Pergamon

Tetrahedron Letters, Vol. 38, No. 44, pp. 7801-7804, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10041-7

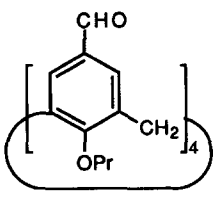
The Assembly of Carbon-Linked Calixarene-Carbohydrate Structures (*C*-Calixsugars) by Multiple Wittig Olefination

Alessandro Dondoni,* Martin Kleban, and Alberto Marra

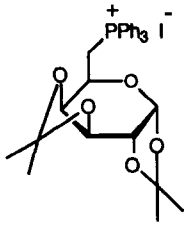
Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, 44100 Ferrara, Italy.

Abstract: The Wittig olefination of the *O*-propyl tetraformylcalix[4]arene **1** with sugar phosphoranes and reduction of the resulting alkenes lead to calixarene derivatives holding three and four carbohydrate units through an ethylene linkage (*C*-calixsugars). © 1997 Elsevier Science Ltd.

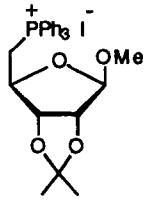
Attention has been focused in recent reports from this laboratory on the use of calixarenes[1] as platforms for the construction of highly ordered polyhydroxylated chiral assemblies through reaction with carbohydrates.[2] The installation of two or four pyranoside units at the upper rim of the macrocycle was carried out in a single step by reaction of di- and tetra(hydroxymethyl)-substituted calix[4]arenes with ethyl 1-thio-β-D-galactopyranoside[2a] and thiazolylgalactopyranose acetate[2b] as glycosyl donors. Because of the limitations on the use of these *O*-calixsugars[3] as molecular receptors under conditions that may cleave the acid sensitive acetal linkage holding the sugar to the macrocycle, we thought that compounds wherein these moieties are linked by an all carbon tether (*C*-calixsugars) can be advantageously employed. We report here a synthetic route to model compounds that involves as the carbon-carbon bond forming reaction the Wittig olefination of the *O*-propyl tetraformylcalix[4]arene[2c] **1** with sugar phosphoranes. The reduction of the double bond of the resulting alkenes leads to the target products. Multiple olefination of the calixarene tetraaldehyde **1** in the presence of excess ylide produced *C*-calixsugars as final products featuring three and four carbohydrate molecules linked to the macrocycle.



1



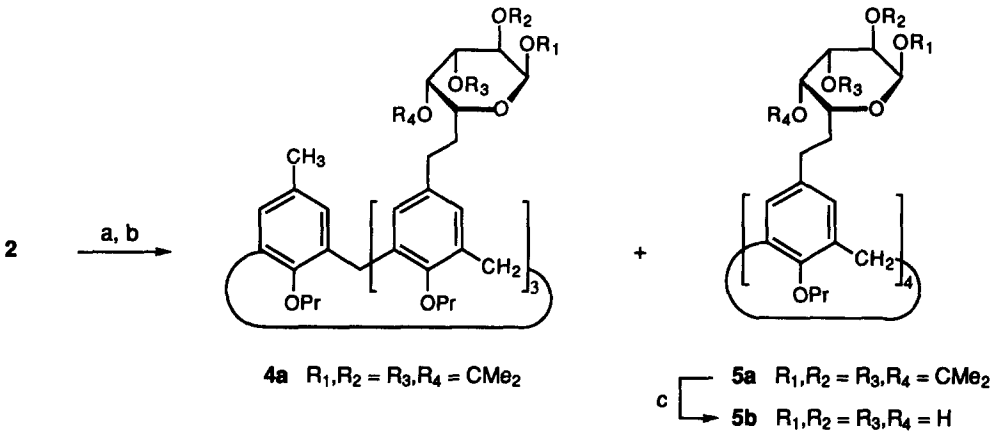
2



3

The generation of the galactose 6-phosphorane from the known triphenylphosphonium iodide[4a] **2** was carried out under the optimised conditions that have been described in recent reports from our laboratory[5] (*n*-BuLi, THF-HMPA, 4Å molecular sieves, -70 °C). The red-coloured solution of the ylide was treated with the tetraaldehyde **1** (0.125 eq) in THF and the mixture stirred for 2 h at -50 °C. Suitable workup and separation of triphenylphosphine oxide and side products[6] afforded a quite complex mixture of alkenes as judged by ^{1}H-NMR analysis. Therefore the mixture was subjected to hydrogenolysis (4 bar) in the presence of $Pd(OH)_2$ on charcoal. Column chromatography (silica, 9:1 cyclohexane-ethyl acetate containing 0.2% of Et_3N) allowed the isolation of the trigalactoside **4a** and tetragalactoside **5a** in 1:1 ratio (34% overall yield). The same reaction mixture was obtained by carrying out the Wittig condensation at higher temperature (-40 °C), while a higher excess of ylide was not tested. The methyl group in the trigalactoside **4a** must arise from the reduction of an unreacted formyl. Evidently the highly congested structure formed by the presence of three sugar moieties has rendered quite difficult the Wittig condensation of the remaining formyl group. The structures of compounds **4a** and **5a** were consistent with their ^{1}H-, ^{13}C-NMR, and mass spectra.[7,8] In particular, the NMR data confirmed the α-D-*galacto* configuration in all the sugar moieties.[9] This is in line with earlier observations[4,5] showing that the formation of the ylide from the galactose phosphonium salt **2** leaves unaltered the configuration at C-5. Finally the removal of the *O*-isopropylidene protecting groups from the sugar moieties of **5a** was carried out by acid hydrolysis to give in almost quantitative yield the unprotected *C*-calixsugar **5b** together with its β-D-anomer (not shown). This compound was soluble in methanol and insoluble in water.

Scheme 1



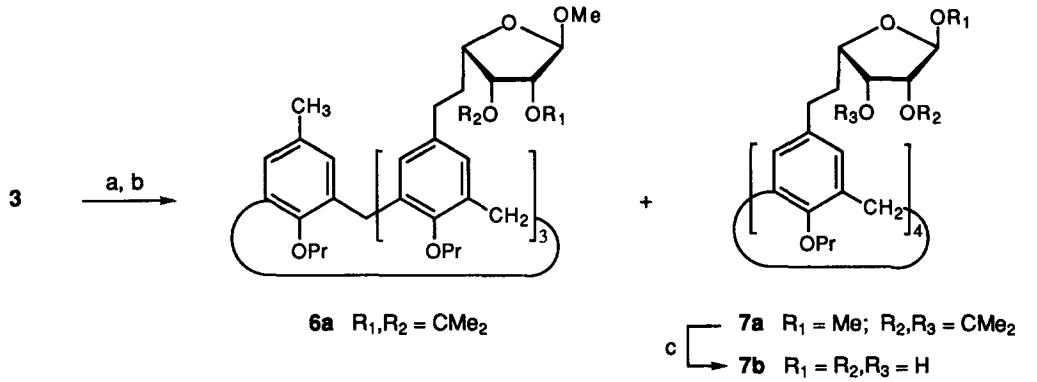
Reagents and conditions: a) *n*-BuLi, THF-HMPA, 4Å MS, -70 °C, then **1** (0.125 equiv.), -50 °C, 2 h; b) H_2 (4 bar), $Pd(OH)_2$/C, MeOH, r. t., 4 h; c) 1M aqueous HCl, THF, reflux 12 h.

The condensation of the calixarene tetraaldehyde **1** with excess of ribose 5-phosphorane, obtained from the known[4b] phosphonium salt **3**, proceeded under the same conditions in a similar way to give a complex mixture of alkenes which after reduction afforded the *C*-linked calixsugars **6a** (15%) and **7a** (24%) featuring three and four furanoside units, respectively. Also these compounds were fully characterised through their NMR and mass spectra.[7,10] The ^{1}H-NMR spectra indicated that the original β-D-*ribo* configuration of the phosphonium salt **3**

($J_{3,4}$ < 0.5 Hz) was not retained in the sugar moieties of compounds **6a** and **7a** ($J_{3,4}$ = 3.2 Hz). According to earlier observations,[4] it is likely that inversion of configuration at C-4 took place by ring opening and closure in the course of the ylide generation from **3**. Therefore the α-L-*lyxo* configuration was assigned to the sugar units of **6a** and **7a**.[11] The removal of all protective groups of the four sugar moieties of **7a** by acid hydrolysis gave in almost quantitative yield the *C*-tetralyxofuranosyl-calixarene **7b** together with its β-L-anomer (not shown). Deceptively, also this compound proved to be insoluble in water, thus confirming the need of more complex calixarene-carbohydrate structures to achieve water solubility.

The feasibility of multiple *O*-glycosylation reactions of calixarene derivatives demonstrated in our earlier reports[2] and the Wittig olefination described here provides the basis for further explorative synthetic work in the field of these interesting molecular receptors.

Scheme 2



Reagents and conditions: a) *n*-BuLi, THF-HMPA, 4Å MS, -70 °C, then **1** (0.125 equiv.), -50 °C, 2 h; b) H_2 (4 bar), $Pd(OH)_2/C$, MeOH, r. t., 4 h; c) 4:1 AcOH-H_2O, reflux, 16 h.

Acknowledgement. Financial support from the United States Army Research Office (N68171-96-C-9097) is gratefully acknowledged.

References and Notes

1. (a) Gutsche, C. D. *Calixarenes*, Stoddart, J. F. Ed.; Royal Society of Chemistry; London, **1989**; (b) Boehmer, V., *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.

2. (a) Marra, A.; Scherrmann, M-C.; Dondoni, A.; Casnati, A.; Minari, P.; Ungaro, R., *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2479; (b) Marra, A.; Dondoni, A.; Sansone, F., *J. Org. Chem.* **1996**, *61*, 5155; (c) Dondoni, A.; Marra, A.; Scherrmann, M-C.; Casnati, A.; Sansone, F.; Ungaro, R., *Chemistry Eur J.* **1997**, in press.

3. For a definition of the trivial name 'calixsugar', see ref. 2b.

4. (a) Secrist III, J. A.; Wu, S.-R., *J. Org. Chem.*, **1979**, *44*, 1434; (b) Secrist III, J. A.; Wu, S.-R. *J. Org. Chem.*, **1977**, *42*, 4084.

5. (a) Dondoni, A.; Boscarato, A.; Zuurmond, H. M., *Tetrahedron Lett.* **1996**, *37*, 7587; (b) Dondoni, A; Zuurmond, H. M.; Boscarato A., *J. Org. Chem.* **1997**, in press.

6. Warming to -10 °C, quenching with phosphate buffer (pH 7), column chromatography (silica, 3:1 cyclohexane-ethyl acetate containing 0.5% of Et_3N). A byproduct of the Wittig olefination was the sugar diphenylphosphine oxide derivative.

7. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix.

8. (**4a**): $[\alpha]_D$ = -51 (*c* 0.99, $CHCl_3$); MS ($C_{80}H_{110}O_{19}$) calcd. 1375.68, found 1399.4 (M^++ Na).
(**5a**): $[\alpha]_D$ = -64 (*c* 0.52, $CHCl_3$); MS ($C_{92}H_{128}O_{24}$) calcd. 1617.94, found 1641.7 (M^++ Na); ^{1}H-NMR (300 MHz, $CDCl_3$) selected data (carbohydrate numbering): δ 1.73-1.93 (m, 16 H, $OCH_2CH_2CH_3$, H-6), 2.33-2.51 (m, 8 H, H-7), 2.99 (d, J = 13.2, 4 H, Heq of $ArCH_2Ar$), 3.59 (dt, $J_{4,5}$ = 1.7, $J_{5,6a}$ = $J_{5,6b}$ = 7.5 Hz, 4 H, H-5), 4.12 (dd, $J_{3,4}$ = 8.0 Hz, 4 H, H-4), 4.26 (dd, $J_{1,2}$ = 5.0, $J_{2,3}$ = 2.3 Hz, 4 H, H-2), 4.32 (d, J = 13.2, 4 H, Hax of $ArCH_2Ar$), 4.56 (dd, 4 H, H-3), 5.52 (d, 4 H, H-1), 6.40 and 6.44 (2 s, 8 H, arom.). The compound showed C4 symmetry, i.e. only one set of signals for all four carbohydrate moieties.

9. This was essentially based on the almost identical values of all coupling constants, particularly that between H-4 and H-5 in the phosphonium salt **2** ($J_{4,5}$ = 2.0 Hz) and in the calixsugar **5a** ($J_{4,5}$ = 1.7 Hz).

10. (**6a**): $[\alpha]_D$ = -38 (*c* 1.14, $CHCl_3$); MS ($C_{71}H_{98}O_{16}$) calcd. 1207.49, found 1231.2 (M^+ + Na).
(**7a**): $[\alpha]_D$ = -38 (*c* 0.64, $CHCl_3$); MS ($C_{80}H_{112}O_{20}$) calcd. 1393.70, found 1394.1 (M^+ + H), 1417.0 (M^++ Na), 1433.4 (M^++ K); ^{1}H-NMR (300 MHz, $CDCl_3$) selected data (carbohydrate numbering): δ 1.31 and 1.45 (2 s, 24 H, 4 CH_3), 1.76-1.86 (m, 8 H, H-5), 2.31-2.56 (m, 8 H, H-6), 3.03 (d, J = 13.2, 4 H, Heq of $ArCH_2Ar$), 3.78-3.85 (m, 4 H, H-4), 4.38 (d, J = 13.2, 4 H, Hax of $ArCH_2Ar$), 4.42 (d, $J_{2,3}$ = 5.9 Hz, 4 H, H-2), 4.55 (dd, $J_{3,4}$ = 3.2 Hz, 4 H, H-3), 4.85 (s, 4 H, H-1), 6.43 and 6.44 (2 s, 8 H, arom.).

11. The observed coupling constants $J_{3,4}$ of compounds **3**, **6a**, and **7a** are in agreement with literature values for 2,3-isopropylidene furanosides, i.e. < 0.5 Hz for methyl-2,3-isopropylidene-*ribo*-β-D-furanosides with different substituents at C-5 and 3.3 Hz for methyl-5-*O*-benzyl-2,3-isopropylidene-α-D-*lyxo*-furanoside. See : Leonard, N. J.; Carraway, K. L., *J. Heterocycl. Chem.* **1966**, *3*, 485. Taniguchi, M.; Koga, K.; Yamada, S., *Tetrahedron* **1974**, *30*, 3547.

(*Received in UK* 18 *July* 1997; *revised* 1 *September* 1997; *accepted* 5 *September* 1997)