Total Synthesis of (+)-Dihydrocompactin[1]

Yuh-Lin Yang, Sukumar Manna, and J. R. Falck*

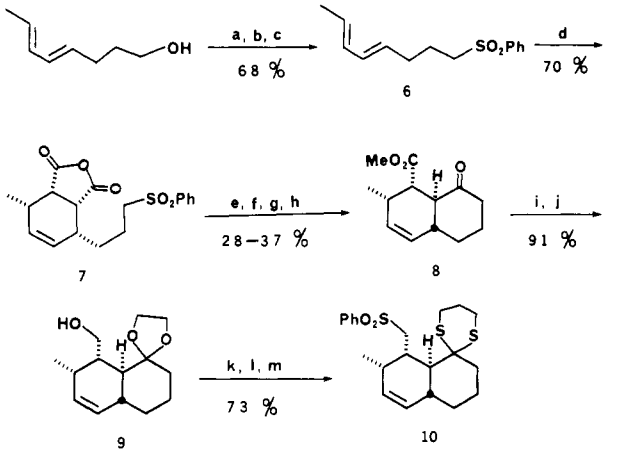
Contribution from the Department of Molecular Genetics, University of Texas Health Science Center at Dallas, Dallas, Texas 75235. *Received December 8, 1983*

Abstract: The potent hypocholesterolemic agent (+)-dihydrocompactin was synthesized by union of the masked lactone **5**, ultimately derived from a carbohydrate precursor with the requisite absolute configuration, and hydronaphthalene **10**, which was obtained from maleic anhydride Diels–Alder adduct **7** by intramolecular sulfone acylation. Extension of this sequence to the hydronaphthalene portion of dihydromevinolin is also described.

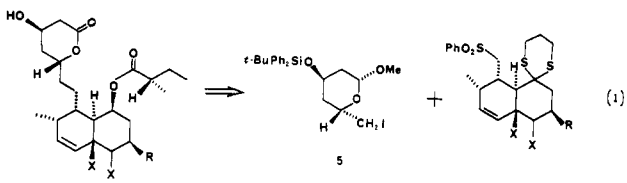
The mevinic acids[2–5] constitute a family of fungal metabolites distinguished by a highly functionalized hexa- or octahydronaphthalene bearing an ethylene-linked β-hydroxy-δ-lactone appendage. The two most prominent mevinic acids, compactin[2] (**1**) and mevinolin[3] (**2**), have attracted much attention[6,7] as hypocholesterolemic agents because of their low toxicity and extremely potent competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase,[8] the rate limiting enzyme in cholesterol biosynthesis. In contrast, their equally potent congeners dihydrocompactin[4] (**3**) and dihydromevinolin[5] (**4**) have been less well studied, due in part to limited availability from natural sources. Disclosed herein is the first total synthesis of (+)-dihydrocompactin by a convergent approach that is adaptable to the preparation of other mevinates and their metabolites.[9]

The overall strategy involves joining a masked form of the common β-hydroxy-lactone appendage to an appropriate hydronaphthalene via the ethylene bridge (eq 1). An added benefit of this approach is the opportunity for independent pharmacological evaluation[7a–c] of the two major fragments. We have previously prepared **5** in the requisite absolute configuration from a carbohydrate precursor and applied it in the synthesis of several mevinate analogues.[7a]

Scheme I[a]



[a] a: TsCl, py. b: NaSPh, MeOH, 2 h. c: 2 equiv CH_3CO_3H, EtOAc, −20 → 0 °C over 2 h. d: maleic anhydride, PhH, 80 °C, 24 h. e: 2 equiv $LiN(SiMe_3)_2$, THF, −78 °C, 5 days, then −40 °C, 8 h. f: CH_2N_2. g: Al(Hg), THF/H_2O 10:1, 3 h. h: NaOMe, MeOH, 40 °C, 24 h. i: $(HOCH_2)_2$, TsOH, PhH, 80 °C, 72 h. j: $LiAlH_4$, THF, room temperature, 2 h. k: Me_3SiCl, NaI, CH_3CN, 1 h. l: $PhSO_2$-Amberlyst A-26, PhH, 80 °C, 3 h. m: $HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 15 h.



1 Compactin: R = H, X = $\Delta^{4a,5}$ 3 Dihydrocompactin: R = X = H
2 Mevinolin: R = Me, X = $\Delta^{4a,5}$ 4 Dihydromevinolin: R = Me, X = H

Construction of the octahydronaphthalene fragment of **3** (Scheme I) commenced with (*E,E*)-octa-4,6-dien-1-ol[10] which was converted to oily sulfone **6** (68%) by sequential tosylation, sodium thiophenoxide displacement, and peracetic acid oxidation. Diels-Alder cyclization with 1 equiv of maleic anhydride in benzene under reflux (24 h) afforded crystalline endo adduct **7** (70%). Intramolecular acylation under carefully controlled conditions using 2 equiv of lithium bis(trimethylsilyl)amide resulted in a mixture of cis- and trans-fused octalones which were purified chromatographically after esterification (CH_2N_2) and aluminum amalgam desulfonylation (30–40% from **7**). Methoxide mediated equilibration[11] gave ketoester **8** (92%) as the exclusive isomer as judged by NMR and chromatographic analysis. The identity of

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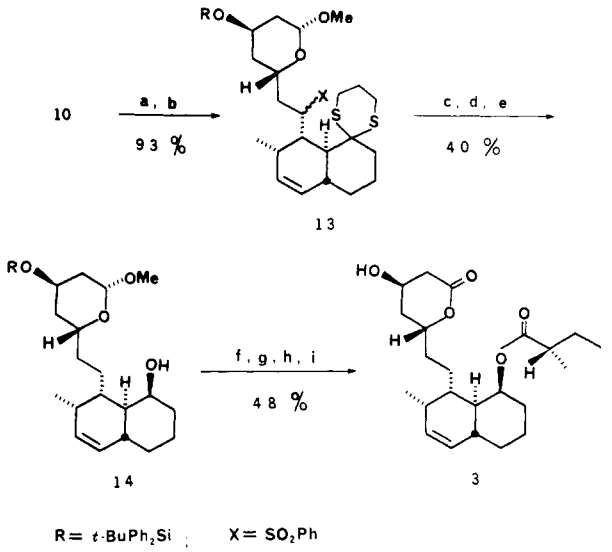
Scheme II[a]



[a] a: 2 equiv BuLi, 20% HMPA/THF, 0 °C, 30 min. b: 5, THF, −78 °C, warm to room temperature, 4 h. c: $HgCl_2$, $CaCO_3$, CH_3CN/H_2O 4:1, 80 °C, 7 h. d: 6% Na(Hg), MeOH, 2 h. e: Li(*sec*-Bu)$_3$BH, THF, 0 °C, 1 h. f: (*S*)-(+)-$CH_3CH_2CH(CH_3)CO_2H$, DCC, DMAP, CH_2Cl_2, 24 h. g: 10% HCl/THF 3:5, 45 °C, 3.5 h. h: PCC-Al_2O_3, CH_2Cl_2. 8 h. i: 48% HF/CH_3CN 1:10, 45 °C, 6 h.

8 was confirmed by lithium aluminum hydride (LiAlH) reduction to diol **11**, identical in all respects with an authentic sample[7f] (mixture mp 78–79 °C). Funk and Zeller have transformed[7f] the primary *tert*-butyldimethylsilyl ether of **11** to **12**, thus offering, in principle, access to the diene mevinates, e.g., **1** and **2**.

11 12

Ketalization of **8** and LiAlH reduction evolved alcohol **9** (91%); however, this alcohol proved unsatisfactory for the preparation of lithium or Grignard reagents by way of the corresponding bromide and iodide. Consequently, **9** was converted to sulfone **10** (73%) by simultaneous ketal cleavage and alcohol–iodide interchange using in situ generated trimethylsilyl iodide[12] (Me_3SiCl/NaI), sulfonylation with benzenesulfinate anion supported on Amberlyst A-26,[13] and boron trifluoride etherate catalyzed thioketalization.

Union of the *dianion*[14,15] of racemic **10** with iodide **5**[7a] secured **13** (93% based on recovered **10**) as a diastereomeric mixture (Scheme II). Selective mercuric chloride hydrolysis[16] of the dithiane in the presence of calcium carbonate followed by sodium amalgam excision[17] of the phenylsulfone and stereospecific ketone reduction[7e] resulted in **14** (40–60%) and an equal amount of diastereomer. Catalytic hydrogenation[7i] of **14** gave rise to a single product spectrally and chromatographically indistinguishable from the major hydrogenation product of degraded natural compactin.[18]

Final elaboration of **14** required *N,N'*-dicyclohexylcarbodiimide (DCC) esterification with (*S*)-(+)-2-methylbutyric acid (Aldrich), acidic methyl lactol hydrolysis, oxidation to the corresponding lactone by pyridinium chlorochromate (PCC) suspended on alumina,[19] and hydrofluoric acid desilylation[7a] yielding **3**, whose 360-MHz ^1H NMR was superimposable with the spectrum of natural material.[20,21]

Repetition of the sequence in Scheme I using the sulfoxide related to **6** and thermal dehydrosulfenylation[22] ($P(OMe)_3$, CCl_4, 55 °C) following intramolecular acylation afforded mainly cis-fused dienone **15** (eq 2). Smooth conjugate addition of methyl

15 16

cuprate (0 °C, Et_2O, 30 min) and sodium methoxide catalyzed equilibration yielded **16** exclusively,[11] suitable for the preparation of dihydromevinolin (**4**). The application of this basic theme to the total synthesis of other mevinates and some key metabolites will be described in due course.

Experimental Section

General. ^1H NMR spectra were measured at 90 MHz in $CDCl_3$ on a JEOL FX90Q spectrometer with tetramethylsilane as internal standard. Chemical shift values are reported as ppm on the δ scale. Low-resolution mass spectra were obtained by chemical ionization with CH_4 as reagent gas on a Finnigan 4021 spectrometer and high-resolution spectra on a MAT-711. Optical rotations were recorded on a Perkin-Elmer 241 MC polarimeter. Melting point determinations were performed with an Electrothermal melting point apparatus and are corrected.

(*E,E*)-Octa-4,6-dien-1-ol. A Me_2SO (250 mL) solution of dimethyl 2,4-hexadienylmalonate[23] (32.44 g, 0.153 mol) and sodium cyanide[24] (11.3 g, 0.23 mol) was heated at 120 °C for 3 h, cooled, poured onto ice, and extracted with hexanes. The organic extract was washed with H_2O and brine and dried over Na_2SO_4, and the solvent was removed leaving methyl 4,6-octadienoate (17.7 g, 75%) which was used without further purification.

The above ester (17 g, 0.11 mol) in dry THF (10 mL) was added dropwise to a 0 °C suspension of LiAlH (4.2 g, 0.11 mol) in THF (300 mL). After 1 h, the reaction was quenched by sequential addition of H_2O (4.2 mL), 15% NaOH solution (4.2 mL), and H_2O (12.6 mL). Filtration and evaporation of the solvent gave (*E,E*)-octa-4,6-dien-1-ol (13.8 g, 99%): bp[10] 105–106 °C (18 mm Hg); NMR 1.70 (3 H, d, $J \sim 7$ Hz), 1.40–1.80 (2 H, m), 2.12 (2 H, q, $J \sim 7.2$ Hz), 3.60 (2 H, t, $J \sim 7.2$ Hz), 5.20–6.20 (4 H, m).

(*E,E*)-4,6-Octadienyl Phenyl Sulfone (6). (*E,E*)-Octa-4,6-dien-1-ol (15 g, 0.119 mol) was treated with tosyl chloride (27.3 g, 0.143 mol) in dry pyridine (50 mL) at 5 °C. After 15 h, the mixture was diluted with H_2O and extracted with Et_2O. The ethereal layer was washed with 1 N HCl and brine, dried, and evaporated to give 31.2 g (95%) of crude tosylate which was used without further purification.

The above tosylate (31.2 g, 0.11 mol) in MeOH (10 mL) was added dropwise with stirring to a methanolic solution of sodium thiophenoxide prepared by addition of thiophenol (18.4 g, 0.167 mol) to a solution of NaOMe (9.0 g, 0.167 mol) in anhydrous methanol (300 mL). The

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methanol was evaporated after 2 h and the residue dissolved in Et_2O and washed with 5% NaOH solution, H_2O, and brine. Evaporation afforded phenyl sulfide (22.48 g, 94%): TLC, SiO_2, 1:1 Et_2O/hexane, $R_f \sim 0.80$; NMR 1.70 (3 H, d, $J \sim 7$ Hz), 1.50–1.90 (2 H, m), 2.18 (2 H, q, $J \sim 7.2$ Hz), 2.88 (2 H, t, $J \sim 7.2$ Hz), 5.20–6.20 (4 H, m), 7.00–7.50 (5 H, m).

To a −20 °C solution of the above sulfide (16.3 g, 0.07 mol) in EtOAc (80 mL) was added dropwise 40% peracetic acid in EtOAc (39.4 mL, 0.187 mol, FMC Corp.) The mixture was warmed to 0 °C over 2 h and then quenched with saturated Na_2SO_3 solution, diluted with brine, and extracted with CH_2Cl_2. The organic extract was washed with saturated $NaHCO_3$ solution and brine and evaporated and the residue purified by column chromatography (SiO_2, 2:1 hexane/EtOAc) to furnish oily sulfone **6** (14 g, 75%): TLC, SiO_2, 1:1 Et_2O/hexanes, $R_f \sim 0.29$; NMR 1.70 (3 H, d, $J \sim 7$ Hz), 1.50–2.00 (2 H, m), 2.10 (2 H, q, $J \sim 7.2$ Hz), 2.90–3.10 (2 H, m), 5.10–6.10 (4 H, m), 7.30–7.60 (3 H, m), 7.62–7.90 (2 H, m); high-resolution mass spectrum calcd for $C_{14}H_{18}O_2S$ 250.1028, found 250.1039.

Diels–Alder Adduct 7. A mixture of **6** (5 g, 20 mmol) and maleic anhydride (2 g, 20 mmol) was dried azeotropically with anhydrous benzene and then heated under reflux in dry benzene for 24 h during which time a white precipitate collected. The reaction mixture was chilled (4 °C) overnight and the white solid collected by filtration to afford adduct **7** (3.5 g, 50%), mp 172–173 °C (CH_2Cl_2/Et_2O). Chromatography of the mother liquor gave an additional 1.4 g (20%) of **7**: NMR 1.44 (3 H, d, $J \sim 7$ Hz), 1.70–2.00 (4 H, m), 2.00–2.60 (2 H, m), 2.90–3.40 (4 H, m), 5.50–5.90 (2 H, m), 7.40–7.70 (3 H, m), 7.70–8.00 (2 H, m); mass spectrum *m/e* (%) 349 ($M^+ + 1$, 85), 303 (23), 275 (36), 209 (54), 207 (65), 179 (23), 157 (24), 143 (29), 135 (44), 125 (23), 111 (100), 109 (49), 99 (35), 93 (28), 85 (45), 83 (77); high-resolution mass spectrum calcd for $C_{18}H_{20}O_5S$ 348.1032, found 348.1025.

Octalone 8. Adduct **7** (4.0 g, 11.5 mmol) was dried by stirring it with hexamethyldisilazane (2 mL) in dry CH_2Cl_2 (100 mL) for 30 min and removing the solvent and excess hexamethyldisilazane under reduced pressure. After a second treatment, the resulting solid was dried in vacuo for 30 min, dissolved in anhydrous THF (120 mL), and cooled to −78 °C. To this was added a 1 M solution of lithium bis(trimethylsilyl)amide (23 mL, 23 mmol) in THF and the resulting deep orange solution maintained at −75 °C for 5 days and then at −40 °C for 8 h. Upon quenching with saturated NH_4Cl solution and acidification with 1 N hydrochloric acid to pH 3, the mixture was saturated with NaCl. Extractive isolation (CH_2Cl_2) gave ~4 g of crude product which as esterified with excess diazomethane. Reduction with freshly prepared aluminum amalgam[25] (4 g, 148 mmol) in THF (100 mL) and H_2O (10 mL) for 3 h, filtration through a Celite bed, and evaporation gave ~2.5 g of crude material which was purified by chromatography (SiO_2, 1:1 Et_2O/hexane) yielding a mixture of cis- and trans-fused octalones (933 mg, 40%). Equilibration in MeOH (15 mL) at 40 °C for 24 h in the presence of a catalytic amount of NaOMe produced **8** (858 mg, 92%) as the sole isomer after solvent evaporation and extractive isolation: TLC, SiO_2, 1:1 Et_2O/hexane, $R_f \sim 0.34$; NMR 0.88 (3 H, d, $J \sim 7$ Hz), 1.40–3.00 (10 H, m), 3.64 (s, 3 H), 5.44 (1 H, br d, $J \sim 10$ Hz), 5.50–5.57 (1 H, m); mass spectrum *m/e* (%) 223 ($M^+ + 1$, 8), 205 (19), 191 (100), 177 (5), 161 (9), 149 (5), 85 (3); high-resolution mass spectrum calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1270; free acid mp 173–174 °C (Et_2O/hexane).

Ketal 9. Octalone **8** (610 mg, 2.75 mmol) was heated for 3 days in benzene (20 mL) under reflux with ethylene glycol (256 mg, 4.12 mmol) and a catalytic amount of tosic acid using a Dean-Stark apparatus filled with 4A molecular sieves for water removal. Washing with saturated $NaHCO_3$ solution and brine and evaporation gave 730 mg (100%) of ketal ester: TLC, SiO_2, 1:20 EtOAc/PhH, $R_f \sim 0.18$; NMR 1.04 (3 H, d, $J \sim 7$ Hz), 1.10–2.90 (10 H, m), 3.60 (3 H, s), 3.70–4.00 (4 H, m), 5.32–5.64 (2 H, m). The above ketal was treated with LiAlH (120 mg, 3.16 mmol) in THF (10 mL) for 2 h. Quenching and isolation as described previously yielded ketal **9** (595 mg, 91%): mp 132–133 °C (Et_2O/hexane); TLC, SiO_2, 1:1 Et_2O/hexane, $R_f \sim 0.17$; NMR 1.06 (3 H, d, $J \sim 7$ Hz), 1.20–2.60 (10 H, m), 3.08 (1 H, dd, $J \sim 4$, 8 Hz), 3.36–3.90 (2 H, m), 3.80–4.20 (4 H, m), 5.32 (1 H, br d, $J \sim 10$ Hz), 5.52 (1 H, ddd, $J \sim 2.5$, 4.5, 10 Hz); mass spectrum *m/e* (%) 239 ($M^+ + 1$, 1), 249 ($M^+ - 18 + 29$, 10), 217 (24), 205 ($M^+ - 33$, 32), 177 (100), 145 (15), 133 (51), 131 (47), 105 (84), 87 (11); high-resolution mass spectrum calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1573.

Sulfone 10. Trimethylsilyl chloride (652 mg, 6 mmol) was added dropwise to a solution of **9** (335 mg, 1.4 mmol) and sodium iodide (900 mg, 6 mmol) in acetonitrile (10 mL). After 1 h, H_2O was added and the mixture extracted with Et_2O. The combined ethereal extracts were washed successively with H_2O, 10% sodium thiosulfate solution, and brine. Evaporation furnished keto iodide as a single product which was immediately treated with benzenesulfinate anion supported on Amberlyst A-26[13] (3.5 mequiv/g, 0.8 g) in benzene under reflux in the dark for 3 h. Filtration and chromatography gave 304 mg (68%) of keto sulfone [TLC, SiO_2, 2:1 Et_2O/hexane, $R_f \sim 0.18$; NMR 1.00 (3 H, d, $J \sim 7$ Hz), 1.20–3.20 (11 H, m), 3.90–4.20 (1 H, m) 5.35 (1 H, br d, $J \sim 9$ Hz), 5.60 (1 H, ddd, $J \sim 2.5$, 4.5, 10 Hz), 7.30–7.60 (3 H, m), 7.70–8.00 (2 H, m)] and 43 mg (10%) of keto sulfinate which could be converted in 50% yield to keto sulfone by treatment as above with trimethylsilyl chloride/sodium iodide and benzenesulfinate anion displacement.

The above keto sulfone (250 mg, 0.75 mmol) in CH_2Cl_2 (6 mL) was subjected to 1,3-propanedithiol (162 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (106 mg, 0.75 mmol) for 15 h. Successive washings with 5% NaOH solution, H_2O, 5% hydrochloric acid, H_2O, saturated $NaHCO_3$ solution, and brine gave, after chromatography, **10** (320 mg, 100%): mp 155–156 °C (CH_2Cl_2/Et_2O); TLC, SiO_2, 2:1 Et_2O/hexane, $R_f \sim 0.38$; NMR 1.01 (3 H, d, $J \sim 10$ Hz), 1.20–2.60 (12 H, m), 2.60–3.16 (4 H, m), 3.29 (1 H, dd, $J \sim 11$, 14 Hz), 5.12 (1 H, dd, $J \sim 2.5$, 14 Hz), 5.20 (1 H, brd, $J \sim 10$ Hz), 5.50 (1 H, ddd, $J \sim 2.5$, 4.5, 10 Hz), 7.32–7.72 (3 H, m), 7.72–8.04 (2 H, m); mass spectrum *m/e* (%) 409 ($M^+ + 1$, 100), 301 (9), 267 (75), 193 (10), 160 (43), 159 (43), 143 (17), 107 (15); high-resolution mass spectrum calcd for $C_{21}H_{28}O_2S_3$ 408.1251, found 408.1260.

Preparation of 13. *n*-BuLi (1.6 M in THF, 0.825 mL, 1.32 mmol) was added dropwise to a −78 °C solution of **10** (280 mg, 0.66 mmol) in THF (5 mL) and HMPA (1 mL). After being stirred at 0 °C for 30 min, the resulting deep orange mixture was cooled to −78 °C and iodide **5**[7a] (490 mg, 0.96 mmol) dissolved in THF (2 mL) was added dropwise. The cooling bath was removed and the mixture stirred at ambient temperature for 4 h. Saturated NH_4Cl solution was added at 0 °C and the mixture extracted with CH_2Cl_2. The organic extract was washed with 5% $NaHCO_3$ solution and brine and evaporated and the residue chromatographed to afford 65 mg (23%) of **10** and 387 mg (93% based on recovered starting material) of **13** as a mixture of diastereomeric alkylation products (SiO_2, 1:1 hexane/EtOAc, $R_f \sim 0.55$–0.64). Resolution of isomers was postponed to a later stage.

Preparation of 14. An acetonitrile (1 mL) solution of the above diastereomeric dithianes (74 mg, 0.094 mmol) was added to an 80% aqueous acetonitrile solution (1.5 mL) of mercuric chloride (56 mg, 0.206 mmol) and calcium carbonate (21 mg). After being heated under reflux for 7 h, the cooled mixture was filtered over a Celite bed and the filtrate washed with 5 M aqueous NH_4OAc, H_2O, and brine and evaporated to give 60 mg (92%) of crude keto sulfone which was subjected to 6% sodium amalgam[26] (200 mg) reduction in MeOH (1 mL) for 2 h. The reaction mixture was filtered into cold NH_4Cl solution and extracted with CH_2Cl_2. Careful chromatography (SiO_2, 1:1 Et_2O/hexane) furnished **14** (7 mg, $R_f \sim 0.32$) and its diastereomer (6 mg, $R_f \sim 0.24$) resulting from stereospecific amalgam reduction of the ketone and a mixture of both corresponding ketones (19 mg, $R_f \sim 0.44$). Stereospecific reduction of the ketones in THF (1 mL) at 0 °C with L-Selectride (Aldrich) (0.11 mmol) for 30 min, extractive isolation, and chromatography gave an additional 9 mg of **14** (total yield 60%), mp 105–106 °C; $[\alpha]^{24}_D$ +9.6° (*c* 0.9, $CHCl_3$) and an equal amount of diastereomer:[21] NMR 0.91 (3 H, d, $J \sim 7$ Hz), 1.13 (9 H, s), 1.20–2.40 (18 H, m), 3.53 (3 H, s), 3.80–4.10 (1 H, m), 4.17 (1 H, br s), 4.20–4.36 (1 H, m), 4.84 (1 H, dd, $J \sim 3$, 10 Hz), 5.40 (1 H, br d, $J \sim 10$ Hz), 5.52–5.74 (1 H, m), 7.28–7.48 (6 H, m), 7.48–7.80 (4 H, m); mass spectrum *m/e* (%) 563 ($M^+ + 1$,2), 407 (2), 381 (2), 355 (2), 327 (9), 315 (10), 288 (39), 286 (97), 285 (100), 251 (35).

(+)-Dihydrocompactin (3). To a solution of **14** (58 mg, 0.104 mmol) in CH_2Cl_2 (6 mL) was added (*S*)-(+)-2-methylbutyric acid (106 mg, 1.04 mmol) followed by *N,N*-dicyclohexylcarbodiimide (214 mg, 1.04 mmol) and 4-dimethylaminopyridine (12 mg, 0.10 mmol). The reaction was diluted with Et_2O (40 mL) after 24 h, filtered through a Celite bed, and washed with cold 5% hydrochloric acid, saturated $NaHCO_3$ solution, and brine. Chromatography (SiO_2, 1:1 Et_2O/hexane) gave unreacted **14** (6 mg) and butyrate ester (58 mg, 97% based on recovered **14**): $[\alpha]^{24}_D$ +52.2° (*c* 0.9, $CHCl_3$), $R_f \sim 0.61$; NMR 0.91 (3 H, d, $J \sim 7$ Hz), 0.95 (3 H, t, $J \sim 7$ Hz), 1.13 (9 H, s), 1.19 (3 H, d, $J \sim 7$ Hz), 1.20–2.60 (21 H, complex m), 3.52 (3 H, s), 3.70–4.10 (1 H, m), 4.12–4.36 (1 H, m), 4.81 (1 H, dd, $J \sim 2.5$, 10 Hz), 5.16 (1 H, br s), 5.41 (1 H, br d, $J \sim 10$ Hz), 5.64 (1 H, ddd, $J \sim 2.5$, 4.5, 10 Hz), 7.28–7.50 (6 H, m), 7.50–7.75 (4 H, m).

The above ester (54 mg, 0.0836 mmol) was stirred with 6 mL of 10% hydrochloric acid and THF (3:5) at 45 °C for 3 h and then poured into cold saturated $NaHCO_3$. Extractive isolation with CH_2Cl_2 gave the

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crude lactol which was immediately added to a vigorously stirring suspension[19] of pyridinium chlorochromate (200 mg) and neutral alumina (200 mg) in CH_2Cl_2 (4 mL). After 8 h, the mixture was diluted with Et_2O (20 mL) and filtered through a short bed of Florisil. The filtrate was washed with 5% $NaHCO_3$ solution and brine and evaporated to an oil: TLC, SiO_2, 1:1 Et_2O/hexane, $R_f \sim 0.32$; NMR 0.91 (3 H, d, $J \sim 7$ Hz), 0.95 (3 H, t, $J \sim 7$ Hz), 1.12 (9 H, s), 1.20 (3 H, d, $J \sim 7$ Hz), 1.20–2.60 (21 H, complex m), 4.12–4.40 (1 H, m), 4.56–4.92 (1 H, m), 5.18 (1 H, br s), 5.42 (1 H, br d, $J \sim 10$ Hz), 5.64 (1 H, ddd, $J \sim 2.5$, 4.5, 10 Hz), 7.30–7.50 (6 H, m), 7.50–7.75 (4 H, m). Desilylation using 48% hydrofluoric acid in acetonitrile (5 mL, 1:10) at 45 °C for 8 h, neutralization with saturated $NaHCO_3$ solution, extractive isolation, and chromatography (SiO_2, Et_2O, $R_f \sim 0.23$) afforded **3** (16 mg, 50%); mp 103–105 °C (benzene/hexane): $[\alpha]^{24}_D + 129°$ (c 1.3, $CHCl_3$), whose 360-MHz ^1H NMR spectrum was identical with that of natural material:[20] NMR 0.83 (3 H, d, $J \sim 7$ Hz), 0.89 (3 H, t, $J \sim 7$ Hz), 1.13 (3 H, d, $J \sim 7$ Hz), 1.30–2.60 (20 H, m), 2.56–2.76 (2 H, m), 4.20–4.42 (1 H, m), 4.42–4.80 (1 H, m), 5.16 (1 H, br s), 5.37 (1 H, br d, $J \sim 10$ Hz), 5.60 (1 H, ddd, $J \sim 2.5$, 4.5, 10 Hz); mass spectrum m/e (%) 393 ($M^+ + 1$, 2), 375 (2), 291 (14), 273 (61), 255 (9), 227 (4), 187 (34), 145 (100); high-resolution mass spectrum calcd for $C_{23}H_{36}O_5$ 392.2560, found 392.2554.

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Registry No. **3**, 78366-44-6; **3** *t*-$BuPh_2Si$ derivative, 90344-22-2; **5**, 86031-03-0; **6**, 90344-09-5; **7**, 90344-10-8; **8**, 90344-11-9; **8** ethylene glycol ketal derivative, 90344-17-5; **9**, 90344-12-0; **9** keto-iodide derivative, 90344-18-6; **9** keto-sulfone derivative, 90367-63-8; **10**, 90344-13-1; **13**, 90344-14-2; **13** keto-sulfone derivative, 90344-19-7; **14**, 90367-62-7; **14** diastereomer, 90410-99-4; **14** ketone derivative, isomer 1, 90367-64-9; **14** ketone derivative, isomer 2, 90411-00-0; **14** (*S*)-(+)-2-methylbutyrate, 90344-20-0; **14** (*S*)-(+)-2-methylbutyrate demethyl derivative, 90344-21-1; dimethyl (*E*,*E*)-2,4-hexadienylmalonate, 75283-60-2; methyl (*E*,*E*)-4,6-octadienoate, 68823-50-7; (*E*,*E*)-octa-4,6-dien-1-ol, 80106-30-5; (*E*,*E*)-octa-4,6-dien-1-ol tosylate, 90344-15-3; sodium thiophenoxide, 930-69-8; (*E*,*E*)-1-(phenylthio)octa-4,6-diene, 90344-16-4; maleic anhydride, 108-31-6; 1,3-propanedithiol, 109-80-8.

Hydrogen Bonded Phosphate Esters. Synthesis and Structure of Catechol-Containing Salts of 2-Hydroxyphenyl Phenylphosphonate[1]

Charles A. Poutasse,[2] Roberta O. Day, and Robert R. Holmes*

Contribution from the Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003. *Received September 8, 1983*

Abstract: The synthesis and X-ray structural analysis of the tetraphenylphosphonium salt of 2-hydroxyphenyl phenylphosphonate ($[(HOC_6H_4O)P(Ph)O_2][PPh_4]\cdot C_6H_4(OH)_2$ (**1**)) and the corresponding pyridinium salt ($[(HOC_6H_4O)P(Ph)O_2][C_5H_5NH]\cdot C_6H_4(OH)_2$ (**2**)) are reported. These substances form unique hydrogen bonded phosphonate ester systems which incorporate catechol molecules of crystallization. The hydrolysis reaction of the benzodioxaphosphole $[(C_6H_4O_2)_2PPh]$ with $KF\cdot 2H_2O$ and Ph_4PCl in acetonitrile gave the ester salt $[HOC_6H_4OP(Ph)O_2][PPh_4]$·catechol (**1**). By a similar method, the pyridinium salt was obtained ($[HOC_6H_4OP(Ph)O_2][C_5H_5NH]$·catechol (**2**)). Single-crystal X-ray analysis showed the phosphonate in **1** contained an intramolecular hydrogen bonded seven-membered ring. The phosphonates are linked by catechol molecules in a chain arrangement. In **2**, the pyridinium ion replaced the intramolecular ring in hydrogen bond formation. As a result, the structure shows dimeric phosphonate units linked together by catechol molecules in a doubly hydrogen bonded chain. **1** crystallizes in the monoclinic space group $P2_1/n$ with $a = 9.996$ (2) Å, $b = 26.858$ (7) Å, $c = 14.160$ (3) Å, $\beta = 109.57$ (1)°, and $Z = 4$. **2** crystallizes in the triclinic space group $P\bar{1}$ with $a = 9.074$ (2) Å, $b = 11.149$ (2) Å, $c = 11.786$ (2) Å, $\alpha = 70.26$ (2)°, $\beta = 87.54$ (2)°, $\gamma = 73.72$ (2)°, and $Z = 2$. A systematic classification of hydrogen bonding in phosphates is obtained regarding the number and types of interactions present in relation to the resultant structures. In addition, the O–X lengths increase with decreasing proton acidity in the hydrogen bonded phosphates, P=O···H—X (X = O, N). Little variation in the P=O bond lengths is apparent.

In modeling phosphoryl transfer enzyme reactions, it is necessary to incorporate hydrogen bonding and electrostatic interactions between the phosphorus-containing substrate and active site residues. The basis for estimating the magnitude of these terms and the conformational changes that are likely to occur as the reaction proceeds is usually limited. Our success in modeling ribonuclease action on uridylyl-(3′,5′)-adenosine[3] was directly dependent on the inclusion of structural parameters into the modeling program[4] based on earlier studies dealing with the structural determination of simpler tetra- and pentacoordinated phosphorus compounds.[5] The first step of action of this enzyme leading to a cyclic intermediate has limited phosphate–hydrogen bonding.[6] In staphylococcal nuclease, a system in which we are currently interested,[7,8] hydrogen bonding is more extensive.[9]

We wish to explore hydrogen bonding to model phosphate substrates that will allow an understanding of structural changes as the system becomes more complex. Examples from the lit-

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