Asymmetric Reduction of αβ-Unsaturated Ketones with Lithium Aluminium Hydride Partially Decomposed by (−)-*N*-Methylephedrine and *N*-Ethylaniline

By SHIRO TERASHIMA,* NORIHIKO TANNO, and KENJI KOGA
(*Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo* 113, *Japan*)

Summary The title asymmetric reaction is found to convert open chain enones into the corresponding optically active allylic alcohols in high optical (78—98% enantiomeric excess) and chemical (92—100%) yields

ASYMMETRIC reductions of achiral ketones with lithium aluminium hydride partially decomposed with various chiral compounds have been extensively studied in recent years [1] While high optical yields have been achieved in the asymmetric reductions of aryl alkyl ketones[2] and acetylenic ketones,[3] the number of methods which afford highly optically active allylic alcohols from αβ-unsaturated ketones (**1**) seems to be quite limited [3a,4]

In our studies on the asymmetric synthesis of optically active anthracyclinones,[5] we found that the hydride originally prepared by the partial decomposition of lithium aluminium hydride with (−)-*N*-methylephedrine and *N*-ethylaniline served as an excellent reducing agent † Thus, the asymmetric reduction of (**1a**) proceeded in a highly stereoselective manner, giving (**1c**), 92% enantiomeric excess (e e), in an almost quantitative yield (see the Table) Since the allylic alcohols (Table) are considered to be quite versa-

TABLE Asymmetric reduction of αβ-unsaturated ketones [a]

αβ-Unsaturated ketones	Alcohol	Optically active allylic alcohols Chemical yield/%[b]	Observed optical rotation/°[c]	Optical yield/% e e	Absolute configuration
(**1a**)	(**1c**)	94[d]	$[\alpha]_{D}^{20}$ −18 9 (*c* 1 77, EtOH)	92[e]	*S*[e]
(**1b**)	(**1d**)	100	$[\alpha]_{D}^{19}$ −33 5 (*c* 5 04, $CHCl_3$)	>90[f]	*S*[g]
(**2a**)	(**2b**)	92	$[\alpha]_{D}^{20}$ −9 8 (*c* 4 25, $CHCl_3$)	78[h]	*S*[h]
(**3a**)	(**3c**)	100	$[\alpha]_{D}^{19}$ +11 1 (*c* 4 40, $CHCl_3$)	>90[f]	—[i]
(**3b**)	(**3d**)	98	$[\alpha]_{D}^{20}$ −24 5 (*c* 5 16, $CHCl_3$)	98[j]	*S*[k]
(**4a**)	(**4b**)	92	$[\alpha]_{D}^{20}$ −8 2 (*c* 3 58, $CHCl_3$)	88[l]	*S*[l]
(**5a**)	(**5d**)	58	$[\alpha]_{577}^{20}$ −52·5 (*c* 2 14, CH_2Cl_2)	32[m]	*S*[m]
(**5b**)	(**5e**)	51	$[\alpha]_{D}^{20}$ −70 2 (*c* 1 41, $CHCl_3$)	58[f]	—[i]
(**5c**)	(**5f**)	88	$[\alpha]_{D}^{20}$ −32 9 (*c* 4 08, $CHCl_3$)	24[f]	—[i]

[a] All reactions were carried out using lithium aluminium hydride (3 3 equiv) partially decomposed with (−)-*N*-methylephedrine (3 4 equiv) and *N*-ethylaniline (6 8 equiv) in ether at −78 °C for 3 h All the reaction products gave satisfactory i r and n m r spectra [b] Calculated on the sample purified by preparative t l c [c] Measured using samples purified successively by preparative t l c and bulb-to-bulb distillation (except for (**1c**) see ref 5) [d] See ref 5 [e] Optically pure (*S*)-(−)-alcohol gives $[\alpha]_{D}^{20}$ −20 5° (*c* 1 07 EtOH, see ref 5) [f] Determined by measuring the n m r spectrum in the presence of $Eu(hfc)_3$ [g] Tentatively assigned by considering the result for the asymmetric reduction of (**1a**) [h] Catalytic hydrogenation of (**2b**) over a platinum catalyst afforded (*S*)-(+)-1-cyclohexylethanol (see table footnote k) which gave α_{D}^{20} +0 408° (l = 0 1 neat) Since optically pure (*S*)-(+)-1-cyclohexylethanol has been reported to give $[\alpha]_{D}^{20}$ + 5·68° (neat), d_{4}^{20} 0 9254 (A Domleo and J Kenyon, *J Chem Soc* , 1926 **128** 1841), the optical yield and absolute configuration of (**2b**) were determined as 78% e e and (*S*), respectively [i] The absolute configuration of this sample could not be determined owing to the lack of a reference compound [j] Based on $[\alpha]_{D}^{20}$ + 24 7° (*c* 5 000, $CHCl_3$) (J Kenyon S M Partridge, and H Phillips, *J Chem Soc* , 1936 85) [k] J Jacques, C Gros, and S Bourcier, Absolute Configurations of 6000 Selected Compounds with One Asymmetric Carbon Atom, in 'Stereochemistry, Fundamentals and Methods,' ed H B Kagan Georg Thieme Publishers Stuttgart 1977, Vol 4, pp 220, 224, and 228 [l] For the determination of the optical yield and absolute configuration of (**4b**), (**4b**) was subjected to catalytic hydrogenation over a platinum catalyst, giving (*S*)-(+) heptan-2 ol, (see table footnote k) $[\alpha]_{D}^{20}$ + 6 9° (*c* 7·50,EtOH) Since optically pure (*S*)-(+)-heptan-2-ol has been reported to give $[\alpha]_{D}^{20}$ + 7 8° (*c* 12 0, EtOH) (J C Craig and S K Roy, *Tetrahedron*, 1965, **21**, 1847), the optical yield and absolute configuration of (**4b**) were determined as 88% e e and (*S*), respectively [m] (*R*)-(+)-cyclohex-2-enol, 13% e e , was reported to give $[\alpha]_{578}^{rt}$ + 21° (CH_2Cl_2) (H Wynberg and B. Marsman, *J Org Chem* , 1980, **45**, 158)

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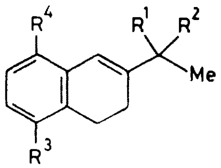
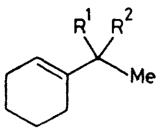
† Detailed examinations of achiral additives, *N*-alkyl substituents of (−)-*N*-alkylephedrines, reaction solvents, and reaction temperatures were carried out for the reduction of (**1a**) See ref 5

tile as optically active synthetic blocks, the asymmetric reduction of various structural types of enones with this new reagent is of interest.



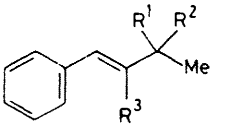
(1)

a, R^1,R^2 = O, R^3 = R^4 = OMe
b, R^1,R^2 = O, R^3 = R^4 = H
c, R^1 = ◀OH, R^2 = ---H, R^3 = R^4 = OMe
d, R^1 = ◀OH, R^2 = ---H, R^3 = R^4 = H



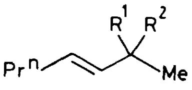
(2)

a, R^1,R^2 = O
b, R^1 = ◀OH, R^2 = ---H



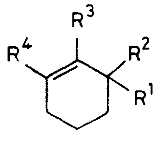
(3)

a, R^1,R^2 = O, R^3 = Me
b, R^1,R^2 = O, R^3 = H
c, R^1 = ◀OH, R^2 = ---H, R^3 = Me
d, R^1 = ◀OH, R^2 = ---H, R^3 = H



(4)

a, R^1,R^2 = O
b, R^1 = ◀OH, R^2 = ---H



(5)

a, R^1,R^2 = O, R^3 = R^4 = H
b, R^1,R^2 = O, R^3 = Me, R^4 = H
c, R^1,R^2 = O, R^3 = H, R^4 = Me
d, R^1 = ◀OH, R^2 = ---H, R^3 = R^4 = H
e, R^1 = ◀OH, R^2 = ---H, R^3 = Me, R^4 = H
f, R^1 = ◀OH, R^2 = ---H, R^3 = H, R^4 = Me

We report here that, amongst the enones examined, (**1b**), (**2a**), (**3a**), (**3b**), and (**4a**), which have similar structural characteristics to those of (**1a**), can be efficiently reduced by the novel chiral hydride to give (**1d**), (**2b**), (**3c**), (**3d**), and (**4b**), respectively, in high optical and chemical yields. The cyclic enones (**5a**), (**5b**), and (**5c**) are not as efficiently reduced as the open chain enones (**1a**), (**1b**), (**2a**), (**3a**), (**3b**), and (**4a**) which may have the *S-cis*-conformation due to C–CO bond rotation (see the Table).‡ To evaluate our reducing agent the asymmetric reduction of (**3b**) was further attempted by employing some reported chiral hydrides. Thus, treatment of (**3b**) with lithium aluminium hydride partially decomposed by (−)-*N*-methylephedrine- and 3,5-dimethylphenol[2b,3b] or by (*S*)-2-anilinomethylpyrrolidine[2c] gave (**3d**) in less than 7% or 75% chemical yields, respectively. The optical yield of (**3b**) obtained by using the latter reagent[2c] was found to be 36% e.e.

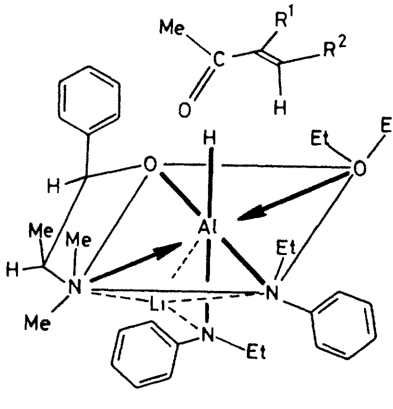


FIGURE. R^1 = H or alkyl; R^2 = aryl or alkyl.

Previously it was reported that the asymmetric reduction of simple achiral aryl alkyl ketones with the above chiral reagent gave similar high optical and chemical yields of the corresponding (*S*)-1-alkylbenzyl alcohols.[2e] Considering the absolute configurations and optical yields of the optically active alcohols obtained in this and the previous studies,[2e] the structure in the Figure might be tentatively assumed as one of the most likely transition states in the asymmetric reduction.

Asymmetric reduction with the chiral hydride developed by us is anticipated to be useful for practical asymmetric syntheses because of various novel aspects including its high optical and chemical yields, operational simplicity, use of readily available chiral source and additive, and so on. Further applications of our reducing agent to various asymmetric reductions are in progress.

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‡ The asymmetric reduction of an acetylenic ketone was attempted using hept-1-yn-3-one as a reduction substrate. In this case, (*S*)-(−)-hept-1-yn-3-ol, $[\alpha]^{25}_{D}$ −15·6° (*c* 3·16, dioxan), 76% e.e., (see ref. 3b) was obtained in 88% yield. The observed optical yield was slightly lower than those reported (see ref. 3).

[1] (a) D. Valentine, Jr. and J. W. Scott, *Synthesis*, 1978, 329; (b) J. W. ApSimon and R. P. Seguin, *Tetrahedron*, 1979, **35**, 2797.

[2] (a) D. Seebach and H. Daum, *Chem. Ber.*, 1974, **107**, 1748; (b) J. P. Vigneron and I. Jacquet, *Tetrahedron*, 1976, **32**, 939; (c) M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn*, 1978, **51**, 1869; (d) R. Noyori, I. Tomino, and Y. Tanimoto, *J. Am. Chem Soc.*, 1979, **101**, 3129; (e) S. Terashima, N. Tanno, and K. Koga, *Chem. Lett.*, 1980, 981.

[3] (a) R S. Brinkmeyer and V. M. Kapoor, *J. Am. Chem. Soc.*, 1977, **99**, 8339; (b) J. P. Vigneron and V. Bloy, *Tetrahedron Lett.*, 1979, **2683**; (c) N. Cohen, R. J. Ropresti, C. Neukom, and G. Saucy, *J. Org. Chem.*, 1980, **45**, 582.

[4] R. Noyori, I. Tomino, and M. Nishizawa, *J. Am. Chem. Soc.*, 1979, **101**, 5843.

[5] S. Terashima, N. Tanno, and K. Koga, *Tetrahedron Lett.*, 1980, **21**, 2749, 2753.