Broad-Spectrum Synthesis of Enantiomerically Pure Lactones. 1. Synthesis of Sex Pheromones of the Carpenter Bee, Rove Beetle, Japanese Beetle, Black-Tailed Deer, and Oriental Hornet[1]

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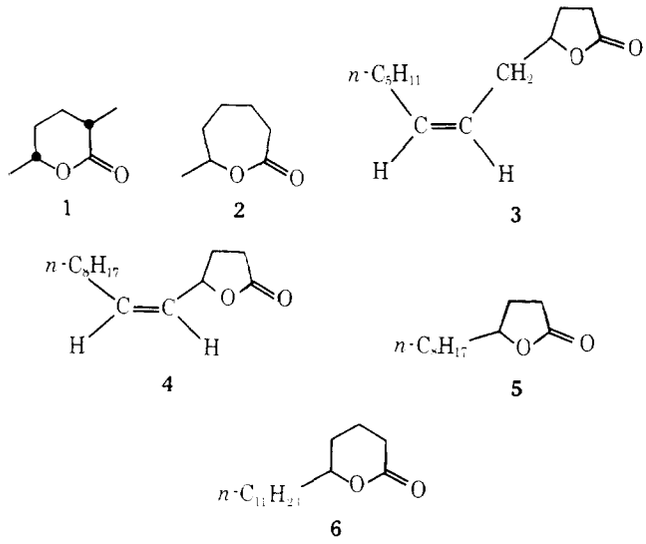
Enantiomerically pure lactonic pheromones, **1**, **3–6**, of the carpenter bee, black-tailed deer, Japanese beetle, rove beetle, and Oriental hornet, respectively, have been synthesized from racemic type **7** cyano alcohols. The key to the success of the overall approach is the facile separation of diastereomeric carbamates derived from type **7** cyano alcohols by automated multigram LC. The approach chosen also facilitates the assignment of absolute configurations to the lactone enantiomers and their precursors. In the case of **1** and **2**, direct determination of enantiomeric purity and absolute configuration is also possible using the chiral solvating agent 2,2,2-trifluoro-1-(9-anthryl)ethanol.

Lactonic functionality is fairly common among natural products and in a variety of biologically active molecules. For those interested in preparing such molecules, the task of assembly of chiral lactonic systems is one often encountered. In this paper, we describe a simple procedure that suffices for the preparation of a series of enantiomerically pure lactones of several ring sizes. Although the procedure is illustrated here by the synthesis of both enantiomers of lactonic pheromones for the carpenter bee (**1**), its isomer (**2**), the black-tailed deer (**3**), the Japanese beetle (**4**), the rove beetle (**5**), and the Oriental hornet (**6**), the approach does provide chiral lactones which might be further elaborated. Several of the aforementioned pheromones have been prepared previously by different methods.



Total syntheses of natural products frequently involve problems of enantiomer separation, enantiomeric purity, and absolute configuration. To alleviate these stereochemical problems, workers often utilize an enantiomerically pure starting material of known absolute configuration. However, this approach may introduce additional difficulties. Even when suitable starting materials of the correct absolute configuration are available, synthetic sequences may be lengthy and failure of key reactions to follow known and totally stereospecific pathways may prove troublesome. A common alternative to the preceding approach involves resolution of the racemic target compound (or a precursor thereof). This approach can have shortcomings also. Most resolutions to date have involved fractional crystallization as a means of separating diastereomeric derivatives of the racemate in question. Such resolutions require a trial-and-error approach, frequently suffer from low overall yields, and possibly afford material of uncertain enantiomeric purity and unknown absolute configuration.

Our recent interest in the use of multigram LC for the convenient and predictable separation of diastereomers has led to methodology that makes routine the resolution of a wide assortment of racemates. In addition to the ease and predictability of these resolutions, questions of enantiomeric purity and absolute configuration are, as a rule, answered concurrently. Such techniques should have considerable impact upon future choices of synthetic routes to chiral natural products, especially since both enantiomers of a substance are often desired for purposes of comparison and testing. In instances where a large amount of but one enantiomer is required, the synthesis of a racemate might be deemed inefficient. We simply point out that methodology that enables one to efficiently, conveniently, and predictably resolve a wide variety of racemates allows one to use short direct synthetic pathways with consequent dividends in effort and overall yield. This philosophy has been employed recently in the synthesis of the chiral sex pheromones of the gypsy moth[3] and of the dried bean weevil.[4]

Results and Discussion

A preliminary report[5] describes the synthesis of the four possible stereoisomers of 2-methyl-5-hydroxyhexanoic acid lactone (*cis*- and *trans*-**1**) by a variation of the general synthetic approach shown in Scheme I. Numerous straightforward synthetic routes are available for obtaining racemic cyano alcohols of general formula **7**. Resolution of these cyano alcohols is almost tantamount to synthesis of the corresponding enantiomerically pure lactone. Resolution of the cyano alcohols involves reaction with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate[6] to afford diastereomeric cyano carbamates **9a** and **9b**. Alternatively, one may obtain the carbamates by allowing the chloroformate of the cyano alcohol to react with (*R*)-(−)-1-(1-naphthyl)ethylamine. We have found these (and many other) carbamate diastereomers to be readily separable by automated multigram LC.[7] Each diastereomer is subsequently subjected to silanolysis with trichlorosilane to retrieve the chiral cyano alcohol.[8] Hydrolysis and lactonization of the enantiomeric cyano alcohols afford the corresponding lactone enantiomers.

2-Methyl-5-hydroxyhexanoic Acid Lactones. Scheme II depicts the approach utilized in the synthesis of the four possible stereoisomers of lactone **1**. The *cis*-lactone has been identified by Wheeler as the major volatile component of the carpenter bee sex attractant.[9] Racemic 5-cyanopentan-2-ol, prepared by the method of Colonge,[10] was converted to diastereomeric cyano carbamates **11a** and **11b**. An α value of 2.8

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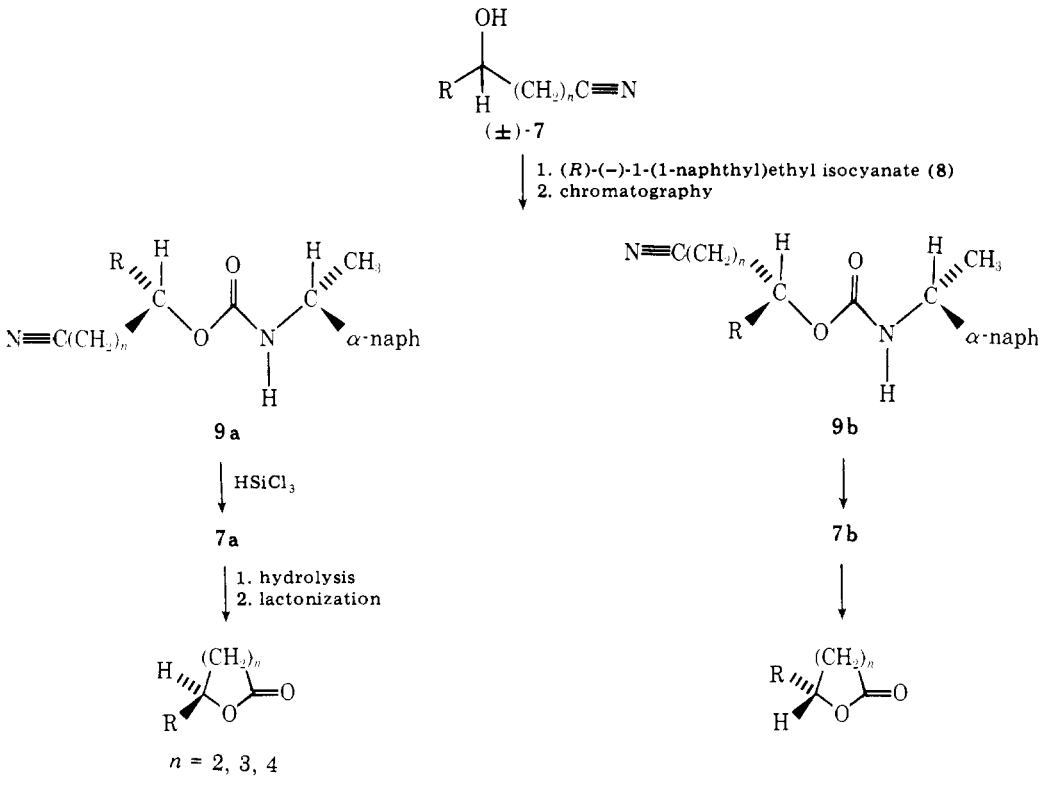
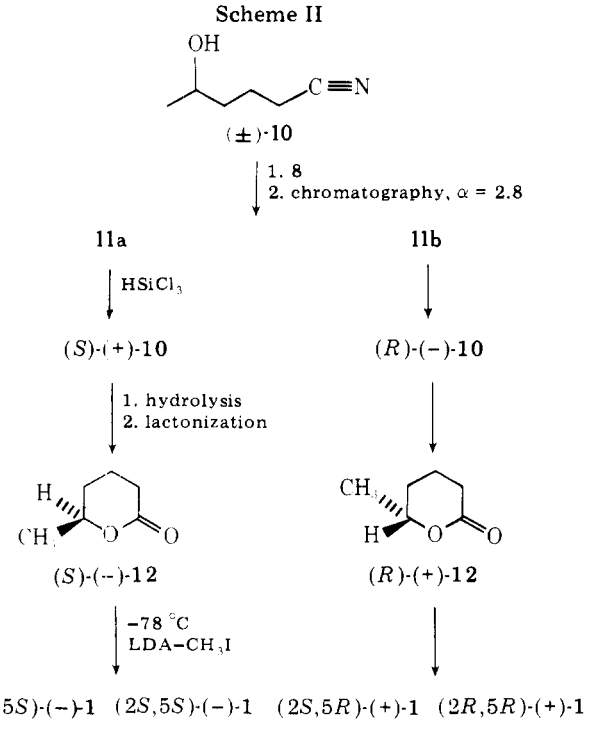
Scheme I. General Sequence for Chiral Lactone Synthesis



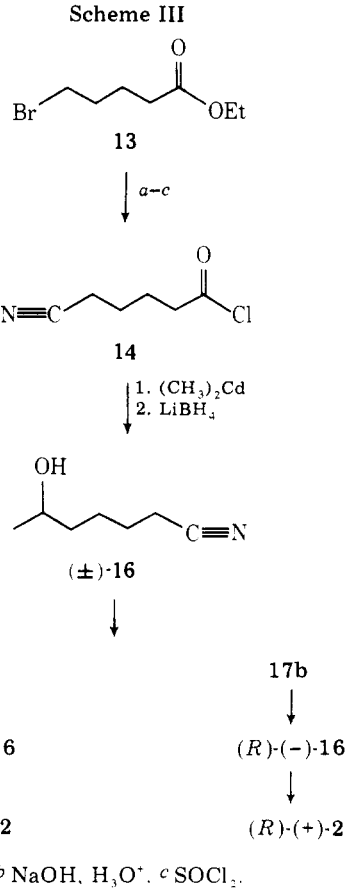
(acidic alumina, 2:1 $CHCl_3$–hexane) was observed for the chromatographic separation of these carbamates. Silanolysis was used to retrieve the enantiomeric cyano alcohols, and these were separately subjected to hydrolysis and lactonization to afford the enantiomers of δ-methyl-δ-valerolactone (**12**). Low temperature methylation (LDA–methyl iodide) of either enantiomer of lactone **12** affords a 1:1 mixture of GLC-separable cis and trans isomers of the corresponding enantiomer of **1**.

ϵ-Caprolactone. Scheme III details our approach to the previously unknown chiral ϵ-caprolactone. A series of quantitative reactions converted ethyl 5-bromovalerate (**13**) into 5-cyanovaleryl chloride (**14**). The cyano acid chloride was allowed to react with dimethylcadmium to afford the corresponding cyano ketone, which was reduced with $LiBH_4$ to give the desired racemic cyano alcohol **16**. The diastereomeric cyano carbamates of **16** exhibit an α value of 1.4 upon chromatography (silica gel, 7:1 benzene–ether). The conversion of the cyano carbamates to the enantiomers of **2** is straightforward.

Scheme II

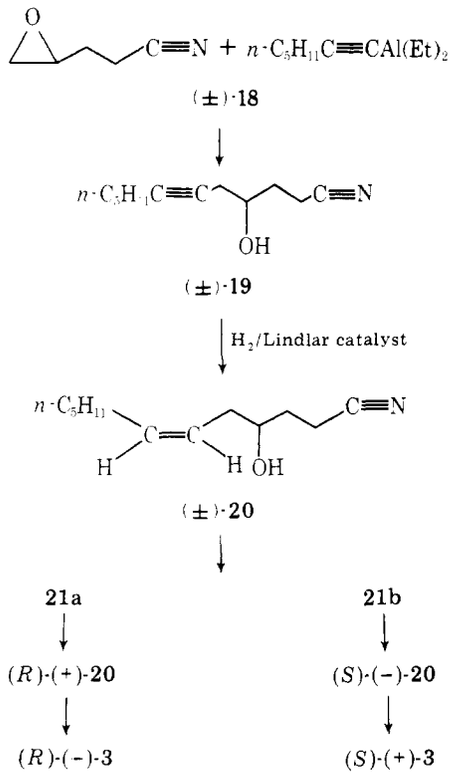


Scheme III



[a] KCN/Me_2SO. [b] NaOH, H_3O^+. [c] $SOCl_2$.

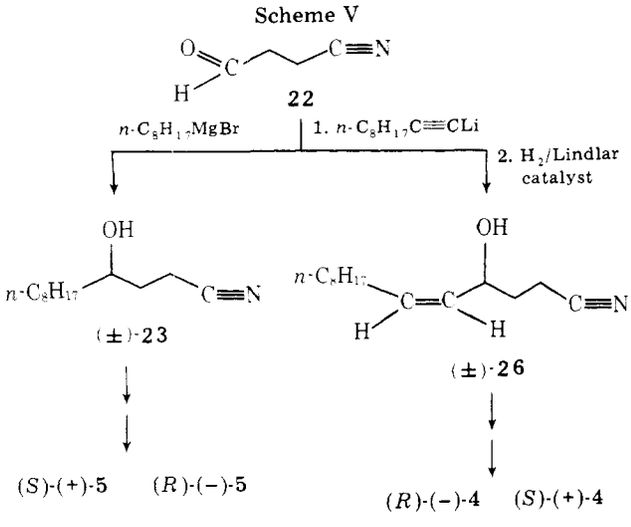
Scheme IV



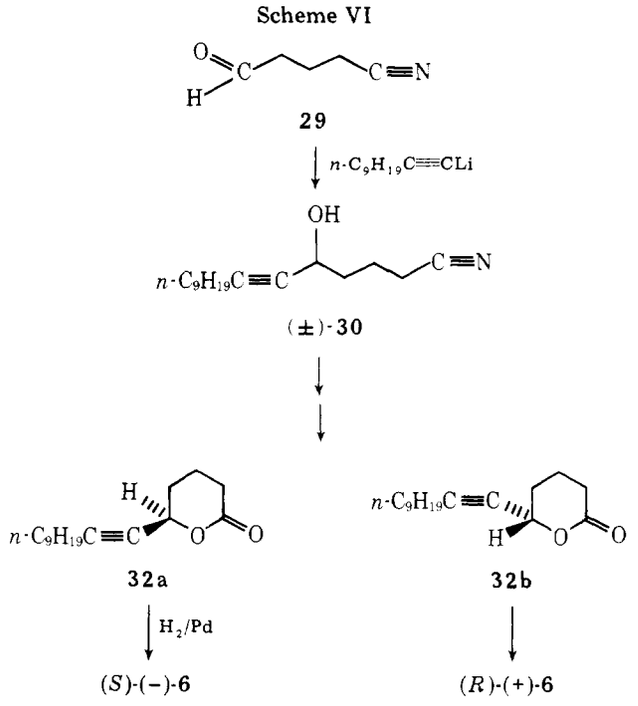
(Z)-6-Dodecen-4-olide. The synthetic sequence (Scheme IV) to the enantiomers of lactone **3** begins with allylacetonitrile epoxide (**18**), prepared by the method of Hall.[11] The cyano epoxide was allowed to react with 1-heptynyldiethylaluminum to afford racemic acetylenic cyano alcohol **19.** Hydrogenation employing Lindlar catalyst gave the appropriately functionalized cis olefin (**20**). A modest α value (1.2) was observed for the chromatographic separation of the cyano carbamates (silica gel, 3:1 hexane–ethyl acetate). Each diastereomer was then converted, as previously described, to the corresponding enantiomer of lactone **3**. The *R*-(−) enantiomer has been identified by Silverstein et al.[12a] as the social pheromone of the black-tailed deer.

γ-*n*-Dodecanolactone and (*Z*)-5-Tetradecen-4-olide. Addition of *n*-octylmagnesium bromide to β-cyanopropionaldehyde (**22**) affords racemic cyano alcohol **23** (Scheme V). The carbinol was resolved (α = 2.0, acidic alumina, 3:1 hexane–ethyl acetate) as previously described and converted to the enantiomers of γ-*n*-dodecanolactone (**5**). This lactone has been identified by Wheeler[13] as being a rove beetle pygidial

Scheme V



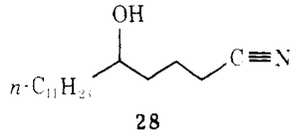
Scheme VI



gland secretion and is also found in various fruits[14] and in butterfat.[15]

The remainder of Scheme V outlines the approach used to obtain both enantiomers of (*Z*)-5-tetradecen-4-olide. Tumlinson and co-workers[16] have identified the *R*-(−) enantiomer as the only component of the Japanese beetle sex attractant. Addition of 1-decynyllithium to β-cyanopropionaldehyde, followed by Lindlar reduction, affords the desired racemic cyano alcohol **26.** Resolution (α = 1.5, silica gel, 7:1 benzene–ether) followed by lactonization in the usual manner affords the enantiomers of **4.** The rotations of the final products are in agreement with those obtained by Tumlinson in his synthesis of **4** from the enantiomers of glutamic acid.[16] This synthesis shows that the present method encompasses allylic (and propargylic) chiral centers, although it should be noted that such compounds should not be subjected to workups involving strongly acidic conditions lest racemization occur.

δ-*n*-Hexadecanolactone. As a final example, we describe the synthesis of the enantiomers of δ-*n*-hexadecanolactone (Scheme VI). Ishay and co-workers[17] have proposed this lactone to be responsible for some aspects of the social behavior of the Oriental hornet. Initially we envisioned that resolution of cyano alcohol **28** would lead directly to the target lactone. In this instance, the cyano carbamates of **28** could not be



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separated by conventional chromatography on alumina or silica gel, although the separation was achieved on an analytical scale using a C_{18} reverse-phase column. The separational difficulty was alleviated by building more rigidity into the linear alkyl chain of **28.** Addition of 1-undecynyllithium to γ-cyanobutyraldehyde[18] (**29**) affords racemic acetylenic cyano alcohol **30.** A striking example of the ease of separation of the corresponding cyano carbamates is shown in Figure 1. The baseline separation of 1.5 g of each diastereomer (α = 1.8, silica gel, 8:1 benzene–ether) was performed automatically in a period of less than 2 h. Conversion of the carbamates to acetylenic lactones (**32a,b**), followed by catalytic reduction

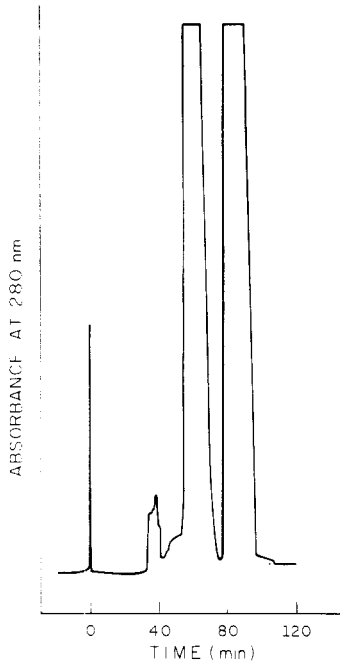

Figure 1. Automated chromatographic separation of the diastereomeric carbamates **31a,b**.

over palladium, completes the synthesis of lactone **6**. The rotations of our enantiomers of **6** represent a nine-fold increase over those obtained by Coke in a prior synthesis.[19]

Assignments of Absolute Configuration and Determinations of Enantiomeric Purity. Diastereomeric carbamates similar to those discussed herein are known to preferentially populate the conformations depicted by **9a** and **9b** and have a more or less rigid backbone.[20] For each of the presently discussed pair of diastereomers, the one having the cyano substituent on the same face of the carbamate backbone as the naphthyl group was expected to be most mobile (high R_f) chromatographically. This presumption stemmed from the expected interaction between the polar cyano group and the adsorbent and the greater ability of the α-naphthyl (compared to methyl) group to impede such interaction. The absolute configuration of the resolving agent utilized is known to be *R*; hence, assignment of absolute configuration to the carbinol portion of the diastereomers was expected to be possible from the observed elution order as well as from NMR spectral differences between a pair of diastereomers. Assignments of absolute configuration so reached extend to the final lactones. Assignments so reached agree uniformly with the prior assignments of absolute configuration to **3, 4, 6,** and **12**.

For those lactones possessing suitable sharp NMR signals, absolute configurations are readily assignable from the sense of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol induced spectral nonequivalence.[21] Assignments made on this basis for the enantiomers of **1** and **2** are in agreement with those assigned from the elution order of the carbamate precursors. Induced NMR nonequivalence usually allows facile NMR determination of the enantiomeric purity of the solute in question. By this criterion, **1** and **2** were enantiomerically pure. However, the remaining lactones have relatively featureless NMR spectra and similar checks of enantiomeric purity and absolute configuration have not been made. However, the chromatographic separation of the diastereomeric carbamates was shown to be total (by rechromatography) and subsequent steps involve no racemization (unchanged rotations in control experiments) so long as strongly acidic conditions and/or high temperatures are avoided. Hence, the presumption is that all of the lactones described herein are of essentially complete enantiomeric purity.

Conclusion

A general approach has been devised whereby both enantiomers of an assortment of enantiomerically pure lactones of various ring sizes can be prepared. Absolute configurational assignments typically attend these syntheses. The chiral lactones so obtained may be structurally elaborated to further extend the scope of the synthetic sequence.

Experimental Section

General. Varian EM 390 and Perkin-Elmer 237B spectrometers were used to obtain NMR and infrared spectra. Optical rotations were obtained using a Zeiss visual polarimeter with a 1.0-dm tube. A Büchi apparatus was used to determine melting points (uncorrected). A Varian Aerograph Series 1800 gas chromatograph was used for some purifications. Carbowax refers to 15% Carbowax 20 M on Chromosorb W. Solvents were reagent grade except for hexane. Microanalyses were performed by J. Nemeth and Associates, University of Illinois. Acetylenes were purchased from Farchan Chemical Co. and were used without further purification. Diastereomeric cyano carbamates were prepared by either of two methods. Procedures A and B are representative.

Chromatography. Liquid chromatographic separations were effected with an automated preparative system which diverts specified bands (e.g., the three major bands of Figure 1) into separate collection vessels. Spent solvent is continuously flash distilled from the collection vessels and returned to the reservoir from which the pump feeds. An earlier version of this system has been described.[7] Columns of 2 in. in diameter and 4.5 ft in length were packed with 58-μm Ventron silica gel or 63–200-μm Brinkman acidic alumina. Typically, 1.0–2.0-g quantities of each diastereomer were separated in a single pass. Larger samples saturate the 280-nm UV detector and interfere with the automatic fraction diversion. The columns themselves were not overloaded. Larger scale automated separations can be accomplished by monitoring at a wavelength where the solutes adsorb less strongly, by using larger columns, or by using the previously described[7] automated repetitive injection technique. TLC was performed with silica gel 60 F-254 plates obtained from EM Reagents. Separation conditions worked out by TLC could be directly transferred to the preparative columns.

1-Methyl-4-cyanobutyl *N*-[1-(1-Naphthyl)ethyl]carbamates (11a,b). Procedure A. A stirred solution of 8.0 g (70.8 mmol) of 5-cyanopentan-2-ol,[10] 13.9 g (70.8 mmol) of (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate,[6] 150 mL of dry PhH, and two drops of dimethylethanolamine catalyst was heated at reflux under N_2 for 24 h. The solvent was removed in vacuo, and the crude diastereomeric carbamates were completely separated by chromatography (acidic alumina with 2:1 $CHCl_3$–hexane) using an automated preparative LC system.[7]

A total of 8.9 g (81%) of the high R_f[(*S,R*)-**11a**] diastereomer was collected as a yellow viscous oil: IR 3310, 2220, 1680–1722 broad, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (broad d, J = 6.0 Hz, 3 H), 1.60 (d, J = 7.0 Hz, 3 H), 1.3–1.7 (m, 4 H), 2.05–2.38 (m, 2 H), 4.45–5.08 (m, 2 H), 5.36–5.68 (m, 1 H), 7.3–8.11 (m, 7 H); $[\alpha]^{22.5}_D$ +8.15° (1.37, EtOH).

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.55; H, 7.10; N, 9.03. Found: C, 73.30; H, 7.11; N, 8.80.

A total of 8.72 g (79.5%) of the low R_f[(*R,R*)-**11b**] diastereomer was isolated as a yellow viscous oil: IR 3305, 2230, 1665–1720 broad, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (d, J = 6.0 Hz, 3 H), 1.60 (d, J = 7.0 Hz, 3 H), 1.3–1.8 (m, 4 H), 2.1–2.47 (m, 2 H), 4.6–5.15 (m, 2 H), 5.35–5.7 (m, 1 H), 7.31–8.16 (m, 7 H); $[\alpha]^{23}_D$ +22.7° (0.76, EtOH).

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.55; H, 7.10; N, 9.03. Found: C, 73.37; H, 7.27; N, 8.85.

The enantiomeric cyano alcohols were retrieved from the cyano carbamates by either of two methods. Procedures C and D are representative.

(*R*)-(−)-5-Cyanopentan-2-ol (10). Procedure C. To a stirred solution of 6.75 g (21.8 mmol) of **11b** and 2.45 g (24.2 mmol) of Et_3N in 50 mL of dry PhH was added 3.28 g (24.2 mmol) of $SiHCl_3$ in 20 mL of PhH over a 10-min period. The reaction was heated at reflux under N_2 for 4 h. After being cooled, the reaction mixture was poured with stirring into 100 mL of saturated aqueous NH_4Cl. An insoluble silicon-containing solid was removed by filtration, and the organic portion of the filtrate was washed with 2 × 100 mL of H_2O. The combined aqueous phases were extracted continuously with ether for 24 h. Drying ($MgSO_4$) and concentration of the ethereal extract afforded 2.25 g (91.5%) of (*R*)-(−)-**10**, which was purified by molecular distillation at 0.2 torr: IR 3450, 2250 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (d J = 6.5 Hz, 3 H), 1.3–1.93 (m, 5 H), 2.38 (t, J = 7.5 Hz, 2 H), 3.65–3.97 (m, 1 H); $[\alpha]^{23.5}_D$ −14.1° (2.0, EtOH).

Anal. Calcd for $C_6H_{11}NO$: C, 63.72; H, 9.73; N, 12.39. Found: C, 63.44; H, 9.96; N, 12.66.

(*S*)-(+)-10. In a manner exactly analogous to the preceding method, **11a** was converted to *S*-(+)-**10**, which possesses spectral and physical properties identical with those of the (−) enantiomer, $[\alpha]^{22.4}_D$ +13.7° (4.3, EtOH).

Procedures E and F are representative for the conversion of the cyano alcohols to lactones.

(*R*)-(+)-δ-Methyl-δ-valerolactone (12). Procedure E. A solution of 1.9 g (16.8 mmol) of (*R*)-(−)-**10**, 2.35 g (42 mmol) of KOH, and 12 mL of H_2O was stirred at reflux under N_2 for 20 h. After being cooled, the reaction was neutralized with dilute hydrochloric acid and continuously extracted for 12 h with ethanol-free ether. Drying ($MgSO_4$) and concentration of the etheral extract afforded crude **12**, which was lactonized in 30 mL of PhH at reflux for 2 h (azeotropic removal of H_2O). The solvent was removed in vacuo, and the residue was molecularly distilled at 0.03 torr to afford 1.86 g (97.4%) of pure (*R*)-(+)-**12**: IR 1737 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (d, *J* = 6.5 Hz, 3 H), 1.46–2.07 (m, 4 H), 2.38–2.64 (m, 2 H), 4.21–4.58 (m, 1 H); $[\alpha]^{22.5}_D$ +30.9° (2.0, EtOH) [lit.[22a] $[\alpha]^{20}_D$ +18.4° (1.7, MeOH)].

Anal. Calcd for $C_6H_{10}O_2$: C, 63.16; H, 8.77. Found: C, 63.08; H, 8.86.

(*S*)-(−)-12. In a manner exactly analogous to the preceding method, (*S*)-(+)-**10** was converted to (*S*)-(−)-**12**, which possesses spectral and physical properties identical with those of the (+) enantiomer, $[\alpha]^{23}_D$ −30.4° (1.6, EtOH) [lit.[22b] $[\alpha]^{19}_D$ −51.4° (EtOH)].

(+)-*cis*- and -*trans*-2-Methyl-5-hydroxyhexanoic Acid Lactones (1). A solution of 1.4 g (12.3 mmol) of *R*-(+)-**12** in 25 mL of ether was added over a 20-min period to a stirred −78 °C solution of 12.3 mmol of lithium diisopropylamide (from 1.24 g of diisopropylamine and 5.85 mL of 2.1 M *n*-butyllithium in 70 mL of dry THF) under an N_2 atmosphere. After being stirred for 2 h at −78 °C, 1.75 g (12.3 mmol) of CH_3I in 15 mL of ether was added over a 10-min period and the stirred solution was maintained at −78 °C for 10 h. The solvent was concentrated in vacuo, and the residue was dissolved in 100 mL of saturated aqueous NaCl. Continuous extraction of the aqueous solution with ethanol-free ether for 12 h afforded, after drying ($MgSO_4$) and concentration of the extract, 1.5 g of crude alkylate. GLC of the crude product (Carbowax, 180 °C) showed 60% conversion to a 1:1 mixture of the cis and trans isomers of **1**. The remainder of the mixture, unreacted starting material, was last to elute and of unchanged specific rotation. A preparative column of 20% Carbowax 20 M on Chromosorb P (20 ft × 0.50 in., 150 °C, 100–120-μL injections) was used to separate the cis and trans isomers of **1**.

trans-(+)-(2*R*,5*R*)-**1** eluted before the cis isomer, consistent with the findings of Wheeler et al.:[9] mp 49–50 °C; IR (Nujol) 1750 cm^{-1}; NMR (CCl_4) δ 1.25 (d, *J* = 7.5 Hz, 3 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 1.4–2.5 (m, 5 H), 4.15–4.45 (m, 1 H); irradiation at 4.36 ppm collapsed the doublet at 1.32 ppm; $[\alpha]^{23.2}_D$ +54.9° (1.2, $CHCl_3$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.62; H, 9.37. Found: C, 65.68; H, 9.45.

cis-(+)-(2*S*,5*R*)-**1**: mp 46.5–48 °C; IR (Nujol) 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (d, *J* = 6.5 Hz, 3 H), 1.34 (d, *J* = 6.1 Hz, 3 H), 1.4–2.7 (m, 5), 4.23–4.51 (m, 1 H); irradiation at 4.33 ppm collapsed the doublet at 1.34 ppm; $[\alpha]^{23.7}_D$ +64.8° (0.73, $CHCl_3$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.62; H, 9.37. Found: C, 65.36; H, 9.47.

(−)-*cis*- and -*trans*-2-Methyl-5-hydroxyhexanoic Acid Lactones (1). In a manner exactly analogous to the preceding method, (*S*)-(−)-**12** was converted to (−)-*cis*- and (−)-*trans*-**1**, both of which possess spectral and physical properties identical with those of the corresponding (+) enantiomers: *cis*-(−)-(2*R*,5*S*)-**1** $[\alpha]^{22.6}_D$ −64.4° (0.51, $CHCl_3$) and *trans*-(−)-(2*S*,5*S*)-**1** $[\alpha]^{23.6}_D$ −54.1° (0.67, $CHCl_3$).

4-Hydroxy-6-dodecynenitrile (19). The method of Fried et al.[23] was used with minor modifications. To a stirred solution of 65.7 mL (0.144 mol, 25% in hexane) of triethylaluminum at 20 °C under N_2 was added 3 mL of Et_3N (20.8 mmol) in 15 mL of dry PhMe and 13.8 g (0.144 mol) of 1-heptyne in 25 mL of PhMe. After 15 min, the temperature was slowly raised to 90 °C and held there until the evolution of ethane had subsided. The cyano epoxide **18**[11] (3.5 g, 36.1 mmol) in 50 mL of PhMe was added to the cooled mixture over a 1-h period. Stirring was continued for 24 h at 25 °C, and the ice-cooled mixture was acidified by the careful addition of dilute hydrochloric acid. The organic layer was collected and the aqueous phase further extracted with 2 × 50 mL of ether. Combined organic layers were washed with H_2O and dried ($MgSO_4$), and the solvent was concentrated in vacuo to afford 3.76 g (54%) of crude **19**. An analytical sample was obtained by preparative GC (Carbowax, 200 °C): IR 3450, 2255 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (broad t, 3 H), 1.16–2.34 (m, 12 H), 2.51 (t, *J* = 7.0 Hz, 2 H), 2.94 (broad s, exchanges with D_2O, 1 H), 3.80 (m, 1 H).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.61; H, 9.84; N, 7.25. Found: C, 74.33; H, 9.75; N, 6.95.

(*Z*)-4-Hydroxy-6-dodecenenitrile (20). A mixture of 3.1 g (16.1 mmol) of **19**, 500 mg of quinoline, 500 mg of 5% Pd on $BaSO_4$, and 20 mL of ether was hydrogenated until approximately 1 equiv of hydrogen had been adsorbed.[24] The catalyst was removed (filtration with Celite) and the organic layer was washed with dilute hydrochloric acid to remove quinoline. Drying ($MgSO_4$) and concentration of the solvent afforded 3.05 g (97%) of crude **20**. An analytical sample was obtained by preparative GC (Carbowax, 200 °C): IR 3440, 2255, 1665, 726 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (broad t, 3 H), 1.06–2.32 (m, 13 H), 2.47 (t, *J* = 7.5 Hz, 2 H), 3.53–3.85 (m, 1 H), 5.07–5.78 (m, 2 H).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.84; H, 10.77; N, 7.18. Found: C, 73.55; H, 10.72; N, 7.03.

(*Z*)-1-(2-Cyanoethyl)-3-nonene *N*-[1-(1-Naphthyl)ethyl]-carbamates (21a,b). Procedure B. To a stirred solution of 5.8 g (58.6 mmol) of phosgene in 75 mL of dry PhMe at −5 °C under N_2 was added 2.8 g (14.3 mmol) of **20** and 1.26 g (15.9 mmol) of dry pyridine in 75 mL of PhMe over a 2-h period. The mixture was allowed to slowly warm to 25 °C, and the solvent and excess phosgene were removed in vacuo under 40 °C. The residue was immediately dissolved in 75 mL of CH_2Cl_2 and blanketed with N_2, and, with stirring, 2.45 g (14.3 mmol) of (*R*)-(−)-1-(1-naphthyl)ethylamine[25] and 1.26 g of pyridine in 30 mL of CH_2Cl_2 was added in one portion (5–10 °C exotherm). The mixture was stirred at 25 °C for 10 h and washed with 2 × 75 mL of 1 M hydrochloric acid and 75 mL of H_2O. Drying ($MgSO_4$) and solvent removal afforded crude **21a** and **21b**, which were chromatographically separated (silica gel with 3:1 hexane–EtOAc).

A total of 1.71 g (61.2%) of the high R_f [(*R*,*R*)-**21a**] diastereomer was collected as a light yellow oil: IR 3310, 2250, 1680–1737 broad, 1605, 735 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (broad t, 3 H), 1.57 (d, *J* = 6.5 Hz, 3 H), 1.06–2.15 (m, 12 H), 2.15 (broad t, *J* = 7.5 Hz, 2 H), 4.5–4.93 (m, 1 H), 4.95–5.78 (m, 4 H), 7.27–8.16 (m, 7 H); $[\alpha]^{22}_D$ +17.5° (4.9, $CHCl_3$).

Anal. Calcd for $C_{25}H_{32}N_2O_2$: C, 76.53; H, 8.16; N, 7.14. Found: C, 76.01; H, 8.34; N, 6.86.

A total of 1.76 g (63%) of the low R_f [(*S*,*R*)-**21b**)] diastereomer was collected as a light yellow oil: IR 3320, 2260, 1680–1737 broad, 1604, 735 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (broad t, 3 H), 1.63 (d, *J* = 6.5 Hz, 3 H), 1.04–2.18 (m, 12 H), 2.28 (broad t, 2 H), 4.58–4.90 (m, 1 H), 5.06–5.72 (m, 4 H), 7.37–8.19 (m, 7 H); $[\alpha]^{22.4}_D$ −21.2° (2.8, $CHCl_3$).

Anal. Calcd for $C_{25}H_{32}N_2O_2$: C, 76.53; H, 8.16; N, 7.14. Found: C, 76.25; H, 8.16; N, 7.03.

(*S*)-(−)-(*Z*)-4-Hydroxy-6-dodecenenitrile (20). Procedure D. To a stirred solution of 870 mg (2.22 mmol) of **21b** and 240 mg (2.46 mmol) of Et_3N in 20 mL of dry PhH under N_2 was added 330 mg (2.46 mmol) of $SiHCl_3$ in 5 mL of PhH over a 10-min period. The mixture was stirred at 25 °C for 20 h and poured with stirring into 50 mL of saturated aqueous NH_4Cl. The organic layer was collected and the aqueous layer was further extracted with 4 × 30 mL of ether. Combined organic layers were dried ($MgSO_4$) and concentrated in vacuo under 30 °C. The residue was chromatographed immediately on neutral alumina (4:1 hexane–EtOAc). (*R*)-(−)-**8** was first to elute,[26] followed by a trace of unreacted carbamate. The desired cyano alcohol eluted immediately after the unreacted carbamate. A 381-mg (88.2%) amount of (*S*)-(−)-**20** was collected and found to possess spectral and physical properties identical with those of (±)-**20**, $[\alpha]^{21.9}_D$ −22.8° (3.0, $CHCl_3$).

(*R*)-(+)-20. In an identical manner, **21a** was converted to (*R*)-(+)-**20**, also found to possess spectral and physical properties identical with those of the racemate, $[\alpha]^{23.5}_D$ +22.2° (2.0, $CHCl_3$).

(*S*)-(+)-(*Z*)-6-Dodecen-4-olide (3). Procedure F. A solution of 310 mg (1.59 mmol) of (*S*)-(−)-**20**, 600 mg (15 mmol) of NaOH, and 30 mL of 3:1 ethanol–water was heated at reflux under N_2 for 12 h. After being cooled, the solution was neutralized with dilute hydrochloric acid and the bulk of the ethanol was concentrated in vacuo. The remaining solution was extracted with 4 × 25 mL of ether, and the extracts were dried ($MgSO_4$) and concentrated to give crude **3**. This crude product was lactonized by heating in 15 mL of PhH at reflux for 3 h (azeotropic removal of H_2O). The solvent was removed in vacuo to give 301 mg (97%) of (*S*)-(+)-**3**. An analytical sample of the lactone was purified by preparative GC (20% SE 30, 175 °C): IR 1778, 1663, 724 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (broad t, 3 H), 1.08–2.83 (m, 14 H), 4.30–4.69 (m, 1 H), 5.02–5.85 (m, 2 H); $[\alpha]^{25.1}_D$ +16.5° (2.6, MeOH) [lit.[12b] $[\alpha]^{20}_D$ +15.0° (0.1, MeOH)].

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.21. Found: C, 73.10; H, 10.03.

(*R*)-(−)-3. In an exactly analogous manner, (*R*)-(+)-**20** was con-

verted to (*R*)-(−)-**3**, which possesses spectral and physical properties identical with those of the (+) enantiomer, $[\alpha]^{24}_D$ −17.2° (2.4, MeOH) [lit.[12b] $[\alpha]^{20}_D$ −16.1° (0.3, MeOH)].

6-Oxoheptanenitrile (15). By a method analogous to that of Cason and Prout,[27] 6.2 g (76.1%) of **15** was prepared: bp 128–131 °C (10 mmHg); IR 2260, 1718 cm^{-1}; NMR ($CDCl_3$) δ 1.32–1.90 (m, 4 H), 2.21 (s, 3 H), 2.38–2.65 (m, 4 H).

Anal. Calcd for $C_7H_{11}NO$: C, 67.20; H, 8.80; N, 11.20. Found: C, 67.14; H, 9.03; N, 11.12.

6-Hydroxyheptanenitrile (16). To a stirred solution of 2.0 g (92 mmol) of $LiBH_4$ in 70 mL of dry THF at 25 °C under N_2 was added 5.0 g (40 mmol) of **15** in 20 mL of THF over a 15-min period. The mixture was stirred at 25 °C for 2 h and acidified by the cautious addition of 2 M hydrochloric acid, followed by dilution to 300 mL with H_2O. This solution was continuously extracted with ether for 10 h, and the ethereal extract was dried ($MgSO_4$) and concentrated to afford 5.1 g (100%) of **16.** An analytical sample was collected by preparative GC (20% SE 30, 140 °C): IR 3450, 2258 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (d, J = 6.7 Hz, 3 H), 1.38–1.97 (m, 7 H), 2.45 (broad t, J = 6.3 Hz, 2 H), 3.72–4.17 (m, 1 H).

Anal. Calcd for $C_7H_{13}NO$: C, 66.14; H, 10.23; N, 11.02. Found: C, 66.01; H, 10.05; N, 11.26.

1-Methyl-5-cyanopentyl *N*-[1-(1-Naphthyl)ethyl]carbamates (17a,b). Procedure A was used to prepare the diastereomeric carbamates, which were chromatographically separated (silica gel with 7:1 benzene–ether).

A total of 3.2 g (85%) of the high R_f [(*S,R*)-**17a**] diastereomer was collected as a light yellow oil: IR 3315, 2243, 1655–1735 broad, 1608 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (broad d, J = 6.0 Hz, 3 H), 1.30–1.72 (m, 6 H), 1.67 (d, J = 7.2 Hz, 3 H), 2.22 (broad t, J = 7.0 Hz, 2 H), 4.75–5.32 (m, 2 H), 5.53–5.98 (m, 1 H), 7.54–8.46 (m, 7 H); $[\alpha]^{24.2}_D$ +10.8° (1.2, $CHCl_3$).

Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.07; H, 7.41; N, 8.64. Found: C, 73.93; H, 7.33; N, 8.52.

A total of 3.3 g (87.7%) of the low R_f [(*R,R*)-**17b**] diastereomer was collected as a white solid: mp 84–85 °C; IR (Nujol) 3290, 2255, 1650–1715 broad, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.19 (d, J = 6.2 Hz, 3 H), 1.30–1.81 (d overlapping m, 9 H), 2.07–2.53 (m, 2 H), 4.70–5.35 (m, 2 H), 5.61–6.00 (m, 1 H), 7.50–8.51 (m, 7 H); $[\alpha]^{25}_D$ −15.2° (6.1, $CHCl_3$).

Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.07; H, 7.41; N, 8.64. Found: C, 74.00; H, 7.50; N, 8.60.

(*S*)-(+)-6-Hydroxyheptanenitrile (16). Procedure C was used to convert **17a** to 880 mg (89.8%) of (*S*)-(+)-**16,** which possesses spectral and physical properties identical with those of the racemic compound, $[\alpha]^{22}_D$ +14.9° (1.6, $CHCl_3$).

(*R*)-(−)-16. Procedure C was used to convert **17b** to 708 mg (86.1%) of (*R*)-(−)-**16,** which possesses spectral and physical properties identical with those of the racemate, $[\alpha]^{22.8}_D$ −14.3° (1.7, $CHCl_3$).

(*S*)-(−)-ε-Caprolactone (2). Procedure E[28] was used to convert (*S*)-(+)-**16** to 655 mg (96.4%) of (*S*)-(−)-**2.** An analytical sample was purified by preparative GC (20% SE 30, 140 °C): IR 1722 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (d, J = 6.1 Hz, 3 H), 1.38–2.07 (m, 6 H), 2.13–2.66 (m, 2 H), 4.13–4.50 (m, 1 H); $[\alpha]^{23.8}_D$ −25.1° (1.7, $CHCl_3$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.63; H, 9.37. Found: C, 65.39; H, 9.18.

(*R*)-(+)-2. In an analogous manner, (*R*)-(−)-**16** was converted to (*R*)-(+)-**2,** which possesses spectral and physical properties identical with those of the (−) enantiomer, $[\alpha]^{23}_D$ +25.0° (1.8, $CHCl_3$).

1-Hydroxydodecanenitrile (23). To a flame-dried flask containing 1.89 g (77.8 mmol) of magnesium turnings was added a solution of 15.0 g (77.8 mmol) of *n*-octyl bromide in 180 mL of dry THF with stirring under N_2. The mixture was stirred at 25 °C until only a trace of magnesium remained unreacted and cooled to −25 °C while a solution of 6.46 g (77.8 mmol) of β-cyanopropionaldehyde[4] in 70 mL of 1:1 ether–THF was added over a 20-min period. The mixture was slowly warmed to 25 °C, held there for 5 h, and then cooled to 0 °C while being acidified by the addition of dilute hydrochloric acid. The aqueous layer was extracted with 4 × 60 mL of ether, and the combined organic layers were washed with saturated aqueous $NaHCO_3$. Drying ($MgSO_4$) and concentration afforded the crude carbinol, which was purified by vacuum distillation. A 6.36-g (41.5%) amount of pure **23** was collected: bp 150–151 °C (0.65 torr); IR 3520 broad, 2250 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (broad t, 3 H), 1.01–1.86 (m, 16 H), 2.17 (broad s, exchanges with D_2O, 1 H), 2.41 (t, J = 7.8 Hz, 2 H), 3.40–3.76 (m, 1 H).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.10; H, 11.67; N, 7.11. Found: C, 72.97; H, 11.67; N, 6.91.

1-(2-Cyanoethyl)nonyl *N*-[1-(1-Naphthyl)ethyl]carbamates (24a,b). Procedure B was used to prepare the diastereomeric carbamates, which were chromatographically separated (acidic alumina with 3:1 hexane–EtOAc).

A total of 3.7 g (84.1%) of the high R_f [(*S,R*)-**24a**] diastereomer was collected as an orange viscous oil: IR 3320, 2230, 1683–1730 broad, 1600 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (broad t, 3 H), 1.10–2.00 (m, 16 H), 1.63 (d, J = 6.3 Hz, 3 H), 2.21–2.49 (m, 2 H), 4.50–4.89 (m, 1 H), 5.00 (broad d, J = 6.8 Hz, 1 H), 5.33–5.73 (m, 1 H), 7.31–8.13 (m, 7 H); $[\alpha]^{19.7}_D$ −5.34° (3.6, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}N_2O_2$: C, 76.14; H, 8.63; N, 7.11. Found: C, 76.03; H, 8.52; N, 6.83.

A total of 3.5 g (79.6%) of the low R_f [(*R,R*)-**24b**] diastereomer was collected as an orange oil: IR 3310, 2230, 1680–1728 broad, 1603 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (broad t, 3 H), 1.07–2.07 (m, 16 H), 1.63 (d, J = 6.3 Hz, 3 H), 2.27 (t, J = 7.0 Hz, 2 H), 4.58–4.88 (m, 1 H), 4.98 (broad d, J = 6.7 Hz, 1 H), 5.38–5.77 (m, 1 H), 7.30–8.18 (m, 7 H); $[\alpha]^{21.4}_D$ −0.65° (5.3, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}N_2O_2$: C, 76.14; H, 8.63; N, 7.11. Found: C, 76.41; H, 8.75; N, 7.40.

(*S*)-(−)-4-Hydroxydodecanenitrile (23). Procedure D was used to convert **24a** to 1.62 g (95.8%) of (*S*)-(−)-**23,** which possesses spectral and physical properties identical with those of the racemate, $[\alpha]^{25}_D$ −15.2° (2.0, EtOH).

(*R*)-(+)-23. In an identical manner, **24b** was converted to (*R*)-(+)-**23,** which possesses spectral and physical properties identical with those of the racemate, $[\alpha]^{23.4}_D$ +16.5° (3.1, EtOH).

(*S*)-(+)-γ-*n*-Dodecanolactone (5). Procedure F was used to convert (*S*)-(−)-**23** to 1.31 g (97.2%) of (*S*)-(+)-**5.** An analytical sample was purified by preparative GC (20% SE 30, 180 °C): IR 1780 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (broad t, 3 H), 1.02–1.98 (m, 16 H), 2.14–2.66 (m, 2 H), 4.35–4.61 (m, 1 H); $[\alpha]^{22.5}_D$ +33.3° (0.73, MeOH).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.73; H, 11.11. Found: C, 73.02; H, 11.37.

(*R*)-(−)-5. In a similar manner, (*R*)-(+)-**23** was converted to (*R*)-(−)-**5,** which possesses spectral and physical properties identical with those of the (+) enantiomer, $[\alpha]^{22.5}_D$ −32.8° (1.6, MeOH).

4-Hydroxy-5-tetradecynenitrile (25). To a stirred solution of 13.8 g (100 mmol) of 1-decyne in 100 mL of dry THF at −78 °C under N_2 was slowly added 45.5 mL of 2.2 M *n*-butyllithium (100 mmol, hexane), and stirring was continued for 10 min. A solution of 8.3 g (100 mmol) of β-cyanopropionaldehyde[4] in 40 mL of 1:1 ether–THF was added over a 10-min period, and the solution was allowed to warm slowly to 25 °C. The solution was cooled to 0 °C and acidified by the addition of dilute hydrochloric acid. The organic phase was collected and the aqueous layer was extracted with 2 × 40 mL of ether. Combined organic layers were washed with saturated $NaHCO_3$ (150 mL), dried ($MgSO_4$), and concentrated to afford crude **25,** which was purified by vacuum distillation. A total of 21.3 g (96.2%) of pure **25** was collected. An analytical sample was collected by preparative GC (20%; SE 30, 220 °C): bp 164–166 °C (0.26 torr); IR 3410, 2250, 2235 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (broad t, 3 H), 1.04–1.67 (m, 12 H), 1.74–2.45 (m, 4 H), 2.59 (t, J = 6.8 Hz, 2 H), 4.28 (broad s, exchanges with D_2O, 1 H), 4.52–4.75 (m, 1 H).

Anal. Calcd for $C_{14}H_{23}NO$: C, 76.02; H, 10.41; N, 6.33. Found: C, 75.92; H, 10.21; N, 6.18.

(*Z*)-4-Hydroxy-5-tetradecenenitrile (26). In a manner exactly analogous to the preparation of **20,** 8.1 g (100%) of **26** was prepared. The crude product was used directly in the conversion to the cyano carbamates.

(*Z*)-1-(2-Cyanoethyl)-2-undecene *N*-[1-(1-Naphthyl)ethyl]-carbamates (27a,b). Procedure A was used to prepare the carbamates, which were subsequently separated by chromatography (silica gel with 7:1 benzene–ether).

A total of 3.66 g (75.8%) of the high R_f [(*R,R*)-**27a**] diastereomer was collected as a colorless oil: IR 3315, 2260, 1690–1732 broad, 1608, 735 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (broad t, 3 H), 0.99–1.42 (m, 12 H), 1.51 (d, J = 6.3 Hz, 3 H), 1.63–2.52 (m, 6 H), 4.52–5.56 (m, 5 H), 6.96–7.90 (m, 7 H); $[\alpha]^{22.9}_D$ −17.8° (2.2, $CHCl_3$).

Anal. Calcd for $C_{27}H_{36}N_2O_2$: C, 77.14; H, 8.57; N, 6.67. Found: C, 76.83; H, 8.85; N, 6.37.

A total of 3.52 g (72.9%) of the low R_f [(*S,R*)-**27b**] diastereomer was collected as a colorless oil: IR 3305, 2250, 1690–1735 broad, 1608, 735 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (broad t, 3 H), 1.12–1.57 (m, 12 H), 1.59 (d, J = 6.5 Hz, 3 H), 1.82–2.74 (m, 6 H), 4.97–6.03 (m, 5 H), 7.52–8.48 (m, 7 H); $[\alpha]^{24.2}_D$ +57.5° (2.8, $CHCl_3$).

Anal. Calcd for $C_{27}H_{36}N_2O_2$: C, 77.14; H, 8.57; N, 6.67. Found: C, 77.00; H, 8.50; N, 6.50.

(*R*)-(+)-(*Z*)-4-Hydroxy-5-tetradecenenitrile (26). Procedure D was used to convert **27a** to 410 mg (89.0%) of (*R*)-(+)-**26**: IR 3500, 2250, 1660, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.84 (broad t, 3 H), 1.08–1.44 (m, 12 H), 1.58–2.27 (m, 5 H), 2.40 (t, J = 7.2 Hz, 2 H), 4.32–4.60 (m,

1 H), 5.10–5.64 (m, 2 H); $[\alpha]^{25.5}_D$ +11.2° (2.5, $CHCl_3$).

Anal. Calcd for $C_{14}H_{25}NO$: C, 75.34; H, 11.21; N, 6.28. Found: C, 74.94; H, 11.44; N, 6.43.

(*S*)-(−)-26. In a similar manner, **27b** was converted to (*S*)-(−)-**26** and found to possess spectral and physical properties identical with those of the (+) enantiomer, $[\alpha]^{26}_D$ −11.9° (4.0, $CHCl_3$).

(*R*)-(−)-(*Z*)-5-Tetradecen-4-olide (4). Procedure F was used with one modification to convert (*R*)-(+)-**26** to 390 mg (95.0%) of (*R*)-(−)-**4**. The basic hydrolysate was neutralized with exactly the theoretical amount of dilute hydrochloric acid.[29] An analytical sample of the lactone was obtained by chromatography (neutral alumina with 4:1 hexane–ethyl acetate): IR 1785, 1665, 725 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (broad t, 3 H), 1.16–1.47 (m, 12 H), 1.73–2.58 (m, 6 H), 5.00–5.87 (m, 3 H); $[\alpha]^{25}_D$ −70.0° (6.4, $CHCl_3$) [lit.[16] $[\alpha]^{26}_D$ −69.6° (5.0, $CHCl_3$)].

Anal. Calcd for $C_{14}H_{24}O_2$: C, 75.00; H, 10.71. Found: C, 74.85; H, 10.67.

(*S*)-(+)-4. In a similar manner, (*S*)-(−)-**26** was converted to (*S*)-(+)-**4**, which was found to possess spectral and physical properties identical with those of the (−) enantiomer, $[\alpha]^{24.1}_D$ +70.3° (6.1, $CHCl_3$) [lit.[16] $[\alpha]^{26}_D$ +70.5° (5.1, $CHCl_3$)].

5-Hydroxy-6-hexadecynenitrile (30). In a manner analogous to the procedure used to prepare **25**, 8.45 g (73.4%) of **30** was prepared from γ-cyanobutyraldehyde[18] and 1-undecynyllithium. The crude carbinol was converted to the carbamates without further purification.

1-(3-Cyanopropyl)-2-dodecyne *N*-[1-(1-Naphthyl)ethyl]-carbamates (31a,b). Procedure B was used to prepare the diastereomeric carbamates, which were chromatographically separated (silica gel with 8:1 benzene–ether).

A total of 2.1 g (74.9%) of the high R_f [(*R*,*R*)-**31a**] diastereomer was collected as a light yellow solid: mp 54.5–55 °C; IR (Nujol) 3320, 2260, 1665–1740 broad, 1610 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (broad t, 3 H), 1.03–1.52 (m, 14 H), 1.65 (d, J = 6.7 Hz, 3 H), 1.53–1.98 (m, 4 H), 2.01–2.50 (m, 4 H), 5.07 (broad d, J = 8.1 Hz, 1 H), 5.25–5.50 (m, 1 H, 5.50–5.71 (m, 1 H), 7.37–8.20 (m, 7 H); $[\alpha]^{24.2}_D$ +15.2° (6.2, $CHCl_3$).

Anal. Calcd for $C_{29}H_{38}N_2O_2$: C, 78.02; H, 8.52; N, 6.28. Found: C, 78.06; H, 8.65; N, 6.24.

A total of 2.04 g (72.7%) of the low R_f [(*S*,*R*)-**31b**] diastereomer was collected as a light yellow oil: IR 3310, 2260, 1688–1742 broad, 1605 cm^{-1}; NMR ($CDCl_3$) δ 0.84 (broad t, 3 H), 0.97–1.47 (m, 14 H), 1.59 (d, J = 6.8 Hz, 3 H), 1.48–1.95 (m, 4 H), 1.96–2.63 (m, 4 H), 4.86–5.78 (m, 3 H), 7.28–8.17 (m, 7 H); $[\alpha]^{23}_D$ −26.3° (1.9, $CHCl_3$).

Anal. Calcd for $C_{29}H_{38}N_2O_2$: C, 78.02; H, 8.52; N, 6.28. Found: C, 77.71; H, 8.50; N, 6.27.

(*R*)-(+)-5-Hydroxy-6-hexadecynenitrile (30). Procedure D was used to convert **31a** to 530 mg (83.6%) of (*R*)-(+)-**30**: IR 3490, 2258 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (broad t, 3 H), 1.10–1.52 (m, 14 H), 1.52–2.52 (m, 9 H), 4.23–4.48 (m, 1 H); $[\alpha]^{22}_D$ +10.2° (3.8, $CHCl_3$).

Anal. Calcd for $C_{16}H_{27}NO$: C, 77.12; H, 10.84; N, 5.62. Found: C, 76.98; H, 10.70; N, 5.36.

(*S*)-(−)-30. In a manner identical with the previous method, **31b** was converted to (*S*)-(−)-**30**, which possesses spectral and physical properties identical with those of the (+) enantiomer, $[\alpha]^{22.4}_D$ −10.9° (8.7, $CHCl_3$).

(*S*)-(−)-δ-*n*-Hexadecanolactone (6). Procedure F[28] was used to convert (*R*)-(+)-**30** to acetylenic lactone **32a**. This material was hydrogenated in ethyl acetate over palladium (5% on carbon) until 2 equiv of hydrogen had been absorbed. The catalyst was removed, and solvent was distilled in vacuo to afford 410 mg (84.1%) of crude (*S*)-(−)-**6**. An analytical sample was obtained by preparative GC (20% SE 30, 197 °C): mp 31–32 °C (lit.[19,30] 26.5 and 29.5–30 °C); IR (Nujol) 1752 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (broad t, 3 H), 1.07–1.37 (m, 20 H), 1.37–1.99 (m, 4 H), 2.16–2.62 (m, 2 H), 4.06–4.38 (m, 1 H); $[\alpha]^{23}_D$ −24.1° (4.0 THF) [lit.[19] $[\alpha]^{23}_D$ −2.65° (1.1, THF)].

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.59; H, 11.81. Found: C, 75.63; H, 12.02.

(*R*)-(+)-6. In a manner exactly analogous to the preceding method, (*S*)-(−)-**30** was converted to (*R*)-(+)-**6**, which possesses spectral and physical properties identical with those of the (−) enantiomer, $[\alpha]^{24.6}_D$ +24.2° (3.6, THF) [lit.[19] $[\alpha]^{24}_D$ +2.69° (0.37, THF)].

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Registry No.—(2*R*,5*R*)-**1**, 65451-95-8; (2*R*,5*S*)-**1**, 65451-94-7; (2*S*,5*R*)-**1**, 65451-92-5; (2*S*,5*S*)-**1**, 65451-93-6; (*R*)-**2**, 69765-34-0; (*S*)-**2**, 69765-35-1; (*R*)-**3**, 63357-99-3; (*S*)-**3**, 63357-98-2; (*R*)-**4**, 64726-91-6; (*S*)-**4**, 64726-93-8; (*R*)-**5**, 69830-91-7; (*S*)-**5**, 69830-92-8; (*R*)-**6**, 59812-96-3; (*S*)-**6**, 59812-97-4; (*R*)-**8**, 42340-98-7; (*R*)-**10**, 65451-91-4; (*S*)-**10**, 65451-90-3; **11a**, 65432-14-6; **11b**, 65432-15-7; (*R*)-**12**, 43112-32-9; (*S*)-**12**, 16320-13-1; **15**, 18214-15-8; (±)-**16**, 69765-36-2; (*R*)-**16**, 69830-93-9; (*S*)-**16**, 69830-94-0; **17a**, 69765-37-3; **17b**, 69765-38-4; **18**, 69765-39-5; **19**, 69765-40-8; (±)-**20**, 69765-41-9; (*R*)-**20**, 69830-95-1; (*S*)-**20**, 69830-96-2; **21a**, 69765-42-0; **21b**, 69765-43-1; (±)-**23**, 69765-44-2; (*R*)-**23**, 69830-97-3; (*S*)-**23**, 69830-98-4; **24a**, 69765-45-3; **24b**, 69765-46-4; **25**, 69765-47-5; (±)-**26**, 69765-48-6; (*R*)-**26**, 69830-99-5; (*S*)-**26**, 69831-00-1; **27a**, 69765-49-7; **27b**, 69765-50-0; (*R*)-**30**, 69765-51-1; (*S*)-**30**, 69765-52-2; (±)-**30**, 69831-01-2; **31a**, 69765-53-3; **31b**, 69765-54-4; **32a**, 69765-55-5; **32b**, 69765-56-6; (±)-5-cyanopentan-2-ol, 65432-13-5; 1-heptyne, 628-71-7; (*R*)-1-(1-napthyl)ethylamine, 3886-70-2; *n*-octyl bromide, 111-83-1; β-cyanopropionaldehyde, 3515-93-3; 1-decyne, 764-93-2; γ-cyanobutyraldehyde, 3350-74-1; 1-undecynyllithium, 69765-57-7.

References and Notes

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