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Determination of the Protons Eliminated in the Regioselective Deprotonation of Some Optically Active 3-Keto Steroids by a Chiral Lithium Amide

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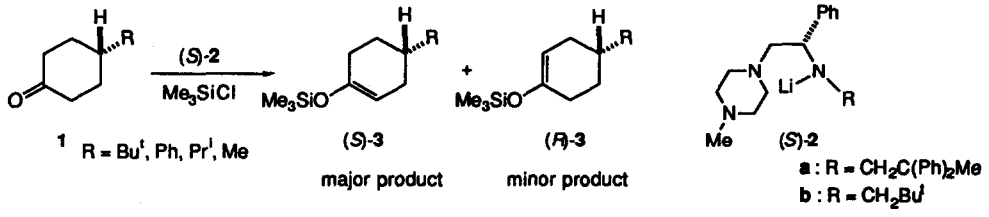
Abstract: Mono-deuterated derivatives of optically active 3-keto steroids (**4**-2α-d, **4**-2β-d, **5**-4α-d, **5**-4β-d, **6**-2α-d, and **6**-2β-d) were treated with a chiral lithium amide ((*S*)- or (*R*)-**2b**) in the presence of excess trimethylsilyl chloride to give the corresponding diastereomeric Δ^2- and Δ^3-silyl enol ethers. It is concluded that the present deprotonation reaction occurs in chair conformation in **6**, while in boat (skew-boat) conformation about the A-rings in **4** and **5**.

We have previously reported that kinetic deprotonation of prochiral 4-substituted cyclohexanones (**1**) by chiral lithium amides ((*S*)- or (*R*)-**2**) in the presence of excess trimethylsilyl chloride occurs enantioselectively to give the corresponding trimethylsilyl enol ethers ((*S*)- or (*R*)-**3**) in reasonably high enantiomeric excesses.[2] The stereochemical course of this reaction was found to be generalized as shown in Scheme 1.



1 R = Bu^t, Ph, Pr^i, Me

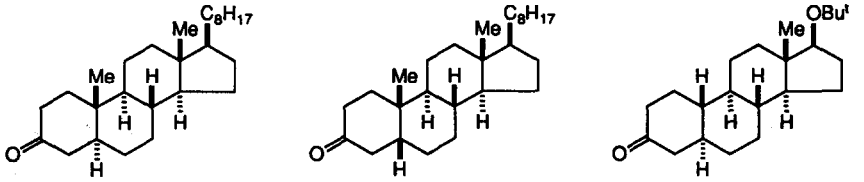
(*S*)-**3** major product

(*R*)-**3** minor product

(*S*)-**2**
a : R = $CH_2C(Ph)_2Me$
b : R = CH_2Bu^t

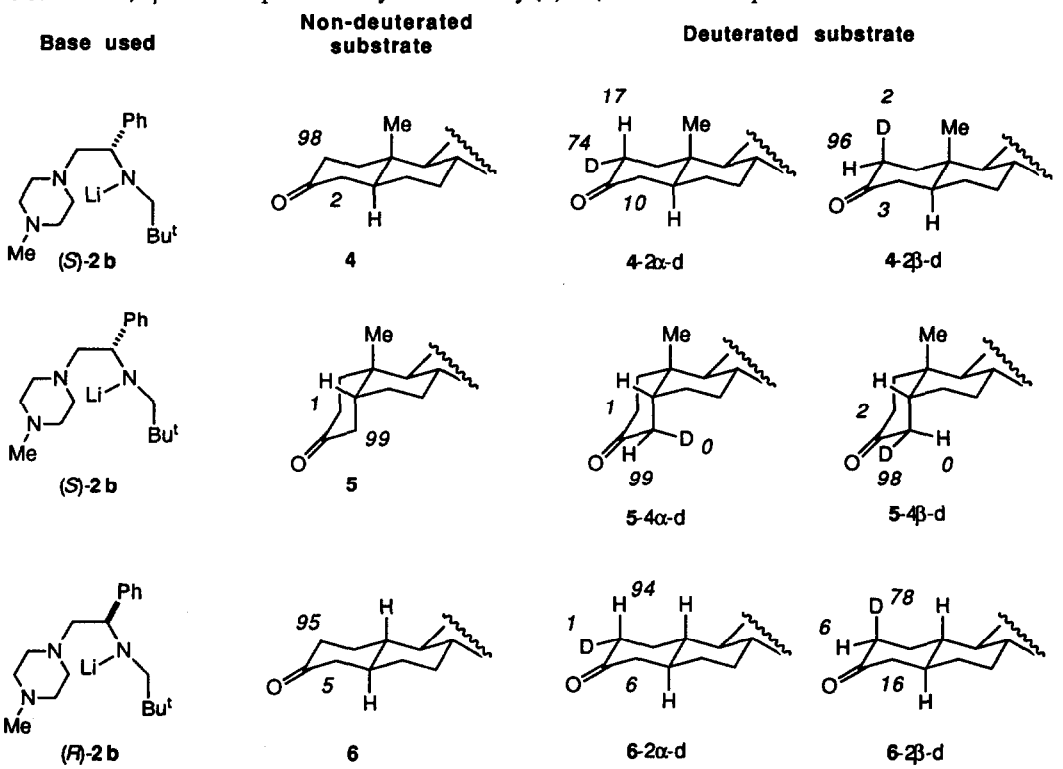
Scheme 1

Selective conversion of an unsymmetrical ketone to either of the two possible regioisomeric enolates plays a valuable and basic role in synthesis. By the same strategy using either enantiomer of **2**, regioselective enolization of optically active 3-keto steroids (**4**, **5**, **6**) was also realized to give Δ^2- or Δ^3-isomers of trimethylsilyl enol ethers in reasonably high selectivities.[3] Some results are shown in Scheme 3. However, in the reactions of **4** and **5**, the sense of regioselectivity is opposite to that predicted from the reaction of **1** shown in Scheme 1, while it is the same as the reaction of **6**. This interesting phenomenon is parallel to the fact that, taking A-rings of these optically active 3-keto steroids as cyclohexanone derivatives in chair conformation, **4** and **5** have an axial carbon substituent at 4-position (cyclohexanone numbering), while **6** has an axial hydrogen there.



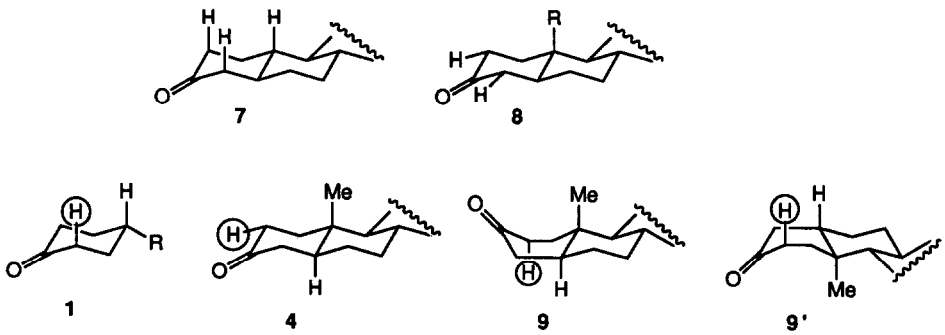
Scheme 2

To determine which protons are actually eliminated in the present deprotonation reaction, optically pure mono-deuterated steroidal ketones (4-2α-d,[4a] 4-2β-d,[4b] 5-4α-d,[4c] 5-4β-d,[4d] 6-2α-d,[4e] and 6-2β-d[4f]) were prepared[5,6] and were subjected to the same reaction condition using **2b** as a base.[7] Some results are summarized in Scheme 3. The numbers written in italics in the structures indicate the actual ratios of eliminated proton or dueteron determined by ^{1}H NMR spectra of the resulting silyl enol ethers.[8] It is thus shown that 2α-H in **4** and 4β-H in **5** are preferentially eliminated by (*S*)-**2b**, and are equatorial protons in their chair conformations. On the other hand, 2β-H in **6** is preferentially eliminated by (*R*)-**2b**, and is an axial proton in chair conformation.



Scheme 3

Evaluating the stereoelectronic effect in deprotonation reaction, which states that carbon-hydrogen σ-bond should be parallel to the carbonyl π-bond for the hydrogen to be eliminated,[9] the results suggest that deprotonation occurs in boat (skew-boat) conformation in **4** and **5**, while it occurs in chair conformation in **6**. This means that, for the present deprotonation reaction, cyclohexanone derivatives should be classified into two groups as substrates. One group is those represented by **7**, which carries an axial hydrogen at 4-position (cyclohexanone numbering) in chair conformation. 4-Substituted cyclohexanones (**1**),[2a,c] 2-substituted cyclohexanones,[10] cis-3,5-disubstituted cyclohexanones,[2b] cis-2,6-disubstituted cyclohexanones,[2b] and **6**[3] belong to this group. In these cyclohexanones, deprotonation by elimination of axial hydrogens in chair conformation predominates. The other group is those represented by **8**, which carries an axial carbon substituent at 4-position (cyclohexanone numbering) in chair conformaiton. Steroidal ketones (**5**, **6**) belong to this group. In these cyclohexanones, elimination of equatorial protons in chair conformation predominates via boat (skew-boat) conformation to satisfy the stereoelectronic requirement.



Scheme 4

Examples using (*S*)-**2** as a base are shown in Scheme 4. Deprotonation of **1** gives (*S*)-**3** as a major product.[3] It is reasonable to assume that the axial proton circled in structure (**1**) is eliminated preferentially. In deprotonation of **4**, it is shown that the equatorial proton circled in structure (**4**) is eliminated preferentially. By changing the conformation of the A-ring from chair (**4**) to boat (skew-boat) (**9**), the circled proton now satisfies the stereoelectronic requirement to be eliminated. Structure (**9'**) is obtained by drawing **9** upside down. It is now clear that (*S*)-**2** abstracts the circled proton in **1**, and the circled proton in **9'**. In this way, the stereochemical sense for the present deprotonation reaction using **2** discussed so far is now generalized.

References and Notes

1. Present Address: Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., Kawagishi, Toda-shi, Saitama 335, Japan.
2. (a) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543. (b) Kim, H.-D.; Shirai, R.; Kawasaki, H.; Nakajima, M.; Koga, K. *Heterocycles* **1990**, *30*, 307. (c) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761.
3. Sobukawa, M.; Nakajima, M.; Koga, K. *Tetrahedron:Asymmetry* **1990**, *1*, 295.

4. Deuterium contents were determined by ^{1}H NMR spectra. (a) 2α-d:2β-d=95:5; (b) 2β-d:2αβ-h_2=99:1; (c) 4α-d:4αβ-h_2=98:2; (d) 4β-d:4α-d:4αβ-h_2=94:2:4; (e) 2α-d:2β-d:2αβ-h_2=78:20:2.
5. Preparation of these mono-deuterated derivatives were carried out by the reported methods[6] or their modifications.
6. (a) Cookson, R. C.; Hamon, D. P. G.; Parker, R. E. *J. Chem. Soc.* **1962** 5104; (b) Valente, C.; Eadon, G. *J. Org. Chem.* **1984**, *49*, 44.
7. A typical experimental procedure (reaction of **4**-2β-d using (*S*)-**2b** in Scheme 3) is as follows. Under argon atmosphere, a solution of n-butyllithium in hexane (1.62 M solution) (0.49 ml, 0.8 mmol) was added to a solution of (*S*)-**2b** (232 mg, 0.8 mmol) in toluene (4 ml) at -78°C, and the resulting solution was stirred for 15 min. After addition of HMPA (0.14 ml, 0.8 mmol), the resulting solution was warmed to room temperature and then re-cooled to -78°C. To this solution was added TMSCl (0.26 ml, 2.0 mmol) in toluene (1 ml), and then a solution of **4**-2β-d[4b] (155 mg, 0.4 mmol) in toluene (5 ml) dropwise during 3 min, and the whole was stirred at -78°C for 20 min. After addition of triethylamine (1 ml) and saturated aqueous sodium bicarbonate (10 ml), the reaction mixture was allowed to warm to room temperature under stirring. Usual work-up using hexane as an extracting solvent gave a crude product, which was subjected to column chromatography (silica gel (5 g), benzene-hexane (1:1)) to isolate a mixture of Δ^2- and Δ^3-regioisomers (181 mg, 98.5 %). ^{1}H NMR spectrum of this sample in C_6D_6 shows olefinic protons at δ 4.92 (Δ^2-isomer) and at δ 4.71 (Δ^3-isomer). Integration of these signals using the signal of the protons of trimethylsilyl group as 9 H, the former signal (Δ^2-isomer) corresponds to be 0.028 H, and the latter signal (Δ^3-isomer) corresponds to be 0.029 H. Therefore, the experimental ratio of the eliminated protons is 94.3:2.8:2.9 for 2α-h, 2β-d, and 3αβ-h_2, respectively, and the corrected[8] ratio is 95.6:1.5:2.9.
8. Data were obtained after correction for the deuterium contents of the substrates.[4] No corrections were made for the deuterium isotope effect.
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