A) gave **21** (trans, 82.1 ± 0.8%) and **20** (cis, 17.9 ± 0.8%).

Ethyl 2-methylcyclohexanecarboxylate (1.4632 g, 8.61 mmol) and lithium (0.0078 g, 1.1 mmol) were used. GC analysis (column B) gave **24** (trans, 76.4 ± 0.6%) and **23** (cis, 23.6 ± 0.6%).

Ethyl 3-methylcyclohexanecarboxylate (1.7093 g, 10.1 mmol) and lithium (0.0090 g, 1.1 mmol) were used. GC analysis (column A) gave **26** (cis, 83.0 ± 1.1%) and **27** (trans, 17.0 ± 1.1%).

Ethyl 4-methylcyclohexanecarboxylate (1.7046 g, 10.03 mmol) and lithium (0.0087 g, 1.2 mmol) were used. GC analysis gave **30** (trans, 78.9 ± 0.1%) and **29** (cis, 21.1 ± 0.1%).

Registry No. 13, 65132-76-5; **14**, 51789-95-8; **15**, 51789-92-5; **16**, 30934-87-3; **17**, 61242-71-5; **18**, 4755-79-7; **19**, 53695-41-3; **20**, 7214-36-0; **21**, 7214-35-9; **22**, 5222-56-0; **23**, 25144-01-8; **24**, 10479-71-7; **25**, 25118-34-7; **26**, 74542-23-7; **27**, 74542-24-8; **28**, 53695-40-2; **29**, 25244-23-9; **30**, 41692-50-6; cyclopentadiene, 542-92-7; diethyl methylenemalonate, 3377-20-6; *p-tert*-butylbenzoic acid, 98-73-7; *cis*-4-*tert*-butylcyclohexanecarboxylic acid, 943-28-2; *trans*-4-*tert*-butylcyclohexanecarboxylic acid, 943-29-3; ethanol, 64-17-5; ethyl chloroformate, 541-41-3; methanol, 67-56-1; methyl *cis*-4-*tert*-butylcyclohexanecarboxylate, 17177-76-3; methyl *trans*-4-*tert*-butylcyclohexanecarboxylate, 17177-75-2; dimethyl 4-*tert*-butylcyclohexanedicarboxylate, 74542-25-9; methyl chloroformate, 79-22-1; *o*-toluic acid, 118-90-1; *cis*-2-methylcyclohexanecarboxylic acid, 7076-91-7; *trans*-2-methylcyclohexanecarboxylic acid, 15177-62-5; *m*-toluic acid, 99-04-7; *cis*-3-methylcyclohexanecarboxylic acid, 73873-48-0; *trans*-3-methylcyclohexanecarboxylic acid, 73873-49-1; *p*-toluic acid, 99-94-5; *cis*-4-methylcyclohexanecarboxylic acid, 934-67-8; *trans*-4-methylcyclohexanecarboxylic acid, 13064-83-0; lithium chloride, 7447-41-8; dimethyl sulfoxide, 67-68-5.

Enantiomerically Pure Lactones. 2.[1] Approaches to Cis or Trans Multicyclic Lactones

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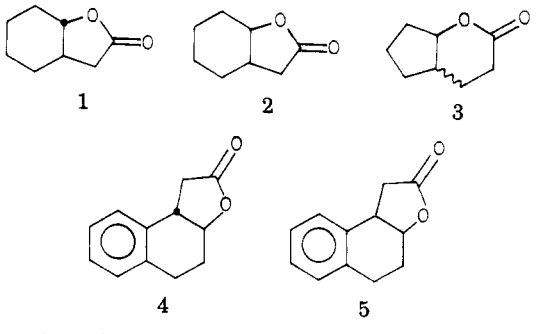
Enantiomerically pure bicyclic lactones **1–3** and tricyclic lactones **4** and **5** have been prepared by either of two procedures, each hinging upon the liquid chromatographic separation of rationally selected diastereomeric derivatives. After separation, the diastereomers are converted by a simple high-yield reaction sequence to the enantiomeric multiring lactones, none of which has been previously reported in optically active form. The relative strengths and weaknesses of each approach are discussed. Lactones **4** and **5** were α-methylated, these derivatives being suitable for the determination of enantiomeric purity and absolute configuration using the chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

Multiringed lactones are widely dispersed throughout nature, literally hundreds of examples being known.[3] This ubiquity, coupled with frequent biological significance,[4] has caused a great deal of effort to be applied toward the synthesis of a host of multiringed lactones. Although most multiringed lactones occur naturally as a single enantiomer, it is interesting to note that most researchers in the field have been content to synthesize racemates. When optically active lactones have been prepared, it has usually been from a related available optically active natural product.

Our interest in developing chromatographic methods for the separation of optical isomers has led to straightforward preparation of a variety of optically active natural products, some of them being simple lactonic pheromones.[1] Accordingly, we sought to extend our basic approach to encompass lactones of greater structural complexity. We now describe two simple procedures for generation of chiral ring-fused lactone moieties of known absolute configuration and high enantiomeric purity. These procedures are illustrated by the synthesis of enantiomers of both bicyclic lactones **1–3** and tricyclic lactones **4** and **5**. None of these



lactones have been previously reported in optically active form. In addition to attesting to the scope of the general approach, lactones **1–5** might themselves be further elaborated to afford more complex systems.

Central to our overall synthetic approach is the multigram chromatographic separation of rationally selected diastereomeric derivatives of a racemic intermediate. The benefits of the chromatographic resolutions discussed herein (i.e., high yields, multigram capability, the obtention of both enantiomers with known absolute configuration and enantiomeric purity) are not always realized with classical resolution methods employing fractional crystallization. These benefits, coupled with the rapidly increasing generality of chromatographic resolution, are causing the latter to become the method of choice for a great many optical resolutions. For example, chromato-

(1) (a) For paper 1 in this series, see: Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169. (b) Presented in part at the Third Biennial Carl S. Marvel Symposium, Tucson, AZ, Mar 1979, No. 16.

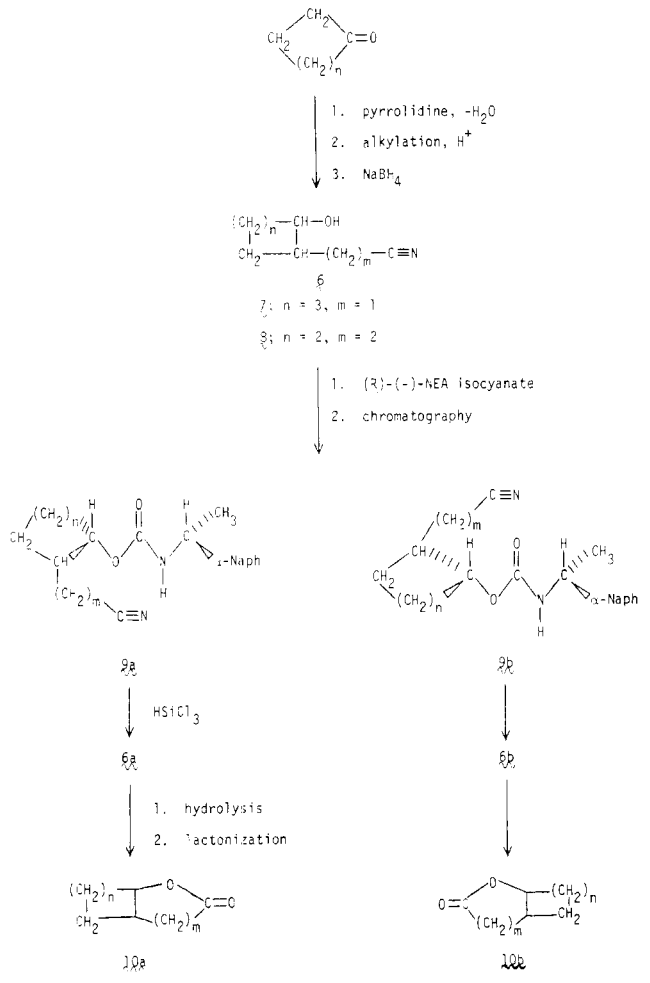
(2) On sabbatical leave from the Lubrizol Corp., 1976–1979. Mobil Oil Corp. Predoctoral Fellow, 1976–1977.

(3) For reviews, see: Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625; Grieco, P. A. *Synthesis* **1975**, 67; Gammil, R. B.; Wilson, C. A. *Synth. Commun.* **1975**, *5*, 245; Yoshioka, H.; Mobry, T. J.; Timmermann, B. N. "Sesquiterpene Lactones"; University of Tokyo Press: Tokyo, 1973; Newaz, S. S. *Aldrichimica Acta* **1977**, *4*, 10.

(4) See for example: Herz, W.; Bhat, S. V. *J. Org. Chem.* **1972**, *37*, 906; Grieco, P. A.; Noguez, J. A.; Masaki, Y. *Ibid.* **1977**, *42*, 495; Martin, J.; Watts, P. C.; Johnson, F. *Chem. Commun.* **1970**, 27; Pettit, G. R.; Budzinski, J. C.; Gragg, G. M.; Brown, P.; Johnston, L. R. D. *J. Med. Chem.* **1974**, *17*, 1013; Kupchan, S. M.; Hemingway, R. J.; Werner, D.; Karim, A. *J. Org. Chem.* **1969**, *34*, 3903, 3908; Herz, W.; Sharma, R. P. *Ibid.* **1975**, *40*, 3118; Weinheimer, A. J.; Schmitz, F. J.; Ciereszko, L. S. "Drugs from the Sea"; Marine Technology Society: Washington, DC, 1968; Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1969**, *91*, 7208.

0022-3263/80/1945-4111$01.00/0

Scheme I

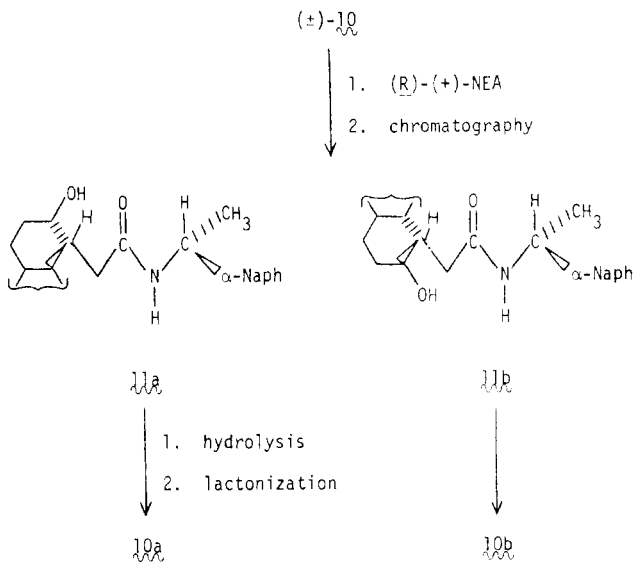


graphic resolution has been recently employed in straightforward approaches that allow one to synthesize optically active lactones,[1,5a-d] alcohols,[6] allenes,[7,8] pyrazolines,[8] and epoxides.[9] Additionally, chromatographic resolution has played a key role in the recently completed syntheses of gibberellic acid[10] and monensin.[11]

Results

A general outline of our first approach, depicted in Scheme I, begins with readily available cyclic ketones. Elaboration of the cyclic ketones to racemic cyano alcohols of general formula **6** is straightforward, amounting to no more than alkylation of the enamine of the ketone with either a cyano halide or acrylonitrile and ultimate reduction of the cyano ketone with borohydride. Although it may be advantageous to control relative stereochemistry

Scheme II



at the reduction stage, this is not required for effective use of the approach. The resolution of the cyano alcohols is similar to the procedures described previously[1] and involves reaction with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate to afford diastereomeric carbamates **9a,b**. The carbamate diastereomers are then separated on silica gel by automated multigram high-pressure LC.[12] Silanolysis of each diastereomer with trichlorosilane[13] regenerates the corresponding enantiomeric cyano alcohols, **6a,b**. Hydrolysis of the cyano function, followed by lactonization of the resulting hydroxy acid, completes the synthetic sequence.

An alternative approach to optically active lactones is one we used earlier[5a] to obtain (−)-γ-benzyl-γ-butyrolactone, an approach later modified and extended by Helmchen and co-workers.[5b-d] As illustrated in Scheme II, (*R*)-(+)-1-(1-naphthyl)ethylamine (α-NEA) is used as a chiral derivatizing agent for racemic lactones of general formula **10** to afford diastereomeric hydroxy amides **11a,b** that, after chromatographic separation, can be converted to optically active lactones. These hydroxy amides can also be obtained by borohydride reduction of the keto amides of α-NEA.

***trans*-Hexahydro-2(3*H*)-benzofuranone (1).** Reduction of 2-(cyanomethyl)cyclohexanone[14] with sodium borohydride afforded racemic trans cyano alcohol **7** almost exclusively. Conversion of cyano alcohol **7** to diastereomeric carbamates was accomplished as previously described,[1] and the diastereomers were separated by chromatography (silica gel, 8:1 PhH–ether, α = 1.20). Silanolysis of each of the carbamate diastereomers regenerated the corresponding cyano alcohol enantiomers, each of which was separately subjected to hydrolysis and lactonization to afford the corresponding enantiomers of trans lactone **1** ((1*S*,2*R*)-**1**, $[\alpha]_D$ −77.6°; (1*R*,2*S*)-**1**, $[\alpha]_D$ +78.5°). The assignment of trans stereochemistry for **1** (and its precursors) is based upon the correspondence of its NMR spectrum with that previously reported for the racemate[15]

(5) (a) Pirkle, W. H.; Sikkenga, D. L. *J. Org. Chem.* **1977**, *42*, 1370. (b) Helmchen, G.; Nill, G.; Flockerzi, D.; Schuhle, W.; Youssef, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 62. (c) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. *Ibid.* **1979**, *18*, 63. (d) Helmchen, G.; Nill, G. *Ibid.* **1979**, *18*, 65.

(6) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904.

(7) Pirkle, W. H.; Boeder, C. W. *J. Org. Chem.* **1978**, *43*, 1950, 2091.

(8) (a) Pirkle, W. H.; Hoover, D. J. Joint Central Great Lakes Regional Meeting of the American Chemical Society, Indianapolis, IN, May 1978, Abstr. ORGN 44. (b) Pirkle, W. H.; Hoover, D. J., to be submitted for publication.

(9) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1978**, *43*, 3803; **1979**, *44*, 1025.

(10) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J. *J. Am. Chem. Soc.* **1978**, *100*, 8031. Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J. *Ibid.* **1978**, *100*, 8034.

(11) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259.

(12) Pirkle, W. H.; Anderson, R. W. *J. Org. Chem.* **1974**, *39*, 3901.

(13) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781.

(14) Boekelheide, V.; Müller, M.; Grossnickle, T. T.; Chang, M. *J. Am. Chem. Soc.* **1959**, *81*, 3955.

(15) Herz, W.; Glick, L. A. *J. Org. Chem.* **1963**, *28*, 2970. Bloomfield, J. J.; Lee, S. L. *Ibid.* **1967**, *32*, 3919. Newman, M. S.; VanderWerf, C. A. *J. Am. Chem. Soc.* **1945**, *67* 233. Meyers, A. I.; Mihelich, E. D.; Nolen, R. L. *J. Org. Chem.* **1974**, *39*, 2783. Sucrow, W.; Klein, U. *Chem. Ber.* **1975**, *108*, 48. Das Gupta, T. K.; Felix, D.; Kempe, U. M.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, 2198.

(carbinyl resonance at 3.8 ppm).

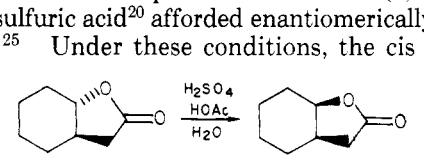
***trans*-Hexahydrocyclopenta[*b*]pyran-1(3*H*)-one (3).** Reduction of 2-(2-cyanoethyl)cyclopentanone[16] with sodium borohydride afforded an approximate 6:1 mixture, respectively, of the trans and cis isomers of cyano alcohol **8**. This mixture was converted to the four possible carbamate diastereomers which were then separated by chromatography on silica gel employing one recycle. An α value of 1.13 was observed for the trans carbamates, each of which was converted to the enantiomers of *trans*-**3** by the previously described procedures with one modification. The corresponding hydroxy acid precursors of both *cis*- and *trans*-**3** were found not to lactonize in refluxing benzene;[17] hence, dicyclohexylcarbodiimide (DCC) was used to effect this transformation ((1*S*,2*R*)-*trans*-**3**, $[\alpha]_D$ −92.5°; (1*R*,2*S*)-*trans*-**3**, $[\alpha]_D$ +91.1°). In a similar manner, one of the cis carbamate diastereomers[18] was converted to *cis*-**3** ((1*S*,2*S*)-**3**, $[\alpha]_D$ +85.2°). Spectral properties of each lactone agree with those previously reported for racemic *cis*- or *trans*-**3** (trans carbinyl resonance at 4.0 ppm and cis resonance at 4.7 ppm).[19]

***cis*-Hexahydro-2(3*H*)-benzofuranone (2).** Racemic lactone **2**, prepared by the method of Klein,[20] was allowed to react with (*R*)-α-NEA to afford the corresponding diastereomeric hydroxy amides (**18a,b**). These easily separable diastereomers (silica gel, 3:1 EtOAc–hexane, α = 1.62) were each hydrolyzed by base to afford the corresponding hydroxy acid enantiomers. Lactonization of these affords, in turn, the corresponding enantiomers of *cis*-**2** ((1*R*,2*R*)-**2**, $[\alpha]_D$ +41.9°; (1*S*,2*S*), $[\alpha]_D$ −40.3°). The NMR spectrum of *cis*-**2** exhibits the expected carbinyl resonance at 4.5 ppm as previously reported for the racemate.[15]

***trans*- and *cis*-(2-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)acetic Acid Lactones (4 and 5).** Reduction of α-(cyanomethyl)-β-tetralone[21] with sodium borohydride afforded a 3:1 mixture of trans and cis cyano alcohols when the reduction was worked up with aqueous base. However, use of an aqueous mineral acid workup reversed the trans to cis ratio owing to acid-catalyzed epimerization. Conversion of the cyano alcohol mixture to a mixture of racemic lactones **4** and **5** was accomplished by hydrolysis and lactonization. Racemic *trans*-**4** was separated from *cis*-**5** by chromatography on silica gel,[22] and each racemate was allowed to react with (*R*)-α-NEA to afford the corresponding pair of diastereomeric hydroxy amides (**19a,b** from *cis*-**5** and **20a,b** from *trans*-**4**). Each pair of diastereomeric amides was then chromatographically separated on silica gel (EtOAc–hexane 3:1; α_{cis} = 1.76, α_{trans} = 1.45). Each of the cis hydroxy amide diastereomers was converted to the enantiomers of cis lactone **5** without incident ((1*R*,2*S*)-**5**, $[\alpha]_D$ −161.1°; (1*S*,2*R*)-**5**, $[\alpha]_D$ +158.6°). However, neither diastereomer of the trans analogue could be similarly hydrolyzed (sodium hydroxide in refluxing aqueous ethanol) until the hydrolysis was conducted at high pressure (4 kbars). Lactonization of each of the resulting trans hydroxy acid enantiomers affords the corresponding enantiomer of trans lactone **4** ((1*S*,2*S*)-**4**, $[\alpha]_D$ −78.2; (1*R*,2*R*)-**4**, $[\alpha]_D$ +76.9°). Cis–trans assignments for the unreported lactones **4** and **5** are based upon the downfield positon of the cis isomer's carbinyl resonance relative to that of the trans compound (4.9 vs. 3.9 ppm). These chemical shift assignments are consistent with those of the other bicyclic lactones described herein.

Assignments of Absolute Configuration and Determinations of Enantiomeric Purity. For the presently discussed pairs of diastereomeric carbamates, assignments of relative and hence absolute configuration are based upon considerations of elution order and proton NMR spectral differences. The arguments used to correlate elution order with stereochemistry are identical with those used earlier[1] and are not repeated here. The chemical shift differences typically observed between diastereomeric carbamates of α-NEA (and correlatable with relative configuration) are obscured by the essentially featureless envelope-like ^{1}H NMR spectra of these particular carbamates. However, for each of the two low-R_f carbamate diastereomers reported herein, several resonances are considerably broadened compared to those of the corresponding high-R_f diastereomers. Similar broadening has been observed for a number of other carbamate diastereomers and has been related to the stereochemistry of the diastereomers and the conformational behavior of carbamates of α-NEA.[23,24] Configurational assignments reached through application of our prior "broadening" arguments[23,24] support those reached from consideration of the elution orders of the diastereomers. Accordingly, we assign the indicated relative (and hence absolute) configuration shown in **9a** to each of the high-R_f carbamate diastereomers, the low-R_f diastereomers having the configuration shown in **9b**. These configurational assignments extend to the final lactones **1** and **3** as well. We also point out that application of the aforementioned broadening and elution order argument to the carbamate diastereomers of the previously discussed monocyclic lactones[1] has been shown to attend the correct stereochemical conclusions.

In the case of the multicyclic lactones resolved via diastereomeric hydroxy amides, the absolute configurations of the carbinol portion of these amides are not easily ascertained either from elution orders of or from NMR spectral differences between the diastereomers. However, the absolute configurations of the enantiomers of *cis*-**2** were assigned as follows. Equilibration of *trans*-(−)-**1** with hot aqueous sulfuric acid[20] afforded enantiomerically enriched *cis*-(+)-**2**.[25] Under these conditions, the cis lactone is

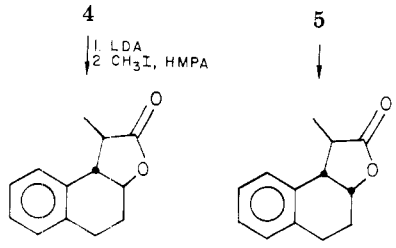


(−)-**1** (+)-**2**

assumed to be derived from the trans compound by inversion of configuration at the carbinyl carbon. Since *trans*-(−)-**1** is derived from the high-R_f α-NEA carbamate, it and *cis*-(+)-**2** must have the indicated absolute configurations.

Assignments of absolute configuration to the enantiomers of *trans*-**4** and *cis*-**5** was made by using a chiral solvating agent. Methylation[26] of (−)-*trans*-**4** or (−)-*cis*-**5** cleanly affords a single monomethylated epimer in each instance. The epimers are assigned structures **12** and **13**,

(16) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
(17) Prolonged reaction times (e.g., several days) lead to formation of the linear polyester.
(18) The other cis carbamate diastereomer was lost and hence not converted to *cis*-(−)-**3**.
(19) Slates, H. L.; Zelawski, Z. S.; Taub, D.; Wendler, N. L. *Tetrahedron* **1974**, 819.
(20) Klein, J. *J. Am. Chem. Soc.* **1959**, *81*, 3611.
(21) Inubushi, Y.; Kitano, M.; Ibuka, T. *Chem. Pharm. Bull.* **1971**, *19*, 1820.
(22) The chromatographic separation of the cis–trans lactone mixture is considerably easier than that of the cis–trans cyano alcohol mixture.
(23) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839.
(24) Pirkle, W. H.; Boeder, C. W.; Simmons, K. *J. Org. Chem.* **1979**, *44*, 4891.
(25) The optical purity of the partially racemized (+)-**2** was approximately 50%.
(26) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1974**, *39*, 120.



12 13

respectively, on the basis of the reasonable presumption that methylation occurs preferentially trans to the adjacent fused ring.[27] Liquid chromatography of either crude product gives no indication of the presence of a second epimer nor do the NMR spectra of either chromatographed **12** or **13** indicate the presence of a second epimer. When the proton NMR spectra of either (−)-enriched **12** or (−)-enriched **13** (some racemate added in each instance) were determined with added (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, a downfield sense of nonequivalence was observed for the methyl resonance of each lactone. This sense of nonequivalence is the basis for the indicated assignments of absolute configuration to (−)-**12** and (−)-**13** (and hence (−)-**4** and (−)-**5** as well as the corresponding hydroxy amide precursors). The logic employed in reaching these assignments is set forth in our prior papers on γ-lactones.[5a,28]

The aforementioned chiral solvating agent has also been used to ascertain the enantiomeric purity of the tricyclic lactones reported here. Methylation of either (−)-**4** or (+)-**5** affords material that, within the limits of the NMR method, is enantiomerically pure.[29] Although similar checks of enantiomeric purity for the remaining lactones have not been made, equally high enantiomeric purity seems likely in view of the chromatographic evidence indicative of complete separation of the relevant diastereomers and the similarity of the subsequent conversions to those previously shown[1] to be nonracemizing.

Discussion

The ability to prepare enantiomerically pure lactones by using either of two types (i.e., cyano carbamate or hydroxy amide) of chromatographically separable diastereomeric precursors is clearly advantageous. Since neither type of diastereomer will always be superior to the other, we shall outline our views on the relative advantages and disadvantages of each approach.

One obvious difference between the two approaches is that one can be used to resolve a racemic lactone that might be in hand, whereas the other resolves a lactone precursor. The aminolysis of a racemic lactone to afford hydroxy amide diastereomers seems to be better suited to γ rather than to δ or larger ring lactones. In the case of several simple lactones, Helmchen[5b-d] has demonstrated that the chromatographic separability of the diastereomeric hydroxy amides decreases drastically when the lactonic chiral center is more than two carbon atoms removed from the amide carbonyl (as might be the case for δ and larger ring lactones). Moreover, we were unable to form the α-NEA hydroxy amides of δ-lactones (i.e., *cis*- or *trans*-**3**), owing to polymerization of these lactones at the high temperatures required for reaction with the amine. In addition to sometimes being difficult to form, the hydroxy amides are sometimes hard to hydrolyze. Helmchen[5b-d] originally employed fairly strong mineral acid at moderately high temperature for hydrolysis, conditions that have been shown to cause racemization of α- or carbinyl-substituted lactones.[5b-d,31] Moreover, several of the lactones discussed herein undergo cis–trans epimerization of the ring junction under strongly acidic conditions. Some of the problems attending acidic hydrolysis can be overcome through use of basic hydrolysis (with careful neutralization subsequently) although basic hydrolysis of amides is often more sluggish than is acidic hydrolysis. We overcame the sluggish hydrolysis of the hydroxy amides derived from *trans*-**4** by conducting these reactions at rather high pressures (4 kbars) in an apparatus not routinely available to most researchers.

In the instances studied, the diastereomeric hydroxy amides were easily separated by chromatography, a definite advantage. On the other hand, no correlation between the elution order of diastereomeric hydroxy amides and their relative stereochemistry is presently obvious. Therefore, the absolute configurations of the final lactones must be adduced in some alternative fashion.

By contrast, the cyano carbamate approach utilizes reagents and reaction conditions that are relatively mild and thus avoid undesired side reactions or stereochemical alterations. However, in some of the instances reported herein, the separation of a pair of diastereomeric cyano carbamates did require careful chromatography with use of the recycle technique. This problem might be ameliorated by use of chiral derivatizing agents more efficacious than α-NEA. Finally, the absolute configurations of the lactones derived from the cyano carbamates will frequently be assignable from considerations of NMR spectral data and chromatographic elution orders.

Conclusion

Two approaches to the synthesis of both enantiomers of bi- and tricyclic lactones have been tested and found viable. Each approach utilizes a chiral derivatizing agent, α-NEA, to afford chromatographically separable diastereomers, each of which can be used to provide a single lactone enantiomer. The use of diastereomeric cyano carbamates of α-NEA often allows assignment of absolute configuration to the product lactones from NMR or chromatographic properties of the diastereomers. While no similar claim is advanced for diastereomeric hydroxy amides of α-NEA, absolute configurations of the product lactones can sometimes be determined through the agency of an NMR chiral solvating agent.

Experimental Section

General Methods. Varian EM-390 and Perkin-Elmer 237B spectrometers were used to obtain NMR and infrared spectra. Optical rotations were obtained by 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 on Chromosorb W (0.25 in. × 10 ft). SE-30 refers to 15% SE-30 on Chromosorb W (0.25 in. × 5 ft).

(27) Grieco[26] adduces evidence that diphenyl diselenide alkylation of the enolate derived from α-methylated **2** introduces an α-phenylseleno group trans to the adjacent fused ring. Moreover, methylation of the enolate from α-(PhSe)-**2** introduces the methyl trans to the adjacent fused ring.

(28) Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.

(29) However, the enantiomeric purity of the final product will reflect that of the resolving agent, unless solid intermediates result which are subjected to recrystallization. We have determined the enantiomeric purity of the (*R*)-α-NEA used in this study to be in the range of 96–98% by a procedure[30] previously described for similar compounds.

(30) Pirkle, W. H.; House, D. W. *J. Org. Chem.* **1979**, *44*, 1957.

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Solvents were reagent grade except for hexane. Microanalyses were performed by J. Nemeth and Associates, University of Illinois. All solutions were dried over anhydrous $MgSO_4$. Liquid chromatographic separations were effected on an automated preparative system fabricated in these laboratories.[12] The chromatographic materials (adsorbents, columns, TLC sheets, etc.) and their sources are the same as those previously described.[1]

(±)-*trans*-2-(Cyanomethyl)cyclohexanol (7). Procedure A. To a stirred 0 °C solution of 5.55 g (146 mmol) of $NaBH_4$ in 100 mL of THF was added a solution of 10.0 g (73 mmol) of 2-(cyanomethyl)cyclohexanone[14] in 50 mL of THF over a 20-min period. The temperature was maintained at 0–5 °C for 1.5 h, and the mixture was acidified to pH 1 with 3 M hydrochloric acid. After being diluted with water, the mixture was continuously extracted with ether for 10 h. Drying and concentration of the ethereal extract afforded crude **7** (9.9 g, 93.4%). An analytical sample was collected by preparative GLC on Carbowax (180 °C): IR 3480, 2265 cm^{-1}; NMR ($CDCl_3$) δ 1.05–1.88 (m, 9 H), 2.42 (AB pattern, 2 H), 2.73 (br s, exchanges with D_2O, 1 H), 3.10–3.43 (m, 1 H).

Anal. Calcd for $C_8H_{13}NO$: C, 69.06; H, 9.35; N, 10.07. Found: C, 68.86; H, 9.47; N, 10.19.

***trans*-2-(Cyanomethyl)cyclohexyl *N*-[1-(1-Naphthyl)ethyl]carbamates (14a,b).** These carbamates were prepared from (±)-**7** and the isocyanate[6] of (*R*)-(+)-α-NEA (**15**) in a manner analogous to the previously described procedure[1] and were completely separated by chromatography (silica gel, 8:1 PhH–ether, $\alpha = 1.20$).

A total of 3.13 g (64.8%) of the high-R_f (1*S*,2*R*,*R*-**14a**) diastereomer was isolated as a white solid: mp 92 °C; IR (Nujol) 3315, 2250, 1670–1732 (br), 1604 cm^{-1}; NMR ($CDCl_3$) δ 0.91–2.02 (br m, 9 H), 1.53 (d overlapping m, $J = 7.0$ Hz, 3 H), 2.03–2.45 (AB pattern, 2 H), 4.09–4.42 (m, 1 H), 5.03–5.24 (br d, 1 H), 5.33–5.68 (m, 1 H), 7.28–8.07 (m, 7 H); $[\alpha]^{22.4}_D$ +30.1° (*c* 13.2, $CHCl_3$).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.00; H, 7.14; N, 8.33. Found: C, 75.04; H, 7.29; N, 8.15.

A total of 3.02 g (62.5%) of the low-R_f (1*R*,2*S*,*R*-**14b**) diastereomer was isolated as a colorless oil: IR 3317, 2245, 1668–1730 (br), 1601 cm^{-1}; NMR ($CDCl_3$) δ 0.88–2.70 (br m, 11 H), 1.60 (d, $J = 6.8$ Hz, 3 H), 4.10–4.53 (m, 1 H), 4.87–5.31 (m, 1 H), 5.40–5.61 (m, 1 H), 7.30–8.13 (m, 7 H); $[\alpha]^{23}_D$ −43.3° (*c* 7.3, $CHCl_3$).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.00; H, 7.14; N, 8.33. Found: C, 74.97; H, 7.36; N, 8.20.

(1*S*,2*R*)-(+)-*trans*-2-(Cyanomethyl)cyclohexanol (7). Procedure B. To a stirred solution of 2.38 g (7.08 mmol) of **14a** and 794 mg (7.8 mmol) of Et_3N in 40 mL of dry PhH under N_2 was added 1.06 g (7.8 mmol) of $SiHCl_3$ in 10 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 ether (4 × 30 mL). Combined organic layers were dried and concentrated in vacuo at less than 30 °C. The residue was immediately chromatographed on neutral alumina (4:1 hexane–EtOAc). (*R*)-(−)-**15** was first to elute,[32] usually followed by a trace of unreacted carbamate. The desired cyano alcohol eluted immediately after the unreacted carbamate. A 910-mg (91.6%) amount of (+)-**7** was collected and found to possess spectral and physical properties identical with those of (±)-**7**, $[\alpha]^{21.9}_D$ +54.7° (*c* 6.1, $CHCl_3$).

(1*R*,2*S*)-(−)-*trans*-7. In a similar manner **14b** was converted to (−)-**7**, which possessed spectral and physical properties identical with those of the racemate, $[\alpha]^{23}_D$ −53.2° (*c* 2.5, $CHCl_3$).

(1*S*,2*R*)-(−)-*trans*-Hexahydro-2(3*H*)-benzofuranone (1). Procedure C. A solution of 805 mg (5.79 mmol) of (+)-**7**, 2.0 g of NaOH, and 50 mL of 3:1 ethanol–water was heated at reflux under N_2 for 20 h. After being cooled to 0 °C, this solution was neutralized with dilute hydrochloric acid, and the bulk of the ethanol was concentrated in vacuo. The remaining solution was extracted with ether (4 × 25 mL), and the extracts were dried and concentrated to give the corresponding hydroxy acid of **1**. This product was lactonized by being heated in 30 mL of PhH at reflux for 3 h (azeotropic removal of water).[33] The solvent was removed to give 740 mg (91.9%) of (−)-**1**. A pure sample of the lactone was isolated by preparative GLC on Carbowax (170 °C): IR 1778 cm^{-1}; NMR ($CDCl_3$) δ 1.12–2.74 (br m, 11 H), 3.57–3.90 (m, 1 H); $[\alpha]^{22.8}_D$ −77.6° (*c* 4.6, $CHCl_3$).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57. Found: C, 68.48; H, 8.72.

(1*R*,2*S*)-(+)-*trans*-1. In an identical manner (−)-**7** was converted to (+)-**1**, which possessed spectral and physical properties identical with those of the (−) enantiomer; $[\alpha]^{23}_D$ +78.5° (*c* 2.9, $CHCl_3$).

(±)-*trans*-2-(2-Cyanoethyl)cyclopentanol (8). Procedure A was used to convert 2-(2-cyanoethyl)cyclopentanone[16] to 10.6 g (91.4%) of (±)-**8**. The crude product was converted directly to the corresponding diastereomeric carbamates.

***trans*-2-(2-Cyanoethyl)cyclopentyl *N*-[1-(1-Naphthyl)ethyl]carbamates (16a,b).** These carbamates were prepared in a manner analogous to the preparation of **14a,b** and were separated completely by chromatography (silica gel, 8:1 PhH–ether, $\alpha = 1.13$). Minor amounts of the corresponding cis carbamates (**17a,b**) were also removed in the chromatography.

A total of 4.9 g (70.4%) of the high-R_f (1*S*,2*R*,*R*-**16a**) diastereomer was isolated as a white solid and was recrystallized from MeOH: mp 133–134 °C; IR (Nujol) 3325, 2262, 1712, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.04–2.01 (br m, 9 H), 1.54 (d overlapping m, $J = 7.2$ Hz, 3 H), 2.24 (t, $J = 7.8$ Hz, 2 H), 4.52–4.70 (m, 1 H), 5.13 (br d, 1 H), 5.35–5.71 (m, 1 H), 7.32–8.17 (m, 7 H); $[\alpha]^{24}$ +17.3° (*c* 5.8, $CHCl_3$).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.00; H, 7.14; N, 8.33. Found: C, 74.65; H, 7.26; N, 8.62.

A total of 4.72 g (67.8%) of the low-R_f (1*R*,2*S*,*R*-**16b**) diastereomer was isolated as a colorless viscous oil: IR (Nujol) 3320, 2265, 1735–1680 (br), 1610 cm^{-1}; NMR ($CDCl_3$) δ 0.99–2.50 (br m, 11 H), 1.59 (d overlapping m, $J = 6.2$ Hz, 3 H), 4.41–4.75 (m, 1 H), 4.88–5.19 (m, 1 H), 5.35–5.70 (m, 1 H), 7.28–8.16 (m, 7 H); $[\alpha]^{23.8}_D$ −23.5° (*c* 0.7, $CHCl_3$).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.00; H, 7.14; N, 8.33. Found: C, 74.62; H, 7.31; N, 8.38.

(1*S*,2*R*)-(+)-*trans*-2-(2-Cyanoethyl)cyclopentanol (8). Procedure B was used to convert **16a** to 864 mg (87.3%) of (+)-*trans*-**8**: IR 3500 (br), 2260 cm^{-1}; NMR ($CDCl_3$) δ 1.34–2.20 (br m, 9 H), 2.43 (t, $J = 7.4$ Hz, 2 H), 3.57 (br s, exchanges with D_2O, 1 H), 3.63–3.97 (m, 1 H); $[\alpha]^{25.2}_D$ +39.8° (*c* 4. 8, $CHCl_3$).

Anal. Calcd for $C_8H_{13}NO$: C, 69.06; H, 9.35; N, 10.07. Found: C, 68.77; H, 9.11; N, 9.89.

(1*R*,2*S*)-(−)-*trans*-8. In a similar manner **16b** was converted to (−)-*trans*-**8** and found to possess spectral and physical properties identical with those of the (+) enantiomer; $[\alpha]^{25.3}_D$ −38.9° (*c* 7.5, $CHCl_3$).

(1*S*,2*R*)-(−)-*trans*-Hexahydrocyclopenta[*b*]pyran-1-(3*H*)-one (3). Procedure D. A stirred solution of 450 mg (3.23 mmol) of (+)-*trans*-**8**, 800 mg (20 mmol) of NaOH, and 30 mL of 3:1 EtOH–H_2O was heated at reflux under N_2 for 24 h. After being cooled, the mixture was neutralized with dilute hydrochloric acid and extracted with ether (4 × 30 mL). Drying and concentration of the combined etheral layers afforded the crude hydroxy acid, which was stirred for 8 h at 25 °C in 15 mL of PhH containing 665 mg (3.23 mmol) of DCC. The mixture was then diluted with 60 mL of hexane and an insoluble white solid (urea) removed by filtration. Concentration of the filtrate afforded 325 mg (72%) of crude (−)-*trans*-**3**. An analytical sample was collected by preparative GLC on Carbowax at 180 °C: IR 1741 cm^{-1}; NMR ($CDCl_3$) δ 1.07–2.30 (br m, 9 H), 2.48–2.77 (m, 2 H), 3.88–4.28 (m, 1 H); $[\alpha]^{21.4}_D$ −92.5° (*c* 1.2, $CHCl_3$).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57. Found: C, 68.53; H, 8.56.

(1*R*,2*S*)-(+)-*trans*-3. In a manner analogous to the preceding method (−)-*trans*-**8** was converted to (+)-*trans*-**3** and found to possess spectral and physical properties identical with those of the (−) enantiomer; $[\alpha]^{23.6}_D$ +91.1° (*c* 3.1, $CHCl_3$).

(1*S*,2*S*)-(+)-*cis*-3. Procedures B and D were used to convert **17a** to 140 mg (61.4% overall) of (+)-*cis*-**3**. A pure sample of the lactone was isolated by preparative GLC on Carbowax (180 °C): IR 1744 cm^{-1}; NMR ($CDCl_3$) δ 1.03–2.48 (br m, 11 H), 4.58–4.81 (m, 1 H); $[\alpha]^{20.3}_D$ +85.2° (*c* 1.6, $CHCl_3$).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57. Found: C, 68.34; H, 8.55.

(32) In this manner the resolving agent is recovered as the isocyanate.
(33) Addition of a crystal of *p*-toluenesulfonic acid increases the rate of lactonization.

(±)-*cis*-Hexahydro-2(3*H*)-benzofuranone (2). Procedure C was used to convert (±)-7 to (±)-*trans*-1. The isomerization of (±)-1 was performed by using the method of Klein[20] with slight modifications. A stirred solution of 23 g (0.164 mol) of (±)-1, 115 mL of 50% aqueous H_2SO_4, and 160 mL of HOAc was heated at reflux under N_2 for 20 h.[34] The mixture was poured over 400 g of ice and extracted with PhH (2 × 200 mL). The combined organic layers were washed with saturated aqueous K_2CO_3 and dried over $MgSO_4$. Concentration of the solvent afforded crude (±)-2, which was purified by molecular distillation at 0.1 torr (12.4 g, 53.9%). This product was converted directly to the corresponding hydroxy amides.

***cis*-1-(2-Hydroxycyclohexyl)methyl *N*-[1-(1-Naphthyl)ethyl]amides (18a,b). Procedure E.** A stirred solution of 2.45 g (17.5 mmol) of (±)-2, 3.0 g (17.5 mmol) of (*R*)-1-(-naphthyl)-ethylamine,[35] and 15 mL of xylene was heated at reflux under N_2 for 30 h. The solvent was concentrated and the diastereomeric amides separated completely by chromatography (silica gel, 3:2 EtOAc–hexane, α = 1.62).

A total of 1.68 g (61.7%) of the high-R_f (1*R*,2*R*,*R*-**18a**) diastereomer was isolated as a white solid: mp 157–158 °C; IR (Nujol) 3510, 3300, 1620 cm^{-1}; NMR $CDCl_3$) δ 1.06–1.68 (br m, 9 H), 1.52 (d overlapping m, J = 6.2 Hz, 3 H), 1.70–2.40 (m, 2 H), 2.42–2.73 (m, 1 H), 3.46–3.63 (m, 1 H), 5.40–5.76 (m, 1 H), 5.84–6.06 (br d, 1 H), 7.02–7.78 (m, 7 H); $[\alpha]^{24.5}_D$ +30.8° (*c* 0.6, $CHCl_3$).

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.17; H, 8.04; N, 4.50. Found: C, 76.91; H, 7.81; N, 4.32.

A total of 1.74 g (64%) of the low-R_f (1*S*,2*S*,*R*-**18b**) diastereomer was isolated as a white solid: mp 145–147 °C; IR (Nujol) 3515, 3310, 1623 cm^{-1}; NMR ($CDCl_3$) δ 1.02–1.73 (br m, 9 H), 1.55 (d overlapping m, J = 6.2 Hz, 3 H), 1.78–2.41 (m, 2 H), 2.48–2.79 (m, 1 H), 3.63–3.78 (m, 1 H), 5.42–5.95 (m, 2 H), 7.01–7.80 (m, 7 H); $[\alpha]^{23.4}_D$ +59.2° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.17; H, 8.04; N, 4.50. Found: C, 76.82; H, 8.01; N, 4.72.

(1*R*,2*R*)-(+)-*cis*-2. Procedure C was used to convert **18a** to 402 mg (81.2%) of (+)-2. A pure sample of the lactone was isolated by preparative GLC on SE-30 at 165 °C: IR 1778 cm^{-1}; NMR ($CDCl_3$) δ 1.04–2.78 (m, 11 H), 4.40–4.60 (m, 1 H); $[\alpha]^{20}_D$ +41.9° (*c* 10.3, $CHCl_3$).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57. Found: C, 68.71; H, 8.54.

(1*S*,2*S*)-(-)-*cis*-2. In a similar manner **18b** was converted to (-)-2 which possessed spectral and physical properties identical with those of the (+) enantiomer; $[\alpha]^{24.3}_D$ -40.3° (*c* 8, $CHCl_3$).

(±)-*trans*- and (±)-*cis*-(2-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)acetic Acid Lactones (4 and 5). Procedure A was used to convert α-(cyanomethyl)-β-tetralone[21] to a 3:1 mixture of the corresponding cis and trans cyano alcohols, respectively.[22] This mixture was directly converted according to procedure C to a mixture of racemic lactones **4** and **5**. The lactones were separated by column chromatography on silica gel with a 254-nm UV detector (4:1 hexane–EtOAc, α = 2.6).

The first major fraction to elute (1.8 g, 15.2%) was the trans isomer (**4**): mp 142–144 °C; IR (Nujol) 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.68–3.31 (m, 7 H), 3.77–4.10 (m, 1 H), 6.54–7.02 (m, 4 H).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.59; H, 6.38. Found: C, 76.35; H, 6.22.

The second major fraction to elute (5.63 g, 47.6%) was the corresponding cis isomer (**5**): mp 59.5–60 °C; IR (Nujol) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.67–3.10 (m, 6 H), 3.43–3.77 (m 1 H), 4.60–4.86 (m, 1 H), 6.68–7.07 (m, 4 H).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.59; H, 6.38. Found: C, 76.31; H, 6.41.

***cis*-1-(2-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)methyl *N*-[1-(1-Naphthyl)ethyl]amides (19a,b).** A mixture of 3.0 g (15.9 mmol) of **5** and 2.72 g of (*R*)-α-NEA (15.9 mmol) was heated at 190 °C under N_2 for 48 h, and the diastereomeric amides were chromatographically separated (silica gel, 3:1 EtOAc–hexane, α = 1.76).

A total of 1.64 g (57.4%) of the high R_f (1*R*,2*S*,*R*-**19a**) diastereomer was isolated as a white solid: mp 168–175 °C dec; IR (Nujol) 3325, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.37–2.98 (m, 6 H), 1.62 (d overlapping m, J = 7.0 Hz, 3 H), 3.20–3.62 (m, 2 H), 3.98–4.27 (m, 1 H), 5.73–6.20 (m, 1 H), 6.33–6.67 (br d, 1 H), 7.04–8.37 (m, 11 H); $[\alpha]^{22.5}_D$ +20.8° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.22; H, 6.96; N, 3.90. Found: C, 79.92; H, 6.81; N, 3.94.

A total of 1.72 g (60.1%) of the low-R_f (1*S*,2*R*,*R*-**19b**) diastereomer was isolated as a white solid: mp 245–250 °C dec; IR (Nujol) 3325, 1648 cm^{-1}; NMR (CD_3SOCD_3) δ 1.28–3.00 (m, 6 H), 1.49 (d overlapping m, J = 7.2 Hz, 3 H), 3.17–3.55 (m, 2 H), 3.85–4.17 (m, 1 H), 4.90–5.13 (m, 1 H), 5.69–6.08 (m, 1 H), 6.76–8.64 (m, 11 H); $[\alpha]^{24.8}_D$ -60.8° (*c* 1.0, DMF).

Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.22; H, 6.96; N, 3.90. Found: C, 79.95; H, 6.94; N, 3.85.

(1*R*,2*S*)-(-)-*cis*-5. Procedure C was used to convert **19a** to 193 mg (92.7%) of (-)-**5**. A pure sample of the lactone was isolated by chromatography on silica gel and found to possess spectral and physical properties identical with those of the racemate; $[\alpha]^{22}_D$ -161.1° (*c* 2.1, $CHCl_3$).

(1*S*,2*R*)-(+)-*cis*-5. In a similar manner **19b** was converted to (+)-**5** and found to possess spectral and physical properties identical with those of the racemate; $[\alpha]^{23}_D$ +158.6° (*c* 3.0, $CHCl_3$).

***trans*-1-(2-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)methyl *N*-[1-(1-Naphthyl)ethyl]amides (20a,b).** Procedure E was used to convert (±)-**4** to the diastereomeric amides which were spearated by chromatography (silica gel, 3:1 EtOAc–hexane, α = 1.45).

A total of 791 mg (63.8%) of the high-R_f (1*S*,2*S*,*R*-**20a**) diastereomer was isolated as a white solid: mp 195–198 °C; IR (Nujol) 3500, 3295, 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.32–2.79 (m, 6 H), 1.44 (d overlapping m, J = 7.0 Hz, 3 H), 2.87–3.16 (m, 1 H), 3.44–3.68 (m, 1 H), 4.61 (br s, exchanges with D_2O, 1 H), 5.33–5.71 (m, 1 H), 5.95 (d, J = 8.2 Hz, 1 H), 6.50–7.78 (m, 11 H); $[\alpha]^{21.8}_D$ -36.9° (*c* 1.8, $CHCl_3$).

Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.22; H, 6.96; N, 3.90. Found: C, 79.91; H, 6.94; N, 3.88.

A total of 820 mg (66.1%) of the low-R_f (1*R*,2*R*,*R*-**20b**) diastereomer was isolated as a white solid: mp 222–228 °C dec; IR (Nujol) 3310, 3220, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.35–2.91 (m, 7 H), 1.50 (d overlapping m, J = 7.0 Hz, 3 H), 2.95–3.23 (m, 1 H), 3.60–3.94 (m, 1 H), 6.41–6.82 (m, 2 H), 6.58–7.86 (m, 11 H); $[\alpha]^{23.5}_D$ -32.9° (*c* 0.73, EtOH).

Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.22; H, 6.96; N, 3.90. Found: C, 80.05; H, 6.97; N, 3.91.

(1*S*,2*S*)-(-)-*trans*-4. High-pressure hydrolysis of a 300-mg (0.84 mmol) portion of **20a** was conducted for 30 h at 110 °C and 4 kbars in a 1-oz screw-cap polyethylene bottle (containing 600 mg of NaOH and 15 mL of 3:1 EtOH–H_2O) in the conventional high-pressure apparatus previously described.[36] After being cooled, the mixture was diluted with H_2O, neutralized with dilute hydrochloric acid, and extracted with ether (3 × 25 mL). Drying and concentration of the combined ethereal layers afforded the crude corresponding hydroxy acid, which was lactonized by heating at reflux for 2 h in 20 mL of PhH containing a crystal of *p*-toluenesulfonic acid (azeotropic removal of H_2O). The solvent was removed to give the crude lactone, which was purified by chromatography on silica gel (114 mg, 72.2%). (-)-**4** possessed spectral and physical properties identical with those of the racemate; $[\alpha]^{23.2}_D$ -78.2° (*c* 2.4, $CHCl_3$).

(1*R*,2*R*)-(+)-*trans*-4. In a manner analogous to the preceding procedure, **20b** was converted to (+)-**4** and found to possess spectral and physical properties identical with those of the racemate; $[\alpha]^{24}_D$ 76.9° (*c* 1.3, $CHCl_3$).

(1*S,2*S**,*S**)-(±)-*trans*-(2-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)-α-methylacetic Acid Lactone (12).** The procedure of Grieco[26] for similar compounds was used to convert (±)-**4** to (±)-**12**. A 42-mg amount (82%) of pure **12** was isolated by column chromatography (silica gel, 6:1 EtOAc–hexane): IR 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (d, J = 7.5 Hz, 3 H), 1.70–3.47 (m, 6 H), 4.38 (m, 1 H), 6.88–7.37 (m, 4 H).

(1*R,2*S**,*S**)-(±)-*cis*-(2-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)-α-methylacetic Acid Lactone (13).** In a manner analogous to the preceding procedure, (±)-**5** was converted to a 33-mg amount (72.3%) of pure (±)-**13**: IR 1770 cm^{-1}; NMR

(34) After 3 h, the reaction was worked up and found to be an 80:20 mixture of cis–trans lactones, respectively.

(35) The resolved amine was purchased from Norse Chemical Co.

(36) Grieger, R. A.; Eckert, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 7149.

($CDCl_3$) δ 1.41 (d, J = 7.3 Hz, 3 H), 1.82–2.55 (m, 4 H), 2.57–2.80 (m, 1 H), 3.10–3.32 (m, 1 H), 4.57–4.84 (m, 1 H), 6.77–7.0 (m, 4 H).

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Registry No. (±)-*trans*-1, 61248-46-2; (1*S*,2*R*)-1, 74741-45-0; (1*R*,2*S*)-1, 74708-14-8; (±)-*cis*-2, 74708-15-9; (1*R*,2*R*)-2, 43119-27-3; (1*S*,2*S*)-2, 74708-16-0; (1*S*,2*R*)-3, 74708-17-1; (1*R*,2*S*)-3, 74708-18-2; (1*S*,2*S*)-3, 74708-19-3; (±)-*trans*-4, 74629-86-0; (1*S*,2*S*)-4, 74708-20-6; (1*R*,2*R*)-4, 74708-21-7; (±)-*cis*-5, 74629-87-1; (1*R*,2*S*)-5, 74708-22-8; (1*S*,2*R*)-5, 74708-23-9; (±)-*trans*-7, 74629-88-2; (1*S*,2*R*)-7, 74708-24-0; (1*R*,2*S*)-7, 74708-25-1; (±)-*trans*-8, 74629-89-3; (1*S*,2*R*)-8, 74708-26-2; (1*R*,2*S*)-8, 74708-27-3; (1*S**,2*S**,*S**)-(±)-12, 74629-90-6; (1*R**,2*S**,-*S**)-(±)-13, 74708-28-4; (1*R*,2*R*,*R*)-14a, 74629-91-7; (1*S*,2*R*,*R*)-14b, 74708-29-5; (*R*)-15, 42340-98-7; (1*R*,2*S*,*R*)-16a, 74629-92-8; (1*S*,2*R*,-*R*)-16b, 74708-30-8; 17a, 74708-31-9; (1*R*,2*R*,*R*)-18a, 74629-93-9; (1*S*,2*S*,*R*)-18b, 74708-32-0; (1*R*,2*S*,*R*)-19a, 74629-94-0; (1*S*,2*R*,*R*)-19b, 74629-95-1; (1*S*,2*S*,*R*)-20a, 74629-96-2; (1*R*,2*R*,*R*)-20b, 74629-97-3; (±)-2-(cyanomethyl)cyclohexanone, 74629-98-4; (*R*)-1-(1-naphthyl)-ethylamine, 3886-70-2; (±)-α-(cyanomethyl)-β-tetralone, 34087-39-3.

Enantiomerically Pure Lactones. 3. Synthesis of and Stereospecific Conjugate Additions to α,β-Unsaturated Lactones

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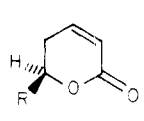
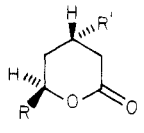
A general synthetic approach to both enantiomers of α,β-unsaturated lactones of general formula 1 has been devised, the first synthesis of the naturally occurring antipode of massoilactone (**1b**) exemplifying the approach. Interestingly, the specific rotation of massoilactone (and its enantiomer) is higher than that of the natural material isolated from formicine ants. A key step in the sequence involves chromatographic separation of rationally selected diastereomeric derivatives of racemic intermediates. Compounding the utility of an approach to optically active, type 1 lactones is the observation that conjugate additions of organometallic reagents to such lactones proceed with a high degree of stereospecificity, affording lactones of general formula 2. The conformational behavior of lactone **1a** is considered as is the solvation of δ-lactones by fluoroalcoholic chiral solvating agents such as 2,2,2-trifluoro-1-(9-anthryl)ethanol (8).

A general synthetic route to configurationally known enantiomerically pure unsaturated lactones of general formula 1 would be of value not only because these lactones are widely occurring natural products (fruits,[1] blossoms,[2] bark oil,[3,4] cane molasses,[5] insects,[4] butter[6]) but also because they are synthetically versatile precursors to other chiral molecules of considerable interest. For example, the naturally occurring enantiomer of parasorbic acid (**1a**) has



1a, R = CH_3
b, R = n-C_5H_{11}
c, R = n-$C_{13}H_{27}$



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served as a convenient starting material for the synthesis of a 4,6-dideoxy-L-ribose derivative,[7] of interest to those concerned with antibiotics. As is often the case with syntheses based upon chiral natural products, only one enantiomer of the product can be obtained for biological testing, owing to unavailability of the unnatural enantiomer of the starting material. Since racemic **1a** has been used to prepare DL-chalcose,[8] DL-desosamine,[8] and various DL-4,6-dideoxy sugars,[9] one presumes that access to either enantiomer of parasorbic acid would allow preparation of either product enantiomer.

Our past interest in the rational resolution of enantiomers by liquid chromatography has led to methodology for the preparation, in high enantiomeric purity, of both enantiomers of an assortment of ring-saturated lactonic pheromones.[10] Our interest in extending our approach to encompass type 1 lactones was additionally stimulated by the possibility that stereospecific 1,4 conjugate additions to these compounds might efficiently afford disubstituted ring-saturated lactones of general formula 2. Such a sequence would complement the asymmetric induction scheme recently described by Meyers and co-workers[11] for the preparation of simple, optically active, monosubstituted β-alkyl lactones.[12]

Since type 2 disubstituted lactones possess a chiral center relatively remote from the synthetically versatile lactone functionality, we deemed them synthetically useful precursors of yet more elaborate chiral molecules. Functionally remote chiral centers are common to many natural products (e.g., pheromones of the German cockroach and pine saw-fly) and often present difficult problems in stereochemical control and assay.

Synthesis of Chiral α,β-Unsaturated Lactones. As a continuation of our studies directed toward the synthesis of enantiomerically pure lactones, we describe a general synthetic approach that affords both enantiomers of α,β-

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