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Synthesis and Reactivity of Some Chiral, Nonracemic 1-Azabicyclo[4.1.0]heptanes Related to the Azinomycins

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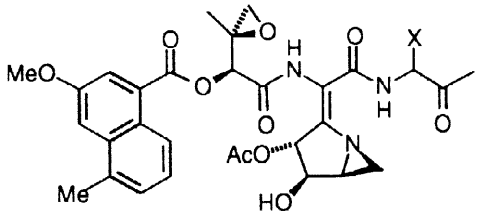
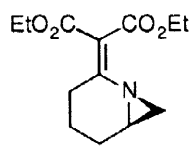
Abstract: Both enantiomers of 1-azabicyclo[4.1.0]heptane 1 have been prepared from a protected form of chiral, nonracemic (6-hydroxymethyl)-2-piperidinone using a strategy involving an Eschenmoser coupling and subsequent ring closure to form the aziridine ring. This ring system undergoes nucleophilic ring opening reactions under acidic (AcOH) and basic (PhSH, Et_3N) conditions. However, neither enantiomer of bicycle 1 possesses significant cytotoxic activity (IC_{50} >25 μM).

Introduction

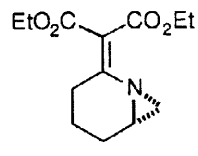
In 1986, azinomycins A and B were isolated from the culture broths of *Streptomyces griseofuscus* S42227 and were found to exhibit potent *in vitro* cytotoxic activity and significant *in vivo* anti-tumour activity (Figure 1).[1,2] Armstrong *et al* have shown that azinomycin B causes interstrand cross-links in the major groove of duplex DNA.[3] While the detailed mechanism of action of these compounds at the molecular level has not yet been fully elucidated, it is most likely that the electrophilic aziridine and epoxide portions of the azinomycins are responsible for the DNA alkylation events which lead to cross-link formation. Unfortunately, while the 1-azabicyclo[3.1.0]hexane ring system would seem to be responsible, in part, for the biological activity of the azinomycins, its propensity to react with nucleophiles makes these compounds highly unstable.[4,5] In an effort to produce more stable analogues of the azinomycins which still possess useful anti-cancer activity, we sought to moderate the reactivity of the 1-azabicyclo[3.1.0]hexane ring system. We reasoned that the introduction of an additional methylene carbon into the five membered ring might lead to a reduction in ring strain producing more chemically robust compounds. In this paper, we describe the preparation of (*R*)- and (*S*)-**1** in enantiomerically pure form and report on the chemical reactivity and cytotoxic activity of such 1-azabicyclo[4.1.0]heptanes.[6]



Azinomycin A (X = H);
Azinomycin B (X = CHO)



(*R*)-**1**



(*S*)-**1**

Figure 1

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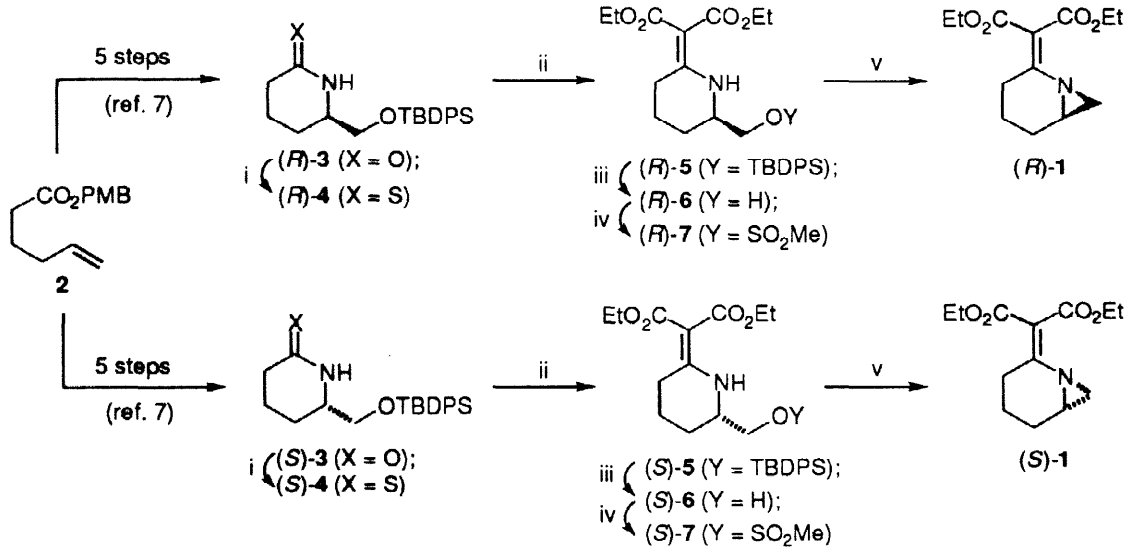
PII: S0040-4020(98)00283-X

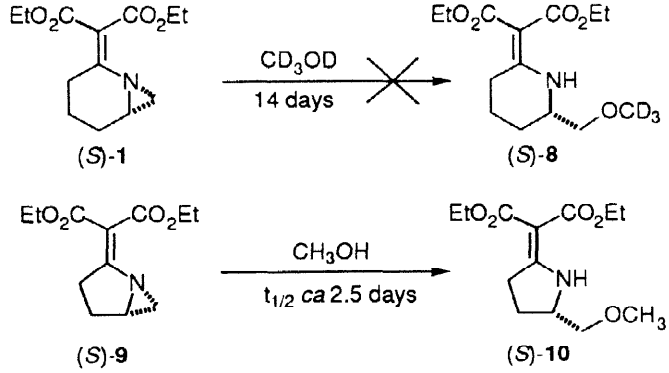
Results and Discussion

We have previously reported an efficient asymmetric route to both antipodes of protected δ-lactam **3** in high enantiomeric excess (≥95%ee) starting from alkenyl ester **2**.[7] By adaptation of the methodology reported by Terashima *et al*,[5b] we have converted this lactam into 1-azabicyclo[4.1.0]heptane **1** in a further five chemical steps. Lactam (*R*)-**3** was transformed into the corresponding thiolactam (*R*)-**4** in near quantitative yield, and then condensed with diethyl bromomalonate by means of an Eschenmoser coupling reaction to give piperidine (*R*)-**5**. Subsequent removal of the silyl ether group from (*R*)-**5** furnished alcohol (*R*)-**6** which was then converted to the corresponding mesylate (*R*)-**7**. Finally, treatment of this mesylate with potassium hydride in tetrahydrofuran at room temperature and subsequent warming to reflux effected ring closure to the desired 1-azabicyclo[4.1.0]heptane system. While the crude ^{1}H NMR spectrum indicated that the reaction had proceeded cleanly, purification of this compound proved very difficult. Careful chromatography on Florisil® was used to obtain pure (*R*)-**1**, although this process yielded the desired product in just 10% yield. Repeating this reaction sequence using (*S*)-**3** furnished (*S*)-**1** in an identical fashion.



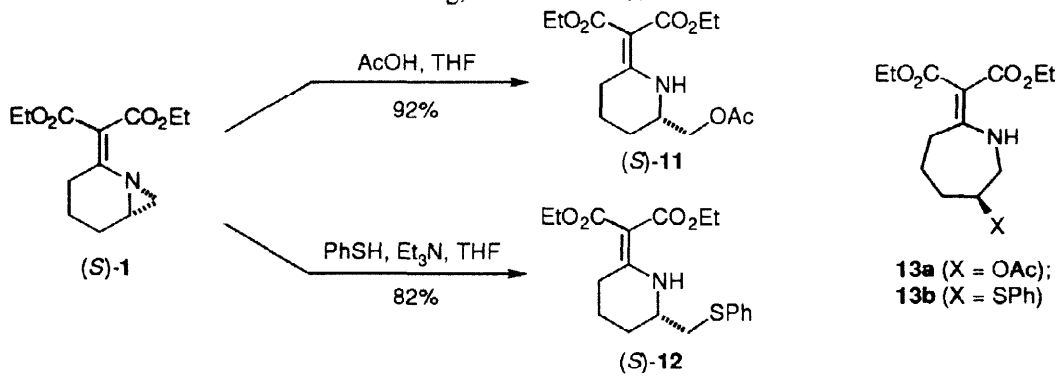
Scheme 1. *Reagents & Conditions:* (i) Lawesson's reagent, toluene, reflux, 1 hr, 98% for (*R*)-**4**, 98% for (*S*)-**4**; (ii) $(EtO_2C)_2CHBr$, CH_2Cl_2, rt then aq K_2CO_3, 80% for (*R*)-**5**, 81% for (*S*)-**5**; (iii) TBAF, THF, 78% for (*R*)-**6**, 78% for (*S*)-**6**; (iv) MsCl, CH_2Cl_2, 0°C, 99% for (*R*)-**7**, 99% for (*S*)-**7**; (v) KH, THF, reflux, 90 min, 10% for (*R*)-**1**, 11% for (*S*)-**1**.

We have determined the reactivity of this 1-azabicyclo[4.1.0]heptane ring system towards nucleophiles under acidic, basic and essentially neutral conditions. Standing (*S*)-**1** in d_4-methanol does not lead to any measurable decomposition over a two week period as monitored by ^{1}H NMR spectroscopy (Scheme 2). This result markedly differs from the findings of Terashima *et al* who have shown that 1-azabicyclo[3.1.0]hexane (*S*)-**9** undergoes ring opening to pyrrolidine (*S*)-**10** under essentially identical conditions.[5b] From this observation, we conclude that the introduction of the extra methylene group has a favourable effect on stability.



Scheme 2

Nevertheless, nucleophilic ring opening of the 1-azabicyclo[4.1.0]heptane ring system does occur under acidic and basic conditions (Scheme 3). Treatment of (*S*)-**1** with acetic acid in THF leads to the production of acetate (*S*)-**11** in 92% yield *via* nucleophilic attack at the least hindered carbon atom of the aziridine. Similarly, reaction with thiophenol in the presence of triethylamine yields thioether (*S*)-**12** in 82% yield. None of the corresponding seven membered ring products **13a** and **13b**, which would have arisen by nucleophilic attack at the more substituted carbon atom of the aziridine ring, were observed.



Scheme 3

In view of the potent biological activity of the azinomycins,[1c] and the significant cytotoxic activity of simple 1-azabicyclo[3.1.0]hexanes such as (*S*)-**9** [IC_{50} (μg/mL) 0.74 (P388 murine leukemia)],[5b] it was of interest to ascertain whether our ring expanded 1-azabicyclo[4.1.0]heptanes possessed any biological activity. We have evaluated the *in vitro* growth inhibitory properties of selected compounds [(*S*)-**6**, (*S*)-**7**, (*S*)-**1**, (*R*)-**6**, (*R*)-**7**, (*R*)-**1**] against a small panel of human tumour cell lines [A2780, A2780cisR, CH1, SKOV-3 (all ovarian) and HT 29 (colon)]. However, essentially no cytotoxic activity was observed (IC_{50} > 25 μM). Thus, it would appear that in contrast to 1-azabicyclo[3.1.0]hexane **8**, 1-azabicyclo[4.1.0]heptane **1** is not able to effectively disrupt DNA replication. Further studies directed towards the development of more potent analogues of the azinomycins are ongoing and these results will be disclosed in due course.

Experimental

General. Reactions requiring anhydrous conditions were performed using oven-dried glassware under a positive pressure of nitrogen. Anhydrous tetrahydrofuran (THF) was prepared by distillation from sodium-benzophenone ketyl under nitrogen immediately prior to use, or purchased from Aldrich in Sure/Seal™ bottles. All other solvents and reagents were purified by standard means. IR spectra were recorded on a Nicolet Magna 550 spectrometer (4000-600 cm^{-1}) with internal calibration. NMR spectra were recorded on a Bruker DRX-400 spectrometer with either TMS or residual protic solvent as internal reference. Mass spectra were recorded under EI conditions on a VG Analytical ZAB-E instrument, or a Kratos Profile HV-3 mass spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN analyser.

(6*R*)-6-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-piperidinethione 4. A stirred mixture of (6*R*)-**3**[7] (8.00 g, 21.8 mmol), *p*-methoxyphenylthionophosphine sulfide dimer (5.28 g, 13.1 mmol) and dry toluene (100 ml) was heated at reflux for 1 hour under a nitrogen atmosphere. After removal of the solvent *in vacuo*, a brown semi-solid remained. Column chromatography (dichloromethane) gave (6*R*)-**4** (8.15 g, 98%) as a pale yellow oil; $[\alpha]_D^{20}$ = +32.4 (*c* 1.0, $CHCl_3$). ν_{max} (thin film) 3371 (NH), 1589, 1520 (aromatic C=C), 1113 (C=S) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.47 (1H, br s, NH), 7.66-7.63 (4H, m, ArH), 7.47-7.38 (6H, m, ArH), 3.65 (1H, dd, *J* = 14.5, 8.7 Hz, OCH), 3.56-3.49 (2H, m, H-6, OCH), 3.01 (1H, m, H-3), 2.74 (1H, m, H-3), 1.82-1.74 (2H, m), 1.65 (1H, m), 1.34 (1H, m), 1.09 (9H, s, $C(CH_3)_3$); δ_C (100.6 MHz, $CDCl_3$) 203.2 (s, C-2), 135.52 (d, ArCH), 135.50 (d, ArCH), 132.6 (s, ArC), 132.5 (s, ArC), 130.1 (d, ArCH), 128.0 (d, ArCH), 66.6 (t, CH_2OSi), 56.9 (d, C-6), 39.4 (t, C-3), 26.9 (q, $C(\underline{C}H_3)_3$), 23.2 (t), 19.3 (t), 19.2 (s, $\underline{C}(CH_3)_3$); *m/z* (EI+) 383 (M^+, 2%), 83 (100). Observed (M^+): 383.1744; $C_{22}H_{29}NOSSi$ requires 383.1739.

(6*S*)-6-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-piperidinethione 4. A stirred mixture of (6*S*)-3[7] (7.97 g, 21.7 mmol), *p*-methoxyphenylthionophosphine sulfide dimer (5.26 g, 13.0 mmol) and dry toluene (100 ml) was heated at reflux for 1 hour under a nitrogen atmosphere. Work-up and purification as described above gave (6*S*)-**4** (8.12 g, 98%) as a pale yellow oil; $[\alpha]_D^{20}$ = -33.1 (*c* 1.0, $CHCl_3$). Spectroscopic data were identical with the corresponding (6*R*)-enantiomer.

(6*R*)-2-Bis(ethoxycarbonyl)methylidene-6-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]piperidine 5. Diethyl bromomalonate (3.74 ml, 21.9 mmol) was added dropwise to a stirred solution of (6*R*)-**4** (7.00 g, 18.3 mmol) dissolved in dichloromethane (100 ml) at 0°C under a nitrogen atmosphere. The reaction mixture was allowed to warm gradually to room temperature and stirred for 18 hours. Saturated aqueous potassium bicarbonate (200 ml) was added to the resulting solution and stirring was continued for a further 4 hours. The organic layer was separated and the aqueous layer further extracted with dichloromethane (3 x 100 ml). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (10% ethyl acetate / light petroleum) gave (6*R*)-**5** (7.46 g, 80%) as a pale yellow oil; $[\alpha]_D^{20}$ = +65.1 (*c* 1.0, $CHCl_3$). ν_{max} (thin film) 3236 (NH), 1699 (C=O), 1647 (olefinic C=C), 1585, 1506 (aromatic C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.43 (1H, br s, NH), 7.69-7.66 (4H, m, ArH), 7.43-7.38 (6H, m, ArH), 4.17 (4H, m, 2 x CO_2CH_2), 3.61-3.53 (3H, m, H-6, CH_2OSi), 2.69 (1H, m, H-3), 2.56 (1H, m, H-3), 1.81-1.72 (2H, m), 1.56 (1H, m), 1.37 (1H, m), 1.29 (3H, t, *J* = 7.1 Hz, CH_3), 1.25 (3H, t, *J* = 7.1 Hz, CH_3), 1.09 (9H, s, $C(CH_3)_3$); δ_C (100.6 MHz, $CDCl_3$) 169.0 (s, C=O), 168.9 (s, C=O), 164.8 (s), 135.72 (d, ArCH), 135.70 (d, ArCH), 133.3 (s, ArC), 133.2 (s, ArC), 129.84 (d, ArCH), 129.82 (d, ArCH), 127.8 (d, ArCH), 90.2 (s), 67.4 (t, CH_2OSi), 60.1 (t, $CO_2\underline{C}H_2$), 59.2 (t, $CO_2\underline{C}H_2$), 53.5 (d, C-6), 27.5 (t, C-3), 26.8 (q, $C(\underline{C}H_3)_3$), 24.2 (t), 19.3 (s, $\underline{C}(CH_3)_3$), 18.4 (t), 14.5 (q, CH_3), 14.3 (q, CH_3); *m/z* (EI$^+$) 509 (M^+, 20%), 406 (100). Found: C: 68.66%; H: 7.39%; N: 2.75%; $C_{29}H_{39}NO_5Si$ requires C: 68.34%; H: 7.71%; N: 2.75%.

(6*S*)-2-Bis(ethoxycarbonyl)methylidene-6-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]piperidine 5. Diethyl bromomalonate (4.01 ml, 23.5 mmol) was added dropwise to a stirred solution of (6*S*)-**4** (7.50 g, 19.6 mmol) dissolved in dichloromethane (100 ml) at 0°C under a nitrogen atmosphere. The reaction mixture was allowed to warm gradually to room temperature and stirred for 18 hours. Saturated aqueous potassium bicarbonate (200 ml) was added to the resulting solution and stirring was continued for a further 4 hours. Work-up and purification as described above gave (6*S*)-**5** (8.05 g, 81%) as a pale yellow oil; $[\alpha]_D^{20}$ = -61.0 (*c* 1.1, $CHCl_3$). Spectroscopic data were identical with the corresponding (6*R*)-enantiomer.

(6*R*)-2-Bis(ethoxycarbonyl)methylidene-6-(hydroxymethyl)piperidine 6. To a stirred solution of (6*R*)-**5** (7.30 g, 14.3 mmol) in dry THF (100 ml) at 0°C under a nitrogen atmosphere was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 15.78 ml, 15.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The resulting red-brown solution was quenched with water (100 ml), causing a colour change to yellow, and extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow-brown oil. Column chromatography (50% ethyl acetate / light petroleum) gave (6*R*)-**6** (3.03 g, 78%) as a pale yellow oil; $[\alpha]_D^{20}$ = +35.6 (*c* 0.85, $CHCl_3$). ν_{max} (thin film) 3450 (OH), 3252 (NH), 1695 (C=O), 1645 (olefinic C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.28 (1H, br s, NH), 4.19 (4H, m, 2 x CO_2CH_2), 3.72-3.46 (3H, m, H-6, CH_2OH), 3.10 (1H, br s, OH), 2.70 (1H, m, H-3), 2.56 (1H, m, H-3), 1.87-1.80 (2H, m), 1.61 (1H, m), 1.38 (1H, m), 1.28 (6H, m, 2 x CH_3); δ_C (100.6 MHz, $CDCl_3$) 169.2 (s, C=O), 168.9 (s, C=O), 165.1 (s), 90.0 (s), 66.1 (t, CH_2OH), 60.2 (t, $CO_2\underline{C}H_2$), 59.3 (t, $CO_2\underline{C}H_2$), 53.6 (d, C-6), 27.4 (t, C-3), 24.0 (t), 18.5 (t), 14.3 (q, CH_3), 14.2 (q, CH_3); *m/z* (EI$^+$) 271 (M^+, 13%), 83 (100). Observed (M^+): 271.1415; $C_{13}H_{21}NO_5$ requires 271.1420.

(6*S*)-2-Bis(ethoxycarbonyl)methylidene-6-(hydroxymethyl)piperidine 6. To a stirred solution of (6*S*)-**5** (7.50 g, 14.7 mmol) in dry THF (100 ml) at 0°C under a nitrogen atmosphere was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 16.21 ml, 16.2 mmol). The reaction mixture was allowed to warm to

room temperature, stirred for 18 hours and quenched with water (100 ml). Work-up and purification as described above gave (6*S*)-**6** (3.10 g, 78%) as a pale yellow oil; $[\alpha]_D^{20}$ = -36.6 (*c* 0.86, $CHCl_3$). Spectroscopic data were identical with the corresponding (6*R*)-enantiomer.

(6*R*)-2-Bis(ethoxycarbonyl)methylidene-6-[[(methanesulfonyl)oxy]methyl]-piperidine 7. To a stirred solution of (6*R*)-**6** (2.95 g, 10.9 mmol) and triethylamine (2.27 ml, 16.3 mmol) in dry dichloromethane (50 ml) at 0°C under a nitrogen atmosphere was added methanesulfonyl chloride (0.88 ml, 11.4 mmol) dropwise. The reaction mixture was stirred at 0°C for 1 hour and then saturated aqueous sodium bicarbonate (100 ml) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow-brown oil. Column chromatography (10% ethyl acetate / dichloromethane) provided (6*R*)-**7** (3.76 g, 99%) as a pale yellow oil; $[\alpha]_D^{20}$ = +43.6 (*c* 1.1, $CHCl_3$). ν_{max} (thin film) 3244 (NH), 1701 (C=O), 1645 (olefinic C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.24 (1H, br s, NH), 4.27 (1H, dd, *J* = 10.1, 4.2 Hz, CH_2OMs), 4.17 (4H, m, 2 x CO_2CH_2), 4.06 (1H, dd, *J* = 10.1, 8.0 Hz, CH_2OMs), 3.77 (1H, m, H-6), 3.11 (3H, s, OSO_2CH_3), 2.71 (1H, m, H-3), 2.57 (1H, m, H-3), 1.95 (1H, m), 1.86 (1H, m), 1.65 (1H, m), 1.47 (1H, m), 1.29 (3H, t, *J* = 7.2 Hz, CH_3), 1.25 (3H, t, *J* = 7.2 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 168.9 (s, C=O), 168.4 (s, C=O), 164.1 (s), 91.6 (s), 71.4 (t, $\underline{C}H_2OMs$), 60.3 (t, $CO_2\underline{C}H_2$), 59.5 (t, $CO_2\underline{C}H_2$), 50.5 (d, C-6), 37.7 (q, OSO_2CH_3), 27.0 (t, C-3), 23.8 (t), 18.0 (t), 14.3 (q, CH_3), 14.2 (q, CH_3); *m/z* (EI^+) 349 (M^+, 10%), 194 (100). Observed (M^+): 349.1191; $C_{14}H_{23}NO_7S$ requires 349.1195.

(6*S*)-2-Bis(ethoxycarbonyl)methylidene-6-[[(methanesulfonyl)oxy]methyl]-piperidine 7. To a stirred solution of (6*S*)-**6** (3.00 g, 11.1 mmol) and triethylamine (2.31 ml, 16.6 mmol) in dry dichloromethane (50 ml) at 0°C under a nitrogen atmosphere was added methanesulfonyl chloride (0.90 ml, 11.6 mmol) dropwise. The reaction mixture was stirred at 0°C for 1 hour and then saturated aqueous sodium bicarbonate (100 ml) was added. Work-up and purification as described above gave (6*S*)-**7** (3.83 g, 99%) as a pale yellow oil; $[\alpha]_D^{20}$ = -43.9 (*c* 1.1, $CHCl_3$). Spectroscopic data were identical with the corresponding (6*R*)-enantiomer.

(6*R*)-2-Bis(ethoxycarbonyl)methylidene-1-azabicyclo[4.1.0]heptane 1. To a stirred solution of (6*R*)-**7** (1.50 g, 4.30 mmol) in dry THF (50 ml) at room temperature under a nitrogen atmosphere was added potassium hydride (344 mg, 8.60 mmol) which gave an orange-brown colouration. This suspension was stirred for 1 hour and then heated at reflux for 90 minutes. After quenching with water (70 ml), the reaction mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to provide a brown oil. Florisil® column chromatography (10% ethyl acetate / light petroleum) gave (6*R*)-**1** (107 mg, 10%) as a pale yellow oil; $[\alpha]_D^{20}$ = +36.0 (*c* 0.55, $CHCl_3$). ν_{max} (thin film) 1707 (C=O), 1653 (olefinic C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.26 (2H, q, *J* = 7.2 Hz, CO_2CH_2), 4.19 (2H, q, *J* = 7.2 Hz, CO_2CH_2), 3.22 (1H, m, H-3), 2.62 (1H, m, H-6), 2.55 (1H, d, *J* = 4.8 Hz, CH_2N), 2.32 (1H, m, H-3), 2.17 (1H, m), 1.77 (1H, m), 1.75 (1H, d, *J* = 4.1 Hz, CH_2N), 1.54 (1H, m), 1.36 (1H, m), 1.31 (3H, t, *J* = 7.2 Hz, CH_3), 1.27 (3H, t, *J* = 7.2 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 168.5 (s), 165.9 (s, C=O), 165.5 (s, C=O), 112.7 (s), 60.5 (t, $CO_2\underline{C}H_2$), 60.3 (t, $CO_2\underline{C}H_2$), 37.3 (t, CH_2N), 34.8 (d, C-6), 26.5 (t), 23.2 (t), 18.5 (t), 14.11 (q, CH_3), 14.07 (q, CH_3); *m/z* (EI^+) 253 (M^+, 26%), 194 (100). Observed (M^+): 253.1319; $C_{13}H_{19}NO_4$ requires 253.1314.

(6*S*)-2-Bis(ethoxycarbonyl)methylidene-1-azabicyclo[4.1.0]heptane 1. To a stirred solution of (6*S*)-**7** (2.00 g, 5.73 mmol) in dry THF (50 ml) at room temperature under a nitrogen atmosphere was added potassium hydride (458 mg, 11.5 mmol) which gave an orange-brown colouration. This suspension was stirred for 1 hour, then heated at reflux for 90 minutes and quenched with water (70 ml). Work-up and purification as described above gave (6*S*)-**1** (155 mg, 11%) as a pale yellow oil; $[\alpha]_D^{20}$ = -35.8 (*c* 0.53, $CHCl_3$). Spectroscopic data were identical with the corresponding (6*R*)-enantiomer.

(6*S*)-2-Bis(ethoxycarbonyl)methylidene-6-(acetoxymethyl)piperidine 11. To a stirred solution of (6*S*)-**1** (20.0 mg, 0.078 mmol) in THF (3 ml) was added glacial acetic acid (0.01 ml, 0.172 mmol). After 5 days the reaction mixture was diluted with ether (10 ml) and washed with saturated sodium bicarbonate (2 x 5 ml), brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10% ethyl acetate / light petroleum) gave (*S*)-**11** (22.8 mg, 92%) as a colourless oil; $[\alpha]_D^{21}$-8.0 (*c* 1.0, $CHCl_3$); ν_{max} (thin film) 3245 (NH), 3129, 2980, 1747 (C=O), 1700, 1646, 1593, 1227 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.42 (1H, bs, NH), 4.25-4.10 (5H, m, 2 x OCH_2, CHOAc), 3.93 (1H, dd, *J* = 11.1, 8.3 Hz, CHOAc), 3.66 (1H, m, H-6), 2.68 (1H, ddt, *J* = 18.0, 1.5, 5.1 Hz, H-3), 2.57 (1H, ddd, *J* = 18.0, 9.9, 5.6 Hz, H-3), 2.13 (3H, s, CH_3), 1.95-1.79 (2H, m), 1.57-1.69 (1H, m), 1.39-1.49 (1H, m), 1.28 (3H, t, *J* = 7.1, CH_3), 1.25 (3H, t, *J* = 7.1, CH_3); δ_C (100.6 MHz, $CDCl_3$) 170.7 (s), 169.0 (s), 168.6 (s), 164.3 (s), 90.9 (s), 67.2 (t), 60.2 (t), 59.3 (t), 50.5 (d), 27.1 (t), 24.3 (t), 20.8 (q), 18.2 (t), 14.4 (q), 14.2 (q); *m/z* (EI^+) 313 (M^+, 13%), 268 (M^+-OEt), 194 (100). Observed (M^+): 313.1525; $C_{15}H_{23}NO_6$ requires 313.1525.

(6*S*)-2-Bis(ethoxycarbonyl)methylidene-6-(phenylsulfanylmethyl)piperidine 12. To a stirred solution of (6*S*)-**1** (16.0 mg, 0.062 mmol) in THF (2 ml) was added thiophenol (6.4 µl, 0.062 mmol) and triethylamine (8.7 µl, 0.062 mmol). After 1 week, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (10% ethyl acetate / light petroleum) to yield (6*S*)-**12** (18.9 mg, 82%) as a colourless oil; ν_{max} (thin film) 2980, 1699 (C=O), 1647, 1589, 1228, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.68 (1H, bs, NH), 7.43 (2H, m, ArH), 7.26 (3H, m, ArH), 4.25-4.12 (4H, m, 2 x OCH_2), 3.44-3.35 (1H, m, H-6), 3.08 (1H, dd, *J* = 13.5, 5.5 Hz, CHSPh), 2.88 (1H, dd, *J* = 13.5, 7.9 Hz, CHSPh), 2.70-2.52 (2H, m), 2.01-1.93 (1H, m), 1.85-1.77 (1H, m), 1.62-1.42 (2H, m), 1.29 (3H, t, *J* = 7.1 Hz, CH_3), 1.26 (3H, t, *J* = 7.1 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 168.9 (s), 168.7 (s), 164.2 (s), 134.5 (s), 131.2 (d), 129.1 (d), 127.1 (d), 90.8 (s), 60.2 (t), 59.3 (t), 50.7 (d), 41.3 (t), 27.7 (t), 27.2 (t), 18.6 (t), 14.4 (q), 14.2 (q); *m/z* (EI^+) 363 (M^+, 41%), 318 (M^+-OEt), 194 (100). Observed (M^+): 363.1504; $C_{19}H_{25}NSO_4$ requires 363.1505.

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References and Notes

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