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Synthesis of enantiopure 1-azaspiro[4.5]dec-6-en-8-ones from L-proline derivatives

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Abstract—An enantioselective synthesis of protected 1-azaspiro[4.5]dec-6-en-8-one derivatives was achieved using an alkylidene carbene 1,5-CH insertion reaction as the key step.

1. Introduction

The 1-azaspiro[4.5]decane[1] skeleton is found in several natural products, such as TAN1251 derivatives, FR901483,[2,3] cylindricines,[4] lepadiformines[5] and lapidilectine B (Fig. 1).[6]

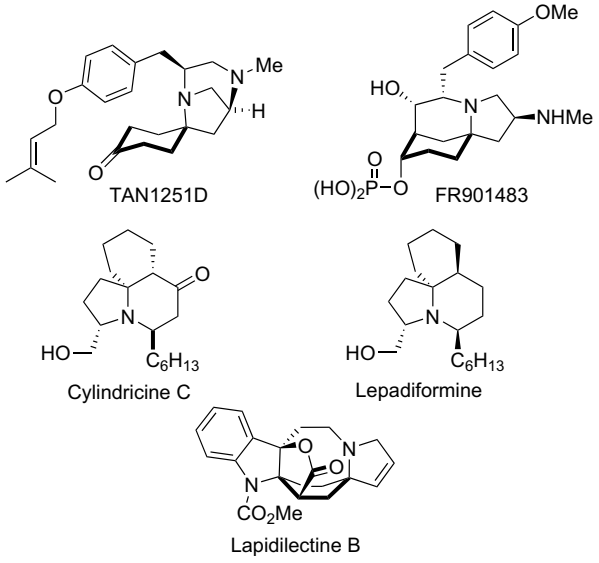
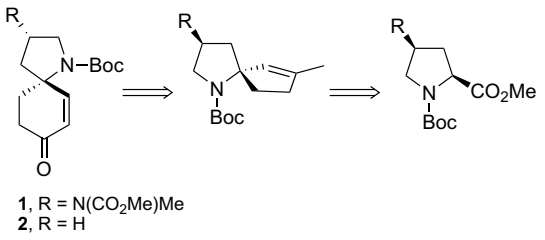


Figure 1.

Following our studies in the FR901483 series starting from 1-azaspiro[4.5]decan-8-ones,[7] we herein report the synthesis of undescribed enantiopure 1-azaspiro[4.5]dec-6-en-8-one[8] derivatives **1** and **2**, which could be considered as building blocks for the enantioselective construction of the azatricyclic ring of some of the aforementioned alkaloids. The synthetic approach follows the methodology recently reported by Hayes,[9] based on the alkylidene carbene 1,5-CH insertion in proline derivatives, which he has also used in a formal synthesis of TAN1251A (see Scheme 1).[10]



Scheme 1.

2. Results and discussion

The synthetic studies were first devoted to the synthesis of **1** using proline **3** as the starting material. Alcohol **3** was converted to the protected 4-methylamino derivative **7a** through a four-step sequence involving a Mitsunobu process[11] to give azide **4**,[12] which was reduced to the primary amine **5**,[13] undergoing subsequent methoxycarbonylation and methylation to give carbamate **7a** (Scheme 2). The methoxycarbonyl group at C-2 of proline **7a** was transformed into the required 3-oxobutyl side chain by an initial

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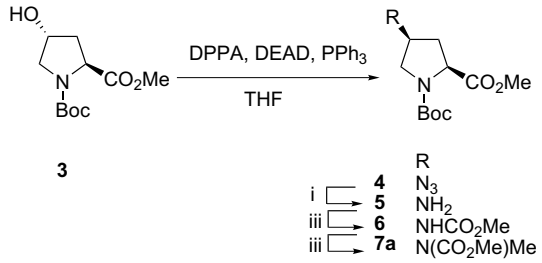


Scheme 2. Reagents and conditions: (i) H_2 (500 psi), Pd/C, MeOH, rt overnight; (ii) $ClCO_2Me$, K_2CO_3, CH_3CN; (iii) NaH, MeI, DMF.

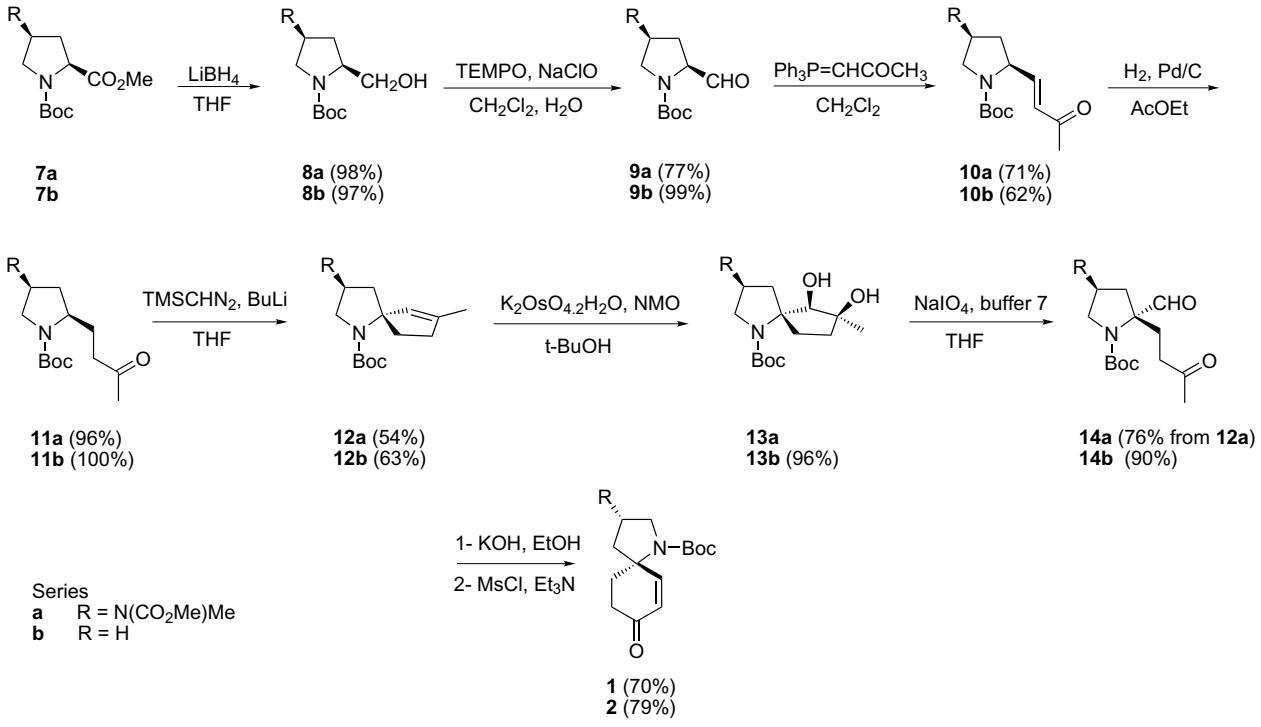
conversion to aldehyde **9a** (TEMPO, NaOCl, NaBr)[14] through alcohol **8a**, followed by a Wittig olefination and hydrogenation of the resulting enone **10a** (Scheme 3).

At this point, the critical construction of the stereogenic quaternary spirocentre was undertaken following the Ohira protocol.[15] Ketone **11a** was added to a preformed solution of lithium(trimethylsilyl)diazomethane at −78 °C to form the corresponding alkylidene carbene and, after the CH insertion,[16] the cyclized azaspiranic compound **12a** was isolated in 54% yield, with the process being stereocontrolled. Cyclopentene **12a** was oxidatively cleaved by a two-step protocol. Treatment with K_2OsO_4 in the presence of NMO provided the dihydroxy derivative **13a** as a single diastereomer with the hydroxy groups being delivered opposite to the bulky Boc-protecting group. Oxidation of **13a** using $NaIO_4$ provided ketoaldehyde **14a,** which was exposed to alkaline conditions and then treated with MsCl[17] to give target compound **1** in 70% overall yield from **14a**.

After these results, we revisited Hayes' synthesis[9] of azaspiranic compound **12b** for two reasons: (i) in order to gain access to an advanced intermediate in the pathway towards target **2**, following the chemistry used in the preparation of **1**, and (ii) to check the level of stereocontrol in the 1,5-CH insertion reaction (**11b**→**12b**), since in the reported process the authors were unable to determine the enantiomeric excess of the synthesized **12b**.

The required cyclization precursor **11b**[18] was prepared as outlined in Scheme 3 starting from proline **7b**, which was sequentially reduced to alcohol **8b**, oxidized to aldehyde **9b** and submitted to a chain extension sequence through a Wittig process followed by hydrogenation.

Ketone **11b** was added over a period of 30 min instead of 15 min[9a] to lithium(trimethylsilyl)diazomethane solution at −78 °C, prepared by the addition of BuLi to a solution of $TMSCHN_2$ in THF at −78 °C. After column chromatography, **12b** was obtained in 63% yield and its specific rotation was −104.8 instead of −78, as reported by Hayes. The time over which the ketone was added to the carbene solution seemed to determine the reaction's stereocontrol, since quick addition of the ketone gave optically inactive cyclopentene **12b**. The latter was used to synthesize the same cyclohexene **2** in a racemic manner to provide reference samples for an enantiomeric excess determination. As occurred in series **a**, the ring enlargement (**12b**→**2**) was carried out by an initial ring cleavage of **12b**, leading to ketoaldehyde **14b**. This underwent the recyclization process by an aldol condensation, which after treatment with MsCl gave target **2** from **12b** in 68% overall yield. Like Hayes, we were initially unable to determine the % ee of



Scheme 3. Preparation of **1** and **2**.

12b using either chiral GC or HPLC. Fortunately, in a later stage of the synthesis, **2** was resolved using a chiral HPLC (Chiracel OD, 2% isopropanol in hexane) and was found to have an enantiomeric excess of 90%.

3. Conclusion

Enantiomerically pure 1-azaspiro[4.5]dec-6-en-8-ones were synthesized from L-proline derivatives using a stereocontrolled 1,5-CH insertion as a key step. These intermediates are suitable precursors of FR901483, cylindricines or lepadiformine.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200, 300, or 400 MHz, and 50.3, 75.4 or 100 MHz, respectively. In addition, chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Infrared spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Optical rotations were taken on a Perkin–Elmer 241 polarimeter with a 1 mL ($L = 1$ dm) cell. TLC was performed on SiO_2 (silica gel 60 F254, Merck). The spots were located by UV light and a 1% $KMnO_4$ solution. Chromatography refers to flash chromatography and carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh). HPLC analyses for the determination of enantiomeric excess were carried out using a daicel Chiralcel OD-H column (250 × 4.6 mm I.D., 5 μm; J. T. Baker) on a Waters model 2487 Dual Absorbance Detector and set at the wavelength of 220 nm. The chromatographic resolution of compound **2** was achieved using 2:98 2-propanol/hexane as the mobile phase in an isocratic run. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Drying of the organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Melting points were determined in a capillary tube on a Büchi apparatus. L-Proline and *trans*-4-hydroxy-L-proline were used as chiral starting materials purchased from Panreac and Fluka, respectively.

4.1. *tert*-Butyl 2-methyl (2*S*,4*S*)-4-[(*N*-methoxycarbonyl)-*N*-methylamino]pyrrolidine-1,2-dicarboxylate 7a

Starting from alcohol **3** (22.6 g, 112.4 mmol), azide **4** was prepared according to the protocol reported by Silverman.[11] After chromatography (hexane–hexane/EtOAc 60:40), **4**[12] was obtained as a viscous yellow oil in a quantitative yield. $[\alpha]_D^{23} = -40.3$ (c 1, $CHCl_3$); IR (NaCl, neat): 2977, 2105, 1755, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 and 1.47 (2s, 9H, CH_3), 2.17 (2t, 1H, $J = 4.4$ Hz, H-3), 2.47 (m, 1H, H-3), 3.48 (m, 1H, H-5), 3.72 (m, 1H, H-5), 3.76 (s, 3H, CH_3O), 4.16 (m, 1H, H-4), 4.33 and 4.43 (2dd, 1H, $J = 8.8$, 4.6 Hz, H-2); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.2 and 28.3 (CH_3), 35.0 and 36.0 (C-3), 50.7 and 51.2 (C-5), 52.2 and 52.4 (CH_3O), 57.3 and 57.6 (CH), 58.2 and 59.2 (CH), 80.5 (CH_3), 153.3 and 153.8 (CO), 171.8 and 172.1 (CO). A suspension of **4** (5.31 g, 19.6 mmol) and Pd/C (0.53 g, 10%) in MeOH (60 mL) was stirred overnight at rt under hydrogen pressure (500 psi). The mixture was then filtered on a Celite pad and concentrated to yield **5**[13] in a quantitative yield and was pure enough to be used in the next step without further purification. To a solution of primary amine **5** (8.83, 36.1 mmol) in CH_3CN were added successively methyl chloroformate (5.6 mL, 72.3 mmol) and K_2CO_3 (10.1 g, 72.3 mmol). The mixture was stirred at rt for 4 h, concentrated, and the residue diluted with CH_2Cl_2 and washed with concentrated $NaHCO_3$. The organic layer was dried and concentrated to yield carbamate **6** as a colourless oil (9.6 g, 88%). $[\alpha]_D^{23} = -23.7$ (c 0.85, $CHCl_3$); IR (NaCl, neat): 3333, 2978, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 and 1.46 (2s, 9H, CH_3), 1.95 (br s, 1H, H-3), 2.48 (m, 1H, H-3), 3.51 (m, 1H, H-5), 3.66 (m, 1H, H-5), 3.66 (s, 3H, CH_3O), 3.77 (s, 3H, CH_3O), 4.28 (m, 1H, H-2), 4.36 (br s, 1H, NH), 5.83 (br s, 1H, H-4); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.2 and 28.3 (CH_3), 35.7 and 36.7 (C-3), 49.5 and 50.5 (CH), 52.1 (CH_3O), 52.3 and 52.5 (CH_3O), 52.8 and 53.4 (C-5), 57.5 and 57.7 (CH), 80.4 (C), 153.2 and 154.0 (CO), 156.2 (CO), 174.3 (CO). To a solution of **6** (5.4 g, 17.9 mmol) in DMF (250 mL) at 0 °C were added NaH (0.86 g, 19.7 mmol) portionwise and then MeI (3.71 mL, 59 mmol). The mixture was stirred overnight at rt and quenched by adding a saturated solution of NH_4Cl. The aqueous phase was extracted with ether and the organics dried and concentrated to yield compound **7a** (4.6 g, 82%). An analytical sample was obtained by chromatography eluting with CH_2Cl_2. $[\alpha]_D^{23} = -44.7$ (c 1, $CHCl_3$); IR (NaCl, neat): 3019, 1748, 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 and 1.45 (2s, 9H, CH_3), 1.98 (m, 1H, H-3), 2.42 (td, 1H, $J = 12.4$, 7.6 Hz, H-3), 2.83 (s, 3H, CH_3N), 3.33 (m, 1H, H-5), 3.71 (m, 1H, H-5), 3.72 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 4.24 (m, 1H, H-2), 4.79 (br s, 1H, H-4); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.2 and 28.3 (CH_3), 28.8 (CH_3N), 31.6 and 32.6 (C-3), 46.2 and 46.6 (C-5), 52.1 and 52.3 (CH_3O), 52.6 and 53.2 (CH), 52.9 (CH_3O), 57.1 and 57.5 (CH), 80.5 (C), 153.4 and 154.1 (CO), 156.7 (CO), 173.1 (CO). Anal. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.86. Found: C, 53.23; H, 7.64; N, 8.62.

4.2. *tert*-Butyl (2*S*,4*S*)-2-(hydroxymethyl)-4-[(*N*-methoxycarbonyl)-*N*-methylamino]pyrrolidine-1-carboxylate 8a

To a solution of **7a** (5.18 g, 16.37 mmol) in THF (75 mL) at 0 °C was added $LiBH_4$ (0.75 g, 32.75 mmol) portionwise and the mixture stirred overnight at rt. The reaction was quenched by the addition of water and the resulting clear solution extracted with ether (5 × 250 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (200 mL), then with brine (200 mL) and dried. Removal of the solvent provided alcohol **8a** as a viscous colourless oil (4.61 g, 98%), which was used in the next step without further purification. $[\alpha]_D^{23} = -43.7$ (c 1, $CHCl_3$); IR (NaCl, neat): 3444, 2977, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46 (s, 9H, CH_3), 1.66 (br s, 1H, H-3), 2.12 (td, 1H, $J = 12.0$, 7.5 Hz, H-3), 2.81 (s, 3H, CH_3N), 3.12 (t, 1H, $J = 10.5$ Hz, H-5), 3.61 (dd, 1H, $J = 11.5$, 6.5 Hz, CH_2OH), 3.71 (s, 3H, CH_3O), 3.71 (m, 1H, H-5), 3.74 (br t, 1H, $J = 11.5$ Hz, CH_2OH), 3.94 (br s, 1H, H-2), 4.63 (br s, 1H, H-4); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.1 (CH_3), 28.6 (CH_3N), 30.1 (C-3), 47.2 (C-5), 52.2

(C-4), 52.5 (CH_3O), 58.7 (C-2), 66.1 (CH_2OH), 80.3 (C), 156.0 (CO), 156.5 (CO).

4.3. *tert*-Butyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate 8b

Operating as above, from ester **7b** (10.3 g, 47.8 mmol) and $LiBH_4$ (2.19 g, 95.6 mmol) in THF (350 mL), **8b**[19] (8.74 g, 97%) was isolated.

4.4. *tert*-Butyl (2*S*,4*S*)-2-formyl-4-[(*N*-methoxycarbonyl)-*N*-methylamino]pyrrolidine-1-carboxylate 9a

To a solution of alcohol **8a** (3.14 g, 10.88 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added successively under vigourous stirring TEMPO (0.035 g, 0.022 mmol) and NaBr (0.13 g, 10.88 mmol). To the resulting mixture was added a solution of $NaHCO_3$ (2.12 g, 25.02 mmol) and 10% NaClO in active chlorine (20.65 mL, 16.64 mmol) in water (50 mL) and the mixture rapidly extracted with ether (4 × 100 mL). The combined organic phase was first washed with a solution of $NaHSO_4$ (10%) and KI (4%), then with brine and dried. After removal of all volatiles in vacuum, aldehyde **9a** (2.40 g, 77%) was obtained as a colourless oil, which was used in the next step without further purification. An analytical sample was obtained by chromatography (hexane/EtOAc 50:50). $[\alpha]_D^{23} = -70.7$ (*c* 1, $CHCl_3$); IR (NaCl, neat): 3017, 2980, 1736, 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.43 and 1.47 (2s, 9H, CH_3), 1.97 (td, 1H, $J = 11.8$, 10.6 Hz, H-3), 2.24 (m, 1H, H-3), 2.84 (s, 3H, CH_3N), 3.31 (td, 1H, $J = 9.6$, 9.2 Hz, H-5), 3.72 (s, 3H, CH_3O), 3.75 (m, 1H, H-5), 4.13 (m, 1H, H-2), 4.76 (br s, 1H, H-4); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 26.9 and 27.0 (CH_3), 28.1 (CH_3N), 28.3 (C-3), 45.4 and 45.7 (C-5), 51.6 (CH_3O), 51.9 and 52.6 (C-4), 61.7 and 62.0 (C-2), 79.4 and 79.8 (C), 152.2 and 153.4 (CO), 155.3 (CO), 197.5 and 197.8 (CO). Anal. Calcd for $C_{13}H_{22}N_2O_5 \cdot 2/3H_2O$: C, 52.33; H, 7.88; N, 9.39. Found: C, 52.56; H, 8.05; N, 8.90.

4.5. *tert*-Butyl (*S*)-2-formylpyrrolidine-1-carboxylate 9b

Operating as above, from alcohol **8b** (23.8 g, 118.5 mmol), TEMPO (0.38 g, 2.37 mmol) and NaBr (12.31 g, 118.5 mmol) in CH_2Cl_2 (550 mL) and then a solution of $NaHCO_3$ (23.12 g, 272.5 mmol) and NaClO (225 mL, 181.3 mmol) in water (550 mL), **9b**[20] (23.3 g, 99%) was isolated.

4.6. *tert*-Butyl (2*S*,4*S*)-2-[(1*E*)-3-oxobut-1-enyl]-4-[(*N*-methoxycarbonyl)-*N*-methylamino]pyrrolidine-1-carboxylate 10a

A solution of aldehyde **9a** (1.06 g, 3.71 mmol) and 1-triphenylphosphoranylidene-2-propanone (1.79 g, 5.57 mmol) in CH_2Cl_2 (30 mL) was stirred overnight at rt. The mixture was concentrated and purified by chromatography, eluting with ethyl acetate, to give enone **10a** (0.86 g, 71%) as a viscous colourless oil. $[\alpha]_D^{23} = -31.8$ (*c* 1, $CHCl_3$); IR (NaCl, neat): 3017, 2980, 1686, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H, CH_3), 1.84 (m, 1H, H-3), 2.28 (s, 3H, CH_3), 2.29 (m, 1H, H-3), 2.83 (s, 3H, CH_3N), 3.22 (t, 1H, $J = 10.2$ Hz, H-5), 3.72 (s, 3H, CH_3O), 3.77 (br t, 1H, $J = 10.2$ Hz, H-5), 4.37 (br s, 1H, H-2), 4.70 (br s, 1H, H-4), 6.13 (d, 1H, $J = 16$ Hz, =CH), 6.70 (dd, 1H, $J = 16$, 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.3 (CH_3), 28.3 (CH_3)$_3$, 29.0 (CH_3N), 34.5 (C-3), 46.6 (C-5), 52.8 (C-4), 52.8 (CH_3O), 56.7 (C-2), 80.3 (C), 129.4 (=CH), 147.5 (=CH), 154.1 (CO), 156.7 (CO), 198.0 (CO). Anal. Calcd for $C_{16}H_{26}N_2O_5 \cdot 1/4\ H_2O$: C, 58.08; H, 8.07; N, 8.47. Found: C, 57.98; H, 7.97; N, 8.33.

4.7. *tert*-Butyl (*S*)-2-[(1*E*)-3-oxobut-1-enyl]pyrrolidine-1-carboxylate 10b

Operating as above, from aldehyde **9b** (10.3 g, 51.83 mmol) and 1-triphenylphosphoranylidene-2-propanone (25 g, 77.7 mmol) in CH_2Cl_2 (300 mL), after chromatography (hexane–hexane/EtOAc 60:40), **10b** was isolated as a viscous colourless oil (7.6 g, 62%). $[\alpha]_D^{23} = -86.9$ (*c* 1.1, $CHCl_3$); IR (NaCl, neat): 3018, 2979, 1686, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.43 and 1.47 (2s, 9H, CH_3), 1.70–1.93 (m, 3H), 2.11 (m, 1H), 2.26 (s, 3H, CH_3), 3.44 (br s, 2H, CH_2-5), 4.41 (br s, 1H, H-2), 6.07 (dd, 1H, $J = 15.6$ Hz, 1.6, =CH), 6.67 (dd, 1H, $J = 15.4$, 5.4 Hz, =CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.8 and 23.3 (C-4), 26.9 (CH_3), 28.1 (CH_3), 30.6 and 31.6 (C-3), 46.1 and 46.3 (C-5), 57.3 and 57.7 (C-2), 79.3 (C), 129.1 (=CH), 147.2 (=CH), 153.9 (CO), 197.9 (CO). Anal. Calcd for $C_{13}H_{21}NO_3 \cdot 0.2H_2O$: C, 64.52; H, 8.87; N, 5.79. Found: C, 64.57; H, 8.74; N, 5.76.

4.8. *tert*-Butyl (2*R*,4*S*)-2-(3-oxobutyl)-4-[(*N*-methoxycarbonyl)-*N*-methylamino]pyrrolidine-1-carboxylate (11a)

A suspension of enone **10a** (1.73 g, 5.30 mmol) and Pd/C (0.18 g, 10%) in ethyl acetate (70 mL) was stirred overnight under hydrogen pressure (500 psi). The mixture was filtered on a Celite pad and concentrated to yield **11a** (1.68 g, 96%). This compound was pure enough for the next step. An analytical sample was obtained by chromatography (hexane–hexane/EtOAc 40:60). $[\alpha]_D^{23} = -47.3$ (*c* 1, $CHCl_3$); IR (NaCl, neat): 2974, 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.46 (s, 9H, CH_3), 1.50–1.90 (m, 2H), 2.02–2.32 (m, 2H), 2.17 (s, 3H, CH_3), 2.45 (t, 2H, $J = 7.2$ Hz), 2.83 (s, 3H, CH_3N), 3.08 (t, 1H, $J = 10.6$ Hz), 3.63–3.90 (m, 2H), 3.71 (s, 3H, CH_3O), 4.55 (br s, 1H, H-4); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.2 (CH_3), 29.0 (CH_3N), 29.0 (CH_2), 29.6 (CH_3), 33.2 (CH_2), 39.6 (CH_2), 46.3 (C-5), 52.6 (CH_3O), 52.8 (CH), 54.9 (CH), 79.5 (C), 154.3 (CO), 156.6 (CO), 207.8 (CO).

4.9. *tert*-Butyl (*S*)-2-(3-oxobutyl)pyrrolidine-1-carboxylate 11b

Operating as above, from enone **10b** (3.7 g, 15.47 mmol) and Pd/C (0.37 g, 10%) in ethyl acetate (70 mL), **11b** was isolated in a quantitative yield (3.7 g). An analytical sample was obtained by chromatography (hexane–hexane/EtOAc 40:60). $[\alpha]_D^{23} = -51.8$ (*c* 1, $CHCl_3$); IR (NaCl, neat): 3019, 2976, 1711, 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H, CH_3), 1.55–1.73 (m, 2H), 1.75–1.99 (m, 4H), 2.15 (s, 3H, CH_3), 2.46 (br s, 2H), 3.30 (br s, 1H), 3.42 (br s, 1H), 3.81 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 23.1 and 23.7 (CH_2), 28.5 (CH_3), 28.7 (CH_2), 29.8 (CH_3), 30.3 and 30.7 (CH_2), 40.7 (CH_2), 46.3 (CH_2), 56.5 (C-2), 79.3 (br s, C), 154.8 (CO), 208.3 and 208.7 (CO).

4.10. *tert*-Butyl (5*R*)-4-[(*N*-methoxycarbonyl)-*N*-methylamino]-7-methyl-1-azaspiro[4.4]non-6-ene-1-carboxylate 12a

To a solution of trimethylsilyldiazomethane (2 M in diethyl ether, 2.48 mL, 4.96 mmol) in dry THF (30 mL) at −78 °C was added BuLi (1.6 M in hexanes, 3.10 mL, 4.96 mmol) and the mixture stirred at this temperature for 30 min. A solution of ketone **11a** (1.09 g, 3.31 mmol) in THF (25 mL) was then added and the mixture stirred at this temperature for 5 h. The reaction was then quenched with water and extracted with ether (5 × 100 mL). The organics were washed with brine, dried and concentrated to yield a yellow oil, which was purified by chromatography (hexane/CH_2Cl_2 50:50–100). Compound **12a** was obtained as a colourless oil (0.58 g, 54%). $[\alpha]_D^{23} = -78.3$ (*c* 1, $CHCl_3$); IR (NaCl, neat): 2973, 2931, 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (s, 9H, CH_3), 1.71 (s, 3H, CH_3-7), 1.80–2.75 (m, 6H), 2.81 (s, 3H, CH_3N), 3.23 (br s, 1H), 3.59 (br s, 1H), 3.70 (s, 3H, CH_3O), 4.62 (br s, 1H, H-3), 5.19 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.5 (CH_3-7), 28.5 (CH_3), 28.8 (CH_3N), 35.7 (CH_2), 35.7 and 37.0 (CH_2), 43.7 and 45.3 (CH_2), 48.1 (CH_2), 51.3 (C-3), 52.7 (CH_3O), 73.9 (C-5), 79.2 (C), 127.0 and 128.4 (C-6), 141.2 and 142.7 (C-7), 153.0 and 154.5 (CO), 157.0 (CO). Anal. Calcd for $C_{17}H_{28}N_2O_4 \cdot 1/2H_2O$: C, 61.24; H, 8.77; N, 8.40. Found: C, 61.47; H, 9.01; N, 8.60.

4.11. *tert*-Butyl (5*R*)-7-methyl-1-azaspiro[4.4]non-6-ene-1-carboxylate 12b

To a solution of trimethylsilyldiazomethane (2 M in diethyl ether, 2 mL) in dry THF (20 mL) at −78 °C was added BuLi (1.6 M in hexanes, 2.5 mL) and the mixture was stirred at this temperature for 1 h. A solution of ketone **11b** (0.80 g, 3.33 mmol) in THF (20 mL) was added over 30 min using a syringe pump. After the addition the reaction mixture was stirred at −78 °C for a further 1 h and then it was allowed to reach 0° over another 1 h. The reaction mixture was quenched with water at 0° and extracted with ether (5 × 50 mL). The combined organic extracts were dried and concentrated to yield a yellow liquid, which was purified by chromatography (hexane–hexane/EtOAc 90:10). Compound **12b** was obtained as a colourless oil (0.471 g, 63%). $[\alpha]_D^{23} = -104.8$ (*c* 1, $CHCl_3$); IR (NaCl, neat): 2970, 2931, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9H, (CH_3)), 1.71 (s, 3H, CH_3-7), 1.67–1.89 (m, 5H), 2.09–2.52 (m, 3H), 3.34 and 3.48 (2br s, 2H, CH_2-2), 5.10 and 5.20 (2br s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.4 (CH_3-7), 22.4 (CH_2), 28.4 (CH_3), 35.3 (CH_2), 36.8 (CH_2), 41.0 (CH_2), 47.4 (CH_2), 74.5 (C-5), 78.2 (C), 129.6 and 130.2 (C-6), 138.9 (C-7), 154.5 (CO). Anal. Calcd for $C_{14}H_{23}NO_2 \cdot 1/5H_2O$: C, 69.79; H, 9.79; N, 5.81. Found: C, 69.79; H, 9.84; N, 5.81. HRMS calcd for $C_{14}H_{23}NO_2$: 237.1729; found: 237.1614.

4.12. *tert*-Butyl (3*S*,5*R*,6*R*,7*S*)-6,7-dihydroxy-4-[(*N*-methoxycarbonyl)-*N*-methylamino]-7-methyl-1-azaspiro[4.4]nonane-1-carboxylate 13a

To a solution of NMO (10 g, 82.35 mmol) in *tert*-BuOH (30 mL) and water (30 mL) were successively added at rt $K_2OsO_4 \cdot 2H_2O$ (0.15 g, 5%) and a solution of **12a** (3 g, 9.25 mmol) in acetone (30 mL). The mixture was stirred overnight at rt, extracted with CH_2Cl_2 (5 × 100 mL) and dried. The crude was pure enough to be used in the next step without further purification (3.3 g, 100%). An analytical sample of **13a** was obtained by column chromatography (CH_2Cl_2–CH_2Cl_2/MeOH 90:10). $[\alpha]_D^{23} = +11.8$ (*c* 1, $CHCl_3$), IR (NaCl, neat): 3422, 2972, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3H, CH_3-7), 1.44 and 1.48 (2s, 9H, $(CH_3)_3C$), 1.60–1.98 (m, 3H), 2.08 (m, 1H), 2.30 and 2.46 (2m, 1H), 2.66 (m, 1H), 2.80 (s, 3H, CH_3N), 3.13 and 3.23 (2t, 1H, $J = 9.9$ Hz, H-2), 3.61 (m, 1H, H-2), 3.70 (s, 3H, CH_3O), 4.10 and 4.27 (2d, 1H, $J = 7.8$ Hz, H-6), 4.86 (br s, 1H, H-3); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.1 and 26.4 (CH_3-7), 28.6 (CH_3), 28.7 (CH_3N), 33.7 and 34.7 (CH_2), 35.6 and 35.7 (CH_2), 39.1 and 40.5 (CH_2), 47.5 (CH_2), 50.9 and 51.5 (C-3), 52.8 (CH_3O), 70.1 and 70.3 (C-5), 77.9 (C-7), 79.2 and 80.3 (C), 80.0 and 81.3 (C-6), 153.3 and 153.7 (CO), 157.2 (CO).

4.13. *tert*-Butyl (5*S*,6*R*,7*S*)-6,7-dihydroxy-7-methyl-1-azaspiro[4.4]nonane-1-carboxylate 13b

Compound **13b** was prepared from **12b** following the same procedure for **13a** with some modifications. Compound **12b** (0.69 g, 2.9 mmol), NMO (2.28 g, 18.85 mmol), $K_2OsO_4 \cdot 2H_2O$ (0.017 g, 2.5%), BuOH (5 mL), water (5 mL) and acetone (5 mL). After extraction with CH_2Cl_2, the organics were placed on a silica gel pad and eluted first with CH_2Cl_2 to eliminate the impurities and then with ethyl acetate to provide the desired compound **13b** (0.76 g, 96%) as a white solid. Mp: 130–131 °C; $[\alpha]_D^{23} = +40.5$ (*c* 1.05, $CHCl_3$), IR (NaCl, neat): 3421, 2972, 2874, 1688, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3H, CH_3-7), 1.45 and 1.48 (2s, 9H, CH_3), 1.56–2.70 (m, 8H), 3.34 (br s, 2H, CH_2-2), 4.32 and 4.58 (2br s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.7 and 22.9 (C-3), 26.9 (CH_3-7), 28.6 (CH_3), 32.4 and 34.1 (CH_2), 35.1 and 36.9 (CH_2), 35.4 (CH_2), 47.9 and 48.0 (CH_2), 70.9 and 71.1 (C-5), 77.0 (C-7), 77.9 and 79.5 (C-6), 78.7 and 79.9 (C), 153.6 and 154.0 (CO). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.65; H, 9.37; N, 5.03.

4.14. *tert*-Butyl (2*R*,4*S*)-2-formyl-4-[(*N*-methoxycarbonyl)-*N*-methylamino]-2-(3-oxobutyl)pyrrolidine-1-carboxylate 14a

To a deoxygenated solution of **13a** (3.3 g, 9.2 mmol) in THF (40 mL) and pH 7 buffer (20 mL) was added $NaIO_4$ (9.21 g, 43.1 mmol) and the mixture stirred at rt for 4 h. Water was then added till all the solid was dissolved and the mixture extracted with CH_2Cl_2 (5 × 100 mL). The combined organic phase was dried and concentrated to yield ketoaldehyde **14a** (2.49 g, 76%). $[\alpha]_D^{23} = +12.5$ (*c* 1, $CHCl_3$); IR (NaCl, neat): 2974, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 and 1.45 (2s, 9H, CH_3), 1.90–2.70 (m, 6H), 2.16 and 2.17 (2s, 3H, CH_3), 2.82 (m, 1H), 2.85 (s, 3H, CH_3N), 3.29 (q, 1H, $J = 10.5$ Hz), 3.70 (s, 3H, CH_3O), 3.82 and 3.94 (2t, 1H, $J = 9.0$ Hz), 4.52 (m, 1H, H-4), 9.56 and 9.62 (2s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.8 (CH_2), 28.2 (CH_3), 28.4 (CH_3N), 29.7

and 30.0 (CH_3), 34.6 and 35.4 (CH_2), 37.6 and 38.2 (CH_2), 47.8 (C-5), 52.0 (br s, C-4), 52.8 (CH_3O), 69.3 and 69.7 (C-2), 80.9 and 81.6 (C), 153.1 and 154.0 (CO), 156.6 (CO), 199.1 and 199.7 (CHO), 207.0, 207.7 (CO).

4.15. *tert*-Butyl (2*S*)-2-formyl-2-(3-oxobutyl)pyrrolidine-1-carboxylate 14b

Operating as above, from diol **13b** (0.7 g, 2.58 mmol) and $NaIO_4$ (1.65 g, 7.74 mmol) in THF (9 mL) and pH 7 buffer (4.5 mL), keto aldehyde **14b** (0.7 g, 90%) was isolated. $[\alpha]_D^{23} = +11.9$ (*c* 1.1, $CHCl_3$); IR (NaCl, neat): 2976, 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 and 1.45 (2s, 9H, CH_3), 1.57–2.31 (m, 6H), 2.13 and 2.17 (2s, 3H, CH_3), 2.39–2.74 (m, 2H), 3.37–3.77 (m, 2H, CH_2-5), 9.35 and 9.38 (2s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.7 and 23.5 (C-4), 26.6 and 26.6 (CH_2), 28.2 and 28.3 (CH_3), 29.8 and 29.9 (CH_3), 33.2 and 33.7 (CH_2), 38.5 and 38.8 (CH_2), 47.7 and 48.1 (C-5), 70.2 and 70.6 (C-2), 80.3 and 81.4 (C), 153.3 and 154.4 (CO), 198.6 and 198.7 (CHO), 207.6, 208.5 (CO). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.52; H, 8.74; N, 5.13.

4.16. *tert*-Butyl (3*S*,5*R*)-4-[(*N*-methoxycarbonyl)-*N*-methylamino]-8-oxo-1-azaspiro[4.5]dec-6-ene-1-carboxylate 1

To a solution of **14a** (0.66 g, 1.86 mmol) in ethanol (50 mL) was added KOH (0.61 g, 9.3 mmol) at 0 °C and the mixture stirred at rt for 2 h. The reaction was then quenched with a saturated aqueous NH_4Cl. Ethanol was then removed under reduced pressure and the mixture extracted with ether (3×50 mL). The combined organic extracts were dried, and the solvent was removed. To a stirred solution of the above azaspiro aldol in CH_2Cl_2 (7 mL) were added MsCl (0.97 mL, 12.27 mmol) and Et_3N (2.1 mL, 15.1 mmol). The mixture was stirred overnight at rt, then a saturated solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2–CH_2Cl_2/MeOH 99:1) providing **1** (0.45 g, 70%). $[\alpha]_D^{23} = -18.3$ (*c* 1.05, $CHCl_3$); IR (NaCl, neat): 2974, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H, CH_3), 1.92 (br s, 1H), 2.24–2.65 (m, 4H), 2.86 (s, 3H, CH_3N), 3.34 (br s, 1H), 3.73 (s, 3H, CH_3O), 3.85 (br s, 1H), 4.72 (br s, 1H, H-3), 5.88 (br d, 1H, H-7), 6.92 (br s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.3 (CH_3), 29.2 (CH_3N), 34.0 (CH_2), 35.5 (CH_2), 40.8 and 41.6 (CH_2), 47.4 (C-2), 51.8 (C-3), 52.8 (CH_3O), 61.0 (C-5), 80.4 and 81.0 (C), 126.6 and 127.4 (C-7), 153.4 (CO), 156.7 (C-6), 197.4 (CO). Anal. Calcd for $C_{17}H_{26}N_2O_5 \cdot 4/5CH_2Cl_2$: C, 56.12; H, 7.25; N, 7.52. Found: C, 56.19; H, 7.34; N, 7.48.

4.17. *tert*-Butyl (5*S*)-8-oxo-1-azaspiro[4.5]dec-6-ene-1-carboxylate 2

Operating as above, from **14b** (0.5 g), gave enone **2** (0.4 g, 79%). **2** was isolated as a colourless viscous liquid, which crystallized on standing: mp: 101–103 °C; $[\alpha]_D^{23} = -111.5$ (*c* 0.95, $CHCl_3$); IR (NaCl, neat): 2972, 2878, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 and 1.45 (2s, 9H, CH_3), 1.75–2.02 (m, 4H), 2.22 (m, 1H), 2.36–2.58 (m, 2H), 2.65 and 2.85 (2dt, 1H, $J = 13.5$, 5.4 Hz), 3.34–3.68 (m, 2H), 5.87 and 5.94 (2d, 1H, $J = 10.2$ Hz, H-7), 6.74 and 6.86 (2d, 1H, $J = 10.2$ Hz, H-6); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.3 and 23.0 (C-3), 28.3 (CH_3), 30.1 and 31.4 (CH_2), 34.7 and 35.3 (CH_2), 35.6 and 35.7 (CH_2), 47.2 (C-2), 61.6 and 61.8 (C-5), 79.7 and 80.4 (C), 126.4 and 126.9 (C-7), 153.4 (CO), 157.3 and 157.4 (C-6), 197.9 and 198.2 (CO). Anal. Calcd for $C_{14}H_{21}NO_3 \cdot 1/5H_2O$: C, 65.96; H, 8.46; N, 5.49. Found: C, 65.99; H, 8.50; N, 5.37. HRMS calcd for $C_{14}H_{21}NO_3$: 251.1521; found: 251.1423.

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