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Stereochemical Studies. XLVII.[1] Asymmetric Reduction of 2-Alkyl-1,3,4-cyclopentanetriones with Lithium Aluminum Hydride decomposed by optically Active β-Aminoalcohols. Syntheses of optically Active Allethrolone and Prostaglandin E_1[2]

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Asymmetric reduction of several kinds of 2-alkyl-1,3,4-cyclopentanetriones (**1**) by the use of lithium aluminum hydride (LAH) partially decomposed by optically active β-aminoalcohols (**7**), was studied. It was found that the reduction of 2-propyl derivative (**1c**) with LAH decomposed by 3.0 eq. of (−)-N-methylephedrine (**7a**), in THF at −70° for 3 hr, followed by acetylation, gave (*R*)(−)-4-acetoxy-2-propyl-1,3-cyclopentanedione ((*R*)(−)-**3c**), 58% e.e., in 42% yield. When the same reduction procedure was applied to 2-allyl derivative (**1b**), (*R*)(−)-4-acetoxy-2-allyl derivative ((*R*)(−)-**3b**), 55% e.e., was obtained in 48% yield. Recrystallization of (*R*)(−)-**3b** from ether could improve the optical purity up to 97% e.e.

The absolute configuration and optical purity of (*R*)(−)-**3b** and (*R*)(−)-**3c** were established by the chemical correlation with (*R*)(−)-allethrolone ((*R*)(−)-**5**).

When 2-(6-carbomethoxyhexyl)-1,3,4-cyclopentanetrione (**1a**) was treated by the exploited reduction condition, the corresponding (*R*)(+)-alcohol ((*R*)(+)-**2a**), 54±6% e.e., from which PGE_1 had been synthesized, was prepared in 58% yield.

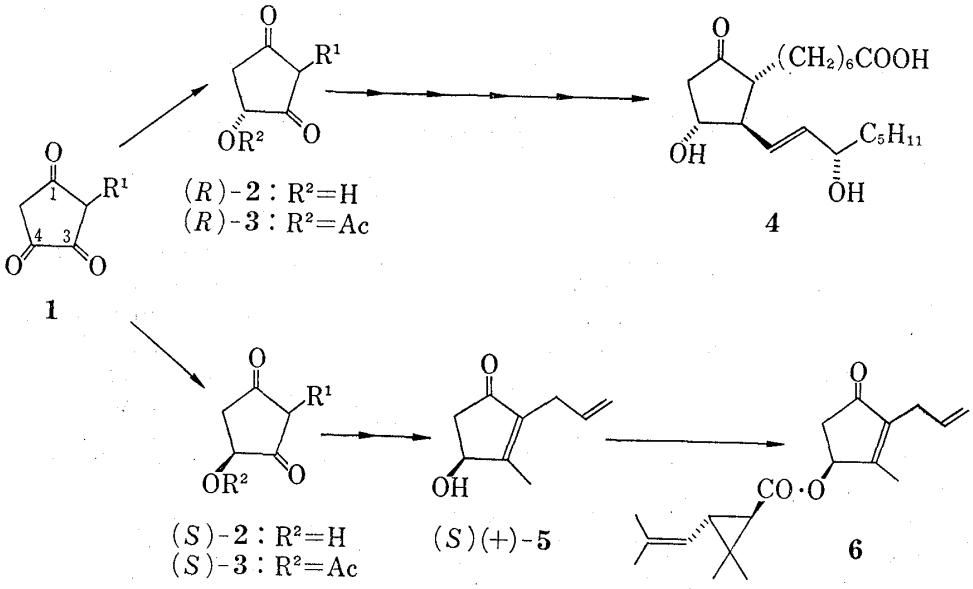
Keywords——asymmetric reduction; 2-alkyl-1,3,4-cyclopentanetriones; lithium aluminum hydride; optically active N,N-dimethyl-β-aminoalcohols; (−)-N-methylephedrine; rethrolones; (*R*)(−)-allethrolone; prostaglandins

There have been developed several kinds of asymmetric reductions which utilized lithium aluminum hydride(LAH) partially decomposed by optically active compounds as reducing agents.[4]

Although these asymmetric syntheses can successfully reduce alkyl aryl ketones such as acetophenone, propiophenone, butyrophenone, *etc.*, giving optically active α-phenylalkanols which have high optical purity (usually 45—75% e.e.,[4] max. 89% e.e.[4c]), their uses for reductions of simple aliphatic ketones regularly afford corresponding optically active alcohols having lower optical purity(usually less than 25% e.e.,[4] max. 31% e.e.[4f]). Due to these reasons, preparation of optically active carbocycles usable for natural product syntheses has never been attempted by the asymmetric reduction mentioned above, except one recent examination in the field of steroid synthesis (max. 23% e.e.).[5]

1) Part XLVI: M. Kitamoto, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **97**, 41 (1977).
2) Part of this report has been a subject of the preliminary communication: S. Yamada, M. Kitamoto, and S. Terashima, *Tetrahedron Letters*, **1976**, 3165.
3) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) *a*) J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1971, pp. 202—218; *b*) D. Seebach and H. Daum, *Chem. Ber.*, **107**, 1748 (1974); *c*) J.P. Vigneron and I. Jacquet, *Tetrahedron Letters*, **1974**, 2065; and *idem*, *Tetrahedron*, **32**, 939 (1976); *d*) S. Yamaguchi and H.S. Mosher, *J. Org. Chem.*, **38**, 1870 (1973); *e*) A.I. Meyers and P.M. Kendall, *Tetrahedron Letters*, **1974**, 1337; *f*) S.R. Landor, B.J. Miller, and A.R. Tatchell, *J. Chem. Soc.*(*C*), **1967**, 197.
5) G. Haffer, U. Eder, G. Sauer, and R. Wiechert, *Chem. Ber.*, **108**, 2665 (1975).

In the course of our studies on asymmetric syntheses of natural products,[6] asymmetric reduction of 2-alkyl-1,3,4-cyclopentanetriones(**1**) was considered as one of the most efficient ways for synthesizing optically active functionalized cyclopentane systems which were present in rethrolones[7] and prostaglandins(PG).[8] As shown in Chart 1, when (*R*) -2-(6-carbomethoxyhexyl)-4-hydroxy-1,3-cyclopentanedione((*R*)-**2a**)is successfully prepared from the achiral 1,3,4-cyclopentanetrione(**1a**) by asymmetric reduction, it can be utilized as a starting material for the synthesis of PGE_1 (**4**).[9] On the other hand, when preparation of (*S*)-



a : $R^1=(CH_2)_6COOMe$
b : $R^1=CH_2\text{-}CH=CH_2$
c : $R^1=CH_2CH_2CH_3$

Chart 1

2-allyl-4-hydroxy-1,3-cyclopentanedione((*S*)-**2b**) is achieved by asymmetric reduction of 2-allyl-1,3,4-cyclopentanetrione(**1b**), it is expected that (*S*) (+)-allethrolone((*S*) (+)-**5**) from which insecticidal allethrin (**6**) has been prepared,[10] can be readily synthesized from (*S*)-**2b**.

Considering the above-mentioned availability of the asymmetric reduction of **1**, an efficient method was sought which would produce (*R*)- or (*S*)-**2** from **1** without reducing other functional groups such as double bond and ester, being present in the side chain(R^1).

We have now found that **1** can be readily reduced to optically active (*R*)-**2**(regularly 55—58% e.e.) by employing LAH partially decomposed by (−)-N-methylephedrine(**7a**) as a reducing agent.[11] Absolute configuration and optical purity of the reduction products

6) T. Sone, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **24**, 1273 (1976), and ref. 5 therein.
7) *a*) R.A. Ellison, *Synthesis*, **1973**, 397; *b*) R.F. Romanet and R.H. Schlessinger, *J. Am. Chem. Soc.*, **96**, 3701 (1974); *c*) G. Büchi, D. Minster, and J.C.F. Young, *ibid.*, **93**, 4319 (1971); *d*) M. Vandewalle and E. Madeleyn, *Tetrahedron*, **26**, 3551 (1970).
8) *a*) S. Terashima, *J. Syn. Org. Chem. Japan*, **31**, 353 (1973); *b*) S. Terashima and S. Yamada, *Metabolism and Disease*, **12**, 1489 (1975); *c*) U. Axen, J.E. Pike, and W.P. Schneider, "The Total Synthesis of Natural Products," ed. by J. ApSimon, Wiley-Interscience, New York, 1973, Vol 1, pp. 81—142.
9) C.J. Sih, J.B. Heather, R. Sood, P. Price, G. Peruzzotti, L.F. Hsu Lee, and S.S. Lee, *J. Am. Chem. Soc.*, **97**, 865 (1975), and its preceding papers.
10) *a*) F.B. LaForge, N. Green, and M.S. Schechter, *J. Org. Chem.*, **19**, 457 (1954); *b*) M.J. Begley, L. Crombie, D.J. Simmonds, and D.A. Whiting, *J. Chem. Soc. Chem. Comm.*, **1972**, 1276.
11) While the asymmetric reduction of **1a** to (*R*)- or (*S*)-**2a** has been examined in the field of PG synthesis by Sih, *et al.*,[9] using enzymic reduction and catalytic hydrogenation over optically active phosphine-rhodium catalyst, studies which aim to develop a versatile preparation method for (*R*)- or (*S*)-**2** by the asymmetric reduction of **1** with LAH partially decomposed by optically active additives, have never been attempted.

((*R*)-**2b** and (*R*)-**2c**) which are isolated as their acetates((*R*)-**3b** and (*R*)-**3c**), have been established by synthesizing (*R*) (−)-allethrolone((*R*)(−)-**5**) from (*R*)-**3b**.[12]

In this report, we wish to describe exploitation of the novel asymmetric reduction, determination of the absolute configuration and optical purity for the reduction products, and application of the new asymmetric synthesis to the preparation of (*R*)-**2a** from which **4** has been synthesized by Sih, *et al.*[9]

Some preliminary experiments which were performed with racemic modifications, were described in detail in experimental part.

Result and Discussion

A. Asymmetric Reduction of 2-Alkyl-1,3,4-cyclopentanetriones(1)

As a substrate for the asymmetric reduction, 2-propyl-1,3,4-cyclopentanetrione(**1c**) was first selected, and was prepared as monohydrate, mp 67.5—69°, according to the reported method.[14–16] Although it is well known that catalytic hydrogenation of **1** over palladium on carbon gives racemic **2** in a high yield,[1,17] reduction of **1** with deactivated LAH has never been reported. However, when **1c** was treated with 2.2 molar equivalents(eq.) of lithium ethylenedioxyaluminum hydride in tetrahydrofuran (THF) at −20——25° for 2.5 hr, *dl*-**2c**[18] was obtained in 78% yield in a similar manner to the catalytic reduction.

Since it became obvious that the C_4-carbonyl group of **1c** was regiospecifically reduced by partially decomposed LAH, asymmetric reduction of **1c** was examined by using LAH partially decomposed with several kinds of optically active N,N-dimethyl-β-aminoalcohols (**7**) and phenol derivatives (**8**) which were depicted in Chart 2.[19]

The reasons why **7** were chosen as chiral additives for decomposing LAH are as follows: 1) These optically active β-aminoalcohols seemed to be readily obtainable from commercially available optically active compounds according to the reported methods; 2) LAH partially decomposed by **7a** and 3,5-dimethylphenol(**8a**) had been used for the asymmetric reduction of alkyl aryl ketones, giving the corresponding alcohols in the highest optical yield(89% e.e.)[4c] among those hitherto reported;[4] 3) Preparation of various new types of **7** was anticipated as possible by using optically active L-α-amino acids as starting materials.

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12) This constitutes the first asymmetric synthesis of optically active rethrolones. Direct chemical resolution of racemic allethrolone (*dl*-**5**) *via* its optically active chrysanthemic acid ester (allethrin) semicarbazone,[10a] and enzymic asymmetric hydrolysis of *dl*-O-acetyl-allethrolone with crude esterase from *Trichoderma sp.*[13] have been reported as methods for preparing optically active rethrolones.

13) T. Oritani and K. Yamashita, *Agr. Biol. Chem.*, **39**, 89 (1975).

14) D.R. Lagidze, S.N. Ananchenko, and I.V. Torgov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, **1965**, 1899 [*C.A.*, **64**, 1973*h* (1966)].

15) Although the melting point of **1c**-monohydrate was different from that reported, mp 46—49°,[14] its structure was definitely confirmed by its spectral and analytical data (see Experimental).

16) Anhydrous (anhyd.) **1c** was used as a substrate for the reduction with deactivated LAH throughout this work (see Experimental).

17) *a*) K. Matoba, K. Yoshii, T. Yamazaki, and Y. Sasaki, *Yakugaku Zasshi*, **89**, 750 (1969); *b*) M. Orchin and L.W. Butz, *J. Am. Chem. Soc.*, **65**, 2296 (1943); *c*) G.D. Searl and Co., Neth. Appl., 6415063 [*C.A.*, **64**, 3377*e* (1966)].

18) J. Katsube and M. Matsui, *Agr. Biol. Chem.*, **35**, 401 (1971).

19) Before these studies were performed, the optical stability of (*R*)- or (*S*)-**2c** was checked by measuring the nuclear magnetic resonance (NMR) spectrum of *dl*-**2c** in time intervals in deuterated solvents (10% deuterium chloride (DCl) in methanol-d_4-deuterium oxide (1: 1) and 13% sodium deuteroxide (NaOD) in methanol-d_4-deuterium oxide (1: 2)). Since the asymmetric hydrogen of the C_4-position of *dl*-**2c** did not incorporate deuterium and appeared at δ 4.8 (in 10% DCl) and 4.3 (in 13% NaOD) even after 10 hr at room temperature, it became evident that (*R*)- or (*S*)-**2c** would not be prone to racemize under highly acidic and basic conditions (M. Kitamoto, S. Terashima, and S. Yamada, unpublished result).

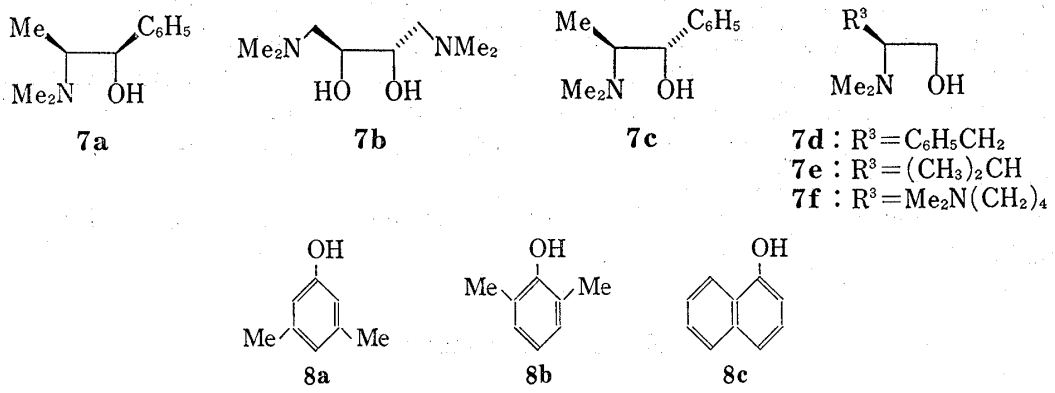

Chart 2

TABLE I. Asymmetric Reduction of 2-Propyl-1,3,4-cyclopentanetrione(**1c**) with LAH partially decomposed by Several Kinds of optically Active N,N-Dimethyl-β-aminoalcohols (**7**) and Phenol Derivatives (**8**)[a]

Run	N,N-Dimethyl-β-aminoalcohols (7)	Phenol derivatives (8) added		Optically active 4-acetoxy-2-propyl-1,3-cyclopentanedione ((*R*)- or (*S*)-**3c**)		
		Nature	Molar ratio to LAH	$[\alpha]_D^{20}$ (*c*, MeOH)	Opt. Yield (%)[b] (Confign.)	Chem. Yield (%)[c]
1	**7b**	**8a**	1	+3.3°(3.25)	6(*S*)	63
2	**7a**[d]	**8a**	2	−14.1°(2.44)	27(*R*)	54
3	**7a**	**8b**	2	−7.1°(3.12)	14(*R*)	70
4	**7a**	**8c**	2	−3.7°(3.33)	7(*R*)	72
5	**7c**	**8a**	2	+1.5°(2.64)	3(*S*)	61
6	**7d**	**8a**	2	−5.5°(3.39)	11(*R*)	56
7	**7e**	**8a**	2	−2.4°(3.98)	5(*R*)	58
8	**7f**	**8a**	2	−9.5°(2.49)	18(*R*)	65

a) All reductions were carried out at −20° (dryice-carbon tetrachloride bath) in ether for 3 hr, using LAH (3.3 molar eq. to **1c**) partially decomposed by **7**(1.0 molar eq. to LAH) and **8**(1.0 or 2.0 molar eq. to LAH).
b) The acetate (**3c**) showing $[\alpha]_D^{20}$ −52° (methanol), has (*R*) -configuration and is 100% optically pure.
c) Based on **1c**.
d) 86% of **7a** was recovered(see Experimental).

Results for the asymmetric reduction were summarized in Table I. In these experiments, LAH(3.3 molar eq. to **1c**) was decomposed by **7**(1.0 molar eq. to LAH) and **8**(1.0(for **7b**) or 2.0(for **7a,c—f**) molar eq. to LAH) to leave one of the four active hydride of LAH in deactivated reducing agents.[20] As complete purification of (*R*)- or (*S*)-**2c** was found to be quite difficult even by the use of preparative thin-layer chromatography (TLC), the reduction product was converted to its acetate((*R*)- or (*S*)- **3c**) by treating with acetic anhydride and pyridine at 0°. The optical rotation was recorded for (*R*)- or (*S*)-**3c** which could be easily purified by preparative TLC. The absolute configuration and optical yield for **3c** were definitely determined, based on the fact that **3c** showing $[\alpha]_D^{20}$−52° (methanol), had (*R*)-configuration and was 100% optically pure (see Section B).

When **1c** was reduced with LAH partially decomposed by 2(*S*),3(*S*)(−)-1,4-bis(dimethylamino)-2,3-butanediol(**7b**)[21](Table I, run 1), (*S*) (+)-**3c**, 6% e.e., was obtained as a colorless

20) Since 1.0 eq. of the active hydride is consumed by the one acidic hydrogen of **1c**, the reducing agents thus obtained, contain active hydride being 2.3 eq. to the ketonic function of **1c**.
21) This was first prepared by Seebach, *et al.*[4b] They succeeded in reducing phenyl *t*-butyl ketone, *etc.*, to the corresponding optically active alcohols in at most 75% optical yield by the use of LAH decomposed by **7b** (1.0 molar eq. to LAH).

solid in 63% yield based on **1c**. Then, we adopted the reduction procedure developed by Vigneron, *et al.*,[4c] which recorded the highest asymmetric induction for the reduction of alkyl aryl ketones(*vide supra*). Treatment of **1c** with LAH decomposed by **7a** and **8a**(Table I, run 2), was found to afford (*R*) (−)-**3c**, $[\alpha]_D^{20}$−14.1° (methanol), 27% e.e., in 54% yield. In order to improve the optical yield of (*R*) (−)-**3c**, the achiral phenols (**8**) were changed from **8a** to 2,6-dimethylphenol (**8b**) and α-naphthol (**8c**) (Table I, runs 3 and 4). However, no improvement of the optical yield was achieved although some increases of the chemical yield for (*R*) (−)-**3c** were observed. When (+)-N-methyl-ψ-ephedrine(**7c**) was used as a chiral additive in place of **7a**(Table I, run 5), the steric course of the asymmetric reduction reversed and (*S*) (+)-**3c** being 3% e.e., was obtained in 61% yield. The uses of (−)-N,N-dimethylphenylalaninol(**7d**), (+)-N,N-dimethylvalinol(**7e**), and (+)-N_α,N_α,N_ε,N_ε-tetramethyllysinol(**7f**), which were readily obtainable from the corresponding L-α-amino acids, as chiral additives, turned out to be again ineffective for improving the optical yield for **3c**(Table I, runs 6,7, and 8).

Aiming to further improve the optival yield for **3c**, the asymmetric reduction of **1c** was examined in ether at −20° by using the reducing agent[20] prepared from LAH(3.3 molar eq. to **1c**) and **7a**(3.0 molar eq. to LAH) without phenol derivatives as shown in Table II, run 1. Surprisingly, it was found that (*R*) (−)-**3c** being 36% e.e., was obtained in 42% yield based on **1c**. When the reaction temperature was changed to −70°, the optical yield of (*R*) (−)-**3c** clearly increased to 43% e.e.(Table II, run 2). No solvent effect was observed when

Table II. Asymmetric Reduction of 2-Alkyl-1,3,4-cyclopentanetriones (**1**) with LAH partially decomposed by (−)-N-Methylephedrine (**7a**)[a]

Run	2-Alkyl-1,3,4-cyclopentanetriones (**1**)	Reac. Temp. (°C)	Solv.	Optically active 4-acetoxy-2-alkyl-1,3-cyclopentanediones (**3**)[b]		
				$[\alpha]_D^{20}$ (*c*, MeOH)	Opt. Yield (%) (Confign.)	Chem. Yield (%)[c]
1[d]	**1c**	−20	ether	−18.5(2.82)	36(*R*)[e]	42
2	**1c**	−70	ether	−22.2(1.60)	43(*R*)[e]	30
3	**1c**	−70	DME	−22.1(1.81)	43(*R*)[e]	32
4[f]	**1c**	−70	THF	−29.9(2.60)	58(*R*)[e]	42
5[g]	**1c**	−100	THF	−29(0.55)	56(*R*)[e]	7
6	**1c**	−70	THF–HMPA[h]	−18.4(2.32)	35(*R*)[e]	41
7	**1c**	−70	THF–DABCO[h]	−26.5(2.00)	51(*R*)[e]	43
8	**1b**	−70	THF	−24.8(1.76)	55(*R*)[i]	48

a) All reductions were performed at the indicated temperature for 3 hr, using LAH (3.3 molar eq. to **1**) partially decomposed by **7a**(3.0 molar eq. to LAH).
b) Identified with corresponding authentic racemic compounds by spectral (IR (in chloroform) and/or NMR) and chromatographic (TLC) comparisons.
c) based on **1**
d) 84% of **7a** was recovered.
e) The acetate (**3c**) showing $[\alpha]_D^{20}$ −52°(methanol), belongs to (*R*) -series and is optically pure.
f) The starting material (**1c**) was obtained in 19% recovery.
g) 71% of the starting material (**1c**) was recovered.
h) After the solution of LAH partially decomposed by **7a**(3.0 molar eq. to LAH) was prepared, HMPA or DABCO (1.0 molar eq. to LAH) was added to the mixture at −70°, and the whole solution was stirred at −70° for 3 hr before a THF solution of **1c** was added.
i) The acetate(**3b**), $[\alpha]_D^{20}$ −45°(methanol), has (*R*)-configuration and is optically pure.

dimethoxyethane(DME) was used as solvent (Table II, run 3), but when the reduction was carried out at −70° in THF(Table II, run 4), (*R*) (−)-**3c**, $[\alpha]_D^{20}$−29.9°(methanol), 58% e.e., was successfully obtained in 42% yield.[22] However, when the reaction temperature was further lowered to −100° in a liquid nitrogen-pentane bath (Table II, run 5), retardation of

22) The starting material was obtained in 19% recovery.

the reduction was simply observed, and 71% of the starting material was recovered. Addition of hexamethylphosphoramide(HMPA) or 1,4-diazabicyclo[2,2,2]octane(DABCO)[23] to the reducing agent was found to be unpromising to further improve the optical yield of (*R*) (−)-**3c**(Table II, runs 6 and 7).

Application of the same reduction condition as that for **1c**(Table II, run 4) to 2-allyl-1,3,4-cyclopentanetrione(**1b**)[24] (Table II, run 8), gave the acetate((−)-**3b**), $[\alpha]_D^{20}$−24.8° (methanol), as a colorless solid in 48% yield after acetylation of the crude reduction product (**2b**).[25] As it had been established as described in Section B that **3b** showing $[\alpha]_D^{20}$−45° (methanol), belonged to (*R*)-series and was optically pure, the absolute configuration and optical yield for (−)-**3b** thus obtained, were determined as (*R*)-configuration and 55% e.e., respectively.

Recrystallization from ether seemed useless for improving the optical purity of (*R*) (−)-**3c**, but when (*R*) (−)-**3b** was recrystallized once from the same solvent, (*R*)(−)-**3b**, mp 126—130°, $[\alpha]_D^{20}$−43.6° (methanol), 97% e.e., was obtained as colorless needles.

Since (+)-N-methylephedrine, the antipode of **7a**, is readily obtainable from commercially available *d*-ephedrine, the use of (+)-N-methylephedrine as a chiral source might afford (*S*)(+)-**3b** and (*S*)(+)-**3c** whose absolute configurations are opposite to those of the samples obtained above.

B. Determination of the Absolute Configuration and Optical Purity for optically Active Reduction Products

In order to establish the steric course and optical yield for the asymmetric reduction studied in Section A, and moreover, to visualize the utility of the asymmetric reduction of **1** for synthesis of optically active rethrolones, the chemical correlation of (−)-**3b** and (−)-**3c** with (*R*)(−)-5 was examined as shown in Chart 3.

Treatment of (−)-**3b**, $[\alpha]_D^{20}$−14.9°(methanol),[26] with excess diazomethane in a mixture of ether and THF, followed by separation with a silica gel column, afforded two sorts of oily enol ether, (−)-**9**, $[\alpha]_D^{20}$−17.2°(chloroform), and (−)-**10**, $[\alpha]_D^{20}$−9.3° (chloroform), in 42% and 40% yields, respectively. Structures of (−)-**9** and (−)-**10** were assigned as depicted in Chart 3 by considering their ultraviolet(UV) spectral difference. 5-Acetoxy derivative ((−)-**9**) exhibited its absorption maximum at 258 nm, which was about 10 nm more bathochromic than that of (−)-**10**. Similar spectral difference had been reported for two sorts of the enol ether prepared from 4-acetoxy-1,3-cyclopentanedione,[1] or *dl*-4-hydroxy-2-methyl- and *dl*-4-hydroxy-2-propyl-1,3-cyclopentanedione.[18,27]

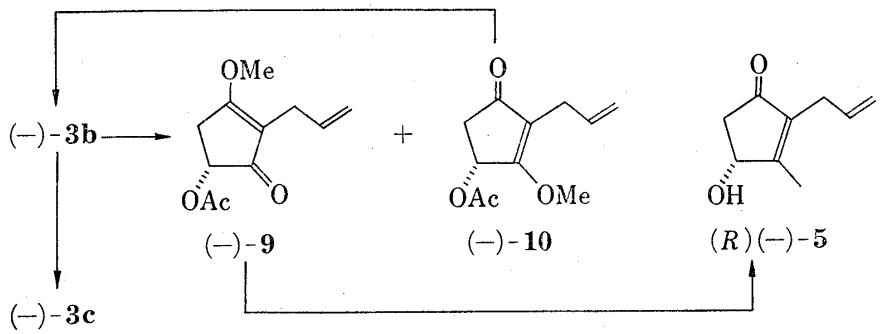

Chart 3

23) These tertiary amines were added for converting the reducing agent, which was assumed to be present as a complex oligomer, into a monomeric form (see for example, T. Sone, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **24**, 1293 (1976)).
24) K. Yoshioka, T. Asako, G. Goto, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **21**, 2195 (1973).
25) Recovery of the starting material was not attempted.
26) This sample was obtained during a study for improving the optical yield.
27) K. Matoba and T. Yamazaki, *Yakugaku Zasshi*, **92**, 213 (1972).

Undesired (−)-**10** could be recycled to (−)-**3b** in 83% yield by successive treatments with 2N hydrochloric acid at room temperature for 24 hr and with acetic anhydride and pyridine at 0° for 4 hr.

Addition of methyllithium (3.0 eq.) to (−)-**9**, and the work-up under acidic condition, gave (−)-**5** as a colorless oil,[28] $[\alpha]_D^{25}$ −2.4° (ethanol), in 57% yield. On the other hand, catalytic reduction of (−)-**3b**, $[\alpha]_D^{20}$ −15.3° (methanol),[26] over 10% palladium on carbon in ethyl acetate, yielded (−)-**3c**, $[\alpha]_D^{20}$ −17.6°(methanol), in 87% yield. Since optically pure (*S*)(+)−**5** was reported to have $[\alpha]_D^{25}$ +7.3°(ethanol),[10] the above correlation clearly established that (−)-**3b** and (−)-**3c** belonged to (*R*)-series and that the optical rotation of optically pure (−)-**3b** and (−)-**3c** could be calculated as $[\alpha]_D^{20}$ −45°(methanol) and $[\alpha]_D^{20}$ −52°(methanol), respectively.

C. Application of the Asymmetric Reduction to Prostaglandin Synthesis

When **1a** prepared according to the reported method,[9] was submitted to the asymmetric reduction developed in Section A, and the reduction product was separated by a silica gel column without acetylation, (*R*)(+)-**2a**, $[\alpha]_D^{23}$ +8.8±1°(chloroform), 54±6% e.e.,[29] was obtained in 58% yield without reduction of the ester group and 27% of the starting **1a** was recovered. One recrystallization from ethyl acetate afforded colorless crystals which showed mp 80—84° and $[\alpha]_D^{23}$ +11.4±1.5°(chloroform), 70±10% e.e.[29] (*R*)(+)-**2a** so obtained, has been transformed into **4** by Sih, *et al.*, as was mentioned in the introduction part.

Although elucidation of the reduction mechanism seems to be quite difficult because LAH partially decomposed by **7** is present as a complex oligomer in ether or THF, the asymmetric reduction developed here might have some practical values due to its fairly high optical yield, operational simplicity and wide applicability.

Further studies for finding out more effective reduction procedure which can afford **2** from **1** in a higher optical yield than those in this report, are under progress in these laboratories.

Experimental[30]

2-Propyl-1,3,4-cyclopentanetrione (1c)——This was prepared according to the reported method.[14] The trione (**1c**) recrystallized from water as monohydrate and pale yellow needles, showed mp 67.5—69°. Although this melting point was clearly different from the reported value (lit.,[14] mp 46—49°), its structure was definitely confirmed by the following spectral behavior and its analytical data. IR ν_{max}^{Nujol} cm^{-1}: 3460, 3340, 2700—2500, 1740, 1680, 1644. NMR (in $CDCl_3$): 0.88 (3H, t, J=7 Hz, $CH_2CH_2C\underline{H}_3$), 1.47 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.24 (2H, t, J=7 Hz, $C\underline{H}_2CH_2CH_3$), 2.84 (2H, s, $COC\underline{H}_2CO$), 4.60 (*ca.* 3H, br s, $\underline{H}OC{=}C{-}CO{+}\underline{H}_2O$). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 277 (4.11). Mass Spectrum *m/e*: 154 (M^+). *Anal.* Calcd. for $C_8H_{10}O_3\cdot H_2O$: C, 55.80; H, 7.03. Found: C, 55.95; H, 6.82. Dissolving **1c**-monohydrate into THF, addition of toluene to the THF solution, and evaporation of the whole solution *in vacuo* were repeated twice, giving anhyd. **1c** as a hygroscopic pale yellow solid. Anhyd. **1c** was directly used as a substrate for the reduction with deactivated LAH.

2-Allyl-1,3,4-cyclopentanetrione (1b)——Prepared according to the reported method.[24] The sample obtained as pale yellow needles (recrystallized from carbon tetrachloride), showed mp 43—46° (lit.,[24] mp 43—45°). Spectral (IR, UV, and NMR) properties of this sample were identical with those reported.[24]

28) This was confirmed by comparing its spectral and chromatographic behavior with that of the authentic racemic compound generously provided by Sumitomo Chemical Co. Ltd.

29) (*R*)(+)-**2a**, $[\alpha]_D^{23}$ +16.2° (c=1.02, chloroform), was assumed to be optically pure (see ref. 9).

30) All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded with a JASCO Infrared Spectrometer Model DS-402G and a JASCO IRA-1 Grating Infrared Spectrometer. NMR spectra were measured with a JNM-PS100 Spectrometer (100 MHz) and a Hitachi R-24 High Resolution NMR Spectrometer (60 MHz). All signals are expressed by the ppm downfield from tetramethylsilane used as an internal standard (δ value). Following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Measurements of optical rotations were carried out using a YANACO OR-50 Automatic Polarimeter. UV spectra were taken with a Hitachi Model EPS-3T Recording Spectrophotometer. Mass Spectra measurements were performed with a JEOL JMS SG-2 Mass Spectrometer.

***dl*-4-Hydroxy-2-propyl-1,3-cyclopentanedione (*dl*-2c)**——a) Preparation by Catalytic Reduction: A mixture of **1c**-monohydrate (1.72 g, 10.0 mmol) and 10% Pd on carbon (0.4 g) in isopropanol (18 ml) was stirred at room temperature under hydrogen atmosphere for 4 hr. The catalyst was filtered off and the alcoholic filtrate was evaporated *in vacuo*, giving crude *dl*-**2c** as a solid. Recrystallization of the crude solid from ethyl acetate afforded *dl*-**2c** as colorless prisms (0.56 g), mp 117.5—119° (lit.,[18] mp 124—126°). Concentration of the mother liquor from the recrystallization gave a further amount of *dl*-**2c** as colorless prisms (0.47 g, total 1.03 g, 66%), mp 112—117°. The melting point of *dl*-**2c** thus obtained, was slightly different from that reported,[18] its structure was clearly established by the following spectral and analytical data. IR ν_{max}^{Nujol} cm^{-1}: 3340, 2700—2500, 1675, 1555. NMR (in DMSO-d_6): 0.84 (3H, t, $J=7$ Hz, $CH_2CH_2C\underline{H}_3$), 1.36 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.00 (2H, t, $J=7$ Hz, $C\underline{H}_2CH_2CH_3$), 2.22 (1H, dd, $J=17$ and 2 Hz, one of $C\underline{H}_2$-CHOH), 2.64 (1H, dd, $J=17$ and 6 Hz, one of $C\underline{H}_2$CHOH), 4.41 (1H, dd, $J=6$ and 2 Hz, C<u>H</u>OH), 7.32 (2H, br s, O<u>H</u>+<u>H</u>OC=C–CO).[31] UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 251 (4.28). Mass Spectrum *m/e*: 156 (M^+), 138. *Anal.* Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.56; H, 7.79.

b) Preparation by the Reduction with Lithium Ethylenedioxyaluminum Hydride: To a suspension of LAH (167 mg, 4.4 mmol) in THF (10 ml) was added a solution of ethylene glycol (273 mg, 4.4 mmol) in THF (5 ml) with stirring under nitrogen atmosphere. Stirring was continued at room temperature for 10 min, giving a THF solution of the reducing agent.

A solution of anhyd. **1c** (308 mg, 2.0 mmol) in THF (5 ml) was gradually added to the stirred THF solution containing the reducing agent in a dryice-carbon tetrachloride bath. After the whole was stirred at −20——25° for 2.5 hr, the reduction was quenched by adding 10% HCl (20 ml) at the same temperature. The lower aqueous phase was saturated with NaCl, then the mixture was extracted with ethyl acetate. The combined organic extracts were washed with satd. NaCl, and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave crude *dl*-**2c** as a solid, which was recrystallized from a mixture of ethyl acetate and ether to afford pure *dl*-**2c** as colorless prisms (213 mg, 68%), mp 117—119°. This compound showed no depression on the mixed melting point measurement with the sample obtained in a), mp 117—119°. Spectral (IR and NMR) properties of this compound were also identical with those of the sample obtained in a). Concentration of the mother liquor from the recrystallization gave a further amount of *dl*-**2c** as colorless prisms (30 mg, total 243 mg, 78%), mp 114—118°. This was similarly identified with the sample prepared in a).

***dl*-4-Acetoxy-2-propyl-1,3-cyclopentanedione (*dl*-3c)**——The racemic alcohol (*dl*-**2c**) (234 mg, 1.5 mmol) was added to a mixture of acetic anhydride (0.34 g, 3.3 mmol) and pyridine (2 ml) in an ice bath with stirring. The mixture was stirred at room temperature overnight, diluted with water (0.3 ml), and was further stirred at room temperature for 20 min. After being acidified (pH<2) with 10% HCl (5 ml), the whole solution was extracted with ethyl acetate. The combined organic extracts were successively washed with satd. $CuSO_4$, water, and satd. NaCl, then was dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* afforded crude *dl*-**3c** as a colorless solid (300 mg), mp 116—119°. Recrystallization from benzene gave pure *dl*-**3c** as colorless crystals (242 mg, 82%), mp 118—119°. IR ν_{max}^{Nujol} cm^{-1}: 2680, 1737, 1605. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2990, 2950, 2920, 2860, 2660, 1743, 1722, 1700, 1655, 1120. NMR (in $CDCl_3$): 0.90 (3H, t, $J=7$ Hz, $CH_2CH_2C\underline{H}_3$), 1.46 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.12 (3H, s, $OCOC\underline{H}_3$), 2.0—2.4 (2H, m, $C\underline{H}_2CH_2CH_3$), 2.40 (1H, d, $J=18$ Hz, one of $C\underline{H}_2CHO$), 2.92 (1H, dd, $J=18$ and 6 Hz, one of $C\underline{H}_2CHO$), 5.55 (1H, d, $J=6$ Hz, C<u>H</u>O), 9.76 (1H, br s, <u>H</u>OC=C–CO). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 251 (4.23). Mass Spectrum *m/e*: 198 (M^+), 138 [$(M-CH_3COOH)^+$]. TLC analysis (silica gel, solvent: benzene: THF: CH_2Cl_2: acetic acid 6: 2: 2: 1, coloring agent: UV, I_2, and aq. $FeCl_3$ solution) of this compound showed a single spot whose *Rf* value was 0.7. *Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.47; H, 7.11.

***dl*-4-Acetoxy-2-allyl-1,3-cyclopentanedione (*dl*-3b)**——This compound was prepared by a slight modification of the reported procedure.[24] To a suspension of sodium borohydride (125 mg, 3.3 mmol) in ethanol (5 ml) was added a mixture of **1b** (500 mg, 3.3 mmol) and triethylamine (360 mg, 3.6 mmol) in ethanol (10 ml) with stirring in an ice bath. After stirring was continued for 1.5 hr, solid sodium hydrogen sulfate (1.2 g, 10 mmol) was added to the reaction mixture. Filtration and evaporation *in vacuo* gave a pale yellow oil, which was acetylated in a similar manner to the case for *dl*-**3c**. The same work-up procedure as that for the preparation of *dl*-**3c**, followed by purification with preparative TLC (silica gel, solvent: benzene: THF: CH_2Cl_2: acetic acid 6: 2: 2: 1) and recrystallization from a mixture of ether and hexane, gave pure *dl*-**3b** as a colorless powder (270 mg, 42%), mp 125—127° (lit.,[24] mp 124—126.5°). Spectral (IR, NMR, and UV) behavior of this sample was identical with that reported.[24] TLC analysis of this compound in a similar fashion to the case for *dl*-**3c**, showed a single spot whose *Rf* value was 0.5.

2(*S*),3(*S*)(−)-1,4-Bis(dimethylamino)-2,3-butanediol (7b)——Prepared as a colorless oil according to the reported method.[4b] bp 90—92° (2 mmHg), mp 40—42°, $[\alpha]_D^{20}$ −33.8° ($c=3.45$, benzene) (lit.,[4b] bp 70° (0.5 mmHg) and $[\alpha]_D^{20}$ −34.8±1° ($c=3.5$, benzene)).

(−)-N-Methylephedrine (7a)——Preparation of this compound was carried out according to the reported procedure.[32] mp 87—88°, $[\alpha]_D^{20}$ −29.7° ($c=4.57$, methanol) (lit.,[32] mp 87—88° and $[\alpha]_D^{20}$ −29.5° ($c=4.5$, methanol)).

31) This signal disappeared when treated with D_2O.

32) K. Nakajima, *Nippon Kagaku Zasshi*, **81**, 1476 (1960).

(+)-N-Methyl-ψ-ephedrine (7c)——This was prepared from (−)-ephedrine *via* (+)-N-benzoyl-ψ-ephedrine, mp 131—132° and $[\alpha]_D^{20}$ +133.5° (c=3.19, chloroform) (lit.,[33] mp 137—137.5° and $[\alpha]_D^{20}$ +135.2° (c=3, chloroform)), and (+)-ψ-ephedrine, mp 114—117° (lit.,[34] mp 117—118°), according to the reported procedure.[33,34] **7c** thus obtained, distilled at bp 125—128° (11 mmHg) and showed $[\alpha]_D^{20}$ +48.4° (c=3.89, methanol)) (lit.,[34] bp 145° (24 mmHg) and $[\alpha]_D^{20}$ −48.3° (c=4, methanol) for (−)-isomer).

(*S*)(−)-N,N-Dimethylphenylalaninol (7d)——This was prepared from (*S*)(−)-phenylalaninol, mp 90—92° and $[\alpha]_D^{25}$ −23.3° (c=1.23, ethanol) (lit.,[35] mp 91—93° and $[\alpha]_D^{25}$ −25.6° (c=1.04, ethanol)).

To a refluxing mixture of (*S*)(−)-phenylalaninol (3.02 g, 20.0 mmol) and 85% formic acid (4.4 g) in water (6 ml) was added dropwise 37% aqueous formalin (2.4 g). After reflux was continued for 4 hr, the mixture was made alkaline (pH>11) with 10% NaOH, and was extracted with chloroform. The combined chloroform extracts were dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo*, followed by fractional distillation, afforded crude **7d** as a colorless oil (3.10 g, 94%), bp 123° (3 mmHg). This oil solidified on standing at room temperature, and showed mp 42—44°. Recrystallization from pentane gave pure **7d** as colorless prisms, mp 44—45°, $[\alpha]_D^{20}$ −2.7° (c=3.37, ethanol) (lit.,[36] mp 51° and $[\alpha]_D^{20}$ −2.34±0.2° (c=3.2, ethanol)). Spectral (IR and NMR) properties of this alcohol were identical with those reported.[36]

(*S*)(+)-N,N-Dimethylvalinol (7e)——The same treatment of (*S*)(+)-valinol (bp 81—83° (9 mmHg) and $[\alpha]_D^{20}$ +17.3° (c=2.72, ethanol))[37] (3.09 g, 30.0 mmol) as that for the preparation of **7d** from (*S*)(−)-phenylalaninol, gave pure **7e** as a colorless oil (2.24 g, 57%), bp 108—110° (70 mmHg), $[\alpha]_D^{20}$ +7.5±0.5° (c=2.13, methanol). IR ν_{max}^{film} cm^{-1}: 3360, 2790, 1600, 1050. NMR (in $CDCl_3$): 0.84 (3H, d, J=7 Hz, one of $(CH_3)_2CH$), 0.98 (3H, d, J=7 Hz, one of $(CH_3)_2CH$), 1.84 (1H, m, $(CH_3)_2CH$), 2.0—2.5 (1H, m, CHN), 2.38 (6H, s, $N(CH_3)_2$), 3.23 (1H, dd, J=12 and 8 Hz, one of CH_2OH), 3.52 (1H, J=12 and 4 Hz, one of CH_2OH), 3.58 (1H, s, OH). Mass Spectrum m/e: 132 [(M+1)$^+$], 131 (M$^+$), 100, 88, 43. This sample was confirmed as its hydrochloride, colorless needles (recrystallized from ethanol–ether), mp 124—126.5°, $[\alpha]_D^{20}$ +12° (c=1.00, methanol). *Anal.* Calcd. for $C_7H_{17}ON\cdot HCl$: C, 50.14; H, 10.82; N, 8.35. Found: C, 49.85; H, 10.99; N, 8.28.

(*S*)(+)-N_α,N_α,N_ε,N_ε-Tetramethyllysinol (7f)——A mixture of commercially available L-lysine hydrochloride (13.6 g, 74.3 mmol), 37% aqueous formalin (50 ml), and 10% Pd on carbon (2 g) in water (75 ml) was stirred at 50° for 20 hr under hydrogen atmosphere (70 atmospheric pressure). After cooling, the catalyst was removed by filtration, and the clear aqueous filtrate was evaporated *in vacuo* to afford a residue. Addition of water to the residue, followed by evaporation *in vacuo*, was repeated twice, then the remaining water was completely removed by azeotropic distillation with benzene. To the evaporation residue thus obtained, was added ethanol (100 ml), and the ethanolic solution was saturated with dry hydrogen chloride gas. After refluxing for 3 hr, the ethanol was removed *in vacuo*, giving a viscous oil which was basified (pH>11) with 10% NaOH and extracted with chloroform. The combined organic extracts were washed with satd. NaCl, then was dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* afforded an orange oil, which on fractional distillation, gave (*S*)(−)-ethyl N_α,N_α,N_ε,N_ε-tetramethyllysinate as a colorless oil (9.33 g, 55%), bp 121° (7 mmHg), $[\alpha]_D^{20}$ −11.0° (c=1.73, ethanol). IR ν_{max}^{film} cm^{-1}: 1730, 1170. NMR (in $CDCl_3$): 1.28 (3H, t, J=7 Hz, OCH_2CH_3), 1.1—2.0 (6H, m, $(CH_2)_3$), 2.18 (6H, s, $(CH_3)_2NCH_2$), 2.31 (6H, s, $(CH_3)_2NCH$), 2.25 (2H, m, $(CH_3)_2NCH_2$), 3.11 (1H, t, J=7 Hz, $(CH_3)_2NCHCOO$), 4.17 (2H, q, J=7 Hz, OCH_2CH_3). Mass Spectrum m/e: 231 [(M+1)$^+$], 230 (M$^+$), 157 [(M−$COOCH_2CH_3$)$^+$].

To a suspension of LAH (1.52 g, 40.0 mmol) in anhyd. THF (200 ml) was added the (*S*)(−)-ester (9.21 g, 40.0 mmol) obtained above, with stirring in an ice bath. The whole mixture was refluxed for 3 hr, then the formed complex was decomposed by successive addition of water (15 ml), 15% NaOH (1.5 ml), and water (4.5 ml). After the mixture was stirred under reflux for 10 min, filtration and evaporation *in vacuo* gave an oily residue, which was submitted to fractional distillation to afford pure **7f** as a colorless oil (6.20 g, 82%), bp 102—104° (3.5 mmHg), $[\alpha]_D^{20}$ +9.8° (c=2.23, ethanol). IR ν_{max}^{film} cm^{-1}: 3400, 1050. NMR (in $CDCl_3$): 1.1—1.6 (6H, m, $NCH_2(CH_2)_3CH$), 2.20 (6H, s, $(CH_3)_2NCH_2$), 2.26 (6H, s, $(CH_3)_2NCH$), 2.2—2.6 (3H, m, NCH_2+NCH), 3.25 (1H, dd, J=10 and 9 Hz, one of CH_2OH), 3.50 (1H, dd, J=10 and 5 Hz, one of CH_2OH), 4.12 (1H, s, CH_2OH). Mass Spectrum m/e: 190 [(M+2)$^+$], 188 (M$^+$), 170 [(M−H_2O)$^+$], 157 [(M−CH_2OH)$^+$].

Asymmetric Reduction of 2-Propyl-1,3,4-cyclopentanetrione (1c) with LAH partially decomposed by Several Kinds of optically Active N,N-Dimethyl-β-aminoalcohols (7) and Phenol Derivatives (8)——a) Table I, Run 2: An ethereal solution (20 ml) of **7a** (1.18 g, 6.6 mmol) was added to a solution of LAH in ether (0.87 mmol/ml)[38] (7.6 ml, 6.6 mmol) at room temperature. After the whole was stirred at room temperature

33) L.H. Welsh, *J. Am. Chem. Soc.*, **71**, 3500 (1949).
34) N. Nagai and S. Kanao, *Ann.*, **470**, 157 (1929).
35) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 995 (1965).
36) E.J. Corey, R.J. McCaully, and H.S. Sachdev, *J. Am. Chem. Soc.*, **92**, 2476 (1970).
37) C.C. Tseng, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 29 (1977).
38) This was prepared as follows. A suspension of LAH (1.90 g, 50 mmol) in ether or THF (75 ml) was stirred at room temperature for 4 hr, and was quickly filtered through a glass funnel to give a clear solution of LAH. The amount of LAH being present in ether or THF, was determined according to the reported method (H. Felkin, *Bull. Soc. Chim. France*, **1951**, 347).

for 30 min, a solution of **8a** (1.61 g, 13.2 mmol) in ether (12 ml) was gradually added to the original ethereal solution. The whole mixture was stirred at room temperature for 1 hr, then was cooled to −20° in a dryice-carbon tetrachloride bath. A solution of anhyd. **1c** (308 mg, 2.0 mmole) in ether (6 ml) was added dropwise to the cooled solution prepared above, over a period of 10 min, and the mixture was stirred at the same temperature for 3 hr. The whole was poured onto a mixture of 10% HCl (20 ml) and ice, and the upper ethereal layer was separated. The lower acidic aqueous phase was extracted with ethyl acetate (30 ml×4), and the combined organic phases were dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo*, afforded an oily residue which was submitted to column chromatography (silica gel 5 g). The column was first eluted with chloroform, then with ethyl acetate. Evaporation of the chloroform eluate gave **8a** as a colorless solid (1.61 g, 100% recovery), which was confirmed by spectral (IR) and chromatographic (TLC) comparisons. Evaporation of the ethyl acetate eluate *in vacuo*, gave crude (*R*)-**2c** as a colorless solid (198 mg, 64%).

The crude (*R*)-**2c** was treated with a mixture of acetic anhydride (0.6 ml) and pyridine (4 ml) in completely the same manner as that of *dl*-**2c**, affording crude (*R*)(−)-**3c** as a solid after evaporation of the ethyl acetate extracts. Purification by preparative TLC (silica gel, solvent: benzene: THF: acetic acid 80: 20: 1) gave pure (*R*)(−)-**3c** as a colorless solid (215 mg, 54%), mp 95—107°, $[\alpha]_D^{20}$ −14.1° (*c*=2.44, methanol). IR (in $CHCl_3$) and NMR spectra of this sample were identical with those of *dl*-**3c** measured in the same states.

The original 10% HCl layer was basified (pH>14) with 10% NaOH after the reduction product was extracted with ethyl acetate, and the colorless solid crystallized out was collected by filtration. The solid was dissolved into ether, and the insoluble material was filtered off. The clear ethereal filtrate was dried over anhyd. $MgSO_4$, and evaporated *in vacuo* to give crude **7a** (1.02 g, 86% recovery). Purification by column chromatography (silica gel, solvent: $CHCl_3$), followed by recrystallization from hexane gave pure **7a** as colorless needles, mp 87—88°, $[\alpha]_D^{20}$ −29.0° (*c*=4.40, methanol).

b) Table I, Run 8: A solution of **7f** (1.24 g, 6.6 mmol) in ether (20 ml) was added dropwise to a stirred ethereal solution of LAH (0.52 mmol/ml)[38] (12.7 ml, 6.6 mmol) at room temperature. After stirring was continued for 1 hr, an ethereal solution (5 ml) of **8a** (1.61 g, 13.2 mmol) was added to the original mixture, and the whole solution was stirred at room temperature for 30 min, then was cooled to −20° in a dryice-carbon tetrachloride bath. To the cooled mixture was added a solution of anhyd. **1c** (308 mg, 2.0 mmol) in ether (5 ml), and the reaction was continued for 3 hr with stirring at the same temperature. The same work- up procedure as that described in a) gave crude **8a** as a colorless solid (1.51 g, 94% recovery) and crude (*R*)-**2c** as a pale yellow solid (301 mg, 97%), after purification by column chromatography (silica gel 5 g, solvent: first chloroform, then ethyl acetate). Acetylation of the crude (*R*)-**2c**, followed by purification by preparative TLC (silica gel, solvent: benzene: THF: acetic acid 80: 20: 1) in a similar manner to the case for a), gave pure (*R*)(−)-**3c** as a colorless solid (258 mg, 65%), $[\alpha]_D^{20}$ −9.5° (*c*=2.49, methanol). Spectral (IR (in $CHCl_3$)) and chromatographic (TLC) behavior of this product was completely identical with that of *dl*-**3c**.

In this case, recovery of the chiral additive (**7f**) was not attempted.

Asymmetric Reduction of 2-Alkyl-1,3,4-cyclopentanetriones (1) with LAH partially decomposed by (−)-N-Methylephedrine (7a)——a) Table II, Run 1: An ethereal solution of **7a** (3.54 g, 19.8 mmol) was added to a stirred solution of LAH (0.86 mmol/ml)[38] (7.7 ml, 6.6 mmol) and the mixture was stirred at room temperature for 1 hr. After cooling in a dryice-carbon tetrachloride bath, a solution of anhyd. **1c** (308 mg, 2.0 mmol) in ether (5 ml) was added dropwise to the solution containing partially decomposed LAH. Stirring was continued at −20° for 3 hr, then the reaction was quenched by adding 10% HCl (20 ml) at −20°. The whole mixture was extracted with ethyl acetate (×3), and the combined organic extracts were washed with satd. NaCl, and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave crude (*R*)-**2c** as a yellow solid (235 mg, 76%). Acetylation of the crude (*R*)-**2c**, followed by separation with preparative TLC (silica gel, solvent: benzene: THF: acetic acid 80: 20: 1), afforded pure (*R*)(−)-**3c** as a colorless solid (167 mg, 42%), mp 115—119°, $[\alpha]_D^{20}$ −18.5° (*c*=2.82, methanol). Spectral (IR (in $CHCl_3$)) and chromatographic (TLC) properties of this sample were identical with those of *dl*-**3c** measured in the same states.

When recovery of **7a** was examined similarly to the case for Table I run 2, **7a** showing mp 87—88° and $[\alpha]_D^{20}$ −28.3° (*c*=4.39, methanol), was obtained in 84% recovery.

b) Table II, Run 4: To a THF solution of LAH (0.65 mmol/ml)[38] (10.2 ml, 6.6 mmol) was added dropwise a solution of **7a** (3.54 g, 19.8 mmol) in THF (25 ml) at room temperature. After stirring was continued for 1 hr at room temperature, the whole solution was cooled to −70° in a dryice–acetone bath. To the cooled solution was gradually added a THF solution (5 ml) of anhyd. **1c** (308 mg, 2.0 mmol) with stirring. The mixture was stirred at −70° for 3 hr, diluted with 10% HCl (20 ml), and extracted with ethyl acetate (30 ml×4) after the lower aqueous phase was saturated with NaCl. The organic extracts were combined, and washed with satd. NaCl. Filtration and evaporation *in vacuo* gave a yellow viscous oil, which was submitted to column chromatography (silica gel 5 g, solvent: first chloroform, then ethyl acetate). The chloroform eluate was evaporated *in vacuo*, giving the starting **1c** as a colorless solid (60 mg, 19% recovery). Evaporation of the ethyl acetate eluate *in vacuo* afforded crude (*R*)-**2c** as a colorless solid (170 mg, 55%). Acetylation of crude (*R*)-**2c** in a similar fashion to the case for the preparation of *dl*-**3c**, followed by purification with preparative TLC (silica gel, solvent: benzene: THF: acetic acid 80: 20: 1), gave pure (*R*)(−)-**3c** as a colorless solid (165 mg, 42%), mp 111—112°, $[\alpha]_D^{20}$ −29.9° (*c*=2.60, methanol). Spectral

(IR (in $CHCl_3$) and NMR) and chromatographic (TLC) properties of this sample were completely identical with those of *dl*-**3c** recorded in the same states. A part of this solid (107 mg) was once recrystallized from ether, yielding colorless crystals (64 mg), mp 118—125°, $[\alpha]_D^{20}$ −30.1° (c=1.07, methanol). Evaporation of the mother liquor from the recrystallization *in vacuo*, afforded a colorless solid showing mp 118—126° and $[\alpha]_D^{20}$ −27.0° (c=0.69, methanol). This experiment clearly shows that recrystallization from ether was useless for improving the optical purity of (*R*)(−)-**3c**.

c) Table II, Run 8: Completely the same treatments of **1b** (304 mg, 2.0 mmol) as those for the case of b), gave (*R*)(−)-**3b** as a colorless solid (190 mg, 48%), $[\alpha]_D^{20}$ −24.8° (c=1.76, methanol), after acetylation and purification by preparative TLC. This sample was similarly comfirmed by spectral (IR (in $CHCl_3$) and chromatographic (TLC) comparisons with *dl*-**3b**. When a part of (*R*)(−)-**3b** (166 mg) thus obtained, was recrystallized once from ether (45 ml), (*R*)(−)-**3b** which showed mp 126—130° and $[\alpha]_D^{20}$ −43.6° (c=1.20, methanol), was obtained as colorless fine needles (71 mg). Evaporation of the mother liquor from the recrystallization *in vacuo*, gave a colorless solid (88 mg) having lower optical purity, mp 112—117° and $[\alpha]_D^{20}$ −9.0° (c=1.18, methanol).

***dl*-5-Acetoxy-2-allyl-3-methoxy-2-cyclopentenone (*dl*-9) and *dl*-4-Acetoxy-2-allyl-3-methoxy-2-cyclopentenone (*dl*-10)**——An ethereal solution of diazomethane was added dropwise to a stirred solution of *dl*-**3b** (140 mg, 0.71 mmol) in THF (2 ml) cooled in a dryice–acetone bath until the yellow color of diazomethane remained. Evaporation of the mixture *in vacuo* gave a yellow oil. TLC analysis of this crude oil (silica gel, solvent: ether: hexane 4: 1) showed two spots whose *Rf* values were 0.33 and 0.18, respectively. Separation by preparative TLC (silica gel, solvent: ether: hexane 6: 1) afforded *dl*-**9** (*Rf* 0.18) as a colorless oil (63 mg, 42%) and *dl*-**10** (*Rf* 0.33) as an oil (52 mg, 35%). These two sorts of enol ether exhibited the following spectral behaviors.

dl-**9**: IR ν_{max}^{film} cm^{-1}: 3060, 1748, 1700, 1623. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3060, 1745, 1700, 1623. NMR (in $CDCl_3$): 2.12 (3H, s, $OCOC\underline{H}_3$), 2.52 (1H, dm, J=18 Hz, one of $C\underline{H}_2CHO$), 2.89 (2H, d, J=6 Hz, $C\underline{H}_2CH{=}CH_2$), 3.23 (1H, dd, J=18 and 7 Hz, one of $C\underline{H}_2CHO$), 3.95 (3H, s, $OC\underline{H}_3$), 4.8—5.2 (3H, m, $CH{=}C\underline{H}_2{+}C\underline{H}O$), 5.7 (1H, m, $CH_2C\underline{H}{=}CH_2$). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 258 (4.20).

dl-**10**: IR ν_{max}^{film} cm^{-1}: 3060, 1745, 1702, 1635. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3060, 1745, 1700, 1634. NMR (in $CDCl_3$): 2.12 (3H, s, $OCOC\underline{H}_3$), 2.22 (1H, dm, J=18 Hz, one of $C\underline{H}_2CHO$), 2.88 (1H, dd, J=18 and 6 Hz, one of $C\underline{H}_2CHO$), 2.95 (2H, d, J=6 Hz, $C\underline{H}_2CH{=}CH_2$), 3.96 (3H, s, $OC\underline{H}_3$), 4.8—5.0 (2H, m, $CH{=}C\underline{H}_2$), 5.5—6.0 (2H, m, $C\underline{H}{=}CH_2{+}C\underline{H}O$). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 249 (4.21).

(−)-5-Acetoxy-2-allyl-3-methoxy-2-cyclopentenone ((−)-9) and (−)-4-Acetoxy-2-allyl-3-methoxy-2-cyclopentenone ((−)-10)——The same treatment of (−)-**3b** ($[\alpha]_D^{20}$ −14.9° (c=1.78, methanol))[26] (3.20 g, 16.3 mmol) as the case for *dl*-**3d** gave two sorts of oily enol ether, (−)-**9** (1.43 g, 42%), $[\alpha]_D^{20}$ −17.2° (c=2.18, chloroform), and (−)-**10** (1.38 g, 40%), $[\alpha]_D^{20}$ −9.3° (c=1.88, chloroform), after separation by a silica gel column (solvent: ether: hexane 6: 1). Spectral (IR and NMR) properties of these enol ethers were superimposable on those of *dl*-**9** and *dl*-**10**, respectively.

(−)-Allethrolone ((−)-5)——To an ethereal solution of methyllithium (23.5 ml, 22.0 mmol) cooled at −18° in a dryice–carbon tetrachloride bath, was gradually added a solution of (−)-**9** ($[\alpha]_D^{20}$ −17.2° (c=2.18, chloroform)) (1.40 g, 6.7 mmol) in ether (20 ml) with stirring. After stirring was continued at −18° for 1 hr, then at 0° for 2 hr, the whole was poured onto a two layer mixture of 1N HCl (200 ml) and ether (200 ml), and was shaken for 1 min. The upper ethereal layer was separated, and the lower aqueous phase was further extracted with ether (×3). The combined ethereal layers were successively washed with 0.1N $Na_2S_2O_3$, water, and statd. NaCl, then was dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave a yellow oil which was purified by column chromatography (silica gel, solvent: $CHCl_3$: ether 1: 1), giving pure (−)-**5** as a pale yellow oil (0.58 g, 57%). Fractional distillation afforded completely pure (−)-**5** as a colorless oil (477 mg, 47%), bp 105—107° (0.1 mmHg), $[\alpha]_D^{25}$ −2.4° (c=9.94, ethanol.[28]) Since optically pure (*S*)(+)-**5** was reported to show $[\alpha]_D^{25}$ +7.3° (c=13.5, ethanol),[10] it was established that (−)-**5** obtained here, had (*R*)-configuration and its optical purity was 33%.

Conversion of (−)-4-Acetoxy-2-allyl-3-methoxy-2-cyclopentenone ((−)-10) into (−)-4-Acetoxy-2-allyl-1,3-cyclopentanedione ((−)-3b)——A mixture of (−)-**10** ($[\alpha]_D^{20}$ −9.3° (c=1.88, chloroform)) (1.10 g, 5.2 mmol) and 2N HCl (3 ml) in THF (10 ml) was stirred at room temperature for 24 hr. Evaporation, addition of benzene, and further azeotropic evaporation of the benzene solution, gave a semisolid, which was dissolved in pyridine (20 ml). After acetic anhydride (3 ml) was added to the pyridine solution under ice-cooling, the mixture was stirred at 0° for 4 hr. Similar work-up of the mixture to the case for the preparation of *dl*-**3b**, gave a pale brown solid (870 mg) after evaporation of the ethyl acetate extracts. Purification by column chromatography (silica gel, solvent: $CHCl_3$) gave pure (−)-**3b** as a colorless solid (851 mg, 83%), $[\alpha]_D^{20}$ −15.3° (c=2.37, methanol). Spectral (IR (in $CHCl_3$) and NMR) behavior of this solid was identical with that of *dl*-**3b** measured in the same states.

(−)-4-Acetoxy-2-propyl-1,3-cyclopentanedione ((−)-3c) from (−)-4-Acetoxy-2-allyl-1,3-cyclopentanedione ((−)-3b)——A heterogeneous mixture of (−)-**3b** ($[\alpha]_D^{20}$ −15.3° (c=2.37, methanol))[26] (200 mg, 1.0 mmole) and 10% Pd on carbon (20 mg) in ethyl acetate (8 ml) was stirred at room temperature under hydrogen atmosphere (1.0 atmospheric pressure) for 4 hr. Filtration and evaporation *in vacuo* gave pure (−)-**3c** as a colorless solid (174 mg, 87%), $[\alpha]_D^{20}$ −17.6° (c=2.62, methanol). IR (in $CHCl_3$) and NMR spectra of this

solid were superimposable on those of *dl*-**3c** measured in the same states. TLC analysis of this sample showed a single spot whose *Rf* value was the same as that of *dl*-**3c**.

2-(6-Carbomethoxyhexyl)-1,3,4-cyclopentanetrione (1a)——Prepared according to the reported procedure.[9] mp 77—81° (lit.,[9] mp 79—81°). Spectral (IR and NMR) behavior of this sample was identical with those reported.

***dl*-2-(6-Carbomethoxyhexyl)-4-hydroxy-1,3-cyclopentanedione(*dl*-2a)**——Catalytic reduction of **1a** (0.30 g, 1.2 mmol) in a similar manner to that of **1c**, followed by recrystallization from a mixture of ether and hexane gave *dl*-**2a** as a colorless powder (0.20 g, 66%), mp 89—91°. Further recrystallization from the same solvent system yielded an analytical sample as a colorless powder, mp 90—91°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 2600, 1745, 1675, 1557. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 2980, 2840, 1725, 1625. NMR (in $CDCl_3$): 1.1—1.8 (8H, $CH_2(C\underline{H}_2)_4$-CH_2COOMe), 2.0—2.5 (5H, m, $C\underline{H}_2(CH_2)_4C\underline{H}_2COOMe$ +one of $C\underline{H}_2CHO$), 2.85 (1H, dd, J=18 and 6 Hz, one of $C\underline{H}_2CHO$), 3.64 (3H, s, $COOC\underline{H}_3$), 4.61 (1H, dm, J=6 Hz, $C\underline{H}O$), 4.8—5.4 (2H, br s, $O\underline{H}$+$\underline{H}OC$=C–CO). TLC analysis (silica gel, solvent: benzene: THF: formic acid 15: 5: 2, coloring agent UV and I_2) of this sample showed a single spot whose *Rf* value was 0.46. *Anal.* Calcd. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.96; H, 7.95.

(*R*)(+)-2-(6-Carbomethoxyhexyl)-4-hydroxy-1,3-cyclopentanedione((*R*)(+)-2a)——The same treatment of **1a** (254 mg, 1.0 mmol) as that of **1c** (Table II, run 4), gave crude (*R*)(+)-**2a** as a solid after evaporation of the ethyl acetate extracts. Separation by column chromatography (silica gel 5 g, solvent: ethyl acetate), afforded **1a** as a colorless solid (68 mg, 27% recovery) and (*R*)(+)-**2a** as a pale yellow solid (155 mg, 61%). The pale yellow color of the product was removed by treating with charcoal after dissolving into methanol. Evaporation of the methanolic filtrate *in vacuo* gave (*R*)(+)-**2a** as a colorless solid (149 mg, 58%), $[\alpha]_D^{23}$ +8.8 ±1° (c=1.00, chloroform). Spectral (IR (in $CHCl_3$)) and chromatographic (TLC) behavior of this solid was completely identical with that of *dl*-**2a** measured in the same states. Recrystallization of (*R*)(+)-**2a** (138 mg) thus obtained, from ethyl acetate gave a pale yellow powder (39 mg) which showed mp 80—84° and $[\alpha]_D^{23}$ +11.4±1.5° (c=0.63, chloroform). Evaporation of the mother liquor from the recrystallization gave (*R*)(+)-**2a**, being less optically active (97 mg), mp 67—79°, $[\alpha]_D^{23}$ +4.4±1° (c=1.04, chloroform).

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