Development of the 1,2-oxaza-Cope Rearrangement

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Supporting Information

Experimental procedures, spectroscopic and analytical data for compounds **1c**, **1f**, **3**, **3a-3g**.

General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware. Proton magnetic resonance spectra were recorded at 300 and 500 MHz on Varian Mercury and Varian Unity Inova spectrometers, respectively. Carbon magnetic resonance spectra were recorded at 75 MHz on a Varian Mercury spectrometer. All chemical shifts were reported in δ units relative to tetramethylsilane. Infrared spectra were recorded on Perkin-Elmer Paragon 1000 FTIR spectrometer. High resolution mass spectral data were obtained by the Mass Spectrometry Laboratory at the Florida State University. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with silica Gel 60 F254 (E. Merck no. 5715-7). Flash column chromatography was performed using 40-63 μ m silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Tetrahydrofuran (THF) was dried by distilling from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, di-iso-propylamine, triethylamine, and chlorotrimethylsilane were distilled from calcium hydride in a continuous still under an atmosphere of argon. All reagents were used as purchased unless noted otherwise.

Compounds **1**,¹ **1a**,^{2,4} **1b**,³ **1d**,⁴ **1e**,⁵ and **1g**⁶ have been prepared according to the literature procedures.

¹ (a) Maskill, H.; Wilson, A. A. *J. Chem. Soc. Perkin Trans 2* **1984**, 119. (b) Inukai, T.; Kasai, M. *J. Org. Chem.* **1965**, 30, 3567. (c) Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, 58, 8219.

² Sudo, A.; Saigo, K. *Chem. Lett.* **1997**, 97.

³ Mirrington, R. N.; Schmalzl, K. J. *J. Org. Chem.* **1969**, 34, 2358.

⁴ Ikota, N. *Chem. Pharm. Bull.* **1989**, 37, 2219.

⁵ Orita, A.; Nagano, Y.; Hirano, J.; Otera, J.; *Syn. Lett.* **2001**, 637.

⁶ Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, 43, 5357.

Esters 1c. To a solution of α,α -dimethoxy-ketone **6**⁷ (610 mg, 1.92 mmol) in methanol (1 mL) was added SmI_2 solution (0.1M in THF) (80 mL, 8 mmol) at room temperature until the blue color of the reaction mixture did not faded. The mixture was stirred for 10 min and then diluted with ethyl acetate, washed with solution of K_2CO_3 . The organic layer was separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. Silica gel chromatography (30% ethyl acetate-hexanes) afforded reduction product **7** (446 mg, 1.73 mmol, 90% yield). ^1H NMR (300 MHz, CDCl_3); δ (ppm): 7.38–7.27 (m, 5H); 6.66 (d, $J=9.0$ Hz, 1H); 6.07 (dd, $J_1=9.0$ Hz, $J_2=6.0$ Hz, 1H); 4.52 (d, $J=12.0$ Hz, 1H); 4.47 (d, $J=12.0$ Hz, 1H); 4.05–4.00 (m, 1H); 3.55 (ddd, $J_1=6.0$ Hz, $J_2=3.0$ Hz, $J_3=1.2$ Hz, 1H); 3.42 (s, 3H); 2.30 (dd, $J_1=17.4$ Hz, $J_2=3.6$ Hz, 1H); 2.21 (dd, $J_1=12.6$ Hz, $J_2=9.0$ Hz, 1H); 2.05 (d, $J=17.4$ Hz, 1H); 1.81 (dt, $J_d=12.6$ Hz, $J_t=3.6$ Hz, 1H). HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{O}_3\text{Na}$ [$\text{M}+\text{Na}$] 281.1154, found 281.1154

To a solution of (methoxymethyl)-triphenylphosphonium chloride (2.1 g, 6.10 mmol) in 10 ml dry toluene was added solution of KHMDS (0.5 M in toluene, 11.1 ml, 5.58 mmol) at 0°C , and the mixture was stirred at 0°C for 30 min. Ketone **7** (410 mg, 1.59 mmol) in toluene (5 ml) was then added and the reaction was warmed to room temperature and was stirred for 5 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted three times with ethyl acetate. The combined organic layers was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. Silica gel chromatography (20% ethyl acetate-hexanes) afforded vinyl ether **8** (277 mg, 0.97 mmol, 61% yield) as 1:1 cis- and trans- isomers, along with 0.11 g (0.164 mmol, 27%) of the starting ketone. ^1H NMR (300 MHz, CDCl_3); δ (ppm): 7.36–7.25 (m, 10H); 6.45 (d, $J=7.8$ Hz, 1H); 6.42 (d, $J=7.8$ Hz, 1H); 6.15–6.09 (m, 2H); 5.95 (t, $J=2.4$ Hz, 1H); 5.84 (t, $J=2.4$ Hz, 1H); 4.58 (d, $J=12.0$ Hz, 1H); 4.49 (s, 2H); 4.48 (d, $J=12.0$ Hz, 1H); 3.96 (dd, $J_1=6.0$ Hz, $J_2=3.0$ Hz, 1H);

⁷ Hou, H.-F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2002**, 4, 2477-2480.

3.80–3.75 (m, 2H); 3.56 (s, 3H); 3.55 (s, 3H); 3.40 (s, 3H); 3.39 (s, 3H); 3.14 (dd, $J_1=6.0$ Hz, $J_2=3.0$ Hz, 1H); 2.15–2.04 (m, 4H); 2.05–1.93 (m, 2H); 1.64–1.54 (m, 2H).

To a solution of vinyl ether **8** (226 mg, 0.79 mmol) in THF (15 ml) at room temperature was added 10 ml aqueous solution of HClO_4 (65% $\text{HClO}_4\cdot\text{H}_2\text{O}=1:1$, v/v), the reaction mixture was stirred 1.5 hr and then diluted with ethyl acetate, quenched by saturated aqueous NaHCO_3 and extracted three times with ethyl acetate. The combined organic layers was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude aldehyde was used directly to next step without purification.

To a solution of the above aldehyde in 11.2 mL of tert-butyl alcohol and 10.5 ml of water at room temperature was added 1.54 mL of 2-methyl-2-butene. A solution of sodium chlorite (80%) (0.735 g, 6.50 mmol) and sodium phosphate monobasic monohydrate (0.710 g, 5.14 mmol) in water was added in portions during 20 min to the reaction mixture, then stirred for an addition hour. The reaction was poured into PH 4.0 buffer and extracted three times with CH_2Cl_2 , the combined organic layers was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude acid was used directly to next step without purification.

To a solution of the above acid in 7.0 mL CH_2Cl_2 and 1.0 mL methanol at 0°C was added TMSCHN_2 (1.0 mL of 2M solution in Et_2O). The resulting reaction mixture was raised to room temperature and stirred for 1 h. The reaction mixture was then concentrated and subjected to column chromatography (silica, 25% ethyl acetate-hexanes) to provide 212 mg (0.708 mmol, 83% yield) of esters **1c**.

Analytical data for each of the diastereoisomers list below:

^1H NMR (500 MHz, CDCl_3); δ (ppm): 7.38–7.26 (m, 5H); 6.49 (d, $J=8.5$ Hz, 1H); 6.04 (dd, $J_1=8.5$ Hz, $J_2=6.0$ Hz, 1H); 4.54 (d, $J=12.0$ Hz, 1H); 4.49 (d, $J=12.0$ Hz, 1H); 3.84–3.81 (m, 1H); 3.67 (s, 3H); 3.40 (s, 3H); 3.29 (t, $J=3.0$ Hz, 1H); 2.59 (ddd, $J_1=10.5$ Hz, $J_2=5.0$ Hz, $J_3=2.0$ Hz, 1H); 1.96–1.88 (m, 2H); 1.65 (dd, $J_1=12.0$ Hz, $J_2=10.5$ Hz, 1H); 1.57 (dt, $J_a=12.5$ Hz, $J_c=3.0$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3); δ (ppm): 174.57, 138.49, 136.06, 128.60, 127.75, 127.18, 77.36, 76.63, 70.17, 52.23,

51.56, 39.61, 39.42, 37.01, 32.77. HRMS (ESI) calcd for $C_{18}H_{22}O_4Na$ [M+Na] 325.1416, found 325.1411.

1H NMR (500 MHz, $CDCl_3$); δ (ppm): 7.37–7.26 (m, 5H); 6.45 (d, $J=8.5$ Hz, 1H); 6.16 (dd, $J_1=8.5$ Hz, $J_2=6.5$ Hz, 1H); 4.46 (s, 2H); 3.82–3.79 (m, 1H); 3.65 (s, 3H); 3.38 (s, 3H); 3.18–3.16 (m, 1H); 2.52 (ddd, $J_1=11.5$ Hz, $J_2=5.5$ Hz, $J_3=3.0$ Hz, 1H); 2.05 (dd, $J_1=12.0$ Hz, $J_2=8.5$ Hz, 1H); 1.94 (dd, $J_1=12.0$ Hz, $J_2=5.5$ Hz, 1H); 1.62 (dt, $J_t=12.0$ Hz, $J_d=4.0$ Hz, 1H); 1.55 (dt, $J_d=12.0$ Hz, $J_t=3.5$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$); δ (ppm): 174.57, 138.56, 136.58, 129.23, 128.51, 127.82, 127.73, 77.66, 73.94, 70.26, 52.20, 51.31, 40.58, 39.70, 36.81, 31.28. HRMS (ESI) calcd for $C_{18}H_{22}O_4Na$ [M+Na] 325.1416, found 325.1411.

Cycloaddition products **10+11**. A mixture of 2,4-cyclohexadienone **9**¹ (0.92 g, 5 mmol) and methyl acrylate (4.5 ml, 50 mmol) was kept in a sealed tube at 100°C for 24 h. The reaction mixture was then cooled to room temperature and subjected to column chromatography (silica, 20% ethyl acetate-hexanes) to give 1.20 g (45 mmol, 90%) of a 1:1 mixture of the two regioisomeric Diels-Alder reaction products **10+11**. Analytical sample of each isomer was separated by column chromatography (silica, 1.5% THF-benzene). Considering the separation is difficult at this stage it is suggested to separate the regioisomers at next step.

Analytical data for **10**: 1H NMR (300 MHz, $CDCl_3$); δ (ppm): 6.51 (d, $J=8.4$ Hz, 1H); 6.18 (dd, $J_1=8.4$ Hz, $J_2=6.6$ Hz, 1H); 3.68 (s, 3H); 3.65 (s, 3H); 3.53 (s, 3H); 3.55–3.52 (m, 1H); 3.42 (s, 3H); 3.17–3.14 (m, 1H); 2.17–2.08 (m, 1H); 1.82 (ddd, $J_1=13.2$ Hz, $J_2=4.8$ Hz, $J_3=3.6$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$); δ (ppm): 199.57, 173.84, 133.84, 123.75, 95.63, 84.18, 54.33, 52.45, 51.70, 51.36, 46.51, 41.63, 26.96. HRMS (ESI) calcd for $C_{13}H_{16}O_6Na$ [M+Na] 293.1001, found 293.1005.

Analytical data for **11**: 1H NMR (300 MHz, $CDCl_3$); δ (ppm): 6.25 (d, $J=8.4$ Hz, 1H); 6.06 (dd, $J_1=8.4$ Hz, $J_2=6.0$ Hz, 1H); 3.70 (s, 3H); 3.51 (s, 3H); 3.49 (s, 3H); 3.47 (s, 3H); 3.52–3.46 (m, 1H); 3.02–2.96 (m,

1H); 2.37 (dd, J1=12.3 Hz, J2=10.2 Hz, 1H); 2.12 (dd, J1=12.3 Hz, J2=5.4 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃); δ(ppm): 198.79, 172.82, 137.49, 122.83, 94.07, 83.00, 52.50, 52.34, 51.94, 51.85, 48.76, 37.02, 27.68. HRMS (ESI) calcd for C₁₃H₁₈O₆Na [M+Na] 293.1001, found 293.1001.

Ketones 12+13. To a solution of α,α-dimethoxy-ketone **10+11** (500 mg, 1.85 mmol) in methanol (2 mL) was added SmI₂ solution (0.1M in THF) (70 mL, 7 mmol) at room temperature until the blue color of the reaction mixture did not faded. The mixture was stirred for 10 min and then diluted with ethyl acetate, washed with solution of K₂CO₃. The organic layer was separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. Silica gel chromatography (20% ethyl acetate-hexanes) afforded reduction products **12** (168 mg, 0.80 mmol, 43% yield) and **13** (172 mg, 0.82 mmol, 44% yield).

Analytical data for **12**: ¹H NMR (300 MHz, CDCl₃); δ(ppm): 6.42 (d, J=9.0 Hz, 1H); 6.27 (dd, J1=9.0 Hz, J2=6.0 Hz, 1H); 3.70 (s, 3H); 3.42 (s, 3H); 3.21-3.16 (m, 1H); 3.12 (dd, J1=9.6 Hz, J2=5.4 Hz, 1H); 2.38 (d, J=17.4 Hz, 1H); 2.22 (d, J=17.4 Hz, 1H); 2.12-2.03 (m, 1H); 1.87 (ddd, J1=13.2 Hz, J2=5.4 Hz, J3=3.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃); δ(ppm): 206.88, 173.49, 135.90, 126.23, 79.94, 51.83, 51.33, 47.72, 45.36, 42.94, 27.78. HRMS (ESI) calcd for C₁₁H₁₄O₄Na [M+Na] 233.0790, found 233.0782.

Analytical data for **13**: ¹H NMR (300 MHz, CDCl₃); δ(ppm): 6.58 (d, J=8.4 Hz, 1H); 6.09 (dd, J1=8.4 Hz, J2=6.0 Hz, 1H); 3.70 (s, 3H); 3.49 (ddd, J1=6.0 Hz, J2=2.4 Hz, J3=1.2 Hz, 1H); 3.43 (s, 3H); 2.95 (ddd, J1=10.2 Hz, J2=5.4 Hz, J3=2.4 Hz, 1H); 2.35 (dd, J1=17.4 Hz, J2=3.6 Hz, 1H); 2.20 (d, J=17.4 Hz, 1H); 2.16 (ddd, J1=12.6 Hz, J2=5.4 Hz, J3=3.6 Hz, 1H); 2.07 (dd, J1=12.6 Hz, J2=10.2 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃); δ(ppm): 206.16, 172.79, 138.75, 123.93, 77.84, 52.34, 51.34, 50.25, 43.34, 38.08, 32.74. HRMS (CI) calcd for C₁₁H₁₅O₄ [M+H] 211.0970, found 211.0977.

Alcohol 14. To a solution of ketone **12** (150 mg, 0.71 mmol) in methanol (2 mL) was added NaBH₄ (19 mg, 0.50 mmol) at room temperature. The mixture was stirred for 10 min and then concentrated, ethyl acetate and 5% HCl was added. The organic layer was separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. Silica gel chromatography (30% to 50% ethyl

acetate-hexanes) afforded alcohol **14** (102 mg, 0.48 mmol, 68% yield) and its diastereoisomer (36 mg, 0.17 mmol, 24% yield).

Alcohol 14: ¹H NMR (300 MHz, CDCl₃); δ(ppm): 6.40 (d, J=9.0 Hz, 1H); 6.20 (dd, J1=9.0 Hz, J2=6.6 Hz, 1H); 4.06–4.03 (m, 1H); 3.65 (s, 3H); 3.38 (s, 3H); 2.80–2.76 (m, 1H); 2.71 (dd, J1=9.6 Hz, J2=5.4 Hz, 1H); 2.11 (dd, J1=12.9 Hz, J2=8.4 Hz, 1H); 1.81 (ddd, J1=13.2 Hz, J2=10.2 Hz, J3=2.4 Hz, 1H); 1.59 (ddd, J1=13.2 Hz, J2=4.8 Hz, J3=3.0 Hz, 1H); 1.50–1.46 (br, 1H, -OH), 1.42 (dd, J1=12.9 Hz, J2=3.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃); δ(ppm): 174.62, 134.08, 128.94, 78.88, 69.33, 51.69, 51.09, 45.03, 41.36, 37.53, 28.24. HRMS (ESI) calcd for C₁₁H₁₆O₄Na [M+Na] 235.0946, found 235.0948.

TBS ether 1f: To a solution of alcohol **14** (80 mg, 0.38 mmol) in dry DMF (3 mL) was added imidazole (51 mg, 0.76 mmol), DMAP (5 mg, 0.038 mmol) and TBSCl (85 mg, 0.56 mmol) at room temperature. The mixture was stirred for 12 hr and then poured to ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. Silica gel chromatography (10% ethyl acetate-hexanes) afforded TBS ether **1f** (114 mg, 0.35 mmol, 92% yield). ¹H NMR (300 MHz, CDCl₃); δ(ppm): 6.31 (d, J=8.4 Hz, 1H); 6.20 (dd, J1=8.4 Hz, J2=6.0 Hz, 1H); 4.03–3.98 (m, 1H); 3.65 (s, 3H); 3.38 (s, 3H); 2.67 (dd, J1=10.2 Hz, J2=5.4 Hz, 1H); 2.61 (dd, J1=6.0 Hz, J2=3.0 Hz, 1H); 1.98 (dd, J1=12.6 Hz, J2=8.4 Hz, 1H); 1.76 (ddd, J1=13.2 Hz, J2=10.2 Hz, J3=3.0, 1H); 1.53 (ddd, J1=13.2 Hz, J2=5.4 Hz, J3=3.0, 1H); 1.44 (dd, J1=11.7 Hz, J2=3.0, 1H); 0.85 (s, 9H); 0.04 (s, 3H); 0.03 (s, 3H). ¹³C NMR (75 MHz, CDCl₃); δ(ppm): 174.83, 132.12, 129.79, 78.86, 70.00, 51.61, 51.13, 45.15, 41.95, 37.87, 28.47, 25.75, 17.99, -4.65, -4.77. HRMS (ESI) calcd for C₁₇H₃₀O₄SiNa [M+Na] 349.1811, found 349.1824.

Nitrosation/1,2-oxaza-Cope rearrangement 1→3 using nitrosonium hexafluoroantimonate.

To a solution of LDA [from *i*-Pr₂NH (79 μ l, 0.564 mmol) and *n*-BuLi (2.65 M in hexanes, 0.19 ml, 0.50 mmol), in THF (0.75 ml), -78°C, 30 min] was added a solution of ester **1** (40 mg, 0.241 mmol) in THF (0.75 ml total with rinses) at -78°C. After stirring for 30 min, TMSCl (69 μ l, 0.54 mmol) was added dropwise at -78°C and, after 30 min, the cooling bath was removed and the reaction mixture was diluted with hexanes and quenched with saturated aqueous sodium bicarbonate. The layers were separated, the organic layer was dried with anhydrous sodium sulfate, filtered and concentrated. The silyl ketene acetal was dissolved in 1.6 ml of dry dichloromethane and triethylamine (67 μ l, 0.48 mmol) was added. The reaction mixture was cooled to -15°C, followed by the dropwise addition of a solution of NOSbF₆ (70 mg, 0.263 mmol) in dry nitromethane (0.40 ml). The reaction mixture immediately turned brilliant green. The solution was stirred for 1 h, during which time it warmed to 0°C. The reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with dichloromethane (2x5 ml). The combined organic layers were washed with water, dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (silica, 10→40% ethyl acetate-hexanes) to afford 14 mg (0.084 mmol, 35%) of ester **1** and its diastereomer and oxazine **3** (14 mg, 0.071 mmol, 30 %).

Nitrosation/1,2-oxaza-Cope rearrangement 1→3 using isoamyl nitrite/TiCl₄. General Procedure.

To a solution of LDA [from *i*-Pr₂NH (0.16 ml, 1.11 mmol) and *n*-BuLi (2.65 M in hexanes, 0.38 ml, 1.01 mmol), in THF (1.5 ml), -78°C, 30 min] was added a solution of ester **1** (80 mg, 0.48 mmol) in THF (1.25 ml total with rinses) at -78°C. After stirring for 30 min, TMSCl (0.14 ml, 1.10 mmol) was added dropwise at -78°C and, after 30 min, the cooling bath was removed and the reaction mixture was diluted with hexanes and quenched with saturated aqueous sodium bicarbonate. The layers were separated, the organic layer was dried with anhydrous sodium sulfate, filtered and concentrated. The silyl ketene acetal was dissolved in 3.2

ml of dry dichloromethane and 2,6-di-*tert*-butyl-4-methylpyridine (30 mg, 0.146 mmol) was added. The reaction mixture was cooled to -45°C and isoamyl nitrite (77 μl , 0.575 mmol) was added, followed by a dropwise addition of a solution of titanium tetrachloride in CH_2Cl_2 (2.0 M, 0.24 ml, 0.48 mmol). The stirred mixture turned bluish green and was allowed to warm to -15°C during 1.5 h. The reaction was quenched by the addition of saturated ammonium chloride. The mixture was extracted with CH_2Cl_2 (2x10 ml), and the combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated. Purification by column chromatography (silica, 35% ethyl acetate-hexanes) afforded oxazine **3** (67 mg, 0.343 mmol, 71 %) as a white crystalline solid.

3

3: mp: $86-87^{\circ}\text{C}$; IR (film, cm^{-1}): 2950, 2348, 1714, 1602, 1516, 1444, 1292, 1216, 1142, 1080, 990, 738, 694; ^1H NMR (300 MHz, CDCl_3); $\delta(\text{ppm})$: 6.01 (dt, $J_d=10.2$ Hz, $J_t=3.6$ Hz, 1H); 5.84 (dq, $J_d=10.2$ Hz, $J_q=2.4$ Hz, 1H); 4.24 (br, 1H); 3.84 (s, 3H); 2.60 (dd, $J_1=19.8$ Hz, $J_2=7.8$ Hz, 1H); 2.28 (dd, $J_1=19.8$ Hz, $J_2=3.6$ Hz, 1H); 2.19–2.11 (m, 3H); 1.63–1.56 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3); $\delta(\text{ppm})$: 164.43, 149.02, 134.44, 124.11, 71.29, 52.85, 27.10, 25.29, 24.72, 23.72. HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3\text{Na}$ [$\text{M}+\text{Na}$] 218.0793, found 218.0801.

3a

NOE 3.4%

Oxazine 3a. Using the general procedure, ester **1a** (81 mg, 0.45 mmol) was converted to oxazine **3a** (75 mg, 0.36 mmol, 80%) obtained after by column chromatography (silica, 25% ethyl acetate-hexanes).

3a: IR (film, cm^{-1}): 2938, 2356, 1738, 1720, 1454, 1298, 1214, 1154, 1088, 992, 736, 674; ^1H NMR (500 MHz, CDCl_3); $\delta(\text{ppm})$: 6.11 (ddd, $J_1=10.0$ Hz, $J_2=5.0$ Hz, $J_3=2.5$ Hz, 1H); 5.93–5.89 (m, 1H); 4.13 (d, $J=5.5$, 1H); 3.84 (s, 3H); 3.03 (quint, $J=7.5$ Hz, 1H); 2.29 (dtt, $J_d=18.5$ Hz, $J_t=5.5$ Hz, $J_t=1.5$ Hz, 1H); 2.16–2.08 (m, 1H); 2.03 (ddt, $J_{d1}=13.0$ Hz, $J_{d2}=7.5$ Hz, $J_t=2.5$ Hz, 1H); 1.73–1.69 (m, 1H); 1.41 (dq, $J_q=13.0$ Hz, $J_d=6.0$ Hz, 1H); 1.18 (d, $J_1=7.5$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3); $\delta(\text{ppm})$: 163.73, 154.10, 135.37, 122.73, 72.39, 52.24, 33.77, 29.78, 25.79, 17.70, 13.08. HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_3\text{Na}$ [$\text{M}+\text{Na}$] 232.0950, found 232.0943.

Oxazine 3b. Using the general procedure, ester **1b** (93 mg, 0.48 mmol) was converted to oxazine **3b** (80 mg, 0.36 mmol, 75%) obtained as a white crystalline solid after by column chromatography (silica, 25% ethyl acetate-hexanes).

3b: mp: 75–76°C; IR (film, cm^{-1}): 2932, 2360, 2340, 1746, 1722, 1440, 1336, 1304, 1280, 1192, 1110, 1000, 964, 668; ^1H NMR (300 MHz, CDCl_3); $\delta(\text{ppm})$: 5.43 (s, 1H); 3.84 (s, 3H); 2.59 (dd, $J_1=19.8$ Hz, $J_2=7.8$ Hz, 1H); 2.30 (dd, $J_1=19.8$ Hz, $J_2=2.4$ Hz, 1H); 2.03 (dd, $J_1=6.6$ Hz, $J_2=5.4$ Hz, 2H); 1.84–1.80 (m, 1H); 1.71 (s, 3H); 1.62–1.43 (m, 2H); 1.27 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3); $\delta(\text{ppm})$: 164.61, 147.66, 140.80, 124.70, 75.71, 52.75, 31.68, 29.64, 25.63, 24.48, 24.40, 23.45. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_3\text{Na}$ [$\text{M}+\text{Na}$] 246.1106, found 246.1107.

Oxazine 3c. Using the general procedure, esters **1c** (exo:endo 1.5:1, 94 mg, 0.311 mmol) were converted to oxazine **3c** (60 mg, 0.193 mmol, 62%) obtained after by column chromatography (silica, 20% ethyl acetate-benzene).

3c: IR (film, cm^{-1}): 2952, 2356, 1722, 1606, 1722, 1454, 1298, 1214, 1154, 1088, 992, 736, 698; ^1H NMR (300 MHz, CDCl_3); $\delta(\text{ppm})$: 7.39–7.27 (m, 5H); 5.95 (dt, $J_d=6.3$ Hz, $J_t=1.2$ Hz, 1H); 5.82 (dt, $J_d=6.3$ Hz, $J_t=1.2$ Hz, 1H); 4.75 (quint, $J=1.2$ Hz, 1H); 4.62 (d, $J=7.2$ Hz, 1H); 4.59 (d, $J=7.2$ Hz, 1H); 4.17–4.12 (m, 1H); 3.86 (s, 3H); 3.29 (s, 3H); 2.53 (dd, $J_1=11.4$ Hz, $J_2=1.2$ Hz, 1H); 2.32 (dd, $J_1=7.8$ Hz, $J_2=4.5$ Hz, 1H); 2.28 (d, $J=11.4$ Hz, 1H); 2.00 (dd, $J_1=7.8$ Hz, $J_2=4.5$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3); $\delta(\text{ppm})$: 163.89, 147.95, 138.01, 131.24, 129.54, 128.73, 128.11, 127.88, 77.44, 72.93, 71.07, 69.43, 53.03, 49.54, 35.03, 26.59. HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_5\text{Na}$ [$\text{M}+\text{Na}$] 354.1317, found 354.1314.

Oxazine 3d. Using the general procedure (exception: the nitrosation/1,2-oxaza-Cope rearrangement were carried out at -78°C for 1h), ester **1d** (0.166 g, 1.00 mmol) was converted to oxazine **3d** (98 mg

mg, 0.502 mmol, 50%) obtained after by column chromatography (silica, 25% ethyl acetate-hexanes).

3d: IR (film, cm^{-1}): 2966, 2358, 1756, 1560, 1412, 1218, 1142, 1078, 996, 748, 690; ^1H NMR (300 MHz, CDCl_3); $\delta(\text{ppm})$: 6.13 (dt, $J_{\text{d}}=5.4$ Hz, $J_{\text{t}}=2.4$ Hz, 1H); 5.90 (ddd, $J_1=5.4$ Hz, $J_2=4.2$ Hz, $J_3=2.4$ Hz, 1H); 4.91 (ddd, $J_1=6.6$ Hz, $J_2=2.4$ Hz, $J_3=1.2$ Hz, 1H); 3.87 (s, 3H); 3.03 (quint, $J=7.5$ Hz, 1H); 2.82 (dq, $J_{\text{q}}=7.2$ Hz, $J_{\text{d}}=0.6$ Hz, 1H); 2.47–2.41 (m, 2H); 1.18 (d, $J=7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3); $\delta(\text{ppm})$: 163.91, 163.86, 137.99, 129.70, 85.53, 52.92, 40.75, 34.32, 27.91, 13.68. HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]$ 218.0793, found 218.0799.

Oxazine 3e. Using the general procedure (exception: the nitrosation/1,2-oxaza-Cope rearrangement were carried out at -78°C for 1h), ester **1e** (0.19 g, 0.83 mmol) was converted to oxazine **3e** (0.143 mg, 0.556 mmol, 67%) obtained as a white crystalline solid after by column chromatography (silica, 25% ethyl acetate-hexanes).

3e: mp: $84\text{--}85^\circ\text{C}$; IR (film, cm^{-1}): 2932, 2360, 2340, 1746, 1722, 1440, 1336, 1304, 1280, 1192, 1110, 1000, 964, 668; ^1H NMR (500 MHz, CDCl_3); $\delta(\text{ppm})$: 7.29–7.22 (m, 3H); 7.16–7.14 (m, 2H); 6.10 (dt, $J_{\text{d}}=6.0$ Hz, $J_{\text{t}}=2.0$ Hz, 1H); 5.95 (ddd, $J_1=6.0$ Hz, $J_2=J_3=2.0$ Hz, 1H); 4.67 (ddd, $J_1=6.0$ Hz, $J_2=J_3=2.0$ Hz, 1H); 4.42 (d, $J=10.0$ Hz, 1H); 3.76 (s, 3H); 2.95–2.89 (m, 1H); 2.09 (ddt, $J_{\text{d}1}=17.5$ Hz, $J_{\text{d}2}=8.5$ Hz, $J_{\text{t}}=2.0$ Hz, 1H); 2.02 (ddq, $J_{\text{d}1}=17.5$ Hz, $J_{\text{d}2}=7.5$ Hz, $J_{\text{q}}=2.5$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3); $\delta(\text{ppm})$: 163.74, 158.81, 139.86, 137.92, 128.92, 128.72, 128.07, 127.53, 83.26, 53.00, 40.06, 39.05, 35.25. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]$ 280.0950, found 280.0946.

Oxazine 3f. Using the general procedure, ester **1f** (95 mg, 0.29 mmol) was converted to oxazine **3f** (60 mg, 0.175 mmol, 61%) obtained as a

white crystalline solid after by column chromatography (silica, 40→60% ethyl acetate-hexanes).

3f: mp: 102–104 °C; ^1H NMR (500 MHz, CDCl_3); $\delta(\text{ppm})$: 4.36–4.34 (m, 1H); 3.88 (s, 3H); 3.73 (dt, $J_t=10.0$ Hz, $J_d=4.5$ Hz, 1H); 2.95 (d, $J=19.5$ Hz, 1H); 2.83 (dt, $J_d=16.0$ Hz, $J_t=2.5$ Hz, 1H); 2.74 (ddd, $J_1=14.0$ Hz, $J_2=4.5$ Hz, $J_3=2.5$ Hz, 1H); 2.60 (dd, $J_1=16.0$ Hz, $J_2=4.0$ Hz, 1H); 2.54 (dd, $J_1=19.5$ Hz, $J_2=7.0$ Hz, 1H); 2.44 (dd, $J_1=14.0$ Hz, $J_2=10.0$ Hz, 1H); 2.32 (ddt, $J_{d1}=10.0$ Hz, $J_{d2}=7.5$ Hz, $J_t=2.0$ Hz, 1H); 0.88 (s, 9H); 0.03 (s, 3H); 0.01 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3); $\delta(\text{ppm})$: 204.75, 163.82, 149.23, 74.12, 67.68, 53.10, 50.27, 43.92, 36.74, 25.85, 23.44, 18.02, -4.19, -4.96. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{27}\text{NO}_5\text{SiNa}$ [M+Na] 364.1556, found 364.1555.

Oxazine 3g. Using the general procedure (exception: the silyl enol ether was prepared by treatment of the aldehyde with TESOTf (3 eq) and triethylamine (10 eq) in dry CH_2Cl_2 (1.0 ml) at rt, 30 min), aldehyde **1g** (26 mg, 0.191 mmol) was converted to oxazine **3g** (11 mg, 0.067 mmol, 35%) obtained after by column chromatography (silica, 15% ethyl acetate-hexanes).

3g: ^1H NMR (300 MHz, CDCl_3); $\delta(\text{ppm})$: 9.54 (s, 1H); 6.07 (dt, $J_d=10.2$ Hz, $J_t=3.6$ Hz, 1H); 5.90 (dq, $J_d=10.2$ Hz, $J_q=2.4$ Hz, 1H); 4.36 (br, 1H); 2.48 (dd, $J_1=19.2$ Hz, $J_2=7.8$ Hz, 1H); 2.21 (dd, $J_1=19.2$ Hz, $J_2=3.0$ Hz, 1H); 2.22–2.13 (m, 3H); 1.62–1.52 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3); $\delta(\text{ppm})$: 191.25, 156.16, 134.76, 123.87, 72.99, 24.46, 26.46, 24.86, 23.64, 22.21. HRMS (CI) calcd for $\text{C}_9\text{H}_{12}\text{NO}_2$ [M+Na] 166.0868, found 166.0866.