Synthesis of α,β -unsaturated 4,5-disubstituted γ -lactones via ring-closing metathesis catalyzed by the first generation Grubbs' catalyst

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SUPPORTING INFORMATION

EXPERIMENTAL

Materials and methods –

Reactions were carried out under argon atmosphere and using Schlenk techniques when appropriate. Solvents were distilled under argon as follows: dichloromethane over P₂O₅, toluene over sodium, and THF over sodium. ¹H-NMR and ¹³C-NMR spectra were recorded on a Varian XL 200 MHz Gemini spectrometer. Chemical shifts are given in ppm, and coupling constants in Hz. IR spectra were run in CHCl₃ solution on a Shimadzu 470 spectrometer. Mass spectra were run on a GC/MS Hewlett Packard 5970. The elemental analyses were performed at the Chemistry Department, Universita' "La Sapienza", Roma. Grubbs catalysts **I** and **II** were purchased from Fluka and Sigma Aldrich, respectively, and used without further purification.

Procedures –

Synthesis of allylic alcohols 3a-e

A solution of methacrolein **4** (or **5** in case of **3e**) (3.0 mmoles) in dry THF (30 ml) was cooled in an ice bath under an argon atmosphere, and R^2MgBr (4.5 mmoles, 2.0M in THF) was added dropwise under stirring. After 4 hours the reaction reached completion (TLC), and the mixture was poured into cold water (10 ml), and HCl 6N was added to completely dissolve the white solid. Dichlorometane (30 ml) was added, and the organic layer was first washed with saturated NaHCO_3 solution, then with water, and finally dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was separated on a silica gel column eluted with light petroleum ether/ Et_2O to afford the desired products as oils.

Preparation of 2-methylene-3-(triisopropylsilyloxy)-propanal (**5**)

1.13 mmol (100 mg) of 2-methylene-propane-1,3-diol were dissolved in 10 ml of dry THF and the solution was cooled to 0°C under argon atmosphere and 34 mg (1.13 mmol) of NaH paraffine oil suspension (80%) were added while stirring; after 1h, 1.13 mmol (0.25 ml, 218 mg) of tri-*iso*-propylsilylchloride were added. The resulting mixture was stirred overnight, then Et_2O was added (20 ml). The organic layer was then washed with saturated K_2CO_3 solution (20 ml), with brine (20 ml), and then dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue

was separated on a silica gel column eluted with light petroleum ether/Et₂O to afford monosilylated compound **6** as an oil (250 mg, 90%).

Alcohol **6** (0.41 mmol, 100 mg) were dissolved in CH₂Cl₂ (10 ml) and pyridinium chlorocromate was added (0.41 mmol, 88 mg). The resulting mixture was stirred for two hours, and filtered on a celite pad. The residue was washed with Et₂O and filtered again on celite, and separated on a silica gel column eluted with light petroleum ether/Et₂O to afford aldehyde **5** (40 mg, 40%) as an oil.

2-Methylene-3-(triisopropylsilyloxy)-propan-1-ol (**6**)

¹H NMR - (CDCl₃, 200 MHz): 0.96-1.41 (21H, m), 2.19 (1H, bs), 4.17 (2H, s), 4.32 (2H, s), 5.07 (1H, m), 5.12 (1H, m).

¹³C NMR - (CDCl₃, 50 MHz): 11.94, 12.33, 17.67, 17.94, 64.70, 65.45, 110.77, 147.55.

IR - (CHCl₃): 3495, 2950, 1471, 1397, 1274, 1055, 1012, 921, 884 cm⁻¹.

GC-MS (EI) *m/z* (rel.int.): 45 (24), 61 (51), 75 (100), 103 (71), 131 (67).

Anal Calcd for C₁₃H₂₈O₂Si: C 63.87, H 11.55. Found : C 63.75, H 11.66

2-Methylene-3-(triisopropylsilyloxy)-propanal (**5**)

¹H NMR - (CDCl₃, 200 MHz): 1.00-1.10 (21H, m), 4.47 (2H, t, J=2.1 Hz), 6.10 (1H, m), 6.58 (1H, m), 9.60 (1H, s).

¹³C NMR - (CDCl₃, 50 MHz): 11.92, 12.29, 17.65, 17.89, 59.85, 132.64, 149.73, 193.52.

IR - (CHCl₃): 2950, 1690, 1470, 1397 cm⁻¹.

GC-MS (EI) *m/z* (rel.int.): 45 (11), 113 (13), 129 (100), 157 (45), 199 (26).

Anal Calcd for C₁₃H₂₆O₂Si : C 64.41, H 10.81. Found : C 64.53, H 10.97.

2-Methyl-hept-1-en-3-ol (3a)

Spectral data are identical to those reported for the same compound in Ref.:

- a) Katzenellenbogen, J.A.; L Crumrine, A. *J. Am. Chem. Soc.* **1976**, 98, 4925-4935.
- b) Courtneidge, J.L.; Bush, M.; Loh, L.S. *Tetrahedron* **1992**, 48, 3835-3856.

2-Methyl-oct-1-en-3-ol (3b)

Spectral data are identical to those reported for the same compound in Ref.:

- a) Kauffmann, T.; Stach, D. *Chem.Ber.* **1992**, 125, 913-922;
- b) Goldmann, S. *Synthesis* **1980**, 8, 640-642.
- c) Sato, T.; Kikuchi, T.; Tsujita, H.; Kaetsu, A.; Sootome, N. et al. *Tetrahedron* **1991**, 47, 3281-3304.

1-Cyclohexyl-2-methyl-2-propen-1-ol (3c)

¹H NMR - (CDCl₃, 200 MHz): 0.82-1.94 (15H, m), 3.71 (1H, d, J=7.2 Hz), 4.85 (2H, m).

¹³C NMR - (CDCl₃, 50 MHz): 17.34, 25.98, 26.18, 26.44, 28.37, 29.61, 40.52, 80.88, 112.17, 146.46.

IR - (CHCl₃): 3625, 3450, 2935, 1716, 1650, 1456, 1390 cm⁻¹.

GC-MS (EI) *m/z* (rel.int.): 43 (20), 57 (20), 58 (20), 71 (100), 83 (39), 97(22).

Anal Calcd for C₁₀H₁₈O : C 77.87, H 11.76. Found : C 77.75, H 11.87

2,4-Dimethyl-1-penten-3-ol (3d)

Structural ^1H -NMR data are identical to those reported in Ref:

Faulkner, D.J.; Petersen, M.R. *J. Am. Chem. Soc.* **1973**, 95, 553-563.

^1H NMR - (CDCl_3 , 200 MHz): 0.82 (6H, d, $J=6.7$ Hz), 1.66 (3H, m), 1.73 (1H, q, overlapped, $J=6.7$ Hz), 3.66 (1H, d, $J=7.2$ Hz), 4.82 (1H, m), 4.87 (1H, m).

^{13}C NMR - (CDCl_3 , 50 MHz): 17.60, 19.38, 30.90, 81.66, 111.98, 146.76.

IR - (CHCl_3): 3825, 3655, 3050, 1459, 1303 cm^{-1} .

GC-MS (EI) - m/z (rel.int.): 41 (32), 43 (55), 55 (60), 57 (17), 67 (14), 71 (96), 72 (100), 83 (34), 111 (25).

Anal Calcd for $\text{C}_7\text{H}_{14}\text{O}$: C 73.63, H 12.36. Found : C 73.58, H 12.44

1-(Triisopropylsilyloxy)-2-methylene-heptan-3-ol (3e)

^1H NMR - (CDCl_3 , 200 MHz): 0.56-1.70 (30H, m), 2.63 (1H, bs), 4.15 (1H, t, $J=6.6$ Hz), 4.32 (2H, m), 5.03 (1H, s), 5.10 (1H, m).

^{13}C NMR - (CDCl_3 , 50 MHz): 11.92, 13.98, 17.67, 22.62, 27.96, 35.47, 64.92, 74.34, 110.94, 149.70.

IR - (CHCl_3): 3690, 3495, 2950, 1470, 1394 cm^{-1} .

GC-MS (EI) m/z (rel.int.): 41 (42), 45 (35), 55 (25), 59 (37), 61 (46), 67 (100), 75 (63), 77 (44), 81 (37), 103 (53), 105 (62), 115 (25), 131 (57), 255 (44), 257 (99).

Anal Calcd for $\text{C}_{17}\text{H}_{36}\text{O}_2\text{Si}$: C 67.94, H 12.07. Found : C 67.75, H 12.22.

Preparation of Esters 1a-e:

1.3 mmol of alcohol **3** and Et₃N (2.6 mmol) were dissolved in 30 ml of anhydrous CH₂Cl₂ and the solution was cooled to 0°C under an argon atmosphere; then a solution of acriloyl chloride (2.0 mmol) in anhydrous CH₂Cl₂ (10 ml) was added dropwise. The resulting mixture was stirred for two hours, then poured into 30 ml of cold water, and then extracted with CH₂Cl₂ (3 x 30 ml). The combined extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was separated on a silica gel column eluted with light petroleum ether/Et₂O to afford the desired acrylates **3** as oils.

[2-Methyl-hept-1-en-3-yl] acrylate (**1a**)

¹H NMR - (CDCl₃, 200 MHz): 0.90 (3H, t, J=7.3 Hz), 1.20-1.40 (4H, m), 1.60-1.75 (2H, m), 1.74 (3H, s), 4.88-5.00 (2H, m), 5.25 (1H, t, J=7.3 Hz), 5.82 (1H, dd, J₁=10.2 Hz, J₂=1.5 Hz), 6.14 (1H, dd, J₁=17.6 Hz, J₂=10.2 Hz), 6.42 (1H, dd, J₁=17.6 Hz, J₂=1.5 Hz).

¹³C NMR - (CDCl₃, 50 MHz): 13.90, 18.02, 22.40, 27.42, 32.28, 77.53, 112.67, 128.23, 130.36, 143.42, 165.98.

IR - (CHCl₃): 2965, 1470, 1440, 1416, 1306 cm⁻¹.

GC-MS (EI) - *m/z* (rel.int.): 41 (14), 55 (100), 67 (10), 68 (21), 81 (17), 95 (28), 110 (26).

Anal Calcd for C₁₁H₁₈O₂ : C 72.49, H 9.95. Found : C 72.42, H 10.02.

[2-Methyl-oct-1-en-3-yl] acrylate (1b)

^1H NMR - (CDCl_3 , 200 MHz): 0.85 (3H, m), 1.26 (6H, m), 1.61 (2H, m), 1.70 (3H, s), 4.86 (1H, m), 4.93 (1H, m), 5.22 (1H, t, $J=6.7$ Hz), 5.77 (1H, dd, $J_1=10.2$ Hz, $J_2=1.7$ Hz), 5.77 (1H, dd, $J_1=17.2$ Hz, $J_2=10.2$ Hz), 6.37 (1H, dd, $J_1=17.2$ Hz, $J_2=1.7$ Hz).

^{13}C NMR - (CDCl_3 , 50 MHz): 13.85, 17.94, 22.41, 28.87, 31.45, 32.50, 77.45, 112.60, 128.79, 130.21, 143.07, 165.36.

IR - (CHCl_3): 3155, 1504, 1454, 1345, 1220 cm^{-1} .

GC-MS (EI) - m/z (rel.int.): 41 (12), 55 (100), 67 (11), 68 (25), 69 (12), 81(16), 82 (21), 95 (23), 124 (20).

Anal Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2$: C 73.43, H 10.27. Found : C 73.37, H 10.33.

[1-Cyclohexyl-2-methyl-2-propenyl] acrylate (1c)

^1H NMR – 0.80-1.77 (15H, m), 4.91 (2H, m), 5.00 (1H, d, $J=7.7$ Hz), 4.85 (2H, m), 5.79 (1H, dd, $J_1=10.2$ Hz, $J_2=1.8$ Hz), 6.11 (1H, dd, $J_1=17.3$ Hz, $J_2=10.2$ Hz), 6.39 (1H, dd, $J_1=17.2$ Hz, $J_2=1.8$ Hz).

^{13}C NMR - (CDCl_3 , 50 MHz): 18.14, 25.81, 25.98, 26.42, 28.38, 29.23, 39.13, 81.75, 113.96, 128.81, 130.16, 141.85, 165.46.

IR - (CHCl_3): 3165, 1754, 1676, 1500, 1455, 1473, 1344, 1286, 1224 cm^{-1} .

GC-MS (EI) - m/z (rel.int.): 41 (8), 55 (100), 56 (6), 81(16), 96 (38).

Anal Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2$: C 74.96, H 9.68. Found : C 75.00, H 9.76.

[2,4-Dimethyl-pent-1-en-3-yl] acrylate (1d)

¹H NMR - (CDCl₃, 200 MHz): (CDCl₃, 200 MHz): 1.07-1.36 (6H, m), 1.71 (3H, s), 1.97 (1H, q, overlapped, J=6.9 Hz), 4.93 (2H, m), 4.97 (1H, d, J=7.6 Hz), 5.81 (1H, dd, J¹=10.2 Hz, J²=1.8 Hz), 6.13 (1H, dd, J¹=17.2 Hz, J²=10.2 Hz), 6.41 (1H, dd, J¹=17.2 Hz, J²=1.8 Hz).

¹³C NMR - (CDCl₃, 50 MHz): 18.13, 25.83, 28.39, 29.23, 39.13, 81.75, 113.97, 128.83, 130.19, 141.85, 165.48.

IR - (CHCl₃): 2935, 1715, 1620, 1457, 1414, 1306 cm⁻¹.

GC-MS (EI) - *m/z* (rel.int.): 41 (11), 55 (100), 81 (9), 121 (17), 136 (29).

HRMS (CI) calcd for [C₁₀H₁₆O₂ + H]⁺: 169.1229. Found : 169.1223

Anal Calcd for C₁₀H₁₆O₂ : C 71.39, H 9.59. Found C 71.26, H 9.72

[1-(Triisopropylsilyloxy)-2-methylene-heptan-3-yl] acrylate (1e)

¹H NMR - (CDCl₃, 200 MHz): 0.85-1.76 (30H, m), 4.26 (2H, s), 5.11 (1H, bs), 5.28 (1H, m), 5.32 (1H, t, J=6.7 Hz), 5.82 (1H, m), 6.11 (1H, dd, J₁=17.2 Hz, J₂=10.2 Hz), 6.38 (1H, m).

¹³C NMR - (CDCl₃, 50 MHz): 12.04, 13.90, 17.98, 22.42, 27.63, 33.27, 63.38, 75.01, 110.97, 128.81, 130.32, 146.95, 165.41.

IR - (CHCl₃): 2960, 1700, 1622, 1470, 1415, 1310 cm⁻¹.

GC-MS (EI) - *m/z* (rel.int.): 55 (15), 67 (13), 73 (29), 75 (10), 185 (100), 186 (20).

Anal Calcd for C₂₀H₃₈O₃Si : C 67.74, H 10.80. Found : C 67.67, H 10.89.

Preparation of 4-Methyl-5-alkyl butenolides (2a-e)

General procedure: 1.6 mmol of ester **1** were dissolved in dry CH_2Cl_2 (160 ml) under argon atmosphere; a 0.01M solution of the catalyst **I** (0.16 mmol in 16 ml of anhydrous CH_2Cl_2) was added very slowly (3-4 hours) and the refluxing mixture stirred overnight. Then the solvent was removed under reduced pressure, and the residue was separated on a silica gel column eluted with light petroleum ether/ Et_2O to afford the desired products as oils.

4-Methyl-5-butyl-2(5H)furanone (2a)

Structural data are identical to those reported for the same compound in Ref:
Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, 55, 12137-12148

4-methyl-5-pentyl-2(5H)furanone (2b)

Structural data are identical to those reported for the same compound in Ref:
Jefford, C.W.; Sledeski, A.W.; Boukouvalas, J. *Helv.Chim.Acta* **1989**, 72, 1362-1370.

4-methyl-5-cyclohexyl-2(5H)furanone (2c)

^1H NMR - (CDCl_3 , 200 MHz): 0.79-1.79 (9H, m), 1.99 (1H, m), 4.72 (1H, m), 5.78 (1H, s).

^{13}C NMR - (CDCl_3 , 50 MHz): 13.95, 23.89, 25.71, 25.78, 26.35, 30.08, 39.09, 88.42, 117.26, 167.48, 173.35.

IR - (CHCl_3): 2975, 1938, 1741, 1646, 1456, 1222 cm^{-1} .

GC-MS (EI) - m/z (rel.int.): 41 (14), 69 (10), 97 (10), 98 (100).

Anal Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2$: C 73.30, H 8.95. Found C 73.15, H 9.04.

4-methyl-5-isopropyl-2(5H)furanone (2d)

¹H NMR - (CDCl₃, 200 MHz): 1.19-1.25 (9H, m), 2.00 (1H, m), 4.72 (1H, m), 5.78 (1H, s).

¹³C NMR - (CDCl₃, 50 MHz): 15.11, 19.61, 29.44, 88.53, 117.50, 167.54, 173.29.

IR - (CHCl₃): 3130, 1686, 1494, 1431, 1369, 1279 cm⁻¹.

GC-MS (EI) - *m/z* (rel.int.): 41 (8), 55 (100), 97 (13), 109 (65).

Anal Calcd for C₈H₁₂O₂ : C 68.54, H 8.63. Found : 68.42, H 8.70.

4-(trisopropylsilyloxy)methylene-5-butyl-2(5H)furanone (2e)

¹H NMR - (CDCl₃, 200 MHz): 0.86-1.97 (30H, m), 4.55 (2H, s), 4.96 (1H, m), 6.00 (1H, m).

¹³C NMR - (CDCl₃, 50 MHz): 11.88, 13.78, 17.88, 22.35, 26.63, 32.46, 59.82, 82.11, 115.29, 170.54, 172.19.

IR - (CHCl₃): 2950, 1745, 1653, 1469, 1394, 1269 cm⁻¹.

GC-MS - *m/z* (rel.int.): 41 (20), 55 (23), 59 (28), 61 (35), 75 (58), 85 (20), 103 (41), 111 (63), 283 (100).

HRMS (CI) calcd for [C₁₈H₃₄O₃Si + H]⁺: 327.2355. Found : 327.2355

Anal Calcd for C₁₈H₃₄O₃Si : C 66.21, H 10.49. Found : C 66.08, H 10.61.

Compound **1a**

Compound **1a**

Compound **1b**

Compound **1c**

Compound **1e**

Compound 2a

Compound 2a

Compound **2b**

Compound **2c**

Compound **2e**

Compound **3a**

Compound **3b**

Compound **3c**

Compound **3e**

Compound 3e

Compound 5

Compound 6

Compound 6