New ring construction strategy in taxane synthesis: stereocontrolled synthesis of taxane CB-ring system

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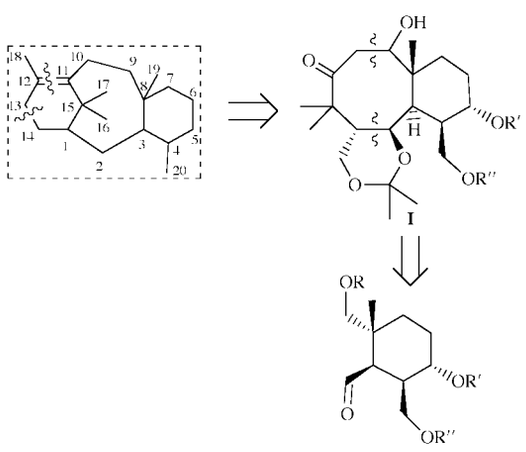
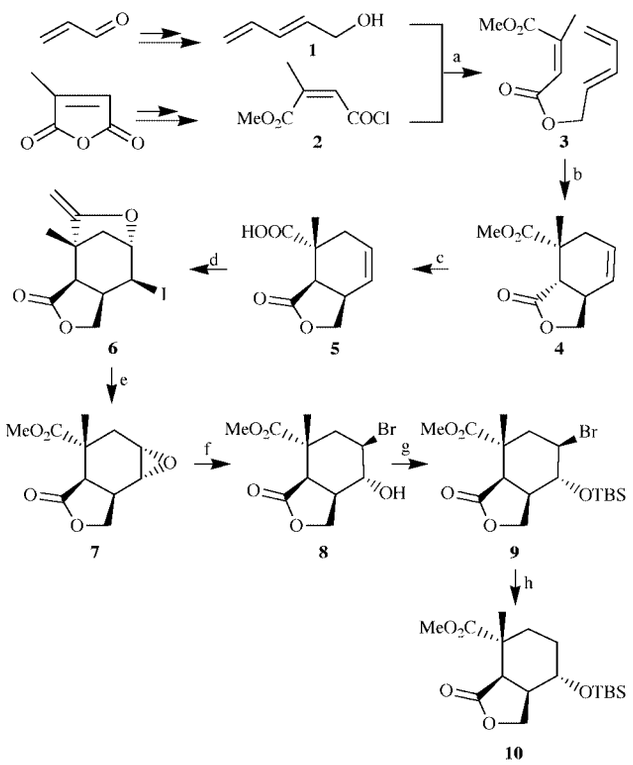
A concise stereocontrolled construction of taxane CB-ring system (C→CB) is described. The key bottom and top linking of the eight-membered B-ring were realized unprecedentedly by way of successive intermolecular aldol condensation and intramolecular aldol cyclization.

Taxol has attracted considerable interest from synthetic organic chemists since it was isolated[1] from the Pacific yew tree owing to its unique structural features, as well as its remarkable anticancer activity and limited supply.[2] To date, six research groups in the world have accomplished the total synthesis of taxol.[3] In spite of these successes, many excellent works on the syntheses of taxol and its analogues are still in progress.[4] Many factors which influence its bioactivity remain to be investigated and it is desirable that simpler analogues with better therapeutic profiles will be synthesized and become useful pharmaceutical products. However, convenient access to the fully functionalized A-ring, C-ring and the construction of the sterically congested eight-membered B-ring remains a challenge in taxol synthesis.

Herein we would like to report a new synthetic strategy which could lead to assembly of all the 20 carbons and essential oxygen functionalities of the taxane diterpene core. The central feature of our strategy involves the synthesis of the appropriately functionalized CB-ring subunit I with the most necessary substituents from the C-ring intermediate II.



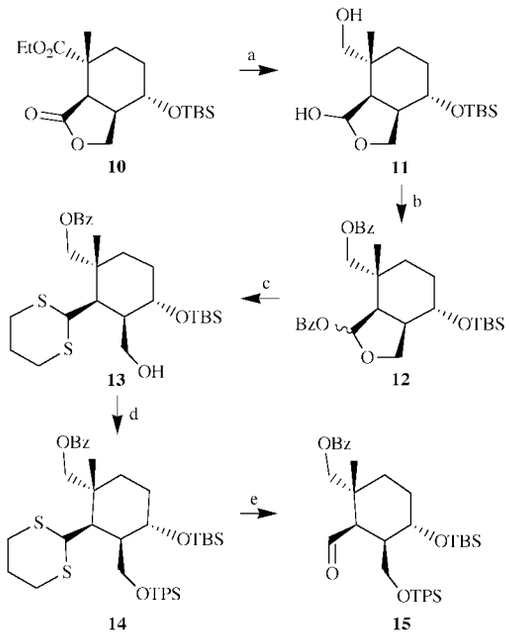
Our key C-ring intermediate was synthesized by successful use of a known intramolecular Diels–Alder reaction, as shown in Scheme 1. The pentadienyl ester **3** was prepared by treatment of penta-2,4-dienol **1**[5] with the *trans*-3-methoxycarbonylbut-2-enoyl chloride **2** which was prepared from citraconic anhydride.[6] After heating at reflux in xylene for 32 h, **3** underwent the intramolecular Diels–Alder reaction exclusively *via* the *exo*-mode to give a single crystalline product which was assigned as the *trans*-fused adduct **4** from NMR data.[7] Both facile epimerization and basic hydrolysis to *cis* lactone **5** could be induced simultaneously with 2 M NaOH (aq.) at reflux for



Scheme 1 *Reagents and conditions*: a. pyridine, benzene, r.t., 90%; b. 2,6-di-*tert*-butyl-*p*-cresol, xylene, reflux, 32 h, 65%; c. 2 M NaOH (aq.), reflux, 3 h, crude 100%; d. 0.5 M $NaHCO_3$ (aq.), KI, I_2, H_2O, r.t., overnight, 85%; e. K_2CO_3, MeOH, r.t., overnight, crude 100%; f. 40% HBr, dioxane, r.t., overnight, 98%; g. TBSCl, imidazole DMF, 92%; h. Bu_3SnH, AIBN, benzene, reflux, 3 h, 94%.

3 h in quantitative yield. The crude carboxylic acid **5**, when treated with potassium iodide–iodine in sodium bicarbonate solution, was transformed into the iodolactone **6** in 85% overall yield. The iodolactone **6** was treated with K_2CO_3 in methanol to open the lactone ring with concomitant formation of the corresponding epoxide **7** in quantitative yield, which on cleavage with HBr (40%) in dioxane at room temp. led to the bromohydrin **8** exclusively in 98% yield. Its structure was confirmed by X-ray crystallographic analysis.[8] Subsequent hydroxy group protection and reductive debromination of **8** gave **10** in 86% overall yield. Attempts to introduce the hydroxy group into compound **8** from the carboxylic ester of **5** by direct hydroboration gave poor regio- and stereo-selectivity.

The intermediate **10,** which already has the exact relative stereochemistry, was used for further group transformations (Scheme 2). Reduction of the dicarbonyl compound **10** with



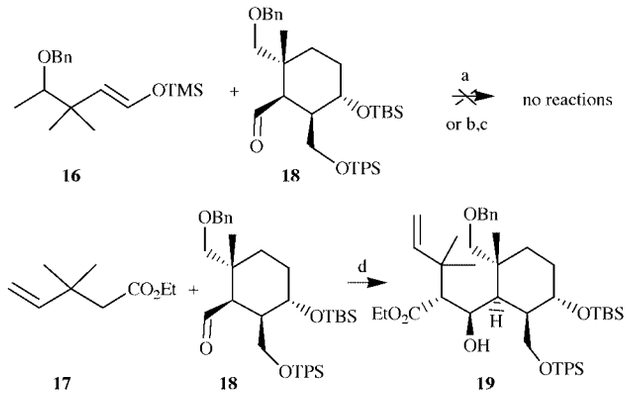
Scheme 2 *Reagents and conditions*: a. DIBAL, CH_2Cl_2, −78 °C, 2 h, 82%; b. BzCl, py, 0 °C, 98%; c. propane-1,3-dithol, $TiCl_4$, CH_2Cl_2, −78 °C, 2 h, 80%; d. TPSCl, imidazole, DMF, r.t., 10 h, 95%; e. $HgCl_2$, HgO, acetone, H_2O, 55 °C, 2 h, 97%.

DIBAL furnished diol **11** as a single isomer in 82% yield. After a four-step sequence: i) benzoylation of the diol **11** (BzCl, pyridine, 98%); ii) opening of the furan ring in **12** (propane-1,3-dithiol, $TiCl_4$, CH_2Cl_2, −78 °C, 80%); iii) protection of the generated hydroxy group in **13** as its *tert*-butyldiphenylsilyl ether (TPSCl, imidazole, DMF, 95%); iv) deprotection of **14** to uncover the aldehyde group ($HgCl_2$, HgO, acetone–H_2O, 97%), compound **15** was achieved in 72% overall yield. This compound has the relative stereochemistry and main functionality needed for the construction of the taxane skeleton.

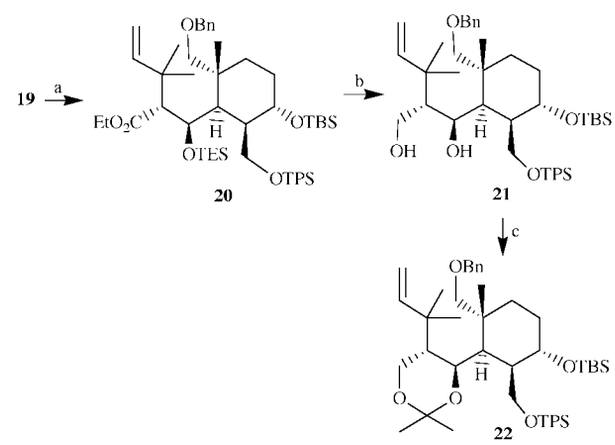
In order to produce a five carbon atom chain containing a quaternary carbon in a single step we chose known 3,3-dimethylpent-4-enoate **17** and its derivative **16** as building blocks. Compound **17** has been used successfully by us in the synthesis of the Taxol A-ring.[9] In our initial trials, the intermolecular Mukaiyama reaction[10] between silyl enol ether **16** and aldehyde **18**[11] did not proceed at all and the reactants were recovered almost quantitatively. Then the traditional aldol condensation induced by LDA–$ZnCl_2$ system was tried. To our delight, the aldol reaction between the unsaturated ester **17** and **18** took place smoothly in the presence of $ZnCl_2$ to furnish the desired β-hydroxyester **19** in 88% yield with good stereoselectivity (Scheme 3).[12]

Protection of aldol **19** was achieved with TESOTf and 2,6-lutidine to give its triethyl silyl ether **20** in 95% yield. DIBAL reduction of compound **20** gave diol **21** in 82% yield, and successive protection of the thus formed hydroxy groups with isopropylidene acetal provided compound in 98% yield (Scheme 4). Attempts to directly reduce the β-hydroxy ester **19** to diol **21** using LAH or DIBAL were both unsatisfactory.

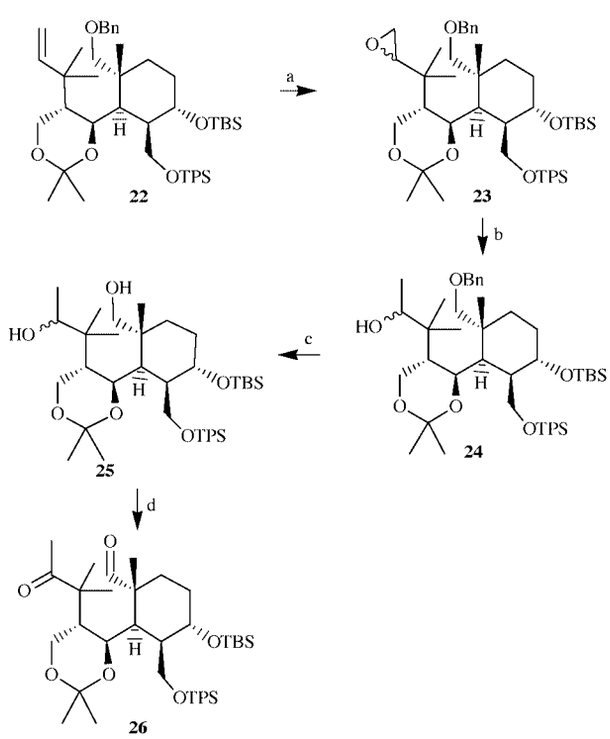
The eight-membered B-ring could be formed from compound **22** by intramolecular aldol cyclization if the terminal double bond could be transformed to an acetyl group and the terminal benzyloxymethyl group could be transformed to a formyl group. However, all attempts to convert the terminal double bond in compound **22** into the desired methyl ketone unit by Wacker oxidation[13] and its modified conditions[14] were ineffective but the reactants were recovered almost quantitatively. Therefore, we had to switch to an alternative four-step sequence as shown in Scheme 5. Epoxidation of compound **22** with MCBPA gave epoxide **23** in 92% yield. Opening this epoxide ring with LAH furnished alcohol **24** in quantitative



Scheme 3 *Reagents and conditions*: a. $TiCl_4$, CH_2Cl_2, −50 °C, 2 h; b. TMSOTf CH_2Cl_2, −20 °C, 2 h; c. $BF_3{\cdot}Et_2O$, CH_2Cl_2, −20 °C, 2 h; d. LDA, THF, −78 °C, 1 h; $ZnCl_2$, −78 °C, 1 h; **18**, −78 °C, 2 h, 88%.



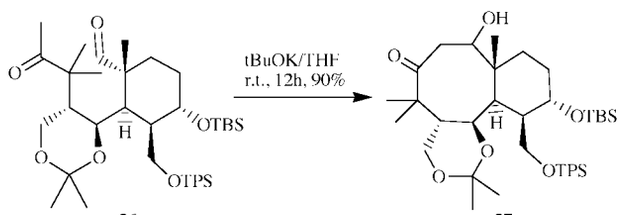
Scheme 4 *Reagents and conditions*: a. TESOTf, 2,6-lutidine, 0 °C, 10 h, 95%; b. DIBAL Ch_2Cl_2, r.t., 12 h, 82%; c. $Me_2C(OMe)_2$, cat. CSA, CH_2Cl_2, r.t., 12 h, 98%.



Scheme 5 *Reagents and conditions*: a. MCBPA, CH_2Cl_2, r.t., 24 h, 92%; b. LAH, THF, 0 °C–r.t., 1 h, 98%; c. 10% Pd–C, EtOAc, r.t., 24 h, 86%; d. TPAP–NMO, 4 Å molecular sieves, CH_2Cl_2, r.t., 2 h, 98%.

yield. Further deprotection of the benzyl group gave the diol **25** in 86% yield. Subsequent oxidation of diol **25** with the TPAP and NMO combined system took place rapidly to afford the desired ring closure precursor ketoaldehyde **26** in 98% yield.

Encouraged by the titanium(IV) chloride induced Mukaiyama type aldol protocol, which was used by Posner,[15] Cockerill[16] and A. B. Smith[17] in the syntheses of medium to large size ring systems, we tried this approach in the synthesis of the key eight-membered B-ring. Without protection of the aldehyde group adjacent to a tertiary carbon, ketoaldehyde **26** was directly converted to its enol trimethylsilyl ether which then underwent intramolecular Mukaiyama cyclization. Unfortunately, all attempts to form the desired eight-membered ring system by a wide variety of different catalysts failed, only complicated mixtures were obtained. Success was finally attained with a more direct aldol approach. Upon treatment with ^{t}BuOK in THF at room temperature for 12 h, ketoaldehyde **26** underwent smooth cyclization to furnish the 8-membered ring product **27** corresponding to the CB-ring system of taxane in 90% isolated yield[18] (Scheme 6).



26 **27**

Scheme 6

Thus, a stereocontrolled synthesis of the taxane CB-ring was unprecedently achieved *via* successive intermolecular aldol condensation and intramolecular aldol cyclization. Our CB-ring subunit with most functionalities and exact relative configuration offers the possibility for further A-ring and oxetane D-ring installation and should prove to be a versatile synthetic intermediate for the taxane diterpenoid skeleton. Synthetic studies on the ABC-ring system of taxane from the present CB-ring system are under active investigation in our laboratories.

Experimental

All ^{1}H NMR spectra were recorded on Bruker AMX-300 or 600 spectrometers and reported in δ units, parts per million (ppm). Mass spectra (EI) were recorded on a HP-5985-A mass spectrometer and HRMS, FABMS and ESIMS were recorded on a Finnigan MAT-95 mass spectrometer.

Infrared (IR) spectra were recorded on Shimadzu IR-440 or Digital FTIR and reported in wave numbers (cm^{-1}). Element analyses were performed on Carlo-ERBA 1106. Flash column chromatography was performed on silica gel H (10–40 μm). THF and Et_2O were distilled from sodium–benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2. DMF was distilled before use. Other reagents were obtained commercially and used as received unless otherwise specified. All water sensitive reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware.

Carboxylic acid 5

A solution of **4** (0.12 g, 0.57 mmol) in 2 M aq. NaOH (3 ml) was stirred at reflux for 3 h. Then the mixture was acidified with 10% H_2SO_4. The aqueous layer was extracted with ether (20 ml × 3) and dried over Na_2SO_4. Removal of the solvent gave the crude carboxylic acid **5** (0.109 g, 99%) as a white solid. The analytical sample was recrystallized from hexane–ethyl acetate. Mp 162–163 °C; IR (film) 3450–2800, 1740, 1200, 1100, 980, 790, 680; ^{1}H NMR (300 MHz, $CDCl_3$), 1.68 (3H, s), 2.18 (1H, m), 2.64 (1H, m), 3.14 (1H, dd, J = 1.1, 7.1 Hz), 3.32 (1H, m), 4.08 (1H, d, J = 9.1 Hz), 4.36 (1H, dd, J = 6.0, 9.0 Hz), 5.60 (1H, dd, J = 2.6, 10.1 Hz), 5.90 (1H, m); EIMS(*m*/*z*) 197 (M^+ + 1), 150, 106, 91; E.A. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.20; H, 6.08%.

Iodolactone 6

To a solution of **5** (0.05 g, 0.26 mmol) in CH_2Cl_2 (0.7 ml) were added 0.5 M aq. $NaHCO_3$ (1 ml), 20% aq. KI (1 ml) and I_2 (0.08 g). Then the mixture was stirred overnight at room temperature. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3), the combined organic layers were washed with saturated aqueous $NaHSO_3$, saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of the solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 5 : 1) gave the title compound **6** (0.071 g, 85%) as a white solid. Mp 189–190 °C; IR (film) 2960, 1780, 1760, 1450, 1190, 1120, 1075, 1060, 960, 940 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (3H, s), 2.26 (1H, m), 2.72 (1H, dd, J = 2.0, 8.0 Hz), 2.90 (1H, m), 2.98 (1H, d, J = 13.2 Hz), 4.44 (2H, m), 4.66 (1H, m), 4.97 (1H, dd, J = 4.0, 6.1 Hz); EIMS(*m*/*z*) 323 (M^+ + 1), 195, 167, 107, 91; E.A. Calcd.for $C_{10}H_{11}O_4I$: C, 37.29; H, 3.44. Found: C, 37.09; H, 3.22%.

Epoxide 7

To a solution of **6** (0.06 g, 0.186 mmol) in methanol (5 ml) was added K_2CO_3 (0.035 g, 0.25 mmol). Then the mixture was stirred overnight at room temperature. The solvent was removed and H_2O (5 ml) was added. The aqueous layer was extracted with ethyl acetate (10 ml × 3), the combined organic layers were washed with brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 5 : 1) gave the title compound **7** (0.041 g, 99%) as a colorless oil. IR (neat) 2960, 1760, 1720, 1460, 1280, 1200, 1140, 1050, 970, 940, 800 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (3H, s), 1.96 (1H, dd, J = 1.0, 15.5 Hz), 2.72 (1H, dt, J = 1.9, 15.4 Hz), 3.02 (2H, m), 3.22 (1H, m), 3.28 (1H, m), 3.72 (3H, s), 4.26 (1H, d, J = 9.6 Hz), 4.40 (1H, dd, J = 6.4, 9.6 Hz); EIMS(*m*/*z*) 227 (M^+ + 1), 194, 167, 141, 105, 95, 91; HREIMS Calcd. for $C_{11}H_4O_5$: 226.0841. Found: 226.0794.

Bromohydrin 8

To a solution of **7** (0.06 g, 0.26 mmol) in acetonitrile (4 ml) was added 40% aq. HBr (0.2 ml) at −40 °C. The mixture was stirred for 2 h. Then the mixture was allowed to warm to room temperature and stirred overnight. H_2O (10 ml) was added to dilute the reaction mixture. The aqueous layers were extracted with ethyl acetate (10 ml × 3), the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 5 : 1) gave the title compound **8** (0.079 g, 98%) as a crystalline solid. Mp 127–128 °C; IR (film) 3503, 2953, 2889, 1759, 1728, 1460, 1371, 1199, 1120, 1068, 1029, 975, 965, 833, 706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (3H, s), 1.95 (1H, dd, J = 13.0, 13.8 Hz), 2.52 (1H, m), 2.69 (1H, ddd, J = 13.8, 3.8, 2.2 Hz), 3.02 (1H, br s), 3.25 (1H, dd, J = 6.6, 2.0 Hz), 3.46 (1H, dd, J = 10.4, 10.2 Hz), 3.75 (3H, s), 3.79 (1H, m), 4.19 (1H, dd, J = 9.3, 4.3 Hz), 4.36 (1H, d, J = 9.3 Hz); EIMS(*m*/*z*) 309 (M^++2), 307 (M^+), 227, 195, 167, 149, 123, 95; E.A. Calcd. for $C_{11}H_{15}O_5Br$: C, 43.02; H, 4.92. Found: C, 43.27; H, 4.62%.

TBS-protected bromohydrin 9

To a solution of **8** (0.061 g, 0.2 mmol) in DMF (1 ml) were added imidazole (0.04 g, 0.6 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl) (0.045 g, 0.3 mmol). The mixture was stirred overnight at room temperature. H_2O (5 ml) was added to dilute the reaction mixture. The aqueous layer was extracted with ether (10 ml × 3), the combined organic layers were washed with brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum

ether : ethyl acetate = 20 : 1) gave the title compound **9** (0.081 g, 92%) as a colorless oil. IR (neat) 2958, 1778, 1725, 1463, 1255, 1117, 861, 834, 777, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (3H, s), 0.21 (3H, s), 0.87 (9H, s), 1.59 (3H, s), 1.95 (1H, dd, J = 12.9, 12.9 Hz), 2.51 (1H, m), 2.69 (1H, ddd, J = 14.0, 3.8, 2.5 Hz), 3.21 (1H, dd, J = 6.7, 2.0 Hz), 3.55 (1H, dd, J = 9.6, 9.6 Hz), 3.69 (1H, m), 3.78 (3H, s), 4.16 (1H, dd, J = 9.4, 4.4 Hz), 4.28 (1H, d, J = 9.4 Hz); EIMS(*m*/*z*) 423 ($M^+ + 2$), 421 (M^+), 365, 319, 305, 259, 237, 179, 149, 105; E.A. Calcd. for $C_{17}H_{29}O_5SiBr$: C, 48.45; H, 6.94. Found: C, 48.45; H, 7.12%.

Debrominated TBS ether 10

To a solution of **9** (0.042 g, 0.1 mmol) in benzene (4 ml) were added AIBN (8 mg, 0.05 mmol) and Bu_3SnH (0.04 ml, 0.15 mmol). The mixture was stirred for 3 h at reflux under N_2. Removal of the solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 20 : 1) gave the title compound **10** (0.032 g, 94%) as a colorless oil. IR (neat) 2932, 2859, 1781, 1723, 1463, 1363, 1271, 1177, 1087, 856, 837, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 1.20 (1H, ddd, J = 13.8, 11.3, 2.7 Hz), 1.40 (1H, ddd, J = 13.8, 13.8, 2.7 Hz), 1.56 (3H, s), 1.78 (1H, ddd, J = 12.8, 7.1, 3.8 Hz), 2.12 (1H, ddd, J = 13.8, 6.2, 2.7 Hz), 2.37 (1H, m), 3.19 (1H, dd, J = 6.3, 2.2 Hz), 3.39 (1H, ddd, J = 10.8, 10.5, 4.5 Hz), 3.72 (3H, s), 4.11 (1H, dd, J = 9.1, 4.1 Hz), 4.17 (1H, d, J = 9.1 Hz); EIMS(*m*/*z*) 341 ($M^+ - 1$), 281, 216, 207, 187, 173, 165, 154, 121; E.A. Calcd. for $C_{17}H_{30}O_5Si$: C, 59.62; H, 8.83. Found: C, 59.34; H, 8.97%.

DIBAL reduction of 10 to semiacetal 11

To a solution of **10** (0.068 g, 0.2 mmol) in CH_2Cl_2 (2 ml) was added 1.0 M DIBAL (0.72 ml, 0.72 mmol) at −78 °C. The mixture was stirred for 2 h and methanol was added to quench the reaction. Then the mixture was allowed to warm to room temperature and 10 ml 1 M HCl was added. The aqueous layers were extracted with CH_2Cl_2 (10 ml × 3), the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 2 : 1) gave the title compound **11** (0.052 g, 82%) as a single isomer. Mp 142–143 °C; IR (film) 3402, 2956, 2858, 1473, 1361, 1256, 1087, 1042, 852, 836, 775 cm^{-1}; ^1H NMR (300 MHz, C_5D_5N) δ −0.09 (3H, s), −0.07 (3H, s), 0.72 (9H, s), 1.28 (1H, m), 1.29 (3H, s), 1.58 (2 H, m), 1.79 (1H, dd, J = 14.0, 1.8 Hz), 2.09 (1H, dd, J = 9.6, 7.7 Hz), 2.39 (1H, dd, J = 6.3, 6.1 Hz), 3.58, 3.72 (2H, AB, J = 10.4 Hz), 3.62 (1H, m), 3.98 (1H, s), 3.99 (1H, s), 5.68 (1H, d, J = 6.5 Hz); FABMS: 315 ($M^+ - 1$), 317 ($M^+ + 1$), 339 ($M^+ + Na$); E.A. Calcd. for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.67; H, 10.29%.

Dibenzoate of semiacetal 12

To a solution of **11** (0.063 g, 0.2 mmol) in pyridine (1 ml) was added benzoyl chloride (0.07 ml, 0.6 mmol) at 0 °C. The mixture was stirred for 30 minutes and methanol was added to quench the reaction. Then the mixture was allowed to warm to room temperature and 10 ml 1 M HCl was added. The aqueous layer was extracted with ethyl acetate (10 ml × 3), the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 10 : 1) gave the title compound **12** (0.103 g, 98%) as a colorless oil. IR (neat) 3064, 1722, 1602, 1452, 1386, 776, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.08 (3H, s), 1.40–1.65 (3H, m), 1.75 (1H, m), 2.29 (1H, m), 2.60 (1H, m), 3.59 (1H, ddd, J = 9.9, 9.9, 4.1 Hz), 4.01 (2H, m), 4.29 (2H, s), 6.38 (1H, d, J = 6.1 Hz), 7.40–7.60 (6H, m), 8.05 (4H, m); EIMS(*m*/*z*) 523 ($M^+ - 1$), 467 ($M^+ - {}^t$Bu); E.A. Calcd. for $C_{30}H_{40}O_6Si$: C, 68.67; H, 7.68. Found: C, 68.46; H, 7.82%.

Dithioacetal 13

A solution of **12** (0.052 g, 0.1 mmol) and propane-1,3-dithiol (0.03 ml, 0.3 mmol) in CH_2Cl_2 (2 ml) was cooled to −78 °C and $TiCl_4$ (0.017 ml, 0.15 mmol) was added dropwise. The mixture was warmed to −40 °C and stirred for 2 h. Saturated aqueous $NaHCO_3$ was added and the mixture was warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3), the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 5 : 1) gave the title compound **13** (0.041 g, 80%) as a white solid. Mp 138–140 °C; IR (film) 3290, 1720, 1472, 1378, 775, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 1.23 (3H, s), 1.51 (2H, m), 1.65–2.00 (4H, m), 2.06 (1H, m), 2.19 (1H, m), 2.62 (1H, m), 2.75–3.00 (3H, m), 3.75 (1H, m), 4.05 (1H, m), 4.18 (1H, m), 4.30 (2H, m), 4.46 (1H, d, J = 3.5 Hz), 7.40–7.60 (3H, m), 8.05 (2H, m); EIMS(*m*/*z*) 509 ($M^+ - 1$), 453 ($M^+ - {}^t$Bu); E.A. Calcd. for $C_{26}H_{42}O_4S_2Si$: C, 61.13; H, 8.29; S, 12.55. Found: C, 61.38; H, 8.48; S, 12.12%.

TBDPS ether of dithioacetal 14

To a solution of **13** (0.051 g, 0.1 mmol) in DMF (1.5 ml) were added imidazole (0.016 g, 0.24 mmol) and TBDPSCl (0.033 g, 0.12 mmol). The mixture was allowed to stand overnight at 50 °C. Water (5 ml) was added to quench the reaction and the aqueous layer was extracted with ether (10 ml × 3), the combined organic layers were washed with brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 20 : 1) gave the title compound **14** (0.071 g, 95%) as a colorless oil. IR (neat) 1722, 1472, 774, 740, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.80 (9H, s), 1.02 (9H, s), 1.10–1.50 (3H, m), 1.50–1.85 (3H, m), 2.01 (1H, m), 2.35 (1H, m), 2.65–2.90 (4H, m), 3.45–4.65 (6H, m), 7.25–7.80 (13H, m), 8.07 (2H, d, J = 8.3 Hz); EIMS(*m*/*z*) 749 ($M^+ + 1$), 691 ($M^+ - {}^t$Bu); E.A. Calcd. for $C_{42}H_{60}O_4S_2Si_2$: C, 67.33; H, 8.07; S, 8.56. Found: C, 67.43; H, 8.33; S, 8.69%.

Deprotection of dithioacetal to 14 aldehyde 15

To a solution of **14** (0.075 g, 0.1 mmol) in acetone (0.6 ml) and water (0.06 ml) were added HgO (0.043 g, 0.2 mmol) and $HgCl_2$ (0.054 g, 0.2 mmol). After stirring for 2 h at 55 °C, the mixture was filtered through a pad of Celite and the solid was washed with acetone. The solvent was removed and the residue was dissolved with CH_2Cl_2, washed with 10% KI and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 20 : 1) gave the title compound **15** (0.064 g, 97%) as a colorless oil. IR (neat) 3072, 1723, 1472, 1429, 776, 740, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.17 (3H, s), −0.04 (3H, s), 0.71 (9H, s), 0.99 (9H, s), 1.18 (3H, s), 1.40–1.80 (5H, m), 2.20 (1H, m), 3.37 (1H, m), 3.48 (1H, dd, J = 9.1, 9.1 Hz), 3.92 (1H, m), 4.20, 4.42 (2H, AB, J = 11.2 Hz), 7.25–7.80 (13H, m), 8.07 (2H, d, J = 9.3 Hz), 9.98 (1H, s); EIMS(*m*/*z*) 658 (M^+), 601 ($M^+ - {}^t$Bu); HREIMS Calcd. for $C_{35}H_{45}O_5Si_2$ ($M^+ - {}^t$Bu): 601.2805. Found: 601.2787.

Intermolecular aldol condensation to unsaturated ester 19

Butyllithium (0.075 ml, 0.12 mmol) was added to a solution of i-Pr_2NH (0.017 ml, 0.12 mmol) in THF (2 ml) at 0 °C, then the mixture was allowed to warm to room temperature and stirred for 20 minutes. The mixture was then cooled to −78 °C, **17** (0.017 g, 0.11 mmol) was added and stirred for 1 h, $ZnCl_2$ (16.5 mg, 0.12 mmol) in THF (1 ml) was added and stirred for 1 h, then **18** (0.064 g, 0.1 mmol) was added and stirred for another 2 h. Saturated aqueous NH_4Cl was added and the mixture was warmed to room temperature. The aqueous layer was extracted

with CH_2Cl_2 (10 ml × 3), the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 20 : 1) gave the title compound **19** (0.072 g, 88%) as a 9 : 1 mixture of two diastereomers. Spectra data of major isomer: IR (neat) 3497, 3072, 1709, 1639, 1473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.06 (3H, s), 0.60 (3H, s), 0.85 (9H, s), 1.00 (3H, s), 1.03 (12H, s), 1.15 (3H, t, J = 7.1 Hz), 1.25–1.40 (3H, m), 1.98 (1H, m), 2.12 (1H, m), 2.31 (1H, dd, J = 10.4, 5.5 Hz), 2.49 (1H, m), 3.04 (1H, d, J = 8.2 Hz), 3.50 (3H, m), 3.68 (1H, d, J = 8.2 Hz), 3.85 (1H, m), 4.14 (2H, m), 4.38, 4.44 (2H, AB, J = 12.3 Hz), 4.82 (1H, d, J = 10.7 Hz), 4.90 (1H, d, J = 17.5 Hz), 5.75 (1H, dd, J = 17.3, 10.7 Hz), 7.20–7.45 (11H, m), 7.65 (4H, m); EIMS(*m*/*z*) 802 (M^+ + 1), 726 (M^+ − ^{t}Bu − H_2O); E.A. Calcd. for $C_{48}H_{72}O_6Si_2$: C, 71.95; H, 9.06. Found: C, 72.36; H, 9.35. Selective spectra data of minor isomer: ^1H NMR (300 MHz, $CDCl_3$) 0.18 (6H, s), 0.82 (9H, s), 0.91 (3H, s), 1.01 (3H, s), 1.08 (9H, s), 1.12 (3H, s), 1.18 (3H, t, J = 7.2 Hz), 1.38 (1H, m), 1.56 (1H, m), 1.86 (2H, m), 2.30 (2H, m), 2.62 (1H, m), 3.12 (1H, m), 3.20 (1H, d, J = 8.8 Hz), 3.62 (1H, m), 3.98, 4.02 (2H, AB, J = 7.2 Hz), 4.22 (1H, m), 4.30 (1H, m), 4.48 (3H, m), 4.82 (1H, d, J = 10.4 Hz), 4.93 (1H, d, J = 17.6 Hz), 5.85 (1H, m), 7.30 (11H, m), 7.68 (4H, m).

TES ether protected unsaturated ester 20

To a solution of **19** (0.08 g, 0.1 mmol) and 2,6-lutidine (0.023 ml, 0.2 mmol) in CH_2Cl_2 (2 ml) was added TESOTf (0.034 ml, 0.15 mmol) at 0 °C. Then the mixture was allowed to stand overnight at room temperature. Saturated aqueous $NaHCO_3$ was added to quench the reaction and the aqueous layer was extracted with CH_2Cl_2 (10 ml × 3), the combined organic layers were washed with brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 50 : 1) gave the title compound **20** (0.089 g, 95%) as a colorless oil. IR (neat) 3072, 1737, 1638, 1473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.39 (6H, m), 0.70 (9H, t, J = 7.7 Hz), 0.75 (3H, s), 0.85 (3H, s), 0.88 (9H, s), 1.00 (3H, s), 1.05 (9H, s), 1.15 (3H, t, J = 7.0 Hz), 1.17 (2H, m), 1.40 (2H, m), 2.00 (1H, m), 2.35 (1H, m), 2.48 (1H, d, J = 5.5 Hz), 2.93 (1H, d, J = 8.5 Hz), 3.21 (1H, d, J = 7.7 Hz), 3.75 (3H, m), 3.80 (1H, m), 4.15 (1H, m), 4.28 (1H, br s), 4.45, 4.65 (2H, AB, J = 11.5 Hz), 4.88 (1H, d, J = 17.6 Hz), 4.97 (1H, d, J = 11.2 Hz), 6.00 (1H, dd, J = 17.6, 11.0 Hz), 7.20–7.45 (11H, m), 7.68 (4H, m); ESIMS(*m*/*z*) 938 (M^+ + Na), 961 (M^+ + 2Na); E.A. Calcd. for $C_{54}H_{86}O_6Si_3$: C, 70.84; H, 9.47. Found: C, 70.94; H, 9.68%.

Reduction of ester to unsaturated diol 21

To a solution of **20** (0.092 g, 0.1 mmol) in CH_2Cl_2 (2 ml) was added 1.0 M DIBAL (0.36 ml, 0.36 mmol) at 0 °C. The mixture was stirred overnight at room temperature. Then the mixture was recooled to 0 °C and methanol was added to quench the reaction and 10 ml 1 M HCl was added. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3), the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 10 : 1) gave the title compound **21** (0.063 g, 82%) as a white solid. Mp 133–134 °C; IR (film) 3365, 3070, 2930, 1634, 1471, 1427 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.06 (3H, s), 0.60 (3H, s), 0.90 (9H, s), 1.05 (12H, s), 1.10 (3H, s), 1.22 (2H, m), 1.34 (2H, m), 1.80 (1H, m), 1.90 (1H, m), 2.38 (1H, m), 3.21 (2H, br s), 3.42 (2H, d, J = 5.8 Hz), 3.83–4.12 (4H, m), 4.42, 4.46 (2H, AB, J = 12.1 Hz), 4.76 (1H, d, J = 10.7 Hz), 4.88 (1H, d, 17.6 Hz), 5.78 (1H, dd, J = 10.7, 17.3 Hz), 7.22–7.45 (11H, m), 7.60 (4H, m); ESIMS(*m*/*z*) 759 (M^+), 782 (M^+ + Na); E.A. Calcd. for $C_{46}H_{70}O_5Si_2$: C, 72.77; H, 9.29. Found: C, 72.60; H, 9.26%.

Isopropylidene protected unsaturated diol 22

To a solution of **21** (0.076 g, 0.1 mmol) in CH_2Cl_2 (1.5 ml) were added $Me_2C(OMe)_2$ (0.05 ml, 0.4 mmol) and CSA (3.75 mg, cat.). The mixture was allowed to stand overnight at room temperature. Saturated aqueous $NaHCO_3$ was added to quench the reaction and the aqueous layer was extracted with CH_2Cl_2 (10 ml × 3), the combined organic layers were washed with brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 20 : 1) gave the isopropylidene acetal **22** (0.078 g, 98%) as a colorless oil. IR (neat) 3076, 2932, 1637, 1472, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (6H, s), 0.90 (3H, s), 0.96 (3H, s), 0.98 (9H, s), 1.02 (3H, s), 1.12 (9H, s), 1.30 (6H, s), 1.35–1.65 (3H, m), 1.85 (1H, m), 2.05 (1H, m), 2.27 (1H, m), 2.45 (1H, m), 3.00 (1H, br s), 3.35–3.70 (4H, m), 3.85 (2H, m), 4.28 (1H, br s), 4.43, 4.47 (2H, AB, J = 11.9 Hz), 4.85 (1H, d, J = 11.6 Hz), 4.90 (1H, d, J = 17.7 Hz), 5.63 (1H, m), 7.30 (11H, m), 7.70 (4H, m); ESIMS(*m*/*z*) 822 (M^+ + Na); E.A. Calcd. for $C_{49}H_{74}O_5Si_2$: C, 73.63; H, 9.33. Found: C, 72.91; H, 9.37%.

Epoxidation of protected unsaturated diol to epoxide 23

To a solution of **22** (0.08 g, 0.1 mmol) in CH_2Cl_2 (2 ml) was added MCBPA (55%, 34.5 mg, 0.11 mmol). The mixture was allowed to stand overnight at room temperature. 1 M Na_2SO_3 was added to quench the reaction and the aqueous layer was extracted with CH_2Cl_2 (10 ml × 3), the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 15 : 1) gave the epoxide **23** (0.075 g, 92%) as a single isomer. IR (neat) 3072, 2931, 1473, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.70–0.95 (21H, m), 1.05 (12H, m), 1.20–1.60 (4H, m), 2.00 (2H, br s), 2.32 (1H, br s), 2.40–2.60 (3H, m), 2.62 (1H, br s), 2.95 (1H, br s), 3.45–3.90 (5H, m), 4.25 (1H, br s), 4.42 (2H, m), 7.30 (11H, m), 7.68 (4H, m); ESIMS(*m*/*z*) 837 (M^+ + Na), 860 (M^+ + 2Na); E.A. Calcd. for $C_{49}H_{74}O_6Si_2$: C, 72.19; H, 9.15. Found: C, 71.82; H, 9.23%.

Reduction of epoxide to alcohol 24

To the suspension of LAH (4 mg, 0.105 mmol) in THF (2 ml) was added **23** (0.082 g, 0.1 mmol) at 0 °C, then the suspension was allowed to warm to room temperature and stirred for 1 h. Aqueous NaOH was added to quench the reaction. The mixture was filtered through a pad of Celite and the solid was washed with ethyl acetate, the combined organic fractions were washed with brine, dried over Na_2SO_4. After removal of solvent, the residue was purified by flash column chromatography (petroleum ether : ethyl acetate = 8 : 1) to give the title compound **24** (0.08 g, 98%) as a white solid. Mp 97–99 °C; IR (film) 3449, 3072, 2931, 1473, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.60–0.95 (18H, m), 1.02 (15H, br s), 1.19 (3H, br s), 1.30 (2H, m), 1.40–1.60 (2H, m), 1.90 (2H, m), 2.21 (1H, br s), 2.42 (1H, m), 2.88 (1H, m), 3.45 (1H, m), 3.60 (2H, m), 3.75 (3H, m), 4.05 (1H, m), 4.10 (1H, m), 4.36 (2H, m), 7.30 (11H, m), 7.60 (4H, m); FABMS(*m*/*z*) 818 (M^+ + 1); E.A. Calcd. for $C_{49}H_{76}O_6Si_2$: C, 72.01; H, 9.37. Found: C, 72.28; H, 9.47%.

Deprotection of alcohol 24 to diol 25

To a solution of **24** (0.082 g, 0.1 mmol) in ethyl acetate (2 ml) was added Pd–C (10%, 8 mg), then the suspension was stirred at room temperature for 24 h under an H_2 atmosphere. The mixture was filtered through a pad of Celite and the solid was washed with ethyl acetate. After removal of solvent, the residue was purified by flash column chromatography (petroleum ether : ethyl acetate = 2 : 1) to give the title compound **25** (0.063 g, 86%) as a white solid. Mp 121–122 °C; IR (film) 3412, 3302,

2932, 1473, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.85 (18H, m), 1.08 (12H, s), 1.18 (6H, m), 1.20–1.40 (2H, m), 1.50–1.60 (2H, m), 2.02 (2H, m), 2.28 (1H, d), 3.32 (1H, m), 3.45 (1H, m), 3.60–3.90 (6H, m), 4.22 (1H, m), 7.40 (6H, m), 7.65 (4H, m); EIMS(*m*/*z*) 670 ($M^+ + 1 - {}^tBu$), 652 ($M^+ + 1 - {}^tBu - H_2O$); HREIMS Calcd. for $C_{38}H_{61}O_6Si_2(M^+ - {}^tBu)$: 669.4007. Found: 669.3998.

Oxidation of diol 25 to ketoaldehyde 26

To a solution of **25** (0.073 g, 0.1 mmol) in CH_2Cl_2 (2 ml) were added 4 Å molecular sieves (50 mg), NMO (17.6 mg, 0.15 mmol) and TPAP (1.76 mg, cat.). The mixture was stirred for 2 h at room temperature, then diluted with CH_2Cl_2, filtered through a pad of Celite and the solid was washed with CH_2Cl_2. After removal of solvent, the residue was purified by flash column chromatography (petroleum ether : ethyl acetate = 5 : 1) to give the title compound **26** (0.075 g, 98%) as a colorless oil. IR (neat) 3073, 2933, 1727, 1704, 1472, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.82 (9H, s), 1.05 (12H, s), 1.20 (4 × CH_3, 4 × s), 1.62 (2H, m), 1.95 (2H, m), 2.10 (2H, m), 2.18 (3H, s), 2.61 (1H, d, J = 3.8 Hz), 3.34 (1H, dd, J = 1.7, 12.4 Hz), 3.66 (1H, dd, J = 5.2, 12.4 Hz), 3.84 (1H, dd, J = 6.0, 10.7 Hz), 3.95 (2H, m), 4.12 (1H, m), 7.40 (6H, m), 7.70 (4H, m), 9.52 (1H, s); EIMS(*m*/*z*) 706 ($M^+ + 1 - CH_3$), 664 ($M^+ - 1 - {}^tBu$); HREIMS Calcd. for $C_{38}H_{57}O_6Si_2(M^+ - {}^tBu)$: 665.3693. Found: 665.3670.

Intramolecular aldol condensation of ketoaldehyde 26 to β-hydroxy ketone 27

To a solution of ^tBuOK (14 mg, 0.12 mmol) in THF (10 ml) was added **26** (0.072 g, 0.1 mmol) in THF (10 ml) over a 2 h period, then the mixture was stirred overnight at room temperature. HCl (1 M) was added to quench the reaction and the aqueous layer was extracted with ethyl acetate (10 ml × 3), the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum ether : ethyl acetate = 3 : 1) gave the title compound **27** (0.065 g, 90%) as a 6.6 : 1.0 mixture of two epimers. Spectra data of major isomer: IR (film) 3477, 3073, 2933, 1690, 1472, 1428 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.19 (3H, s), 0.08 (3H, s), 0.64 (3H, s), 0.95 (9H, s), 1.05 (15H, m), 1.30 (6H, m), 1.60 (2H, br s), 1.75–2.25 (4H, m), 2.30–2.75 (3H, m), 3.02–4.70 (7H, m), 7.42 (6H, m), 7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 135.7, 133.8, 129.6, 127.6, 98.7, 79.4, 77.5, 77.0, 76.6, 75.5, 67.6, 63.1, 55.6, 48.0, 47.3, 46.6, 42.1, 37.1, 29.7, 27.2, 27.0, 26.2, 25.9, 25.7, 24.3, 24.0, 20.5, 18.6, 18.4, −4.5, −4.9; EIMS(*m*/*z*) 722 (M^+), 666 ($M^+ + 1 - {}^tBu$), 648 ($M^+ + 1 - {}^tBu - H_2O$), 607 ($M^+ - 724; 1 - 2{}^tBu$); HREIMS Calcd. for $C_{38}H_{57}O_6Si_2(M^+ - {}^tBu)$: 665.3693. Found: 665.3685.

Oxidation of compound 27

To a solution of **27** (0.072 g, 0.1 mmol) in CH_2Cl_2 (2 ml) were added 4 Å molecular sieves (50 mg), NMO (17.6 mg, 0.15 mmol) and TPAP (1.76 mg, cat.). The mixture was stirred for 2 h at room temperature, then diluted with CH_2Cl_2, filtered through a pad of Celite and the solid was washed with CH_2Cl_2. After removal of solvent, the residue was purified by flash column chromatography (petroleum ether : ethyl acetate = 10 : 1) to give the 1,3-dicarbonyl compound (0.071 g, 98%) as a colorless oil. IR (neat) 2931, 1708, 1683, 1471, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (6H, s), 0.98 (9H, s), 1.05 (9H, s), 1.00–1.20 (4 × CH_3, 4 × s), 1.25 (3H, s), 1.20–1.30 (1H, m), 1.35–1.50 (2H, m), 1.95 (1H, m), 2.10 (2H, m), 2.52 (1H, d, J = 4.0 Hz), 3.58, 3.62 (2H, AB, J = 16.7 Hz), 3.68 (2H, m), 3.80 (2H, m), 4.13 (1H, dd, J = 10.6, 3.3 Hz), 4.35 (1H, br s), 7.40 (6H, m), 7.64 (4H, m); EIMS(*m*/*z*) 664 ($M^+ + 1 - {}^tBu$), 606 ($M^+ - 2{}^tBu$).

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11 Several synthetic trials launched from compound **15** have failed. In the end, we changed the benzoyl ester in compound **15** to the benzyl ether in compound **18.** Compound **18** was prepared from compound **14** through a successive deprotection (Bz), protection (Bn) and aldehyde deprotection procedure.

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18 Compound **27** was determined to be a 6.6 : 1.0 mixture of two epimers from the HPLC analysis. This was verified by further oxidation of both epimers to the same 1,3-dicarbonyl product.

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