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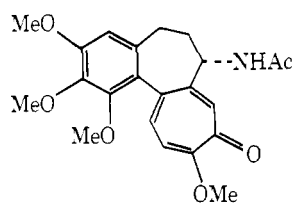
Communications to the Editor

A New Approach to the Synthesis of Tropolones: Syntheses of Colchicine and β-Dolabrin

Sir:

Colchicine (**1**), one of the major alkaloid constituents of the autumn crocus (*Colchicum automnale L.*), has attracted the attention of synthetic organic chemists for over two decades.[1-3] Renewed interest in the pharmacology of colchicine, in particular its antimitotic activity,[4] has encouraged us to develop a convergent synthesis of this natural product which would also be readily amenable to the synthesis of structural analogues. The purpose of this communication is to outline our preliminary efforts in the area of tropolone synthesis which have culminated in an efficient synthesis of desacetamidoisocolchicine (**2**), a common intermediate in all but two of the numerous syntheses of colchicine which have been reported to date.[2,3] The



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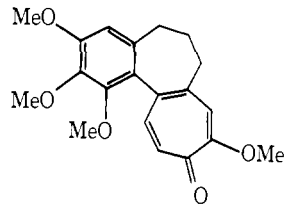

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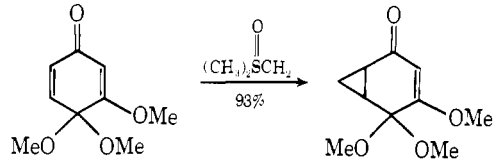
present approach to **2**, as well related tropolones, has focused upon the design of a suitably functionalized tropolone "equivalent" which could be employed in annelation reactions with binucleophilic reagents to construct polycyclic ring systems such as **1** and **2**. The cyclopropyl ketone **4** has been found to serve admirably in this capacity.

Quinone monoketal **3**,[5,6] upon treatment with dimethyloxosulfonium methylide[7,8] (2 equiv), afforded crystalline cyclopropyl ketone **4** in a 93% yield (mp 94-95 °C).[9] When **4** was



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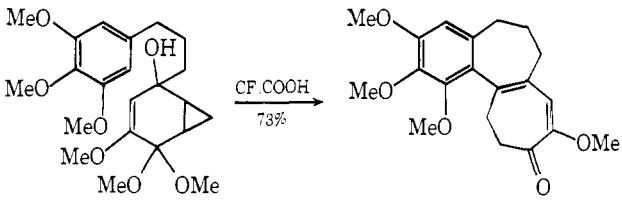

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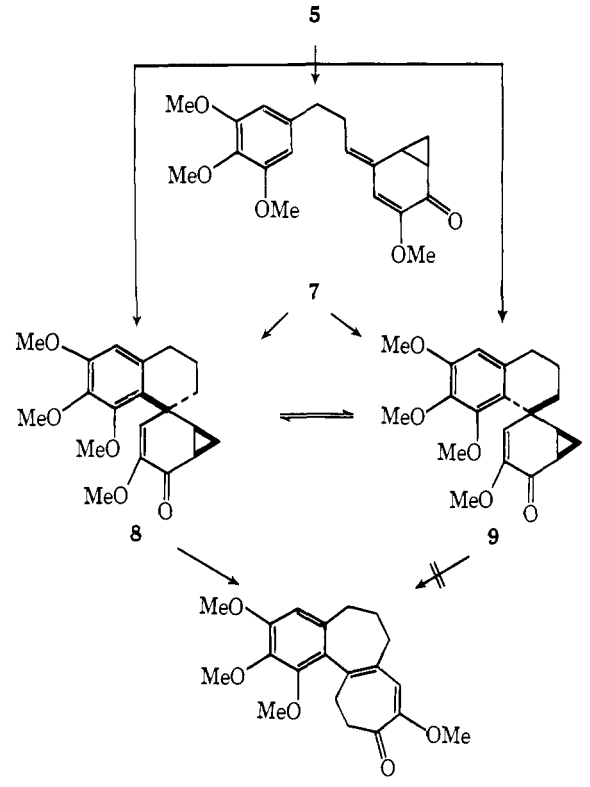
allowed to react with 3-(3,4,5-trimethoxyphenyl)-*n*-propylmagnesium bromide (1.5 equiv), prepared from the appropriate bromide,[2f] the vinylogous hemiketal **5** was obtained in a 70-90% yield after chromatography over silica gel. When ketal **5** was treated with neat trifluoroacetic acid, 11,12-dihydrodesacetamidoisocolchicine (**6**) was obtained in a 73% yield (mp 111-112 °C).[9] The structure of **6** was established by oxidation to desacetamidoisocolchicine (**2**) with DDQ (72%).[10]

Table I. Trifluoroacetic Acid Induced Rearrangements[a]

Substrate	Time, min (h)	Products ratio, % (yield)[b]
5	1	**7**:**8**:**9** (10:3:7)[c]
5	60	**6**:**8**:**9** (22:16:62)[c]
5	(15)	**6** (73)
7	40	**6** (11) + **8**:**9** (1:5, 56)
8	30	**6**:**8**:**9** (1:1:1)[c]
9	30	**6**:**8**:**9** (1:1:8)[c]
9	(9)	**6** (81)

[a] All reactions were run at 25 °C in neat trifluoroacetic acid. [b] Isolated yields. [c] Products were not separated; ratio was determined by ^{1}H NMR.

From a mechanistic standpoint the acid-catalyzed transformation of ketal **5** to dihydrotropolone **6** is highly interesting. The complex series of events that intervene during this transformation were revealed by examining the behavior of ketal **5** upon treatment with trifluoroacetic acid for abbreviated time periods. It is evident from the results documented in Table I that **5** rapidly affords a mixture of dienone **7**[11] and diastereomeric spirans **8** (mp 169-172 °C) and **9** (mp 155-157 °C).[11]



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The minor spiran (**8**) was found to be identical with an intermediate prepared by Tobinaga and co-workers during their synthesis of **2**.[2g,10] The stereochemical assignments of **8** and **9** are based on an analysis of their modes of synthesis, spectroscopic properties, and respective behavior upon treatment with strong acids.[2g,12] Over a period of several minutes dienone **7** cyclizes to a mixture of **8** and **9** which then slowly rearrange with aryl migration to afford dihydrotropolone ether **6**. *It is*

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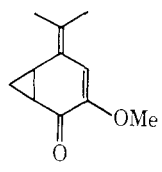
also noteworthy that spirans **8** *and* **9** *interconvert upon being treated independently with trifluoroacetic acid.* Furthermore, the observation that spiran **8** rearranges to **6** more rapidly than does spiran **9** suggests that the conversion of **5** to **6** proceeds entirely through spiran **8.** This notion is supported by the discovery that, while spiran **8** is converted to **6** (40%) upon treatment with boron trifluoride etherate in nitromethane, spiran **9** is recovered unchanged (1.0 equiv, 25 °C, 60 min). Although it is not readily apparent from an inspection of molecular models, these results indicate that only spiran **8** is able to adopt the stereoelectronic arrangement required for facile aryl migration. It is apparent that the aforegoing synthetic sequence to **2** embodies sufficient flexibility to incorporate the C-7 acetamido group or its equivalent at an early stage of the synthesis.

The general utility of cyclopropyl ketone **4** as a precursor to monocyclic tropolones has been demonstrated within the context of a synthesis of β-dolabrin (**13**).[13] Treatment of **4** with isopropylmagnesium bromide and subsequent dehydration-deketalization with acid (BF_3·Et_2O, CH_3NO_2) afforded dienone **10** (50%). Ring expansion of **10** to **11** was effected with base (KH, THF) followed by Me_3SiCl (90%). This transformation is viewed as proceeding via the electrocyclic ring opening of the enolate derived from **10.**[14] Oxidation of **11** with chloranil to **12** (60–70%) and subsequent demethylation (BBr_3) afforded β-dolabrin (**13**), mp 56.5–57 °C.



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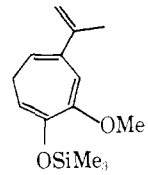

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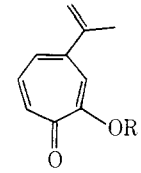

12, R = Me
13, R = H

Acknowledgment. Support from the National Institutes of Health is gratefully acknowledged.

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(6) For a general method of preparing quinone ketals such as **3**, see A. M. McKillop, D. H. Perry, M. Edwards, S. Antus, L. Farkas, M. Nogradi, and E. C. Taylor, *J. Org. Chem.,* **41,** 282 (1976).
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(9) Spectral data of all new compounds reported herein are in accord with the assigned structures. All new solids gave satisfactory combustion analyses.
(10) We wish to thank Professor S. Tobinaga for supplying us with authentic samples of (±)-**2** and (±)-**8.** Samples of **2** and **8** prepared as described herein were identical (melting point, NMR, IR, TLC) with the samples provided by Professor Tobinaga. Hydrolysis of **2** afforded desacetamidocolchiceine whose spectral and physical characteristics were in accord with those reported elsewhere.[2a]
(11) The stereoisomeric dienones and spirans were separated by liquid chromatographic techniques.
(12) We reason that in the cyclization reaction the aryl group will predominantly attack the convex face of the bicyclo[4.1.0] system thus affording **9** as the major product. A careful analysis of the Tobinaga synthesis,[2g] which gives only one of the diastereomeric spirans, predicts that **8** should be produced. Also in accord with the stereochemical assignment, the cyclopropyl methylene resonates at 14.5 and 12.4 ppm relative to Me_4Si in the ^{13}C spectra of **8** and **9,** respectively. A downfield shift is expected in **8** because of deshielding by the aryl group.
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Proton Affinity of Dichlorocarbene

Sir:

In a recent study of Levi et al.[1] employing the bracketing proton-transfer technique, the proton affinity of CCl_2 was estimated to be ~7 kcal/mol above that of NH_3. This is in contradiction to an earlier study of the proton affinity of CCl_2 from this laboratory,[2] in which the proton-transfer reaction

$$CCl_2D^+ + NH_3 \rightarrow CCl_2 + NH_3D^+ \qquad (1)$$

was reported to occur with a relatively high efficiency ($k = 4.4 \times 10^{-10}$ cm^3/(molecule s)). The occurrence of reaction 1 would suggest that the proton affinity of CCl_2D^+ is lower than that of NH_3. It is possible that the cause for this discrepancy could be that, instead of the sought-after proton-transfer reactions, there occur other, energetically more favorable, competing reactions between CCl_2H^+ and the bases (*i*-Pr_2O, *i*-Pr_2S, aniline) examined by Levi et al.,[1] even though all these compounds have proton affinities above that of NH_3.

It has been shown in previous studies[2,3] that halomethyl ions undergo a multitude of reactions with organic molecules. It is clear that the task of pinpointing the bases (B) for which the proton-transfer reaction

$$CX_2H^+ + B \rightarrow CX_2 + BH^+ \qquad (2)$$

(where $CX_2 = CF_2$, CCl_2, CFCl, etc.) turns from endothermic to exothermic can only be expected to be entirely successful if energetically and sterically more favorable reaction channels are not available to the reaction pair. It will be shown here that slightly exothermic proton transfer reactions do not always occur when a favorable competing channel is available.

We wish to report new ICR data on CCl_3D–B (20:1) mixtures carried out at 325 K, a total pressure of $3–5 \times 10^{-6}$, and an electron energy of 13 eV. We concentrated on the reactions with ethers, sulfides, and NH_3. The results are summarized in Table I.

The occurrence of reaction 1 was confirmed. The determination of the actual efficiency of this reaction was, as before, complicated by the occurrence of a competing reaction sequence[8] resulting ultimately in the formation of the same product ion:

$$CCl_2D^+ + NH_3 \rightarrow NH_2CDCl^+ + HCl \qquad (3)$$

$$NH_2CDCl^+ + NH_3 \rightarrow NH_3D^+ + NH_2CCl \qquad (4)$$

However, the occurrence of reaction 1 was verified in an experiment in which the precursors of NH_3D^+ were individually removed from the system (CCl_3D–NH_3 = 50:1) through double resonance ion ejection.