Synthesis of phalluside-1 and Sch II using 1,2-metallate rearrangements†

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(4*E*,8*E*,10*E*)-9-Methyl-4,8,10-sphingatrienine, a core component of marine sphingolipids, was synthesised for the first time using a copper(I)-mediated 1,2-metallate rearrangement of a lithiated glycal as a key step. It was converted to phalluside-1, a cerebroside isolated from the ascidian *Phallusia fumigate*. By an analogous route, (4*E*,8*E*)-9-methyl-4,8-sphingadiene was synthesised and converted to Sch II, a cerebroside that induces fruiting body formation in the basidiomycete *Schizophyllum commune*.

Introduction

Cerebrosides such as the ubiquitous β-D-glucosylceramide **3** (Scheme 1) consist of three components: a hydrophilic hexapyranose head group, a hydrophobic fatty acid-derived *N*-acyl chain and a serine-derived sphingoid base. Cerebrosides are an essential component of eukaryotic cells and they are present in some prokaryotic organisms and viruses. They are predominantly found in cell membranes where they serve as structural support and texture determinants.[1,2] Cerebrosides are involved in a broad range of biological functions including cell–cell signalling, cell recognition and adhesion.[3,4] In addition, the products of cerebroside metabolism act as second messengers in cell signalling pathways.[5]

Most of the cerebrosides of the plant and animal kingdoms share a common biosynthetic precursor in the *N*-acylsphinganines **1a** and **1b**.[6] Subsequent enzymatic transformations then create a diverse array of unsaturated cerebrosides whose properties and biological function are determined by the number, position and configuration of their double bonds. Thus, in mammals, the *N*-acylsphinganine **1a** is dehydrogenated by a Δ^4-desaturase[7-9] to ceramide (**2**) which is then glycosylated[10] to afford β-D-glucosylceramide **3**. The cerebrosides of plants, fungi and marine organisms are more highly functionalised than their mammalian counterparts. Cerebroside B_{1b} (**4**) typifies the additional transformations wrought in higher plants. By the action of Δ^8-desaturase, an additional double bond is installed in the sphingoid base and the *N*-acyl chain is hydroxylated at the 2 position.[11] In the case of the cerebrosides from fungi and some marine organisms, a methyl branch is appended to C9 by an *S*-adenosylmethionine-dependent enzyme (C9-methyltransferase) to generate a trisubstituted (*E*)-alkene.[12] Sch II (**5**), a cerebroside isolated from the basidiomycete *Schizophyllum commune*[13] and the sea anemone *Metridium senile*,[14] exemplifies the range of structural modifications and their probable order (Scheme 1). Desaturase modification is most prevalent in the sphingoid bases but it has also been observed in the *N*-acyl chain as in fusaruside (**6**).[15] Recently a 2-hydroxy fatty *N*-acyl-Δ^3(*E*)-desaturase from the plant pathogen *Fusarium graminearum* has been identified and cloned.[16]

Many cerebrosides display useful biological activity. The active anti-ulcerogenic components of the plant *Tetragonia tetragonoides* used in traditional Chinese herbal medicine are cerebroside B_{1b} (**4**) and its (8*E*) diastereoisomer, cerebroside B_{1a}.[17] Cerebroside B_{1b} binds Ca^{2+} ions and participates in active ion transport across human erythrocyte cell membranes.[18,19] Sch II (**5**) induces fruiting body formation in *Schizophyllum commune*[13,20] probably due to inhibition of replicative DNA polymerase-α.[21] Fusaruside (**6**), from an endophytic *Fusarium* fungus,[15] exhibits antibacterial activity and the closely related ophidiacerebrosides A–D from the starfish *Ophidiaster ophidiamus*[22] are cytotoxic towards L1210 murine leukemia cells *in vitro* whilst agelasphin-10 from the sponge *Agelas mauritianus*[23] is active *in vivo* against B16 murine melanoma.[24]

Numerous syntheses of β-D-glucosylceramide (**3**), ceramide (**2**) and their precursor D-*erythro*-sphingosine have been reported.[25-31] In contrast, syntheses of the cerebrosides based on (4*E*,8*E*)-9-methyl-4,8-sphingadiene such as Sch II are rare. Sch II was first synthesised by Mori and Funaki[32,33] in 1985 and a revised route was published in 1996 as part of a synthesis of Pen II.[34] Murakami and co-workers[35] described a synthesis of Sch II which is akin to the Mori–Funaki synthesis in a common early key step: the nucleophilic addition of an alkenylmetal reagent to Garner's aldehyde. Wu and co-workers[36] accomplished a synthesis of (4*E*,8*E*)-9-methyl-4,8-sphingadiene in which the diene was constructed by an S_N2' reaction of an allylic cuprate with an allylic mesylate. We now report the first total synthesis of (4*E*,8*E*,10*E*)-9-methyl-4,8,10-sphingatrienine[37] and its conversion to phalluside-1 (**7**, Scheme 2), a cerebroside from the Mediterranean ascidian *Phallusia fumigate*[38] and the starfish *Allostichaster inaequalis*[39] and *Cosmasterias lurida*.[40] We also describe a synthesis of Sch II by a related route.

Results and discussion

According to the retrosynthetic analysis shown in Scheme 2, phalluside-1 was constructed from the glucosyl trichloroacetimidate **8**, the (*R*)-2-hydroxyhexadecanoic acid derivative **9** and the azidosphingatrienine derivative **10**. Key steps in our synthesis are two Cu(I)-mediated 1,2-metallate rearrangements deployed in the construction of two strategic bonds in the azidosphingatrienine **10**.

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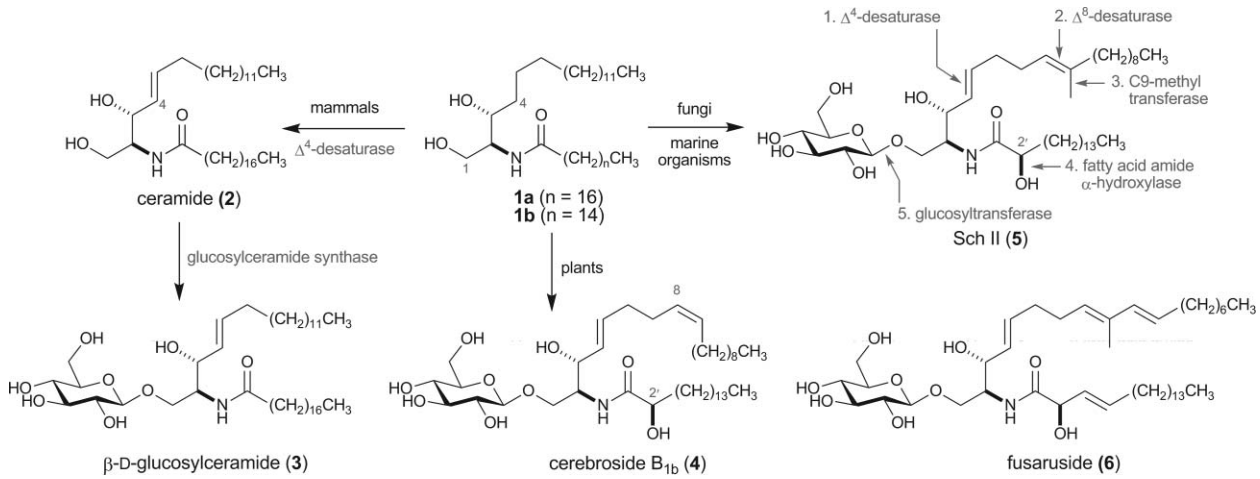
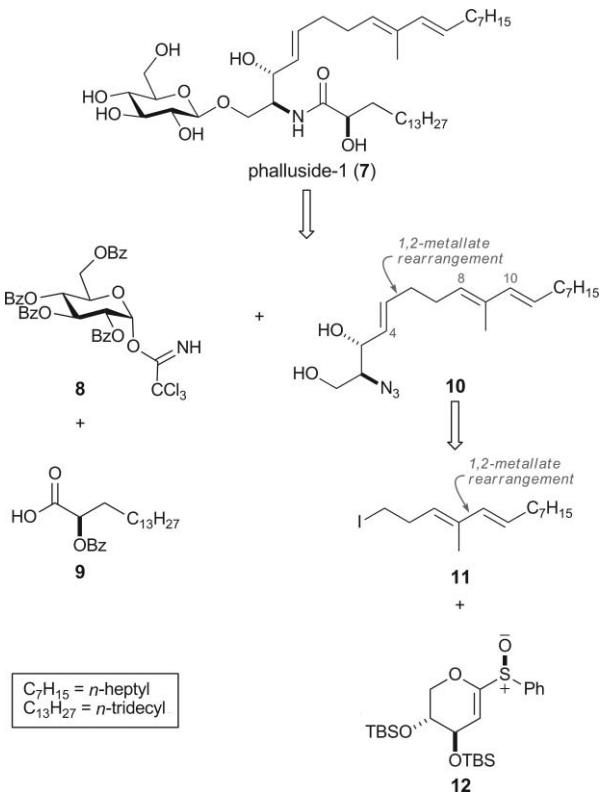
† Electronic supplementary information (ESI) available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/b920285d

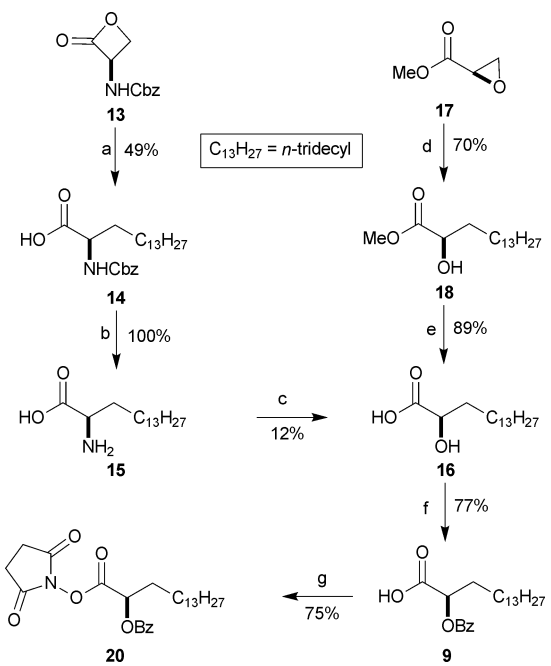


Scheme 1



Scheme 2

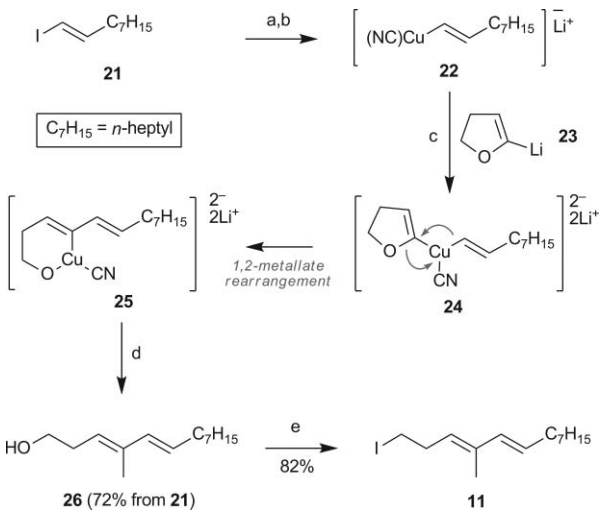
We begin our account with the synthesis of the benzoate ester **9**. Its precursor, (*R*)-2-hydroxyhexadecanoic acid (**16**), had been prepared from hexadecanoic acid by the action of α-oxidase enzymes extracted from germinating peas.[41,42] It had also been prepared from racemic 2-hydroxyhexadecanoic acid by classical resolution[43,44] and by kinetic resolution through lipase-catalysed enantioselective acetylation.[45,46] Mori and Funaki[32] synthesised (*R*)-2-hydroxyhexadecanoic acid by diazotisation of (*R*)-2-aminohexadecanoic acid which, in turn, had been derived from kinetic resolution of racemic 2-(chloroacetamido)hexadecanoic acid using an *Aspergillus* amino acylase. However, we required a short synthesis of enantiopure 2-hydroxyalkanoic acids from a single precursor which could be easily adapted to the synthesis of homologues. Our efforts are summarised in Scheme 3. Enantiopure β-lactone **13** is readily available in 2 steps from D-serine[47] and it reacted with the organocuprate derived from *n*-tridecyllithium by an S_N2 mechanism[48–50] to give (*R*)-*N*-Cbz-2-aminohexadecanoic acid (**14**) in 49% yield. Following hydrogenolysis of the Cbz group, the (*R*)-2-aminohexadecanoic acid (**15**) in aq. HCl–dioxane was treated with excess nitrous acid at r.t. to give the desired (*R*)-2-hydroxyhexadecanoic acid (**16**) in a meagre 12% yield.[51]



Scheme 3 *Reagents and conditions*: (a) $(n\text{-}C_{13}H_{27})_2CuLi$ (5.0 equiv), Et_2O–SMe_2, −25 °C, 49%; (b) H_2, Pd/C, HOAc–H_2O, r.t., 100%; (c) $NaNO_2$ (60 equiv), dioxane–0.5 M HCl, 0 °C → r.t., 12%; (d) $(n\text{-}C_{13}H_{27})_2CuLi$ (2.5 equiv), Et_2O–SMe_2, −78 → −60 °C, 70%; (e) LiOH, THF–H_2O–MeOH, r.t., 89%; (f) BzCl, PhMe–py (4 : 1), r.t., (77%); (g) *N*-hydroxysuccinimide (1.2 equiv), DCC (1.1 equiv), THF, 0 °C → r.t., 75%.

The low yield in the forgoing series prompted us to examine a related sequence involving reaction of commercial methyl (*R*)-2,3-epoxypropionate (**17**)[52,53] with the organocuprate derived from *n*-tridecyllithium. By conducting the reaction at −78 °C in the presence of dimethylsulfane to stabilise the cuprate, methyl (*R*)-2-hydroxyhexadecanoate (**18**) was obtained in 70% yield. Hydrolysis of the methyl ester with LiOH and esterification of the C2 hydroxyl gave the desired benzoate ester **9**. The carboxylic acid was then converted to its crystalline *N*-succinimidyl ester **20**.

Azidosphingatrienine **10** was constructed from two fragments: the iodoalkane **11** and the glycal sulfoxide **12**. The glycal sulfoxide **12** was prepared from D-xylose in 6 steps (25% overall) by a published procedure.[54] The iodoalkane was synthesised as shown in Scheme 4 using the first of two 1,2-metallate rearrangements[55] to install the trisubstituted alkene. To a solution of the lower order cyanocuprate **22** in Et_2O at −20 °C was added a solution of the lithiated dihydrofuran **23** to give the higher order cyanocuprate **24**. On warming to r.t., the requisite 1,2-metallate rearrangement occurred to afford the higher order oxycuprate **25** which was quenched with excess iodomethane to afford the pure (*E*,*E*)-homoallylic alcohol **26** in 72% overall yield from (*E*)-1-iodononene (**21**).[56,57] Conversion of the alcohol **26** to the iodoalkane **11** was accomplished under standard conditions in 82% yield.



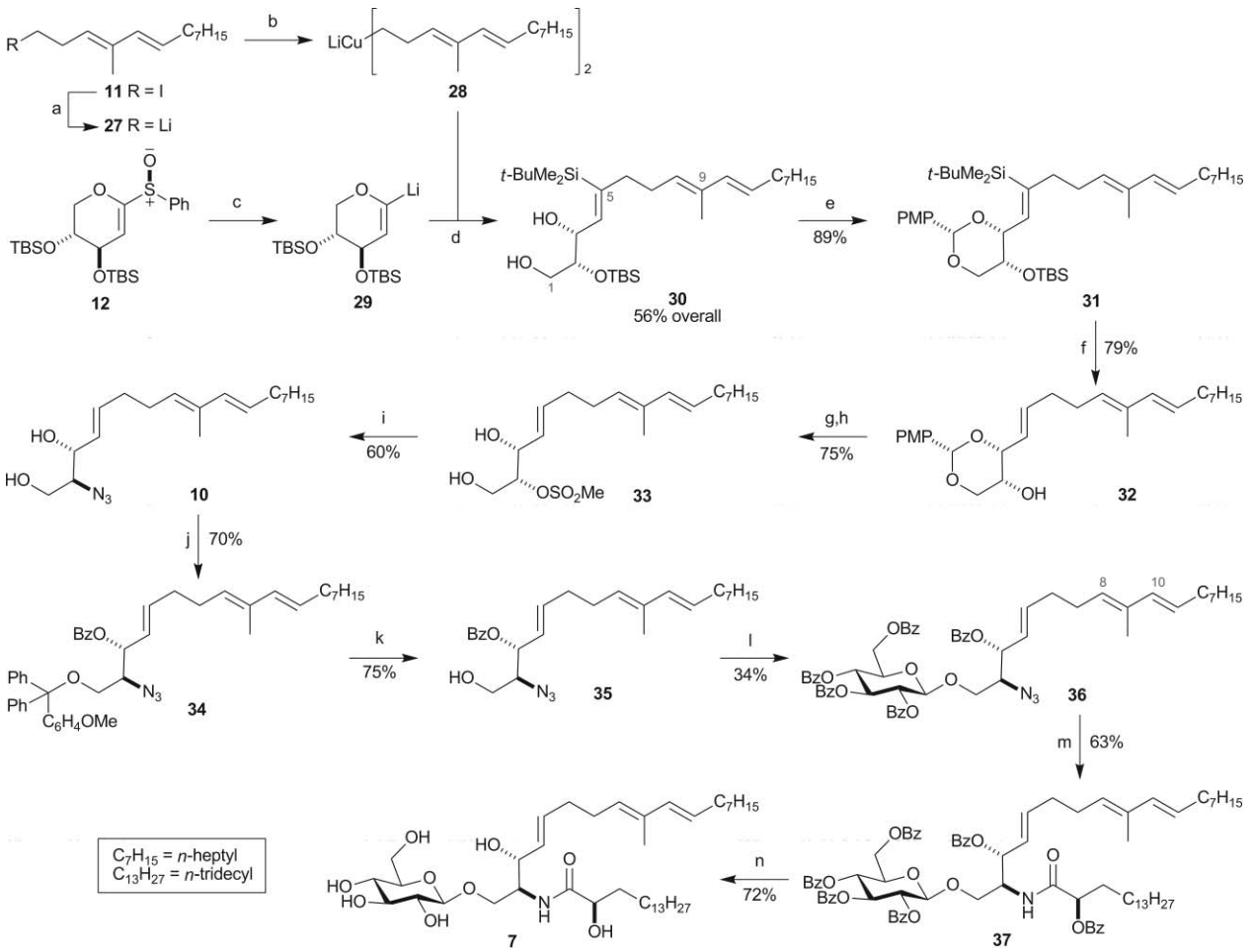
Scheme 4 *Reagents and conditions*: (a) **21** (1.5 equiv), *t*-BuLi (3.0 equiv), pentane–Et_2O, −78 °C, 30 min then 0 °C, 1 h; (b) CuCN (1.0 equiv), Et_2O, −78 °C then −20 °C, 30 min; (c) add a solution of 2-lithiodihydrofuran (**23**, 1.0 equiv) in Et_2O to cyanocuprate **22** at −20 °C; (d) add MeI (10 equiv), −78 °C → r.t., 72% overall from **21**; (e) I_2 (1.5 equiv), PPh_3 (1.5 equiv), imidazole (1.5 equiv), THF, r.t., 82%.

The union of the 4 fragments to give phalluside-1 is depicted in Scheme 5. The sequence began with the second 1,2-metallate rearrangement using conditions previously established in a prototypical synthesis of D-*erythro*-sphingosine.[58] Thus the lithiated glycal **29** generated by a sulfoxide–lithium exchange reaction of sulfoxide **12** with *tert*-butyllithium[54] was added to a solution of the homocuprate **28** in Et_2O at −35 °C. On warming to 0 °C the 1,2-metallate rearrangement occurred to give the alkenylsilane **30** in 56% yield by a mechanism that will be discussed below. After protecting the diol as its *p*-methoxyphenyl acetal **31**, the two *tert*-butyldimethylsilyl groups were expunged by brief treatment with excess TBAF in DMF at 110 °C. The hydroxyl group in **32** was converted to its methanesulfonate ester whereupon methanolysis of the labile *p*-methoxyphenyl acetal with trifluoroacetic acid (pK_a 0.23) gave the diol **33**. Earlier attempts to deploy a more robust benzylidene acetal foundered because the conditions required for its methanolysis at room temperature (*p*-toluenesulfonic acid, pK_a −6.62) isomerised the trisubstituted alkene. The final step in the sequence leading to the azidosphingatrienine **10** entailed nucleophilic substitution of the methanesulfonate ester in **33**. The reaction was slow and best results were achieved using tetramethylguanidinium azide in DMF at 50 °C for 4 days during which a small amount of isomerisation to the (8*Z*) alkene was observed.

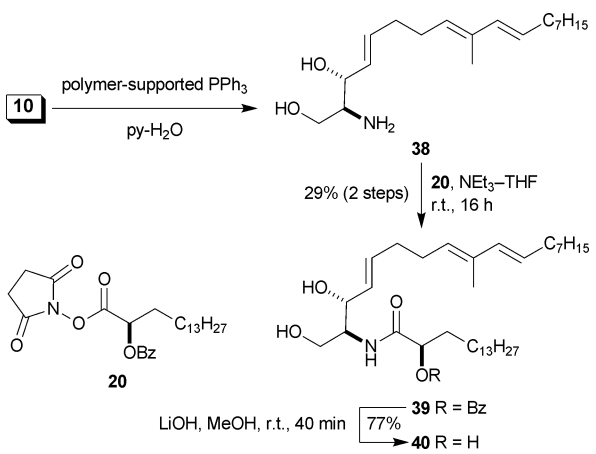
Our decision to perform a Schmidt glycosylation on the azidoshingatrienine before appending the *N*-acyl group[59] was informed by earlier experience of Schmidt and Zimmermann[60] in their synthesis of cerebrosides based on D-*erythro*-sphingosine. However, attempts to glycosylate the primary alcohol[61] in systems closely related to **10** were complicated by low yields and competing glycosylation of the secondary alcohol as well. We therefore reluctantly adopted a more oblique approach (Scheme 5) involving first protection of the primary alcohol in **10** as its monomethoxytrityl ether **34** followed by protection of the secondary alcohol as its benzoate ester then methanolysis of the monomethoxytrityl protecting group using pyridinium tosylate as the acid catalyst. This 3-step detour was expensive giving primary alcohol **34** with the (8*E*) alkene intact in 52% yield from **10**.

Schmidt glycosylaton[62] of the alcohol **35** with the donor **8** using 1 equivalent of $BF_3{\cdot}OEt_2$ gave a mixture of products from which the glycoside **36** was isolated in a paltry 34% yield. A Staudinger reaction transformed the azide **36** to the primary amine which was then *N*-acylated with (*R*)-2-(benzoyloxy)hexadecanoic acid (**9**) mediated by dicyclohexylcarbodiimide to give **37** in 63% yield for the two steps. Finally, global deprotection of the 6 benzoate esters with sodium methoxide in methanol gave phalluside-1 (**7**) displaying $[\alpha]_D$, ^1H NMR and ^{13}C NMR data consistent with literature data recorded on the natural product isolated from *Phallusia fumigate*.[39] The ceramide of phalluside-1 (**40**, Scheme 6) was also synthesised in 3 steps from azidosphingatrienine **9** in anticipation of its isolation from natural sources.

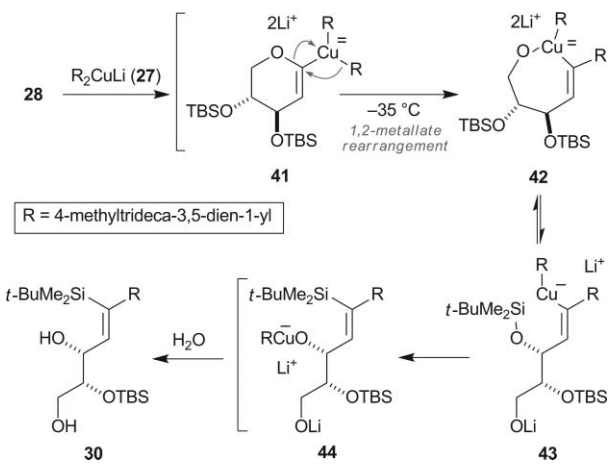
We now return to the mechanism by which the alkenylsilane **30** was generated. The product can be explained (Scheme 7) by two consecutive anionic rearrangements, the first being a 1,2-metallate rearrangement of the higher order cuprate **41** with inversion of configuration to give the higher order alkenyl oxycuprate **42**. Equilibration of **42** to the open chain tautomer **43** enables a second anionic rearrangement, an intramolecular 1,4-O → C(sp^2) silyl migration[63,64] of the C3O–silyl group, to give the lower order oxycuprate **44**. Precedent suggests that the 1,4-O → C(sp^2) silyl migration (retro-Brook rearrangement[65,66]) is reversible with the greater stability of the oxyanion *vs.* the carbanion prevailing over the energy difference between the Si–O and Si–C bonds.[67] Crucial to the success of the reaction were conditions that favoured the stability of the putative higher order cuprate intermediate **41**: (a) low initial reaction temperature; (b) use of Et_2O rather than THF as solvent; (c) the presence of a large excess of SMe_2 and (d) the use of $CuBr{\cdot}SMe_2$ freshly prepared by reduction of $CuBr_2$ with sodium sulfite.[68] A further factor that contributed to good yields



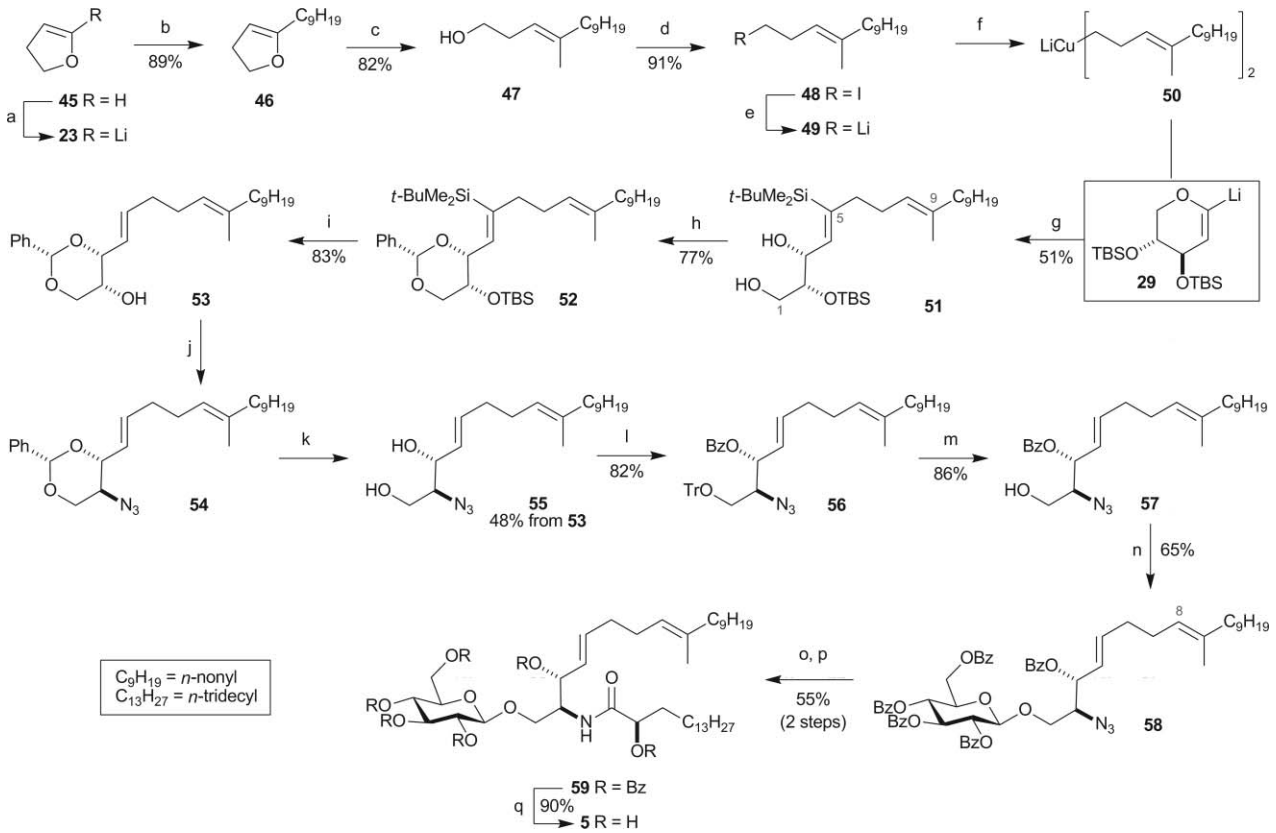
Scheme 5 *Reagents and conditions*: (a) **11** (4.4 equiv), *t*-BuLi (8.8 equiv), pentane–Et_2O, –78 °C, 30 min then 0 °C, 1 h then r.t., 1 h; (b) CuBr·SMe_2 (1.1 equiv), Et_2O–SMe_2, 0 °C, 1 h; (c) *t*-BuLi (1.0 equiv), THF (2.0 equiv), Et_2O, –78 °C, 30 min; (d) add **29** to cuprate **28**, –35 °C 30 min then 0 °C, 3 h, 56% from **12**; (e) 4-$MeOC_6H_4CH(OMe)_2$ (5.0 equiv), *p*-TsOH (cat.), CH_2Cl_2, r.t., 89%; (f) Bu_4NF (2.4 equiv), DMF, 120 °C, 10 min, 79%; (g) MsCl (1.5 equiv), NEt_3 (1.9 equiv), CH_2Cl_2, 0 °C; (h) CF_3CO_2H (25 mol%), MeOH–CH_2Cl_2 (2.4 : 1), r.t., 5 h, 75% from **32**; (i) tetramethylguanidinium azide (5.0 equiv), DMF, 50 °C, 4 d, 60%; (j) 4-$MeOC_6H_4(Ph)_2CCl$ (4.4 equiv), DMAP (5 mol%), NEt_3 (6.0 equiv), CH_2Cl_2, r.t., 3 d then BzCl (10 equiv), py–PhMe, r.t., 10 h, 70% from **10**; (k) PPTS (1.0 equiv), MeOH–CH_2Cl_2 (5 : 1), r.t., 24 h, 75%; (l) **8** (2.5 equiv), BF_3·OEt_2 (1.1 equiv), 4 Å MS, CH_2Cl_2, 0 °C, 10 min then r.t., 2 h, 34%; (m) PPh_3 (3.0 equiv), THF–H_2O, 45 °C, 5 h then **9** (1.5 equiv), DCC (1.5 equiv), HOBt (1.4 equiv), CH_2Cl_2, r.t., 3 d, 63% (2 steps); (n) NaOMe (1.9 equiv), MeOH–THF, 0 °C → r.t., 2.5 h, 72%.



Scheme 6



Scheme 7



Scheme 8 *Reagents and conditions*: (a) add *t*-BuLi (1.6 equiv) to **45** (1.9 equiv) THF–pentane, –40 → –5 °C; (b) add 1-iodononane (1.0 equiv), –20 °C → r.t., 89% from 1-iodononane; (c) MeMgBr (2.2 equiv), $NiCl_2[PPh_3]_2$ (2 mol%), Et_2O–PhMe, reflux, 4 h, 82%; (d) I_2 (1.2 equiv), PPh_3 (1.2 equiv), imidazole (1.2 equiv), THF, –10 °C, 1 h then r.t., 3 h, 91%; (e) add **48** (4.4 equiv) to *t*-BuLi (8.8 equiv) in Et_2O–pentane, –78 °C, 30 min then 0 °C, 1 h then r.t., 1 h; (f) **49** (4.4 equiv), $CuBr{\cdot}SMe_2$ (1.1 equiv), Et_2O–SMe_2, 0 °C, 1 h; (g) add **29** (1.0 equiv) to the solution of **50** (1.1 equiv) and **49** (2.2 equiv), –35 °C, 30 min then 0 °C, 3 h, 51%; (h) $PhCH(OMe)_2$ (5.0 equiv), *p*-TsOH (cat.), CH_2Cl_2, r.t., 89%; (i) Bu_4NF (2.4 equiv), DMF, 120 °C, 10 min, 83%; (j) $(PhO)_2P(O)N_3$ (6.0 equiv), PPh_3 (2.0 equiv), DIAD (2.0 equiv), PhMe, r.t.; (k) *p*-TsOH, MeOH, r.t., 48% from **53**; (l) Ph_3CCl (3.0 equiv), NEt_3 (3.6 equiv), EtOAc, r.t. then add BzCl, py–PhMe, r.t., 82%, 2 steps; (m) $BF_3{\cdot}OEt_2$ (3.0 equiv), PhMe–MeOH (3 : 2), r.t., 86%; (n) **8** (2.5 equiv), $BF_3{\cdot}OEt_2$ (1.0 equiv), 4 Å MS, CH_2Cl_2, r.t., 65%; (o) PPh_3 (3.0 equiv), THF–H_2O, 45 °C, 5 h; (p) **9** (1.5 equiv), DCC (1.5 equiv), HOBt (1.5 equiv), r.t., 3 d, 55% (2 steps); (q) NaOMe (2.0 equiv), MeOH–THF, 0 °C, r.t., 90%.

in the transformation depicted in Scheme 7 was the use of 4.4 equiv. of (*E*)-4-methyltrideca-3,5-dien-1-yllithium (**27**).

Scheme 8 depicts a synthesis of Sch II using a 1,2-metallate rearrangement involving the lithiated glycal **29** and the organocuprate **50** as the key step. The route began with the alkylation of the lithiated dihydrofuran **23** with 1-iodononane. The resultant dihydrofuran **46** (89% yield) underwent a Ni(0)-catalysed coupling reaction[69–72] with MeMgBr in refluxing toluene to give the homoallylic alcohol **47** as a single isomer in 82% yield. Hereafter the route resembles the synthesis of phalluside-1 save in one significant aspect: the relative stability of the single trisubstituted alkene at C8 in the Sch II 4,8-sphingadienine base compared with the conjugated diene in the 4,8,10-sphingatrienine resulted in higher tolerance towards acid and consequently cleaner reactions and higher yields, especially in the glycosidation step (**57** → **58**). Our synthetic Sch II displayed ^1H NMR and ^{13}C NMR spectroscopic data (recorded at 500 and 125 MHz respectively in pyridine-d_5) consistent with literature data recorded at 400 and 100 MHz respectively on the natural product isolated from *Tuber indicum*.[73]

Conclusion

The 1,2-metallate rearrangement of lithiated glycals derived from D-xylose provides a general route to three of the most common sphingolipid bases: D-*erythro*-sphingosine,[58] D-*erythro*-9-methyl-4,8-sphingadienine and D-*erythro*-9-methyl-4,8,10-sphingatrienine. One of the virtues of our approach is the ease with which structural diversity can be attained through the use of different metallated glycals[74] and organocuprate ligands including unsaturated ligands that would otherwise be incompatible with cross metathesis reactions.[75–77] Efforts are currently underway to show that glycals derived from all the common monosaccharides participate in 1,2-metallate rearrangements with a wide variety of organocuprates.

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