Chelation-Controlled Reduction of α-Methylated 8-Oxabicyclo[3.2.1]oct-6-en-3-ones with Samarium Diiodide. Diastereoselective Preparation of Secondary Alcohols

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The title reduction has been effected with high stereocontrol using samarium diiodide in the presence of a proton source. It is concluded that chelation of samarium by the ether oxygen of the substrate directs and facilitates the reduction to equatorial alcohol.

The stereoselective reduction of cyclohexanones and their six-membered heteroanalogs to *equatorial* cyclohexanols is a problem which is far from trivial. There are numerous methods for preparing axial alcohols, taking advantage of bulky metal hydrides such as selectrides and DIBAH. In bridged bicyclic cyclohexanones such as 8-oxabicyclo[3.2.1]oct-6-en-3-ones the concave/convex directing effect tends to further enhance attack from the less hindered face, with potential formation of axial alcohol in high diastereomeric purity. Thus the reduction of a ketone to an axial alcohol is a consequence of substrate and reagent control. In contrast the preparation of equatorial alcohols, which are thermodynamically more stable than the axial epimers, has remained unsatisfactory.

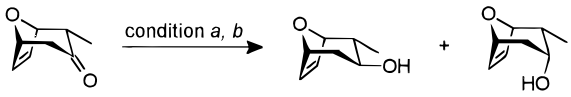
For preparing the equatorial alcohol in excess it is known to be advantageous to change the mechanism. The SET, radical anion route (e.g., Li, liquid NH_3, *t*-BuOH) with axial protonation of the intermediate anion tends to give equatorial alcohols predominantly.[1] We observed that either the diastereoselectivity was disappointing (condition *a*) or the chemical yield of alcohol was low (condition *b*) (Scheme 1).

Furthermore, the resulting epimeric alcohols are often known to be difficult to separate and the method frequently fails in total synthesis, for example, when dealing with small quantities of polyfunctional ketones.

A three-step conversion of ketone into equatorial alcohol *via* (i) axial alcohol, (ii) Mitsunobu inversion, and (iii) saponification[2] has therefore been used. The additional steps and problems of scale-up are, of course, a drawback. We now show that the title reduction is simple, efficient, and circumvents some of the previous difficulties.

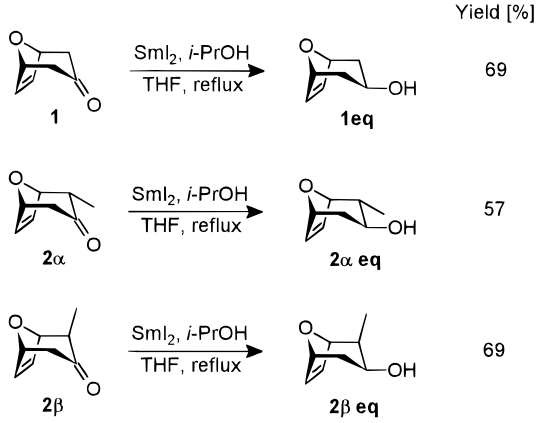
Results. 8-Oxabicyclo[3.2.1]oct-en-3-ones **1**, **3**, and **4** have been prepared by published procedures. Monomethylated ketones[3] **2**α and **2**β could not be separated. Therefore, diastereomerically pure axial **2**β was prepared by monomethylation of deprotonated parent ketone **1**.

Scheme 1



Conditions *a*: Li. liq. NH_3, THF, EtOH, -78 °C, 89%, ratio 1 : 2
b: Na, EtOH, reflux, 41%, ratio 4 : 1

Scheme 2



Equatorial ketone **2**α was obtained epimerically pure by reaction of 1,1,3,3-tetrabromo-2-butanone in the presence of $(EtO)_3B$/zinc followed by zinc/copper/NH_4Cl-mediated reduction of the brominated cycloaddition intermediate.[3] For the first time, oxabicyclic ketone **5** was also obtained epimerically pure by stereocontrolled axial monomethylation of geminally dimethylated ketone **4**. The preparation of tetramethylated ketone **6** has been improved and simplified, using the NaI/Cu procedure.

SmI_2-mediated reduction for the parent oxabicycle **1** and the monomethylated α- and *β*-derivatives (**2**α, **2**β) in the presence of 2-propanol was completely diastereoselective (Scheme 2). No axial alcohol was detected.

Dimethylated oxabicyclic ketones reacted differently. α,α′-Dimethylated oxabicycle **3** was reduced easily in high chemical yield and gave the equatorial epimer **3eq** in

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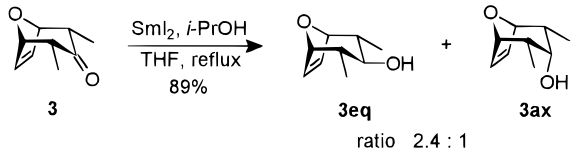
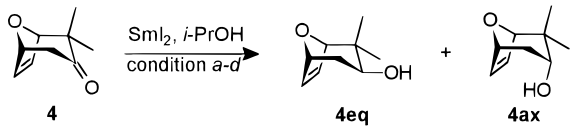
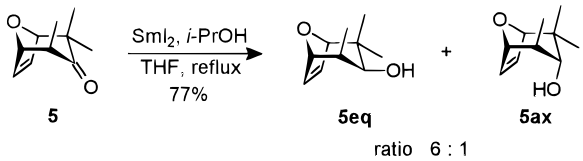
Scheme 3



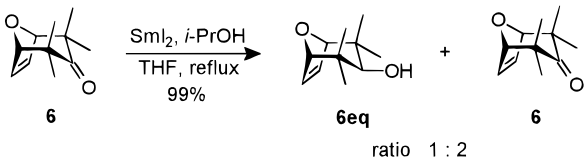


Conditions *a*: THF, reflux, 79%, ratio 2 : 1
b: THF, reflux to 50 °C to reflux, 70%, ratio 3 : 1
c: THF, r.t. to 40 °C to reflux, 41%, ratio 4 : 1
d: THF, ultrasound, 0 °C to 25°C to 40 °C, 57%, ratio 3 : 1

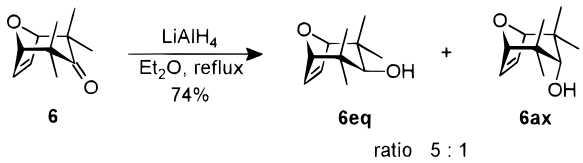
Scheme 4



Scheme 5



Scheme 6



excess (**3eq**:**3ax** = 2.4:1) (Scheme 3). Oxabicycle **4** with its geminal dimethyl group provided only an inseparable mixture of equatorial **4eq** and axial alcohol **4ax**.

Trimethylated bicycle **5** reacted smoothly with SmI_2, giving equatorial **5eq** and axial alcohol **5ax** not only in good yield but also as a separable mixture (6:1) (Scheme 4).

No doubt due to steric hindrance, reduction of ketone **6** was sluggish. Interestingly, the equatorial epimer **6eq** was formed exclusively in addition to recovered starting material (Scheme 5). Unfortunately, starting ketone **6** and product alcohol **6eq** were not separable by chromatography.

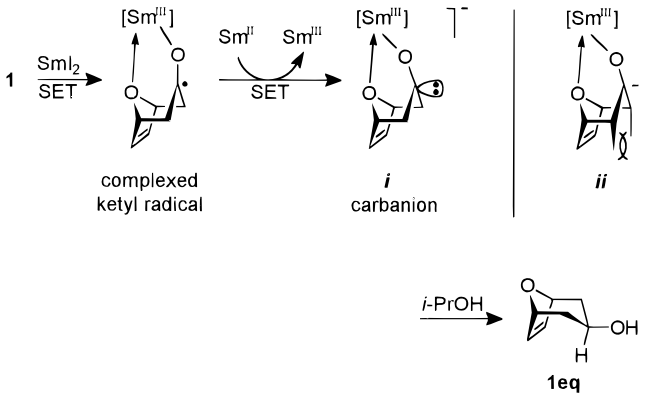
As a control on the stereochemistry of this reaction, we reduced ketone **6** under conventional conditions with $LiAlH_4$. In this case, equatorial alcohol **6eq** also predominated clearly over the axial epimer **6ax** (5:1) (Scheme 6).

Assignment of Axial and Equatorial Alcohols. For the oxabicyclic alcohol **2**α**eq** we performed NOE experiments to elucidate the configuration at C-3. Another hint for the configuration at C-3 is provided by the characteristic vicinal coupling ^3J between the protons H-4/H-2 and H-3. The equatorial epimer shows $^3J_{aa} = 10-13$ Hz ($\phi = 180°$), while the axial epimer has $^3J_{ee/ae} = 2-5$ Hz ($\phi = 60°$). The signals of the olefinic protons H-6 and H-7 for the axial epimer showed a significant downfield shift. We have previously found a similar difference for bicyclo[3.2.1]oct-6-en-3-ols[1c] and attribute the downfield shift to intramolecular hydrogen bonding

Table 1. ^{13}C and IR Data for Ketones 1−6

ketone	**1**	**2**α	**2**β	**3**	**4**	**5**	**6**
IR [cm^{-1}]	1713	1713	1714	1713	1709	1704	1700
^{13}C [ppm]	205.3	207.3	209.4	208.9	210.6	215.6	217.5

Discussion. The high diastereoselectivity of the SmI_2-promoted reduction, especially for the parent oxabicycle **1** and also for monomethylated derivatives **2**α and **2**β, is a consequence of chelation of samarium by the ether oxygen[4] of the oxabicycle. The oxacyclic six-membered moiety of the postulated intermediate anion assumes a boat-like conformation (**i**) and directs protonation to the endo face.



In ketone **3** the analogous complex places the methyl groups into a conformationally unfavorable, quasi-axial position (**ii**). Thus, of all oxabicycles investigated by us, ketone **3** is the least favored candidate for a diastereoselective reduction. However, even in this case the equatorial epimer **3eq** predominates by a factor of 2.4:1. For sterically hindered ketone **6** SmI_2-reduction furnishes **6eq** exclusively, although the reduction is incomplete and the product cannot be separated from the educt. In this instance, even $LiAlH_4$ reduction provides the equatorial epimer predominantly (**6eq**:**6ax** = 5:1). We suggest that a change in ground state conformation of the starting oxabicyclic ketone **6** is responsible. Spectroscopic data on the series of ketones **1**−**6** show that the IR carbonyl stretching frequency drops progressively with increasing methylation, from 1713 cm^{-1} for **1** to 1700 cm^{-1} for ketone **6**. Clearly, the six-membered oxacyclic ketone moiety flattens progressively from **1** to **6** (conversely, the ^{13}C carbonyl signal shifts in the opposite direction, Table 1). For tetramethylated ketone **6** flattening has proceeded to such an extent that endo attack is very much preferred, irrespective of the mechanism, i.e., hydride ion attack by $LiAlH_4$ and also SET path.

Conclusions. We have reduced 8-oxabicyclo[3.2.1]oct-6-en-3-ones to equatorial alcohols with high diastereoselectivity using SmI_2. The SET, radical anion pathway together with chelation of samarium is thought to be responsible for these favorable results. Oxidation of the axial alcohol to ketone allows recycling of the undesired epimer. For example, *cis*-dimethylated alcohol **3ax** is

oxidized readily with PCC to yield ketone **3** (71%). 8-Oxabicyclo[3.2.1]oct-6-en-3-ols are valuable building blocks in stereoselective natural products synthesis.[5a−d]

Experimental Section

General Remarks. APT (attached proton test): spin echo-based selection of multiplicities of ^{13}C signals. Quaternary C and CH_2 carbon atoms give positive signals (+), while CH and CH_3 give negative signals (−). Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30−60 μm). Analytical TLC was carried out on aluminum-backed 0.2-mm silica gel 60 F_{254} plates (E. Merck). All reactions were carried out under nitrogen in dried glassware.

General Procedure for the Reduction with SmI_2.[6] A 25-mL two-necked flask equipped with gas inlet and reflux condenser was charged with Sm (740.5 mg, 4.93 mmol) and diiodoethane (1.11 g, 3.94 mmol). The reaction apparatus was alternately evacuated with an oil pump and flushed with N_2. Then the mixture was cooled to 0 °C, and 10 mL of THF was added slowly under a stationary atmosphere of N_2. The mixture was stirred for 10 min at 0 °C and 10 min at rt and heated to reflux, while the color of the solution turned to dark blue. The ketone (300 mg, 1.97 mmol) was mixed with 1 equiv of 2-propanol (0.15 mL, 1.97 mmol) and dissolved in 5 mL of THF. The mixture was added slowly to the refluxing SmI_2 solution.

After complete reaction and cooling to rt, the still dark blue reaction mixture was treated with distilled H_2O and 1 N HCl. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was freed from iodine by treatment with saturated aqueous $Na_2S_2O_3$ solution and dried ($MgSO_4$). After removal of the solvent, the crude product was chromatographed.

8-Oxabicyclo[3.2.1]oct-6-en-3-ol (1eq). Oxabicyclic ketone **1** (300 mg, 2.4 mmol) was allowed to react according to the general procedure to afford after 3 h **1eq** (210 mg, 69%), yellowish crystals: mp 34 °C; IR (KBr) ν 3644, 3296 cm^{-1}; ^1H NMR δ 6.11 (s, 2 H, H-6, H-7), 4.81 (d, J = 3 Hz, 2 H, H-1, H-5), 3.95−3.8 (m, 1 H, H-3), 2.48 (br s, 1 H, OH), 1.96−1.89 (m, 2 H, H-2 (eq), H-4 (eq)), 1.66−1.55 (m, 2 H, H-2 (ax), H-4 (ax)); ^{13}C NMR δ 130.88 (C-6, C-7), 78.04 (C-5, C-1), 63.95 (C-3), 35.55 (C-2, C-4); MS m/z 127 ($M^+ + 1$, 2), 126 (M^+, 14), 82 (100); HRMS calcd for $C_7H_{10}O_2$ 126.0681, found 126.0681.

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Supporting Information Available: Preparation and spectroscopic data for ketones **1, 2**α, **2**β, **3**, **4**, **5**, and **6** and alcohols **2**α**eq**, **2**β**eq**, **3eq**, **3ax**, **4eq**, **4ax**, **5eq**, **5ax**, **6eq**, and **6ax** and table with comparative NMR signals of equatorial and axial alcohols (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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