Pergamon

Tetrahedron Letters 39 (1998) 5199–5200

TETRAHEDRON LETTERS

Stereoselective Synthesis of Sphinganine by Means of Modified Asymmetric Borane Reduction

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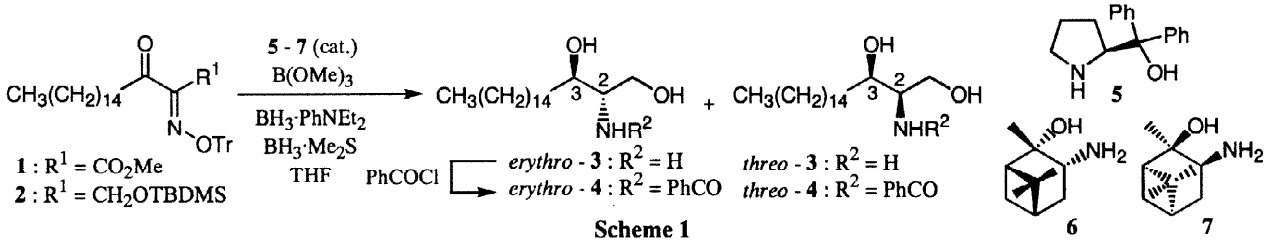
Received 3 March 1998; revised 11 May 1998; accepted 13 May 1998

Abstract: Efficient stereoselective synthesis of sphinganine by the asymmetric borane reduction of α-oxoketoxime trityl ethers is described. Both *threo* and *erythro* sphinganine could be obtained with high enantioselectivities by using borane-*N,N*-diethylaniline complex as a reducing agent.

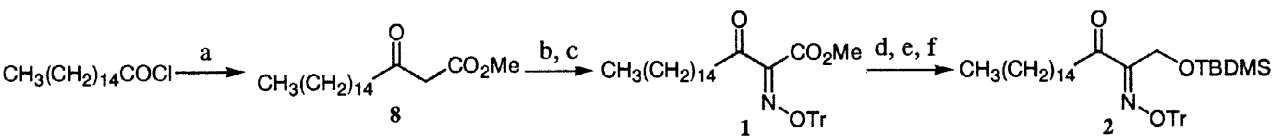
Keywords: Asymmetric synthesis; Ketones; Oximes; Reduction

Sphinganine (dihydrosphingosine, **3**) is an intermediate in the biosynthesis of sphingolipids (e.g., ceramides, sphingomyelin, cerebrosides, and gangliosides) which play important roles in cell regulation and signal transduction,[1] with sphinganine itself found to be an inhibitor of protein kinase C.[2] In this paper we describe a simple and efficient route for the preparation of four stereoisomers of sphinganine. The key step in the procedure is the asymmetric borane reduction of α-oxoketoxime trityl ethers **1** and **2** using catalysts generated *in situ* from trimethyl borate and chiral amino alcohols **5**-**7**.[3]



Scheme 1

Preparation of **1** was accomplished without any expensive reagents or complex procedures by the pathway of Scheme 2. Condensation of palmitoyl chloride with malonic acid half ester potassium salt gave β-ketoester **8**.[4] Nirosation of **8** by butylnitrite was followed by *O*-tritylation to afford the desired ester **1**. Substrate **2** was prepared from **1** in high yield by a three-step procedure which involves reduction with sodium borohydride, protection of the primary alcohol with *tert*-butyldimethylsilyl chloride, and Swern oxidation.



Scheme 2. *Reagents and Conditions*: a) $KO_2CCH_2CO_2Me$, $MgCl_2$, Et_3N, CH_3CN, r.t. 18h (52 %); b) BuONO, c-H_2SO_4, Et_2O, r.t. 15h (85 %); c) TrCl, Et_3N, CH_2Cl_2, r.t. 2h (99 %); d) $NaBH_4$, EtOH, r.t. 1 h (99 %); e) TBDMSCl, imidazole, DMF, r.t. 24 h (85 %); f) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C 15min; then Et_3N, r.t. 1 h (99 %)

The initial experiment for the asymmetric reduction of **1** was conducted with 0.1 equivalent (eq) of amino alcohol **5** and 0.12 eq of trimethyl borate by using 10 eq of borane-dimethyl sulfide complex (BMS) as a reducing agent in dry THF. The mixture was stirred for 2 h at 0~5 °C and then heated under reflux for 65 h (Method A). After being quenched with 2N HCl, the solution was treated with benzoyl chloride in the presence of NaOH to isolate the sphinganine produced. The desired *N*-benzoylsphinganine (**4**) was obtained in 90% yield. However, *threo*-(2*R*, 3*R*)-**4** and *erythro*-(2*S*, 3*R*)-**4** were obtained at the ratio of 80:20 with only 46 and 16 % ee, respectively. We therefore examined alternative reduction conditions.

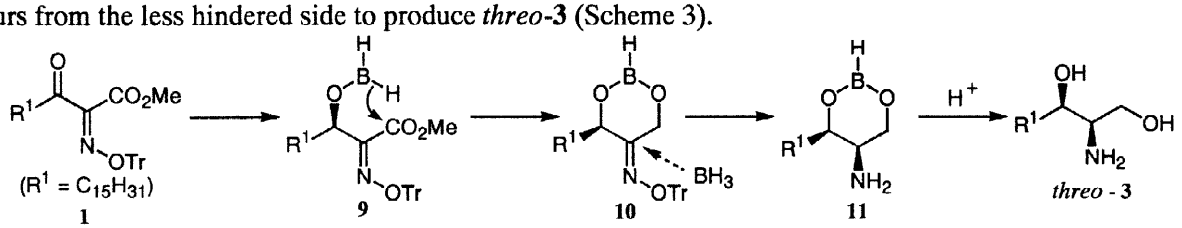
0040-4039/98/$19.00
PII: S0040-4039(98)01020-X

Table 1 Asymmetric Borane Reduction of Oxime Ethers 1 and 2

Run	Starting material	Amino alcohol (eq)	Method	Yield (%)	*erythro* : *threo* [a]	% ee [a] (Config.)	
						erythro	*threo*
1	**1**	**5** (0.1)	A	90	20 : 80	16 (2*S*, 3*R*)	46 (2*R*, 3*R*)
2	**1**	**5** (0.1)	B	92	13 : 87	75 (2*S*, 3*R*)	89 (2*R*, 3*R*)
3	**1**	**6** (0.1)	B	89	21 : 79	91 (2*R*, 3*S*)	90 (2*S*, 3*S*)
4	**1**	**7** (0.1)	B	90	22 : 78	91 (2*S*, 3*R*)	90 (2*R*, 3*R*)
5	**1**	**7** (0.2)	B	90	20 : 80	93 (2*S*, 3*R*)	95 (2*R*, 3*R*)
6	**2**	**5** (0.1)	C	94	97 : 3	87 (2*S*, 3*R*)	58 (2*R*, 3*R*)
7	**2**	**6** (0.1)	C	94	96 : 4	91 (2*S*, 3*R*)	79 (2*R*, 3*R*)
8	**2**	**7** (0.1)	C	95	97 : 3	91 (2*R*, 3*S*)	71 (2*S*, 3*S*)
9	**2**	**7** (0.2)	C	94	98 : 2	97 (2*S*, 3*R*)	91 (2*R*, 3*R*)

a) Determined by HPLC analysis using a Chiralcel OJ-R (Daicel) and a YMC Chiral NEA (R) (YMC) column connected in series.

Enantioselectivity was improved by using borane-*N,N*-diethylaniline complex (BEA). The modified reaction was commenced with reduction of the carbonyl group by 2 eq of BEA. After the mixture was stirred at room temperature until **1** had disappeared on TLC, 8 eq of BMS was added. The solution was then heated under reflux for 65 h for complete reduction of the ester and oxime groups (Method B). Enhanced enantioselectivities were obtained; for example, the reduction of **1** with 0.1 eq of **5** afforded *threo*-(2*R*, 3*R*)-**4** and *erythro*-(2*S*, 3*R*)-**4** at the ratio of 87:13 with 89 and 75 % ee, respectively (Run 2). Amino alcohols **6** and **7** also led to high enantioselective reduction of **1** by the modified procedure, and both enantiomers of **4** were obtained from these reactions with over 90 % ee (Runs 3,4). By using 0.2 eq of **7**, enantiomeric excess of the predominant *threo* isomer increased to 95 % ee (Run 5). Contrary to our expectation from previous results on the reduction of α-oxoketoxime ethers,[3] the reduction of **1** proceeded with *threo* selectivity. Substrate **1** might be reduced to the six-membered cyclic intermediate **10**, where the attack by borane on the oxime group occurs from the less hindered side to produce *threo*-**3** (Scheme 3).



Scheme 3

Reduction of **2** was conducted by stirring for 1-3 h at room temperature with 2 eq of BEA and subsequent heating under reflux for 18 h after the addition of 2 eq of BMS (Method C). Silyl ether was deprotected while the reaction mixture was quenched with 2N HCl. In all the cases examined, the desired product **4** was formed in high yields with excellent *erythro* selectivity and high enantiomeric excess (Runs 6-8). The highest diastereo- and enantioselectivity was obtained using 0.2 eq of amino alcohol **7**, where *erythro*-(2*S*,3*R*)- **4** was afforded at 96 % de with 97 % ee (Run 9).[5]

In conclusion, we have demonstrated that the stereoselective synthesis of sphinganine can be accomplished by asymmetric borane reduction of α-oxoketoxime trityl ethers. Each of the four stereoisomers of sphinganine could be obtained with high enantioselectivity by changing the combination of the substrate and chiral amino alcohol in the key step.

References and Notes

1. Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500.
2. Schwartz, G. K.; Jiang, J.; Kelsen, D.; Albino, A. P. *J. Nat. Cancer Inst.* **1993**, *85*, 402.
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4. Clay, R. J.; Collom, T. A.; Karrick, G. L., Wemple, J. *Synthesis* **1993**, 290.
5. Sphiganine usually occurs in nature as its *erythro*-(2*S*, 3*R*) isomer.