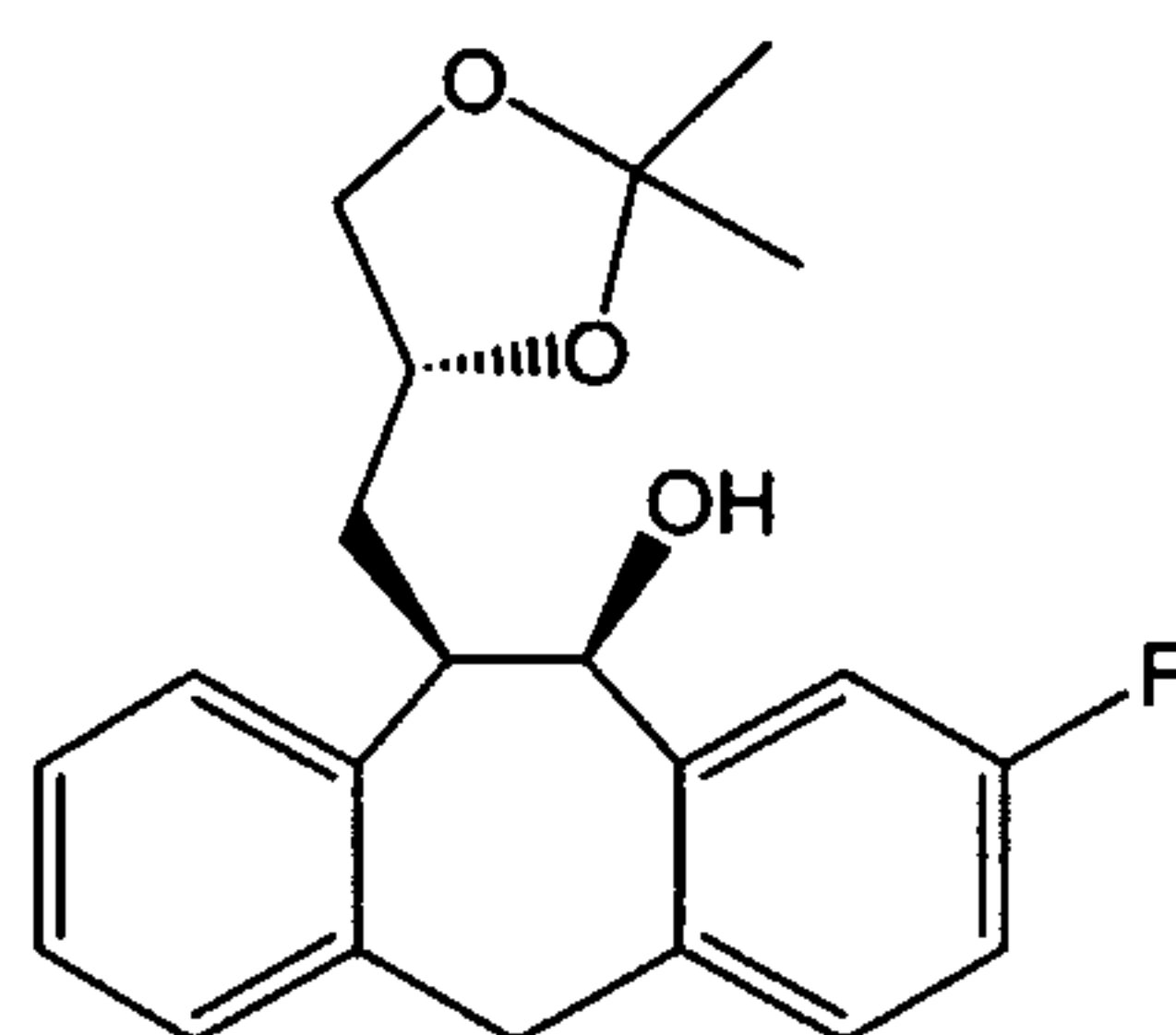
-18-

b. Conversion of intermediate 8 to intermediate 7.

Intermediate 6 (1.00 g, 2.96 mmol) was dissolved in i-PrOH (30 ml). Et₃N (0.63 ml, 4.50 mmol) and Pd/C were added and the hydrogenation was performed for 6 hr. Then the mixture was filtrated through celite and washed 4 times with CH₂Cl₂. After
5 evaporation, i-PrOH (5ml), Et₃N (1.20 ml) was added and stirred at 40°C for 1 hr. The reaction mixture was cooled to room temperature and allowed to crystallisation. The crystals were filtered off and dried under vacuum to afford pure ketone as white crystalline powder. Yielding intermediate 7 (0.86 g, 86%) (mp. 144-146°C).

Example A3a

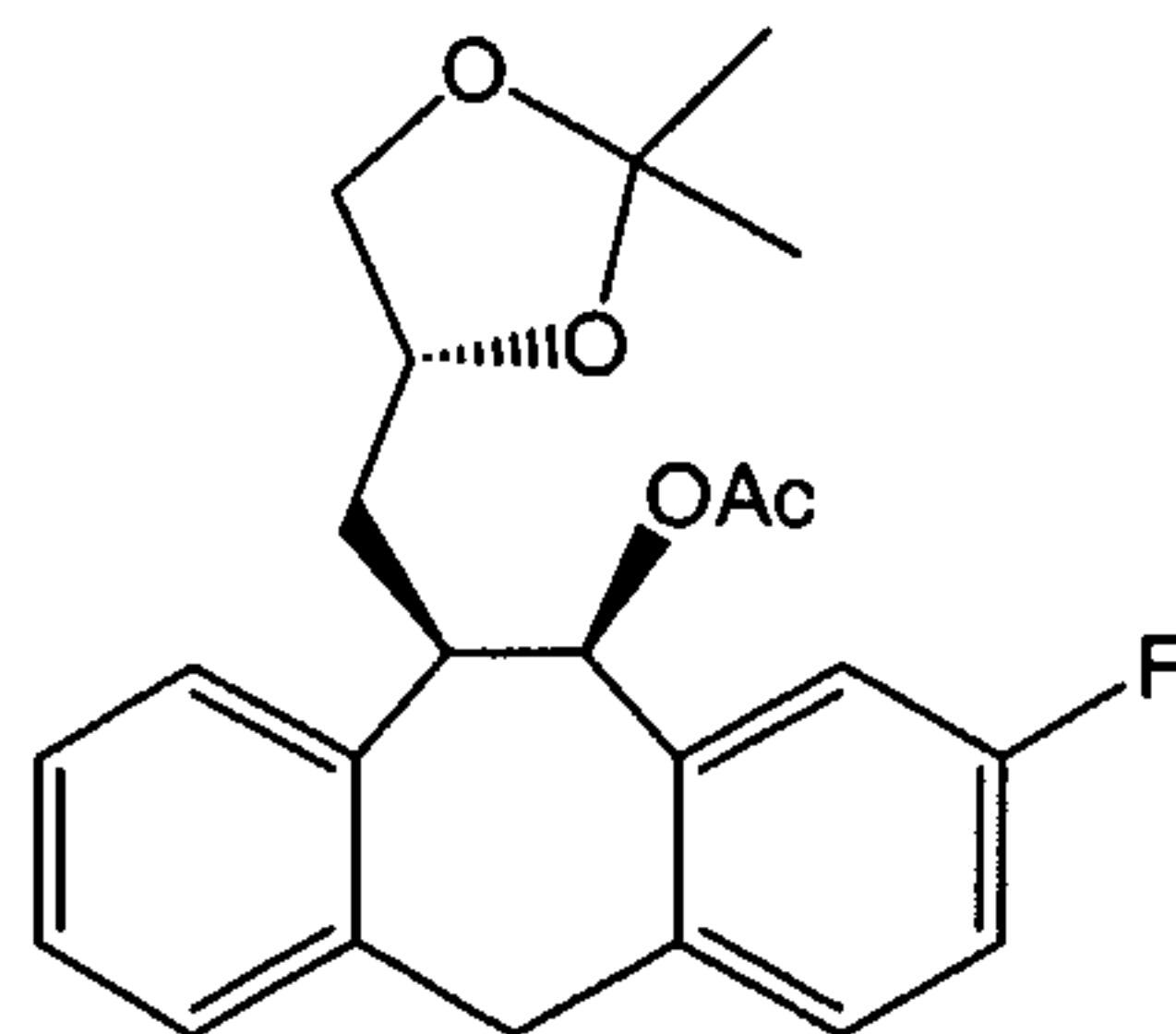
Preparation of intermediate 9



10 In THF (1.4L/mol), a buffer solution of pH 7 containing potassium dihydrogen-phosphate and disodium hydrogenphosphate, 0.3L/mol was added. The mixture was cooled down to 0-5°C and intermediate 7 was added. Lithium borohydride 2N in THF (0.48eq.) was added and the temperature was maintained under 10°C. After the addition, the reaction mixture was stirred during 2h at 0-5°C. Acetone (1.7eq.) was
15 cautiously added and the reaction mixture was stirred to room temperature. Water (0.7L/mol) was added at 10-25°C and the reaction mixture was stirred 30min. at room temperature. Acetic acid (2.2eq.) and 200ml toluene were added. After stirring during 10min., the organic layer was washed with water (0.36L/mol) and NaOH 50% (2.2eq.), then washed again twice with water (0.45L/mol). The solution was evaporated (a
20 viscous oil was obtained) and dichloromethane (1L/mol) was added. The solution was used further in the next step, assuming that 100% intermediate 9 had been obtained.

Example A3b

Preparation of intermediate 10



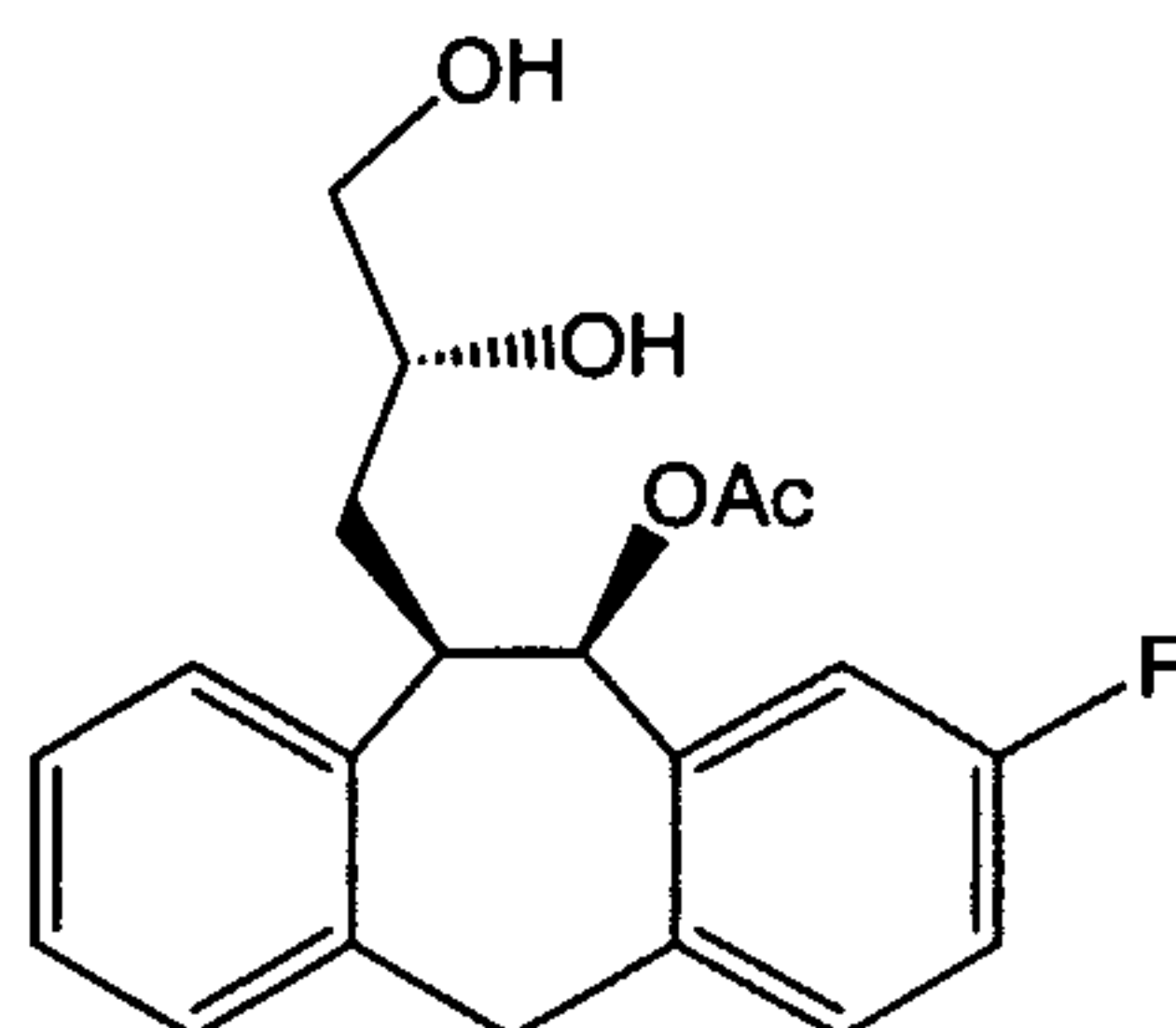
Dimethylaminopyridine (0.05eq.) and triethylamine (1.1eq.) were added to intermediate 9 (solution in CH₂Cl₂). Acetic anhydride (1.1eq.) was added dropwise.
25 The temperature was allowed to rise to 40°C. The reaction mixture was stirred during

-19-

2h and NH_4Cl 1N (0.5eq.). About 90% of the solvent was distilled off (atmospheric pressure) and isopropanol (1L/mol) was added. About one fifth of the solvent was evaporated (atmospheric pressure) and the reaction mixture was slowly cooled down to room temperature and stirred overnight. After cooling down further to 0-5°C and stirring at that temperature during 8-16h, the precipitate was filtered off and washed with isopropanol (0.2L/mol). The product was dried for 16h at 50°C under vacuum. Active yield: 80% of intermediate 10.

Example A3c

Preparation of intermediate 11

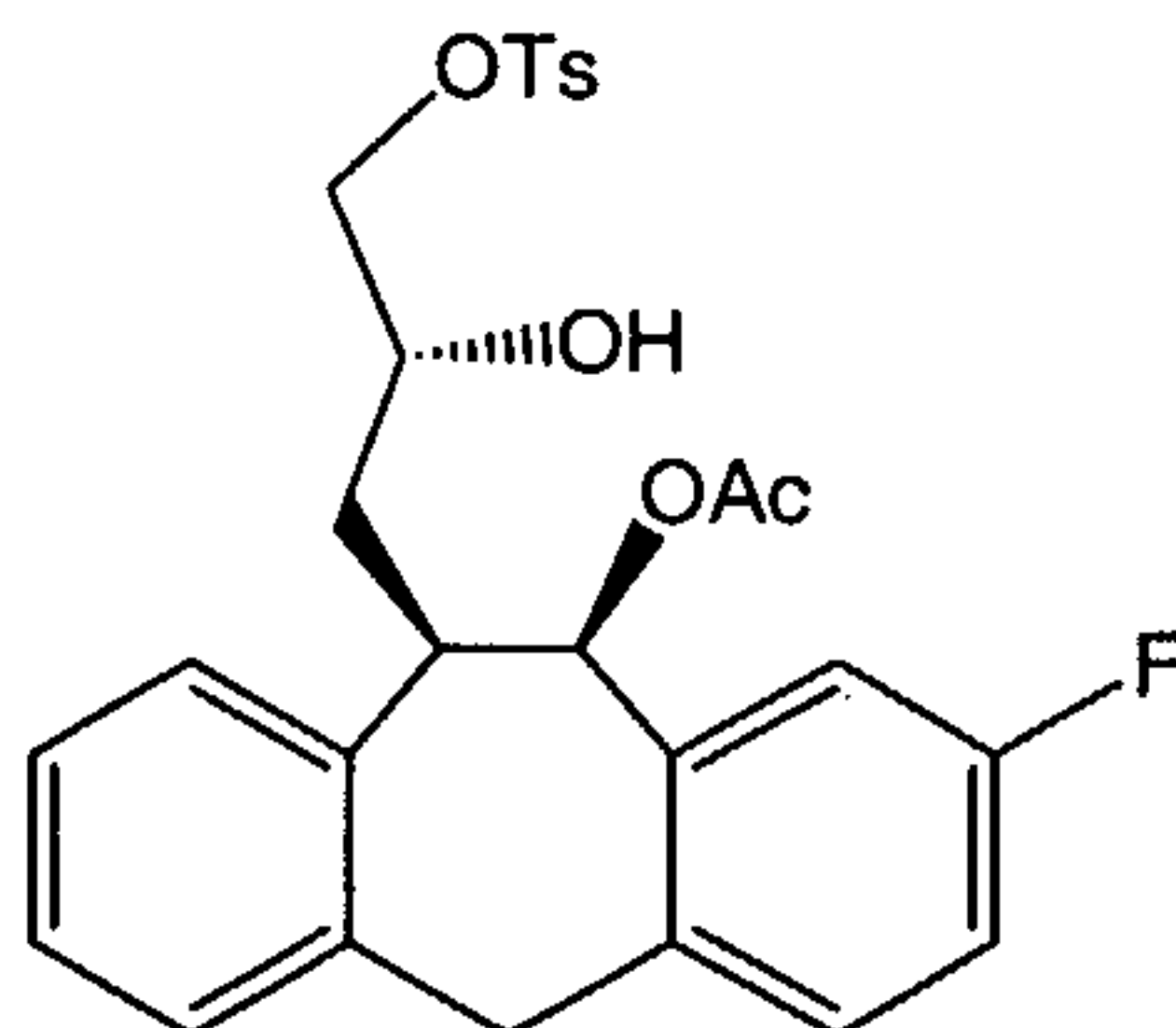


Intermediate 10 was suspended in water (0.3L/mol) and glacial acetic acid (0.45L/mol) was added. This mixture was stirred at 55 °C for 8 hours. The reaction proceeded to 93% conversion. The reaction mixture was cooled to ambient temperature. Water (1.5L/mol) and methylene chloride (0.8L/mol) were charged and the mixture was stirred for 15 minutes. The water phase was separated and extracted three times with methylene chloride (each time with 0.6L/mol). The combined organic phases were washed with water (1L/mol) and dried over sodium sulfate. The solvent was evaporated, yielding a fluffy white solid.

Active yield: 94% of intermediate 11.

Example A3d

Preparation of intermediate 12

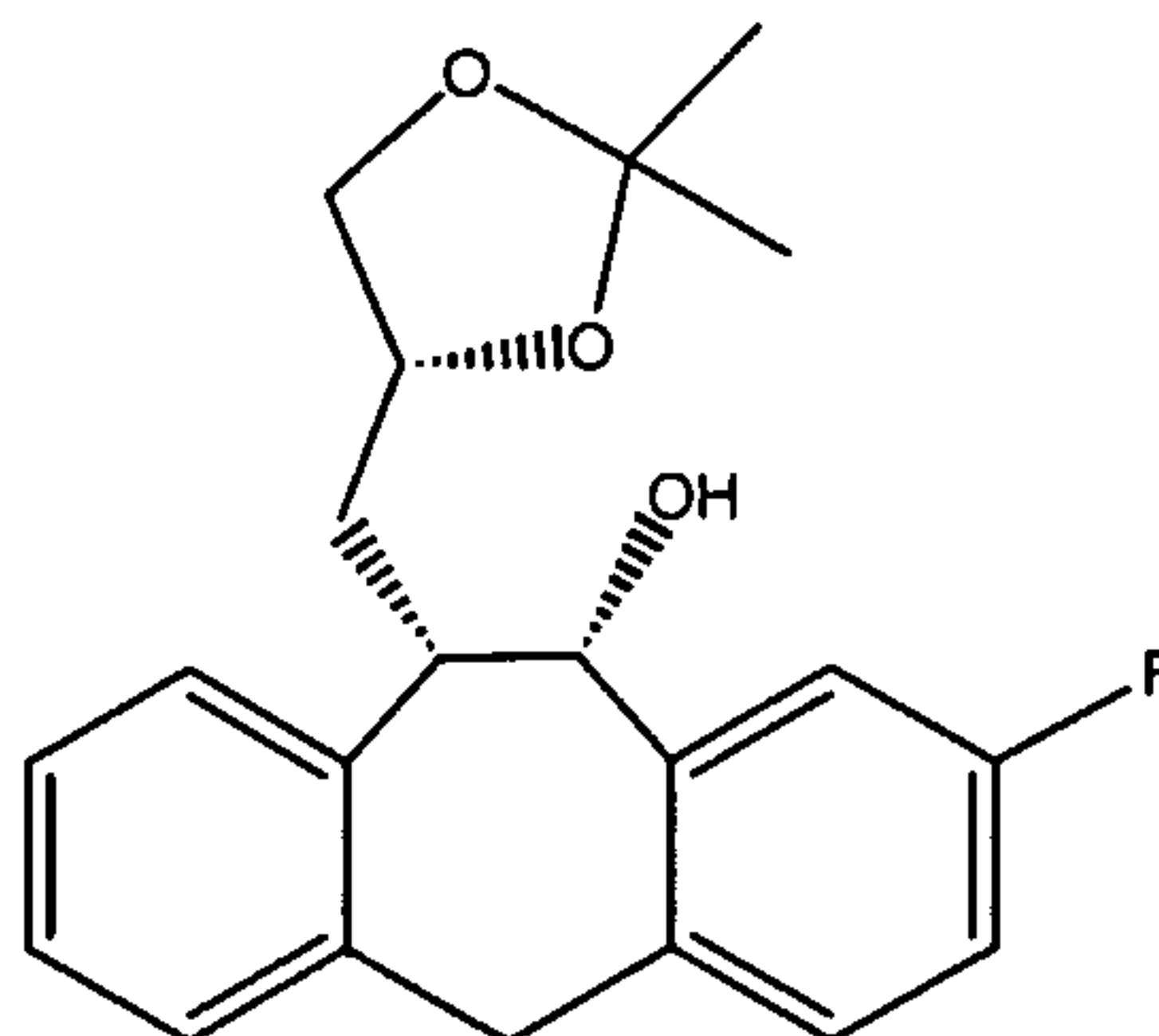


Intermediate 11 was dissolved in toluene (3.5L/mol) and *p*-toluenesulfonyl chloride (1.5eq.) was added in one portion. To this mixture, pyridine (10eq.) was added dropwise. The reaction mixture was stirred 4h at 40°C. Water (1.5L/mol) was added, followed by 1 M ammonium chloride (1.3eq.). After drying the organic phase over sodium sulfate, the organic solvent was evaporated yielding crude product, which was a mixture of starting material (8%), mono-tosylate (76%) and di-tosylate (16%) (LC area%). Yield: 61% of intermediate 12.

-20-

Example A4a

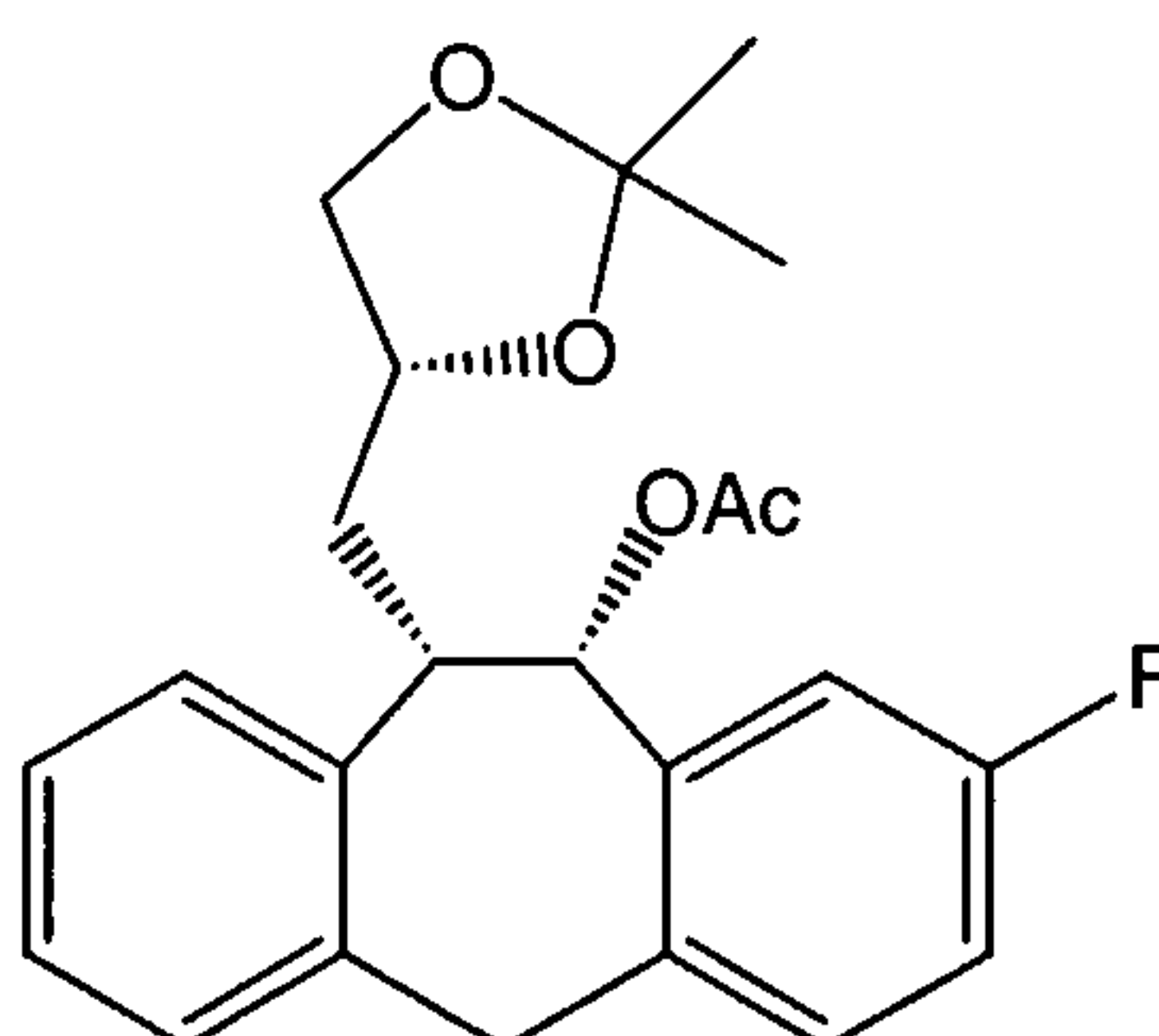
Preparation of intermediate 13



Solid sodium borohydride (2.50g, 66 mmol) was added in small portions within 15 min. into a magnetically stirred, ice-cooled solution of (11R) and (11S)-11-{[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-8-fluoro-5,11-dihydro-10H-dibenzo[a,d]cyclohepten-10-one (reaction mixture of intermediate 7 and 8 before separation) (65:35, 1278 mg, 3.75 mmol) in isopropanol (160 mL) and 0.5 M phosphate buffer (pH 7, 63 mL). Reaction mixture was stirred at 0°C for additional 15 min., quenched with saturated aqueous NH₄Cl (30 mL); organic phase was separated, aqueous solution extracted with ether (2×30mL), combined organics washed with water (2×50mL), then brine (50 mL), dried (MgSO₄), evaporated *in vacuo*, to furnish crude mixture of two alcohols. HPLC separation (Waters 515 pump, 2 mL injection loop, Merck Hibar[®] 250 × 25 mm column LiChrosorb[®] SI 60 7μm, Waters 2410 refractive index detector, EtOAc-hexane 30:70, 15 mL/min) gave pure intermediate 13 (10S,11S)-11-{[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-8-fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-10-ol (449 mg, 1.31 mmol, 35%) as a colorless oil.

Example A4b

Preparation of intermediate 14



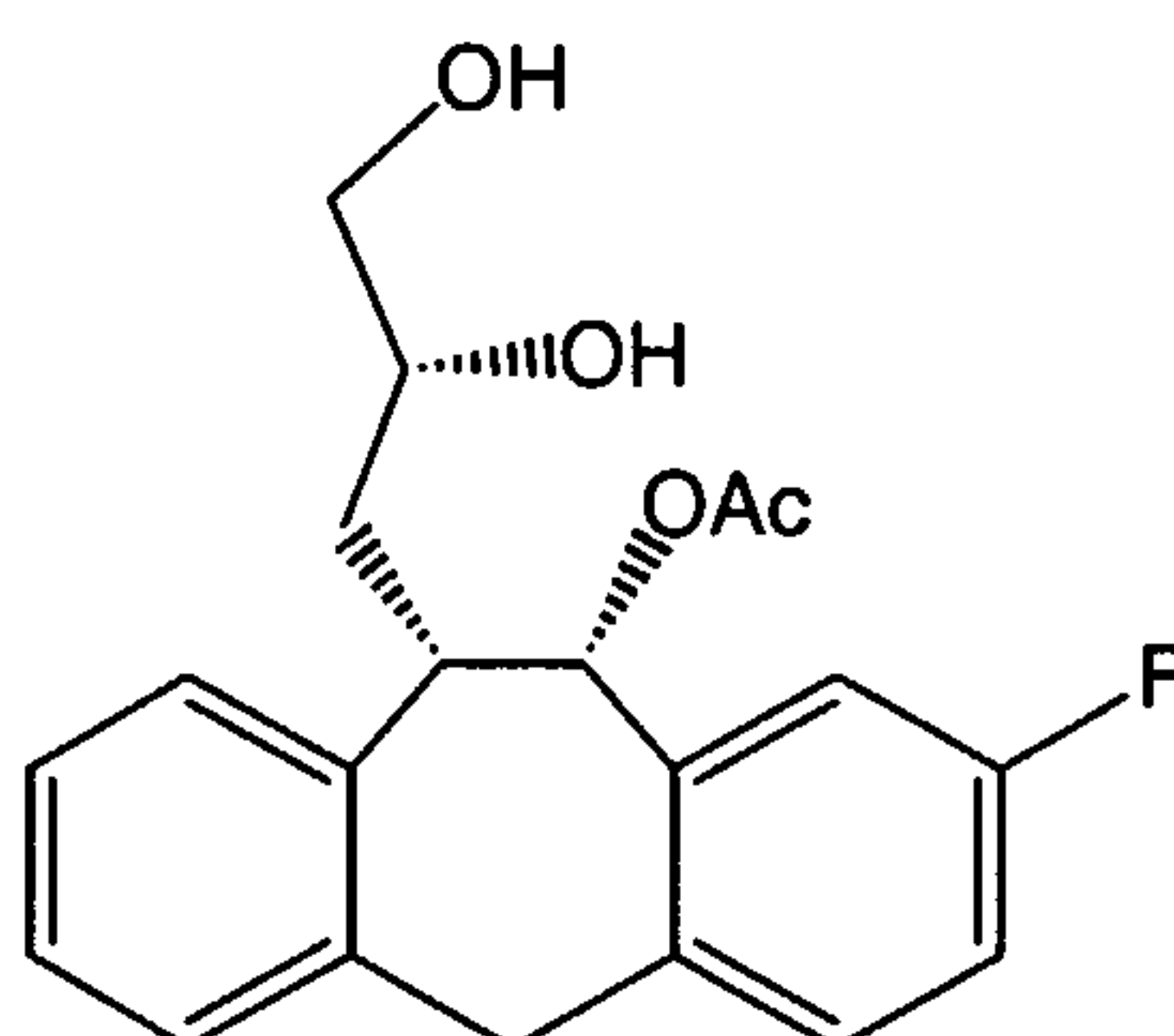
A mixture of the alcohol (intermediate 13) (449 mg, 1.31 mmol), triethylamine (728 μL, 530 mg, 5.24 mmol, 4 equiv.), DMAP (160 mg, 1.31 mmol, 1 equiv.), and acetic anhydride (318 μL, 343 mg, 3.36 mmol, 2.56 equiv) in dichloromethane (20 mL) was stirred at room temperature under N₂ for 2h, then quenched with saturated aqueous NH₄Cl (12 mL), organic phase was separated, aqueous solution extracted with CH₂Cl₂ (15 mL), combined organics washed with water (2 × 20 mL), 0.5N HCl (10 mL), then water

-21-

(2 × 20 mL), dried (MgSO₄) and evaporated *in vacuo* to furnish crude intermediate 14 (10*S*,11*S*)-11-[[*(4R)*-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-10-yl acetate (478 mg, 1.24 mmol, 95%) as a yellowish oil, which was converted without further purification.

5 Example A4c

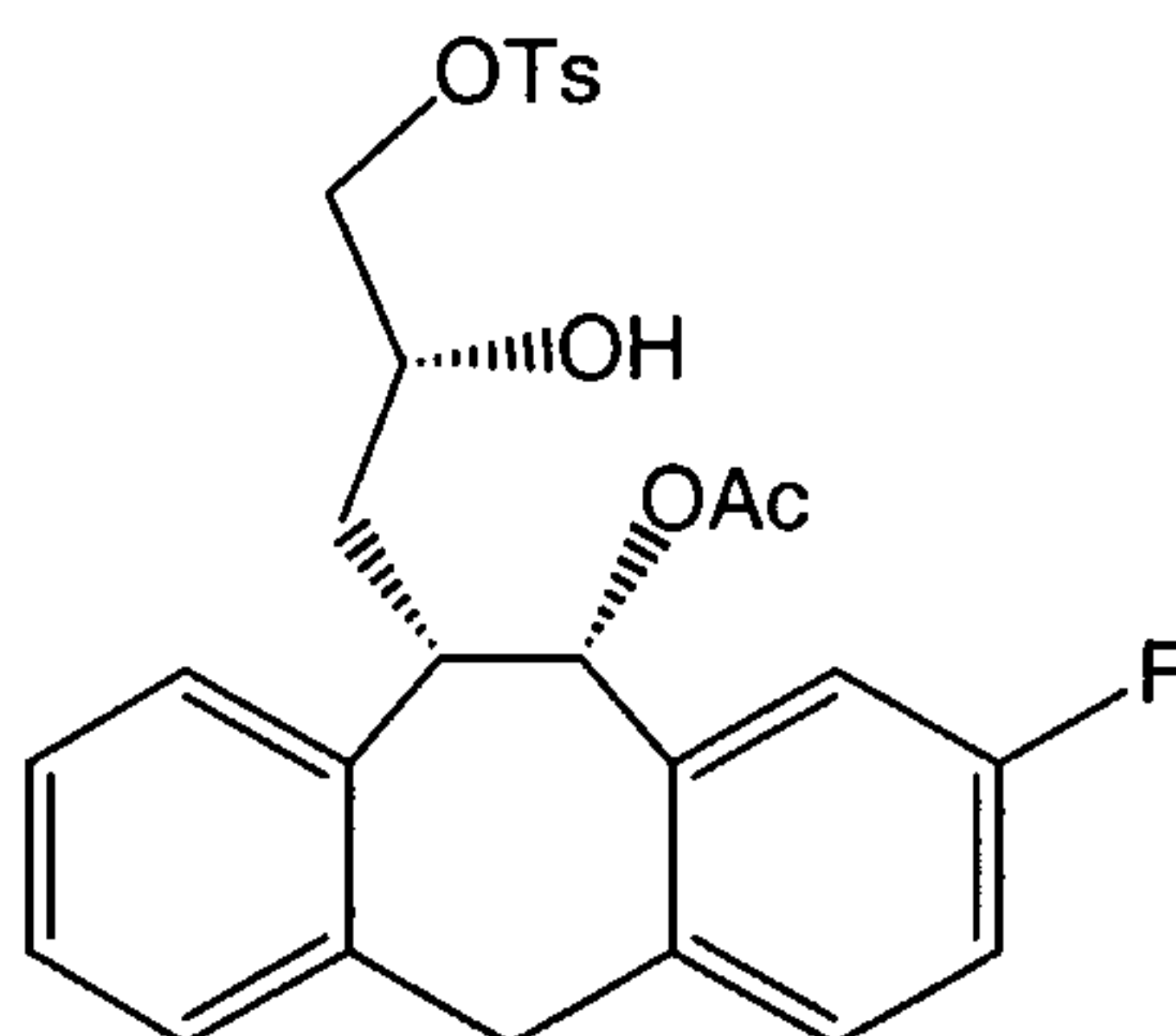
Preparation of intermediate 15



A mixture of acetal (intermediate 14) (478 mg, 1.24 mmol), 1N HCl (20 mL) and THF (20 mL) was stirred at room temperature under N₂ until starting material disappeared (*ca.* 6h, TLC control, EtOAc-hexane 80:20), then 25% aqueous K₂CO₃ (20 mL) was added, organic phase separated, aqueous solution extracted with ether (2×15 mL),
 10 combined organics washed with water (3×20 mL), dried (MgSO₄) and evaporated *in vacuo*. Crude product was purified by column chromatography (EtOAc-hexane 65:35) to obtain intermediate 15 (10*S*,11*S*)-11-[(2*R*)-2,3-dihydroxypropyl]-8-fluoro-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-10-yl acetate (389 mg, 1.13 mmol, 91%) as a colorless oil.

15 Example A4d

Preparation of intermediate 16



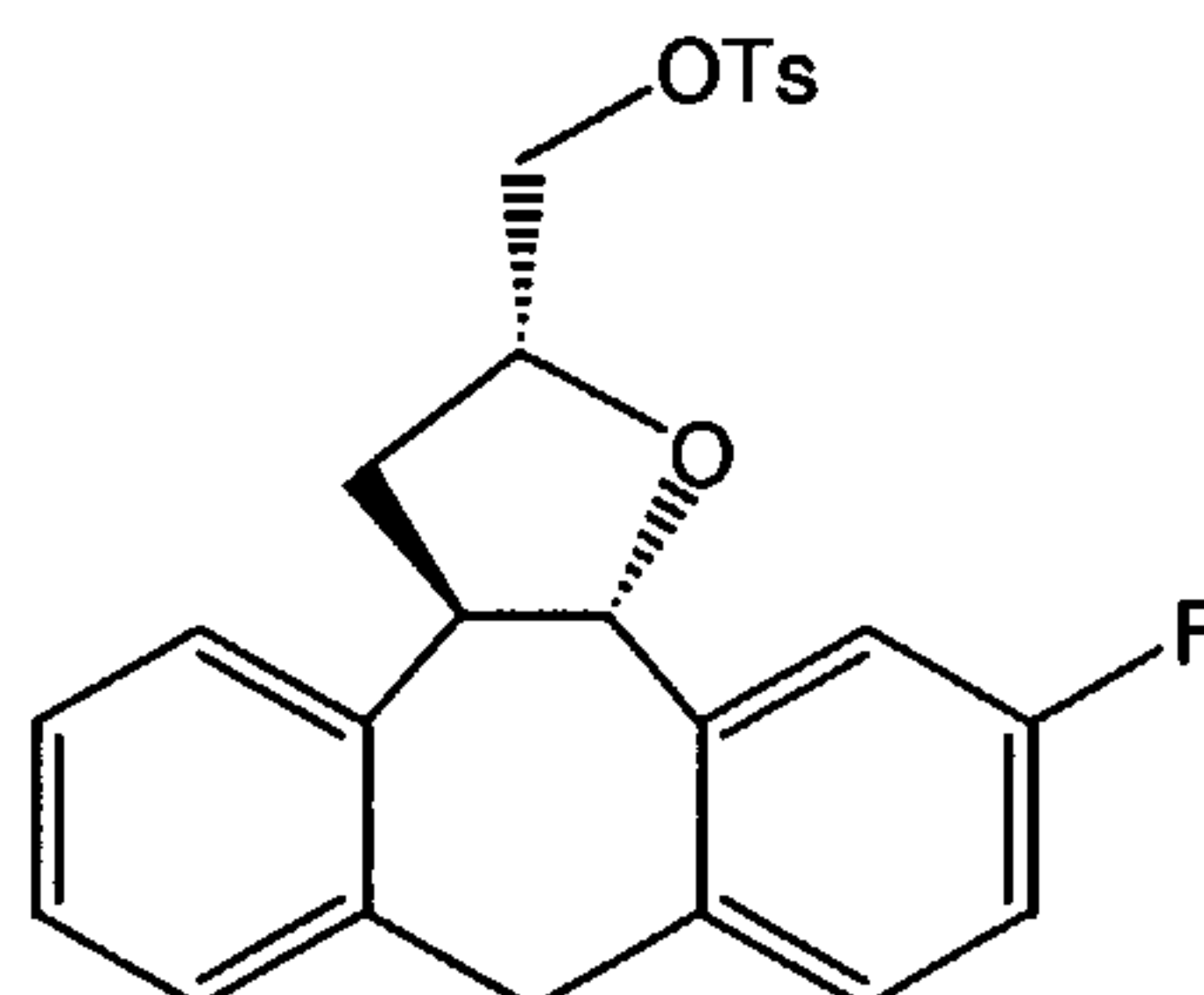
A mixture of the diol (intermediate 15) (389 mg, 1.13 mmol), triethylamine (628 μL, 457 mg, 4.52 mmol, 4 equiv.), DMAP (138 mg, 1.13 mmol, 1 equiv.), dibutyl(oxo)stannane (141 mg, 0.566 mmol, 0.5 equiv.), and tosyl chloride (431 mg, 2.26 mmol, 2.0 equiv) in dichloromethane (20 mL) was stirred at room temperature
 20 under N₂ for 12h, then quenched with saturated aqueous NH₄Cl (15 mL), organic phase was separated, aqueous solution extracted with CH₂Cl₂ (2 × 15 mL), combined organics washed with water (3 × 20 mL), filtered through 5 cm layer of MgSO₄, and evaporated *in vacuo* to furnish crude intermediate 16 (10*S*,11*S*)-8-fluoro-11-[(2*R*)-2-

-22-

hydroxy-3-{[(4-methylphenyl)sulfonyl]oxy}propyl)-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-10-yl acetate (406 mg, 0.814 mmol, 72%) as a yellowish semisolid mass, which was converted without further purification.

Example A5

Preparation of intermediate 17

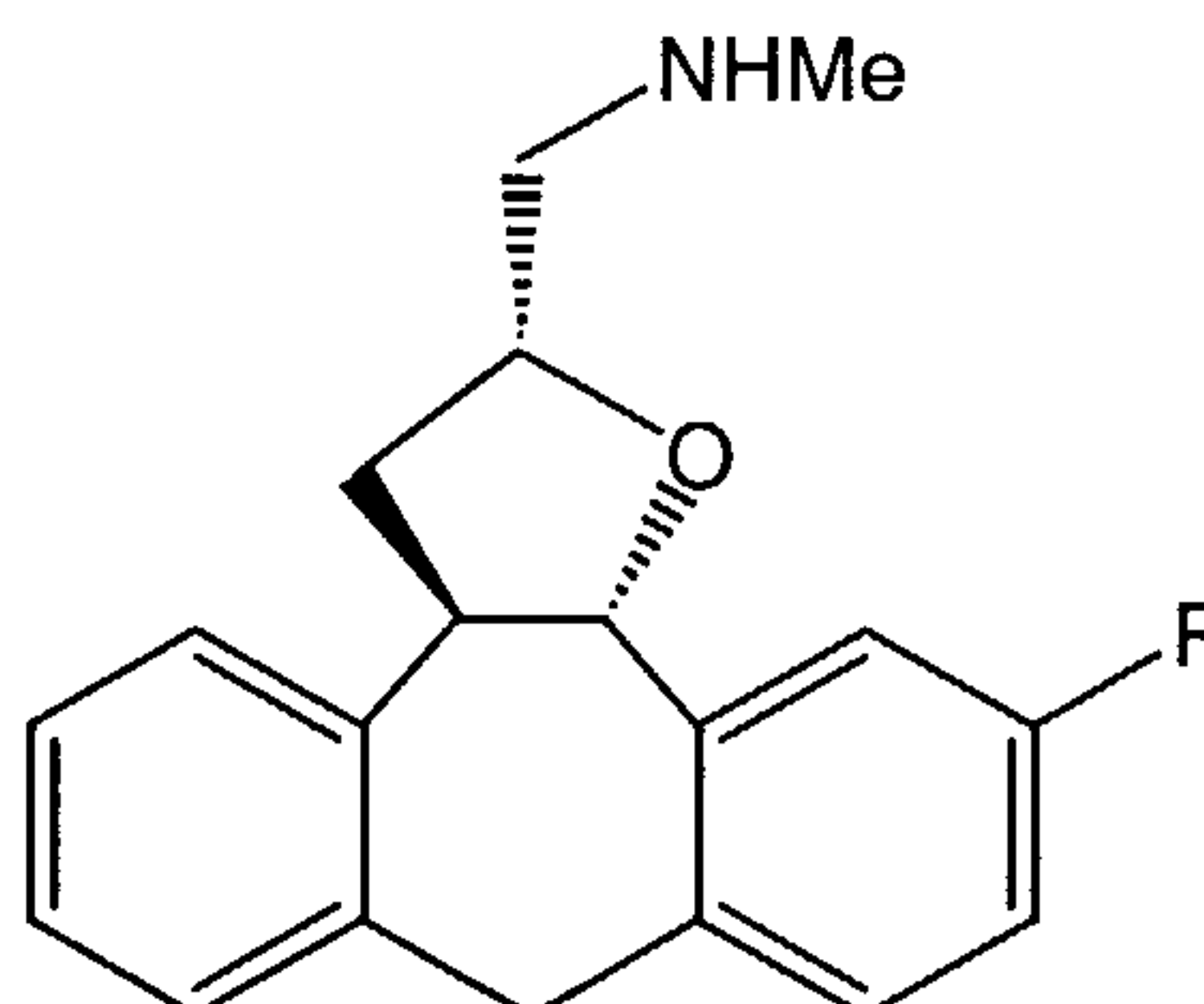


- 5 Intermediate 12 (prepared according to A3d) (0.15 g, 0.298 mmol) was dissolved in dry toluene. $\text{CH}_3\text{SO}_3\text{H}$ (19 μl , 0.149 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. Then Na_2CO_3 (sat. aq. sol.) was added. After extracting 3 times with CH_2Cl_2 the combined organic phases were dried with MgSO_4 . After removal of the solvent, the residue was purified on silica gel column with ether/hexane (50/50), which gave a yellowish oil. Yield: 0.11 g of intermediate 17, 82%.

B. Preparation of the final compounds

Example B

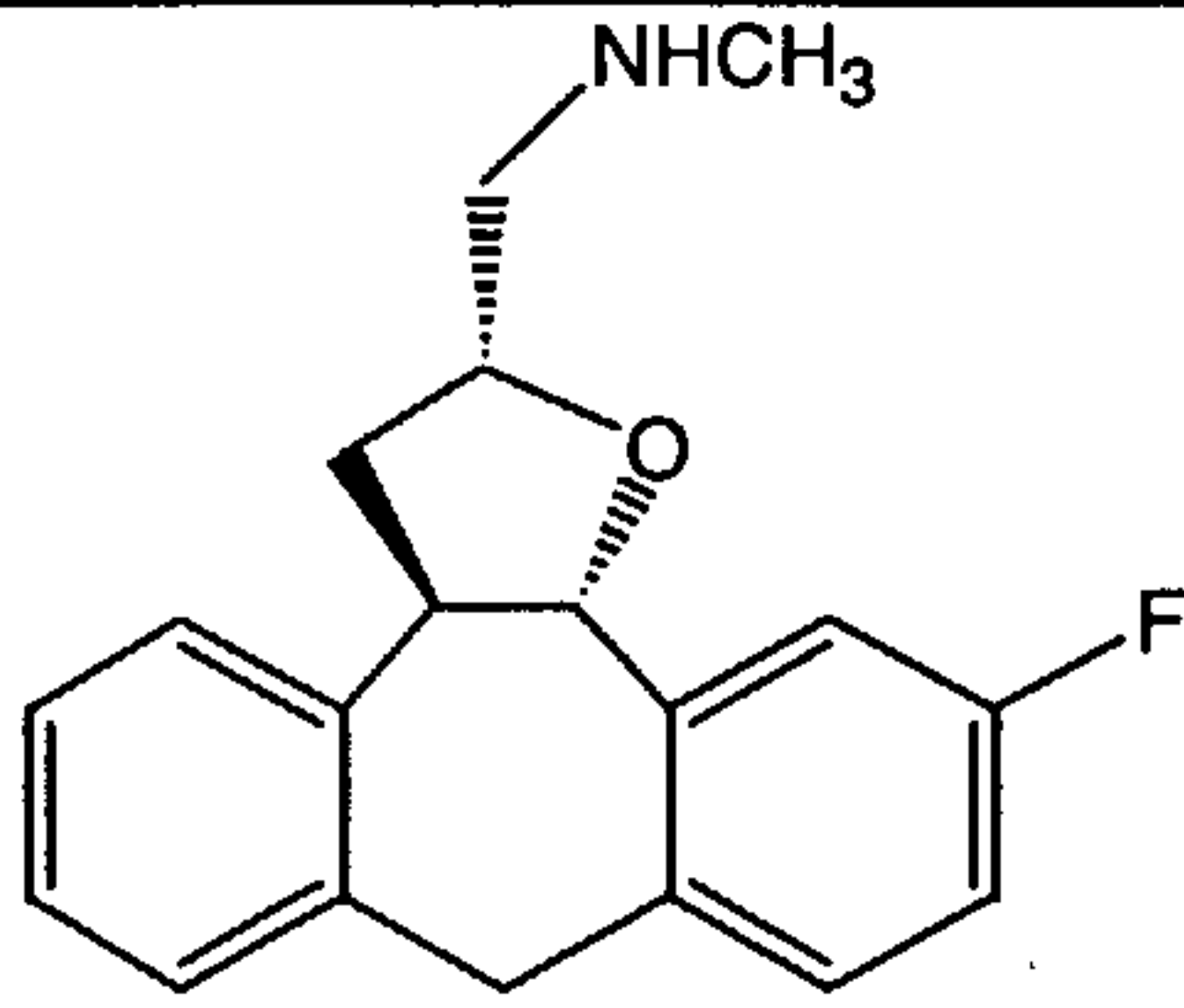
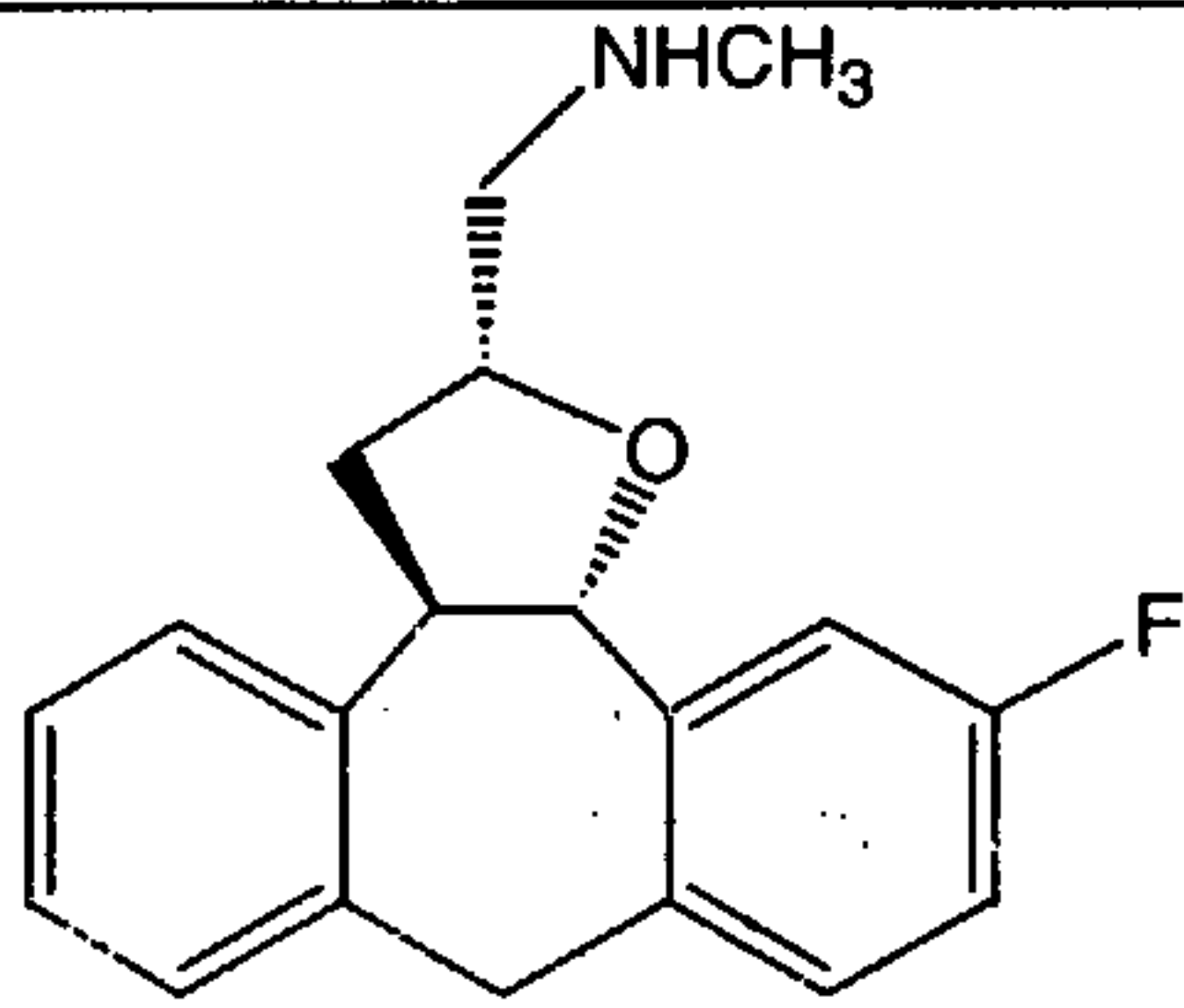
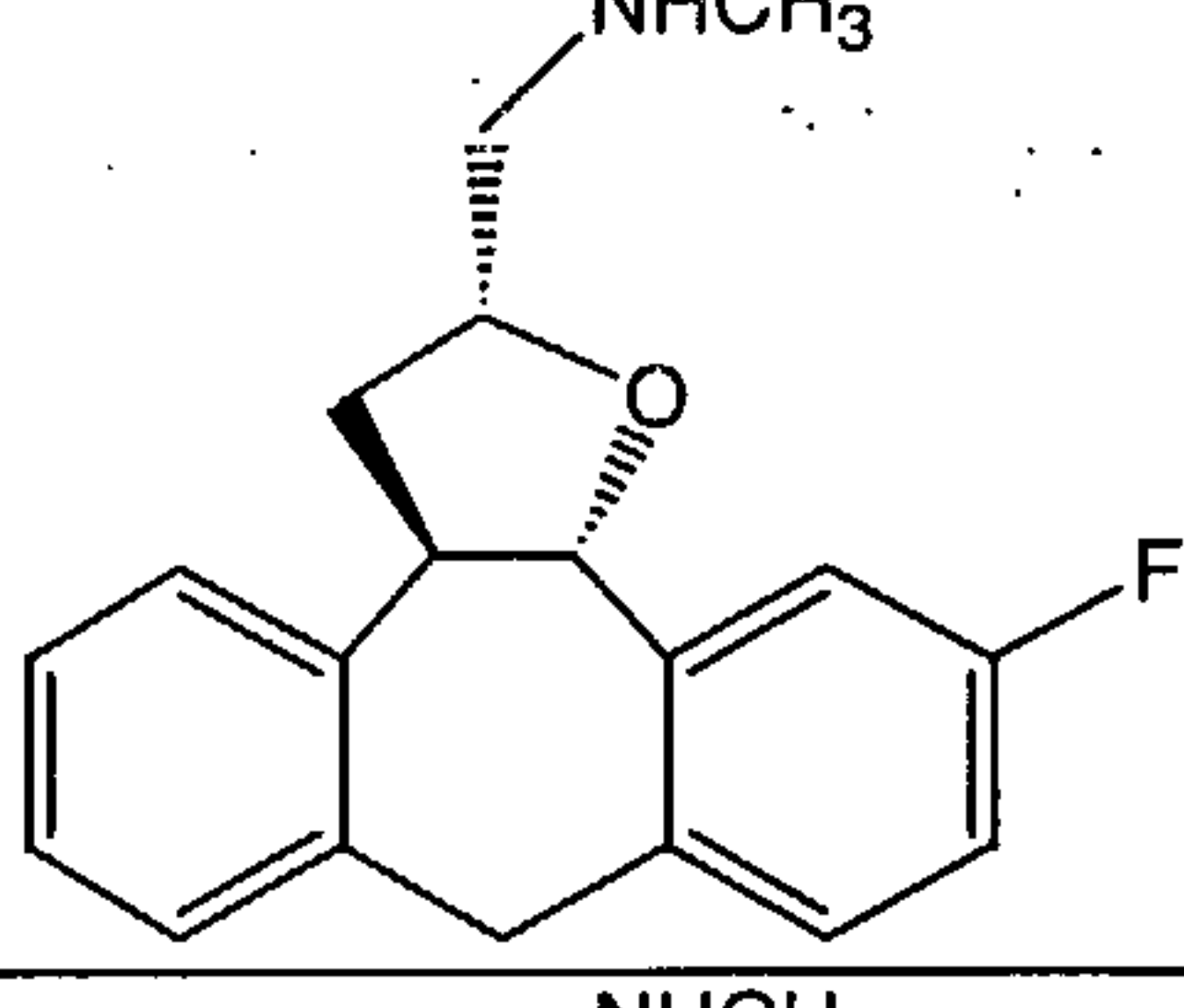
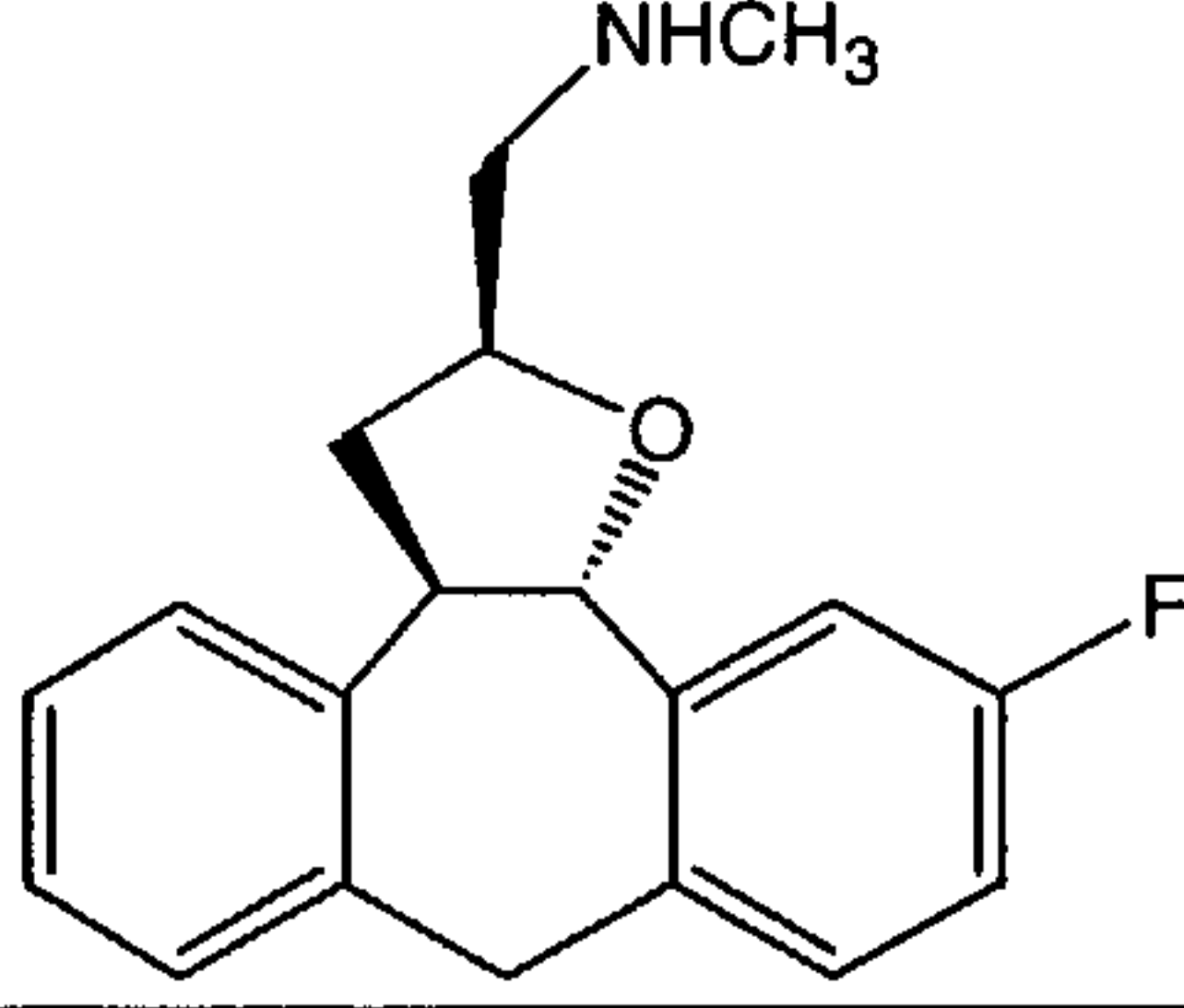
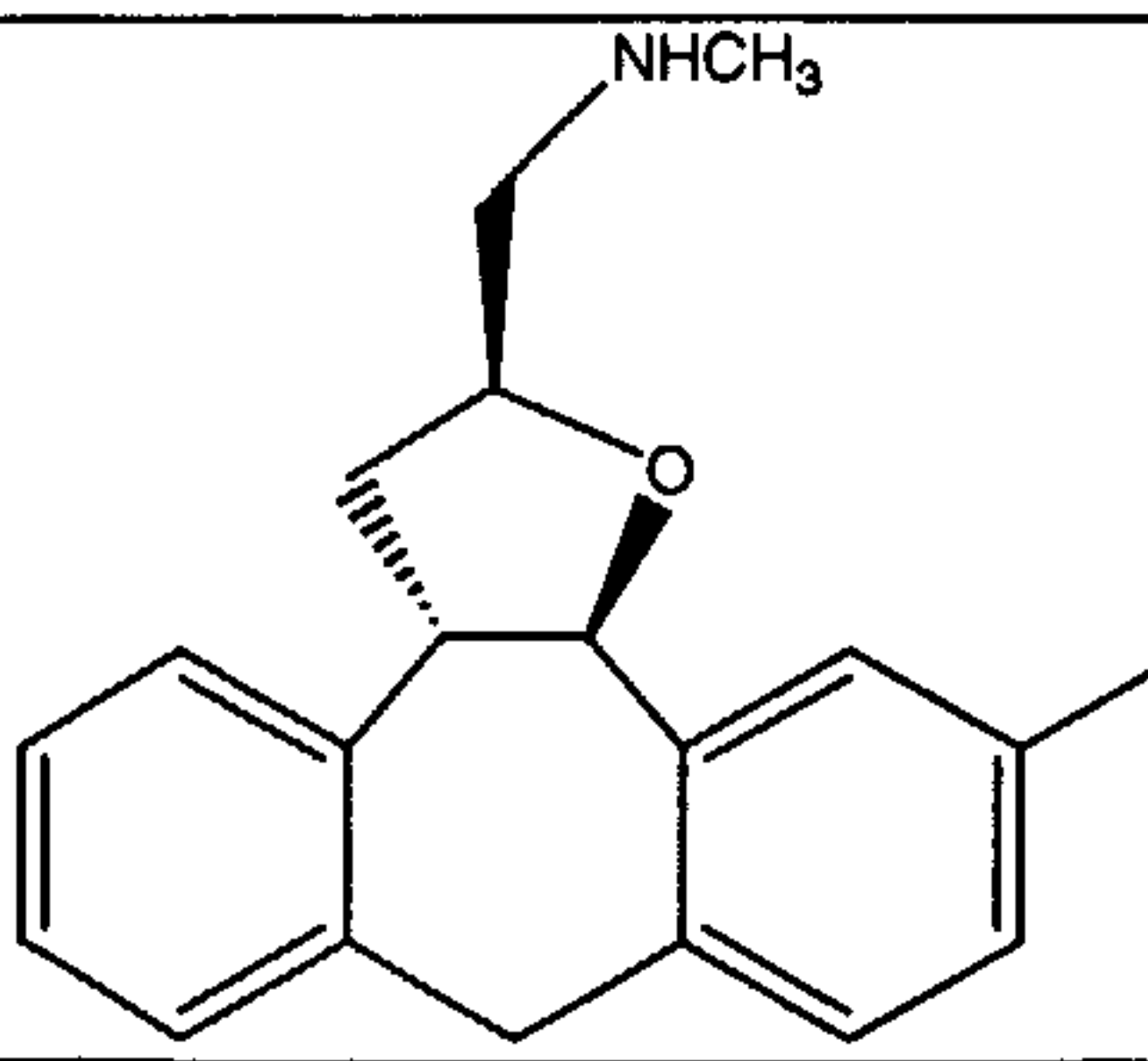
Preparation of compound 1

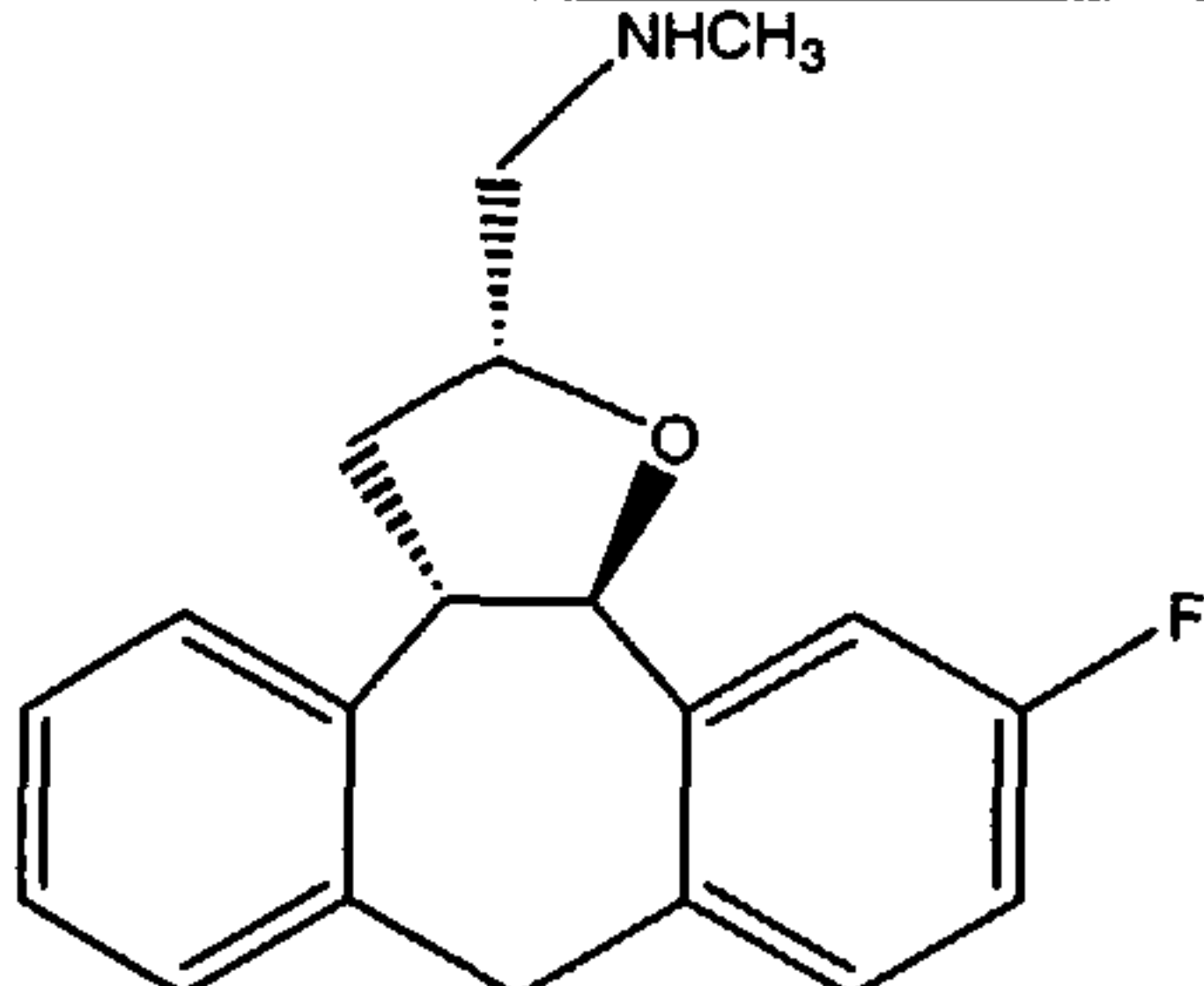


- 15 Intermediate 17 (prepared according to A5) (0.10 g, 0.228 mmol) was dissolved in THF (10 ml) and 40% CH_3NH_2 (10 ml) was added. The solution was put in a tightly sealed steel vessel and heated at 130°C for 12 hr. The reaction mixture was cooled down to room temperature, NH_4Cl (sat. aq. sol.) was added. The reaction mixture was extracted 3 times with CH_2Cl_2 and dried with MgSO_4 . After evaporation, the residue was purified on silica gel column chromatography with $\text{MeOH}/\text{CHCl}_3$ (15/85), yielding a yellowish oil (60 mg of compound 1, 88%).

Table 1 lists the compounds that were prepared according to one of the above Examples.

Table 1:

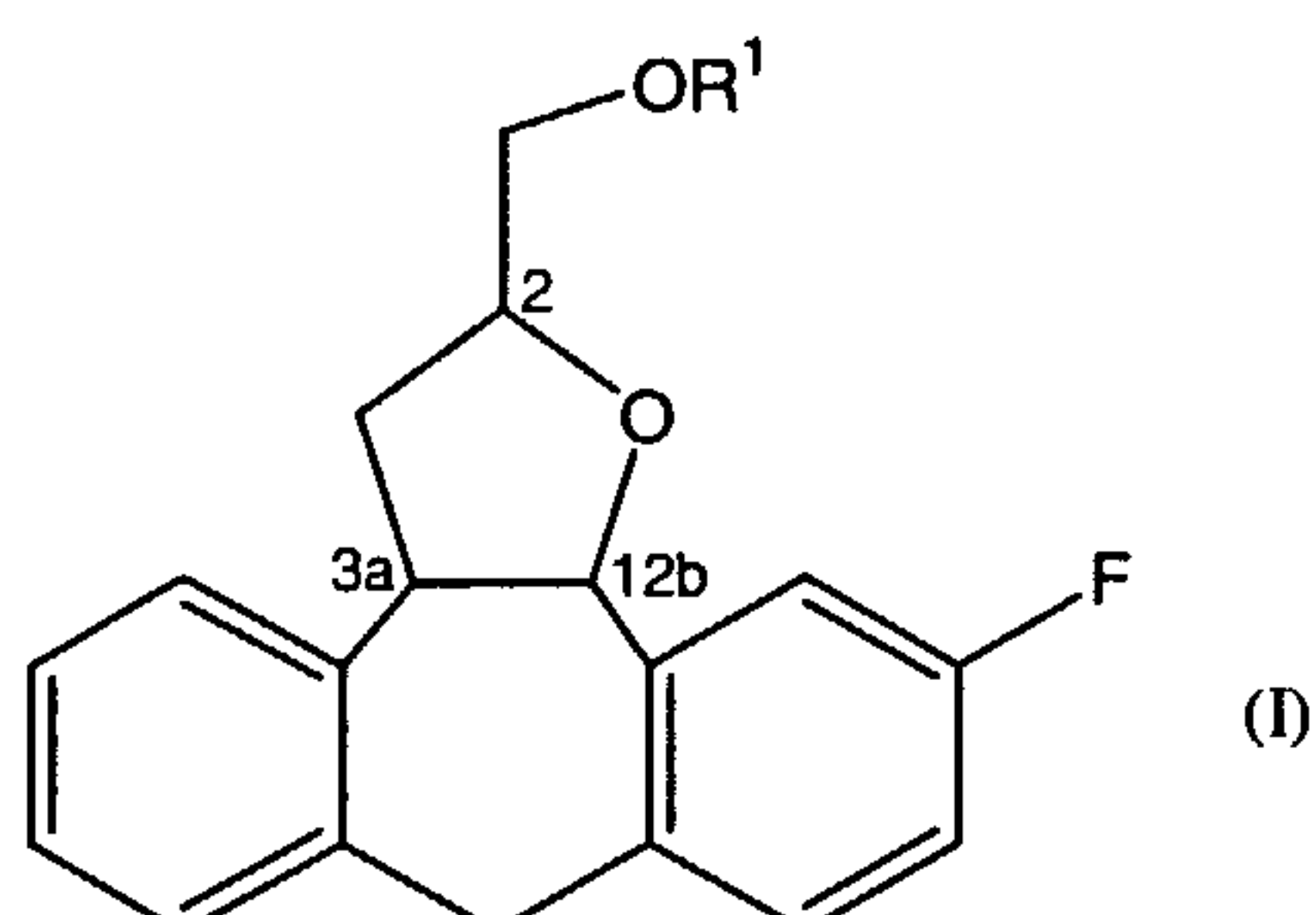
Comp. No.	Ex. No.	Structure	Physical data
1	B		2R, 3aR, 12bS: <u>Mass spectrum</u> : -CI m/z (assignment, relative intensity) 298 (MH ⁺ , 100%) -EI: m/z (assignment, relative intensity) 297 (M ⁺ , 3%), 279 (M ⁺ -H ₂ O, 6%), 248 (M ⁺ -H ₂ O-CH ₃ NH ₂ , 3%) -High resolution EI Calculated C ₁₉ H ₂₀ FNO (M ⁺): 297.1529 Found: 297.1527 (100%)
2	B		.(+)-[R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1); [2R-(2a, 3aα, 12bβ)]
3	B		.(S)-Alpha-hydroxybenzeneacetate (1:1); [2R-(2a, 3aα, 12bβ)]
4	B		2S, 3aR, 12bS;
5	B		2S, 3aS, 12bR;

Comp . No.	Ex. No.	Structure	Physical data
6	B		2R, 3aS, 12bR;

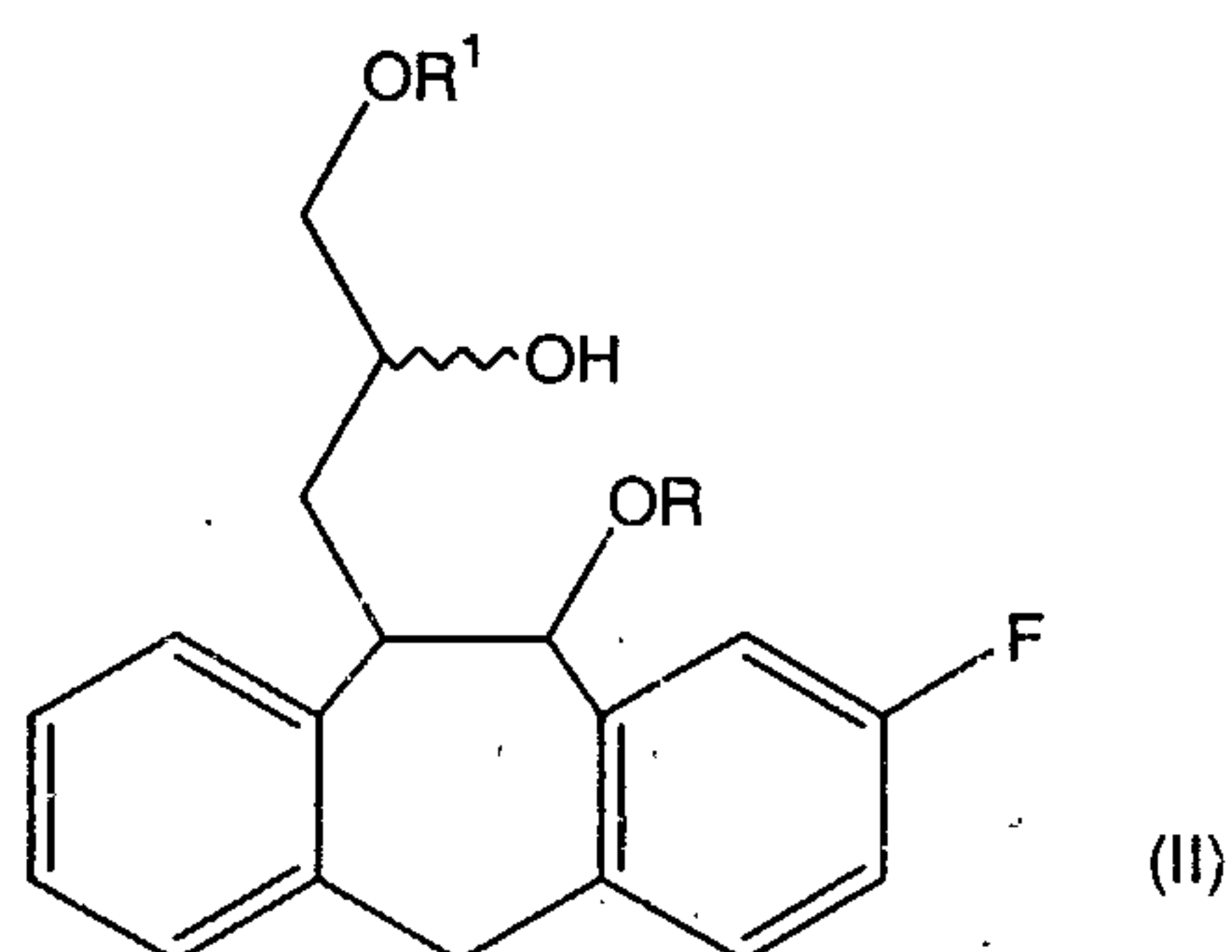
-25-

Claims

1. A process for preparing each individual diastereoisomer of formula (I):



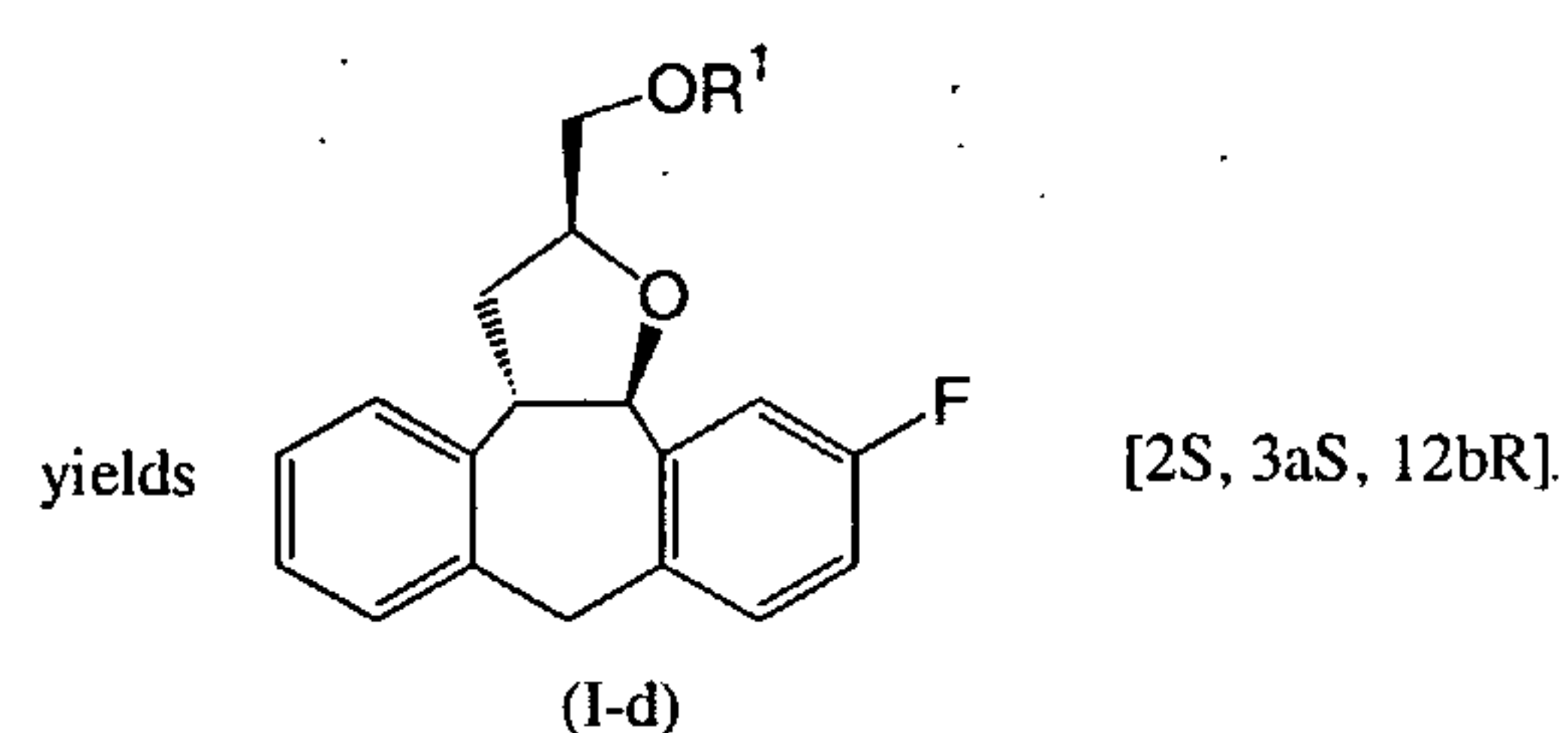
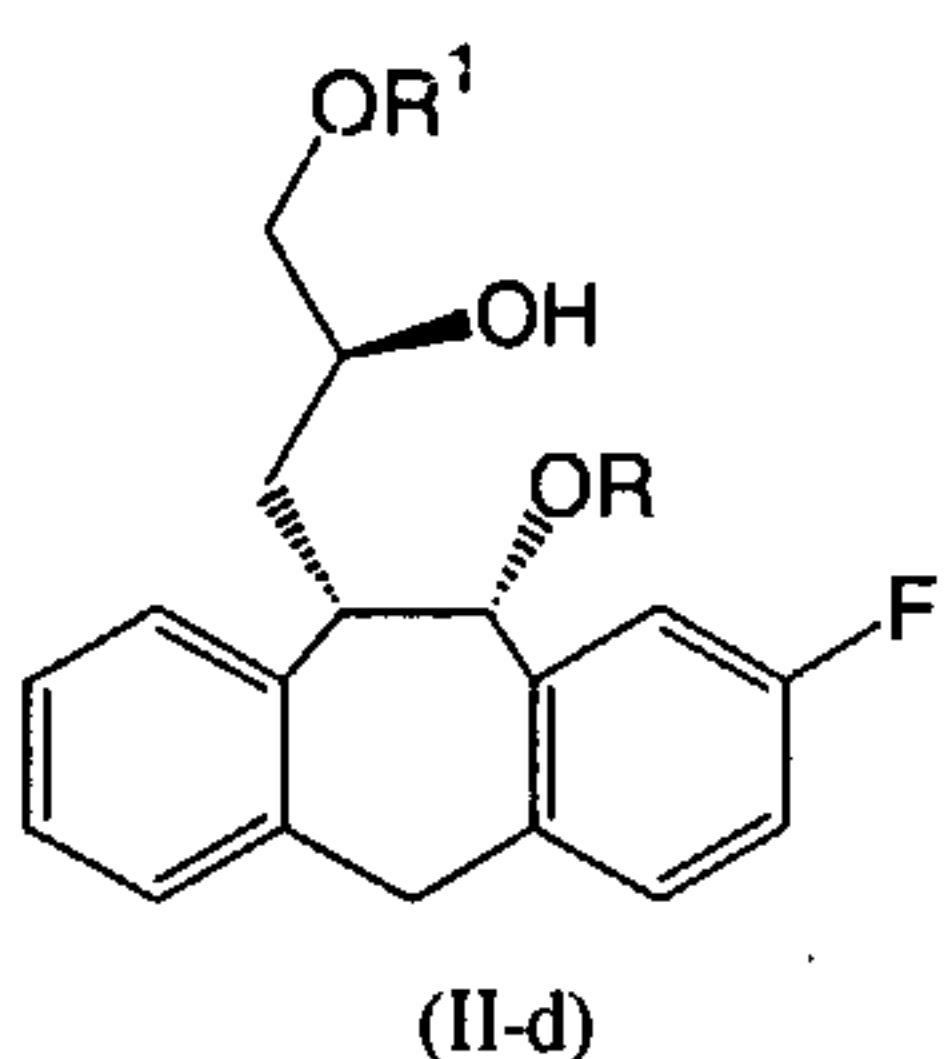
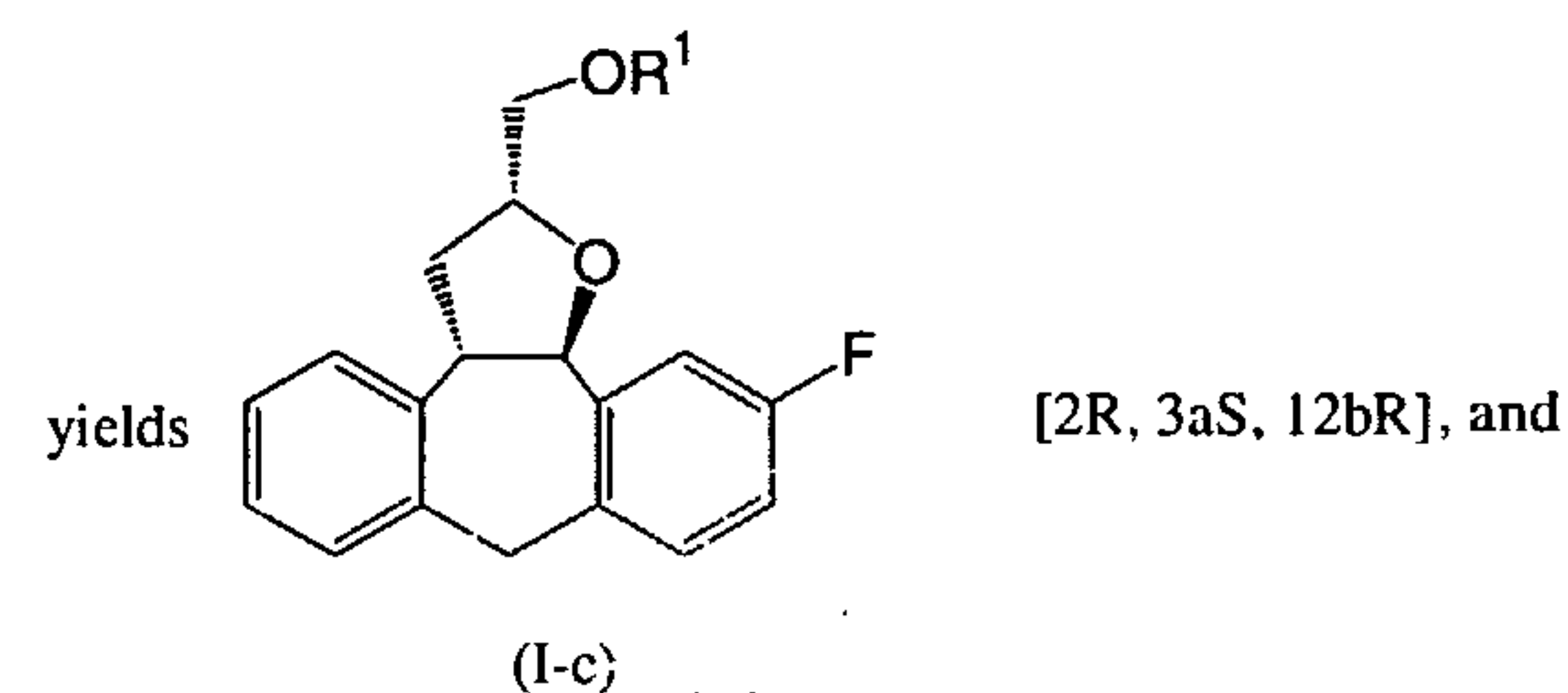
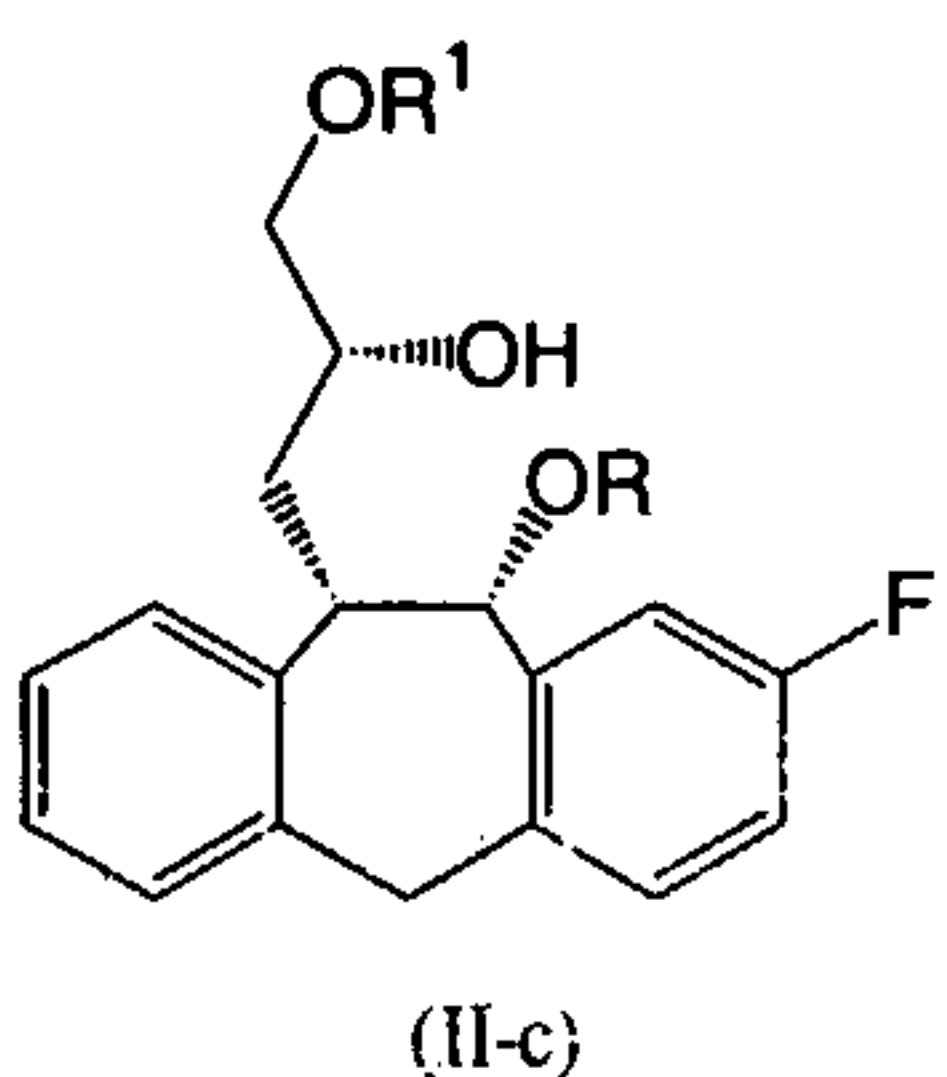
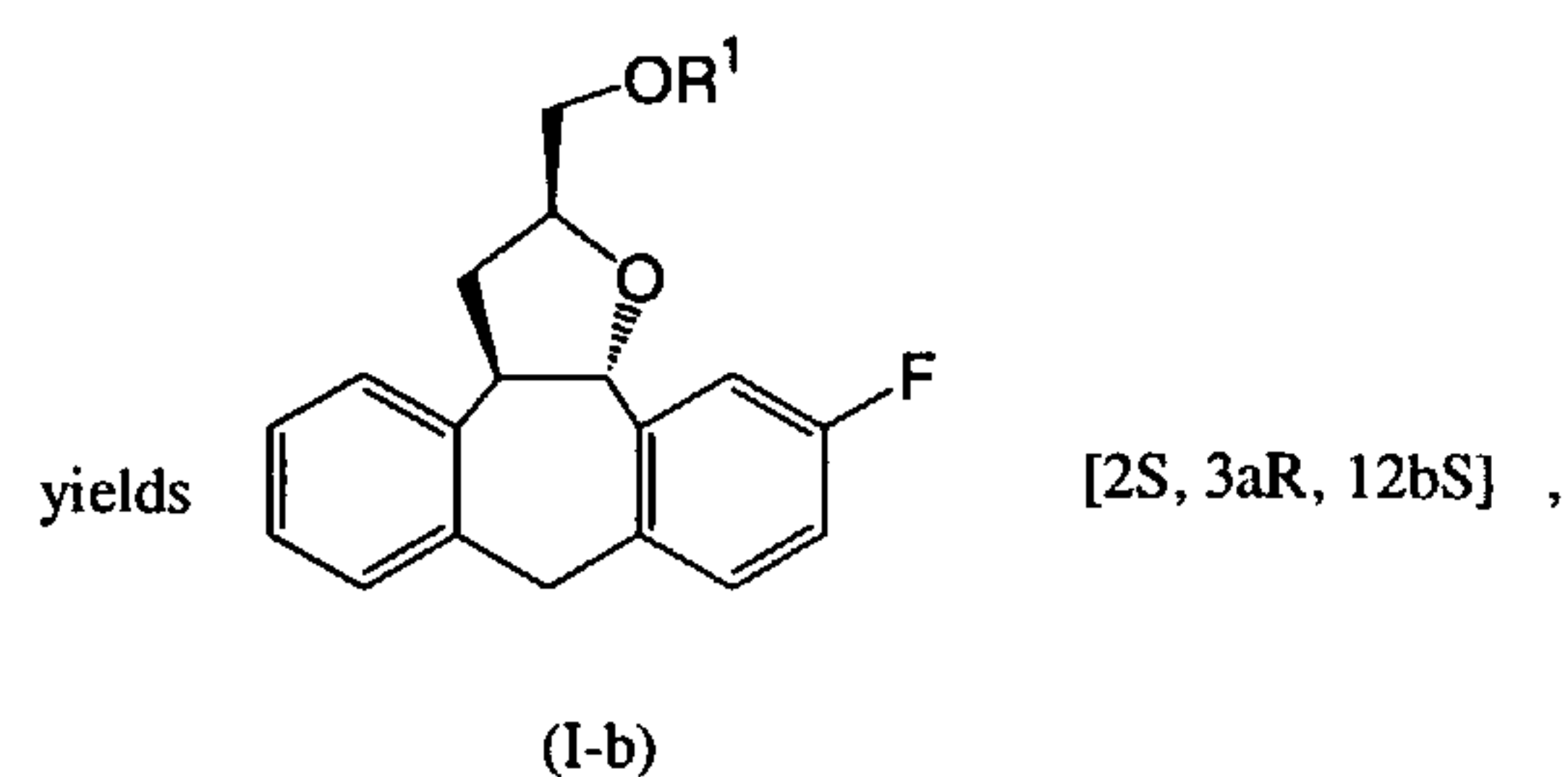
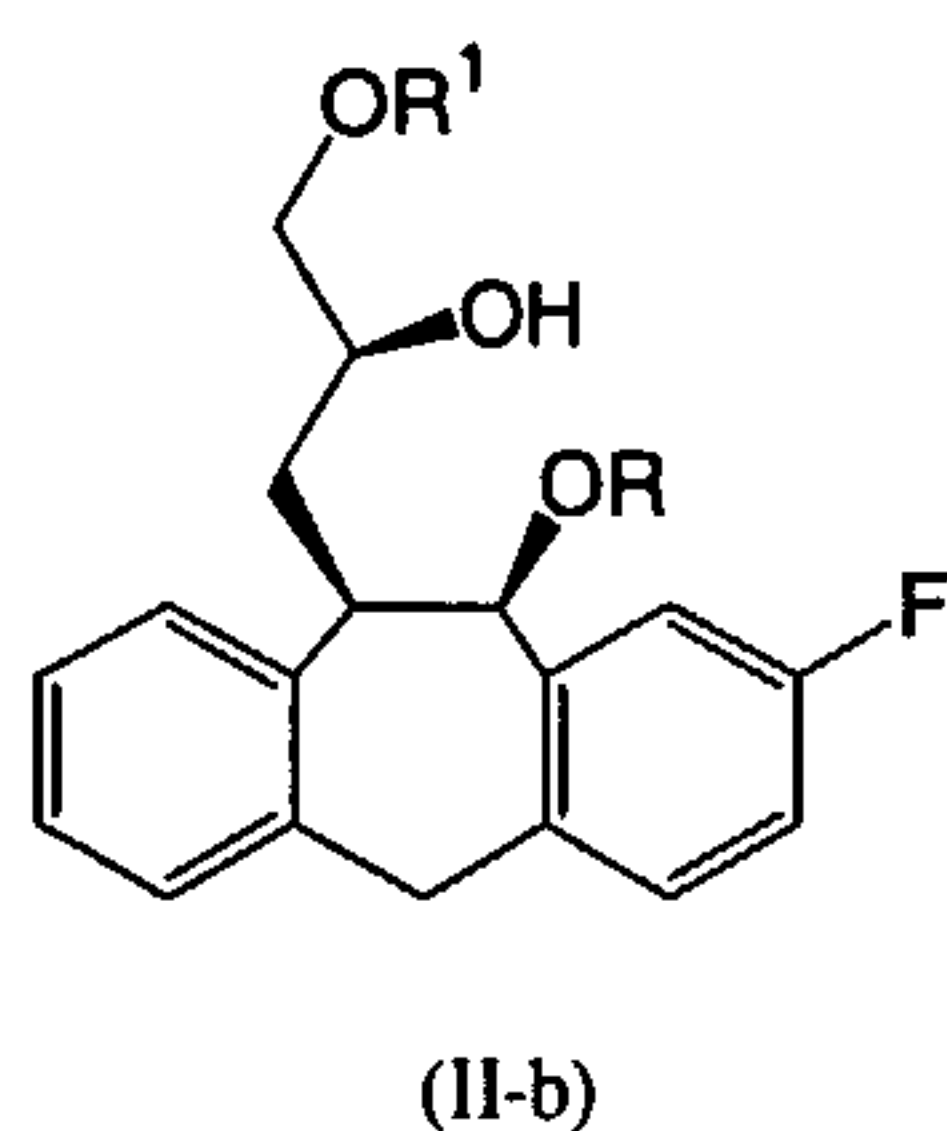
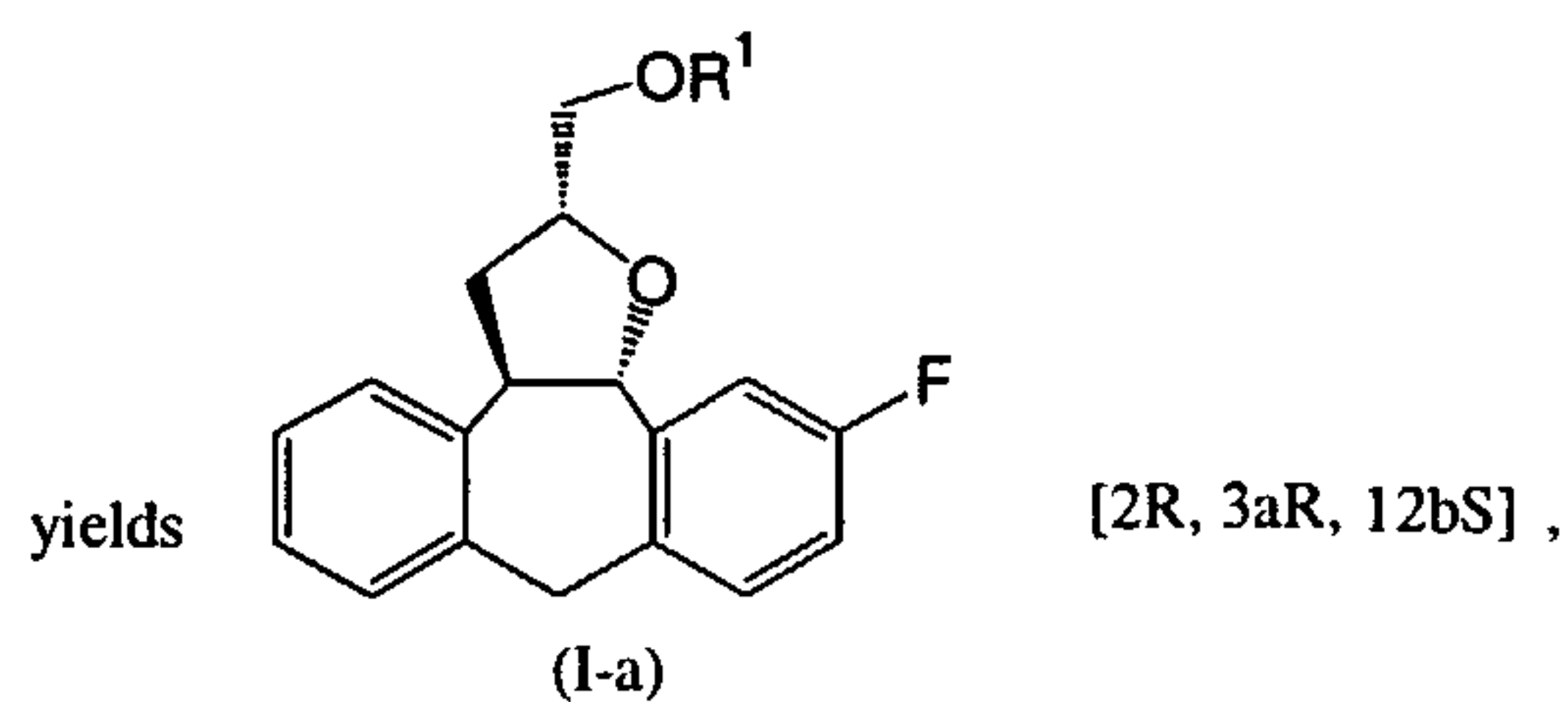
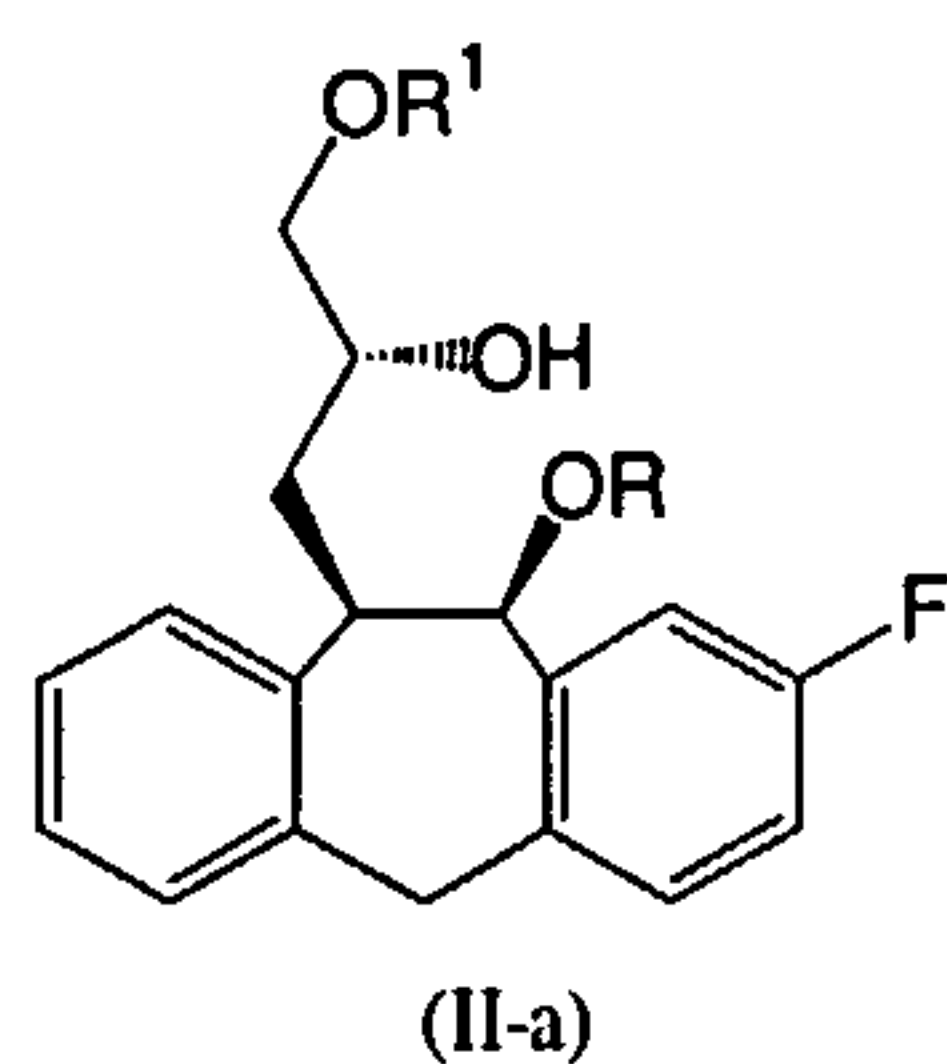
- 5 wherein the substituents on carbon atoms 3a and 12b have the trans configuration, the substituent on carbon atom 2 may have the R or the S configuration, comprising the step of cyclizing a compound of formula (II)



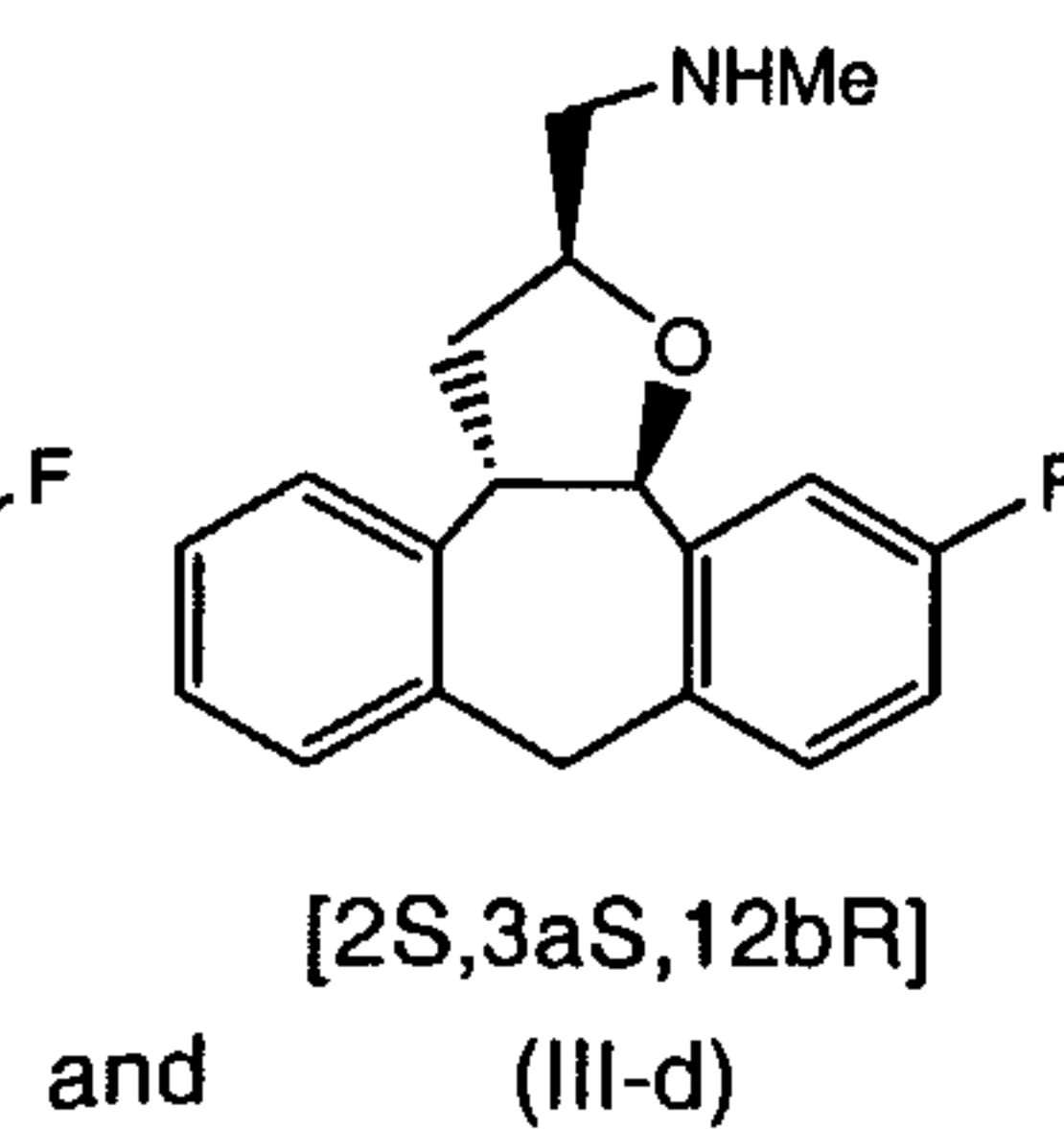
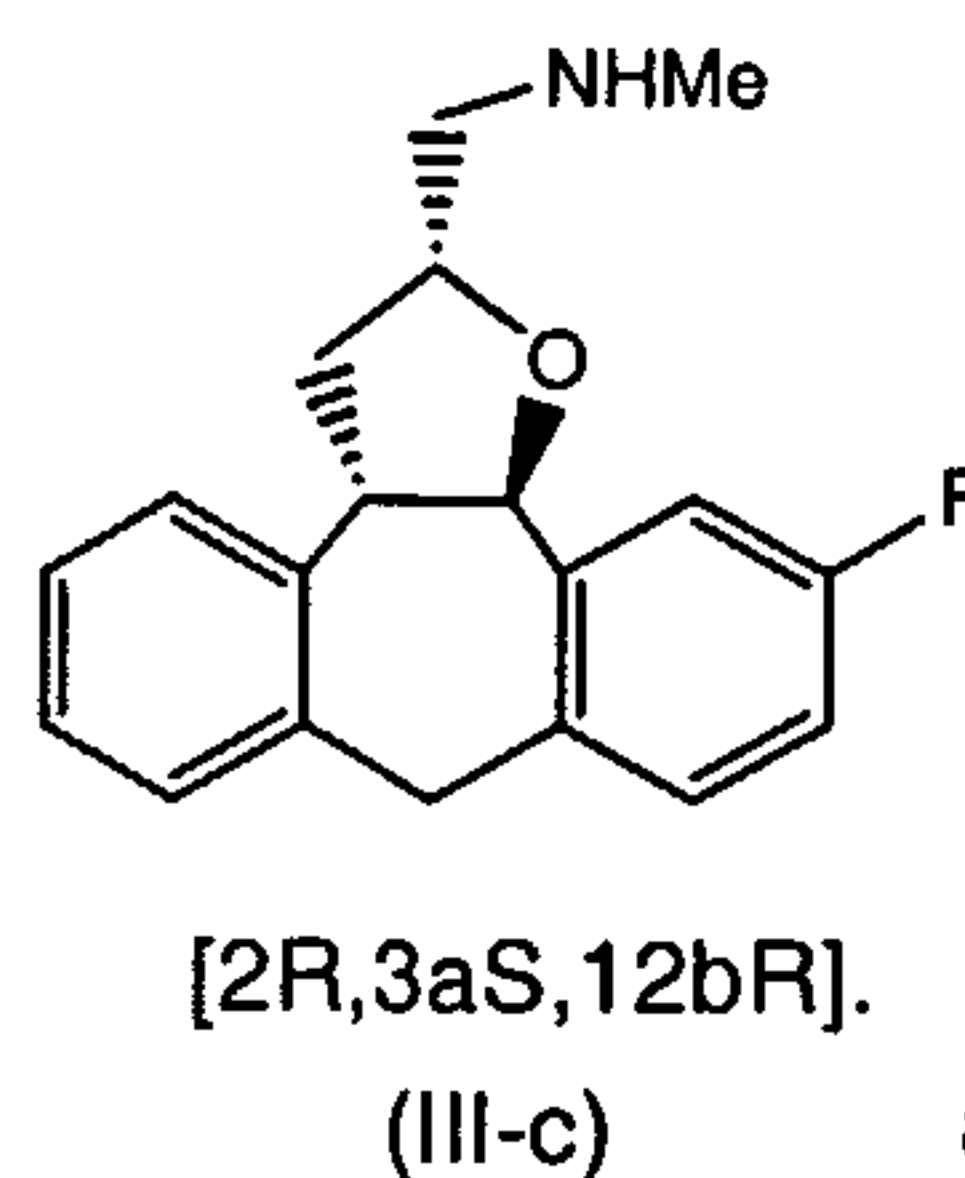
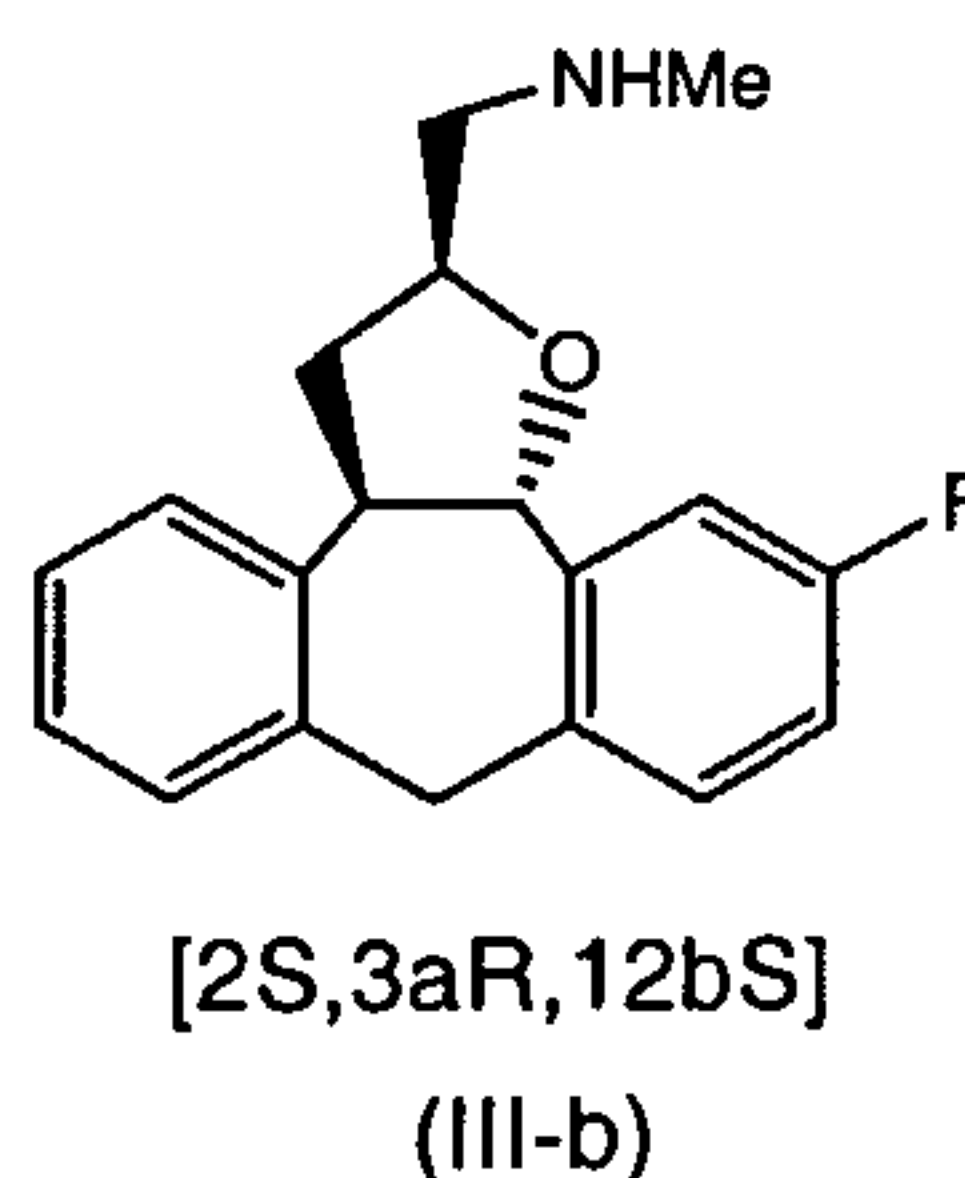
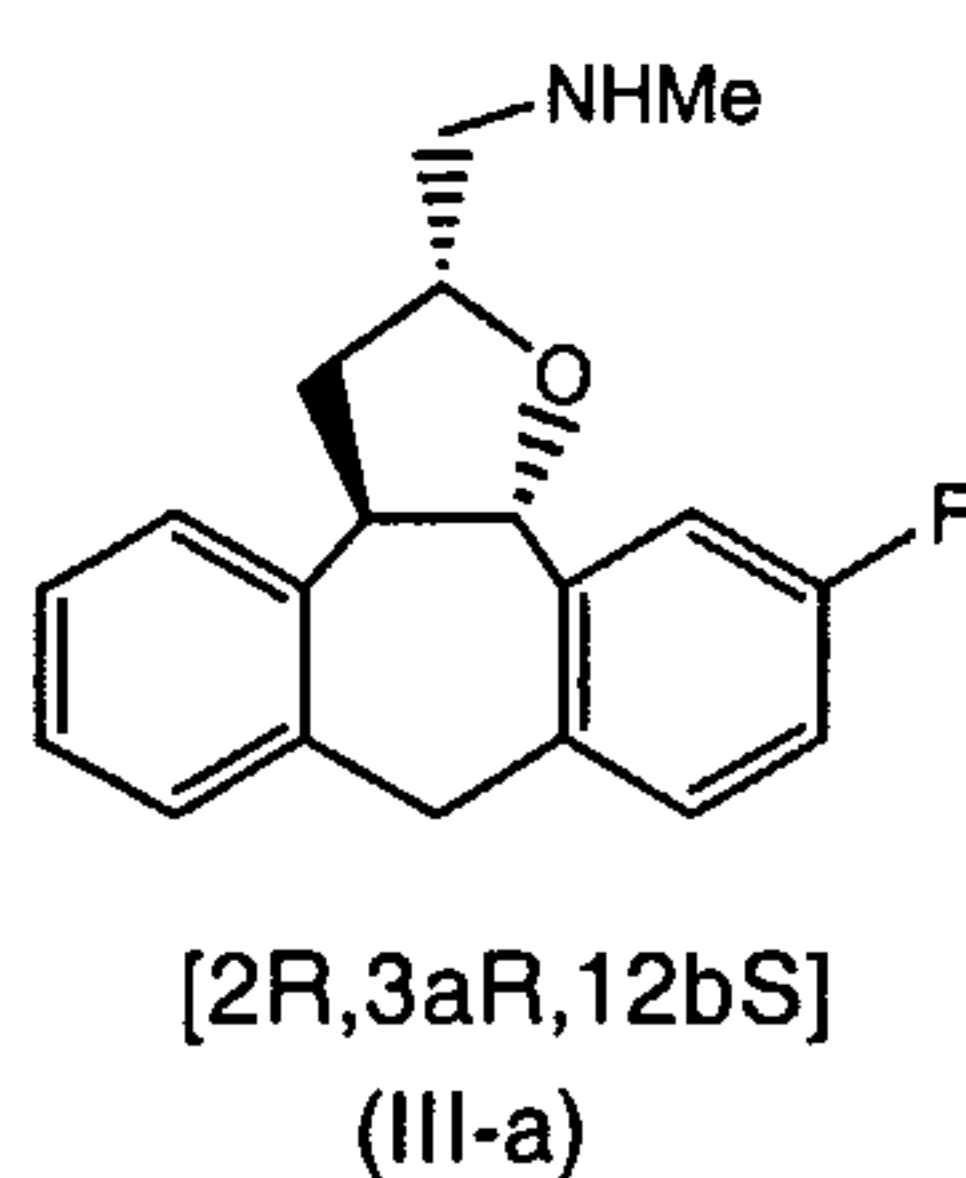
wherein R represents C₁₋₃ alkylcarbonyl;

- 10 OR¹ represents a leaving group and
the substituents -OR and -CH₂-CHOH-CH₂OR¹ have the cis configuration, in a reaction inert solvent in the presence of an acid, whereby

-26-

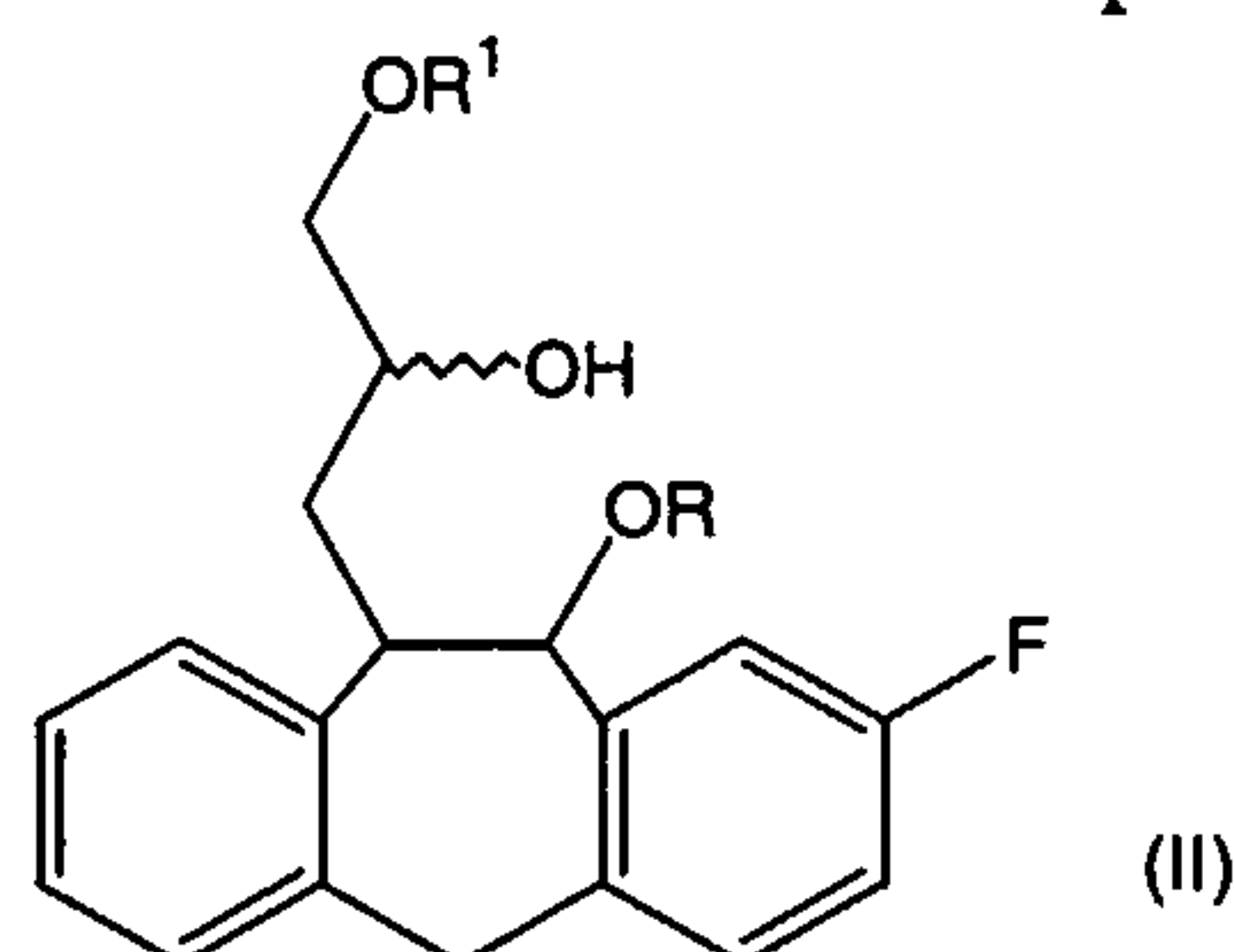


2. A process according to claim 1 wherein each individual diastereomer of formula (I) is converted further into a target compound of formula (III) comprising the further steps of
- 5 reacting the intermediate compound of formula (I) with aqueous or gaseous methylamine in an organic solvent at an elevated temperature, thus yielding



-27-

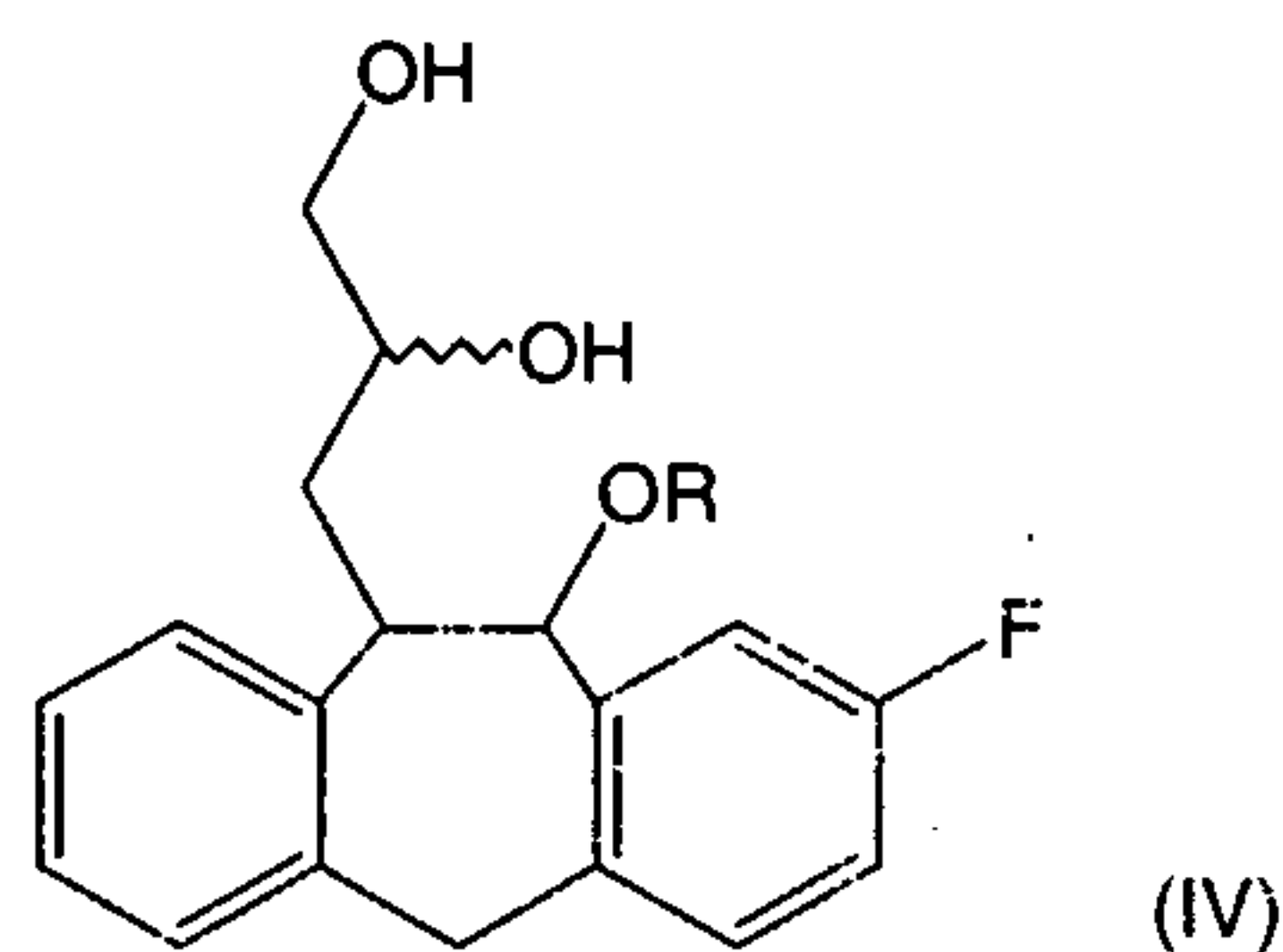
3. A process according to claim 1 wherein the compound of formula (II)



wherein

- 5 OR¹ is a leaving group
and the substituents -OR and -CH₂-CHOH-CH₂-OR¹ have the cis
configuration

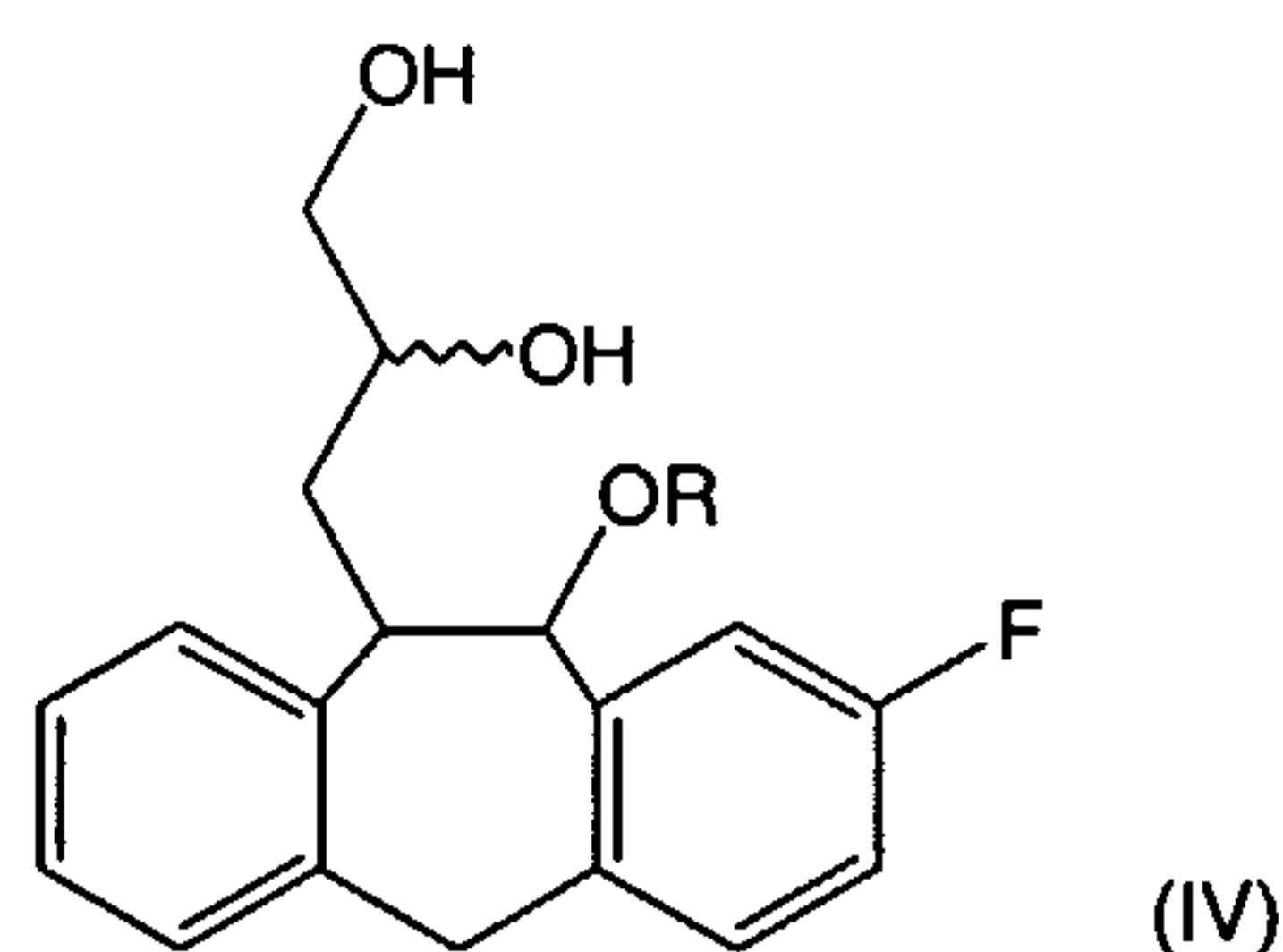
is prepared from a diol of formula



- 10 wherein the substituents -OR and -CH₂-CHOH-CH₂-OH have the cis
configuration by selective conversion of the primary hydroxyl group into a
leaving group, through reaction with a sulfonylchloride in a reaction-inert
solvent, in the presence of an excess of base, and optionally in the presence of
dimethylaminopyridine and/or dibutyl(oxo)stannane.

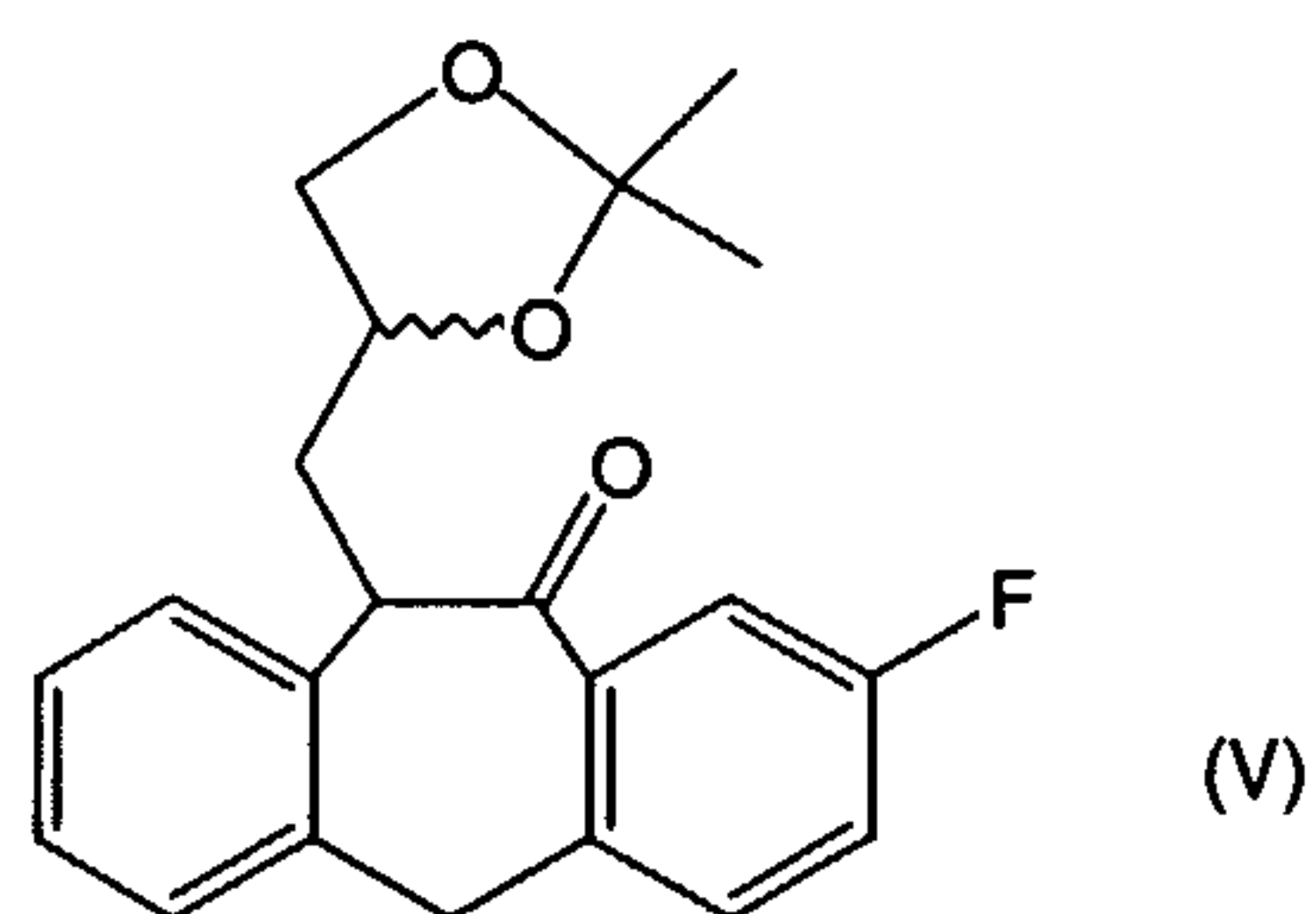
15

4. A process according to claim 3 wherein the intermediate diol of formula (IV)



wherein the substituents have the cis configuration is prepared from a ketone of
formula (V)

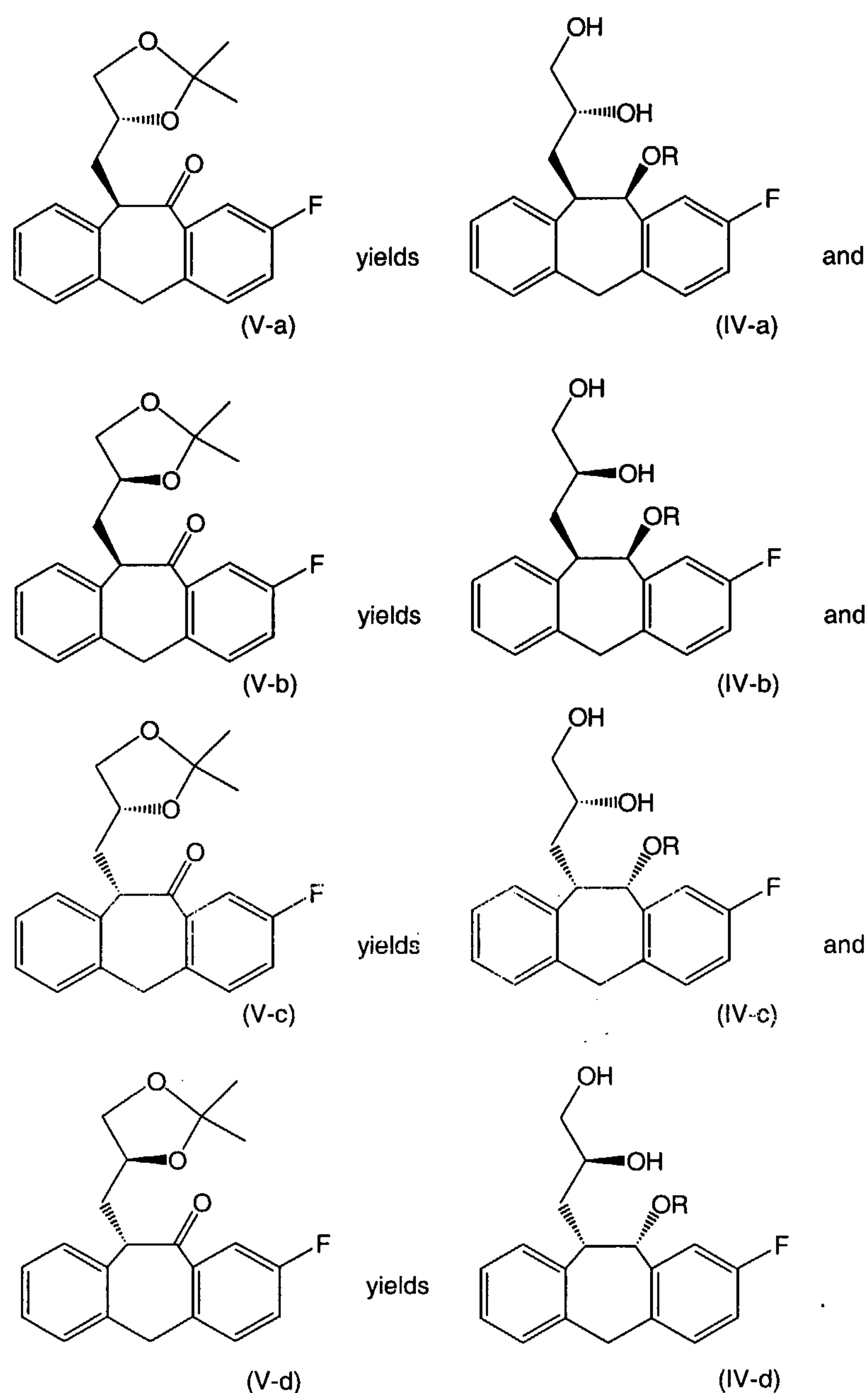
-28-



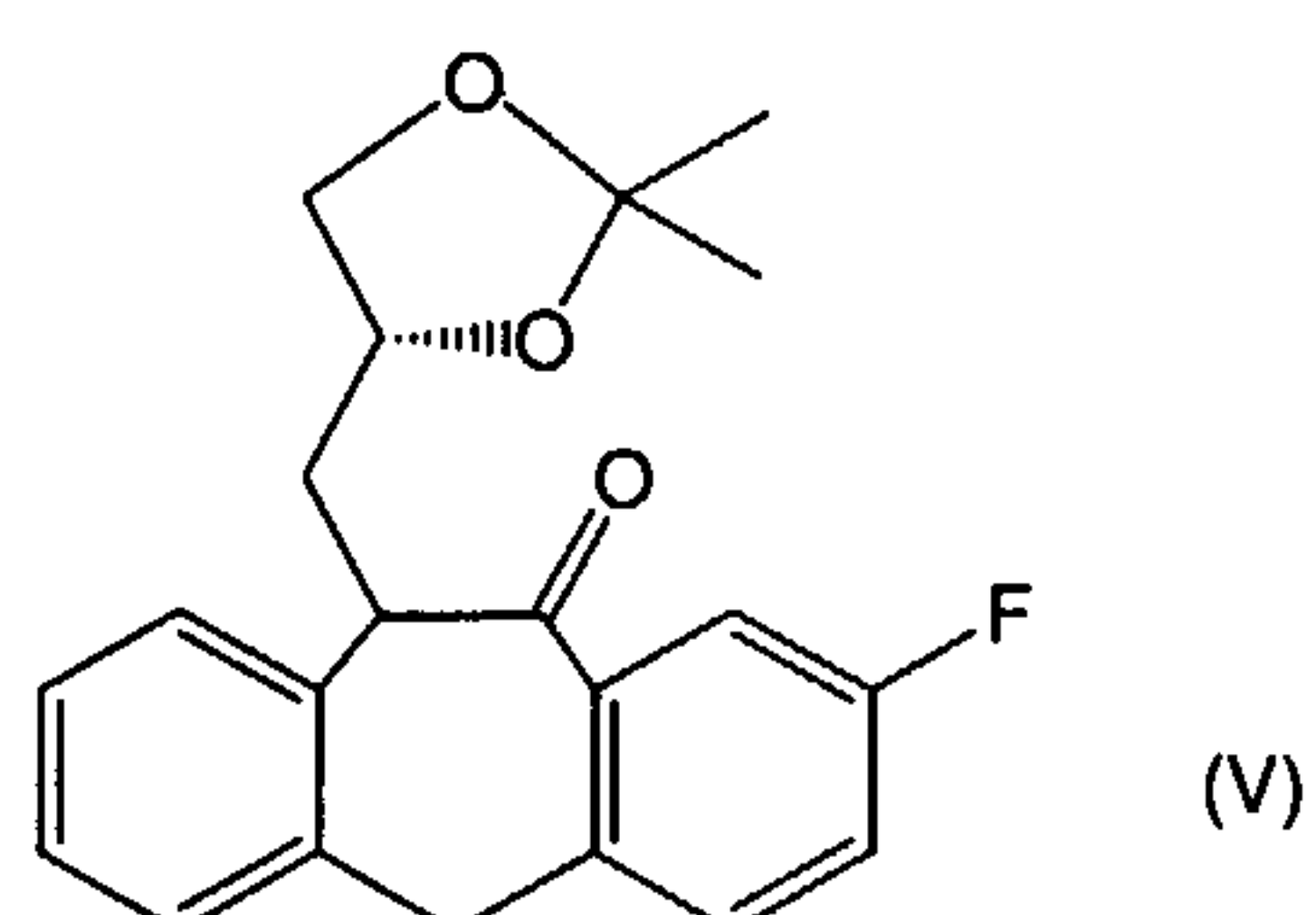
by the following series of reaction steps

- 5 (a) reduction of the ketone to the cis-oriented hydroxyl group by reaction with lithium or sodium borohydride in a mixture of an organic solvent and an aqueous buffer having a pH of about 7 at a temperature below ambient temperature;
- (b) acylation of the hydroxyl group following art-known procedures; and
- 10 (c) deacetalisation in an organic solvent in the presence of an acid, whereby

-29-

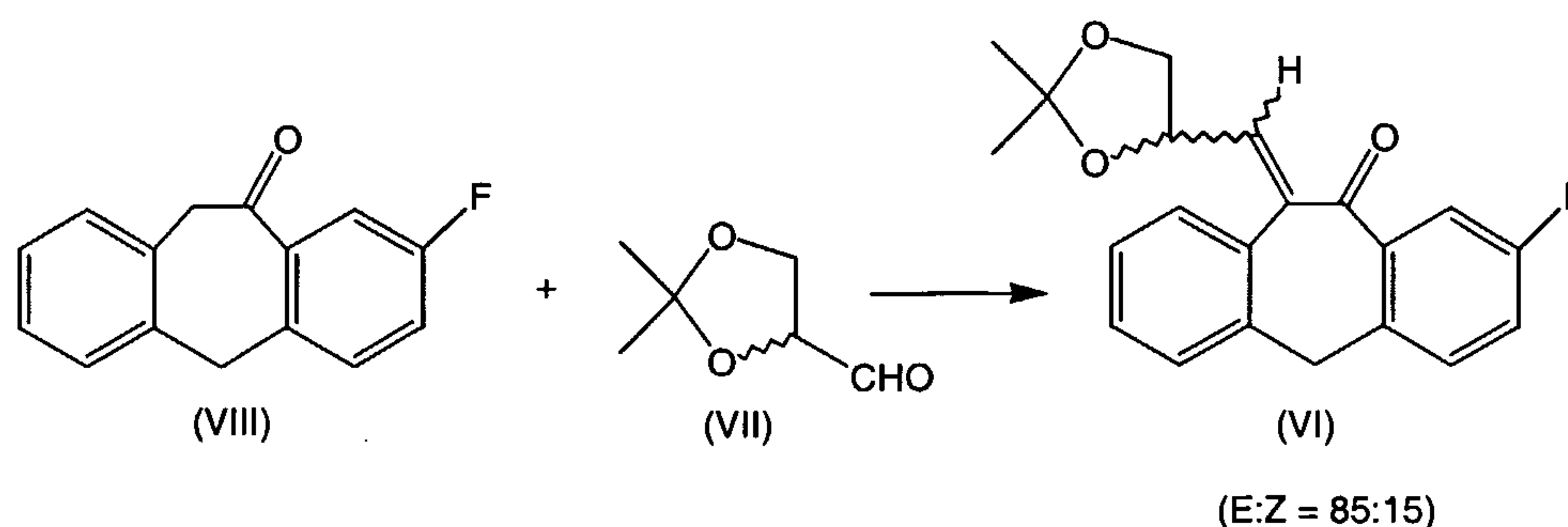


5. A process according to claim 4 wherein the ketone of formula (V)



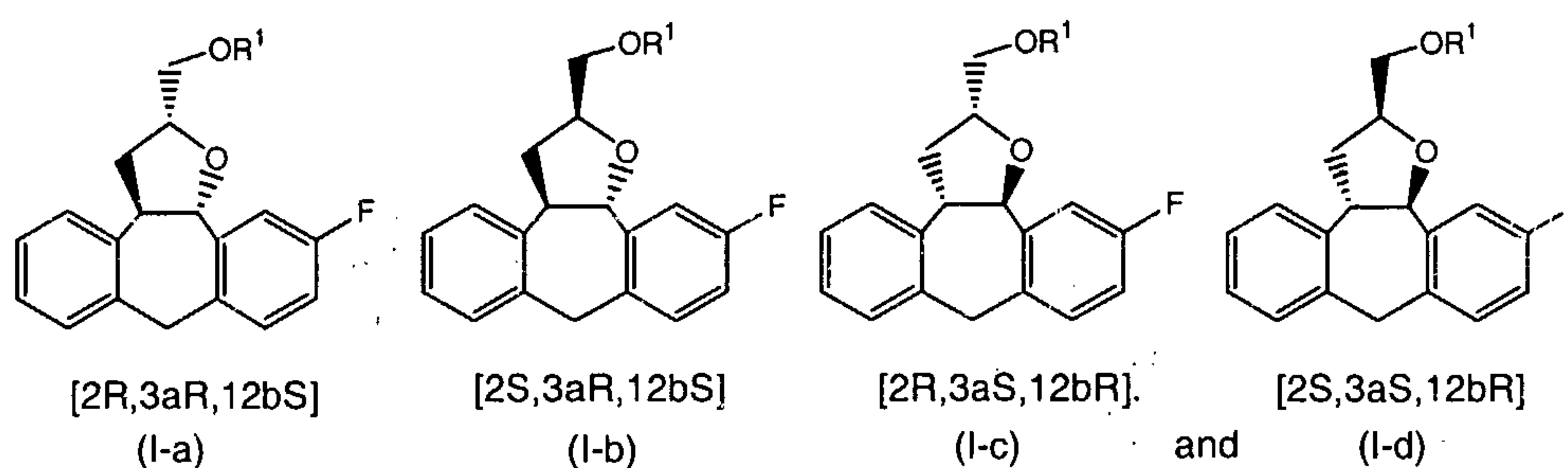
- 5 is prepared from a pro-chiral ketone of formula (VIII) and (4S)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde or (4R)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (VII) in an aldol reaction,

-30-



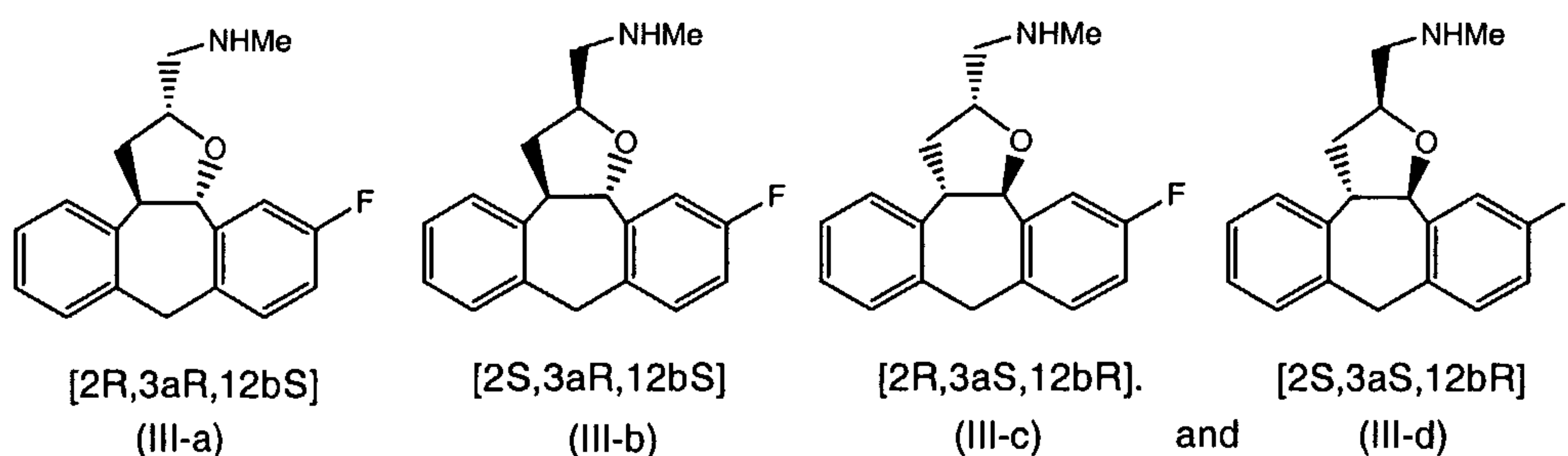
yielding unsaturated ketone (VI) and reducing said unsaturated ketone to a mixture of epimeric ketones (V-a) and (V-c) or (V-b) and (V-d), and optionally converting (V-c) into (V-a), or (V-b) into (V-d) by treatment with a base in a suitable solvent at a temperature in the range of 35°C-45°C.

6. An intermediate compound of formula (I) having the formula



wherein OR^1 represents a leaving group.

10 7. A compound of formula (III) having the formula



in free base form or a pharmaceutically acceptable acid addition salt form thereof.

8. A compound of formula (III) according to claim 7 for use as a medicine.

9. A compound according to claim 8 for use as a CNS active medicine.

