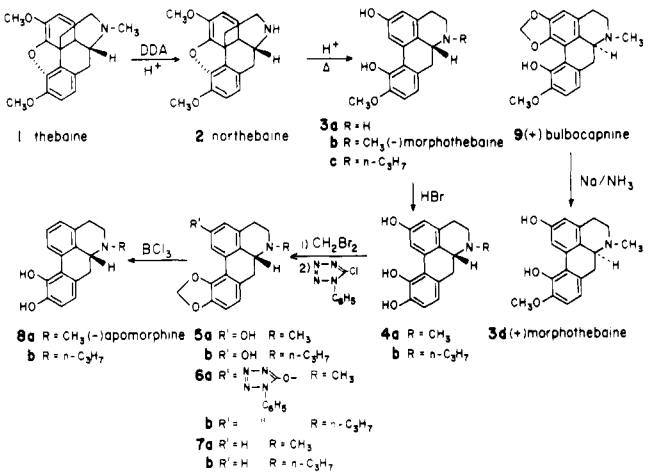
Scheme I. Transformation of Thebaine, (*R*)-Apomorphine, and (*S*)-Bulbocapnine to (*S*)-Apomorphine



evaluate binding of DA-agonists[12] to their presumed receptors in forebrain tissue preparations.

This communication describes a procedure for the transformation of the opioid thebaine (1) to the aporphines (-)-apomorphine (**8a**) and (-)-*N*-*n*-propylnorapomorphine (**8b**) as well as the preparation of (+)-apomorphine from the naturally occurring aporphine alkaloid (*S*)-(+)-bulbocapnine (Scheme I).

Northebaine (**2**)[13] was treated with concentrated HCl in a pressure bottle as described for the thebaine (**1**) → morphothebaine (**3b**)[14] conversion to give normorphothebaine (**3a**). *N*-*n*-Propylnormorphothebaine was prepared from **3a** with propyl iodide in acetonitrile. O-Demethylation of **3b** and **3c** was achieved by heating with 48% HBr to give **4a** and **4b** in quantitative yields.[15] The catechol-protected derivatives **5a** and **5b** were secured by treatment of triphenols **4a** and **4b** with methylene dibromide in alkaline aqueous Me_2SO[16] [for **5a**·HCl: mp 245–246 °C; mass spectrum, *m/e* 295; NMR (Me_2SO-d_6) δ 7.45 (d, 1 H, C_1 H), 6.85 (m, 2 H, C_8 H), 6.65 (d, 1 H, C_3 H), 6.05 and 6.2 (d, 2 H, CH_2), 2.8–3.23 (m, 7 H), 2.5 (s, 3 H, NCH_3)].[17] Removal of the phenolic hydroxyl group at the 2-position of the aporphine ring in **5a** and **5b** was achieved in two steps by formation of the phenyl tetrazolyl ethers **6a**·HCl (mp 224–27 °C; mass spectrum, *m/e* 439) and **6b**·HCl (mp 167–175 °C; mass spectrum, *m/e* 467) followed by hydrogenolysis over 5% Pd/C in acetic acid at 40 °C for 48 h to give **7a** and **7b** in greater than 90% yields[18] [**7a**·HCl, mp 270–273 °C (lit.[16] 273–279 °C); **7b**·HCl, mp 238–244 °C; mass spectrum, *m/e* 307]. Comparison samples of **7a** and **7b** were prepared from the disodium salt of the aporphines **8a** and **8b** with methylene dibromide in Me_2SO–H_2O. The products thus obtained were identical with respect to their mass spectra, R_f values, and melting points.

The removal of the methylenedioxy group in **7a** and **7b** was carried out in quantitative yields with boron trichloride in CH_2Cl_2 by methods recently described.[19] The mass spectrum as well as the optical rotation of **8a** and **8b** was in agreement with authentic samples obtained by the rearrangement of the corresponding morphine derivatives.[4,20]

The aporphine alkaloid (*S*)-bulbocapnine, isolated from the roots of *Corydalis cava*, has been converted to (+)-morphothebaine (**3d**).[21,22] By a sequence of reactions described for the transformation of (-)-morphothebaine (**3b**) to (-)-apomorphine (**8a**) described above, a facile route to (+)-apomorphine has thus been effected.

This approach to the synthesis of the enantiomers of apomorphine from readily available natural products containing the desired chirality appears to be superior to the procedure involving an involved multistep process followed by separation of the racemic mixture[5] and thus provides an alternative process for the preparation of apomorphine and *N*-propylnorapomorphine for biochemical and clinical use.

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Registry No. **1**, 115-37-7; **2**, 2579-67-1; **3a**, 61774-59-2; **3b**, 478-53-5; **3c**, 77629-99-3; **3d**, 77630-00-3; **4a**, 77630-01-4; **4b**, 77630-02-5; **5a**·HCl, 77630-03-6; **5b**, 77630-04-7; **6a**·HCl, 77630-05-8; **6b**·HCl, 77630-06-9; **7a**·HCl, 40609-94-7; **7b**·HCl, 77630-07-0; **8a**·2Na, 77630-08-1; **8b**·2Na, 77630-09-2; **9**, 298-45-3.

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Asymmetric Induction in Additions to Epoxides. Addition of α-Anions of N,N-Disubstituted Carboxamides

Summary: The addition of α-anions of monosubstituted *N,N*-dialkylacetamides to monosubstituted epoxides has been shown to give significant 1,3 asymmetric induction at the carbanionic center when the alkyl substituents are large.

Sir: Asymmetric induction during carbon–carbon bond formation has been[1] and continues to be[2-4] a topic of great

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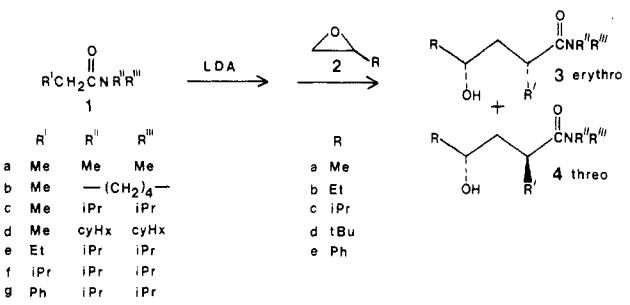
Table I. Products of Additions to Epoxides

entry	amide	epoxide	solvent[a]	time, h	temp, °C	% completion[b]	ratio of diastereomers
1	a	a	a	2	35	82	1.04
2	b	a	a	2	35	100	1.2
3	c	a	a	5	35	93	1.9
4	c	a	a	5	0	81	2.9
5	c	a	a	24	−23.5	66	3.3
6	c	a	a	6	−78	1-2	>20
7	d	a	a	6	0	49	2.9
8	c	a	b	5	0	75	1.7
9	e	a	c	5	0	77	2.3
10	c	a	d	5	25	89	1.3
11	c	b	a	5	0	58	3.8
12	c	c	a	5	0	40	5.3
13	c	d	a	5	0	48	9
14	c	e	a	5	0	78	9
15	e	a	a	5	0	84	3.5
16	f	a	a	5	0	59	2.1
17	g	a	a	6	0	90	1.3

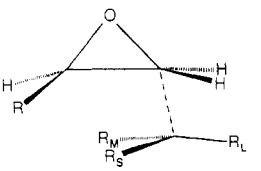
[a] Solvents: a, ether; b, tetrahydrofuran; c, ether plus 1 equiv of 12-crown-4; d, ether plus 1 equiv of HMPT. [b] Approximately estimated by comparison of ^{13}C NMR peak heights of starting materials and products.

interest. Although the addition of carbanions to epoxides is an important method for the formation of carbon–carbon bonds, asymmetric induction at the nucleophilic center has never been systematically studied. Asymmetric induction should be observed whenever a carbanion with enantiotopic faces is added to an epoxide which lacks a plane of symmetry in the epoxide ring plane.[5] Reactions of this type have been done on many occasions[6-8] but the similarity of the product properties has made analysis of the proportions of the diastereomers present difficult enough that the relative amounts of the two products have been measured in only a few cases.[8] If a monosubstituted epoxide is used, any asymmetric induction observed would be of the remote 1,3 type. General methods which produce 1,3 asymmetric induction are rare,[2,4] and a new approach would have considerable synthetic value. In this publication, we report the useful stereoselectivity obtained when α-anions from N,N-disubstituted carboxamides are added to monosubstituted epoxides and describe the effects of structural change in the amide and in the epoxide on the stereoselectivity of the reaction.

Scheme I



α-Anions derived from N,N-disubstituted carboxamides were chosen as nucleophiles because these anions are known to be particularly stable and to react with a variety of electrophiles including epoxides.[7,9] Conformational considerations suggest that the favored direction of approach for a trigonal nucleophile having enantiotopic faces is as shown in the structure below. The maximum possible



stereoselectivity for the simplest case, the addition of the α-anion of an N,N-disubstituted propanamide to propylene oxide, can be estimated by assuming that the transition state resembles the initially formed product and that the $CONR_2$ group is infinitely larger than methyl. An approach as shown would lead to a transition state with two butane gauche interactions whereas an approach with R_M and R_S reversed would lead to a transition state with a 1,3-diaxial interaction between methyl groups. The 2 kcal mol^{-1} difference in stability would give a rate ratio of 40:1 at 0 °C.

In the present study, anions were generated under nitrogen by adding the amide to lithium diisopropylamide in ether or THF at 0 °C. In some cases, the initial solvent and the amine were removed under vacuum before the

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reaction solvent was added. Then the temperature was adjusted and the epoxide added. Reactions were quenched with 1 M acetic acid in ether. Analyses of the resulting mixtures were performed by integration of ^{13}C NMR signals of the γ-carbons recorded under conditions where these should be an accurate measure of concentration.[10,11] Comparison of these results with GLC integration in two cases gave identical (±2%) diastereomeric ratios. The results are shown in Table I.

As previously observed,[7,9] the addition of carboxamide α-anions to terminal epoxides proceeded readily at 0 °C. The product γ-hydroxy amides were highly crystalline compounds. In every case where significant asymmetric induction was observed (see below), the major diastereomer crystallized from the product mixture (after the unreacted amide had been removed by distillation under reduced pressure) and could be recrystallized to high purity. Although the product N,N-disubstituted γ-hydroxy amides with large groups on nitrogen (from amides c–g, Scheme I) hydrolyzed with more difficulty than did the *N,N*-dimethyl-γ-hydroxy amides, treatment of the former products with 6 M HCl at 50 °C for 72 h gave γ-butyrolactones in moderate yields. The major diastereomer produced from the reaction of **1c** and **2a** yielded only *trans*-2,4-dimethyl-γ-butyrolactone on hydrolysis[12] in agreement with the mechanism proposed above. This lactone was identified by comparison of its ^1H NMR spectra with the distinctly different spectra reported[13] for the authentic cis and trans isomers. Thus, the major diastereomeric product had the erythro configuration **3**.

Significant asymmetric induction (diastereomeric ratios ≥2) was observed only when the substituents on nitrogen were large (see Table I, entries 1–4 and 7) probably because only then was the amide group significantly larger than methyl. The stereoselectivity obtained increased markedly as the temperature was lowered (entries 3–6), and excellent selectivity was obtained at −78 °C. Unfortunately, the rate of reaction was very slow at this temperature. The reaction was more stereoselective in ether than in THF (compare entries 4 and 8), and the addition of cation complexing reagents lowered the stereoselectivity (compare entries 3 and 4 with 9 and 10, respectively). These results suggest that the structure of the anion is closer to a contact ion pair than a solvent-separated ion pair in ether[14] than under the other conditions examined. Contact ion pairs are known to be larger than solvent separated ion pairs.[14] Stereoselectivity for the erythro product increased as the size of the R group on the epoxide increased (entries 4, 11–14) consistent with increased differentiation between R_M and R_S (see structure I) and perhaps also between R_M and R_L. When the size of R_M was increased (entries 4 and 15–17), the stereoselectivity initially increased (for R_M = ethyl), but further gain in size brought decreased stereoselectivity. These observations suggest a conflict between increased differentiation between R_M and R_S and decreased differentiation between R_M and R_L as R_M is increased in steric bulk.

The results herein indicate that additions of carbanions to monosubstituted epoxides constitute a promising approach to the difficult problem of 1,3 asymmetric induction. Investigations of other carbanion stabilizing groups are in progress to extend the usefulness of the method.

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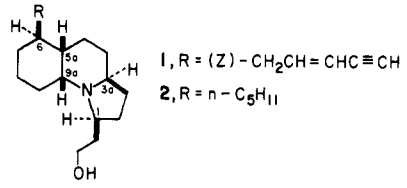
Short Total Synthesis of (±)-Perhydrogephyrotoxin

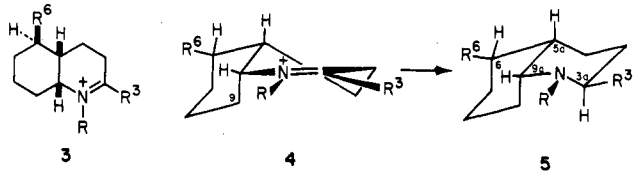
Summary: Preparation of the dendrobatid poison-frog alkaloid toxin (±)-perhydrogephyrotoxin from benzyl *trans*-1,3-butadiene-1-carbamate is described; the synthesis features the stereoselective reduction of *cis*-octahydroindole **9** from the sterically hindered concave face.

Sir: Gephyrotoxin (1), the parent member of a new class of skin alkaloids from tropical poison frogs of the genus *Dendrobates*, was first described by Daly, Witkop, and co-workers in 1977.[1] Last year we reported[2] a stereoselective total synthesis of (±)-perhydrogephyrotoxin (**2**), and



more recently Kishi and co-workers[3] recorded the first total synthesis of (±)-gephyrotoxin. In conjunction with our interest in the biological activity[1,4] of this series, we have been investigating simplified approaches to gephyrotoxin and gephyrotoxin analogues. In this communication we describe a new concise approach to these alkaloids and specifically report a short, stereocontrolled total synthesis of (±)-perhydrogephyrotoxin.

Our preliminary investigations in the gephyrotoxin area[2,5] indicated that it might be possible to reduce bicyclic iminium ion **3** (R = electrophilic metal species) from the



sterically more congested concave α face. We anticipated that iminium ion **3** would be preferentially reduced via a transition-state conformer related to **4**, since the alternate conformer would be destabilized by $A^{1,2}$ interactions between R and C-9.[6] A stereoelectronic preference[7] for initial

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