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Synthesis of D-*erythro*-sphingosine and D-*erythro*-ceramide

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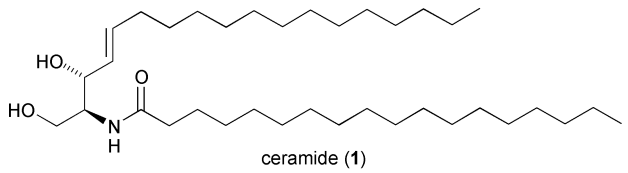
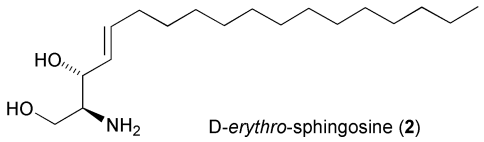
A 1,2-metallate rearrangment of a higher order cuprate derived from an α-lithiated xylal derivative and tridecyllithium is the key step in a synthesis of D-*erythro*-sphingosine and ceramide. A convenient method for preparing α-lithiated glycals from α-phenylsulfinyl glycals is also described.

Sphingolipids anchor carbohydrates to cell surfaces. Enzymatic cleavage of sphingolipids releases ceramide (**1**), which plays a central role in signal transduction; it inhibits cell growth and induces apoptosis. Strip ceramide of its *N*-acyl group and the residual D-*erythro*-sphingosine (**2**) is itself an inhibitor of protein kinase C.[1,2] We now add a fresh brick to the pyramid of sphingosine syntheses[3–5] that is noteworthy for three reasons. We report (a) two efficient methods for the synthesis of α-lithiated glycals; (b) the first example of a 1,2-metallate rearrangement of glycal derivatives; and (c) a rare O–C–O silicon shuttle that imparts strategic benefit to our approach.



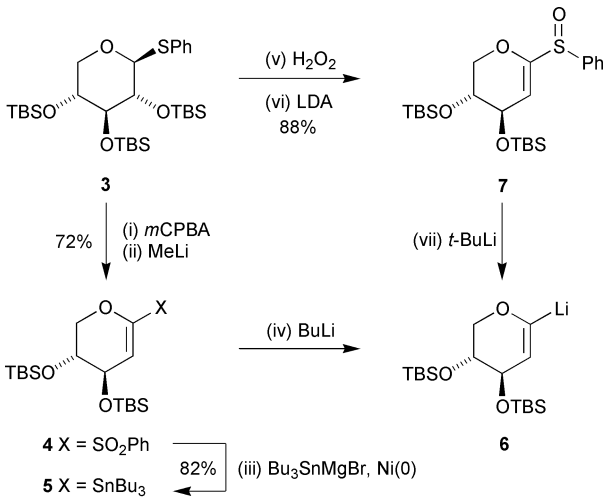
ceramide (**1**)



D-*erythro*-sphingosine (**2**)

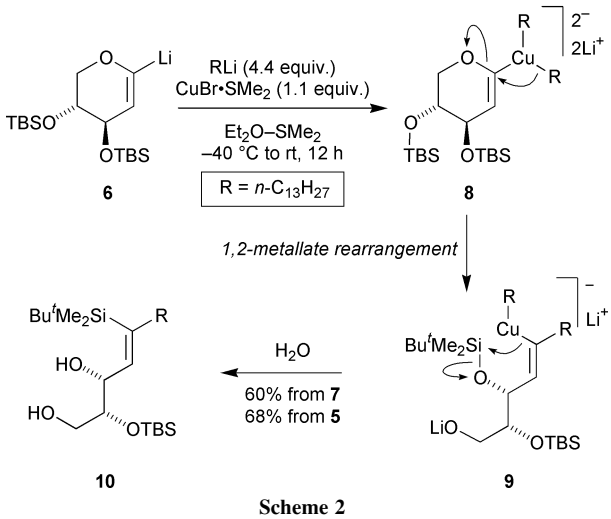
The synthesis of the crucial α-lithiated glycal intermediate **6** is summarised in Scheme 1. 1-Thio-β-D-xylopyranoside, protected as its tris(*tert*-butyldimethylsilyl) ether **3**, was oxidised to the corresponding sulfone. Subsequent β-elimination using MeLi as base afforded the α-phenylsulfonyl glycal derivative **4** in 72% yield. A new Ni(0)-catalysed coupling of tributylstannylmagnesium bromide converted the sulfone **4** to the corresponding stannane **5** in 82% yield on a 20 mmol scale.[6] Transmetallaton with BuLi then gave the desired lithium derivative **6**. A shorter synthesis of **6** from the thioglycoside **3** that avoided tin intermediates began with oxidation of the thioether to the corresponding sulfoxide with hydrogen peroxide catalysed by ammonium molybdate and subsequent β-elimination of *t*-BuMe$_2$SiOLi with LDA to give the stable, storable α-phenylsulfinyl glycal **7** in 69% yield from **3**. Reaction of sulfoxide **7** with *t*-BuLi at −78 °C resulted in phenylsulfinyl-lithium exchange and generation of α-lithiated glycal **6** in less than 5 min. The latter process is an adaptation of a recent synthesis of glycosyllithiums from glycosyl sulfoxides based on phenylsulfinyl–lithium exchange and solves a long-standing problem in metallated glycal chemistry.[7]

The key step in our synthesis is a Cu(I)-mediated 1,2-metallate rearrangement shown in Scheme 2.[8,9] Reaction of the α-lithiated glycal **6** with CuBr·SMe$_2$ (1.1 equiv.) and *n*-



Scheme 1 *Reagents and conditions*: (i) *m*CPBA (2.1 equiv.), NaHCO$_3$ (7.5 equiv.), CH$_2$Cl$_2$, 0 °C to rt, 12 h (80%); (ii) MeLi (1.5 equiv.), THF, −78 °C, 20 min (89%); (iii) Bu$_3$SnMgBr·LiBr (2 equiv.), Ni(0) (0.1 equiv.), PPh$_3$ (0.2 equiv.), THF–Et$_2$O, −78 to 20 °C, 12 h (82%); (iv) BuLi (1 equiv.), THF–Et$_2$O, −78 °C, 15 min; (v) H$_2$O$_2$ (3 equiv.), (NH$_4$)$_2$MoO$_4$ (6 mol%), EtOH, 0 °C, 12 h; (vi) LDA (2.5 equiv.), THF, −78 °C, 2 h (97%); (vii) *t*-BuLi (1 equiv.), THF–Et$_2$O, −78 °C, 5 min.

tridecyllithium (4.4 equiv.) generated the alkenylsilane **10** in 60–68% overall yield after aqueous workup. The product can be explained by a 1,2-metallate rearrangement of the higher order cuprate **8** with inversion of configuration to give the alkenyl cuprate **9** which undergoes a selective intramolecular O→C silyl transfer of the C3O–silyl group. Crucial to the success of the reaction were conditions that favoured the stability of the putative higher order cuprate intermediate **8**: (a) low initial reaction temperature; (b) use of Et$_2$O rather than THF as solvent; (c) the presence of a large excess of SMe$_2$[10] and (d) the use of CuBr·SMe$_2$ freshly prepared[11] by reduction of CuBr$_2$



Scheme 2

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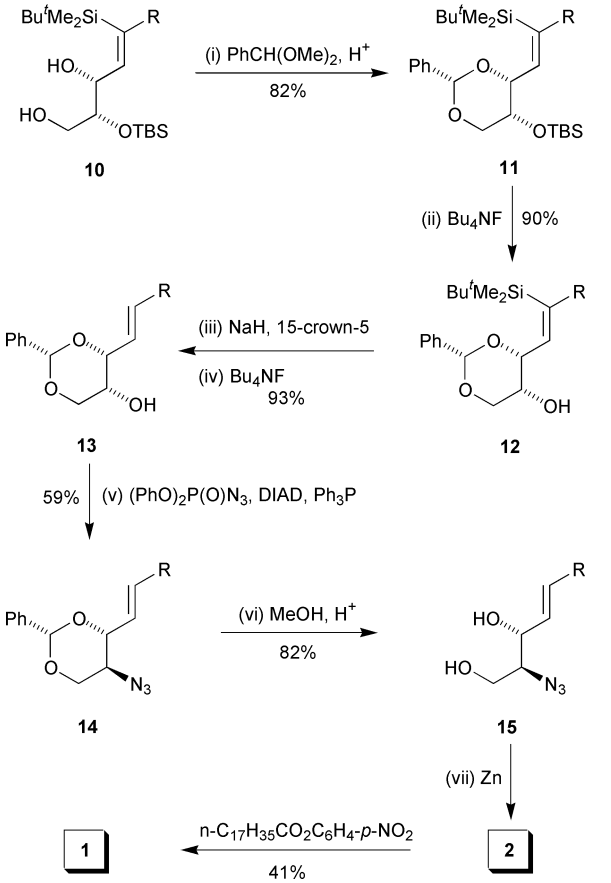
with sodium sulfite.[12] A further factor that contributed to good yields in the transformation depicted in Scheme 2 was the use of 4.4 equiv. of tridecyllithium.

To complete the synthesis (Scheme 3), the 1,3-diol **10** was protected as its benzylidene acetal derivative **11** and the remaining *O*-TBS ether cleaved with tetrabutylammonium fluoride. The *C*-TBS group was then transferred back to oxygen (Brook rearrangement)[13,14] by treating alcohol **12** with sodium hydride and 15-crown-5 in refluxing THF to give a mixture of alcohol **13** and its *O*-TBS ether derivative. The mixture was treated with tetrabutylammonium fluoride to give the known alcohol **13**[15] in 93% yield whence a Mitsunobu reaction using diphenylphosphoryl azide[16] afforded the inverted azide **14**[15] in 59% yield. Reduction of the azide **15**, derived from methanolysis of the benzylidene acetal **14**,[15] using standard literature procedures (Ph_3P, H_2S)[15,17] was either slow or gave several products and modest yields at best but reduction with Zn and ammonium chloride (40 equiv. each) in methanol afforded D-*erythro*-sphingosine (**2**) as a white waxy solid. Owing to the instability of **2** towards recrystallisation and column chromatography, it was characterised as the ceramide **1**, prepared by reaction of crude **2** with *p*-nitrophenyl stearate.[18] Synthetic **1** gave mp 96–97 °C (lit mp 97–98 °C),[19] $[\alpha]_D$ −3.0 (lit $[\alpha]_D$ −3.1),[19] 500 MHz ^{1}H and 125 MHz ^{13}C NMR spectroscopic data were consistent with data reported for the natural product.[19]



Scheme 3 *Reagents and conditions*: (i) $PhCH(OMe)_2$ (5 equiv.), *p*-TsOH (12 mol%), CH_2Cl_2, rt, 2 h (82%); (ii) Bu_4NF (1.2 equiv), THF, rt, 12 h (90%); (iii) NaH (60 mol%), 15-crown-5 (60 mol%), THF, reflux, 14 h; (iv) Bu_4NF (1.2 equiv.) (93%): (v) PPh_3 (2 equiv.), diphenylphosporyl azide (2 equiv.), diisopropyl azodicarboxylate (3 equiv.), PhMe, rt, 12 h, (59%); (vi) *p*-TsOH (42 mol%), MeOH, rt, 12 h (82%); (vii) Zn powder (40 equiv.), NH_4Cl (40 equiv.), MeOH, rt, 12 h.

In conclusion, we have devised a 9-step synthesis of the known D-*erythro*-sphingosine intermediate **13** (9–12% overall) from cheap D-xylose using a 1,2-metallate rearrangement as the key step. We have also described a method for making α-lithiated glycals from α-phenylsulfinyl glycals that is fast, efficient and devoid of tin.

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