Enantiospecific Synthesis of the C-9 to C-18 Fragment of Macbecins I and II

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The synthesis of the C-9 to C-18 fragment of macbecins I and II has been accomplished *via* a novel cyclisation and stereospecific cuprate opening of a chiral epoxide.

Macbecins I (**1**) and II (**2**) are new antibiotics isolated from the fermentation broth of Nocardia sp. (No. C-14919) exhibiting antibacterial, antifungal, antiprotozoal, and antitumour activities.[1,2] Their structure and absolute configuration have been determined by Muroi *et al.*[3] and they have been assigned to the ansamycin group of antibiotics which includes geldanamycin,[4] herbimycin,[5] and ansamitocin.[6] There has been a steadily growing interest in macbecin both clinically[7] and synthetically,[8] although to date no synthesis has been reported. We now report a synthesis of a fragment of macbecins I and II.

Retrosynthetic analysis divided the C-9—C-18 fragment of macbecin into two segments, the epoxide (**3**) and the vinyl iodide (**4**). It was anticipated that formation of the C-15–C-16 bond would be by reaction of the appropriate vinyl cuprate reagent with the chiral epoxide (**3**). The required epoxide was obtained in two steps from (*E*)-crotyl alcohol (**5**). Sharpless epoxidation[9] [(+)-di-isopropyl tartrate, $Ti(OPr^i)_4$, Bu^tOOH, CH_2Cl_2, −20 °C, 24 h] afforded the epoxy alcohol in 40% yield and in 95% enantiomeric excess (e.e.), b.p. (Kugelrohr) 78 °C at 15 mm Hg; $[\alpha]_D^{22}$ −53.1° (*c* 6.0, benzene) lit.[9] $[\alpha]_D^{22}$ −54.5° (*c* 0.24, benzene), which was subsequently protected as the t-butyldimethylsilyl ether in quantitative yield to afford the required epoxide (**3**) (Scheme 1) $[\alpha]_D^{22}$ −23.2° (*c* 0.11, CH_2Cl_2); δ_H (360 MHz; $CDCl_3$) 3.72 (1H, dd, *J* 11.6, 2.5 Hz), 3.59 (1H, dd, *J* 11.6, 2.5 Hz), 2.83 (1H, dq, *J* 5, 2.4 Hz), 2.73 (1H, m), 1.32 (3H, d, *J* 5 Hz), 0.88 (9H, s), 0.06 (3H, s), 0.05 (3H, s); 95% e.e. [determined by 360 MHz ^1H n.m.r. using $Eu(fod)_3$ shift reagent; fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate].

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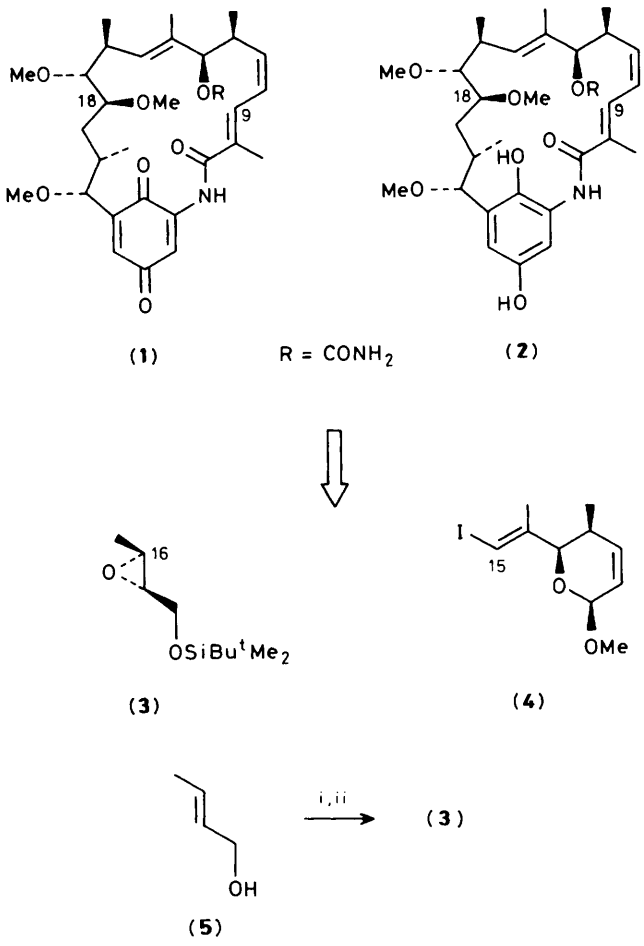

Scheme 1. *Reagents:* i, $Ti(OPr^i)_4$, (+)-di-isopropyl tartrate, Bu^tOOH, CH_2Cl_2, −20 °C, 24 h; ii, Bu^tMe_2SiCl, imidazole.

The synthesis of the C-9—C-15 fragment is shown in Scheme 2;‡ carboalumination[10] of propargyl alcohol [$(C_5H_5)_2ZrCl_2$, Me_3Al, $ClCH_2CH_2Cl$, room temp., 12 h, quench at −30 °C, I_2] gave the expected (*E*)-trisubstituted allylic alcohol in 43% yield. Manganese dioxide oxidation in dichloromethane yielded the extremely unstable and volatile aldehyde (**6**), which was not normally isolated but filtered in dichloromethane through Celite to remove the MnO_2. The solution was dried over freshly activated 4 Å molecular sieves and used directly in the next step. The enantioselective aldol[11] required to yield the appropriate stereochemistry at C-12 and C-13 was conducted between (**6**) and the preformed (*Z*)-9-borabicyclo[3.3.1]nonane (9-BBN) enolate of propanoyl oxazolidinone [(*Z*)-enolate formation: propanoyl oxazolidinone (**7**), 9-BBN·trifluoromethanesulphonyl (·Tf), Pr^i_2NEt, CH_2Cl_2, 0 °C, 1.5 h]. The aldol was conducted with the (*Z*)-enolate and (**6**) in CH_2Cl_2 at −78 °C for 1.5 h followed by the same time at room temperature. The reaction was quenched with NaH_2PO_4 and worked-up with excess of H_2O_2 at 0 °C. This yielded the expected *erythro* isomer (**8**) in 95% e.e. and 58% chemical yield as a white crystalline solid, m.p. 106 °C, $[\alpha]_D^{22}$ + 134° (*c* 1.3, CH_2Cl_2); δ_H (360 MHz; $CDCl_3$) 7.40 (5H, m), 6.43 (1H, s), 5.71 (1H, d, *J* 7.3 Hz), 4.78 (1H, dq, *J* 7.3, 7.0 Hz), 4.52 (1H, s), 4.02 (1H, dq, *J* 6.4, 2.3 Hz), 3.18 (1H, d, *J* 2.8 Hz; removable with D_2O), 1.79 (3H, s), 1.12 (3H, d, *J* 7.0 Hz), 0.85 (3H, d, *J* 6.4 Hz). Protection of the alcohol as its t-butyldimethylsilyl ether gave (**9**) in quantitative yield $[\alpha]_D^{22}$ −10.43° (*c* 0.94, CH_2Cl_2). Removal of the chiral

‡ All isolated compounds described were characterised by 360 MHz n.m.r., i.r., and mass spectrometric data which were in accord with the assigned structures.

Scheme 2. *Reagents:* i, $(C_5H_5)_2ZrCl_2$, Me_3Al, $ClCH_2CH_2Cl$, room temp., 12 h; quench −30 °C, I_2; ii, MnO_2, CH_2Cl_2, room temp., 12 h; iii, (**7**), 9-BBN·Tf, Pr^i_2NEt, CH_2Cl_2, (**6**), −78 °C; iv, Bu^tMe_2Si·Tf, 2,6-lutidine, 0 °C, 2 h; v, $LiBH_4$, THF, room temp., 18 h; vi, $(COCl)_2$, dimethyl sulphoxide, Et_3N, −60 °C, 1.5 h; vii, Bu^tOAc, LDA, THF, −78 °C, 2 h; viii, TFA·H_2O, 9 : 1, CH_2Cl_2, room temp., 96 h; ix, MsCl, Et_3N, CH_2Cl_2 reflux, 12 h; x, DIBAL, toluene, −78 °C, 1 h; xi, Amberlite-H^+, MeOH, room temp., 18 h; xii, (**4**), Bu^tLi (2 equiv.), Et_2O, −80 °C, CuCN (1 equiv.), (**3**) (2 equiv.), Et_2O, −40 °C, 4 h, −20 °C, 24 h.

auxiliary with $LiBH_4$, and Swern oxidation[12] of the resulting alcohol afforded the aldehyde (**10**) $[\alpha]_D^{22}$ + 33.8° (*c* 0.9, CH_2Cl_2), in 71% overall yield.

The aldehyde (**10**) was then treated with lithio-t-butyl acetate [formed from t-butyl acetate, lithium di-isopropylamide (LDA), tetrahydrofuran (THF), −78 °C, 20 min] under argon to yield the aldol product (**11**) in quantitative yield. These epimeric β-hydroxyesters were then treated with a 9 : 1 trifluoroacetic acid (TFA)–water mixture at 25 °C for 96 h to yield the hydroxylactones (**12b**,**a**) in 68% yield in a 5 : 1 axial/equatorial ratio at C-11; δ_H (360 MHz; $CDCl_3$) (equatorial isomer) 6.49 (1H, s), 4.70 (1H, s), 4.32 (1H, ddd, *J* 7.0, 9.5, 4.5 Hz), 2.91 (1H, dd, *J* 18.2, 7.0 Hz), 2.53 (1H, dd, *J* 18.2, 9.5 Hz), 2.40 (1H, m), 1.81 (3H, s), 0.84 (3H, d, *J* 6.8 Hz); (axial isomer) 6.48 (1H, s), 5.23 (1H, s), 4.15 (1H, m), 2.83 (1H, dd, *J* 18.3, 5.2 Hz), 2.60 (1H, dd, *J* 18.3, 2.5 Hz), 2.19 (1H, m), 1.81 (3H, s), 0.80 (3H, d, *J* 6.7 Hz), thus achieving two deprotections and a lactonisation in one step. It had been hoped that elimination would occur under these conditions to yield the α,β-unsaturated lactone. However, further treatment with mesyl chloride (MsCl) and Et_3N in refluxing dichloromethane for 12 h was necessary to achieve this transformation yielding (**13**) in 83% yield, $[\alpha]_D^{25}$ +81.4° (*c* 0.17, CH_2Cl_2). It was noted that the major axial isomer (**12b**) eliminated within minutes while the equatorial isomer (**12a**) required the refluxing conditions, thus confirming our original assignment.

The lactone was then reduced with di-isobutylaluminium hydride (DIBAL) to give one anomer; $[\alpha]_D^{22}$ +279.2° (*c* 0.27, CH_2Cl_2) and the lactol protected as a methyl acetal (Amberlite–H^+, MeOH, room temp., 12 h) to afford (**4**) as a colourless oil in 90% overall yield; $[\alpha]_D^{22}$ +485° (*c* 0.11, CH_2Cl_2), δ_H (360 MHz; $CDCl_3$) 6.28 (1H, s), 5.96 (1H, dd, *J* 9.6, 5.9 Hz), 5.61 (1H, dd, *J* 2.4, 9.6 Hz), 4.82 (1H, d, *J* 2.4 Hz), 4.36 (1H, s), 3.32 (3H, s), 2.15 (1H, m), 1.72 (3H, s), 0.71 (3H, d, *J* 7.1 Hz). This was then converted into the higher order cuprate[13] by treatment with two equivalents of Bu^tLi in diethyl ether at −80 °C under argon for 1.5 h to form the vinyl lithium which was then transferred *via* a cannula into a stirred suspension of CuCN (one equiv.) in diethyl ether at −40 °C and stirred for 1.5 h to form the higher order cuprate $[R_2Cu(CN)Li_2]$. The cuprate was then treated with the epoxide (**3**) (two equiv.) at −40 °C for 4 h then −20 °C for 24 h to yield the C-9—C-18 fragment (**14**) of macbecin in 35% yield§ as a colourless oil; $[\alpha]_D^{22}$ + 23.14° (*c* 0.15, CH_2Cl_2); δ_H (360 MHz; $CDCl_3$) 6.08 (1H, dd, *J* 9.6, 5.9 Hz), 5.70 (1H, dd, *J* 2.4, 9.6 Hz), 5.11 (1H, s), 4.92 (1H, br. s), 4.36 (1H, s), 3.77 (1H, m), 3.70 (1H, m), 3.48 (1H, m), 3.41 (3H, s), 2.27—2.13 (2H, m), 1.72 (3H, s), 1.29 (3H, d, *J* 5.2 Hz), 0.90 (9H, s), 0.83 (3H, d, *J* 7.0 Hz), 0.07 (6H, s).

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§ Based on the vinyl iodide.