An Asymmetric Synthesis of Acyclic and Macrocyclic α-Alkyl Ketones. The Role of (*E*)- and (*Z*)-Lithioenamines

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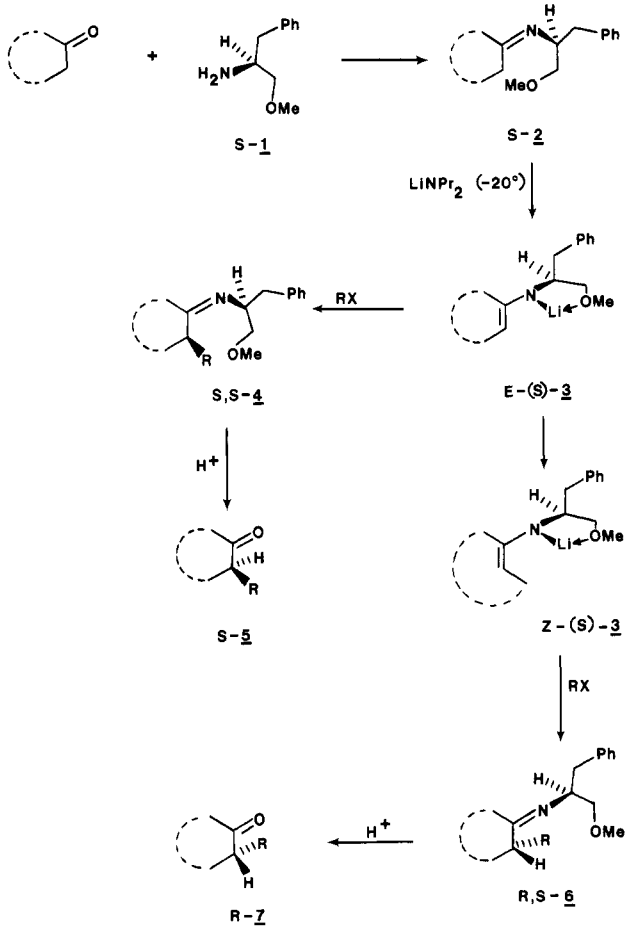
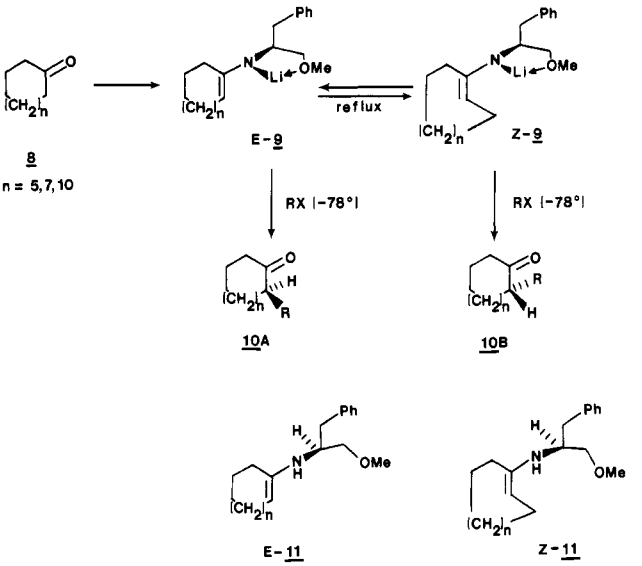
Abstract: Metalation and alkylation of chiral imines derived from C_{10}, C_{12}, and C_{15} cyclic ketones gave, under kinetic metalation conditions, 2-alkylcycloalkanones of absolute configuration opposite to that formed from thermodynamic metalation. Thus, (*S*)-(−)-2-methylcyclododecanone is formed kinetically in 60% ee, whereas (*R*)-(+)-2-methylcyclododecanone is reached in 80% ee under thermodynamic conditions. In a similar fashion, acyclic ketones **20**, via their chiral imines **17**, are alkylated enantioselectively under both kinetic and thermodynamic modes. The kinetic metalation gives exclusively the (*Z*)-lithioenamines (**19**), while reflux of this lithio anion gives only the (*E*)-lithioenamine (**19**). Chiral α-substituted ketones are produced in 18–97% ee.

The enantioselective alkylation of cyclic ketones leading to α-substituted cycloalkanones in high enantiomeric purity has been described in the preceding paper.[2] The success of this method depended mainly on the chiral imine (*S*)-**2** derived from various cyclic ketones and the methoxyamine (*S*)-**1**. Metalation of **2** with



LDA in THF at −20 °C led to the lithioenamine **3** which upon alkylation gave (*S,S*)-**4** in high diastereomeric ratio and after hydrolysis produced the α-alkyl ketones **5**. The purpose of the present study was to evaluate the key intermediate, lithioenamine **3**, which possessed rigid topological features due to the chelation

Scheme I



of lithium ion by the methoxyl group. Since the cyclic ketones previously studied[2] were all C_6–C_8, there was little concern for the C=C geometry in **3** being other than *E*. However, it should be possible to generate a (*Z*)-enamine moiety if the ketones were of the acyclic variety or even if they were cyclic and contained more than 10 carbons. Large cycloolefins have been studied and appear to have their stability favored in either the cis or trans form depending, of course, on the ring size.[3] For example, *trans*-cyclooctene is highly unstable with respect to the cis isomer, whereas, for the C_9 and C_{10} cycloolefins, the energy difference is smaller. However, for C_{11} and C_{12} cycloolefins, the trans isomers are more stable by approximately 1 kcal/mol. Assuming comparable cis–trans energies in the lithioenamines, it should be feasible to isomerize (*E*)-**3** to (*Z*)-**3**, causing a reversal in the prochiral face which then would lead to the optical antipodes **7**.

In this report we will show that *E*–*Z* isomerization does indeed occur and leads to optical antipodes with moderate to excellent enantiomeric purity.[4] Three medium-ring ketones **8** (cyclodecanone, cyclododecanone, and cyclopentadecanone) were studied (Scheme I) in regard to their ability to furnish either optical antipodes of the α-alkyl ketones **10A** and **10B**. These ketones were transformed into their imines with (*S*)-**1** and metalated with LDA

(1) (a) A portion of this work was taken from the Ph.D. thesis of D.R.W, 1978. (b) National Research Award Postdoctoral Fellow.

(2) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S. *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) Cope, A. C.; Moore, W. R. *J. Am. Chem. Soc.* **1959**, *81*, 3153. Turner, R. B.; Meador, W. R. *Ibid.* **1957**, *79*, 4133.

(4) A portion of this work was reported in preliminary form: Meyers, A. I.; Williams, D. R. *J. Org. Chem.* **1978**, *43*, 3245.

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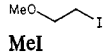
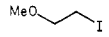
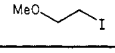
Table I. Alkylation of Cyclic Ketones and the *E,Z* Ratios of Metalloenamines

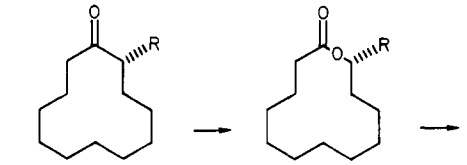
imine (*S*)-**2** from	metalation condtns[d]	ratio of metalloenamine[b] *E*-**9**/*Z*-**9**	alkyl[c] halide	% yield of **10**	$[\alpha]^{23}_D$[d]	% ee,[e] (confn)[f]
cyclodecanone (C_{10})	LDA, −78 °C	45:55	MeI	80	−3.14	30 (*S*)
	LDA, −25 °C	33:66	MeI	71	−3.24	31 (*S*)
	LDA, reflux	0:100	MeI	77	−3.16	30 (*S*)
	t-BuLi, −78 °C	*g*		79	−12.10	31 (*R*)
cyclododecanone (C_{12})	LDA, −78 °C	100:0	MeI	88	−6.90	59 (*S*)
	LDA, −25 °C	100:0	*h*			
	LDA, reflux	0:100	MeI	83	+10.30	81 (*R*)
	t-BuLi, reflux	*g*		85	+1.88	79 (*S*)
cyclopentadecanone (C_{15})	LDA, −20 °C	100:0	MeI	75	−4.31	37 (*S*)
	LDA, reflux	0:100	MeI	78	+7.90	81 (*R*)
	LDA, reflux	*c*		70	+1.17	82 (*S*)

[a] Solutions of imine were 0.05 M in THF. [b] Ratios determined by quenching in MeOH at −78 °C and integrating the respective vinyl proton of isolated product **11** (Experimental Section). [c] Alkyl halide added at −78 °C. [d] Solutions of chloroform, concentrations given in Experimental Section under each compound. [e] Determined by Optishift II (Aldrich); tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III). [f] Predicted absolute configuration on the basis of reaction mechanics. [g] Not determined. [h] Alkylation not performed in this experiment.

at −20 °C in THF to give the lithioenamine (*E*)-**9**. Addition of an alkyl halide (−78 °C) followed by hydrolysis (NaOAc/HOAc, water/pentane) gave the optically active ketone **10A**. However, if the initially formed THF solution of the lithioenamine is heated to reflux for 30–60 min and the resulting solution of (*Z*)-**9** cooled down to −78 °C, treated with an alkyl halide, and hydrolyzed, there was obtained the optically active ketone **10B**. Except for cyclodecanone, the major enantiomer was different from each route. As can be seen from Table I, the enantiomer of C_{12} and C_{15} ketone from the low-temperature metalation is opposite to that obtained from heating the lithioenamine, whereas the same enantiomer was formed from cyclodecanone regardless of the method employed. For determination of the *E*–*Z* ratios of **9** under low-temperature formation (kinetic conditions) and after heating of **9** (thermodynamic conditions), the lithioenamines were quenched with MeOH (−78 °C), employing the technique of Knorr.[5] Proton magnetic resonance spectra of the protonated material showed virtually exclusive (*E*)-vinyl amine **11** from the cold-treated lithioenamine (*E*)-**9** and only the (*Z*)-vinyl amine **11** from the heated lithioenamine (*Z*)-**9**. However, the C_{10} ketone again exhibited diverse behavior when compared to the C_{12} and C_{15} ketones. Although the C_{10} imine gave 100% (*Z*)-vinyl amine (**11**) after reflux of its lithium salt, the kinetic ratio for **11** was about 2:1 favoring the *Z* isomer (Table I). Thus, the *Z* isomer appeared to be favored both kinetically and thermodynamically. No meaningful explanation can be offered at this time other than lengthy conjecture concerning the lack of response of the C_{10} ketone to kinetic and thermodynamic effects since both lithioenamines of C_{10} gave the (−)-2-methylcyclodecanone. Presumably, the alkylation step is not stereoselective in the *Z* isomer even though it was exclusively present as the thermodynamic lithio salt.

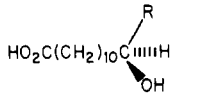
A comment on the C_{12} and C_{15} ketones and their respective asymmetric alkylation is in order. Even though exclusive (*E*)-lithioenamines are formed kinetically and (*Z*)-lithioenamines are formed thermodynamically, the % ee of the α-alkyl ketones is 40–60% in the former and ~80% in the latter. This simply means that once again the selectivity of the alkylation step still leaves something to be desired and this could be the result of the yet unknown ring conformations in the (*E*)- and (*Z*)-lithioenamines. In a further attempt to manipulate the *E,Z* ratios of the lithioenamines **11**, the kinetic deprotonation was examined with bases of various steric bulk. Thus, *t*-BuLi, $LiNEt_2$, LDA/HMPA, and lithium tetramethylpiperidide were employed to increase the % ee of the kinetic product. However, little was gained and the % ee's were not significantly affected or gave even poorer enantiomeric purities. Some of these results were due to the extremely strong bases which affected varying degrees of racemization (epimerization) of the alkylated imines **6**. Irradiation (Pyrex) at 330 nm, the maximum absorbance band of lithioenamines (azaallyl anions), also failed to effect the ratios of the asymmetric alkylation although light induced cis–trans isomerization of anionic species has been described.[6]

Since the chiral α-substituted ketones had not been previously described in enantiomerically pure form, it was necessary, in addition to assessing the ee's, to also determine the absolute configuration. The ee's were determined within 4–5% by using chiral shift reagents by observing, in the case of the methyl derivative, the methyl doublets. In the case of the methoxyethyl derivative, the methoxyl singlet proved to be a useful probe. The absolute configuration was a more difficult task. The CD spectrum of the C_{12} and C_{15} ketones gave a double Cotton effect, a phenomenon that is relatively rare.[8] This has been attributed to different conformations due to solvation about a lone chromophore. This behavior made the correlation to the cyclohexanone series virtually impossible, and an alternative approach was therefore required. Baeyer–Villiger oxidation of (+)-2-methylcyclododecanone **10a** gave the lactone **13a** which was hydrolyzed with

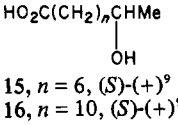


(+)-**10a**, R = Me
(+)-**10b**, R = *n*-hexyl

13a, R = Me
13b, R = *n*-hexyl



(*R*)-(−)-**14a**, R = Me
(*R*)-(−)-**14b**, R = *n*-hexyl



15, *n* = 6, (*S*)-(+)[9]
16, *n* = 10, (*S*)-(+)[9]

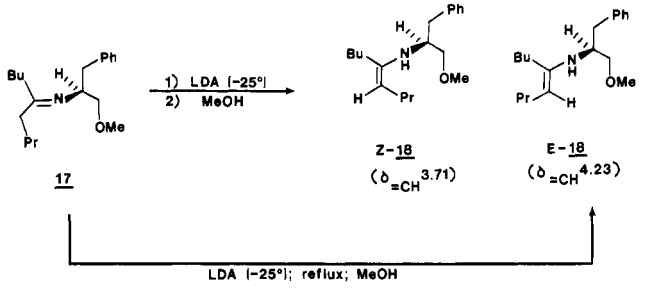
ethanolic/KOH to 12-hydroxytridecanoic acid **14a** which had $[\alpha]_D$ −4.30°. Unfortunately, this compound could not be found in the

(5) Knorr, P.; Low, P. *J. Am. Chem. Soc.* **1980**, *102*, 3241.

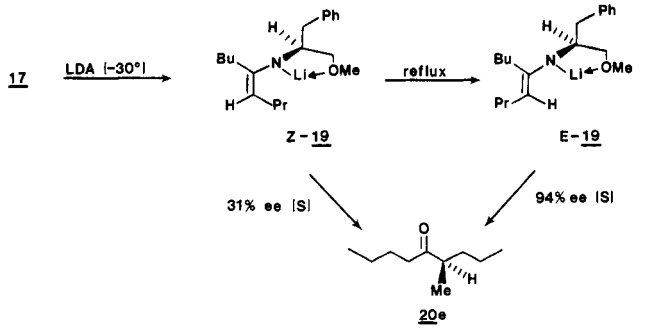
(6) Parkes, H. M.; Young, R. N. *J. Chem. Soc., Perkin Trans. 2* **1978**, 249.
(7) Boche, G.; Bieberbach, A. *Tetrahedron Lett.* **1976**, 1021.
(8) Wellman, K. M.; Laur, P. H. A.; Briggs, W. S.; Moscowitz, A.; Djerassi, C. *J. Am. Chem. Soc.* **1965**, *87*, 66.
(9) Gorin, P. A. J.; Spencer, J. F. T.; Tulloch, A. P. *Can. J. Chem.* **1961**, *39*, 846.

literature but comparison with two known hydroxy acids, 8-hydroxynonanoic **15** and 17-hydroxy stearic **16** being reported as (*S*)-(+), suggested a similar configurational assignment. Although this is not direct proof of the absolute configuration, it may be taken as good indication that (−)-acid **14a** obtained possesses the *R* configuration in agreement with the mechanistic proposals put forth for this asymmetric synthesis. Unequivocal proof for the absolute configuration of these chiral ketones was gathered by the synthesis of the known 12-hydroxystearic acid **14b**,[10] obtained by the enantioselective alkylation of cyclododecanone to the 2-hexyl derivative **10b**. The latter was formed via the thermodynamic lithioenamine in 85% yield with $[\alpha]_D$ +4.3°. When this ketone was subjected to the Baeyer–Villiger oxidation and **13b** was produced, it was hydrolyzed to the 12-hydroxystearic acid (−)-**14b**, $[\alpha]_D$ −0.2°. The known (*S*)-(+)-**14b** confirmed that (−)-**14b** possessed the expected *R* configuration.[11]

Our attention was next turned to acyclic ketones and their enantioselective alkylation via (*E*)- or (*Z*)-lithioenamines **3**. The imine of 5-nonanone **17** was metalated at −25 °C with LDA in

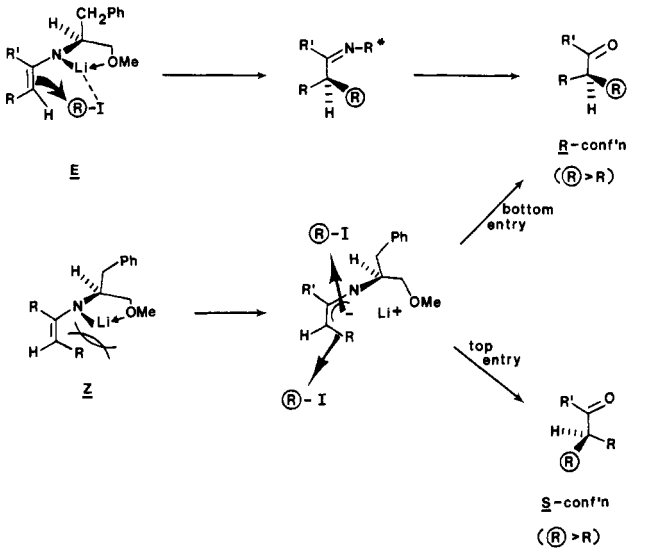


ether and quenched with methanol to give the kinetic vinyl amine (*Z*)-**18**. The ^{1}H NMR spectrum exhibited a clean triplet for the vinyl proton at δ 3.71 along with phenyl protons (δ 7.30) and the methoxyl singlet (δ 3.42). When the imine **17** was metalated, then heated to reflux, and quenched with methanol, the thermodynamic vinyl amine, (*E*)-**18** was cleanly formed. The ^{1}H NMR spectrum showed the vinyl proton at δ 4.23 with no signal from the *Z* isomer at δ 3.71 visible. Also, the phenyl protons (δ 7.15) and the methoxyl singlet (δ 3.32) were also distinctly different from those observed for the *Z* isomer. The vinyl protons observed for *E* and *Z* vinyl amines are consistent with those reported by Knorr.[5] With the confidence that the (*E*)- or (*Z*)-lithioenamines can be formed with very high selectivity, we proceeded to alkylate these intermediates in an effort to generate either (*R*)- or (*S*)-2-alkyl ketones similar to the medium-ring ketones discussed earlier. Table II summarizes the enantioselective alkylation studies of chiral lithioenamines produced kinetically (method A) or thermodynamically (method B). It was surprising that methyl iodide addition to the lithioenamine of 5-nonanone ((*Z*)-**19**) kinetically formed gave only

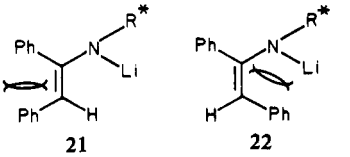


31% ee of the *S* enantiomer **20e**, whereas similar alkylation of the thermodynamic species (*E*)-**19** gave **20e** in 94% ee as the *S* enantiomer. The latter result was expected since the ^{1}H NMR

Scheme II



of the corresponding vinylamine (*E*)-**18** indicated a single isomer, which should alkylate with high enantioselectivity. However, the *Z* isomer, also pure from its ^{1}H NMR spectrum, gave the ketone in poor ee and the same major enantiomer. From Table II, it can be seen that this behavior is repeated in the first three entries (a–c) wherein the kinetic lithioenamine leads to poor ee's of the ketone, while the thermodynamic lithioenamine furnishes the ketone in much higher ee's of the same absolute configuration. If it can be assumed that the lithioenamines of these other ketones (entries a–c) are produced exclusively as the *E* or *Z* isomer under the conditions used, then the poor ee's of ketones from the kinetic preparation must be due to poor selectivity in the alkylation step. This can be understood by considering the structure given in Scheme II. The (*E*)-lithioenamine is seen to be free of any severe nonbonded interactions and allows bond formation with the alkyl halide R–I to take place in an unencumbered manner, keeping the rigid chelate intact. This operational mechanism has been used successfully in aldehyde imines[12] as well and indeed predicts the proper configuration of the chiral 2-alkyl ketones and aldehydes observed. On the other hand, the (*Z*)-lithioenamine possesses (via CPK models) severe interactions between the vinyl R group and the amine portion of the salt. Thus, (*Z*)-lithioenamine may simply open to the aza-allyl species which has lost its rigidity and allows entry of the alkyl halide, R–I, from several directions. Since the *Z* anion gives the same absolute configuration, in lower ee's, as the *E* anion, entry of R–I must predominate from the bottomside, an approach which seems from models to be more accessible. Although other reasons for the diverse behavior of E and *Z* anions may be considered, the factors discussed above appear to be the most reasonable. Further examination of Table II reveals more support for the relative kinetic and thermodynamic products observed. For example, when the starting ketones possess a large substituent (e.g., phenyl), the relative stabilities of the *E* and *Z* anions become closer due to severe cisoid interactions in either isomer (entries f–i). For entry j, the *E* anion possesses a *cis*-stilbene moiety **21**, whereas the *Z* anion experiences the severe interactions shown in **22**. In neither case is there a stable conformer and this results in the chiral ketone **20j** in only 18% ee.



21 22

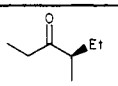
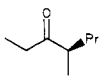
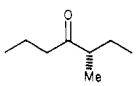
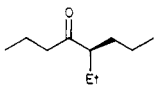
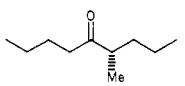
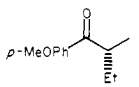
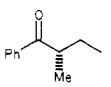
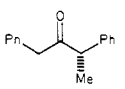
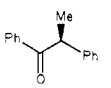
In summary, the enantioselective alkylation of acyclic ketones is a viable synthetic route within the constraints set forth by the

(10) Serck-Hassen, K. *Chem. Ind.* **1958**, 1554.

(11) In addition to (*S*)-(+)-12-hydroxystearic acid, the CD spectrum of the lactone **13b** has been reported (Vorbruggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 876) to be λ(dioxane) 218 nm, Δε −0.681 for the (*R*)-(−)-lactone of 12-hydroxysteric acid. The lactone **13b** obtained from (+)-**10b** gave λ(dioxane) = 218 nm, Δε −0.412).

(12) Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892.

Table II. Alkylation of Acyclic Ketones **20** via Imines (*S*)-**2**

entry	ketone	RX	product **20**	% yield	method A[a] % ee	confn	method B[b] % ee	confn
a	3-pentanone	EtI		69	3	*R*	77	*R*
b	3-pentanone	*n*-PrI[c]		60	43	*R*	88	*R*
c	4-heptanone	MeI		84	31	*S*	82–97[f]	*S*
d	4-heptanone	*n*-PrI[c]		69	*d*		*g*	*R*
e	5-nonanone	MeI[c]		75	25	*S*	94	*S*[e]
f	propiophenone	EtI		71	44	*R*	58	*R*
g	*p*-methoxypropiophenone	EtI		75	*d*		80	*R*
h	butyrophenone	MeI		77	*d*		51	*S*
i	dibenzyl ketone	MeI		88	25	*S*	38	*S*[h]
j	desoxybenzoin	MeI		78	*d*		18	*S*

[a] Method A: imine **2** metalated at −20 °C, and alkyl halide added at −78 °C. [b] Method B: imine **2** metalated at −20 °C, heated to reflux for 1 h, cooled to −78 °C, and alkyl halide added. [c] Reaction performed in ethyl ether, % ee slightly higher (~5%) than in THF. [d] Not attempted under these conditions. [e] Maximum rotation not reported. Physical data for each compound given in Experimental Section. [f] See Table IV, footnote *c*. [g] See Table IV, footnote *d*. [h] Absolute configuration determined by Baeyer–Villiger oxidation, see Experimental Section.

substituents on the starting ketone. The method fares well in comparison with the beautiful work of Enders[13] insofar as simple acyclic ketones are concerned. However, low ee's are also observed in Enders' technique by using the chiral proline hydrazones when large substituents are present. It should also be stated that racemization of the ketonic products never exceeded 5% during the isolation procedures utilized and, therefore, the varying ee's observed are not subject to this phenomenon to any great extent.

Experimental Section

Imines of C_{10}, C_{12}, and C_{15} Cyclic Ketones (*S*)-2. The following procedure is identical for the chiral imines of cyclodecanone, cyclododecanone, and cyclopentadecanone. A solution of the cyclic ketone (34.8 mmol), (*S*)-**1** (40.0 mmol), and 0.25 g of trifluoroacetic acid in 100 mL of toluene was heated for 35 h in a flask equipped with a Dean–Stark trap for azeotropic water removal. Potassium carbonate (1 g) was added and the solution filtered and concentrated to give the crude imine whose IR spectrum showed the complete absence of any carbonyl stretch (1690–1710 cm^{-1}). Fractional distillation through a short-path Vigreaux column gave the imines (*S*)-**2**. Physical data are given below.

(a) (2*S*)-(−)-(*N*-Cyclodecylidine)-1-methoxy-3-phenyl-2-propylamine: bp 119 °C (0.1 torr); 6.35 g (61%), light yellow oil; ^1H NMR ($CDCl_3$) δ 1.45 (br s, 14), 2.00 (m, 2), 2.45 (m, 2), 2.95 (m, 2), 3.45 (m, 5), 4.00 (m, 1), 7.30 (s, 5); IR (film) 1645 cm^{-1}; $[\alpha]^{23}D$ −45.0° (*c* 3.4, $CHCl_3$). The air and moisture sensitivity of these imines precluded any attempts at elemental analysis.

(b) (2*S*)-(−)-(*N*-Cyclododecylidine)-1-methoxy-3-phenyl-2-propylamine: bp 135–140 °C (0.05 torr); straw colored oil; ^1H NMR ($CDCl_3$) δ 1.36 (br s, 18), 1.50–3.30 (m, 8), 3.30 (s, 3), 3.50–4.00 (m, 1), 7.20 (s, 5); IR (film) 1655 cm^{-1}; $[\alpha]^{23}D$ −48.6° (*c* 4.9, $CHCl_3$).

(c) (2*S*)-(−)-(*N*-Cyclopentadecylidine)-1-methoxy-3-phenyl-2-propylamine: bp 68–70 °C (0.005 torr); 5.7 g (69%), light yellow oil; ^1H NMR ($CDCl_3$) δ 1.30 (s, 24), 2.00–2.50 (m, 4), 2.70–2.90 (m, 2), 3.37 (s, 3), 3.50 (m, 2), 3.55–4.00 (m, 1), 7.22 (s, 5); IR (film) 1660 cm^{-1}; $[\alpha]^{23}D$ −38.9° (*c* 5.4, $CHCl_3$).

Kinetic ((*E*)-11) Lithioenamines. The C_{10}, C_{12}, and C_{15} imines prepared above were subjected to metalation and methanol quench by the following general procedure. The imine (*S*)-**2** (1 mmol) in 1–2 mL of anhydrous THF was added to a THF solution of LDA (1 mmol) at −78, −40, or −20 °C and stirred at the respective temperatures for 1 h. The solutions at −78 °C were then treated with 2–5 equiv of anhydrous methanol and immediately put on a rotary evaporator to remove excess methanol and THF. The residue, now at ambient temperature, was dissolved in 0.5 mL of CCl_4 and its ^1H NMR spectrum examined immediately. The *E*–*Z* ratio for this kinetic formation was assessed by integration (±2%) of the vinyl signal (triplet). The half-life of the vinyl amines was 1–2 h at which time isomerization to the imine became noticeable by slow disappearance of the vinyl signal; pertinent ^1H NMR data are given below.

Vinylamines 11 from Methanol Quench of C_{10} Imine. The vinyl signal for the (*E*)-vinylamine appeared at δ 4.38 and the (*Z*)-vinylamine at δ 4.10. Metalation at −78 °C gave 45% *E* and 55% *Z*, whereas metalation at −25 °C gave 33% *E* and 66% *Z* by virtue of the signal integral.

C_{12} Imine. The vinyl signal for the (*E*)-vinylamine appeared at δ 4.35 (100%) with no signal present for the (*Z*)-vinylamine which appears at δ 4.05.

C_{15} Imine. The vinyl signal for the (*E*)-vinylamine appeared at δ 4.20 (100%) with no signal present for the *Z* isomer (δ 4.10).

Thermodynamic ((*Z*)-11) Lithioenamines. Lithioenamines (1 mmol) prepared as described in the kinetic metalations were heated to reflux for 30 min to 1 h and cooled to −78 °C, and methanol was added (5 equiv) followed by addition of K_2CO_3 (1 g), filtered, and concentrated at room

(13) Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 397.

temperature, in vacuo. The ^1H NMR spectrum in CCl_4 was examined immediately.

Vinylamines ((*Z*)-11) from Methanol Quench of C_{10} Imine. The vinyl signal for the (*Z*)-vinylamine appeared at δ 4.10 (100%) with no *E* isomer (δ 4.38) visible.

C_{12} Imine. The vinyl signal for the (*Z*)-vinylamine appeared at δ 4.05 (100%) with no *E* isomer (δ 4.35) visible.

C_{15} Imine. The vinyl signal for the (*Z*)-vinylamine appeared at δ 4.10 (100%) with no *E* isomer (δ 4.20) visible.

(*R*)-(+)-2-Methylcyclopentadecanone (Thermodynamic Product). This procedure is typical of the alkylation of C_{10}, C_{12}, and C_{15} ketones via thermodynamic lithioenamines.

To a dry 50-mL 3-necked flask fitted with a magnetic stir bar, reflux condenser, a nitrogen inlet tube, and a pressure equalizing dropping funnel was added 3.8 mmol (10% excess) diisopropylamine and 10 mL of dry THF. The flask was cooled to 0 °C and 3.5 mmol *n*-butyllithium was introduced via syringe. The resulting solution was stirred for 5 min, then cooled to −40 °C, and stirred an additional 10 min. A solution of 3.5 mmol of imine from cyclopentadecanone (*S*)-**2** in 10 mL of THF was added to the LDA solution over 15 min at −40 °C and then the mixture allowed to warm ambient and heated to reflux for 1 h. After being cooled to ambient, the mixture was cooled further to −78 °C and, after 30 min, a solution of 3.8 mmol methyl iodide in 10 mL of THF was added dropwise over 25–30 min. The reaction mixture was stirred at −78 °C for 2.5 h and then poured into 150 mL of brine. The aqueous layer was extracted with ether (3 × 20 mL), and the organics were combined with the THF layer. The ethereal THF solution was washed once with brine, the latter discarded, and the organic layer concentrated in vacuo. The residue (crude imine) was hydrolyzed by addition of 20 mL of pentane, 10 mL of water, and 10 mL of sodium acetate/acetic acid buffer[14] (16.5 g of NaOAc, 37.5 mL of HOAc, 37.5 mL of H_2O) and stirred at 25 °C for 12 h. The aqueous layer was extracted with pentane (3 × 30 mL), and the combined organics were washed with saturated sodium bicarbonate and then brine. The aqueous layer containing the buffer solution also contained the chiral methoxyamine which was recovered as previously described.[2]

The washed organic layer was dried (Na_2SO_4) and concentrated to give an oily residue of the crude 2-methylcyclopentadecanone. Distillation by Kugelrohr apparatus (85–90 °C (0.01 torr)) gave 0.63 g (78%) of product containing 9–10% cyclopentadecanone $[\alpha]^{25}_D$ +7.90° (*c* 6.1, $CHCl_3$)), corrected for the unalkylated ketone: ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 7 Hz, 3), 1.20–1.60 (m, 24), 2.20–2.55 (m, 3); IR (film) 1708 cm^{-1}. The enantiomeric excess was determined as 80–82% by using tris[(3-heptafluoropropyl)hydroxymethylene-*d*-camphorato]europium-(III) and observing the splitting of the methyl doublet at δ 1.0. Circular dichroism spectrum: $[\theta]_{312}$ −125, $[\theta]_{281}$ +656. 2,4-DNP of 2-methylcyclopentadeconane: mp 95.0–96.5 °C (EtOH); reported[15] mp 97–98 °C.

(R)-(+)-2-Methylcyclododecanone (Thermodynamic Product). Using the procedure described immediately above gave the ketone via Kugelrohr distillation: 80–90 °C (0.1 torr); 0.81 g (83%); bp 100–101 °C (0.05 torr);[16] $[\alpha]^{25}_D$ +10.30° (*c* 4.7, $CHCl_3$); CD $[\theta]_{307}$ −589, $[\theta]_{273}$ +487; ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 6 Hz, 3), 1.30 (br s, 16), 1.45–1.85 (m, 2), 2.20–2.40 (m, 3); IR(film) 1700 cm^{-1}. The enantiomeric excess based on the methyl doublet splitting by using Eu(III) shift reagent was 80–82%. The 2,4-DNP was prepared: mp 178–179 °C (EtOH); reported[15] mp 179.5–180.5 °C.

(*S*)-(−)-2-Methylcyclodecanone (Thermodynamic Product). Using the standard procedure under thermodynamic conditions as described above gave 0.58 g (77%) after Kugelrohr distillation (50–55 °C (0.1 torr); $[\alpha]^{25}_D$ −3.16° (*c* 4.5, $CHCl_3$)) corrected for 22% cyclodecanone: IR (film) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 7 Hz, 3), 1.30–1.50 (br, s, 12), 1.50–2.00 (m, 2), 2.40–2.65 (m, 3). Enantiomeric excess by using Eu(III) shift reagent and by observing the split of the methyl doublet was 29–31% 2,4-DNP; mp 102–103 °C (EtOH); reported[15] mp 104.5–105.5 °C.

(*S*)-(+)-2-(2-Methoxyethyl)cyclopentadecanone (Thermodynamic Product). Following the typical procedure described above and employing 2-methoxyethyl iodide gave 0.53 g (70%) of a light yellow oil after Kugelrohr distillation; $[\alpha]^{23}_D$ +1.17° (*c* 4.2, $CHCl_3$) corrected for 5% unalkylated cyclopentadecanone; CD $[\theta]_{317}$ −49, $[\theta]_{2,3}$ +97.2; IR (film) 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.80 (m, 26), 2.15–2.50 (m, 3), 3.15–3.20 (m, 5), 3.20 (s, 3). The enantiomeric excess was determined to be 83 ± 2% by splitting of the methoxyl signal at 3.20 ppm by using Eu(III) shift reagent. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.60; H, 12.06. Found: C, 76.48; H, 12.28.

(*S*)-(+)-2-(2-Methoxyethyl)cyclododecanone (Thermodynamic Product). Using the general procedure described above employing 2-methoxyethyl iodide gave, after Kugelrohr distillation (90–115 °C (0.50 torr)), 0.89 g (85%) of a clear liquid: $[\alpha]^{23}_D$ +1.88 (*c* 5.4, $CHCl_3$) corrected for 1% cyclododecanone; ^1H NMR (CCl_4) δ 3.2 (t, 2), 3.20 (s, 3), 3.0–1.2 (m, 23); IR (film) 1700 cm^{-1}. The enantiomeric excess was determined as 78.6% by observing the methoxy singlet splitting with Eu(III) shift reagent. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.87, H, 11.91.

(*R*)-(−)-2-(2-Methoxyethyl)cyclodecanone (Thermodynamic Product). Reaction of the imine of cyclodecanone with 2-methoxyethyl iodide gave after Kugelrohr distillation: 0.32 g (79%) light yellow oil; $[\alpha]^{25}_D$ −12.10 (*c* 3.3, $CHCl_3$) corrected for 18% cyclodecanone; IR (film) 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35–1.85 (m, 16), 2.35–2.60 (m, 3), 3.20 (s, 3), 3.30 (m, 2). The enantiomeric excess was determined by observing the splitting of the methoxyl signal at δ 3.20 by using Eu(III) shift reagent and found to be 31 ± 2%.

General Procedure for the Kinetic Products of C_{10}, C_{12}, and C_{15} Ketones. The following procedure for (*S*)-(−)-2-methylcyclopentadecanone is typical of all the kinetically generated products given in Table I. A solution of the imine (*S*)-**2** (2.8 mmol) in 10 mL of THF was added dropwise over 10 min to a solution of LDA (3.0 mmol in 10 mL of THF) at −20 °C under nitrogen. This was stirred for 1 h between −20 and −25 °C and then cooled to −78 °C. After 20 min, a solution of methyl iodide (3.1 mmol) in 10 mL of THF was added over 15 min and stirred for 2.5 h at −78 °C. The mixture was poured into brine and the organic layer separated. The aqueous layer was extracted with ether (3 × 30 mL), and the organics were combined, washed with brine and water, and then dried (Na_2SO_4). Concentration gave the oil alkylated imine. Hydrolysis was performed by using the sodium acetate buffer and pentane system (as detailed for the thermodynamic product) with stirring at ambient for 12 h. The acidic layer was washed with pentane, combined with the original pentane layer, and washed with saturated bicarbonate and then brine. Drying (Na_2SO_4) concentration, and distillation of the residue (Kugelrohr, 76–80 °C (0.002 torr)) gave 0.48 g (75%) of a clear oil, (*S*)-(−)-2-methylcyclopentadecanone: $[\alpha]^{25}_D$ −4.31° (*c* 4.4, $CHCl_3$). Physical constants were the same as for the *S*-(+)-enantiomer. The enantiomeric excess was determined as 37% by use of the Eu(III) shift reagent: CD $[\theta]_{312}$ +103, $[\theta]_{281}$ −431.

The kinetic methods for forming the ketones in Table I were all performed in the same manner.

Baeyer–Villiger Oxidation of (+)-2-Methylcyclododecanone was carried out by heating a solution of the ketone (1.20 g, 6.12 mmol) and *m*-chloroperbenzoic acid (3.0 equiv, 17.2 mmol) in 1,2-dichloroethane for 5 days. The solution was cooled and stirred overnight with an equal volume of saturated sodium bisulfite ($NaHSO_3$). The organic layer was washed successively with saturated $NaHCO_3$ (3 × 30 mL), 5% KOH (3 × 30 mL), and brine (3 × 30 mL) and dried over K_2CO_3. Concentration gave 1.25 g of a mixture of 2-methylcyclododecanone (40%) and the lactone (60%) as determined by VPC. Without further purification, the mixture was hydrolyzed by heating at reflux for 3 h a solution of 1 g of KOH in ethanol/water (1:1). The basic solution was extracted (3 × 30 mL) with ether and the aqueous solution acidified to pH 2 with concentrated HCl. The acidic solution was extracted (3 × 30 mL) with ether, and the ethereal extracts were washed with brine and dried (Na_2SO_4). Concentration gave a colorless waxy solid, 307 mg (21% from ketone), whose purity was determined (>98%) by HPLC: reverse phase column, methanol/water (7:3), $[\alpha]^{25}_D$ −4.30° (*c* 2.44, $CHCl_3$).

(*R*)-(+)-2-*n*-Hexylcyclododecanone. Following the standard conditions for alkylation of cyclododecanone imine (*S*)-**2** under thermodynamic conditions (heating the lithium salt in THF at 65 °C for 1 h) and adding *n*-hexyl iodide at −78 °C gave after workup 2.40 g (94%) of the 2-*n*-hexyl derivative: $[\alpha]^{25}_D$ +4.50° (*c* 2.75, $CHCl_3$) corrected for 19% unalkylated cyclododecanone (via VPC); CD $[\theta]_{307}$ −326, $[\theta]_{277}$ +398 (MeOH); ^1H NMR ($CDCl_3$) δ 0.85 (t, 3), 1.10–1.30 (br s) and 1.30–1.85 (br, shoulder) for a total of 28 protons, 2.45 (t, 2), 3.15–3.55 (m, 1); IR (film) 1692 cm^{-1}. No elemental analysis was performed on this 81:19 mixture which was used directly for the oxidation.

Baeyer–Villiger Oxidation of (*R*)-(+)-2-*n*-Hexylcyclododecanone. The mixture from above (893 mg) was dissolved in 20 mL of chloroform containing 0.5 mL of BF_3/etherate and cooled to 0 °C. A solution of 2.50 mL of 40% peracetic acid in 10 mL of chloroform was added dropwise at 0 °C and the solution allowed to warm to room temperature and then heated at 45 °C for 48 h under nitrogen in the presence of a reflux condenser. After being cooled, the mixture was stirred with saturated sodium bisulfite ($NaHSO_3$) for 1 h. The chloroform layer was washed with water, saturated $NaHCO_3$, and water successively. After

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(15) Muller, E.; Bauer, M. *Justus Liebigs Ann. Chem.* **1962**, *654* 92.
(16) Lafont, R.; Bonnet, Y.; Vivant, G.; Rhone-Poulanc, S. A.; Fr. Patent 1 308 579, 1961; *Chem. Abstr.* **1963**, *58*, 35*c*.

Table III. Physical Data for Imines 17

entry	imine (*S*)-2 from	bp, °C (*p*, torr)	$[\alpha]^{23}_D$ (*c* 3-4, MeOH)	IR (film), cm^{-1}
a	3-pentanone	69-71 (0.02)	−58.8°	1670
b	4-heptanone	85-88 (0.02)	−54.0°	1663
c	5-nonanone	96-100 (0.02)	−52.7°	1663
d	propiophenone	111-115 (0.02)	−126.0°	1640
e	*p*-methoxypropiophenone	133-137 (0.02)	−195.0°	1630
f	butyrophenone	121-125 (0.02)	−84.7°	1635
g	dibenzyl ketone	169-170 (0.02)	−46.2°	1665
h	disoxybenzoin	164-171 (0.02)	−115.0°	1630

the mixture was dried (Na_2SO_4) and concentrated, the lactone **13b** was isolated by using medium-pressure liquid chromatography[17] (50% $CHCl_3$/hexane) to give 0.47 g of the lactone (49%) and 0.30 g of unreacted ketone (33%). The lactone **13b** showed a CD spectrum where $\Delta\epsilon$ −0.412, λ(dioxane) = 218 nm, which is in agreement with the reported CD spectrum for the (*R*)-(−)-lactone.[11] Since the Baeyer–Villiger reaction proceeds with retention, this confirms that the ketone **10a** also possessed the *R* configuration. Hydrolysis of **10a** to the 12-hydroxysteric acid **14b** was accomplished by stirring with KOH/water/EtOH overnight, at room temperature, acidification with HCl, extraction with ether, and isolation of the ether residue by preparative layer chromatography (3% acetic acid in chloroform). The purified **14b** had $[\alpha]^{25}_D$ −0.2° (*c* 0.5, acetic acid), $[\alpha]^{25}_{365}$ −2.89°. The literature[10] reports that the *S* enantiomer is (+) and, therefore, the isolated material herein must be the *R* enantiomer in agreement with the lactone isolated above.

Chiral Imines (17) from Acyclic Ketones. General Procedure. In general, formation of imines using acyclic ketones and (*S*)-1 was quite slow; two to three drops of trifluoroacetic acid were normally used to initiate the reaction which often took several days in refluxing benzene or toluene. The procedure given here for 3-pentanone is a representative example.

In a system containing a Dean–Stark trap arranged for azeotropic removal of water, methoxyamine **1** (8 g, 48.5 mmol) and 3-pentanone (8.4 g, 97 mmol) were dissolved in benzene (100 mL) and after addition of three drops of trifluoroacetic acid were heated to reflux (oil bath) for 2 days. After being shaken with solid K_2CO_3 and filtered, the solution was evaporated to give a yellow oil which upon distillation gave 11.3 g (100%) of colorless oil; physical properties and spectral data are given in Table III.

Due to the air and moisture sensitivity of these compounds, no elemental analyses were performed.

Kinetic ((*Z*)-18)- and Thermodynamic ((*E*)-18)-Lithioenamines. Methanol Quench. To a solution of 2.35 mmol of LDA in 20 mL of THF cooled to −30 °C was added the imine of 5-nonanone **17c** (2.30 mmol) in 10 mL of THF, and the solution was stirred at −25 ± 5 °C for 1 h. Approximately one-third of the volume of the mixture was cannulated into another flask containing 5 mL of methanol at −78 °C. This methanolic solution was concentrated in vacuo, $CDCl_3$ added, and a 60-MHz NMR spectrum recorded. The vinyl triplet at 3.71 ppm indicative of the *Z* isomer was clearly present.

The remainder of the lithium anion solution was heated to reflux for 1 h and then cooled to −78 °C. To this was added 5 mL of methanol at a slow dropwise rate, and after the solution was warmed to room temperature evaporation and examination of a $CDCl_3$ solution at 60 MHz showed the vinyl triplet at 4.23 ppm.

Alkylation of Acyclic Imines and Preparation of α-Alkyl Ketones 20. General Method B. An oven-dried 50-mL 3-necked flask equipped with pressure-equalizing dropping funnel, reflux condenser, nitrogen inlet, magnetic stirrer, and vacuum takeoff adapter was evacuated (vacuum pump) and refilled three times with nitrogen. THF (10 mL) and diisopropylamine (0.735 ml, 0.53 g, 5.25 mmol) were then added via double-edged needle. The solution was cooled to 0 °C, and *n*-butyllithium (2.2 mL of a 2.4 M solution in *n*-hexane, 5.25 mmol) was added. the LDA was allowed to form at 0 °C for 15 min and was then cooled to −20 °C. Imine **17** (5 mmol) in THF (5 mL) was added (5 min) and anion formation allowed to continue for 1 h at −20 °C. The anion solution was then heated to reflux for 2 h and cooled to −78 °C. A solution of alkyl iodide (5.25 mmol) in THF (5 mL) was then added, and alkylation was allowed to proceed at −78 °C for 1 h. Workup and hydrolysis as described previously for the cyclic ketones yielded the α-alkyl ketones given in Table II. Rotation data for these products are shown in Table IV.

Table IV. Rotation Data for Ketones 20 in Table II

ketone (from Table II)	configuratn 20	$[\alpha]^{23}_D$ (*c*, solv)	$[\alpha]_D$ (lit.)
20a	*R*	−24.7° (5.0, Et_2O)	31.9°[a]
20b	*R*	−19.5° (2.2, hexane)	22.2°[b]
20c	*S*	+17.1° (2, Et_2O)	17.5°[c]
20d	*R*	−0.914° (3.60, Et_2O)	1.11°[d]
20e	*S*	+14.8° (3.0 Et_2O)	[e]
20f	*R*	−27.1° (5.0, Et_2O)	46.2°[f]
20g	*R*	−22.5° (5.0, EtOH)	15.4°[g]
20h	*S*	+15.3° (5.0, Et_2O)	43.7°[f]
20i	*S*	+113.0° (3, C_6H_6)	296°[h]
20j	*S*	−43.3° (5.0, EtOH)	240°[i]

[a] Nerdel, F.; Henkel, E. *Chem. Ber.* **1953**, *86*, 1002. [b] Riley, R.; Silverstein, R.; Moser, J. *Science (Washington, D.C.)* **1974**, *183*, 760. [c] Seebach, D.; Ehrig, V.; Teschner, M. *Justus Liebigs Ann. Chem.* **1976**, 1357. However, Eu(III) shift reagent indicates that the % ee obtained is ~80%; thus the $[\alpha]_D$ for pure ketone **20c** may be ~21–22°. [d] Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 397 report 1.11 for the *S* enantiomer, % ee unknown. [e] Not previously reported, % ee determined by using $Eu(hfbc)_3$. Configuration assumed to be *S* by CD; $[\theta]^{MeOH}_{285}$ + 345.2° and compared to **20c**, $[\theta]^{MeOH}_{285}$ + 314.1. [f] Seebach, D.; Steinmuller, D.; Demuth, F. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 620. [g] Korver, O. *Tetrahedron* **1971**, *27*, 4643. The author warns that the optical purity is suspect. Use of $Eu(hfbc)_3$ in this study gave the % ee as 80 ± 5%. [h] Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 549. Absolute configuration not reported by these authors. [i] Cervinka, O.; Hub, L. *Collect. Czech. Chem. Commun.* **1968**, *33*, 1911.

Absolute Configuration of 20j via Baeyer–Villiger Oxidation. To a suspension of 85% *m*-chloroperbenzoic acid (Aldrich) (2.10 g, 10.1 mmol) under nitrogen in 10 mL of 1,2-dichloroethane at room temperature was added 1,3-diphenyl-2-butanone (**20j**). After the solution was stirred for 72 h, TLC (15% ethylacetate/hexane) indicated no further reaction. The reaction mixture was washed successively with 10% sodium sulfite, 5% sodium bicarbonate, and brine. The organic solution was dried (Na_2SO_4), filtered, and concentrated to give 0.7 g of a light yellow oil: IR (film) 1735, 1715 cm^{-1}; ^1H NMR (CCl_4) δ 7.22 (br s), 3.75 (q), 3.62 (s), 3.50 (s), 1.50 (d), 1.25 (d). VPC showed two peaks of approximately equal area due to ester and starting ketone. The crude mixture of ketone and ester was hydrolyzed with 10 mL of ethanol, 10 mL of water, and 1.5 g of KOH and heated for 3 h at reflux. On being cooled, the mixture was extracted with ether and the ether extracts were washed with 1 N HCl, water, and brine, dried (K_2CO_3), and concentrated to give 0.45 g of an oil: $[\alpha]^{23}_D$ −3.97° (*c* 8.5, benzene). VPC and ^1H NMR indicated a 1:1 mixture of 1-phenylethanol and starting ketone **20i**. Preparative TLC (20% ethyl acetate/hexane) gave 0.2 g pure (*S*)-(−)-1-phenylethanol: $[\alpha]^{23}_D$ −7.95° (*c*, 3.1, benzene); lit.[18] $[\alpha]^{25}_D$ +43.6° for the *R* enantiomer.

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