analogues of **6** with encapsulated functionality covalently bound either to the floor (i.e., **1**) or the roof of the cavity.

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Claisen-Based Strategy for the de Novo Construction of Basmane Diterpenes. Enantiospecific Synthesis of (+)-7,8-Epoxy-2-basmen-6-one

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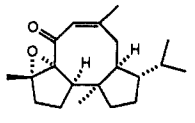
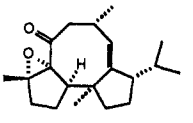
For reasons yet incompletely understood, Virginia and Burley tobaccos contain only diterpenoids of the cembrane type (more than 40 have been characterized) while Oriental tobaccos normally elaborate both cembranoids and labdanoids.[1] The vast majority of these compounds appear not to be present in other sources (plant or animal) and hence may be specific to tobacco. Until 1983, the cembranoids and labdanoids were the only diterpenoids known to occur in tobacco. At that time, the isolation and structure determination of **1**, having a previously unknown tricyclic ring system to which the class name basmane was assigned, was reported.[2]



1



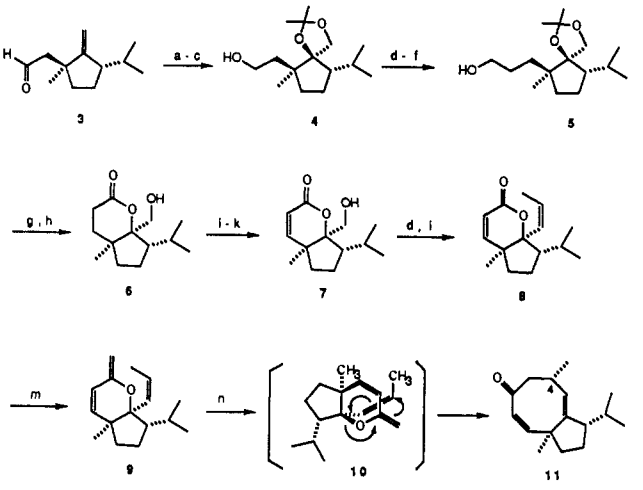
2

In this communication, we detail an enantiospecific route to **2**, the first member of the basmenone class to yield to total synthesis. Our approach showcases the capacity of the Claisen rearrangement for providing convenient stereocontrolled access to annulated 2,5-cyclooctadienones that carry multiple stereogenic centers.[3]

The ready availability of aldehyde **3** from (*R*)-(+)-limonene[4] prompted its utilization as the cornerstone of our approach. Reduction with sodium borohydride, followed by osmylation and regioselective acetonide formation, led to **4** (80%, Scheme I).[5] Chain extension was next accomplished by sequential PDC oxidation, Wittig olefination, and hydroboration. The overall yield of **5** based on **4** after purification by silica gel chromatography was 62%. Once conversion to the carboxylic acid had been achieved, hydrolysis with 10% hydrochloric acid in THF delivered a 15:1 mixture of **6** and its epimer (80%). Consequently, osmylation of the alcohol derived from **3** proceeds with a pronounced preference for attack from that face syn to the 2-hydroxyethyl substituent.

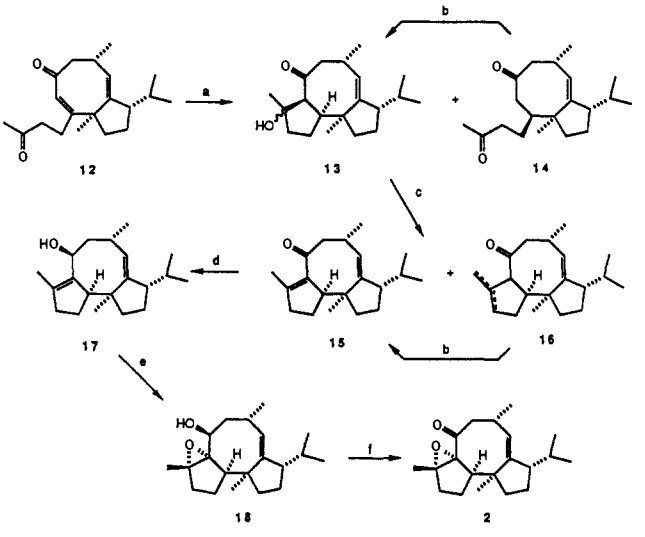
Enantiomerically homogeneous **6** was next transformed into **7** with high efficiency (86%). The use of benzeneseleninic anhydride for this purpose[6] necessitated that the hydroxyl group be transiently protected by silylation. With arrival of **7**, we had nearly completed the *indirect* construction of ring B. Homologative generation of two additional sights of unsaturation, one with high stereocontrol, was now required to reach this major plateau of the synthesis. In fact, PDC oxidation and condensation with ethylidenetriphenylphosphorane[7] (THF, 0 °C) led uniquely to **8** (77%), the stereochemistry of which was confirmed by X-ray analysis.[8]

Scheme I[a]



[a] (a) $NaBH_4$, EtOH, THF; (b) OsO_4, NMO, aqueous acetone; (c) $CH_3C(OCH_3)_2CH_3$, (TsOH), acetone; (d) PDC, 3-Å sieves, CH_2Cl_2; (e) $Ph_3P{=}CH_2$, THF, 0 °C; (f) 9-BBN,THF; NaOH, 30% H_2O_2; (g) PDC, DMF; (h) 10% HCl, THF; (i) *t*-$BuMe_2SiCl$, imidazole, DMF, 48 h; (j) $(PhSeO)_2O$, C_6H_5Cl, 135 °C, 16 h; (k) $Bu_4N^+F^-$, THF, DMF; (l) $Ph_3P{=}CHCH_3$, THF, 0 °C; (m) $Cp_2TiCl(CH_2)Al(CH_3)_2$, (py), THF, C_6H_6; (n) $C_6H_5CH_3$, 180 °C, 24 h (see text).

Scheme II[a]



[a] (a) H_2, PtO_2, C_2H_5OH; (b) K_2CO_3, CH_3OH; (c) $SOCl_2$, py, CH_2Cl_2; (d) $LiAlH_4$, THF, 0 °C; (e) MCPBA, CH_2Cl_2, 0 °C; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −70 °C.

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(5) All formulas are drawn in their proper absolute configuration. In addition, all structural assignments are in accord with individual 300-MHz ^1H NMR, 75-MHz ^{13}C NMR, and high-resolution mass spectra. Key intermediates have also given acceptable combustion analysis data. All recorded yields are based upon isolated material of >97% purity.
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(8) The crystals of compound **8** belong to the space group $P2_12_12_1$ (No. 19) with a = 8.457 (1) Å, b = 12.753 (2) Å, and c = 12.951 (2) Å with four molecules per unit cell, D_{calcd} = 1.114 g cm^{-3}; data collected = $h,k,\pm l$, unique data = 1180, unique data with $F_o^2 > \sigma(F_o^2)$ = 905, final number of variables = 155, $R(F)$ = 0.094, $R_w(F)$ = 0.078, R = 0.055, and R_w = 0.064.

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The conversion of **8** to **9** was effected with the Tebbe reagent[9] (91%). Significantly for our purposes, the structural features in **9** effectively preclude possible prototropic isomerization of the vinyl ether double bond.[3] The thermal rearrangement of this intermediate (180 °C, 24 h, NaOH-washed Carius tubes) was consequently not plagued by this competing side reaction and delivered **11** together with its 4-methyl epimer in a ratio of 15:1 (34–60%). These isomers could be distinguished spectroscopically (NOE). Pure **11** exhibits an $[\alpha]_D$ of −2.7° (*c* 2.3, $CHCl_3$) at 19 °C. This stereochemical outcome is in agreement with dominant utilization by **9** of the chair transition state **10**.

With the structure and stereochemistry of **11** secure, attention was turned to regiospecific cyclopentannulation and installation of the four remaining stereogenic centers. Addition to **11** of the 4-bromo-2-butanone ethylene ketal Grignard reagent in the presence of $CuBr{\cdot}SMe_2$, direct O-silylation of the resulting enolate, phenylselenenylation (PhSeCl, THF, 0 °C), and oxidation (30% H_2O_2) generated **12** in 84% yield after acid hydrolysis. As a consequence of the conformation adopted by **12**, hydrogenation over platinum proceeded stereoselectively from the α-face. The mixture of **13** (42%) and **14** (48%, 9:1 mixture with its epimer) so produced was directly cyclized and then dehydrated (Scheme II). To arrive exclusively at **15** (62%), the initially formed **15**/**16** mixture was stirred for 1 week in the presence of methanolic K_2CO_3.

Well aware of the topography inherent to **15**, we reduced this ketone cleanly to **17** (95%) in order to take subsequent advantage of the known anti epoxidation mode to which 3-cyclooctenols are normally subject.[10] In the case of **17**, the exocyclic double bond responded analogously such that **18** was isolated at the 86% level from reaction with MCPBA. Swern oxidation led conventionally to **2** [mp, 135–137 °C; $[\alpha]^{19}_D$ = +138° (*c* 3.09, $CHCl_3$)]. Single-crystal X-ray analysis[11] of this ketone unambiguously confirmed its identity.

Presently work is underway to synthesize **1** from one or more of the intermediates or directly from **2**. It is already clear, however, that the availability of **11** should allow access to some interesting epoxybasmenones not available from natural sources for biological evaluation.

Acknowledgment. We thank the National Institutes of Health (Grants GM-30827 and CA-12115) for generous financial support and Dr. Judith C. Gallucci for the X-ray crystallographic analyses.

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(11) The crystals of compound **2** belong to the space group $P2_12_12_1$ with a = 13.490 (3) Å, b = 13.993 (3) Å, and c = 9.552 (2) Å with four molecules per unit cell, D_{calcd} = 1.11 g cm^{-3}; data collected = *hkl*, unique data = 1851, unique data with $F_o^2 > \sigma(F_o^2)$ = 1150, final number of variables = 199, $R(F)$ = 0.103, $R_w(F)$ = 0.063, and R = 0.049.

Total Synthesis of Calicheamicinone: A Solution to the Problem of the Elusive Urethane

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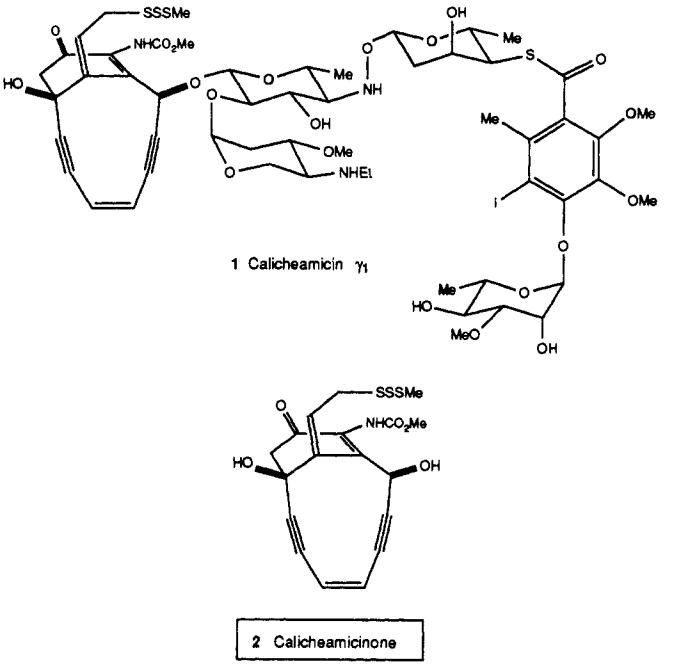
Recently there has been discovered a growing collection of antibiotics bearing novel patterns of interactive unsaturation. The antimicrobial and antitumor properties of these compounds[1] follow from their capacity to cut double-stranded DNA.[2] Evidence has been accumulated that the effector species for DNA degradation in vitro are diyls arising from chemically induced Bergman type[3] bond reorganizations[4] of the unsaturated loci. In a suitable setting,

Scheme I



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