(quantitatively by TLC), which was treated at 0–5 °C during 0.5 h with 1.05 equiv of recrystallized *N*-bromoacetamide (NBA) to afford essentially pure bromo ketal **12** after neutralization with NH_3 gas, solvent evaporation, and workup with $CHCl_3$–H_2O. Bromo ketal **12**, mp 182.5–184 °C (EtOAc), could be readily isolated in 88% yield but was most efficiently deketalized in 6 volumes of 5:1 88% HCO_2H–H_2O (25 °C, 1 h) followed by $CHCl_3$–aqueous $NaHCO_3$ workup to afford **13** (mp 203.5–206.5 °C (DMF–EtOAc); IR ($CHCl_3$) 1717 (C=O), 1665 (NCHO) cm^{-1}) in 90% yield from **10**. Bromo ketone **13** underwent Grewe-type cyclization to (±)-1-bromo-*N*-formylnordihydrothebainone (**17**), mp 229.5–231.5 °C (DMF–H_2O), in 60% isolated yield when treated in a screw-capped, high-density polyethylene bottle with 14% NH_4F·HF in dry CF_3SO_3H (0 °C, under argon for 72–96 h until **13** had essentially disappeared by TLC).[23] Also, isomerization of **13** occurred to give (TLC) the α,β-unsaturated bromo ketone **16**.[24] Pure **16** afforded (TLC) only traces of morphinan **17** and β,γ-unsaturated ketone **13** under the conditions used to cyclize **13** to **17**. Treatment of pure morphinan **17** under these conditions gave no **13** or **16** (TLC); apparently the acid-catalyzed equilibrium of **13** and **16** lies nearly exclusively toward the side of the latter, which undergoes little, if any, morphinan cyclization under these conditions.[14] Refluxing isolated **17** in 10:1 MeOH–37% aqueous HCl for 18 h afforded (±)-1-bromonordihydrothebainone (**18**), mp 220–223 °C, which was easily isolated in 92% yield by workup with NH_3–H_2O–2-propanol. (±)-Dihydrothebainone (**19**), mp 173–175 °C (lit.[4] mp 176 °C), was obtained directly and quantitatively from **17** by hydrolysis as above, evaporation to dryness, and hydrogenation[15,16] of the residue in 2 N AcOH containing 50 mg of 10% Pd/C, 0.3 mL of 37% HCHO, and 5 mmol of NaOAc per mmol of **17**, followed by workup with $CHCl_3$–aqueous NH_3. Bromination (1.1 mol of Br_2, 25 °C, 2 h) of an AcOH solution of the dry residue from hydrolysis of **17**, evaporation, treatment of the residue with $CHCl_3$–1 N NaOH[16] and hydrogenation as above without addition of HCHO afforded an 80% yield (from **17**) of (±)-nordihydrocodeinone (**21**), that was readily isolated (2-propanol, 1.1 equiv of 37% aqueous HCl) as **21**·HCl·$0.5H_2O$, mp 292–295 °C dec; anhydrous **21** base, mp 136.5–138 °C ($PhCH_3$). This appears to be the first example of closure of the oxide bridge in the basic N-nor series and is of potential interest in the synthesis of narcotic antagonists. When **17** was treated as in the preparation of **21** and 0.3 mL of 37% HCHO/mmol of **17** was added to the hydrogenation medium, (±)-dihydrocodeinone (**22**), mp 158–160 °C (lit.[25] mp 163 °C), was readily isolated as **22**·TsOH, mp 248–251 °C, in 79% yield from **17**.

This straightforward total synthesis of (±)-dihydrothebainone (**19**), (±)-nordihydrocodeinone (**21**), and (±)-dihydrocodeinone (**22**) in 37, 30, and 29% overall yields, respectively, from readily available 3-methoxyphenethylamine (**4**) requires isolation of only six intermediates; these are directly obtained sufficiently pure for further transformation. In view of these results, the high-yielding conversion[16] of (–)-**19** to (–)-thebaine (**3**) and (–)-codeine (**1**) discussed above and the facile O-demethylation[26a] of the latter to (–)-morphine (**2**), a practical total synthesis of these alkaloids (and the thebaine-based drugs) appears to be in hand.[27]

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Registry No. **4**, 2039-67-0; **5**, 1131-94-8; **6**, 74007-21-9; (±)-**7**, 23180-27-0; (*R*)-**7**, 74035-73-7; (*S*)-**7**, 74035-74-8; (±)-**8**, 23180-28-1; (±)-**10**, 58780-17-9; (±)-**11**, 74007-22-0; (±)-**12**, 74007-23-1; (±)-**13**, 74007-24-2; (±)-**14**, 74007-25-3; (±)-**14**·TSOH, 74007-26-4; **15**, 54186-35-5; **16**, 54186-36-6; (±)-**17**, 74007-27-5; (±)-**18**, 74007-28-6; (±)-**19**, 15172-51-7; (±)-**21**, 74007-29-7; (±)-**21**·HCl, 74007-30-0; (±)-**22**, 74035-75-9; (±)-**22**·TSOH, 74035-76-0.

(23) A lower melting form of **17**, mp ~140 °C, which gave the higher melting form when boiled briefly in EtOAc, was occasionally obtained. It has been shown in this study that the carbamate function can be used instead of the *N*-formyl substitution in this step and others; however, the *N*-formyl derivatives are preferred since the amide function is readily cleaved by mild acid hydrolysis and the formyl derivatives usually crystallize more readily than the corresponding carbamates.

(24) Similar ketalization of **8** with 2.5% (v/v) TFA in MeOH (25 °C, 2 h), bromination with 1.05 equiv of NBA (0 °C), evaporation, deketalization by warming the residue in 5 volumes of H_2O, and addition of 5 volumes of acetone and concentrated aqueous NH_3 to pH 9–9.5 afforded labile amine **14** (69%), mp 160–164 °C dec (**14**·TsOH, mp 194–195.5 °C dec), containing minor amounts of **15**. Isomerization of this crude **14** with 48% HBr (25 °C, 48 h), under conditions similar to those[20] used for preparation of the debromo derivative of **15** from **8**, gave **15** (70%), mp 224.5–226 °C dec (lit.[13] mp 204–209 °C). Formylation of crude **14** and pure **15** (PhOCHO, refluxing $CHCl_3$) afforded **13** (65%) and **16** (87%), mp 205.5–207 °C, IR ($CHCl_3$) 1668 (C=O and NCHO) cm^{-1} (lit.[13] foam), respectively. Brief treatment of **16** with base (e.g., NaOMe in MeOH) resulted predominately in isomerization to **13**.

(25) Goto, K.; Takubo, K.; Mitsui, S. *Justus Liebigs Ann. Chem.* **1931**, *489*, 86.

(26) (a) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164. (b) For application of this method in the 14-hydroxy series, see: Iijima, I.; Minamikawa, J.; Jacobson, A. E.; Brossi, A.; Rice, K. C. *J. Med. Chem.* **1978**, *21*, 398.

(27) Optical resolution of (±)-**7** and application of the reaction sequence described here to the *R* enantiomer of **7** will afford entry into the natural morphine series. This resolution has readily been accomplished to give (+)-**7**, mp 217.5–219 °C, $[\alpha]^{23}_D$ +37.8° (*c* 0.25, DMF), and (–)-**7**, mp 218–219.5 °C, $[\alpha]^{23}_D$ –38.1° (*c* 0.25, DMF). The optical purity of these was demonstrated as for the 7-hydroxy derivatives[17] (norreticulines) by NMR analysis of the urea derivatives formed with (*S*)-(–)-α-methylbenzyl isocyanate. The chemical shifts of the methyl doublets ($\Delta\delta$ = 0.25) of the ureas from (*R*)-(+)- and (*S*)-(–)-norreticuline were δ 1.26 and 1.01[17] and for those of (+)- and (–)-**7**, δ 1.28 and 1.04 ($\Delta\delta$ = 0.24), respectively. The absolute configuration of (+)- and (–)-**7** can tentatively be assigned as *R* and *S*, respectively, if one assumes the compounds with corresponding chemical shifts have the same absolute configuration. Transformation of the *R* enantiomer of **7** to (–)-dihydrothebainone [(–)-**19**] is now in progress and will be reported in due course. Similarly, the *S* enantiomer affords entry into the unnatural morphine series, some members of which are of considerable importance as neuropharmacological research tools. See, for example, ref 26b and references cited therein.

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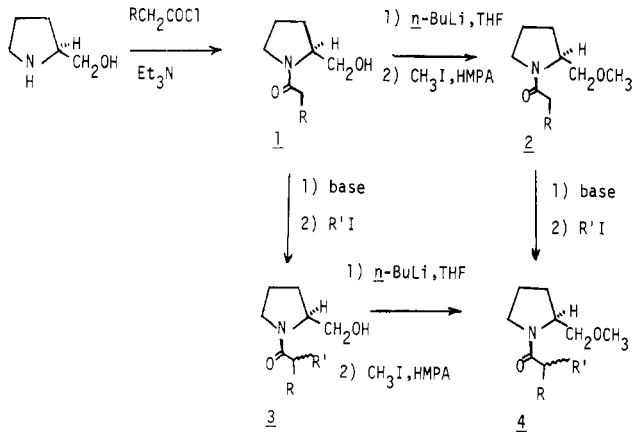
Asymmetric Alkylation of Amide Anions. Product Analysis by GLC Using Cholesteryl Cinnamate, a Liquid Crystal Phase

Summary: Chiral amides derived from (*S*)-(–)-prolinol and its methyl ether were metalated and alkylated to afford α-alkyl amides in 12–82% ee. The configuration induced by (*S*)-(–)-prolinol, as the chiral auxiliary reagent, was opposite to that induced by its methyl ether. Diastereomer compositions of the alkylated products were readily, in fact, uniquely, assessed by GLC by using a capillary column coated with cholesteryl cinnamate.

Scheme I



	R	R'
1a	n-C_8H_{17}	CH_3
1b	CH_3	n-C_8H_{17}
2	n-C_8H_{17}	CH_3
3a	n-C_8H_{17}	CH_3
3b	n-C_8H_{17}	C_2H_5
3c	n-C_8H_{17}	n-C_4H_9
4a	n-C_8H_{17}	C_2H_5

Sir: Highly successful syntheses of chiral α-alkyl alkanoic acids have been accomplished by metalation–alkylation of chiral oxazolines[1] (45–85% ee) and amides of ephedrine[2] (80–100% ee). The pioneering efforts of Meyers have demonstrated the utility of employing chiral nucleophiles that impose their asymmetry in the transition state for alkylation by chelation of the nucleophilic carbon with an additional heteroatom of the chiral auxiliary reagent. Related reactions of metalloenamines[3] and chiral metalated hydrazones[4] that produce chiral α-alkylated aldehydes and ketones have in common with the alkylation of oxazolines metalated azaenolate intermediates which predispose one face of an azaenolate double bond to reaction with the electrophile.[3d,4] Asymmetric induction was highest in these systems when the additional substituent necessary for chelation was methoxyl, while the oxyanion (formed from a hydroxyl substituent) was much less effective. Alkylation of α-C-metalated amides of (−)-ephedrine, however, proceeded with greater asymmetric induction with a hydroxyl substituent than with a methoxyl substituent.[2] We communicate our results of the alkylations of amides of (*S*)-(−)-prolinol and its methyl ether which we feel complement and amplify the results obtained with amides of ephedrine. We also demonstrate the utility of liquid crystal cap columns for analysis of product diastereomer composition.

Table I. Alkylation of Amides

compd	conditions[a]	product	% ee[b]	config
1a	$Li(iPr)_2N$, Et_2O, −100 °C, CH_3I	3a	56	*S*
1a	*t*-BuLi, HMPA/THF, −60 °C, CH_3I	3a	54	*S*
1a	*t*-BuLi, THF, −10 °C, CH_3I	3a	66	*S*
1a	*t*-BuLi, THF, −100 °C, CH_3I	3a	72	*S*
1a	*t*-BuLi, THF, −120 °C, CH_3I	3a	80[c]	*S*
1a	*t*-BuLi, MgI_2,[d] THF, 25 °C, CH_3I	3a	50	*S*
1a	*t*-BuLi, CuI, THF, −100 °C, CH_3I	3a	62	*S*
1a	*t*-BuLi, CuI·$P(OMe)_3$,[e] THF, −100 °C, CH_3I	3a	70	*S*
1b	*t*-BuLi, THF, −100 °C, n-$C_8H_{17}I$	3a	66	*R*
2	$Li(iPr)_2N$, Et_2O, −100 °C, CH_3I	4a	12	*R*
2	*t*-BuLi, THF, −100 °C, CH_3I	4a	82	*R*
1a	*t*-BuLi, THF, −100 °C, C_2H_5I	3b	68	*S*
1a	*t*-BuLi, THF, −100 °C, n-C_4H_9I	3c	52	*S*
2	*t*-BuLi, THF, −100 °C, C_2H_5I	4b	82	*R*
5[e]	*t*-BuLi, THF, −100 °C, CH_3I	6[f]	62	*S*
7[e]	*t*-BuLi, THF, −100 °C, CH_3I	8[f]	68	*R*

[a] Temperatures indicated refer to the alkylation step; anions were allowed to attain 25 °C prior to alkylation. [b] Satisfactory spectral data (IR, ^1H NMR, ^{13}C NMR, mass spectra) were obtained for all alkylation products. [c] (*S*)-(+)-2-Methyldecanoic acid was obtained after hydrolysis (concentrated HCl/hexane, reflux, 8 h) in 63% yield: bp 105 °C (30 mm); $[\alpha]^{23}_D$ +9.4° (*c* 10.4, $CHCl_3$); mass spectrum, *m/e*, 212 (M^+); combustion analysis. A byproduct of the alkylation was *tert*-butyl *n*-nonyl ketone (30%). [d] Ethereal MgI_2 was prepared according to Summerbell and Umhoefer (*J. Am. Chem. Soc.* **1939**, *61*, 3016) and used as soon as possible. [e] Dave, V.; Warnhoff, E. W. *Org. React.* **1970**, *18*, 217. [f] 5 is the decanamide of (−)-ephedrine, 6 is the corresponding α-methyldecanamide, 7 is the decanamide of (−)-ephedrine methyl ether, and 8 is the corresponding α-methyldecanamide.

Such methodology should considerably enhance studies of asymmetric synthesis.

Deprotonation of 1 (Scheme I) with ≥2 equiv of lithium diisopropylamide (LDA) in THF or THF–HMPA was very slow (dianion formation was incomplete after 2 h at 25 °C). Hence, *t*-BuLi was employed routinely as the base, using 3.6 equiv for 1 and 2.6 equiv for **2** and allowing 1 h at 25 °C. The alkyl halide was then added neat at the indicated temperature (Table I). Control experiments indicated that C-methylation of the dianion of 1 was essentially complete after 0.5 h at −100 °C and that the diastereomer composition was unaltered by delaying workup by 4 h at 25 °C. Moreover, the α-alkylated product could be O-methylated either in situ (HMPA, CH_3I, 25 °C, 1 h) or as a separate step (THF, HMPA, 1.1 equiv of *n*-BuLi, CH_3I, 25 °C, 1 h) without significantly altering (≤3%) the configuration of the α carbon. Analysis of diastereomer content was performed on the amide alcohols directly or on the subsequently prepared methyl ethers. The latter procedure permitted a direct comparison of the alkylations of **1** and **2**. Interestingly, addition of Mg^{2+} to the reaction

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(4) Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, B.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654, and references cited therein.

did not have the expected exalting effect on diastereomer ratio,[2] and the enantiomeric excess was also reduced slightly by the increased bulk of the alkyl iodide.

Alkylation of the dianion of (*S*)-(−)-prolinol propionamide with 1-iodooctane gave the opposite configuration for **3**, as expected, though the enantiomeric excess was slightly less than that for the comparably alkylated decanamide (66% vs. 72%). A most striking observation was that the opposite configuration was also induced upon alkylating the α anion of prolinol methyl ether. *Thus, methylation of the dianion of 1 at −120 °C in THF gave the S configuration (80% ee), but methylation of the anion of 2 at −100 °C in THF gave the R configuration (82% ee).*[5] It is therefore possible to induce asymmetry equally in either configurational sense with a single chiral auxiliary reagent and the same alkyl iodide. In contrast, alkylation of the dianion of (−)-ephedrine propionamide (LDA as base) reportedly[2] produced an enantiomeric excess of 90% (in the presence of Mg^{2+}), and the alkylation of the methyl ether simply reduced the degree of asymmetry, though inducing an excess of the same configuration, when LDA was employed as the base.[2] For comparison, therefore, we prepared and alkylated the dianion of (−)-ephedrine decanamide and the anion of the corresponding methyl ether. The alkylation product derived from the amide alcohol (*t*-BuLi, THF, CH_3I, −100 °C, 0.5 h) was 81:19 (*S*:*R*); that from the methyl ether was 16:84. The configuration induced by (−)-ephedrine was the same as that induced by (*S*)-(−)-prolinol, though the enantiomeric excess induced in this instance was slightly less when ephedrine was the chiral auxiliary. Clearly, however, the methyl ether again induced asymmetry in the opposite sense, an observation not previously made.[2]

The alkylated products (prolinol and ephedrine amides) were hydrolyzed in a two-phase system (concentrated HCl, hexane, reflux, 8 h) to produce the acids without affecting the configuration. Although the chiral auxiliaries were not recovered, one expects that they could be recycled.

The mechanistic picture for these and related alkylations is not clear. Preliminary work by us with amides of (*S*)-α-methylbenzylamine indicated that alkylation of the corresponding amide anions occurred without any significant configurational preference. The failure of α-methylbenzylamine as a chiral auxiliary strongly suggests chelation as the induction-activating factor for chiral β-hydroxy (methoxy) amides.[6] Further experimental detail, however, is required to define the several species that may be present and to explain the dramatic reversal of induced configuration due to change of functional group.

We have recently described the preparation and some of the column characteristics of capillary columns coated with the liquid crystal, cholesteryl cinnamate.[7] The effective temperature range for such columns is 160–210 °C, which corresponds to the mesophase range of the liquid crystal. In Table II, pertinent details are given of the analyses for the diastereomeric pairs of compounds. Complete resolution was not achieved by using capillary columns coated with either OV-101 (apolar) or SP-2340 (polar); thus, in this instance, the liquid crystal phase uniquely served to analyze the alkylation products.

Table II. Analytical Data for Diastereomeric Pairs of Alkylated Amides

compd	column temp	R^a	$K_{S,S'}{}^a$	$K_{R,S'}{}^a$
3a	200	1.36	9.8	10.2
4a	180	1.50	11.1	11.5
3b	200	3.19	11.8	12.9
4b	180	3.08	12.5	13.4
4c[b]	190	0.75	16.2	16.4
8[c]	185	0.92	11.7	11.9

[a] Ettre, L. S. *J. Gas Chromatogr.* **1963**, *1*, 36. [b] **4c** was obtained by O-methylation of **3c**. [c] **8** is the α-methyl decanamide of (−)-ephedrine methyl ether.

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Registry No. 1a, 74036-65-0; **1b**, 74036-66-1; **2**, 74036-67-2; (*R*,*S*)-**3a**, 74036-68-3; (*S*,*S*)-**3a**, 74036-69-4; (*R*,*S*)-**3b**, 74036-70-7; (*S*,*S*)-**3b**, 74036-71-8; (*S*,*S*)-**3c**, 74036-72-9; (*R*,*S*)-**4a**, 74036-73-0; (*S*,*S*)-**4a**, 74036-74-1; (*R*,*S*)-**4b**, 74036-75-2; (*S*,*S*)-**4b**, 74036-76-3; (*R*,*S*)-**4c**, 74036-77-4; (*S*,*S*)-**4c**, 74036-78-5; **5**, 74036-79-6; (*S*)-**6**, 74036-80-9; **7**, 74036-81-0; (*R*)-**8**, 74036-82-1; (*S*)-**8**, 74080-81-2; (−)-ephedrine, 299-42-3; (*S*)-(−)-prolinol, 23356-96-9; (*S*)-(+)-2-methyldecanoic acid, 74036-83-2; *tert*-butyl *n*-nonyl ketone, 74036-84-3; CH_3I, 74-88-4; *n*-$C_8H_{17}I$, 629-27-6; C_2H_5I, 75-03-6; *n*-C_4H_9I, 25267-27-0; *n*-$C_8H_{17}CH_2COCl$, 112-13-0; CH_3CH_2COCl, 79-03-8.

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(5) An inversion in stereoselectivity involved in asymmetric hydrogenation of *o*-acylcinnamic acid derivatives catalyzed by a chiral aminophosphine–rhodium complex has been recently reported: Onuma, K.; Ito, T.; Nakamura, A. *Chem. Lett.* **1979**, 905.

(6) Since this manuscript was submitted for publication, we have learned of Professor David Evans' (California Institute of Technology, Pasadena, CA) studies of this anion system. We are grateful for information he has related to us, and more definitive data concerning the nature of the anionic species will be forthcoming from his laboratory.

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Cyclization of Substituted 5-Hexenyl Radicals as a Model for Photocyclization of 1,5-Hexadien-3-ones

Summary: An examination of substituent effects upon the photochemistry of a number of 1,5-hexadien-3-ones reveals a close parallel with those observed in the cyclization of 5-hexenyl radicals and permits for the first time a rationalization for variations in the regiospecificity of the intramolecular [2 + 2] cycloaddition reactions of these dienones.

Sir: Over a decade ago, in two studies of intramolecular photocyclizations of hydrocarbons, Srinivasan and Carlough[1] and Liu and Hammond[2] noted that when the reacting double bonds were in a 1,5-relationship the photochemistry seemed to be largely controlled by initial C(1)–C(5) bonding, giving a five-membered-ring biradical intermediate which afforded products through disproportionation and closure. Liu and Hammond[2] also sug-

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(2) Liu, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 4936.

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