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# SYNTHESIS OF FLUORINE-CONTAINING ISOSTERES OF SPHINGOSINE AS INACTIVATORS OF PROTEIN KINASE C

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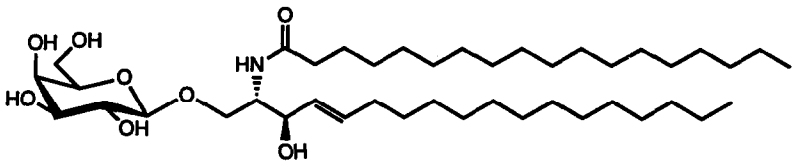
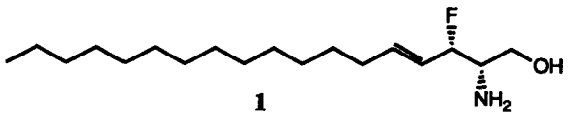
***Summary:*** Syntheses of isosteres of D-sphingosine in which either the primary or the secondary hydroxyl group of the parent compound has been replaced by a fluorine substituent are described.

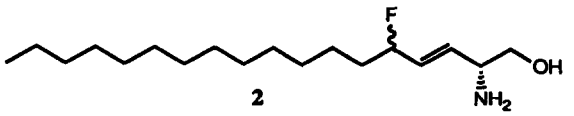
Sphingosine is a key component of more complex classes of biomolecules such as the cerebrosides which are one of the main constituents of brain membranes.[1] Sphingosine has attracted considerable interest recently as a consequence of its potent and reversible inhibitory effects on protein kinase C.[2] Protein kinase C is a ubiquitous, multifaceted enzyme system which plays important roles in biological processes including signal transduction, cellular differentiation and tumor promotion.[2] As a part of a broader program[3] aimed at discovering clinically useful inactivators of this kinase, we have developed synthetic procedures to gain access to several fluorine containing isosteres **1**, **2**, and **3** of sphingosine. The fluoro isosteres were deemed particularly valuable since fluorine can serve as a useful isosteric replacement for the hydroxyl group, even possibly participating to some degree as a hydrogen bond acceptor.[4]



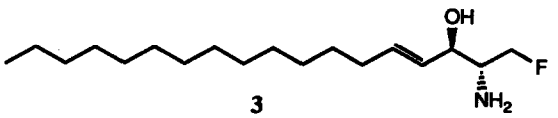

**Cerebroside**




**1**



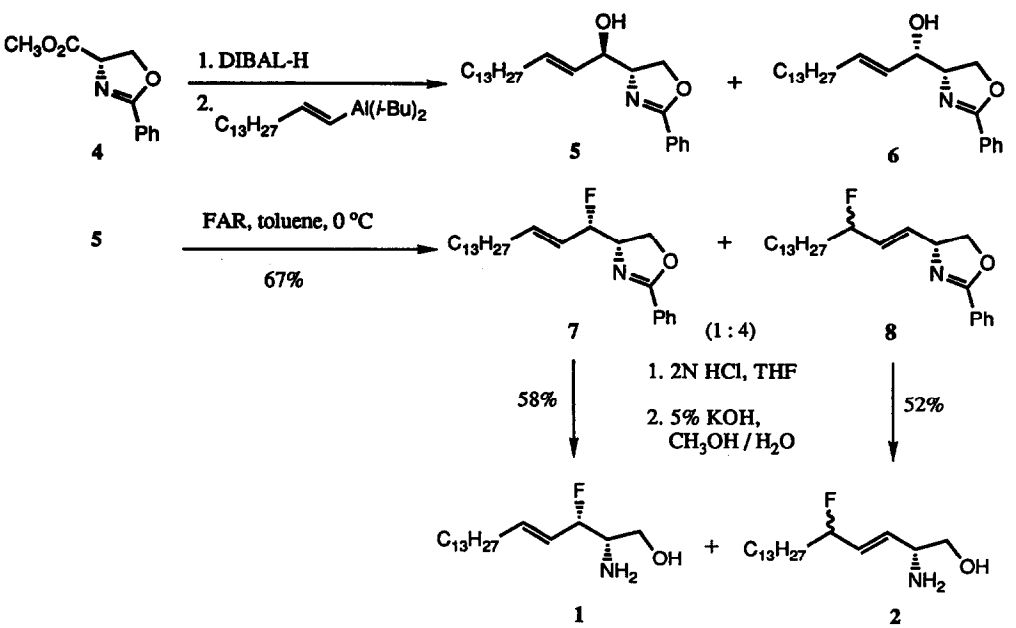

**2**




**3**

While initial efforts were made to prepare the fluoro compounds starting from *N/O*-protected versions of sphingosine, these attempts proved fruitless. Therefore, *de novo* synthetic approaches were examined. Following the procedure of Tkaczuk and Thornton[5] the methyl ester of L-serine was converted to the oxazoline derivative **4** by reaction with benziminoethyl ether. Next the ester group was converted to aldehyde by reduction with Dibal followed by careful quenching with methanol and potassium sodium tartrate. This aldehyde was coupled with the *E*-vinylalane prepared from the reaction of 1-pentadecyne with Dibal[6] to provide a mixture of the erythro and threo oxazoline derivatives of sphingosine **5** and **6** (erythro/threo ≅ 1:1). The isomers were separated by chromatography on silica gel and a study of the reaction of the pure erythro isomer **5** with several different fluorinating reagents was made. By far, the fluoroalkylamine (FAR) reagent 2-chloro-1,1,2-trifluorotriethylamine[7] provided the best yield of the desired fluoro derivative **7** in addition to the allylic rearrangement product **8**. Due to the fact that **7** was isolated as a single stereoisomer, we assume that it was formed by an $S_N2$ mechanism, a stereochemical pathway commonly observed for this reagent, and thus possesses threo stereochemistry ($J_{H_2, H_3}$ = 5.0 Hz). The allylic rearrangement product **8** constituted the major product of the FAR reaction (**8**:**7** ≅ 4:1), and it was obtained as a mixture of diastereomers (ratio ≅ 1:1). The oxazoline group was removed from **7** and **8** by treatment first with 2N HCl in THF at room temperature for 24 h, followed by reaction with 5% KOH in a 9:1 mixture of MeOH / $H_2O$. The amino alcohols **1** and **2** were obtained as white solids possessing the following optical rotations: **1**, $[\alpha]_D^{22}$ -10.8° (c 0.4, $CCl_4$); **2**, $[\alpha]_D^{22}$ + 2.2 ° (c 2.6, $CCl_4$).[12] Since Tkaczuk and Thornton[5] have shown previously that the serine derived oxazoline **4** is converted to *erythro*- and *threo*-sphingosine without racemization, it can be safely assumed that the stereochemistry of the amine bearing center of **1** and **2** is as depicted.

**Scheme 1. Synthesis of Sphingosine Analogues 1 and 2**

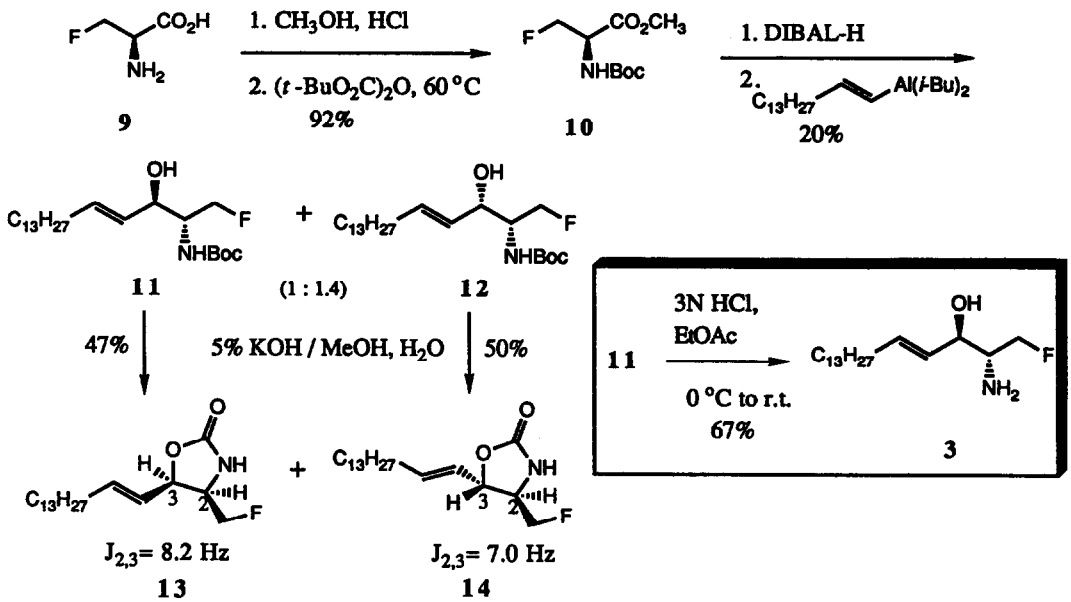


To procure the fluoro isostere **3**, (*S*)-3-fluoroalanine[8] was employed as the starting material. This compound was first transformed to its methyl ester by reaction with methanol and HCl gas. The amino group was then protected as its *t*-Boc derivative using di-*tert*-butyl dicarbonate to provide **10**, $[\alpha]_D^{22}$ + 18.8 ° (c 5.7, $CCl_4$).

The ester group was reduced to the aldehyde using Dibal in toluene and the crude aldehyde was reacted immediately with the *E*-vinylalane prepared from 1-pentadecyne. A chromatographically separable mixture of the erythro and threo isomers **11** and **12** was obtained (ratio ≅ 1:1.4). The assignment of stereochemistry to these products was made by transforming them to their corresponding cyclic urethanes **13** and **14** by 5% KOH, $MeOH/H_2O$ treatment. Based upon literature precedent, erythro stereochemistry was assigned to that isomer exhibiting the larger $J_{2,3}$ coupling constant.[9] Cleavage of the *t*-Boc group from **11** and **12** was accomplished by treatment with 3N HCl in ethyl acetate. The desired fluoro isostere **3**[12] was obtained in 67% yield, $[\alpha]_D^{22}$ -6.7 ° (c 0.15, $CCl_4$). Since the camphanic acid ester derivative of (-)-**3** was found to exhibit a single set of peaks in its $^1H$ NMR spectrum, while the ester derivative of racemic **3** prepared from (±)-**9** exhibited a doubling of peaks, the stereochemical integrity of the amine bearing center originating from (*S*)-**9** is ensured.

The work reported herein provides the first total synthesis approaches to the fluorine containing isosteres of sphingosine. While details of the biological action of these analogues will be published in full elsewhere, it is of interest to note that all three compounds were found to be inhibitors of PKC.[10,11]

**Scheme 2. Synthesis of Sphingosine Analogue 3**

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10. We thank Dr. A. Guidotti of the Fidia-Georgetown Institute for Neurosciences for conducting the biological assays on the sphingosine analogues.
11. For other synthetic routes to the sphingosines, see inter alia, H. Newman, *J. Am. Chem. Soc.*, **95**, 4098-4099 (1973); R. H. Boutin and H. Rapoport, *J. Org. Chem.*, **51**, 5320-5327 (1986); K. Ohashi, Y. Yamagiwa, T. Kamikawa and M. Kates, *Tetrahedron Lett.*, **29**, 1185-1188 (1988); B. Bernet and A. Vasella, *Tetrahedron Lett.*, **24**, 5491-5494 (1983); R. S. Garigipati and S. M. Weinreb, *J. Am. Chem. Soc.*, **105**, 4499-4501 (1983); W. R. Roush and M. A. Adam, *J. Org. Chem.*, **50**, 3752-3757 (1985); P. Herold, *Helv. Chim. Acta*, **71**, 354-362 (1988); S. Nimbar, D. Menaldino, A. H. Merrill and D. Liotta, *Tetrahedron Lett.*, **29**, 3037-3040 (1988).
12. Spectral data for compound **1**, **2** and **3** follow:
    **1**: IR (KBr) 3330, 3272, 3195, 3120, 1630, 932 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300MHz) $\delta$ 5.86 (1H, m), 5.53 (1H, m), 4.80 (0.5H, t, $J$=6.7 Hz), 4.64 (0.5H, t, $J$=6.7 Hz), 3.61 (1H, dd, $J$=4.1, 10.8 Hz), 3.44 (1H, dd, $J$=6.9, 10.8 Hz), 2.93 (1H, m), 2.07 (2H, m), 1.96 (3H, m), 1.25 (22H, m), 0.87 (3H, t, $J$=6.7 Hz); mass spectrum: m/z (isobutane CI) 302 ($MH^+$), 282, 252.
    **2**: IR (KBr) 3329, 3273, 3194, 3120, 1630, 1466 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300MHz) $\delta$ 5.73 (2H, m), 4.95 (0.5H, m), 4.78 (0.5H, m), 3.62 (1H, dd, $J$=4.4, 10.3 Hz), 3.49 (1H, m), 3.35 (1H, dd, $J$=7.7, 10.4 Hz), 1.63 (5H, m), 1.25 (22H, m), 0.88 (3H, t, $J$=6.6 Hz); mass spectrum m/z (70 ev) 270 ($M^+$-$CH_2OH$), 250, 82; exact mass calcd for $C_{17}H_{33}NF$ ($M^+$-$CH_2OH$) 270.2597, found 270.2598.
    **3**: IR (neat) 2500-3300 (broad), 3360, 3292, 2919, 1686, 1677, 1467 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300MHz) $\delta$ 5.77 (1H, dt, $J$=15.6, 6.9 Hz), 5.44 (1H, dd, $J$=15.6, 7.2 Hz), 4.59 (0.5 H, dd, $J$=4.0, 9.2 Hz), 4.48 (0.5H, dd, $J$=6.9, 8.9 Hz), 4.42 (0.5H, dd, $J$=4.0, 9.2 Hz), 4.32 (0.5H, dd, $J$=6.8, 8.9 Hz), 4.07 (1H, dd, $J$=6.2, 6.7 Hz), 3.10 (1H, m), 2.05 (2H, m), 1.93-1.65 (3H, m), 1.25 (22H, m), 0.88 (3H, t, $J$=6.5 Hz); mass spectrum m/z (70 ev) 282 ($M^+$-F), 268 ($M^+$-$CH_2F$), 239, 207; exact mass calcd for $C_{17}H_{34}NO$ ($M^+$-$CH_2F$) 268.2640, found 268.2640.


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