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A Formal, Enantiospecific Synthesis of Pseudoguaianolides

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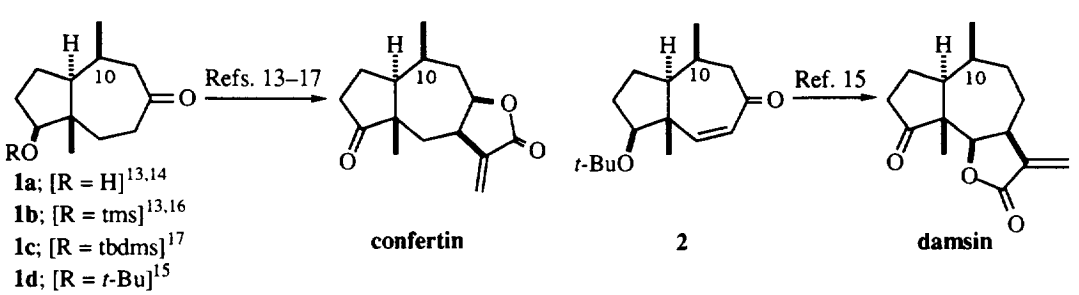
Abstract: The preparation of ketal-enone (**3**) and hydroxy-ketones (**1a**), (**16**), and (**4a**), from (–)-camphor (**6**) represents a formal enantiospecific synthesis of (+)-carpesiolin, (+)-confertin, (–)-damsin, (–)-helenalin, (+)-bigelovin, (+)-mexicanin I, and (+)-linifolin A.

The pseudoguaianolides[1] are a relatively large group of sesquiterpenoid tricyclic lactones that are classified as helenanolides or ambrosanolides on the basis of the respective α- and β- configuration of the methyl group at the C(10) position [*cf.* Schemes 1 and 2]. The development of synthetic routes[2,3] to pseudoguaianolides has been stimulated by the discovery that many members of the group display anti-leukemic, anti-tumor, anti-inflammatory, anti-bacterial, dermatological, and insect anti-feedant properties[4-8].

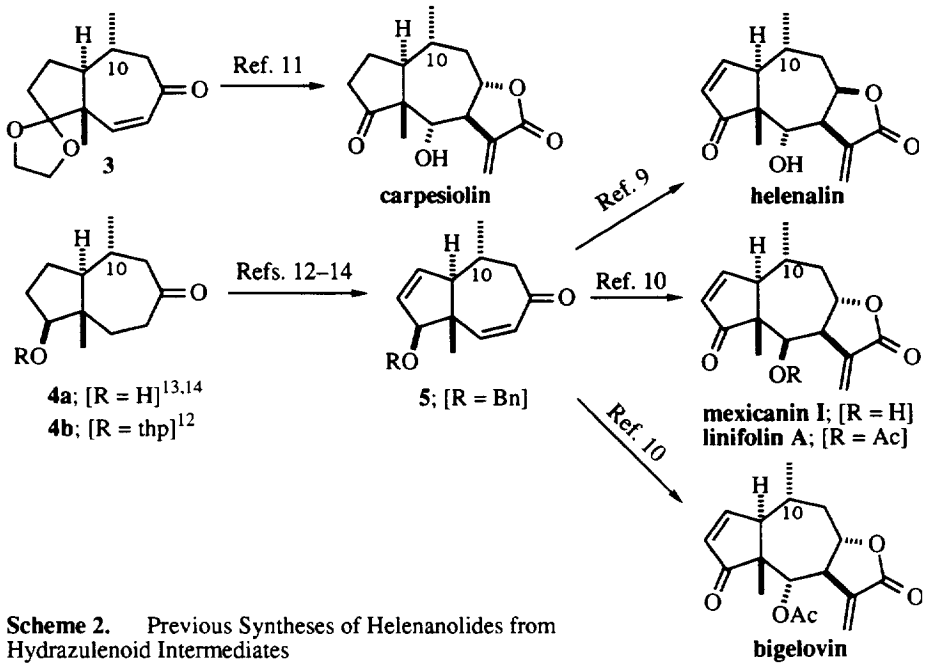
Key intermediates in several reported syntheses of helenanolides[9-14] and ambrosanolides[13-17] are the hydrazulenoid compounds (**1**) – (**5**) shown in Schemes 1 and 2, and this report describes synthetic routes that can provide these compounds[18] in either enantiomeric form. The only previous enantiospecific routes to pseudoguaianolides, specifically ambrosanolides, were reported by Quinkert and co-workers[16] (confertin) and recently by Asaoka and co-workers[18t] (neoambrosin, parthenin, and dihydroisoparthenin).



1a; [R = H][13,14]
1b; [R = tms][13,16]
1c; [R = tbdms][17]
1d; [R = *t*-Bu][15]

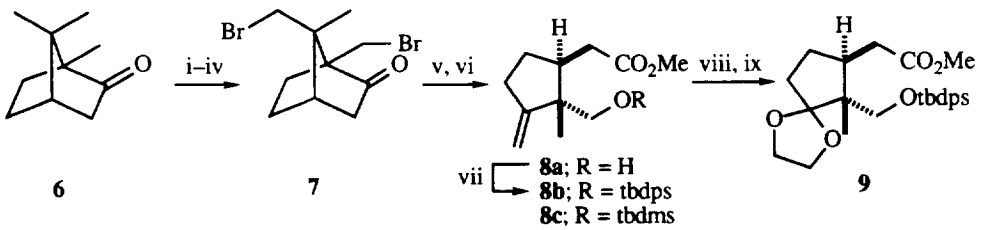
confertin **2** **damsin**

Scheme 1. Previous Syntheses of Ambrosanolides from Hydrazulenoid Intermediates

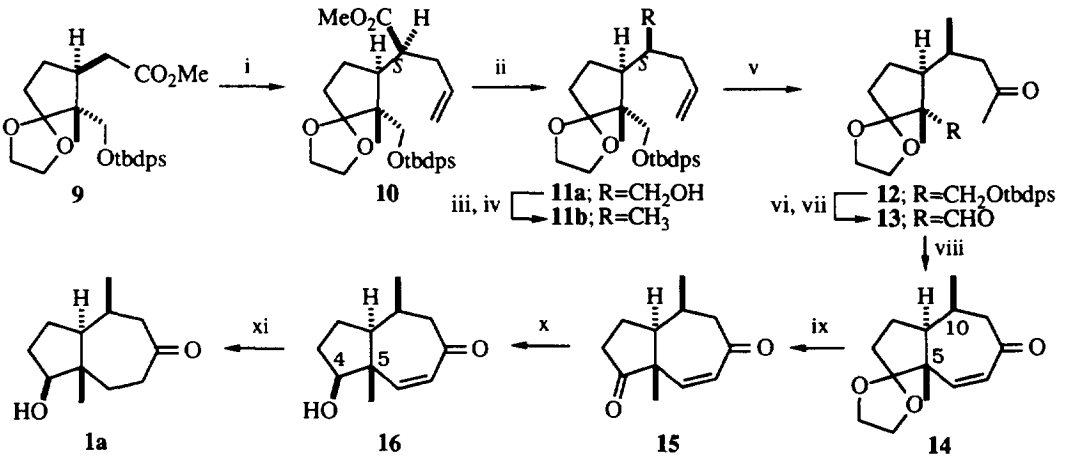


Scheme 2. Previous Syntheses of Helenanolides from Hydrazulenoid Intermediates

The synthetic routes [Schemes 3–5] we have developed to helenanolide and ambrosanolide intermediates (**1a**), (**2**), (**3**), and (**4a**) involve the use of (–)-ketal-ester (**9**), derived from (–)-camphor (**6**) [Scheme 3], as a common monocyclic intermediate. Previous reports from our laboratory have described the synthesis of (–)-9,10-dibromocamphor (**7**)[19,20] and its efficient cleavage[20,21] to provide the monocyclic hydroxy-ester (**8a**) in >90% yield. We have also shown that ester (**8c**) undergoes stereoselective alkylation[22] and thus it was assumed that the derived ketal-ester (**9**) [Scheme 3] would behave in a similar manner.



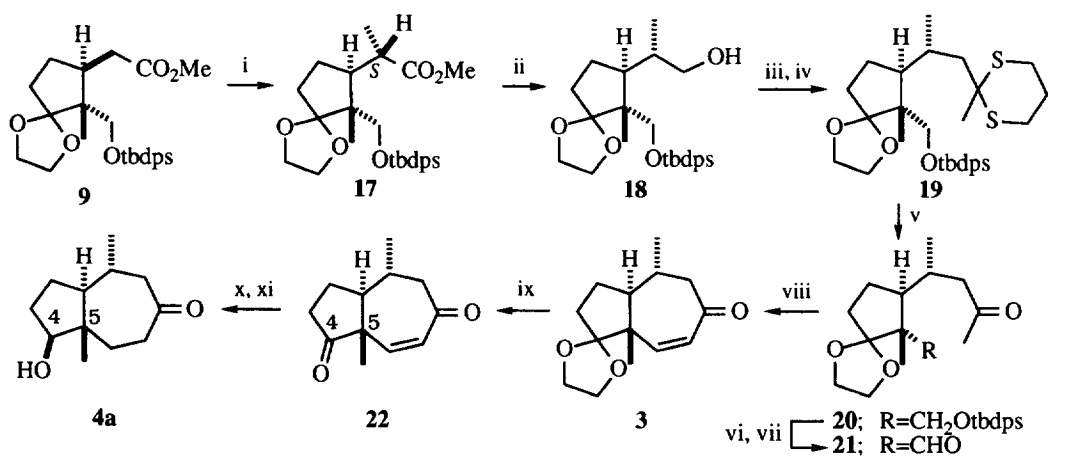
Scheme 3. (i) Br_2, HOAc, 80 °C [80%] (ii) Br_2, $ClSO_3H$, 5 h [75%] (iii) Br_2, $ClSO_3H$, 5 d (iv) Zn, HOAc–Et_2O (1:1), 0 °C [60% over two steps] (v) KOH, DMSO–H_2O (9:1), 90 °C [85%] (vi) K_2CO_3, DMF; CH_3I [94%] (vii) *t*-$BuPh_2SiCl$, imidazole, DMF [95%] (viii) O_3, CH_2Cl_2–MeOH (1:1), –78 °C; Me_2S, –78 °C —> r.t. [92%] (ix) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, reflux [92%].



Scheme 4. (i) LDA, THF, –78 °C; $H_2C{=}CHCH_2Br$, –78 °C—>r.t. [95%] (ii) $LiAlH_4$, THF, 0 °C [96%] (iii) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C [97%] (iv) $LiEt_3BH$, THF; 3 M NaOH, 30% H_2O_2 [88%] (v) $PdCl_2$, CuCl, O_2, DMF–H_2O (9:1) [91%] (vi) TBAF, THF, reflux [90%] (vii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; Et_3N, –78 °C—>r.t [95%] (viii) 10% KOH, MeOH, 12 days; MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C; DBU [70%] (ix) 1 M HCl, Me_2CO [90%] (x) $NaBH_4$, EtOH, –10 °C [87%] (xi) H_2, Pd-C, EtOH [93%].

In the event, stereoselective alkylation[22] of (**9**) with allyl bromide [LDA, THF; allyl bromide; *cf.* Scheme 4] provided ester (**10**) as a single diastereomer in 95% yield. The diastereomeric purity of (**10**) [>99%] was supported by its glc characteristics and by the absence of signals due to the undesired diastereomer of (**10**) in the 400 MHz ^{1}H-nmr spectrum. Treatment of (**10**) with $LiAlH_4$ at 0 °C yielded ketal-alcohol (**11a**) in excellent yield [96%]. Mesylation of (**11a**) [MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C; 97%] followed by reductive removal of the mesyloxy group [$LiEt_3BH$, THF; NaOH, H_2O_2; 88%][23] provided ketal-alkene (**11b**). Subsequent conversion of (**11b**) to (10*S*)-methyl ketone (**12**) was readily accomplished by application of the Wacker reaction[24] [$PdCl_2$, CuCl, O_2, DMF–H_2O (9:1); 91%]. Hydrolysis of the silyl protective group in (**12**) [TBAF, THF, reflux; 90%] followed by Swern oxidation[25] gave the air-sensitive keto-aldehyde (**13**) [95%]. It was presumed at this point that the desired ketal-enone (**14**) could be prepared from (**13**) through an intramolecular aldol condensation reaction. In our initial experiments, treatment of (**13**) with aqueous KOH in methanol or 1% KOH/Et_2O[26] resulted in only minimal (<10%) conversion of (**13**) to the desired ketal-enone (**14**). Likewise, treatment of (**13**) with a variety of basic [Bu_4NOH/MeOH; NaOMe/MeOH; KOBu^t/HOBu^t; LiI/Et_2O[27]; Et_2AlOEt, toluene[28]] and acidic [*p*-TsOH/C_6H_6; PPTS/C_6H_6; H_3BO_3/toluene[29]; HOAc/piperidine/C_6H_6[30]; and HCl/HOAc[31]] condensing agents failed to promote the required intramolecular aldol condensation in acceptable yield. Presumably the low efficiency of these reactions is due to steric interactions between the C(5) and C(10) methyl groups in the transition state. Interestingly, in one case, treatment of the keto-aldehyde (**13**) with tetrabutylammonium hydroxide in refluxing DME provided the alternative aldol condensation product, a strained, *trans*-fused bicyclo[3.3.0]octenone, as the major product (64%, based on recovered starting material). Fortunately, after

considerable experimentation, it was found that treatment of (**13**) with 10% aq. KOH (5 equivalents)/MeOH for 12–16 days at room temperature, followed by dehydration [MsCl, DMAP, NEt_3; DBU], provided (10*S*)-ketal-enone (**14**) in 70% yield. The *syn* relationship between the C(5) and C(10) methyl groups in (**14**) was confirmed by the results of an n.O.e. experiment [400 MHz] in which irradiation of the C(5) methyl signal [1.19 ppm (s, 3H)] resulted in enhancement of the C(10) methyl signal [1.06 (s, 3H)], and vice versa. Subsequent hydrolysis [1 M HCl, Me_2CO] provided enedione (**15**) in 90% yield. By analogy with other related bicyclic enedione systems[32], regioselective and stereoselective (>98%) reduction [$NaBH_4$, EtOH, –10 °C; 87%] of (**15**) provided (–)-hydroxy-enone (**16**). The corresponding *t*-butyl ether (**2**) has been used as an intermediate in the synthesis of damsin[15]. Irradiation of the C(4) proton in (**16**) [3.69 ppm (dd, J = 8.0, 8.0 Hz, 1H)] in a difference n.O.e. experiment did not result in enhancement of the C(5)-methyl signal [1.09 ppm (s, 3H)]. Although this result does not necessarily provide conclusive evidence to support the configurational assignment at C(4), we have assigned the β-stereochemistry to the C(4) hydroxyl group in (**16**) on the basis of analogous stereoselective sodium borohydride reductions[18b,d,j–l,u;32b,c]. In any case, the exact stereochemistry at C(4) in hydroxy-enone (**16**) is not crucial to its subsequent use in ambrosanolide synthesis, as there is a carbonyl group at C(4) of all the ambrosanolides under consideration (*cf.* Scheme 1). Finally, catalytic hydrogenation [H_2, Pd-C, EtOH; 93%] of (**16**) yielded (–)-hydroxy-ketone (**1a**), an intermediate previously used in the synthesis of confertin[13-17].



Scheme 5. (i) LDA, THF, –78 °C; CH_3I, –78 °C—>r.t. [95%] (ii) $LiAlH_4$, THF, 0 °C [96%] (iii) I_2, PPh_3, imidazole, Et_2O–CH_3CN (5:3) [85%] (iv) 2-methyl-1,3-dithiane, BuLi, THF, –25 °C [85%] (v) $Hg(ClO_4)_2$, $CaCO_3$, H_2O, THF [93%] (vi) TBAF, THF, reflux [90%] (vii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; Et_3N, –78 °C—>r.t [95%] (viii) 10% KOH, MeOH; MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C; DBU [82%] (ix) 1 M HCl, Me_2CO [90%] (x) $NaBH_4$, EtOH, –10 °C [85%] (xi) H_2, Pd-C, EtOH [95%].

Access to the helenanolide series [Scheme 5] was gained through a reaction sequence that involved initial stereoselective methylation[22] of ester (**9**) [LDA, THF; CH_3I; 95%]. The diastereomeric purity [>99%] of the resulting ester (**17**) was established by glc and 400 MHz ^{1}H-nmr characteristics. Reduction of (**17**)

[$LiAlH_4$, THF, 0 °C; 96%] followed by conversion of the resulting primary alcohol (**18**) to the corresponding iodide [I_2, PPh_3, imidazole, Et_2O–CH_3CN (5:3); 85%][33] and then exposure of the iodide to 2-lithio-2-methyl-1,3-dithiane[34] yielded the ketal-dithiane (**19**) [85%]. Subsequent chemoselective hydrolysis of the dithiane group in (**19**) [$Hg(ClO_4)_2$, $CaCO_3$, H_2O, THF; 93%][35] provided (10*R*)-methyl ketone (**20**). Hydrolysis of the *t*-butyldiphenylsilyl protective group in (**20**) [TBAF, THF, reflux; 90%] followed by Swern oxidation[25] yielded the air-sensitive keto-aldehyde (**21**). Treatment of (**21**) in MeOH with 10% aq. KOH (3 equivalents) promoted intramolecular aldol condensation and, after mesylation [MsCl, DMAP, Et_3N, CH_2Cl_2] and elimination [DBU] of methanesulfonic acid, provided (10*R*)-(–)-ketal-enone (**3**) [82% from (**21**)], a key intermediate in the synthesis of carpesiolin[11]. In contrast to the twelve days required for the corresponding aldol condensation step in the ambrosanolide series [*cf.* Scheme 4], the aldol addition step involving (**21**) was complete after only 2 h. The stereochemistry of the C(10) methyl group in ketal-enone (**3**) was confirmed by means of a difference n.O.e. experiment. Once again, we are aware that the absence of an n.O.e. between the C(5) and C(10) methyl groups does not necessarily suggest that the two methyl groups are oriented *anti* to each other. However, in view of the fact that an n.O.e. is observed between the corresponding methyl groups of the diastereomer (**14**), which differs from ketal-enone (**3**) *only at C(10)*, the absence of an n.O.e. betwen the C(5) and C(10) methyl groups confirms the 10α-stereochemistry of (**3**). Hydrolysis of enone (**3**) [1 M HCl, Me_2CO; 90%] provided enedione (**22**). Regioselective and stereoselective reduction of enedione (**22**) with $NaBH_4$ in EtOH provided a hydroxy-enone whose diastereomeric purity was determined by glc and ^{1}H-nmr spectroscopy [400 MHz] to be greater than 98%. The configuration of the C(4) hydroxyl group was assigned in the same manner as that of (**16**), described above, and also in view of the fact that no n.O.e. was observed between the C(4) proton and C(5) methyl protons. Finally, catalytic hydrogenation [H_2, Pd-C, EtOH; 95%] provided (–)-hydroxy-ketone (**4a**), and hence[12] enone (**5**), an intermediate previously used in the synthesis of helenalin[9,12,13], bigelovin[10], mexicanin I[10], and linifolin A[10] [*cf.* Scheme 2].

Spectroscopic data for all relay compounds were in agreement with those reported previously in the literature[11,13,16,17]. Minor modifications of this versatile synthetic route could lead to the enantiospecific synthesis of other pseudoguaianolides and pseudoguaianolide analogues. It is envisaged, for example, that protection of the hydroxyl group of ketal-alcohol (**11a**) [Scheme 4] will provide an intermediate that could be of value in a projected synthesis of enantiopure hysterin[18b]. In summary, the synthesis of hydroazulenoid ketones (**1a**), (**3**), (**4a**), and (**16**) from (–)-camphor (**6**) represents a formal synthesis of (+)-confertin, (–)-damsin, (+)-carpesiolin, (–)-helenalin, (+)-bigelovin, (+)-mexicanin I, and (+)-linifolin A.

ACKNOWLEDGMENT

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EXPERIMENTAL

General Experimental

All reactions involving air- or moisture-sensitive reagents were conducted under argon atmosphere. Unless specified otherwise, THF and diethyl ether were distilled over sodium/benzophenone while

dichloromethane, benzene, acetonitrile, triethylamine, diisopropylamine, piperidine and dimethyl sulfoxide were distilled over calcium hydride. Methanesulfonyl chloride was distilled over phosphorus pentoxide. Ethylene glycol was distilled over calcium oxide and stored over 4 Å molecular sieves. Methyl iodide, allyl bromide, 2-methyl-1,3-dithiane, and DBU were passed through a short (~5 × 0.5 cm) column of oven-dried (160 °C) basic alumina (Brockmann Activity I) immediately prior to use. For ozonolysis reactions, ozone was generated (~4% O_3 in O_2) using a Welsbach Model T-23 laboratory ozonator. Extraction solvents and all other reagents were used as received.

All 400 MHz ^1H and 100 MHz ^{13}C nmr spectra were recorded on a Bruker WH-400 spectrometer while 75 MHz ^{13}C nmr spectra were recorded on a Varian XL-300 spectrometer and 50 MHz ^{13}C nmr spectra on an Bruker AC-200 spectrometer. Nmr signal positions (δ) are reported in parts per million and are referenced to the residual proton signal of $CDCl_3$ (7.24 ppm) or the carbon signal of $^{13}\underline{C}DCl_3$ (77.0 ppm), as appropriate. Infrared spectra were recorded on a Perkin-Elmer Model 1710 Fourier transform spectrophotometer. Low and high resolution electron impact mass spectra were acquired on a Kratos MS-50 mass spectrometer while desorption chemical ionization mass spectra were recorded on a Delsi Nermag R-10-10C instrument. Melting points were measured on a Reichert hot stage and are uncorrected. Specific rotations were recorded on a Jasco J-710 or Perkin-Elmer 141 spectropolarimeter in a 0.1 or 1.0 dm cell, respectively. Flash column chromatography was performed according to the method reported by Still and co-workers[36]. Microanalyses were performed by Mr. P. Borda of the UBC Microanalytical Laboratory on a Carlo-Erba CHN elemental analyzer, model 1106.

***tert*-Butyldiphenylsilyloxy-ester (8b)**

To a solution of hydroxy-ester (**8**)[20–22] (6.4421 g, 32.49 mmol) and imidazole (11.06 g, 162.4 mmol) in spectro grade DMF (40 mL) was added *t*-butyldiphenylsilyl chloride (9.9 mL, 11 g, 39 mmol). The reaction mixture was stirred at room temperature for 5 h after which it was partitioned between water (200 mL) and Et_2O (100 mL). The aqueous phase was extracted further with Et_2O (2 × 50 mL). The combined extracts were then washed with water (50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to a colorless oil. Further purification by flash column chromatography (5% EtOAc–pet. ether) yielded pure silyloxy-ester (**8b**) as a colorless oil (13.4679 g, 95%).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.65–7.72 (m, 4H), 7.35–7.45 (m, 6H), 4.89 (bs, 1H), 4.72 (bs, 1H), 3.68 (s, 3H), 3.49 (d, J = 10.0 Hz, 1H), 3.44 (d, J = 10.0 Hz, 1H), 2.61 (dd, J = 15.0, 4.0 Hz, 1H), 2.49–2.59 (m, 1H), 2.23–2.44 (m, 2H), 2.12 (dd, J = 15.0, 10.0 Hz, 1H), 1.85–1.94 (m, 1H), 1.24–1.37 (m, 1H), 1.06 (s, 9H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0, 157.9, 135.7, 133.5, 129.5, 127.6, 105.5, 70.8, 51.4, 48.6, 42.2, 35.9, 32.2, 29.2, 26.8, 19.7, 19.3; IR (neat film) 3071, 3060, 2956, 2894, 2858, 1741, 1650, 1590, 1472, 1429, 1194 cm^{-1}; Exact mass calcd for $C_{27}H_{36}O_3Si$ 436.2434 found 436.2428; Anal. Calcd for $C_{27}H_{36}O_3Si$: C, 74.27; H, 8.31. Found: C, 74.31; H, 8.27.

Keto-ester (23)

A stream of ozonized oxygen (~4% O_3 in O_2) was bubbled into a solution of silyloxy-ester (**8b**) (12.4231 g, 28.45 mmol) in 1:1 CH_2Cl_2–MeOH (200 mL) at –78 °C until a faint blue color persisted (~1 h). Excess ozone was purged with oxygen gas (~10 min). Dimethyl sulfide (20 mL) was added and the reaction mixture was allowed to warm to room temperature over 12 h. The solution was concentrated to a clear, pale

yellow oil that was then purified by flash column chromatography (20% Et_2O–pet. ether) to yield pure keto-ester (**23**) as a viscous, clear, colorless oil (11.4776 g, 92%)

^1H NMR ($CDCl_3$, 400 MHz) δ 7.61–7.67 (m, 4H), 7.33–7.44 (m, 6H), 3.78 (d, J = 9.2 Hz, 1H), 3.68 (s, 3H), 3.32 (d, J = 9.2 Hz), 3.02–3.12 (m, 1H), 2.34–2.48 (m, 2H), 2.12–2.30 (m, 3H), 1.44–1.58 (m, 1H), 0.99 (s, 9H), 0.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 217.5, 172.3, 135.7, 132.3, 129.7, 127.7, 66.2, 53.0, 51.6, 38.2, 37.2, 35.0, 26.8, 25.4, 19.2, 13.8; IR (neat film) 3073, 3050, 2948, 2858, 1741, 1467, 1428, 1101 cm^{-1}; Exact mass calcd for $C_{22}H_{25}O_4Si$ (M – t-Bu)$^+$ 381.1522 found 381.1523 Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 70.99; H, 7.91.

Ketal-ester (9)

To a solution of keto-ester (**23**) (11.3824 g, 25.95 mmol) in dry, distilled benzene (200 mL) was added dry ethylene glycol (29 mL, 32 g, 519.0 mmol) and p-toluenesulfonic acid (0.4936 g, 2.595 mmol). The heterogeneous mixture was stirred vigorously at reflux in a Dean-Stark apparatus for 18 h. The reaction mixture was cooled to room temperature, diluted with Et_2O (200 mL) and poured into water (~250 mL). The organic phase was separated while the aqueous phase was extracted once more with Et_2O (200 mL). The combined organic solutions were washed with water (250 mL), saturated aq. $NaHCO_3$ (250 mL), and brine (3 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated to yield a clear, straw yellow oil. Subsequent purification by flash column chromatography (20% EtOAc–pet. ether) yielded pure ketal-enone (**9**) as a viscous, clear, colorless syrup (11.4846 g; 92%); $[\alpha]_D^{25}$ –17.7 (c 0.793, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.76 (m, 4H), 7.32–7.46 (m, 6H), 3.72–3.84 (m, 4H), 3.62 (s, 3H), 3.60–3.70 (m, 2H), 2.72 (dd, J = 14.8, 3.4 Hz, 1H), 2.51–2.62 (m, 1H), 2.17 (dd, J = 14.8, 11.2 Hz, 1H), 1.64–2.01 (m, 3H), 1.27–1.40 (m, 1H), 1.06 (s, 9H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6, 135.6, 133.6, 129.5, 127.5, 118.8, 68.1, 64.6, 64.2, 51.2, 49.5, 40.0, 36.9, 33.4, 26.9, 25.9, 19.3, 13.6; IR (neat film) 3072, 3055, 2949, 2873, 1739, 1589, 1470, 1429, 1152, 1099, 1005 cm^{-1}; Exact mass calcd for $C_{24}H_{29}O_5Si$ (M – t-Bu)$^+$ 425.1784, found 425.1786; Anal. Calcd for $C_{28}H_{38}O_5Si$: C, 69.67; H, 7.93. Found: C, 69.58; H, 7.96.

Ketal-ester (10)

n-Butyllithium (5.8 mL, 1.55 M in hexane, 8.9 mmol) was added dropwise over 5 min to a solution of diisopropylamine (1.3 mL, 0.90 g, 8.9 mmol) in THF (15 mL) at 0 °C. The solution was stirred at 0 °C for 30 min and then cooled to –78 °C. Ketal-ester (**9**) (3.3224 g, 6.883 mmol), dissolved in THF (25 mL), was added and the reaction mixture was stirred at –78 °C for 45 min. Allyl bromide (0.77 mL, 1.1 g, 8.9 mmol) was then added and the mixture was stirred at –78 °C for a further 2 h before being allowed to warm to room temperature over 15 h. The solution was partitioned between ether (50 mL) and water (50 mL). The aqueous layer was further extracted with ether (2 × 50 mL) and the combined extracts were washed with brine (3 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to provide a pale yellow oil. Purification of the crude product by flash chromatography (10% EtOAc–pet. ether) yielded the ketal-ester (**10**) (3.4002 g; 95%) as a viscous, colorless oil.

^1H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.70 (m, 4H), 7.30–7.42 (m, 6H), 5.60–5.71 (m, 1H), 4.90–5.00 (m, 2H), 3.79–3.91 (m, 4H), 3.69 (d, J = 8.0 Hz, 1H), 3.34 (d, J = 8.0 Hz, 1H), 3.20 (s, 3H), 2.46 (ddd, J = 9.5, 9.5, 3.0 Hz, 1H), 2.27–2.36 (m, 2H), 2.09–2.19 (m, 1H), 1.75–1.86 (m, 3H), 1.31–1.41 (m, 1H), 1.04 (s, 9H), 1.00 (s,

3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.4, 135.8, 135.7, 135.2, 134.0, 133.8, 122.4, 127.6, 119.0, 116.6, 67.9, 64.6, 64.5, 50.8, 50.0, 47.3, 43.6, 35.4, 33.4, 27.0, 24.0, 19.4, 13.6; IR (neat film) 3073, 3050, 2948, 2858, 1735, 1642, 1590, 1472, 1429, 1391, 1371, 1318, 1112 cm^{-1}; Exact mass calcd for $C_{31}H_{42}O_5Si$ 522.2801, found 522.2807; Anal. Calcd for $C_{31}H_{42}O_5Si$: C, 71.23; H, 8.10. Found: C, 71.30; H, 8.03.

Ketal-alcohol (11a)

To a suspension of lithium aluminum hydride (0.3703 g, 9.757 mmol) in THF (10 mL) at 0 °C was added the ester (**10**) (3.4002 g, 6.504 mmol) in THF (50 mL). The reaction was allowed to proceed at 0 °C for 2 h before being quenched by cautious, dropwise addition of water (~10 mL). The two-phase mixture was stirred for a further 30 min, and the aqueous phase was then extracted with ether (5 × 25 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to a viscous, colorless oil. Purification of this crude product by flash chromatography (20% EtOAc–pet. ether) yielded the ketal-alcohol (**11a**) (3.0497 g; 95%) as a colorless syrup.

^1H NMR ($CDCl_3$, 400 MHz) δ 7.63–7.72 (m, 4H), 7.32–7.42 (m, 6H), 5.77–5.89 (m, 1H), 4.98–5.09 (m, 2H), 3.57–3.74 (m, 6H), 3.50–3.57 (m, 1H), 3.42–3.50 (m, 1H), 2.18–2.32 (m, 2H), 1.97–2.07 (m, 1H), 1.88 (bs, 1H; exchanges with D_2O), 1.61–1.83 (m, 4H), 1.38–1.48 (m, 1H), 1.09 (s, 9H), 0.95 (s, 3H); IR (neat film) 3479, 3072, 3050, 2956, 2870, 1639, 1590, 1472, 1428, 1392, 1365, 1318, 1190, 1112, 1085 cm^{-1}; Exact mass calcd for $C_{30}H_{42}O_4Si$ 494.2852, found 494.2844; Anal. Calcd for $C_{30}H_{42}O_4Si$: C, 72.83; H, 8.56. Found: C, 72.87; H, 8.65.

Ketal-mesylate (24)

To a solution of alcohol (**11a**) (2.2749 g, 4.598 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added DMAP (0.2808 g, 2.299 mmol), triethylamine (0.77 mL, 0.56 g, 5.5 mmol), and methanesulfonyl chloride (0.43 mL, 0.63 g, 5.5 mmol). The colorless solution was stirred at 0 °C for 2.5 h, then diluted with CH_2Cl_2 (50 mL), washed with water (1 × 100 mL), ice-cold 0.1 M HCl (2 × 100 mL), water (3 × 100 mL), and brine (3 × 100 mL), and dried over anhydrous $MgSO_4$. Concentration of the organic layer under reduced pressure yielded chromatographically pure ketal-mesylate (**24**) (2.5584 g; 97%) that could be used in the subsequent reaction without further purification. For characterization purposes, a small quantity of the crude ketal-mesylate (**24**) (~20 mg) was purified by radial chromatography (20% EtOAc–pet. ether).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.61–7.68 (m, 4H), 7.34–7.42 (m, 6H), 5.70–5.82 (m, 1H), 5.03–5.12 (m, 2H), 4.21 (dd, J = 8.0, 4.0 Hz, 1H), 4.07 (dd, J = 8.0, 4.0 Hz, 1H), 3.63–3.81 (m, 4H), 3.60 (d, J = 10.5 Hz, 1H), 3.55 (d, J = 10.5 Hz, 1H), 2.78 (s, 3H), 2.37 (ddd, J = 13.4, 6.0, 0.9 Hz, 1H), 2.22–2.30 (m, 1H), 1.93–2.09 (m, 2H), 1.62–1.79 (m, 3H), 1.42–1.52 (m, 1H), 1.05 (s, 9H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.8, 135.6, 113.5, 113.5, 129.6, 128.0, 127.7, 127.6, 127.4, 118.7, 117.2, 71.2, 68.7, 64.3, 64.1, 49.9, 42.5, 38.1, 36.5, 33.0, 32.1, 27.0, 22.6, 19.3, 14.0; IR (neat film) 3072, 3050. 2957, 2884, 2858, 1640, 1590, 1472, 1428, 1360, 1177, 1112 cm^{-1}; Exact mass calcd for $C_{31}H_{44}O_6SSi$ 572.2628, found 572.2619.

Ketal-alkene (11b)

To a solution of mesylate (**24**) (2.5560 g, 4.462 mmol) in THF (50 mL) at 0 °C was added lithium triethylborohydride (SuperHydride®; 9.8 mL, 1.0 M in THF, 9.8 mmol). The clear, colorless solution was stirred at 0 °C for 5 min and at room temperature for 18 h. The cloudy reaction mixture was cooled to 0 °C, at which 3 M NaOH (2.0 mL) and 30% hydrogen peroxide (2.0 mL) were added successively. The solution was stirred at room temperature for 1 h, during which a white precipitate formed, and then partitioned between Et_2O (50 mL) and H_2O (50 mL). The aqueous layer was extracted once more with Et_2O (50 mL). The combined extracts were washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide a colorless oil. Subsequent purification of the oil by flash chromatography (5% EtOAc–pet. ether) yield pure ketal-alkene (**11b**) as a clear, colorless oil (1.9033 g, 89%).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.73 (m, 4H), 7.34–7.46 (m, 6H), 5.18–5.30 (m, 1H), 4.93–5.00 (m, 2H), 3.71–3.83 (m, 4H), 3.65 (d, J = 9.0 Hz, 1H), 3.58 (d, J = 9.0 Hz, 1H), 2.23 (partially resolved ddd, J = 14.0, 6.0, 1.5 Hz, 1H), 1.61–1.85 (m, 5H), 1.50–1.60 (m, 1H), 1.32–1.42 (m, 1H), 1.05 (m, 9H), 0.98 (s, 3H), 0.82 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.8, 135.7, 134.0, 133.8, 129.4, 127.5, 123.1, 119.7, 67.9, 64.6, 64.3, 50.1, 48.0, 45.4, 38.3, 33.6, 33.4, 27.0, 25.5, 24.4, 23.6, 21.6, 19.4, 18.0, 14.0; IR (neat film) 3072, 3050, 2959, 2880, 1640, 1590, 1472, 1428, 1113 cm^{-1}; Exact mass calcd for $C_{30}H_{42}O_3Si$ 478.2903, found 478.2901.

Silyloxy-ketone (12)

A suspension of palladium(II) chloride (0.1282 g, 0.7228 mmol), copper(I) chloride (0.3582 g, 0.3618 mmol) in 7:1 DMF–H_2O (10 mL) was stirred under oxygen atmosphere for 2 h. To this green-brown suspension was added a solution of the ketal-alkene (**11b**) (1.7303 g, 3.6142 mmol) in 9:1 DMF–H_2O (40 mL). The mixture was stirred under oxygen for 18 h and filtered through a pad of Celite®. The Celite® pad was washed with Et_2O (~50 mL). The filtrate was extracted with Et_2O (3 × 50 mL). The combined extracts were washed with $NaHCO_3$ (2 × 50 mL), H_2O (2 × 50 mL), and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to provide the crude product as a golden-yellow oil. Subsequent purification by flash chromatography (20% EtOAc–pet. ether) yielded pure silyloxy-ketone (**12**) as a clear, colorless oil (1.5412 g, 86%).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.62–7.71 (m, 4H), 7.32–7.42 (m, 6H), 3.72–3.84 (m, 4H), 3.60 (d, J = 10.0 Hz, 1H), 3.55 (d, J = 10.0 Hz, 1H), 2.56 (partially resolved ddd, J = 20.0, 9.0, 2.5 Hz, 1H), 2.06–2.16 (m, 1H), 2.09 (s, 3H), 1.88 (dq, J = 8.0, 2.0 Hz, 1H), 1.62–1.78 (m, 3H), 1.19–1.34 (m, 2H), 1.07 (s, 9H), 0.97 (s, 3H), 0.82 (d, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.0, 135.8, 133.8, 133.6, 129.6, 127.6, 119.6, 68.2, 64.6, 64.3, 51.1, 50.1, 48.1, 32.9, 30.3, 27.0, 23.6, 19.4, 18.1, 13.8; IR (neat film) 3070, 3050, 2958, 2882, 1716, 1472, 1428, 1361, 1153, 1112 cm^{-1}; Exact mass calcd for $C_{26}H_{33}O_4Si$ $(M - t\text{-}Bu)^+$ 437.2148, found 437.2145; Anal. Calcd for $C_{30}H_{42}O_4Si$: C, 72.83; H, 8.56. Found: C, 72.62; H, 8.56.

Hydroxy-ketone (25)

A solution of silyl ketone (**12**) (1.4361 g, 2.9027 mmol) and tetrabutylammonium fluoride (87 mL, 1.0 M in THF, 87 mmol) was refluxed for 3.0 h. The reaction mixture was then poured into brine (100 mL) and extracted with Et_2O (5 × 50 mL). The combined extracts were washed with brine (3 × 150 mL), dried over anhydrous $MgSO_4$ and concentrated to provide a golden-yellow oil. Purification of the oil by flash

chromatography (60% EtOAc-pet. ether) yielded pure hydroxy-ketone (**25**) as a clear, colorless syrup (0.7029 g, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84–4.01 (m, 4H), 3.60 (dd, J = 12.7, 3.0 Hz, 1H; collapses to d (J = 12.7 Hz) upon addition of D_2O), 3.38 (dd, J = 12.7, 9.8 Hz, 1H; collapses to d (J = 12.7 Hz) upon addition of D_2O), 2.91 (dd, J = 9.8, 3.0 Hz, 1H; exchanges with D_2O), 2.51 (dd, J = 16.0, 1.5 Hz, 1H), 2.21 (dd, J = 16.0, 9.0 Hz, 1H), 2.10 (s, 3H), 2.00–2.15 (m, 2H), 1.74–1.85 (m, 1H), 1.58–1.74 (m, 2H), 1.26–1.37 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.6, 120.8, 66.1, 64.4, 63.2, 49.4, 48.8, 43.3, 31.6, 30.9 30.4, 24.2, 18.8, 13.4; IR (neat film) 3534, 2969, 2882, 1713, 1467, 1412, 1151, 1068, 1043 cm^{-1}; Exact mass calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1677; Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.69; H, 9.52.

Keto-aldehyde (13)

To a solution of oxalyl chloride (0.27 mL, 0.39 g, 3.1 mmol) in dry CH_2Cl_2 (5.0 mL) at –78 °C was added dropwise over 10 min a solution of dry DMSO (0.24 mL, 0.26 g, 3.4 mmol) in CH_2Cl_2 (5.0 mL). The clear, colorless solution was stirred at –78 °C for 30 min after which a solution of the hydroxy-ketone (**12**) (0.6646 g, 2.5926 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise by cannula over 5 min. The reaction mixture was stirred at –78 °C for a further hour. Triethylamine (1.8 mL, 1.3 g, 13 mmol) was added and the solution was allowed to warm to room temperature over approximately 2 h and was stirred subsequently at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (~100 mL), washed with ice-cold 0.5 M HCl (2 × 25 mL), water (2 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to provide the crude product as a pale yellow oil. Purification of the oil by flash chromatography (75% Et_2O–pet. ether) provided pure keto-aldehyde (**13**) as clear, colorless oil (0.5844 g, 89%) [N.B. Due to the air sensitivity of (**13**), this compound was stored at –10 °C under argon].

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.74 (s, 1H), 3.69–3.89 (m, 4H), 2.51 (dd, J = 16.0, 3.0 Hz, 1H), 2.29 (dd, J = 16.0, 10.0 Hz), 2.12 (s, 3H), 1.88–2.04 (m, 4H), 1.76–1.85 (m, 1H), 1.33–1.45 (m, 1H), 1.07 (s, 3H), 0.69 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 208.2, 207.5, 121.6, 65.5, 64.2, 59.5, 48.9, 48.6, 34.5, 31.5, 30.7, 25.4, 19.5, 10.3; IR (neat film) 2977, 2882, 2731, 1718, 1468, 1362, 1158, 1069 cm^{-1}; Exact mass calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1511.

Ketal-enone (14)

To a solution of keto-aldehyde (**13**) (0.1184 g, 0.4655 mmol) in spectro. grade methanol (5.0 mL) was added, in one portion, a 10% aqueous potassium hydroxide solution (1.3 mL, 130 mg, 2.3 mmol). The reaction mixture was stirred at room temperature under argon for 12 days after which it was neutralized by addition of 1 M HCl (~2.7 mL). The mixture was extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated to yield the intermediate aldol as a viscous, colorless syrup that could be used in the subsequent part without further purification. A small sample was further purified by flash chromatography (75% Et_2O–pet. ether) for characterization purposes.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (bs, 1H), 3.97–4.02 (m, 1H), 3.89–3.97 (m, 4H), 3.36 (dd, J = 11.0, 4.0 Hz, 1H), 2.83–2.92 (m, 1H), 2.58–2.65 (m, 2H), 2.34 (dd, J = 11.0, 5.5 Hz, 1H), 2.10–2.22 (m, 1H), 1.73–1.90 (m, 3H), 1.61–1.72 (m, 1H), 0.96 (d, J = 8.5 Hz, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.9, 121.2, 68.4, 64.9, 63.4, 52.4, 50.0, 46.5, 42.0, 32.8, 31.2, 22.3, 15.8, 14.9; IR (neat film) 3513, 2958, 2924, 2878, 1692, 1476, 1457, 1436, 1391, 1351, 1328, 1315, 1253, 1215 cm^{-1}; Exact mass calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1510.

To an ice-cold solution of aldol, triethylamine (97 μL, 0.071 g, 0.70 mmol), and DMAP (0.0568 g, 0.4649 mmol) in dry CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (54 μL, 0.080 g, 0.70 mmol). The cloudy, straw yellow solution was stirred at 0 °C for 2 h after which DBU (140 μL, 0.142 g, 0.931 mmol), pre-purified by passage down a column of basic alumina, was added and the solution was allowed to warm to room temperature. The clear, pale yellow solution was stirred for 2 h and then poured into a 1:1 diethyl ether-water mixture (50 mL). The aqueous layer was extracted further with diethyl ether (2 × 25 mL). Combined extracts were washed with water (3 × 25 mL), saturated aqueous $NaHCO_3$ (3 × 25 mL), and brine (3 × 25 mL), dried over anhydrous $MgSO_4$, and concentrated to a pale yellow oil. Subsequent purification of the oil by flash column chromatography (70% Et_2O–pet. ether) yielded pure ketal-enone (**14**) as a colorless oil (0.0768 g, 70% from the keto-aldehyde (**13**))

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.36 (d, J = 12.0 Hz, 1H), 5.95 (dd, J = 12.0, 1.3 Hz, 1H), 3.86–3.99 (m, 4H), 2.62–2.72 (m, 2H), 2.44–2.52 (m, 1H), 2.23–2.30 (m, 1H), 1.75–1.89 (m, 3H), 1.61–1.71 (m, 1H), 1.19 (s, 3H), 1.06 (d, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.6, 149.4, 130.3, 119.1, 65.4, 64.0, 53.4, 51.9, 45.2, 31.6, 30.7, 22.0, 18.1, 16.4; IR (neat film) 2959, 2878, 1672, 1629, 1460, 1286, 1241, 1165, 1061 cm^{-1}; Exact mass calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1415; Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.24; H, 8.57.

Keto-enone (15)

Ketal-enone (**3**) (33.5 mg, 0.142 mmol) was dissolved in acetone (2.0 mL) and 1 M HCl (2.0 mL) was added. The colorless solution was stirred at room temperature for 3 h after which it was diluted with water (10 mL) and extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with water (1 × 50 mL), saturated $NaHCO_3$ solution (1 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a colorless oil. Subsequent purification of the oil by flash chromatography (70% Et_2O–pet. ether) yielded pure keto-enone (**15**) as a colorless film (24.4 mg, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (d, J = 11.6 Hz, 1H), 6.00 (dd, J = 11.6, 1.6 Hz, 1H), 2.72 (d, J = 11.7 Hz, 1H), 2.66 (ddd, J = 11.7, 7.1, 1.5 Hz, 1H), 2.12–2.58 (m, 4H), 1.89–1.98 (m, 2H), 1.22 (s, 3H), 1.12 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.8, 201.9, 148.8, 131.3, 55.2, 51.2, 47.5, 36.4, 30.9, 22.5, 18.3, 17.2; IR (neat film) 2965, 2930, 2876, 2860, 1740, 1677, 1625, 1464, 1396, 1381 cm^{-1}; Exact mass calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1144.

Hydroxy-enone (16)

To a solution of keto-enone (**15**) (15.7 mg, 81.6 μmol) in absolute ethanol (1.0 mL) at –10 °C was added solid sodium borohydride (0.9 mg, 22 μmol) in one portion. The resulting clear, colorless solution was

stirred at –10 °C for 10 min, and then neutralized by addition of 1 M HCl (3 drops). The reaction mixture was diluted with diethyl ether (50 mL) and poured into water (25 mL). The aqueous phase was extracted further with diethyl ether (2 × 15 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (1 × 25 mL) and brine (1 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to yield a colorless film. Flash column chromatography (90% diethyl ether–pet. ether) yielded the desired hydroxy-enone (**16**) (13.4 mg; 85%) as a clear, colorless film; $[\alpha]_D^{25}$ –20 (*c* 0.67, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz) δ 6.58 (d, *J* = 11.7 Hz, 1H), 5.91 (dd, *J* = 11.7, 1.6 Hz, 1H), 3.69 (dd, *J* = 8.0, 8.0 Hz, 1H), 2.73 (dd, *J* = 11.0, 11.0 Hz, 1H), 2.59 (partially resolved ddd, *J* = 11.0, 7.7, 1.6 Hz, 1H), 2.20–2.30 (m, 1H), 1.95–2.11 (m, 2H), 1.84 (ddd, *J* = 19.0, 12.5, 5.3 Hz, 1H), 1.43–1.66 (m, 3H), 1.09 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.8, 152.0, 129.5, 79.3, 51.4, 45.1, 31.2, 29.7, 28.8, 22.7, 18.0, 11.7; IR (neat film) 3363, 2956, 2873, 1687, 1622, 1458, 1376 cm^{-1}; Exact mass calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1298.

Hydroxy-ketone (1a)

To a solution of hydroxy-enone (**16**) (10.2 mg, 51.9 μmol) in absolute ethanol (1.5 mL) was added 10% palladium on charcoal (2.5 mg). The mixture was stirred under an atmosphere of hydrogen (ambient pressure) for 4 h, then diluted with Et_2O (50 mL) and filtered through a pad of Celite®. The Celite® pad was washed further with Et_2O (50 mL). The filtrate was concentrated to yield a clear, colorless film. Purification by flash column chromatography (90% Et_2O–pet. ether) yielded pure hydroxy-ketone (**1a**) as a clear, colorless film (9.4 mg; 93%); $[\alpha]_D^{25}$ –15 (*c* 0.47, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz) δ 3.60 (dd, *J* = 12.5, 8.5 Hz, 1H; collapses to a dd (*J* = 8.5, 8.5 Hz) upon treatment with D_2O), 2.78 (dd, *J* = 11.2, 4.1 Hz, 1H), 2.40–2.52 (m, 3H), 2.03–2.14 (m, 2H), 1.89 (ddd, *J* = 14.7, 4.5, 4.5 Hz, 1H), 1.65–1.79 (m, 2H; simplifies upon addition of D_2O), 1.36–1.61 (m, 4H), 0.93 (d, *J* = 7.5 Hz, 3H), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.6, 80.8, 51.7, 49.8, 46.6, 41.2, 32.7, 31.4, 29.2, 23.4, 14.3, 11.3; IR (neat film) 3425, 2965, 2870, 1695, 1475, 1391, 1112, 1075 cm^{-1}; Exact mass calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1472.

Ketal-ester (17)

To an ice-cold solution of diisopropylamine (0.73 mL, 0.53 g, 5.2 mmol) in THF (5 mL) was added n-butyllithium (3.35 mL, 1.55 M in hexane, 5.19 mmol) in one portion. The colorless solution was stirred at 0 °C for 40 min and then cooled to –78 °C. After ~5 min, a solution of ketal-ester (**9**) (2.0879 g, 4.326 mmol) in THF (10 mL) was added by cannula. After a further 1.0 h, methyl iodide (0.32 mL, 0.74 g, 5.2 mmol) was added. The reaction mixture was stirred at –78 °C for 2 h and then allowed to warm to room temperature, at which it was stirred for 15 h. Water (20 mL) was added, cautiously at first, and the organic phase was separated. The aqueous phase was extracted with ether (3 × 20 mL). The combined extracts were washed with brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to a pale yellow oil. Subsequent purification by flash column chromatography (10% EtOAc–pet. ether) yielded ketal-ester (**17**) as a clear, colorless oil (2.0409 g, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.70 (m, 4H), 7.33–7.44 (m, 6H), 3.79–3.92 (m, 4H), 3.68 (d, J = 8.0 Hz, 1H), 3.36 (d, J = 8.0 Hz, 1H), 3.27 (s, 3H), 2.47 (dq, J = 9.5, 7.0 Hz, 1H), 2.32 (partially resolved dd, J = 9.5, 1.7 Hz, 1H), 1.71–1.85 (m, 3H), 1.28–1.38 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 1.04 (s, 9H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.1, 135.8, 135.8, 135.7, 134.0, 133.8, 129.4, 127.6, 127.5, 119.1, 68.0, 64.6, 64.5, 51.2, 50.0, 44.4, 41.0, 33.5, 27.0, 23.7, 19.5, 16.5, 13.7; IR (neat film): 3072, 3022, 2951, 2883, 2850, 1737, 1590, 1470, 1462, 1429, 1391, 1161, 1112, 1068 cm^{-1}; Exact mass calcd for $C_{25}H_{31}O_5Si$ (M – Bu^t)$^+$ 439.1941, found 439.1944; Exact mass calcd for $C_{28}H_{37}O_4Si$ (M – OMe)$^+$ 465.2461, found 465.2480; Anal. Calcd for $C_{29}H_{40}O_5Si$: C, 70.12; H, 8.12. Found: C, 70.04; H, 8.05.

Ketal-alcohol (18)

To an ice-cold suspension of $LiAlH_4$ (0.1471 g, 3.876 mmol) in THF (10 mL) was added by cannula an ice-cold solution of ketal-ester (**17**) (1.9254 g, 3.876 mmol) in THF (30 mL). The grey suspension was stirred at 0 °C for 1 h, then diluted with dry Et_2O (30 mL) and quenched cautiously with water (10 mL). The mixture was stirred at room temperature for 1 h. The organic layer was then separated while the aqueous layer was extracted further with ether (4 × 10 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to provide a colorless syrup. Subsequent purification by flash column chromatography (15% acetone–pet. ether) yielded pure ketal-alcohol (**18**) as a clear, viscous syrup (1.5588 g, 97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63–7.73 (m, 4H), 7.34–7.45 (m, 6H), 3.66–3.77 (m, 4H), 3.64 (d, J = 10.5 Hz, 1H), 3.60 (d, J = 10.5 Hz, 1H), 3.39–3.50 (m, 2H; simplifies to overlapping dd upon addition of D_2O), 2.02–2.10 (m, 1H), 1.62–1.82 (m, 5H), 1.39–1.50 (m, 1H), 1.09 (s, 9H), 0.94 (s, 3H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.9, 135.8, 133.6, 129.6, 127.6, 119.4, 68.2, 67.5, 64.5, 64.1, 50.0, 43.4, 36.6, 33.0, 27.1, 23.0, 19.4, 15.3, 14.3; IR (neat film): 3451, 3072, 3049, 2975, 2961, 2890, 2880, 1590, 1473, 1428, 1391, 1113, 1080 cm^{-1}; Exact mass calcd for $C_{28}H_{41}O_4Si$ [(M + H)$^+$; DCI]: 469.2774, found 469.2791; Anal. Calcd for $C_{28}H_{40}O_4Si$: C, 71.75; H, 8.60. Found: C, 71.80; H, 8.73.

Ketal-iodide (26)

To an ice-cold, colorless solution of ketal-alcohol (**18**) (1.3929 g, 2.972 mmol), triphenylphosphine (1.1692 g, 4.458 mmol) and imidazole (0.3035 g, 4.458 mmol) in 5:3 diethyl ether-acetonitrile (30 mL) were added iodine crystals (0.9806 g, 3.863 mmol) in several portions over 5 min until a pale yellow endpoint was reached. The ice bath was removed and the solution was stirred at room temperature for 5 h. The reaction mixture was partitioned between H_2O (50 mL) and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (50 mL). The combined extracts were washed successively with saturated aqueous $NaHSO_3$ (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), and brine (3 × 50 mL) dried over anhydrous $MgSO_4$. Removal of solvent by rotary evaporation yielded a white, pasty oil. Subsequent purification of the crude product by flash chromatography (10% Et_2O–pet. ether) yielded pure ketal-iodide (**26**) as a clear, colorless, viscous oil (1.3736 g, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.73 (m, 4H), 7.34–7.44 (m, 6H), 3.73–3.80 (m, 3H), 3.56–3.66 (m, 3H), 3.44 (dd, J = 9.3, 3.7 Hz, 1H), 3.11 (dd, J = 9.3, 7.6 Hz, 1H), 1.94 (partially resolved ddd, J = 17.5, 8.0, 1.0 Hz, 1H), 1.61–1.77 (m, 4H), 1.34–1.45 (m, 1H), 1.06 (s, 9H), 0.99 (d, J = 6.6 Hz, 3H), 0.92 (s, 3H); ^{13}C

NMR ($CDCl_3$, 75 MHz): δ 135.8, 133.5, 129.5, 127.6, 119.4, 67.9, 64.7, 64.2, 50.1, 48.2, 36.1, 32.9, 27.1, 23.4, 19.4, 18.5, 13.6; IR (neat film): 3070, 3052, 2952, 2885, 1590, 1470, 1391, 1115, 1075 cm^{-1}; Exact mass calcd for $C_{28}H_{40}IO_3Si$ [$(M + H)^+$; DCI]: 579.1751, found 579.1766.

Ketal-dithiane (19)

To a solution of 2-methyl-1,3-dithiane (0.88 mL, 0.99 g, 7.4 mmol; CAUTION: STENCH!) in THF (15 mL) at –25 °C was added *n*-butyllithium (5.3 mL, 1.55 M in hexane, 8.2 mmol), dropwise over 15 min. The colorless solution was stirred at –25 °C for 3 h. A solution of ketal-iodide (**26**) (2.3765 g, 4.1072 mmol) in THF (50 mL) was cooled to –25 °C and added dropwise to the reaction mixture by cannula over ~10 min. The pale yellow solution was stirred at (–25 ± 5) °C for 12 h after which it was allowed to warm to room temperature and partitioned between H_2O (50 mL) and Et_2O (50 mL). The aqueous layer was extracted further with Et_2O (3 × 50 mL). The combined ether extracts were washed successively with H_2O (50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield a pale yellow oil. Purification of the crude product by flash chromatography (10% EtOAc–pet. ether) yielded pure ketal-dithiane (**19**) as a clear, colorless, viscous oil (2.0746 g, 86%).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.73 (m, 4H), 7.32–7.41 (m, 6H), 3.74–3.84 (m, 4H), 3.65 (d, J = 10.5 Hz, 1H), 3.60 (d, J =10.5 Hz, 1H), 2.67–2.83 (m, 4H), 1.93–2.08 (m, 4H), 1.83–1.91 (m, 2H), 1.68–1.80 (m, 3H), 1.57 (s, 3H), 1.51–1.65 (m, 1H), 1.08 (s, 9H), 1.02 (d, J = 7.3 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.9, 135.8, 133.9, 133.8, 129.4, 127.5, 119.1, 68.8, 64.5, 50.8, 49.9, 49.7, 49.3, 34.1, 29.7, 28.1, 27.1, 26.7, 25.2, 20.3, 19.4, 19.3, 14.5; IR (neat film): 3076, 3045, 2960, 2932, 2880, 2850, 1590, 1472, 1428, 1390, 1280, 1112, 1082 cm^{-1}; Exact mass calcd for $C_{33}H_{48}O_3S_2Si$: 584.2814, found 584.2818.

Silyloxy-ketone (20)

To a mixture of ketal-dithiane (**19**) (1.3063 g, 2.233 mmol) and calcium carbonate (0.5588 g, 5.583 mmol) in THF (15 mL) was added dropwise over 5 min a solution of mercuric perchlorate trihydrate (1.5193 g. 3.349 mmol) in water (4 mL). The reaction mixture was stirred for another 5 min, then diluted with Et_2O (80 mL) and poured into water (100 mL). The organic layer was washed further with water (100 mL) and brine (2 × 100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield a viscous, clear, colorless syrup. Subsequent purification by flash column chromatography (30% Et_2O–pet. ether) provided pure silyloxy-ketone (**20**) as a clear, colorless syrup (1.0281 g, 93%).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.62–7.70 (m, 4H), 7.32–7.42 (m, 6H), 3.74–3.82 (m, 3H), 3.65–3.72 (m, 1H), 3.59 (d, J = 10.0 Hz, 1H), 3.55 (d, J = 10 Hz, 1H), 2.61–2.71 (m, 1H), 2.05–2.17 (m, 1H), 1.97 (s, 3H), 1.59–1.86 (m, 5H), 1.33–1.44 (m, 1H), 1.08 (s, 9H), 0.97 (s, 3H), 0.82 (d, J = 5.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.9, 135.8, 133.8, 133.6, 129.6, 127.6, 119.5, 68.2, 64.6, 64.3, 51.1, 50.1, 48.0, 32.9, 30.2, 27.0, 23.5, 19.4, 18.0, 13.8; IR (neat film): 3072, 3045, 2960, 2928, 2881, 2850, 1717, 1590, 1472, 1428, 1361, 1309, 1151, 1113, 1076 cm^{-1}; Exact mass calcd for $C_{30}H_{43}O_4Si$ [$(M + H)^+$; DCI]: 495.2931, found 493.2939; Anal. Calcd for $C_{30}H_{42}O_4Si$: C, 72.83; H, 8.56. Found: C, 72.65; H, 8.51.

Hydroxy-ketone (27)

TBAF (9.7 mL, 1 M in THF, 9.735 mmol) was added to a solution of silyl ketone (**20**) (0.9633 g, 1.947 mmol) in THF (25 mL) and the resulting pale yellow solution was refluxed for 3 h. The reaction

mixture was allowed to cool to room temperature, diluted with diethyl ether (100 mL), washed with water (3 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to provide a clear, colorless oil. Purification of the oil by flash column chromatography (60% EtOAc–pet. ether) yielded pure hydroxy-ketone (**27**) as a clear, viscous, colorless oil (0.4658 g, 93%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84–3.99 (m, 4H), 3.61 (dd, J = 12.4, 2.8 Hz, 1H; collapses to d (J = 12.4 Hz) upon addition of D_2O), 3.27 (dd, J = 12.4, 10.5 Hz, 1H; collapses to d (J = 12.4 Hz) upon addition of D_2O), 2.95 (dd, J = 10.5, 2.8 Hz, 1H; exchanges with D_2O), 2.67 (dd, J = 17.0, 2.8 Hz, 1H), 2.34 (dd, J = 17.0, 9.0 Hz, 1H), 2.15 (s, 3H), 2.02–2.18 (m, 2H), 1.62–1.83 (m, 3H), 1.38–1.48 (m, 1H), 0.83 (d, J = 6.1 Hz, 3H), 0.80 (s, 3H); IR (neat film) 3533, 2970, 2881, 1713, 1413, 1361, 1324, 1152, 1069, 1043 cm^{-1}; Exact mass calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1669; Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.71; H, 9.49.

Keto-aldehyde (21)

To a solution of oxalyl chloride (93 μL, 0.13 g, 1.1 mmol) in dry CH_2Cl_2 (5.0 mL) at –78 °C was added dropwise over 10 min a solution of dry DMSO (82 μL, 0.90 g, 1.1 mmol) in CH_2Cl_2 (5.0 mL). The clear, colorless solution was stirred at –78 °C for 30 min after which a solution of the hydroxy-ketone (**27**) (0.2265 g, 0.8835 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise by cannula over 5 min. The reaction mixture was stirred at –78 °C for a further hour. Triethylamine (0.62 mL, 0.45 g, 4.4 mmol) was added and the solution was allowed to warm to room temperature over 1 h, and was stirred subsequently at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 (~100 mL), washed with ice-cold 0.5 M HCl (2 × 25 mL), water (2 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to provide the crude product as a pale yellow oil. Purification of the oil by flash chromatography (50% Et_2O–pet. ether) provided pure keto-aldehyde (**21**) as a clear, colorless oil (0.2038 g, 91%) [N.B. Due to the air sensitivity of (**13**), it was necessary to store this compound at –10 °C under argon].

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1H), 3.68–4.92 (m, 4H), 2.51 (ddd, J = 19.0, 10.5, 3.1 Hz, 1H), 2.06 (s, 3H), 1.76–2.15 (m, 6H), 1.36–1.50 (m, 1H), 1.07 (s, 3H), 0.89 (d, J = 6.5 Hz, 3H); IR (neat film) 2970, 2885, 2735, 1715, 1469, 1370, 1160, 1058 cm^{-1}; Exact mass calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1515.

Ketal-enone (3)

To a solution of keto-aldehyde (**21**) (0.1931 g, 0.7592 mmol) in spectro. grade methanol (6.5 mL) was added, in one portion, a 10% aqueous potassium hydroxide solution (1.3 mL, 130 mg, 2.3 mmol). The reaction mixture was stirred at room temperature under argon for 2 h after which it was neutralized by addition of 1 M HCl (~2.5 mL). The mixture was extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated to yield the crude aldol intermediate as a viscous, colorless syrup (0.1831 g) that was used in the subsequent reaction without further purification.

To an ice-cold solution of aldol (0.1831 g, 0.7199 mmol), triethylamine (180 μL, 0.109 g, 1.08 mmol), and DMAP (0.0879 g, 0.7199 mmol) in dry CH_2Cl_2 (8 mL) was added methanesulfonyl chloride (84 μL, 0.12

g, 1.08 mmol). The cloudy, straw yellow solution was stirred at 0 °C for 1.5 h after which DBU (215 μL, 0.219 g, 1.44 mmol) was added and the solution was allowed to warm to room temperature. The clear, pale yellow solution was stirred for 2.5 h and then poured into a 1:1 diethyl ether-water mixture (50 mL). The aqueous layer was extracted further with diethyl ether (2 × 25 mL). Combined extracts were washed with water (3 × 25 mL), saturated aqueous $NaHCO_3$ (3 × 25 mL), and brine (3 × 25 mL), dried over anhydrous $MgSO_4$, and concentrated to a pale yellow oil. Subsequent purification of the oil by flash column chromatography (50% Et_2O–pet. ether) yielded pure ketal-enone (**3**) as a colorless oil (0.1472 g, 82% from the keto-aldehyde (**21**)); $[\alpha]_D^{25}$ −15.7 (*c* 0.896, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz): δ 6.40 (d, J = 12.0 Hz, 1H), 5.91 (dd, J = 12.0, 1.3 Hz, 1H), 3.86–4.04 (m, 4H), 2.92 (dd, J = 13.0, 6.5 Hz, 1H), 2.29 (dd, J = 13.0, 4.6 Hz, 1H), 1.89–2.06 (m, 3H), 1.72–1.86 (m, 2H), 1.36–1.46 (m, 1H), 1.12 (s, 3H), 1.01 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.4, 148.4, 130.5, 119.3, 65.5, 63.9, 51.8, 49.9, 31.6, 31.1, 25.2, 20.7, 15.9; IR (neat film): 2959, 2878, 1672, 1626, 1460, 1439, 1390, 1344, 1165, 1061 cm^{-1}; Exact mass calcd for $C_{14}H_{20}O_3$: 236.1412, found 236.1410; Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.05; H, 8.48.

Keto-enone (22)

Ketal-enone (**3**) (53.6 mg, 0.227 mmol) was dissolved in acetone (3.0 mL) and 1 M HCl (3.0 mL) was added. The colorless solution was stirred at room temperature for 3 h after which it was diluted with water (10 mL) and extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with water (1 × 50 mL), saturated $NaHCO_3$ solution (1 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a colorless oil. Subsequent purification of the oil by flash chromatography (50% Et_2O–pet. ether) yielded pure keto-enone (**22**) as a white, crystalline solid (38.7 mg, 89%); mp = 71.5–72.5 °C.

^1H NMR ($CDCl_3$, 400 MHz): δ 6.81 (d, J = 12.7 Hz, 1H), 5.98 (dd, J = 12.7, 1.4 Hz, 1H), 3.03 (dd, J = 13.0, 7.8 Hz, 1H), 2.45–2.58 (m, 1H), 2.33 (ddd, J =13.0, 3.5, 1.4 Hz, 1H), 2.12–2.24 (m, 2H), 2.02–2.12 (m, 1H), 1.82–1.91 (m, 1H), 1.55–1.66 (m, 1H), 1.14 (s, 3H), 1.12 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 217.2, 202.3, 147.2, 131.6, 54.6, 51.4, 50.7, 35.7, 31.0, 24.3, 20.3, 15.8; IR (thin film, from $CDCl_3$): 2965, 2925, 2860, 1742, 1672, 1458, 1406, 1371 cm^{-1}; Exact mass calcd for $C_{12}H_{16}O_2$: 192.1150, found 192.1148.

Hydroxy-enone (28)

To a solution of keto-enone (**22**) (22.1 mg, 115 μmol) in absolute ethanol (1.0 mL) at −10 °C was added solid sodium borohydride (1.2 mg, 31 μmol) in one portion. The resulting clear, colorless solution was stirred at −10 °C for 10 min, and then neutralized by addition of 1 M HCl (3 drops). The reaction mixture was diluted with diethyl ether (50 mL) and poured into water (25 mL). The aqueous phase was extracted further with diethyl ether (2 × 15 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (1 × 25 mL) and brine (1 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to yield a white, sticky foam. Subsequent purification by flash column chromatography (90% diethyl ether–pet. ether) yielded the desired hydroxy-enone (**28**) (18.9 mg; 85%) as a clear, colorless film.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.62 (d, J = 11.6 Hz, 1H), 5.91 (dd, J = 11.6, 1.5 Hz, 1H), 3.58–3.64 (m, 1H), 3.06 (dd, J = 12.4, 7.8 Hz, 1H), 2.25 (ddd, J = 12.7, 3.5, 1.5 Hz, 1H), 1.99–2.09 (m, 1H), 1.82–1.98 (m, 2H), 1.62 (bs, 1H; exchanges with D_2O), 1.34–1.58 (m, 3H), 1.03 (s, 3H), 1.00 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.3, 151.0, 130.1, 79.0, 50.7, 49.8, 49.4, 32.2, 28.7, 26.0, 20.7, 10.5; IR (neat film): 3363, 2956, 2925, 2873, 1687, 1458, 1376, 1262, 1142, 1107, 1072, 1025 cm^{-1}; Exact mass calcd for $C_{12}H_{18}O_2$: 194.1307, found 194.1311.

Hydroxy-ketone (4a)

To a solution of hydroxy-enone (**16**) (12.5 mg, 63.0 μmol) in absolute ethanol (1.5 mL) was added 10% palladium on charcoal (5 mg). The mixture was stirred under an atmosphere of hydrogen (ambient pressure) for 3 h, then diluted with Et_2O (50 mL) and filtered through a pad of Celite®. The Celite® pad was washed further with Et_2O (50 mL). The filtrate was concentrated to yield a clear, colorless film. Purification by flash column chromatography (90% Et_2O–pet. ether) yielded pure hydroxy-ketone (**4a**) as a clear, colorless film (11.6 mg; 95%); $[\alpha]_D^{25}$ −14 (*c* 0.58, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.48 (dd, J = 8.0, 8.0 Hz, 1H), 2.82 (dd, J = 10.5, 3.5 Hz, 1H), 2.45–2.60 (m, 3H), 2.00–2.14 (m, 2H), 1.82–1.95 (m, 1H), 1.60–1.75 (m, 2H), 1.20–1.57 (m, 4H), 0.89 (d, J = 6.0 Hz, 3H), 0.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.0, 79.8, 50.7, 49.5, 45.4, 41.5, 40.9, 35.6, 30.1, 23.3, 13.2, 10.5; IR (neat film) 3420, 2970, 2880, 1692, 1478, 1391, 1119 cm^{-1}; Exact mass calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1468.

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