Pergamon

Tetrahedron Letters 43 (2002) 375–377

TETRAHEDRON LETTERS

A concise route to D-*erythro*-sphingosine from *N*-Boc-L-serine derivatives via sulfoxide or sulfone intermediates

Jiong Chun, Guoqing Li, Hoe-Sup Byun and Robert Bittman*

Department of Chemistry and Biochemistry, Queens College of The City University of New York, Flushing, NY 11367-1597, USA

Received 11 September 2001; accepted 30 October 2001

Abstract—Sulfoxide and sulfone intermediates **7** and **15**, respectively, were employed to synthesize synthons **3** and **4**, which are readily converted to the naturally occurring (2*S*,3*R*,4(*E*))-sphingosine **1** and (2*S*,3*R*)-sphinganine **2**.

Sphingolipids have been implicated in a vast variety of physiological functions but are not readily obtained from natural sources in homogeneous form.[1] Therefore, there is a great demand for chemical methods that provide sphingolipids in sufficient amounts and high chiral purity for use in biological and biochemical studies. Since the first report of the synthesis of racemic sphingosine in 1951,[2] many different methods have been employed for the chemical synthesis of naturally occurring (2*S*,3*R*)-sphingosine (**1a**, Chart 1)[3] and sphinganine (**2**).[4] However, because of the need to generate two stereogenic centers with high stereoselectivity, as well as an (*E*)–C(4)–C(5) double bond, most of the synthetic procedures are quite lengthy. An efficient synthetic route to D-*erythro*-sphingosine (**1a**) in only four steps (two of which take place in one pot, with no intermediate being isolated) is reported here that involves the use of β-keto-sulfoxide or sulfone intermediates for C–C bond formation. The latter have not been previously used for the preparation of sphingolipids, even though the reactions of sulfur-containing carbanions have been used extensively in organic synthesis.[5] Our method provides facile access to synthon **3** from L-serine methyl ester derivative **5**; synthon **4** is readily obtained in only three steps from L-serinal derivative **12**. It has previously been shown that synthons **3** and **4** afford naturally occurring D-*erythro*-sphingosine **1a** and D-*erythro*-sphinganine (**2**).[6,7]

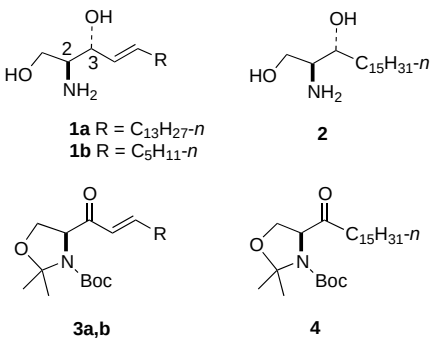


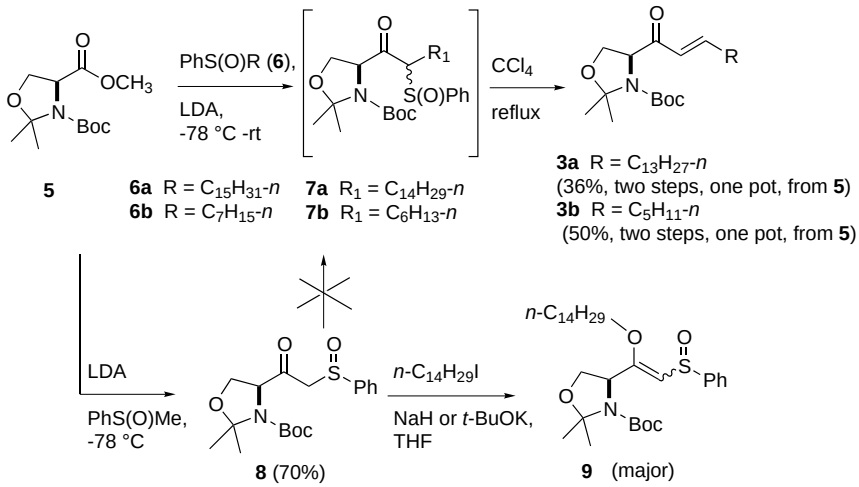
Chart 1.

The synthesis of **1a** began with the reaction of L-serine-derived *N*-Boc-oxazolidine methyl ester **5**[8] with an alkyl phenyl sulfoxide (**6**) (Scheme 1). Sulfoxides **6a**,**b** were prepared in high yield by the reaction of thiophenol with (a) *n*-pentadecyl bromide or (b) *n*-heptyl bromide in the presence of Li_2CO_3 in DMF, followed by brief treatment of the resulting sulfide with MCPBA in CH_2Cl_2 at −78°C.[9] Nucleophilic addition of the anion of sulfoxide **6a**,**b** (2 equiv.) to ester **5** gave sulfoxide intermediates **7a**,**b**,[10] which were not isolated. On heating in CCl_4 overnight, **7a**,**b** afforded enones **3a**,**b** in 36 and 50% overall yield, respectively.[11]

β-Ketosulfoxide **8** was prepared in 70% yield from **5** by using 2 equiv. of the carbanion of methyl phenyl sulfoxide (Scheme 1). Attempts to carry out the *C*-alkylation of **8** with long-chain alkyl halides mediated by different bases have not been successful. When a strong base such as NaH or *t*-BuOK in THF was used, *O*-alkylation was the major reaction, providing enol ether **9**.

* Corresponding author. Tel.: (718) 997-3279; fax: (718) 997-3349; e-mail: robert_bittman@qc.edu

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02145-1

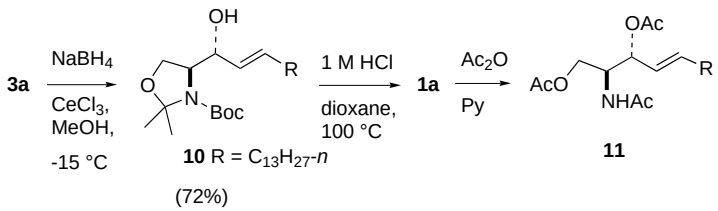


Scheme 1. Synthesis of sphingosine **1a** via sulfoxide **6** and enone **3**.

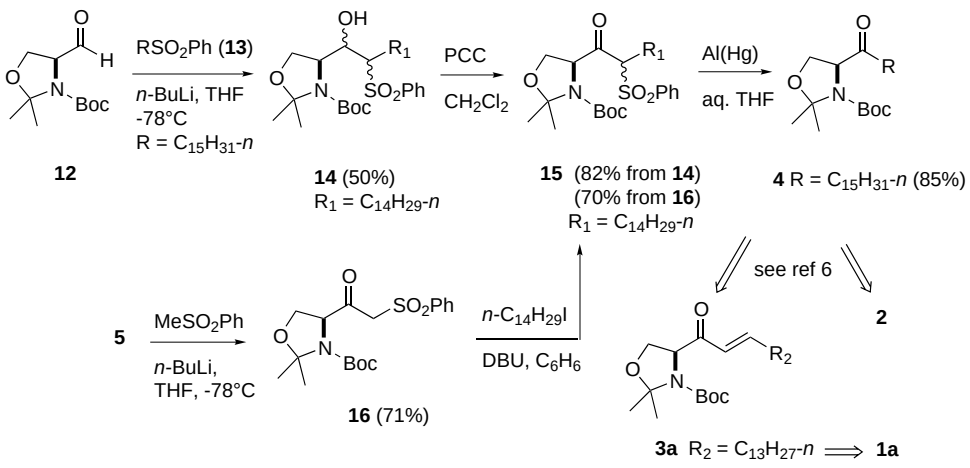
When a relatively weak base such as Cs_2CO_3 or K_2CO_3 in DMF or DBU in benzene was used, the yield of **7a** was low.

The synthesis of sphingosine from **3a** was completed in two steps. Diastereoselective reduction of **3a** ($NaBH_4$, $CeCl_3$, MeOH, −15°C) provided alcohol **10** in 72% yield (Scheme 2).[6,12] Hydrolysis of **10** (1 M HCl, dioxane, 100°C) afforded D-*erythro*-sphingosine (**1a**), which was characterized as the triacetate derivative **11**.[13]

As depicted in Scheme 3, the preparation of synthon **4** began with *N*-Boc-oxazolidine L-serinal **12**.[8] Reaction of methyl ester **5** with 2 equiv. of the anion of *n*-pentadecyl phenyl sulfone (**13**)[14] gave a low yield of β-ketosulfone **15**; furthermore, it was difficult to separate product **15** from starting sulfone **13**. Therefore, sulfone intermediate **14** was prepared by addition of the anion of sulfone **13** to aldehyde **12**. Oxidation of alcohol **14** (PCC, rt) provided β-ketosulfone **15** in 82% yield.[15] Aluminum amalgam[16] was used to effect the desulfonyl-



Scheme 2. Conversion of enone **3a** to sphingosine **1a**.



Scheme 3. Synthesis of ketone **4**, a precursor of **1a** and **2**, via β-ketosulfone **15**.

ation of β-ketosulfone **15**, affording ketone **4** (85% yield), which has been used to prepare enone **3a** and sphinganine **2**.[6]

Scheme 3 also shows that direct addition of the carbanion derived from 2 equiv. of methyl phenyl sulfone to ester **5** gave sulfone **16**,[17] which was alkylated with *n*-tetradecyl iodide, providing an alternative route to β-ketosulfone intermediate **15**.

In summary, the sphingoid base of the naturally occurring lipids **1** and **2** has been conveniently synthesized from the commercially available L-serine-derived synthons **5** and **12** by employing β-keto-sulfoxide and sulfone intermediates **7** and **15**. The *S* configuration of the stereocenter at C-2 in products **1** and **2** is derived from the configuration at C-2 of L-serine. Diastereoselective reduction of enone **3** provides the requisite *R* configuration at C-3 of D-*erythro*-sphingosine (**1**), as demonstrated by the agreement of the specific rotation of triacetate derivative **11** with literature values.[13] This practical method can be applied to the construction of sphingoid bases containing a modified aliphatic chain.[18] This approach is well suited to the preparation of isotopically labeled sphingoid bases derived from commercially available labeled serine.[19]

Acknowledgements

This work was supported by National Institutes of Health Grant HL 16660.

References

1. (a) Hannun, Y. A. *Science* **1996**, *274*, 1855–1859; (b) Ariga, T.; Jarvis, W. D.; Yu, R. K. *J. Lipid Res.* **1998**, *39*, 1–16; (c) Perry, D. K.; Hannun, Y. A. *Biochim. Biophys. Acta* **1998**, *1436*, 233–243.
2. Grob, C. A.; Jenny, E. F.; Utzinger, H. *Helv. Chim. Acta* **1951**, *34*, 2249–2254.
3. For reviews, see: (a) Byun, H.-S.; Bittman, R. In *Phospholipids Handbook*; Cevc, G., Ed.; Marcel Dekker: New York, 1993; pp. 97–140; (b) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, *8*, 1075–1091; (c) Jung, K.-H.; Schmidt, R. R. In *Lipid Synthesis and Manufacture*; Gunstone, F. D., Ed.; Sheffield Academic Press: Sheffield, UK; CRC Press: Boca Raton, FL, 1999; pp. 208–249; (d) Curfman, C.; Liotta, D. *Methods Enzymol.* **1999**, *311*, 391–457; (e) Koskinen, P. M.; Koskinen, A. M. P. *Methods Enzymol.* **1999**, *311*, 458–479.
4. (a) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4797–4802; (b) Villard, R.; Fotiadu, F.; Buono, G. *Tetrahedron: Asymmetry* **1998**, *9*, 607–611; (c) Masui, M.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 5199–5200; (d) He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7618–7626.
5. (a) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019–2045; (b) Block, E. *Reactions of Organosulfur Compounds*; Academic: New York, 1978; (c) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363–382; (d) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon: Oxford, 1993.
6. Tao, J.; Hoffman, R. V. *J. Org. Chem.* **1998**, *63*, 3979–3985.
7. Koskinen, A. M. P.; Koskinen, P. M. *Synlett* **1993**, 501–502.
8. L-Oxazolidine methyl ester **5** and aldehyde **12**, which are commercially available, are readily prepared from L-serine: Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18–28.
9. Dodson, R. M.; Srinivasan, V.; Sharma, K. S.; Sauers, R. F. *J. Org. Chem.* **1972**, *37*, 2367–2372.
10. For the formation of an β-ketosulfoxide by reaction of an ester with an β-sulfinyl carbanion, see: Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345–1353.
11. Experimental procedures for the preparation of enones (−)-**3a**,**b**. **3a**: To a solution of diisopropylamine (470 μL, 3.3 mmol) in 4 mL of dry THF was added 1.3 mL (3.3 mmol) of *n*-BuLi (a 2.5 M solution in hexane,) at −15°C under N_2. After the mixture was stirred for 30 min, a solution of phenyl sulfoxide **6a** (1.0 g, 3.0 mmol) in 5 mL of THF was added dropwise. After 30 min at −15°C, the reaction mixture was brought to −78°C and a solution of ester **5** (389 mg, 1.5 mmol) in 5 mL of THF was added slowly. The reaction mixture was stirred at −78°C for 2 h and allowed to warm to room temperature overnight, then quenched with saturated aqueous NH_4Cl solution (10 mL). The product was extracted with EtOAc, washed with brine, and dried ($MgSO_4$). Concentration gave crude β-ketosulfoxide **7a**, which was dissolved in 25 mL of CCl_4 and heated at reflux for 12 h. Concentration and purification by flash chromatography (hexane/EtOAc, 4:1, R_f 0.80) gave 236 mg (36%, two steps) of **3a** as a colorless oil; $[\alpha]_D^{25}$ −30.0° (*c* 0.85, $CHCl_3$) (lit.[6] $[\alpha]_D^{25}$ −27.3° (*c* 0.54, $CHCl_3$); lit.[3e] $[\alpha]_D^{20}$ −21.0° (*c* 0.85, $CHCl_3$)). **3b**: This compound was prepared by the procedure described above in 50% yield (two steps from ester **5**); $[\alpha]_D^{25}$ −7.4° (*c* 1.5, $CHCl_3$).
12. For an example of stereoselective sulfoxide-mediated reduction of a ketone in a chiral *N*-Boc-oxazolidine derivative with DIBAL-H, see: Khiar, N.; Singh, K.; García, M.; Martín-Lomas, M. *Tetrahedron Lett.* **1999**, *40*, 5779–5782.
13. Triacetyl D-*erythro*-sphingosine (−)-**11** was obtained as a white solid: mp 104.0–105.2°C (lit.,[20a] mp 104.5–105.0°C; lit.,[20b] mp 101–102°C); $[\alpha]_D^{25}$ −12.0° (*c* 0.9, $CHCl_3$) (lit.,[20a] $[\alpha]_D^{25}$ −12.9° (*c* 1.0, $CHCl_3$); lit.,[20b] $[\alpha]_D^{25}$ −12.8° (*c* 1.0, $CHCl_3$)).
14. Sulfone **13** was obtained in 90% yield by MCPBA oxidation (CH_2Cl_2 at 0°C) of the corresponding sulfide.
15. Sulfone **15**: ^1H NMR (C_6D_6) δ 0.88 (t, 3H, $J=7.0$ Hz), 0.9–2.0 (m, 44H), 3.70–3.90 (m, 1H), 4.27 (m, 1.5H), 4.36, 4.73 (two sets of br s, 1H),[21] 5.10, 5.35 (two sets of d, 0.5H, $J=6.6$, 6.8 Hz), 6.90–7.05 (m, 3H), 7.86 (d, 1H, $J=7.4$ Hz), 7.84, 8.13 (two sets of d, 1H, $J=7.4$, 5.1 Hz).
16. Troyansky, E. I. In *Encyclopedia for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; pp. 150–153.
17. House, H. O.; Larson, J. K. *J. Org. Chem.* **1968**, *33*, 61–65.
18. Chun, J.; Li, G.; Byun, H.-S.; Bittman, R., unpublished results.
19. Various starting materials have been used in other efficient syntheses of **1a** (He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7627–7633 and references cited therein); however, serine is the only common starting material available with ^{13}C, ^{14}C, and ^{15}N labels.
20. (a) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354–362; (b) Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 368–373.
21. The pairs of signals arise from the conformers present in the compound containing the oxazolidine ring system.