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A New Synthesis of Substituted Tropolones

Ching-Pong Mak and George Büchi*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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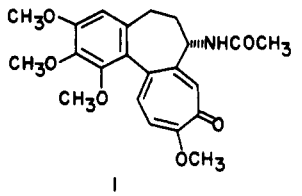
The bicyclic tropolone methyl ether 17, structurally related to colchinine (1), was prepared from the bicyclo[3.2.1]octane derivative 3 by a five-step sequence. Hydrolysis of 3 with base yielded the carboxylic acid 6 which on treatment with *N*-bromosuccinimide afforded the bromo γ-lactone 12. Hydrolysis, followed by methylation of enol 14, and oxidation of the resulting 15 with DDQ led to the tropolone 17. Bicyclooctanes of type 3 are accessible by cycloaddition of *p*-quinone monoketals to olefins.

Crude extracts of the autumn crocus (*Colchicum autumnaline L.*) have been used in the treatment of gout for several centuries. More recent interest in the biological properties of colchicine (1), the active principle, centers on its potent and highly specific antimitotic activity.[1] In the course of structure–activity relationship studies it was discovered that the structurally less complex trimethoxyphenyl-substituted tropolone methyl ether 2 retains the antimitotic properties of the alkaloid 1.[2]



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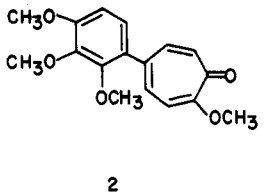

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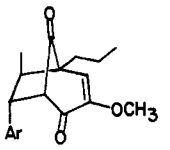
It occurred to us that excision of the bridging carbonyl group in bicyclo[3.2.1]octanes, such as 3, followed by adjustment in the oxidation level should lead to a short synthesis of what turned out to be 4-aryltropolone methyl ethers. The bicyclooctanes required are readily available from acid-catalyzed addition of *p*-quinone monoketals to olefins, and we have prepared a number of these previously in connection with the synthesis of neolignans,[3] gymnomitrol,[4] and megaphone.[5]

Condensation of quinone ketal 4[6] with isosafrole 5 in acetonitrile, catalyzed by 2,4,6-trinitrobenzenesulfonic acid, gave the crystalline bicyclooctane 3 in 61% yield.[3] As anticipated, this nonenolizable β-diketone was unstable to base, and treatment with methanolic potassium hydroxide at ambient temperatures yielded the keto carboxylic acid 6 in quantitative yield. At elevated temperature, in the same medium, this vinylogous β-keto acid suffered decarboxylation to give 8. The singlets attributed to the



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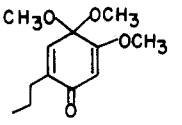

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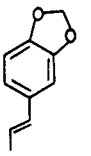

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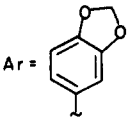
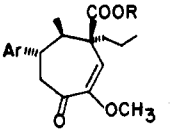
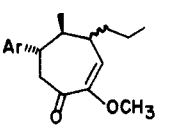




6 R=H
7 R=CH$_3$



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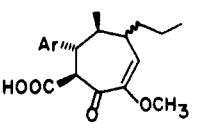

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vinyl proton in the ^{1}H NMR spectra of acid 6 and its methyl ester 7 were replaced by a doublet in the decarboxylated ketone 8, and structure 9 which could have been formed by hydrolytic cleavage of the vinylogous β-diketone 3 was thus excluded. Oxidation of both 6 and 8 with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), as well as catalytic dehydrogenations, failed to yield a tropolone. Dienone 10 only could be isolated from these reactions, but yields never exceeded 5%. Oxidation of ester 7 with DDQ, on the other hand, turned out to be efficient, furnishing the yellow-colored dienone 11 in 90% yield. Efforts to

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(2) Fitzgerald, T. J. *Biochem. Pharm.* **1976**, *25*, 1383.
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(5) Büchi, G.; Chu, P.-S., to be published.
(6) Büchi, G.; Chu, P.-S.; Hoppmann, A.; Mak, C.-P.; Pearce, A. *J. Org. Chem.* **1978**, *43*, 3983.

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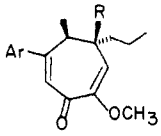
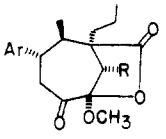
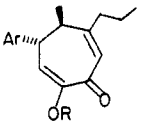
convert the latter to a tropolone unfortunately failed. It was then decided to attempt the introduction of the missing two double bonds via halogen-containing intermediates. Bromo γ-lactone **12** was formed when the un-



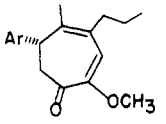
10 R = H
11 R = $COOCH_3$



12 R = Br
13 R = H



14 R = H
15 R = CH_3



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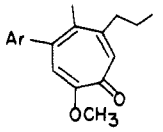

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saturated acid **6** was treated with *N*-bromosuccinimide. Facile formation of a γ-lactone was observed again when heating acid **6** and triphenylphosphine in carbon tetrachloride afforded **13**. When submitted to the action of aqueous potassium hydroxide the bromo lactone **12** underwent smooth decarboxylation with concomitant elimination of hydrobromic acid. According to spectral data the resulting unstable α-diketone exists entirely in the enol form **14**. The much more stable methyl ether **15** was prepared by methylation with methyl iodide and silver oxide. Its ^1H NMR spectrum exhibited a methyl doublet at δ 1.33 (J = 7 Hz) in agreement with structure **15** but in disagreement with **16** resulting from an alternate mode of enolization within the hypothetical α-diketone. We attribute the exclusive formation of a single enol to the nonplanarity of the α,β-unsaturated ketone moiety in the seven-membered ring. While it was not possible to introduce two double bonds into **8** by oxidation with DDQ, exposure of the more highly unsaturated ketone **16** to this reagent caused rapid and efficient conversion to the tropolone **17**.

The sequence described constitutes a novel method for the synthesis of tropolones. Both the availability of various substituted quinone monoketals and their facile cycloaddition to a wide variety of olefins should assure the versatility of this new route.

Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are corrected. The following spectrometers were used: IR, Perkin-Elmer 247; ^1H NMR, Perkin-Elmer R32 (90 MHz) (chemical shifts are reported in parts per million (δ) downfield from Me_4Si); UV, Perkin-Elmer 202; mass spectra, Varian-Mat 44 (results are quoted as m/e). Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ.

3-Methoxy-6-*exo*-methyl-7-*endo*-(3,4-(methylenedioxy)-phenyl)-5-propylbicyclo[3.2.1]oct-3-ene-2,8-dione (3). To a stirred mixture of quinone ketal **4** (2.3 g, 10 mmol) and isosafrole (1.8 g, 11 mmol) in anhydrous acetonitrile (50 mL) at 0 °C was added, all at once, under argon, 2,4,6-trinitrobenzenesulfonic acid (3 g). After 15 min, the reaction mixture was poured into a saturated solution of sodium bicarbonate and this was extracted throughly with methylene chloride. The combined organic extracts were washed twice with saturated sodium dithionite solution, followed by a saturated solution of sodium bicarbonate, and brine and dried ($MgSO_4$). Removal of solvent in vacuo gave an oil which ws chromatographed on silica gel (200 g, 30% ethyl acetate in hexane) to afford 2.1 g of crystalline **3** in 61% yield. Recrystallization from ether-hexane gave a pure product: mp 125 °C; IR ($CHCl_3$) 1760, 1690, 1615, 1505, 1495 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (d, 3, J = 7 Hz), 1.10–1.30 (m, 3), 1.45–2.18 (m, 4), 2.51 (m, 1, J = 7 Hz), 3.10 (t, 1, J = 7 Hz), 3.74 (s, 3), 3.75 (d, 1, J = 7 Hz), 5.96 (s, 2), 6.27 (s, 1), 6.56 (d, 1, J = 1 Hz), 6.58 (d of d, 1, J = 1 Hz, 8 Hz), 6.76 (d, 1, J = 8 Hz); UV (95% EtOH) 235 nm (ε 7450), 275 (8400); exact mass calcd for $C_{20}H_{22}O_5$ 342.146 72, found 342.147 27.

3-Methoxy-7β-methyl-6α-(3,4-(methylenedioxy)phenyl)-4-oxo-1α-propyl-2-cycloheptene-1β-carboxylic Acid Methyl Ester (7). A solution of bicyclooctanone **3** (342 mg, 1 mmol) and potassium hydroxide (1.5 g) in methanol (12 mL) was stirred at room temperature under an argon atmosphere for 1 h. The solution was then diluted with saturated sodium bicarbonate and washed twice with ether. The aqueous solution was then acidified with dilute hydrochloric acid and extracted thoroughly with ether. The combined organic layer was dried ($MgSO_4$) and concentrated to give 360 mg (100%) of the keto acid **6** as a foam. This was again taken up in 5 mL of ether and treated with excess diazomethane, followed by the usual workup to afford 370 mg (100%) of the foamy methyl ester **7**: NMR (CCl_4) δ 0.80–1.58 (m, 8), 1.73–2.26 (m, 3), 2.60–3.08 (m, 3), 3.62 (s, 3), 3.68 (s, 3), 5.73 (s, 1), 5.90 (s, 2), 6.46–6.72 (m, 3); IR ($CHCl_3$) 1752, 1685, 1510, 1490, 1445, 1250, 1040 cm^{-1}; UV (95% EtOH) 240, 280 nm; mass spectrum (70 eV), m/e (relative intensity) 374 (M^+, 11), 232 (15), 167 (38), 162 (12), 155 (52), 41 (100).

2-Methoxy-5β-methyl-6α-(3,4-(methylenedioxy)phenyl)-4α-propyl-2-cycloheptenone (8). Bicyclooctanone **3** (50 mg, 0.146 mmol) and potassium hydroxide (0.3 g) were dissolved in 5 mL of methanol and the resulting solution was heated at reflux under an argon atmosphere for 1 h. After cooling to ambient temperature, the mixture was diluted with saturated sodium bicarbonate and extracted thoroughly with ether. Organic layers were combined and washed once with brine, dried ($MgSO_4$), and concentrated to an oil, which was then chromatographed on a 20 × 20 × 0.05 cm silica gel plate with 25% ethyl acetate in hexane as solvent. This provided **8** (27 mg, 58%) as a viscous oil: NMR (CCl_4) δ 0.78 (d, 3, J = 7 Hz), 0.87–1.11 (m, 3), 1.20–2.00 (m, 5), 2.25–3.07 (m, 4), 3.56 (s, 3), 5.04 (d, 1, J = 7 Hz), 5.91 (s, 2), 6.47–6.73 (m, 3); IR ($CHCl_3$) 1685, 1630, 1520, 1505, 1455, 1260, 1160, 1140, 1125 cm^{-1}; UV (95% EtOH) 236, 277 nm; mass spectrum (70 eV), m/e (relative intensity) 316 (M^+, 11), 168 (14), 162 (9), 148 (26), 55 (100). Anal. ($C_{19}H_{24}O_4$) C, H.

Methyl 3-Methoxy-7β-methyl-6α-(3,4-(methylenedioxy)-phenyl)-4-oxo-1α-propylcyclohepta-2,5-diene-1β-carboxylate (11). A mixture of methyl ester **7** (370 mg, 1 mmol) and 2,3-dichloro-5,3-dicyano-1,4-benzoquinone (625 mg, 2.5 mmol) in dry benzene (15 mL) was heated at reflux under a nitrogen atmosphere for 5 h. This was cooled, diluted with ether, then washed twice with saturated sodium bicarbonate and once with brine, and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave 400 mg of a foam, which was filtered through a short column of silica gel (4 g, 2:1 hexane–ethyl acetate) to give 334 mg (90%) **12** as foam. Crystallization from ether followed by one recrystallization from ether–hexane gave pale yellow crystals: mp 132–133 °C; NMR ($CDCl_3$) δ 0.84 (br t, 3, J = 7 Hz), 1.0–1.58 (m, 2), 1.10 (d, 3, J = 7 Hz), 1.80–2.10 (m, 2), 3.46 (br q, 1, J = 7 Hz), 3.73 (s, 3), 3.82 (s, 3), 6.02 (s, 2), 6.27 (br s, 1), 6.35 (s, 1), 6.82 (d, 1, J = 8 Hz), 6.99 (br s, 1), 7.03 (d, 1, J = 8 Hz, with fine spiltting); IR ($CHCl_3$) 1740, 1620, 1515, 1500, 1450, 1260, 1230, 1000 cm^{-1}; UV (95% EtOH) 247 nm (sh, ε 9800), 259 (10, 400), 295 (5500), 352 (9800); mass spectrum (70 eV), m/e (relative intensity) 372 (M^+, 6), 242 (12), 155 (30), 141 (18), 59 (100). Anal. ($C_{21}H_{24}O_6$) C, H.

Bromo γ-Lactone 12. To a solution of the crude keto acid **6** (803 mg, 2.23 mmol) in chloroform (15 mL) was added *N*-bromosuccinimide (440 mg, 2.47 mmol). After being stirred at room temperature for 30 min, the solvent was evaporated in vacuo and the residue was taken up in ether; this was washed three times with saturated sodium bicarbonate and then dried ($MgSO_4$). Ether was removed under reduced pressure and 921 mg (94%) of **12** was obtained as a solid. Crystallization from methylene chloride–heptane gave white rods: mp 152–154 °C; NMR ($CDCl_3$) δ 0.70–1.10 (m, 6), 1.22–1.95 (m, 4), 2.47–2.87 (m, 3), 3.05–3.40 (m, 1), 3.72 (s, 3), 4.58 (s, 1), 5.98 (s, 2), 6.50–6.80 (m, 3); IR ($CHCl_3$) 1790, 1740, 1515, 1500, 1450 cm^{-1}; UV (95% EtOH) 235 nm (ε 4800), 288 (4500); mass spectrum (70 eV), m/e (relative intensity)

440 ($M^+ + 2$, 8), 438 (M^+, 8), 299 (26), 175 (92), 167 (33), 155 (87), 148 (96), 41 (100). Anal. ($C_{20}H_{23}BrO_6$) C, H.

γ-Lactone 13. A mixture of crude keto acid **6** (55 mg, 0.15 mmol) and triphenylphosphine (50 mg, 0.15 mmol) in 5 mL of carbon tetrachloride was first heated at 45 °C for 24 h and then at reflux for 6 h. Solvent was then removed in vacuo to give a foamy residue, which was dissolved in ether and saturated sodium bicarbonate. After the layers were separated, the organic fraction was dried ($MgSO_4$) and then concentrated to give an oil. This was chromatographed on a 20 × 20 × 0.1 cm silica gel plate with 25% ethyl acetate in hexane as solvent. γ-Lactone **13** was isolated (48 mg, 87%) as an oil which crystallized on storage. Recrystallization from methylene chloride–heptane gave white needles: mp 126–128 °C; NMR ($CDCl_3$) δ 0.82 (d, 3, J = 7 Hz); 0.96–1.70 (m, 7), 1.90–2.20 (m, 1), 2.53 (br s, 2), 2.51–3.20 (m, 3), 3.62 (s, 3), 6.00 (s, 2), 6.59 (d, 1, J = 8 Hz), 6.62 (br s, 1), 6.80 (d, 1, J = 8 Hz); IR ($CHCl_3$) 1785, 1740, 1515, 1500, 1455, 1260 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 360 (M^+, 7), 176 (20), 162 (9), 149 (32), 148 (100). Anal. ($C_{20}H_{24}O_6$) C, H.

2-Methoxy-5β-methyl-4α-(3,4-(methylenedioxy)phenyl-6-propylcyclohepta-2,6-dienone (15). A solution of the bromo γ-lactone **12** (439 mg, 1 mmol) and 0.5 N potassium hydroxide (16 mL) in tetrahydrofuran (10 mL) was stirred under an argon blanket for 1 h and then diluted with brine. The aqueous mixture was extracted thoroughly with ether; the ethereal solution was dried ($MgSO_4$) and evaporated in vacuo to give 271 mg of oily enol **14**: NMR ($CDCl_3$) δ 3.76 (d of d, 1, J = 4 Hz, 9 Hz); IR ($CHCl_3$) 3400, 1645, 1600 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 300 (M^+, 16), 135 (100).

The crude product was dissolved in 7 mL of dimethylformamide and to this was added excess silver(I) oxide (0.8 g) and methyl iodide (1 mL). The resulting suspension was stirred vigorously at room temperature for 20 h; insoluble materials were filtered and washed thoroughly with ethyl acetate and water. After the layers were partitioned, the organic phase was washed three times with water and then dried ($MgSO_4$). Removal of solvent gave a pale oil. Filtration through a short column of silica gel with 25% ethyl acetate in hexane gave dienone **15** (213 mg, 68% from **12**) as an oil which crystallized on storage. Recrystallization from ether–hexane gave an analytical sample: mp 75–77 °C; NMR (CCl_4) δ 0.69 (br t, 3, J = 7 Hz), 0.81–1.22 (m, 2), 1.33 (d, 3, J = 7 Hz), 1.84 (br t, 2, J = 7 Hz), 2.40–2.73 (m, 1), 3.62 (s, 3), 3.66 (d of d, 1, J = 4 Hz, 9 Hz; one set is underneath the methyl signal), 5.42 (d, 1, J = 9 Hz), 5.81 (br s, 1), 5.93 (s, 2), 6.64 (br s, 3); IR ($CHCl_3$) 1655, 1640, 1510, 1495, 1260 cm^{-1}; UV (95% EtOH) 255 nm (ε 11 900), 283 (6500) 315 (sh, 3100); mass spectrum (70 eV), m/e (relative intensity) 314 (M^+, 69), 300 (10), 299 (49), 271 (28), 175 (100). Anal. ($C_{19}H_{22}O_4$) C, H.

2-Methoxy-5-methyl-4-(3,4-(methylenedioxy)phenyl)-6-propyltropone (17). A mixture of the dienone **15** (43 mg, 0.137 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (37 mg, 0.16 mmol) in dry benzene (8 mL) was heated at reflux for 6 h under an atmosphere of nitrogen. After the mixture cooled, ether was added and the solution was washed successively with saturated sodium bicarbonate and brine and then dried ($MgSO_4$). Evaporation of the solvent gave an oil which was chromatographed on a 20 × 20 × 0.1 cm silica gel plate with 50% ethyl acetate in methylene chloride as solvent. Pure tropone **17** (33.9 mg, 80%) was isolated as an oily solid. Crystallization from ether–hexane–methylene chloride gave small plates: mp 148–50 °C; NMR ($CDCl_3$) δ 1.02 (br t, 3, J = 7 Hz), 1.46–1.80 (m, 2), 2.09 (s, 3), 2.62 (br t, J = 7 Hz), 3.84 (s, 3), 6.07 (s, 2), 6.58–6.73 (m, 3), 6.90 (d, 1, J = 8 Hz), 7.30 (s, 1); IR ($CHCl_3$) 1605, 1595, 1560, 1510, 1500, 1480, 1440, 1245, 1200 cm^{-1}; UV (95% EtOH) 248 nm (ε 35 000), 320 (sh, 10 600), 348 (11 600); mass spectrum (70 eV), m/e (relative intensity) 312 (M^+, 47), 285 (21), 284 (100). Anal. ($C_{19}H_{20}O_4$) C, H.

Acknowledgment. We thank the National Institutes of Health (GM 09868) and the Hoffmann-La Roche Foundation for financial support. High-resolution mass spectra were provided by the facility, supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources.

Registry No. 3, 75522-10-0; **4**, 67271-93-6; **5**, 120-58-1; **6**, 75522-11-1; **7**, 75522-12-2; **8**, 75522-13-3; **11**, 75522-14-4; **12**, 75522-15-5; **13**, 75522-16-6; **14**, 75533-61-8; **15**, 75522-17-7; **17**, 75522-18-8; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 84-58-2.

Synthetic, Structural, and Chemical Study of the 1,2-Diphosphetene Ring

Claude Charrier,[1a] Jean Guilhem,[1b] and François Mathey*[1a]

Laboratoire CNRS-SNPE, 94320 Thiais, France, and Institut de Chimie des Substances Naturelles, 91190 Gif-Sur-Yvette, France

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Synthesis of the diphosphetene ring by reaction of substituted acetylenes with cyclopolyphosphines was reinvestigated. In addition, a conversion of triphospholenes into diphosphetenes by lithium cleavage followed by ring closure with phosgene was devised. Thus, the two first alkyl-*C*-substituted diphosphetenes were obtained. The X-ray crystal structure of tetraphenyldiphosphetene is described. No cyclic delocalization takes place within the ring. The cyclic strain is probably minimized owing to a P—P bent bond and a predistorsion of the C=C double bond geometry by the bulky C substituents. Some reactions of tetraphenyldiphosphetene are also described including their ring cleavage by lithium and their complexation by iron carbonyls. At 150 °C, $Fe_2(CO)_9$ and $Fe_3(CO)_{12}$ cleave the P—P bond to yield a phosphido-bridged $LFe_2(CO)_6$ complex through an intermediate complex of unknown structure. An excess of iron carbonyl then causes expulsion of the tolane subunit and gives a previously described phenylphosphinidene complex, $(PhP)_2[Fe(CO)_3]_3$.

Among the various carbon–phosphorus monocyclic compounds known up to now only a few possess a 6π-electron system capable of giving rise to a cyclic delocalization. Phospholes and phosphorins have been studied in depth mainly in view of their possible aromaticity. On the other hand, practically nothing is known about the chemistry of the 1,2-diphosphetene ring **1** in spite of its discovery in 1964.[2] In fact, only two such compounds are known where R = R^1 = CF_3 (**1a**)[2] and R = R^1 = Ph (**1b**).[3] Besides this, a brief study has appeared on the metal

(1) (a) Laboratoire CNRS-SNPE. (b) Institut de Chimie des Substances Naturelles.

(2) W. Mahler, *J. Am. Chem. Soc.*, **86**, 2306 (1964).
(3) A. Ecker and U. Schmidt, *Chem. Ber.*, **106**, 1453 (1973).

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