New Access to Unsaturated Keto Carba Sugars (Gabosines) Using an Intramolecular Nozaki−Kishi Reaction as the Key Step

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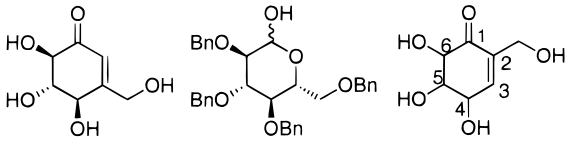
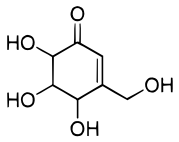
We report here the first synthesis of gabosine I **1** in nine steps from tetra-*O*-benzyl-D-glucose **2** (Scheme 1). The gabosines, the majority of which are trihydroxylated cyclohexenone derivatives, have been isolated from *Streptomyces* strains.[1] These unsaturated keto carbasugars present a great structural diversity due to variations at three asymmetric centers and differing substitutions at C-2 or C-3 such as for example in **3** or **4**. Isolation of 10



1 Gabosine I gluco-configuration

2

3



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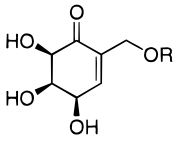
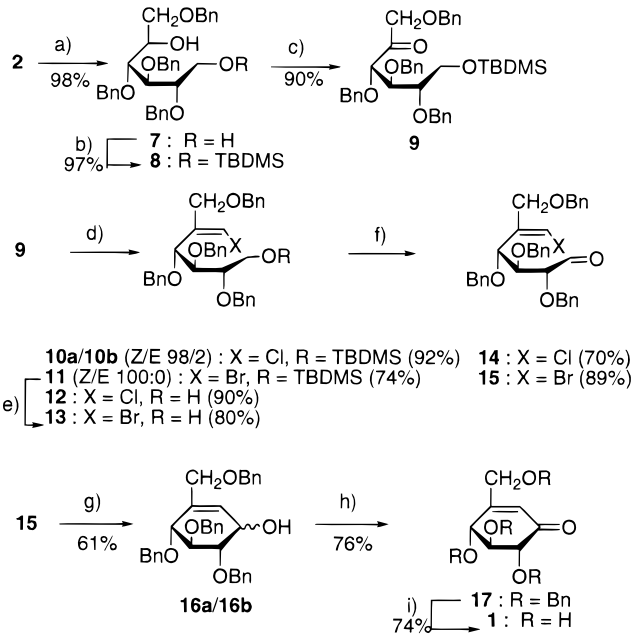


5 R = Crotonyl ester (COTC)
6 R = H (KD16-U1)

gabosines has been reported, and to these may be added the glyoxylase I inhibitor (COTC)[2] **5** and the antibiotic KD16-U1[3] **6** (gabosine C). Several methods for the synthesis of **5** and **6** have been developed.[4,5] Moreover, gabosine-related derivatives have been used as intermediates for the synthesis of biological active compounds (i.e., a L-fucosyl-transferase inhibitor,[6] valienamine and derivatives,[7] and a "pseudo sugar C-disaccharide" [8]). Considering their versatily as synthons, we are interested in developing a new general access to the gabosines

Scheme 1



Reagents and conditions : a) $NaBH_4$, THF/H_2O ; b) TBDMSCl, Pyr.; c) PCC, AcONa, MS 4A°, CH_2Cl_2 ; d) Ph_3PCHX (X = Cl or Br), THF ; e) $N(Bu)_4F$, THF ; f) DMP, CH_2Cl_2 for **14** ; Swern oxidation for **15** ; g) $CrCl_2$, $NiCl_2$ (0.1%), DMF ; h) PCC, AcONa, MS 4A°, CH_2Cl_2 : i) BCl_3, CH_2Cl_2.

skeleton and have focused on the preparation of gabosine I **1**,[9] which could serve as a precursor of various glucosidase inhibitors. A key step in our synthesis was a Nozaki−Kishi mediated cyclization[10] which provides a new and efficient access to functionalized cyclohexene derivatives.[11]

Results and Discussion

Starting from tetra-*O*-benzyl-D-glucose **2**, the silylated D-glucitol **8** was prepared, upon sodium borohydride reduction[12] followed by silylation (Scheme 1). Oxidation of **8** with either PCC in the presence of AcONa[13] or with the Dess−Martin periodinane[14] (DMP) gave the L-sorbose derivative **9** (90%). This ketone reacted with chloromethylenetriphenylphosphorane[15] at −70 °C in THF to give **10a/10b** in 92% yield, while the bromo analogue **11** was obtained in 74% yield by reaction of **9** with bromo-

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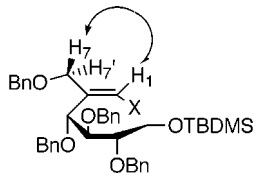

10a : X = Cl
11 : X = Br

Figure 1.

methylenetriphenylphosphorane.[16,17] The Wittig reaction turned out to be very stereoselective,[14,18] yielding exclusively the Z-isomer for the vinyl bromide **11** and a 98:2 *Z*/*E* mixture for the vinyl chlorides **10a/10b**. The presence of **10b** (*E*-isomer) in the mixture has been evidenced by a second vinylic proton NMR signal at δ 6.22. The configurations of **10a** and **11** were assigned on the basis of NOE data. The NOESY spectra of **10a/10b** and **11** show a NOE between the vinylic proton H-1 and the allylic proton H-7 and H-7′ but not between H-1 and H-3, suggesting a *Z* configuration (Figure 1). The vinyl halogenides **10a** and **11** were then desilylated with tetrabutylammonium fluoride[19] to afford the alcohols **12** (90%) and **13** (80%), respectively. Oxidation of **12**, with DMP,[12] and of **13**, under Swern conditions,[20] yielded the aldehydes **14**[21] (70%) and **15** (89%). We failed to cyclize **14** under Barbier conditions,[22] using magnesium as the metal. Turning to the more reactive bromide **15**, with lithium activation, the problem was not solved, and at room temperature no reaction was detected, while at 40 °C, a β-elimination occurred. The Nozaki−Kishi reaction[10] is known to promote the addition of vinyl halogenides or triflate to aldehydes. Examples of macrocyclizations using this reagent have been reported,[23] but to the best of our knowledge it has never been applied to the synthesis of cyclohexenes. Very pleasingly, the Cr/Ni catalysis smoothly promoted the cyclization of the vinyl bromide **15** and gave **16a/16b**[24] in 61% yield. Oxidation of the allylic alcohols **16a/16b** with MnO_2[25] or the DMP[12] gave the enone **17**[26] in only moderate yields (ca. 50%). Better yields (76%) were obtained by using PCC in the presence of AcONa.[11] Debenzylation of **17** by hydrogenolysis could not be envisaged, and we therefore used BCl_3[27] at −78 °C and obtained gabosine I **1** in 74% yield. In this latter step neither epimerization at C-6 or β-elimination were observed. Compound **1** was obtained as a hygroscopic brown solid compound which prevented us from getting a reliable melting point, but it was fully characterized through a high-resolution mass spectrum and ^{1}H and ^{13}C NMR spectra which confirm its homogeneity and which were found to be identical to those already described.[1] Finally, the negative value of the specific rotation, although smaller than the reported one, gave indication that the natural compound[1] has the *gluco* configuration.

In conclusion, we have prepared gabosine I **1** in nine steps from tetra-*O*-benzyl-D-glucose via a Nozaki−Kishi reaction. The cyclization of vinyl bromide **15** using this reaction provides a novel and efficient access to functionalized cyclohexene derivatives. Moreover, this method could be extended in principle to other sugars and should allow the preparation of a large number of gabosine type compounds.

Experimental Section

General. Chemical shifts are reported in δ vs Me_4Si for ^{1}H NMR spectra and relative to the $CDCl_3$ resonance at 77.00 ppm for ^{13}C NMR spectra. Solvents were distilled just before use: THF from sodium/benzophenone, CH_2Cl_2 and DMF from CaH_2. Oxygen free DMF was obtained by passing argon under ultrasound. Elemental analyses were performed at the service central de microanalyses du CNRS at Gif-sur-Yvette.

1-*O*-*tert*-Butyldimethylsilyl-2,3,4,6-tetra-*O*-benzyl-D-glucitol (8). Pyridine (90 mL) was added to a mixture of **7**[10] (4.90 g, 9.04 mmol) and *t*-Bu(Me)$_2$SiCl (1.93 g, 10.8 mmol) at 0 °C. The reaction mixture was then slowly warmed to room temperature and stirred overnight. The mixture was then concentrated and the residue dissolved in CH_2Cl_2 (100 mL). The organic phase was washed with water (100 mL), filtered on phase separator filter, and then concentrated. Flash chromatography (hexane/AcOEt 9:1) of the residue (6.20 g) gave 5.72 g (97%) of **8** as colorless syrup. ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 6H, $(CH_3)_2$-Si); 0.87 (s, 9H, $(CH_3)_3$C); 3.10 (br d, 1H, J = 4.5 Hz, OH); 3.61 (br d, 2H, J = 4.5 Hz, H-1, H1′); 3.66−3.90 (m, 5H, H-6, H-6′, H-2, H-3, H-4); 3.98 (m, 1H, H-5); 4.47 (d, 1H, J = 12.0 Hz, PhCH); 4.53 (d, J = 12.0 Hz, 1H, PhCH); 4.55 (s, 2H, $PhCH_2$); 4.61 (d, J = 11.5 Hz, 1H, PhCH); 4.64 (s, 2H, $PhCH_2$); 4.73 (d, J = 11.5 Hz, 1H, PhCH); 7.15−7.40 (m, 20 H aromatic). ^{13}C NMR ($CDCl_3$): δ -5.5, 18.1, 25.8, 62.8, 70.9, 71.1, 73.1, 73.3, 74.1, 77.41, 78.08, 79.60, 127.5−128.4, 138.0, 138.1, 138.2, 138.4. IR (neat): 3500 cm^{-1} (OH). $[\alpha]^{24}_D$ = +20 (*c* 1.75, CH_2Cl_2). Anal. Calcd for $C_{40}H_{52}O_6Si$ (656.94): C, 73.13; H, 7.98. Found: C, 72.99; H, 7.97.

1,3,4,5-Tetra-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-L-sorbose (9). A suspension of AcONa (2.25 g, 27.4 mmol), PCC (2.95 g, 13.6 mmol), and 4 Å molecular sieves (5.30 g) in CH_2Cl_2 (30 mL) was stirred for 1 h at room temperature; then a solution of **8** (3.00 g, 4.56 mmol) in CH_2Cl_2 (15 mL) was added. After 2 h, the mixture was diluted with Et_2O (90 mL) and hexane (45 mL) and the mixture was stirred for a further 15 min. The suspension was filtered through a silica gel (70−200 μm) column which was further eluted with Et_2O (400 mL). The organic phase was concentrated to 100 mL, washed with water (100 mL), and then dried ($MgSO_4$). After evaporation, flash chromatography (hexane/AcOEt 9:1 with Et_3N 0.2%) of the residue (3.10 g) gave 2.55 g of **9** (89%) as colorless syrup. ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 6H, $(CH_3)_2$Si); 0.85 (s, 9H, $(CH_3)_3$C); 3.60 (dd, 1H, J = 7.5, 12.0 Hz, H-6); 3.74 (m, 2H, H-6′, H-5); 3.97 (t, 1H, J = 4.0 Hz, H-4); 4.18 (d, 1H, J = 17.5 Hz, H-1); 4.19 (d, 1H, J = 4.0 Hz, H-3); 4.26 (d, 1H, J = 17.5 Hz, H-1′); 4.39 (s, 2H, $PhCH_2$); 4,44 (d, 1H, J = 12.0 Hz, PhCH); 4.49 (d, 1H,J = 12.0 Hz, PhCH); 4.56 (d, 1H, J

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= 18.0 Hz, PhCH); 4.59 (s, 2H, $PhCH_2$); 4.60 (d, 1H, J = 18.0 Hz, PhCH); 7.17−7.39 (m, 20H, H aromatic). ^{13}C NMR ($CDCl_3$): δ −5.4, 18.1, 25.8, 62.4, 73.1, 73.3, 73.4, 74.2, 74.3, 79.1, 79.3, 81.7, 127.5−128.4, 137.0, 137.4, 137.6, 138.4, 207.00. IR (neat): 1731 cm^{-1} (CO). $[\alpha]^{24}_D = -2.9$ (c 1.35, CH_2Cl_2). Anal. Calcd for $C_{40}H_{50}O_6Si$ (654.94): C, 73.36; H, 7.70. Found: C, 73.58; H, 7.64.

1-Chloro-2-[(phenylmethoxy)methyl]-3,4,5-tris(phenylmethoxy)-6-*O*-*tert*-butyldimethylsilylhex-1-ene (10a/10b). A chloromethylenetriphenylphosphorane solution (0.3 M) was prepared just before its use as follows: A solution of potassium *tert*-butylate (411 mg, 3.66 mmol) in THF was added at 0 °C to a stirred suspension of chloromethylenetriphenylphosphonium chloride (1.06 g, 3.06 mmol) in THF (6.5 mL). After 1 h at 0 °C, the mixture was warmed to room temperature and kept under stirring for a further 1 h. The resulting solution of phosphorane was then added to a cooled (−70 °C) solution of **9** (1.00 g, 1.53 mmol) in THF (4.5 mL). After 2 h at −70 °C, the mixture was warmed to −30 °C (30 min) and pentane (75 mL) was added. The resulting suspension was filtered, and the filtrate was washed with H_2O (75 mL). The aqueous phase was extracted twice with pentane (2 × 75 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/AcOEt 95:5) of the residue (1.2 g) gave 0.973 g of **10a/10b** (*Z*/*E* 98:2) as a colorless syrup (92%). The ratio *Z*/*E* was determined by integration of both vinylic H-1 signals (*E*-isomer δ 6.22 ppm). ^1H NMR ($CDCl_3$): δ 0.00 (s, 6H, $(CH_3)_2Si$); 0.90 (s, 9H, $(CH_3)_3C$); 3.54 (dd, J = 5.0, 10.0 Hz, H-6); 3.63 (q, J = 5.0 Hz, H-5); 3.73 (dd, J = 5.0, 10.0 Hz, H-6′); 3.90 (dd, J = 5.0, 6.0 Hz, H-4); 4.16 (dd, J = 1.5, 14.0 Hz, H-7); 4.26 (dd, J = 1.5, 14.0 Hz, H-7′); 4.40 (d, J = 12.5 Hz, 1H, PhCH); 4.50 (s, 2H, $PhCH_2$); 4.55 (d, J = 12.5 Hz, 1H, PhCH); 4.66 (s, 2H, $PhCH_2$); 4.70 (s, 2H, $PhCH_2$); 4.99 (d, J = 6.0 Hz, H-3); 6.50 (br s, H-1); 7.20−7.40 (m, 20H, H aromatic). ^{13}C NMR ($CDCl_3$): δ −5.4, 18.2, 25.9, 62.5, 68.8, 71.6, 72.9, 73.2, 75.4, 77.0, 79.8, 80.6, 118.85, 127.3−128.4, 137.4, 137.8, 138.5, 139.0. IR (neat): 2856, 2957, 3030, 3064, 3088 cm^{-1} (CH aromatic and CH double bond). Anal. Calcd for $C_{41}H_{51}O_5SiCl$ (687.39): C, 71.64; H, 7.48; Cl, 5.16. Found: C, 71.90; H, 7.58; Cl, 5.27.

1-Bromo-2-[(phenylmethoxy)methyl]-3,4,5-tris(phenylmethoxy)-6-*O*-*tert*-butyldimethylsilylhex-1-ene (11). A Bromomethylenetriphenylphosphorane solution (3 M) was prepared just before its use as follows: To a suspension of bromomethylenephosphonium bromide (2.66 g, 6.10 mmol) in THF (14 mL) was added dropwise at −5 °C a 1 M potassium *tert*-butylate solution in 2-methylpropanol (6.1 mL). The resulting orange solution was then immediately added to a solution of **9** (2.00 g, 3.05 mmol) in THF (20 mL) at −70 °C. The reaction went to completion after adding two times more of the orange bromomethylenetriphenylphosphorane solution prepared in the same conditions. After the third addition, the mixture was slowly warmed to room temperature (2 h) and diluted with hexane (100 mL). The resulting suspension was filtered through a silica gel (70−200 μm) column which was further eluted with Et_2O (600 mL). The organic phase was concentrated and the residue triturated with hexane (3 × 150 mL). The resulting suspension was then filtered and concentrated. Flash chromatography (hexane/Et_2O 98:2 and then hexane/AcOEt 95:5) of the residue (2.21 g) gave 1.62 g of **11** (*Z*-isomer) as colorless syrup (74%). ^1H NMR ($CDCl_3$): δ 0.00 (s, 3H, $(CH_3)Si$); 0.05 (s, 3H, $(CH_3)Si$); 0.90 (s, 9H, $(CH_3)_3C$); 3.56 (dd, J = 4.5, 10.5 Hz, H-6); 3.65 (q, J = 4.5 Hz, H-5); 3.75 (dd, J = 4.5, 10.5 Hz, H-6′); 3.91 (t, J = 4.5 Hz, H-4); 4.16 (dd, J = 1.5,12.0 Hz, H-7); 4.26 (dd, J = 12.0, 1.5 Hz, H-7′); 4.40 (d, J = 10.5 Hz, 1H, PhCH); 4.50 (s, 2H, $PhCH_2$); 4.55 (d, J = 10.5 Hz, 1H, PhCH); 4.66 (d, J = 10.5 Hz, 1H, PhCH); 4.70 (s, 2H, $PhCH_2$); 4.73 (d, J = 10.5 Hz, 1H, PhCH); 4.92 (d, J = 4.5 Hz, H-3); 6.65 (br s, H-1); 7.25−7.45 (m, 20H, H aromatic). ^{13}C NMR ($CDCl_3$): δ −5.4, 18.2, 25.9, 62.5, 69.8, 71.6, 72.9, 73.3, 75.4, 78.9, 79.8, 80.6, 107.4, 127.3−128.4, 137.6, 137.9, 138.4, 138.9, 140.2. IR (neat): 2856, 2927, 2953, 3031, 3064, 3088 cm^{-1} (CH aromatic and CH double bond). $[\alpha]^{29}_D = -11.3$ (c 1.5, CH_2Cl_2). Anal. Calcd for $C_{41}H_{51}O_5SiBr$ (731.85): C, 67.29; H, 7.02. Found: C, 67.84; H, 6.99.

1-Chloro-2-[(phenylmethoxy)methyl]-3,4,5-tris(phenylmethoxy)-6-hydroxyhex-1-ene (12). A solution of TBAF in THF (1 M, 1.23 mL) was added at room temperature to a stirred solution of **10a**/**10b** (0.842 g, 1.23 mmol) in THF (11 mL). After 16 h, the mixture was concentrated and flash chromatography (hexane/AcOEt 8:2) of the crude residue (1.2 g) gave 0.64 g of pure **12** as colorless syrup (90%) with no trace of the *E*-isomer. ^1H NMR ($CDCl_3$): δ 3.42 (m, 1H, H-6); 3.60 (m, 1H, H-6′); 3.67 (q,1H, J = 7.5 Hz, H-5); 3.86 (t, 1H, J = 7.5 Hz, H-4); 4.09 (dd, 1H, J = 1.5, 16.5 Hz, H-7); 4.25 (dd, 1H, J = 1.5, 16.5 Hz, H-7′); 4.33 (d, 1H,J = 13.5 Hz, PhCH); 4.44 (s, 2H, $PhCH_2$); 4.51 (d, 1H, J = 13.5 Hz, PhCH); 4.54 (d, 1H, J = 13.5 Hz, PhCH); 4.63 (d, 1H, J = 13.5 Hz, PhCH); 4.67 (d, 1H, J = 13.5 Hz, PhCH); 4.71 (d, 1H, J = 13.5 Hz, PhCH); 4.88 (d, 1H, J = 7.5 Hz, H-3); 6.43 (br s, 1H, H-1); 7.20−7.40 (m, 20H, H aromatic). ^{13}C NMR ($CDCl_3$): δ 61.5, 68.8, 71.7, 72.9, 75.2, 76.1, 79.3, 80.4, 118.8, 127.59−128.46, 137.3, 137.5, 137.8, 137.9, 138.3. IR (neat): 3434 cm^{-1} (OH). $[\alpha]^{23}_D = -17$ (c 1, CH_2Cl_2). Anal. Calcd for $C_{35}H_{37}O_5Cl$ (572.50): C, 73.35; H, 6.51; Cl, 6,19. Found: C, 72.56; H, 6.51, Cl, 6,91.

1-Bromo-2-[(phenylmethoxy)methyl]-3,4,5-tris(phenylmethoxy)-6-hydroxyhex-1-ene (13). A solution (1 M) of TBAF in THF (1 M, 2.36 mL) was added to a stirred solution of **11** (1.55 g, 2.14 mmol) in THF (21 mL) at 0 °C. The solution was warmed slowly to room temperature and stirred overnight. Et_2O (75 mL) was added, and the organic phase was washed with water (100 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (hexane/AcOEt 95:5 to 85:15) of the residue (1.59 g) gave 1.06 g of **13** as colorless syrup (80%). ^1H NMR ($CDCl_3$): δ 2.10 (br s, 1H, OH); 3.42 (m, 1H, H-6); 3.60 (m, 1H, H-6′); 3.68 (q, 1H, J = 5.0 Hz, H-5); 3.87 (dd, 1H, J = 4.0, 5.0 Hz, H-4); 4.07 (dd, 1H, J = 2.0, 14.0 Hz, H-7); 4.25 (dd, 1H, J = 2.0, 14.0 Hz, H-7′); 4.30 (d, 1H, J = 11.0 Hz, PhCH); 4.42 (s, 2H, $PhCH_2$); 4.50 (d, 1H, J = 11.0 Hz, PhCH); 4.53 (d, 1H, J = 11.0 Hz, PhCH); 4.58 (d, 1H, J = 11.0 Hz, PhCH); 4.70 (d, 1H,J = 11.0 Hz, PhCH); 4.71 (d, 1H, J = 11.0 Hz, PhCH); 4.79 (d, 1H, J = 4.0 Hz, H-3); 6.56 (br s, 1H, H-1); 7.18−7.40 (m, 20H, H aromatic). ^{13}C NMR ($CDCl_3$): δ 61.5, 69.9, 71.6, 72.8, 72.90, 75.17, 78.0, 79.5, 80.3, 107.5, 127.5−128.3, 137.1, 137.8, 138.2, 140.3. IR (neat): 3500 cm^{-1} (OH). $[\alpha]^{23}_D = -25.9$ (c 1.35, CH_2Cl_2). Anal. Calcd for $C_{35}H_{37}O_5Br$ (617.58): C, 68.07; H, 6.04. Found: C, 67.98; H, 6.19.

6-Chloro-2,3,4-tris(phenylmethoxy)-5-[(phenylmethoxy)methyl]hex-5-enal (14). A solution of **12** (0.66 g, 1.15 mmol) in CH_2Cl_2 (3.5 mL) was added to a cooled (0 °C) solution of Dess−Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one) (0.98 g, 2.30 mmol) in CH_2Cl_2 (4 mL). The mixture was then brought to 10 °C, and wet CH_2Cl_2 (55 mL containing 1.15 mmol (1 equiv) of water) was added dropwise over 1 h. The mixture was then concentrated. Then, Et_2O (50 mL) was added, followed by a 1:1 mixture (50 mL) of saturated $NaHCO_3$ solution and sodium thiosulfate solution (20%). The mixture was then stirred for 20 min further. The two phases were separated, and the aqueous phase extracted twice with Et_2O (2 × 50 mL). The combined organic phases were washed with H_2O (100 mL), dried ($MgSO_4$), filtered, and then concentrated. Flash chromatography (hexane/AcOEt 9:1) of the crude residue (0.70 g) gave 0.47 g of **14** as a colorless syrup (70%) which was shown to be relatively unstable at room temperature. ^1H NMR ($CDCl_3$): δ 3.86 (d, 1H, J = 4.5 Hz, H-2); 4.02 (dd, 1H, J = 1.5, 13.0 Hz, H-7); 4.05 (t, 1H, J = 4.5 Hz, H-3); 4.25 (dd, 1H, J = 1.5, 13.0 Hz, H-7′); 4.33 (d, 1H, J = 14.5 Hz, PhCH); 4.41 (d, 1H, J = 14.5 Hz, PhCH); 4.45 (s, 2H, $PhCH_2$); 4,48−4.68 (4d, 4H, J = 14.5 Hz, 4 PhCH); 5.01 (d, 1H, J = 4.5 Hz, H-4); 6.40 (m, 1H, H-6); 7.15−7.40 (m, 20H, H aromatic); 9.54 (br s, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 68.8, 72.1, 72.9, 73.2, 74.5, 76.0, 80.8, 81.5, 118.8, 127.6−128.3, 136.9, 137.2, 137.3, 139.7, 201.05. IR (neat): 1701 cm^{-1} (CO).

6-Bromo-2,3,4-tris(phenylmethoxy)-5-[(phenylmethoxy)methyl]hex-5-enal (15). To a stirred solution of oxalyl chloride (86 μL, 1.10 mmol) in CH_2Cl_2 (3.5 mL) was added DMSO (0.38 mL) at −78 °C. After 15 min, a solution of **13** (334 mg, 0.54 mmol) in CH_2Cl_2 (1.25 mL) was added dropwise and the stirring was continued at the same temperature for 15 min before addition of NEt_3 (7.56 × 10^{-1} mL, 5.40 mmol). The mixture was then slowly warmed to room temperature, diluted with Et_2O (20 mL), washed with 0.1 M HCl (20 mL), water (20 mL), and brine (20 mL), and finally dried ($MgSO_4$). Flash chromatography (hexane/AcOEt 98:02 to 9:1) of the residue (0.34 g) gave 0.30 g of **15** as a colorless syrup (89%). ^1H NMR ($CDCl_3$): δ 3.85 (d, 1H, J = 4.5 Hz, H-2); 4.01 (dd, 1H, J = 2.0, 14.0 Hz, H-7); 4.07 (t, 1H, J = 4.5 Hz, H-3); 4.23 (dd, 1H, J = 2.0, 14 Hz, H-7′); 4.33

(d, 1H, J = 11.0 Hz, PhCH); 4.41 (d, 1H, J = 11.0 Hz, PhCH); 4.45 (s, 2H, $PhCH_2$); 4,50 (d, 1H, J = 11.0 Hz, PhCH); 4.58 (d, 1H, J = 11.0 Hz, PhCH); 4.59 (d, 1H,J = 11.0 Hz, PhCH); 4,67 (d, 1H, J = 11.0 Hz, PhCH); 4.93 (d, 1H, J = 4.5 Hz, H-4); 6.52 (br s, 1H, H-6); 7.10−7.40 (m, 20H, H aromatic); 9.60 (br s, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 69.9, 72.2, 72.9, 73.1, 74.5,77.9, 80.7, 81.3, 107.5, 127.5−128.4, 137.0, 137.2, 137.3, 139.8, 200.6. IR (neat): 1726 cm^{-1} (CO). $[\alpha]^{23}_D = -18.7$ (c 1.55, CH_2Cl_2). Anal. Calcd for $C_{35}H_{35}O_5Br\cdot 0.5H_2O$ (624.77): C, 67.31; H, 5.81. Found: C, 67.86; H, 5.82.

(1*RS*,4*R*,5*S*,6*S*)-4,5,6-Tris(phenylmethoxy)-3-[(phenylmethoxy)methyl]cyclohex-2-enol (16a/16b). A stirred mixture of $CrCl_2$ (617 mg, 5 mmol) and $NiCl_2$ (0.1%) was dried under reduce pressure (≈30 mmHg) at 160 °C. After 1 h, the gray powder was cooled to room temperature and DMF (oxygene free, 5 mL) was added under argon. The resulting green suspension was stirred at room temperature for a further 30 min, before a solution of **15** (124 mg, 0.20 mmol) in DMF (oxygene free, 5 mL) was added. After 22 h of stirring at 40 °C, cold water (30 mL) was added, and the mixture was extracted with Et_2O (4 × 30 mL). The combined organic phases were dried and concentrated. Flash chromatography (hexane/AcOEt 9:1) of the residue (118 mg) gave 65 mg of **16a/16b** (1/1 mixture) as a colorless syrup (61%). ^{1}H NMR ($CDCl_3$), data of (1*S*) **16a**: δ 2.60 (br d, 1H, OH); 3.60 (dd, 1H, J = 4.2, 9.2 Hz, H-6); 3.94 (d, 1H, J = 12.0 Hz, H-7); 4.06 (dd, 1H, J = 7.0, 12.0 Hz, H-5); 4.16 (br d, 1H, J = 7.0 Hz, H-4); 4.24 (br d, 1H, J = 12.0 Hz, H-7′); 4.30 (m, 1H, H-2); 4.50 (d, 1H, J = 11.0 Hz, PhCH); 4.53 (d, 1H, J = 11.0 Hz, PhCH); 4.62−5.93 (6d, 6H, J = 11.0 Hz, 6 PhCH); 5.91 (br d, 1H, J = 4.7 Hz, H-2); 7.20−7.40 (m, 20H, H aromatic). ^{1}H NMR ($CDCl_3$), data of (1*R*) **16b**: δ 2.12 (br d, 1H, OH); 3.57 (dd, 1H, J = 7.0, 10.0 Hz, H-6); 3.85 (dd, 1H, J = 7.0, 10.0 Hz, H-5); 3.91 (br d, 1H, J = 10 Hz, H-7); 4.25 (br d, 1H, J = 10.0 Hz, H-7′); 4.29 (br d, 1H, J = 10.0 Hz, H-4); 4.29−4.36 (m, 1H, H-2); 4.44 (d, 1H, J = 11.0 Hz, PhCH); 4.52 (d, 1H, J = 11.0 Hz, PhCH); 4.67−5.02 (6d, 6H, J = 11.0 Hz, 6 PhCH); 5.73 (br s, 1H, H-1); 7.18−7.40 (m, 20H, H aromatic). ^{13}C NMR ($CDCl_3$), (1*R* and 1*S*): δ 65.0, 71.2, 69.9, 70.9, 72.2, 72.5, 72.8, 74.0, 74.6, 74.7, 74.9, 75.1, 78.7, 78.7, 79.0, 79.6, 83.5, 83.7, 124.6, 127.1, 127.7−128.6, 137.9, 138.0, 138.3, 138.5, 139.9, 139.7, 200.6. IR (neat): 3500 cm^{-1} (OH). Anal. Calcd for $C_{35}H_{36}O_5\cdot 0.25\ H_2O$ (541.17): C, 77.68; H, 6.80; O, 15.52. Found: C, 77.52; H, 6.89; O, 15.49.

(4*R*,5*S*,6*R*)-4,5,6-Tris(phenylmethoxy)-3-[(phenylmethoxy)methyl]cyclohex-2-enone (17). A suspension of AcONa (245 mg, 3.0 mmol), PCC (323 mg, 1.5 mmol), and 4 Å molecular sieves (1.80 g) in CH_2Cl_2 (5 mL) was stirred for 30 min at room temperature; then a solution of **16a/16b** (0.40 g, 0.75 mmol) in CH_2Cl_2 (45 mL) was added. After 2 h, Et_2O (15 mL) and hexane (7.5 mL) were added and the reaction mixture was stirred for 15 min. The resulting suspension was filtered through a silica gel (70−200 μm) column which was further eluted with Et_2O (150 mL). The organic phase was then concentrated to 50 mL, washed with water (50 mL), dried ($MgSO_4$), and finally concentrated. Flash chromatography (hexane/AcOEt 93:3 to 95:5 with Et_3N 0.3%) of the residue (0.31 g) gave 305 mg of **17** as a colorless syrup (76%). ^{1}H NMR ($CDCl_3$): δ 4.05 (dd, 1H, J = 7.0, 11.0 Hz, H-5); 4.04 (d, 1H, J = 10.0 Hz, H-6); 4.08 (br d, 1H, J = 16.0 Hz, H-7); 4.27 (br d, 1H, J = 16.0 Hz, H-7′); 4.38 (br d, 1H, J = 7.0 Hz, H-4); 4.51 (s, 2H, $PhCH_2$); 4.65−4.80 (3d, 3H, J = 11.0 Hz, 3 PhCH); 3.88−5.15 (3d, 3H, J = 11.0 Hz, 3 PhCH); 6.23 (q, 1H, J = 1.5 Hz, H-2); 7.20−7.47 (m, 20H, H aromatic). ^{13}C NMR ($CDCl_3$): δ 68.9, 73.1, 74.4, 75.6, 75.7, 79.1, 83.9, 84.9, 123.88, 127.7−128.5, 137.4, 137.6, 137.7, 138.0, 159.1, 196.7. $[\alpha]^{28}_D = -9$ (c 1, $CHCl_3$) (lit. $[\alpha]^{23}_D = -12$ (c 1, $CHCl_3$)). Anal. Calcd for $C_{35}H_{34}O_5$: C, 78.63; H, 6.41; O, 14.96. Found: C, 77.93; H, 6.52; O, 15.18.

(4*R*,5*S*,6*R*)-4,5,6-Trihydroxy-3-(hydroxymethyl)cyclohex-2-enone (1). A solution (1 M) of BCl_3 in CH_2Cl_2 (2.25 mL) was added to a cooled solution (−70 °C) of **17** (0.30 g, 0.56 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was then warmed slowly to 0 °C (2 h) and then cooled to −70 °C before addition of pyridine (1.45 mL, 18 mmol) and MeOH (0.730 mL, 18 mmol). The mixture was then warmed to room temperature and concentrated. Water (1 mL) was added to the residue, and the solution was passed first through a column of Dowex resin (1 × 8) (HCO_3^- form) and then through a column of Dowex resin (1 × 50) (H^+ form). The aqueous phase was reduced to 10 mL, washed with Et_2O (10 mL), and then concentrated. Flash chromatography (AcOEt/2-propanol/H_2O 8:2:1) of the residue followed by filtration through a polyacrylamide gel column gave 72 mg of **1** as a hygroscopic brown solid (74%). ^{1}H NMR (CD_3OD): δ 3.59 (dd, 1H, J = 8.4, 10.9 Hz, H-5); 4.01 (d, 1H, J = 10.9 Hz, H-6); 4.32−4.50 (2d, 2H, 2H-7); 4.36 (m, 1H, H-4); 6.16 (q, 1H, J = 2.0 Hz, H-2). ^{13}C NMR ($CDCl_3$): δ 62.0, 73.7, 78.1, 79.4, 121.3, 167.9, 199.4. $[\alpha]^{27}_D = -40$ (c 1, MeOH) (lit.[1] $[\alpha]^{20}_D = -61.4$ (c 1, MeOH)). EI-MS: M^+ calcd = 174.0528; found 174.0524 (0.25), 156 (1.2), 138 (18.0), 126 (19.5), 114 (68.11), 96 (100), 68 (85.98).

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