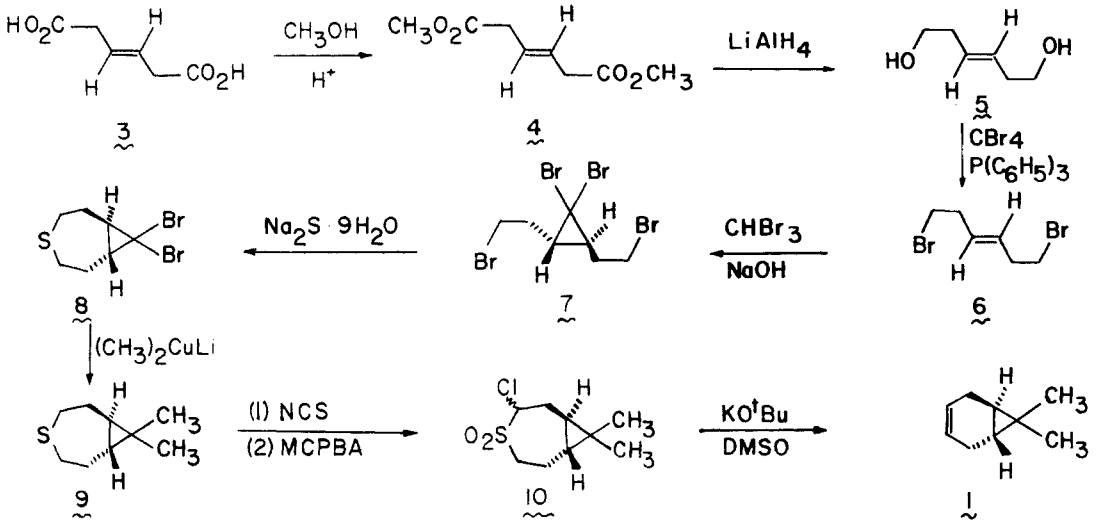
Scheme I



rearrangement product was identical in all respects with an authentic sample of **2** prepared by the addition of 1 equiv of dibromocarbene to 1,4-cyclohexadiene, followed by replacement of the bromines by methyl groups through the use of lithium dimethylcuprate.[12] At 110 °C the thermal rearrangement of **1** to **2** occurred 8 times faster than the rearrangement of the parent hydrocarbon.

In view of our interest in the electrochemical[15] and photoinduced electron-transfer-promoted reactions[16] of highly strained polycyclic molecules, we examined the oxidation of **1** under single-sweep cyclic voltammetry conditions which showed that **1** had an $E_{1/2}$ vs. a saturated calomel electrode of 1.34 V.[17] This value was sufficiently low that electron transfer from **1** to a variety of excited state photosensitizers was anticipated. Irradiation of a solution of **1** in methanol-d_4 containing 5 mol % of 1-CN as photosensitizer for 3.5 h with a Rayonet photochemical reactor containing 16 300-nm, 21-W lamps gave a 78% yield of **2**. Since this photochemistry was carried out in Pyrex glassware, only the 1-CN was excited. We believe that a tight cation radical–anion radical pair, which could be represented by **11** is formed.[18] Isomerization of the cation radical of **1** (**11**) to the cation radical of **2**, followed by back electron transfer from the anion radical of 1-CN would then produce **2**.

Lastly, we indicate that **1** is extremely acid-sensitive. It was rapidly isomerized to **12** in the presence of trace amounts of acid. We are continuing to explore the chemistry of **1** and of related derivatives of trans-fused bicyclic alkanes.

Acknowledgment. We are indebted to the National Science Foundation for Grant CHE-8414359 which supported this investigation.

Registry No. **1**, 101934-24-1; **2**, 36168-41-9; **3**, 29311-53-3; **4**, 25126-93-6; **5**, 71655-17-9; **6**, 59533-63-0; **7**, 101934-25-2; **8**, 101934-26-3; **9**, 101934-27-4; **10** (isomer 1), 101934-28-5; **10** (isomer 2), 102044-02-0; **12**, 26325-89-3; 1-CN, 86-53-3; $CHBr_3$, 75-25-2; Na_2S, 1313-82-2; $(CH_3)_2CuLi$, 15681-48-8; 8-methyl-4-thiabicyclo[5.1.0]octane, 101934-29-6.

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(14) In addition to 93% of **2**, the formation of ca. 7% of **12** was observed. In the absence of Dabco, the percentage of **12** varied, ranging up to 30% of the reaction mixture. This implies that **12** was formed in an acid-catalyzed process (vide post).

(15) Gassman, P. G.; Yamaguchi, R. *J. Am. Chem. Soc.* **1979**, *101*, 1308. Gassman, P. G.; Mullins, M. J.; Richtsmeier, S.; Dixon, D. A. *Ibid.* **1979**, *101*, 5793. Gassman, P. G.; Mullins, M. J. *Tetrahedron Lett.* **1980**, *21*, 2219.

(16) Gassman, P. G.; Olson, K. D.; Walter, L.; Yamaguchi, R. *J. Am. Chem. Soc.* **1981**, *103*, 4977. Gassman, P. G.; Olson, K. D. *Ibid.* **1982**, *104*, 3740. Gassman, P. G.; Hay, B. *Ibid.* **1985**, *107*, 4075.

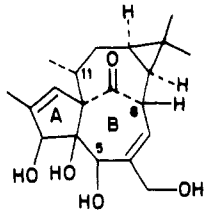
(17) This value can be compared to $E_{1/2}$ = 1.52 V measured for *trans*-bicyclo[4.1.0]hept-3-ene.[6] The effect of the methyl groups at C7 is consistent with the HOMO being associated with the C1–C6 bond.[15] All $E_{1/2}$ values were determined by single-sweep cyclic voltammetry and are nonreversible.

(18) While we show the C1–C6 bond as a one-electron bond in **11**, we cannot rule out the possibility that the isomerization of **1** to **2**, under the described photochemical conditions, involves a cation radical derived from removal of an electron from the C1–C7 bond. Also, on the basis of presently available data, we are unable to determine whether the photoinduced isomerization of **1** to **2** is a cation radical–chain process.

Synthetic Studies on the Ingenane Diterpenes. Inter- and Intramolecular [6 + 4] Tropone–Diene Cycloaddition Reactions†

Summary: Thermally allowed inter- and intramolecular [6 + 4] tropone–diene cycloadditions have been employed for the construction of intermediates in the synthesis of the cocarcinogenic diterpene ingenol.

Sir: The ingenanes represent a structurally unique class of highly oxygenated tetracyclic diterpene esters which exhibit potent tumor-promoting properties.[1] Ingenol (**1**) serves as the parent diterpene nucleus from which many of these biologically active esters are derived.



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†Portions of this work were presented at the 190th American Chemical Society National Meeting in Chicago, IL, September 10, 1985, Abstract ORGN102.

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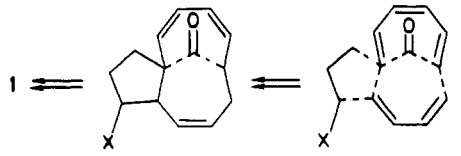
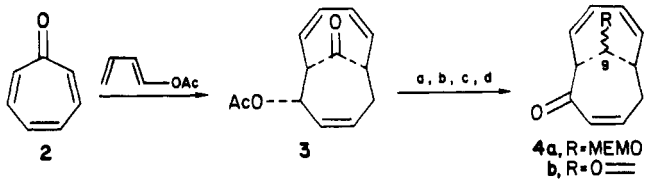
Scheme I



Scheme II[a]



[a] (a) $NaBH_4$, MeOH, room temperature; (b) MEMCl, $(i\text{-Pr})_2EtN$; (c) K_2CO_3, MeOH; (d) PDC, CH_2Cl_2.

The unusual bicyclo[4.4.1]undecanone moiety comprising the B and C rings in this series is of particular interest. The strategy disclosed in this paper addresses the construction of this relatively rare and challenging ring system via the thermally allowed [6 + 4] cycloaddition of tropone derivatives with diene partners.[2,3] The general approach is depicted in Scheme I.[4]

Our initial efforts to effect periselective [6 + 4] cycloaddition of substituted butadienes with various 2-substituted tropones were on the whole disappointing. Adducts from the [4 + 2] mode of cycloaddition were the principal products obtained in these reactions. In contrast to these results, heating 1-acetoxybutadiene with tropone (**2**) in refluxing xylene provided the desired bicyclo[4.4.1]undecanone **3** exclusively as the α-acetoxy epimer in 55% yield[5,6] (Scheme II).

The necessity of employing the parent tropone as the six-electron partner in this sequence required that a method be developed for the efficient introduction of an appropriate three-carbon unit amenable to elaboration into the requisite A ring of ingenol. Toward this end, acetoxy ketone **3** was converted via a four-step sequence into the two enones **4a**[5] (ν_{max} 1665 cm^{-1}) in a ratio of 2:1 in 36% overall yield. Only the major isomer with the stereochemistry at C_9 (ingenol numbering) undefined, was carried through the remainder of the sequence described below. These manipulations established a substrate onto which the elements of the five-membered A ring could be added.

Critical to the success of this endeavor was the subsequent alkylation of a regioselectively generated bridgehead enolate. At the outset of this work little was known about these anions; however, treatment of enone **4a** with LDA at −78 °C gave a deep wine-red solution, which upon addition of excess 2-methoxyallyl bromide[7] in 15% HMPA/THF, and subsequent warming to room temperature provided the ketone **5**[5] in 66% yield. No evidence for the formation of isomeric alkylation products was observed, and, interestingly, the corresponding dione **4b** provided only unidentifiable products under similar conditions. Finally, a methyl group, which serves as a model for the hydroxymethyl group at C_6 in ingenol, was introduced by the smooth conjugate addition of Me_2CuLi at 0 °C to provide dione **6**[5] as a single isomer in 71% yield after aqueous acid workup. The relative configuration of this newly generated stereocenter was ascertained by single-crystal X-ray analysis on dione **8** (vida infra). Significantly, only the α-epimer was obtained, which augues well for future stereocontrolled manipulations of substituents on this ring system.

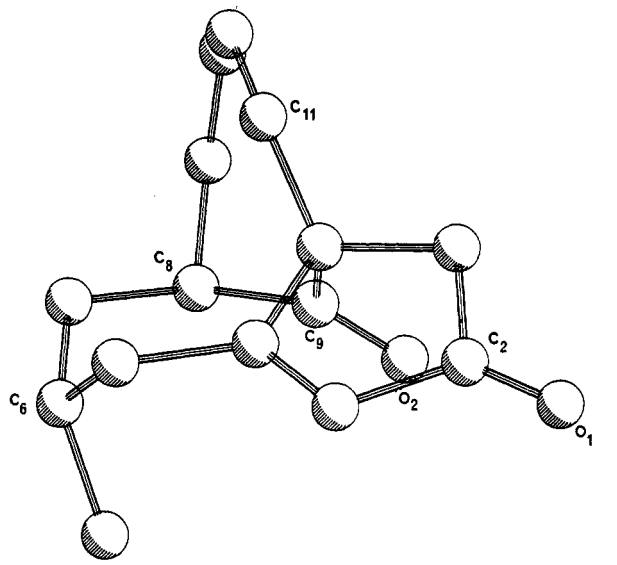
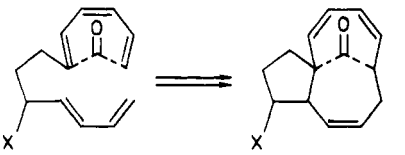
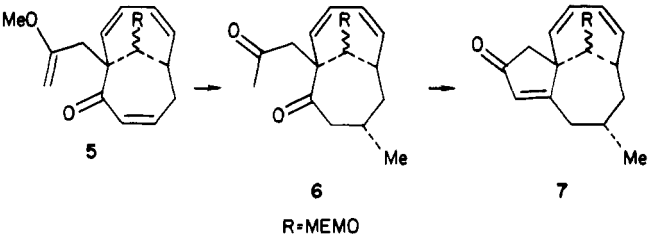


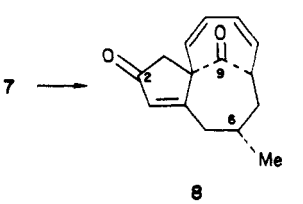
Figure 1. X-ray structure of dione 8.

Scheme III





The requisite cyclopentane A ring was assembled by dropwise addition of dione **6** to a suspension of excess NaH in refluxing toluene. This aldol reaction furnished the key tricyclic enone **7**[5] (mp 60–61.5 °C) in 67% yield. Unventful removal of the (methoxyethoxy)methyl protection



(1) (a) Evans, F. J.; Kinghorn, A. D. *Phytochemistry* **1974**, *13*, 1011. (b) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423. (c) Evans, F. J.; Soper, C. J. *Lloydia* **1978**, *41*, 193.

(2) (a) Garst, M. E.; Roberts, V. A.; Prussin, C. *Tetrahedron* **1983**, *39*, 581. (b) Garst, M. E.; Roberts, V. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 3882.

(3) For another synthetic approach to the ingenanes, see: Paquette, L. A.; Nitz, T. J., Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446.

(4) This approach initially provides the isoingenol series, epimeric to ingenol at C_8 only. Further manipulation of this center will be required for synthesis of the ingenol series.

(5) This compound gave spectral (^1H NMR, ^{13}C, NMR, IR, MS) and analytical data in accord with the assigned structure.

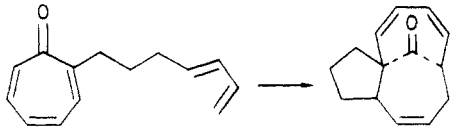
(6) Fujise, Y.; Shiokawa, T.; Mazaki, Y.; Fukazawa, Y.; Fujii, M.; Ito, S. *Tetrahedron Lett.* **1982**, *23*, 1601.

(7) Jacobson, R. M.; Raths, R. A.; McDonald, J. H., III *J. Org. Chem.* **1977**, *42*, 2545.

(8) Rigby, J. H.; Wilson, J. Z. *Tetrahedron Lett.* **1984**, 1429.

with Me_3SiCl/NaI[8] followed by PDC oxidation gave dione 8[5] (mp 159–160 °C) in 56% yield for the two steps. The structure of this compound was unambiguously established by X-ray analysis (Figure 1). This intermediate appears to be most attractive as a potential precursor to ingenol in view of the well-positioned functional groups suitable for selective elaboration of the remaining structural features common to the ingenane system.

An equally fascinating entry into the ring system of ingenol can be envisioned to arise from an *intra*molecular [6 + 4] cycloaddition process as seen in Scheme III.[9] This possibility was particularly intriguing to us in view of the recalcitrant behavior of substituted tropones toward *inter*molecular [6 + 4] cycloaddition. Heating the readily accessible 2-substituted tropone **9**[5,10] in xylene at reflux for 6 h provided tricyclic ketone **10**[5] in 81% yield, as a single product uncontaminated with materials derived from the [4 + 2] cycloaddition mode. Again the assigned



9 **10**

stereochemistry of the adduct was based on the well-established propensity for tropone–diene [6 + 4] cycloadditions to proceed through an exo transition state.[2] Thus the ingenane skeleton can be assembled in only two steps from readily available 2-chlorotropone.

The viability of both intra- and intermolecular [6 + 4] cycloadditions in the tropone series for application to natural product synthesis has been clearly established, and work is currently under way to elaborate these intermediates into the ingenane diterpenes.

Acknowledgment. We thank the National Institutes of Health (CA-36543) for support of this research. We would also like to thank Dr. Mary Jane Heeg for obtaining the X-ray structure of compound 8.

(9) While this manuscript was in preparation, another example of an intramolecular [6 + 4] tropone cycloaddition surfaced: Funk, R. L., personal communication.

(10) 2-Substituted tropones are relatively difficult to prepare. Compound **9** is available in 61% from the reaction of 2-chlorotropone[11] and the Grignard reagent derived from 1-bromohept-4,6-diene. Details of this procedure will be reported in a separate paper: Rigby, J. H., Kierkus, P.; Moore, T. L.; Rege, S., manuscript in preparation.

(11) TerBorg, A. P.; Van Helden, R.; Bickel, A. F. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 177.

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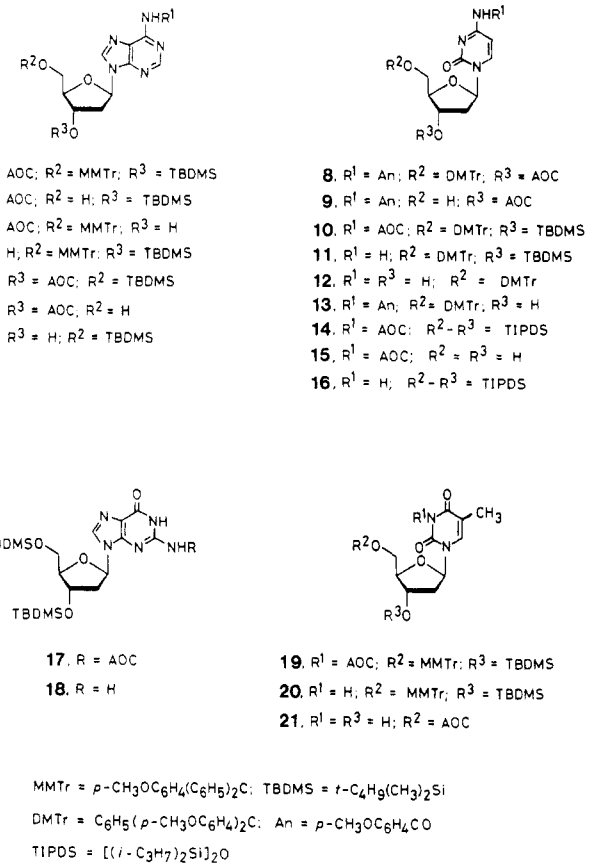
Allyloxycarbonyl Group: A Versatile Blocking Group for Nucleotide Synthesis

Summary: Allyloxycarbonyl (AOC) is excellent for the protection of sugar hydroxyls and amino and imide moieties of nucleoside bases. The deblocking is easily performed by brief treatment with a palladium catalyst and a variety of nucleophiles at room temperature.

Sir: Efficient functional group protection is one of the most fundamental and crucial problems in nucleotide synthesis.[1] Protectors requiring harsh deblocking conditions are not appropriate for the highly functionalized synthetic intermediates. Acyl groups, for instance, are the most widely employed for the amino group protection, but removal of such groups is frequently accompanied by undesired side reactions including cleavage of the internucleotide linkage, resulting in serious loss of the products. We disclose here that the allyloxycarbonyl (AOC) group serves as an extremely useful protecting group in nucleoside and nucleotide synthesis. AOC can block amino and imide moieties of nucleoside bases and sugar hydroxyls and is removable by brief treatment with a palladium catalyst.[2]

Chart I



First, the sensitivity of AOC-protected nucleoside bases was examined. Conditions for deblocking of the MMTr or DMTr and TBDMS protecting groups do not affect the AOC protection. For example, when the adenosine nucleoside **1** (Chart I), having three kinds of protecting groups, was treated with dichloroacetic acid in dichloromethane at room temperature, only MMTr group was removed to give the 5′-O-unprotected derivative **2** in 84% yield. Exposure of **1** to tetrabutylammonium fluoride (TBAF) in THF furnished selectively the 3′-O-free nucleoside **3** in 97% yield. Similarly, the 5′-O-*tert*-butyldimethylsilylated adenosine nucleoside **5** underwent the selective deblocking of TBDMS protection by treatment with TBAF to give quantitatively the 5′-O-free derivative **6**. TBAF treatment of N^4-allyloxycarbonylated deoxycytidine **14** removed selectively the 3′,5′-cyclic silyl pro-

(1) Comprehensive reviews: Reese, C. B. *Tetrahedron* **1978**, *34*, 3143. Ikehara, M.; Ohtsuka, E.; Markham, A. F. *Adv. Carbohydr. Chem. Biochem.* **1979**, *36*, 135. Crockett, G. C. *Aldrichimica Acta* **1983**, *16* (3), 47. Hata, T. *J. Synth. Org. Chem. Jpn.* **1984**, *42*, 429. Zhdanov, R. I.; Zhenodarova, S. M. *Synthesis* **1975**, 222. Amarnath, V.; Broom, A. D. *Chem. Rev.* **1977**, *77*, 183. Ishido, Y.; Hata, T. *Kagaku Sosetsu* **1978**, *19*, 207. Ohtsuka, E. *Ibid.* **1985**, *46*, 209.

(2) For a comprehensive review: Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Pergamon: Oxford, 1983; Vol. 8, pp 799–938.

0022-3263/86/1951-2400$01.50/0