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Synthesis of caryophyllose. Use of *n*-BuLi/Na-*O*-*t*-Bu in the coupling of highly functionalized ketones and dithioacetals

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Abstract

The C-4 branched monosaccharide caryophyllose **2a** was synthesized by a convergent approach relying on the coupling of metalated dithioacetal **4b** with ketone **3**. Combined use of *n*-BuLi and *t*-Bu-ONa as deprotonation system for **4b** turned out to be decisive for the success of this coupling.

Caryose **1** and caryophyllose **2a** are two structurally peculiar monosaccharides isolated[1–3] from the phitopathogenic bacterium *Pseudomonas caryophylli* as components of cell wall lipopolysaccharides. We have recently reported[4] the first total synthesis of caryose, a unique example of a carbocyclic monosaccharide to date. In this paper we report the synthesis of caryophyllose, one of the few members in the family of C-4 branched monosaccharides. Recently, Prandi et al.[5] have reported the synthesis of various natural and unnatural C-4 branched monosaccharides possessing a functionalized seven-carbon side chain. For this purpose the attachment of the side chain onto the pyranoid ring was performed elegantly by SmI_2-mediated addition of a suitably functionalized acyl chloride to ketone **3** in tetrahydropyran. During the preparation of this manuscript the use of this strategy for the first synthesis of methyl α-caryophylloside **2b** using acyl chloride **4a** was reported.[6] Herein, we propose an efficient alternative approach for the synthesis of caryophyllose relying on the coupling of the metalated dithioacetal **4b** with ketone **3**. This approach could be attractive in view of the easier manipulation of the branching precursor as well as its high yielding and ready preparation (two steps from commercially available D-digitoxose). In Prandi's synthesis compound **4a** was prepared from D-digitoxose through **4c**, the silylated analogue of **4b**.

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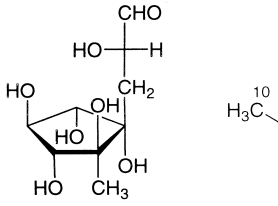
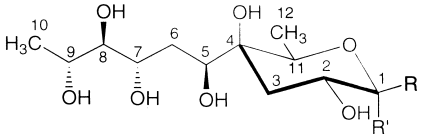
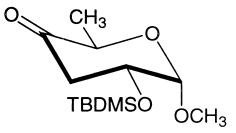


1



2a R,R' = H,OH
2b R = H, R' = OCH_3



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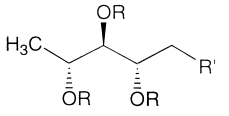
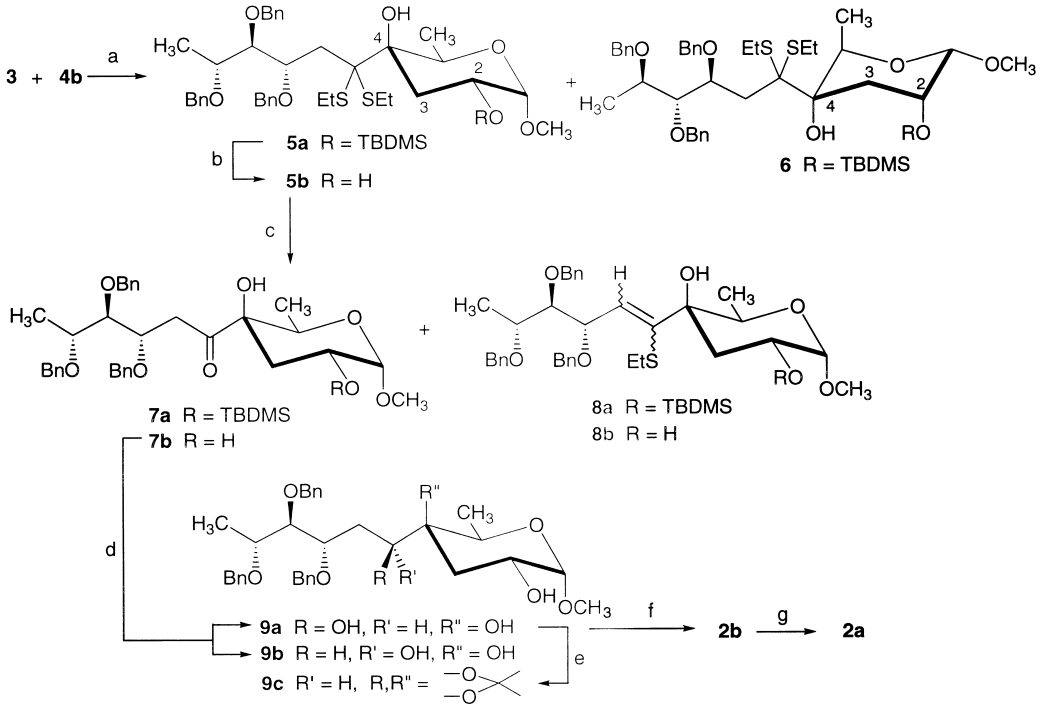


4a R = TBDMS, R' = COCl
4b R = Bn, R' = $CH(SEt)_2$
4c R = TBDMS, R' = $CH(SEt)_2$

Utilization of lithiated dithioacetals (more commonly, 1,3-dithianes) as nucleophiles in organic transformations is well known.[7] However, the exploitation of this chemistry has often been plagued in the case of functionalized substrates by the low yielding or even ineffective initial deprotonation with alkyl-lithium bases.[8,9] In our hands any attempted deprotonation of **4b** with *n*-BuLi failed, even at rt,[8] as shown by the lack of deuterium incorporation at C-1 after D_2O quenching. However Lipshutz has demonstrated[9] that partially or fully protected hydroxylated dithianes can be quantitatively metalated by combined use of *n*-BuLi and *t*-Bu-ONa. Under this protocol, the coupling step between the caryophyllose building blocks **4b**[5] and **3** was performed (Scheme 1) to provide the desired adduct **5a** together with minor amounts of epimer **6** (60% yield, **5a**:**6**, 3.5:1).[10] The configuration at the position 4 of these compounds was inferred by ^{1}H NMR analysis, which showed that the bulky appendage was equatorially oriented in both **5a** and **6**, which possess a $^4C_1$ and a $^1C_4$ conformation of the ring, respectively. In fact, the spectrum of the major product displayed a *trans*-diaxial relationship between one H-3 proton and the H-2 proton ($J_{2ax,3ax} = 11.0$ Hz). On the other hand, the spectrum of the minor epimer **6** did not display any *trans*-diaxial relationship for the H-2 proton, as shown by the small values (< 4 Hz) of both $J_{2,3}$ constants. In addition, a long-range W-coupling (< 2 Hz) between H-11 and one H-3 proton of the minor compound was observed. The expected stereochemistry of the major product has been also confirmed unambiguously on a later intermediate of the synthesis (see below).

After the key coupling step, hydrolysis of the dithioketal function was attempted by exposure of **5a** to HgO/$HgCl_2$ in several aqueous solvents (MeOH, MeCN, Me_2CO) but in all cases predominant formation of thioenol ether **8a** [undetermined double-bond configuration; ^{1}H NMR ($CDCl_3$): δ 5.06 (d, $J_{6,7} = 8.1$ Hz, 6-H); ^{13}C NMR ($CDCl_3$): δ 145.4 (C-5), 125.3 (C-6)] was observed besides minor amounts of the desired ketone **7a** [^{13}C NMR ($CDCl_3$) : δ 209.8 (5-C=O)]. This unfavourable outcome, not unusual for other desulfurization systems,[12] was mainly ascribed to the low solubility of **5a** in mixtures containing amounts of water higher than 5%. This consideration led us to remove, before the hydrolytic step, the apolar silyl protecting group (1.5 eq. TBAF in THF, room temperature, 8 h, 90% yield) to obtain **5b**. Exposure of **5b** to HgO/$HgCl_2$ in 9:1 MeCN:H_2O furnished ketone **7b** [52% yield; ^{13}C NMR ($CDCl_3$): δ 209.7 (5-C=O)] predominantly even though substantial amounts of the corresponding elimination product **8b** [^{1}H NMR ($CDCl_3$): δ 5.05 (d, $J_{6,7} = 8.1$ Hz, 6-H); ^{13}C NMR ($CDCl_3$): δ 144.8 (C-5), 125.0 (C-6)] were



Scheme 1. (a) See Ref. 10; (b) TBAF (1.5 equiv.), THF, 8 h, rt, 90%; (c) $HgCl_2$ (2 equiv.), 9:1 MeCN:H_2O, 0.5 h, rt, 79% (**7b**) and 13% (**8b**); (d) $NaBH_4$, MeOH, 0°C, 2 h, **9a**:**9b** 9:1, 66%; (e) 1:2 $Me_2C(OMe)_2$:Me_2CO, Dowex-50WX8/H^+, 8 h, rt, >95%, (f) 9:1 MeOH:HCOOH, C/Pd, sonication, 2 h, 10°C, >95%; (g) 0.125 M CF_3COOH, 100°C, 1.5 h, >95%

again isolated (29% yield). However, when the reaction was performed in the same solvent system but in the absence of the basic HgO, in order to minimize elimination to **8b**, compounds **7b** and **8b** were obtained in 79 and 13% yields, respectively.

Compound **7b** was reduced diastereoselectively with $NaBH_4$ in MeOH at 0°C. In contrast to the corresponding persilylated intermediate of Prandi's synthesis, this reduction was not sluggish on our substrate and proceeded with higher diastereoselectivity (66% yield; **9a**:**9b** = 9:1, in favour of the desired epimer: ^{1}H NMR ($CDCl_3$): δ 3.58, dd, $J_{5,6a} = 10.2$ Hz, $J_{5,6b} = 1.2$ Hz, 5-H). The stereochemistry of this compound was confirmed by ^{1}H NMR NOESY analysis (see Fig. 1) of the corresponding acetonide **9c** (acetone:2,2-dimethoxypropane 2:1, Dowex 50WX8/H^+, 8 h, >95%). At this stage it should be noted that the choice of two differently protected building blocks **3** and **4b**, initially dictated by considerations of preparative convenience, was beneficial for the final purpose. As a matter of fact, selective removal of the protecting group from *O*-2 immediately after the coupling step, in addition to the efficient hydrolysis of the dithioketal function, allowed us to achieve high diastereoselectivity in the reduction step to **9a** exploiting the chelation control arising from the vicinal location of 5-C=O and 4-OH. Preservation of protecting groups at *O*-7, *O*-8 and *O*-9 avoided alternative and unpredictable chelation effects which could operate.

Finally, debenzylation of **9a** afforded almost quantitatively methyl α-caryophylloside **2b**,[1] whose conversion into the corresponding monose **2a** was performed quantitatively by hydrolysis with 0.125 M aqueous trifluoroacetic acid (100°C, 1 h). Synthetic monose **2a** was identical (TLC, ^{1}H and ^{13}C NMR) to the natural product.[1,2]

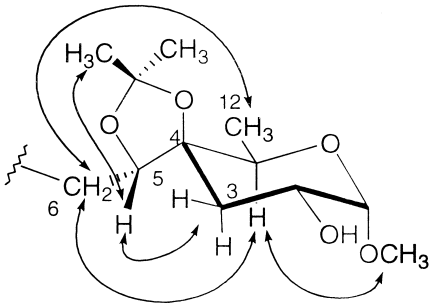


Figure 1. Selected NOE contacts observed for **9c** (NOESY, 400 MHz, $CDCl_3$)

This paper highlights the notable synthetic potential of the coupling between a functionalized dithioacetal and a functionalized ketone in the convergent assemblage of complex structures. In this regard, use of the *t*-Bu-ONa/*n*-BuLi system was found to be crucial for the in situ generation of a highly reactive carbanionic nucleophile from **4b**.

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10. *n*-BuLi [1.45 M in hexanes (determined by titration),[11] 550 μL, 0.80 mmol] is added at 0°C to a suspension of *t*-Bu-ONa (77 mg, 0.80 mmol) in anhydrous hexane (2.0 mL). The mixture is stirred for 1 h at 0°C and one additional hour at rt. After cooling to –78°C, a solution of **4b** (462 mg, 0.88 mmol) in anhydrous THF (5 mL) is added dropwise in 10 min. The resulting dark red solution is left for 1 h at –78°C under stirring and then a solution of **3** (110 mg, 0.40 mmol) in anhydrous THF (1.5 mL) is added dropwise. During the addition (5 min), the red colour of the solution turns gradually to a pale yellow. After stirring for an additional 10 min at –78°C, the reaction is quenched with water. The mixture is diluted with chloroform and the organic phase is washed with brine and water. Removal of chloroform under reduced pressure and column chromatography (silica gel, hexane:ethyl acetate, 95:5) affords unreacted **4b** (253 mg), **6** (41 mg, 13% yield), and **5a** (150 mg, 47% yield). Compound **5a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.08 and –0.05 (6H, 2 s, -Si(CH_3)$_2$-*t*-Bu), 0.81 (9H, s, -Si(CH_3)$_2$C(CH_3)$_3$), 1.06 and 1.14 (6H, 2 t, J = 7.4 Hz, 2×-SCH_2CH_3), 1.34 (3H, d, $J_{9,10}$ = 5.9 Hz, H-10), 1.43 (3H, d, $J_{11,12}$ = 6.4 Hz, H-12), 2.1–2.25

(3H, H-3_{ax}, H-3_{eq} and H-6_a), 2.35–2.8 (5H, 2×-SC*H*$_2$CH$_3$ and H-6_b), 3.40 (3H, s, -OCH$_3$), 3.65 (1H, dq, $J_{8,9}$ = 7.2 Hz, H-9), 3.75 (1H, bd, H-8), 3.99 (1H, ddd, $J_{1,2}$ = 3.7 Hz, $J_{2,3ax}$ = 11.0 Hz, $J_{2,3eq}$ = 5.7 Hz, H-2), 4.10 (1H, bs, exchange with D_2O, 4-OH), 4.34 (1H, q, H-11), 4.50 (2H, H-1 and H-8), 4.4–4.9 (6H, 3 ABq, 3x-O-C*H*$_2$-Ph), 7.2–7.5 (15H, 3×-Ph). ^{13}C NMR ($CDCl_3$): δ –4.9 and –4.6 (-Si(*C*H$_3$)$_2$-*t*-Bu), 13.3 and 13.8 (2×-SCH$_2$*C*H$_3$), 16.7 and 17.5 (C-10 and C-12), 18.1 (-Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 22.6 (2×-S*C*H$_2$CH$_3$), 25.9 (-Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 37.3 and 37.8 (C-3 and C-6), 67.4, 68.4, 75.2, 78.2, 82.9 (C-2, C-7, C-8, C-9, and C-11), 70.0 and 79.2 (C-4 and C-5), 70.6, 71.4 and 73.9 (3×-O*C*H$_2$Ph), 99.1 (C-1), 127.2–128.5 (aromatic *C*H), 134.5–138.3 (quaternary aromatic carbons).

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