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COMPARATIVE GAS CHROMATOGRAPHIC SEPARATION OF SIMPLE DIASTEREOMERIC AMIDES AND CARBAMATES USING ISOTROPIC AND CHOLESTERIC LIQUID CRYSTAL PHASES

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SUMMARY

A series of diasteromeric amides and carbamates have been prepared, and comparisons are made between the gas–liquid chromatographic separations obtained with several stationary phases in capillary columns. These are: SE-54 as a non-polar phase, polyethylene glycol polar phase, and a liquid crystal phase, cholesteryl *para*-chlorocinnamate (CpCC). For the compounds studied, the CpCC column provided greater separation factors than the other two columns. Since the elution order of pairs of diasteromers was the same on all three columns, the enhanced separation with CpCC suggests greater sensitivity of the ordered mesophase to the shape of the solution conformers of solute molecules.

INTRODUCTION

Application of liquid crystals as stationary phases for the gas–liquid chromatographic (GLC) separation of insect sex pheromones and related aliphatics has generally resulted in resolution of these compounds superior to that achieved on polar and non-polar isotropic phases[1–3]. The ordered character of the liquid phase is eminently suited to discriminating these substrates, many of which are aliphatics bearing one or two olefinic links and a chain-terminating oxygenated functionality. An occasional structure has a methyl branch. These materials tend to occur in nature as complicated mixtures whose exact composition is crucial for eliciting insect sexual behavior[4].

We have also found that capillary columns that have been coated with the liquid crystal, cholesteryl cinnamate, were particularly valuable in connection with the synthesis of a series of diasteromeric amides[5]. Because of current interest in asymmetric organic synthesis[6–9], rapid chromatographic analysis of diastereomeric intermediates to determine configurational purity (and absolute configuration) is also important in chromatography. We wish to extend our observations of cinnamate ester liquid crystal columns to commonly employed diastereomeric derivatives, and describe here the preparation, configurational analysis, and chromatographic properties of a series of diastereomeric pairs of amides and carbamates. Comparisons are

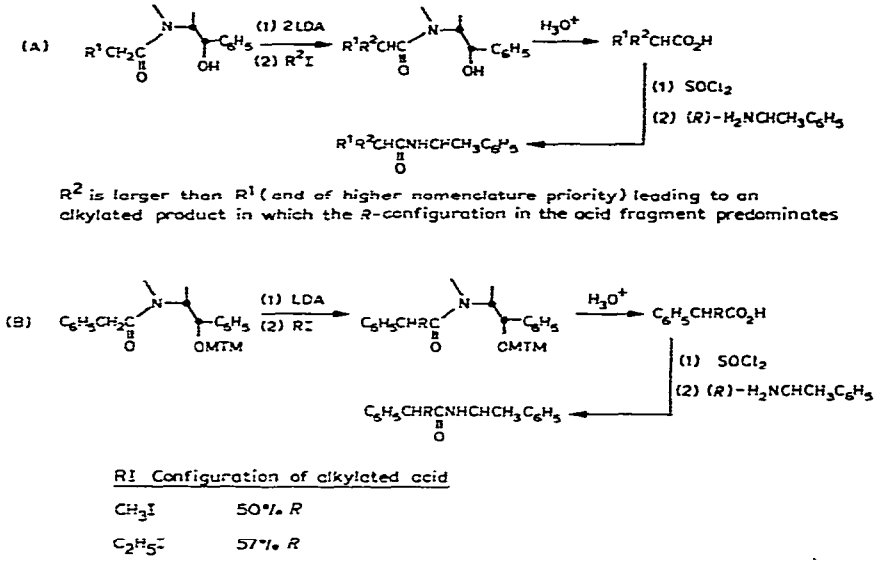

Fig. 1. Syntheses of configurationally biased amides I–XIII from (1)-ephedine. LDA = Lithium diisopropylamide, MTM = methyl thiomethyl.

made between the separations obtained with the following stationary phases: SE-54 as a non-polar phase, Carbowax 20M as a polar phase, and cholesteryl *para*-chlorocinnamate (CpCC) as a typical cholesteric liquid crystal phase[10]*.

EXPERIMENTAL

Capillary columns

The SE-54 fused-silica column was 15 m × 0.25 mm I.D. and was purchased from J. W. Scientific (Rancho Cordoba, CA, U.S.A.). The Carbowax 20M fused-silica column was 15 m × 0.20 mm I.D. and was obtained from Hewlett-Packard (Avondale, PA, U.S.A.). The CpCC columns were 20 m × 0.20 mm I.D. and were prepared in our laboratories from etched soft glass coated by the static method. Column A was prepared with a 0.25% (w/v) CpCC in methylene chloride, and column B was prepared with 0.10% (w/v) solution. Each column was conditioned for 2 h at 200°C prior to use.

All work was done on a Varian 3700 or Varian 1400 instrument with a user-designed all-glass capillary system. The carrier was helium and the linear flow velocity was 18 cm/sec. The inlet split ratio was *ca.* 100:1 and detector make-up flow was 30 ml of nitrogen/min.

The amides I–XI (Table I) were prepared as follows. Amides derived from (1)-ephedrine were alkylated in the manner recently described for (S)-prolinol and (1)-ephedrine (Fig. 1A)[5,11,12]. The resulting amides were hydrolyzed producing acids of known configurational bias (see Appendix). The acids then were converted via acid

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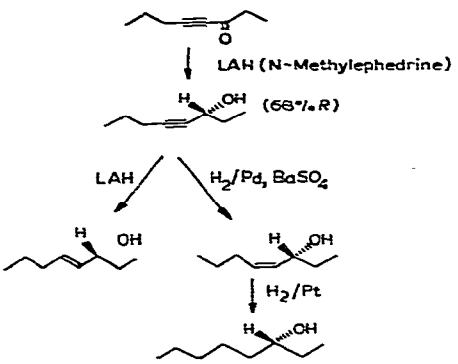


Fig. 2. Synthesis of the *R*-enriched carbinols for carbamates XV–XVIII.

halides to amides of (*R*)-α-methylbenzylamine*.

Alkylation of phenylacetamides of chiral β-aminoalcohols such as (1)-ephedrine (Fig. 1B) have not been discussed, therefore, the assignment of configurations for amides XII and XIII (Table I) was based on high-performance liquid chromatography (HPLC) elution order[13] and ^{1}H nuclear magnetic resonance (NMR) analysis of the purified diastereomers (Table II).

The urethanes XIV–XXI (Table I) were prepared from the appropriate secondary carbinol by sequential treatment with phosgene-triethylamine in ether, and (*R*)-α-methylbenzylamine-triethylamine. Samples of (*R*)- and (*S*)-2-octanols (Aldrich) were employed to prepare XIV. The related 3-octanols that were used to make carbamates XV–XVIII were synthesized as shown in Fig. 2. The 5-octyn-3-one was prepared by standard methods from 1-pentyne and propionaldehyde. Reduction of that ketone with lithium aluminum hydride (LAH) modified with (1)-N-methylephedrine produced 5-octyn-3-ol with an enantiomeric excess of 36% R (ref. 14). The ratio of enantiomers was determined by esterification with (*S*)-α-methoxy trifluoromethylphenyl acetyl chloride (MTPA-chloride)[15,16]. Samples of the *R*-enriched alkynol were reduced with $Ni(OAc)_2/NaBH_4$ (ref. 17) to give the predominantly *cis*-alkenol and with LAH to give the *trans*-alkenol. Finally, hydrogenation of the alkenols over Pt in propionic acid yielded the *R*-enriched saturated 3-octanol. Carbamate XIX was prepared as a mixture of four diastereomers from commercial 4-methyl-3-heptanol. The phenyl carbamates XX and XXI were synthesized from the racemic carbinols, and configuration assignment was based on HPLC elution order and, in the case of XXI, ^{1}H NMR evaluation of the purified diastereomers[13].

RESULTS AND DISCUSSION

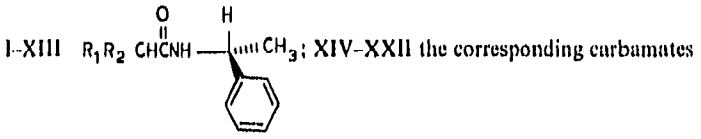
Investigations by Dewar and Schroeder[18–20] using packed columns and various azoxybiphenyl derivatives for stationary liquid phases indicated the utility of ordered phases for the separation of simple benzenoid derivatives. Their observations

* Commercial (*R*)-α-methylbenzylamine (Aldrich, Milwaukee, WI, U.S.A.) was ≥92% enantiomeric excess (ee) as judged by the diastereomeric amides formed with (*S*)-MTPA-chloride, and was employed without further purification.

TABLE I

GAS-LIQUID CHROMATOGRAPHIC DATA FOR DIASTEREOMERIC AMIDES AND CARBAMATES

Column temperatures were as follows for A:SE-54; 170°C for I-XI; 190°C for XII and XIII; Carbowax 20M; 160°C for I-XI; 180°C for XII and XIII; CpCC column A; 145°C, Column temperatures were as follows for B: SE-54; 200°C for XIV-XIX; 210°C for XX and XXI; Carbowax 20M; 170°C for XIV-XIX; 190°C for XX and XXI; CpCC column B; 145°C for XIV and XV; 155°C for XIX; 160°C for XVI-XVIII, XX, and XXI.



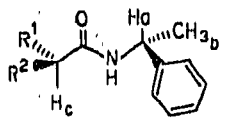
Compound; R_1,R_2	*SE-54*			*Carbowax 20M*			*CpCC (column A)*		
	k' (R,R)	*k'(S,R)*	α	*k'(R,R)*	*k'(S,R)*	α	*k'(R,R)*	*k'(S,R)*	α
I; CH_3, C_2H_5	3.03	3.09	1.021	4.36	4.44	1.018	6.93	7.18	1.036
II; I-N-methyl	4.95	4.95	1.000				3.05	3.09	1.013
III; CH_3, *iso*-C_3H_7	3.91	4.06	1.040	4.64	4.86	1.046	7.76	8.26	1.064
IV; CH_3, *n*-C_3H_7	4.18	4.44	1.060	5.07	5.36	1.056	8.50	9.13	1.071
V; IV-N-methyl	6.82	6.75	1.019				4.18	5.17	1.059
VI; CH_3, *n*-C_4H_9	5.97	6.31	1.058	6.79	7.25	1.068	12.95	14.24	1.100
VII; C_2H_5, *iso*-C_3H_7	5.06	5.16	1.018	4.39	4.53	1.033	10.18	10.63	1.044
VIII; C_2H_5, *n*-C_3H_7	5.50	5.68	1.034	4.93	5.14	1.044	11.50	12.08	1.050
IX; C_2H_5, *n*-C_4H_9	7.81	8.18	1.048	6.50	6.86	1.055	17.11	18.21	1.065
X; *n*-C_4H_9, *n*-C_5H_{11}							7.47	7.60	1.017
XI; *n*-C_5H_{11}, *n*-C_6H_{13}	5.47	5.47	1.000				15.62	15.79	1.011
XII; CH_3, C_6H_5	6.76	7.35	1.088	6.93	7.93	1.144	7.00	8.00	1.143
XIII; C_2H_5, C_6H_5	8.47	9.29	1.097	7.57	8.64	1.141	8.70	9.90	1.138
XIV; CH_3, *n*-C_6H_{13}	4.13	4.33	1.048	4.65	4.96	1.066	16.36	17.86	1.09
XV; C_2H_5, *n*-C_5H_{11}	3.87	4.03	1.043	2.00	2.08	1.039	10.71	11.5	1.07
XVI; C_2H_5, *n*-$C_3H_7C{\equiv}C$-	4.63	4.80	1.036	8.92	9.23	1.037	10.21	10.57	1.04
XVII; C_2H_5, *n*-$C_3H_7CH{=}CH$-(*Z*)	3.60	3.73	1.037	4.12	4.38	1.065	6.28	6.64	1.06
XVIII; C_2H_5, *n*-$C_3H_7CH{=}CH$-(*E*)	3.93	4.07	1.034	5.08	5.27	1.038	7.82	8.18	1.05

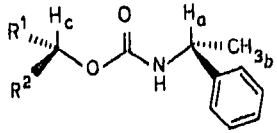
XIX; C_2H_5, n-$C_3H_7CH(CH_3)$–	3.40	3.50	1.029	(3.31,	3.46	3.58)	1.047 1.033	(12.52, 13.20	12.99 13.50)	1.038 1.017 1.027
XX; CH_3, C_6H_5	4.43	4.57	1.030	7.96		8.31	1.044	20.10	21.8	1.08
XXI, CF_3, C_6H_5	2.73	2.67	1.025	4.31		4.31	1.000	8.89	8.43	1.07

TABLE II

^{1}H NMR DATA FOR PHENYL SUBSTITUTED ACID AND CARBINOL DERIVATIVES

^{1}H NMR data were obtained in dilute C^2HCl_3 solution with a Nicolet 300 MHz spectrometer. Shifts are reported in ppm downfield from $(CH_3)_4Si$. Values of $\Delta\delta$ are obtained from δ_1–δ_2. HPLC collections were made with a 250 mm × 18 mm I.D. column of Biosil-A, 2–10 μm, employing hexane–ethyl acetate (9:1) at a flow-rate of 9.9 ml/min. Carbamate XX was not resolved by HPLC and collections of material during peak elution were employed to establish relative rates of elution of the diastereomers on LC *versus* GLC.





Compound	*Elution order***	R^1	R^2	M_p(°C)	δ_a	δ_b	δ_c	$\Delta\delta_a$	$\Delta\delta_b$	$\Delta\delta_c$
XII	1 (*S,R*)*	C_6H_5	CH_3	132–134	5.09	1.35	3.53			
	2 (*R,R*)*	CH_3	C_6H_5	111–114	5.08	1.39	3.57	0.01	−0.04	−0.04
XIII	1 (*S,R*)	C_6H_5	C_2H_5	116–119	5.09	1.35	3.21			
	2 (*R,R*)	C_2H_5	C_6H_5	66–68	5.09	1.41	3.24	0.00	−0.06	−0.03
XXI	1 (*R,R*)	C_6H_5	CF_3	73–74	4.84	1.54	6.07			
	2 (*S,R*)	CF_3	C_6H_5	132–135	4.82	1.48	6.05	0.02	0.06	0.02

* δ $C_6H_5CHCH_3C{=}O$ for XII-1 = 1.51; XII-2 = 1.51.

** The first configuration designator represents the acid residue. The second designator represents the (unvaried) chiral auxiliary.

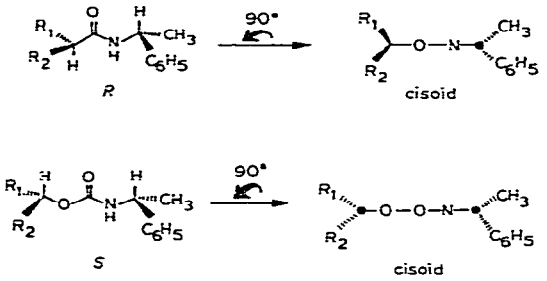


Fig. 3. Solution conformers of diastereomeric amides and carbamates[13]. R_1 and R_2 are saturated alkyl groups with R_2 longer than R_1.

suggested that the more rod-shaped molecule of a set of isomeric molecules would be preferentially dissolved (partitioned) by the ordered phase. This seemed consistent with the separations of olefins[1–3]; the *cis*-isomers which are "kinked" tend to elute first, and the separation for *cis–trans* pairs increases as the site of the double bond is shifted toward the middle of the chain.

Lochmüller and Souter[21] have investigated optically active liquid crystal phases for the separation of enantiomers. Although this polyamide ("ureide") phase provided excellent separation of chiral amides, the low mesophase transition temperature has precluded more extensive use of the phase. More recently Frank *et al.*[22] have described an optically active isotropic, hence temperature-stable, phase that provided excellent separations of enantiomeric amino acid derivatives. The diastereomeric pairs listed in Tables I and II were, in fact, analyzed with a chirasil-val column (25 m × 0.20 mm I.D.) obtained from Applied Science Labs., and the separations were always less than those obtained on CpCC columns. The performance of the chirasil-val column was intermediate to that of the two columns with isotropic phases in most cases. Thus we were led to make a comparison of the CpCC column with conventional isotropic phases, namely SE-54 and Carbowax 20M with a view to examining elution orders as well as relative separations.

The chromatographic elution orders of diasteromeric amides, carbamates, and esters have been discussed in terms of solution conformations such as those depicted in Fig. 3[23–29]. Briefly, the carbonyl-containing functional group serves to create a plane between the asymmetric centers, and these centers extend alkyl (aryl) groups to either side of that plane. Those diastereomers which feature the largest group on each asymmetric center to the same side of the plane have been referred to as *cisoid* in Fig. 3. An explanation based on a combination of steric bulk and hydrophobicity has been advanced to explain HPLC elution orders for diastereomeric carbamates[13], namely the *cisoid* diastereomer of a carbamate ($S^*_{alcohol}$, R^*_{amine}) can make easier approach to the stationary phase doing so from that planar face having the smaller alkyl (aryl) residues exposed. This model is tempered by the degree of repulsion (hydropobicity) experienced by these substituents, and in extreme cases the usual elution order is reversed. This situation for amides is quite analogous; asymmetric centers are separated by one less atom and *cisoid* corresponds to an R^*R^* diastereomer. Although substantive criticism has been offered by way of demonstrated exceptions[30,31], for simple (otherwise unfunctionalized) substrates such as ours the model described[13] was quite adequate and elution orders followed the proposed model for HPLC elution.

The elution orders were exactly reversed in gas chromatography from that in HPLC with the *transoid* diastereomers being retained longest. More to the point, elution orders were the same for all three liquid phases indication that the mechanisms of separation for isotropic and ordered phases were perhaps quite similar. Methylation of the amide nitrogen (see II *vs.* I, and V *vs.* IV in Table I) produced a dramatic reduction in separations (α) on all GLC columns. A similar reduction in HPLC α was observed for N-methylated (as opposed to N–H) carbamates for which a higher content of the 180° rotamer about the N–C bond was suggested[13]. Such a rotamer would contribute in an opposite sense to those factors crucial to α in HPLC since the substituents on the amine asymmetric center would now be deployed on the alternative sides of the carbonyl. If one takes GLC resolutions of diastereomers to be a matter of relative solution energies of preferred solution conformations, then the N-methylated derivatives would on the same grounds as just described for HPLC separations become (solution) energetically more equivalent. Although capacity factors (k') for II and V (Table I) are greater than for their unmethylated counterparts on SE-54, they are dramatically reduced by a factor of >2 on the CpCC column, *i.e.*, solution energies have been greatly reduced for both pairs of diastereomers. Hydrogen bonding involving the N–H of amides and carbamates is an obvious suspect cause for larger k' values, but further investigation would be required to determine the existence of specific solute–solvent interactions involving the relatively apolar cholesterol ester solvent.

The trifluoromethyl substituted diastereomeric carbamates XXI were both eluted much more rapidly on all GLC columns than their methyl counterparts. The elution orders were the same with the *cisoid* isomer being retained more. This striking inversion of elution order on substituting CF_3 for CH_3 was first noted in reference to HPLC resolution[13] and was ascribed to the considerable hydrophobicity of a CF_3 group. Although the group is small, repulsion from Si-OH of the stationary phase causes both the observed inversion of elution order and smaller k' values of both diastereomers. The same observation is made with GLC elution order/k' values, and the phenomenon here would therefore need to be considered in terms of solution energetics as part of a more thorough investigation.

As part of this study we examined the diastereomers of the carbamate of 4-methyl-3-heptanol. This alcohol is the major component of the aggregation pheromone of the large European elm bark beetle, *Scolytus scolytus* (F.)[32,33], and is a minor component of the pheromonal complex of the small European elm bark beetle, *Scolytus multistriatus* (Marsham)[34]. Analyses of the MTPA esters[15,16] of the commercial alcohol had been performed on a Carbowax 20M glass column to provide separation into three peaks. (The (−)-*threo* and (−)-*erythro* derivatives of (−)-MTPA coincided. The four esters were only separated into two peaks (*ca.* 1:1 by CpCC. The carbamate XIX, however, was separated albeit incompletely into the four diastereomers by the CpCC column (Fig. 4).

In conclusion we can summarize the data in the following manner. For the compounds studied, the CpCC column provided the greatest separation factors Tables I and II). Since the elution order of pairs of diastereomers was the same on all three columns, the previously described models seem applicable to this cholesteric phase although the enhanced α with CpCC suggests greater sensitivity of this phase to the shape of the solution conformers of substrate molecules.

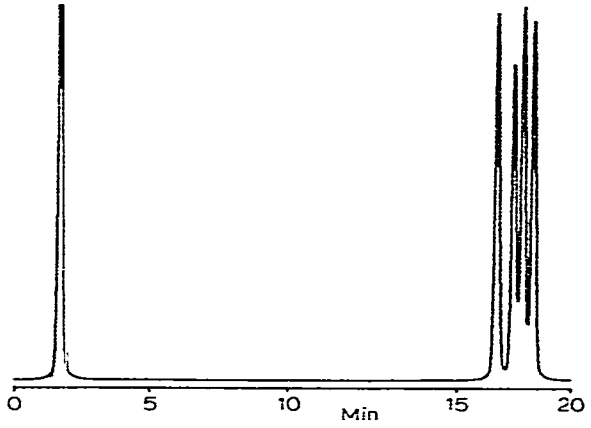


Fig. 4. Separation of diastereomeric carbamates of 4-methyl 3-heptanol, XIX on 15 m × 0.02 I.D. CpCC (column B) at 155°C, carrier gas (helium) at 18 cm/sec.

One should note also that the operating temperatures for several separations reported here were well above the meso-phase transition for CpCC. Thus the reported α values are not maximal. By reducing film thickness of liquid crystal phases, the chromatographer has a variable that permits lower operating temperatures in order to further enhance a given separation[32,33].

APPENDIX

Amides of (*S*)-prolinol and (1)-ephedrine are deprotonated by non-nucleophilic bases such as lithium diisopropylamide to produce enolate ions[5,11,12]. The example in Fig. 1A depicts the enolate (presumably *Z*, ref. 12) derived from (1)-ephedrine propionamide after reaction with more than 2 equivalents of the base. Although the detailed structure of these intermediate anions is still under investigation[12], the observation made by several independent laboratories is that the new center is created in this instance with strong *R* preference. When the hydroxyl group of the amino-alcohol is etherified bond formation between enolate and alkyl halide occurs mainly from the other face of the double bond and, for a reaction involving a propionamide with ethyl iodide, results in a strong *S* bias in the new center. Using this reaction and its predictable stereochemical consequences we were able to obtain products of known configurational bias.

In order to obtain amides XII and XIII, (1)-ephedrine was treated with phenylacetyl chloride. The resulting phenylacetamide was then allowed to react with (1) NaH, and (2) methyl thiomethyl chloride in order to convert the ephedrine hydroxyl

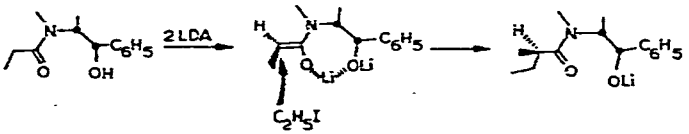


Fig. A1.

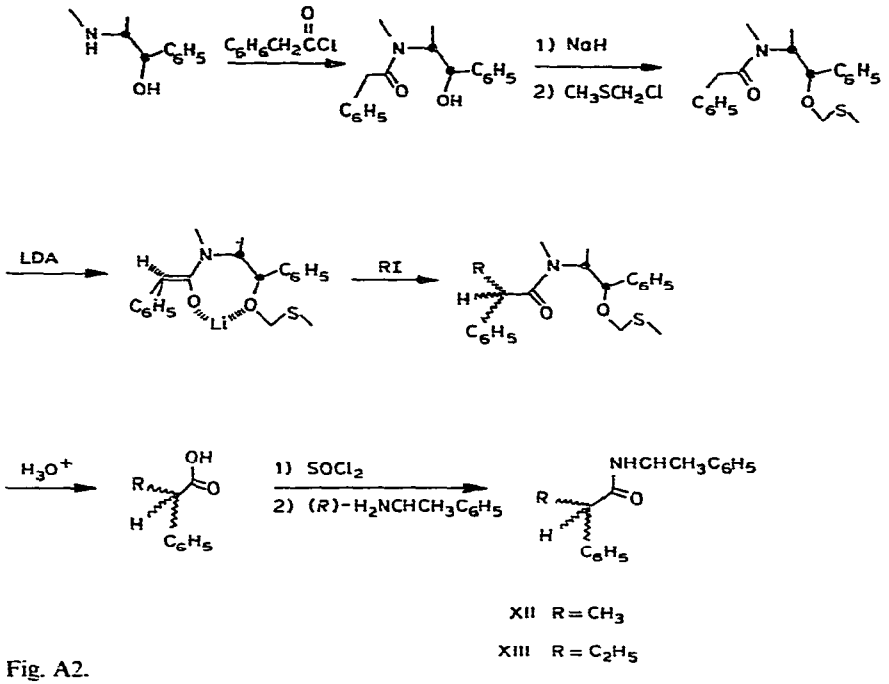


Fig. A2.

group to a methyl thiomethyl ether (Fig. A2). This amide then served as the substrate for production of XII and XIII. The deprotonation by lithium diisopropylamide was followed by reaction either with methyliodide (→ → XII) or ethyliodide (→ → XIII). The methylation product was a 1:1 ratio of diastereomers while ethylation produced a 2:1 ratio that was shown subsequently to be *R*-predominant. As was the case for amides I–XI, the alkylated ephedrine amides were hydrolyzed (1 *N* HCl, 90°, 2–4 h), and the resulting acids where then converted to amides of (*R*)-α-methylbenzylamine. The diastereomer ratios obtained were independent of the temperature employed for deprotonation; alkylation was conducted at −78°C.

The ^{1}H NMR data in Table I of the text are consistent with the relative shift data presented for closely analogous compounds[13]. Briefly, the principal solution conformers of amides and carbamates such as those described are as indicated by the structures associated with Table I. Aryl groups on the acid-based center of asymmetry in opposition to a methyl group on the other center will shield that methyl group. Thus for XII, the CH_3 signal (absorption b) of the first-eluted (HPLC) diastereomer is shielded by 0.04 ppm relative to that of the later eluting diastereomer. A shift difference of 0.06 ppm is observed for the XIII pair. These observations in conjunction with HPLC elution order[13] and mechanistic rationalization for XIII (as per amides I–XI) led to our configuration assignments.

For urethans, or carbamates, XIV–XXI the assignment of configuration follows from the many asymmetric reductions of conjugated alkynones provided in the literature (*e.g.*, ref. 14); however, the configuration assignments for the phenyl carbamates XX and XXI were based on expected HPLC elution[13]. In addition, the ^{1}H NMR data for the purified diastereomers of XXI (Table I) were rationalized as they

had been for the phenyl-substituted amides XII and XIII. The second-eluted (HPLC) diastereomer would be expected to have the *S,R*-configuration[13] and is the diastereomer in which the CH_3 signal "b" is shifted upfield (by 0.06 ppm) by virtue of opposition to a phenyl substituent as R_1.

All new compounds were characterized by ^1H NMR and mass spectrometry.

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