Efficient Chirality Transfer between a Chiral 4-Methyl-1,4-dihydropyridine and Benzoylformic Ester. An Example of a Pure Intermolecular Self-Immolative Process

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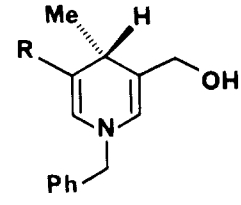
Abstract: The efficient asymmetric synthesis of several 4-methyl-1,4-dihydropyridines (**5a–c**) in greater than 95% ee is described. These substances are prepared by diastereofacial addition to chiral 3-oxazolinylpyridines and after removal of the oxazoline moiety furnish optically active 4-methyl-1,4-dihydropyridines. The latter have been evaluated as NADH mimics by reduction of benzoylformic ester **17** and produced (*S*)-(+)-methyl mandelate in 90–95% ee. Substituents placed at the 3- and 5-positions of the dihydropyridine, none of which have any stereocenters, have resulted in both changes in the enantiomeric excess and absolute configuration of methyl mandelate. A mechanistic model, involving dipolar interactions between the 1,4-dihydropyridine and benzoylformic ester, is presented to account for this self-immolative chiral-transfer process.

The extensive studies performed in recent years to develop an efficient NADH mimic have ranged through a host of structurally diverse 1,4-dihydropyridines with varying degrees of success.[1] The basic process which has intrigued organic chemists is the nonenzymic, metal-catalyzed redox system shown in eq 1. The net chemical change is the transfer of a hydride ion to a reducible group in the presence of a divalent metal ion (e.g., Mg^{2+} and Zn^{2+}) to afford the reduced species and a pyridinium ion. So much has been written and discussed concerning the scope and mechanism (direct hydride vs. stepwise electron transfer[1e,2]) that it need not be reiterated here.

The main purpose of this report is to describe some experiments which attempted to simplify this redox process and gain some insight into its stereochemical aspects. Therefore, we will only concern ourselves with those processes dealing with chiral 1,4-dihydropyridines and reduction of prochiral carbonyls to optically active alcohols. The major contributions to asymmetric reductions via chiral 1,4-dihydropyridines have been by Ohno and Ohnishi,[3] Inouye,[4] and Kellogg[5] who have shown in a number of brilliant studies that stereoselective reductions of prochiral groups, mainly carbonyl, were indeed within reach. These workers have explored a variety of chiral 1,4-dihydropyridines **1–3** in the presence of divalent metal ions (e.g., Mg^{2+} and Zn^{2+}) to reduce highly electrophilic substrates, e.g., benzoylformic esters (eq 2). The enantiomeric excesses of the mandelates **4** ranged as high as 98% when **2**[6] was employed, and ee's of 90% were achieved when the appended macrocycle **3** (X = $(CH_2)_5$, R = *i*-Pr) was the reducing agent. All the above, **1–3**, were rationally designed dihydropyridines, containing for various reasons the specific substituents shown. The system of interest to us (**2**) was that utilized by Ohno,[6] wherein the stereocenter has a stereochemically defined hydrogen to be transferred to the reducible group. It was reported by Ohno that the stereocenters on the side chain in **2** derived from an (*R*)- or (*S*)-amine did not affect the stereochemical result observed for the benzoylformic ester. Thus, only the absolute configuration of the 4-position (Me vs. H) dictated which enantiomer of mandelic ester **4** was obtained. Enantiomerically pure **2** was obtained as four distinct diastereomers by recrystallization of the amides derived from (*S*)- and (*R*)-amines.

It became of interest to us to assess the feasibility of chiral 4-methyl-1,4-dihydropyridines (**5**) as reducing agents, which were indeed devoid of any other stereochemical elements, such as **2**.



5a, R = H
5b, R = CO_2Et
5c, R = $CONMe_2$

In this manner, one could simplify the process without the added complexity of a second stereocenter and determine if a simple chiral transfer would lead to enantiomerically enriched mandelate esters. If this were accomplished, it would illustrate the process by using the least complex chiral dihydropyridine yet reported and represent a pure self-immolative transformation, examples of which are still rather rare.[7]

The synthetic routes to desired dihydropyridines **5** were available via the chiral oxazoline derived from the appropriate 3-cyanopyridines. Thus, 3-cyanopyridine (**6**) or the 5-carboethoxy derivative **7** was transformed into their imidates (**8** and **9**) and treated with the chiral amino alcohol **10**,[8] furnishing the pyridyloxazolines (+)-**11** and (+)-**12** in 65–80% yields (eq 3). A third pyridyloxazoline (+)-**13** was also prepared (88%) by treatment of the ester **12** with ammonia followed by geminal nitrogen alkylation with KOH–Me_2SO–MeI.[9] With the pyridyloxazolines **11**, **12**, and **13** in hand, the addition of methyllithium was attempted in order to introduce the 4-methyl substituent with some reasonable degree of diastereoselectivity. In the event, an ethereal solution of methyllithium (1.1 equiv) was introduced into a THF solution of **11**, **12**, or **13** at −78 °C followed by excess methyl chloroformate to give **14** as a mixture of diastereomers (**14A** and **14B**). HPLC analysis indicated that the ratio of diastereomers was in the range 96:4 ± 2. From a previous study,[10] wherein methyllithium or

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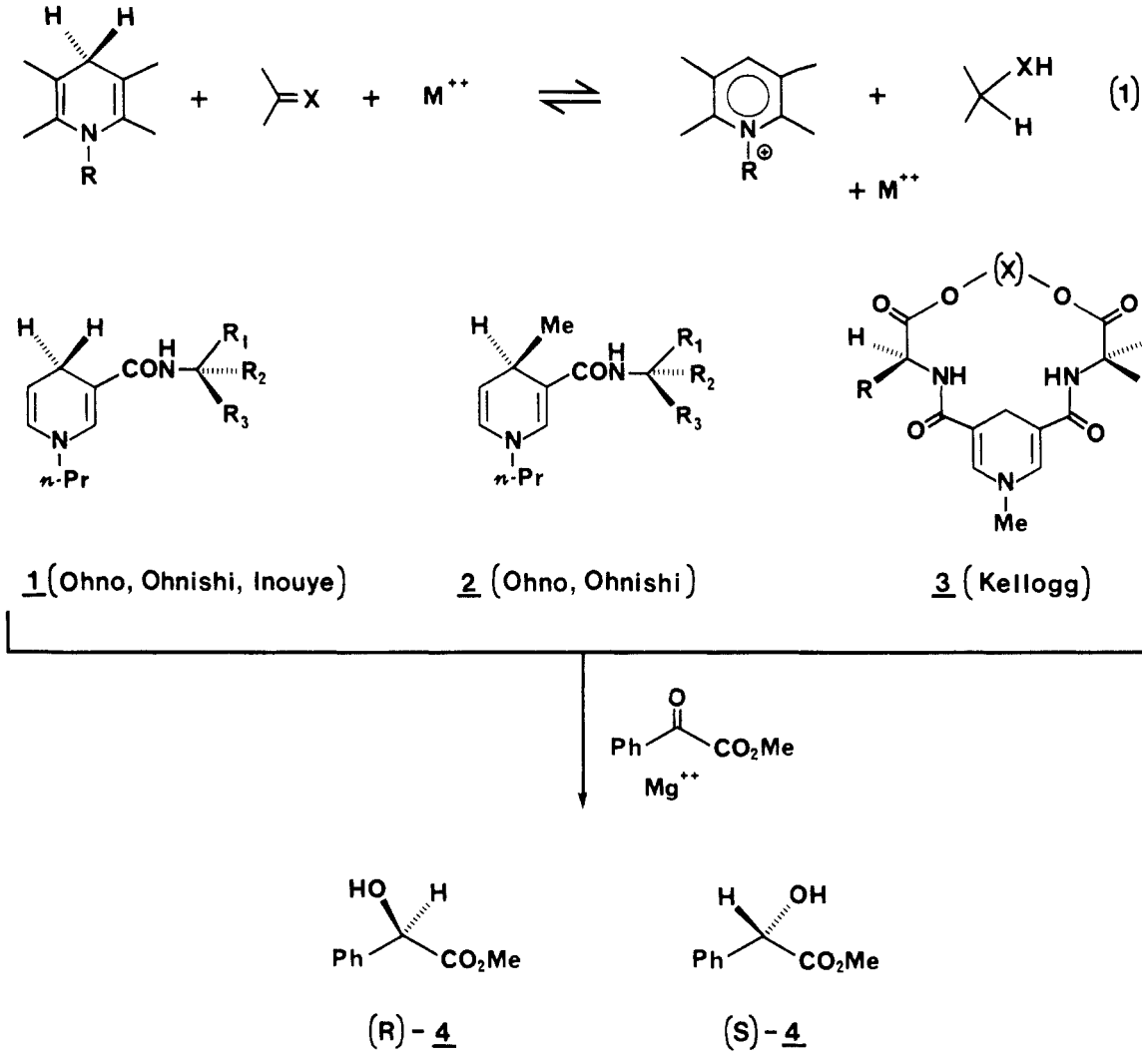

methylmagnesium bromide was added to (+)-**11**, an X-ray structure on the amide, derived from **14A** (after hydrogenation) showed **14A** to possess the S configuration at C-4. Thus, the additions were highly selective, affording **14A** as the predominant product. The oxazoline auxiliary was smoothly removed by using a procedure previously reported by us.[11] This involved quaternization of **14** with methane fluorosulfonate, reduction with sodium borohydride, and hydrolytic cleavage of the oxazolidine with oxalic acid to furnish **15** in 75–83% yield for the three sequential steps. The *N*-carbomethoxy group in **15** was replaced by benzyl by using phase-transfer conditions and producing **16** in 40–71% yields. The target 1,4-dihydropyridines **5a–c** were reached by lithium aluminum hydride reduction of the 3-formyl derivative **16**. Verification of the enantiomeric purity of **5** was obtained by forming the Mosher ester via (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride[12] and after ^{19}F NMR analyses indicated that **5b** was a 94:6 mixture, in excellent agreement with the 95:5 ratio of **14A** and **14B** (R = CO_2Et) observed via HPLC. Thus, no racemizattion had taken place during the synthetic sequence leading to **5**.

Asymmetric Reduction with 5. The reduction of benzoylformic ester **17**, using the dihydropyridine **5a**, in the presence of 1.0 equiv of magnesium perchlorate, was attempted under the conditions found suitable in many of the earlier studies. To our delight, the process proceeded with a high degree of stereoselectivity, affording (*S*)-(+)-methyl mandelate (**18**) in 94% yield with an enantiomeric excess of 95% (Table I). Furthermore, **5b**, when subjected to the same conditions, gave (*S*)-(+)-**18** in 61% yield and 91% ee (eq 4). However, when **5c** was utilized in the reduction, the (*S*)-(+)-mandelate **18** was not obtained, but instead the (*R*)-(−) enantiomer was formed in 98% yield but with enantiomeric excess of only 62%. This reversal in the stereochemistry of the product caused us to consider further modification in the dihydropyridines **5a–c** by transforming the hydroxyl group to its methyl ether **19**. This was accomplished by treating **5a–c** with potassium hydride in THF followed by addition of methyl iodide. When these methyl ethers were incorporated into the reduction sequence, the chemical

Table I. Asymmetric Reduction of Methyl Benzoylformate (**17**)[a]

		18			
entry	dihydropyridine	conversion, %[b]	ee, %[c]	*n*[d]	config
1	**5a**	94	95	3	(*S*)-(+)
2	**19a**	69	62	3	(*S*)-(+)
3	**5b**	61	91	6	(*S*)-(+)
4	**19b**	58	52	3	(*S*)-(+)
5	**5c**	98	62	3	(*R*)-(−)
6	**19c**	84	52	2	(*R*)-(−)
7	**5b**	<1[f]	*e*	2	
8	**19b**	32[f]	7.4	2	(*S*)-(+)

[a] Reductions were performed in 0.1–0.2 M acetonitrile containing 1.0 equiv of $Mg(ClO_4)_2 \cdot 1.5H_2O$, in the dark under an argon atmosphere for 5–10 days. [b] Determined by calibrated capillary gas chromatography. [c] Based on the optical rotation of pure methyl mandelate, $[\alpha]_D$ 141.4° (*c* 1.0, MeOH), and corrected for the enantiomeric purity of the dihydropyridines **5 a–c** or **19a–c**. [d] Number of experiments performed; the ee's given contain an estimated error of ±5%. [e] The alcohol could not be isolated for further determination. [f] Performed in the absence of $Mg(ClO_4)_2$.

(10) Meyers, A. I.; Natale, N. R.; Wettlaufer, D. G. *Tetrahedron Lett.* **1981**, *22*, 5123.
(11) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1965.
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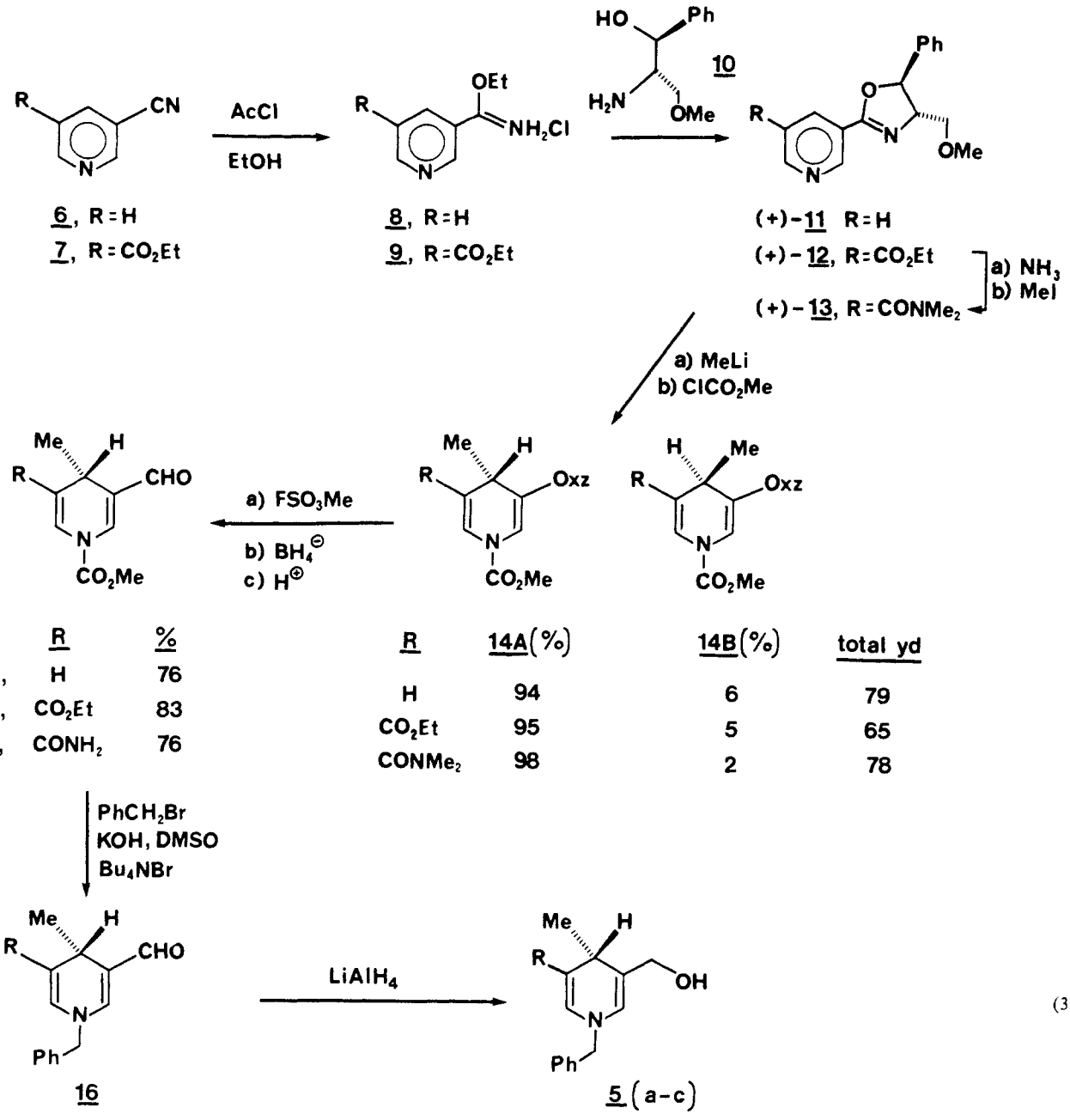


	R	%
15a,	H	76
15b,	CO_2Et	83
15c,	$CONH_2$	76

R	14A(%)	14B(%)	total yd
H	94	6	79
CO_2Et	95	5	65
$CONMe_2$	98	2	78

(3)

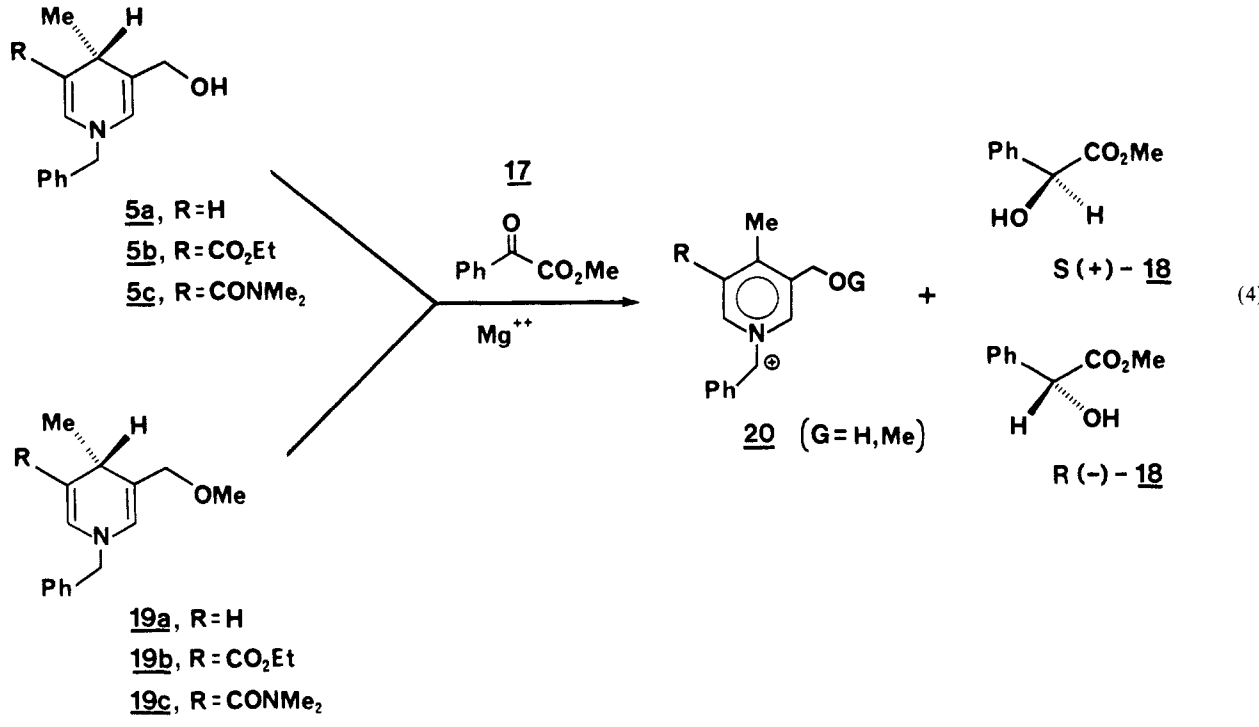
yields of the mandelate were generally unaffected but gave surprising alterations in the stereoselectivity (Table I). As can be seen from the data, replacing the hydroxyl (**5a**) by methoxyl (**19a**) caused the ee's of the mandelate to drop from 95 to 62%. Similarly, the ee's dropped from 91 to 52% when the ester-containing dihydropyridine **5b** was changed to **19b**. The major change in stereochemical outcome arose when the 3-[(dimethylamino)-carbonyl)]pyridine **5c** was examined (entries 5 and 6). In this instance, the mandelate was formed as the R enantiomer in 62% ee, and replacing the hydroxyl with methoxy (**19c**) again gave the R enantiomer in slightly lower enantiomeric purity (52%). In addition, the chemical yields were consistently higher when the carboxamide-containing pyridines were employed, a fact previously observed.[4] Also seen from Table I is the poor reduction efficiency of the keto ester **17** in the absence of magnesium ion (entries 7 and 8). No significance is attached to the ee's and configuration in the latter experrment due to the very low conversion efficiency.

In light of previous studies[4] on NADH mimics, wherein the concentration of the magnesium ion was found to have a profound effect on the reduction efficiency as well as the stereoselectivity, we examined this aspect of the process by using the 5-carboethoxydihydropyridine **5b**. The results are given in Table II. Within the limits of error, we found no meaingful effect on the asymmetric reduction by changing the magnesium ion concentration over a 12-fold range.

Table II. Effect of Asymmetric Reduction as a Function of Magnesium Perchlorate Concentration Using **5b** and **17**

		(*S*)-**18**			
ratio $Mg(ClO_4)_2$/**5b**	yield (%)[a] of (*S*)-(+)-**18**	α_{OBS},[b] deg	concn,[c] g/100 mL	$[\alpha]_D$, deg	ee, %[e]
0.25	29	+0.053	0.044	120.5	94.7
0.50	41	+0.347	0.302	114.9	90.3
1.00	61	+0.466	0.397	117.3	92.2
2.00	51	+0.440	0.383	114.9	90.3
3.00	30	+0.350	0.311	112.5	88.4

[a] Determined via capillary gas chromatography; yields are relative to consumed starting material, **17**. [b] Measured in a 1-dm cell (1 mL), Perkin-Elmer Model 240, using 589 nm. [c] Determined after measuring rotation by calibrated HPLC, error ±2%. [d] Test runs on authentic (*S*)-(+)-methyl mandelate (Aldrich) confirmed that the specific rotation was not concentration-dependent over the range 0.1–1.0 g/100 mL (MeOH). [e] Based on maximum rotation; see Table I, footnote *c*.



(4)

These results on the chiral transfer from 4-methyl-1,4-dihydropyridines **5a–c** to the keto ester support the following conclusions: (a) magnesium ion catalysis is essential for the reductions, (b) the substituent in the 5-position (H, CO_2Et, or $CONME_2$) strongly influences the stereoselectivity and absolute configuration of the mandelate ester, (c) the methyl ethers **19a** and **19b** have a deleterious effect on the stereoselectivity but not the absolute configuration, and (d) the amide substitution **5c** leads to a reversal in the absolute configuration, and the effect of the methyl ether in **19c** is minimal.

At this juncture of our studies, the stereochemical results obtained thus far may be explained as outlined in Scheme I. It appears that the hydroxyl group in **5a** and **5b** interacts with the carbonyl of the ester group, either by hydrogen bonding or nonbonding electron pair donation (or both) as shown in A. This forces the benzoylformic ester to assume a conformation wherein the carbomethoxy group and the hydroxymethyl (or methoxymethyl) substituent are facing each other in the magnesium ion-containing ternary complex (A). As a result of this conformation leading to the transition state, similar to that proposed by Ohno,[6] the hydride is transferred from the rear of the carbonyl (*re* face) producing the mandelate (*S*)-(+)-**18** as the major enantiomer. Since the hydroxymethyl group in A (R_2 = H) leads to the mandelate in 95% ee, whereas the methoxymethyl group in A (R_2 = Me) provides the (*S*)-mandelate in 62% ee, one can assume that the hydrogen bond is a factor in aligning the ternary complex, A. However, models indicate that the hydrogen bond cannot assume colinearity for the maximum strength (5–6 kcal) and thus one must also consider electron donation (dipole–dipole interactions). The drop in ee of the mandelate from 95 to 62% when the hydrogen bond is absent could be due to the difference in size between hydrogen and methyl, resulting in a weaker dipole interaction with the carbonyl group of the carbomethoxy group. Additional experiments employing the deuteriooxymethyl groups (A, R_2 = D) or bulkier alkyl groups on the ether of the dihydropyridine should clarify this point. As shown in Table I, the presence of a hydrogen or carboethoxy group at C-5 (R_1 = H and CO_2Et) in A has no effect on the stereochemical outcome of the chirality transfer. When the 5-substituent is the carboxamide (A, R_1 = $CONMe_2$), the ternary complex assumes a conformation (B) due to the enhanced electron-donating properties of the dimethylamino moiety toward the ester carbonyl. Thus, the amido group competes favorably with the hydroxy (or methoxy) methyl group in the 3-position, resulting in a reversal of stereochemistry. Furthermore, molecular models strongly support the out-of-plane twisting of the carboxamide in B as well as in the starting dihydropyridines **5c** and **19c**.[13] Although it is expected that the highest site of the electron density in the amide would reside on oxygen, the stereochemical environment prohibits the carbonyl of the amide from facing the ester carbonyl but rather faces away from the carbonyl. This is primarily due to severe nonbonded interaction of the dimethylamino group with the 4-methyl group of the dihydropyridine. This leaves the electron donation to the ester carbonyl arising from the dimethylamino group, as shown for B. The fact that the loss in stereoselectivity is minimal for the carboxamide (R_1 = $CONMe_2$) when the hydroxymethyl (R_2 = H, 62% ee) is changed to methoxymethyl (R_2 = Me, 52% ee) is also a reflection of the stronger dipole (electron donation) present in the carboxamide vs. the hydroxy or methoxymethyl substituent. It is, therefore, expected that replacing the latter by methyl or other nonpolar groups should lead to high enantioselectivity for the R entiomer of **18**. This will require further assessment to determine whether or not this is indeed the case.

In summary, there are rather subtle electronic factors operating in this self-immolative process, and we continue to probe this system with the goal of obtaining either enantiomer of prochiral carbonyls (and other reducible groups) by appropriate choice of substituents in the 1,4-dihydropyridine ring.

Experimental Section

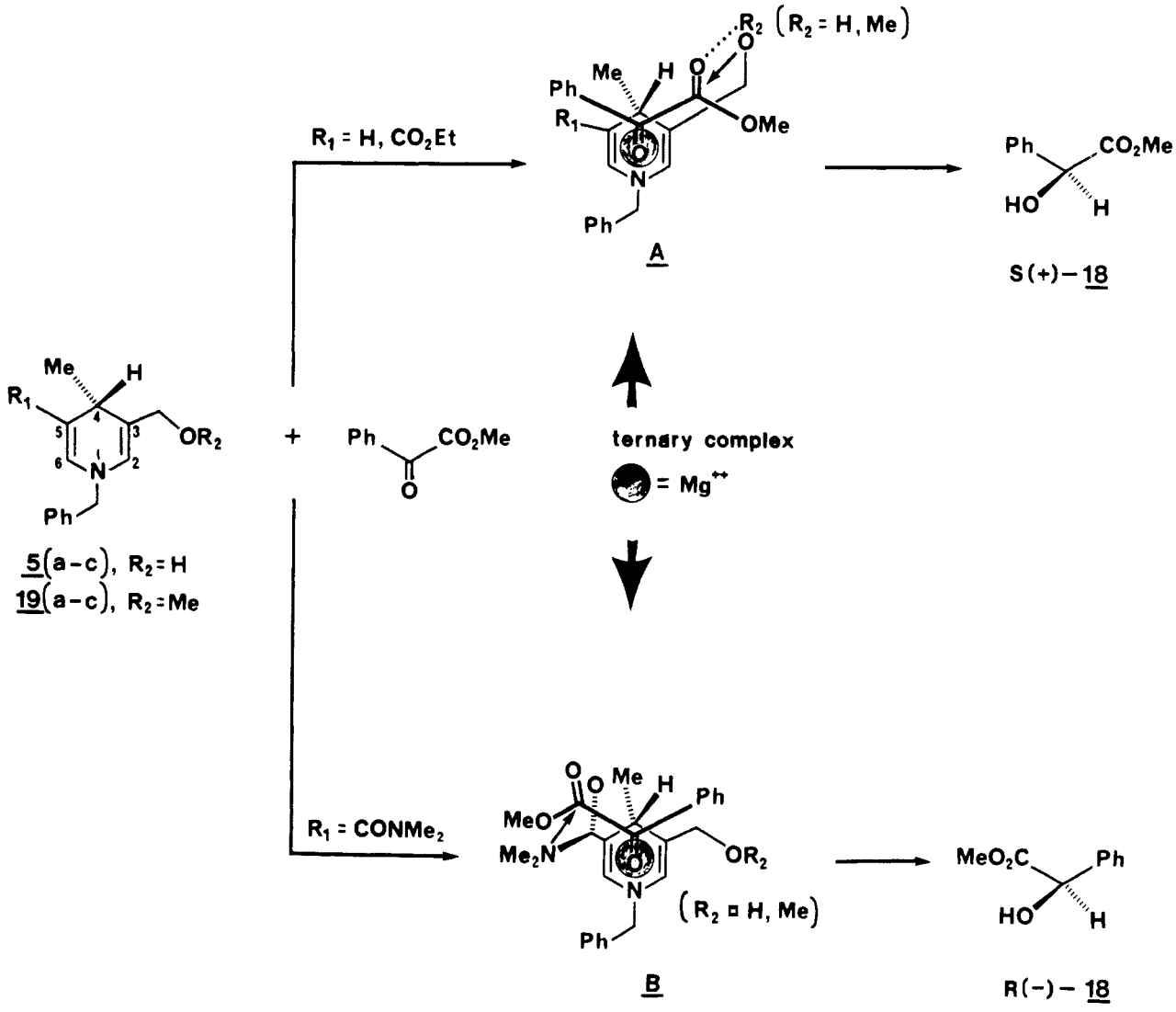
General. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 and/or a Rudolph Research Autopol III polarimeter using a 1 dm cell with a total volume of 1 mL. IR spectra were recorded on a Beckman 4240 spectrophotometer and are reported in wavenumbers (cm^{-1}).

Quantitative capillary gas chromatography (CGC) was performed by using a Hewlett-Packard gas chromatograph 5890 equipped with a 5% phenyl methyl silicone fused silica column (column i.d. 0.25 mm, column length 25 m). Acetonitrile was distilled once over phosphorus pentoxide, and magnesium perchlorate (anhydrous, Fisher Scientific Co.) was stored in a vacuum desiccator after drying for 3 h at 100 °C/0.1 mmHg. Methyl benzoylformate (95%, Aldrich) was purified by radial chromatography (50% ether/hexanes) followed by Kugelrohr distillation (bp 110–112 °C, 6 mmHg, purity 99%, CGC).

Proton and ^{13}C NMR spectra were measured on a Bruker WP-270 SY instrument at 270 and 67.9 MHz, respectively. ^{19}F NMR spectra

(13) Donkersloot, M. C. A.; Buck, H. M. *J. Am. Chem. Soc.* **1981**, *103*, 6554.

Scheme I



were measured at 188.3 MHz by using a Bruker WP-200 SY spectrometer with $CFCl_3$ as the internal standard. Elemental analysis was performed by MicAnal, Tucson, AZ. Analytical HPLC was done by using a Waters instrument equipped with an UV detector (254 nm).

All 1,4-dihydropyridines were isolated from their crude reaction mixtures by radial chromatography using a Harrison Research Chromatotron 7924 and silica gel plates (No. 7749, Kieselgel 60 PF_{254}, Merck).

(+)-(1S,2S)-Phenyl-2-amino-3-methoxy-1-propanol (10) was prepared as previously described:[14] mp 49–51 °C, $[\alpha]_D^{20}$ +25.7° (*c*, 10.4 $CHCl_3$).

Ethyl (3-Pyridyl)imidate Dihydrochloride (8). To an oven-dried 1-L three-necked flask fitted with a magnetic stirrer bar, septum, reflux condensor, pressure equalizing addition funnel, and argon inlet was added absolute EtOH (80 mL, 1.37 mmol) and $CHCl_3$ (100 mL). After the solution was cooled to 0 °C, acetyl chloride (80 mL, 1.13 mmol, Fisher) was added dropwise, followed by addition, via cannula, of a solution consisting of 3-cyanopyridine (10.4 g, 100 mmol) and $CHCl_3$ (300 mL). The resulting solution was allowed to warm to room temperature overnight (25 h) at which time dry ether (225 mL) was added and the mixture was placed in the freezer (−15 °C) overnight (16 h). The precipitated imidate was recovered by filtration through a sintered glass funnel and washed with dry ether. Residual HCl was removed under aspirator vacuum (1–2 days) to afford 20.5 g (92%) of a finely divided white powder: mp 230–232 °C [lit.[15] 233 °C]; IR (KBr) (cm^{-1}) 3200–2400 (br), 1610 (br).

2-(3-Pyridyl)-4(*S*)-(methoxymethyl)-5(*S*)-phenyl-Δ^2-oxazoline (11). To an oven-dried 500-mL round-bottomed flask fitted with a magnetic stirrer bar, reflux condensor, and argon inlet was added dry 1,2-dichloroethane (300 mL), and pyridylimidate **8** (10.5 g, 47 mmol). The resulting suspension was treated with dry triethylamine (6 mL, 43 mmol) and amino alcohol **10** (8.33 g, 46 mmol). The reaction mixture was heated to reflux (24 h), cooled to room temperature, and poured into water (200 mL). Upon separation of the layers, the organic layer was washed with water (4 × 75 mL) and the aqueous layers were back-extracted with $CHCl_3$ (3 × 75 mL). The combined organic layers were washed with brine (3 × 100 mL) and dried (K_2CO_3). Filtration and concentration gave the crude yellow–brown oxazoline, which upon Kugelrhor distillation under reduced pressure afforded 10.1 g (79%) of a light-orange oil: bp 147–149 °C (0.013 mmHg), $[\alpha]_D^{20}$ +42.9° (*c* 7.4, $CHCl_3$); 1H NMR ($CDCl_3$) δ 9.22 (d, *J* = 2 Hz, 1 H), 8.67 (dd, *J* = k, 2 Hz, 1 H), ,.26 (dt, *J* v 8, 2 Hz, 1 H), 7.48–7.10 (m, 1 H), 7.34 (s, 5 H), 5.48 (d, *J* = 7 Hz, 1 H), 4.53–49.16 (m, 1 H), 3.83–3.25 (m, 2 H), 3.42 (s, 3 H); IR (film) (cm^{-1}): 1665, 1593, 1570.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01. Found: C, 71.35; H, 6.10.

2-[5-(Ethoxycarbonyl)-3-pyridyl]-4(*S*)-methoxymethyl-5(*S*)-phenyl-Δ^2-oxazoline (12). A solution of 3-cyano-5-(ethoxycarbonyl)pyridine[16] (1.00 g, 5.68 mmol) in absolute chloroform (5 mL) was added carefully to a cooled (0 °C) mixture of freshly distilled acetyl chloride (4.0 mL, 56.3 mmol) and absolute ethanol (4.0 mL, 68.2 mmol) in chloroform (50 mL) over a period of 30 min. After the solution was stirred for 30 min at 0 °C, a white precipitate was formed. The resulting suspension was allowed to warm to room temperature over a period of 12 h. The precipitated ethyl [5-(ethoxycarbonyl)-3-pyridyl]imidate dihydrochloride (**9**)

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(15) Karrar, P.; Schwarzenbach, G.; Benz, F.; Solmssen, U. *Helv. Chem. Acta* **1936**, *19*, 811.

(16) Kuthan, J.; Janeckova, E.; Havel, M. *Collect. Czech. Chem. Commun.* **1964**, *29*, 143.

was isolated by filtration through a sintered glass funnel and washed with absolute ether (3 × 10 mL). Drying over KOH under aspirator vacuum afforded the white crystalline imidate **9** (1.60 g, 95%), mp 181–183 °C.

A suspension of freshly prepared imidate **9** (1.00 g, 3.39 mmol) in dry 1,2-dichloroethane (60 mL) was treated with distilled triethylamine (0.50 mL, 3.59 mmol). To the resulting mixture was added (+)-(1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol (**10**) (0.61 g, 3.37 mmol), and the resulting white suspension was heated to reflux for 12 h. After cooling to room temperature the reaction mixture was washed with five 10-mL portions of distilled water and the aqueous layers were back-extracted with chloroform (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL) and dried (K_2CO_3). Filtration and concentration gave the crude oxazoline **12**, which upon purification by column chromatography using Kieselgel 60 PF_{254} (No. 7747, Merck) and 30% THF/hexanes as solvent afforded the pure oxazoline **12** (0.88 g, 76%) as a pale-yellow oil: $[\alpha]_D^{20}$ +49.5° (*c* 0.92, $CHCl_3$): IR (neat) 3062, 3035, 2985, 1730, 1658, 1607, 1580, 753, 711, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.939 (d, *J* = 2.0 Hz, 1 H), 9.33 (d, *J* = 2.4 Hz, 1 H), 8.88 (t, *J* = 2.0 Hz, 1 H, 4′-H), 7.50–7.21 (m, 5 H, C_6H_5), 5.55 (d, *J* = 7.3 Hz, 1 H, 5-H), 4.43 (q, *J* = 7.3 Hz, 2 H, CH_3CH_2O), 4.50–4.29 (br m, 1 H, 4-H), 3.80–3.60 (m, 2 H, CH_2OMe), 3.46 (s, 3 H, OMe), 1.42 (t, *J* = 7.i Hz, 3 H, CH_3CH_2O); ^{13}C NMR ($CDCl_3$) δ 164.47 (s), 161.30 (se, 152.92 (d), 140.16 (s), 136.52 (d), 128.80 (2 × d), 128.38 (d), 126.16 (s), 125.58 (d), 123.68 (s), 84.03 (d), 75.10 (d), 73.99 (t), 61.57 (t), 59.29 (q), 14.13 (q).

Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92. Found: C, 66.70; H, 5.97.

2-(5-(*N*,*N*-Dimethylcarbamoyl)-3-pyridyl)-4(*S*)-(methoxymethyl)-5-(*S*)-phenyl-2-oxazoline (13). A solution of 1.00 g (2.94 mmol) of 5-(ethoxycarbonyl)oxazoline **12** in 50 mL of absolute ethanol was saturated with gaseous ammonia at room temperature. The flask was sealed and the mixture was allowed to react for 7 days. After this period, the solution was concentrated to about 5 mL of total volume and treated with hexanes (100 mL). The white plates, formed at −20 °C overnight, were collected via suction filtration and dried under reduced pressure to yield 0.90 g (98%) of pure primary amide: mp 173.5–174 °C $[\alpha]_D^{20}$ +38.9° (*c* 0.93, $CHCl_3$); IR (KBr) 3365, 3170, 3055, 2920, 2890, 2820, 1670, 1647, 1620, 1569, 1450, 1403, 1092, 911, 759, 690, 615 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.32 (d, *J* = 1.9 Hz, 1 H), 9.22 (d, *J* = 2.1 Hz, 1 H), 8.74 (t, *J* = 2.0 Hz, 1 H, 4′-H), 1.42-1.30 (m, 5 H, C_6H_5), 6.88 (br s, 1 H, NH), 6.64 (br s, 1 H, NH), 5.51 (d, *J* = 7.4 Hz, 1 H, 5 H), 4.37 (mc, 1 H, 4-H), 3.73–3.63 (m, 2 H, CH_2OMe), 3.44 (s, 3 H, OMe); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 166.80 (s), 161.53 (s), 152.11 (d), 151.37 (d), 140.10 (s), 134.57 (d), 129.01 (s), 128.91 (d), 128.48 (d), 125.63 (d), 123.72 (s), 84.24 (d), 75.04 (d), 74.20 (t), 59.29 (q).

Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.63; H, 5.49; N, 13.58.

N,N-Dimethylation[9] of the above amide was achieved by addition (50 mg, 0.161 mmol) to a suspension of powdered KOH (72.1 mg, 1.28 mmol, 8 equiv) in Me_2SO (2 mL) at room temperature followed by addition of methyl iodide (91.2 mg, 40 μL, 0.642 mmol, 4 equiv). The reaction was complete after 5 min (TLC, 70% THF/hexanes), and the reaction mixture was poured into water (20 mL) and extracted with chloroform (5 × 10 mL). The combined organic extracts were washed with water and brine and dried (K_2CO_3). Evaporation of the solvent gave a pale-yellow oil which was purified via radial chromatography (50% ether/hexanes to 70% THF/hexanes) to yield 49.1 mg (90%) of the pure oxazoline 13: $[\alpha]_D^{20}$ +40.3° (*c* 0.38, $CHCl_3$); IR (neat) 3060, 3030, 2922, 2880, 2823, 1645, 1598, 1494, 1075, 708, 691 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.27 (d, *J* = 2.0 Hz, 1 H, 2′-H), 8.80 (d, *J* = 2.2 Hz, 1 H, 6′-H), 8.37 (t, *J* = 2.0 Hz, 1 H, 4′-H), 7.43–7.29 (m, 5 H, C_6H_5), 5.53 (d, *J* = 7.3 Hz, 1-H, 5 H), 4.40–4.34 (m, 1 H, 4 H), 3.75–3.63 (AB m, 2 H, CH_2OMe), 3.45 (s, 3 H, OMe), 3.313, 3.03 (br s, 6 H, NMe_2-rotamers); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 168.01 (s), 161.31 (s), 150.10 (d), 140.21 (s), 134.29 (d), 131.97 (s), 128.75 (d), 128.27 (d), 125.47 d), 125.31 (d), 123.57 (s), 84.03 (d), 75.04 (d), 74.09 (t), 59.18 (q), 30.32 (q).

Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.16; H, 6.41; N, 11.36.

Addition of Methyllithium to 11, 12, and 13. Formation of 14A and 14B (R = H). To a solution of oxazolinylpyridine **11** (0.299 g, 1.12 mmol) and THF (70 mL) cooled to −78 °C was added dropwise methyllithium (1.4 M, 2.4 mL, 2.36 mmol). Stirring was continued for 6.5 h, at which time the bright-yellow solution was placed in a 0 °C bath for 2 min. The flask was recooled to −78 °C and the reaction quenched with methyl chloroformate (0.52 mL, 6.72 mmol). The reaction mixture was concentrated, slurried in CH_2Cl_2 (60 mL), and washed with dilute aqueous bicarbonate (3 × 50 mL) and brine. Drying (K_2CO_3), filtration, and concentration gave the crude dihydropyridine. Purification on radial chromatography (silica gel, 20% EtOAc/hexanes) afforded 0.310 g (79%) of the product. Analysis by HPLC (normal phase, 30% EtOAc/hexanes, 4 mL/min) indicated a diastereomeric ratio of 94:6 (**14a**/**14B**): ^1H NMR ($CDCl_3$, 60 MHz) δ 7.73 (br s, 1 H), 7.38 (s, 5 H), 6.80 (br d, *J* = 8 Hz, 1 H), 5.35 (d, *J* = 6 Hz, 1 H), 5.10 (dd, *J* = 8, 5 Hz, 1 H), 4.45–3.97 (m, 1 H), 3.83 (s, 3 H), 3.60–3.30 (m, 3 H), 3.43 (s, 3 H), 1.25 (d, *J* = 7 Hz, 3 H) (diastereomeric proton signals were not detected in the spectrum); ^{13}C NMR (C_6D_6) δ 162.9, 151.3, 140.8, 128.4, 128.1 127.7, 125.2, 120.6, 113, 1, 110.4, 82.6, 74.6, 74.2, 59.1, 53.6, 27.8, 23.6; IR (film) (cm^{-1}): 1720, 1672, 1622, 1430, 1330; MS (70 eV), *m*/*e* 342, 327, 311, 295, 283.

Formation of 14A and 14B (R = CO_2Et). To a solution of 5-(ethoxycarbonyl)-3-oxazolinylpyridine **12** (0.50 g, 1.47 mmol) in dry THF (100 mL) cooled to −78 °C was added dropwise, via syringe, a methyllithium solution (ether, 1.3 M, 1.1 equiv) over a period of 1 h. Stirring was continued at −78 °C for 3–4 h, and the dark-green fluorescing mixture was quenched with methyl chloroformate (0.568 mL, 7.35 mmol) at −78 °C. After warming to room temperature, the yellow reaction mixture was washed with saturated aqueous bicarbonate (2 × 20 mL) and extracted with chloroform (5 × 20 mL). Drying (K_2CO_3) followed by filtration and evaporation of the solvents afforded the crude 1,4-dihydropyridines **14A** and **14B** (R = CO_2Et) as a yellow oil. Purification was achieved by radial chromatography using 50% ether/hexanes as the solvent to yield a pale-yellow foam (396 mg, 65%): $[\alpha]_D^{20}$ +86.6° (*c* 0.41, $CHCl_3$); IR (neat) 3115, 3030, 2988, 2924, 2822, 1750, 1710, 1680, 1624, 1617, 1440, 1225, 752, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92 (br s, 1 H, 6-H), 7.70 (br s, 1 H, 2-H), 7.50–7.20 (m, 5 H, C_6H_5), 5.36 (d, *J* = 6.5 Hz, 1 H, 5′-H), 4.40–4.10 (m, 3 H, CH_3CH_2O, 4′-H), 3.92 (q, *J* = 6.5 Hz, 1 H, 4-H), 3.89 (s, 3 H, CO_2Me), 3.72–3.45 (AB m, 2 H, CH_2OMe), 3.41 (s, 3 H, OMe), 1.31 (m, 6 H, CH_3CH_2O and CH_3, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 166.06 (s), 162.51 (s), 151.27 (s), 140.96 (s), 130.72 (d), 128.70 (d), 128.06 (d), 127.03 (d), 125.41 (d), 115.53 (s), 113.26 (s), 83.07 (d) 74.84 (d), 74.28 (t), 60.43 (t), 59.22 (q), 54.28 (q), 27.76 (d), 229.69 (q), 14.26 (nq).

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.42; H, 5.95; N, 6.20. Diastereomeric ratio, 95:5 (HPLC, normal phase, Zorbax SIL, Du Pont Instruments using 10% THF/hexanes).

Formation of 14A and 14B (R = $CONMe_2$). In the manner described above, methyllithium was added to **13**: yield 78%, colorless oil; $[\alpha]_D^{20}$ +108.6° (*c* 0.42, $CHCl_3$); IR (neat) 3056, 3014, 2955, 2920, 2820, 1735, 1685, 1630, 1493, 792, 750, 692 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.71 (br s, 1 H, 2-H), 7.38–7.30 (m, 5 H, C_6H_5), 6.98 (br s, 1 H, 6-H), 5.34 (d, *J* = 6.4 Hz, 1 H, 5′-H), 4.27–4.21 (m, 1 H, 4′-H), 3.86 (s, q, 4 H, CO_2Me, 4-H), 3.57 (AB m, 2 H, CH_2OMe), 3.41 (s, 3 H, OMe), 3.06 (s, 6 H, NMe_2), 1.31 (d, *J* = 6.6 Hz, 3 H, CH_3), diastereomeric ratio, 98:2 (HPLC, reverse phase, Altex, Beckman, Ultrasphere, 20% MeOH/H_2O).

5-(Ethoxycarbonyl)-3-formyl-*N*-(methoxycarbonyl)-4(*R*)-methyl-1,4-dihydropyridine (15b). The reductive removal of the oxazoline auxiliary was achieved in an analogous manner to literature procedures[11] by treating a solution of oxazoline **14** (R = CO_2Et) as a 95:5 mixture of diastereomers (300.0 mg, 0.72 mmol) in dry methylene chloride (100 mL) with methyl fluorosulfonate (83 μL, 1.03 mmol) at room temperature. Stirring was continued for 16 h at which time the resulting yellow solution was cooled to 0 °C and treated with a solution of sodium borohydride (82.2 mg, 2.17 mmol) in THF (2 mL) and absolute ethanol (1 mL). The mixture was allowed to warm to room temperature over a period of 3–4 h and was quenched by the addition of water (1 mL) and saturated aqueous ammonium chloride (2 mL). Upon further dilution was ether (25 mL), the layers were separated. The aqueous layer was extracted with ether (2 × 20 mL), and the combined organic layers were washed with brine and dried (K_2CO_3). Filtration and concentration gave the crude oxazolidine which was immediately hydrolyzed by dissolving it in THF (10 mL) and treatment with 50% aqueous oxalic acid (2 mL). After 3 h, potassium carbonate (1.5 g) was added and the solution was filtered and concentrated to give the crude aldehyde which was purified by radial chromatography (50% ether/hexanes) to yield **15b** as a colorless oil (152.0 mg, 83%): $[\alpha]_D^{20}$ +51.4° (*c* 0.42, $CHCl_3$); IR (neat) 2975, 2930, 2870, 1750, 1708, 1673, 1614, 1440, 1230, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.46 (s, 1 H, CHO), 7.87 (br s, 1 H, 6-H), 7.65 (br s, 1 h, 2-H), 4.26 (AB m, 2 H, CH_3CH_2O), 4.00 (s, 3 H, CO_2Me), 3.78 q, *J* = 6.7 Hz, 1 H, 4-H), 1.33 (t, 3 H, CH_3CH_2O), 1.16 (d, *J* = 6.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 189.49 (d), 165.40 (s), 150.68 (s), 138.79 (d), 130.19 (d), 126.58 (s), 116.96 (s), 60.52 (t), 54.64 (q), 25.14 (d), 21.90 (q), 14.03 (q).

Anal. Calcd for $C_{12}H_{15}NO5$: C, 56.91; H, 5.97. Found: C, 57.23; H, 5.64.

***N*-(Methoxycarbonyl)-3-formyl-4(*R*)-methyl-1,4-dihydropyridine (15a).** In a similar manner, the dihydropyridine mixture **14a** and **14b** (R = H) (0.103 g, 0.30 mmol) was quaternized with methyl fluorosulfonate (0.049 mL, 0.06 mmol, 12 h) and reduced with sodium boro-

hydride. Hydrolysis of the resulting oxazolidine to the aldehyde **15a** was performed by using a mixture of CH_2Cl_2 (20 mL) and 10% aqueous oxalic acid (10 mL) for 12 h with rapid stiirring. The mixture was diluted with ether (30 mL), and the layers were separated. The organic layer was washed with dilute NH_4Cl/H_2O (3 × 40 mL) and brine. Drying (K_2CO_3) followed by filtration and concentration yielded the crude product. Purification via radial chromatography (silica gel, 10% THF/hex) afforded 0.041 g (76%) of the desired aldehyde as a yellow oil. Analysis by TLC (50% THF/hexanes) indicated that the yellow was contamination. Repurification by PTLC (50% ether/pentane) separated the yellow and gave the analytical sample: $[\alpha]_D^{20}$ +143.9° (*c* 0.62, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.35 (s, 1 H), 7.60 (br s, 1 H), 6.74 (br d, J = 8 Hz, 1 H), 5.14 (dd, J = 8, 4 Hz, 1 H), 3.91 (s, 3 H), 3.50–3.08 (m, 1 H), 1.16 (d, J = 7 Hz, 3 H); ^1H NMR (C_6D_6) δ 9.04 (s, 1 H), 7.16 (br s, 1 H), 6.49 (br s, 1 H), 4.62 (dd, J = 8, 4 Hz, 1 H), 3.38–3.08 (m, 1 H), 3.32 (s, 3 H), 1.11 (d, J = 7 Hz, 3 H); ^{13}C NMR (C_6D_6) δ 189.8, 150.9, 140.1, 124.8, 12099, 114.6, 53.7, 26.2, 23.0; IR (film) (cm^{-1}) 1743, 1677, 1618, 1348, 1318.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12. Found: C, 60.20; H, 6.32.

5-(*N*,*N*-Dimethylcarbamoyl)-3-formyl-*N*-(methoxycarbonyl)-4(*R*)-methyl-1,4-dihydropyridine (15c). In the manner employed for **15a** and **15b**, the reductive cleavage was performed to yield **15c**, 76%, as a pale-yellow oil: $[\alpha]_D^{20}$ +42.6° (*c* 0.23, $CHCl_3$); IR (neat) 3010, 2943, 2916, 2855, 1670, 1645, 1608, 1575, 1408, 1384, 1166 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.41 (s, 1 H, CHO), 7.63 (br s, 1 H, 2-H), 6.95 (br s, 1 H, 6-H), 3.94 (s, 3 H, CO_2Me), 3.76 (q, J = 6.7 Hz, 1 H, 4-H), 3.05 (s, 6 H, NMe_2), 1.18 (d, J = 6.8 Hz, 3 H, CH_3).

***N*-Benzyl-3-formyl-4-methyl-1,4-dihydropyridines 16. General Procedure.** A mixture of *N*-(methoxycarbonyl)-1,4-dihydropyridines **15a–c** (0.1 M, 1 equiv) and benzyl bromide (2.0 equiv) in absolute THF was injected to a rapidly stirred suspension of solid KOH (2.2 equiv) and phase-transfer catalyst (tetrabutylammonium bromide, 10 mol %) at room temperature. The reaction mixture was heated to 50 °C by means of an oil bath for 48 h after which a white precipitate appeared. The yellow mixture was treated with water (10 equiv) and diluted with ether, filtered, and washed with saturated aqueous sodium bicarbonate and brine. Drying (K_2CO_3) and concentration afforded the crude *N*-benzyl-1,4-dihydropyridines **16a–c** as yellow oils. Purification was achieved by radial chromatography using 50% ether/hexanes as eluent.

***N*-Benzyl-3-formyl-4(*S*)-methyl-1,4-dihydropyridine (16a)**: yield 40%, air-sensitive yellow oil; $[\alpha]_D^{20}$ +439.2° (*c* 0.26, $CHCl_3$); IR (neat) 3055, 3030, 2950, 2920, 2860, 2718, 1669, 16428 1573, 1176, 1140, 690, 662 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.06 (s, 1 H, CHO), 7.38–7.20 (m, 5 H, C_6H_5), 6.75 (s, 1 H, 2-H), 5.77 (d, J = 7.8 Hz, 1 H, 6-H), 4.91 (dd, J_1 = 7.7, J_2 = 7.8 Hz, 1 H, 5-H), 4.40 (s, 2 H, $CH_2C_6H_5$), 3.47 (mc, 1 H, 4-H), 1.13 (d, J = 6.6 Hz, 3 H, CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 188.46 (d), 148.99 (d), 136.14 (s), 128.61 (d), 127.70 (d), 126.79 (d), 126.58 (d), 117.38 (s), 112.52 (d), 5734 (t), 25.20 (d), 23.82 (q).

***N*-Benzyl-5-(ethoxycarbonyl)-3-formyl-4(*R*)-methyl-1,4-dihydropyridine (16b)**: yield, 71%, pale-yellow oil; $[\alpha]_D^{20}$ +99.2° (*c* 0.38, $CHCl_3$); Ir (neat) 3060, 3025, 2970, 2920, 2863, 1697, 1658, 1575, 1400, 1180, 758, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.23 (s, 1 H, CHO), 7.50–7.15 (m, 5 H, C_6H_5), 7.12 (d, J = 1.0 Hz, 1 H, 6-H), 6.74 (d, J = 1.1 Hz, 1 H, 2-H), 4.58 (s, 2 H, $CH_2C_6H_5$), 4.18 (AB m, 2 H, CH_3CH_2O), 3.90 (q, J = 6.4 Hz, 1 H, 4-H), 1.27 (t, 3 H, CH_3), 1.12 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 188964 (d), 166.48 (s), 146.44 (d), 137.57 (d), 135.71 (s), 129.19 (d), 128945 (d), 127.08 (d), 122.35 (s), 112.71 (s), 60.08 (t), 58.15 (t), 24.80 (d), 23.06 (q), 14.24 (q).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 69.97; H, 6.49.

***N*-Benzyl-5-(*N*,*N*-dimethylcarbamoyl)-3-formyl-4(*R*)-methyl-1,4-dihydropyridine (16c)**: yield, 51%, pale-yellow air-sensitive oil; $[\alpha]_D^{20}$ 80.6° (*c* 0.18, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 9.17 (s, 1 H, CHO), 7.42–7.21 (m, 5 H, C_6H_5), 6.82 (s, 1 H, 2-H), 6.3 (s, 1 H, 6-H), 4.52 (s, 2 H, $CH_2C_6H_5$), 3.86 (q, J = 6.6 Hz, 1 H, 4-H), 2.97 (s, 6 H, NMe_2), 1.13 (d, J = 6.6 Hz, 3 H, CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 188.33 (d), 170.24 (s), 147.42 (d), 135.72 (s), 128.96 (d), 128.85 (d), 128.22 (d), 127.00 (d), 118.90 (s), 118.39 (s), 57.71 (t), 36.78 (q), 27.10 (d), 22.24 (q).

Dihydropyridines 5a–c. *N*-Benzyl-5-(ethoxycarbonyl)-3-(hydroxymethyl)-4(*R*)-methyl-1,4-dihydropyridine (5b). A solution of lithium aluminum hydride (57.2 mg, 1.51 mmol) in absolute THF (50 mL) was cooled to 0 °C and treated with a solution of 1,4-dihydropyridine **16b** (0.43 g, 1.51 mmol) in absolute THF (10 mL). After 1 h at 0 °C, the reaction was quenched with water (5 mL) and 20% aqueous potassium hydroxide (10 mL). The phases were separated, the water layer was back-extracted with chloroform (3 × 20 mL), and the combined organic layers were dried (K_2CO_3). Filtration and concentration gave the crude product which was purified by radial chromatography using 50% ether/hexanes as the eluent to yield **5b** as a colorless oil (245 mg, 57%): $[\alpha]_D^{20}$ −164.5° (*c* 0.38, $CHCl_3$); IR (neat) 3680–3120, 3060, 3030, 29758 2965, 2920, 2865, 1683, 1598, 1180, 1097, 760, 749, 725, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.00 (m, 6 H, C_6H_5, 6-H), 5.87 (br s, 1 H 2-H), 4.35 (s, 2 H, $CH_2C_6H_5$), 4.17 (AB m, 2 H, CH_3CH_2O), 4.03 (AB q, 2 H, CH_2OH), 3.45 (q, J = 6.J Hz, 1 H, 4-H), 2.93 (br s, 1 H, OH), 1.23 (t, 3 H, CH_3CH_2O), 1.11 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.95 (s), 140.13 (d), 137.20 (s), 128.64 (d), 127.58 (d), 126.85 (d), 124.47 (d), 121.03 (s), 103.44 :s), 63.10 (t), 59.19 (t), 57.44 (t), 28.21 (d), 22.72 (q), 14.26 (q).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.88. Found: C, 70.54; H, 6.94; N, 4.30.

***N*-Benzyl-3-(hydroxymethyl)-4(*S*)-methyl-1,4-dihydropyridine (5a).** In a similar manner, the 3-formyl derivative **16a** was reduced to give **5a**, yield 69%, which was purified by trituration of the crude material with hot hexanes to afford a colorless oil which decomposes on TLC and turns dark green on exposure to air. However, solutions of **5a** in $CDCl_3$, under argon, are stable for several months: $[\alpha]_D^{20}$ +56.7° (*c* 0.27, $CHCl_3$); IR (neat) 3680–3110, 3050, 3010, 2945, 2910, 2855, 1670, 1616, 1492, 1450, 716, 684 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.33–7.18 (m, 5 H, C_6H_5), 5.85 (s, 1 H, 2-H), 5.78 (d, J = 7.7 Hz, 1 H, 6-H), 4.43 (dd, J_1 = 7.8, J_2 = 7.8 Hz, 1 H 5-H), 4.14 (s, 2 H, CH_2-C_6H_5), 3.96 (AB q, 2 H, CH_2OH), 3.21 (mc, 1 H, 4-H), 2.04 (br s, 1 H, OH), 1.11 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 138.63 (s), 129.17 (d), 128.43 (d), 128.38 (d), 127.11 (d), 126.95 (d), 113.95 (s), 104.33 (d), 64.26 (t), 56.65 (t), 28.68 (d), 24.19 (q).

***N*-Benzyl-5-(*N*,*N*-dimethylcarbamoyl)-3-(hydroxymethyl)-4(*R*)-methyl-1,4-dihydropyridine (5c).** Following the procedure for **5b**, the product **5c** was obtained by purification via radial chromatography (50% THF–hexanes changing to 70% THF–hexanes) to furnish **5c** in 58% yield, as a colorless oil: $[\alpha]_D^{20}$ +13.5° (*c* 0.17, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.39–7.19 (m, 5 H, C_6H_5), 6.23 (s, 1 H, 6-H), 5.95 (s, 1 H, 2-H), 4.31 (s, 2 H, $CH_2C_6H_5$), 4.07 (AB q, 2 H, CH_2OH), 3.55 (q, J = 6.6 Hz, 1 H, 4-H), 2.99 (s, 6 H, NMe_2), 2.68–2.53 (br s, 1 H, OH), 1.08 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 172.67 (s), 137.89 (s), 132.97 (d), 128.69 (d), 127.53 (d), 127.00 (d), 126.27 (d), 117.33 (s), 109.00 (°), 63.73 (t), 57.18 (t), 3736 (q), 30.44 (d), 22.56 (q).

Methyl Ethers 19a–c. General Procedure. To a suspension of potassium hydride in absolute THF (1.2 equiv washed several times with dry pentane prior to use) was added a solutionof the dihydropyridines **5a–c** (1.0 equiv) at 0 °C. After the solution was stirred for 30 min at this temperature, methyl iodide (2 equiv) was added to the reaction mixture. The mixture was allowed to warm to room temperature over a period of 1 h, at which time the excess hydride was quenched by addition of water (2 equiv). Extractive work up ($CHCl_3$), drying (K_2CO_3), and evaporation of the solvent gave pale-yellow air-sensitive oils of the corresponding methyl ethers **19a–c**. These compounds turn dark green when exposed to air and should be handled and stored under argon.

***N*-Benzyl-3-(methoxymethyl)-4(*S*)-methyl-1,4-dihydropyridine (19a)**: yield 96%; $[\alpha]_D^{20}$ +65.8° (*c* 1.06, $CHCl_3$); IR (neat) 3025, 2590, 2915, 2860, 2805, 1682, 1618, 1494, 688 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5 H, C_6H_5), 5.87 (s, 1 H, 2-H), 5.79 (d, J = 7.8 Hz, 1 H, 6-H), 4.44 (dd, J_1 = 7.7, J_2 = 7.7 Hz, 1 H, 5-H), 4.19 (s, 2 H, $CH_2C_6H_5$), 3.80 (AB q, 2 H, CH_2OMe), 3.25 (s, 3 H, OMe), 3.15 (mc, 1 H, 4 H), 1.11 (d, J = 6.6 Hz, 3 H, CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 138.68 (s), 129.39 (d), 129.07 (d), 128.38 (d), 127.09 (d), 126.89 (d), 110.61 (s), 104.52 (d), 74.20 (t), 56.66 (t), 56.66 (q), 29.27 (d), 24.07 (q).

***N*-Benzyl-5-(ethoxycarbonyl)-3-(methoxymethyl)-4(*R*)-1,4-dihydropyridine (19b)**: yield 64%, pale-yellow oils; $[\alpha]_D^{20}$ −189.3° (*c* 0.15, $CHCl_3$); IR (neat) 3065, 3030, 2980, 2925, 2870, 2820, 1688, 1600, 1495, 1450, 1199, 7618 724, 692 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.38–7.20 (m, 6 H, C_6H_5, 6-H), 5.87 (s, 1 H, 2-H), 4.40 (s, 2 H, $CH_2C_6H_5$), 4.16 (AB m, 2 H, CH_6CH_2O), 3.86 (AB q, 2 H, CH_2OMe), 3.43 (q, J = 6.4 Hz, 1 H, 4-H), 3.29 (s, 3 H, OMe), 1.26 (t, 3 H, CH_3CH_2O), 1.13 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 167.96 (s), 140.11 (d), 137.41 (s), 128.85 (d), 127.79 (d), 127.00 (d), 125.89 (d), 117.97 (s), 104.17 (s), 73.36 (t), 59.35 (t), 57.62 (t), 57.52 (q), 28.79 (d), 22.71 (q), 14.47 (q).

***N*-Benzyl-5-(*N*,*N*-dimethylcarbamoyl)-3-(methoxymethyl)-4(*R*)-1,4-dihydropyridine (19c)**: yield 72%; $[\alpha]_D^{20}$ +3.6° (*c* 0.11, $CHCl_3$); IR (neat) 3380, 30208, 2940, 2910, 2855, 1680, 1597, 1486, 1161, 687 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37–7.19 (m, 5 H, C_6H_5), 6.25 (s, 1 H, 6-H), 5.93 (s, 1 H, 2-H), 4.32 (s, 2 H, $CH_2C_6H_5$), 3.86 (AB q, 2 H, CH_2OMe), 3.48 (q, J = 6.5 Hz, 1 H, 4-H), 3.28 (s, 3 H, OMe), 2.99 (s, 6 H, NMe_2), 1.09 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 172.57 (s), 137.89 (s), 132.80 (d), 128.67 (d), 127.61 (d), 127.45 (d), 126.97 (d), 113.88 (s), 109.30 (s), 73.78 (t), 57.12 (t + q), 37.29 (q), 30.91 (d).

Asymmetric Reduction of Benzoylformic Ester to Methyl Mandelate (*S*)- or (*R*)-18. General Procedure for 20–50-mg Scale. An ampule (2 mL) containing magnesium perchlorate ($Mg(ClO_4)_2 \cdot 1.5\ H_2O$, 1.0 equiv) sealed with a small rubber septum was evacuated and flushed with argon several times. Methyl benzoylformate (1.0 equiv) was injected via syringe, followed by a solution of the 1,4-dihydropyridine (1.0 equiv) in freshly distilled acetonitrile (1 mL). The ampule was kept in the dark and the reduction allowed to proceed for 5–10 days monitored by TLC. After this period, water (100–200 μL) was added, and the reaction mixture was concentrated in vacuo. The residue was triturated with boiling chloroform (2–3 mL) and the relative yield of methyl mandelate **18**, as a chloroform solution, was determined by using capillary GC.[17] The chloroform solution was concentrated to about 0.1 mL, and the alcohol **18** was isolated via preparative TLC using 20% ethyl acetate–hexanes as the eluent. Extraction of the silica gel bands, with ethyl acetate, gave methyl mandelate after filtration through a millipore filter, and concentration gave the crystalline alcohol **18**. After dissolving this material in 1.0 mL of methanol, the specific rotation of the sample was measured, followed by determination of the accurate concentration of **18** in the alcohol using HPLC calibration.[18]

Pyridinium Salt 20. Isolation of the pyridinium salt **20** was achieved during the preparative TLC by extraction of the base-line silica gel layers with ethyl acetate (5 mL). Filtration and concentration gave the orange salt **20** (40–50% recovery): ^1H NMR (CD_3CN) δ 9.08 (br s, 1 H, 6-H), 8.79 (br s, 1 H, 2-H), 7.60–7.40 (m, 5 H, C_6H_5), 5.77 (s, 2 H, $CH_2C_6H_5$), 4.82 (d, J = 5.2 Hz, 2 H, CH_2OH), 4.68 (br s, OH), 4.42 (q, J = 7.2 Hz, 2 H, CH_3CH_2O), 2.66 (ns, 3 H, CH_3), 1.39 (t, J = 7.1 Hz, 3 H, CH_3CH_2O).

Determination of Enantiomeric Purity of 5b via Mosher Ester. Verification of the ee for **5a–c** as a cross check for the HPLC determination on **14A** and **14B** was obtained in the case of **5b** by the independent method which follows: (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride[12] (44.0 mg, 0.174 mmol) was added to a solution of alcohol **5b** (10.0 mg, 0.35 mmol) in freshly distilled pyridine (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over a period of 3 h and was diluted with methylene chloride (10 mL). Washing with water (2 × 5 mL) and brine (2 × 5 mL), drying (K_2CO_3), filtrating, and concentrating gave the crude Mosher ester: ^1H NMR ($CDCl_3$) δ 7.85–7.05 (m, 11 H, C_6H_5, 6-H), 6.01 (br s, 1 H, 2-H), 4.76 (AB q, 2 H, CH_2O), 4.39 (s, 2 H, $CH_2C_6H_5$), 4.14 (AB m, 2 H, CH_3CH_2O), 3.53 (s, 3 H, OMe), 3.30 (q, J = 6.1 Hz, 1 H, 4-H), 1.25 (t, 3 H, CH_3CH_2O), 1.04 (d, J = 6.5 Hz, 3 H, CH_3); ^{19}F NMR ($CDCl_3$ + $CFCl_3$, internal standard) δ −71.88, −72.05, ratio = 6:94.

Determination of Enantiomeric Purity of Methyl Mandelate (+)-18 via Mosher Ester. Independent verification of the enantiomeric purity of **18**, obtained via the asymmetric reductions with **5** and **19** was obtained by the following: A solution of (+)-methyl mandelate **18** (91% ee via specific rotation, 30.8 mg, 0.185 mmol) in pyridine–carbon tetrachloride (5 mL, 1:1) was treated with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (70.2 mg, 0.278 mmol) and stirred at room temperature for 1 h. The reaction mixture was washed with water (3.5 mL), and the separated organic phase was dried ($MgSO_4$) and concentrated, leaving a pale-yellow oil: 67.3 mg, 95%; ^{19}F NMR ($CDCl_3$–$CFCl_3$) δ −72.20 (s), −72.52 ns), ratio of the peaks = 94:6 (88% ee); ^1H NMR n$CDCl_3$, 270 MHz) δ 6.13 (s), 6.11 (s), ratio of methoxyl peaks = 94.4:5.6 (89% ee). This is in good agreement with the optical purity obtained via polarimetric determination (91% ee) when **5b** was employed.

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(17) Capillary gas chromatography calibration was determined for methyl benzoylformate and racemic methyl mandelate using 1,4-dimethoxybenzene as the internal standard. The calibration factors, f_i = 0.85 ± 0.03 and f_i = 0.93 ± 0.08, were determined using column, injector, and detector temperatures of 110, 210, and 250 °C, respectively, and a carrier gas flow (N_2) of 10 psi.

(18) HPLC calibration to determine the concentration of **18** in methanol was performed using (±)-**18** and 1,4-dimethoxybenzene as an internal standard, giving a calibration factor, f_i = 0.843 ± 0.017, on a normal phase column (4.6 mm × 25 cm), Zorbax Sil, Du Pont Instruments, with 10% THF–hexanes as the eluent.

A Novel Cyclophane. Host–Guest Complexation and Selective Inclusion of Aromatic Guests from Nonaqueous Solution

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Abstract: A novel cyclophane, 2,2,20,20-tetramethyl-11,29-dinitro-7,15,25,33-tetraoxaheptacyclo-[32.2.2.2^{3,6}.2^{16,19}.2^{21,24}.1^{9,13}.1^{27,31}]hexatetraconta-3,5,9(44),10,12,16,18,21,23,27(39),28,30,34,36,37,40,42,45-octadecaene (**1**), was synthesized by the reaction of 3,5-bis(bromomethyl)nitrobenzene (**2**) with bisphenol A (**3**). Both stepwise 2:2 cyclization of **2** and **3** via U-shaped precursor **4** and direct 2:2 cyclization of **2** and **3** were performed under several reaction conditions. With the coexistence of benzene in the reaction solvent, relatively high yield of **1** was achieved even without operation under high dilution conditions. This can be explained in term of a "template" effect of benzene in the cyclization step. The cyclophane **1** formed a "column-type" cave and included aromatic guests in this cave. This was confirmed by X-ray crystal structure analysis of the complex with benzene. The stoichiometry and the stability of the various inclusion complexes at high temperatures and under reduced pressure were examined. The remarkable discrimination selectivity in the inclusion complex formation from mixtures of guests is reasonably explained by the "packing-size relationship".

Incipient studies of the chemistry of cyclophanes by Cram and others were largely concerned with the chemical and physical properties of the small-membered cyclophanes.[1] However, during the past decade, great effort was devoted to the synthesis of large-membered cyclophanes, and consequently a number of novel and interesting cyclophanes were prepared. It was observed that some of these cyclophanes formed inclusion complexes with various neutral molecules.[2] Selective inclusion complex formation with organic guests is of great significance in many respects. One of the fundamental problems is to design cyclophanes which show

Table I. Comparison of the Yield of **1** by Stepwise and Direct Methods

stepwise 2:2 condensation via U-type precursor **4**	direct 2:2 condensation		
without C_6H_6 H.D.[a]	without C_6H_6 H.D.[a]	with C_6H_6 H.D.[a]	
28%	4%	23%	21%

[a] H.D. = high dilution method.

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