A novel approach to bis-isoxazolines using a latent form of cyclopentadienone

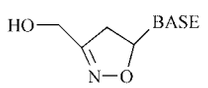
Sanjivanjit K. Basra,[a] Michael G. B. Drew,[a] John Mann *[a]† and Peter D. Kane[b]

[a] *Department of Chemistry, Reading University, Whiteknights, Reading, UK RG6 6AD*
[b] *Novartis Ltd., Wimblehurst Road, Horsham, UK RH12 4AB*

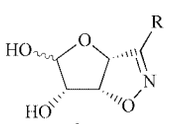
Received (in Cambridge, UK) 10th July 2000, Accepted 25th August 2000
First published as an Advance Article on the web 16th October 2000

We describe the synthesis of a range of both racemic and homochiral 4-alkyl- and 4-aryl-8-hydroxy-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-ones (isoxazolines) from the 1,3-dipolar cycloaddition reactions between alky- and aryl-nitrile oxides and 4-alkoxycyclopent-2-enones. Elimination of the 8-hydroxy group and subsequent additional cycloaddition reactions provided 5,9-disubstituted-3,11-dioxa-4,10-diazatricyclo[6.3.0^{1,8}.0^{2,6}]undeca-4,9-dien-7-ones (bis-isoxazolines) formally derived from cyclopentadienone.

The 1,3-dipolar cycloaddition of nitrile oxides to alkenes to produce isoxazolines has become a popular route to key intermediates for the construction of both natural products and novel biologically active molecules.[1] The isoxazoline ring not only provides access to β-hydroxyketones, β-hydroxynitriles, or γ-aminoalcohols, depending upon subsequent chemistry, but also has biological interest in its own right. The recent syntheses of the anti-viral nucleoside analogues **1**[2] and the β-galactoside



1



2

inhibitors **2**,[3] are but two examples of compounds that exemplify this fact. Our aim was to prepare a range of compounds that possessed two isoxazoline rings fused to a cyclopentanone, but which also carried a number of functional groups that would allow the production of a 'library' of more complex structures for possible biological evaluation. An overview of this approach is shown in Scheme 1.

Results and discussion

The starting material for our synthetic endeavours was the well-known 4-hydroxycyclopent-2-enone **3**, which is available on the multigram scale from furfural using the Bac–Piancatelli rearrangement.[4] Conversion of this compound into its *tert*-butyldimethylsilyl ether **4** was then achieved by standard means (TBDMSCl, imidazole, DCM, 63%). This racemic compound was then used for all of the initial studies, but it was also prepared in homochiral form *via* the route shown in Scheme 2. This uses well-established chemistry[5] including a highly stereoselective ester hydrolysis with electric eel acetylcholine esterase to produce (1*R*,3*S*)-1-acetoxycyclopent-4-en-3-ol. These investigators went on to prepare the (4*R*)-enantiomer of compound **4**. We employed a novel sequence involving silyl ether protection, acetate removal (1 M K_2CO_3–MeOH), and oxidation with PCC in dichloromethane to provide the (4*S*)-enantiomer of **4** in an overall yield of 54% for these three steps. The oxidation was complete within 1.5 hours which compares very favourably with previous efforts involving MnO_2,[6] where reaction times were as high as 2 days. This compound was obtained with an optical rotation that was higher than others recorded in the literature.[6]

Reaction of **4** with nitropropane in the presence of phenyl isocyanate and triethylamine[7] (in benzene) yielded the anticipated isoxazoline **5** in yields ranging from 50–78%, while a similar reaction with 2-(tetrahydropyranyloxy)nitroethane provided the adduct **6** in 46% yield. Alternatively, a variety of aryl-isoxazolines **7** could be produced through reaction of **4** with the oximes of aryl aldehydes in the presence of sodium hypochlorite[8] (in DCM). The best yield was obtained with the oxime of 4-bromobenzaldehyde (typically 65%). The ^{1}H NMR data for these compounds did not allow a clear-cut decision as to their relative stereochemistry, both in terms of *J* values and after extensive NOE studies. However, an X-ray crystallographic study on both compounds **5** and **7b** confirmed the *anti*-stereochemistry of these adducts (Fig. 1 and Table 1).

Adduct **7b** also provided an opportunity for further elaboration, and although an attempted Heck reaction[9] using Pd(II) acetate and methyl acrylate failed to yield the desired product, Suzuki reactions[10] with Pd(II) acetate and both phenylboronic acid and thiophene-2-boronic acid, provided the anticipated products **8** and **9** (24% and 18% respectively, unoptimised).

The feasibility of using compound **4** as a cyclopentadienone equivalent was then explored using adduct **7b**, and to this end the TBDMS group was first removed (5% aq. HF in MeCN, 52%) to provide alcohol **10**. This was dehydrated ($SOCl_2$, pyridine, 47–74%) to produce the cyclopentenone **11**, and thence the bis-isoxazoline **12** through reaction with nitropropane in the presence of phenyl isocyanate and triethylamine (45%). The *anti*-arrangement of the two isoxazoline rings was established through an X-ray structural analysis.

This chemistry was then repeated with adduct **5** to produce the cyclopentenone **13** which reacted with the THP-ether of 2-nitroethanol in the presence of triethylamine and phenyl isocyanate to yield the bis-isoxazoline **14**. Most of these reactions were then repeated using the pure (4*S*)-form of compound **4**.

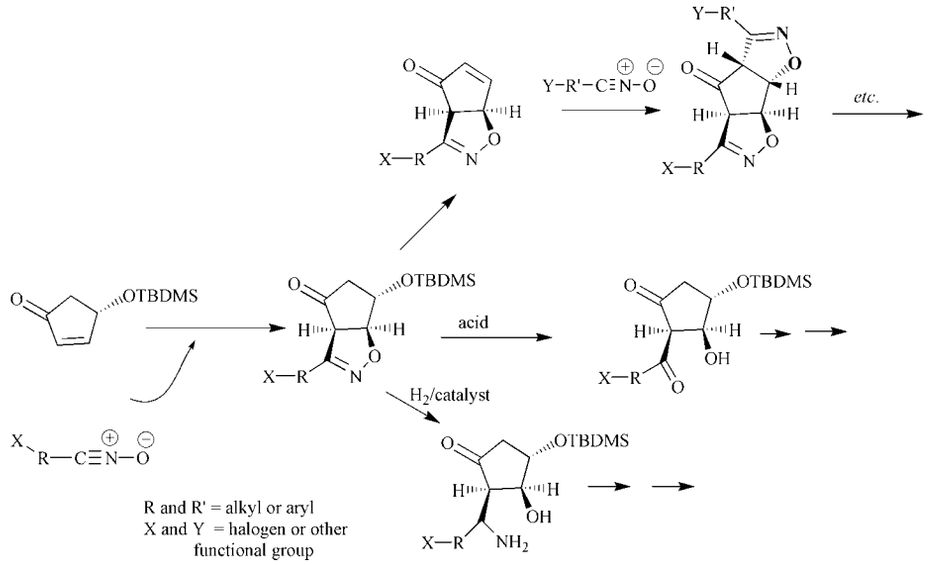
Overall this methodology offers the possibility of preparing a large number of stereochemically pure bis-isoxazolines where the extent of structural variety will be limited only by the availability of the nitroalkanes or aryl oximes. We are exploring the production of such libraries and also the subsequent chemical transformation of these adducts.

Experimental

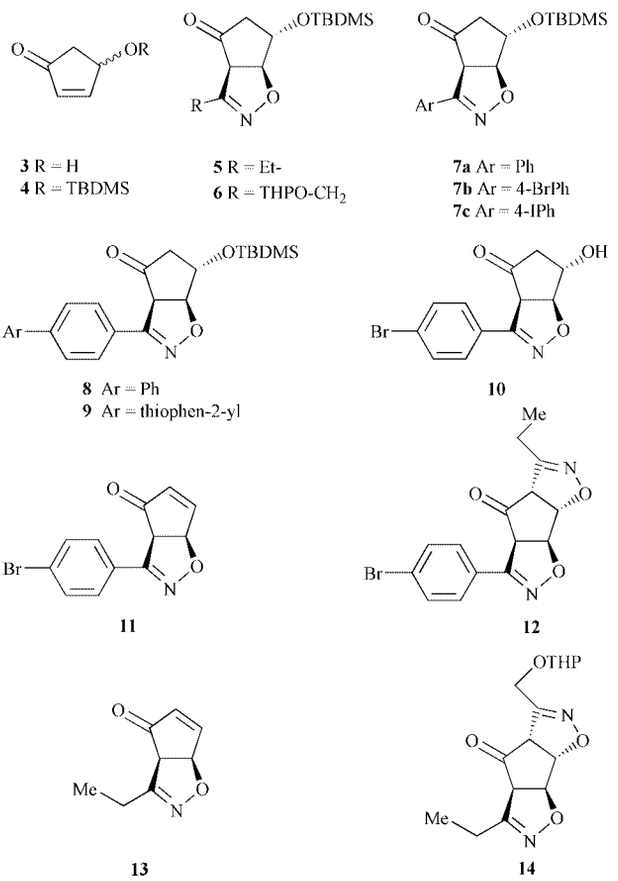
IR spectra were recorded using a Perkin-Elmer 881 series

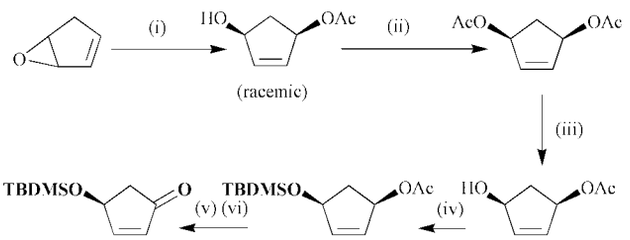
† *Present address*: School of Chemistry, Queen's University Belfast, Belfast, UK BT9 5AG.

 DOI: 10.1039/b005520o



Scheme 1





Scheme 2 (i) $(Ph_3P)_4Pd$, HOAc, THF (78%); (ii) Ac_2O, py, DCM (84%); (iii) electric eel acetylcholine esterase, NaN_3, phosphate buffer pH 6.9 (93%); (iv) TBDMSCl, imidazole, DCM (83%); (v) K_2CO_3, MeOH (86%); (vi) PCC, DCM, NaOAc (89%).

double beam spectrophotometer, and samples were run as thin films or in solution using NaCl plates. Low resolution and accurate mass data were recorded on a VG Autospec. Instrument. Elemental analyses were carried out by Medac Ltd., Brunel University, on those compounds that were stable. All compounds for which exact mass data are provided were homogeneous by TLC using three different solvent systems, and exhibited no spurious signals in their ^{1}H NMR spectra at 400 MHz. NMR spectra were recorded using JEOL EX-400, Bruker DPX 250, or Bruker WM 250 spectrometers. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Solvents were dried by distillation from calcium hydride (DCM, dichloromethane) or from sodium–benzophenone (diethyl ether, THF).

Crystal data for compounds **5**, **7b** and **12** were collected with Mo-Kα radiation using the MARresearch Image Plate System at room temperature. The crystals were positioned at 70 mm from the Image Plate. 100 Frames were measured at 2° intervals with a counting time of 2 minutes. Data analysis was carried out with the XDS programme.[11] The structures were solved using direct methods with the SHELX 86 programme.[12] The *tert*-butyl group was disordered in **7b** and two sets of methyl groups were redefined with occupation factors of x and $1 - x$ with x refining to 0.52(2). In the three structures the non-hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atoms to which they were attached. There were two molecules in the asymmetric unit of **12**. Compounds **7b** and **12** were corrected for absorption using the DIFABS programme.[13] The high R value for **7b** is a consequence of the disorder of the *tert*-butyl group and the poor quality of the crystal. The quality of the crystal of **12** was also poor but in both cases the structure determinations were of sufficient quality to identify unequivocally the relevant stereochemistry of the molecules. The structures were refined on F^2 using SHELXL.[14] ‡

3,4-Epoxycyclopent-1-ene

An ice-cooled mixture of anhydrous sodium carbonate (108.24 g, 1.02 mol), dichloromethane (450 mL), and cyclopentadiene (70 mL, 0.85 mol) were stirred mechanically. A solution of 39% peracetic acid (116 mL, 681 mmol) treated with anhydrous sodium acetate (2.094 g, 26 mmol) was slowly added to the mixture over 45 min. After stirring this solution for 2.5 h, below 25 °C, the solution was allowed to warm up to room temperature, and stirred until starch-iodide paper indicated the absence of oxidising agent. The white solid was filtered off and

‡ CCDC reference number 207/479. See http://www.rsc.org/suppdata/p1/b0/b005520o for crystallographic files in .cif format.

Table 1 Crystal data and structure refinement for **5**, **7b** and **12**

Identification code	**5**	**7b**	**12**
Empirical formula	$C_{14}H_{25}NO_3Si$	$C_{18}H_{24}NO_3Si$	$C_{15}H_{13}BrN_2O_3$
Formula weight	283.44	410.38	349.68
Crystal system, space group	Monoclinic, $P2_1$	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/n$
Unit cell dimensions a/Å	7.150(9)	7.091(9)	5.513(8)
b/Å	9.834(11)	25.43(3)	49.82(6)
c/Å	12.116(13)	11.529(14)	10.840(14)
β/deg	94.66(1)	96.49(1)	103.71(1)
Volume/Å^3	849	2065	2892
Z, Calculated density/Mg m^{-3}	2, 1.109	4, 1.320	8, 1.604
Data/restraints/parameters	2837/0/179	2619/31/204	5394/0/382
Final R indices [$I > 2\sigma(I)$] $R1$	0.0645	0.1249	0.1080
$wR2$	0.1513	0.2598	0.2013
R indices (all data) $R1$	0.0964	0.3276	0.2553
$wR2$	0.1650	0.3912	0.2893

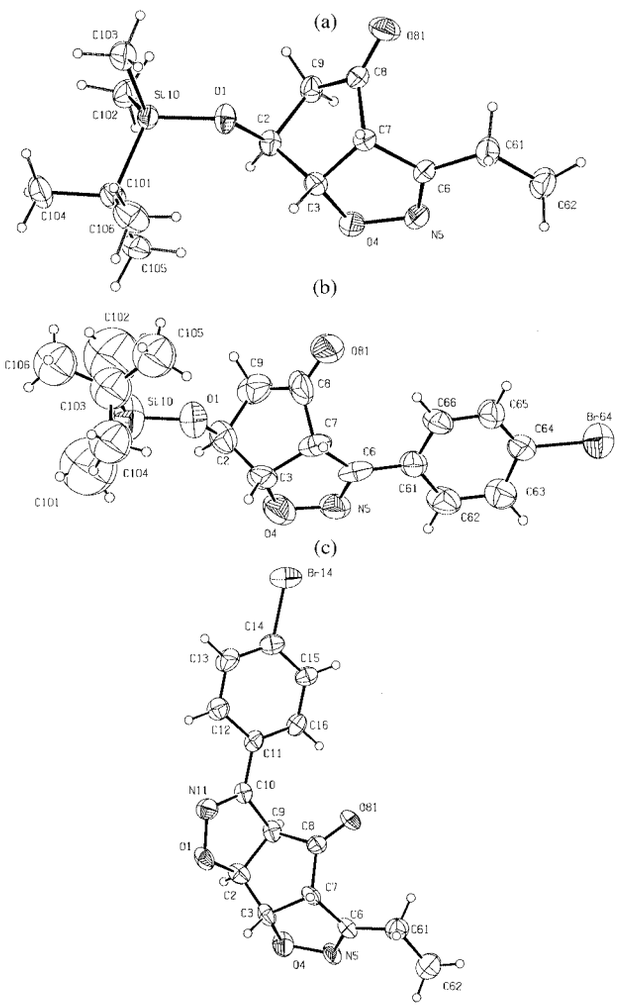


Fig. 1 (a) The structure of **5** with ellipsoids at 30% probability; (b) the structure of **7b** with ellipsoids at 30% probability. The *tert*-butyl group is disordered and only one set of positions is shown; (c) the structure of **12** with ellipsoids at 30% probability. There are two molecules in the asymmetric unit with similar conformations. Only one molecule is shown.

washed thoroughly with DCM. The solvent was removed by distillation, and the residue purified by reduced pressure distillation (35–44 °C, 35–40 mmHg) to provide a colourless oil (27.74 g, 50%), which was stored below −20 °C. $R_f = 0.7$ (1 : 1 petroleum ether (bp 40–60 °C)–ethyl acetate); ν_{max}/cm^{-1} 3048 (s), 2911 (s), 2819 (w), 1284 (s), 914 (s), 814 (s), 715 (s); δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.48 (2 H, m, CH_2), 3.87 (2 H, m, H-1/2), 6.05 (2 H, m, H-3/4); δ_C (100 MHz; $CDCl_3$; Me_4Si) 35.2 (C-5), 56.3 (C-1), 58.6 (C-2), 130.9 (C-4), 137.4 (C-3).

cis-1-Acetoxycyclopent-4-en-3-ol

Tetrakis(triphenylphosphine)palladium (0.242 g) was dissolved in dry THF (110 mL) under an Ar atmosphere at room temperature. Dry acetic acid (6.1 mL) was added to the ice-cooled solution. A solution of 3,4-epoxycyclopentene (8.71 g, 106.1 mmol) in dry THF (35 mL) was added slowly to the catalyst solution *via* a dropping funnel. After 10 min the solvent was removed under reduced pressure and the resulting reddish-brown oil passed through a plug of silica (50 g, 70–200 mesh) with diethyl ether (450 mL) as eluant. The solution was dried ($MgSO_4$) and solvent removed under reduced pressure to yield a pale yellow oil (6.8 g, 78% yield). ν_{max}/cm^{-1} 3400 (s) OH, 1735 (s) C=O; crude δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.64 (1 H, dt, J 14.5 and 3.8 Hz, H-2), 1.68 (1 H, dt, J 14.5 and 3.9 Hz, H-2), 1.9–2.1 (1 H, br s, OH), 2.06 (3 H, s, CH_3), 4.70 (1H, m, H-3), 5.50 (1 H, m, H-1), 5.99 (1 H, m, HC=), 6.12 (1 H, m, HC=).

cis-1,3-Diacetoxycyclopent-4-ene

The crude monoacetate (6.338 g, 34.8 mmol) was dissolved in DCM (75 mL) and dry pyridine (14.9 mL) was added under Ar. Acetic anhydride (15.0 mL) was added to the ice-cooled solution and the solution left stirring for 48 hours until the reaction had reached completion. The mixture was extracted with water (100 mL) and diethyl ether (100 mL), then the ethereal layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a dark orange–brown liquid. This mixture was chromatographed (130 g flash silica, 3 : 1 petroleum spirit–ethyl acetate), to give a pale yellow oil (5.3 g, 84%). $R_f = 0.4$ (3 : 1 petroleum ether–ethyl acetate); ν_{max}/cm^{-1} 3069 (m), 2946 (m), 1735 (s) C=O, 733 (w), 694 (w); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.74 (1 H, dt, J 15.0 and 3.9 Hz, H-2), 2.08 (6 H, s, CH_3), 2.89 (1 H, dt, J 15.0 and 7.5 Hz, H-2), 5.55 (2 H, dd, J 7.5 and 3.9 Hz, H-1/3), 6.10 (2 H, s, H-4 and 5); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.2 (acetate Me), 37.2 (C-2), 76.7 (C-1 and 3), 134.7 (C-4 and 5), 170.7 (2 × C=O); m/z (CI) 184.0744 ($C_9H_{12}O_4$ M^+ requires 184.0736).

Resolution using electric eel acetylcholine esterase

(1*R*,3*S*)-(+)-1-Acetoxycyclopent-4-en-3-ol. Phosphate buffer solution, pH 6.9 (1.45 M, 215 mL), was made up to 535 mL with water, and to this solution was added sodium azide (0.052 g, 0.80 mmol) followed by the electric eel acetylcholine esterase (0.004 g, 2112 units), and finally 1,3-diacetoxycyclopent-4-ene (10.84 g, 59.4 mmol). The two-phase mixture was gently stirred for 9 h, then extracted with diethyl ether (3 × 100 mL) and a 1 : 1 mixture of diethyl ether–ethyl acetate (15 × 100 mL). The organic extracts were combined, dried ($MgSO_4$), concentrated and the residue chromatographed to yield colourless crystals (6.42 g, 93%). Mp 48.8–51.5 °C [1 : 1 petrol–ether (5 mL g^{-1})] (lit.[5] 50.7–51.3 °C). $R_f = 0.3$ (1 : 1 petroleum ether–ethyl acetate); $[\alpha]_D^{20}$ +65.7 (c 1.03, chloroform) (lit.[5] $[\alpha]_D^{23}$ +73.8,

chloroform); ν_{max}/cm^{-1} 3395 (m) OH, 2924 (w) CH_2, 1732 (s) C=O, 1358 (w), 1257 (s), 1007 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.66 (1 H, dt, *J* 14.7 and 3.8 Hz, H-2), 2.06 (3 H, s, CH_3 of acetate), 2.81 (1 H, overlapping dt, *J* 14.7 and 7.3 Hz, H-2), 4.72 (1 H, m, H-3), 5.50 (1 H, m, H-1), 5.99 (1 H, m, H-4), 6.13 (1 H, m, H-5); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.2 (*C*H_3), 40.5 (C-2), 74.8 (C-3), 77.0 (C-1), 132.6 (C-4), 138.5 (C-5), 170.8 (C=O of acetate).

4-Hydroxycyclopent-2-enone (from furfuryl alcohol) (3)

Furfuryl alcohol (32.70 g, 300 mmol) was dissolved in water (1000 mL) and the solution de-gassed prior to addition of hydroquinone (0.35 g, 3.2 mmol) and sodium dihydrogen orthophosphate (1.63 g, 10.5 mmol). The pH of the solution was adjusted to 4.1 using 0.25 M orthophosphoric acid before the reaction mixture was heated under reflux under Ar for 16.5 h. A brown oil developing in the solution after this time was dispersed with 1,4-dioxane (200 mL). After a further 23 h the reaction mixture was allowed to cool to room temperature and extracted with toluene (3 × 100 mL). The remaining aqueous phase was concentrated to 150 mL and extracted with ethyl acetate (6 × 100 mL), dried ($MgSO_4$) and concentrated to give a crude brown oil (17.258 g, 53% yield). No further purification was undertaken. R_f = 0.28 (2:1 ethyl acetate–petroleum ether); ν_{max}/cm^{-1} 3388 (br s) OH, 2925 (w) CH_2, 1713 (s) C=O, 1586 (w) C=C, 1404 (w), 1342 (m), 1190 (m), 1104 (m), 1045 (m), 947 (w), 797 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.29 (1 H, dd, $J_{5,5}$ 18.7, $J_{5,4}$ 2.2 Hz, H-5), 2.78 (2 H, m, $J_{5,5}$ 18.7, $J_{5,4}$ 5.9 Hz, H-5 and OH), 5.06 (1 H, m, H-4), 6.23 (1 H, dd, $J_{3,2}$ 5.5, $J_{2,4}$ 1.3 Hz, H-2), 7.59 (1 H, dd, $J_{2,3}$ 5.5, $J_{3,4}$ 2.2 Hz, H-3); δ_C (100 MHz; $CDCl_3$; Me_4Si) 44.2 (CH_2), 70.4 (C-4), 135.1 (C-2), 163.4 (C-3), 207.1 (C-1).

(1*R*,4*S*)-(−)-1-Acetoxy-4-*tert*-butyldimethylsilyloxycyclopent-2-ene

To a solution of (1*R*,4*S*)-(+)-1-acetoxy-4-hydroxycyclopent-2-ene (5.3 g, 42.0 mmol) in dry DCM (60 mL) was added imidazole (4.005 g, 58.8 mmol) and this solution was cooled to 0 °C. A solution of *tert*-butyldimethylchlorosilane (7.599 g, 50.4 mmol) in dry DCM (40 mL) was added to the reaction mixture which was allowed to warm to RT, and stirred under N_2 for 1 h. The reaction mixture was extracted from water (50 mL) with DCM (3 × 25 mL). The organic extracts were combined, dried and concentrated and the residue chromatographed to yield a colourless oil (8.91 g, 83%). R_f = 0.3 (0.5:9.5 diethyl ether–petroleum ether); $[a]_D^{20}$ −7.2 (*c* 0.59, chloroform) (lit.,[6] $[a]_D^{20}$ −1.32, *c* 1.52, MeOH); ν_{max}/cm^{-1} 2931 and 2857 (m) CH_2, CH_3, 1735 (s) C=O, 1369 (m), 1239 (s), 1107 (m) Si–O, 1050 (m), 1022 (m), 837 (m), 778 (m); δ_H (250 MHz; $CDCl_3$; Me_4Si) 0.09 (3 H, s, Me of TBS), 0.09 (3 H, s, Me of TBS), 0.90 (9 H, s, *t*-Bu of TBS), 1.56–1.66 (1 H, m, H-5), 2.05 (3 H, s, Me of acetate), 2.75–2.87 (1 H, m, H-5), 4.69–4.74 (1 H, m, H-4), 5.44–5.49 (1 H, m, H-1), 5.87–5.98 (2 H, m, H-2 and 3); δ_C (63 MHz; $CDCl_3$; Me_4Si) −4.7 and −4.6 (Me of TBS), 18.2 (*t*-Bu quaternary), 21.2 (Me of acetate), 25.9 (*t*-Bu), 41.2 (C-5), 74.9 (C-4), 77.2 (C-1), 131.2 and 138.9 (C-2 and 3), 171.0 (C=O); *m*/*z* (CI) 197.1372 ($C_{13}H_{24}O_3Si$ M − acetate$^+$ requires 197.1362).

(4*S*)-(−)-1-*tert*-Butyldimethylsiloxycyclopent-2-en-1-ol

To a solution of (1*R*,4*S*)-(−)-1-acetoxy-4-*tert*-butyldimethylsiloxycyclopent-2-ene (8.911 g, 34.8 mmol) in AR methanol (150 mL) was added a solution of potassium carbonate (1 M, 35.0 mL) at RT. The mixture was stirred for 1.5 h and concentrated. The residue was taken up into DCM (50 mL) and extracted from brine (30 mL) with DCM (5 × 30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated to yield a colourless oil (6.419 g, 86%) which was used without further purification. R_f = 0.29 (3:7 diethyl ether–petroleum ether); $[a]_D^{20}$ −30.4 (*c* 0.5, chloroform); ν_{max}/cm^{-1} 3905–3367 (br s) OH, 2955, 2929 and 2858 (m) CH_2, CH_3, 1363 (m), 1252 (s), 1070 (s), 1020 (m), 906 (m), 837 (m), 776 (m); δ_H (250 MHz; $CDCl_3$; Me_4Si) 0.09 (6 H, s, Me of TBS), 0.90 (9 H, s, *t*-Bu of TBS), 1.52 (1 H, dt, $J_{5,5}$ 13.8, $J_{5,1/4}$ 4.5 Hz, H-5), 1.63 (1 H, br s, OH), 2.64–2.75 (1 H, dt, $J_{5,5}$ 13.8, $J_{5,1/4}$ 7.0 Hz, H-5), 4.56–4.69 (2 H, m, H-1 and 4), 5.88–5.97 (2 H, m, H-2 and 3); δ_C (63 MHz; $CDCl_3$; Me_4Si) −4.3 (Me of TBS), 18.6 (*t*-Bu quaternary), 26.3 (*t*-Bu), 45.1 (C-5), 75.5 and 75.7 (C-1 and 4), 136.0 and 137.4 (C-2 and 3); *m*/*z* (CI) 214.1389 ($C_{11}H_{22}O_2Si$ M$^+$ requires 214.1389).

(4*S*)-(−)-4-*tert*-Butyldimethylsilyloxycyclopent-2-en-1-one (−)-(4)

To a solution of the alcohol **3** (6.419 g, 29.9 mmol) in dry DCM (140 mL) were added anhydrous sodium acetate (0.737 g, 9.0 mmol) and powdered 4 Å sieves (10.9 g). This mixture was cooled prior to the portion-wise addition of PCC (9.678 g, 44.9 mmol). The mixture was allowed to warm to RT under N_2 and stirred for 10 min. The chromate salts were precipitated out with ether (100 mL) and the mixture filtered through Celite–silica plug and washed thoroughly with ethyl acetate. The combined organic extracts were dried (brine, $MgSO_4$), concentrated and the residue chromatographed (1.5:8.5 ether–petrol) to yield colourless crystals (5.661 g, 89%). Mp 29–31 °C; lit.,[6] 32–33 °C; R_f = 0.31 (8.5:1.5 petroleum ether–diethyl ether); $[a]_D^{20}$ −72.0 (*c* 0.50, methanol) (lit.,[6] $[a]_D^{23}$ −65.1, *c* 0.94, methanol); δ_H (250 MHz; $CDCl_3$; Me_4Si) 0.13 (3 H, s, Me), 0.14 (3 H, s, Me), 0.91 (9 H, s, *t*-Bu), 2.25 (1 H, dd, $J_{5,5}$ 18.2, $J_{5,4}$ 2.2 Hz, H-5), 2.71 (1 H, dd, $J_{5',5}$ 18.2, $J_{5,4}$ 6.0 Hz, H-5), 4.96–5.02 (1 H, m, H-4), 6.18 (1 H, dd, $J_{2,3}$ 5.7, $J_{2,4}$ 1.3 Hz, H-2), 7.45 (1 H, dd, $J_{3,2}$ 5.7, $J_{3,4}$ 2.3 Hz, H-3); *m*/*z* (CI) 212.1284 ($C_{11}H_{20}O_2Si$ M$^+$ requires 212.1283).

General procedure for formation of isoxazolines under Mukaiyama conditions: (1*S*,5*S*,8*S*)-4-ethyl-8-(*tert*-butyldimethylsiloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (5)

To a solution of (4*S*)-*tert*-butyldimethylsilyloxycyclopent-2-en-1-one (0.500 g, 2.35 mmol), dry triethylamine (0.164 mL, 1.18 mmol) and nitropropane (0.53 mL, 5.94 mmol) in dry benzene (7 mL), was added a solution of phenyl isocyanate (1.60 mL, 9.90 mmol) in dry benzene (6 mL) *via* a motorised syringe pump over 6 h. The clear yellow solution became opaque and slightly viscous during the isocyanate addition. The mixture was stirred overnight at room temp. and quenched with water (15 mL). The mixture was filtered through a plug of Celite and then gravity filtered prior to extraction with benzene. The organic extracts were combined, dried (brine, $MgSO_4$), concentrated and chromatographed to yield a pale yellow crystalline solid (0.336 g, 50%). Mp 42.0–44.0 °C; R_f = 0.50 (1.5:8.5 diethyl ether–petroleum ether); $[a]_D^{20}$ −500.6 (*c* 0.54, chloroform); ν_{max}/cm^{-1} 2930 and 2857 (s) CH_2, CH_3, 1755 (s) C=O, 1610–1660 (br w) C=N, 1463 (m) CH_2, CH_3, 1257.8 (m) Si–Me, 1134 (s), 1089.1 (m) Si–O, 1044 (m), 922 (m) Si–Me, 836 (s), 780 (m); δ_H (250 MHz; $CDCl_3$; Me_4Si) 0.10 (3 H, s, Me of TBS), 0.12 (3 H, s, Me of TBS), 0.87 (9 H, s, *t*-Bu), 1.20 (3 H, t, *J* 7.3 Hz, CH_3 ethyl), 2.31 (2 H, m, H-7 and 1 H from ethyl CH_2), 2.46 (1 H, m, 1 H from ethyl CH_2), 2.60 (1 H, dd, $J_{7,7'}$ 17.4, $J_{7,8}$ 4.9 Hz, H-7), 3.79 (1 H, m, H-5), 4.51 (1 H, m, $J_{8,7'}$ 4.9 Hz, H-8), 5.04 (1 H, unresolved ddd, $J_{1,8}$ 8.6, $J_{1,5}$ 8.6, $J_{1,7}$ 1.5 Hz, H-1); δ_C (63 MHz; $CDCl_3$; Me_4Si) −5.0 (Me of TBS), 10.5 (C-ethyl CH_3), 17.9 (quaternary of *t*-Bu), 19.8 (C-ethyl CH_2), 25.6 (*t*-Bu), 44.8 (C-7), 61.4 (C-5), 71.8 (C-8), 89.9 (C-1), 156.4 (C-4), 208.7 (C-6); *m*/*z* (CI) 283.1603 ($C_{14}H_{25}NO_3Si$ M$^+$ requires 283.1604).

Protection of 2-nitroethanol: 2-(2′-nitroethoxy)tetrahydropyran

To a solution of 2-nitroethanol (0.201 g, 2.2 mmol) in dry DCM (2.5 mL) was added PTSA (0.044 g, 0.23 mmol). This

colourless solution was cooled to 0 °C prior to the dropwise addition of 3,4-dihydro-2*H*-pyran (0.220 mL, 2.4 mmol). The colourless solution became opaque, and the reaction mixture was allowed to warm to RT. The solution went through a series of colour changes—blue, green, then brown as the solution was stirred overnight under N_2. The mixture was extracted from water (2 mL) with DCM, the organic extracts were combined, dried, concentrated and the residue purified by column chromatography to yield a colourless oil (0.242 g, 63%). $R_f = 0.27$ (3:7 diethyl ether–petroleum ether); δ_H (250 MHz; $CDCl_3$; Me_4Si) 1.49–1.63 (4 H, m, H-4 and H-5), 1.65–1.83 (2 H, m, H-6), 3.50–3.58 (1 H, m, H-3), 3.76–3.85 (1 H, m, H-3), 3.94–4.03 (1 H, m, H-2′), 4.19–4.27 (1 H, m, H-2′), 4.55–4.59 (2 H, m, H-1′), 4.66–4.68 (1 H, m, H-2).

(1*S*,5*S*,8*S*)-4-(Tetrahydropyran-2′-yloxymethyl)-8-(*tert*-butyldimethylsilyloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (6)

Procedure as for **5**, but using THP protected nitroethanol, and reaction time was approximately 48 h. Reaction carried out on 0.500 g (alkene) scale, to yield a colourless oil (0.296 g, 33%). $R_f = 0.27$ (3:7 diethyl ether–petroleum ether); $[\alpha]_D^{20}$ −243.8 (*c* 0.53, chloroform); ν_{max}/cm^{-1} 2952 (s) CH_2, CH_3, 2858 (s) CH_2, CH_3, 1755 (s) C=O, 1616 (w) C=N, 1472 (m) CH_2, CH_3, 1391 (m), 1362 (m), 1301.4 (m), 1260 (s), 1202 (w), 1129 (s) Si–Me, 1078 (s) Si–O, 1037 (s), 921 (m) Si–Me, 837 (s), 780 (m); δ_H (250 MHz; $CDCl_3$; Me_4Si) 0.10 (3 H, s, Si–Me), 0.12 (3 H, s, Si–Me), 0.87 (9 H, s, *t*-Bu), 1.43–1.88 (6 H, m, 3 × CH_2 of THP), 2.34 (1 H, m, $J_{7,7}$ 17.4 Hz, H-7), 2.55 (1 H, dd, $J_{7,7}$ 17.4, $J_{7,8}$ 4.9 Hz, H-7), 3.46–3.61 (1 H, m, 1 H from CH_2 of THP), 3.79–3.97 (1 H, m, 1 H from CH_2 of THP), 4.01 (1 H, m, $J_{5,1}$ 8.7 Hz, H-5), 4.14–4.31 (1 H, m, CH_2-OTHP), 4.38–4.50 (1 H, m, CH_2-OTHP), 4.50–4.55 (1 H, m, C*H* of THP), 4.68–4.76 (1 H, m, H-8), 5.09–5.14 (1 H, m, $J_{1,5}$ 8.7 Hz, H-1); δ_C (100 MHz; $CDCl_3$; Me_4Si) −4.9 (Si–Me), 17.9 (*t*-Bu quaternary), 18.8 and 18.9 (CH_2 of THP), 25.2 (CH_2 of THP), 25.6 (Me of *t*-Bu), 30.1 and 30.2 (CH_2 of THP), 44.9 (C-7), 59.6 (C-5), 60.3 (*C*H_2-OTHP), 61.7 and 62.0 (CH_2 of THP), 71.6, 71.7 and 71.9 (*C*H of THP), 90.6 (C-1), 97.8 and 99.1 (C-8), 152.9 and 153.3 (C-4), 208.0 and 208.2 (C-6); *m*/*z* (CI) 369.1957 ($C_{19}H_{30}NO_5Si$ M^+ requires 369.1972).

General procedure for the formation of isoxazolines using sodium hypochlorite: *rac*-(1*S**,5*S**,8*S**)-4-phenyl-8-(*tert*-butyldimethylsilyloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (7a)

To a solution of *rac*-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-en-1-one (**4**) (0.11 g, 0.52 mmol) and benzaldoxime in DCM (8 ml) at 0 °C was added sodium hypochlorite solution (4% aq., 7.5 ml) dropwise over 15 min. The reaction mixture was allowed to warm to room temperature and stirred vigorously for 18 h. The reaction mixture was then extracted with DCM, the organic extracts combined, dried and concentrated prior to chromatography that yielded a white crystalline solid. Mp 102–104 °C; $R_f = 0.42$ (1:9 diethyl ether–petroleum ether); ν_{max}/cm^{-1} 3064 (w) aromatic C–C, 2955, 2930 and 2857 (s) CH_2 and CH_3, 1758 –C=O, 1593 (m) aromatic C–C, 1506 (w), 1472 and 1446 (m) CH_2 and CH_3, 1392 (w), 1362 (w) CH_3, 1344 (m), 1259 (s) Si–Me, 1178 (w), 1156 (m), 1131 (s), 1080 (s), 1049 (s), 1023 (w), 100 (w), 976 (w), 920 (m), 836 (s), 780 and 691 (m) monosubstituted benzene; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.00 (3 H, s, Me), 0.18 (3 H, s, Me), 0.76 (9 H, s, *t*-Bu), 2.22 (1 H, unresolved dd, $J_{7,7'}$ 16.9 Hz, H-7), 2.54 (1 H, dd, $J_{7',7}$ 16.9, $J_{7',8}$ 4.4 Hz, H-7′), 4.15 (1 H, d, $J_{5,1}$ 8.6 Hz, H-5), 4.47 (1 H, m, H-8), 5.11 (1 H, d, $J_{1,5}$ 8.6 Hz, H-1), 7.28 (3 H, m, H-aromatic), 7.77 (2 H, m, H-aromatic); δ_C (63 MHz; $CDCl_3$; Me_4Si) −4.9 (Si–Me), 17.9 and 18.0 (quaternary of *t*-Bu), 25.6 (*t*-Bu), 45.0 (C-7), 58.8 (C-5), 71.1 (C-8), 91.4 (C-1), 128.3 (C-aromatic), 128.7 (C-aromatic), 130.4 (C-aromatic quaternary), 153.5 (C-4), 208.0 (C-6); *m*/*z* (CI) 331.1604 ($C_{18}H_{25}NO_3Si$ M^+ requires 331.1604).

(1*S*,5*S*,8*S*)-4-(4′-Bromophenyl)-8-(*tert*-butyldimethylsiloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (7b)

Preparation as for **7a**, using (4*S*)-4-(*tert*-butyldimethylsiloxy)-cyclopent-2-enone (**4**) (1.003 g, 4.7 mmol) to yield a white solid (1.295 g, 73%). Mp 88–94 °C; $C_{18}H_{24}BrNO_3Si$ requires C 52.68, H 5.89, N 3.41%; found C 52.51, H 6.06, N 3.85%; $R_f = 0.56$ (1:9 diethyl ether–petroleum ether); $[\alpha]_D^{20}$ −52.2 (*c* 0.51, chloroform); ν_{max}/cm^{-1} 2927 (s) CH_2 and CH_3, 1752 (s) C=O, 1399 (m), 1257 (m), 1133 (s), 1072 (s), 918 (s), 836 (s), 470 (m); δ_H (250 MHz; $CDCl_3$; Me_4Si) 0.13 (3 H, s, Si–Me), 0.15 (3 H, s, Si–Me), 0.89 (9 H, s, *t*-Bu), 2.36 (1 H, m, $J_{7,7}$ 17.1 Hz, H-7), 2.65 (1 H, dd, $J_{7',7}$ 17.1, $J_{7',8}$ 4.7 Hz, H-7′), 4.23 (1 H, m, $J_{5,1}$ 8.6 Hz, H-5), 4.60 (1 H, m, $J_{8,7'}$ 4.7 Hz, H-8), 5.24 (1 H, m, $J_{1,5}$ 8.6 Hz, H-1), 7.53 (2 H, d, $J_{3',2'}$ 8.9 Hz, H-3′), 7.75 (2 H, d, $J_{2',3'}$ 8.9 Hz, H-2′); δ_C (100 MHz; $CDCl_3$; Me_4Si) −4.9 (2 × Si–Me), 17.9 (*t*-Bu quaternary C), 25.6 (*t*-Bu), 45.0 (C-7), 58.7 (C-5), 71.0 (C-8), 91.6 (C-1), 125.0 and 126.7 (C-1′ and C-4′), 129.2 (C-3′), 131.9 (C-2′), 152.8 (C-4), 207.9 (C-6); *m*/*z* (CI) 409.0720 ($C_{18}H_{24}BrNO_3Si$ M^+ − H requires 409.0709).

(1*S*,4*S*,8*S*)-4-(4′-Iodophenyl)-8-(*tert*-butyldimethylsilyloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (7c)

To a solution of (4*S*)-(−)-4-*tert*-butyldimethylsiloxycyclopent-2-en-1-one (**4**) (0.201 g, 0.95 mmol) and 4-iodobenzaldoxime (0.448 g, 1.8 mmol) in DCM (10 mL) was added triethylamine (0.014 mL, 0.1 mmol). The pale yellow solution was cooled to 0 °C prior to dropwise addition of NaOCl solution (5%, 15 mL) over 1 h. The opaque mixture was allowed to warm to RT and stirred vigorously for 43 h. The mixture was extracted with DCM (3 × 15 mL). The organic extracts were combined, dried (brine, $MgSO_4$), concentrated and the residue chromatographed (gradient elution: 100% petroleum ether to 1% diethyl ether in petroleum ether, to 2% diethyl ether) to yield a white solid (0.197 g, 45%). Mp 99–106 °C; $R_f = 0.54$ (1:9 diethyl ether–petroleum ether); $[\alpha]_D^{20}$ −48.0 (*c* 0.52, chloroform); ν_{max}/cm^{-1} 2954, 2928 and 2857 (s) CH_2, CH_3, 1756 (s) C=O, 1584 (w), 1488 (w), 1472 (w), 1396 (m), 1332 (w), 1259 (m), 1156 (w), 1131 (m), 1081 (m), 1048 (m), 1006 (m), 920 (m), 836 (m) *para*-disubstituted benzene, 780 (m); δ_H (250 MHz; $CDCl_3$; Me_4Si) 0.13 (3 H, s, Me), 0.14 (3 H, s, Me), 0.89 (9 H, s, *t*-Bu), 2.33–2.40 (1 H, m, $J_{7,7}$ 17.1 Hz, H-7), 2.65 (1 H, dd, $J_{7,7}$ 17.1, $J_{7,8}$ 4.6 Hz, H-7), 4.21–4.25 (1 H, m, $J_{5,1}$ 8.5 Hz, H-5), 4.60 (1 H, d, $J_{8,7}$ 4.6 Hz, H-8), 5.22–5.27 (1 H, m, $J_{1,5}$ 8.5 Hz, H-1), 7.61 (2 H, dt, $J_{2',3'}$ 8.7, $J_{2',2'} \equiv J_{2',3a'}$ 2.0 Hz, H-aromatic), 7.76 (2 H, dt, $J_{3',2'}$ 8.7, $J_{3',3'} \equiv J_{3',2a'}$ 2.0 Hz, H-aromatic); δ_C (63 MHz; $CDCl_3$; Me_4Si) −4.4 (2 × Me), 18.4 (*t*-Bu quaternary), 26.1 (*t*-Bu), 45.4 (C-7), 59.0 (C-5), 71.4 (C-8), 92.1 (C-1), 97.5 (C-aromatic), 127.6 (C-aromatic quaternary), 129.6 (C-aromatic), 138.3 (C-aromatic), 153.4 (C-4), 208.4 (C-6); *m*/*z* (CI) 457.0570 ($C_{18}H_{24}NO_3SiI$ M^+ requires 457.0570).

(1*S*,5*S*,8*S*)-4-(4′,4″-Biphenylyl)-8-(*tert*-butyldimethylsilyloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (8)

To a stirred solution of the 4-(4′-bromophenyl)-8-(*tert*-butyldimethylsiloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (**7b**) (0.099 g, 0.24 mmol) and phenylboronic acid (0.031 g, 0.25 mmol) in DME (1 mL) under Ar, was added triphenylphosphine (0.02 g, 0.08 mmol) and palladium(II) acetate (0.005 g, 0.02 mmol), followed by sodium carbonate solution (2 M, 0.145 mL, 0.29 mmol) and water (0.1 mL). The reaction mixture was heated under gentle reflux for 6.5 h, and during this time the solution underwent colour changes from yellow to orange, and finally brown. The reaction mixture was extracted from water (2 mL) with ethyl acetate. The organic extracts were washed with dilute sodium bicarbonate solution, dried ($MgSO_4$, brine), concentrated and chromatographed (gradient elution from 100% petroleum ether to 25% diethyl ether in petroleum ether) to yield a colourless crystalline solid (0.018 g, 24% yield). Mp

135–149 °C; R_f = 0.68 (2.5 : 7.5 diethyl ether–petroleum ether); $[\alpha]_D^{20}$ −16.2 (*c* 1.2, chloroform); ν_{max}/cm^{-1} 2955 and 2855 (m) –CH_2, –CH_3, 1753 (s) –C=O, 1488 (w), 1462 (w), 1408 (w), 1336 (w), 1260 (m), 1131 (m), 1079 and 1046 (m) Si–O, 1007 (w), 915 (s), 843 (s) *p*-substituted benzene, 783 (m), 764 (s) monosubstituted benzene, 728 (w), 698 (s) monosubstituted benzene; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.14 (3 H, s, Si–Me), 0.16 (3 H, s, Si–Me), 0.90 (9 H, s, *t*-Bu), 2.37 (1 H, unresolved m, $J_{7,7}$ 17.1 Hz, H-7), 2.70 (1 H, dd, $J_{7,7}$ 17.1, $J_{7,8}$ 4.7 Hz, H-7), 4.31 (1 H, ddd, $J_{5,1}$ 8.5, $J_{5,7}$ 1.6, $J_{5,8}$ 0.5 Hz, H-5), 4.62 (1 H, m, $J_{8,7}$ 4.7 Hz, H-8), 5.26 (1 H, m, $J_{1,5}$ 8.5 Hz, H-1), 7.26–7.47 (3 H, m, H-aromatic), 7.56–7.68 (4 H, m, H-aromatic), 7.94–7.99 (2 H, m, H-aromatic); δ_C (63 MHz; $CDCl_3$; Me_4Si) −4.8 (Si–Me), 18.0 (C-*t*-Bu), 25.7 (Me of *t*-Bu), 45.0 (C-7), 58.9 (C-5), 71.2 (C-8), 91.5 (C-1), 126.6 (C-aromatic quaternary), 127.1 and 127.4 (C-aromatic), 127.9, 128.2 and 128.9 (C-aromatic), 140.1 and 143.2 (C-aromatic quaternary), 153.4 (C-4), 208.2 (C-1); *m*/*z* (CI) 407.1912 ($C_{24}H_{29}NO_3Si$ M^+ requires 407.1917).

rac-(1*S**,5*S**,8*S**)-4-(4′-Thiophen-2″-ylphenyl)-8-(*tert*-butyldimethylsilyloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (9)

To a stirred solution of the 4-(4′-bromobenzyl)-8-(*tert*-butyldimethylsiloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (**7b**) (0.099 g, 0.24 mmol) and thiophene-2-boronic acid (0.033 g, 0.26 mmol) in DME (1 mL) under Ar, was added triphenylphosphine (0.019 g, 0.07 mmol) and palladium(II) acetate (0.005 g, 0.02 mmol) which gave a yellow solution. Addition of sodium carbonate solution (2 M, 0.145 mL, 0.29 mmol) and water (0.1 mL) led to colour changes: yellow to orange; to red–orange; to red. The reaction mixture was heated under gentle reflux for 5.5 h, which caused a colour change from red to brown. The reaction mixture was cooled in air and extracted from water (1 mL) with ethyl acetate. The organic extracts were washed with dilute sodium bicarbonate solution, dried ($MgSO_4$, brine), concentrated and chromatographed (gradient elution from 100% petroleum ether to 25% diethyl ether in petroleum ether) to yield a colourless crystalline solid (0.012 g, 14% yield). Mp 111–120 °C; $C_{22}H_{27}NO_3SSi$ requires C 63.89, H 6.58, N 3.38%; found C 63.40, H 6.37, N 3.23%; R_f = 0.62 (2.5 : 7.5 diethyl ether–petroleum ether); ν_{max}/cm^{-1} 2954 (m) and 2929 (m) CH_2, CH_3, 2857 (m) CH_2, CH_3, 1756 (s) C=O, 1605.5 (w), 1471 (w), 1413 (w), 1339 (w), 1260 (m), 1131 (s), 1080 (m), 1048 (m), 1000 (w), 921 (m), 836 (s) *para*-substituted benzene, 781 (m), 696.2 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.13 (3 H, s, Si–Me), 0.15 (3 H, s, Si–Me), 0.90 (9 H, s, *t*-Bu), 2.36 (1 H, unresolved m, $J_{7,7}$ 17.1 Hz, H-7), 2.68 (1 H, dd, $J_{7,7}$ 17.1, $J_{7,8}$ 4.7 Hz, H-7), 4.28 (1 H, unresolved ddd, $J_{5,1}$ 8.5, $J_{5,7}$ 1.6 Hz, H-5), 4.70 (1 H, m, $J_{8,7}$ 4.7 Hz, H-8), 5.25 (1 H, m, $J_{1,5}$ 8.5, $J_{1,7/1,8}$ 1.5 Hz, H-1), 7.1 (1 H, dd, *J* 5.1, *J* 3.6 Hz, H-4″ thiophene), 7.32 (1 H, dd, *J* 5.1, *J* 1.2 Hz, H-3″/5″ thiophene), 7.38 (1 H, dd, *J* 3.6, *J* 1.2 Hz, H-3″/5″ thiophene), 7.63–7.68 (2 H, d, *J* 8.4 Hz, H-aromatic), 7.88–7.92 (2 H, d, *J* 8.4 Hz, H-aromatic); δ_C (63 MHz; $CDCl_3$; Me_4Si) −4.8 (2 Si–Me), 18.0 (quart. *t*-Bu), 25.7 (3 Me from *t*-Bu), 45.1 (C-7), 58.9 (C-5), 71.2 (C-8), 91.5 (C-1), 124.0 and 125.8 (C-3″ and 5″ thiophene), 126.0 (C-3′ aromatic), 126.6 (C-aromatic quaternary), 128.3 (C-4″ thiophene), 128.4 (C-2′ aromatic), 136.4 and 143.4 (C-4′ aromatic quaternary and C-2″ thiophene quaternary), 153.3 (C-4), 208.1 (C-6); *m*/*z* (CI) 413.1484 ($C_{24}H_{29}NO_3Si$ M^+ requires 413.1481).

rac-4-Ethyl-8-hydroxy-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one

To *rac*-(1*R**,5*R**,8*R**)-4-ethyl-8-(*tert*-butyldimethylsilyloxy)-2-oxa-3-azabicyclo[3.3.0]oct-3-en-6-one (0.100 g, 0.35 mmol) was added a 5% solution of HF (40% aqueous solution, 0.5 mL) in acetonitrile (2 mL). The orange solution was stirred at RT for 2.5 h. Water (2 mL) was added to the reaction mixture, which was then extracted with chloroform. The organic extracts were combined, dried, concentrated and the residue chromatographed (column packed in 1 : 1 diethyl ether–petroleum ether, run in 6 : 4 diethyl ether–petroleum ether) to yield a yellow oil (0.032 g, 59% yield). R_f = 0.34 (8 : 4 diethyl ether–petroleum ether); ν_{max}/cm^{-1} 3388 (br s) –OH, 2977 (m) –CH_2, –CH_3, 1748 (s) –C=O, 1616 (w) C=N, 1393 (w), 1288 (w), 1135 (m), 1021 (w), 982 (w), 892 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.21 (3 H, t, *J* 7.5 Hz, CH_3 of ethyl), 2.20 (1 H, br s, OH), 2.24–2.58 (3 H, m, CH_2 of ethyl and 1 × H-7), 2.64 (1 H, dd, $J_{7,7}$ 17.9, $J_{7,8}$ 5.1 Hz, H-7), 3.85 (1 H, d, $J_{5,1}$ 8.8 Hz, H-5), 4.61 (1 H, br d, $J_{8,7}$ 5.1 Hz, H-8), 5.14 (1 H, unresolved dd, $J_{1,5}$ 8.8, $J_{1,8}$ 1.4 Hz, H-1); δ_C (63 MHz; $CDCl_3$; Me_4Si) 10.261 (CH_3), 19.7 (CH_2), 44.0 (C-7), 61.5 (C-5), 71.0 (C-8), 89.2 (C-1), 156.6 (C-4), 208.81 (C-6); *m*/*z* (CI) 169.0745 ($C_8H_{11}NO_3$ M^+ requires 169.0739).

(1*S*,5*S*,8*S*)-4-(4′-Bromophenyl)-8-hydroxy-2-oxa-3-azabicyclo-[3.3.0]oct-3-en-6-one (10)

Procedure as for 4-ethyl-8-hydroxy-2-oxa-3-azabicyclo[3.3.0]-oct-3-en-6-one, using 0.28 g of silyl ether to yield a white solid (0.104 g, 52%). Mp 138–145 °C. R_f = 0.26 (6 : 4 diethyl ether–petroleum ether; $[\alpha]_D^{20}$ −74.0 (*c* 0.50, chloroform); ν_{max}/cm^{-1} ~3500 (br s) OH, 2943 (m) CH_2, CH_3, 1753 (s) C=O; δ_H (250 MHz; $CDCl_3$; Me_4Si) 2.18 (1 H, br s, OH), 2.43–2.52 (1 H, m $J_{7,7}$ 17.7 Hz, H-7), 2.73 (1 H, dd, $J_{7,7}$ 17.7, $J_{7,8}$ 4.8 Hz, H-7), 4.27–4.31 (1 H, m, $J_{5,1}$ 8.7 Hz, H-5), 4.72 (1 H, d, $J_{8,7}$ 4.8 Hz, H-8), 5.32–5.37 (1 H, m, $J_{1,5}$ 8.7 Hz, H-1), 7.53–7.57 (2 H, m, J_3 8.8 Hz, H-aromatic), 7.74–7.78 (2 H, m, *J* 8.8 Hz, H-aromatic); δ_C (63 MHz; $CDCl_3$; Me_4Si) 44.4 (C-7), 58.7 (C-5), 70.5 (C-8), 91.0 (C-1), 125.2 and 126.4 (C-aromatic quaternary), 129.2 and 132.1 (C-aromatic), 152.8 (C-4), 207.7 (C-6); *m*/*z* (CI) 294.9848 ($C_{12}H_{10}NO_3Br$ M^+ requires 294.9844).

rac-(1*S**,5*S**)-4-Ethyl-2-oxa-3-azabicyclo[3.3.0]octa-3,7-dien-6-one (13)

To a solution of 4-ethyl-8-hydroxy-2-oxa-3-azabicyclo[3.3.0]-oct-3-en-6-one (0.130 g, 0.77 mmol) in dry DCM (3 mL), was added dry pyridine (0.124 mL, 1.5 mmol). This yellow solution was cooled to 0 °C under Ar, prior to the dropwise addition of thionyl chloride (0.06 mL, 0.82 mmol). The reaction mixture was allowed to warm to RT, and stirred for 2 h. Water (5 mL) was added to the reaction mixture which was then extracted with DCM. The organic extracts were combined, dried ($MgSO_4$, brine), concentrated and the residue chromatographed to yield a pale yellow oil (0.084 g, 72%). R_f = 0.38 (7 : 3 diethyl ether–petroleum ether); ν_{max}/cm^{-1} 2975 and 2349 (m) CH_2, CH_3, 1716 (s) C=O, 1699 (w), 1683 (w), 1652 (w), 1335 (w), 1174 (w), 965 (w), 878 (w), 671 (w); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.21 (3 H, t, *J* 7.5 Hz, CH_3 of ethyl), 2.23–2.39 (1 H, m, CH_2 of ethyl), 2.43–2.58 (1 H, m, CH_2 of ethyl), 3.84 (1 H, d, $J_{5,1}$ 7.4 Hz, H-5), 5.69 (1 H, dd, $J_{1,5}$ 7.4, $J_{1,8}$ 2.0 Hz, H-1), 6.26 (1 H, d, $J_{7,8}$ 5.7 Hz, H-7), 7.58 (1 H, dd, $J_{8,7}$ 5.7, $J_{8,1}$ 2.0 Hz, H-8); δ_C (63 MHz; $CDCl_3$; Me_4Si) 10.3 (C-2′), 19.9 (C-1′), 59.6 (C-5), 82.7 and 133.8 (C-7), 156.1 (C-4), 159.3 (C-8), 201.3 (C-6); *m*/*z* (CI) 151.0638 ($C_8H_9NO_2$ M^+ requires 151.0633).

(1*S*,5*S*)-4-(4′-Bromophenyl)-2-oxa-3-azabicyclo[3.3.0]octa-3,7-dien-6-one (11)

Procedure as for 4-ethyl-2-oxa-3-azabicyclo[3.3.0]octa-3,7-dien-6-one using 0.098 g of alcohol to yield a white solid (0.063 g, 68%). Mp 83–86 °C; R_f = 0.38 (6 : 4 diethyl ether–petroleum ether); $[\alpha]_D^{20}$ +201.3 (*c* 0.51, chloroform); ν_{max}/cm^{-1} 2925 (w) CH_2, CH_3, 1721 (s) C=O, 1590 (m) C=N, 1491 (m), 1398 (m), 1388 (m), 1168 (m), 1072 (m), 1009 (m), 895 (m) *p*-substituted benzene, 823 (w), 785 (w); δ_H (250 MHz; $CDCl_3$; Me_4Si) 4.31 (1 H, m, $J_{5,1}$ 7.6 Hz, H-5), 5.90–5.95 (1 H, m, $J_{1,5}$ 7.6 Hz, H-1), 6.32 (1 H, d, $J_{7,8}$ 5.7 Hz, H-7), 7.52–7.58 (2 H, m, *J* 8.8 Hz, H-aromatic), 7.64–7.67 (2 H, m, $J_{8,7}$ 5.7 Hz, H-8), 7.78–7.83 (2 H, m, *J* 8.8 Hz, H-aromatic); δ_C (63 MHz; $CDCl_3$; Me_4Si) 57.7 (C-5), 85.2 (C-1), 125.4 and 127.2 (C-aromatic quaternary), 129.6 and 132.3 (C-aromatic), 134.8 (C-7), 152.5 (C-4),

158.7 (C-8), 200.8 (C-6); *m/z* (CI) 277.9819 ($C_{12}H_8NO_2Br$ M^+ requires 277.9817).

rac-(1*S**,2*S**,6*R**,8*R**)-5-(Tetrahydropyran-2′-yloxymethyl)-9-ethyl-3,11-dioxa-4,10-diazatricyclo[6.3.0^{1,8}.0^{2,6}]undeca-4,9-dien-7-one (14)

To a solution of *rac*-4-ethyl-2-oxa-3-azabicyclo[3.3.0]octa-3,7-dien-6-one (**13**) (0.08 g, 0.53 mmol) in dry benzene (1.5 mL) were added the THP protected 2-nitroethanol (0.23 g, 1.31 mmol) and dry triethylamine (0.041 mL, 0.29 mmol). A solution of phenyl isocyanate (0.40 mL, 0.29 mmol) in dry benzene (2.5 mL) was added to this pale yellow solution over 4 h *via* a motorised syringe pump. The reaction mixture was stirred under N_2 for 72 h and quenched with water (4 mL). This mixture was filtered through Celite then filter paper before extracting with benzene. The organic extracts were combined, dried (brine, $MgSO_4$), concentrated and the residue chromatographed to yield a pale yellow oil (0.08 g, 50%). $R_f = 0.21$ (4 : 5 diethyl ether–petroleum ether); ν_{max}/cm^{-1} 2942 (s) $-CH_2$, $-CH_3$, 1753 (s) –C=O, 1596 (w) C=N, 1547 (w), 1500 (w), 1443 (m), 1262 (m), 1202 (m), 1123 (s), 1077 (m) C–O–C, 1036 (s), 968 (w), 885 (s); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.22 (3 H, t, *J* 7.4 Hz, Me of ethyl), 1.43–1.83 (6 H, m, CH_2 of THP), 2.28–2.42 (1 H, m, CH_2 of ethyl), 2.45–2.64 (1 H, m, CH_2 of ethyl), 3.44–3.78 (1 H, m, H-3′ of THP), 3.83–3.94 (1 H, CH_2O of THP), 3.96 (1 H, app. d, $J_{8,1/6,2}$ 7.5 Hz, H-6/8), 4.02 (1 H, m, H-6/8), 4.21–4.59 (2 H, m, CH_2-O-THP), 4.65–4.74 (1 H, m, H-2′ of THP), 5.40 (2 H, app. t, H-1 and H-2); δ_C (63 MHz; $CDCl_3$; Me_4Si) 10.4 (ethyl CH_3), 19.1 (CH_2 of THP), 19.6 (ethyl CH_2), 25.2, 30.2 and 30.2 (C-6′/3′/4′ of THP), 59.5 and 60.2 (C-6 and C-8), 61.0 and 62.5 (*C*H_2-O-THP and C-3′ of THP), 87.6 and 87.7 (C-2′ of THP), 88.6 (C-1), 98.4 (C-2), 152.7 and 152.4 (C-5), 155.0 and 155.1 (C-8), 203.4 and 203.6 (C-7); *m/z* (CI) 308.1377 ($C_{15}H_{20}N_2O_5$ M^+ requires 308.1372).

rac-(1*S**,2*S**,6*R**,8*R**)-5-(*p*-Bromophenyl)-9-ethyl-3,11-dioxa-4,10-diazatricyclo[6.3.0^{1,8}.0^{2,6}]undeca-4,9-dien-7-one (12)

To a solution of *rac*-4-(4′-bromophenyl)-2-oxa-3-azabicyclo-[3.3.0]octa-3,7-dien-6-one (**11**) (0.065 g, 0.23 mmol) in dry benzene (1 mL) were added the nitropropane (0.052 mL, 0.58 mmol) and dry triethylamine (0.016 mL, 0.11 mmol). A solution of phenyl isocyanate (0.16 mL, 0.99 mmol) in dry benzene (2 mL) was added to this pale yellow solution over 3 h *via* a motorised syringe pump. The reaction mixture was stirred under N_2 for 45 h and quenched with water (4 mL). This mixture was filtered through Celite then filter paper before extracting with benzene. The organic extracts were combined, dried, concentrated and the residue chromatographed to yield a colourless crystalline solid (0.029 g, 44%). Mp 157–159 °C. $R_f = 0.22$ (3 : 7 diethyl ether–petroleum ether); ν_{max}/cm^{-1} 2940 (s) $-CH_2$, $-CH_3$, 1751 (s) –C=O, 896 (s) *p*-substituted benzene; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.22 (3 H, t, *J* 7.4 Hz, Me of ethyl), 2.34–2.45 (1 H, m, CH_2 of ethyl), 2.51–2.61 (1 H, m, CH_2 of ethyl), 4.04 (1 H, d, $J_{8,1}$ 9.6 Hz, H-8), 4.46 (1 H, d, $J_{6,2}$ 9.6 Hz, H-6), 5.47 (1 H, d, $J_{1,8}$ 9.6 Hz, H-1), 5.59 (1 H, d, $J_{2,6}$ 9.6 Hz, H-2), 7.57 (2 H, m, *J* 8.9 Hz, H-3′ aromatic), 7.71 (2 H, m, *J* 8.9 Hz, H-2′ aromatic); δ_C (63 MHz; $CDCl_3$; Me_4Si) 10.4 (ethyl CH_3), 19.7 (ethyl CH_2), 60.0 (C-6), 62.5 (C-8), 87.0 (C-1), 90.0 (C-2), 125.4 and 126.0 (C-1′ and C-4′ aromatic), 129.3 and 132.0 (C-2′ and C-3′ aromatic), 152.0 (C-5), 155.4 (C-9), 203.4 and 203.6 (C-7); *m/z* (CI) 349.0186 ($C_{14}H_{13}N_2O_3Br$ M^+ requires 349.0188).

Acknowledgements

S. K. B. thanks Novartis Ltd. for financial support, and we thank the EPSRC and the University of Reading for funds for the Image Plate System.

References

1 A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410; K. Bougrin, M. Lamiri and M. Soufiaoui, *Tetrahedron Lett.*, 1998, **39**, 4455; W. J. Haap, D. Kaiser, T. B. Walk and G. Jung, *Tetrahedron*, 1998, **54**, 3705; S. Moutel and M. Shipman, *Synlett*, 1998, 1333.
2 H.-J. Gi, Y. Xiang, R. F. Schinazi and K. Zhao, *J. Org. Chem.*, 1997, **62**, 88.
3 C. Schaller, R. Demange, S. Picasso and P. Vogel, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 277.
4 G. Piancatelli, M. D'Auria and F. D'Onofrio, *Synthesis*, 1994, 867.
5 D. R. Deardorff, C. Q. Windham and C. L. Craig, *Org. Synth.*, 1995, **73**, 25.
6 L. A. Paquette and T. M. Heidelbaugh, *Org. Synth.*, 1995, **73**, 44.
7 T. Hoshion and M. Mukaiyama, *J. Am. Chem. Soc.*, 1960, **82**, 5339.
8 S. Cicchi, M. Corsi and A. Goti, *J. Org. Chem.*, 1999, **64**, 7243.
9 W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2.
10 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
11 W. Kabsch, *J. Appl. Crystallogr.*, 1988, **21**, 916.
12 SHELX86, G. M. Sheldrick, *Acta Crystallogr.*, *Sect. A*, *Fundam. Crystallogr.*, 1990, **46**, 467.
13 N. Walker and D. Stuart, *Acta Crystallogr.*, *Sect. A*, *Fundam. Crystallogr.*, 1983, **39**, 158.
14 SHELXL, G. M. Sheldrick, 1993, programme for crystal refinement, University of Göttingen.