0.2 g of K_2CO_3 for 2.5 h. The mixture was filtered, evaporated, taken up in CH_2Cl_2, and washed successively with H_2O and brine. Chromatography (EtOAc/*i*-PrOH 98.5:1.5) gave 0.022 g of starting material **6** and 0.468 g of alcohol **7a**. The analytical sample was distilled bulb-to-bulb [oven at 145 °C (0.025 mmHg)]: Anal. for $C_{16}H_{29}NO_2$: C, H; $[\alpha]_D$ = -113.1° (*c* = 0.55, $CHCl_3$); ^1H NMR δ 5.28 (br s, 1 H), 3.64 (m, 2 H), 3.00 (s, 3 H), 2.95 (s, 3 H), 2.68 (m, 1 H), 2.35 (dd, *J* = 5.9, 14.4 Hz, 1 H), 2.11 (dd, *J* = 8.7, 14.4 Hz, 1 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR δ (C) 172.8, 136.3, (CH) 125.6, 35.8, 30.4, 27.5, (CH_2) 60.8, 45.8, 39.5, 35.0, 27.8, 26.6, (CH_3) 37.5, 35.5, 19.8, 16.1.

Ene Reaction of 7b to 8. To a solution of 0.412 g (1.55 mmol) of **7b** in 18 mL of CH_2Cl_2 at -20 °C was added 3.89 mL of Me_2AlCl solution (1.0 M in hexanes) over 1.5 min. The mixture was stirred for 20 min and then quenched by addition of H_2O. The mixture was taken up in CH_2Cl_2 and washed with brine. Chromatography (EtOAc/*i*-PrOH 98.5:1.5) gave 0.3622 g of **8**. The analytical sample was recrystallized from ether: mp 152-153 °C; $[\alpha]_D$ = -29.6° (*c* = 0.50, $CHCl_3$); Anal. for $C_{16}H_{27}NO_2$, C, H, N; ^1H NMR δ 5.44 (br s, 1 H), 3.81 (br s, 1 H), 3.65 (br s, 1 H, OH), 3.01 (s, 3 H), 2.95 (s, 3 H), 1.06 (d, *J* = 7.0 Hz, 3 H), 0.87 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR δ (C) 173.4, 133.6, (CH) 121.7, 68.5, 45.8, 34.0, 32.0, 28.0, (CH_2) 40.8, 38.5, 36.9, 32.6, (CH_3) 37.2, 35.8, 21.0, 14.5.

Cyclocondensation of 10 with 1-Methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene. To a solution of 0.9051 g (3.25 mmol) of aldehyde **10** in 26 mL of CH_2Cl_2 at -78 °C was added 3.58 mL of 1.0 M $TiCl_4$ in CH_2Cl_2 (Aldrich) over 4.5 min. After 2 min flask was set in a bath at -40 °C and stirring continued for 5 min; then 1.1219 g of 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (ca. 95% purity by NMR) in 7.8 mL of CH_2Cl_2 was added dropwise over 16 min. The mixture was stirred for 40 min and then quenched by the addition of saturated $NaHCO_3$. The mixture was taken up in EtOAc and washed successively with saturated $NaHCO_3$ and brine. The residue was stirred with 24 mL of THF and 2.8 mL of trifluoroacetic acid for 1 h. After aqueous workup, the residue was chromatographed (hexanes/EtOAc 1:1) to give 0.7451 g of pyranones **11** and **12** as an inseparable 90:10 mixture as judged from ^{13}C NMR. **11**: ^1H NMR δ 7.31 (d, *J* = 6.0 Hz, 1 H), 5.44 (br s, 1 H), 5.35 (d, *J* = 6.0 Hz, 1 H), 5.18 (ddd, *J* ~ 3.2 Hz, 1 H), 4.32 (m, 1 H), 2.49 (dd, *J* = 12.3, 17.1 Hz, 1 H), 2.37 (dd, J = 4.8, 17.1 Hz, 1 H), 1.96 (s, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.78 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR for **11** with the distinguishing resonances for **12** in parentheses δ (C) 192.7, 170.7, 132.1, (CH) 163.3, 122.2, 106.9, 79.4(79.7), 72.3(72.6), 43.2, 38.1(38.7), 27.8, 27.6, (CH_2) 41.9(41.7), 40.7, 35.8, 32.1, 31.8, 24.0, CH_3: 21.4, 20.2, 14.0.

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Registry No. 1a, 75330-75-5; **2a**, 3391-90-0; **2b**, 118760-35-3; **2c**, 118759-44-7; **2d**, 118682-25-0; **3a**, 118682-26-1; **3a** (epimer), 118682-27-2; **3b**, 118682-28-3; **3c**, 118682-29-4; **3d**, 118682-30-7; **3e**, 118713-57-8; **4**, 118682-31-8; **5**, 118682-32-9; **6**, 118682-33-0; **7a**, 118682-34-1; **7b**, 118682-35-2; **8**, 118682-36-3; **9a**, 118713-58-9; **9b**, 118682-37-4; **9c**, 118682-38-5; (*E*)-**9d**, 118713-59-0; (*Z*)-**9d**, 118682-51-2; (*E*)-**9e**, 118722-37-5; (*Z*)-**9e**, 118713-60-3; **10**, 118682-39-6; **11**, 118682-40-9; **12**, 118682-41-0; **13a**, 118682-42-1; **13a** (H = α), 118759-45-8; **13b**, 118682-43-2; **13c**, 118682-44-3; **14a**, 118682-45-4; **14b**, 118682-46-5; **14c**, 118682-47-6; **14c** ((*S*)-α-methylbutyrate), 85613-99-6; **15a**, 118682-48-7; **15b**, 85614-07-9; **15b** (β-epoxide), 85648-19-7; **16a**, 118682-49-8; **16b**, 118682-50-1; **17**, 79691-11-5; i, 118682-52-3; ii, 118682-53-4; $Ph_3P{=}CH_2$, 3487-44-3; $CH_3C(OMe)_2NMe_2$, 18871-66-4; $Ph_3P{=}CHOMe$, 20763-19-3; $[(S)\text{-}C_2H_5CH(CH_3)CO]_2O$, 84131-91-9; $TMSCH_2CH{=}CH_2$, 762-72-1; Danishefsky's diene, 54125-02-9.

Supplementary Material Available: Spectral data (including ^{13}C NMR) for **2b,c**, **3b-e**, **5**, **6**, **9a-e**, **10**, **13a-c**, **14a,c**, **16a,b**, and **17** (3 pages). Ordering information is given on any current masthead page.

Total Syntheses of ML-236A and Compactin by Combining the Lactonic (Silyl) Enolate Rearrangement and Aldehyde-Diene Cyclocondensation Technologies

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Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received September 9, 1988. Revised Manuscript Received December 1, 1988*

Abstract: The sequence of a lactonic Claisen rearrangement and a Lewis acid catalyzed cyclocondensation of an aldehyde with an appropriate diene affords a new route to the title series.

The lowering of human blood serum cholesterol levels by mevinoids,[1] through suppression of HMG-CoA reductase (HMGR), already finds growing application in cardiovascular medicine.[2] Since the HMGR-mediated reductive conversion of 3-hydroxy-3-methylglutarate to mevalonate is a rate-limiting step in de novo cholesterol biosynthesis in humans, its inhibition is a prime target for medical intervention. Not surprisingly, the challenge of providing new routes to the compactin-mevinolin family has stimulated many approaches and successes.[3a,b] We have been developing some new ideas with a view to this objective.[4a-c] Total syntheses of ML-236A and of enantiomerically pure compactin are described below.

Our stereochemical strategy centers on four key processes. The first takes advantage of the remarkable syn selectivity exhibited

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(2) Endo, A. *J. Med. Chem.* **1985**, *28*, 401, and references therein.

(3) (a) For a review, see: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909. (b) The work described herein was described at the 7th IUPAC Conference on Organic Synthesis (Nancy, France) July 7, 1988. For a discussion of the background and synthetic logic, see: Danishefsky, S. J.; Simoneau, B. *Pure Appl. Chem.* **1988**, *60*, 1555.

(4) (a) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6889. (b) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (c) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981.

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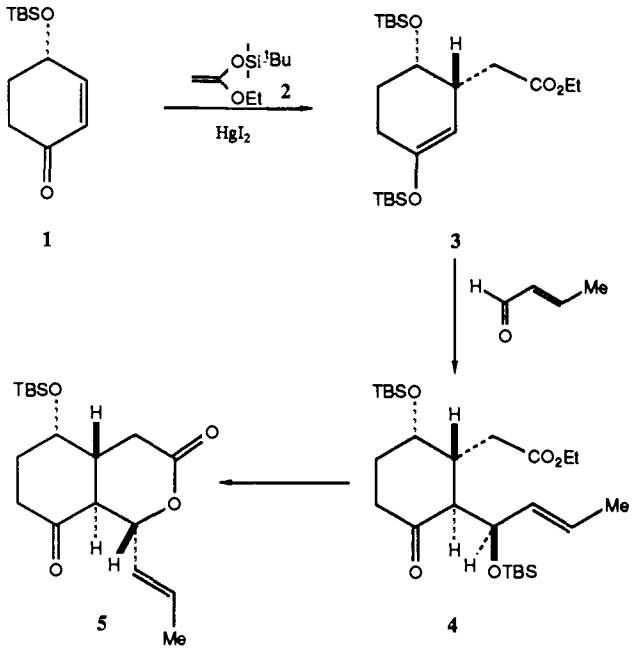
Scheme I



by compound **1** in several Lewis acid catalyzed additions to the double bond.[5] Included among these is a Mukaiyama group-transfer reaction with silyl ketene acetal **2** to give **3**, as substantially the only product.[6] A second silatropic group-transfer reaction (**3** → **4**), this time in the aldol mode, with essentially perfect trans-erythro specificity sets the stage for a lactonic variation[7] of the Ireland[8] (silyl) enolate rearrangement. This bond reorganization reaction (**5** → **6** → **7**) occurred with the perfect suprafaciality and fidelity to a boatlike transition state which are its hallmarks.[9a,b] The final component is the selectivity realized in the Lewis acid catalyzed cyclocondensation of aldehyde **17** with diene **18**,[10,11] While the selectivity margin in the desired sense is modest (4:1), it is very useful synthetically. Since the aldehyde group is insulated from the nearest stereogenic center by an "ethano spacer", any significant preference is remarkable. The synthesis we describe is linear in the sense that *all stereochemistry is introduced by communication from the single stereogenic center at C_4 of compound 1*. While we have developed an excellent route to the *S* enantiomer of this compound from quinic acid,[12,13] the experiments leading to ML-236A, described here in detail, were actually conducted on racemic material. The project, which culminated in a total synthesis of compactin, was indeed carried out on the *S* system.

Reaction of **1** with **2** (HgI_2 catalysis) followed by reaction of **3** (BF_3 etherate catalysis) with crotonaldehyde gave, with very high stereoselection, the siloxy aldol **4** (Scheme I). After desilylation and lactonization (trifluoroacetic acid–aqueous acetic acid–THF), keto lactone **5** is obtained. The overall yield of **5** from **1** is presently 35–38%.[14] While process improvements are certainly being studied, the conciseness of the route already renders it very attractive, particularly for analogue work.

Compound **5** was converted to its bis(TMS) derivative **6**, which upon heating in toluene at 105 °C gave rise to **7**.[9] However, for purposes of this synthesis, **7** was converted to the keto methyl ester **8** by hydrolysis (HCl–THF) and esterification (diazomethane). The overall yield from **5** → **8** is ca. 80%. The β,γ-unsaturated ketone was converted to the 3(4),4a(5)-diene via (i) L-Selectride reduction, (ii) mesylation, and (iii) elimination with DBU.[3] Compound **9**, thus available in 65% yield from **8**, was readied for chain extension by (i) reduction with DIBAH and (ii) Swern oxidation[15] of the alcohol to the aldehyde **11** (80% overall yield) (Scheme II).

Emmons-like elongation of **11** gave a 95% yield of **12**. Conjugate reduction (magnesium–methanol)[16] followed by reduction of the ester linkage with DIBAH gave rise to alcohol **14** (75%). Based on the findings of Wovkulich and Uskokovic,[10] it seemed preferable to conduct the cyclocondensation reaction on a C_8[17] acetoxy rather than silyloxy function. Our goal substrate was therefore the acetoxyaldehyde **17**. Desilylation of **14** (HF, MeCN) and selective silylation (TBSCl; Et_3N; DMAP) afforded **15**. Acetylation of **15** followed by desilylation (HF–MeCN) gave **16** and, after subsequent oxidation, the desired aldehyde **17** (60% overall from **14**).

Cyclocondensation of **17** with diene **18** ($TiCl_4$ in methylene chloride at −40 °C) gave a mixture of aldols (**19** and **20**)[18a] and dihydropyrones (**21** and **22**).[18b] Treatment of **19**:**20** with trifluoroacetic acid in THF gave the **21**:**22** mixture. The overall ratio of **21**:**22** (obtained in 70%) by treating the total **19**–**22** reaction mixture with TFA was 4:1 (Scheme III).

From **21**, the route to ML-236A took advantage of protocols developed in model systems.[4b,c] Addition of ethanol under the influence of HCl afforded an 80% yield of axial glycoside **23**, which upon L-Selectride reduction gave cleanly the axial alcohol **24**. Hydrolysis of the acetal followed by Fetizon oxidation[19] and deacylation afforded fully synthetic ML-236A. The high-field (500-MHz) NMR spectrum of the racemate and that of an authentic sample were identical. By contrast, the spectrum of the bis epi compound **26**, prepared in the same way from **22**, was similar to that of ML-236A, but clearly differed in nuance and detail.

In a very recent extension of this work, the optically pure version of **1** was employed.[13] The synthesis described herein was repeated and, with some modification, led to the total synthesis of the naturally occurring enantiomer of compactin.[17] We note that during the course of that synthesis, the cyclocondensation of diene **18** was conducted with optically pure aldehyde ester **27** (Scheme IV). The ratio of **28**:**29** obtained after this process was 3.7:1, The factors that go into controlling the extent of stereochemical communication have also been evaluated in several related systems by the Hoffmann La Roche group.[10] We also note that the silyl enol ether functionality available in the rearrangement product **7** can be exploited. For instance, reaction of **7** with *m*-chloro-

(5) High syn selectivity was also observed with allyltrimethylsilane (catalyzed by $TiCl_4$) and in a Diels–Alder reaction with 1,3-butadiene (catalyzed by $AlCl_3$). Conversely, high anti selectivity was encountered in the reaction of **1** with lithium dimethylcuprate. (Cabal, M. P.; Yamaguchi, M., Yale University, unpublished results.) The same remarkable effect of Lewis acid catalysts in directing syn stereochemistry of addition has also been observed with the corresponding cyclopentenone. This area is being actively investigated as to its theoretical basis, and with respect to other applications to synthesis.

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(7) For novel enhancements and applications of the lactonic variation of the Ireland process, cf. inter alia: (a) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030. (b) Funk, R. L.; Munger, J. D., Jr. *J. Org. Chem.* **1984**, *49*, 4320. (c) Funk, R. L.; Daily, W. J.; Parvez, M. *J. Org. Chem.* **1988**, *53*, 4141. (d) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298. (e) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, *49*, 4322. (f) Burke, S. D.; Armistead, D. M.; Fevig, J. M. *Tetrahedron Lett.* **1985**, *26*, 1163. (g) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* **1986**, *42*, 2787.

(8) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *Ibid.* **1976**, *98*, 2868.

(9) Danishefsky, S.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 6891. (b) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371.

(10) Higher facial selectivities were realized in the same sort of cyclocondensation reaction with related substrates by a Hoffmann La Roche group. See: Wovkulich, P. M.; Tang, P. C.; Chada, N. K.; Batcho, A. D.; Barrish, J. C.; Uskoković, M. R. *J. Am. Chem. Soc.*, preceding paper in this issue.

(11) Diene **18** prepared according to general method: Danishefsky, S.; Bednarski, M.; Izawa, T.; Maring, C. *J. Org. Chem.* **1984**, *49*, 2290.

(12) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986** *51*, 2332.

(13) Audia, J. E.; Boisvert, L.; Patten, A. D., Yale University, unpublished results.

(14) The major losses occur in the desilylation and lactonization reactions.

(15) Mancuso, A. J.; Huang, S.-H.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

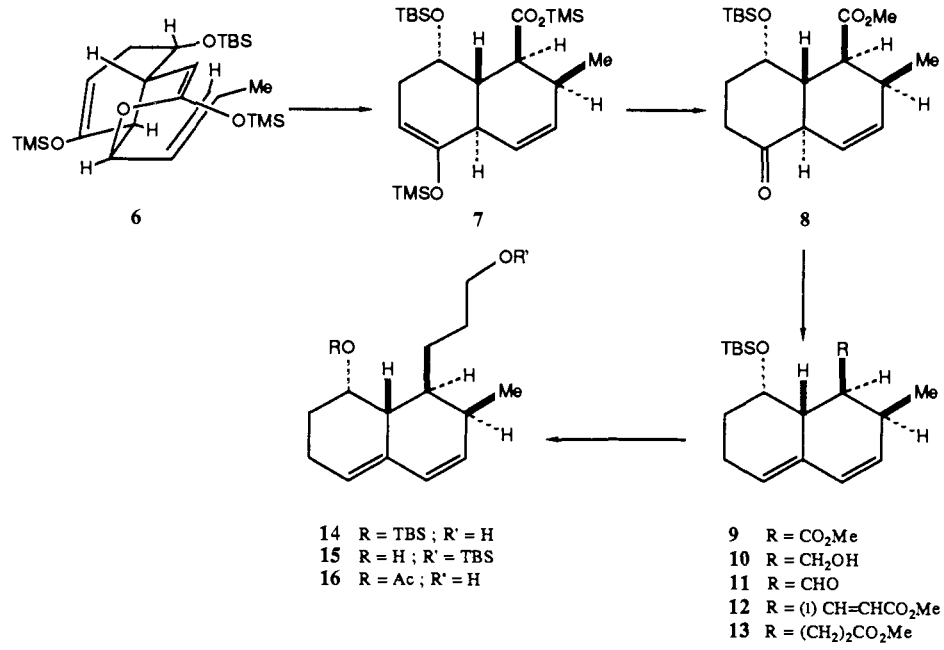
(16) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409.

(17) For a description of the numbering system, see: Brown, A. G.; Smale, T. C.; King, T. G.; Hasenkamp, R.; Thomson, R. H. *J. Chem. Soc., Perkin Trans 1* **1976**, 1165.

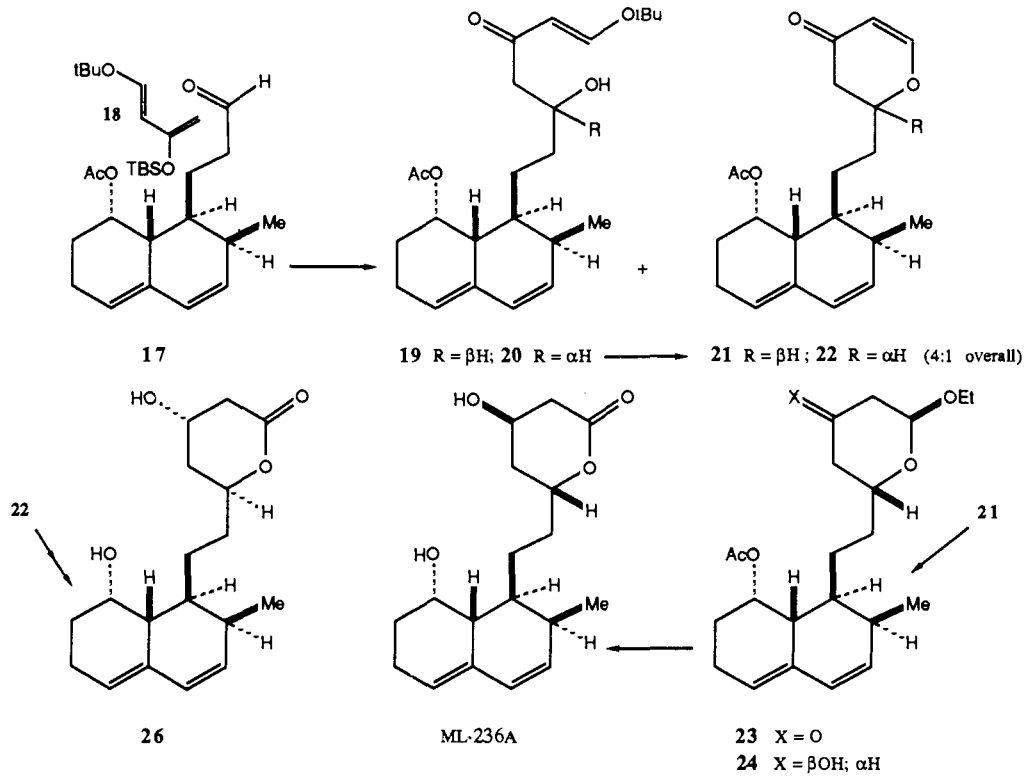
(18) (a) The ratio of aldols **19**:**20** was 5:1. (b) The ratio of dihydropyrones **21**:**22** was 3:1.

(19) Fetizon, M.; Golfier, M. *Compt. Rend.* **1968**, *267*, 900.

Scheme II



Scheme III



peroxybenzoic acid in hexanes, followed by acidic workup and esterification with diazomethane, affords ester **30** (75% overall from **5**). In principle this transformation might be of value with respect to a synthesis of the related cholesterol inhibitor pravastatin.[20]

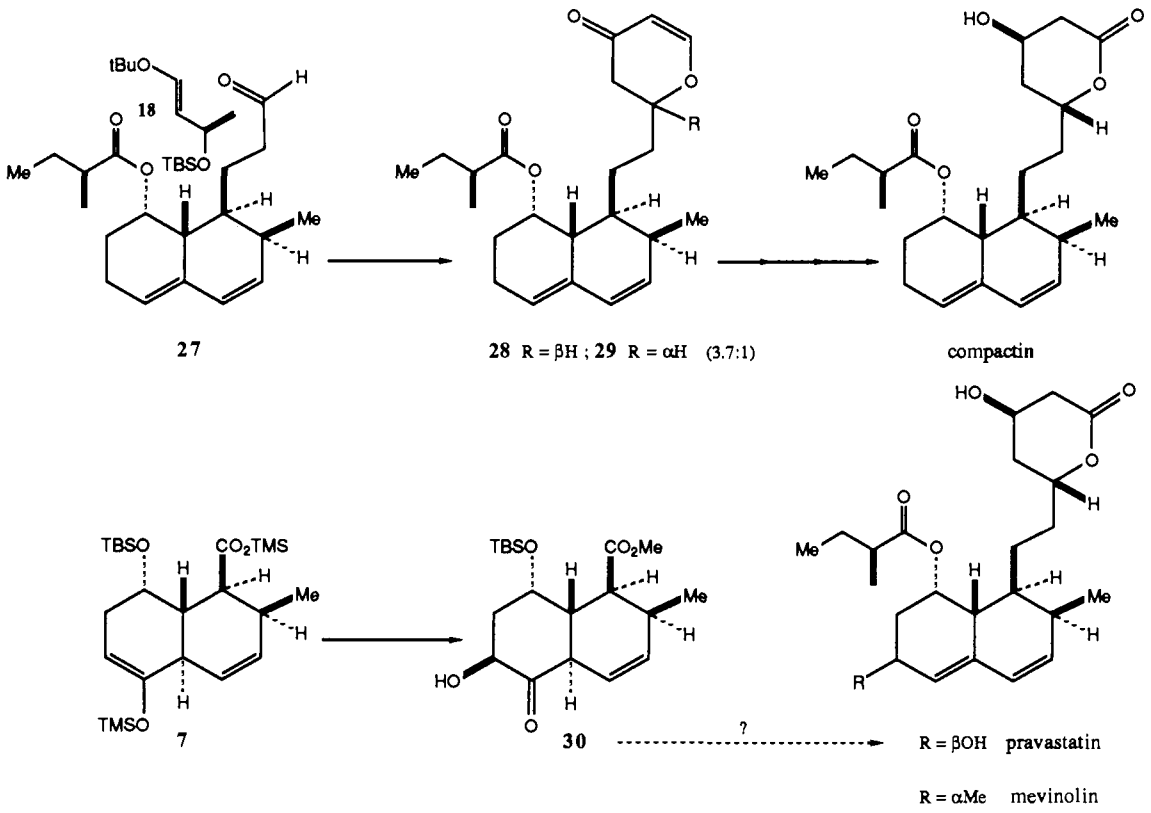
Additional work in this area is focusing on (i) applications to the synthesis of other naturally occurring mevinoids (cf. mevinolin and pravastatin), (ii) application to the syntheses of analogue systems not available for the natural products themselves,[21] and (iii) experiments directed toward achieving a better understanding of the basis of stereochemical transmission in the cyclocondensation reaction.

Experimental Section

4-Hydroxy-2-cyclohexen-1-one. To a solution of 3-cyclohexen-1-one[22] (38.45 g, 0.40 mol) in CH_2Cl_2 (800 mL) was added slowly (50 min) mCPBA (89.33 g, 0.44 mol) in CH_2Cl_2 (800 mL). The reaction mixture was stirred at room temperature for 14 h. The suspension was filtered and the solution washed with 10% $Na_2S_2O_3$ (375 mL), saturated $NaHCO_3$ (500 mL), H_2O (500 mL) and brine (500 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in a 1:1 mixture of ether–CH_2Cl_2 (760 mL) and stirred for 1 h with basic alumina[23] (activity

(20) Serizawa, W.; Nakagawa, K.; Hamano, K.; Tsujita, Y.; Terahara, A.; Kuwano, H. *J. Antibiot.* **1983**, *36*, 604.
(21) Boisvert, L., Yale University, unpublished results.
(22) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1977**, *42*, 1051.

Scheme IV



I, 147 g). The solid was filtered and thoroughly washed with CH_2Cl_2. Purification of the residue by flash chromatography (AcOEt–hexane, 5:3) gave 4-hydroxy-2-cyclohexen-1-one (26.30 g, 59%) as a thick oil: bp 98–100 °C (1 mmHg); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.95 (ddd, J = 10.2, 2.3, 1.7 Hz, 1 H, 3-H), 5.97 (ddd, J = 10.2, 2.0, 1.0 Hz, 1 H, 2-H), 4.54–4.63 (m, 1 H, 4-H), 2.59 (dtd, J = 17.2, ~4.9, 1.0 Hz, 1 H, 6-H), 2.30–2.45 (m, 2 H, 5,6-H), 2.00 (tdd, J = 12.7, 9.3, ~4.9 Hz, 1 H, 5-H), 1.81 (s, 1 H, 4-OH); IR ($CHCl_3$) 3580, 3400 (br), 3000, 2940, 1670, 1410, 1370, 1120, 1055, 960, 935, 855 cm^{-1}; MS m/e 112 (M^+).

4-(*tert*-Butyldimethylsiloxy)-2-cyclohexen-1-one (1). DBU (22.3 g, 21.9 mL, 147 mmol) was added dropwise (20 min) to a solution of 4-hydroxy-2-cyclohexen-1-one (14.94 g, 133 mmol) and (TBS)Cl (21.08 g, 140 mmol) in C_6H_6 (270 mL).[24] After 1.5 h at room temperature, the reaction mixture was diluted with ether (750 mL) and washed with H_2O (200 mL), 0.1 N HCl (2 × 250 mL), saturated $NaHCO_3$ (200 mL), and brine (200 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (hexane–AcOEt, 20:1) gave **1** (27.73 g, 92%) as a colorless oil; bp 120–122 °C (5 mmHg); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.83 (ddd, J = 10.2, 2.4, 1.7 Hz, 1 H, 3-H), 5.92 (ddd, J = 10.2, 2.0, 1.0 Hz, 1 H, 2-H), 4.53 (dddd, J = 9.1, 4.7, 2.4, 2.0 Hz, 1 H, 4-H), 2.58 (dtd, J = 16.7, 4.7, 1.0 Hz, 1 H, 6-H), 2.35 (ddd, J = 16.7, 12.7, 4.7 Hz, 1 H, 6-H), 2.21 (dqd, J = 12.7, 4.7, 1.7 Hz, 1 H, 5-H), 2.00 (tdd, J = 12.7, 9.1, 4.7 Hz, 1 H, 5-H), 0.92 (s, 9 H, 4-OSi(t-C_4H_9)), 0.13, 0.12 (2 s, 2 × 3 H, 4-OSi(CH_3)$_2$); IR ($CHCl_3$) 3010, 2960, 2930, 2890, 2860, 1685, 1470, 1385, 1260, 1135, 1110, 1070, 1000, 990, 975, 960, 875, 865, 845 cm^{-1}; MS m/e 226 (m^+).

Ethyl (1*RS*,6*SR*)[3,6-Bis(*tert*-butyldimethylsiloxy)-2-cyclohexen-1-yl]acetate (3). A solution of enone **1** (4.50 g, 19.9 mmol) and HgI_2 (452 mg, 0.99 mmol) was stirred at room temperature for 15 min and then cooled to −78 °C. Ketene acetal **2**[25] (5.03 g, 5.70 mL, 24.8 mmol) was added dropwise (15 min). The reaction mixture was stirred at −78 °C for 2 h, quenched with Et_3N (416 μL, 302 mg, 2.98 mmol), and allowed to warm to room temperature. The mixture was filtered through a short column (2 in.) of silica gel (deactivated with a 5% Et_3N solution of hexane–AcOEt, 10:1) eluting with hexane–AcOEt (10:1) and concentrated in vacuo. Purification of the crude material by flash chromatography (hexane–AcOEt, 30:1) gave **3** (cis to trans, 20:1) as a colorless oil (7.98 g, 94%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.68 (d, J = 3.8 Hz, 1 H, 2-H), 4.14, 4.13 (2 q, J = 7.1 Hz, 2 H, 1′-OCH_2CH$_3$), 3.99 (ddd, J = 8.1, 4.5, 2.6 Hz, 1 H, 6-H), 2.75 (br s, 1 H, 1-H), 2.63 (dd, J = 15.7, 6.2 Hz, 1 H, 2′-H), 2.15 (dd, J = 15.7, 8.5 Hz, 1 H, 2′-H), 2.13 (m, 1 H, 4-H), 2.01 (dtt, J = 17.2, 6.6, 1.5 Hz, 1 H, 4-H), 1.78 (dddd, J = 13.2, 6.6, 6.6, 8.1 Hz, 1 H, 5-H), 1.66 (dddd, J = 13.2, 6.6, 6.6, 2.6 Hz, 1 H, 5-H), 1.27 (t, J = 7.1 Hz, 3 H, 1′-OCH$_2$CH_3), 0.92, 0.89 (2 s, 2 × 9 H, 3,5-OSi(t-C_4H_9)), 0.13 (s, 6 H, 3-OSi(CH_3)$_2$), 0.07, 0.04 (2 s, 2 × 3 H, 6-OSi(CH_3)$_2$); IR ($CHCl_3$) 2960, 2930, 2890, 2860, 1725, 1665, 1475, 1465, 1380, 1260, 1180, 1100, 1065, 1010, 915, 890, 845 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{44}O_4Si_2$ 428.2778, found 428.2742.

(1*RS*,4a*RS*,5*SR*,8a*SR*)-5-(*tert*-Butyldimethylsiloxy)-4a,6,7,8a-tetrahydro-1-[(*E*)-1-propen-1-yl]-1*H*-2-benzopyran-3,8(4*H*,5*H*)-dione (5). To a cold (−78 °C) solution of crotonaldehyde (2.59 g, 2.99 mL, 36.9 mmol) in CH_2Cl_2 (95 mL) was added dropwise (2 min) BF_3·OEt_2 (2.62 g, 2.27 mL, 18.4 mmol). After 5 min, a solution of enol ether **3** (7.91 g, 18.4 mmol) in CH_2Cl_2 (15 mL) was added slowly (15 min). The reaction mixture was stirred at −78 °C for 12 min, then quenched by addition of saturated $NaHCO_3$ (30 mL), allowed to warm to room temperature, and diluted with saturated $NaHCO_3$ (70 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude aldol **4** (9.07 g) was treated with a mixture of AcOH–THF–H_2O–TFA (100 mL:20 mL:20 mL:20 mL) for 4.5 h at room temperature. The reaction mixture was poured in H_2O (1.7 L). Extraction with CH_2Cl_2 (3 × 300 mL) gave a combined organic phase which was washed with saturated $NaHCO_3$ (2 × 250 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (hexane–AcOEt, 4:1) of the residue gave lactone **5** (2.62 g, 42%) as a thick colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.91 (dqd, J = 15.3, 6.6, 1.0 Hz, 1 H, 2′-H), 5.50 (ddq, J = 15.3, 6.3, 1.6 Hz, 1 H, 1′-H), 5.08 (dd, J = 10.4, 6.3 Hz, 1 H, 1-H), 3.92 (br s, 1 H, 5-H), 2.84 (td, J = 14.1, 5.9 Hz, 1 H, 7-H), 2.82 (dd, J = 12.4, 10.4 Hz, 1 H, 8a-H), 2.68 (dd, J = 17.4, 12.5 Hz, 1 H, 4-H), 2.49 (dd, J = 17.4, 4.4 Hz, 1 H, 4-H), 2.13–2.31 (m, 3 H, 4a,6,7-H), 1.91 (tdd, J = 14.1, 4.3, 2.1 Hz, 1 H, 6-H), 1.72 (ddd, J = 6.6, 1.6, 0.8 Hz, 1 H, 3′-H$_3$), 0.96 (s, 9 H, 5-OSi(t-C_4H_9)), 0.14, 0.14 (2 s, 2 × 3 H, 5-OSi(CH_3)$_2$); IR ($CHCl_3$) 3020, 2960, 2930, 2880, 2860, 1720, 1330, 1300, 1260, 1240, 1195, 1165, 1135, 1125, 1090, 1060, 1010, 995, 840 cm^{-1}; HRMS (CI) calcd for $C_{18}H_{31}O_4Si$ 339.1992, found 339.2006.

Methyl (1*SR*,2*SR*,4a*RS*,8*SR*,8a*SR*)-8-(*tert*-Butyldimethylsiloxy)-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-5-oxo-1-naphthalenecarboxylate (8). To a solution of LDA (30.7 mmol) [prepared at 0 °C from 1.6 M n-BuLi solution in hexanes (19.2 mL, 30.7 mmol) and dry diisopropylamine (3.11 g, 4.30 mL, 30.7 mmol) in THF (60 mL)] cooled to −78 °C was added (10 min) (TMS)Cl (5.00 g, 5.85 mL, 46.1 mmol) followed by a solution

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of lactone **5** (2.45 g, 7.24 mmol) in THF (15 mL) (45 min). The reaction mixture was stirred at −78 °C for 30 min and then warmed slowly to room temperature. The volatiles were removed in vacuo and replaced with dry toluene (72 mL). The reaction mixture was heated at 105 °C for 4 h, whereupon the solution was cooled to room temperature and the solvent removed. The residue was taken up in THF (220 mL) and treated with 1 N HCl (22.0 mL). After 15 min, the reaction mixture was poured in water (1 L) and extracted with CH_2Cl_2 (4 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude acid in dry ether (100 mL) was esterified with an excess of a ethereal CH_2N_2 solution (0 °C, 1.5 h). The crude product was purified by chromatography (hexane–AcOEt, 10:1) to give the keto ester **8** (1.94 g, 76%): mp 100 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.03 (d, *J* = 10.1 Hz, 1 H, 4-H), 5.70 (ddd, *J* = 10.1, 4.6, 2.7 Hz, 1 H, 3-H), 4.48 (br s, 1 H, 8-H), 3.70 (s, 3 H, 1-CO_2CH_3), 3.48 (br d, *J* = 12.0 Hz, 1 H, 4a-H), 2.95 (dd, *J* = 11.5, 6.1 Hz, 1 H, 1-H), 2.71 (dt, *J* = 14.0, 6.6 Hz, 1 H, 6-H), 2.58–2.66 (m, 1 H, 2-H), 2.27 (ddd, *J* = 14.0, 4.9, 2.1 Hz, 1 H, 6-H), 2.09 (dm, *J* = 14.0 Hz, 1 H, 7-H), 2.01 (~ddd, *J* = 12.0, 11.5, ~1.5 Hz, 1 H, 8a-H), 1.91 (tdd, *J* = 14.0, 4.9, 2.2 Hz, 1 H, 7-H), 0.91 (s, 9 H, 8-OSi(*t*-C_4H_9)), 0.84 (d, *J* = 7.1 Hz, 3 H, 2-CH_3), 0.09, 0.02 (2 s, 2 × 3 H, 8-OSi$(CH_3)_2$); IR ($CHCl_3$) 3030, 3020, 2960, 2930, 2860, 1730, 1715, 1370, 1290, 1260, 1235, 1180, 1145, 1135, 1100, 1090, 1070, 1000, 840 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{32}O_4Si$ 352.2070, found 352.2096. Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.73; H, 9.15. Found: C, 65.36; H, 9.12.

Methyl (1*SR*,2*SR*,4a*RS*,5*SR*,8*SR*,8a*SR*)-8-(*tert*-Butyldimethylsiloxy)-1,2,4a,5,6,7,8,8a-octahydro-5-hydroxy-2-methyl-1-naphthalenecarboxylate (8b). To a cold (−78 °C) solution of keto ester **8** (1.88 g, 5.33 mmol) in THF (48 mL) was added dropwise a 1 M L-Selectride solution in THF (16.0 mL, 16.00 mmol). The reaction mixture was stirred at −78 °C for 9 h. The reaction was quenched by addition of H_2O (1 mL) and warmed to 0 °C. A 2.5 N NaOH solution (6.7 mL) and a 30% H_2O_2 solution (5.7 mL) were added cautiously. After 1 h at room temperature, the reaction mixture was poured in H_2O (600 mL + 2 mL of 10% NaS_2O_3) and extracted with CH_2Cl_2 (6 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (hexane–AcOEt, 4:1) gave starting material **8** (131 mg, 7%), a trace of the corresponding α,β-unsaturated ketone (69 mg, 4%), and the axial alcohol **8b** (1.55 g, 82%): mp 105.5 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.74 (ddd, *J* = 9.9, 4.5, 2.7 Hz, 1 H, 3-H), 5.49 (br d, *J* = 9.9 Hz, 1 H, 4-H), 4.31 (br s, 1 H, 8-H), 4.00 (br s, 1 H, 5-H), 3.67 (s, 3 H, 1-CO_2CH_3), 2.80 (dd, *J* = 11.8, 5.8 Hz, 1 H, 1-H), 2.58 (br d, *J* = 11.0 Hz, 2 H, 2,4a-H), 2.07 (ddd, *J* = 11.8, 11.0, 1.5 Hz, 1 H, 8a-H), 1.83–1.97 (m, 2 H, 6,7-H), 1.55–1.71 (m, 2 H, 6,7-H), 1.30 (d, *J* = 2.1 Hz, 1 H, 5-OH), 0.89 (d, *J* ~ 7 Hz, 3 H, 2-CH_3), 0.87 (s, 9 H, 8-OSi(*t*C_4H_9)), 0.03, −0.05 (2 s, 2 × 3 H, 8-OSi$(CH_3)_2$); IR ($CHCl_3$) 3580, 3020, 2950, 2930, 2880, 2860, 1730, 1440, 1255, 1175, 1145, 1095, 1075, 1045, 1030, 840 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{35}O_4Si$ 355.2304, found 355.2297. Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.67. Found: C, 64.47; H, 9.79.

(1*SR*,2*SR*,8*SR*,8a*RS*,6′*RS* and 6′*SR*)-6-[2-(8-Acetoxy-1,2,6,7,8,8a-hexahydro-2-methyl-1-naphthalenyl)ethyl]-5,6-dihydro-4*H*-pyran-4-one (21 and 22). To a solution of **17** (55.3 mg, 0.21 mmol) in CH_2Cl_2 (1.75 mL) at −78 °C was added (2 min) a 1 M $TiCl_4$ solution in CH_2Cl_2 (245 μL, 0.24 mmol). After being stirred at −78 °C for 2 min, the reaction mixture was warmed to −40 °C (~1 min) and a solution of diene **18** (114 mg, 128 μL, 0.443 mmol) in CH_2Cl_2 (550 μL) was added dropwise (5 min). The reaction mixture was stirred at −40 °C for 45 min and then quenched by addition of MeOH (1.1 mL) and saturated $NaHCO_3$ (3.0 mL). The mixture was kept at −40 °C for 10 min, then was allowed to warm to room temperature, and was taken up in AcOEt (50 mL). The organic phase was washed with brine (15 mL). The aqueous layer was extracted with AcOEt (2 × 10 mL), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was dissolved in dry THF (3.7 mL) and TFA (637 mg, 430 μL, 5.58 mmol) was added. After 2.5 h at room temperature, solid $NaHCO_3$ (350 mg) was added in one portion followed (5 min) by a dropwise addition of saturated $NaHCO_3$ (3.5 mL). The mixture was taken up in AcOEt (60 mL) and washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The dark residue was purified by flash chromatography (hexane–ether, 1:1) to give a 4:1 mixture (by ^{1}H NMR 250 MHz) of dihydropyrones **21** and **22** (48.8 mg, 70%). HPLC separation (Waters μ-Porasil column; hexane–ether 1:1; 3 mL/min; 5 mg/injection) gave **22** (8.3 mg, 21 min) and **21** (34.5 mg, 22.2 min). **21**: mp 114.5–116 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.33 (d, *J* = 6.0 Hz, 1 H, 2′-H), 5.99 (d, *J* = 9.7 Hz, 1 H, 4-H), 5.75 (dd, *J* = 9.7, 5.9 Hz, 1 H, 3-H), 5.58 (br s, 1 H, 5-H), 5.40 (dd, *J* = 6.0, 0.7 Hz, 1 H, 3′-H), 5.34 (br s, 1 H, 8-H), 4.34–4.46 (m, 1 H, 6′-H), 2.53 (dd, *J* = 16.8, 12.3 Hz, 1 H, 5′-H), 2.05 (s, 3 H, 8-OAc), 1.27–2.47 (complex, 12 H), 0.92 (d, *J* = 7.0 Hz, 3 H, 2-CH_3); IR ($CHCl_3$) 3010, 2990, 2950, 2910, 2870, 2860, 1720, 1660, 1590, 1400, 1370, 1265, 1245, 1230, 1185, 1030, 1020 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{26}O_4$ 330.1832, found 330.1819. **22**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35 (d, *J* = 6.0 Hz, 1 H, 2′-H), 6.00 (d, *J* = 9.6 Hz, 1 H, 4-H), 5.76 (dd, *J* = 9.6, 6.1 Hz, 1 H, 3-H), 5.59 (br s, 1 H, 5-H), 5.40 (dd, *J* = 6.0, 0.8 Hz, 1 H, 3′-H), 5.33 (br s, 1 H, 8-H), 4.34–4.41 (m, 1 H, 6′-H), 2.52 (dd, *J* = 16.6, 12.6 Hz, 1 H, 5′-H), 2.15–2.44 (m, 6 H), 2.07 (s, 3 H, 8-OAc), 1.60–1.82 (m, 5 H), 1.15–1.29 (m, 1 H), 0.90 (d, *J* = 7.0 Hz, 3H, 2-CH_3); IR ($CHCl_3$) 3000, 2940, 2910, 2870, 2860, 1720, 1660, 1585, 1400, 1370, 1260 (sh), 1250, 1185, 1030 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{26}O_4$ 330.1832, found 330.1846.

(1*SR*,2*SR*,8*SR*,8a*RS*,2′*SR*,6′*RS*)-6-[2-(8-Acetoxy-1,2,6,7,8,8a-hexahydro-2-methyl-1-naphthalenyl)ethyl]-2-ethoxytetrahydro-4*H*-pyran-4-one (23). A 1 M HCl solution in EtOH[4b,c,26] (prepared from 12 M HCl and EtOH) (5.75 mL) was added to dihydropyrone **21** (71.8 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 20 min. Excess of saturated $NaHCO_3$ (20 mL) was added, and the mixture was diluted with H_2O (50 mL). The aqueous solution was extracted with AcOEt (3 × 35 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude mixture gave ethyl glycoside **23** (42.3 mg, 52%; a:e, 12:1) and the starting material **21** (23.6 mg, 33%). **23**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.99 (d, *J* = 9.6 Hz, 1 H, 4-H), 5.76 (dd, *J* = 9.6, 5.8 Hz, 1 H, 3-H), 5.57 (br s, 1 H, 5-H), 5.31 (br s, 1 H, 8-H), 5.21 (dd, *J* = 3.9, 0.6 Hz, 1 H, 2′-H), 3.95–4.05 (m, 1 H, 6′-H), 3.45, 3.71 (2 dq, *J* = 9.7, 7.1, Hz, 2 × 1 H, 2′-OCH_2CH_3), 2.62 (dd, *J* = 14.6, 4.7 Hz, 1 H, 3′-H), 2.09–2.51 (m, 8 H), 2.05 (s, 3 H, 8-OAc), 1.60–1.79 (m, 3 H), 1.26–1.53 (m, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H, 2′-OCH_2CH_3), 0.92 (d, *J* = 7.0 Hz, 3 H, 2-CH_3).

(1*SR*,2*SR*,8*SR*,8a*RS*,2′*SR*,4′*RS*,6′*RS*)-6-[2-(8-Acetoxy-1,2,6,7,8,8a-hexahydro-2-methyl-1-naphthalenyl)ethyl]-2-ethoxytetrahydro-4-hydroxy-2*H*-pyran (24). To a solution of ethyl glycoside **23** (59.7 mg, 0.16 mmol) in THF (3.15 mL) at −78 °C was added (5 min) a 1 M L-Selectride solution in THF (396 μL). After 4 h at −78 °C, H_2O was added dropwise; the reaction mixture was allowed to warm to room temperature and was diluted with saturated $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with AcOEt (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (hexane–AcOEt, 2:1) of the crude residue gave **24** (33.4 mg, 56%) (the product decomposes on silica; a very quick chromatography gave yield of 80–87%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.98 (d, *J* = 9.6 Hz, 1 H, 4-H), 5.76 (dd, *J* = 9.6, 6.1 Hz, 1 H, 3-H), 5.56 (br s, 1 H, 5-H), 5.31 (br s, 1 H, 8-H), 4.96 (br d, *J* = 2.9 Hz, 1 H, 2′-H), 4.05 (dm, *J* = 10.0 Hz, 1 H, 4′-H), 3.92–4.00 (m, 1 H, 6′-H), 3.85 (d, *J* = 10.0 Hz, 1 H, 4′-OH), 3.43, 3.78 (2 dq, *J* = 9.7, 7.1 Hz, 2 × 1 H, 2′-OCH_2CH_3), 1.30–2.44 (complex, 15 H), 2.05 (s, 3 H, 8-OAc), 1.26 (t, *J* = 7.1 Hz, 3 H, 2′-OCH_2CH_3), 0.91 (d, *J* = 7.0 Hz, 3 H, 2-CH_3); IR ($CHCl_3$) 3480, 3000, 2940, 2920, 2860, 1720, 1365, 1245, 1110, 1090, 1045, 1030, 1010 cm^{-1}: HRMS (EI) calcd for $C_{22}H_{34}O_5$ 378.2406, found 378.2375.

(1*SR*,2*SR*,8*SR*,8a*RS*,4′*RS*,6′*RS*)-6-[2-(8-Acetoxy-1,2,6,7,8,8a-hexahydro-2-methyl-1-naphthalenyl)ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (25). To a solution of **24** (33.2 mg, 0.088 mmol) in THF (4.10 mL) was added 10% HCl (2.45 mL). The reaction mixture was stirred at room temperature for 35 min, cooled to 0 °C, and poured into cold saturated $NaHCO_3$ solution (80 mL). The aqueous solution was extracted with CH_2Cl_2 (4 × 25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was dissolved in dry C_6H_6 (5.25 mL) and heated at reflux for 1 h with freshly prepared Fetizon's reagent[19] (Ag_2CO_3–Celite; 505 mg, 0.88 mmol).[27] The reaction mixture was cooled to room temperature and filtered through Celite. Purification of the crude residue by flash chromatography (AcOEt–CH_2Cl_2, 1:1) gave **25** (17.9 mg, 59%) as a thick oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.99 (d, *J* = 9.7 Hz, 1 H, 4-H), 5.75 (dd, *J* = 9.7, 6.0 Hz, 1 H, 3-H), 5.58 (br s, 1 H, 5-H), 5.35 (br s, 1 H, 8-H), 4.61–4.70 (m, 1 H, 6′-H), 4.39 (br s, 1 H, 4′-H), 2.75 (dd, *J* = 17.6, 5.0 Hz, 1 H, 3′-H), 2.61 (ddd, *J* = 17.6, 3.8, 1.5 Hz, 1 H, 3-H), 2.07 (s, 3 H, 8-OAc), 1.35–2.41 (complex, 14 H), 0.91 (d, *J* = 7.0 Hz, 3 H, 2-CH_3); IR ($CHCl_3$) 3580, 3410 (br), 3010, 2950, 2920, 1720, 1375, 1250, 1185, 1075, 1035, 1020 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{28}O_5$ 348.1937, found 348.1926.

(1*SR*,2*SR*,8*SR*,8a*RS*,4′*RS*,6′*RS*)-6-[2-(1,2,6,7,8,8a-Hexahydro-8-hydroxy-2-methyl-1-naphthalenyl)ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one [(±)-ML-236A]. A solution of **25** (6.0 mg, 0.017 mmol) and LiOH·H_2O (7.2 mg, 0.17 mmol) in H_2O (1.20 mL) was heated at reflux for 2.5 h. The reaction mixture was cooled to 0 °C and 10% HCl (3.0 mL) and CH_2Cl_2 (5 mL) were added. After 2 h at room temperature, the mixture was poured in H_2O (25 mL) and extracted with AcOEt (3

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× 25 mL). The organic layers were washed with H_2O (20 mL), and the aqueous phase was extracted with AcOEt. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (AcOEt) afforded the desired compound (4.4 mg, 83%): mp 129-131 °C (hexane-AcOEt); ^1H NMR ($CDCl_3$, 490 MHz) δ 5.97 (d, J = 9.7 Hz, 1 H, 4-H), 5.75 (dd, J = 9.7, 5.9 Hz, 1 H, 3-H), 5.57 (br s, 1 H, 5-H), 4.70-4.76 (m, 1 H, 6'-H), 4.39 (dt, J = 8.6, 3.7 Hz, 1 H, 4'-H), 4.24 (br s, 1 H, 8-H), 2.75 (dd, J = 17.6, 5.1 Hz, 1 H, 3'-H), 2.63 (ddd, J = 17.6, 3.7, 1.7 Hz, 1 H, 3'-H), 2.29-2.40 (m, 2 H), 2.14-2.24 (m, 1 H), 1.46-2.07 (complex, 12 H), 0.92 (d, J = 7.1 Hz, 3 H, 2-CH_3); IR ($CHCl_3$) 3580, 3400 (br), 3010, 2950, 2920, 1720, 1390, 1370, 1250, 1075, 1045 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{26}O_4$ 306.1832, found 306.1839. The synthetic compound was indistinguishable (NMR, IR, TLC) from the natural material [obtained from (+)-compactin[28]].

Methyl (1*SR*,2*SR*,4a*RS*,6*SR*,8*SR*,8a*SR*)-8-(*tert*-Butyldimethylsilyoxy)-1,2,4a,5,6,7,8,8a-octahydro-6-hydroxy-2-methyl-5-oxo-1-naphthalenecarboxylate (30). To a solution of mCPBA (306.7 mg, 1.42 mmol) in hexanes (20.3 mL), cooled to -20 °C, was added (2 min) a solution of silyl enol ether **7** [prepared from lactone **5** (321 mg, 0.95 mmol), as mentioned above (see preparation of **8**) [LDA, -78 °C, toluene 105 °C (2.5 h), filtration of salt from hexanes solution]] in hexanes (3.5 mL).[29] The reaction mixture was stirred at -20 °C for 5 min and allowed to warm to room temperature. After 2 h, a second portion of mCPBA (100 mg, 0.46 mmol) was added. After 3 h at room temperature, dimethyl sulfide (1.5 mL) was added and the mixture was stirred for 10 min. Most of the acid was removed by filtration and the solvent evaporated. The residue was taken up in THF (35 mL) and treated with 1 N HCl (3.1 mL). After 20 min, the reaction mixture was poured in H_2O (250 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The organic phases were washed with brine (50 mL + 3 mL of 10% $Na_2S_2O_3$). The aqueous layer was extracted with CH_2Cl_2 (50 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude acid in dry ether (30 mL) was esterified with an excess of a ethereal CH_2N_2 solution (0 °C, 45 min). After concentration, the residue was purified by flash chromatography (hexane-AcOEt, 6:1) to give **30** (263.2 mg, 75%): mp 53.0-54.5 °C (hexane); ^1H NMR ($CDCl_3$, 250 MHz) δ 6.00 (dt, J = 10.1, 1.6 Hz, 1 H, 4-H), 5.77 (ddd, J = 10.1, 4.5, 2.7 Hz, 1 H, 3-H), 4.55 (br s, 1 H, 8-H), 4.52 (ddd, J = 11.9, 7.2, 3.7 Hz, 1 H, 6-H), 3.70 (s, 3 H, 1-CO_2CH_3), 3.57 (br d, J = 11.8 Hz, 1 H, 4a-H), 3.44 (d, J = 3.7 Hz, 1 H, 6-OH), 2.95 (11.5, 6.1 Hz, 1 H, 1-H), 2.62-2.71 (m, 1 H, 2-H), 2.58 (ddd, J = 13.6, 7.2, 3.4 Hz, 1 H, 7-H), 2.02 (~ddd, J = 11.8, 11.5, 1.6 Hz, 1 H, 8a-H), 1.70 (ddd, J = 13.6, 11.9, 2.0 Hz, 1 H, 7-H), 0.91 (s, 9 H, 8-OSi(t-C_4H_9)), 0.85 (d, J = 7.1 Hz, 3 H, 2-CH_3), 0.14, 0.01 (2 s, 2 × 3 H, 8-$OSi(CH_3)_2$); IR ($CHCl_3$) 3480 (br), 3010, 2950, 2930, 2880, 2850, 1730, 1715 (sh), 1470, 1460, 1435, 1375, 1290, 1260, 1245, 1205, 1175, 1145, 1095, 1065, 1010, 970, 960, 930, 865, 840, 815 cm^{-1}; MS m/e 311 $(M - 57)^+$.

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Supplementary Material Available: Experimental conditions for the preparation of racemic compounds **9-17** and for the concluding steps from (+)-**14** to (+)-compactin, spectral data for compounds **9-17**, spectral and rotation data for (+)-**14** to (+)-compactin, and rotation and melting point data for (+)-**3**-(+)-**14** (12 pages). Ordering information is given on any current masthead page.

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The Copigmentation Reaction of Anthocyanins: A Microprobe for the Structural Study of Aqueous Solutions

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Abstract: By means of visible absorption spectrometry, we have demonstrated that, in acidic aqueous solutions, chlorogenic acid (5-*O*-caffeoylquinic acid) gives a loose 1:1 complex with the flavylium cation of malvin (malvidin 3,5-diglucoside) chloride. The molecular interaction taking place between these two chemical species is characteristic of the copigmentation reaction of anthocyanins. For the first time the mechanism associated with this reaction is established. The equation describing the copigment effect is also given. The copigmentation reaction is a very fast process that is extremely influenced by temperature. Increasing the temperature or adding methanol, formamide, or sodium chloride always reduces the copigment effect. In fact, we demonstrate that the extent of copigmentation is strictly under the control of the unique molecular structure of liquid water. Finally, the copigmentation phenomenon, which is widespread in higher plants, constitutes a simple, inexpensive, and very sensitive microprobe for the structural studies of aqueous solutions.

As part of the general effort to improve our knowledge of the phenomena involved in plant pigmentation, we now report results on the copigmentation reaction of anthocyanins. Many factors are known to influence the color of anthocyanins.[1] Among these factors, copigmentation is one of the most important and perhaps the least understood. Copigments have a strong stabilizing effect on the color of anthocyanins. In their absence and, under the physico-chemical conditions prevailing in the natural media in which anthocyanins occur, the common anthocyanins exist es-

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