Acknowledgment. We gratefully acknowledge The Robert A. Welch Foundation and Eli Lilly and Co. for support of this work.

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(4) G. A. Olah and J. M. Bollinger, *J. Amer. Chem. Soc.*, **90**, 6082 (1968); S. Arora and P. Binger, *Synthesis*, 801 (1974).
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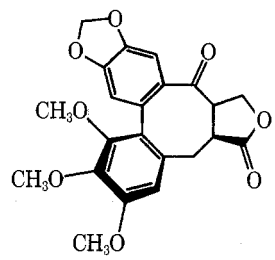
W. E. Billups,*[9] Andrew J. Blakeney
William T. Chamberlain
Department of Chemistry, Rice University
Houston, Texas 77001
Received June 14, 1976

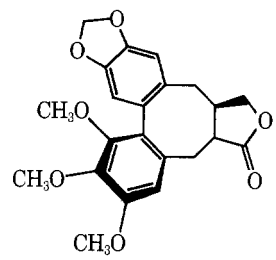
A Short Synthesis of (±)-Isostegane[1]

Summary: (±)-Isostegane has been prepared in a three-step sequence utilizing sequential substitution of the β and α positions of an electron-deficient olefin followed by nonphenolic oxidative coupling.

Sir: Kupchan and coworkers recently described an unusual and highly cytotoxic class of dibenzocyclooctadiene lactones exemplified by the ketone lactone steganone (**1**).[2] Two total syntheses of **1** have been reported and another group has described synthetic efforts in this area.[3] Our retro-synthetic analysis of **1** suggested that the dibenzocyclooctadiene skeleton might be efficiently constructed by sequential substitution of the β and α positions of an electron-deficient olefin using a conjugate addition alkylation sequence followed by nonphenolic oxidative coupling to yield a tetracyclic debenzocyclooctadiene structure.[4] Herein, we wish to describe a three-step construction of isostegane (**2**)[1] which demonstrates the validity of this strategy and which proceeds in 55% overall yield.



1



2

Compound **2** was prepared in the following manner. The carbonyl anion equivalent **3** was generated from piperonal dithiomethyl acetal[5] (1 equiv, 1 M in THF, −78 °C) by treatment with *n*-butyllithium (1 equiv). After stirring for 40 min at −78°C, the butenolide **4**[6] (1 equiv, 1 M in THF) was slowly added over a period of 30 min. The resulting white suspension was stirred for 3 h at −78 °C whereupon the bromide **5**[7] (1 equiv, 1 M in THF) was rapidly added followed immediately by tetramethylethylenediamine (1 equiv).[8] The temperature of the reaction mixture was then raised to −20 °C and stirring continued for 10 to 12 h. Standard workup gave the adduct **6** as an amorphous yellow solid in 99% crude yield.[9] Without purification, adduct **6** (2.5 g) was treated with a suspension of W-4 Raney Nickel (25 g) in acetone (100 ml) at reflux for 30 min. Vacuum filtration of the crude desulfurized product through silica gel gave compound **7** as a clear oil in 85% overall yield from **3**.

Cyclization of **7** into **2** was accomplished by slowly adding (10 min) compound **7** (1 equiv, 0.02 M in methylene chloride) to VOF_3 (3 equiv.) suspended in a 2:1 mixture of methylene chloride and trifluoroacetic acid (0.16 M) at −45 °C.[10] The reaction mixture was stirred at −45 °C for 7 h and then worked up by addition of saturated sodium carbonate solution. The crude dark yellow product was purified by vacuum filtration through silica gel followed by crystallization from chloroform–methanol to give pure isostegane (mp 172–172.5 °C) as the sole reaction product in 65 to 70% yield.[11]

The spectral characteristics of compound **2** (uv, ir, NMR, and mass spectrum) clearly indicated it to be a tetracyclic dibenzocyclooctadiene lactone. However, the stereochemical configuration of **2** could not be assigned from these data. As a result, the bromide **8** was prepared[12] and an x-ray structure determination undertaken.

The crystals of compound **8** were monoclinic, space group $P2_1/a$, with a = 22.699 (9), b = 7.433 (6), c = 11.984 (5) Å; β = 95.16 (2)° and d_{calcd} = 1.574 g cm^{-1} for Z = 4. The intensity data were measured on a Hilger-Watts diffractometer (Ni filter Cu Kα radiation, θ–2θ scans,

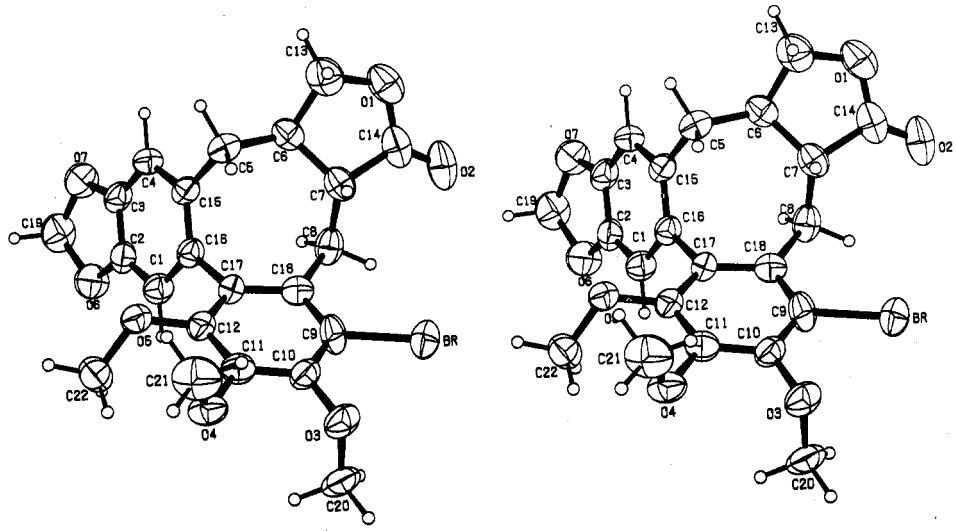
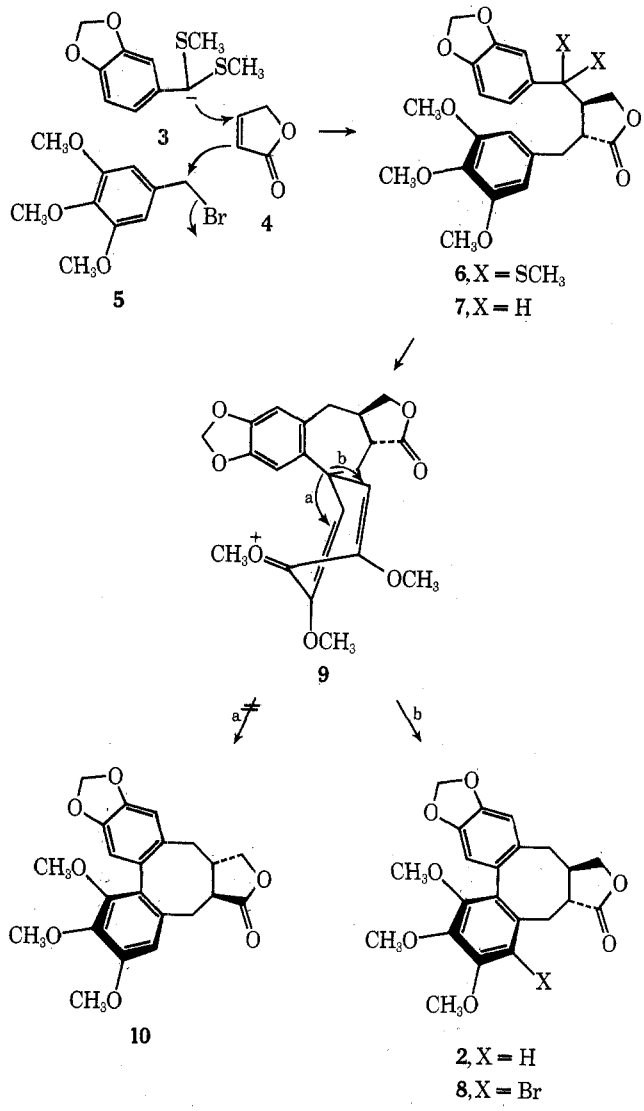


Figure 1.



pulse height discrimination). The size of the crystal used for data collection was approximately 00.2 × 0.25 × 0.30 mm; the data were corrected for absorption (μ = 34.5 cm^{-1}). Of the 2706 independent reflections with $\theta < 57°$, 1859 were considered to be observed. The structure was solved by a multiple solution procedure[13] and was refined by full matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.059 and wR = 0.056 for the 1859 observed reflections. The final difference map has no peaks greater than ±0.4 e A^{-3}. The computer drawing of compound **8** (Figure 1) clearly indicates that **8**, and therefore compound **2**, possess the unnatural biphenyl configuration.[14]

The exclusive formation of **2** as opposed to compound **10** (the natural biphenyl configuration) must occur during the VOF_3 cyclization of compound **7**. One possible explanation for this stereochemical result involves the intermediacy of the spirodiene **9**.[15] Phenyl migration in **9** via path a leads to stegane (**10**) whereas phenyl migration via path b gives rise to isostegane (**2**). Inspection of molecular models indicate path b is considerably more favored on the basis of configurational interactions than is path a.[16]

Acknowledgment. We would like to thank the National Institutes of Health and the Hoffmann-La Roche Corporation for support of this work. We also thank Professor A. S. Kende and Mr. L. S. Liebeskind for several helpful discussions during the course of this work.

References and Notes

(1) We suggest the name isostegane instead of deoxyisosteganone to denote both the lack of ketonic oxygen and the unnatural biphenyl twist. The name stegane is used instead of deoxysteganone.
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(4) We have been involved with this type of multi carbon–carbon bond forming reaction sequence using two electrophiles and one nucleophile for some time. See for example (a) J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **95**, 7923 (1973); (b) R. F. Romanet and R. H. Schlessinger, *ibid.*, **96**, 3701 (1974). A similar conjugate addition alkylation reaction has been reported in ref 3c.
(5) This compound was prepared in essentially quantitative yield from piperonal using standard reaction conditions.
(6) Prepared in 75% overall yield starting from butyrolactone using a modified procedure based on the reported by C. C. Price and J. M. Judge, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 255.
(7) Compound **5** (mp 73 °C) was prepared in 62% overall yield from gallic acid using standard reaction procedures.
(8) It is important to note that the alkylation segment of this reaction sequence occurs in good yield only if tetramethylethylenediamine is added, and, further, only if this reagent is added after the alkylating agent.
(9) All new compounds exhibited satisfactory spectral and physical data.
(10) Transformation **7** to **2** represents the second example of this type of cyclization successfully applied to the preparation of a cyclooctadiene system; the first example of this reaction type is described in ref 3b. It should be noted however, that the conversion of **7** into **2** is the only example of this cyclization reaction which leads directly to a tetracyclic cyclooctadiene system.
(11) This reaction may be carried out at significantly higher concentrations with a minimal loss in yield (5 to 10%). The remainder of the reaction mixture consists of phenolic substances which have not been fully characterized. A wide variety of other two-electron-transfer oxidants failed to bring about the conversion of **7** into **2**.
(12) Compound **8** (mp 173–174 °C) was prepared from **2** using pyridinium hydrobromide perbromide in chloroform: procedure of L. S. Liebeskind.
(13) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr.*, **A27**, 368 (1971).
(14) A similar phenomenon has been observed by Kende and coworkers. We thank Professor Kende for a preprint describing these results.
(15) Intermediates like **9** have been suggested for other nonphenolic coupling reactions. For examples see (a) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973); (b) S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *ibid.*, **97**, 5622 (1975); and (c) S. M. Kupchan and C. Kim, *ibid.*, **97**, 5623 (1975).
(16) Molecular models strongly suggest that the configuration depicted in structure **9** represents an energy minimum for this species.

R. E. Damon, R. H. Schlessinger*
Department of Chemistry, University of Rochester
Rochester, New York 14627

J. F. Blount
Research Division, Hoffman-La Roche Inc.
Nutley, New Jersey 07110
Received August 4, 1976

Anhydrocholine

Summary: Choline, $(CH_3)_3N^+CH_2CH_2OH\ OH^-$, was found to exist in water-poor media mainly in the form of anhydrocholine, $(CH_3)N^+CH_2CH_2O^-$.

Sir: A characteristic feature of enzyme systems appears to be the existence of highly reactive regions on the enzyme surface. In these regions acidic or basic groups often function as if their pK's were much greater (or smaller) than they are in aqueous solution.[1] It is likewise possible that some small biomolecules might be particularly susceptible to such changes in acidity, either on an enzyme surface or in some other cellular environment, and that this variability might be a vital part of their function.

The effect of polar, water-poor mixed solvents on the binding of various substrates to an enzyme cavity model has been reported recently.[2] We wish to report a remarkable