Table III. Cyclic Ethers

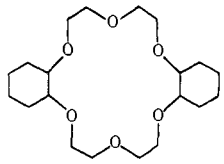
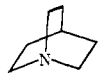
Compound	ΔH_{obsd}, kcal/mol
Tetrahydrofuran 	−0.08 ± 0.007
1,4-Dioxane 	−0.06 ± 0.003
1,3-Dioxolane 	−0.08 ± 0.003
Trioxane 	−0.04 ± 0.06
Triacetonemannitol	−0.21 ± 0.10
Dicyclohexyl-18-crown-6 ether 	−5.99 ± 0.36

Table IV. Amines

Compound	ΔH_{obsd}, kcal/mol
Primary amines react with system	
Diethylamine	−0.68 ± 0.03
Triethylamine	0 ± 0.02
Quinuclidine 	−0.26 ± 0.05
N,N,N′,N′-Tetramethyl-1,2-propanediamine	−0.71 ± 0.02
N,N,N′,N′-Tetramethylethylenediamine	−0.75 ± 0.01
Pyridine	−0.16 ± 0.004

(4) The cyclic polyethers show that the orientation of vicinal oxygen atoms in the proper conformation is important; note the low value for vicinal oxygens in 1,3-dioxolane.[9]

(5) Table V shows that by themselves acetate ester

Table V. Esters

Compound	ΔH_{obsd}, kcal/mol
Ethyl acetate	−0.02 ± 0.006
Ethylene diacetate	0
Glycerol triacetate	−0.03 ± 0.016
Glycerol diacetate	−0.15 ± 0.005
Glucose pentaacetate	−0.014 ± 0.08
Maltose octaacetate	−0.60 ± 0.11
Cellobiose octaacetate	−0.62 ± 0.14

groups are very poor ligands for Na^+ under our conditions, although an accumulation of them has some additive effect. However, comparison of glycerol diacetate with glycerol triacetate shows that the cooperative effect of a hydroxyl group and a vicinal acetate is superior to three vicinal acetates (in glycerol triacetate) or a lone hydroxyl group in ethanol. It is well known that completely acetylated cellulose is a poor reverse osmosis membrane material compared to the partially hydrolyzed polymer.[4,5] The data in Table V suggest that the hydrolyzed material might also complex cations better than the completely acetylated form. Comparison of acetylated glucose, maltose, and cellobiose suggests again that a cooperative effect between acetate and ether linkages could assist in binding sodium to cellulose acetate.

Table VI. Other Assorted Solvents with Ligand Groups

Compound	ΔH_{obsd}, kcal/mol
Acetonitrile	+0.06 ± 0.01
Dimethyl sulfoxide	−0.34 ± 0.01
N,N-Dimethylformamide	−0.23 ± 0.01
N,N-Dimethylacetamide	−0.30 ± 0.01
Hexamethylphosphoramide	−0.58 ± 0.02

The relatively high values for DMSO and the amides shown in Table VI accord with their use as dipolar aprotic solvents.[9]

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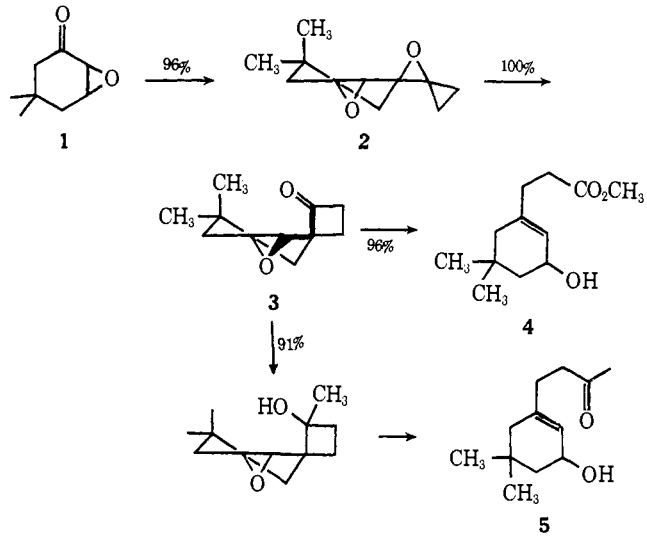
New Synthetic Reactions. Secoalkylation

Sir:

The Michael reaction constitutes one of the most useful synthetic reactions.[1] In essence, it involves the incorporation of alkyl groups as $C^+CC(=O)$ fragments. We wish to report a new alkylation reaction in which the electronic sense of the Michael acceptor is reversed, that is, introduction of alkyl groups utilizing $C^-CC(=O)$ as the synthetic unit. Application of this method led to a new annelation procedure complementary to the widely employed Robinson procedure.

Scheme I outlines the approach. Spiroannelation

Scheme I. Secoalkylation of 2,3-Epoxy-5,5-dimethylcyclohexanone



of α,β-epoxy ketone **1**[2] with diphenylsulfonium cyclopropylide, generated reversibly from potassium hydroxide and diphenylcyclopropylsulfonium fluoroborate,[3]

(1) For general discussions see E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179 (1959); H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Menlo Park, Calif., 1972, pp 595–623.

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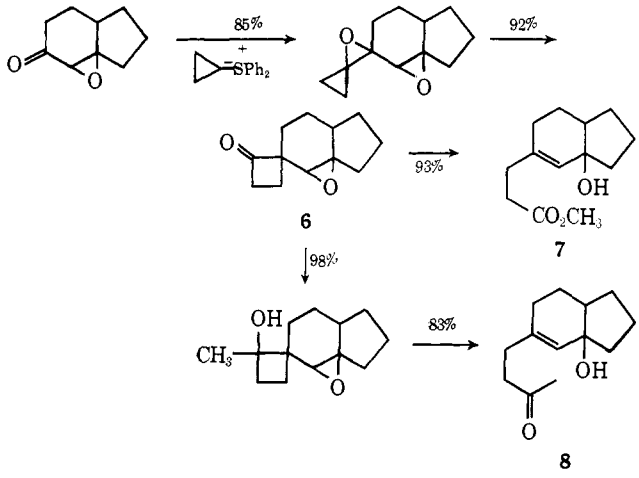
produced diepoxide **2**, bp 74° (1 mm).[4,5] Selective epoxide rearrangement to cyclobutanone **3** succeeded by washing a pentane solution of **2** with 1 *M* aqueous fluoroboric acid.[3,6] Spectral and chromatographic properties of **3** indicated its stereohomogeneity. The stereochemistry depicted is based upon the least hindered approach of cyclopropylide and inversion of configuration at the migration terminus in the epoxide rearrangement.

In the conformation of epoxycyclobutanone **3** depicted, the cyclobutyl and epoxy bonds emboldened bear an approximate trans diaxial relationship. Conversion of the carbonyl group into a good electron source by addition of nucleophiles should initiate fragmentation[7] accompanied by the release of 54 kcal/mol, the combined strain energies of cyclobutyl and epoxide rings.[8] In the event, allowing a methanolic solution of sodium methoxide and epoxycyclobutanone **3** to stand at room temperature resulted in nearly quantitative isolation of the ester allylic alcohol **4**.[5] Alternatively, methyllithium addition in ether at −78° followed by treatment of the resultant cyclobutanol with sodium methoxide in methanol generated the 3-oxobutylallylic alcohol **5** in 91% isolated yield for the two steps.[5] Since the process involves the introduction of the alkyl group C⁻CC(=O) by ring formation (spiroannelation) followed by ring cleavage, we term the overall process secoalkylation.

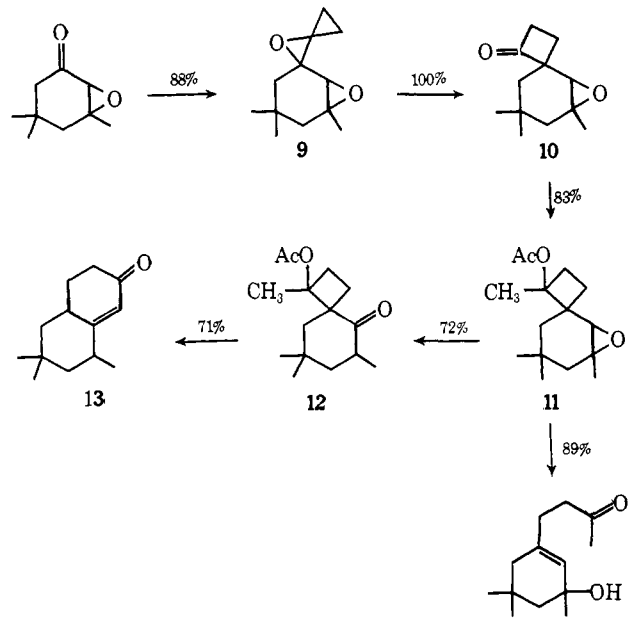
To test the generality of the concept and the applicability to steroid synthesis (in particular the ecdysones), 1,2-epoxybicyclo[4.3.0]nonan-3-one[9] was examined (Scheme II). Selective epoxide rearrangement to epoxycyclobutanone **6** was highly successful employing 10 mol % oxalic acid in acetonitrile at room temperature. Under these conditions, nmr studies indicated the half-life of the diepoxide at 37° to be 11 min. Although **6** was presumably a mixture of two isomers (indistinguishable in **6** but observable in its diepoxide precursor) both fragmented smoothly in reactions with nucleophiles. Thus, methanolic sodium methoxide treatment at 25° or methyllithium addition in ether at −78° followed by reaction with methanolic sodium methoxide gave the ester **7**[5] (93%) and the ketone **8**[5] (82% overall), respectively. Presumably other nucleophiles would initiate similar fragmentations and this process is therefore a general method for introduction of C⁻CC(=O)-Nucl.

Scheme II. Secoalkylation of Epoxybicyclo[4.3.0]nonan-3-one

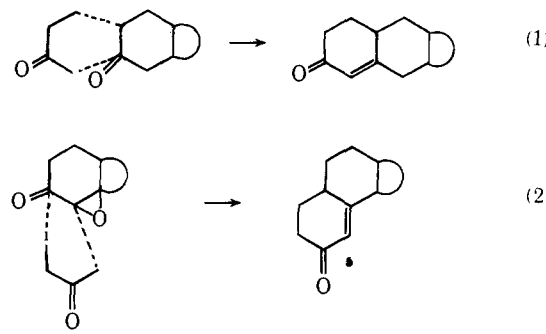


To illustrate the synthetic utility of such an alkylation reaction, a new annelation procedure based upon secoalkylation was developed as outlined in Scheme III.

Scheme III. Secoalkylative Annelation



Spiroannelation of isophorone oxide[9b] with diphenylsulfonium cyclopropylide generated initially diepoxide **9**[5] (bp 31° (0.01 mm), mp 34–35°) and subsequently epoxycyclobutanone **10**[5] (mp 35.5–36.0°) after treatment with 1 *M* aqueous fluoroboric acid at 25°. Methyllithium addition in ether at −78° followed by work-up with acetyl chloride gave acetoxycyclobutane **11**. This cyclobutane participated smoothly in the fragmentation reaction as illustrated by the room temperature cleavage with sodium methoxide in methanol. Refluxing a benzene solution of the epoxide **11** with 10 mol % anhydrous lithium perchlorate[10] produced keto



(4) The procedure involved utilization of 1.0 equiv of epoxy ketone, 1.25 equiv of cyclopropyldiphenylsulfonium fluoroborate, and 2.0 equiv of potassium hydroxide in DMSO at 25° for 2 hr.

(5) All new compounds were characterized by spectral means and correct determinations of elemental compositions.

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acetate **12**. Sodium ethoxide (0.01 *M*) in 1:2 ethanol–benzene at reflux effected fragmentation and *in situ* aldol cyclization to generate trimethyloctalone **13**. This regioselective annelation procedure complements the normal Robinson process (eq 1) in that the two-carbon arm is bonded to the carbonyl carbon and the one-carbon arm to the α carbon (eq 2).

The immensity of the applications of the Michael reaction foreshadows the potentiality of this new electronically reversed Michael-type alkylation.

Acknowledgment. We wish to express our appreciation to the National Science Foundation and the National Institutes of Health for their generous support of our programs.

(11) Camille and Henry Dreyfus Foundation Teacher–Scholar Grant recipient.

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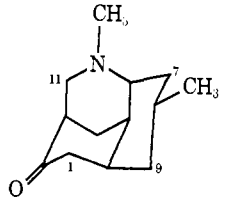
The Total Synthesis of (±)-Luciduline

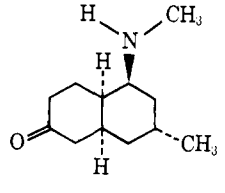
Sir:

The known *Lycopodium* alkaloids constitute a diverse class of skeletal types[1] which appear to be linked biogenetically to lysine,[2] the primary source of structural atoms in this group of naturally occurring bases. We report herein a stereoselective synthesis of (±)-luciduline (**1**)[3] which features several generally useful methods of carbocycle synthesis.[4,5]

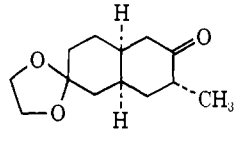


1

Systematic analysis of the possible synthetic routes to **1** readily suggests that the tricyclic skeleton of luciduline can be established from ketoamine **2** *via* an intramolecular Mannich reaction, C-11 being derived from formaldehyde. Consequently, the stereoselective synthesis of **2** became our primary objective.



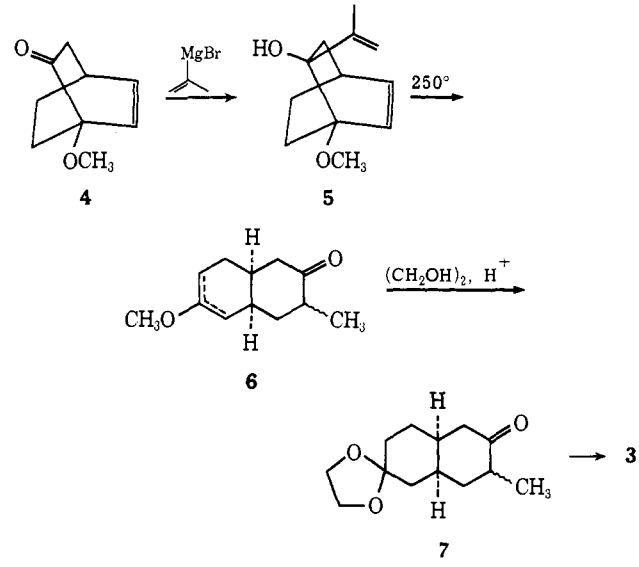
2



3

Although potential routes to **2** may be visualized from 5-methylcyclohexane-1,3-dione, we felt that the controlled introduction of the required sites of asymmetry in **2** could best be achieved through ketal ketone **3**, the synthesis of which may be accomplished as summarized in Scheme I.

Scheme I



4 **5** **6** **7**

As previously reported by us, bicyclo[2.2.2]oct-5-en-2-one derivatives such as **4** may be conveniently synthesized in good yield from 2,5-dihydroanisole and the useful ketene equivalent 2-chloroacrylonitrile.[4] Furthermore, oxy-Cope rearrangement[6] of **5** followed by ketalization of **6** affords **7** in greater than 65% yield.[5] Contrary to our earlier report,[5] the ketal ketone **7** obtained on chromatography is an equilibrium 60:40 mixture of methyl epimers in which the desired α isomer **3** predominates. The lack of stereochemical definition at this stage was readily overcome by a single recrystallization of **7** (hexane) affording the desired α-methyl epimer **3**, mp 117–118°, in good yield. A simple re-equilibration–crystallization recycle of the isomer mixture **7** obtained from the filtrate yielded additional amounts of **3** with negligible losses of material.

Treatment of ketal ketone **3** with 1 equiv of *p*-toluenesulfonylhydrazine in anhydrous methanol for 3 hr at 25° afforded a quantitative yield of tosylhydrazone **8**, mp 137–139°, without epimerization of the methyl group. Tosylhydrazone **8** was converted to the single ketal olefin **9** with 2 equiv of methyllithium in anhydrous ether. The high regioselectivity of this reaction has been previously demonstrated.[7] Crude **9** was stereoselectively oxidized to epoxide **10**, mp 51–53°, in 80% overall yield from **3**, with *m*-chloroperbenzoic acid in chloroform.

Cleavage of **10** with sodium thiophenoxide in refluxing methanol (12 hr) proceeded regioselectively to **11**, mp 95–96° (85% yield), which was cleanly desulfurized to ketal alcohol **12**, mp 95–97° (82% yield), with Raney nickel[8] in refluxing ethanol. The entire sequence **3**–**12**

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