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Synthesis of methyl α-caryophylloside

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Abstract

The convergent synthesis of caryophyllose, a new C-4 branched dodecose isolated from *Pseudomonas caryophylli*, is described from two monosaccharidic precursors. The key step is the diiodosamarium-promoted coupling of two six-carbon fragments: an acid chloride and a cyclic ketone.

Caryophyllose **1** (see Fig. 1) is a member of the family of C-4 branched sugars[1–3] and was isolated in 1995 from the cell wall of a strain of *Pseudomonas caryophylli*, the causal agent of the bacterial wilt of carnation.[4] The complete structure of this dodecose has been elucidated early after[5] as 3,6,10-trideoxy-4-C-(D-*glycero*-1-hydroxyethyl)-D-*erythro*-D-*gulo*-decose and it was later shown to occur in the cell wall as a highly unusual homopolysaccharidic chain with (1→7)-α and -β linkages.[6,7]

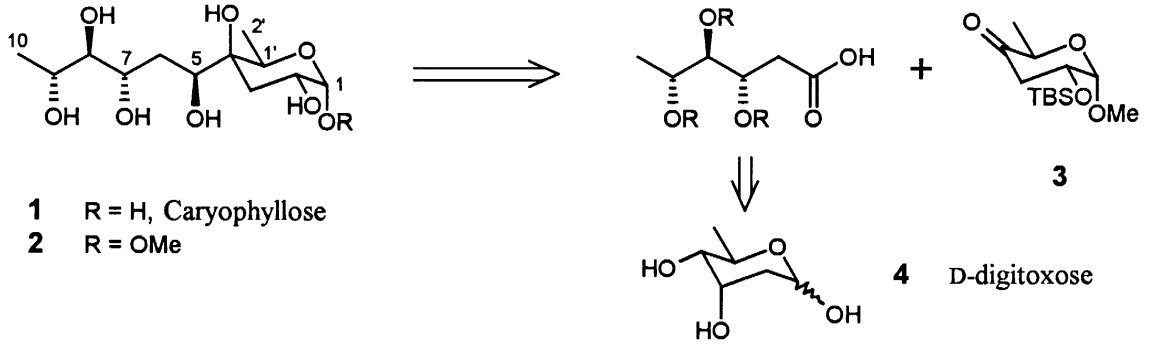

Fig. 1.

Pursuing our work on the synthesis of C-4 branched sugars,[8] we now report the stereoselective preparation of methyl α-D-caryophylloside **2**, starting from ketone **3**[8] and a six-carbon carboxylic acid derived from 2,6-dideoxy-D-*ribo*-hexose **4**, D-digitoxose (Fig. 1).

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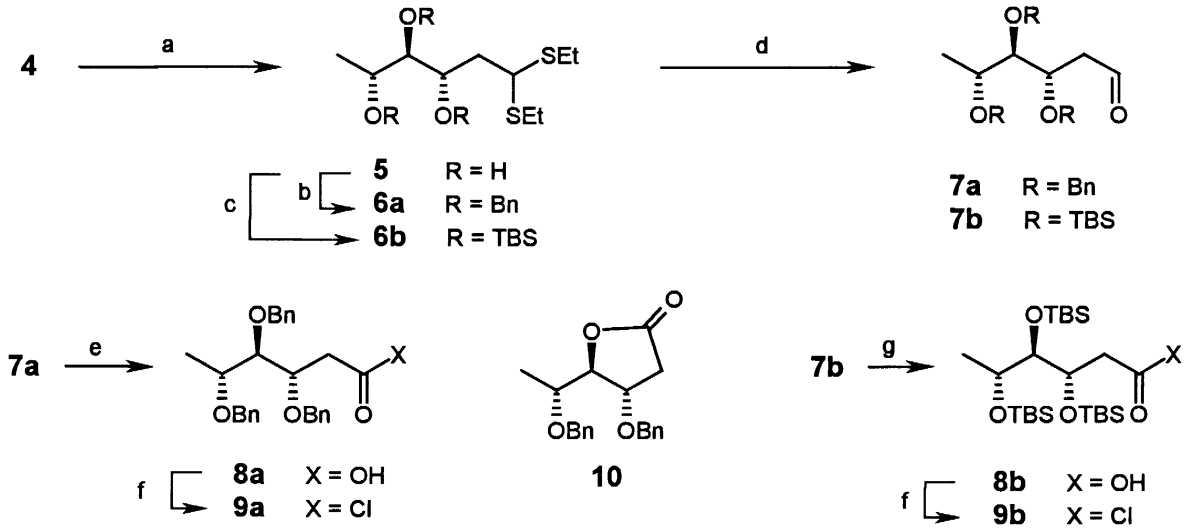
Treatment of **4**, easily prepared from methyl α-D-glucopyranoside,[9] with an excess of ethanethiol and concentrated HCl gave the diethyldithioacetal **5** in 81% yield after three hours (see Scheme 1).[10] Perbenzylation (NaH, BnBr, DMF) and dithioacetal hydrolysis with mercuric chloride and mercuric oxide[10,11] in aqueous acetone gave the aldehyde **7a** in 69% yield from **5**. This aldehyde was smoothly oxidized to the carboxylic acid **8a** with Jones reagent[12] in acetone (92%). All attempts to prepare the acid chloride **9a** from **8a** were plagued by intramolecular nucleophilic attack of the oxygen atom of the C-4 benzyloxy group on the carbonyl bond[13] and formation of the five-membered lactone **10**; only low yields of **9a** were obtained (<10%).

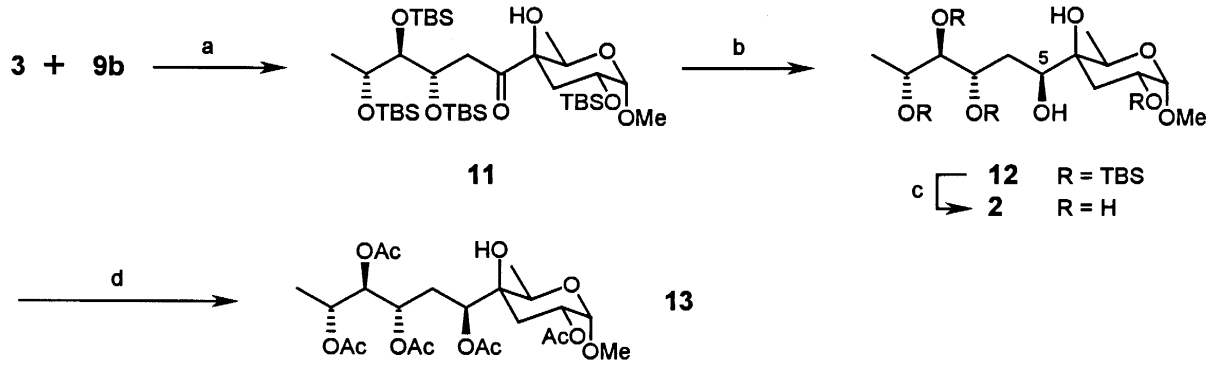


Scheme 1. (a) EtSH, concd HCl, 0°C, 3 h, 81%. (b) BnBr, NaH, DMF, rt, 2 h. (c) TBDMSOTf, pyridine, CH_2Cl_2, rt, 24 h, 90%. (d) HgO, $HgCl_2$, acetone:water 10:1, rt, 3 h. (e) Jones reagent, acetone, 0°C, 30 min, 92%. (f) $(COCl)_2$, pyridine, THP, 0°C. (g) $KMnO_4$, 5% NaH_2PO_4, *t*-BuOH, rt, 1 h, 83%

We assumed that steric crowding should lower the nucleophilicity of this C-4 oxygen atom and introduced the bulky *tert*-butyldimethylsilyl ethers as protecting groups for the hydroxyl functions of **5**. Thus, **5** was treated with an excess of *tert*-butyldimethylsilyltriflate and pyridine in CH_2Cl_2 and gave the trisilylated dithioacetal derivative **6b** in 90% yield. Unmasking of the aldehydic group was effected as above in excellent yield with $HgCl_2$ and HgO in aqueous acetone and gave **7b** in 93% yield. The presence of the acid-sensitive silyl protecting groups precluded the use of the Jones reagent on **7b** but oxidation to the carboxylic acid **8b** could be accomplished in 83% yield with buffered $KMnO_4$ in aqueous *t*-BuOH.[14] In this case, formation of the acid chloride **9b** from **8b** proceeded cleanly with oxalyl chloride and pyridine in CH_2Cl_2.[15]

Ketone **3**[8] was treated at room temperature with 1.3 equiv. of crude **9b** and 5 equiv. of samarium diiodide in tetrahydropyran[16] to give the expected coupling products in 63% yield (based on **3**) and in an 8:1 diastereoisomeric ratio[8,17] (Scheme 2). Reduction of the keto group of the major equatorial isomer **11** was done in chelating conditions[18] with sodium borohydride in methanol at 0°C and was very slow; some starting material was still present after 24 hours at room temperature but a mixture of the 5*S* alcohol **12** and its 5*R* epimer was obtained in 73% isolated yield.

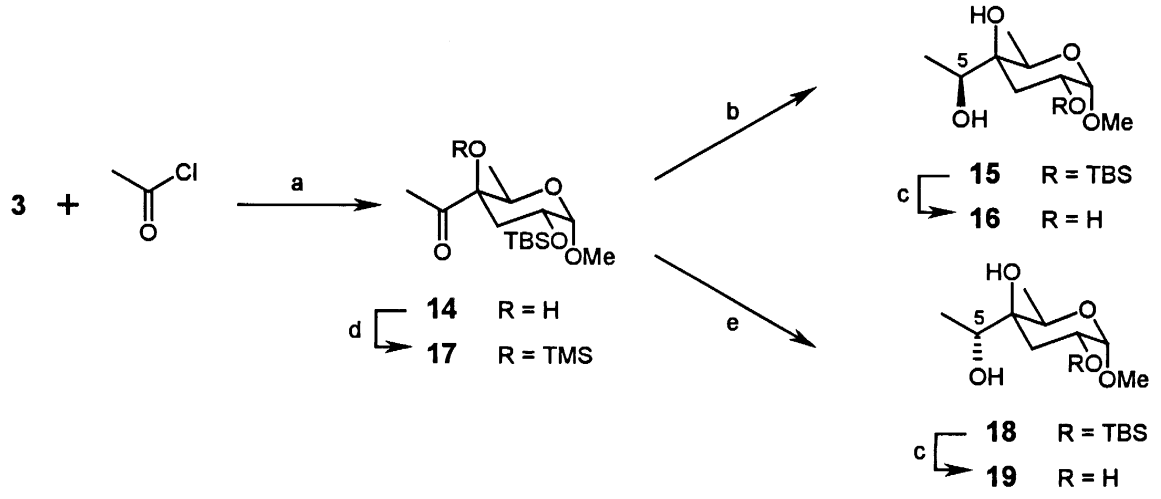
Due to the higher reaction temperature, the observed diastereoselectivity of the reduction was 5 to 1 in favor of the desired alcohol **12**, which is somewhat lower than our previous results on related compounds.[8] The silyl ethers were removed with dilute HCl in aqueous methanol and gave methyl α-



Scheme 2. (a) 1 equiv. **3**, 1.3 equiv. **9b**, 5 equiv. SmI_2, THP, rt, 10 min, 63%, 8/1. (b) $NaBH_4$, MeOH, rt, 24 h, 73% and 10% recovered **11**. (c) HCl, MeOH/water, rt, 3 h, 77%. (d) Ac_2O, pyridine, 80°C, 30 min, 82%

D-caryophylloside **2**[19] in 77% yield which was fully characterized as the pentaacetylated derivative **13**. Comparison of the spectral data for **2** and **13** with the natural product derivatives[4] showed their identity.

Finally, methyl yersiniosides A and B[1,2] were also synthesized in good yields from the reaction of ketone **3** and acetyl chloride with SmI_2 (Scheme 3). Reduction of ketone **14** (obtained in 79% yield and 13:1 diastereoselectivity) with $NaBH_4$ under chelating conditions as above gave **15** with the 5*S* configuration (75%, 7:1). This compound was deprotected with acidic aqueous methanol to methyl yersinioside A **16**.[1] The other diastereoisomer with the 5*R* configuration was also synthesized from **14** after trimethylsilyl protection of the tertiary C-4 hydroxyl group of **14** and Red-Al® reduction of the TMS ether **17**.[17] Compound **18** was obtained as a single diastereoisomer in 78% yield. Acid hydrolysis of the silyl ether gave methyl yersinioside B **19**[2] (69%).



Scheme 3. (a) 1 equiv. **3**, 3 equiv. AcCl, 3 equiv. SmI_2, THP, rt, 15 min, 79%, 13/1. (b) $NaBH_4$, MeOH, 0°C, 20 min, 75%, 7/1. (c) HCl, MeOH. (d) TMSOTf, pyridine, CH_2Cl_2, 0°C, 3 h, 67%. (e) Red-Al®, toluene, 0°C, 4 h, 78%

In conclusion, a short and convergent synthesis of the complex sugar caryophyllose from readily available precursors was devised. The diiodosamarium-promoted coupling reaction of a ketone with an acid chloride proved to be very valuable for the rapid and efficient synthesis of various C-4 branched sugars[8] and should be generally applicable in complex natural products synthesis.

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19. Selected data for **2**. $[\alpha]_D^{20}$=+56 (c 0.82, water). ^{1}H NMR (CD_3OD) δ 4.68 (d, 1H, J 3.5 Hz, H-1); 4.24 (q, 1H, J 6.5 Hz, H-1′); 4.05 (m, 1H, H-2); 4.00–3.86 (m, 2H, H-7, H-9); 3.82 (dd, 1H, J 4.0, 5.0 Hz, H-5); 3.50 (s, 3H, OCH_3); 3.49 (m, 1H, J 6.0 Hz, H-8); 3.44 (s, 1H, OH-4); 2.03 (dd, 1H J 12.0 Hz, H-3ax); 1.89–1.74 (m, 3H, H-3eq, H-6); 1.31 (d, 3H, J 6.5 Hz, H-10); 1.24 (d, 3H, J 6.5 Hz, H-2′). ^{13}C NMR (CD_3OD) δ 100.55, 79.67, 75.93, 71.64, 70.47, 69.62, 67.99, 66.50, 55.81, 34.15, 32.72, 18.91, 13.75. **13**. $[\alpha]_D^{20}$=+49 (c 0.88, chloroform). ^{1}H NMR (C_6D_6) δ 5.53 (dd, 1H, J 6.5, 3.5 Hz, H-8); 5.37 (ddd, 1H, J 11.5, 3.5, 2.5 Hz, H-7); 5.35 (dd, 1H, J 11.5, 2.5 Hz, H-5); 5.28 (m, 1H, J 6.5 Hz, H-9); 5.15 (ddd, 1H, J 12.5, 6.0, 3.5 Hz, H-2); 4.93 (d, 1H, J 3.5 Hz, H-1); 4.00 (q, 1H, J 6.5 Hz, H-1′); 3.05 (s, 3H, OMe); 2.48 (ddd, 1H, J 14.5, 11.5, 2.5 Hz, H-6); 2.39 (dd, J 12.5 Hz, H-3ax); 2.09 (ddd, 1H, J 14.5, 11.5, 2.5 Hz, H-6); 2.04 (dd, 1H, J 12.5, 6.0 Hz, H-3eq); 1.88, 1.75, 1.74, 1.72, 1.70 (5s, 5×3H, Ac); 1.34 (d, 3H, J 6.5 Hz, H-2′); 1.19 (d, 3H, J 6.5 Hz, H-10). ^{13}C NMR ($CDCl_3$) δ 96.21, 74.15, 73.59, 70.03, 68.23, 67.70, 67.51, 66.06, 55.38, 29.63, 27.44, 16.26, 13.34. Anal. calcd for $C_{23}H_{36}O_{13}$: C, 53.07; H, 6.97. Found: C, 53.31; H, 6.87.