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Synthesis of Caryose, the Carbocyclic Monosaccharide Component of the Lipopolysaccharide from *Pseudomonas caryophylli*[1]

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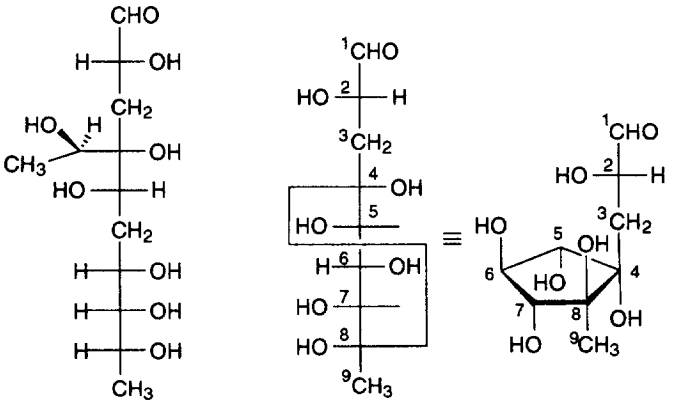
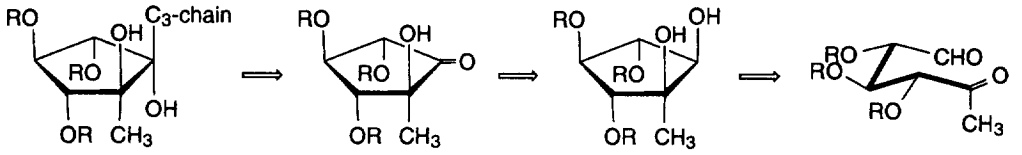
Abstract : The structure of the novel natural carbocylic monosaccharide caryose (4,8-cyclo-3,9-dideoxy-L-*erythro*-D-*ido*-nonose) has been confirmed through a synthesis whose key steps are the SmI_2-mediated cyclization of a ketoaldehyde derived from 3,4,5-tri-*O*-benzyl-1-deoxy-D-iditol, the mild oxidation of the obtained *cis*-1,2-diol and the diastereoselective allylation of the resulting ketol.

Two novel monosaccharides, caryophyllose (3,6,10-trideoxy-4-*C*-(D-*glycero*-1-hydroxyethyl)-D-*erythro*-D-*gulo*-decose, **1**) and caryose (4,8-cyclo-3,9-dideoxy-L-*erythro*-D-*ido*-nonose, **2**) have been recently isolated[2-5] as components of the cell wall lipopolysaccharides of *Pseudomonas caryophylli*, a bacterium responsible for the wilting of carnation.[6,7] The former is a twelve carbon C-4 branched sugar, the latter presents a carbocyclic skeleton, a unique feature for monosaccharides. Both structures **1** and **2** were mainly established by a combination of NMR experiments, mass spectroscopic and circular dichroic data. Now we present a synthesis of caryose that affords a chemical confirmation of the peculiar structure of the sugar.



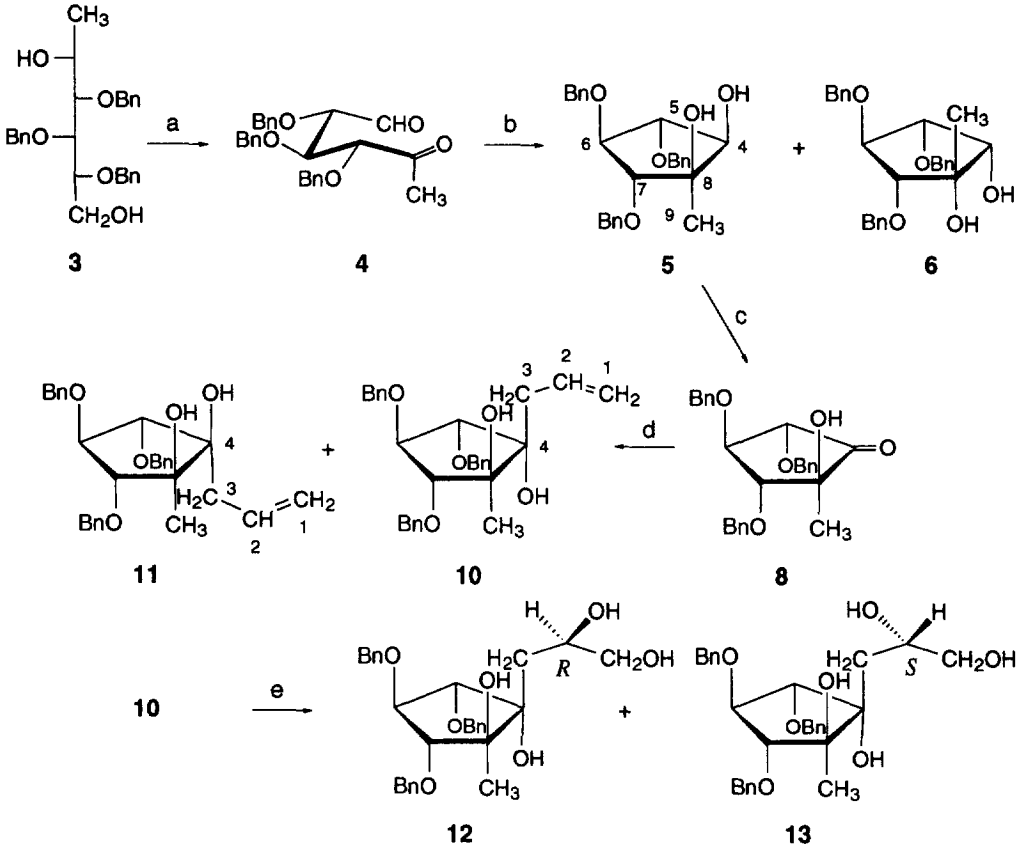
1 **2**

The synthesis was devised on the basis of the retroanalysis summarized in the Scheme 1, which took advantage of the availability of reliable procedures for Samarium(II) diiodide mediated cyclization of keto aldehydes to obtain *vic*-diols.[8, 9] The diol **A** in the Scheme had to possess both the same functionalization and stereochemistry as caryose at the positions C-5, C-6, C-7, and C-8 and a secondary carbinol grouping suitable to be utilized for attaching the C_3 chain after oxidation to carbonyl group.

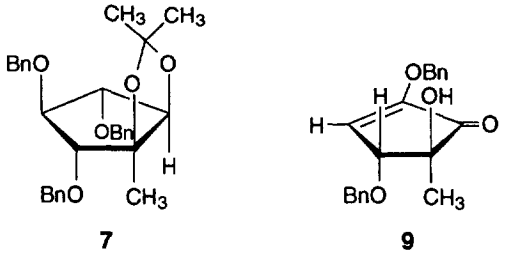


Scheme 1 **A**

Construction of the caryose ring started from the easily available 3,4,5-tri-*O*-benzyl-1-deoxy-D-iditol **3** (Scheme 2).[10] Swern oxidation[11] ($(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C) gave keto aldehyde **4** (relevant NMR signals: δ 2.11 s, CH_3CO-; δ 210.4, CH_3CO-; δ 9.77, -CH=O; δ 200.2, -CH=O). As chromatography caused extensive alteration, crude **4** was submitted to cyclization with SmI_2/*t*-BuOH/THF to give a 93:7 (^1H NMR) mixture of two *vic*-diols in a 64 % yield from **3**. Recently, cyclization of dialdehydes carrying one alkoxy substituent on each of the carbon atoms adjacent to the carbonyl groups has been shown[9, 12] to afford as the preponderant product the *cis vic*-diol with each OH group *trans*-oriented with respect to the α-alkoxy group, when the two substituents can be located on the same side of the ring. On this basis, the major diol from **4** could be expected to be the desired *cis*-diol **5**. However, because of the essential relevance of the stereochemical outcome of the cyclization step for the synthesis of **2**, the configuration of the carbinol centres of the two diols was analyzed by NMR experiments. Thus, in the ^1H NMR spectrum in C_6D_6 of the major diol, two signals due to the hydroxyl protons (D_2O exchange) were displayed at δ 2.30 and δ 2.10. A broad doublet at δ 3.72 was identified as due to the 4-proton[13] as it was shown to be coupled with the former. Scalar connectivity starting from 4-H hence assigned the δ 4.04 t, 4.01 t and 3.98 d signals to 5-H, 6-H and 7-H, respectively. NOE contact (Fig. 1) of the methyl group with the 6-H then showed that it was located at the same side of the ring as 6-H, as depicted in **5**. In addition, a sample of the major diol was readily converted to the 4,8-isopropylidene derivative **7** (three methyl singlets at δ 1.40, 1.46 and 1.49: (9)CH_3 and $>C(CH_3)_2$), that supports the expected *cis* relation of the two hydroxyl groups. Conversely, for the minor diol, NOE correlations (Fig. 1) between the methyl protons and 5-H and between 4-OH and 6-H, whose signals were identified as described for compound **5**, put these groups oriented as depicted in **6**.



Scheme 2. a) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2; b) SmI_2/*t*-BuOH/THF; c) TEMPO/KBr/ 0.9 M NaOCl/CH_2Cl_2/H_2O; d) AllylTMS/$TiCl_4$/CH_2Cl_2; e) NMO/OsO_4/THF/H_2O



Oxidation of the secondary hydroxyl group of **5** was performed only after exploring a number of methods. Treatment of **5** with *N*-chlorosuccinimide/Me_2S/Et_3N,[14] Ag_2CO_3/Celite,[15] or $(COCl)_2$/DMSO/Et_3N[11] gave only complex mixtures. The use of Bu_2SnO/MeOH followed by Br_2/Bu_3SnOMe, specific for 1,2-diols,[16] did afford ketone **8** (^1H NMR), but any chromatography procedure

needed to remove co-products and organotin compounds caused the extensive conversion of **8** into an elimination product (probably **9**: the ^{1}H NMR spetrum displayed an alkene proton at δ 6.24 d and the signals for only two benzylic methylene groups). Satisfactory results were achieved with sodium hypochloride TEMPO-mediated oxidation,[17, 18] that gave the crude α-hydroxy-ketone **8** (^{13}C NMR: $\delta_{C=O}$ 212.7; IR: $\nu_{C=O}$ 1761 cm^{-1}) enough pure to be used in the subsequent synthetic step. NOE correlation between 9-H_3 and 6-H confirmed the configuration at C-8.

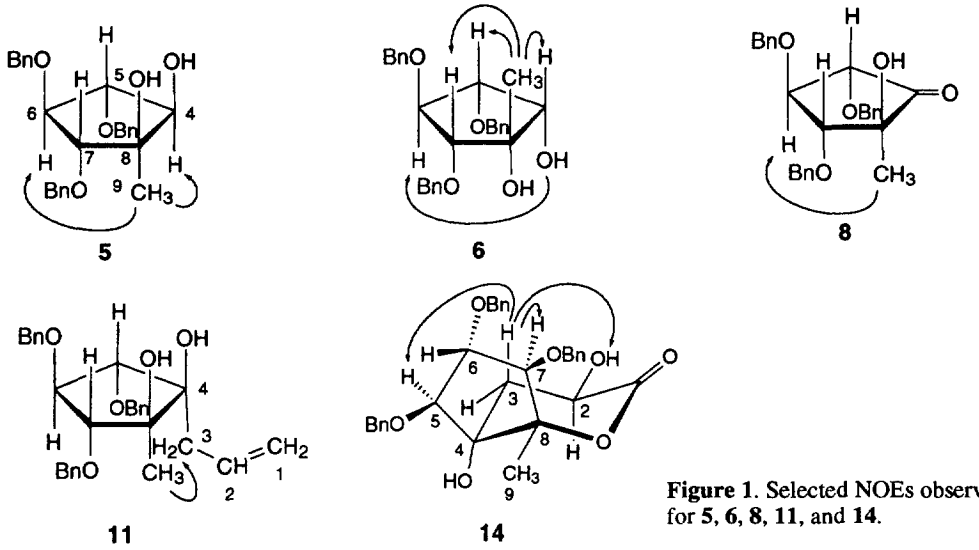
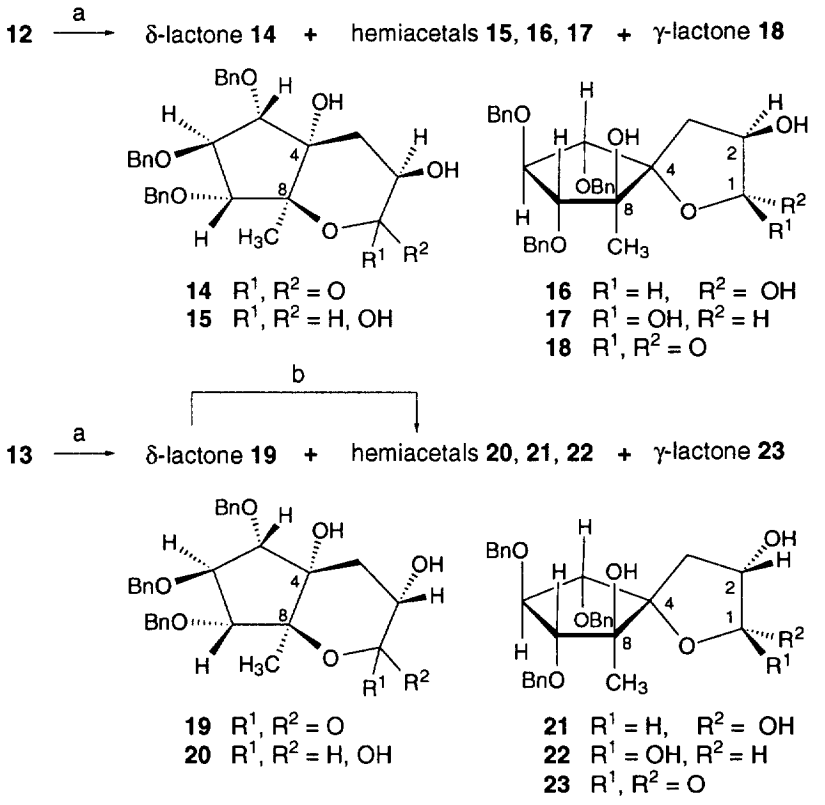


Figure 1. Selected NOEs observed for **5**, **6**, **8**, **11**, and **14**.

The attachment of a C_3 chain at C-4 of **8** was attempted by allylation without any protection of the tertiary hydroxyl group both to avoid further steps in the synthesis and because a directing effect exerted by that group to maximize the introduction of the chain from that side could be relied on.[19] This effect could cooperate with the larger crowding at the other side of the C=O grouping (due to 8-CH_3 and 5-OBn) to attain the desired stereochemistry at C-4. The additions of allylmagnesium bromide and of allyltrimethylsilane/$TiCl_4$[20] both gave two homoallilic alcohols in the ratio 3:2 (38 % yield from **5**) and 19:1 (61 % yield from **5**), respectively. As expected, the major product (C*H*= at δ 5.96, =CH_2 at δ 5.14) was **10**, with the same configuration at C-4 as caryose, and the minor one (C*H*= at δ 5.82, =CH_2 at δ 5.21) was **11**. This was established from the strong NOE correlation (Fig. 1) between 9-H_3 and 3-H_2 measured for the latter but quite absent for the former. Such a higher diastereoselectivity in the addition of allyltrimethylsilane might be accounted for by chelation of $TiCl_4$ to both carbonyl and hydroxyl oxygen atoms with consequent transfer of a chloride ion to the silicon atom and attack of the allyl group to C-4 occurring from that side.

Dihydroxylation of **10** (scheme 2) with osmium tetroxide/*N*-methylmorpholine oxide[21, 22] in 1:1 THF/water at r.t. afforded a 3:2 mixture (95% yield) of two epimeric tetrols (2-C*H*OH at δ 3.87 m, 1-CH_2OH at δ 3.42 dd and 3.53 dd for the minor isomer (**12** or **13**); 2-C*H*OH at δ 4.03 m, 1-CH_2OH at δ 3.46 dd and 3.57 dd for the major isomer (**13** or **12**)), easily resolved by column chromatography. Because of the conformational mobility of the side chain in **10**, no surmise could be ventured as for the preferential attack to the C=C double bond and, therefore, as for the configuration at C-2 of the two epimers. This point was resolved after both tetrols were submitted to two-phase reaction (Scheme 3) with sodium hypochloride, mediated by TEMPO, to achieve the selective oxidation of the primary hydroxyl group to aldehyde in presence of the secondary one.[23]



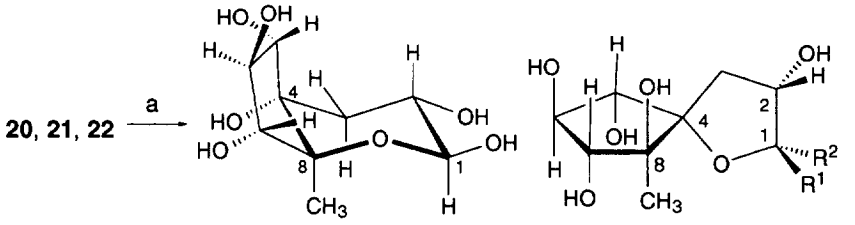
Scheme 3. a) TEMPO/KBr/TBAC/sat $NaHCO_3$/1.95 M NaOCl/CH_2Cl_2; b) DIBAL/$PhCH_3$.

Actually, oxidation of the minor isomer gave, beside a sustantial amount of unreacted material (36 %), two main compounds: an aldehyde (27 %) as the mixture of three hemiacetal forms (anomeric carbons at δ 94.7 (pyranose), δ 103.8 and 97.1 (furanoses)),[4] and a δ-lactone (32 %; $\delta_{C=O}$ 173.4; $\nu_{C=O}$ 1735 cm^{-1}). A trace

of a γ-lactone ($\nu_{C=O}$ 1783 cm^{-1}) was also recovered. The *R*-configuration as in **14** could be safely assigned to the C-2 centre of the δ-lactone on the basis of NMR considerations. In fact, the large coupling (13.2 Hz) between the 2-H and the 3-H at δ 2.03 t (as compared to the smaller coupling, 5.9 Hz, with the other 3-H at δ 2.33 dd) and the NOE correlations (Fig. 1) of the latter with 5-H, 7-H and also with 2-OH (identified as being displayed as a doublet at δ 3.07, coupled with the 2-H at δ 4.58 m) indicated that the δ-lactone possesses the conformation depicted in **14** with the 2-H axially and the 2-OH equatorially oriented. Therefore, the *2R* configuration, opposite to the configuration assigned[4] to caryose at that centre, must be possessed by δ-lactone **14**, the hemiacetals, **15**, **16**, and **17**, the γ-lactone, **18**, and, therefore, by the minor tetrol, **12**, from which they had been obtained.

Oxidation of the major tetrol **13**, which thus possesses the *2S* configuration at C-2, afforded, beside unreacted material (34 %), δ-lactone **19** (33 %; $\nu_{C=O}$ 1740 cm^{-1}; $\delta_{C=O}$ 171.2; $\delta_{3\text{-}H_2}$ 2.09 dd (14.0 and 8.5 Hz) and 2.25 dd (14.0 and 5.8 Hz); $\delta_{2\text{-}H}$ 4.06 dd), the mixture of hemiacetals **20-22** (31 %; anomeric carbons at δ 94.8 (pyranose), δ 103.8 and 98.3 (furanoses)), and a trace of the γ-lactone **23** ($\nu_{C=O}$ 1789 cm^{-1}). Attempt to obtain the complete conversion of **13** by using larger proportions of oxidant only increased the ratio δ-lactone/hemiacetals. To this regard, it may be noted that the hydrophylic nature of the hemiacetals could favour overoxidation in aqueous phase.[23] However, δ-lactone **19** was easily converted to the hemiacetal mixture **20-22** by treatment with DIBAL at -70 °C.

When asymmetric dihydroxylation was attempted, the compound **10** was found to react only very sluggishly both with AD-mix-α and with AD-mix-β[24] during 48h, even at r.t., due probably to presence of the bulky carbocycle. In both cases TLC monitoring showed that the undesired tetrol **12** would be the predominant dihydroxylation product.



Scheme 4. a) Pd-C/HCOOH/MeOH.

Finally, the hemiacetal mixture **20-22** obtained from **13** was quantitatively debenzylated by catalytic transfer hydrogenolysis using formic acid (Scheme 4).[25] The product ($[\alpha]_D$ +10.5° in water) was identical

(TLC, ^1H and ^{13}C NMR) with the mixture of the hemiacetals forms **24-26** of caryose ($[\alpha]_D$ +9.5°)[4] obtained from the natural source.

EXPERIMENTAL

^1H NMR spectra were recorded using a Bruker DRX-400 (400 MHz) or AM-250 (250 MHz) spectrometer. ^{13}C NMR spectra were recorded using a Bruker AM-250 (62.89 MHz) spectrometer. ^1H and ^{13}C chemical shifts in $CDCl_3$ or C_6D_6 were measured relative to TMS. ^1H and ^{13}C chemical shifts in D_2O were measured relative to sodium 3-trimethylsilylpropionate-*2,2,3,3-d*$_4$ and 1,4-dioxane (δ 67.40), respectively. Multiplicities in the ^{13}C spectra were determined by DEPT experiments using a polarization transfer pulse of 135° and a delay adjusted to an average C,H-coupling of 160 Hz. Assignment of ^1H NMR signals was obtained by decoupling experiments. NOE experiments were performed with a standard NOEDIFF sequence. IR spectra were recorded in $CHCl_3$ with a Perkin Elmer 1760 spectrometer. Optical rotations were determined on a Perkin Elmer 141 polarimeter at 18-22 °C. TLC and PLC were performed using silica gel plates F_{254} (Merck), column chromatography on silica gel 60 (Merck). Whenever anhydrous reaction conditions were required, dry solvents (dichloromethane, tetrahydrofuran, methanol) stored over molecular sieves were used, under dry argon atmosphere.

Swern oxidation of 2,3,4-tri-*O*-benzyl-6-deoxy-D-iditol 3 to L-*xylo*-6-deoxy-hexos-5-ulose 4

A solution of DMSO (1.6 mL, 22.5 mmol) in CH_2Cl_2 (4.8 mL) was added dropwise to a solution of oxalyl chloride (940 mL, 10.6 mmol) in CH_2Cl_2 (17 mL) at -60 °C under argon. After 10 min stirring, compound **3**[10] (2 g, 4.6 mmol) in CH_2Cl_2 (5 mL) was added in 5 min. After 15 min stirring, Et_3N (6.4 mL, 46 mmol) was added dropwise. The reaction mixture was left ro raise gradually to r.t., diluted with water (20 mL) and extracted with CH_2Cl_2 (3x20 mL). Evaporation to dryness *in vacuo* of the combined organic layers gave crude compound **4** (1.89 g) which was used without purification for the following step, as chromatography on silica gel caused alteration.

Compound 4: ^1H NMR (250 MHz, $CDCl_3$) δ 2.11 (3H, s, C*H*$_3$CO-), 3.92 (1H, bd, $J_{2,3}$ = 5.2 Hz, 2-H), 4.08 (1H, d, $J_{3,4}$ = 2.8 Hz, 4-H), 4.12 (1H, dd, 3-H), 4.45-4.81 (6H, benzylic), 7.3-7.4 (Ph), 9.77 (1H, s, -C*H*O); ^{13}C NMR δ 27.9 (*C*H$_3$-CO-), 200,2 (-CH=O), 210,4 (CH$_3$-*C*O-).

Cyclization of 4

SmI_2 (0.1 M soln in THF, 110 mL, 11.0 mmol) and t-BuOH (410 μL, 4.4 mmol) were added to the above crude compound **4** dissolved in THF (30 mL) at -78 °C under argon. After 4 h stirring the reaction mixture was left to raise to r.t overnight. Neutralization of the resulting yellow mixture with sat aq $NaHCO_3$, evaporation, extraction (EtOAc, 3 x 100 mL), washing of the combined organic layers with 10% $Na_2S_2O_3$ (50 mL) and then water, drying, evaporation, and chromatography on silica gel (EtOAc/hexane 1:4) afforded **6** as an oil (91 mg, 5% from **3**) and, successively, **5** as white needles (1.175 g, 59% from **3**). By treatment with 1:1 2,2-dimetoxypropane/acetone and a trace of Amberlite IR-120 (H^+ form) at r.t for 1 h, a sample of diol **5** was converted to the 4,8-isopropylidene derivative **7**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.40, 1.46, and 1.49 ((9)CH_3 and >$C(CH_3)_2$), 3.88-3.98 (3H, m) and 4.09 (1H, d, J = 1.7 Hz), 4.55-4.85 (6H, 3 x benzylic CH_2), 7.25-7.4 (15 H, 3 x Ph).

Compound 5: m.p. 66-69 °C from Et_2O/hexane, $[\alpha]_D$ -17.9° ($CHCl_3$, c 1.7); ^1H NMR (250 MHz, C_6D_6) δ 1.33 (3H, s, 9-H_3), 2.10 (1H, s, exchange with D_2O, 8-OH), 2.30 (1H, bs, exchange with D_2O, 4-OH), 3.72 (1H, bd, sharpened after exchange with D_2O, $J_{4,5}$ = 4.4 Hz, 4-H), 3.98 (1H, d, $J_{6,7}$ = 4.4 Hz, 7-H), 4.01 (1H, t, $J_{5,6}$ = 4.4 Hz, 6-H), 4.04 (1H, t, 5-H), 4.58-4.71 (6H, benzylic), 7.1-7.5 (15 H, Ph); ^{13}C NMR (C_6D_6) δ 20.9 (C-9), 71.75, 71.8, and 72.4 (3 x benzylic CH_2), 79.4, 85.0, 87.4, and 87.45 (C-4, C-5, C-6, and C-7), 77.8 (C-8), 127.5-128.3 and 138-138.5 (Ph). Anal. Calcd for $C_{27}H_{30}O_5$: C 74.63; H 6.96. Found: C 74.80; H 7.01.

Compound 6: ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, s, 9-H_3), 2.83 (1H, d, $J_{OH,4-H}$ = 7.85 Hz, exchange with D_2O, 4-OH), 3,09 (1H, s, exchange with D_2O, 8-OH) , 3.54 (1H, d, $J_{6,7}$ = 4.5 Hz, 7-H), 3.78 (1H, dd, $J_{4,5}$ = 5.8 Hz, 4-H), 3.87 (1H, dd, $J_{5,6}$ = 4.5 Hz, 5-H), 4.09 (1H, t, 6-H), 4.45-5,30 (6H, benzylic), 7.3-7.5 (15 H, Ph). Anal. Calcd for $C_{27}H_{30}O_5$: C 74.63; H 6.96. Found: C 74.71; H 7.08.

Oxidation of diol 5 to ketone 8

a) Compound **5** (23 mg, 0,051 mmol) and dibutyltin oxide (14 mg, 0.056 mmol) in dry MeOH (0.5 mL) were refluxed 90 min under argon. Solvent was removed with a stream of the gas. To the residue dissolved in CH_2Cl_2 (350 μL) and cooled to -10 °C tributyltin methoxide (7.5 μL, 0.026 mmol) and then, in 30 min, bromine (2.6 μL, 0.051 mmol) in CH_2Cl_2 (110 μL) was added. The reaction mixture was warmed to r.t, diluted with CH_2Cl_2 (5 mL), washed with 10% aq $Na_2S_2O_3$, dried and evaporated. ^1H NMR of the residue displayed mainly the signals of unreacted **5** and of ketone **8** (see later). Chromatography on silica gel (EtOAc: hexane 1:4) afforded **5** (7 mg) and a product (4 mg) wich could be assigned structure **9** on the basis of the ^1H

NMR (250 MHz, $CDCl_3$) signals at δ 1.47 (3H, s, 9-H_3), 4.50 (1H, d, $J_{6,7}$ = 2.7 Hz, 7-H), 4.70 and 4.87 (2H, AB, J = 12.1 Hz, CH_2-OPh), 4.97 and 5.02 (2H, AB, J = 12.0 Hz, CH_2-OPh), 6.24 (1H, d, J=2.7, 6-H), 7.3-7.5 (10H, Ph).

b) 0.9 M NaOCl (2.7 mL, 2.4 mmol, buffered at pH 9.5) was added in 5 min to a cooled (0°C) and well stirred mixture of diol **5** (0.97 g, 2.24 mmol), CH_2Cl_2 (8 mL), TEMPO (3.6 mg, 0.02 mmol), KBr (27 mg, 0.22 mmol) and water (0.4 mL). After 10 min stirring, the organic phase was separated, washed with 10% aq $Na_2S_2O_3$ (5 mL) and water (5 mL), dried and evaporated to give crude ketone **8** (966 mg) as a colourless oil, which was used for the following step directly.

*Compound **8***: ^{1}H NMR (400 MHz, C_6D_6) δ 1.17 (3H, s, 9-H_3), 3.82 (1H, d, J = 7.6 Hz, 5-H or 7-H), 3.94 (1H, d, J = 7.6 Hz, 7-H or 5-H), 4.03 (1H, t, J = 7.6 Hz, 6-H), 4.58-4.94 (6H, benzylic), 6.9-7.4 (15H, Ph); ^{13}C NMR (C_6D_6) δ 19.4 (C-9), 72.8, 72.9, and 73.1 (3 x benzylic CH_2), 80.1 (C-8), 82.1, 82.4, and 82.4 (C-5, C-6, and C-7), 127.5-129 and 137.9-138.9 (Ph), 212.7 (C=O); IR ($CHCl_3$) $\nu_{C=O}$ 1761 cm^{-1}.

Allylation of 8

a) Allylmagnesium bromide (1.0 M in Et_2O, 438 μL, 0.438 mmol) was added dropwise to a solution of crude **8** (prepared from **5** with method ***b***, 53 mg) in THF (300 μL) at -78 °C under argon. After 30 min stirring, sat aq NH_4Cl (0.5 mL) and then AcOEt (10 mL) were added. The residue from evaporation of the dried organic layer was chromatographed on silica gel (EtOAc/hexane 1:4) to give compounds **10** (13 mg, 23 % from **5**) and **11** (9 mg, 15 % from **5**), both as colourless oils.

b) $TiCl_4$ (1.0 M in CH_2Cl_2, 3.7 mL, 3.7 mmol) was added to a solution of crude **8** (prepared from **5** with method ***b***, 910 mg) in CH_2Cl_2 (16.5 mL) at r.t. under argon. After 1 min stirring, the solution was cooled to 0 °C and allyltrimethylsilane (854 μL, 5.3 mmol) was added. The mixture was stirred for 3 h, neutralized with sat aq $NaHCO_3$, diluted with EtOAc (100 mL) and centrifuged. The clear supernatant was washed with water (3 x 40 mL) and evaporated to give a 19:1 (^{1}H NMR) mixture of compounds **10** and **11**. Chromathography on silica gel (EtOAc/hexane 1:4) gave compounds **11** (30 mg, 3 % from **5**) and **10** (580 mg, 58 % from **5**).

*Compound **10***: $[\alpha]_D$ +23.9° ($CHCl_3$, c 3.6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s, 9-H_3), 1.80 (1H, bs, exchange with D_2O, 4-OH or 8-OH), 2.20 (1H, dd, $J_{3a,3b}$ = 14.9 Hz, $J_{3a,2}$ = 8.5 Hz, 3-H_a), 2.71 (1H, dd, $J_{3b,2}$ = 6.4 Hz, 3-H_b), 2.97 (1H, bs, exchange with D_2O, 8-OH or 4-OH), 3.78 (2H, m, 5-H and 7-H), 3.87

(1H, dd, J = 3.8 Hz, J = 5.4 Hz, 6-H), 4.45-4.85 (6H, benzylic), 5.14 (2H, m, 1-H_2), 5.96 (1H, m, 2-H), 7.27-7.42 (15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 18.8 (C-9), 38.9 (C-3), 71.9, 72.7, and 72.7 (3 x benzylic CH_2), 79.4 and 82.4 (C-4 and C-8), 84.0, 86.7, and 87.8 (C-5, C-6, and C-7), 118.3 (C-1), 134.4 (C-2) , 127.8-128.4 and 137.5-138.3 (Ph). Anal. Calcd for $C_{30}H_{34}O_5$: C 75.92; H 7.22. Found: C 75.78; H 7.34.

Compound 11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, s, 9-H_3), 2.58 (1H, bs, exchange with D_2O, 4-OH or 8-OH), 2.21 (1H, dd, $J_{3a,3b}$ = 13.7 Hz, $J_{3a,2}$ = 9.3 Hz, 3-H_a), 2.67 (1H, dd, $J_{3b,2}$ = 5.5 Hz, 3-H_b), 2.70 (1H, bs, exchange with D_2O, 8-OH or 4-OH), 3.58 (1H, d, J = 2.4 Hz, 5-H or 7-H), 3.82 (1H, dd, J = 6.1 Hz, 6-H), 4.19 (1H, d, 7-H or 5-H), 4.37-4.96 (6H, benzylic), 5.21 (2H, m, 1-H_2), 5.82 (1H, m, 2-H), 7.2-7.5 (15 H, Ph); ^{13}C NMR ($CDCl_3$)δ 17.1 (C-9), 35.0 (C-3), 71.3, 71.6, and 72.4 (3 x benzylic CH_2), 80.6 and 81.2 (C-4 and C-8), 85.9, 86.3, and 90.3 (C-5, C-6, and C-7), 120.5 (C-1), 133.2 (C-2), 127.6-128.3 and 137.8-138.1 (Ph). Anal. Calcd for $C_{30}H_{34}O_5$: C 75.92; H 7.22. Found: C 76.03; H 7.36.

Dihydroxylation of 10

Compound **10** (565 mg, 1.1 mmol), *N*-methylmorpholine-*N*-oxide monohydrate (165 mg, 1.22 mmol) and osmium tetroxide (0.016 M in H_2O, 1.25 mL, 0.02 mmol) were stirred in 1:1 THF-water (18 mL) at r.t overnight. The reaction mixture was treated with $Na_2S_2O_5$ (4 mg) and extracted with EtOAc. The organic layer was washed with water, dried and evaporated. Chromatography of the residue on silica gel (EtOAc/hexane 3:2) gave tetrols **13** (321 mg, 57 %, white crystals) and **12** (214 mg, 38 %, oil).

Compound 12: $[\alpha]_D$ +4.3° ($CHCl_3$, c 6.2); ^{1}H NMR (400 MHz, $CDCl_3$, exchanged with D_2O) δ 1.38 (3H, s, 9-H_3), 1.74 (1H, dd, $J_{3a,3b}$ = 14.9 Hz, $J_{3a,2}$ = 9.3 Hz, 3-H_a), 1.83 (1H, dd, $J_{3b,2}$ = 2.3 Hz, 3-H_b), 3.42 (1H, dd, $J_{1a,1b}$ = 11.0 Hz, $J_{1a,2}$ = 6.9, 1-H_a), 3.53 (1H, dd, $J_{1b,2}$ = 3.5 Hz, 1-H_b), 3.71 (1H, d, J = 2.9 Hz, 5-H or 7-H), 4.08 (1H, d, J = 4.0 Hz, 7-H or 5-H), 3.87 (1H, m, 2-H), 3.99 (1H, t, 6-H), 4.45-4.7 (6H, benzylic), 7.2-7.4 (15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 18.2 (C-9), 37.0 (C-3), 68.3 (C-2), 67.0, 72.0, 72.6, and 72.8 (1-CH_2 and 3 x benzylic CH_2), 81.3 and 81.6 (C-4 and C-8), 86.3, 87.2, and 88.4 (C-5, C-6, and C-7), 127.9-128.5 and 137.4-137.6 (Ph). Anal. Calcd for $C_{30}H_{36}O_6$: C 70.85; H 7.13. Found: C 70.99; H 7.26.

Compound 13: $[\alpha]_D$ +15.5° ($CHCl_3$, c 5.1); m.p. 107-9 °C (from benzene-hexane); ^{1}H NMR (400 MHz, $CDCl_3$, exchanged with D_2O) δ 1.35 (3H, s, 9-H_3), 1.52 (1H, d, $J_{3a,3b}$ = 14.9 Hz, 3-H_a), 2.04 (1H, dd, $J_{3b,2}$ = 10.8 Hz, 3-H_b), 3.46 (1H, dd, $J_{1a,1b}$ = 11.1 Hz, $J_{1a,2}$ = 6.7, 1-H_a), 3.57 (1H, dd, $J_{1b,2}$ = 3.2 Hz, 1-H_b), 3.74 (1H, d, J = 4.9 Hz, 5-H or 7-H), 3.78 (1H, d, J = 3.8 Hz, 7-H or 5-H), 3.92 (1H, t, 6-H), 4.03 (1H, m, 2-H), 4.45-4.8 (6H, benzylic), 7.2-7.4 (15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 18.3 (C-9), 36.3 (C-3), 68.6 (C-2),

67.1, 72.1, 72.8, and 72.8 (1-CH_2 and 3 x benzylic CH_2), 81.0 and 81.9 (C-4 and C-8), 85.4, 86.0, and 87.8 (C-5, C-6, and C-7), 127.8-128.5 and 137.2-137.9 (Ph). Anal. Calcd for $C_{30}H_{36}O_6$: C 70.85; H 7.13. Found: C 70.75; H 7.08.

Oxidation of compound 13

TEMPO (0.8 mg, 0.005 mmol) and sat aq $NaHCO_3$ (800 µL) containing KBr (6 mg, 0.05 mmol) and tetrabutylammonium chloride (6 mg, 0.02 mmol) were added to compound **13** (230 mg, 0.45 mmol) dissolved in CH_2Cl_2 (1 mL). To the cooled (0 °C) and stirred mixture, a solution made of aq NaOCl (1.95 M, 300 µL), sat aq $NaHCO_3$ (450 µL) and iced water (900 µL) was added dropwise in 30 min. After 15 min stirring at 0 °C and warming to r.t., the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). Washing with water of the combined organic phases, drying, evaporation and chromathography on silica gel (EtOAc/hexane 1:4) afforded unreacted **13** (77 mg, 34%), the mixture of hemiacetals **20**, **21**, and **22** (71 mg, 31%), δ-lactone **19** (75 mg, 33%, oil), and traces of the γ-lactone **23**.

*Hemiacetals **20**, **21**, and **22**:* $[\alpha]_D$ +9.6° ($CHCl_3$, c 1,4). ^{13}C NMR ($CDCl_3$) : 9-CH_3 at δ 15.6, 17.8, and 19.1; 3-CH_2 at δ 34.6, 36.4, and 36.7; C-4 and C-8 at δ 75.0, 80.4, 84.4, 85.9, 90.7, and 92.8; CH at δ 66.4, 68.0, 71.4 and overlapping signals in the range 75.5-90.5; benzylic CH_2 in the range δ 71.9-73.6; C-1 at δ 94.8 (pyranose form)[4], 98.3 and 103.8 (furanose forms)[4]; Ph signals at δ 127-130 and δ 136.5-138.5. In the ^1H NMR (400 MHz, $CDCl_3$) spectrum, because of the overlapping of the signals, only the anomeric furanoses protons at δ 5.33 bs and δ 5.16 d (3.2 Hz), the 9-H_3 signals at d 1.38 s, 1.36 s, and 1.35 s, and the 3-H_2 signals in the range δ 1.7-2.6 could be clearly identified.

*δ-lactone **19***: $[\alpha]_D$ +11.9° ($CHCl_3$, c 1.8); IR ($CHCl_3$) $\nu_{C=O}$ 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (3H, s, 9-H_3), 2.09 (1H, dd, $J_{3a,3b}$ = 14.0 Hz, $J_{3a,2}$ = 8.5 Hz, 3-H_a), 2.25 (1H, dd, $J_{3b,2}$ = 5.8 Hz, 3-H_b), 3.5 (2H, exchange with D_2O, 8-OH and 4-OH), 3.70 (1H, d, J = 5.3 Hz, 5-H or 7-H), 3.86 (1H, d, J = 6.4 Hz, 7-H or 5-H), 3.90 (1H, dd, 6-H), 4.06 (1H, dd, 2-H), 4.5-4.9 (6H, benzylic), 7.25-7.45 (15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 17.8 (C-9), 37.1 (C-3), 64.8 (C-2), 73.2, 72.6, and 72.6 (3 x benzylic CH_2), 73.7 and 93.7 (C-4 and C-8), 82.5, 84.8, and 87.6 (C-5, C-6, and C-7), 127.7-128.6 and 136.6-137.5 (Ph), 171.2 (C=O). Anal. Calcd for $C_{30}H_{32}O_7$: C 71.41; H 6.39. Found: C 71.64; H 6.50.

*γ-lactone **23***: IR ($CHCl_3$) $\nu_{C=O}$ 1789 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.37 (3H, s, 9-H_3), 2.00 (1H, dd, $J_{3a,3b}$ = 14.3 Hz, $J_{3a,2}$ = 5.4 Hz, 3-H_a), 2.74 (1H, dd, $J_{3b,2}$ = 8.3 Hz, 3-H_b), 3.15 (1H, d, $J_{OH,2-H}$ = 5

Hz, exchange with D_2O, 2-OH), 3.76 (1H, d, J = 5.4 Hz, 5-H or 7-H), 4.00 (1H, d, J = 5.4 Hz, 7-H or 5-H), 4.06 (1H, t, 6-H), 4.46 (1H, m, 2-H), 4.45-4.80 (6H, benzylic), 7.20-7.50 (15 H, Ph).

Oxidation of compound 12

Oxidation of compound **12** (51 mg, 0.1 mmol), in the very same experimental conditions as for oxidation of **13**, afforded unreacted **12** (18 mg, 36%), the mixture of hemiacetals **15**, **16**, and **17** (14 mg, 27%), δ-lactone **14** (16 mg, 32%, oil) and traces of the γ-lactone **18**.

*Hemiacetals **15**, **16**, and **17***: ^{13}C NMR ($CDCl_3$) DEPT: 9-CH_3 at δ 15.2, 18.6, and 18.9; 3-CH_2 at δ 35.4, 38.3, and 39.2; CH at δ 65.4, 68.1, 71.4 and overlapping signals in the range75.9-91.1; benzylic CH_2 in the range δ 71.9-72.9; C-1 at δ 94.7 (pyranose form)[4], 97.1 and 103.8 (furanose forms)[4]; Ph signals at δ 127.0-129.0. In the ^1H NMR (400 MHz, $CDCl_3$) spectrum, because of the overlapping with the benzylic proton signals, only the anomeric furanose protons at δ 5.29 d (J = 4,5 Hz) and 5.12 bs, the 9-H_3 signals at δ 1.43 s, 1.31 s, and 1.26 s, and the 3-H_2 signals in the range δ 1.8-2.4 could be clearly identified.

*δ-lactone **14***: $[\alpha]_D$ +12.1° ($CHCl_3$, c 1.5); IR ($CHCl_3$) $\nu_{C=O}$ 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, s, 9-H_3), 2.03 (1H, t, $J_{3ax,3eq} = J_{3ax,2}$ = 13.2 Hz, 3-H_{ax}), 2.33 (1H, dd, $J_{3eq,2}$ = 5.9 Hz, 3-H_{eq}), 3.07 (1H, d, $J_{OH,2-H}$ = 1.65 Hz, exchange with D_2O, 2-OH), 3.50 (1H, s, exchange with D_2O, 4-OH), 3.52 (1H, d, J = 3.2 Hz, 5-H or 7-H), 3.99 (1H, d, J = 6.7 Hz, 7-H or 5-H), 3.77 (1H, dd, 6-H), 4.58 (1H, m, 2-H), 4.47-4.95 (6H, benzylic), 7.20-7.50 (15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 17.3 (C-9), 39.4 (C-3), 62.9 (C-2), 72.3, 72.9, and 72.9 (3 x benzylic CH_2), 73.7 and 94.5 (C-4 and C-8), 84.0, 84.3, and 87.9 (C-5, C-6, and C-7), 127.8-128.7 and 136.5-137.2 (Ph), 173.4 (C=O). Anal. Calcd for $C_{30}H_{32}O_7$: C 71.41; H 6.39. Found: C 71.57; H 6.27.

*γ-lactone **18***: IR ($CHCl_3$) $\nu_{C=O}$ 1783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, exchanged with D_2O) δ 1.37 (3H, s, 9-H_3), 2.26 (1H, dd, $J_{3a,3b}$ = 13.5 Hz, $J_{3a,2}$ = 8.8 Hz, 3-H_a), 2.35 (1H, dd, $J_{3b,2}$ = 8.8 Hz, 3-H_b), 3.77 (1H, d, J = 4.62 Hz, 5-H or 7-H), 4.00 (1H, d, J = 6.9 Hz, 7-H or 5-H), 4.07 (1H, dd, 6-H), 4.5-4.8 (7H, benzylic CH_2 and 2-H), 7.3-7.5 (Ph).

Reduction of δ-lactone 19 to hemiacetals 20, 21, and 22

DIBAL (1.6 M in toluene, 210 μL, 0.34 mmol) was added to compound **19** (50 mg, 0.1 mmol) dissolved in dry toluene (1 mL) at -70 °C under argon. After 30 min stirring, quenching with methanol, addition of cold 10% aq HCl and then of EtOAc (5 mL), the organic phase was washed with water, dried and

evaporated. Chromatography of the residue on silica gel (EtOAc/hexane 3:2) afforded the mixture of hemiacetals **20**, **21**, and **22** (46 mg, 92%).

Debenzylation of hemiacetals 20, 21 and 22

The mixture of hemiacetals **20**, **21** and **22** (57 mg, 0.11 mmol) was dissolved in a mixture of methanol (9 mL) and formic acid (1 mL). Palladium on activated charcoal (10%, 285 mg, moistened with methanol) was added under argon atmosphere. The mixture was kept in a sonic bath for 2 h at 20° C and then filtered and concentrated to dryness to give pure caryose (26 mg, 100%, vitreous oil), $[\alpha]_D$ +10.5° (water, c 2) (lit.: +9.5°). ^1H NMR (400 MHz, D_2O) spectrum was superimposable with that of the mixture of the hemiacetals forms **24-26** obtained from the natural source.[4] ^{13}C NMR (D_2O): C-9 at δ 17.9, 17.1, and 12.6; C-3 at δ 35.9, 35.1, and 34.0; anomeric CH at δ 94.2 (α-pyranose)[4], 97.4 and 103.6 (furanoses)[4]; other CH at δ 83.4, 83.1, 82.7, 82.4, 81.8, 81.2, 78.7, 78.5, 76.2, 75.5, 71.0, and 68.4; C-4 and C-8 at δ 93.0, 90.7, 84.7, 80.1, 79.9, and 77.6.

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