1′-H), 4.4 (t, 1, ribH), 4.2 (t, 1, ribH), 4.1 (g, 1, ribH), 3.8 (m, 2, 5′-CH_2).

Anal. Calcd for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.43. Found: C, 52.92; H, 4.55.

Similar treatment of **19** gave **13**: UV $\lambda_{max}^{pH\ 7}$ (0.1 M phosphate) 336, 322, 310, 283, 264 nm.

***lin*-Benzoxanthosine (4b).** To a solution of 0.05 M aqueous TEAB (pH 7.6, 970 mL, made by diluting 0.5 M aqueous TEAB)[25] was added a solution of *lin*-benzoinosine (**3b**) (100 mg, 0.31 mmol) in 0.05 M aqueous TEAH (30 mL). A solution of xanthine oxidase (20 units in 1.5 mL of 2.3 M aqueous ammonium sulfate, Sigma Grade I) was added, and the solution was agitated for 1 min. After 30 min, there was no further decrease in A_{298} and the solution was diluted with an equal volume of methanol and immersed in a dry ice–acetone bath for 30 min. Removal of the solvent in vacuo at 0–5 °C gave a yellow glass which solidified on successive coevaporations with methanol (250 mL) and ethanol (250 mL). The residue was dissolved in 0.1 M aqueous TEAH (10 mL), applied to a TEAE cellulose column (3 × 40 cm), and eluted with a pH gradient from 0.04 M (1 L) aqueous TEAH to 0.08 M (1 L) aqueous TEAB (pH 7.6). Appropriate fractions (by A_{320}) were concentrated in vacuo at 25 °C and dried by evaporation with pyridine (3 × 50 mL) to yield 102 mg (98%) of **4b**: UV $\lambda_{max}^{pH\ 7.6}$ (0.05 M TEAB) 321 (ϵ 6300), 285 (4700), 270 (6900) nm; field desorption MS m/e 334 (M^+).

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Registry No. 2b, 70631-11-7; **3b**, 60189-63-1; **4a**, 60189-64-2; **4b**, 60189-65-3; **5**, 70631-12-8; **6**, 70631-13-9; **7**, 70631-14-0; **8**, 70631-15-1; **8** ammonium salt, 70631-16-2; **9**, 70631-17-3; **10**, 70631-18-4; **11**, 70631-19-5; **12**, 70631-20-8; **13**, 70631-21-9; **14**, 63243-77-6; **15**, 70631-22-0; **16**, 70631-23-1; **17**, 70631-24-2; **18**, 70631-25-3; **19**, 70631-26-4; **20**, 70631-27-5; 4-nitroanthranilic acid, 619-17-0; ethyl chloroformate, 541-41-3; 6,8-dithio-*lin*-benzoanthine, 70631-28-6; 1-bromotri-*O*-acetyl-β-D-ribofuranose, 39925-22-9; ethyl 4-chloroanthranilate, 60064-34-8; 7-methyl-*lin*-benzoinosine, 70631-29-7.

Reduction–Elimination of Some Vicinal Cycloalkyl Cyanohydrin Derivatives. Stereoselective Synthesis of Cycloalkenes

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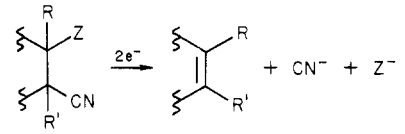
The isomeric 2-cyano-2-methylcyclododecanols, 2-cyano-1,2-dimethylcyclododecanols, and 2-cyano-1,2-dimethylcyclohexanols were prepared from the corresponding cyano ketones. Reduction of the methanesulfonate, (methylthio)methyl, and (methanesulfonyl)methyl derivatives with lithium in ammonia (Li/NH_3) or sodium naphthalenide ($NaC_{10}H_8$) gave rise to *cis*- and/or *trans*-1-methylcyclododecene, 1,2-dimethylcyclododecene, and 1,2-dimethylcyclohexene, respectively. The cyclododecyl systems showed a high preference for syn elimination with $NaC_{10}H_8$ whereas Li/NH_3 gave products of both syn and anti elimination. The findings suggest a preferred coplanar transition state for the elimination reactions.

We have found the reductive elimination of vicinal cyanohydrin derivatives to be a useful method for the synthesis of tri- and tetrasubstituted cycloalkenes (Scheme I).[1,2] We recently noted that sodium naphthalenide in hexamethylphosphoramide ($NaC_{10}H_8$/HMPA) effected a highly stereoselective syn elimination of certain cyclododecyl cyanohydrin derivatives in high yield.[2] We now report additional studies along these lines which show that the elimination reaction can also take place via an anti pathway under some circumstances.

The cyanohydrin derivatives chosen for these studies were prepared as follows (Chart I). Reduction of 2-cyano-2-methylcyclododecanone (**1a**) with sodium borohydride in isopropyl alcohol afforded the crystalline trans and cis cyanohydrins **2a** and **3a** as a 55:45 mixture in nearly quantitative yield. This mixture, and the derived methanesulfonates **4a** and **5a**, could be separated conveniently by high-pressure liquid chromatography (LC).

Scheme I



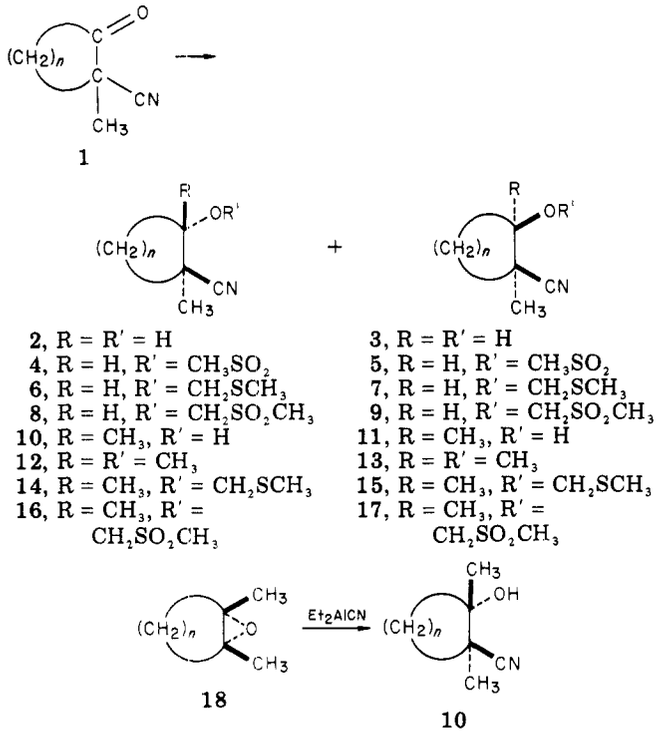
The (methylthio)methyl (MTM) ethers **6a** and **7a** were formed nearly quantitatively upon treatment of the cyanohydrins **2a** and **3a** with dimethyl sulfoxide in acetic anhydride–acetic acid.[3] These could also be separated by LC. Oxidation with *m*-chloroperoxybenzoic acid gave the crystalline sulfones **8a** and **9a**.

The ditertiary cyanohydrins **10a** and **11a** were produced as a 75:25 mixture in 88% yield upon addition of methylmagnesium bromide to ketone **1a**. Earlier we had found that cyano ethers such as I (R = R′ = CH_3, Z = OCH_3) underwent reductive elimination to olefins with dissolving metals.[1] Accordingly we prepared ethers **12a**

(1) J. A. Marshall and L. J. Karas, *Synth. Commun.*, 8, 65 (1978).
(2) J. A. Marshall and L. J. Karas, *J. Am. Chem. Soc.*, **100**, 3615 (1978).
(3) P. M. Pojer and S. Angyal, *Tetrahedron Lett.*, 3067 (1976).

0022-3263/79/1944-2994$01.00/0

Chart I[a]



[a] For the a series, $n = 10$; for the b series, $n = 4$.

and **13a** to study their reduction. However, all attempts at direct methylation of cyanohydrins **10a** and **11a** failed because of retroaldolization. The MTM ethers **14a** and **15a**, on the other hand, were readily prepared in nearly quantitative yield by treatment of cyanohydrins **10a** and **11a** with dimethyl sulfoxide in acetic anhydride.[3] Reduction with Raney nickel yielded the requisite methyl ethers **12a** and **13a**.[4] Oxidation of the MTM ethers **14a** and **15a** wih *m*-chloroperoxybenzoic acid afforded the crystalline sulfones **16a** and **17a**.

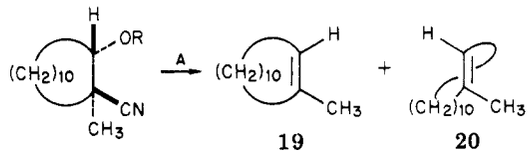
Cyanohydrins **10a** and **11a** could be converted to a mixture of methanesulfonate derivatives. However, this could not be separated and proved difficult to purify. Reduction with lithium in ammonia gave rise to hydrocarbon products, but only in 30% yield. We therefore decided not to pursue methanesulfonates in this series.

The cyclohexyl cyanohydrins **10b–15b** were prepared from cyano ketone **1b** analogously. Addition of methyllithium gave rise to a 70:30 mixture of cyanohydrins **10b** and **11b**. Interestingly, methylmagnesium bromide showed increased stereoselectivity and produced only the trans cyanohydrin **10b**. Direct methylation of the mixture **10b,11b** with methyl iodide in tetrahydrofuran–HMPA gave the trans cyano ether **12b** with no recovery of cyanohydrin. Evidently, the cis isomer **11b** must retroaldol preferentially under the reaction conditions. Treatment of the cyanohydrin mixture with dimethyl sulfoxide–acetic anhydride afforded both MTM ethers **14b** and **15b**. These were readily separated by LC. Reduction with Raney nickel then yielded the methyl ethers **12b** and **13b**.[4]

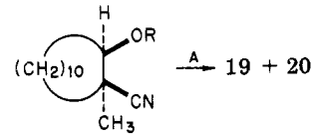
We have previously described our stereochemical proof for the trisubstituted cyclodecyl cyanohydrins **2a** and **3a**.[2] At that time we were unable to offer a rigorous assignment for the tetrasubstituted homologues **10a** and **11a**. In the interim, we have found that the epoxide **18a** reacts with Nagata's diethylaluminum cyanide reagent[5] to give cyanohydrin **10a**, thus substantiating our previous assumed configurations. Since 1,2-dimethylcyclohexene oxide (**18b**) affords cyanohydrin **10b** upon treatment with the cyanide reagent, the stereochemistry of cyanohydrins **10b–15b** can likewise be assigned.

(4) N. A. Hughes, *Carbohydr. Res.*, 7, 474 (1968).

Table I. Reduction-Eliminations Yielding (*E*)- and (*Z*)-1-Methylcyclododecene



R	A	% anti (19)	% syn (20)	% yield
(1) CH_3SO_2 (4a)	Li/NH_3	10	80[a]	90
(2) CH_3SO_2 (4a)	$NaC_{10}H_8$/HMPA	14	78[b]	82
(3) $CH_2SO_2CH_3$ (8a)	$NaC_{10}H_8$/HMPA	6	94	71



R	A	% anti (20)	% syn (19)	% yield
(4) CH_3SO_2 (5a)	Li/NH_3	71	23[c]	87
(5) CH_3SO_2 (5a)	$NaC_{10}H_8$/HMPA	11	88[d]	82
(6) $CH_2SO_2CH_3$ (9a)	$NaC_{10}H_8$/HMPA	0	100	85

[a] 10% methylcyclododecane was formed in addition to the alkenes. [b] 8% methylcyclododecane was formed in addition to the alkenes. [c] 6% methylcyclododecane was formed in addition to the alkenes. [d] 1% methylcyclododecane was formed in addition to the alkenes.

Reductions of the various cyanohydrin derivatives were carried out by using lithium in ammonia–tetrahydrofuran at −33 °C or with sodium naphthalenide in hexamethylphosphoramide or tetrahydrofuran at room temperature. Other combinations of metals, solvents, and radical anion reagents were either less selective or gave lower yields of alkene products.[6] Among the less attractive systems examined were lithium/ethylamine, calcium/ammonia, and lithium/HMPA–tetrahydrofuran.[6]

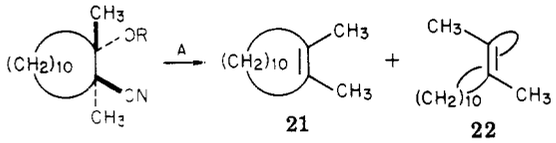
Tables I–III highlight some of our reduction–elimination findings. The results suggest that Li/NH_3 reductions tend to be *product* oriented favoring (*E*)-1-methylcyclododecene and (*Z*)-1,2-dimethylcyclododecene (Table I, entries 1 and 4, Table II, entries 1, 2, 6, and 7),[7] whereas $NaC_{10}H_8$ reductions tend to be *process* oriented showing a remarkable preference for syn elimination (Table I, entries 2, 3, 5, and 6) especially in the ditertiary cyclododecyl system (Table II, entries 3, 4, 5, 8, and 9). Molecular models indicate that an anti coplanar transition state for eliminations of the cis

(5) Cf. W. Nagata, M. Yoshioka, and T. Okumura, *Chem. Commun.*, 2365 (1970), for an example of trans diaxial opening of a tetrasubstituted steroidal epoxide.

(6) A detailed account of these experiments may be found in L. J. Karas, Ph.D. Dissertation, Northwestern University, 1979.

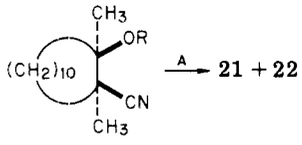
(7) T. C. Flood, Ph.D. Dissertation, Massachusetts Institute of Technology, 1972; A. L. Runquist, Ph.D. Dissertation, Northwestern University, 1974. Upon equilibration at 100 °C 1-methylcyclododecene was found to give a 60:40 mixture of *Z* and *E* isomers; 1,2-dimethylcyclododecene yielded 75% of isomeric 1,12-dimethylcyclododecenes and 25% of an 80:20 mixture of (*Z*)- and (*E*)-1,2-dimethylcyclododecene.

Table II. Reduction-Eliminations Yielding (*E*)- and (*Z*)-1,2-Dimethylcyclododecene



21 22

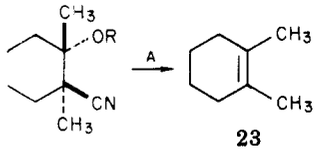
R	A	% anti (21)	% syn (22)	% yield
(1) CH_3 (12a)	Li/NH_3	100	0	50[a]
(2) $CH_2SO_2CH_3$ (16a)	Li/NH_3	90	10	99
(3) CH_2SCH_3 (14a)	$NaC_{10}H_8$/HMPA	0	100	99
(4) CH_2SCH_3 (14a)	$NaC_{10}H_8$/THF	0	100	85
(5) $CH_2SO_2CH_3$ (16a)	$NaC_{10}H_8$/HMPA	0	100	83



R	A	% anti (22)	% syn (21)	% yield
(6) CH_3 (13a)	Li/NH_3	0	100	50[a]
(7) $CH_2SO_2CH_3$ (17a)	Li/NH_3	0	100	97
(8) CH_2SCH_3 (15a)	$NaC_{10}H_8$/HMPA	0	100	75
(9) $CH_2SO_2CH_3$ (17a)	$NaC_{10}H_8$/HMPA	0	100	74

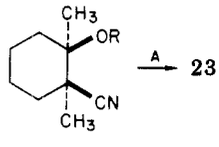
[a] 50% 1-methoxy-1,2-dimethylcyclododecane was formed in addition to the alkene.

Table III. Reduction-Eliminations Yielding 1,2-Dimethylcyclohexene



23

R	A	% yield
(1) CH_3 (12b)	Li/NH_3	89
(2) CH_2SCH_3 (14b)	Li/NH_3	75
(3) CH_2SCH_3 (14b)	$NaC_{10}H_8$/HMPA	90

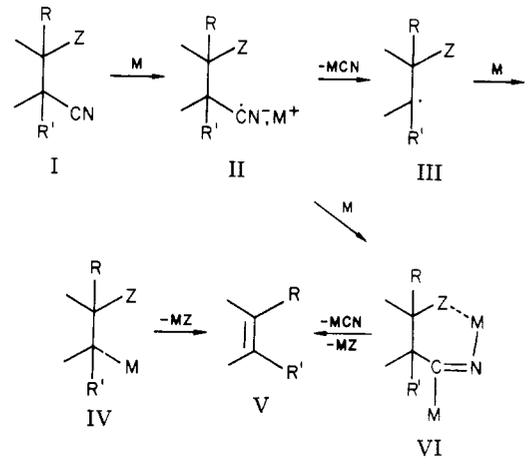


R	A	% yield
(4) CH_3 (13b)	Li/NH_3	30[a]
(5) CH_2SCH_3 (15b)	Li/NH_3	55[b]
(6) CH_2SCH_3 (15b)	$NaC_{10}H_8$/HMPA	50[c]

[a] 70% 1-methoxy-1,2-dimethylcyclohexane was formed in addition to the alkene. [b] 10% 1-[(thiomethyl)-methoxy]-1,2-dimethylcyclohexane was formed in addition to the alkene. [c] Side products could not be identified owing to the presence of naphthalene.

ditertiary cyanohydrin derivatives **13a**, **15a**, and **17a** (Table II, entries 6–9) requires one of the four substitutents to become oriented inside the cyclododecane ring, a situation resulting in excessive nonbonded interactions. Thus no (*E*)-1,2-dimethylcyclododecene (anti elimination) would be expected from these derivatives. In the analogous cis

Scheme II



secondary, tertiary derivatives **5a** and **9a** (Table I, entries 4–6), the hydrogen substituent can adopt the inside position, and thus the formation of (*E*)-1-methylcyclododecene (**20**) by an anti coplanar process is not energetically prohibited.

In the cyclohexane **b** series only the *Z* cycloalkene can be formed, so the tendency for syn vs. anti elimination must be gauged by the yield of 1,2-dimethylcyclohexene (**23**), as shown in Table III. Here both Li/NH_3 and $NaC_{10}H_8$/HMPA reveal a distinct preference for anti (entries 1–3) as opposed to syn elimination (entries 4–6). These findings suggest a preferred coplanar arrangement in the transition state. While not energetically prohibitive, syn elimination of the cis cyanohydrin derivatives **13b** and **15b** (Table III, entries 4–6) requires a boat transition state conformation and would be expected to occur less readily.

The reduction–elimination of vicinal cyanohydrin derivatives involves the net transfer of two electrons as summarized in Scheme I. A possible reaction pathway, depicted in Scheme II, entails the initial formation of the nitrile radical anion II.[8] Loss of cyanide would lead to the radical III which would expectedly undergo rapid electron transfer to give the associated anion IV. Loss of MZ would then lead to the olefin product V. Clearly attempts at direct comparison of results obtained with such diverse reagents as Li/NH_3 vs. $NaC_{10}H_8$ can shed little light on mechanistic details of the reaction. However, in view of the synthetically significant differences in product ratios, and in order to provide guidelines for applications to other systems, some speculation seems warranted. The Li/NH_3 results seem best accommodated by the sequence I → II → III → IV → V, especially where the Z group has low election affinity. Here a common intermediate (IV) might be expected from each of the two stereoisomeric cyanohydrin derivatives I. Thus the two methyl ethers **12a** and **13a** (Table II, entries 1 and 6) give identical product mixtures. In the **b** series, the highly favored anti coplanar CN/OMe arrangement of the trans isomer **12b** may facilitate elimination, as opposed to protonation, thus accounting for the differing amounts of these two products from cyano ethers **12b** and **13b** (Table III, entries 1 and 4).

If the Z group has a high electron affinity [e.g., **4a** and **5a** (Z = CH_3SO_3)] alternative pathways II → V or III → V involving electron transfer to Z may account for some of the olefin product (Table I, entries 1, 2, 4, and 5). In these cases hydrogenolysis of the Z group could also take place, thus accounting for the formation of methyl-

(8) Cf. P. G. Arapakos, M. K. Scott, and F. E. Huber, Jr., *J. Am. Chem. Soc.*, 91, 2059 (1969), and references cited therein.

cyclododecane from **4a** and **5a**.[9]

In HMPA, dissociation of the initial nitrile radical anion (II → III) might be relatively disfavored owing to the low anion solvating properties of that solvent.[10] Moreover, effective cation solvation by HMPA would expectedly increase the reducing ability of $NaC_{10}H_8$. Therefore the electron transfer II → VI might be feasible. Subsequent syn elimination of the chelated dianion VI would afford the olefinic product V. The observed anti eliminations for mesylates **4a** and **5a** (Table I, entries 2 and 5) could be accommodated by the pathway II → V. Of course, anti eliminations could also occur via a competing sequence involving anion IV (Scheme II) or a nonchelated dianion intermediate analogous to VI.

In the cyclohexane series a chelated intermediate such as VI could yield 1,2-dimethylcyclohexene (**23**) via a coplanar elimination pathway in the cis isomer **15b** but not the trans isomer **14b**. Since elimination of the trans isomer **14b** proceeds in higher yield (90% vs. 50%) (Table III, entries 6 and 3), chelation may be of rather minor importance in stabilizing dianion VI, if indeed this intermediate is crucial to the $NaC_{10}H_8$ reduction–elimination pathway. At least one unifying element of the $NaC_{10}H_8$ reductions seems to be a decided preference for a low energy coplanar (syn or anti) alignment of the adjacent CN/Z groupings.

Experimental Section[11]

2-Cyano-2-methylcyclododecanone (1a). A solution of 45.6 g (0.25 mol) of cyclododecanone in 150 mL of ether was added dropwise to a stirred mixture of 6.6 g (0.27 mol) of hexane-washed sodium hydride and 100 mL (1.25 mol) of ethyl formate in 300 mL of ether at 0 °C. The mixture was allowed to reach room temperature with stirring overnight. Water was carefully added and the basic solution was extracted with 10% sodium hydroxide. The combined basic extracts were washed with ether and acidified with cold concentrated HCl, and the product was isolated by ether extraction.

The resultant crude 2-(hydroxymethylene)cyclododecanone was dissolved in 500 mL of *tert*-butyl alcohol, 19.1 g (0.275 mol) of hydroxylamine hydrochloride was added, and the mixture was stirred at reflux for 1 h. The mixture was concentrated and distilled [120–125 °C (bath temperature) at 0.3 torr], and the distillate was recrystallized from hexane to give 30 g (63%) of isoxazole; mp 55–56 °C.[12]

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.6; H, 10.2; N, 6.6.

A mixture of 5.2 g (25 mmol) of the aforementioned isoxazole, 8.5 g (75 mmol) of KO-*t*-Bu, and 75 mL of *t*-BuOH was stirred at reflux for 15 min, whereupon 4.8 mL (75 mmol) of methyl iodide was added by syringe. Additional 1.6-mL (25 mmol) portions were added at 15-min intervals. The mixture was cooled, water was added, and the product was isolated by ether extraction, affording 5.1 g (92%) of a white solid. Recrystallization from ethyl acetate–hexane gave 4.0 g (72%) of cyano ketone 1; mp 98–101 °C. The analytical sample, mp 106–107 °C, was secured after column chromatography on silica gel and recrystallization.[12]

Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.1; H, 10.5; N, 6.2.

2-Cyano-2-methylcyclododecanol (2a, 3a). A mixture of 3.32 g (15 mmol) of cyano ketone **1a** and 0.58 g (15 mmol) of sodium borohydride in 50 mL of isopropyl alcohol was stirred overnight at room temperature. The mixture was carefully treated with 10% aqueous HCl and the product was isolated with ether, affording 3.05 g (91%) of a solid 55:45 mixture of cyanohydrins **2a** and **3a** according to the gas chromatogram. This mixture was separated by LC and the resultant pure isomers were recrystallized from hexane.

***trans*-2-Cyano-2-methylcyclododecanol (2a)**: mp 112–113 °C; λ_{max}^{KBr} 2.88, 3.47, 4.46, 6.81, 9.35, 9.50 μm; $\delta_{Me_4Si}^{CDCl_3}$ 3.89 (H-1, d, J = 8 Hz), 2.09 (OH), 1.29 (CH_2 envelope), 1.22 (CH_3).

Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.4; H, 11.4; N, 6.1.

***cis*-2-Cyano-2-methylcyclododecanol (3a)**: mp 131–131.5 °C; λ_{max}^{KBr} 2.83, 3.47, 4.46, 6.82, 9.39, 9.48 μm; $\delta_{Me_4Si}^{CDCl_3}$ 3.49 (H-1, d, J = 9 Hz), 1.90 (OH), 1.37 (CH_3), 1.29 (CH_2 envelope).

Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.5; H, 11.4; N, 6.1.

2-Cyano-2-methylcyclododecyl Methanesulfonate (4a, 5a). A solution of 2.26 g (10 mmol) of the 55:45 cyanohydrin mixture **2a,3a** and 2.0 mL (25 mmol) of methanesulfonyl chloride in 20 mL of pyridine was stirred at 0 °C for 15 min, allowed to reach room temperature over 5 h, and stored in a freezer overnight. Water was added and the product was isolated with ether giving 3 g of yellow oil shown by LC to consist of a 55:45 mixture of isomers. The mixture was separated using LC, and the resultant pure isomers were recrystallized from hexane.

***trans*-2-Cyano-2-methylcyclododecyl Methanesulfonate (4a)**: mp 81–82 °C; λ_{max}^{KBr} 3.46, 4.46, 6.80, 7.37, 7.42, 8.48, 10.3, 10.5, 11.6 μm; $\delta_{Me_4Si}^{CCl_4}$ 5.02 (H-1, m), 3.13 (CH_3), 1.36 (CH_2 envelope).

Anal. Calcd for $C_{15}H_{27}NO_3S$: C, 59.77; H, 9.03; N, 4.65; S, 10.64. Found: C, 59.95; H, 9.2; N, 4.6; S, 10.8.

***cis*-2-Cyano-2-methylcyclododecyl Methanesulfonate (5a)**: mp 82–83 °C; λ_{max}^{KBr} 3.47, 4.46, 6.79, 7.43, 8.51, 10.3, 10.5, 11.3 μm; $\delta_{Me_4Si}^{CCl_4}$ 4.69 (H-1, m), 3.04 (CH_3), 1.38 (CH_2 envelope), 1.44 (CH_3).

Anal. Calcd for $C_{15}H_{27}NO_3S$: C, 59.77; H, 9.03; N, 4.65; S, 10.64. Found: C, 59.9; H, 9.2; N, 4.5; S, 10.8.

2-Cyano-2-methylcyclododecyl (Methylthio)methyl Ether (6a, 7a). A solution of 3.35 g (15 mmol) of the 55:45 cyanohydrin mixture **2a,3a** in 60 mL of dimethyl sulfoxide, 40 mL of acetic anhydride, and 12 mL of acetic acid was stirred at room temperature for 48 h. The solution was poured into a stirred mixture of 400 mL of saturated sodium bicarbonate and 150 mL of hexane at 0 °C. After 1 h the product was isolated by hexane extraction to give 4.25 g of a yellow oil shown to be a 55:45 mixture of isomers. Separation by LC gave material with the following properties.

***trans*-2-Cyano-2-methylcyclododecyl (Methylthio)methyl Ether (6a)**: λ_{max}^{film} 3.38, 3.48, 4.46, 9.50, 9.60 μm; $\delta_{Me_4Si}^{CCl_4}$ 4.80 (OCH_2), 3.89 (H-1, d, J = 7 Hz), 2.16 (CH_3), 1.37 (CH_2 envelope), 1.26 (CH_3).

Anal. Calcd for $C_{16}H_{29}NOS$: C, 67.79; H, 10.31; N, 4.94; S, 11.31. Found: C, 68.0; H, 10.4; N, 5.1; S, 11.2.

***trans*-2-Cyano-2-methylcyclododecyl (Methylthio)methyl Ether (7a)**: λ_{max}^{film} 3.38, 3.48, 4.46, 9.40, 9.80 μm; $\delta_{Me_4Si}^{CCl_4}$ 4.77 (OCH_2), 3.53 (H-1, m), 2.14 (CH_3), 1.39 (CH_3 and CH_2 envelope).

Anal. Calcd for $C_{16}H_{29}NOS$: C, 67.79; H, 10.31; N, 4.94; S, 11.31. Found: C, 68.2; H, 10.1; N, 4.8; S, 11.2.

***trans*-2-Cyano-2-methylcyclododecyl (Methanesulfonyl)methyl Ether (8a).** A solution of 6.0 g (30 mmol) of 85% *m*-chloroperoxybenzoic acid and 2.8 g (10 mmol) of trans cyano ether **6a** in 115 mL of chloroform at 0 °C was allowed to reach room temperature with stirring over 1 h. Saturated sodium bisulfite solution was added and the product was isolated with ether and recrystallized from ethyl acetate–hexane, affording 2.12 g (67%) of sulfone **8a** as white needles: mp 96–97 °C; λ_{max}^{KBr} 3.38, 3.48, 4.47, 7.58, 7.72, 8.75, 9.1 μm; $\delta_{Me_4Si}^{CDCl_3}$ 4.73 (OCH_2, AB q, J_{AB} = 12 Hz, $\Delta\nu$(AB) = 15 Hz), 2.98 (CH_3), 2.58 (CH_2 envelope), 1.35 (CH_3).

(9) Control experiments showed that the 1-methylcyclododecenes **19a** and **20a** were only negligibly reduced to 1-methylcyclododecane under the reaction conditions.[6]

(10) Cf. G. Fraenkel, S. H. Ellis, and D. T. Dix, *J. Am. Chem. Soc.*, **87**, 1406 (1965); E. J. Panek, *ibid.*, **95**, 8460 (1973).

(11) The apparatus described by Johnson and Schneider (W. S. Johnson and W. P. Schneider, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132) was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with water and saturated brine solution, and drying the extracts over anhydrous sodium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories. Nuclear magnetic resonance spectra were recorded with a Varian CFT-20 or Perkin-Elmer R20B spectrometer. Signals are reported as the chemical shift downfield from tetramethylsilane (Me_4Si) in parts per million of the applied field. Coupling constants are reported in hertz. Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected. High-pressure liquid chromatography (LC) was performed on Waters Associates ALC-201 Model 6000 and Model LC500 instruments with Porasil, μ-Porasil, and Corasil II columns.

(12) The procedure of P. Beak and T. L. Chaffin, *J. Org. Chem.*, **35**, 2275 (1970), was employed.

Anal. Calcd for $C_{16}H_{29}NO_3S$: C, 60.92; H, 9.27; N, 4.44; S, 10.16. Found: C, 61.2; H, 9.5; N, 4.2; S, 10.4.

***cis*-2-Cyano-2-methylcyclododecyl (Methanesulfonyl)-methyl Ether (9a).** The above procedure was followed using 4.2 g (21 mmol) of 85% *m*-chloroperoxybenzoic acid and 2.0 g (7.0 mmol) of cis cyano ether **7a** in 100 mL of chloroform to give 1.85 g (84%) of sulfone **9a** as small white plates, mp 94–95 °C, from ethyl acetate–hexane: λ_{max}^{KBr} 3.40, 3.48, 4.46, 7.60, 7.70, 8.80, 9.1 μm; $\delta_{Me_4Si}^{CDCl_3}$ 4.57 (OCH_2), 3.82 (H-1, m), 2.95 (CH_3), 1.51 (CH_3), 1.36 (CH_2 envelope).

Anal. Calcd for $C_{16}H_{29}NO_3S$: C, 60.92; H, 9.27; N, 4.44; S, 10.16. Found: C, 61.2; H, 9.4; N, 4.6; S, 10.2.

2-Cyano-1,2-dimethylcyclododecanol (10a, 11a). To a solution of 7 mL (21 mmol) of 3 M ethereal methylmagnesium bromide in 15 mL of tetrahydrofuran (THF) at −5 °C was added a cooled (0 °C) solution of 2.21 g (10 mmol) of cyano ketone **1a** in 15 mL of THF dropwise with stirring. The mixture was allowed to reach room temperature over 0.5 h. Saturated ammonium chloride was added and the product was isolated with ether, affording 2.35 g (99%) of yellow oil shown to contain 10% of unreacted cyano ketone **1a** and 90% of a 3:1 mixture of trans and cis cyanohydrins **10a** and **11a**. Chromatography on silica gel with 10% ethyl acetate–hexane as the eluant yielded 2.1 g (88%) of the cyanohydrin mixture: λ_{max}^{film} 2.85, 3.46, 4.45, 9.15 μm.

***trans*-2-Cyano-1,2-dimethylcyclododecanol (10a).** A stirred suspension of 0.625 g (2.1 mmol) of cyano ether **14a**, 1.71 g (6.3 mmol) of mercuric chloride, and 2.17 g (12.6 mmol) of cadmium carbonate in 30 mL of 10:1 acetonitrile–water was heated to 50 °C for 3 h. The cooled mixture was filtered and the product was isolated by ether extraction and distilled to give 0.45 g (91%) of oil, bp 120–130 °C (bath temperature) at 0.1 torr, which solidified on standing. Recrystallization from hexane afforded the trans cyanohydrin **10a** as a white solid: mp 126–127 °C; λ_{max}^{film} 2.86, 3.39, 4.48, 8.90, 9.20, 9.50 μm.

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 11.46; N, 5.90. Found: C, 75.8; H, 11.7; N, 5.8.

***cis*-2-Cyano-1,2-dimethylcyclododecanol (11a).** The procedure described above for the trans cyanohydrin **10a** was followed exactly, using 0.14 g (0.47 mmol) of cyano ether **15a**. Cyanohydrin **11a**, mp 82–82.5 °C from hexane, was thereby secured in 82% yield: λ_{max}^{film} 2.90, 3.39, 3.48, 4.46, 8.98, 9.30, 9.55 μm; $\delta_{Me_4Si}^{CDCl_3}$ 2.78 (OH), 1.38 (CH_2 envelope), 1.33 and 1.20 (CH_3's).

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 11.46; N, 5.90. Found: C, 76.0; H, 11.6; N, 5.9.

***trans*-2-Cyano-1,2-dimethylcyclododecyl Methyl Ether (12a).** A suspension of 5 mL of freshly prepared W-2 Raney nickel[13] in 100 mL of ethanol containing 0.70 g (2.36 mmol) of MTM ether **14a** was stirred for 1 h at room temperature. The mixture was filtered through Celite, and the ethanol was distilled under reduced pressure to give 0.55 g (93%) of colorless oil: λ_{max}^{film} 3.37, 3.42, 3.51, 4.46, 6.84, 7.25, 8.95 μm; $\delta_{Me_4Si}^{CCl_4}$ 3.11 (OCH_3), 1.37 (CH_2 envelope), 1.27 (CH_3).

Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.23; H, 11.72; N, 5.32.

***cis*-2-Cyano-1,2-dimethylcyclododecyl Methyl Ether (13a).** The above procedure was applied to 0.44 g (1.5 mmol) of MTM ether **15a**, using 6 mL of W-2 Raney nickel[13] in 50 mL of ethanol to give 0.29 g (77%) of colorless oil: λ_{max}^{film} 3.36, 3.42, 3.51, 4.46, 6.84, 7.25, 9.25 μm; $\delta_{Me_4Si}^{CCl_4}$ 3.22 (OCH_3), 1.38 (CH_2 envelope), 1.23 (CH_3), 1.10 (CH_3).

Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.3; H, 11.4; N, 5.4.

***trans*-2-Cyano-1,2-dimethylcyclohexyl Methyl Ether (12b).** To a stirred suspension of 0.5 mL of freshly prepared W-2 Raney nickel[13] in 5 mL of ethanol was added 0.10 g (0.47 mmol) of MTM ether **14b** in 5 mL of ethanol. After 1.5 h, the mixture was filtered through Celite, and the ethanol was distilled under reduced pressure to give 0.075 g (96%) of colorless oil: λ_{max}^{film} 3.34, 3.40, 3.49, 4.46, 6.84, 7.25, 8.50, 9.19 μm; $\delta_{Me_4Si}^{CCl_4}$ 3.07 (OCH_3) and 1.23 (CH_3).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.82; H, 10.25; N, 8.38. Found: C, 71.53; H, 10.34; N, 8.48.

***cis*-2-Cyano-1,2-dimethylcyclohexyl Methyl Ether (13b).** Desulfurization of 0.60 g (2.8 mmol) of cis MTM ether **15b** was achieved using 2 mL of W-2 Raney nickel[13] suspension in 50 mL of ethanol as described above to yield 0.35 g (76%) of yellow oil: λ_{max}^{film} 3.34, 3.41, 3.49, 4.46, 6.80, 7.21, 8.42, 8.81, 9.24 μm; $\delta_{Me_4Si}^{CCl_4}$ 3.20 (OCH_3), 1.28 (CH_3), 1.12 (CH_3).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.82; H, 10.25; N, 8.38. Found: C, 71.6; H, 10.2; N, 8.1.

2-Cyano-1,2-dimethylcyclododecyl (Methylthio)methyl Ethers (14a, 15a). A. From Cyanohydrins 10a and 11a. A solution of 0.71 g (3.0 mmol) of the 3:1 cyanohydrin mixture **10a,11a** in 15 mL of dimethyl sulfoxide and 15 mL of acetic anhydride was stirred at room temperature for 64 h. The solution was poured into 150 mL of saturated sodium bicarbonate and 75 mL of hexane at 0 °C and the resultant mixture was vigorously stirred for 1 h. The product (0.88 g, 98%) was isolated with hexane and purified by preparative LC to afford material with the following properties.

***trans*-2-Cyano-1,2-dimethylcyclododecyl(Methylthio)-methyl Ether (14a):** λ_{max}^{film} 3.47, 4.48, 9.10, 9.70 μm; $\delta_{Me_4Si}^{CCl_4}$ 4.51 (OCH_2), 2.13 (CH_3), 1.48 (CH_3), 1.43 (CH_2 envelope), 1.35 (CH_3).

Anal. Calcd for $C_{17}H_{31}NOS$: C, 68.63; H, 10.50; N, 4.71; S, 10.78. Found: C, 68.8; H, 10.6; N, 4.6; S, 10.6.

***cis*-2-Cyano-1,2-dimethylcyclododecyl (Methylthio)methyl Ether (15a):** mp 51–52 °C from methanol–water; λ_{max}^{film} 3.47, 4.48, 9.60, 9.70 μm; $\delta_{Me_4Si}^{CCl_4}$ 4.58 (OCH_2), 2.21 (CH_3), 1.41 (CH_2 envelope), 1.30 (CH_3), 1.21 (CH_3).

Anal. Calcd for $C_{17}H_{31}NOS$: C, 68.63; H, 10.50; N, 4.71; S, 10.78. Found: C, 68.7; H, 10.8; N, 4.9; S, 10.8.

B. From Epoxide 18a. To a solution of 0.41 g (2.0 mmol) of epoxide **18a** (contaminated by 10% of the trans isomer)[15] in 5 mL of benzene was added 5 mL (8.4 mmol) of 1.7 M diethylaluminum cyanide in toluene. After 48 h, the solution was cooled to 0 °C and acidified with 10% aqueous HCl. The product isolated by ether extraction was dissolved in 10 mL of dimethyl sulfoxide and 10 mL of acetic anhydride at room temperature. After 48 h this product was isolated by hexane extraction as described above to give the trans cyano ether **14a** identical with material previously prepared.

***trans*-2-Cyano-1,2-dimethylcyclohexyl (Methylthio)-methyl Ether (14b). A. From Cyano Ketone 1b.** To a well-stirred solution of 2.95 mL (8.9 mmol) of ethereal methylmagnesium bromide in 20 mL of THF and 10 mL of ethyl ether at 0 °C was added 0.400 g (2.92 mmol) of cyano ketone **1b** in 10 mL of THF. After 0.5 h at 0 °C and 0.5 h at room temperature, the stirred mixture was treated with 15 mL of saturated ammonium chloride solution, and the product was isolated by ether extraction to give 0.365 g (82%) of cyanohydrin **10b**, a yellow oil: λ_{max}^{film} 2.86, 3.36, 3.48, 4.46, 6.84, 7.25, 11.00 μm.

This material was stirred with 12 mL of acetic anhydride and 12 mL of dimethyl sulfoxide at room temperature for 48 h. The resulting solution was poured into a well-stirred mixture of 50 mL of saturated sodium bicarbonate and 50 mL of hexane at 0 °C. After 1 h, the product was isolated by hexane extraction to give 0.447 g (88%) of the trans MTM ether **14b**: λ_{max}^{film} 3.33, 3.38, 3.48, 4.46, 6.84, 7.24, 8.50, 9.30, 9.60 μm; $\delta_{Me_4Si}^{CCl_4}$ 4.30 (OCH_2), 2.09 (CH_3), 1.35 (CH_3), 1.30 (CH_3).

Anal. Calcd for $C_{11}H_{19}NOS$: C, 61.95; H, 8.98; N, 6.57; S, 15.03. Found: C, 61.81; H, 9.09; N, 6.37; S, 15.24.

B. From Epoxide 18b. A solution of 0.97 g (7.7 mmol) of epoxide **18b**[15] in 15 mL of benzene was stirred with 23 mL (35 mmol) of 1.5 M diethylaluminum cyanide in toluene at reflux for 4 h and at room temperature for an additional 14 h. The mixture was poured into 35 mL of cold 10% HCl and, after stirring for 0.5 h, was extracted with ether to yield 0.61 g (52%) of yellow oil whose spectral properties were identical with those of the trans cyanohydrin **10b**, obtained as described above in A. This material afforded the corresponding MTM ether **14b** in 87% yield by the above procedure.

***cis*-2-Cyano-1,2-dimethylcyclohexyl (Methylthio)methyl Ether (15b).** To a stirred solution of 1.00 g (7.29 mmol) of cyano ketone **1b** in 160 mL of THF at −78 °C was added 6.6 mL (9.9 mmol) of 1.5 M ethereal methyllithium. After 0.5 h at −78 °C

(13) R. Mozingo, "Organic Synthesis", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 181.

(14) J. Sicher, M. Svoboda, M. Pankova, and J. Zavada, *Collect. Czech. Chem. Commun.*, **36**, 3637 (1971).

(15) Secured from the corresponding alkene via epoxidation with *m*-chloroperoxybenzoic acid in chloroform.[6]

the mixture was treated with 5 mL of saturated ammonium chloride, and the product was isolated by ether extraction to give 1.05 g (94%) of colorless oil.

A 4.20-g sample of the above mixture of cyanohydrins was converted to the MTM ethers **14b** and **15b** by the procedure described above for **14b**. The resulting product (5.7 g, 97%), a yellow oil, was shown to be a 65:35 mixture by gas chromatography and NMR analysis. Separation was easily effected using preparative LC to afford the previously described trans isomer **14b** (major product) and the minor cis isomer **15b**: λ_{max}^{film} 3.35, 3.42, 3.48, 4.46, 6.84, 7.24, 8.95, 9.30, 9.60, 9.94 μm; $\delta_{Me_4Si}^{CCl_4}$ 4.47 (OCH_2), 2.17 (CH_3), 1.33 (CH_3), 1.27 (CH_3).

Anal. Calcd for $C_{11}H_{19}NOS$: C, 61.95; H, 8.98; N, 6.57; S, 15.03. Found: C, 61.78; H, 8.96; N, 6.49; S, 15.27.

***trans*-2-Cyano-1,2-dimethylcyclododecyl (Methanesulfonyl)methyl Ether (16a).** The procedure described for sulfone **8a** was employed, using 0.90 g (4.5 mmol) of *m*-chloroperoxybenzoic acid and 0.45 g (1.5 mmol) of cyano ether **14a** in 25 mL of chloroform. The sulfone **16a** (0.42 g, 85% yield) was secured as white needles: mp 105–106 °C from ethyl acetate–hexane; λ_{max}^{film} 3.29, 3.47, 4.48, 7.60, 8.78, 9.01, 10.7, 13.2 μm; $\delta_{Me_4Si}^{CDCl_3}$ 4.45 (OCH_2), 2.88 (CH_3), 2.55 (CH_3), 1.45 (CH_3 and CH_2 envelope).

Anal. Calcd for $C_{17}H_{31}NO_3S$: C, 61.97; H, 9.48; N, 4.25; S, 9.73. Found: C, 62.1; H, 9.5; N, 4.1; S, 9.9.

***cis*-2-Cyano-1,2-dimethylcyclododecyl (Methanesulfonyl)methyl Ether (17a).** The procedure described for sulfone **8a** was employed, using 0.30 g (1.5 mmol) of *m*-chloroperoxybenzoic acid and 0.14 g (0.47 mmol) of cyano ether **15a** in 10 mL of chloroform. The sulfone **17a** (0.093 g, 60% yield), mp 152–153 °C from ethyl acetate–hexane, was secured as a white solid: λ_{max}^{KBr} 3.49, 4.48, 7.58, 7.64, 8.84, 9.10 μm; $\delta_{Me_4Si}^{CDCl_3}$ 4.44 (OCH_2), 2.95 (CH_3), 1.39 (CH_3 and CH_2 envelope), 1.23 (CH_3).

Anal. Calcd for $C_{17}H_{31}NO_3$: C, 61.97; H, 9.48; N, 4.25; S, 9.73. Found: C, 62.1; H, 9.5; N, 4.1; S, 9.8.

Typical Procedures for Reduction–Elimination of Cyanohydrin Derivatives. A. Lithium in Ammonia. To a stirred solution of 84 mg (12 mg-atoms) of lithium in 20 mL of liquid ammonia and 5 mL of THF was added a solution of 0.31 g (1.05 mmol) of cyano ether **14a** in 3 mL of THF. After 1 min, the solution was cooled to −78 °C with a dry ice bath and solid ammonium chloride was added to discharge the blue color. The ammonia was allowed to evaporate and the product was isolated by hexane extraction, affording 0.22 g (100%) of a colorless oil. Distillation at 90–100 °C (bath temperature) at 0.15 torr afforded 0.17 g (83%) of a 35:65 mixture of (*E*)- and (*Z*)-1,2-dimethylcyclododecene (**22** and **21**) according to gas chromatographic analysis.[16]

B. Sodium Naphthalenide in Hexamethylphosphoramide. A mixture of sodium (0.45 g, 19.6 mg-atoms) and naphthalene (2.80 g, 22.0 mmol) in 15 mL of HMPA was stirred overnight. To the resulting green solution was added 0.165 g (0.50 mmol) of cyano ether **14a** in 2 mL of HMPA. After 24 h, water and aqueous HCl were added and the product was isolated by hexane extraction. Chromatography on silica gel, using hexane as the eluant, afforded 0.081 g (83%) of (*E*)-1,2-dimethylcyclododecene (**22**).[16]

Characteristics of the Cycloalkene Products. (*E*)-1-Methylcyclododecene (20):[14] λ_{max}^{film} 3.38, 3.48, 6.88, 6.95, 7.25 μm; $\delta_{Me_4Si}^{CCl_4}$ 5.28 (H-2, t, J = 8 Hz), 2.04 (allylic CH_2's, m), 1.60 (CH_3), 1.28 (CH_2 envelope).

(*Z*)-1-Methylcyclododecene (19):[14] λ_{max}^{film} 3.40, 3.48, 6.82, 6.90, 7.25 μm; $\delta_{Me_4Si}^{CCl_4}$ 5.05 (H-2, t, J = 8 Hz), 2.05 (allylic CH_2's), 1.64 (CH_3), 1.34 (CH_2 envelope).

(*E*)-1,2-Dimethylcyclododecene (22): λ_{max}^{film} 3.40, 3.46, 6.84, 6.90, 7.25 μm; $\delta_{Me_4Si}^{CCl_4}$ 2.72–2.02 (allylic CH_2's), 1.67 (CH_3's), 1.21 (CH_2 envelope).

(*Z*)-1,2-Dimethylcyclododecene (21): λ_{max}^{film} 3.40, 3.48, 6.80, 6.91, 7.15 μm; $\delta_{Me_4Si}^{CCl_4}$ 2.17–1.75 (allylic CH_2's), 1.54 (CH_3's), 1.32 (CH_2 envelope).

Acknowledgments. We are grateful to the National Science Foundation for support of this work through a research grant (MPS75-07777).

(16) The analysis was performed by using a 6 ft × 1/8 in. column of 5% (w/w) 1:10 silver nitrate–Carbowax 20M on 80–100 mesh Chromosorb W.

Tetracyclic Analogues of the Rosane Lactones from *Eupatorium album*[1]

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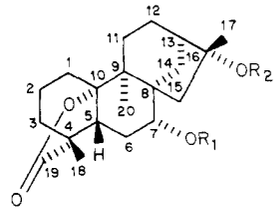
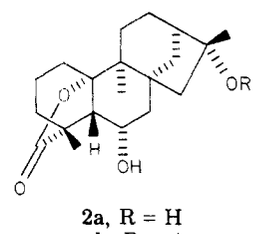
Isolation and structure determination of eupatalbin and eupatoralbin, two tetracyclic diterpenoids of a new skeletal type, from *Eupatorium album* L. are reported. Eupatalbin, details of whose structure and stereochemistry were established by X-ray crystallography, is *ent*-7β-hydroxy-9,10-friedokauran-19,10β-olide **1a**. Eupatoralbin is the *ent*-6β-hydroxy analogue **2a**. Comments are offered on the biogenesis. An earlier study (ref 2) dealt with *E. petaloideum* Britt., not *E. album*.

In an earlier article[2] we described isolation and structure determination of several new hydroxylated *ent*-kauranoic acids from what was presumed to be *Eupatorium album* L. Subsequent examination of the vouchers showed that the collection actually represented the morphologically very similar but geographically highly restricted *E. petaloideum* Britt. We now report isolation and structure determination from authentic *E. album* of eupatalbin (**1a**) and eupatoralbin (**2a**), two tetracyclic diterpenoids of a new skeletal type.[3] Eupatorin (3′,5-dihydroxy-4′,6,7-trimethoxyflavone) was also found.[5]



1a, $R_1 = R_2 = H$
b, R_1 = Ac; R_2 = H
c, $R_1 = R_2$ = Ac



2a, R = H
b, R = Ac

(1) Work at Florida State University supported in part by U.S. Public Health Service Grant CA-1312 through the National Cancer Institute.
(2) W. Herz and R. P. Sharma, *J. Org. Chem.*, 41, 1021 (1976).

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