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ENANTIOSELECTIVE REDUCTION OF KETONES WITH (+)-(1R,4S)-3-EXO-ANILINO-2-EXO-HYDROXYBORNANE-LITHIUM ALUMINIUM HYDRIDE COMPLEX

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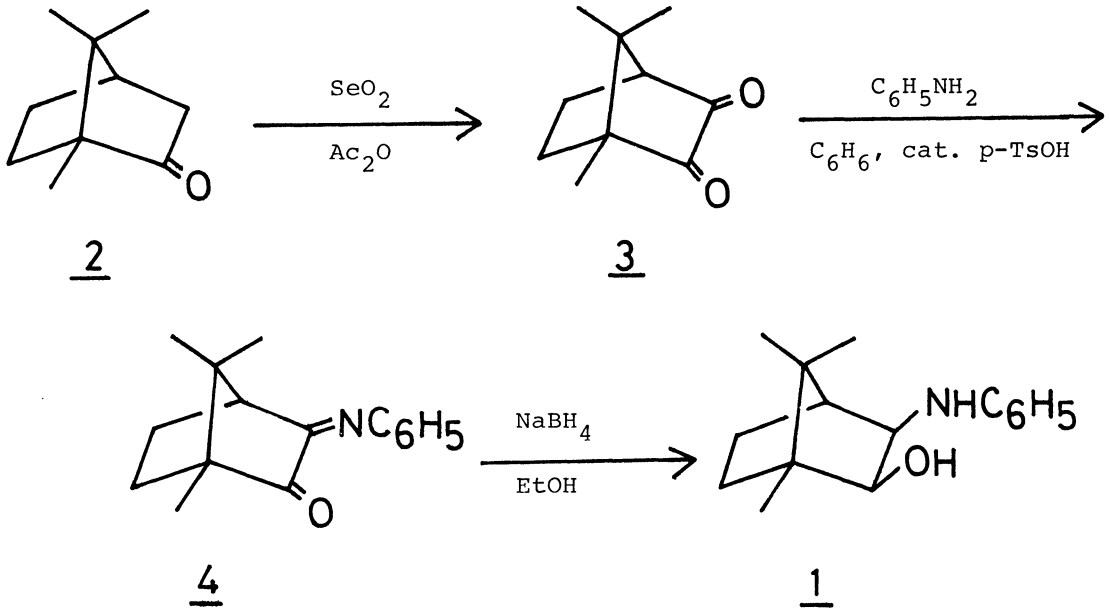
(+)-(1R,4S)-3-Exo-anilino-2-exo-hydroxybornane (1) was synthesized in moderate yield in three steps from commercially available (+)-camphor. Asymmetric reduction of prochiral ketones such as acetophenone, propiophenone, and butyrophenone with the chiral hydride reagent prepared from 1 and lithium aluminium hydride gave optically active alcohols having the R-configuration in 26-43% e.e.

Asymmetric reduction of carbonyl compounds with chiral metallic hydride complexes has been reported.[1] In particular, chiral lithium aluminium hydride complexes obtained by the reaction of lithium aluminium hydride with chiral agents such as alkaloids,[2] sugar derivatives,[3] amino alcohols,[4,5] oxazolines,[6] and diamines[7] reduced acetophenone in high optical yields. On the other hand, (+)-camphor-10-sulfonic acid having the bornane skeleton is widely used to resolve racemic amines and amino acids, and bornane skeleton is considered to be useful for asymmetric synthesis and induction. We have synthesized a new chiral amino alcohol, (+)-(1R,4S)-3-exo-anilino-2-exohydroxybornane (1) and applied its lithium aluminium hydride complex to the enantioselective reduction of ketones.[8]

From readily available (+)-camphor, 1 was easily prepared as follows: (+)-Camphor (2) was converted to (-)-(1R,4S)-2,3-bornanedione (3) [83%, mp 200.5-202°C, $[\alpha]_{589}^{28}$ -108.3° (c 1.86, $CHCl_3$)] by oxidation with SeO_2 in acetic anhydride.[9] It was then condensed with aniline by azeotropic distillation of water formed from a benzene solution containing a small amount of p-toluenesulfonic acid as catalyst to give (+)-(1R,4S)-3-phenyliminobornan-2-one (4) in 93% yield [mp 108-109°C, $[\alpha]_{589}^{30}$ +704.9° (c 0.70, $CHCl_3$)].[10] Reduction of 4 with sodium borohydride in absolute

alcohol[11] followed by the purification of the crude product by column chromatography on silica gel gave 1[12] in 74% yield [bp 159-162°C / 0.35 Torr, $[\alpha]_{589}^{27.5}$ +46.3° (c 1.91, $CHCl_3$)].



2 3 4 1

Asymmetric reduction of ketones was carried out using 1-$LiAlH_4$ complex, and the effects of temperature and ratio of reactants upon the enantioselectivity in the reduction were examined. The results are summarized in the Table.

The molar ratio of 1 to $LiAlH_4$ was found to affect optical yield, namely, optical yield was improved when the molar ratio increased from 1.0:1.0 to 1.1:1.0. Moreover, by lowering the reaction temperature from -78°C to -98°C, optical yield increased slightly.

A general procedure for the reduction is as follows; to an ethereal solution of $LiAlH_4$ (4.0 mmol)[15] was added dropwise 1 (1080 mg, 4.4 mmol) in ether (8 ml) over 30 min at room temperature under an argon atmosphere. Hydrogen evolution was completed after stirring for 1 hr. Then the solution was cooled to -78°C to form a white precipitate. Ketone (2.0 mmol) in ether (5 ml) was added to the suspension. After stirring for 2-3 hr at -78°C, the mixture was treated with water (0.5 ml), followed by 4N HCl (100 ml), and ethereal layer was washed with sat. NaCl solution. The oily product obtained from the ethereal solution was purified by thin layer chromatography (developed with CH_2Cl_2) followed by bulb to bulb distillation.

The structure of 1-$LiAlH_4$ complex was not studied.

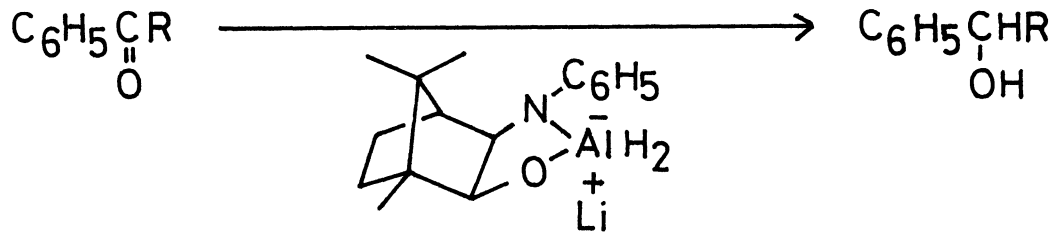


Table Reduction of ketones with 1-$LiAlH_4$ Complex

Run	R	Molar Ratio			Reduction	Alcohol			
		$LiAlH_4$	1	Ketone	Temp.(°C)	Yield(%)	$[\alpha]_{589}$(°)	e.e.	Config.
1	CH_3	2.0	2.0	1.0	-78	80	+13.2[a]	31[f]	R
2	CH_3	2.0	2.2	1.0	-78	89	+16.5[b]	38[f]	R
3	CH_3	2.0	2.2	1.0	-98	94	+18.4[c]	43[f]	R
4	C_2H_5	2.0	2.2	1.0	-78	87	+11.9[d]	26[g]	R
5	n-C_3H_7	2.0	2.2	1.0	-78	82	+11.5[e]	26[h]	R

a) (c 7.28, cyclopentane) b) (c 8.07, cyclopentane) c) (c 7.38, cyclopentane) d) (c 5.15, $CHCl_3$) e) (c 4.24, C_6H_6) f) Based on $[\alpha]_{589}^{20}$ -43.1° (c 7.19, cyclopentane)[4] g) Based on $[\alpha]_{589}$ 45.45° (c 5.15, $CHCl_3$)[13] h) Based on $[\alpha]_{589}^{20}$ +43.6° (c 4.18, C_6H_6)[14]

References and Notes

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8) It was mentioned that $LiAlH_4$ complex with (1R,4S)-3-endo-anilino-2-exo-hydroxybornane or (1R,4S)-3-endo-anilino-2-hydroxynorbornane was used in the asymmetric reduction of (-)- and (+)-dehydropestalotin, but the detail is ambiguous. E. L. Eliel and N. L. Allinger, "Topics in Stereochemistry" Vol. 10, John Wiley & Sons, N. Y., 1978, pp. 207, 208.

9) Lit. mp 198°C, $[\alpha]_{589}$ -110° (c 1.9, $CHCl_3$). A. Marquet, M. Dvolaitzky, and D. Arigoni, Bull. Soc. Chim. Fr., 1966, 2956.

10) Lit. mp 109°C, $[\alpha]_{589}$ +726° ($CHCl_3$). M. O. Forster and T. Thornlly, J. Chem. Soc., 95, 942 (1909). NMR($CDCl_3$) δ= 0.90 (s, 3H), 0.97 (s, 3H), 1.09 (s, 3H), 1.40-2.37 (m, 4H), 2.83 (d-d, 1H, J= 1 Hz and J'= 4 Hz), and 6.81-7.10 (m, 5H).

11) Reduction with $LiAlH_4$ gave nearly equal amounts of 2-exo,3-exo and 2-exo,3-endo isomers of 3-anilino-2-hydroxybornane. The determination of the stereochemistry was made on NMR spectra.

12) NMR($CDCl_3$) δ= 0.76 (s, 3H, 9-Me), o.91 (s, 3H, 10-Me), 1.06 (s, 3H, 8-Me), 1.17-1.89 (m, 5H), 3.26 (d, 1H, J= 7.5 Hz, 2-H), 3.66 (d, 1H, J= 7.5 Hz, 3-H), 3.68 (br s, 2H, OH and NH), and 6.43-7.33 (m, 5H, Ph).

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