Enantioselective Synthesis of the $C_{1,6}$-$C_{21,16}$ Segment of Macbecins I and II

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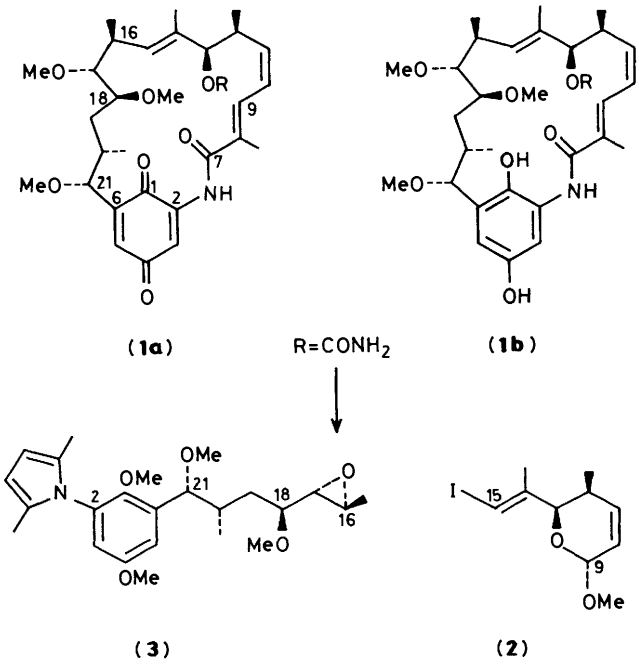
A highly efficient and stereocontrolled enantioselective synthesis of the $C_{1,6}$–$C_{21,16}$ segment of macbecins I and II has been performed in 19 steps and 28.5% overall yield.

Macbecin I (**1a**) and II (**1b**) are new antibiotics isolated[1] from the fermentation broth of Nocardia sp. (No. C-14919) whose structure and absolute configuration were determined by Muroi *et al.* in 1980.[2] These novel compounds were shown to be 2,6-disubstituted benzoquinone and hydroquinone respectively and assigned to the ansamycin group of antibiotics which also includes geldanamycin,[3] herbimycin,[4] and ansamitocin.[5] The antifungal, antibacterial, and antiprotozoal properties of (**1a**) and (**1b**) together with the antitumor activity of macbecin I in



(**1a**) (**1b**) (**3**) (**2**)

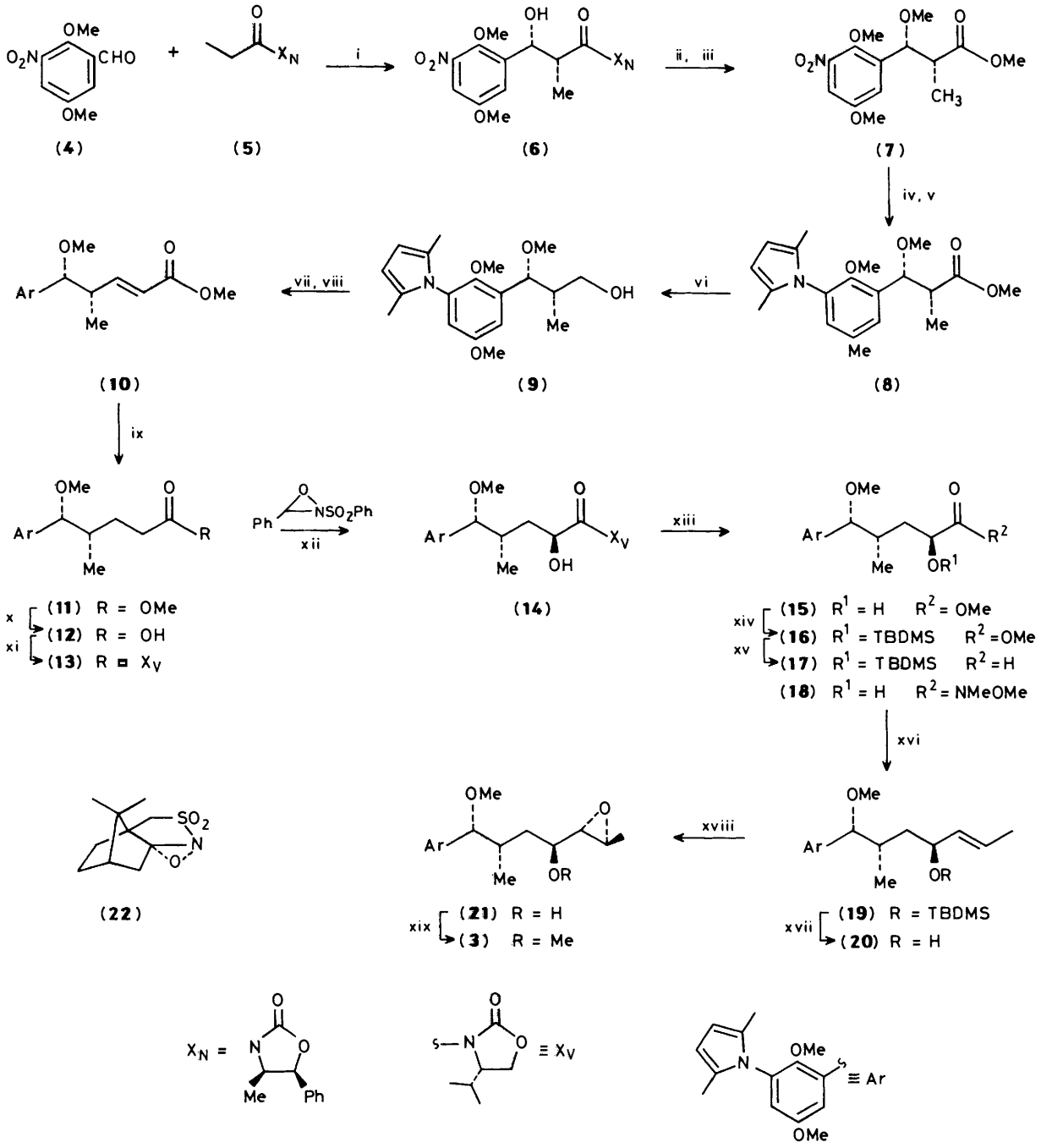
the P388 leukemia test[6] have attracted substantial interest.[7] As a part of our ongoing synthetic studies toward the macbecins we describe here an enantiospecific synthesis of the $C_{1,6}$–$C_{21,16}$ segment. Our retrosynthesis of macbecin involves disconnection between the C_{15}–C_{16} bond to give rise to the vinyl iodide (**2**)[8] and the epoxide (**3**).

It was apparent that the required absolute stereochemistry at C_{20} and C_{21} in (**3**) could be achieved by an enantioselective aldol condensation[9] and the C_{16}–C_{17} epoxy unit by Sharpless epoxidation.[10] The remaining stereocentre at C_{18} was considered to be accessible *via* the recently developed asymmetric hydroxylations of enolates.[11]

Preparation of 2,5-dimethoxy-3-nitrobenzaldehyde (**4**) was achieved from *p*-methoxyphenol by a Reimer-Teimann reaction followed by nitration and methylation.[12] Reaction of (**4**) with the (*Z*)-boron enolate of (**5**) (generated with Et_2BOTf and Et_3N) according to the methodology of Evans *et al.*[13] gave the required *erythro* alcohol (**6**), m.p. 201—203 °C, in 88% isolated yield.[14] The chiral auxiliary was then removed under the usual conditions (NaOMe, MeOH–CH_2Cl_2) and the β-hydroxy group methylated with NaH–Me_2SO_4 to give the ester (**7**) in 88% overall yield.

To avoid possible future complications, the nitro group was converted into the 2,3-dimethylpyrrole[15] by successive catalytic hydrogenation and condensation with acetonylacetone (90.6% for two steps). The protected compound (**8**) could now be quantitatively reduced to the alcohol (**9**) using $LiAlH_4$. Swern oxidation [$(COCl)_2$, DMSO, Et_3N, −60 °C] of (**9**) gave less than 2% of the required aldehyde with no recovery of the starting alcohol, probably owing to reaction of the pyrrole moiety with the activated DMSO. Fortunately the aldehyde could be isolated in 89% yield when a solution of the alcohol in DMSO–Et_3N–THF was treated at 25 °C with solid Py·SO_3 complex (3 equiv.) for 40 min. Homologation was achieved by Wittig reaction of the above aldehyde with $Ph_3P{=}CHCO_2Me$ in refluxing CH_2Cl_2. Thus, the α,β-unsaturated ester (**10**) was obtained in excellent yield and with more than 98% *E*-selectivity. Reduction of the double bond using 10% Pd–C in ethanol cleanly afforded the ester (**11**), the basic material for introduction of the hydroxy group at C-18.

Although oxidation of the lithium enolate (LDA, −78 °C, THF, 30 min) of (**11**) with the chiral camphor oxaziridine (**22**) (THF, −78 °C, 50 min) gave a 64% isolated yield of hydroxylated compounds, the diastereoisomeric ratio was only 78:22 in favour of the required hydroxy ester (**15**).[11g] The use of dimethylethyleneurea (DMEU; 5.5 equiv.) for generation of the *Z*-lithium enolate of (**11**) (LDA, DMEU, THF, −78 °C) decreased the overall yield (41%) and also the diastereoisomeric ratio to 58:42. Amongst other possibilities for executing the same transformation, the hydroxylation of acyl oxazolidinones[11d] was chosen in view of its high degree of enantioselection. Thus, the ester (**11**) was quantitatively hydrolysed to



Reagents: i, (**5**) (1.0 equiv.), Et_2BOTf (1.1 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, −2 °C, 1 h; RCHO (1.0 equiv.), 0.5 h at −78 °C and 1 h at 0 °C, 88%; ii, NaOMe (1.2 equiv.), MeOH–CH_2Cl_2, −17 °C, 15 min, 97%; iii, NaH, (1.1 equiv.), Me_2SO_4 (2 equiv.), THF–DMF (3:1), −5 °C, 16 h, 90%; iv, H_2, 10% Pd–C, EtOH, 1 atm, 2.5 h, 100%; v, acetonylacetone (3 equiv.), isobutyric acid (catalyst), refluxing toluene, Dean-Stark trap, 65 h, 91%; vi, $LiAlH_4$ (1 mol equiv.), THF, −5 °C, 3 h, 100%; vii, SO_3·Py (3 equiv.), Et_3N (7 equiv.), DMSO–THF (6.5:1), 25 °C, 45 min, 89%; viii, $Ph_3P{=}CHCO_2Me$ (2 equiv.), CH_2Cl_2, 40 °C, 24 h, 99.5%; ix, H_2, 10% Pd–C, EtOH, 1 atm, 40 min, 99%; x, LiOH (5 equiv.), MeOH–H_2O–THF (3:1:1), 25 °C, 18 h, 100%; xi, pivaloyl chloride (1.01 equiv.), Et_3N (1.01 equiv.), toluene, 20 min at −10 °C and 40 min at 0 °C; Xv–Li (2.3 equiv.), THF, −78 °C, 1 h, 89%; xii, $NaN(SiMe_3)_2$ (1.3 equiv.), THF, −78 °C, 25 min; 2-phenylsulphonyl-3-phenyloxaziridine (1.8 equiv.), −78 °C, 20 min; AcOH (10 equiv.), −78 °C to 25 °C, 82.5%; xiii, MeOMgCl (2.2 equiv.), CH_2Cl_2–MeOH (3.5:1), −10 °C, 1 h, 86%; xiv, TBDMS–OTF (1.5 equiv.), 2,6-lutidine (2.5 equiv.), CH_2Cl_2, 0 °C, 1 h, 97.0%; xv, DIBAL-H (1.6 equiv.), toluene, −80 °C, 2 h, methanol quenching (20 equiv.) at −80 °C; xvi, $CrCl_2$ (8 equiv.), CH_3CHI_2 (2 equiv.), THF, 25 °C, 2.5 h, 91% from (**16**); xvii, Bu_4NF (2 equiv.), THF, 25 °C, 16 h, 96%; xviii, (+)-DIPT [(1.2 equiv.), $Ti(OiPr)_4$ (1.0 equiv.)], TBHP (2.0 equiv.), CH_2Cl_2, −20 °C, 22 h, 99%; xix, NaH (1.3 equiv.), MeI (5 equiv.), THF −15 to 0 °C, 2 h, 87% from (**20**)

the acid (**12**) and this was coupled with the lithium salt (BuLi, THF, −78 °C) of the oxazolidinone (Xv–H) either by activating the acid with carbonyldi-imidazole, di-2-pyridyl disulphide or with pivaloyl chloride to give (**13**) in 50, 75, and 89% yield, respectively. Treatment of the sodium enolate of (**13**) with 3-phenyl-2-phenylsulphonyloxaziridine afforded the required hydroxy compound (**14**) in 82.5% isolated yield, m.p. 131.5—132 °C, after flash chromatography. Removal of the chiral

auxiliary from (**14**) required some investigation. The use of NaOMe in MeOH–CH_2Cl_2 at −50 °C gave substantial amounts of a product arising from acyl transfer rearrangement and transamidation[16] using Me_3Al–MeNHOMe afforded the amide (**18**) in only 40% yield. Successful removal of the chiral auxiliary was achieved, however, by reaction with MeOMgCl in MeOH–CH_2Cl_2 which gave (**15**) in 82—86% yield; *ca.* 15% of the acyl transfer rearrangement product was also observed.[11d] After protection of the hydroxyl group of (**15**) as the TBDMS derivative, the ester (**16**) was cleanly reduced to the aldehyde (**17**) (DIBAL, −80 °C) which was used in the next step without further purification. The required olefin (**19**) was prepared in 91% yield from (**16**) and with more than 99% *E*-selectivity by reaction of (**17**) with $CrCl_2$–CH_3CHI_2.[17]. Under these extremely mild conditions no epimerisation of the aldehyde was observed and we believe that this method offers one of the best alternatives to the Schlosser modification[18] of the Wittig reaction for preparing *E*-olefins. Deprotection of the hydroxy group under standard conditions followed by Sharpless epoxidation using (+)-DIPT gave the epoxide (**21**) and the corresponding epoxy isomer in a ratio of 95:5 and in 96% overall yield. Methylation of this mixture followed by flash chromatography gave the pure epoxide (**3**) in 88% yield as a colourless viscous oil; $[\alpha]^{23}$ +48.2° (*c* 0.56 in CH_2Cl_2); δ_H(360 MHz, $CDCl_3$) 6.94 (1 H, d, *J* 3.1 Hz, 5-H), 6.63 (1 H, d, *J* 3.1 Hz, 3-H), 5.90 (2 H, s, ArH), 4.39 (1 H, d, *J* 5.9 Hz, 21-H), 3.79 (3 H, s, 4-OMe), 3.34 (3 H, s, 18-OMe), 3.26 (3 H, s, 21-OMe), 3.16 (3 H, s, 1-OMe), 3.06 (2 H, ddd, *J* 9.9, *J′* 5.8, *J″* 3.1 Hz, 18-H), 2.97 (1 H, dq, *J* 5.2, *J′* 2.1 Hz, 16-H), 2.51 (1 H, dd, *J* 5.8, *J′* 2.1 Hz, 17-H), 2.07 (3 H, s, Ar-Me), 2.02 (3 H, s, Ar-Me), 2.10—1.98 (1 H, m, 20-H), 1.56 (1 H, ddd, *J* 14.0, *J′* 9.9, *J″* 4.2 Hz, 19 H) 1.43 (1 H, ddd, *J* 14.0, *J′* 9.9, *J″* 3.1 Hz, 19-H), 1.30 (3 H, d, *J* 5.2 Hz, 16-Me), and 0.93 (3 H, d, *J* 6.7 Hz, 20-Me). The epoxide (**3**) has the correct absolute stereochemistry at all of its asymmetric centres.

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