

## Synthesis of ( $\pm$ )-7,8-Epoxy-4-basmen-6-one by a Transannular Cyclization Strategy

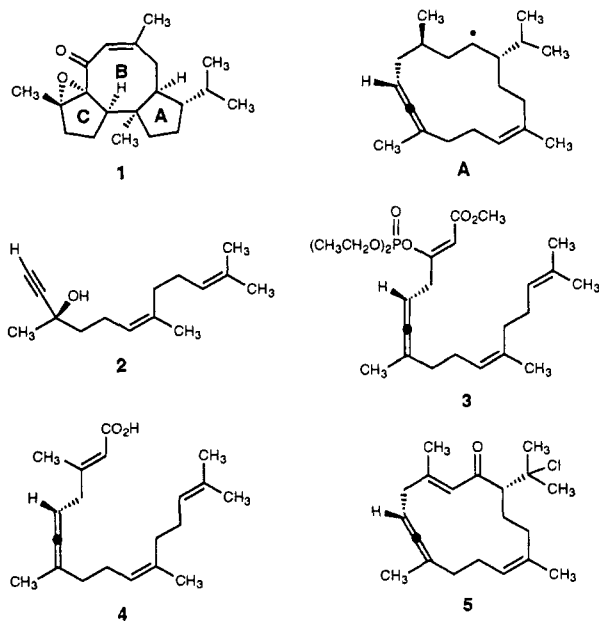
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The diterpenoid tobacco isolate 7,8-epoxy-4-basmen-6-one (**1**)<sup>1</sup> possesses a carbon skeleton that is thus far unique in nature and presents a complex synthetic problem in which to explore the use of transannular cyclization as a strategy for synthetic simplification. In this work we illustrate the use of such a strategy in the first synthesis of this natural product.

The tricyclic skeleton of **1** was envisioned to be formed from the macrocyclic free radical **A** by 5-*exo*-trig closure of the radical onto the (*Z*)-olefin via a chairlike conformer in which the isopropyl substituent is equatorially oriented, thus setting the problematic stereocenters within the A ring of **1**.<sup>2,3</sup> The allene functional group was incorporated so as to direct a second closure reaction to form the 5-8-5 tricyclic ring system. The following sequence has provided synthetic ( $\pm$ )-**1** via the intermediate **A**.



Addition of lithium acetylide (1.5 equiv) to commercial neryl acetone in tetrahydrofuran (THF) at  $-78$  °C afforded the alcohol **2** in 99% yield. The corresponding mesylate was prepared in the usual way<sup>4</sup> and was stored briefly at 0 °C as a solution in THF (1 M). Addition of the crude mesylate solution to a reagent prepared from cuprous iodide (0.6 equiv) and the dianion of methyl acetoacetate (1.2 equiv) in THF (0 °C for 1 h, then cooled to  $-78$  °C) led to the stereocontrolled formation of an allenyl  $\beta$ -keto ester enolate, which was trapped in situ by the addition of

diethylchlorophosphate (2.0 equiv,  $-78 \rightarrow 0$  °C), thus producing the (*Z*)-enol phosphate **3** in 85% yield from **2**. Treatment of **3** with lithium dimethylcuprate (2.3 equiv) in diethyl ether ( $-78 \rightarrow 0$  °C)<sup>5</sup> and saponification of the product with aqueous sodium hydroxide in *tert*-butyl alcohol at 75 °C afforded the acid **4** with complete stereospecificity (67% yield for the two steps). Using a modification of methodology developed by Kato et al.,<sup>6</sup> the crude acid chloride formed from **4** and oxalyl chloride was treated with stannic chloride (1.1 equiv) in dichloromethane at  $-78$  °C for 0.5 h to produce the macrocycle **5** in 60% yield (10:1 ratio of diastereomers).<sup>7,8</sup> The macrocycle **5** has proven to be a versatile synthetic intermediate, providing access to each of the four diastereomers of **A** for study. Discussion here is limited to the synthesis and cyclization of the specific diastereomer **A**, which proved optimum with respect to a synthesis of **1**.

Conjugate reduction of **5** with lithium *sec*-butylborohydride (2.0 equiv) in THF at  $-78$  °C afforded the ketone **6** (mp 54 °C) as a single diastereomer in 91% yield.<sup>8,9</sup> Heating **6** in a mixture of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and THF at reflux for 36 h afforded a thermodynamic distribution of readily separable, crystalline  $\alpha,\beta$ - and  $\beta,\gamma$ -unsaturated ketones in a 4:1 ratio (mg 44 and 35 °C, respectively, 73% yield). The major, conjugated product was reduced with  $\text{SmI}_2$  (2.5 equiv)<sup>10</sup> in THF-methanol at 25 °C for 1 h, producing the  $\beta$ -isopropyl epimer of **7** as the sole product (mp 36 °C). Treatment of the latter with DBU in toluene at reflux for 48 h produced **7** (mp 49 °C) as the major product and lesser amounts of recovered  $\beta$ -isopropyl epimer (2:1, respectively, 81% yield for the two steps).<sup>11</sup> Reduction of the ketone **7** with lithium aluminum hydride in THF at  $-78$  °C for 2 h and acylation of the resulting epimeric mixture of alcohols with *m*-(trifluoromethyl)benzoyl chloride (2.0 equiv) and (*N,N*-dimethylamino)pyridine (3.0 equiv) in dichloromethane at 23 °C for 18 h gave the esters **8** in 95% yield for the two steps.

Irradiation of a mixture of esters **8**, *N*-methylcarbazole (1.1 equiv), and 1,4-cyclohexadiene (0.2 M) in THF-water (10:1) at 55 °C for 5 h with Pyrex-filtered light from a 450-W medium-pressure mercury vapor lamp led to the efficient generation and cyclization of **A** to form a mixture of olefin isomers arising from the trapping of **D** at either allylic terminus (51% combined yield, Scheme I).<sup>12,13</sup> This isomeric mixture is readily equilibrated upon heating in thiophenol:heptane (1:3 v/v, AIBN catalysis) at 50 °C for 30 min to afford the single isomer **9** (91%). The formation of tricyclic products from **8** is believed to occur as depicted in Scheme I, where **A** undergoes 5-*exo*-trig cyclization to form **B**, which then undergoes conformational isomerization to **C** prior to cyclization to form **D**. Importantly, we have found that the theoretical method of Spellmeyer and Houk accurately predicts the outcome of this cyclization reaction.<sup>14</sup> Thus, the initial

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(7) The product of chloride elimination (2-propenyl derivative) was also observed (<10%). Neither this impurity nor the minor diastereomer of **5** was routinely separated from **5**, because all three compounds are processed identically in the next step and converge upon intermediate **7**.

(8) Stereochemical assignments for **5** and **6** were determined by X-ray crystallographic analysis of the C4-epimer of **6** (mp 69 °C), prepared by the treatment of **5** with diisobutylaluminum hydride in THF at  $-78$  °C.

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(11) Both the  $\beta$ -isopropyl epimer of **7** and the  $\beta,\gamma$ -unsaturated ketone formed from **6** were readily and routinely recycled by base treatment.

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(13) X-ray crystallographic analysis of an epoxidation product obtained upon treatment of the olefinic mixture with *m*-chloroperoxybenzoic acid (MCPBA) secured stereochemical assignments in the cyclization reaction (see supplementary material).

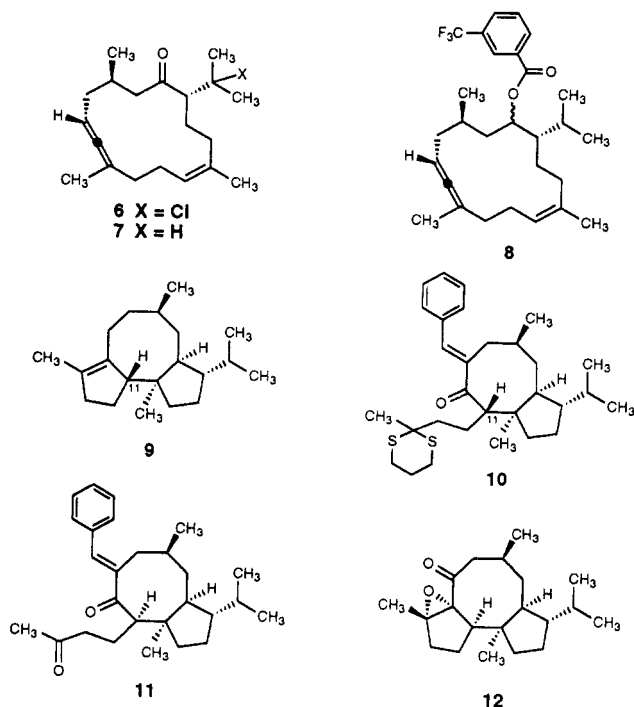
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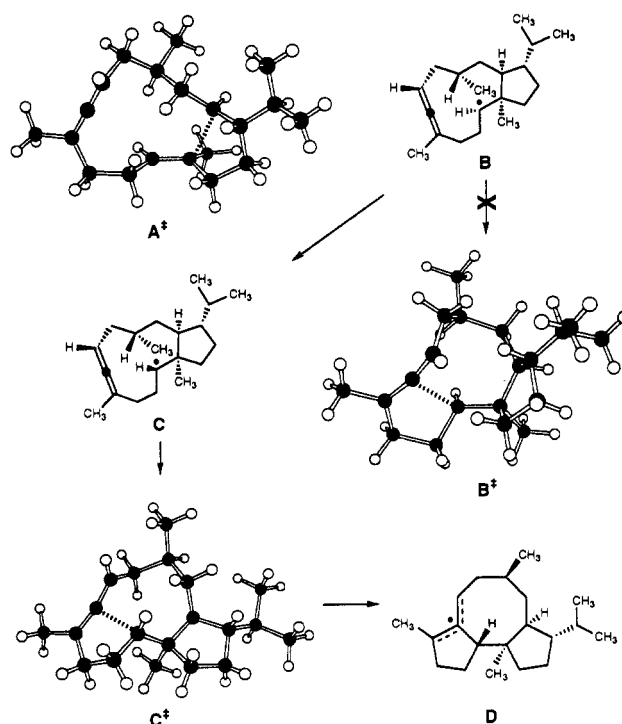
(4) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.



cyclization of **A** and **B** via  $A^\ddagger$  (Scheme I) is calculated to be energetically favored over all alternative 5-*exo*-trig or 6-*endo*-trig cyclizations by  $\geq 4.2$  kcal/mol. Similarly, calculations for the subsequent cyclization of the radical **B** have determined the transition structure  $C^\ddagger$  to be favored over  $B^\ddagger$  by more than 4.0 kcal/mol.

To complete the synthesis of **1** it was necessary to invert the configuration of C11 within intermediate **9** and to introduce the requisite functionality in the B and C rings. Toward this end, oxidative cleavage of **9** with  $\text{RuO}_4^{15}$  produced a diketone which underwent selective thioketalization of the acyclic carbonyl group [1,3-propanedithiol (10 equiv),  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (0.74 equiv),  $\text{CH}_2\text{Cl}_2$ , 5 min, 23 °C]. Condensation of the latter product with benzaldehyde (10 equiv), employing sodium hydroxide as catalyst (0.01 equiv), in ethanol at 23 °C for 24 h provided the enone **10** in 60% yield from **9**. Epimerization of **10** at C11 was accomplished by the initial conversion of **10** to the corresponding trimethylsilyl enol ether with excess trimethylsilyl iodide and triethylamine in dichloromethane at 50 °C in a sealed tube. Treatment of the resulting trimethylsilyl enol ether with 0.5 M methanolic hydrochloric acid at 23 °C for 10 min afforded 11-*epi*-**10** as a crystalline solid (mp 162 °C, 95% for the two steps, 2:1 11-*epi*-**10**:**10**; **10** is easily removed by trituration with hexanes and is recycled). Removal of the dithiane protecting group within 11-*epi*-**10** was readily accomplished with methyl iodide (4 M) in 25% aqueous acetonitrile at 23 °C for 15 h, providing the crystalline diketone **11** (mp 99 °C) in 96% yield.<sup>16</sup> Subjection of **11** to  $\text{TiCl}_3$ -dimethoxyethane complex (19 equiv) and zinc-copper couple (75 equiv) in refluxing dimethoxyethane for 1.5 h led to smooth carbonyl coupling to furnish a sensitive diene product.<sup>17</sup> Epoxidation of this diene with MCPBA afforded an acid-labile allylic epoxide, which was directly treated with  $\text{RuO}_4^{15}$  forming the epoxy ketone **12** in 65% yield for the three steps. Deprotonation of **12** with lithium diisopropylamide in THF at -78 °C and quenching of the resultant enolate with phenylselenenyl chloride formed a single  $\alpha$ -phenylselenenyl ketone diastereomer. Direct treatment of this product with 30% aqueous

Scheme I



hydrogen peroxide in dichloromethane buffered with pyridine<sup>18</sup> at 23 °C for 20 min provided racemic **1** as a crystalline solid (mp 122 °C, lit. mp (for (+)-**1**)<sup>1</sup> 109–110 °C) in 75% yield from **12**. Synthetic ( $\pm$ )-**1** provided spectral data indistinguishable from those obtained from the natural substance (<sup>1</sup>H NMR, <sup>13</sup>C NMR, FTIR, and HRMS), and the structure was established unequivocally by X-ray crystallographic analysis (see supplementary material).

In summary, several noteworthy transformations have served to simplify the synthesis of the natural product **1**. The conversion of **2** to the enol phosphate **3** in a two-step operation, employing an organocopper reagent derived from acetoacetate, introduced the allene functional group in high yield, and cationic cyclization of the olefinic acid **4** produced the macrocycle **5** stereoselectively. The transannular radical cyclization of **8** by a photochemical method led to the stereoselective construction of the tricyclic product **9**. The ability of theory to accurately predict the outcome of the latter transformation is encouraging for the future use of transition-state molecular modeling in the design of synthetic schemes employing a transannular radical cyclization strategy.

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**Supplementary Material Available:** Tabulated <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and high-resolution mass spectral data, reproductions of <sup>1</sup>H NMR spectra for synthetic intermediates **1**–**12**, and thermal ellipsoid plots with experimental procedures and crystal structure data for compounds analyzed by X-ray crystallography (65 pages). Ordering information is given on any current masthead page.

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