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# Reductive and Base-Induced Cleavage Reactions of Oxabicyclic Compounds

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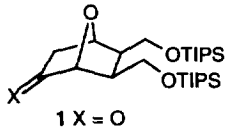
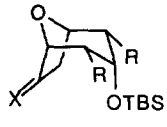
***Abstract:*** The 2-methylene-7-oxabicyclo[2.2.1]heptane **2** and 6-methylene-8-oxabicyclo[3.2.1]octanes **15** and **16** were prepared in enantiomerically enriched form, and shown to undergo a base-induced β-elimination of the oxygen bridge leading to substituted methylenecyclohexenols and methylenecycloheptenediols. Li/$NH_3$ induced an α-reduction of 7-oxabicyclo[2.2.1]heptan-2-one **1** and afforded β-hydroxy cyclohexanone **19**.

7-Oxabicyclo[2.2.1]heptenes and 8-oxabicyclo[3.2.1]octenes have been shown to be useful building blocks in organic synthesis.[1] For example, functionalized cyclohexenols and cycloheptenols are obtained after nucleophile induced cleavage of the bridging carbon-oxygen bond in these systems.[2] Recently Arjona and Plumet reported that methylenecyclohexenediols are formed by treatment of 1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-enes with LDA.[3] We have observed a similar reaction pathway upon treatment of enantiomerically enriched methyleneoxabicyclic compounds with organolithium reagents and report the results herein.

In order to prepare the enantiomerically enriched oxabicyclo[2.2.1] and [3.2.1] ketones **1**, **3** and **5**, we utilized an asymmetric hydroboration-oxidation of the corresponding 7-oxabicyclo[2.2.1]heptenes and 8-oxabicyclo[3.2.1]octenes (Figure 1). The alternative routes to enantiomerically enriched ketones which we considered were the diastereoselective Diels-Alder reaction developed by Vogel and co-workers or an enantioselective Diels-Alder reaction between furan and α-bromoacrolein using a chiral Lewis acid catalyst reported by Corey.[4,5] However, these routes are most efficient for the preparation of the 7-oxabicyclic ketones and we sought a common strategy to both the 7- and 8-oxabicyclic families of ketones.



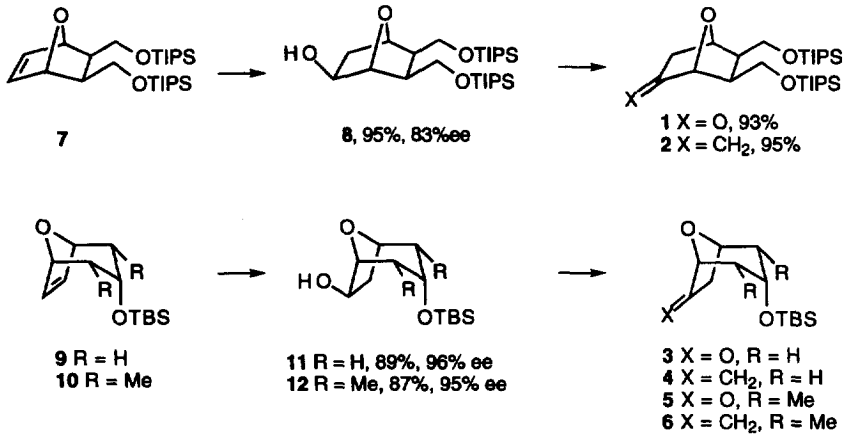

**1** X = O
**2** X = $CH_2$




**3** X = O, R = H
**4** X = $CH_2$, R = H
**5** X = O, R = Me
**6** X = $CH_2$, R = Me

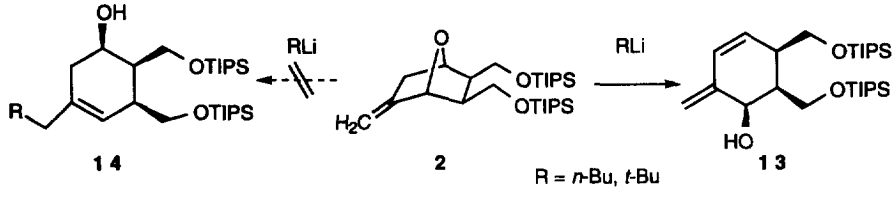
**Figure 1**

Brown's enantioselective hydroboration method was used to induce the asymmetry.[6,7] Alcohol **8** was obtained in 83% ee upon treatment of alkene **7** with 1.2 equivalents of (-)-$Ipc_2BH$ in THF at 0 °C for 30 min followed by oxidation with alkaline hydrogen peroxide. The ee was determined by $^{19}F$ NMR at 300 MHz of the corresponding Mosher's ester. Analysis of the Mosher's ester and prediction based on Brown's studies indicated that the absolute configuration at the newly formed carbinol stereocenter is (*S*).[8] Oxidation of resulting *exo* alcohol with PCC, NaOAc afforded **1** in 93% yield. Subsequent Wittig reaction (NaHMDS, $Ph_3PCH_3Br$, toluene, reflux) gave compound **2** in 95% yield.[9] Hydroboration of oxabicyclic[3.2.1] compound **9** and **10** with (-)-$Ipc_2BH$ in THF at -25 °C for 14 h gave **11** and **12** in >85% yield and >95% ee and once again the ee was determined by $^1H$ NMR at 400 MHz of the corresponding Mosher's esters. Oxidation and olefination were equally efficient providing **4** and **6** in 85% and 84% yield respectively for the two steps (Scheme 1).




**Scheme 1**

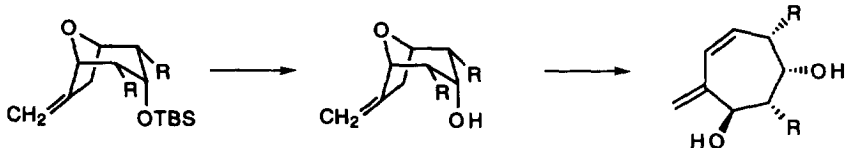
Treatment of **2** with 5.0 equivalents of *n*-BuLi in $Et_2O$ at 0 °C for 4 h or 10.0 equivalents of *t*-BuLi in $Et_2O$ at -78 °C to -40 °C for 8 h afforded the ring opened product **13** in 86% and 80% yields respectively.[10] The alternative reaction pathway, wherein addition of the alkyllithium to the exocyclic olefin would induce the ring opening and give **14**, was not observed (Scheme 2).[11]




**Scheme 2**

Reaction of **4** and **6** under identical conditions (*n*-BuLi or *t*-BuLi) gave complex mixtures of products. However, reaction of the alcohols **15** and **16** produced by treatment with $Bu_4NF$ in THF was much cleaner.

For example, treatment of **15** with 6.0 equivalents of *t*-BuLi in THF at -78 °C for 2 h gave **17** in 73% yield and reaction of **16** with 10.0 equivalents of *n*-BuLi in THF at -61 °C for 1 h gave **18** in 84% yield, eq. 1.



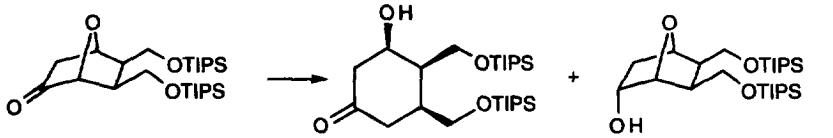
**4** R = H
**6** R = Me

**15** R = H
**16** R = Me

**17** R= H
**18** R = Me

(1)

Finally we should note that reductive ring opening of ketone **1** to cyclohexanone **19** has also been achieved in 72% yield in the presence of excess Li/$NH_3$, THF, -78 °C, 1 h. This transformation is closely related to that reported by De Clercq in the synthesis of precursor to 1α-hydroxyvitamin D. In their case samarium iodide was shown to induce the reduction of an oxabicyclic[2.2.1] ketone.[12] When we treated **1** with $SmI_2$ under various reaction conditions (with or without MeOH in THF, with or without HMPA added to THF), the best result obtained was a 28% of **19** accompanied by **20** (23%) and recovered starting material **1** (18%) (4.0 equivalent $SmI_2$, THF:MeOH 6:1, -90 °C, 1 h). Treatment of compound **1** with Na/Hg and $Na_2HPO_4$ in 1:1 THF:MeOH gave *endo* alcohol **20** exclusively (eq. 2). Unfortunately this methodology appears to be restricted to oxabicyclo[2.2.1]ketones since Li/$NH_3$ did not lead to ring opening in oxabicyclic ketones **3** or **5**.[13]



**1** **19** **20**

(2)

Both antipodes of the ketones and methyleneoxabicycles are readily available using the enantiomeric chiral boranes, which means that access to a variety of enantiomerically enriched methylenecyclohexenols and methylenecycloheptenediols is now in hand.

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6. (-)-$Ipc_2BH$ was synthesized according to Brown, H.C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945. For the hydroboration of oxabicyclic systems using achiral borane regents, see: a) Brown, H.C.; Vara Prasad, J.V.N. *J. Org. Chem.* **1985**, *50*, 3002. b) Rama Rao, A.V.; Yadav, J.S.; Vidyasagar, V. *J. Chem. Soc. Chem. Commun.* **1985**, 55.
7. Following completion of our work, several improvements in asymmetric hydrometallation have been reported. Hayashi described a very efficient route to compounds closely related to **8** in 90-95% ee using a Pd-MOP catalyzed enantioselective hydrosilylation-oxidation sequence, see: Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2335. Catalytic asymmetric hydroboration has also been reported, see: Schnyder, A.; Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 931 and references therein.
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9. Corey, E.J.; Mehrotra, M.M. *Tetrahedron Lett.* **1986**, *27*, 5173.
10. There are reports in the literature that strong bases such as NaOMe, LDA or $LiN(SiMe_3)_2$ deprotonate 7-oxabicyclo[2.2.]heptane-2-carboxylates or 7-oxabicyclo[2.2.1]hept-2-yl alkyl ketones and give ring opening products. a) Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299. b) Campbell, M.M.; Kaye, A.D.; Sainsbury, M. *Tetrahedron Lett.* **1983**, *24*, 4745. c) Van Royen, L.A.; Mijngheer, R.; De Clercq, P.J. *Tetrahedron Lett.* **1983**, *24*, 3145. d) Rajapaksa, D.; Keay, B.A.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 826. e) Campbell, M.M.; Kaye, A.D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron Lett.* **1984**, *25*, 1629. f) Ager, D.J.; East, M.B. *J. Chem. Research (S)* **1986**, 462. also see: Jung, M.E.; Street, L.J. *Tetrahedron Lett.* **1985**, *26*, 3639. Experimental procedure for the ring opening of compound **16**: To a stirred suspension of compound **16** (25 mg, 0.15 mmol) in THF (0.9 mL) at -61 °C was added *n*-BuLi (2.5 M, 0.60 mL, 1.49 mmol) dropwise. The mixture was stirred for 1 h and the reaction was quenched with sat. $NH_4Cl$ at same temperature. After warm to room temperature, the $H_2O$ layer was extracted with EtOAc and dried over $Na_2SO_4$. The crude product was purified by flash chromatography on silica gel (50% $Et_2O$ in hexanes) to afford 21 mg (84%) of **18** as viscous oil. $[\alpha]^{24}_D$ -120.5 (*c* 1.9, $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 6.08 (1H, ddm, $J$ = 11.7, 3.0 Hz), 5.34 (1H, dm, $J$ = 11.7 Hz), 5.21 (1H, s), 5.04 (1H, s), 4.01 (1H, m), 3.57 (1H, ddm, $J$ = 10.4, 4.4 Hz), 3.06 (1H, m), 2.10 (1H, qdd, $J$ = 7.3, 4.4, 3.0 Hz), 1.89 (1H, br s), 1.59 (1H, d, $J$ = 10.4 Hz), 1.18 (3H, d, $J$ = 7.5 Hz), 1.05 (3H, d, $J$ = 7.3 Hz).
11. For $S_N2'$ ring openings of oxabicyclic systems using alkyllithiums, see a) Arjona, O.; Fernandez de la Pradilla, R.; Garcia, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, *30*, 6437. b) Lautens, M.; Abd-El-Aziz, A.S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305. c) Arjona, O.; Fernandez de la Pradilla, R.; Mallo, A.; Plumet, J.; Viso, A. *Tetrahedron Lett.* **1990**, *31*, 1475.
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13. The reaction is messy, and the only isolated product was the *endo* oxabicyclic alcohol from the reduction of the carbonyl group.

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