Substituent Effects on Regioselective Intramolecular Oxidation of Unactivated C–H Bonds: Stereoselective Synthesis of Substituted Tetrahydropyrans

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Supporting Information

General Methods. All reactions were performed in oven-dried apparatus. Air and moisture-sensitive compounds were introduced via syringes through a rubber septum. Diethyl ether and THF were distilled from sodium-benzophenone. Dichloromethane, toluene, and triethylamine were distilled over calcium hydride. Flash column chromatography was performed using the indicated solvent system on E. Merck silica gel 60 (230–400 mesh ASTM).

Preparation of Ketone 1.

(a) Pd/C , H_2 ; (b) $\text{Ph}_3\text{P}=\text{CHCN}$, EDCI, DMAP, CH_2Cl_2 ; (c) dimethyldioxirane, MeOH , CH_2Cl_2 .

Ketone **1** was synthesized from acid **1d** according to a literature procedure (Wong, M.-K.; Yu, C.-W.; Yuen, W.-H.; Yang, D. *J. Org. Chem.* **2001**, *66*, 3606).

Acid **1d** was prepared from **1e** according to a literature procedure (Mori, K.; Kuwahara, S.; Levinson, H. Z.; Levinson, A. R. *Tetrahedron* **1982**, *38*, 2291). ^1H NMR (300 MHz, CDCl_3) δ 2.36 (dd, $J = 14.9, 5.9$ Hz, 1H), 2.14 (dd, $J = 14.9, 8.2$ Hz, 1H), 1.90–2.00 (m, 1H), 1.53 (septet, $J = 6.6$ Hz, 1H), 1.10–1.39 (m, 6H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 180.21, 41.72, 39.02, 36.91, 30.18, 27.94, 24.66, 22.66, 22.58, 19.71; EIMS (20 eV) m/z 172 (M^+ , 2), 129 (7), 113 (17); HRMS (EI) for $\text{C}_{10}\text{H}_{20}\text{O}_2$ (M^+), calcd 172.1463, found 172.1449.

To a solution of **1d** (0.63 g, 3.66 mmol) in dry CH_2Cl_2 was added $\text{Ph}_3\text{P}=\text{CHCN}$ (1.66 g, 5.52 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.06 g, 5.52 mmol), and DMAP (0.05 g, 0.37 mmol) under nitrogen atmosphere at room temperature. After stirring overnight, the reaction mixture was diluted with CH_2Cl_2 (18 mL), washed with 5% NaHCO_3 solution, brine, and water. The organic layer was separated, dried over anhydrous MgSO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc in hexane) to give **1c** as a syrup (0.60 g, 0.66 mmol, 36% yield). Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.55$; ^1H NMR (270 MHz, CDCl_3) δ 7.46–7.65 (m, 15H), 2.64 (dd, $J = 14.2, 6.3$ Hz, 1H), 2.54 (dd, $J = 14.2, 7.9$ Hz, 1H), 2.26–2.37 (m, 1H), 1.46–1.57 (m, 1H), 1.13–1.32 (m, 15H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (68 MHz, CDCl_3) δ 197.05 (d, $J = 3.3$ Hz), 133.51 (d, $J = 10.6$ Hz), 132.86 (d, $J = 3.4$ Hz), 128.96 (d, $J = 12.9$ Hz, 6C), 123.52 (d, $J = 93.3$ Hz, 3C), 122.70 (d, $J = 19.6$ Hz, CN), 49.55 (d, $J = 125.7$ Hz), 46.95 (d, $J = 6.7$ Hz), 39.34, 37.32,

30.79, 28.02, 24.88, 22.83, 22.70, 19.92; IR (CH₂Cl₂) 2174, 1582 cm⁻¹; EIMS (20 eV) 455 (M⁺, 37), 370 (23), 343 (100), 328(26); HRMS (EI) for C₃₀H₃₄OPN (M⁺), calcd 455.2378, found 455.2374.

To a solution of **1c** (0.22 g, 0.36 mmol) in dry MeOH (20 mL) was added dimethyldioxirane (0.04 M in acetone, 18 mL, 0.72 mmol). After stirring for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc in hexane) to give **1** as a white solid (57 mg, 0.27 mmol, 74% yield). Mp 115–116 °C. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, R_f = 0.62; ¹H NMR (300 MHz, CDCl₃) δ 3.86 (s, 3H), 2.83 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.64 (dd, *J* = 17.0, 8.0 Hz, 1H), 2.04–2.09 (m, 1H), 1.46–1.59 (m, 1H), 1.11–1.32 (m, 6H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 194.18, 161.71, 52.80, 46.39, 39.90, 36.96, 28.78, 27.83, 24.55, 22.58, 22.49, 19.69; IR (CH₂Cl₂) 1729 cm⁻¹; EIMS (20 eV) 214 (M⁺, 8); HRMS (EI) for C₁₂H₂₂O₃ (M⁺), calcd 214.1569, found 214.1583.

Preparation of Ketone 2.

(a) i, oxalyl chloride, CH₂Cl₂; ii, (CF₃CO)₂O, pyridine, CH₂Cl₂.

Ketone **2** was synthesized from acid **1d** according to a literature procedure (Boivin, J.; Kaim, L. E.; Zard, S. Z. *Tetrahedron Lett.* **1992**, 33, 1285).

To a solution of acid **1d** (2.0 g, 11.6 mmol) in CH₂Cl₂ was added oxalyl chloride (2.0 mL, 23.3 mmol) at room temperature under nitrogen atmosphere. Stirring was continued for 2 h. The solvent and excess oxalyl chloride were evaporated off under reduced pressure. The resulting acid chloride was dissolved in CH₂Cl₂ and treated successively with trifluoroacetic anhydride (9.9 mL, 69.8 mmol) and pyridine (7.5 mL, 93.0 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h and quenched slowly with water at 0 °C. Then the mixture was diluted with CH₂Cl₂ washed with diluted HCl and saturated NaHCO₃ solution. The organic layer was dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by vacuum distillation (b.p. 41–42 °C at

ca. 2 mmHg) to afford ketone **2** (1.33 g, 51% yield) as a colourless liquid: ^1H NMR (300 MHz, CDCl_3) δ 2.69 (dd, $J = 17.8, 5.6$ Hz, 1H), 2.51 (dd, $J = 17.8, 7.8$ Hz, 1H), 2.07–2.16 (m, 1H), 1.53 (septet, $J = 6.6$ Hz, 1H), 1.15–1.37 (m, 6H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 191.36 (q, $^2J_{\text{C},\text{F}} = 34.3$ Hz), 115.59 (q, $^1J_{\text{C},\text{F}} = 292.7$ Hz), 43.64, 38.96, 36.86, 28.44, 27.96, 24.63, 22.65, 22.57, 19.59; EIMS (20 eV) m/z 155 ($\text{M}^+ - \text{CF}_3$, 14); HRMS (EI) for $\text{C}_{10}\text{H}_{19}\text{O}$ ($\text{M}^+ - \text{CF}_3$), calcd 155.1436, found 155.1457.

Preparation of Ketone **3**.

(a) $\text{Ph}_3\text{P}=\text{CHCN}$, EDCI, DMAP, CH_2Cl_2 ; (b) dimethyldioxirane, MeOH, CH_2Cl_2 .

Ketone **3** was synthesized from 2-methylhexanoic acid according to a literature procedure (Wong, M.-K.; Yu, C.-W.; Yuen, W.-H.; Yang, D. *J. Org. Chem.* **2001**, 66, 3606).

To a solution of 2-methylhexanoic acid (0.65 g, 5.0 mmol) in dry CH_2Cl_2 (25 mL) was added $\text{Ph}_3\text{P}=\text{CHCN}$ (2.40 g, 8.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.54 g, 8.0 mmol), and 4-dimethylaminopyridine (60 mg, 0.5 mmol) under nitrogen atmosphere at room temperature. After stirring overnight, the reaction mixture was washed with 5% NaHCO_3 solution. The aqueous layer was extract with CH_2Cl_2 . The organic layer was separated, dried over anhydrous MgSO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc in hexane) to give **3c** as white solid (1.00 g, 2.4 mmol, 48% yield). M.p. 130 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, $R_f = 0.55$; ^1H NMR (300 MHz, CDCl_3) δ 7.47–7.63 (m, 15H), 3.14–3.22 (m, 1H), 1.63–1.73 (m, 1H), 1.28–1.33 (m, 5H), 1.13 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (68 MHz, CDCl_3) δ 201.11, 133.41 (d, $J = 14.0$ Hz, 6C), 132.83 (d, $J = 13.4$ Hz, 3C), 128.92 (d, $J = 12.9$ Hz, 6C), 123.46 (d, $J = 93.9$ Hz, 3C), 122.30 (d, $J = 16.2$ Hz, CN), 48.8 (d, $J = 125.2$ Hz), 42.06 (d, $J = 6.7$ Hz), 33.69, 29.83, 22.89, 17.90, 14.17; IR (CH_2Cl_2) 2172,

1559 cm^{-1} ; EIMS (20 eV) 413 (M^+ , 20), 328 (100); HRMS (EI) for $\text{C}_{27}\text{H}_{28}\text{ONP}$ (M^+), calcd 413.1909, found 413.1925.

To a solution of **3c** (0.32 g, 0.80 mmol) in dry MeOH (16 mL) was added dimethyldioxirane (0.02 M in acetone, 80 mL, 1.60 mmol). After stirring for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc in hexane) to give **3** as a colorless oil (0.13 g, 0.76 mmol, 95% yield). Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, R_f = 0.42; ^1H NMR (300 MHz, CDCl_3) δ 3.87 (s, 3H), 3.80 (m, 1H), 1.67–1.78 (m, 1H), 1.24–1.40 (m, 5H), 1.14 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 197.86, 162.24, 52.75, 42.03, 31.52, 29.09, 22.56, 15.02, 13.82; IR (CH_2Cl_2) 1730 cm^{-1} ; EIMS (20 eV) 157 ($\text{M}^+ - \text{CH}_3$, 38), 113 (61); HRMS (EI) for $\text{C}_8\text{H}_{13}\text{O}_3$ ($\text{M}^+ - \text{CH}_3$), calcd 157.0865, found 157.0867.

Preparation of Ketone 4.

(a) LiAlH_4 , Et_2O , rt; (b) p -TsCl, pyridine, 0 $^\circ\text{C}$; (c) NaCN, DMSO, 60 $^\circ\text{C}$;
(d) NaOH, $\text{EtOH}/\text{H}_2\text{O}$, reflux; (e) i, oxalyl chloride, CH_2Cl_2 ; ii, $(\text{CF}_3\text{CO})_2\text{O}$, pyridine, CH_2Cl_2 .

Acid **4c** was prepared from acid **1d** according to a literature procedure (Mori, K.; Kuwahara, S.; Levinson, H. Z.; Levinson, A. R. *Tetrahedron* **1982**, 38, 2291).

4f: ^1H NMR (300 MHz, CDCl_3) δ 3.60–3.73 (m, 2H), 1.77 (br s, 1H), 1.08–1.66 (m, 10H), 0.89 (d, J = 7.1 Hz, 3H), 0.86 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 61.17, 39.99, 39.28, 37.41, 29.54, 27.99, 24.71, 22.71, 22.61, 19.65; CIMS m/z 157 ($\text{M}^+ - 1$, 40), 141 (100).

4d: ^1H NMR (300 MHz, CDCl_3) δ 2.25–2.43 (m, 2H), 1.09–1.75 (m, 10H), 0.91 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 120.03, 39.12, 36.48, 32.31, 32.02, 27.94, 24.52, 22.68, 22.57, 18.83, 14.93; CIMS m/z 168 ($\text{M}^+ + 1$, 100).

4c: ^1H NMR (300 MHz, CDCl_3) δ 2.26–2.44 (m, 2H), 1.09–1.75 (m, 10H), 0.88 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 180.95, 39.25, 36.88, 32.35, 31.96, 31.64, 27.97, 24.65, 22.70, 22.61, 19.26; EIMS (20 eV) m/z 186 (M^+ , 3), 127 (44); HRMS (EI) for $\text{C}_{11}\text{H}_{22}\text{O}_2$ (M^+), calcd 186.1619, found 186.1613.

Ketone **4** was synthesized from acid **4c** according to a literature procedure (Boivin, J.; Kaim, L. E.; Zard, S. Z. *Tetrahedron Lett.* **1992**, 33, 1285). As a colourless liquid (41% yield); b.p. 46 °C at ca. 2 mm Hg; ^1H NMR (300 MHz, CDCl_3) δ 2.52–2.80 (m, 2H), 1.09–1.75 (m, 10H), 0.89 (d, J = 5.8 Hz, 3H), 0.87 (d, J = 6.5 Hz, 6H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 191.91 (q, $^2J_{\text{C},\text{F}}$ = 34.7 Hz), 115.73 (q, $^1J_{\text{C},\text{F}}$ = 292.2 Hz), 39.25, 36.89, 34.24, 32.21, 29.33, 28.03, 24.72, 22.70, 22.61, 19.25; EIMS (20 eV) m/z 238 (M^+ , 6), 181 (29), 169 (100); HRMS (EI) for $\text{C}_{12}\text{H}_{21}\text{OF}_3$ (M^+), calcd 238.1544, found 238.1503.

Preparation of Ketone 5.

(a) phthalic anhydride, Et_3N , toluene, overnight; (b) $\text{Ph}_3\text{P}=\text{CHCN}$, DMAP, EDCI, CH_2Cl_2 , r.t., overnight; (c) dimethyldioxirane, MeOH, r.t., 3 h

To a solution of **5d** (2 g, 15 mmol) in dry toluene (50 mL) was added Et_3N (6.2 mL, 45 mmol) and phthalic anhydride (2.9 g, 19.5 mmol). After refluxing overnight, the organic solvent was evaporated under reduced pressure. The reaction mixture was acidified with dilute hydrochloric acid to pH 2 at 0 °C, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in hexane) to provide **5c** as a white solid (2.2 g, 8.9 mmol, 59% yield). M.p. 105 –106 °C. Analytical TLC (silica gel 60), 75% EtOAc in n-hexane, R_f = 0.44; ^1H NMR (300 MHz, CDCl_3) δ 7.87 (m, 2H), 7.74 (m, 2H), 4.90 (dd, J = 5 Hz, 1H), 2.25 (m, 2H), 1.34 (m, 4H), 0.86 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.32, 167.73, 134.32, 132.02, 131.61, 123.62, 51.95,

28.38, 28.07, 21.94, 13.78; IR (CH₂Cl₂) 3445, 1777, 1720, 1635 cm⁻¹; EIMS (20 eV) 261 (M⁺, 10), 216 (100), 160 (82); HRMS (EI) for C₁₄H₁₅O₄ (M⁺), calcd 261.1001, found 261.1002.

5b as a white solid (3.4 g, 6.2 mmol, 71% yield). M.p. 207.5 – 208 °C. Analytical TLC (silica gel 60), 75% EtOAc in n-hexane, R_f = 0.67; ¹H NMR (300 MHz, CDCl₃) δ 7.84 (m, 2H), 7.60 (m, 16H), 5.20 (t, *J* = 7.8 Hz, 1H), 2.32 (m, 2H), 1.30 (m, 4H), 0.85 (t, *J* = 6.4 Hz, 3H); ¹³C NMR (67 MHz, CDCl₃) δ 191.36 (d, *J* = 3.8 Hz), 168.31, 133.72, 133.53 (d, *J* = 10.2 Hz, 6C), 133.08 (s, 3C), 133.02, 129.51, 129.10 (d, *J* = 12.8 Hz, 6C), 123.22, 122.86 (d, *J* = 93.6 Hz, 3C), 120.87 (d, *J* = 15.2 Hz, CN), 57.33 (d, *J* = 7.9 Hz), 46.73 (d, *J* = 127.48 Hz), 28.69, 27.95, 22.20, 19.71, 13.96; IR (CH₂Cl₂) 2175, 1714, 1597 cm⁻¹; FABMS *m/z* 545 (M⁺+1, 100); EIMS (20 eV) 544 (M⁺, 2), 328 (100), 277 (19); HRMS (EI) for C₃₄H₂₉PN₂O₃ (M⁺), calcd 544.1915 found 544.1931.

5 as a colourless oil (340 mg, 1.12 mmol, 98% yield). Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R_f = 0.40; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (m, 2H), 7.79 (m, 2H), 5.26 (dd, *J* = 5 Hz, 1H), 3.81 (s, 3H), 2.16 (m, 2H), 1.36 (m, 4H), 0.87 (t, *J* = 7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 188.73, 167.34, 160.76, 134.31, 131.44, 123.52, 55.89, 52.94, 27.74, 26.92, 21.88, 13.58; IR (CH₂Cl₂) 1779, 1737, 1718, 1614 cm⁻¹; EIMS (20 eV) 303 (M⁺, 0.48), 216 (100), 160 (78); HRMS (EI) for C₁₆H₁₇NO₅ (M⁺), calcd 303.1107, found 303.1129.

Preparation of ketone 6.

(a) phthalic anhydride, Et₃N, toluene, overnight; (b) ClCOOEt, Et₃N, THF, -25 °C, 15 min; CH₂N₂, 0 °C, overnight; (c) PhCOOAg, Et₃N, THF : H₂O (9 : 1), -25 °C to 0 °C, overnight, exclusion of light; (d) Ph₃P=CHCN, DMAP, EDCl, dry CH₂Cl₂, r.t., overnight; (e) DMSO, MeOH, 0 °C, 30 min

To a solution of **6f** (1.2 g, 10 mmol) in dry toluene (80 mL) was added Et₃N (4 mL, 30 mmol) and phthalic anhydride (2 g, 13 mmol). After refluxing for overnight, the organic solvent was evaporated under reduced pressure. The reaction mixture was acidified with dilute hydrochloric acid to

pH 2 at 0 °C, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in hexane) to provide **6e** as a white solid (2.24 g, 9.9 mmol, 98% yield). M.p. 103–104 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R_f = 0.45; ¹H NMR (300 MHz, CDCl₃) δ 11.25 (br s, 1H), 7.85 (m, 2H), 7.75 (m, 2H), 4.94 (dd, *J* = 11.0, 4.0 Hz, 1H), 2.30 (m, 2H), 1.34 (m, 2H), 0.93 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.44, 167.76, 134.34, 131.70, 123.66, 51.72, 30.37, 19.58, 13.34; IR (CH₂Cl₂) 3473, 1775, 1717, 1615 cm⁻¹; EIMS (20 eV) 247 (M⁺, 7), 202 (48), 160 (99); HRMS (EI) for C₁₃H₁₃NO₄ (M⁺), calcd 247.0845, found 247.0845.

To a solution of **6e** (2.0 g, 8.1 mmol) in dry THF (80 mL) was added Et₃N (1.2 mL, 8.9 mmol) and ClCOOEt (1.0 g, 8.9 mmol) at room temperature under nitrogen atmosphere. After stirring for 15 min, CH₂N₂ (0.3 M in ether, 40 mL, 12 mmol) was added at -25 °C until the yellow color of the solution was persistent. Then the reaction mixture was heated to 0 °C and stirred for overnight. The reaction mixture was acidified with dilute hydrochloric acid to pH 2 at 0 °C, and extracted with Et₂O. The combined organic layers were washed with water, brine and dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc in hexane) to provide **6d** as a yellow oil (1.8 g, 6.6 mmol, 82% yield). Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R_f = 0.73; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (m, 2H), 7.72 (m, 2H), 5.36 (br s, 1H), 4.74 (m, 1H), 3.18 (m, 1H), 2.78 (m, 1H), 2.03 (m, 1H), 1.67 (m, 1H), 1.27 (m, 1H), 0.90 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 189.97, 167.70, 134.21, 131.44, 123.37, 56.86, 53.91, 29.70, 19.38, 13.24; IR (CH₂Cl₂) 2114, 1775 cm⁻¹; FABMS 272 (M⁺+1); EIMS (20 eV) 243 (M⁺-N₂, 8), 202 (85), 160 (100); HRMS (EI) for C₁₄H₁₃NO₃ (M⁺-N₂), calcd 243.0895, found 243.0891.

To a solution of **6d** (1.7 g, 6.2 mmol) in THF:H₂O (9:1, 30 mL) was added Et₃N (2.5 mL, 18 mmol) and PhCOOAg (0.156 g, 0.68 mmol) at -25 °C with exclusion of light. After stirring from -25 °C to 0 °C overnight, the organic solvent was evaporated under reduced pressure. The reaction mixture

was diluted with Et₂O and extracted with saturated NaHCO₃ (4 × 30 mL), Then the aqueous layer was acidified with dilute hydrochloric acid to pH 2 at 0 °C, and extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in hexane) to provide **6c** as a white solid (1.3 g, 4.9 mmol, 81 % yield). M.p. 104–106 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R_f = 0.49; ¹H NMR (300 MHz, CDCl₃) δ 8.08 (br s, 1H), 7.80 (m, 2H), 7.71 (m, 2H), 4.67 (m, 1H), 3.21 (m, 1H), 2.80 (dd, *J* = 16.0, 5.0 Hz, 1H), 2.04 (m, 1H), 1.68 (m, 1H), 1.30 (m, 2H), 0.89 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 176.39, 168.16, 134.11, 131.84, 123.41, 47.60, 36.87, 34.57, 19.61, 13.65; IR (CH₂Cl₂) 3473, 1774, 1713, 1614 cm⁻¹; EIMS (20 eV) 261 (M⁺, 13), 215 (4), 200 (15), 149 (100).

6b as a white solid (0.8 g, 1.4 mmol, 79% yield). M.p. 152.5–153 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R_f = 0.64; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (m, 2H), 7.65 (m, 16H), 7.39 (m, 15H), 4.82 (m, 1H), 3.40 (m, 1H), 3.19 (m, 1H), 2.07 (m, 1H), 1.31 (m, 1H), 1.23 (m, 4H), 0.88 (t, *J* = 7 Hz, 3H); ¹³C NMR (67 MHz, CDCl₃) δ 191.34 (d, *J* = 3.8 Hz), 168.21, 133.73 (d, *J* = 48.9 Hz, 3C), 133.50 (d, *J* = 10.2 Hz, 6C), 133.08 (s, 3C), 129.15 (d, *J* = 12.8 Hz, 6C), 123.22, 122.86 (d, *J* = 93.6 Hz, 3C), 120.69 (d, *J* = 15.2 Hz, CN), 57.52 (d, *J* = 8 Hz), 46.7 (d, *J* = 127.4 Hz), 28.69, 27.95, 22.20, 19.71, 13.96; IR (CH₂Cl₂) 3435, 2178, 1708 cm⁻¹; EIMS (20 eV) 544 (M⁺, 15), 328 (94), 277 (100), 160 (70); HRMS (EI) for C₃₄H₂₉PN₂O₃ (M⁺), calcd 544.1915, found 544.1921.

6 as a colourless oil (0.03 g, 0.1 mmol, 46% yield). Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R_f = 0.79; ¹H NMR (400 MHz, CDCl₃) δ 7.74 (m, 2H), 7.63 (m, 2H), 4.67 (m, 1H), 3.76 (s, 3H), 3.62 (dd, *J* = 9 Hz, 1H), 3.33 (dd, *J* = 5 Hz, 1H), 1.96 (m, 1H), 1.64 (m, 1H), 1.17 (m, 2H), 0.83 (t, *J* = 7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 191.35, 168.32, 160.68, 133.99, 131.61, 123.23, 53.05, 46.17, 41.76, 34.47, 19.40, 13.49; IR (CH₂Cl₂) 1773, 1710 cm⁻¹; EIMS (20 eV) 303 (M⁺), 244 (100), 202 (98); HRMS (EI) for C₁₆H₁₇NO₅ (M⁺), calcd 303.1107, found 303.1125.

Preparation of ketone 7.

(a) ClCOOEt, Et₃N, THF, -25 °C, 15 min; CH₂N₂, 0 °C, overnight; (b) PhCOOAg, Et₃N, THF : H₂O (9 : 1), -25 °C to 0 °C, overnight, exclusion of light; (c) Ph₃P=CHCN, DMAP, EDCI, CH₂Cl₂, r.t., overnight; (d) dimethyldioxirane, MeOH, 0 °C, 30 min

7b as a yellow oil (0.62 g, 2.2 mmol, 44% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.71–7.84 (m, 4H), 5.37 (s, 1H), 4.72–4.80 (m, 1H), 3.17–3.20 (m, 1H), 2.77–2.82 (m, 1H), 2.01–2.07 (m, 1H), 1.64–1.71 (m, 1H), 1.28–1.33 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 191.84, 168.43, 134.00, 133.28, 128.37, 123.24, 55.24, 47.75, 42.75, 34.59, 19.52, 13.58; IR (CH₂Cl₂) 2113, 1774, 1715, 1647 cm⁻¹; FABMS 286 (M⁺+1).

7a as a white solid (0.23 g, 0.4 mmol, 34% yield). M.p. 204–205 °C. Analytical TLC (silica gel 60), 65% EtOAc in n-hexane, R_f = 0.47; ¹H NMR (300 MHz, CDCl₃) δ 7.50–7.79 (m, 19H), 4.22–4.27 (m, 1H), 2.62–2.76 (m, 2H), 2.04–2.19 (m, 2H), 1.67–1.69 (m, 1H), 1.20–1.28 (m, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.42, 168.84, 133.69, 133.62 (d, *J* = 10.4 Hz, 6C), 131.93 (d, *J* = 2.5 Hz, 3C), 129.17 (d, *J* = 12.8 Hz, 6C), 123.28 (d, *J* = 93.6 Hz, 3C), 123.13, 122.38 (d, *J* = 16.5 Hz, CN), 51.46, 48.45 (d, *J* = 127.1 Hz), 35.98, 34.44, 27.60, 19.80, 13.69; IR (CH₂Cl₂) 2177, 1708, 1629 cm⁻¹; EIMS (20 eV) 558 (M⁺, 9), 343 (100), 328 (14); HRMS (EI) for C₃₅H₃₁N₂O₃P (M⁺), calcd 558.2072 found 558.2069.

7 as a colourless oil (0.09 g, 0.29 mmol, 70% yield). Analytical TLC (silica gel 60), 65% EtOAc in n-hexane, R_f = 0.63; ¹H NMR (300 MHz, CDCl₃) δ 7.80–7.86 (m, 2H), 7.69–7.77 (m, 2H), 4.18–4.28 (m, 1H), 3.82 (s, 3H), 2.72–2.94 (m, 2H), 2.05–2.47 (m, 1H), 1.63–1.77 (m, 2H), 1.58–1.60 (m, 1H),

1.21–1.38 (m, 3H), 0.90 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 190.04, 168.69, 161.18, 134.11, 131.73, 123.30, 53.02, 51.08, 36.45, 34.43, 25.72, 19.77, 13.68; IR (CH_2Cl_2) 1772, 1709 cm^{-1} .

Preparation of Ketone 8.

(a) NaH, MeI, DMF, 0 °C; (b) LiOH, THF / MeOH / H_2O ; (c) $\text{Ph}_3\text{P}=\text{CHCN}$, EDCl, DMAP, CH_2Cl_2 ; (d) dimethyldioxirane, MeOH, CH_2Cl_2 .

To a solution of ethyl-2-hydroxycaproate (1.6 g, 10 mmol) in dry DMF (10 mL) was added NaH (0.32 g, 12 mmol) under nitrogen atmosphere at 0 °C. After stirring for 30 min, MeI (0.75 mL, 12 mmol) was added to above reaction mixture. The reaction progress was monitored by TLC. After stirring for 1 h, the reaction mixture was quenched with H_2O and then extracted with EtOAc. The organic layer was washed with H_2O , dried with MgSO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in hexane) to give **8e** as colorless oil (0.46 g, 2.6 mmol, 26% yield). Analytical TLC (silica gel 60), 15% EtOAc in n-hexane, $R_f = 0.31$; ^1H NMR (300 MHz, CDCl_3) δ 4.21 (q, $J = 7.2$ Hz, 1H), 3.72 (t, $J = 6.3$ Hz, 1H), 3.37 (s, 3H), 1.68–1.75 (m, 2H), 1.25–1.43 (m, 4H), 1.29 (t, $J = 7.2$ Hz, 3H), 0.89 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.8, 80.60, 60.60, 57.90, 32.45, 27.14, 22.32, 14.19, 13.78; IR (CH_2Cl_2) 1736 cm^{-1} (ref: Toshinari, T.; Isao, Y.; Noriyoshi, I.; Hidenori, I.; Yoshio, I.; Osamu, L.; Hideya, M. Tetsuya, S.; Tokuichi, T.; et al. *Yamanouchi Seiyaku Kenkyu Hokoku*, **1977**, 3, 50).

To a solution of **8e** (0.44 g, 2.5 mmol) in THF/ MeOH / H_2O (3.75 / 1.25 / 1.25 mL) was added LiOH· H_2O (0.21 g, 5 mmol). After stirring for 1 h, the reaction mixture was diluted with EtOAc, acidified with 1M HCl to pH 2. The aqueous layer was extracted with EtOAc, and the combined organic layer was dried over anhydrous MgSO_4 and concentrated under vacuum to give **8d** as colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 3.81 (dd, $J = 16.3, 5.5$ Hz, 1H), 3.45 (s, 3H), 1.73–1.84 (m, 2H), 1.27–1.47

(m, 4H), 0.92 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.07, 80.22, 58.30, 32.01, 26.99, 22.37, 13.80; IR (CH_2Cl_2) 3406, 1722 cm^{-1} (ref: Compere, E. L., Jr.; Shockravi, A. *J. Org. Chem.* **1978**, *43*, 2702).

8c as white solid (0.35 g, 8.10 mmol, 91% yield). M.p. 125 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, $R_f = 0.55$; ^1H NMR (300 MHz, CDCl_3) δ 7.40–7.68 (m, 15H), 4.26 (dd, $J = 7.4$, 5.2 Hz, 1H), 3.40 (s, 3H), 1.75–1.86 (m, 2H), 1.33–1.43 (m, 4H), 0.90 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 196.07 (d, $J = 2.3$ Hz), 133.56 (d, $J = 10.3$ Hz, 6C), 133.13 (d, $J = 2.9$ Hz, 3C), 129.08 (d, $J = 12.9$ Hz, 6C), 123.04 (d, $J = 93.6$ Hz, 3C), 121.45 (d, $J = 15.3$ Hz, CN), 83.32 (d, $J = 8.3$), 57.49, 48.16 (d, $J = 124.3$ Hz), 32.74, 27.55, 22.62, 14.05; IR (CH_2Cl_2) 2176, 1607 cm^{-1} ; EIMS (20 eV) 429 (M^+ , 17), 328 (100); HRMS (EI) for $\text{C}_{27}\text{H}_{28}\text{O}_2\text{NP}$ (M^+), calcd 429.1858, found 429.1864.

8 as a colorless oil (0.13 g, 0.76 mmol, 95% yield). Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.42$; ^1H NMR (300 MHz, CDCl_3) δ 4.25 (dd, $J = 7.7$, 4.5 Hz, 1H), 3.89 (s, 3H), 3.41 (s, 3H), 1.65–1.85 (m, 2H), 1.23–1.46 (m, 4H), 0.91 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 195.35, 162.74, 83.89, 58.70, 52.77, 29.68, 27.19, 23.38, 13.78; IR (CH_2Cl_2) 1734 cm^{-1} ; CIMS 188 (M^+ , 8).

Preparation of ketones **9** and **10**.

For the preparation of ketones **9** and **10**, see: Wong, M.-K.; Yu, C.-W.; Yuen, W.-H.; Yang, D. *J. Org. Chem.* **2001**, *66*, 3606.

Preparation of ketone **11**.

(a) $\text{Ph}_3\text{P}=\text{CHCN}$, EDCI, DMAP, CH_2Cl_2 ; (b) N-methylmorpholine N-oxide, OsO_4 , H_2O / acetone; (c) acetyl chloride, $35\text{ }^\circ\text{C}$, CH_2Cl_2 ; (d) dimethyldioxirane, MeOH, CH_2Cl_2 ; (e) Pt/C, EtOH

Ylid **11d** was synthesized from acid **11e** according to a literature procedure (ref: Wong, M.-K.; Yu, C.-W.; Yuen, W.-H.; Yang, D. *J. Org. Chem.* **2001**, *66*, 3606). Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, $R_f = 0.33$; ^1H NMR (300 MHz, CDCl_3) δ 7.46–7.65 (m, 15H), 5.59–5.75 (m, 2H), 3.40 (d, $J = 5.1$ Hz, 2H), 2.02–2.12 (m, 2H), 0.99 (t, $J = 7.5$ Hz, 3H).

To a solution of **11d** (0.65 g, 16.3 mmol) in acetone (30 mL) / water (5 mL) was added an OsO_4 solution (2% w/v in water) (0.2 mL, 0.16 mmol) followed by N-methylmorpholine N-oxide (0.44 g, 39.2 mmol). After stirring overnight, the solvent was removed under vacuum. The residue was purified by flash column chromatography (90% EtOAc in hexane) to give **11c** as a white solid (0.58 g, 13.5 mmol, 83% yield). M.p. $210\text{ }^\circ\text{C}$. Analytical TLC (silica gel 60), 70% EtOAc in n-hexane, $R_f = 0.39$; ^1H NMR (300 MHz, CDCl_3) δ 7.51–7.68 (m, 15H), 3.70–3.90 (m, 1H), 3.34–3.49 (m, 1H), 3.04 (dd, $J = 16.9, 3.2$ Hz, 1H), 2.85 (dd, $J = 16.9, 9.8$ Hz, 1H), 1.44–1.64 (m, 2H), 0.99 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 196.65, 133.43 (d, $J = 10.1$ Hz, 6C), 133.25 (d, $J = 13.5$ Hz, 3C), 129.18 (d, $J = 12.8$ Hz, 6C), 122.60 (d, $J = 93.9$ Hz, 3C), 121.49 (d, $J = 15.1$ Hz, CN), 75.40, 71.58, 50.69 (d, $J = 124.6$ Hz), 41.25 (d, $J = 6.7$ Hz), 26.33, 10.21; IR (CH_2Cl_2) 2180, 1565 cm^{-1} ; EIMS (20 eV) 431 (M^+ , 17), 328 (71); HRMS (EI) for $\text{C}_{26}\text{H}_{26}\text{O}_3\text{NP}$ (M^+), calcd 431.1650, found 431.1655.

To a solution of **11c** (0.86 g, 2.0 mmol) in CH_2Cl_2 was added acetyl chloride (0.86 mL, 12.0 mmol). Then the reaction mixture was heated up to $35\text{ }^\circ\text{C}$. After stirring overnight, the solvent and

excess acetyl chloride were removed under reduced pressure. The residue was purified by flash column chromatography (60% EtOAc in hexane) to give **11b** as a syrup (0.68 g, 13.3 mmol, 66% yield). Analytical TLC (silica gel 60), 80% EtOAc in n-hexane, R_f = 0.56; mp 173–175 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.49–7.64 (m, 15H), 5.46–5.51 (m, 1H), 4.98–5.04 (m, 1H), 3.07 (dd, J = 15.3, 6.7 Hz, 1H), 2.89 (dd, J = 15.3, 6.7 Hz, 1H), 2.04 (s, 6H), 1.53–1.63 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 192.07 (d, J = 4.0 Hz), 170.77, 170.83, 133.60 (d, J = 10.3 Hz, 6C), 133.11 (d, J = 2.9 Hz, 3C), 129.13 (d, J = 12.9 Hz, 6C), 122.85 (d, J = 93.8 Hz, 3C), 122.11 (d, J = 18.5 Hz, CN), 74.75, 70.93, 49.55 (d, J = 126.5 Hz), 39.92 (d, J = 7.5 Hz), 23.79, 20.99, 20.94, 9.7; IR (CH_2Cl_2) 2177, 1739 cm^{-1} ; EIMS (20 eV) 515 (M^+ , 25), 395 (28), 328 (100); HRMS (EI) for $\text{C}_{30}\text{H}_{30}\text{O}_5\text{NP}$ (M^+), calcd 515.1862, found 515.1864.

To a solution of **11b** (0.21 g, 0.40 mmol) in dry MeOH was added dimethyldioxirane (0.44 M in acetone, 18 mL, 0.80 mmol). After stirring for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc in hexane) to give **11a** as a pale yellow oil (0.05 g, 0.25 mmol, 63% yield). Analytical TLC (silica gel 60), 80% EtOAc in n-hexane, R_f = 0.57; ^1H NMR (300 MHz, CDCl_3) δ 7.09 (dd, J = 16.0, 4.9 Hz, 1H), 6.79 (dd, J = 6.0, 1.5 Hz, 1H), 5.40–5.47 (m, 1H), 3.90 (s, 3H), 2.14 (s, 3H), 1.70–1.81 (m, 2H), 0.95 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 182.16, 170.05, 161.98, 150.03, 123.81, 73.59, 53.02, 26.75, 20.09, 9.23; IR (CH_2Cl_2) 1724 cm^{-1} ; CIMS 183 ($\text{M}^+ - \text{OMe}$, 3).

To a solution of **11a** (0.05 g, 0.25 mmol) in dry MeOH was added platinum on activated carbon (18 mL, 0.80 mmol). After stirring for 90 min under hydrogen atmosphere, the reaction mixture was filtered through a short pad of celite and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc in hexane) to give **11** as a colorless oil (0.05 g, 0.23 mmol, 93% yield). Analytical TLC (silica gel 60), 80% EtOAc in n-hexane, R_f = 0.57; ^1H NMR (300 MHz, CDCl_3) δ 4.79–4.88 (m, 1H), 3.89 (s, 3H), 2.79–2.99 (m, 2H), 2.05 (s, 3H), 1.56–1.76 (m, 2H),

0.91 (d, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 193.29, 170.84, 161.21, 74.22, 52.95, 35.29, 26.95, 26.82, 21.04, 9.50; IR (CH_2Cl_2) 1732 cm^{-1} ; CIMS 185 ($\text{M}^+ - \text{OMe}$, 5).

Preparation of ketone 12.

(a) $\text{Ph}_3\text{P}=\text{CHCN}$, EDCI, DMAP, CH_2Cl_2 ; (b) dimethyldioxirane, MeOH, CH_2Cl_2 .

Acids **12d** and **13d** were synthesized according to a literature procedure (Flippin, L. A.; Brown, P. A.; Jalali-Araghi, K. *J. Org. Chem.* **1989**, *54*, 3588).

12c as a white solid (0.54 g, 1.00 mmol, 67% yield). M.p. 188–190 °C. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.43$; ^1H NMR (400 MHz, CDCl_3) δ 7.46–7.63 (m, 15H), 4.18–4.23 (m, 1H), 2.83 (d, $J = 8.2$ Hz, 2H), 1.41–1.50 (m, 2H), 1.06–1.11 (m, 1H), 0.85–0.96 (m, 6H), 0.85 (s, 9H), 0.00 (s, 3H), -0.3 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 194.79 (d, $J = 13.6$ Hz), 133.45 (d, $J = 10.2$ Hz, 6C), 132.82 (d, $J = 2.8$ Hz, 3C), 128.86 (d, $J = 12.9$ Hz, 6C), 123.18 (d, $J = 93.6$ Hz, 3C), 122.38 (d, $J = 16.7$ Hz, CN), 72.42, 49.06 (d, $J = 126.1$), 43.70 (d, $J = 6.8$ Hz), 40.36, 25.76, 24.03, 17.86, 14.78, 12.07, -4.62 , -4.88 ; IR (CH_2Cl_2) 2174 , 1585 cm^{-1} ; EIMS (20 eV) 543 (M^+ , 1), 486 (100), 328 (58); HRMS (EI) for $\text{C}_{33}\text{H}_{42}\text{O}_2\text{NPSi}$ (M^+), calcd 543.2722, found 543.2724.

12 as a colorless oil (0.25 g, 0.82 mmol, 89% yield). Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.76$; ^1H NMR (300 MHz, CDCl_3) δ 4.15–4.24 (m, 1H), 3.84 (s, 3H), 2.97 (dd, $J = 8.9$, 15.5 Hz, 1H), 2.66 (dd, $J = 3.4$, 15.5 Hz, 1H), 1.47–1.56 (m, 1H), 1.00–1.35 (m, 2H), 0.75–0.91 (m, 6H), 0.79 (s, 9H), 0.01 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 193.35, 161.30, 71.55, 52.69, 41.64, 41.05, 25.64, 25.61, 17.83, 13.21, 11.96, -4.70 , -5.09 ; IR (CH_2Cl_2) 1732 cm^{-1} ; EIMS (20 eV) 245 ($\text{M}^+ - t\text{Bu}$, 40), 243 (6); HRMS (EI) for $\text{C}_{11}\text{H}_{21}\text{O}_4\text{Si}$ ($\text{M}^+ - \text{COOCH}_3$), calcd 243.1780, found 243.1790.

Preparation of Ketone 13.

(a) $\text{Ph}_3\text{P}=\text{CHCN}$, EDCI, DMAP, CH_2Cl_2 ; (b) dimethyldioxirane, MeOH, CH_2Cl_2 .

13c as white solid (0.49 g, 0.91 mmol, 60% yield). M.p. 188–190 °C. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.43$; ^1H NMR (300 MHz, CDCl_3) δ 7.42–7.61 (m, 15H), 4.18–4.22 (m, 1H), 2.91 (dd, $J = 8.1, 14.3$ Hz, 1H), 2.77 (dd, $J = 5.4, 14.3$ Hz, 1H), 1.33–1.98 (m, 2H), 1.04–1.25 (m, 1H), 0.78–0.96 (m, 6H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 194.76 (d, $J = 3.5$ Hz), 133.54 (d, $J = 10.3$ Hz, 6C), 133.01 (d, $J = 2.8$ Hz, 3C), 129.01 (d, $J = 12.8$ Hz, 6C), 123.25 (d, $J = 93.6$ Hz, 3C), 122.42 (d, $J = 16.7$ Hz, CN), 72.12, 49.72 (d, $J = 125.4$), 44.94 (d, $J = 6.8$ Hz), 39.85, 26.32, 25.90, 18.01, 12.99, 12.31, $-4.26, -4.83$; IR (CH_2Cl_2) 2175, 1583 cm^{-1} ; EIMS (20 eV) 543 (M^+ , 1), 486 (100), 328 (58); HRMS (EI) for $\text{C}_{33}\text{H}_{42}\text{O}_2\text{NPSi}$ (M^+), calcd 543.2722, found 543.2730.

13 as a colorless oil (0.27 g, 0.89 mmol, 99% yield). Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.76$; ^1H NMR (300 MHz, CDCl_3) δ 4.07–4.19 (m, 1H), 3.83 (s, 3H), 2.99 (dd, $J = 8.0, 16.0$ Hz, 1H), 2.77 (dd, $J = 4.3, 16.0$ Hz, 1H), 1.23–1.63 (m, 3H), 0.73–1.10 (m, 6H), 0.81 (s, 9H), 0.02 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 193.21, 161.32, 71.80, 52.76, 43.03, 40.93, 25.67, 24.16, 17.90, 14.25, 12.07, $-4.72, -4.91$; IR (CH_2Cl_2) 1732 cm^{-1} ; EIMS (20 eV) 245 ($\text{M}^+ - t\text{Bu}$, 40), 243 (2); HRMS (EI) for $\text{C}_{11}\text{H}_{21}\text{O}_4\text{Si}$ ($\text{M}^+ - t\text{Bu}$), calcd 245.1209, found 245.1215.

Characterization Data of Hemiketals

1a and **1b** could not be separated by flash column chromatography. As a colorless oil. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.41$; ^1H NMR (300 MHz, CDCl_3) δ 4.13 (m, 1.0/11.0H), 4.03 (m, 10.0/11.0H), 3.82 (s, 3H), 3.60 (s, OH), 1.96–2.10 (m, 1H), 1.41–1.78 (m, 6H), 1.11–1.32 (m, 2H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ **1a** 171.85, 95.55, 69.22, 53.08, 44.92, 40.00, 38.69, 24.24, 24.08, 23.04, 22.30, 22.06; IR (CH_2Cl_2) 1741 cm^{-1} , δ **1b** 171.16, 94.85, 69.24, 53.09, 44.81, 39.72, 38.67, 25.07, 24.11, 22.98, 22.37, 22.07; EIMS (20 eV) 171 ($\text{M}^+ - \text{COOMe}$, 10), 153 (100); HRMS (EI) for $\text{C}_{10}\text{H}_{19}\text{O}_2$ ($\text{M}^+ - \text{COOMe}$), calcd 171.1395, found 171.1385.

2a and **2b** could not be separated by flash column chromatography. As a colorless oil. Analytical TLC (silica gel 60), 10% EtOAc in n-hexane, $R_f = 0.4$; ^1H NMR (500 MHz, CDCl_3) δ 3.94–3.99 (m, 1H), 2.49 (d, $J = 2.6$ Hz, 1H), 1.98–2.07 (m, 1H), 1.85 (dd, $J = 13.0, 3.6$ Hz, 1H), 1.76 (septet, $J = 6.6$ Hz, 1H), 1.61–1.65 (m, 1H), 1.46–1.51 (m, 1H), 1.20–1.27 (m, 2H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.88–0.91 (m, 1H); ^{13}C NMR (125.77 MHz, CDCl_3) δ 122.91 (q, $^1J_{\text{C},\text{F}} = 285.2$ Hz), 94.67 (q, $^2J_{\text{C},\text{F}} = 31.6$ Hz), 70.02, 44.69, 39.37, 34.78, 24.67, 24.32, 23.06, 22.52, 21.87, 1b; EIMS (20 eV) m/z 222 ($\text{M}^+ - \text{H}_2\text{O}$, 6), 183 (70); HRMS (EI) for $\text{C}_7\text{H}_{10}\text{O}_2\text{F}_3$ ($\text{M}^+ - \text{C}_4\text{H}_9$), calcd 183.0633, found 183.0629.

To determine the trans/cis ratio, **2a** and **2b** were converted to the corresponding lactones **2c** and **2d** (**2c** : **2d** = 1 : 14.7) via basic hydrolysis.

As a colourless liquid. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R_f = 0.56; ^1H NMR (300 MHz, CDCl_3) δ 4.42–4.51 (m, 1.0/15.7H), 4.30–4.39 (m, 14.7/15.7H), 2.59–2.73 (m, 1H), 1.80–2.23 (m, 4H), 1.60–1.70 (m, 1H), 1.29–1.38 (m, 1H), 1.11–1.20 (m, 1H), 1.03 (d, J = 6.2 Hz, 3H), 0.93 (t, J = 6.3 Hz, 6H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 171.61, 78.88, 45.26, 38.08, 37.56, 26.76, 23.93, 23.03, 22.06, 21.68; CIMS m/z 171 ($\text{M}^+ + 1$, 100), 113 (6); HRMS (EI) for $\text{C}_6\text{H}_9\text{O}_2$ ($\text{M}^+ - \text{C}_4\text{H}_9$), calcd 113.0603, found 113.0632. (ref: Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 8692.)

3a

3a as a colorless oil. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, R_f = 0.50; ^1H NMR (300 MHz, CDCl_3) δ 4.00–4.11 (m, 1H), 3.80 (s, 3H), 3.77 (s, OH), 2.06–2.13 (m, 1H), 1.57–1.67 (m, 3H), 1.32–1.47 (m, 1H), 1.15 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ **3a** 171.60, 97.83, 67.45, 52.54, 32.93, 28.37, 24.50, 21.65, 14.81; IR (CH_2Cl_2) 1742 cm^{-1} ; EIMS (20 eV) 170 ($\text{M}^+ - \text{H}_2\text{O}$, 11), 129 (43), 111 (37); HRMS (EI) for $\text{C}_9\text{H}_{14}\text{O}_3$ ($\text{M}^+ - \text{H}_2\text{O}$), calcd 170.0942, found 170.0940.

3b

3b and **3b'** could not separated by column. As a colorless oil. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, R_f = 0.50; ^1H NMR (300 MHz, CDCl_3) δ 3.92–3.98 (m, 1H), 3.80 (s, 3H), 3.77 (s, OH), 2.06–2.13 (m, 1H), 1.57–1.67 (m, 3H), 1.32–1.47 (m, 1H), 1.15 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ **3b** 171.74, 97.55, 70.17, 52.82, 32.51, 29.25, 26.95, 22.01,

14.68; IR (CH₂Cl₂) 1743 cm⁻¹; EIMS (20 eV) 170 (M⁺-H₂O, 11), 129 (43), 111 (37); HRMS (EI) for C₉H₁₄O₃ (M⁺-H₂O), calcd 170.0943, found 170.0940.

4a and **4b** could not be separated by flash column chromatography. As a colourless liquid. Analytical TLC (silica gel 60), 10% EtOAc in n-hexane, $R_f = 0.5$; ¹H NMR (300 MHz, CDCl₃) δ 3.92–3.96 (m, 1.0/4.6H), 3.47–3.53 (m, 3.6/4.6H), 2.50 (br s, 1 H), 1.10–1.90 (m, 10H), 0.86–0.95 (m, 9H); ¹³C NMR (67.94 MHz, CDCl₃) δ **4a** 122.97 (q, ¹J_{C, F} = 284.4 Hz), 93.99 (q, ²J_{C, F} = 32.2 Hz), 76.57, 33.95, 33.81, 30.16, 28.04, 26.98, 26.69, 22.84, 22.35, 17.56; **4b** 122.97 (q, ¹J_{C, F} = 284.4 Hz), 94.25 (q, ²J_{C, F} = 31.1 Hz), 73.83, 34.78, 30.27, 29.17, 28.08, 25.37, 22.72, 22.43, 21.19, 10.27; EIMS (20 eV) m/z 254 (M⁺, 2), 236 (38).

4a' and **4b'** could not be separated by flash column chromatography. As a colourless liquid. Analytical TLC (silica gel 60), 10% EtOAc in n-hexane, $R_f = 0.16$; ¹H NMR (300 MHz, CDCl₃) δ 4.21–4.30 (m, 1.0/4.6H), 3.93 (ddd, $J = 10.0, 8.0, 3.0$ Hz, 3.6/4.6H), 2.61 (ddd, $J = 18.0, 7.0, 5.0$ Hz, 1 H), 2.47 (ddd, $J = 18.0, 10.0, 7.0$ Hz, 1 H), 1.20–2.00 (m, 8H), 1.00 (d, $J = 6.5$ Hz, 3H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.89 (d, $J = 6.5$ Hz, 3H); ¹³C NMR (67.94 MHz, CDCl₃) δ **4a'** 171.87, 86.08, 33.30, 32.09, 31.17, 29.47, 27.81, 27.74, 22.67, 22.19, 17.38; **4b'** 171.87, 83.28, 34.55, 29.81, 29.23, 26.67, 26.12, 22.46, 22.38; EIMS (20 eV) m/z 184 (M⁺, 4); HRMS (EI) for C₁₁H₂₀O₂ (M⁺), calcd 184.1463, found 184.1455.

5a as a white solid. M.p. 170–171 °C. Analytical TLC (silica gel 60), 66% EtOAc in n-hexane, $R_f = 0.45$; ^1H NMR (300 MHz, CDCl_3) δ 7.83 (m, 2H), 7.74 (m, 2H), 5.66 (s, *OH*), 4.74 (dd, $J = 13, 4$ Hz), 4.35 (m, 1H), 3.76 (s, 3H), 2.94 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.61 (m, 1H), 1.26 (d, $J = 6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.06, 168.95, 134.58, 131.55, 123.81, 95.90, 66.87, 53.41, 53.09, 32.99, 22.83, 21.16; IR (CH_2Cl_2) 3343, 1744, 1710, 1612 cm^{-1} ; EIMS (20 eV) 319 (M^+ , 2), 301 (5), 173 (100); HRMS (EI) for $\text{C}_{16}\text{H}_{17}\text{NO}_6$ (M^+), calcd 319.1055, found 319.1048.

6a as a white solid. M.p. 173–175 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, $R_f = 0.70$; ^1H NMR (300 MHz, CDCl_3) δ 7.83 (m, 2H), 7.71 (m, 2H), 4.82 (m, 1H), 3.85 (s, 3H), 2.97 (t, $J = 12$ Hz, 1H), 2.30 (q, $J = 12$ Hz, 1H), 1.80 (m, 2H), 1.25 (d, $J = 6$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.64, 168.10, 134.01, 123.21, 95.03, 67.12, 53.36, 43.98, 36.01, 33.39, 29.68, 21.18; IR (CH_2Cl_2) 3435, 1636 cm^{-1} ; EIMS (20 eV) 301 ($\text{M}^+ - \text{H}_2\text{O}$, 24), 260 (100); HRMS (EI) for $\text{C}_{16}\text{H}_{15}\text{NO}_5$ ($\text{M}^+ - \text{H}_2\text{O}$), calcd 301.0950, found 301.0946.

8a and **8b** could not be separated by flash column chromatography. As a colorless oil. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, $R_f = 0.24$; ^1H NMR (300 MHz, CDCl_3) δ 3.97 (s, $\frac{1}{2} \times 3\text{H}$), 3.95 (s, $\frac{1}{2} \times 3\text{H}$), 3.85 (s, *OH*), 3.62–3.71 (m, 1H), 3.60 (s, $\frac{1}{2} \times 3\text{H}$), 3.43 (s, $\frac{1}{2} \times 3\text{H}$), 1.31–1.79 (m, 5H), 0.94 (t, $J = 6.9$ Hz, $\frac{1}{2} \times 3\text{H}$), 0.92 (t, $J = 6.9$ Hz, $\frac{1}{2} \times 3\text{H}$); ^{13}C NMR (75 MHz, CDCl_3) δ **8a** 179.50, 109.85, 85.22, 59.90, 54.53, 30.08, 27.97, 22.48, 13.87, **8b** 179.60, 109.57, 84.25, 61.38, 54.48, 29.67,

27.98, 22.15, 13.78; IR (CH₂Cl₂) 3493, 1759, 1743 cm⁻¹; EIMS (20 eV) 204 (M⁺, 3); HRMS (EI) for C₉H₁₆O₅ (M⁺), calcd 204.0998, found 204.1001.

9a as a colourless liquid. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, R_f = 0.37; ¹H NMR (300 MHz, CDCl₃) δ 6.25 (s, 1H, OH), 4.37–4.46 (m, 2H), 3.81 (s, 3H), 2.09 (dd, *J* = 14.0, 2.6 Hz, 1H), 2.01 (ddd, *J* = 14.0, 3.2, 3.2 Hz, 1H), 1.67–1.74 (m, 1H), 1.49–1.59 (m, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ¹³C NMR (75.48 MHz, CDCl₃) δ 169.36, 96.01, 66.76, 61.32, 52.82, 39.21, 36.70, 25.65, 21.32, 17.83, –5.06, –5.28; IR (CH₂Cl₂) 3412, 1749 cm⁻¹; EIMS (20 eV) 247 (M⁺–C₄H₉, 30), 187 (100); HRMS (EI) for C₁₀H₁₉SiO₅ (M⁺–C₄H₉), calcd 247.1002, found 247.1002.

9b as a colourless liquid. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, R_f = 0.38; ¹H NMR (300 MHz, CDCl₃) δ 4.05–4.17 (m, 2H), 3.83 (s, 3H), 3.66 (d, *J* = 2.1 Hz, 1H, OH), 1.96 (ddd, *J* = 12.6, 4.9, 1.8 Hz, 1H), 1.81–1.91 (m, 3H), 1.32 (q, *J* = 12.3 Hz, 1H), 1.20 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C NMR (67.94 MHz, CDCl₃) δ 171.01, 95.71, 66.57, 64.79, 53.33, 42.92, 39.90, 25.81, 21.35, 18.06, –4.63; IR (CH₂Cl₂) 3524, 1742 cm⁻¹; CIMS 305 (M⁺+1, 5), 247 (40); HRMS (EI) for C₁₀H₁₉SiO₅ (M⁺–C₄H₉), calcd 247.1002, found 247.1020.

10a as a white solid; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.21$; ^1H NMR (300 MHz, CDCl_3) δ 6.56 (s, 1H, *OH*), 4.35–4.46 (m, 1H), 4.20–4.24 (m, 1H), 3.81 (s, 3H), 1.93–2.18 (m, 2H), 1.64–1.71 (m, 1H), 1.45–1.54 (m, 1H), 1.26 (d, $J = 5.9$ Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 169.53, 96.09, 75.64, 65.05, 61.88, 52.75, 38.77, 36.50, 27.79, 21.36; IR (CH_2Cl_2) 3434, 1748 cm^{-1} ; CIMS m/z 229 (10), 187 (5), 173 (100); HRMS (EI) for $\text{C}_{10}\text{H}_{19}\text{O}_3$ ($\text{M}^+ - \text{COOMe}$), calcd 187.1334, found 187.1330.

10b as a colourless liquid; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.29$; ^1H NMR (300 MHz, CDCl_3) δ 4.09–4.20 (m, 1H), 3.92–4.02 (m, 1H), 3.82 (s, 3H), 3.71 (d, $J = 2.0$ Hz, 1H, *OH*), 1.79–1.96 (m, 3H), 1.33 (q, $J = 12.6$ Hz, 1H), 1.20 (d, $J = 6.3$ Hz, 3H), 1.20 (s, 9H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 171.06, 95.81, 73.97, 66.91, 63.72, 53.28, 42.25, 39.36, 28.38, 21.41; IR (CH_2Cl_2) 3493, 1747 cm^{-1} ; CIMS m/z 247 ($\text{M}^+ + 1$, 25), 229 (36), 187 (6), 173 (100); HRMS (EI) for $\text{C}_{10}\text{H}_{19}\text{O}_3$ ($\text{M}^+ - \text{COOMe}$), calcd 187.1334, found 187.1327.

12a as a colourless syrup; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.59$; ^1H NMR (300 MHz, CDCl_3) δ 5.96 (s, 1H, *OH*), 3.96–4.08 (m, 2H), 3.76 (s, 3H), 2.00–2.35 (m, 2H), 1.46–1.53 (m, 1H), 1.20 (d, $J = 6.3$ Hz, 3H), 1.04–0.81 (m, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 169.36, 95.55, 70.94, 66.54, 52.62, 40.77, 37.87, 25.66, 18.95, 17.77, 14.47, –4.70, –5.08; IR (CH_2Cl_2) 3422, 1747 cm^{-1} ; EIMS (20 eV) 261 ($\text{M}^+ - \text{C}_4\text{H}_9$, 9); HRMS (EI) for $\text{C}_{15}\text{H}_{30}\text{SiO}_5$ ($\text{M}^+ - \text{C}_4\text{H}_9$), calcd 261.1158, found 261.1166.

12b as a colourless oil; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.59$; ^1H NMR (300 MHz, CDCl_3) δ 4.17–4.25 (m, 2H), 3.82 (s, 3H), 3.81 (s, 1H, OH), 2.03–2.11 (m, 1H), 1.61–1.76 (m, 1H), 1.55 (d, $J = 6.6$ Hz, 3H), 0.82–0.98 (m, 3H), 0.92 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 171.04, 95.53, 68.74, 67.56, 53.19, 40.10, 34.04, 25.75, 18.18, 18.00, 13.74, -4.74 , -4.80 ; IR (CH_2Cl_2) 3541, 1742 cm^{-1} ; EIMS (20 eV) 261 ($\text{M}^+ - \text{C}_4\text{H}_9$, 40); HRMS (EI) for $\text{C}_{15}\text{H}_{30}\text{SiO}_5$ ($\text{M}^+ - \text{C}_4\text{H}_9$), calcd 261.1158, found 261.1162.

13a as a white solid. M.p. 101 °C. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.57$; ^1H NMR (300 MHz, CDCl_3) δ 6.09 (s, 1H, OH), 4.48–4.55 (m, 1H), 4.02–4.08 (m, 1H), 3.78 (s, 3H), 2.21 (dd, $J = 14.4, 2.6$ Hz, 1H), 2.01 (dd, $J = 14.4, 3.3$ Hz, 1H), 1.51–1.60 (m, 1H), 1.17 (d, $J = 6.6$ Hz, 3H), 0.83–0.97 (m, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 169.22, 95.81, 72.57, 62.70, 52.66, 38.45, 32.03, 25.70, 25.56, 17.90, 17.73, 10.18, -5.17 , -5.36 ; IR (CH_2Cl_2) 3423, 1751 cm^{-1} ; EIMS (20 eV) 261 ($\text{M}^+ - \text{C}_4\text{H}_9$, 40); HRMS (EI) for $\text{C}_{15}\text{H}_{30}\text{SiO}_5$ ($\text{M}^+ - \text{C}_4\text{H}_9$), calcd 261.1158, found 261.1160.

13b as a colourless oil; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.57$; ^1H NMR (300 MHz, CDCl_3) δ 3.83 (s, 3H), 3.83–3.58 (m, 2H), 1.96 (d, $J = 7.5$ Hz, 1H), 1.55–1.85 (m, 1H), 1.04–1.50 (m, 1H), 1.20 (d, $J = 6.2$ Hz, 1H), 0.89–0.98 (m, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H);

^{13}C NMR (75.48 MHz, CDCl_3) δ 170.94, 95.25, 71.77, 69.84, 53.22, 45.56, 40.13, 25.74, 25.60, 19.18, 17.93, 13.21, -4.24, -4.83; IR (CH_2Cl_2) 3530, 1742 cm^{-1} ; EIMS (20 eV) 261 ($\text{M}^+ - \text{t-Bu}$, 40); HRMS (EI) for $\text{C}_{15}\text{H}_{30}\text{SiO}_5$ ($\text{M}^+ - \text{t-Bu}$), calcd 261.1158, found 261.1164.

Table 1. 2D NOESY studies of cyclohemiketals

Trans-product		Cis-product
<p>1a: R = COOMe 2a: R = CF_3</p>	<p>no NOE observed between H_3 and H_5</p>	<p>1a: R = COOMe 2a: R = CF_3</p>	<p>NOE signal between H_3 and H_5</p>
<p>3a: R = CH_3 8a: R = OMe</p>	<p>NOE signal between H_2 and H_4; H_3 and H_5</p>	<p>3a: R = CH_3 8a: R = OMe</p>	<p>NOE signal between H_2 and H_5</p>
<p>5a</p>	<p>NOE signal between H_2 and H_4</p>	<p>6a</p>	<p>NOE signal between H_3 and H_5</p>
<p>9a: R = TBDMS 10a: R = tBu</p>	<p>no NOE between H_3 and H_5</p>	<p>9b: R = TBDMS 10b: R = tBu</p>	<p>NOE signal between H_3 and H_5</p>
<p>12a</p>	<p>no NOE between H_3 and H_5</p>	<p>12b</p>	<p>NOE signal between H_3 and H_5</p>

Determination of the stereochemistry of **4a** and **4b**:

The stereochemistry of **4a** and **4b** was determined by comparing ¹H NMR shifts and coupling patterns of protons H₅ of trans and cis hydrolysis products **4a'** and **4b'** with similar compounds reported in literature (reference S. A. Kozmin; *Org. Lett.* **2001**, 3, 755).

Dilution Studies of **12a** and **13a**

Figure 1. Dilution Study of **12a**.

Figure 2. Dilution Study of **13a**.