A Facile Synthesis of Chiral α-Methylene-δ-Valerolactones

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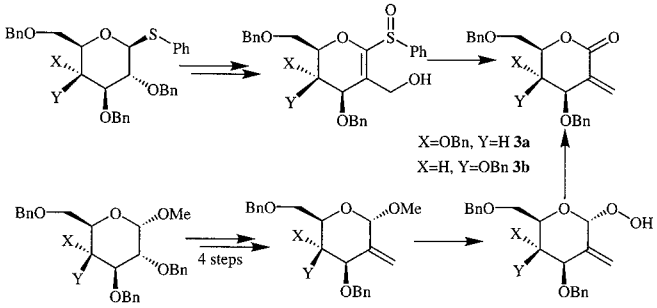
Abstract: Chiral α-methylene-δ-valerolactones have been obtained from 1,2-cyclopropanated sugars in one pot by reaction with iodonium di(*s*-collidine)perchlorate (IDCP).

The significance of stereocontrolled carbon-carbon bond formation involving conjugate addition of carbon nucleophiles and radicals in organic synthesis has been well recognised. However, its appreciation in carbohydrates has commenced only recently.[1] The C-disaccharide synthesis developed by Giese and Schmidt[2a,b] permits the connection of two pyranoses by a methylene group, involving the addition of an anomeric pyranosyl radical derived from a pyranosyl halide to sugar derived α-methylene-δ-valerolactones. Other potential synthetic applications of α-methylene-δ-valerolactones include Michael addition with different nucleophiles and reduction of the methylene unit in a stereospecific manner to give α-methyl-δ-valerolactones. The two procedures[2c,d] available for the synthesis of sugar derived α-methylene-δ-valerolactones are both multistep processes and their large scale synthesis is laborious.

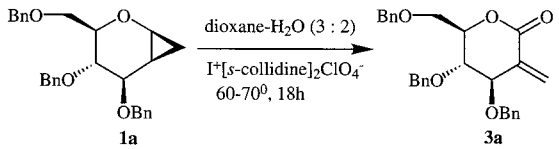
Schmidt's[2b,c] procedure involves oxidation of a phenyl tetra-O-benzyl-1-thioglyco pyranoside to its sulfoxide which on treatment with 2eq. of lithium diisopropylamide (LDA) followed by the addition of formaldehyde gives the 2-hydroxymethyl-1-phenylsulfinyl-hex-1-enitol derivative. This is on heating with *p*-toluenesulfonic acid (*p*-TsOH) yields the required α-methylene-δ-valerolactones. In Chmielewski's[2d] method, a benzyl protected 2-*exo*-methylene glycoside is oxidised with H_2O_2\MoO_3 and the resulting pyranosyl hydroperoxide is treated with acetic anhydride and pyridine to furnish the α-methylene-δ-valerolactone.

Recently, we reported the diastereospecific synthesis of 1,2-cyclopropanated sugars.[3] Our interest in the synthetic utility of these 1,2-cyclopropanated sugars led us to examine their reactions with different electrophiles. In this communication, we wish to report the synthesis of α-methylene-δ-valerolactones derived from 1,2-cyclopropanated sugars. This transformation was achieved in one pot by the reaction of cyclopropanated sugars with an excess of iodonium di(*s*-collidine)perchlorate ($I^+[s\text{-collidine}]_2ClO_4^-$, IDCP).



Scheme 1

Recently, Cossy[4] reported the oxidative ring opening of cyclopropylcarbinols with NBS yielding γ-halocarbonyl derivatives. The reaction of cyclopropane **1a** with NBS in aq.dioxane at rt yielded only the 3,4,6-tri-*O*-benzyl-2-deoxy-2-bromomethyl-D-mannopyranose accompanied by concomitant benzyl ether cleavage. Electrophilic activation of the cyclopropane ring with the iodonium ion was next investigated. While the reaction of **1a** with iodine in aq.dioxane at 70°C once again provided the iodolactol **2a**, use of N-iodosuccinimide in methanol at rt resulted in incomplete cleavage of the cyclopropane ring. Prompted by a report[5] on the reaction of olefins with a combination of iodonium di(*s*-collidine)tetrafluoroborate and DMSO to yield α-halocarbonyl compounds, we looked at the reaction of **1a** and IDCP in aq.dioxane. Gratifyingly, and most suprisingly, the desired α-methylene-δ-valerolactone **3a** was obtained in 57% yield, involving a sequence of ring opening, oxidation and elimination. The optimum conditions are treatment of the cyclopropane **1a** with 6eq. of IDCP in 3:2 water-dioxane at 60-70°C for 18h. The ^{1}H-NMR spectrum and optical rotation data of compound **3a** were in agreement with that reported by Schmidt[2c] and the DEPT-135 ^{13}C-NMR spectrum showed a methylene carbon at 129.92 ppm, thus confirming the presence of the excocyclic double bond.

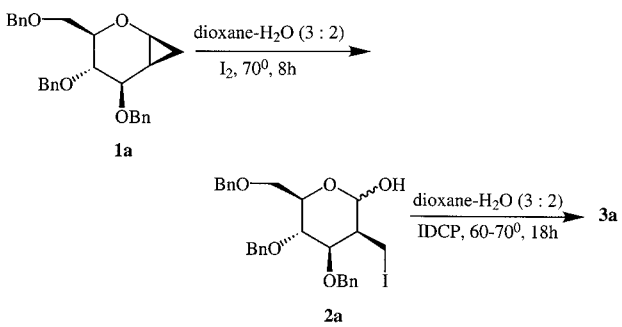


1a **3a**

Scheme 2

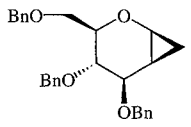
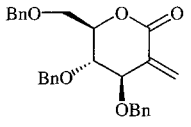
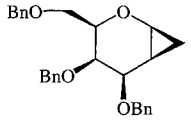
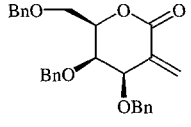
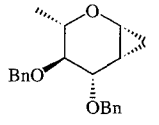
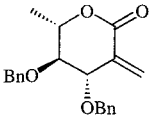
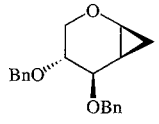
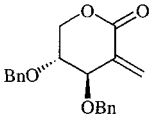
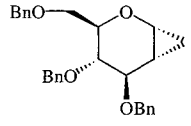
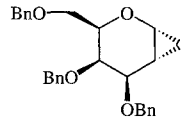
In order to generalise this reaction (Table 1), cyclopropanes **1b**, **1c** and **1d** were treated under similar conditions as above and the corresponding α-methylene-δ-valerolactones **3b**, **3c** and **3d** were obtained in 41, 83 and 68% yields, respectively. The low yield obtained in the case of **1b** may be due to the more sterically crowded environment around the β-cyclopropane, which precludes the attack of I^+. This was substantiated by the reaction of its α-diastereomer **1f** under similar conditions to provide **3b** in 82% yield. In a similar fashion, **3a** was obtained in 75% yield from the cyclopropane **1e**. The physical data of compound **3b** was in agreement with that reported earlier[2c] and the identities of compounds **3c** and **3d** were established by their spectral (IR, ^{1}H and ^{13}C-NMR) as well as mass spectral data.[6]

As already mentioned, when cyclopropane **1a** was treated with I_2 in dioxane-water (3 : 2) mixture at 70°C for 8h, iodolactol **2a** was obtained in 79% yield and no iodolactone was found. Subsequent reaction of **2a** with IDCP (5 eq.) resulted in **3a** in 77% yield, thus implying **2a** as an intermediate in the tandem three step sequence of ring opening, oxidation and elimination, the last step being brought about by *s*-collidine.



Scheme 3

Table 1

Entry	Substrate	Product (yield %)
1	 **1a**	 **3a** (57%)
2	 **1b**	 **3b** (41%)
3	 **1c**	 **3c** (83%)
4	 **1d**	 **3d** (68%)
5	 **1e**	**3a** (75%)
6	 **1f**	**3b** (82%)

In conclusion, we have developed a simple method for the synthesis of chiral α-methylene-δ-valerolactones from 1,2-cyclopropanated sugars which themselves can be prepared in one, or otherwise in two steps, from easily available glycals.

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References and Notes

(1) (a) Herradon, B.; Fenude, E.; Bao, R.; Vaverde, S. *J. Org. Chem.*, **1996**, *61*, 1143. (b) Csuk, R.; Schaade, M.; Krieger, C. *Tetrahedron*, **1996**, *52*, 6397. (c) Lopez, J.C.; Gómez, A.M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.*, **1994**, 1533. (d) Hsia, K.Y.; Ward, P.; Lamont, R.B.; de Q. Lilley, P.M.; Watkin, D.J.; Fleet, G.W.J. *Tetrahedron Lett.*, **1994**, *35*, 4823.

(2) (a) Giese, B.; Witzel, T. *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 450. (b) Giese, B.; Hoch, M.; Lamberth, C.; Schmidt, R.R. *Tetrahedron Lett.*, **1988**, *29*, 1375. (c) Kast, J.; Hoch, M.; Schmidt, R.R. *Liebigs Ann. Chem.*, **1991**, 481. (d) Hamann, H.-J; Höft, E.; Mostowicz, D.; Mishnev, A.; Urbanczyl-Lipkowska, Z.; Chmielewski, M. *Tetrahedron*, **1997**, *53*, 185.

(3) (a) Murali, R.; Ramana, C.V.; Nagarajan, M. *J. Chem. Soc., Chem. Commun.*, **1995**, 217. (b) Bozell, J.J.; Hoberg, J.O. *Tetrahedron Lett.*, **1995**, *36*, 6831.

(4) Cossy, J.; Furet, N. *Tetrahedron Lett.*, **1995**, *36*, 3691.

(5) Evans, R.D.; Schauble, J.H. *Synthesis*, **1986**, 727.

(6) **General procedure for the conversion of 1c to 3c:** To a solution of **1c** (163 mg, 0.5 mmol) in 7.5 ml of 3 : 2 dioxane-H_2O was added IDCP (1.410 g, 3 mmol) and the resulting solution was heated at 60-70^0 C for 18h. The reaction mixture was cooled and diluted with ether and the ether solution was subsequently washed successively with 5% HCl, water, sat.$NaHSO_3$ and brine and dried over anhydrous $MgSO_4$. The crude product obtained on evaporation of the solvent was purified by column chromatography on silica gel (Acme 100-200 mesh) using 10% ethyl acetate-hexane as eluent. 3,4-Di-*O*-benzyl-2,6-dideoxy-2-methylene-L-arabino-hexono-1,5-lactone (**3c**) was obtained as a colourless oil (141 mg, 83%).

Spectral data of 3c IR (neat) 3032, 2876, 1730, 1167, 696 cm^{-1}; $[\alpha]_D^{25}$ -51.0° (c, 1.3, $CHCl_3$); ^{1}H-NMR(200 MHz, $CDCl_3$) δ 7.36-7.26 (m, 10H), 6.49 (bs, 1H), 5.88 (bs, 1H), 4.81-4.55 (m, 4H), 4.29-4.27 (m, 2H), 3.61-3.59 (m, 1H), 1.48-1.45 (d, J=6.7 Hz, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) 165.76, 137.29, 134.83, 129.82, 128.61, 128.03, 127.78, 81.09, 79.05, 75.84, 73.46, 71.86, 18.73 ppm; MS m/e (relative intensity) 338 (M^+, 7), 180 (39), 91 (100).

Spectral data of 3d. IR (neat) 3032, 2924, 1726, 1165, 698 cm^{-1}; $[\alpha]_D^{25}$ -44.6° (c, 1.3, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.39-7.25 (m, 10H), 6.72-6.71 (d, J=1.36 Hz, 1H), 5.78-5.77 (dd, J=1.26, 0.7 Hz, 1H), 4.71-4.61 (m, 4H), 4.46-4.45 (m, 1H), 4.39 (bs, 1H), 4.28-4.26 (m, 1H), 3.68-3.61 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) 164.14, 137.22, 133.73, 132.46, 128.61, 128.09, 127.81, 127.76, 126.99, 75.29, 72.79, 71.09, 70.09, 67.39 ppm; MS m/e (relative intensity) 324 (M^+, 12), 232 (39), 181 (59), 127 (70), 107 (100).