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A new diorganozinc-based enantioselective access to truncated D-*ribo*-phytosphingosine

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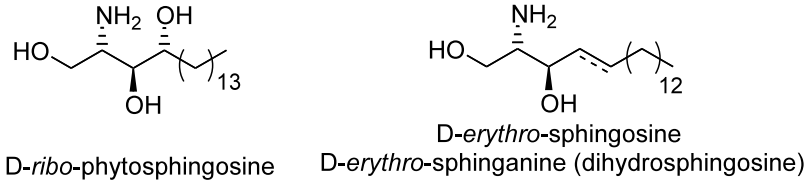
Abstract—The use of a *trans* α,β-epoxyaldehyde as a precursor of D-*ribo*-phytosphingosines was studied. The highly stereoselective alkylation of the aldehyde with a diorganozinc reagent was ensured through double asymmetric induction. The regioselective opening of the epoxide in turn gives access to an azide from which a C_{10} phytosphingosine can be easily prepared.

D-*ribo*-Phytosphingosine represents, along with D-*erythro*-sphinganine and sphingosine, the three main classes of sphingoid bases (Fig. 1). These long-chain (typically C_{18}) amino polyols, once *N*-acylated with a fatty acid to form a ceramide, constitute the backbone of sphingolipids, major components of eukaryotic cell membranes.[1] Originally isolated from mushrooms,[2] phytosphingosine is the most frequently encountered sphingoid base in yeasts[3] and plants.[4] In mammals, phytosphingosine-containing ceramides are present in many different tissues, especially in skin.[5] The phytosphingosine base has also recently been proposed to be a signaling molecule in yeast where it plays a key function in heat stress response[6] and endocytosis.[7] In addition, glycosyl ceramides embedding a phytosphingosine backbone have been isolated from marine sources.[8] Among them, the α-galactosyl ceramides agelasphins[9] and their synthetic congener KRN 7000[10] are strong immunostimulatory agents displaying promising antitumor[11] and antimalaria activities.[12]

In light of their significance, a variety of synthetic methods have been directed toward phytosphingosines.[13] Interestingly, however, very few chain-modified phytosphingosines have been described to date.[14] A possible general synthetic approach relies on the *anti*-selective addition of a long-chain nucleophile to a chiral α-alkoxyaldehyde. Only few syntheses based on this disconnection have been reported. They make use of chiral pool derived aldehydes and of alkynyl lithium[15] or titanium[16] and alkyl magnesium[17] or cerium[18] organometallic species. The (2*S*,3*R*)-α,β-epoxyaldehyde thus represents a potential four carbon electrophilic synthon for the preparation of D-*ribo*-phytosphingosines (Scheme 1). The epoxide moiety could act as a Felkin–Ahn directing chirality control element and allows in turn the introduction of the amino group via opening with an amine equivalent. The methodology of dialkyzinc reagents[19,20] seemed adapted to the synthesis of truncated, and possibly functionalized, new analogs of phytosphingosine.[21] We wish to report here our efforts to put this synthetic plan into practice.

Access to the required α,β-epoxyaldehyde **3** was secured via a Sharpless asymmetric epoxidation and a Doering oxidation from the *t*-butyldiphenylsilyl derivative **2** of



D-*ribo*-phytosphingosine D-*erythro*-sphingosine
D-*erythro*-sphinganine (dihydrosphingosine)

Figure 1.

Keywords: phytosphingosine; diorganozinc reagent; double asymmetric induction.
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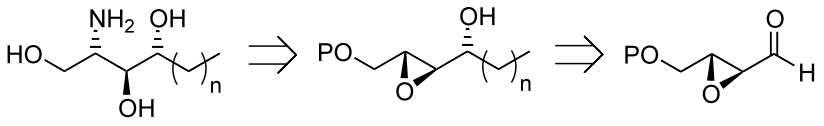


Scheme 1.

trans butene-1,4-diol (Scheme 2).[22] The latter was prepared by a two-step sequence: reduction of butyne-1,4-diol with LAH (80% yield) and monosilylation of the resulting *trans* allylic alcohol by slow addition of *t*-butylchlorodiphenylsilane (0.8 equiv.) in DMF in the presence of imidazole (56% yield based on the chlorosilane).[23]

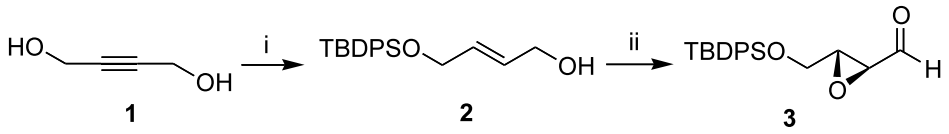
Preliminary studies used the commercially available diethylzinc. Treatment of aldehyde **3** in the absence of any external catalyst (2 equiv. Et_2Zn, toluene, 0°C, 26 h) led to the expected epoxyalcohols as a 85/15 diastereomeric mixture (73% yield) (not shown). The unwanted *syn* configuration was attributed to the major adduct on the basis of the ^{13}C NMR data of the acetonide (two distinct acetonide methyl signals at 19.8 and 30.1 ppm)[24] obtained after reduction with Red-Al to the corresponding 1,3-diol. This selectivity agrees with related studies where it has been proposed that diethylzinc only reacts when activated through chelation with the substrate.[25] Attempts to reverse selectivity adding $Ti(O\textit{i}\text{-}Pr)_4$ failed,[26] resulting in the absence of any reaction.

We then turned our attention to the disulfonamide–$Ti(O\textit{i}\text{-}Pr)_4$ catalytic system (Scheme 3).[27] First experiments conducted with racemic 1,2-*N*,*N*′-bis(trifluoromethanesulfonylamino)cyclohexane (0.05 equiv. catalyst, 1.2 equiv. $Ti(O\textit{i}\text{-}Pr)_4$, 2.2 equiv. Et_2Zn, degassed toluene, −20°C, 20 h) afforded the required *anti* diastereomer **4a** as the major ethylation product (70% de) in 75% yield, based on recovered starting material (BRSM), at 45% of conversion. More interesting data were obtained evaluating, under identical reaction conditions, the distinct contribution of each enantiomer of the catalyst to the asymmetric induction. While the (1*R*,2*R*) derivative only gave 20% de and 70% yield BRSM at 45% of conversion, the (1*S*,2*S*) gave almost complete stereoselection (95% de) and conversion (78% yield BRSM at 85% of conversion). This observation is coherent with the fact that (1*S*,2*S*) catalyst induces an *R* configuration.[27] The reaction was pushed to completion (using 2.4 equiv. of Et_2Zn either at −20°C for 20 h or at −10°C for 12 h) without affecting the stereoselectivity. The utility of this transformation was tested with the stereocontrolled addition of a hexyl radical through the use of the corresponding dialkylzinc reagent (0.2 equiv. catalyst, 3.5 equiv. Hex_2Zn, degassed toluene, −10°C, 20 h). The *anti* alkylation product, which was in this case the only diastereomer detectable, could be isolated in 40% yield.

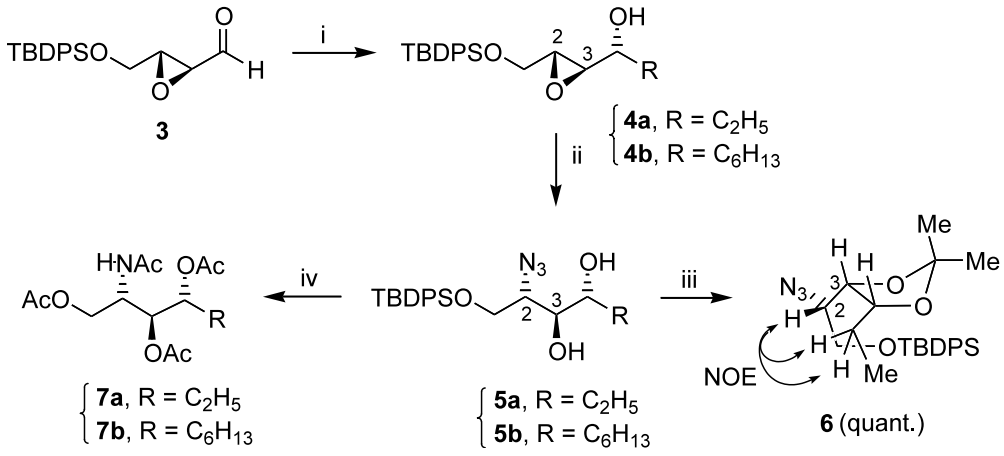
Introduction of the nitrogen atom was then studied. Direct opening of the epoxide ring in β of the newly formed secondary alcohol appeared to be the simplest option. Treatment of the *anti* epoxyalcohol **4a** under Sharpless conditions[28] (5 equiv. NaN_3, 2 equiv. NH_4Cl, methoxyethanol/H_2O, 120°C, 5 h) gave the two expected regioisomeric azidodiols (75/25 ratio) in 80% yield.[29,30] The structure of the major compound was attributed to the desired C-2 opening product on the basis of the NMR study of the corresponding acetonide. Resonance of the quaternary ketalic carbon at 108.3 ppm,[31] characteristic of a five-membered acetonide, unambiguously indicated the 1,2 relationship of the two alcohols.[32] Interestingly, a strong NOE correlation between H-2 and the C-5 methylene protons confirmed the *anti* configuration of these two alcohols. When applied to the epoxyalcohol resulting of the addition of dihexylzinc, these conditions led to the desired azidodiols in reasonable yield (65% BRSM at 80% of conversion) and with comparable regioselectivity.[33]

The C_2 and C_{10} D-*ribo*-phytoshingosines were generated from these azidodiols after smooth desilylation of the primary alcohol with the $Et_3N{\cdot}3HF$ complex in THF and hydrogenolysis of the azido group in good overall yield (85–90%, two steps). They were characterized as their peracetylated derivatives.[34]

In conclusion, we have explored a new enantioselective access to the D-*ribo*-phytosphingosine pattern. This route is based on the highly stereoselective alkylation of a chiral α,β-epoxyaldehyde which represents, to the best of our knowledge, the first case of double asymmetric induction involving a dialkylzinc reagent. Medium length phytosphingosines, thus accessible, are direct precursors of truncated ceramides which represent use-



Scheme 2. *Reagents and conditions*: (i) (a) LAH (2.2 equiv.), THF, reflux, 18 h, 80%; (b) *trans* butene-1,4-diol (1.3 equiv.), TBDPSCl (1 equiv., addition over 12 h), imidazole (2.5 equiv.), DMF, rt, 20 h, 56% based on the chlorosilane; (ii) (a) Sharpless epoxidation, (b) Doering oxidation (see Ref. 22).



Scheme 3. *Reagents and conditions*: (i) (1*S*,2*S*)-1,2-*N*,*N*′-bis(trifluoromethanesulfonylamino)cyclohexane (0.05 equiv. for R = C_2H_5, 0.2 equiv. for R = C_6H_{13}), Ti(O*i*-Pr)$_4$ (1.2 equiv.) R_2Zn (2.4 equiv. for R = C_2H_5, 3.5 equiv. for R = C_6H_{13}), degassed toluene, −20°C for R = C_2H_5, −10°C for R = C_6H_{13}, 20 h, 80% (95% de) for R = C_2H_5, 40% (100% de) for R = C_6H_{13}; (ii) NaN_3 (5 equiv.), NH_4Cl (2 equiv.), methoxyethanol/H_2O, 120°C, 5 h, 80% for R = C_2H_5, 65% BRSM at 80% of conversion for R = C_6H_{13}, C-2/C-3 opening ratio 75/25; (iii) dimethoxypropane, CSA (cat.), rt, overnight, quant.; (iv) (a) $Et_3N{\cdot}3HF$ (4 equiv.), THF, rt, 24 h, (b) 10% Pd/C (cat.), MeOH, rt, 18 h, (c) Ac_2O/pyridine (1/1), rt, 24 h, 90% (three steps) for R = C_2H_5, 85% (three steps) for R = C_6H_{13}.

ful biological tools.[35] Thanks to the mildness of diorganozinc reagents, this approach opens the way to the preparation of novel functionalized phytosphingosine analogs.

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30. In situ prepared $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ gave a better regioselectivity (92/8 ratio based on ^1H NMR) but only 63% yield BRSM at 43% conversion using standard Sharpless conditions.[28b]
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34. Separation of the two regioisomers was accomplished at that stage for the C_{10} derivative by means of reverse phase HPLC (Hypersil Hyperprep C_{18} 10 μm, acetonitrile/water, 55/45). Selected data for **7b**: $[\alpha]_D^{20}$ +33 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 0.86 (t, $J=6.3$ Hz, 3H), 1.10–1.45 (m, 8H), 1.55–1.75 (m, 2H), 2.01 (s, 3H), 2.03 (s, 6H), 2.07 (s, 3H), 3.99 (dd, $J=3.0$, 11.7 Hz, 1H), 4.28 (dd, $J=4.7$, 11.7 Hz, 1H), 4.40–4.52 (m, 1H), 4.92 (dt, $J=3.4$, 9.1 Hz, 1H), 5.09 (dd, $J=3.0$, 8.2 Hz, 1H), 6.01 (d, $J=9.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 14.0, 20.8×2, 21.0, 22.6, 23.3, 25.4, 28.1, 28.9, 31.6, 47.6, 62.8, 71.9, 72.9, 169.7, 170.1, 170.9, 171.2; MS (DCI, NH_3) m/z 391 $[M+NH_4]^+$.
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