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Stereochemical Studies. XXIX.[1] Asymmetric Synthesis of 2-Alkylcyclohexanones *via* optically Active Lithioenamines[2]

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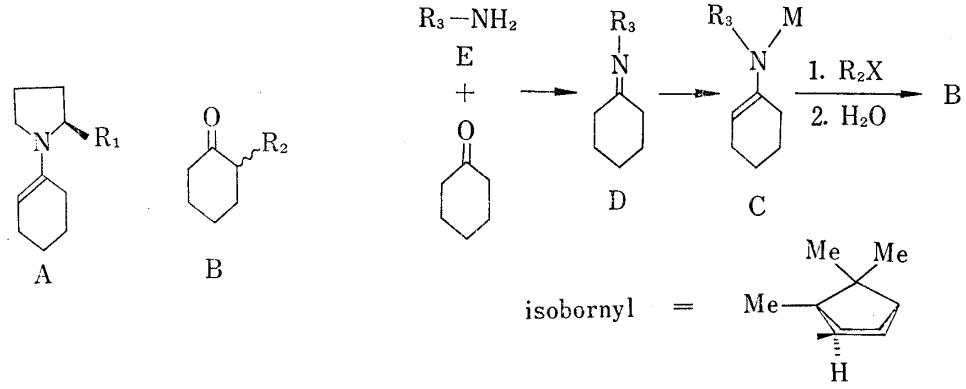
Recently, we undertook fundamental studies on the asymmetric alkylations of cyclohexanone 2-substituted pyrrolidine enamines (A: R_1=COOMe, COOEt and COO*t*-Bu), and explored an unique versatility of enamine alkylations in the field of asymmetric synthesis.[4]

However, as it could be expected from the original studies on enamine alkylation conducted by Stork, *et al.*,[5] we also observed that the asymmetric alkylations of A ($R_1 \neq H$) afforded desired optically active 2-alkylcyclohexanones (B: R_2=α-alkyl) (at most 59% optical yield) in moderate yields only when electrophilic olefins, *i.e.* acrylonitrile and methyl acrylate, or strongly electrophilic alkyl halides, *i.e.* allyl bromide and ethyl bromoacetate, were employed as an electrophile.[6]



In order to circumvent these difficulties in the enamine reaction, Stork, *et al.*[5c] developed a new method in which the metalloenamines (C: R_3=*t*-Bu, M=MgBr) prepared with the imine (D) (R_3=*t*-Bu) and Grignard reagent, could be easily alkylated with primary and secondary alkyl halide to afford 2-alkylcyclohexanone (B: R_2=*n*-Bu, *etc.*). This novel method was subsequently applied by Horeau, *et al.*[7] to the asymmetric synthesis of *S*(+)-2-methylcyclo-

1) Part XXVIII: T. Sone, K. Hiroi, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2331 (1973).
2) A part of this report was presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972.
3) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) *a*) S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Letters*, **1969**, 4233; *b*) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 246 (1972); *c*) K. Hiroi and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 47 (1973).
5) *a*) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954); *b*) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963); *c*) G. Stork and S.R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).
6) Although A(R_1=H) could be successfully alkylated with methyl iodide or *n*-butyl iodide according to ref. 5*b*), similar treatment of A($R_1 \neq$H) gave no trace amount of the desired B(R_2=α-alkyl) (S. Yamada and K. Hiroi, unpublished results).
7) D. Mea-Jacheet and A. Horeau, *Bull. Soc. Chim. France*, **1968**, 4571.

hexanone (B: R_2=β-Me) by using metalloenamine (C: R_3=isobornyl, M=MgBr) and methyl iodide.

In this reaction, C(R_3=isobornyl, M=MgBr) was derived from cyclohexanone and isobornylamine by way of the imine (D: R_3=isobornyl), and B(R_2=β-Me) having 72% optical integrity, could be successfully obtained in 58% yield.[7,8] However, it was also stated by Horeau, *et al.*[7] that the same asymmetric reaction attempted with *S*(+)-amphetamine or *R*(+)-α-phenethylamine in place of isobornylamine afforded B(R_2=Me) having less than 10% optical activity.

Since it was recently found[9] that the metallation of the imine (D) could be also accomplished by treating D with lithium diisopropylamide, we attempted the asymmetric alkylation of C(M=Li) which were obtainable from cyclohexanone and optically active primary amines (E) by way of D, as was done by Horeau, *et al.*[7]

This report concerns with the preliminary results for these attempts, which were obtained using *S*(−)-α-phenethylamine (*S*(−)-**1a**), and *S*(+)-*sec*-butylamine (*S*(+)-**1b**) as an optically active primary amine counterpart.

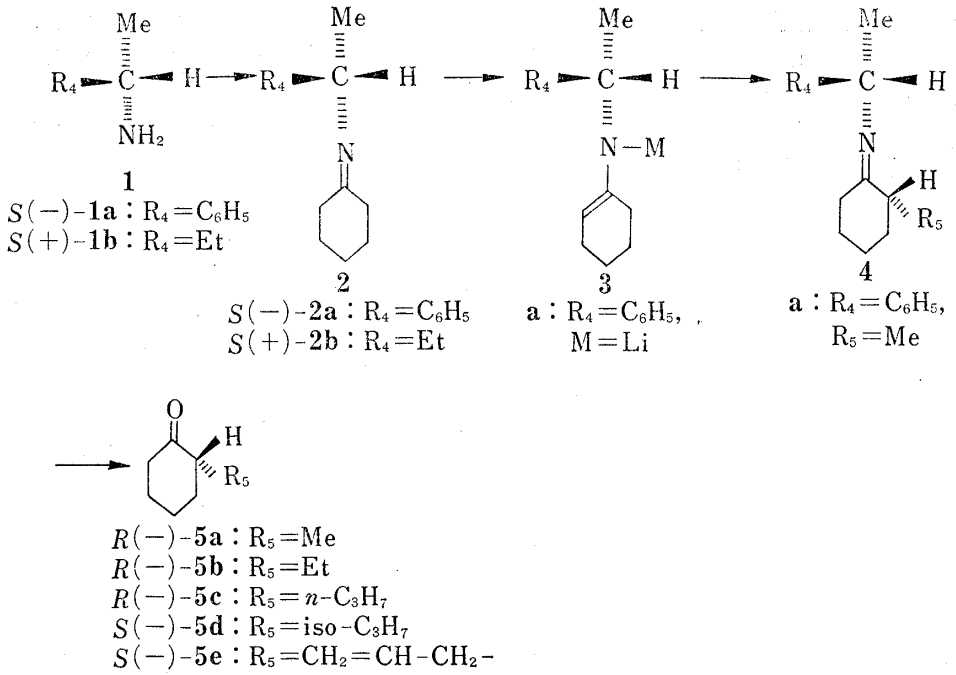


Chart 1

As shown in Chart 1, condensation of *S*(−)-**1a**, α_D^{20} −3.79° (*l*=0.1, neat), $[\alpha]_D^{20}$ −39.4° (benzene), 100% optically pure[10] and cyclohexanone in benzene under an azeotropic condition afforded the imine (*S*(−)-**2a**), α_D^{20} −5.44° (*l*=0.1, neat), in 90% yield. No racemization during the preparation of *S*(−)-**2a** from *S*(−)-**1a**, was clearly established by reconverting *S*(−)-**2a** to *S*(−)-**1a**, $[\alpha]_D^{20}$ −39.6° (benzene) on treatment with water. *S*(−)-**2a** was converted to the lithioenamine (**3a**), *in situ*, by adding to a tetrahydrofuran solution of lithium diisopropylamide (1.2 eq.)[9] below −20°. Treatment of **3a** with methyl iodide (1.3 eq.) at −60— −50° for 0.75 hr gave the alkylated imine (**4a**), which without isolation, was hydrolyzed after the reaction was neutralized (pH=7.0) with 1N hydrochloric acid, to give

8) J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall Inc., New Jersey, 1971, p. 286.
9) *a*) D.A. Evans, *J. Am. Chem. Soc.*, **92**, 7593 (1970); *b*) G. Stork and J. Benaim, *J. Am. Chem. Soc.*, **93**, 5938 (1971).
10) *a*) S. Terashima, M. Wagatsuma, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **18**, 1137 (1970); *b*) S. Terashima, K. Takashima, T. Sato, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 1135 (1973).

TABLE I. Asymmetric Synthesis of 2-Alkylcyclohexanone (5) Using Various Alkyl Halides[a)]

Run	Optically active imines (2) used			Alkyl halides used[c)]	Formed optically active 2-alkylcyclohexanones (5)						
	Compds	R_4	Optical[b)] purity (%)		Compds	R_5	Isolated yield (%) based on 2[d)]	bp °C (mmHg)	$[\alpha]_D$ (c, t, MeOH)	Optical yield (%)	Absolute confign. at C_2[e)]
1	*S*(−)-**2a**	C_6H_5	100	MeI	**5a**	Me	42 (A)	109 (150)	−3.7° (1.534, 25)	26[f)]	*R*
2	*S*(−)-**2a**	C_6H_5	100	EtI	**5b**	Et	44 (A and B)	119—120 (150)	−16.0° (2.059, 20)	—[g)]	*R*
3	*S*(−)-**2a**	C_6H_5	100	*n*-C_3H_7I	**5c**	*n*-C_3H_7	48 (A)	119—120 (120)	−10.0° (2.610, 20)	37[h)]	*R*
4	*S*(+)-**2b**	Et	84	*n*-C_3H_7I	**5c**	*n*-C_3H_7	47 (A and B)	130 (115)	−1.7° (4.462, 20)	6[h)]	*R*
5	*S*(−)-**2a**	C_6H_5	100	iso-C_3H_7I	**5d**	iso-C_3H_7	26 (A and B)	124—125 (95)	−20.2° (1.566, 23)	27[i)]	*S*
6	*S*(−)-**2a**	C_6H_5	100	CH_2=CH–CH_2Br	**5e**	CH_2=CH–CH_2	51 (A)	110 (55)	−4.5° (2.219, 20)	33[d)]	*S*

a) All alkylations were carried out under the same reaction condition as that for run 1 (see Experimental).
b) Optical purity of the starting amines was used since no racemization during preparation of *S*(−)-**2a** from *S*(−)-**1a** was clearly established.
c) 1.3 eq. of alkyl halides were used.
d) After purified by fractional distillation (A) and/or by silica gel column chromatography (solvent: petr. ether: ether=4:1) (B). All samples are completely homogeneous by gas-liquid chromatography (15% SE-30 on Diasolid L, 2.25 m, 60°) and/or thin-layer chromatography (TLC) analysis (silica gel petr. ether:ether=4:1).
e) Determined based on the octant rule. For ORD curves of these compounds, see Experimental.
f) (+)-**5a** showing $[\alpha]_D$ +14° (*c*=0.23, MeOH) was assumed to be 100% optically pure (see ref. 11).
g) not determined
h) (−)-**5c** showing $[\alpha]_D^{20}$ −27.9° (MeOH) was assumed to be 100% optically pure (see ref. 6*b*).
i) (+)-**5d** showing $[\alpha]$ (MeOH): +2126° (312 mμ), −2126° (272 mμ), and amplitude 43 in the ORD measurement, was assumed to be 100% optically pure (see C. Djerassi, P.A. Haat and C. Beard, *J. Am. Chem. Soc.*, **86**, 85 (1964)). (−)-**5d** obtained here showed $[\alpha]$ (*c*=1.566, MeOH): −575° (310 mμ), +575° (270 mμ), and amplitude −11.5°.
j) (−)-**5e** showing $[\alpha]_D^{27.5}$ −13.7° (*c*=2.046, MeOH) was assumed to be 100% optically pure (see ref. 6*b*).

(−)-2-methylcyclohexanone ((−)-**5a**), $[\alpha]_D^{25}$ −3.7° (methanol), in 42% yield based on *S*(−)-**2a**. The absolute configuration of (−)-**5a** has been already established to be *R*-configuration by the studies on optical rotatory dispersion (ORD) undertaken by Djerassi, *et al.*[11] Optical yield of *R*(−)-**5a** for this alkylation was elucidated to be 26%, based on the assumption that *S*(+)-**5a** reported to have [α] +14° (methanol)[12] was optically pure.

Similarly, as shown in Table I, alkylations of **3a** with ethyl iodide, *n*-propyl iodide, isopropyl iodide, and allyl bromide afforded optically active 2-alkylcyclohexanones (*R*(−)-**5b**, *R*(−)-**5c**, *S*(−)-**5d**, and *S*(−)-**5e**). The absolute configurations of these ketones were determined by measuring their ORD curves which showed a negative Cotton effect around 285—290 mμ in methanol as did *R*(−)-**5a**.[13] Optical yields for these asymmetric alkylations could be calculated by the assumption described in the foot notes of Table I.[14] Result obtained with *S*(+)-**1b**, α_D^{20} +0.459° (*l*=0.1, neat), 84% optically pure,[15] and *n*-propyl iodide was also shown in the Table.

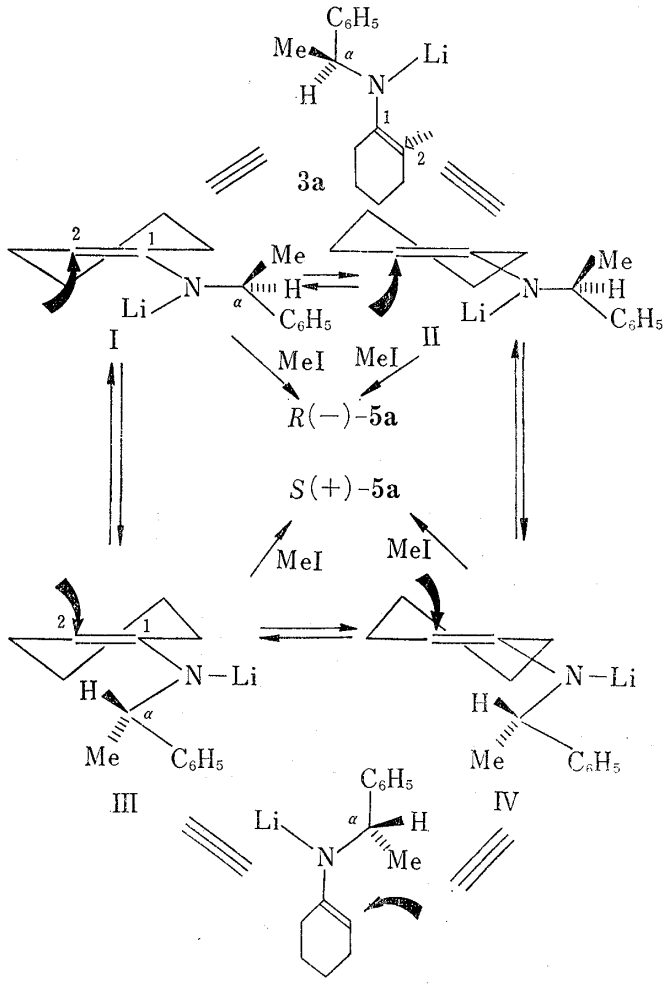
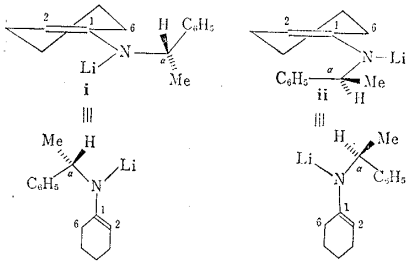


Chart 2

From results summarized in the Table, it is evident that absolute configuration of the formed **5** can be cleanly correlated to that of **1** employed. That is, optically active amines **1** having *S*-configuration generally afford **5** possessing α-alkyl substituent even though sign of absolute configuration of **5** was variable.

Many possible explanations might be anticipated for this asymmetric alkylation. However, as shown in Chart 2, four conformers, I, II, III, and IV could be drawn for **3a** by assuming the coplanality in N–C_1–C_2 bond system due to stereoelectronic reason,[4b] and the cisoid coplanarity in Li–N–C_α–C_6H_5 bond system because of steric factor.[16] Arrows in conformers I, II, III, and IV represent the direction of prefered attack by alkyl halide, which

11) C. Beard, C. Djerassi, T. Elliott, and R.C.C. Tao, *J. Am. Chem. Soc.*, **84**, 874 (1962).
12) C. Beard, C. Djerassi, J. Sicher, F. Šipoš, and M. Tichy, *Tetrahedron*, **19**, 919 (1963).
13) See also ref. 4*b*).
14) Optical yield of *R* (−)-**5b** could not be determined because of lack of the optical rotation for optically pure sample.
15) *a*) P. Bruck, I.N. Denton, and A.H. Labberton, *J. Chem. Soc.*, **1956**, 921; *b*) L. Verbit and P.J. Heffron, *J. Org. Chem.*, **32**, 3199 (1967).
16) Transoid coplanality such as **i** or **ii** in Li-N-Cα-C_6H_5 bond system might be excluded due to the steric interaction between phenyl group and C_6 or C_2-hydrogens.



is expected by comparing the steric bulkiness of C_α-methyl group and C_α-hydrogen. Considering the absolute configuration of *S*(−)-**1a** and the formed **5**, prefered alkylation in the conformers I and/or II should be responsible for this novel asymmetric synthesis.

Further exploitation of this asymmetric reaction to more complex system is under progress.

Experimental[17]

Preparations of Schiff Bases (*S*(−)-2a, and *S*(+)-2b)——*S*(−)-**2a**: A benzene solution (30 ml) of cyclohexanone (4.66 g, 0.0384 mole) and *S*(−)-**1a** (α_D^{20} −3.79° (*l*=0.1, neat), $[\alpha]_D^{20}$ −39.4° (*c*=5.104, benzene), 100% optically pure[10]) (3.78 g, 0.0384 mole) was refluxed under an azeotropic condition for 3.5 hr, then was evaporated *in vacuo* to give an oily residue. The residue was distilled under reduced pressure to afford pure *S*(−)-**2a** (6.93 g, 90%) as a colorless oil, bp 119—120° (3 mmHg), α_D^{20} −5.44° (*l*=0.1, neat). IR ν_{max}^{film} cm^{-1}: 1655 ($\nu_{C=N}$). NMR (in $CDCl_3$): 1.3—1.85 (9H, m, other protons), 2.3 (4H, m, $C\underline{H}_2$-C=N), 4.68 (1H, q, *J*=6.7 cps, C<u>H</u>-N), 7.1—7.4 (5H, m, aromatic protons). This oil was immediately used for the next step. Treatment of *S*(−)-**2a** thus prepared, with water followed by extractive isolation and purification by fractional distillation afforded *S*(−)-**1a**, $[\alpha]_D^{20}$ −39.6° (*c*=2.600, benzene), which was identified with the starting *S*(−)-**1a** by comparing their IR spectra.

S(+)-**2b**: A mixture of cyclohexanone (1.47 g, 0.015 mole), *S*(+)-**1c** (α_D^{20} +0.459° (*l*=0.1, neat), 84% optically pure[15]) (1.10 g, 0.015 mole) and molecular sieves 4A (*ca.* 2 g) in ether (20 ml) was stirred at room temperature for 12 hr.[18] Filtration and evaporation *in vacuo* gave an oily residue, which was submitted for fractional distillation to give pure *S*(+)-**2b** (1.67 g, 72%) as a colorless oil, bp 114—117° (91 mmHg), α_D^{20} + 3.60° (*l*=0.1, neat). IR ν_{max}^{film} cm^{-1}: 1660 ($\nu_{C=N}$). NMR (in $CDCl_3$): 0.80 (3H, t, *J*=7.0 cps, $C\underline{H}_3CH_2$), 1.05 (3H, d, *J*=7.6 cps, $C\underline{H}_3CH$-), 1.30—2.00 (8H, m, other protons), 2.30 (4H, m, $C\underline{H}_2$-C=N), 3.42 (1H, m, CH_3-C<u>H</u>-). This oil was directly used for the next step.

Alkylations of Schiff Bases with Alkyl Halides——Reaction procedure for the alkylation of *S*(−)-**2a** with methyl iodide (Table I, run 1) was described as an example. Other alkylations were conducted under the same condition as that described here. *n*-Butyl lithium (1.43M solution in hexane) (8.40 ml, 0.012 mole) was added to a tetrahydrofuran solution (8 ml) of di-isopropylamine (1.21 g, 0.012 mole) with stirring under nitrogen atmosphere below −20°. The whole was stirred at the same temperature for 0.16 hr to afford a solution of lithium di-isopropylamide,[9] to which was added a tetrahydrofuran solution (3 ml) of *S*(−)-**2a** (2.10 g, 0.010 mole). After stirring for 1.0 hr in an ice bath, the reaction mixture was cooled to −60° in a dry ice-acetone bath. Then, a tetrahydrofuran solution (3 ml) of methyl iodide (1.84 g, 0.013 mole) was gradually added to a cooled solution of the lithioenamine (**4a**) over 0.25 hr at *ca.* −60°. After stirred at −50°——60° for 0.75 hr, the whole reaction mixture was neutralized to pH=7.0 with 1N hydrochloric acid, then was stirred at room temperature for 0.25 hr. The aqueous solution was diluted with benzene (150 ml), and was successively washed with 1N hydrochloric acid (2 ml×2), 5% $Na_2S_2O_3$, satd. $NaHCO_3$, and satd. NaCl solution. After drying over anhyd. Na_2SO_4, filtration and evaporation *in vacuo* gave an oily residue, which was distilled under reduced pressure to give pure *R*(−)-**5a** (0.47 g, 42% based on *S*(−)-**2a**, bp 109° (150 mmHg). α_D^{20} −0.407° (*l*=0.1, neat) $[\alpha]_D^{25}$ −3.7° (*c*=1.534, MeOH). IR ν_{max}^{film} cm^{-1}: 1715 ($\nu_{C=O}$). NMR (in $CDCl_3$): 1.00 (3H, d, *J*=7.0 cps, $C\underline{H}_3$), 1.10—2.60 (9H, m, other protons). ORD (*c*=1.534, MeOH) $[\alpha]^{25}$ (mμ): −2.3° (700), −3.7° (589), −4.7° (550). −6.5° (500), −10.7° (450), −18.8° (400), −49.4° (350), −227° (304) (trough), 0° (285), +228° (265) (peak).

Semicarbazone[19]: mp 195° (recrystallized from ethanol). *Anal.* Calcd. for $C_8H_{15}ON_3$: C, 56.78; H, 8.94; N, 24.83. Found: C, 56.71; H, 8.93; N, 24.85.

Physical Data of Optical Active 2-Alkylcyclohexanones (5), Other Than Those Shown in the Table I——*R*(−)-**5b**: IR ν_{max}^{film} cm^{-1}: 1715 ($\nu_{C=O}$). NMR (in $CDCl_3$): 0.85 (3H, t, *J*=7.0 cps, $C\underline{H}_3CH_2$), 1.1—2.5 (11H, m, other protons). ORD (*c*=2.059, MeOH) $[\alpha]^{20}$(mμ): −10.7° (700), −16.0° (589), −19.4° (550), −27.2° (500), −41.8° (450), −72.4° (400), −203° (350), −816° (304) (trough), 0° (288), +893° (266) (peak). 2,4-

17) All melting and boiling points are uncorrected. IR spectra measurements were performed with a Spectrometer, Model IR-S, Japan Spectroscopic Co., Ltd. NMR spectra were measured with a Spectrometer Model JNM-TS-100 (100 Mc), Japan Electron Optics Lab., and data are reported in parts per million (ppm) downfield from internal tetramethylsilane. Following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were determined with a Yanaco OR-50 Automatic Polarimeter, and ORD curve measurements were carried out with a Spectrometer, Model ORD/UV-5, Japan Spectroscopic Co., Ltd. Gas chromatographic analyses were made with a Yanagimoto Gas chromatograph, Model GCG-550T.

18) T. Taguchi and F.H. Westheimer, J. *Org. Chem.*, **36**, 1570 (1971).

19) Measurement of optical rotation was not attempted for this sample.

Dinitrophenylhydrazone[19]: mp 162° (recrystallized from EtOH). *Anal.* Calcd. for $C_{14}H_{18}O_4N_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.90; H, 6.05; N, 18.06.

R(−)-**5c**: IR ν_{max}^{film} cm^{-1}: 1710 ($\nu_{C=O}$). NMR (in $CDCl_3$): 0.90 (3H, t, J=6.0 cps, $C\underline{H}_3CH_2CH_2$), 1.0—2.6 (13H, m, other protons). IR and NMR spectra of *R*(−)-**5c** prepared with *S*(−)-**2a** and *S*(+)-**2b** were identical when measured in the same states. ORD (c=2.610, MeOH) $[\alpha]^{20}(m\mu)^{20}$: −7.3° (700), −10.2° (589), −11.9° (550), −16.9° (500), −24.6° (450), −41.4° (400), −107° (350), −376° (305) (trough), 0° (289), +346° (274) (peak). Semicarbazone[19]: mp 130° (recrystallized from EtOH). *Anal.* Calcd. for $C_{10}H_{19}O_2N_3$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.80; H, 9.61; N, 21.48.

S(−)-**5d**: IR ν_{max}^{film} cm^{-1}: 1710 ($\nu_{C=O}$). NMR (in $CDCl_3$): 0.90 (6H, d, J=7.0 cps, $(C\underline{H}_3)_2CH$), 1.1—2.5 (10H, m, other protons). ORD (c=1.566, MeOH) $[\alpha]^{23}(m\mu)$: −14.0° (700), −21.7° (589), −27.4° (550), −35.0° (500), −47.8° (450), −79.8° (400), −179° (350), −575° (310) (trough), 0° (290), +575° (270) (peak). Semicarbazone[19]: mp 185° (recrystallized from EtOH). *Anal.* Calcd. for $C_{10}H_{19}ON_3$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.89; H, 9.70; N, 21.54.

S(−)-**5e**: IR ν_{max}^{film} cm^{-1}: 1716 ($\nu_{C=O}$), 1640 ($\nu_{C=C}$). NMR (in $CDCl_3$): 1.10—2.80 (11H, m, other protons), 4.91 (1H, d, J=1 cps $_{H}\!>\!C\!=\!C\!<^{H}_{H}$), 5.05 (1H, d, J=6 cps, $_{H}\!>\!C\!=\!C\!<^{H}_{H}$), 5.5—6.0 (1H, m, $-C\underline{H}\!=\!CH_2$). ORD (c=2.219, MeOH) $[\alpha]^{20}(m\mu)$: −3.6° (700), −4.5° (589), −6.3° (550), −9.0° (500), −14.9° (450), −27.0° (400), −76.5° (350), −302 (306) (trough), 0° (288), +306° (264) (peak). Semicarbazone[19]: mp 172° (recrystallized from EtOH). *Anal.* Calcd. for $C_{10}H_{17}ON_3$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.53; H, 8.63; N, 21.34.

Acknowledgement The authors are grateful to the members of the Central Analysis Room of this Faculty for elemental analyses and spectral data.

20) This ORD curve was measured for *R*(−)-**5c** prepared with *S*(−)-**2a**.

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Conversion of Digitoxigenin to Uzarigenin

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A great number of cardenolide aglycones have been found in nature, the majority of which belong to *cis*- or *trans*-A/B steroids.[2] There are several instances where both type cardenolides isomeric only at the C-5 position are known. Between 5β- and 5α-cardenolide, however, the former far predominates over the latter. It is to be desired, therefore, to devise a simple, convenient method of converting 5β-cardenolide to 5α-cardenolide. This paper describes the conversion of digitoxigenin (I) to uzarigenin (IIa), which represent 5β- and 5α-cardenolide respectively.

Previously[3] it was reported that 3-hydroxy-5β-steroids undergo epimerization at the C-5 position to provide 3-keto-5α-compounds on heating under reflux with freshly prepared Raney nickel in a solvent such as *p*-cymene. This procedure has been successfully applied to 5β-cholanoates for the preparation of 5α-cholanoates.[4–7] The attempt[8] to prepare IIa,

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