

Enantioselective Enzymatic Desymmetrization of Highly Functionalized *Meso* Tetrahydropyranyl Diols

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Supporting informations

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I- General experimental

Anhydrous dichloromethane, diethylether, toluene and tetrahydrofuran were obtained from the Solvent Purification System BRAUN MB-SPS800. All experiments using anhydrous solvents were performed under inert atmosphere of argon, using dried apparatus and employing standard techniques for handling air-sensitive materials.

All reagents were obtained from commercial suppliers unless otherwise stated.

Lipase from *Candida rugosa* type VII (CRL) was purchased from Sigma (St. Quentin Fallavier, France). Lipase from porcine pancreas (PPL) was purchased from Fluka (Buchs, Switzerland). Lipase AK (from *Pseudomonas fluorescens*, PFL) was a gift from Amano Pharmaceutical (Nagoya, Japan). Novozyme 435 (from *Candida antarctica* B lipase, CAL-B) and Lipozyme RM IM (from *Rhizomucor miehei* lipase, RML) were gifts from Novo Nordisk A/S (Bagsværd, Denmark).

Para-methoxybenzyltrichloroacetimidate (PMBTCA) was prepared following the procedure described by Paquette *et al.*¹

Zinc was activated as follow: 1N HCl was added to zinc dust and the resulting suspension was stirred at room temperature for 30 min. It was then filtered, washed with water, absolute ethanol and dried under high vacuum for 2 h. Activated zinc dust was used rapidly after activation.

Flash chromatography was performed using Merck 40-63 μm particle-sized silica gel (230-400 mesh) and eluted with EtOAc in petroleum ether (PE, bp 40-60 °C). Analytical thin layer chromatography was performed using 0.20 mm silica gel 60 plates. Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with various stains (*p*-anisaldehyde, phosphomolybdic acid...)

Melting points (m.p.) were determined with a Büchi Melting-point B-450 apparatus and were not corrected. High resolution mass spectra (HRMS) were obtained from a QStar Elite spectrometer (Applied Biosystems SCIEX) by electrospray ionisation.

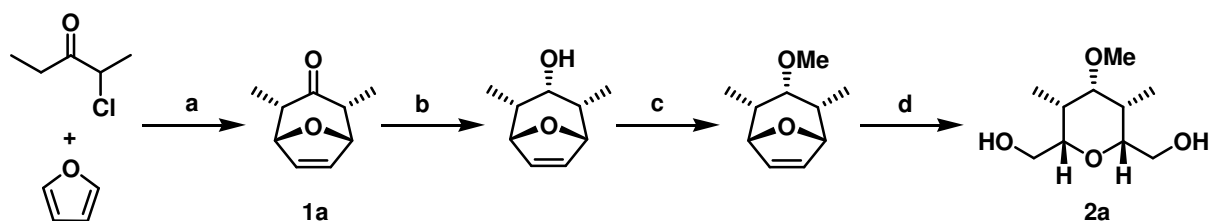
Proton NMR (¹H) spectra were recorded at 300.13 MHz on a Bruker AC-300 spectrometer using as internal standard the residual CHCl₃ signal for ¹H NMR ($\tau^{\text{M}} = 7.26$). Carbon NMR (¹³C) spectra were similarly recorded at 75.47 MHz on a Bruker AC-300 spectrometer, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence and as internal standard the deuteriochloroform (CDCl₃) solvent signal for ¹³C NMR ($\tau^{\text{M}} = 77.0$). Chemical shifts (δ) are reported in parts per million (ppm). The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet or massif, brs: broad signal. Coupling constants (*J*) are reported in Hertz (Hz).

The analytical chiral HPLC experiments were performed on a unit composed of a Merck D 7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV-detector, and on-line Jasco OR-1590 polarimeter. Hexane and 2-PrOH, HPLC grade, were degassed and filtered on a 0.45 μm membrane before use. The column used is Chiralpak IA (250 x 4.6 mm) from Chiral Technologies Europe (Illkirch, France). Retention times *R_t* are given in minutes. The sign given by the on-line polarimeter is the sign of the product in the solvent used for the chromatographic separation. The analyses were performed at 25 °C, with hexane/2-PrOH as mobile phase, with UV (220 nm) and polarimeter as detectors.

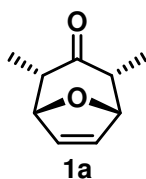
¹ Paquette, L.A.; Guevel, R.; Sakamoto, S.; Kim, I.H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096-6107.

II- Syntheses of diols 2a-2i

Synthesis of diol 2a



a- Et₃N, H₂O, rt. **b-** NaBH₄, MeOH, 0°C. **c-** KH, THF, 0°C then MeI. **d-** O₃, CH₂Cl₂ / MeOH (2/1.5) then NaBH₄ (4 equiv) -60°C to 0°C.

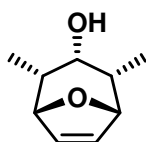


(1R,2S,4S,5S)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (1a)²: To a vigorously stirred emulsion of 2-chloropentan-3-one (64.0 g, 530 mmol) and furan (154 mL, 2.12 mol) in distilled water (530 mL) was added triethylamine (77 mL, 550 mmol) dropwise over a period of 30 min. The resulting orange emulsion was then stirred at room temperature for 12 h. The reaction mixture was subsequently quenched with a saturated aqueous solution of NH₄Cl (200 mL). The aqueous layer was extracted with dichloromethane (3 x 200 mL) and the combined organic layers were washed with brine (2 x 200 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford the crude product as an orange oil which was cooled to -20°C for 12 h. The resulting white crystals were filtered off, washed with cold pentane and dried in high vacuum. The filtrate was concentrated in *vacuo* and the procedure was repeated once to afford a total of 28.44 g (34%) of pure **1a** as white crystals. m.p. 44-46°C; *R_f* = 0.70 (PE/EtOAc : 7/3).

¹H NMR (300 MHz, CDCl₃): δ 6.32 (s, 2H), 4.84 (d, *J* = 4.5 Hz, 2H), 2.79 (dq, *J* = 7.2, 4.5 Hz, 2H), 0.96 (d, *J* = 7.2 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 208.9, 133.5 (2C), 82.7 (2C), 50.3 (2C), 10.1 (2C).

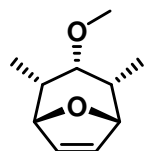
² Foehlich, B. ; Gehrlach, E. ; Stezawski, J. ; Kollat, P.; Martin, E.; Gottstein, W. *Chem. Berich.* **1986**, *119*, 1661-1682.



(1R,2R,3r,4S,5S)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol³: To a stirred solution of **1a** (5.0 g, 32.89 mmol) in methanol (50 mL) was added sodium borohydride (2.49 g, 65.78 mmol) portionwise at 0 °C. The reaction mixture was stirred at this temperature for 2 h and quenched with a saturated aqueous solution of NH₄Cl (30 mL). Methanol was evaporated in *vacuo*, the aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic layers were washed with brine (2 x 20 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford 4.87 g (98%) of pure hydroxyoxabicyclo, as white crystals without the need of further purification. m.p. 42-43 °C; *R_f* = 0.23 (PE/EtOAc : 8/2).

¹H NMR (300 MHz, CDCl₃): δ 6.52 (s, 2H), 4.48 (d, *J* = 3.2 Hz, 2H), 3.69 (dt, *J* = 11.3, 4.9 Hz, 1H), 2.25 (m, 2H), 1.55 (d, *J* = 11.3 Hz, 1H_{OH}), 0.99 (d, *J* = 7.4 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 136.1 (2C), 82.0 (2C), 72.6, 38.1 (2C), 12.8 (2C).



(1R,2R,3r,4S,5S)-3-methoxy-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-ene⁴: In a flame dried 500 mL one-necked round bottomed flask, under an argon atmosphere, potassium hydride (3.99 g, 99.5 mmol) was washed with pentane (3 x 5 mL) before 150 mL of THF were added. To this stirred suspension was added dropwise at 0 °C a solution of (1R,2R,3r,4S,5S)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol (7.67 g, 49.74 mmol) in 50 mL of THF. The resulting pale yellow solution was stirred at room temperature for 1 h and cooled to 0 °C. Iodomethane (14.83 g, 6.56 mL, 104 mmol) was added dropwise at this temperature and the resulting white suspension was stirred for an additional 3 h at room temperature. The reaction mixture was quenched at 0 °C by adding 5 mL of methanol, 50 mL of a saturated aqueous solution of NH₄Cl (50 mL) and 50 mL of water. The aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic layers were washed with brine (2 x 50 mL), dried (anhydrous MgSO₄), and concentrated *in vacuo*. The crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 95/5 to 90/10) to afford 7.70 g (92%) of pure methoxyoxabicyclo, as a pale yellow oil. *R_f* = 0.75 (PE/EtOAc : 8/2).

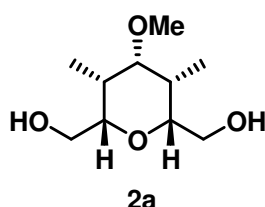
¹H NMR (300 MHz, CDCl₃): δ 6.29 (s, 2H), 4.35 (d, *J* = 3.2 Hz, 2H), 3.28 (s, 3H), 3.20 (t, *J* = 5.0 Hz, 1H), 2.23 (m, 2H), 0.92 (d, *J* = 7.4 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 133.9 (2C), 82.9, 82.0 (2C), 62.7, 38.5 (2C), 12.5 (2C).

³ Millward, D.B. ; Sammis, G. ; Waymouth, R.M. *J. Org. Chem.* **2000**, *65*, 3902-3909.

⁴ De Almeida Barbosa, L.-C. ; Culter, D. ; Mann, J. ; Crabbe, M.J. ; Kirky, G.C. ; Warhurst, D.C. *J. Chem. Soc. Perkin Trans. 1*, **1996**, 1101-1106.

General procedure for ozonolysis: To a stirred solution of alkene (10 mmol) in a 2/1.5 dichloromethane / methanol mixture (100 mL) were added few drops of Sudan III dissolved in dichloromethane. The resulting purple solution was cooled to -60°C and ozone was bubbled until the purple coloration turned to pale yellow. Air was bubbled for 5 min and then argon for 1 min to purge the remaining ozone. Sodium borohydride (1.5g, 40 mmol) was added portionwise. The reaction mixture was stirred at -60°C for 30 min, warmed up to 0°C , stirred for an additional 30 min and quenched with a saturated aqueous solution of NH_4Cl (30 mL). The aqueous layer was extracted with dichloromethane (4 x 50 mL) and the combined organic layers were washed with brine (2 x 50 mL), dried (anhydrous MgSO_4), and concentrated in *vacuo* to afford the crude product which was purified by silica gel column flash chromatography.



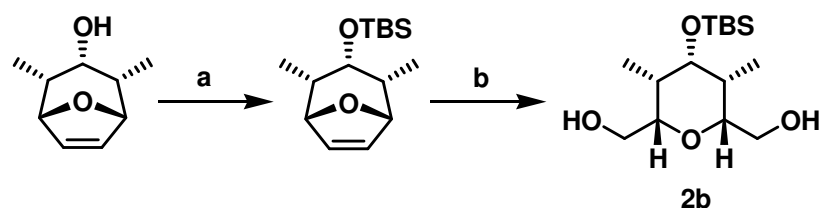
((2S,3R,4r,5S,6R)-4-methoxy-3,5-dimethyl-tetrahydro-2H-pyran-2,6-diyl)-dimethanol (2a): Following the general procedure for ozonolysis, the crude material was purified by silica gel column flash chromatography (EtOAc/MeOH, gradient elution: 100/0 to 90/10) to afford pure diol **2a** as white crystals. (78% yield); m.p. $114-115^{\circ}\text{C}$; $R_f = 0.46$ (EtOAc : 100%).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 4.30 (brs, 2H_{OH}), 3.77 (m, 2H), 3.52 (m, 4H), 3.35 (t, $J = 5.3$ Hz, 1H), 3.31 (s, 3H), 2.03 (m, 2H), 0.84 (d, $J = 7.2$ Hz, 6H).

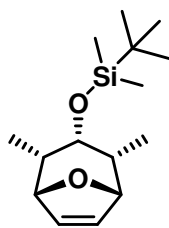
$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 81.08, 81.03 (2C), 64.3 (2C), 55.3, 33.6 (2C), 8.5 (2C)

Elemental analysis: calcd for $\text{C}_{16}\text{H}_{24}\text{O}_4$ C 58.80%, H 9.87%, found C 56.85%, H 10.02%.

Synthesis of diol **2b**



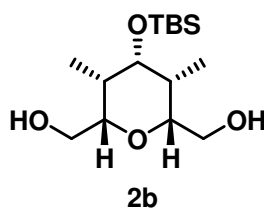
a- KH, THF, 0°C then TBSOTf, 0°C to rt. **b-** O_3 , CH_2Cl_2 / MeOH (2/1.5) then NaBH_4 (4 equiv) -60°C to 0°C .



((1R,2S,3s,4R,5S)-3-(tert-butyldimethylsilyloxy)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene⁵: In a flame dried 25 mL one-necked round bottomed flask, under an argon atmosphere, potassium hydride (60 mg, 1.5 mmol) was washed with pentane (3 x 1 mL) before 2 mL of THF were added. To this stirred suspension was added dropwise at 0°C a solution of (1R,2R,3r,4S,5S)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (154 mg, 1.0 mmol) in 1.5 mL of THF. The resulting pale yellow solution was stirred at room temperature for 1 h and cooled to 0°C. A solution of TBSOTf (317 mg, 1.2 mmol) in 1.5 mL of THF were added dropwise at this temperature and the resulting white suspension was stirred for an additional 12 h at room temperature. The reaction mixture was quenched at 0°C by adding 0.5 mL of methanol, 5 mL of a saturated aqueous solution of NH₄Cl and 5 mL of water. The aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic layers were washed with brine (2 x 5 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo*. The crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 98/2 to 90/10) to afford 149 mg (55%) of pure silyloxyoxabicyclo, as a colourless oil. *Rf* = 0.85 (PE/EtOAc : 8/2).

¹H NMR (300 MHz, CDCl₃): δ 6.23 (s, 2H), 4.36 (d, *J* = 2.6 Hz, 2H), 3.86 (t, *J* = 4.2 Hz, 1H), 2.14 (m, 2H), 0.90 (s, 9H), 0.86 (d, *J* = 7.4 Hz, 6H) -0.03 (s, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 133.6 (2C), 82.5 (2C), 72.0, 38.5 (2C), 26.1 (3C), 18.5, 14.1 (2C), -3.6 (2C).



((2S,3R,4r,5S,6R)-4-(tert-butyldimethylsilyloxy)-3,5-dimethyl-tetrahydro-2H-pyran-2,6-diyl)-dimethanol (2b) : Following the general procedure for ozonolysis, the crude material was purified by silica gel column flash chromatography (EtOAc/MeOH, gradient elution: 100/0 to 90/10) to afford pure **2b** as white crystals. (81% yield); m.p. 89-90 °C; *Rf* = 0.56 (EtOAc : 100%).

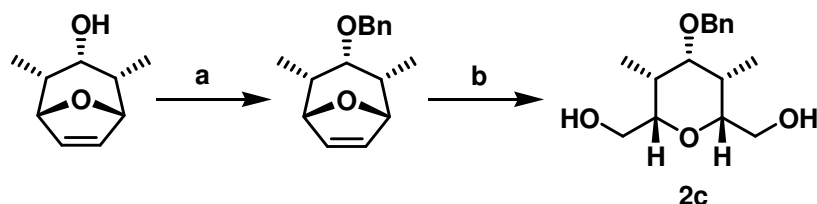
¹H NMR (300 MHz, CDCl₃): δ 3.85 (brs, 2H_{OH}), 3.83 (t, *J* = 5.5 Hz, 1H), 3.78 (m, 2H), 3.51 (m, 4H), 1.77 (m, 2H) 0.90 (s, 9H), 0.86 (d, *J* = 7.2 Hz, 6H) 0.04 (s, 6H).

⁵ Lautens, M.; Abd-El-Aziz, A.S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305-5306.

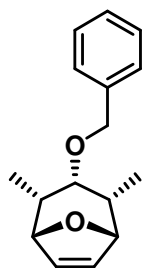
^{13}C NMR (75 MHz, CDCl_3): δ 81.0 (2C), 72.7, 64.4 (2C), 37.4 (2C), 25.7 (3C), 18.1, 8.5 (2C), -4.8 (2C).

HRMS (ESI TOF) calcd for $\text{C}_{15}\text{H}_{33}\text{O}_4\text{Si}$ ($\text{M}+\text{H}$) $^+$ 305.2143, found 305.2143.

Synthesis of diol **2c**



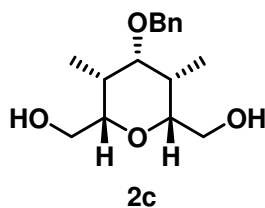
a- KH, THF, 0°C then BnBr and *n*-Bu₄NI (cat.), 0°C to rt. **b**- O₃, CH₂Cl₂ / MeOH (2/1.5) then NaBH₄ (4 equiv) -60°C to 0°C.



(1R,2R,3r,4S,5S)-3-(benzyloxy)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-ene²: In a flame dried 250 mL one-necked round bottomed flask, under an argon atmosphere, potassium hydride (960 mg, 23.9 mmol) was washed with pentane (3 x 1 mL) before 40 mL of THF were added. To this stirred suspension was added dropwise at 0°C a solution of (1R,2R,3r,4S,5S)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol (2.46 g, 15.9 mmol) in 20 mL of THF. The resulting pale yellow solution was stirred at room temperature for 1 h and cooled to 0°C. A solution of benzyl bromide (3.55 g, 2.53 mL, 20.7 mmol) in 20 mL of THF were added dropwise at this temperature followed by tetrabutylammonium iodide (600 mg, 1.6 mmol) and the resulting white suspension was stirred for an additional 12 h at room temperature. The reaction mixture was quenched at 0°C by adding 2 mL of methanol, 20 mL of a saturated aqueous solution of NH₄Cl and 20 mL of water. The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic layers were washed with brine (2 x 20 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo*. The crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 98/2 to 90/10) to afford 3.31g (85%) of pure benzyloxyoxabicyclo, as a colourless oil. *R*_f = 0.67 (PE/EtOAc : 8/2).

^1H NMR (300 MHz, CDCl_3): δ 7.33-7.29 (m, 5H), 6.32 (s, 2H), 4.42 (s, 2H), 4.40 (d, *J* = 3.2 Hz, 2H), 3.53 (t, *J* = 4.7 Hz, 1H), 2.28 (m, 2H), 0.94 (d, *J* = 7.4 Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3): δ 139.2, 133.8 (2C), 128.1 (2C), 127.0, 126.8 (2C), 82.1 (2C), 81.2, 75.9, 38.85 (2C), 12.8 (2C).



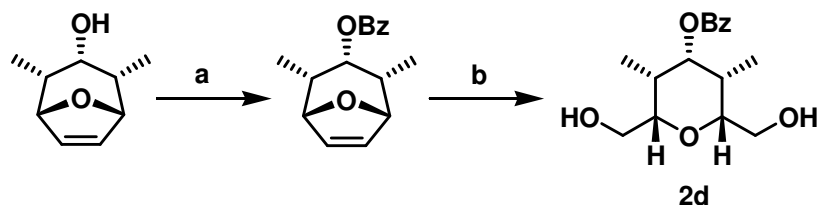
((2*S*,3*R*,4*r*,5*S*,6*R*)-4-(benzyloxy)-3,5-dimethyl-tetrahydro-2*H*-pyran-2,6-diyl)-dimethanol (2c**):** Following the general procedure for ozonolysis, the crude material was purified by silica gel column flash chromatography (EtOAc/MeOH, gradient elution: 100/0 to 90/10) to afford pure **2c** as white crystals. (89% yield); m.p. 121-122°C; *R*_f = 0.48 (EtOAc : 100%).

¹H NMR (300 MHz, CDCl₃): δ 7.35-7.25 (m, 5H), 4.51 (s, 2H), 4.35 (brs, 1H_{OH}), 3.79 (dd, *J* = 11.7, 9.6 Hz, 2H), 3.58 (t, *J* = 5.3 Hz, 1H), 3.52-3.44 (m, 4H), 2.07 (m, 2H), 0.92 (d, *J* = 7.2 Hz, 6H).

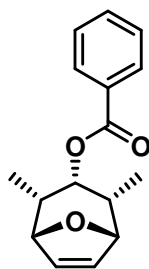
¹³C NMR (75 MHz, CDCl₃): δ 138.6, 128.3 (2C), 127.4, 127.2 (2C), 81.0 (2C), 78.8, 69.1, 64.26 (2C), 33.9 (2C), 8.8 (2C)

HRMS (ESI TOF) calcd for C₁₆H₂₅O₄ (M+H)⁺ 281.1747, found 281.1741.

Synthesis of diol **2d**



a- KH, THF, 0°C then BzCl, 0°C to rt. **b-** O₃, CH₂Cl₂ / MeOH (2/1.5) then NaBH₄ (4 equiv) -60°C to 0°C.



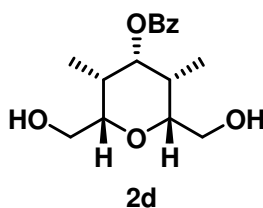
(1*R*,2*S*,3*s*,4*R*,5*S*)-3-(benzyloxy)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-ene: In a flame dried 250 mL one-necked round bottomed flask, under an argon atmosphere, potassium hydride (1.91 g, 47.7 mmol) was washed with pentane (3 x 3 mL) before 60 mL of THF were added. To this stirred suspension was added a solution of (1*R*,2*R*,3*r*,4*S*,5*S*)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol (4.32 g, 28.0 mmol) in 30 mL of THF dropwise at 0°C. The resulting pale yellow solution was stirred at room temperature for 1 h and cooled to 0°C. A solution of benzoyl chloride (6.70 g,

5.55 mL, 47.7 mmol) in 30 mL of THF were added dropwise at this temperature and the resulting white suspension was stirred for an additional 12 h at room temperature. The reaction mixture was quenched at 0°C by adding 3 mL of methanol, 30 mL of a saturated aqueous solution of NH₄Cl and 30 mL of water. The aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic layers were washed with brine (2 x 30 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo*. The crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 98/2 to 80/20) to afford 6.01g (84%) of pure benzyloxyoxabicyclo, as pale yellow crystals. m.p. 95-96°C; *R_f* = 0.61 (PE/EtOAc : 8/2).

¹H NMR (300 MHz, CDCl₃): δ 8.05 (dt, *J* = 7.3, 1.3 Hz, 2H), 7.58 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.46 (t, *J* = 7.3, 2H), 6.51 (s, 2H), 5.53 (t, *J* = 4.9 Hz, 1H), 4.52 (d, *J* = 3.2 Hz, 2H), 2.46 (m, 2H), 0.83 (d, *J* = 7.4 Hz, 6H)

¹³C NMR (75 MHz, CDCl₃): δ 166.4, 133.7 (2C), 132.9, 130.1, 129.6 (2C), 128.4 (2C), 81.8 (2C), 72.8, 36.7 (2C), 12.3 (2C).

HRMS (ESI TOF) calcd for C₁₆H₁₉O₃ (M+H)⁺ 259.1329, found 259.1328.



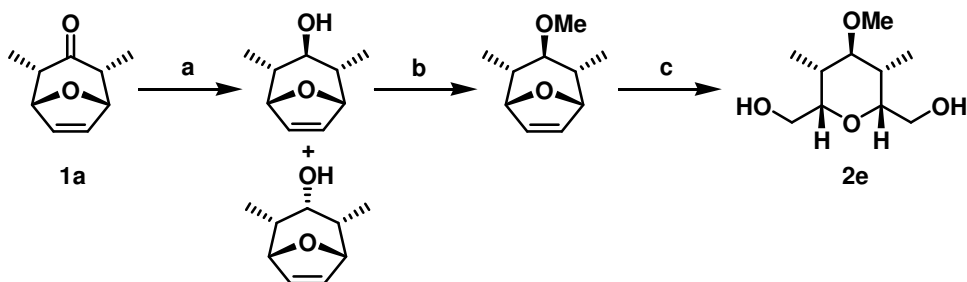
((2*R*,3*S*,4*r*,5*R*,6*S*)-3-(benzyloxy)-3,5-dimethyl-tetrahydro-2H-pyran-2,6-diyl)-dimethanol (2d**):** Following the general procedure for ozonolysis, the crude material was purified by silica gel column flash chromatography (EtOAc/MeOH, gradient elution: 100/0 to 90/10) to afford pure the diol **2d** as white crystals. (77% yield); m.p. 175-176°C; *R_f* = 0.40 (EtOAc : 100%).

¹H NMR (300 MHz, CDCl₃): δ 8.08 (dt, *J* = 7.2, 1.3 Hz, 2H), 7.58 (tt, *J* = 7.2, 1.3 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 5.26 (t, *J* = 5.7 Hz, 1H), 3.83-3.71 (m, 6H), 3.60-3.56 (m, 2H), 2.24 (m, 2H), 1.05 (d, *J* = 7.4 Hz, 6H).

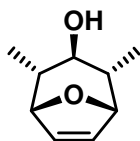
¹³C NMR (75 MHz, CDCl₃): δ 165.4, 133.1, 130.3, 129.5 (2C), 128.4 (2C), 80.7 (2C), 74.8, 64.1 (2C), 34.0 (2C), 9.5 (2C).

HRMS (ESI TOF) calcd for C₁₆H₂₃O₅ (M+H)⁺ 295.1540, found 295.1543.

Synthesis of diol **2e**



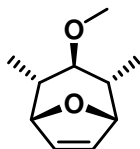
a- NaBH₄, *n*-BuOH, 0°C. **b-** KH, THF, 0°C then MeI. **c-** O₃, CH₂Cl₂ / MeOH (2/1.5) then NaBH₄ (4 equiv) -60°C to 0°C.



(1*R*,2*R*,3*s*,4*S*,5*S*)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol⁶: To a stirred solution of **1a** (8.0 g, 52.56 mmol) in *n*-butan-1-ol (240 mL) was added sodium borohydride (5.97 g, 157 mmol) portionwise at room temperature. The reaction mixture was stirred at this temperature for 24 h and quenched with a saturated aqueous solution of NH₄Cl (200 mL). The layers were separated, the aqueous one was extracted with dichloromethane (3 x 70 mL) and the combined organic layers were washed with brine (2 x 50 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford a 61/39 mixture of the two diastereomers with no trace of starting material according to ¹H NMR of the crude product. These two compounds were separated by silica gel column flash chromatography (PE/EtOAc mixture : 70/30) to afford 2.64 g of pure (1*R*,2*R*,3*s*,4*S*,5*S*)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol as white crystals, 4.23 g of (1*R*,2*R*,3*r*,4*S*,5*S*)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol and 980 mg of the mixture of both diastereomers (97% global yield). m.p. 72-73°C ; *R*_f = 0.13 (PE/EtOAc : 8/2).

¹H NMR (300 MHz, CDCl₃): δ 6.22 (s, 2H), 4.55 (d, *J* = 3.6 Hz, 2H), 2.87 (t, *J* = 8.7 Hz, 1H), 1.67 (dq, *J* = 8.7, 7.0, 3.6 Hz 2H), 1.41 (brs, 1H_{OH}), 0.95 (d, *J* = 7.0 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 130.8 (2C), 82.7 (2C), 77.6, 40.4 (2C), 14.0 (2C).



(1*R*,2*R*,3*s*,4*S*,5*S*)-3-methoxy-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-ene: In a flame dried 100 mL one-necked round bottomed flask, under an argon atmosphere, sodium hydride (1.03 g, 42.8 mmol) was washed with pentane (3 x 3 mL) before 35 mL of THF were added. To this stirred suspension was added a solution of

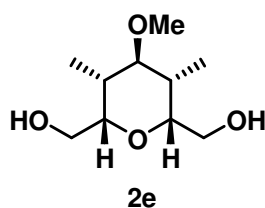
⁶ Treu, J. ; Hoffmann, H.M. *J. Org. Chem.* **1997**, *62*, 4650-4652.

(1*R*,2*R*,3*s*,4*S*,5*S*)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol (2.20 g, 14.28 mmol) in 10 mL of freshly distilled THF dropwise at 0°C. The resulting pale yellow solution was stirred at room temperature for 1 h and cooled to 0°C. Neat iodomethane (4.05 g, 1.77 mL, 28.56 mmol) was added dropwise at this temperature and the resulting white suspension was stirred for an additional 12 h at room temperature. The reaction mixture was quenched at 0°C by adding a saturated aqueous solution of NH₄Cl (20 mL) and 20 mL of water. The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic layers were washed with brine (2 x 20 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo*. The crude product was purified by silica gel column flash chromatography (PE/ EtOAc mixture, gradient elution: 98/2 to 90/10) to afford 2.32 g (97%) of pure methoxyoxabicyclo, as a colourless oil. *R_f* = 0.60 (PE/EtOAc : 9/1).

¹H NMR (300 MHz, CDCl₃): δ 6.20 (s, 2H), 4.50 (d, *J* = 3.6 Hz, 2H), 3.40 (s, 3H), 2.55 (t, *J* = 8.9 Hz, 1H), 1.81 (m, 2H), 0.92 (d, *J* = 7.0 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 130.7 (2C), 87.1, 82.7 (2C), 59.7, 38.0 (2C), 14.5 (2C).

HRMS (ESI TOF) calcd for C₁₀H₁₇O₂ (M+H)⁺ 169.1223, found 169.1223.



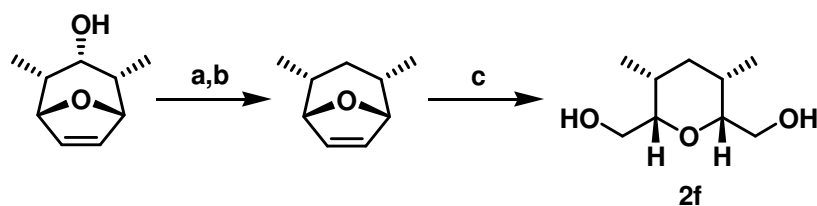
((2*S*,3*R*,4*s*,5*S*,6*R*)-4-methoxy-3,5-dimethyl-tetrahydro-2H-pyran-2,6-diyl)-dimethanol (2e**):** Following the general procedure for ozonolysis, the crude material was purified by silica gel column flash chromatography (EtOAc/MeOH, gradient elution: 100/0 to 90/10) to afford pure diol **2e** as a pale yellow oil. (72% yield); *R_f* = 0.41 (EtOAc : 100%).

¹H NMR (300 MHz, CDCl₃): δ 4.01 (brs, 2H_{OH}), 3.90 (dt, *J* = 9.3, 2.6 Hz, 2H), 3.70 (dd, *J* = 11.7, 9.3 Hz, 2H), 3.48 (dd, *J* = 11.7, 2.6 Hz, 2H), 3.32 (s, 3H), 3.03 (t, *J* = 2.0 Hz 1H) 1.84 (m, 2H), 0.94 (d, *J* = 7.5 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 86.3, 77.49 (2C), 64.4 (2C), 56.5, 33.2 (2C), 12.5 (2C).

HRMS (ESI TOF) calcd for C₁₀H₂₁O₄ (M+H)⁺ 205.1434, found 205.1439.

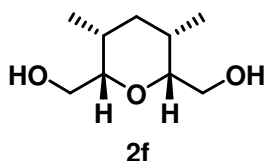
Synthesis of diol **2f**



a- KH, CS₂ then MeI, THF, 0 °C to rt. **b-** Bu₃SnH, AIBN (cat.), toluene, 100 °C. **c-** O₃, CH₂Cl₂ / MeOH (2/1.5) then NaBH₄ (4 equiv) -60 °C to 0 °C.



(1S,2R,4S,5R)-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-ene: this compound was prepared according to the literature procedure described by De Almeida *et al.*⁴



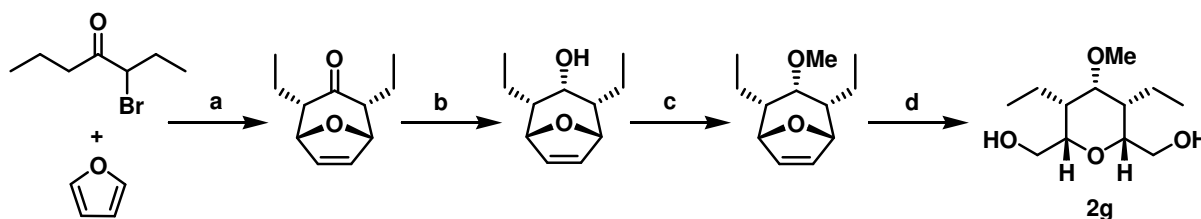
((2S,3R,5S,6R)-3,5-dimethyl-tetrahydro-2H-pyran-2,6-diyl)dimethanol: Following the general procedure for ozonolysis, the crude material was purified by silica gel column flash chromatography (EtOAc/MeOH, gradient elution: 100/0 to 90/10) to afford pure diol **2f** as white crystals (50% yield); m.p. 102-103 °C; *R_f* = 0.51 (EtOAc : 100%).

¹H NMR (300 MHz, CDCl₃): δ 3.78-3.58 (m, 4H), 3.50-3.46 (m, 2H), 3.17 (brs, 2H_{OH}), 2.01 (dt, *J* = 13.8, 5.7 Hz, 1H), 1.73 (m, 2H), 1.51 (dt, *J* = 13.8, 1.9 Hz, 1H), 0.97 (d, *J* = 7.4 Hz, 6H).

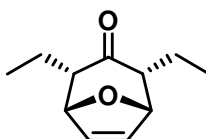
¹³C NMR (75 MHz, CDCl₃): δ 81.9 (2C), 64.6 (2C), 38.3, 29.0 (2C), 15.8 (2C).

HRMS (ESI TOF) calcd for C₉H₁₉O₃ (M+H)⁺ 175.1329, found 175.1324.

Synthesis of diol **2g**



a- Et₃N, H₂O, rt. **b-** NaBH₄, MeOH, 0°C. **c-** KH, THF, 0°C then MeI. **d-** O₃, CH₂Cl₂ / MeOH (2/1.5) then NaBH₄ (4 equiv) –60°C to 0°C.

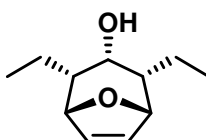


(1*R*,2*S*,4*R*,5*S*)-2,4-diethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one⁷: To a vigorously stirred emulsion of 3-bromoheptan-4-one (14.12 g, 73.16 mmol) and furan (21.3 mL, 292.6 mmol) in distilled water (130 mL) was added dropwise over a period of 30 min triethylamine (11.2 mL, 80.5 mmol). The resulting orange emulsion was then stirred at room temperature for 12 h. The reaction mixture was subsequently quenched with a saturated aqueous solution of NH₄Cl (200 mL). The aqueous layer was extracted with dichloromethane (3 x 200 mL) and the combined organic layers were washed with brine (2 x 200 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford an orange oil. This crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 95/5 to 90/10) to afford 1.97 g of pure oxabicyclic, (15%) as a pale yellow oil. *R_f* = 0.55 (PE/EtOAc : 9/1).

¹H NMR (300 MHz, CDCl₃): δ 6.26 (s, 2H), 4.95 (d, *J* = 4.5 Hz, 2H), 2.58 (m, 2H), 1.82 (m, 2H), 1.05 (m, 2H), 0.99 (t, *J* = 4.9 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 208.2, 133.1 (2C), 80.9 (2C), 57.1 (2C), 18.5 (2C), 12.0 (2C).

HRMS (ESI TOF) calcd for C₁₁H₁₇O₂ (M+H)⁺ 181.1223, found 181.1224.



(1*R*,2*R*,3*r*,4*S*,5*S*)-2,4-diethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol: To a stirred solution of (1*R*,2*S*,4*R*,5*S*)-2,4-diethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (815 mg, 4.5 mmol) in methanol (25 mL) was added portionwise at 0°C sodium borohydride (345

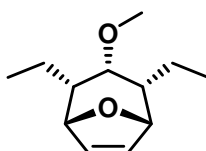
⁷ Herter, R. ; Foehlich, B. *Synthesis* **1982**, 976-979.

mg, 9.0 mmol). The reaction mixture was stirred at this temperature for 2 h and quenched with a saturated aqueous solution of NH_4Cl (20 mL). Methanol was evaporated in *vacuo*, the aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were washed with brine (2 x 5 mL), dried (anhydrous MgSO_4), and concentrated in *vacuo* to afford 815 mg (99%) of pure hydroxyoxabicyclo, as white crystals without the need for further purification; m.p. 28-30 °C; R_f = 0.47 (PE/EtOAc : 8/2).

^1H NMR (300 MHz, CDCl_3): δ 6.48 (s, 2H), 4.57 (d, J = 3.2 Hz, 2H), 3.90 (t, J = 4.1 Hz, 1H), 1.96 (m, 2H), 1.61 (brs, 1H_{OH}), 1.43-1.37 (m, 4H), 0.99 (t, J = 7.3 Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3): δ 136.1 (2C), 81.3 (2C), 68.9, 45.1 (2C), 20.7 (2C), 11.6 (2C).

HRMS (ESI TOF) calcd for $\text{C}_{11}\text{H}_{19}\text{O}_2$ ($\text{M}+\text{H}$)⁺ 183.1380, found 183.1374.

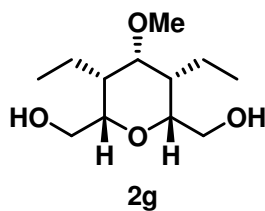


(1*R*,2*R*,3*r*,4*S*,5*S*)-2,4-diethyl-3-methoxy-8-oxa-bicyclo[3.2.1]oct-6-ene: In a flame dried 100 mL one-necked round bottomed flask, under an argon atmosphere, potassium hydride (280 mg, 6.91 mmol) was washed with pentane (3 x 1 mL) before 20 mL of THF were added. To this stirred suspension was added dropwise at 0 °C a solution of (1*R*,2*R*,3*r*,4*S*,5*S*)-2,4-diethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol (630 mg, 3.45 mmol) in 10 mL of THF. The resulting pale yellow solution was stirred at room temperature for 1 h and cooled to 0 °C. Neat iodomethane (981 mg, 430 μL , 6.91 mmol) was added dropwise at this temperature and the resulting white suspension was stirred for an additional 4 h at room temperature. The reaction mixture was quenched at 0 °C by adding 1 mL of methanol, 20 mL of a saturated aqueous solution of NH_4Cl and 20 mL of water. The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic layers were washed with brine (2 x 20 mL), dried (anhydrous MgSO_4), and concentrated in *vacuo*. The crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 98/2 to 90/10) to afford 620 mg (91%) of pure methoxyoxabicyclo, as a colourless oil. R_f = 0.50 (PE/EtOAc : 9/1).

^1H NMR (300 MHz, CDCl_3): δ 6.26 (s, 2H), 4.53 (d, J = 3.2 Hz, 2H), 3.41 (t, J = 4.6 Hz, 1H), 3.34 (s, 3H), 1.98 (m, 2H), 1.41-1.35 (m, 4H), 0.98 (t, J = 7.5 Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3): δ 133.7 (2C), 81.2, 80.6 (2C), 63.2, 46.3 (2C), 20.5 (2C), 12.1 (2C).

HRMS (ESI TOF) calcd for $\text{C}_{12}\text{H}_{21}\text{O}_2$ ($\text{M}+\text{H}$)⁺ 197.1536, found 197.1531.



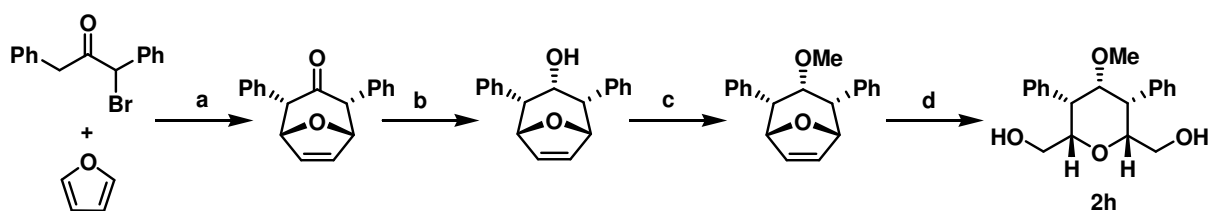
((2S,3R,4r,5S,6R)-3,5-diethyl-4-methoxy-tetrahydro-2H-pyran-2,6-diyol)-dimethanol (2g): Following the general procedure for ozonolysis, the crude material was purified by silica gel column flash chromatography (EtOAc/MeOH, gradient elution: 100/0 to 90/10) to afford pure diol **2g** as white crystals. (70% yield); m.p. 94-95 °C; $R_f = 0.27$ (EtOAc : 100%).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 4.60 (brs, 2 H_{OH}), 3.79 (t, $J = 10.4$ Hz, 2H), 3.59-3.49 (m, 4H), 3.37 (t, $J = 4.51$ Hz, 1H), 3.31 (s, 3H), 1.69 (m, 2H), 1.55 (m, 2H), 1.17 (m, 2H), 0.84 (t, $J = 7.4$ Hz, 6H).

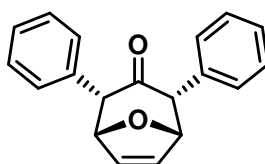
$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 82.3, 82.2 (2C), 64.4 (2C), 55.6, 42.6 (2C), 16.6 (2C), 15.8 (2C).

HRMS (ESI TOF) calcd for $\text{C}_{12}\text{H}_{25}\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 233.1747, found 233.1747.

Synthesis of diol **2h**



a- Et_3N , H_2O , rt. **b-** NaBH_4 , MeOH , 0°C. **c-** KH , THF , 0°C then MeI . **d-** O_3 , CH_2Cl_2 / MeOH (2/1.5) then NaBH_4 (4 equiv) -60°C to 0°C.



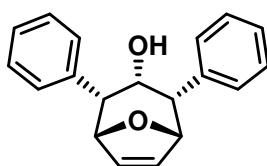
(1R,2S,4R,5S)-2,4-diphenyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one: To a vigorously stirred emulsion of 1-bromo-1,3-diphenylpropan-2-one (4.22 g, 14.6 mmol) and furan (4.2 mL, 58.4 mmol) in distilled water (14 mL) was added dropwise over a period of 30 min triethylamine (2 mL, 15.3). The resulting orange emulsion was then stirred at room temperature for 12h. The reaction mixture was subsequently quenched with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were washed with

brine (2 x 20 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford the crude product as an orange oil. The residue was purified by flash chromatography on silica gel (PE/EtOAc : 95/5 to 8/2). The oxabicyclo was obtained as white crystals (1.63 g) in 43% yield. m.p. 129-130 °C ; *R*_f = 0.49 (PE/EtOAc : 8/2).

¹H NMR (300 MHz, CDCl₃): δ 7.40-7.33 (m, 6H), 7.19 (m, 4H), 6.50 (s, 2H), 5.09 (d, *J* = 4.6 Hz, 2H), 4.17 (d, *J* = 4.6 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃): δ 204.5, 134.7 (2C), 133.7 (2C), 129.9 (4C), 128.5 (4C), 127.4 (2C), 83.1 (2C), 61.4 (2C).

HRMS (ESI TOF) calcd for C₁₉H₂₀NO₂ (M+NH₄)⁺ 294.1489, found 294.1487.

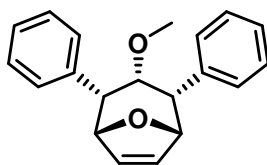


(1*R*,2*R*,3*r*,4*S*,5*S*)-2,4-diphenyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol: To a stirred solution of (1*R*,2*S*,4*R*,5*S*)-2,4-diphenyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (815 mg, 4.5 mmol) in methanol (25 mL) was added portionwise at 0 °C sodium borohydride (345 mg, 9.0 mmol). The reaction mixture was stirred at this temperature for 2 h and quenched with a saturated aqueous solution of NH₄Cl (20 mL). The methanol was concentrated in *vacuo* before the aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were washed with brine (2 x 5 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford 815 mg (99%) of the pure hydroxyoxabicyclo, as white crystals without the need for further purification. m.p. 187-188 °C ; *R*_f = 0.31 (PE/EtOAc : 8/2).

¹H NMR (300 MHz, CDCl₃): δ 7.37-7.23 (m, 10H), 6.77 (s, 2H), 4.97 (d, *J* = 3.0 Hz, 2H), 4.49 (dt, *J* = 5.9, 4.4 Hz, 1H), 3.64 (dd, *J* = 4.4, 3.0 Hz, 2H), 1.39 (d, *J* = 5.9 Hz, 1H_{OH}).

¹³C NMR (75 MHz, CDCl₃): δ 138.5 (2C), 134.9 (2C), 128.7 (4C), 128.5 (4C), 126.8 (2C), 80.6 (2C), 72.1, 49.1 (2C).

HRMS (ESI TOF) calcd for C₁₉H₂₂NO₂ (M+NH₄)⁺ 296.1645, found 296.1642.



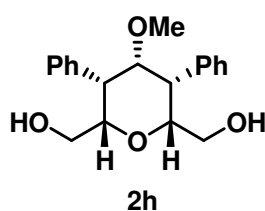
(1*R*,2*R*,3*r*,4*S*,5*S*)-3-methoxy-2,4-diphenyl-8-oxa-bicyclo[3.2.1]oct-6-ene: In a flame dried 25 mL one-necked round bottomed flask, under an argon atmosphere,

potassium hydride (115 mg, 2.9 mmol) was washed with pentane (3 x 1 mL) before 8 mL of THF were added. To this stirred suspension was added portionwise at 0°C pure (1*R*,2*R*,3*r*,4*S*,5*S*)-2,4-diphenyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol (400 mg, 1.43 mmol). The resulting pale yellow solution was stirred at room temperature for 1 h and cooled to 0°C. Iodomethane (304 mg, 133 μ L, 2.14 mmol) was added dropwise at this temperature and the resulting white suspension was stirred for an additional 14 h at room temperature. The reaction mixture was quenched at 0°C by adding 1 mL of methanol, 10 mL of a saturated aqueous solution of NH₄Cl and 10 mL of water. The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (2 x 10 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo*. The crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 98/2 to 90/10) to afford 345 mg (83%) of the pure methoxyoxabicyclo, as white crystals. m.p. 121-122°C; *R*_f = 0.80 (PE/EtOAc : 8/2).

¹H NMR (300 MHz, CDCl₃): δ 7.34-7.25 (m, 10H), 6.76 (s, 2H), 4.70 (d, *J* = 4.7 Hz, 2H), 3.76 (t, *J* = 4.4 Hz, 1H), 3.59 (dd, *J* = 4.7, 4.4 Hz, 2H), 2.34 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 138.9 (2C), 134.4 (2C), 129.4 (4C), 128.2 (4C), 126.6 (2C), 83.8, 81.0 (2C), 61.6, 50.1 (2C).

HRMS (ESI TOF) calcd for C₂₀H₂₁O₂ (M+H)⁺ 293.1536, found 293.1537.



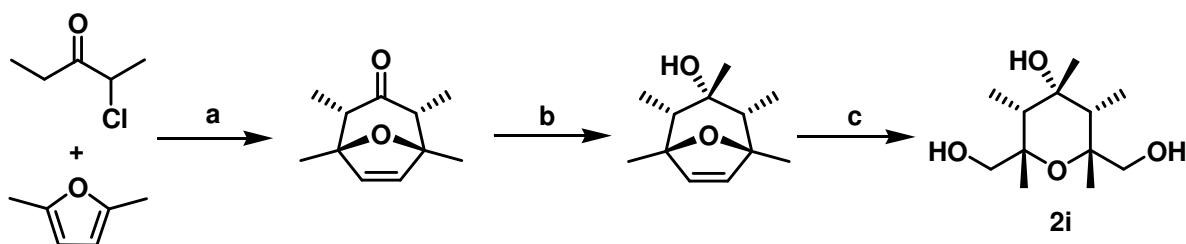
((2*S*,3*R*,4*r*,5*S*,6*R*)-4-methoxy-3,5-diphenyl-tetrahydro-2H-pyran-2,6-diyl)-dimethanol (2h**):** Following the general procedure for ozonolysis, the crude material was purified by silica gel column flash chromatography (EtOAc/MeOH, gradient elution: 100/0 to 90/10) to afford pure diol **2h** as white crystals. (94% yield); m.p. 190-191°C; *R*_f = 0.50 (EtOAc : 100%).

¹H NMR (300 MHz, CDCl₃): δ 7.42-7.39 (m, 4H), 7.28-7.22 (m, 6H), 4.27 (ddd, *J* = 6.7, 6.6, 2.8 Hz, 2H), 3.85 (t, *J* = 4.7 Hz, 1H), 3.74 (dd, *J* = 6.7, 11.5 Hz, 2H), 3.46 (m, 2H), 3.42 (dd, *J* = 6.6, 4.7 Hz, 2H), 3.37 (brs, 2H_{OH}), 2.91 (s, 3H).

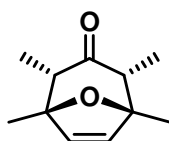
¹³C NMR (75 MHz, CDCl₃): δ 136.8 (2C), 130.3 (4C), 128.0 (4C), 127.0 (2C), 80.9, 78.4 (2C), 63.1 (2C), 59.8, 47.4 (2C).

HRMS (ESI TOF) calcd for C₂₀H₂₅O₄ (M+H)⁺ 329.1747, found 329.1755.

Synthesis of diol **2i**



a- Et₃N, H₂O, rt. **b-** MeLi, Et₂O, 0 °C. **c-** O₃, CH₂Cl₂ / MeOH (2/1.5) then NaBH₄ (4 equiv) –60 °C to 0 °C.

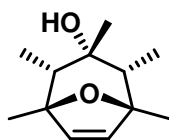


(1R,2S,4R,5S)-1,2,4,5-tetramethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one: To a vigorously stirred emulsion of 2-chloropentan-3-one (31.0 g, 257 mmol) and 2,5-dimethylfuran (22.5 g, 25 mL, 234 mmol) in distilled water (260 mL) was added dropwise over a period of 30 min triethylamine (26.0 g, 36 mL, 257 mmol). The resulting orange emulsion was then stirred at room temperature for 12 h. The reaction mixture was subsequently quenched with a saturated aqueous solution of NH₄Cl (50 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were washed with brine (2 x 50 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford the crude product as an orange oil which was cooled to –20 °C for 12 h. The resulting white crystals were filtered off, washed with cold pentane and dried in high vacuum. The filtrate was concentrated in *vacuo* and the procedure was repeated once. The second filtrate was concentrated in *vacuo* and the rest of the crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 95/5 to 90/10) to afford a total of 10.55 g (23 %) of oxabicyclic as white crystals; m.p. 60-61 °C; *R_f* = 0.64 (PE/EtOAc : 8/2).

¹H NMR (300 MHz, CDCl₃): δ 6.01 (s, 2H), 2.44 (q, *J* = 7.1 Hz, 2H), 1.48 (s, 6H), 1.01 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 209.5, 136.1 (2C), 87.4 (2C), 54.8 (2C), 21.9 (2C), 10.2 (2C).

HRMS (ESI TOF) calcd for C₁₁H₁₇O₂ (M+H)⁺ 181.1223, found 181.1221.

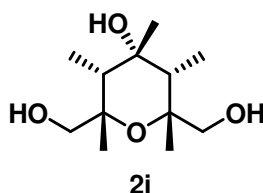


(1R,2R,3r,4S,5S)-1,2,3,4,5-pentamethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol: To a stirred solution of (1R,2S,4R,5S)-1,2,4,5-tetramethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (800 mg, 4.43 mmol) in dry diethyl ether (20 mL) was added dropwise at 0°C methyl lithium 1.6 M solution in diethyl ether (3.05 mL, 4.88 mmol). The reaction mixture was stirred for 10 min at this temperature and then quenched with a saturated aqueous solution of NH₄Cl (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (2 x 10 mL), dried (anhydrous MgSO₄), and concentrated *in vacuo* to afford pure hydroxyoxabicyclic, 865 mg, (99%) as a white powder without the need for further purification. m.p. 81-82°C; *R_f* = 0.33 (PE/EtOAc : 9/1).

¹H NMR (300 MHz, CDCl₃): δ 6.22 (s, 2H), 1.86 (brs, 1H_{OH}), 1.81 (q, *J* = 7.1 Hz, 2H), 1.34 (s, 6H), 1.09 (s, 3H), 0.94 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 138.0 (2C), 87.0 (2C), 73.4, 48.4 (2C), 27.2, 22.4 (2C), 10.9 (2C).

HRMS (ESI TOF) calcd for C₁₂H₂₁O₂ (M+Na)⁺ 197.1536, found 197.1533.



(2R,3S,4r,5R,6S)-2,6-bis-hydroxymethyl-2,3,4,5,6-pentamethyltetrahydropyran-4-ol (2i): Following the general procedure for ozonolysis, the crude material was purified by silica gel column flash chromatography (EtOAc/MeOH, gradient elution: 100/0 to 80/20) to afford pure triol **2i** as white crystals. (40% yield); m.p. 137-138°C; *R_f* = 0.13 (PE/EtOAc : 1/1).

¹H NMR (300 MHz, CDCl₃): δ 4.08 (d, *J* = 11.7 Hz, 2H), 3.35 (d, *J* = 11.7 Hz, 2H), 1.65 (q, *J* = 7.2 Hz, 2H), 1.26 (s, 6H), 1.18 (s, 3H), 1.05 (d, *J* = 7.2 Hz, 6H).

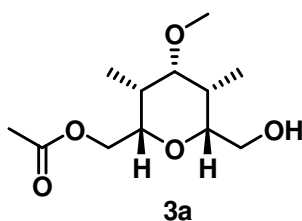
¹³C NMR (75 MHz, CDCl₃): δ 77.9 (2C), 70.8, 65.9 (2C), 47.8 (2C), 27.7 (2C), 26.1, 9.9 (2C).

HRMS (ESI TOF) calcd for C₁₂H₂₄O₄ (M+H)⁺ 233.1747, found 233.1749.

III- Enantioselective desymmetrization of diols **2a-2i**

General procedure for the synthesis of racemic monoacetate: To a stirred solution of *meso* diol (1.0 mmol) in dry dichloromethane (10 mL) were successively added at 0°C triethylamine (121 mg, 168 μ L, 1.2 mmol), DMAP (25 mg, 0.2 mmol) and acetic anhydride (102 mg, 95 μ L, 1.0 mmol). The solution was stirred at this temperature for 1 h and then 12 h at room temperature. The reaction mixture was then quenched with a saturated aqueous solution of NH₄Cl (10 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were washed with brine (2 x 5 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford a mixture of monoacetate (intermediate polar compound), diacetate (less polar compound) and unreacted starting material (most polar compound). The desired monoacetate was isolated by silica gel column flash chromatography (EP/EtOAc mixture, gradient elution: 80/20 to 50/50).

General Procedure for Lipase Screening for desymmetrization of tetrahydropyran diols **2a-i:** The lipase (30 mg) was added to a solution of **2a** (50 mg, 0.245 mmol) in *i*Pr₂O (2 mL) and vinyl acetate (2 mL) and the mixture was stirred magnetically in a hermetically stoppered one-necked flask at room temperature. The course of the reaction was monitored by TLC. After the period indicated in Table 1, the reaction mixture was filtered through a pad of Celite ®, and the cake was washed with dry Et₂O. The filtrate was concentrated in *vacuo* and purified by flash chromatography on a silica gel column. Results of the lipase-mediated acylations are reported in Table 1. As indicated in Table 1, a chiral HPLC analysis showed that the formed acetate **3a** (90% yield) had an ee > 98% when the experiment was conducted with *Rhizomucor miehei* lipase. This procedure was realized with the tetrahydropyran diols **2b-i** using *Rhizomucor miehei* lipase and results are reported in Table 2.



((2S,3R,4R,5S,6R)-6-(hydroxymethyl)-4-methoxy-3,5-dimethyl-tetrahydro-2H-pyran-2-yl)methyl acetate (3a**):**

Following the general procedure for the synthesis of racemic monoacetate, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure racemic monoacetate **3a** as white crystals. (50% yield).

Following the general procedure for enzymatic desymmetrization, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure monoacetate **3a** as white crystals. (90% yield) ; m.p. 80-81 °C ; *R_f* = 0.28 (PE/EtOAc : 1/1).

$[\alpha]_D^{25} = +13.5$ (c 0.20, CHCl_3)

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 4.12 (m, 2H), 3.76 (dd, $J = 12.1, 9.5$ Hz, 1H), 3.62 (m, 1H), 3.51 (m, 2H), 3.36 (t, $J = 5.3$ Hz, 1H), 3.32 (s, 3H), 2.09 (m, 2H), 2.06 (s, 3H), 0.90 (d, $J = 7.2$ Hz, 3H), 0.86 (d, $J = 7.2$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 171.0, 80.8, 80.7, 77.4, 65.2, 63.7, 55.3, 33.6, 33.2, 20.9, 8.5, 8.2.

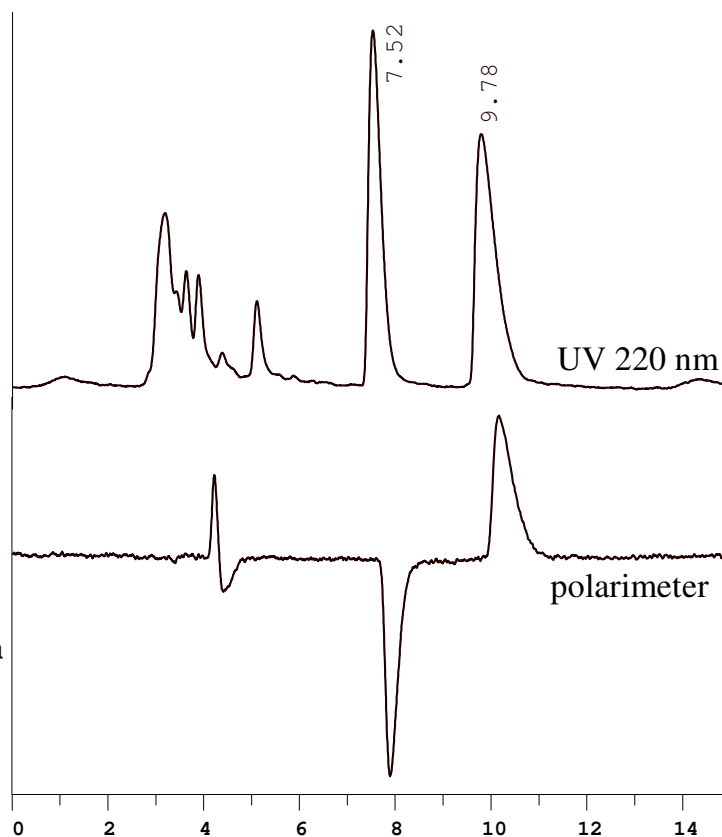
HRMS (ESI TOF) calcd for $\text{C}_{12}\text{H}_{23}\text{O}_5$ (M+H) $^+$ 247.1540, found 247.1543.

Racemic mixture

Column : Sepapak-2-HR
Mobile phase : Hexane/
Isopropanol 80/20, 1 mL/min
Temperature : 25°C
Detection : UV 220 nm and
Polarimeter

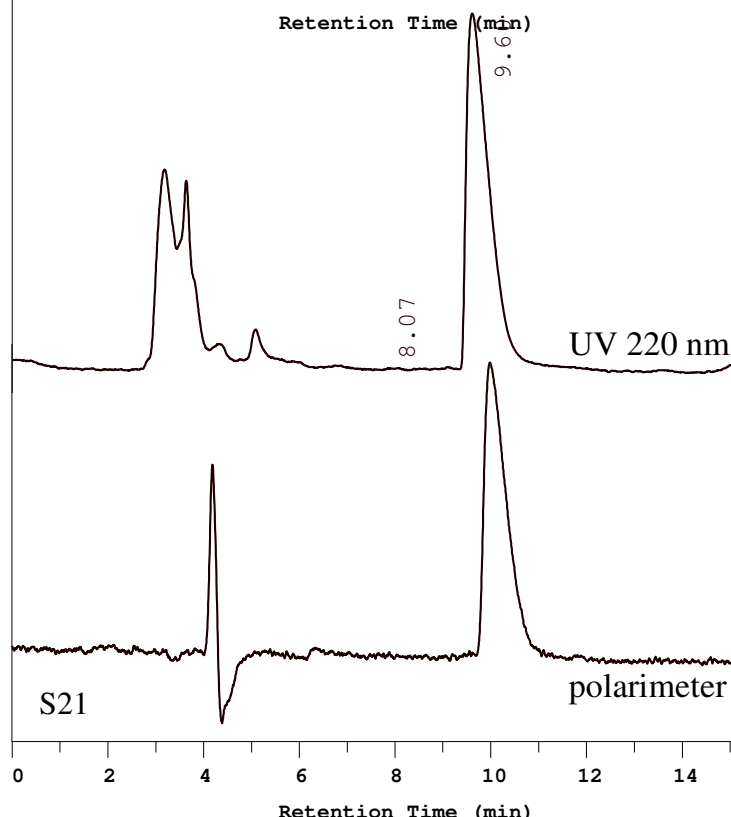
No.	RT	Area	Conc 1	BC
1	7.52	1321649	46.747	BB
2	9.78	1505600	53.253	BB
		2827249	100.000	

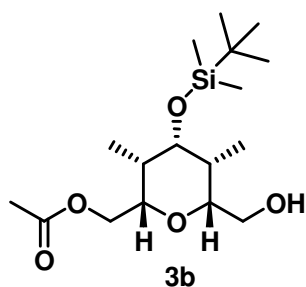
RT (min)	k'	Asym	N (USP)	N (JP)	Res (USP)	Res (JP)	Alpha
7.52	1.47	1.87*	---	3789*	---	---	---
9.78	2.22	2.54*	---	2499*	---	3.55	1.50



Enantioselective desymmetrization

No.	RT	Area	Conc 1	BC
1	8.07	3099	0.144	MC
2	9.60	2155717	99.856	BB





((2*S*,3*S*,4*R*,5*R*,6*R*)-4-(tert-butyldimethylsilyloxy)-6-(hydroxymethyl)-3,5-dimethyl-tetrahydro-2*H*-pyran-2-yl)methyl acetate (3b**):**

Following the general procedure for the synthesis of racemic monoacetate, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure racemic monoacetate **3b** as white crystals. (44% yield).

Following the general procedure for enzymatic desymmetrization, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure monoacetate **3b** as white crystals. (82% yield) ; m.p. 74-75 °C ; $R_f = 0.56$ (PE/EtOAc : 1/1).

$[\alpha]_D^{25} = +11.4$ (c 1.50, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ 4.12-4.10 (m, 2H), 3.83 (t, $J = 5.5$ Hz, 1H), 3.75 (m, 1H), 3.63 (m, 1H), 3.52-3.45 (m, 2H), 2.06 (s, 3H), 1.79 (m, 2H), 0.91 (d, $J = 7.2$ Hz, 3H), 0.90 (s, 9H), 0.87 (d, $J = 7.2$ Hz, 3H), 0.04 (s, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 171.0, 80.6, 77.4, 72.5, 65.4, 63.8, 37.4, 37.0, 25.7 (3C), 20.9, 18.0, 8.5, 8.2, -4.9 (2C).

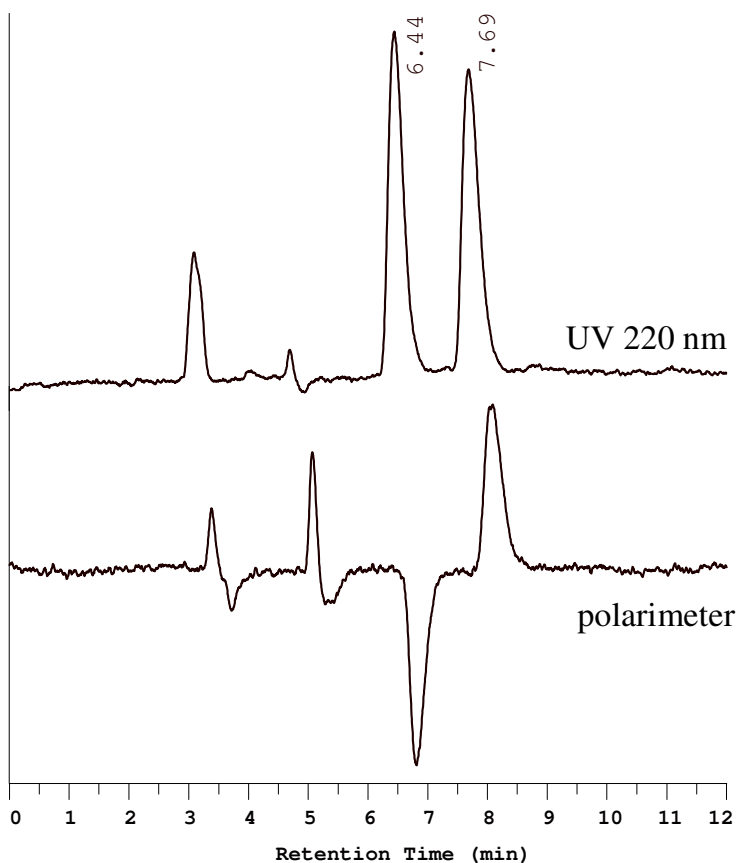
HRMS (ESI TOF) calcd for C₁₇H₃₅O₅Si (M+H)⁺ 347.2248, found 347.2246.

Racemic mixture

Column : Sepapak-2-HR
Mobile phase : Hexane/
Isopropanol 90/10, 1 mL/min
Temperature : 25°C
Detection : UV 220 nm and
polarimeter

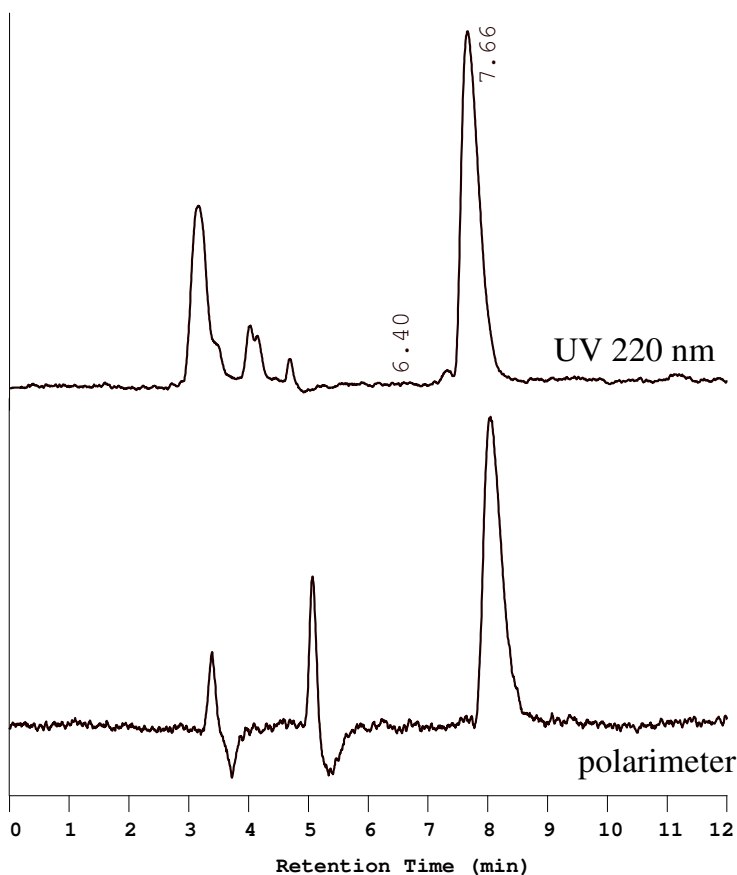
No.	RT	Area	Conc 1	BC
1	6.44	355075	50.968	BB
2	7.69	341587	49.032	BB

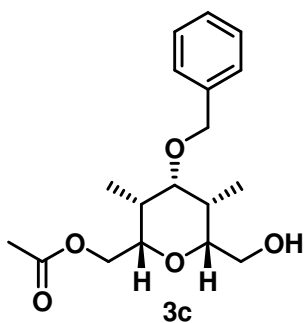
696662 100.000



*Enantioselective
desymmetrization*

No.	RT	Area	Conc 1	BC
1	6.40	2089	0.393	BB
2	7.66	530213	99.607	VB





((2*S*,3*R*,4*R*,5*S*,6*R*)-4-(benzyloxy)-6-(hydroxymethyl)-3,5-dimethyl-tetrahydro-2H-pyran-2-yl)methyl acetate (3c**):**

Following the general procedure for the synthesis of racemic monoacetate, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure racemic monoacetate **3c** as white crystals. (40% yield).

Following the general procedure for enzymatic desymmetrization, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure monoacetate **3c** as white crystals. (88% yield) ; m.p. 83-84 °C ; $R_f = 0.42$ (PE/EtOAc : 1/1).

$[\alpha]_D^{25} = +5.9$ (c 1.50, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ 7.35 (m, 4H), 7.30 (t, $J = 3.8$ Hz, 1H), 4.53 (s, 2H), 4.14 (m, 2H), 3.79 (dd, $J = 12.1, 9.4$ Hz, 1H), 3.66-3.61 (m, 1H), 3.60 (t, $J = 5.3$ Hz, 1H), 3.52 (m, 2H) 2.14 (m, 2H), 2.07 (s, 3H), 0.99 (d, $J = 7.4$ Hz, 3H), 0.95 (d, $J = 7.2$ Hz, 3H).

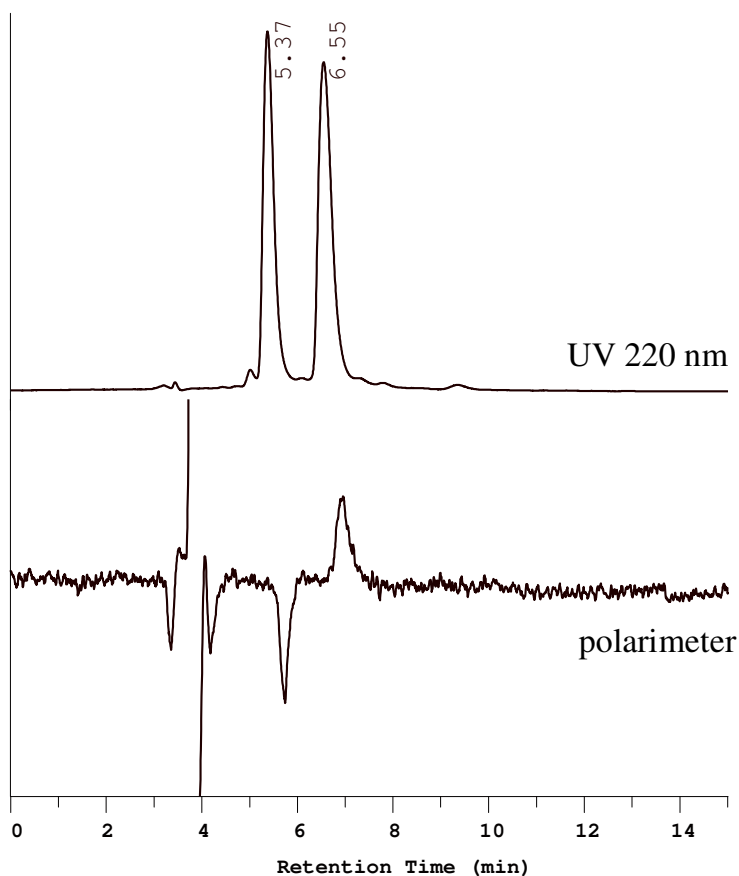
¹³C NMR (75 MHz, CDCl₃): δ 171.0, 138.5, 128.4 (2C), 127.5, 127.2 (2C), 80.7, 78.5, 77.4, 69.2, 65.2, 63.8, 34.0, 33.6, 20.9, 8.9, 8.5.

HRMS (ESI TOF) calcd for C₁₈H₂₇O₅ (M+H)⁺ 323.1853, found 323.1849.

Racemic mixture

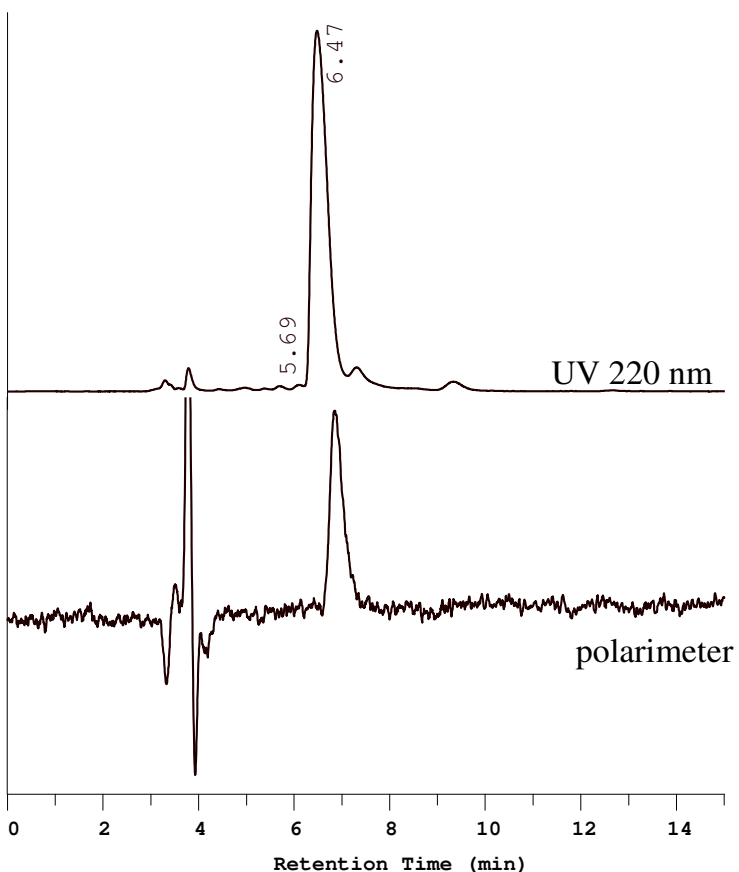
Column : Sepapak-2-HR
Mobile phase : Hexane/
Isopropanol 60/40, 1 mL/min
Temperature : 25°C
Detection : UV 220 nm and
polarimeter

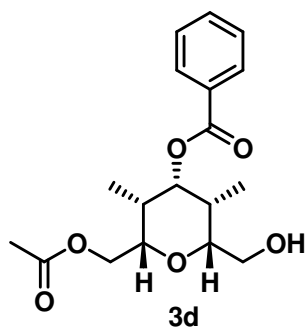
No.	RT	Area	Conc 1	BC
1	5.37	6613272	48.365	MC
2	6.55	7060500	51.635	MC
		13673772	100.000	



*Enantioselective
desymmetrization*

No.	RT	Area	Conc 1	BC
1	5.69	58335	0.464	VB
2	6.47	12504729	99.536	VV





(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(acetoxymethyl)-6-(hydroxymethyl)-3,5-dimethyl-tetrahydro-2H-pyran-4-yl benzoate (3d):

Following the general procedure for the synthesis of racemic monoacetate, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure racemic monoacetate **3d** as white crystals. (71% yield).

Following the general procedure for enzymatic desymmetrization, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure monoacetate **3d** as white crystals. (89% yield); m.p. 127-128°C ; *R_f* = 0.40 (PE/EtOAc : 1/1).

$[\alpha]_{\text{D}}^{25} = -4.1$ (c 1.50, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ 8.08 (dd, *J* = 7.3, 1.3 Hz, 2H), 7.59 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 2H), 5.26 (t, *J* = 5.5 Hz, 1H), 4.21 (dd, *J* = 11.5, 7.9 Hz, 1H), 4.14 (dd, *J* = 11.5, 4.3 Hz, 1H), 3.85-3.77 (m, 2H), 3.72 (dt, *J* = 8.5, 2.8 Hz, 1H), 3.56 (brs, 1H), 2.28 (m, 2H), 2.08 (s, 3H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 3H).

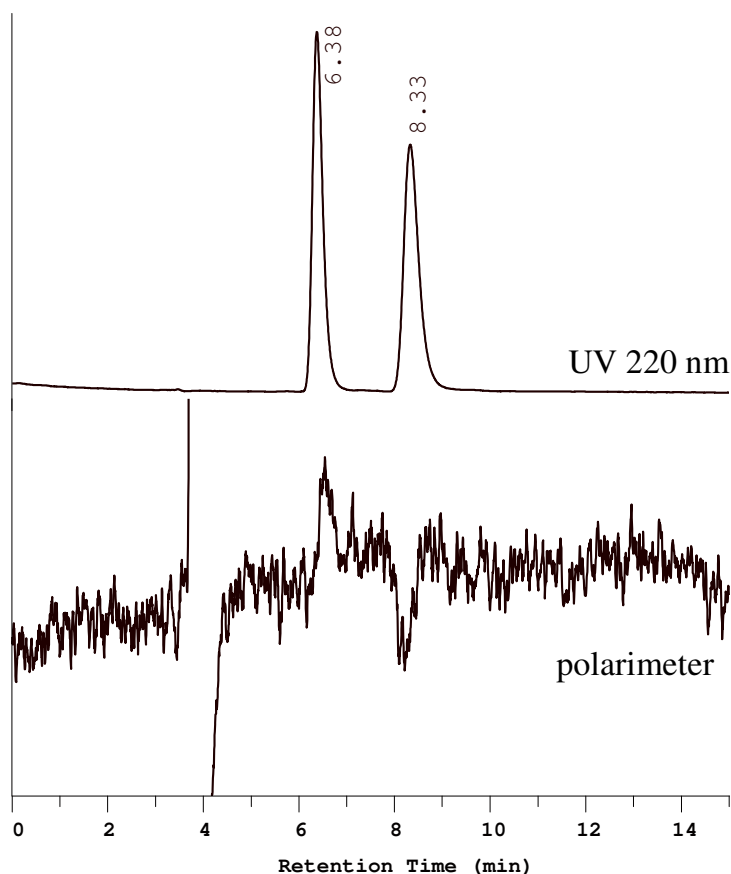
¹³C NMR (75 MHz, CDCl₃): δ 170.9, 165.4, 133.2, 130.2, 129.5 (2C), 128.5 (2C), 80.4, 77.1, 74.4, 64.7, 63.6, 34.0, 33.8, 20.9, 9.5, 9.1.

HRMS (ESI TOF) calcd for C₁₈H₂₅O₆ (M+H)⁺ 337.1646, found 337.1637.

Racemic mixture

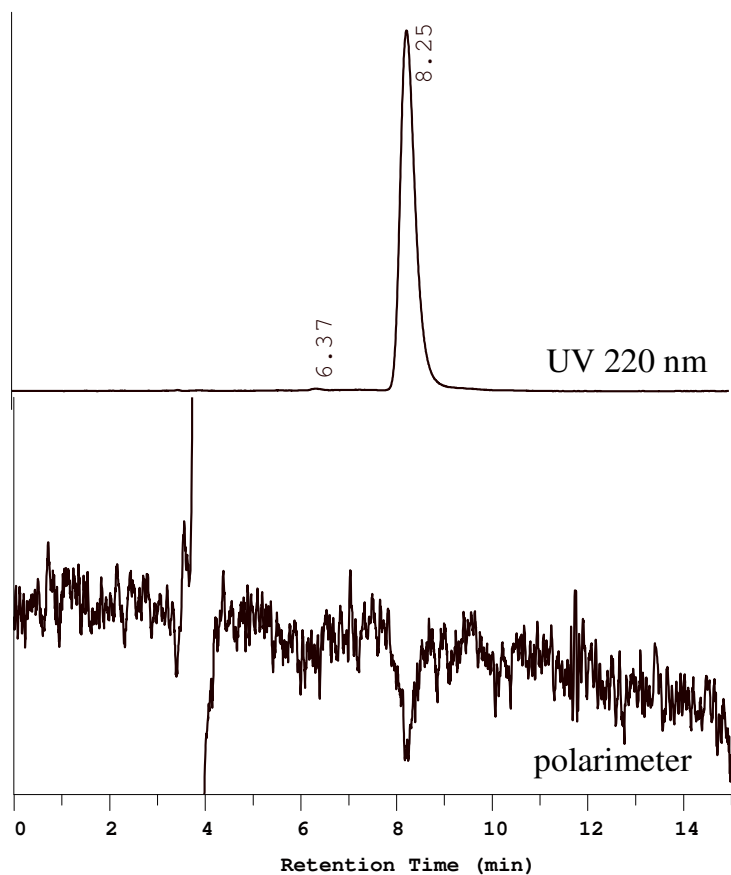
Column : Sepapak-2-HR
Mobile phase : Hexane/
Isopropanol 50/50, 1 mL/min
Temperature : 25°C
Detection : UV 220 nm and
polarimeter

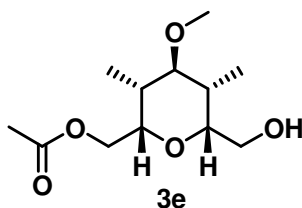
No.	RT	Area	Conc 1	BC
1	6.38	6831706	49.846	BV
2	8.33	6873835	50.154	BB
		13705541	100.000	



*Enantioselective
desymmetrization*

No.	RT	Area	Conc 1	BC
1	6.37	41171	0.295	BB
2	8.25	13922241	99.705	BB





((2*S*,3*R*,4*S*,5*S*,6*R*)-6-(hydroxymethyl)-4-methoxy-3,5-dimethyl-tetrahydro-2H-pyran-2-yl)methyl acetate (3e**) :**

Following the general procedure for the synthesis of racemic monoacetate, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure racemic monoacetate **3e** as a colourless oil. (48% yield).

Following the general procedure for enzymatic desymmetrization, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure monoacetate **3e** as a colourless oil. (58% yield); $R_f = 0.26$ (PE/EtOAc : 1/1).

$[\alpha]_D^{30} = +6.0$ (c 0.8, CHCl₃).

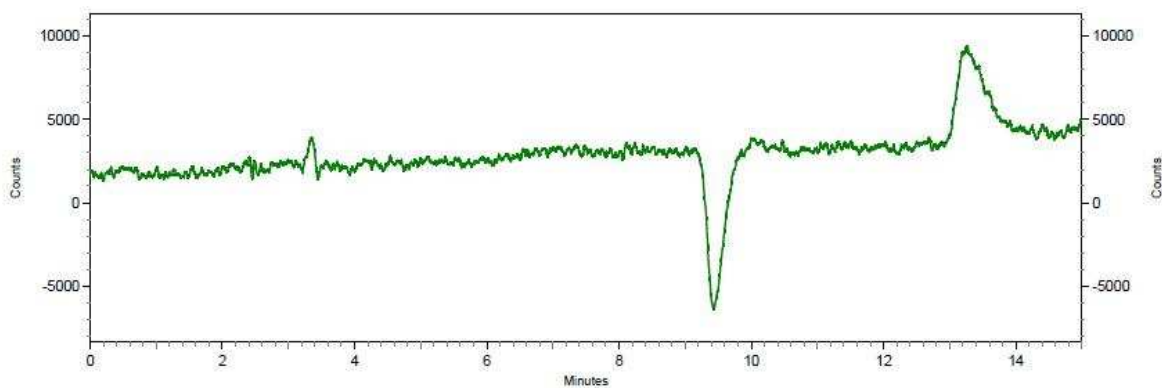
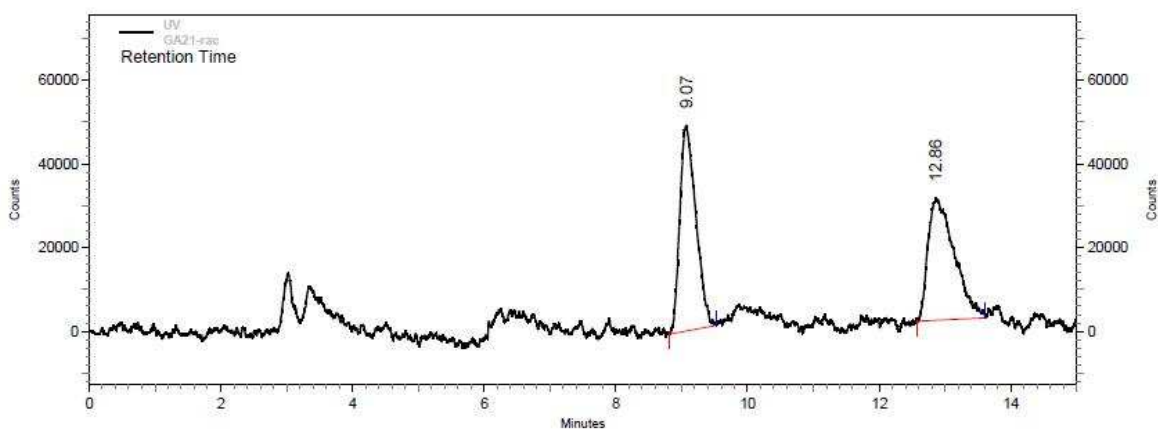
¹H NMR (300 MHz, CDCl₃): δ 4.06 (m, 2H), 3.99 (m, 1H), 3.90 (ddd, $J = 8.9, 3.2, 3.2$ Hz, 1H), 3.69 (dd, $J = 11.3, 8.9$ Hz, 1H), 3.47 (dd, $J = 11.3, 3.2$ Hz, 1H), 3.33 (s, 3H), 3.08 (dd, $J = 2.1, 2.1$ Hz, 1H), 2.06 (s, 3H), 2.03 (brs, 1H_{OH}), 1.88 (m, 2H), 1.00 (d, $J = 7.5$ Hz, 3H), 0.97 (d, $J = 7.7$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 171.1, 85.8, 77.0, 73.9, 65.5, 63.9, 56.6, 33.4, 32.8, 20.9, 12.6, 12.2.

HRMS (ESI TOF) calcd for C₁₂H₂₃O₅ (M+H)⁺ 247.1540, found 247.1532.

Racemic mixture

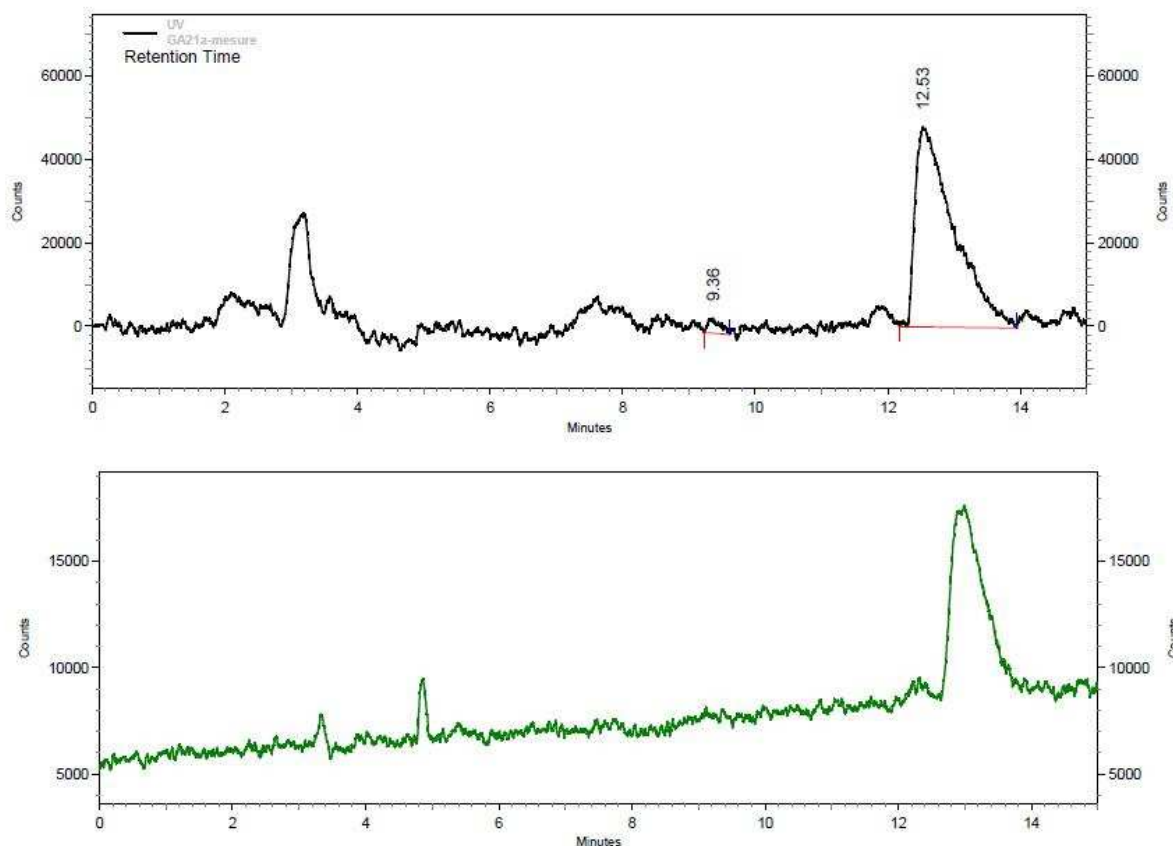
Method description : Sepapak-2HR, Hexane/isopropanol 80/20, 1 ml/min, UV 220 nm et polarimètre



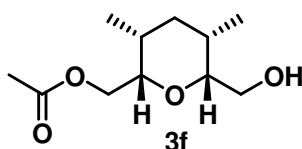
UV Results					
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.07	835837	50.86	2.02	1.00	0.00
12.86	807670	49.14	3.29	1.62	6.21
Totals	1643507	100.00			

Enantioselective desymmetrization

Method description : Sepapak-2HR, Hexane/isopropanol 80/20, 1 ml/min, UV 220 nm et polarimètre



UV Results					
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.36	45078	2.28	2.12	1.00	0.00
12.53	1928555	97.72	3.18	1.50	0.00
Totals	1973633	100.00			



((2*S*,3*R*,5*S*,6*R*)-6-(hydroxymethyl)-3,5-dimethyl-tetrahydro-2H-pyran-2-yl)methyl acetate (3f**) :**

Following the general procedure for the synthesis of racemic monoacetate, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure racemic monoacetate **3f** as a colourless oil. (32% yield).

Following the general procedure for enzymatic desymmetrization, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure monoacetate **3f** as a colourless oil. (67% yield); $R_f = 0.38$ (PE/EtOAc : 1/1).

$[\alpha]_D^{30} = +6.2$ (c 1.00, CHCl_3).

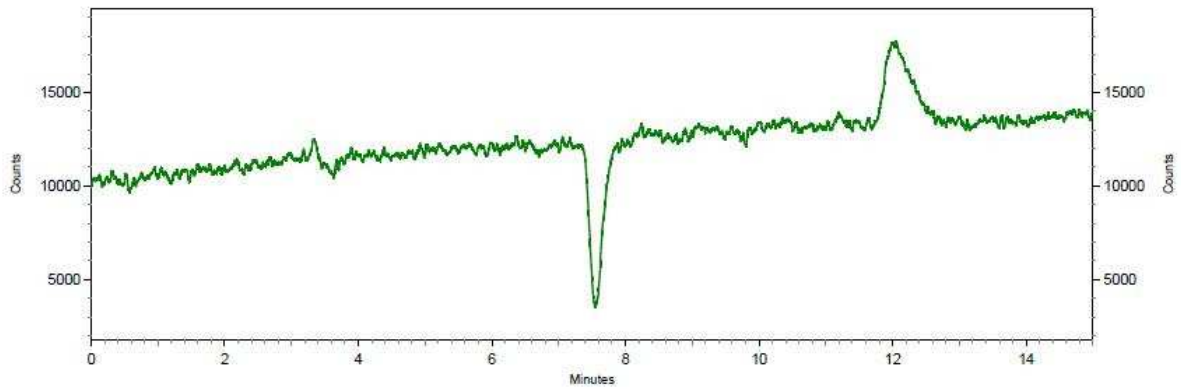
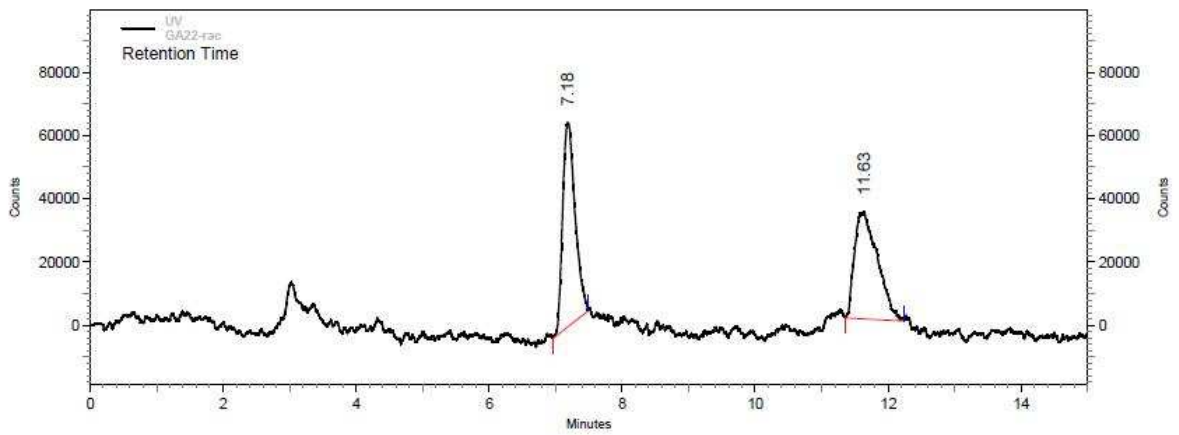
$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 4.08 (dd, $J = 6.4, 1.0$ Hz, 2H), 3.71 (m, 1H), 3.69 (dd, $J = 11.0, 8.8$ Hz, 1H), 3.61 (dt, $J = 8.8, 2.8$ Hz, 1H), 3.49 (d, $J = 11.0$ Hz, 1H), 2.08 (brs, 1 H_{OH}), 2.06 (s, 3H), 2.02 (m, 1H), 1.79 (m, 2H), 1.57 (dt, $J = 13.8, 2.1$ Hz, 1H), 1.03 (d, $J = 7.4$ Hz, 3H), 0.99 (d, $J = 7.4$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 171.1 (C), 81.6 (C), 78.3 (C), 65.8 (C), 64.2 (C), 38.0 (C), 29.0 (C), 28.6 (C), 20.9 (C), 15.9 (C), 15.5 (C).

HRMS (ESI TOF) calcd for $\text{C}_{11}\text{H}_{24}\text{NO}_4$ ($\text{M}+\text{NH}_4$)⁺ 234.1700, found 234.1694.

Racemic mixture

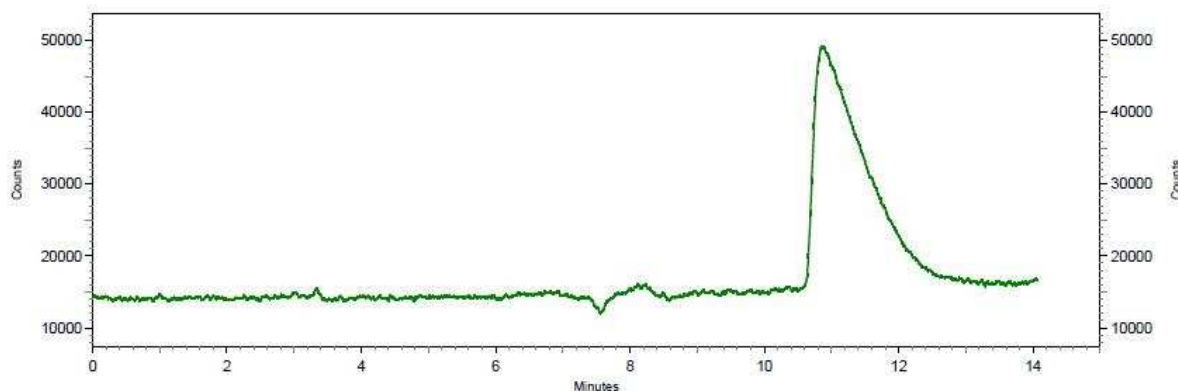
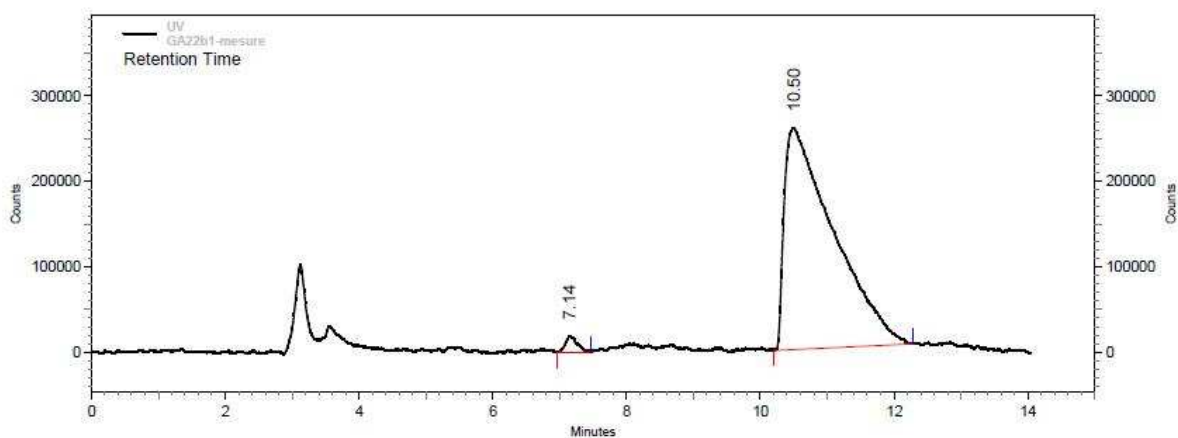
Method description : Sepapak-2HR, Hexane/isopropanol 80/20, 1 ml/min, UV 220 nm et polarimètre



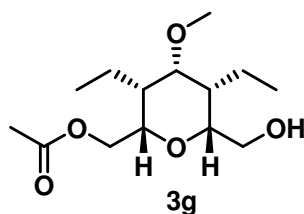
UV Results					
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.18	841886	50.79	1.39	1.00	0.00
11.63	815551	49.21	2.88	2.06	8.65
Totals					
	1657437	100.00			

Enantioselective desymmetrization

Method description : Sepapak-2HR, Hexane/isopropanol 80/20, 1 ml/min, UV 220 nm et polarimètre



UV Results					
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.14	241592	1.79	1.38	1.00	0.00
10.50	13233338	98.21	2.50	1.81	3.85
Totals		13474930	100.00		



((2*S*,3*R*,4*R*,5*S*,6*R*)-3,5-diethyl-6-(hydroxymethyl)-4-methoxy-tetrahydro-2H-pyran-2-yl)methyl acetate (3g) :

Following the general procedure for the synthesis of racemic monoacetate, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient

elution: 80/20 to 60/40) to afford pure racemic monoacetate **3g** as a colourless oil. (68% yield).

Following the general procedure for enzymatic desymmetrization, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure monoacetate **3g** as a colourless oil. (82% yield); $R_f = 0.32$ (PE/EtOAc : 1/1)

$[\alpha]_D^{25} = +10.5$ (c 0.20, CHCl_3).

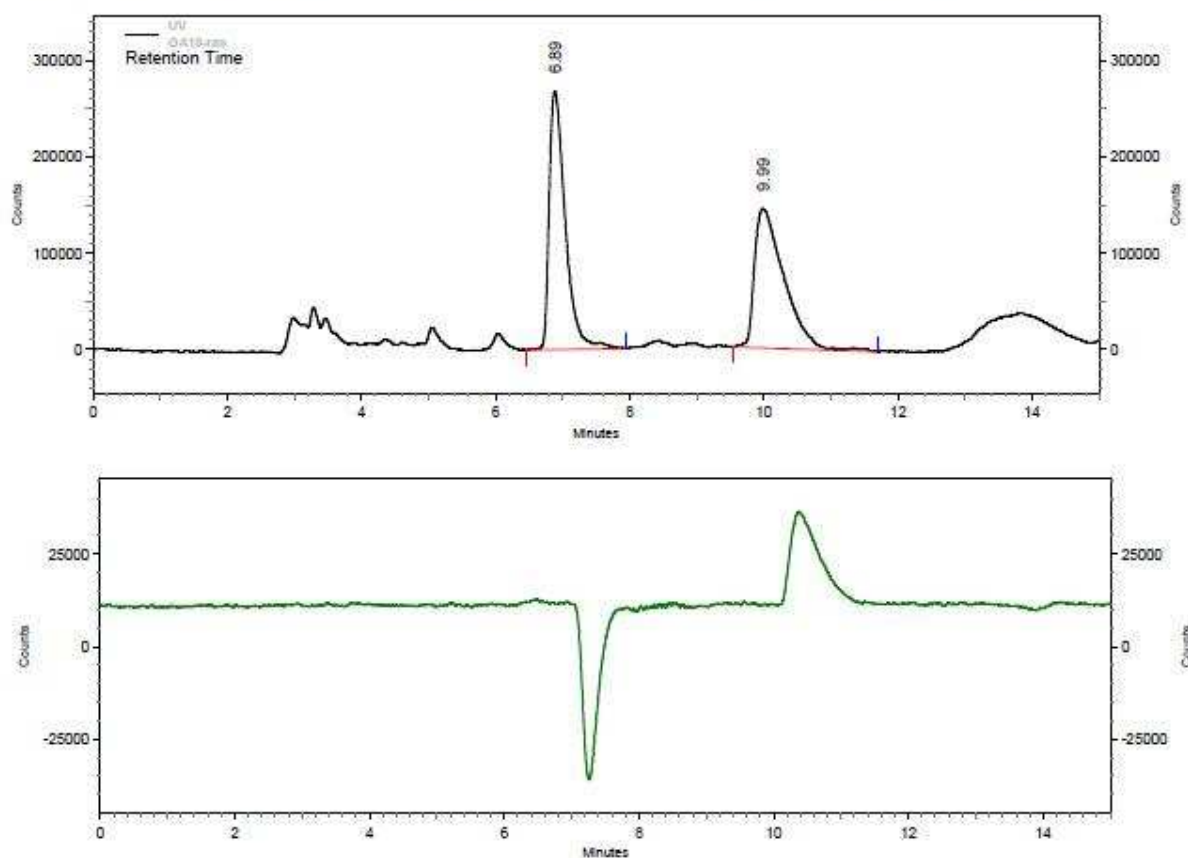
$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 4.19 (d, $J = 5.7$ Hz, 2H), 3.79 (t, $J = 11.1$ Hz, 1H), 3.55 (m, 3H), 3.88 (t, $J = 4.9$ Hz, 1H), 3.34 (s, 3H), 2.07 (s, 3H), 1.79 (m, 1H), 1.73 (m, 1H), 1.71 (m, 2H), 1.23 (m, 2H), 0.91 (t, $J = 7.7$ Hz, 3H), 0.86 (t, $J = 7.6$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 170.8, 81.7, 81.5, 78.2, 65.3, 63.8, 55.8, 42.4, 42.3, 20.8, 16.6 (2C), 15.6 (2C).

HRMS (ESI TOF) calcd for $\text{C}_{14}\text{H}_{27}\text{O}_5$ (M+H) $^+$ 275.1853, found 275.1855.

Racemic mixture

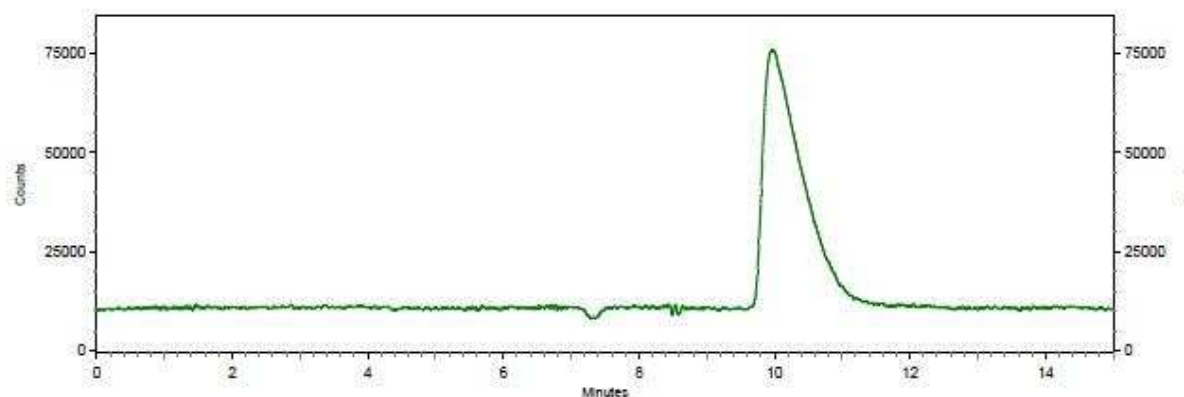
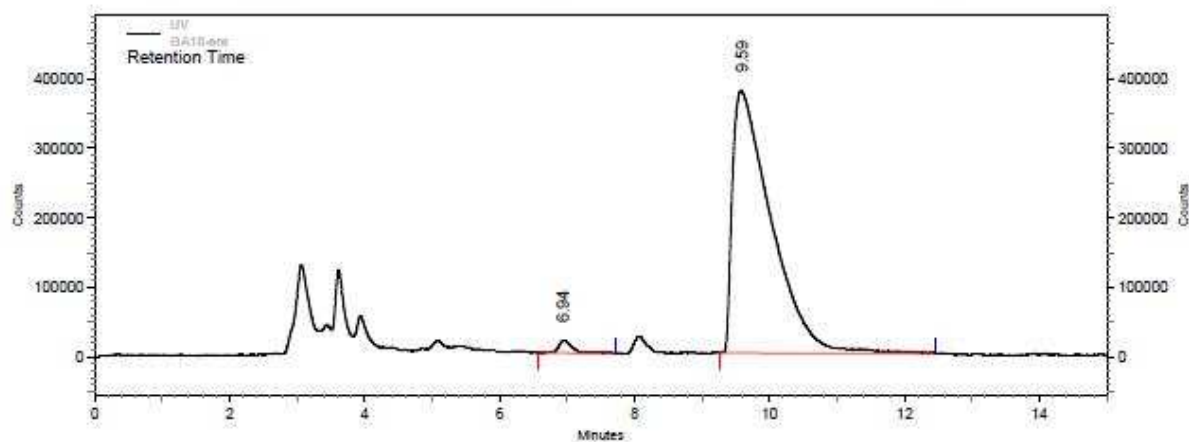
Method description : Sepapak-2-HR, Hexane/isopropanol 80/20, 1 ml/min, UV 220 nm et polarimètre



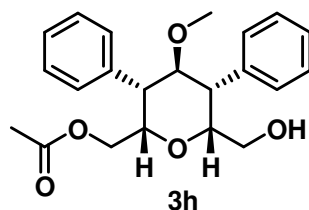
UV Results						
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)	
6.89	4502403	50.39	1.30	1.00	0.00	
9.99	4433361	49.61	2.33	1.80	5.05	

Enantioselective desymmetrization

Method description : Sepapak-2-HR, Hexane/isopropanol 80/20, 1 ml/min, UV 220 nm et polarimètre



UV Results						
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)	
6.94	271699	1.76	1.31	1.00	0.00	
9.59	15129708	98.24	2.20	1.67	3.74	



((2S,3R,4R,5S,6R)-3,5-diphenyl-6-(hydroxymethyl)-4-methoxy-tetrahydro-2H-pyran-2-yl)methyl acetate (3h) :

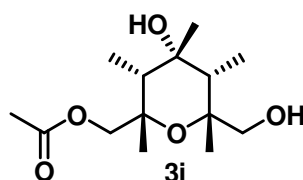
Following the general procedure for the synthesis of racemic monoacetate, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure racemic monoacetate **3h** as a white powder. (49% yield).

Following the general procedure for enzymatic desymmetrization (reaction time 72h), the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure monoacetate **3h** as a white powder. (Yield: 21%), m.p. 94-95 °C; *R_f* = 0.40 (PE/EtOAc : 1/1)

¹H NMR (300 MHz, CDCl₃): δ 7.44-7.36 (m, 4H), 7.27-7.19 (m, 6H), 4.34 (ddd, *J* = 8.3, 5.9, 3.8 Hz, 1H), 4.26 (ddd, *J* = 7.2, 5.7, 2.9 Hz, 1H), 4.23 (dd, *J* = 12.0, 8.3 Hz, 1H), 4.00 (dd, *J* = 12.0, 3.8 Hz, 1H), 3.87 (dd, *J* = 5.9, 3.8 Hz, 1H), 3.70 (dd, *J* = 11.9, 5.7 Hz, 1H), 3.56 (dd, *J* = 11.9, 2.9 Hz, 1H), 3.46 (dd, *J* = 7.2, 3.8 Hz, 1H), 3.38 (dd, *J* = 5.9, 5.9 Hz, 1H), 3.24 (brs, 1H_{OH}), 2.91 (s, 3H), 2.01 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 170.8, 137.1, 135.9, 130.6 (2C), 129.9 (2C), 128.1 (2C), 127.8 (2C), 127.0, 126.9, 80.7, 78.9, 75.2, 66.1, 62.4, 59.6, 47.5, 46.6, 20.9.

HRMS (ESI TOF) calcd for C₂₂H₂₇O₅ (M+H)⁺ 371.1853, found 371.1853.



((2S,3R,4R,5S,6R)-4-hydroxy-6-(hydroxymethyl)-2,3,4,5,6-pentamethyl-tetrahydro-2H-pyran-2-yl)methyl acetate (3i**):**

Following the general procedure for the synthesis of racemic monoacetate, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure racemic monoacetate **3i** as white crystals. (56% yield).

Following the general procedure for enzymatic desymmetrization, the crude material was purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford pure monoacetate **3i** as white crystals. (72% yield) ; m.p. 140-141 °C ; *R_f* = 0.56 (PE/EtOAc : 1/1)

[α]²⁵_D = -21.6 (c 0.25, CHCl₃).

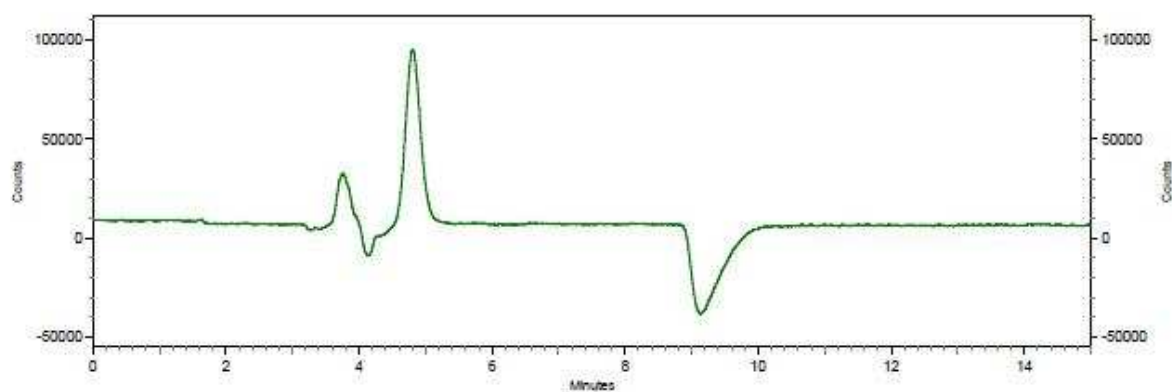
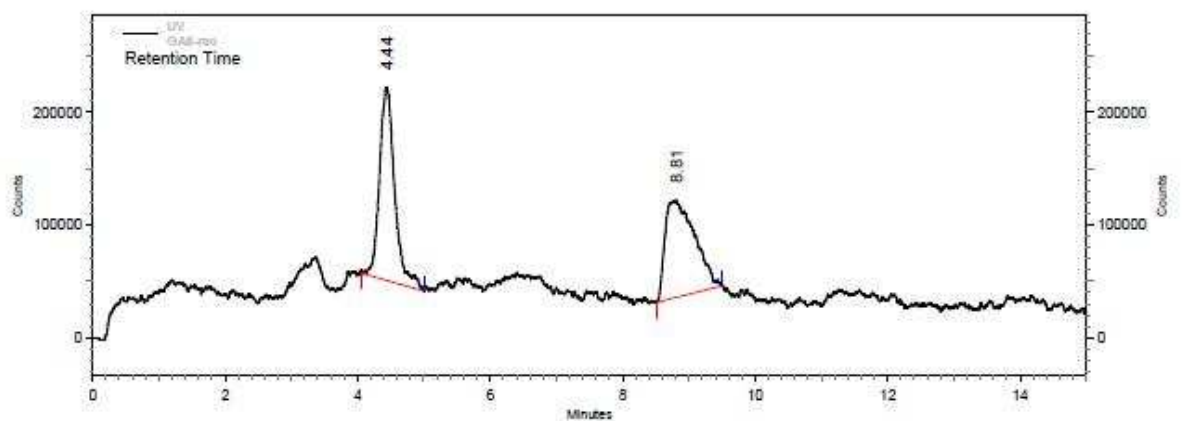
¹H NMR (300 MHz, CDCl₃): δ 4.72 (d, *J* = 12.3 Hz, 1H), 4.18 (d, *J* = 12.3 Hz, 1H), 4.06 (d, *J* = 11.6 Hz, 1H), 3.23 (d, *J* = 11.6 Hz, 1H), 3.21 (brs, 1H_{OH}), 2.12 (s, 3H), 1.62 (m, 2H), 1.26 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.08 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 171.3, 77.3, 75.4, 70.7, 67.3, 65.0, 47.6, 47.1, 27.7, 27.5, 26.2, 21.0, 10.0, 9.6.

HRMS (ESI TOF) calcd for C₁₄H₂₅O₅ (M+H)⁺ 275.1853, found 275.1858

Racemic mixture

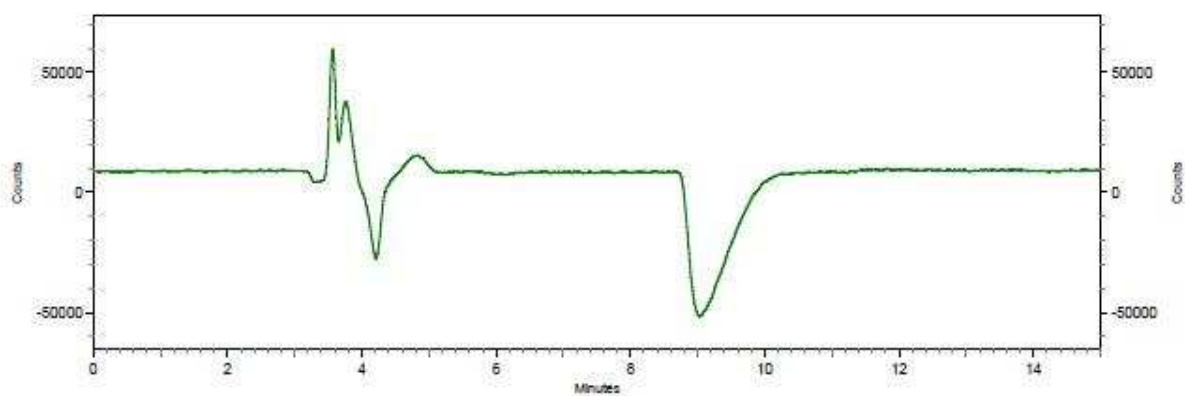
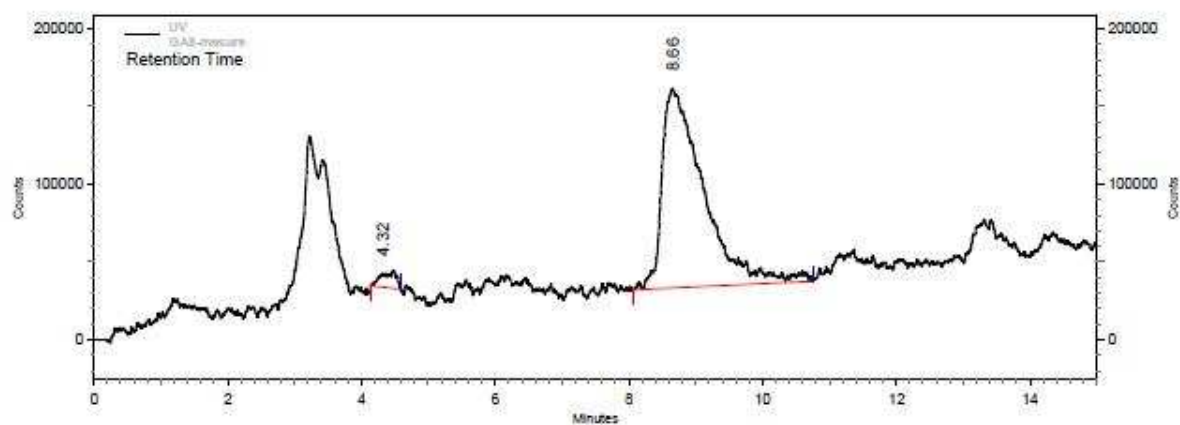
Method description : Sepapak-2-HR, Hexane/isopropanol 70/30, 1 ml/min, UV 210 nm et polarimètre



UV Results					
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
4.44	2726324	50.56	0.48	1.00	0.00
8.81	2665815	49.44	1.94	4.04	7.05

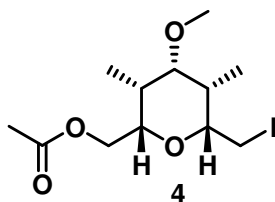
Enantioselective desymmetrization

Method description : Sepapak-2-HR, Hexane/isopropanol 70/30, 1 ml/min, UV 210 nm et polarimètre



UV Results					
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
4.32	166805	2.93	0.44	0.00	0.00
8.66	5524568	97.07	1.89	0.00	0.00

IV- Syntheses of the stereotetrades **7** and *ent-7*



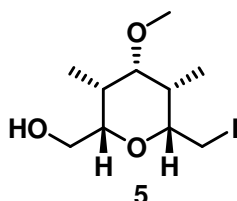
((2S,3R,4S,5S,6R)-6-(iodomethyl)-4-methoxy-3,5-dimethyl-tetrahydro-2H-pyran-2-yl)methyl acetate (4**):** In a flame dried 50 mL one-necked round bottomed flask, equipped with reflux condenser under an argon atmosphere, **3a** (400 mg, 1.62 mmol) was dissolved in 25 mL of freshly distilled toluene. To this stirred solution were added successively imidazole (335 mg, 4.87 mmol), triphenylphosphine (1.29 g, 4.87 mmol) and iodine (828 mg, 3.24 mmol). The resulting brown suspension was refluxed for 1 h, cooled to room temperature before a 50/50 mixture of petroleum ether / diethyl ether (20 mL) was added. The white precipitate was filtered off, washed with a 50/50 mixture of petroleum ether and diethyl ether (20 mL) and the filtrate was concentrated in vacuo to afford the crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 98/2 to 80/20) to afford 526 mg (91%) of pure iodoacetate **4**, as white crystals. m.p. 104-105 °C; R_f = 0.51 (PE/EtOAc : 8/2).

$[\alpha]_D^{25} = +3.6$ (c 1.50, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ 4.18 (dd, J = 11.7, 8.3 Hz, 1H), 4.09 (dd, J = 11.7, 4.1 Hz, 1H), 3.61 (ddd, J = 8.3, 4.1, 2.8 Hz, 1H), 3.56 (td, J = 7.2, 2.6 Hz, 1H), 3.35 (t, J = 5.3 Hz, 1H), 3.34 (s, 3H), 3.29 (dd, J = 10.0, 7.2 Hz, 1H), 3.12 (dd, J = 10.0, 7.2 Hz, 1H), 2.34 (m, 1H), 2.08 (s, 3H), 2.02 (m, 1H), 0.89 (d, J = 7.4 Hz, 3H), 0.86 (d, J = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 171.0, 81.0, 80.1, 77.8, 64.9, 55.5, 34.5, 33.1, 20.9, 8.2, 7.0, 4.9.

HRMS (ESI TOF) calcd for C₁₂H₂₂O₄I (M+H)⁺ 357.0557, found 357.0558.



((2S,3R,4S,5S,6R)-6-(iodomethyl)-4-methoxy-3,5-dimethyl-tetrahydro-2H-pyran-2-yl)methanol (5**):** In a 25 mL one-necked round bottomed flask, iodoacetate **4** (210 mg, 0.59 mmol) was dissolved in 6 mL of methanol. To this stirred solution was added potassium carbonate (163 mg, 1.18 mmol) in one portion. The resulting white suspension was stirred at room temperature for 20 min and quenched with a saturated aqueous solution of NH₄Cl (10 mL). Methanol was evaporated in vacuo, the aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined

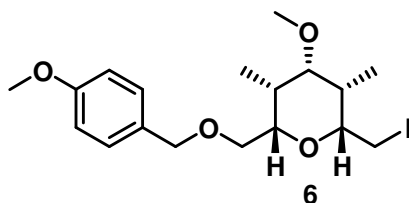
organic layers were washed with brine (2 x 10 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford the crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 80/20 to 60/40) to afford 184 mg (99%) of pure iodoalcohol **5**, as a colourless oil. *R*_f = 0.56 (PE/EtOAc : 1/1).

$[\alpha]_D^{25} = -9.2$ (c 0.75, CHCl₃)

¹H NMR (300 MHz, CDCl₃): δ 3.79 (dd, *J* = 12.3, 10.0 Hz, 1H), 3.58 (ddd, *J* = 8.3, 6.0, 2.6 Hz, 1H), 3.54-3.47 (m, 2H), 3.36 (t, *J* = 5.3 Hz, 1H), 3.34 (s, 3H), 3.31 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.14 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.31 (m, 1H), 2.01 (m, 1H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 81.2, 81.1, 80.0, 63.8, 55.5, 35.1, 33.0, 8.6, 7.2, 5.7.

HRMS (ESI TOF) calcd for C₁₀H₂₀O₃I (M+H)⁺ 315.0452, found 315.0445.



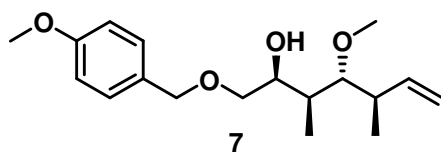
(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(iodomethyl)-4-methoxy-6-((4-methoxybenzyloxy)methyl)-3,5-dimethyl-tetrahydro-2H-pyran (6**):** In a 25 mL one-necked round bottomed flask, under an argon atmosphere, iodoalcohol **5** (155 mg, 0.49 mmol) was dissolved in 5 mL of freshly distilled toluene. To this stirred solution was added PMBTCA (154 mg, 0.54 mmol), followed by ytterbium triflate (15 mg, 0.024 mmol). The resulting solution was stirred at room temperature for 2 h and quenched with a saturated aqueous solution of NH₄Cl (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (2 x 10 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford the crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 95/5 to 90/10) to afford 164 mg (77%) of pure iodopyran **6**, as a colourless oil. *R*_f = 0.70 (PE/EtOAc : 8/2).

$[\alpha]_D^{25} = -11.5$ (c 1.00, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.61 (m, 3H), 3.46 (m, 1H), 3.35 (t, *J* = 5.3 Hz, 1H), 3.34 (s, 3H), 3.31 (dd, *J* = 10.0, 6.6 Hz, 1H), 3.12 (dd, *J* = 10.0, 7.6 Hz, 1H), 2.35 (m, 1H), 2.04 (m, 1H), 0.86 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 159.2 (C₁₂), 130.3, 129.4 (2C), 113.8 (2C), 81.2, 80.0, 79.3, 73.1, 70.3, 55.4, 55.3, 34.5, 33.1, 8.1, 7.0, 5.0.

HRMS (ESI TOF) calcd for C₁₈H₃₁NO₄I (M+NH₄)⁺ 452.1292, found 452.1292.



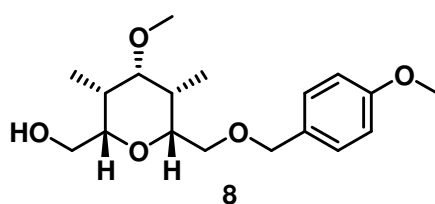
(3R,4R,5S,6S)-4-methoxy-7-(4-methoxybenzyloxy)-3,5-dimethylhept-1-en-6-ol (7): In a 10 mL one-necked round bottomed flask, iodopyran **6** (110 mg, 0.25 mmol) was dissolved in 4 mL of 96.5% ethanol. To this stirred solution was added freshly activated zinc dust (167 mg, 2.5 mmol) and the resulting suspension was refluxed for 2 h. After been cooled to room temperature, the reaction mixture was then filtered through a short pad of Celite® and washed thoroughly with ether (3 x 10 mL). The filtrate was concentrated in *vacuo* to afford the crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 90/10 to 80/20) to afford 71 mg (92%) of pure tetrade **7**, as a colourless oil. *R_f* = 0.42 (PE/EtOAc : 8/2).

$[\alpha]_D^{25} = -8.0$ (c 1.00, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.83 (ddd, *J* = 16.9, 11.0, 8.1 Hz, 1H), 5.06-5.00 (m, 2H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.18 (m, 1H), 3.80 (s, 3H), 3.48 (s, 3H), 3.46 (dd, *J* = 9.4, 6.8 Hz, 1H), 3.39 (dd, *J* = 9.4, 4.9 Hz, 1H), 3.05 (dd, *J* = 6.8, 4.9 Hz, 1H), 2.87 (brs, 1H_{OH}), 2.49 (m, 1H), 1.71 (pd, *J* = 7.0, 1.7 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 159.2, 140.4, 130.3, 129.3 (2C), 114.8, 113.8 (2C), 88.8, 73.0, 72.9, 69.4, 61.6, 55.2, 40.5, 37.1, 17.5, 10.8.

HRMS (ESI TOF) calcd for C₁₈H₂₉O₄ (M+H)⁺ 309.2060, found 309.2060.



((2S,3R,4S,5S,6R)-4-methoxy-6-((4-methoxybenzyloxy)methyl)-3,5-dimethyl-tetrahydro-2H-pyran-2-yl)methanol (8): In a 25 mL one-necked round bottomed flask, under an argon atmosphere, the monoacetate **4** (200 mg, 0.81 mmol) was dissolved in 8 mL of toluene. To this stirred solution was added PMBTCA (260 mg, 0.89 mmol), followed by ytterbium triflate (25 mg, 0.04 mmol). The resulting solution was stirred at room temperature for 2 h and quenched with a saturated aqueous solution of NH₄Cl (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (2 x 10 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo* to afford the crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient

elution: 80/20 to 60/40) to afford 390 mg of intermediate acetate contaminated with trichloroacetamide resulting from PMBTCA, as a colourless oil. This compound was used in the next step without further purification. $R_f = 0.66$ (PE/EtOAc : 1/1).

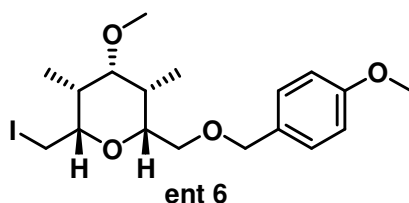
In a 25 mL one-necked round bottomed flask, the crude intermediate acetate contaminated with trichloroacetamide (390 mg, 0.81 mmol) was dissolved in 8 mL of methanol. To this stirred solution was added potassium carbonate (223 mg, 1.62 mmol), in one portion. The resulting white suspension was stirred at room temperature for 20 min and quenched with a saturated aqueous solution of NH_4Cl (10 mL). Methanol was evaporated in *vacuo*, the aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic layers were washed with brine (2 x 10 mL), dried (anhydrous MgSO_4), and concentrated in *vacuo* to afford the crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 70/30 to 50/50) to afford 218 mg (83% over two steps) of pure alcohol **8**, as a white solid. m.p. 92-93 °C ; $R_f = 0.39$ (PE/EtOAc : 1/1).

$[\alpha]_{\text{D}}^{25} = +7.9$ (c 1.00, CHCl_3).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.27 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 4.55 (d, $J = 11.6$ Hz, 1H), 4.48 (d, $J = 11.6$ Hz, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.61 (m, 2H), 3.52 (m, 1H), 3.46 (m, 2H), 3.35 (t, $J = 5.3$ Hz, 1H), 3.32 (s, 3H), 2.12 (m, 2H), 0.86 (d, $J = 7.2$ Hz, 6H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 159.2, 130.1, 129.4 (2C), 113.8 (2C), 81.1, 80.8, 78.5, 73.1, 70.41, 63.9, 55.3, 55.2, 33.5, 33.5, 8.6, 8.2.

HRMS (ESI TOF) calcd for $\text{C}_{18}\text{H}_{32}\text{NO}_5$ ($\text{M}+\text{NH}_4$)⁺ 342.2275, found 342.2272.

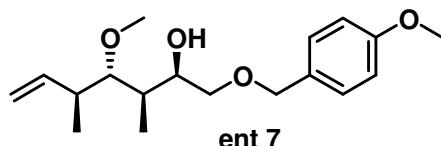


(2S,3R,4R,5S,6R)-2-(iodomethyl)-4-methoxy-6-((4-methoxybenzyloxy)methyl)-3,5-dimethyl-tetrahydro-2H-pyran (ent-6): In a flame dried 50 mL one-necked round bottomed flask, equipped with reflux condenser under an argon atmosphere, alcohol **8** (130 mg, 0.40 mmol) was dissolved in 6 mL of toluene. To this stirred solution were added successively imidazole (83 mg, 1.2 mmol), triphenylphosphine (318 mg, 1.2 mmol) and iodine (204 mg, 0.8 mmol). The resulting brown suspension was refluxed for 1 h, cooled to room temperature before a 50/50 mixture of petroleum ether / diethyl ether (10 mL) was added. The white precipitate was filtered off, washed with a 50/50 mixture of petroleum ether and diethyl ether (20 mL) and the filtrate was concentrated in *vacuo* to afford the crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 98/2 to 90/10) to afford 159 mg (92%) of pure iodopyran **ent-6**, as a colourless oil. $R_f = 0.70$ (PE/EtOAc : 8/2).

$[\alpha]_{\text{D}}^{25} = +11.5$ (c 1.00, CHCl_3).

¹H NMR (300 MHz, CDCl₃): δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.61 (m, 3H), 3.46 (m, 1H), 3.35 (t, *J* = 5.3 Hz, 1H), 3.34 (s, 3H), 3.31 (dd, *J* = 10.0, 6.6 Hz, 1H), 3.12 (dd, *J* = 10.0, 7.6 Hz, 1H), 2.35 (m, 1H), 2.04 (m, 1H), 0.86 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 159.2 (C₁₂), 130.3, 129.4 (2C), 113.8 (2C), 81.2, 80.0, 79.3, 73.1, 70.3, 55.4, 55.3, 34.5, 33.1, 8.1, 7.0, 5.0.



(3*S*,4*S*,5*R*,6*R*)-4-methoxy-7-(4-methoxybenzyloxy)-3,5-dimethylhept-1-en-3-ol (ent-7): In a 10 mL one-necked round bottomed flask, iodopyran **ent-6** (119 mg, 0.27 mmol) was dissolved in 4 mL of 96.5% ethanol. To this stirred solution was added freshly activated zinc dust (179 mg, 2.7 mmol) and the resulting suspension was refluxed for 2 h. After been cooled to room temperature, the reaction mixture was then filtered through a short pad of Celite ® and washed thoroughly with ether (3 x 10 mL). The filtrate was concentrated in *vacuo* to afford the crude product which was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 90/10 to 80/20) to afford 75 mg (90%) of pure tetrad **ent-7**, as a colourless oil. *R_f* = 0.42 (PE/EtOAc : 8/2).

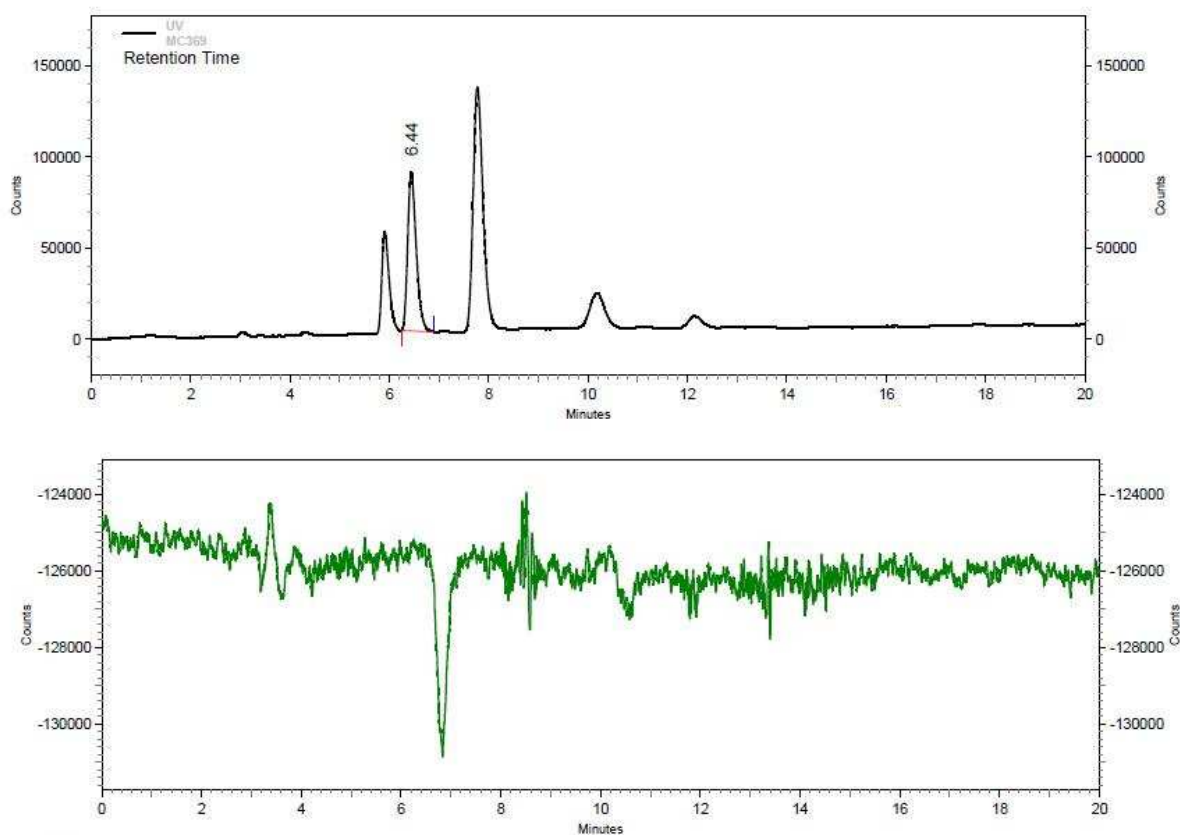
[α]_D²⁵ = +8.0 (c 1.00, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.83 (ddd, *J* = 16.9, 11.0, 8.1 Hz, 1H), 5.06-5.00 (m, 2H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.18 (m, 1H), 3.80 (s, 3H), 3.48 (s, 3H), 3.46 (dd, *J* = 9.4, 6.8 Hz, 1H), 3.39 (dd, *J* = 9.4, 4.9 Hz, 1H), 3.05 (dd, *J* = 6.8, 4.9 Hz, 1H), 2.87 (brs, 1H_{OH}), 2.49 (m, 1H), 1.71 (pd, *J* = 7.0, 1.7 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 159.2, 140.4, 130.3, 129.3 (2C), 114.8, 113.8 (2C), 88.8, 73.0, 72.9, 69.4, 61.6, 55.2, 40.5, 37.1, 17.5, 10.8.

Compound *ent-7*

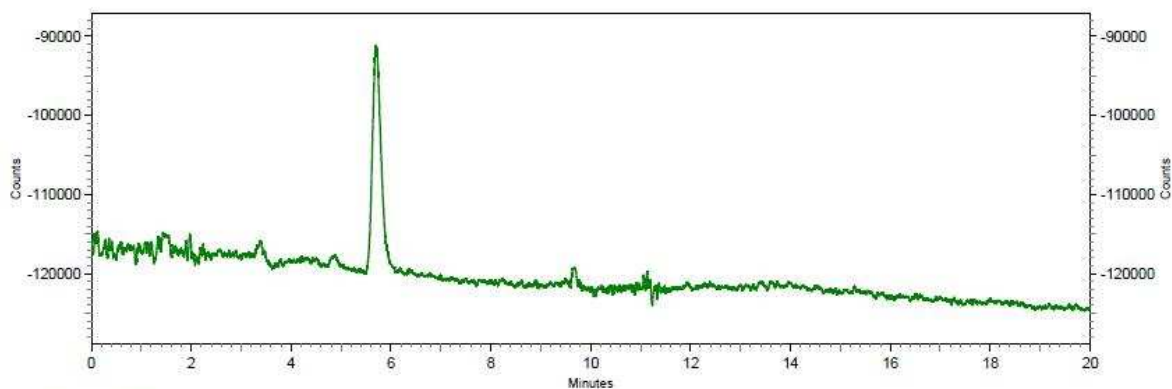
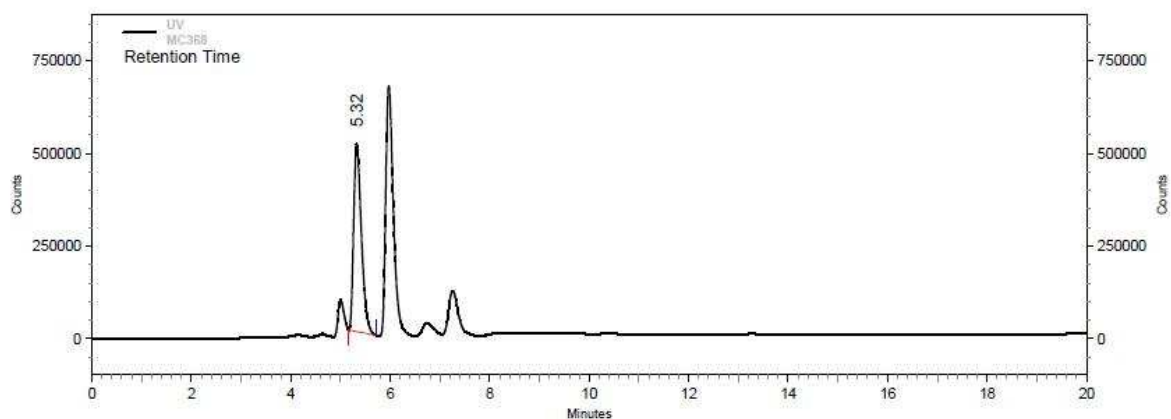
Method description : Chiralpak AD-H, Hexane/isopropanol 80/20, 1 ml/min, UV 254 nm et polarimètre



UV Results					
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.44	1046905	100.00	1.15	1.00	0.00
Totals		1046905	100.00		

Compound 7

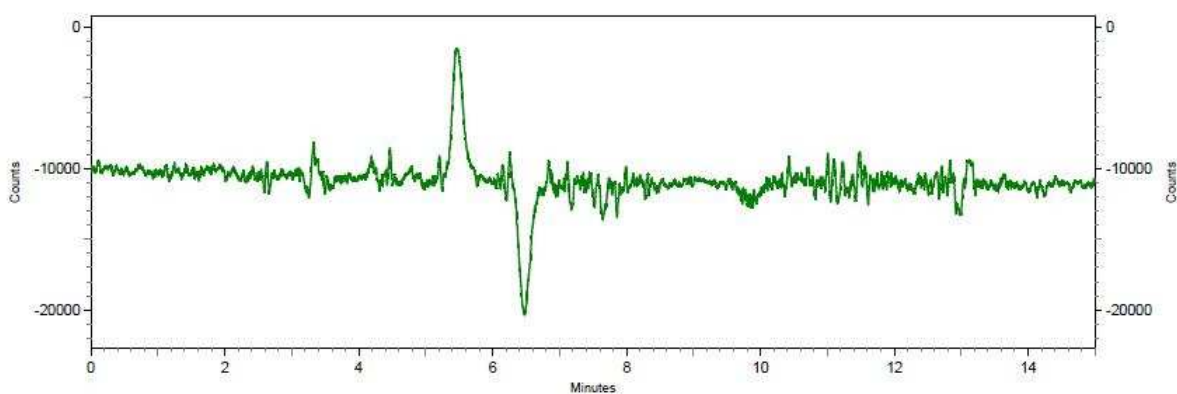
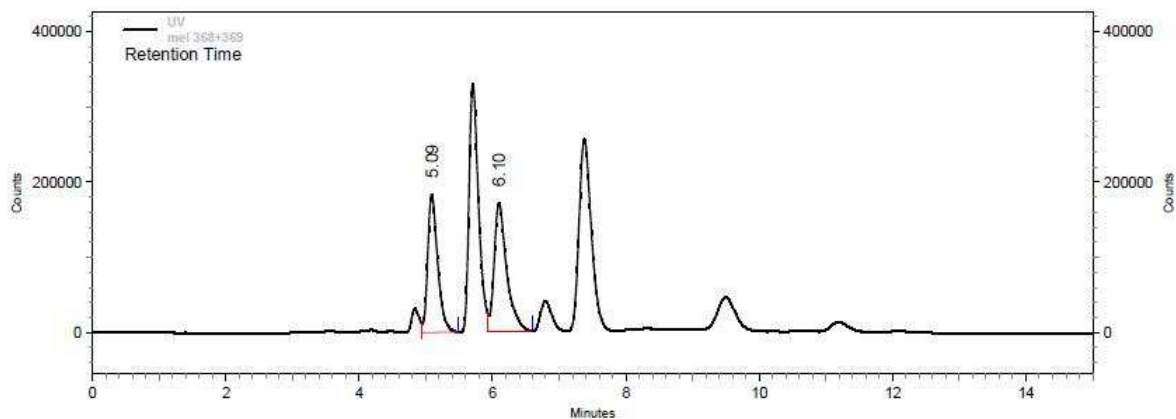
Method description : Chiralpak AD-H, Hexane/isopropanol 80/20, 1 ml/min, UV 254 nm et polarimètre



UV Results						
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)	
5.32	5523919	100.00	0.77	1.00	0.00	
Totals		5523919	100.00			

Compounds 7 + ent-7

Method description : Chiralpak AD-H, Hexane/isopropanol 80/20, 1 ml/min, UV 254 nm et polarimètre



UV Results					
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
5.09	1897032	45.84	0.70	1.00	0.00
6.10	2241611	54.16	1.03	1.48	3.37

Totals	4138643	100.00			
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V- Copies of ^1H NMR and ^{13}C NMR

