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Heterocyclic ring scaffolds as small-molecule cholesterol absorption inhibitors

Tobias Ritter,[a] Lisbet Kværnø,[a] Moritz Werder,[b] Helmut Hauser[b] and Erick M. Carreira*[a]

[a] *Laboratorium für Organische Chemie, ETH-Hönggerberg, CH-8093 Zürich, Switzerland. E-mail: carreira@org.chem.ethz.ch; Fax: +41 44 632 1328; Tel: +41 44 632 2830*

[b] *Lipideon Biotechnology AG, Hermann-Hiltbrunnerweg 25, CH-8713 Uerikon, Switzerland*

Received 15th July 2005, Accepted 1st August 2005
First published as an Advance Article on the web 24th August 2005

Enantio- and diastereoselective syntheses of a substituted oxazolidinone, isoxazoline and pyrazoline as β-lactam surrogates are described. The substituted heterocycles were designed to incorporate side chains closely resembling those found in the β-lactam cholesterol absorption inhibitor ezetimibe (**1**). Additionally, the *in vitro* inhibitory efficacy of the novel compounds as cholesterol absorption inhibitors is reported using a brush border membrane vesicle assay.

Introduction

Enantio- and diastereoselective methods for the synthesis of substituted non-aromatic heterocycles are of prime importance. When incorporating multiple derivatization sites such methods facilitate diversity oriented synthesis. A recent example is the drug ezetimibe (**1**, Fig. 1),[1] which inhibits cholesterol absorption and contains a non-aromatic heterocycle in the form of a β-lactam ring. In the development of ezetimibe, the β-lactam was proposed to be essential for inhibitory activity,[2,3] with the corresponding ring-opened β-amino acid derivative being completely inactive.[3] In the course of an ongoing project aimed at the characterization and further study of intestinal cholesterol uptake, we became interested in the design of structurally well-defined, non-aromatic heterocycles which can mimic the β-lactam scaffold. The β-lactam ring is a rigid, almost planar heterocycle that defines out of plane vectors from a central core. Given our objectives of identifying structural congeners of β-lactams, we focused on generating structures in which the geometrical alignment of the three exit vectors of the substituents in the β-lactam are conserved (Fig. 1). Importantly, we additionally wished to identify β-lactam mimics that would not be prone to undergo hydrolysis as seen for β-lactams in general. In this report, we document the enantio- and diastereoselective syntheses of three β-lactam surrogates, namely an oxazolidinone, an isoxazoline, and a pyrazoline, which do not suffer from hydrolytic instability and display a set of exit vectors closely resembling those found in the β-lactam scaffold. We furthermore report their activities as cholesterol absorption inhibitors using our recently developed brush border membrane vesicle assay.[4]

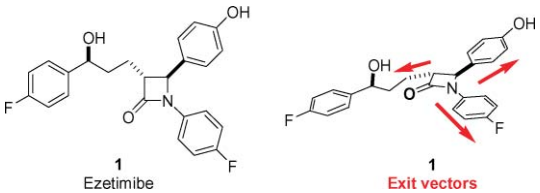


Fig. 1 Ezetimibe and the exit vectors of the β-lactam core.

Results and discussion

The oxazolidinone scaffold **2** has previously been suggested to serve as a structural mimic of the β-lactam of ezetimibe (**1**).[2] Our *ab initio* geometry optimizations[5] (Fig. 2) additionally suggested that the isoxazoline **3** and the pyrazoline **4** position three out of plane exit vectors in a manner that corresponds well to the β-lactam ring of ezetimibe. The excellent overlaps of the substituents are illustrated by superposition of each of the three heterocycles **2–4** with the β-lactam core found in ezetimibe. In order to focus on the exit vectors from the heterocyclic core, the flexible hydroxypropyl side chain in ezetimibe, which is not expected to strongly favor any single conformation, was replaced by a methyl group in the calculations.

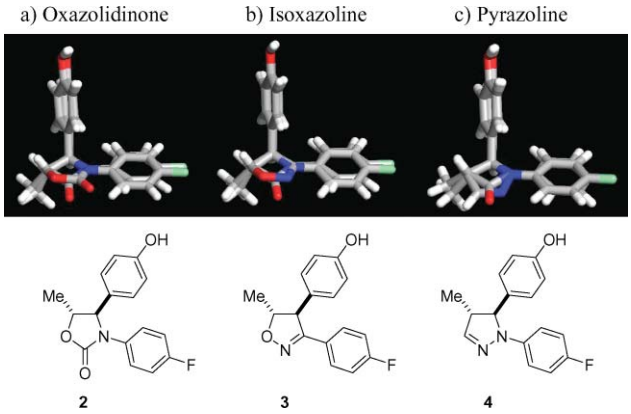
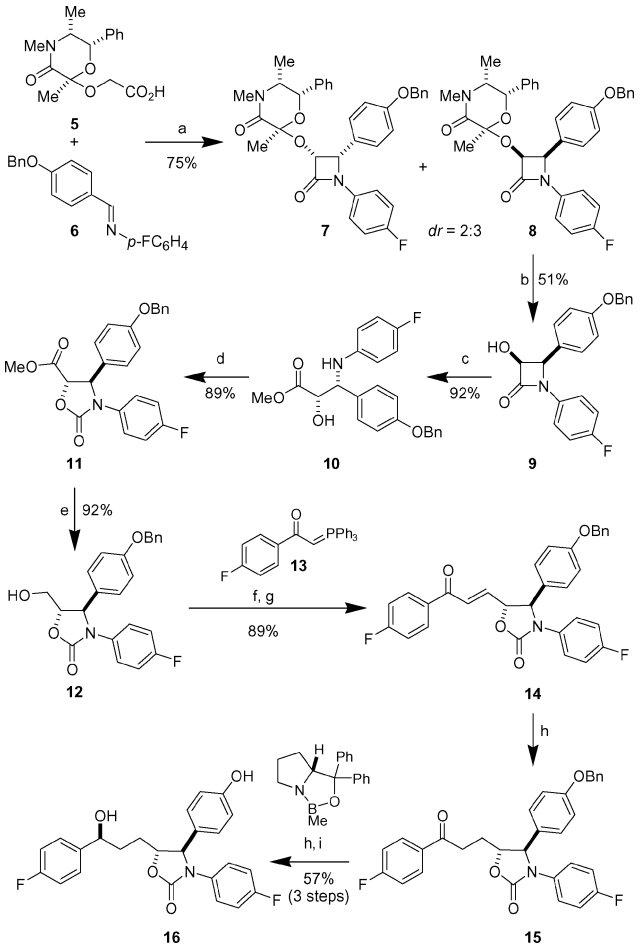


Fig. 2 Geometric overlap of oxazolidinone **2** (a), isoxazoline **3** (b), and pyrazoline **4** (c) with the β-lactam core structure of ezetimibe (**1**).

The synthesis of the desired oxazolidinone **16** commenced with a Staudinger cycloaddition of imine **6**[6] and the ketene derived from acid **5**[7] (Scheme 1). The reaction proceeded in 75% yield (*cis*:*trans* = 95:5) to give a mixture of *cis*-diastereomers **7** and **8** (dr = 2:3 as determined by ^{1}H NMR spectroscopy).[8] These were separable by silica gel chromatography and afforded **8** as a single isomer. Acid-mediated cleavage of the ketal furnished α-hydroxy-β-lactam **9** in enantiomerically pure form and 51% yield. Although yield and diastereoselectivity were modest, the ready availability of the inexpensive starting materials as well as the straightforward and scalable reaction protocol were decisive in our synthetic plan. Cleavage of the β-lactam under alkaline conditions delivered amino alcohol **10** in 92% yield, which was converted to oxazolidinone **11** in 89% yield using triphosgene.

The methyl ester in **11** served as an appropriate handle to attach the 3′-aryl-3′-hydroxypropyl side chain found in ezetimibe (**1**). Initially, we envisaged reduction of the ester to the aldehyde and subsequent introduction of the side chain by an aldol condensation reaction. However, all attempts to isolate the aldehyde derived from **11** failed. Reduction of ester **11** or the corresponding Weinreb amide[9] with DIBAL-H resulted only in decomposition products, attributed to the presumed instability of the product aldehyde. In 1985 Ireland documented the manipulation

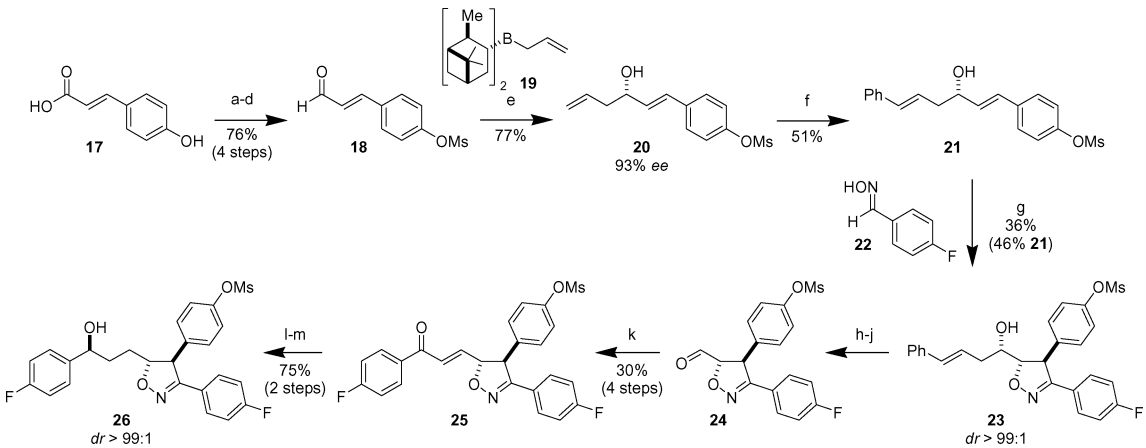
DOI: 10.1039/b510100j



Scheme 1 *Reagents and conditions:* a) triphosgene, Et_3N, CH_2Cl_2, 0 °C to 23 °C. b) CSA, THF–H_2O, reflux. c) NaOMe, MeOH. d) Triphosgene, iPr_2NEt, DMAP, CH_2Cl_2, −78 °C to 23 °C. e) $NaBH_4$, EtOH. f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C. g) **13**. h) H_2, Pd/C, EtOH. i) (*R*)-CBS catalyst, $BH_3{\cdot}SMe_2$, CH_2Cl_2, −20 °C to 0 °C.

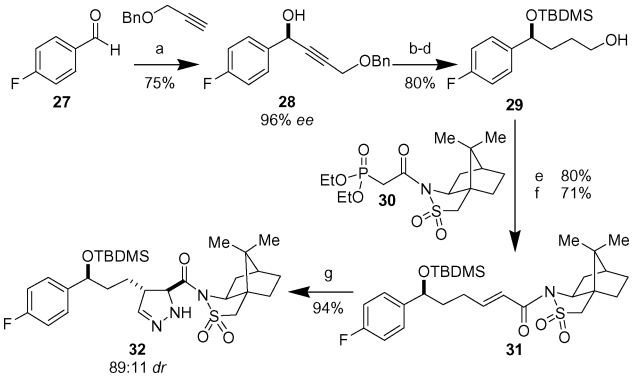
of unstable aldehydes through *in situ* Swern oxidation of the corresponding alcohols and subsequent Wittig reaction.[10] Consequently, ester **11** was reduced to the corresponding alcohol **12** by treatment with $NaBH_4$ in ethanol at 23 °C. Subsequent Swern oxidation[11] at −78 °C for 5 min furnished the intermediate aldehyde, which was subjected to *in situ* reaction with stabilized phosphorous ylide **13**.[12] The unusual low reaction temperature for this Wittig reaction (< −40 °C)[13] underscores the high electrophilicity of the intermediate aldehyde. Through this procedure *trans*-enone **14** could be conveniently prepared in 89% yield. Hydrogenation of the conjugated double bond afforded ketone **15**, which was diastereoselectively reduced using the (*R*)-CBS catalyst[14] (dr > 99:1 according to ^{19}F-NMR). Finally hydrogenolysis of the benzyl ether furnished the targeted oxazolidinone **16** in 57% yield over three steps. The above route thus furnished a rapid and straightforward access to the oxazolidinone scaffold with the desired side chains.

The stereoselective synthesis of the desired isoxazoline **26** was then pursued (Scheme 2) through a diastereoselective dipolar cycloaddition reaction of nitrile oxides and optically active allylic alcohols, which provides access to chiral optically active isoxazolines.[15] However, at the outset of our synthesis it was far from clear whether allylic alcohols wherein the olefin is conjugated to a functionalized aromatic ring could be used as dipolarophiles in this cycloaddition, since the vast majority of the described magnesium-mediated cycloadditions have been conducted with non-conjugated allylic alcohols. In order to test the strategy, the cinnamyl aldehyde **18** was prepared from commercially available 4-hydroxycinnamic acid (**17**) in 76% yield over 4 steps. Subsequent Brown allylation using (+)-β-allyldiisopinocampheyl borane (**19**)[16] afforded homoallylic alcohol **20** in 77% yield and 93% ee as determined by chiral HPLC. Cycloaddition of this allylic alcohol with the nitrile oxide derived from **22** delivered the product isoxazoline largely derived from cycloaddition to the terminal double bond. We speculated that this undesired regioselectivity could be circumvented by conversion of the terminal double bond to a corresponding di-substituted olefin, thereby reducing the rate of the cycloaddition reaction at this site. In this regard, **20** was subjected to Heck arylation[17] to give **21** in 51% yield. In initial investigations of the cycloaddition reaction we noted a major by-product resulting from dimerization of the nitrile oxide. In order to minimize the formation of this by-product, the reaction was conducted at low concentration of the nitrile oxide in the reaction mixture by slow addition of the hydroximinoyl chloride (generated from oxime oxidation with *tert*-butyl hypochloride) to the dipolarophile over a period of 30 h. Thus, cycloaddition of allylic alcohol **21** with the nitrile oxide derived from **22** proceeded completely regio- and diastereoselectively (dr > 99:1 as determined by NMR) to give isoxazoline **23** in 36% yield with 46% recovered starting material. Installation of the desired substituents commenced by conversion of **23** to aldehyde **24**. In analogy to the synthesis of the oxazolidinone **16** described earlier, aldehyde **24** was allowed to react with phosphorous ylide **13**[12] to afford enone **25** (30% over 4 steps). Hydrogenation of the double bond followed by diastereoselective ketone reduction (dr > 99:1 as determined by ^{1}H NMR) using the (*R*)-CBS catalyst[14] afforded the desired isoxazoline **26** in 75% yield over two steps.



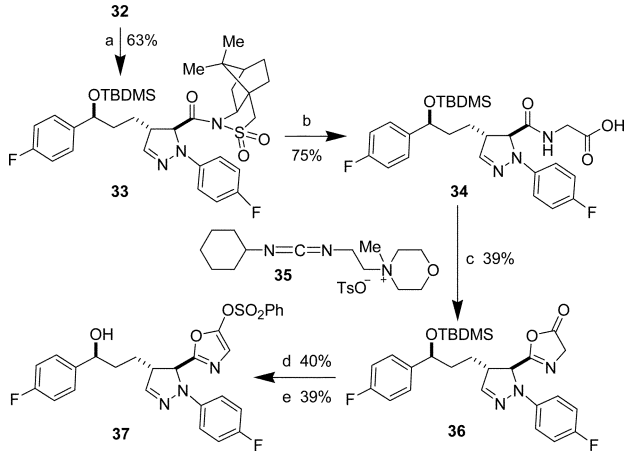
Scheme 2 *Reagents and conditions:* a) $SOCl_2$, MeOH. b) MsCl, Et_3N, THF. c) DIBAL-H, CH_2Cl_2, 0 °C. d) MnO_2, CH_2Cl_2. e) **19**, Et_2O, −78 °C. f) C_6H_5I, $Pd(OAc)_2$, PPh_3, Et_3N, MeCN. g) **22**, *t*BuOCl, *i*PrOH, EtMgBr, CH_2Cl_2. h) MsCl, pyr, CH_2Cl_2. i) DBU, CH_2Cl_2, reflux. j) $K_2OsO_4{\cdot}2H_2O$, $NaIO_4$, THF–H_2O. k) **13**. l) H_2, Pd/C, MeOH. m) (*R*)-CBS catalyst, $BH_3{\cdot}SMe_2$, CH_2Cl_2, −20 °C to 0 °C.

In the approach to the desired substituted pyrazolines, a diastereoselective 1,3-dipolar cycloaddition of TMS-diazomethane[18] was utilized to construct the heterocyclic core (Scheme 3). The synthesis commenced with a Zn-mediated enantioselective alkyne addition[19] to *p*-fluorobenzaldehyde **27** to give propargylic alcohol **28** in 75% yield (96% ee as determined by chiral HPLC). The yields were higher when the reaction was conducted slightly below room temperature (8–13 °C). Subsequent silylation was immediately followed by sequential reduction of the triple bond and removal of the benzyl group to give alcohol **29** in 80% overall yield. This was necessary because the intermediary propargylic silyl ether proved unstable and difficult to isolate. The propensity of the benzylic and propargylic C–OSi bond to undergo hydrogenolytic cleavage necessitated stepwise hydrogenation of the alkyne prior to removal of the benzyl group. Subsequent Dess–Martin oxidation[20] (80% yield) and Horner–Wadsworth–Emmons olefination using the camphorsultam derived phosphonate **30**[21,22] and LiCl–DBU[23] afforded the (*E*)-olefin **31** in 71% yield. The pyrazoline heterocyclic core was generated using a diastereoselective 1,3-dipolar cycloaddition of TMS-diazomethane,[18] which furnished the desired pyrazoline **32** in 94% combined yield (89:11 dr based on the yields of the isolated diastereomers). The diastereomeric products were readily separated by chromatography on silica gel to afford diastereomerically pure **32**.



Scheme 3 *Reagents and conditions:* a) $Zn(OTf)_2$, (+)-*N*-methylephedrine, Et_3N, toluene, 8–13 °C. b) TBDMSCl, imidazole, DMF. c) H_2, Pd/C, Na_2CO_3, EtOH. d) H_2, Pd/C, EtOH. e) Dess–Martin periodinane, CH_2Cl_2. f) **30**, DBU, LiCl, MeCN. g) $TMSCHN_2$, toluene–hexane; then TFA, CH_2Cl_2.

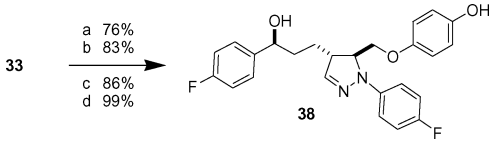
Typical conditions employed in Pd-mediated *N*-arylations[24] proved incompatible with the camphorsultam imide. However, a Cu-mediated *N*-arylation proceeded successfully employing either a boronic acid[25] or a triarylbismuth derivative[26] (Scheme 4).



Scheme 4 *Reagents and conditions:* a) $(p\text{-}FC_6H_4)_3Bi$, $Cu(OAc)_2$, Et_3N, CH_2Cl_2. b) Glycine, KCN, MeOH, 50 °C. c) **35**, CH_2Cl_2, reflux. d) $PhSO_2Cl$, Et_3N, CH_2Cl_2. e) HF·pyr, pyr, THF.

Optimal yields (63%) were obtained using the organobismuth reagent, $(p\text{-}FC_6H_4)_3Bi$, which was readily obtained by reaction of *p*-fluorophenylmagnesium bromide with $BiCl_3$. With this intermediate **33** in hand, we envisioned a rapid synthesis of various analogues by conversion of the carboxylic acid derivative into an oxazole as a substitute for the phenol substituent of ezetimibe. In this regard, substitution of the camphorsultam auxiliary with glycine catalyzed by KCN[27] (75%) and dehydration using the water-soluble DCC analogue **35**[28] afforded the desired, but rather unstable, oxazolone **36** in 39% isolated yield. Generation of the oxazole **37** was effected by benzene sulfonate ester formation and desilylation in 40% and 39% yields, respectively.

As an alternative pyrazoline derivatization, the chiral camphorsultam auxiliary of **33** was reductively removed ($LiAlH_4$, 76% yield) to give a primary alcohol which, following tosylation (83% yield), was subjected to nucleophilic displacement of the sulfonate by hydroquinone in 86% yield (Scheme 5). Subsequent desilylation afforded the pyrazoline **38** in 99% yield featuring an oxymethylene linker between the pyrazoline and the aromatic ring substituent.



Scheme 5 *Reagents and conditions*: a) $LiAlH_4$, THF, −78 °C. b) TsCl, DMAP. Et_3N, CH_2Cl_2. c) Hydroquinone, Cs_2CO_3, DMF, 80 °C. d) HF·pyr, pyr, THF.

The heterocyclic compounds **16**, **26**, and **37–38** were subsequently evaluated for inhibition of intestinal cholesterol uptake using our recent brush border membrane vesicle *in vitro* assay (Fig. 3).[4] We were pleased to observe that oxazolidinone **16** showed a similar *in vitro* activity (19% inhibition) to ezetimibe (**1**) (16% inhibition). Despite previous promising *in vitro* results for a wide range of sulfonate ester phenolic derivatives of ezetimibe,[4b] the sulfonate ester substituted isoxazoline (**26**) and pyrazoline (**37**) did not show any activity as cholesterol absorption inhibitors. The remaining pyrazoline **38** was likewise void of inhibitory activity. This attests that small changes of the

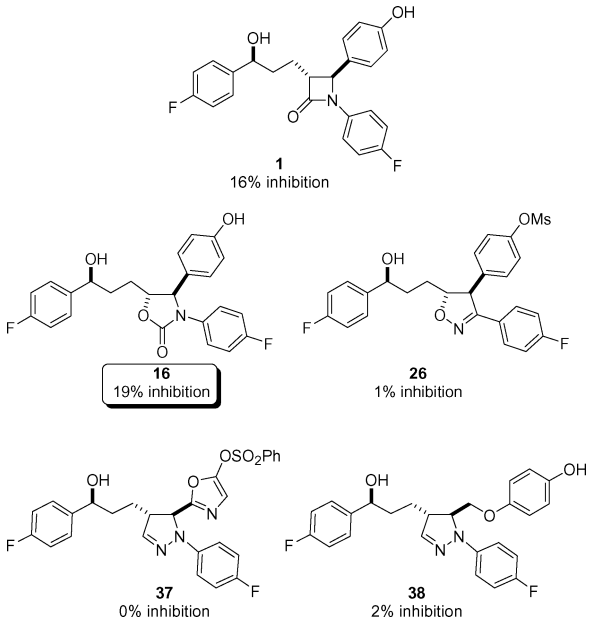


Fig. 3 Percentage inhibition in the brush border membrane vesicle assay using rabbit small intestine at nominal concentrations of 6 μM.[4] The average standard deviations were ±3% inhibition.

heterocyclic core can result in marked differences as cholesterol absorption inhibitors even though the geometric deviations of the exit vectors are only subtle (Fig. 2).

Conclusions

We have documented the enantio- and diastereoselective syntheses of three β-lactam surrogates with side chains resembling those found in the cholesterol absorption inhibitor ezetimibe (**1**). In the course of these investigations we expanded the substrate scope of the highly diastereoselective hydroxyl-directed nitrile oxide cycloadditions. The pyrazoline synthesis featured a diastereoselective dipolar cycloaddition of TMS-diazomethane and a copper-mediated *N*-arylation using an organobismuth reagent as the key steps. When evaluated in the brush border membrane vesicle assay, the oxazolidinone **16** showed similar activity as ezetimibe (**1**) as a cholesterol absorption inhibitor. This promising result suggests that an oxazolidinone ring scaffold could effectively replace the β-lactam of ezetimibe. Synthesis of additional analogues and their biological evaluation are underway and will be reported in due course.

Experimental

General experimental details

Reactions in anhydrous solvents were all performed using oven dried glassware under an atmosphere of argon. Reagent grade solvents were all purchased from chemical companies and used without prior purification. Anhydrous THF, ether, toluene, CH_3CN and CH_2Cl_2 were dried and purified through activated alumina columns as described.[29] Diisopropylamine, triethylamine and pyridine were distilled from KOH. For chromatographic purification, technical grade solvents were distilled prior to use. TLC was performed using Machery-Nagel Alugram Sil G/UV$_{254}$ or Merck 0.25 mm silica gel 60 F_{254} TLC glass plates. Visualization of the developed chromatogram was performed by UV fluorescence at 254 nm and oxidative stain by either ceric ammonium molybdate solution, $KMnO_4$–$NaHCO_3$ water solution, phosphomolybdic acid or H_2SO_4–MeOH. Chromatographic purification of products was accomplished by dry column vacuum chromatography[30] on either Merck silica gel 60 (15–40 μm) or Brunschwig silica 18–32, 60 Å (18–32 μM) or by flash chromatography on silica gel 60 (230–400 mesh, 0.04–0.063 mm) from Merck at rt and 0.3–0.5 mbar air pressure. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and the purified compounds were subsequently dried under high vacuum (<0.5 Torr). NMR spectra were recorded on a Varian Mercury 300 MHz apparatus operating at 300 MHz, 75 MHz and 282 MHz for ^{1}H, ^{13}C/DEPT and ^{19}F, respectively, and chemical shifts (δ) were referenced to the internal solvent signals for ^{1}H and ^{13}C. Multiplicities are reported as follows: ^{1}H: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; ^{13}C: C, CH, CH_2, CH_3 (determined by DEPT); coupling constants are reported in Hz. Melting points were measured on a Büchi 510 apparatus in open capillaries and all melting points are uncorrected. IR-Spectra were recorded in $CHCl_3$ on a Perkin Elmer Spectrum RX I FT-IR apparatus (thin films on NaCl plates) and are reported as absorption maxima in cm^{-1}. Optical rotations are reported in 10^{-1}deg cm^2 g^{-1}. Elemental analysis was performed by the Mikroelementaranalytisches Laboratorium at the ETH, Zürich. High resolution matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) and electrospray ionization (ESI-MS) were performed by the mass spectrometry service of the LOC at the ETH, Zürich.

(2*S*,5*R*,6*S*)-2-[(1*S*,2*R*)-2-(4-Benzyloxyphenyl)-3-(4-fluorophenyl)-4-oxocyclobutoxy]-2,4,5-trimethyl-6-phenylmorpholin-3-one (8). To a solution of acid **5**[7] (30.0 g, 102 mmol, 1.11 eq.) in CH_2Cl_2 (600 ml) was added triethylamine (64.0 ml, 461 mmol, 5.00 eq.) followed by imine **6**[6] (28.1 g, 92.1 mmol, 1.00 eq.). The solution was cooled to −20 °C and triphosgene (16.4 g, 55.8 mmol, 0.600 eq.) was added in 50 ml CH_2Cl_2 over a period of 20 min. The solution was warmed to 23 °C over a period of 8 h and stirred for an additional 10 h at this temperature. The solution was poured onto 600 ml ice water and 200 ml CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with hexane–EtOAc (3:2 to 1:2 gradient) and then chromatography on silica gel eluting with EtOAc–CH_2Cl_2 (7:1 to 3:1 gradient) to afford β-lactam **8** as a colorless solid in 45% yield along with 30% yield of the undesired diastereomer **7**. Mp: 132 °C. R_f = 0.38 [hexane–EtOAc 1:1 (v/v)]. $\alpha_D^{30.5}$ = +77°, (*c* 1.075 in $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.46–7.07 (16 H, m), 6.92–6.84 (2 H, m), 5.34 (1 H, d, *J* = 5.3 Hz), 5.06 (2 H, s), 4.95 (1 H, d, *J* = 5.3 Hz), 4.60 (1 H, d, *J* = 2.5 Hz), 3.23–3.14 (1 H, m), 2.90 (3 H, s), 1.70 (3 H, s), 0.83 (3 H, d, *J* = 6.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.4, 165.0, 159.3 (d, *J* = 244 Hz), 159.1, 137.1 (d, *J* = 5 Hz), 133.7, 129.9, 128.9, 128.6, 128.3, 128.0, 127.7, 125.7, 119.0 (d, *J* = 8 Hz), 116.0 (d, *J* = 23 Hz), 115.1, 100.1, 76.9, 71.2, 70.1, 62.2, 59.0, 33.8, 23.6, 12.4. IR (thin film): 2938, 1756, 1667, 1612, 1511, 1382, 1223, 1177, 1112, 1092, 834, 734. HRMS (EI): found, 580.2369. $C_{35}H_{33}FN_2O_5^+$ requires 580.2374.

(3*S*,4*R*)-4-(4-Benzyloxyphenyl)-1-(4-fluorophenyl)-3-hydroxyazetidin-2-one (9). To a solution of ketal **8** (17.0 g, 29.0 mmol, 1.00 eq.) in THF (242 ml) and water (48 ml) was added *p*-toluenesulfonic acid monohydrate (55.7 g, 293 mmol, 10.0 eq.). The solution was heated to reflux for 5 h. The solution was concentrated to an approximate volume of 60 ml and then poured onto EtOAc (150 ml) and water (250 ml). The aqueous phase was extracted with EtOAc (4 × 100 ml). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (3:2 to 2:3 gradient), to afford β-lactam **9** as a colorless solid in 51% yield. Mp: 168 °C. R_f = 0.26 [hexane–EtOAc 3:2 (v/v)]. $\alpha_D^{29.5}$ = −129°, (*c* 1.22 in acetone). ^{1}H-NMR (300 MHz, acetone-d_6): δ 7.50–7.47 (2 H, m), 7.42–7.29 (5 H, m), 7.10–7.01 (4 H, m), 5.33 (1 H, d, *J* = 5.3 Hz), 5.27 (1 H, dd, *J* = 7.2 Hz, 5.3 Hz), 5.11 (2 H, s), 5.07 (1 H, d, *J* = 7.2 Hz). ^{13}C-NMR (75 MHz, acetone-d_6): δ 166.5, 159.2, 159.0 (d, *J* = 241 Hz), 137.7, 134.7, 129.6, 128.6, 128.0, 127.8, 118.9 (d, *J* = 8 Hz), 115.8 (d, *J* = 23 Hz), 114.8, 78.0, 69.8, 62.3. IR (thin film): 3120, 1756, 1667, 1612, 1511, 1382, 1223, 1177, 1112, 1092, 834, 734. HRMS (EI): found, 363.1268. $C_{22}H_{18}FNO_3^+$ requires 363.1271. Anal.: found, C, 77.73; H, 5.20; N, 3.91. $C_{22}H_{18}FNO_3$ requires C, 72.72; H, 4.99; N, 3.85%.

(2*S*,3*R*)-3-(4-Benzyloxyphenyl)-3-(4-fluorophenylamino)-2-hydroxypropionic acid methyl ester (10). To a suspension of β-lactam **9** (2.00 g, 5.50 mmol, 1.00 eq.) in methanol (55.0 ml) was added sodium methoxide (1.49 g, 27.5 mmol, 5.00 eq.). The suspension was stirred at 23 °C for 2 h. To the forming solution was added $NH_4Cl_{(s)}$ and the suspension was concentrated *in vacuo*. To the solid was added EtOAc (50 ml) and water (50 ml). The aqueous phase was extracted with EtOAc (3 × 20 ml). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (3:2 to 1:1 gradient), to afford amino alcohol **10** as a colorless solid in 89% yield. Mp: 103 °C. R_f = 0.45 [hexane–EtOAc 3:2 (v/v)]. $\alpha_D^{25.3}$ = +13.9°, (*c* 1.10 in CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.44–7.24 (4 H, m), 6.97–6.91 (2 H, m), 6.84–6.76 (2 H, m), 6.53–6.46 (2 H, m), 5.02 (2 H, s), 4.81 (1 H, s), 4.60 (1 H, s), 4.46 (1 H, m), 3.79 (3 H, s), 3.07 (1 H, d, *J* = 3.7 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 158.2, 155.8 (d, *J* = 233 Hz), 142.5, 136.8, 131.0, 128.5, 127.9, 127.9, 127.4, 155.5 (d, *J* = 22 Hz), 114.9, 114.8, 74.6, 70.0, 59.1, 53.1, 114.8, 78.0, 69.8,

62.3. IR (thin film): 3390, 1737, 1610, 1510, 1221, 1113, 823. MS (EI): 306.1748 (2.54%), 186.2356 (18.8%), 91.0908 (100%). Anal.: found, C, 69.88; H, 5.78; N, 3.54. $C_{23}H_{22}FNO_4$ requires C, 69.86; H, 5.61; N, 3.54%.

(4*R*,5*S*)-4-(4-Benzyloxyphenyl)-3-(4-fluorophenyl)-2-oxooxazolidine-5-carboxylic acid methyl ester (11). To a solution of amino alcohol **10** (1.92 g, 4.86 mmol, 1.00 eq.) in CH_2Cl_2 (24.0 ml) was added diisopropylethylamine (2.54 ml, 14.6 mmol, 3.00 eq.) and 4-*N*,*N*-dimethylaminopyridine (59.0 mg, 0.486 mmol, 0.10 eq.). The solution was cooled to −78 °C and triphosgene (1.44 g, 4.86 mmol, 1.00 eq.) in CH_2Cl_2 (4.0 ml) was added over a period of 5 min. The solution was warmed to 23 °C over 8 h and stirred at this temperature for an additional 5 h. To this solution was added water (50 ml) and concentrated aqueous ammonium hydroxide solution (3 ml). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (2:1 to 1:1 gradient), to afford methyl ester **11** as a colourless solid in 82% yield. Mp: 118 °C. $R_f = 0.54$ [hexane–EtOAc 3:2 (v/v)]. $\alpha_D^{29.3} = +18°$, (*c* 1.10 in $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40–7.32 (7 H, m), 7.29–7.22 (2 H, m), 6.98–6.93 (4 H, m), 5.33 (1 H, d, $J = 4.4$ Hz), 5.03 (2 H, s), 4.73 (1 H, d, $J = 4.4$ Hz), 3.89 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.9, 160.1 (d, $J = 244$ Hz), 159.7, 154.3, 136.7, 132.7, 129.5, 128.9, 128.4, 127.8, 127.7, 123.2 (d, $J = 8$ Hz), 116.1 (d, $J = 22$ Hz), 116.0, 77.9, 70.3, 36.6, 53.5. IR (thin film): 1769, 1552, 1388, 1227, 1099, 834. HRMS (MALDI): found, 444.1224. $C_{24}H_{20}FNO_5Na^+$ requires 444.1224. Anal.: found, C, 68.18; H, 4.91; N, 3.38. $C_{24}H_{20}FNO_5$ requires C, 68.40; H, 4.78; N, 3.32%.

(4*R*,5*S*)-4-(4-Benzyloxyphenyl)-3-(4-fluorophenyl)-5-hydroxymethyloxazolidin-2-one (12). To a suspension of methyl ester **11** (1.68 g, 3.99 mmol, 1.00 eq.) in ethanol (27.0 ml) was added, at 23 °C, sodium borohydride (226 mg, 5.98 mmol, 1.50 eq.). The suspension was stirred for 2 h at this temperature after which point all solids had dissolved. To this solution was added $NH_4Cl_{(s)}$ and the volume was concentrated to 5 ml *in vacuo*. To this suspension was added water (50 ml) and EtOAc (50 ml). The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (1:1 to 2:3 gradient), to afford alcohol **12** as a colorless solid in 92% yield. Mp: 143 °C. $R_f = 0.40$ [hexane–EtOAc 2:3 (v/v)]. $\alpha_D^{32.4} = -16°$, (*c* 1.54 in $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42–7.19 (9 H, m), 6.97–6.90 (4 H, m), 5.26 (1 H, d, $J = 6.5$ Hz), 5.02 (2 H, s), 4.39 (1 H, m), 3.99 (1 H, d, $J = 12.5$ Hz), 3.74 (1 H, d, $J = 12.5$ Hz), 2.77 (1 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.7 (d, $J = 245$ Hz), 159.0, 136.4, 132.7, 129.4, 128.5, 128.0, 127.9, 127.4, 123.6 (d, $J = 8$ Hz), 115.6 (d, $J = 22$ Hz), 115.6, 82.0, 70.1, 61.6, 61.2. IR (thin film): 3418, 2930, 2871, 1748, 1611, 1512, 1394, 1234. HRMS (EI): found, 393.1389. $C_{23}H_{20}FNO_4^+$ requires 393.1376. Anal.: found, C, 70.26; H, 5.21; N, 3.61. $C_{23}H_{20}FNO_4$ requires C, 70.22; H, 5.12; N, 3.56%.

(4*R*,5*R*)-4-(4-Benzyloxyphenyl)-3-(4-fluorophenyl)-5-[(*E*)-3-(4-fluorophenyl)-3-oxopropenyl]oxazolidin-2-one (14). To a solution of oxalyl chloride (508 mg, 4.00 mmol, 2.00 eq.) in CH_2Cl_2 (15.0 ml) was added, at −78 °C, dimethyl sulfoxide (0.355 ml, 5.00 mmol, 2.50 eq.). After 10 min at −78 °C, alcohol **12** (787 mg, 2.00 mmol, 1.00 eq.) in CH_2Cl_2 (15.0 ml) was added over a period of 5 min. After an additional 5 min at this temperature, triethylamine (1.14 ml, 8.00 mmol, 8.00 eq.) was added. After 5 min, 1-(4-fluorophenyl)-2-(triphenyl-λ^5-phosphanylidene)ethanone **13**[12] was added and the resulting suspension was warmed to 20 °C and stirred for an additional 30 min. To the solution was added saturated aqueous Na_2HCO_3 solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (2:1 to 1:1 gradient), to afford enone **14** as a colorless solid in 89% yield. Mp: 152 °C. $R_f = 0.56$ [hexane–EtOAc 3:2 (v/v)]. $\alpha_D^{25.6} = +100°$, (*c* 0.60 in $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.06–7.99 (2 H, m), 7.42–7.06 (14 H, m), 7.00–6.92 (4 H, m), 5.05–5.00 (4 H, m). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 187.1, 165.9 (d, $J = 254$ Hz), 159.8 (d, $J = 243$ Hz), 159.4, 154.8, 140.0, 136.2, 133.2, 132.3, 131.4 (d, $J = 9$ Hz), 128.6, 128.1, 128.1, 127.9, 127.4, 125.8, 123.5 (d, $J = 9$ Hz), 115.9 (d, $J = 24$ Hz), 115.8 (d, $J = 24$ Hz), 115.8, 80.5, 70.2, 66.0. IR (thin film): 1760, 1675, 1597, 1511, 1385, 1227. HRMS (MALDI): found, 534.1482. $C_{31}H_{23}F_2NO_4Na^+$ requires 534.1493. Anal.: found, C, 72.51; H, 4.78; N, 2.73. $C_{31}H_{23}F_2NO_4$ requires C, 72.79; H, 4.53; N, 2.74%.

(4*R*,5*R*)-3-(4-Fluorophenyl)-5-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)oxazolidin-2-one (16). To enone **14** (910 mg, 1.78 mmol, 1.00 eq.) in ethanol (15.0 ml) was added, at 23 °C, Pd on carbon (10%) (100 mg). The suspension was vigorously stirred under 1 atm of hydrogen gas for 3 h. The suspension was filtered through a pad of celite, eluting with EtOAc, concentrated and the residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (2:1 to 1:1 gradient). A portion of the resulting benzyl ether **15** (310 mg, 0.604 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 and cooled to −20 °C. (*R*)-3,3-Diphenyl-1-methyltetrahydro-3*H*-pyrrolo-oxazaborole-2-methyl oxazaborolidine [solution in toluene (0.5 M) 0.600 ml, 0.302 mmol, 0.50 eq.] was added, followed by borane–dimethylsulfide complex (0.080 ml, 0.905 mmol, 1.50 eq.). The solution was stirred at −20 °C for 2 h, then warmed to 0 °C and quenched with methanol. To the solution was added saturated aqueous Na_2HCO_3 solution and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (3:2 to 1:1 gradient). A portion of the resulting alcohol (53 mg, 0.10 mmol, 1.0 eq.) was dissolved in ethanol and Pd on carbon (10 mg) was added. The suspension was vigorously stirred under an atmosphere of hydrogen for 2.5 h. The suspension was filtered through a plug of celite eluting with EtOAc. The residue was purified by chromatography on silica gel eluting with hexane–EtOAc (1:1 to 1:2 gradient) to afford oxazolidinone **16** as a colorless solid in 57% yield from enone **14**. Mp: 98 °C. $R_f = 0.41$ [hexane–EtOAc 2:3 (v/v)]. $\alpha_D^{27.6} = -1°$, (*c* 0.84 in $CHCl_3$). ^{1}H-NMR (300 MHz, acetone-d_6): δ 7.47–7.35 (4 H, m), 7.29–7.24 (2 H, m), 7.09–6.97 (4 H, m), 6.85–6.79 (2 H, m), 5.15 (1 H, d, $J = 6.7$ Hz), 4.76–4.68 (1 H, m), 4.43–4.34 (2 H, m), 2.02–1.76 (4 H, m). ^{13}C-NMR (75 MHz, acetone-d_6): δ 162.0 (d, $J = 243$ Hz), 159.5 (d, $J = 242$ Hz), 157.9, 155.3, 142.2 (d, $J = 3$ Hz), 134.3 (d, $J = 2$ Hz), 129.1, 128.7, 127.8 (d, $J = 8$ Hz), 123.8 (d, $J = 9$ Hz), 116.1, 115.2 (d, $J = 23$ Hz), 114.9 (d, $J = 21$ Hz), 82.4, 72.3, 65.6, 35.0, 30.3. IR (thin film): 3316, 2925, 1726, 1603, 1511, 1224, 835. HRMS (MALDI): found, 448.1326. $C_{24}H_{21}F_2NO_4Na^+$ requires 448.1337. The diastereoselectivity of the CBS reduction was established by integration of the fluorine signals in the ^{19}F-NMR spectrum by comparison to a mixture of **16** and *(4*R*,5*R*)-3-(4-fluorophenyl)-5-[(*R*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)oxazolidin-2-one*, obtained by $NaBH_4$ reduction of the corresponding ketone.

Methanesulfonic acid 4-[(*E*)-3-oxopropenyl]phenyl ester (18). To a suspension of 4-hydroxycinnamic acid **17** (8.85 g, 53.5 mmol, 1.00 eq.) in methanol (70 ml) at 0 °C was added dropwise thionyl chloride (6.40 g, 53.5 mmol, 1.00 eq.). The ice bath was removed and the solution was stirred at 23 °C for 16 h. A stream of air was bubbled through the solution

for 2 h and the solution was concentrated *in vacuo* to afford an off-white solid. This solid was dissolved in THF (75 ml) and triethylamine (6.05 g, 60.0 mmol, 1.20 eq.) was added and the solution was cooled to 0 °C. To this solution was added methanesulfonyl chloride (6.30 g, 55.0 mmol, 1.10 eq.). The ice bath was removed and the suspension was stirred at 23 °C for 2 h. This suspension was poured onto saturated, aqueous NH_4Cl (25 ml), water (50 ml), and EtOAc (150 ml). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 30 ml). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was recrystallized from hexane–EtOAc (1:3, 200 ml) to afford a colorless solid. The solid was suspended in CH_2Cl_2 (100 ml) and the suspension was cooled to 0 °C. To this suspension was added, over a period of 15 min, DIBAl-H (15.3 g, 108 mmol, 2.15 eq.) and the solution was stirred at 0 °C for 15 min. To this solution was added saturated, aqueous NaK-tartrate solution (100 ml) followed by Et_2O (100 ml). This emulsion was vigorously stirred for 12 h. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow solid. This solid was dissolved in CH_2Cl_2 (200 ml) and MnO_2 (34.7 g, 400 mmol, 8.00 eq.) was added and the suspension was stirred for 6 h. The suspension was filtered over a plug of celite, eluting with CH_2Cl_2. The filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (1:1 to 2:3 gradient), to afford the target compound as a bright yellow solid in 76% yield (four steps). R_f = 0.35 [hexane–EtOAc 1:1 (v/v)]. Mp: 78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.69 (1 H, d, J = 7.5 Hz), 7.62–7.60 (2 H, m), 7.45 (1 H, d, J = 15.9 Hz), 7.36–7.33 (2 H, m), 6.67 (1 H, dd, J = 15.6 Hz, 7.8 Hz), 3.18 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.6, 151.0, 150.8, 133.5, 130.4, 129.7, 123.0, 38.0. IR (thin film) 3035, 2939, 2826, 2744, 1678, 1627, 1600, 1504, 1367, 1177, 1155, 1126, 974, 873, 775, 693, 526 (cm^{-1}). HRMS-EI (m/z): found, 226.0301. $C_{10}H_{10}O_4S$ requires 226.0300. Anal.: found, C, 53.14; H, 4.56. $C_{10}H_{10}O_4S$ requires C, 53.09; H, 4.45%.

Methanesulfonic acid 4-[(*E*)-(*S*)-3-hydroxyhexa-1,5-dienyl]-phenyl ester (20). To (+)-β-chloro diisopinocampheyl borane (8.24 g, 25.6 mmol, 1.25 eq.) in Et_2O (50 ml) at −78 °C was added allylmagnesium bromide (1.0 M in Et_2O, 24.7 ml, 24.7 mmol, 1.20 eq.). The emulsion was warmed to 23 °C and stirred at this temperature for 2 h to afford a grey slurry. This slurry was cooled to −78 °C and aldehyde **18** was added portionwise over a period of 15 min. The yellow slurry was stirred at −78 °C for 2 h. The reaction was quenched with methanol (1.0 ml), 10% aqueous NaOH (25 ml), and H_2O_2 (30%) (25 ml). The emulsion was vigorously stirred for 20 h. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (2:1 to 1:2 gradient), to afford the target compound as a colorless oil (77% yield, 93% ee). R_f = 0.35 [hexane–EtOAc 1:1 (v/v)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.38 (2 H, m), 7.24–7.20 (2 H, m), 6.59 (1 H, d, J = 16.2 Hz), 6.22 (1 H, dd, J = 15.9 Hz, 5.9 Hz), 5.91–5.77 (1 H, m), 5.22–5.15 (2 H, m), 4.39–4.32 (1 H, m), 3.13 (3 H, s), 2.44–2.36 (2 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 136.0, 133.7, 132.9, 128.5, 127.8, 122.1, 118.7, 71.3, 42.0, 37.4. IR (thin film) 3370, 3029, 1501, 1375, 1356, 1178, 1151, 969, 872, 695 (cm^{-1}). HRMS-EI (m/z): found, 268.0760. $C_{13}H_{16}O_4S$ requires 268.0769. Chiral HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH = 9:1, flow rate = 1.00 ml min^{-1}) t_R = 21.0 min (major), t_R = 18.9 min (minor).

Methanesulfonic acid 4-[(1*E*,5*E*)-(*S*)-3-hydroxy-6-phenylhexa-1,5-dienyl]phenyl ester (21). To $Pd(OAc)_2$ (82.0 mg, 0.365 mmol, 0.10 eq.) in acetonitrile (14.0 ml) at 25 °C was added triphenylphosphine (192 mg, 0.730 mmol, 0.20 eq.), triethylamine 140 (7 ml), iodobenzene (820 mg, 4.02 mmol, 1.10 eq.), and allyl alcohol **20** (980 mg, 3.65 mmol, 1.00 eq.). The suspension was heated at reflux for 4 h. The solution was concentrated *in vacuo* and the residue was dissolved in EtOAc (20 ml) and filtered over a plug of silica gel, eluting with EtOAc. The solution was concentrated *in vacuo* and the residue was recrystallized from toluene (4 ml). The crystals were filtered off, washed with toluene (3 ml), and dried *in vacuo* to afford the target compound as a beige solid (51% yield). R_f = 0.35 [hexane–EtOAc 1:1 (v/v)]. Mp (toluene) 134 °C. $\alpha_D^{29.0}$ −4° (*c* 0.85 in CH_2Cl_2). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.55–7.51 (2 H, m), 7.40–7.37 (2 H, m), 7.30–7.16 (5 H, m), 6.68 (1 H, dd, J = 15.9 Hz, 1.0 Hz), 6.53–6.33 (3 H, m), 4.46–4.38 (1 H, m), 4.10 (1 H, d, J = 4.7 Hz), 3.26 (3 H, s), 2.55–2.51 (2 H, m). ^{13}C NMR (75 MHz, acetone-d_6): δ 149.4, 138.4, 137.3, 135.3, 132.7, 129.1, 128.4, 128.2, 127.6, 127.5, 126.7, 123.0, 72.3, 42.3, 37.5. IR (thin film) 3370, 3029, 2935, 1501, 1375, 1356, 1197, 1178, 1151, 969, 872, 777, 748, 695 (cm^{-1}). HRMS-EI (m/z): 157.0344 (84.80%), 114.0275 (62.10%), 113.0204 (54.88%), 17.9497 (100%). Anal.: found, C, 66.41; H, 5.84. $C_{19}H_{20}O_4S$ requires C, 66.26; H, 5.85%.

Methanesulfonic acid 4-{(4*S*,5*S*)-3-(4-fluorophenyl)-5-[(*E*)-(*S*)-1-hydroxy-4-phenylbut-3-enyl]-4,5-dihydroisoxazol-4-yl}phenyl ester (23). To allyl alcohol **21** (600 mg, 1.74 mmol, 1.00 eq.) in CH_2Cl_2 (8.5 ml) at 0 °C was added isopropanol (345 mg, 5.75 mmol, 3.30 eq.) followed by ethylmagnesium bromide (3.0 M) (1.74 ml, 5.23 mmol, 3.00 eq.). The solution was allowed to warm to 23 °C. Separately, 4-fluorobenzaldehyde oxime **22** (303 mg, 2.18 mmol, 1.25 eq.) was dissolved in CH_2Cl_2 (8.5 ml). This solution was cooled to −78 °C and *tert*-butyl hypochloride (239 mg, 2.18 mmol, 1.25 eq.) was added. The ice bath was removed and the solution allowed to reach 23 °C. This solution was added over a period of 30 h by syringe pump to the solution containing allyl alcohol **23**. To the solution was added 10% aqueous HCl (10 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. The residue was purified by chromatography on silica gel, eluting with toluene–EtOAc (4:1 to 2:1 gradient), to afford the target compound as a colorless solid (36% yield, dr > 99:1) and starting material **21** (46%). R_f = 0.37 [hexane–EtOAc 1:1 (v/v)]. Mp 78 °C. $\alpha_D^{29.0}$ +147° (*c* 0.65 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.50 (2 H, m), 7.36–7.18 (9 H, m), 7.00–6.93 (2 H, m), 6.51 (1 H, d, J = 15.9 Hz), 6.24 (1 H, dd, J = 15.9 Hz, 6.2 Hz), 4.79 (1 H, d, J = 5.6 Hz), 4.51 (1 H, dd, J = 5.6 Hz, 3.4 Hz), 3.90–3.82 (1 H, m), 3.13 (3 H, s), 2.62–2.58 (2 H, m), 2.14 (1 H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2 (d, J = 242 Hz), 157.4, 148.4, 138.0, 136.8, 133.6, 129.2, 129.1, 128.5, 127.4, 126.1, 124.7, 123.0, 115.8 (d, J = 24 Hz), 91.9, 72.1, 55.9, 37.7, 37.3. IR (thin film) 3387, 3027, 2936, 1603, 1512, 1502, 1368, 1235, 1177, 1151, 969, 913, 871, 838, 772, 749 (cm^{-1}). HRMS-EI (m/z): found, 481.1355. $C_{26}H_{24}FNO_5$ requires 481.1359.

Methanesulfonic acid 4-{(4*S*,5*R*)-3-(4-fluorophenyl)-5-[(*E*)-3-(4-fluorophenyl)-3-oxopropenyl]-4,5-dihydroisoxazol-4-yl}phenyl ester (25). To homoallyl alcohol **23** (80.0 mg, 0.155 mmol, 1.00 eq.) in CH_2Cl_2 (1.5 ml) at 25 °C was added pyridine (24.6 mg, 0.310 mmol, 2.00 eq.) followed by methanesulfonyl chloride (26.7 mg, 0.233 mmol, 1.50 eq.). The solution was stirred at 23 °C for 16 h, then diluted with CH_2Cl_2 and water. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in EtOAc and passed over a small plug of silica gel, eluting with EtOAc. The solution was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.0 ml) and DBU (0.10 ml) was added. The solution was heated at reflux for 12 h, then cooled and diluted with saturated aqueous NH_4Cl and CH_2Cl_2. The phases were separated and the aqueous phase was extracted

with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in EtOAc and passed over a small plug of silica gel, eluting with EtOAc. The solution was concentrated *in vacuo*. The residue was dissolved in THF (2.6 ml) and water (2.6 ml) and $NaIO_4$ (222 mg, 1.04 mmol, 8.00 eq.) was added followed by $K_2OsO_4 \cdot 2H_2O$ (9.5 mg, 26 μmol, 0.20 eq.). The suspension was stirred for 14 h, then diluted with EtOAc and saturated aqueous Na_2SO_3. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was immediately dissolved in CH_2Cl_2 (2.0 ml) and 1-(4-fluorophenyl)-2-(triphenyl-λ_5-phosphanylidene)ethanone **13**[12] (200 mg, 0.516 mmol, 3.30 eq.) was added. The solution was stirred at 23 °C for 30 min and then concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (3:2 to 1:1 gradient), to afford the target compound as a colorless solid (30% yield, four steps). $R_f = 0.51$ [hexane–EtOAc 1:1 (v/v)]. Mp (MeOH) 64 °C. $a_D^{27.8}$ +255° (*c* 1.00 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03–7.99 (2 H, m), 7.58–7.54 (2 H, m), 7.35–6.96 (8 H, m), 5.20 (1 H, ddd, $J = 4.7$ Hz, 4.7 Hz, 1.6 Hz), 4.62 (1 H, d, $J = 5.0$ Hz), 3.16 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 165.7 (d, $J = 255$ Hz), 163.6 (d, $J = 251$ Hz), 156.6, 148.6, 142.6, 136.9, 133.4, 131.3 (d, $J = 9$ Hz), 129.2 (d, $J = 9$ Hz), 129.0, 125.2, 123.9, 123.2, 116.0 (d, $J = 22$ Hz), 115.8 (d, $J = 22$ Hz), 88.4, 59.4, 37.8. IR (thin film) 3028, 2938, 1672, 1626, 1598, 1511, 1369, 1235, 1153, 972, 872, 838 (cm^{-1}). HRMS-EI (*m*/*z*): found, 483.0948. $C_{25}H_{19}F_2NO_5S$ requires 483.0952.

Methanesulfonic acid 4-{(4*S*,5*R*)-3-(4-fluorophenyl)-5-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4,5-dihydroisoxazol-4-yl}-phenyl ester (26). To alkene **25** (6.7 mg, 14 μmol) in methanol (1.3 ml) was added Pd on carbon (10%) (2 mg). The atmosphere was changed to hydrogen (1 atm) and the suspension was stirred for 10 min at 23 °C. The suspension was diluted with EtOAc (15 ml) and filtered through a plug of silica gel, eluting with EtOAc. The filtrate was concentrated *in vacuo* and redissolved in CH_2Cl_2 (0.50 ml). The solution was cooled to −20 °C and (*R*)-3,3-diphenyl-1-methyltetrahydro-3*H*-pyrrolo-oxazaborole-2-methyl-oxazaborolidine (solution in toluene, 0.5 M) (10 μl, 5.0 μmol, 0.50 eq.) was added, followed by borane–dimethylsulfide complex (1.5 mg, 20 μmol, 2.0 eq.). The solution was stirred at −20 °C for 2 h, then warmed to 0 °C and stirred for an additional 1 h. To this solution was added methanol (50 μl) followed by saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (1:1 to 1:2 gradient), to afford the target compound as a colorless solid (75% yield, two steps). $R_f = 0.44$ [hexane–EtOAc 1:2 (v/v)]. Mp 68 °C. $a_D^{26.2}$ +135° (*c* 0.25 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55–7.51 (2 H, m), 7.33–7.24 (6 H, m), 7.06–6.95 (4 H, m), 4.75–4.71 (1 H, m), 4.52–4.46 (1 H, m), 4.36 (1 H, d, $J = 5.0$ Hz), 3.14 (3 H, s), 1.99–1.82 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8 (d, $J = 250$ Hz), 162.5 (d, $J = 245$ Hz), 157.1, 148.7, 140.2, 138.4, 129.3 (d, $J = 9$ Hz), 129.2, 127.6 (d, $J = 8$ Hz), 125.0, 123.3, 116.2 (d, $J = 22$ Hz), 115.7 (d, $J = 22$ Hz), 90.7, 73.7, 59.3, 37.8, 35.1, 31.6. IR (thin film) 3388, 2930, 1604, 1151, 1368, 1222, 1151, 871, 837 (cm^{-1}). HRMS-EI (*m*/*z*): found, 487.1256. $C_{25}H_{23}F_2NO_5S$ requires 487.1265.

4-Benzyloxy-1-(4-fluorophenyl)but-2-yn-1-ol (28). A 50 ml Schlenk flask was charged with $Zn(OTf)_2$ (12.647 g, 34.79 mmol) and heated to 120 °C under high-vacuum (0.2 Torr) for 3.5 h. After cooling, (+)-*N*-methylephedrine (6.595 g, 36.79 mmol) was added and the flask was purged with Ar for 15 min. Anhydrous toluene (14 ml) followed by Et_3N (3.874 g, 38.3 mmol) were added and, after 3 h stirring, benzyl propargyl ether[31] (5.556 g, 38.00 mmol) was added in one portion. After 20 min stirring, the mixture was transferred to a pre-cooled acetone bath (8 °C), stirred for 5 min and *p*-FC_6H_4CHO (3.632 g, 29.26 mmol) was added in one portion. After 15 h stirring at 9–12 °C, the suspension was diluted with EtOAc (125 ml) and washed with sat. aq. NH_4Cl (2 × 30 ml) and brine (30 ml). The organic layer was evaporated on celite and purified by dry column vacuum chromatography (5.4 × 5.5 cm) on silica gel, eluting with a gradient of 0–50% EtOAc in hexane (v/v), to give alcohol **28** (5.896 g, 75%) as a light yellow oil. Enantiomeric excess as determined by HPLC analysis: 96% ee; t_R 20 min (*R*-**28**), 28 min (*S*-**28**) (Chiracel OD-H 25 cm, 6% *i*PrOH in hexane, flow 1.0 ml min^{-1}, 254 nm). R_f [EtOAc–hexane 1:3 (v/v)] 0.28. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.50 (2 H, dd, $J = 5.6$, 8.7 Hz), 7.38–7.32 (5 H, m), 7.06 (2 H, t, $J = 8.7$ Hz), 5.48 (1 H, s), 4.60 (2 H, s), 4.26 (2 H, s), 2.84 (1 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.01, 160.75, 136.95, 136.04 (C), 128.30, 128.21, 127.92, 127.81, 115.43, 115.13 (CH), 86.13, 82.62 (C), 71.74 (CH_2), 63.74 (CH), 57.35 (CH_2). ^{19}F-NMR (282 MHz, $CDCl_3$): δ −113.28 (1 F, septet, $J = 4.3$ Hz). IR (cm^{-1}): 3390, 3066, 3032, 2859, 1604, 1508, 1455, 1413, 1386, 1355, 1224, 1158, 1121, 1096, 1072, 1028, 1014, 842, 772, 744, 699, 592, 561, 498. MALDI-MS: found, 293.0947 $[MNa]^+$. $C_{17}H_{15}FO_2Na$ requires 293.0954. Anal.: found, C, 75.39; H, 5.62. $C_{17}H_{15}FO_2$ requires C, 75.54; H, 5.59%.

4-(*tert*-Butyldimethylsilanyloxy)-4-(4-fluorophenyl)butan-1-ol (29). Alcohol **28** (4.108 g, 15.20 mmol) was dissolved in anhydrous DMF (50 ml). Imidazole (2.123 g, 31.1 mmol) and TBDMSCl (3.590 mg, 23.8 mmol) were added sequentially and the solution was stirred for 3.5 h, followed by addition of 50% sat. aq. $NaHCO_3$ (150 ml). After extraction with ether (4 × 50 ml), the combined organic phase was washed successively with sat. aq. $NaHCO_3$ (50 ml) and H_2O (50 ml), evaporated and dried shortly under high vacuum. The residue was dissolved in EtOH (40 ml). Na_2CO_3 (3.229 g, 30.5 mmol) and Pd/C [10% (w/w), 223 mg] were added and the suspension was evacuated 4 times with H_2 and stirred under an H_2 atmosphere for 19 h. The suspension was diluted with 10% EtOAc–hexane [250 ml (v/v)] and filtered through a short plug of silica gel [2 × 25 ml 20% EtOAc–hexane washings (v/v)], evaporated and dried shortly under high vacuum. The residue was dissolved in EtOH (40 ml). Pd/C [10% (w/w), 142 mg] was added and the suspension was evacuated 4 times with H_2 and stirred under an H_2 atmosphere for 1 h. Additional Pd/C [10% (w/w), 190 mg] was added and the suspension was evacuated 4 times with H_2 and stirred under an H_2 atmosphere for 1.25 h. The suspension was evaporated on celite and purified by dry column vacuum chromatography (5.2 × 5.5 cm) on silica gel, eluting with a gradient of 0–25% EtOAc in hexane (v/v), to give alcohol **29** (3.643 g, 80%) as a light yellow oil. R_f [EtOAc–hexane 1:3 (v/v)] 0.37. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.24 (2 H, dd, $J = 5.6$, 8.7 Hz), 6.97 (2 H, t, $J = 8.7$ Hz), 4.69 (1 H, dt, $J = 1.2$, 5.0 Hz), 3.59 (2 H, dt, $J = 1.2$, 6.2 Hz), 2.18 (1 H, bs), 1.77–1.45 (4 H, m), 0.87 (9 H, s), 0.02 (3 H, s), −0.15 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 163.37, 160.13, 140.96, 140.91 (C), 127.32, 127.23, 114.94, 114.64, 74.16 (CH), 62.76, 37.19, 28.47 (CH_2), 25.76 (CH_3), 18.15 (C), −4.71, −5.05 (CH_3). IR (cm^{-1}): 3339, 2954, 2930, 2885, 2858, 1606, 1510, 1472, 1463, 1362, 1252, 1223, 1156, 1092, 1060, 984, 890, 836, 776, 668, 560. MALDI-MS: found, 321.1643 $[MNa]^+$. $C_{16}H_{27}FO_2SiNa$ requires 321.1662. Anal.: found, C, 64.36; H, 9.15. $C_{16}H_{27}FO_2Si$ requires C, 64.39; H, 9.12%.

Olefin (31). Alcohol **29** was dissolved in CH_2Cl_2 (50 ml). Dess–Martin periodinane (5.658 g, 13.3 mmol) was added and the milky solution was stirred at room temperature for 1.5 h. Sat. aq. Na_2SO_3 (100 ml) was added and the layers were swirled until the solid had dissolved. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 ml). The combined organic phase was evaporated on celite and purified by

dry column vacuum chromatography (5.1 × 5.5 cm) on silica gel, eluting with a gradient of 0–10% EtOAc in hexane (v/v), to give the intermediary aldehyde (2.093 g, 80%) as a light yellow oil. R_f [EtOAc–hexane 1:3 (v/v)] 0.63. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.73 (1 H, d, J = 1.5 Hz), 7.25 (2 H, dd, J = 5.6, 8.7 Hz), 6.99 (2 H, t, J = 9.0 Hz), 4.74 (1 H, dt, J = 5.0, 6.8 Hz), 2.52–2.35 (2 H, m), 2.06–1.88 (2 H, m), 0.88 (9 H, s), 0.02 (3 H, s), −0.16 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 201.91 (CH), 163.35, 160.10, 140.13 (C), 127.20, 127.10, 115.04, 114.75, 73.03 (CH), 39.69, 33.11 (CH_2), 25.85 (CH_3), 18.21 (C), −4.61, −4.95 (CH_3). IR (cm^{-1}): 2955, 2938, 2888, 2858, 2720, 1727, 1606, 1509, 1472, 1464, 1412, 1390, 1362, 1254, 1223, 1156, 1090, 1014, 837, 776, 670, 540. Anal.: found, C, 64.95; H, 8.36. $C_{16}H_{25}FO_2Si$ requires C, 64.82; H, 8.50%. LiCl (140.8 mg, 3.32 mmol) was heated shortly with a heat gun under high-vacuum and, after cooling, anhydrous CH_3CN (5 ml), phosphonate **30**[21] (660 mg, 1.68 mmol) and DBU (221 mg, 1.45 mmol) were added sequentially. After 3 min stirring, the aldehyde (407.3 mg, 1.37 mmol) was added and the suspension was stirred at room temperature for 2.5 h, followed by addition of 50% sat. aq. $NaHCO_3$ (60 ml). After extraction with ether–hexane [1:1 (v/v), 4 × 25 ml], the combined organic phase was washed with brine (25 ml), evaporated on celite and purified by dry column vacuum chromatography (4.6 × 3.3 cm) on silica gel, eluting with a gradient of 0–20% EtOAc in hexane (v/v), to give olefin **31** (520.7 mg, 71%) as a colourless oil. R_f [EtOAc–hexane 1:3 (v/v)] 0.43. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.25 (2 H, dd, J = 5.6, 8.7 Hz), 7.10–6.94 (3 H, m), 6.53 (1 H, d, J = 14.9 Hz), 4.65 (1 H, dd, J = 5.0, 7.5 Hz), 3.91 (1 H, dd, J = 5.6, 6.8 Hz), 3.50 (1 H, d, J = 13.7 Hz), 3.42 (1 H, d, J = 13.7 Hz), 2.30–2.23 (2 H, m), 2.09–2.02 (2 H, m), 1.90–1.70 (5 H, m), 1.43–1.30 (2 H, m), 1.15 (3 H, s), 0.95 (3 H, s), 0.85 (9 H, s), 0.01 (3 H, s), −0.20 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 163.88, 163.39, 160.14, 150.06, 140.63 (C), 127.35, 127.26, 120.91, 114.98, 114.69, 73.24, 64.99 (CH), 53.04 (CH_2), 48.33, 47.67 (C), 44.58 (CH), 38.61, 38.39, 32.71, 28.32, 26.40 (CH_2), 25.72, 20.72, 19.78 (CH_3), 18.04 (C), −4.74, −5.10 (CH_3). IR (cm^{-1}): 2956, 2885, 2859, 1684, 1640, 1605, 1509, 1472, 1414, 1374, 1332, 1295, 1250, 1220, 1165, 1134, 1083, 1049, 995, 970, 860, 836, 774, 544. MALDI-MS: found, 558.2479 [MNa]$^+$. $C_{28}H_{42}FNO_4SSiNa$ requires 558.2486. Anal.: found, C, 62.84; H, 7.78; N, 2.58. $C_{28}H_{42}FNO_4SSi$ requires C, 62.77; H, 7.90; N, 2.61%.

Pyrazoline (32). Olefin **31** was dissolved in anhydrous toluene (2.0 ml). $TMSCHN_2$ (2 M in hexanes, 1.50 ml, 3.0 mmol) was added and the solution was stirred at room temperature for 64 h. After evaporation, the residue was dissolved in CH_2Cl_2 (10 ml). TFA (202 mg, 1.77 mmol) was added and the solution was stirred for 20 min. Sat. aq. $NaHCO_3$ (1.5 ml) was added and the mixture was evaporated on celite and purified by dry column vacuum chromatography (4.5 × 3.3 cm) on silica gel, eluting with a gradient of 0–40% EtOAc in hexane (v/v), to give diastereomeric pyrazolines **32** (468 mg, 84%) and **32A** (54.3 mg, 10%) as light yellow foams. **32**: R_f [EtOAc–hexane 1:3 (v/v)] 0.25. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.21 (2 H, dd, J = 5.6, 8.7 Hz), 6.95 (2 H, t, J = 8.7 Hz), 6.60 (1 H, s), 6.16 (1 H, d, J = 5.6 Hz), 4.65 (1 H, t, J = 5.0 Hz), 4.33 (1 H, dd, J = 5.9, 9.7 Hz), 3.87 (1 H, dd, J = 5.0, 7.5 Hz), 3.67–3.62 (1 H, bs), 3.53 (1 H, d, J = 13.7 Hz), 3.44 (1 H, d, J = 13.7 Hz), 2.15–1.99 (2 H, m), 1.91–1.86 (3 H, m), 1.66–1.51 (3 H, m), 1.47–1.21 (3 H, m), 1.14 (3 H, s), 0.95 (3 H, s), 0.86 (9 H, s), 0.01 (3 H, s), −0.17 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.96, 163.12, 159.89 (C), 146.91 (CH), 140.52, 140.49 (C), 127.15, 127.05, 114.83, 114.54, 73.37, 66.44, 65.09 (CH), 52.81 (CH_2), 48.91 (C), 48.04 (CH), 47.79 (C), 44.33 (CH), 37.98, 37.79, 32.55, 26.76, 26.45 (CH_2), 25.82, 20.68, 19.84 (CH_3), 18.16 (C), −4.64, −4.90 (CH_3). IR (cm^{-1}): 3360, 2955, 2857, 1700, 1604, 1509, 1472, 1390, 1329, 1273, 1250, 1236, 1221, 1166, 1134, 1086, 1066, 994, 939, 836, 775, 694, 542. MALDI-MS: found, 600.2691 [MNa]$^+$. $C_{29}H_{44}FN_3O_4SSiNa$ requires 600.2704. Anal.: found, C, 60.25; H, 7.83; N, 7.16. $C_{29}H_{44}FN_3O_4SSi$ requires C, 60.28; H, 7.67; N, 7.27%. **32A**: R_f [EtOAc–hexane 1:3 (v/v)] 0.11. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.21 (2 H, dd, J = 5.3, 8.4 Hz), 6.96 (2 H, t, J = 8.7 Hz), 6.62 (1 H, s), 6.14 (1 H, d, J = 3.1 Hz), 4.59 (1 H, dd, J = 5.0, 6.8 Hz), 4.39 (1 H, dd, J = 3.1, 7.5 Hz), 3.90 (1 H, dd, J = 5.0, 7.5 Hz), 3.52 (1 H, d, J = 13.7 Hz), 3.45 (1 H, d, J = 13.7 Hz), 3.37 (1 H, dd, J = 6.2, 13.7 Hz), 2.08–1.13 (2 H, m), 1.00 (3 H, s), 0.96 (3 H, s), 0.85 (9 H, s), 0.00 (3 H, s), −0.19 (3 H, s). MALDI-MS: found, 600.2691 [MNa]$^+$. $C_{29}H_{44}FN_3O_4SSiNa$ requires 600.2704.

(p-FC_6H_4)$_3$Bi. p-FC_6H_4Br (5.446 g, 31.1 mmol) dissolved in anhydrous ether (100 ml) was added to Mg turnings (844 mg, 34.7 mmol) and I_2 (28 mg, 0.11 mmol) and the suspension was refluxed for 1 h 20 min and cooled to 0 °C. $BiCl_3$ (3.931 g, 12.5 mmol) was added and, after 15 min stirring at 0 °C, the suspension was refluxed for 4 h. The suspension was cooled, H_2O (3 ml) was added and the suspension was evaporated on celite and purified by dry column vacuum chromatography (4.8 × 5.5 cm) on silica gel, eluting with a gradient of 0–14% EtOAc in hexane (v/v), to give (p-FC_6H_4)$_3$Bi (2.862 g, 56%) as a light yellow solid. R_f [EtOAc–hexane 1:9 (v/v)] 0.42. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (2 H, dd, J = 6.2, 8.1 Hz), 7.13 (2 H, t, J = 9.0 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.19, 160.92, 149.36 (C), 139.02, 138.92, 117.96, 117.70 (CH). ^{19}F (282 MHz, $CDCl_3$): δ −111.97 (1 F, m).

***N*-Aryl pyrazoline (33).** Pyrazoline **32** (409.8 mg, 0.709 mmol), $Cu(OAc)_2$ (296 mg, 1.63 mmol) and (p-FC_6H_4)$_3$Bi (950 mg, 1.92 mmol) were dissolved in anhydrous CH_2Cl_2 (5 ml). Anhydrous Et_3N (165 mg, 1.63 mmol) was added and the dark green suspension was stirred at room temperature for 12.5 h. After evaporation on celite the residue was purified by dry column vacuum chromatography (4.5 × 3.3 cm) on silica gel, eluting with a gradient of 0–30% EtOAc in hexane (v/v), to give pyrazoline **33** (320.8 mg, 63%) as a light yellow foam. R_f [EtOAc–hexane 1:3 (v/v)] 0.33. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.24 (2 H, dd, J = 5.3, 8.4 Hz), 7.01–6.94 (4 H, m), 6.89 (2 H, t, J = 8.7 Hz), 6.68 (1 H, d, J = 1.9 Hz), 5.05 (1 H, d, J = 3.7 Hz), 4.62 (1 H, t, J = 5.3 Hz), 3.85 (1 H, dd, J = 4.4, 7.5 Hz), 3.59 (1 H, d, J = 14.3 Hz), 3.58 (1 H, d, J = 14.3 Hz), 3.41–3.35 (1 H, m), 1.98–1.78 (5 H, m), 1.72–1.60 (3 H, m), 1.41–1.23 (3 H, m), 1.21 (3 H, s), 0.98 (3 H, s), 0.88 (9 H, s), 0.04 (3 H, s), −0.17 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 169.54, 163.38, 160.14, 158.46, 155.30 (C), 142.10 (CH), 140.75 (C), 127.32, 127.22, 115.71, 115.40, 114.96, 114.67, 114.22, 114.12, 73.99, 65.48, 64.93 (CH), 53.02 (CH, CH_2), 49.05, 47.77 (C), 44.31 (CH), 37.98, 36.95, 32.76, 27.79, 26.25 (CH_2), 25.75, 20.37, 19.77 (CH_3), 18.07 (C), −4.77, −5.01 (CH_3). ^{19}F (282 MHz, $CDCl_3$): δ −116.27 (1 F, m), −125.73 (1 F, septet, J = 4.3 Hz). IR (cm^{-1}): 2957, 2857, 1699, 1606, 1510, 1471, 1413, 1362, 1334, 1268, 1250, 1221, 1166, 1136, 1113, 1088, 1063, 987, 836, 776, 759, 538. MALDI-MS: found, 540.2127 [MH − TBDMSOH]$^+$. $C_{29}H_{32}F_2N_3O_3S$ requires 540.2132; found, 694.2909 [MNa]$^+$. $C_{35}H_{47}F_2N_3O_4SSiNa$ requires 694.2922. Anal.: found, C, 62.37; H, 7.05; N, 6.03. $C_{35}H_{47}F_2N_3O_4SSi$ requires C, 62.56; H, 7.05; N, 6.25%.

Carboxylic acid (34). Pyrazoline **33** (228.5 mg, 0.340 mmol) was dissolved in anhydrous MeOH (5 ml), glycine (226 mg, 3.01 mmol) and KCN (305 mg, 4.68 mmol) were added and the suspension was stirred at 50 °C in a sealed flask for 19 h. After cooling, the suspension was evaporated on celite and purified twice by dry column vacuum chromatography (4.8 × 2.0 cm) on silica gel, eluting first with a gradient of 0–60% MeOH in EtOAc and second with 0–20% MeOH in CH_2Cl_2 (v/v), to give carboxylic acid **34** (135.6 mg, 75%) as a light yellow oil. R_f [MeOH–EtOAc 1:3 (v/v)] 0.38. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33 (2 H, dd, J = 5.6, 8.7 Hz), 7.01–6.93 (6 H, m), 6.80 (1 H, s), 4.78–4.73 (1 H, m), 3.95–3.78 (3 H, m), 3.40–3.32 (1 H, m), 1.88–1.65 (4 H, m), 0.86 (9 H, s), 0.04 (3 H, s), −0.17 (3 H, s).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 174.55, 165.01, 161.79, 160.58 (C), 145.83 (CH), 144.14, 144.11, 142.57, 142.53 (C), 128.94, 128.82, 116.58, 116.34, 116.24, 115.95, 115.66, 74.91, 70.88, 55.50 (CH), 42.25, 38.40, 30.07 (CH_2), 26.38 (CH_3), 19.06 (C), −4.40, −4.71 (CH_3). ^{19}F (282 MHz, $CDCl_3$): δ −116.75 (1 F, m), −125.36 (1 F, septet, J = 4.3 Hz). IR (cm^{-1}): 3325, 2954, 2930, 2858, 1737, 1671, 1606, 1508, 1472, 1410, 1361, 1252, 1224, 1157, 1088, 1006, 984, 835, 776, 760, 668, 608, 554. MALDI-MS: 576.2 $[M - H + 2Na]^+$.

2-{2-(4-Fluorophenyl)-4-[3-(4-fluorophenyl)-3-hydroxypropyl]-3,4-dihydro-2*H*-pyrazol-3-yl}-4*H*-oxazol-5-one (36). Carboxylic acid **34** (22.0 mg, 0.041 mmol) was dissolved in anhydrous CH_2Cl_2 (5 ml), *N*-cyclohexyl-*N*′-2-(*N*-methylmorpholinio)ethylcarbodiimide *p*-toluenesulfonate **35** (19.0 mg, 0.045 mmol) was added and the mixture was stirred at reflux for 2 h. The solution was cooled, diluted with CH_2Cl_2 (10 ml), washed with sat. aq. $NaHCO_3$ (10 ml) and H_2O (10 ml), dried (Na_2SO_4), filtered through a short plug of silica gel [15 ml EtOAc–hexane washings, 1:1 (v/v)] and evaporated to give the oxazolone **36** (8.3 mg, 39%) as a colourless oil. R_f [EtOAc–hexane 1:1 (v/v)] 0.58. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.23 (2 H, dd, J = 5.6, 8.7 Hz), 7.06–6.93 (6 H, m), 6.73 (1 H, s), 4.68–4.64 (1 H, m), 4.39 (1 H, d, J = 6.2 Hz), 4.21 (2 H, s), 3.47–3.39 (1 H, m), 1.80–1.57 (4 H, m), 0.86 (9 H, s), 0.00 (3 H, s), −0.17 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 174.69, 165.28, 163.58, 160.32, 159.11, 155.94, 142.46, 141.30, 140.28, 127.29, 127.18, 115.89, 115.60, 115.26, 114.97, 114.87, 114.76, 73.61, 63.26, 54.23, 52.64, 37.50, 29.70, 27.96, 25.78, 18.14, −4.63, −5.0. ^{19}F (282 MHz, $CDCl_3$): δ −115.81 (1 F, m), −124.45 (1 F, septet, J = 4.3 Hz). IR (cm^{-1}): 2930, 2858, 1835, 1674, 1606, 1509, 1472, 1362, 1252, 1224, 1157, 1088, 1021, 905, 836, 777, 736, 608, 553. MALDI-MS: 429.2 $[M - C_3H_2NO_2]^+$.

Benzenesulfonic acid 2-{2-(4-fluorophenyl)-4-[3-(4-fluorophenyl)-3-hydroxypropyl]-3,4-dihydro-2*H*-pyrazol-3-yl}oxazol-5-yl ester (37). Oxazolone **36** (24 mg, 0.047 mmol) was dissolved in anhydrous CH_2Cl_2 (5 ml), Et_3N (0.2 ml, 1.4 mmol) followed by $PhSO_2Cl$ (0.1 ml, 0.78 mmol) were added and the mixture was stirred at room temperature for 22 h. Sat. aq. $NaHCO_3$ (1 ml) was added and the mixture was evaporated on celite and purified by dry column vacuum chromatography (4.5 × 2.0 cm) on silica gel, eluting with a gradient of 0–60% EtOAc in hexane (v/v), to give the intermediary oxazole (12.2 mg, 40%) as a yellow oil. R_f [EtOAc–hexane 1:3 (v/v)] 0.29. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.76 (2 H, d, J = 8.1 Hz), 7.63 (1 H, tt, J = 1.2, 7.5 Hz), 7.42 (2 H, dd, J = 7.5, 8.7 Hz), 7.21 (2 H, dd, J = 5.3, 8.4 Hz), 6.99 (2 H, t, J = 8.7 Hz), 6.91 (4 H, d, J = 6.2 Hz), 6.66 (1 H, d, J = 1.2 Hz), 6.52 (1 H, s), 4.64–4.60 (1 H, m), 4.51 (1 H, d, J = 7.5 Hz), 3.35–3.30 (1 H, m), 1.74–1.53 (4 H, m), 0.85 (9 H, s), 0.01 (3 H, s), −0.18 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 157.31, 142.38, 135.27, 129.41, 128.62, 127.29, 127.18, 115.73, 115.44, 115.21, 114.90, 114.81, 112.25, 73.56, 63.05, 53.78, 27.75, 25.78, 18.14, −4.65, −5.02. ^{19}F (282 MHz, CD_3OD): δ −115.91 (1 F, m), −124.69 (1 F, p, J = 6.4 Hz). IR (cm^{-1}): 2930, 2857, 1606, 1509, 1451, 1398, 1224, 1193, 1157, 1090, 999, 914, 829, 777, 752, 685, 618, 578, 554. This oxazole (12.0 mg, 0.018 mmol) was dissolved in anhydrous THF (1.0 ml, teflon bottle), anhydrous pyridine (0.20 ml) followed by HF·pyridine complex (0.20 ml) were added and the solution was stirred at room temperature for 10 h, diluted with ether (10 ml) and washed with sat. aq. $NaHCO_3$ (2 × 5 ml). The organic layer was evaporated on celite and purified by dry column vacuum chromatography (3.2 × 2.0 cm) on silica gel, eluting with a gradient of 0–100% EtOAc in hexane (v/v), to give oxazole **37** (3.9 mg, 39%) as a light brown oil. R_f [EtOAc–hexane 1:1 (v/v)] 0.19. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.76 (2 H, d, J = 7.5 Hz), 7.64 (1 H, t, J = 7.5 Hz), 7.44 (2 H, t, J = 7.8 Hz), 7.34–7.25 (2 H, m), 7.03 (2 H, t, J = 8.4 Hz), 6.92 (4 H, d, J = 6.2 Hz), 6.69 (1 H, d, J = 1.9 Hz), 6.52 (1 H, s), 4.66–4.62 (1 H, m), 4.57 (1 H, d, J = 7.5 Hz), 3.42–3.36 (1 H, m), 1.90–1.53 (4 H, m). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 142.30, 139.76, 135.32, 129.44, 128.62, 127.39, 115.76, 115.65, 115.45, 115.37, 114.92, 114.82, 112.28, 73.17, 63.09, 53.68, 35.69, 28.19. ^{19}F (282 MHz, CD_3OD): δ −114.03 (1 F, m), −123.73 (1 F, p, J = 6.4 Hz). IR (cm^{-1}): 3300, 2926, 1606, 1509, 1450, 1396, 1224, 1192, 1090, 998, 828, 736, 685, 618, 578.

4-{2-(4-Fluorophenyl)-4-[3-(4-fluorophenyl)-3-hydroxypropyl]-3,4-dihydro-2*H*-pyrazol-3-ylmethoxy}phenol (38). Pyrazoline **33** (101.5 mg, 0.151 mmol) was dissolved in anhydrous THF (5 ml) −78 °C, $LiAlH_4$ (33 mg, 0.87 mmol) was added and the suspension was stirred at −78 °C for 4.5 h. Sat. aq. $NaHCO_3$ (1 ml) was added and the mixture was evaporated on celite and purified twice by dry column vacuum chromatography (4.6 × 2.0 cm) on silica gel, eluting with a gradient of 0–30% EtOAc in hexane (v/v), to give the intermediary alcohol (52.7 mg, 76%) as a light yellow oil. R_f [EtOAc–hexane 1:3 (v/v)] 0.23. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.23 (2 H, dd, J = 5.6, 8.7 Hz), 7.04–6.92 (6 H, m), 6.67 (1 H, d, J = 1.2 Hz), 4.64 (1 H, t, J = 5.9 Hz), 3.81 (1 H, dd, J = 4.0, 11.5 Hz), 3.68–3.58 (2 H, m), 3.12 (1 H, dd, J = 6.2, 6.8 Hz), 1.86 (1 H, bs), 1.77–1.67 (2 H, m), 1.58–1.48 (2 H, m), 0.86 (9 H, s), 0.00 (3 H, s), −0.17 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 163.47, 160.22, 158.83, 155.68 (C), 144.84 (CH), 142.35, 140.67, 140.62 (C), 127.26, 127.16, 115.75, 115.46, 115.11, 115.06, 114.96, 114.83, 73.76, 66.81 (CH), 62.37 (CH_2), 50.05 (CH), 37.72, 28.28 (CH_2), 25.75 (CH_3), 18.12 (C), −4.67, −5.01 (CH_3). ^{19}F (282 MHz, $CDCl_3$): δ −115.25 (1 F, septet, J = 4.3 Hz), −124.25 (1 F, septet, J = 4.3 Hz). IR (cm^{-1}): 3401, 2953, 2930, 2885, 2858, 1672, 1605, 1509, 1472, 1463, 1416, 1362, 1296, 1252, 1223, 1156, 1086, 1006, 979, 938, 861, 835, 776, 666, 608, 554. MALDI-MS: found, 429.2175 $[M - CH_2OH]$. $C_{24}H_{31}F_2N_2O_2Si$ requires 429.2174. Found, 459.2279 $[M - H]^+$. $C_{25}H_{33}F_2N_2O_2Si$ requires 459.2279. This alcohol (70.8 mg, 0.154 mmol) was dissolved in anhydrous CH_2Cl_2 (5 ml), anhydrous Et_3N (0.50 ml, 3.9 mmol), DMAP (6.8 mg, 0.056 mmol) and TsCl (69 mg, 0.36 mmol) were added and the solution was stirred at room temperature for 12.5 h, evaporated on celite and purified by dry column vacuum chromatography (4.4 × 2.0 cm) on silica gel, eluting with a gradient of 0–20% EtOAc in hexane (v/v), to give the intermediary tosylate (78.4 mg, 83%) as a colourless oil. R_f [EtOAc–hexane 1:3 (v/v)] 0.44. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.68 (2 H, d, J = 8.7 Hz), 7.25 (4 H, t, J = 8.1 Hz), 6.99 (2 H, t, J = 8.7 Hz), 6.92–6.80 (4 H, m), 6.64 (1 H, d, J = 1.2 Hz), 4.65 (1 H, dd, J = 4.4, 6.8 Hz), 4.12 (1 H, dd, J = 2.5, 9.3 Hz), 3.92–3.81 (2 H, m), 3.08–3.01 (1 H, m), 2.42 (3 H, s), 1.80–1.43 (4 H, m), 0.87 (9 H, s), 0.01 (3 H, s), −0.17 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 163.49, 160.24, 158.59, 155.43, 145.16 (C), 143.40 (CH), 140.54, 132.21 (C), 129.84, 127.82, 127.32, 127.21, 115.79, 115.48, 115.12, 114.83, 114.31, 114.22, 73.50 (CH), 67.45 (CH_2), 62.42, 50.74 (CH), 37.35, 27.87 (CH_2), 25.77, 21.59 (CH_3), 18.10 (C), −4.67, −5.01 (CH_3). ^{19}F (282 MHz, $CDCl_3$): δ −116.01 (1 F, m), −125.40 (1 F, septet, J = 4.3 Hz). IR (cm^{-1}): 3055, 3034, 2953, 2930, 2886, 2857, 1603, 1509, 1472, 1463, 1365, 1307, 1294, 1252, 1223, 1190, 1177, 1156, 1096, 979, 862, 835, 775, 666, 608, 555. MALDI-MS: found, 483.1559 $[MH - TBDMSOH]^+$. $C_{26}H_{25}F_2N_2O_3S$ requires 483.1554. Found, 637.2330 $[MNa]^+$. $C_{32}H_{40}F_2N_2O_4SSiNa$ requires 637.2344. This tosylate was dissolved in anhydrous DMF (2.5 ml), hydroquinone (263 mg, 2.39 mmol) and Cs_2CO_3 (102.1 mg, 0.313 mmol) were added and the suspension was stirred at 80 °C for 12 h. EtOAc (30 ml) was added and the organic phase was washed with sat. aq. $NaHCO_3$ (10 ml) and H_2O (10 ml), evaporated on celite and purified by dry column vacuum chromatography (4.5 × 2.0 cm) on silica gel, eluting with a gradient of 0–30% EtOAc in hexane (v/v), to give the intermediary phenol (70.9 mg, 86%) as a colourless oil. R_f [EtOAc–hexane 1:3 (v/v)] 0.33. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.24 (2 H, dd, J = 5.3, 8.4 Hz), 7.06–6.93 (6 H, m), 6.75–6.68 (5 H, m), 4.67 (1 H, dd, J = 4.4, 6.8 Hz), 4.10–3.98 (2 H, m), 3.74 (1 H, dd, J = 1.2, 7.5 Hz),

3.17–3.11 (1 H, m), 1.86–1.54 (4 H, m), 0.88 (9 H, s), 0.02 (3 H, s), −0.15 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 163.32, 160.08, 158.48, 155.35, 152.31, 149.86 (C), 143.85 (CH), 141.52, 141.49, 140.63 (C), 127.23, 127.12, 115.99, 115.73, 115.51, 115.44, 115.04, 114.75, 114.67, 114.57, 73.78 (CH), 67.79 (CH_2), 63.88, 51.51 (CH), 37.77, 28.38 (CH_2), 25.89 (CH_3), 18.25 (C), −4.46, −4.80 (CH_3). ^{19}F (282 MHz, $CDCl_3$): δ −115.31 (1 F, m), −124.71 (1 F, septet, J = 4.3 Hz). IR (cm^{-1}): 3350, 3056, 2953, 2930, 2885, 2858, 1605, 1509, 1472, 1462, 1362, 1297, 1226, 1156, 1100, 1086, 1050, 1006, 939, 828, 776, 667, 609, 553, 518. MALDI-MS: found, 421.1720 $[MH - TBDMSOH]^+$. $C_{25}H_{23}F_2N_2O_2$ requires 421.1728. Found, 553.2677 $[MH]^+$. $C_{31}H_{39}F_2N_2O_3Si$ requires 553.2698. Found, 575.2505 $[MNa]^+$. $C_{31}H_{38}F_2N_2O_3SiNa$ requires 575.2517. This phenol (18.4 mg, 0.0333 mmol) was dissolved in anhydrous THF (1.0 ml, teflon bottle) at 0 °C, anhydrous pyridine (0.20 ml) followed by HF·pyridine complex (0.20 ml) were added and the solution was allowed to warm to room temperature over several hours and stirred at room temperature for 22 h. Ether (20 ml) was added and the solution was washed with sat. aq. $NaHCO_3$ (2 × 5 ml), evaporated on celite and purified by dry column vacuum chromatography (4.5 × 2.0 cm) on silica gel, eluting with a gradient of 0–60% EtOAc in hexane (v/v), to give diol **38** (14.4 mg, 99%) as a colourless oil. R_f [EtOAc–hexane 1:1 (v/v)] 0.27. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.29 (2 H, dd, J = 5.3, 8.4 Hz), 7.06–6.93 (6 H, m), 6.75–6.67 (5 H, m), 4.70 (1 H, t, J = 6.5 Hz), 4.09–4.03 (2 H, m), 3.72 (1 H, t, J = 10.0 Hz), 3.18 (1 H, dd, J = 4.4, 6.2 Hz), 1.99–1.50 (4 H, m). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 163.72, 160.47, 155.31, 152.26, 149.95 (C), 143.53 (CH), 141.41, 139.78 (C), 127.41, 127.29, 116.01, 115.77, 115.51, 115.23, 114.54, 114.42, 73.49 (CH), 67.60 (CH_2), 63.67, 51.35 (CH), 35.89, 28.70 (CH_2). ^{19}F (282 MHz, $CDCl_3$): δ −114.89 (1 F, septet, J = 4.3 Hz), −124.64 (1 F, septet, J = 4.3 Hz). IR (cm^{-1}): 3320, 2927, 1604, 1508, 1453, 1366, 1225, 1157, 1102, 1044, 910, 826, 733, 609. MALDI-MS: found, 421.1717 $[MH - H_2O]^+$. $C_{25}H_{23}F_2N_2O_2$ requires 421.1728. Found, 438.1755 $[M]^+$.$C_{25}H_{24}F_2N_2O_3$ requires 438.1755. Found, 439.1825 $[MH]^+$. $C_{25}H_{25}F_2N_2O_3$ requires 439.1833. Found, 461.1650 $[MNa]^+$. $C_{25}H_{24}F_2N_2O_3Na$ requires 461.1653.

Acknowledgements

This research was supported by a KTI grant (6813.2 BTS-LS) and Lipideon AG. L. K. was supported by a fellowship from The Technical University of Denmark. T. R. thanks the Fonds der Chemischen Industrie for a Kekulé Fellowship.

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