Copper(I)-Mediated 1,2-Metallate Rearrangements of 1-Metallated Glycals

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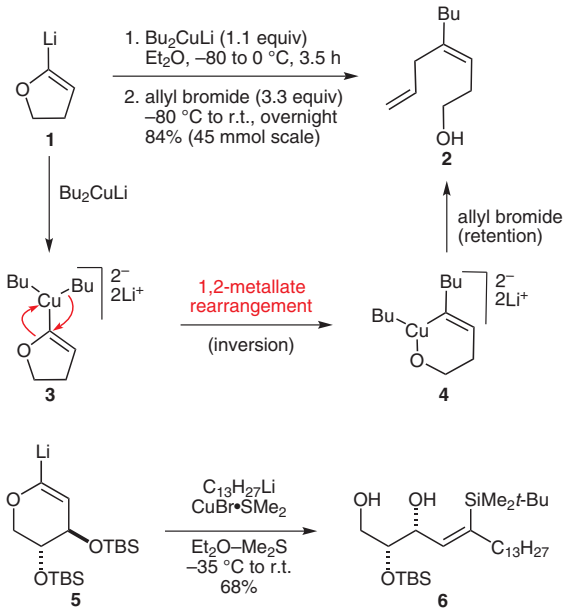
Abstract: 1,2-Metallate rearrangements involving reaction of 1-metallated glycals with organolithium reagents under copper(I) mediation give alkenylpolyol chains in 45–91% yield (19 examples). The reaction was applied to a formal synthesis of KRN7000 as well as a synthesis of a $\Delta^{5,6}$-ceramide derivative.

Key words: 1,2-metallate rearrangement, retro-[1,4]-Brook rearrangement, 1-metallated glycals, cuprates, organolithiums, KRN7000

We have previously described a one-pot connective synthesis of trisubstituted alkenes involving the reaction of α-metallated cyclic enol ethers with organocuprates[1] which was inspired by an earlier report by Sato and co-workers.[2] The key step in the sequence exemplified in Scheme 1 is a 1,2-metallate rearrangement[3,4] of the putative higher order cuprate **3**. The sequence has practical value – it can be performed on a 45 mmol scale[5] – and it has broad scope: five-,[6–8] six-,[9] and seven-membered-ring α-metallated enol ethers[10,11] participate. A noteworthy feature of the 1,2-metallate rearrangement depicted in Scheme 1 is the connection of two organometallic reagents – α-lithiated dihydrofuran **1** and *n*-BuLi – under copper(I) mediation to generate the alkenylmetal species **4** which is capable of further elaboration. Formally, the 1,2-metallate rearrangement is equivalent to the stereospecific insertion of a vinylidenecarbene derived by α-elimination of **1** into a C–Cu bond. Early attempts to implement this chemistry in the glycal series were thwarted by the low reactivity of the 1-lithiated glycal substrates compared with their lithiated dihydropyran counterparts; however, in 2002 we were able to achieve the first copper(I)-mediated 1,2-metallate rearrangement of a glycal derivative **5** in the context of a synthesis of D-*erythro*-sphingosine.[12] We now show that the reaction is applicable to 1-lithiated glycals derived from the common monosaccharides as a general procedure for appending carbon chains to carbohydrates.

Synthesis of 1-Lithiated Glycals

The 1-lithiated glycals at the heart of our investigation were prepared by transmetallation of the corresponding 1-tributylstannyl glycals with *n*-BuLi as first described by Beau and co-workers.[13] Two routes were used for the synthesis of the requisite stannanes as illustrated in Scheme 2 by the synthesis of 1-tributylstannyl glucal derivative **9**. Both routes start from the same 1-thio-β-D-glucopyranoside **7**. The first route is based on a nickel(0)-catalysed coupling reaction to substitute the sulfone **8** by $Bu_3SnMgBr{\cdot}LiBr$.[14] This route conserves the virtues of stability and crystallinity typical of the unsaturated sulfones and the reaction is easily scalable. The prime detraction to route 1 is the volume of tin waste: 2 equivalents of the $Bu_3SnMgBr{\cdot}LiBr$ are required for complete reaction and the $Bu_3SnMgBr{\cdot}LiBr$ is generated from Bu_3SnLi which in turn is generated from the reaction of BuLi with $Bu_3SnSnBu_3$. Hence there are 3 atoms of tin waste for each coupling reaction. The second route is based on a sulfoxide–lithium exchange of the sulfoxide **10** to generate a 1-lithiated glycal intermediate **11** which is then quenched by the addition of 1.3 equivalents of Bu_3SnCl. It benefits from the cheaper source of tin and only 0.3 equivalent of tin waste is generated at best.



Scheme 1

Optimisation Studies Using 1-Tributylstannyl Glucal 9

Our investigation of the 1,2-metallate rearrangement of carbohydrate derivatives began with the effects of solvent, temperature, stoichiometry, and copper(I) source on the reaction of 1-tributylstannyl glucal derivative **9** with *n*-BuLi. After extensive experiments, we ascertained that optimal conditions (procedure 1) entailed the addition of a solution of 1-tributylstannyl glucal **9** (1.0 equiv) in Et_2O to a mixture of CuCN (1.2 equiv) and *n*-BuLi (5.4 equiv)

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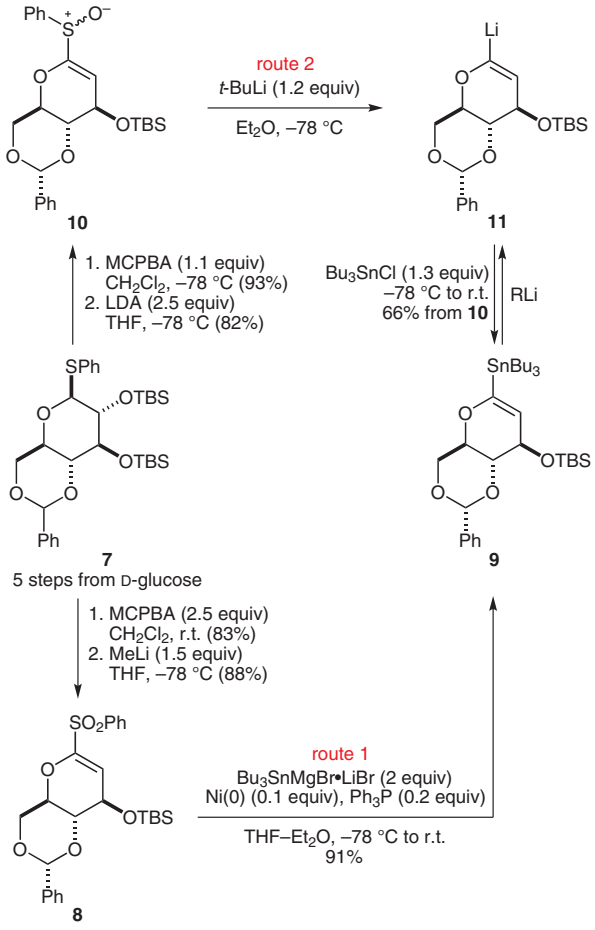
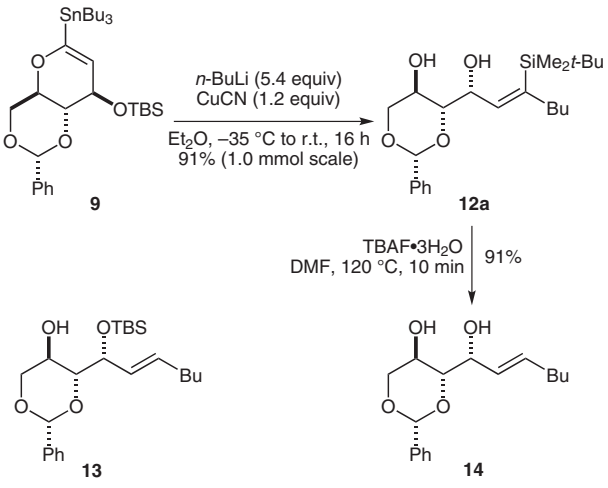


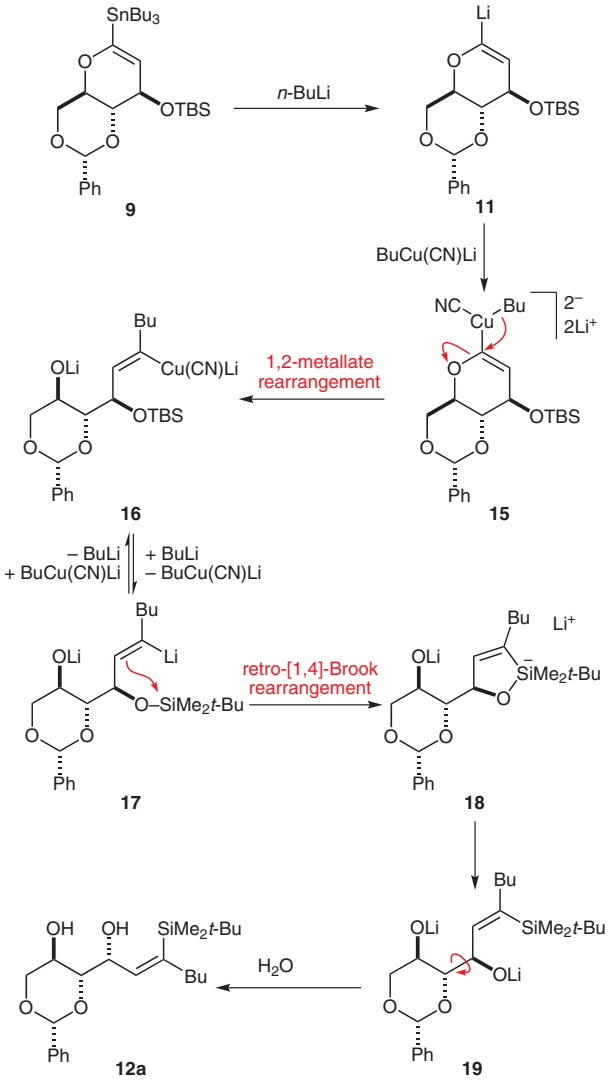
Scheme 2



Scheme 3

in Et_2O at –35 °C (Scheme 3). The mixture was then allowed to warm gradually to room temperature overnight whereupon a standard aqueous workup gave the crystalline *Z*-alkenylsilane **12a** in 91% yield. None of the expected *E*-alkene **13** was observed. The *Z*-stereochemistry of the alkenylsilane **12a** was established by C-desilylation using TBAF in DMF at 120 °C to give the *E*-alkene **14** in 91% yield. The conversion of **9** into **12a** could also be effected in 80% yield using freshly recrystallised $CuBr{\cdot}SMe_2$ (1.2 equiv) in a mixture of Et_2O and Me_2S in place of CuCN (procedure 2).

A mechanism for the formation of alkenylsilane **12a** is given in Scheme 4. Under the reaction conditions, the stannane **9** transmetallates in situ to the corresponding lithiated glycal **11** which then adds to BuCu(CN)Li to give the higher order cuprate **15**. A 1,2-metallate rearrangement of the putative higher order cuprate **15** is then followed by transmetallation of the alkenyl cuprate **16** to the alkenyllithium **17** whereupon a retro-[1,4]-Brook rearrangement via the pentacoordinate siliconate **18** gives the alkenylsilane **19**, the final intermediate in the sequence. Similar retro-[1,4]-Brook rearrangements of alkenyllithiums have been observed previously.[12,15–20] A potentially significant consequence of the transmetallation of alkenyl cuprate **16**, is the liberation of BuCu(CN)Li suggesting that the 1,2-metallate rearrangement could be catalytic in Cu(I). Thus, when 0.2 equivalent of CuCN was used together with 5.4 equivalents of BuLi, **12a** was formed in 71% yield.



Scheme 4

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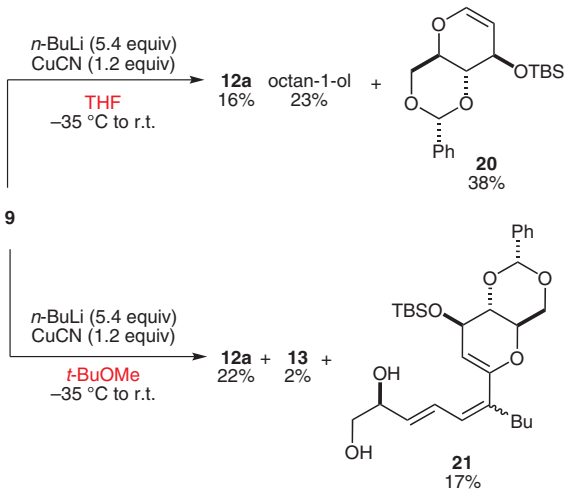
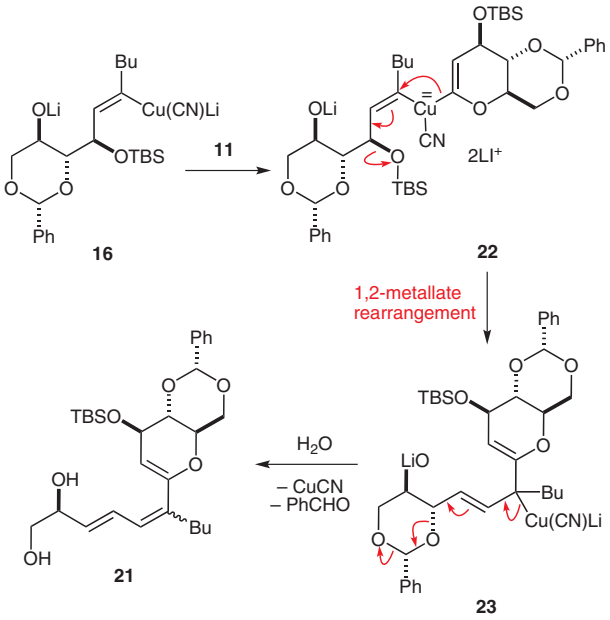
The solvent plays a crucial role in the course of the reaction. When the 1,2-metallate rearrangement was performed in THF (Scheme 5), only 16% of **12a** was isolated along with octan-1-ol (23%); the major product was the glucal **20** (38%) derived from protonation of **11** or **15**. When the identical reaction was performed in *t*-BuOMe, 22% of **12a** was obtained along with 2% rearrangement product **13** and an unstable conjugated triene **21** (17%) that incorporated two molecules of the glycal (one of them minus the benzylidene acetal) and one butyl group.



Scheme 5

A possible mechanism for the formation of **21** is depicted in Scheme 6. We suggest that the initial alkenyl cyanocuprate **16** derived from 1,2-metallate rearrangement of the higher order cyanocuprate **15** adds the lithiated glucal **11** to give the higher order cyanocuprate **22** which then undergoes a second 1,2-metallate rearrangement with elimination of *t*-BuMe_2SiOLi to give allylcuprate **23**. Finally, 1,4-elimination of CuCN and concomitant cleavage of the benzylidene acetal gave the triene **21** as a single stereoisomer after aqueous workup together with benzaldehyde (see below).

To complement the solvent studies described above, a number of experiments were performed to ascertain the optimum stoichiometry of the reaction. The 1,2-metallate rearrangement shown in Scheme 3 employed 5.4 equivalents of *n*-BuLi. One equivalent is consumed in the transmetallation of the stannane **9** to the corresponding lithium reagent **11** and 1.2 equivalents are consumed in the formation of the BuCu(CN)Li leaving a further 3.2 equivalents of excess *n*-BuLi. When the same reaction was performed with 4.4 equivalents of BuLi, the yield of **12a** decreased to 79% but when 3.4 equivalents of *n*-BuLi was used, none of the alkenylsilane **12a** was formed and instead the protonated glycal **20** (41%) was isolated along with an 8% yield of the rearrangement product **13** and 1-phenylpentan-1-ol (9%), a product that is presumably generated from the addition of *n*-BuLi to benzaldehyde resulting from destruction of the benzylidene acetal moiety.



Scheme 6

Scope of the 1,2-Metallate Rearrangement of 1-Lithiated Glycal Derivatives

All of the foregoing optimisation experiments were conducted solely with 1-tributylstannyl glucal derivative **9** and *n*-BuLi. We next explored the reactions of **9** with various organolithiums using both CuCN (procedure 1) and CuBr (procedure 2) mediation. The temperature, time, and stoichiometry were identical in both procedures but the solvents were Et_2O in the case of CuCN and Et_2O–Me_2S in the case of CuBr.[21] The results are summarised in the table provided in Scheme 7. All eight of the organolithiums examined gave the corresponding alkenylsilanes **12a–h** in 45–91% yield. Entries 1–6, using *n*-BuLi, MeLi, and PhLi, reveal that the yields were 7–11% higher with CuCN compared with CuBr.[22] When *t*-BuLi was employed as the nucleophilic partner the alkenylsilane **12d** resulting from 1,4-O → C silicon migration was obtained in 45% yield, but it was accompanied by 25% of a second 1,2-metallate rearrangement product, the *E*-alkene **25**, suggesting steric impedance of the retro-[1,4]-Brook rearrangement. In one case (entry 3) a conjugated triene **24** was observed resulting from a double 1,2-metallate rearrangement akin to that described in Scheme 6.

The examples depicted in Scheme 8 show that a variety of TBS-protected 1-tributylstannyl glycals derived from the common monosaccharides undergo a Cu(I)-mediated 1,2-metallate rearrangement together with a regioselective retro-[1,4]-Brook rearrangement to afford alkenylsilanes in modest to good yield (48–79%). For purposes of comparison, *n*-BuLi was used as the nucleophilic partner in all cases. The 1-tributylstannyl glycals were prepared from the following precursors as described previously:[23] **27** and **29** from D-galactose, **31** from L-rhamnose, **33** from D-xylose, **35** from D-arabinose, and **37** from D-ribose.

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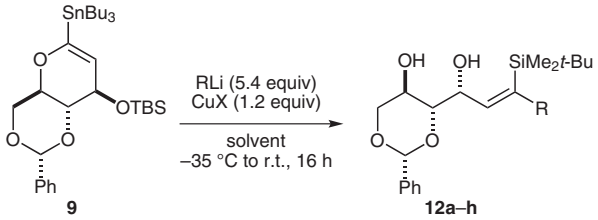
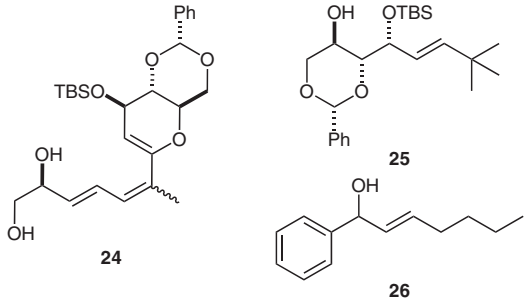


Entry	R	CuX	Product(s) and yields
1	*n*-Bu	CuCN[a]	**12a** (91%)
2	*n*-Bu	CuBr•SMe_2[b]	**12a** (80%)
3	Me	CuCN[a]	**12b** (60%) + **24** (13%)
4	Me	CuBr•SMe_2[b]	**12b** (53%)
5	Ph	CuCN[a]	**12c** (90%)
6	Ph	CuBr•SMe_2[b]	**12c** (83%)
7	*t*-Bu	CuBr•SMe_2[b]	**12d** (45%) + **25** (25%)
8	*trans*-hex-1-enyl	CuCN[a]	**12e** (55%) + **26** (15%)
9	*cis*-hex-1-enyl	CuCN[a]	**12f** (57%)
10	Bu_3Sn	CuCN[a]	**12g** (65%)
11	Me_3SiCH_2	CuCN[a]	**12h** (49%)

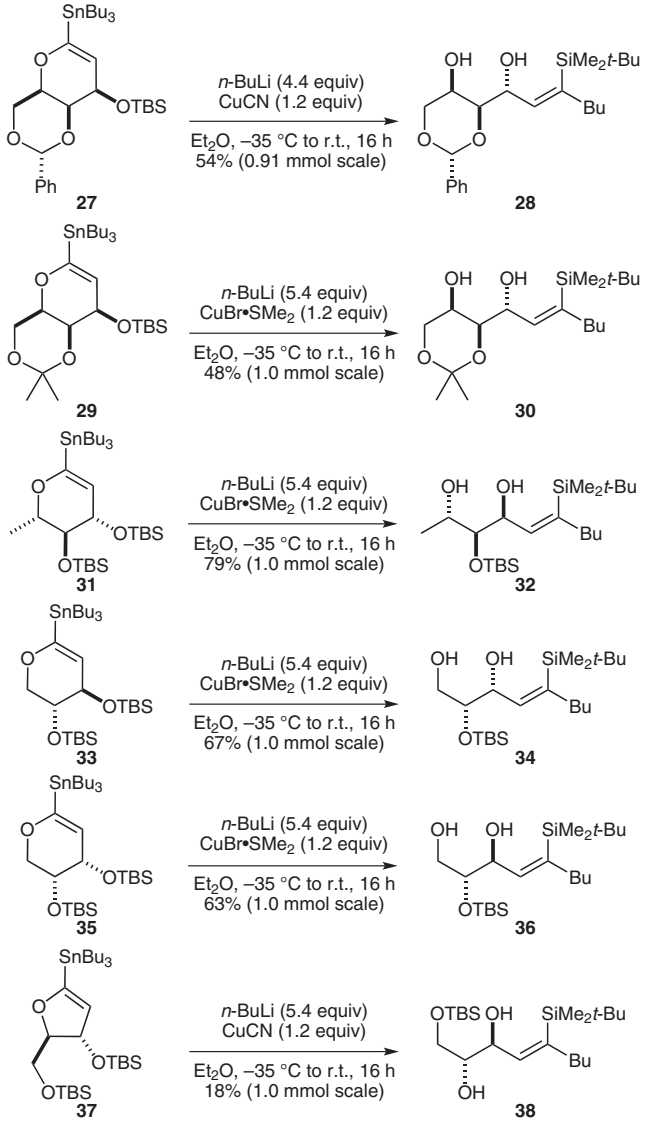
[a] Procedure 1 using Et_2O as solvent.
[b] Procedure 2 using Et_2O–Me_2S (3:5) as solvent.



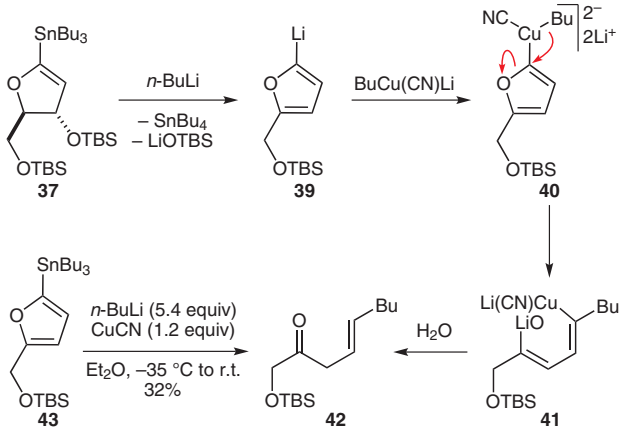
Scheme 7 Reaction of 1-tributylstannyl glucal **9** with various organolithiums under Cu(I) mediation

The 1,2-metallate rearrangement of the furanoid glycal **37** afforded a low yield (18%) of the expected product **38** together with significant quantities of a by-product which was identified as the β,γ-unsaturated ketone **42** (Scheme 9) by NMR spectroscopy of an impure sample isolated by column chromatography. We surmise that the furanoid glycal **37** undergoes both transmetallation and elimination of TBSOLi by the excess *n*-BuLi to the lithiated furan **39** which can then participate in a 1,2-metallate rearrangement via intermediates **40** and **41** to give the observed ketone after protonation and tautomerisation. Evidence for this process derives from reaction of the furan **43** with *n*-BuLi and CuCN according to procedure 1 to give the ketone **42** in 32% yield. The easy aromatisation of furanoid glycals has been observed previously.[23,24]

In all the foregoing examples, the glycal substrates bore a TBS ether protecting group at C3 that underwent a tandem 1,2-metallate rearrangement followed by a regiospecific O → C silyl migration (retro-[1,4]-Brook rearrangement) to give a trisubstituted alkenylsilane. Whether the O → C silyl migration is a boon or nuisance will depend on circumstances. In those cases where it is a nuisance, the TBS group in the alkenylsilane can be excised by treatment with TBAF in DMF at elevated temperature. However, in order to avoid the vexation of an additional step, we examined 1-tributylstannyl glycal substrates either with no protecting group or a non-transferrable protecting group



Scheme 8



Scheme 9

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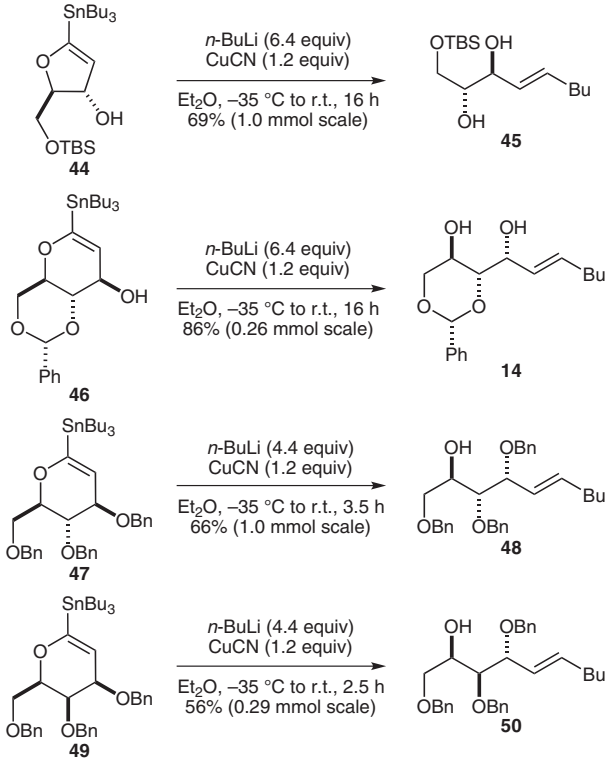
at C3. The results are shown in Scheme 10. In all four cases, the 1,2-metallate rearrangement proceeded normally to give 56–86% yields of *trans*-alkenes directly. The high yield of alkene **45** from the furanoid glycal **44** is markworthy because it shows that deprotonation of the C3-OH group effectively blocked the easy aromatisation reaction observed with substrate **37**.



Scheme 10

Formal Synthesis of KRN7000 and Synthesis of $\Delta^{5,6}$-Ceramide 59

KRN7000 (**55**, Scheme 11) is a synthetic α-galactosyl ceramide analogue of the agelasphins isolated from the Okinawan sponge *Agelas mauritianus* in 1993.[25,26] It is a potent immunostimulant that displays remarkable activity in animal models against a diverse range of diseases including various cancers, malaria, hepatitis B, juvenile diabetes, and autoimmune encephalomyelitis.[27–29] The first synthesis of KRN7000 was reported by Koezuka and coworkers of the Kirin Brewery Company in 1995[30] and since then intense effort has been invested in the synthesis of KRN7000 itself as well as a myriad of analogues.[31,32] We now describe an application of our 1,2-metallate rearrangement methodology to a formal synthesis KRN7000 as well as a synthesis of the $\Delta^{5,6}$-ceramide derivative **59** of $\Delta^{5,6}$-KRN7000.

1-Tributylstannyl galactal **51** bearing a free hydroxy group at C3, was treated with *n*-dodecyllithium (6.4 equiv) and CuCN (1.2 equiv) in Et_2O according to procedure 1 to afford the 1,2-metallate rearrangement product **52** in 89% yield (Scheme 11). Subsequent selective mesylation of the C2-OH followed by hydrogenation on Pd/C gave mesylate **54** – an advanced intermediate in Schmidt's total synthesis of KRN7000.[33] The synthesis of intermediate **54** was thus accomplished in 12 steps and in 16% overall yield from commercially available D-galactose pentaacetate. The synthesis of 1-tributylstannyl galactal **51** is presented in the Supporting Information.

The diol **52** was also incorporated into a synthesis of the $\Delta^{5,6}$-ceramide derivative **59** of $\Delta^{5,6}$-KRN7000 in which the alkene function introduced during the 1,2-metallate rearrangement is retained.[34] An attempt to introduce an azide moiety via displacement of the mesylate **53** with sodium azide in DMF or DMSO or with tetramethylguanidinium azide in DMF or MeCN over several days failed. However, by first selectively protecting the C4-OH group in diol **52** as its TBS ether, the remaining C2-OH was then converted into its triflate derivative that underwent substitution by NaN_3 in DMF to give **57** in 82% yield over two steps. The azide was reduced with zinc in the presence of NH_4Cl. The resulting amine was fairly unstable; therefore, it was directly coupled with hexacosanoic acid without purification, to give amide **58** in about 51% yield over two steps. ^1H NMR and ^{13}C NMR spectroscopy of the amide purified by column chromatography revealed that the product was only 90% pure and the unknown impurity could not be removed by column chromatography or by recrystallisation from various solvents. Therefore, the contaminated material was treated with TBAF to remove the TBS group and then with TsOH in methanol to cleave the benzylidene acetal. The desired $\Delta^{5,6}$-ceramide **59** (≥95% pure according to ^1H NMR spectroscopic analysis) was obtained as a white amorphous solid (mp 93–95 °C from MeOH) in a lamentable 9% yield from azide **57** (4 steps) after column chromatography.

In conclusion, we have shown that 1-metallated glycals derived from the common monosaccharides D-glucose, D-galactose, L-rhamnose, D-xylose, D-arabinose, and D-ribose react with a variety of organolithium reagents under Cu(I) mediation to give alkenylpolyol chains in 45–91% yield (19 examples). The reaction can be divided into 2 classes depending on the structure of the 1-metallated glycal. In class 1 reactions, 1-metallated glycals bearing either no protecting group at C3 or a non-transferrable protecting group undergo 1,2-metallate rearrangements to alkenylcuprate intermediates that hydrolyse to give *trans*-alkenes. In class 2 reactions, 1-metallated glycals bearing a TBS ether at C3 undergo a tandem 1,2-metallate rearrangement followed by a regiospecific retro-[1,4]-Brook rearrangement to give *Z*-alkenylsilanes after aqueous workup. Crucial to the success of both class 1 and class 2 reactions is the use of an excess of the nucleophilic organolithium partner.[35] Application of the 1,2-metallate rearrangement to the total syntheses of sphingolipids D-*erythro*-ceramide,[12] Sch II, and phalluside-1[36] as well as the syntheses of KRN7000 and the $\Delta^{5,6}$-ceramide reported herein attest to its practical value.

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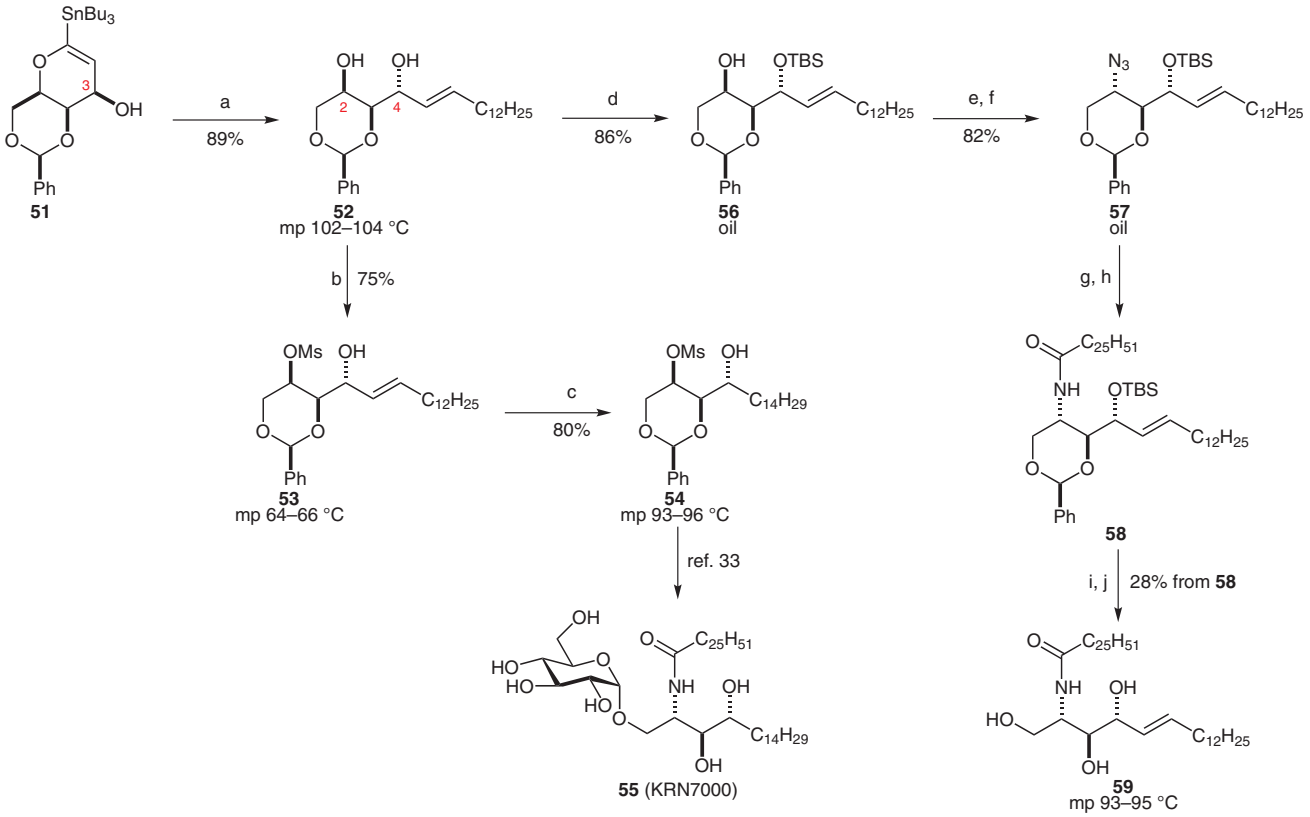

Scheme 11 *Reagents and conditions*: (a) *n*-$C_{12}H_{25}Li$ (6.4 equiv), CuCN (1.2 equiv), Et_2O, –35 to 10 °C, 3 h, 89%; (b) MsCl (1.1 equiv), Py–CH_2Cl_2, –15 °C, 5 h, 75%; (c) H_2 (1 bar), 10% Pd/C, MeOH–CH_2Cl_2, r.t., 16 h, 80%; (d) TBSCl (1.4 equiv), DBU (1.6 equiv), THF, r.t., 3 h, 86%; (e) Tf_2O (1.4 equiv), Py (2.0 equiv), CH_2Cl_2, –15 °C, 20 min; (f) NaN_3 (5.0 equiv), DMF, r.t., 80 min, 82% from **56**; (g) Zn (10.4 equiv), NH_4Cl (10.4 equiv), THF–H_2O, r.t., 3 h; (h) *n*-$C_{25}H_{51}CO_2H$ (2.3 equiv), HOBT (3.2 equiv), EDC·HCl (3.2 equiv), DMAP (3.2 equiv), CH_2Cl_2, r.t., 16 h; (i) TBAF·$3H_2O$ (1.2 equiv), THF, r.t., 3 h; (j) *p*-TsOH·H_2O (6.5 equiv), CH_2Cl_2–MeOH, r.t., 1 h, 9% from **57**.

For general information and materials, see the Supporting Information.

CuCN Mediation; Procedure 1

To a stirred suspension of CuCN (Fluka, 0.107 g, 1.2 mmol) in Et_2O (8.0 mL) cooled to –78 °C was added dropwise *n*-BuLi (1.56 M in hexanes, 3.4 mL, 5.4 mmol). The mixture was allowed to warm to 0 °C, stirred for 6 min, and then cooled to –35 °C. A solution of stannane **9** (0.64 g, 1.0 mmol) in Et_2O (3.0 mL) was added by cannula with an additional amount of Et_2O (2.0 mL) being used for washing. The reaction was allowed to warm gradually to r.t. over 16 h and then quenched with sat. aq NH_4Cl (20 mL). The organic layer was separated from the blue aqueous layer which was then extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated. The residue was purified by column chromatography (SiO_2, hexanes–Et_2O) to give the title compound **12a** (0.37 g, 0.91 mmol, 91%).

CuBr Mediation; Procedure 2

To a stirred suspension of freshly recrystallised CuBr·SMe_2 (0.247 g, 1.2 mmol) in Et_2O (3.0 mL) and Me_2S (5.0 mL) cooled to –78 °C was added dropwise *n*-BuLi (1.8 M in hexanes, 3.0 mL, 5.4 mmol). The mixture was allowed to warm to 0 °C and stirred for 6 min. The yellow solution was then cooled to –35 °C and a solution of a 1-tributylstannyl glucal **9** (1.0 mmol) in Et_2O (3.0 mL) was added by cannula with an additional amount of Et_2O (2.0 mL) being used for washing. The reaction was allowed to warm gradually to r.t. during 16 h and then quenched with sat. aq NH_4Cl (20 mL). Aqueous extractive workup as described in procedure 1 gave diol **12a** (0.325 g, 0.80 mmol, 80%).

(2*R*,4*S*,5*R*)-4-[(*R*,*Z*)-1-Hydroxy-3-(*tert*-butyldimethylsilyl)hept-2-enyl]-2-phenyl-1,3-dioxan-5-ol (12a)

White solid; mp 121.0–122.0 °C (hexane); $[\alpha]_D^{25}$ –45 (*c* 1.00, $CHCl_3$).

IR (diamond compression system): 3372 (br s), 2955 (s), 2928 (s), 2856 (s), 1461 (m), 1389 (m), 1077 (s), 1014 (s), 822 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.47 (2 H, m, ArH), 7.41–7.36 (3 H, m, ArH), 6.30 (1 H, dt, *J* = 10.1, 1.1 Hz, C5H), 5.52 (1 H, s, CHPh), 4.56 (1 H, ddd, *J* = 10.0, 5.6, 4.1 Hz, C4H), 4.30 (1 H, dd, *J* = 10.8, 5.4 Hz, C1H_AH_B), 4.04–3.96 (1 H, m, C2H), 3.62 (1 H, t, *J* = 10.6 Hz, C1H_AH_B), 3.59 (1 H, dd, *J* = 9.2, 4.1 Hz, C3H), 2.55 (1 H, d, *J* = 3.6 Hz, HOC2), 2.35 (1 H, d, *J* = 5.8 Hz, HOC4), 2.17–2.06 (2 H, m, C7H_2), 1.43–1.27 (4 H, m, C8H_2 + C9H_2), 0.94 [9 H, s, $(CH_3)_3C$], 0.91 (3 H, t, *J* = 7.1 Hz, C10H_3), 0.21 (3 H, s, CH_3Si), 0.20 (3 H, s, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8 (C6), 140.5 (C5H), 137.9 (C_{Ar}), 129.4 ($C_{Ar}H$), 128.6 (2$C_{Ar}H$), 126.5 (2$C_{Ar}H$), 101.3 (CHPh), 84.3 (C3H), 71.1 (C1H_2), 70.3 (C4H), 62.4 (C2H), 38.3 (C7H_2), 33.1 (C8H_2), 27.4 [$CH_3)_3C$], 23.1 (C9H_2), 17.9 [$C(CH_3)_3$], 14.4 (C10H_3), –2.3 (CH_3Si), –3.4 (CH_3Si).

Anal. Calcd for $C_{23}H_{38}O_4Si$: C, 67.94; H, 9.42. Found: C, 68.20; H, 9.45.

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References

(1) Kocieński, P.; Wadman, S.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363.
(2) Fujisawa, T.; Kurita, Y.; Kawashima, M.; Sato, T. *Chem. Lett.* **1982**, 1642.
(3) Kocieński, P. J.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933.
(4) Kocieński, P. In *Organic Synthesis via Organometallics*; Enders, D.; Gais, H.-J.; Keim, W., Eds.; Verlag Vieweg: Wiesbaden, **1993**, 203.
(5) Jarowicki, K.; Kocieński, P. J.; Qun, L. *Org. Synth. Coll. Vol. 10*; Wiley: New York, **2004**, 662.
(6) Jarowicki, K.; Kocieński, P.; Norris, S.; O'Shea, M.; Stocks, M. *Synthesis* **1995**, 195.
(7) Pommier, A.; Stepanenko, V.; Jarowicki, K.; Kocieński, P. J. *J. Org. Chem.* **2003**, *68*, 4008.
(8) Fargeas, V.; Ménez, P. L.; Berque, I.; Ardisson, J.; Pancrazi, A. *Tetrahedron* **1996**, *52*, 6613.
(9) Ashworth, P.; Broadbelt, B.; Jankowski, P.; Kocieński, P.; Pimm, A.; Bell, R. *Synthesis* **1995**, 199.
(10) Hareau-Vittini, G.; Kocieński, P.; Reid, G. *Synthesis* **1995**, 1007.
(11) Hareau-Vittini, G.; Kocieński, P. *Synlett* **1995**, 893.
(12) Milne, J. E.; Jarowicki, K.; Kocieński, P. J.; Alonso, J. *Chem. Commun.* **2002**, 426.
(13) Lesimple, P.; Beau, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1985**, 894.
(14) Gunn, A.; Jarowicki, K.; Kocieński, P.; Lockhart, S. *Synthesis* **2001**, 331.
(15) Braun, M.; Mahler, H. *Justus Liebigs Ann.* **1995**, 29.
(16) Bures, E.; Spinazzé, P. G.; Beese, G.; Hunt, I. R.; Rogers, C.; Keay, B. A. *J. Org. Chem.* **1997**, *62*, 8741.
(17) Comanita, B. M.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1999**, *40*, 5283.
(18) Simpkins, S. M. E.; Kariuki, B. M.; Aricó, C. S.; Cox, L. R. *Org. Lett.* **2003**, *5*, 3971.
(19) Yamago, S.; Fujita, K.; Miyoshi, M.; Kotani, M.; Yoshida, J. *Org. Lett.* **2005**, *7*, 909.
(20) Mori, H.; Matsuo, T.; Yoshioka, Y.; Katsumura, S. *J. Org. Chem.* **2006**, *71*, 9004.
(21) In all of our earlier studies we routinely used Me_2S as a cosolvent on the assumption that it stabilised the higher order cuprate intermediates. However, we later discovered that Me_2S is deleterious to the CuCN-mediated reactions in some cases. In the case of CuBr-mediated reactions, the presence of Me_2S as a co-solvent generally had a neutral or beneficial effect.
(22) A further advantage to procedure 1 is that CuCN is stable in its Cu(I) oxidation state and hence requires no further purification whereas CuBr should be purified as its Me_2S complex since Cu(II) contamination can cause messy reactions and low yields.
(23) Jarowicki, K.; Kilner, C.; Kocieński, P. J.; Komsta, Z.; Milne, J. E.; Wojtasiewicz, A.; Coombs, V. *Synthesis* **2008**, 2747.
(24) Zhang, H.-C.; Brakta, M.; Daves, G. D. Jr. *Tetrahedron Lett.* **1993**, *34*, 1571.
(25) Natori, T.; Koezuka, Y.; Higa, T. *Tetrahedron Lett.* **1993**, *34*, 5591.
(26) Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771.
(27) Banchet-Cadeddu, A.; Hénon, E.; Dauchez, M.; Renault, J.-H.; Monneaux, F.; Haudrechy, A. *Org. Biomol. Chem.* **2011**, *9*, 3080.
(28) Chen, G.; Chien, M.; Tsuji, M.; Franck, R. W. *ChemBioChem* **2006**, *7*, 1017.
(29) Franck, R. W.; Tsuji, M. *Acc. Chem. Res.* **2006**, *39*, 692.
(30) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J. Med. Chem.* **1995**, *38*, 2176.
(31) Enders, D.; Terteryan, V.; Paleček, J. *Synthesis* **2010**, 2979.
(32) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461.
(33) Figueroa-Pérez, S.; Schmidt, R. R. *Carbohydr. Res.* **2000**, *328*, 95.
(34) During their pioneering studies on the synthesis of agelasphin analogues that led to the discovery of KRN7000, Koezuka and co-workers had prepared $\Delta^{5,6}$-sphinganine precursors (see ref. 30).
(35) By contrast 1,2-metallate rearrangements of simple lithiated dihydrofurans and dihydropyrans mediated by CuCN require only 1.1–1.5 equivalents of the organolithium reagent or 2.2 equivalents if the corresponding stannane is used.
(36) Black, F. J.; Kocieński, P. J. *Org. Biomol. Chem.* **2010**, *8*, 1188.

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