Fluoride Ion-Promoted α-Ketol Rearrangement during Unmasking of Silyl-Protected Medium-Ring Dihydroxy Ketones

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Received: January 5, 2004; Accepted: April 2, 2004

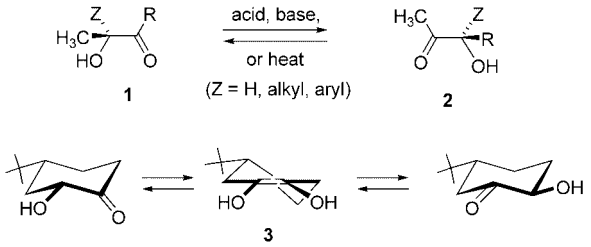
Dedicated to Joe P. Richmond on the occasion of his 60th birthday.

Abstract: A new strategy for implementing α-ketol rearrangements under mild conditions is presented. The reactants are mono- and disilylated stereoisomers of α,α′- and α,β-dihydroxycycloheptanones and -cyclooctanones. Compounds of this class experience ready deprotection upon treatment with tetrabutylammonium fluoride. In certain examples, this process is accompanied by structural isomerization. Since the product diols are stable to the reaction conditions, these chemical changes have been attributed to kinetically controlled events following transient alkoxide generation resulting from cleavage of the O–Si bond proximal to the carbonyl group. The experimental findings are evaluated against a backdrop of calculated (MM3) steric energies of the silicon-free products and their response to equilibration under strongly basic conditions.

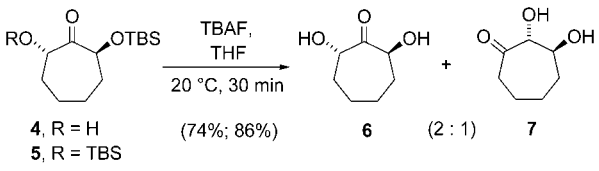
Keywords: desilylation; fluoride ion; α-ketols; medium-sized rings; MM3 calculations; rearrangement

Many α-hydroxy ketones have the capacity for conversion to an isomeric α-ketol. Catalysis by a base,[1] inorganic salt,[2] Brønsted acid,[3] or Lewis acid[4] is generally required. Two mechanistic pathways are possible depending on structural features. When the hydroxy group forms part of a tertiary carbinol, a 1,2-alkyl or aryl shift as depicted for **1** ⇌ **2** operates.[5] Secondary α-keto carbinols can also isomerize *via* an enediol intermediate typified by **3**.[6–10] In both cases, the rearrangement is reversible, such that thermodynamic control is operative and the more stable isomer results. If the enthalpically advantaged member of the pair is already in hand, a chemical transformation will not likely operate under the predescribed conditions provided that the energy difference is sufficiently great.

Extensive attention has been accorded to acyclic, cyclic, bridged, and steroidal α-ketols, such that ring-size effects and the impressively high levels of attainable selective bond migration are well appreciated.[5] In contrast, heteroatomic substituent effects in the vicinity of the carbonyl group appear not to have been given prior attention. The recent availability of monosilylated medium-ring α,α′-dihydroxycycloalkanones in our laboratory[11] has prompted a probe of the manner in which the individual *cis*- and *trans*-isomers react when desilylated. The generation of tautomeric α-ketol products has been found to occur under conditions sufficiently mild[1d,12] that the resulting dihydroxy ketones are not concurrently equilibrated. These observations constitute a previously unrecognized means for implementing α-ketol rearrangements.



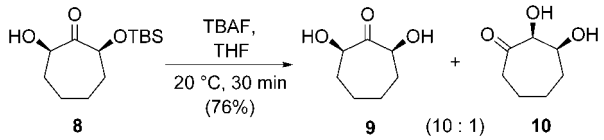
We first addressed the direct desilylation of **4** and its diprotected congener **5** with tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran at room temperature for 30 min. In the event, the dihydroxy ketones **6** and **7** were formed in an identical ratio of 2:1 in these examples. The structural assignments to the products are based upon direct spectral comparisons with authentic samples. The *trans* relationship of the hydroxy substituents in **7** presumably stems from operation of a suprafacial 1,2-hydride shift in the alkoxide intermediate(s).



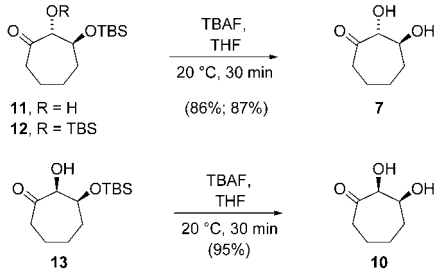
cis-Isomer **8** exhibits less of a driving force to isomerize. Under entirely comparable reaction conditions, **9** and **10** are formed with a distribution of 10:1. Product formation in the case of both cycloheptanone stereo-

 DOI: 10.1002/adsc.200404002

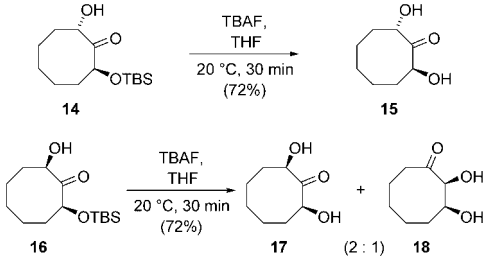
isomers appears to be under kinetic control, as **6**, **9**, and **10** undergo no further chemical change when reexposed to TBAF for the same time periods.



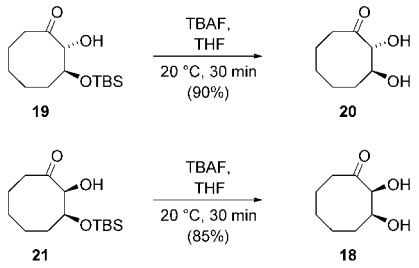
Beyond this, the 2,3-dihydroxy derivatives **11** and **12** were found to undergo desilylation smoothly without rearrangement to furnish exclusively **7**. When the reactivity of **13** was likewise scrutinized, high-yield conversion to **10** (95% yield) was noted. Since the desilylations of **11** and **13** do not proceed *via* an α-ketol alkoxide, the absence of isomerization is not unexpected. This mechanistic scenario does not apply to **12**, thereby signaling the lack of a driving force for the isomerization of *trans*-2,3-dihydroxycycloheptanone to its *trans*-2,7-dihydroxy tautomer.



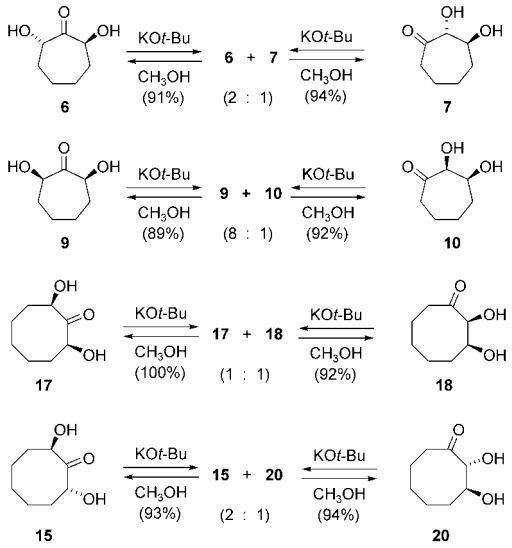
In light of the conformational and reactivity differences known to distinguish medium rings of different size, several structurally related cyclooctanone derivatives were also studied. Ketone **14** was the lead-off eight-membered candidate to be treated with fluoride ion. Unlike **4**, this α-ketol provided only **15** and exhibited no detectable tendency to isomerize. This adherence to a non-isomerative pathway was not shared by the corresponding *cis*-isomer **16**. In this instance, activation with TBAF led reproducibly to a 2:1 mixture of **17** and **18**. As before, systematic spectroscopic comparisons were made to achieve unequivocal definition of stereochemistry and structure.



In line with expectations based on our earlier rationale, neither **19** nor **21** experienced rearrangement when desilylated. Also, resubmission of **9**, **10**, **15**, **17**, **18**, and **20** to the standard protocol resulted in no further chemical change. When control experiments were conducted instead with methanolic potassium *tert*-butoxide in an effort to simulate more conventional α-ketol rearrangement conditions, both **6** and **7** were independently converted into a 2:1 mixture of the *trans* tautomers with the predominant component being **6**.



Noteworthily, **9** was equilibrated with **10** (ratio 8:1), while **17** was equilibrated with **18** (1:1 ratio). Comparable treatment of **15** and **20** in independent experiments gave rise to a 2:1 mixture of **15** and **20** in both cases.



To gain a different vantage point regarding this matter, the global minimum energy conformations and the associated steric energies were calculated for each dihydroxy ketone by the MM3 method using 1500 Monte Carlo simulations in MacroModel version 5.0. For convenient reference, the 7- and 8-membered ring systems are grouped separately in Figures 1 and 2, respectively. As concerns the dihydroxycycloheptanones, two important relationships can be readily derived from these data: a) the *cis*- and *trans*-isomers in both the 2,3- and

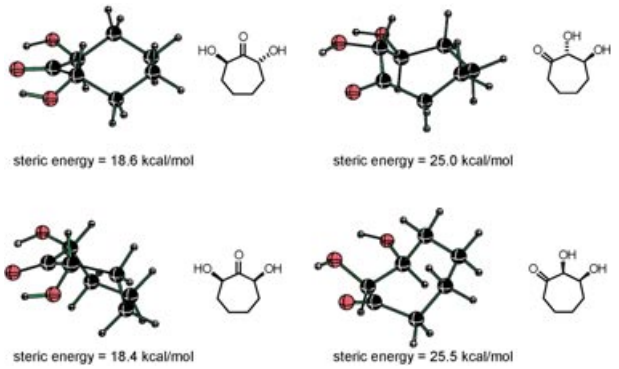


Figure 1. Global minimum energy conformations of the 2,3- and 2,7-dihydroxycycloheptanones.

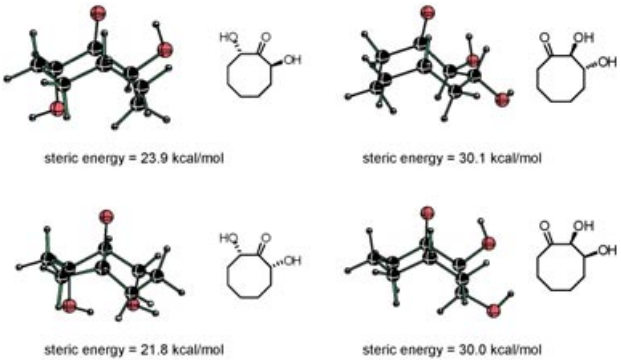


Figure 2. Global minimum energy conformations of the 2,3- and 2,8-dihydroxycyclooctanones.

2,7-disubstituted series are essentially isoenergetic; and b) the 2,7-dihydroxy arrangement is thermodynamically favored in both substrates irrespective of diol stereochemistry. Intramolecular hydrogen bonding is available to both structural classes, with the 7-membered ring possessing sufficient flexibility to accommodate the necessary topological arrangements. All hydroxy groups are projected pseudoequatorially.

The energetic interrelationships determined in the cyclooctyl series are entirely parallel (Figure 2). There is little difference between configurational diastereomers, and the 2,8-dihydroxycyloooctanones are seen to be less sterically disadvantaged than the 2,3 isomers.

Our global experimental results reflect a tendency on the part of **4** and **8** to undergo structural isomerization to some degree upon treatment with fluoride. The process operates more extensively in the *trans* series than the *cis*. The converse is true for the related cyclooctanones. While *trans*-ketone **14** exhibits no proclivity for conversion to the 2,3-isomer, *cis*-derivative **16** leads only to modest amounts of **18**. While the rearrangement is stereospecific in all cases, the calculations do not corroborate perfectly with the experimental results.

Experimental Section

For Desilylation of Mono-TBS Protected Substrates; General Procedure A

The reactant (1 mmol) was dissolved in dry THF (25 mL), treated with a 1 M solution of TBAF in THF (1.05 mmol), and stirred for 30 min prior to solvent evaporation. The residue was directly submitted to chromatography on silica gel (elution with 1:1 hexane/ethyl acetate).

For Desilylation of Di-TBS Protected Substrates; General Procedure B

As above, except that 2.5 equivs. of TBAF were added.

Control Experiments Involving TBAF

Identical to procedure A.

Control Experiments Involving Potassium *tert*-Butoxide

The reactant (1 mmol) was dissolved in methanol (25 mL), treated with potassium *tert*-butoxide (1.1 mmol), and stirred for 30 min prior to solvent evaporation. The residue was directly submitted to chromatography on silica gel (elution with 1:1 hexane/ethyl acetate).

Spectral Data of Products

For **6**: yellowish oil; IR (neat): $\nu = 3414, 1710, 1452, 1270\ cm^{-1}$; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 4.25$ (dd, $J = 9.8, 2.9$ Hz, 2H), 3.10 (s, 2H), 2.12–2.04 (m, 2H), 1.98–1.90 (m, 2H), 1.79–1.25 (series of m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 214.2$, 77.4 (2C), 32.2 (2C), 26.9 (2C); ES HRMS: *m/z* $(M+Na)^+$ calcd.: 167.0678; obsd.: 167.0674.

For **7**: colorless oil; IR (neat): $\nu = 3418, 1703, 1647, 1451\ cm^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.45$ (d, $J = 1.5$ Hz, 1H), 4.26–4.22 (m, 1H), 2.75–2.69 (m, 1H), 2.53–2.46 (m, 1H), 2.23–2.18 (m, 1H), 1.99–1.93 (m, 1H), 1.88–1.79 (m, 2H), 1.74–1.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 212.2$, 80.8, 73.1, 41.0, 34.2, 23.0, 22.9; ES HRMS: *m/z* $(M+Na)^+$ calcd.: 167.0678; obsd.: 167.0669.

For **9**: white solid, mp 87 °C; IR (neat): $\nu = 3406$, 1711, 1451 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.41$ (dd, $J = 7.6$, 4.5 Hz, 2H), 3.39 (br s, 2H), 2.06–2.00 (m, 2H), 1.83–1.76 (m, 2H), 1.69–1.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 214.9, 74.9 (2C), 33.7 (2C), 24.8 (2C); ES HRMS: *m/z* $(M+Na)^+$ calcd.: 167.0678; obsd.: 167.0684.

For **15**: white solid, mp 78–79 °C; IR (neat): $\nu = 3419$, 1700, 1653 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.62$ (dd, $J = 6.0$, 2.9 Hz, 2H), 2.47–2.40 (m, 2H), 2.09–2.01 (m, 2H), 1.79–1.71 (m, 2H), 1.60–1.54 (m, 2H), 1.39–1.31 (m, 2H) (OH not seen); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 218.7$, 75.7 (2C), 33.5 (2C), 24.9 (2C), 21.0; ES HRMS: *m/z* $(M+Na)^+$ calcd.: 181.0835; obsd.: 181.0837.

For **17**: white solid, mp 120–121 °C; IR (neat): ν = 3693, 1705, 1246 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.41 (dd, *J* = 7.7, 3.7 Hz, 2H), 3.26 (s, 2H), 2.33–2.27 (m, 2H), 1.97–1.90 (m, 2H), 1.84–1.66 (m, 4H), 1.48–1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 218.2, 74.1 (2C), 33.4 (2C), 24.6, 21.9 (2C); ES HRMS: *m/z* $(M+Na)^+$ calcd.: 181.0835; obsd.: 181.0829.

For **18**: white solid, mp 79 °C; IR (neat): ν = 3614, 1477, 1236 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.03–3.99 (m, 2H), 3.96 (d, *J* = 2.5 Hz, 1H), 2.37 (s, OH), 2.10–2.04 (m, 2H), 1.92–1.80 (m, 4H), 1.71–1.34 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.6, 76.1 (2C), 32.6 (2C), 29.1, 22.9 (2C); ES HRMS: *m/z* $(M+Na)^+$ calcd.: 183.0991; obsd.: 183.0993.

For **20**: colorless oil; IR (neat): ν = 3394, 1703, 1478 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.28 (t, *J* = 8.2 Hz, 1H), 3.38 (d, *J* = 8.7 Hz, 1H), 3.31–3.26 (m, 1H), 3.18 (s, 2H), 2.72–2.66 (m, 1H), 2.51–2.44 (m, 1H), 2.11–2.04 (m, 1H), 1.93–1.80 (m, 2H), 1.67–1.57 (m, 2H), 1.54–1.47 (m, 1H), 1.02–0.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.7, 79.7, 77.6, 41.6, 29.2, 28.2, 21.0, 20.7; ES HRMS: *m/z* $(M+Na)^+$ calcd.: 181.0835; obsd.: 181.0841.

Acknowledgements

This investigation was made possible by the receipt of unrestricted funds from the S. T. Li Foundation.

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