JOC*Note*

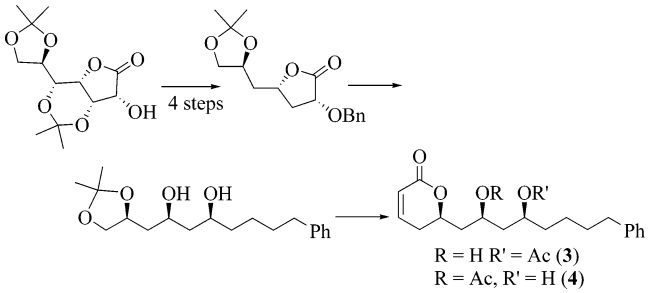
A Carbohydrate-Based Approach for the Total Synthesis of 1,3-Polyol/α-Pyrone Antifungal Natural Products

C. V. Ramana,* Burgula Srinivas, Vedavati G. Puranik, and Mukund K. Gurjar

National Chemical Laboratory, Dr. Homi Bhabha Road, Pune - 411 008, India

vr.chepuri@ncl.res.in

Received May 16, 2005



An elimination and stereoselective hydrogenation of α-D-glucoheptonic-γ-lactone derivative has been applied to prepare a differentially protected *anti*,*anti*-1,3,5-triol system, the utility of which has been extended for the total synthesis of *anti*-fungal 1,3-polyol/α-pyrone natural products.

The 5,6-dihydro-δ-pyrones with an integrated 1,3-skipped polyol system form a basic skeleton of several natural products represented by cryptocarya diacetate (**1**),[1] passifloricin (**2**),[2] 1,3-polyol/α-pyrones (**3** and **4**),[3] and strictifolione (**5**)[4] (Figure 1). The broad range of biological activities associated with these natural products was ascribed to their inherent ability to act as good Michael acceptors.[5] Natural products **3** and **4**,[3] isolated from *Ravensara anisata*, possess inhibitory activity against *C. cucumerinum* which was comparable to miconazole and propiconazole. The synthesis of **3** and **4** reported by Shibasaki and co-workers turned out to be their enantiomers.[6] Herein, we report the first synthesis of the natural occurring **3** and **4** by adopting the chiral pool approach.

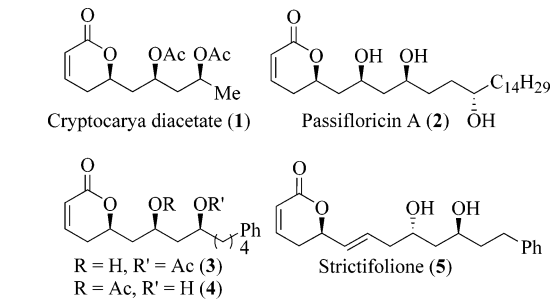


FIGURE 1. Representative skipped polyol natural products with an integrated α-pyrone moiety.

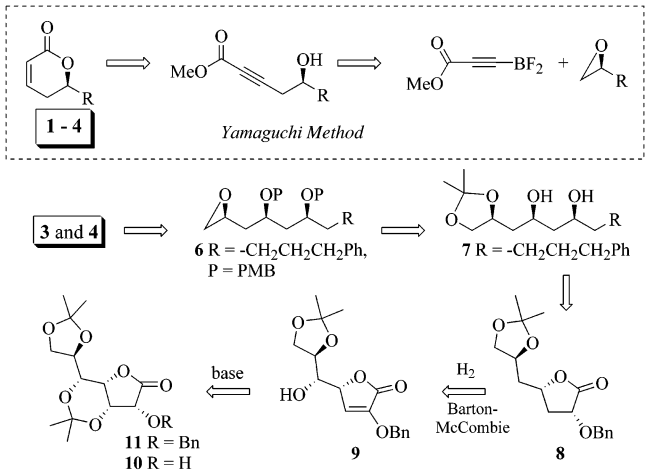


FIGURE 2. Retrosynthetic strategy for the key *syn*,*syn*-1,3,5-triol synthesis and of the α-pyrone moiety.

The structural analysis of **3** and **4** revealed that the diacetonide (**10**)[7] of commercially available α-D-glucoheptonic-γ-lactone would be an ideal starting point as depicted in Figure 2. The deoxygenation at C-3 by base-mediated elimination and stereocontrolled reduction[8] and Barton−McCombie radical deoxygenation[9] of C-5 followed by an inversion at C-4 are the key steps to secure the preparation of the key intermediate (**7**). Coupling reaction between the advanced intermediate (**6**) and methyl propiolate by the Yamaguchi method,[10] partial hydroge-

* Corresponding author. Tel: +91-20-25882456. Fax: +91-20-25893614.

(1) (a) Collett, L. A.; Davies-Coleman, M. T.; Rivett, D. E. A.; Drewes, S. E.; Horn, M. M. *Phytochemistry* **1997**, *44*, 935. (b) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777. (c) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959.

(2) (a) Echeverri, F.; Arango, V.; Quiñones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881. For synthesis, see: (b) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 7909. (c) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *J. Org. Chem*. **2004**, *69*, 7277.

(3) Andrianaivoravelona, J. O.; Sahpaz, S.; Terreaux, C.; Hostettmann, K.; Stoeckli-Evans, H.; Rasolondramanitra, J. *Phytochemistry* **1999**, *52*, 265.

(4) (a) Juliawaty, L. D.; Kitajima, M.; Takayama, H.; Achmad, S. A.; Aimi, N. *Phytochemistry* **2000**, *54*, 989. (b) Juliawaty, L. D.; Watanabe, Y.; Kitajima, M.; Achmad, S. A.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002,** *43*, 8657. (c) BouzBouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*, 1995. (d) Enders, D.; Lenzen, A.; Müller, M. *Synthesis* **2004**, 1486. (e) Ramana C. V.; Raghupathi, N.; Gurjar, M. K.; Chorghade, M. S. *Tetrahedron Lett.* **2005**, *46*, 4073.

(5) (a) Davies-Coleman, M. T.; Rivett, D. E. A. *Fortschr. Chem. Org. Naturst.* **1989**, *55*, 1. (b) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed*. **1985**, *24*, 94.

(6) Tosaki, S.-Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett*. **2003**, *5*, 495.

(7) (a) Brimacombe, J. S.; Tucker, L. C. N. *Carbohydr. Res.* **1966**, *2*, 341. (b) Shing, T. K. M.; Tsui, H. C.; Zhou, Z.-H.; Mak, T. C. W. *J. Chem. Soc*., *Perkin Trans. 1* **1992**, 887. (c) Baudat, A.; Picasso, S.; Vögel, P. *Carbohydr. Res.* **1996**, *281*, 277. (d) Xu, D. D.; Waykole, L.; Calienni, J. V.; Ciszewski, L.; Lee, G. T.; Liu, W.; Szewczyk, J.; Vargas, K.; Prasad, K.; Repiè, O.; Blacklock, T. J. *Org. Process Res.* Dev. **2003**, *7*, 856.

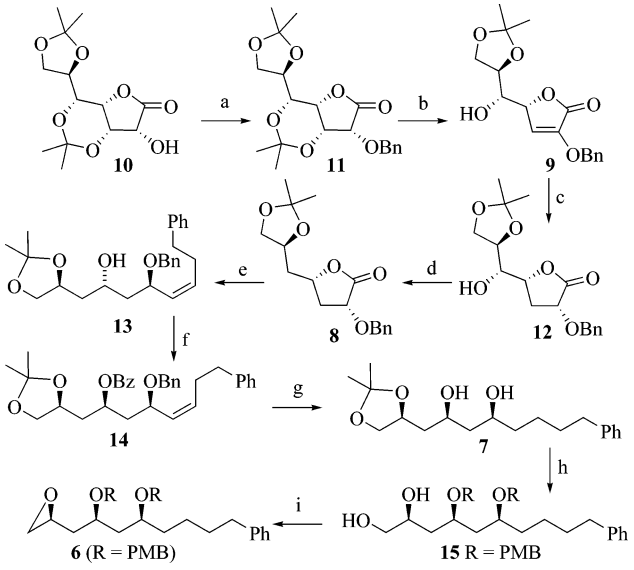
(8) Bock, K.; Lundt, I.; Pedersen, C.; Sonnichsen, R. *Carbohydr. Res*. **1988**, *174*, 331.

(9) Barton, D. H. R.; McCombie, W. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(10) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

10.1021/jo050972v CCC: $30.25
Published on Web 09/07/2005

SCHEME 1. Synthesis of the Epoxide 6[a]



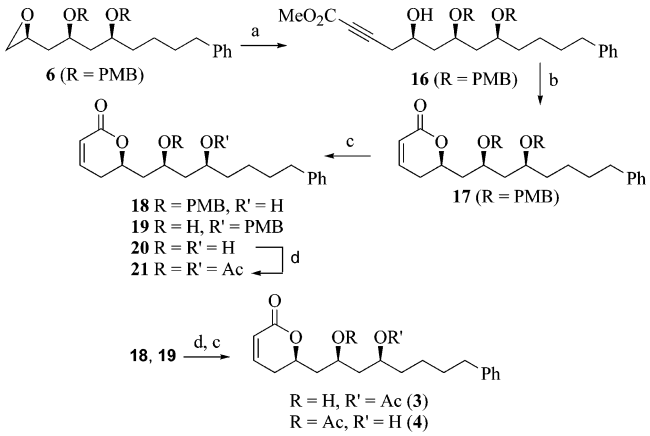
[a] Reagents and conditions: (a) Ag_2O, BnBr, CH_2Cl_2, reflux, 6 h, 84%; (b) KO-*t*-Bu, THF, −78 °C, 0.25 h, 81%; (c) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, methanol, 0 °C, 1.5 h, 61%; (d) NaH, CS_2, MeI, THF, −15 °C→rt, 12 h, 93%, followed by *n*-Bu_3SnH, AIBN, toluene, reflux, 5 h, 71%; (e) DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h, followed by $[C_6H_5CH_2CH_2CH_2PPh_3]^+I^-$, *n*-BuLi, THF, 0 °C → rt, 12 h, 93%; (f) DEAD, TPP, benzoic acid, THF, 0 °C, 2 h, 69%; (g) H_2-Raney-Ni, ethanol, 20 psi, 12 h, followed by NaOMe, MeOH, rt, 2 h, 91%; (h) NaH, PMBCl, DMF, 0°C → rt, 6 h, followed by PPTS, methanol, 24 h, 85%; (i) (i) TsCl, Bu_2SnO (cat.), triethylamine, DMAP, CH_2Cl_2, rt, 1 h, followed by (ii) K_2CO_3, MeOH, 0 °C→rt, 0.5 h, 78%.

nation, and lactonization should complete the total synthesis of the natural products **3** and **4**.

Protection of the hydroxyl group at C-2 with silver oxide and benzyl bromide gave the benzyl ether **11**. After substantial experimentation of the elimination step, we concluded that potassium *tert*-butoxide provided satisfactory yield.[7d,8] Selective conjugate reduction of the lactone **9** with −OBn intact was achieved with $NiCl_2$−$NaBH_4$.[11] The spectral and analytical data of **12** were in agreement with the assigned structure, which was further substantiated by single-crystal X-ray crystallography.[12] Subsequent reduction of **8** with DIBAL-H and Wittig olefination with 3-phenylpropyltriphenylphosphorane furnished **13**. The *Z*-configuration of **13** was evident from the coupling constant (J = 10.3 Hz). Mitsunobu reaction of **13** using DEAD and benzoic acid was facile to give the benzoate derivative **14**. Hydrogenation of the double bond present in **14** by using Raney-Ni followed by saponification with catalytic NaOMe gave the diol **7**. The diol **7** was protected with *p*-methoxybenzyl chloride−NaH, and then the 1,2-isopropylidene group hydrolyzed in the presence of PPTS in MeOH to obtain the terminal diol **15**. The primary hydroxyl group of **15** was selectively tosylated by using TsCl, Bu_2SnO, and triethylamine in dichloromethane followed by cyclization with K_2CO_3 in methanol to afford the epoxide **6** (Scheme 1).

Our next concern involved the construction of the key pyrone ring for which the lithium salt of methyl propiolate was reacted with the epoxide **6** in THF at −78 °C to furnish the β-hydroxy alkyne derivative **16**. The latter compound (**16**) was successively subjected to partial reduction in the presence of Lindlar catalyst and lactonization resulting in the formation of the α-pyrone intermediate **17**.

SCHEME 2. Total Synthesis of Anti-fungal Natural Products 3/4[a]



[a] Reagents and conditions: (a) methyl propiolate, *n*-BuLi, $BF_3 \cdot Et_2O$, THF, −78 °C, 1 h, 93%; (b) H_2, $Pd/CaCO_3$, quinoline, benzene, 1 NTP, 0.5−1 h, 72%, followed by PPTS, $CHCl_3$, reflux, 6 h, 95%; (c) TFA, DCM, 0 °C, 0.5 h, 78% (**18/19** and **20**) and 90% (**3/4**); (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 6 h, 94%.

Attempted deprotection of PMB ethers of **17** using TFA in dichloromethane provided a (1:1) regiomeric mixture of mono-PMB ethers **18** and **19** along with the diol **20**. The diol **20** was converted to the diacetate **21** which showed spectral data identical with the reported values.[7] The acetylation of **18/19** followed by treatment with TFA gave a mixture of **3** and **4** (3:1), separated by preparative HPLC. The spectral and analytical data of **3** and **4** were identical with the data reported for the natural products. Notably, a periodic examination of ^{1}H NMR spectra of pure isomers **3** and **4** indicated the migratory aptitudes of acetyl group in these compounds, however with different rate of migration. For example, the interconversion of **4** → **3** was substantially faster than **3** → **4** (Scheme 2).

In summary, we report a simple strategy for the synthesis of *anti*,*anti*- and *syn*,*syn*-1,3,5-polyol systems using a chiral pool approach. This study enabled us to carry out the first total synthesis of antifungal natural 1,3-polyol/α-pyrones **3** and **4**.

Experimental Section

2-Benzyloxy-3-deoxy-6,7-*O*-isopropylidine-D-*arabino*-hept-2-enoic-γ-lactone (9). At −78 °C, a suspension of KO-*t*-Bu (1.48 g, 13.2 mmol) in anhydrous THF (50 mL) was treated with a solution of **11** (5 g, 13.2 mmol) in anhydrous THF (80 mL) and stirred for 15 min at −78 °C. The reaction mixture was quenched with a solution of acetic acid (0.8 mL, 13.2 mmol) in THF (5 mL) and allowed to reach rt. The contents were filtered (Celite) and concentrated, and the crude product was purified by crystallization from ethyl acetate/hexane (1:3) to procure **9** (3.43 g, 81%) as a colorless solid. Mp: 162 °C. $[\alpha]^{25}_D$ = +31.7 (c = 1, $CHCl_3$). IR ($CHCl_3$): ν 3420, 3020, 2400, 1760, 1652, 1381, 1215, 1059, 756, 668 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.40−7.36 (m, 5H), 6.17 (d, J = 2.1 Hz, 1H), 5.09 (dd, J = 4.1, 2.1 Hz, 1H), 5.02 (s, 2H), 4.16 (dd, J = 6.2, 4.1 Hz, 1H), 4.12 (dt, J = 6.2, 3.5 Hz, 1H), 3.99 (dd, J = 7.6, 3.5 Hz, 1H), 3.55 (dd, J =

(11) (a) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817. (b) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996,** *61,* 8356.

(12) G. M. Sheldrick, SHELX-97 Program for Crystal Structure Solution and Refinement, University of Gottingen, Germany, 1997.

7.6, 4.1 Hz, 1H), 2.40 (br.s, 1H), 1.37 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (50 MHz) δ: 25.1 (q), 26.7 (q), 67.1 (t), 72.8 (t), 73.1 (d), 75.3 (d), 79.5 (d), 109.7 (s), 115.9 (d), 127.6 (d), 128.5 (d), 128.6 (d), 134.7 (s), 145.9 (s), 167.8 (s) ppm. Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.80; H, 6.03.

2-*O*-Benzyl-3-deoxy-6,7-*O*-isopropylidine-D-*gluco*-heptoic-γ-lactone (12). At 0 °C, a solution of **9** (1 g, 3.1 mmol) in methanol (30 mL) was treated with $NiCl_2 \cdot 6H_2O$ (220 mg, 0.9 mmol) and stirred for 30 min. To this solution were added $NaBH_4$ (342 mg, 9.1 mmol) and acetic acid (to maintain pH = 7) in three portions during a 10 min interval. After the addition was complete, stirring was continued for another 30 min at 0 °C. The contents were filtered (Celite), concentrated, dissolved in ethyl acetate (25 mL), washed with water and brine, dried (Na_2SO_4), and concentrated to get a white solid. The crude product was purified by crystallization in CH_2Cl_2/hexane to get a white crystalline solid **12** (615 mg, 61%). Mp: 116 °C. $[\alpha]^{25}_D$ = +32.4 (c = 1, $CHCl_3$). IR ($CHCl_3$): ν 3442, 2992, 2881, 1787, 1455, 1370, 1216, 848, 755 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.38−7.32 (m, 5H), 4.96 (d, J = 11.8 Hz, 1H), 4.75 (d, J = 11.8 Hz, 1H), 4.59 (ddd, J = 8.9, 6.4, 2.9 Hz, 1H), 4.24 (dd, J = 9.2, 8.4 Hz, 1H), 4.19−3.96 (m, 3H), 3.45 (br.d, J = 4.4 Hz, 1H), 2.51 (ddd, J = 13.1, 8.3, 6.4 Hz, 1H), 2.30 (dt, J = 13.1, 9.1 Hz, 1H), 1.38 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (75 MHz) δ: 25.1 (q), 26.7 (q), 31.1 (t), 67.2 (t), 72.1 (t), 72.9 (d), 73.2 (d), 75.3 (d), 76.4 (d), 109.4 (s), 128.0 (d), 128.4 (d), 136.9 (s), 174.5 (s) ppm. Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.38; H, 7.14.

Crystal Data. A colorless platelike crystal of approximate size 0.48 × 0.24 × 0.02 mm was used for data collection on a Bruker SMART APEX CCD diffractometer using Mo Kα radiation with fine focus tube with 50 kV and 30 mA. Crystal to detector distance 6.05 cm, 512 × 512 pixels/frame, multiscan data acquisition. Total scans = 3, total frames = 1212, oscillation/frame −0.3°, exposure/frame = 10.0 s/frame, maximum detector swing angle = −30.0°, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.52−25.0°, completeness to θ of 23.33° is 99.2%. SADABS correction applied, $C_{17}H_{22}O_6$, M = 322.35. Crystals belong to monoclinic, space group $P2_1$, a = 9.195(1) Å, b = 6.1777(8) Å, c = 15.004(2) Å, β = 93.846(2)°, V = 850.4 (2) Å^3, Z = 2, D_c = 1.259 mg m^{-3}, μ (Mo Kα) = 0.095 mm^{-1}, T = 295(2) K, 4283 reflections measured, 2795 unique [$I > 2\sigma(I)$], R value 0.0594, wR2 = 0.1375. All of the data were corrected for Lorentzian, polarization, and absorption effects. SHELX-97 (ShelxTL)[12] was used for structure solution and full-matrix least-squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

Treatment of Epoxide 6 with Methyl Propiolate. Methyl propiolate (590 μL, 6.6 mmol) was taken in a flame-dried two-neck round-bottom flask (50 mL) and dissolved in anhydrous THF (15 mL). The reaction mixture was cooled to −78 °C, treated with n-BuLi (4.2 mL, 6.64 mmol, 1.6 M in hexane) dropwise, stirred for 15 min, treated with $BF_3 \cdot Et_2O$ (0.84 mL, 6.6 mmol), and stirred for an additional 15 min. Once the formation of dark black alkyne borane was observed, a solution of epoxide **6** (335 mg, 0.66 mmol) in anhydrous THF (10 mL) was added and stirred for 30 min at −78 °C. The reaction was quenched at −78 °C by addition of satd Na_2SO_4 (20 mL) and taken in ethyl acetate−water, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Purification by column chromatography (20% ethyl acetate in petroleum ether) gave **16** (365 mg, 93%). $[\alpha]^{25}_D$ = +56.7 (c = 1, $CHCl_3$). IR ($CHCl_3$): ν 3457, 3011, 2936, 2859, 2238, 1714, 1612, 1586, 1513, 1454, 1435, 1302, 1250, 1075, 1035, 822, 755, 667 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.31−7.14 (m, 9H), 6.83 (br.d, J = 8.4 Hz, 4H), 4.52 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 11.2 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.27 (d, J = 11.2 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.90−3.73 (m, 2H), 3.71 (s, 3H), 3.44−3.33 (m, 1H), 2.66−2.58 (t, J = 7.5 Hz, 2H), 2.47−2.26 (m, 2H), 2.03−1.90 (m, 1H), 1.71−1.33 (m, 10H). ^{13}C NMR (50 MHz) δ: 24.6 (t), 27.3 (t), 31.6 (t), 33.9 (t), 35.9 (t), 38.3 (t), 39.9 (t), 52.4 (q), 55.1 (q), 69.3 (d), 70.0 (t), 70.5 (t), 74.5 (s), 74.8 (d), 76.4 (d), 86.2 (s), 113.7 (d), 113.9 (d), 125.7 (d), 128.3 (d), 128.4 (d), 129.6 (d), 129.7 (d), 130.5 (s), 142.3 (s), 153.8 (s), 159.2 (s), 159.4 (s) ppm. Anal. Calcd for $C_{36}H_{44}O_7$: C, 73.44; H, 7.53. Found: C, 73.14; H, 7.80.

PMB Deprotection of 17. A solution of compound **17** (145 mg, 0.26 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with TFA (50 μL) and stirred for 30 min at 0 °C. The reaction was quenched by addition of saturated bicarbonate solution, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (40% → 50% ethyl acetate in petroleum ether) to afford a 1:1 mixture of alcohols **18** and **19** (61 mg, 54%) and diol **20** (20 mg, 24%).

Data for 18 and 19. $[\alpha]^{25}_D$ = +54.8 (c = 1, $CHCl_3$). IR ($CHCl_3$): ν 3462, 3019, 2937, 2860, 1719, 1612, 1514, 1454, 1390, 1251, 1215, 1035, 757, 668 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.19−7.07 (m, 7H), 6.82−6.70 (m, 3H), 5.96−5.88 (m, 1H), 4.59−4.21 (m, 3H), 3.92−3.77 (m, 1H), 3.71 (s, 3H), 3.68−3.54 (m, 1H), 2.59−2.49 (m, 2H), 2.33−2.18 (m, 2H), 2.14−1.67 (m, 2H), 1.67−1.45 (m, 6H), 1.41−1.28 (m, 3H). ^{13}C NMR (50 MHz) δ: 24.1 (t), 25.1 (t), 29.1 (t), 29.7 (t), 31.5 (t), 31.6 (t), 33.1 (t), 35.8 (t), 35.9 (t), 37.6 (t), 38.8 (t), 40.7 (t), 41.8 (t), 55.1 (q), 68.0 (d), 70.2 (t), 70.4 (t), 70.6 (d), 74.7 (d), 75.2 (d), 75.5 (d), 79.5 (d), 113.9 (d), 121.2 (d), 121.4 (d), 125.6 (d), 125.7 (d), 128.2 (d), 128.3 (d), 129.5 (d), 129.6 (d), 129.8 (s), 142.2 (s), 142.5 (s), 144.8 (d), 145.2 (d), 159.3 (s), 159.4 (s), 163.9 (s), 164.3 (s) ppm. Anal. Calcd for $C_{27}H_{34}O_5$: C, 73.94; H, 7.81. Found: C, 74.05; H, 7.63.

Data of Diol 20. $[\alpha]^{25}_D$ = +62.1 (c = 1, $CHCl_3$). IR ($CHCl_3$): ν 3684, 3020, 2934, 1725, 1522, 1476, 1215, 1055, 759, 669 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.30−7.11 (m, 5H), 6.89 (dt, J = 9.8, 4.5, 3.8 Hz, 1H), 6.02 (dt, J = 9.8, 1.8 Hz, 1H), 4.72−4.57 (br.ddt, J = 8.9, 7.5, 5.5 Hz, 1H), 4.15−4.03 (m, 1H), 3.90−3.79 (m, 1H), 3.50 (b, 2H), 2.62 (t, J = 7.5 Hz, 2H), 2.45−2.39 (m, 2H), 2.08−1.94 (m, 1H), 1.81−1.32 (m, 9H). ^{13}C NMR (50 MHz) δ: 24.9 (t), 29.4 (t), 31.4 (t), 35.8 (t), 38.1 (t), 42.3 (t), 42.7 (t), 69.5 (d), 72.7 (d), 76.2 (d), 121.2 (d), 125.7 (d), 128.2 (d), 128.3 (d), 142.4 (s), 145.4 (d), 164.2 (s) ppm. Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.66; H, 8.23. Found: C, 71.39; H, 8.81.

Diacetate 21. Treatment of **20** (29 mg, 0.09 mmol) in CH_2Cl_2 (6 mL) with Ac_2O (85 μL, 0.91 mmol), triethylamine (126 μL, 0.91 mmol), and DMAP (5 mg) and usual workup after 6 h of stirring followed by purification by column chromatography (30% ethyl acetate in petroleum ether) gave **21** (34 mg, 94%) as a yellow oil: $[\alpha]^{25}_D$ = +48.6 (c = 1, $CHCl_3$). IR ($CHCl_3$): ν 3020, 2936, 2861, 1730, 1496, 1374, 1242, 1216, 1152, 1038, 758, 668 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28−7.25 (m, 2H), 7.18−7.15 (m, 3H), 6.87−6.84 (m, 1H), 6.02−6.00 (dd, J = 9.7, 1.9 Hz, 1H), 5.07−5.02 (m, 1H), 4.95−4.90 (m, 1H), 4.50−4.45 (m, 1H), 2.61−2.58 (t, J = 7.5 Hz, 2H), 2.46−2.40 (m, 1H), 2.33−2.27 (m, 1H), 2.16−2.10 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.99−1.89 (m, 2H), 1.84−1.79 (m, 1H), 1.66−1.57 (m, 4H), 1.39−1.28 (m, 2H). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 21.1 (q), 24.6 (t), 29.1 (t), 31.0 (t), 34.1 (t), 35.6 (t), 38.9 (t), 38.9 (t), 67.8 (d), 70.8 (d), 74.9 (d), 121.3 (d), 125.7 (d), 128.2 (d), 128.4 (d), 142.3 (s), 144.7 (d), 163.7 (s), 170.6 (s), 170.8 (s) ppm. MALDI-TOF (MS): calcd for $C_{23}H_{30}O_6Na$ 425.19, found 425.19 (M + Na). Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.89; H, 7.61.

Synthesis of α-Pyrone Natural Products 3 and 4. In a manner similar to that used in the deprotection of **17**, treatment of **18**-Ac/**19**-Ac (58 mg, 0.12 mmol) in CH_2Cl_2 (6 mL) with TFA (20 μL), stirring at 0 °C for 30 min, usual workup, and purification by column chromatography (40% ethyl acetate in petroleum ether) gave an equilibrium mixture of natural regioisomers **3** and **4** (39 mg, 90%) as a yellow oil. $[\alpha]^{25}_D$ = +39 (c = 0.4, MeOH) [lit.[3] $[\alpha]^{25}_D$ = +35 (c = 0.05, MeOH)]. IR ($CHCl_3$): ν 3440, 3019, 2934, 2859, 1724, 1513, 1496, 1384, 1250, 1216, 1043, 757, 668 cm^{-1}. MALDI-TOF (MS): calcd for $C_{21}H_{28}O_5Na$ 383.18, found 383.17 (M + Na). Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.79; H, 7.96.

A portion of the **3/4** mixture was subjected to preparative HPLC separation, and the ^{1}H and ^{13}C NMR of the separated **3** and **4** were recorded. In case of the minor isomer **4**, we found the equilibration is facile and the difference in the ratio of **4/3** changed from 1:0.14 (^{1}H NMR) to ∼1:0.75 (^{13}C NMR), the later being recorded overnight.

Major Isomer 3. $[\alpha]^{25}_D = +33$ ($c = 0.3$, MeOH) [lit.[4] $[\alpha]^{25}_D = +35$ ($c = 0.05$, MeOH)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27−7.24 (m, 2H), 7.18−7.14 (m, 3H), 6.87 (dt, $J = 9.8$, 4.2 Hz, 1H), 6.01 (br dt, $J = 9.5$, 1.7 Hz, 1H), 4.97−4.92 (m, 1H), 4.66−4.60 (m, 1H), 3.90−3.86 (m, 1H), 2.59 (t, $J = 7.5$ Hz, 2H), 2.40−2.37 (m, 2H), 2.02 (s, 3H),1.95−1.41 (m, 10H). ^{13}C NMR (125 MHz) δ: 21.3 (q), 24.8 (t), 29.4 (t), 31.1 (t), 34.5 (t), 35.7 (t), 41.7 (t), 42.3 (t), 67.0 (d), 72.3 (d), 76.6 (d), 121.2 (d), 125.7 (d), 128.3 (d), 128.4 (d), 142.3 (s), 145.2 (d), 163.9 (s), 171.3 (s) ppm.

Minor Isomer 4. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27−7.24 (m, 2H), 7.18−7.14 (m, 3H), 6.87−6.84 (ddd, $J = 9.7$, 6.1, 2.4 Hz, 1H), 6.01 (ddd, $J = 9.7$, 2.6, 0.7 Hz, 1H), 5.24−5.19 (m, 1H), 4.54−4.48 (m, 1H), 3.72−3.67 (m, 1H), 2.61 (t, $J = 7.5$ Hz, 2H), 2.48−2.43 (m, 1H), 2.34−2.26 (m, 1H), 2.18 (ddd, $J = 14.6$, 8.4, 6.3 Hz, 1H), 2.05 (s, 3H), 1.95 (ddd, $J = 14.6$, 6.8, 4 Hz, 1H), 1.82−1.71 (m, 2H), 1.66−1.42 (m, 6H). ^{13}C NMR (125 MHz) δ: 21.3 (q), 25.0 (t), 29.2 (t), 31.3 (t), 35.8 (t), 37.7 (t), 39.3 (t), 41.7 (t), 69.0 (d), 69.2 (d), 75.1 (d), 121.4 (d), 125.7 (d), 128.3 (d), 128.4-(d), 142.4(s), 144.7 (d), 163.9 (s), 170.9 (s).

Acknowledgment. B.S. thanks CSIR, New Delhi, for the financial assistance in the form of a research fellowship.

Supporting Information Available: Experimental procedures and spectral and analytical data for all new compounds (**3/4**, **6**−**21**), representative ^{1}H, ^{13}C, and DEPT spectra (**3/4**, **6**−**8**, **12**, **13**, **17**, **20**, and **21**), and crystallographic information file (CIF) of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050972V