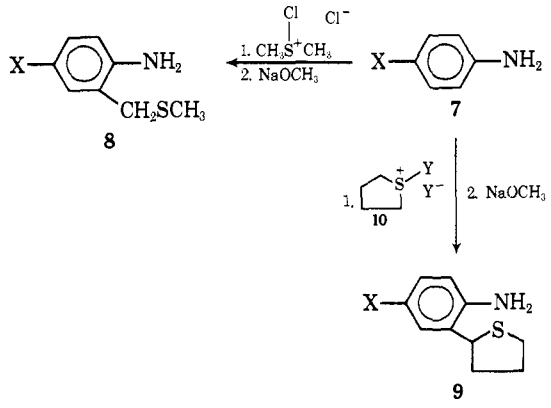
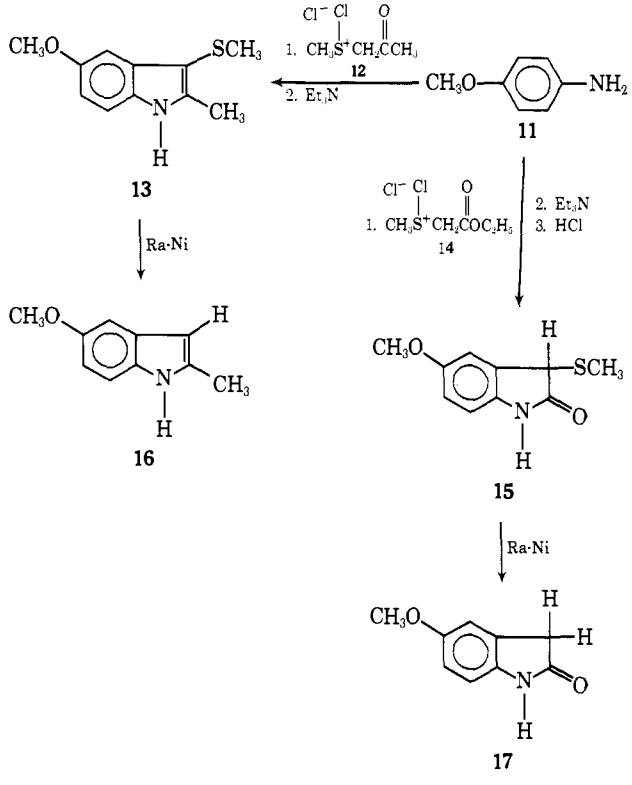


The use of β-keto sulfides and α-carboalkoxy sulfides in this reaction provided a simple route to indoles and oxindoles. Treatment of *p*-anisidine (**11**) with **12** followed by triethylamine, according to the general procedure, gave **13** in 38% yield.[8] The reaction of **11** with **14**, followed by treatment of the intermediate azasulfonium salt with triethylamine and then with hydrochloric acid, gave the oxindole **15** in 53% yield.[9] Raney-nickel desulfurization of **13** and **15** gave **16** and **17** in 72 and 71% yields, respectively.



In summary, the use of halosulfonium halides with substituted anilines provides a simple process for the preparation of ortho-alkylated anilines, indoles, and oxindoles. The process is of particular importance in the synthesis of methoxylated indoles, which constitute a portion of numerous indole alkaloids, and in the synthesis of methoxylated oxindoles. Variation of the substitution patterns of the β-keto sulfides and α-carboalkoxy sulfides used in our prototype studies should provide a ready access to a wide variety of methoxylated indoles of value as key intermediates in the synthesis of certain natural products.

Acknowledgment. We are indebted to the National Cancer Institute of the Public Health Service for a grant which partially supported this investigation.

(8) The reaction was not restricted to *p*-anisidine. With aniline, *p*-chloroaniline, and benzocaine, we obtained the corresponding 2-methyl-3-methylthioindoles in 68, 45, and 33% yields, respectively.

(9) Other substituted oxindoles can be prepared *via* this procedure. With aniline, *o*-toluidine, and 4-nitroaniline, we obtained the corresponding 3-methylthiooxindoles in 65, 62, and 12% yields, respectively.

(10) Fellow of the Netherlands Organization for the Advancement of Pure Research (Z. W. O., 1972–1973).

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A Stereoselective Approach to Eremophilane Sesquiterpenes. A Synthesis of (±)-Nootkatone

Sir:

The sesquiterpene nootkatone (**6**) is a principal flavor component of grapefruit peel oil.[1] Syntheses to date[2-4] have relied on the Robinson annelation reaction, with subsequent establishment of the cis (*C*)-4,5-dimethyl structure.

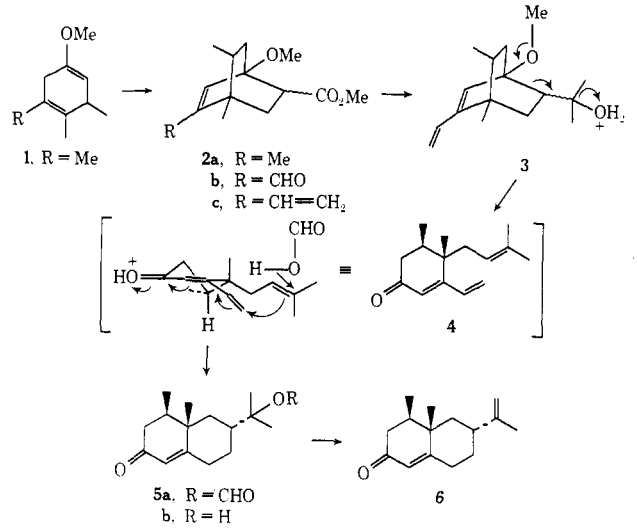
The present approach to construction of the ring system and steric control in this important area depends on the Diels–Alder reaction. The catalyzed production of Diels–Alder adducts directly from available 1-methoxycyclohexa-1,4-dienes[5] and acid catalyzed conversion of derived tertiary carbinols into 4-substituted cyclohexenones[6] have been noted.

Synthesis of the adduct **2a** from diene **1** and methyl acrylate is the initial requirement for the present route to **6**. The indicated stereochemistry of the bridge methyl group would be expected to predominate owing to the steric interactions arising in the transition state between **1** and the dienophile in the Diels–Alder reaction. Acid catalyzed ring opening[6] of the carbinol **3** derived from **2a** would be expected to lead to the trienone **4**, in which a cis relationship exists between the adjacent methyl groups (Scheme I). It was conceived, however, that in formic acid this compound would directly undergo further cyclization[7] to the eremophilane derivative **5a**.

The diene **1** was obtained from the aromatic precursor by Birch reduction[8] (NH_3, THF, *t*-BuOH, 90%). Subsequent *in situ* Diels–Alder reaction with methyl acrylate in the presence of dichloromaleic anhydride[5] gave the adduct **2a** (85% based on 33% recovered **1**). Selective functionalization of the vinylic methyl group of **2a** to give **2b** was accomplished by selenium dioxide in refluxing dioxane[9] (70%), due to the absence of any other

(1) W. D. MacLeod and N. M. Buignes, *J. Food Sci.*, **29**, 565 (1964).
(2) M. Pesaro, G. Bozzato, and P. Schudel, *Chem. Commun.*, 1152 (1968).
(3) J. A. Marshall and R. A. Ruden, *Tetrahedron Lett.*, 1239 (1970).
(4) A. Van Der Gen, L. M. Van Der Linde, J. G. Witeveen, and H. Boelens, *Recl. Trav. Chim. Pays-Bas*, **90**, 1034 (1971).
(5) A. J. Birch and K. P. Dastur, *Tetrahedron Lett.*, 4195 (1972), and references therein.
(6) A. J. Birch and J. S. Hill, *J. Chem. Soc. C*, 419 (1966).
(7) For a somewhat analogous process see J. A. Marshall, N. Cohen, and A. R. Hochstetter, *J. Amer. Chem. Soc.*, **88**, 3408 (1966).
(8) A. J. Birch and G. Subba Rao, "Advances in Organic Chemistry," Vol. 8, E. C. Taylor, Ed., Wiley, New York, N. Y., 1972, p 1.
(9) N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron Lett.*, 1281 (1962).

Scheme I[a]



[a] All compounds have satisfactory spectral data.

allylic position. Dropwise addition of ethereal methylenetriphenylphosphorane[10] to **2b** gave the diene **2c** (50%) which was converted to the carbinol **3** by the action of ethereal methyllithium at room temperature (96%).

Stirring of **3** with excess formic acid for 1 hr at room temperature gave rise to **5a** (50% after purification). Saponification (aqueous NaOH, *t*-BuOH, 20°) of **5a** produced **5b** (90%). The spectral properties of **5b** were identical with those reported for 11-hydroxy-11,12-dihydronootkatone.[4] Refluxing of **5a** in pure collidine for 15 hr in the presence of 30% by weight of neutral alumina (with respect to **5a**) gave a mixture of elimination products (70% after purification). A sample of the major component (75% by nmr and glc) obtained by preparative glc was found to be spectrally identical and superimposable on glc with an authentic sample of nootkatone.[11] The remaining 25% of the elimination product consisted mainly of α-vetivone (nmr analysis[12]). No 7-*epi*-nootkatone could be detected by careful pmr analysis,[13] showing that the final ring closure step (Scheme I) is stereospecific. The functionalized isopropyl side chain of **5a** therefore exists in the thermodynamically preferred equatorial configuration, as in natural nootkatone. Furthermore, since no trans (*C*)-4,5-dimethyl compound could be detected[14] the Diels–Alder reaction to give **2a** is stereoselective as previously discussed.

A full paper bearing experimental details will appear at a later date.

Acknowledgments. The author is indebted to Professor A. J. Birch for the suggestion that the Diels–Alder reaction should give the correct configuration of the methyl groups. The award of a Research Scholarship from the Australian National University is gratefully acknowledged.

(10) G. Wittig and U. Schoellkopf, *Org. Syn.*, **40**, 66 (1960).

(11) The author is indebted to Dr. M. Pesaro, Givaudan-Esrolko, Zurich, for a gift sample of nootkatone.

(12) K. Endo and P. de Mayo, *Chem. Pharm. Bull.*, **17**, 1324 (1969).

(13) The pmr signal of the C(5)-methyl group is shifted 3 Hz downfield going from nootkatone to 7-*epi*-nootkatone. No signal corresponding to the latter compound could be detected at optimum resolution on a JEOL 100 MHz nmr spectrometer. Similar analysis has been employed previously.[4]

(14) In *trans*-4,5-dimethyleremophilanes the pmr signal of the C(5)-methyl group is shifted up to 30 Hz upfield with respect to the corresponding cis isomers.[4] No such signal is observed for **5b** and **6**.

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Additions and Corrections

A Bell-Shaped pH–Rate Profile for an Oxidation. The Reaction of Permanganate with Hydroxycyclohexanecarboxylic Acids [*J. Amer. Chem. Soc.*, **93**, 4271 (1971)]. By Ross Stewart* and J. Anthony MacPhee, Department of Chemistry, University of British Columbia, Vancouver 8, Canada.

The value of k_1 for compound **3** in Table I should be 731 ± 25. The units on the *y* axes of Figures 2 and 3 should be l. mol^{-1} min^{-1}.

The Mechanism of Reactions Involving Schiff Base Intermediates. Thiazolidine Formation from L-Cysteine and Formaldehyde [*J. Amer. Chem. Soc.*, **93**, 6236 (1971)]. By Roland G. Kallen, Department of Biochemistry, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Equations 9 and 10 should read as shown below.

$$k_{obsd} = \frac{(k_{1a}\alpha_3 + k_{1b}\alpha_{13})[F]\alpha_{RNH_2T}/(\alpha_3 + \alpha_{13})}{\left\{\frac{k_{1a}\alpha_3/K_1 + k_{1b}\alpha_{13}/K_1}{(\alpha_3 + \alpha_{13})(k_2 + k_2'a_{H^+})}\right\} + 1} \quad (9)$$

$$k_{obsd} = \frac{(k_{1a}\alpha_3 + k_{1b}\alpha_{13})[F]\alpha_{RNH_2T}/(\alpha_3 + \alpha_{13})}{\left\{\frac{k_{1a}\alpha_3/K_1 + k_{1b}\alpha_{13}/K_1}{(\alpha_3 + \alpha_{13})(k_2 + k_2'a_{H^+} + k_2''[HA])}\right\} + 1} \quad (10)$$

Determination of the Tautomeric Form of the Imidazole Ring of L-Histidine in Basic Solution by Carbon-13 Magnetic Resonance Spectroscopy [*J. Amer. Chem. Soc.*, **95**, 328 (1973)]. By W. F. Reynolds,* I. R. Peat, M. H. Freedman, and J. R. Lyerla, Jr., Department of Chemistry and the Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada, M5S 1A1.

In Table II, the entries listed for 3-methylhistidine are