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An unusual acetonide group migration

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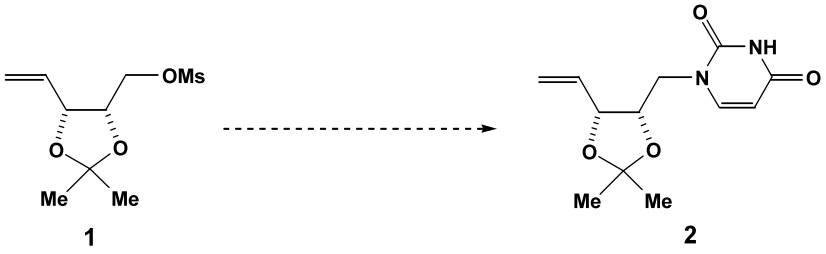
Abstract—Treatment of (2*S*,3*R*)-2,3-*O*-isopropyliden-4-penten-1,2,3-triol mesylate with uracil, K_2CO_3 did not provide the product of S_N2 displacement, but an interesting acetonide group migration product **8**. The structure of **8** was secured by spectral analysis and single crystal X-ray analysis. The desired product **2** could be ultimately obtained by Mitsunobu reaction of the alcohol **6** with 3-*N*-benzoyl uracil followed by basic hydrolysis.

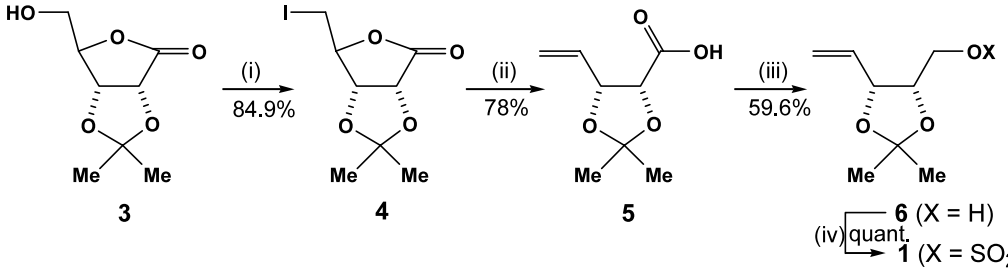
In connection with an ongoing medicinal chemistry program we sought to prepare **2** from **1**.



The precursor (2*S*,3*R*)-2,3-*O*-isopropyliden-4-penten-1,2,3-triol mesylate **1** could be conveniently obtained from D-ribonolactone by slight modification of procedure originally described by Jager.[1] The iodolactone **4** was produced from D-ribonolactone by a one step reaction with *N*,*N*′-carbonyldiimidazole and an excess of methyl iodide. The remaining steps were carried out according to Scheme 1.[2–4]

However, when **1** was treated with uracil and anhydrous K_2CO_3 in DMF, the product obtained was not **2** but an interesting acetonide migration product **8**, mp 126–27°C[5] (Scheme 2).

The structure of **8** was determined by MS, ^{13}C and ^{1}H



Scheme 1. *Reagents and conditions*: (i) ImCOIm, MeI, MeCN, Δ, 2 h; (ii) Zn, KH_2PO_4, THF, rt; (iii) $LiAlH_4$, EtOEt; (iv) $MeSO_2Cl$, pyridine, CH_2Cl_2.

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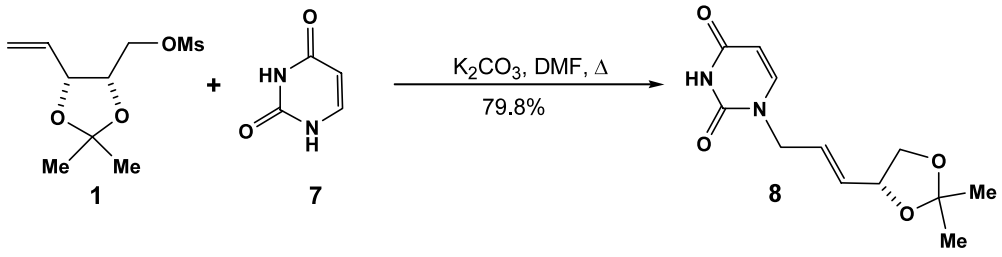


Scheme 2.

NMR. Analysis of the 2D (^{1}H–^{1}H) cosy and (^{1}H–^{13}C) cosy NMR data led to the above assignment. In addition 1D NOE data confirmed the assignment.[7]

Single crystal X-ray crystallographic analysis established the structure and relative stereochemistry of **8**. The asymmetric crystal unit consists of two independent molecules which are hydrogen bonded [N(3)–O(8′) = 2.822 (3) A, N(3′)–O(8) = 2.865 (3) A] in the manner shown in Figure 1. The conformations of the individual molecules differ significantly around their C(9)–C(10) bonds [torsion angles: N(1)–C(9)–C(10)–C(11) = −125.7 (6)°, N(1′)–C(9′)–C(10′)–C(11′) = 126.5 (5)°], and their 1,3-dioxa cyclopentane rings approximate to envelope and half chair forms in the unprimed and primed molecules, respectively.[10]

It appears that this unprecedented rearrangement of acetonide group takes place by breakage of the bond 'a' leading to the hemiacetal intermediate **9** which displaces the mesylate (Scheme 3). Note that bond 'b' remains intact throughout this process. Confirmation for this came from chiral shift reagent studies on the alcohol **10** prepared by ozonolysis of **8** followed by reduction. The absolute stereochemistry of **10** was assigned as *R*-(−) on the basis of results presented below.[8]

Finally the desired **2** could be prepared by Mitsunobu reaction of 3-*N*-benzoyl uracil **12** with the alcohol **6** to provide **13** (Scheme 4). Hydrolysis of the *N*-benzoyl group provided **2**, mp 148–50°C.[6,9]

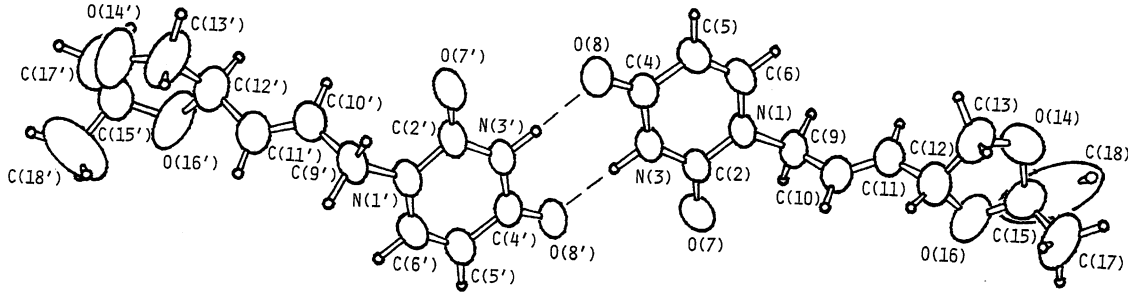
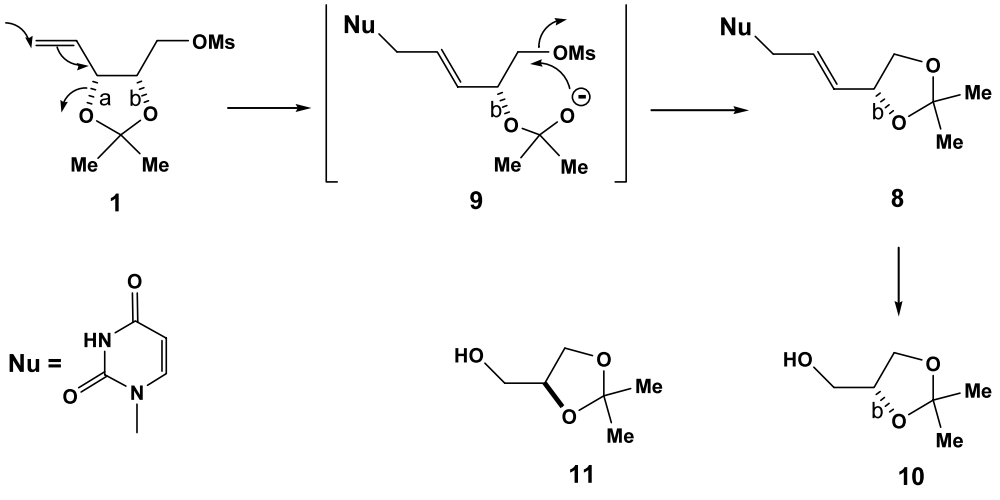
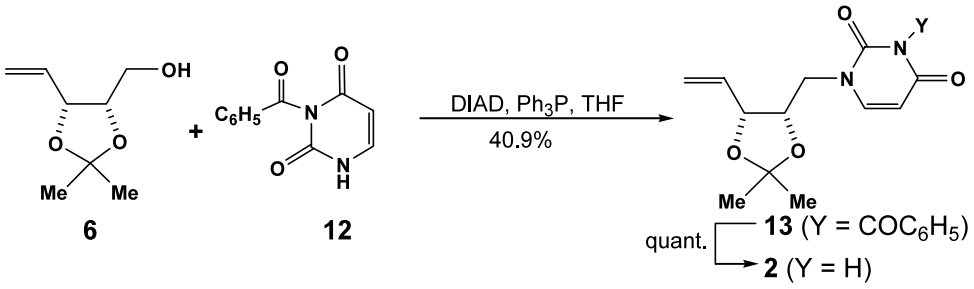


Figure 1.



Scheme 3.



Scheme 4.

We have presented here an unusual example of an acetonide group migration. To the best of our knowledge we are not aware of any such example in the literature.

References

1. Jager, V.; Hafele, B. *Synthesis* **1987**, 801–806.
2. All new compounds were characterized by ^{1}H, ^{13}C NMR and high-resolution mass spectra. When necessary 1D NOE and 2D NOESY NMR spectra were obtained to confirm relative stereochemistry. Elemental analysis were obtained for crystalline compounds only. Yields refer to isolated products and have not been optimized. Selective spectral data is given here.
3. Preparation of **4**: A solution of ribonolactone acetonide (10 g) in dry acetonitrile (50 ml) was treated with carbonyl diimidazole (8.59 g; 1 equiv.). After a clear solution was obtained, MeI (37.6 g; 5 equiv.) was added. The reaction mixture was stirred at room temprature for 30 min followed by heating under reflux for 2 h. After cooling, the product was isolated by extractive work-up with ether. The ether extract was washed with water, aqueous $Na_2S_2O_3$, dried over Na_2SO_4 and evaporated to dryness to provide a solid 13.7 g. It was filtered through a column of silica gel (300 g) using $CHCl_3$ as eluent to yield a crystalline solid, mp 91–93°C.
4. Prepation of **5**: An efficiently stirred solution of the iodolactone (25 g) in THF (250 ml) was treated with zinc dust (50 g). To this stirred suspension was added in one portion 1 M KH_2PO_4. After an induction period of ~2 min, gentle reflux of THF was observed. After stirring for 20–25 min, zinc was removed by filtration and washed with additional THF to bring the total volume of combined filtrates to ~800 ml. To these combined filtrates was added with stirring Amberlite IRC-50 resin (250 g). After stirring for 1 h, the resin was removed by filtration, washed with more THF. The filtrates were evaporated in vacuo to leave a aqueous medium containing polymeric suspensions. This aqueous medium was extracted with CH_2Cl_2 (400 ml total after 3 extractions). The combined CH_2Cl_2 extract was dried (Na_2SO_4) and evaporated to dryness in vacuo to provide a thick yellow oil (11.29 g) which was suitable for the next reaction.
5. Preparation of **8**: Uracil (3.46 g) was suspended in dry DMF (100 ml) and dry K_2CO_3 (4.2 g), and the mesylate **1** (7.3 g) were added. The reaction mixture was subjected to magnetic stirring and it was then heated (bath temp. ~130°C). Uracil initially dissolved followed by separation of a thick gel. The heating was continued for ~20 h, water (~100 ml) added to dissolve the gel and the reaction mixture extracted with CH_2Cl_2. The organic phase containing substantial DMF was evaporated in vacuo to dryness and the gummy residue azeotroped with toluene. The resulting thick brownish mass was purified by chromatography on a coarse SiO_2 (150 g) column to provide in 10% *n*-hexane/EtOAc eluents the product **8** (2.95 g), mp 126–27°C.
6. Preparation of **2**: A stirred suspension of the alcohol **6** (3.18 g), 3-*N*-benzoyl uracil (4.25 g) and Ph_3P (5.3 g) in THF (50 ml) was treated (under argon atmosphere) with diisopropylazodicarboxylate (4.24 ml). Immediate dissolution of the contents followed by slightly exothermic reaction took place. The reaction mixture was stirred overnight, evaporated to dryness in vacuo to provide a gummy residue which was subjected to chromatography on TLC grade silica gel (200 g). Elution with 60% EtOAc/*n*-hexane provided in some of the fractions pure **13** (2.93 g). It was dissolved in methanol (100 ml) and treated with 10% aqueous K_2CO_3 (50 ml). The reaction mixture was stirred overnight, the solvents evaporated in vacuo and the residue extracted with CH_2Cl_2. The crude product containing methyl benzoate was crystallized from EtOAc/*n*-hexane to provide a crystalline solid **2**, mp 148–50°C.
7. **8**: ^{13}C NMR [$CDCl_3$, δ, ppm] 163.8 (s), 150.7 (s), 143.7 (d, CH), 133.1 (d, CH), 126.8 (d, CH), 102.7 (d, CH), 109.7 (s), 75.8 (d, CHO), 69.2 (t, CH_2O), 48.9 (t, CH_2), 26.6 (q, CH_3) and 25.8 (q, CH_3). ^{1}H NMR [$CDCl_3$, δ, ppm] 1.32 (s, CH_3), 1.39 (s, CH_3), 7.12 (d, CH), 5.80 (m, CH), 5.67 (d, CH), 5.65 (m, CH), 4.50 (dd, CHO), 4.30 (m, CH_2), 4.08 (m, $CH_{2A}O$) and 3.52 (m, $CH_{2B}O$).
8. Absolute stereochemistry of **10**: A mixture of **10** (*R*) and **11** (*S*) acetal (18.0 mg) was dissolved in 1.0 ml of dry $CDCl_3$. Quantitative additions of chiral shift reagent, Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), [Eu(hfPC)$_3$], led to the differentiation of *R* and *S* enatiomers at a concentration of 18 mg of the reagent. Addition of *S*-(+)-enantiomer **11** to the above solution (18 mg of *R*/*S* mixture+18 mg of the chiral shift reagent) led to the identification of the *S*-(+)-enatiomer as a slow moving component. Finally, a fresh solution of 9.2 mg of *R*-(−)-enantiomer **10** and 9.1 mg of *S*-(+)-enantiomer **11** was prepared. To this solution 18.7 mg of chiral shift reagent was added to observe CH_3 splitting. When a sample (~1 mg) of the unknown dioxolane was added, the spectrum indicated an increase in the intensity of the *R*-(−)-**10** (fast moving) component.

9. **2**: ^{13}C NMR [$CDCl_3$, δ, ppm] 119.5 (t), 132.0 (d), 77.8 (d), 75.3 (d), 50.0 (t), 150.8 (s), 163.6 (s), 101.8 (d), 145.5 (d), 109.5 (s), 25.2/27.9 (q, q). ^1H NMR [$CDCl_3$, δ, ppm] 5.47 (d of t, 17 Hz, 1 Hz, 1 Hz, CH), 5.34 (d of t, 10 Hz, 1 Hz, 1 Hz, CH), 5.81 (d of q, 17 Hz, 10 Hz, 7 Hz, CH), 4.72 (t of t, 7 Hz, 7 Hz, 1 Hz, 1 Hz, CH), 4.43 (d of q, 10 Hz, 7 Hz, 2 Hz, CH), 4.20 (d of d, 14 Hz, 2 Hz, CH), 3.17 (d of d, 14 Hz, 10 Hz, CH), 5.68 (d of d, 8 Hz, 1.5 Hz, CH), 7.25 (d, 8 Hz, CH), 1.54/1.36 (s, s, CH_3, CH_3), 8.97 (broad).
10. Atomic parameters, bond lengths, bond angles and torsion angles for **15** have been deposited at the Cambridge Crystallographic Data Center, Cambridge, CB2 1EZ, UK. Any request should be accompanied by full literature citation for this communication.