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Asymmetric synthesis of spiro 2-pyrrolidin-5-ones, 2-piperidin-6-ones and 1-isoindolin-3-ones. Part 2: *N*-Acyliminium ion cyclisations with an internal alkene nucleophile

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Abstract—Chiral non-racemic bicyclic and tricyclic oxylactams obtained in two steps from *N*-(2-hydroxy-1(*R*)-phenylethyl)-succinimide and phthalimide are cyclised diastereoselectively in formic acid to give spiro[cyclohexane-1,2′-pyrrolidin]-5-ones and spiro[cyclohexane-1,1′-isoindolin]-3-ones, respectively.
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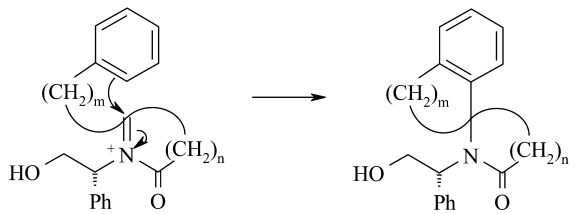
1. Introduction

In the preceding paper,[1] we have shown how Meyers's chiral bicyclic lactam methodology[2] can be used for the diastereoselective cyclisation of *N*-acyliminium ion intermediates **1** to form spiro lactams **2** (Scheme 1). In this paper, we describe similar cyclisations in which the internal nucleophile is an alkene rather than an arene group.



1 **2**

Scheme 1.

Spiro cyclisations of *N*-acyliminium ions with an internal alkene nucleophile were first described by Speckamp and co-workers (Scheme 2).[3] In their spiro lactams **5** the relative stereochemistry of O- and N-substituents *cis*-diequatorial in the cyclohexane ring is a consequence of anti alignment of bonds made and broken in a chair-like transition state **4** in a favoured 6-*endo-exo-trig* cyclisation.[4] The less favoured 5-*exo-exo-trig* process accounts for the formation of 5,5-spiro lactam by-products in some related cases[3] or as the main product in one case.[5] (Note that for spiro cyclisation of an iminium ion the C=N bond must always be *exo*.) There are more recent examples of spiro cyclisations of *N*-acyliminium ions with an internal alkene nucleophile;[6–8] some are based on the use of oxylactams as precursors for the cyclisation step,[9] although there is no control over the configuration at the resulting spiro carbon atom.

2. Results and discussion

Bicyclic oxylactams **9** and **10** were prepared in two steps from the succinimide **6** (Scheme 3). Each of **9** and **10** was obtained as a single diastereoisomer, which is assigned (*S*)-stereochemistry at C-7a from numerous precedents in other work.[2,10] Treatment of **9** with acid under various conditions failed to give spiro lactam products, and this accords with previous failures of attempted 5-*endo-exo-trig* cyclisation via an *N*-acyliminium ion intermediate.[11] However, experiments with **10** were more successful. Treatment of **10** with aluminium trichloride in 1,2-dichloroethane afforded 45% yield of a product oil, which was a ca 3:1 mixture of diastereoisomeric 6,5-spiro lactams **11a** and **b**, containing also a small amount of a 5,5-spiro lactam **12**. The mass spectrum showed the correct molecular ion peaks *m*/*z* 307 and 309, together with other pairs of peaks indicating the presence of one chlorine atom and fragment ions (including loss of 18 and 30 mass units corresponding to H_2O and CH_2O, respectively) which indicate that the oxazolidine ring of **10** has opened to give the $HOCH_2CHPh$ side chain in **11a**,**b**. The ^{13}C NMR spectrum showed resonances for the spiro carbons at δ 65.1 and 64.8 for **11a** and **b** and at δ 77.2 for **12** (cf. ref. 1). The major diastereoisomer is presumably **11a** with (*S*)-configuration at the spiro carbon to accord with our previous results for cyclisation to 6,5-spiro lactams.[1] In

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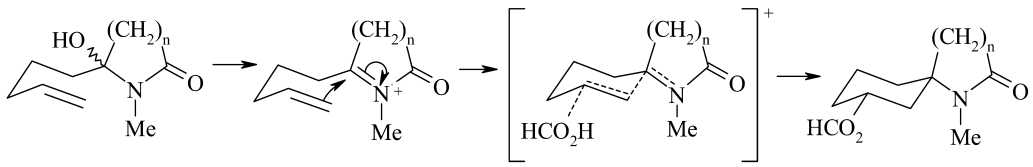
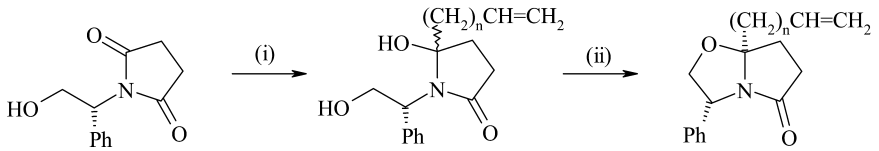


3 **4** **5**

Scheme 2.



6 **7** n = 2, **8** n = 3 **9** n = 2, **10** n = 3

Scheme 3. *Reagents:* (i) $CH_2{=}CH(CH_2)_nMgBr$; (ii) TFA/DCM.

the ^{1}H NMR spectrum the signal assigned to CHCl appeared as a triplet of triplets, J=4.3 and 11.4 Hz; the larger coupling constant is consistent with *trans*-diaxial coupling of CHCl to adjacent ring hydrogens and hence with chlorine being in an equatorial position (cf. ref. 3). Unfortunately, this mixture of **11a**,**b** and **12** was inseparable by chromatography, so we next examined alternative conditions for cyclisation of **10** with a view to obtaining crystalline spiro products.

Treatment of the bicyclic lactam **10** with formic acid at room temperature gave a product mixture which was separated chromatographically into two fractions. The less polar material (7% yield) appeared to be a mixture of diastereoisomeric spiro lactams (^{13}C NMR signals for the spiro carbon at δ 64.8 and 65.4) containing one rather than two formate ester groups. In the mass spectrum a strong fragment ion at m/z 240 corresponds to the loss of CH_2OCHO, suggesting that the formate group is in the side chain. Hence structure **13** is assigned. Although the position of the ring double bond is uncertain, a comparison of ^{13}C chemical shifts for the spiro carbon in **13** with the values for **14a**,**b** suggests that **13** is a cyclohex-3-ene rather than a cyclohex-2-ene. The more polar fraction was the main product (78% yield), which was shown to be a 4:1 mixture of spiro lactams **14a** and **b** (^{13}C NMR spectrum). The mass spectrum showed the correct molecular ion m/z 345, the fragment ion at m/z 286 (loss of CH_2OCHO), and the base peak at m/z 106 (the same as for **11a**,**b**). Also, as for **11a**,**b** the ^{1}H NMR signal for C*H*OCHO (δ 4.9) in the

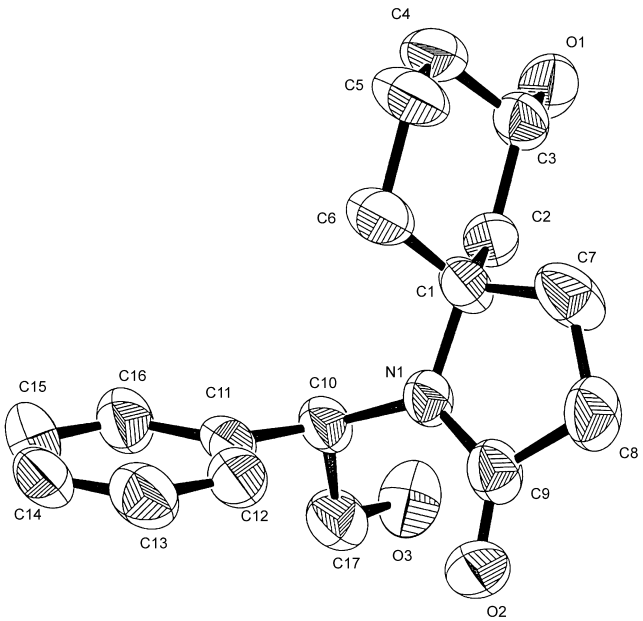
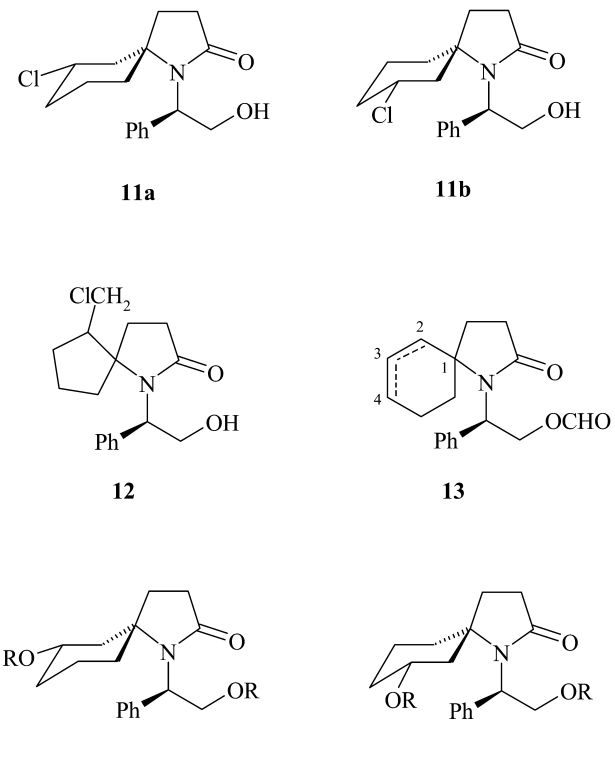


Figure 1. ORTEP drawing of the crystal structure of spiro lactam **15a** with crystallographic numbering scheme (hydrogen atoms omitted).

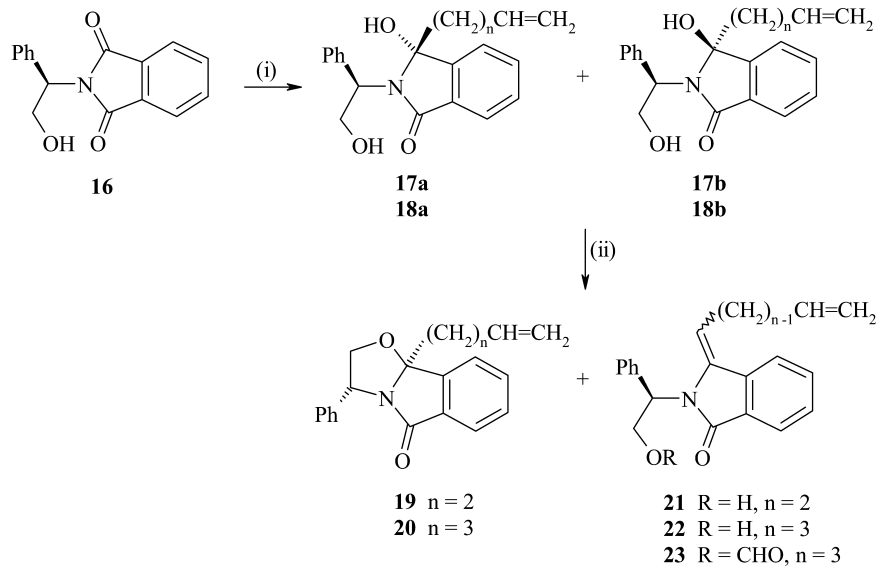


11a **11b**

12 **13**

14a R = CHO
15a R = H

14b R = CHO
15b R = H



Scheme 4. *Reagents:* (i) $CH_2{=}CH(CH_2)_nMgBr$; (ii) TFA/DCM.

cyclohexane ring was a triplet of triplets, J=4.6 and 11.0 Hz, with the larger coupling constant consistent with *trans*-diaxial couplings and hence with the formate group equatorial. Hydrolysis of this mixture of diformates gave the corresponding diols **15a**,**b**, from which the major diastereoisomer was separated by fractional crystallisation. It was shown by X-ray diffraction to have the structure **15a** (Fig. 1) with (*S*)-configuration at the spiro centre. Therefore, the major diformate diastereoisomer is **14a**, and the selectivity of spiro cyclisation from **10** with an alkene nucleophile is the same as that already established for similar cyclisations to 6,5-spiro lactams with an arene nucleophile.[1]

The scope of this approach to spiro lactams was extended to include compounds derived from phthalimide **16**. Addition of ω-alkenyl Grignard reagents to **16** gave, as expected, hydroxy lactams **17** and **18**, in each case as a mixture of diastereoisomers (Scheme 4). These were separable by chromatography, with the major diastereoisomer being the more polar component (eluted second) in each case. The structure **17a** for the major isomer was established by X-ray crystal structure determination (Fig. 2).

Treatment of **17a** with TFA in DCM afforded the tricyclic lactam **19** as the major product (78% yield) as a single diastereoisomer, which has α*R*,9b*S* stereochemistry as in **24**[12] and other related examples.[1] By-products, which were incompletely separated from one another, included probably the enelactam **21**. The same mixture of products was obtained from **17b** with TFA in DCM, consistent with cyclisation via a *N*-acyliminium ion intermediate in which C-3 of **17a**,**b** becomes planar. Consequently, separation of diastereoisomeric hydroxy lactams is unnecessary (where this is possible), and a mixture of **18a** and **b** was treated with TFA in DCM to give the corresponding bicyclic lactam **20** (71% yield), again as a single diastereoisomer, alongside a very small amount of a by-product, probably the enelactam **22** (Scheme 4).

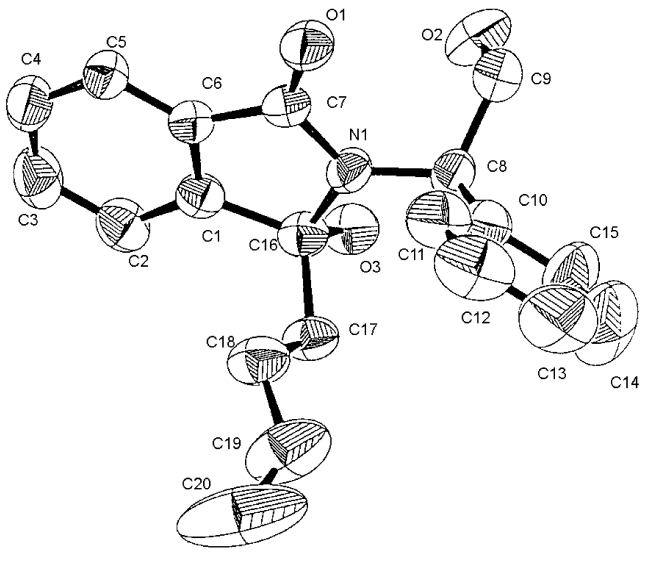
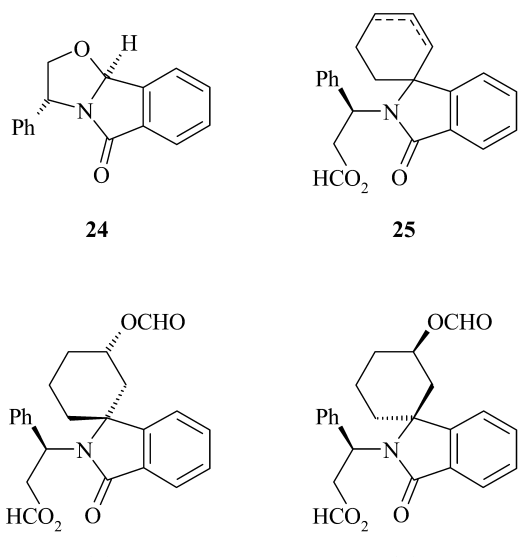


Figure 2. ORTEP drawing of the crystal structure of compound **17a** with crystallographic numbering scheme (hydrogen atoms omitted).



From **19** in formic acid we were unable to obtain a 5,5-spiro lactam, but only very small amounts of unidentified products (cf. **9**). However, from **20** in formic acid we obtained a 4:1 mixture of spiro lactams **26a** and **b** (47% yield), in which **26a** must be the major diastereoisomer. In addition, less polar material eluted in an earlier column fraction was a mixture of at least two by-products, in which the major component was tentatively identified as the enelactam **23** and the minor component as the spirocyclohexene **25** (^{13}C NMR spectra and other evidence).

In conclusion, we have demonstrated several examples of diastereoselective cyclisation of *N*-acyliminium ion intermediates to spirocyclohexane[1,2′]-pyrrolidin-5′-ones and spirocyclohexane[1,1′]isoindolin-3′-ones. The stereochemical preference for formation of the new quaternary carbon centre follows the same pattern as that found for similar *N*-acyliminium ion cyclisations with an internal arene nucleophile.[1] The same approach was not successful for the preparation of corresponding spirocyclopentane derivatives by cyclisations with an internal alkene nucleophile.

3. Experimental

NMR spectra were recorded at 90 MHz for ^{1}H (22.5 MHz for ^{13}C) on JEOL 90Q or at 270 MHz for ^{1}H (67.5 MHz for ^{13}C) on JEOL FX270 spectrometers for solutions in deuteriochloroform (unless otherwise stated) with tetramethylsilane as internal standard. Assignments of ^{13}C NMR signals were assisted by use of DEPT spectra. In ^{13}C NMR spectra lines enclosed in | | are assigned to the minor diastereoisomer of a pair. Mass spectra were obtained by electron impact at 70 eV on a VG Autospec spectrometer; high resolution spectra were obtained in EI mode or in CI mode using ammonia. Chromatographic separations were performed on MN-silica (230–400 mesh). THF and diethyl ether were dried before use. Light petroleum refers to the fraction bp 40–60 °C (unless otherwise stated). DCM refers to dichloromethane.

3.1. Hydroxy lactams 17a,b and 18a,b

3.1.1. (α*R*,3*R*)- and (α*R*,3*S*)-3-(But-3-enyl)-3-hydroxy-2-(2-hydroxy-1-phenylethyl)-2,3-dihydroisoindol-1(1*H*)-ones 17a,b. The Grignard reagent was prepared from magnesium (0.13 g) and 4-bromo-1-butene (0.73 g, 5.4 mmol) in THF (30 mL) and added rapidly to (*R*)-*N*-(2-hydroxy-1-phenylethyl)phthalimide **16**[1] (0.46 g, 1.72 mmol) in THF (20 mL) with stirring at 0 °C. The crude product isolated after aqueous work up was then chromatographed on silica and two products eluted with ethyl acetate/chloroform (1:1 v/v).

(α*R*,3*S*)-*Hydroxy lactam* **17b**: yield 105 mg (19%), viscous oil (HREIMS found M^+ 323.1516. $C_{20}H_{21}NO_3$ requires *M* 323.1521); ^{1}H NMR (270 MHz) δ 1.30 and 1.60 (each 1H, m, H_A and H_B of CH_2 at C-3), 2.07 (2H, m, CH_2), 3.57 (1H, s br, OH), 4.02 (2H, m, C*H*$_2$OH), 4.33 (1H, m, C*H*Ph), 4.67 (1H, s, OH), 4.73 and 4.83 (each 1H, m, H_A and H_B of CH=C*H*$_2$), 5.41 (1H, m, C*H*=CH$_2$) and 7.08–7.72 (9H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 27.6 (CH_2), 35.6 (CH_2), 58.1 (CH), 63.8 (CH_2), 92.7 (C-3), 114.9 (CH_2), 121.6 (CH), 123.5 (CH), 127.6 (CH), 127.9 (2×CH), 128.5 (2×CH), 129.6 (CH), 130.7 (C), 132.7 (CH), 136.7 (C), 138.9 (C), 146.5 (C) and 168.8 (C=O); MS *m*/*z* 324 (MH^+, 2%), 305 (M−H_2O, 4), 292 (M−CH_2OH, 46), 250 (24), 187 (61), 106 (100), 91 (60) and 78 (92).

(α*R*,3*R*)-*Hydroxy lactam* **17a**: yield 420 mg (76%), mp 126–129 °C (from ethyl acetate/hexane) (HREIMS found M^+ 323.1516. $C_{20}H_{21}NO_3$ requires *M* 323.1521); ^{1}H NMR (270 MHz) δ 1.16 (2H, dd, *J*=7.6, 15.7 Hz, CH_2), 1.77–1.88 (1H, m), 2.00–2.19 (1H, m), 3.75–3.84 (1H, m), 4.42 (1H, dd, *J*=1.7, 17.1 Hz), 4.63–4.68 (3H, m), 4.77–4.89 (1H, m), 5.11–5.26 (1H, m), 5.40 (1H, s) and 7.30–7.65 (9H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 28.0 (CH_2), 36.0 (CH_2), 59.0 (CH), 62.9 (CH_2), 92.2 (C-3), 114.9 (CH_2), 122.1 (CH), 123.3 (CH), 128.1 (CH), 128.7 (2×CH), 128.9 (2×CH), 129.8 (C), 131.7 (CH), 132.8 (CH), 136.8 (CH), 138.9 (C), 146.7 (C) and 169.1 (C=O); MS *m*/*z* 324 (MH^+, 2%), 305 (M−H_2O, 2), 292 (M−CH_2OH, 46), 250 (18), 187 (65), 106 (100), 91 (59) and 78 (89).

3.1.2. (α*R*,3*R*)- and (α*R*,3*S*)-3-Hydroxy-2-(2-hydroxy-1-phenylethyl)-3-(pent-4-enyl)-2,3-dihydroisoindol-1(1*H*)-ones 18a,b. The Grignard reagent was prepared from magnesium (165 mg, 6.8 mmol) and 5-bromo-1-pentene (1.02 g, 6.8 mmol) in THF (30 mL). This was added to the phthalimide **21** (454 mg, 1.7 mmol) in THF (20 mL) at 0 °C with stirring. After aqueous work up, the crude product was chromatographed on silica, from which two fractions were eluted with EtOAc/$CHCl_3$ (1:1 v/v).

(α*R*,3*S*)-*Hydroxy lactam* **18b**: 166 mg (29%), mp 90–93 °C (from toluene/light petroleum) (HREIMS found M^+ 337.1667. $C_{21}H_{23}NO_3$ requires *M* 337.1678); ^{1}H NMR (270 MHz) δ 0.68 and 0.95 (each 1H, m, H_A and H_B of CH_2 at C-3), 1.54–2.09 (4H, m, 2×CH_2), 4.09 (1H, m), 4.36 (3H, m), 4.85–5.07 (3H, m), 5.54 (1H, m) and 7.21–7.67 (9H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 22.6 (CH_2), 33.0 (CH_2), 35.8 (CH_2), 57.6 (CH_2), 63.5 (CH_2), 92.9 (C-3), 115.0 (CH_2), 121.5 (CH), 123.4 (CH), 127.5 (CH), 128.0 (2×CH), 128.3 (2×CH), 129.4 (CH), 130.6 (C), 132.5 (CH), 137.7 (CH), 138.7 (C), 146.7 (C) and 168.9 (C=O); MS *m*/*z* 337 (M^+, 1%), 307 (31), 306 (M−CH_2OH, 49), 250 (34), 183 (34), 159 (47), 106 (100) and 77 (30).

(α*R*,3*R*)-*Hydroxy lactam* **18a**: 409 mg (71%), viscous oil (HREIMS found M^+ 337.1667. $C_{21}H_{23}NO_3$ requires *M* 337.1678); ^{1}H NMR (270 MHz) δ 0.41 (2H, quint, *J*=7.0 Hz, CH_2), 1.39–1.47 (1H, m), 1.55–1.66 (1H, m), 1.81–1.94 (1H, m), 3.69 (1H, br d, *J*=10.8 Hz), 4.53–4.70 (5H, m), 5.06–5.21 (1H, m), 5.35 (1H, s) and 7.23–7.55 (9H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 22.8 (CH_2), 33.0 (CH_2), 35.9 (CH_2), 58.9 (CH), 62.9 (CH_2), 92.2 (C), 114.7 (CH_2), 121.8 (CH), 123.2 (CH), 127.9 (CH), 128.3 (2×CH), 128.5 (2×CH), 129.5 (CH), 131.5 (C), 132.5 (CH), 137.9 (CH), 138.9 (C), 146.7 (C) and 168.9 (C=O); MS *m*/*z* 337 (M^+, 1%), 307 (31), 306 (M−CH_2OH, 53), 250 (32), 183 (34), 159 (49), 106 (100), 91 (25) and 77 (32).

3.2. General procedure for bicyclic/tricyclic oxylactams 9, 10, 19 and 20

A two to threefold excess of the Grignard reagent was

freshly prepared from the appropriate ω-alkenyl bromide and magnesium in THF and added rapidly with stirring to the imide **6** or **16** dissolved in THF at 0 °C. This solution was stirred during 1 h and allowed to warm to room temperature before aqueous work up and extraction with ether to give the crude hydroxy lactam. This was redissolved in DCM, cooled in ice, and treated with TFA. After stirring for 1 h at 0 °C, the solution was allowed to warm to room temperature, saturated ammonium chloride solution was added, the organic layer was separated, washed with water, dried ($MgSO_4$), and the solvent evaporated. The crude product was chromatographed on silica using ethyl acetate/chloroform (1:4 v/v) as eluent.

3.2.1. (3*R*,7a*S*)-7a-(But-3-enyl)-3-phenyl-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one 9. From 4-bromo-1-butene (0.93 g, 6.9 mmol) and (*R*)-*N*-(2-hydroxy-1-phenylethyl) succinimide **6** (0.50 g, 2.28 mmol); the hydroxy lactam **7** treated with TFA (2.60 g, 22.8 mmol). Bicyclic oxylactam **9** was obtained (183 mg, 31%) as a viscous oil (HREIMS found M^+ 257.1419. $C_{16}H_{19}NO_2$ requires *M* 257.1416); ^{1}H NMR (270 MHz) δ 1.71–1.95 (2H, m, CH_2), 2.21–2.33 (3H, m), 2.42–2.51 (1H, m), 2.68 (1H, ddd, *J*=17.3, 10.2, 2.7 Hz), 2.93 (1H, dt, *J*=17.3, 9.9 Hz), 4.16 (1H, td, *J*=8.5, 1.1 Hz), 4.73 (1H, t, *J*=8.5 Hz), 5.00–5.10 (2H, m, =CH_2), 5.28 (1H, t, *J*=7.8 Hz), 5.83 (1H, ddt, *J*=17.0, 10.2, 6.6 Hz, =CH) and 7.31–7.45 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 28.3 (CH_2), 30.8 (CH_2), 33.1 (CH_2), 35.4 (CH_2), 57.5 (CH), 72.8 (CH_2), 102.3 (C-7a), 115.0 (CH_2), 125.4 (2×CH), 127.4 (CH), 128.6 (2×CH), 137.2 (CH), 140.0 (C) and 179.3 (C=O); MS *m*/*z* 257 (M^+, 4%), 202 ($M-C_4H_7$, 100), 120 (18), 103 (13), 91 (11) and 55 (12).

3.2.2. (3*R*,7a*S*)-7a-(Pent-4-enyl)-3-phenyl-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one 10. From 5-bromo-1-pentene (1.09 g, 7.3 mmol) and (*R*)-*N*-(2-hydroxy-1-phenylethyl)succinimide **6** (0.40 g, 1.8 mmol); the hydroxy lactam **8** treated with TFA (2.08 g, 18.3 mmol). Bicyclic oxylactam **10** was obtained (278 mg, 56%) as a viscous oil (HREIMS found M^+ 271.1575. $C_{17}H_{21}NO_2$ requires *M* 271.1572); ^{1}H NMR (270 MHz) δ 1.41–1.75 (4H, m, 2×CH_2), 1.90–2.07 (2H, m, CH_2), 2.17 (1H, dt, *J*=13.5, 10.2 Hz), 2.36 (1H, ddd, *J*=13.2, 9.9, 2.6 Hz), 2.59 (1H, ddd, *J*=17.2, 10.2, 2.6 Hz), 2.83 (1H, dt, *J*=17.2, 10.2 Hz), 4.08 (1H, dd, *J*=8.6, 7.3 Hz), 4.62 (1H, t, *J*=8.6 Hz), 4.90–4.99 (2H, m, CH=CH_2), 5.18 (1H, t, *J*=7.6 Hz), 5.71 (1H, ddt, *J*=17.2, 13.2, 6.6 Hz, C*H*=CH_2) and 7.21–7.38 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 23.6 (CH_2), 31.3 (CH_2), 33.6 (CH_2), 33.8 (CH_2), 36.0 (CH_2), 57.8 (CH), 73.1 (CH_2), 102.9 (C-7a), 115.4 (CH_2), 115.4 (CH), 125.8 (2×CH), 127.7 (CH), 129.0 (2×CH), 138.2 (CH), 140.4 (C) and 179.6 (C=O); MS *m*/*z* 271 (M^+, 2%), 102 ($M-C_5H_9$, 100), 120 (14) and 55 (10).

3.2.3. (3*R*,9b*S*)-9b-(But-3-enyl)-3-phenyl-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-5-one 19. TFA (195 mg, 1.7 mmol) was added to hydroxy lactam **17a** (275 mg, 0.85 mmol) in DCM (25 mL) at 0 °C. After the usual work up and chromatography, as above, tricyclic lactam **19** was obtained (200 mg, 74%) as a viscous oil (HREIMS found M^+ 305.1419. $C_{20}H_{19}NO_2$ requires *M* 305.1416); ^{1}H NMR (270 MHz) δ 1.61–1.74 (1H, m), 1.99–2.24 (3H, m), 4.42 (1H, dd, *J*=8.7, 6.8 Hz), 4.78–4.88 (3H, m), 5.33 (1H, dd, *J*=7.7, 7.3 Hz), 5.54–5.69 (1H, m)7.28–7.42 (5H, m, aryl H) and 7.52–7.67 (3H, m, aryl H) and 7.81–7.85 (1H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 28.4 (CH_2), 33.4 (CH_2), 58.2 (CH), 75.7 (CH_2), 101.6 (C-9b), 114.9 (CH_2), 122.3 (CH), 124.5 (CH), 125.6 (2×CH), 127.5 (CH), 128.7 (2×CH), 130.3 (CH), 132.3 (C), 133.3 (CH), 136.8 (CH), 140.1 (C), 145.4 (C) and 174.6 (C=O); MS *m*/*z* 305 (M^+, 8%), 250 ($M-C_4H_7$, 100), 232 (31), 214 (26), 130 (11), 103 (22) and 49 (13). The same product **19** with identical spectra was obtained in similar yield starting from hydroxy lactam **17a** or from a mixture of **17a** and **b**. A later fraction from the column afforded an impure sample of the isomeric enelactam **21** (16 mg).

3.2.4. (3*R*,9b*S*)-9b-(Pent-4-enyl)-3-phenyl-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-5-one 20. The mixture of hydroxy lactams **18a**,**b** (523 mg, 1.55 mmol) in DCM (30 mL) was treated with TFA (265 mg, 2.33 mmol) at 0 °C. After aqueous work up and chromatography, as above, tricyclic lactam **20** was obtained (350 mg, 71%) as a viscous oil (HREIMS found M^+ 319.1578. $C_{21}H_{21}NO_2$ requires *M* 319.1572); ^{1}H NMR (270 MHz) δ 0.92–1.08 (1H, m), 1.21–1.42 (1H, m),1.86–2.15 (4H, m, 2×CH_2), 4.41 (1H, dd, *J*=8.7, 6.7 Hz), 4.79 (1H, t, *J*=8.5 Hz), 4.83–4.91 (2H, m, CH=CH_2), 5.59 (1H, ddt, *J*=17.7, 9.6, 6.7 Hz, C*H*=CH_2), 7.25–7.39 (5H, m, aryl H), 7.50–7.57 (2H, m, aryl H), 7.59–7.66 (1H, m, aryl H) and 7.80–7.84 (1H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 23.3 (CH_2), 33.2 (CH_2), 33.5 (CH_2), 58.2 (CH), 75.6 (CH_2), 101.8 (C-9b), 115.1 (CH_2), 122.3 (CH), 124.4 (CH), 125.6 (2×CH), 127.4 (CH), 128.6 (2×CH), 130.2 (CH), 132.2 (C), 133.2 (CH), 137.7 (CH), 140.1 (C), 145.6 (C), and 174.6 (C=O); MS *m*/*z* 319 (M^+, 5%), 250 ($M-C_5H_9$, 100), 232 (22), 130 (12), 103 (23) and 77 (12). A later fraction from the column afforded an impure sample of the isomeric enelactam **22** (7 mg); ^{13}C NMR (67.5 MHz) δ 27.2 (CH_2), 34.3 (CH_2), 61.6 (CH), 64.7 (CH_2), 115.2 (CH), 116.5 (CH_2), 123.9 (CH), 124.3 (CH), 127.4 (2×CH), 128.3 (CH), 129.1 (CH), 129.4 (2×CH), 130.7 (C), 132.9 (CH), 137.6 (CH), 138.4 (C) and 168.8 (C=O); MS *m*/*z* 319 (M^+, 22%), 288 (11), 278 (30), 246 (8), 200 (10), 158 (100), 103 (14), 91 (23) and 77 (10).

3.3. Spiro lactams 11a,b, 14a,b, 15a,b and 26a,b. General procedure for cyclisation in formic acid

The hydroxy lactam in freshly distilled formic acid was allowed to stand at room temperature or heated under reflux until reaction was complete (tlc). The solvent was evaporated in vacuo and the residue redissolved in chloroform, which was washed with aqueous sodium bicarbonate solution, then with water, dried ($MgSO_4$), and evaporated to dryness. The crude product was chromatographed on silica with ethyl acetate/chloroform (1:4 v/v) as eluent.

3.3.1. (α*R*,3*S*,spiro*S*)- and (α*R*,3*R*,spiro*R*)-3-Hydroxy-1′-(2-hydroxy-1-phenylethyl) spiro[cyclohexane-1,2′-pyrrolidin]-5′-ones 15a,b and diformates 14a,b; (α*R*, spiro*S*)- and (α*R*,spiro*R*)-1′-(2-formyloxy-1-phenylethyl)spiro[cyclohex-3-ene-1,2′-pyrrolidin]-5′-ones 13. From bicyclic lactam **10** (223 mg, 0.82 mmol) in formic acid (10 mL) 10 h at room temperature. First material eluted

from the column was a mixture of spirocyclohexene diastereoisomers **13** (17 mg, 7%) as a viscous oil (HREIMS found M^+ 299.1527. $C_{18}H_{21}NO_3$ requires *M* 299.1521); ^{1}H NMR (270 MHz) δ 1.24–2.62 (10H, m), 4.33–4.43 (3H, m), 5.65 (2H, m), 7.23–7.48 (5H, m, aryl H), 8.01 (1H, s, CHO) and |8.09 (1H, s, CHO)|; ^{13}C NMR (67.5 MHz) δ 23.1 (CH_2), |23.2 (CH_2)|, 29.6 (CH_2), |29.7 (CH_2)|, 29.8 (CH_2), |30.1 (CH_2)|, |31.2 (CH_2)|, 32.8 (CH_2), 32.9 (CH_2), |33.0 (CH_2)|, |56.6 (CH)|, 60.5 (CH), |64.0 (CH_2)|, |64.8 (spiro C)|, 65.0 (CH_2), 65.4 (spiro C), 124.5 (CH), 124.6 (CH), 126.6 (CH), 126.7 (CH), 127.2 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.6 (CH), 128.8 (CH), |138.5 (C)|, 138.9 (C), |160.9 (CHO)|, 163.0 (CHO), |176.7 (lactam C=O)| and 177.7 (lactam C=O); MS *m/z* 299 (M^+, 36%), 253 ($M-HCO_2H$, 10), 245 (64), 240 ($M-CH_2OCHO$, 47), 200 (60), 186 (30), 148 (25), 121 (58), 106 (74), 98 (100), 91 (73) and 77 (60). Later column fractions afforded a mixture of spiro lactams **14a**,**b** (220 mg, 78%, 4:1 ratio) as a viscous oil (HREIMS found M^+ 345.1579. $C_{19}H_{23}NO_5$ requires *M* 345.1576); ^{1}H NMR (270 MHz) δ 1.22–2.19 (10H, m), 2.35–2.60 (2H, m), 4.44 (1H, dd, *J*=9.3, 6.0 Hz), 4.71 (1H, dd, *J*=11.0, 5.8 Hz), 4.92 (1H, tt, *J*=11.0, 4.6 Hz), 5.18 (1H, apparent td, *J*=9.7, 2.8 Hz), 7.28–7.37 (3H, m, aryl H), 7.48 (2H, d *J*=7.7 Hz, aryl H), |7.90 (s, CHO|, 8.03 and 8.07 (each 1H, s, CHO); ^{13}C NMR (67.5 MHz) δ 19.9 (CH_2), |20.5 (CH_2)|, 30.3 (CH_2), |30.5 (CH_2)|, 31.1 (CH_2), |32.9 (CH_2)|, 36.5 (CH_2), 39.5 (CH_2), |42.9 (CH_2)|, |56.7 (CH)|, 56.8 (CH), 64.1 (CH_2), |64.2 (CH_2)|, 65.9 (spiro C), |70.1 (CH)|, 70.7 (CH), 128.3 (2×CH), 128.5 (CH), 129.2 (2×CH), |129.3 (CH)|, |138.5 (C)|, 138.7 (C), |160.8 (CHO)|, 160.9 (CHO), 161.3 (CHO), |161.4 (CH)|, |176.0 (lactam C=O)| and 176.1 (lactam C=O); MS *m/z* 345 (M^+, 7%), 300 (48), 299 ($M-HCO_2H$, 57), 286 ($M-CH_2OCHO$, 73), 198 (28), 152 (40), 121 (62), 106 (100), 103 (51), 91 (47) and 77 (34).

The mixture of diformates **14a**,**b** (178 mg) was added to potassium hydroxide (0.33 g) dissolved in water (3 mL) and ethanol (3 mL) and stirred at room temperature for 8 h. The solution was acidified by addition of dilute hydrochloric acid and extracted several times with chloroform. The combined organic extract was washed, dried ($MgSO_4$), and the solvent evaporated in vacuo. The crude product was a mixture of the spiro lactam diols **15a**,**b** (4:1 ratio from ^{13}C NMR spectrum). The first crop obtained after fractional crystallisation was diol **15a** (85 mg), mp 226–228 °C (from ethanol) (HREIMS found M^+ 289.1672. $C_{17}H_{23}NO_3$ requires *M* 289.1678. Found $M-CH_2O$ 259.1570. $C_{16}H_{21}NO_2$ requires 259.1572); ^{1}H NMR (270 MHz) ($CHCl_3$-*d*/MeOH-d_4) δ 1.06–1.96 (9H, m), 2.10 (1H, ddd, *J*=12.9, 8.9, 4.5 Hz), 2.40–2.60 (2H, m), 3.61–3.71 (1H, m), 3.91–4.00 (1H, m), 4.08 (2H, s, OH, exchanged with MeOH-d_4), 4.34–4.45 (2H, m) and 7.23–7.40 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 19.4 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 33.7 (CH_2), 35.5 (CH_2), 42.0 (CH_2), 59.6 (CH), 63.8 (CH_2), 66.6 (spiro C), 67.2 (CH), 127.0 (2×CH), 127.1 (CH), 128.2 (2×CH), 138.5 (C) and 176.9 (C=O); MS *m/z* 289 (M^+, <1%), 259 ($M-CH_2O$, 75), 258 ($M-CH_2OH$,73), 216 (13), 170 (36), 106 (100) and 91 (32). The sample of diol **15a** submitted to X-ray analysis was further recrystallised from hexane/ethyl acetate. The second crop of crystals (27 mg) from ethanol was relatively enriched in diol **15b**, which showed additional ^{13}C NMR signals δ 20.0 (CH_2), 29.7 (CH_2), 31.7 (CH_2), 45.5 (CH_2), 59.5 (CH), 64.0 (CH_2), 66.6 (CH), 126.9 (CH), 138.3 (C) and 178.0 (C=O).

3.3.2. (α*R*,3*S*,spiro*R*)- and (α*R*,3*R*,spiro*S*)-3-Formyloxy-2′-(2-formyloxy-1-phenylethyl)-2′,3′-dihydrospiro[cyclohexane-1,1′-isoindol]-3′-ones 26a,b. Tricyclic oxylactam **20** (287 mg, 0.90 mmol) was dissolved in formic acid (10 mL) and stirred at room temperature for 32 h. After work up and chromatography, as above, a first fraction was obtained (93 mg, 32%) of viscous oil which was the 3-(pent-4-enylidene)isoindolin-1-one **23** admixed with other component(s) (HREIMS found M^+ 347.1516. $C_{22}H_{21}NO_3$ requires *M* 347.1521); ^{1}H NMR (270 MHz) δ 1.81–2.69 (4H, m, 2×CH_2), 4.77–5.45 (5H, m, 2×C=C*H* and PhC*H*CH_2O), 5.64–5.90 (2H, m, CH=CH_2), 7.28–7.94 (9H, m, aryl H) and 8.03 (1H, s, CHO); ^{13}C NMR (67.5 MHz) δ 26.5 (CH_2), 33.7 (CH_2), 53.5 (CH), 62.5 (CH_2), 113.4 (CH), 115.8 (CH_2), 123.4 (CH), 123.6 (CH), 126.9 (2×CH), 127.9 (CH), 128.7 (CH), 128.8 (2×CH), 132.2 (CH), 137.0 (C), 138.2 (C), 160.6 (CHO) and 167.2 (lactam C=O); MS *m/z* 347 (M^+, 47%), 306 ($M-C_3H_5$, 54), 293 (30), 288 (30), 249 (40), 236 (100), 234 (28),158 (82), 149 (32), 130 (33), 121 (66), 103 (66), 91 (42) and 77 (50). Additional weaker ^{13}C NMR signals attributable to the isomeric spiro enelactam **25**: δ 24.0 (CH_2), 30.6 (CH_2), 32.8 (CH_2), |53.4 (CH)|, 56.4 (CH), |61.7 (CH_2)|, 64.1 (CH_2), 64.7 (C), 122.6 (CH), 123.5 (CH), 125.2 (CH), 127.0 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 128.6 (CH), 129.7 (CH), 131.8 (CH), 133.9 (C), 134.2 (CH), 135.5 (C), 136.5 (C), 137.0 (CH), 138.0 (C), |138.4 (C)|, 150.3 (C), 160.3 (CHO), |160.9 (CHO)|, |168.1 (lactam C=O)| and 168.9 (lactam C=O).

Further elution afforded the spiro lactams **26a**,**b** (165 mg, 47%, 4:1 ratio) as a viscous oil (HREIMS found M^+ 393.1573. $C_{23}H_{23}NO_5$ requires *M* 393.1576); ^{1}H NMR (270 MHz) δ 1.35–2.33 (8H, m), 4.81–4.91 (2H, m), 5.40–5.56 (2H, m), 7.28–8.09 (9H, m, aryl H), 8.02, 8.05 |and 8.09| (each 1H, s, CHO); ^{13}C NMR (67.5 MHz) δ|18.5 (CH_2)|, 19.9 (CH_2)|, 30.2 (CH_2), |32.7 (CH_2)|, 32.8 (CH_2), |38.6 (CH_2)|, 38.7 (CH_2), |55.9 (CH)|, 56.0 (CH), 63.8 (CH_2), |64.0 (CH_2)|, |66.2 (spiro C)|, 67.0 (spiro C), |69.1 (CH)|, 69.2 (CH), 122.9 (CH), 124.1 (CH), 127.5 (CH), 127.6 (2×CH), 127.9 (CH), 128.4 (CH), 128.6 (2×CH), |130.9 (C)|, 131.1 (C), |131.5 (CH)|,131.7 (CH), |137.4 (C)|, 137.6 (C), 149.1 (C), |150.1 (C)|, |160.0 (CHO)|, 160.1 (CHO), 160.8 (CHO), |160.9 (CHO)|, 168.3 (lactam C=O) and |168.6 (lactam C=O)|; MS *m/z* 393 (M^+, 1%), 347 ($M-HCO_2H$, 36), 334 ($M-CH_2OCHO$, 100), 246 (22), 200 (12), 183 (42), 165 (21), 103 (25), 91 (27) and 77 (18).

3.3.3. (α*R*,3*S*,spiro*S*)- and (α*R*,3*R*,spiro*R*)-3-Chloro-1′-(2-hydroxy-1-phenylethyl)spiro [cyclohexane-1,2′-pyrrolidin]-5′-ones 11a,b. Bicyclic oxylactam **10** (0.19 g, 0.70 mmol) in 1,2-dichloroethane (10 mL) was added with stirring to a cold (−5 °C) solution of aluminium trichloride (0.28 g) in 1,2-dichloroethane (10 mL). Cooling and stirring were maintained for 4 h, after which the mixture was poured onto ice, acidified with dilute sulfuric acid, and extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution and with water, dried

($MgSO_4$), and the solvent evaporated in vacuo. The residue was chromatographed on silica, and products eluted with ethyl acetate/chloroform (1:1 v/v). The 6,5-spiro lactam **11a**,**b** was obtained as an oil (97 mg, 45%, ca 3:1 ratio), containing a small amount of the 5,5-spiro lactam **12**; ^{1}H NMR (270 MHz) δ 1.06–2.31 (10H, m), 2.48–2.57 (2H, m), 3.74 (1H, tt, J=11.4, 4.3 Hz, CHCl), 3.92–4.03 (1H, m, PhC*H*), 4.29–4.46 (2H, m, CH_2OH) overlapping 4.54 (1H, br s, OH), and 7.25–7.36 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 26.9 (CH_2), 29.3 (CH_2), |29.4 (CH_2)|, 29.7 (CH_2), 30.2 (CH_2), 31.0 (CH_2), |32.8 (CH_2)|, |33.1 (CH_2)|, 33.7 (CH_2), |57.1 (CHCl)|, 57.3 (CHCl), |60.0 (CH)|, 60.1 (CH), |64.8 (C)|, 65.1 (CH_2), |65.4 (C)|, 65.5 (CH_2), 127.1 (CH), 127.2 (2×CH), |127.3 (CH)|, 128.4 (2×CH), |128.5 (CH)|, |138.7 (C)|, 139.0 (C), 176.6 C=O) and |176.7 (C=O)|; MS m/z 307 (M^+, <1%), 279, 277 (M−CH_2O, 14, 43), 278, 276 (M−CH_2OH, 24, 56), 242 (33), 200 (18), 188 (29), 120 (16), 106 (100) and 91 (29). Additional, weaker ^{13}C NMR signals attributed to **12** δ 32.3, 32.5, 33.0, 35.8, 42.3, 43.2, 47.2, 55.1, 65.3, 77.2 (spiro C), 126.9, 127.4, 138.6 and 171.2 (C=O).

3.4. Crystallographic structure determinations

X-ray analysis of **15a** and **17a** was carried out on a Rigaku AFC6S four-circle diffractometer with graphite-monochromated Mo Kα radiation, λ=0.710.70 at 20 °C. The structures were solved by direct methods using SHELX-76 and refined on F^2 using SHELXL.

3.4.1. Crystal data for 15a.[13] $C_{17}H_{23}NO_3$, M=289.36 The crystal size was 0.50×0.50×0.40 mm; monoclinic, space group $C2$, with unit cell a=16.402(3), b=8.955(7), c=10.899 4(1) Å, β=103.51°, V=1556.7(12) Å^3, Z=4, D_c=1.269 g cm^{-1} 1521 reflections were collected in the range 5<2θ<50°, of which 1465 were independent (R_{int}=0.0170). Full matrix least squares refinement on F^2 with 192 parameters for 1465 reflections with I>2σI gave final values of R_1=0.0349 and wR_2=0.0892.

3.4.2. Crystal data for 17a.[13] $C_{20}H_{21}NO_3$, M=323.38 The crystal size was 0.30×0.10×0.05 mm; orthorhombic, space group $P2_12_12_1$, with unit cell a=25.502(6), b=8.1085(1), c=8.708(2) Å, V=1800.6(6) Å^3, Z=4, D_c=1.193 g cm^{-1} 2769 reflections were collected in the range 5<2θ<55°, of which 2343 were independent (R_{int}=0.0081). Full matrix least squares refinement on F^2 with 220 parameters for 2337 reflections with I>2σI gave final values of R_1=0.0318 and wR_2=0.0820.

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References and notes

1. Bahajaj, A. A.; Moore, M. H.; Vernon, J. M. *Tetrahedron* **2004**, *60*, 1235–1246.
2. (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569, and references therein. (b) Meyers, A. I. In *Stereocontrolled organic synthesis*; Trost, B. M., Ed.; Blackwell Scientific: Oxford, 1994; pp 145–161. (c) Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1–8.
3. (a) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 1515. (b) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 951.
4. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
5. Schoemaker, H. E.; Kruk, C.; Speckamp, W. N. *Tetrahedron Lett.* **1979**, 2437.
6. Inoue, Y.; Tazawa, N.; Watanabe, A.; Aoki, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn* **1992**, *65*, 2866–2868.
7. Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507–3510.
8. Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem. Intl Ed.* **2002**, *41*, 3017–3020.
9. Ito, T.; Yamazaki, N.; Kibayashi, C. *Synlett* **2001**, 1506–1509.
10. (a) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294–2296. (b) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859. (c) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656–1662.
11. Lochead, A. W.; Proctor, G. R.; Caton, M. P. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2477.
12. Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1997**, *38*, 3627–3630.
13. Crystallographic data for compounds **15a** and **17a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 213792 and 213791, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).