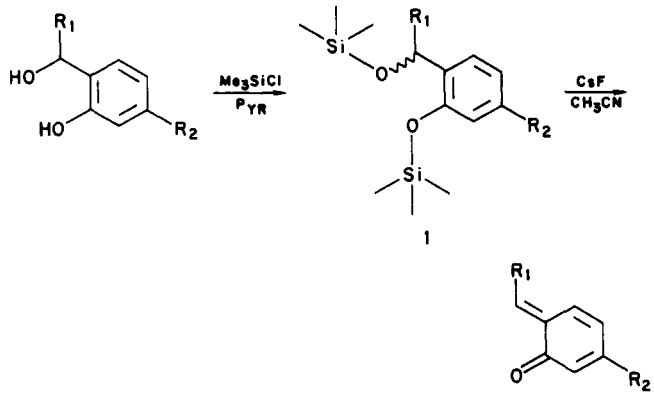
An Efficient Desilylation Method for the Generation of *o*-Quinone Methides: Application to the Synthesis of (+)- and (-)-Hexahydrocannabinol

Summary: The bis-silylated *o*-hydroxybenzyl alcohol derivative **1** undergoes regiospecific 1,4-desilylation–elimination to an incipient *o*-quinone methide that is trapped in an intramolecular Diels–Alder reaction to yield (+)- or (-)-hexahydrocannabinols.

Sir: The widespread occurrence of phenolic compounds as precursors to polycyclic aromatic natural products has stimulated efforts directed toward the synthetic exploitation of *o*- and *p*-quinone methides. While *p*-quinone methides are inherently easier to generate by oxidation processes, their *o*-quinone methide counterparts are more difficult to access and trap in an efficient manner. There are several elegant syntheses already reported that are based on the intramolecular Diels–Alder trapping of *o*-quinone methide intermediates.[1] In addition to oxidations, *o*-quinone dimethides have been recently accessed by 1,4-elimination processes induced by desilylation sequences.[2] To date, there is no simple methodology based on 1,4-eliminations for the generation of *o*-quinone methides. We report herein a simple and efficient procedure for *o*-quinone methides via fluoride-induced desilylation of disilyl derivatives **1** of *o*-hydroxybenzyl alcohols.



We have applied this methodology to an asymmetric synthesis of (+)- and (-)-hexahydrocannabinol (HHC). Tietz and co-workers[3] have recently reported the synthesis of HHC via an intramolecular Diels–Alder reaction of an appropriately substituted α-alkylidene 1,3-cyclohexanedione. Tietz's synthesis requires the subsequent aromatization of the cyclohexanedione derivative. In our synthetic sequence we have efficiently trapped an *o*-quinone methide intermediate to directly produce an aromatic system. The overall synthetic scheme is shown in Scheme I.

In order to differentiate the phenolic hydroxyl groups, olivetol monomethyl ether, **2**, was protected with 2-(trimethylsilyl)ethoxymethyl chloride[4] (SEM-Cl, 2 equiv) in diisopropylethylamine (2.1 equiv) and methylene chloride. Metalation of the SEM ether **3** was readily accomplished with *tert*-butyllithium (1.1 equiv) in hexane at room temperature (2.5 h). Subsequent addition of (+)-citronellal[5]

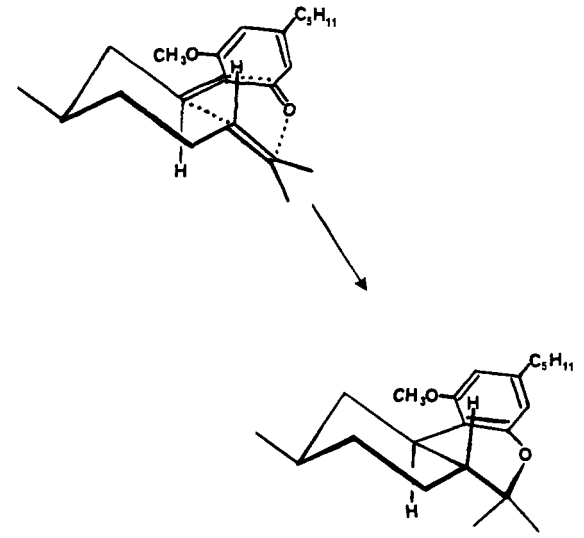
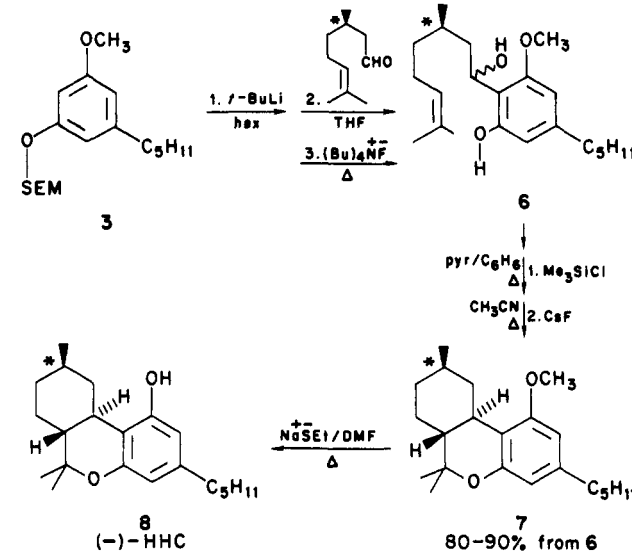


Figure 1.

Scheme I



in tetrahydrofuran and removal of solvents yielded a red oil, **5**, which was not purified. The crude adduct **5** was added dropwise to a refluxing THF solution of tetra-*n*-butylammonium fluoride[6] to remove the SEM protecting group. After an aqueous workup and column chromatography, the citronellal–olivetol adduct, **6**, was isolated in 40% yield.[7]

Adduct **6** was bis-silylated with trimethylsilyl chloride and pyridine in refluxing benzene. The entire reaction mixture was then added dropwise to a suspension of cesium fluoride (7 equiv) in refluxing acetonitrile. The heterogeneous reaction mixture was refluxed for 40 h under an argon atmosphere. After workup and silica gel chromatography, the hexahydrocannabinol methyl ether, **7**, was isolated in high yield (80–90%) as a yellow oil.[8] Deme-

(1) (a) Chapman, O. L.; et al. *J. Am. Chem. Soc.* **1971**, *93*, 6696. (b) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1981**, *22*, 4437. (c) Begley, M. J.; Crombie, L.; et al. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2402.
(2) Ito, Y.; et al. *J. Am. Chem. Soc.* **1983**, *105*, 1586.
(3) Tietze, L. F.; et al. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1021.
(4) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
(5) (+)-Citronellal was available from Fluka Chemical Corp. (85–90%), $[\alpha]^{25}_D$ +11.9°, *c* 0.04. (-)-Citronellal (-)-Citronellal was obtained via the oxidation of (-)-citronellol (available from Fluka Chemical Corp., ~98%) with pyridinium dichromate (1.5 equiv) in methylene chloride at room temperature (>95% yield), $[\alpha]^{25}_D$ -12.7° (*c* 0.04).
(6) Available from Aldrich Chemical Co. as a 1 M solution in tetrahydrofuran. The solvent was rotary evaporated prior to use to give a thick colorless oil.
(7) IR ($CHCl_3$): 3580 (m), 3450–3370 (br), 3050–2800 (s), 1600 (s), 1350 (m), 1210 (m), 1080 (m) cm^{-1}; NMR ($CDCl_3$, 360 MHz): δ 0.88 (t, 3 H), 0.95 (d, 3 H), 1.29–1.40 (m, 7 H), 1.57 (m, 2 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.92–2.05 (m, 3 H), 2.42 (s, 1 H), 2.49 (t, 3 H), 3.75 (s, 3 H), 5.07 (m, 1 H), 5.41 (m, 1 H), 6.20 and 6.33 (2 s, 2 H), 8.45 and 8.52 (2 s, 1 H).
(8) IR ($CHCl_3$): 3050–2850 (s), 1640 (m), 1580 (m), 1450 (w), 1425 (m), 1350 (w), 1260 (s), 1240 (w), 1150–1000 cm^{-1}; NMR ($CDCl_3$, 360 MHz): δ 0.88 (t, 3 H), 0.90 (d, 3 H), 1.04 (s, 3 H), 1.25–1.50 (m, 8 H), 1.35 (s, 3 H), 1.60 (m, 2 H), 1.80 (m, 3 H), 2.35–2.52 (t and m, 3 H), 2.97 (d, J = 12.7 Hz, 1 H), 3.79 (s, 3 H), 6.22–6.27 (m, 2 H).

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thylation of 7 with sodium ethyl thiolate[9] gave the optically active (−)-HHC, 8 (α_D −73.9°, c = 0.014).[10] An identical sequence was carried out on (−)-citronellal and (+)-HHC (α_D +82.9°, c = 0.024) was obtained.

Several points in this desilylation–cyclization methodology are noteworthy. Firstly, the bis-silylated derivative need not be isolated and the *o*-quinone methide can be generated slowly. Secondly, the success of the process for generating the *o*-quinone methide requires the regioselective desilylation of the phenol silyl ether with concomitant elimination of trimethylsilanoxide. Finally, the asymmetric induction during the intramolecular Diels–Alder reaction is controlled by the preference for a pseudo-chair conformation in the transition state as shown in Figure 1. This latter aspect was previously manifested in Tietze's work.[3]

Acknowledgment. We thank Professor E. F. Domino of the Medical School, University of Michigan, for a sample of (−)-THC for spectral comparisons.

(9) Feutrill, G. I.; Mirrington, R. N. (*Tetrahedron Lett.* **1970**, *16*, 1327.

(10) IR ($CHCl_3$): 3580 (s), 3050–2850 (s), 1638 (m), 1580 (m), 1450 (w), 1355 (w), 1140 (w) cm^{-1}; NMR ($CDCl_3$, 360 MHz): δ 0.88 (t, 3 H), 0.90 (d, 3 H), 1.06 (s, 3 H), 1.25–1.65 (m, 11 H), 1.36 (s, 3 H), 1.85 (m, 2 H), 2.35–2.52 (t and m, 3 H), 3.04 (dm, J = 12.9 Hz, 1 H), 4.68 (s, 1 H), 6.08 (d, 1 H) and 6.24 (d, 1 H). Based upon the optical purities of the starting citronellal and citronellol,[5] the optical rotations of both (−)-HHC and (+)-HHC are within experimental error of the values reported by Tietze et al.[3]

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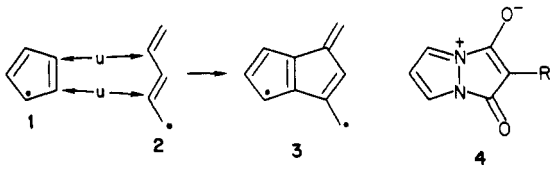
New Heterocyclic Betaines

Summary: Several new types of cross-conjugated, heterocyclic betaines have been prepared from (chlorocarbonyl)phenylketene and, e.g., 1-methylimidazole and pyridine; in an alternative synthetic approach, reaction of 1-(substituted-acetyl)-3,5-dimethylpyrazole with NaH and the electrophilic reagents phosgene, thiophosgene, and other activated geminal dichlorides allowed variation of the exocyclic substituents in new examples of the pyrazolo[1,2-*a*]pyrazole system.

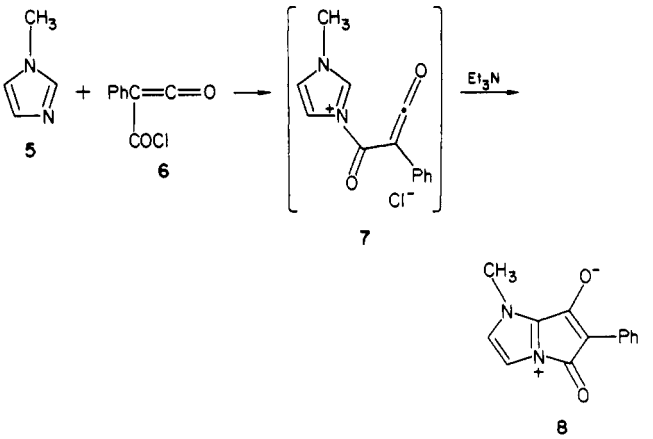
Sir: In several recent publications,[1,2] attention has focused on new classes of heterocyclic betaines. The interesting, deep red anhydro-1-hydroxy-3-oxo-2-phenylpyrazolo[1,2-*a*]pyrazolium hydroxide[1] (4; R = Ph) and related derivatives are cross-conjugated systems which may be formally derived from the diradical 3 considered to be formed by union of a cyclopentadienyl radical 1 and a pentadienyl radical 2. Replacement of two carbon atoms with two



1 2 3 4

two-electron nitrogen atoms in the diradical 3 leads to the betaine 4, which is isoelectronic with the 1,3-dimethylenepentalenyl dianion.[3] In this manner one can derive six general types of cross-conjugated betaines containing a [5,5] ring-fused system.[7] In this paper we describe additional representatives of these cross-conjugated betaines as well as a new route to 4 which enables variation of the exocyclic heteroatoms.

Reaction of 1-methylimidazole (5) with (chlorocarbonyl)phenylketene[8] (6) in THF at room temperature in the presence of Et_3N gave anhydro-1-hydroxy-7-methyl-3-oxo-2-phenylpyrrolo[1,2-*a*]imidazolium hydroxide[9] (8) [red spears from EtAc, mp 188–190 °C dec; ν_{CO} (KBr) 1730 cm^{-1}; M^+· 226 (100%)]. Reaction occurred via the N-3 acylated derivative 7 as this colorless product, on treatment with Et_3N, readily formed 8. Ring closure of



5 6 7

8

7 in the alternative sense to form the isomeric pyrrolo[1,2-*c*]imidazole system was excluded by failure of 1,2-dimethylimidazole to form an analogous product. The intermediacy of 7 is consistent with the mechanism proposed for the acid-catalyzed D_2O exchange of H-2 in imidazoles.[10]

Our earlier synthesis[1] of 4 from (chlorocarbonyl)-phenylketene (6) and pyrazole in the presence of Et_3N excluded exocyclic substituents other than oxygen and nonaromatic substituents at position 2 due to difficulties in preparing the appropriate highly reactive species analogous to 6. An alternative synthesis, involving ring closure of substituted 1-acetylpyrazoles with suitable 1,1-bielectrophiles in the presence of base now provides ready access to additional representatives of 4 with the variety

(1) Potts, K. T.; Kanemasa, S.; Zvilichovsky, G. *J. Am. Chem. Soc.* **1980**, *102*, 3971.

(2) Friedrichsen, W. *Z. Naturforsh.* **1980**, *35B*, 1002. Zvilichovsky, G.; David, M. *J. Org. Chem.* **1982**, *47*, 295. Friedrichsen, W.; Bottcher, A.; Debaerdemaeker, T. *Heterocycles* **1983**, *20*, 23. Friedrichsen, W.; Kappe, T.; Bottcher, A. *Heterocycles* **1982**, *19*, 1083.

(3) Heterosubstitution of a *m*-quinodimethane diradical formed from a propenyl radical and a pentadienyl radical results in cross-conjugated six-membered ring betaines containing pyrimidine,[4] thiazine,[5] and triazine[6] rings.

(4) Potts, K. T.; Sorm, M. *J. Org. Chem.* **1972**, *37*, 1422. Potts, K. T.; Hsia, R. K. C. *J. Org. Chem.* **1973**, *38*, 3485. Kappe, T.; Lube, W. *Monatsh. Chem.* **1971**, *102*, 781.

(5) Potts, K. T.; Ehlinger, R.; Nichols, W. M. *J. Org. Chem.* **1975**, *40*, 2596. Kappe, T.; Golser, W. *Synthesis* **1972**, 312.

(6) Kappe, T.; Golser, W.; Stadlbauer, W. *Chem. Ber.* **1978**, *111*, 2173. Coburn, R. A.; Bhooshan, B. *J. Heterocycl. Chem.* **1975**, *12*, 187; *J. Org. Chem.* **1973**, *38*, 3868. Stadlbauer, W.; Kappe, T. *Chem. Ber.* **1976**, *109*, 3661.

(7) In our evaluations, systems differing by replacement of one or more carbon atoms by one-electron nitrogen atoms are considered representatives of the same type. Consequently, variation of the exocyclic oxygen atoms between S, Se, NR, and CR_2 in the six systems containing nitrogen results in 90 possible systems. When two-electron heteroatoms other than nitrogen (O, S, and Se) are included in the ring-fused skeleton, the total number of possible betaines is increased to 1035.

(8) Nakanishi, S.; Butler, K. *Org. Prep. Proced. Int.* **1975**, *7*, 155.

(9) All compounds reported gave satisfactory analytical results (±0.4% C, H, N) and compatible ^1H NMR spectra.

(10) Elvidge, J. A.; Jones, J. R.; O'Brien, C.; Evans, E. A.; Sheppard, H. C. *Adv. Heterocycl. Chem.* **1974**, *16*, 5.

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