0.2 g of K<sub>2</sub>CO<sub>3</sub> for 2.5 h. The mixture was filtered, evaporated, taken up in CH<sub>2</sub>Cl<sub>2</sub>, and washed successively with H<sub>2</sub>O 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-tobulb [oven at 145 °C (0.025 mmHg)]: Anal. for C<sub>16</sub>H<sub>29</sub>NO<sub>2</sub>: C, H; [ $\alpha$ ]<sub>D</sub> = -113.1° (c = 0.55, CHCl<sub>3</sub>); <sup>1</sup>H NMR  $\delta$  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), 0.86 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.0 Hz, 3 H); <sup>13</sup>C NMR  $\delta$  (C) 172.8, 136.3, (CH) 125.6, 35.8, 30.4, 27.5, (CH<sub>2</sub>) 60.8, 45.8, 39.5, 35.0, 27.8, 26.6, (CH<sub>3</sub>) 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<sub>2</sub>Cl<sub>2</sub> at -20 °C was added 3.89 mL of Me<sub>2</sub>AlCl solution (1.0 M in hexanes) over 1.5 min. The mixture was stirred for 20 min and then quenched by addition of H<sub>2</sub>O. The mixture was taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed with brine. Chromatography (EtOAc/*i*-PrOH 98.51.5) gave 0.3622 g of 8. The analytical sample was recrystallized from ether: mp 152-153 °C;  $[\alpha]_D = -29.6^\circ$  (c = 0.50, CHCl<sub>3</sub>); Anal. for C<sub>16</sub>H<sub>27</sub>NO<sub>2</sub>, C, H, N; <sup>1</sup>H NMR  $\delta$  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); <sup>13</sup>C NMR  $\delta$  (C) 173.4, 133.6, (CH) 121.7, 68.5, 45.8, 34.0, 32.0, 28.0, (CH<sub>2</sub>) 40.8, 38.5, 36.9, 32.6, (CH<sub>3</sub>) 37.2, 35.8, 21.0, 14.5.

Cyclocondensation of 10 with 1-Methoxy-3-[(trimethylsily])oxy]-1,3butadiene. 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<sub>4</sub> 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<sub>3</sub>. The mixture was taken up in EtOAc and washed successively with saturated NaHCO<sub>3</sub> 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 pyraAcknowledgment. We express our gratitude to the members of the Physical Chemistry Department of Hoffmann-La Roche, Inc., for determination of spectral and analytical data, and to A. Williams for technical assistance.

**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, 118713-60-3; **10**, 118682-39-6; **11**, 118682-40-9; **12**, 118682-41-0; **13a**, 118682-42-1; **13a** (H =  $\alpha$ ), 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*)- $\alpha$ -methylbutyrate), 85613-99-6; **15a**, 118682-48-7; **15b**, 85614-07-9; **15b** ( $\beta$ -epoxide), 85648-19-7; **16a**, 118682-48-7; **15b**, 118682-50-1; **17**, 79691-11-5; i, 118682-53-3; ii, 118682-53-4; **Ph**<sub>3</sub>P=CH<sub>2</sub>, 3487-44-3; CH<sub>3</sub>C(OMe)<sub>2</sub>NMe<sub>2</sub>, 18871-66-4; Ph<sub>3</sub>P=CHOMe, 20763-19-3; [(*S*)-*C*<sub>2</sub>H<sub>3</sub>CH(CH<sub>3</sub>)CO]<sub>2</sub>O, 84131-91-9; TMSCH<sub>2</sub>CH=CH<sub>2</sub>, 762-72-1; Danishefsky's diene, 54125-02-9.

Supplementary Material Available: Spectral data (including <sup>13</sup>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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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,<sup>1</sup> through suppression of HMG-CoA reductase (HMGR), already finds growing application in cardiovascular medicine.<sup>2</sup> 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.<sup>3a,b</sup> We have been developing some new ideas with a view to this objective.<sup>4a-c</sup> 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

<sup>(1) (</sup>a) Endo, A.; Kuroda, M.; Tsujita, Y. J. Antibiot. 1976, 29, 1346. (b) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, G.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schönberg, G.; Hensens, D.; Hirshfeld, J.; Hoogsteen, K.; Liesch, J.; Springer, J. Proc. Natl. Acad. Sci. U.S.A. 1980, 77, 3957.

<sup>(2)</sup> Endo, A. J. Med. Chem. 1985, 28, 401, and references therein.

<sup>(3) (</sup>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.

 <sup>(4) (</sup>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.

Scheme I



by compound 1 in several Lewis acid catalyzed additions to the double bond.<sup>5</sup> Included among these is a Mukaiyama grouptransfer reaction with silyl ketene acetal 2 to give 3, as substantially the only product.<sup>6</sup> A second silatropic group-transfer reaction  $(3 \rightarrow 4)$ , this time in the aldol mode, with essentially perfect trans-erythro specificity sets the stage for a lactonic variation<sup>7</sup> of the Ireland<sup>8</sup> (silyl) enolate rearrangement. This bond reorganization reaction  $(5 \rightarrow 6 \rightarrow 7)$  occurred with the perfect suprafaciality and fidelity to a boatlike transition state which are its hallmarks.<sup>9a,b</sup> The final component is the selectivity realized in the Lewis acid catalyzed cyclocondensation of aldehyde 17 with diene 18.<sup>10,11</sup> 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

(7) For novel enhancements and applications of the lactonic variation of (1) For novel ennancements and applications of the factoric 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.; Schoener, F. J. Evic, L. M. Catterkers 1996, 42, 2727. 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 cyclo-(10) Figure 1 acta's selectivities were realized in the same sort of cyclo-condensation 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. Boiyert J. Patter A. D. Vale Usivarity upsublished

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

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<sub>2</sub> catalysis) followed by reaction of 3 (BF<sub>3</sub> etherate catalysis) with crotonaldehyde gave, with very high stereoselection, the siloxy aldol 4 (Scheme I). After desilvlation and lactonization (trifluoroacetic acid-aqueous acetic acid-THF), keto lactone 5 is obtained. The overall yield of 5 from 1 is presently 35-38%.<sup>14</sup> 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  $5 \rightarrow 8$  is ca. 80%. The  $\beta,\gamma$ -unsaturated ketone was converted to the 3(4),4a(5)-diene via (i) L-Selectride reduction, (ii) mesylation, and (iii) elimination with DBU.<sup>3</sup> Compound 9, thus available in 65% yield from 8, was readied for chain extension by (i) reduction with DIBAH and (ii) Swern oxidation<sup>15</sup> 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)<sup>16</sup> followed by reduction of the ester linkage with DIBAH gave rise to alcohol 14 (75%). Based on the findings of Wovkulich and Uskokovic,<sup>10</sup> 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 silvlation (TBSCl; Et<sub>3</sub>N; 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<sub>4</sub> in methylene chloride at -40 °C) gave a mixture of aldols (19 and 20)<sup>18a</sup> and dihydropyrones (21 and 22).<sup>18b</sup> 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.<sup>4b,c</sup> 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<sup>19</sup> 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.<sup>13</sup> The synthesis described herein was repeated and, with some modification, led to the total synthesis of the naturally occurring enantiomer of compactin.<sup>17</sup> 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.<sup>10</sup> 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-

(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.

<sup>(5)</sup> High syn selectivity was also observed with allyltrimethylsilane (catalyzed by TiCl4) and in a Diels-Alder reaction with 1,3-butadiene (catalyzed by AlCl<sub>3</sub>). 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. (6) Kobayashi, S.; Mukaiyama, T. Chem. Lett. 1986, 1805

<sup>(14)</sup> 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.

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

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

<sup>(19)</sup> Fetizon, M.; Golfier, M. Compt. Rend. 1968, 267, 900.

#### Scheme II

Scheme III



24  $X = \beta OH; \alpha H$ 

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.<sup>20</sup>

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,<sup>21</sup> and (iii) experiments directed toward achieving a better understanding of the basis of stereochemical transmission in the cyclocondensation reaction.  $% \left( {{{\bf{r}}_{\rm{s}}}} \right)$ 

#### **Experimental Section**

**4-Hydroxy-2-cyclohexen-1-one.** To a solution of 3-cyclohexen-1-one<sup>22</sup> (38.45 g, 0.40 mol) in CH<sub>2</sub>Cl<sub>2</sub> (800 mL) was added slowly (50 min) mCPBA (89.33 g, 0.44 mol) in CH<sub>2</sub>Cl<sub>2</sub> (800 mL). The reaction mixture was stirred at room temperature for 14 h. The suspension was filtered and the solution washed with 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (375 mL), saturated NaH-CO<sub>3</sub> (500 mL), H<sub>2</sub>O (500 mL) and brine (500 mL), dried (MgSO<sub>4</sub>), and concentrated in vacuo. The residue was dissolved in a 1:1 mixture of ether-CH<sub>2</sub>Cl<sub>2</sub> (760 mL) and stirred for 1 h with basic alumina<sup>23</sup> (activity

<sup>(20)</sup> Serizawa, W.; Nakagawa, K.; Hamano, K.; Tsujita, Y.; Terahara, A.; Kuwano, H. J. Antibiot. 1983, 36, 604.

<sup>(21)</sup> Boisvert, L., Yale University, unpublished results.

<sup>(22)</sup> Rubottom, G. M.; Gruber, J. M. J. Org. Chem. 1977, 42, 1051.

Scheme IV



 $R = \alpha Me$  mevinolin

I, 147 g). The solid was filtered and thoroughly washed with CH<sub>2</sub>Cl<sub>2</sub>. 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); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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,  $J = 17.2, \sim 4.9, 1.0$  Hz, 1 H, 6-H), 2.30-2.45 (m, 2 H, 5.6-H), 2.00 (tdd,  $J = 12.7, 9.3, \sim 4.9$  Hz, 1 H, 5-H), 1.81 (s, 1 H, 4-OH); IR (CHCl<sub>3</sub>) 3580, 3400 (br), 3000, 2940, 1670, 1410, 1370, 1120, 1055, 960, 935, 855 cm<sup>-1</sup>; MS m/e 112 (M<sup>+</sup>).

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).<sup>24</sup> After 1.5 h at room temperature, the reaction mixture was diluted with ether (750 mL) and washed with H<sub>2</sub>O (200 mL), 0.1 N HCl (2 × 250 mL), saturated NaHCO<sub>3</sub> (200 mL), and brine (200 mL), then dried (MgSO<sub>4</sub>), 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); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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<sub>4</sub>H<sub>9</sub>)), 0.13, 0.12 (2 s, 2 × 3 H, 4-OSi(CH<sub>3</sub>)<sub>2</sub>); IR (CHCl<sub>3</sub>) 3010, 2960, 2930, 2890, 2860, 1685, 1470, 1385, 1260, 1135, 1110, 1070, 1000, 990, 975, 960, 875, 865, 845 cm<sup>-1</sup>; MS m/e 226 (m<sup>+</sup>).

Ethyl (1RS,6SR)[3,6-Bis(terr-butyldimethylsiloxy)-2-cyclohexen-1yl]acetate (3). A solution of enone 1 (4.50 g, 19.9 mmol) and HgI<sub>2</sub> (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<sub>3</sub>N (416  $\mu$ L, 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<sub>3</sub>N solution of hexane-AcOEt, 10:1) eluting with hexane-AcOEt (10:1) and concentrated in vacuo. Purification of the crude material by flash chromatogo i (7.98 g, 94%): 'H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  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<sub>2</sub>CH<sub>3</sub>), 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, 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<sub>2</sub>CH<sub>3</sub>), 0.92, 0.89 (2 s, 2 × 9 H, 3,5-OSi(*t*-C<sub>4</sub>H<sub>9</sub>)), 0.13 (s, 6 H, 3-OSi(CH<sub>3</sub>)<sub>2</sub>), 0.07, 0.04 (2 s, 2 × 3 H, 6-OSi(CH<sub>3</sub>)<sub>2</sub>); IR (CHCl<sub>3</sub>) 2960, 2890, 2860, 1725, 1665, 1475, 1465, 1380, 1260, 1180, 1100, 1065, 1010, 915, 890, 845 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>22</sub>H<sub>44</sub>O<sub>4</sub>Si<sub>2</sub> 428.2778, found 428.2742.

(1RS,4aRS,5SR,8aSR)-5-(tert-Butyldimethylsiloxy)-4a,6,7,8atetrahydro-1-[(E)-1-propen-1-yl]-1H-2-benzopyran-3,8(4H,5H)-dione (5). To a cold (-78 °C) solution of crotonaldehyde (2.59 g, 2.99 mL, 36.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (95 mL) was added dropwise (2 min) BF<sub>3</sub>·OEt<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> (30 mL), allowed to warm to room temperature, and diluted with saturated NaHCO<sub>3</sub> (70 mL). The organic layer was separated and the aqueous layer was extracted with CH2Cl2  $(4 \times 50 \text{ mL})$ . The combined organic fractions were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The crude aldol 4 (9.07 g) was treated with a mixture of AcOH-THF-H<sub>2</sub>O-TFA (100 mL:20 mL:20 mL:20 mL) for 4.5 h at room temperature. The reaction mixture was poured in H<sub>2</sub>O (1.7 L). Extraction with  $CH_2Cl_2$  (3 × 300 mL) gave a combined organic phase which was washed with saturated NaHCO<sub>3</sub> (2 × 250 mL), dried (MgSO<sub>4</sub>), 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: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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<sub>3</sub>), 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 (CH-Cl<sub>3</sub>) 3020, 2960, 2930, 2880, 2860, 1720, 1330, 1300, 1260, 1240, 1195, 1165, 1135, 1125, 1090, 1060, 1010, 995, 840 cm<sup>-1</sup>; HRMS (CI) calcd for C<sub>18</sub>H<sub>31</sub>O<sub>4</sub>Si 339.1992, found 339.2006.

Methyl (1SR,2SR,4aRS,8SR,8aSR)-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

 <sup>(23)</sup> Suzuki, M.; Oda, Y.; Noyori, R. J. Am. Chem. Soc. 1979, 101, 1623.
 (24) Aizpurua, J. M.; Palomo, C. Tetrahedron Lett. 1985, 26, 475.
 (25) Kita V. Segawa L. Haruta, J. V. Sauda, H. Tamura, V. J. Chem.

<sup>(25)</sup> Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y. J. Chem. Soc., Perkin Trans 1 1982, 1099.

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<sub>4</sub>), filtered, and concentrated in vacuo. The crude acid in dry ether (100 mL) was esterified with an excess of a ethereal CH<sub>2</sub>N<sub>2</sub> 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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, -1.5Hz, 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<sub>3</sub>), 0.09, 0.02 (2 s, 2 × 3 H, 8-OSi(CH<sub>3</sub>)<sub>2</sub>); IR (CHCl<sub>3</sub>) 3030, 3020, 2960, 2930, 2860, 1730, 1715, 1370, 1290, 1260, 1235, 1180, 1145, 1135, 1100, 1090, 1070, 1000, 840 cm<sup>-1</sup>; HRMS (EI) calcd for  $C_{19}H_{32}O_4Si$  352.2070, found 352.2096. Anal. Calcd for C<sub>19</sub>H<sub>32</sub>O<sub>4</sub>Si: C, 64.73; H, 9.15. Found: C, 65.36; H. 9.12.

Methyl (1SR,2SR,4aRS,5SR,8SR,8aSR)-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<sub>2</sub>O (1 mL) and warmed to 0 °C. A 2.5 N NaOH solution (6.7 mL) and a 30% H<sub>2</sub>O<sub>2</sub> 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<sub>2</sub>O<sub>3</sub>) and extracted with  $CH_2Cl_2$  (6 × 150 mL). The combined organic layers were dried (MgSO<sub>4</sub>), 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  $\alpha,\beta$ -unsaturated ketone (69 mg, 4%), and the axial alcohol 8b (1.55 g, 82%): mp 105.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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<sub>2</sub>CH<sub>3</sub>), 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,  $J \sim 7$  Hz, 3 H, 2-CH<sub>3</sub>), 0.87 (s, 9 H, 8-OSi( $tC_4H_9$ )), 0.03, -0.05 (2 s, 2 × 3 H, 8-OSi(CH<sub>3</sub>)<sub>2</sub>); IR (CHCl<sub>3</sub>) 3580, 3020, 2950, 2930, 2880, 2860, 1730, 1440, 1255, 1175, 1145, 1095, 1075, 1045, 1030, 840 cm<sup>-1</sup>; HRMS (CI) calcd for  $C_{19}H_{35}O_4Si$  355.2304, found 355.2297. Anal. Calcd for C<sub>19</sub>H<sub>34</sub>O<sub>4</sub>Si: C, 64.36; H, 9.67. Found: C, 64.47; H, 9.79.

(1SR,2SR,8SR,8aRS,6'RS and 6'SR)-6-[2-(8-Acetoxy-1,2,6,7,8,8ahexahydro-2-methyl-1-naphthalenyl)ethyl]-5,6-dihydro-4H-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<sub>4</sub> solution in CH<sub>2</sub>Cl<sub>2</sub> (245  $\mu$ L, 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  $\mu$ L, 0.443 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (550  $\mu$ L) 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<sub>3</sub> (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 ( $2 \times 10$  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  $\mu$ L, 5.58 mmol) was added. After 2.5 h at room temperature, solid NaHCO3 (350 mg) was added in one portion followed (5 min) by a dropwise addition of saturated NaHCO<sub>3</sub> (3.5 mL). The mixture was taken up in AcOEt (60 mL) and washed with brine (3  $\times$  20 mL), dried (MgSO<sub>4</sub>), 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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, 5.9 Hz, 1 H, 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, 12.3Hz, 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<sub>3</sub>); IR (CHCl<sub>3</sub>) 3010, 2990, 2950, 2910, 2870, 2860, 1720, 1660, 1590, 1400, 1370, 1265, 1245, 1230, 1185, 1030, 1020 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>20</sub>H<sub>26</sub>O<sub>4</sub> 330.1832, found 330.1819. **22**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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<sub>3</sub>); IR (CHCl<sub>3</sub>) 3000, 2940, 2910, 2870, 2860, 1720, 1660, 1585, 1400, 1370, 1260 (sh), 1250, 1185, 1030 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>20</sub>H<sub>26</sub>O<sub>4</sub> 330.1832, found 330.1846.

(1SR,2SR,8SR,8aRS,2'SR,6'RS)-6-[2-(8-Acetoxy-1,2,6,7,8,8ahexahydro-2-methyl-1-naphthalenyl)ethyl]-2-ethoxytetrahydro-4Hpyran-4-one (23). A 1 M HCl solution in EtOH<sup>4b,c,26</sup> (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 NaHCO3 (20 mL) was added, and the mixture was diluted with H<sub>2</sub>O (50 mL). The aqueous solution was extracted with AcOEt ( $3 \times 35$  mL), and the combined organic layers were dried (MgSO<sub>4</sub>), 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: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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,  $2 \times 1$  H, 2'-OCH<sub>2</sub>CH<sub>3</sub>), 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<sub>2</sub>CH<sub>3</sub>), 0.92 (d, J = 7.0 Hz, 3 H, 2-CH<sub>3</sub>)

(1SR, 2SR, 8SR, 8aRS, 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-2H-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  $\mu$ L). After 4 h at -78 °C, H<sub>2</sub>O was added dropwise; the reaction mixture was allowed to warm to room temperature and was diluted with saturated NaHCO<sub>3</sub> solution (50 mL). The aqueous phase was extracted with AcOEt ( $3 \times 30$  mL). The combined organic layers were dried (MgSO<sub>4</sub>), 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%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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, $2 \times 1$  H, 2'-OCH<sub>2</sub>CH<sub>3</sub>), 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<sub>2</sub>CH<sub>3</sub>), 0.91 (d, J = 7.0 Hz, 3 H, 2-CH<sub>3</sub>); IR (CHCl<sub>3</sub>) 3480, 3000, 2940, 2920, 2860, 1720, 1365, 1245, 1110, 1090, 1045, 1030, 1010 cm<sup>-1</sup>: HRMS (EI) calcd for C<sub>22</sub>H<sub>24</sub>O<sub>5</sub> 378.2406, found 378.2375.

(1SR,2SR,8SR,8aRS,4'RS,6'RS)-6-[2-(8-Acetoxy-1,2,6,7,8,8ahexahydro-2-methyl-1-naphthalenyl)ethyl]tetrahydro-4-hydroxy-2Hpyran-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<sub>3</sub> solution (80 mL). The aqueous solution was extracted with  $CH_2Cl_2$  (4 × 25 mL), dried (MgSO<sub>4</sub>), 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<sup>19</sup>  $(Ag_2CO_3-Celite; 505 \text{ mg}, 0.88 \text{ mmol}).^{27}$  The reaction mixture was cooled to room temperature and filtered through Celite. Purification of the crude residue by flash chromatography (AcOEt-CH<sub>2</sub>Cl<sub>2</sub>, 1:1) gave 25 (17.9 mg, 59%) as a thick oil:  $^1H$  NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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<sub>3</sub>); IR (CHCl<sub>3</sub>) 3580, 3410 (br), 3010, 2950, 2920, 1720, 1375, 1250, 1185, 1075, 1035, 1020 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>20</sub>H<sub>28</sub>O<sub>5</sub> 348.1937, found 348.1926.

(1SR, 2SR, 8SR, 8aRS, 4RS, 4RS, 6'RS)-6-[2-(1,2,6,7,8,8a-Hexahydro-8-hydroxy-2-methyl-1-naphthalenyl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one [(±)-ML-236A]. A solution of 25 (6.0 mg, 0.017 mmol) and LiOH-H<sub>2</sub>O (7.2 mg, 0.17 mmol) in H<sub>2</sub>O (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<sub>2</sub>Cl<sub>2</sub> (5 mL) were added. After 2 h at room temperature, the mixture was poured in H<sub>2</sub>O (25 mL) and extracted with AcOEt (3

<sup>(26)</sup> Kozikowski, A. P.; Li, C. S. J. Org. Chem. 1985, 50, 778.

<sup>(27)</sup> Keck, G. E.; Kachensky, D. F. J. Org. Chem. 1986, 51, 2487.

× 25 mL). The organic layers were washed with H<sub>2</sub>O (20 mL), and the aqueous phase was extracted with AcOEt. The combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. Purification by flash chromatography (AcOEt) afforded the desired compound (4.4 mg, 83%): mp 129–131 °C (hexane-AcOEt); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 490 MHz)  $\delta$  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<sub>3</sub>); IR (CHCl<sub>3</sub>) 3580, 3400 (br), 3010, 2950, 2920, 1720, 1390, 1370, 1250, 1075, 1045 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>18</sub>H<sub>26</sub>O<sub>4</sub> 306.1832, found 306.1839. The synthetic compound was indistinguishable (NMR, IR, TLC) from the natural material [obtained from (+)-compactin<sup>28</sup>].

Methyl (15R,2SR,4aRS,6SR,8SR,8aSR)-8-(tert-Butyldimethylsiloxy)-1,2,4a,5,6,7,8,8a-octahydro-6-hydroxy-2-methyl-5-oxo-1naphthalenecarboxylate (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).<sup>29</sup> 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 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<sub>2</sub>S<sub>2</sub>O<sub>3</sub>). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The crude acid in dry ether (30 mL) was esterified with an excess of a ethereal CH<sub>2</sub>N<sub>2</sub> 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); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  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, 3.7Hz, 1 H, 6-H), 3.70 (s, 3 H, 1-CO<sub>2</sub>CH<sub>3</sub>), 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 ( $\sim$ 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 = 7.1Hz, 3 H, 2-CH<sub>3</sub>), 0.14, 0.01 (2 s,  $2 \times 3$  H, 8-OSi(CH<sub>3</sub>)<sub>2</sub>); IR (CHCl<sub>3</sub>) 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<sup>-1</sup>; MS m/e 311 (M - 57)<sup>+</sup>.

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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.

# 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.<sup>1</sup> 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-

<sup>(28)</sup> Willard, A. K.; Smith, R. L. J. Labelled Compd. Radiopharm. 1982, 19, 337.

<sup>(29)</sup> Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. Tetrahedron Lett. 1974, 4319.

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<sup>(1)</sup> Brouillard, R. In *The Flavonoids. Advances in Research*; Harborne, J. B., Ed.; Chapman and Hall: London, 1988; p 525.