for a further 30 min in the cold and 1 h at room temperature. Usual workup gave a light yellow oil, which was chromatographed over silica gel (100–200 mesh). Elution with light petroleum ether–ethyl acetate (97:3) afforded **2d** (110 mg; 42%) as a colorless oil: IR (neat) 1720, 760, 730 cm^{-1}; ^1H NMR δ 7.00–7.40 (m, 4 H, Ar-H), 4.14 (q, 2 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.28 (t, 3 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.28 (s, 3 H, 4-CH_3), 1.06 (s, 3 H, 10-CH_3). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.75, H, 8.92.

Further elution with the same solvent mixture (9:1) furnished unreacted lactone **9a** (130 mg, 54%) as a colorless oil: IR (neat) 1750 cm^{-1}; ^1H NMR δ 7.02–7.48 (m, 5 H, Ar-H), 4.36–4.60 (m, 1 H, OCH-), 1.16 (s, 3 H, CH_3), 1.11 (d, 3 H, J = 6.5 Hz, CH_3). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.82; H, 8.69.

Methyl (±)-*O*-Methylpodocarpate (2e) and δ-Lactone 9b. Similarly, the saturated keto ester **7b** (0.5 g) on sodium borohydride reduction in methanol yielded the mixture of cyclohexanol carboxylate **8b** and δ-lactone **9b** as a colorless oil (0.495 g): IR (neat) 3490, 1750, and 1720 cm^{-1}. The mixture (0.49 g) was treated with P_2O_5–$MeSO_3H$ (1:10, 7 g) under the same reaction conditions as above. After usual workup, the product was chromatographed over silica gel (100–200 mesh). Elution with light petroleum ether–ethyl acetate (9:1) yielded **2e** (0.192 g, 40%) as a white solid: mp 138–139 °C (lit.[9] mp 136–138 °C); IR (Nujol) 1720 and 1615 cm^{-1}; ^1H NMR δ 6.98 (dd, 1 H, J = 8 and 1 Hz, 14-H), 6.82 (d, 1 H, J = 7 Hz, 11-H), 6.67 (dd, 1 H, J = 8 and 2 Hz, 13-H), 3.76 (s, 3 H, Ar-OCH_3), 3.65 (s, 3 H, CO_2CH_3), 1.32–2.48 (m, 9 H), 1.26 (s, 3 H, 4-CH_3), and 1.03 (s, 3 H, 10-CH_3); MS, m/z (relative intensity) 302 (M^+, 93), 287 (6), 229 (32), 228 (100), 173 (29), 147 (34), 121 (36), 91 (20). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.57; H, 8.51.

Further elution of the column with the same solvent mixture (3:1) furnished the lactone **9b** (0.25 g, 55%) as a colorless oil, which solidified on scratching: mp 80–82 °C; IR (Nujol) 1745, 1615 cm^{-1}; ^1H NMR δ 7.09 and 6.79 (m, AA'BB', 4 H, Ar-H), 4.42 (m, 1 H, OCH-), 3.76 (s, 3 H, Ar-OCH_3), 1.14 (s, 3 H, CCH_3) and 1.09 (d, 3 H, J = 7 Hz, $CHCH_3$). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.91; H, 8.48.

(±)-Deoxypodocarpic Acid (2c) and Methyl (±)-Deoxypodocarpate (2b). (±)-Ethyl deoxypodocarpate (**2d**) (0.5 g, 1.7 mmol) and potassium hydroxide (1.0 g) in diethylene glycol (90%; 25 mL) was refluxed for 20 h under nitrogen. The reaction mixture was diluted with water and extracted with ether (4 × 50 mL). The ether layer was washed with brine and dried. After removal of the solvent a light yellow oil (0.415 g) was obtained, which was characterized as the starting material **2d**.

The basic aqueous solution was acidified with sulfuric acid (2 N) and extracted with ether (4 × 50 mL). The ethereal solution treated as above furnished a light yellow solid, which on crystallization from methanol–water afforded white crystals of **2c** (70 mg, 91% on the basis of recovered starting material): mp 234–235 °C (lit.[3a] mp 232–233 °C); IR (KBr) 1705 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.88; H, 8.62.

The above acid **2c** (50 mg) was esterified with an excess of ethereal diazomethane to afford **2b** (47 mg) as white crystals: mp 134–135 °C (lit.[10] mp 131–132 °C); IR (KBr) 1720, 770, 735 cm^{-1}; ^1H NMR δ 7.00–7.40 (m, 5 H, Ar-H), 3.64 (s, 3 H, CO_2CH_3), 1.26 (s, 3 H, 4-CH_3), and 1.03 (s, 3 H, 10-CH_3); MS, m/z (relative intensity) 272 (M^+, 36), 257 (67), 197 (100), 141 (38), 91 (12). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.33; H, 8.95.

(±)-*O*-Methylpodocarpic Acid (2f). Methyl (±)-*O*-methylpodocarpate (**2e**) (0.1 g, 0.33 mmol) on hydrolysis furnished **2f** (52 mg, 91% on the basis of recovered starting material) as white crystals: mp 193–194 °C (lit.[9] mp 194–195 °C); IR (KBr) 1705, 1610 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.92; H, 8.44.

Cyclization of δ-Lactone 9a to (±)-Deoxypodocarpic Acid (2c). The δ-lactone (0.5 g, 2 mmol) was mixed with glacial acetic acid (9 mL) and concentrated sulfuric acid (1 mL), and the solution was gently refluxed for 10 h under nitrogen. The dark brown solution obtained was poured into crushed ice and extracted with ethyl acetate (4 × 50 mL). The combined ethyl acetate extract was washed thoroughly with potassium hydroxide solution (2%, 100 mL). The aqueous alkaline solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate (400 mL). Usual workup gave a light brown solid, which on treatment with Norite in methanol furnished white microcrystals of **2c** (142 mg, 28%).

Cyclization of δ-Lactone 9b to (±)-*O*-Methylpodocarpic Acid (2f). The δ-lactone (0.24 g, 0.83 mmol) on similar cyclization as above furnished **2f** (80 mg, 33%) as white crystals.

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Registry No. (±)-**2b**, 16957-27-0; (±)-**2c**, 5708-75-8; (±)-**2d**, 122571-56-6; (±)-**2e**, 41437-72-3; (±)-**2f**, 80408-73-7; (±)-**3a**, 122571-50-0; (±)-**3b**, 126753-78-4; (±)-**5a**, 122571-53-3; (±)-**5b**, 126753-79-5; **6**, 122571-52-2; **7a**, 122571-57-7; **7b**, 126753-80-8; **8a**, 122571-55-5; **8b**, 126753-81-9; **9a**, 122571-54-4; **9b**, 126753-82-0; (±)-$EtO_2CCHMeCOMe$, 64854-05-3; (±)-$MeO_2CCHMeCOMe$, 59057-05-5; PhCHO, 100-52-7; 4-$MeOC_6H_4CHO$, 123-11-5; $EtCO(CH_2)_2N^+Et_2MeI^-$, 52103-30-7.

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A Stereoselective Synthesis of *d,l*-16-Oxa-15α-methyl-19-nortestosterone

Phillip A. Zoretic,* Byung-Chan Yu, Michael S. Biggers, and Myron L. Caspar

Department of Chemistry, East Carolina University, Greenville, North Carolina 27858

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Recently we reported that stereoselective copper-catalyzed vinylation[1] of **1** followed by trapping the regiospecifically generated enolate with formaldehyde gas afforded an excellent yield of alcohol **2**, which contains the prerequisite functionality for further elaboration of the transfused C,D ring system[2] in steroids. Of particular interest to us was the utilization of **2** in the construction of various 16-substituted testosterone derivatives[3] for biological evaluation. We report herein a facile synthesis of the 16-oxa analogue **13** as delinated below.

Reaction of alcohol **2**[4] (Scheme I) with methanesulfonyl chloride in the presence of triethylamine gave a 97% yield of mesylate **3**. Subsequent treatment of **3** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene afforded the exocyclic methylene **4** (90%). The resonance signals at δ 6.04 and 5.19 are consistent with an intact exocyclic methylene.

Construction of the potential A and B ring systems in **13** was in turn realized by Michael addition of ethyl 7,7-(ethylenedioxy)-3-oxooctanoate (**5**)[5] to **4** (Scheme II). Thus reaction of **5** with **4** in the presence of 0.1 N sodium methoxide in methanol at 0 °C and subsequent acidifica-

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(2) Zoretic, P. A.; Yu, B.-C.; Caspar, M. L. *Synth. Commun.* **1989**, *19*, 1859.

(3) For synthetic approaches to 16-oxatestosterone derivatives and related analogues, see: Barton, D. H. R.; Akhtar, M. *J. Am. Chem. Soc.* **1962**, *84*, 1496. Kierstead, R. W.; Faraone, A. *J. Org. Chem.* **1966**, *32*, 704. Pappo, R. *Chem. Abstr.* **1967**, *67*, 54354V. Baran, J. S. *J. Med. Chem.* **1967**, *10*, 1039. Kierstead, R. W. *Chem. Abstr.* **1969**, *71*, 61657g; U.S. Pat. 3, 448,123. Baran, J. S. *Chem. Abstr.* **1970**, *72*, 44002T.

(4) Approximately 5% of an isomer was present in **2**.

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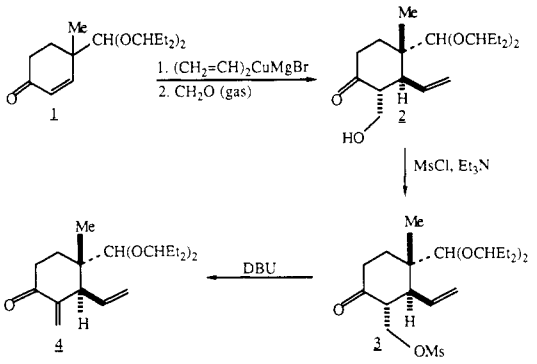
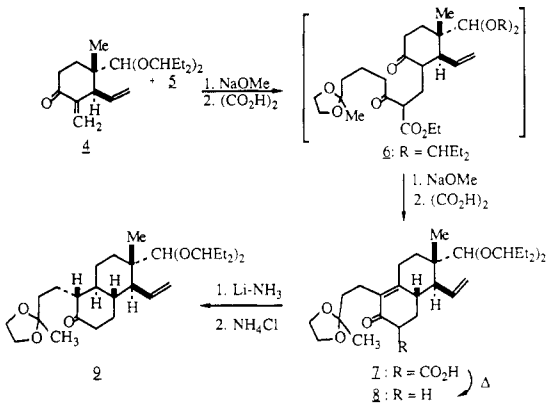
0022-3263/90/1955-3954$02.50/0

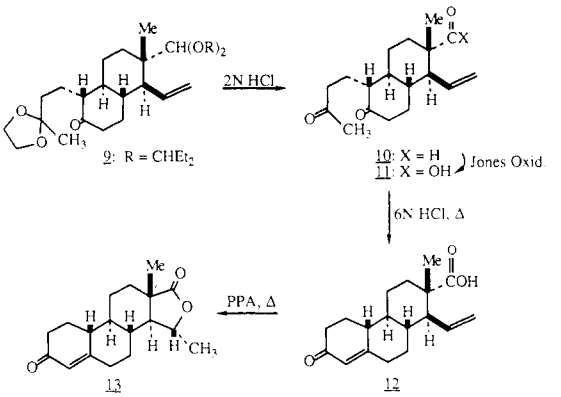
Scheme I



Scheme II



Scheme III



tion with oxalic acid gave the crude intermediate **6**. Concomitant treatment of **6** with NaOMe in methanol at 40 °C followed by acidification afforded a product consisting mainly of enones **7** and **8**. Only a trace amount of the corresponding ester could be detected. Complete decarboxylation to yield **8** (40%) was effected in refluxing toluene.

Lithium ammonia reduction[6] of **8** at −33 °C followed by destroying the excess lithium with a catalytic amount of $FeCl_3$ and subsequent acidification with NH_4Cl afforded, after chromatography, a 61% yield of the desired *trans*-decalin **9**. Unreacted **8** (15%) was also receovered from the reaction mixture. Hydrolysis of **9** (Scheme III) with 2 N HCl–THF (1:3) at room temperature gave a 91% yield of the crude aldehyde **10** and subsequent Jones oxidation at 0 °C gave acid **11** in 68% yield. Cyclization of **11** in a refluxing solution of 6 N HCl–THF afforded the 2-phenanthrenecarboxylic acid **12** (74%). Treatment of **12** with hot polyphosphoric acid afforded the desired *d,l*-16-oxa-15α-methyl-19-nortestosterone (**13**) in 89% yield, after chromatography. The configuration assignment at C-15 in **13** is consistent with the observed 10.3-Hz coupling constant between the trans-disposed C-14 and C-15 methines.

Experimental Section

General. ^1H NMR spectra were obtained at 200 or 500 MHz. All melting points and boiling points are uncorrected. Preparative chromatography was performed on Merck silica gel G 60 (70–230 mesh) and Merck silica gel G (230–400 mesh, for pressure chromatography). Thin layer chromatography was performed with Sybron/Brinkmann silica gel G/UV_{254} plates, 0.25 mm (analytical). Compounds on chromatography plates were visualized by spraying with 4% phosphomolybdic acid in isopropyl alcohol followed by heating. The purity of the title compounds were judged to be ≥90% by ^1H NMR determinations. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Commercial reagent-grade solvents and chemicals were used as obtained unless otherwise noted.

(2α,3β,4α)-3-Ethenyl-4-[bis(1-ethylpropoxy)methyl]-2-(hydroxymethyl)-4-methylcyclohexanone (2). To $CuBr{\cdot}Me_2S$ (4.15 g, 20.2 mmol) in dry THF (10 mL) was added vinylmagnesium bromide (1.12M in THF, 36 mL, 40.5 mmol) over 30 min at −78 °C under N_2. The reaction mixture was stirred for an additional 30 min. Enone[1] **1** (3.0 g, 10.1 mmol) in 5 mL of dry THF was added over 20 min. The reaction mixture was stirred for an additional 5 h at −78 °C. Formaldehyde gas [generated by heating paraformaldehyde (1.82 g, 60.72 mmol) at 150 °C] was passed into the reaction mixture by a stream of N_2 over 20 min. After stirring another 20 min, water was added. The reaction mixture was allowed to come to room temperature and filtered through Celite. The salts were washed with CH_2Cl_2 and the filtrate was extracted with three (50 mL) portions of CH_2Cl_2. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel, eluting with an ethyl acetate–hexane solution, gave 2.98 g (83%) of **2**: ^1H NMR (200 MHz, $CDCl_3$) δ 5.52–5.72 (m, 1 H), 4.93–5.22 (m, 2 H), 4.42 (s, 1 H) 3.63–3.72 (m, 2 H, OCH_AH_B), 3.34–3.60 (m, 2 H, $OCHEt_2)_2$, 2.82 (dd, 1 H, OH, J = ~6.4 and ~7.9 Hz), 5.71 (dd, 1 H, $CHCH{=}CH_2$, J = ~9.7 and ~12.4 Hz), 2.41 (m, C-2 methine) and 2.30–2.52 (m) [3 H], 2.04–2.23 (m, 1 H), 1.78–1.93 (m, 1 H), 1.21–1.69 (m, 8 H), 1.14 (s, 3 H), and 1.28–1.98 (m, 12 H); IR (neat) 3500, 1700, and 1640 cm^{-1}; mass spectrum calcd for $C_{21}H_{38}O_4$ 354.2769 [M^+, under CI conditions no (M^+ + 1) peak was observed], found 354.2813. The chemical shift assignments were deduced from a ^1H COSY spectrum; approximately 5% of an isomeric compound [δ 4.64 (s)] was also present in the chromatographed sample.

Irradiation [^1H NMR (500 MHz, $CDCl_3$)] of the CH_2OH protons at δ 3.68 caused the C-3 methine at δ 2.41 to collapse into a doublet, J = 12.4 Hz; the OH proton at δ 2.82 also collapsed into a singlet, δ 2.82. An NOE experiment [^1H NMR (500 MHz, $CDCl_3$)] showed that irradiation of the angular CH_3 at δ 1.14 gave significant enhancement for the C-3, vinyl, and acetal methines.

(2α,3β,4α)-3-Ethenyl-4-[bis(1-ethylpropoxy)methyl]-4-methyl-2-[[(methylsulfonyl)oxy]methyl]cyclohexanone (3). To a solution of alcohol **2** (1.02 g, 2.88 mmol) in 12 mL of dry CH_2Cl_2 under N_2 at 0 °C was added dry Et_3N (10.5 mL, 3.45 mmol) followed by dropwise addition (syringe) of CH_3SO_2Cl (0.25 mL, 3.23 mmol). The reaction mixture was stirred for an additional 3.5 h at 0 °C. Saturated $NaHCO_3$ was added and the resulting mixture was extracted with three (20 mL) portions of CH_2Cl_2. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford 1.21 g (97%) of crude **3**. TLC analysis indicated a slower moving compound when compared to **2** and the labile mesylate was used directly in the next step.

(3α,4β)-3-Ethenyl-4-[bis(1-ethylpropoxy)methyl]-4-methyl-2-methylenecyclohexanone (4). To crude mesylate **3** (1.21 g, 2.80 mmol) in 7 mL of dry benzene under N_2 at room temperature was added DBU (473 μL, 3.16 mmol) dropwise (syringe). The reaction mixture was stirred for 1.0 h at room temperature and then diluted with CH_2Cl_2 (70 mL). The organic

(6) Stork, G.; Darling, S. D. *J. Am. Chem. Soc.* **1960**, *82*, 1512. Stork, G.; McMurry, J. E. *Ibid.* **1967**, *89*, 5464.

layer was washed with cold 0.15 N HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 850 mg (90%) of **4**: ^1H NMR ($CDCl_3$) δ 6.04 (sharp m, 1 H), 5.67–5.86 (m, 1 H), 5.19 (br s) and 5.02–5.26 (m) [3 H], 4.52 (s, 1 H), 3.34–3.57 (m, 2 H), and 0.8–1.0 (5 CH_3). The labile exocyclic methylene ketone was not characterized further but submitted directly to the Michael addition reaction.

1,3-Dioxolane-2-hexanoic Acid, 2-Methyl-β-oxo-, Ethyl Ester (5). To a 50% suspension of NaH–mineral oil (852 mg, 17.8 mmol) in 20 mL of dry THF at 0 °C under N_2 was added via a syringe dry HMPA (0.646 mL, 3.7 mmol), followed by dropwise addition of ethyl acetoacetate (2.0 mL, 6.1 mmol). The reaction mixture was stirred for 10 min. *n*-Butyllithium[7] (2.3M in hexane, 7.37 mL, 16.9 mmol) was added dropwise via a syringe and the rection mixture was stirred for an additional 10 min during which time the reaction turned yellow. 1-Bromo-3,3-(ethylenedioxy)butane[8] (3.30 g, 16.94 mmol) in THF (2 mL) was added dropwise at 0 °C. After an additional hour the reaction mixture was quenched with 3% oxalic acid. Saturated $NaHCO_3$ was added and the resulting mixture was extracted with three (60 mL) portions of CH_2Cl_2. The organic solution was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Distillation gave 2.07 g (53%) of **5**: bp 148–50 °C (1.2 mm); lit.[5] bp 125–144 °C (0.2 mm); ^1H NMR ($CDCl_3$) δ 4.19 (q, 2 H, J = 7 Hz), 3.95 (m, 4 H), 3.44 (s, 2 H), 2.59 (t, 2 H, J = 7 Hz), 1.69 (m, 4 H), and 1.28 (t, 3 H, J = 7 Hz); IR (neat) 1725 br cm^{-1}.

(4aα,5α,6β)-5-Ethenyl-1-[3,3-(ethylenedioxy)-1-butyl]-6-[bis(1-ethylpropoxy)methyl]-6-methyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (8). A mixture of crude enone **4** (1.58 g, 4.70 mmol) and keto ester **5** (1.31 g, 5.37 mmol) was cooled to 0 °C under N_2. Sodium methoxide (0.1 N, 19.4 mL, 0.938 mmol) was added dropwise and the reaction mixture was stirred for an additional 60 h at 0 °C. A 3% oxalic acid solution was added dropwise at 0 °C until the pH was 7.5, and then the reaction was diluted with 100 mL of CH_2Cl_2. The organic solution was washed with water (50 mL), two (50 mL) portions of 10% $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo to afford 2.68 g of the crude intermediate **6**, which was subjected to cyclization.

To crude **6** (2.10 g) in 20 mL of methanol was added NaOMe (215 mg, 3.98 mmol) under N_2. The resulting reaction mixture was stirred at 40 °C for 4 h and then allowed to cool to room temperature. Methanol was removed in vacuo; the residue was diluted with cold water (30 mL) and then carefully acidified with 3% oxalic acid. The mixture was extracted with three (75 mL) portions of CH_2Cl_2. The organic solution was washed with water (65 mL) and brine (65 mL), dried (Na_2SO_4), and concentrated in vacuo to afford an oil. The crude product consisted mainly of the carboxylic acid **7** (δ 12.52) and the decarboxylated compound **8**. To effect complete decarboxylation, the crude product was dissolved in toluene (20 mL) and refluxed for 1.5 h. The solvent was removed in vacuo to afford an oil. Chromatography on silica gel, eluting with an ethyl acetate–hexane solution, gave 714 mg (40%) of **8**: ^1H NMR ($CDCl_3$) δ 5.47–5.67 (m, 1 H), 4.96–5.20 (m, 2 H), 4.39 (s, 1 H), 3.95 (s, 4 H), 3.35–3.55 (m, 2 H), 1.37 (s) and 1.26–2.83 (m) [25 H], 1.02 (s, 3 H), and 0.80–0.98 (m, 12 H); IR (neat) 1665 cm^{-1}; mass spectrum (CI, isobutane), m/z 491 (M^+ + 1), 403 and 333; HRMS calcd for $C_{30}H_{50}O_5$ (M^+ + 1), 491.3736, found 491.3730. Anal. Calcd for $C_{30}H_{50}O_5$: C, 73.41; H, 10.29. Found: C, 73.23; H, 10.70.

(1α,4aβ,5β,6α,8aα)-5-Ethenyl-1-[3,3-(ethylenedioxy)butyl]-6-[bis(1-ethylpropoxy)methyl]-6-methyl-1,4,4a,5,6,7,8,-8a-octahydro-2(3*H*)-naphthalenone (9). Lithium (49 mg, 7.06 mmol) was added in small pieces to 60 mL of dry liquid NH_3 at −33 °C under N_2, and the blue solution was stirred for 30 min. Enone **8** (680 mg, 1.38 mmol) in dry THF (6 mL) was added dropwise over 1 h. The addition funnel was washed with 1.0 mL of THF and the reaction mixture was stirred for an additional 2 h at −33 °C. Two small portions (several crystals) of anhydrous $FeCl_3$ were added (Li → $LiNH_2$, approximately 20 min). Solid NH_4Cl was added and the NH_3 was allowed to evaporate. The residue was diluted with CH_2Cl_2 (100 mL). The organic solution was washed with two (25 mL) portions of water, cold 1% HCl (20 mL), 10% $NaHCO_3$ (20 mL), and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel, eluting with 5% ethyl acetate–hexane, gave 415 mg (61%) of **9**: ^1H NMR ($CDCl_3$) δ 5.65–5.42 (m, 1 H), 4.91–5.16 (m, 2 H), 4.35 (s, 1 H), 3.94 (s, 4 H), 3.30–3.54 (m, 2 H), 1.34 (s) and 1.09–2.51 (m) [27 H], and 0.94 (s) and 0.78–0.97 (m) [15 H]; IR (neat) 1710 cm^{-1}; mass spectrum (CI, isobutane), m/z 493 (M^+ + 1), 405, 335; HRMS calcd for $C_{30}H_{52}O_5$ (M^+ + 1) 493.3892, found 493.3903. In addition there was obtained 103 mg (15%) of unreacted **8**.

(1α,2β,4aβ,5β,8aα)-1-Ethenyl-2-methyl-6-oxo-5-(3-oxo-1-butyl)octahydro-2-naphthalenecarboxaldehyde (10). Diacetal **9** (390 mg, 0.793 mmol) was dissolved in 2 N HCl–THF (1:3; 10 mL) and the reaction mixture was stirred at room temperature for 4.5 h. Solid $NaHCO_3$ was added until the reaction mixture was slightly basic. THF was removed in vacuo and CH_2Cl_2 (50 mL) and H_2O (40 mL) were added to the reduced residue. The layers were separated and the aqueous solution was extracted with two (50 mL) portions of CH_2Cl_2. The organic solution was washed with brine (40 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 210 mg (91%) of crude keto aldehyde **10**: ^1H NMR ($CDCl_3$) δ 9.38 (s), 2.14 (s), and 1.15 (s). Intermediate **10** was not characterized further but submitted to Jones oxidation.

(1α,2β,4aβ,5β,8aα)-1-Ethenyl-2-methyl-6-oxo-5-(3-oxo-1-butyl)octahydro-2-naphthalenecarboxylic Acid (11). To crude aldehyde **10** (210 mg, 0.723 mmol) in acetone at 0 °C was added Jones reagent (2.67 M, 0.352 mL, 0.940 mmol) dropwise (syringe). The reaction mixture was stirred an additional 20 min at 0 °C and then diluted with CH_2Cl_2 (50 mL). Water (50 mL) was added and the organic layer was separated. The aqueous solution was extracted with three (50 mL) portions of CH_2Cl_2. The organic solution was washed with brine (40 mL), dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel, eluting with an ethyl acetate–hexane solution, gave 151 mg (68%) of **11**: ^1H NMR ($CDCl_3$) δ 5.47–5.69 (m, 1 H), 5.0–5.19 (m, 2 H), 2.13 (s, 3 H), 1.22 (s, 3 H), and 1.20–2.68 (m, 17 H); IR (neat) 1710 cm^{-1}; mass spectrum (EI) m/z 306 (M^+, 23.9), 288 (21.1), 263 (6.5), 235 (28), and 43 (100); HRMS calcd for $C_{18}H_{26}O_4$ 306.1830, found 306.1821.

(1α,2β,4aβ,4bα,10aα)-1-Ethenyl-2-methyl-7-oxo-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydro-2-phenanthrenecarboxylic Acid (12). Diketone **11** (132 mg, 0.455 mmol) was dissolved in a 6 N HCl–THF solution (1:1; 5 mL), and the reaction mixture was refluxed for 2 h. No starting material was detected by TLC analysis. The reaction mixture was diluted with CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted with two (15 mL) portions of CH_2Cl_2. The organic solution was washed with water (20 mL) and the aqueous solution was backwashed with two (30 mL) portions of CH_2Cl_2. The combined organic solution was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel, eluting with an ethyl acetate–hexane solution, gave 92 mg (74%) of **12**: mp (softens 156 °C) 158–161 °C (triturated, EtOAc–hexane–ether solution); ^1H NMR ($CDCl_3$) δ 5.85 (s, 1 H), 5.46–5.65 (m, 1 H), 4.89–5.12 (m, 2 H), 1.20 (s) and 0.96–2.48 (m) [19 H]; IR (KBr) 3500 (br), 2500 (br) and 1680 (br) cm^{-1}; mass spectrum (EI), m/z 288 (M^+, 100), 273 (7.6), 270 (4.2), 260 (10.9), 243 (12.6), and 215 (10.1); HRMS calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1735. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.95; H, 8.40. Found: C, 74.59; H, 8.28.

***d,l*-16-Oxa-15α-methyl-19-nortestosterone (13).** To enone acid **12** (25.1 mg, 0.087 mmol) was added polyphosphoric acid (~3 g). The reaction mixture was heated in a hot water bath for 45 min during which time the reaction flask was rotated on a rotary evaporator under slight vacuum. The reaction mixture was cooled in an ice bath and cold water (~10 mL) was added dropwise.

An additional 10 mL of cold water was added and the resulting mixture was extracted with three (40 mL) portions of CH_2Cl_2. The organic solution was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL) and concentrated in vacuo to afford a solid. Chromatography on silica gel, eluting with an ethyl acetate–hexane solution, gave 22.4 mg (89%) of **13**: mp 166–168 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 (s, 1 H), 4.46 (dq, 1 H, J = 5.9 and 10.3

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Hz), 1.45 (d, 3 H, J = 5.9 Hz), and 1.21 (s, 3 H); IR (KBr) 1750 and 1650 cm^{-1}; mass spectrum (EI), m/z 288 (M^+, 37.5), 260 (31.7), 244 (41.7), 215 (21.7), and 82 (100); HRMS calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1732.

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Registry No. 1, 126724-79-6; 2, 126786-76-3; 3, 126724-80-9; 4, 126724-81-0; 5, 27428-41-7; 6, 126724-82-1; 7, 126724-83-2; 8, 126724-84-3; 9, 126724-85-4; 10, 126724-86-5; 11, 126724-87-6; 12, 126724-88-7; 13, 126724-89-8; vinylmagnesium bromide, 1826-67-1; formaldehyde, 50-00-0; ethyl acetoacetate, 141-97-9; 1-bromo-3,3-(ethylenedioxy)butane, 37865-96-6.

Supplementary Material Available: ^1H NMR spectra of compounds 2, 4, 5, 8, 9, 11–13 (12 pages). Ordering information is given on any current masthead page.

[2 + 2 + 2] Cycloaddition Reaction of 1-Methylpyrrole with Diethyl Azodicarboxylate

Chang Kiu Lee* and Yu Mi Ahn

Department of Chemistry, Kangweon National University, Chuncheon 200-701, S. Korea

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Reactions of bimolecular [2 + 2 + 2] cycloaddition are of interest since they serve as examples of orbital interactions that can be explained by the Woodward–Hoffmann rules.[1] However, concerted [2 + 2 + 2] cycloadditions involving three molecules are rare. For example, trimerization of acetylene to benzene needs a catalyst such as $AlCl_3$ and a 1:1 adduct is involved in the course of formation, indicating a stepwise process.[2] Although few reports are found in the literature, termolecular [2 + 2 + 2] cycloaddition reactions seem to be useful synthetic processes if a suitable catalyst is employed.[3-7] We report an example of an uncatalyzed cycloaddition reaction that appears to involve 6 π electrons from three double bonds in three molecules.

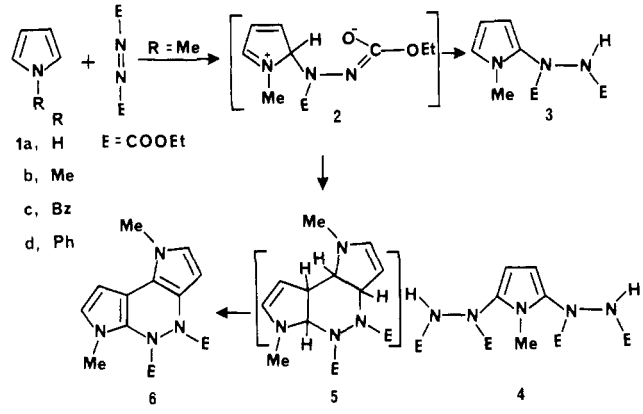
In the course of our investigation of reactions of five-membered heteroaromatic compounds with dienophiles, we repeated the reaction of 1-methylpyrrole (**1b**) with diethyl azodicarboxylate (DADC). In ethanol, the Michael-type 1:2 adduct **4** formed as reported previously.[8] However, when the reaction was carried out in thoroughly dried ether, new compound **8** precipitated out in ca. 4% yield together with **3** (32%) and **4** (53%). The use of anhydrous ether was critical since the yield of **8** was variable, depending on the quality of the solvent employed. Furthermore, the yield could not be improved by using other solvents than ether. Michael-type adduct **4** was always the major product (Table I).

Table I. Yields of 4 and 8 in Various Solvents[a]

	40 °C		80 °C	
solvent	4, %	8, %	4, %	8, %
diethyl ether	53[b]	4	40[c]	0
tetrahydrofuran	17	5	*d*	*d*
benzene	37	0	40	0
carbon tetrachloride	40	3	60	0
dioxane	23	3	60	0
dimethyl sulfoxide	86	0	80	0

[a] Molar ratio of **1b** and DADC was 1:2. [b] 1:1 Michael-type adduct **3** was also isolated in 32% yield. [c] Heated in a sealed stainless steel tube (inner volume = 40 mL). [d] Not tried.

Scheme I



Reaction temperature was also critical: that is, the yield of **8** was maximum when the reaction was carried out at 40 °C in various aprotic solvents. At higher temperature (80 °C) only the Michael-type adduct (**4**) was formed. When excess amounts of **1b** (10 molar equiv) were used, only the Michael-type adduct was isolated. The optimum ratio for the formation of **8** was a 1:2 molar ratio of **1b** and DADC.

1*H*-Pyrrole (**1a**) and other N-substituted pyrroles (**1c,d**) did not give adducts similar to **8**. Only the Michael-type adducts similar to **4** were obtained regardless of solvents or reaction temperature.

The structure of **8** was established by IR, UV, ^1H NMR, ^{13}C NMR (DEPT), and EI- and CI-mass spectra together with elemental analysis. It has a new type of dipyrrolopyridazine skeleton. A structure such as **6** would be logical if the reaction is stepwise and **2** is the intermediate leading to **3**, **4**, **5**, or **6** (Scheme I) because C_2 in pyrrole is much more nucleophilic than C_3.[9] But the ^{13}C NMR spectrum clearly indicated the presence of only eight carbon atoms, in spite of the molecular formula of $C_{16}H_{20}N_4O_4$ (from high resolution mass spectrum), which is consistent with the elemental analysis. Therefore, the molecule must be symmetric. Two other structures, **9** and **10**, which have C_2 symmetry, may also be considered. An AB pattern at δ 7.33 and 7.50 with J = 6.0 Hz was the only signal that appeared in the aromatic region. The coupling constants of 6.0 Hz is unusually large compared to 2.6–3.1 Hz for $J_{2,3}$ of pyrrole or indole.[10] This large value may be due to the electronic and field effects of the ethoxycarbonyl group on the nitrogen atom of the ring. In fact, $J_{2,3}$ of dimethyl 1-methylindole-4,6-dicarboxylate is 8.0 Hz.[11] This data

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