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A SYNTHESIS OF GYMNOMITROL

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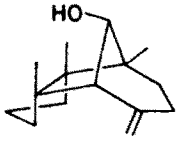
Abstract—Condensation of 1,2 - dimethylcyclopentene **10** with 2 - methyl - 4, 4, 5 - trimethoxycyclohexa - 2, 5 - dienone **7** in methylene chloride - nitromethane with added stannic chloride gave a mixture of the two diastereomeric bicyclo[3.2.1]octanes **13** and **14** by ionic [4+2]cycloaddition. After selective reduction of the saturated carbonyl group with sodium borohydride, and hydrogenation of the double bond the two epimers **18** and **20** (ratio 3.3:1) were separable by chromatography. Protection of the hydroxy group in **18** with dihydropyran and, reduction of the α-methoxyketone **19** with calcium in liquid ammonia gave ketone **21**. Gymnomitrol **1** was then prepared by Wittig olefination followed by deprotection of the hydroxy group.

Gymnomitrol **1**, together with seven related sesquiterpenes, including the presumed biogenetic parent gymnomitrene **2** were isolated from the liverwort *Gymnomitrion obtusum* (Lindb.) Pears.[1-3] Because gymnomitrol **1** contains the rare 4, 8 - methanoazulene[4] carbon skeleton with five adjacent chiral centers, three of them quaternary, its synthesis has attracted attention, and indeed five different syntheses were reported in a period of two months.[5-9]



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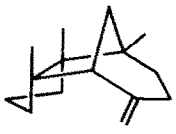
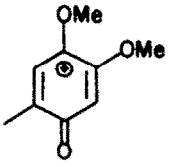


2

To test the generality of a newly discovered method[10] for the preparation of bicyclo[3.2.1]octanes by acid catalyzed addition of *p*-quinonemonoketals to olefins, we explored a synthesis of gymnomitrol which utilizes this strategy. Details are presented in this paper. The first phase of the synthesis was concerned with the preparation of the quinoneketal **7**, one of the partners in the projected cycloaddition. Wolff–Kishner reduction of 3, 4 - dimethoxybenzaldehyde **3** gave 3, 4 - dimethoxytoluene **4** which by formylation[11] afforded the known 6 - methylveratraldehyde **5**[12] in 77% yield. Oxidation of **5** with *m*-chloroperbenzoic acid was followed by hydrolysis of the resulting formate to the phenol **6**.[13] Dicyanodichlorobenzoquinone in methanol[14] transformed phenol **6** to the quinoneketal **7**. After 1, 2 - dimethylcyclopentene **10** had been prepared from cyclopentanone[15] we were ready to investigate the critical cycloaddition.

Early attempts to condense quinoketal **7** with olefin **10** (5–6 equivalents) using catalytic amounts of trinitrobenzenesulfonic acid in acetonitrile[10] gave none of the desired adduct. Similarly, no tricyclic adducts were detectable when condensations were tried with methanesulfonic acid in methylene chloride. Attention was then shifted to Lewis acids, and when performed in methylene chloride at −30° in the presence of one equivalent of boron trifluoride etherate a condensation product, surprisingly lacking carbonyl absorption in the infrared spectrum, was produced in 36% yield. Structure **12** was derived from spectroscopic measurements, and the formation of this pyran can be rationalized if the initially formed carbonium ion **8** is deprotonated to give the *o*-quinonemethide **9** which subsequently undergoes a well precedented [4+2] cycloaddition. It should be pointed out that analogous products were not observed when less highly substituted olefins, such as β-substituted styrenes were partners in these cycloadditions.[10]



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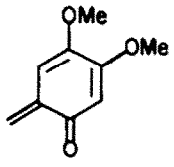

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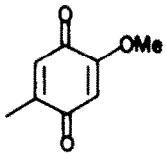

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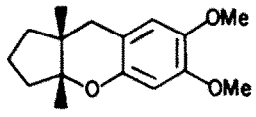

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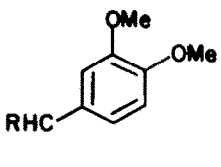
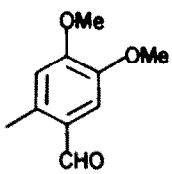


3 R=O
4 R=H_2



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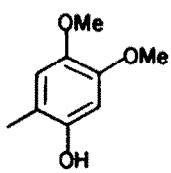

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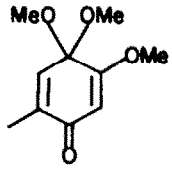
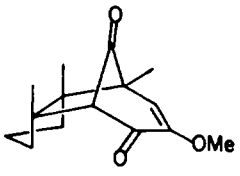


7

Crowding in the transition state, and, as will be shown later, angle strain in the carbotricyclic products seem to decelerate the condensation and force it to take a different course.

A search for minor products produced in the condensation of **7** with **10** uncovered less than 3% of the bicyclo[3.2.1]octanes **13** and **14**.[16] Replacements of boron trifluororide etherate with stannic chloride in methylene chloride gave similar results, but when using stannic chloride (one equivalent) in nitromethane-methylene chloride[17] approximately 10% of what turned out to be a mixture of **13** and **14** was obtained. Other Lewis acids, such as titanium tetrachloride as well as trimethyloxonium tetrafluoroborate gave even poorer yields. The hypothesis that additional ring strain created by the third cyclopentane ring is to a good measure responsible for the disappointing yield, received support when it was found that condensation of **7** with the equally substituted 2, 3 - dimethyl - 2 - butene afforded adduct **15** in 35% yield. In all these reactions the cycloadducts were accompanied by the phenol **6** and 2 - methoxy - 5 - methylbenzoquinone **11** probably formed by reduction and electrophilic attack on the *o*-methyl group, respectively, within intermediate **8**. The two diasteromeric adducts **13** and **14** could not be separated from each other, nor from quinone **11** by column chromatography, and in the hope that more polar derivatives would be more easily separable the mixture was reduced with the required amount of sodium borohydride. The isolated carbonyl group was reduced selectively. The hydroquinone resulting from the reduction of the quinone **11** was now removable by extraction with base, but separation of the diastereomers **16** and **17** by thin layer chromatography failed. Fortunately, the major isomer crystallized from ether, and **16** was available in better than 90% purity after a single recrystallization. Configurational assignments are based on the assumption that endo-oriented methyl groups are shielded by the proximate double bond and pertinent chemical shifts, obtained at 270 MHz, are indicated in structures **16** and **17**.[18] Confirmatory evidence was procured by measuring proton spectra in the presence of tris - 2, 2, 6, 6 - tetramethyl - 3, 5 - heptane - 4, 6 - dionate europium. The shifts (change in δ values) of the three methyl singlets in isomer **16** per mg of shift reagent were measured and calculated (by least square method of six points) to be 0.069 0.098 and 0.069. All three methyl signals were shifted downfield by approximately the same amount suggesting that these substituents are nearly equidistant from the hydroxy group, a situation prevailing in isomer **16** but not in **17**. Catalytic hydrogenation of the two unsaturated ketones **16** and **17** gave the stereochemically homogeneous dihydroderivatives **18** and **20**. These were readily separable by flash chromatography,[19] and in preparative runs mixtures of **16** and **17** were hydrogenated prior to separation. Isomers **18** and **20**, both unstable oils were thus obtained in a ratio of 3.3:1.

Presumably due to the instability of the β-hydroxyketone functionality (retroaldol cleavage?) the remaining steps in the synthesis could only be accomplished after the hydroxy group had been protected. The tetrahydropyranyl ether **19** was reduced with calcium in liquid ammonia,[20] and the resulting ketone **21** condensed with triphenylphosphonium methylide to afford olefin **22**. Deprotection gave racemic gymnomitrol (**1**), m.p. 105–108°, whose infrared, and proton nuclear magnetic resonance spectra were identical with those of natural, optically active material.[21]



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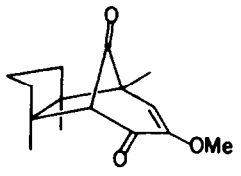

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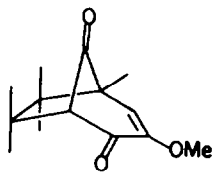

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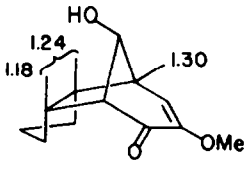

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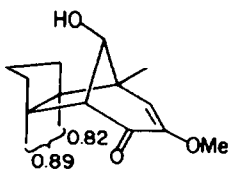

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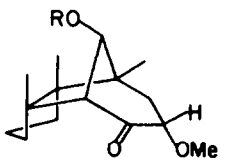
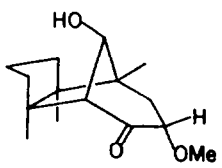


18 R = H
19 R = THP



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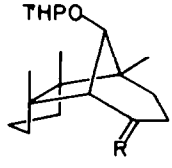

21 R = O
22 R = CH_2

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 237B or 397 grating spectrophotometer and are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were measured on a Varian T–60, Hitachi Perkin–Elmer R–24B or a Bruker–270 MHz FT–spectrometer and are given in parts per million (δ) downfield from tetramethylsilane as an internal standard; the abbreviations *br, s, d, q,* and *m* refer to broad, singlet, doublet, quartet and multiplet, respectively. Ultraviolet (UV) spectra were determined on a Hitachi Perkin–Elmer 200 spectrophotometer, and wavelengths are reported in nanometers (nm). The high-resolution mass spectrum (HRMS) was measured on a DuPont CEC–110B instrument, and low-resolution mass spectra (MS) were determined on a Varian Mat 44 instrument. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J. Flash chromatographic separations[19] were performed using silica gel obtained from ICN Life Sciences Group, Cleveland, Ohio, cat. no. 402826 (particle size 32–63 μm).

4, 5 - *Dimethoxy* - 2 - *methylphenol* (**6**)

To a cooled (ice bath) and stirred suspension of MCPBA (13.0 g; tech, approx. 80–90%; 63 mmol) in dry dichloromethane (100 mL) was added dropwise a solution of 4, 5 - dimethoxy - 2 - methylbenzaldehyde **5** (10.0 g; 55.5 mmol) in dry dichloromethane (120 mL). After the addition was complete the ice bath was removed, and the mixture was stirred at room temperature for 5 hr. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed twice with saturated $NaHCO_3$ solution, once with brine and concentrated *in vacuo*. The crude formate was then dissolved in methanol (100 mL), and the solution was cooled in an ice bath under argon. A 10% aqueous KOH solution (65 mL) was added dropwise to the stirring solution. Stirring was continued for 30 min while the solution was cooled with an ice bath. The basic solution was then neutralized with 1N aqueous HCl until pH < 7 and was then extracted three times with ether. The combined ethereal solutions were washed twice with H_2O, three times with saturated $NaHCO_3$ solution, once with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude phenol was purified by flash chromatography on a 50 mm column eluting with hexane–EtOAc (1:1 v/v). Fractions judged to be identical by tlc were pooled to give 7.9 g (85%) of **6**: m.p. 87–88° (hexane/ether); IR ($CHCl_3$) 3600, 3400, 1620, 1515, 1465, 1195, 1110, 1000 cm^{-1}; NMR ($CDCl_3$) δ 2.17 (s, 3) 3.77 (s, 3), 3.80 (s, 3), 4.70 (s, 1), 6.37 (s, 1), 6.57 (s, 1); MS *m/e* (relative intensity, %) 168 (M^+, 88), 153 (79), 125 (78). Anal ($C_9H_{12}O_3$) C, H.

2 - *Methyl* - 4, 4, 5 - *trimethoxycyclohexa* - 2, 5 - *dienone* (**7**)

To a cooled (ice bath) and stirred solution of phenol **6** (1.00 g, 5.9 mmol) in methanol (20 mL) was added dropwise a solution of DDQ (1.50 g, 6.6 mmol) in methanol (20 mL). After the addition was completed, methanol was removed *in vacuo*, and the residue was dissolved in ether, then washed with saturated $NaHCO_3$. After conventional workup the ether solution was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane–EtOAc (1:1 v/v). Fractions judged to be identical by tlc were pooled to give 0.74 g (63%) of **7**: m.p. 103–104° (CH_2Cl_2/ether); IR ($CHCl_3$) 1680, 1640, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.93 (d, 3, J = 2 Hz), 3.33 (s, 6), 3.83 (s, 3), 5.63 (s, 1), 6.40 (q, 1, J = 2 Hz); UV (95% EtOH) 234 mn (ϵ 12,400), 293 (3500); MS *m/e* (relative intensity, %) 198 (M^+, 5), 183 (52, 167 (100). Anal. ($C_{10}H_{14}O_4$) C, H.

cis - 1, 2, 3, 3a, 9, 9a-*Hexahydro* - 6, 7 - *dimethoxy* - 3a, 9a-*dimethylcyclopenta*[*b*][1]*benzopyran*[12][22]

A mixture of *p*-quinone ketal **7** (105 mg, 0.5 mmol) and 1,2 - dimethylcyclopentene **10** (0.30 mL, 0.24 g, 2.5 mmol) in dichloromethane (2 mL) was stirred and cooled to −40° (Dry Ice-acetone). Boron trifluoride etherate (65 μl, 75 mg, 0.5 mmol) was added via a syringe and the mixture was then kept at −40° to −20° for 1 hr. Saturated $NaHCO_3$ solution was then added; the solution was extracted three times with ether, and the combined ether extracts were washed twice with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was chromatographed on a 20 × 20 × 0.1 cm silica gel plate using CH_2Cl_2–EtOAc (19:1 v/v) as solvent to give 49 mg (36%) of **12**: m.p. 64–66° (hexane); IR (CCl_4) 1620, 1600, 1510, 1230, 1040 cm^{-1}; NMR (CCl_4) δ 0.97 (s, 3), 1.15 (s, 3), ~1.00–2.23 (m, 6), 2.45 (br s, 2), 3.68 (s, 3), 3.72 (s, 3), 6.18 (s, 1), 6.35 (s, 1); MS *m/e* (relative intensity, %) 262 (M^+, 9), 167 (100), 95 (62). Anal ($C_{16}H_{22}O_3$) C, H.

(3aα, 4aα, 8aα, 8aaα, 9R*) - 2, 3, 3a, 4, 8, 8a - *Hexahydro* - 9 - *hydroxy* - 6 - *methoxy* - 3a, 8, 8a - *trimethyl* - 4, 8 - *methanoazulen* - 5 (1H) - *one* **16**

A mixture of *p*-quinone ketal **7** (210 mg, 1.1 mmol), 1, 2 - dimethylcyclopentene (**10**) (0.65 mL, 0.51 g, 5.3 mmol) in nitromethane (6 mL), and dichloromethane (1 mL) was stirred and cooled under argon to −20° (Dry Ice-acetone). Anhydrous stannic chloride (120 μl, 0.27 g, 1.0 mmol) was then added via a syringe and the mixture was kept at −20° with stirring for 10 min. 1N HCl (10 mL) was added to the mixture and the solution was extracted three times with ether. The combined ether extracts were then washed once with saturated $NaHCO_3$ solution and once with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on a 20 mm column, eluting with CH_2Cl_2–EtOAc (14:1 v/v). Fractions containing 2 - methoxy - 5 - methyl benzoquinone **11** **13** and **14** were combined (60 mg). The mixture was then dissolved in methanol (4 mL), and cooled with stirring under argon to −20° (Dry Ice-acetone). Sodium borohydride (11 mg, 0.3 mmol) was added, and the mixture was kept at −20° for 10 min. Water (4 mL) was added and the solution was extracted three times with ether. The combined ether extracts were washed once with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography on a 20 mm column eluting with CH_2Cl_2–EtOAc (4:1 v/v). Fractions containing **16** and **17** were combined (26 mg; 10% overall). Preparative GC separations of the two isomers could be achieved on a 15% SE–30 column [8 ft × 6 mm (OD)] at 250°. Isomer free alcohol **16** was further purified by flash chromatography on a 20 mm column eluting with CH_2Cl_2–EtOAc (3:1 v/v). Fractions containing **16** were combined and concentrated. Crystallization from ether gave prisms: m.p. 175.5–177.5° IR ($CHCl_3$) 3620, 3450, 1680, 1620, 1140 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 1.18, 1.24, 1.30, (all s, 3 × CMe), 2.47 (d, J = 4 Hz, –OH), 2.75 (s, –COCH–), 3.60 (s, –OMe), 3.88 (d, J = 4Hz, –CHOH), 5.67 (s, vinyl–CH); UV (95% EtOH) 267 nm (ϵ 6,700); MS *m/e* (relative intensity, %) 250 (M^+, 5). Anal ($C_{15}H_{22}O_3$) C, H.

(3aα, 4aα, 6β, 8aα, 8aaα, 9R*) - *Octahydro* - 9 - *hydroxy* - 6 - *methoxy* - 3a, 8, 8a - *trimethyl* - 4, 8 - *methanoazulen* - 5 (1H) - *one* (**18**)

A mixture of alcohols **16** and **17** (33 mg, 0.13 mmol) in absolute ethanol (2 mL) was hydrogenated with 19 mg 10% Pd/C at atmospheric pressure, at room temp. After 1 hr, the mixture was filtered through a thin pad of Celite, and the catalyst was washed thoroughly with dichloromethane. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on a 20 mm column eluting with CH_2Cl_2–EtOAc (4:1 v/v). Fractions 7 and 8 contained 6 mg (18%) of alcohol **20** and fractions 10 to 14 contained 20 mg (59%) of alcohol **18**: IR (CCl_4) 3620, 3475, 1720, 1125 cm^{-1}; NMR (CCl_4) δ 1.05, 1.08, 1.23 (all s, 3 × CMe), 2.22 (s, –COCH–), 3.42 (s, –OMe), 4.12 (s, CH–OH). Due to its instability alcohol **18** was used immediately after isolation.

(3aα, 4aα, 8α, 8aaα, 9R*) - *Octahydro* - 3a, 8, 8a - *trimethyl* - 9 - [(*tetrahydro* - 2H - *pyran* - 2 - *yl*)*oxy*] - 4, 8 - *methanoazulen* - 5 (1H) - *one* (**21**)

To a stirred solution of alcohol **18** (32 mg, 0.13 mmol) and DHP (35 μL, 32 mg, 0.38 mmol) in dichloromethane (0.75 mL) was added a catalytic amount of d - 10 - camphorsulfonic acid. The mixture was then stirred at room temperature for 1 hr and allowed to stand at 0° for 2 hr. Degassed saturated $NaHCO_3$ solution was added and the solution was diluted with dichloromethane. After workup the crude THP ether **19** (54 mg) was used directly without further purification. Ammonia (about 4 to 5 mL) was first condensed from a cold finger (Dry Ice-acetone)

into a three-necked flask equipped with a stirrer. Calcium turnings (28 mg, 0.70 mmol) were added and the solution was stirred for 5 min. The crude THP ether **19** in dry THF (1 mL) was added via syringe and the mixture was stirred for 10 min. Solid NH_4Cl (100 mg, 1.9 mmol) was added in one portion causing the blue color of the solution to be discharged immediately. Ether was added followed by water, and the ammonia was allowed to evaporate. The organic layer of the resulting solution was separated from the aqueous layer which was extracted twice with ether. The combined ether extracts were washed once with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on a 20 mm column eluting with hexane–EtOAc (3:1 v/v). Fractions containing THP ether **21** (as a pair of diastereoisomers according to NMR) were pooled to give 31 mg (78%) of a colorless oil: IR (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.50–2.83 (m, 26), 3.17–4.07 (m, 3), 4.50–4.73 (m, 1); MS *m/e* (relative intensity, %) 85 (100), no M^+.

(3aα, 4a, 8α, 8aα, 9R*) - *Decahydro* - 3a, 4, 8a - *trimethyl* - 7 - *methylene* 4, 8 - *methanoazulen* - 9 - *ol(gymnomitrol)* (**1**)

To a stirred suspension methyltriphenylphosphonium bromide (0.292 g, 0.82 mmol) in dry THF (2 mL) under argon was added dropwise via a syringe 0.2 mL of n-BuLi (2.57 M in hexane; 0.51 mmol). The resulting solution was stirred for 10 min and THP ether **21** (31 mg, 0.10 mmol) in dry DMSO (1 mL) was added via a syringe. The mixture was then stirred and kept at 80° (oil bath) for 3.5 hr. After it had been cooled half saturated NH_4Cl solution (10 mL) was added, and the mixture was extracted five times with ether. The combined ether extracts were washed once with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was passed through a short column of silica gel to remove the residual DMSO. The crude olefin **22** was taken up in HOAc/H_2O/THF (3:2:2, V/V, 7 mL), and the solution was heated at 60° (oil bath) for 7 hr. After workup with ether the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on a 20 mm column eluting with hexane–EtOAc (14:1 v/v). Fractions judged to be identical by tlc were pooled and gave 17 mg of (±) gymnomitrol **1** (76%). Gas chromatography of synthetic gymnomitrol revealed the presence of small amounts of impurities. Further purification on a preparative GC column [15% SE-30, 8 ft × 6 mm(OD)] at 210°, sublimation (75–80°/0.02 mm), followed by crystallization gave racemic gymnomitrol (**1**): m.p. 105–108° (EtOH–H_2O); IR (CCl_4) 3620, 3070, 1640, 1060, 890 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 0.957, 1.094, 1.242 (all s, 3 × CMe), 2.335 (s, bridge head proton), 3.719 (s, CHOH), 4.645, 4.654 (both s, methylene protons); MS *m/e* (relative intensity, %) 220 (M^+, 1). Anal Calc. for $C_{15}H_{24}O$: 220.18271. Found: 220.18106.

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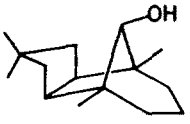

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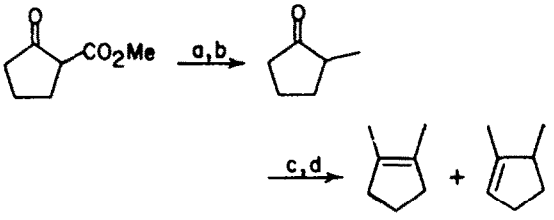
[15]1, 2 - Dimethylcyclopentene was prepared according to the following scheme:



[a](i) NaH/THF/0°/30 min; (ii) CH_3I/RT/overnight; [b] LiCl/H_2O/DMSO/160°/8 hr; 40% overall[a]; [c]MeMgI/Et_2O/RT/4 hr; [d]I_2/100°/2–4 hr; 35–50% overall.[b] A mixture of isomeric olefins containing mainly the desired isomer (approx. 85% by GC) was isolated and subject to spinning band distillation.[c] 1, 2 - dimethylcyclopentene (≥ 90% pure) was then obtained in 35–50% overall yield from 2 - methylcyclopentanone. [a]A. P. Krapcho. J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, Jr, A. J. Lovey and W. P. Stephens, *J. Org. Chem.* **43**, 138 (1978) and Refs. cited therein; [b]M. Guisnet, P. Canesson and R. Mauvel, *Bull. Soc. Chim. France* 3566 (1970), [c]According to A. P. I. Research Project 44, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons*, p. 47. Carnegie Press, Pittsburgh, (1953), boiling point of 1, 2 - dimethylcyclopentene is 105.8° and 1, 5 - dimethycyclopentene is 102.0°.

[16]Detection of the desired condensation product was most conveniently carried out by scanning the IR spectrum of the crude

products. The carbonyl group of the tricyclic products gives rise to an unusually high frequency band at 1760 cm^{-1}.

[17]1, 2 - Dimethylcyclopentene appears to be immiscible with nitromethane but adding methylene chloride produced homogeneous solutions.

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[21]We are indebted to Prof. Connolly for spectra of natural and to Prof. Coates of synthetic (±)-gymnomitrol.

[22]The names of the compounds were kindly provided by Dr. Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service, Columbus, OH 43210, U.S.A.