Preparation of cis-fused tetrahydropyranyl lactones via Pd-catalysed cyclocarbonylation of enediols

Daniela Cintulová,¹ Monika Slahúčková,¹ Juraj Paštrnák,¹ Naďa Prónayová² and Peter Szolcsányi¹,*

¹ Department of Organic Chemistry and ² Department of NMR Spectroscopy
Faculty of Chemical and Food Technology, Slovak University of Technology
Radlinského 9, SK-812 37 Bratislava, Slovakia

E-mail: peter.szolcsanyi@stuba.sk

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General Experimental

All chemicals and reagents were purchased from commercial sources (Alfa Aesar, Sigma-Aldrich) and were used without further purification, unless otherwise noted. All solvents were distilled prior the use. Anhydrous solvents were prepared either by filtration through column of activated alumina or by standing over activated 4Å molecular sieves and stored under argon atmosphere.\(^1\) Hexanes refer to a mixture of C-6 alkanes (b.p. 60–80°C). Yields refer to chromatographically and spectroscopically (\(^1\)H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on aluminium sheets pre-coated with silica gel 60 F\(_{254}\) (Merck) or aluminium oxide 60 F\(_{254}\) (neutral, Merck). Visualisation was performed using shortwave UV light followed by dipping TLC plates in either basic solution of KMnO\(_4\), acidic solution of vanillin or acidic solution of ceric ammonium nitrate followed by heating with heat gun. Flash column chromatography (FLC) was performed using Silica Gel 60 (particle size 0.040–0.063 mm). NMR spectra were recorded in CDCl\(_3\) on Varian Mercury Plus (300 MHz for \(^1\)H, 75MHz for \(^{13}\)C) or Varian Unity Inova 600 (600 MHz for \(^1\)H, 151 MHz for \(^{13}\)C) and were calibrated using residual non-deuterated solvent or tetramethylsilane as an internal reference (CDCl\(_3\): 7.26 ppm \(^1\)H NMR, 77.16 ppm \(^{13}\)C NMR, TMS: 0.00 ppm). Chemical shifts (\(\delta\)) are quoted in ppm and following abbreviations were used to explain NMR peak multiplicities: \(s\) = singlet, \(d\) = doublet, \(t\) = triplet, \(q\) = quartet, \(pent\) = pentet, \(sext\) = sextet, \(m\) = multiplet, \(br\) = broad signal. Liquid chromatography–mass spectrometry (LC-MS) analyses were performed on Agilent 1200 Series instrument equipped with a multimode MS detector using the MM ESI/APCI ionisation method (column Zorbax Eclipse XDB-18, 150 x 4.6 mm, particle size 5 \(\mu\)m, eluent water with 0.1% HCO\(_2\)H /CH\(_3\)CN, 70:30, flow 1.5 ml/min). High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Orbitrap Velos mass spectrometer with a heated electrospray ionisation (HESI) source in positive and/or negative mode. Optical rotations were measured with a JASCO P-2000 polarimeter and are given in units of \(10^{-1}\) deg·cm\(^2\)·g\(^{-1}\). FTIR spectra were obtained on a Nicolet 5700 spectrometer (Thermo Electron) equipped with a Smart Orbit (diamond crystal ATR) accessory using the reflectance technique (4000–400 cm\(^{-1}\)).

Synthetic Procedures

(±)-cis/trans-5-Methyltetrahydrofuran-2-ol (rac-6)

To a cooled (-78°C) soln. of γ-valerolactone rac-7 (2.1 g, 21 mmol) in anhydrous CH₂Cl₂ (53 mL) was slowly added DIBAL (28 ml, 1M in heptane, 28 mmol, 1.3 eq) over 1.5 h via syringe pump under argon. The mixture was then stirred at -78°C for another 1 h until the full conversion of substrate (TLC control). Reaction was quenched by dropwise addition of MeOH (7 ml) followed by sat. aq. soln. of sodium potassium tartrate (50 ml). The generated white suspension was stirred at r.t for 2 hrs, the mixture was filtered through Celite and washed with CH₂Cl₂ (50 ml). Separated water layer was extracted with CH₂Cl₂ (4 x 40 ml) and combined organic phases were washed with sat. aq. NaCl soln. (2 x 40 mL). Combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. Due to undesired co-distillation of product on rotary evaporator (40°C, 700 mbar), solvent was carefully removed by atmospheric distillation (45°C bath) using Vigreux column (2 x 44 cm) and crude product (1.94 g) was purified by short-path (bulb-to-bulb, Kugelrohr) distillation (108–115°C, 23 Torr) affording pure γ-valerolactol rac-6 as colourless liquid (1.86 g, 87%) containing racemic cis-/trans-diastereomers in a ratio ~ 1:1.5 as determined by integration of Me-signals in ¹H NMR spectra.

Rᶠ= 0.21 (EtOAc/hexanes/2% aq. NH₃ = 1:1:0.1), C₅H₁₀O₂ (M.W. = 102.13 g/mol).

¹H NMR (300 MHz, CDCl₃): δ = 1.22 (d, 3H, J = 6.2 Hz, trans-Me), 1.35 (d, 3H, J = 6.2 Hz, cis-Me), 1.65–2.23 (m, 4 x 2H, H-3, H-4), 3.73 (brs, 2 x 1H, 2 x OH, exchangeable with D₂O), 4.07–4.20 (m, 1H, cis-H-5), 4.26–4.43 (m, 1H, trans-H-5), 5.46 (d, 1H, J = 3.1 Hz, cis-H-2), 5.55 (dd, 1H, J = 4.7, 1.6 Hz, trans-H-2).

Data are in accordance with the literature.³

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(±)-syn/anti-Hept-6-ene-2,5-diol (rac-1)

\[ \text{rac-6} \xrightarrow{\text{Mg-nucleophile}} \text{rac-1} \]

**a) Addition of Mg-nucleophile**

To a cooled (-5°C) soln. of vinylmagnesium bromide (15 ml, 1M in THF, 15 mmol, 3 eq) was slowly added a THF (5 ml) soln. of lactol rac-6 (0.5 g, 4.87 mmol) over 15 min via syringe under argon. The cooling bath was removed and the mixture was stirred at r.t. for 12 hrs until the full conversion of substrate (TLC control). The cooled (0°C) reaction mixture was quenched by addition of sat. aq. soln. of NH₄Cl (15 ml), diluted with AcOEt (40 ml) and H₂O (20 ml). Separated water layer was extracted with AcOEt (8 x 40 ml) and the combined organic phases were dried over anhydrous Na₂SO₄. Filtration and evaporation of volatiles in vacuo afforded dark yellow oil (773 mg) that was purified by FLC (20 g SiO₂, hexanes/EtOAc = 4:1) yielding pure mixture (~ 1:1) of diastereomeric syn/-anti-diols rac-1 (545 mg, 86%) as viscous pale yellow oil. Their ratio was approximately determined by integration of partially overlapping doublets of H-1 protons (1.17 vs. 1.19 ppm).

**b) Addition of Zn-nucleophile**

To a cooled (-5°C) soln. of vinylmagnesium bromide (12 ml, 1M in THF, 12 mmol, 4 eq) was slowly added a soln. of freshly dried (1 mbar, 300 → 450°C, 15 min) ZnBr₂ (1.32 g, 5.84 mmol, 2 eq) in anhydrous THF (5 ml) over 15 min via syringe under argon. The cooling bath was removed and the mixture was stirred at r.t. for 45 min. The reaction mixture was then cooled to 0°C and a soln. of lactol rac-6 (0.3 g, 2.939 mmol) in anhydrous THF (5 ml) over 30 min. The mixture was stirred at r.t. for 36 hrs until the full conversion of substrate (TLC control). The cooled (0°C) reaction mixture was quenched by addition of sat. aq. soln. of NH₄Cl (10 ml), diluted with AcOEt (10 ml). The separated organic layer was sequentially washed with 5% aq. HCl (4 ml), sat. aq. NaHCO₃ soln. (10 ml), and water (10 ml). The combined water phases were back-extracted with AcOEt (6 x 20 ml) and the combined organic extracts were dried over anhydrous Na₂SO₄. Filtration and evaporation of volatiles in vacuo afforded dark yellow viscous oil (356 mg) that was purified by FLC (25 g SiO₂, hexanes/EtOAc = 4:1) yielding pure mixture (~ 1:1) of diastereomeric syn/-anti-diols rac-1 (325 mg, 85%) as a pale yellow oil. Their ratio was approximately determined by integration of partially overlapping doublets of H-1 protons (1.17 vs. 1.19 ppm).

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c) Addition of Ce-nucleophile

To a freshly dried (1 mbar, 100 → 400°C, 20 min) CeCl₃ (1.03 g, 4.14 mmol, 3 eq) was added a soln. of vinylmagnesium chloride (2.6 ml, 1.6M in THF, 4.94 mmol, 3.6 eq) at r.t. and the mixture was then cooled to 0°C. Next, a soln. of lactol rac-6 (141 mg, 1.38 mmol) in anhydrous THF (3 ml) was slowly added dropwise over 15 min under argon. The cooling bath was removed and the mixture was stirred at r.t. for 12 hrs until the full conversion of substrate (TLC control). The cooled (0°C) reaction mixture was quenched by addition of sat. aq. soln. of NH₄Cl (5 ml), diluted with AcOEt (10 ml) and H₂O (10 ml). Separated organic layer was filtered through Celite to remove solids, water layer was extracted with AcOEt (5 x 30 ml) and combined organic phases were dried over anhydrous Na₂SO₄. Filtration and evaporation of volatiles in vacuo afforded dark yellow oil (276 mg) that was purified by FLC (9 g SiO₂, hexanes/EtOAc = 4:1 → 2:1) yielding pure mixture (~ 1:1) of diastereomeric syn-/anti-diols rac-1 (146 mg, 81%) as yellowish oil. Their ratio was approximately determined by integration of partially overlapping doublets of H-1 protons (1.17 vs. 1.19 ppm).

(R)-Hex-5-ene-2-ol (9)

Alkenol 9 was prepared via modification of procedure by Marco et al.⁶ Thus, finely powdered CuI (0.947 g, 4.97 mmol, 0.1 eq) was carefully dried under vacuum (0.1 mbar, 100°C, 20 min) until it became light yellow. Then, anhydrous Et₂O (80 ml) was added and the suspension was cooled to -30°C. Next, allylmagnesium chloride (2M in THF, 24 ml, 48 mmol, 1.3 eq) was added over 15 min with vigorous stirring. After 30 min, a solution of (R)-2-methyloxirane 8 (2.14 g, 36.84 mmol) in anhydrous Et₂O (20 ml) was slowly added via syringe pump over 45 min. The resulting yellow suspension was stirred at -30°C for 12 h. The reaction mixture was quenched by addition of sat. aq. NH₄Cl soln. (40 ml) and the blue mixture was diluted with Et₂O (50 ml). The separated organic phase was repeatedly washed with sat aq. NH₄Cl soln. until its discoloration (3 x 50 ml), the combined water fractions were back-extracted with Et₂O (4 x 50 ml) and the combined organic phase was dried over MgSO₄. Due to undesired co-distillation of product, solvent was carefully removed by atmospheric distillation (40°C bath) using Vigreux column (2 x 44 cm) and the crude product was purified by short-path (bulb-to-bulb, Kugelrohr) distillation (144 mbar, 100–125°C) affording alkenol 9 as a colourless oil (3.28 g, 90%).

Rf = 0.56 (EtOAc/hexanes = 2:1), C₆H₁₂O (M.W. = 100.16 g/mol).

¹H NMR (300 MHz, CDCl₃): δ = 1.18 (d, 3H, J = 6.8 MHz, H-1), 1.48–1.61 (m, 2H, H-3), 2.05–2.27 (m, 2H, H-4), 3.77–3.90 (sext, 1H, H-2), 4.94–5.11 (ddt, 2H, H-6), 5.77–5.92 (ddt, 1H, H-5).

Data are in accordance with the literature.⁷

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