Synthesis of a *trans*-Fused Tricyclic Ether Using a Novel Differentially Protected Glucal

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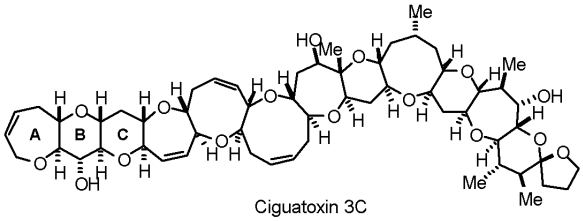
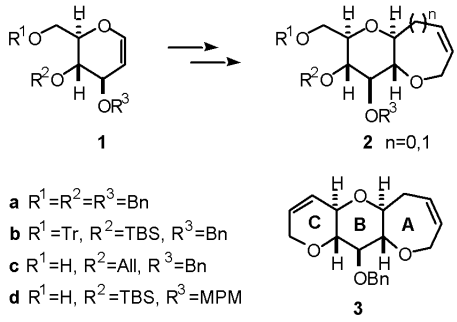
Abstract: The construction of the *trans*-fused 7,6,6-ABC fragment (**3**) of ciguatoxin 3C, starting from the novel carbohydrate derivative 3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-D-glucal, is reported. The formation of the A- and C-rings can be effected by executing two individual ring-closing metathesis steps in a sequential or a one-pot procedure.

Key words: ring-closing metathesis, fused ethers, ciguatoxin 3C, carbohydrate, glucal



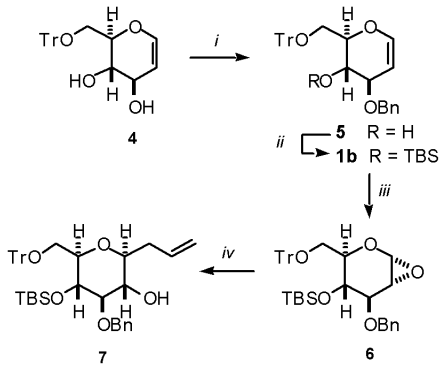
Figure

Studies from our[1] and other[2] laboratories revealed that sugars are useful starting compounds for the generation of scaffolds featuring two olefin functions suitable for ring-closing metathesis (RCM). The general usefulness of this concept was nicely illustrated by us in the synthesis of functionalised oxepines,[1a] spiroketals,[1b] as well as carbocycles.[1c,d] We also showed[1e,f] that tri-*O*-benzyl-D-glucal (**1a**) could be converted into the *trans*-fused bicyclic ether **2a** via stereoselective epoxidation followed by the installation of a *trans*-1-vinyl-2-*O*-allyl configuration and subsequent RCM. It seemed evident that the masking of H*O*-6 and H*O*-4 by an orthogonal set of temporary protecting groups as in the differentially protected[3] glucal **1b** would open the way to the construction of an additional *trans*-fused cyclic ether unit. For instance, removal of the *t*-butyldimethylsilyl (TBS) group in the RCM product **2b** followed by sequential allylation of the secondary H*O*-group and detritylation will provide **2c**, the primary hydroxyl of which can be readily transformed into a terminal alkene function. The viability of our concept will be demonstrated in the synthesis of the *trans*-fused 7,6,6-tricyclic fragment **3**, which features the ABC ring framework of ciguatoxin 3C,[4] starting from glucal **1b**.



Scheme 1

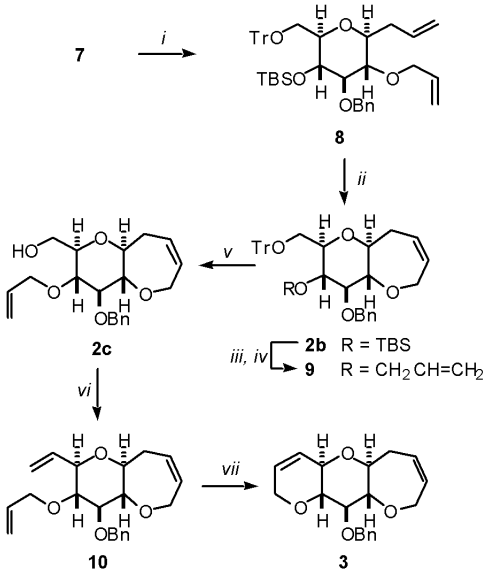
The synthesis of glucal **1b** commences with the regioselective benzylation of the allylic hydroxyl group of known[5] 6-*O*-trityl-D-glucal **4**. Thus, treatment of the stannylidene acetal of **4** (see Scheme 2) with benzyl bromide in the presence of cesium fluoride[6] gave 3-*O*-benzyl derivative **5**. Silylation of H*O*-4 with *t*-butyldimethylsilyl chloride (TBSCl), followed by stereoselective epoxidation of fully protected **1b** with 3,3-dimethyldioxirane,[7] afforded the stable α-epoxide **6** in 65% yield (based on **4**).[8] Ring-opening of epoxide **6** under the influence of allylmagnesium bromide led, in contrast to expectation,[9] to an unacceptable α,β-mixture of both *C*-glucosides in a near equal amount. It was therefore gratifying to establish that the use of allylmagnesium chloride resulted in the main formation (i.e. α/β = 1:9) of the required β-*C*-glucoside.[10] Separation of the latter mixture could be readily effected by silica gel chromatography to give the crucial intermediate **7** in 77% yield.



Reagents and conditions: *i*. a) Bu_2SnO, MeOH, reflux; b) BnBr, CsF, DMF, 73%. *ii*. TBSCl, imidazole, DMF, 50 °C, 90%. *iii*. 3,3-dimethyldioxirane (1.2 equiv.), CH_2Cl_2/acetone, 0 °C, 30 min, quant. *iv*. allylmagnesium chloride (2 equiv.), THF, 10 min, 77%.

Scheme 2

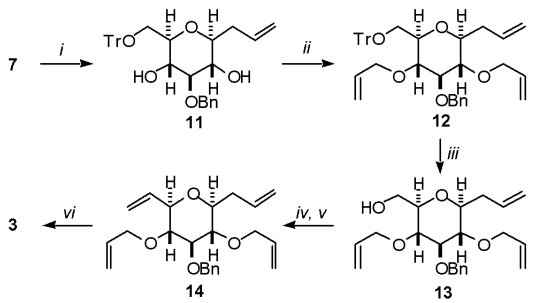
The transformation of **7** into the target compound **3** (Scheme 3) starts with the allylation of H*O*-2 in **7**. Subsequent RCM of the resulting *trans*-allyl-*O*-allyl setting in **8** using Grubbs' catalyst $(PCy_3)_2Cl_2Ru{=}CHPh$[11] provided the *trans*-fused 7,6-bicyclic system **2b** in near quantitative yield. Introduction of the second and similarly fused ring could be realised by executing the following simple and straightforward six-step procedure. Desilylation of **2b** followed by allylation of the secondary hydroxyl group gave, after detritylation of **9**, the primary alcoholic derivative **2c**. Dess-Martin periodinane oxidation[12] of **2c** and subsequent Wittig olefination with methyltriphenylphosphonium bromide in the presence of *n*-butyllithium led to the isolation of RCM precursor **10**. RCM of the latter derivative using the same ruthenium catalyst also proceeded smoothly at room temperature to give the *trans*-fused tricyclic ether **3**,[8] as evidenced by NO*E*-experiments, in 43% yield based on **7**.



Reagents and conditions: *i*. allyl bromide, NaH, DMF, 97%. *ii*. $Cl_2(PCy_3)_2R{=}CHPh$ (5 mol%), 0.02 M diene conc., CH_2Cl_2, 2h, 99%. *iii*. TBAF, THF, 84%. *iv*. allyl bromide, NaH, DMF, 88%. *v*. TsOH, MeOH/CH_2Cl_2 (1:1), 94%. *vi*. a) Dess-Martin periodinane, CH_2Cl_2; b) $MePh_3P^+Br^-$, *n*-BuLi, THF, –40 °C to r.t., 80%. *vii*. $Cl_2(PCy_3)_2R{=}CHPh$ (5 mol%), 0.02 M diene conc., CH_2Cl_2, 3h, 82%.

Scheme 3

The relatively high efficacy of both metathesis steps (i.e. **8**→**2b** and **10**→**3**) urged us to explore whether the formation of **3** could be achieved in one step using the bis-*O*-allyl derivative **14** (Scheme 4) as the substrate. The bis-*O*-allyl ether functions could be easily installed (Scheme 4) by desilylation of **7** (→**11**), allylation of both secondary hydroxyl groups (**11**→**12**), detritylation of **12** and conversion of **13** by the same sequence of events mentioned earlier for the transformation of **2c** into **10**. Ruthenium catalysed RCM of **14** was uneventful to give **3** in a similar overall yield.



Reagents and conditions: *i*. TBAF, THF, 94%. *ii*. allyl bromide, NaH, DMF, 87%. *iii*. TsOH, MeOH/CH_2Cl_2 (1:1), 92%. *iv*. a) Dess-Martin periodinane, CH_2Cl_2; b) $MePh_3P^+Br^-$, *n*-BuLi, THF, –40 °C to r.t., 78% (two steps). v. $Cl_2(PCy_3)_2R{=}CHPh$ (5 mol%), 0.02 M diene conc., CH_2Cl_2, 3h, 78%.

Scheme 4

The results presented in this paper clearly indicate that the differentially protected glucal **1b** is a valuable and versatile building unit in the design and synthesis of *trans*-fused cyclic ethers. Moreover, the protecting group strategy described here can be easily adapted for the preparation of other appropriately protected glucal derivatives, e.g., compound **1d** in which the benzyl group is replaced by a 4-methoxybenzyl (MPM) group. In this respect, it is of interest to mention that glucal **1b** may be an attractive alternative for the preparation of the recently reported[2g] intermediate **2** (n = 1, R^1 = H, R^2 = MPM, R^3 = Bn). The implementation of our strategy in the assembly of more extended cyclic ether frameworks of ciguatoxin 3C and other structurally related marine toxins will be reported in due course.

Acknowledgement

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References and Notes

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(8) All new compounds were fully characterised by ^{1}H NMR, ^{13}C NMRand HR-mass spectrometry. Spectroscopic data of relevant examples:
1b: ^{1}H NMR (300 MHz, $CDCl_3$): 7.58-7.18 (m, 20H), 6.49 (d, 1H, *J* = 6.6 Hz), 4.84 (dd, 1H, *J* = 2.9 Hz), 4.49 (AB, 2H), 4.18-4.07 (m, 1H), 3.92 (t, 1H), 3.82-3.76 (m, 1H), 3.47-3.36 (m, 2H), 0.70 (s, 9H), -0.16, -0.35 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 144.7, 144.0, 138.2, 128.8, 128.2, 127.7, 127.4, 126.9, 98.9, 86.9, 70.0, 78.7, 76.1, 68.8, 63.5, 25.8, 17.8, -3.8, -5.0. [α_D] -22° (*c* 1, $CHCl_3$).
3: ^{1}H NMR (300 MHz, $CDCl_3$): 7.44-7.26 (m, 5H), 5.88-5.71 (m, 4H), 4.93-4.82 (AB, 2H), 4.27 (dd, 1H, J_1 = 15.7 Hz, J_2 = 5.5 Hz), 4.24 (dd, 2H), 3.98 (ddd, 1H, *J* = 5.3 Hz), 3.80 (app. d, 1H, *J* = 8.7 Hz), 3.57 (app. t, 1H, $J_1 = J_2$ = 8.8 Hz), 3.40-3.35 (m, 2H), 3.28 (t, 1H), 2.67 (ddd, 1H, J_1 = 16.3 Hz, J_2 = 2.9 Hz), 2.35 (m, 1H). ^{13}C NMR(75 MHz, $CDCl_3$): 139.2, 131.1, 128.0, 126.4, 125.9, 128.1, 127.5, 127.3, 87.7, 81.9, 78.0, 77.2, 74.8, 71.6, 68.4, 66.0, 34.7.[α_D]+34.6 ° (*c* 1, $CHCl_3$).

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(10) It is of interest to note that ring opening of α-1,2-anhydro-tri-*O*-benzyl-D-glucose with either allylmagnesium chloride or bromide both gave exclusively the corresponding β-*C*-glucoside (see ref. 9) in good yield.

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