Na^+: 6.71×10^{-3} (2×10^{-3}), 5.56×10^{-3} (4×10^{-3}), 3.59×10^{-3} (1×10^{-2}), 2.36×10^{-3} (2×10^{-2}), 8.71×10^{-4} (0.1), 5.05×10^{-4} (0.2); $r = 0.9907$.

K^+: 6.75×10^{-3} (1×10^{-2}), 5.22×10^{-3} (4×10^{-2}), 3.21×10^{-3} (0.1), 2.26×10^{-3} (0.2).

Rb^+: 5.99×10^{-3} (4×10^{-2}), 4.11×10^{-3} (0.1), 2.91×10^{-3} (0.2).

Cs^+: 5.69×10^{-3} (4×10^{-2}), 4.18×10^{-3} (0.1), 3.17×10^{-3} (0.2).

Et_4N^+: 8.12×10^{-3} (1×10^{-2}), 8.93×10^{-3} (0.2), 8.71×10^{-3} (0.4).

Appendix

Neglect of the activity coefficient term $\gamma_\pm^2$ led to a very poor fit of eq 5 to the data. As a first approximation, $\gamma_\pm$ was calculated from the Debye-Hückel limiting law

$$\log \gamma_\pm = -1.115\mu^{1/2} \tag{19}$$

With the term $\gamma_\pm^2$ thus calculated, the fit was significantly better but not yet fully satisfactory. It was nevertheless apparent that for a given number of reactions k_{ip} was negligibly small. These were all the reactions carried out in the presence of Li^+, reactions 3 and 2 (R = H and OCH_3) as carried out in the presence of Na^+, and reactions 3 and 2 (R = OCH_3) as carried out in the presence of K^+. In all these cases, eq 7 may be rewritten in the form

$$K_O^{app} = \frac{k_i - k_{obsd}}{k_{obsd}[M^+]} \tag{20}$$

where $K_O^{app} = K_O\gamma_\pm^2$ is the concentration association constant for ion pairing. Upon introduction of experimental data into eq 20 for each reaction, sets of concentration dependent K_O^{app} values were obtained. By assuming that log $\gamma_\pm$ is given by a power series in $\mu^{1/2}$,[36] with the first coefficient given by the Debye-Hückel theory for neat Me_2SO, the second coefficient C was determined from plots of the left-hand side of eq 21 against μ. The coefficient

$$\log K_O^{app} + 2.23\mu^{1/2} = \log K_O + 2C\mu \tag{21}$$

C was found to vary somewhat for the varying phenoxide-cation pairs, but since no systematic trend was apparent, the average value of 1.65 ± 0.25 was assumed to apply to all ionic species including the Rb and Cs phenoxides. It is worth noting that up to $\mu \simeq 0.1$ M the $\gamma_\pm$ values calculated from eq 8 are indistinguishable within the precision of the data from those calculated from the extended Debye-Hückel equation

$$\log \gamma_\pm = -\frac{1.115\mu^{1/2}}{1 + 2.34\mu^{1/2}} \tag{22}$$

which has been used by Kolthoff[37] and corresponds to a value of 6 Å for the adjustable parameter.

Registry No. 1, 65845-47-8; **1**·Li, 83897-22-7; **1**·Na, 83897-23-8; **1**·K, 83897-24-9; **1**·Rb, 83897-25-0; **1**·Cs, 83897-26-1; **1**·Et_4N, 83897-27-2; **2**, 3229-70-7; **2**·Li, 555-24-8; **2**·Na, 139-02-6; **2**·K, 100-67-4; **2**·Rb, 15589-78-3; **2**·Cs, 1120-91-8; **2**·Et_4N, 32580-85-1; **3**, 54976-95-3; **3**·Li, 20246-64-4; **3**·Na, 13052-77-2; **3**·K, 5633-98-7; **3**·Rb, 83897-28-3; **3**·Cs, 1194-05-4; **3**·Et_4N, 83897-29-4; **4**, 83897-41-0; **4**·Li, 83897-30-7; **4**·Na, 83897-31-8; **4**·K, 83897-32-9; **4**·Rb, 83897-33-0; **4**·Cs, 83897-34-1; **5**, 83897-39-6; **5**·Li, 83897-35-2; **5**·Na, 83897-36-3; **5**·K, 76670-16-1; **5**·Rb, 83897-37-4; **5**·Cs, 83897-38-5; **5**·Et_4N, 83897-40-9; B18C6, 14098-24-9; BuBr, 109-65-9; *o*-$BuOC_6H_4(OCH_2CH_2)_4OMe$, 83897-42-1; 2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1,14-benzodioxacyclohexadecin, 62587-29-5; butoxybenzene, 1126-79-0; 1-butoxy-2-methoxybenzene, 51241-33-9.

(36) Reference 12, Chapter 7.

(37) Kolthoff, I. M.; Chantooni, M. K., Jr.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23.

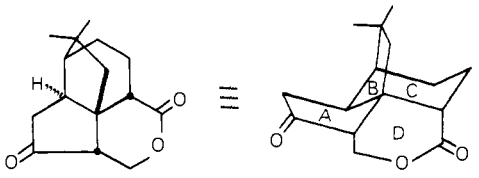
A Short-Step Entry to (±)-Quadrone

Kei Takeda, Yukari Shimono, and Eiichi Yoshii*

Contribution from the Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Toyama 930-01, Japan. *Received April 26, 1982*

Abstract: A new synthetic route to (±)-quadrone (**1**) starting with 7,7-dimethyl-*cis*-bicyclo[4.2.0]octan-2-one (**2**) via Danishefsky's intermediate **5** is reported, in addition to the preliminary model study dealing with the synthesis of the tricyclic enone **9**. 2-(2-Propynyl)bicyclo[4.2.0]octan-2-ol (**6**) obtained from **2** was subjected to rearrangement in refluxing formic acid to produce the isomeric bicyclo[3.2.1]octanol **7** in good yield, which could have been transformed to **9** through a conventional three-step sequence of reactions in an overall yield of 47% from **2**. For the synthesis of **5**, the 3-methoxymethyl derivative of **6** derived from **2** was subjected to formolysis, yielding mainly four products: **12**-**15**. The product ratio was found to be very sensitive to the reaction conditions, and especially lowering the temperature favored increased formation of the objective compound **14**. The product mixture obtained at 25 °C was treated with PCC followed by chromatographic separation to give the [3.2.1] bicyclic ketone **17** in 31% yield from **11**. The compound **17** was then transformed to the tricyclic enone **19** according to the procedure established in the model experiment. Oxidation of the side chain of **19** to the carboxyl group by a two-step reaction afforded the key intermediate **5** in an overall yield of 4% from **2**.

Quadrone (**1**), a novel sesquiterpene reported as a fungal metabolite from *Aspergillus terreus* in 1978, exhibits inhibitory activity in vitro against human epidermoid carcinoma of the nasopharynx (KB) and in vivo against P-338 lyphocytic leukemia in mice (PS).[1] Its unique structural features embodying a quadracyclic fused ring system and its reported biological activity have received considerable attention from synthetic chemists, yielding three independent entries in recent years. The first total synthesis of (±)-**1** by Danishefsky,[2a] which was communicated in 1980, and the second one by Helquist[2b] have shared a general synthetic strategy in which the quadracyclic ring system is as-



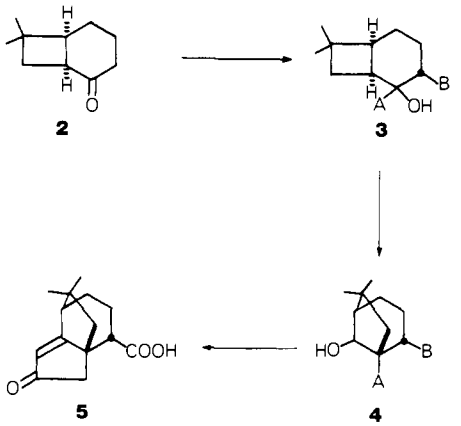
1

(1) (a) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499-502. (b) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38-42.

(2) (a) Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136-4141; **1980**, *102*, 4262-4263. (b) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *Ibid.* **1981**, *103*, 4647-4648. (c) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S. *Ibid.* **1982**, *104*, 872-874.

0002-7863/83/1505-0563$01.50/0

Scheme I[a]



[a] A = acetonyl group equivalent; B = carboxyl group equivalent.

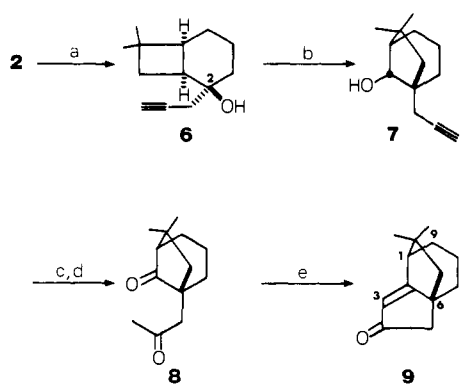
sembled by a stepwise annelation sequence of B → A → C → D. In contrast, the more recent work by Burke[2c] features a novel and efficient A → B → C annelation route to reach the tricyclic keto ester **20** which is an intermediate in Danishefsky's synthesis.

A particularly attractive approach occurred to us in our investigation in this area that was quite different from those already published. As illustrated in Scheme I, we envisioned that the tricyclic enone acid **5**, which had already been converted to quadrone (**1**) by an additional three steps by Danishefsky,[2a] would be obtainable from an appropriately substituted bicyclo[4.2.0]-octanol **3** by solvolytic rearrangement[3] followed by cyclopentenone annelation. The compound **3** itself would be readily accessible from 7,7-dimethyl-*cis*-bicyclo[4.2.0]octan-2-one (**2**). In order to test the feasibility of the indicated cyclobutylcarbinyl cation rearrangement (**3** → **4**) and also of the subsequent reaction sequence for the cyclopentenone annelation, we have performed a preliminary experiment dealing with the synthesis of the decarboxy tricyclic compound **9**. This paper describes the successful result obtained in the model study and application of the strategy to the synthesis of the compound **5**, leading to a short formal total synthesis of (±)-**1** by an unprecedented C → B → A → D annelation approach.

Results and Discussions

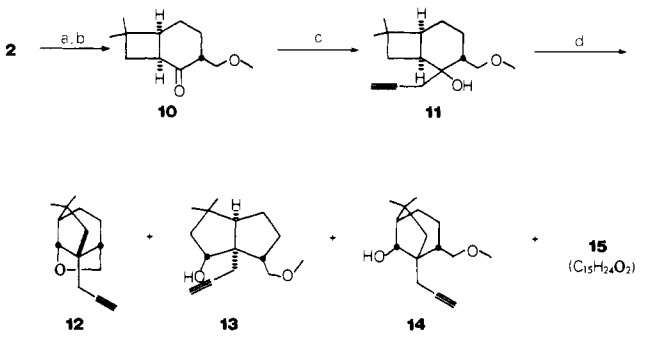
As a latent functionality equivalent to the acetonyl group (A in structure **3**) (Scheme I), we selected the propargyl group. Thus, 7,7-dimethyl-*cis*-bicyclo[4.2.0]octan-2-one (**2**),[4a] readily available by photocycloaddition of isobutene to 2-cyclohexenone in good yield by an improved procedure,[4b] was allowed to react with properglylaluminum sesquibromide[5] in tetrahydrofuran at 40 °C to give the propargyl carbinol **6** in 81% yield as a single stereoisomer. The stereochemistry at the C(2) center as indicated in the structure (Scheme II) was assigned by considering the reagent attack on the less hindered convex side of the substrate. When the carbinol **6** was heated in refluxing formic acid, the formolysis proceeded smoothly. An alcohol obtained in 75% yield after saponification of the resulting formate was fentatively assigned to the structure **7**, the carbon framework of which was later confirmed by transformation into the tricyclic compound **9**. Orientation of the hydroxyl group was assigned by consideration of the mechanism of the reaction.[3] Oxidation of **7** with pyridinium

Scheme II[a]



[a] (a) Al, HC≡C–CH_2Br. (b) HCO_2H, reflux, 30 min; K_2CO_3, MeOH–H_2O. (c) $PyHCrO_3Cl$, CH_2Cl_2. (d) HgO, H_2SO_4, MeOH–H_2O. (e) *tert*-$C_5H_{11}OH$, NaH, PhH, reflux.

Scheme III[a]



[a] (a) LDA, Me_3SiCl. (b) $MeOCH_2Cl$, CH_2I_2, Zn–Cu. (c) Al, HC≡C–CH_2Br. (d) HCO_2H.

chlorochromate (PCC)[6] in dichloromethane followed by hydration of the triple bond in the usual manner afforded the diketone **8** in 86% yield, which was characterized by the carbonyl bands (1745, 1720 cm^{-1}) in the infrared spectrum.

Base-catalyzed internal aldol cyclization of **8** was attempted by a variety of known methods, among which the most effective was the use of sodium hydride in the presence of a trace amount of *tert*-amyl alcohol in benzene at reflux,[7] affording the desired tricyclic enone **9** in 90% yield. The bridged structure of **9** was now determined on the basis of the mass spectrum, which showed the base peak at *m/e* 134 due to loss of isobutene from M^+, and the ^1H NMR spectral data in which the most informative were a broad triplet for C(1)–H at δ 2.45 ($J \simeq 3$ Hz, $J_{1,3} = 0$ Hz) and a couple of doublets due to the C(11) bridge methylene protons at δ 1.80 and 1.32 ($J = 13$ Hz). Recently, Smith et al.[8] have prepared the compound **9** starting with 3-methyl-2-cyclopentenone in the course of the synthesis of (±)-descarboxyquadrone, a biologically active analogue of quadrone. When compared with this reported 13 step synthesis in 4.7% yield, the efficiency of our 5 step access to **9** in 47% yield should be noted.

With the tricarbocyclic nucleus of quadrone successfully constructed, we were encouraged to apply our strategy to the synthesis of the quadrone precursor **5** possessing an axial carboxyl group. As the one carbon synthon required for the carboxyl group, we selected the methoxymethyl group. Thus, 3-(methoxymethyl)-7,7-dimethyl-*cis*-bicyclo[4.2.0]octan-2-one (**10**) was prepared after the method of Shono[9] by the reaction of the trimethylsilyl enol ether of **2** with chloromethyl methyl ether in the presence of

(3) (a) Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1964**, *86*, 1652–1653. (b) Cope, A. C.; Gleason, R. W.; Moon, S.; Park, C. H. *J. Org. Chem.* **1967**, *32*, 942–946. (c) Manh, D. K.; Fetizon, M.; Flament, J. P. *Tetrahedron* **1975**, *31*, 1897–1902. (d) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 2869–2872. (e) Manh, D. K.; Fetizon, M.; Kone, M. *Tetrahedron* **1978**, *34*, 3513–3523. (f) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82–87; **1979**, *101*, 7130–7131. (g) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Helv. Chim. Acta* **1981**, *64*, 1347–1364; *Chem. Lett.* **1978**, 1301–1304.

(4) (a) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485–492; **1963**, *85*, 362–363. (b) Owsley, D. C.; Bloomfield, J. J. *J. Chem. Soc. C* **1971**, 3445–3447.

(5) Laeuger, P.; Prost, M.; Charlier, R. *Helv. Chim. Acta* **1959**, *42*, 2379–2393.

(6) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.

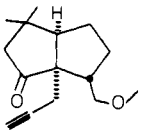
(7) McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, M. A. *J. Am. Chem. Soc.* **1979**, *101*, 1330–1332.

(8) Smith, A. B., III; Wexler, B. A.; Slade, J. *Tetrahedron Lett.* **1982**, *23*, 1631–1634.

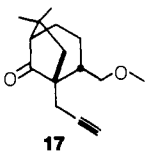
(9) Shono, T.; Nishiguchi, I.; Komamura, T.; Sasaki, M. *J. Am. Chem. Soc.* **1979**, *101*, 984–987.

zinc–copper couple and diiodomethane in 59% yield from **2** (Scheme III). The stereochemistry of the methoxymethyl group was tentatively assigned as having the desired cis orientation relative to the junction hydrogens on the basis of the sterically favored attack of the alkylating reagent on the convex face of the substrate, and this was later confirmed by conversion to **5**. The key intermediate alcohol **11** was obtained as a single stereisomer by treatment of **10** with propargylaluminum sesquibromide at −78 °C in 50% yield.[10]

Formolysis of compound **11** was first attempted in refluxing formic acid, i.e., the reaction condition employed for the corresponding desmethoxymethyl compound **6**. The reaction product isolated after treatment with aqueous sodium hydroxide was, however, rather complex in contrast to the case of **6**. It was shown by vapor-phase chromatography (VPC) to be a mixture of mainly four products (in the order of elution): the tricyclic ether **12**, two isomeric cyclopentanols **13** and **14**, and a bicyclic unsaturated ketone **15** in a ratio of ca. 4:3:1:4. The structures of these listed products except the unidentified **15** were supported by spectral data.[11] The cyclopentanol structure for **13** and **14** was proved by converting them to the corresponding ketones **16** and **17** by



16



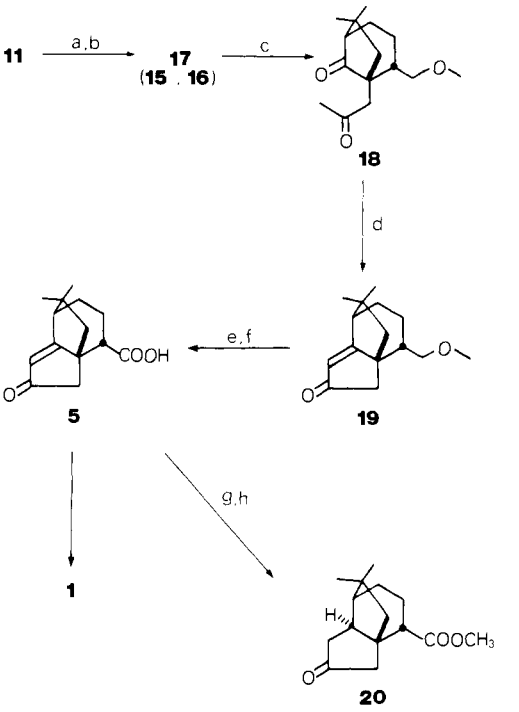
17

oxidation with PCC and observing their infrared spectra for five-membered ring ketone bands: **16**, 1740 cm^{-1}; **17**, 1745 cm^{-1}. Differentiation of the isomers **13** and **14** was readily made through the use of ^1H NMR spectroscopy by observing for **14** a pair of doublet at δ 1.44 and 1.68 (J = 14 Hz) due to the bridge methylene protons and by comparison of the coupling patterns of the carbinyl protons: **13**, a doublet of doublets at δ 4.05 (J = 11, 6 Hz); **14**, a doublet at δ 3.87 (J = 5 Hz).

The observation made by a separate experiment that the ether **12** had been formed by cyclization of **14** indicated the methoxymethyl group in **14** to occupy an axial position on the cyclohexane ring as expected. Furthermore, it was suggested that the relative yield of **14** would be increased by changing the solvolysis to milder conditions. Indeed, the expectation was realized by running the reaction at lower temperatures, approximate VPC ratio of **12**/**13**/**14**/**15** being 0.6:1:1:1 at 40 °C (18 h) and 0.1:0.6:1:0.5 at 20 °C (4 days). Thus, we could have secured ca. 40% VPC yield of **14**, but difficulty was encountered in its separation from the remaining products. After several experimentations, it has been found that isolation of the desired [3.2.1] bicyclic compound is best accomplished at the next stage. Thus, the bicyclic ketone **17** was readily obtained in an overall yield of 31% from **11** by performing the following three-step sequence of reactions without isolation of intermediates: (i) formolysis at 25 °C for 40 h, (ii) hydrolysis of the formates with aqueous sodium hydroxide, and (iii) oxidation with PCC followed by chromatography (Scheme IV). Hydration of the triple bond in **17** followed by base-catalyzed cyclization of the resulting diketone **18** produced the tricyclic enone **19** in nearly quantitative yield. The gross structure of **19** was supported by the mass spectrum (base peak, m/e 133 (M^+ − isobutene − CH_2OCH_3)) and the ^1H NMR spectrum (δ 5.79 (s) for C(3)–H, 2.42 (br t, J = 3 Hz) for C(1)–H (cf. data for **9**)).

Compound **19** was now subjected to demethylation with boron tribromide in dichloromethane, and the resulting primary alcohol was directly oxidized with Jones reagent to give the enone carboxylic acid **5**, mp 146–147 °C (lit.[2a] mp 142–146 °C) in 49% yield from **19**. The identity of **5** with the Danishefsky's intermediate of the same structure was established by comparison of our ^1H NMR spectral data with those reported.[2a] The structure of **5** was further confirmed by a reaction leading to the dihydro methyl ester **20**, mp 48–49 °C (lit. mp 49–51 °C,[2a] 47–49 °C[2c]), which was proved to be identical (IR, MS, ^1H NMR, TLC) with an authentic sample.

Scheme IV[a]



[a] (a) HCO_2H, 25 °C, aqueous NaOH. (b) $PyHCrO_3Cl$, CH_2Cl_2. (c) HgO, H_2SO_4, MeOH–H_2O. (d) *tert*-$C_5H_{11}OH$, NaH, PhH, reflux. (e) BBr_3, CH_2Cl_2. (f) Jones reagent. (g) CH_2N_2. (h) H_2, 10% Pd–C.

Since the compound **5** has already been converted into (±)-quadrone (**1**) by three steps,[2a] our preparation of this compound constitutes a formal total synthesis of (±)-**1**. When compared to the reported syntheses, the significance of our synthesis will lie in its conciseness, i.e., requiring relatively short 12 steps to reach **1** from our starting material **2**, even though rather low overall yield of 2.6%.

Experimental Section

Infrared spectra (IR) were recorded on a Jasco IRA-1 grating spectrophotometer and were calibrated with the 1601-cm^{-1} absorption of polystyrene. Nuclear magnetic resonance spectra (NMR) was taken on a Varian XL-200 spectrometer (200 MHz for ^1H and 50.3 MHz for ^{13}C) in deuteriochloroform. Chemical shifts were reported in parts per million (δ) downfield from internal tetramethylsilane. Resonance patterns in ^1H NMR are reported as s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. In ^{13}C NMR, when multiplicities were determined by off-resonance decoupling, they are reported by using the abbreviations given above. Mass spectra (MS) at 70 eV were obtained on a JEOL JMS-D300 spectrometer combined with a JMA-2000 data processing system. Vapor-phase chromatography (VPC) data were obtained on a Shimadzu GC-6A (TC detector) with the following columns: a glass column of 3 mm × 3 m packed with 5% OV-17 on Shimalite for analytical VPC; a stainless steel column of 5 mm × 1 m packed with 10% OV-17 on Shimalite for preparative-scale VPC. Other VPC conditions are reported in the text.

A Büchi Kugelrohr apparatus was used for vacuum distillation and all boiling points are uncorrected. Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this university. For chromatography, the following adsorbents were used: column, Merck silica gel 60 (70–230 mesh); analytical thin layer, Merck precoated silica gel 60 F-254.

Dry tetrhydrofuran (THF) was obtained by distilling the commercial reagent over calcium hydride first and then from lithium aluminum hydride under an argon atmosphere. Dry dichloromethane was obtained

(10) The observed low yields were largely caused by the concomitant formation of demethoxylated products of unknown structures. As the reaction temperature was raised, this serious side reaction was more favored. Use of propargylmagnesium bromide did not afford **11**.

(11) Orientation of the hydroxyl groups in **13** and **14** was tentatively assigned on the basis of mechanistic consideration of the solvolysis reaction.[3]

by distillation from phosphorus pentoxide. Other dry solvents were obtained by using standard procedures. Anhydrous magnesium sulfate was used for drying all organic solvent extracts in workup, and removal of the solvents was performed with a rotary evaporator at a reduced pressure.

7,7-Dimethyl-*cis*-bicyclo[4.2.0]octan-2-one (2). This compound was prepared according to the method of Bloomfield.[4b] A solution of 2-cyclohexenone (10 g) in degassed dichloromethane (100 mL) was placed in a modified Hanovia immersion photoreactor and under cooling with a dry ice–acetone bath; isobutene gas was introduced into the solution to collect ca. 100 mL of the liquid olefin. The solution was then subjected to irradiation at −78 °C by a 400-W high-pressure mercury arc lamp through a Pyrex filter. After 7 h, the reaction mixture was allowed to warm to room temperature, and the solvent and unreacted isobutene were removed in vacuo. The residual oil was dissolved in a mixture of 10% aqueous potassium hydroxide (40 mL) and methanol (100 mL), and the solution was refluxed for 2 h. It was then concentrated in vacuo and extracted with ether after addition of water. The ether extract was washed with water, dried, and concentrated. The residue was subjected to column chromatography (silica gel, 200 g) with hexane–ether (7:1) to give 10.6 g (67%) of **2** as a homogeneous clear oil: bp 56–60 °C (1.6 mmHg).

(1*R,2*R**,6*S**)-7,7-Dimethyl-2-(2-propynyl)-*cis*-bicyclo[4.2.0]octan-2-ol (6).** An aluminum amalgam was prepared from aluminum foil (592 mg, 21.9 mmol) and mercuric chloride (10 mg) in dry THF (5 mL) by vigorously stirring the mixture at room temperature for 30 min. A solution of propargyl bromide (3.92 g, 32.9 mmol) in dry THF (10 mL) was added slowly to the stirred suspension in such a rate to keep the temperature at 30–40 °C, and after the addition, stirring at 40 °C was continued for 1 h. The resulting solution was then allowed to cool to room temperature, and after addition of **2** (5.0 g, 32.9 mmol) in dry ether (5 mL), it was again heated at 40 °C for 30 min. The reaction mixture was poured into icewater and extracted with ether. The ether solution was washed with brine, dried, and concentrated. The residual oil was distilled to give 5.09 g (81%) of **6**: bp 125–135 °C (2 mmHg); IR (film) 3460, 3330, 2140 cm^{-1}; MS, *m/e* 192 (M^+), 191, 175, 153, 135, 119, 118, 97, 82, 79, 67, 55, 41 (base); ^1H NMR δ 0.94 (3 H, s), 1.20 (3 H, s), 1.84 (1 H, t, J = 10 Hz), 2.08 (1 H, t, J = 3 Hz), 2.37 (2 H, d, J = 3 Hz), 2.52 (2 H, dd, J = 18, 8 Hz); exact mass calcd for $C_{13}H_{20}O$, 192.1515; found, 192.1537.

(1*R,5*S**,8*S**)-6,6-Dimethyl-1-(2-propynyl)bicyclo[3.2.1]octan-8-ol (7).** A solution of **6** (4.88 g, 25.4 mmol) in 90% formic acid (25 mL) was heated under reflux for 30 min and then allowed to cool to room temperature. The solution was concentrated in vacuo, and after addition of water, it was neutralized by addition of potassium carbonate and extracted with ether. The ether solution was washed with brine, dried, and concentrated. Distillation of the residual oil afforded 4.31 g (77%) of the formate of **7**: bp 90–100 °C (0.9 mmHg); ^1H NMR δ 1.12 (3 H, s), 1.13 (3 H, s), 1.98 (1 H, t, J = 3 Hz), 2.12 (2 H, m), 5.23 (1 H, d, J = 5 Hz), 8.18 (1 H, s).

To a solution of the formate in methanol (20 mL) was added 4% aqueous potassium carbonate (10 mL), and the mixture was stirred at room temperature. After 1 h, it was diluted with water and extracted with ether. The ether extract was washed with brine, dried, and concentrated to give 3.64 g (97%) of **7** as a clear oil: bp 105–111 °C (0.8 mmHg); IR (film) 3420, 3330, 2140 cm^{-1}; ^1H NMR δ 1.06 (3 H, s), 1.10 (3 H, s), 2.01 (1 H, t, J = 2 Hz), 2.12 (1 H, dd, J = 16, 2 Hz), 2.17 (1 H, dd, J = 16, 2 Hz), 4.24 (1 H, d, J = 6 Hz); MS, *m/e* 192 (M^+), 177, 153, 135, 109 (base), 41; exact mass calcd for $C_{13}H_{20}O$, 192.1512; found, 192.1487.

(1*R,5*S**)-6,6-Dimethyl-1-(2-oxopropyl)bicyclo[3.2.1]octan-8-one (8).** A solution of **7** (2.87 g, 14.9 mmol) in dry dichloromethane (10 mL) was added to a stirred suspension of PCC (4.7 g, 21.8 mmol) in dry dichloromethane (15 mL), and stirring at room temperature was continued for 30 min. The reaction mixture was diluted with ether (25 mL), and the organic phase was filtered through a layer of Florisil (10 g). The filtrate and ether washings were combined and concentrated to give an oil, which was subjected to distillation to afford 2.64 g (93%) of (1*R**,5*S**)-6,6-dimethyl-1-(2-propynyl)bicyclo[3.2.1]octan-8-one: bp 108–112 °C (0.8 mmHg); IR (film) 3300, 1745 cm^{-1}; MS, *m/e* 190 (M^+), 175, 147, 41 (base); exact mass calcd for $C_{13}H_{18}O$, 190.1356; found, 190.1339.

A solution of the above acetylenic ketone (2.15 g, 11.3 mmol) in methanol (4 mL) was added to a stirred suspension of mercuric oxide (140 mg, 0.646 mmol) in 4% sulfuric acid (6 mL), and the mixture was heated at 60 °C for 1 h. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with brine, dried, and concentrated to give 2.18 g (93%) of **8** as a clear oil which was pure enough for the next step. Distillation afforded 1.82 g (78%) of **8**: bp 126–131 °C (0.8 mmHg); IR (film) 1745, 1720 cm^{-1}; ^1H NMR δ 1.07 (3 H, s), 1.19 (3 H, s), 1.72 (1 H, d, J = 14 Hz), 1.93 (1 H, d, J = 14 Hz), 2.14 (3 H, s), 2.57 (1 H, d, J = 18 Hz), 2.68 (1 H, d, J = 18 Hz); MS, *m/e* 208 (M^+), 193, 179, 165 (base), 151, 82, 81, 43, 42; exact mass calcd for $C_{13}H_{20}O_2$, 208.1462; found, 208.1452.

(1*R,6*S**)-10,10-Dimethyltricyclo[4.3.2.0^{2,6}]undec-2-en-4-one (9).** To sodium hydride (50% dispersion in mineral oil; 44 mg, 0.92 mmol) that was previously washed with dry benzene under an argon atmosphere was added dry benzene (5 mL) and a trace amount of *tert*-amyl alcohol. The mixture was stirred and heated under reflux for 5 min, and then **8** (158 mg, 0.76 mmol) in dry benzene (1 mL) was added to it. After continued refluxing for 2.5 h, the reaction mixture was allowed to cool to room temperature, quenched by addition of water, and extracted with ether. The organic phase was washed with brine, dried, and concentrated to give **9** (153 mg) as an essentially homogeneous oil. Purification of this material was performed by column chromatography (silica gel, 1.5 g) with hexane–ether (2:1) to afford an analytical sample (130 mg, 90%): IR ($CHCl_3$) 1690, 1630 cm^{-1}; IR (film) 1710, 1640 cm^{-1}; ^1H NMR δ 0.93 (3 H, s), 1.24 (3 H, s), 1.32 (1 H, d, J = 13 Hz), 1.80 (1 H, d, J = 13 Hz), 1.9–2.05 (2 H, m), 2.23 (1 H, d, J = 18 Hz), 2.30 (1 H, d, J = 18 Hz), 2.45 (1 H, br t, J = ca. 3 Hz), 5.77 (1 H, s); ^{13}C NMR δ 21.26 (t), 25.33 (q), 30.91 (t), 35.43 (q), 43.72 (t), 49.84 (t), 51.05 (d), 52.12 (t, s), 52.99 (t), 121.6 (d), 126.4 (s), 194.4 (s); MS, *m/e* 190 (M^+), 148, 134 (base), 119, 106, 105, 101; exact mass calcd for $C_{13}H_{18}O$, 190.1357; found, 190.1326.

3-(Methoxymethyl)-7,7-dimethyl-*cis*-bicyclo[4.2.0]octan-2-one (10). A solution of **2** (16.0 g, 0.105 mol) in dry THF (20 mL) was slowly added at −78 °C to a solution of lithium diisopropylamide which was prepared by usual way from *n*-butyllithium (10% hexane solution, 80.8 mL) and diisopropylamine (12.8 g, 0.126 mol) in dry THF (50 mL) under an argon atmosphere. The mixture was stirred at the same temperature for 30 min, and then trimethylsilyl chloride (13.7 g, 0.126 mol) was added dropwise to it. After 1 h, the reaction mixture was allowed to warm to room temperature, poured into ice water containing excess hydrochloric acid, and extracted with ether. The organic phase was washed with brine, dried, and concentrated to afford 23.0 g (98%) of the crude trimethylsilyl enol ether of **2** as a clear oil, which was used directly in the following reaction.

A suspension of zinc dust (1.67 g, 25.7 mmol) and cuprous chloride (0.255 g, 2.58 mmol) in dry dichloromethane under an argon atmosphere was heated under reflux with stirring for 30 min. The mixture was then allowed to cool to room temperature, and after addition of diiodomethane (3.42 g, 12.8 mmol), it was again refluxed for 1 h. The resulting solution was cooled in an ice–water bath, and the trimethylsilyl enol ether of **2** (prepared above) (2.85 g, 12.7 mmol) in dry dichloromethane (5 mL) and then chloromethyl methyl ether (1.13 g, 14.0 mmol) in dry dichloromethane (5 mL) were added to it. The cooling bath was removed, and the mixture was stirred at room temperature for 2 h and the refluxed for 2 h. The reaction mixture was cooled in an ice–water bath, treated with 10% sulfuric acid (8 mL) and ether (ca. 20 mL), and filtered after stirring for several minutes. The filtrate was transferred into ether, and the organic phase was successively washed with brine, saturated aqueous sodium bicarbonate and brine, and dried. Removal of the solvent afforded the crude **10**, which was purified by column chromatography (silica gel, 150 g) with hexane–ether (3:1) to give 1.50 g (60%) of **10**: bp 71–81 °C (0.3 mmHg); IR (film) 1705, 1110 cm^{-1}; MS, *m/e* 196 (M^+), 164, 151, 141, 109, 108, 95, 81, 68 (base), 55, 45, 41; ^1H NMR δ 0.97 (3 H, s), 1.17 (3 H, s), 1.5-2.2 (6 H, m), 2.35-2.65 (2 H, m), 3.00 (1 H, dd, J = 18, 9 Hz), 3.33 (3 H, s), 3.57 (2 H, d, J = 5 Hz); exact mass calcd for $C_{12}H_{20}O_2$, 196.1462; found, 196.1461.

3-(Methoxymethyl)-7,7-dimethyl-2-(2-propynyl)-*cis*-bicyclo[4.2.0]octan-2-ol (11). A solution of propargyl bromide (2.78 g, 23.4 mmol) in dry THF (7 mL) was added to an aluminum amalgam prepared from aluminum foil (408 mg, 15.1 mmol) and mercuric chloride (several mg) in dry THF (7 mL). Stirring of the mixture at 40 °C was continued until a dark gray solution was formed (ca. 1 h). The propargylaluminum sesquibromide solution thus obtained was added to a stirred solution of **10** (4.04 g, 20.6 mmol) in dry ether (150 mL) at −78 °C, and stirring of the reaction mixture at the same temperature was continued for 30 min. It was then poured into ice water and extracted with ether. The ether extract was washed with brine, dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 250 g) with hexane–ether (2:1) to give 2.45 g (50%) of **11**: bp 117–125 °C (0.7 mmHg); IR (film) 3500, 3330, 2120 cm^{-1}; ^1H NMR δ 0.94 (3 H, s), 1.22 (3 H, s), 1.4–2.1 (6 H, m), 1.86 (1 H, t, J = 11 Hz), 2.06 (1 H, t, J = 2.5 Hz), 2.37 (1 H, dd, J = 15, 2.5 Hz), 2.44 (1 H, dd, J = 15, 2.5 Hz), 2.87 (1 H, t, J = 8 Hz), 2.93 (1 H, t, J = 8 Hz), 3.21 (1 H, s), 3.36 (3 H, s), 3.42 (1 H, dd, J = 9, 6 Hz), 3.53 (1 H, t, J = 9 Hz); ^{13}C NMR δ 23.44, 24.29, 24.90, 26.45, 28.22, 33.63, 33.73, 36.62, 42.46, 43.07, 59.11, 71.02, 72.33, 74.64, 81.63; MS, *m/e* 197 ($M^+ - CH_2C{\equiv}CH$, base), 147, 141, 131, 117, 109, 95, 91, 81, 55, 45, 41. Anal. Calcd for

$C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.17; H, 10.13.

Formolysis of 11 at 40 °C. A solution of **11** (72 mg, 0.305 mmol) in a reagent grade anhydrous formic acid (3 mL) was stirred at 40 °C for 16.5 h. The solution was poured into a mixture of 10% aqueous sodium hydroxide (40 mL) and crushed ice (ca. 10 g), and the mixture was stirred at room temperature for 30 min. It was extracted with ether, and the ether phase was washed with brine, dried, and concentrated. The VPC analysis (210 °C: He 32 mL/min) of the residual oil (65 mg) showed that is contained **12** (14%), **13** (23%), **14** (22%), and **15** (24%) in the order of elution (relative retention times: 0.44, 0.82, 1.00, and 1.25). The analytical samples of these four products were obtained by first subjecting them to column chromatography over silica gel and then performing preparative VPC.

(1*R,2*R**,5*R**,6*R**)-8,8-Dimethyl-6-(2-propynyl)-3-oxatricyclo[3.3.2.0^{2,6}]decane (12).** A clear oil: ^{1}H NMR δ 1.01 (3 H, s), 1.03 (3 H, s), 1.61 (1 H, d, J = 13 Hz), 1.76 (1 H, d, J = 13 Hz), 1.97 (1 H, t, J = 2.5 Hz), 2.09 (1 H, br s), 2.26 (1 H, dd, J = 16, 2.5 Hz), 2.44 (1 H, dd, J = 16, 2.5 Hz), 3.85 (1 H, d, J = 8.5 Hz), 4.09 (1 H, ddd, J = 8.5, 8, 1.5 Hz), 4.49 (1 H, d, J = 5.5 Hz); MS, m/e 204 (M$^+$), 203, 148, 140, 105, 91, 79, 41 (base), 39; exact mass calcd for $C_{14}H_{20}O$, 204.1513; found, 204.1468.

(1*R,2*S**,5*S**,8*R**)-8-(Methoxymethyl)-4,4-dimethyl-1-(2-propynyl)bicyclo[3.3.0]octan-2-ol (13)**: mp 52 °C; IR (KBr) 3445, 3235, 1085 cm^{-1}; ^{1}H NMR δ 0.96 (3 H, s), 1.06 (3 H, s), 1.35–1.9 (6 H, m), 1.98 (1 H, t, J = 3 Hz), 2.17 (1 H, br t, J = 8 Hz), 2.34 (1 H, dd, J = 17, 3 Hz), 2.50 (1 H, m), 2.59 (1 H, dd, J = 17, 3 Hz), 3.40 (3 H, s), 3.57 (2 H, m), 4.05 (1 H, dd, J = 11, 6 Hz); MS, m/e 236 (M$^+$), 221, 218, 173, 147, 121, 119, 117, 91, 84, 79, 71, 45, 41 (base). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 7.43; H, 10.17.

(1*R,2*R**,5*S**,8*S**)-2-(Methoxymethyl)-6,6-dimethyl-1-(2-propynyl)bicyclo[3.2.1]octan-8-ol (14)**: mp 91 °C after recrystallization from chloroform–hexane; IR (KBr) 3420, 3325, 2120, 1090 cm^{-1}; ^{1}H NMR δ 1.08 (3 H, s), 1.10 (3 H, s), 1.44 (1 H, d, J = 14 Hz), 1.68 (1 H, d, J = 14 Hz), 1.95 (1 H, t, J = 3 Hz), 2.23 (1 H, dd, J = 18, 3 Hz), 2.51 (1 H, dd, J = 18, 3 Hz), 3.38 (1 H, dd, J = 10, 4 Hz), 3.41 (3 H, s), 3.57 (1 H, d, J = 10 Hz), 3.87 (1 H, dd, J = 11, 5 Hz; d, J = 5 Hz on D_2O addition), 4.91 (1 H, d, J = 11 Hz; disappears on D_2O addition); MS, m/e 236 (M$^+$), 204, 203, 189, 171, 130, 91, 45, 41 (base). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 76.02; H, 10.09.

15. A clear oil: IR (film) 1695 cm^{-1}; ^{1}H NMR δ 0.85 (3 H, s), 1.04 (3 H, s), 1.5–1.65 (1 H, m), 1.65–1.9 (2 H, m), 1.95–2.1 (2 H, m), 2.13 (2 H, br s), 2.23 (1 H, d, J = 12 Hz), 2.49 (3 H, m), 2.80 (1 H, d, J = 12 Hz), 3.33 (2 H, d, J = 7 Hz), 3.36 (3 H, s), 5.46 (1 H, br t, J = ca. 3.5 Hz); MS, m/e 236 (M$^+$), 204, 191, 176, 161, 148, 135, 120, 107 (base), 105, 91, 55, 45, 41; exact mass calcd for $C_{15}H_{24}O_2$, 236.1774; found, 236.1768.

(1*R,5*S**,8*R**)-8-(Methoxymethyl)-4,4-dimethyl-1-(2-propynyl)bicyclo[3.3.0]octan-2-one (16) and (1*R**,2*R**,5*S**)-2-(Methoxymethyl)-6,6-dimethyl-1-(propynyl)bicyclo[3.2.1]octan-8-one (17).** A solution of **11** (1.41 g, 5.97 mmol) in a reagent grade anhydrous formic acid (50 mL) was set aside at 25 °C for 40 h. The solution was then poured into a mixture of 10% aqueous sodium hydroxide (600 mL) and crushed ice (ca. 200 g), and the mixture was stirred at room temperature for 30 min. It was extracted with ether, and the ether extract was washed with brine, dried, and concentrated to give a clear oil (1.41 g). A solution of this oil in dry dichloromethane (5 mL) was added to a stirred mixture of PCC (1.95 g, 9.0 mmol) and dry dichloromethane (5 mL), and stirring at room temperature was continued for 10 h. The reaction mixture was diluted with ether, and the organic phase was filtered through a layer of Florisil (5 g). Concentration of the filtrate afforded an oil, which was subjected to column chromatography (silica gel, 130 g) with hexane–ether (3:1) to give **17** (433 mg, 31%), **16** (404 mg, 29%), and **15** (235 mg, 17%) in the order of elution. The analytical samples of **16** and **17** were obtained by recyrstallization of the solid products from hexane–chloroform. The compounds **16** and **17** were also obtained by PCC oxidation of the corresponding alcohols **13** and **14**, respectively.

16: mp 50–51 °C; IR (neat) 1740 cm^{-1}; ^{1}H NMR δ 1.08 (3 H, s), 1.12 (3 H, s), 2.03 (1 H, t, J = 3 Hz), 2.03 (1 H, d, J = 16 Hz), 2.14 (1 H, dd, J = 18, 3 Hz), 2.58 (1 H, d, J = 16 Hz), 2.64 (1 H, dd, J = 18, 3 Hz), 3.38 (3 H, s), 3.57 (1 H, t, J = 4.5 Hz), 3.69 (1 H, dd, J = 9, 4.5 Hz); ^{13}C NMR δ 21.97 (t), 24.92 (q), 28.23 (t), 30.96 (q), 31.61 (t), 34.74 (s), 47.58 (d), 50.53 (t), 57.01 (d), 58.97 (q), 59.33 (s), 70.94 (d), 72.43 (t), 82.54 (s), 219.9 (s); MS, m/e 234 (M$^+$), 219, 202, 191, 189, 187, 178, 133, 117, 105, 91, 45 (base), 41. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40. Found: C, 76.96; H, 9.46.

17: mp 57–58 °C; IR (neat) 3330, 1745 cm^{-1}; ^{1}H NMR δ 0.92 (3 H, s), 1.21 (3 H, s), 1.21 (1 H, d, J = 14 Hz), 1.77 (1 H, d, J = 14 Hz), 1.98 (1 H, t, J = 3 Hz), 2.29 (1 H, dd, J = 17, 3 Hz), 2.43 (1 H, br m), 2.50 (1 H, dd, J = 17, 3 Hz), 3.08 (1 H, t, J = 8.5 Hz), 3.29 (3 H, s), 3.36 (1 H, dd, J = 8.5, 4 Hz); MS, m/e 234 (M$^+$), 202, 187, 148 (base), 133, 109, 105, 91, 84, 69, 55, 45, 41. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40. Found: C, 76.67; H, 9.54.

(1*R,5*S**)-2-(Methoxymethyl)-6,6-dimethyl-1-(2-oxopropyl)bicyclo[3.2.1]octan-8-one (18).** A solution of **17** (90 mg, 0.385 mmol) in methanol (1 mL) was added to a stirred suspension of mercuric oxide (5 mg) in 4% sulfuric acid (1 mL), and the mixture was heated at 60 °C for 1 h. The reaction mixture was allowed to cool to room temperature, diluted with water, and extracted with ether. The ether extract was washed with brine, dried, and concentrated to give the crude **18** (96 mg, 100%), which was directly used in the next experiment. An analytic sample was obtained by preparative VPC at 215 °C: IR (film) 1740, 1715 cm^{-1}; ^{1}H NMR δ 1.00 (3 H, s), 1.25 (3 H, s), 2.17 (3 H, s), 2.24 (1 H, d, J = 14 Hz), 2.46 (1 H, d, J = 18 Hz), 3.08 (1 H, d, J = 18 Hz), 3.13 (1 H, t, J = 9 Hz), 3.32 (3 H, s), 3.41 (1 H, dd, J = 9, 5 Hz); exact mass calcd for $C_{15}H_{24}O_3$, 252.1724; found, 252.1704.

(1*R,6*S**,7*S**)-7-(Methoxymethyl)-10,10-dimethyltricyclo[4.3.2.0^{2,6}]undec-2-en-4-one (19).** Sodium hydride (50% dispersion in mineral oil; 116 mg, 2.42 mmol) was washed with dry benzene under an argon atmosphere to remove mineral oil and covered with dry benzene (10 mL). After addition of a few drops of *tert*-amyl alcohol, the mixture was stirred and heated under reflux for 5 min, and then **18** (508 mg, 2.02 mmol) in dry benzene (2 mL) was added to it. After continued refluxing for 3.5 h, the reaction mixture was allowed to cool to room temperature, quenched by addition of water, and extracted with ether. The organic extract was washed with brine, dried, and concentrated to give the crude **19** (493 mg, 105%, 85% VPC purity), which was used in the next experiment without further purification. An analytical sample was obtained by preparative VPC: IR (film) 1705, 1640 cm^{-1}; ^{1}H NMR δ 0.92 (3 H, s), 1.15 (1 H, d, J = 13 Hz), 1.20 (3 H, s), 1.86 (1 H, d, J = 13 Hz), 2.14 (1 H, d, J = 18 Hz), 2.42 (1 H, br t, J = 3 Hz), 2.74 (1 H, d, J = 18 Hz), 3.22 (1 H, dd, J = 9, 6.5 Hz), 3.30 (3 H, s), 3.41 (1 H, dd, J = 9, 5 Hz), 5.79 (1 Hz, s); ^{13}C NMR δ 25.91 (q), 26.23 (t), 35.98 (q), 43.75 (s), 47.19 (t), 50.28 (t), 50.93 (d × 2, s), 61.68 (q), 78.30 (t), 122.9 (d), 128.3 (s), 193.1 (s); MS, m/e 234 (M$^+$), 219, 206, 202, 178, 161, 159, 147, 146, 133 (base), 105, 91, 79, 77, 45, 41; exact mass calcd for $C_{15}H_{22}O_2$, 234.1620; found, 234.1630.

(1*R,6*S**,7*S**)-10,10-Dimethyl-4-oxotricyclo[4.3.2.0^{2,6}]undec-2-ene-7-carboxylic Acid (5).** Boron tribromide (0.4 mL, 4.23 mmol) was added to a stirred solution of **19** (106 mg, 0.453 mmol) in dry dichloromethane (2 mL) at −78 °C, and the mixture was kept at −78 °C for 12 h and then at −20 °C for 12 h. The reaction mixture was poured into a mixture of saturated aqueous sodium bicarbonate and crushed ice and extracted with dichloromethane. The organic phase was washed with brine, dried, and concentrated to afford (1*R**,6*S**,7*S**)-7-hydroxymethyl-10,10-dimethyltricyclo[4.3.2.0^{2,6}]undec-2-en-4-one as a clear oil: ^{1}H NMR δ 0.92 (3 H, s), 1.14 (1 H, d, J = 14 Hz), 1.20 (3 H, s), 1.85 (1 H, d, J = 14 Hz), 2.15 (1 Hz, d, J = 19 Hz), 2.42 (1 H, t, J = 3 Hz), 2.73 (1 H, d, J = 19 Hz), 3.51 (1 H, dd, J = 10, 7 Hz), 3.72 (1 H, dd, J = 10, 5 Hz), 5.79 (1 H, s); MS, m/e 220 (M$^+$), 147, 133, 105, 91, 18, 17 (base); exact mass calcd for $C_{14}H_{20}O_2$, 220.1462; found, 220.1425.

This alcohol (100 mg, 0.455 mmol) in acetone (2 mL) was treated with a slight excess of Jones reagent[12] at room temperature for 30 min. The reaction mixture was diluted with brine and extracted with ether. The ether phase was repeatedly extracted with 5% aqueous sodium hydroxide, and the combined aqueous phase was acidified with hydrochloric acid and extracted with ether. The ether phase was washed with brine, dried, and concentrated to give **5** (52 mg, 49% from **19**) as a crystalline solid. Recrystallization from hexane–chloroform afforded a pure sample: mp 146–147 °C; IR ($CHCl_3$) 1700, 1630, 1200 cm^{-1}; ^{1}H NMR δ 0.95 (3 H, s), 1.25 (3 H, s), 1.42 (1 H, d, J = 13 Hz), 2.21 (1 H, d, J = 18 Hz), 2.50 (1 H, br t), 2.80 (1 H, d, J = 18 Hz), 2.97 (1 H, br d, J = 5 Hz), 5.90 (1 H, s); MS, m/e 234 (M$^+$), 219, 206, 192, 147, 133 (base), 105, 91.

Methyl (1*R,2*S**,6*S**,7*S**)-10,10-Dimethyl-4-oxotricyclo[4.3.2.0^{2,6}]undecane-7-carboxylate (20).** A solution of **5** (25 mg, 0.128 mmol) in methanol (0.5 mL) was treated with an excess amount of ethereal diazomethane at room temperature for 30 min. The crude methyl ester obtained by removal of the solvent was dissolved in methanol (1 mL), and the solution was stirred at room temperature under a hydrogen atmosphere in the presence of 10% Pd–C (10 mg) until the reaction was completed as judged by TLC. The mixture was diluted with methanol and filtered. The filtrate was concentrated to give an oil, which was purified by column chromatography (silica gel, ca. 1 g) with hexane–ether (3:2) to give **20** as a crystalline solid. Recrystallization from petroleum ether afforded an analytical sample: mp 48–49 °C; IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR δ 1.16 (3 H, s), 1.19 (3 H, s), 1.56 (1 H, d, J = 14 Hz), 1.75 (1 H, d, J = 14 Hz), 1.76–2.0 (5 H, m), 2.23 (1 H,

(12) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 263–264.

d, J = 18 Hz), 2.36 (1 H, d, J = 18 Hz), 2.48 (2 H, d, J = 10 Hz), 2.76 (1 H, d, J = 7 Hz), 2.88 (1 H, t, J = 10 Hz), 3.68 (3 H, s); MS, m/e 250 (M^+), 235 (base), 149, 107, 91, 41. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.77; H, 8.98.

Acknowledgment. We express our appreciation to Professor Steven D. Burke (University of South Carolina) for providing the ^{1}H NMR and IR spectra and an authentic sample of the compound **20**.

Note Added in Proof. Subsequent confirmation of the structures of the compounds **5** and **9** was made respectively by comparison of their ^{1}H NMR spectra with those generously provided by Professor S. Danishefsky (Yale University) and Professor A. B. Smith, III (University of Pennsylvania).

Registry No. (±)-**1**, 74807-65-1; (±)-**2**, 84057-30-7; (±)-**5**, 78739-64-7; (±)-**6**, 84057-31-8; (±)-**7**, 84057-32-9; (±)-**7** formate, 84057-33-0; (±)-**8**, 82652-82-2; (±)-**9**, 82652-83-3; (±)-**10**, 84057-34-1; (±)-**11**, 84057-35-2; (±)-**12**, 84057-36-3; (±)-**13**, 84057-37-4; (±)-**14**, 84057-38-5; (±)-**16**, 84057-39-6; (±)-**17**, 84057-40-9; (±)-**18**, 84057-41-0; (±)-**19**, 84057-42-1; (±)-**20**, 78739-62-5; 2-cyclohexenone, 930-68-7; isobutene, 115-11-7; propargyl bromide, 106-96-7; (±)-(1R*,5S*)-6,6-dimethyl-1-(2-propynyl)bicyclo[3.2.1]octan-8-one, 84057-43-2; (±)-(1R*,6S*,7S*)-7-hydroxymethyl-10,10-dimethyltricyclo[4.3.2.0^{2,6}]undec-2-en-4-one, 84057-44-3.

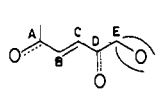
Palladium-Assisted Macrocyclization Approach to Cytochalasins: A Synthesis of Antibiotic A26771B

Barry M. Trost* and Steven J. Brickner

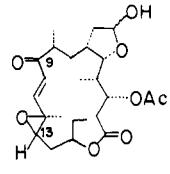
Contribution from the McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received June 28, 1982*

Abstract: A synthetic strategy to macrocycles possessing a γ-oxo-δ-hydroxy-, γ,δ-dihydroxy-, and γ-hydroxy-α,β-unsaturated carbonyl system derives from a palladium-catalyzed C–C bond-forming reaction. In this approach, the macrocyclization employs a β-keto sulfone as an electrofugal group and a 2-ethoxyallyl acetate as a nucleofugal group mediated by a phosphine–palladium(0) complex. In addition to facilitating anion formation and nucleophilic attack on the (π-allyl)palladium intermediate, the benzenesulfonyl group serves as a stereochemical control element which permits relay of stereochemical information between remote centers. The total synthesis of antibiotic A26771B is completed in 12 steps from 10-undecenal to illustrate the applicability of this methodology. The utility of conformational biases of large rings in synthesis and the mechanism of the macrocyclization are also discussed.

The highly oxidized structural fragment represented by formula **1** populates many naturally occurring macrocycles. For example,

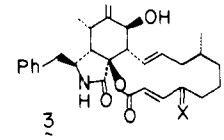


1

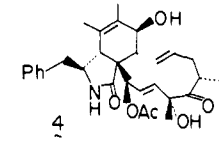


2

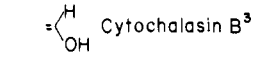
the aglycon **2** of the antibiotic rosaramycin possesses such a unit [C(9)–C(13)].[1] The cytochalasins, a group of fungal metabolites noted for inhibitory activity against bacteria and fungi and for unusual cytostatic activity,[2] prominently display this grouping in a richly diverse fashion as **3**–**6** illustrate. Among this family of compounds, both lactones and macrocyclic ketones are found.[3-6]



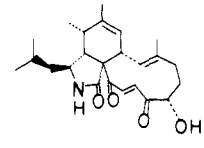
3 X = O Cytochalasin A[3]



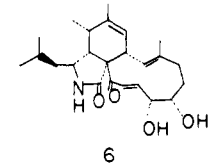
4 Cytochalasin C[4]



Cytochalasin B[3]



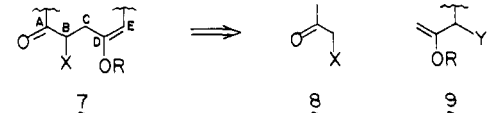
5 Aspochalasin B[5]



6 Aspochalasin C[5]

Furthermore, the sensitivity of the 2-ene-1,4-dione functionality as found in **3** and **5** make it desirable to introduce such a structural grouping at the final stages of synthesis. For these reasons, in searching for a general solution to these macrocycles, we focused on methods that would generate the macrocycle via C–C bond formation and simultaneously create the appropriate juxtaposition of functionality to permit the elaboration of **1** with the flexibility to adjust selectively the oxidation state at each carbon A → E.

With the goal of a general solution to this problem, we envisioned the fragment **7** as such a flexible unit. For example,



(1)

7 **8** **9**

hydrolysis and carbonyl reduction (or simple double bond reduction) followed by elimination of HX produces **3**. Hydroxylation and elimination produces **5** and with a minor modification **6**. The

(1) Ganguly, A. K.; Liu, Y. T.; Sarre, D.; Jaret, R. S.; McPhail, A. T.; Onun, K. K. *Tetrahedron Lett.* **1980**, *21*, 4699.
(2) Tamm, Ch. *Front. Biol.* **1978**, *46*, 15. For some recent examples, see: Probst, A.; Tamm, Ch. *Helv. Chim. Acta* **1981**, *64*, 2056. Fex, T. *Tetrahedron Lett.* **1981**, *22*, 2703.
(3) Rothweiler, W.; Tamm, Ch. *Experientia* **1966**, *22*, 750. Scott, P. M.; Harwig, J.; Chen, Y.-K.; Kennedy, B. P. C. *J. Gen. Microbiol.* **1975**, *87*, 177. Aldridge, D. C.; Armstrong, J. J.; Speake, R. N.; Turner, W. B. *Chem. Commun.* **1967**, 26.
(4) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc.* **1969**, 923; *Jpn. J. Antibiot.* **1969**, *22*, 170.
(5) Keller-Schierlein, W.; Kupfer, E. *Helv. Chim. Acta* **1979**, *62*, 1501. Heberle, W.; Loeffler, W.; Konig, W. A. *Arch. Microbiol.* **1974**, *100*, 73.
(6) For synthetic efforts, see: Kim, M. Y.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Org. Chem.* **1981**, *96*, 5383. Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534. Bailey, S.; Thomas, E. J.; Turner, B. W.; Jarvis, J. A. J. *J. Chem. Soc., Commun.* **1978**, 474. Owens, C.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1504. Brettle, R.; Cummins, D. P. *Ibid.* **1977**, 2835. Pyne, S. G.; Hensel, M. J.; Byrn, S. R.; McKengie, A. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 5960. Sttork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *Ibid.* **1978**, *100*, 7775. Schmidlin, T.; Tamm, Ch. *Helv. Chim. Acta* **1978**, *61*, 2096. Schmidlin, T.; Zurcher, W.; Tamm, Ch. *Helv. Chim. Acta* **1981**, *64*, 235.

0002-7863/83/1505-0568$01.50/0