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ENANTIOSELECTIVE SYNTHESIS OF D-*erythro*-SPHINGOSINE

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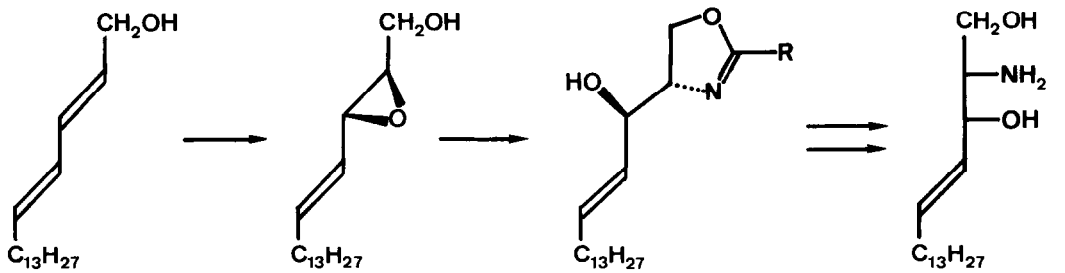
Abstract: D-*erythro*-sphingosine (4) and the 3-amino-2-hydroxy-L-*erythro* isomer 15 were synthesized in a highly enantio- and regioselective manner by a modified Sharpless asymmetric epoxidation.

Several syntheses of the racemic *erythro*-sphingosine are known. [1,2,3,4] The D-*erythro* enantiomer 4 has been obtained by resolution of racemic 4 [5] or of one of its synthetic intermediates. [6] The syntheses from an enantiomerically pure starting material - from L-serine [7,8] and from D-glucose [9] - contain each a low yield step: the former in the addition of a trans vinylalane to an aldehyde derived from L-serine, the latter in the preparation of 3-amino-3-deoxy-di-O-isopropylidene-*α*-D-allofuranose. We desired to obtain 4 by an enantioselective procedure on a gram scale. Sharpless' asymmetric epoxidation, [10] known for its high enantioselectivity, appeared a good method. [11] Attachment of a potential *N*-nucleophile to the hydroxy group should then allow a regioselective opening of the oxirane ring (see Scheme 1).

Scheme 1



1 **2** **3** **4**

To the best of our knowledge, no Sharpless epoxidation of a conjugated dienol such as 1 has been published. Under standard conditions, [10] 1 [4] was initially transformed into a single product, which subsequently decomposed to several unidentified products. [12] This behaviour was rationalized by assuming first an epoxide migration [13] of the initially obtained epoxide 2 to a secondary allylic alcohol and then its further epoxidation to an unstable diepoxy alcohol. Propargylic alcohols are known to be epoxidized much slower

than allylic alcohols.[14] Hence, the enynol 6 (mp 56°C) [15] was chosen as starting material (see Scheme 2). It was obtained in 80% yield, along with the dimer 23 (mp 55°C, 11%) by the Sonogashira reaction [16] of pentadecyne (5) [17] with (*E*)-3-bromo-prop-2-en-1-ol. [18,19] Sharpless epoxidation of 6, catalyzed by titanium tetra-*t*-butoxide [20] and D-(-)-diethyl tartrate in 2,3-dimethyl-2-butene/CH_2Cl_2 1:1 [21] yielded the desired epoxide 7 (72% with 97% ee [22]), the *t*-butyl ether 26 (8%) and starting material 6 (4%). [23] Two recrystallisations from hexane at 5°C gave enantiomerically pure 7 (mp 55°C, $[\alpha]_D^{25}$ -2.2° (c=2, $CHCl_3$), 64% from 6). Treatment of the trichloroimidate 8 with triethyl aluminium in diethyl ether led to a single product 11 (mp 71°C, $[\alpha]_D^{25}$ -128.7° (c=1, $CHCl_3$), 78% from 7). The ^1H NMR spectra of 11 and of its acetate 12 suggested a dihydro oxazine structure. Assuming a *trans* configuration, the small coupling constants ($J_{4,5}$ = 2.5 Hz in 11 and 2 Hz in 12) could only be explained by a pseudoaxial arrangement of the substituents. The *trans* configuration and a pseudoaxial conformation in the solid state were evident from an X-ray analysis of 11. [24] Acidic hydrolysis and Li/NH_3 reduction furnished the slightly impure L-*erythro* 15 (90%). The amorphous amino diols 13 and 15 were characterized as their triacetates 14 (mp 83°C, $[\alpha]_D^{25}$ +49.5° (c=1, $CHCl_3$)) and 16 (mp 94°C, $[\alpha]_D^{25}$ +30.2° (c=1, $CHCl_3$)).

To obtain the desired regioisomer, the benzyl urethane 10 (mp 61°C, $[\alpha]_D^{25}$ +10.3° (c=1, $CHCl_3$)) was prepared in 92% yield *via* the *p*-nitrophenyl carbonate 9 (one-pot reaction) and treated with potassium *t*-butoxide in *t*-butanol at -5°C according to Kishi. [25] This leads to the desired oxazolidinone 17 (mp 52°C, $[\alpha]_D^{25}$ -26.9° (c=1, $CHCl_3$)), which, however, decomposed partially during the reaction. A better yield of 17 (89%) was obtained by treating 10 with 5 equivalents of sodium bis-trimethylsilyl amide in oxolane at -20°C. Lithium in liquid NH_3 at -20°C cleaved the *N*-benzyl group, while the (selective) reduction of the triple bond was incomplete even after a second Birch reduction leading to the alcohols 19 (mp. 73°C, $[\alpha]_D^{25}$ -1.8° (c=2, $CHCl_3$), 79% yield) [26] and 18 (mp. 67°C, $[\alpha]_D^{25}$ -5.9° (c=1.9, $CHCl_3$), 19% yield), which were separated by column chromatography. Hydrolysis of the carbamates gave in almost quantitative yield the amino diols 4 and 21, respectively. They were characterized as the triacetates 20 (mp. 103°C, $[\alpha]_D^{25}$ -12.9° (c=1, $CHCl_3$); lit. 8): mp. 103.5-104.5°C, $[\alpha]_D^{24}$ -12.9° ($CHCl_3$)) and 22 (mp. 64°C, $[\alpha]_D^{25}$ -55.4° (c=1, $CHCl_3$)) [27]. This synthesis leads to D-*erythro*-sphingosine in 6 steps from 5 and in an overall yield of 33%.

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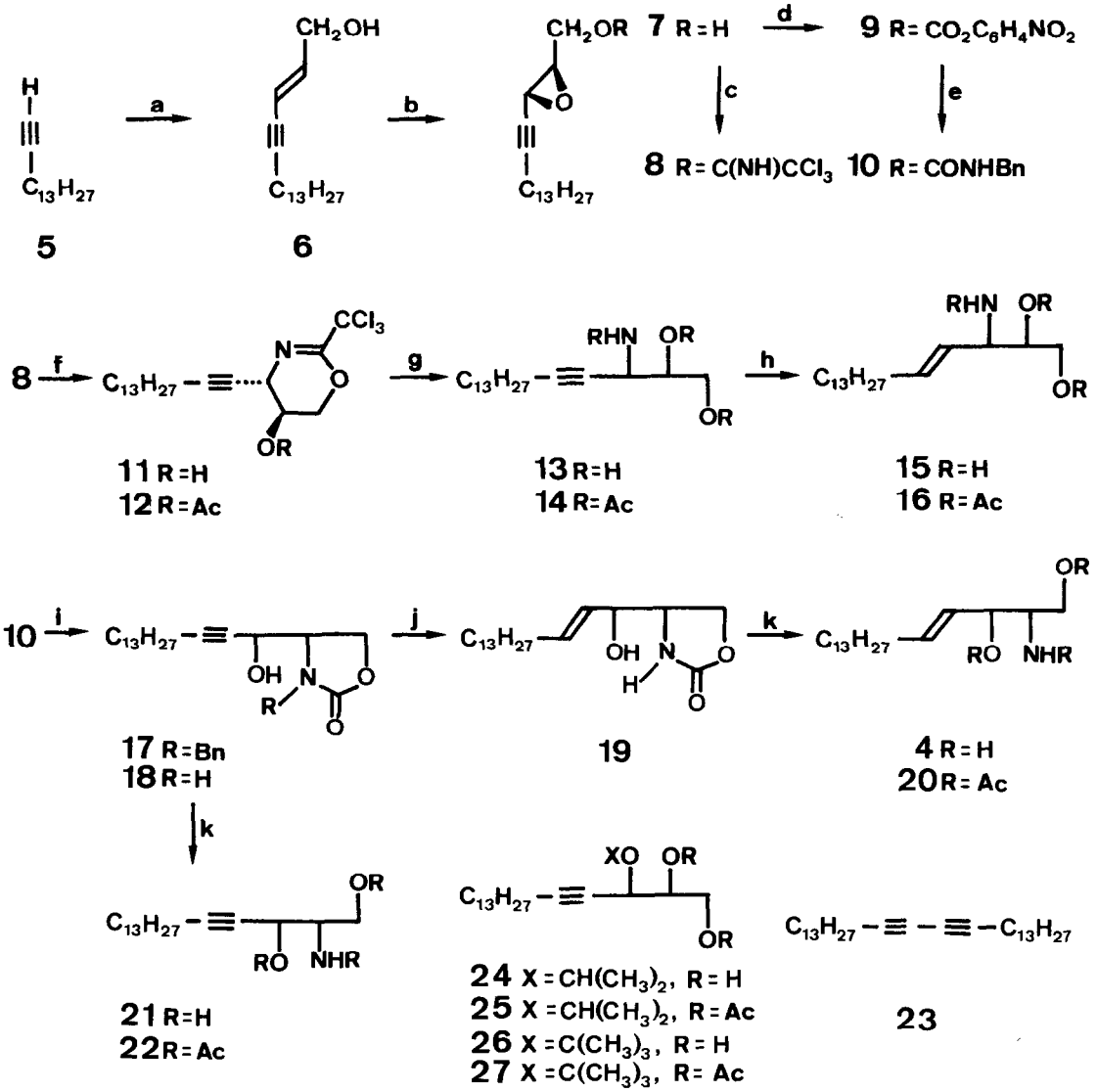
Scheme 2



Conditions: a) 1.3 eq. (*E*)-3-bromo-prop-2-en-1-ol, 0.005 eq. $PdCl_2(P\phi_3)_2$, 0.02 eq. CuI, $HNEt_2$, 40°C, 5h (80%); b) 1.9 eq. $Ti(OBu^t)_4$, 2 eq. D-(-)-diethyl tartrate, 2.2 eq. Bu^tOOH, 2,3-dimethyl-2-butene/CH_2Cl_2 1:1, -20°C, 4h (72%); c) 3 eq. CCl_3CN, 3.5 eq. DBU, toluene, r.t., 10 min; d) 1.2 eq. $ClCOO\text{-}C_6H_4\text{-}pNO_2$, pyridine/$CH_2Cl_2$, r.t., 70 min; e) 3 eq. $BnNH_2$, CH_2Cl_2, r.t., 10 min (92% from 7); f) 4 eq. $AlEt_3$, Et_2O, 0°C → r.t., 30 min (78% from 7); g) CH_3OH /H_2O/conc. H_2SO_4 50:24:1, reflux, 70 min; h) Li/NH_3, HMPA, -10°C, 1h (90% from 11); i) 5 eq. $NaN[Si(CH_3)_3]_2$, THF, -20°C, 90 min (89%); j) Li/NH_3, -20°C, 90 min. (79% after 2 sequential reductions); k) EtOH/2*N* NaOH, 80°C, 150 min; acetylations: Ac_2O, NEt_3, cat. DMAP, CH_2Cl_2.

References and Footnotes

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23) Using titanium tetraisopropoxide 7 (48%), 6 (23%) and 24 (19%) were isolated. Acetylation of 24 and 26 gave the diacetates 25 and 27.

24) We thank Dr. J.H. Bieri and R. Prewo for the X-ray analysis.

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27) For racemic 22 see 2).

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