(Scheme II), in which LDA replaces reducing metals as the electron donor. It is important to note that in many cases one-electron reduction of the (hetero) aromatic moiety may be more facile than the reacting carbonyl compound, providing an alternate mechanistic pathway not previously considered.[14]

A brief review of the literature reveals reactions with other anions which are candidates for the SET mechanism. The reactions of pyridine with Na/NH_3,[10] Na^+-(α-methylstyrene)$_4^-$ Na^+,[15] and alkyl-substituted dithiane anion,[16] of quinoxaline with $NaNH_2$ in *N,N*-dimethylaniline,[17] and of NaOMe with 5-azacinnoline[18] and substituted 1,2,4-triazines[19] all form coupled products which can be envisioned as proceeding through radical-anion intermediates. Studies are currently underway to extend the synthetic utility of this process and to (re)discover hidden anionic one-electron donor systems.

Acknowledgment. We are indebted to the National Science Foundation for financial support of this work and we also thank the referees, especially Professor Cal Meyers, for their helpful comments.

Registry No. 2, 34516-74-0; 3, 29685-07-2; 4, 553-26-4; pyridine, 110-86-1; lithium diisopropylamide, 4111-54-0; 2,4'-bipyridine, 581-47-5.

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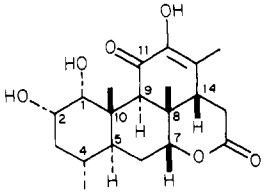
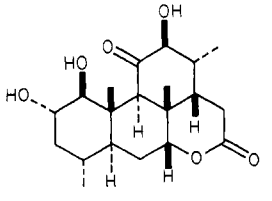
Synthetic Studies on Quassinoids: Total Synthesis of *dl*-Castelanolide

Summary: The quassinoid castelanolide (1) has been synthesized from tetracyclic alcohol 4, thereby confirming the original structural assignment.

Sir: As a result of a detailed examination of *Castela nicholsoni* (Simaroubacaea), a plant known to exhibit antiamebic activity, Geissman and co-workers isolated in the early seventies two new quassinoids, castelanolide (1) and chaparrolide (2).[1] Much attention continues focused on



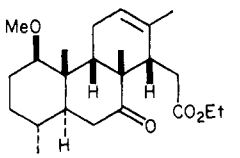
1



2

quassinoids[2,3] because of their potent in vivo antineoplastic activity,[4] recently observed antimalarial properties,[5] and their ability to inhibit cell transformation.[6] Despite the vast number of quassinoids which have been fully characterized during the last 20 years,[2] success at total synthesis has been limited to one published account.[7] We record herein the total synthesis of racemic castelanolide which confirms the structural assignment made via classical methods by Geissman over 10 years ago.

The location of the nine chiral centers in castelanolide coupled with its highly oxygenated carbon backbone suggested as a possible starting point the tetracyclic alcohol 4 prepared previously[7] by a four-step sequence from the known Diels-Alder adduct 3.[3k,8] The use of 4 ensures the



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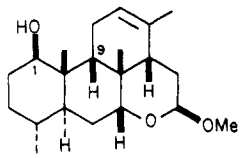

4

proper configuration at six [C(4), C(5), C(7), C(8), C(10), and C(14)] of the nine chiral centers. Transformation of 4 into castelanolide requires the following: (a) elaboration of the ring C diosphenol moiety, (b) inversion of configuration at C(9), (c) introduction of the C(1)-C(2) α oriented vicinal diol unit, and (d) unmasking of the δ-lactone. Toward this end, tetracyclic alcohol 4,[7] mp 161-163 °C, was subjected to tetrahydropyranylation (DHP, PPTS,[9] CH_2Cl_2, 25 °C, 2.5 h) followed by hydroboration (B_2H_6, THF, 0 → 25 °C, 3 h; 30% H_2O_2, OH^-, 50 °C, 2 h) of the C(12)-C(13) olefinic bond, giving rise (80% overall) to

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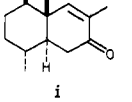

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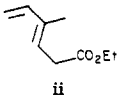

ii

ature (30 h) in benzene containing 0.25 equiv of aluminum chloride and 0.02 equiv of 4,4'-thiobis(6-*tert*-butyl-3-methylphenol). The yield of this remarkable Diels-Alder reaction has been improved to 64% (based on isolated crystalline material) by substituting ethylaluminum dichloride in place of aluminum chloride and allowing the reaction to proceed over a 72-h period.
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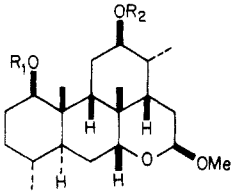
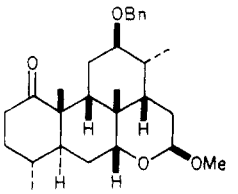
tetracyclic alcohol **5**.[10] Benzylation (NaH, THF, $C_6H_5CH_2Br$, n-Bu_4NI, HMPA, 55 °C, 17 h) of **5** and subsequent cleavage (MeOH, PPTS,[9] THF, 55 °C, 3.5 h) of the THP protecting group provided (72%) crystalline alcohol **6**,[10] mp 140–141 °C, as colorless prisms. Collins oxidation of **6** afforded (92%) ketone **7**,[10] mp 150.5–152.0 °C, which was directly transformed [LDA, THF, HMPA, −78 °C; $(Me_2N)_2POCl$, 0 °C (1.5 h) → 25 °C (2.0 h)] into **8** [R = $OPO(NMe_2)_2$, R′ = Bn],[10] mp 176–177 °C, in 77% yield.

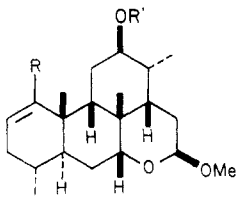


5, R_1 = THP; R_2 = H
6, R_1 = H; R_2 = Bn



7

Reductive cleavage [Li (15 equiv), $EtNH_2$/THF (2:1), t-BuOH (3.0 equiv), 1 h][11] of the C–O bond of enol phosphorodiamidate **8** [R = $OPO(NMe_2)_2$, R′ = Bn] with simultaneous removal of the benzyl ether protecting group generated tetracyclic olefinic alcohol **8** (R = R′ = H),[10] mp 129–130 °C, in 90% yield.



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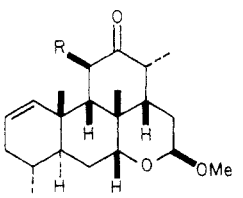
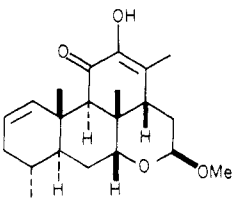


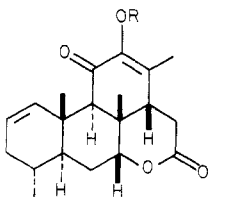
9

Construction of the ring C diosphenol moiety was achieved via a three-step sequence. Oxidation (CrO_3·2Py, CH_2Cl_2) of alcohol **8** (R = R′ = H) provided (91%) crystalline ketone **9** (R = H),[10] mp 138.5–140.0 °C, whose enolate, generated at −78 °C with lithium diisopropylamide in tetrahydrofuran, was treated (5 min) at −10 °C with 1.5 equiv of MoO_5·Py·HMPA.[12] Workup provided a 45% yield (77% based on recovered starting material) of the crystalline hydroxy ketone **9** (R = OH),[10] mp 183–184 °C. Compound **9** was smoothly transformed (91%) with concomitant inversion of configuration at C(9) into diosphenol **10**,[10] mp 168.5–169 °C, upon treatment [55 °C (1 h) → 95 °C (1.5 h)] with excess sodium methoxide in dimethyl sulfoxide containing methanol.[13] This simple one-pot procedure permits facile elaboration of the trans,anti,trans, arrangement of the ABC ring system found in castelanolide.

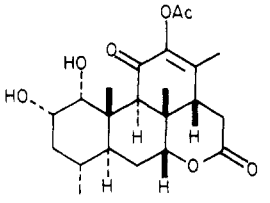
With the basic carbon skeleton of castelanolide secured, we focused our efforts on introduction of the C(1)–C(2) α oriented vicinal diol unit. However, prior to glycolation of the olefinic bond, it was necessary to unmask the δ-lactone and protect the sensitive diosphenol unit. Hydrolysis (10% HCl, THF, 1 h, reflux) of protected lactol **10** followed by mild oxidation (Ag_2CO_3,[14] PhH, 2.5 h, reflux) gave rise to tetracyclic lactone **11**,[10] mp 152–153 °C, which was readily converted (Ac_2O, Py, 1.25 h) into acetate **12**,[10] mp 160–161 °C, in 73% overall yield from **10**. Treatment (25 min) of **12** with 1.1 equiv of osmium tetraoxide in pyridine afforded (98%) crystalline racemic monoacetate **13**,[10] mp 207–209 °C, whose spectral properties were identical with those recorded in the literature for a sample of **13** derived from naturally occurring castelanolide.[1] Treatment of **13** with potassium carbonate in methanol (15 min) provided (91%) crystalline racemic castelanolide (**1**),[10,15] mp 135–137 °C, identical with a sample of natural castelanolide[16,17] by comparison of spectral properties [^{1}H NMR (220 MHz), IR] and thin-layer mobility in several solvent systems.



10



11, R = H
12, R = Ac



13

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (CA 28865) from the National Cancer Institute and, in part, by G.D. Searle and Co. We are grateful to Professor Giovanni Vidari for numerous discussions during the early stages of this work and Drs. J. C. Huffman and K. Folting for carrying out a single-crystal X-ray analysis of monoacetate **13**.

Registry No. **1**, 80326-84-7; **4**, 75924-46-8; **5**, 80326-85-8; **6**, 80326-86-9; **7**, 80326-87-0; **8** (R = $OPO(NMe_2)_2$), 80326-88-1; **8** (R = H), 80326-89-2; **9** (R = H), 80326-90-5; **9** (R = OH), 80326-91-6; **10**, 80326-92-7; **11**, 80326-93-8; **12**, 80326-94-9; **13**, 80326-95-0.

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(15) IR (KBr) 3500, 3400, 1730, 1685, 1655, 1235, 1040 cm^{-1}; NMR (220 MHz, acetone-d_6) δ 0.89 (d, 3 H, J = 6.5 Hz), 1.10 (s, 3 H), 1.23 (s, 3 H), 1.85 (s, 3 H), 3.48 (s, 1 H), 3.96 (m, 1 H), 4.36 (br s, 1 H), 4.52 (d, 1 H, J = 2.5 Hz).
(16) We are grateful to Professor Robert V. Stevens for providing us with a sample of natural castelanolide.
(17) We were indeed fortunate to obtain a sample of natural castelanolide, since the ^{1}H NMR spectrum reported [1] for **1** was incorrectly recorded.

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Received September 14, 1981