(d, 12 H, CH_3 of *i*-Bu), 1.2-2.3 (m, 2 H, CH of *i*-Bu), 2.5-3.0 (featureless m, 1 H, benzylic CHAl), 3.15-3.65 (featureless m, 2 H, benzylic CH_2), 6.6-7.1 (br, featureless signal, 1.0 H, H_3), and at 7.2 (br m) and at 7.45 ppm (br d) (total of 4.7-5.0 H. Trace signals of dissolved isobutene were detected at 1.67 and 4.78 ppm. As this spectrum was recorded at successively higher temperatures, the signals due to **4** sharpened very markedly: at 112 °C, the benzylic signals between 2.5-3.0 and 3.15-3.65 ppm resolved into a triplet and doublet, respectively (J = 7 Hz), the broad signal at 6.6-7.1 became a doublet at 6.88 (J = 4 Hz), and the signal at 7.2 ppm became a four-line multiplet. The ratio of the signal at 6.88 vs. the other aromatic signals was 1.0:4.85.

(b) Effect of Added *i*-Bu_2AlR. Each of the other three portions of **4** prepared above were admixed either with 0.98 equiv of *i*-Bu_2AlD, 0.86 equiv of *i*-Bu_2AlCl, or 0.55 equiv of *i*-Bu_3Al. The ^1H NMR spectra were recorded and the ratio of the shielded aromatic resonance at 6.88 ppm (SAR) to the other aromatic signals (OAR) was determined.

(c) Effect of Added Lewis Bases. Another portion of **4** was prepared as in section a. The ratio of all aromatic resonances to the isobutyl resonances revealed an excess of 0.22 equivalence of *i*-Bu_2AlH. This solution was apportioned among several samples that were treated with various amounts of ethyl ether or *N*-methylpyrrolidine. The amount of donor added was ascertained by noting how the ratio of aromatic area to the area between 1.0 and 5.0 ppm changed upon adding the donor aliquot. The resulting ratios of SAR to OAR are given in Table I.

(d) Effect of 5-Deuteration of Acenaphthylene and Concentration of 4-d_2. A sample of acenaphthylene-*1,5*-d_2, which was 72% deuterated at C_5 (0.269 g, 1.7 mmol) was hydraluminated in toluene-d_8 as in section a (0.35 mL of *i*-Bu_2AlH in 0.5 mL of toluene). The ^1H NMR spectra of the resulting sample and of various samples made by dilution with toluene-d_8 were recorded. The relative positions and areas of the SAR and OAR were noted.

^1H NMR Spectra of Other Benzylic Aluminum Systems. The spectrum of tribenzylaluminum in mesitylene solution showed a ten-line multiplet for the benzyl group downfield from the mesitylene's aromatic singlet. The two upfield (ortho CH) lines sharpened to a clean doublet between 100 °C and 149 °C (6.80 ppm, J = 4 Hz) and shifted downfield from the mesitylene signal by 5 Hz.

Diisobutyl(1,1-dimethyl-3-indanyl)aluminum in toluene-d_8[6b] was examined by ^1H NMR spectroscopy between 37 °C and 97 °C. The aromatic region consisted of a singlet at 6.8 ppm (~3,5 H) and a broad singlet at 6.95 ppm (~0.5 H), and these resonances did not vary with temperature. It should be noted that in the ^1H NMR spectrum of 1,1-dimethylindan the aromatic protons display a singlet at 6.99 ppm.

Acknowledgment. We are grateful to the Public Health Service and to the National Science Foundation for the support of this research through Grant GM-20304 and Grant CHE7918188, respectively. The technical advice of Drs. Harsh Gopal and Sue-Goo Rhee has been deeply appreciated.

Registry No. **4**, 51754-77-9; **8**, 208-96-8; **9**, 1191-15-7; **10**, 56819-67-1; **11**, 75-77-4; **12**, 71582-71-3; **13**, 71582-67-7; **14**, 92669-60-8; **14**-d_6, 92669-75-5; **15**, 92669-61-9; **16**, 92669-62-0; **17**, 1136-10-3; **17**-1,3,5-$(NO_2)_3C_6H_3$, 92669-77-7; **18**, 81-84-5; **19**, 92669-63-1; **19a**, 92669-76-6; **21**, 93-55-0; **22**, 92669-64-2; **23**, 92669-65-3; **24**, 92669-66-4; (*E*)-**25**, 92669-67-5; (*Z*)-**25**, 92669-68-6; **26**, 92669-69-7; **27**, 55720-25-7; (*E*)-**28**, 92669-70-0; (*Z*)-**28**, 92669-71-1; **29**, 92669-84-6; **29a**, 92669-72-2; **32**, 486-25-9; *cis*-**33**, 92669-73-3; *trans*-**33**, 92669-74-4; **33** (dedeuterio deriv), 92669-81-3; *cis*-**34**, 50442-54-1; *trans*-**34**, 50442-53-0; **35**, 7434-96-0; **36**, 7424-61-5; **37**, 72976-61-5; **44**, 92669-82-4; Me_2CO, 67-64-1; $(CD_3)_2CO$, 666-52-4; Et_2CO, 96-22-0; MeCOCl, 75-36-5; PhCOCl, 98-88-4; EtCOCl, 79-03-8; PhBr, 108-86-1; 1-(2-propenyl)acenaphthalene, 54759-30-7; 3-(3-hydroxy-3-pentyl)-1,3-dihydroacenaphthylene, 92669-78-8; 1-(3-hydroxy-3-pentyl)acenaphthalene, 92669-79-9; cyclopentanone, 120-92-3; 3-(1-hydroxy-1-cyclopentyl)-1,3-dihydroacenaphthylene, 92669-80-2; 3-(1-hydroxy-1-propyl)-acenaphthalene, 92669-83-5.

Enantiomers of the Biologically Active Components of the Insect Attractant Trimedlure

Philip E. Sonnet,* Terrence P. McGovern,† and Roy T. Cunningham‡

Insect Attractants, Behavior, and Basic Biology Research Laboratory, Agricultural Research Service, U.S. Department of Agriculture, Gainesville, Florida 32604

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The biologically most active components of a synthetic lure that is used to attract male Mediterranean fruit flies are the *tert*-butyl esters of *cis*-4-(and *trans*-5-)chloro-*trans*-2-methylcyclohexanecarboxylic acids (**1-A** and **1-C**). These compounds have been synthesized enantiomerically pure (≥99.6% ee) from resolved *trans*-6-methyl-3-cyclohexenecarboxylic acid. Configurations were assigned on the basis of literature analogy, proton chemical shift data, and high-pressure liquid chromatographic elution orders of selected diastereomeric adducts of the acids.

The best tool currently available for monitoring infestations of Mediterranean fruit fly, *Ceratitis capitata* (Wiedemann), is a synthetic attractant mixture known as trimedlure **1** (Scheme I). Discovered in a screening program conducted by the U.S. Department of Agriculture during the sixties,[1] its commercial synthesis involves a Diels-Alder reaction between butadiene and crotonic acid that produces primarily *trans*-6-methyl-3-cyclohexenecarboxylic acid (**2**) generally less than 5% of the cis isomer). Hydrogen chloride addition to the double bond produces a mixture of monochlorides **3** in which axially oriented chlorine predominates at both positions 4 and 5 and in which the methyl and carboxyl substituents are equatorial.[2] Esterification of the acid mixture with isobutylene and acid produces the mixture of *tert*-butyl esters referred to as trimedlure. The designations of the individual isomers in Scheme I are those of the authors who made the original assignments and refer to gas chromatographic elution orders.[2] The most attractive isomers

† Organic Chemicals Synthesis Laboratory, Beltsville, MD 20705.
‡ Tropical Fruit and Vegetable Laboratory, Honolulu, HI 96804.

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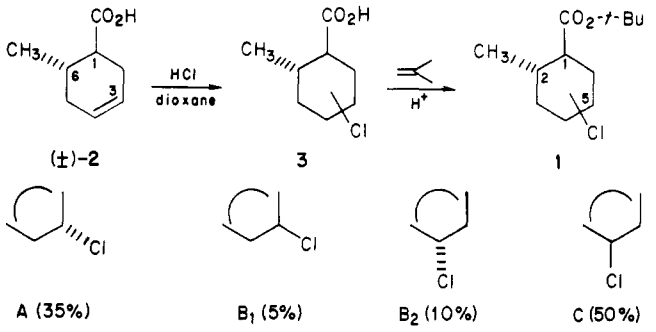
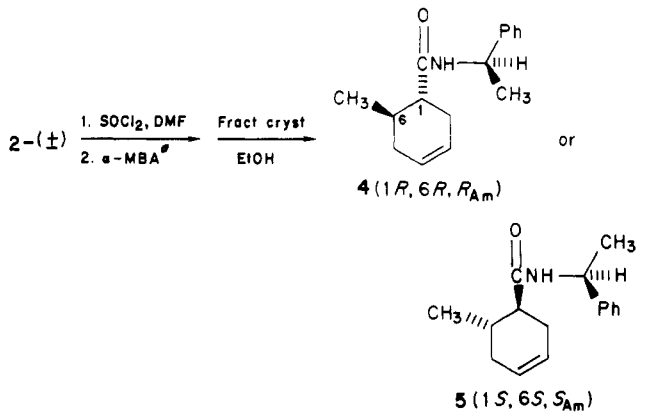
(2) McGovern, T. P.; Beroza, M. *J. Org. Chem.* **1966**, *31*, 1472.

Scheme I



Scheme II



[a] (*R*)- or (*S*)-α-methylbenzylamine.

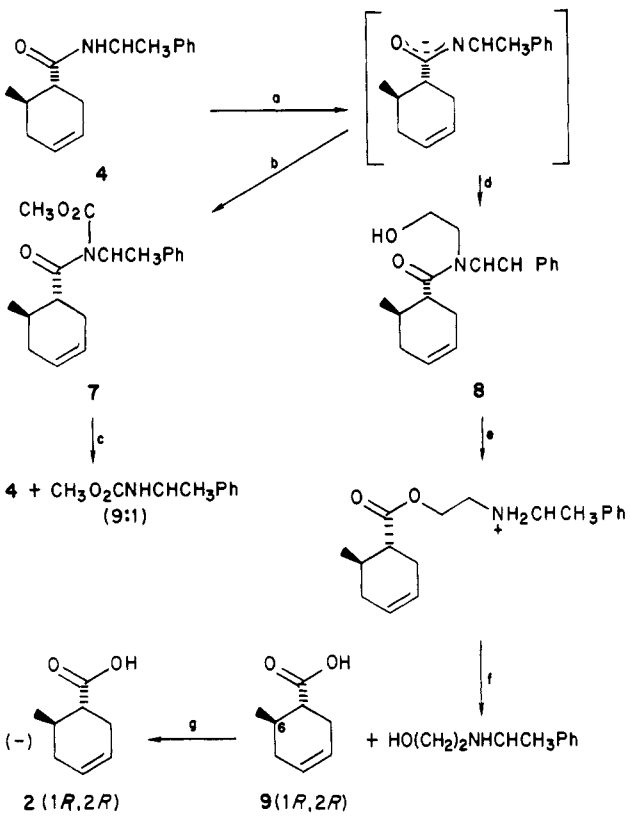
appear to be **1-C**, and to a lesser extent **1-A**, which are the two isomers bearing axial chlorine.[3] We describe here the syntheses and configurational assignments for the enantiomers of these structures.

We opted to resolve derivatives of acids **2** and **3-C**; the latter acid can be obtained in crystalline from the hydrochlorination mixtures.[2] Our initial attempts to resolve these acids as salts of configurationally pure α-methylbenzylamines were unrewarding, resolution being incomplete for **2**, for example, after nine recrystallizations. An alternative was to resolve the acids as amides of the same chiral amine auxiliaries. The amide of **3-C** also was slow to resolve by recrystallization, and in addition, methods employed to labilize the amide toward cleavage (vide infra) failed to produce acceptable yields of a clean product. In contrast, diastereomeric amides of the acid **2**, namely, **4** and **5** (Scheme II), were resolved easily; they were obtained in ≥99.8% purity (GLC) after four–five recrystallizations from ethanol (Scheme II).

It was found that addition of bromine to each pure diastereomer yielded a single adduct, **6**, in which both bromines were axially oriented (δ 4.61, 4.66 for equatorial CHBr). The relative solubilities of the dibromides were inverted from that of the original diastereomers. Thus we were able to employ amide mother liquors from recrystallizations (enriched in the more soluble diastereomers of **4** or **5**) and by bromination, recrystallization, and zinc debromination obtain that more soluble diastereomer in pure form. A cycle was established whereby both enantiomers of **2** could be obtained from a single enantiomer of the chiral auxiliary.

Although amides are well-known for their resistance to hydrolysis, a number of methods are now available for labilizing secondary amides to cleavage. Replacement of

Scheme III[a]



[a] (a) LDA, THF, ≤0 °C; (b) CH_3O_2CCl, ≤0 °C; (c) 1.25 N NaOH/EtOH, 25 °C, 3 h; (d) ethylene oxide, HMPT, 25 °C, 16 h; (e) 2 equiv of HCl/THF, reflux, 5-6 h; (f) LAH/THF, reflux, 16 h; (g) Jones' reagent/acetone, 0-5 °C.

the nitrogen-bound proton by *t*-BOC [$(t\text{-}BuO_2C)_2O$, Et_3N, DMAP, 25 °C, 8 h],[4] CH_3O_2C (LDA, CH_3O_2CCl, −78 °C, 0.5 h),[5] or $(HOCH_2CH_2)_2$ (LDA, ethylene oxide, 25 °C, overnight)[6] in each case provides a derivative that readily undergoes preferential cleavage of the original acyl carbon–nitrogen bond. The N-carbethoxylated amide **7**, an acylurethane (IR 1670, 1730 cm^{-1}) (Scheme III), was prepared, assuming that its reactivity would be similar to that of the acyloxazolidones described by Evans,[7] namely, that brief treatment with cold ethanolic NaOH or reaction with Me_3SiI[5] would result in "acid cleavages". In fact the reaction of **7** with base resulted in predominant urethane cleavage (9:1). Evidently reactions of acylurethanes, at least, are quite dependent on the steric environment of the amide carbonyl group.

Hydroxyethylation of amide **4** to **8** (Scheme III) proceeded in good yield but the hydrolysis of **8** in a two-phase system composed of concentrated HCl and hexane or in HCl–dioxane (both under reflux) were complicated by concurrent addition of HCl to the cyclohexene double bond. This addition could, of course, have shortened the synthetic sequence but was unfortunately neither complete nor avoidable. Treatment of **8** with aqueous HCl in THF under reflux (16 h) resulted in complete hydrolysis to the acid **2** although the yield was disappointing (40–45%). Instead the reaction was allowed to continue until **8** had been consumed, and the crude intermediate amino ester was isolated as its hydrochloride salt (Scheme III) and reduced with LAH to the alcohol **9**. Oxidation of a sample

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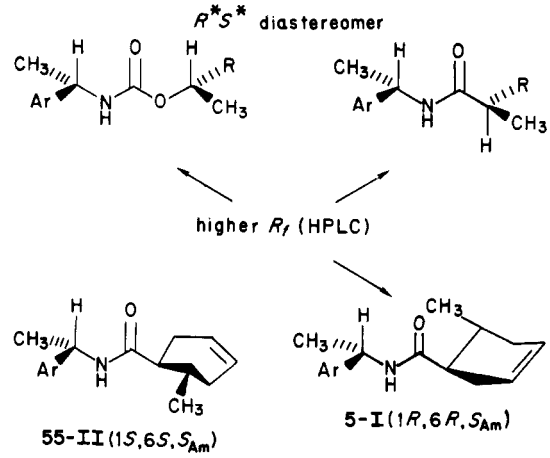
Scheme IV



of **9** with Jones reagent gave acid **2**, the purity of which was confirmed by conversion to the original amide **4**. This sequence was then applied to the diastereomerically pure amide **5**.

The assignments of absolute configuration for **2** and **9** were made initially by applying Brewster's rules[8] to the optical rotations. Thus the (+) enantiomers of **2** and **9** that had been obtained as the less soluble diastereomers by using (*R*)-α-methylbenzylamine were assigned the 1*R*,6*R* configuration. Additional evidence was obtained from ^{1}H NMR data and HPLC elution orders of diastereomeric derivatives. Pirkle has shown that in solution carbamate and amide diastereomers (Scheme IV) tend to prefer conformations in which the central functional group and attendant carbinyl hydrogens are coplanar.[9,10] The diastereomer elution order and any differential shielding of substituents on the asymmetric centers is predictable from this structure. The expected elution order for diastereomers of an α-methylalkanoic acid–(*S*)-α-methylbenzamide is *R***S** (shown in Scheme IV), then *R***R**. In addition, the methyl substituents of the acid residue in the *R***S** isomer experience an upfield shift from the phenyl ring though the effect in this system is small.[11] Although some criticism of these models has been offered by demonstrated exceptions,[12,13] the conceptualization holds well for simple (otherwise functionally unsubstituted) amides and carbamates.

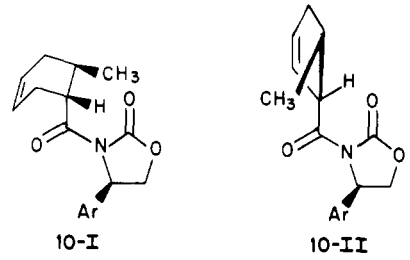
Presuming the same general solution conformation preferences of amides such as **5-I** and **5-II**, the expected lower R_f diastereomer is the one in which the more hydrophobic substituents extend from the same side of the central amide backbone (**5-II**, aryl and methyl-branched), thereby exposing the other side more completely to the adsorbent. This in fact was the case (α = 1.309, 10% EtOAc–hexane, see Experimental Section for additional HPLC data). In addition the ring-CH_3 of **5-II** was shifted upfield by 0.1 ppm relative to that of **5-I**. This shift

Table I. ^{1}H NMR Shifts of Ring-CH_3 in Amide Diastereomers[a]

compd	CH_3CH[b]
4-I(1*R*,6*R*,R_{Am}), **5-II**(1*S*,6*S*,S_{Am})	0.84
4-II(1*S*,6*S*,R_{Am}), **5-I**(1*R*,6*R*,S_{Am})	0.96
3-C-amide(1*S*,2*S*,S_{Am})	0.81
3-C-amide(1*R*,2*R*,S_{Am})	0.91
6-II(1*S*,6*S*,S_{Am} + Br_2)	0.84[c]
6-I(1*R*,6*R*,S_{Am} + Br_2)	0.99[c]
N-Hydroxyethyl derivatives,	
8(1R,6R,R_{Am})	0.99
8(1R,2R,S_{Am})	1.02
6-I → NCH_2CH_2OH	0.93
6-II → NCH_2CH_2OH	0.93

[a] Shifts are in ppm relative to Me_4Si ($CDCl_3$). Am refers to configuration of α-methylbenzylamine. [b] Each is a doublet; J = 6.5 Hz. [c] CHBr shifts are 4.73 and 4.62, consistent with equatorial C-H.

Scheme V



difference was noted routinely (Table I) and is consistent with these configurational assignments. The diminished proton shift difference noted in the N-hydroxyethylated amines **8** (0.03 ppm) is probably a result of considerable intramolecular H-bonding as inferred from infrared data. The amide I band of **8** is at 1600–1605 cm^{-1} while those of **4** and **5** are at 1655 cm^{-1}. The structure of such a chelate inverts the relationship of the ring-CH_3 to the substituents of the N-based asymmetric carbon and acts thereby to reduce the proton shift difference of the diastereomers.

Recently Pirkle described the use of chiral oxazolidones and their conversion to diastereomeric allophanates with amines as a method of determining configuration and configurational purity of amines.[14] The oxazolidone based on (*R*)-phenylglycinol and (±)-α-arylethylamines have been depicted (Scheme V) with antiperiplanar alignment of allophanate carbonyls and concurrent hydrogen bonding involving the amide proton and ring oxygen as suggested by the investigations of Krieg and Lautenschlager.[15] The particular diastereomer shown (Scheme V) exposes the amine-based methyl substituent to the phenyl ring of the oxazolidone unit, thereby shifting that methyl doublet by 0.1 ppm upfield. In addition, this diastereomer which places both the methyl and phenyl substituents to the same side of the general plane of the molecular backbone has the higher R_f. The oxazolidone of (*R*)-phenylglycinol was acylated with the acid halides obtained from **2** to produce the diastereomeric derivatives **10-I** and **10-II**. In analogy to the allophanates, the expectation was that the cyclohexene ring would prefer to align (more for steric reasons than for reasons of carbinyl hydrogen bonding) with the carbinyl hydrogen oriented toward the ring oxygen. The 1*S*,6*S* diastereomer **10-II** places the ring methyl and oxazolidone phenyl substituents to the same side of the proposed diastereomer backbone. For this substitution pattern, **10-II** was the lower R_f diastereomer (α = −1.45, 10% EtOAc–hexane), but the methyl doublet was fully

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(11) The solution conformation preferences of amides and carbamates are enhanced by increasing the acidity of the carbinyl hydrogens on either asymmetric center to legitimize carbinyl hydrogen bonding and results in greater ^{1}H NMR shift differences and HPLC separation factors: (a) ref 11b. (b) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2436. (c) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1983**, *15*, 263–331.
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Table II. ^{13}C NMR of Trimedlure Components[a]

compd	C_1	C_2	C_3	C_4	C_5	C_6	$CHCH_3$	*t*-Bu	C=O
(±)-3-A	46.26 d (45.8)	34.28 d (34.6)	28.05[b] (28.3)	33.55 t (33.5)	58.62 d (57.8)	36.98 t (36.9)	20.27 q	28.05 q, 80.43 s	174.97
(±)-3-B_1	52.30 d (52.8)	34.09 d (33.6)	33.60 t (35.2)	37.03 t (37.1)	58.26 d (58.1)	40.01 t (40.5)	19.76 q	28.30 q, 80.71 s	173.59
(±)-3-B_2	50.98 d (50.2)	35.09 d (36.1)	44.86 t (45.8)	58.20 d (58.6)	36.31 t (36.6)	29.68 t (29.9)	20.14 q	28.30 q, 80.46 s	174.72
(±)-3-C	51.76 d (51.2)	28.30[b] (29.0)	41.56 t (42.2)	58.78 d (58.3)	33.24 t (33.0)	23.85 t (22.9)	19.89 q	28.30 q, 80.27 s	174.71

[a] Values given in ppm ($CDCl_3$); values in parentheses are calculated.[15] [b] Coincidence with *t*-Bu CH_3.

0.20 ppm to higher field than that of the 1*R*,2*R* diastereomer. These data were consistent with our assignments of configuration for **2** and **9** based on Brewster's rules. Thus we concluded that (+)-**2** is (1*R*,6*R*)-6-methyl-3-cyclohexenecarboxylic acid.

The synthesis of the HCl adducts **3** and the corresponding *tert*-butyl esters **1** from enantiomerically pure **2** was performed as previously described with racemic **2**.[2] Individual components **1-A,B_1,B_2,C** were isolated by preparative HPLC and were identical in all respects with the known racemates. The mixture of configurationally pure chloro acids **3** could be purified to give the acid **3-C** by recrystallization of its salt of α-methylbenzylamine ((*S*)-amine, for example, was employed successfully with chloro acids obtained from (1*S*,2*S*)-**2**). Although this amine failed to resolve (±)-**3-C**, it succeeded in separating positionally isomeric materials.

Finally, the ^{13}C NMR shifts of the four *tert*-butyl esters have been tabulated (Table II) along with calculated shifts.[16] These data act to confirm the assignments of (±)-**3-A,B_1,B_2C** that were made originally on the basis of HCl elimination studies and somewhat limited spectral data that were available at the time.[2]

Preliminary field tests have been conducted in Hawaii that show that the 1*S*,2*S*,4*R* enantiomer of **3-C** is very attractive to male Mediterranean fruit flies while the 1*R*,2*R*,4*S* enantiomer is essentially inactive. Both enantiomers of **3-A** show much reduced activity though they seem equally attractive.

Experimental Section

Gas–liquid chromatography was performed with a Varian 1400 instrument using the following capillary columns: column A, OV-1 0.04% (0.25 mm × 3.3 m); column B, Durabond-fused silica (0.25 mm × 31 m); and column C, cholesteryl *p*-chlorocinnamate coated fused silica (0.25 mm × 45 m) with helium carrier (A and B) and hydrogen carrier (C) and operated at temperatures as indicated. Infrared data were obtained with a Perkin-Elmer Model 467 spectrophotometer using 3% solutions in CCl_4 or $CHCl_3$. A Nicolet 300-MHz FT NMR spectrometer was employed to obtain ^1H NMR and ^{13}C data with 1% solutions and 20% solutions in $CDCl_3$, respectively. Shifts are reported in ppm relative to Me_4Si. Mass spectra were obtained with a Finnegan Model 3200 spectrometer operated for CIMS (isobutane) and that was equipped with chromatographic inlet that was served by a Varian 1400 instrument and a 3% OV-101 glass column (3.2 cm × 1.5 m). Optical rotations were obtained with a Randolph Model 85 polarimeter with a sodium vapor lamp. The HPLC columns employed were as follows: A, 5-μm Lichrosorb Si-60 (6.3 mm × 25 cm) for analytical work; and B, 2–10-μm Biosil-A (25 mm × 25 cm). They were operated with a Waters Associates Model 6000 pump and RI detection as described below. The α-methylbenzylamines were purchased from Hexcel Corp., Zeeland, MI. The *S* enantiomer was judged to be 99.6% pure by GLC analysis of its methoxy(trifluoromethyl)phenyl acetate[17] (column A: 150 °C, *R*R**:*R*St* = 1.125) and the *R* enantiomer (98.7%) was purified by recrystallization of the L-tartrate salt to ≥99.6% purity. (*R*)-(+)-Phenylglycinol was purchased from Aldrich Chemical Co. and converted to an oxazolidone by the method of Pirkle and Simmons.[14]

Synthesis and Resolution of α-Methylbenzylamides 4 and 5 and the (*S*)-α-Methylbenzylamide of 3-C. The carboxylic acids (1 equiv) were converted to acid halides with $SOCl_2$ (1.2 equiv) and DMF (0.12 equiv) in anhydrous Et_2O (16 h, 25 °C).[18] The reaction mixtures were concentrated on a flash evaporator, the residues taken up in hexane and filtered through Na_2SO_4, and the filtrates were again concentrated. The crude acid halides were converted to the solid amides (≥95% yield) in CH_2Cl_2 by using 1.1 equiv each of one of the α-methylbenzylamines and Et_3N (ice bath). The amides **4**(1*R*,6*R*) and **5**(1*S*,6*S*) were obtained in ≥99.5% diastereomeric purity after four recrystallizations from EtOH using 3 mL/g for the first crystallization and ca. 2 mL/g initial weight thereafter. The recovery was 50–55% of theory. The procedures were the same for the (*S*)-α-methylbenzylamide of acid **3-C** except that either diastereomer could be induced to separate from solution and complete purification required at least seven recrystallizations with much lower yields (20–25%). Purifications of amides **4** and **5** were monitored by GLC (column B, 160 °C). Gas–liquid chromatography for **4,5**: k'(1*R**,6*R**,R^*_{Am}) = 15.50, k'(1*S**,6*S**,R^*_{Am}) = 16.07; α = 1.037°; *R* = 1.59[19] Purification of **3-C** amides required ^1H NMR monitoring (Table I). Data for amides **4** and **5**: mp 170–6 °C (more soluble diastereomers, 120–5 °C); IR ($CHCl_3$) 3440, 1655 cm^{-1}; NMR δ 0.84 (d, *J* = 6.5 Hz, 3 H, CH_3CHC), 1.48 (d, *J* = 6.9 Hz, 3 H, CH_3CHN), 1.6–2.4 (m, ~6 H, ring H), 5.14 (m, 1 H, CH_3CHN), 5.65 (bs, 2 H, vinyl H), 7.3 (m, 5 H, aryl H) ppm; CIMS, *m/e* 244 (P + 1), 140 (P + 1 − $C_6H_5CH{=}CH_2$); $[\alpha]^{22}_D$ −31.4° (1*S*,2*S*,S_{Am}; *c* 4.31, $CHCl_3$) (more soluble diastereomer, namely, 1*R*,6*R*,S_{Am}) $[\alpha]^{22}_D$ −109.7° (*c* 4.06, $CHCl_3$); HPLC column A (10% EtOAc–hexane); *k'*s **4**(1*S*,6*S*), 8.90; **4**(1*R*,6*R*) 11.65, α = 1.31. Anal. **5**(1*R*,6*R*,S_{Am}). Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.04; H, 8.93; N, 5.67.

Data for amides of **3-C**. 1*R*,2*R*,4*S*,S_{Am}: mp 164–5 °C; IR and NMR as described above and in Table II; $[\alpha]^{24}_D$ −97.7° (*c* 2.66, $CHCl_3$). 1*S*,2*S*,4*R*,S_{Am}: mp 179 °C; $[\alpha]^{24}_D$ −50.5° (*c* 2.77, $CHCl_3$).

Bromination–Debromination Sequence To Prepare 5-A and 5-B. Addition of bromine (1 equiv) to pure **5**(1*R*,6*R*) or **5**(1*S*,6*S*) (1 equiv) was conducted in CH_2Cl_2 (ice bath). Removal of solvent produced quantitative yields of adducts **6-I** and **6-II**, respectively, that were judged homogeneous based on the following spectral data, **6-I**(1*R*,2*R*,4*R*,5*R*,S_{Am}): mp 192–3 °C; IR ($CHCl_3$) 1650 cm^{-1}; NMR δ 0.99 (d, *J* = 6.0 Hz, 3 H, CH_3CHC), 1.48 (d, *J* = 6.9 Hz, 3 H, CH_3CHN), 1.6–2.4 (m's, 6 H, ring H), 4.61 and 4.66 (bs, 2 H, equatorial CHBr), 5.13 (m, 1 H, CH_3CHN), 7.3 (m, 5 H, aryl H); $[\alpha]^{22}_D$ −78.5° (*c* 4.02, $CHCl_3$). **6-II**(1*S*,2*S*,4*S*,5*S*,S_{Am}): mp 142–144 °C; IR and NMR as for **6-I** except as noted in Table I.

Bromine was removed by stirring the dibromides in a propionic or acetic acid suspension of zinc (5 equiv) for 2 h/25–30 °C and then filtering the zinc, diluting the filtrate with H_2O, and filtering the debrominated amide. For example, 80.0 g of **5** (0.33 mol) was recrystallized from EtOH (5×) as described, giving pure **5**(1*S*,6*S*) (22.5 g, 54.0% of theory) (GLC column B 160 °C, *k'* = 19.31, 19.54, α = 1.012, *R* = ~1.1). The amide mixture recovered from the mother liquors was brominated and the dibromide was crystallized (4×) from EtOH to give pure **6**(1*R*,6*R*) (32.8 g, 47.4% of theory). Debromination gave pure **5**(1*R*,6*R*) (18.7 g, 44.8%). Each diastereomer of **5** was ≥99.8% (GLC column B as described above). The process could be continued to further maximize use of the chiral auxiliary.

N-Hydroxyethylation of Diastereomerically Pure Amides 4 and 5. The hydroxyethylations of the amides (1 equiv) were

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conducted essentially as previously described[6] by employing LDA (1.5 equiv) in THF, ethylene oxide (2 equiv), and HMPT (2 equiv/Li^+) initially at ≥0 °C and warming to 25 °C overnight. The usual workup procedure gave the N-hydroxyethylated derivatives as oils or semisolids, **8**(1*R**,6*R**,R^*_{Am}): mp 107–117 °C (heptane, contains a few percent original amide); IR ($CHCl_3$) 3500, 1600–1605 cm^{-1}; NMR δ 0.99 (d, 3 H, *J* = 7.1, CH_3CHC), 1.64 (d, 3 H, *J* = 6.9, CH_3CHN), 1.8–2.8 (m's, ~6 H, ring H) 3.5 (m, 2 H, CH_2OH), 5.69 (bs, 2 H, vinyl H), 7.3 (m, 5 H, aryl H); CIMS, *m/e* 288 (P + 1), 184 (P + 1 - $C_6H_5CH{=}CH_2$); data for less soluble diastereomer (oil) as above and in Table II. Data for *N*-hydroxyethylated-(*S*)-α-methylbenzylamide of **3-C** (oil): IR ($CHCl_3$) 3500, 1620 cm^{-1}; NMR δ 0.93 (d, *J* = 6.5 Hz, 3 H, CH_3CHC), 1.64 and 1.65 (d's due to diastereomers, *J* = 6.6 Hz, 3 H, CH_3CHN), 3.5 (m, 2 H, CH_2OH).

(1*R*,6*R*)-(+)- and (1*S*,6*S*)-(−)-6-Methyl-3-cyclohexenylmethanol (9). The crude hydroxyethylated amine **7** (1 equiv) was heated under reflux in THF containing HCl (1.5 equiv) for 6 h. The mixture was concentrated on a flash evaporator to an oil and then water was removed azeotropically with benzene. After removal of the benzene, the resulting oil was dissolved in THF and added dropwise to excess LAH in THF (ice bath). The resulting mixture was heated under reflux for 16 h, excess hydride was decomposed with 1.25 N NaOH, and the organic products were extracted in the usual fashion. The organic layer (Et_2O) was washed with 2 N HCl from which one could subsequently recover the hydroxyethylated α-methylbenzylamine. The alcohols **9** were obtained in 35–40% yields: bp 100–109 °C (21 mm); IR ($CHCl_3$) 3560 cm^{-1}; NMR δ 0.99 (d, *J* = 6.5 Hz, 2 H, CH_3CHC), 1.8–2.4 (m's, 6 H, ring H), 3.57–3.75 (m, ~2 H, CH_2OH), 5.64 (bs, 2 H, vinyl H); CIMS, *m/e* 127 (P + 1), 109 (P + 1 - H_2O); (1*R*,6*R*)-**9**, $[\alpha]^{23}_D$ −75.4° (*c* 6.63, $CHCl_3$); (1*S*,6*S*)-**9**, $[\alpha]^{23}_D$ +70.6° (*c* 6.82, $CHCl_3$). Difficulties were encountered in achieving a reliable rotation because of variable impurities, although the signs of rotation were reproduced in several preparations.

(1*R*,6*R*)-(−)- and (1*S*,6*S*)-(+)-6-Methyl-3-cyclohexenecarboxylic Acid (2). The alcohols **9** were oxidized by using Jones' reagent[18] to the acids **2** in 68–71% yield: bp 70–75 °C (0.02 mm) identical in all respects with the racemic acid: (1*R*,6*R*)-**2**, $[\alpha]^{24}_D$ −84.2° (*c* 24.06, $CHCl_3$); (1*S*,6*S*)-**2**, $[\alpha]^{24}_D$ +76.7° (*c* 9.78, $CHCl_3$). Reconversion of the acids to amides of (*R*)- or (*S*)-α-methylbenzylamine and GLC analysis revealed no detectable racemization or epimerization.

3-[(6-Methyl-3-cyclohexenyl)carbonyl]-4-phenyl-2-oxazolidinone (10-I and 10-II). The 4(*R*)-phenyl-2-oxazolidone[14] (0.36 g, 2.2 mmol) was dissolved in 10 mL of dry THF under nitrogen and cooled to ≤30 °C. The lithio derivative was prepared with butyllithium (0.81 mL of 2.7 M). The acid halide (±)-**2** was prepared from the acid (0.30 g, 2.1 mmol) in anhydrous ether (vide supra) and the reaction mixture was concentrated on a flash evaporator with hexane to remove HCl and $SOCl_2$. The crude acid halide was then dissolved in 1 mL of hexane and added to the lithiated oxazolidone. After 0.25 h, the reaction mixture was worked up with water and ether in the usual manner. The crude produce was purified by column chromatography (10 g of silica gel) eluting with 15% EtOAc–hexane and was obtained as a solid (0.42 g, 71%). In similar fashion, **2**(1*R*,6*R*) was converted to **10-I** on a smaller scale by using excess lithiated oxazolidone for GLC and HPLC comparisons. **10-I**: mp 96–98 °C; IR (CCl_4) 1710, 1790 cm^{-1}; NMR δ 0.97 (3 H, d, *J* = 6.4 Hz, CH_3), 1.6–2.4 (ca. 5 H, m), 3.74 (1 H, dt, *J* = 5.3, 10.4 Hz, CHC=O), 4.25 (1 H, q, *J* = 8.7, 3.6 Hz, OCH), 4.69 (1 H, t, *J* = 8.7 Hz, OCH), 5.48 (1 H, dt, *J* = 8.7, 3.6 Hz, NCH), 5.63 (2 H, s, =CH), 7.2–7.4 (5 H, m, C_6H_5); CIMS, *m/e* 286 (P + 1). Compound **10-II**: mp 101–102 °C; all spectral data as for **10-I** except NMR δ 0.71 (3 H, d, *J* = 6.3 Hz, CH_3) and 4.25 and 4.69; HPLC column A (10% EtOAc–hexane) *k'*(**10-I**) = 5.30, *k'*(**10-II**) = 7.70, α = 1.45. Anal. **10-II** Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.72; H, 6.91; N, 479.

Preparation of Enantiomeric Trimedlure Components, 1-A and 1-C. The addition of HCl to (+)- and (−)-**2** was accomplished in dioxane at 90–95 °C as previously described.[2] The crude mixture of acids **3** was dissolved in EtOH (4 mL/g) containing α-methylbenzylamine (1 equiv). The (*S*)-amine was employed for mixtures of 1*S*,2*S* acid HCl adducts, for example, and four crystallizations produced the 1*S*,2*S*,4*R* (+)-acid **3**, accompanied by varying amounts of residual unsaturated acid (+)-**2**: $[\alpha]^{24}_D$ +29.5° (*c* 3.05, $CHCl_3$). Similarly obtained was 1*R*,2*R*,4*S* (−)-acid **3**: $[\alpha]^{24}_D$ −33.0° (*c* 3.19, $CHCl_3$). Yields were 0.4–0.5 g of impure **3-C** from 3–4 g of acids **2**.

Esterifications of impure **3-C** and of crude HCl adduct mixtures were accomplished by first converting the acids to acid halides with $SOCl_2$/DMF as described above. The acid halides were dissolved in anhydrous Et_2O that contained *t*-BuOH and *N,N*-dimethylaniline (2 equiv each) and heated under reflux overnight. After the usual workup procedure, esters from impure **3-C** were further purified by silica gel chromatography eluting with 2% Et_2O–hexane. In this manner 80–85 mg of (+)- and (−)-**1-C** were obtained from 0.4–0.5 g of **3-C** that were pure (GLC analysis using columns B and C).

Esterifications of mixed acids **3** produced the mixed esters **1** that as racemates constitute commercial trimedlure. These were analyzed with HPLC column A (1% Et_2O–hexane) at 1 mL/min: *k'* = 2.29 (B_1), 3.00 (B_2), 3.46 (A), 3.79 (C), each resolved to base line and obtained preparatively with HPLC column B (2% Et_2O–hexane) at 6 mL/min: *k'* = 2.87 (B_1), 3.90 (B_2), 4.40 (A), 4.70 (C). Recently published GLC data for trimedlure[20] prompts this additional GLC data: GLC column B (110 °C) *k'* = 8.538 (A), 9.231 (C), α = 1.08, *R* = >5 (B_1 and B_2 were not resolved from A); column C (100 °C) *k'* = 6.882 (A), 7.941 (C), 8.118 (B_1), 9.500 (B_2)—a dramatic alteration of elution orders was observed compared to GLC columns coated with isotropic liquids such as Carbowax 20M[20] in that isomers bearing equatorial chlorine were retained longer on the liquid crystal phase. The rotations (GLC purities) of the materials collected by HPLC were as follows: (1*R*,2*R*,5*S*)-(−)-**1-A** (7% of related **1-C**), $[\alpha]^{22}_D$ −4.7° (*c* 6.4, $CHCl_3$); (1*S*,2*S*,5*R*)-(+)-**1-A** (5% of related **1-C**), $[\alpha]^{22}_D$ +6.7° (*c* 6.7, $CHCl_3$); (1*R*,2*R*,5*R*)-(−)-**1-B**$_1$ (~100%), $[\alpha]^{22}_D$ +25.7° (*c* 1.4, $CHCl_3$); (1*R*,2*R*,4*R*)-(−)-**1-B**$_2$ (~100%), $[\alpha]^{22}_D$ −19.2° (*c* 2.9, $CHCl_3$); (1*S*,2*S*,4*S*)-(+)-**1-B**$_2$ (~100%), $[\alpha]^{22}_D$ +27.9° (*c* 3.1, $CHCl_3$); (1*R*,2*R*,4*S*)-(−)-**1-C** (7% of related **1-A**) $[\alpha]^{22}_D$ −20.4° (*c* 14.4, $CHCl_3$); (1*S*,2*S*,4*R*)-(+)-**1-C** (9% of related **1-A**) $[\alpha]^{22}_D$ +19.6° (*c* 8.4, $CHCl_3$). Recrystallized samples of **B**$_2$ melted 66–7 °C (lit.[2] mp 71–2 °C); **C** melted 56–8 °C (lit.[2] mp 57–8 °C).

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Registry No. (±)-**1-A**, 92284-32-7; (−)-**1-A**, 92344-63-3; (+)-**1-A**, 92344-64-4; (±)-**1-B**$_1$, 92314-24-4; (−)-**1-B**$_1$, 92344-65-5; (±)-**1-B**$_2$, 92284-33-8; (−)-**1-B**$_2$, 92344-66-6; (+)-**1-B**$_2$, 92344-67-7; (±)-**1-C**, 92284-34-9; (−)-**1-C**, 92344-68-8; (+)-**1-C**, 92344-69-9; (±)-**2**, 92284-35-0; (+)-**2**, 92344-70-2; (−)-**2**, 92344-71-3; (±)-**2** (acid chloride), 92284-36-1; (±)-**3-A**, 92284-37-2; (±)-**3-A** (acid chloride), 92284-41-8; (±)-**3-B**$_1$, 92284-38-3; (±)-**3-B**$_1$ (acid chloride), 92284-42-9; (±)-**3-B**$_2$, 92284-39-4; (±)-**3-B**$_2$ (acid chloride), 92284-43-0; (±)-**3-C**, 92284-40-7; (−)-**3-C**, 92344-72-4; (−)-**3-C** (*N*-hydroxymethylated-(*S*)-α-methylbenzylamide), 92284-52-1; (+)-**3-C**, 92344-73-5; (+)-**3-C** (*N*-hydroxymethylated-(*S*)-α-methylbenzylamide), 92284-51-0; (±)-**3-C** (acid chloride), 92284-44-1; (1*R*,2*R*,4*S*,S_{AM})-**3-C** (α-methylbenzylamide), 92284-45-2; (1*S*,2*S*,4*R*,S_{AM})-**3-C** (α-methylbenzylamide), 92284-46-3; **5-I**, 92284-47-4; **5-II**, 92344-74-6; **6-I**, 92284-48-5; **6-II**, 92344-75-7; (1*R*,6*R*,R_{AM})-**8**, 92284-49-6; (1*R*,6*R*,R_{AM})-**8** (amino ester), 92284-53-2; (1*R*,2*R*,S_{AM})-**8**, 92344-76-8; (1*R*,2*R*,S_{AM})-**8** (amino ester), 92344-80-4; (−)-**9**, 92344-77-9; (+)-**9**, 92344-78-0; **10** (isomer 1), 92284-50-9; **10** (isomer 2), 92344-79-1; (*R*)-α-methylbenzylamine, 3886-69-9; (*S*)-α-methylbenzylamine, 2627-86-3; ethylene oxide, 75-21-8; 4-(*R*)-phenyl-2-oxazolidone, 7480-32-2.

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