5,6,7,8-Tetrachloro-2-methoxy-5,8-dimethoxymethano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (3b). A solution of 2-methoxy-*p*-benzoquinone (54 mg)[6] and 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene (excess) in benzene (5 mL) was stirred and refluxed until the dienophile disappeared as indicated by TLC. The solvent was removed in vacuo and the residue was chromatographed on silica gel (1:5 ethyl acetate–hexane eluent), affording the Diels–Alder cycloadduct **3b** (154 mg, 98%). It was identical in melting point and spectral data with **3b** obtained from the reaction of epoxide **2** with base as described above.

2-Hydroxy-5,6,7,8-tetrachloro-4a-methoxy-5,8-dimethoxymethano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4a). To a solution of epoxide **2** (3 g, 7.7 mmol) in methanol (15 mL) was added dropwise an aqueous solution of 2 M NaOH (15 mL) over a period of 30 min. The mixture was stirred at room temperature until the suspended epoxide totally disappeared. Another portion of 2 M NaOH solution (15 mL) was then added, and the brown reaction mixture was stirred overnight. The resulting precipitate was collected by filtration and washed with methanol (5 mL), affording colorless solids (salts of **4**) which were dissolved in water and acidified with dilute HCl solution to give pale yellow solids of **4a** (1.2 g, 37%). The filtrate was concentrated to remove most of methanol and extracted with dichloromethane. The organic layer was washed with water, dried, and concentrated to give an additional portion of oily **4a** (1.1 g, 35%). Recrystallization of crude product from ethyl acetate afforded pure colorless crystalline **4a** (2 g, 70%): mp 216–217 °C; IR (KBr) 3550, 3470, 2500, 1675, 1610, 1450, 1380, 1220, 1185 cm^{-1}; ^1H NMR (acetone-d_6) δ 10.4 (br s, =COH), 6.38 (s, 1 H, vinyl proton), 3.97 (s, 1 H, methine proton), 3.75 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3); ^{13}C NMR (acetone-d_6) δ 189.7 (s), 188.4 (s), 161.6 (s), 131.4 (s), 129.9 (s), 117.7 (d) 112.5 (s), 85.8 (s), 80.6 (s), 77.4 (s), 59.0 (d), 54.0 (q), 52.4 (q), 51.6 (q); MS (12 eV), *m/e* (relative intensity) 420 (1), 418 (2), 416 (2) [M^+], 385 (18), 383 (56), 381 (57), 353 (4), 351 (10), 349 (11), 347 (6), 345 (10), 287 (18), 283 (16), 266 (14), 264 (23), 262 (18), 185 (11), 143 (8), 105 (100), 75 (8).

Anal. Calcd for $C_{14}H_{12}Cl_4O_6$: C, 40.20; H, 2.89; O, 22.97. Found: C, 40.16; H, 2.95; O, 23.26.

Compound **4a** (0.57 g, 1.4 mmol) was converted to **2,4a-dimethoxy-5,6,7,8-tetrachloro-5,8-dimethoxymethano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4b)** in 88% yield by treatment with diazomethane as described above: mp 196–197 °C; IR (KBr) 1685, 1655, 1590, 1450, 1435, 1180, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.15 (s, 1 H, =CH), 3.83 (s, 1 H, methine proton), 3.81 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.26 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) 189.3 (s), 186.4 (s), 163.2 (s), 130.5 (s), 129.8 (s), 115.1 (d), 112.0 (s), 85.6 (s), 80.2 (s), 76.9 (s), 59.2 (d), 56.7 (q), 54.4 (q), 52.5 (q), 52.0 (q); MS (12 eV), *m/e* (relative intensity) 434 (5), 432 (11), 430 (9) [M^+], 399 (52), 397 (96), 395 (100), 287 (3), 285 (8), 283 (8), 266 (14), 264 (17), 262 (8), 111 (11), 109 (31), 105 (87), 85 (27), 83 (45).

Anal. Calcd for $C_{15}H_{14}Cl_4O_6$: C, 41.68; H, 3.27; Cl, 32.83. Found: C, 41.74; H, 3.27; Cl, 32.71.

Photocyclization of 3b. Preparation of 5. A solution of **3b** (10 g, 25 mmol) in acetone (500 mL) was irradiated for 2 h with a 450-W Hanovia medium-pressure Hg lamp (Pyrex filter). The reaction mixture was concentrated to leave a solid residue which was recrystallized from chloroform to give colorless crystalline **5** (7.3 g, 73%): mp 148–150 °C; IR (KBr) 3495, 3300, 1440, 1320, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.21 (br s, 2 H, disappeared upon addition of D_2O), 3.67 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 3.39 (d, J = 2.5 Hz, 1 H), 3.25 (s, 1 H), 3.21 (d, J = 2.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 108.7 (s), 106.9 (s), 106.8 (s), 88.2 (s), 78.7 (s), 76.5 (s), 74.4 (s), 73.7 (s), 59.0 (d), 58.9 (d), 55.5 (d), 53.8 (q), 51.0 (q), 50.9 (q); MS (75 eV), *m/e* (relative intensity) 404 (2), 402 (2), 400 (4) [$M^+ - H_2O$], 371 (3), 369 (33), 367 (98), 365 (100), 331 (8), 329 (11), 305 (3), 303 (11), 301 (15), 279 (3), 257 (6), 255 (15), 253 (17), 189 (4), 187 (13), 159 (5), 157 (6), 109 (7), 69 (10), 59 (21).

Anal. Calcd for $C_{14}H_{14}Cl_4O_6$: C, 40.01; H, 3.36; Cl, 33.77. Found: C, 39.79; H, 3.32; Cl, 34.13.

Photocyclization of 4b. Preparation of 6. Compound **4b** (0.33 g) was dissolved in acetone (10 mL) and irradiated for 2 h with a 450-W Hanovia medium-pressure Hg lamp (Pyrex filter). Removal of solvent left semisolids which were recrystallized from ethyl acetate to afford colorless crystals of **6** (0.15 g). Further chromatography of the residue on silica gel (1:3 ethyl acetate–hexane) gave additional product (0.13 g, total yield 81%): mp 180–182 °C; IR (KBr) 3400, 1460, 1450, 1305, 1235, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 and 4.08 (br s, both disappeared upon addition of D_2O), 3.68 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3), 3.55 (s, 1 H), 3.40 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 108.8 (s), 106.3 (s), 106.2 (s), 90.5 (s), 89.1 (s), 78.5 (s), 78.2 (s), 74.6 (s), 70.7 (s), 57.8, 56.5, 54.3, 52.9, 50.9, and 50.5; MS (12 eV), *m/e* (relative intensity) 452 (3), 450 (4), 448 (2) [M^+], 434 (5), 432 (9), 430 (7) [$M^+ - H_2O$], 399 (32), 397 (98), 395 (100), 385 (11), 383 (28), 381 (29), 219 (10), 218 (16), 217 (21), 109 (21), 105 (36).

Anal. Calcd for $C_{15}H_{16}Cl_4O_7$: C, 40.01; H, 3.58; Cl, 31.52. Found: C, 40.11; H, 3.65; Cl, 31.26.

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Registry No. 1, 50874-38-9; 2, 114301-84-7; 3a, 114301-85-8; 3b, 114301-86-9; 4a, 114301-87-0; 4b, 114301-88-1; 5, 114301-89-2; 6, 114324-37-7; 2-hydroxy-3-methoxybenzaldehyde, 148-53-8; pyrogallol 1-monomethyl ether, 934-00-9; 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene, 2207-27-4; 2-methoxy-1,4-benzoquinone, 2880-58-2.

Supplementary Material Available: X-ray crystallographic analysis (crystal data and data collection parameters, structure drawings, bond lengths and angles) for **4b** (6 pages). Ordering information is given on any current masthead page.

Useful Route to Partially Saturated Isocoumarins. Biomimetic Syntheses of Mellein, Ramulosin, and Epiramulosin†

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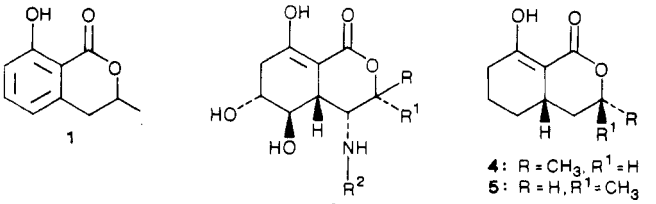
Many of the substituted 8-hydroxy-3-methyl-3,4-dihydroisocoumarins are naturally occurring substances of ascertained biological activity.[1] The parent system, mellein (**1**), is widespread in nature and was isolated from a number of different microorganisms.[2,3] One recent report indicates, however, its biological importance among the higher organisms as well.[4] More highly oxidized naturally occurring 8-hydroxy-3-methylisocoumarins have already been assessed as having considerable therapeutic value. Actinobolin (**2**)[5] and bactobolin (**3**),[6] for example, are potent broad-spectrum antibiotics and antitumor agents.[7,8] Ramulosin (**4**), the corresponding unsubstituted saturated system, was also identified in nature[9] and was later suggested to be biogenetically related to mellein.[10]



1

2: R = H, R^1 = CH_3, R^2 = L-alanyl
3: R = CH_3, R^1 = $CHCl_2$, R^2 = L-alanyl

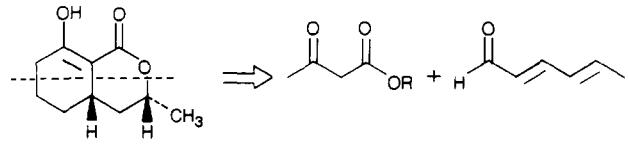
4: R = CH_3, R^1 = H
5: R = H, R^1 = CH_3

Many different syntheses of mellein including preparation of natural (–)-mellein[11] have been reported to date.[12] As for ramulosin, only two very recent syntheses are available: one of (±)-ramulosin by Cordova and Snider[13]

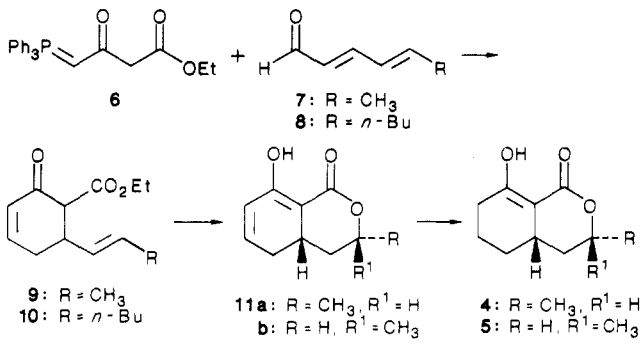
† Dedicated to Prof. Ernest L. Eliel on the occasion of his 65th birthday.

0022-3263/88/1953-2837$01.50/0

Scheme I



Scheme II



and another one by Mori and Gupta,[12] who prepared the naturally occurring 3*R*,4a*S*-(+) isomer. In one earlier synthetic attempt by Findlay et al.,[14] a preponderant formation of epiramulosin resulted.

Retrosynthetic consideration of ramulosin according to Scheme I points readily to acetoacetic ester and sorbaldehyde as its likely primary biogenetic precursors.[13] We report simple three-step preparations of ramulosin, epiramulosin, and mellein which follow from this consideration and which utilize ethyl γ-(triphenylphosphoranylidene)acetoacetate (**6**) in the key annulation step. The choice of this reagent stems from our previous work[15,16] which has identified **6** as the synthetic equivalent of ethyl acetoacetate. The successful use of **6** for the direct "3 + 3" annulation of cyclohexenones on enals[16,17] prompted us to examine its selectivity in reactions with dienals which, if they followed the same pattern, would produce, in one step, cyclohexenones possessing vicinal alkenyl and carbethoxy functionalities fitted for the subsequent intramolecular lactonization. In the case of sorbaldehyde (**7**), a single reduction step following lactonization should then lead to ramulosin as visualized in Scheme II.

Results and Discussion

Reaction of **6** with sorbaldehyde (**7**) under the originally developed conditions[16] (i.e., sodium hydride activated with a small amount of water as a base, room temperature, THF) produced a mixture of products resulting from initial 1,2- and 1,4-reactivity in only 10.8% and 12.5% yields, respectively. Use of catalytic amounts of potassium hydride instead of water for activation of NaH[17] under otherwise identical reaction conditions improved both the selectivity and the yield and lead to the formation of the desired cyclohexenone **9** as the sole isolable product in 38–46% yield.[18] Other dienals reacted in similar fashion. For example, 2,4-nonadienal (**8**) was readily transformed into **10** with comparable efficiency. In these experiments, two isomers were discerned in the ^{1}H NMR spectra of **9** and **10**, with the trans isomer predominating significantly (ca. 85%) as judged from the value $^3J_{H_5-H_6}$ = 12.5 Hz in the main isomer in both cases.

A subsequent lactonization of **9** was conveniently achieved with neat concentrated sulfuric acid at 0 °C. It provided isomeric bicyclic lactones **11a** and **11b** as a ca. 4:3 mixture in 73–79%[18] isolated yield and, more importantly, without detectable formation of any γ-lactone byproducts.[13]

The isomeric lactones **11a** and **11b** turned out to be easily separable by chromatography. The cis (ramulosin) configuration was assigned to the predominant (crystalline) isomer **11a** on the basis of the detailed ^{1}H and ^{13}C NMR analysis of both individual components. Dramatic differences in chemical shifts of the H_3 protons of **11a** and **11b** allowed an immediate distinction of the two isomers. The pseudoaxial H_3 in **11a** resonated at δ 4.36 while the pseudoequatorial H_3 in **11b** was at δ 4.76. An interesting observation of a long-range coupling between Me protons and the pseudoaxial H_4 in only one isomer, **11b**, suggested additionally the pseudoaxial position of Me in this epimer.[19] Accordingly, ^{13}C NMR signals of C_{4a} and, to a

(1) Steyn, P. S. In *Microbial Toxins*; Cigler, A., et al., Eds.; Academic: New York, 1971; Vol. VI, pp 179–205.

(2) First Isolation: Nishikawa, H. *Nippon Nogei Kagaku Kaishi* **1933**, *9*, 772 from *Aspergillus melleus*. Yabuta, T.; Sumiki, Y. *Nippon Nogei Kagaku Kaishi* **1933**, *9*, 1264 from *Aspergillus ochraceus*.

(3) From *Aspergillus oniki*: Sasaki, M.; Kaneko, Y.; Oshita, K.; Takamatsu, H.; Asao, Y.; Yokotsuka, T. *Agric. Biol. Chem.* **1970**, *34*, 1296. From *Lasiodiplodia theobromae*: Aldridge, D. C.; Galt, S.; Giles, D.; Turner, W. B. *j. Chem. Soc. C* **1971**, 1623. From *Fusarium larvarum*: Grove, J. F.; Pople, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2048. From *Pestalotia ramulosa*, see ref 10.

(4) Nishida, R.; Baker, T. C.; Roelofs, W. L.; Acree, T. E. *Abstracts of Papers*, 186th National Meeting of the American Chemical Society, Washington, DC; American Chemical Society: Washington, DC, 1983; PEST 100. For published account (a review), cf.: *Chem Abstr.* **1985**, *102*, 201375z.

(5) Isolation: Haskell, T. H.; Bartz, Q. R. *Antibiot. Annu.* **1960**, 505. Structure: Wetherington, J. B.; Moncrief, J. W. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *B31*, 501. Antosz, F. J.; Nelson, D. B.; Herald, D. L., Jr.; Munk, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 4933 and references cited therein.

(6) Isolation: Kondo, S.; Horiuchi, J.; Hamada, M.; Takeuchi, T.; Umezawa, H. . *Antibiot.* **1979**, *32*, 1069. Structure: Ueda, I.; Munakata, T.; Sakai, A. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1980**, *B36*, 3128.

(7) Pittillo, R. F.; Fisher, M. W.; McAlpine, R. J.; Thompson, P. E.; Ehrlich, J.; Anderson, L. E.; Fiskin, R. A.; Galbraith, M.; Kohberger, D. L.; Manning, M. C.; Reutner, T. F.; Roll, D. R.; Weston, K. *Antibiot. Annu.* **1960**, *1958/1959*, 497. Ishizaka, M.; Fukasawa, S.; Masuda, T.; Sato, J.; Kanbayashi, N.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1980**, *33*, 1054.

(8) For total syntheses of actinobolin, *N*-acetylactinobolamine, and 5,6,10-triepiacetinobolin, see: Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133. Yoshioka, M.; Nakai, H.; Ohno, M. *Heterocycles* **1984**, *21*, 151. Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790. Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1985**, *50*, 5005. Rahman, Md. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576. Kozikowski, A. P.; Nieduzak, T. R.; Springer, J. P. *Tetrahedron Lett.* **1986**, *27*, 819. To our knowledge, total synthesis of bactobolin has not been reported as yet.

(9) Stodola, F. H.; Cabot, C.; Benjamin, C. R. *Biochem. J.* **1964**, *93*, 92.

(10) Tanenbaum, S. W.; Agarwal, S. C.; Williams, T.; Pitcher, R. G. *Tetrahedron Lett.* **1970**, 2377.

(11) Both enantiomers of mellein occur in nature. For isolation of (+)-mellein, see: Patterson, E. L.; Andres, W. W.; Bohonos, N. *Experientia* **1966**, *22*, 209. Grove, J. F.; Pople, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2048. The latter report proves also that 3-substituted dihydroisocoumarins with either absolute configuration at C_3 can be produced by a single species.

(12) Mori, K.; Gupta, A. K. *Tetrahedron* **1985**, *41*, 5295 and references cited therein.

(13) Cordova, R.; Snider, B. B. *Tetrahedron Lett.* **1984**, *25*, 2945.

(14) Findlay, J. A.; Matsoukas, J. M.; Krepinsky, J. *Can. J. Chem.* **1976**, *54*, 3419.

(15) Pietrusiewicz, K. M.; Monkiewicz, J. *Tetrahedron Lett.* **1986**, *27*, 739.

(16) Pietrusiewicz, K. M.; Monkiewicz, J.; Bodalski, R. *J. Org. Chem.* **1983**, *48*, 788.

(17) Pietrusiewicz, K. M.; Salamończyk, I.; Monkiewicz, J., Manuscript in preparation.

(18) The upper yield limit was usually attained in runs in which *tert*-butyl γ-(triphenylphosphoranylidene)acetoacetate δ-(triphenylphosphoranylidene)acetoacetate was used in lieu of **6**. A detailed description of the use of this reagent for annulation purposes will be published elsewhere.[17]

(19) Jackman, L. M.; Sternhell, S. *Application of Nuclear Resonance Spectroscopy in Organic Chemistry*; Pergamon: Oxford, 1969; Chapter 4-4.

somewhat lesser extent,[23] of Me carbon were observed significantly more upfield in **11b** than in **11a**. Different stereochemistry at C_3 in **11a** and **11b** was also reflected in the positions of H_{4a} and pseudoaxial H_4 signals being significantly upfield in the cis **11a** epimer, $\Delta\delta$ = 0.17 and 0.39 ppm, respectively.

The cis configuration of **11a** was finally evidenced by the straightforward conversion of this isomer into ramulosin in a simple reductive operation. This was accomplished cleanly with Ph_2SiH_2 under $Pd^0/ZnCl_2$ catalysis conditions[20] and provided hydrogenated product **4** in practically quantitative yield (one spot by TLC, 91% yield after Kugelrohr distillation). The structure of our synthetic **4** was rigorously established by MS, ^{13}C NMR, and ^1H NMR analysis aided by 2D COSY experiments as well as by a direct comparison with the data similarly obtained for epiramulosin.[21]

As expected, analogous reduction of **11b** provided epiramulosin (**5**) with equal efficiency. This material was in turn found to be identical with previously synthesized epiramulosin.[22]

The dehydro compounds **11a** and **11b**, which served as the direct precursors of ramulosin and epiramulosin, were likewise envisioned as useful as the half-way intermediates in a synthesis aimed at mellein. In fact, standard DDQ oxidation of **11a** and **11b** (either as a mixture or as individual compounds) furnished quantitative amounts of mellein with extreme facility (eq 1). Interestingly, **11b**

$$\textbf{11a} \text{ and/or } \textbf{11b} \xrightarrow[\text{benzene, room temperature}]{\text{DDQ}} \textbf{1} \qquad (1)$$

undergoes slow oxidation to mellein even upon simple exposure of the sample to air during its prolonged storage either as the pure oil or in solution.[26] Physical and spectral data of the product were identical with those reported for (±)-mellein.[12,28]

The demonstrated facility of the synthesis of mellein and ramulosin from a common precursor, when combined with the reported isolation of ramulosin and mellein (and also 6-hydroxyramulosin) from a common microbial source, i.e., *Pestalotia ramulosa*,[10] and with the unexpectedly high selectivity in the formation of only **11a** and **11b** from **9** under rudimentary protic conditions, makes it tempting to conjecture that the dehydro compounds **11a** and **11b** are indeed true intermediates in the biosynthesis of the title compounds, either being only of transient existence or still awaiting isolation.

Thus, the syntheses of (±)-mellein and (±)-ramulosin (and its epimer) starting from sorbaldehyde in three simple steps have been accomplished. Moreover, the similarly successful use of **8** in lieu of **7** in the key annulation step suggests that our approach will be amenable to useful modifications of the dienal structure. Dihydroisocoumarins with C_3 substituents different from Me also occur in nature.[25]

Experimental Section

Melting points and boiling points are uncorrected. Solvents and reagents were purified by standard methods. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl before use. ^1H NMR spectra were recorded on 300-MHz and 200-MHz Bruker spectrometers. ^{13}C NMR spectra were obtained on a Bruker MSL-300 spectrometer at 75 MHz. To facilitate spectral assignment, additional 2D COSY and DEPT experiments were performed with compounds **4**, **5**, **11a**, **11b**. Mass spectra were obtained on a LKB-2091 mass spectrometer under standard 70-eV electron-impact conditions. All the compounds described in this study were of at least 97% purity as judged from their ^1H and ^{13}C NMR spectra.

6-Carbethoxy-5-(1-propenyl)-2-cyclohexen-1-one (9). To a magnetically stirred mixture of 1.56 g (4 mmol) of ylide **6**[16,27] and 96 mg (4 mmol) of sodium hydride in 25 mL of dry tetrahydrofuran was added under argon a catalytic amount of potassium hydride. After evolution of hydrogen had ceased, 0.53 mL (5 mmol) of sorbaldehyde was added in one portion and the resulting mixture was kept at room temperature. When the ylide was completely consumed, as indicated by TLC (chloroform–acetone, 5:1), the reaction mixture was quenched with dilute HCl and then partitioned between ether and brine. The aqueous phase was further extracted with ether, and the combined ethereal extracts were washed with dilute aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude cyclohexenone **9** was then Kugelrohr distilled at 150 °C (0.8 mmHg) and gave 350 mg of practically pure product. Short column chromatography on silica gel (hexane–ether, 5:1) provided 312 mg (38%) of an analytically pure sample of **9** (an oil). This was identified as a ca. 85:15 mixture of trans and cis isomers. Structural assignment was facilitated by a direct comparison of the spectrum of **9** with those obtained previously for a series of 6-carbethoxy-5-substituted-cyclohexenones:[16,17] ^1H NMR (200 MHz, $CDCl_3$) δ (major isomer) 1.25 (t, J = 7.2, 3 H), 1.65 (dd, J = 6.2, 1.3, 3 H), 2.28 (ddt, J = 16.4, 10.4, 2.5, $H_{4(ax)}$), 2.52 (dt, J = 16.4, 5.5, $H_{4(eq)}$), 3.09 (m, H_5), 3.26 (d, J = 12.5, H_6), 4.21 (q, J = 7.2, 2 H), 5.36 (ddd, J = 16, 7.8, 1.3, propenyl H), 5.59 (br dq, J = 16, 6.2, propenyl H), 6.08 (ddd, J = 10.5, 2.4, 1.1, H_2), 7.02 (ddd, J = 10.5, 5.6, 2.6, H_3).

6-Carbethoxy-5-(1-hexenyl)-2-cyclohexen-1-one (10). This compound was prepared from the ylide **6** (1.6 g, 4 mmol) and nonadienal **8** (0.83 g, 0.96 mL, 6 mmol) by exactly the same procedure as for **9**. The crude product was Kugelrohr distilled at 150 °C (0.8 mmHg) and yielded 450 mg (45%) of pure oily material, again as a ca. 85:15 mixture of trans and cis isomers: MS, m/e 250 (M^+), 204, 177, 147 (base peak), 107, 68; ^1H NMR (300 MHz, $CDCl_3$) δ (major isomer) 0.88 (t, J = 7.1, 3 H), 1.27 (t, J = 7, 3 H), 1.21–1.35 (m, 4 H), 1.95 (m, 2 H), 2.28 (ddt, J = 19.1, 10.2, 2.7, $H_{4(ax)}$), 2.52 (br dt, J = 19.1, 5.4, $H_{4(eq)}$), 3.1 (m, H_5), 3.27 (d, J = 12.1, H_6), 4.2 (q, J = 7.1, 2 H), 5.32 (ddt, J = 15.3, 7.9, 1.4, H), 5.58 (br dt, J = 15.3, 6.6, H), 6.08 (ddd, J = 10.1, 2.7, 1.1, H_2), 6.99 (ddd, J = 10.1, 5.6, 2.5, H_3); ^{13}C NMR ($CDCl_3$) δ (major isomer) 13.95, 14.29, 22.14, 31.48, 31.77, 32.15, 41.41, 60.25, 61.00, 129.09, 129.68, 133.51, 149.42, 169.51, 194.03.

8-Hydroxy-3-methyltetrahydroisocoumarins 11a and 11b. To 1 mL of concentrated sulfuric acid chilled to 0 °C was added 344 mg (1.65 mmol) of **9**, and the resulting mixture was kept at this temperature for 24 h. The reaction mixture was poured onto ice and extracted with ether. The combined ethereal extracts were washed with dilute aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The oily residue was then Kugelrohr distilled, bp 150 °C (0.2 mmHg), to give 220 mg (74%) of isomeric tetrahydroisocoumarins **11a** and **11b** in a 4:3 ratio. Efficient separation of the isomers by means of a short column chromatography (silica gel; hexane–ether, 5:1,

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(21) Most of the shift and coupling differences seen in the NMR spectra of the pair of dehydro compounds **11a** and **11b** recurred in the spectra of ramulosin and epiramulosin and were again highly diagnostic; cf. Experimental Section.
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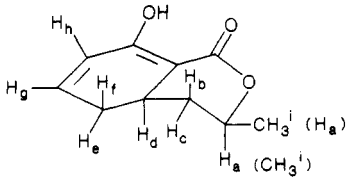
as eluent) provided pure compounds. **11a** (major): 114 mg, mp 102–103 °C; R_f 0.19 (hexane–ether, 5:2); MS, m/e 180 (M^+), 139, 121 (base peak), 107, 95, 94, 77, 41, 39; ^{1}H NMR (200 MHz, $CDCl_3$)



δ 1.36 (d, J_{ia} = 6.5, 3 H_i), 1.46 (dt, J_{bc} = 13.5, J_{ba} = J_{bd} = 11.7, H_b), 1.95 (tt, J_{fe} = J_{fd} = 17.2, J_{fh} = J_{fg} = 2.8, H_f), 1.99 (ddd, J_{cb} = 13.5, J_{cd} = 4.5, J_{ca} = 2.2, H_c), 2.3 (dt, J_{ef} = 17.2, J_{ed} = J_{eg} = 6.5, H_e), 2.83 (dddd, J_{db} = 11.7, J_{dc} = 4.5, J_{de} = 6.5, H_{df} = 17.2, H_d), 4.36 (dqd, J_{ab} = 11.7, J_{ac} = 2.2, J_{ai} = 6.5, H_a), 6.05 (dd, J_{hg} = 10, J_{hf} = 2.8, H_h), 6.4 (ddd, J_{gh} = 10, J_{ge} = 6.5, J_{gf} = 2.8, H_g), 9.78 (s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C_8), 168.15 (C_1), 139.52 (C_6), 124.68 (C_7), 92.7 (C_{8a}), 75.62 (C_3), 36.89 (C_4), 30.47 (C_{4a}), 30.43 (C_5), 21.46 (CH_3). **11b** (minor): 91 mg; an oil; R_f 0.16 (hexane–ether, 5:2); MS, m/e 180 (M^+), 139, 121 (base peak), 107, 95, 94, 77, 39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (dd, J_{ia} = 6.7, J_{ib} = 1.3, 3 H_i), 1.85 (m, H_b, H_c), 1.99 (britt, J_{fe} = J_{fd} = 17.1, J_{fg} = J_{fn} = 2.8, H_f), 2.29 (dtd, J_{ef} = 17.1, J_{ed} = J_{eg} = 6.4, J_{eh} = 0.5, H_e), 2.92 (m, H_d), 4.72 (m, H_a), 6.06 (ddd, J_{he} = 0.5, J_{hf} = 2.8, J_{hg} = 10, H_h), 6.46 (dddd, J_{ge} = 6.3, J_{gf} = 2.8, J_{gh} = 10, J_{gd} = 0.8, H_g), 9.75 (s, OH); accidental magnetic equivalence of protons H_b, H_c precluded full first-order treatment; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.25 (C_8), 168.03 (C_1), 140.2 (C_6), 124.24 (C_7), 92.14 (C_{8a}), 74.4 (C_3), 33.31 (C_4), 30.31 (C_5), 25.35 (C_{4a}), 19.9 (CH_3).

(±)-Ramulosin (4). To a chloroform solution containing 164 mg (0.91 mmol) of **11a**, 184 mg (0.19 mL, 1 mmol) of diphenylsilane, and 49 mg (0.36 mmol) of zinc chloride was added 21 mg (0.018 mmol) of $Pd(Ph_3)_4$, and the mixture was stirred at room temperature until the total consumption of **11a** was evidenced by TLC monitoring (hexane–ether, 5:1). The mixture was then filtered through a short column of silica gel using CH_2Cl_2 as eluent, and the crystalline product was finally purified by a Kugelrohr distillation at 150 °C (0.2 mmHg): 151 mg (91%); mp 112–115 °C (lit.[13] mp 115–116 °C); R_f 0.25 (hexane–ether, 5:2); MS, m/e 182 (M^+), 154, 136, 126, 123 (base peak), 95, 84, 55, 43, 41, 39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (m, pseudoaxial H_5), 1.24 (ddd (apparent br q), J_{gem} = 13.5, $J_{H_4-H_3}$ = 11.5, pseudoaxial H_4), 1.32 (d, J = 6.3, 3 H, Me), 1.45–1.69 (m, 2 H_6), 1.77–1.90 (m, pseudoequatorial H_5), 1.86 (ddd, J_{gem} = 13.5, $J_{H_4-H_3}$ = 2.4, $J_{H_4-H_{4a}}$ = 3.9, pseudoequatorial H_4), 2.31 (m, 2 H_7), 2.44 (ttt, J_{vic} = 12.2, J_{vic} = 3.9, $J_{homoallylic}$ = 1.9, H_{4a}), 4.39 (ddq, J = 11.5, 2.4, 6.3, pseudoaxial H_3), 9.33 (s, OH); the assignment given follows from a 2D COSY spectrum of **4**; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (C_8), 171.76 (C_1), 96.75 (C_{8a}), 76.51 (C_3), 37.41 (C_4), 32.9 (C_{4a}), 29.48 (C_7 or C_5), 28.98 (C_5 or C_7), 21.69 (CH_3), 20.83 (C_6); cf. ref 12.

(±)-Epiramulosin (5) was obtained from **11b** in 90% isolated yield by exactly the same procedure as described above: mp 65 °C (lit.[14] mp 65 °C); R_f 0.22 (hexane–ether, 5:2); MS m/e 182 (M^+), 154, 136, 126, 123 (base peak), 86, 84, 55, 41, 39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (m, pseudoaxial H_5), 1.36 (d, J = 6.7, Me; additional coupling with pseudoaxial H_4 is evidenced in the 2D COSY spectrum), 1.56–1.97 (m, 5 H; these protons appear in the spectrum in the order pseudoaxial H_4, pseudoaxial H_6, pseudoequatorial H_4, pseudoequatorial H_5, and pseudoequatorial H_6, when going from upper- to lower-field region, and were assigned from the 2D COSY spectrum of **5**), 2.32–2.38 (m, 2 H_7), 2.54–2.68 (m, H_{4a}), 4.72 (m, pseudoequatorial H_3), 9.3 (s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.88 (C_8), 170.3 (C_1), 96.8 (C_{8a}), 74.76 (C_3), 34.15 (C_4), 29.49 (C_7 or C_5), 28.98 (C_5 or C_7), 27.51 (C_{4a}), 21.01 (C_6), 20.52 (CH_3).

(±)-Mellein (1). To a 5-mL solution of 100 mg (0.56 mmol) of **11a** (and/or **11b**) in dry benzene was added 189 mg (0.84 mmol) of DDQ, and the resulting mixture was stirred at room temperature for 2 h. The product was then readily isolated by filtration through a short column of silica gel using hexane–ether (5:1) as eluent in practically quantitative yield. Kugelrohr distillation at 150 °C C (0.4 mmHg) gave 89 mg (90%) of analytically pure 1: mp 35–38 °C (lit.[28] mp 37–38 °C); R_f 0.29 (hexane–ether, 5:2); MS, m/e 178 (M^+), 160, 134 (base peak), 106, 104, 78, 77, 51; ^{1}H NMR (200 MHz, $CDCl_3$)[29] δ 1.51 (d, $J_{CH_3-H_3}$ = 6.3, 3 H, Me), 2.93 (m, $J_{H_{4A}-H_3}$ = 8.4, $J_{H_{4B}-H_3}$ = 6.5, J_{gem} = 16.4, 2 H_4), 4.72 (m, $J_{H_3-H_{4A}}$ = 8.4, $J_{H_3-H_{4B}}$ = 6.5, $J_{H_3-CH_3}$ = 6.3, H_3), 6.71 (dd, $J_{H_7-H_6}$ = 8.4, $J_{H_7-H_5}$ = 1.0, H_7), 6.86 (dd, $J_{H_5-H_6}$ = 7.4, $J_{H_5-H_7}$ = 1.0, H_5), 7.42 (dd, $J_{H_6-H_5}$ = 7.4, $J_{H_6-H_7}$ = 8.4, H_6), 11.01 (s, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.88 (C_1), 162.28 (C_8), 139.37 (C_{4a}), 136.09 (C_6), 117.84 (C_5), 116.28 (C_7), 108.35 (C_{8a}), 76.04 (C_3), 34.68 (C_4), 20.73, (CH_3); cf. ref 12.

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Registry No. **1**, 1200-93-7; **4**, 92611-81-9; **5**, 62232-14-8; **6**, 13148-05-5; **8**, 5910-87-2; **9** (isomer 1), 112348-30-8; **9** (isomer 2), 112420-28-7; **10** (isomer 1), 112348-31-9; **10** (isomer 2), 112420-29-8; **11a**, 112348-29-5; **11b**, 112348-32-0; sorbaldehyde, 142-83-6.

Supplementary Material Available: 300-MHz ^{1}H NMR 2D COSY spectra of **11a**, **11b**, (±)-ramulosin, and (±)-epiramulosin (4 pages). Ordering information is given on any current masthead page.

(29) Recording of this spectrum at the NMR laboratory of the Max-Planck-Institut für Kohlenforschung, Mülheim, FRG, is gratefully acknowledged.

Superacid-Catalyzed Near-Quantitative Isomerization of $C_{4n+6}H_{4n+12}$ (n = 1–3) Polycyclic Precursors to Diamondoid Cage Hydrocarbons Promoted by 1-Haloadamantanes and Sonication

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Introduction

The polycyclic diamandoid cage hydrocarbons[1] $C_{4n+6}H_{4n+12}$ composition, whose three-dimensional topography is based on the regular repetitious array of tetrahedral carbon atoms similar to those found in diamond, are of substantial significance and interest. Adamantane and later diamantane (originally named congressane[2]), the first two members of the adamantalogue series, were isolated by Landa et al. from crude oil.[3] Chemical synthesis including their higher homologues, e.g., triamantane and tetramantane, allowed the fascinating chemistry of diamandoid cage hydrocarbons to develop.

The development of the synthesis of adamantane by rearrangements of isomeric $C_{10}H_{16}$ precursors was first achieved by Schleyer and is well reviewed.[1,4,5] The first successful synthesis of diamantane[6] was also achieved by Schleyer by $AlCl_3$-catalyzed isomerization of isomeric $C_{14}H_{20}$ norbornene photodimers **2**[7] (Chart I) but only in

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