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A NEW ENTRY INTO VERSATILE RING OPENING OF O-BENZYL GLYCALS AND RELATED COMPOUNDS *via* $Tl(NO_3)_3$ and $NaBH_4$

Pietro Passacantilli

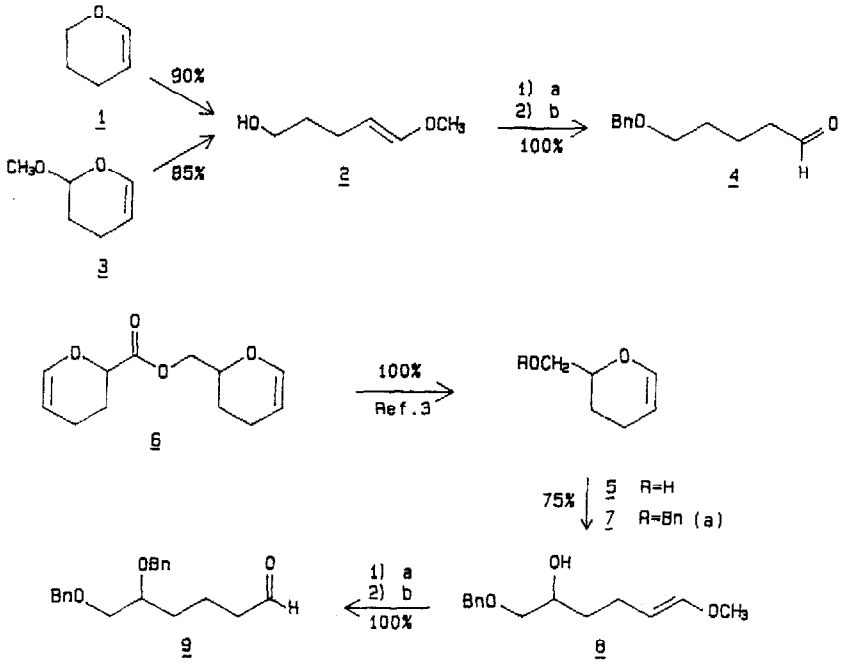
Centro di Studio per la Chimica delle Sostanze Organiche Naturali del C.N.R. - Dipartimento di Chimica, Universita' "La Sapienza" di Roma - P.le A. Moro, 5 - 00185 ROMA

Abstract: A new, one pot procedure for the preparation of chiral building blocks, by treatment of O-benzyl glycals **10**, **11**, **12** and cyclic enol-ethers **1**, **3** and **7** with the system $Tl(NO_3)_3$ and $NaBH_4$ is described.

In connection with a project aimed to broaden the synthetic exploitation of enol-ether systems, we studied the reactivity of cyclic enol-ethers under the action of thallium (III) nitrate and $NaBH_4$ (molar ratio 1 : 4). This original system had never been used before on this class of compounds. In a typical experiment, dihydropyran (**1**) in methanol was first allowed to react with thallium (III) nitrate, then $NaBH_4$ was immediately added before the formation of the insoluble reduced $TlNO_3$[1].
Thus the linear methoxy alcohol **2**[2] was isolated in excellent yield (90%). The obtained product shows to be synthetically interesting because of the different functional groups present at the ends of the molecule.

In order to verify the efficacy of this unusual behaviour of the system thallium salt and hydride, we applied this procedure to other dihydropyran derivatives. First of all, the 3,4-dihydro-2-methoxy-2H-pyran (**3**) showed the same reactivity of **1**, giving **2** in high yield (85%). The O-benzyl derivative of **2** was easily and quantitatively transformed into the

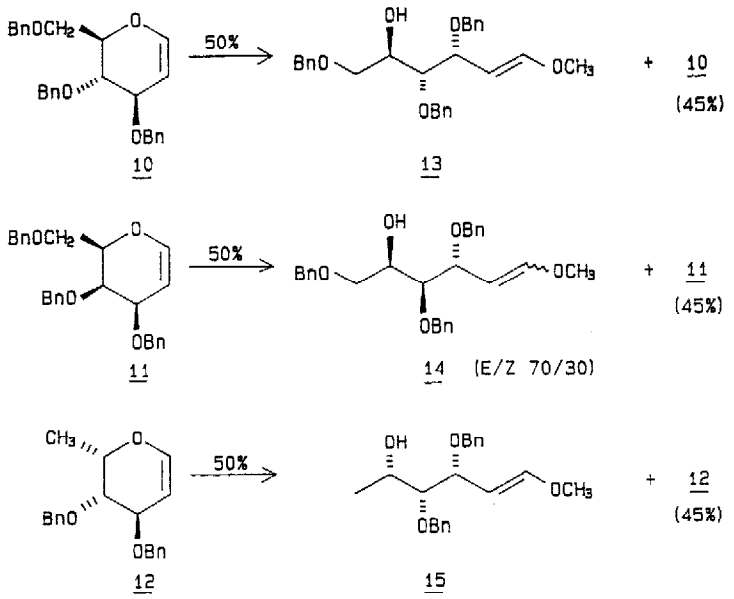
aldehyde **4**[2]. Furthermore **7**, the O-benzyl ether derivative of **5** obtained from the ester **6** by $NaBH_4$ reduction[3], furnished in good yield (75%) **8**[4], whose O-benzyl ether derivative was quantitatively converted into the aldehyde **9**[4].



a) $C_6H_5CH_2Br$, THF, NaH, reflux, 2h,

b) Dioxane/H_2O (10:1), H^+, 6h.

Owing to these promising results, we focused our attention on glycals, widely employed in the stereospecific synthesis of natural compounds[5,6]. The O-benzyl ether derivatives **10**, **11** and **12** gave *chiral opening products* **13**[7], **14**[7] and **15**[7] with selectively protected hydroxy groups; the yields (50%) could be considered satisfactory, since starting materials (45%) were recovered unchanged. It was interesting to note that all chiral centres have been conserved unlike the previous procedure for glycal derivatives ring opening by acids which gave α,β-unsaturated aldehydes[8,9] losing a chiral centre.



These preliminary results confirm the great reactivity and utility of cyclic enol-ethers in organic synthesis and stimulate further studies in this field. Work is now in progress to apply this methodology to the preparation of other chiral building blocks.

ACKNOWLEDGMENTS

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General Procedure

A solution of $Tl(NO_3)_3$ (1 mmol) in methanol (5 ml) is added to the enol-ether (or to its O-benzyl ether derivative) (0.5 mmol) dissolved in methanol (20 ml); immediately after $NaBH_4$ (4 mmol) is added. The suspension, diluted with H_2O (20 ml) was extracted then twice with Et_2O (50 ml). Combined extracts were dried (Na_2SO_4), evaporated and crude product was chromatographed on silica gel. Yields are calculated after purification.

References and Notes

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2. ^{1}H-NMR ($CDCl_3$, 200 MHz), Spectral data for **2**: δ 6.29 (d, $J_{1,2}$=12.6 Hz, 1H), 4.68 (q, $J_{2,1}$=12.6, $J_{2,3a}$=7.7 Hz, 1H), 3.58 (t, $J_{5,4}$=6.7 Hz, 2H), 3.43 (s, OCH_3), 2.5-1.8 (m, 2H), 1.62-1.48 (m, 2H); **4**: δ 9.74 (t, $J_{1,2}$= 1.6 Hz, 1H), 7.31 (s, 5H), 4.47 (s, CH_2-Ph), 3.46 (t, $J_{5,4}$=6.0 Hz, 2H), 2.43 (dt, $J_{2,1}$=1.6, $J_{2,3}$=7.0 Hz, 2H), 1.80-1.55 (m, 4H); selected spectral data from ^{13}C-NMR ($CDCl_3$, 50,3 MHz) δ 203.27 (C-1), 70.08 (C-5), 73.29 (CH_2-Ph).
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4. Spectral data for **8**: ^{13}C-NMR ($CDCl_3$, 50,3 MHz) δ 148.04 (C-1), 102.64 (C-2), 34.27 (C-3), 23.94 (C-4), 65.61 (C-5), 70.00 (C-6), 56.18 (OCH_3), 73.70 (CH_2-Ph), 138.69, 128.95 and 128.22 (CH_2-Ph); **9**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 9.70 (d, $J_{1,2a}$=1,4 Hz, 1H), 7.34 (fs, CH_2-Ph, 10H), 4.71 and 4.55 (q, $J_{A,B}$=11,8 Hz, CH_2-Ph), 4.56 (s, CH_2-Ph), 3.56 (m, H-C5 and 2H-C6), 2.37 (dt, $J_{2a,1}$=1.4, $J_{2,3}$=7 Hz, 2H), 1.90-1.50 (m, 4H).
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7. Spectral data for **13**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 6.42 (d, $J_{1,2}$=12.8 Hz, 1H), 4.80 (dd, $J_{2,1}$=12.8, $J_{2,3}$=9,5 Hz 1H), 4.58 (bs, CH_2-Ph), 4.58, 4.28 (A'B', $J_{A',B'}$=12.0 Hz, CH_2'-Ph), 4.48 (bs, CH_2"-Ph), 3.92 (dd, $J_{3,2}$= 9.5, $J_{3,4}$=3.8 Hz, 1H), 3.57 (fs, H-C4, 2H-C6, 3H), 3.50 (s, OCH_3), 2.96 (bs, H-C5), 7.33-7.23 (fs, CH_2-Ph); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 151.45 (C-1), 99.36 (C-2), 81.39, 79.41 (C-3 and C-4), 66.03 (C-5), 69.19 (C-6), 74.99, 73.05, 72.90 (CH_2-Ph), 138.38, 138.33, 138.30, 128.32, 128.26, 128.12, 128.03, 127.66, 127.59, 127.38 (CH_2-Ph).

   Selected spectral data for isomer E and Z of **14** : ^{1}H-NMR ($CDCl_3$,200 MHz) δ 6.45 (d, $J_{1,2}$=12.6 Hz, isomer E), 6.38 (d, $J_{1',2'}$=6.5 Hz, isomer Z), 4.01-3.80 (m, E and Z, H-C3), 2.88 (m, E and Z, H-C5), 3.55 (s, OCH_3, isomer E), 3.50 (s, OCH_3, isomer Z).

   Spectral data for **15**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.31 (fs, CH_2-Ph, 10H), 6.48 (d, $J_{1,2}$=12.8 Hz, 1H), 4.77 (dd, $J_{2,1}$=12.8, $J_{2,3}$=9.5 Hz, 1H), 4.76, 4.60 (AB, $J_{A,B}$= 11.9 Hz, CH_2-Ph), 4.60, 4.32 (A'B', $J_{A',B'}$=11.9, CH_2'-Ph), 3.98-3.80 (m, H-C3 and H-C4), 3.55 (s, OCH_3), 3.37 (t, $J_{4,3}$= $J_{4,5}$=5.3 Hz, 1H), 2.83 (d, $J_{OH,5}$=6.3 Hz, OH), 1.13 (d, $J_{6,5}$=6.3 Hz, 3H)
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