Synthesis of the 16α,17α,21-Trimethyl Corticosteroid Rimexolone from Prednisolone

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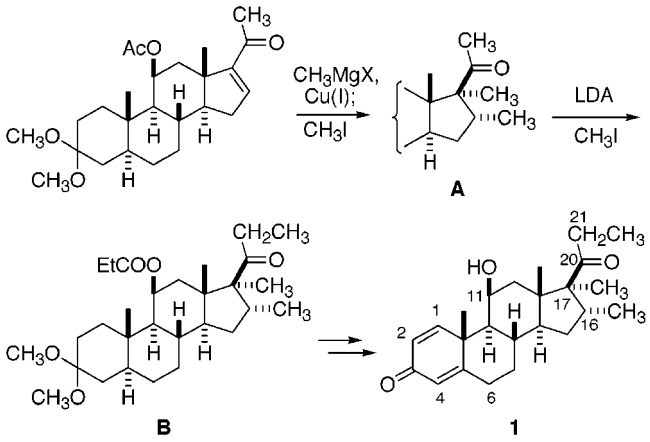
Rimexolone (**1**, Scheme 1), a corticosteroid first prepared by Organon, was introduced in 1995 by Alcon as Vexol ophthalmic suspension for topical treatment of anterior uveitis and postsurgical ocular inflammation. Rimexolone represents an important therapeutic advance because it does not significantly elevate intraocular pressure, a side effect of traditional corticosteroids such as dexamethasone.[1]

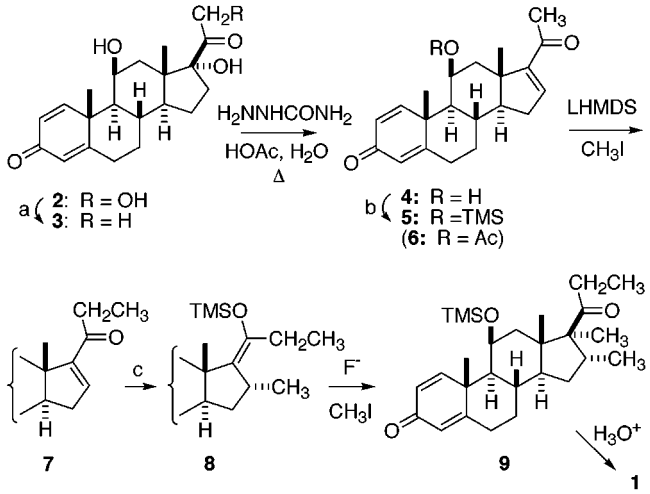
The previously published sapogenin-based synthesis of **1** is summarized in Scheme 1.[2] The current shift toward utilization of soy-derived 17-oxo steroids as starting materials[3] prompted consideration of alternative routes to **1** employing early construction[4] of the D-ring ethyl enone (see **7**, Scheme 2). Complexities associated with the Δ^1 and 11β-OH functional group introductions would, however, remain.[2,5] In contrast, a synthesis of **1** from abundant, inexpensive ($1500/kg) prednisolone (**2**) would obviate these concerns. The key issue would then be the compatibility of anion-mediated methylations with the unprotected A-ring dienone. Here we report the results of small-scale investigations that validate this approach.

Prednisolone (**2**) was converted to the 21-deoxy derivative **3**,[6a] via the primary tosylate and iodide, in 88% yield (Scheme 2).[6] The previously unreported dehydration of **3** to **4**[7] was effected by Kövendi's catalytic[8a] semicarbazone-mediated method.[8] Silylation of crude **4** facilitated chromatographic removal of polar materials, and intermediate **5**[9] was thereby secured in 57% yield from **3**.

Scheme 1



Scheme 2



(a) 1. TsCl, py, 5 °C (→ R =OTs); 2. NaI (6 equiv), acetone, rt (→ R = I), add HOAc, Δ.
(b) TMSCl, py, DMAP.
(c) $(CH_3)_2Cu(CN)Li_2$, TMSCl, THF, -45°C.

Concurrent studies on acetate **6** revealed an interesting sidelight. Prednisolone triacetate (**10**)[10] is known to yield acetoxy enone **12** upon heating with KOAc in DMF at 105 °C.[10a] In turn, deacetoxylation of **12** can be effected with Zn−HOAc, but the yield is low.[11] As the reduction of **2** to **3** was efficient, we subjected the derived diacetate **11** to the KOAc−DMF conditions, but the expected product **6** did not form. At 140 °C, cyclodehydration occurred, giving spirobutenolide **13**.[12] The loss of

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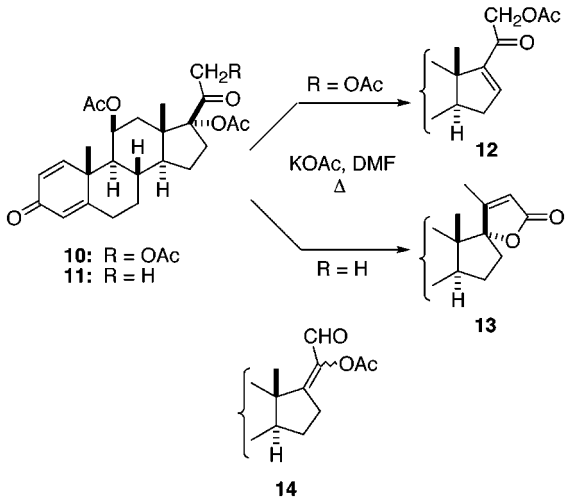
HOAc from **10** therefore likely occurs in the course of a Mattox rearrangement, giving enal **14** which isomerizes[3d,13] to **12**.



In principle, C-21 methylation could be performed on **5** or deferred until after vicinal C-16/C-17 methylation as in Scheme 1 (**A** → **B**; note the concurrent methylation of the 11*β*-acetate). Either sequence had worked well in the absence of a second keto group.[2] We perceived the former sequence to be more favorable here.[14] Kinetic enolization of **5**, by slow addition to base,[15] would surely form some 6,21-dianion, as a 1,4-dien-3-one is known to enolize at −78 °C on exposure to $NaN(TMS)_2$.[16] Also, the extended D-ring enolate could be a significant constituent.[15b] We were therefore pleased to find that slow addition of $LiN(TMS)_2$[3a] to a solution of **5** in THF−HMPA at −65 °C, followed by quenching with CH_3I, provided ethyl enone **7** in 82% yield after chromatography. The remaining material consisted largely of **5** and mixed **5**/**7** fractions.

Copper-catalyzed conjugate additions of Grignard reagents to compounds configured as in **12** (e.g., 9α-F, $\Delta^{9(11)}$) are used in the commercial production of 16α-methyl corticosteroids.[3a,17] Inclusion of TMSCl in the reaction mixture enhances regioselectivity and intercepts the enolate as the silyl ether, which can be epoxidized to effect 17α-hydroxylation.[17a−c] Although these precedents were encouraging, extrapolation to the more demanding[18,19] 17α-methylation without A-ring involvement required experimentation. We found that addition of the stoichiometric cuprate $(CH_3)_2Cu(CN)Li_2$[20] to a solution of **7** and TMSCl in THF at −45 °C reliably gave silyl enol ether **8** in 85% yield. Addition of **8** dissolved in CH_3I to a suspension of dry benzyltrimethylammonium fluoride and molecular sieves in THF[19] delivered rimexolone TMS ether (**9**). Only the enolic silyl ether was cleaved. The mass spectrum of crude **9** showed only 0.2% polyalkylation,[19] an important consideration in light of the difficulty of removing such materials from related intermediates.[2] Recrystallization gave **9** in 63% yield (unoptimized). Desilylation of **9** with dilute HCl[9] afforded rimexolone (**1**) (97%).

In conclusion, a route to **1** from **2** has been demonstrated. Supplies of **2**, a commodity corticosteroid, are assured. The reactions leading from **2** to **5** are economical and well suited to scale-up, as is the final desilylation. The methylations work well, furnish highly crystalline intermediates, and should be amenable to process variations. The current average yield is >80% per step.

Experimental Section

General Methods. THF was freshly distilled from $K/Ph_2C{=}O$ under Ar. HMPA was dried under N_2 over 4A molecular sieves. Anhydrous pyridine and DMF were used as received from Aldrich. Temperatures are external unless otherwise indicated. Concentration refers to removal of volatile components by rotary evaporation in vacuo. Melting points are uncorrected. Coupling constants (*J*) are reported in Hz. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. High-resolution mass spectroscopy was performed by Analytical Instrument Group, Raleigh, NC.

11*β*-Hydroxypregna-1,4,16-trien-3,20-dione (4).[7] A stirred solution of 21-deoxyprednisolone (**3**)[6] (2.15 g, 6.25 mmol) and semicarbazide·HCl (4.75 mL of a 5.0% aqueous solution, 2.14 mmol) in HOAc (72 mL) was heated to 80−85 °C for 4.2 h under Ar.[8a] Water (75 mL) was added, and heating (85 °C) was continued for 5.5 h. The solution was cooled to room temperature over 11 h and poured into water (850 mL), and the resulting suspension was chilled in ice. The light yellow solid was collected by filtration and dried under vacuum at room temperature to give 1.40 g of **4**. A sample was purified by elution through Florisil (20% acetone−CH_2Cl_2) followed by recrystallization from EtOAc: mp 262−266.5 °C (dec); ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 1.0−2.7 (m, 12H), 4.38 (br q, 1H, J = 2.5), 6.00 (s, 1H), 6.25 (dd, 1H, J = 10, 2), 6.66 (q, 1H, J = 2), 7.32 (d, 1H, J = 10); ^{13}C NMR ($CDCl_3$) δ 18.43, 21.20, 26.97, 30.26, 31.94, 32.41, 33.65, 44.35, 44.89, 45.60, 56.54 (2C), 70.47, 122.51, 127.94, 143.88, 155.68, 156.30, 169.77, 186.64, 196.64; $[\alpha]^{23}_D$ +158° (c = 0.50, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.02; H, 8.07.

11*β*-(Trimethylsiloxy)-pregna-1,4,16-trien-3,20-dione (5).[9] TMSCl (1.4 mL, 11 mmol) was added to a stirred, ice-cooled solution of unpurified **4** (1.40 g, nominally 4.3 mmol) and DMAP (0.12 g, 1.0 mmol) in anhydrous pyridine (14 mL) under Ar. The cooling bath was removed, and the mixture was stirred for 23 h. TMSCl (1.0 mL, 7.9 mmol) was added, and stirring was continued for 2 h. The solution was cooled in ice and quenched with CH_3OH (1 mL). After 0.5 h, EtOAc was added and the solution was washed with water, saturated $CuSO_4$ (twice), water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue (1.69 g) was purified by flash chromatography (140 g silica, CH_2Cl_2 to apply, 30% EtOAc−hexane) to give 1.42 g of **5** (57.5% from **3**) as an off-white solid. A sample was recrystallized from diisopropyl ether: mp 193−195 °C, lit.[9] mp 196−197.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9H), 1.0−1.4 (m, 4H), 1.17 (s, 3H), 1.42 (s, 3H), 2.0−2.8 (m, 7H), 2.24 (s, 3H), 4.37 (br q, 1H, J = 2.5), 6.01 (s, 1H), 6.27 (dd, 1H, J = 10, 2), 6.65 (q, 1H, J = 2), 7.13 (d, 1H, J = 10); ^{13}C NMR ($CDCl_3$) δ 0.92, 18.10, 20.61, 26.94, 30.31, 31.97, 32.36, 33.68, 42.69, 44.16, 45.80, 56.84, 57.34, 71.40, 122.46, 128.08, 143.45, 155.51, 155.71, 169.88, 186.41, 196.40; $[\alpha]^{23}_D$ +128° (c = 0.33, $CHCl_3$). Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 72.31; H, 8.60. Found: C, 72.31; H, 8.52.

21-Methyl-11*β*-(trimethylsiloxy)-pregna-1,4,16-trien-3,-20-dione (7). $LiN(TMS)_2$ (0.9 M in THF, 2.1 mL, 1.9 mmol) was added over 8 min to a stirred solution of **5** (0.73 g, 1.83 mmol)

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(14) Two examples of **A** → **B** type alkylation in the presence of the A-ring dienone have been recorded: **24** → **25** in ref 2 (30% yield); Example 19 in U.S. Patent 3,862,194 (yield unspecified).

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in THF (12.0 mL) and HMPA (3.0 mL) at −60 to −65 °C (internal) under Ar. After 2 min, CH_3I (2.5 mL, 40 mmol) was added rapidly. The solution was warmed over 2 min to 10 °C, quenched with saturated KH_2PO_4, and extracted with EtOAc. The organic solution was dried ($MgSO_4$), filtered, and concentrated. The residue (1.9 g) was purified by flash chromatography (80 g silica, 25% to 50% EtOAc−hexane) to give 0.62 g (82%) of **7**: mp 178−182 °C (dec); ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 9H), 1.05 (t, 3H, J = 7.3), 1.18 (s, 3H), 1.41 (s, 3H), 1.0−1.4 (m, 4H), 2.0−2.8 (m, 7H), 2.6 (q, 2H), 4.37 (br q, 1H, J = 2.5), 5.99 (s, 1H), 6.25 (dd, 1H, J = 10, 2), 6.64 (q, 1H, J = 2), 7.12 (d, 1H, J = 10); ^{13}C NMR ($CDCl_3$) δ 0.97, 8.14, 18.18, 20.62, 30.28, 31.99, 32.00, 32.33, 33.70, 42.74, 44.17, 45.92, 56.80, 57.38, 71.43, 122.45, 128.08, 142.01, 155.13, 155.53, 169.92, 186.43, 199.44; $[\alpha]^{23}_D$ +144° (c = 0.05, $CHCl_3$). Anal. Calcd for $C_{25}H_{36}O_3Si$: C, 72.76; H, 8.79. Found: C, 72.57; H, 8.73. Further elution provided 0.08 g (11%) of a 3:1 mixture of **5** and **7**.

16α,21-Dimethyl-11β,20-bis(trimethylsiloxy)-pregna-1,4,-17(20)-trien-3-one (8). Methyllithium (1.0 M in 9:1 cumene−THF, 4.0 mL, 4.0 mmol) was added dropwise via syringe over 5 min to a stirred, ice-cooled suspension of CuCN powder (187 mg, 2.09 mmol) in THF (6.0 mL) under Ar. A yellow precipitate formed and then dissolved during the addition of the first 2.0 mmol of CH_3Li. The resulting 0.2 M solution of $(CH_3)_2Cu(CN)Li_2$ was kept in an ice bath. To a stirred, cooled (−45 °C) solution of **7** (0.395 g, 0.96 mmol) in 9.0 mL of THF under Ar was added TMSCl (0.50 mL, 4.0 mmol), followed by dropwise addition over 3 min of 5.0 mL (1.0 mmol) of the above THF solution of $(CH_3)_2Cu(CN)Li_2$. After 10 min, the mixture was quenched at −45 °C by rapid addition of a solution of 0.5 mL (12 mmol) of CH_3OH and 1.5 mL (11 mmol) of Et_3N and then warmed to 0 °C. Water and EtOAc were added, and the solution was stirred vigorously. The pH was adjusted from 9 to 7 with saturated KH_2PO_4, and stirring was continued for 0.5 h. The layers were separated, and the organic solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (40 g silica, 15% EtOAc−hexane) giving 0.41 g (85.5%) of **8** as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9H), 0.24 (s, 9H), 0.96 (d, 3H, J = 6.9), 1.01 (t, 3H, J = 7.4), 1.07 (s, 3H), 1.39 (s, 3H), 0.9−2.4 (m, 11H), 2.6 (br m, 3H), 4.38 (br s, 1H), 6.01 (s, 1H), 6.28 (dd, 1H, J = 10, 2), 7.12 (d, 1H, J = 10); $[\alpha]^{23}_D$ +65.4° (c = 0.51, $CHCl_3$). A sample was recrystallized from diisopropyl ether giving an *E*/*Z* mixture (NMR): mp 194−206 °C. Anal. Calcd for $C_{29}H_{48}O_3Si_2$: C, 69.54; H, 9.66. Found: C, 69.66; H, 9.73.

11β-(Trimethylsiloxy)-16α,17α,21-trimethylpregna-1,4-dien-3,20-dione (9). Molecular sieves (4A, $^1/_{16}$ in. spheres, 2.7 g, dried at 250 °C) and dry[19] benzyltrimethylammonium fluoride (0.8 g) were weighed under Ar (glovebag) into an oven-dried Ar-flushed 25-mL flask containing a stir bar. THF (3.0 mL) was added via syringe, and the mixture was stirred rapidly for 6 h. To the resulting paste was added via syringe a solution of **8** (47 mg, 0.094 mmol) in CH_3I (1.3 mL, 21 mmol, dried over 4A molecular sieves). After 45 min of stirring at room temperature, EtOAc was added and the suspension was filtered. The filtrate was washed with half-saturated brine, dried ($MgSO_4$), eluted through Florisil with EtOAc, and concentrated to give 46.5 mg of an oil that solidified. Crystallization from 12% EtOAc−hexanes (6 mL) at −25 °C followed by drying under vacuum at 75 °C afforded 26 mg (63%) of **9** as a white solid. A chromatographically purified sample of **9** showed the following characteristics: mp 207.5−210 °C; ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9H), 0.87 (d, 3H, J = 7.2); 0.94 (s, 6H), 1.04 (t, 3H, J = 7.1), 1.37 (s, 3H); 2.34 (q, 2H, J = 7), 1.1−2.7 (m, 11H), 3.07 (m, 1H), 4.46 (br t, 1H, J = 3), 6.00 (s, 1H), 6.27 (dd, 1H, J = 10, 2), 7.10 (d, 1H, J = 10); ^{13}C NMR ($CDCl_3$) δ 0.95, 8.17, 14.59, 17.24, 18.14, 20.45, 31.58, 32.06, 32.42, 32.65, 33.38, 33.94, 40.90, 43.90, 45.77, 50.68, 56.29, 63.67, 71.14, 122.35, 128.03, 155.38, 170.14, 186.33, 214.20; $[\alpha]^{23}_D$ +64.6° (c = 0.50, $CHCl_3$). Anal. Calcd for $C_{27}H_{42}O_3Si$: C, 73.25; H, 9.56. Found: C, 73.00; H, 9.65.

11β-Hydroxy-16α,17α,21-trimethylpregna-1,4-dien-3,20-dione (Rimexolone, 1).[2] To a stirred, ice-cooled suspension of **9** (92 mg, 0.21 mmol) in 8 mL of CH_3OH under Ar was added dropwise 0.40 mL of 6 M HCl. The mixture was allowed to warm to room temperature over 1 h, and then 2.5 mL of THF was added, whereupon the solid dissolved. After another 1.5 h, the solution was diluted with water (100 mL), and the suspension was extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give 88 mg of crude product, which was triturated twice with 5 mL of 2% ether−hexane and dried under vacuum (Abderhalden, EtOH) to give 77 mg (97%) of **1** as a white solid: mp 269−272 °C (dec), lit.[2] mp 230−273 °C (dec); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, J = 7), 0.96 (s, 3H), 1.00 (s, 3H), 1.03 (t, 3H, J = 7), 1.46 (s, 3H), 2.36 (q, 2H, J = 7), 1.1−2.7 (m, 12H), 3.05 (m, 1H), 4.48 (br t, 1H, J = 3), 6.01 (s, 1H), 6.27 (dd, 1H, J = 10, 2), 7.30 (d, 1H, J = 10); ^{13}C NMR ($CDCl_3$) δ 8.10, 14.93, 17.33, 18.44, 20.97, 31.54, 32.01, 32.62, 32.87, 33.50, 33.90, 42.79, 44.09, 45.74, 50.19, 55.49, 63.47, 70.41, 122.36, 127.88, 156.10, 170.03, 186.53, 214.65; $[\alpha]^{25}_D$ +94.1° (c = 0.50, py), lit.[2] +100° (c = 0.92, py). Anal. Calcd for $C_{24}H_{34}O_3 \cdot H_2O$: C, 74.19; H, 9.34. Found: C, 74.08; H, 8.98.

11β,17α-Diacetoxypregna-1,4-dien-3,20-dione (11). *p*-Toluenesulfonic acid monohydrate (0.03 g, 0.16 mmol) was added to a stirred solution of TFAA (1.3 mL, 9.2 mmol) in HOAc (8 mL). The solution was heated at 37 °C for 5 min. Diol **3** (0.34 g, 1.0 mmol) was added, and heating (37 °C) and stirring were continued for 5 h. The solution was poured cautiously into saturated $NaHCO_3$ (foaming, vigorous CO_2 evolution), and the product was isolated by EtOAc extraction. The EtOAc solution was washed with water and brine, dried (MgSO4), filtered, and concentrated. The crude product (0.39 g) was purified by chromatography (50% EtOAc−hexane) to remove aromatized material. The product was triturated with 1:1 ether−hexane to afford 0.17 g (40%) of **11** as a white solid: mp 233−239 °C; ^{1}H NMR (DMSO-d_6) δ 0.70 (s, 3H), 1.21 (s, 3H), 1.91 (s, 3H), 1.0−2.4 (m, 12H), 2.02 (s, 3H), 2.04 (s, 3H), 2.75 (dist t, 1H), 5.39 (br s, 1H), 5.95 (s, 1H), 6.21 (dd, 1H, J = 10, 2), 6.91 (d, 1H, J = 10); ^{13}C NMR ($CDCl_3$) δ 16.61, 20.81, 21.23, 21.87, 24.07, 26.39, 30.19, 31.77, 31.92, 33.65, 36.42, 42.97, 46.02, 51.96, 53.77, 71.18, 96.08, 123.04, 128.59, 154.27, 168.32, 169.81, 170.42, 185.96, 203.27. $[\alpha]^{23}_D$ +75.6° (c = 0.39, $CHCl_3$). Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.88; H, 7.46.

3-(11β-Acetoxy-17α-hydroxy-3-oxo-1,4-pregnadien-17β-yl)-2-butenoic Acid γ-Lactone (13). A stirred solution of **11** (68 mg, 0.16 mmol) and KOAc (0.15 g, 1.5 mmol) in anhydrous DMF (1.2 mL) was heated under Ar to 105 °C for 1.5 h and then to 120 °C for 1 h. TLC showed only starting **11**. KOAc (0.2 g, 2 mmol) was added, and heating was continued for 15 h, during which time the temperature rose to 143 °C. The cooled mixture was partitioned between EtOAc and water; the organic solution was dried ($MgSO_4$), filtered, and concentrated; and the residue was purified by flash chromatography on silica (50% EtOAc−hexanes) to afford 17.5 mg (26%) of **11**, followed by 31 mg (47.5%) of **13** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 3H), 1.28 (s, 3H), 1.1−2.7 (m, 12H), 2.10 (s, 3H), 2.13 (d, 3H, J = 1.5), 5.39 (br s, 1H), 5.50 (br q, 1H, J = 3), 5.81 (d, 1H, J = 1.5), 6.04 (s, 1H), 6.27 (dd, 1H, J = 10, 2), 6.90 (d, 1H, J = 10); ^{13}C NMR ($CDCl_3$) δ 16.47, 18.41, 20.85, 21.83, 24.31, 31.66, 31.84, 32.34, 33.40, 34.88, 42.83, 48.96, 51.57, 53.46, 71.21, 99.33, 120.15, 123.00, 128.49, 154.05, 168.00, 168.05, 169.62, 170.92, 185.89; HRMS Calcd for $C_{25}H_{30}O_5$ 410.20932, found 410.20837.

Supporting Information Available: Infrared and mass spectra (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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