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Synthesis of 7-oxa-phomopsolide E and its C-4 epimer

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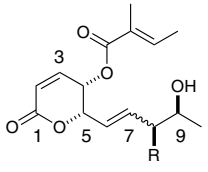
Abstract—A flexible, enantioselective route to highly functionalized α,β-unsaturated δ-lactones has been applied to the synthesis of 7-oxa-phomopsolide E and its C-4 epimer. This approach relies on the application of the Noyori asymmetric hydrogenation of furyl ketone to produce the secondary furyl alcohol in high enantioexcess, which can be stereoselectively transformed into α,β-unsaturated-δ-lactones by a short, highly diastereoselective oxidation and reduction sequence. DCC and Mitsunobu coupling were used to introduce the side chains of the two natural product analogs.

1. Introduction

The American elm tree thrives in a wide range of soils and climatic conditions, making it one of the most widely planted street trees in North America.[1] Unfortunately, a completely healthy 100-year-old American elm can be killed in as little as two weeks if infected with Dutch elm disease,[2] and over 40 million elm trees in the United States have been killed since the arrival of Dutch elm disease.[3] The fungus responsible for Dutch elm is spread from tree to tree by the elm bark beetle (*Scolytid beetle*).

The devastation caused by Dutch elm disease brought about research to find natural compounds that have antiboring/antifeeding activity against the elm bark beetle. As a result, Grove,[4] and later Stierle,[5] found a series of related 6-substituted 5,6-dihydro-5-hydroxy-pyran-2-ones, the phomopsolides (Fig. 1), which possess the desired deterrent activity for *Scolytid beetles* as well as potent antimicrobial activity against *Staphylococcus aureus*.

As part of a continuing program directed at the discovery of new antibiotics, we have investigated the enantioselective syntheses of various biologically important pyranone natural products both from dienoates[6] and furan alcohols.[7,8] In the case of the phomopsolide class of natural products, our furan



1a: cis, R = O; **Phomopsolide A**
1b: trans, R = OH; **Phomopsolide B**
1c: trans, R = O; **Phomopsolide C**
1d: 6,7-dihydro, R = OH; **Phomopsolide D**
1e: 6,7-dihydro, R = O; **Phomopsolide E**

Figure 1. Structures of phomopsolides.

methodology was successfully applied to the synthesis of phomopsolide C (**1c**).[9] Our approach derives its asymmetry from (*S*)-lactic acid and the application of the Sharpless asymmetric dihydroxylation of vinylfuran. The resulting secondary furan alcohol is produced in high enantioexcess and can be stereoselectively transformed into α,β-unsaturated-δ-lactones via a short highly diastereoselective oxidation and reduction sequence. In our previous synthesis of phomopsolide C (Scheme 1), a Wittig olefination reaction was used to introduce the side chain and was further elaborated into the target structure.

Because of our motivation to test similar compounds as antibiotics and against Dutch elm disease, we felt that a related approach to our synthesis could easily generate structural analogs of the phomopsolide family for biological testing. To these ends the syntheses of the two C-4 diastereomers of 7-oxa-phomopsolide E (**7a** and **7b**) were undertaken. The two targets can easily be envisioned being prepared in a convergent manner from the

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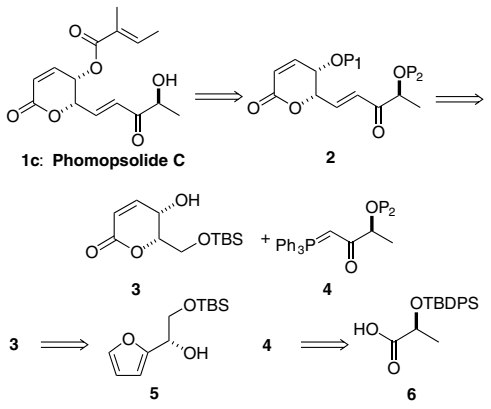
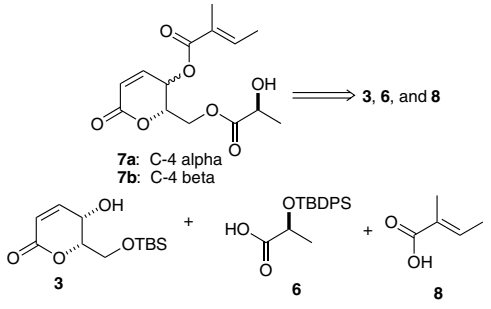


Scheme 1. Retrosynthesis of phomopsolide C.

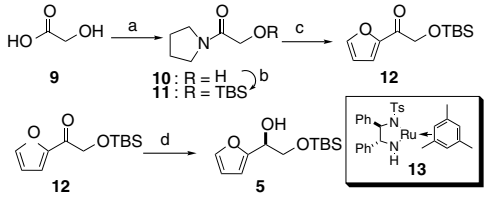
three intermediates pyranone **3**, protected lactic acid **6**, and tiglic acid **8** (Scheme 2).



Scheme 2. Retrosynthetic analysis of 7-oxa-phomopsolide D.

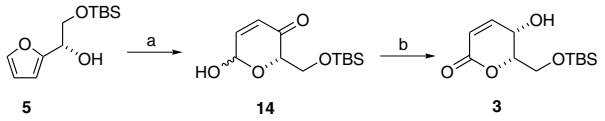
In our previous furan approaches we derived the pyranone asymmetry by means of the Sharpless asymmetric dihydroxylation of vinylfuran.[8,10] Because the enantioselectivity of the dihydroxylation reaction was less than perfect,[11] we searched for a better asymmetric reaction and settled on the Noyori reduction of acylfurans. Thus, the furyl alcohol **5** was enantioselectively prepared from a Noyori asymmetric hydrogenation of furyl ketone **12**, which occurred in high yield (84%) and ideal enantioexcess (>96% ee). In turn, the acylfuran **12** could easily be prepared in three steps from glycolic acid **9** via a 2-lithiofuran addition to the TBS-protected amide **11** (Scheme 3).[12]

The synthesis of both 7-oxa-phomopsolide E **7a** and its 4-*epi* isomer **7b** began with the conversion of furyl



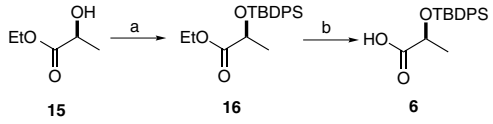
Scheme 3. Reagents and conditions: (a) pyrrolidine, xylene, 150 °C (83%); (b) TBSCl, DMF, Imid., rt (83%); (c) furan/*n*-BuLi, THF, −78 °C (87%); (d) (*1S,2S*) Noyori catalyst (**13**), HCO_2H/Et_3N (1:1) (84%).

alcohol **5** to pyranone **3** (Scheme 4). Treatment of furyl alcohol **5** with NBS[13] in aqueous THF (Achmatowicz reaction),[14] gave pyranone **14** in 92% yield. The reaction of **14** with Jones reagent gave a ketolactone intermediate, which was taken on without purification to a Luche reduction[15] with $NaBH_4$ and $CeCl_3$ in MeOH, to give pyranone **3** in 83% yield from **14**.



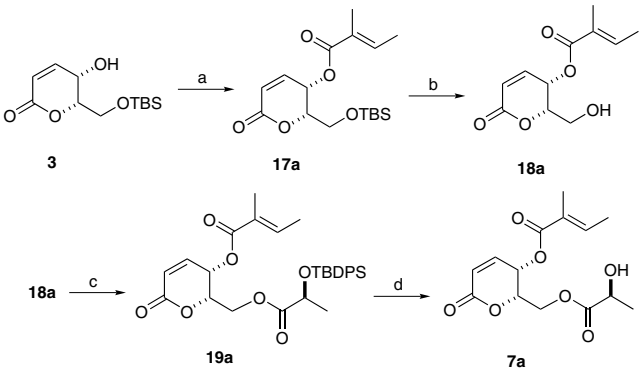
Scheme 4. Reagents and conditions: (a) NBS, $NaHCO_3$, NaOAc, THF, H_2O, 0 °C (92%); (b) Jones reagent, acetone, 0 °C, then $NaBH_4/CeCl_3$, $MeOH/CH_2Cl_2$, −78 °C (83%).

The desired carboxylic acid **6** was synthesized from (*S*)-ethyl lactate **15** in two steps and 78% yield. This sequence involved hydroxyl group protection of **15** with TBDPSCl to give **16** followed by ester hydrolysis to form the acid **6** (Scheme 5).

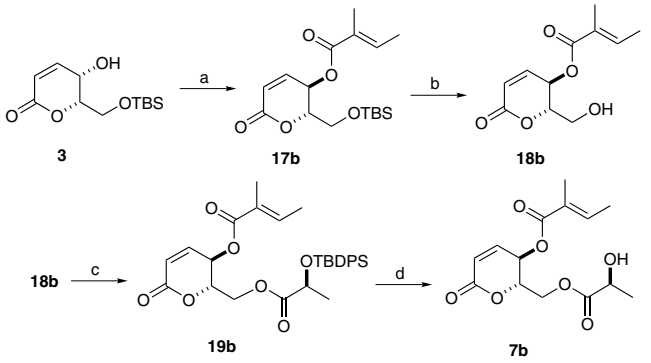


Scheme 5. Reagents and conditions: (a) TBDPSCl, DMF, Imid., rt (95%); (b) KOH, MeOH, rt (82%).

The synthesis of 7-oxa-phomopsolide E **7a** was then pursued using a DCC-mediated coupling between pyranone **3** and tiglic acid **8** to yield ester **17a** (Scheme 6). A subsequent TBS-group deprotection using HF gave a 74% yield (two steps) of alcohol **18a**. Once again, resorting to a DCC coupling reaction establishes the remaining carbons of analog **7a**. Thus, a DCC coupling of **18a** with acid **6** resulted in the protected natural product analog **19a**, which was deprotected with HF/Py (2:1) complex providing 7-oxa-phomopsolide E **7a** in 91% yield.



Scheme 6. Reagents and conditions: (a) **8**, DCC, DMAP, CH_2Cl_2 (85%); (b) HF, CH_3CN (87%); (c) **6**, DCC, DMAP, CH_2Cl_2 (89%); (d) HF/Py (2:1), CH_3CN (91%).



Scheme 7. Reagents and conditions: (a) **8**, PPh_3, DEAD (61%); (b) HF, CH_3CN (82%); (c) **6**, DCC, DMAP, CH_2Cl_2 (86%); (d) HF/Py (2:1), CH_3CN (88%).

The 4-*epi* isomer of **7a** (**7b**) was similarly prepared beginning with the esterification of pyranone **3** and tiglic acid **8** but this time under the Mitsunobu conditions (Scheme 7).[16] Thus simply exposing pyranone **3** and tiglic acid **8** to a mixture of PPh_3 and DEAD gave ester **17b** in a 61% yield. Ester **17b** was deprotected with HF to give a 82% yield of alcohol **18b**. DCC coupling between alcohol **18b** and acid **6** gave protected 4-*epi*-7-oxa-phomopsolide E **19b**, and HF/Py (2:1) deprotection gave the natural product analog **7b** in 88% yield.

In conclusion, the highly enantio- and diastereocontrolled route to the α,β-unsaturated δ-lactone natural products developed in our laboratory was successfully applied to the syntheses of the natural product analogs 7-oxa-phomopsolide E and its 4-*epi* isomer, thus demonstrating the flexibility of the method. The synthesis of both **7a** and **7b** were completed in only six steps from furan **5** (10 steps from glycolic acid).

2. Experimental section

2.1. 1-(2′-Furyl)-2-*tert*-butyldimethylsilanyloxyethanone (12)

A solution of 2-lithiofuran (0.5 M, 26 ml, 13 mmol) was added dropwise to a solution of amide **11** (2.43 g, 10 mmol) in THF (50 mL) at −78 °C. After stirring for 1 h, the reaction was quenched by addition of satd NH_4Cl (20 mL). It was then diluted with Et_2O (200 mL) and water (100 mL). The organic layer was separated, washed with brine (50 mL), and dried (Na_2SO_4). Concentration afforded a residue that was purified by flash chromatography (10% EtOAc/hexane) to give the desired ketone **12** (2.09, 8.7 mmol, 87%), as a light yellow oil: R_f (20% EtOAc/hexane) = 0.61; IR (thin film, cm^{-1}) 2952, 2929, 2856, 1698, 1471, 1255, 1150, 1017, 839; ^1H NMR (270 MHz, $CDCl_3$) δ 7.58 (dd, $J = 1.7$, 0.7 Hz, 1H), 7.32 (dd, $J = 3.5$, 0.7 Hz, 1H), 6.54 (dd, $J = 3.5$, 1.7 Hz, 1H), 4.73 (s, 2H), 0.94 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 187.0, 150.9, 146.3, 118.0, 112.1, 67.1, 25.8, 18.5, −5.4; CI HRMS calcd for $[C_{12}H_{20}O_3Si+Na]^+$: 263.1074, found: 263.1076.

2.2. 1-(2′-Furyl)-2-*tert*-butyldimethylsilanyloxyethan-1*S*-ol (5)

To a 20 ml flask was added ketone **12** (1.42 g, 5.9 mmol), formic acid/triethylamine (1:1, 8 ml), CH_2Cl_2 (3 mL), and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6-mesitylene)-(*S*,*S*)-TsDPEN **13** (18 mg, 0.5 mol %). The resulting solution was stirred at room temperature for 24 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude alcohol. Flash chromatography (30% EtOAc/hexane) on silica gel yielded 1.20 g (5.0 mmol, 84%) of alcohol **5** as a light yellow oil: R_f (30% EtOAc/hexane) = 0.54; $[\alpha]_D^{25}$ −15.4° (*c* 1.01, CH_2Cl_2); IR (thin film, cm^{-1}) 3447, 2954, 2930, 2884, 2857, 1471, 1473, 1361; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37 (dd, $J = 1.7$, 0.7 Hz, 1H), 6.34 (dd, $J = 3.2$, 1.7 Hz, 1H), 6.30 (dd, $J = 3.2$, 0.7 Hz, 1H), 4.75 (dd, $J = 6.4$, 4.5 Hz, 1H), 3.85 (dd, $J = 10.1$, 4.5 Hz, 1H), 3.83 (dd, $J = 10.1$, 6.4 Hz, 1H), 2.89 (d, $J = 4.2$ Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 153.6, 142.0, 110.2, 107.0, 68.3, 65.6, 25.8, 18.2, −5.5; calcd for $[C_{12}H_{22}O_3Si-H_2O]^+$: 225.1310, found: 225.1296.

2.3. (5*S*,6*S*)-5-(2-Methyl-2-butenoyloxy)-6-(*tert*-butyldimethylsilanyloxymethyl)-5,6-dihydropyran-2-one (17a)

Alcohol **3** (136 mg, 0.53 mmol), tiglic acid (105 mg, 1.05 mmol), dicyclohexylcarbodiimide (217 g, 1.05 mmol), and dimethylaminopyridine (catalytic amount) were dissolved in 64 ml of CH_2Cl_2. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then filtered through a pad of Celite with excess Et_2O and concentrated. The crude product was purified by silica gel flash chromatography eluting with 10% EtOAc/hexane to yield 152 mg (0.45 mmol, 85%) of **17a** as a clear oil: R_f (30% EtOAc/hexane) = 0.78; $[\alpha]_D^{25}$ +250° (*c* 1.10, CH_2Cl_2); IR (thin film, cm^{-1}) 2955, 2930, 2857, 1715, 1253, 1134, 1096, 1068, 837; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (dd, $J = 10.0$, 6.0 Hz, 1H), 6.86 (dd, $J = 14.0$, 6.0 Hz, 1H), 6.17 (d, $J = 9.5$ Hz, 1H), 5.33 (dd, $J = 6.0$ Hz, 2.5 Hz, 1H), 4.56 (ddd, $J = 7.0$, 7.0, 2.5 Hz, 1H), 3.88 (d, $J = 7.0$ Hz, 1H), 1.81–1.76 (m, 6H), 0.83 (s, 9H), 0.01 (d, $J = 16.5$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 162.4, 141.0, 139.3, 127.7, 124.9, 78.5, 60.9, 60.2, 25.7, 18.1, 14.5, 12.0, −5.5, −5.6; CI HRMS calcd for $[C_{17}H_{28}O_5Si+H]^+$: 341.1784, found: 341.1772.

2.4. (5*S*,6*S*)-5-(2-Methyl-2-butenoyloxy)-6-hydroxymethyl-5,6-dihydropyran-2-one (18a)

Ester **17a** (140 mg, 0.41 mmol), 1 mL of CH_3CN, and HF (5%, 2 ml, ~5.0 mmol) were added to a plastic vial and stirred at rt for 10 h. The reaction was quenched with saturated $NaHCO_3$, the aqueous layer was extracted with EtOAc (2 × 30 mL), and the organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude alcohol. Flash chromatography (60%

EtOAc/hexane) on silica gel yielded 81 mg (0.36 mmol, 87%) of alcohol **18a** as a colorless oil: R_f (50% EtOAc/hexane) = 0.23; $[\alpha]_D^{25}$ +285° (*c* 1.02, CH_2Cl_2); IR (thin film, cm^{-1}) 3446, 2934, 1712, 1649, 1382, 1256, 1131, 1066; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (dd, $J = 9.6$, 6.0 Hz, 1H), 6.95–6.85 (m, 1H), 6.24 (d, $J = 9.6$ Hz, 1H), 5.41 (dd, $J = 6.0$, 2.7 Hz, 1H), 4.64 (ddd, $J = 6.5$, 6.5, 2.7 Hz, 1H), 3.94 (dd, $J = 12.0$ Hz, 6.9 Hz, 1H), 3.75 (dd, $J = 12.0$ Hz, 6.3 Hz, 1H), 1.82–1.78 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 162.3, 140.2, 139.1, 127.1, 125.0, 79.1, 61.9, 60.3, 14.5, 11.9; ESI HRMS calcd for $[C_{11}H_{14}O_5+Na]^+$: 249.0739, found: 249.0751.

2.5. (5*S*,6*S*)-5-(2-Methyl-2-butenoyloxy)-6-[(2*S*)-2-(*tert*-butyldiphenylsilanyloxy)propionyloxymethyl]-5,6-dihydro-pyran-2-one (19a)

Alcohol **18a** (79 mg, 0.35 mmol), (2*S*)-(*tert*-butyldiphenylsilanoxy)propionic acid (228 mg, 0.70 mmol), dicyclohexylcarbodiimide (143 mg, 0.70 mmol), and dimethylaminopyridine (catalytic amount) were dissolved in 8 ml of CH_2Cl_2. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then filtered through a pad of Celite with Et_2O (40 mL) and concentrated. The crude product was purified by silica gel flash chromatography eluting with 20% EtOAc/hexane to yield 164 mg (0.31 mmol, 89%) of **19a** as a colorless oil: R_f (30% EtOAc/hexane) = 0.47; $[\alpha]_D^{25}$ +107° (*c* 1.02, CH_2Cl_2); IR (thin film, cm^{-1}) 3069, 2962, 2936, 2860, 1750, 1717, 1651, 1428, 1248, 1135, 824; ^1H NMR (270 MHz, $CDCl_3$) δ 7.69–7.62 (m, 4H), 7.44 (m, 6H), 6.99 (dd, $J = 9.7$, 5.7 Hz, 1H), 6.87 (m, 1H), 6.20 (d, $J = 9.7$ Hz, 1H), 5.03 (dd, $J = 5.7$, 2.7 Hz, 1H), 4.46 (ddd, $J = 6.4$, 6.4, 2.7 Hz, 1H), 4.31 (q, $J = 6.7$ Hz, 1H), 4.20 (m, 2H), 1.83–1.79 (m, 6H), 1.38 (d, $J = 6.7$ Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.2, 166.3, 161.6, 140.3, 140.0, 135.9, 135.7, 133.2, 133.0, 129.9, 127.7, 127.6, 127.2, 124.8, 75.8, 68.6, 61.5, 61.0, 26.7, 21.2, 19.2, 14.6, 12.0; calcd for $[C_{30}H_{36}O_7Si+Na]^+$: 559.2123, found: 559.2137.

2.6. 7-Oxa-phomopsolide E (7a)

Ester **19** (153 mg, 0.29 mmol), 2 ml of CH_3CN, and HF/Py (2:1) (2.5 M, 3 mL, ~7.5 mmol) were added to a plastic vial and stirred at rt for 24 h. The reaction was quenched with saturated $NaHCO_3$, and the aqueous layer was extracted with EtOAc (2 × 40 mL). The organic layer was washed with HCl (1 M, 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude alcohol. Flash chromatography (60% EtOAc/hexane) on silica gel yielded 78 mg (0.26 mmol, 91%) of 7-oxa-phomopsolide E **7a** as a colorless oil: R_f (50% EtOAc/hexane) = 0.21; $[\alpha]_D^{25}$ +243° (*c* 1.20, CH_2Cl_2); IR (thin film, cm^{-1}) 3468, 2933, 1715, 1648, 1450, 1381, 1254, 1132, 1099, 1068; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (dd, $J = 9.5$, 5.9 Hz, 1H), 6.99–6.87 (m, 1H), 6.27 (d, $J = 9.9$ Hz, 1H), 5.40 (dd, $J = 5.9$, 3.0 Hz, 1H), 4.85 (ddd, $J = 6.0$, 3.0, 0.9 Hz, 1H), 4.47 (ddd, $J = 11.7$, 6.0, 6.0, 2H), 4.34 (q, $J = 6.9$ Hz, 1H), 1.87–1.79 (m, 6H), 1.43 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 166.2, 161.5, 140.4, 138.9, 127.0, 124.8, 76.6, 66.6, 62.3, 61.2, 20.0, 14.3, 11.9; ESI HRMS calcd for $[C_{14}H_{18}O_7+Na]^+$: 321.0950, found: 321.1188.

2.7. (5*R*,6*S*)-5-(2-Methyl-2-butenoyloxy)-6-(*tert*-butyldimethylsilanyloxymethyl)-5,6-dihydropyran-2-one (17b)

Alcohol **3** (235 mg, 0.91 mmol) was dissolved in 6 mL of benzene. The solution was cooled to 0 °C and triphenylphosphine (358 mg, 1.37 mmol), tiglic acid (136 mg, 1.36 mmol), and diethyl azodicarboxylate (238 mg, 1.37 mmol) were added to the solution. The solution was stirred for 12 h, quenched with saturated aqueous sodium bicarbonate (30 mL), and extracted with EtOAc (2 × 30 mL). The organic fractions were combined, washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Purification on silica gel (EtOAc/hexane, 3:7) yielded 188 mg (0.55 mmol, 61%) of ester **17b** as a colorless oil: R_f (30% EtOAc/hexane) = 0.65; $[\alpha]_D^{25}$ −155° (*c* 1.20, CH_2Cl_2); IR (thin film, cm^{-1}) 2954, 2932, 2856, 1742, 1716, 1651, 1253, 1130, 837; ^1H NMR (270 MHz, $CDCl_3$) δ 6.93 (q, $J = 6.9$ Hz, 1H), 6.82 (dd, $J = 9.9$, 3.7 Hz, 1H), 6.10 (dd, $J = 9.9$, 1.2 Hz, 1H), 5.60 (ddd, $J = 5.2$, 4.0, 1.2 Hz, 1H), 4.57 (dd, $J = 7.9$, 4.0 Hz, 1H), 3.85 (dd, $J = 4.2$, 1.5 Hz, 2H), 1.83–1.80 (m, 6H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 166.7, 161.9, 142.1, 139.4, 127.6, 122.9, 80.4, 63.4, 62.5, 25.7, 18.2, 14.5, 12.0, −5.6; calcd for $[C_{30}H_{36}O_7Si+Na]^+$: 559.2123, found: 559.2133.

Acknowledgements

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14. An Achmatowicz reaction is the oxidative rearrangement of furfuryl alcohols to 2-substituted 6-hydroxy-2*H*-pyran-3(6*H*)-ones, see: (a) Ref. 13, Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165–176; (b) For its use in carbohydrate synthesis, see Ref. 12 and Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863–866; (c) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033–4036.
15. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *110*, 2226–2227.
16. Previously we have shown that the Mitsunobu esterification reaction works well on pyranone **3**, see Ref. 7, Mitsunobu, O. *Synthesis* **1981**, 1.