



(86) Date de dépôt PCT/PCT Filing Date: 2003/04/24

(87) Date publication PCT/PCT Publication Date: 2003/11/13

(45) Date de délivrance/Issue Date: 2011/02/22

(85) Entrée phase nationale/National Entry: 2004/10/27

(86) N° demande PCT/PCT Application No.: GB 2003/001763

(87) N° publication PCT/PCT Publication No.: 2003/093252

(30) Priorités/Priorities: 2002/05/01 (GB0209996.8);
2002/10/14 (GB0223873.1); 2002/11/07 (US60/424,608)

(51) Cl.Int./Int.Cl. *C07D 285/14* (2006.01),
A61K 31/433 (2006.01), *A61P 25/28* (2006.01),
C07D 417/04 (2006.01), *C07D 417/14* (2006.01),
C07D 491/04 (2006.01)

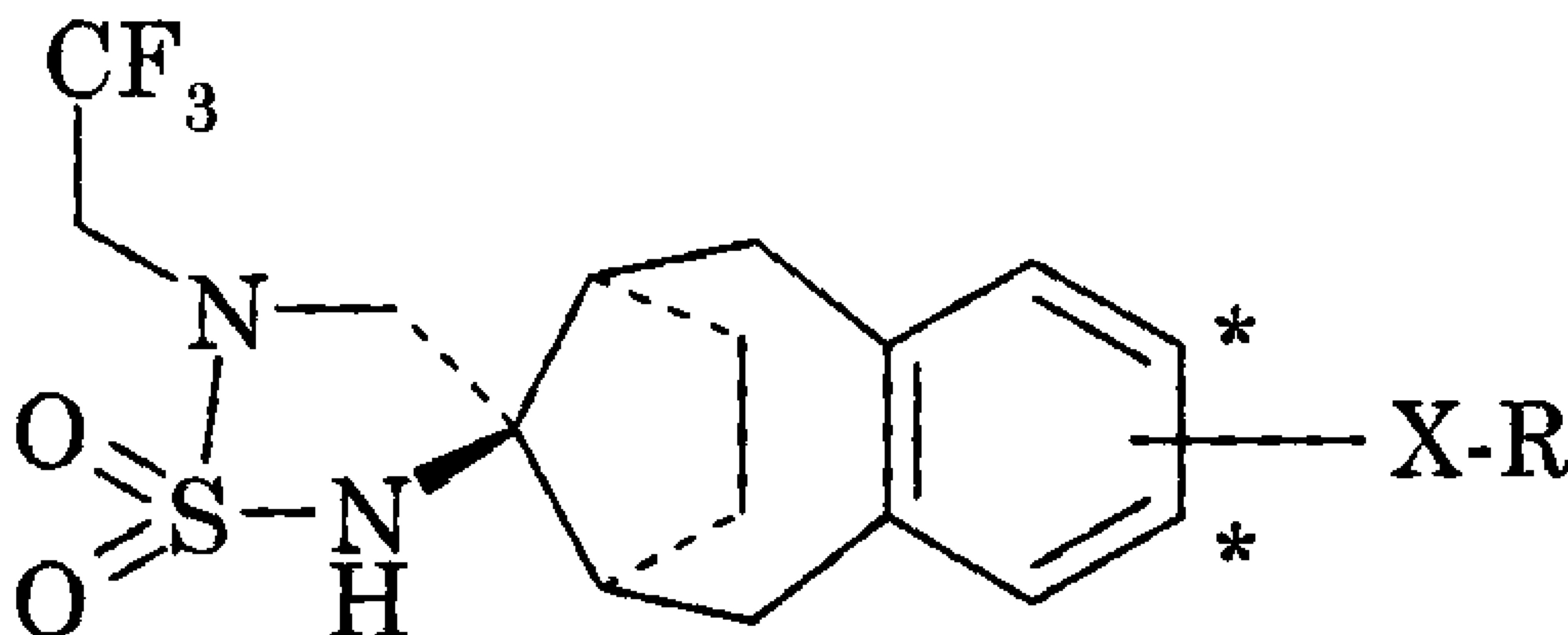
(72) Inventeurs/Inventors:
COLLINS, IAN JAMES, GB;
COOPER, LAURA CATHERINE, GB;
HARRISON, TIMOTHY, GB;
KEOWN, LINDA ELIZABETH, GB;
MADIN, ANDREW, GB;
RIDGILL, MARK PETER, GB

(73) Propriétaire/Owner:
MERCK SHARP & DOHME LIMITED, GB

(74) Agent: OGILVY RENAULT LLP/S.E.N.C.R.L.,S.R.L.

(54) Titre : SULFAMIDES SPIROCYCLIQUES SUBSTITUES PAR HETEROARYLE UTILISES COMME INHIBITEURS DE
LA GAMMA-SECRETASE

(54) Title: HETEROARYL SUBSTITUTED SPIROCYCLIC SULFAMIDES FOR INHIBITION OF GAMMA SECRETASE



I

(57) **Abrégé/Abstract:**

Compounds of formula I are disclosed: in which X is a 5-membered heteroaryl ring and R is as defined herein. The compounds are inhibitors of the processing of APP by gamma-secretase, and hence are useful in the treatment or prevention of Alzheimer's disease.

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 November 2003 (13.11.2003)

PCT

(10) International Publication Number
WO 03/093252 A1

(51) International Patent Classification⁷: **C07D 285/14**,
417/04, 417/14, A61K 31/433, A61P 25/28

Road, Harlow, Essex CM20 2QR (GB). **RIDGILL, Mark, Peter** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(21) International Application Number: PCT/GB03/01763

(22) International Filing Date: 24 April 2003 (24.04.2003)

(74) Agent: **BUCHAN, Gavin, MacNicol**; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0209996.8 1 May 2002 (01.05.2002) GB
0223873.1 14 October 2002 (14.10.2002) GB
60/424,608 7 November 2002 (07.11.2002) US

(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, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, 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*): **MERCK SHARP & DOHME LIMITED** [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **COLLINS, Ian, James** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). **COOPER, Laura, Catherine** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). **HARRISON, Timothy** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). **KEOWN, Linda, Elizabeth** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). **MADIN, Andrew** [GB/GB]; Terlings Park, Eastwick

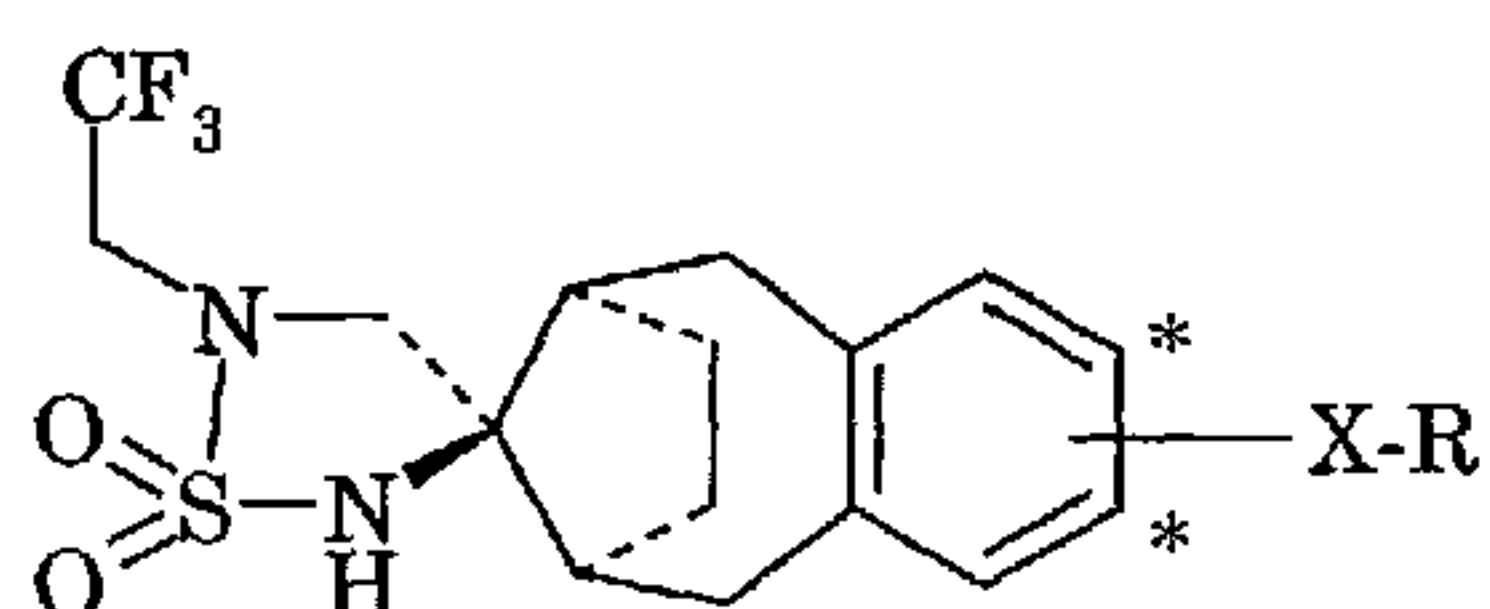
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ,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

Published:

— with international search report

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: HETEROARYL SUBSTITUTED SPIROCYCLIC SULFAMIDES FOR INHIBITION OF GAMMA SECRETASE



(I)

(57) Abstract: Compounds of formula I are disclosed: in which X is a 5-membered heteroaryl ring and R is as defined herein. The compounds are inhibitors of the processing of APP by gamma-secretase, and hence are useful in the treatment or prevention of Alzheimer's disease.



WO 03/093252 A1

HETEROARYL SUBSTITUTED SPIROCYCLIC SULFAMIDES FOR
INHIBITION OF GAMMA SECRETASE

The present invention relates to a novel class of compounds, their salts, pharmaceutical compositions comprising them, processes for making
5 them and their use in therapy of the human body. In particular, the invention relates to compounds which modulate the processing of APP by γ -secretase, and hence are useful in the treatment or prevention of Alzheimer's disease.

Alzheimer's disease (AD) is the most prevalent form of dementia.
10 Although primarily a disease of the elderly, affecting up to 10% of the population over the age of 65, AD also affects significant numbers of younger patients with a genetic predisposition. It is a neurodegenerative disorder, clinically characterized by progressive loss of memory and cognitive function, and pathologically characterized by the deposition of
15 extracellular proteinaceous plaques in the cortical and associative brain regions of sufferers. These plaques mainly comprise fibrillar aggregates of β -amyloid peptide ($A\beta$), and although the exact role of the plaques in the onset and progress of AD is not fully understood, it is generally accepted that suppressing or attenuating the secretion of $A\beta$ is a likely means of
20 alleviating or preventing the condition. (See, for example, *ID research alert* 1996 1(2):1-7; *ID research alert* 1997 2(1):1-8; *Current Opinion in CPNS Investigational Drugs* 1999 1(3):327-332; and *Chemistry in Britain*, Jan. 2000, 28-31.)

$A\beta$ is a peptide comprising 39-43 amino acid residues, formed by
25 proteolysis of the much larger amyloid precursor protein. The amyloid precursor protein (APP or $A\beta$ PP) has a receptor-like structure with a large ectodomain, a membrane spanning region and a short cytoplasmic tail. Different isoforms of APP result from the alternative splicing of three exons in a single gene and have 695, 751 and 770 amino acids respectively.

30 The $A\beta$ domain encompasses parts of both extra-cellular and transmembrane domains of APP, thus its release implies the existence of

two distinct proteolytic events to generate its NH₂- and COOH-termini. At least two secretory mechanisms exist which release APP from the membrane and generate the soluble, COOH-truncated forms of APP (APP_s). Proteases which release APP and its fragments from the
5 membrane are termed "secretases". Most APP_s is released by a putative α -secretase which cleaves within the A β domain (between residues Lys¹⁶ and Leu¹⁷) to release α -APP_s and precludes the release of intact A β . A minor portion of APP_s is released by a β -secretase, which cleaves near the NH₂-terminus of A β and produces COOH-terminal fragments (CTFs) which
10 contain the whole A β domain. Finding these fragments in the extracellular compartment suggests that another proteolytic activity (γ -secretase) exists under normal conditions which can generate the COOH-terminus of A β .

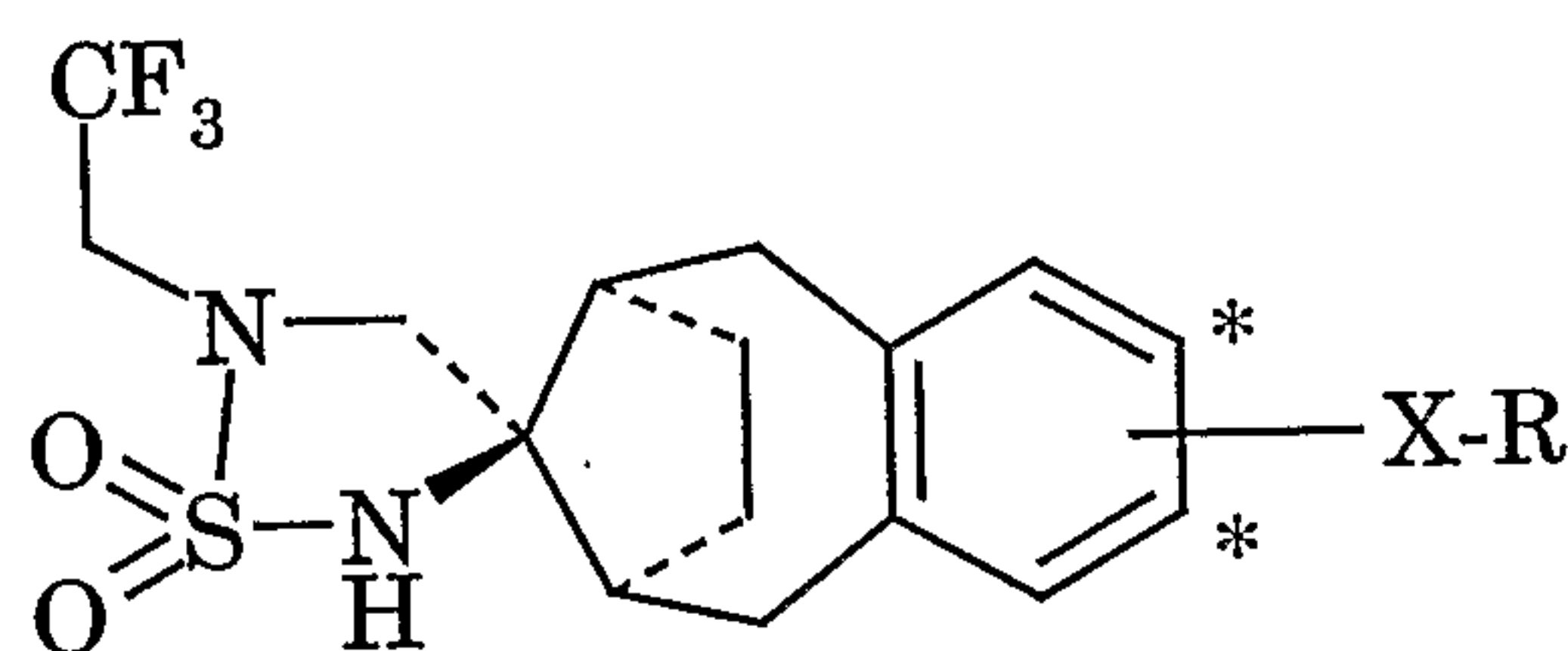
It is believed that γ -secretase itself depends for its activity on the
15 presence of presenilin-1. In a manner that is not fully understood presenilin-1 appears to undergo autocleavage.

There are relatively few reports in the literature of compounds with inhibitory activity towards β - or γ -secretase, as measured in cell-based assays. These are reviewed in the articles referenced above. Many of the
20 relevant compounds are peptides or peptide derivatives.

WO 01/70677 discloses certain sulphonamido-substituted bridged bicycloalkyl derivatives which are useful in the treatment of Alzheimer's disease, but neither discloses nor suggests the compounds of the present invention.

25 The present invention provides a novel class of non-peptidic compounds which are useful in the treatment or prevention of AD by modulating the processing of APP by the putative γ -secretase, thus arresting the production of A β and preventing the formation of insoluble plaques.

30 According to the invention there is provided a compound of formula I:



I

wherein the moiety X-R is attached at one of the positions indicated by an asterisk;

X is a bivalent pyrazole, imidazole, triazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole or 1,3,4-oxadiazole residue optionally bearing a hydrocarbon substituent comprising 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

R is selected from:

- (i) CF_3 or a non-aromatic hydrocarbon group of up to 10 carbon atoms, optionally substituted with halogen, CF_3 , CHF_2 , CN , OH , CO_2H , $\text{C}_{2-6}\text{acyl}$, $\text{C}_{1-4}\text{alkoxy}$ or $\text{C}_{1-4}\text{alkoxycarbonyl}$;
 - (ii) a non-aromatic heterocyclic group comprising up to 7 ring atoms of which up to 3 are chosen from N, O and S and the remainder are carbon, bearing 0-3 substituents independently selected from oxo, halogen, CN , $\text{C}_{1-6}\text{alkyl}$, OH , CF_3 , CHF_2 , CH_2F , $\text{C}_{2-6}\text{acyl}$, CO_2H , $\text{C}_{1-4}\text{alkoxy}$ and $\text{C}_{1-4}\text{alkoxycarbonyl}$;
 - (iii) phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF_3 , CHF_2 , CH_2F , NO_2 , CN , OCF_3 , $\text{C}_{1-6}\text{alkyl}$ and $\text{C}_{1-6}\text{alkoxy}$; and
 - (iv) $\text{N}(\text{R}^a)_2$ where each R^a independently represents H or $\text{C}_{1-6}\text{alkyl}$ which is optionally substituted with halogen, CF_3 , CHF_2 , CN , OH , CO_2H , $\text{C}_{2-6}\text{acyl}$, $\text{C}_{1-4}\text{alkoxy}$ or $\text{C}_{1-4}\text{alkoxycarbonyl}$;
- or a pharmaceutically acceptable salt thereof.

In a subset of the compounds of formula I, X is a bivalent pyrazole, imidazole, triazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole or 1,3,4-oxadiazole residue wherein, in the case of pyrazole, imidazole and triazole, one of the ring nitrogen atoms optionally bears a hydrocarbon

substituent comprising 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

R is selected from:

(i) a non-aromatic hydrocarbon group of up to 10 carbon atoms, optionally substituted with halogen, CF₃, CHF₂, CN, OH, CO₂H, C₂₋₆acyl, C₁₋₄alkoxy or C₁₋₄alkoxycarbonyl;

(ii) a non-aromatic heterocyclic group comprising up to 7 ring atoms of which up to 3 are chosen from N, O and S and the remainder are carbon, bearing 0-3 substituents independently selected from oxo, halogen, CN, C₁₋₆alkyl, OH, CF₃, CHF₂, CH₂F, C₂₋₆acyl, CO₂H, C₁₋₄alkoxy and C₁₋₄alkoxycarbonyl;

(iii) phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF₃, CHF₂, CH₂F, NO₂, CN, OCF₃, C₁₋₆alkyl and C₁₋₆alkoxy; and

(iv) N(R^a)₂ where each R^a independently represents H or C₁₋₆alkyl which is optionally substituted with halogen, CF₃, CHF₂, CN, OH, CO₂H, C₂₋₆acyl, C₁₋₄alkoxy or C₁₋₄alkoxycarbonyl.

It will be readily apparent to those skilled in the art that the compounds of formula I exist in two enantiomeric forms, depending on which of the ring positions indicated by an asterisk is bonded to the moiety -X-R. Attachment at the position indicated by the upper asterisk in formula I gives rise to a 2-substituted-[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-decahydro-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide. Conversely, attachment at the position indicated by the lower asterisk in formula I gives rise to a 2-substituted-[6R,9S,11S] 2',3',4',5,5',6,7,8,9,10-decahydro-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide. It is to be emphasised that the invention, for each identity of -X-R, encompasses both enantiomers, either as homochiral compounds or as mixtures of enantiomers in any proportion. Furthermore, structural formulae depicting attachment of -X-R or a synthetic precursor thereof at

one of the said ring positions shall hereinafter be indicative of attachment at either of said ring positions, unless expressly stated otherwise.

Where a variable occurs more than once in formula I or in a substituent thereof, the individual occurrences of that variable are
5 independent of each other, unless otherwise specified.

As used herein, the expression "C_{1-x}alkyl" where x is an integer greater than 1 refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.
10 Derived expressions such as "C₂₋₆alkenyl", "hydroxyC₁₋₆alkyl", "heteroarylC₁₋₆alkyl", "C₂₋₆alkynyl" and "C₁₋₆alkoxy" are to be construed in an analogous manner. Most suitably, the number of carbon atoms in such groups is not more than 4.

The expression "C₃₋₆cycloalkyl" as used herein refers to nonaromatic
15 monocyclic hydrocarbon ring systems comprising from 3 to 6 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclohexenyl.

The expression "C₃₋₆ cycloalkyl(C₁₋₆)alkyl" as used herein includes cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and
20 cyclohexylmethyl.

The expression "C₂₋₆acyl" as used herein refers to (C₁₋₅alkyl)carbonyl groups, such as acetyl, propanoyl and butanoyl, including cycloalkyl derivatives such as cyclopentanecarbonyl and cyclobutanecarbonyl, and fluorinated derivatives such as trifluoroacetyl.

25 The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

For use in medicine, the compounds of formula I may be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their
30 pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which

may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, benzenesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Alternatively, where the compound of the invention carries an acidic moiety, a pharmaceutically acceptable salt may be formed by neutralisation of said acidic moiety with a suitable base. Examples of pharmaceutically acceptable salts thus formed include alkali metal salts such as sodium or potassium salts; ammonium salts; alkaline earth metal salts such as calcium or magnesium salts; and salts formed with suitable organic bases, such as amine salts (including pyridinium salts) and quaternary ammonium salts.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In the compounds of formula I, X is a bivalent pyrazole, imidazole, triazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole or 1,3,4-oxadiazole residue, optionally bearing a hydrocarbon substituent as defined previously. X may be bonded to R and to the fused benzene ring via any of the available ring positions of X. Typically, X is bonded both to R and to the fused benzene ring via carbon atoms, but when X is a pyrazole, imidazole or triazole residue, one of the points of attachment may be a nitrogen atom. Preferably, the points of attachment do not occupy adjacent ring atoms of X.

The ring represented by X optionally bears a hydrocarbon substituent comprising 1 to 5 carbon atoms, optionally substituted with up to 3 halogen atoms. Said optional hydrocarbon substituent may be

attached to one of the ring carbon atoms of X, or when X is a pyrazole, imidazole or triazole residue and both of its points of attachment are carbon atoms, it may be attached to one of the ring nitrogen atoms of X. In either case, the optional hydrocarbon substituent may comprise cyclic
5 or acyclic hydrocarbon residues or combinations thereof, saturated or unsaturated, up to a maximum of 5 carbon atoms in total. The optional hydrocarbon substituent is preferably unsubstituted or is substituted with up to 3 fluorine atoms. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, fluoromethyl, difluoromethyl,
10 trifluoromethyl, 2,2,2-trifluoroethyl, cyclopropyl, cyclopropylmethyl and allyl. A preferred example is methyl.

When X is a triazole or thiadiazole residue, both of the possible isomeric forms are within the scope of the invention. Thus, the definition of X encompasses both 1,2,3- and 1,2,4-triazole residues, and both 1,2,4-
15 and 1,3,4-thiadiazole residues.

Suitable identities for X include 1,3,4-oxadiazol-2-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-1-yl, 1,2,4-triazol-3-yl, 1-methyl-1,2,4-triazol-3-yl, oxazol-2-yl, pyrazol-3-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-5-yl, 1-ethylpyrazol-3-yl, 1-(2,2,2-trifluoroethyl)pyrazol-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, isoxazol-5-yl,
20 isoxazol-3-yl, imidazol-2-yl, imidazol-4-yl and imidazol-1-yl, wherein the numbering indicates the ring atom of X which is attached to the fused benzene ring in formula I.

Preferred identities for X include 1-methyl-1,2,4-triazol-3-yl, 1-methylpyrazol-3-yl, 1-ethylpyrazol-3-yl, oxazol-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl, in which R is attached to the 5-position of X. A further preferred identity for X is imidazol-4-yl in which R is attached to the 1-position of X. Another preferred identity for X is 1,2,4-triazol-3-yl in which R is attached to the 1-position of X.

30 A particularly preferred identity for X is 1-methylpyrazol-3-yl in which R is attached to the 5-position.

In one embodiment, R is CF₃ or a non-aromatic hydrocarbon group of up to 10 carbon atoms, optionally substituted with halogen, CF₃, CHF₂, CN, OH, CO₂H, C₂₋₆acyl, C₁₋₄alkoxy or C₁₋₄alkoxycarbonyl. Within this definition, R may comprise cyclic or acyclic hydrocarbon residues or
5 combinations thereof, saturated or unsaturated, up to a maximum of 10 carbon atoms in total, and may bear a substituent as detailed above. Within this embodiment, R typically contains up to 6 carbon atoms. Suitable examples include alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl and 2-methylpropyl, cycloalkyl groups
10 such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, cycloalkylalkyl groups such as cyclopropylmethyl and cyclopentylmethyl, alkenyl groups such as allyl, cyclopentenyl and cyclohexenyl, and alkynyl groups such as propargyl. Within this embodiment, R very aptly represents CF₃ or t-butyl or isopropyl.

15 In a second embodiment, R represents a non-aromatic heterocyclic group comprising up to 7 ring atoms of which up to 3 are chosen from N, O and S and the remainder are carbon, bearing 0-3 substituents independently selected from oxo, halogen, CN, C₁₋₆alkyl, OH, CF₃, CHF₂, CH₂F, C₂₋₆acyl, CO₂H, C₁₋₄alkoxy and C₁₋₄alkoxycarbonyl. Suitable
20 heterocyclic groups include azetidine, pyrrolidine, piperidine, tetrahydropyridine, piperazine, morpholine, thiomorpholine, thiomorpholine-1,1-dioxide, pyran and thiopyran. Heterocyclic groups containing one or more nitrogen atoms may be bonded to X via carbon or via nitrogen. Within this embodiment, R very aptly represents piperidin-
25 1-yl, 4-trifluoromethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 3,3-difluoropiperidin-1-yl, 3,3-difluoroazetidin-1-yl, morpholin-4-yl, 1-acetylpiperidin-4-yl, 1-trifluoroacetylpiperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, 1-trifluoroacetyl-1,2,3,6-tetrahydropyridin-4-yl or 1-(t-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl. In a particular
30 embodiment, when R represents an N-heterocyclyl group, X is an oxazole

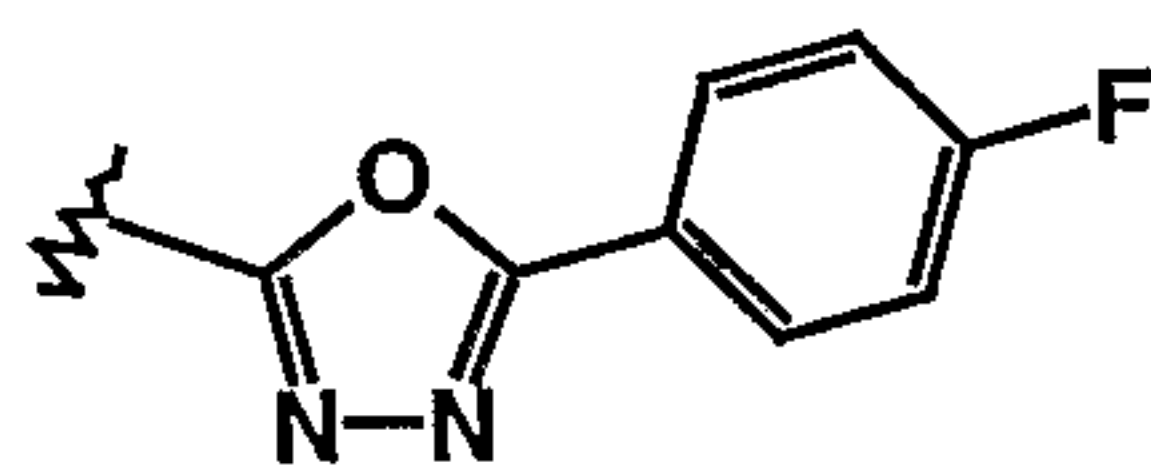
or thiazole residue, preferably thiazol-2-yl in which R is attached to the 5-position.

- In a third embodiment, R represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF₃, CHF₂, CH₂F, NO₂, CN, OCF₃, C₁₋₆alkyl and C₁₋₆alkoxy. Examples of suitable 6-membered heteroaryl groups represented by R include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and triazinyl. Preferably, the phenyl or heteroaryl ring bears 0 to 2 substituents. Phenyl groups represented by R preferably bear at least one substituent.
- Preferred substituents include halogen (especially chlorine and fluorine), CN, C₁₋₆alkyl (especially methyl), C₁₋₆alkoxy (especially methoxy), OCF₃ and CF₃. If two or more substituents are present, preferably not more than one of them is other than halogen or alkyl. Within this embodiment, examples of groups represented by R include phenyl, monohalophenyl, dihalophenyl, trihalophenyl, cyanophenyl, methylphenyl, methoxyphenyl, trifluoromethylphenyl, trifluoromethoxyphenyl, pyridyl, monohalopyridyl and trifluoromethylpyridyl, wherein "halo" refers to fluoro or chloro. Suitable specific values for R include 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 3,4,5-trifluorophenyl, 4-cyanophenyl, 4-methylphenyl, 4-methoxyphenyl, 2-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 4-(trifluoromethoxy)phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, 5-methylpyridin-2-yl, 5-fluoropyridin-2-yl, 5-chloropyridin-2-yl, 5-(trifluoromethyl)pyridin-2-yl and 6-(trifluoromethyl)pyridin-3-yl.
- Preferred examples include 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-(trifluoromethyl)phenyl, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.
- In a fourth embodiment, R represents N(R^a)₂ where each R^a independently represents H or C₁₋₆alkyl which is optionally substituted as

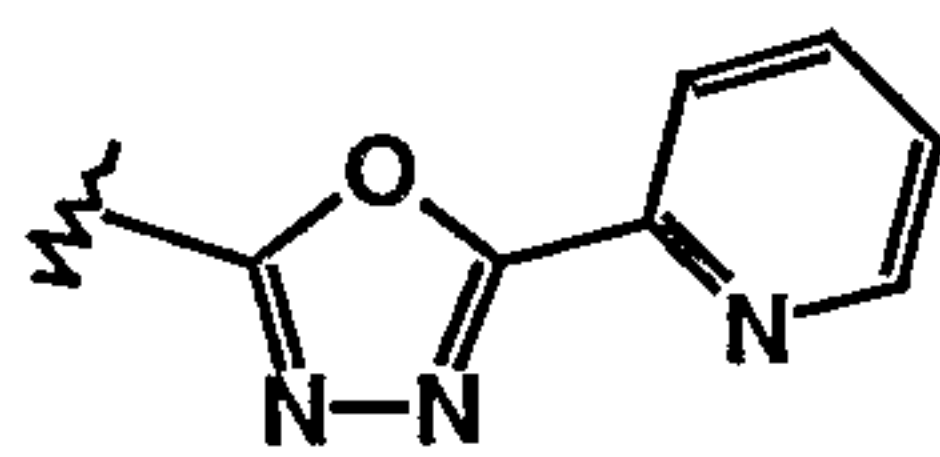
defined previously. R^a aptly represents H, unsubstituted alkyl such as methyl, ethyl, propyl or butyl, or haloalkyl such as mono-, di- or trifluoroethyl. Within this embodiment, R very aptly represents dimethylamino. In a particular embodiment, when R represents $N(R^a)_2$, X
 5 is an oxazole or thiazole residue, preferably thiazol-2-yl wherein R is attached to the 5-position.

In one preferred embodiment of the invention, X represents a bivalent pyrazole residue and R represents phenyl or 6-membered heteroaryl which is optionally substituted as defined above.

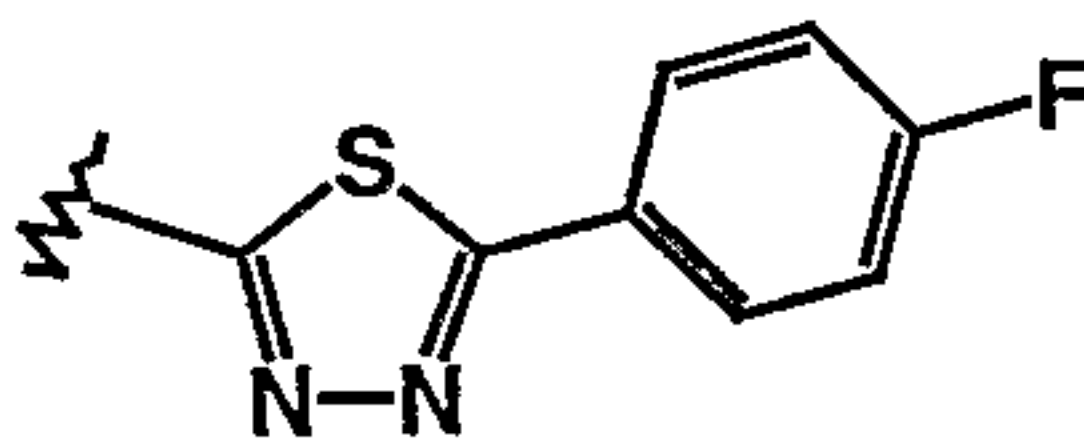
10 Representative compounds in accordance with the invention include those in which the moiety $-X-R$ is selected from:



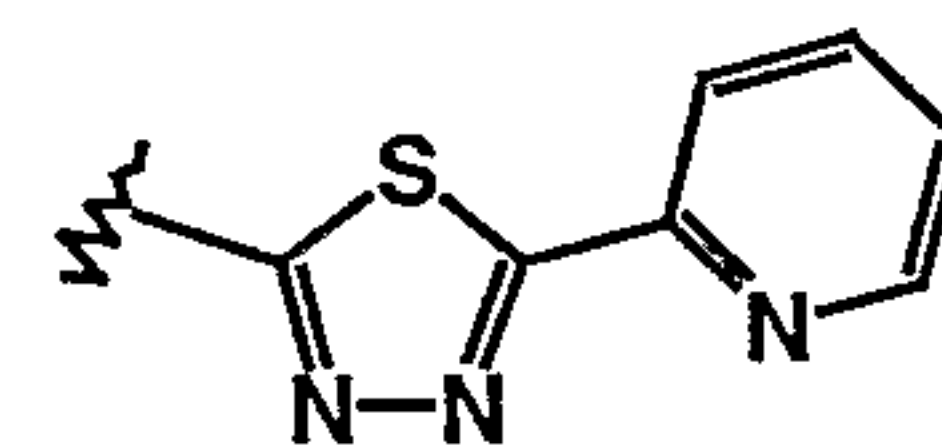
;



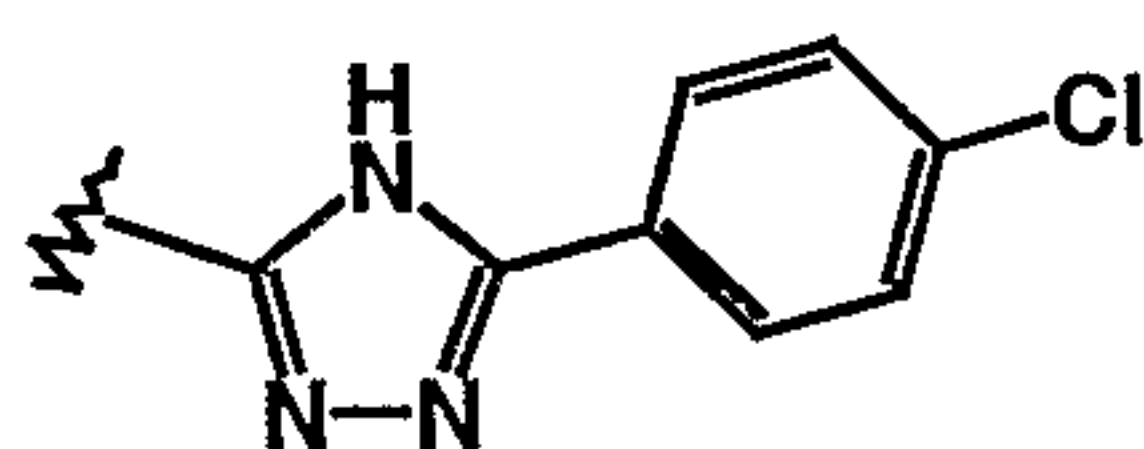
;



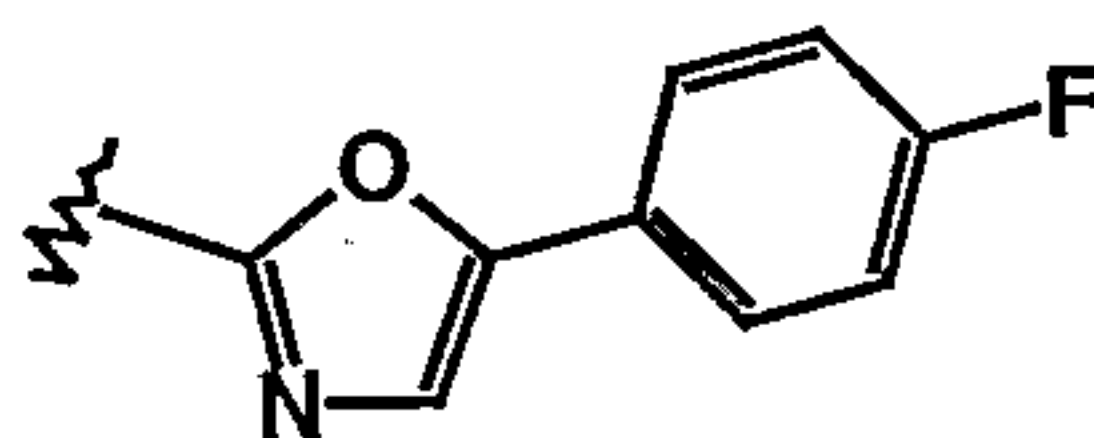
;



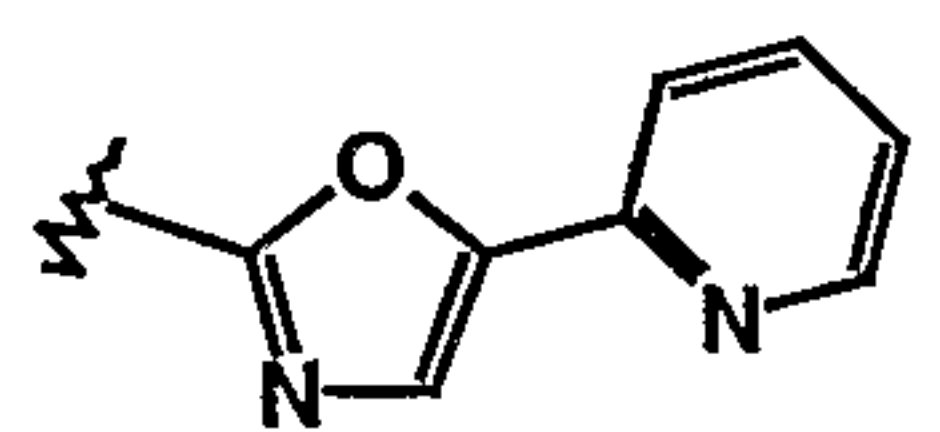
;



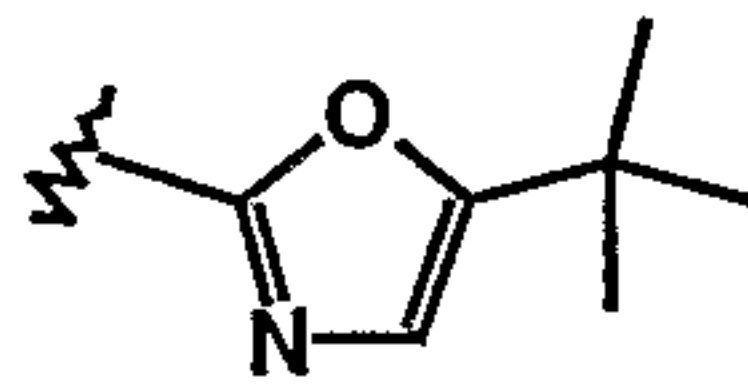
;



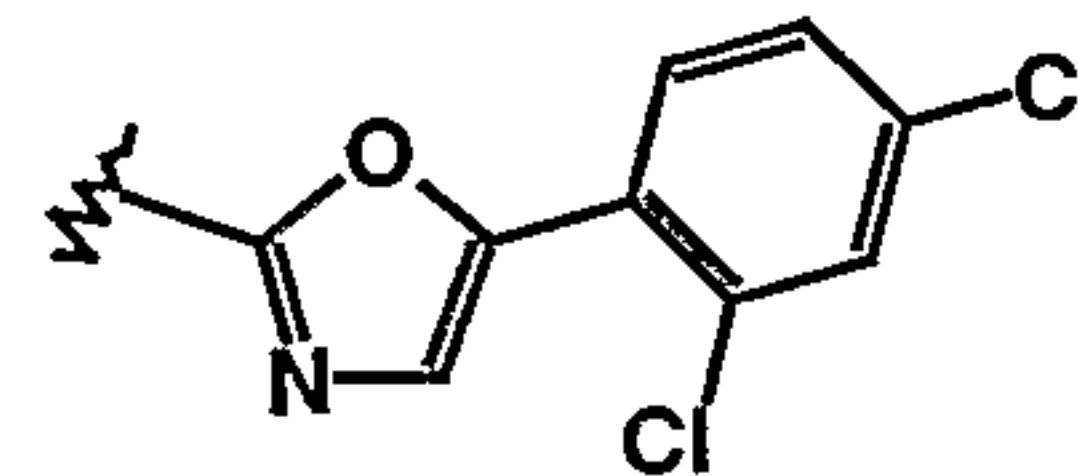
;



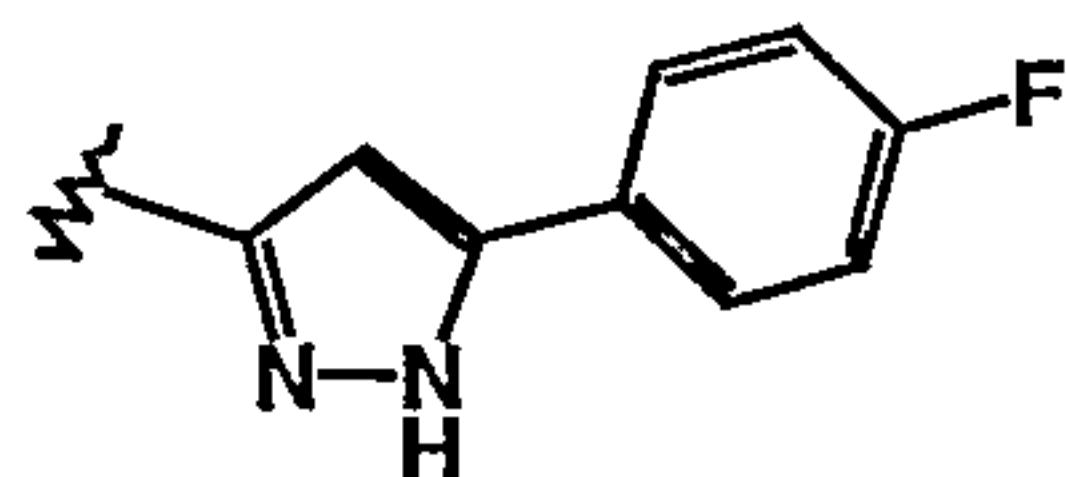
;



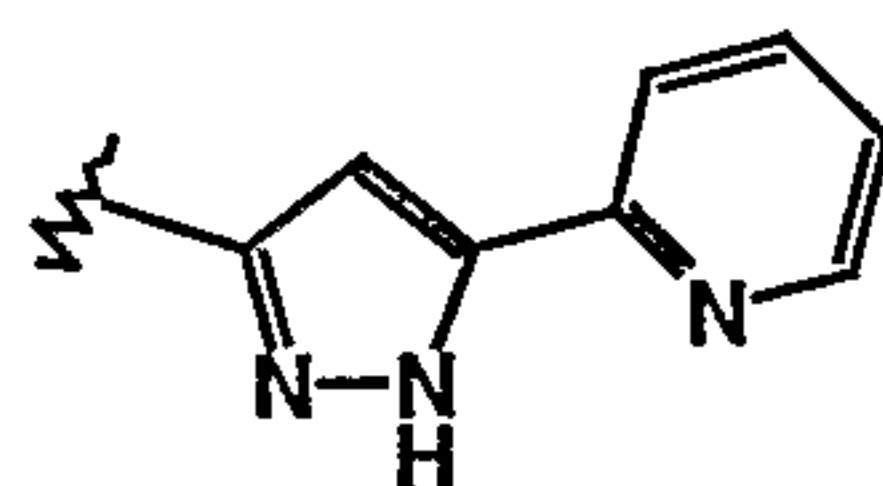
;



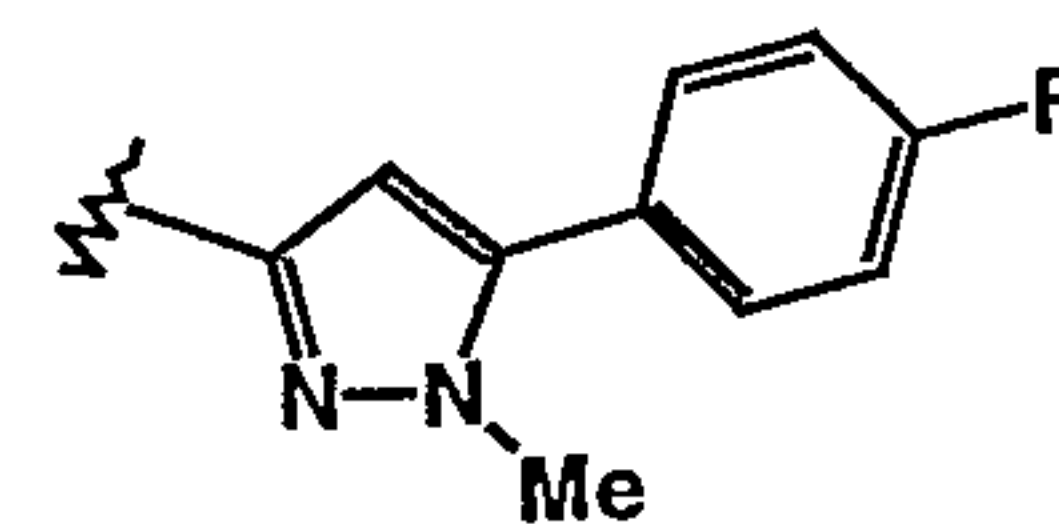
;



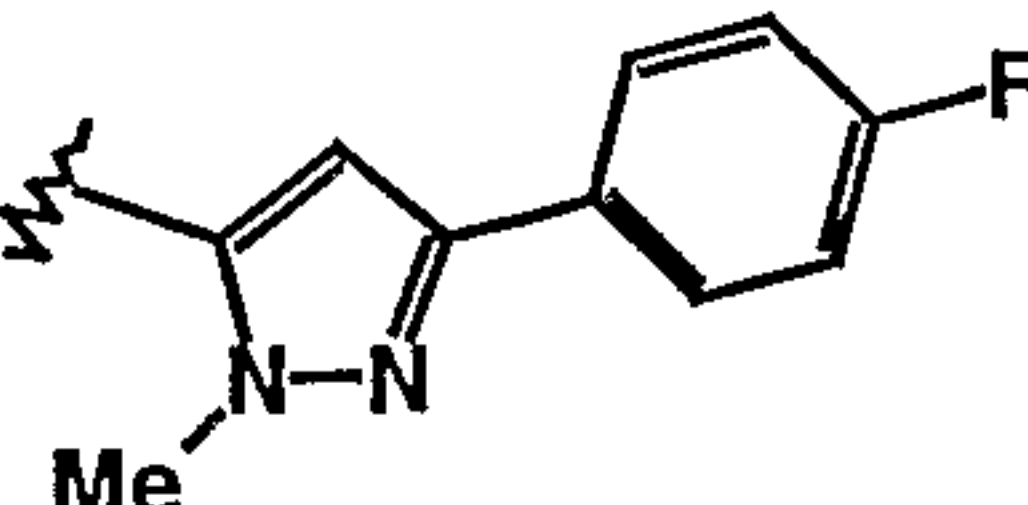
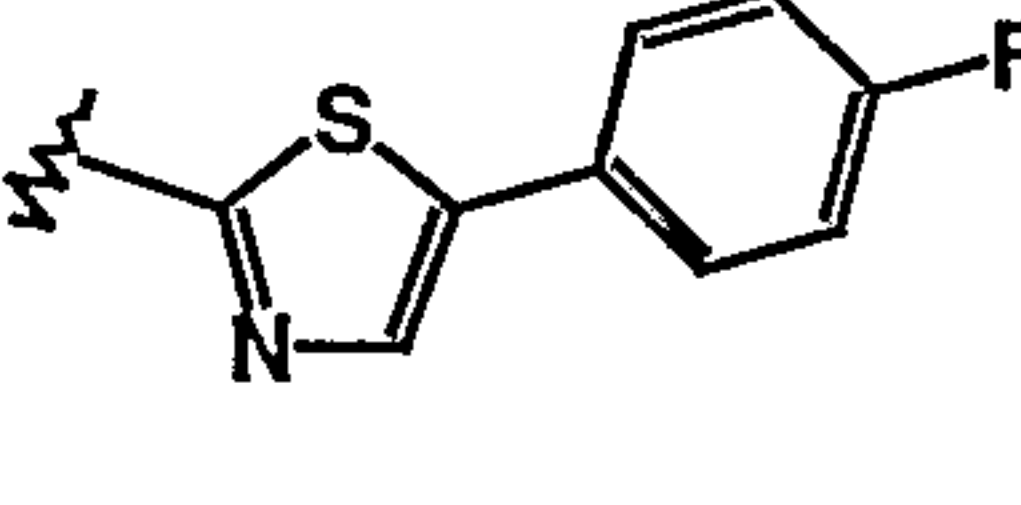
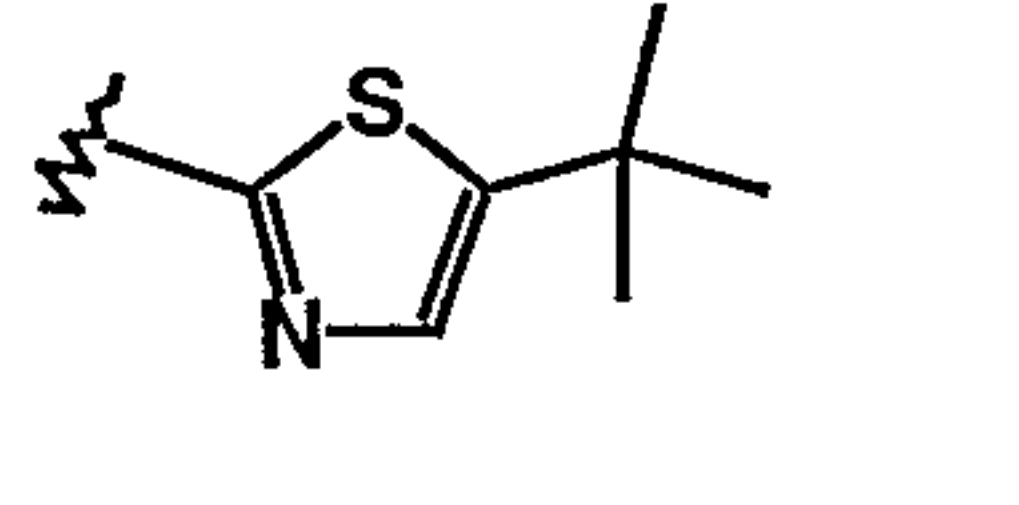
;

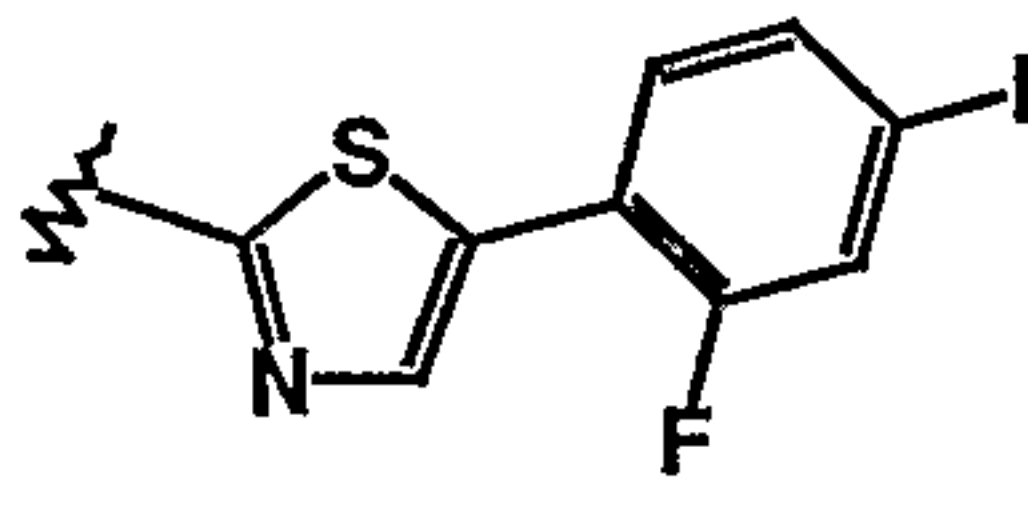
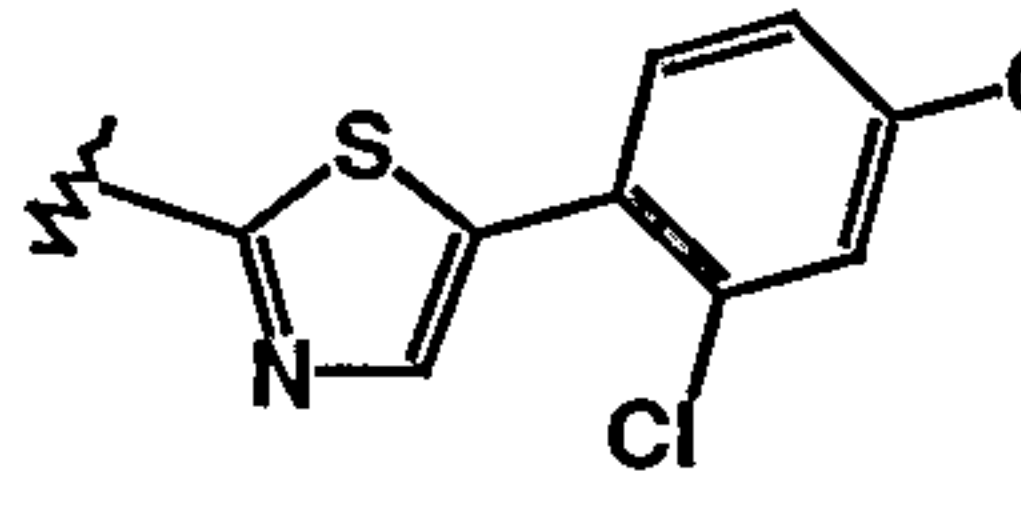
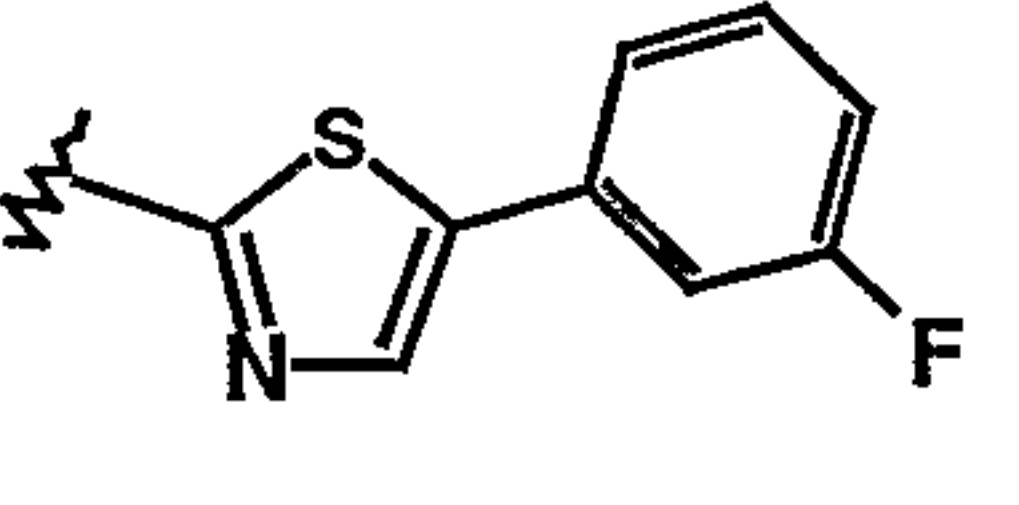


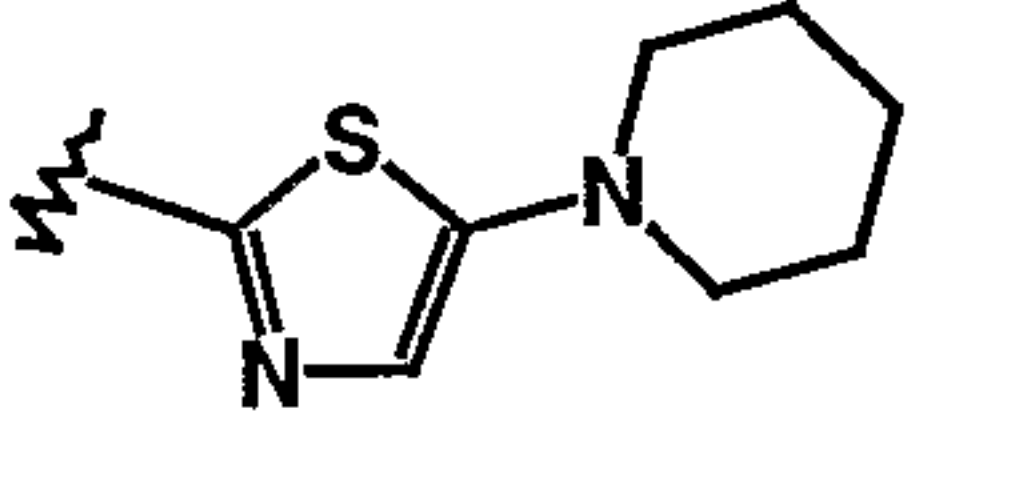
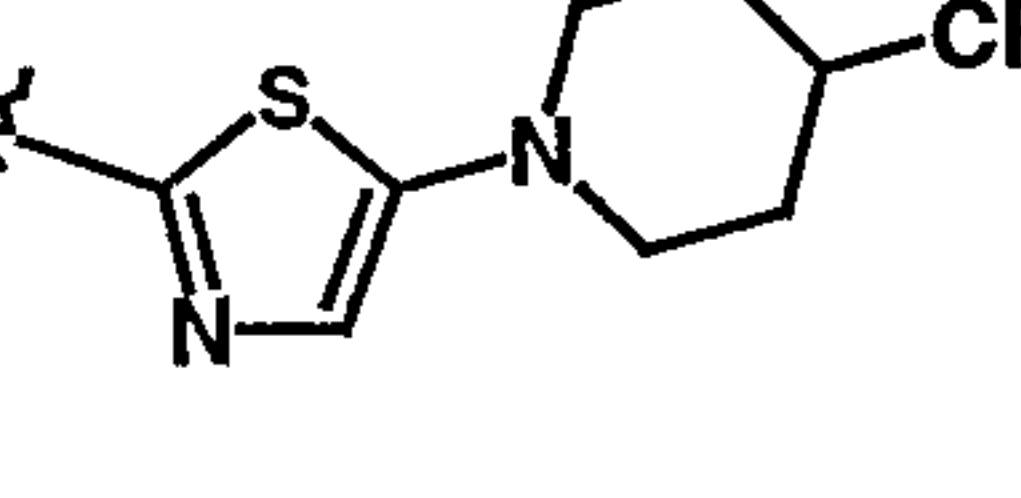
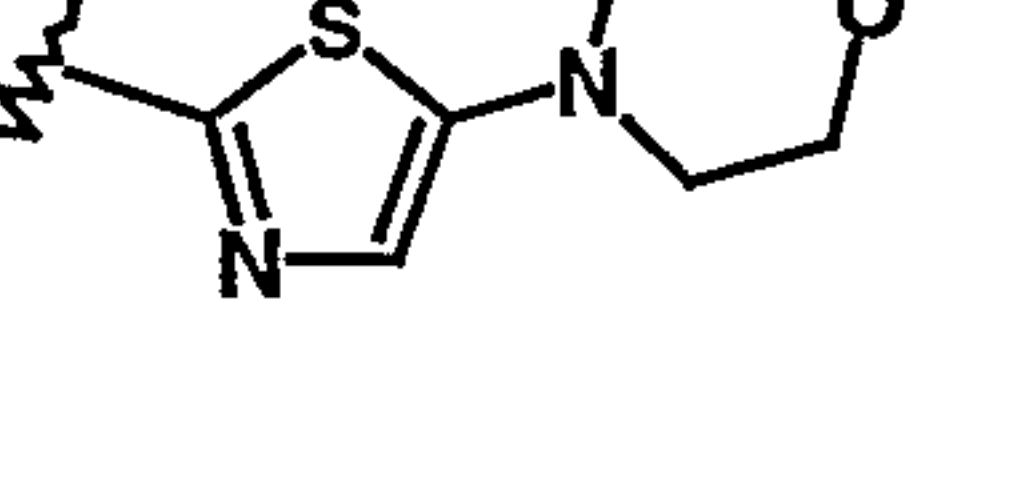
;

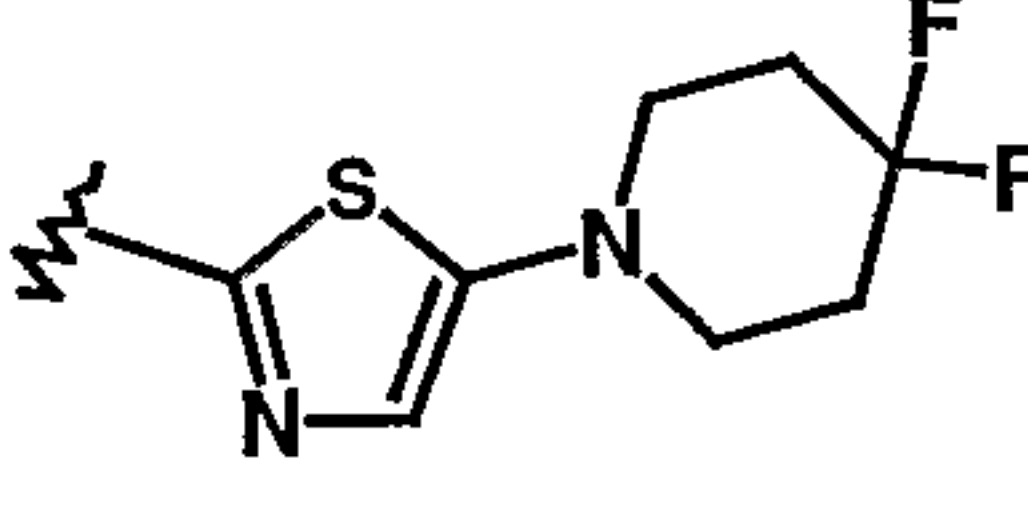
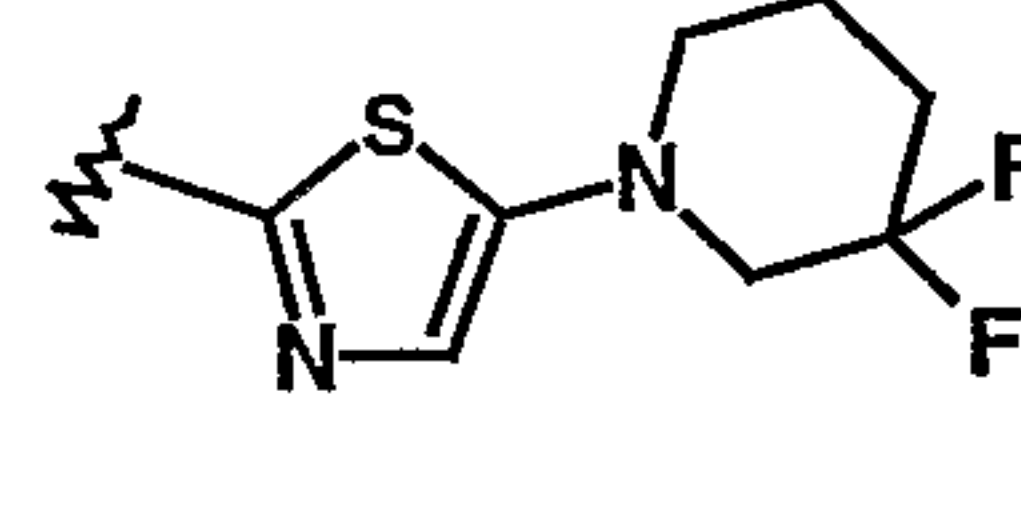
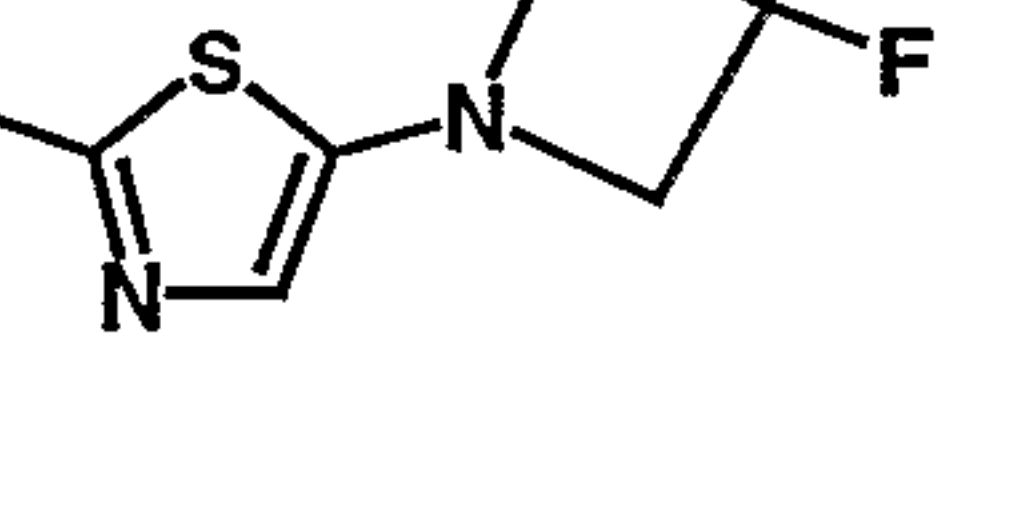


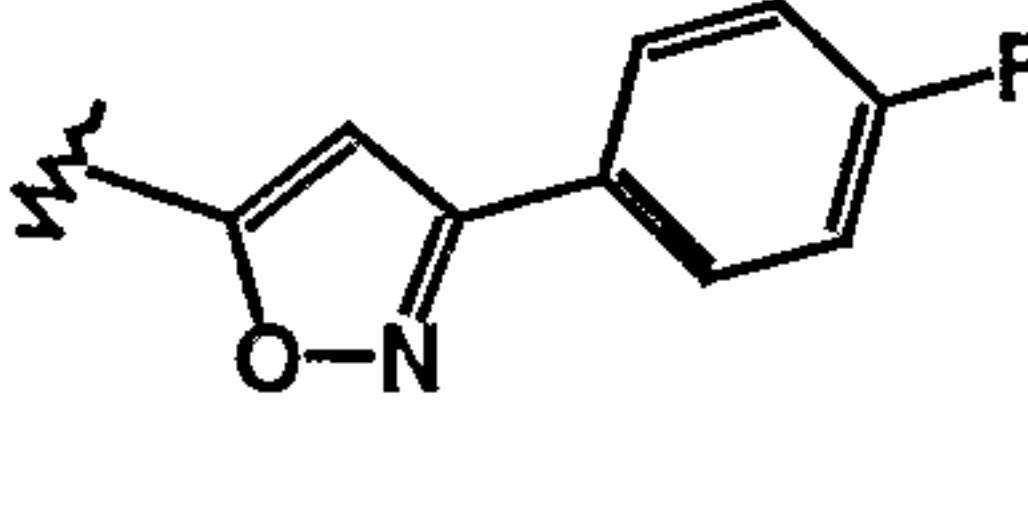
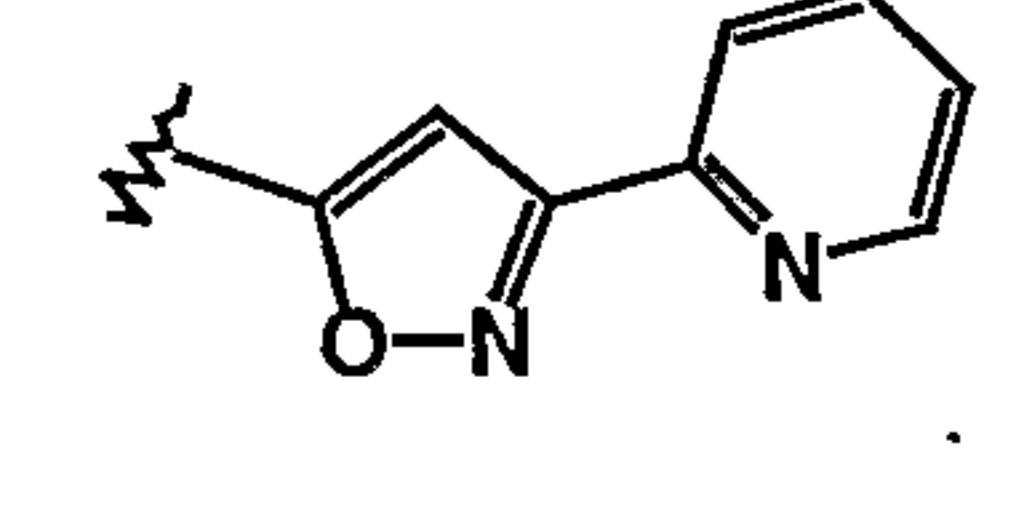
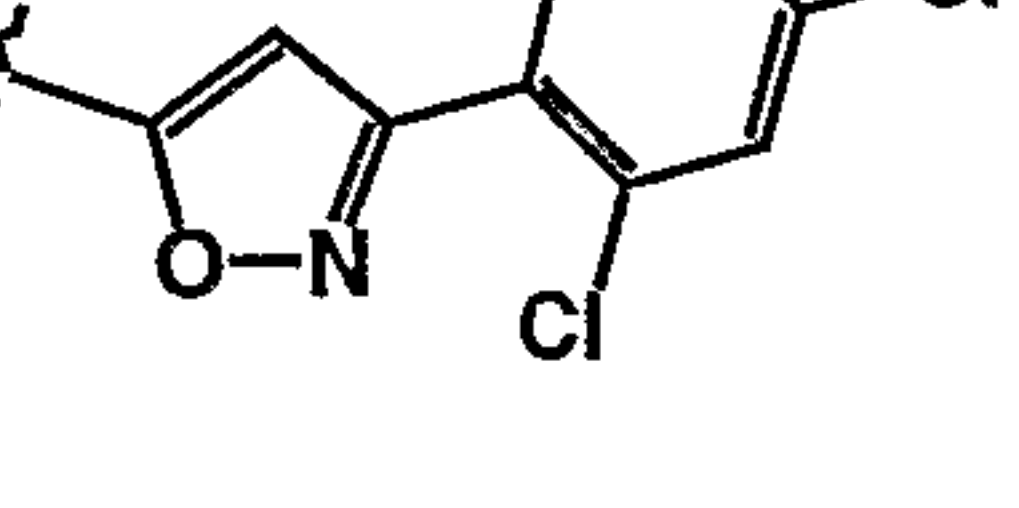
;

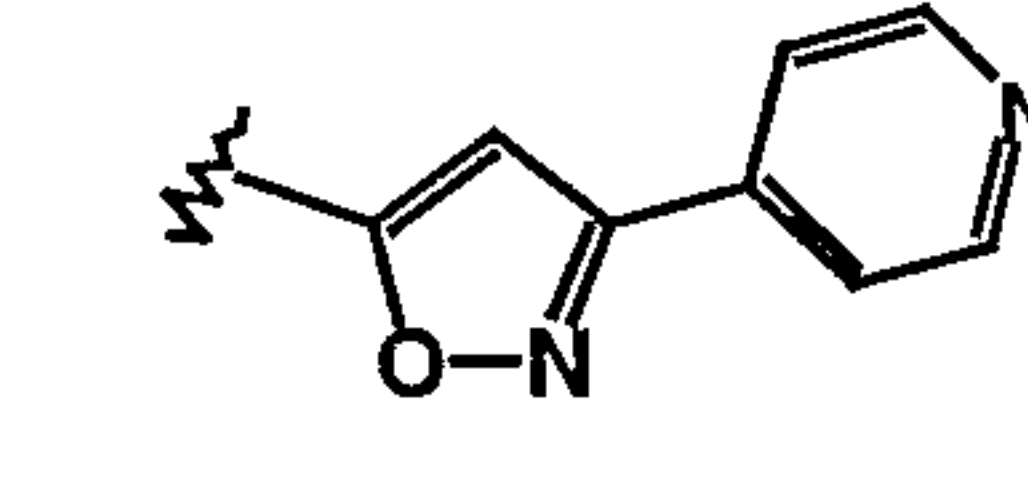
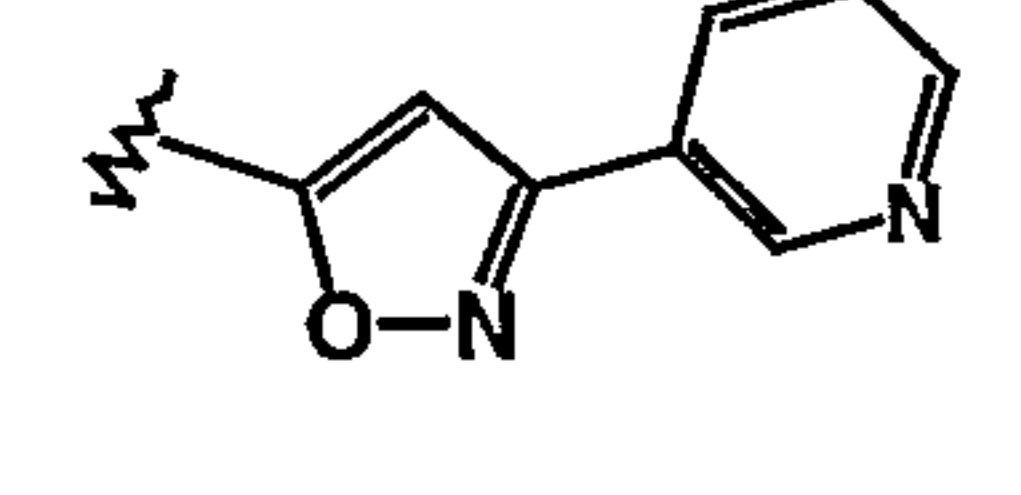
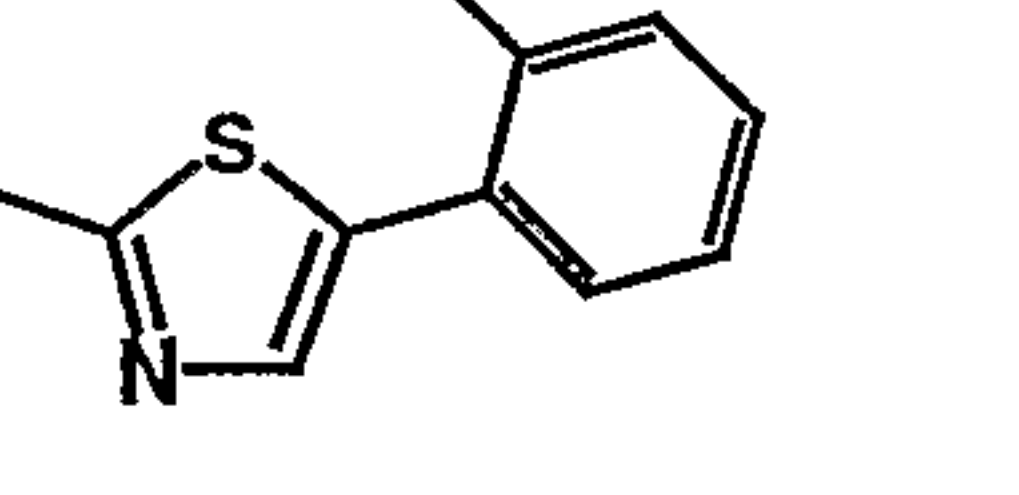
 ;
 ;
 ;

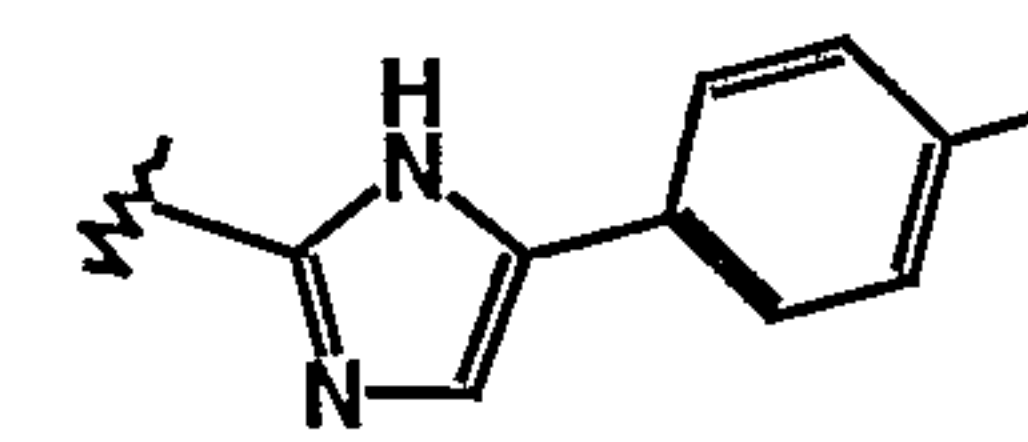
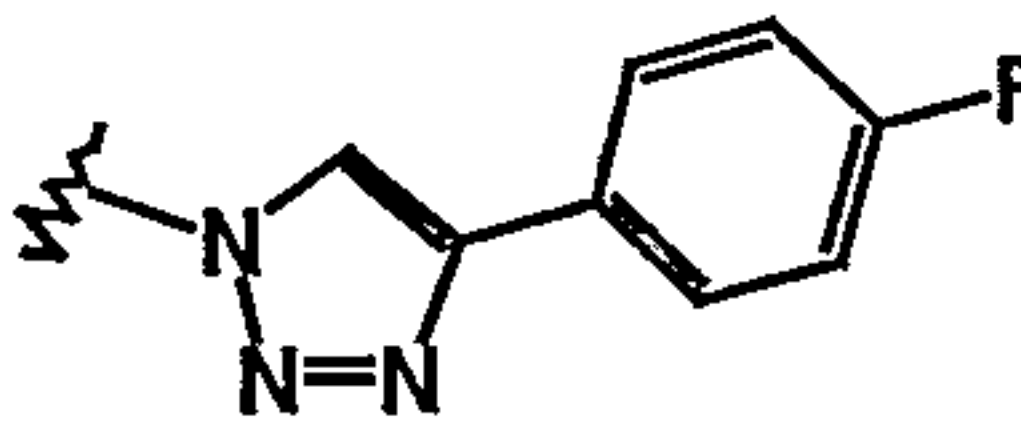
 ;
 ;
 ;

 ;
 ;
 ;

 ;
 ;
 ;

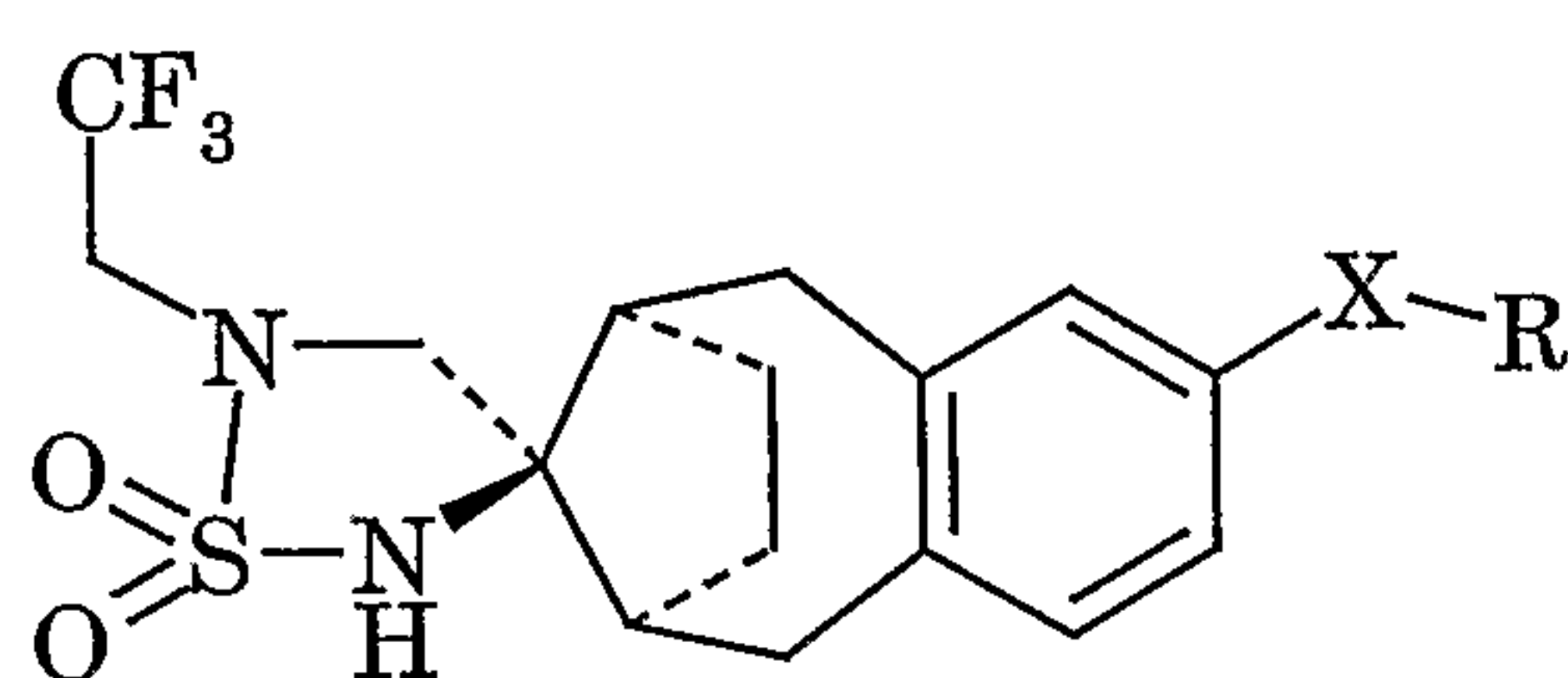
 ;
 ;
 ;

 ;
 ;
 ;

 ;


and

A preferred subclass of the compounds of the invention are the 2-substituted-[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-decahydro-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxides of formula I(a):



I(a)

wherein R and X have the same meanings and preferred identities as before;

and pharmaceutically acceptable salts thereof.

5 Within this subclass, X is very aptly 5-substituted-thiazol-2-yl, 5-substituted-4-methylthiazol-2-yl, 5-substituted-1-methylpyrazol-3-yl, 1-substituted-imidazol-4-yl or 1-substituted-1,2,4-triazol-3-yl.

Preferably, R represents optionally-substituted phenyl or heteroaryl as described previously.

10 Particularly preferred identities of R-X- include 5-(4-fluorophenyl)-1-methylpyrazol-3-yl and 1-(4-fluorophenyl)imidazol-4-yl.

The compounds of the present invention have an activity as inhibitors of γ secretase.

The invention also provides pharmaceutical compositions

15 comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or

20 suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. The principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate and dicalcium phosphate,

25 or gums or surfactants such as sorbitan monooleate, poly(ethylene glycol), and other pharmaceutical diluents, e.g. water, to form a homogeneous preformulation composition containing a compound of the present

invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. Tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, liquid- or gel-filled capsules, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous solutions, gels or suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(ethylene glycol), poly(vinylpyrrolidone) or gelatin.

The present invention also provides a compound of the invention or a pharmaceutically acceptable salt thereof for use in a method of

treatment of the human body. Preferably the treatment is for a condition associated with the deposition of β -amyloid. Preferably the condition is a neurological disease having associated β -amyloid deposition such as Alzheimer's disease.

5 The present invention further provides the use of a compound of the present invention or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing Alzheimer's disease.

10 The invention further provides the use of a compound as defined herein or a pharmaceutically acceptable salt thereof for treatment or prevention of Alzheimer's disease.

 The invention further provides a composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

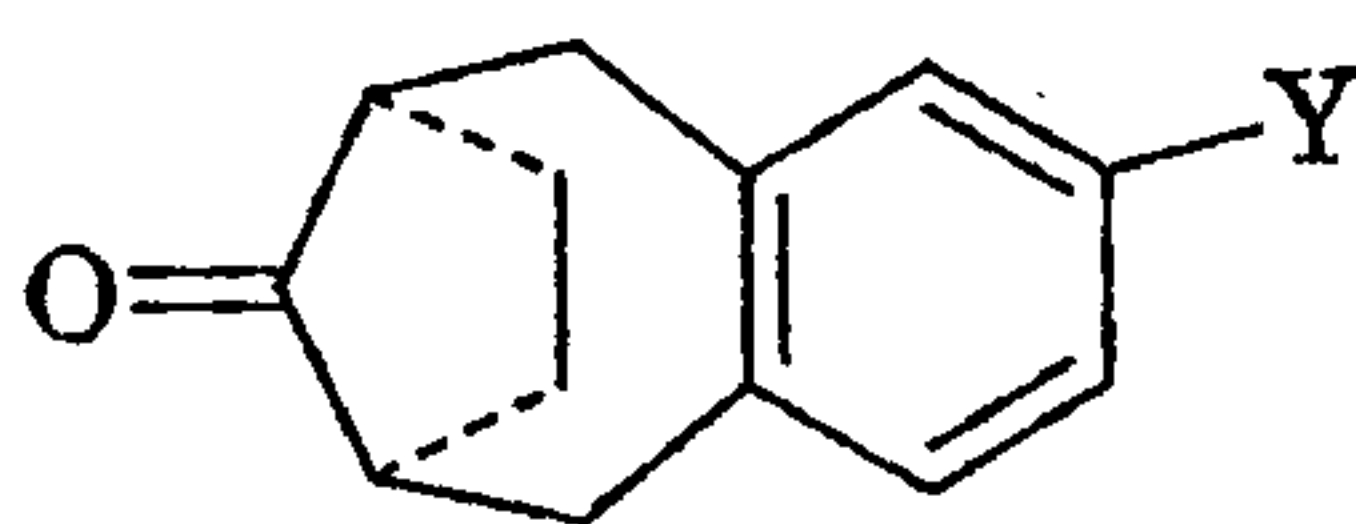
15 Also disclosed is a method of treatment of a subject suffering from or prone to Alzheimer's disease which comprises administering to that subject an effective amount of a compound according to the present invention or a pharmaceutically acceptable salt thereof.

 For treating or preventing Alzheimer's Disease, a suitable dosage
20 level is about 0.01 to 250 mg/kg per day, preferably about 0.01 to 100 mg/kg per day, more preferably about 0.05 to 50 mg/kg of body weight per day, and for the most preferred compounds, about 0.1 to 10 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, a dosage outside these limits
25 may be used.

 The compounds of the invention are particularly suitable for oral administration.

 Suitable starting materials for the preparation of the compounds of formula I are the ketones II:

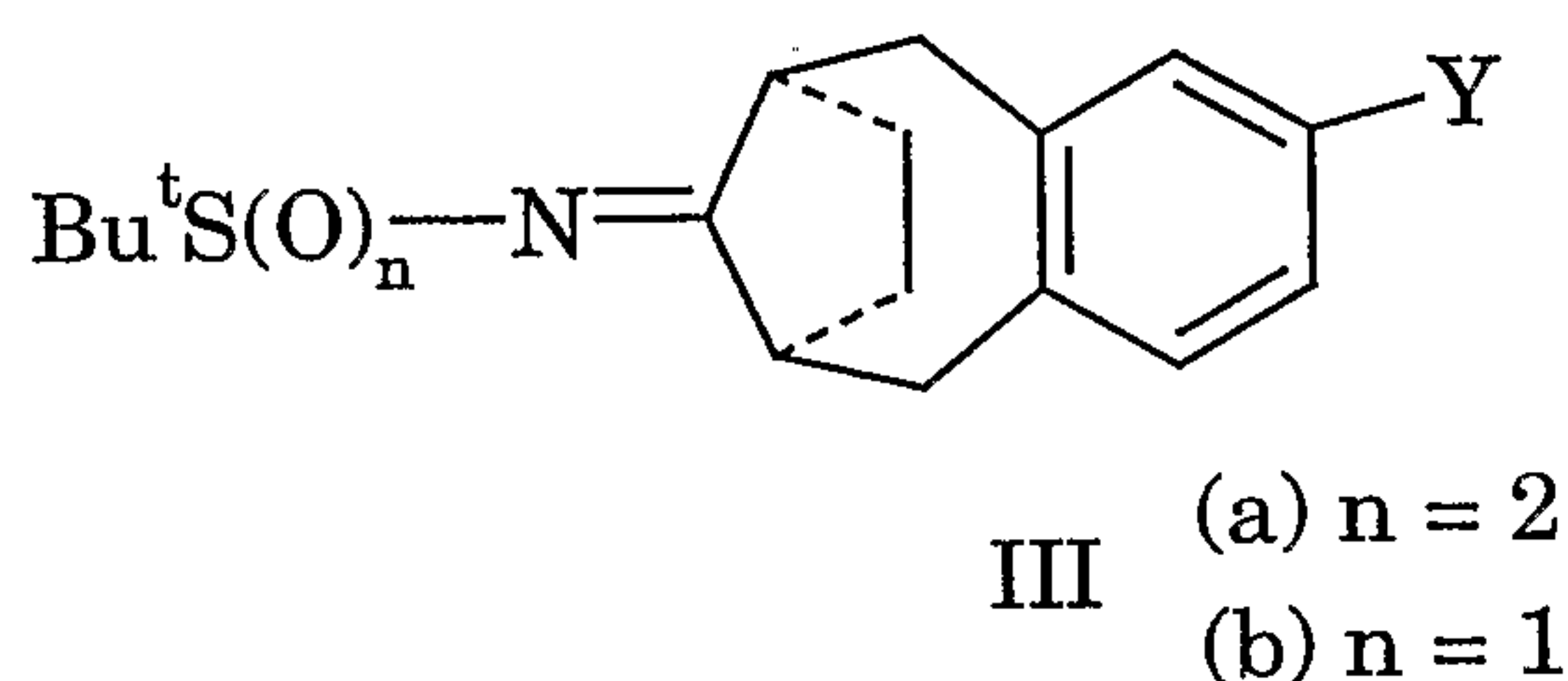
- 14a -



II

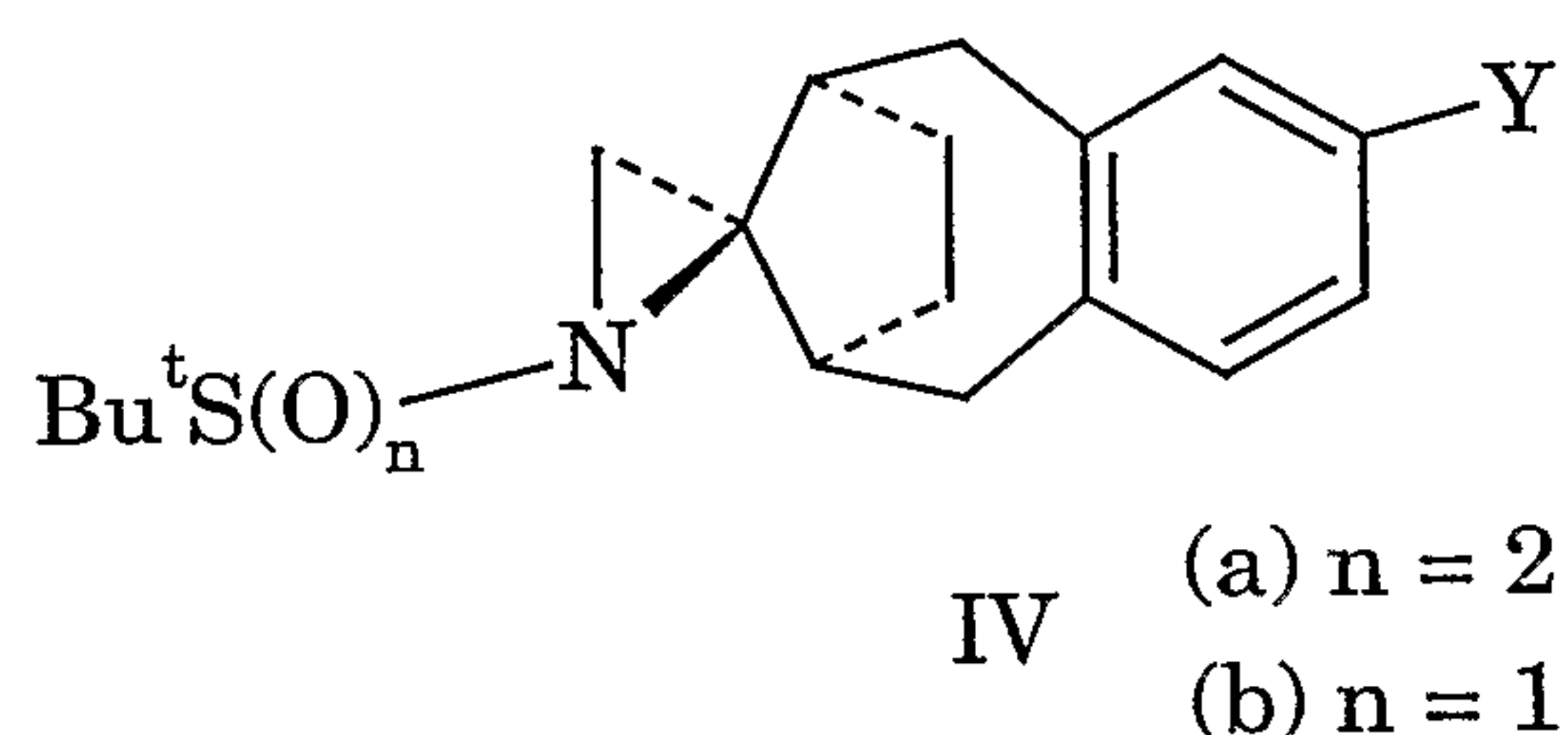
- 5 wherein Y represents alkoxycarbonyl (especially CO₂Me or CO₂Et), nitro or benzyloxy. Treatment of the ketones II with t-butylsulphonamide in the presence of TiCl₄ and triethylamine in refluxing dichloroethane provides the sulphonylimines III(a):

- 15 -



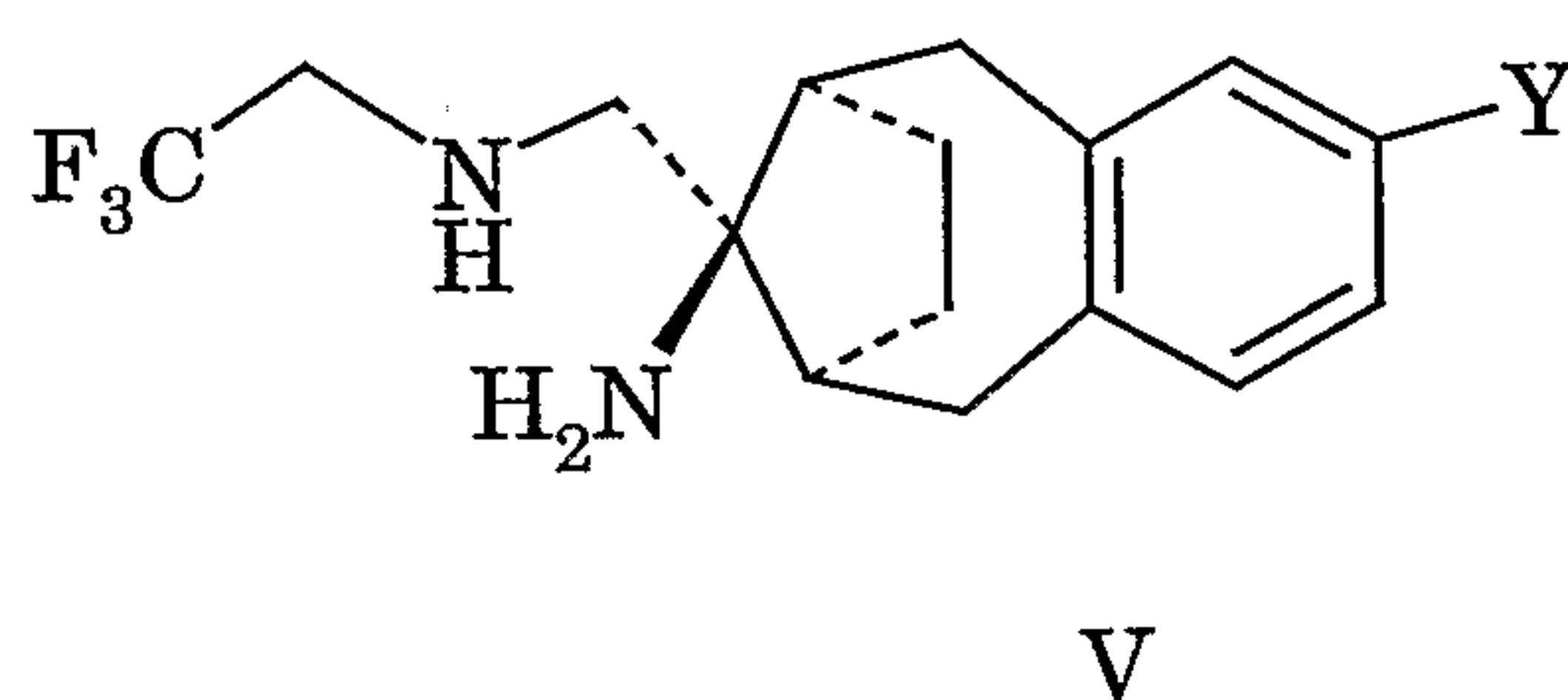
where Y has the same meaning as before. Alternatively, treatment of the ketones II with t-butylsulphinamide in the presence of $\text{Ti}(\text{OEt})_4$ in refluxing tetrahydrofuran provides the sulphonylimines III(b).

5 Both types of imine III react with trimethylsulphoxonium iodide to provide aziridines IV:



where Y has the same meaning as before. The reaction takes place in the presence of sodium hydride at ambient temperature in a THF-DMSO mixture or at 0°C in DMSO.

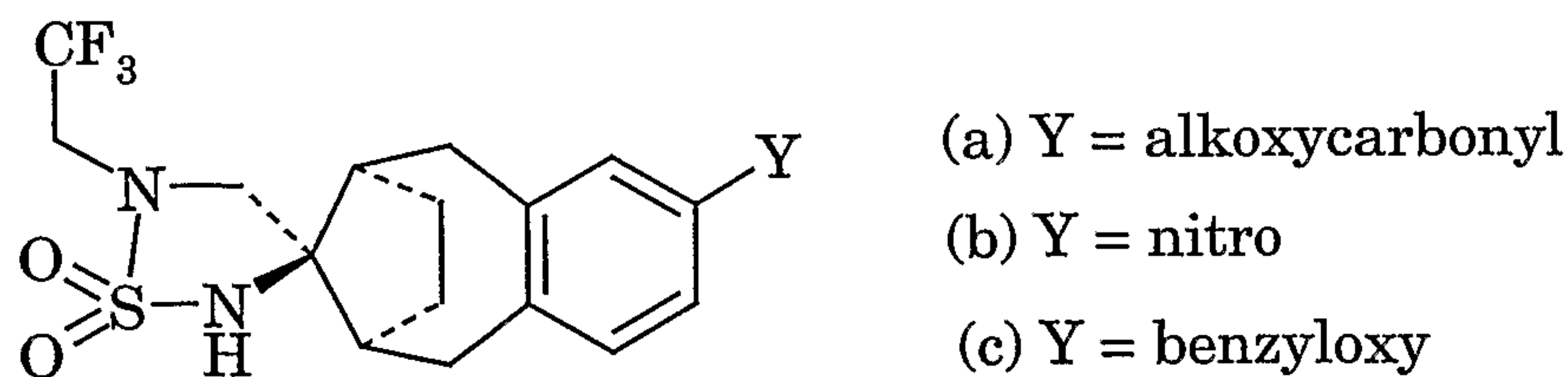
10 Reaction of sulphonamides IV(a) with $\text{CF}_3\text{CH}_2\text{NH}_2$, followed by cleavage of the t-butylsulphonyl group, provides diamines V:



where Y has the same meaning as before. Ring-opening of the aziridine is typically effected by heating with $\text{CF}_3\text{CH}_2\text{NH}_2$ at 100°C in DMF or DMSO in a sealed tube, while cleavage of the t-butylsulphonyl group may be effected by treatment with trifluoromethanesulphonic acid at 0-20°C.

Alternatively, the diamines V may be formed directly by reaction of the sulphinamides IV(b) with $\text{CF}_3\text{CH}_2\text{NH}_2$ in the presence of zinc iodide in dichloroethane at 75°C.

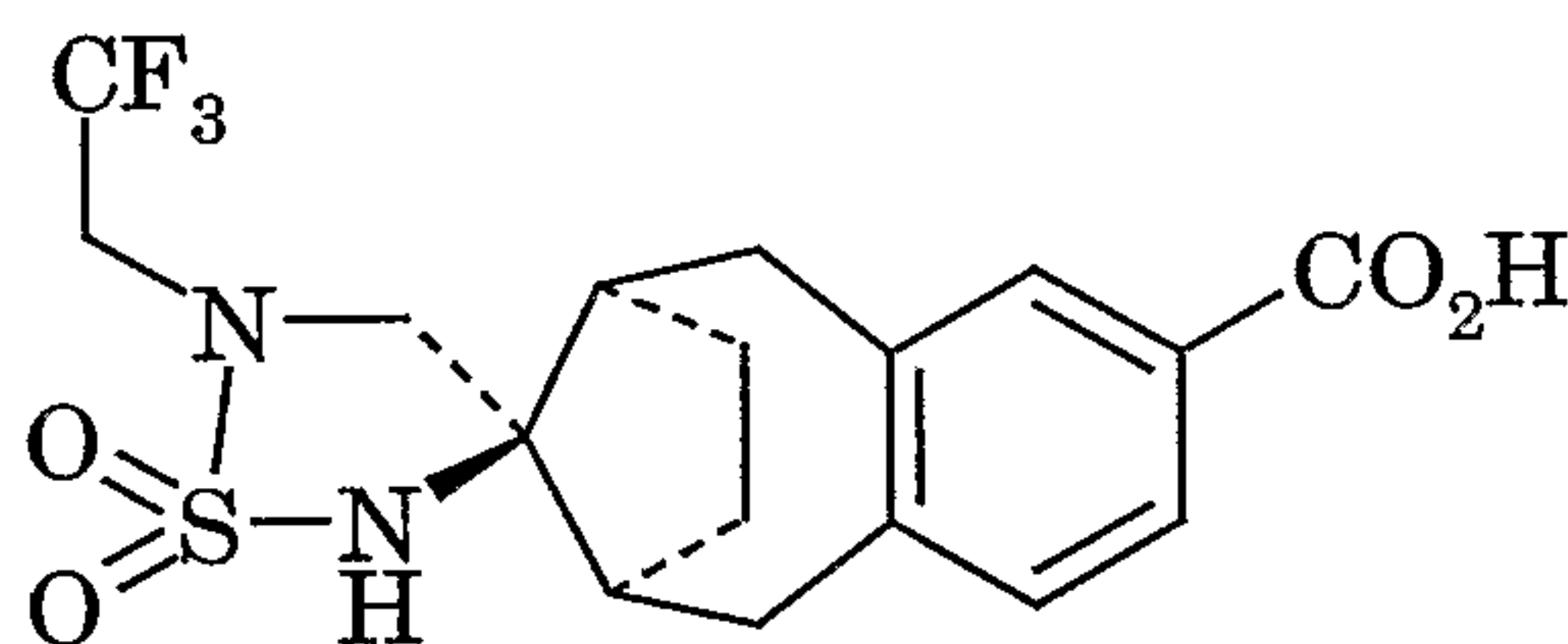
Reaction of diamines V with sulphamide ($\text{H}_2\text{NSO}_2\text{NH}_2$) in refluxing anhydrous pyridine provides the cyclic sulphamides VI(a)-(c):



VI

Compounds VI(a)-(c) are key intermediates for the preparation of compounds of formula I since the substituent Y may be transformed into the moiety $-\text{X}-\text{R}$ by various standard synthetic techniques.

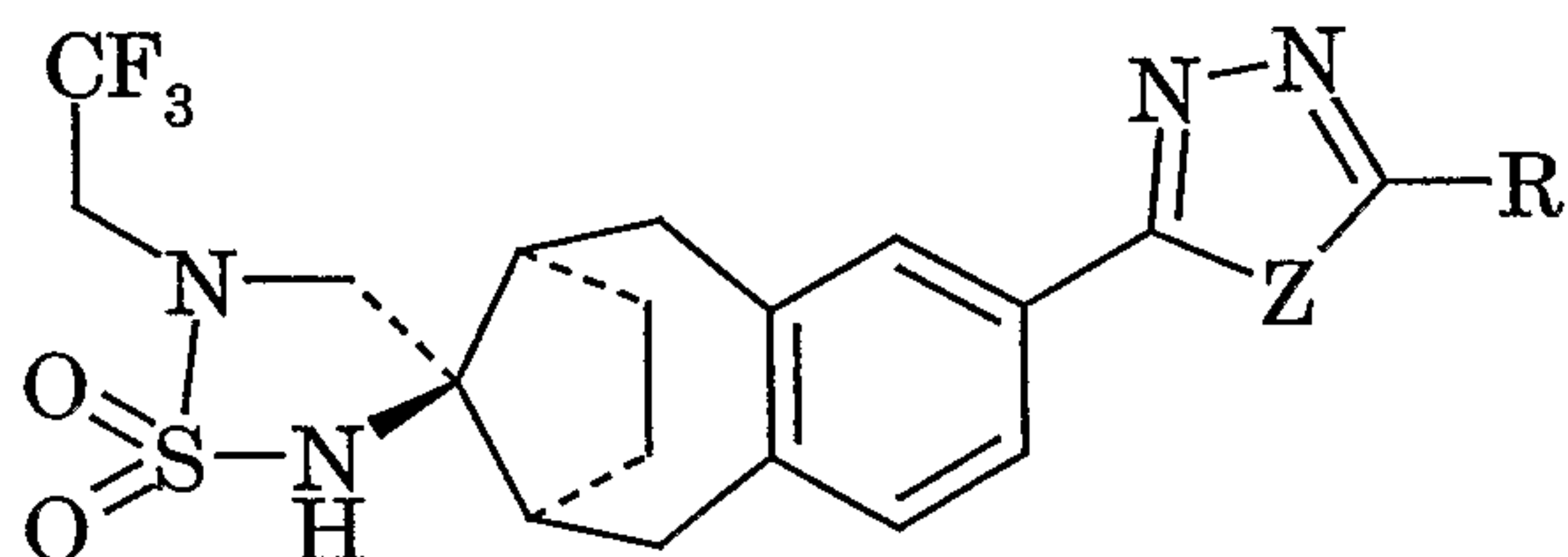
Hydrolysis of the esters VI(a) (for example, using sodium hydroxide in aqueous THF at 60°C) provides the acid VII which serves as the precursor for a variety of heteroaryl structures.



VII

10

In one process, the acid VII is coupled with a hydrazide $\text{R}-\text{CO}-\text{NHNH}_2$ and then reacted (a) with Burgess reagent or (b) with diphosphorus pentasulphide or Lawesson's reagent to provide, respectively, a 1,3,4-oxadiazole derivative IX(a) or a 1,3,4-thiadiazole derivative IX(b):



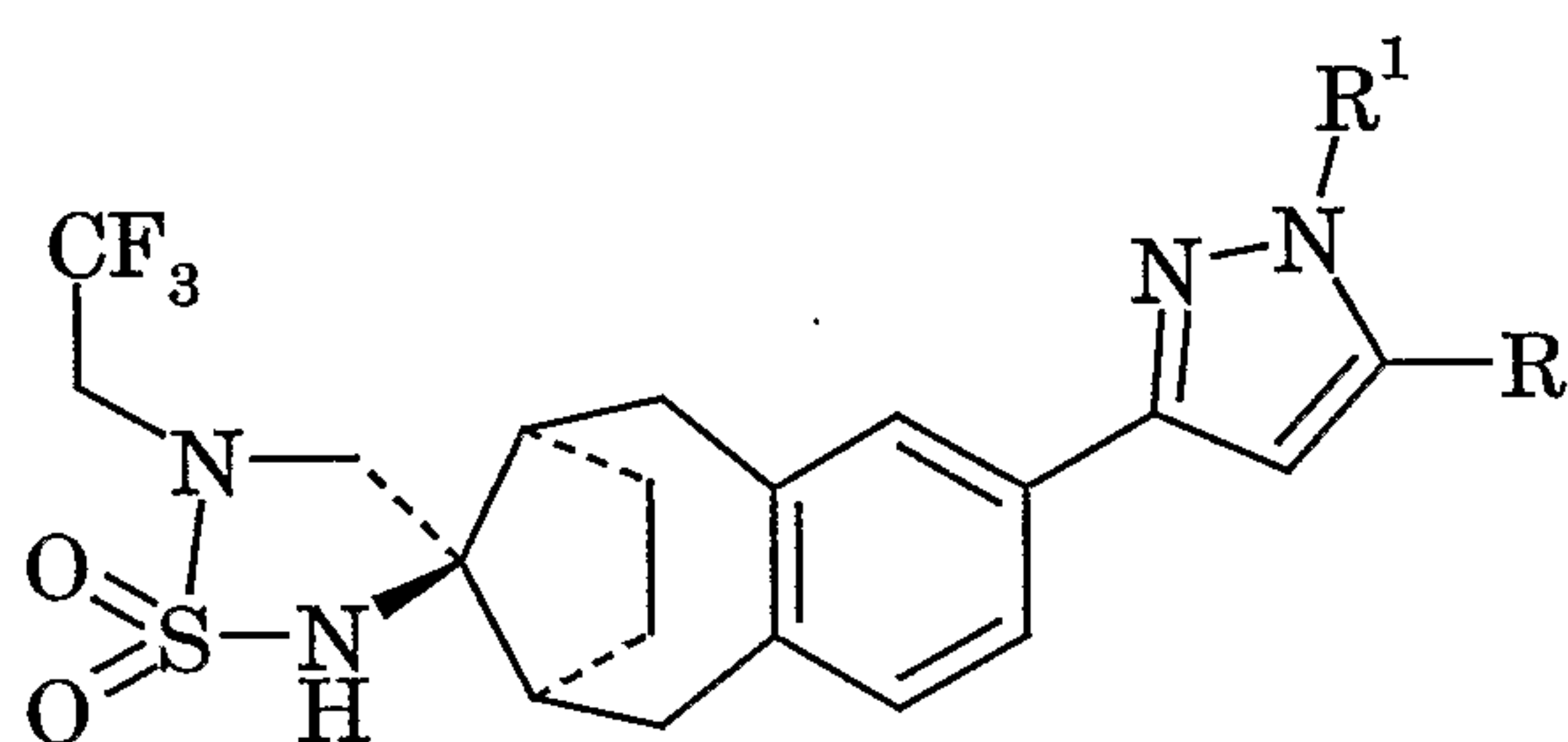
IX
(a) Z = O
(b) Z = S

where R has the same meaning as before. The initial coupling may be effected using HBTU in the presence of a tertiary amine in acetonitrile at

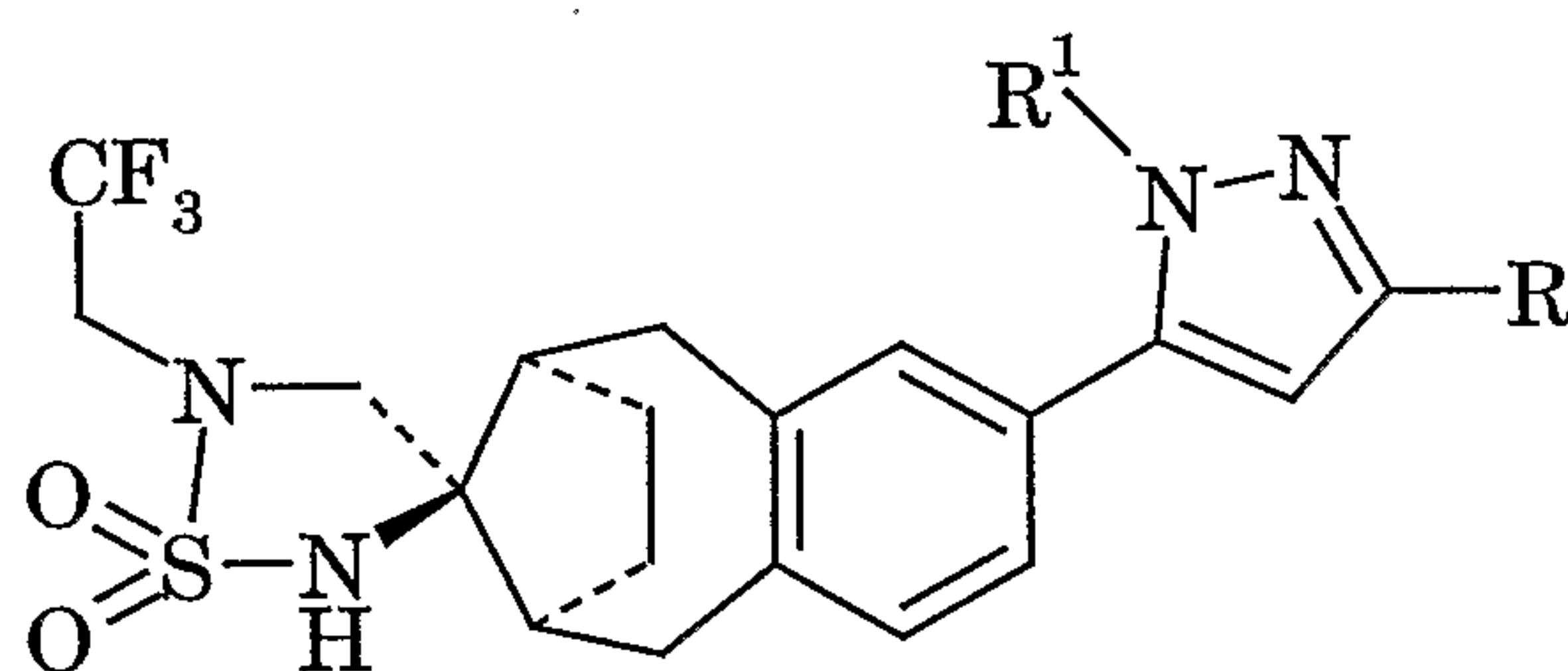
15

40°C. Treatment with Burgess reagent may be carried out in THF using microwave heating, and treatment with diphosphorus pentasulphide may be carried out in refluxing pyridine.

In another process, the acid VII is first reacted with
 5 carbonyldiimidazole and then with an anion derived from an acetyl derivative $R\text{-COCH}_3$. Treatment of the resulting β -diketone with $R^1\text{NHNH}_2$ then provides the preferred pyrazoles X(a) and X(b):



X(a)

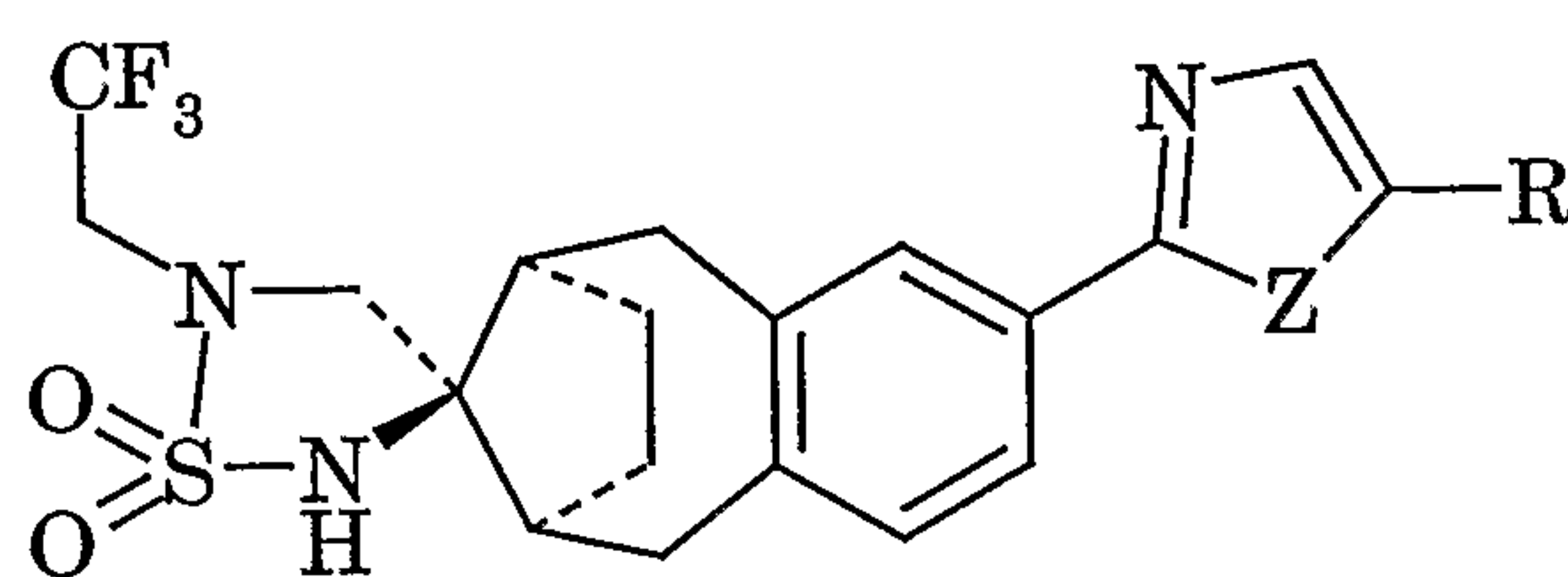


X(b)

where R^1 is H or a hydrocarbon group of up to 5 carbon atoms optionally
 10 substituted with up to 3 halogen atoms (preferably methyl) and R has the same meaning as before (preferably substituted phenyl). The anion is typically generated by treatment of $R\text{-COCH}_3$ with lithium diisopropylamide in THF at -78°C and reacted *in situ*. Reaction with the hydrazine is conveniently carried out in refluxing ethanol. When R^1 is
 15 other than H, the positional isomers X(a) and X(b) are formed in approximately equal proportions, and may be separated by preparative HPLC.

In another process, the acid VII is coupled with an amine $R\text{-COCH}_2\text{NH}_2$, then treated (a) with Burgess reagent or (b) with
 20 Lawesson's reagent to provide, respectively, an oxazole derivative XI(a) or a thiazole derivative XI(b):

- 18 -

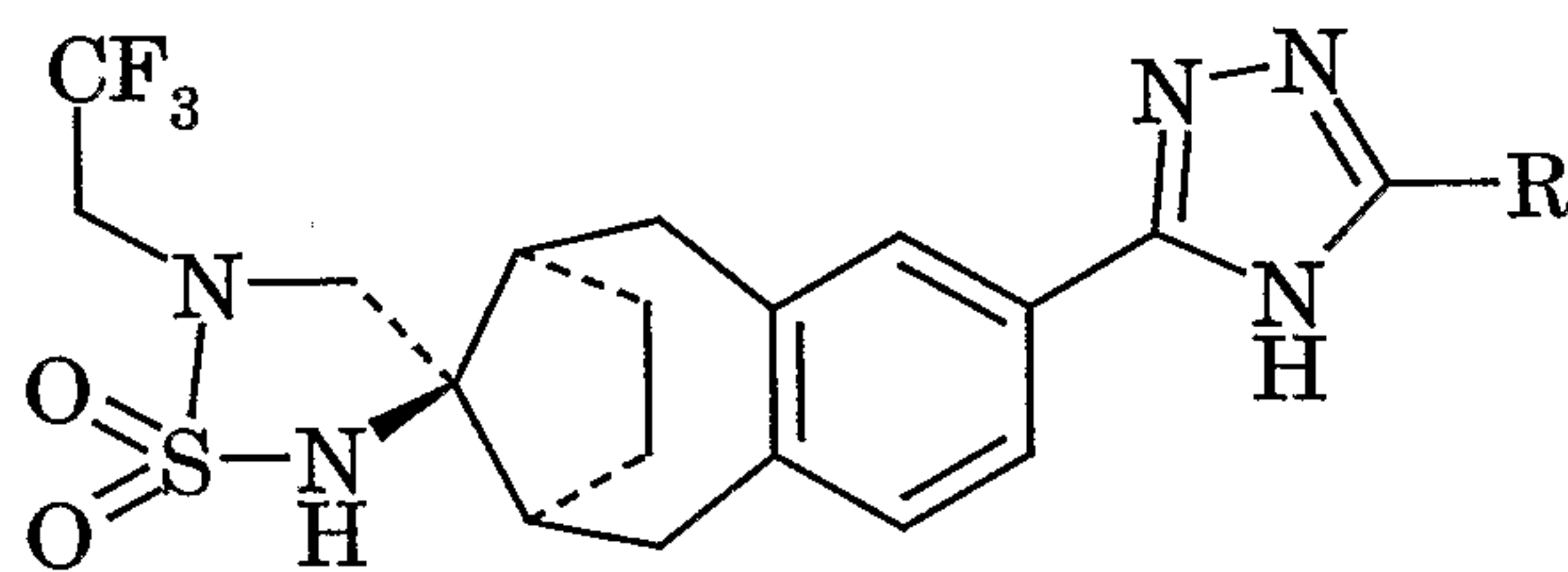


XI (a) Z = O
(b) Z = S

where R has the same meaning as before. The initial coupling may be effected using HBTU in the presence of a tertiary amine in acetonitrile at 50°C. Treatment with Burgess reagent may be carried out in THF using microwave heating, and treatment with Lawesson's reagent may be carried out in refluxing toluene.

For the synthesis of oxazoles or thiazoles of formula XI in which R is N(R^a)₂ or N-heterocyclyl, it is advantageous to carry out the initial coupling of the acid VII with glycine ethyl ester, and to react the product with (R³)₂NH, where the R³ groups represent R^a (as defined previously) or complete a heterocyclic ring within the definition of R. Treatment of the resulting bis-amides with Burgess reagent or Lawesson's reagent, as described above, then provides the desired oxazoles or thiazoles.

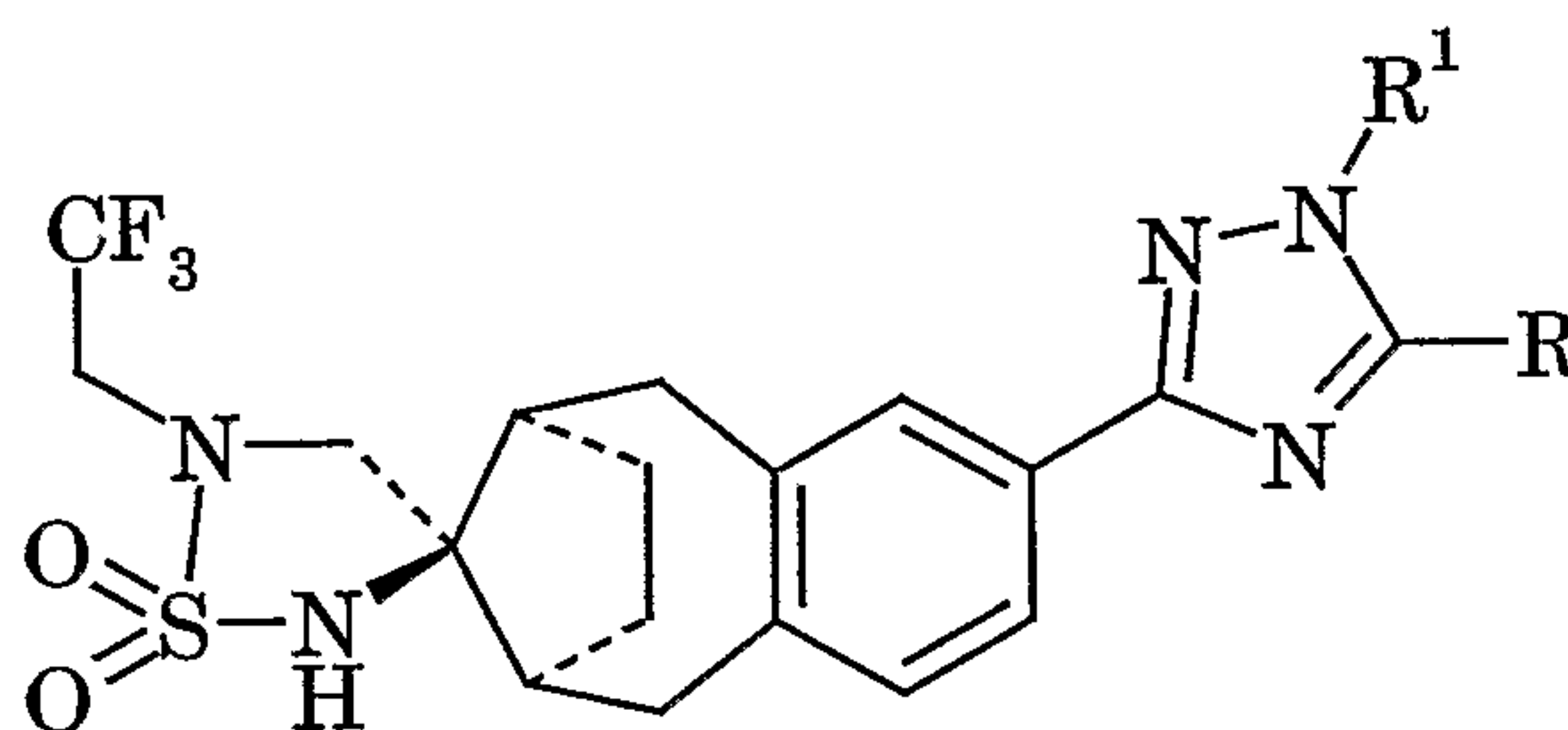
In another process, the acid VII is converted to the corresponding hydrazide, then reacted with a thioamide R-CS-NH₂ to form a 1,2,4-triazole derivative XII:



XII

where R has the same meaning as before. Conversion of VII to the hydrazide is conveniently effected by treatment with BOC-NHNH₂ in the presence of HBTU and a tertiary amine in acetonitrile at 20°C, followed by cleavage of the BOC protecting group with HCl at ambient temperature in ethyl acetate. Reaction with R-CS-NH₂ is carried out at elevated temperature, e.g. 200°C.

Alternatively, the acid VII (or its ester precursor VI(a)) may be reduced to the corresponding aldehyde and treated with R^1NHNH_2 to provide the corresponding hydrazone, then reacted with a hydroximinoyl chloride $R-C(Cl)=NOH$ to provide a 1,2,4-triazole XIII:



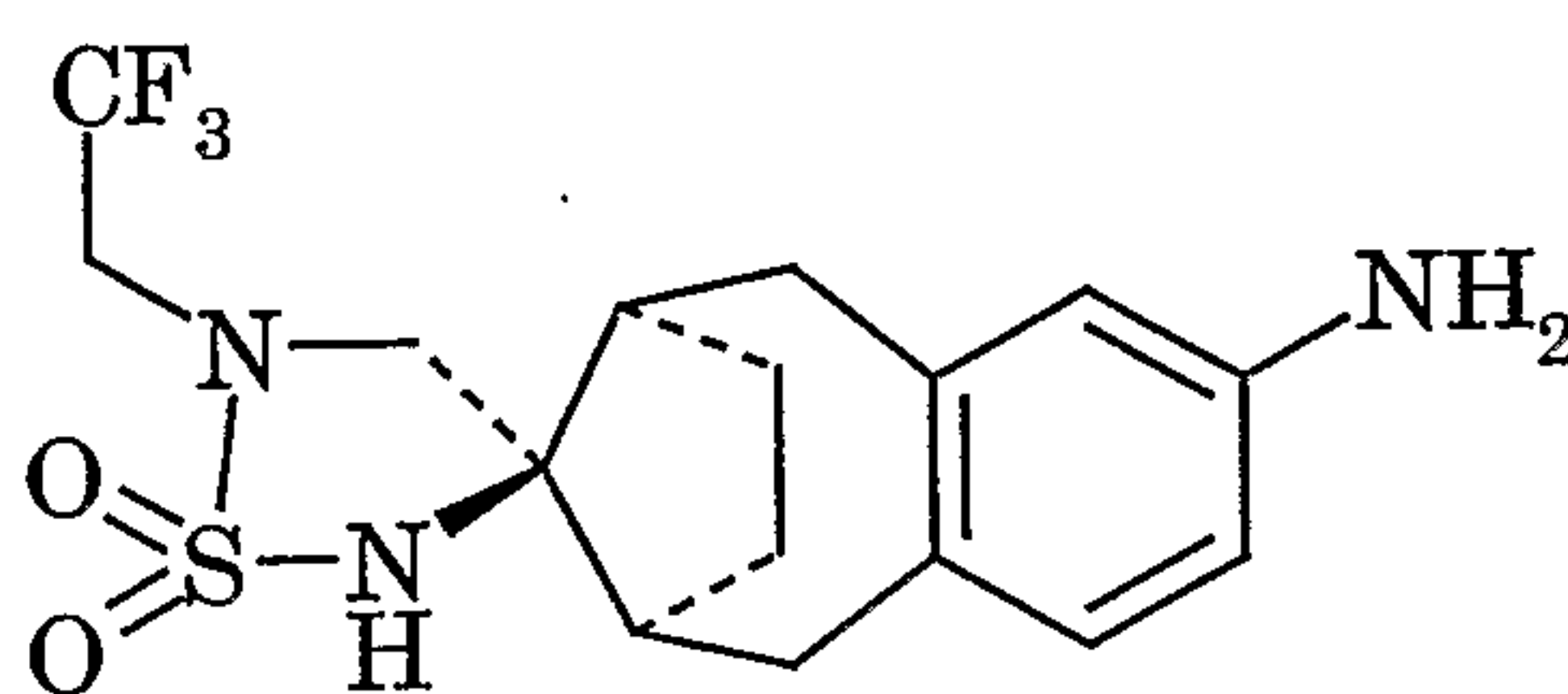
XIII

5

where R and R^1 have the same meanings as before. The aldehyde is conveniently formed by reduction of VI(a) with diisobutylaluminium hydride at -78 to -10°C in THF to provide the benzyl alcohol, which is then oxidised to the aldehyde using pyridinium dichromate in dichloromethane at room temperature. Formation of the hydrazone takes place in THF at room temperature, while the final step may be carried out in THF at -10 to 20°C in the presence of triethylamine, followed by refluxing in acetic acid.

The nitro derivative VI(b) may be reduced (e.g. using zinc and acetic acid) to the aniline XV:

15

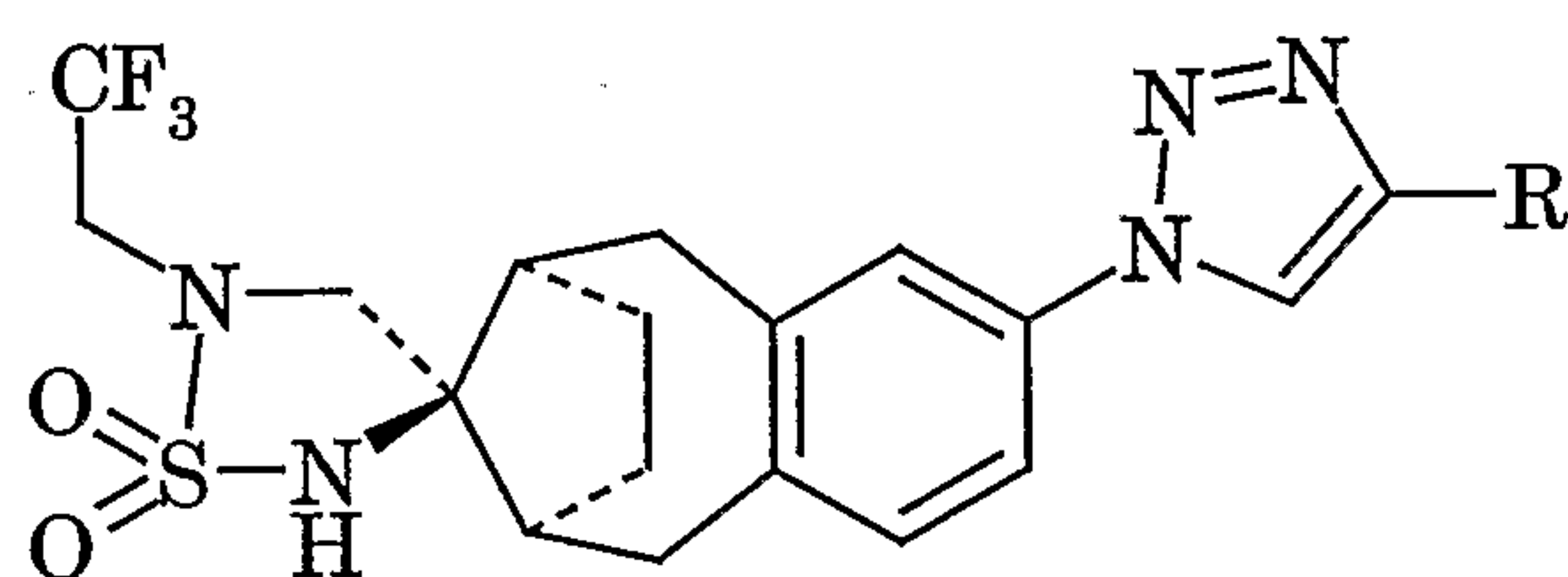


XV

which is a precursor for certain compounds of formula I in which X is bonded through nitrogen. For example, diazotisation of XV followed by reaction with azide ion provides the corresponding azide, which may undergo cycloaddition with an alkyne $R-C\equiv CH$ to form a 1,2,3-triazole XVI:

20

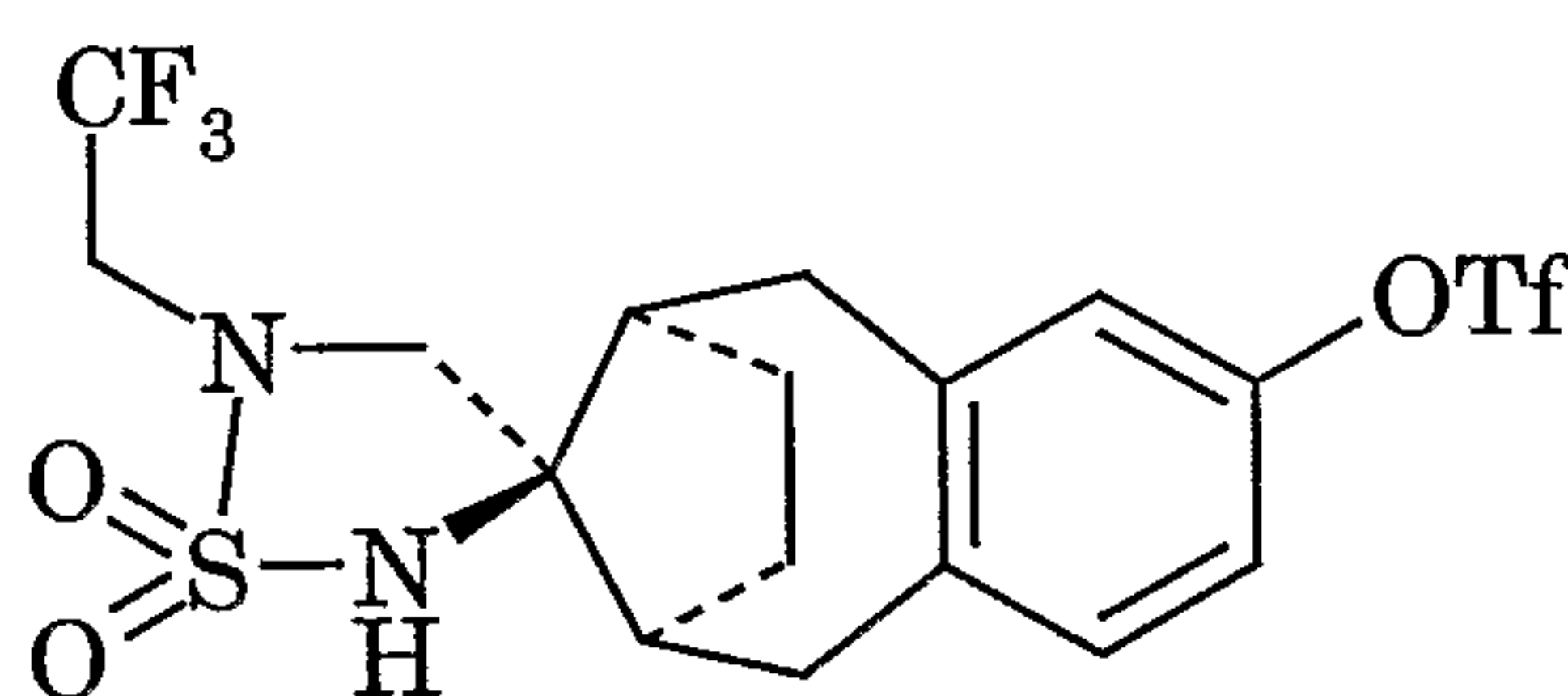
- 20 -



XVI

where R has the same meaning as before. Diazotisation may be carried out under standard conditions (sodium nitrite in aqueous HCl at 0°C), and reaction of the diazonium salt with azide ion is typically carried out *in situ*. Cycloaddition with R-C≡CH may be carried out by refluxing in xylene.

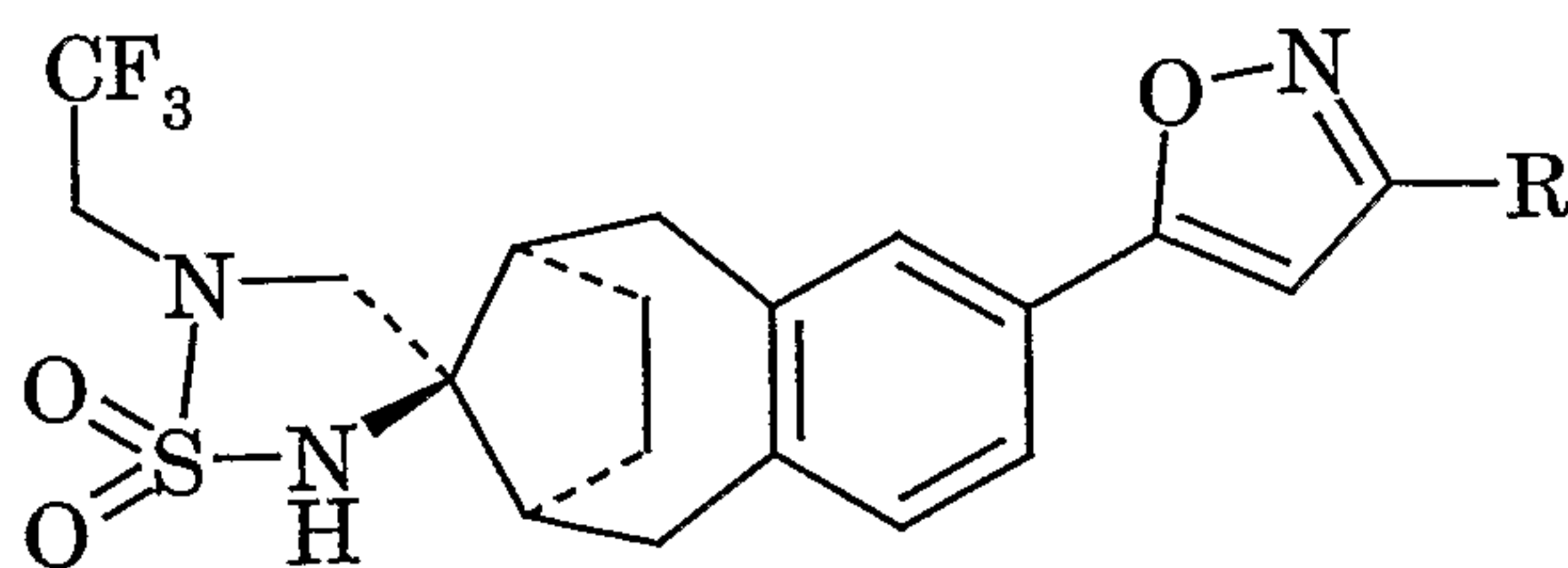
The benzyl ether VI(c) may be converted to the corresponding phenol by hydrogenation over Pd/C, and thence to the triflate XVII by treatment with triflic anhydride in the presence of pyridine in dichloromethane at 0-20°C:



XVII

where Tf represents triflyl (i.e. trifluoromethanesulphonyl). The triflate XVII is another precursor of compounds in accordance with formula I.

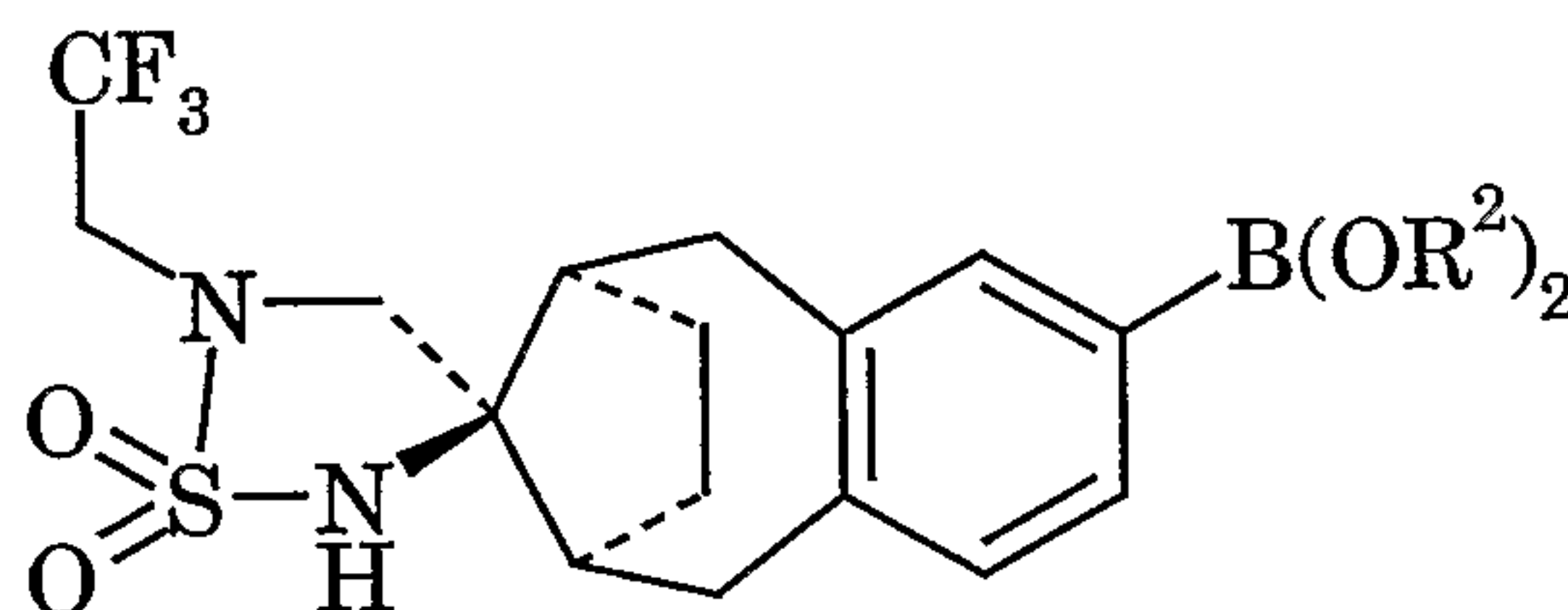
For example, treatment of XVII with trimethylsilylacetylene in the presence of a Pd(0) catalyst, CuI and an amine, followed by treatment with lithium hydroxide, provides the corresponding acetylene derivative, which undergoes cycloaddition with nitrile oxides R-C≡N⁺-O⁻ to provide isoxazoles XVIII:



XVIII

where R has the same meaning as before. Cycloaddition of R-N₃ to the aforesaid acetylene derivative (e.g. by refluxing in xylene) provides the 1-(R-substituted)-1,2,3-triazol-4-yl isomers of XVI, where R is preferably optionally-substituted hydrocarbon, C-heterocyclyl, phenyl or heteroaryl.

5 Alternatively, XVII may be converted to a boronic acid derivative XIX:

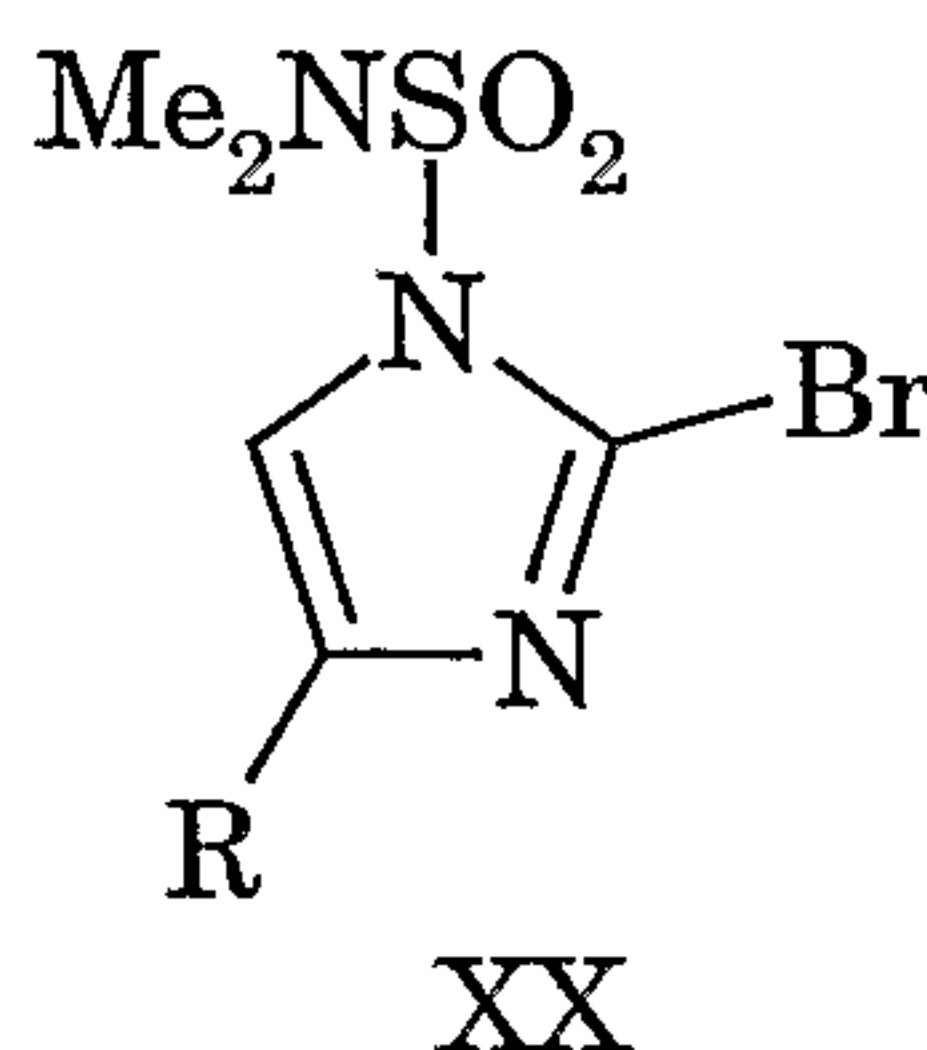


XIX

where R² represents H or alkyl, or the two OR² groups complete a cyclic boronate ester such as the pinacolate or the neopentyl glycolate. The conversion may be achieved by conventional means using a suitable boron reagent, such as bis(pinacolato)diboron, in the presence of a Pd catalyst such as bis(diphenylphosphinoferrocene)dichloropalladium(II) or tetrakis(triphenylphosphine)palladium(0), typically in the presence of an inorganic base such as potassium acetate or sodium carbonate, in a solvent
10 such as DMF or toluene at about 100°C.

Reaction of boronates XIX with R-X-L, where L is a suitable leaving group (such as halogen, especially bromine or iodine, triflate or nonaflate) and R and X have the same meanings as before, provides compounds of formula I directly. The reaction takes place under similar conditions in
20 the presence of the same Pd catalysts as used in the preparation of XIX.

As an example of this strategy, boronate XIX may be reacted with a bromoimidazole XX:



XX

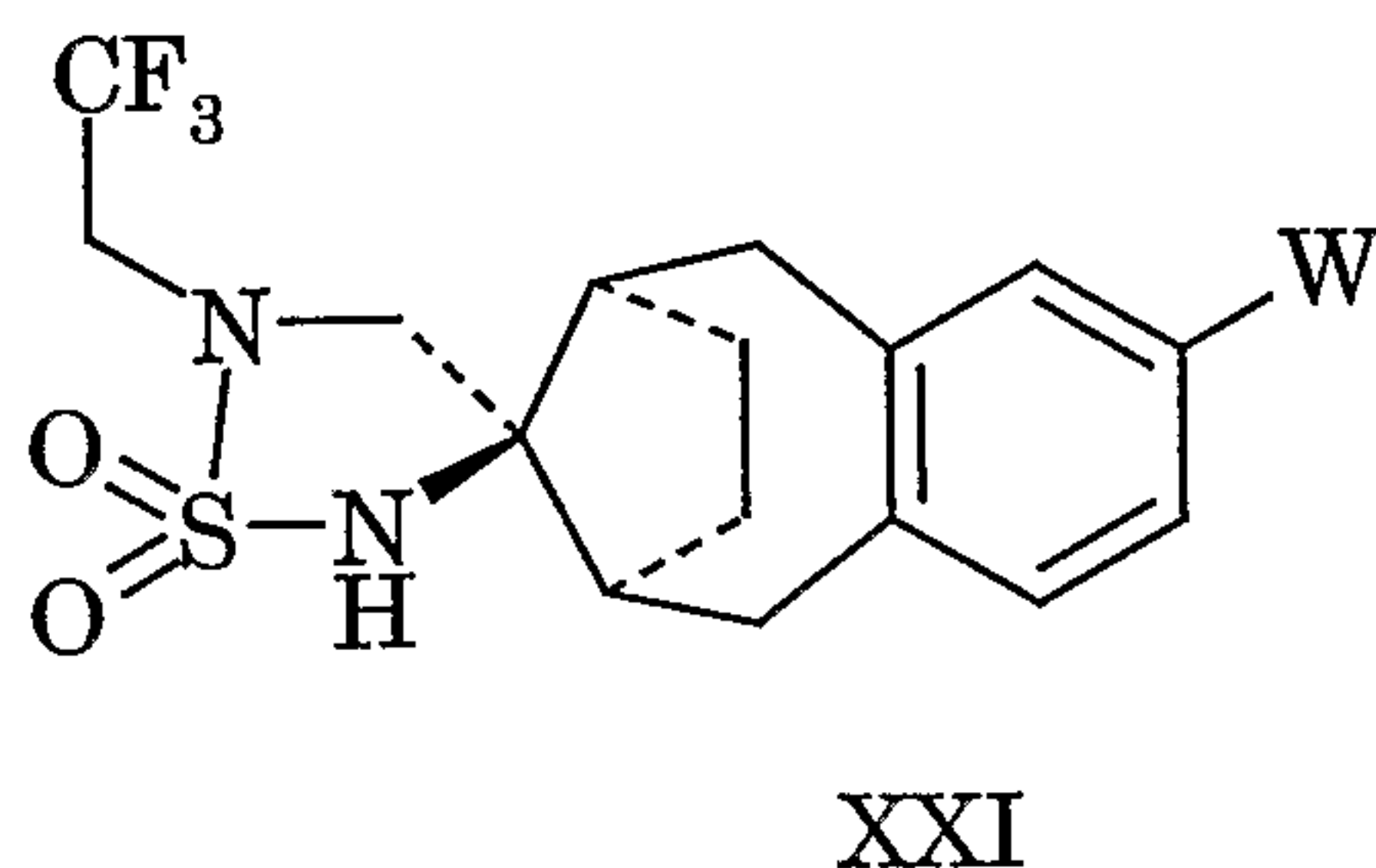
where R has the same meaning as before. Removal of the dimethylaminosulphonyl protecting group (e.g. by reflux in a mixture of THF and hydrochloric acid) then provides a compound of formula I in which R-X- represents a 4-substituted-1H-imidazol-2-yl moiety.

5 Other notable examples of compounds R-X-L which may similarly undergo coupling via boronates XIX include 4-bromo-1-(R-substituted) imidazoles and 3-bromo-1-(R-substituted)-1,2,4-triazoles, where R is preferably optionally-substituted hydrocarbon, C-heterocyclyl, phenyl or heteroaryl.

10 When the group X comprises an NH functionality in the ring (as in imidazole, for example), reaction of boronic acid XIX ($R^2 = H$) with R-X-H provides compounds of formula I in which X is bonded to the fused benzene ring through nitrogen. The reaction takes place at ambient temperature in dichloromethane in the presence of di- μ -hydroxo-bis(*N,N,N',N'*-
15 tetramethylethylenediamine)copper(II) chloride.

Alternatively, the R-X moiety may be assembled in a three-stage process in which firstly an HX- group is introduced by reaction of boronate XIX with HX-L, where L and X have the same meanings as before; secondly, the resulting product is brominated to convert the HX- group to
20 Br-X-; and thirdly, reaction with R-B(OR²) provides a compound of formula I, where R and R² have the same meanings as before.

In another process, the triflate VI(c) is reacted with tributyl(1-ethoxyvinyl)tin to form the acetyl derivative XXI(a):



- (a) W = COCH₃
- (b) W = COCH₂CHOH-R
- (c) W = COCH=CH-R
- (d) W = COCH₂CO₂Et

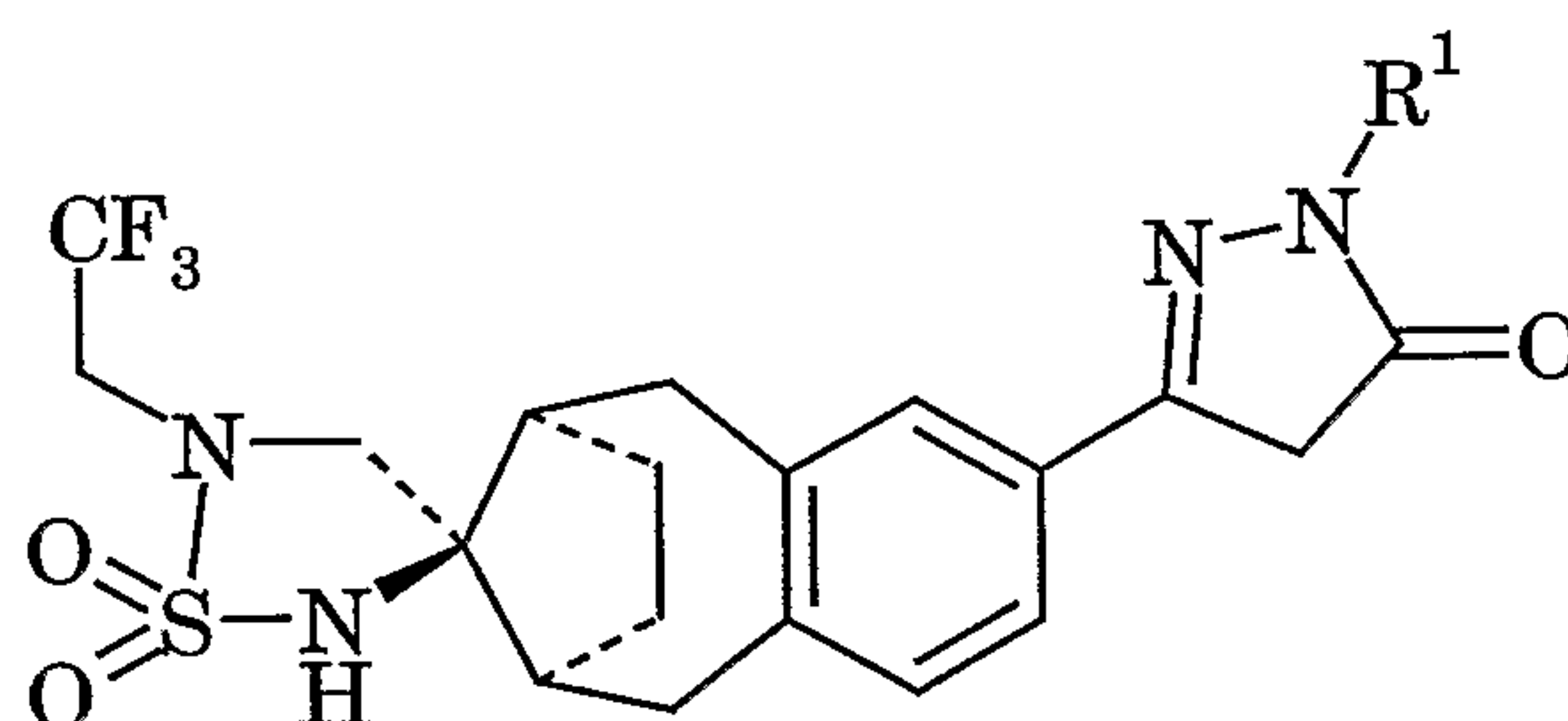
25

The reaction takes place in DMF in a sealed tube at 100°C in the presence of LiCl, triphenylphosphine and Pd(II)acetate. Aldol

condensation of XXI(a) with R-CHO provides the hydroxyketone XXI(b), which may be dehydrated to the enone XXI(c), where R has the same meaning as before. The aldol condensation takes place at low temperature (e.g -78°C) in THF in the presence of a strong base such as lithium
 5 bis(trimethylsilyl)amide. The dehydration may be effected by treatment with cerium(III) chloride and sodium iodide in refluxing acetonitrile.

Reaction of the enones XXI(c) with hydrazines R^1NHNH_2 , where R^1 has the same meaning as before, followed by oxidation of the resulting adduct with DDQ, provides an alternative route to the pyrazoles X(a) and
 10 X(b), with X(a) as the major product. The reaction with the hydrazine takes place at ambient temperature in ethanol under nitrogen, while the oxidation may be carried out in THF at ambient temperature.

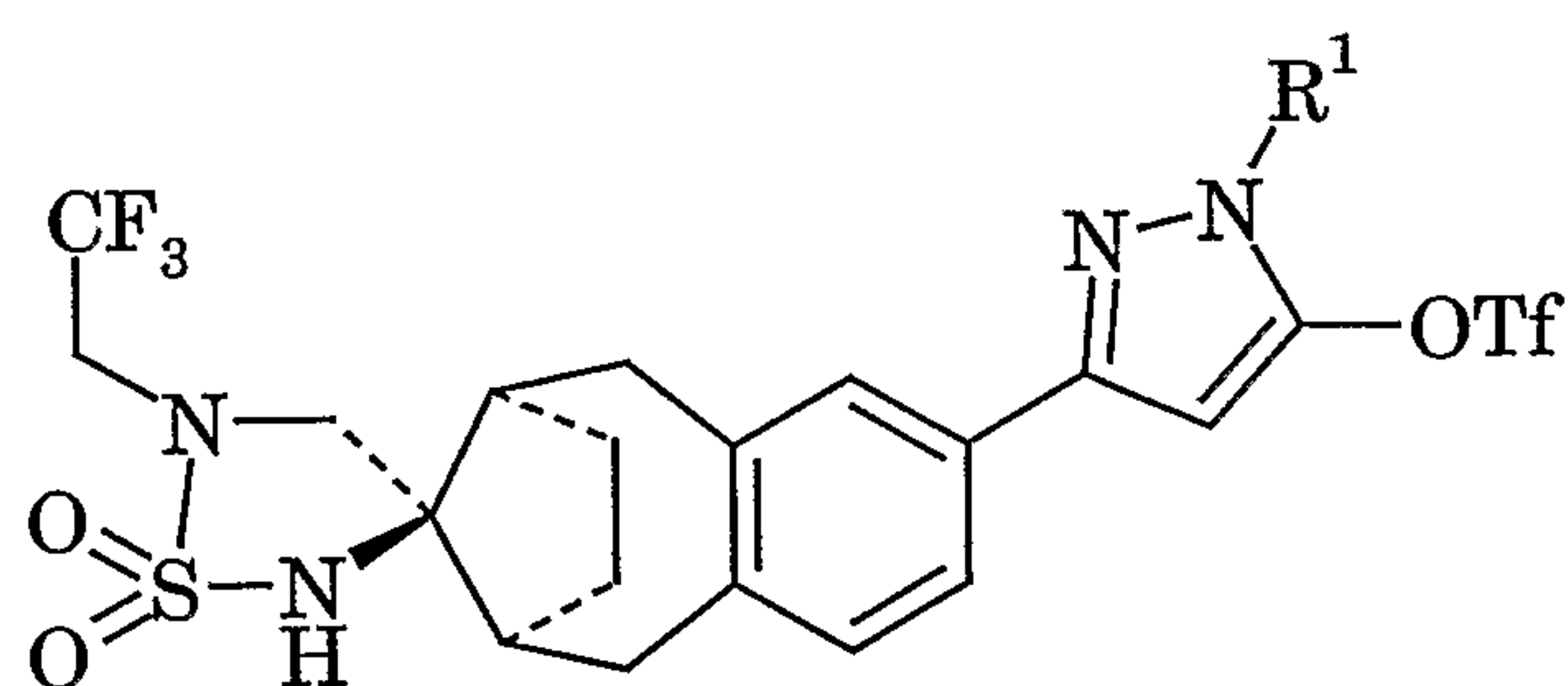
In another route to the pyrazoles X(a), the carboxylic acid VII is converted to the acid chloride, then added to a mixture of ethyl hydrogen
 15 malonate and isopropylmagnesium bromide at -78°C in THF, followed by treatment with aqueous HCl, to form the β -ketoester XXI(d). Reaction of this intermediate with R^1NHNH_2 (e.g. in acetic acid at ambient temperature) provides pyrazolones XXII:



XXII

20 where R^1 has the same meaning as before, which form the triflates XXIII by treatment with triflic anhydride and pyridine in dichloromethane at -78°C :

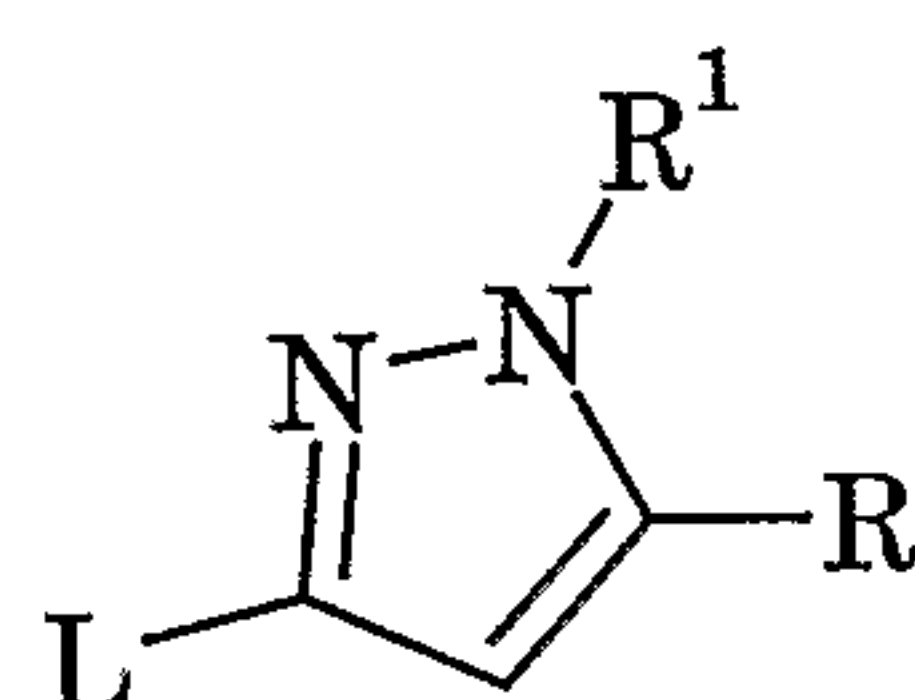
- 24 -



XXIII

where R^1 has the same meaning as before. Triflates XXIII react with $R-B(OR^2)_2$ as described previously to form pyrazoles X(a).

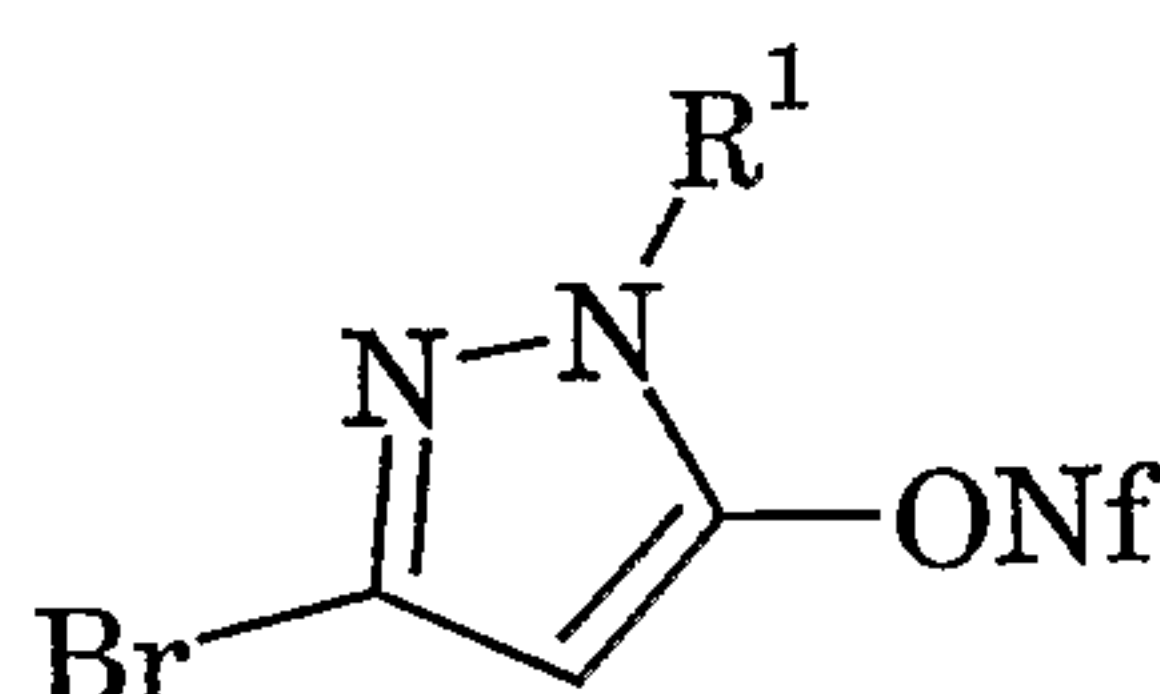
In another route to the pyrazoles X(a), boronic acid derivative XIX is
 5 reacted with a compound XXIV under the conditions described previously:



XXIV

where L, R and R^1 have the same meanings as before. Compounds XXIV
 10 in which L is triflate or nonaflate are accessible from the reaction of
 alkynes $R-C\equiv C-CO_2Me$ with R^1NHNH_2 and treatment of the resulting
 pyrazolones with triflic anhydride or nonafluorobutanesulfonyl fluoride
 respectively. Compounds XXIV in which L is Br are available by reaction
 of nonaflates XXV with $RZnBr$:

15



XXV

where Nf represents nonafluorobutanesulfonyl, and R and R^1 have the
 same meaning as before.

It will be apparent to those skilled in the art that in the above-described routes to compounds of formulae IX, X, XII, XIII, XVI and XVIII, or in the routes involving R-B(OR²)₂, R is most suitably an optionally-substituted hydrocarbon, C-heterocyclyl, phenyl or heteroaryl group, and
5 in particular an optionally-substituted phenyl or heteroaryl group.

It is emphasised that the above formulae II – VII, IX – XIII, XV – XIX and XXI – XXIII represent both of the enantiomeric forms arising from the overall asymmetry of the molecules, either singly or in mixtures of any proportion.

10 It will be apparent to those skilled in the art that, in many cases, the steps in the synthetic schemes described above may be carried out in a different order. Thus, if desired, the group Y in ketones II may be converted to the moiety R-X- by one of the described routes prior to the construction of the spiro-linked sulphamide ring.

15 It will also be appreciated that where more than one isomer can be obtained from a reaction then the resulting mixture of isomers can be separated by conventional means.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of
20 stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by
25 standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric
30 esters or amides, followed by chromatographic separation and removal of

the chiral auxiliary. Alternatively, such techniques may be carried out on racemic synthetic precursors of the compounds of interest.

In a preferred route to enantiomerically pure compounds of formula I, racemic intermediates VI(a) or VI(c) are subjected to preparative chiral HPLC to provide the corresponding homochiral intermediates, which are then converted to homochiral compounds of formula I by the routes indicated above.

Alternatively, intermediate II (Y = nitro) is reduced to the corresponding racemic aniline, and resolved via salt formation with (+) or (-) mandelic acid. The resulting homochiral aniline is converted to the corresponding phenol (via the corresponding diazonium salt) and thence to the homochiral benzyl ether II (Y = benzyloxy), which may then be converted to homochiral compounds of formula I by the methods outlined above.

Where they are not commercially available, the starting materials and reagents used in the above-described synthetic schemes may be prepared by conventional means. The ketones II may be prepared by the method described in *J.Org.Chem.*, **47**, 4329-34, 1982.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

An assay which can be used to determine the level of activity of compounds of the present invention is described in WO01/70677. A preferred assay to determine such activity is as follows:

- 1) SH-SY5Y cells stably overexpressing the β APP C-terminal fragment SPA4CT, are cultured at 50-70% confluency. 10mM sodium butyrate is added 4 hours prior to plating.
- 2) Cells are plated in 96-well plates at 35,000 cells/well/100 μ L in
5 Dulbeccos minimal essential medium (DMEM) (phenol red-free) + 10% foetal bovine serum (FBS), 50mM HEPES buffer (pH7.3), 1% glutamine.
- 3) Make dilutions of the compound plate. Dilute stock solution 18.2x to 5.5% DMSO and 11x final compound concentration. Mix compounds vigorously and store at 4°C until use.
- 10 4) Add 10 μ L compound/well, gently mix and leave for 18h at 37°C, 5% CO₂.
- 5) Prepare reagents necessary to determine amyloid peptide levels, for example by Homogeneous Time Resolved Fluorescence (HTRF) assay.
- 6) Plate 160 μ L aliquots of HTRF reagent mixture to each well of a
15 black 96-well HTRF plate.
- 7) Transfer 40 μ L conditioned supernatant from cell plate to HTRF plate. Mix and store at 4°C for 18 hours.
- 8) To determine if compounds are cytotoxic following compound administration, cell viability is assessed by the use of redox dye reduction.
20 A typical example is a combination of redox dye MTS (Promega) and the electron coupling reagent PES. This mixture is made up according to the manufacturer's instructions and left at room temperature.
- 9) Add 10 μ L/well MTS/PES solution to the cells; mix and leave at 37°C.
- 25 10) Read plate when the absorbance values are approximately 0.4 – 0.8. (Mix briefly before reading to disperse the reduced formazan product).
- 11) Quantitate amyloid beta 40 peptide using an HTRF plate reader. Alternative assays are described in *Biochemistry*, 2000, 39(30), 8698-8704.
- 30 See also, *J. Neuroscience Methods*, 2000, 102, 61-68.

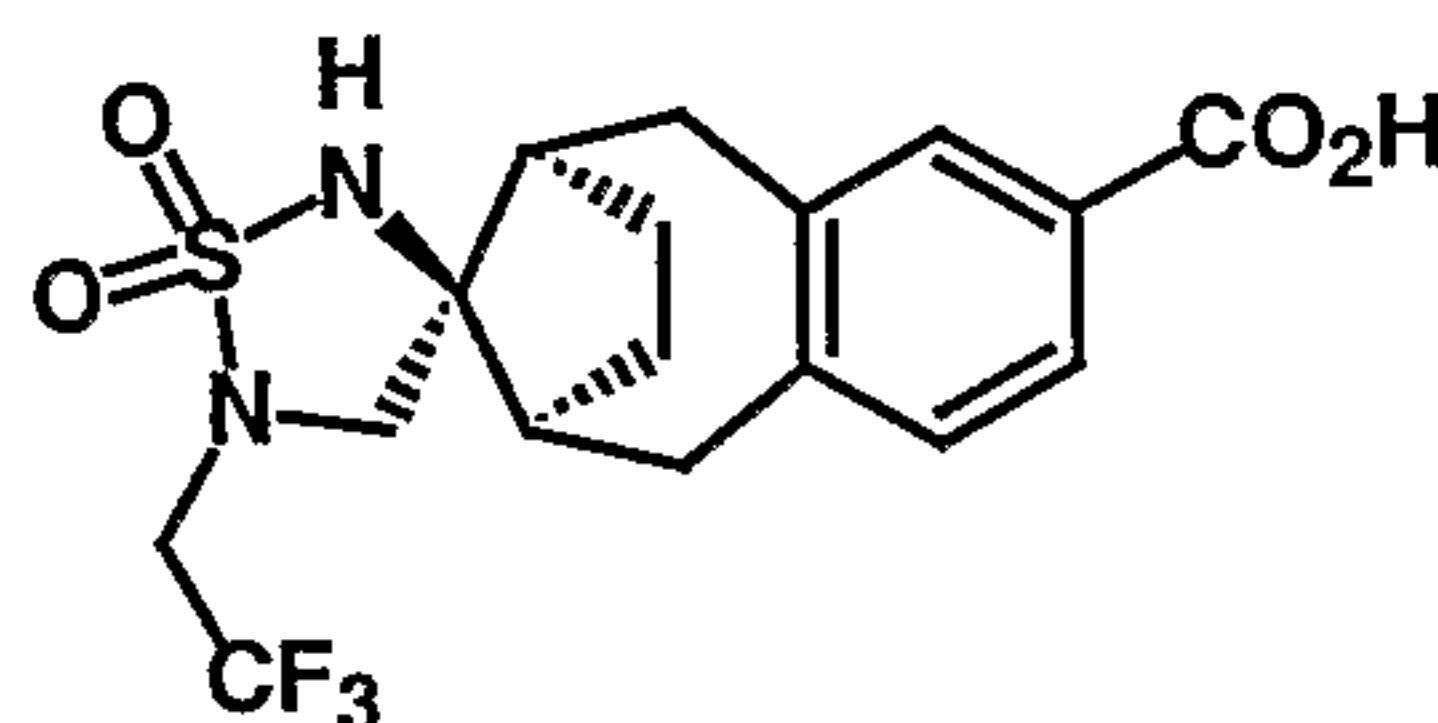
The compounds of the present invention show unexpectedly high affinities as measured by the above assays. Thus the following Examples all had an ED₅₀ of less than 50nM, typically less than 10nM, and frequently less than 1nM in at least one of the above assays. In general, the compounds also exhibit good oral bioavailability and/or brain penetration, and are largely free from undesirable biological interactions likely to lead to toxic side effects.

The following examples illustrate the present invention.

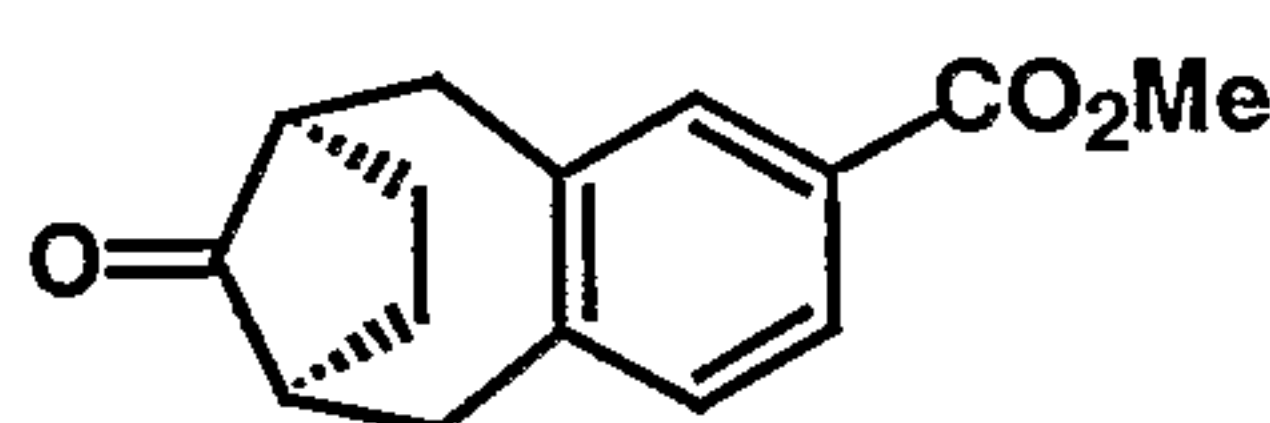
EXAMPLES

Intermediate A

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-carboxy-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

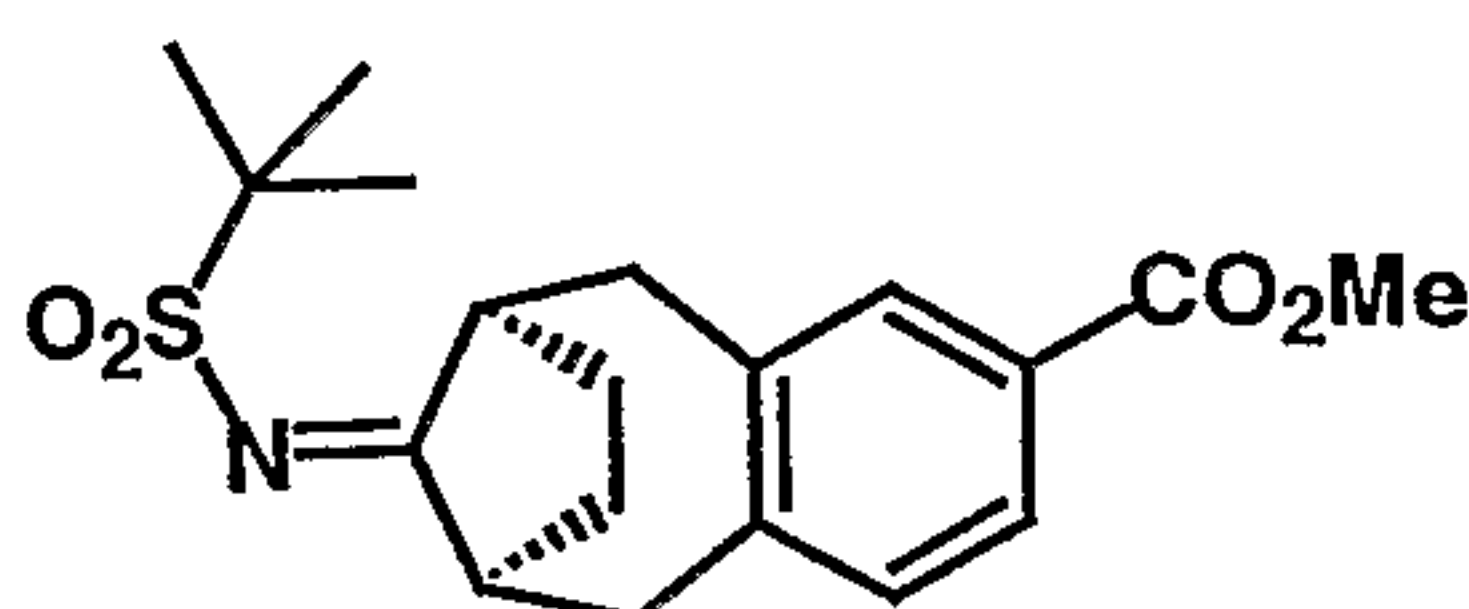


Step 1: Methyl 11-Oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene-2-carboxylate



Prepared using the procedure described for 11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (Justus Liebigs Ann. Chem. **1961**, 650, 115) using methyl 3,4-bis(bromomethyl)benzoate in place of 1,2-bis(bromomethyl)benzene.

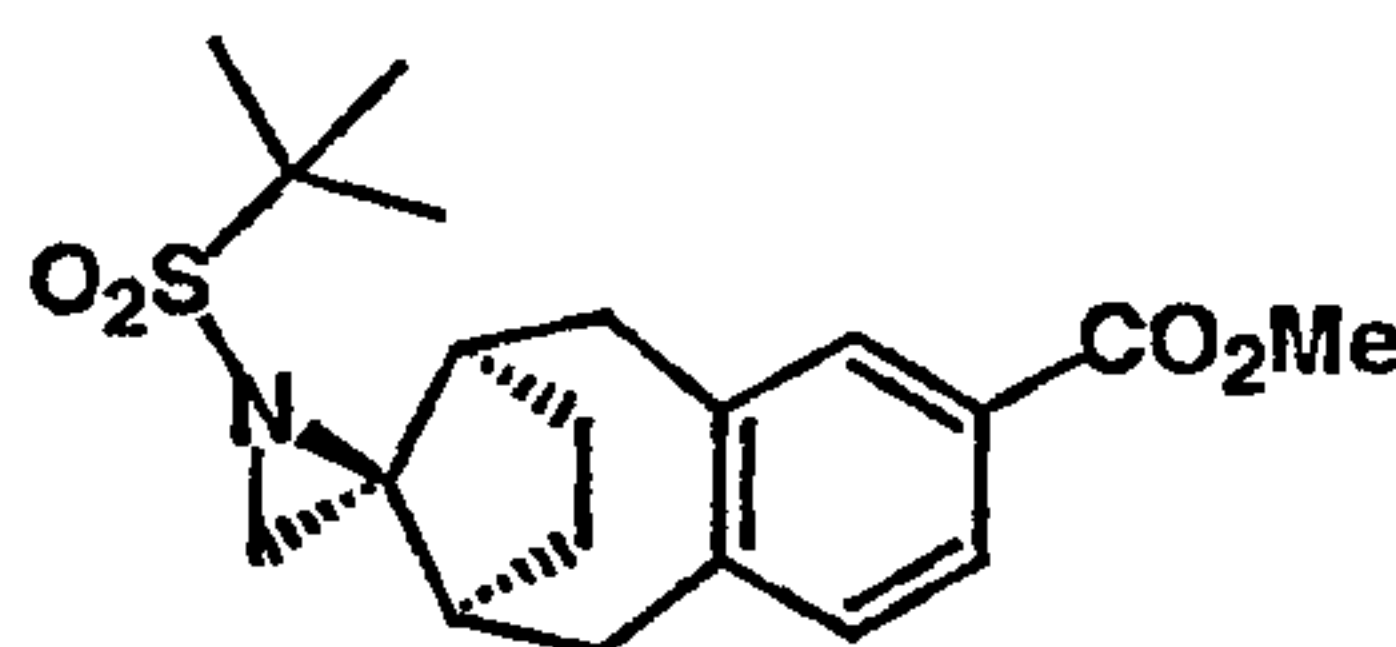
Step 2: Methyl 11-(2'-Methyl-propane-2'-sulfonylimino)-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene-2-carboxylate



- 29 -

A solution of titanium (IV) chloride (25 mL, 1M in DCM) was added at r.t. to a stirred suspension of the ketone from Step 1 (10.0 g), *tert*-butyl sulfonamide (5.8 g) and triethylamine (11.6 mL) in 1,2-dichloroethane (100 mL). The yellow suspension was stirred under nitrogen for 30 minutes,
 5 then refluxed for 8 hours. The mixture was diluted with dichloromethane (400 mL) and saturated aqueous sodium hydrogencarbonate (400 mL) and filtered through a pad of Celite™. The organic phase was dried (Na₂SO₄), filtered and concentrated to give the sulfonimine (15.5 g, quantitative) as a brown gum. δ (¹H, 360MHz, CDCl₃) 1.20-1.40 (2H, m), 1.50 (9H, s), 1.75-
 10 2.00 (2H, m), 2.90-2.95 (2H, m), 3.05-3.20 (3H, m), 3.92 (3H, s), 3.95-4.05 (1H, m), 7.24-7.28 (1H, m), 7.84-7.87 (2H, m).

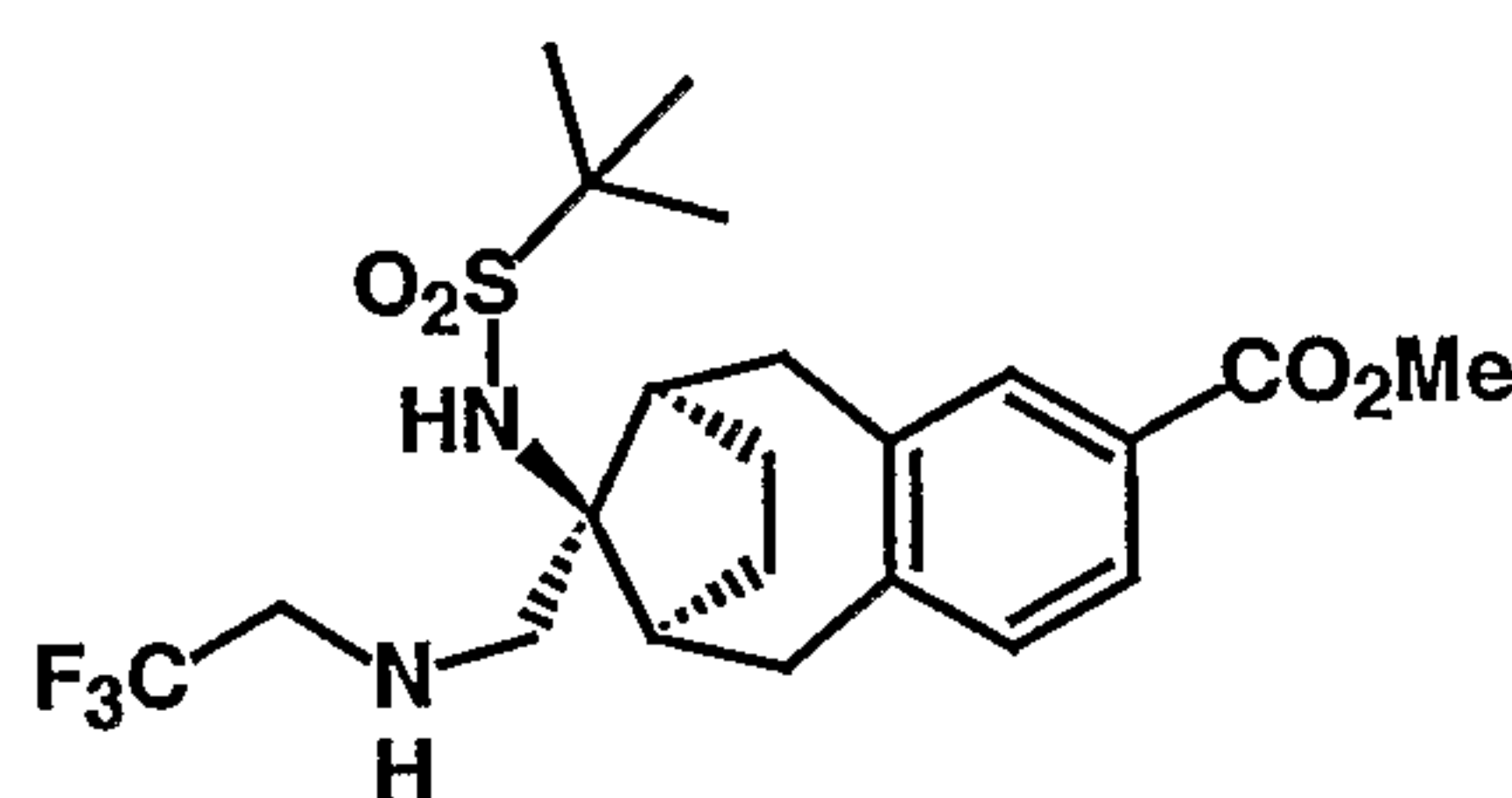
Step 3: Methyl [6S/R,9R/S,11R/S]-11-[(2'-Methyl-propane-2'-sulfonyl)-1'-
aza-spiro[2.4]]-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene-2-
 15 carboxylate



Sodium hydride (55%, 1.75 g) was added portionwise at room temperature to a stirred suspension of trimethylsulfoxonium iodide (8.8 g) in DMSO (70 mL) under nitrogen. After stirring for 2 hours, the solution was cooled in
 20 an ice-bath and a solution of the sulfonimine from Step 2 (10.0 g) in DMSO (80 mL) was added. The mixture was stirred at room temperature for 2.5 hours then poured onto ice (500 mL) and diluted with water (200 mL). The white solids were collected, rinsed with diethyl ether and dried under vacuum at room temperature to give the aziridine (8.16 g, 79%). MS (ES+)
 25 400 ([MNa]⁺).

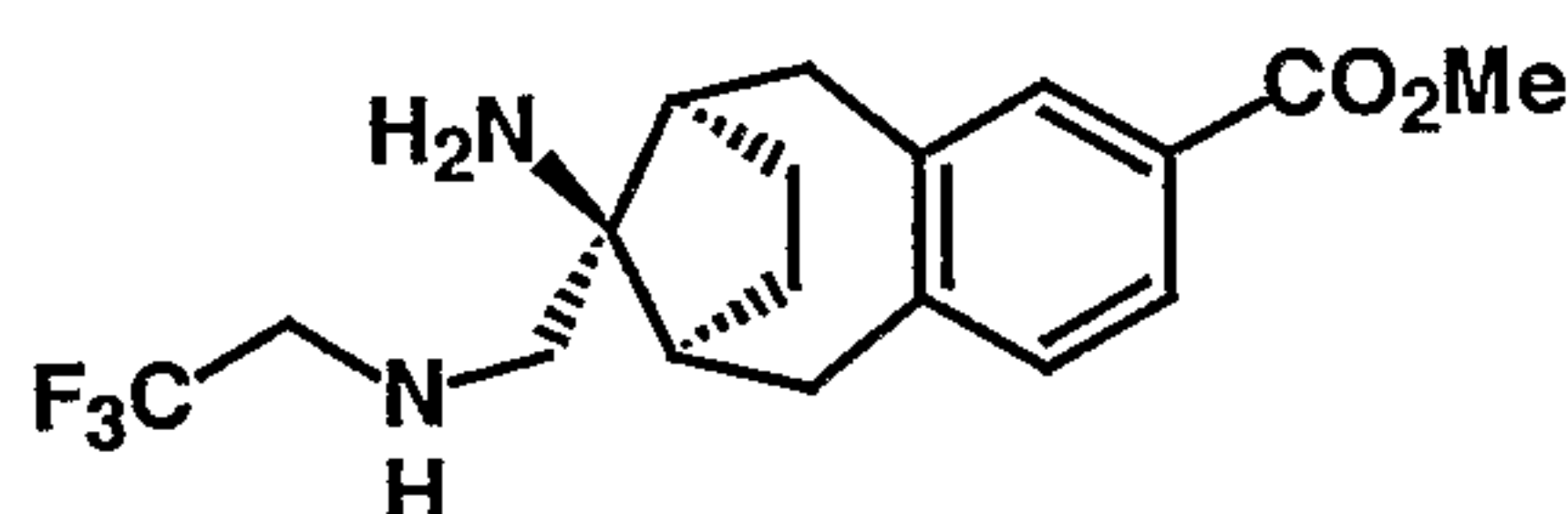
Step 4: Methyl [6S/R,9R/S,11R/S]-11-(2'-Methyl-propane-2'-
sulfonylamino)-11-(2,2,2-trifluoroethyl)aminomethyl-5,6,7,8,9,10-
hexahydro-6,9-methanobenzocyclooctene-2-carboxylate

- 30 -



A solution of the aziridine from Step 3 (8.16 g) and 2,2,2-trifluoroethylamine (10.2 mL) in DMSO (45 mL) was divided into 3 equal portions and stirred at 100°C in sealed tubes for 6 days. The cooled
 5 solutions were combined and poured into water (250 mL). The white crystalline solid was collected, rinsed with diethyl ether and dried under vacuum at room temperature to give the amine (7.43 g, 72%). MS (ES+) 477 ([MH]⁺).

10 Step 5: Methyl [6S/R,9R/S,11R/S] 11-Amino-11-(2,2,2-trifluoroethyl)aminomethyl-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene-2-carboxylate

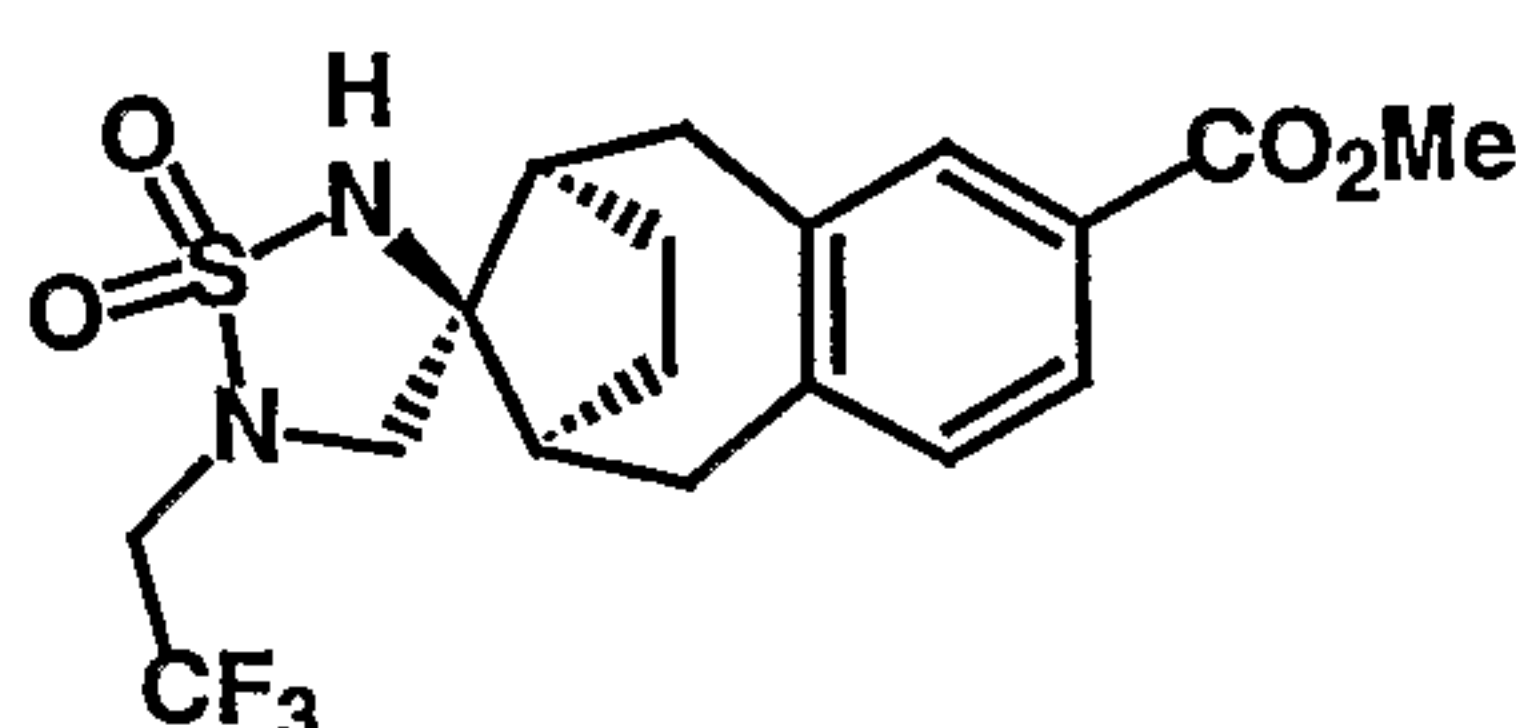


Trifluoromethanesulfonic acid (11 mL) was added dropwise at 0°C to a
 15 stirred suspension of the sulfonamide from Step 4 (7.43 g) in dichloromethane (100 mL) under nitrogen. The mixture was stirred at 0°C for 20 minutes, then at room temperature for 4 hours. The mixture was poured into saturated aqueous sodium hydrogencarbonate (600 mL) and extracted with 10% methanol-dichloromethane (2x 300 mL). The extracts
 20 were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated to give the diamine (6.5 g, quantitative) as a yellow oil. MS (ES+) 357 ([MH]⁺).

Step 6: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-carbomethoxy-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

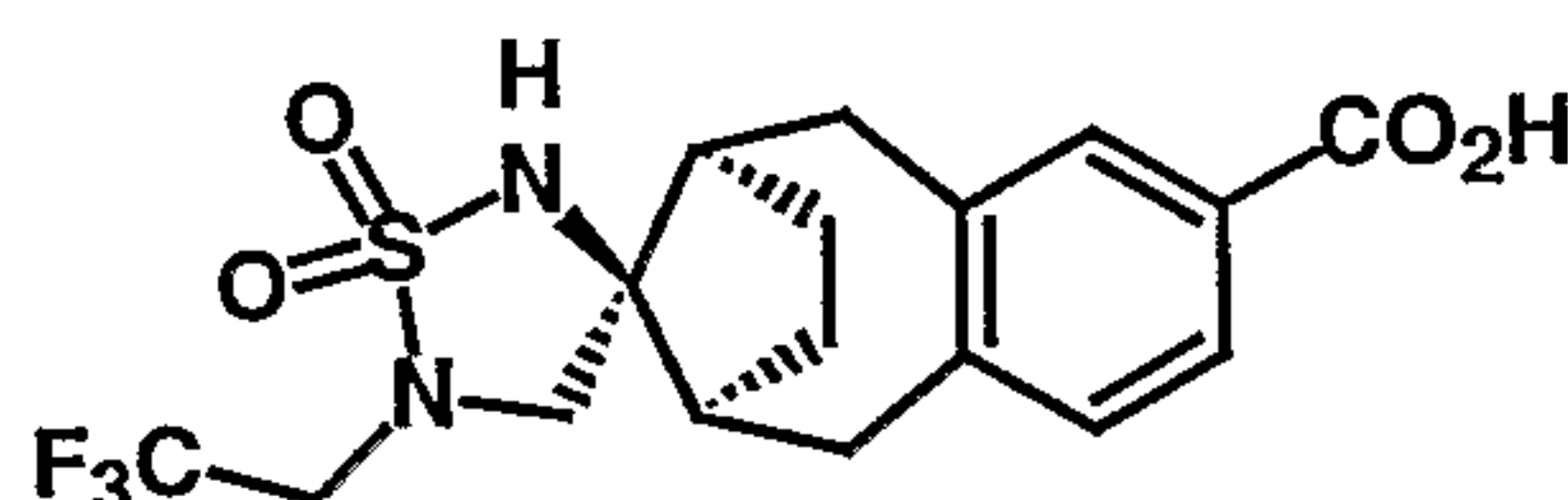
25

- 31 -



A solution of the diamine from Step 5 (6.5 g) and sulfamide (4.5 g) was refluxed in pyridine (120 mL) for 6 hours. Solvent was removed by evaporation. The residue was partitioned between 1M HCl (200 mL) and
 5 10% methanol-dichloromethane (500 mL). The organic extract was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The solid was rinsed with diethyl ether to give the cyclic sulfamide (5.26 g, 80%) as an off-white powder. δ (¹H, 360MHz, CDCl₃) 1.26-1.30 (2H, m), 1.70-1.75 (2H, m), 2.47-2.50 (2H, m), 2.74-2.82 (2H, m), 3.21-3.29 (2H, m),
 10 3.41-3.47 (2H, m), 3.68 (2H, q, *J*=9 Hz), 3.90 (3H, s), 4.78 (1H, s), 7.17 (1H, d, *J*=8 Hz), 7.78-7.80 (2H, m)

Step 7: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-carboxy-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

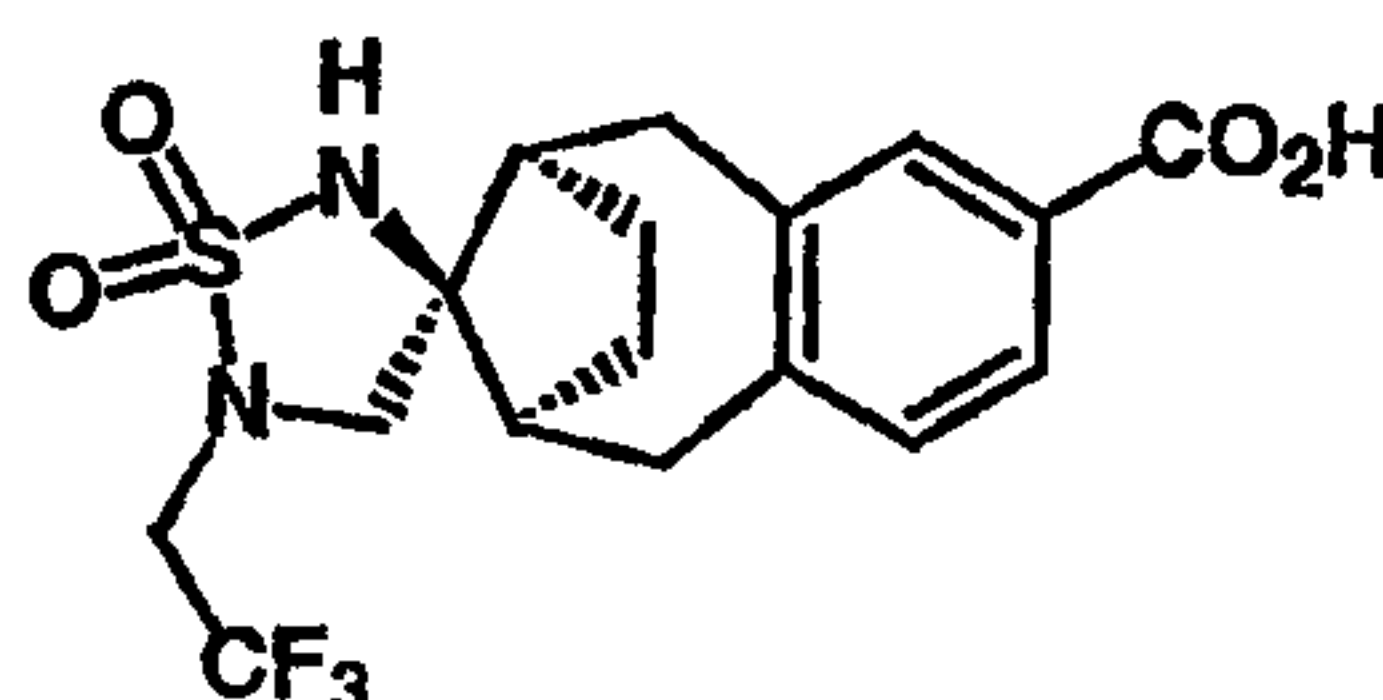


A mixture of 4M sodium hydroxide (3 mL) and the ester from Step 6 (2.33 g) in tetrahydrofuran (30 mL) was stirred at 60°C for 3.5 hours. The mixture was diluted with 1M citric acid (10 mL) and 1M hydrochloric acid
 20 (20 mL) and extracted with dichloromethane (2 x 100 mL). The extracts were washed with water (100 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated. Trituration with diethyl ether – isohexane gave the acid (1.96 g, 88%) as an off-white solid. δ (¹H, 360MHz, d₆-DMSO) 0.95-1.05 (2H, m), 1.65-1.75 (2H, m), 2.35-2.42 (2H, m), 2.62-2.72 (2H, m), 3.18-3.23 (2H, m), 3.47 (2H, s), 4.02 (2H, q, *J*=10 Hz), 7.23 (1H, d, *J*=8 Hz),
 25 7.62-7.70 (2H, m), 8.03 (1H, s), 12.60 (1H, s).

Intermediate B

- 32 -

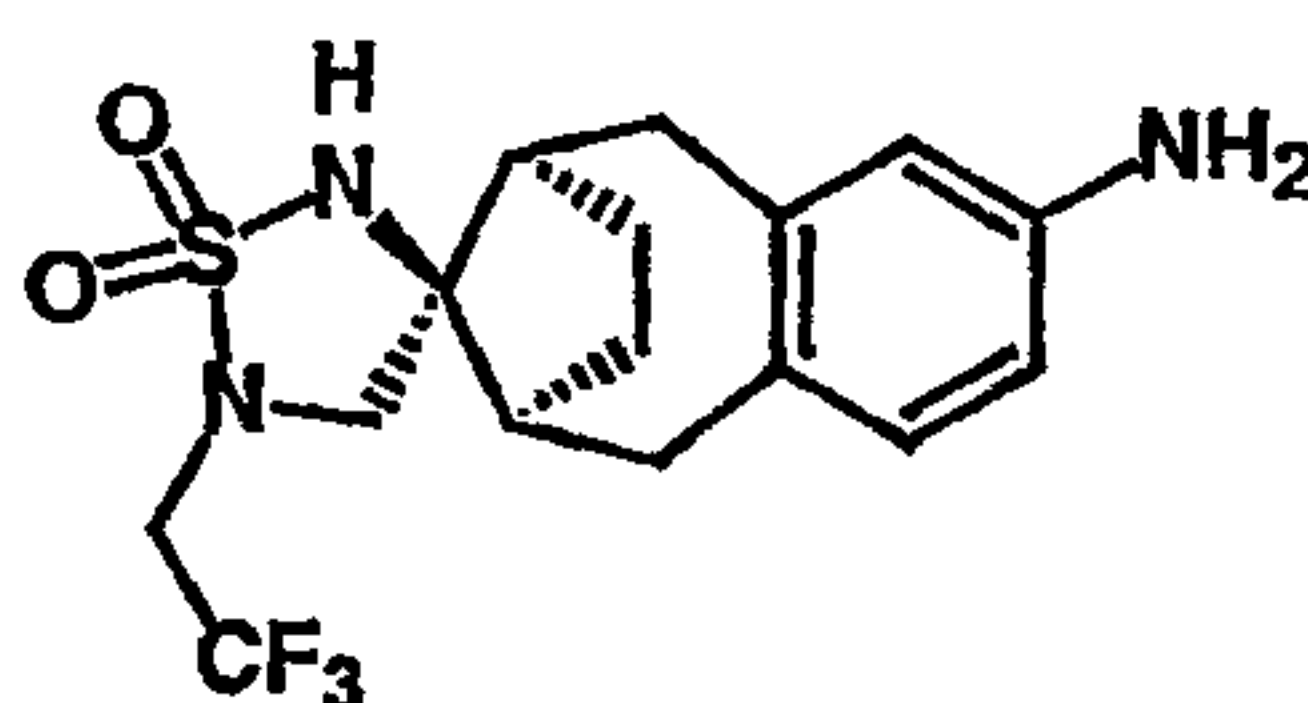
(-)- [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-carboxy-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



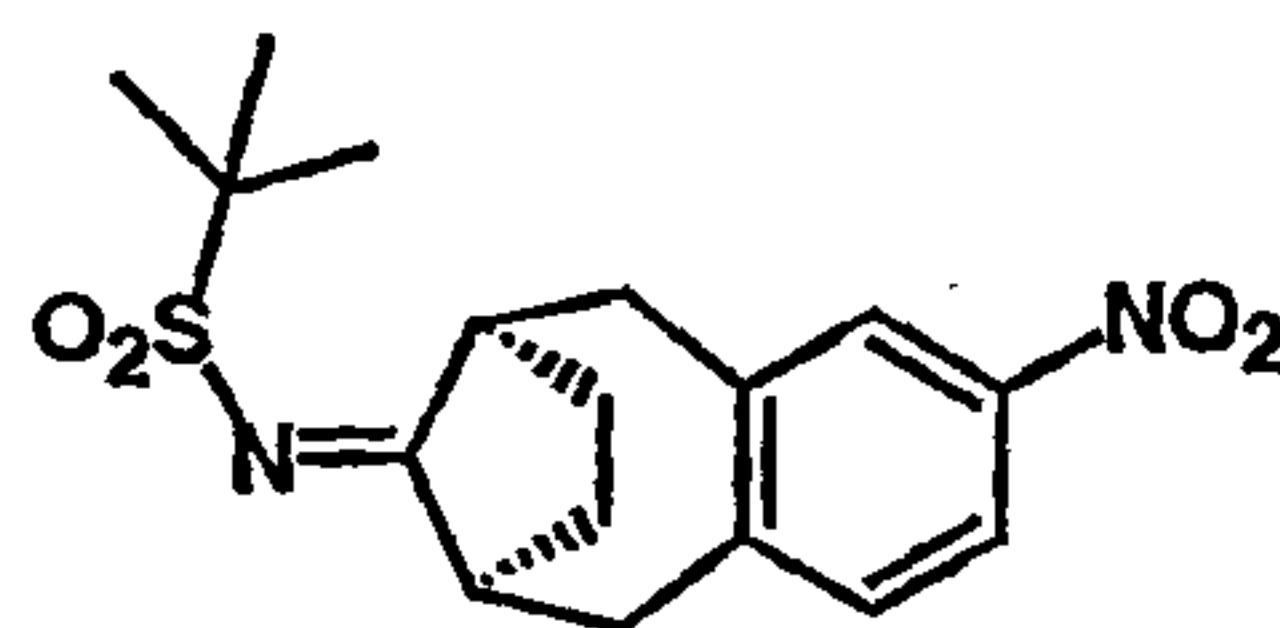
- 5 The racemic acid Intermediate A was resolved by supercritical fluid chromatographic separation on a Chiralcel™ OD (20 μ m) column using 22% methanol - sc-CO₂ (with 0.1% trifluoroacetic acid) as eluant at 35°C, 100 bar and UV detection at 250 nm. The first eluted compound under these conditions was the (-)-enantiomer of the acid. $[\alpha]_D = -8$ (c=1, Methanol, 10 23°C).

Intermediate C

- [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-amino-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



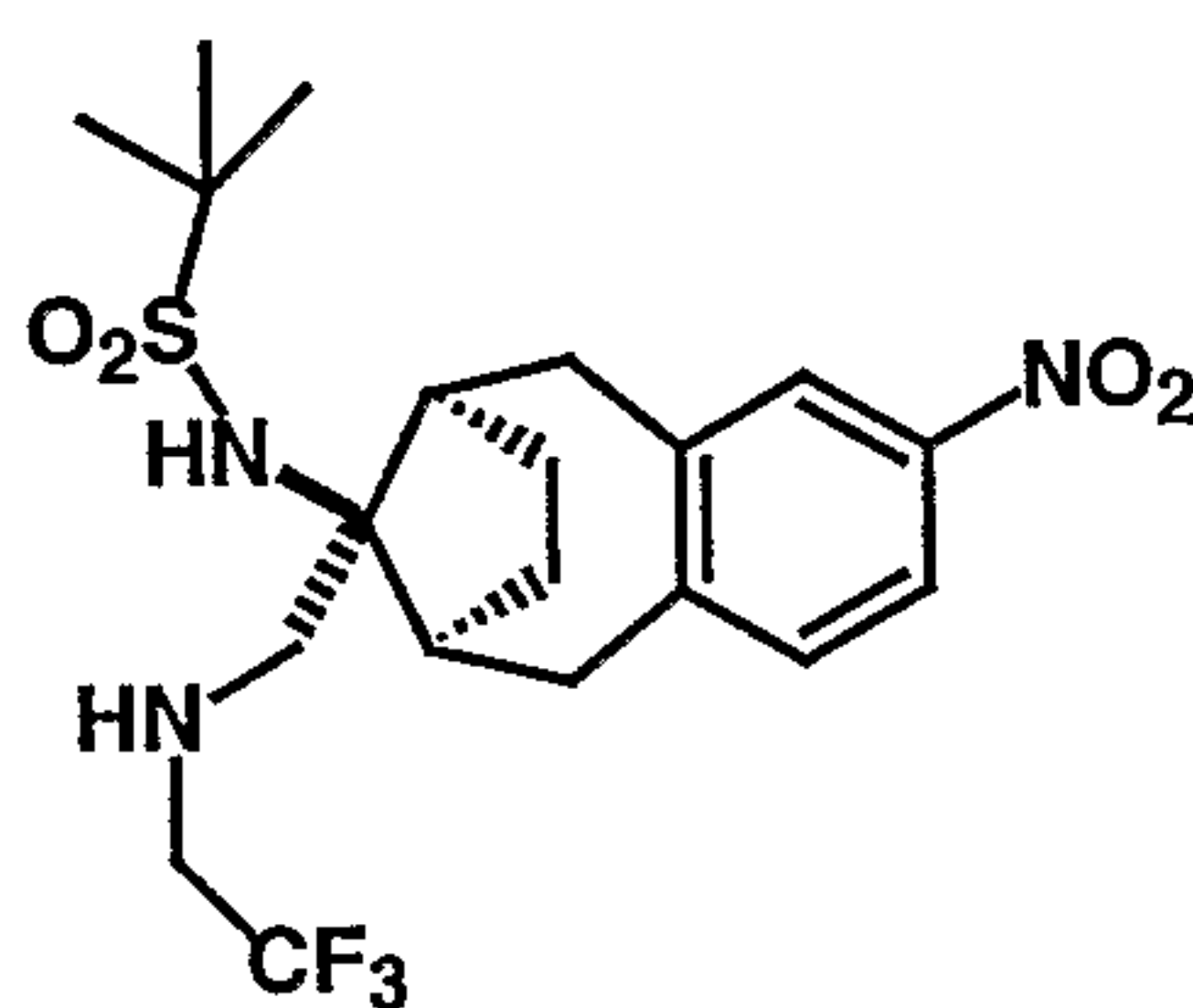
Step 1 : 11-(2'-Methyl-propane-2'-sulfonylimino)-5,6,7,8,9,10-hexahydro-2-nitro-6,9-methanobenzocyclooctene



- 20 Triethylamine (6 mL, 43.2 mmol) was added to a stirred suspension of 11-oxo-5,6,7,8,9,10-hexahydro-2-nitro-6,9-methanobenzocyclooctene (5.0 g, 21.6 mmol; *J. Org. Chem.* **47**, 4329, 1982), *tert*-butyl sulphonamide (2.97 g, 21.6 mmol) and titanium (IV) chloride (1.0 M in dichloromethane, 13 mL, 13 mmol) in 1,2-dichloroethane (50 mL) at room temperature under

nitrogen. The reaction was heated under reflux for 6.5 hours then allowed to cool to room temperature. The reaction mixture was poured into water (250 mL), hydrochloric acid (2 M, 100 mL) and dichloromethane (200 mL) and filtered through Celite®. The layers were separated and the organic
 5 layer washed with brine, dried over Na₂SO₄ and concentrated to give the imine (6.85 g containing 5% starting nitroketone, 87% yield of imine). MS (ES⁺) 231 ([MH]⁺).

Step 2 : [6S/R,9R/S,11R/S]-11-(2'-Methyl-propane-2'-sulfonylamino)-11-
 10 (2,2,2-trifluoroethyl)aminomethyl-5,6,7,8,9,10-hexahydro-2-nitro-6,9-
methanobenzocyclooctene

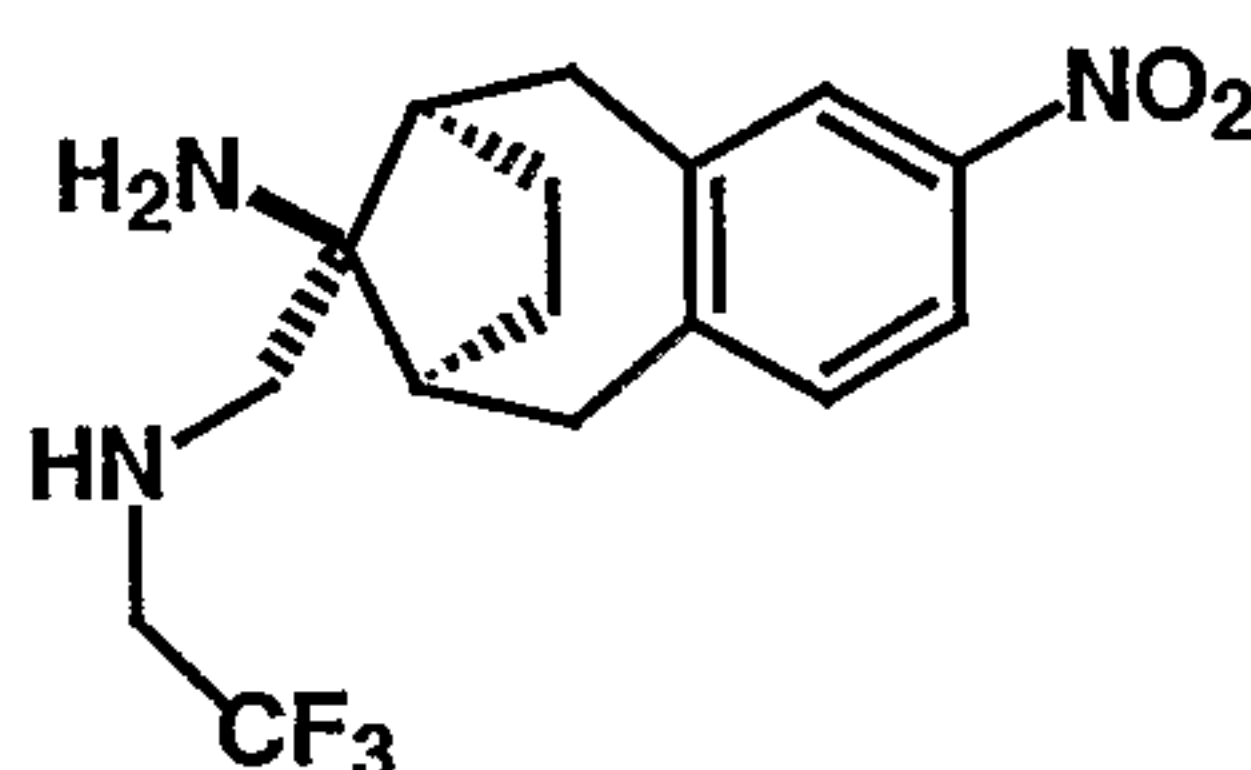


Sodium hydride (60 % dispersion in mineral oil, 1.1 g, 27.4 mmol) was added portionwise to a suspension of trimethylsulphoxonium iodide (6.0 g, 27.4 mmol) in dry dimethylsulphoxide (35 mL) at room temperature under
 15 nitrogen and stirred for 1.5 hours. The solution was cooled in an ice-bath (resulting in partial freezing) and a solution of the imine from Step 1 (6.85 g containing 5% starting material, 18.9 mmol) in warm dry dimethylsulphoxide (45 mL) was added dropwise over 15 mins. The
 20 resulting partially frozen mixture was allowed to warm to room temperature and stirred for 18 hours. The mixture was poured onto ice (250 mL) and diluted with ice-cold water (250 mL). The resulting precipitate was collected by filtration and washed with water, then dissolved in dichloromethane. This organic layer was washed with water
 25 and brine, dried over Na₂SO₄ and evaporated. The residue was purified by flash column chromatography on silica, eluting with 20% ethyl acetate –

isohexane to give clean aziridine (3.1g, 45%) and some containing 12% epoxide (1.72 g, approx. 23% yield of aziridine).

A mixture of 2.05 g (5.6 mmol) of the aziridine and 2,2,2-trifluoroethylamine (2.9 mL, 36.5 mmol) in dimethylsulphoxide (10 mL) was heated at 100°C in a sealed tube behind a blast shield for 4 days. Another 1 mL of 2,2,2-trifluoroethylamine was added and the mixture heated at 100°C in a sealed tube behind a blast shield for 18 hours. The cooled reaction mixture was diluted with ethyl acetate (50 mL), washed with water (3 x 50 mL) and brine, dried over Na₂SO₄ and evaporated to give the product sulphonamide (2.18 g, 84%). MS (ES+) 464 ([MH]⁺).

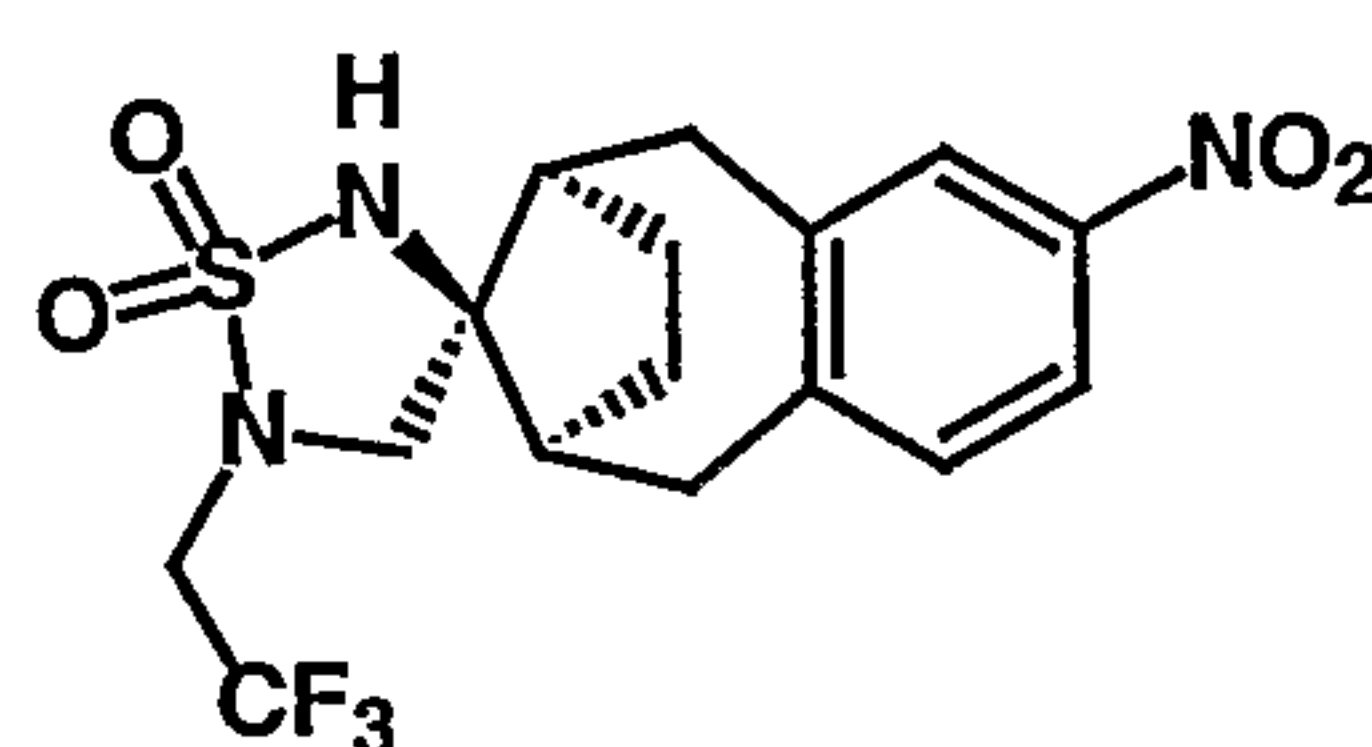
Step 3 : [6S/R,9R/S,11R/S] 11-Amino-11-(2,2,2-trifluoroethyl)aminomethyl-5,6,7,8,9,10-hexahydro-2-nitro-6,9-methanobenzocyclooctene



The sulphonamide from Step 2 (2.18 g, 4.7 mmol) was dissolved in dry dichloromethane (30 mL) under nitrogen and cooled to 0°C. Trifluoromethanesulphonic acid (3.33 mL, 37.6 mmol) was added dropwise and the resulting orange solution stirred at 0°C for 10 mins then allowed to warm to room temperature for 1 hour. The reaction was carefully quenched with NaHCO₃ (sat. aq; 200 mL) and extracted with dichloromethane (2 x 150 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and evaporated to give diamine (1.6 g, 99%). MS (ES+) 344 ([MH]⁺).

Step 4 : [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-nitro-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

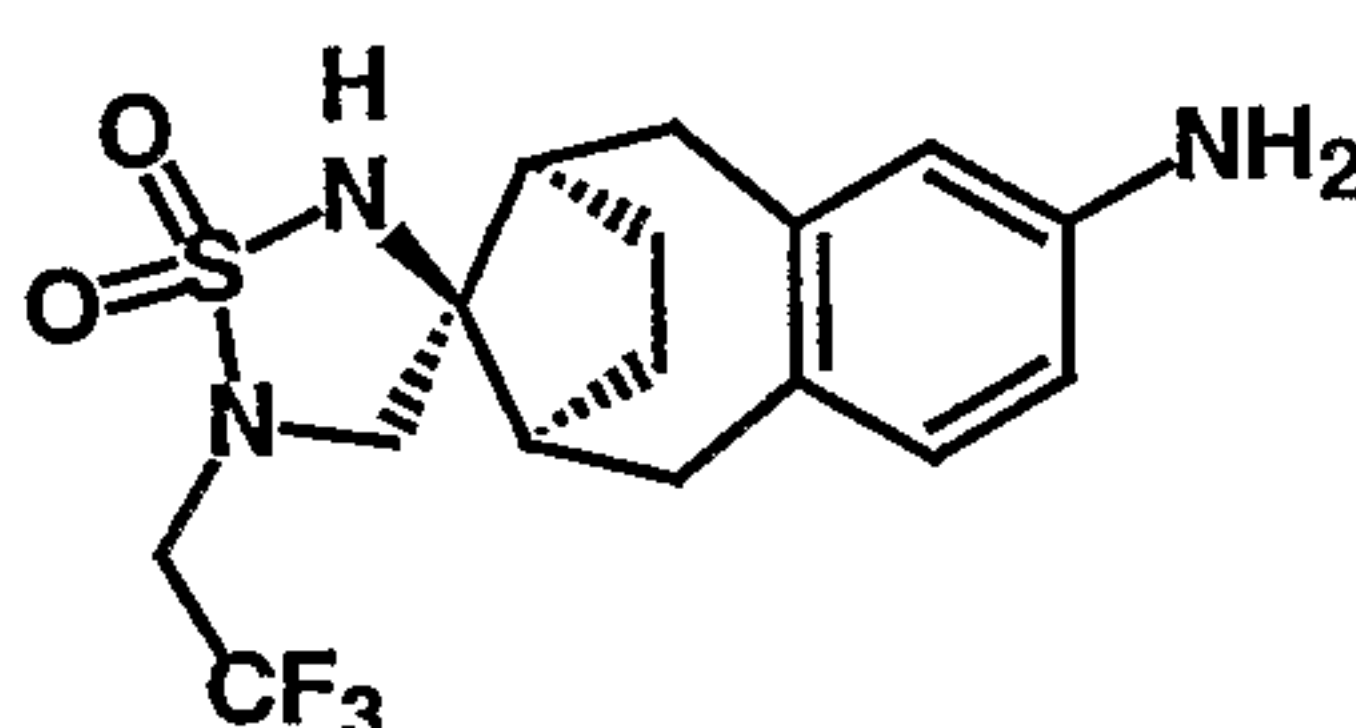
- 35 -



A mixture of diamine from Step 3 (1.6 g, 4.7 mmol) and sulphamide (1.36 g, 14.1 mmol) in pyridine (30 mL) was heated under reflux for 18 hours. The pyridine was removed *in vacuo*. The residue was partitioned between ethyl acetate (200 mL) and hydrochloric acid (1 M, 200 mL). The aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were washed with water and brine, dried over Na₂SO₄ and evaporated. The residue was triturated in diethyl ether to give the cyclic sulphamide nitro compound (1.36 g, 71%).

δ (¹H, 400MHz, CDCl₃) 1.24-1.32 (2H, m), 1.77-1.81 (2H, m), 2.51-2.55 (2H, m), 2.82-2.88 (2H, m), 3.29 (1H, d, J=11 Hz), 3.33 (1H, d, J=11 Hz), 3.42-3.48 (2H, m), 3.70 (2H, q, J=9 Hz), 4.69 (1H, s), 7.27 (1H, d, J=8 Hz), 7.97-7.99 (2H, m).

Step 5 : [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-amino-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



The nitro compound from Step 4 (1.36 g, 3.35 mmol) was dissolved in tetrahydrofuran (20 mL). Acetic acid (20 mL) followed by water (10 mL), were added. The solution was stirred vigorously while activated zinc (2.96 g, 45.2 mmol) was added portionwise. The reaction was stirred at room temperature for 1 hour. The zinc was removed by filtration and the filtrate concentrated *in vacuo*. The residue was taken up in ethyl acetate (50 mL) and carefully washed with NaHCO₃ (sat. aq; 50 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined

- 36 -

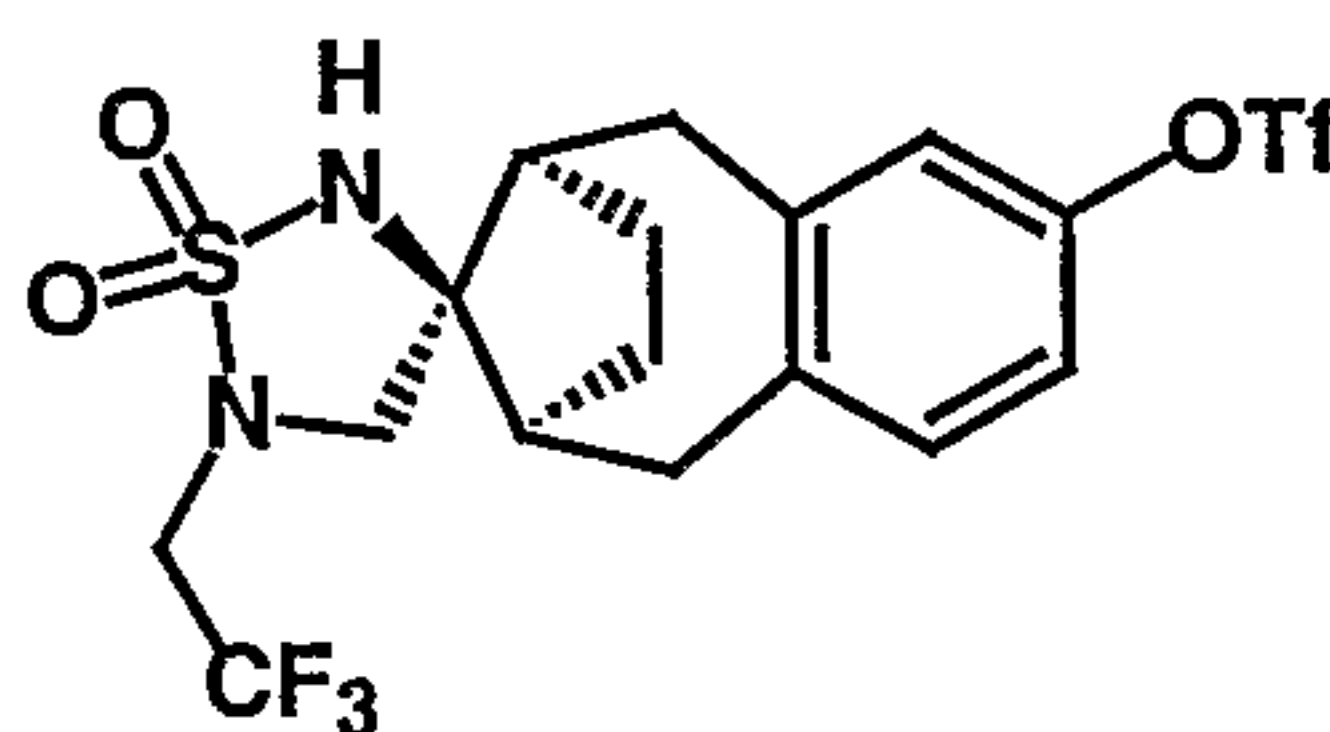
organic layers were washed with brine, dried over Na₂SO₄ and evaporated to give the title compound (1.23 g, 98%).

5 δ (¹H, 400MHz, CDCl₃) 1.34-1.39 (2H, m), 1.65-1.71 (2H, m), 2.35-2.42 (2H, m), 2.51-2.60 (2H, m), 3.05 (1H, d, J=16 Hz), 3.15 (1H, d, J=16 Hz), 3.41 (2H, q, J=8.8 Hz), 3.55 (2H, s), 3.61-3.74 (2H, m), 4.64 (1H, s), 6.45-6.48 (2H, m), 6.86 (1H, d, J=7 Hz).

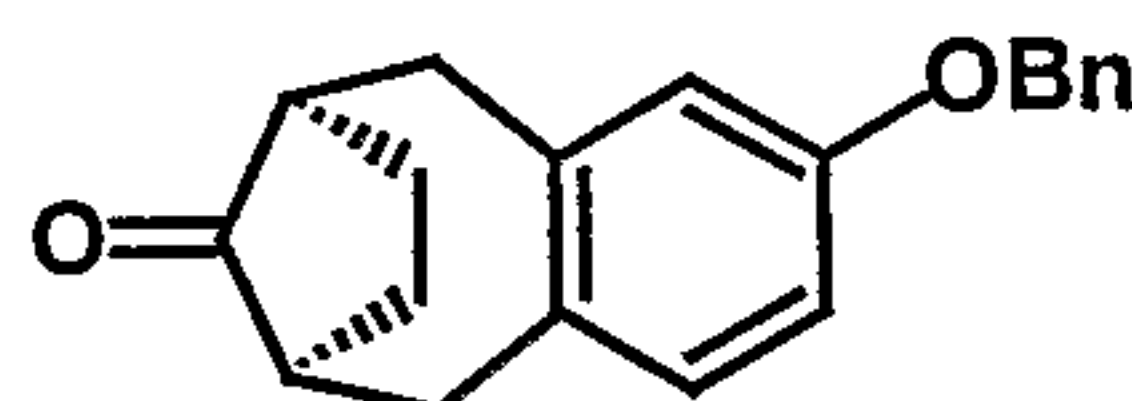
MS (ES+) 376 ([MH]⁺).

Intermediate D

10 [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-trifluoromethanesulphonate-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

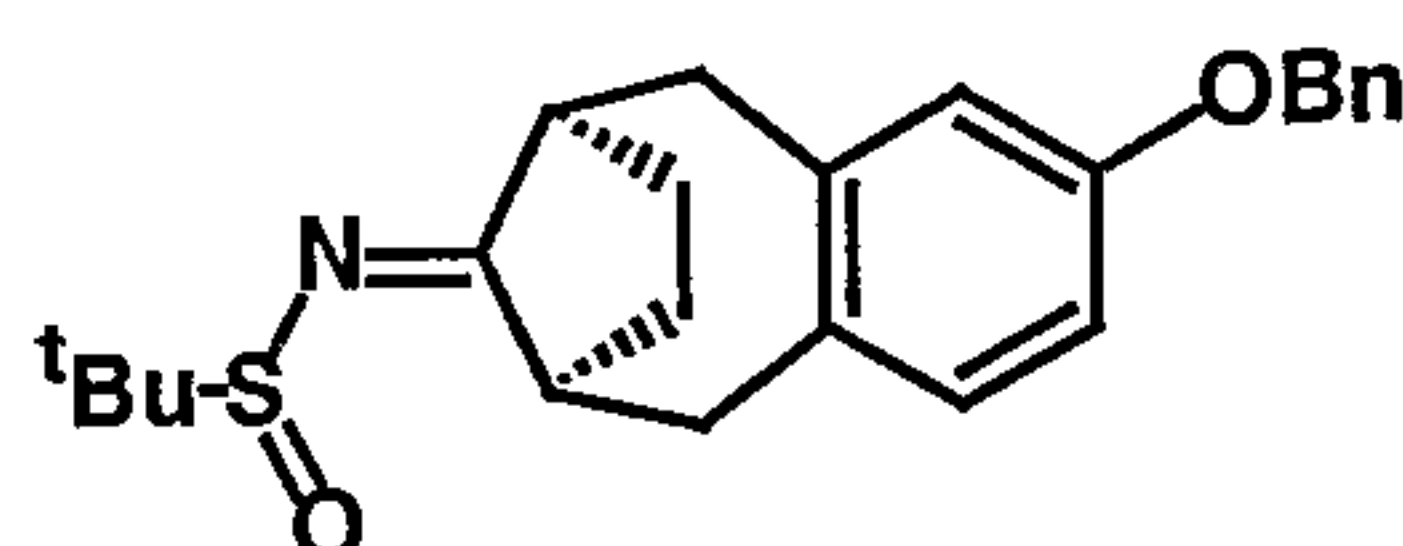


15 Step 1 : 11-Oxo-5,6,7,8,9,10-hexahydro-2-benzyloxy-6,9-methanobenzocyclooctene



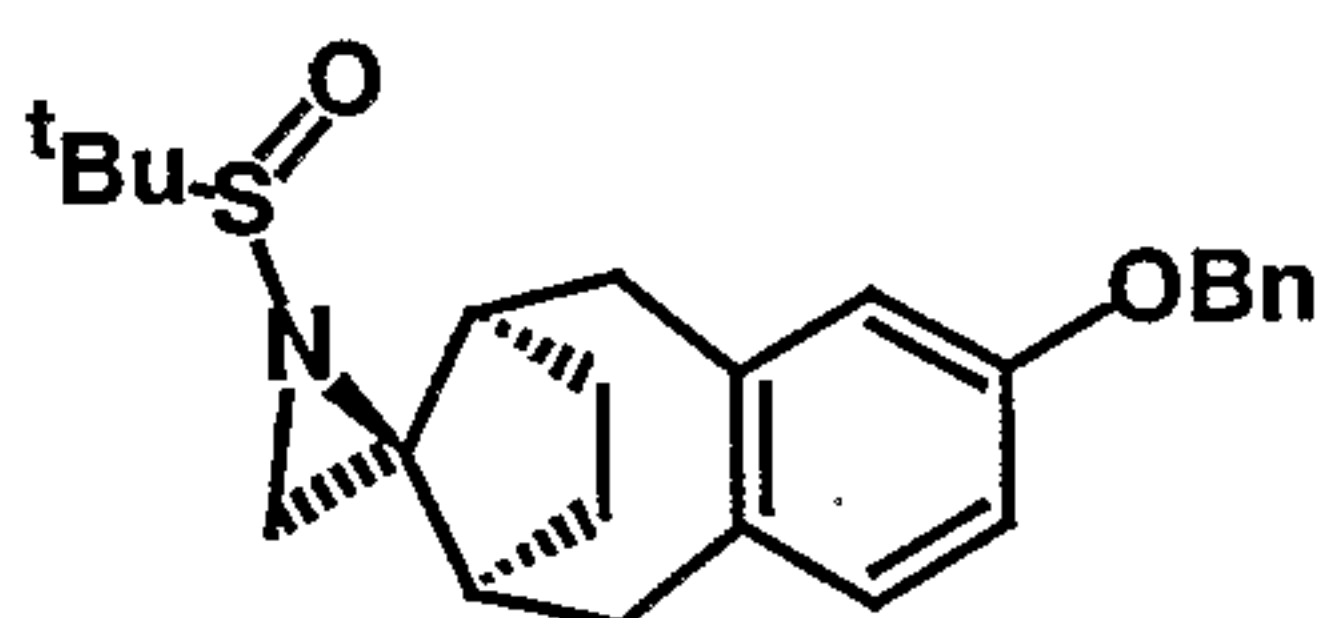
A mixture of 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[α][8]annulen-11-one (15 g; J. Org. Chem **1982**, *47*, 4329), K₂CO₃ (20.5 g) and benzyl bromide (10.6 ml) in DMF (100 ml) was stirred for 48 hrs at room temperature. The reaction was diluted with water (500 ml) and extracted with EtOAc (3x 150 ml). The combined organic phases were washed with water (2x 300 ml), brine (150 ml), dried and concentrated to give a gummy oil which crystallized on standing and after trituration with ether gave the title benzyl ether (19.5 g, 90%) as a white solid. δ (¹H, 360MHz, CDCl₃) 1.32 (2H, m), 1.85 (2H, m), 2.57 (2H, m), 2.87 (4H, m), 5.05 (2H, s), 6.82 (2H, m), 7.11 (1H, d, J=8.2 Hz), 7.37 (5H, m).

Step 2 : 11-(2'-Methyl-propane-2'-sulfinylimino)-5,6,7,8,9,10-hexahydro-2-benzyloxy-6,9-methanobenzocyclooctene



5 A solution of the product from Step 1 (20 g, 68 mmol), (+/-)tert-butyl sulfinamide (9.2 g, 76 mmol) and titanium (IV) ethoxide (tech., 29.2 mL, 140 mmol) in dry THF (140 mL) was stirred and heated at reflux under nitrogen for 4 hours. The reaction was allowed to cool to room temperature and poured into rapidly stirred brine (160 mL). The mixture
10 was stirred for 20 minutes, then filtered through Hyflo[®], washing with ethyl acetate. The filtrate was transferred to a separating funnel. The layers were separated, and the aqueous layer was extracted with ethyl acetate (x1). The combined organic extracts were washed with brine, then dried (Na₂SO₄), filtered and evaporated. The residue was purified by
15 chromatography on silica, eluting with 20→30% ethyl acetate / hexanes, to give the imine (24.9 g, 93%) as a colourless solid. MS (ES+) 396 ([MH]⁺).

Step 3: [6S/R,9R/S,11R/S] 11-[(2'-Methyl-propane-2'-sulfinyl)-1'-aza-spiro[2.4]]-5,6,7,8,9,10-hexahydro-2-benzyloxy-6,9-methanobenzocyclooctene

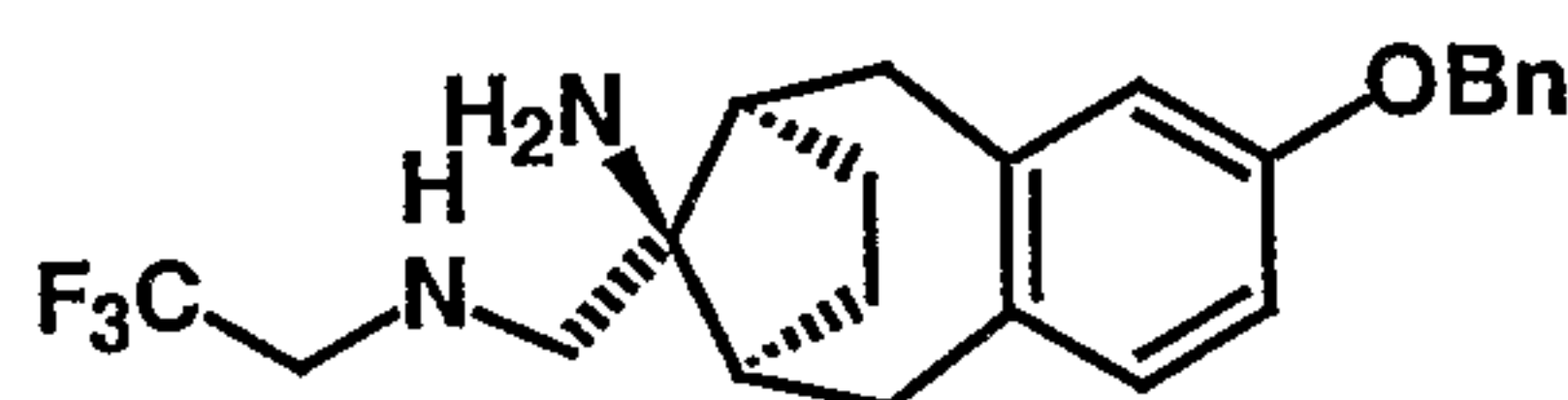


Sodium hydride (60% dispersion in oil, 3.8 g, 95 mmol) was added portionwise to a stirred suspension of trimethyl sulfoxonium iodide (21 g, 95 mmol) in dry DMSO (150 mL) at room temperature under nitrogen.
25 After 90 minutes at room temperature, a solution of the product from Step 2 (24.9 g, 95 mmol) in dry DMSO (250 mL) was added such that the internal temperature remained below 30°C. The mixture was stirred at room temperature for 4 hours, then quenched with water (1 L). The

- 38 -

precipitate was collected by filtration. The solid was taken up in dichloromethane and washed with brine. The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 5→10% ethyl acetate / dichloromethane, to give the aziridine (23.2 g, 90%) as a colourless solid. MS (ES+) 410 ([MH]⁺).

Step 4 : [6S/R,9R/S,11R/S] 11-Amino-11-(2,2,2-trifluoroethyl)aminomethyl-5,6,7,8,9,10-hexahydro-2-benzyloxy-6,9-methanobenzocyclooctene



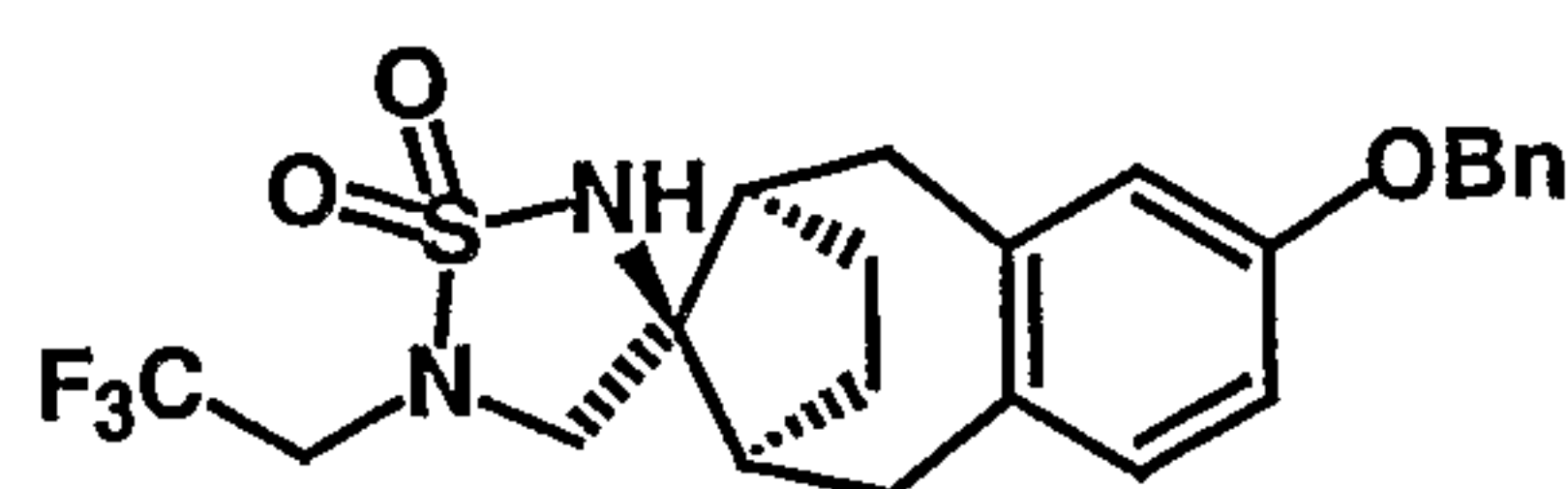
10

Trifluoroethyl amine (70 mL, 880 mmol) was added to a stirred suspension of the product from Step 3 (68.4 g, 167 mmol) and anhydrous zinc iodide (54 g, 170 mmol) in dry 1,2-dichloroethane (300 mL) at room temperature under nitrogen. The resulting solution was heated at 75°C, protected from light, for 24 hours. An additional portion of trifluoroethyl amine (70 mL, 880 mmol) was added and the reaction was maintained at 75°C for a further 16 hours. The reaction was allowed to cool, then diluted with dichloromethane (500 mL) and water (400 mL). Sufficient sodium carbonate was then added to adjust the aqueous layer to ~pH 11. The small amount of precipitate was removed by filtration through Hyflo[®]. The layers were separated and the aqueous layer was extracted with dichloromethane (x3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 5→10% ethyl acetate / dichloromethane, then with 10→20% methanol / dichloromethane, to give the diamine (59.6g, 88%) as a thick oil. MS (ES+) 405 ([MH]⁺).

Step 5 : [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-benzyloxy-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

30

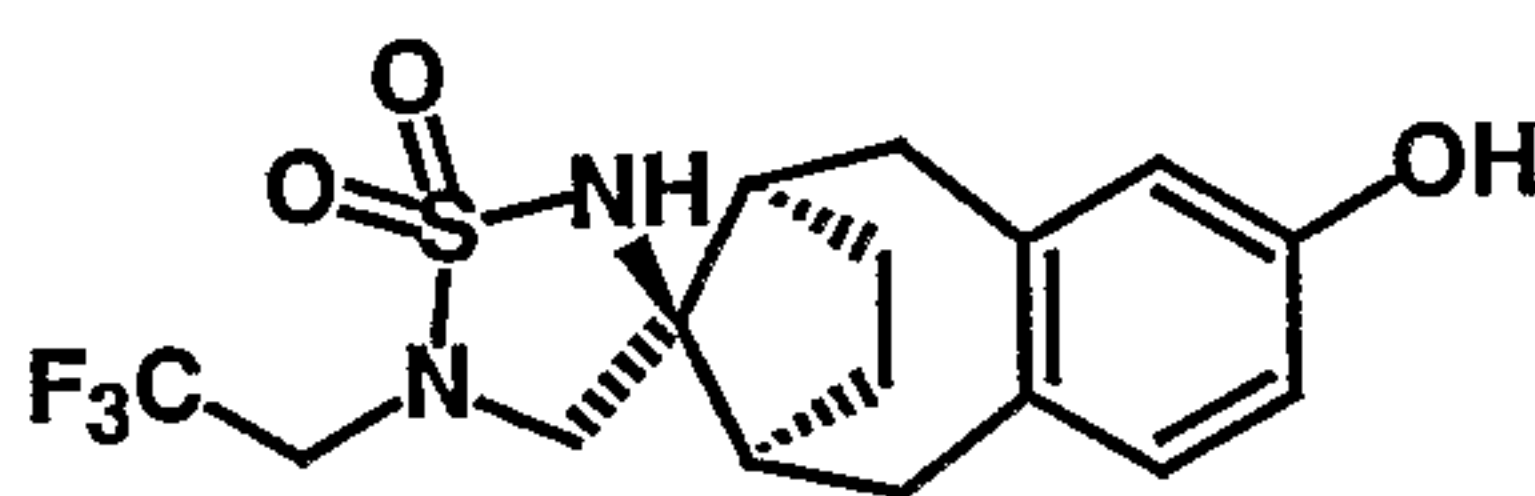
- 39 -



A solution of the product from Step 4 (59.6 g, 147 mmol) and sulfamide (42.5g, 442 mmol) in dry pyridine (350 mL) was stirred and heated at reflux under nitrogen for 4 hours. The reaction was allowed to cool, then the pyridine was removed in vacuo. The residue was azeotroped with toluene (x2). The residue was then partitioned between dichloromethane (400 mL) and 1N hydrochloric acid (400 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (x3). The combined organic extracts were dried (Na₂SO₄), filtered and evaporated.

The residue was purified by chromatography on silica, eluting with dichloromethane, then 1→2→4% ethyl acetate / dichloromethane to give the cyclic sulfamide (53 g, 80%) as a colourless solid. δ (¹H, 360MHz, CDCl₃) 1.34 (2H, m), 1.70 (2H, m), 2.41 (2H, m), 2.62 (2H, m), 3.11 (1H, d, J=15.9 Hz), 3.20 (1H, d, J=15.9 Hz), 3.42 (2H, ABq, J=9.3, 13.3 Hz), 3.67 (2H, dq, J=2.2, 8.7 Hz), 4.76 (1H, s), 5.02 (2H, s), 6.72 (2H, m), 6.99 (1H, d, J=7.8 Hz), 7.37 (5H, m).

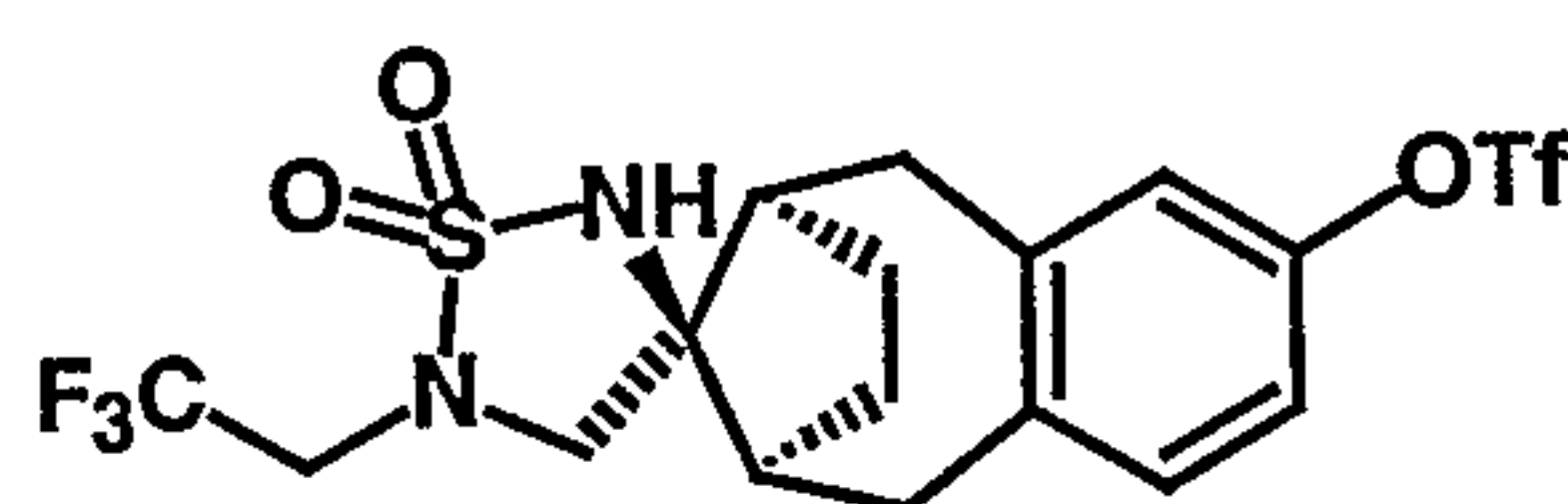
Step 6 : [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-hydroxy-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



A solution of the product from Step 5 (3.9 g, 8.4 mmol) in methanol/ethyl acetate (4:1, 150 mL) was hydrogenated at 35 psi over 10% palladium on carbon (500 mg) for 4 hours at room temperature. The catalyst was removed by filtration through Hyflo[®]. The filtrate was evaporated, and the residue was purified by filtration through a pad of silica, eluting with 50% ethyl acetate/dichloromethane to give the phenol (3.2g) as a colourless solid. δ (¹H, 360MHz, d₆-DMSO) 1.06 (2H, m), 1.65 (2H, m), 2.29 (2H, m),

2.42 (2H, m), 3.04 (1H, d, J=15.6 Hz), 3.11 (1H, d, J=15.6 Hz), 3.43 (2H, s), 3.99 (2H, brq, J=9.6 Hz), 6.47 (2H, m), 6.85 (1H, d, J=8 Hz), 7.93 (1H, s), 9.02 (1H, s).

5 Step 7 : [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-trifluoromethanesulphonate-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

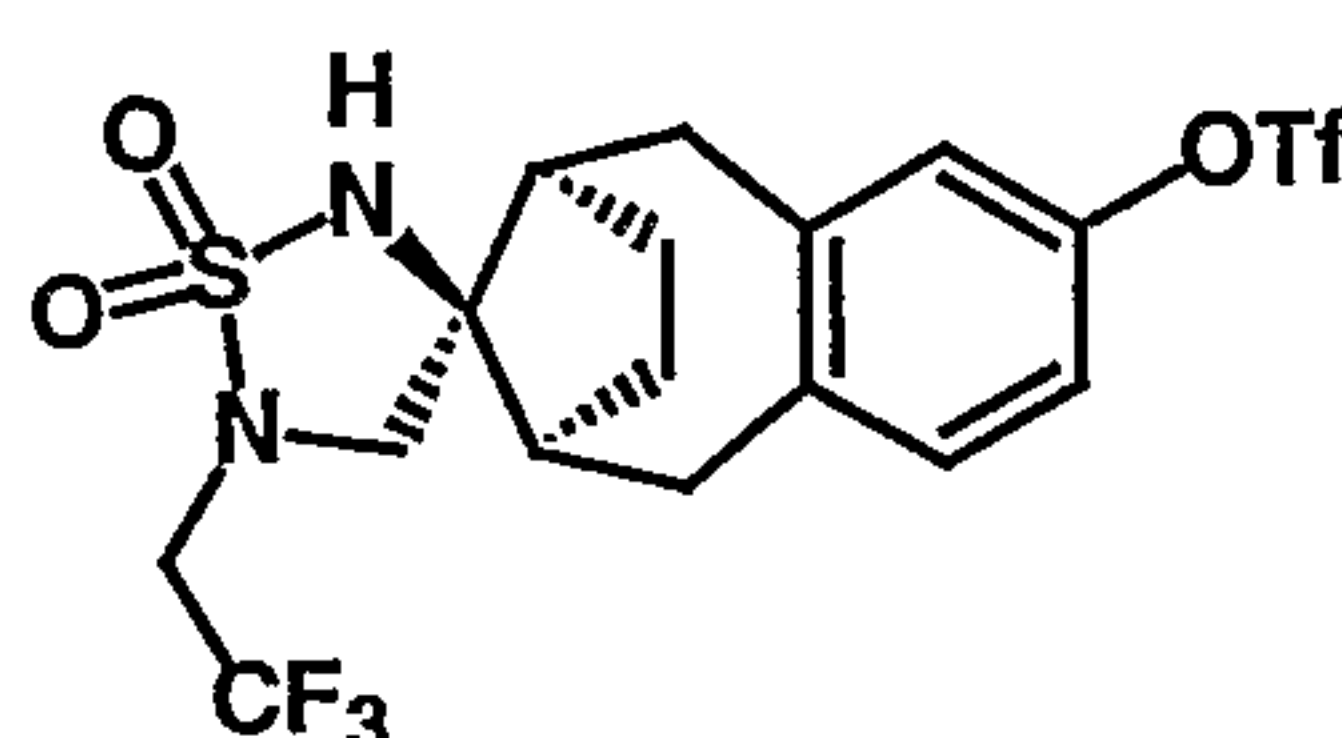


Trifluoromethanesulfonic anhydride (3.8 ml, 23 mmol) was added dropwise to a cold (0°C) solution of the phenol from Step 6 (5.1 g, 12.8 mmol), in dichloromethane (400 ml), under a nitrogen atmosphere. Once the addition was complete the mixture was stirred at room temperature for one hour. The reaction was cooled to 0°C and pyridine (1.9 ml, 23 mmol) was added dropwise, and the mixture was stirred at 0°C for 15 minutes and at room temperature for 16 hours. The reaction was diluted with water (200 ml) and extracted with dichloromethane (2 x 200 ml). The extracts were washed with brine, dried (MgSO₄) and evaporated *in vacuo* to give a pinkish solid (5.25 g). The solid was triturated with diethyl ether to give the title compound as an off white solid (4.3 g, 66%).

20 δ (¹H, 400MHz, *d*₆-DMSO) 0.97-1.01 (2H, m), 1.70-1.74 (2H, m), 2.32-2.41 (2H, m), 2.66-2.74 (2H, m), 3.15 (1H, d, J=6.2 Hz), 3.19 (1H, d, J=6.2 Hz), 3.46 (2H, m), 3.98-4.05 (2H, m), 7.20 (1H, dd, J = 8.4 & 2.6 Hz), 7.28 (2H, t, J = 8.4 Hz) and 8.04 (1H, s).

Intermediate E

25 [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-trifluoromethanesulphonate-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



The benzyl ether from Step 5 of the Intermediate D synthesis was resolved by preparative HPLC using a Chiralcel OD column (25 x 2 cm), 25%MeOH/CO₂ @ 50 ml/min; 288nm; 35 C; 100 bar. The second enantiomer collected was converted to the title compound using the procedures described in Steps 6 and 7 of the Intermediate D synthesis.

Alternative Method

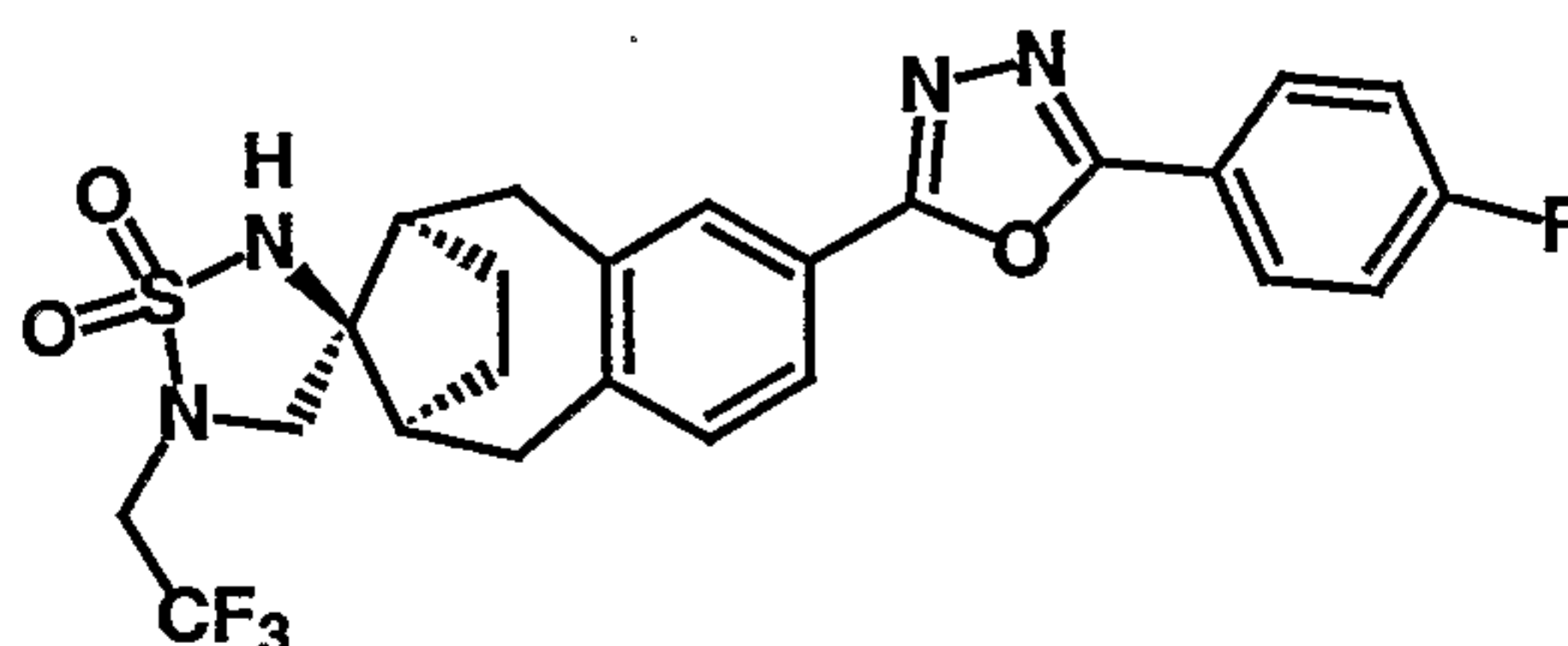
2-Amino-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (*J. Org. Chem.* **47**, 4329, 1982), (17.16 g, 0.085 mol) was dissolved in ethanol (430 mL) and *R*-(-)-mandelic acid (7.14 g, 0.047 mol) was added in one portion. The solution was slowly added into toluene (650 mL) whilst distilling the azeotrope under vacuum such that the volume was kept constant. When all of the ethanol had been added and the solution was concentrated to approximately 500 mL, the mixture was seeded with enantiopure salt (800 mg). The resulting slurry was concentrated further to a volume of 343 mL via vacuum distillation and then allowed to stir overnight. The solids were filtered, washed with toluene (53 mL) and dried. This product (16.07 g, 87% ee) was added to a 95:5 mixture of toluene and THF (402 mL) and aged at 50 °C overnight. The solids were filtered, washed with toluene (60 mL) and dried, to afford enantiopure light-orange salt (11.59 g, 38% yield, 97% e.e.). δ (¹H, 250 MHz, CD₂Cl₂): δ (ppm) 1.20 (m, 2H), 1.73 (m, 2H), 2.37 (m, 2H), 2.56 (d, 1H, *J* = 15.3 Hz), 2.60 (d, 1H, *J* = 14.6), 2.76 (dd, 1H, *J* = 8.3, 15.1 Hz), 2.77 (dd, 1H, *J* = 8.3, 15.3 Hz), 5.00 (s, 1H), 6.54 (m, 2H), 6.88 (d, 1H, *J* = 7.8), 7.28 (m, 5H).

Treatment of this salt with base released the homochiral aniline, which could be converted to the corresponding homochiral phenol by the

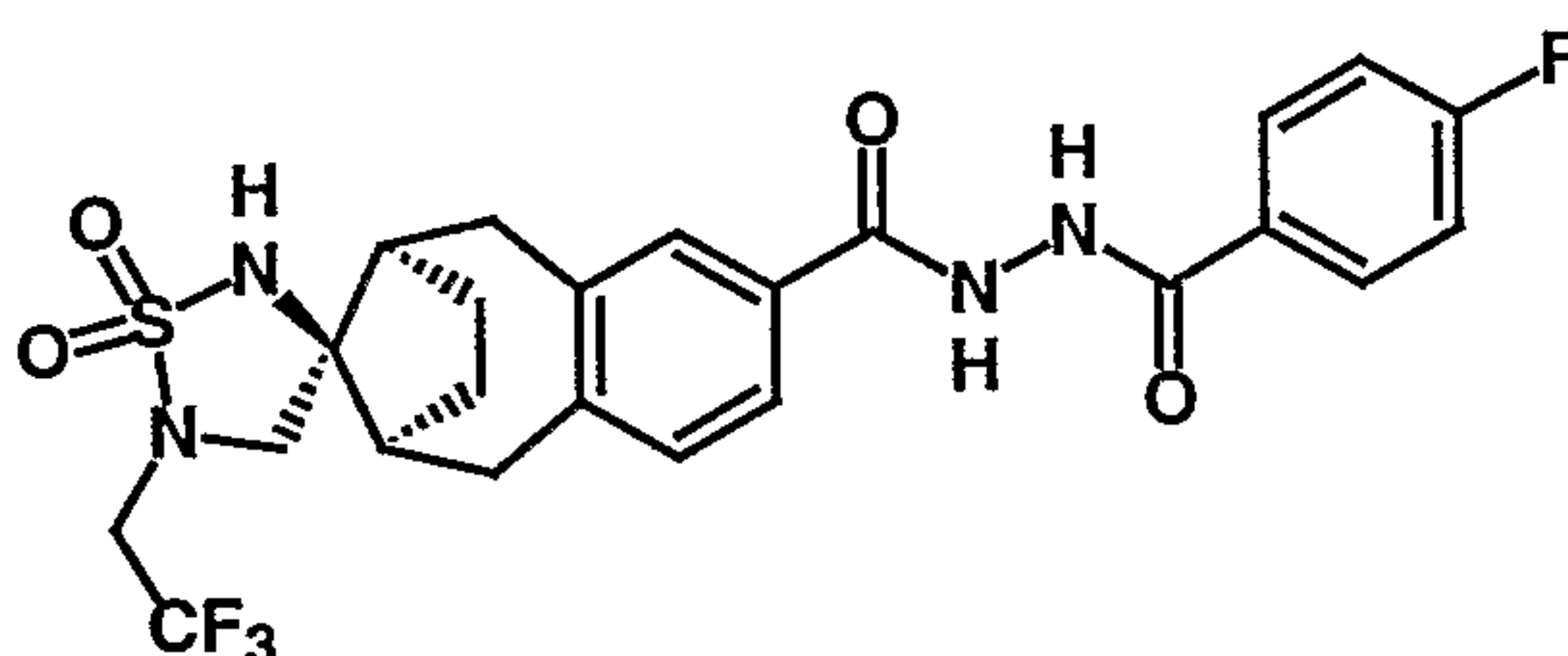
procedure described in *J. Org. Chem.* **47**, 4329, 1982, and thence to Intermediate E by the procedures described for Intermediate D.

Example 1

- 5 **[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-5'-trifluoroethyl-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.**

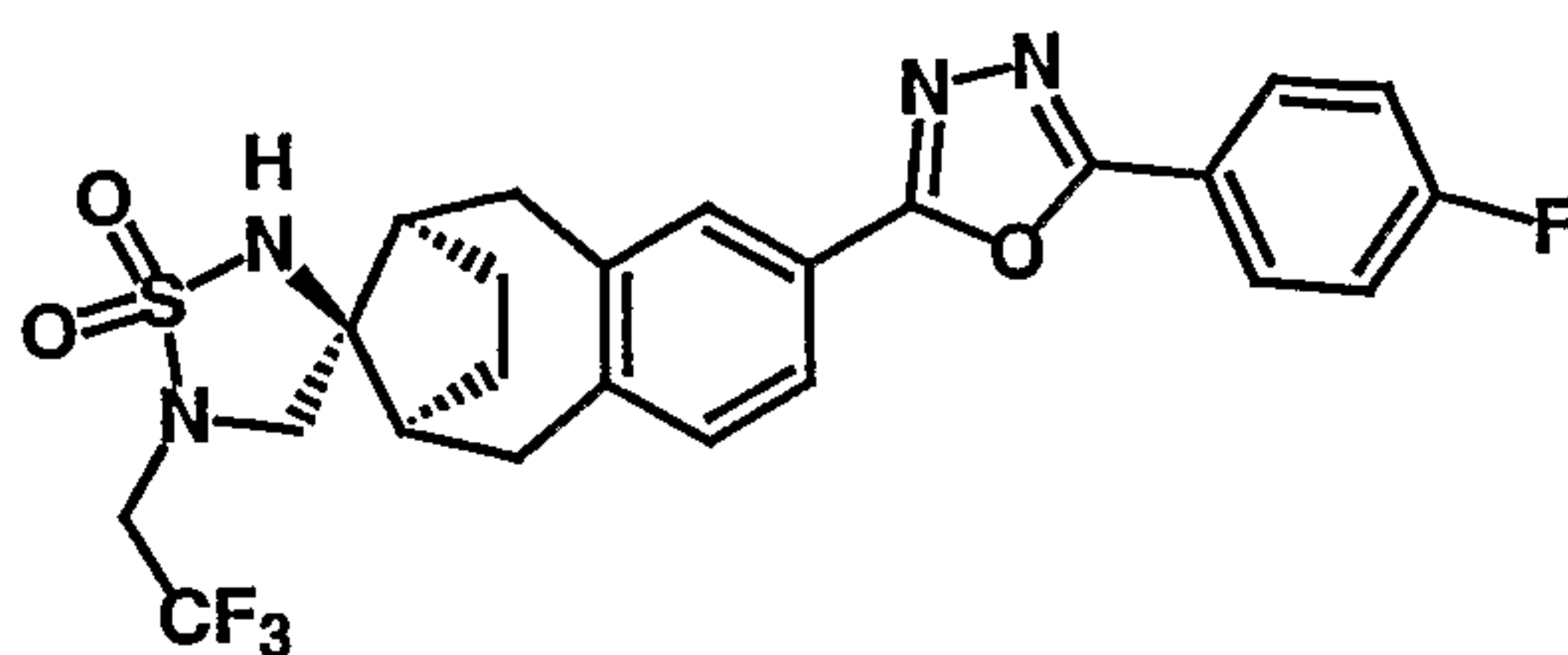


- 10 Step 1 [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(carboxylic acid N'-4-fluorobenzoyl hydrazido)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



- Diisopropylethylamine (83 μ L) was added to a suspension of Intermediate A (160 mg) in acetonitrile (3 mL). To the resulting solution was added HBTU (180 mg) followed by 4-fluorobenzhydrazide (73 mg). The reaction mixture was heated at 40°C for 2 h. The mixture was allowed to cool to ambient temperature and was then partitioned between water and ethyl acetate. The layers were separated and the organic extract was washed sequentially with 10% citric acid solution, water and brine. The organic phase was dried (Na_2SO_4) and concentrated to give the diacyl hydrazide. MS (ES⁺) 541 ([MH]⁺), 563 ([M+Na]⁺).

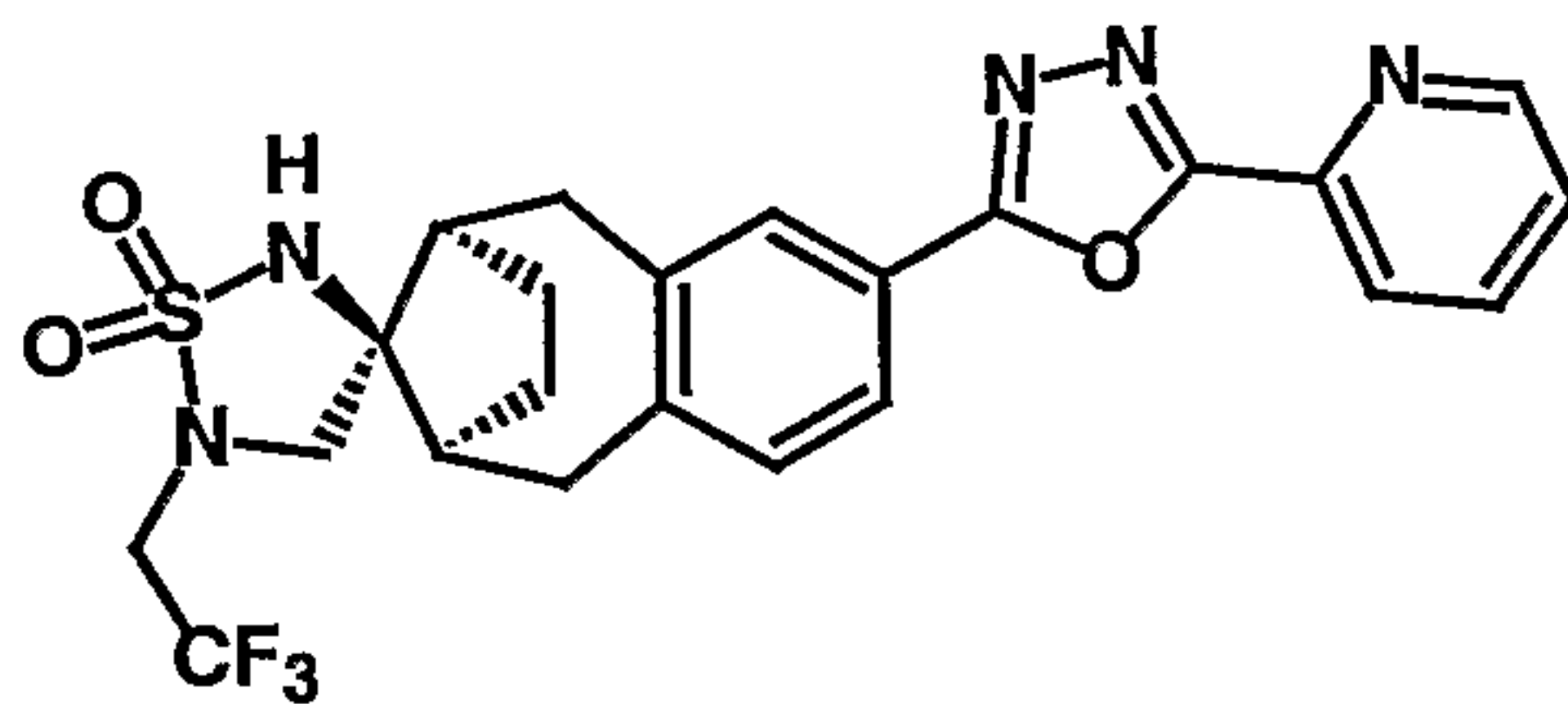
- 25 Step 2 : [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-5'-trifluoroethyl-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



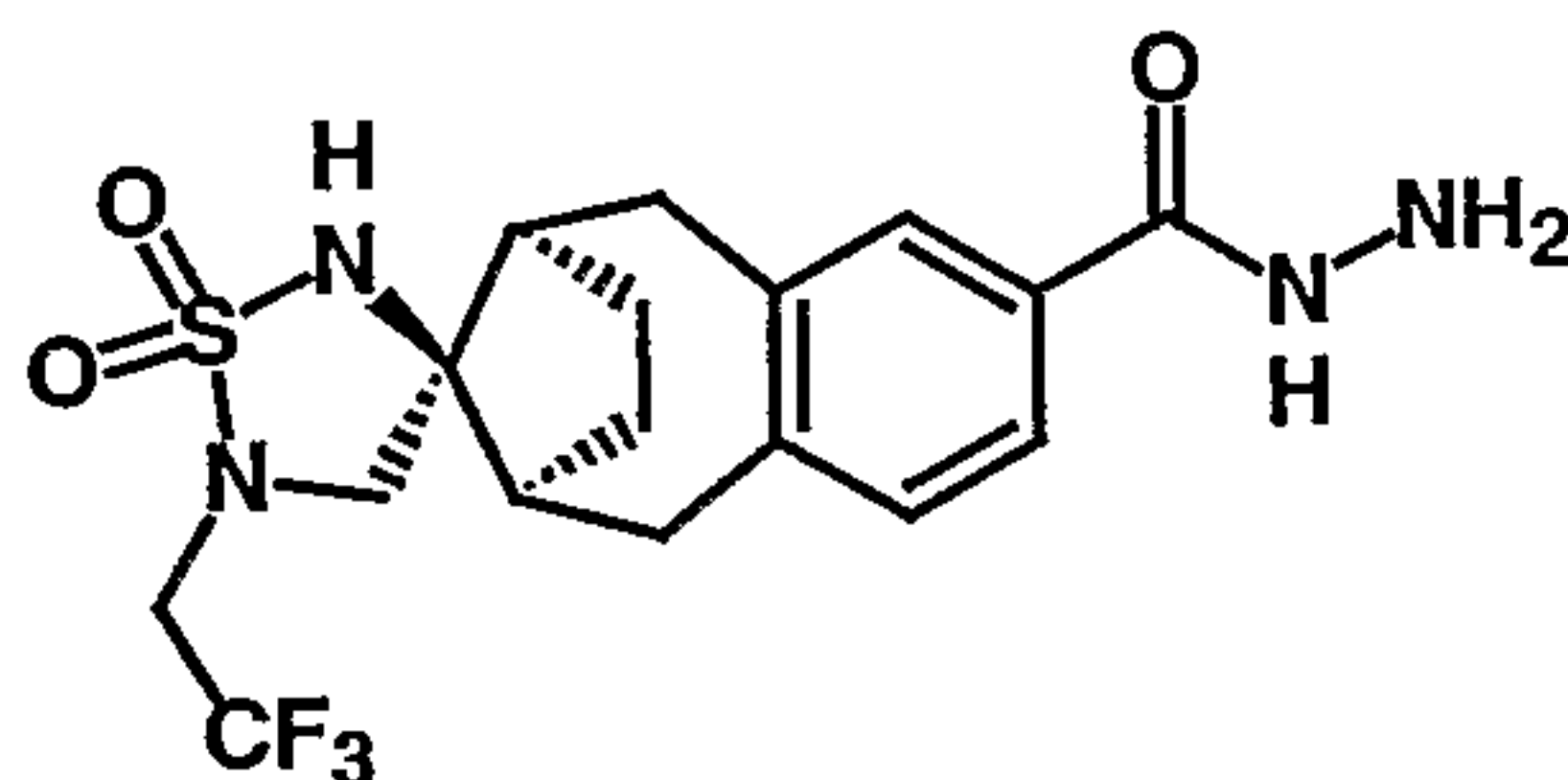
Burgess' reagent (183 mg) was added to a solution of the diacyl hydrazide from Step 1 (138 mg) in THF (2 mL) in a microwave reaction tube. The mixture was irradiated in a microwave for 600 s at 120°C. The mixture was washed into a flask using ethyl acetate and was then concentrated *in vacuo*. The product was purified by chromatography on silica eluting with 2 to 3 to 5% MeOH in dichloromethane. The white solid obtained was triturated with diethyl ether to give 68 mg (51% yield) of the title compound. δ (^1H , 400MHz, CDCl_3) 1.31-1.39 (2H, m), 1.75-1.79 (2H, m), 2.51-2.54 (2H, m), 2.77-2.88 (2H, m), 3.29 (1H, d, $J=5.6$ Hz), 3.33 (1H, d, $J=5.6$ Hz), 3.46 (2H, s), 3.70 (2H, q, $J = 8.7$ Hz), 4.87 (1H, br s), 7.21-7.29 (3H, m), 7.86-7.89 (2H, m), 8.13-8.17 (2H, m).

Example 2

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(2-(2-pyridyl)-1,3,4-oxadiazol-5-yl)-5'-trifluoroethyl-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Step 1 [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-hydrazido-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

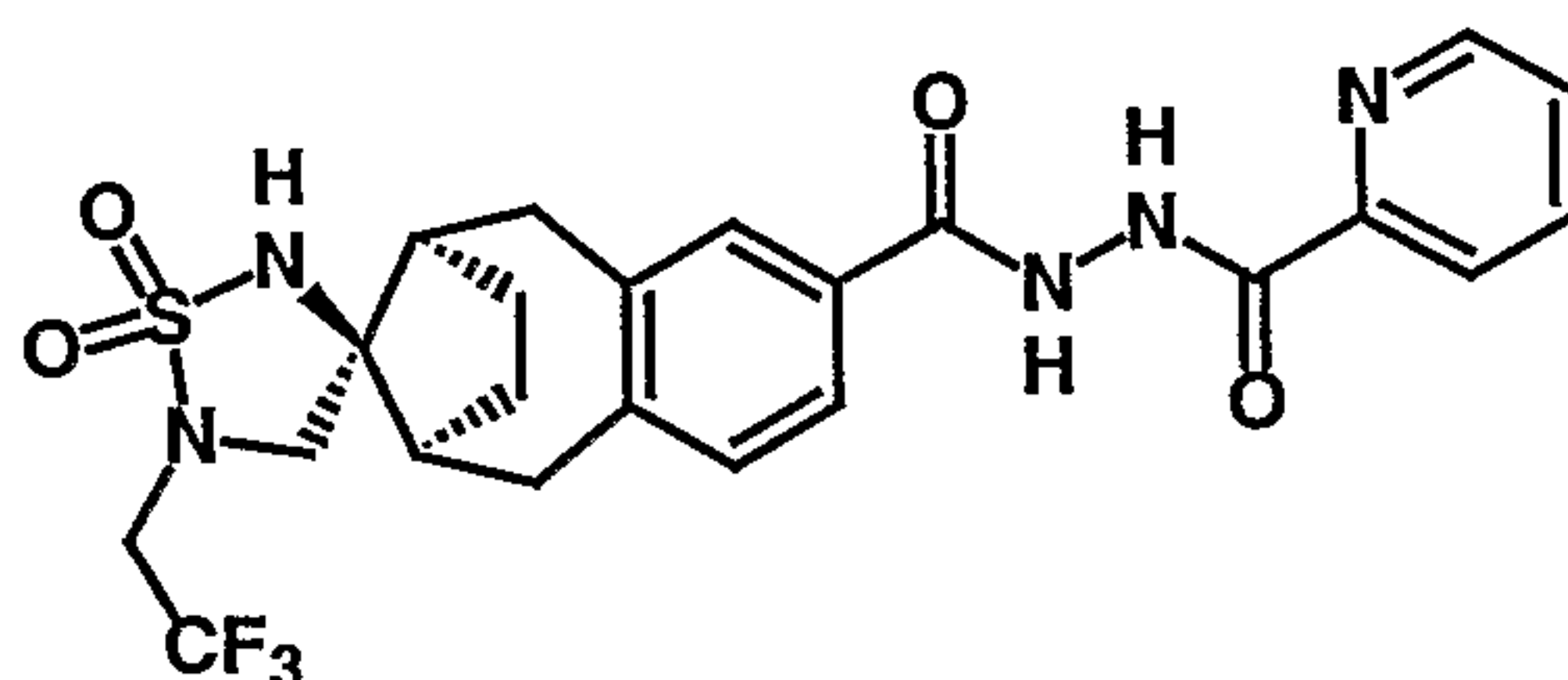


- 44 -

A mixture of Intermediate A (238 mg), diisopropylethylamine (113 μ L), HBTU (246 mg) and BOC-hydrazine (86 mg) in acetonitrile (7 mL) was stirred at room temperature under nitrogen for 65 h. The reaction mixture was partitioned between EtOAc and water. The layers were separated and the organic extract was washed sequentially with 10% citric acid solution, water and brine. The organic phase was dried (MgSO_4) and concentrated. The residue was chromatographed on silica eluting with 3% methanol in dichloromethane to give 328 mg (assumed quantitative) of the BOC-hydrazide.

The protected hydrazide (328 mg) was dissolved in EtOAc (5 mL) and to this solution was added HCl in diethyl ether (2 mL of a 2M solution). The mixture was stirred at room temperature overnight. After aqueous work-up, it became apparent that deprotection was incomplete. Therefore the crude material was dissolved in EtOAc (5 mL) and to this solution was added saturated HCl in methanol (3 mL). The mixture was stirred for 72 h. The mixture was diluted with EtOAc and washed with satd. $\text{NaHCO}_{3(\text{aq})}$ (x2) and then brine before being dried (MgSO_4) and concentrated. The hydrazide was obtained as a solid (255 mg, 96% yield). MS (ES+) 419 ([MH]⁺).

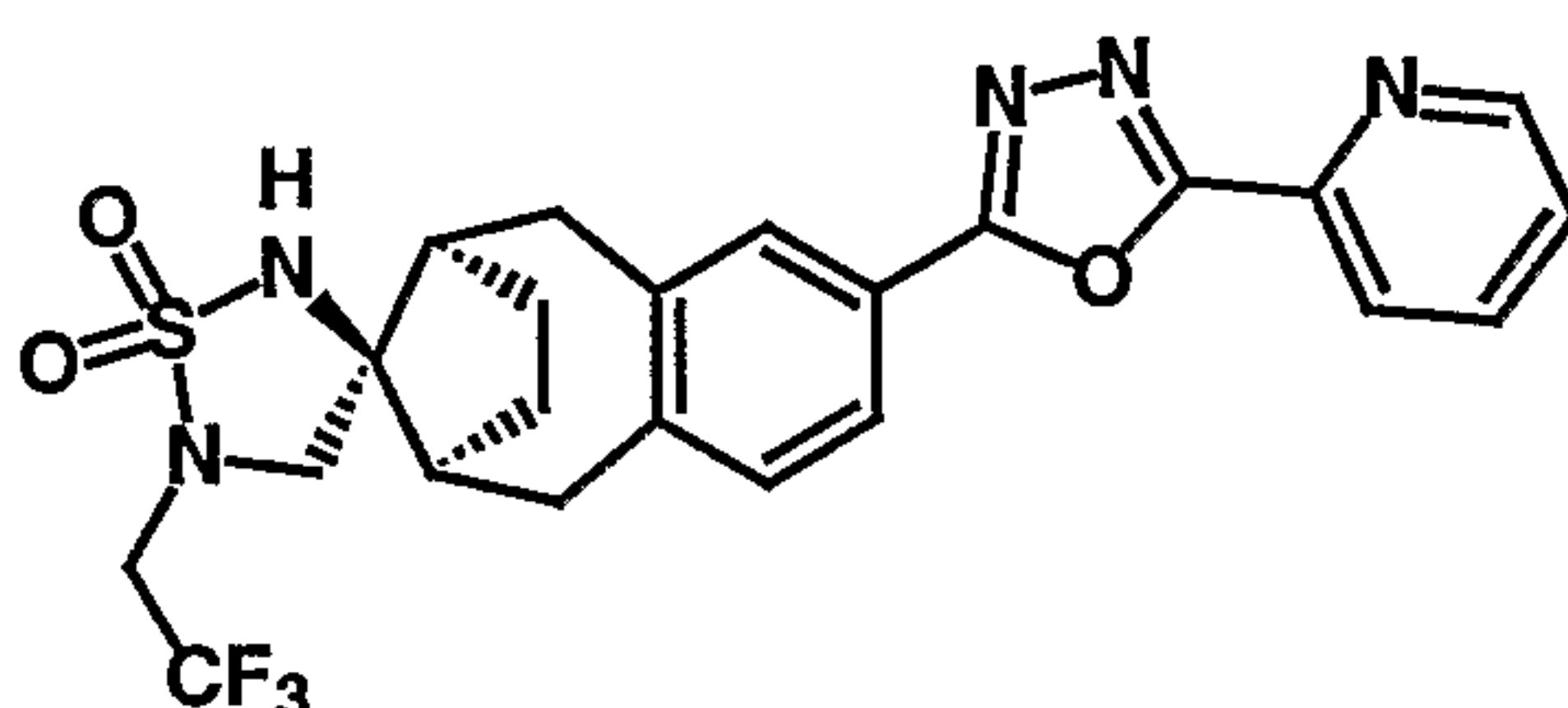
Step 2 6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(carboxylic acid N'-2-pyridinecarbonyl hydrazido)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



with water and extracted into EtOAc (X2). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated. Trituration with EtOAc/Et₂O afforded predominantly the diacyl hydrazide (190 mg, 60% yield). MS (ES⁺) 524 ([MH]⁺).

5

Step 3 : [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(2-(2-pyridyl)-1,3,4-oxadiazol-5-yl)-5'-trifluoroethyl-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



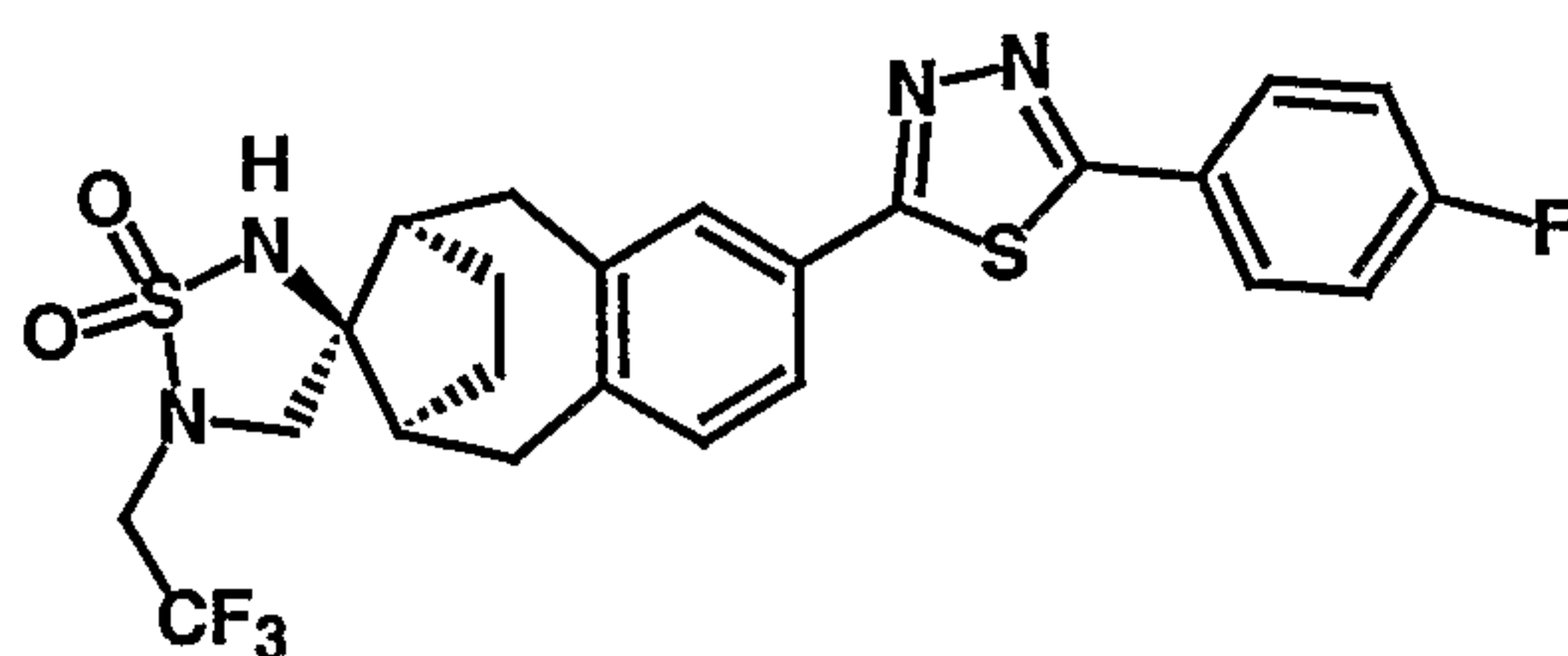
- 10 Burgess' reagent (85 mg) was added to a solution of the diacyl hydrazide (62 mg) in THF (1 mL). The mixture was irradiated in a microwave for 300s at 120°C. The reaction mixture was washed out of the reaction tube using ethyl acetate, and concentrated. Chromatography on silica eluting with 2% methanol in dichloromethane was followed by trituration with
- 15 diethyl ether to give the title compound (25 mg, 42%) and some slightly impure material (20 mg). δ (¹H, 400MHz, CDCl₃) 1.32-1.35 (2H, m), 1.74-1.78 (2H, m), 2.49-2.52 (2H, m), 2.77-2.89 (2H, m), 3.25-3.33 (2H, m), 3.45 (2H, s), 3.69 (2H, q, *J* = 8.7 Hz), 4.70 (1H, s), 7.25-7.28 (1H, m), 7.46-7.49 (1H, m), 7.89-7.93 (1H, m), 7.97-7.99 (2H, m), 8.33 (1H, d, *J* = 8.2 Hz), 8.82
- 20 (1H, d, *J* = 4.3 Hz); MS (ES⁺) 506 ([MH]⁺).

Example 3

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)-5'-trifluoroethyl-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.

25

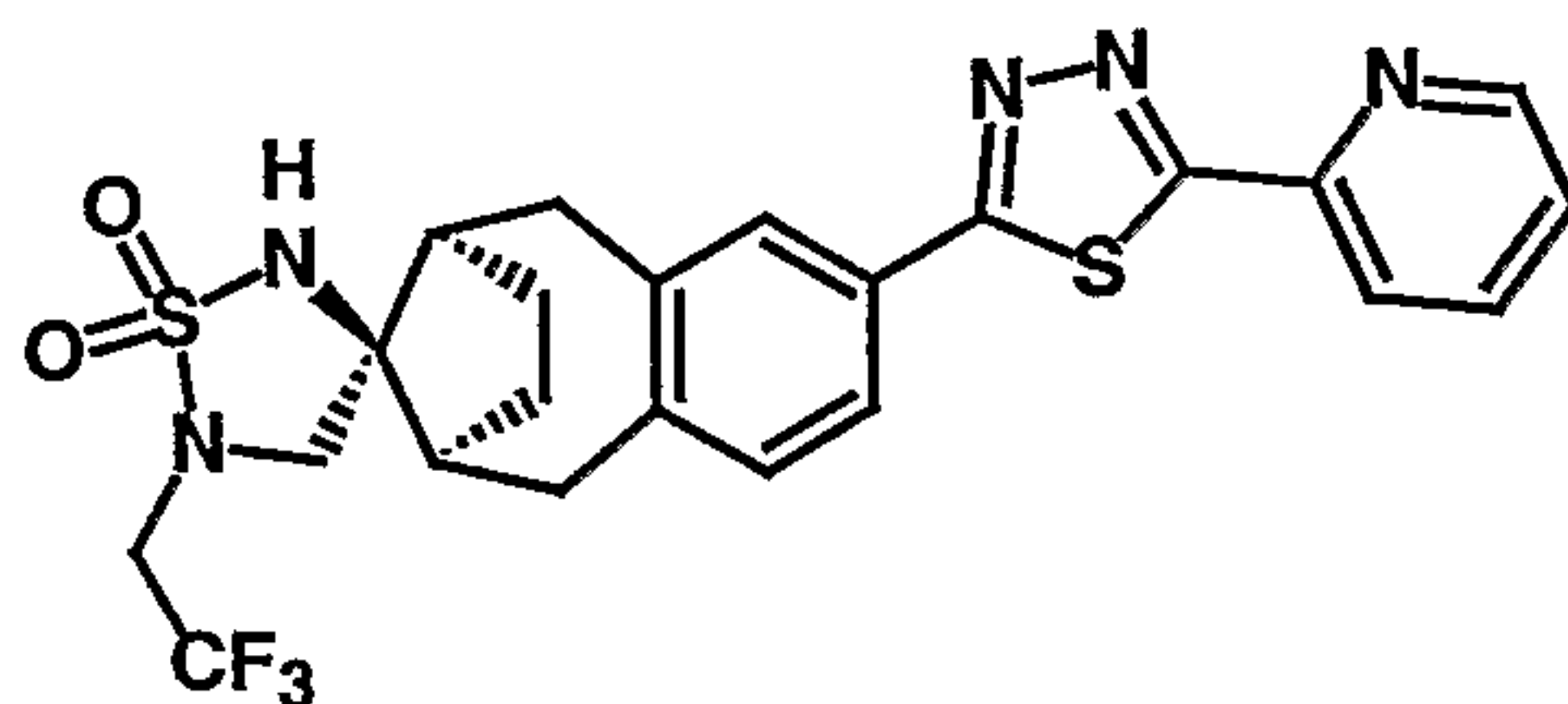
- 46 -



Diphosphorus pentasulphide (58 mg) was added to a solution of the diacyl hydrazide described in Example 1, Step 1 (47 mg) in pyridine (3 mL). The mixture was heated at reflux for 16 h. The mixture was allowed to cool and partitioned between EtOAc and water. The organic extract was washed sequentially with 10% citric acid solution, water and brine before being dried (MgSO₄) and concentrated. Chromatography eluting with 3% methanol in dichloromethane afforded the title compound (31 mg, 66% yield) as a white solid. δ (¹H, 400MHz, *d*₆-DMSO) 1.06-1.10 (2H, m), 1.71-1.74 (2H, m), 2.41 (2H, br s), 2.68-2.80 (2H, m), 3.16-3.21 (2H, m), 3.48 (2H, s), 3.99-4.06 (2H, m), 7.33 (1H, d, *J* = 7.8 Hz), 7.41-7.46 (2H, m), 7.73-7.78 (2H, m), 8.06-8.09 (3H, m); MS (ES⁺) 539 ([MH]⁺).

Example 4

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(2-(2-pyridyl)-1,3,4-thiadiazol-5-yl)-5'-trifluoroethyl-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

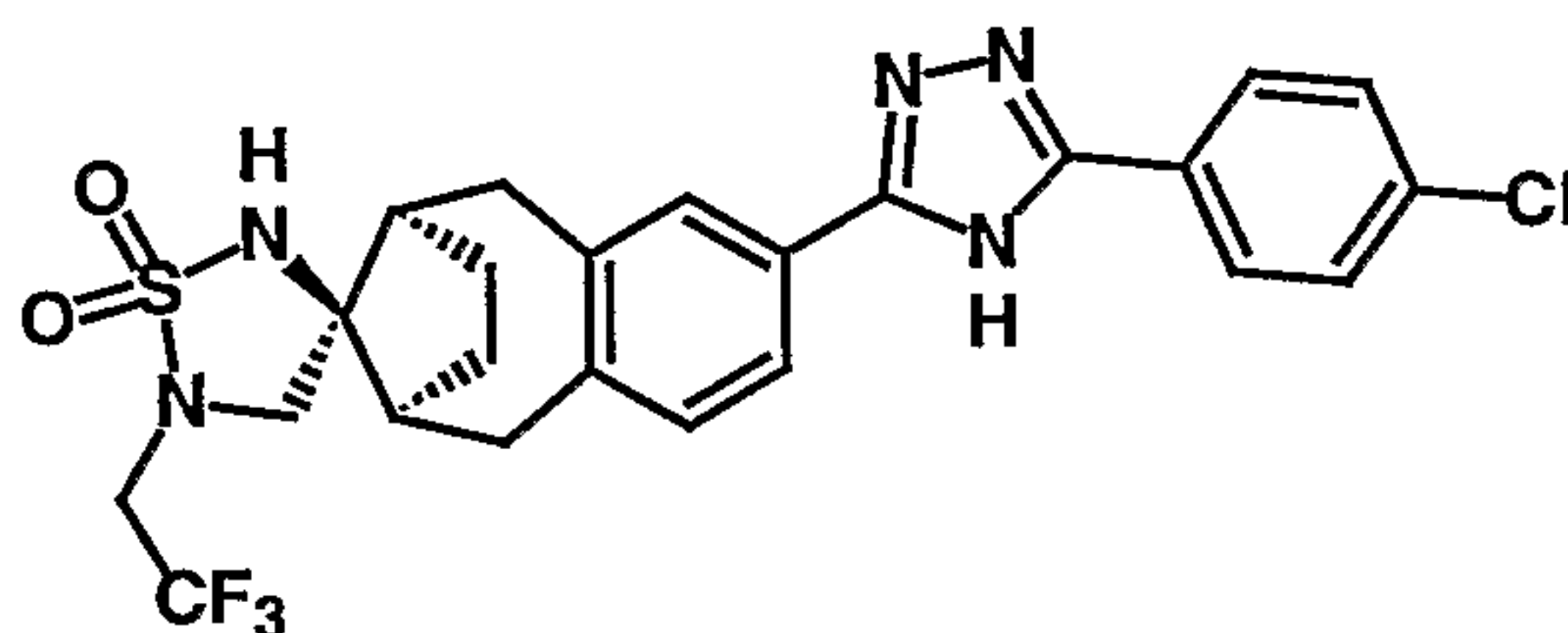


The diacyl hydrazide (80 mg) described in Example 2, Step 2 was dissolved in pyridine (4 mL) and to the solution was added diphosphorus pentasulphide (102 mg). The mixture was heated at reflux for 17 h then allowed to cool and partitioned between ethyl acetate and water. The layers were separated and the organic extract was washed sequentially with 0.5 M HCl_(aq) (X2), water and brine before being dried (MgSO₄) and concentrated. The product was purified by chromatography on silica

eluting with 3% methanol in dichloromethane. Trituration with 10% ethyl acetate in dichloromethane afforded the title compound as an off-white solid. δ (^1H , 400MHz, d_6 -DMSO); 1.07-1.11 (2H, m), 1.73-1.75 (2H, m), 2.42 (2H, br s), 2.68-2.82 (2H, m), 3.22-3.31 (2H, m), 3.49 (2H, s), 4.04 (2H, q, $J = 9.4$ Hz), 7.34 (1H, d, $J = 7.8$ Hz), 7.59-7.62 (1H, m), 7.79 (1H, d, $J = 7.8$ Hz), 7.84 (1H, s), 8.05-8.07 (2H, m), 8.31 (1H, d, $J = 7.8$ Hz), 8.74 (1H, d, $J = 4.7$ Hz); MS (ES+) 522 ([MH]⁺).

Example 5

10 **[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-chlorophenyl)-1,2,4-triazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**

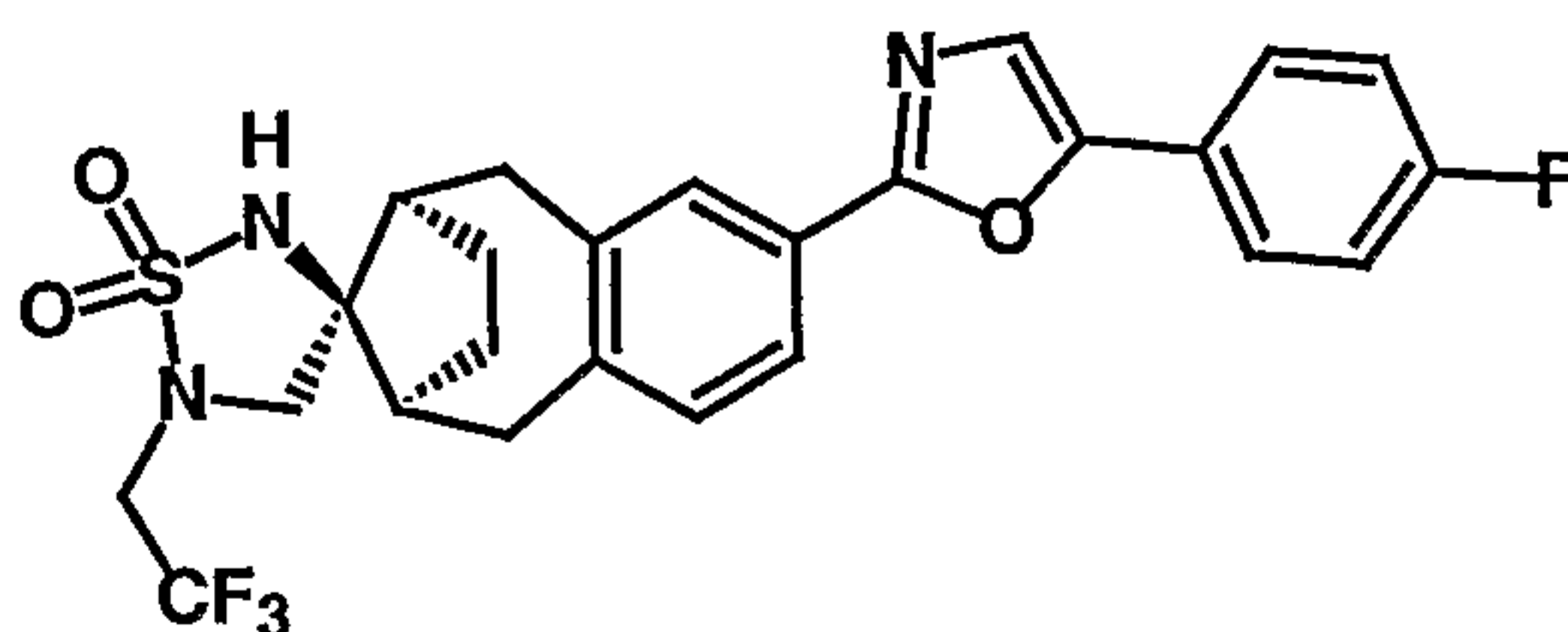


A mixture of the hydrazide from Example 2, Step 1 (0.188 g) and 4-chlorobenzenethiocarboxamide (0.086 g) was heated to 200°C under N₂ for 2 hours. The mixture was cooled and dissolved in dichloromethane (2 mL). Flash column chromatography, eluting with 2% methanol-dichloromethane, then preparative thin layer chromatography, eluting with 40% ethyl acetate-isohexane, gave the triazole (0.026 g, 11%) as a white powder. δ (^1H , 360MHz, CDCl₃) 1.23-1.32 (2H, m), 1.71-1.79 (2H, m), 2.46-2.50 (2H, m), 2.74-2.83 (2H, m), 3.24-3.31 (2H, m), 3.45 (2H, s), 3.70 (2H, q, $J = 9$ Hz), 4.91 (1H, s), 7.22 (1H, d, $J = 8$ Hz), 7.45 (2H, d, $J = 8$ Hz), 7.73-7.78 (2H, m), 8.03 (2H, $J = 8$ Hz). MS (ES+) 540, 538 ([MH]⁺).

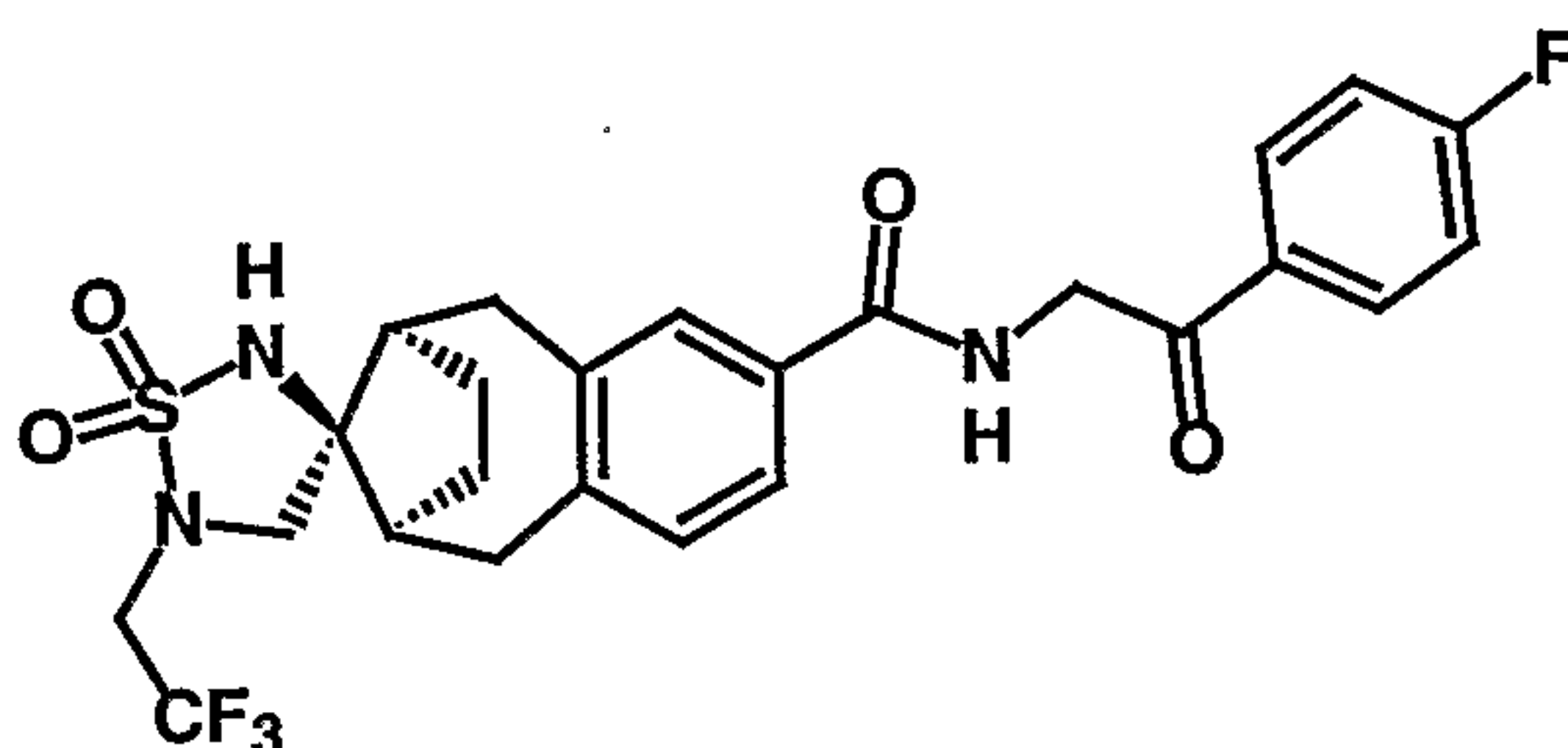
25 Example 6

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-oxazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

- 48 -

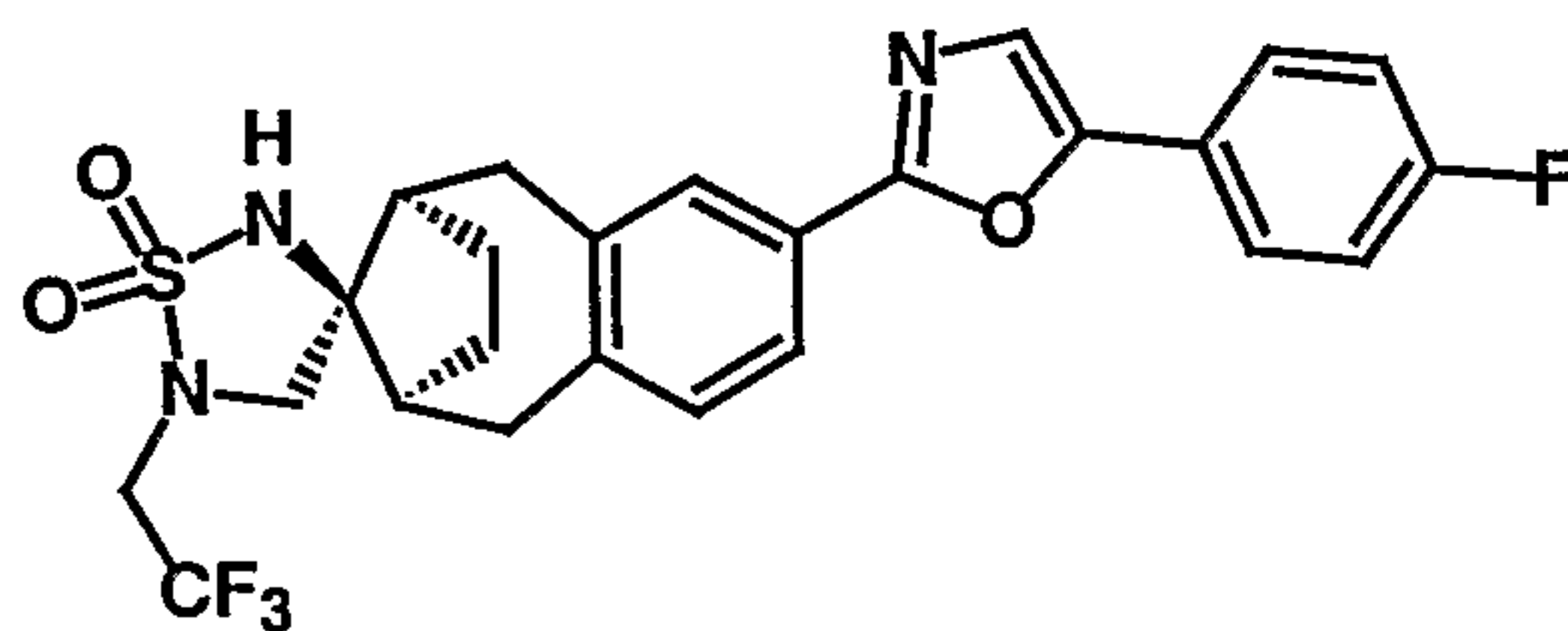


Step 1: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-([2-(4-fluorophenyl)-2-oxo-ethyl]carboxamido) -5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



A mixture of the acid Intermediate A (0.30 g), HBTU (0.34 g), diisopropylethylamine (0.12 mL) and 2'-amino-(4-fluoroacetophenone) hydrochloride (0.16 g) in acetonitrile (5 mL) was stirred at 50°C under nitrogen for 18 hours. The cooled suspension was diluted with water (50 mL) and the yellow solids were collected and rinsed with water and ethyl acetate. The solid was dried under vacuum at room temperature to give the ketoamide as a white powder (0.306 g, 76%). MS (ES+) 357 ([MH]⁺).

Step 2: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-oxazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

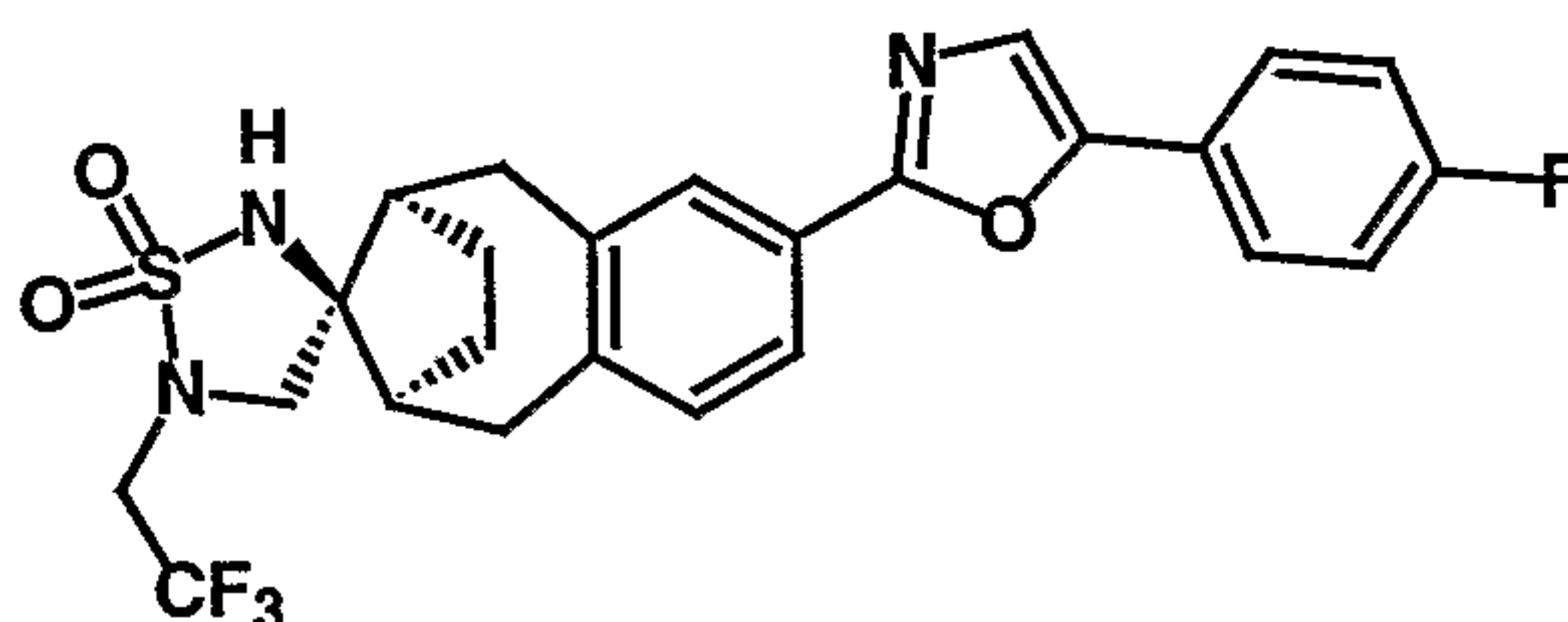


A solution of the ketoamide from Step 1 (0.30 g) and Burgess Reagent (0.30 g) in dry tetrahydrofuran (4 mL) was divided into two portions which were separately heated by microwave irradiation to give an internal temperature of 120°C for 600 seconds. The cooled solutions were combined, diluted with water (20 mL) and extracted with ethyl acetate (2

x 40 mL). The combined extracts were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, eluting with 5% methanol-dichloromethane, gave a yellow foam. Trituration and rinsing with diethyl ether gave the oxazole (0.129 g, 44%) as a pale yellow solid. δ (¹H, 360MHz, d₆-DMSO) 1.03-1.16 (2H, m), 1.55-1.70 (2H, m), 2.41-2.42 (2H, m), 2.66-2.80 (2H, m), 3.07-3.41 (4H, m), 4.04 (2H, q, *J*=9 Hz), 7.29-7.38 (3H, m), 7.79-7.82 (2H, m), 7.86-7.92 (3H, m), 8.07 (1H, s). MS (ES⁺) 522 ([MH]⁺).

10 Example 7

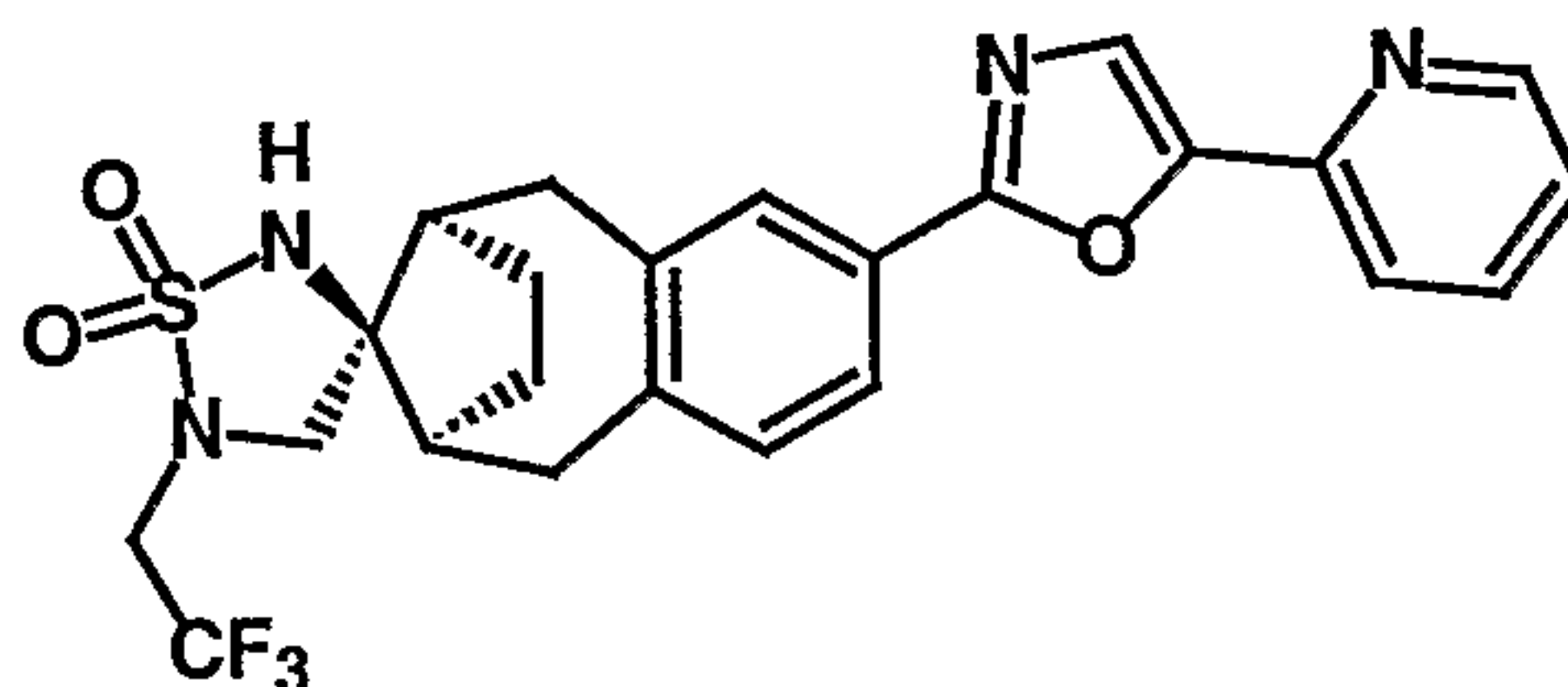
(-)- [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-oxazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



15 Prepared from the homochiral acid, Intermediate B, and 2'-amino-(4-fluoroacetophenone) hydrochloride by the method described for Example 6. MS (ES⁺) 522 ([MH]⁺); [α]_D = -19 (c=0.52, DMSO, 23°C).

Example 8

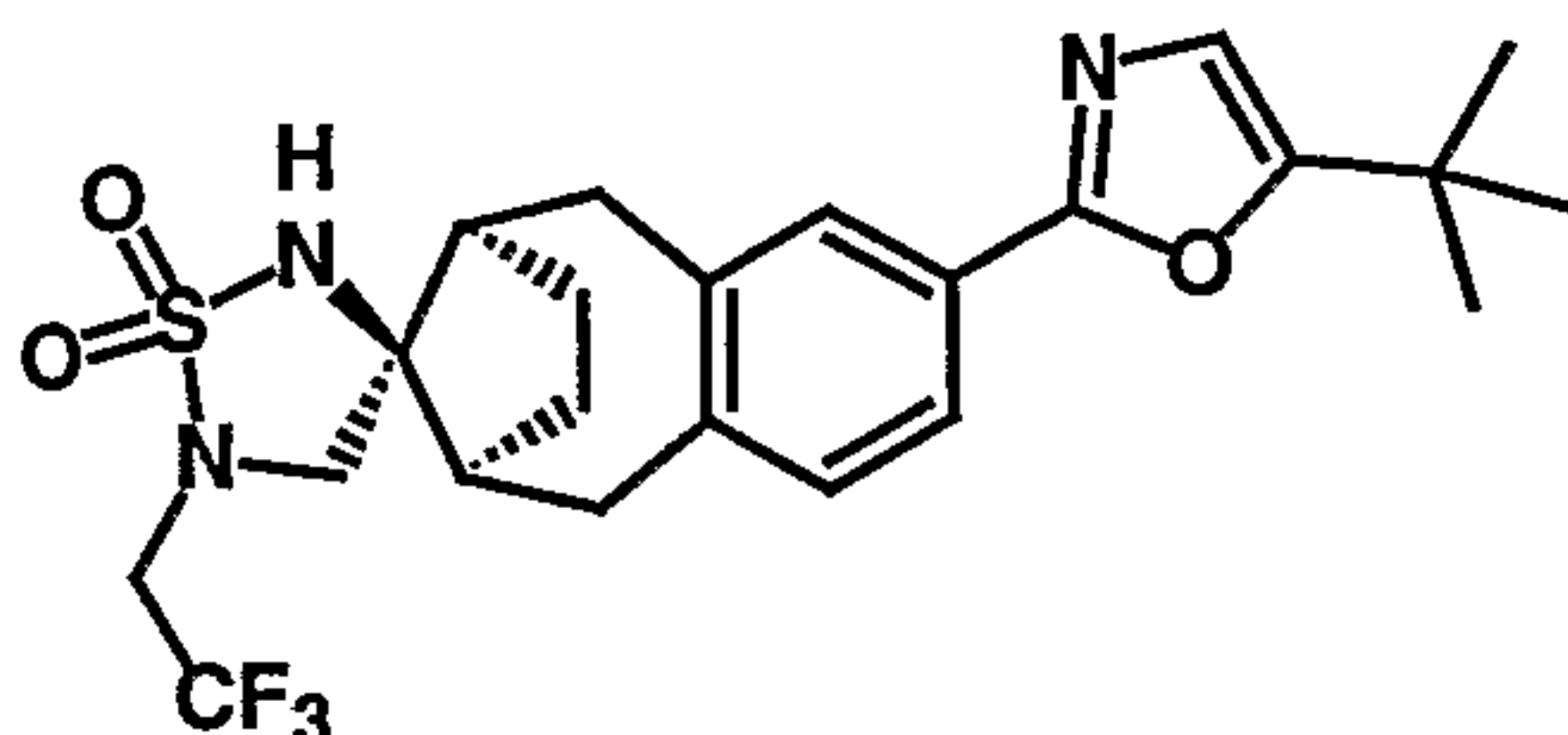
20 [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2-pyridyl)-oxazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.



Prepared from the acid, Intermediate A, and 2-amino-1-(2-pyridyl)-1-ethanone dihydrochloride by the method described for Example 6. MS (ES⁺) 505 ([MH]⁺).

Example 9

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(1,1-dimethyl-1-ethyl)-oxazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



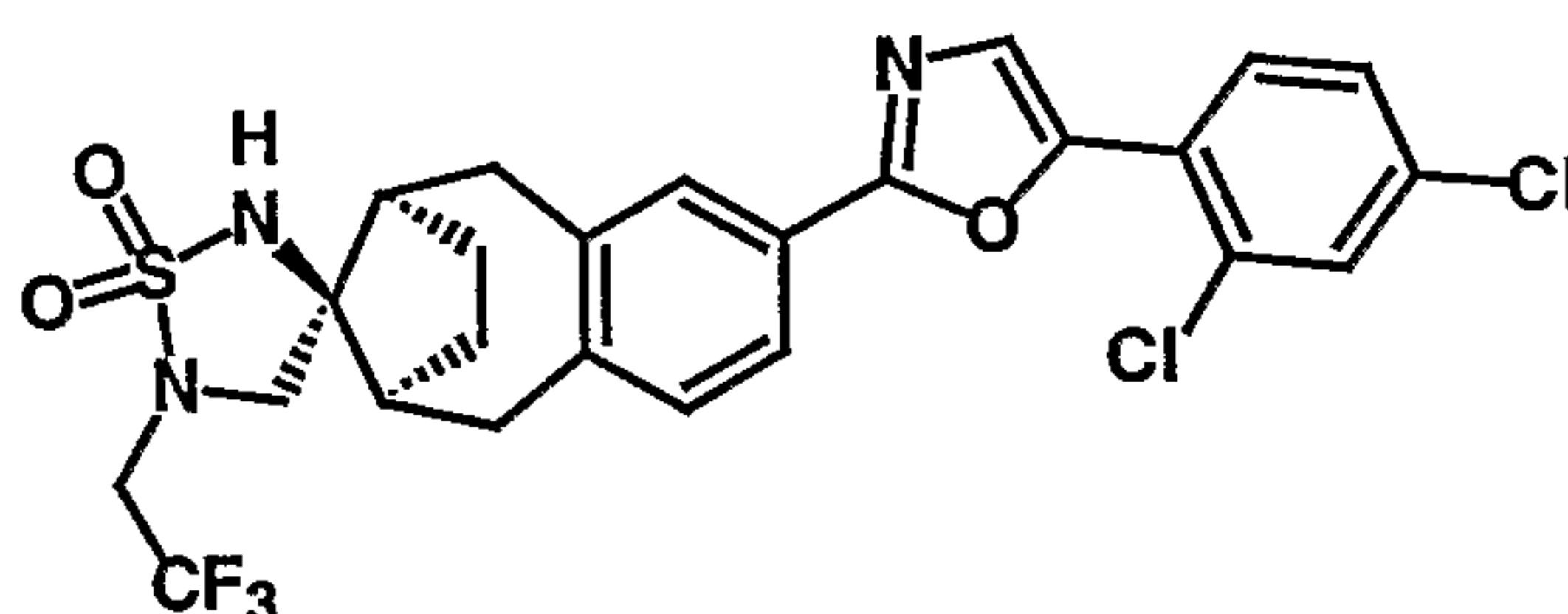
Prepared from the acid, Intermediate A, and 1-amino-3,3-dimethyl-2-butanone hydrochloride by the method described for Example 6. MS (ES+) 484 ([MH]⁺).

10

Example 10

(-)-[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2,4-dichlorophenyl)-oxazol-2-yl)-5'-(2,2,2-trifluoroethyl)spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

15



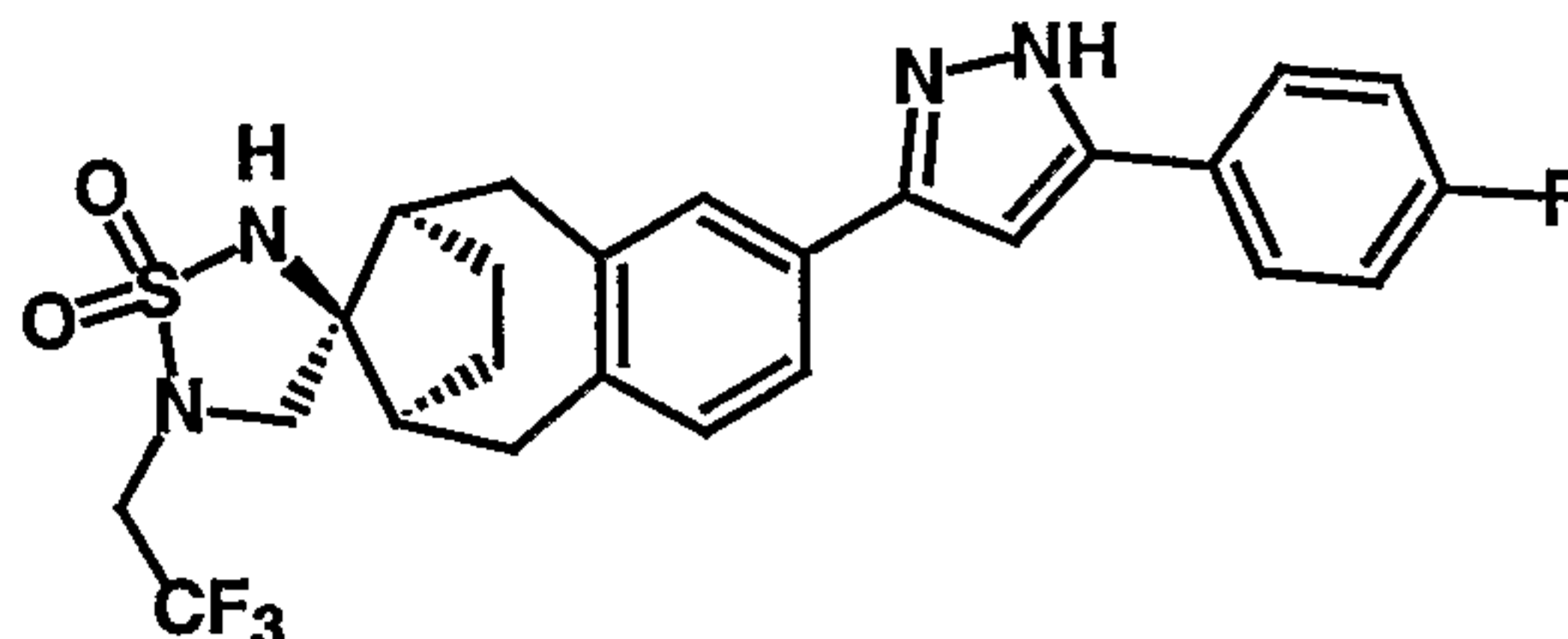
Prepared in the same way as Example 6 using 0.25 g of the acid, Intermediate B, and 2'-amino-(2,4-dichloroacetophenone) to give the title compound (0.032 g, 9% over 2 steps).

20 MS (ES+) 572, 574, 575 ([MH]⁺).

$\alpha_D -20$ (c=0.57, DMSO).

Example 11

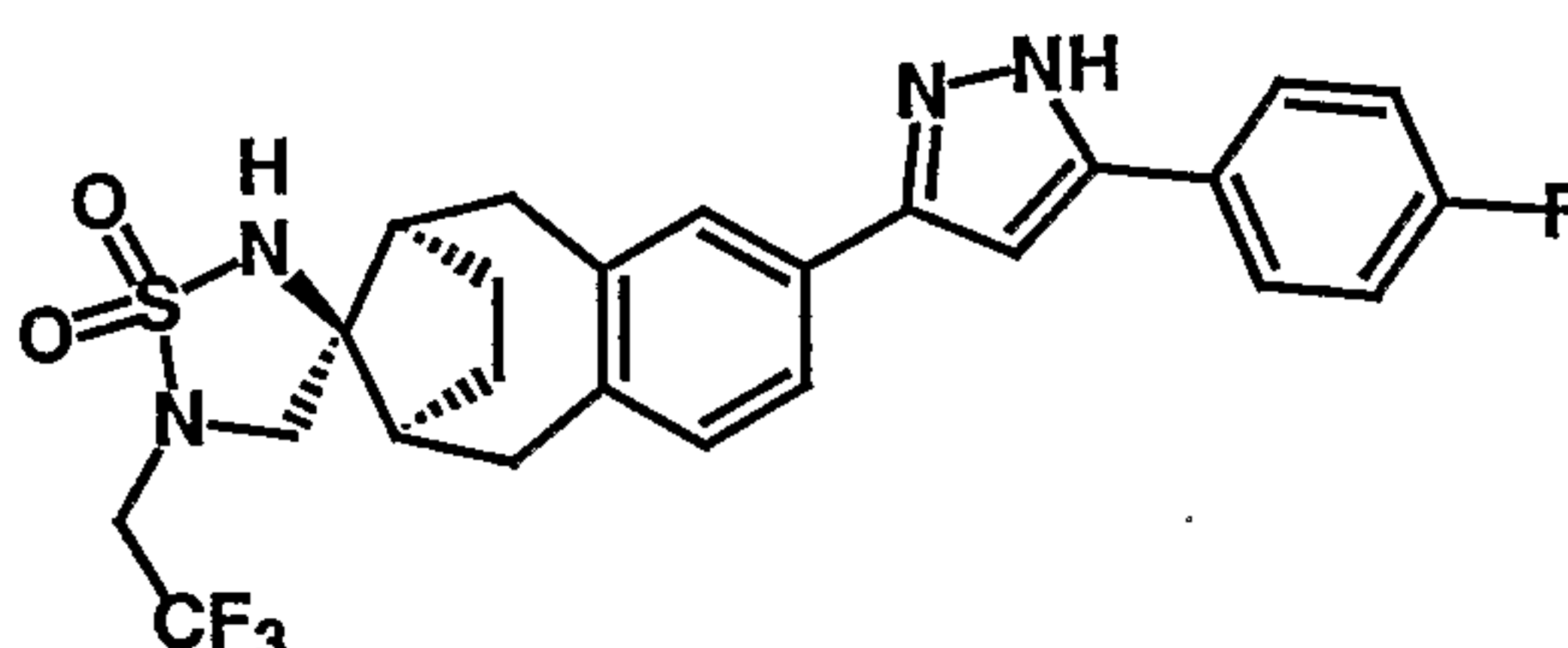
[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1H-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



- 5 A solution of the acid, Intermediate A (0.179 g) and 1,1'-carbonyldiimidazole (0.080 g) in dry tetrahydrofuran (3 ml) was stirred at room temperature under N₂ for 1.5 hours. A solution of lithium diisopropylamide in dry tetrahydrofuran (3 mL) was prepared from n-butyllithium (1.6M in hexanes, 0.90 mL) and diisopropylamine (0.20 mL)
- 10 at -78°C under N₂. 4'-Fluoroacetophenone (0.17 mL) was added dropwise to the stirred solution of lithium diisopropylamide at -78°C. After 1 hour, the imidazolide solution was added in a single portion to the enolate solution at -78°C. The white suspension was immediately warmed to room temperature. After 2.5 hours, the solution was diluted with 1M
- 15 aqueous citric acid (20 mL) and extracted with ethyl acetate (30 mL). The extract was dried, filtered and concentrated. Flash column chromatography on silica gel, eluting with 20% ethyl acetate – hexanes, gave partially purified β-diketone (0.15 g) as a pink foam. The material was redissolved in ethanol (3 mL) with hydrazine hydrate (0.5 mL) and
- 20 refluxed under N₂ for 7 hours. The solution was cooled, poured into water (30 mL) and extracted with dichloromethane (2 x 15 mL). The extracts were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, eluting with 98:2 then 95:5 dichloromethane – methanol, gave the pyrazole as white powder (0.053 g, 23%). δ (¹H, 360MHz, CDCl₃)
- 25 1.33-1.36 (2H, m), 1.70-1.75 (2H, m), 2.43-2.49 (2H, m), 2.67-2.75 (2H, m), 3.23-3.27 (2H, m), 3.44 (2H, s), 3.49 (1H, s), 3.70 (2H, q, *J*=9 Hz), 5.20 (1H, s), 6.77 (1H, s), 7.11-7.16 (3H, m), 7.42-7.44 (2H, m), 7.70 (2H, dd, *J*=9, 5 Hz); MS (ES⁺) 521 ([MH]⁺).

Example 12

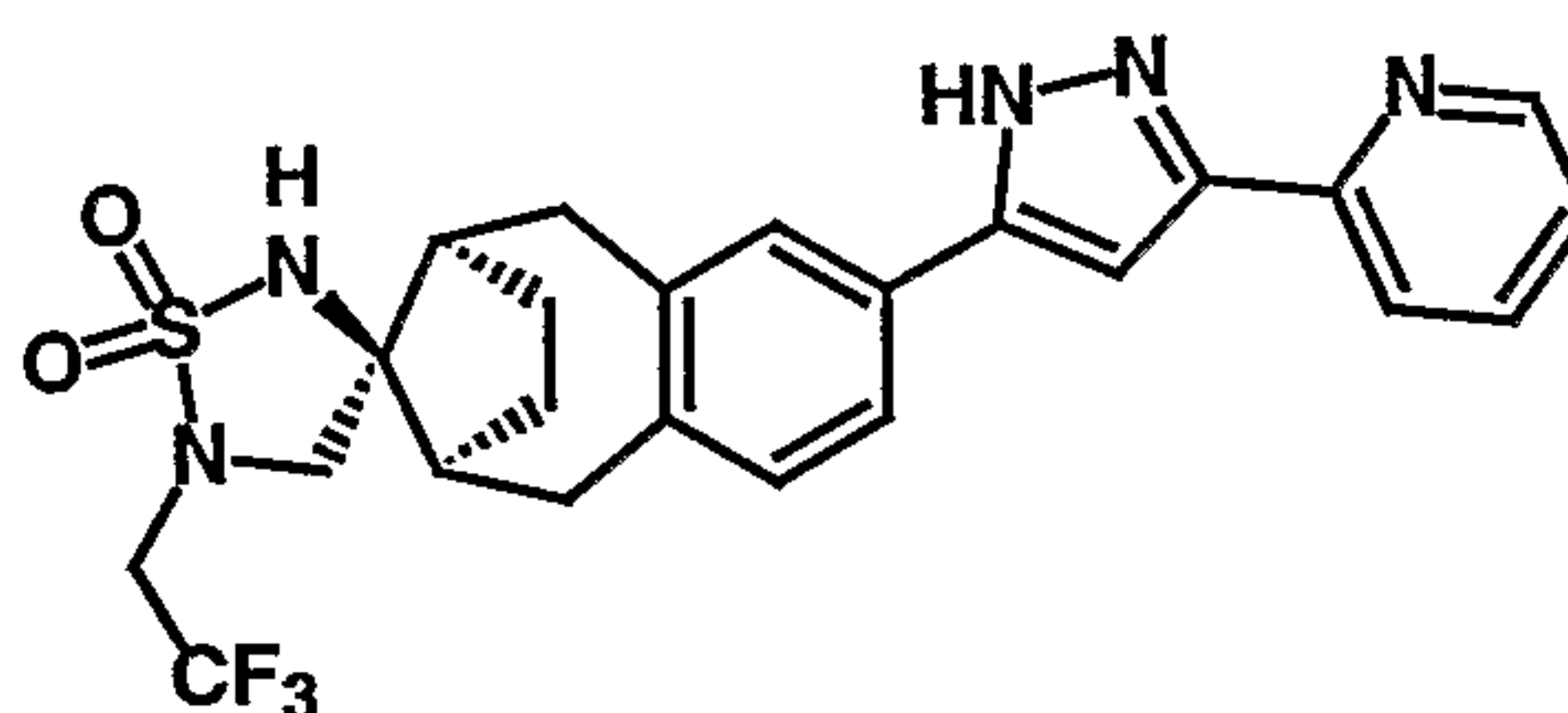
[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1H-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



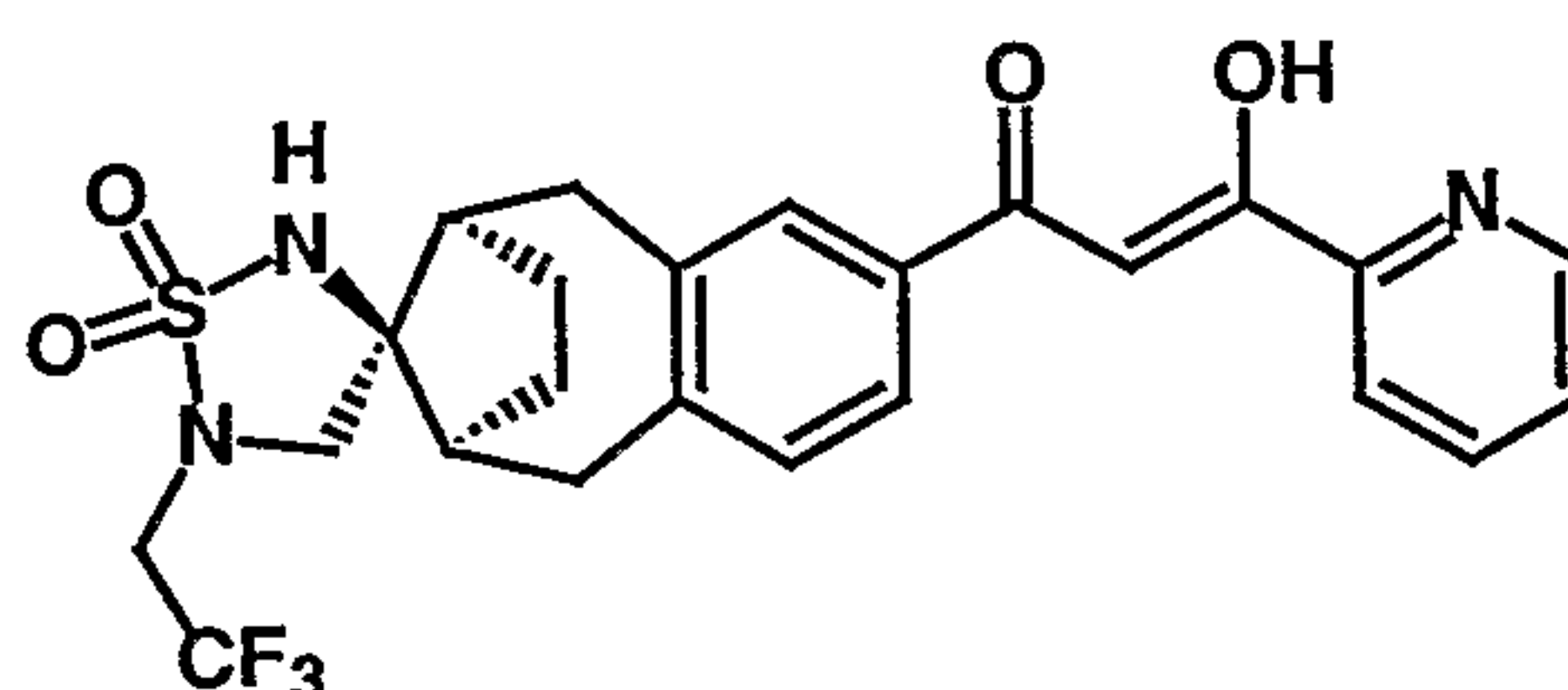
The racemic pyrazole from Example 11 was resolved by supercritical fluid chromatographic separation on a Chiralcel OD column using 35% methanol - sc-CO₂ as eluant at 35°C, 100 bar, 50 mL/min and UV detection at 250 nm. The first eluted compound under these conditions was the title compound (98%ee). MS (ES⁺) 521 ([MH]⁺).

Example 13

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(2-pyridyl)-1H-pyrazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Step 1 : [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(pyrid-2-yl)-propane-1,3-dione)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

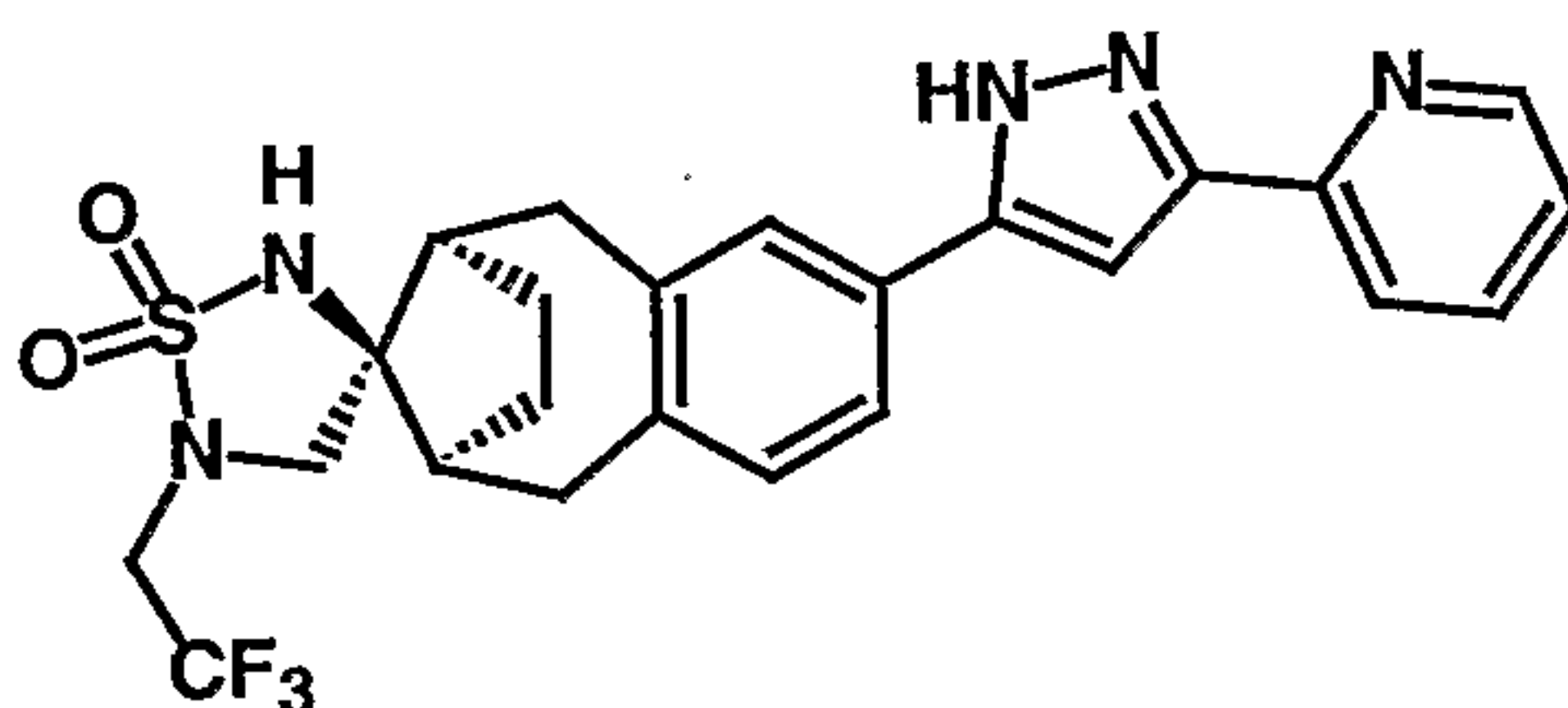


1,1'-Carbonyldiimidazole (51 mg) was added to a solution of Intermediate A (115 mg) in THF (3 mL) and the mixture stirred for 1 h. Meanwhile,

- 53 -

lithium bis(trimethylsilyl)amide solution (0.85 mL of a 1M solution in THF) was added to a solution of 2-acetylpyridine (96 μ L) in THF (2 mL) at -78°C . After the enolate solution had been stirred for 1 h, to it was added the imidazolidine solution (+ 1 mL washing) *via* syringe. The mixture was stirred overnight, warming to ambient temperature. The reaction was quenched by addition of satd. $\text{NH}_4\text{Cl}_{(\text{aq})}$, then diluted with water and ethyl acetate. The layers were separated and the aqueous phase extracted a second time with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO_4) and concentrated. Chromatography on silica eluting with 1 to 2 to 5% methanol in dichloromethane provided the diketone contaminated with 2-acetylpyridine.

Step 2 : [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(2-pyridyl)-1H-pyrazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



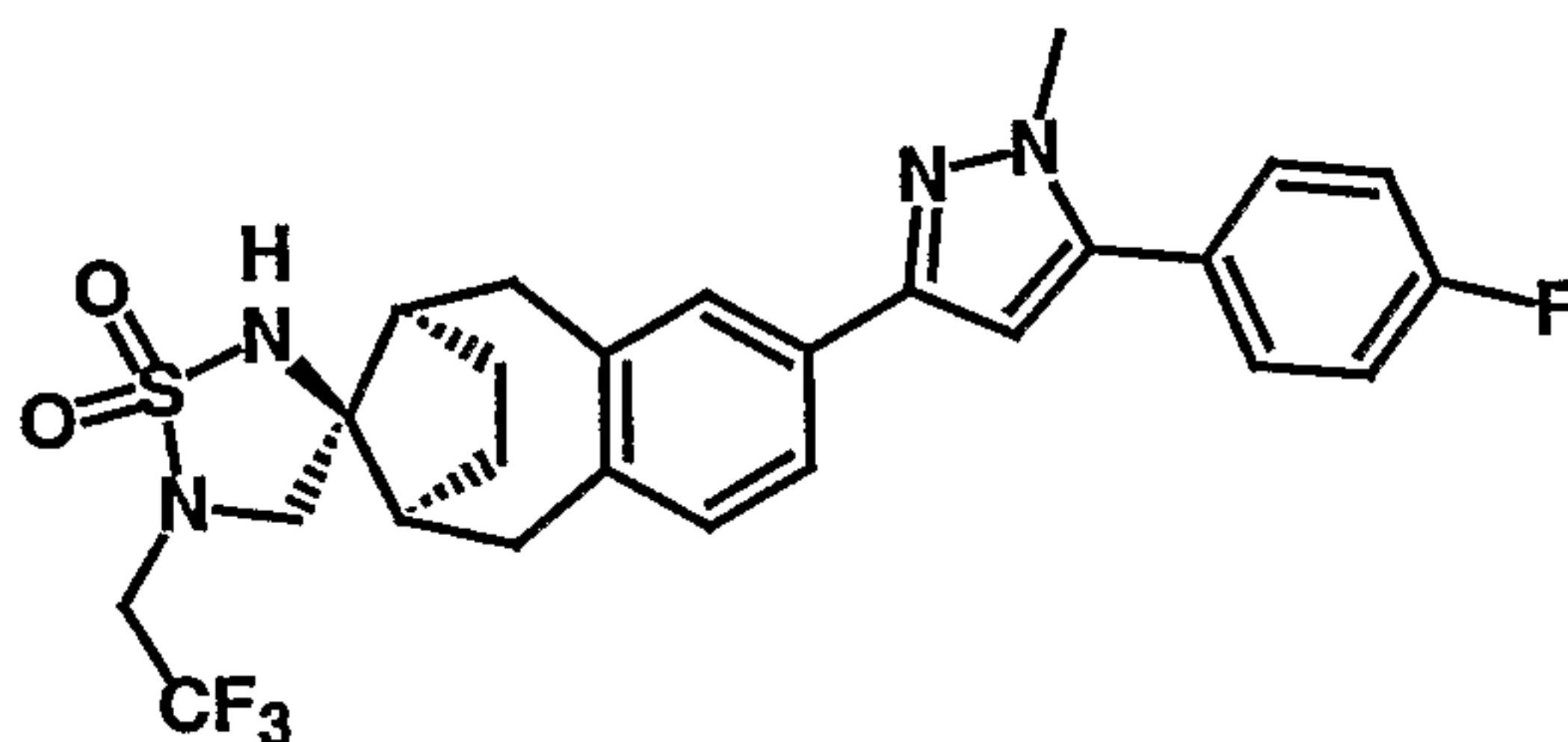
To a suspension of the semi-crude diketone (123 mg) in ethanol (5 mL) was added hydrazine solution (2.4 mL of a 1M solution in THF). The mixture was heated for 4 h at which time thin-layer chromatography indicated incomplete reaction. Further hydrazine solution (2.4 mL of a 1M solution in THF) was added and the mixture heated at reflux for 2h. The solvent was removed *in vacuo* and the residue partitioned between water and ethyl acetate. The layers were separated and the organic phase washed sequentially with 10% citric acid solution, water and brine before being dried (MgSO_4) and concentrated. Purification by trituration with dichloromethane provided the title compound. δ (^1H , 400MHz, d_6 -DMSO) 1.09-1.11 (2H, m), 1.70-1.72 (2H, m), 2.38-2.40 (2H, m), 2.59-2.69 (2H, m), 3.18-3.32 (2H, m), 3.48 (2H, s), 3.99-4.06 (2H, m), 7.19 (1H, br d, J

- 54 -

δ 7.8 Hz), 7.26 (1H, br s), 7.34 (1H, br s), 7.56 (1H, br d, J = 7.7 Hz), 7.61 (1H, s), 7.88 (2H, br s), 8.03 (1H, s), 8.61 (1H, br s); MS (ES+) 504 ([MH]⁺).

Example 14

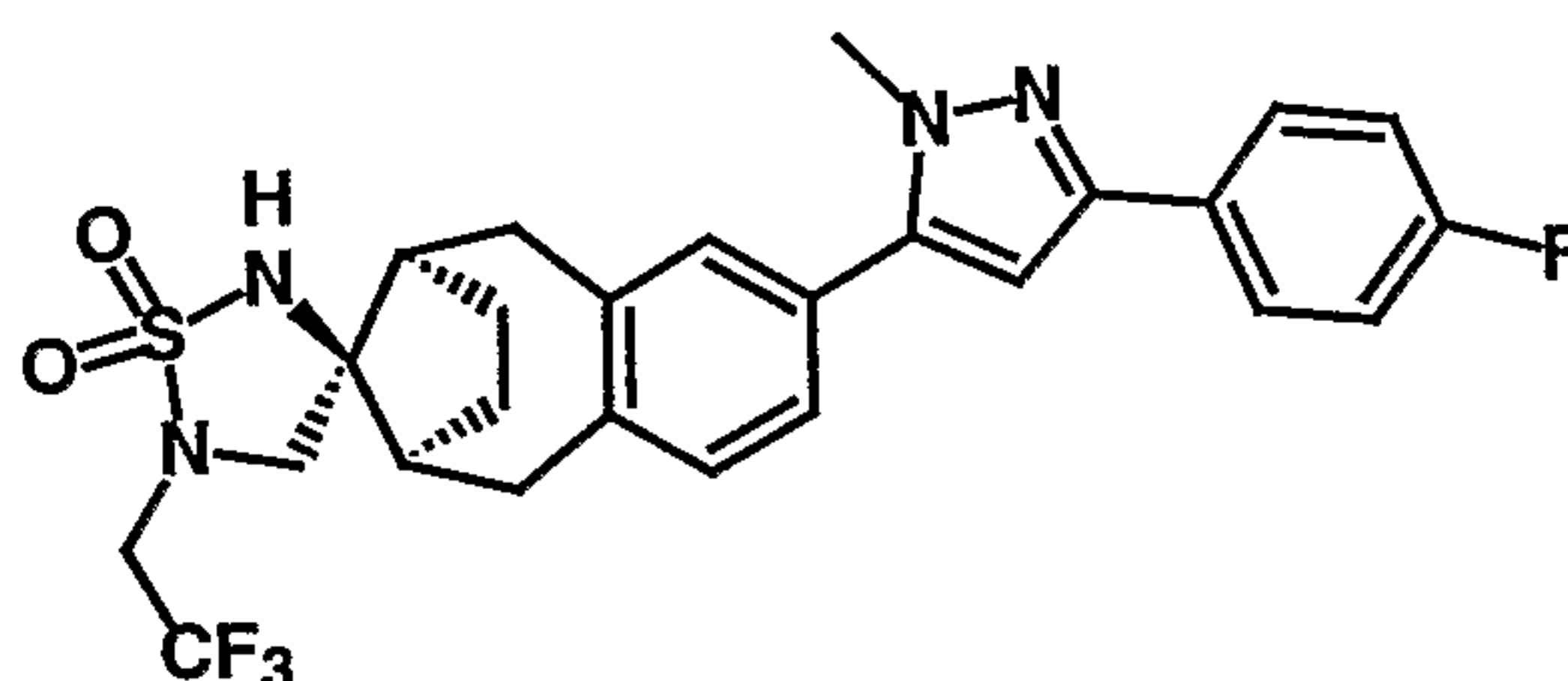
- 5 **[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**



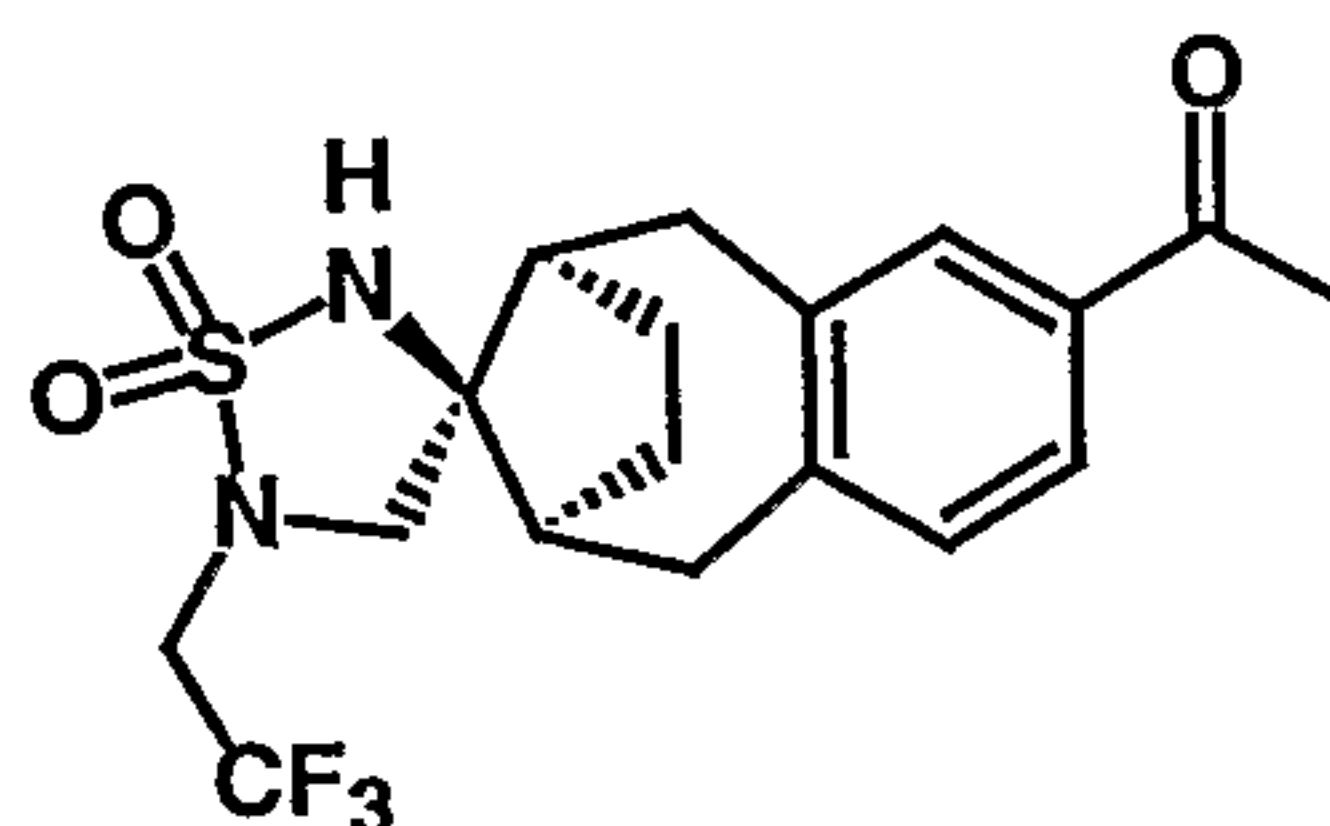
and

10 **Example 15**

- [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(4-fluorophenyl)-1-methyl-pyrazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**



- 15 Step 1: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-acetyl-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

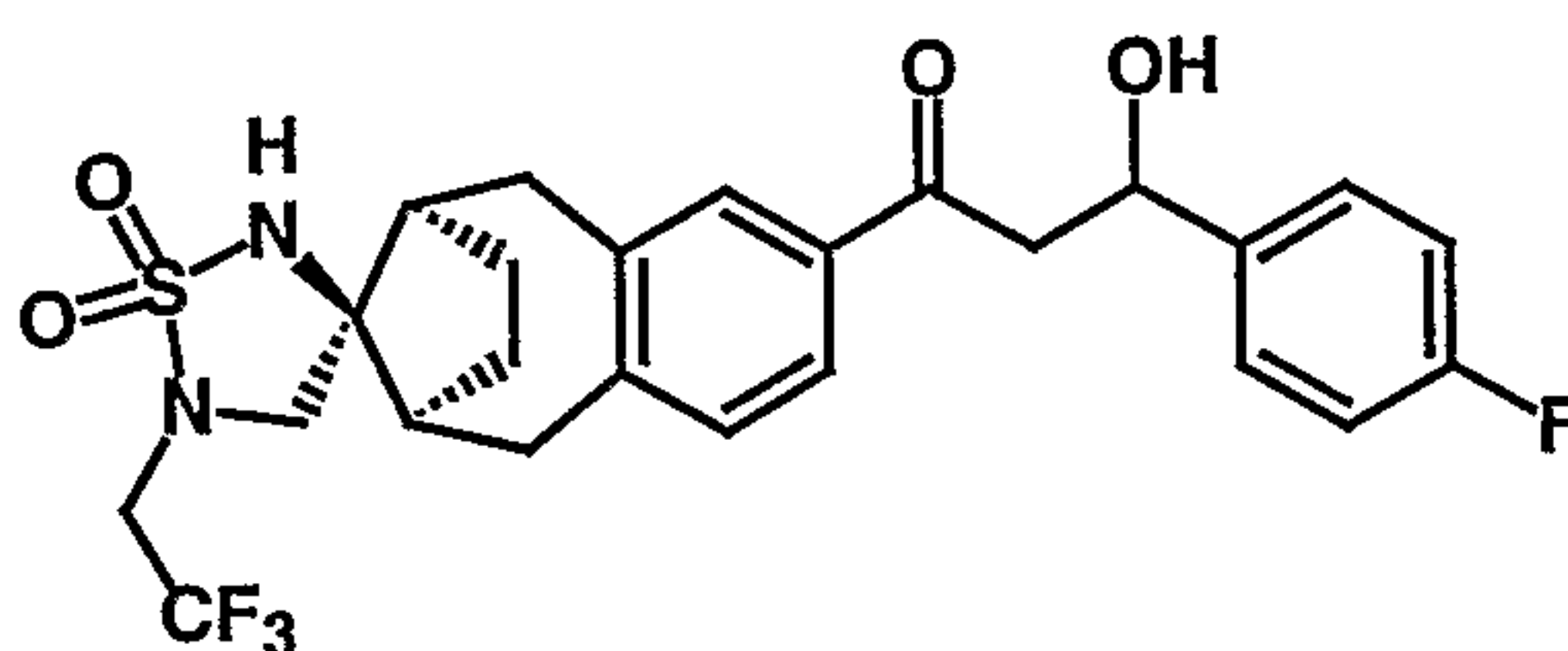


- 20 To a de-gassed solution of Intermediate E (0.5 g) in DMF (5 mL) in a tube was added tributyl(1-ethoxyvinyl)tin (0.40 mL) followed by lithium chloride (125 mg), triphenylphosphine (31 mg) and palladium (II) acetate (13 mg). The tube was sealed and heated at 100°C for 3 h. The cooled

- 55 -

mixture was diluted with 1M HCl_(aq) (30 mL) and extracted with ethyl acetate (70 mL). The organic extract was dried (Na₂SO₄) and concentrated. Chromatography on silica eluting with 20 to 40% ethyl acetate in hexane provided the methyl ketone as a white foam (332 mg, 84% yield). δ (¹H, 400MHz, CDCl₃) 1.24-1.31 (2H, m), 1.72-1.76 (2H, m), 2.48-2.50 (2H, m), 2.58 (3H, s), 2.76-2.83 (2H, m), 3.22-3.29 (2H, m), 3.43 (1H, d, J = 9.4 Hz), 3.46 (1H, d, J = 9.4 Hz), 3.69 (2H, q, J = 8.7 Hz), 4.68 (1H, s), 7.19-7.21 (1H, m), 7.70-7.72 (2H, m).

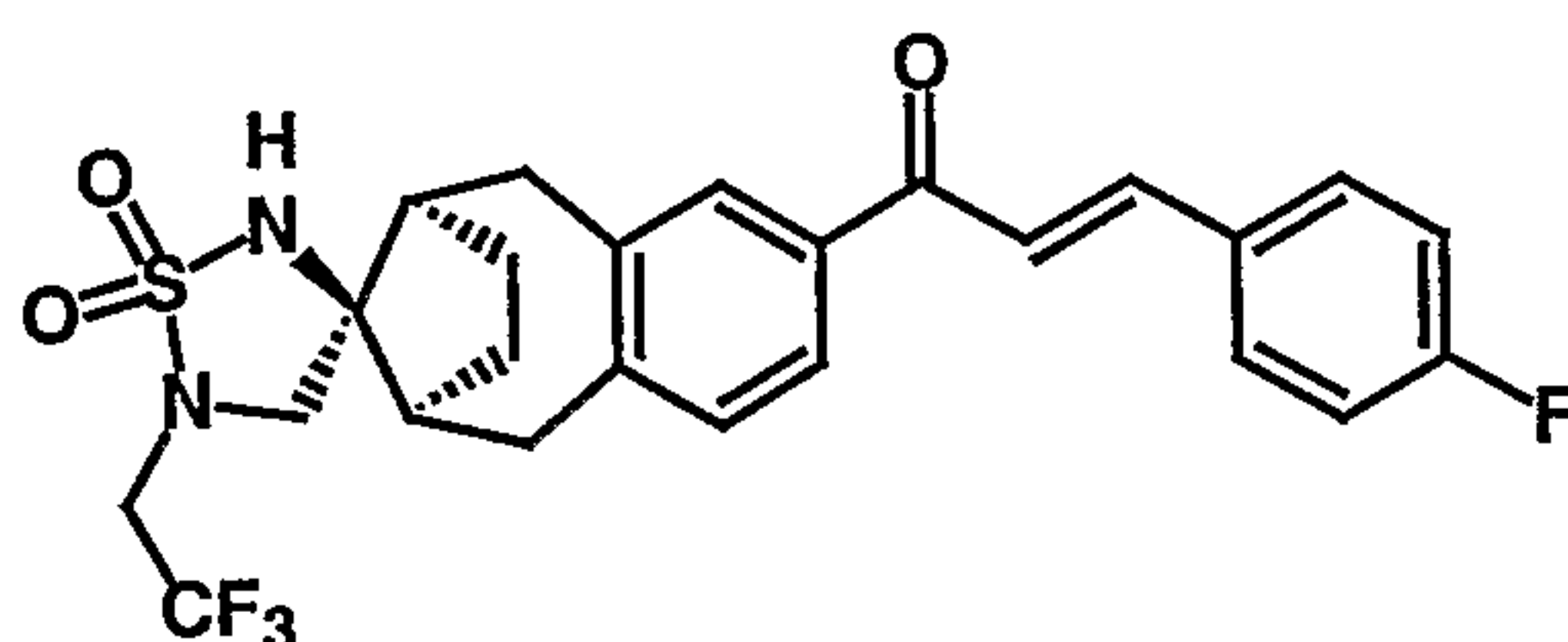
Step 2: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-[4-fluorophenyl]-3-hydroxy-propan-1-one)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Lithium bis(trimethylsilyl)amide solution (1.7 mL of a 1M solution in THF) was added dropwise to a solution of the ketone from Step 1 (325 mg) in THF (4 mL) at -78°C . After 30 min, 4-fluorobenzaldehyde (0.13 mL) was added dropwise. The reaction mixture was stirred for 2.5 h at -78°C , then quenched by addition of satd. NH₄Cl_(aq). The mixture was diluted with water and extracted into ethyl acetate (X2). The combined organic extracts were dried (MgSO₄) and concentrated. Chromatography on silica eluting with 10 to 20 to 40% ethyl acetate in hexane afforded the aldol adduct (364 mg, 86% yield) as a white foam. δ (¹H, 400MHz, CDCl₃) 1.22-1.27 (2H, m), 1.69-1.74 (2H, m), 2.45-2.50 (2H, m), 2.70-2.78 (2H, m), 3.22-3.32 (4H, m), 3.42 (1H, d, J = 9.4 Hz), 3.45 (1H, d, J = 9.4 Hz), 3.66-3.72 (3H, m), 5.29-5.33 (2H, m), 7.02-7.07 (2H, m), 7.18 (1H, d, J = 7.8 Hz), 7.39-7.42 (2H, m), 7.66-7.69 (2H, m).

- 56 -

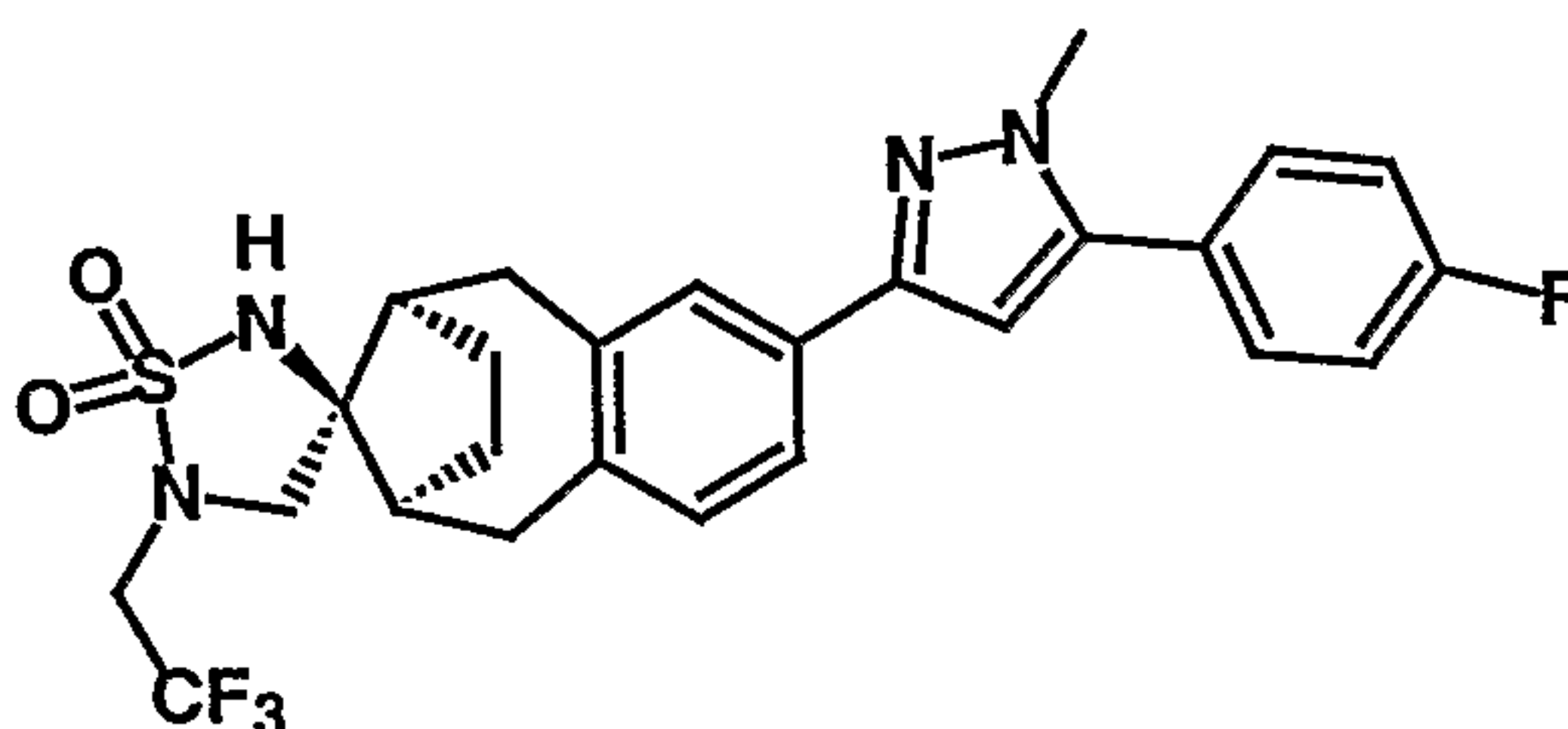
Step 3: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-[4-fluorophenyl]-propenone)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



5 To a solution of the aldol adduct from Step 2 (364 mg) in acetonitrile (10 mL) was added cerium(III) chloride heptahydrate (0.39 g). To the resulting suspension was added sodium iodide (0.16 g) and the reaction mixture was stirred at reflux for 20 h. The mixture was allowed to cool and partitioned between 0.5 M HCl_(aq) and ethyl acetate. The layers were
10 separated and the organic phase washed with satd. NaHCO_{3(aq)} (X2) and then brine before being dried (Na₂SO₄) and concentrated.

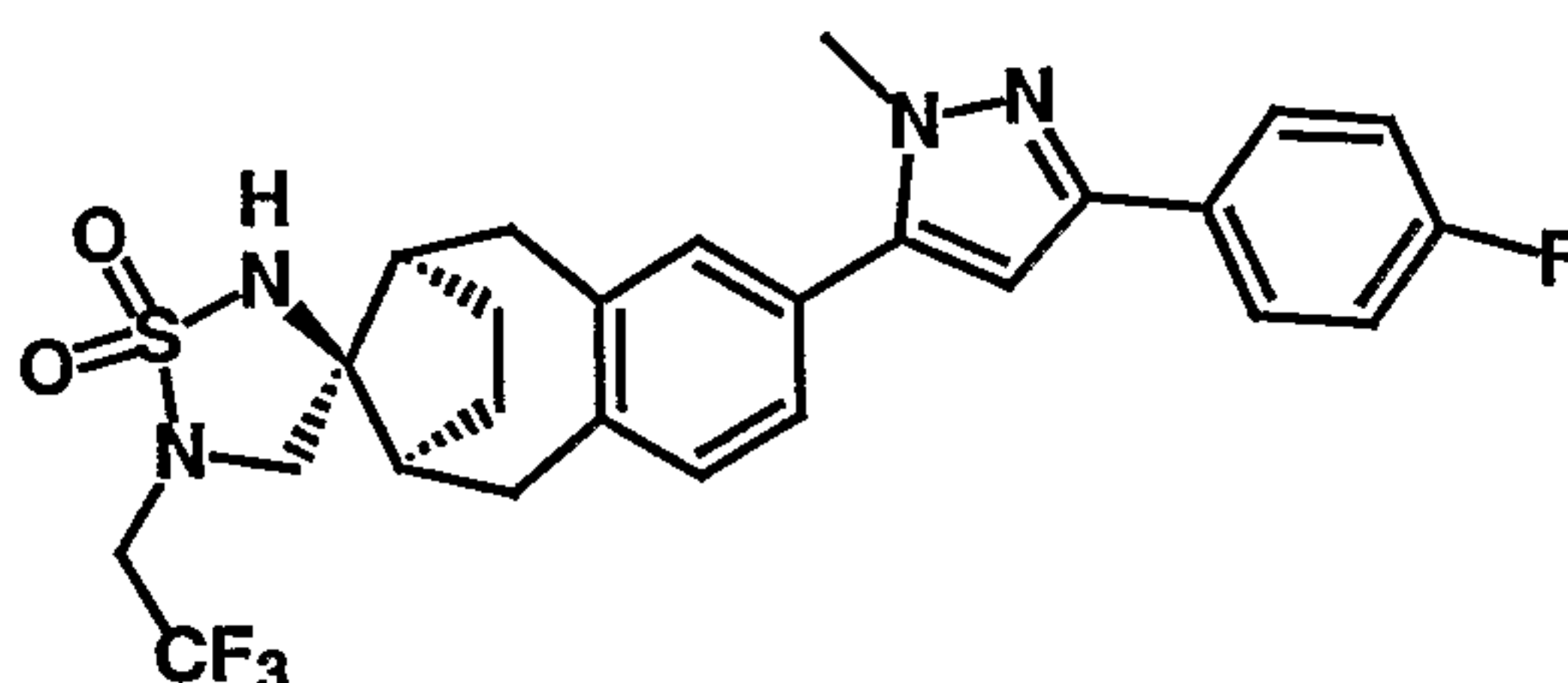
Chromatography on silica eluting with 15 to 20 to 30% ethyl acetate in hexane provided the enone (242 mg, 69% yield). δ (¹H, 400MHz, CDCl₃) 1.30-1.37 (2H, m), 1.73-1.77 (2H, m), 2.50-2.51 (2H, m), 2.78-2.87 (2H, m),
15 3.26-3.32 (2H, m), 3.44 (1H, d, *J* = 9.3 Hz), 3.47 (1H, d, *J* = 9.3 Hz), 3.69 (2H, q, *J* = 8.7 Hz), 4.77 (1H, s), 7.10-7.14 (2H, m), 7.24 (1H, d, *J* = 8.0 Hz), 7.45 (1H, d, *J* = 15.7 Hz), 7.63-7.66 (2H, m), 7.76-7.80 (3H, m).

Step 4 [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



and

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(4-fluorophenyl)-1-methyl-pyrazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



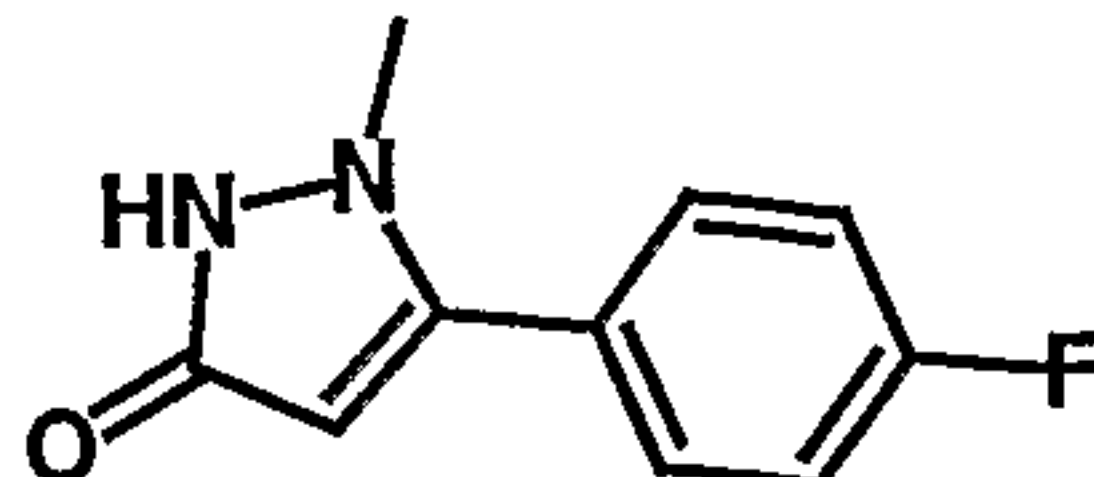
5 Methyl hydrazine (30 μ L) was added to a suspension of the enone from Step 3 (185 mg) in ethanol (15 mL) under nitrogen. The mixture was stirred at room temperature overnight, during which time the material went into solution. The mixture was concentrated *in vacuo*.

To a solution of the residue in THF (4 mL) was added 2,3-dichloro-5,6-
 10 dicyano-1,4-benzoquinone (124 mg) and the resulting suspension was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate and washed with satd. $\text{NaHCO}_3(\text{aq})$ (X2) and then brine before being dried (MgSO_4) and concentrated. Chromatography on silica afforded a 5:1 mixture of N-Me pyrazole isomers (167 mg, 86% yield). The isomers
 15 were separated by preparative HPLC using an acetonitrile/aqueous buffer gradient system.

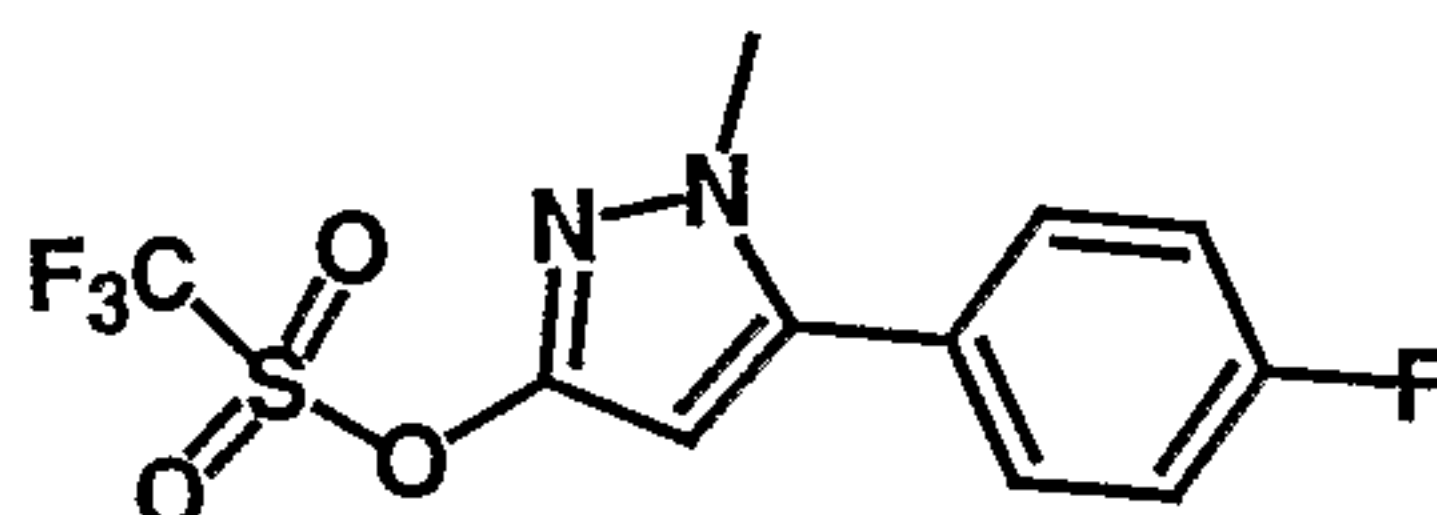
The first eluted compound, the major isomer, was the title compound

Example 14. δ (^1H , 400MHz, CDCl_3) 1.33-1.43 (2H, m), 1.69-1.73 (2H, m), 2.46 (2H, br s), 2.69-2.83 (2H, m), 3.19 (1H, d, $J=3.7\text{Hz}$), 3.25 (1H, d, $J=3.7\text{Hz}$), 3.44 (2H, s), 3.68 (2H, q, $J = 8.7 \text{ Hz}$), 3.90 (3H, s), 4.68 (1H, s), 6.56 (1H, s), 7.12-7.20 (3H, m), 7.41-7.45 (2H, m), 7.54 (1H, d, $J = 8.0 \text{ Hz}$), 7.60 (1H, s); MS (ES+) 535 ($[\text{MH}]^+$).

The minor regioisomer, Example 15, was isolated by preparative HPLC and was the second eluted compound. δ (^1H , 400MHz, CDCl_3) 1.36-1.41
 25 (2H, m), 1.76-1.79 (2H, m), 2.50 (2H, br m), 2.73-2.81 (2H, m), 3.25-3.31 (2H, m), 3.46 (2H, s), 3.70 (2H, q, $J = 8.7 \text{ Hz}$), 3.92 (3H, s), 4.67 (1H, br s), 6.54 (1H, s), 7.09 (2H, t, $J = 8.7 \text{ Hz}$), 7.20-7.24 (3H, m), 7.77-7.80 (2H, m); MS (ES+) 535 ($[\text{MH}]^+$).

Alternative route to Example 14**Step 1 5-(4-Fluorophenyl)-1-methyl-1,2-dihydropyrazol-3-one**

- 5 To a solution of methyl 4-(fluorophenyl)propynoate (J. Org. Chem. (1987), 52(16), 3662-8) (13g, 73mmol) in methanol (60ml) was added water (60ml) followed by methylhydrazine (4ml, 77mmol), the mixture was stirred for 6hrs at 60°C then left to stand overnight. The solid was filtered and washed with water then a minimum volume of methanol and dried
- 10 overnight, affording 7.7g of pure product (55%). δ (^1H , 500MHz, CDCl_3) 3.68 (3H, s), 5.68 (1H, s), 7.13-7.17 (2H, m), 7.37-7.40 (2H, m).

Step 2 Trifluoromethanesulfonic acid 5-(4-fluorophenyl)-1-methyl-1H-pyrazol-3-yl ester

- 15 To a cooled suspension of 5-(4-fluorophenyl)-1-methyl-1,2-dihydropyrazol-3-one (15.5g, 81 mmol) in dry pyridine (100ml) was added in three portions trifluoromethanesulfonic anhydride (24g, 85 mmol) maintaining the temperature below 5°C. After addition the cooling bath was removed and
- 20 the reaction was stirred for two hours before pouring into 2M hydrochloric acid and extracting into ethyl acetate. The organic layer was washed with brine, saturated sodium hydrogen carbonate, and dried (sodium sulphate), filtered and evaporated to yield a residue which was dissolved in toluene and evaporated and then dissolved in isohexane and filtered through a
- 25 plug of silica, eluting with dichloromethane. The solvent was evaporated to yield product as a colourless oil (23.4g, 89%) δ (^1H , 500MHz, CDCl_3) 3.80 (3H,s), 6.14 (1H, s), 7.15-7.19 (2H, m), 7.38-7.42 (2H, m).

Step 3

The homochiral boronate from Example 24 Step 1 (10.9g, 22.42 mmol) and the triflate from the above Step 2 (10.9g, 33.6 mmol) in THF (112 ml) were treated with 33.6ml of 2M sodium carbonate and LiCl (2.85 g, 66 mmol).

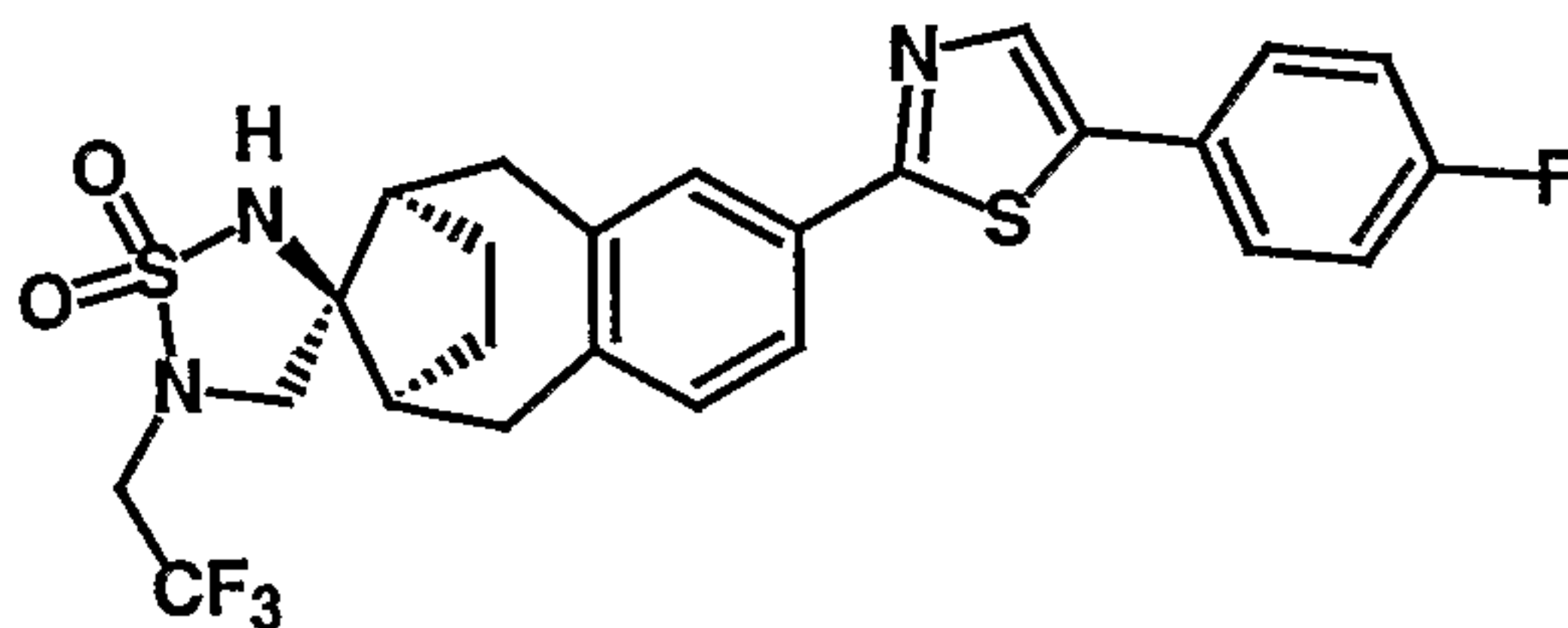
- 5 The reaction mixture was degassed using a flow of nitrogen, *tetrakis*(triphenylphosphine)palladium(0) (560mg, 0.56 mmol) was added, and the reaction was heated to reflux for 16 hours. The reaction was cooled, diluted with ethyl acetate and was washed with water, dried (sodium sulphate), filtered and evaporated. The residue was purified by
- 10 column chromatography on silica eluting with 25% ethyl acetate/isohexane. The product obtained was crystallized from ethanol and then evaporated from dichloromethane (x 3) and dried at 60° C to yield 6.5g of product. ¹H nmr and mass spectrometry data as before.

A portion of this product was dissolved in excess diethyl ether.

- 15 Isohexane was added and the solution was allowed to stand for several hours to form crystals. These were filtered and dried to give a white crystalline solid containing flat rectangular platelike crystals ranging from 2 to 226 micrometers with an average size of *ca.* 41 micrometers. DSC gave an onset of melting at 185° C with a peak at 188° C. Found: C, 58.29; H, 4.90; N, 10.48 C₂₆H₂₆F₄N₄O₂S requires C, 58.42; H, 4.90; N, 10.48.
- 20

Example 16

- [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.
- 25



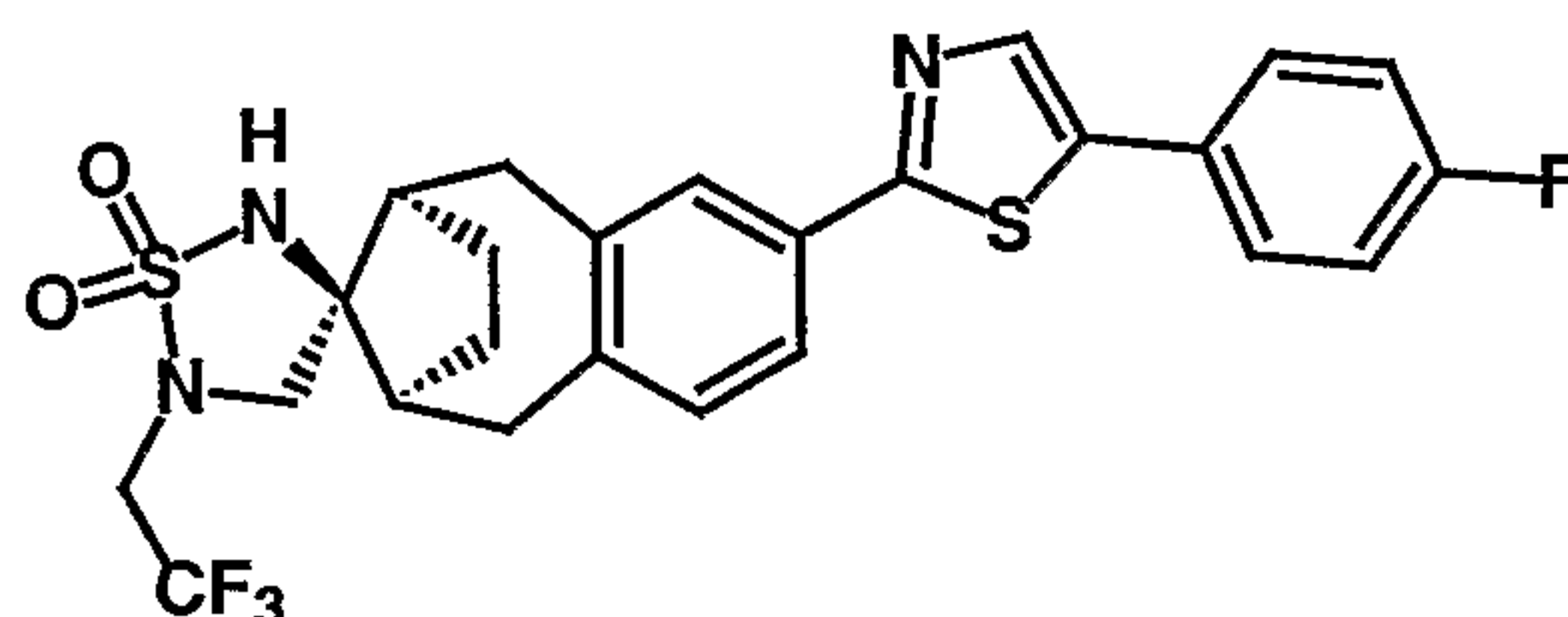
A solution of the ketoamide from Example 6, Step 1 (0.10 g) and Lawesson's reagent (0.15 g) in toluene (3 mL) was refluxed under N₂ for 18

- 60 -

hours. The mixture was cooled, absorbed onto silica gel and evaporated to dryness. Flash column chromatography, eluting with 97:3 dichloromethane – methanol, then preparative thin-layer chromatography, eluting with 98:2 dichloromethane – methanol, gave the thiazole as a pale yellow solid (0.030 g, 30%). δ (^1H , 360MHz, CDCl_3) 1.32-1.43 (2H, m), 1.68-1.78 (2H, m), 2.45-2.51 (2H, m), 2.73-2.85 (2H, m), 3.24-3.28 (2H, m), 3.45 (2H, s), 3.69 (2H, q, $J=9$ Hz), 4.66 (1H, s), 7.12 (2H, dd, $J=9$, 9 Hz), 7.19 (1H, d, $J=8$ Hz), 7.55-7.59 (2H, m), 7.68 (1H, d, $J=8$ Hz), 7.74 (1H, s), 7.93 (1H, s); MS (ES+) 538 ($[\text{MH}]^+$).

Example 17

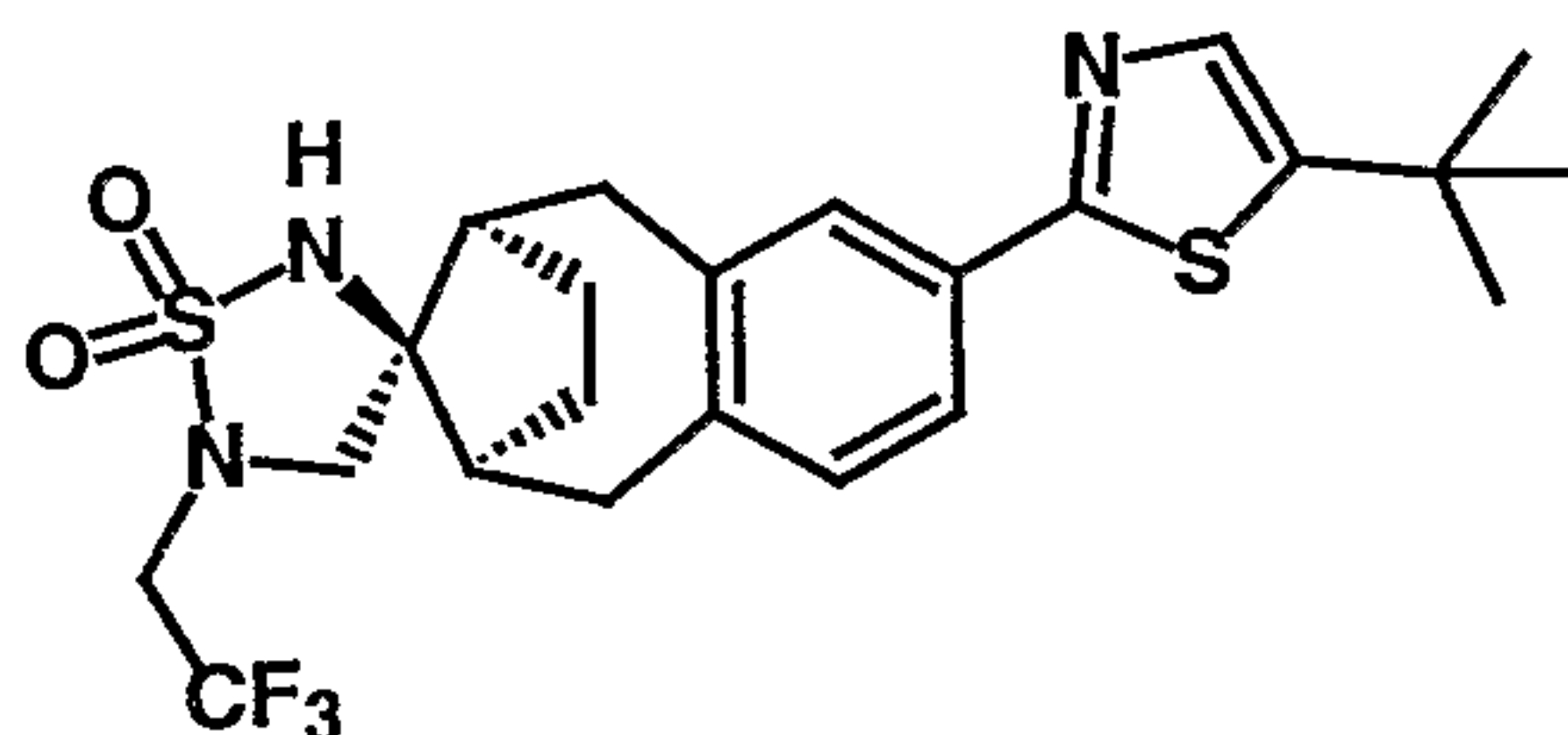
(-)- [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Prepared from the homochiral acid, Intermediate B and 2'-amino-(4-fluoroacetophenone) hydrochloride by the procedures described in Example 6, Step 1 and Example 16. MS (ES+) 538 ($[\text{MH}]^+$). $[\alpha]_D = -18$ ($c=0.54$, methanol, 23°C).

Example 18

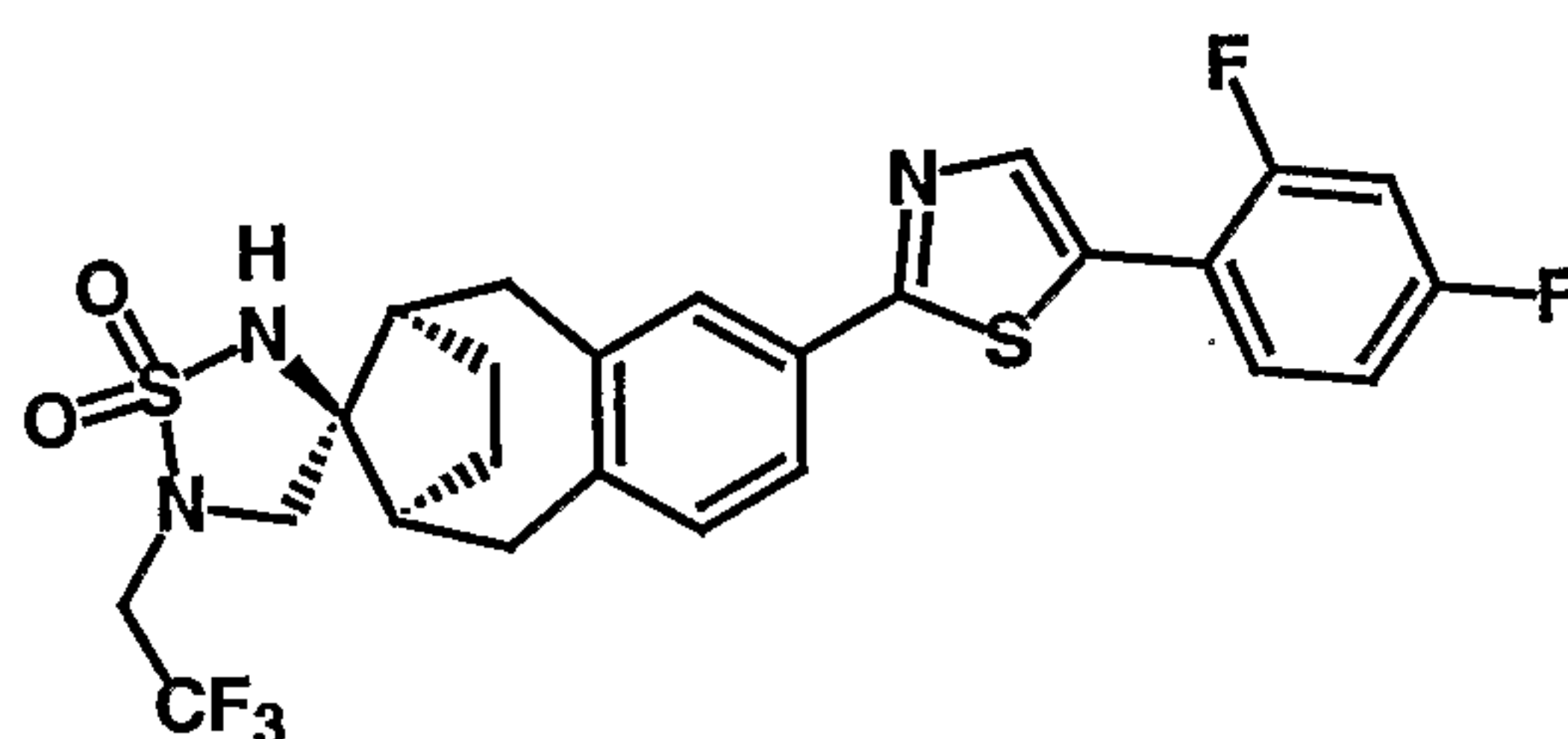
[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(1,1-dimethyl-1-ethyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.



Prepared from the racemic acid, Intermediate A and 1-amino-3,3-dimethyl-2-butanone hydrochloride by the method described for Example 6 Step 1 and Example 16. MS (ES+) 500 ([MH]⁺).

5 Example 19

(-)-[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2,4-difluorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



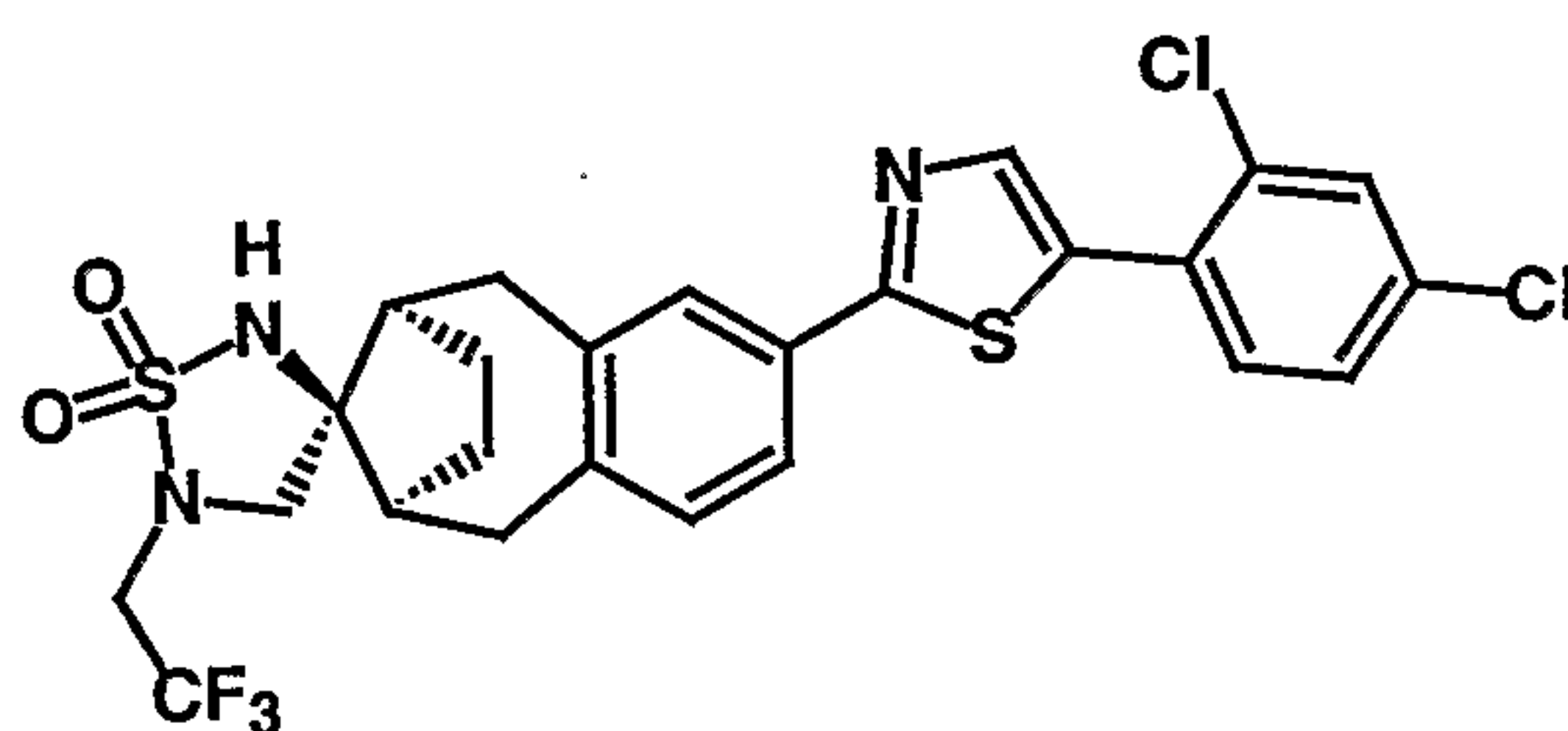
10

Prepared from 0.2 g of acid, Intermediate B, and 2'-amino-(2,4-difluoroacetophenone) hydrochloride by the method described for Example 6 Step 1 and Example 16 to give the title compound (0.075 g, 28% over 2 steps). MS (ES+) 556 ([MH]⁺). $\alpha_D -15$ (c=0.56, DMSO).

15

Example 20

(-)-[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2,4-dichlorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.

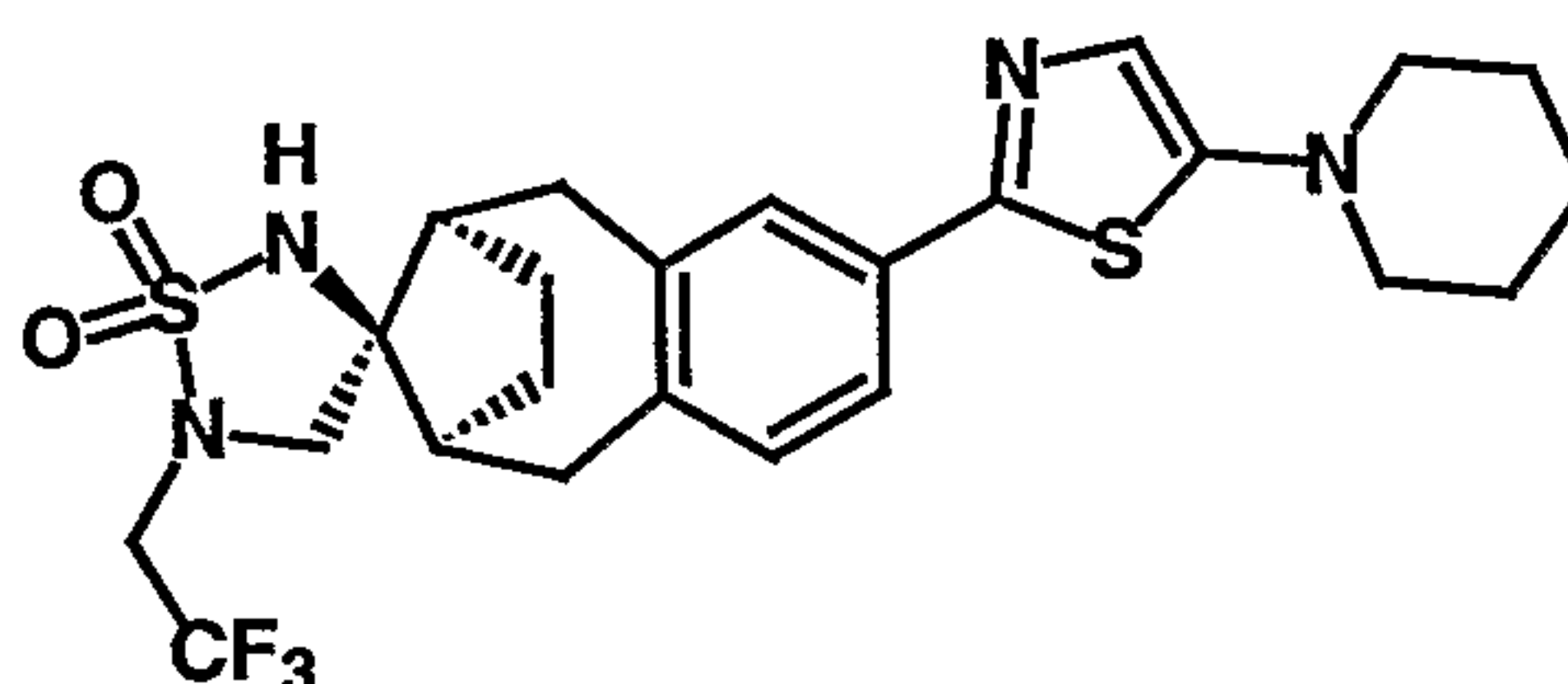


20

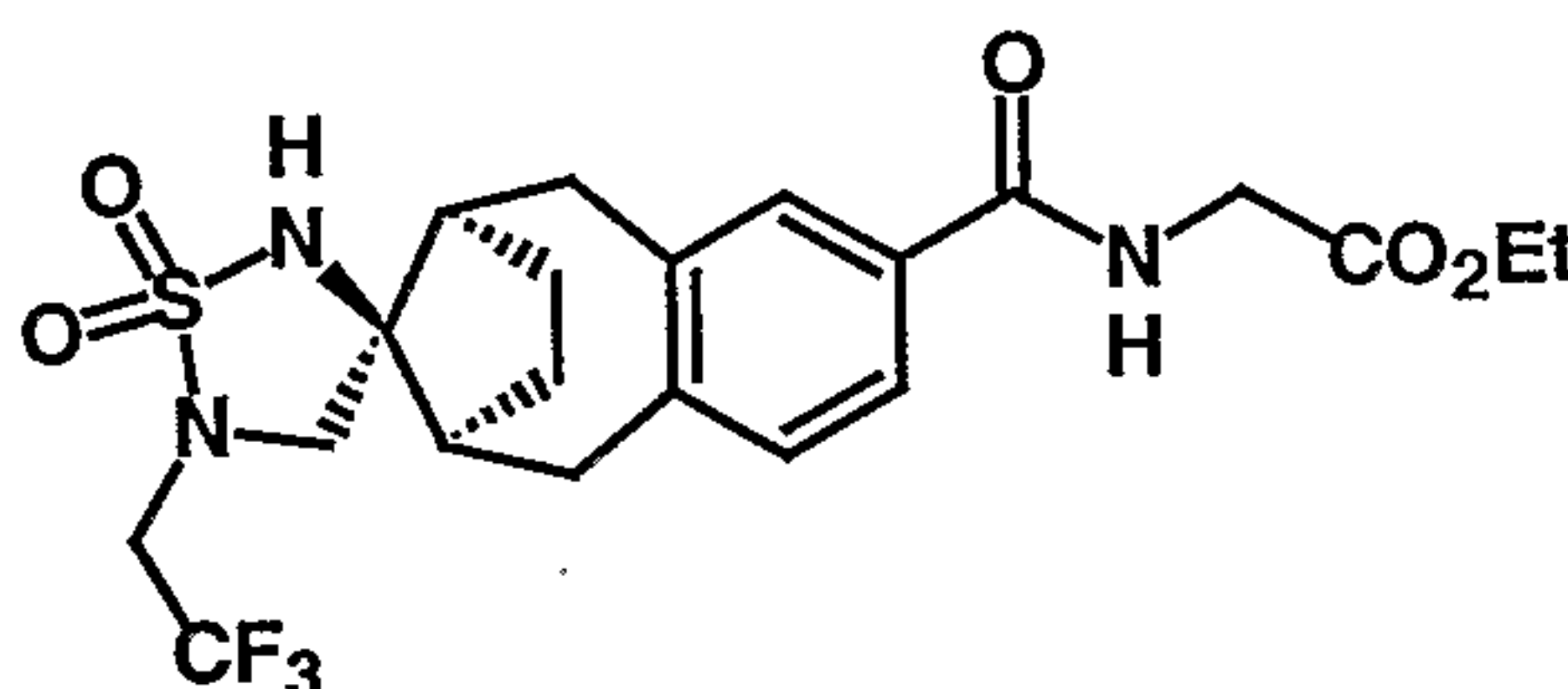
Prepared from 0.2 g of acid, Intermediate B, and 2'-amino-(2,4-dichloroacetophenone) hydrochloride by the method described for Example 6 Step 1 and Example 16 to give the title compound (0.098 g, 34% over 2 steps). MS (ES+) 588, 590, 592 ([MH]⁺). $\alpha_D -19$ (c=0.59, DMSO).

Example 21

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(piperidin-1-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Step 1: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(carboxyamino-acetic acid ethyl ester)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



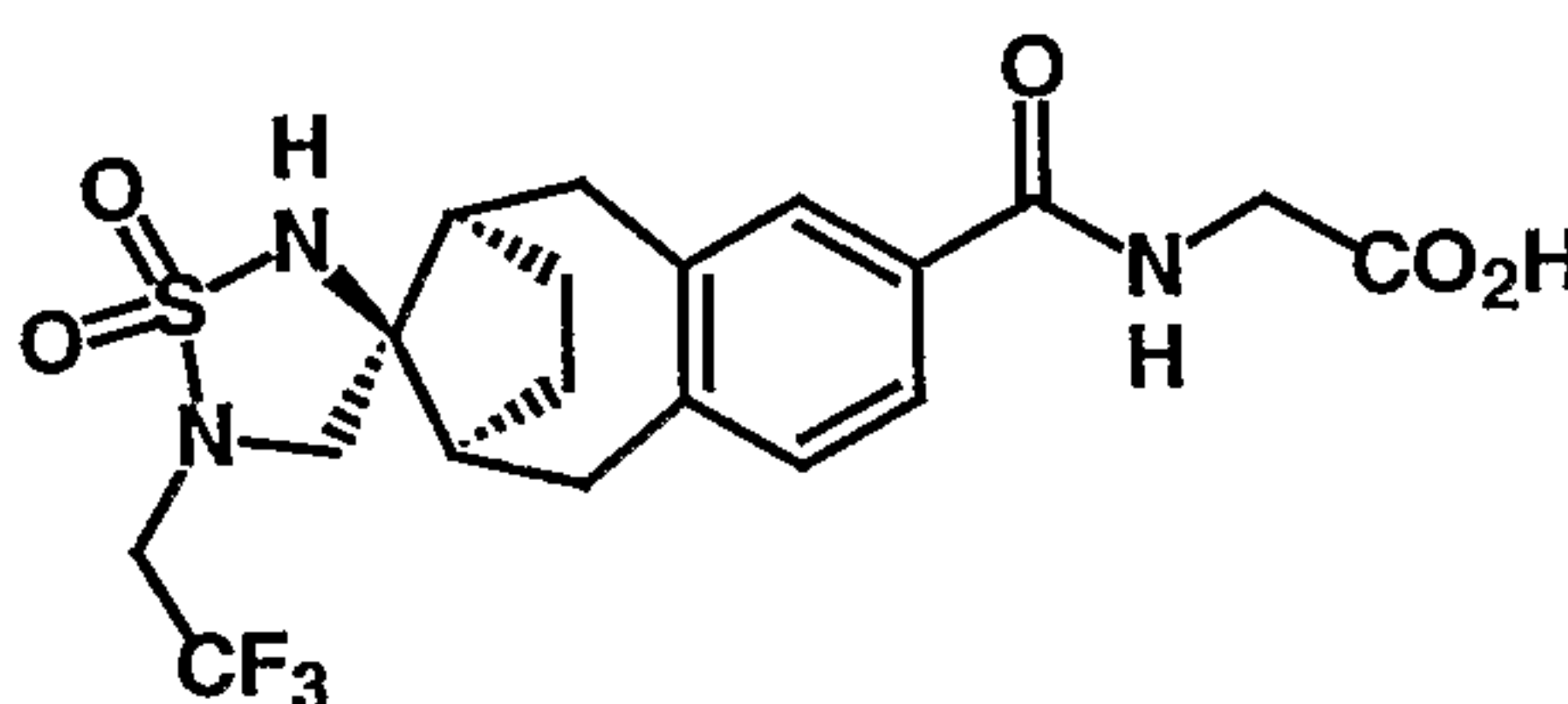
10

Prepared from the acid Intermediate A and glycine ethyl ester hydrochloride by the method described for Example 6, Step 1. δ (^1H , 360MHz, CDCl_3) 1.22-1.34 (5H, m), 1.69-1.74 (2H, m), 2.45-2.50 (2H, m), 2.71-2.78 (2H, m), 3.18-3.27 (2H, m), 3.43 (2H, s), 3.68 (2H, q, $J=9$ Hz), 4.11-4.30 (4H, m), 4.92 (1H, s), 6.66 (1H, t, $J=5$ Hz), 7.15 (1H, d, $J=8$ Hz), 7.52-7.55 (2H, m).

15

Step 2: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(carboxyamino-acetic acid)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

20

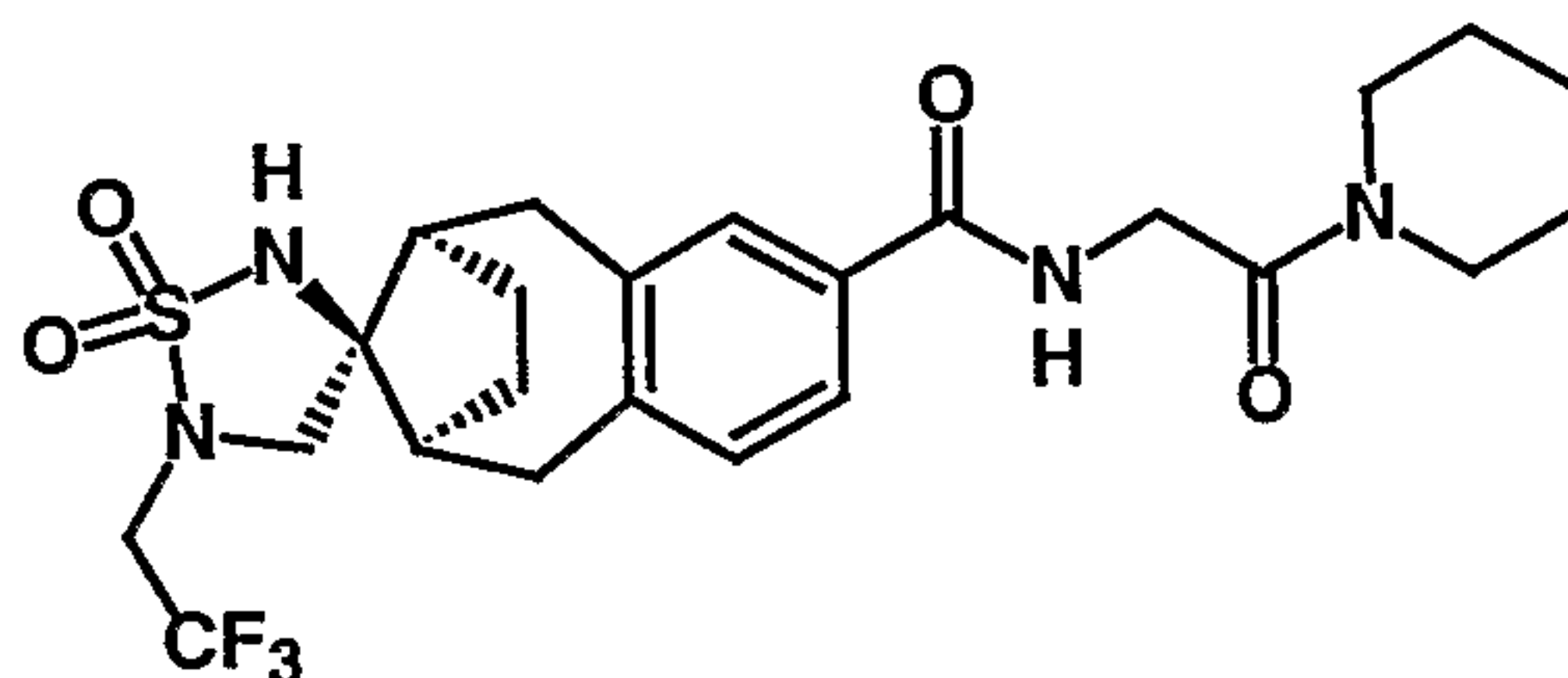


A solution of the ester from Step 1 (0.45 g) and 4M aqueous NaOH (0.75 mL) in THF (4 mL) was stirred at 50°C under N_2 for 5.5 hours. The

mixture was cooled, acidified with 1M hydrochloric acid (20 mL) and extracted with ethyl acetate (20 mL). The extract was dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, eluting with 10% methanol-dichloromethane, then with 0.2% trifluoroacetic acid-10% methanol-dichloromethane, gave the acid as a white powder (0.213 g, 50%). δ (¹H, 360MHz, DMSO) 0.97-1.09 (2H, m), 1.69-1.72 (2H, m), 2.36-2.40 (2H, m), 2.60-2.70 (2H, m), 3.15-3.22 (2H, m), 3.47 (2H, s), 3.90 (2H, d, $J=6$ Hz), 3.98-4.06 (2H, m), 7.21 (1H, d, $J=8$ Hz), 7.55-7.62 (2H, m), 8.03 (1H, s), 8.70 (1H, t, $J=6$ Hz).

10

Step 3: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(N-[2-oxo-2-piperidin-1-yl-ethyl]carboxamido)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



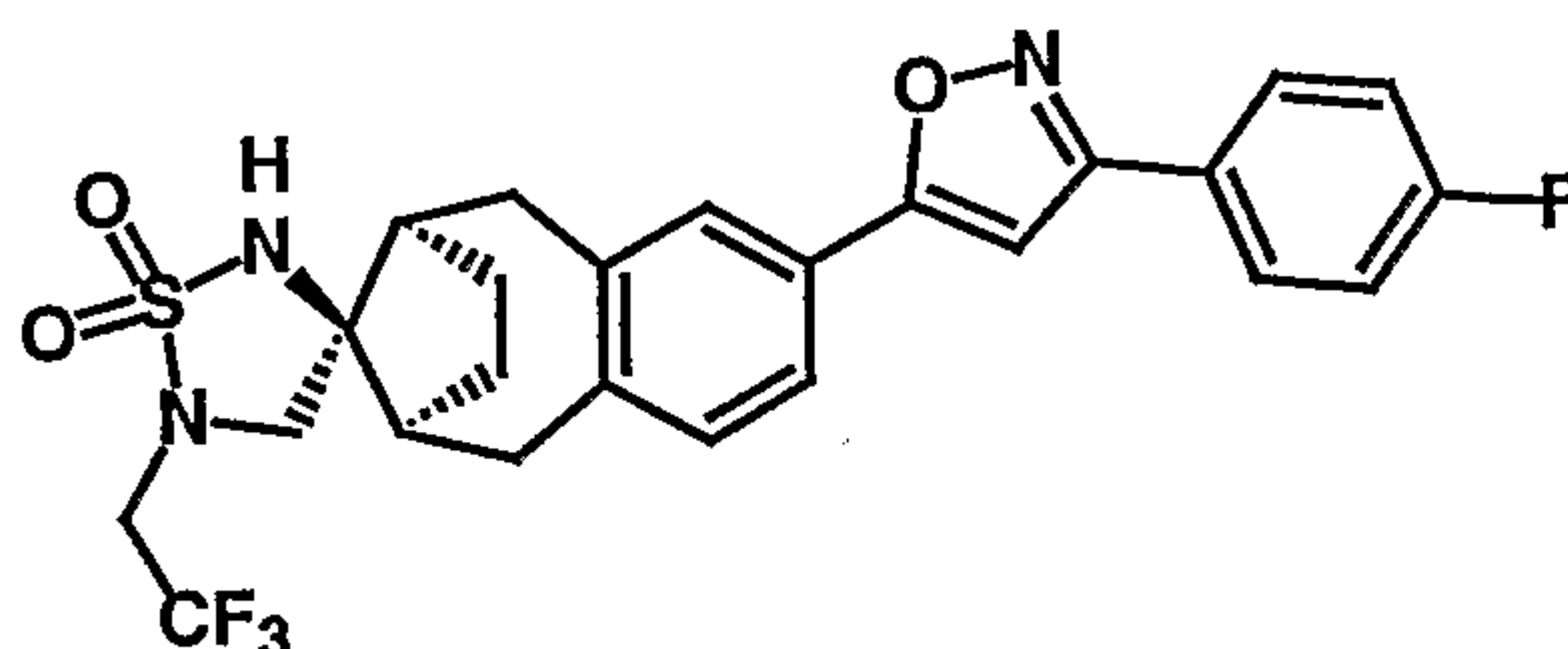
15 Prepared from the acid, Step 2 and piperidine by the method described for Example 6, Step 1. MS (ES⁺) 551 ([MNa]⁺), 529 ([MH]⁺).

Step 4: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(piperidin-1-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.

20 Prepared from the amide, Step 3, by the method described for Example 16. δ (¹H, 360MHz, CDCl₃) 1.31-1.41 (2H, m), 1.57-1.62 (2H, m), 1.71-1.77 (6H, m), 2.43-2.48 (2H, m), 2.68-2.80 (2H, m), 3.14-3.24 (6H, m), 3.43 (2H, s), 3.68 (2H, q, $J=9$ Hz), 3.90 (2H, d, $J=6$ Hz), 4.67 (1H, s), 6.94 (1H, s), 7.10 (1H, d, $J=8$ Hz), 7.49 (1H, d, $J=8$ Hz), 7.58 (1H, s). MS (ES⁺) 527 ([MH]⁺).

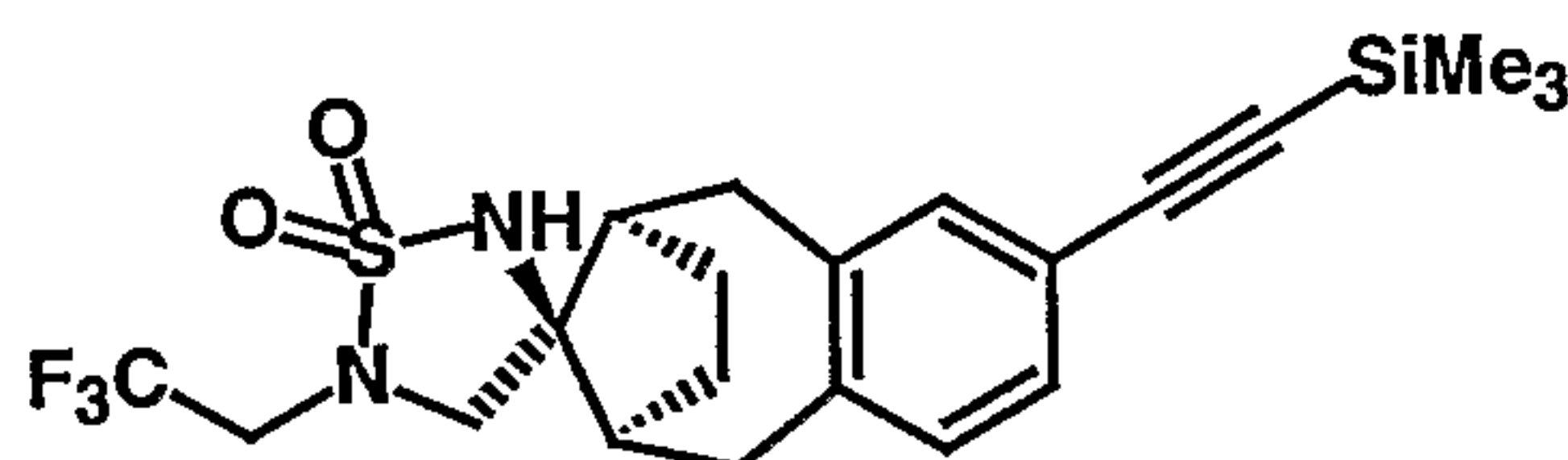
Example 22

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(4-fluorophenyl)-isoxazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



5

Step 1 [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(trimethylsilylethynyl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

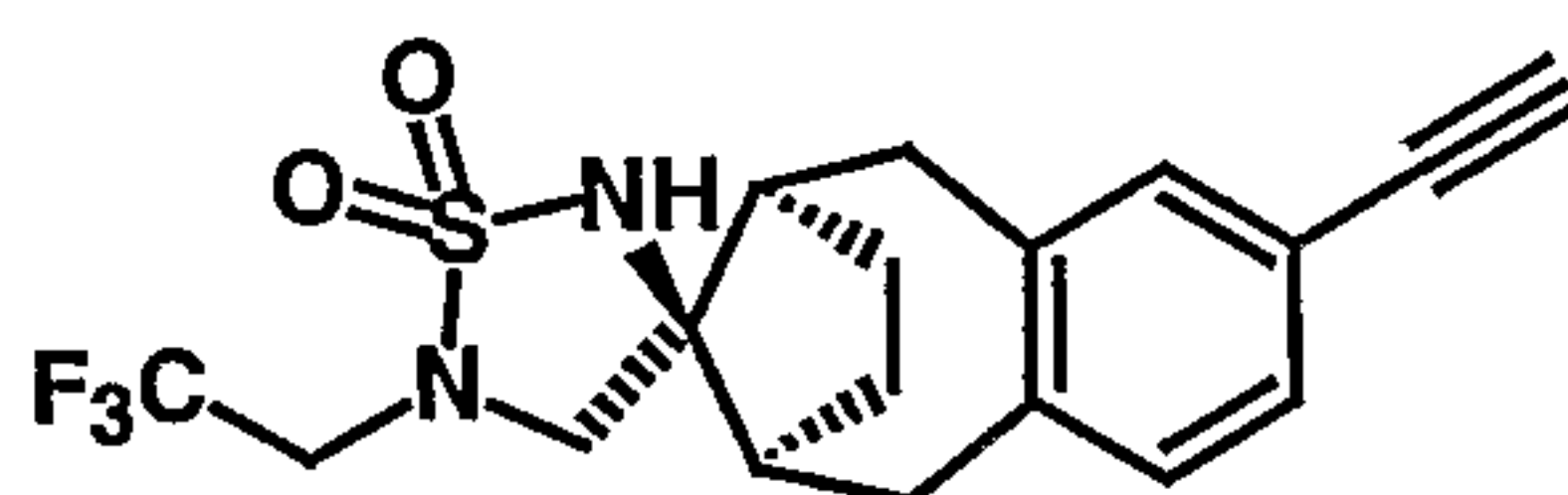


10

A solution of triflate, Intermediate D, (200 mg, 0.39 mmol), TMS acetylene (112 μ L, 0.78mmol), tetrakis-triphenylphosphine palladium(0) (20 mg, 5 mol%), triphenyl phosphine (10 mg, 10 mol%) and copper iodide (7.6 mg, 10 mol%) was made up in 2mL of dry piperidine and added to a crimp top microwave vial, the reaction mixture was sealed, purged with nitrogen and then irradiated in the Smith Synthesizer Microwave to 150°C for 10 minutes. After this time the reaction was diluted with EtOAc (100 mL) and the mixture washed successively with dilute NaHCO₃, 1M HCl solution and then saturated brine solution. The organic layer was then separated, dried (MgSO₄) and evaporated *in vacuo* giving a crude residue which was purified by flash column chromatography using 25% EtOAc in isohexane as eluant to give the title compound as a white solid (156 mg, 86% yield). δ (¹H, 400 MHz, CDCl₃) 0.23 (9H, s), 1.25-1.30 (2H, m), 1.68-1.72 (2H, m), 2.42-2.45 (2H, m), 2.62-2.71 (2H, m), 3.15-3.22 (2H, m), 3.42 (2H, s), 3.67 (2H, q, J = 8.7 Hz), 4.68 (1H, brs), 7.03 (1 H, d, J = 8.2Hz) and 7.22-7.24 (2 H, m).

25

Step 2 [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-ethynyl-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



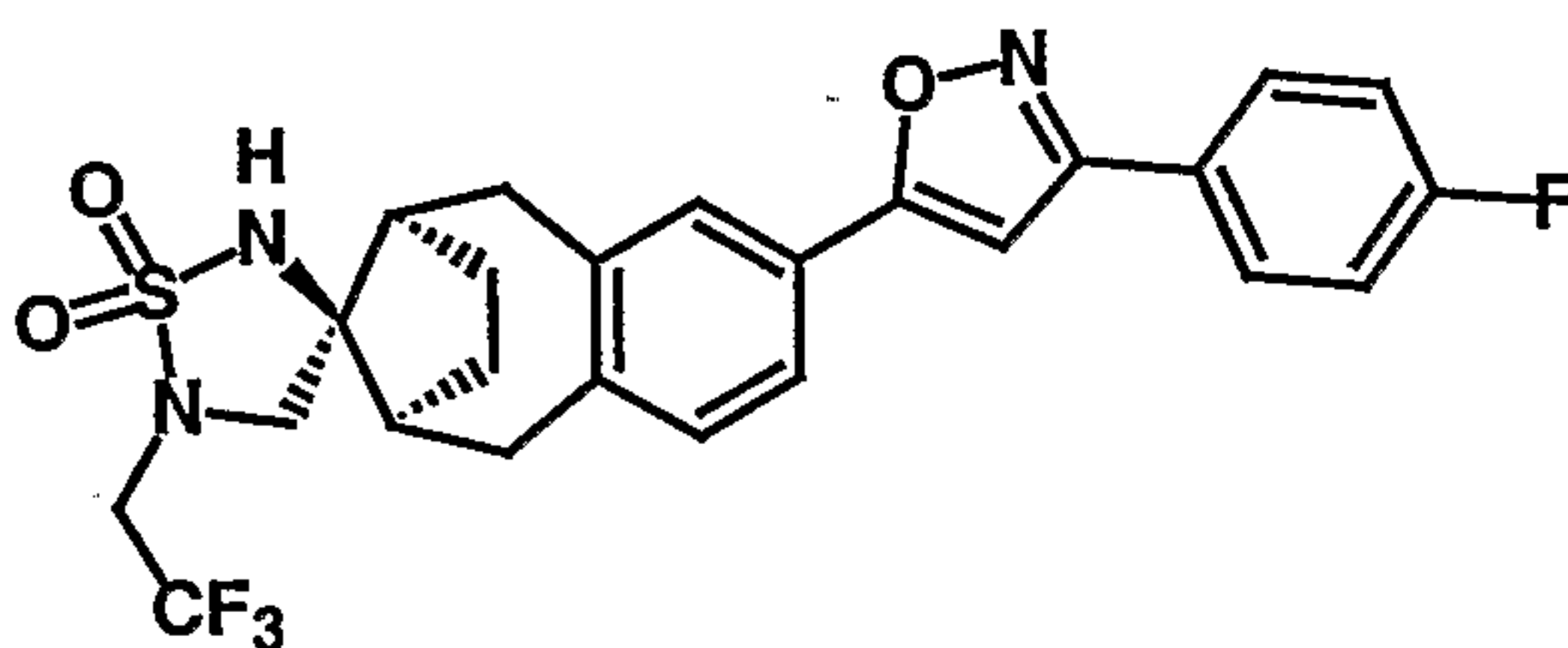
5

A solution of the TMS acetylene compound from Step 1 (156 mg, 0.34 mmol) in a 10:1 tetrahydrofuran/water mixture (10 mL) was treated with lithium hydroxide (41 mg, 1.71 mmol) and stirred at room temperature for 1.5 hours. After this time the reaction mixture was diluted with 50 mL dichloromethane and washed with saturated brine solution. The organic phase was dried (MgSO₄) and evaporated to dryness before purification by flash column chromatography using 20% ethyl acetate in isohexane as eluant to give the title compound as a colourless film (86mg, 66%). δ (¹H, 400 MHz, CDCl₃) 1.28-1.32 (2H, m), 1.68-1.72 (2H, m), 2.42-2.46 (2H, m), 2.62-2.71 (2H, m), 3.05 (1H, s), 3.15-3.22 (2H, m), 3.43 (2H, s), 3.67 (2H, q, J = 8.7 Hz), 4.66 (1H, brs), 7.03 (1 H, d, J = 8.2Hz) and 7.22-7.24 (2 H, m).

15

20

Step 3 [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(4-fluorophenyl)-isoxazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



A solution of *N*-bromosuccinimide (208 mg, 1.17 mmol) in *N,N*-dimethylformamide (1 mL) was added to a solution of 4-fluorobenzaldoxime (113 mg, 0.26 mmol) in *N,N*-dimethylformamide (4 mL) at 0°C and the reaction mixture was stirred, under nitrogen, for 3 hours at 0°C. Triethylamine (163 μ L, 1.17 mmol) was added and the mixture was stirred, under nitrogen, for a further 20 minutes at 0°C. A

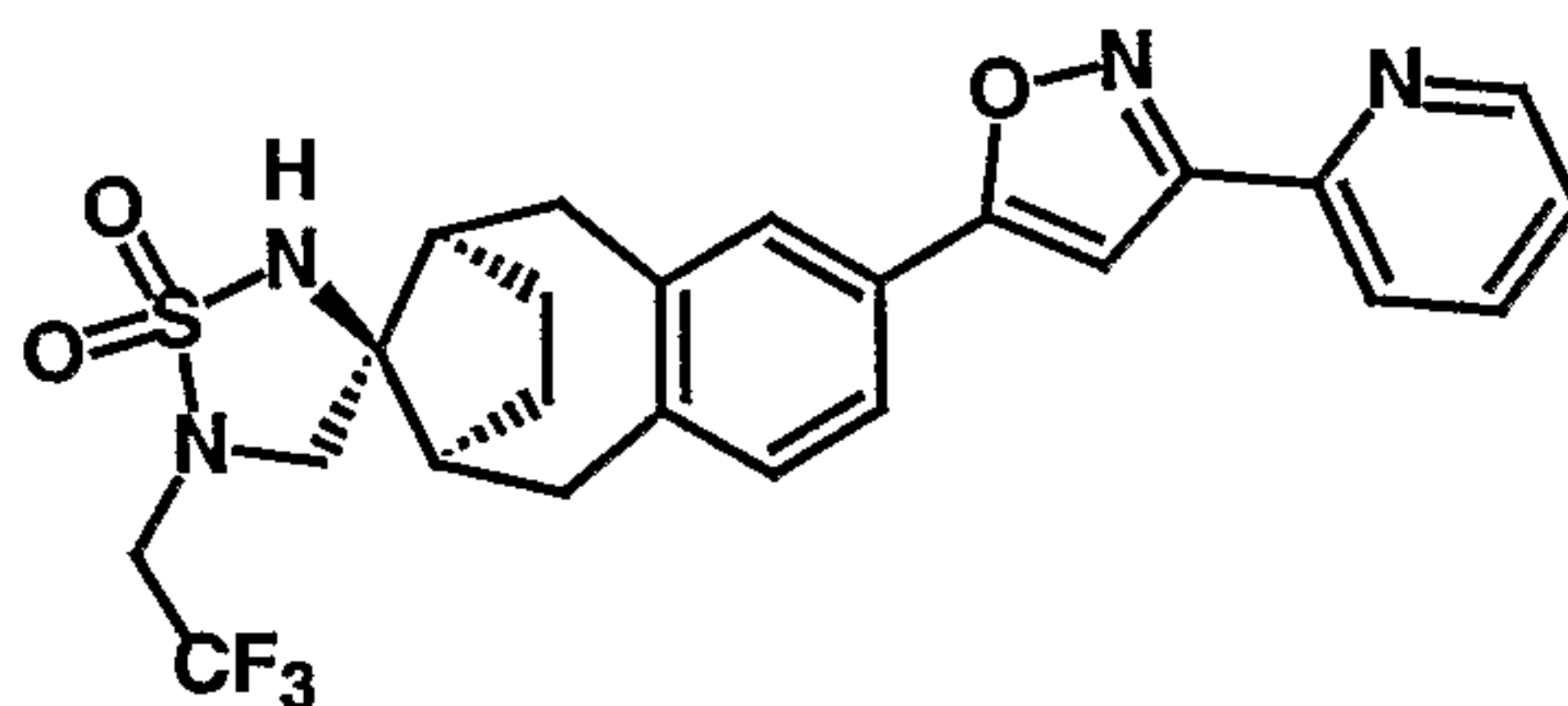
25

solution of the acetylene from Step 2 (100 mg, 0.81 mmol) in DMF (1 mL) was added dropwise and the reaction mixture was stirred, under nitrogen, for 1 hour at 0°C. The reaction mixture was diluted with sodium

5 The organics were washed with brine (25 mL), dried (MgSO₄) and evaporated *in vacuo* to give an orange solid. The solid was purified by chromatography on SiO₂ eluting with ethyl acetate / hexane (1:9, 1:6, 1:3 and 1:2) to give the title compound (121 mg, 90%) as a cream solid after drying *in vacuo* (80°C, 2 hours). δ (¹H, 400MHz, *d*₄-MeOH: 1.22-1.30 (2H, m), 1.77-1.80 (2H, m), 2.49-2.50 (2H, m), 2.71-2.81 (2H, m), 3.35 (1H, d, J=10Hz), 3.39 (1H, d, J=10Hz), 3.52 (2H, s), 3.87 (2H, q, *J* = 9.2 Hz), 7.18 (1H, s), 7.22-7.28 (3H, m), 7.63-7.66 (2H, m) and 7.92-7.96 (2H, m); MS (ES⁺) 522 ([MH]⁺).

15 Example 23

[6S/R,9R/S,11R/S]-2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(2-pyridyl)-isoxazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

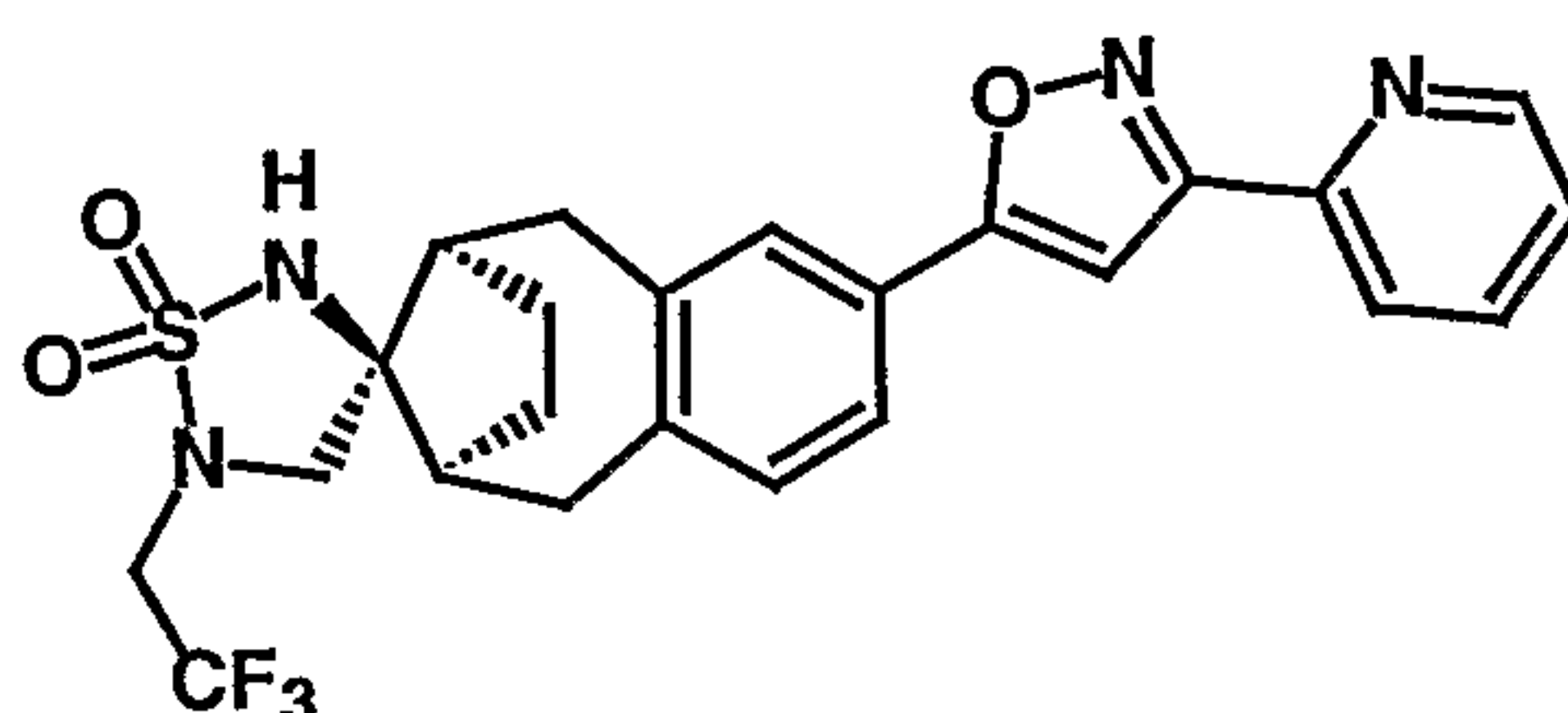


20 The title compound was prepared in the same way as Example 22 using 2-pyridinealdoxime. MS(ES⁺) 505 ([MH]⁺).

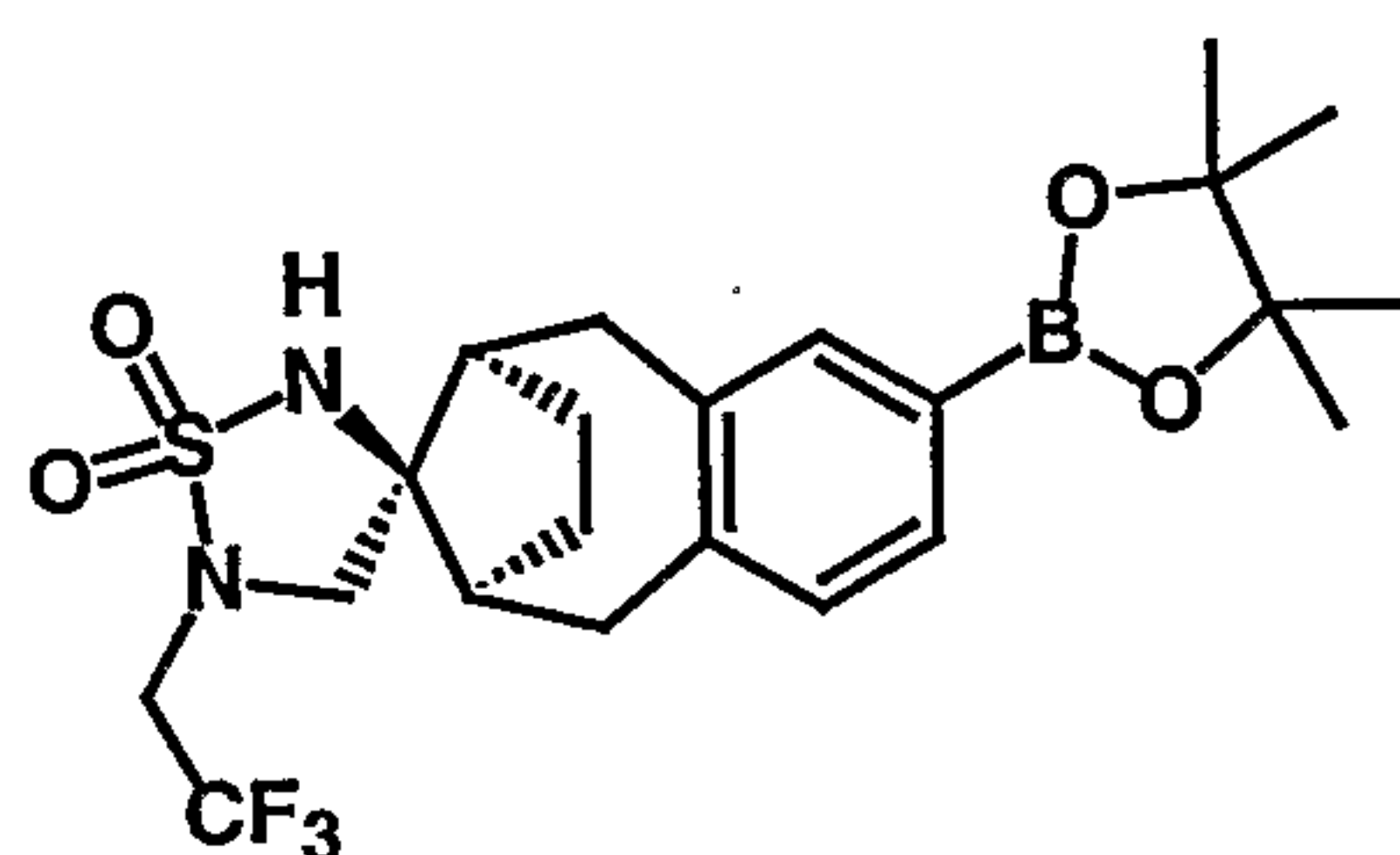
Example 24

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(2-pyridyl)-isoxazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

- 67 -



Step 1 [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-5'-(2,2,2-trifluoroethyl)spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



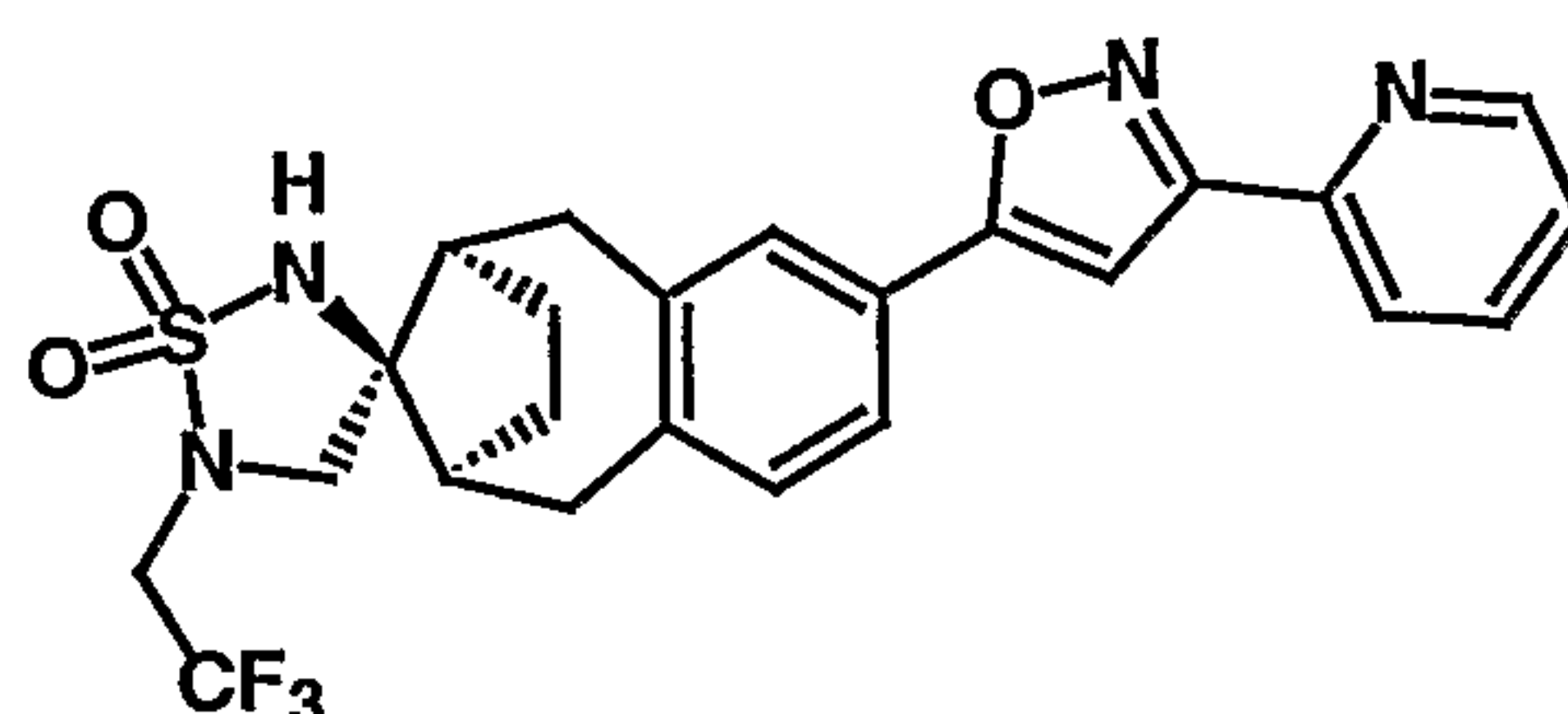
5

A solution of the homochiral triflate, Intermediate E, (508 mg, 1.0 mmol), bis pinacolatodiboron (279 mg, 1.1 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloro palladium (II) dichloromethane complex (82 mg, 0.1 mmol), 1,1'-bis(diphenylphosphino)ferrocene (55 mg, 0.1 mmol) and potassium acetate (294 mg, 3.0 mmol) in dimethylformamide (7 mL) was degassed via a stream of nitrogen before heating at 100°C for 3 hours. The reaction was cooled to room temperature, diluted with water (30 ml) and extracted with ethylacetate (2 x 40 mL). The extracts were washed with brine, dried (MgSO₄) and evaporated *in vacuo* to give a black oil, which was purified by column chromatography, eluting with ethyl acetate:iso-hexane (1:5) to give the title compound as a white solid (480 mg, 99%). δ (¹H, 400MHz, CDCl₃) 1.30-1.34 (14H, m), 1.65-1.75 (2H, m), 2.40-2.50 (2H, m), 2.69-2.80 (2H, m), 3.14-3.25 (2H, m), 3.40-3.45 (2H, m), 3.65-3.71 (2H, m), 4.66 (1H, brs), 7.10 (1H, d, J = 7.4 Hz), 7.53 (1H, s) and 7.56 (1H, d, J = 7.4 Hz).

20

Step 2 [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(2-pyridyl)-isoxazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

- 68 -

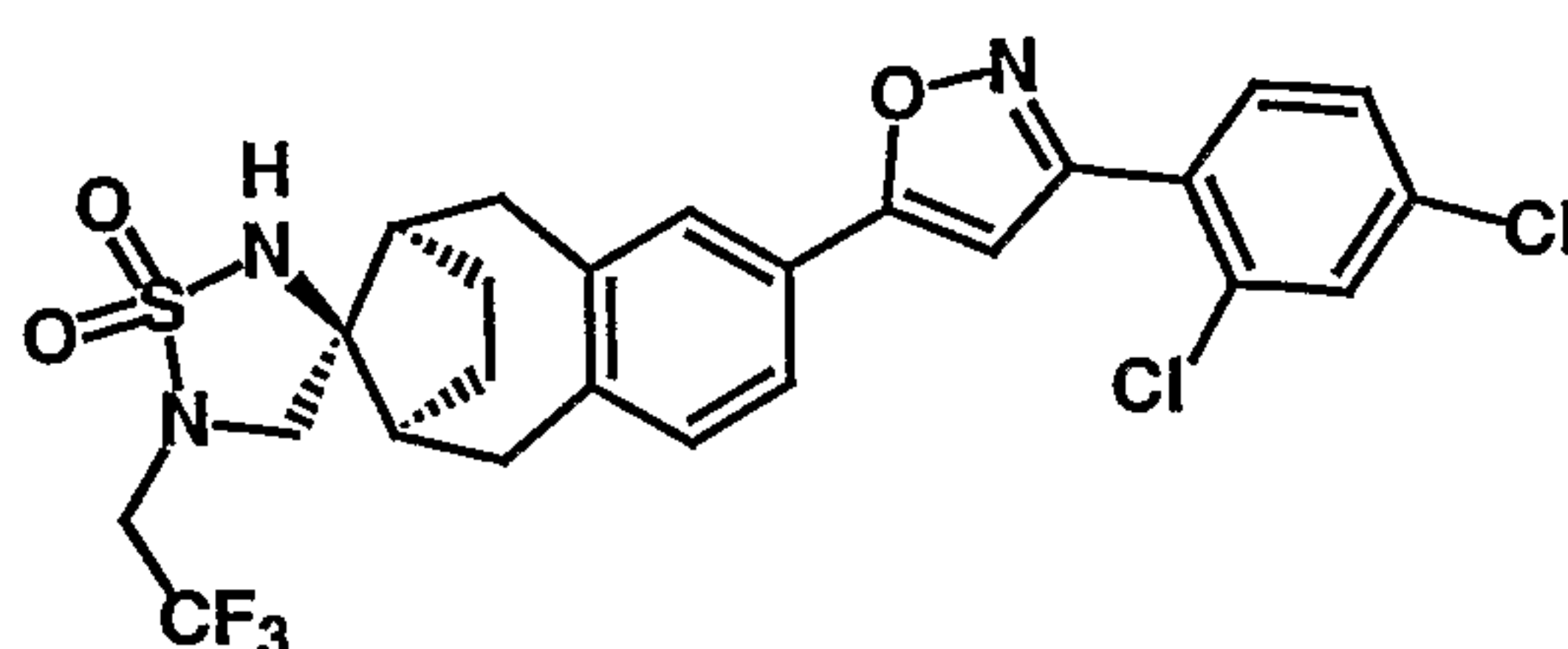


A mixture of 2-(5-iodoisoxazol-3-yl)pyridine (prepared in the manner of Ku
et al Org. Lett. 3 (26), 4185-4187, 2001.) (90 mg, 0.3 mmol), the homochiral
 boronate from Step 1 (100 mg, 0.2 mmol) potassium carbonate (135 mg, 1
 5 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloro palladium (II)
 dichloromethane complex (5 mg) in toluene (2 mL), ethanol (1 mL) and
 water (1mL) was heated under microwave conditions at 100°C for 5
 minutes. More [1,1'-bis(diphenylphosphino)ferrocene] dichloro palladium
 (II) dichloromethane complex (5 mg) was added and the mixture was again
 10 heated under microwave conditions at 100°C for 5 minutes. The reaction
 was diluted with sodium bicarbonate (half sat, 20 mL) and extracted with
 ethylacetate (2 x 30 mL). The extracts were washed with brine, dried
 (MgSO₄) and evaporated *in vacuo* to give a brown gum, which was purified
 by column chromatography, eluting with ethylacetate:iso-hexane (1:4) to
 15 give the title compound as a white solid (70 mg, 69%). δ (¹H, 400MHz,
 CDCl₃) 1.32-1.40 (2H, m), 1.74-1.78 (2H, m), 2.48-2.52 (2H, m), 2.74-2.83
 (2H, m), 3.26-3.31 (2H, m), 3.46 (2H, s), 3.70 (2H, q, J = 8.7 Hz), 4.83 (1H,
 brs), 7.17 (1H, s), 7.23 (1H, d, J = 8.3 Hz), 7.36-7.40 (1H, m), 7.60-7.62 (2H,
 m), 7.81-7.85 (1H, m), 8.12-8.14 (1H, m), and 8.71-8.72 (1H, m). MS (ES+)
 20 505 ([MH]⁺).

Example 25

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(2,4-
 dichlorophenyl)-isoxazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-
 25 methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

- 69 -

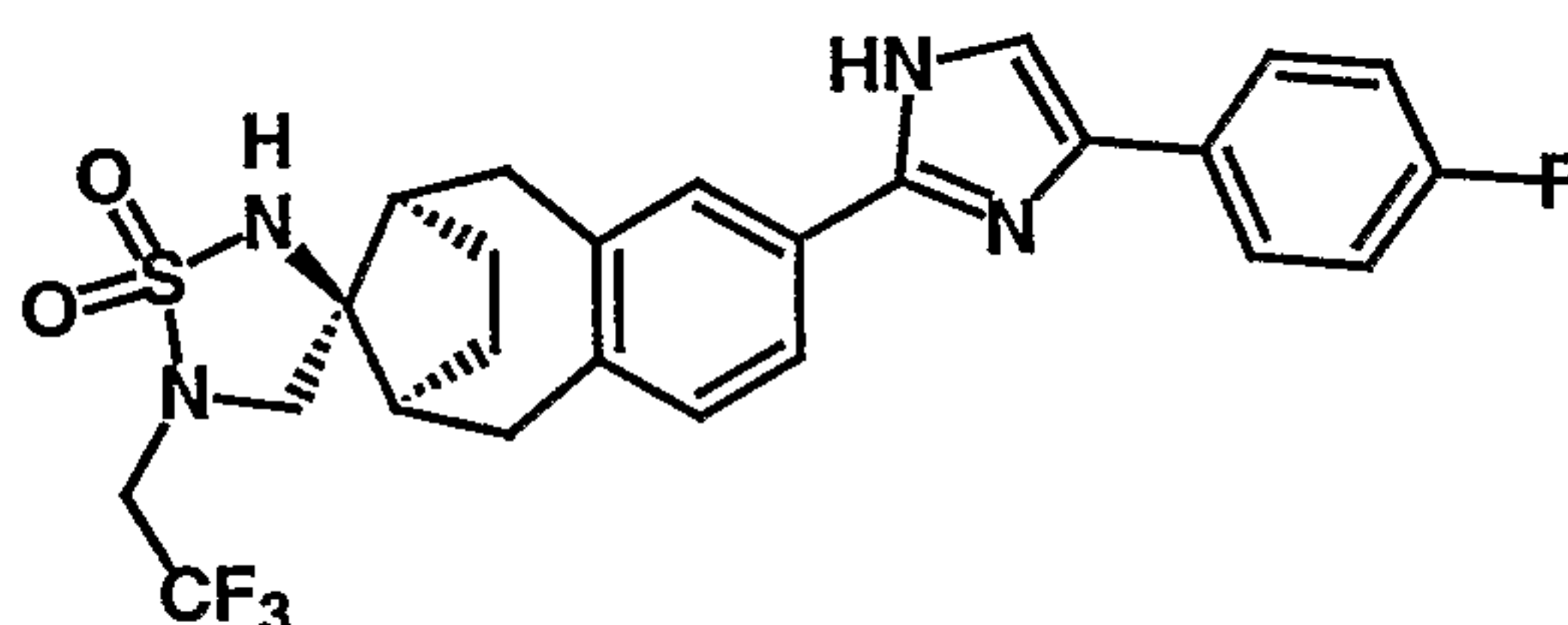


The title compound was prepared from Intermediate D using the method described in Example 22 and with 2,4-dichlorobenzaldehyde oxime. MS (ES+) 572, 574, 575 ([MH]⁺).

5

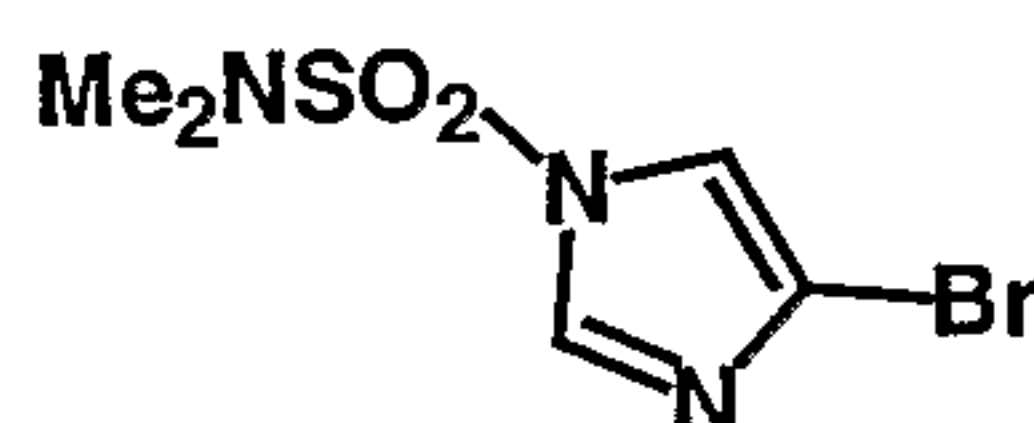
Example 26

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(4-(4-fluorophenyl)-1H-imidazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



10

Step 1: 1-(Dimethylaminosulfonyl)-4-bromoimidazole



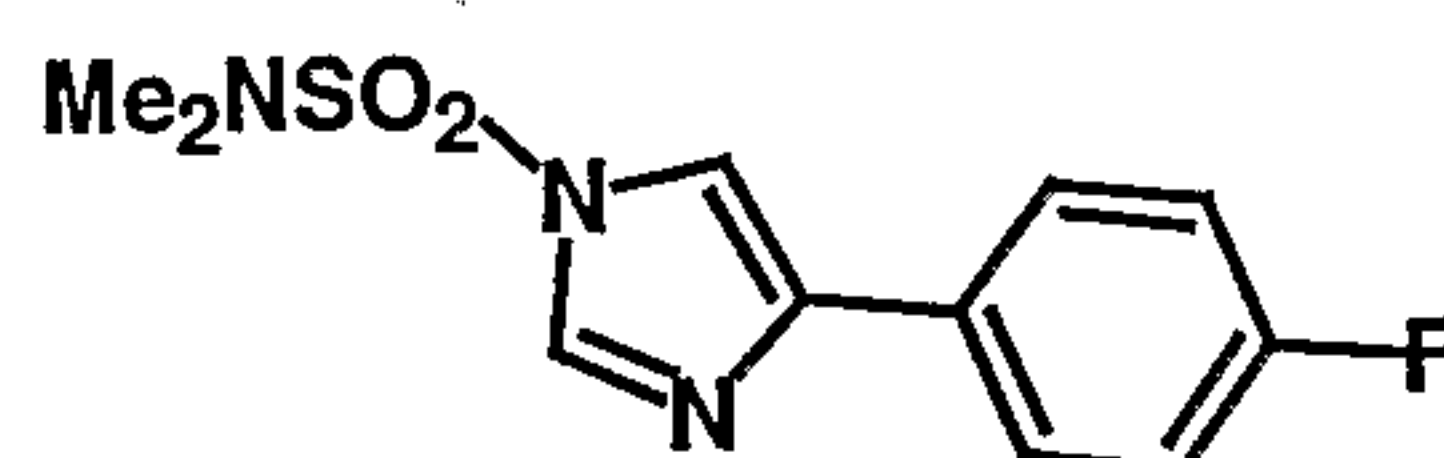
Sodium hydride (55% in oil, 0.31 g) was added to a stirred solution of 4-bromo-1H imidazole (1.02 g) in dry tetrahydrofuran (20 mL) at room temperature under N₂. After 10 minutes, dimethylsulfamoyl chloride (0.81 mL) was added. After stirring for 5 hours, the mixture was diluted with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (20 mL). The extract was dried over Na₂SO₄, filtered and concentrated. The white solid was rinsed with diethyl ether and dried to give 1-(dimethylaminosulfonyl)-4-bromoimidazole (1.53 g, 87%). MS (ES+) 256, 254 ([MH]⁺).

15

20

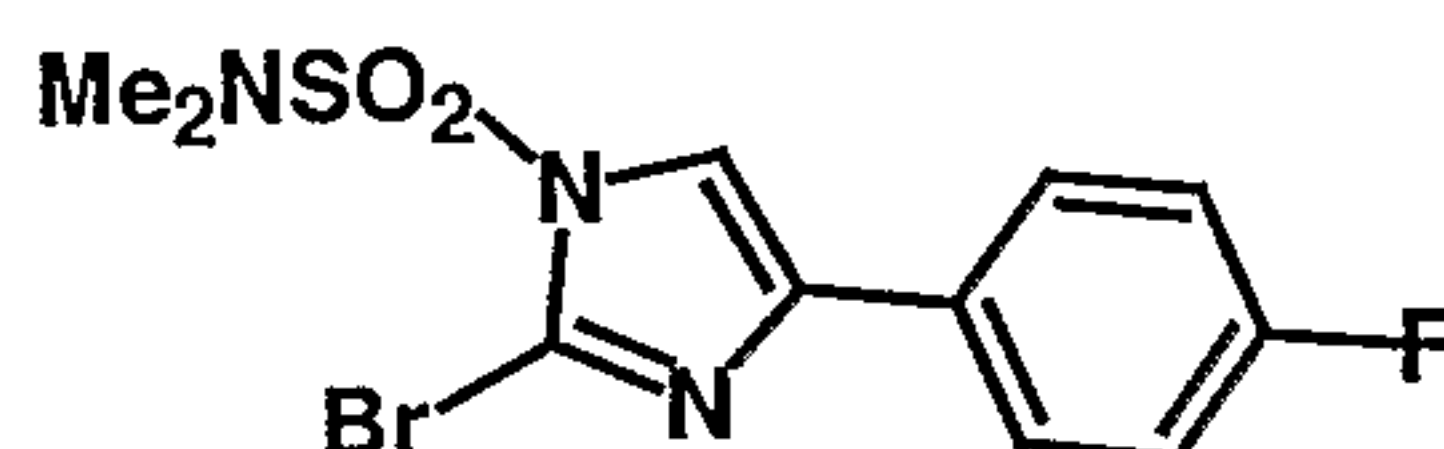
Step 2: 1-(Dimethylaminosulfonyl)-4-(4-fluorophenyl)imidazole

- 70 -



A mixture of the bromide from Step 1 (0.543 g), 4-fluorophenylboronic acid (0.31 g), tetrakis(triphenylphosphine) palladium (0) (0.2 g), 2M aqueous sodium carbonate (2.2 mL) and toluene (10 mL) was refluxed under N₂ for 5 1.5 hours. The mixture was cooled, poured into water (75 mL) and extracted with ethyl acetate (2 x 25 mL). The extracts were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, eluting with 40% ethyl acetate-isohexane, gave 1-(dimethylaminosulfonyl)-4-(4-fluorophenyl)imidazole (0.417 g, 72%) as a yellow solid. MS (ES+) 270 10 ([MH]⁺).

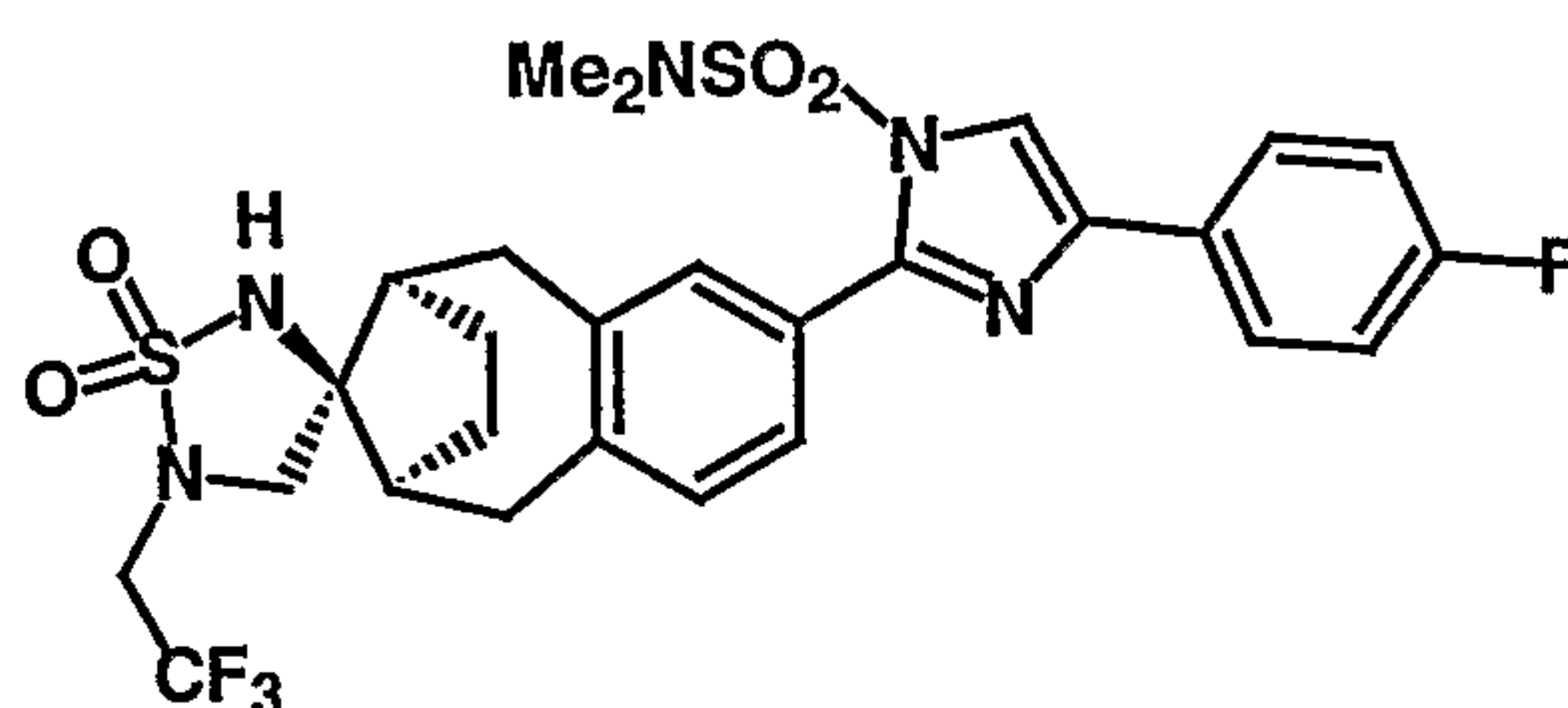
Step 3: 1-(Dimethylaminosulfonyl)-2-bromo-4-(4-fluorophenyl)imidazole



A solution of n-butyllithium (1.6M, 0.35 mL) was added dropwise at -78°C 15 to a stirred solution of the imidazole from Step 2 (0.20 g) in dry tetrahydrofuran (4 mL) under N₂. After 7 hours, 1,2-dibromotetrafluoroethane (0.12 mL) was added and the mixture was stirred for 18 hours, warming to room temperature. The solution was evaporated onto silica gel and flash column chromatography, eluting with 20 20% ethyl acetate-isohexane, gave the bromide (0.152 g, 59%) as a yellow oil. MS (ES+) 348, 350 ([MH]⁺).

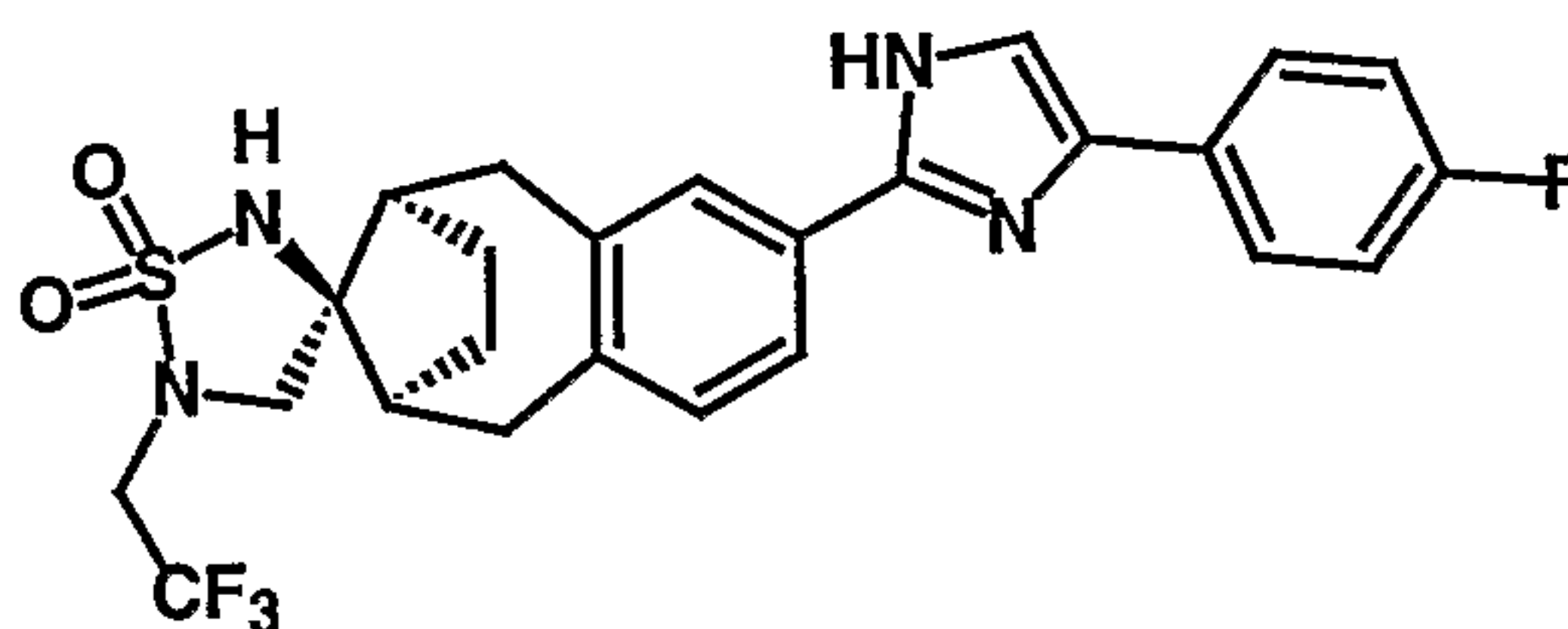
Step 4: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-[1-(dimethylaminosulfonyl)-4-(4-fluorophenyl)-imidazol-2-yl]-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.

- 71 -



A mixture of the bromide from Step 3 (0.075 g), the homochiral boronate ester from Example 24, Step 1 (0.105 g), tetrakis(triphenylphosphine) palladium (0) (0.1 g), 2M aqueous sodium carbonate (0.22 mL) and toluene
 5 (3 mL) was refluxed for 4 hours. The mixture was cooled, diluted with ethyl acetate (15 mL) and washed with water (10 mL). The organic phase was filtered through a Teflon membrane and concentrated. Flash column chromatography, eluting with 20% then 30% then 50% ethyl acetate-
 isohexane, gave the product as a yellow oil (0.085 g, 63%). MS (ES+) 628
 10 ([MH]⁺).

Step 5: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(4-(4-fluorophenyl)-1H-imidazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.



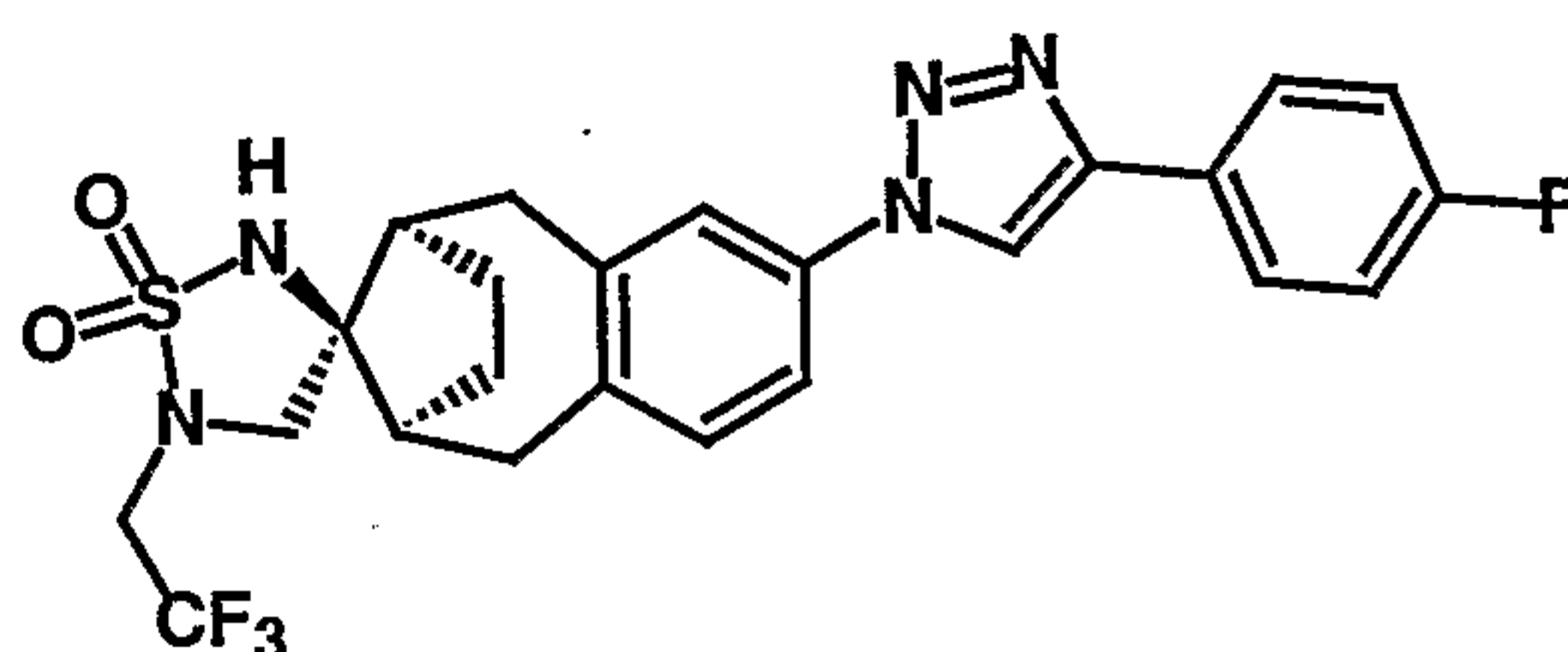
15

A solution of the product from Step 4 (0.085 g) and 2M hydrochloric acid (1 mL) in tetrahydrofuran (5 mL) was refluxed under N₂ for 1 hour. The solution was cooled, poured into saturated aqueous sodium hydrogen carbonate (30 mL) and extracted with ethyl acetate (2 x 30 mL). The
 20 extracts were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, eluting with 50% ethyl acetate-isohexane, then preparative thin layer chromatography, eluting with 50% ethyl acetate-
 isohexane, gave the imidazole as a waxy solid (0.014 g, 20%). δ (¹H, 360MHz, CDCl₃) 1.21-1.25 (2H, m), 1.60-1.70 (2H, m), 2.30-2.40 (2H, m),
 25 2.55-2.66 (2H, m), 3.05-3.14 (2H, m), 3.39 (2H, s), 3.68 (2H, q, *J*=9 Hz),

5.12 (1H, s), 7.04-7.09 (3H, m), 7.30 (1H, s), 7.54 (1H, d, $J=8$ Hz), 7.61 (1H, s), 7.69-7.77 (2H, m). MS (ES+) 521 ([MH]⁺).

Example 27

- 5 **[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(4-(4-fluorophenyl)-1,2,3-triazol-1-yl)-5'-(2,2,2-trifluoroethyl)spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.**



- 10 Intermediate C (0.5 g, 1.33 mmol) was suspended in concentrated HCl (10 mL) and water (10 mL) and cooled in an ice-salt bath. A solution of sodium nitrite (0.092 g, 1.33 mmol) in water (5 mL) was added dropwise, maintaining the internal temperature below 0°C. The orange solution was stirred at a temperature below 0°C for 20 mins. This diazonium salt
- 15 solution was added dropwise to a solution of sodium azide (0.087 g, 1.33 mmol) and acetic acid sodium salt (1.09 g, 13.3 mmol) in water (10 mL) at room temperature. Nitrogen evolution was observed. The reaction was stirred at room temperature for 18 hours. The pale green solid was collected by filtration, washed well with water and dried at room
- 20 temperature. Purification by flash column chromatography on silica, eluting with 25% ethyl acetate – isohexane gave the azide (0.27 g, 51%). 0.26 g (0.65 mmol) of this and 1-ethynyl-4-fluorobenzene (0.078 g, 0.65 mmol) in xylene (10 mL) were heated under reflux for 18 hours. Another 0.078 g of 1-ethynyl-4-fluorobenzene was added and heating continued for
- 25 7 hours. Another 0.078 g of 1-ethynyl-4-fluorobenzene was added and heating continued for 18 hours. The solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica, eluting

- 73 -

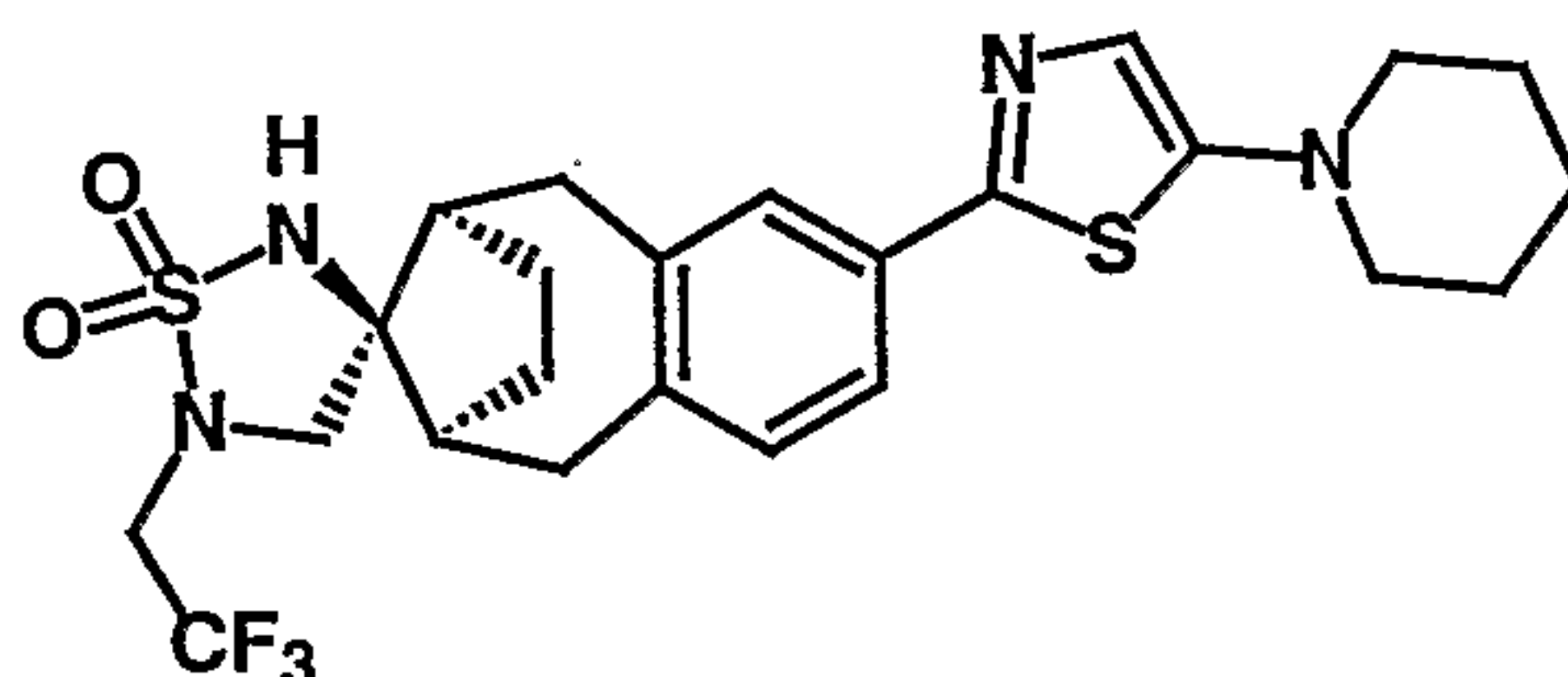
with 25% ethyl acetate – isohexane, followed by trituration in dichloromethane to give the title compound (0.016 g, 5%).

δ (^1H , 400MHz, CDCl_3) 1.33-1.43 (2H, m), 1.75-1.82 (2H, m), 2.50-2.54 (2H, m), 2.77-2.85 (2H, m), 3.27-3.35 (2H, m), 3.46 (2H, s), 3.70 (2H, q, $J=8.7$ Hz), 4.66 (1H, s), 7.14-7.18 (2H, m), 7.26-7.29 (1H, m), 7.52 (1H, dd, $J=2.2, 8$ Hz), 7.58 (1H, d, $J=2$ Hz), 7.86-7.90 (2H, m), 8.12 (1H, s).

MS (ES+) 522 ($[\text{MH}]^+$).

Example 28

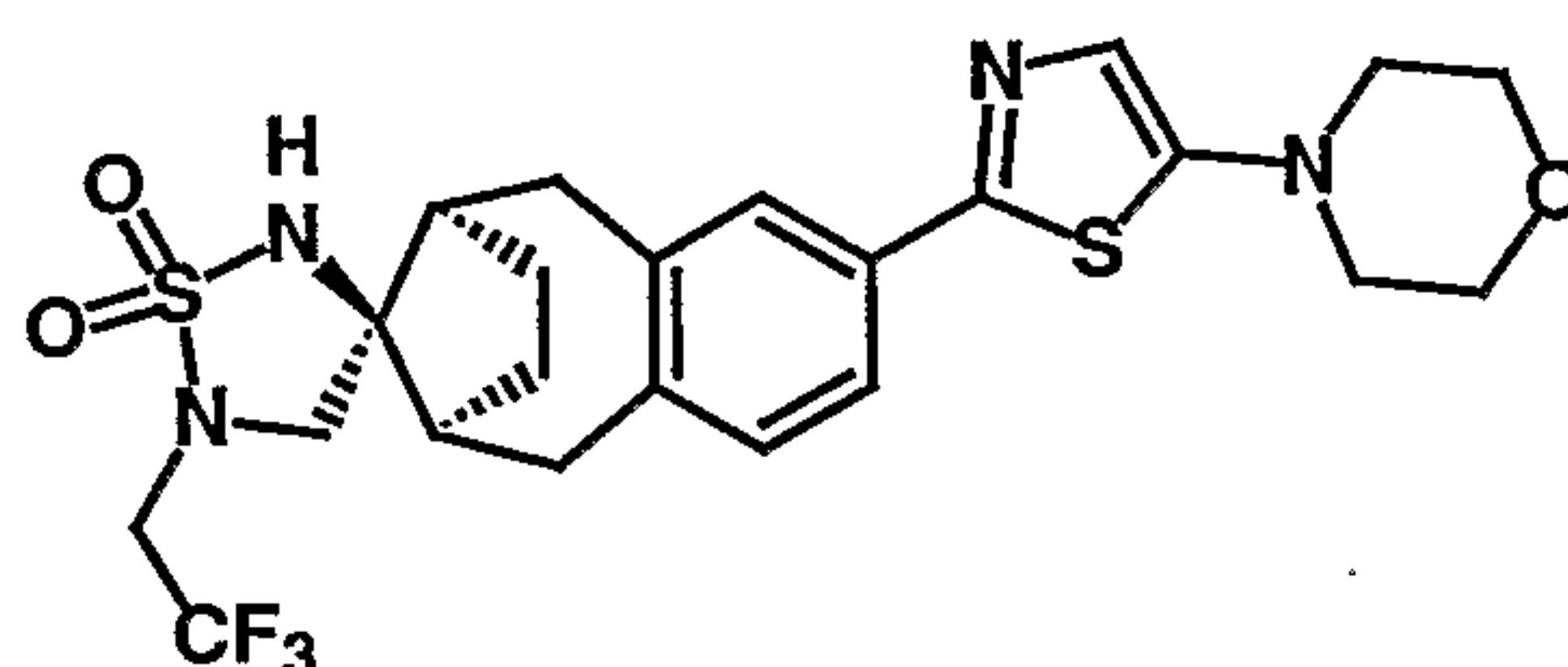
10 **[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(piperidin-1-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**



Prepared from the homochiral acid Intermediate B by the method described for Example 21. MS (ES+) 527 ($[\text{MH}]^+$). $[\alpha]_D = -25$ ($c=0.526$, DMSO)

Example 29

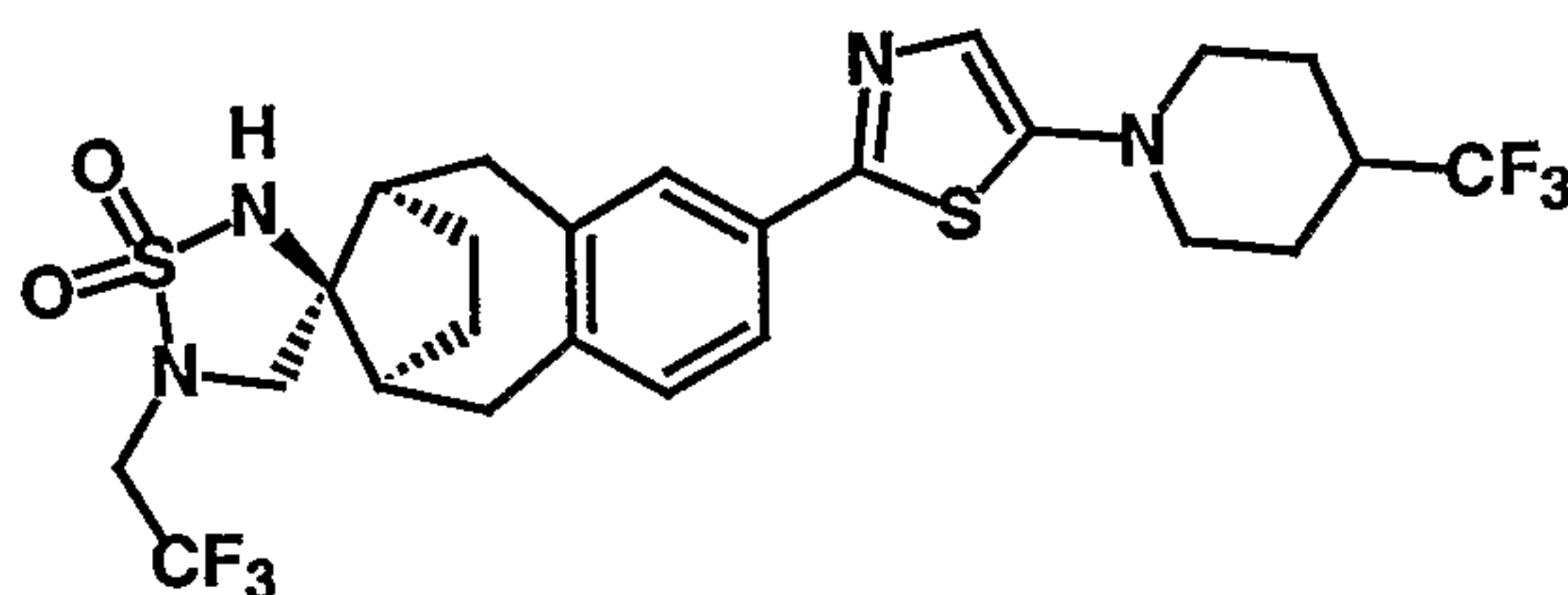
20 **[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(morpholin-4-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**



Prepared from the homochiral acid Intermediate B and morpholine by the method described for Example 21. MS (ES+) 529 ($[\text{MH}]^+$).

Example 30

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-trifluoromethyl-piperidin-1-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

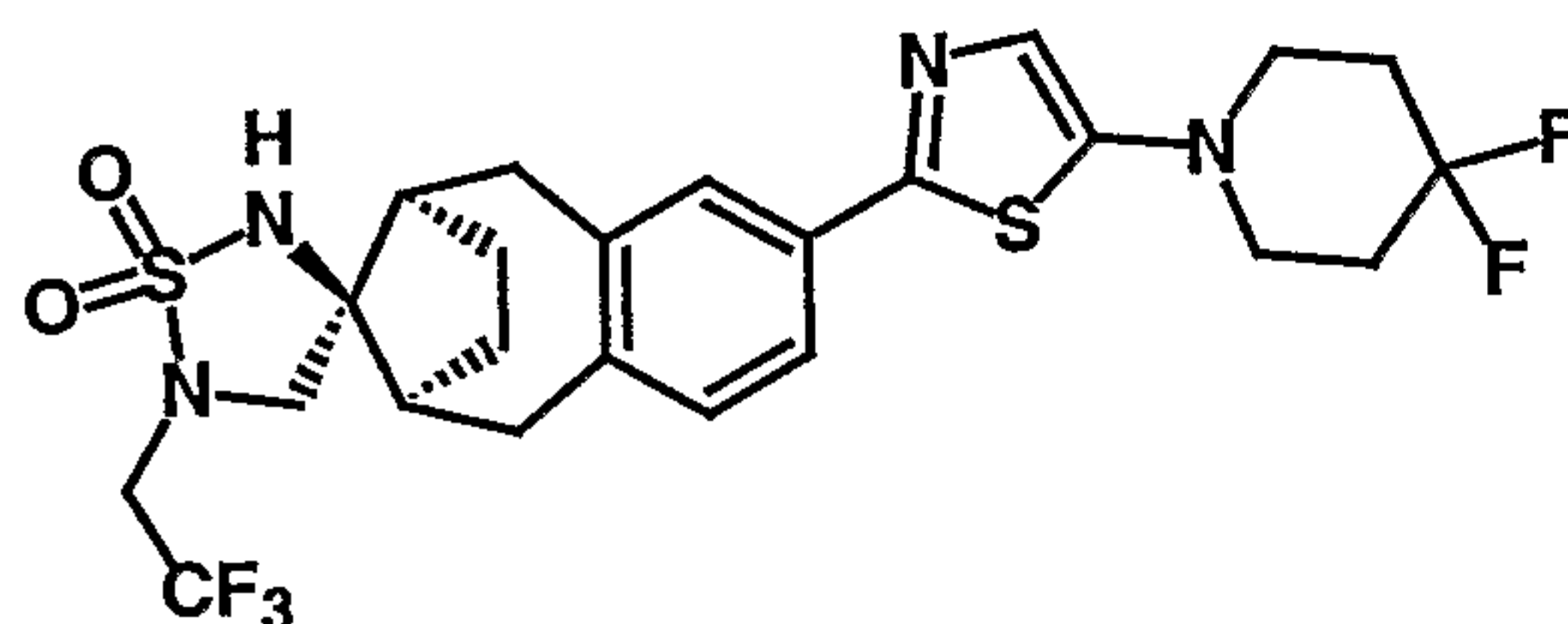


5

Prepared from the homochiral acid Intermediate B and 4-trifluoromethylpiperidine by the method described for Example 21. MS (ES+) 595 ([MH]⁺).

10 **Example 31**

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4,4-difluoropiperidin-1-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



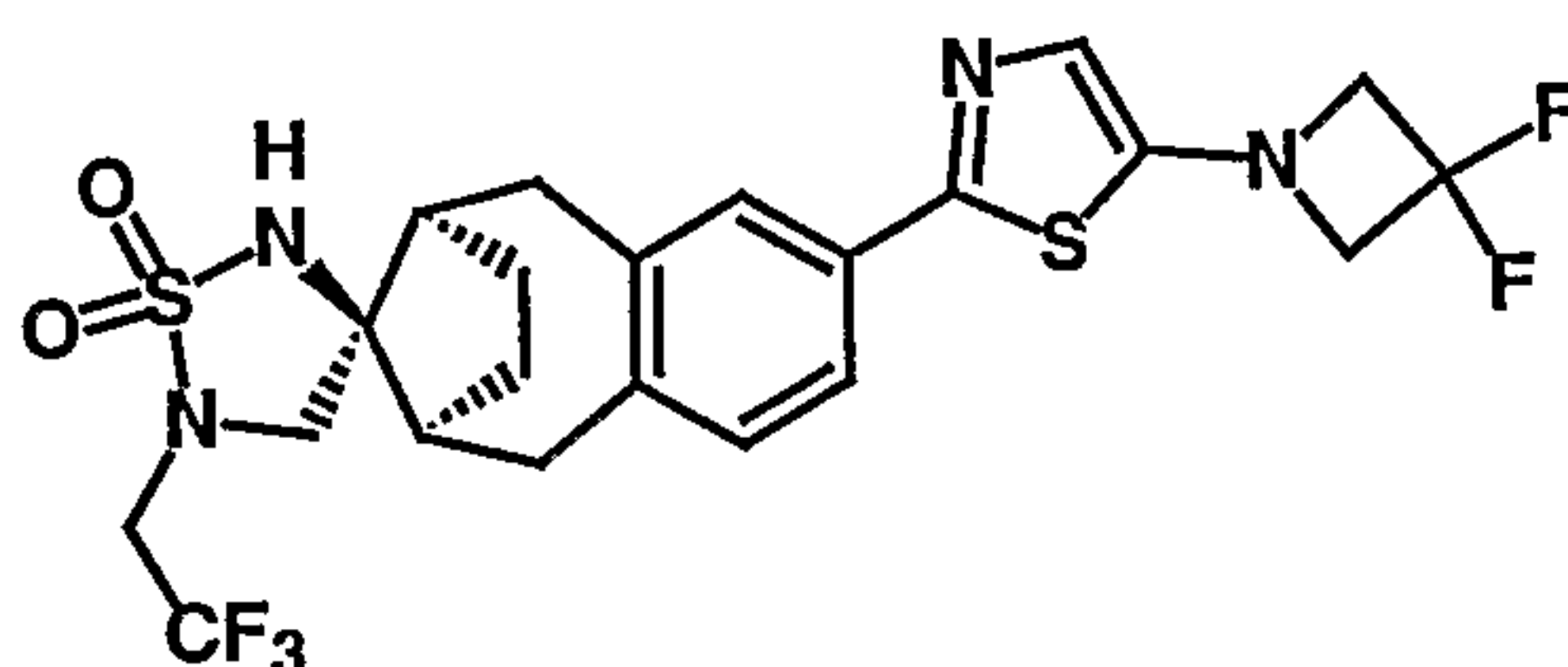
15

Prepared from the homochiral acid Intermediate B and 4,4-difluoropiperidine by the method described for Example 21. MS (ES+) 563 ([MH]⁺).

20 **Example 32**

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3,3-difluoroazetidin-1-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

- 75 -



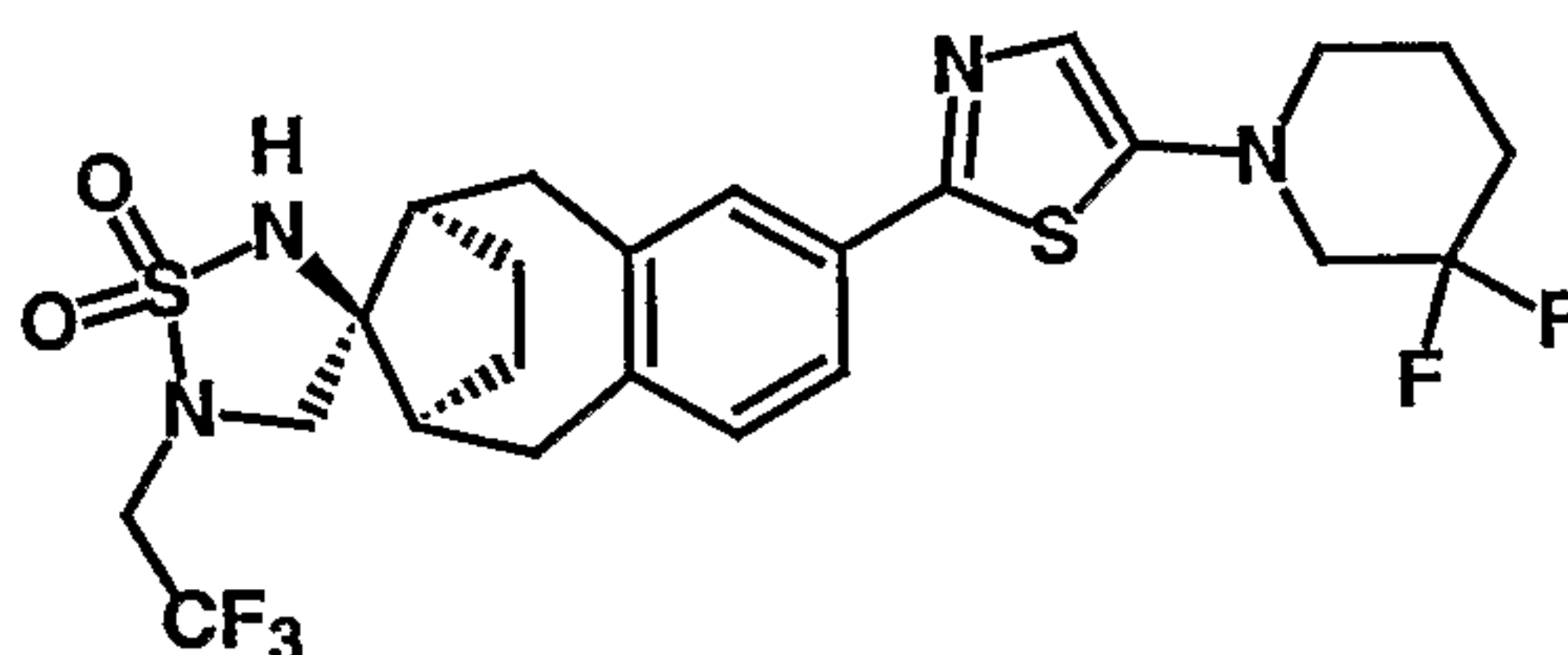
Prepared from the homochiral acid Intermediate B and 3,3-difluoroazetidine hydrochloride by the method described for Example 21. MS (ES+) 535 ([MH]⁺).

5

Example 33

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3,3-difluoropiperidin-1-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide.

10

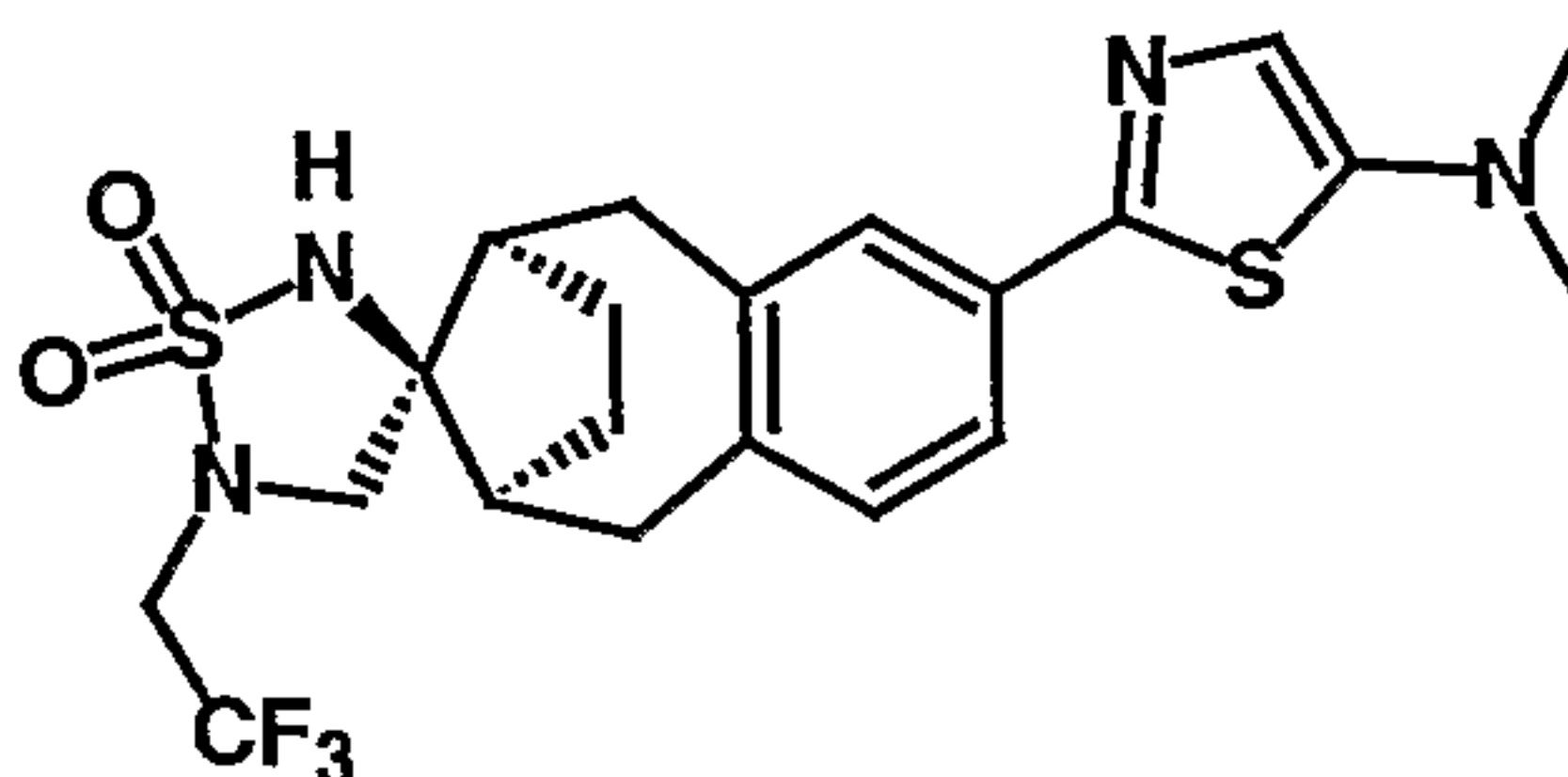


Prepared from the homochiral acid Intermediate B and 3,3-difluoropiperidine hydrochloride by the method described for Example 21. MS (ES+) 563 ([MH]⁺).

15

Example 34

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(dimethylamino)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

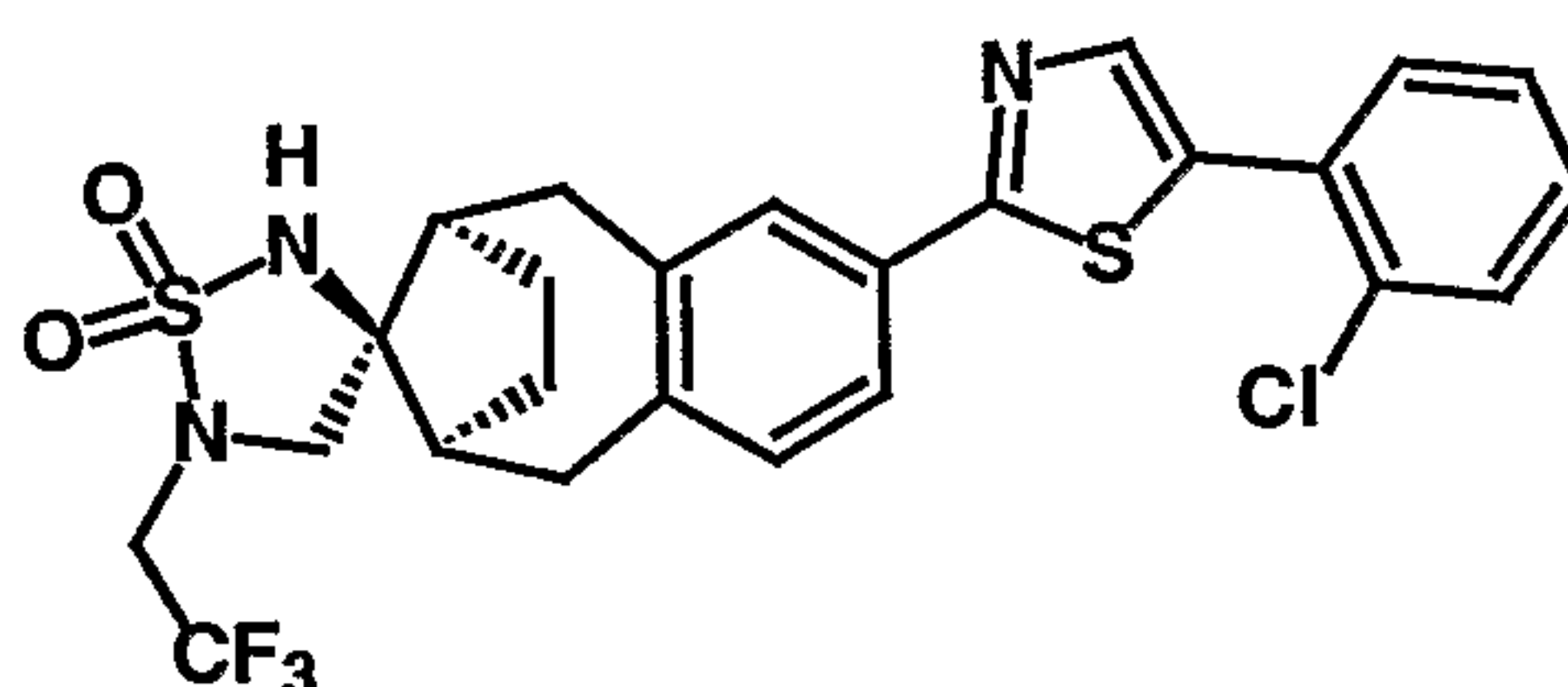


20

Prepared from the homochiral acid Intermediate B and dimethylamine hydrochloride by the method described for Example 21. MS (ES+) 563 ([MH]⁺).

Example 35

(-)-[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2-chlorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



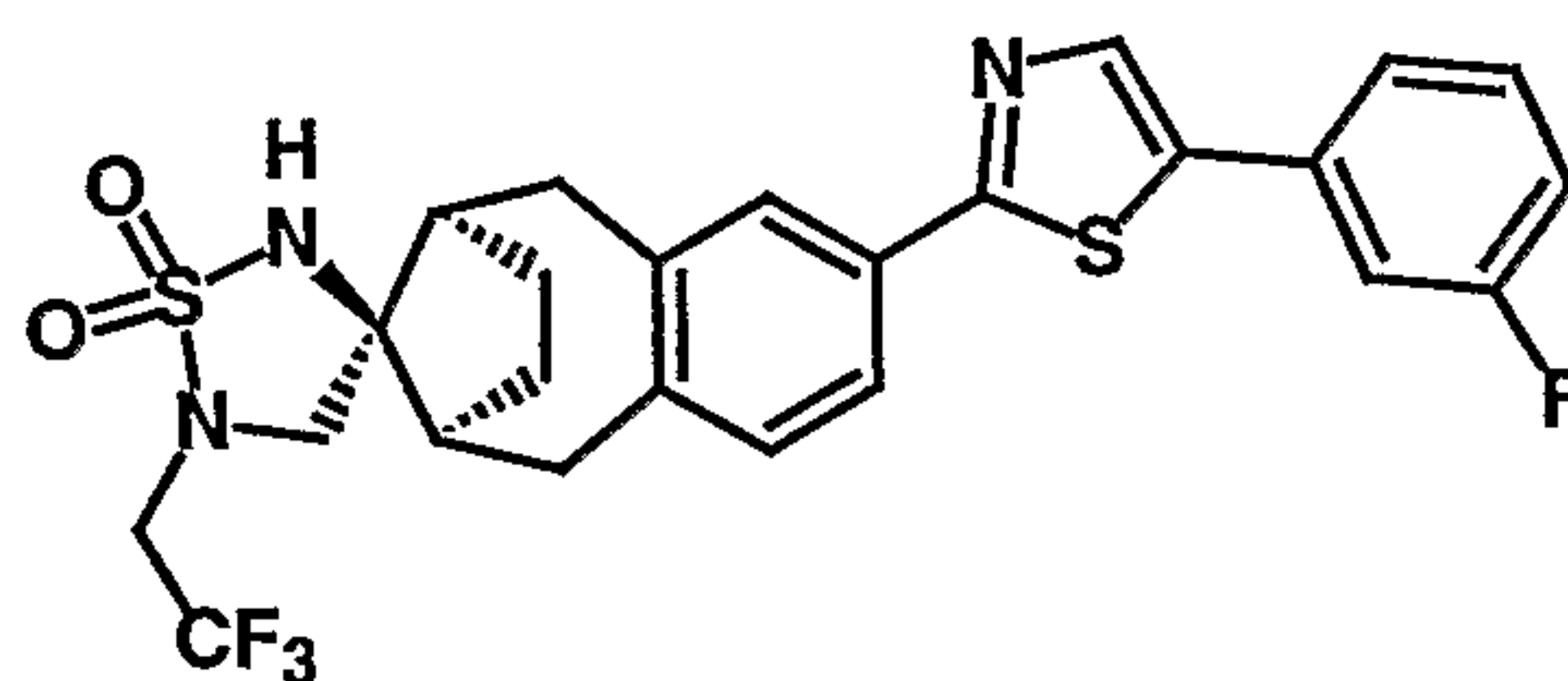
Prepared from the acid, Intermediate B, and 2'-amino-(2-chloroacetophenone) hydrochloride by the method described for Example 6 Step 1 and Example 16 to give the title compound.

MS (ES+) 554, 556 ([MH]⁺).

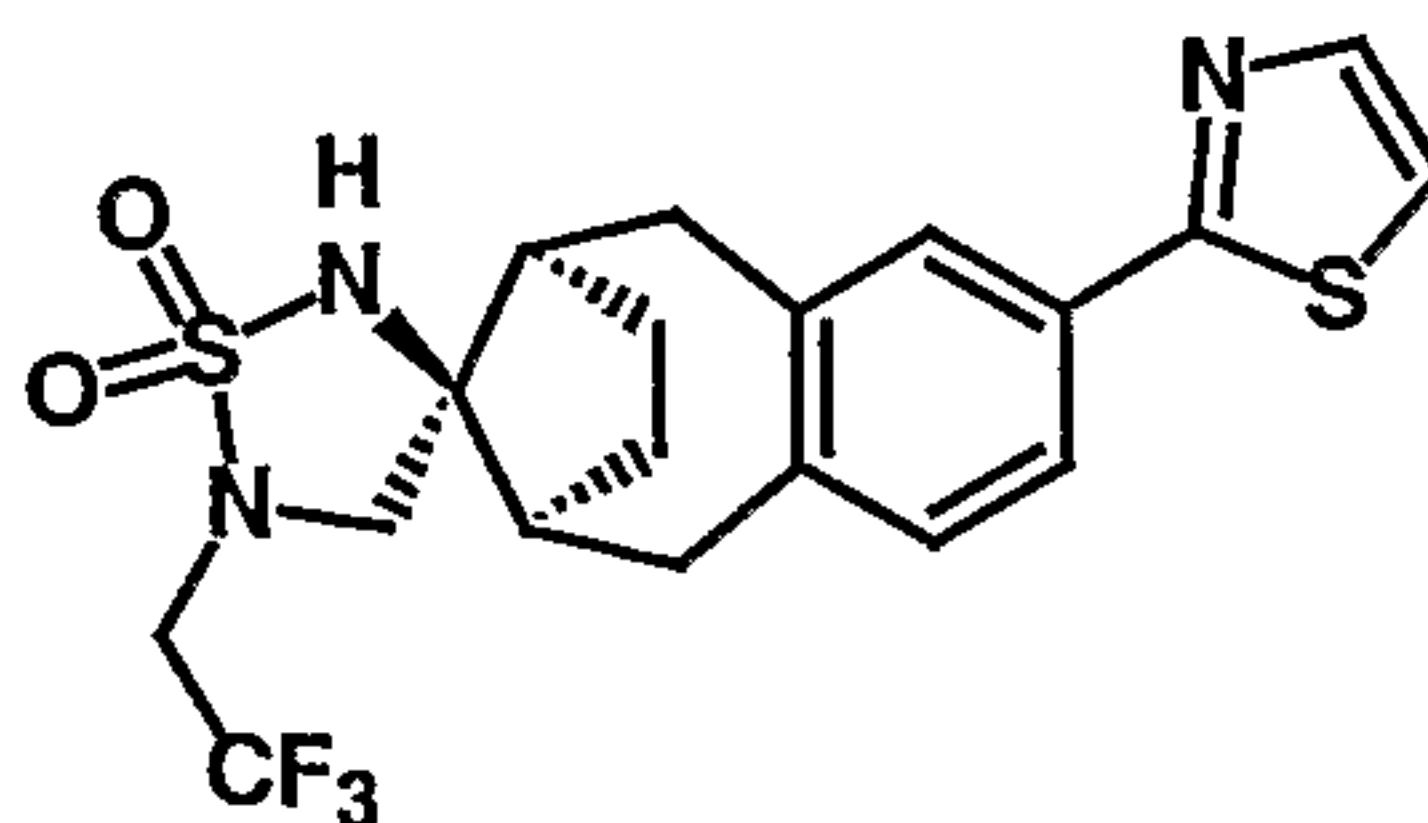
$\alpha_D -18$ (c=0.55, DMSO).

Example 36

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3-fluorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Step 1: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

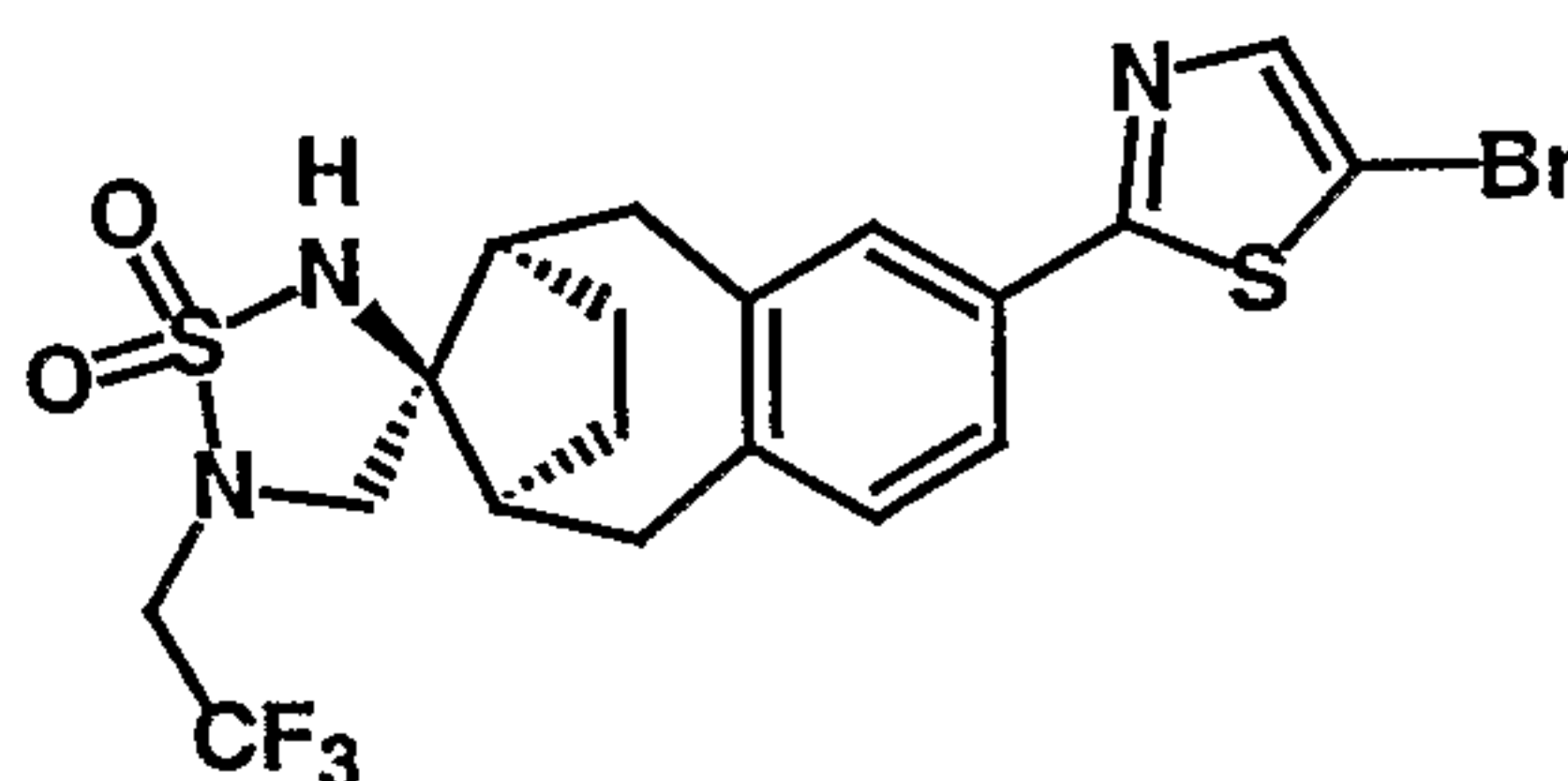


[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-5'-(2,2,2-trifluoroethyl)spiro[6,9-

- 77 -

methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide was synthesised from the triflate Intermediate D using the method described in Example 24, Step 1. Three portions of 100 mg of the aforementioned boronate were weighed into separate microwave reaction tubes. To each tube were added toluene (2 mL), ethanol (1 mL), water (1 mL), 2-bromothiazole (28 μ L), potassium carbonate (142 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (17 mg). The reaction tubes were sealed and the mixtures heated in a microwave at 100°C for 5 min. Thin-layer chromatographic analysis indicated incomplete reaction, therefore a spatula tipful of the palladium catalyst was added to each reaction mixture before re-sealing and heating for a further 5 min at 100°C. The reaction mixtures were combined, poured into satd. NaHCO₃(aq) and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to give a brown gum. Chromatography on silica eluting with 25% ethyl acetate in hexane gave the title compound (200 mg, 72% yield). δ (¹H, 400MHz, CDCl₃) 1.33-1.39 (2H, m), 1.71-1.76 (2H, m), 2.46-2.50 (2H, m), 2.72-2.84 (2H, m), 3.23-3.28 (2H, m), 3.44 (2H, s), 3.69 (2H, q, J = 8.7 Hz), 4.78 (1H, s), 7.17 (1H, d, J = 7.8 Hz), 7.32 (1H, d, J = 3 Hz), 7.69 (1H, dd, J = 7.8, 1.7 Hz), 7.74 (1H, s), 7.85 (1H, d, J = 3 Hz); MS (ES+) 444 ([MH]⁺).

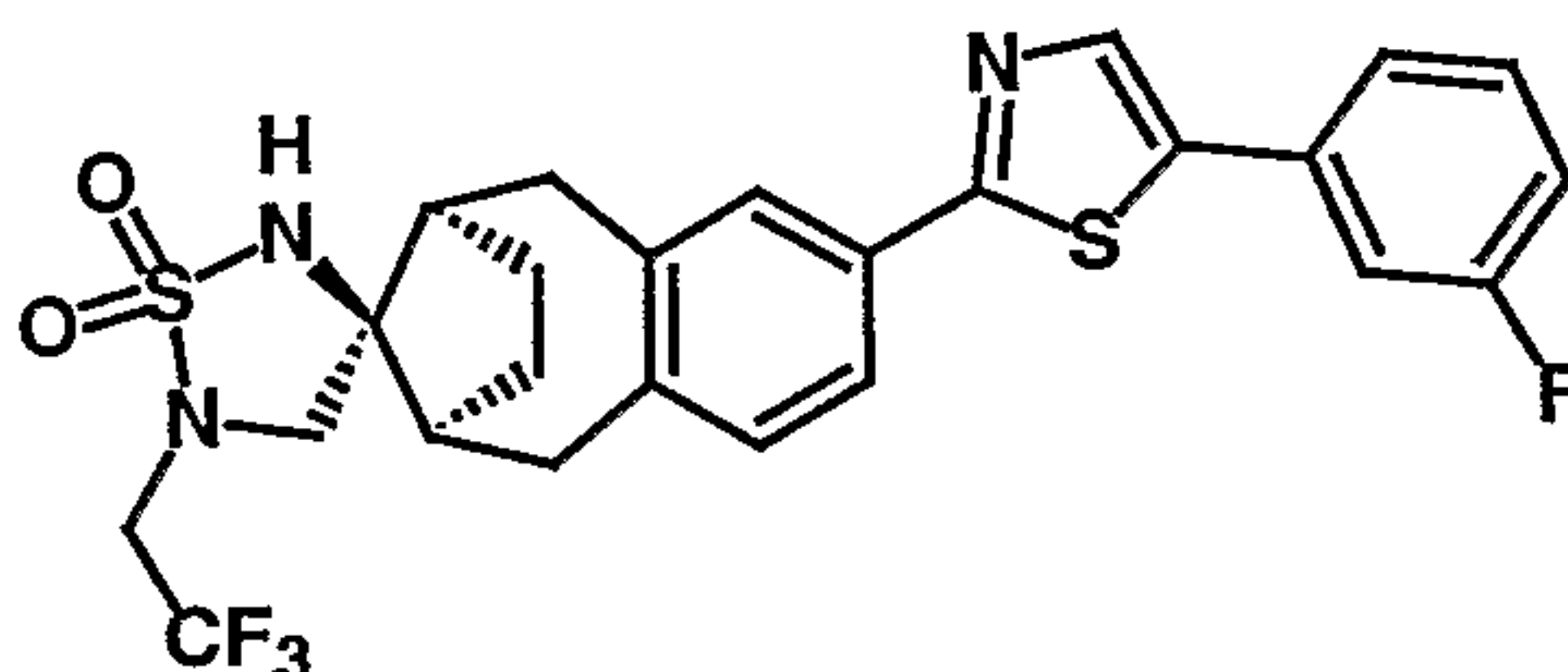
Step 2: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-bromothiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



To the thiazole from Step 1 (400 mg) was added acetic acid (5 mL) followed by bromine (46 μ L). The reaction mixture was stirred at room

temperature overnight. Cold water was added and the precipitate was collected by filtration, washing with water. The solid was dissolved in ethyl acetate, washed with 10% Na₂CO₃ solution_(aq) and then brine before being dried over Na₂SO₄ and concentrated. Chromatography on silica
 5 eluting with 25% ethyl acetate in hexane provided the title compound (240 mg, 51% yield) together with recovered starting material (33%). δ (¹H, 400MHz, CDCl₃) 1.33-1.37 (2H, m), 1.72-1.76 (2H, m), 2.47-2.50 (2H, m), 2.72-2.82 (2H, m), 3.23-3.27 (2H, m), 3.44 (2H, s), 3.69 (2H, q, J = 8.7 Hz), 4.77 (1H, s), 7.17 (1H, d, J = 7.8 Hz), 7.58 (1H, dd, J = 7.8, 1.6 Hz), 7.63
 10 (1H, d, J = 1.6 Hz), 7.72 (1H, s); MS (ES+) 522, 524 ([MH]⁺).

Step 3: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3-fluorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



15

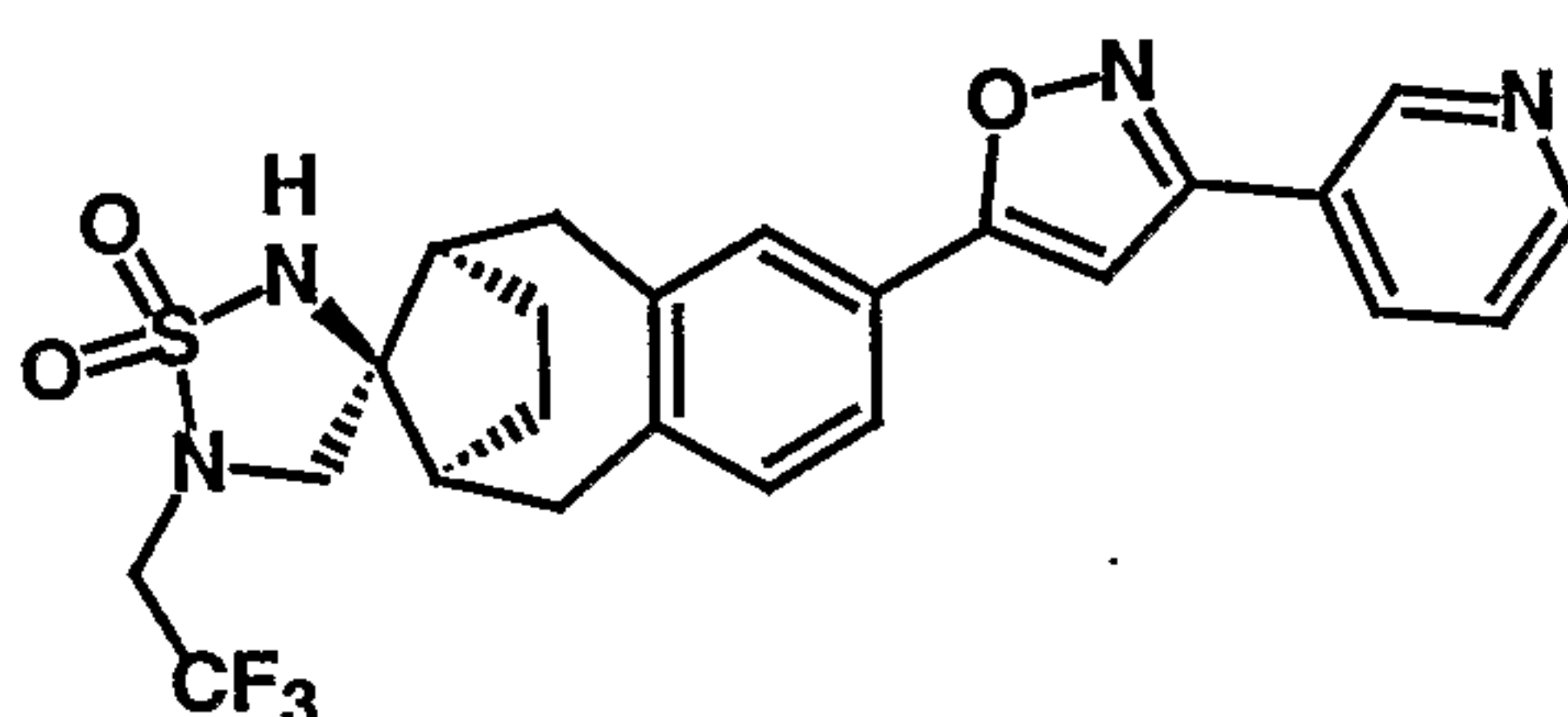
To a solution of the bromide from Step 2 (20 mg) in toluene (0.5 mL), ethanol (0.25 mL) and water (0.25 mL) were added 3-fluorophenylboronic acid (8 mg), potassium carbonate (26 mg) and
 [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with
 20 dichloromethane (3 mg). The mixture was heated in a microwave at 100°C for 5 min. Additional catalyst was added and the mixture was heated at 100°C for a further 10 min. The reaction mixture was poured into satd. NaHCO_{3(aq)} and extracted with ethyl acetate (X2). The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated.
 25 Chromatography on silica eluting with 25% ethyl acetate in hexane gave the title compound (5.5 mg, 27%). δ (¹H, 400MHz, CDCl₃) 1.31-1.41 (2H, m), 1.71-1.77 (2H, m), 2.47-2.51 (2H, m), 2.72-2.84 (2H, m), 3.25-3.29 (2H, m), 3.45 (2H, s), 3.70 (2H, q, J = 8.7 Hz), 4.93 (1H, s), 7.01-7.06 (1H, m),

- 79 -

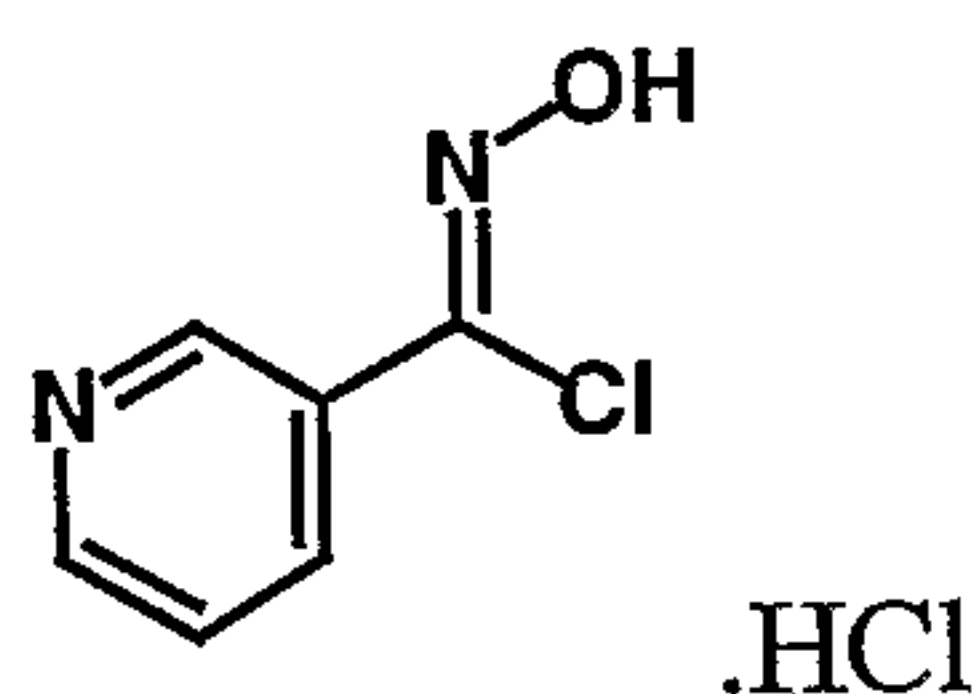
7.18 (1H, d, $J = 7.8$ Hz), 7.28-7.31 (1H, m), 7.37-7.41 (2H, m), 7.68 (1H, dd, $J = 7.8, 1.6$ Hz), 7.73 (1H, d, $J = 1.2$ Hz), 8.00 (1H, s); MS (ES+) 538 ([MH]⁺).

5 Example 37

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(3-pyridyl)-isoxazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



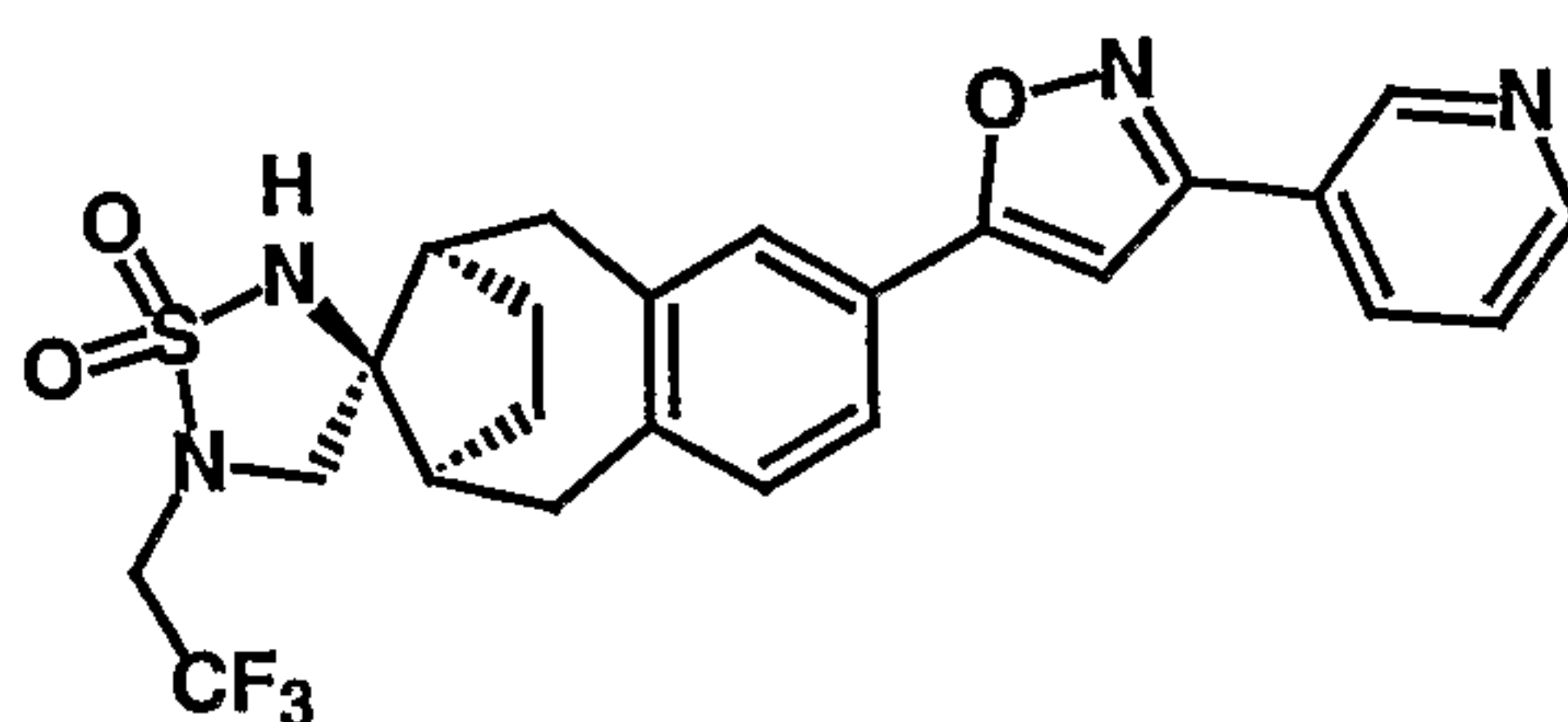
10 Step 1: α -Chloro-3-pyridinealdoxime hydrochloride



Chlorine gas was bubbled through a cold (0°C) suspension of pyridine-3-aldoxime (5.0 g, 40.9 mmol) in dichloromethane (150 mL) until the solution was saturated. The reaction vessel was stoppered and stirred, whilst allowed to warm to room temperature, for 16 hours. The excess chlorine was blown off by a stream of nitrogen and the solids collected by filtration, washed with dichloromethane and dried *in vacuo* to give the chloro-oxime hydrochloride as a white solid (7.5 g, 94%). δ (¹H, 400 MHz, d6-DMSO) 7.69 (1 H, dd, $J = 8.4$ & 5.3 Hz), 8.31-8.34 (1 H, m), 8.76 (1 H, dd, $J = 4.9$ & 1.4 Hz), 9.02 (1 H, d, $J = 0.5$ Hz) and 12.86 (1 H, s). MS (ES+) 157 ([MH]⁺).

Step 2: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(3-pyridyl)-isoxazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

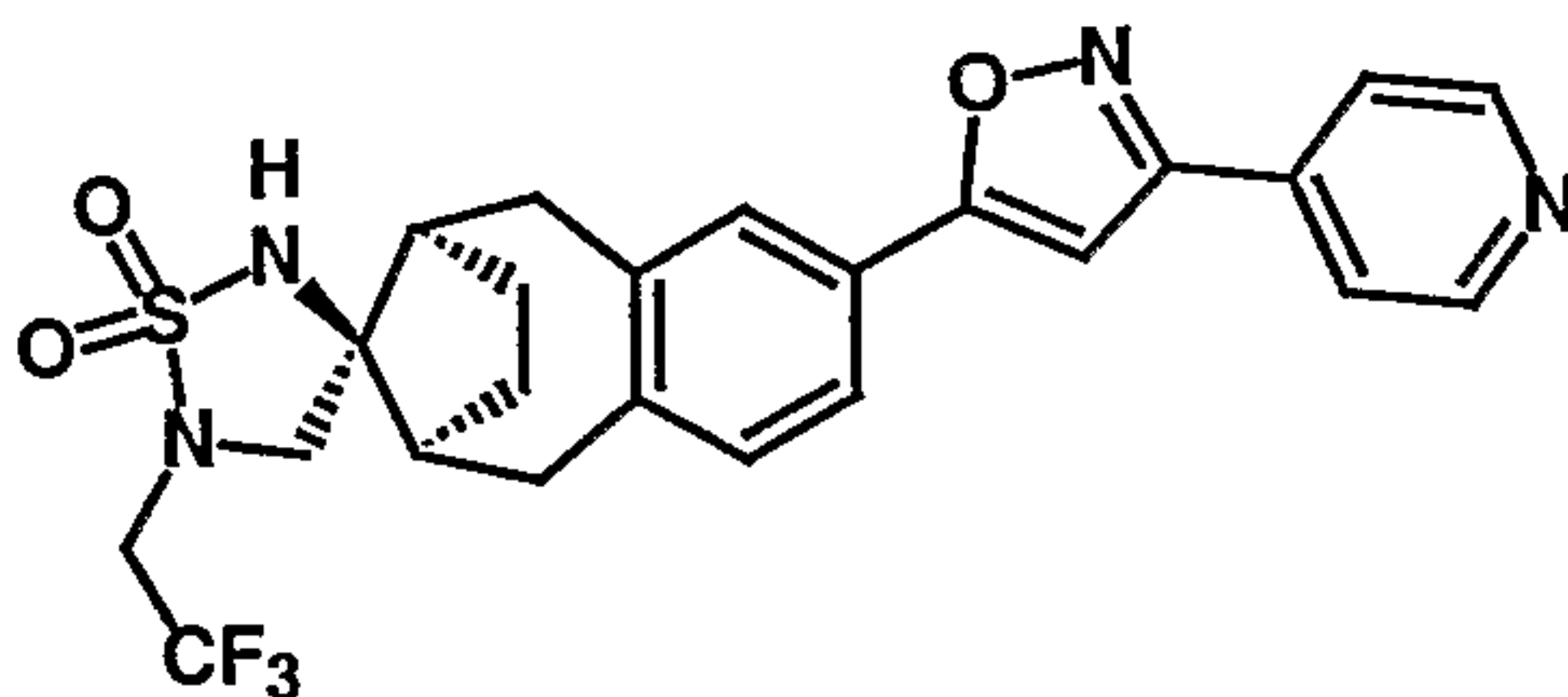
- 80 -



[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-ethynyl-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide was synthesised from the homochiral triflate Intermediate E using the method described in Example 22, Steps 1 and 2. Triethylamine (78 μ L, 0.56 mmol) was added dropwise to a mixture of the aforementioned acetylene (54 mg, 0.14 mmol) and the chloro-oxime from Step 1 (54 mg, 0.28 mmol) in dichloromethane (10 mL) and the reaction was stirred at room temperature for 65 hours. The reaction was diluted with sodium bicarbonate (sat, 25 mL) and extracted with dichloromethane. The extracts were washed with water, dried (MgSO_4) and evaporated *in vacuo* to give a yellow solid, which was purified by column chromatography, eluting with ethyl acetate:iso-hexane (2:1) to give the title compound as a white solid (38 mg, 54%). δ (^1H , 400MHz, d_6 -DMSO) 1.04-1.09 (2H, m), 1.72-1.75 (2H, m), 2.39-2.44 (2H, m), 2.68-2.75 (2H, m), 3.21-3.29 (2H, m), 3.43 (2H, s), 4.03 (2H, q, $J = 9.6$ Hz), 7.34 (1H, d, $J = 7.8$ Hz), 7.63-7.69 (4H, m), 8.07 (1H, s), 8.41-8.45 (1H, m), 8.79 (1H, s), 9.17 (1H, s). MS (ES+) 505 ($[\text{MH}]^+$).

20 Example 38

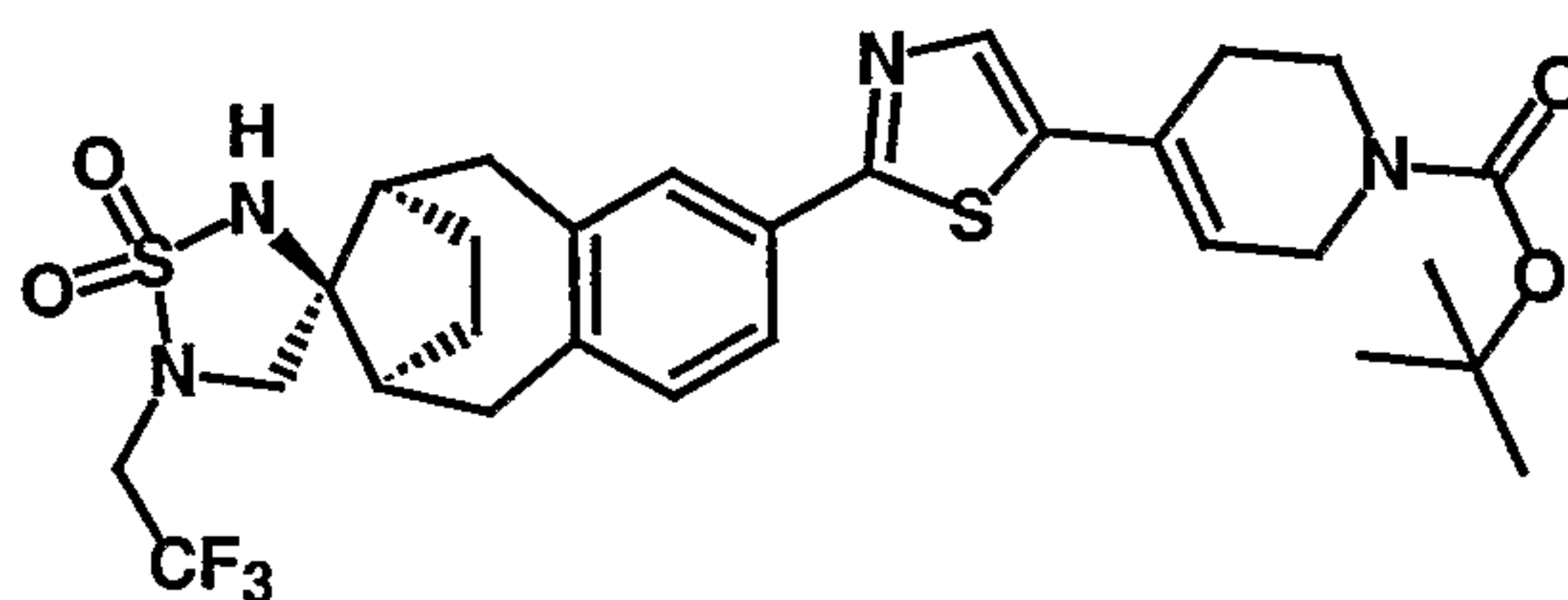
[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(3-(4-pyridyl)-isoxazol-5-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



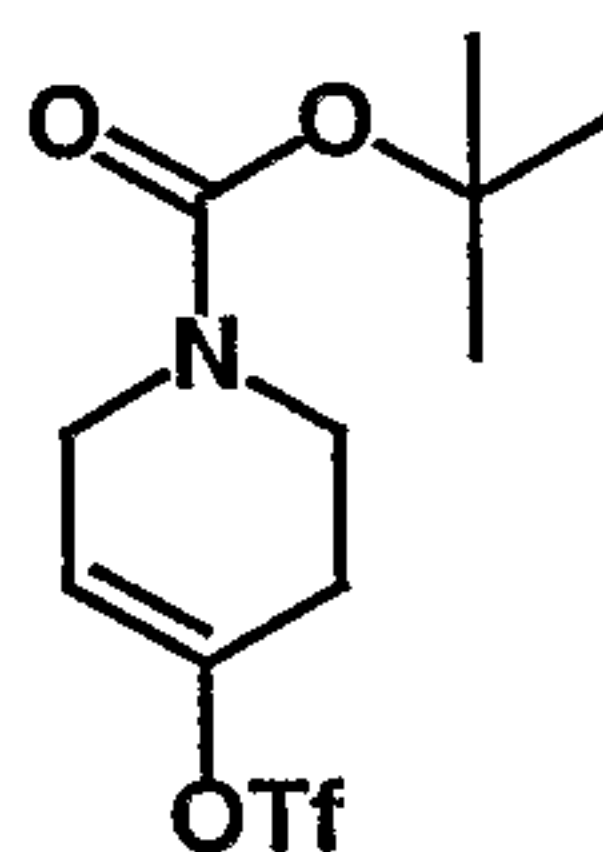
Prepared by the method described in Example 37, using pyridine-4-aldoxime. MS (ES+) 505 ([MH]⁺).

Example 39

5 [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

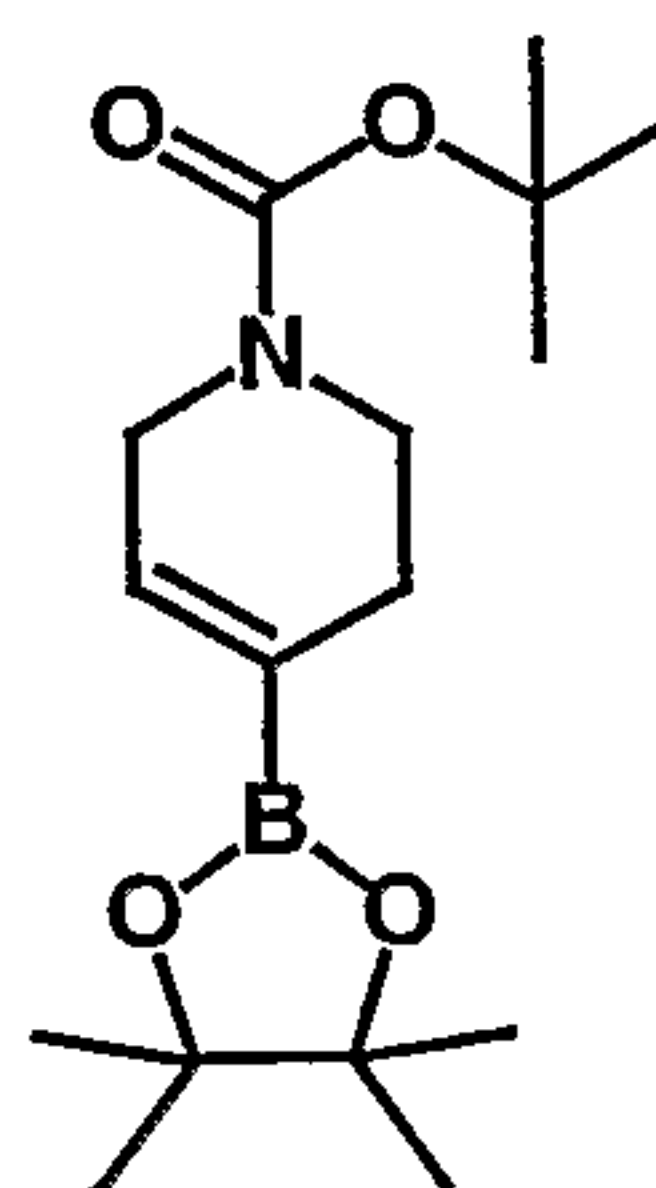


10 Step 1: 1-*tert*-Butoxycarbonyl-4-trifluoromethanesulphonyloxy-1,2,3,6-tetrahydropyridine



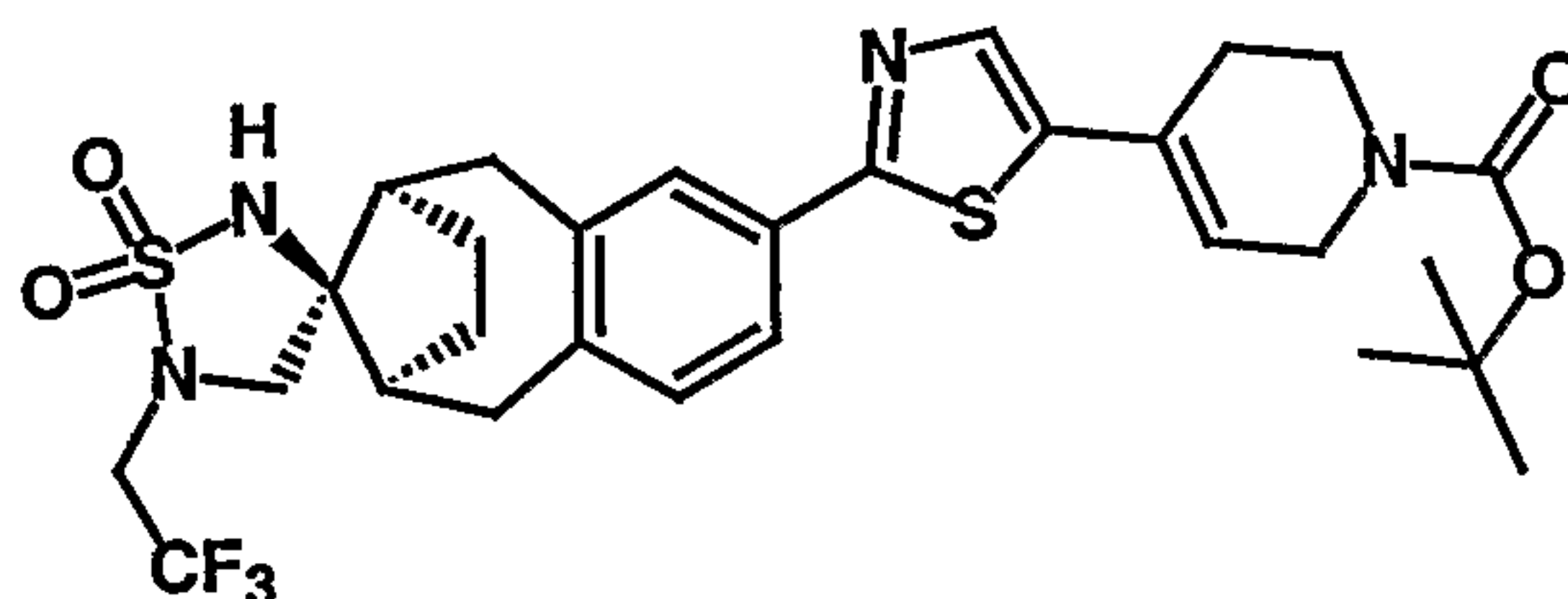
Prepared using the procedure described in Synthesis 1991, 993.

15 Step 2: 1-*tert*-Butoxycarbonyl-4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolanyl)-1,2,3,6-tetrahydropyridine



20 Prepared from the triflate from Step 1 by the method described for Example 24, Step 1.

Step 3: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



5

Prepared from the boronate from Step 2 and the bromide from Example 36, Step 2 by the method described for Example 36, Step 3. Contains ~10% unsubstituted thiazole.

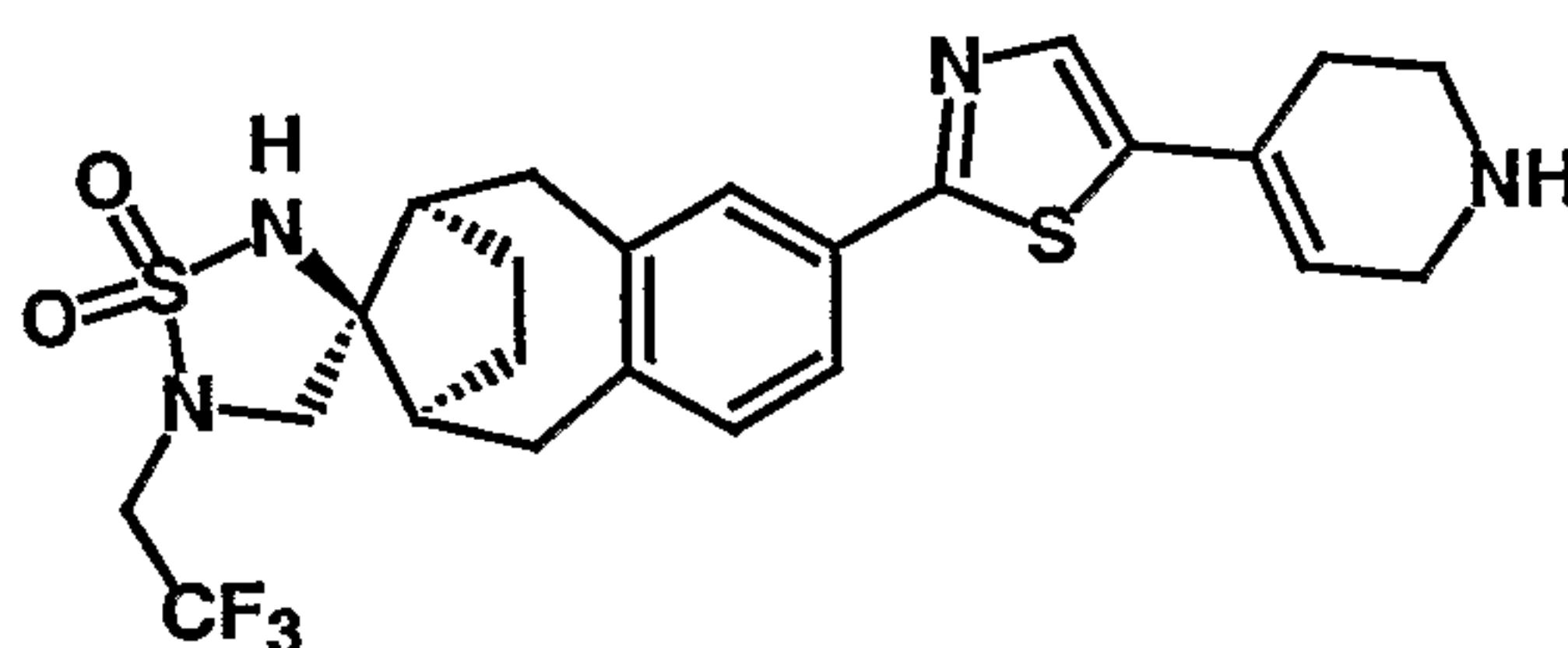
MS (ES+) 444, 625 ([MH]⁺).

10

Example 40

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(1,2,3,6-tetrahydro-1*H*-pyridin-4-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

15



20

A solution of the 1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridine from Example 39 Step 3 (0.11 g, 0.18 mmol) and trifluoroacetic acid (1 mL) in dichloromethane (1 mL) was stirred at room temperature for 90 minutes. The reaction was diluted with ethyl acetate (25 mL), washed with 10% aqueous sodium carbonate (25 mL) and brine (25 mL), dried over Na₂SO₄ and evaporated to give the title compound (0.06 g, 64%).

25

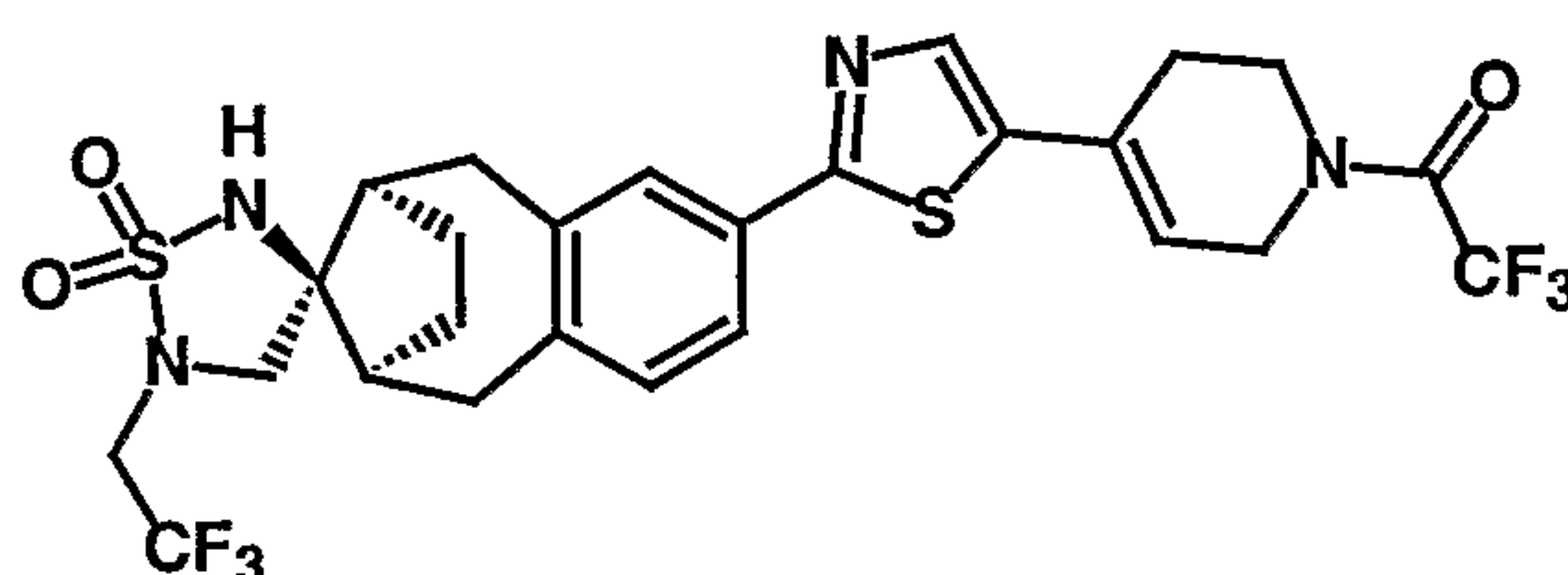
δ (¹H, 400MHz, MeOD) 1.21-1.28 (2H, m), 1.76-1.79 (2H, m), 2.46-2.50 (2H, m), 2.58-2.62 (2H, m), 2.69-2.77 (2 H, m), 3.15 (2H, t, *J* = 6 Hz), 3.31-3.38

(2H, m), 3.51 (2H, s), 3.55-3.57 (2H, m), 3.87 (2H, q, $J = 8.7$ Hz), 6.21-6.23 (1H, m), 7.21 (1 H, d, $J = 7.8$ Hz), 7.62-7.66 (2H, m), 7.73 (1H, s). MS (ES+) 525 ([MH]⁺).

5 Example 41

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(1-trifluoroacetyl-1,2,3,6-tetrahydropyridin-4-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

10



15

A solution of the tetrahydropyridine from Example 40 (0.05 g, 0.095 mmol) and triethylamine (54 μ L, 0.38 mmol) in dichloromethane (2 mL) was cooled to 0°C under nitrogen. Trifluoroacetic anhydride (80 μ L, 0.57 mmol) was added dropwise and the reaction allowed to warm to room temperature overnight. The reaction was diluted with ethyl acetate (25 mL), washed with 10% aqueous sodium carbonate (25 mL) and brine (25 mL), dried over Na₂SO₄ and evaporated to give the title compound as a 2:1 mixture of rotamers (0.034 g, 58%). MS (ES+) 621 ([MH]⁺).

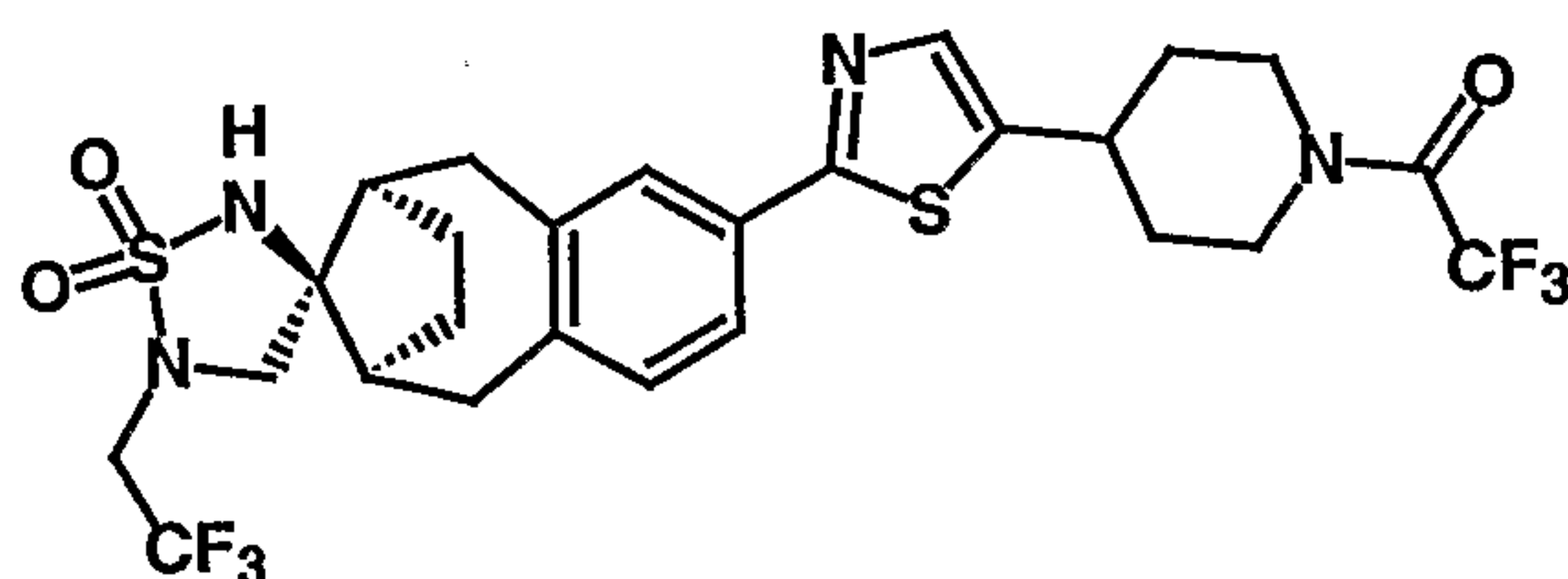
20

Example 42

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(1-trifluoroacetylpiperidin-4-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

25

- 84 -

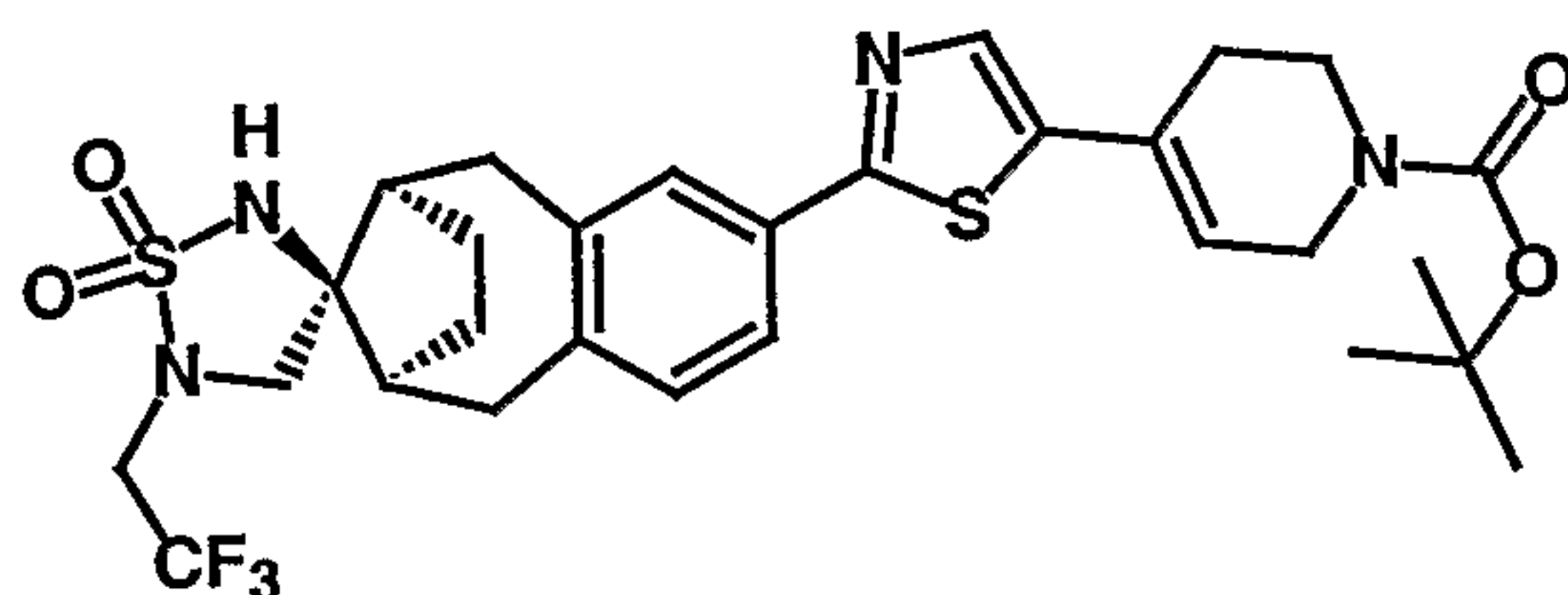


A mixture of the tetrahydropyridine from Example 41 (0.018 g, 0.029 mmol), palladium on carbon (0.01 g) and ethyl acetate (2 mL) was stirred under 1 atmosphere of hydrogen for 16 hours. The catalyst was removed by filtration through a glass fibre pad and the solvent removed *in vacuo* to give the title compound (0.018 g, quant.).

δ (^1H , 400MHz, CDCl_3) 1.29-1.38 (2H, m), 1.68-1.82 (4H, m), 2.16-2.20 (2H, m), 2.46-2.49 (2H, m), 2.70-2.80 (2H, m), 2.92-2.98 (1 H, m), 3.18-3.33 (4H, m), 3.44 (2H, s), 3.64-3.72 (2H, m), 4.11-4.15 (1H, m), 4.64 (1H, d, $J = 14$ Hz), 4.91 (1H, s) 7.15 (1H, d, $J = 7.8$ Hz), 7.55 (1 H, d, $J = 0.7$ Hz), 7.61 (1H, dd, $J = 1.5$ & 7.8 Hz), 7.66 (1H, s). MS (ES+) 623 ([MH] $^+$).

Example 43

(-)-[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



20

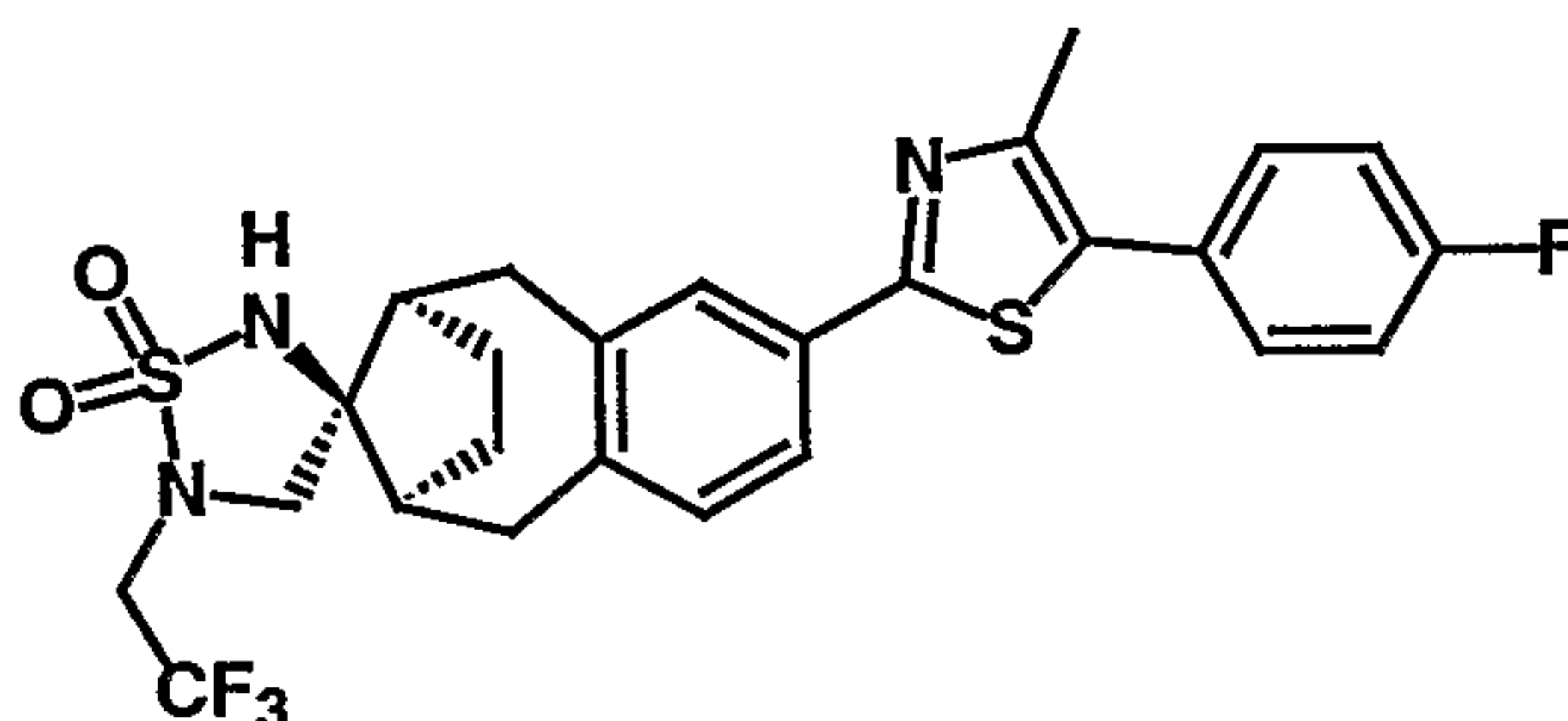
Prepared using [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-bromothiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide (prepared using the homochiral boronate from Example 24 Step 1 by the method described for Example 36 Steps 1-2) and the boronate from Example 39

25

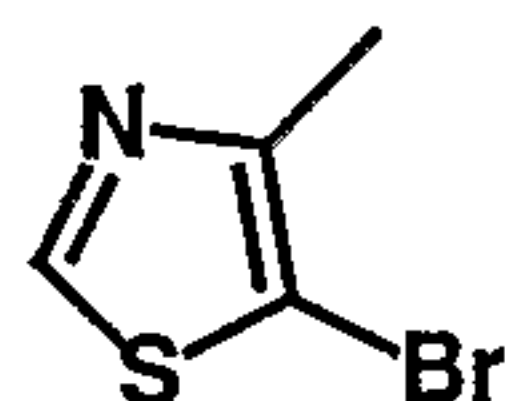
Step 2 using the method described for Example 36 Step 3. MS (ES+) 625 ([MH]⁺).; $[\alpha]_D = -11$ (c=0.62, DMSO, 23°C).

Example 44

- 5 **[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(4-methyl-5-(4-fluorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**



Step 1: 4-methyl-5-bromothiazole



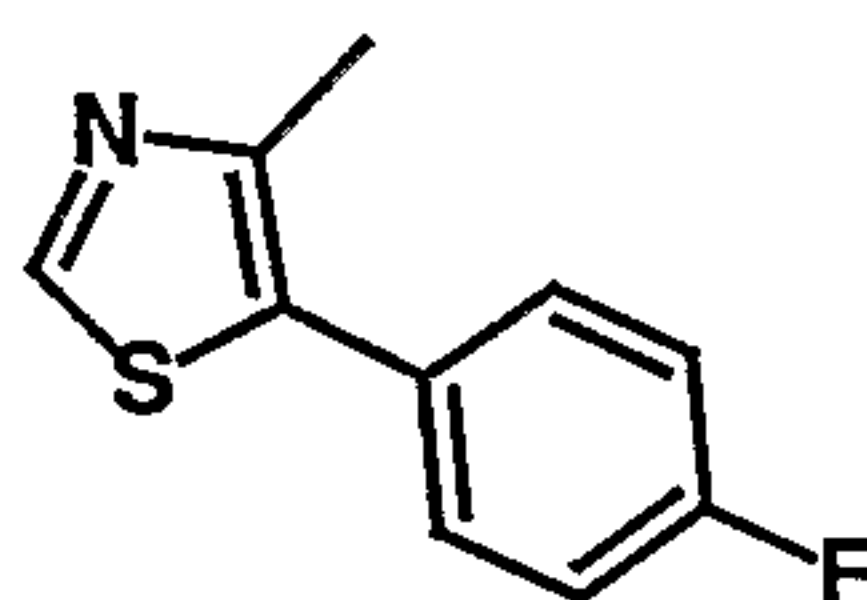
10

- 4-methylthiazole (200 μ L, 2.2mmol) and bromine (112 μ L, 2.2mmol) in acetic acid (2 mL) were protected from the light and stirred for 16 hours at room temperature. The mixture was washed with 10% aqueous sodium carbonate and extracted with ethyl acetate. The organic layers were washed with brine, dried over Na₂SO₄ and evaporated to give 4-methyl-5-bromothiazole (0.085 g, 22%).

15

δ (¹H, 400MHz, CDCl₃) 2.45 (3H, s), 8.69 (1H, s).

Step 2: 4-methyl-5-(4-fluorophenyl)thiazole

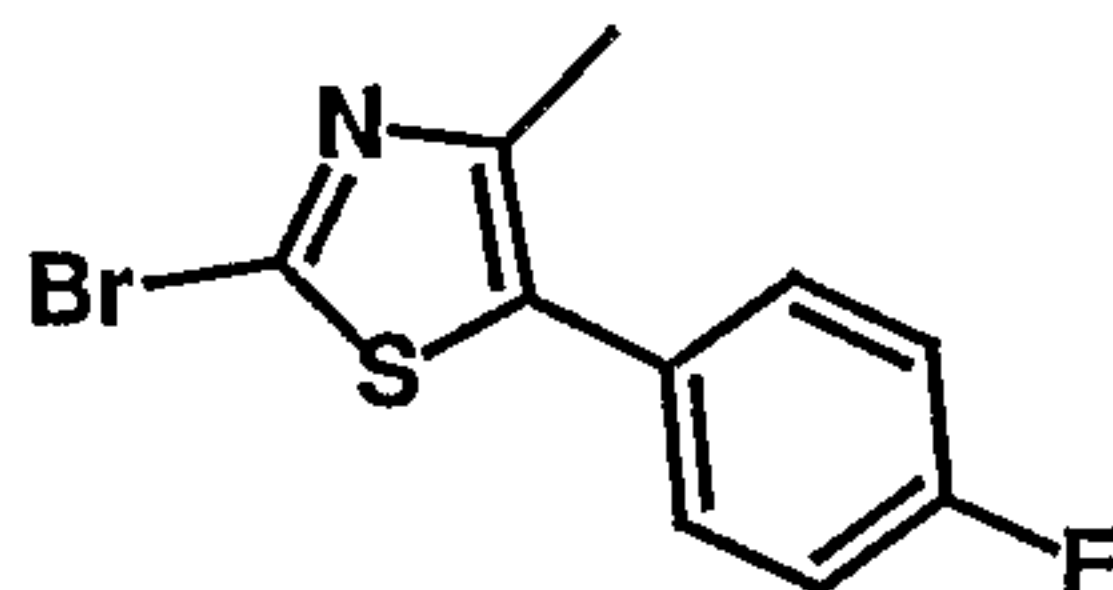


20

Prepared from the bromothiazole from Step 1 and 4-fluorobenzeneboronic acid by the method described for Example 36 Step 3.

δ (¹H, 400MHz, CDCl₃) 2.51 (3H, s), 7.10-7.15 (2H, m), 7.39-7.43 (2H, m), 8.68 (1H, s). MS (ES+) 194 ([MH]⁺).

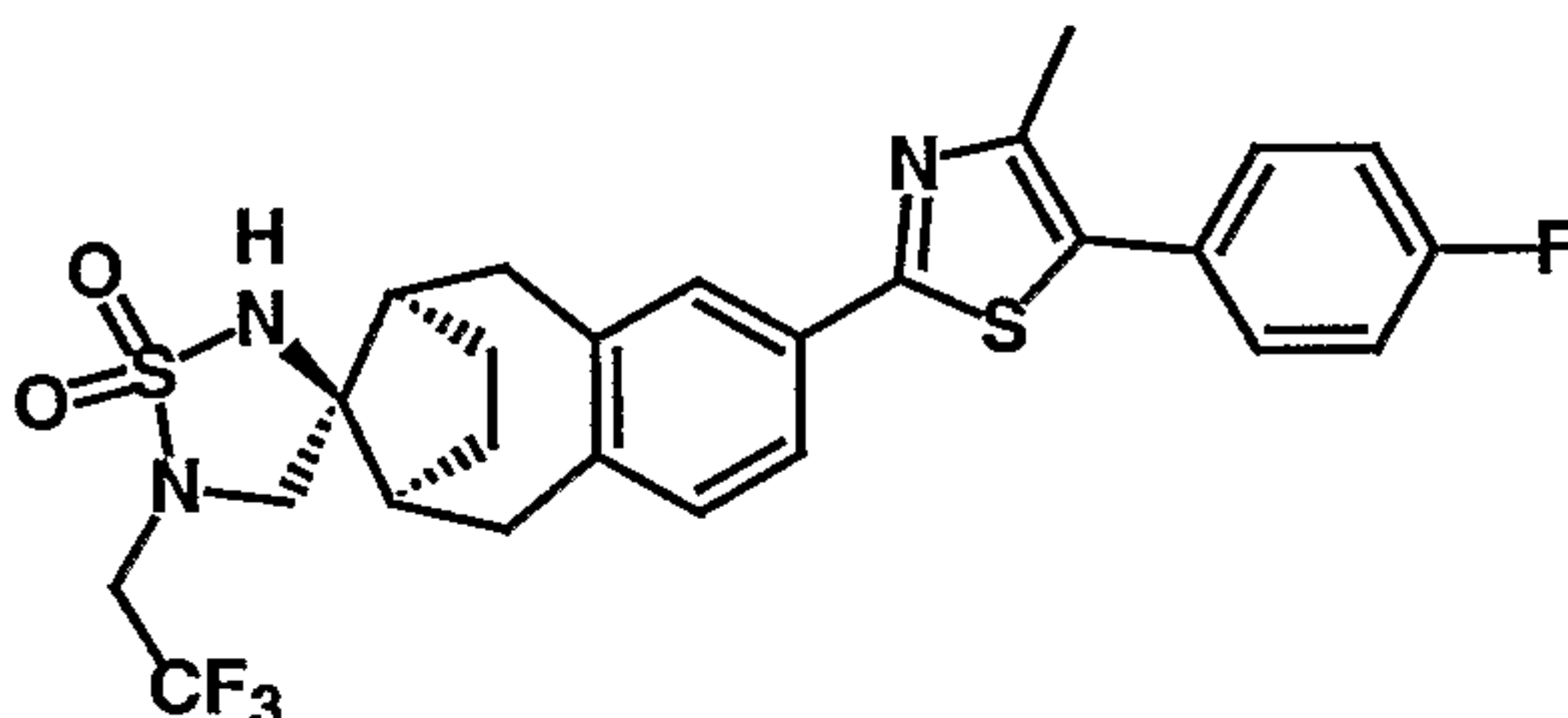
25

Step 3: 2-bromo-4-methyl-5-(4-fluorophenyl)thiazole

Prepared from the thiazole from Step 2 by the method described for Example 36 Step 2.

5 δ (^1H , 400MHz, CDCl_3) 2.43 (3H, s), 7.10-7.15 (2H, m), 7.34-7.37 (2H, m).
MS (ES+) 272, 274 ($[\text{MH}]^+$).

10 Step 4: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(4-methyl-5-(4-fluorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Prepared from the bromothiazole from Step 3 and the homochiral boronate from Example 24 Step 1 by the method described for Example 36 Step 3.

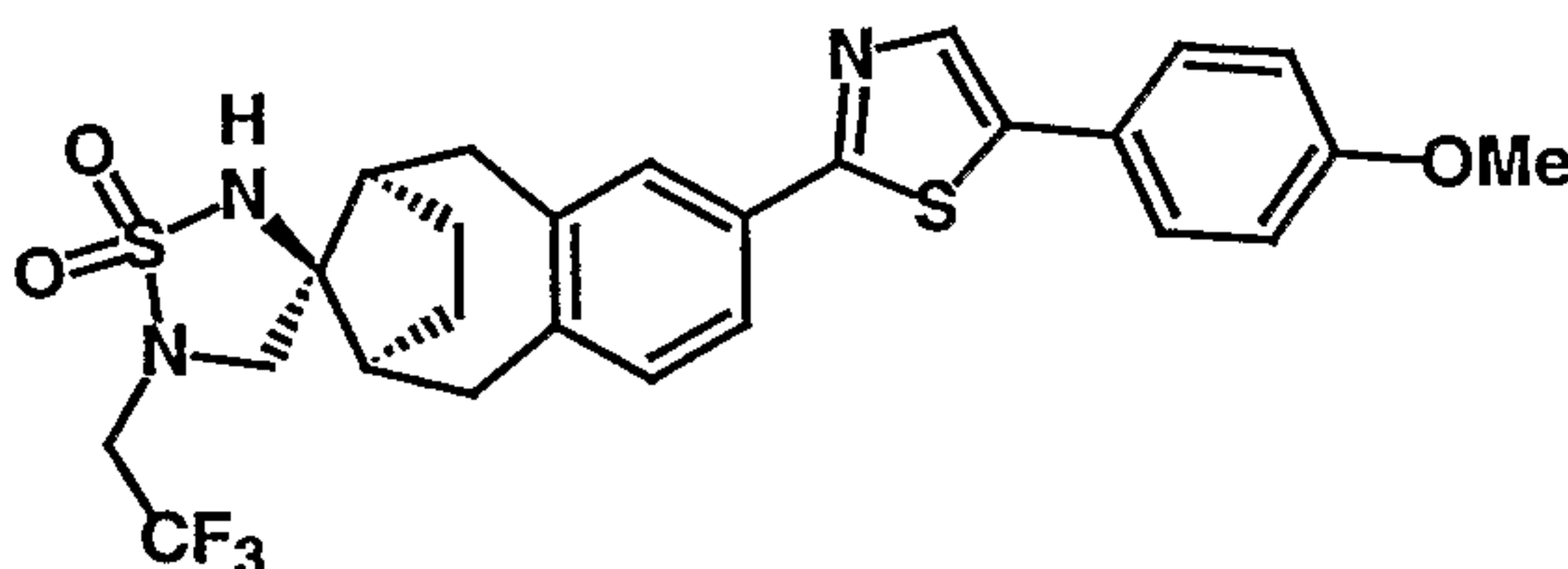
MS (ES+) 552 ($[\text{MH}]^+$).

15

Example 45

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-methoxyphenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

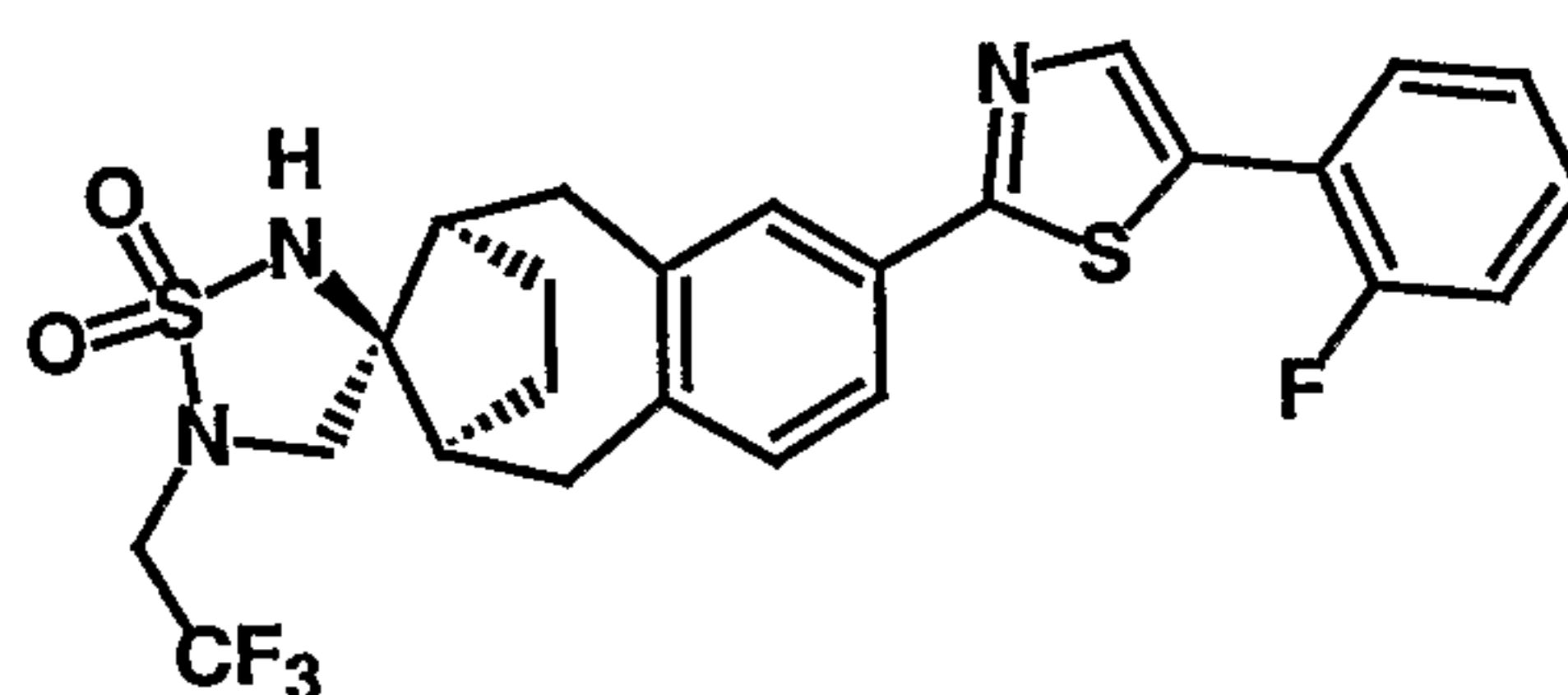
20



Prepared using the bromide from Example 36 Step 2 and 4-methoxybenzeneboronic acid by the method described for Example 36 Step 3. MS (ES+) 550 ([MH]⁺).

5 Example 46

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2-fluorophenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



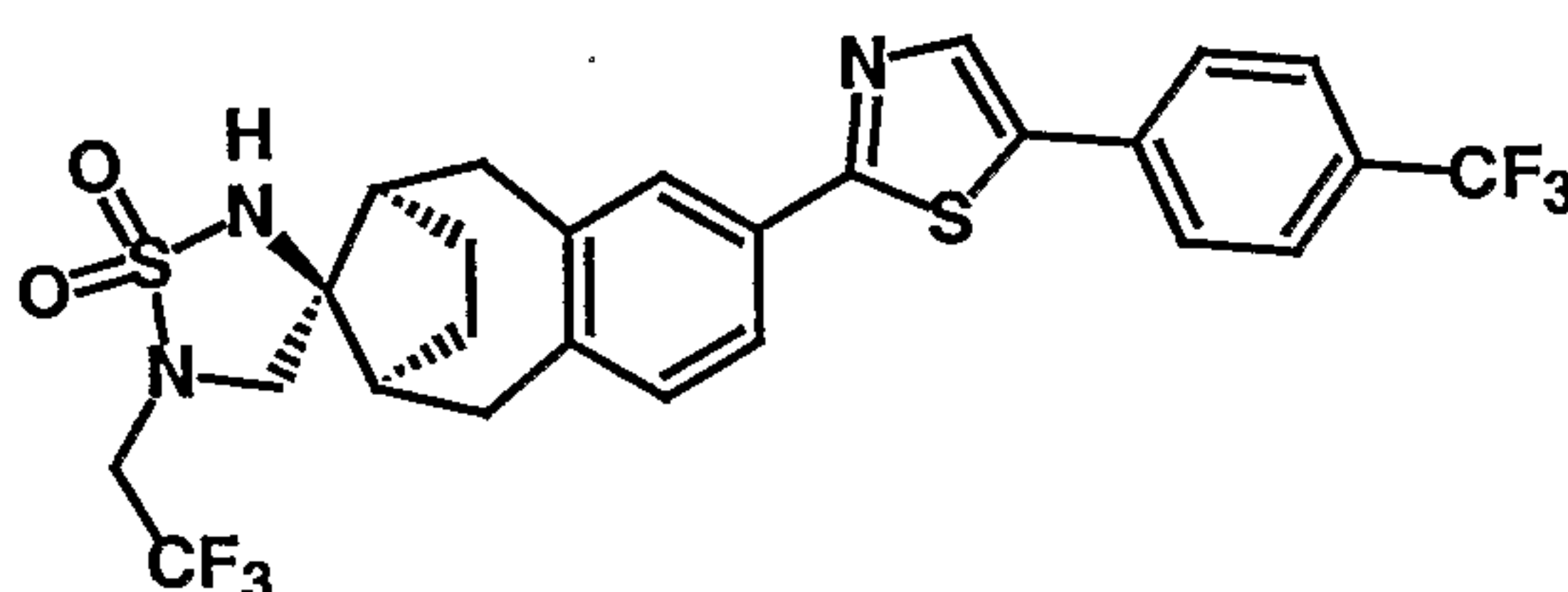
10

Prepared using the bromide from Example 36 Step 2 and 2-fluorobenzeneboronic acid by the method described for Example 36 Step 3. MS (ES+) 538 ([MH]⁺).

15 Example 47

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-trifluoromethylphenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

20



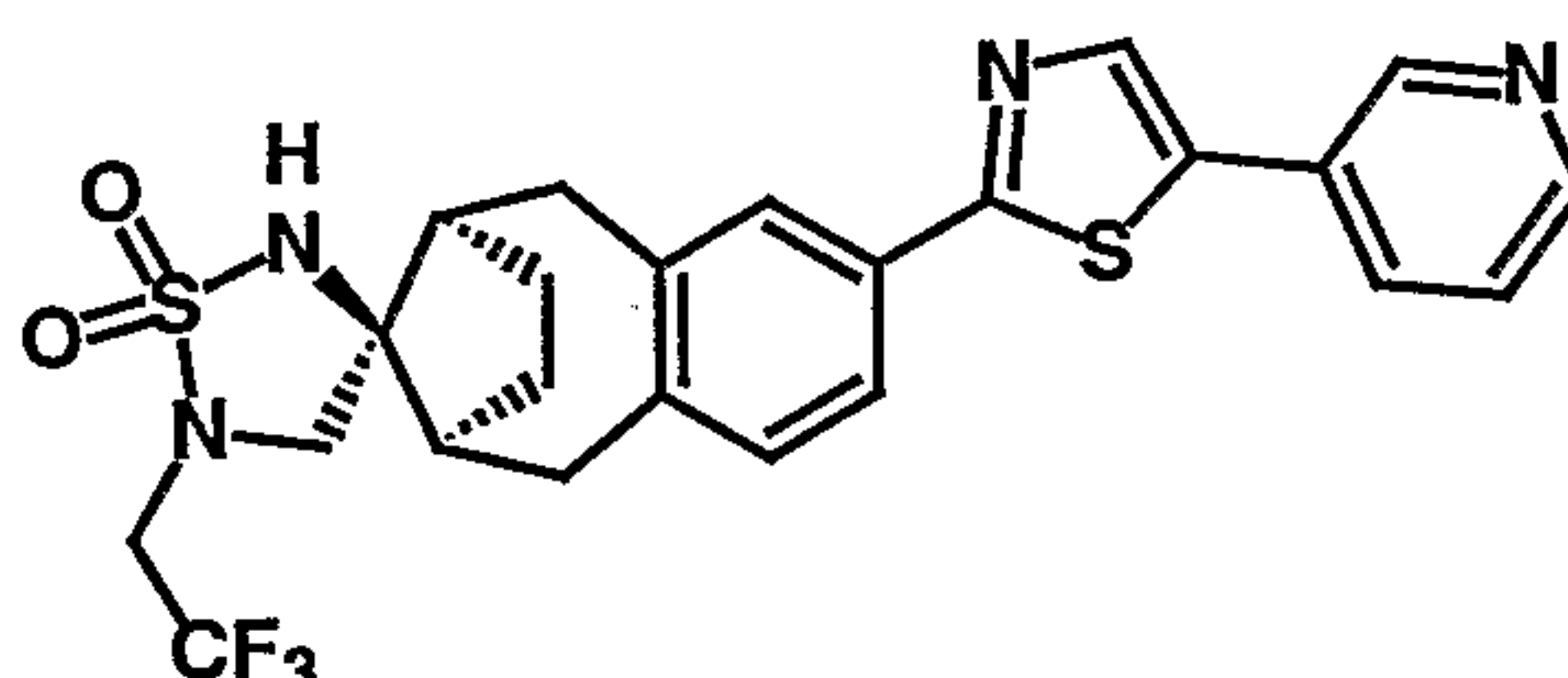
Prepared using the bromide from Example 36 Step 2 and 4-trifluoromethylbenzeneboronic acid by the method described for Example 36 Step 3. MS (ES+) 588 ([MH]⁺).

25

Example 48

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3-pyridyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

5



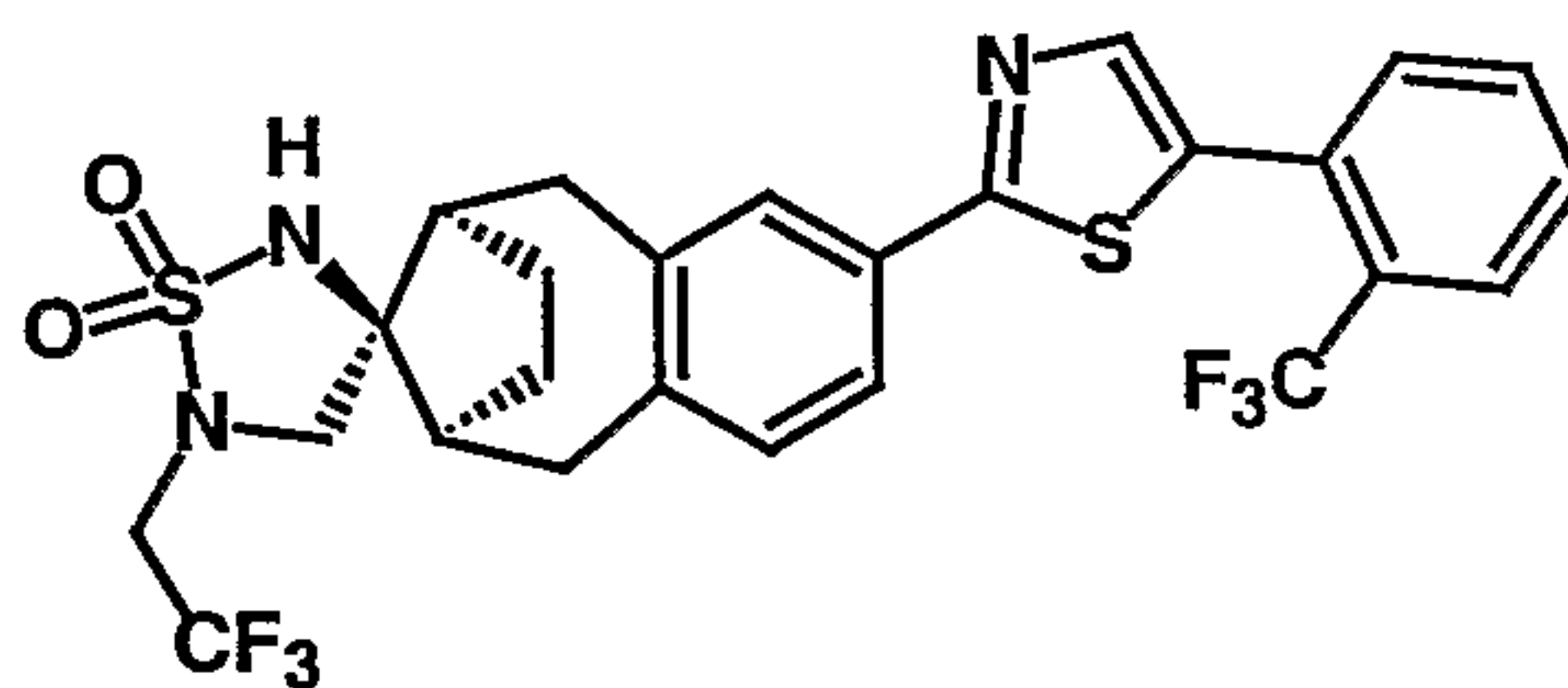
Prepared using the bromide from Example 36 Step 2 and 3-pyridylboronic acid by the method described for Example 36 Step 3. MS (ES+) 521 ([MH]⁺).

10

Example 49

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2-trifluoromethylphenyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

15



Prepared using the bromide from Example 36 Step 2 and 2-trifluoromethylbenzeneboronic acid by the method described for Example 36 Step 3. MS (ES+) 588 ([MH]⁺).

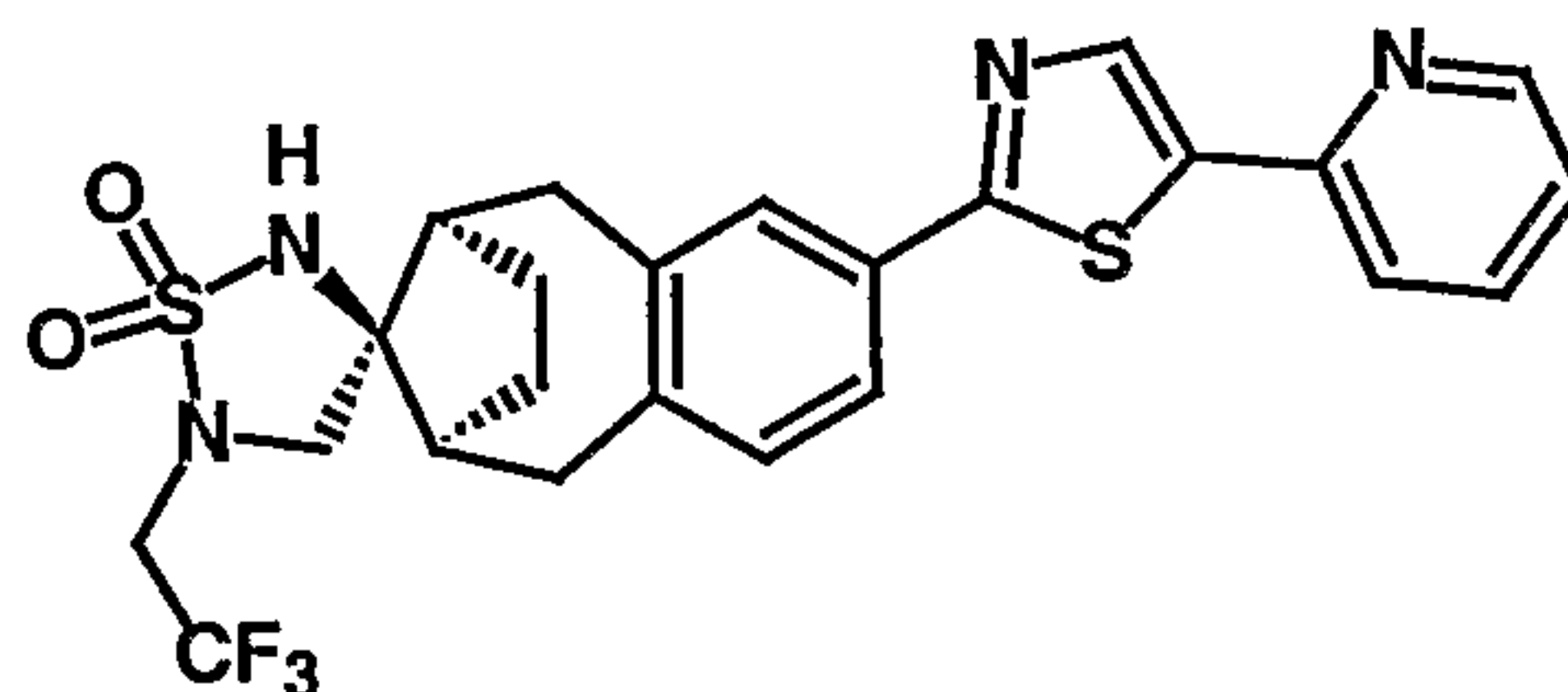
20

Example 50

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2-pyridyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

25

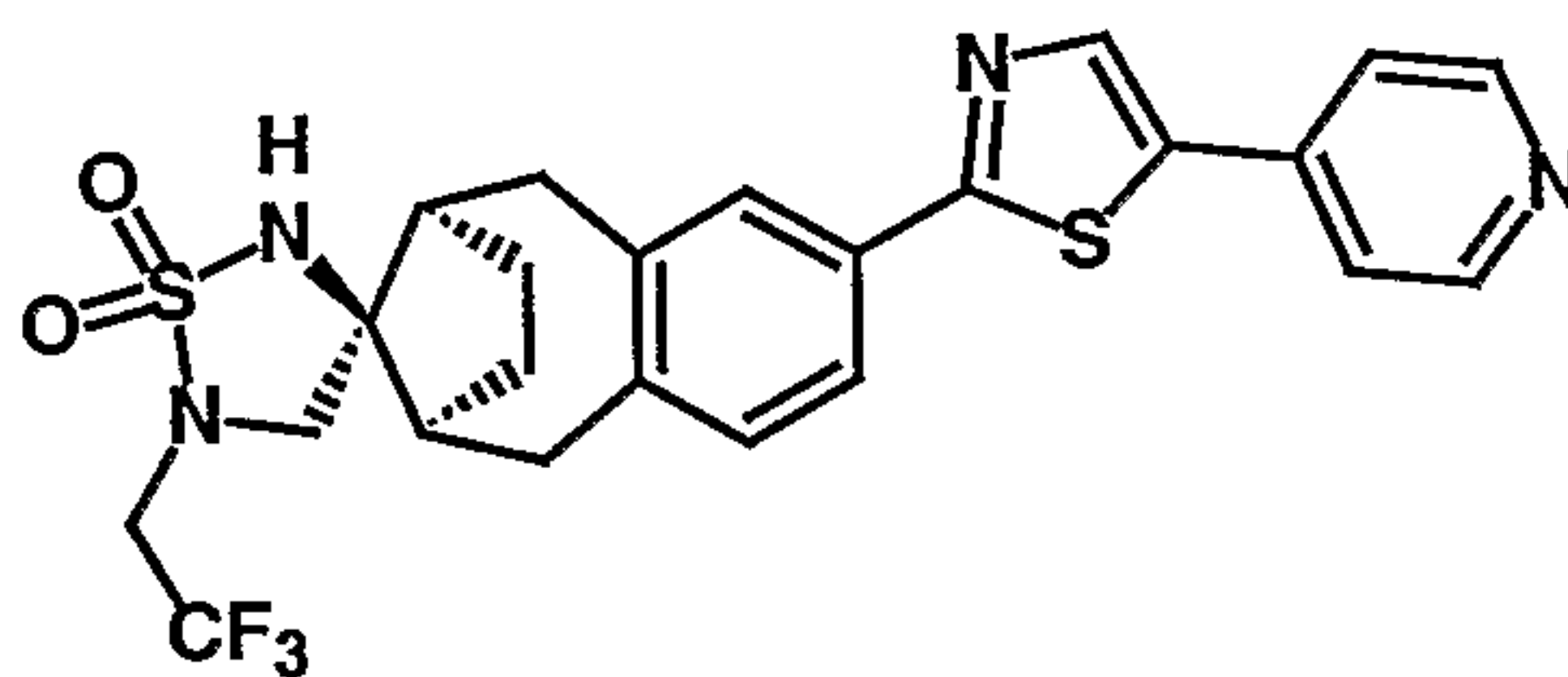
- 89 -



Prepared using the bromide from Example 36 Step 2 and 2-pyridylboronic acid by the method described for Example 36 Step 3. MS (ES+) 521 ([MH]⁺).

Example 51

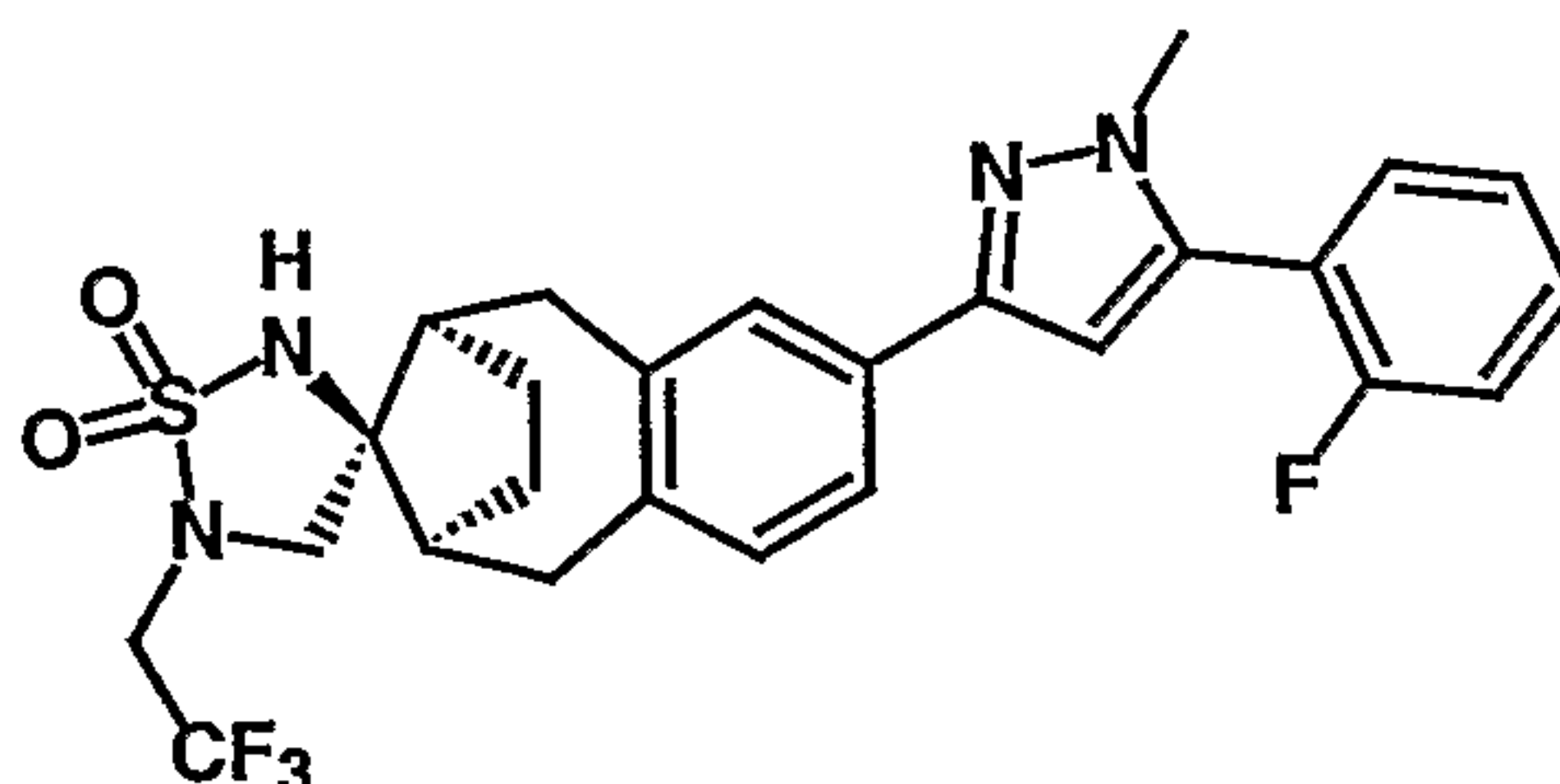
[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-pyridyl)-thiazol-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



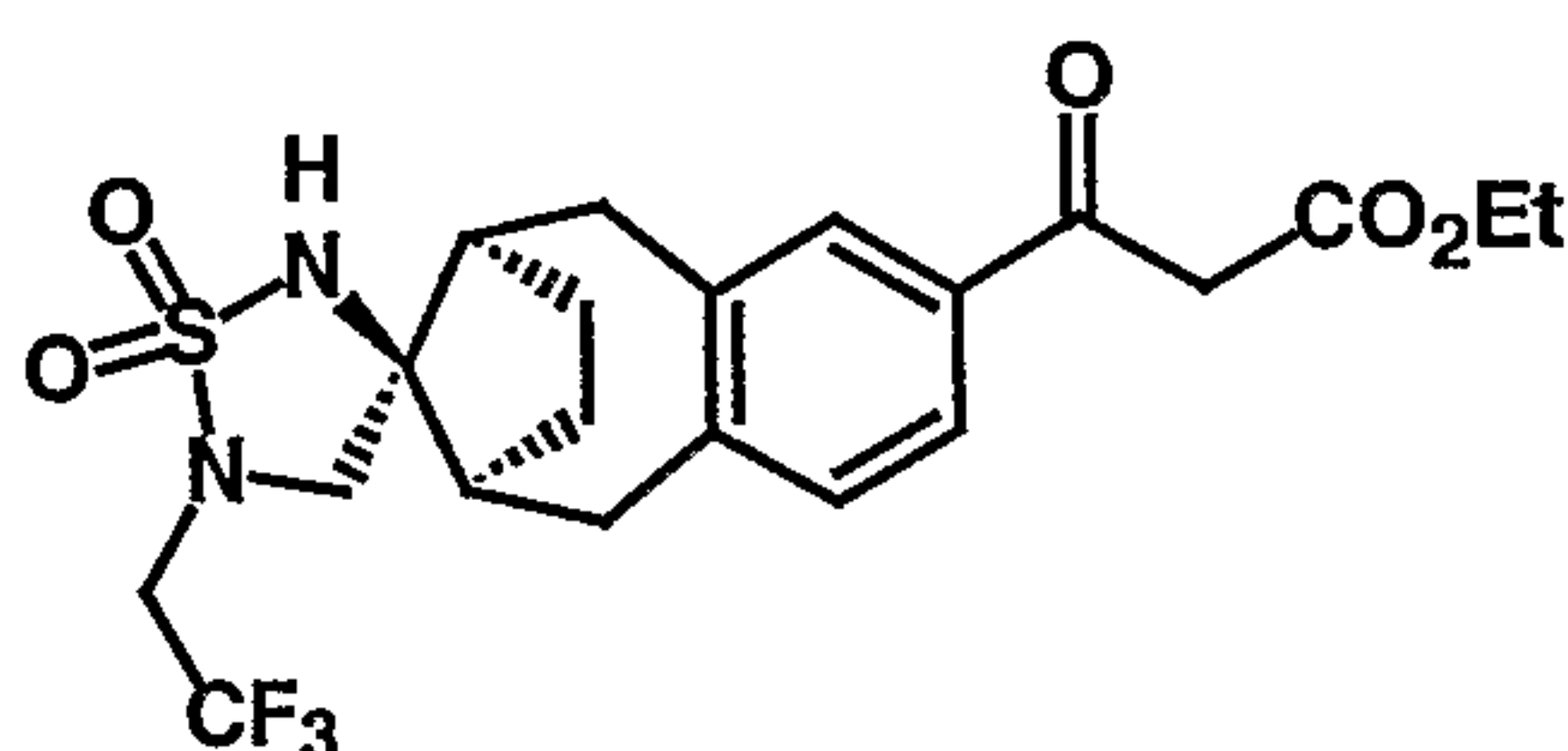
Prepared using the bromide from Example 36 Step 2 and 4-pyridylboronic acid by the method described for Example 36 Step 3. MS (ES+) 521 ([MH]⁺).

Example 52

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2-fluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Step 1: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(2-ethoxycarbonylacetyl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

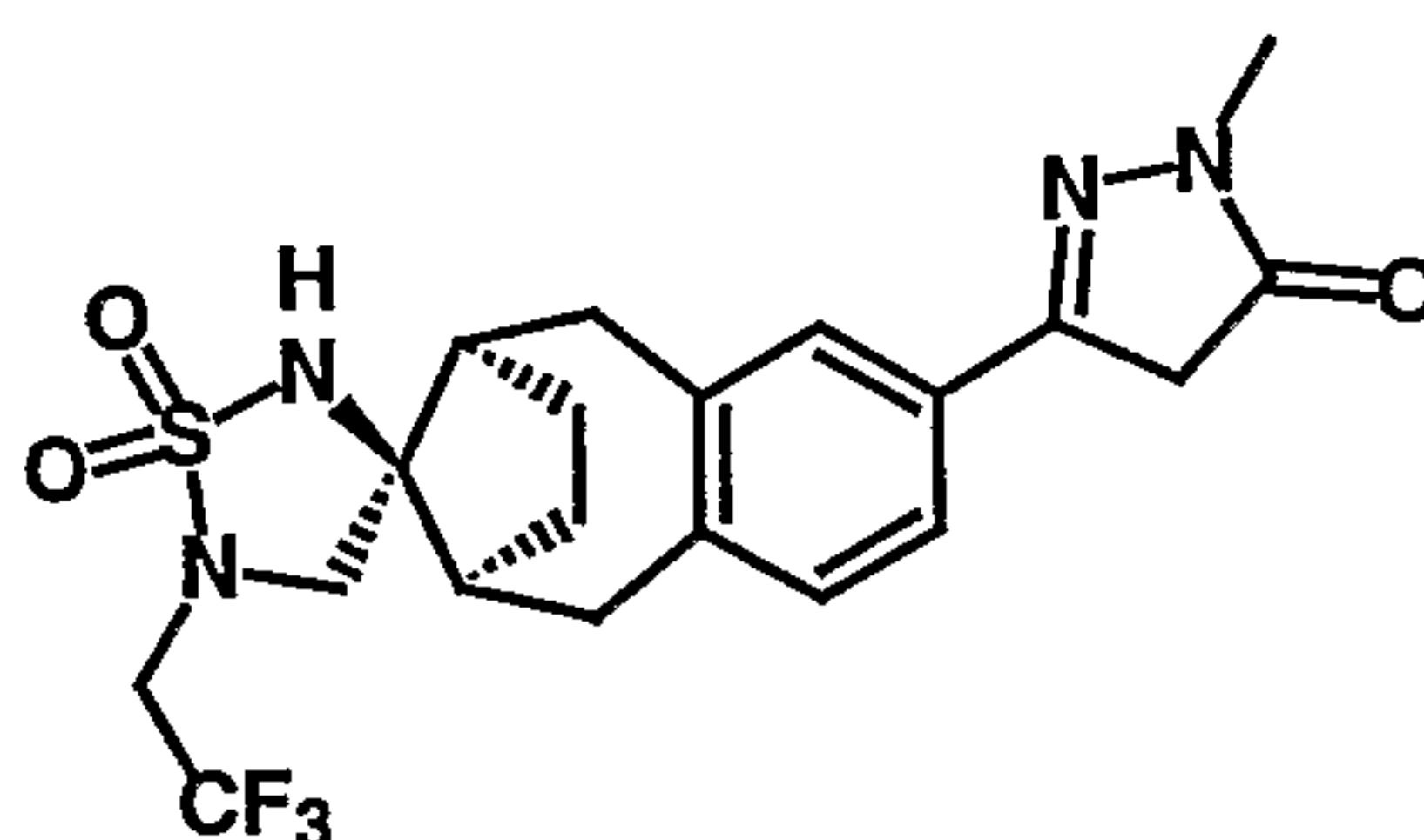


5 Catalytic *N,N*-dimethylformamide (2 drops) was added to a stirred solution of the acid Intermediate A (0.75 g, 1.86 mmol) and oxalyl chloride (0.65 mL, 7.4 mmol) in dry dichloromethane (20 mL) at room temperature under nitrogen. The effervescent mixture was stirred at room temperature for 18 hours. Solvents and excess reagents were removed *in vacuo* to give
10 the acid chloride as an orange foam.

A solution of isopropylmagnesium chloride (2M in THF; 5.6 mL, 11.2 mmol) was added at -78°C to a stirred solution of ethyl hydrogen malonate (0.74 g, 5.6 mmol) in dry tetrahydrofuran (20 mL) under nitrogen. After 25 minutes stirring at -78°C, a solution of the acid chloride in tetrahydrofuran
15 (10 mL) was added. The orange solution was warmed to room temperature. After stirring at room temperature for 1.5 hours, 1 M aqueous hydrochloric acid (45 mL) was added. When effervescence had subsided, the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with 0.2 M aqueous sodium
20 hydroxide (2 x 30 mL) and brine (20 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica, eluting with 50% ethyl acetate - isohexane, to give the keto-ester as a pale yellow foam (0.732 g, 83%). NMR shows ~5:1 keto:enol forms.

Keto form: δ (¹H, 360MHz, CDCl₃) 1.26 (3H, t, *J* = 7 Hz), 1.26-1.33 (2H, m),
25 1.72-1.77 (2H, m), 2.48-2.50 (2H, m), 2.76-2.82 (2H, m), 3.22-3.31 (2H, m), 3.41-3.47 (2H, m), 3.69 (2H, q, *J* = 8.7 Hz), 3.96 (2H, s), 4.22 (2H, q, *J* = 7 Hz), 4.75 (1H, s), 7.21 (1H, d, *J* = 7.6 Hz), 7.68-7.70 (2H, m).

Step 2: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-methyl-pyrazol-5-on-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



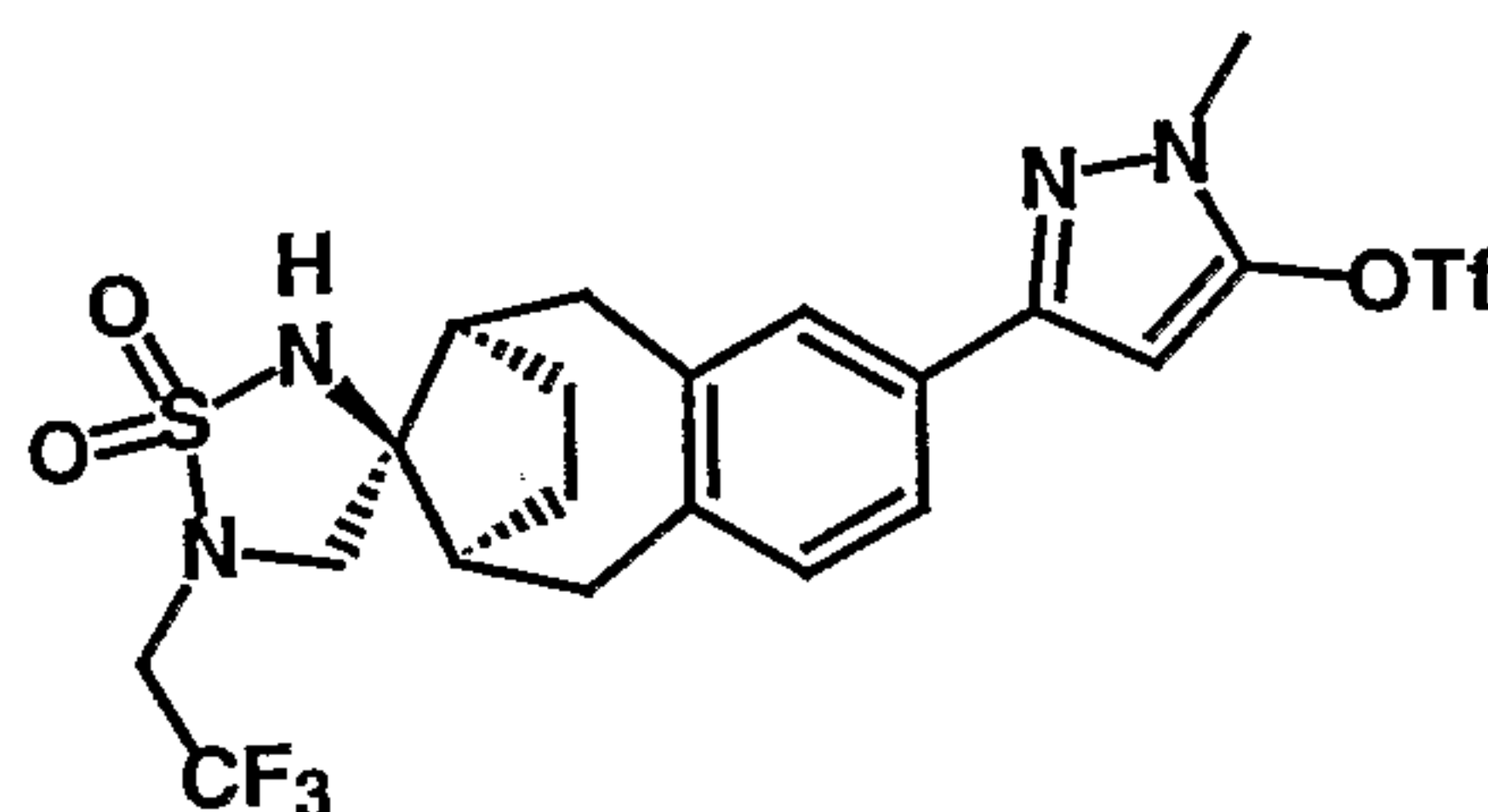
5

Methylhydrazine (0.5 mL, 9 mmol) was added dropwise to a stirred solution of the keto-ester from Step 1 (0.44 g, 0.93 mmol) in acetic acid (3 mL), moderating the exotherm with water-bath cooling. The reaction was stirred at room temperature for 18 hours. Water (50 mL) was added and the orange precipitates were collected, dissolved in ethyl acetate (100 mL), washed with water (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate, to give the pyrazolone as a yellow solid (0.504 g, 54%).
 δ (¹H, 360MHz, CDCl₃) 1.27-1.33 (2H, m), 1.71-1.76 (2H, m), 2.45-2.50 (2H, m), 2.70-2.79 (2H, m), 3.22-3.27 (2H, m), 3.40 (3H, s), 3.44 (2H, s), 3.54-3.3.59 (2H, m), 3.69 (2H, q, *J* = 8.7 Hz), 4.85 (1H, s), 7.15 (1H, d, *J* = 7.8 Hz), 7.37 (1H, d, *J* = 7.8 Hz), 7.44 (1H,s).

15

20

Step 3: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-trifluoromethanesulphonyloxy-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



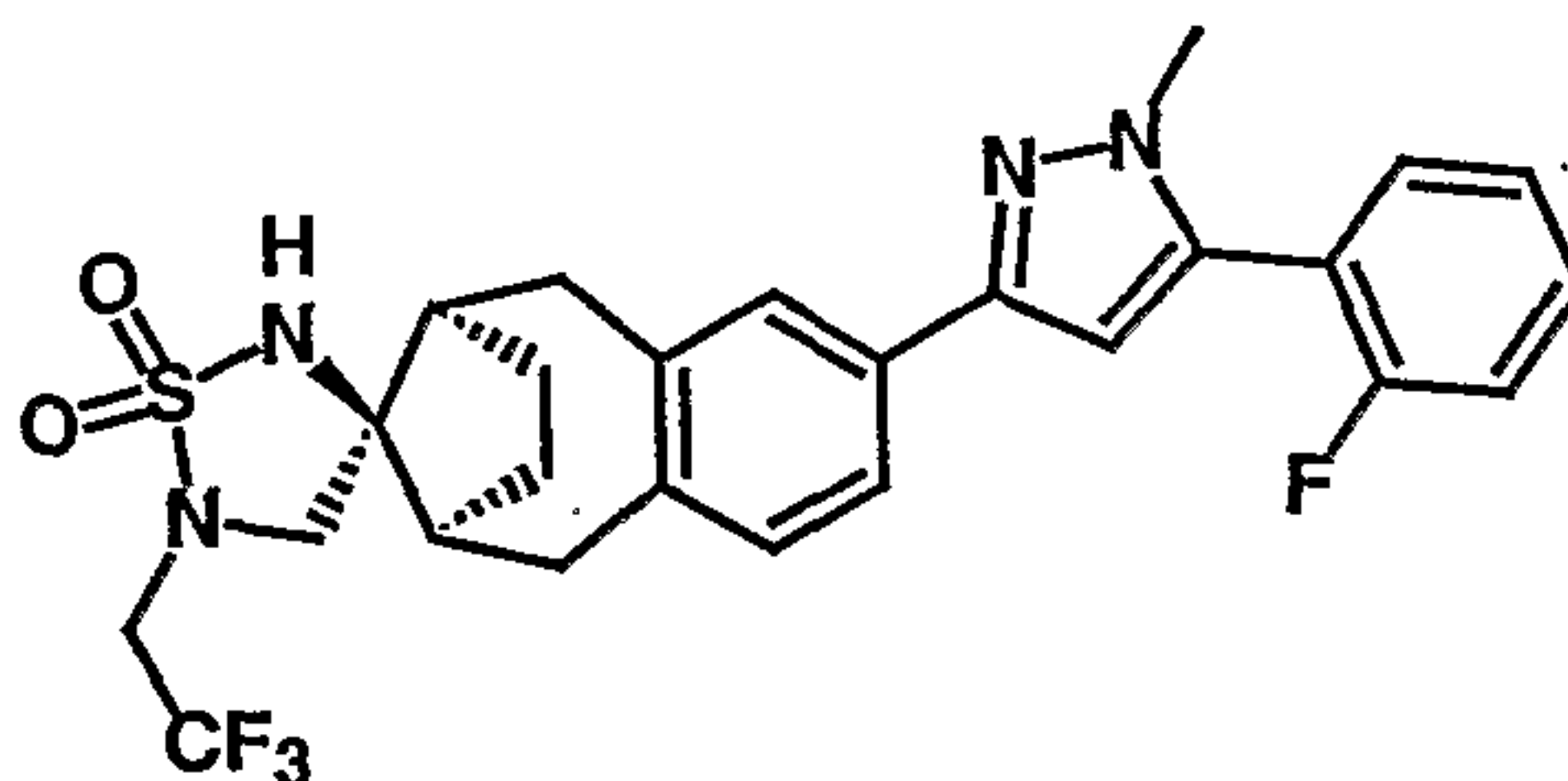
- 92 -

Trifluoromethanesulfonic anhydride (0.12 mL, 0.71 mmol) was added dropwise to a stirred suspension of the pyrazolone from Step 2 (0.15 g, 0.329 mmol) and pyridine (0.07 mL, 0.80 mmol) in dichloromethane (3 mL) at -78°C under nitrogen. After stirring for 3 hours, the reaction was

5 quenched at -78°C with saturated aqueous sodium hydrogencarbonate (25 mL) and extracted with dichloromethane (25 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica, eluting with 30% ethyl acetate - isohexane, to give the triflate as a pink oil (0.114 g, 59%).

10 δ (¹H, 360MHz, CDCl₃) 1.32-1.37 (2H, m), 1.69-1.74 (2H, m), 2.42-2.49 (2H, m), 2.69-2.81 (2H, m), 3.20-3.25 (2H, m), 3.44 (2H, s), 3.68 (2H, q, *J* = 8.7 Hz), 3.86 (3H, s), 4.66 (1H, s), 6.41 (1H, s) 7.14 (1H, d, *J* = 7.8 Hz), 7.47 (1H, d, *J* = 7.8 Hz), 7.51 (1H, s).

15 Step 4: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2-fluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



A mixture of the triflate from Step 3 (0.054 g, 0.092 mmol),

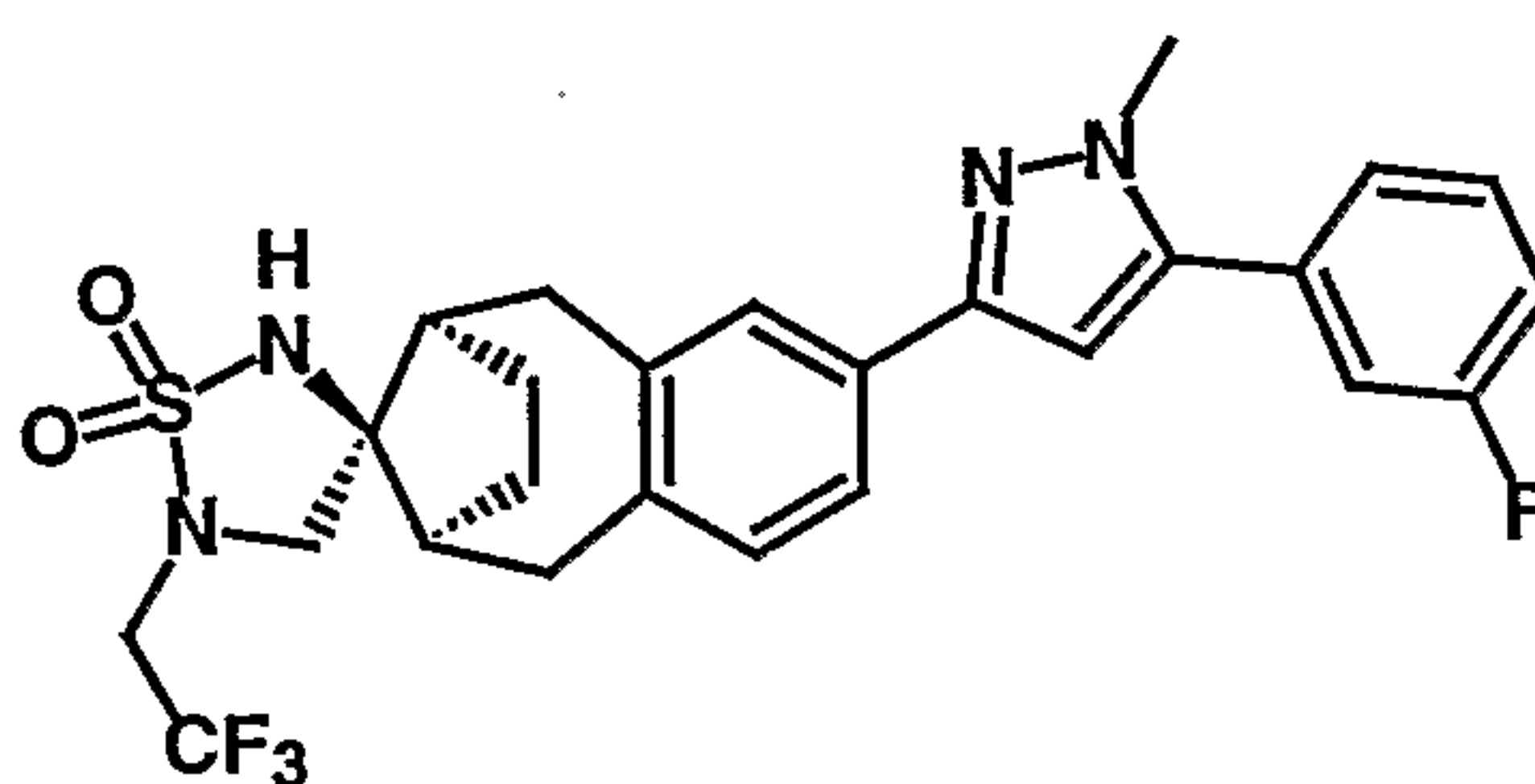
20 tetrakis(triphenylphosphine)palladium(0) (0.025 g, 0.022 mmol), 2-fluorophenylboronic acid (0.025 g, 0.17 mmol) and 2 M aqueous sodium carbonate (0.15 mL, 0.3 mmol) in toluene (2 mL) was degassed and flushed with nitrogen at room temperature. The reaction was heated to reflux for 18 hours. The cooled reaction mixture was diluted with water (15 mL) and

25 ethyl acetate (15 mL) and filtered. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica, eluting with 30% ethyl acetate - isohexane, to give the product as a white solid (0.029 g, 59%).

δ (^1H , 400MHz, CDCl_3) 1.36-1.40 (2H, m), 1.69-1.73 (2H, m), 2.42-2.49 (2H, m), 2.69-2.83 (2H, m), 3.21-3.25 (2H, m), 3.44 (2H, s), 3.68 (2H, q, $J = 8.7$ Hz), 3.85 (3H, d, $J = 1.4$ Hz), 4.68 (1H, s), 6.61 (1H, s), 7.13 (1H, d, $J = 7.8$ Hz), 7.19-7.28 (2H, m), 7.38-7.46 (2H, m), 7.55 (1H, dd, $J = 1.6$ & 7.8 Hz),
 5 7.61 (1H, s). MS (ES+) 535 ($[\text{MH}]^+$)

Example 53

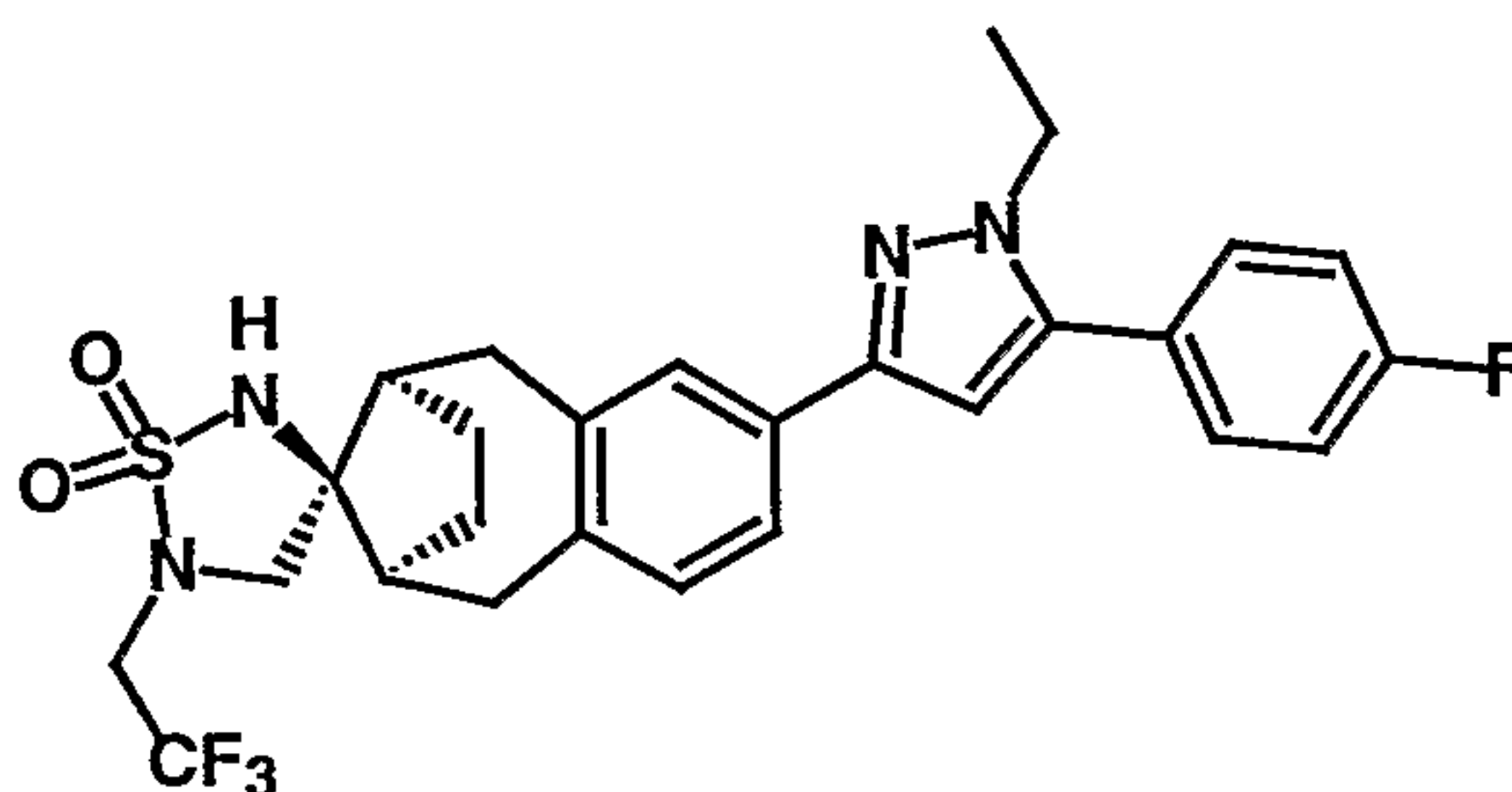
[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3-fluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-
 10 spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Prepared using Intermediate A and 3-fluorobenzenboronic acid by the method described for Example 52. MS (ES+) 535 ($[\text{MH}]^+$).
 15

Example 54

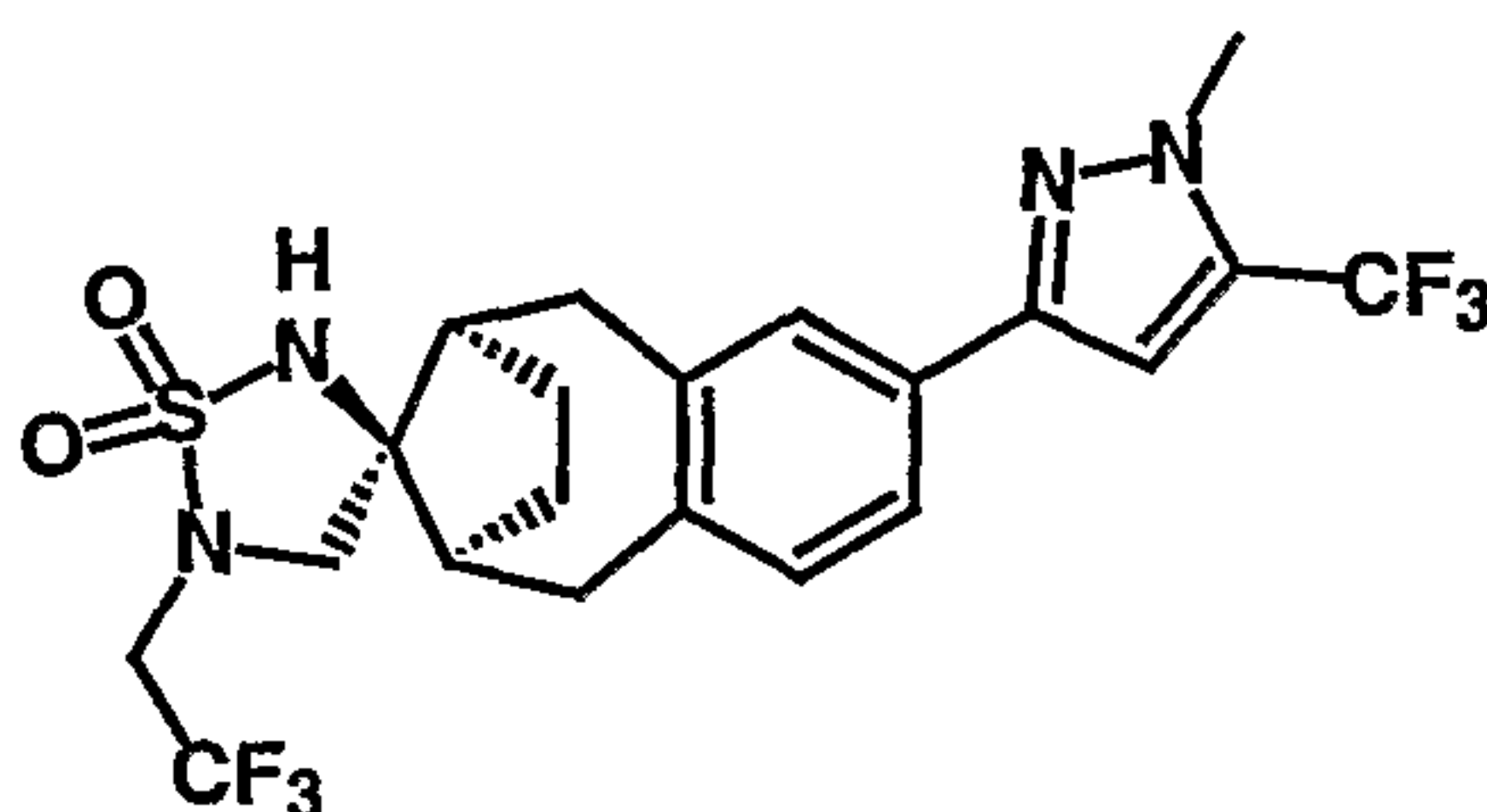
[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1-ethyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-
 20 spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



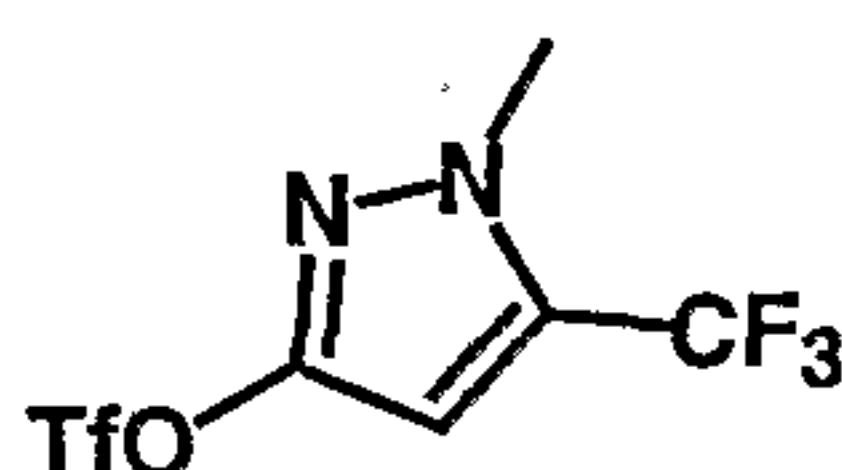
Prepared using Intermediate A, ethylhydrazine oxalate and 4-fluorobenzenboronic acid by the method described for Example 52. MS (ES+) 549 ($[\text{MH}]^+$).

Example 55

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-trifluoromethyl-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



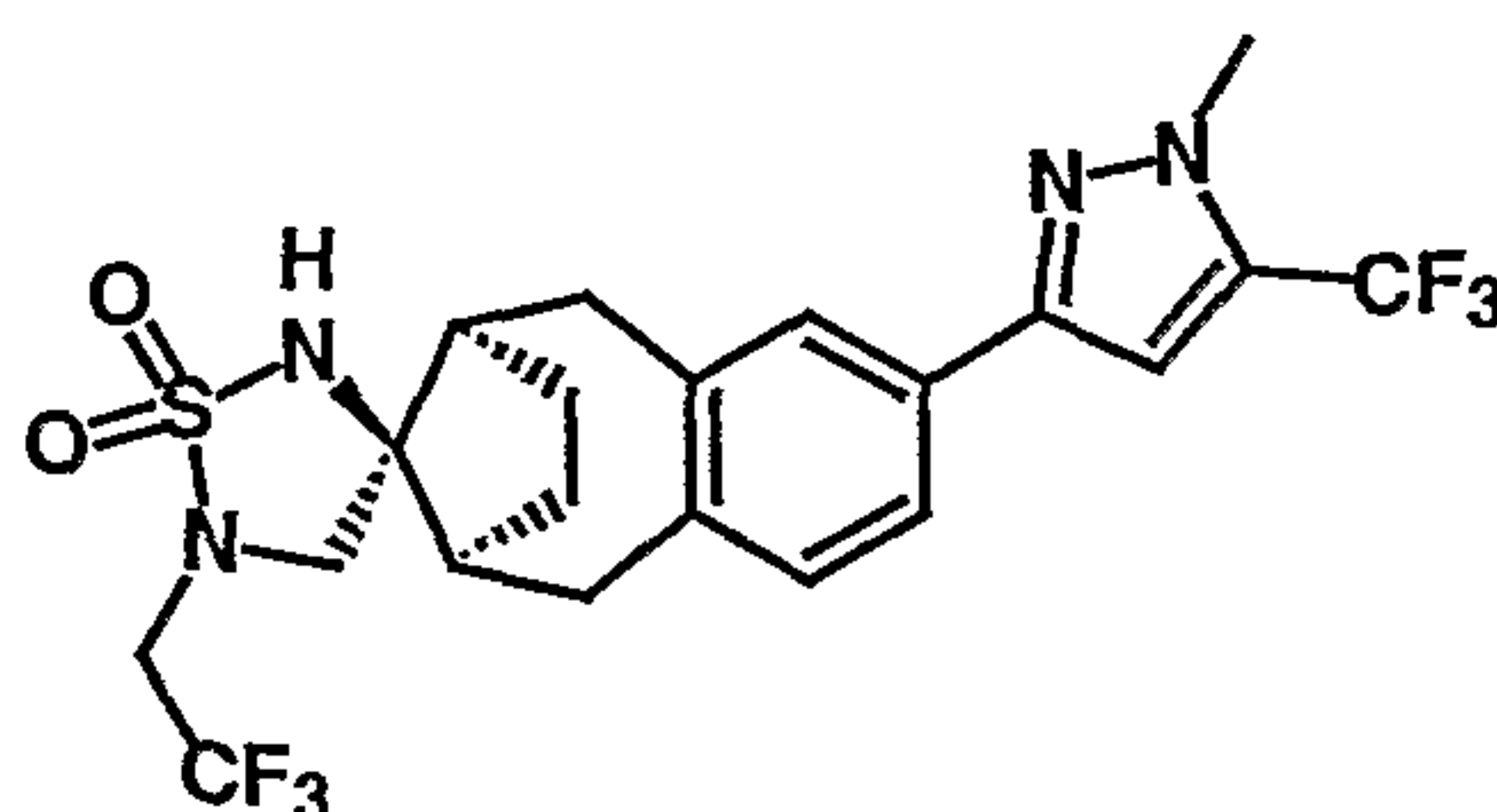
Step 1: 3-trifluoromethanesulphonyloxy-1-methyl-5-(trifluoromethyl)pyrazole



A solution of 3-hydroxy-1-methyl-5-(trifluoromethyl)pyrazole (0.227 g, 1.37 mmol), 2,6-lutidine (0.18 mL, 1.5 mmol) and trifluoromethanesulfonic anhydride (0.25 mL, 1.5 mmol) in dichloromethane (5 mL) was stirred for 18 hours at room temperature under nitrogen. The reaction mixture was washed with water (5 mL), dried over Na₂SO₄ and evaporated. The residue was purified by flash column chromatography on silica, eluting with 50% ethyl acetate – isohexane to give the triflate as a mobile yellow oil (0.18 g, 44%).

δ (¹H, 400MHz, CDCl₃) 3.97 (3H, s), 6.50 (1H, s).

Step 2: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-trifluoromethyl-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

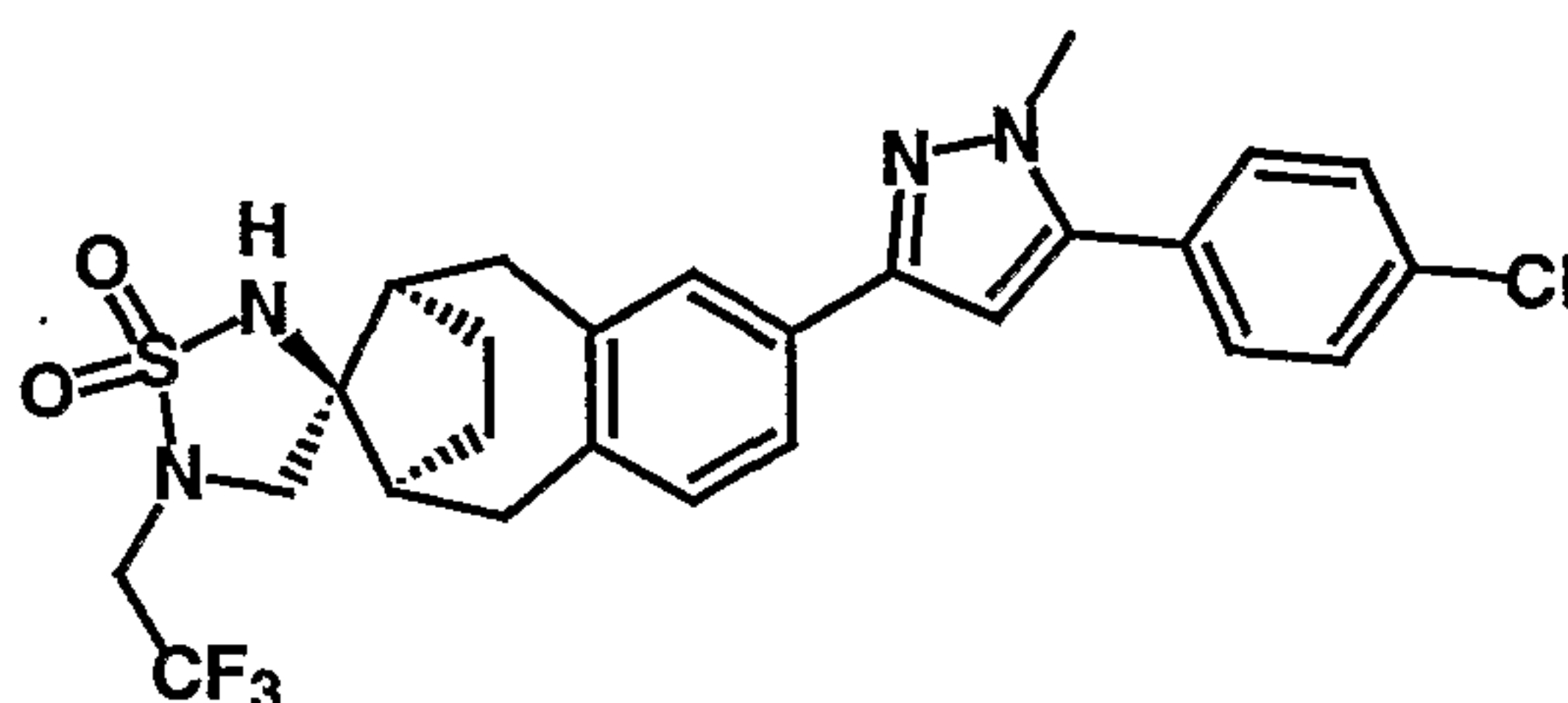


Prepared using the triflate from Step 1 and the homochiral boronate from Example 24 Step 1 by the method described for Example 52 Step 4.

MS (ES+) 509 ([MH]⁺).

5 Example 56

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-chlorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

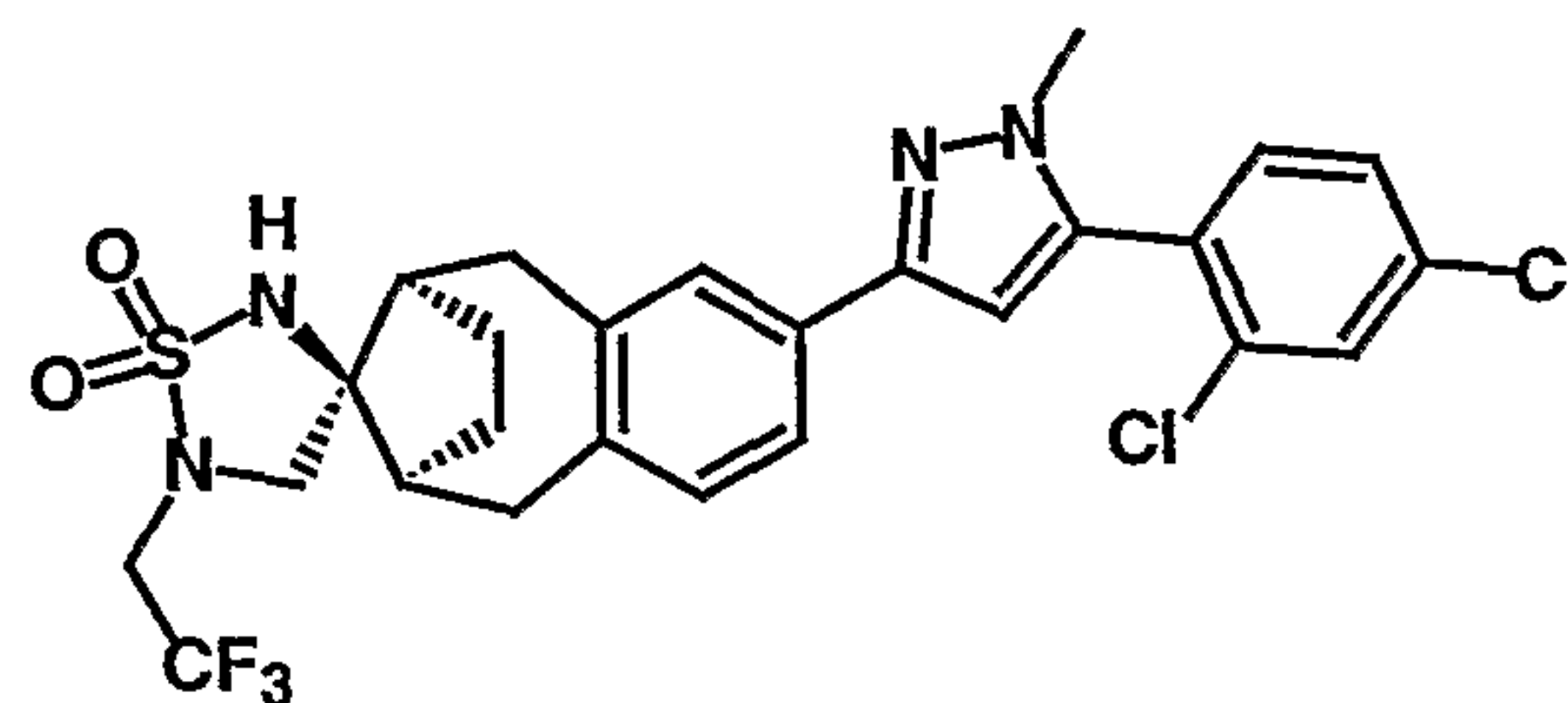


10

Prepared using Intermediate A and 4-chlorobenzeneboronic acid by the method described for Example 52. MS (ES+) 551 ([MH]⁺).

Example 57

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2,4-dichlorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



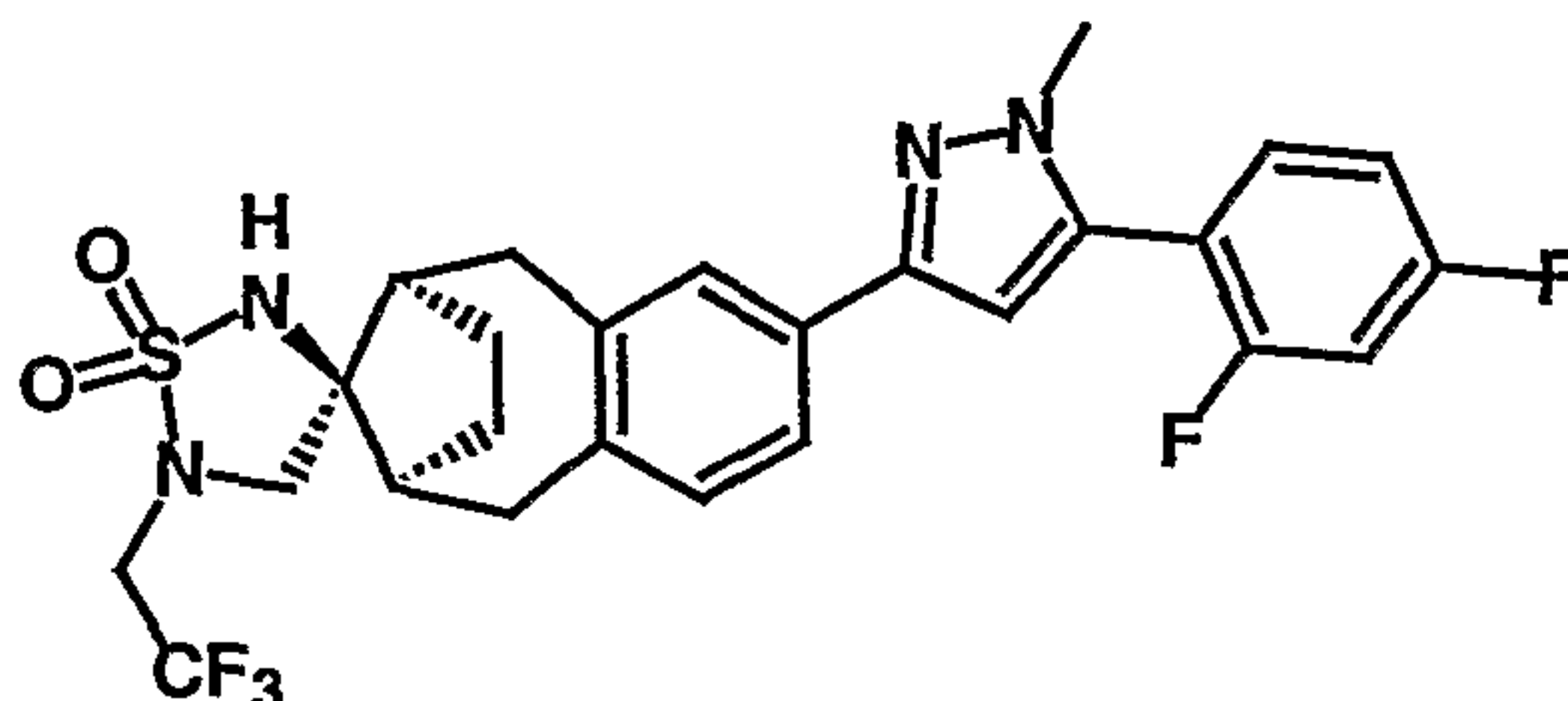
20

Prepared using Intermediate A and 2,4-dichlorobenzeneboronic acid by the method described for Example 52. MS (ES+) 585 ([MH]⁺).

Example 58

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2,4-difluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

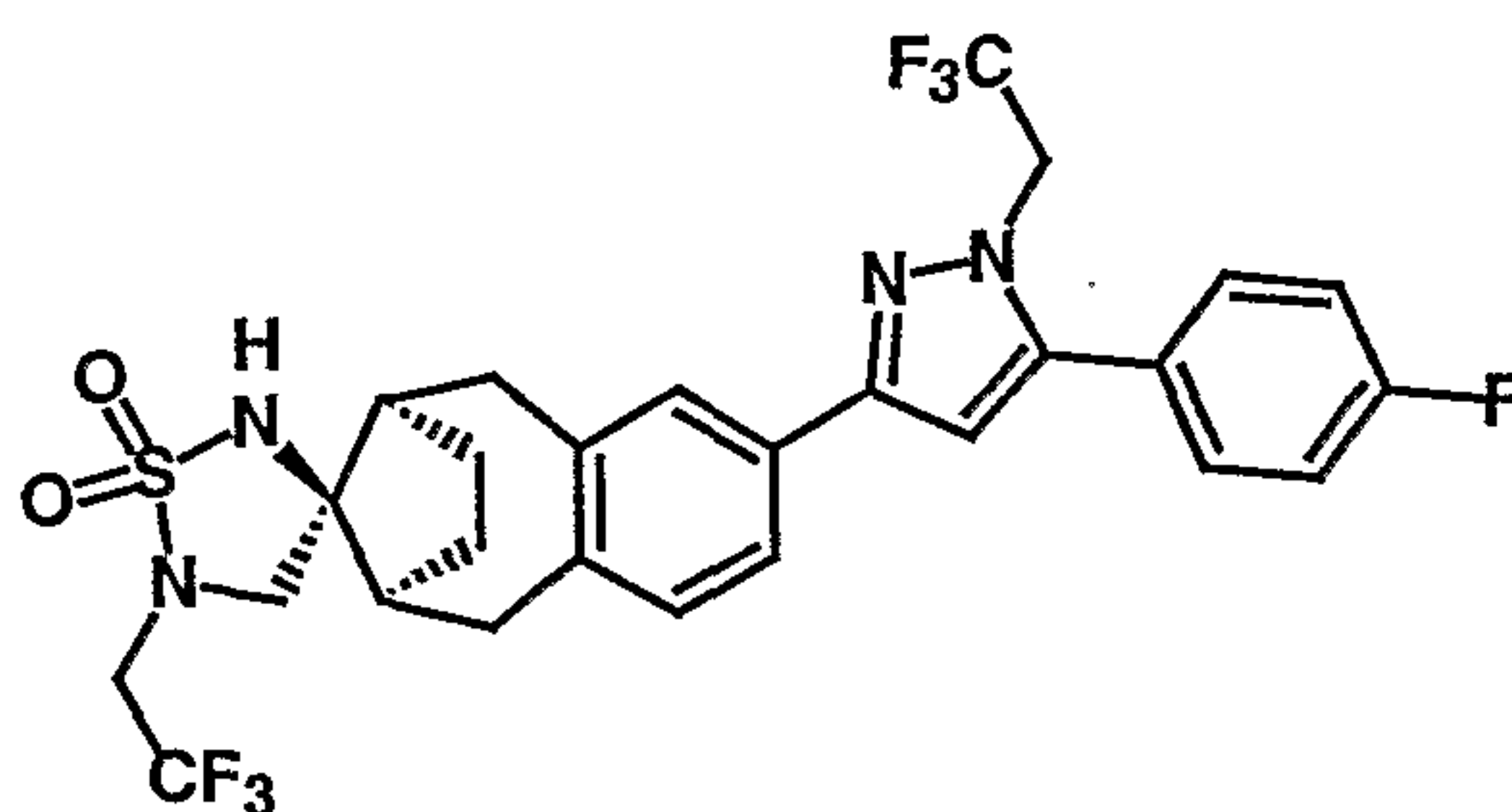
5



Prepared using Intermediate A and 2,4-difluorobenzeneboronic acid by the method described for Example 52. MS (ES+) 553 ([MH]⁺).

Example 59

10 **[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1-(2,2,2-trifluoroethyl)-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**

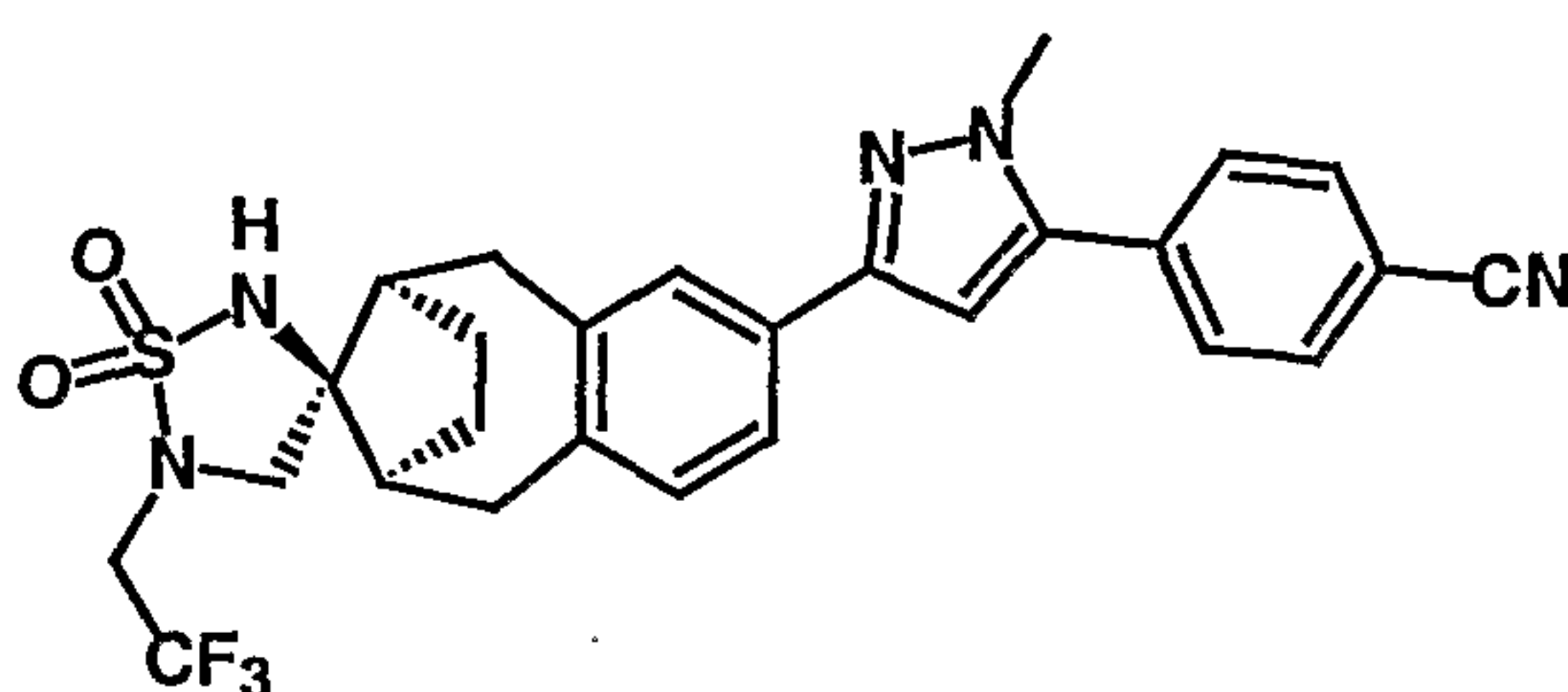


15 Prepared using Intermediate A, trifluoroethylhydrazine and 4-fluorobenzeneboronic acid by the method described for Example 52. MS (ES+) 603 ([MH]⁺).

Example 60

20 **[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-cyanophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**

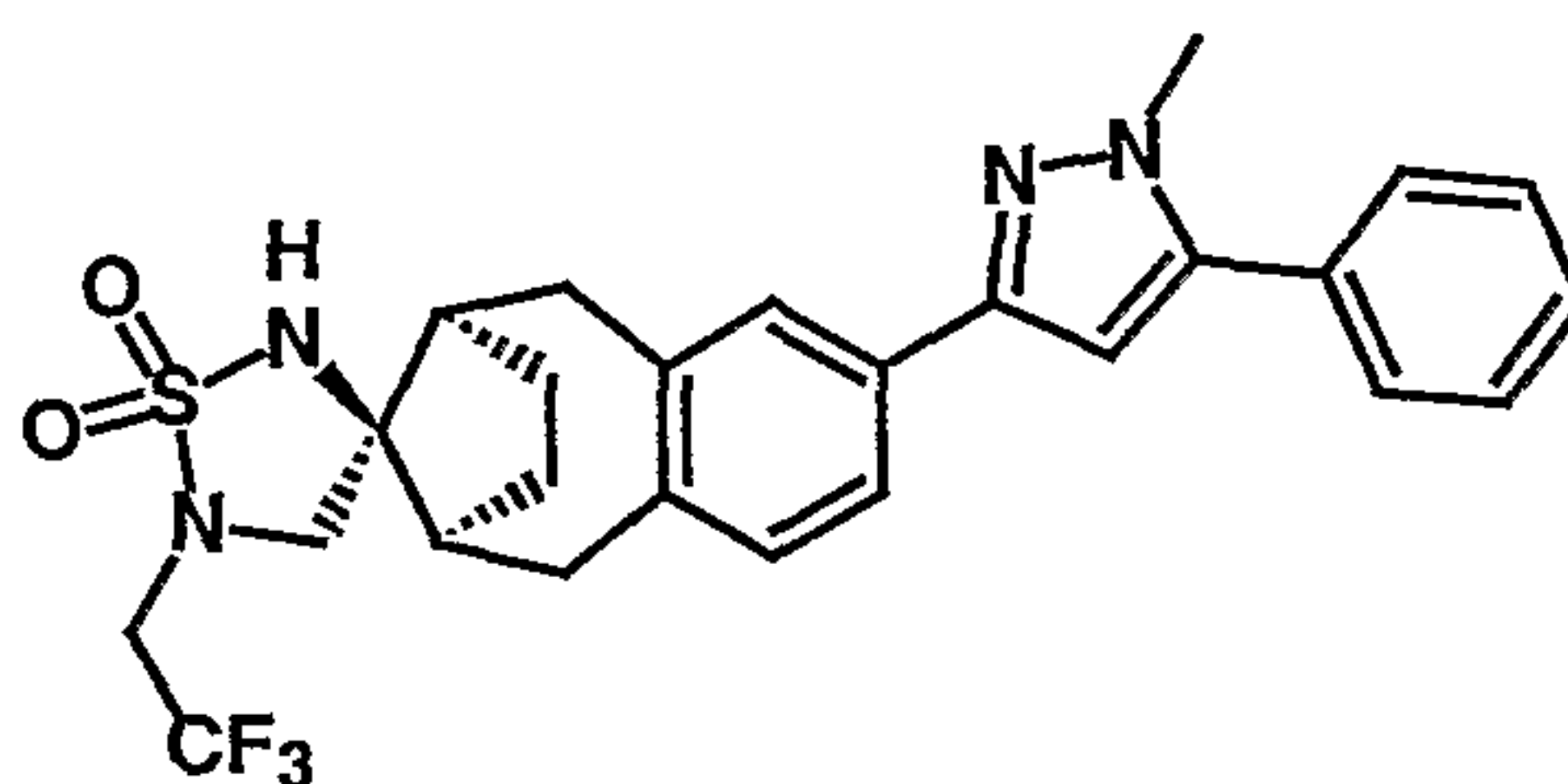
- 97 -



Prepared using Intermediate A and 4-cyanobenzeneboronic acid by the method described for Example 52. MS (ES+) 542 ([MH]⁺).

5 Example 61

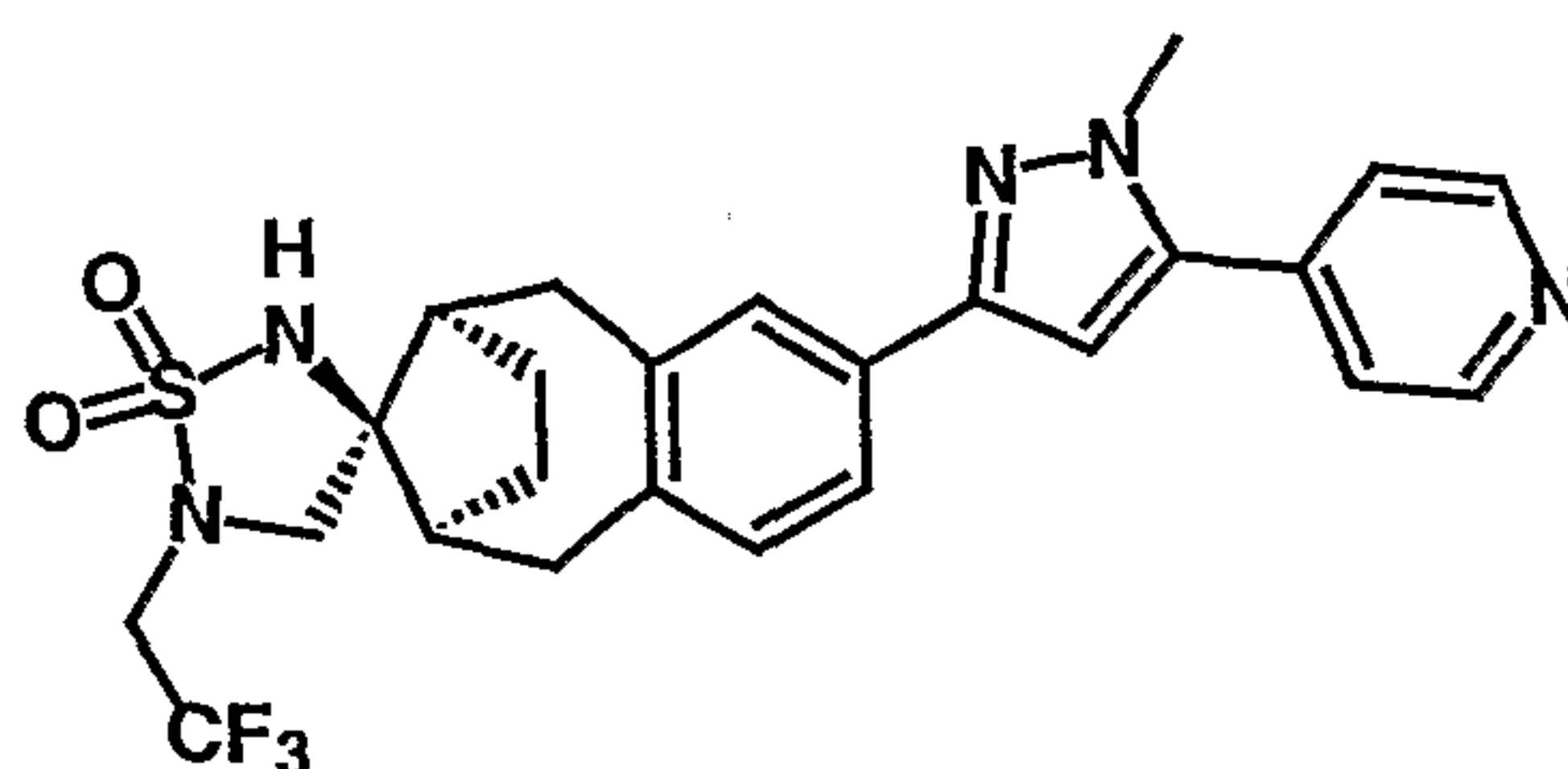
[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-phenyl-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



10 Prepared using Intermediate A and benzeneboronic acid by the method described for Example 52. MS (ES+) 517 ([MH]⁺).

Example 62

15 **[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-pyridyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**

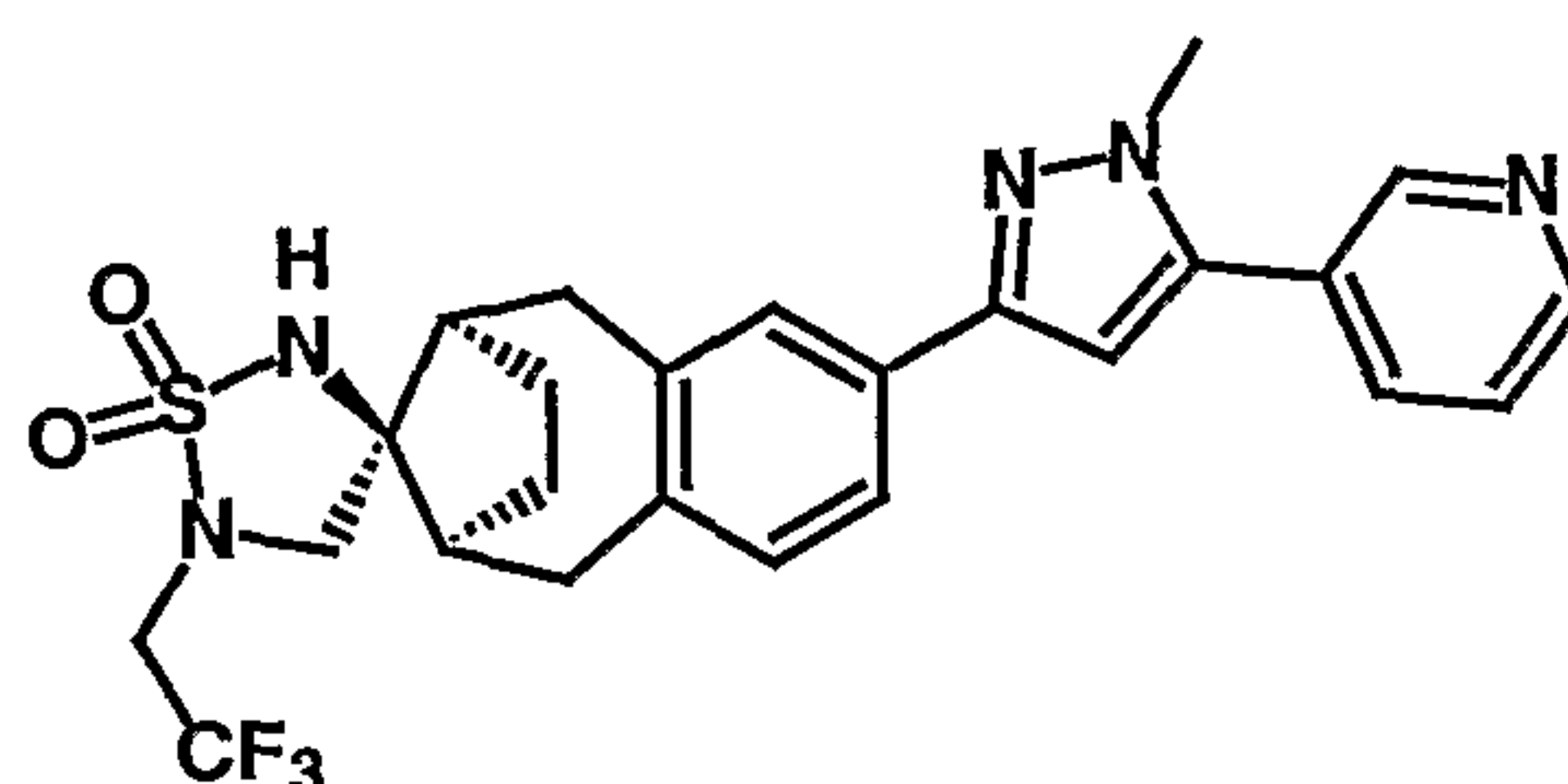


Prepared from Intermediate B and 4-pyridylboronic acid by the method described for Example 52. MS (ES+) 518 ([MH]⁺).

20

Example 63

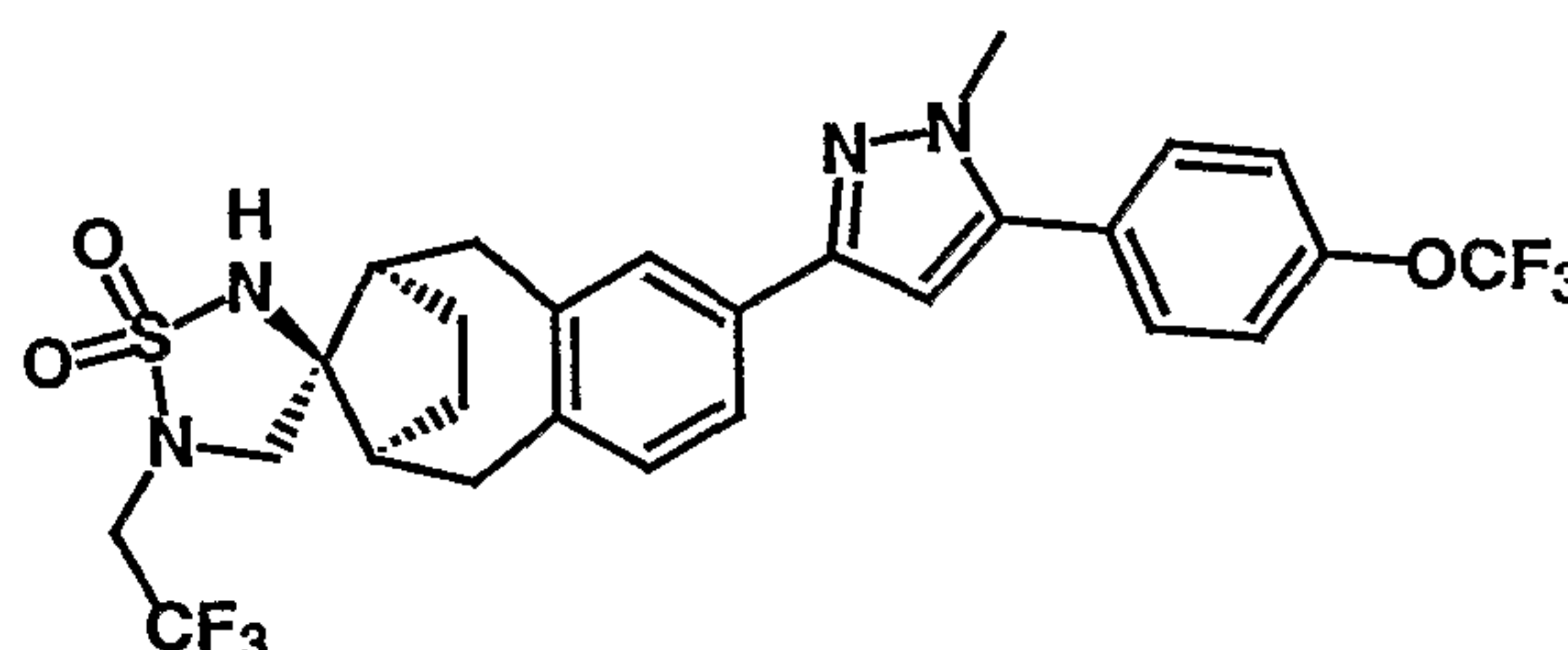
[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3-pyridyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



- 5 Prepared from Intermediate B and 3-pyridylboronic acid by the method described for Example 52. MS (ES+) 518 ([MH]⁺).

Example 64

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-trifluoromethoxyphenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

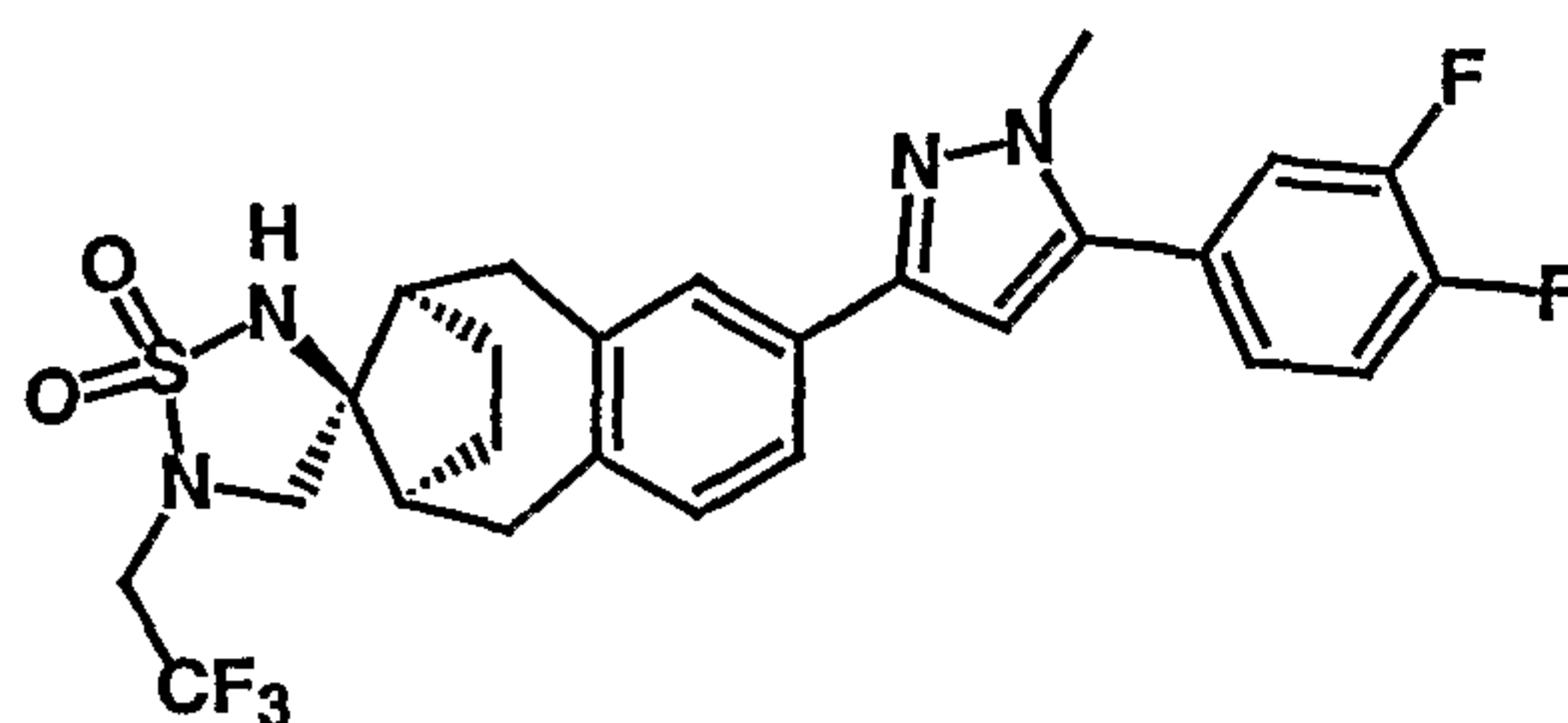


- 15 Prepared from Intermediate B and 4-trifluoromethoxybenzeneboronic acid by the method described for Example 52. MS (ES+) 601 ([MH]⁺).

Example 65

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3,4-difluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

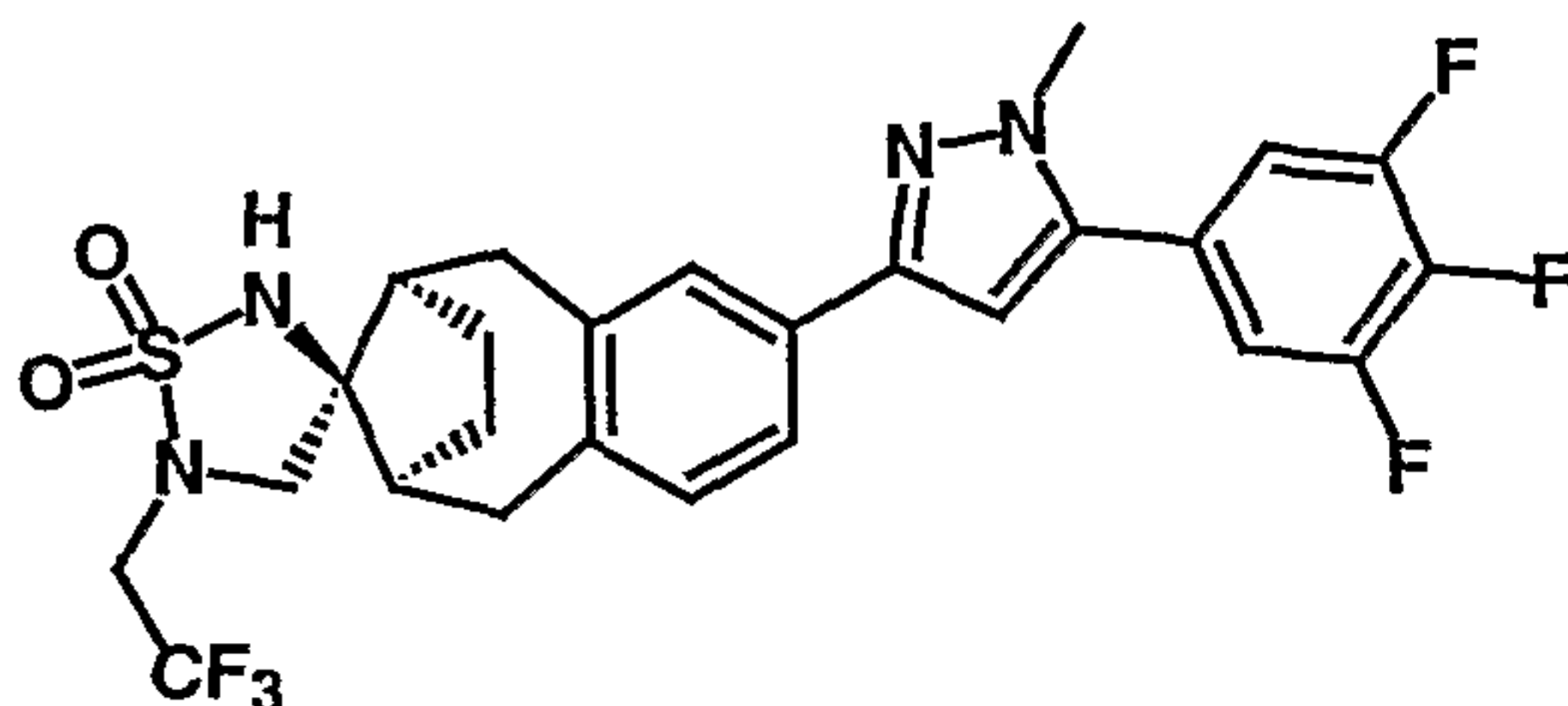
20



Prepared from Intermediate B and 3,4-difluorobenzenboronic acid by the method described for Example 52. MS (ES+) 553 ([MH]⁺).

5 Example 66

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3,4,5-trifluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

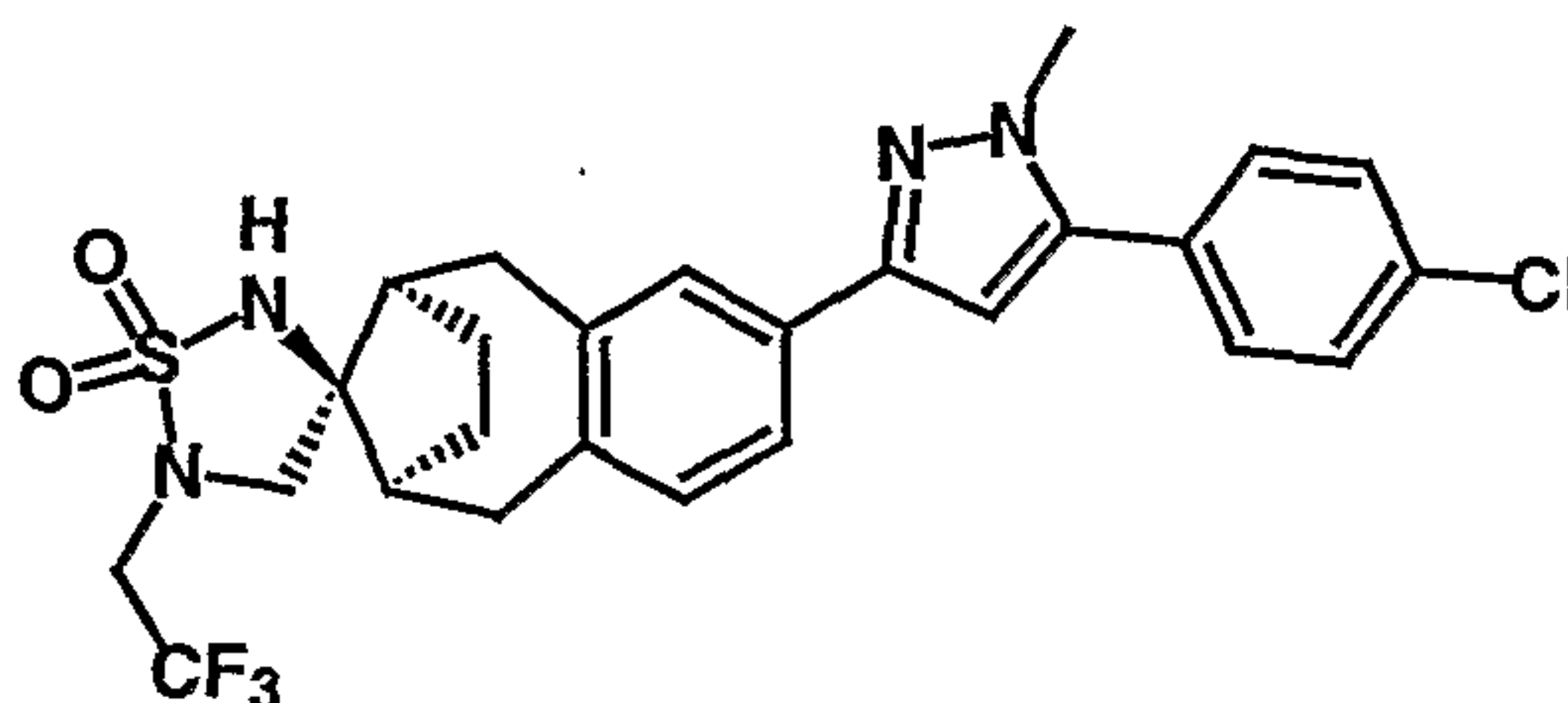


10

Prepared from Intermediate B and 3,4,5-trifluorobenzenboronic acid by the method described for Example 52. MS (ES+) 571 ([MH]⁺).

Example 67

15 [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-chlorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

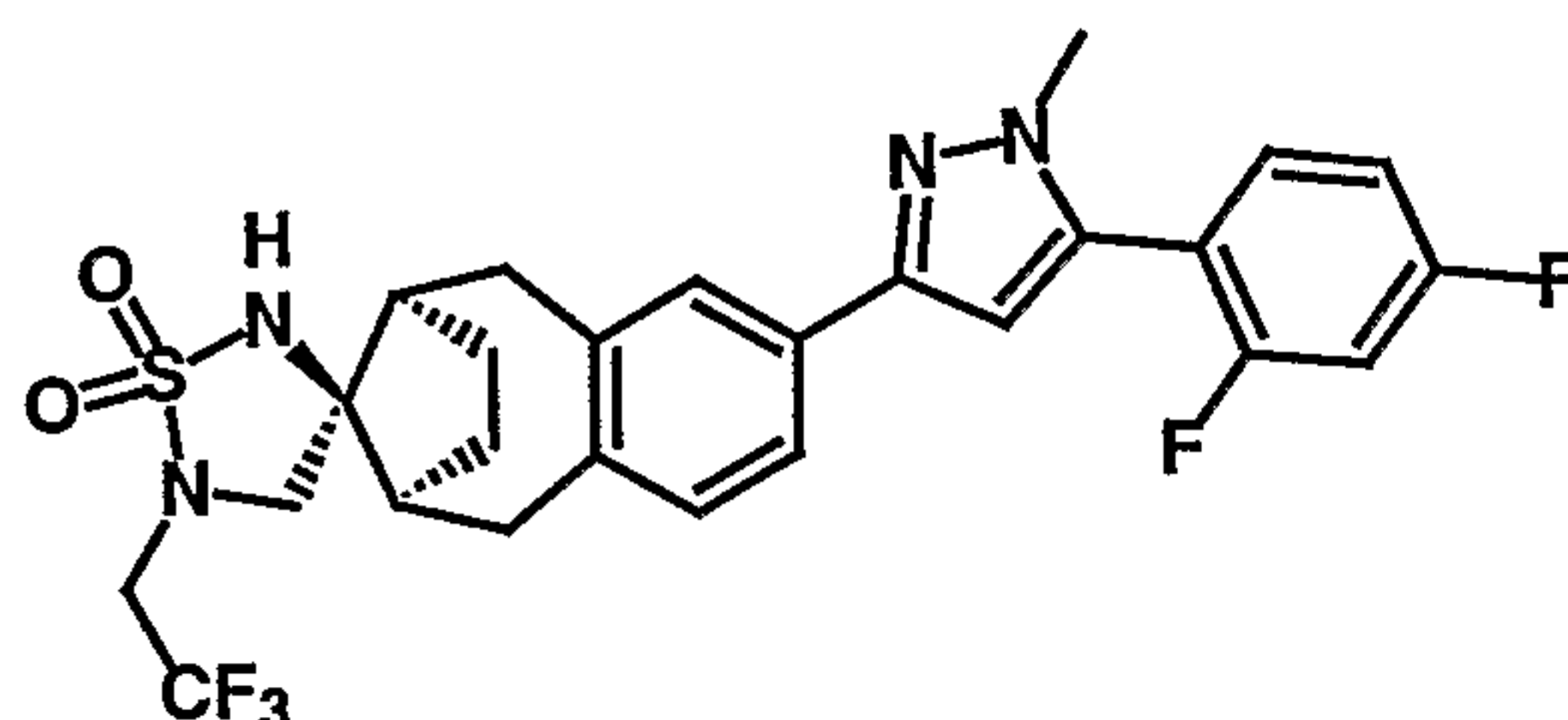


20

Prepared from Intermediate B and 4-chlorobenzenboronic acid by the method described for Example 52. MS (ES+) 551 ([MH]⁺).

Example 68

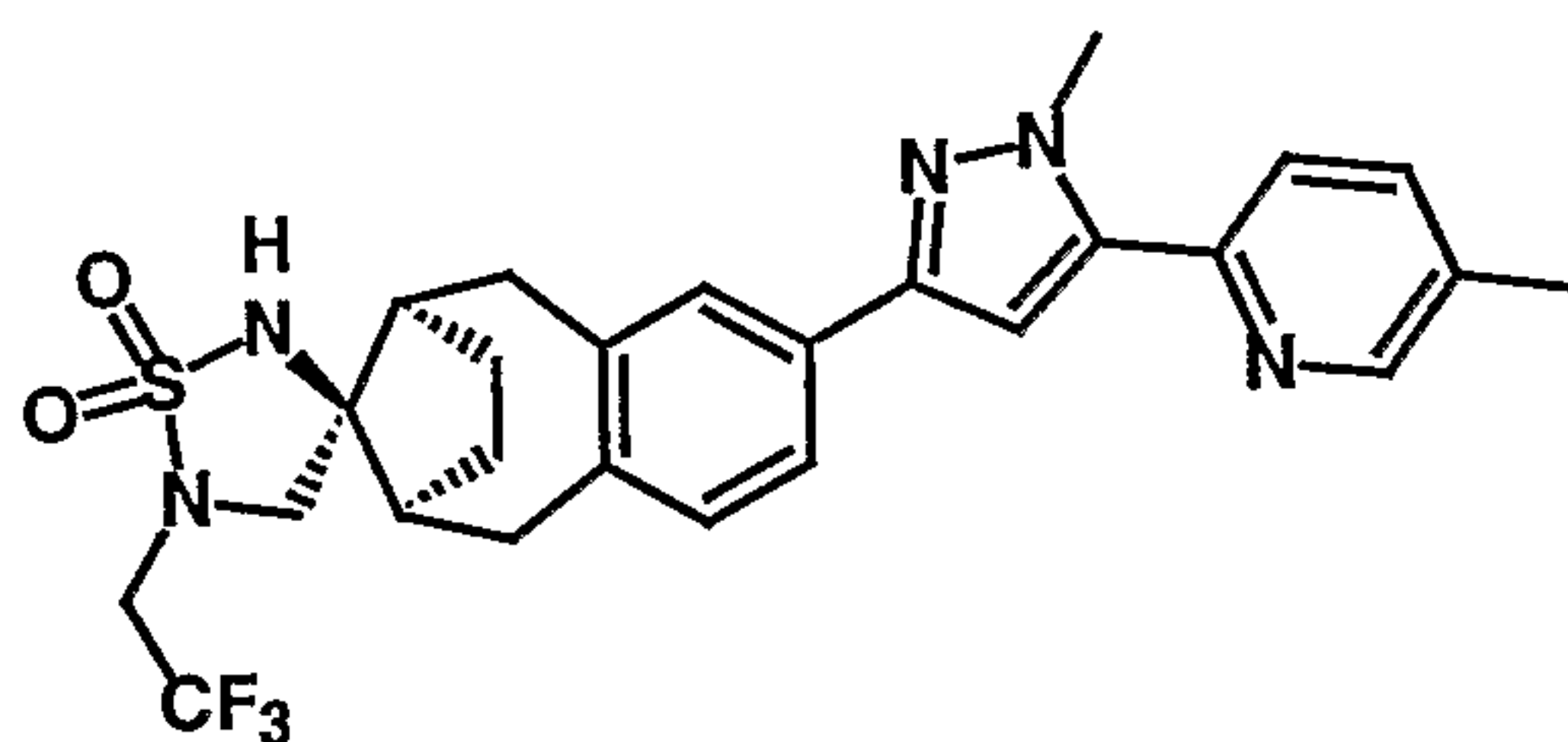
[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2,4-difluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



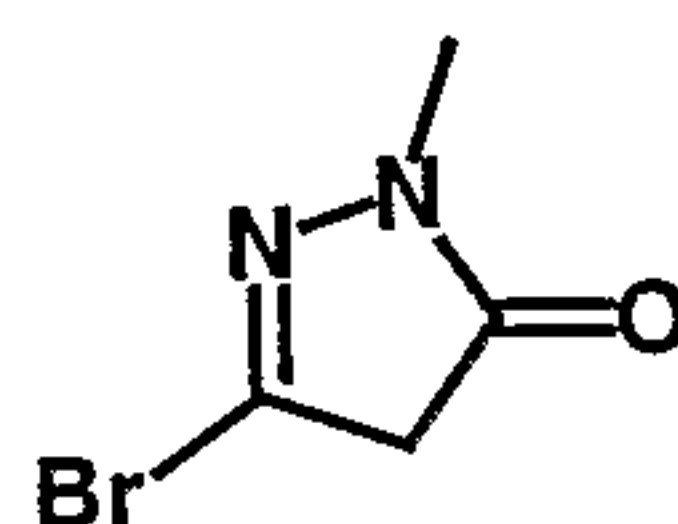
Prepared from Intermediate B and 2,4-difluorobenzeneboronic acid by the method described for Example 52. MS (ES+) 553 ([MH]⁺).

10 **Example 69**

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(5-methylpyrid-2-yl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



15 **Step 1: 1-methyl-3-bromo-5-pyrazolone**

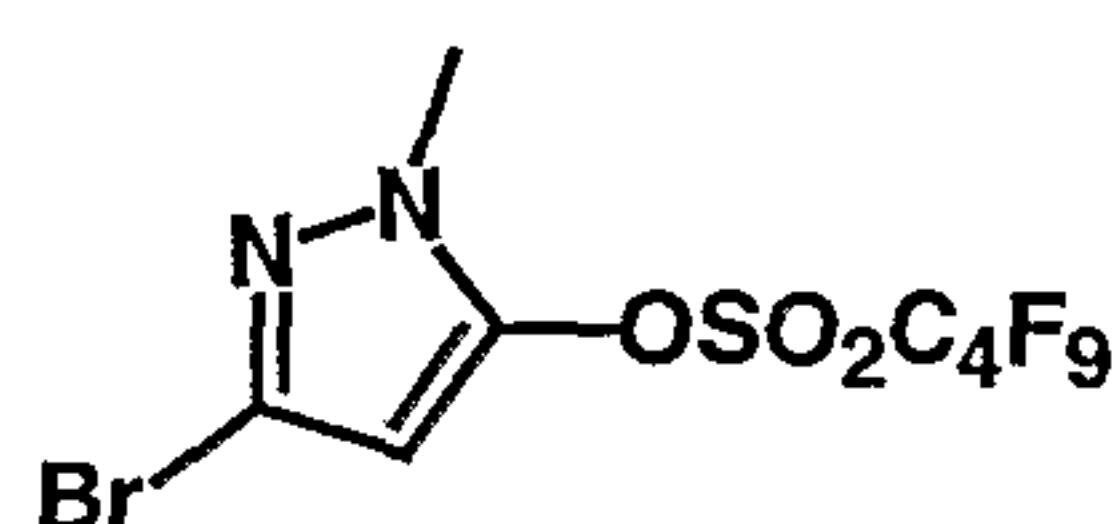


A solution of 3,3-dibromoprop-2-enoyl chloride (1.60 g, 6.44 mmol) (prepared as described in *Synthesis*, 1984, 434) in dry dichloromethane (10 mL) was added dropwise by syringe to a stirred solution of ethyl 3-methylcarbazate (0.77 g, 6.50 mmol) (prepared as described in *Arch. Pharm.* 1971, **304**, 706) and triethylamine (0.90 mL, 6.50 mmol) in dry dichloromethane (10 mL) at 0°C under nitrogen. After 2 hours, the solution was washed with 0.2M hydrochloric acid (30 mL). The aqueous washings

were extracted with dichloromethane (20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to give a pink oil (2.01 g). A solution of sodium hydroxide (2.10 g, 53 mmol) in water (42 mL) was warmed to 60°C and added to the oil. The mixture
5 was stirred at 60°C for 25 min, then cooled slowly to room temperature over 1 hour and allowed to stand at room temperature for 1 hour. The solution was acidified by dropwise addition of concentrated hydrochloric acid. After chilling for 30 min, the white precipitate was collected. The aqueous layer was extracted with 10% methanol – dichloromethane (60
10 mL). The collected solids were dissolved in the organic extract, and the solution was dried (Na_2SO_4) and concentrated to give a yellow solid. The solid was rinsed with diethyl ether and dried under vacuum to give 1-methyl-3-bromo-5-pyrazolone as a yellow powder (0.56 g, 49%).
 δ (^1H , 400MHz, CDCl_3) 3.33 (3H, s), 3.47 (2H, s).

15

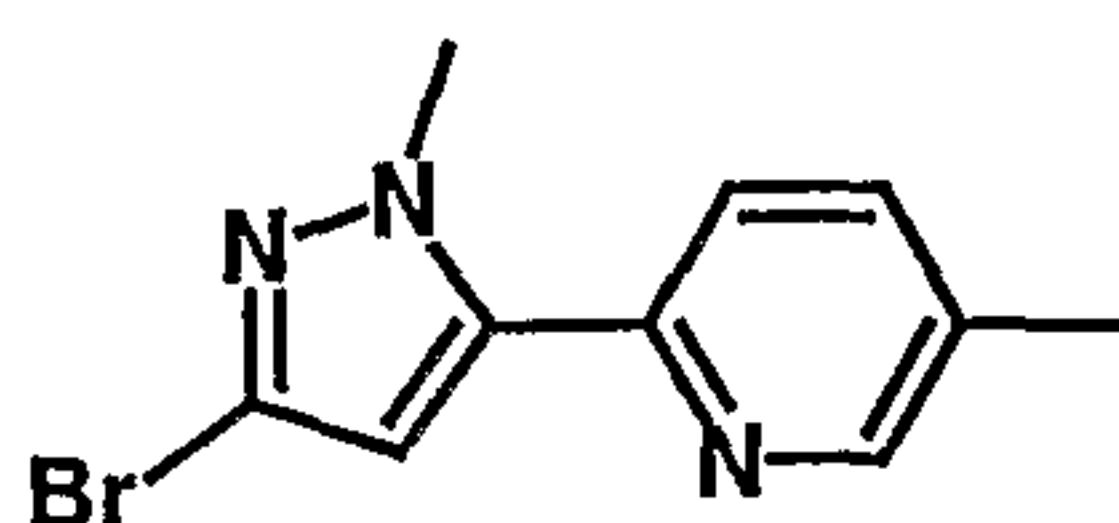
Step 2: 1-methyl-3-bromo-5-(nonafluorobutanesulfonyloxy)pyrazole



A solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (1M, 0.70 mL, 0.70 mmol) was added at -78°C under nitrogen to a stirred solution of
20 1-methyl-3-bromo-5-pyrazolone from Step 1 (0.10 g, 0.565 mmol) in dry tetrahydrofuran (2 mL). After 10 min, nonafluorobutanesulfonyl fluoride (0.13 mL, 0.70 mmol) was added dropwise. The resulting gel was warmed to room temperature and stirred for 1 hour. The solution was diluted with water (10 mL) and extracted with ethyl acetate (2 x 10 mL). The extracts
25 were dried (Na_2SO_4) and concentrated. Flash column chromatography on silica, eluting with 10% ethyl acetate – isohexane, gave 1-methyl-3-bromo-5-(nonafluorobutanesulfonyloxy)pyrazole (0.204 g, 79%) as a colourless oil.
 δ (^1H , 500MHz, CDCl_3) 3.80 (3H, s), 6.19 (1H, s).

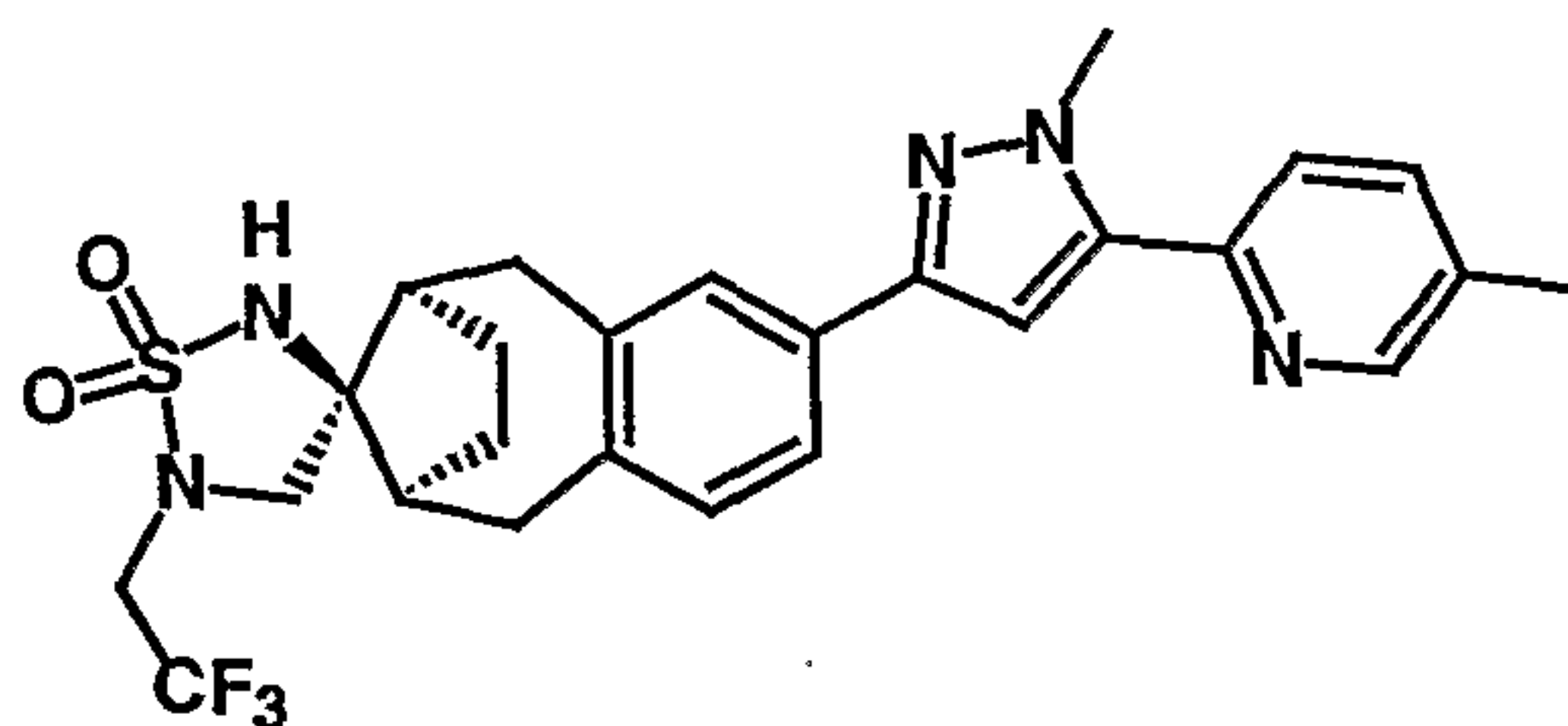
30 Step 3: 1-methyl-3-bromo-5-(5-methylpyridin-2-yl)pyrazole

- 102 -



A solution of 1-methyl-3-bromo-5-(nonafluorobutanesulfonyloxy)pyrazole from Step 2 (0.36 g, 0.784 mmol) and *tetrakis*(triphenylphosphine) palladium (0) (0.09 g, 10 mol%) in dry *N,N*-dimethylformamide (2 mL) was stirred under nitrogen at 60°C for 10 min, followed by addition of a solution of 5-methylpyridin-2-ylzinc bromide in tetrahydrofuran (0.5M, 1.8 mL, 0.9 mmol). The solution was stirred at 60°C for 18 hours then cooled, diluted with water (30 mL), and extracted with ethyl acetate (2 x 20 mL). The extracts were dried (Na₂SO₄) and concentrated. Flash column chromatography on silica, eluting with 10% ethyl acetate – isohexane, gave 1-methyl-3-bromo-5-(5-methylpyridin-2-yl)pyrazole (0.081 g, 41%) as a yellow solid. MS (ES⁺) 252, 254 ([MH]⁺).

Step 4: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-decahydro-2-(5-(5-methylpyrid-2-yl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



A mixture of 1-methyl-3-bromo-5-(5-methylpyridin-2-yl)pyrazole from Step 3 (0.081 g, 0.321 mmol), the homochiral boronate from Example 24 Step 1 (0.156 g, 0.321 mmol), cesium carbonate (0.10 g, 0.32 mmol) and *tetrakis*(triphenylphosphine) palladium (0) (0.04 g, 10mol%) in *N,N*-dimethylformamide (3 mL) and water (1 mL) was degassed and flushed with nitrogen, then stirred at 100°C under nitrogen for 18 hours. The cooled mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL). The extract was dried (Na₂SO₄), filtered through a plug of silica gel and concentrated. The residual oil was partitioned between

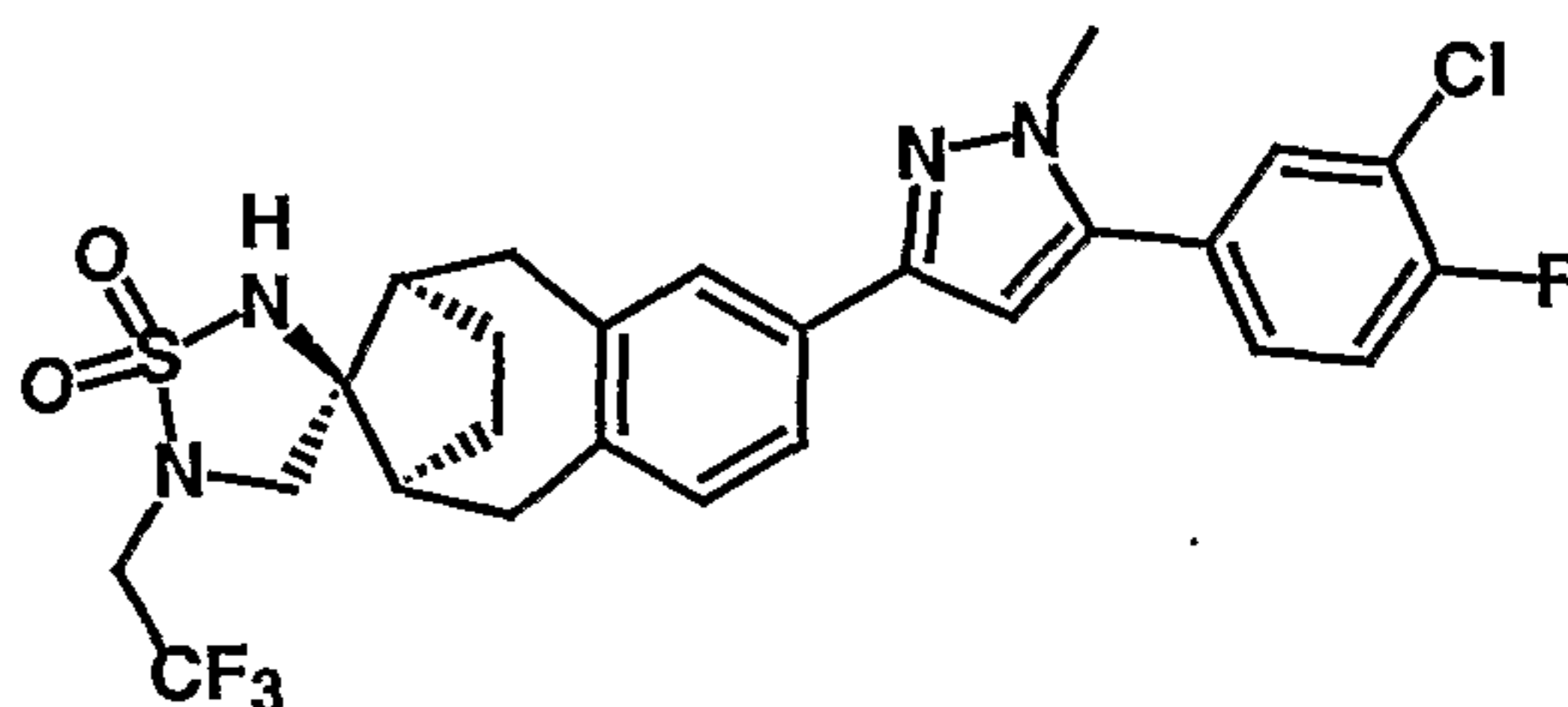
water (10 mL) and diethyl ether (10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The material was purified by normal-phase preparative HPLC, eluting with ethyl acetate – isohexanes, to give the title compound (0.039 g, 23%) as a beige solid.

5 δ (^1H , 400MHz, CDCl_3) 1.34-1.43 (2H, m), 1.68-1.74 (2H, m), 2.40 (3H, s), 2.44-2.48 (2H, m), 2.69-2.83 (2H, m), 3.21-3.25 (2H, m), 3.44 (2H, s), 3.68 (2H, q, $J = 8.7$ Hz), 4.24 (3H, s), 4.68 (1H, s), 6.81 (1H, s), 7.13 (1H, d, $J = 7.6$ Hz), 7.51-7.59 (3H, m), 7.62 (1H, d, $J = 1.6$ Hz), 8.52 (1H, d, $J = 1.6$ Hz). MS (ES+) 532 ($[\text{MH}]^+$).

10

Example 70

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3-chloro-4-fluorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-
15 dioxide

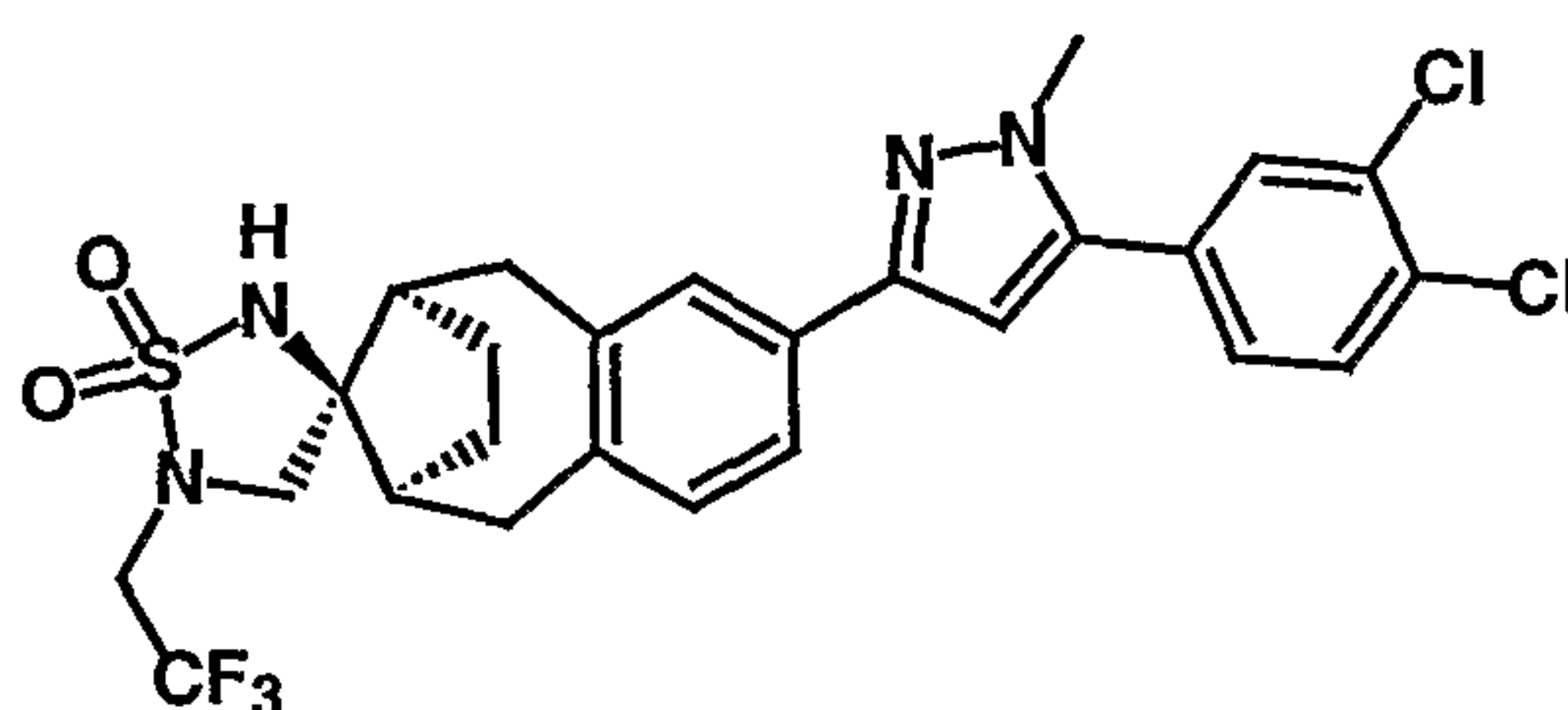


Prepared by the method described for Example 69, using 3-chloro-4-fluorophenylzinc iodide in Step 3. MS (ES+) 569 ($[\text{MH}]^+$).

20

Example 71

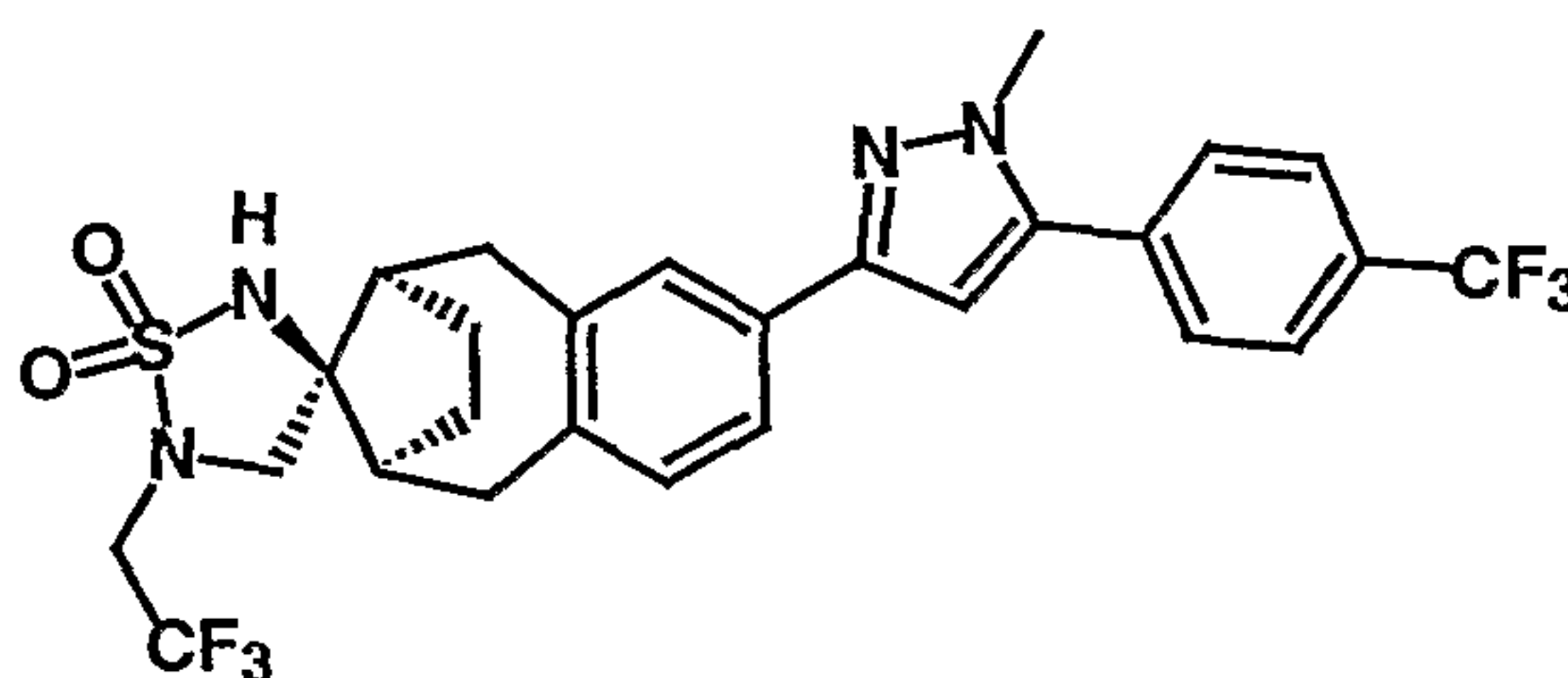
[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(3,4-dichlorophenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-
dioxide



Prepared by the method described for Example 69, using 3,4-dichlorophenylzinc iodide in Step 3. MS (ES+) 551 ([MH]⁺).

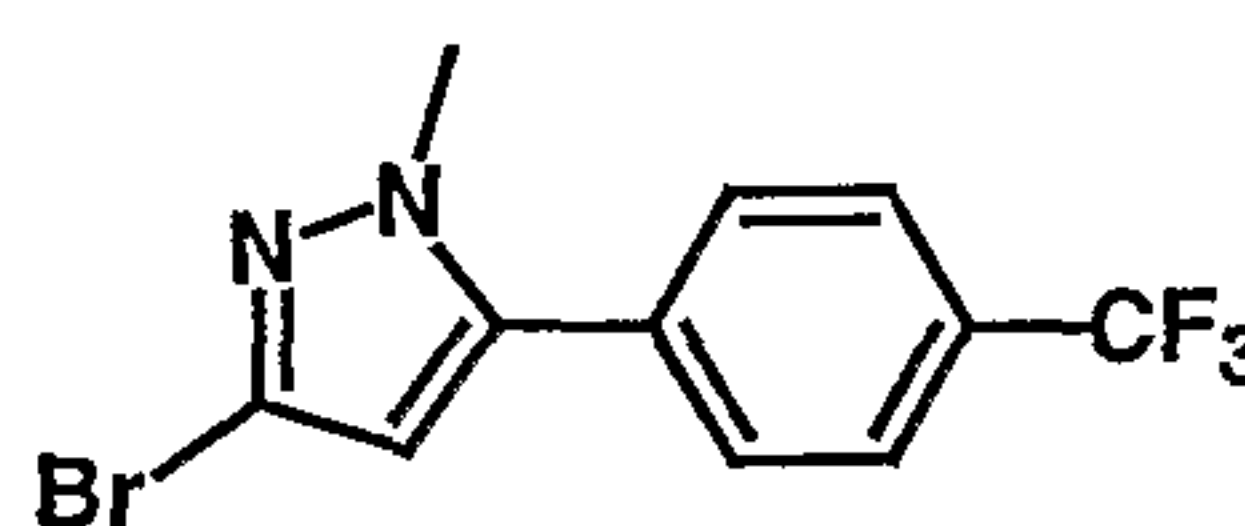
5 Example 72

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-trifluoromethylphenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



10

Step 1: 1-methyl-3-bromo-5-(4-trifluoromethylphenyl)pyrazole



A solution of 1-methyl-3-bromo-5-(nonafluorobutanesulfonyloxy)pyrazole from Example 69 Step 2 (0.16 g, 0.35 mmol), 4-

15 trifluoromethylbenzeneboronic acid (0.07 g, 0.36 mmol), *tetrakis*(triphenylphosphine) palladium (0) (0.04 g, 10 mol%), sodium carbonate (0.04 g, 0.38 mmol) in dry *N,N*-dimethylformamide (2 mL) was stirred under nitrogen at 40°C for 18 hours. The cooled reaction mixture was poured into 1M hydrochloric acid (10 mL) and extracted with diethyl
20 ether (2 x 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated to give an oil which was purified by flash column chromatography on silica eluting with 5% ethyl acetate – isohexane to give

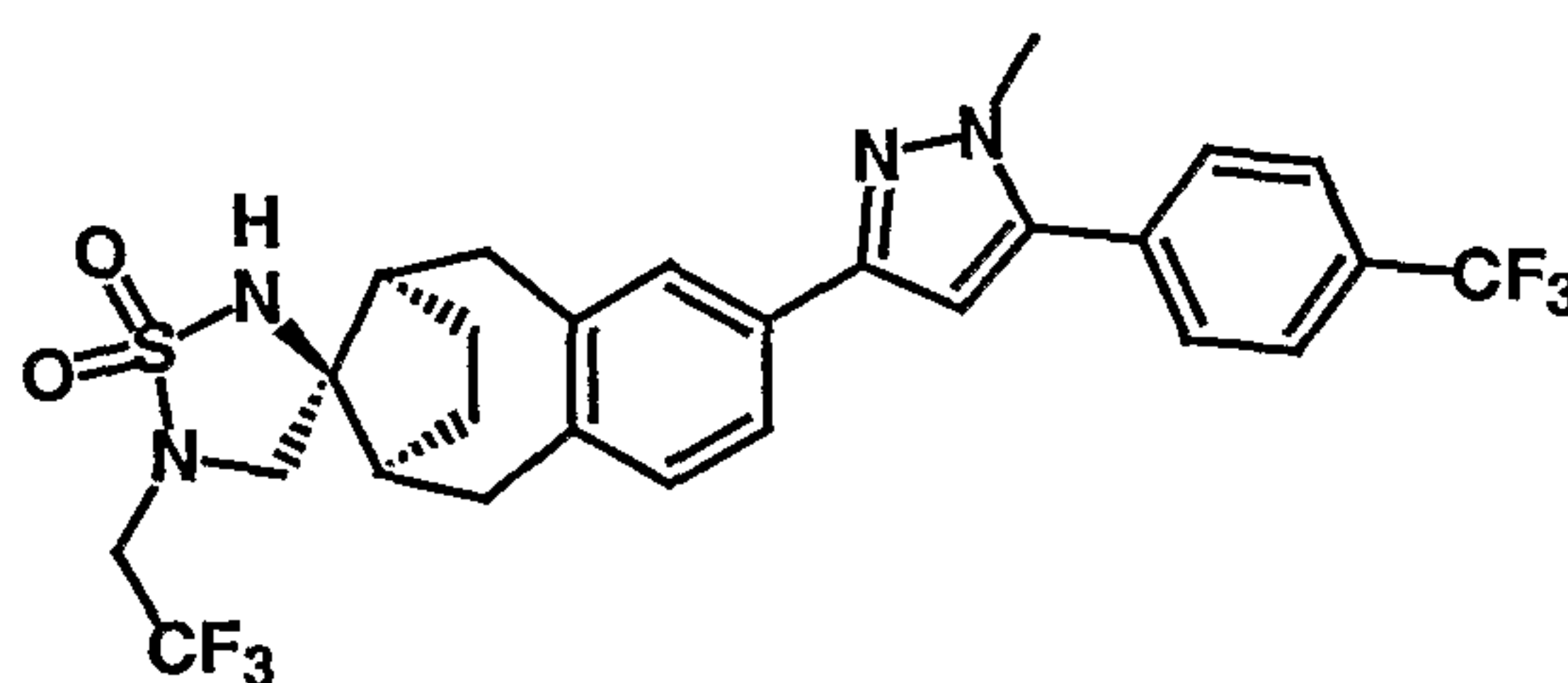
- 105 -

1-methyl-3-bromo-5-(4-trifluoromethylphenyl)pyrazole as a white solid (0.06 g, 56%).

δ (^1H , 400MHz, CDCl_3) 3.86 (3H, s), 6.37 (1H, s), 7.53 (2H, d, $J = 8$ Hz), 7.74 (2H, d, $J = 8$ Hz).

5

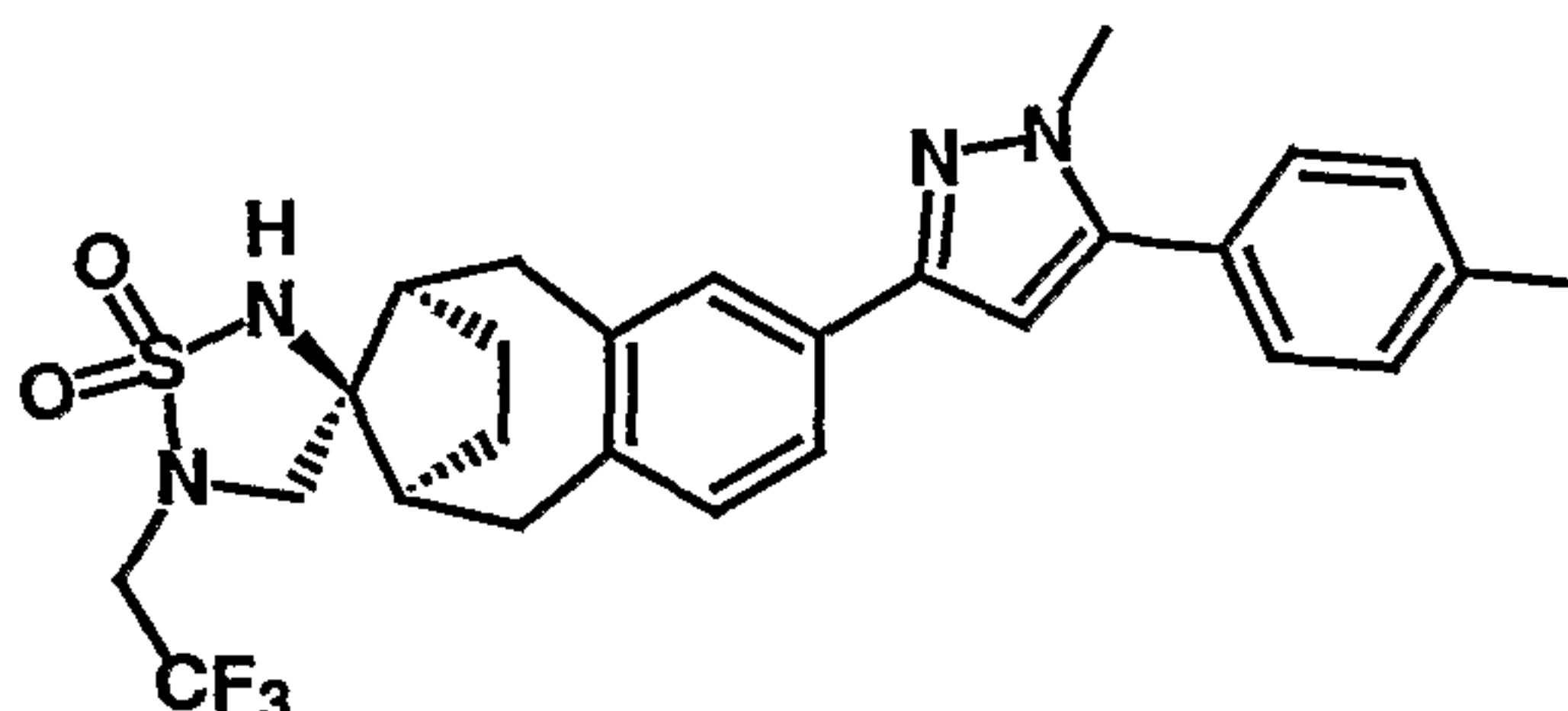
Step 2: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-decahydro-2-(5-(4-trifluoromethylphenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



10 Prepared by the method of Example 69 Step 4. MS (ES+) 451 ($[\text{MH}]^+$).

Example 73

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-methylphenyl)-1-methyl-pyrazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

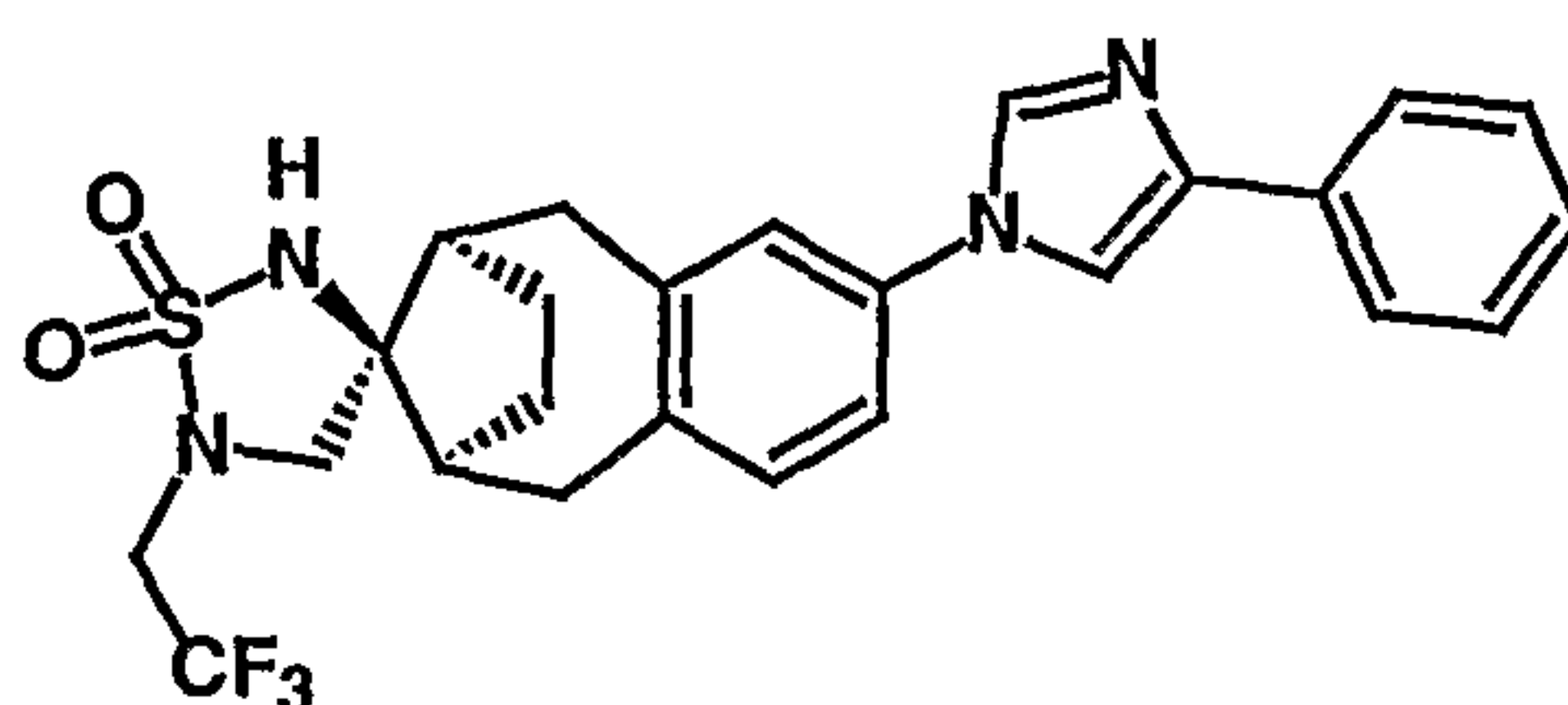


Prepared by the method described for Example 72, using 4-methylbenzeneboronic acid at 100°C in Step 1. MS (ES+) 531 ($[\text{MH}]^+$).

20 Example 74

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(4-phenylimidazol-1-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

- 106 -

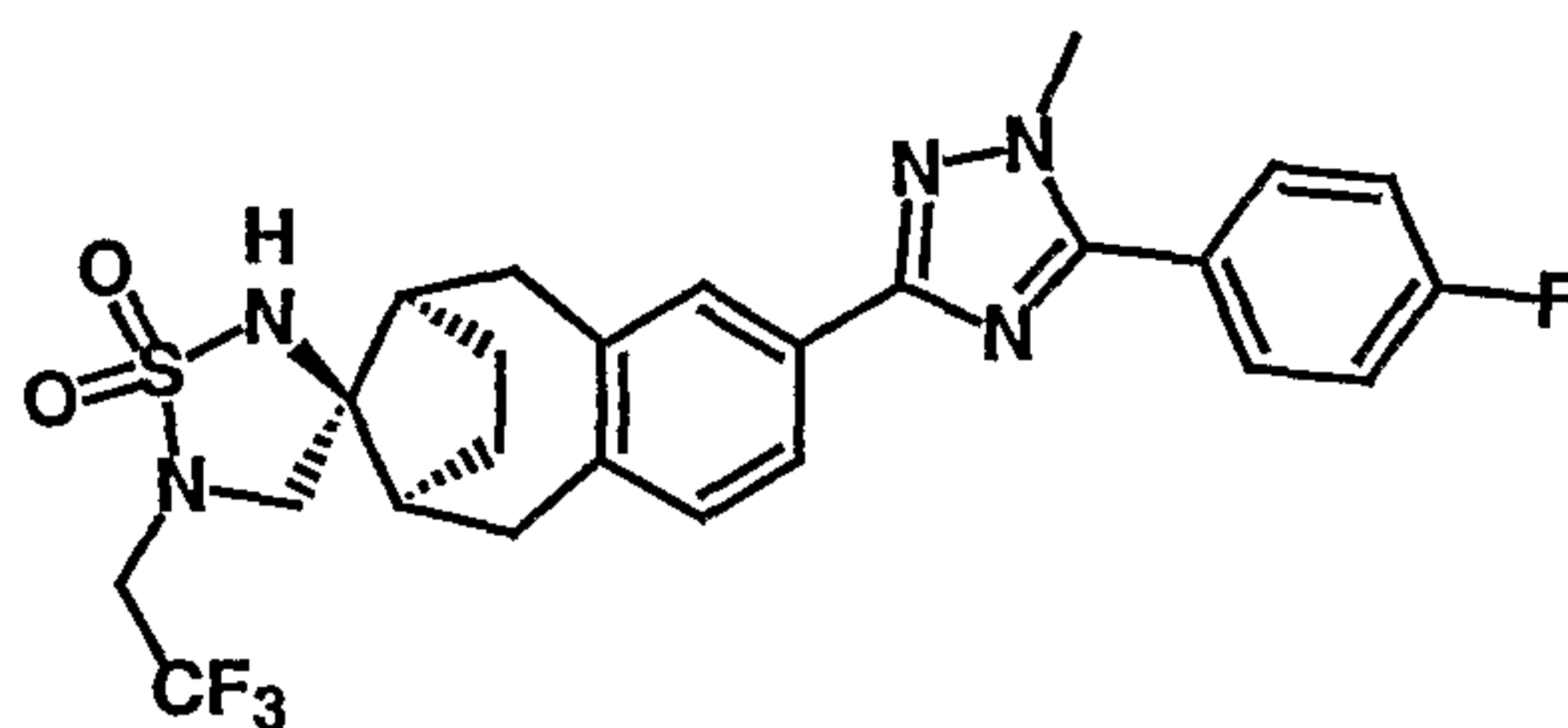


Sodium periodate (99 mg, 0.46 mmol) was added to a solution of the racemic boronate from Example 36 Step 1 (75 mg, 0.15 mmol) in tetrahydrofuran (2 mL) and water (0.5 mL) and stirred for 2 hours at room temperature. 2M aqueous hydrochloric acid (50 μ L) was added and stirred for 18 hours at room temperature. The reaction was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated to give the crude boronic acid. 62 mg (0.15 mmol) of this, 4-phenylimidazole (22 mg, 0.15 mmol) and (di- μ -hydroxo-bis(*N,N,N',N'*-tetramethylethylenediamine)copper(II) chloride (7 mg, 0.02 mmol) in dichloromethane (4 mL) were stirred in an open flask for 18 hours at room temperature. The mixture was filtered through Celite® and washed with ethyl acetate. The filtrate was concentrated and the residue purified by flash column chromatography on silica eluting with ethyl acetate/isohexane (gradient 50% to 70% to neat ethyl acetate) to give the title compound as a white solid (34 mg, 44%).

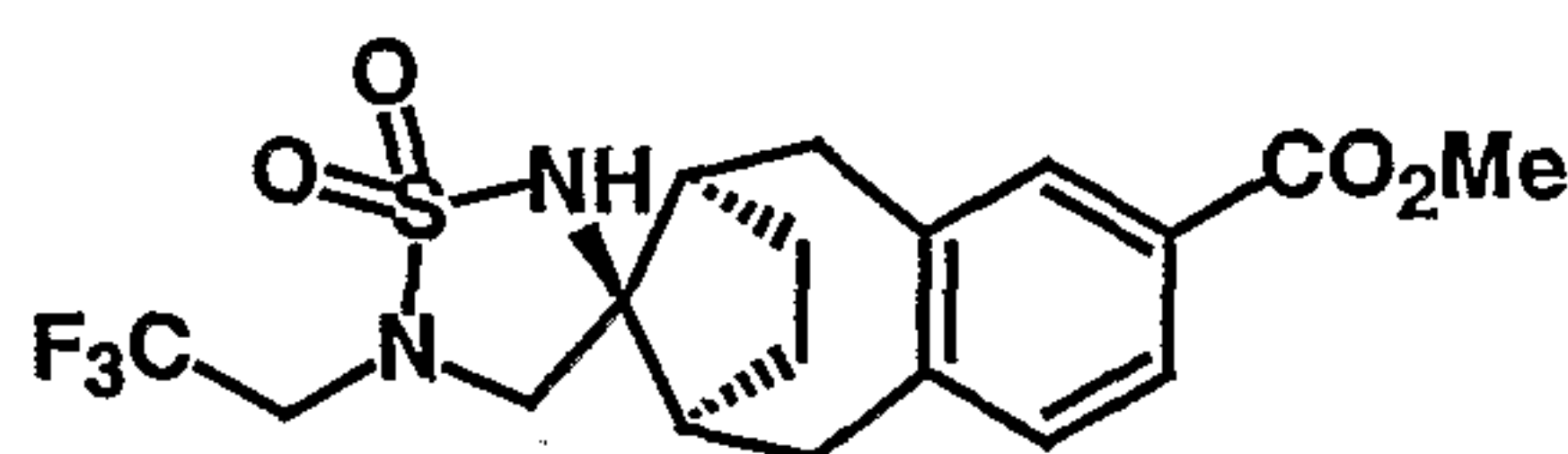
δ (^1H , 500MHz, CDCl_3) 1.32-1.40 (2H, m), 1.77-1.79 (2H, m), 2.49-2.53 (2H, m), 2.74-2.80 (2H, m), 3.26 (1H, d, $J = 16$ Hz), 3.3.1 (1H, d, $J = 16$ Hz), 3.44-3.48 (2H, m), 3.67-3.72 (2H, m), 4.72 (1H, s), 7.20-7.29 (4H, m), 7.41 (2H, t, $J = 7.4$ Hz), 7.54 (1H, d, $J = 1.1$ Hz), 7.84 (2H, d, $J = 7.4$ Hz), 7.87 (1H, d, $J = 1.1$ Hz). MS (ES+) 503 ($[\text{MH}]^+$).

Example 75

[6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1-methyl-1,2,4-triazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



Step 1: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-carbomethoxy-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

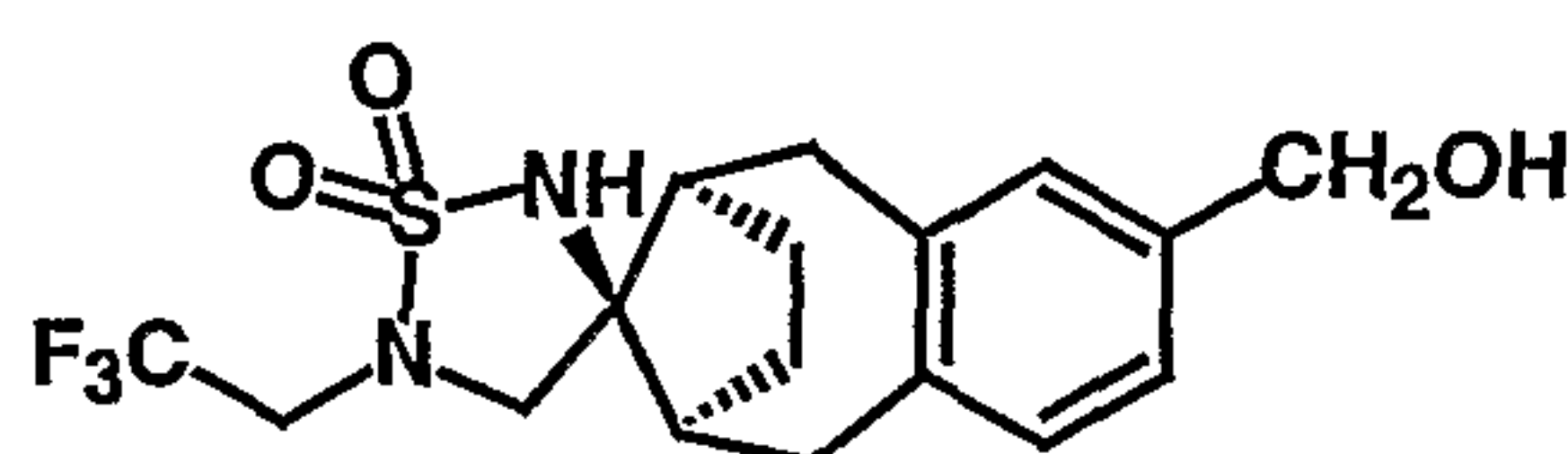


5

A solution of Intermediate D (6.7g, 13 mmol), 1,3-bis (diphenylphosphino)propane (540 mg, 1.3 mmol) and triethylamine (25 mL, 180 mmol) in dry dimethylsulfoxide (180 mL) and methanol (120 mL) was deoxygenated by bubbling carbon monoxide through the solution for 15 minutes. Palladium (II) acetate (300 mg, 1.3 mmol) was added and deoxygenation was continued for a further 5 minutes. The reaction was then heated at 80°C for 4 hours, with a slow stream of carbon monoxide bubbling through the solution. The reaction was allowed to cool, then diluted with water (1 L). The mixture was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography on silica, eluting with 100% dichloromethane to 5% ethyl acetate/dichloromethane, to give the ester (4.8g, 88%) as a pale yellow solid.

20 δ (¹H, 360MHz, CDCl₃) 1.28 (2H, m), 1.72 (2H, m), 2.48 (2H, brm), 2.78 (2H, m), 3.23 (1H, d, J=15.4 Hz), 3.27 (1H, d, J=15.4 Hz), 3.43 (2H, ABq, J=9.5, 11.1 Hz), 3.68 (2H, q, J=8.7 Hz), 3.90 (3H, s), 4.79 (1H, s), 7.17 (1H, d, J=8.3 Hz), 7.78 (2H, m).

Step 2: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-hydroxymethyl-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



5

Diisobutylaluminium hydride (1M in toluene, 49 mL, 49 mmol) was added slowly to a stirred solution of the product from Step 1 (5.1g, 12.2 mmol) in dry tetrahydrofuran (100 mL) at -78°C under nitrogen. After 30 minutes the reaction was allowed to warm to -10°C and maintained at this temperature for 3 hours. The reaction was quenched with methanol and allowed to warm to room temperature. 1M Aqueous hydrochloric acid (100 mL) was added slowly. The mixture was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to give a dark foam (5.2 g) which was used without further purification.

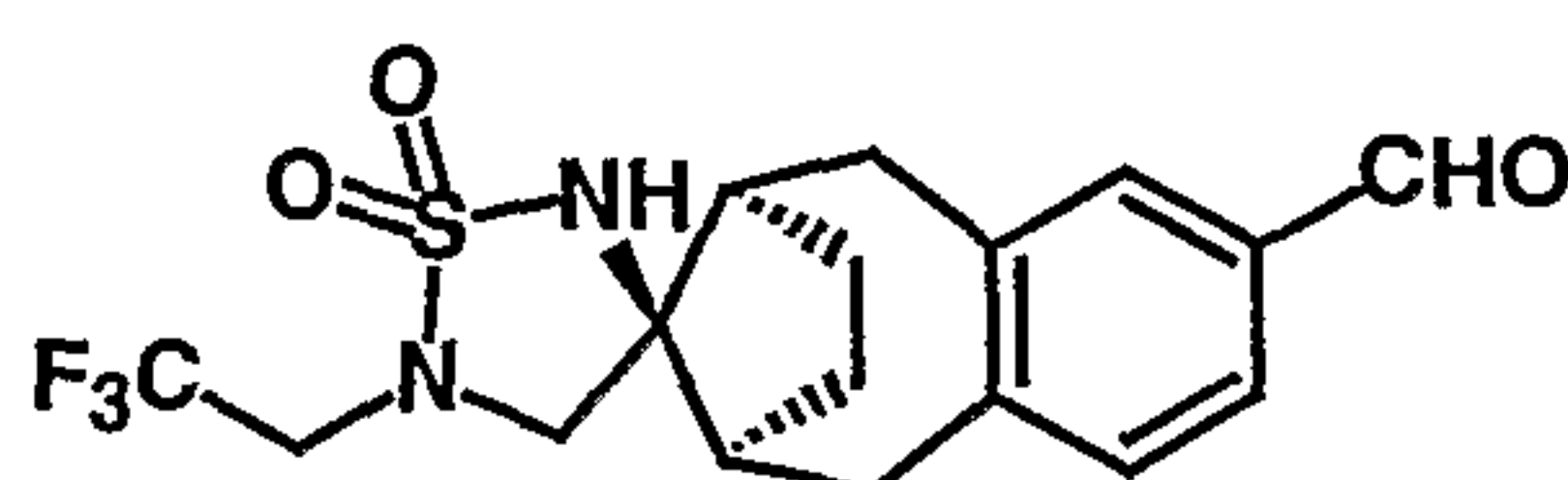
10

15

δ (^1H , 360MHz, CDCl_3) 1.35 (2H, m), 1.71 (2H, m), 2.43 (2H, brm), 2.68 (1H, d, $J=16.1$), 2.70 (1H, d, $J=16.1$ Hz), 3.17 (1H, d, $J=15.9$ Hz), 3.20 (1H, d, $J=15.9$ Hz), 3.43 (2H, s), 3.69 (2H, q, $J=8.7$ Hz), 4.65 (2H, brs), 4.73 (1H, s), 7.10 (3H, m).

20

Step 3: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-carboxaldehyde-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



25

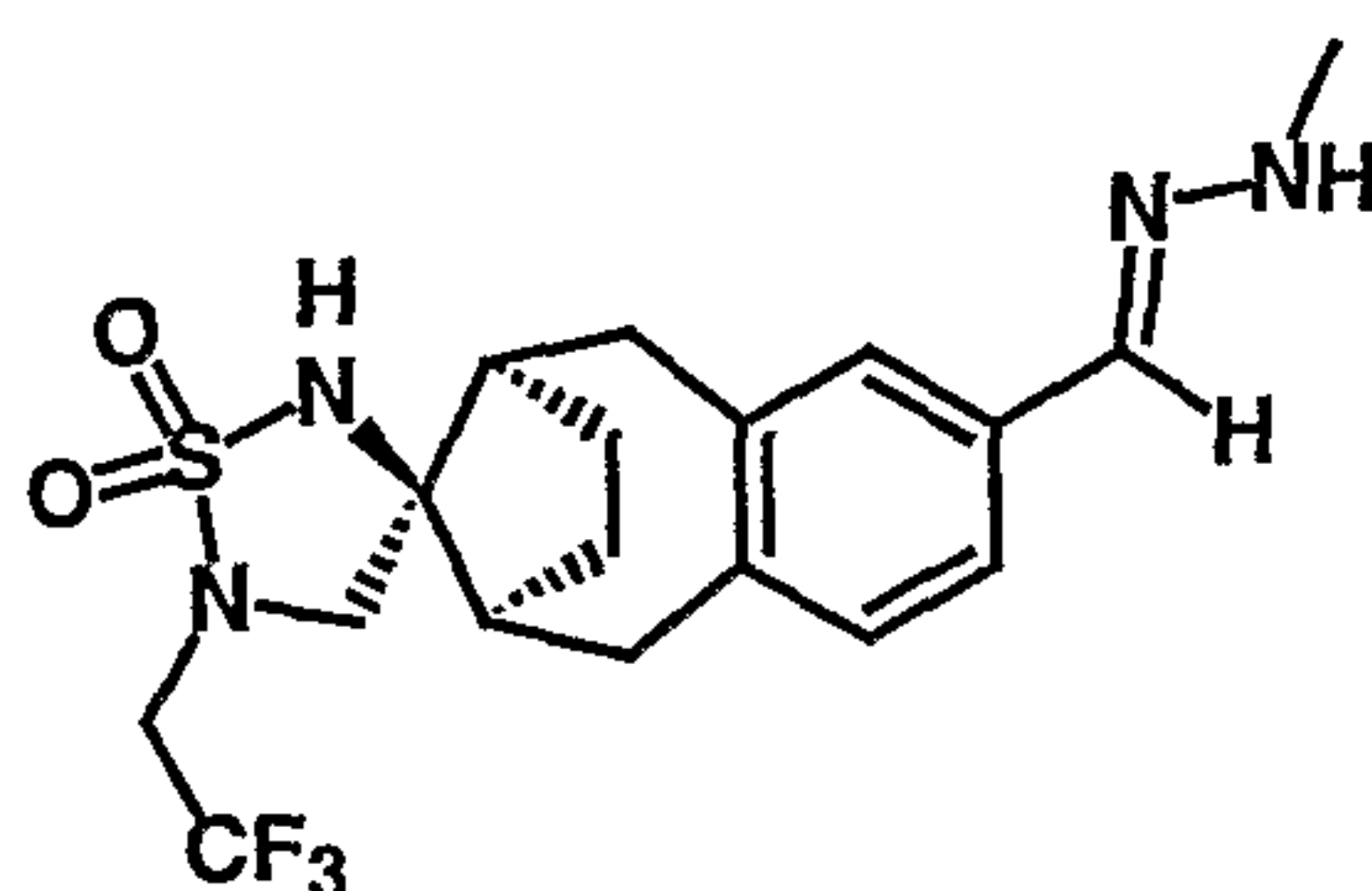
Pyridinium dichromate (6.9 g, 18 mmol) was added to a stirred solution of the product from Step 2 (5.2 g) in dry dichloromethane (120 mL) at room temperature. The mixture was stirred at this temperature overnight, then loaded directly on to a pad of silica. The pad was eluted with

- 109 -

dichloromethane, then 20% ethyl acetate/dichloromethane to give the aldehyde (4.2 g, 89%) as a pale yellow solid.

δ (^1H , 360MHz, CDCl_3) 1.27 (2H, m), 1.74 (2H, m), 2.50 (2H, brm), 2.82 (2H, m), 3.26 (1H, d, $J=13.9$ Hz), 3.30 (1H, d, $J=13.9$ Hz), 3.45 (2H, Abq, $J=9.4, 11.5$ Hz), 3.69 (2H, q, $J=8.7$ Hz), 4.79 (2H, s), 7.28 (1H, d, $J=7.6$ Hz), 7.64 (2H, m), 9.96 (1H, s).

Step 4: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-carboxaldehydemethylhydrazone-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

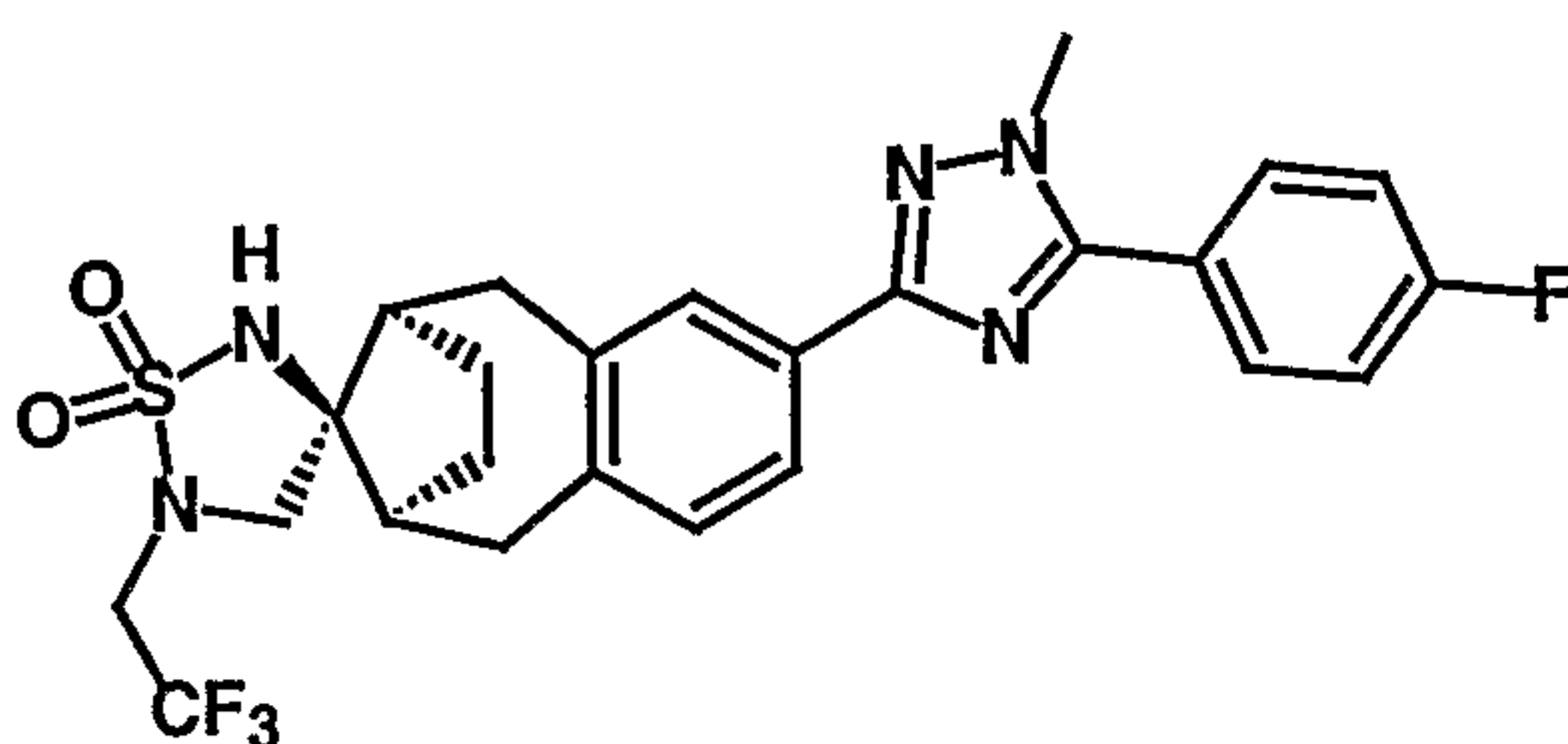


To a suspension of the aldehyde from Step 3 (106 mg, 0.27 mmol) in diethyl ether (4 mL) was added methylhydrazine (15 μL , 0.27 mmol). Tetrahydrofuran (1 mL) was added to aid dissolution. The reaction was stirred at room temperature for 1.5 hours, then the solvent was removed *in vacuo* to give the title compound as a white foam (112 mg, quant.).

δ (^1H , 500MHz, CDCl_3) 1.29-1.37 (2H, m), 1.68-1.71 (2H, m), 2.43 (2H, br s), 2.66-2.2.74 (2H, m), 2.97 (3H, s), 3.19 (2H, d, $J = 16$ Hz), 3.42 (2H, s), 3.68 (2H, q, $J = 8.7$ Hz), 4.78 (1H, br s), 7.06 (1H, d, $J = 7.7$ Hz), 7.27 (1H, d, $J = 7.7$ Hz), 7.33 (1H, s), 7.49 (1H, s). MS (ES+) 417 ($[\text{MH}]^+$).

Step 5: [6S/R,9R/S,11R/S] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-1-methyl-1,2,4-triazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

- 110 -

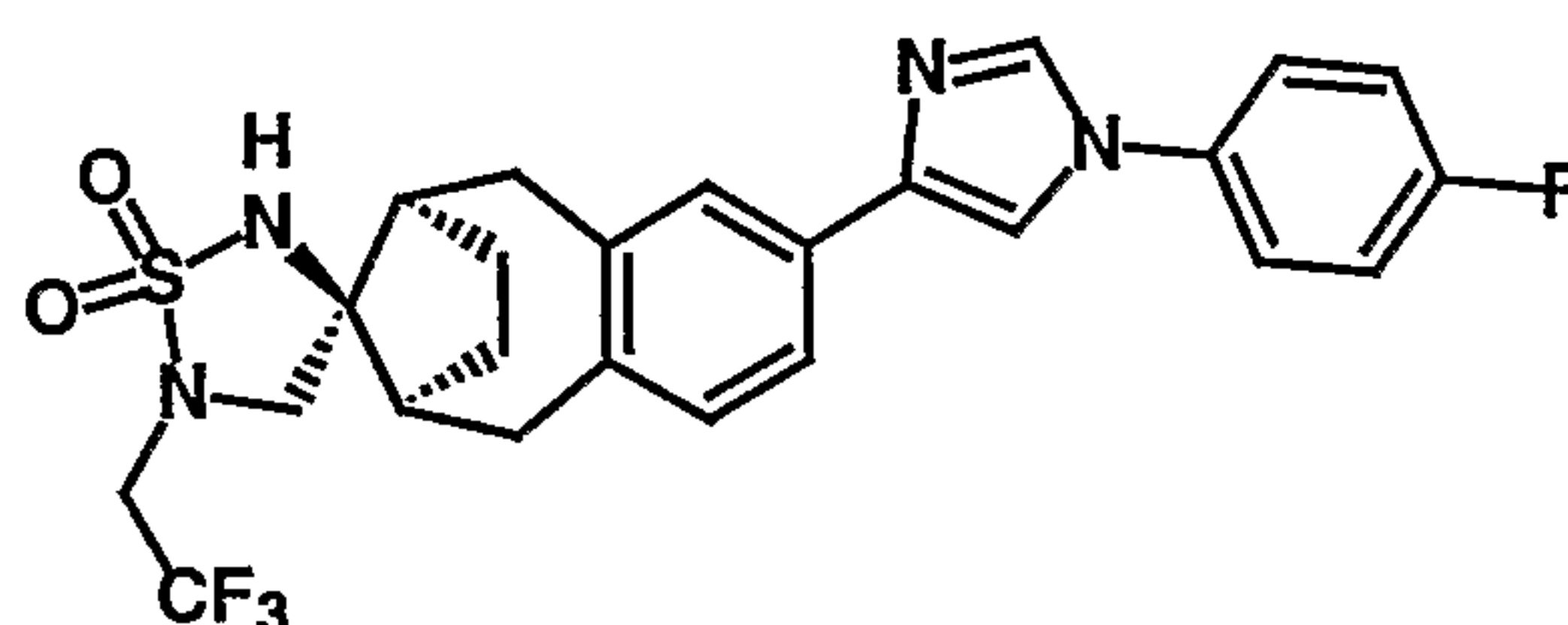


A solution of 4-fluorobenzohydroximinoyl chloride (69 mg, 0.4 mmol) (prepared from *syn*-4-fluorobenzaldoxime using the general procedure for the synthesis of benzohydroximinoyl chlorides described in *J. Org. Chem.* 1980, 45, 3916) in tetrahydrofuran (2 mL) was added dropwise to a stirred solution of the methylhydrazone from Step 4 (110 mg, 0.26 mmol) and triethylamine (74 μ L, 0.53 mmol) in tetrahydrofuran (4 mL) at -10°C. The mixture was stirred at between -10 and 0°C for 1.5 hours then at ambient temperature for 1 hour. A further 2 equivalents of triethylamine (74 μ L) were added, the mixture was cooled to -10°C and a further 1.5 equivalents of the chloro-oxime (69 mg) added as a solution in tetrahydrofuran (1 mL). The mixture was stirred at between -10 and 0°C for 0.5 hours then at ambient temperature for 1 hour. The mixture was cooled to -10°C and a further 4 equivalents of triethylamine (147 μ L) and 3 equivalents of chloro-oxime (138 mg) in tetrahydrofuran (1 mL) were added. The mixture was stirred at between -10 and -5°C for 0.5 hours then at ambient temperature for 18 hours. The reaction was partitioned between ethyl acetate and water. The organic layer was dried (MgSO₄) and concentrated on the rotary evaporator without heating. The yellow residue was partially dissolved in acetic acid (7 mL) and heated at reflux for 1 hour. The cooled solution was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium hydrogencarbonate (x 3), dried (MgSO₄) and concentrated. The residue was purified by flash column chromatography on silica eluting with 40 to 50% ethyl acetate/isohexane to give almost pure product (74 mg). This was further purified by flash column chromatography on silica eluting with 1% methanol/dichloromethane followed by recrystallisation from diethyl ether/isohexane to give the product (33 mg, 24%).

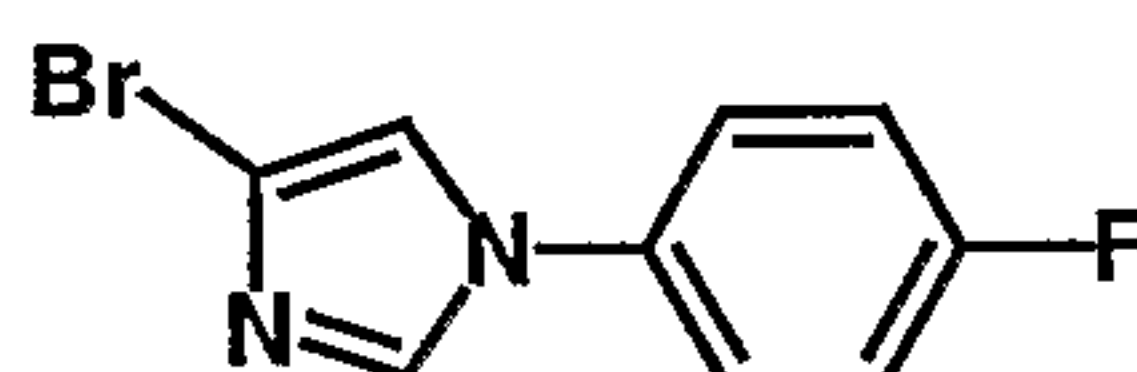
δ (^1H , 500MHz, CDCl_3) 1.32-1.42 (2H, m), 1.69-1.73 (2H, m), 2.45-2.48 (2H, m), 2.73-2.77 (1H, m), 2.81-2.86 (1H, m), 3.23 (1H, d, $J = 7$ Hz), 3.26 (1H, d, $J = 7$ Hz), 3.44 (2H, s), 3.68 (2H, q, $J = 8.7$ Hz), 4.00 (3H, s), 4.69 (1H, s), 7.18 (1H, d, $J = 8.4$ Hz), 7.23 (2H, t, $J = 8.4$ Hz), 7.71-7.74 (2H, m), 7.88 (2H, d, $J = 5.5$ Hz). MS (ES+) 536 ($[\text{MH}]^+$).

Example 76

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(4-fluorophenyl)-imidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



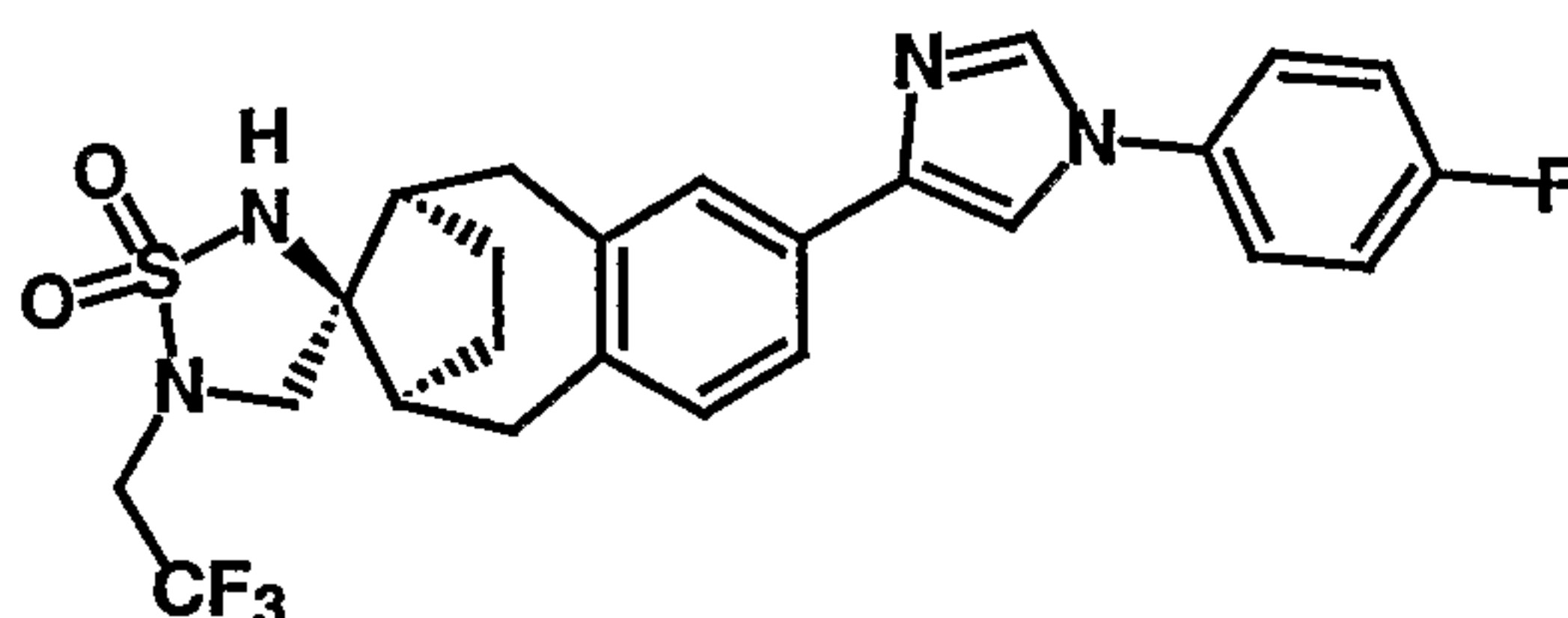
Step 1: 4-Bromo-1-(4-fluorophenyl)imidazole



A mixture of 4-bromo-1*H*-imidazole (223 mg, 1.52 mmol), 4-fluorophenylboronic acid (425 mg, 3.03 mmol), copper(II) acetate (413 mg, 2.28 mmol), pyridine (0.25 mL) and powdered 4Å molecular sieves (1 g) in 1,2-dichloroethane (7mL) was stirred at room temperature under a slow stream of air for 44 hours. The reaction mixture was filtered through Celite®, washing with ethyl acetate. The filtrate was concentrated and the residue purified by flash column chromatography on silica eluting with 10 to 20% ethyl acetate/isohexane to give the product as a white solid (135 mg, 37%).

δ (^1H , 400MHz, CDCl_3) 7.16-7.22 (3H, m), 7.32-7.37 (2H, m), 7.65 (1H, d, $J = 1.5$ Hz). MS (ES+) 241, 243 ($[\text{MH}]^+$).

Step 2: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(4-fluorophenyl)-imidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



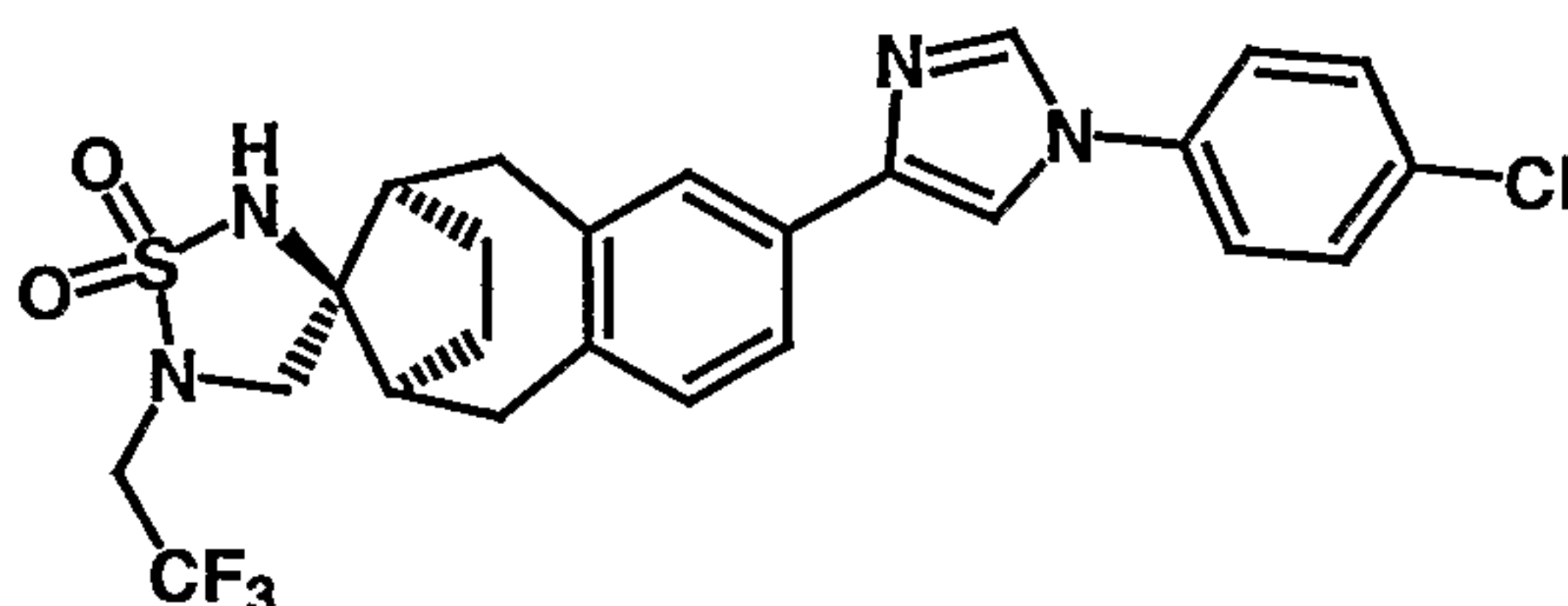
- 5 To a degassed solution of 4-bromo-1-(4-fluorophenyl)imidazole from Step 1 (50 mg, 0.21 mmol) and the homochiral boronate from Example 24 Step 1 (100 mg, 0.21 mmol) in *N,N*-dimethylformamide (3 mL) and water (1 mL) was added cesium carbonate (67 mg, 0.21 mmol) followed by *tetrakis*(triphenylphosphine) palladium (0) (24 mg, 0.02 mmol). The
- 10 reaction was heated at 100°C for 19 hours. The cooled reaction mixture was diluted with ethyl acetate. The organic layer was washed with water (x 3) and brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica eluting with ethyl acetate/isohexane (gradient 20 to 30 to 50% to neat ethyl acetate) followed by
- 15 recrystallisation from dichloromethane/diethyl ether to give the product (13 mg, 12%).

δ (¹H, 500MHz, CDCl₃) 1.34-1.42 (2H, m), 1.70-1.72 (2H, m), 2.43-2.48 (2H, m), 2.68-2.82 (2H, m), 3.21-3.25 (2H, m), 3.43 (2H, s), 3.68 (2H, q, *J* = 8.7 Hz), 4.82 (1H, s), 7.12 (1H, d, *J* = 7.8 Hz), 7.19-7.22 (2H, m), 7.40-7.43 (2H, m), 7.48 (1H, d, *J* = 1.1 Hz), 7.54 (1H, d, *J* = 7.8 Hz), 7.61 (1H, s), 7.82 (1H, d, *J* = 1.1 Hz). MS (ES⁺) 521 ([MH]⁺).

20

Example 77

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(4-chlorophenyl)-imidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



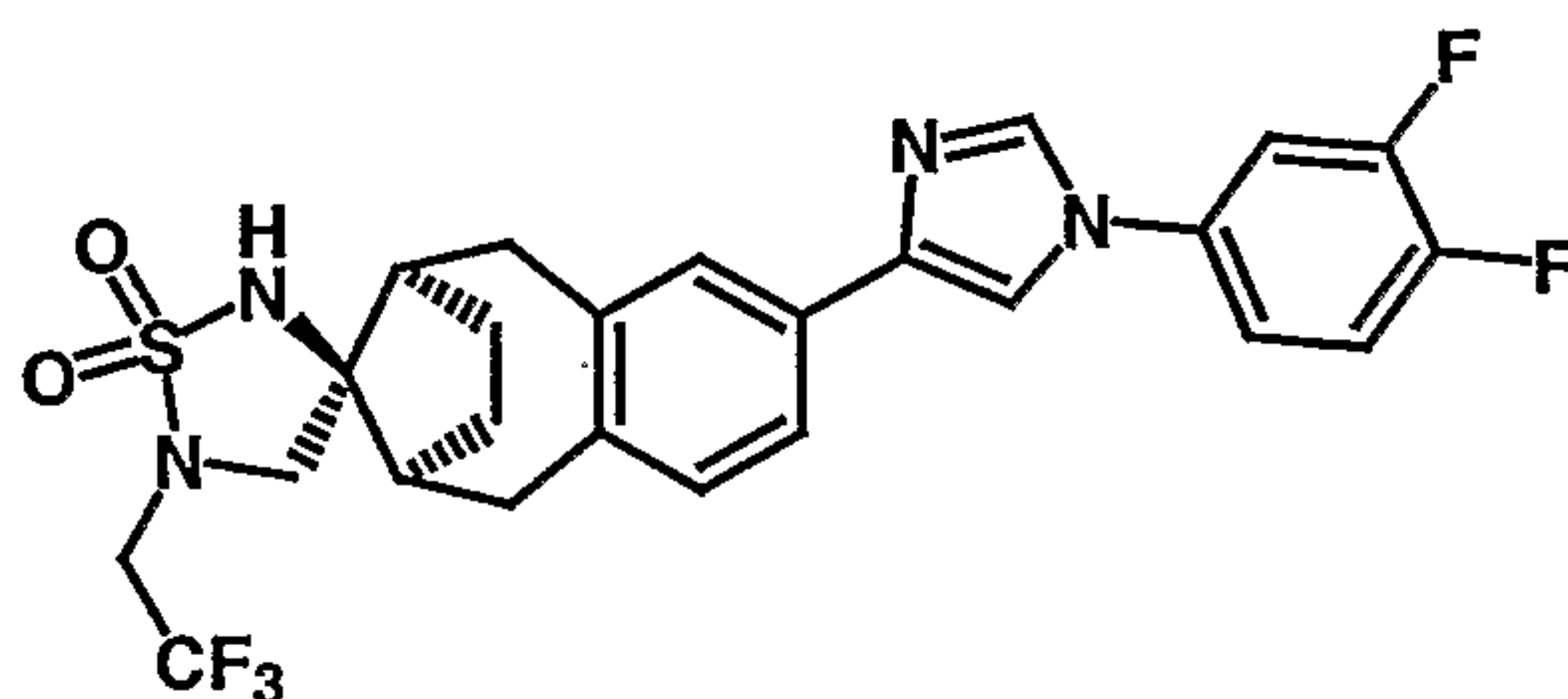
5

Prepared from 4-bromo-1*H*-imidazole, 4-chlorophenylboronic acid and homochiral boronate from Example 24 Step 1 following the procedures in Example 76 Steps 1 and 2.

10 δ (^1H , 500MHz, CDCl_3) 1.34-1.42 (2H, m), 1.68-1.75 (2H, m), 2.42-2.50 (2H, m), 2.70-2.82 (2H, m), 3.20-3.28 (2H, m), 3.44 (2H, s), 3.68 (2H, q, $J = 8.7$ Hz), 4.68 (1H, s), 7.12 (1H, d, $J = 7.8$ Hz), 7.38 (2H, d, $J = 8.7$ Hz), 7.47-7.51 (3H, m), 7.56 (1H, d, $J = 7.8$ Hz), 7.62 (1H, s), 7.86 (1H, s). MS (ES+) 537, 539 ($[\text{MH}]^+$).

15 **Example 78**

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(3,4-difluorophenyl)-imidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



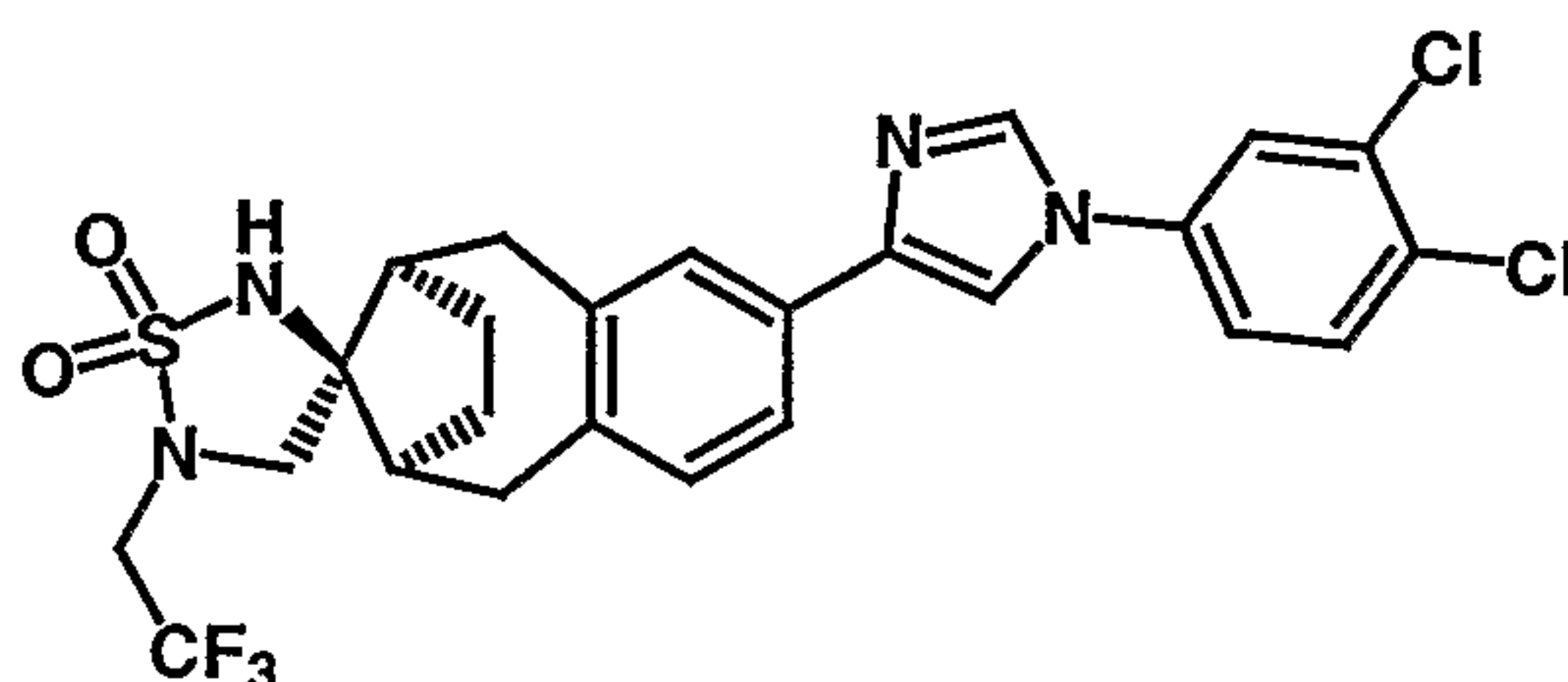
20 Prepared from 4-bromo-1*H*-imidazole, 3,4-difluorophenylboronic acid and homochiral boronate from Example 24 Step 1 following the procedures in Example 76 Steps 1 and 2.

25 δ (^1H , 400MHz, CDCl_3) 1.18-1.24 (2H, m), 1.70-1.73 (2H, m), 2.43-2.49 (2H, m), 2.69-2.81 (2H, m), 3.20-3.26 (2H, m), 3.44 (2H, s), 3.68 (2H, q, $J = 8.7$ Hz), 4.72 (1H, s), 7.13 (1H, d, $J = 7.8$ Hz), 7.19-7.22 (1H, m,) 7.28-7.35 (2H,

m), 7.48 (1H, d, $J = 1$ Hz), 7.54 (1H, dd, $J = 7.7, 2$ Hz), 7.61 (1H, s), 7.83 (1H, d, $J = 1$ Hz). MS (ES+) 539 ([MH]⁺).

Example 79

5 [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(3,4-dichlorophenyl)-imidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

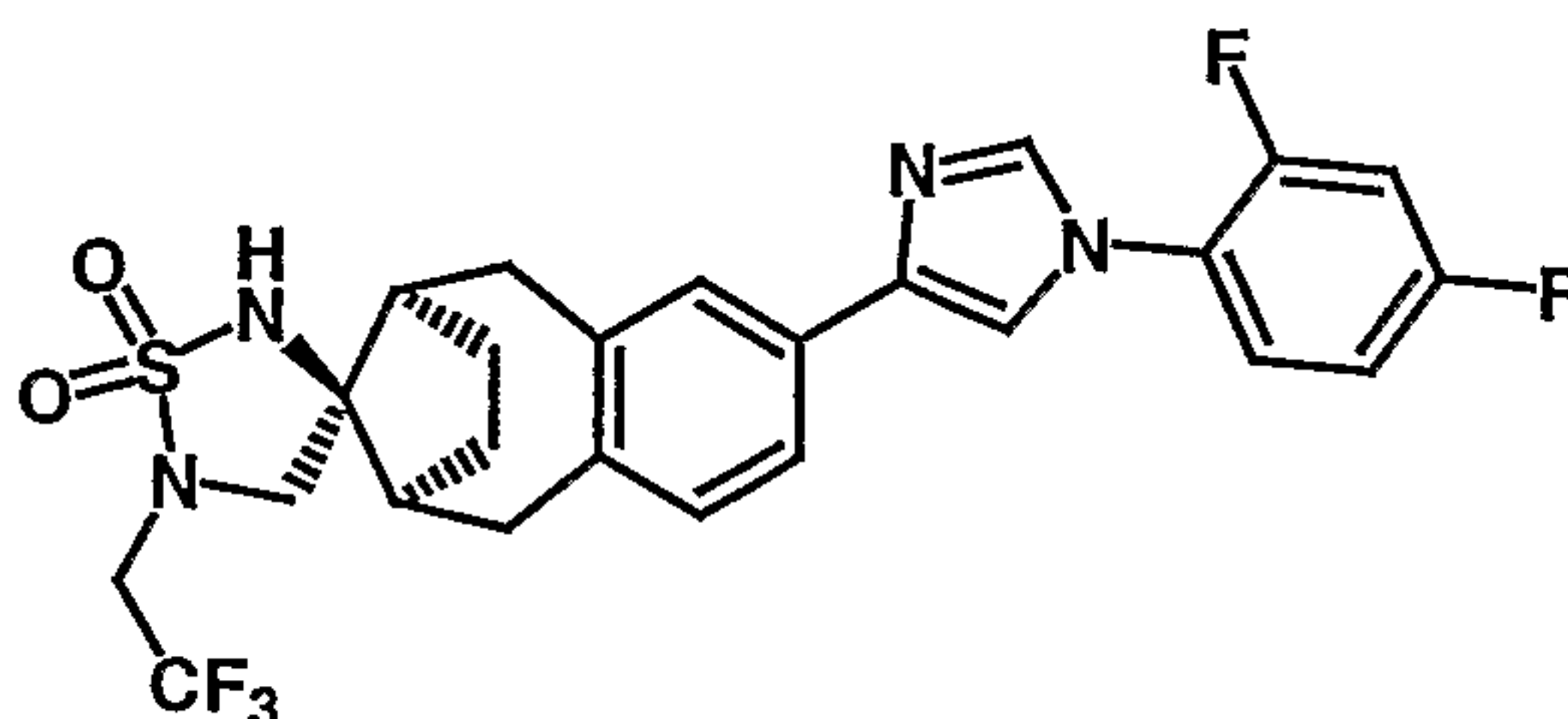


Prepared from 4-bromo-1*H*-imidazole, 3,4-dichlorophenylboronic acid and
10 homochiral boronate from Example 24 Step 1 following the procedures in Example 76 Steps 1 and 2.

δ (¹H, 400MHz, CDCl₃) 1.24-1.28 (2H, m), 1.70-1.74 (2H, m), 2.42-2.49 (2H, m), 2.69-2.81 (2H, m), 3.20-3.26 (2H, m), 3.44 (2H, s), 3.68 (2H, q, $J = 8.7$ Hz), 4.73 (1H, s), 7.13 (1H, d, $J = 7.8$ Hz), 7.31 (1H, dd, $J = 8.6, 2.6$ Hz),
15 7.50-7.61 (5H, m), 7.87 (1H, d, $J = 1$ Hz). MS (ES+) 571, 573, 575 ([MH]⁺).

Example 80

20 [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(2,4-difluorophenyl)-imidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



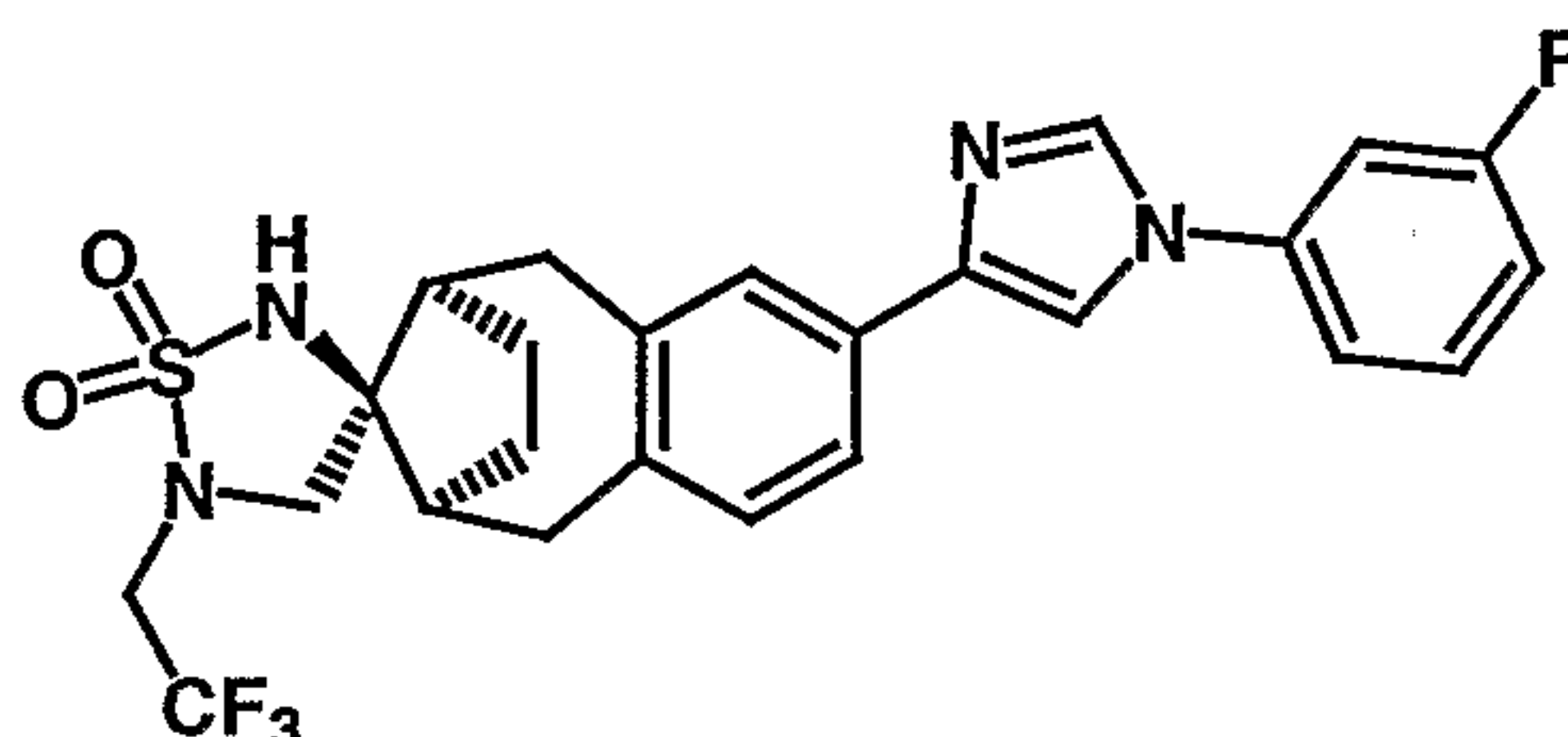
Prepared from 4-bromo-1*H*-imidazole, 2,4-difluorophenylboronic acid and homochiral boronate from Example 24 Step 1 following the procedures in Example 76 Steps 1 and 2.

δ (^1H , 360MHz, CDCl_3) 1.20-1.27 (2H, m), 1.69-1.73 (2H, m), 2.45-2.47 (2H, m), 2.68-2.82 (2H, m), 3.20-3.26 (2H, m), 3.43 (2H, s), 3.68 (2H, q, $J = 8.7$ Hz), 4.71 (1H, s), 7.00-7.13 (3H, m), 7.40-7.45 (2H, m), 7.54 (1H, d, $J = 7.9$ Hz), 7.61 (1H, s), 7.78 (1H, s). MS (ES+) 539 ($[\text{MH}]^+$).

5

Example 81

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(3-fluorophenyl)-imidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



10

Prepared from 4-bromo-1*H*-imidazole, 3-fluorophenylboronic acid and homochiral boronate from Example 24 Step 1 following the procedures in Example 76 Steps 1 and 2.

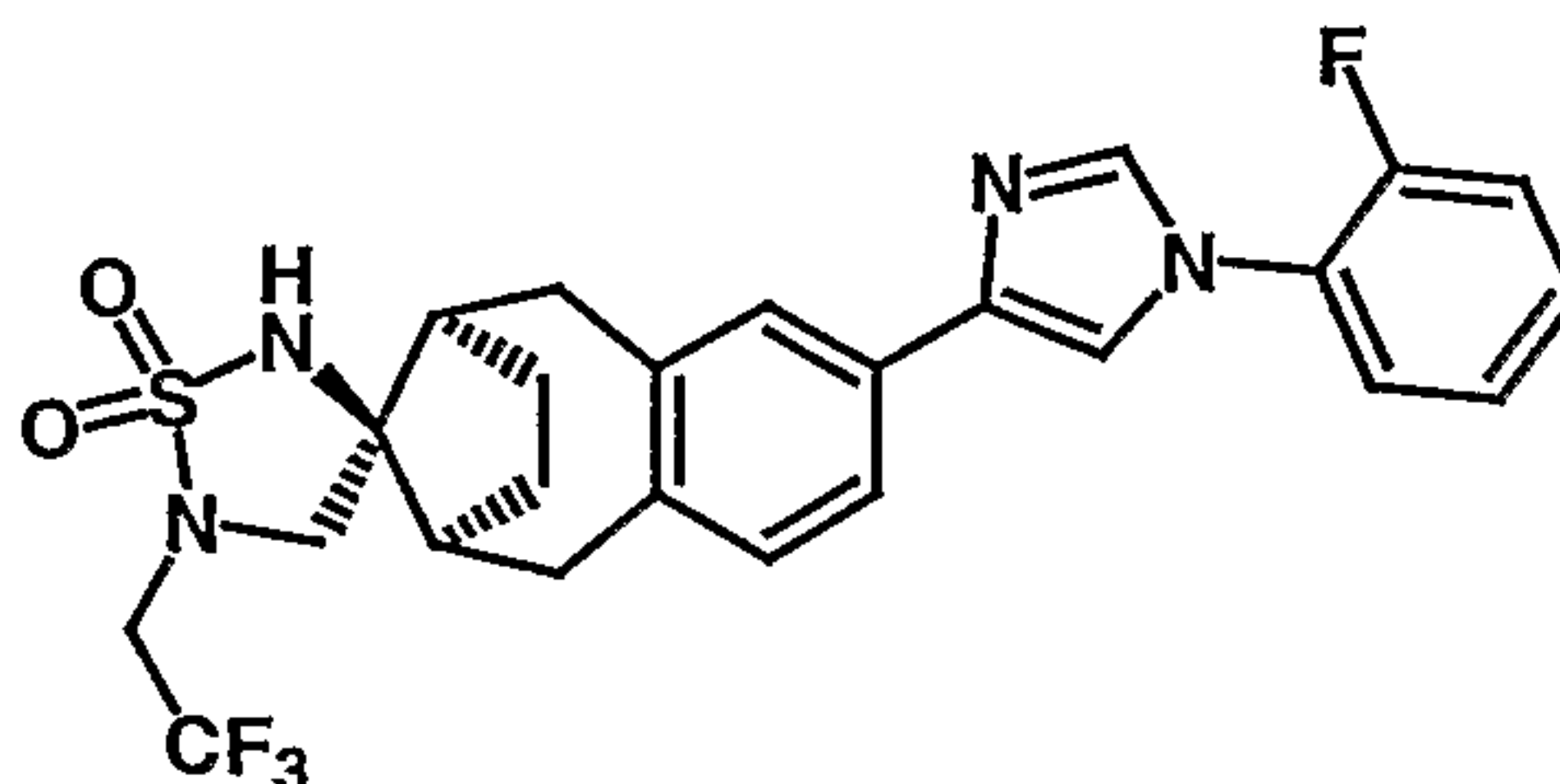
δ (^1H , 360MHz, CDCl_3) 1.33-1.43 (2H, m), 1.69-1.73 (2H, m), 2.45-2.48 (2H, m), 2.68-2.82 (2H, m), 3.20-3.26 (2H, m), 3.44 (2H, s), 3.68 (2H, q, $J = 8.7$ Hz), 4.75 (1H, s), 7.07-7.20 (3H, m), 7.24 (1H, s), 7.45-7.56 (3H, m), 7.61 (1H, s), 7.89 (1H, s). MS (ES+) 521 ($[\text{MH}]^+$).

15

Example 82

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(2-fluorophenyl)-imidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

20

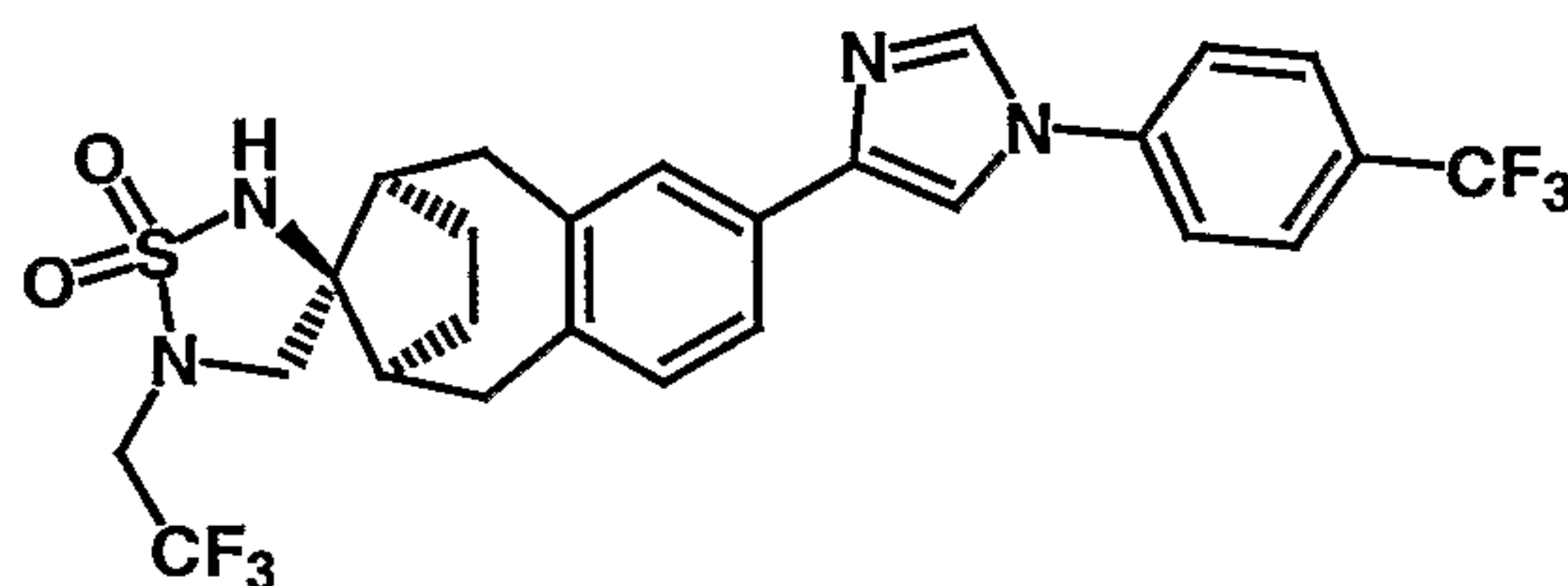


Prepared from 4-bromo-1*H*-imidazole, 2-fluorophenylboronic acid and homochiral boronate from Example 24 Step 1 following the procedures in Example 76 Steps 1 and 2.

5 δ (¹H, 360MHz, CDCl₃) 1.92-1.97 (2H, m), 2.26-2.29 (2H, m), 3.01-3.03 (2H, m), 3.29-3.36 (2H, m), 3.76-3.82 (2H, m), 4.00 (2H, s), 4.24 (2H, q, *J* = 8.8 Hz), 5.28 (1H, s), 7.69 (1H, d, *J* = 7.8 Hz), 7.84-7.88 (2H, m), 7.90-7.98 (1H, m), 7.99-8.05 (1H, m), 8.08-8.13 (2H, m), 8.19 (1H, s), 8.42 (1H, s). MS (ES+) 521 ([MH]⁺).

10 Example 83

[6*S*,9*R*,11*R*] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(4-(trifluoromethyl)phenyl)-imidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



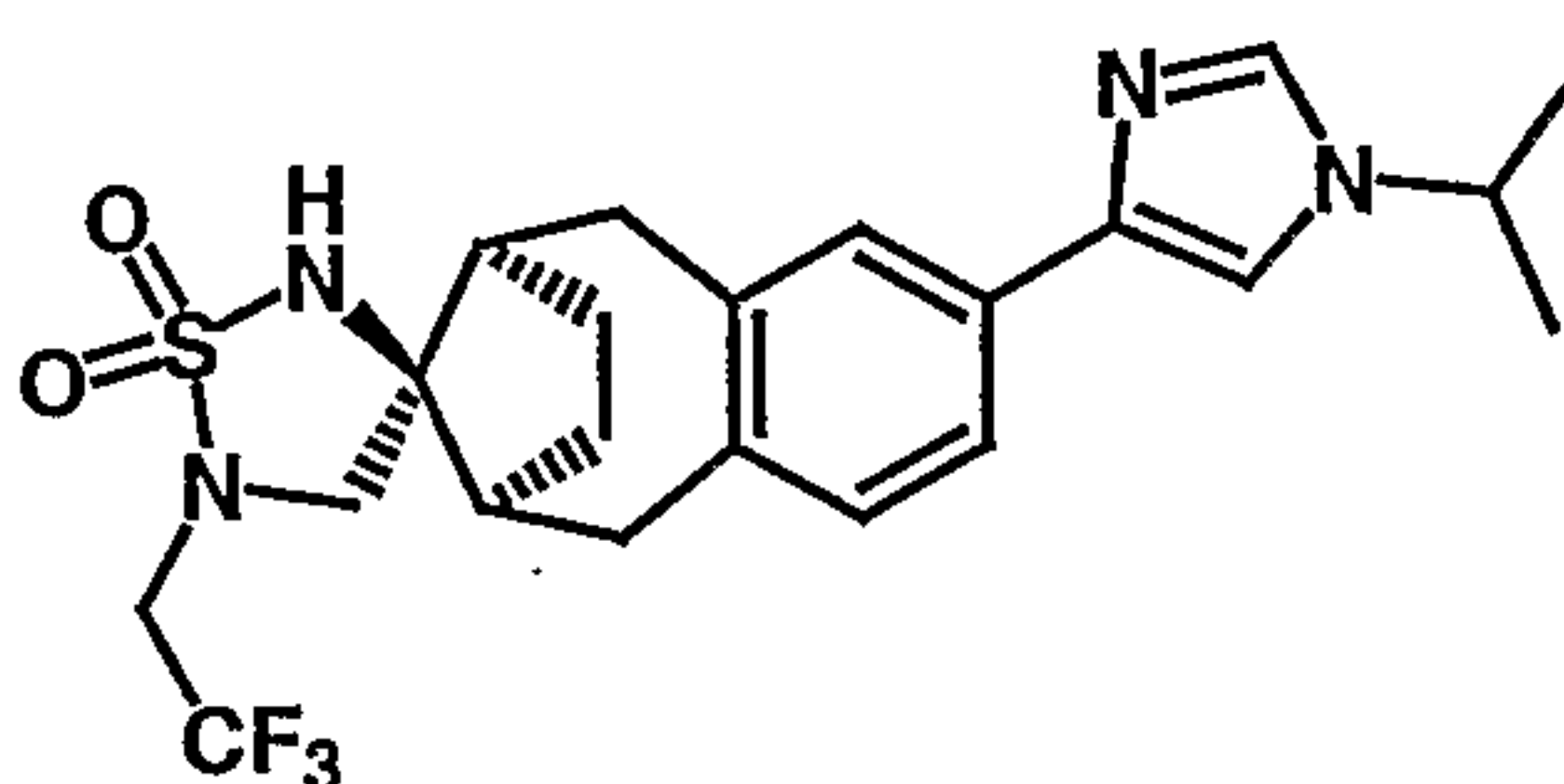
15

Prepared from 4-bromo-1*H*-imidazole, 4-(trifluoromethyl)phenylboronic acid and homochiral boronate from Example 24 Step 1 following the procedures in Example 76 Steps 1 and 2.

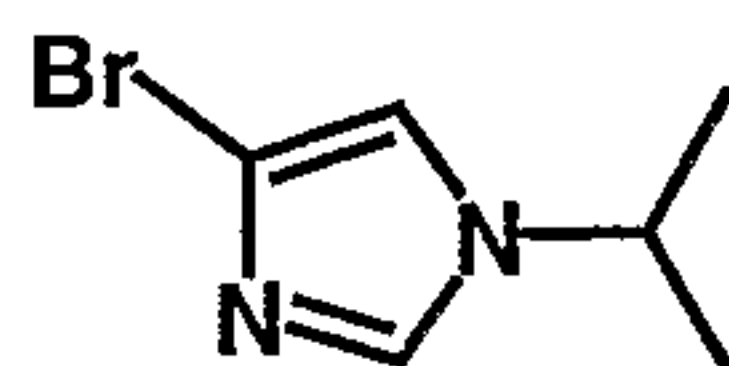
20 δ (¹H, 360MHz, DMSO) 1.08-1.11 (2H, m), 1.67-1.75 (2H, m), 2.35-2.38 (2H, m), 2.56-2.70 (2H, m), 3.15-3.20 (2H, m), 3.46 (2H, s), 4.00-4.05 (2H, m), 7.15 (1H, d, *J* = 7.2 Hz), 7.56-7.62 (2H, m), 7.90-8.05 (4H, m), 8.36 (1H, s), 8.49 (1H, s). MS (ES+) 571 ([MH]⁺).

Example 84

25 **[6*S*,9*R*,11*R*] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-isopropylimidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**



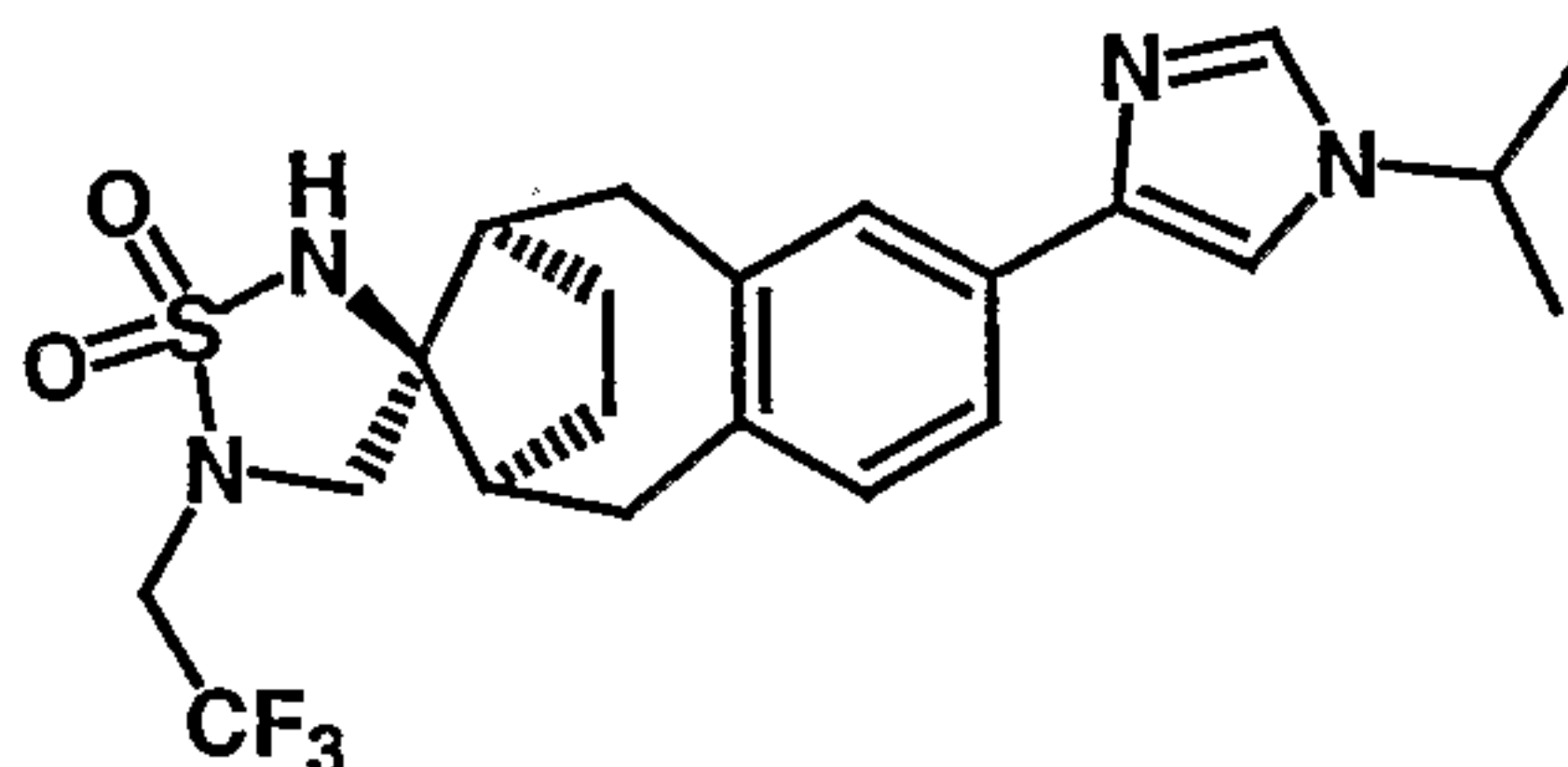
Step 1: 4-Bromo-1-isopropyl-1H-imidazole



A mixture of 4-bromo-1H-imidazole (1.0 g, 6.80 mmol) in
 5 dimethylformamide (5 mL) was stirred at 0°C, to which was added sodium
 hydride, 60% suspension in oil, (326 mg, 8.20 mmol). The reaction mixture
 was warmed to room temperature and stirred for 30 minutes, followed by
 dropwise addition of 2-bromopropane (0.70 mL, 7.48 mmol). The reaction
 mixture was stirred at room temperature for 15 hours under nitrogen,
 10 then quenched with water (10 mL) and extracted with ethyl acetate (3 x 15
 mL). The combined organic extracts were washed with water (20 mL) and
 extracted with 1M hydrochloric acid (3 x 20 mL). The combined acidic
 extracts were washed with ethyl acetate (20 mL), then basified with
 ammonium hydroxide (pH 12), and extracted with ethyl acetate (3 x 20
 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered and
 concentrated. Preparative HPLC, eluting with an ethyl acetate –
 isohexane gradient, gave the product as a pale brown oil (380 mg, 30%)
 δ (¹H, 400MHz, CDCl₃) 1.47 (6H, d, *J* = 6.8Hz), 4.28-4.32 (1H, m), 6.92
 (1H, d, *J* = 1.5 Hz), 7.40 (1H, d, *J* = 1.5 Hz). MS (ES⁺) 189, 191 ([MH]⁺).

20

Step 2: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-isopropylimidazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

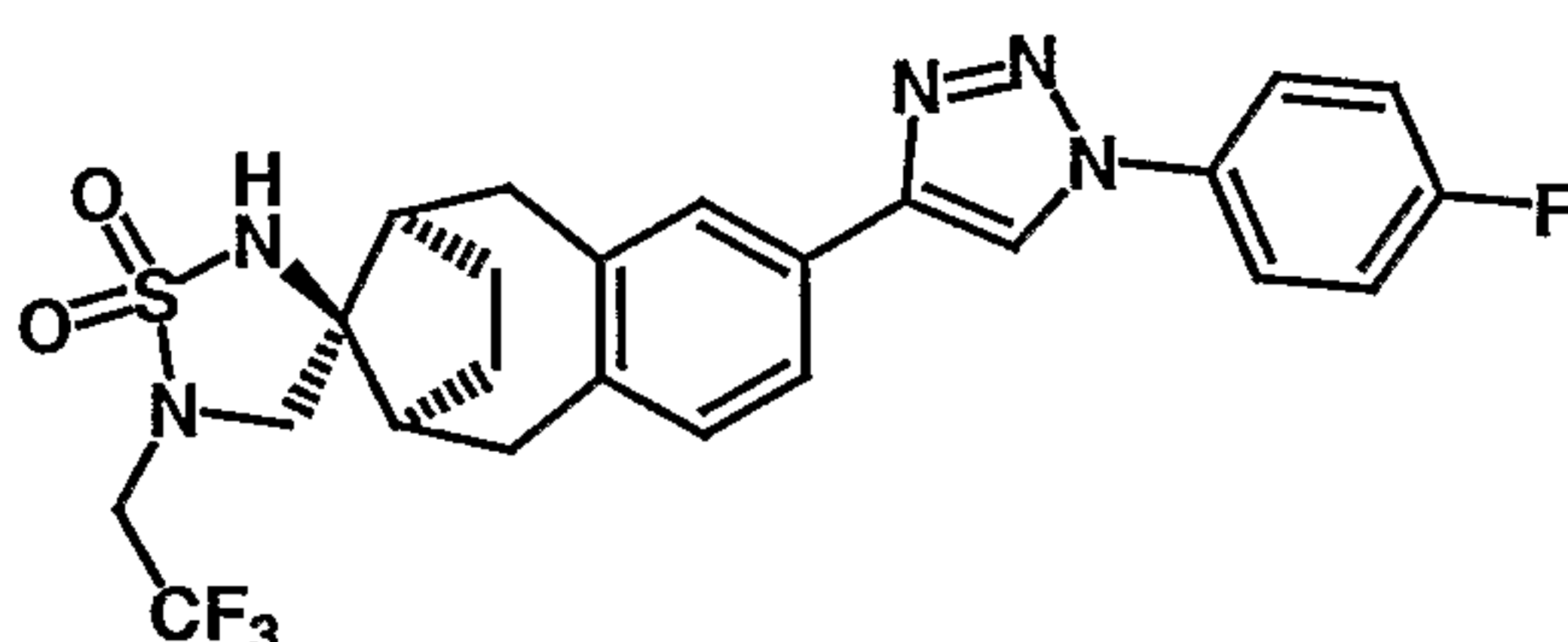


Prepared from 4-bromo-1-isopropyl-1*H*-imidazole (Step 1) and homochiral boronate from Example 24 Step 1 by the procedure described for Example 76 Step 2.

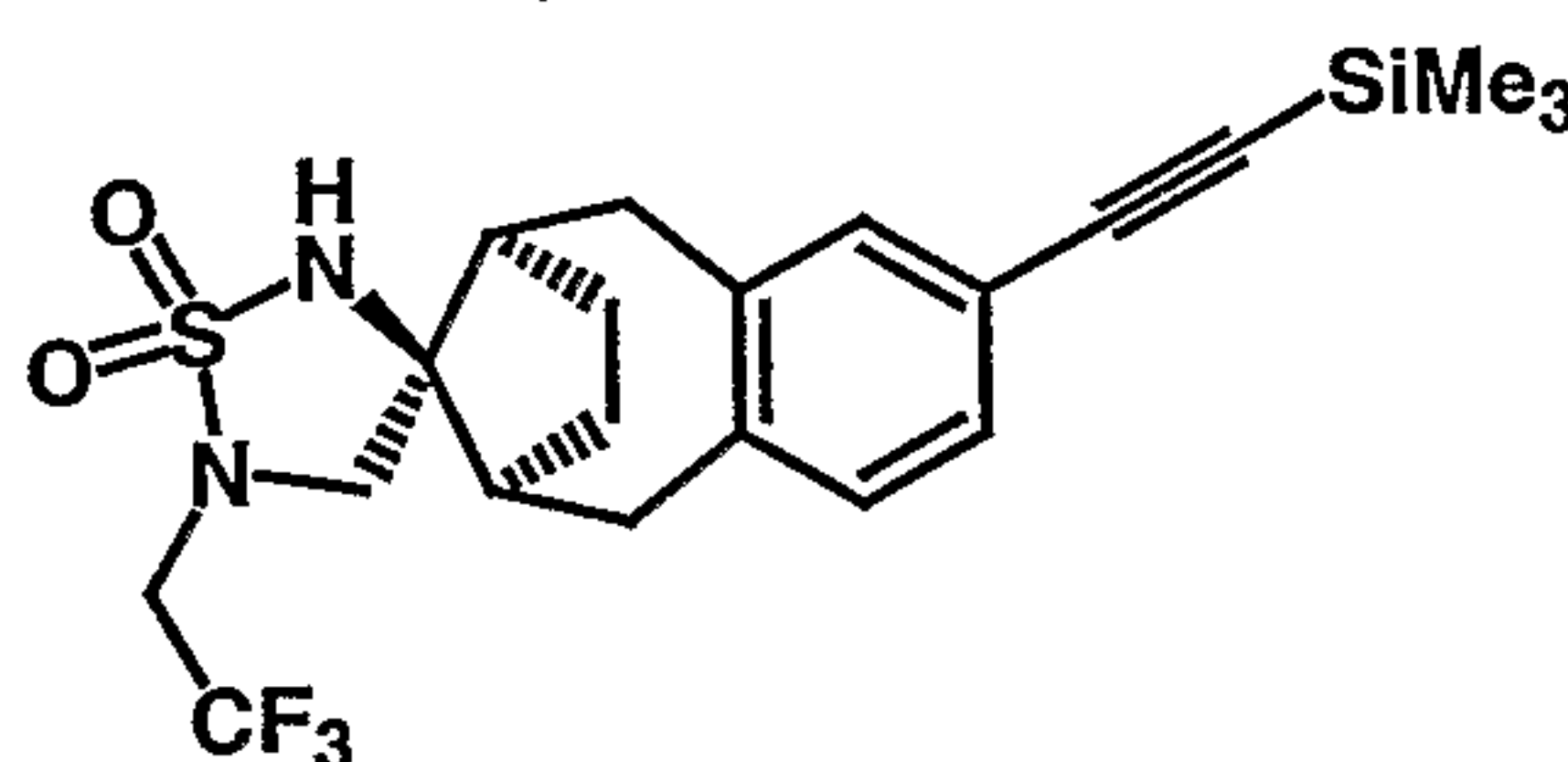
5 δ (¹H, 400MHz, CDCl₃) 1.30-1.40 (2H, m), 1.53 (6H, d, *J* = 6.8 Hz), 1.67-1.75 (2H, m), 2.40-2.50 (2H, m), 2.66-2.80 (2H, m), 3.18-3.24 (2H, m), 3.42 (2H, s), 3.67 (2H, q, *J* = 8.7 Hz), 4.32-4.42 (1H, m), 4.65 (1H, s), 7.10 (1H, d, *J* = 8 Hz), 7.23 (1H, d, *J* = 1.4 Hz), 7.45 (1H, d, *J* = 8 Hz), 7.55-7.58 (2H, m). MS (ES+) 469 ([MH]⁺).

10 Example 85

[6*S*,9*R*,11*R*] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(4-fluorophenyl)-1,2,3-triazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



15 Step1: [6*S*,9*R*,11*R*] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-trimethylsilylethyn-2-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

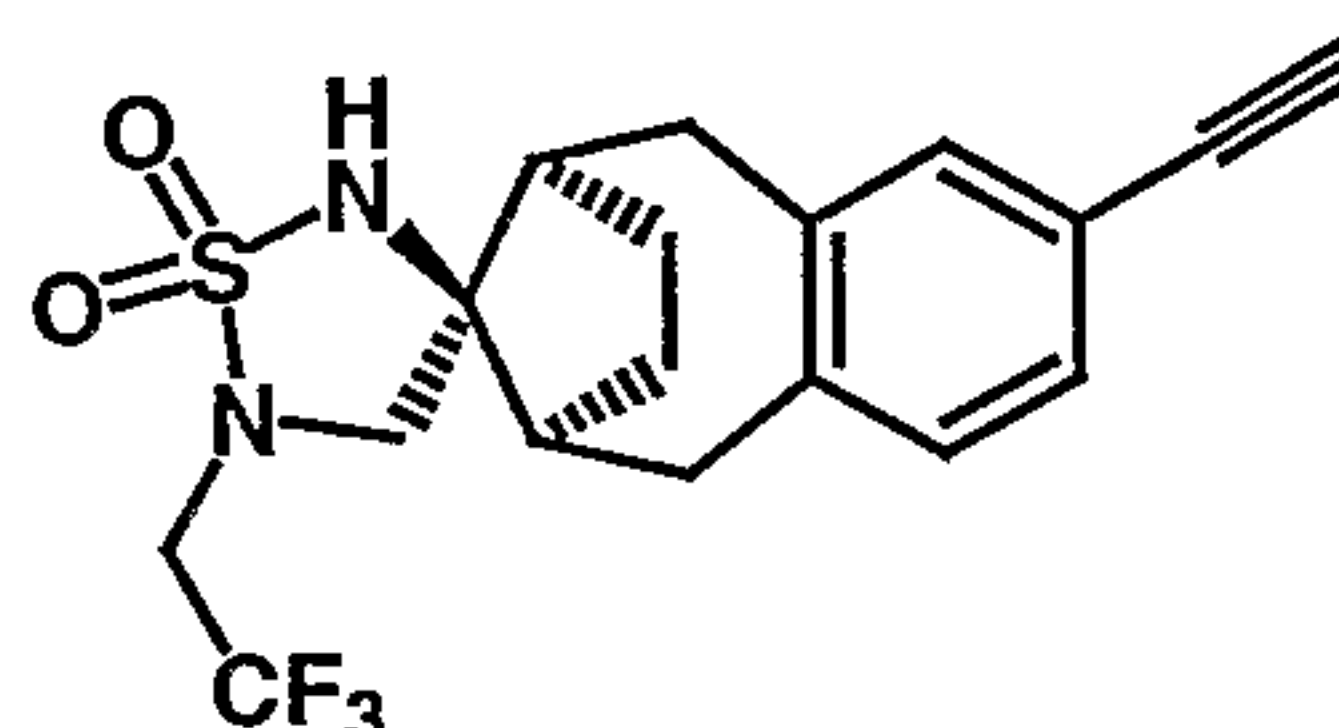


A solution of the homochiral triflate Intermediate E (0.25 g, 0.49 mmol),
 20 trimethylsilylacetylene (0.20 mL, 1.4 mmol), copper (I) iodide (0.01 g, 10 mol%), triphenylphosphine (0.025 g, 20 mol%) and *tetrakis*(triphenylphosphine) palladium (0) (0.03g, 5mol%) in piperidine (2 mL) and 1,4-dioxane (1 mL) was heated to 150°C for 10 min in a microwave heater. The black solution was diluted with 1M hydrochloric
 25 acid (20 mL) and extracted with ethyl acetate (20 mL). The extract was dried (Na₂SO₄), and concentrated. Flash column chromatography on silica

gel, eluting with 20% ethyl acetate – isohexane gave the trimethylsilylalkyne as a yellow glass (0.185 g, 83%).

δ (^1H , 500MHz, CDCl_3) 0.24 (9H, s), 1.24-1.34 (2H, m), 1.68-1.74 (2H, m), 2.42-2.46 (2H, m), 2.62-2.72 (2H, m), 3.15-3.21 (2H, m), 3.42 (2H, s), 3.67 (2H, q, $J = 8.7$ Hz), 4.62 (1H, s), 7.02 (1H, d, $J = 8$ Hz), 7.20-7.26 (2H, m).

Step 2: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-ethynyl-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



10

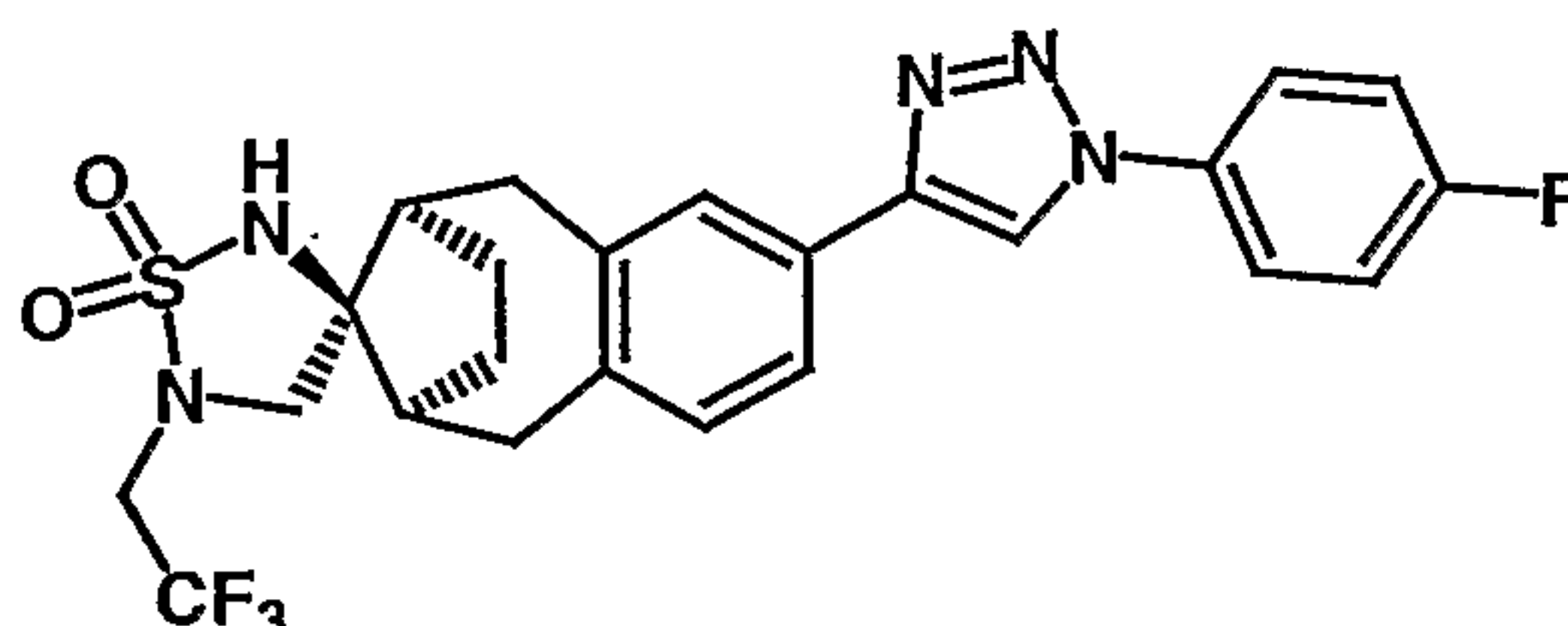
A mixture of the trimethylsilylalkyne from Step 1 (0.27 g, 0.592 mmol) and potassium carbonate (0.1 g, 0.72 mmol) in methanol (2 mL) and tetrahydrofuran (1 mL) was stirred at room temperature for 23 hr. The mixture was diluted with 1M hydrochloric acid (50 mL) and extracted with ethyl acetate (50 mL). The extract was dried (Na_2SO_4) and concentrated. Preparative HPLC on a normal phase column, eluting with an ethyl acetate – isohexane gradient, gave the alkyne as a brown foam (0.114 g, 51%).

δ (^1H , 400MHz, CDCl_3) 1.27-1.33 (2H, m), 1.68-1.73 (2H, m), 2.41-2.49 (2H, m), 2.62-2.73 (2H, m), 3.04 (1H, s), 3.16-3.23 (2H, m), 3.43 (2H, s), 3.67 (2H, q, $J = 8.7$ Hz), 4.64 (1H, s), 7.05 (1H, d, $J = 8$ Hz), 7.25-7.27 (2H, m).

20

Step 3: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(4-fluorophenyl)-1,2,3-triazol-4-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

25



A solution of the alkyne from Step 2 (0.075 g, 0.195 mmol) and 4-fluorophenylazide (0.035 g, 0.25 mmol) in *p*-xylene (5 mL) was refluxed under nitrogen for 21 hr. The solution was evaporated to dryness.

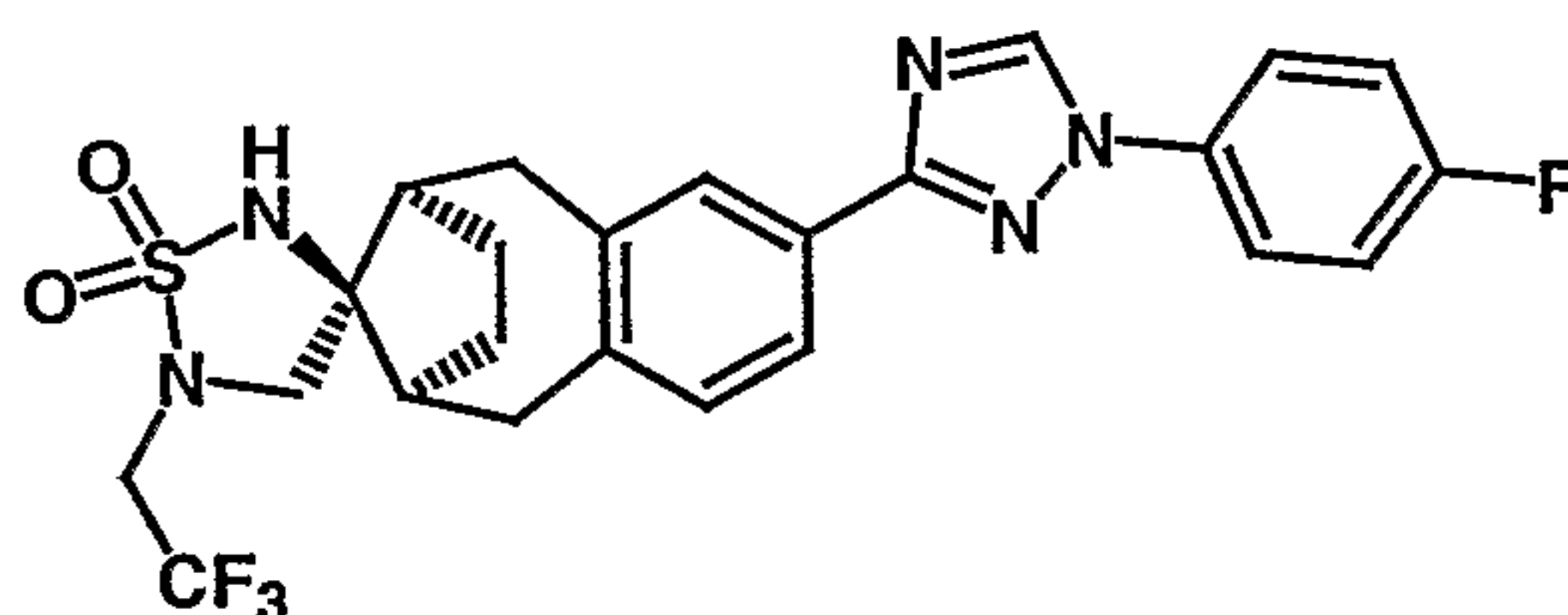
Preparative HPLC on a normal phase column, eluting with an ethyl

5 acetate – isohexane gradient gave the major cycloadduct (0.022 g). Further purification by reverse phase HPLC, eluting with an acetonitrile – pH3 buffer gradient, gave the triazole as yellow solid, which was rinsed with diethyl ether and dried to give a pale yellow powder (0.010 g, 10%).

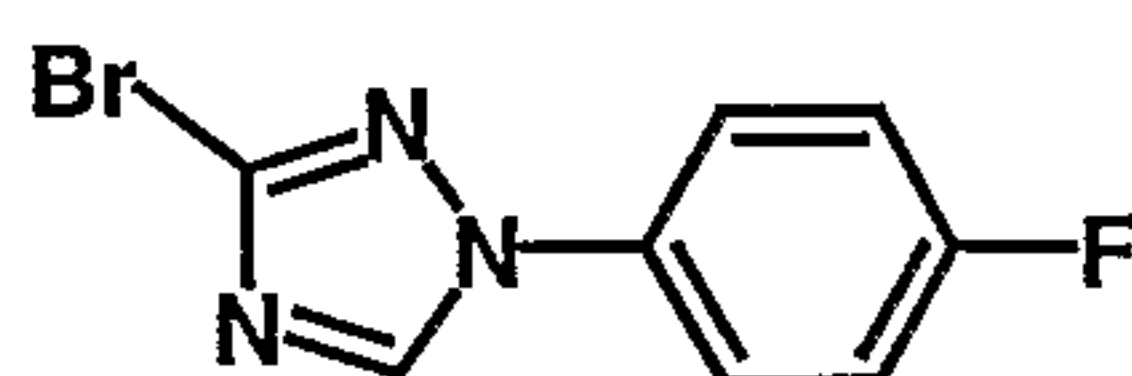
10 δ (^1H , 400MHz, CDCl_3) 1.35-1.42 (2H, m), 1.61-1.68 (2H, m), 2.45-2.52 (2H, m), 2.72-2.86 (2H, m), 3.22-3.30 (2H, m), 3.45 (2H, s), 3.69 (2H, q, $J = 8.7$ Hz), 4.66 (1H, s), 7.21-7.27 (3H, m), 7.62 (1H, d, $J = 8$ Hz), 7.70 (1H, s), 7.75-7.79 (2H, m), 8.12 (1H, s). MS (ES+) 522 ($[\text{MH}]^+$).

Example 86

15 **[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(4-fluorophenyl)-1,2,4-triazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide**



Step 1: 1-(4-Fluorophenyl)-3-bromo-1,2,4-1*H*-triazole



20

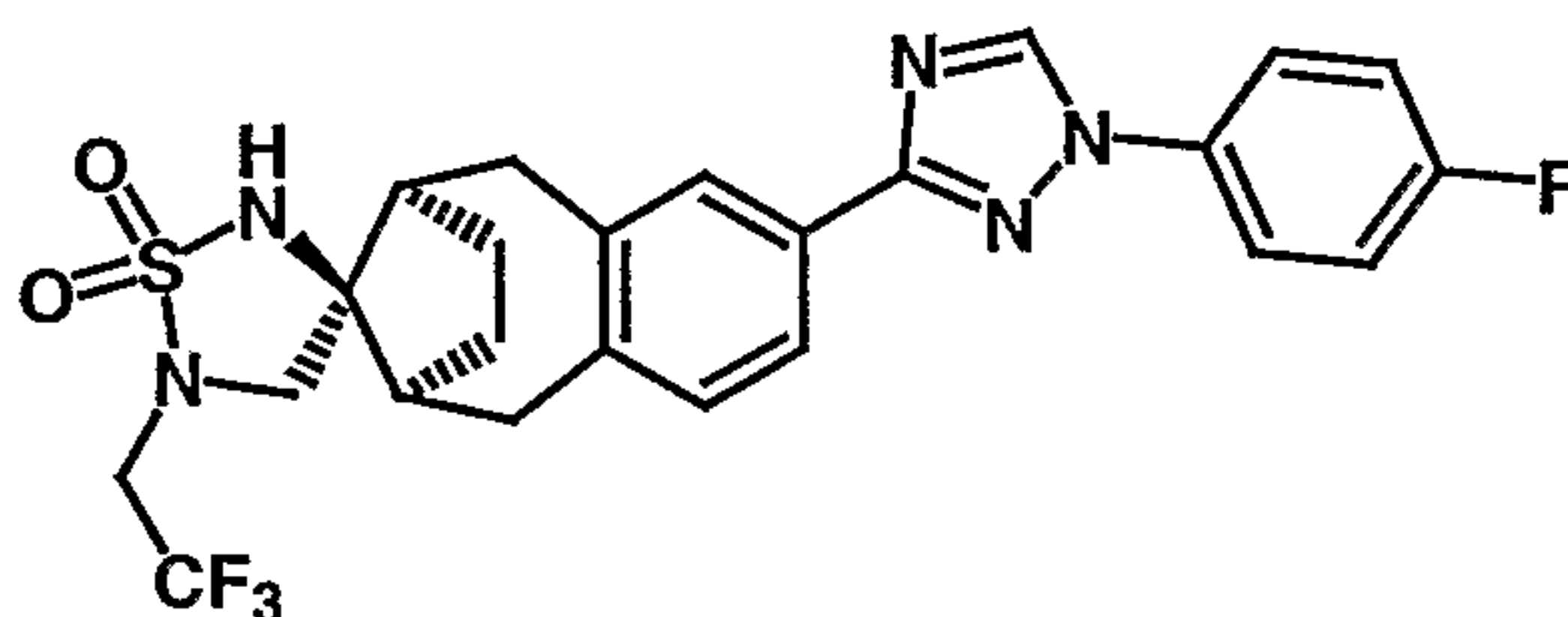
A mixture of 3-bromo-1,2,4-1*H*-triazole (prepared as described in *Chemische Berichte* 1967, 100, 2250) (1.0 g, 6.76 mmol), tri(4-fluorophenyl)bismuth diacetate (prepared by the method described in *Synthetic Communications* 1996, 4569) (4.53 g, 7.4 mmol), copper (II) acetate (0.25 g, 20mol%) and *N,N,N',N'*-tetramethylguanidine (1.7 mL, 13.5 mmol) in dry tetrahydrofuran (30 mL) was stirred at 50°C under a balloon of air for 16 hr. The suspension was poured into water (100 mL) and 1M citric acid (30 mL) to give a suspension of pH 3-4. Ethyl acetate

25

(100 mL) was added and the mixture was filtered through Celite®, washing the filter cake with ethyl acetate (100 mL). The two phases of the filtrate were separated and the organic layer was dried (Na₂SO₄) and concentrated. Flash column chromatography on silica gel, eluting with 25% then 40% ethyl acetate – isohexane, gave 1-(4-fluorophenyl)-3-bromo-1,2,4-1*H*-triazole as an off-white solid (0.74 g, 45%).

δ (¹H, 400MHz, CDCl₃) 7.18-7.24 (2H, m), 7.60-7.65 (2H, m), 8.37 (1H, s). MS (ES⁺) 242, 244 ([MH]⁺).

Step 2: [6*S*,9*R*,11*R*] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(1-(4-fluorophenyl)-1,2,4-triazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

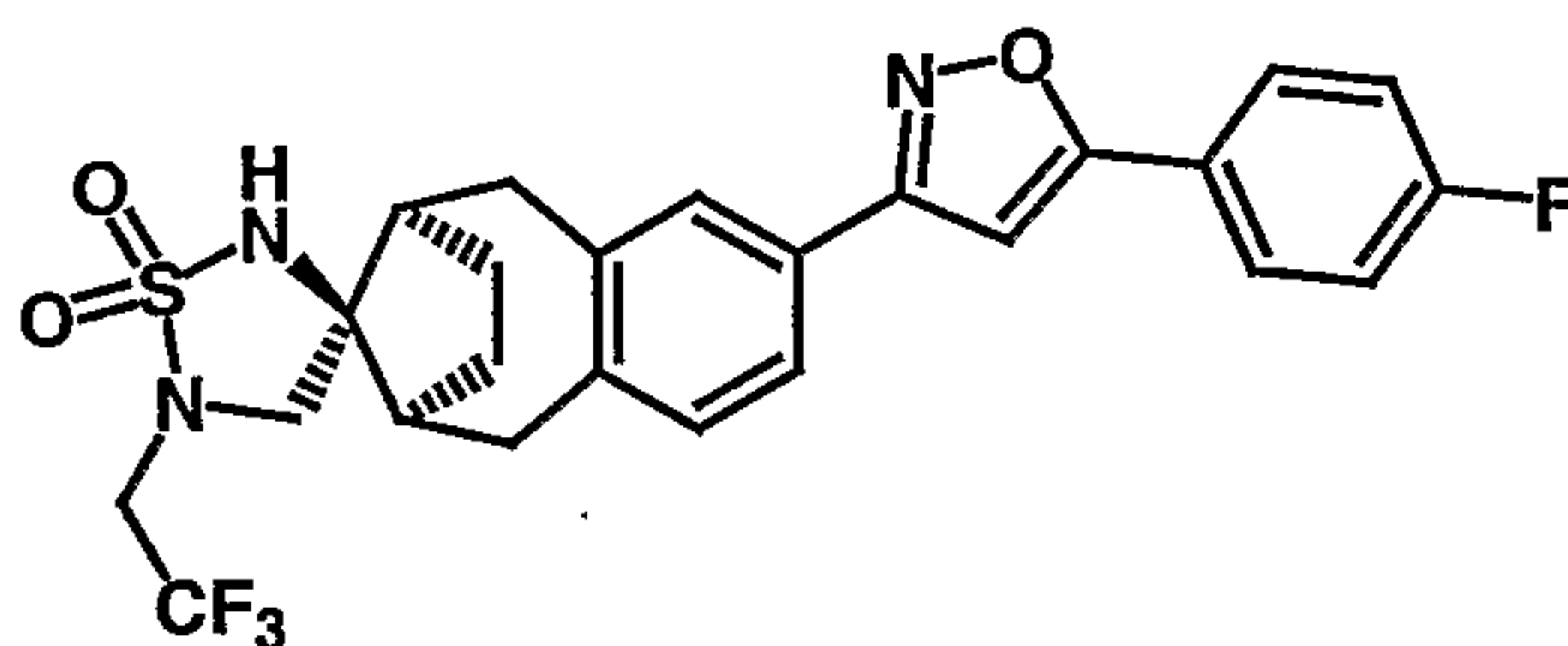


A solution of the bromotriazole from Step 1 (0.10 g, 0.41 mmol), homochiral boronate from Example 24 Step 1 (0.15 g, 0.32 mmol), cesium carbonate (0.25 g, 0.7 mmol) and *tetrakis*(triphenylphosphine) palladium (0) (0.045 g, 10 mol%) in 1,2-dimethoxyethane (2 mL) and water (1 mL) was refluxed under nitrogen for 15 hr. The mixture was diluted with 1M citric acid (10 mL) and extracted with ethyl acetate (20 mL). The extract was filtered through a plug of silica gel and concentrated. Preparative HPLC on a normal phase column, eluting with an ethyl acetate – isohexane gradient, gave the product as an oil. Trituration with diethyl ether gave the triazole as a white solid (0.084 g, 50%).

δ (¹H, 500MHz, CDCl₃) 1.33-1.43 (2H, m), 1.70-1.75 (2H, m), 2.45-2.51 (2H, m), 2.74-2.88 (2H, m), 3.24-3.28 (2H, m), 3.45 (2H, s), 3.68 (2H, q, *J* = 8.7 Hz), 4.68 (1H, s), 7.20-7.25 (3H, m), 7.70-7.75 (2H, m), 7.93-7.95 (2H, m), 8.51 (1H, s). MS (ES⁺) 522 ([MH]⁺).

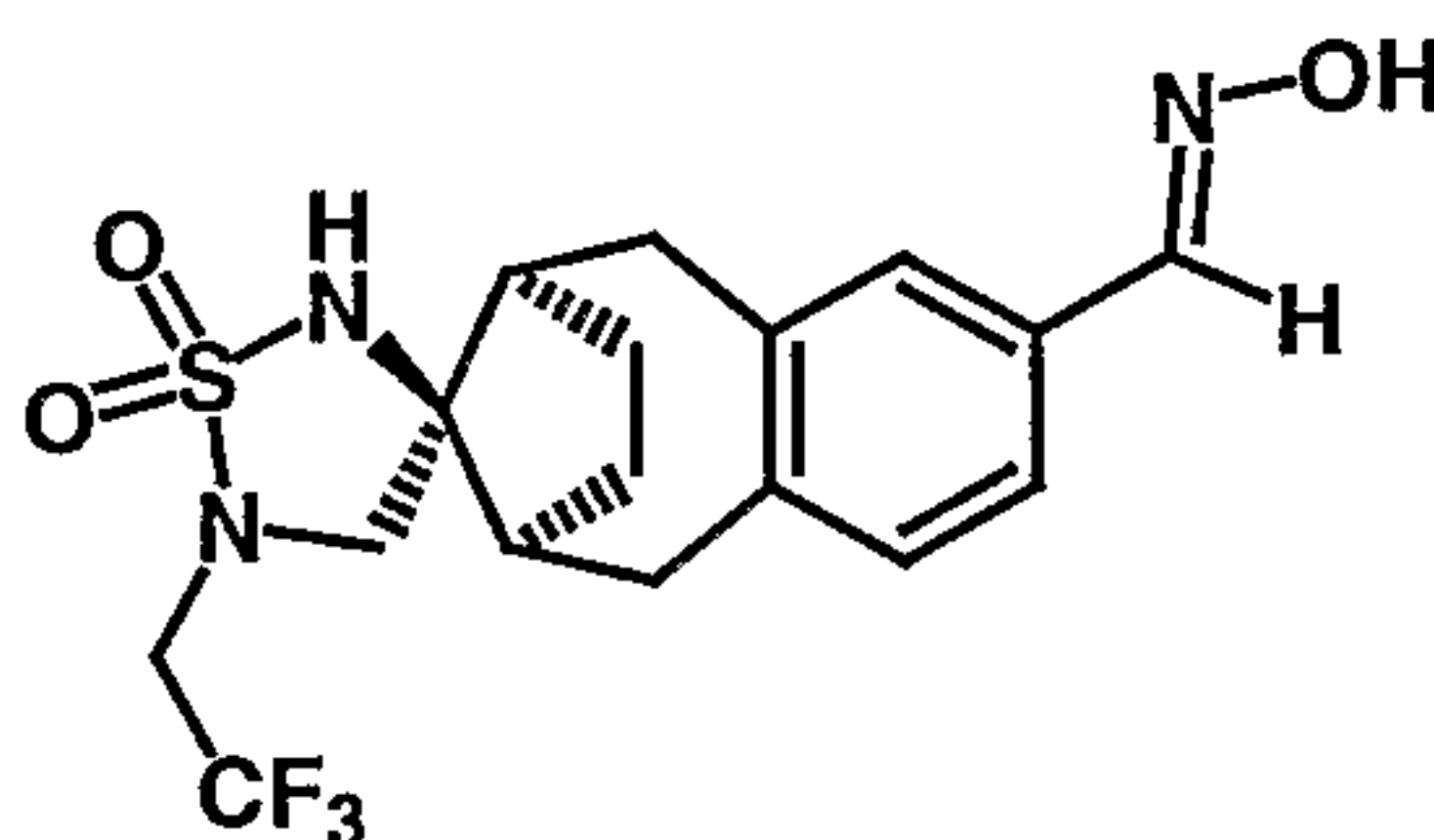
Example 87

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-isoxazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



5

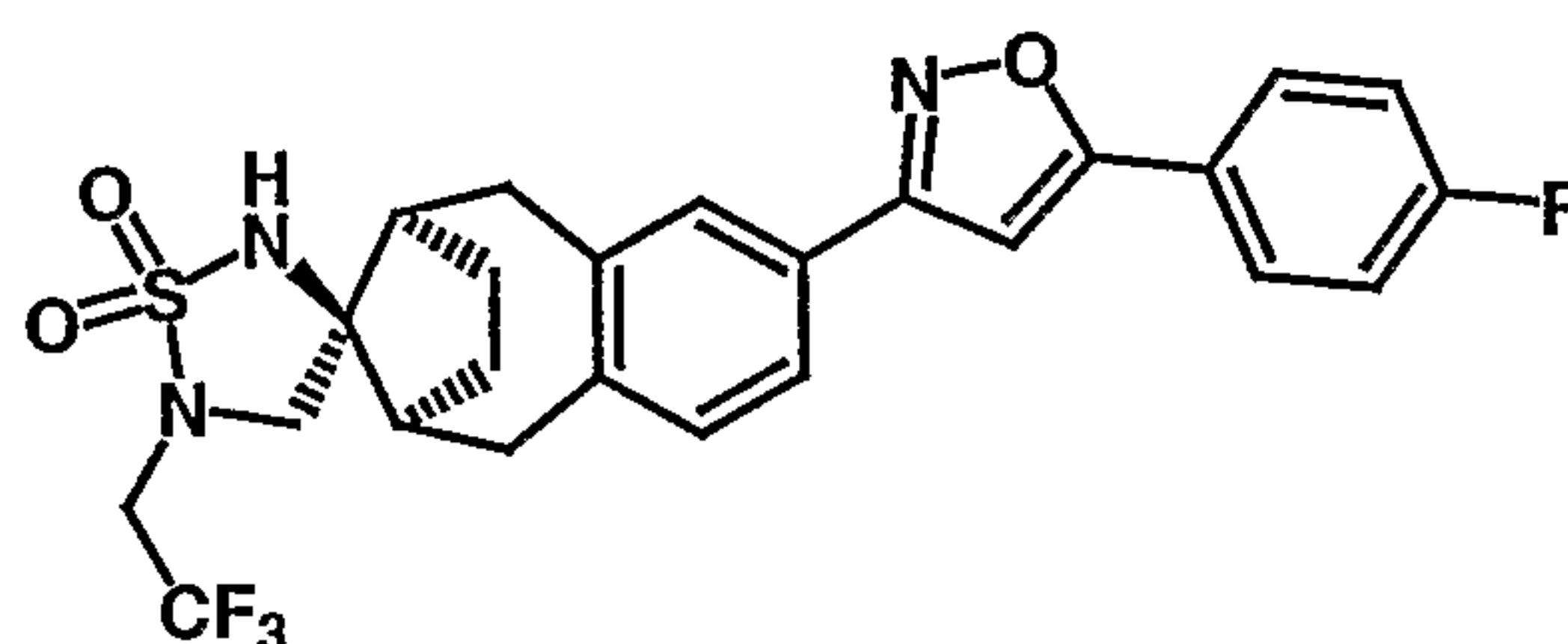
Step 1: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(carboxaldehyde oxime)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide



- 10 A mixture of the aldehyde Example 75, Step 3 (192 mg, 0.5 mmol), hydroxylamine hydrochloride (104 mg, 1.5 mmol) and sodium acetate (204 mg, 1.5 mmol) in dioxane (4 mL) was stirred at room temperature for 16 hours. The reaction was diluted with sodium hydrogen carbonate (half saturated 30 mL) and extracted with ethyl acetate (2 x 30 mL). The
- 15 extracts were washed with brine, dried (MgSO₄) and evaporated *in vacuo* to a clear gum (200 mg, >99%).
- 20 δ (¹H, 400MHz, CDCl₃) 1.23-1.32 (2H, m), 1.68-1.77 (2H, m), 2.40-2.50 (2H, m), 2.67-2.73 (2H, m), 3.19 (2H, d, *J* = 16.1 Hz), 3.43 (2H, s), 3.67-3.72 (2H, m), 4.89 (1H, br s), 7.09 (1H, d, *J* = 7.6 Hz); 7.29-7.31 (2H, m), 7.53 (1H, br s) and 8.09 (1H, s).

Step 2: [6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(4-fluorophenyl)-isoxazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

25

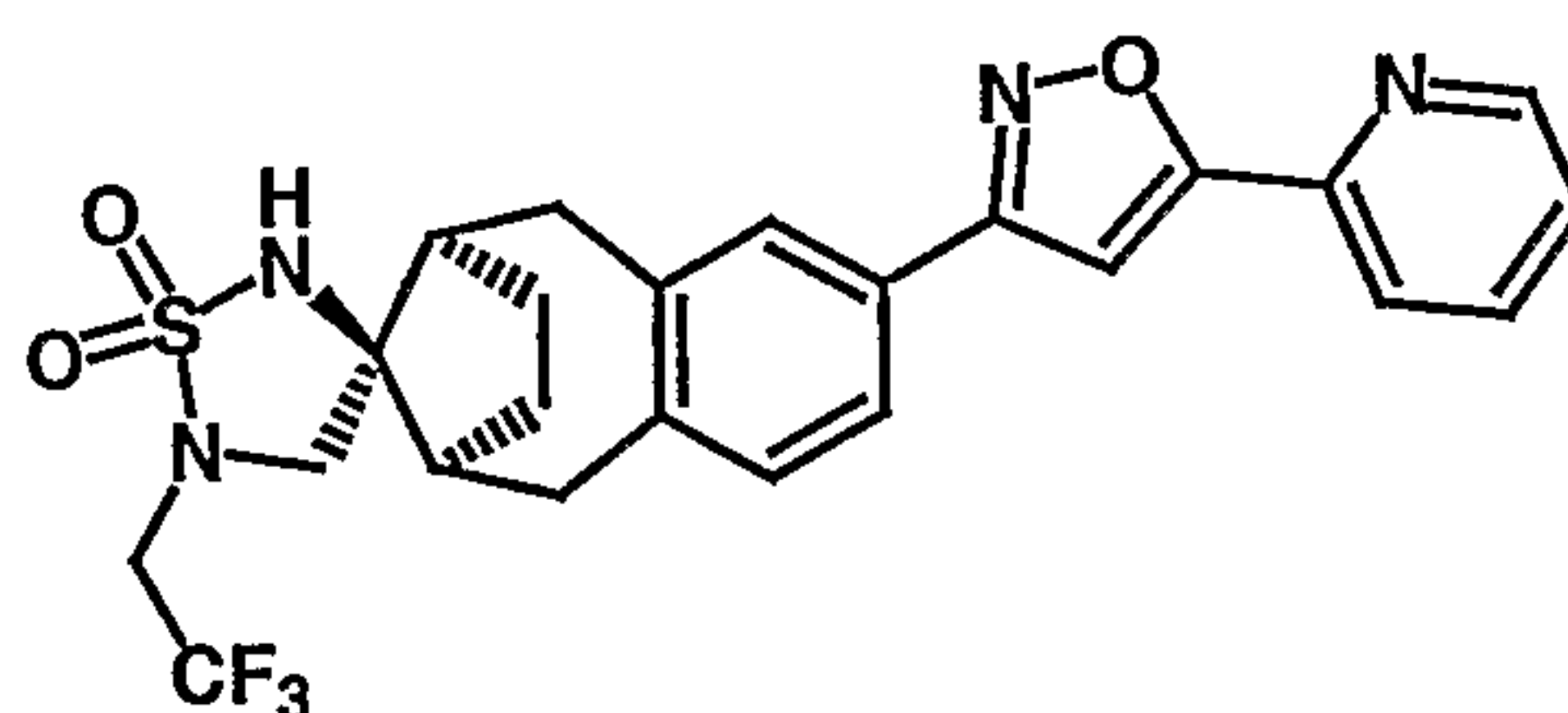


The title compound was prepared following the procedure of Moriya *et al.* (JCS Perkin 1, 1994, 413). A solution of sodium hypochlorite (13 mg, 0.12 mmol) in dichloromethane (1 mL) was added to a solution of the oxime from step 1 (50 mg, 0.12 mmol), bis(tributyl tin) oxide (31 μ L, 0.06 mmol) and 4-fluorophenyl acetylene (55 μ L, 0.24 mmol) in dichloromethane (1 mL), under a nitrogen atmosphere, at $<-20^{\circ}\text{C}$. The reaction was allowed to warm to room temperature and was stirred for 16 hours. The reaction was treated with potassium fluoride in methanol (sat. 0.5 mL), diluted with water (20 mL) and extracted with ethyl acetate (2 x 15 mL). The extracts were washed with brine, dried (MgSO_4) and evaporated *in vacuo* to a clear gum which was purified by column chromatography on silica eluting with ethyl acetate : iso hexane (1:3) to give a white solid. The solid was dissolved in acetonitrile and washed with iso hexane (x3). The solvent was evaporated *in vacuo* to provide the title compound as a white solid 25 mg, 40%). δ (^1H , 400MHz, CDCl_3) 1.33-1.40 (2H, m), 1.70-1.79 (2H, m), 2.46-2.54 (2H, m), 2.73-2.85 (2H, m), 3.27 (2H, d, $J = 16.1$ Hz), 3.45 (2H, s), 3.69 (2H, q, $J = 8.7$ Hz), 4.69 (1H, br s), 6.76 (1H, s), 7.19 (3H, q, $J = 8.6$ Hz), 7.58-7.63 (2H, m) and 7.81-7.85 (2H, m). M/Z (ES^+) 522 ($[\text{MH}]^+$).

Example 88

[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-Decahydro-2-(5-(2-pyridyl)-isoxazol-3-yl)-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide

- 124 -



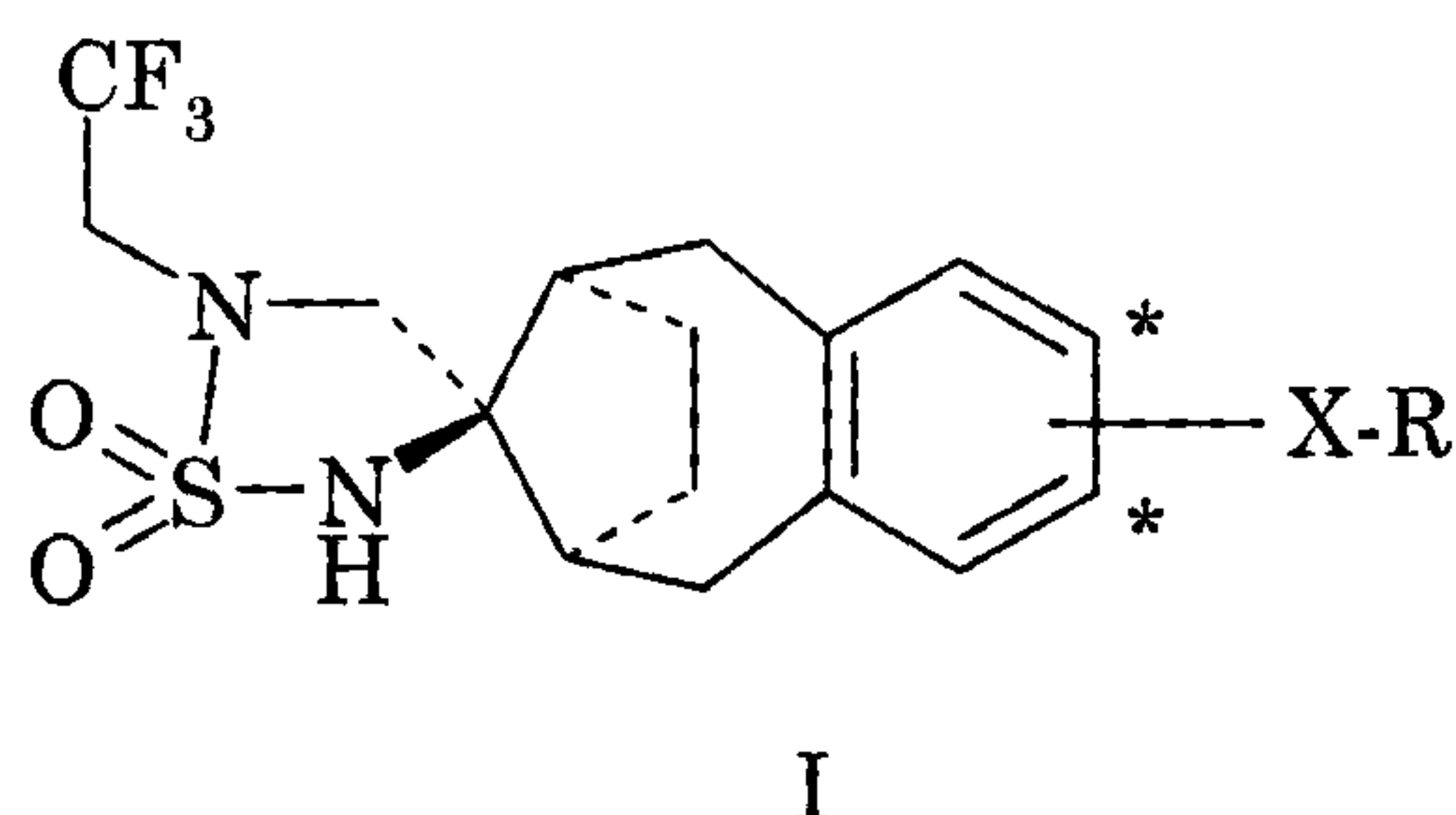
The title compound was prepared in a manner analogous to example 87.

The crude product was purified by column chromatography on silica

5 eluting with ethyl acetate : isohexane (1:2) to give a white solid 13 mg,
22%). M/Z (ES+) 505 ([MH]⁺).

CLAIMS :

1. A compound of formula I:



wherein the moiety X-R is attached at one of the positions indicated by an asterisk;

X is a bivalent pyrazole, imidazole, triazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole or 1,3,4-oxadiazole residue optionally bearing a hydrocarbon substituent comprising 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

R is selected from:

(i) CF_3 or a non-aromatic hydrocarbon group of up to 10 carbon atoms, optionally substituted with halogen, CF_3 , CHF_2 , CN , OH , CO_2H , $\text{C}_{2-6}\text{acyl}$, $\text{C}_{1-4}\text{alkoxy}$ or $\text{C}_{1-4}\text{alkoxycarbonyl}$;

(ii) a non-aromatic heterocyclic group comprising up to 7 ring atoms of which up to 3 are chosen from N, O and S and the remainder are carbon, bearing 0-3 substituents independently selected from oxo, halogen, CN , $\text{C}_{1-6}\text{alkyl}$, OH , CF_3 , CHF_2 , CH_2F , $\text{C}_{2-6}\text{acyl}$, CO_2H , $\text{C}_{1-4}\text{alkoxy}$ and $\text{C}_{1-4}\text{alkoxycarbonyl}$;

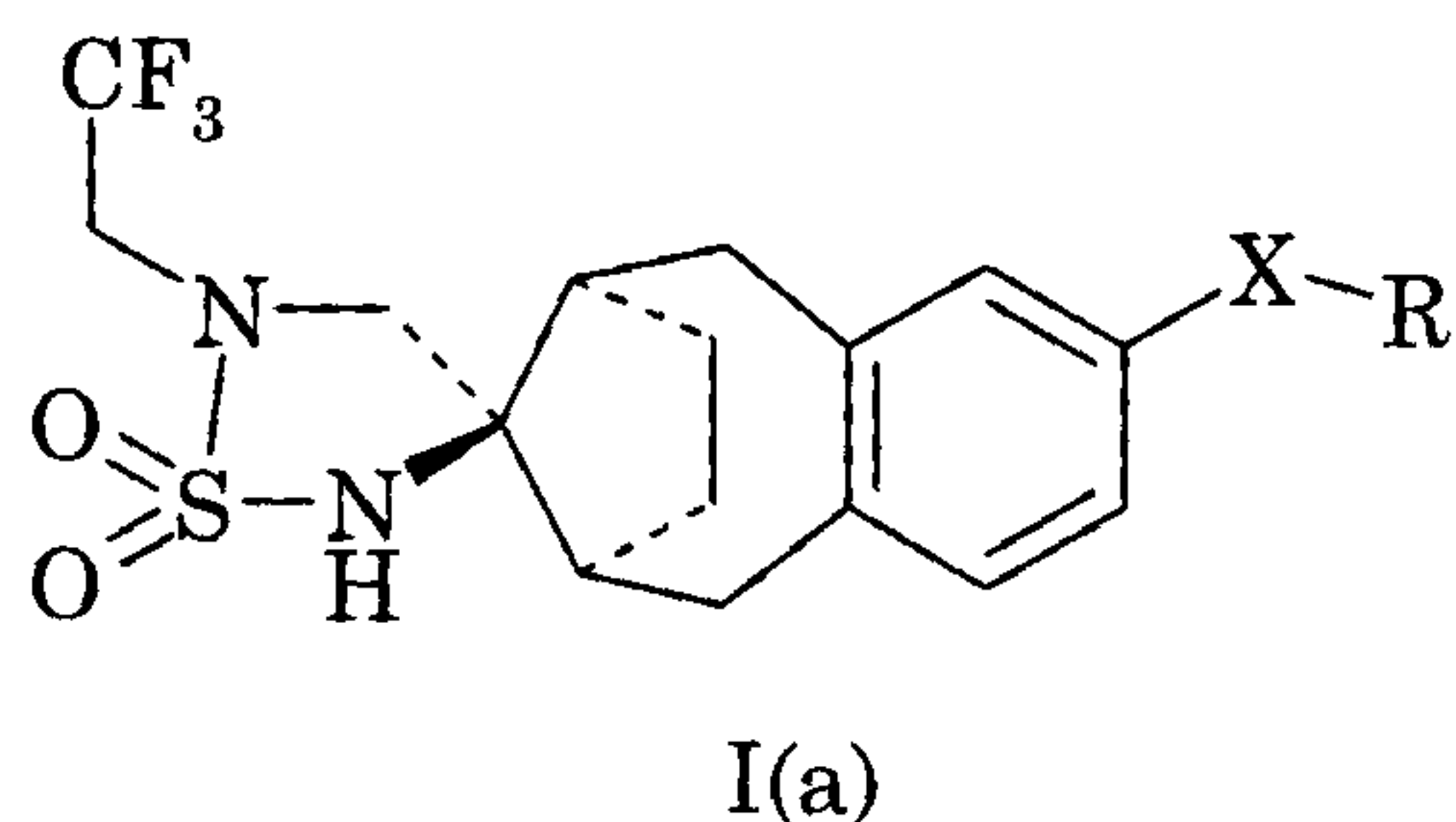
(iii) phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF_3 , CHF_2 , CH_2F , NO_2 , CN , OCF_3 , $\text{C}_{1-6}\text{alkyl}$ and $\text{C}_{1-6}\text{alkoxy}$; and

(iv) $\text{N}(\text{R}^a)_2$ where each R^a independently represents H or $\text{C}_{1-6}\text{alkyl}$ which is optionally substituted with halogen, CF_3 , CHF_2 , CN , OH , CO_2H , $\text{C}_{2-6}\text{acyl}$, $\text{C}_{1-4}\text{alkoxy}$ or $\text{C}_{1-4}\text{alkoxycarbonyl}$;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X is selected from the group consisting of 1,3,4-oxadiazol-2-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-1-yl, 1,2,4-triazol-3-yl, 1-methyl-1,2,4-triazol-3-yl, oxazol-2-yl, pyrazol-3-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-5-yl, 1-ethylpyrazol-3-yl, 1-(2,2,2-trifluoroethyl)pyrazol-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, isoxazol-5-yl, isoxazol-3-yl, imidazol-2-yl, imidazol-4-yl and imidazol-1-yl, wherein the numbering indicates the ring atom of X which is attached to the fused benzene ring in formula I; or a pharmaceutically acceptable salt thereof.
3. A compound according to claim 2 wherein X is selected from the group consisting of 1-methyl-1,2,4-triazol-3-yl, 1-methylpyrazol-3-yl, 1-ethylpyrazol-3-yl, oxazol-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl, in which R is attached to the 5-position of X; or a pharmaceutically acceptable salt thereof.
4. A compound according to claim 2 wherein X is imidazol-4-yl or 1,2,4-triazol-3-yl in which R is attached to the 1-position of X; or a pharmaceutically acceptable salt thereof.
5. A compound according to any one of claims 1 to 4 wherein R is CF₃, t-butyl or isopropyl; or a pharmaceutically acceptable salt thereof.
6. A compound according to any one of claims 1 to 4 wherein R represents a non-aromatic heterocyclic group comprising up to 7 ring atoms of which up to 3 are chosen from N, O and S and the remainder are carbon, bearing 0-3 substituents independently selected from oxo, halogen, CN, C₁₋₆alkyl, OH, CF₃, CHF₂, CH₂F, C₂₋₆acyl, CO₂H, C₁₋₄alkoxy and C₁₋₄alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 6 wherein R represents piperidin-1-yl, 4-trifluoromethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 3,3-difluoropiperidin-1-yl, 3,3-difluoroazetidin-1-yl, morpholin-4-yl, 1-acetylpiperidin-4-yl, 1-trifluoroacetylpiperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, 1-trifluoroacetyl-1,2,3,6-tetrahydropyridin-4-yl or 1-(t-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl; or a pharmaceutically acceptable salt thereof.
8. A compound according to any one of claims 1 to 4 wherein R represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF₃, CHF₂, CH₂F, NO₂, CN, OCF₃, C₁₋₆alkyl and C₁₋₆alkoxy; or a pharmaceutically acceptable salt thereof.
9. A compound according to any one of claims 1 to 4 wherein R is selected from phenyl, monohalophenyl, dihalophenyl, trihalophenyl, cyanophenyl, methylphenyl, methoxyphenyl, trifluoromethylphenyl, trifluoromethoxyphenyl, pyridyl, monohalopyridyl and trifluoromethylpyridyl, wherein "halo" refers to fluoro or chloro; or a pharmaceutically acceptable salt thereof.
10. A compound according to claim 8 wherein R is selected from 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-(trifluoromethyl)phenyl, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl; or a pharmaceutically acceptable salt thereof.
11. A compound according to claim 1 which is a 2-substituted-[6S,9R,11R] 2',3',4',5,5',6,7,8,9,10-decahydro-5'-(2,2,2-trifluoroethyl)-spiro[6,9-methanobenzocyclooctene-11,3'-[1,2,5]thiadiazole] 1',1'-dioxide of formula I(a):



or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 11 wherein X is selected from 5-substituted-thiazol-2-yl, 5-substituted-4-methylthiazol-2-yl, 5-substituted-1-methylpyrazol-3-yl, 1-substituted-imidazol-4-yl and 1-substituted-1,2,4-triazol-3-yl; or a pharmaceutically acceptable salt thereof.

13. A compound according to claim 11 or claim 12 wherein R represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF_3 , CHF_2 , CH_2F , NO_2 , CN , OCF_3 , C_{1-6} alkyl and C_{1-6} alkoxy; or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 13 wherein R is selected from 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-(trifluoromethyl)phenyl, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl; or a pharmaceutically acceptable salt thereof.

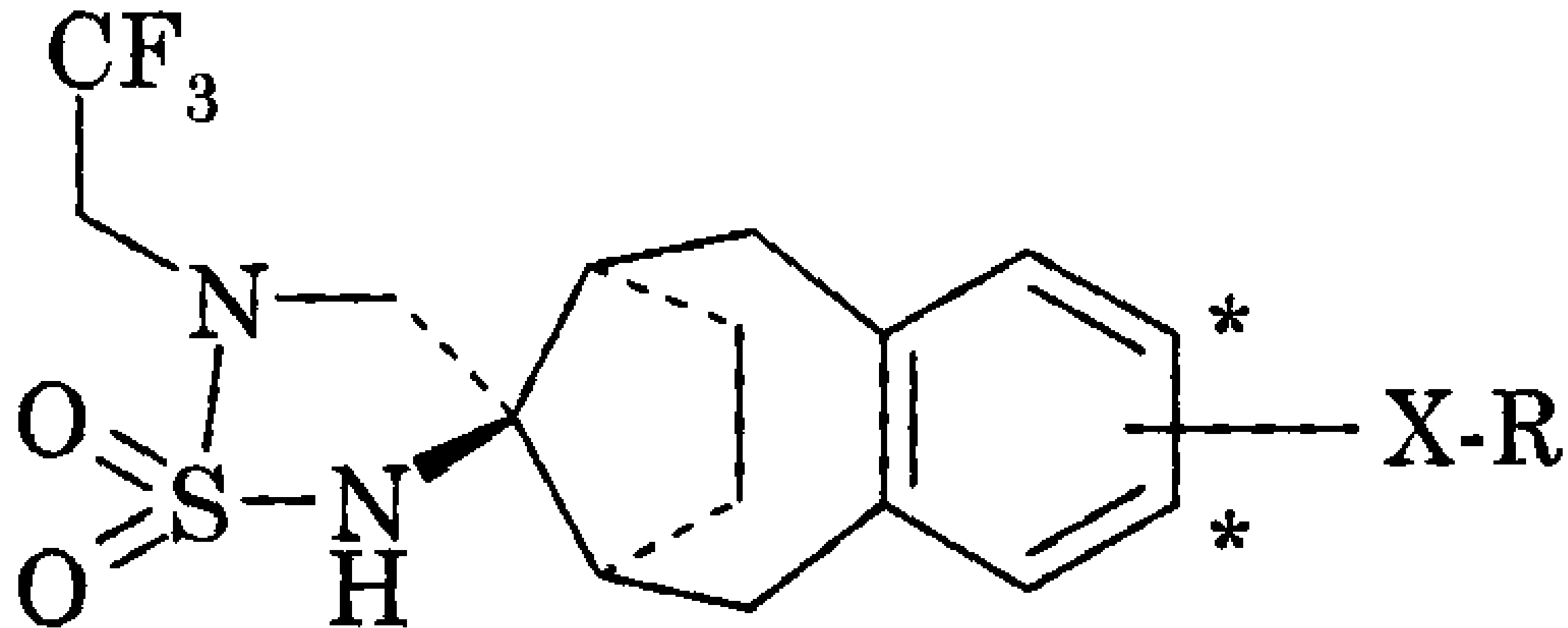
15. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 14; or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

- 129 -

16. Use of a compound as defined in any one of claims 1 to 14; or a pharmaceutically acceptable salt thereof for treatment or prevention of Alzheimer's disease.

17. Use of a compound as defined in any one of claims 1 to 14; or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treatment or prevention of Alzheimer's disease.

18. The composition of claim 15 for use in the treatment of a subject suffering from or prone to Alzheimer's disease.



I