An enantiodivergent synthesis of N-Boc-protected (R)- and (S)-4-amino cyclopent-2-en-1-one

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Abstract
Routes are reported for the synthesis of both (1R)- and (1S)-tert-butyl-(4-oxocyclopent-2-en-1-yl)carbamate 2. Featuring Mitsunobu reactions with di-tert-butyl iminodicarbonate, both syntheses begin from (S)-4-[(tert-butyl(dimethyl)silyl)oxy] cyclopent-2-en-1-one (3) and take advantage of the 1,4-cyclopentenyl dioxygenation pattern of this optically active starting material. Thus both (−) and (+)-2 have been accessed from 3 in an enantiodivergent manner in 11% and 10% overall yield over five and seven reaction steps, respectively.

Keywords
Mitsunobu reaction, O-protecting groups, prostaglandin analogue, reduction, stereoselective transformation

Introduction
Substituted cyclopentyl and cyclopentenyl compounds are useful building blocks for the construction of natural products and other compounds of interest: many of which feature heteroatom substituents. In relation to this, we have recently reported the preparation of aza-analogues of the unsaturated prostaglandin Δ12,14,15-deoxy-PGJ₂ (Scheme 1). This type of prostaglandin possesses an interesting biological profile and attempts to explore how the structure of this compound affects its activity are hampered because it is not amenable to ready synthetic divergence from an advanced intermediate. In relation to this point, we demonstrated that incorporation of a nitrogen atom at the 4-position in the cyclopentenone enabled ready modification of the α-prostanoid side chain. In addition, alkylidination/arylidination was successfully used to install the unsaturated exocyclic side chain present in the natural product analogue 1.

This enables 1 to be traced to the optically active N-Boc-protected functionalised cyclopentenone 2. Since some compounds of the type 1 demonstrated comparable activities to Δ12,14,15-deoxy-PGJ₂ in assays relevant to inflammation and anticancer activity, a robust supply of optically active compound (R)-2 was required. In addition, we were also interested to explore how the stereogenicity of the α-side chain affected biological action, and consequently also required access to the (S)-enantiomer of compound 2. It should be noted that several methods for the synthesis of optically active forms of 2 have been reported, and in this article, we show how (S)-4-[(tert-butyldimethylsilyl)oxy]cyclopent-2-en-1-one (3) can be used to prepare both (R)- and (S)-2.

Results and discussion
Optically active (−)-3 is commercially available and can be prepared with high levels of enantioexcess in several
and has scarce literature precedence. Alternative activated form of 4-hydroxycyclopentenone is problematic -dioxygenation takes advantage of the symmetrical 1,4-
Consequently, an alternative approach was employed which yielded (12%) for this two-step process was unacceptably low. 

\[
\text{Experimental}
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Starting materials were obtained from commercial suppliers and were used without further purification unless otherwise stated. CAS number for (S)-4-[(tert-butyldimethylsilyl)oxy]cyclopent-2-en-1-yl]carbamic acid (2). These optically active compounds are of broad utility for the synthesis of 1,4-difunctionalised cyclopentenyl compounds which are of synthetic and biological interest. It should be noted again that the direct nucleophilic attack on activated forms of 3 has been infrequently reported due to competitive formation of cyclopentadienone (which subsequently undergoes cycloaddition chemistry). 

\[
\text{Conclusion}
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In conclusion, routes are described for the synthesis of both enantiomers of tert-butyl-(4-oxocyclopent-2-en-1-yl)carbamate (2). These optically active compounds are of broad utility for the synthesis of 1,4-difunctionalised cyclopentenyl compounds which are of synthetic and biological interest. It should be noted again that the direct nucleophilic attack on activated forms of 3 has been infrequently reported due to competitive formation of cyclopentadienone (which subsequently undergoes cycloaddition chemistry). 

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\text{General directions}
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Starting materials were obtained from commercial suppliers and were used without further purification unless otherwise stated. CAS number for (S)-4-[(tert-butyldimethylsilyl)oxy]cyclopent-2-en-1-one (3): 61305-36-0. All commercially available solvents were used as supplied unless otherwise stated. All ‘dry’ solvents were dried and distilled by standard procedures. Glassware was either dried in an oven, flame-dried with a Bunsen burner before use and assembled hot then cooled to room temperature under a stream of nitrogen. Oxygen-free, anhydrous nitrogen was obtained from BOC. Thin-layer chromatography (TLC) was carried out on Merck silica gel aluminium sheets (60 F254). Ultraviolet (UV) light and a mixture of KMnO₄ (1.5 g), K₂CO₃ (10 g), 10% NaOH (1.25 mL) in water (200 mL) was used to visualise spots. Merck silica 60 Å (230–400 mesh) 9385 was used for flash column chromatography. Nuclear magnetic resonance (NMR) spectra were recorded on Varian Unit 300, 400 or 500 MHz spectrometers as specified. Spectra were calibrated using trimethylsilylane (TMS) or the residual protiated solvent. Coupling constants (J) are quoted in Hertz. ¹H and ¹³C NMR chemical shift assignments are based on two-dimensional NMR techniques, including ¹H-¹H-gCOSY and heteronuclear single quantum coherence (HSQC) experiments. All values are reported in parts per million (ppm). Infrared (IR) spectra were recorded on a Bruker Alpha Fourier-transform infrared (FTIR) spectrometer. High-resolution mass spectrometry (HRMS) was
performed using a Waters Crop, Micromass LCT, electrospray ionisation (ESI) spectrometer. Melting points were determined in an open capillary on a Gallenkamp melting point apparatus and are uncorrected. Compound names were generated using ChemDraw software. Known compounds are referenced accordingly.

\[(1R,4S)-4-\text{[(tert-Butyldimethylsilyl)oxy]cyclopent-2-enol (4a) and (1S,4S)-4-\text{[(tert-Butyldimethylsilyl)oxy]cyclopent-2-enol (4b)}\]

Cerium chloride heptahydrate (1.76 g, 4.72 mmol, 1.0 equiv.) was added to a solution of ((S)-4-((tert-butyldimethylsilyl)oxy)cyclopent-2-enone (3) (1.01 g, 4.76 mmol, 1.0 equiv.) in MeOH (15 mL) and the resulting suspension was stirred vigorously for 5 min until fully dissolved. The solution was cooled to \(-20^\circ C\) (adjusted with dry ice in acetone) and sodium borohydride (0.18 g, 4.76 mmol, 1.0 equiv.) was added slowly. After stirring at this temperature for 10 min, the cooling bath was removed and the suspension was stirred at room temperature for an additional 20 min. Following this, sat. NH₄Cl (40 mL) was added dropwise and the mixture was then extracted with CH₂Cl₂ (3 \(\times\) 50 mL). The combined organic phases were dried over MgSO₄, filtered and the solvent removed in vacuo, which resulted in the formation of the desired product 4 (0.79 g, 78%) as a colourless oil and as

**Scheme 2.** Asymmetric synthesis of (−)-2 from (−)-3.

**Scheme 3.** The Mitsunobu reaction for the epimerisation of 4a into 4b.

**Scheme 4.** Asymmetric synthesis of (+)-2 from 4a.
a mixture of diastereomers. The crude mixture, containing 15% of the diastereomer 4b (as determined by 1H NMR spectroscopy), was purified by column chromatography (c-Hex/EtOAc; 9:1), affording the desired product (−)-5 (0.295 g, 42%) as a colourless oil. Rf=0.5 (c-Hex/EtOAc; 9:1). IR (neat): v_max = 3079, 2976, 2925, 2857, 1743, 1473, 1391, 1346, 1252, 1149, 1113 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 0.07 (br s, 6H, CH₃), 0.89 (s, 9H, CH₃), 1.48 (s, 18H, CH₃), 2.06 (dd, J=14.0, 8.5, 2.5 Hz, 1H, CH₂), 2.24 (dd, J=14.0, 7.5, 5.0 Hz, 1H, CH₂), 5.03–5.09 (m, 1H, CH), 5.41–5.47 (m, 1H, CH), 5.78–5.85 (m, 2H, CH₂) ppm; 13C NMR (101 MHz, CDCl₃): δ 4.46 (CH₂), 22.9 (CH), 75.3 (CH), 135.8 (CH), 152.3 (CH) ppm; HRMS (ES⁺): m/z C₁₉H₂₇NO₃SiNa (MNa⁺) calcd. 340.1471; found 340.1469; [α]D = −112.6 (c=0.1, CHCl₃).

Di-tert-butyl[(1S,4S)-4-hydroxycyclopent-2-en-1-yl]imidodicarboxylate [(−)-6]

A 1 M solution of TBAF in THF (3.02 mL, 3.02 mmol, 1.0 equiv.) was added to a solution of TBS ether 5 (831 mg, 2.01 mmol, 1.0 equiv.) in dry THF (30 mL). The solution was stirred at room temperature for 1 h 30 min. After this time, the reaction mixture was concentrated under a flow of air and the resulting residue was directly purified by column chromatography (c-Hex/EtOAc; 2:1), affording the desired product (−)-6 (498 mg, 83%) as a white solid. M.p. = 60–62 °C; Rf=0.5 (c-Hex/EtOAc; 1:1). IR (neat): v_max = 3250, 2980, 2933, 1746, 1706, 1477, 1456, 1390, 1345 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 1.49 (s, 18H, CH₃), 2.11 (dd, J=14.0, 8.5, 2.0 Hz, 1H, CH₂), 2.34 (dd, J=14.0, 7.5, 5.5 Hz, 1H, CH), 5.06 (br s, 1H, CH), 5.44–5.53 (m, 1H, CH₂), 5.91 (dd, J=5.5, 2.0, 1.0 Hz, 1H, CH), 5.93–5.98 (m, 1H, CH) ppm; 13C NMR (101 MHz, CDCl₃): δ 28.1 (CH₃), 39.3 (CH), 61.8 (CH), 76.8 (CH), 82.6 (C), 134.8 (CH), 135.6 (CH) ppm; HRMS (ES⁺): m/z C₁₅H₂₃NO₂ (M⁺) calcd. 300.1805; found 300.1806; [α]D = −142.6 (c=0.1, CHCl₃).

Di-tert-butyl[(1S)-4-oxocyclopent-2-en-1-yl]imidodicarboxylate [(−)-7]

Dess–Martin periodinane (651 mg, 1.53 mmol, 1.0 equiv.) was added to a solution of alcohol 6 (441 mg, 1.47 mmol, 1.0 equiv.) in dry CH₂Cl₂ (40 mL). The solution was stirred at room temperature for 2.5 h. (The reaction was monitored by TLC.) An additional aliquot of Dess–Martin periodinane (126 mg, 0.30 mmol, 0.2 equiv.) was added, and the reaction mixture was stirred for a further 45 min. The reaction mixture was filtered through Celite and concentrated under a flow of air. The resulting residue was purified by column chromatography (c-Hex/EtOAc; 4:1), affording the desired product (−)-7 (216 mg, 49%) as a colourless solid. M.p. = 62–64 °C; Rf=0.3 (c-Hex/EtOAc; 4:1). IR (neat): v_max = 2976, 2925, 2852, 1750, 1705, 1345, 1262, 1232, 1134, 1101 cm⁻¹; 1H NMR (500 MHz, CDCl₃): δ 0.50 (s, 18H, CH₃), 2.42 (dd, J=18.0, 7.5, 5.0 Hz, 1H, CH), 2.73 (dd, J=18.0, 7.0 Hz, 1H, CH₂), 5.48–5.53 (m, 1H, CH), 6.22 (dd, J=5.5, 2.5 Hz, 1H, CH₂), 7.52 (dd, J=5.5, 2.5 Hz, 1H, CH) ppm; 13C NMR (101 MHz, CDCl₃): 28.1 (CH), 40.6 (CH₂), 56.1 (CH), 83.7 (C), 134.1 (CH), 152.3 (CH), 163.0 (CO), 206.3 (CO) ppm; HRMS (ES⁺): m/z C₁₅H₂₃NO₂Na (MNa⁺) calcd. 320.1468; found 320.1471; [α]D = −82.4 (c=0.1, CHCl₃).

(S)-tert-Butyl (4-oxocyclopent-2-en-1-yl) carbamate [(−)-2]

Trifluoroacetic acid (70 μL, 0.97 mmol, 1.9 equiv.) was added to a solution of cyclopentone (−)−7 (152 mg, 0.51 mmol, 1.0 equiv.) in dry CH₂Cl₂ (7 mL) and the solution was stirred under an inert atmosphere for 1.5 h. After this, the solution was diluted with CH₂Cl₂ (8 mL) and washed with NaHCO₃ (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic phases were dried over MgSO₄ and the solvent removed in vacuo. Purification by column chromatography (c-Hex/EtOAc; 2:1) afforded the desired product (−)-2 (83 mg, 83%) with data as reported.11–15 M.p. = 110–111 °C; Rf=0.2 (c-Hex/EtOAc; 2:1). IR (neat): v_max = 3325, 2981, 2932, 1719, 1673, 1539, 1366, 1252, 1159 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 1.46 (s, 9H, CH₃), 2.16 (dd, J=18.5, 2.5 Hz, 1H, CH), 2.86 (dd, J=18.5, 6.5 Hz, 1H, CH), 4.73 (br s, 1H, NH), 4.95 (br s, 1H, CH), 6.24 (dd, J=5.5, 2.0 Hz, 1H, CH), 7.53 (dd, J=5.5, 2.5 Hz, 1H, CH) ppm; 13C NMR (101 MHz, CDCl₃): 28.5 (CH), 42.6 (CH), 51.2 (CH), 80.4 (C), 135.4 (CH), 155.2 (CH), 162.3 (CO), 206.6 (CO) ppm; HRMS (ES⁺): m/z C₁₀H₁₅NO₃Na (MNa⁺) calcd. 220.0944; found 220.0945; [α]D = −73.5 (c=0.1, CHCl₃), [lit.11] [α]D = −73 (c=0.1, CHCl₃).

(1S,4S)-4-[(tert-Butyldimethylsilyl)oxy]cyclopent-2-enol (4b)

Alcohol 4 (100 mg, 0.47 mmol, 1.0 equiv.) was added to a solution of triphenylphosphine (241 mg, 0.92 mmol, 1.5 equiv.) and benzoic acid (88 mg, 0.71 mmol, 1.5 equiv.) in dry THF (5 mL). The solution was cooled to 0 °C and DIAD (0.2 mL, 0.94 mmol, 2.0 equiv.) was added. Following this,
the reaction was allowed to warm to room temperature and stirred for 16 h under an inert atmosphere. After this time, the solvent was removed under a flow of air and the residue was diluted with Et₂O (10 mL) and washed with NaHCO₃ (3 × 10 mL). The organic phase was dried over MgSO₄ and the solvent was removed in vacuo. The intermediate was then diluted in methanol (5 mL) and K₂CO₃ (326 mg, 2.35 mmol, 5.0 equiv.) was added. The resulting suspension was stirred under an inert atmosphere for 4 h, after which the suspension was filtered and concentrated in vacuo. The resulting residue was dissolved in Et₂O (10 mL) and water (10 mL) and washed with water (3 × 10 mL) and brine (10 mL). The organic phase was dried over MgSO₄ and the solvent removed in vacuo. Purification by column chromatography (c-Hex/EtOAc; 3:1) afforded the desired product 4b (12 mg, 12%) with data as reported.¹¹ H NMR (400 MHz, CDCl₃): δ 0.06–0.10 (m, 6H, CH₃), 0.89 (s, 9H, CH₃), 1.96–2.10 (m, 2H, CH₂), 5.02 (s, 1H, CH), 5.06–5.12 (m, 1H, CH), 5.91–5.97 (m, 2H, CH) ppm; ¹³C NMR (101 MHz, CDCl₃): −4.5 (CH₃), 18.4 (C), 26.1 (CH₃), 44.7 (CH₂), 76.4 (CH), 76.7 (CH), 135.6 (CH), 138.6 (CH) ppm.

(1R,4S)-4-((tert-Butyldimethylsilyl)oxy) cyclopent-2-en-1-yl acetate (8)

DMAP (cat.) was added to a solution of alcohol 4 (785 mg, 3.66 mmol, 1.0 equiv.) in dry CH₂Cl₂ (30 mL). The solution was cooled to 0 °C and Et₃N (0.70 mL, 5.02 mmol, 1.3 equiv.) was added, followed by acetic anhydride (0.40 mL, 4.23 mmol, 1.2 equiv.). The cooling bath was removed, and the solution was stirred for 2.5 h. After this time, NH₄Cl (20 mL) was added to the solution and the resulting mixture was stirred for 10 min. The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic phase was washed with NaHCO₃ (40 mL) and dried over MgSO₄. Filtration and solvent removal in vacuo gave the desired product 8 (782 mg, 3.05 mmol, 83%) as a yellow liquid. The crude product (8), with data as described above for (−)-α-Di-butyl-iminodicarboxylate (10), was purified by column chromatography (c-Hex/EtOAc; 3:1) affording the desired product 10 (0.287 g, 41%) as a colourless oil. Rₚ = 0.4 (c-Hex/EtOAc; 9:1); IR (neat): νmax = 2980, 2936, 1736, 1701, 1344, 1234, 1146, 1112 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 6.148 (s, 18 H, CH₃), 2.02 (s, 3H, CH₃), 2.19 (dd, J = 14.5, 8.0, 2.0 Hz, 1H, CH), 2.35 (dd, J = 14.5, 7.5, 5.5 Hz, 1H, CH), 5.41–5.51 (m, 1H, CH), 5.77–5.82 (m, 1H, CH), 5.89–5.96 (m, 1H, CH), 6.02 (dd, J = 5.5, 2.0 Hz, 1H, CH) ppm; ¹³C NMR (101 MHz, CDCl₃): 61.4 (CH), 79.4 (CH), 82.7 (C), 130.5 (CH), 138.3 (CH), 152.8 (CO), 171.1 (CO) ppm; HRMS (ES⁺): m/z C₂₁H₂₆NO₃Na (MNa⁺) calcd. 364.1731; found 364.1732; [α]D = +150.4 (c = 0.1, CHCl₃).

Di-tert-butyl[(1R,4S)-4-acetoxy-cyclopent-2-en-1-yl]-imidodicarboxylate (+-6)

K₂CO₃ (172 mg, 1.24 mmol, 2.0 equiv.) was added to a solution of acetate 10 (210 mg, 0.62 mmol, 1.0 equiv.) in MeOH (5 mL). The solution was stirred for 2 h, after which NaHCO₃ (15 mL) was added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over MgSO₄ and the solvent removed in vacuo. Purification by column chromatography (c-Hex/EtOAc; 3:1) afforded the desired product (+)-6 (134 mg, 71%) as a colourless waxy solid with data as described above for (−)-6. Rₚ = 0.2 (c-Hex/EtOAc; 3:1); [α]D = +142.6 (c = 0.1, CHCl₃).

Di-tert-butyl[(1S)-4-oxocyclopent-2-en-1-yl]-imidodicarboxylate (+-7)

Dess–Martin periodinane (561 mg, 1.32 mmol, 3.0 equiv.) was added to a solution of alcohol (+)-6 (328 mg, 1.10 mmol, 1.0 equiv.) in dry CH₂Cl₂ (30 mL) and the solution was stirred at room temperature for 2.5 h. Following this, the reaction mixture was filtered through Celite, concentrated in vacuo and the resulting residue was purified by column chromatography (c-Hex/EtOAc; 4:1), affording the desired product (+)-7 (251 mg, 77%) as a colourless solid with data as previously stated for (−)-7. [α]D = +79.3 (c = 0.1, CHCl₃).
(R)-tert-Butyl (4-oxocyclopent-2-en-1-yl) carbamate [(+)-2]:

Trifluoroacetic acid (0.10 mL, 1.31 mmol, 1.9 equiv.) was added to a solution of cyclopentenone (+)-7 (206 mg, 0.69 mmol, 1.0 equiv.) in dry CH$_2$Cl$_2$ (10 mL), and the solution was stirred under an inert atmosphere for 2.5 h. After this time, the solution was diluted with CH$_2$Cl$_2$ (10 mL) and washed with NaHCO$_3$ (15 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3×15 mL) and the combined organic phases were dried over MgSO$_4$ and the solvent removed in vacuo. Purification by column chromatography (c-Hex/EtOAc; 2:1) afforded the desired product (+)-2 (111 mg, 82%) with data as described above for (−)-2. 

$\alpha_D$ = +74.4 ($c$ = 0.1, CHCl$_3$), {Lit.$^13$ $\alpha_D$ = +66.8 ($c$ = 1.0, CHCl$_3$)}.

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