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Note

Consequences of rigidity and conformational locking in a 4,4-dimethyl-1,3-dioxolane ring system during protection of internal diol

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Dedicated to Professor R. R. Schmidt

Abstract

The presence of an isopropylidene ketal protection of an internal diol in 3,4-*O*-isopropylidene-D-*arabino*-1-*C*-phenyl hexanone locks it in a conformation that prevents its cyclization to a pyranose ring.

Keywords: Glucopyranosyl compounds; Umpolung; Isopropylidene ketal protection; Internal diol; Conformational locking

2-Deoxy-*C*-aryl glycosyl derivative **1** (Scheme 1)(Fig. 1), a special class of *C*-aryl glycosyl compounds[1] constitutes a common structural feature of several groups of antitumour antibiotics[2] such as the angucyclines, pluramycins, gilvocarcins and the vineomycins and have attracted great attention from the synthetic organic chemists.[3] Recently, we disclosed a novel route based on the unexplored umpolung strategy for the synthesis of methyl 2-deoxy-*C*-aryl glucopyranosyl derivatives **2**.[4] The route involved synthesis of ketones of the type **3a** and its ready cyclization to the target **2** under neutral condition of 1% I_2 in methanol. The simplicity in the synthesis of **3b** as for **3a**, and the possibility of the selective removal of the terminal isopropylidene ketal[5] prompted us to investigate the synthesis of **1** starting from **3b**. A completely different behaviour of **3b** in arriving at the pyranoside structure forms the basis of this note.

The representative aryl ketone **3b** required for the investigation was synthesized as depicted in Scheme 2. The umpoled benzaldehyde in the form of aminonitrile **4**[6] on alkylation with protected arabinitol iodide **5**[7] followed by hydrolysis[8] using $CuSO_4 \cdot 5\ H_2O$ in aqueous methanol at 60 °C afforded the ketone **3b**. For the possible ring closure in **3b** to the pyranose structure **7**, selective removal of the terminal isopropylidene protection became necessary. Considering that Dowex-50W-X8 in 9:1 MeOH–water[5a] or catalytic HCl in MeOH,[5b] have been used for selective hydrolysis of terminal isopropylidene ketals, we subjected **3b** to both these conditions. Unfortunately the only isolated product was the furan derivative **8** (Scheme 3). The facile formation of **8** was an indication that de isopropylidenation conditions were indiscriminate and the internal isopropylidene group was hydrolyzed under the experimental conditions, following which cyclization occurred leading to the formation of a furan ring.

To circumvent the formation of the furan ring and facilitate ring closure to the pyranose form, exclusive removal of the terminal isopropylidene protection became mandatory. This could be easily achieved by using a solution of $Zn(NO_3)_2 \cdot 6\ H_2O$ in MeCN,[5c] which furnished **9** in 88% yield as a crystalline solid (Scheme 3). On heating **9** in toluene for 24 h no cyclization occurred, with complete recovery of **9** in quantitative yield. The failure is probably due to the large distance of the cyclization termini across a rigid dioxolane ring. The speculation was confirmed by the X-ray crystallographic structure of compound **9** ((Table 1, Fig. 1). The carbon

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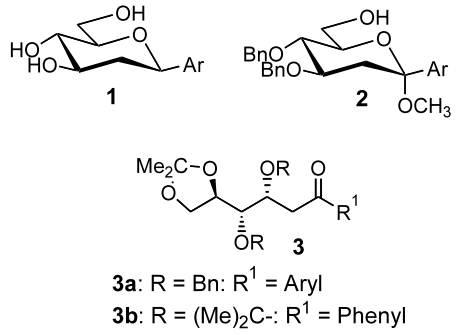


Scheme 1. Substrate **3a** and **3b**; precursor for synthesis of **1**.

atoms of the alkyl chains (C-2, C-5: C-2′, C-5′) across the (C-3, C-4: C-3′, C-4′) bond are in mutually perpendicular orientation as shown by the torsion angles τ(C-2, C-3, C-4, C-5) = 94.2(4)° and τ(C-2′, C-3′, C-4′, C-5′) = 94.8(4)° in the two molecules (incidentally in compound **3b** Fig. 1, the precursor to the compound **9**, the torsion angles across the (C-3, C-4: C-3′, C-4′) bond are τ(C-2, C-3, C-4, C-5) = −102.3(5)° and τ(C-2′, C-3′, C-4′, C-5′) = −104.3(5)° indicating that the two alkyl chains are mutually perpendicular to each other) Also the atoms necessary for cyclization to a six-membered pyranose ring in compound **9**, O-4 and C-1 are too far away for the attack to occur (O-4 and C-1; $d_{O\text{-}4\text{-}C\text{-}1}$ = 4.82 Å: O-4′ and C-1′; $d_{O\text{-}4'\text{-}C\text{-}1'}$ = 4.47 Å). Any attempt to promote this cyclization under protic and non-aqueous conditions either in benzene or toluene, only led to extensive decomposition. The rationale to use non-aqueous conditions was based on the fear for de-isopropylidenation under aqueous condition.

To conclude, the thermal cyclization of **3b** to the 2-deoxy *C*-aryl pyranosyl skeleton is not possible due to the rigid conformational locking in the internal dioxolane ring. Under protic conditions, transitory opening of the dioxolane ring occurs to furnish the furan derivative **8** or results in extensive decomposition (Table 1).

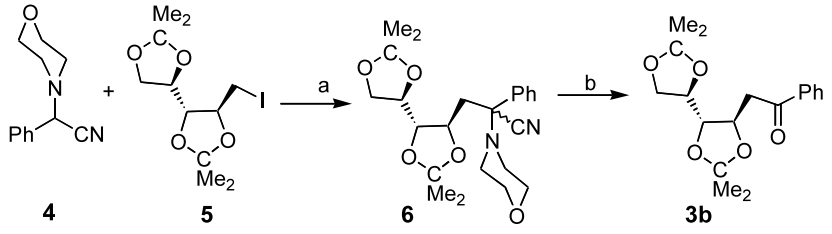
1. Experimental

1.1. General procedure

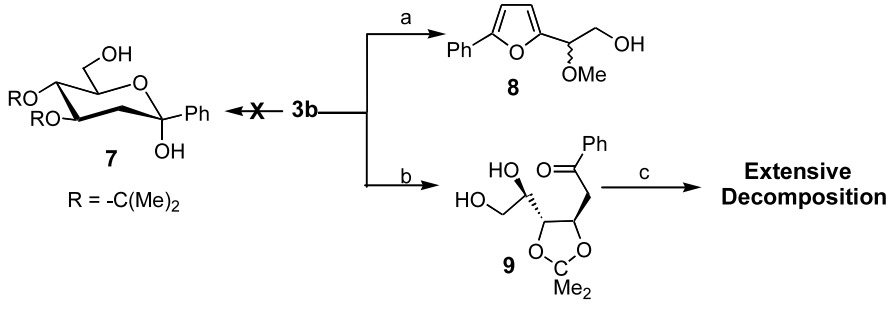
IR spectra were determined in $CHCl_3$ solution using a Shimadzu IR 470 model instrument. ^1H and ^{13}C NMR spectra were recorded on a JEOL-GSX 400 spectrometer in $CDCl_3$ using Me_4Si as internal standard. X-Ray data were collected on Enraf Nonius CAD4F diffractometer at 293 K using Cu K_α radiation (λ = 1.5418 Å) in the $\omega 2\theta$ scan mode.

1.2. 3,4:5,6-Di-*O*-isopropylidene-D-*arabino*-1-*C*-phenyl hexanone (3b)

To a soln of NaH (0.143 g, 5.96 mmol) in dry DMF (2 mL) under inert nitrogen atmosphere, was added dropwise a soln of the α-phenyl aminonitrile 4 (1.104 gm, 5.46 mmol) in dry DMF (4 mL) at room temperature. After stirring the reaction mixture at room temperature for 30 min, a soln of the iodo compound **5** (1.70 g, 4.97 mmol) in dry DMF (4 mL) was added.



Scheme 2. Conditions: (a) NaH, Dry DMF, 1 h, 77%; (b) $CuSO_4 \cdot 5H_2O$, (3:1) MeOH–water, 1.5 h, 60 °C, 68%.



Scheme 3. Reagents: (a) Dowex-H^+, (9:1) CH_3OH–water, rt, 24 h, 50%; (b) $Zn(NO_3)_2 \cdot 6\ H_2O$, MeCN, 18 h, 88%; (c) anhyd *p*-TsOH, benzene (or) toluene, 2 h.

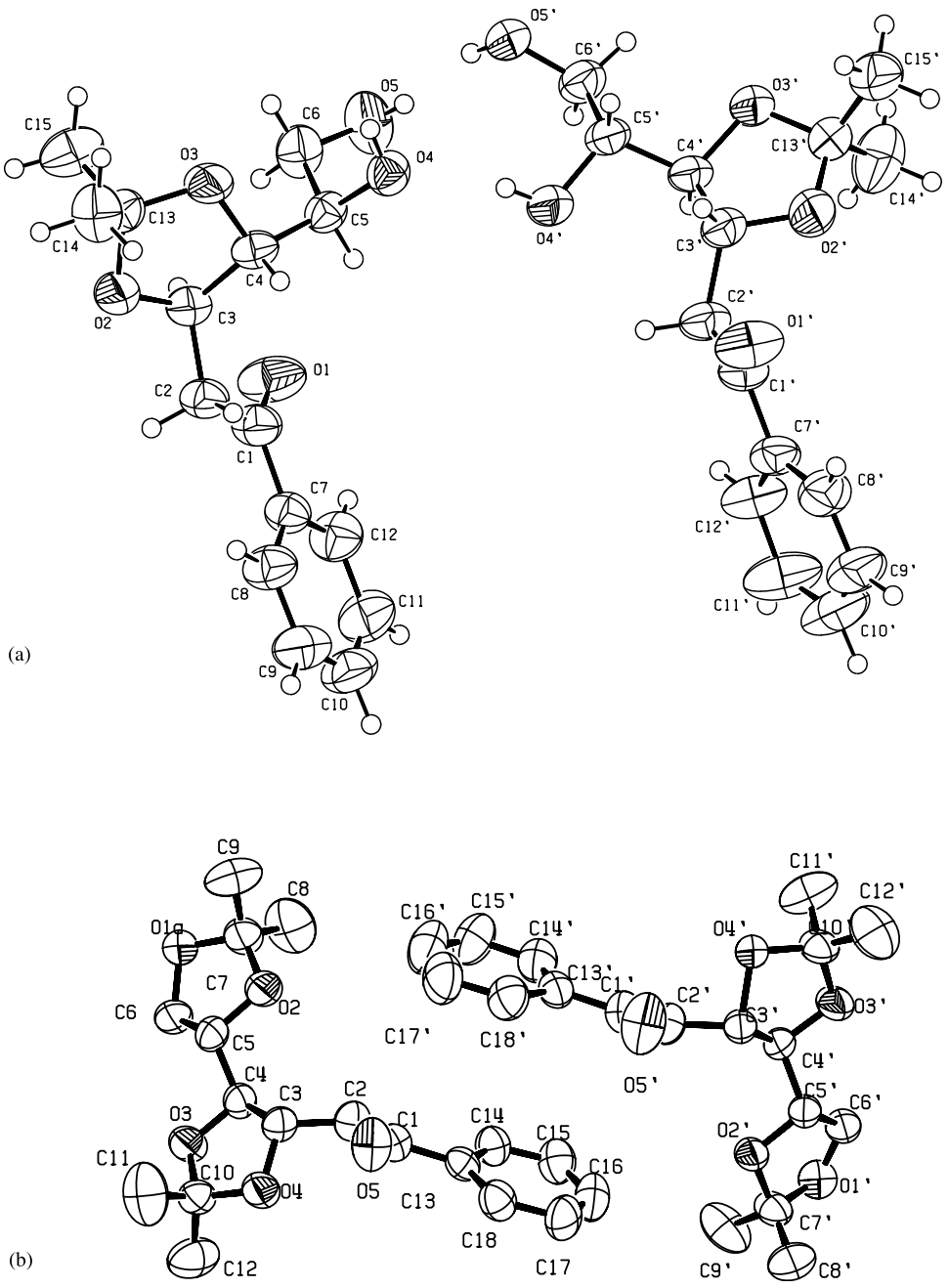


Fig. 1. (a) Perspective view[9] of two independent molecules of **9** in a unit cell. Intramolecular hydrogen bonding:[10] O(5)–H···O(4) = 2.744 Å and ∠O(5)–H···O(4) = 166.2°. (b) Perspective view[9] of two independent molecules of **3b** in a unit cell. Intermolecular H-bonding: C(8′)–H···O(4) = 3.490 Å and ∠C(8′)–H···O(4) = 174.4°. C(11′)–H···O(1A) = 3.502 Å and ∠C(11′)–H···O(1A) = 169.2°.

After stirring the reaction mixture for 1 h at room temperature, a saturated ammonium chloride soln (20 mL) was added. The aq layer was extracted with Et_2O (3 × 15 mL). The combined Et_2O layer was dried over anhyd Na_2SO_4 and evaporated to obtain the alkylated compound **6** as a diastereoisomeric mixture (1.612 g, 3.87 mmol, 78%). Without further purification, a soln of $CuSO_4 \cdot 5\ H_2O$ (1.15 g, 4.61 mmol) in 3:1 MeOH–water (16 mL) was added and the reaction was heated at 60 °C. After 1 h, the solvents were evaporated on a rotary evaporator and water (10 mL) was added. The aq layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layer was dried over Na_2SO_4. The solvent was removed under diminished pressure and the residue was purified by a filtration column (9:1, hexane–EtOAc) affording compound **3b** (0.836 g, 2.61 mmol,

Table 1
Summary of crystal data and data collection parameters for 3,4:5,6-di-*O*-isopropylidene-D-*arabino*-1-*C*-phenyl hexanone (**3b**) and for 3,4-*O*-isopropylidene-D-*arabino*-1-*C*-phenyl hexanone (**9**)

Chemical formula	$C_{18}H_{24}O_5$ (**3b**)	$C_{15}H_{20}O_5$ (**9**)
Formula weight	320.37	280.31
Crystal system	monoclinic	monoclinic
Space groups	$P2_1$	$C2$
Unit cell dimensions		
a (Å)	17.2001(2)	33.298(8)
b (Å)	5.647(2)	5.873(1)
c (Å)	18.587(2)	15.257(5)
β (°)	100.746(10)	98.79(3)
V (Å)^3	1773.9(7)	2948.5(13)
Z	4	8
D_{calcd} (mg m^{-3})	1.200	1.263
Absorption Coefficient μ (mm^{-1})	0.711	0.782
$F(000)$	688	1200
Index ranges	$-20 \le h \le 20$, $-6 \le k \le 0$, $-9 \le l \le 22$	$-40 \le h \le 0$, $0 \le k \le 7$, $-18 \le l \le 18$
Crystal size (mm)	$0.3 \times 0.3 \times 0.15$	$0.4 \times 0.3 \times 0.3$
Measured data	3879	3113
Unique data	3580	2980
Parameters	418	366
Restraints	4	1
R (all data)	0.0922	0.0672
wR_2	0.1818	0.1715
Goodness-of-fit	1.023	1.064
Mean and maximum shift/esd	0.003–0.011	0.000–0.008
Maximum and minimum difference electron density (e Å^{-3})	0.203, −0.150	0.233, −0.292

68%) as a white solid; mp 322–325 °C, $[\alpha]_D^{26}$ +42.26° (*c* 1, $CHCl_3$); IR (ν, cm^{-1}): 2944, 1680; ^{1}H NMR(400 MHz, $CDCl_3$) δ_H 1.33, 1.39, 1.40 (3 s, 12 H, $C(Me)_2$), 3.27 (dd, 1 H, $J = 16.6$, 8.8 Hz, H-C (2)), 3.40 (dd, 1 H, $J = 16.6$, 2.9 Hz, H-C (2′)), 3.68 (t, 1 H, $J = 7.8$, 8.3 Hz, H-C (4)), 3.98 (dd, 1 H, $J = 8.5$, 5.4 Hz, H-C (6)), 4.10 (m, 1 H, H-C (3)), 4.17 (dd, 1 H, $J = 8.3$, 5.9 Hz, H-C (6)), 4.56 (dt, $J = 8.3$, 2.9 Hz, 1 H, H-C (5)), 7.26–7.59 (m, 3 H, C-(ϕ)), 7.98 (d, 2 H, C-(ϕ)); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 25.19, 26.70, 26.89, 27.15 (-C(Me)$_2$), 42.27 (C-2), 67.77 (C-6), 76.24 (C-4), 77.38 (C-3), 80.67 (C-5), 109.53 & 109.65 (-C-(Me)$_2$), 128.29, 128.55, 133.16, 136.94 (C-Ar), 199.23 (C=O).

X-Ray suitable crystals of **3b** were grown from 0.5:9.5 EtOAc–hexane. The structure was solved using direct methods and refined by full-matrix least-squares on F^2.[11]

1.3. 3,4-*O*-Isopropylidene-D-*arabino*-1-*C*-phenyl hexanone (9)

To a soln of **3b** (0.320 g, 1 mmol) in MeCN (0.5 mL) was added $Zn(NO_3)_2 \cdot 6\ H_2O$ (0.059 g, 0.2 mmol). The mixture was stirred at 27 °C for 24 h. The solvent was evaporated under diminished pressure and the oily residue was diluted with CH_2Cl_2 (15 mL). The organic layer was washed with water (10 mL) and dried over anhyd Na_2SO_4. The solvent was removed under diminished pressure, the residue purified by a filtration column on silica gel to yield the product as a white solid (0.246 g, 0.878 mmol, 88%); mp 68 °C, $[\alpha]_D$ + 25.20° (*c* 1, $CHCl_3$), IR (ν, cm^{-1}): 3520, 1683; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.40 & 1.41 (2 s, each 3 H, -C (Me)$_2$), 1.67 (brs, 2 H, 2 × -OH), 3.40 (1 H, dd, $J =$ 17.1, 5.4 Hz, H-C (2)/H-C (2′)), 3.47 (1 H, dd, $J = 17.6$, 5.8 Hz, H-C (2′)/H-C (2)), 3.73–3.88 (m, 4 H), 4.64 (m, 1 H), 7.45–7.61(m, 3 H), 7.97–7.99 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 26.9 and 27.2 ($C(Me)_2$), 43.2 (C-2), 64.2 (C-6), 73.2 (C-5),76.0 (C-4), 80.7 (C-3), 109.4 (C-(Me)$_2$), 128.3, 128.5, 128.6, 133.6, 136.6 (C-(ϕ)), 198.8 (C=O). HRMS: calcd for $C_{15}H_{20}O_5$ 280.1560, Found 280.1576.

X-Ray suitable crystals of **9** were grown from 1:9 EtOAc–hexane. The structure was solved using direct methods and refined by full matrix least-squares on F^2.[11]

2. Supplementary material

Full crystallographic details, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos: 203804 and 203805 for compounds **3b** and **9** respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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