Synthesis of (±)-7,8-Epoxy-4-basmen-6-one by a Transannular Cyclization Strategy

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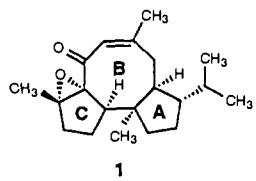
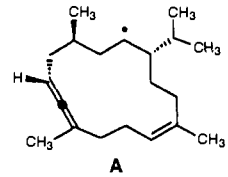
The diterpenoid tobacco isolate 7,8-epoxy-4-basmen-6-one (**1**)[1] possesses a carbon skeleton that is thus far unique in nature and presents a complex synthetic problem in which to explore the use of transannular cyclization as a strategy for synthetic simplification. In this work we illustrate the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

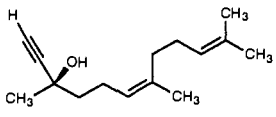
The tricyclic skeleton of **1** was envisioned to be formed from the macrocyclic free radical **A** by 5-*exo*-trig closure of the radical onto the (*Z*)-olefin via a chairlike conformer in which the isopropyl substituent is equatorially oriented, thus setting the problematic stereocenters within the A ring of **1**.[2,3] 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 (±)-**1** via the intermediate **A**.



1



A



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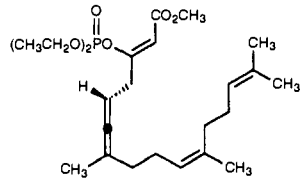

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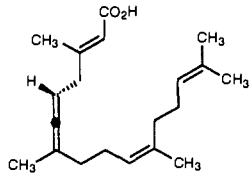

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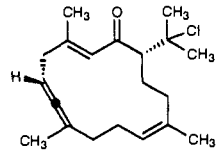

5

Addition of lithium acetylide (1.5 equiv) to commerical neryl acetone in tetrahydrofuran (THF) at −78 °C afforded the alcohol **2** in 99% yield. The corresponding mesylate was prepared in the usual way[4] 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 β-keto ester enolate, which was trapped in situ by the addition of diethylchlorophosphate (2.0 equiv, −78 → 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 → 0 °C)[5] 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.,[6] 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).[7,8] 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 tri-*sec*-butylborohydride (2.0 equiv) in THF at −78 °C afforded the ketone **6** (mp 54 °C) as a single diastereomer in 91% yield.[8,9] 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 α,β- and β,γ-unsaturated ketones in a 4:1 ratio (mg 44 and 35 °C, respectively, 73% yield). The major, conjugated product was reduced with SmI_2 (2.5 equiv)[10] in THF–methanol at 25 °C for 1 h, producing the β-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 β-isopropyl epimer (2:1, respectively, 81% yield for the two steps).[11] 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).[12,13] 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.[14] Thus, the initial

(1) Wahlberg, I.; Eklund, A.-M.; Nishida, T.; Enzell, C. R.; Berg, J.-E. *Tetrahedron Lett.* **1983**, *24*, 843.

(2) Leading references, radical cyclizations: (a) Curran, D. P. *Synthesis* **1988**, 417, 489. Transannular radical cyclizations: (b) Cope, A. C.; Martin, M. M.; McKervey, M. A. *Q. Rev., Chem. Soc.* **1966**, *20*, 119. (c) Winkler, J. D. *J. Am. Chem. Soc.* **1986**, *108*, 1708. (d) Curran, D. P. *Tetrahedron* **1993**, *49*, 755.

(3) Previous work directed toward the synthesis of **1**: (a) Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252. (b) Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610.

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

(5) (a) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082. (b) Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431.

(6) Kato, T.; Suzuki, M.; Kobayashi, T.; Moor, B. P. *J. Org. Chem.* **1980**, *45*, 1126.

(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.

(9) (a) Ganem, B.; Fortunato, J. M. *J. Org. Chem.* **1975**, *40*, 2846. (b) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.

(10) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

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

(12) (a) Saito, I.; Ikehira, H.; Kasatani, R.; Watanabe, M.; Matsuura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3115. (b) Suzuki, M.; Koyano, H.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 5583.

(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).

(14) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

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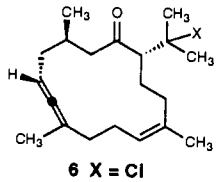
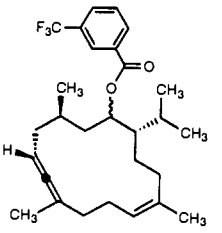
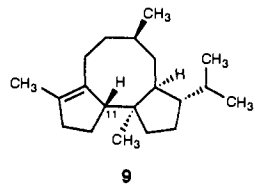
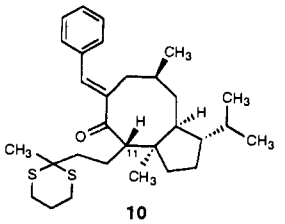
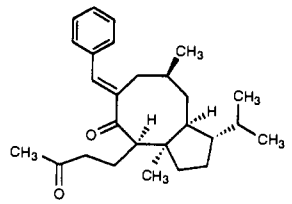
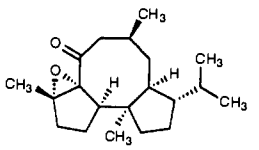








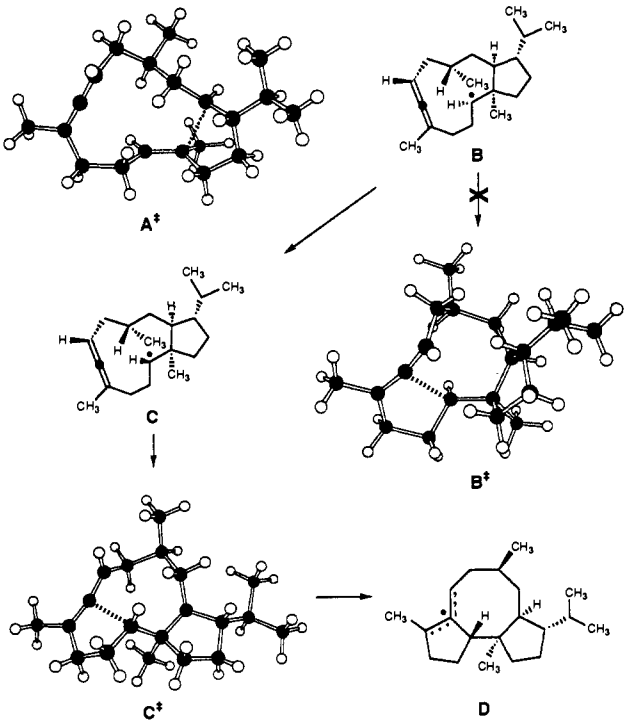




cyclization of **A** and **B** via **A**‡ (Scheme I) is calculated to be energetically favored over all alternative 5-*exo*-trig or 6-*endo*-trig cyclizations by ≥4.2 kcal/mol. Similarly, calculations for the subsequent cyclization of the radical **B** have determined the transition structure **C**‡ to be favored over **B**‡ 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 RuO_4[15] produced a diketone which underwent selective thioketalization of the acyclic carbonyl group [1,3-propanedithiol (10 equiv), $BF_3{\cdot}Et_2O$ (0.74 equiv), CH_2Cl_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.[16] Subjection of **11** to $TiCl_3$–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.[17] Epoxidation of this diene with MCPBA afforded an acid-labile allylic epoxide, which was directly treated with 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 α-phenylselenenyl ketone diastereomer. Direct treatment of this product with 30% aqueous hydrogen peroxide in dichloromethane buffered with pyridine[18] at 23 °C for 20 min provided racemic **1** as a crystalline solid (mp 122 °C, lit. mp (for (+)-**1**)[1] 109–110 °C) in 75% yield from **12**. Synthetic (±)-**1** provided spectral data indistinguishable from those obtained from the natural substance (^1H NMR, ^{13}C NMR, FTIR, and HRMS), and the structure was established unequivocally by X-ray crystallographic analysis (see supplementary material).

Scheme I



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.

Acknowledgment. We thank Dr. Curt Enzell for kindly providing spectra of **1**, and we acknowledge Dr. Marc Labgold for his contributions to the synthesis of **5**. We are grateful for financial support from the National Science Foundation and for a Bristol-Myers Company Grant of Research Corporation.

Supplementary Material Available: Tabulated ^1H NMR, ^{13}C NMR, IR, and high-resolution mass spectral data, reproductions of ^1H 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.

(15) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(16) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1977**, 68.
(17) (a) McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748. (b) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.
(18) (a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, *39*, 2133. (b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (c) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.