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trans couplings, rather than as the observed broadened singlet. This requirement, which implies cis couplings, could be met by either 16 or the more highly strained isomer 18. Subsequent transformations, now described, eliminate the latter.

Ketopyranoses such as 16 can be conveniently degraded by Baeyer-Villiger oxidation using *m*-CPBA,²³ oxygen being inserted chemoselectively into the electron rich

C4-C5 bond. Sodium chromate²⁴ achieved a similar result with accompanying allylic oxidation to give the α -enone 17. Upon methanolysis the acylal function was cleaved leading to lactone 4 whose ¹H NMR data were identical to those described by Ruveda^{10b} for the racemic modification.

Use of the above strategy for various synthetic targets is underway and will be described in due course.

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Asymmetric Synthesis of Macbecin I

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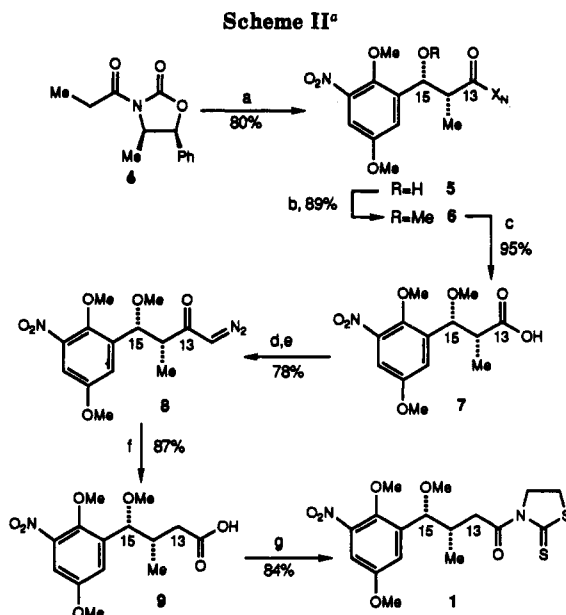
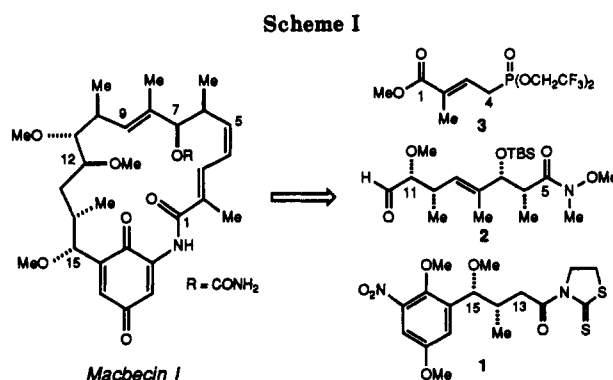
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Summary: The asymmetric synthesis of macbecin I is described wherein the absolute stereochemical relationships were established through the use of chiral boron aldol bond constructions and internally directed α -methoxy ketone reduction, while the *E,Z* dienic amide moiety was installed in one step using a vinylogous phosphonate reagent.

The benzoquinoid antibiotics, the macbecins,¹ herbimycins,² and geldanamycin,³ are representatives of an emerging class of ansa-bridged macrocyclic lactams possessing a significant range of antitumor activity.⁴ We describe in this paper our studies culminating in the successful total synthesis of macbecin I. Our retrosynthetic analysis is shown in Scheme I. Both the structural complexity and the promising antitumor potential of these molecules have made them attractive as targets for total synthesis. To date, one total synthesis of macbecin I⁵ and one of herbimycin A have appeared.⁶

The synthesis of 1 was initiated with the C₁₄-C₁₅ aldol bond construction that establishes the two stereogenic centers resident in the fragment (Scheme II). Treatment of the (*Z*)-boron enolate of imide 4,⁷ derived from the (4*R*,5*S*)-norephedrine-based oxazolidinone (X_NH), with 2,5-dimethoxy-3-nitrobenzaldehyde⁸ according to the standard conditions⁹ afforded the desired aldol adduct 5 (80%, >97% diastereomeric purity).¹⁰ Methylation of the C₁₅-hydroxyl was accomplished by reaction of the aldol adduct with trimethyloxonium tetrafluoroborate (Proton



^a Key: (a) *n*-Bu₃BOTf, Et₃N, 2,5-dimethoxy-3-nitrobenzaldehyde; (b) Me₃O BF₄, Proton Sponge, CH₂Cl₂, 25 °C; (c) LiOOH, THF/H₂O, 0 °C; (d) (ClCO)₂, DMF, CH₂Cl₂, 25 °C; (e) CH₂N₂, Et₂O/CH₂Cl₂, 0-25 °C; (f) AgNO₃, THF/H₂O, 25 °C; (g) 2-mercaptothiazoline, EDC, DMAP, CH₂Cl₂.

Sponge, CH₂Cl₂, 25 °C, 5 days).¹¹ Subsequently, a one-carbon homologation was effected using the Arndt-Eistert sequence.¹² Thus, imide 6 was treated with lithium hy-

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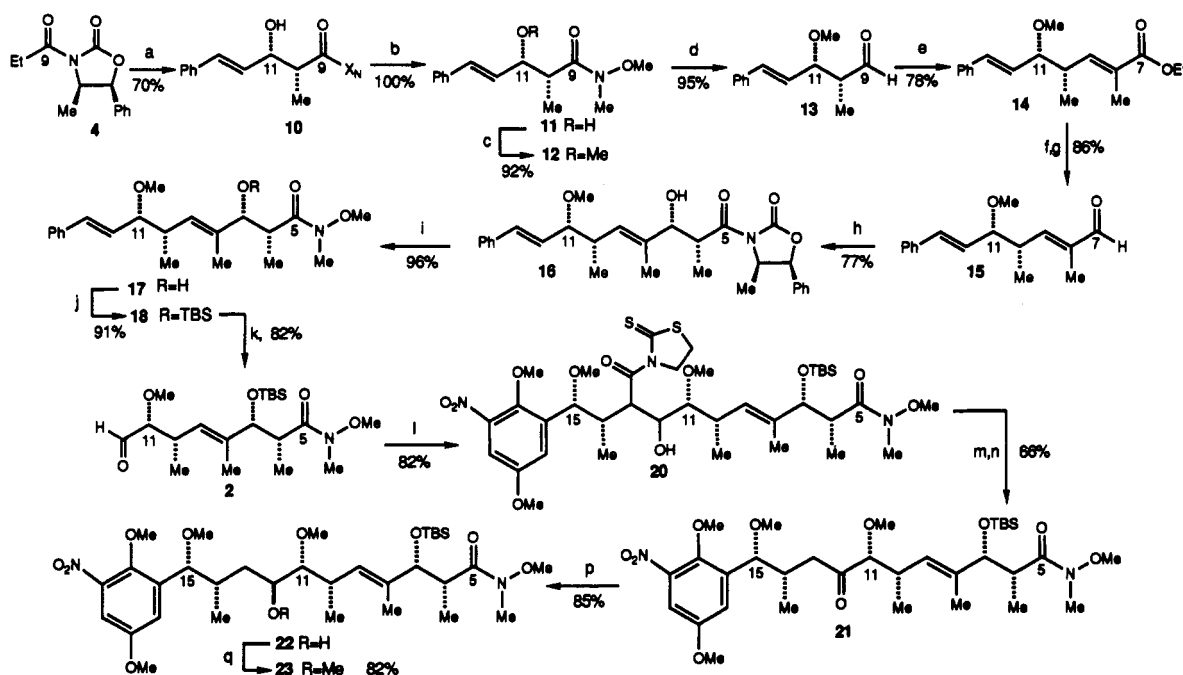
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Scheme III^a

^a Key: (a) *n*-Bu₂BOTf, Et₃N, *trans*-cinnamaldehyde; (b) AlMe₃, MeONHMe·HCl, CH₂Cl₂, -10 °C; (c) MeI, NaH, THF/DMF, 0 °C; (d) DIBAL-H, CH₂Cl₂, -78 °C; (e) Ph₃P=C(Me)CO₂Me, toluene, 100 °C; (f) DIBAL-H, CH₂Cl₂, -78 °C; (g) (COCl)₂, DMSO, CH₂Cl₂; Et₃N, -60 °C; (h) 4, *n*-Bu₂BOTf, Et₃N; (i) AlMe₃, MeONHMe·HCl, CH₂Cl₂, -10 °C; (j) TBSCl, imidazole, DMF, 25 °C; (k) OsO₄, NMO, *t*-BuOH/THF/H₂O; NaIO₄, NaHCO₃, 25 °C; (l) 1, TiCl₄, Et₃N, 0 °C; (m) Dess–Martin periodinane, pyridine/CH₂Cl₂, 25 °C; (n) LiOH, THF/H₂O, 25 °C; (p) Zn(BH₄)₂, cyclohexane, Et₂O, -78–20 °C; (q) Me₃BOF₄, Proton Sponge, CH₂Cl₂, 25 °C.

drogen peroxide¹³ to provide acid 7 (95%). Diazo ketone 8 was prepared in 86% yield from 7 by formation of the corresponding acid chloride (1.1 equiv of (COCl)₂, cat. DMF, 25 °C) and subsequent treatment with excess diazomethane (Et₂O/CH₂Cl₂ 0–25 °C). Wolff rearrangement (AgNO₃, THF/H₂O, 25 °C, 24 h) then afforded the homologated acid 9 in 88% yield. Finally, treatment of the acid with 2-mercaptothiazoline (EDC, DMAP, CH₂Cl₂, 25 °C) furnished the completed synthon 1 in 84% yield.

With fragment 1 in hand, we addressed the C₅–C₁₂ synthon 2 (Scheme III). As with the aromatic synthon, the construction of this fragment centered around the incorporation of the four stereocenters using chiral boron enolate methodology. Treatment of *trans*-cinnamaldehyde with the enolate derived from imide 4 afforded the aldol adduct 10 (70%, >95% one diastereomer by ¹H NMR analysis). Transamination of 10 according to the conditions of Weinreb,¹⁴ followed by methylation (MeI, NaH, THF/DMF, 0 °C), and DIBAL reduction furnished 13 in 87% yield for the three-step sequence. The C₈–C₉ tri-substituted olefin was then stereoselectively incorporated (78%, 94:6 *trans*-*cis* by capillary GLC) by treatment of 13 with (carbethoxymethylene)triphenylphosphorane¹⁵ in refluxing toluene. Sequential DIBAL reduction and Swern oxidation¹⁶ (86% for two steps) afforded aldehyde 15 to set up the final boron aldol reaction. Addition of the (*Z*) enolate derived from imide 4 to 15 thus afforded the aldol adduct 16 in 77% yield (>95% one diastereomer by ¹H NMR analysis). At this point, six of seven of the stereo-

genic centers resident in the macbecins had been established via the common imide precursor 4.

Elaboration of 16 to the completed C₅–C₁₂ synthon 2 was then accomplished by successive transamination and subsequent silylation of the secondary alcohol (TBSCl, imidazole, DMF, 25 °C) to provide 18 in 87% overall yield. The C₁₂ aldehyde moiety was then revealed by selective oxidation of the disubstituted olefin with osmium tetroxide (20 mol %, NMO, *t*-BuOH/THF/H₂O).¹⁷ Oxidative cleavage of the intermediate diol with sodium periodate afforded the desired aldehyde 2 in 82% yield.

The aldol coupling of fragments 1 and 2 was accomplished using a modification of the recently reported TiCl₄/Et₃N enolization procedure.¹⁸ It is noteworthy that attempts to activate 1 toward enolization with other mild enolization reagents such as *n*-Bu₂BOTf resulted in loss of the C₁₅-methoxyl group. In a similar manner, Sn(OTf)₂-based procedures also resulted in low yields of coupled product. However, enolization of 1.0 equiv of 1 (1.05 equiv of TiCl₄, 1.10 equiv of Et₃N, CH₂Cl₂, 0 °C, 1 h) followed by addition of aldehyde 2 (0.9 equiv, 0 °C, 3.3 h) afforded 73% of aldol adduct 20 as a single diastereomer (9% of recovered 2, complete recovery of unreacted 1). Although the absolute stereochemistry of this aldol adduct remains to be established, we have determined that the relative stereochemistry is that of an anti aldol adduct.¹⁹

Elaboration to the completed C₅–C₁₅ synthon began with oxidation of 20 to the corresponding β-ketoimide (90%) using the pyridine-buffered Dess–Martin oxidation.²⁰ Subsequent lithium hydroxide hydrolysis and in situ thermal decarboxylation (THF/H₂O, 25 °C) afforded the desired ketone 21 in 73% yield. Chelate-controlled re-

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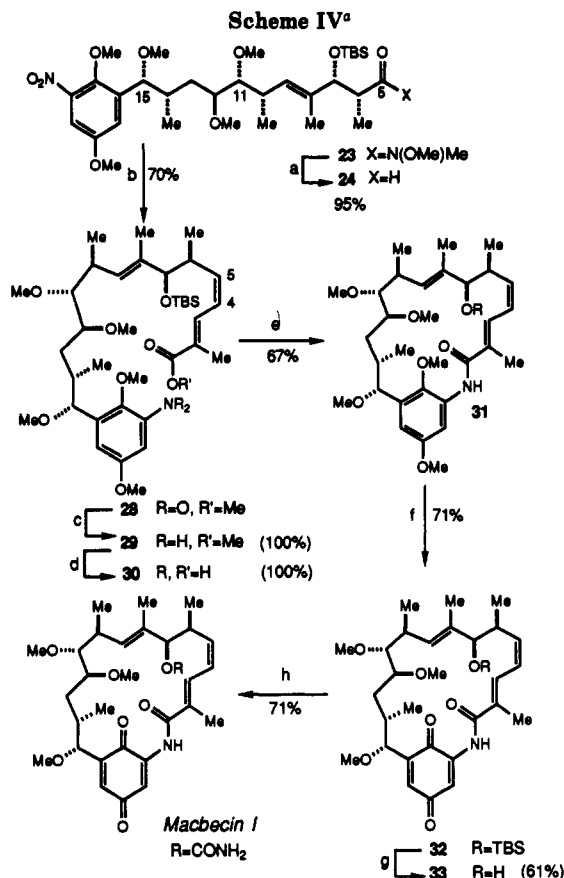
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^a Key: (a) DIBAL; (b) 3, *n*-BuLi, Et₂O, -78 °C; (c) H₂, quinoline, Pd(CaCO₃), PbO, EtOH; (d) LiOH, THF/MeOH/H₂O; (e) BOP-Cl, Hunig's base, PhCH₃, 85 °C; (f) CAN, H₂O/CH₃CN; (g) TBAF, THF, 25 °C, 48 h; (h) NaOCN, TFA, CH₂Cl₂.

duction of 21 with Zn(BH₄)₂²¹ (4.0 equiv of cyclohexene, Et₂O, -78 to -20 °C) provided the secondary alcohol 22 as a single isomer (85%, >95:5 by ¹H NMR analysis). Although we did not rigorously prove the stereochemistry of the newly created C₁₂-hydroxyl center, we felt that the high diastereoselectivity of the reaction reflected the anticipated high degree of chelate organization in the transition state.²² Methylation of the C₁₂-alcohol using trimethyloxonium tetrafluoroborate and proton sponge (CH₂Cl₂, 25 °C) then afforded the completed C₅-C₁₅ synthon 23 (83% yield).

The stereoselective incorporation of the C₁-C₄ diene and the completion of the synthesis were then addressed (Scheme IV). It is known that conventional vinylogous phosphorous-based reagents undergo selective (*E,E*) olefination with aldehydes.²³ Our plan was to employ a vinylogous phosphonate that would undergo selective (*E,Z*) olefin formation by using activating substituents on phosphorus.²⁴ Treatment of γ -bromomethyl tiglate²⁵ with

neat trimethyl phosphite afforded the corresponding dimethylphosphonate. Subsequent treatment with neat PCl₅ and then 2,2,2-trifluoroethanol (Hunig's base, PhH, 0-25 °C) provided 3 (38% for two steps). Horner-Emmons olefination (8 equiv of 3, *n*-BuLi, Et₂O, -78 °C) with aldehyde 24 (prepared by DIBAL reduction of 23 in 95% yield), then provided a 73:27 mixture of (*E,Z*)-(*E,E*) unsaturated esters from which the desired (*E,Z*) isomer 28 was isolated in 70% yield.²⁶

With the macbecin skeleton assembled, the nitro group was selectively reduced (H₂, Lindlar's catalyst²⁷) to provide the anilinic ester 29 in 94% yield (6% recovered 28) without any reduction of the diene moiety. Subsequent hydrolysis of the methyl ester (LiOH, THF/MeOH/H₂O) afforded the derived acid 30 in quantitative yield. Macrocyclization according to the Baker conditions with *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride²⁸ in the presence of Hunig's base (0.001 M in PhCH₃, 85 °C, 67%) provided the macrocycle 31. Oxidation of 31 to quinone 32 (CAN, CH₃CN/H₂O, 71%)²⁹ and subsequent desilylation (TBAF, THF, 25 °C, 48 h, 51%, 10% recovered 32) afforded decarbamoyl macbecin 33. Finally, acylation of the C₇ hydroxyl group (NaOCN, TFA, 71%) provided synthetic macbecin I whose spectroscopic and physical properties agreed in all respects with the data (¹H NMR, IR, [α]_D, HR FABMS) reported in the literature for the natural product.³⁰ In addition, direct comparison to a natural sample (¹H NMR, ¹³C NMR, IR, [α]_D, HR FABMS, TLC, *R_f* in several solvent systems) confirmed the identity of the natural and synthetic samples.³¹

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Supplementary Material Available: Full experimental details for all reactions, as well as analytical data for all intermediates in the synthesis (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(26) Attempts to effect this reaction with fewer equivalents of 3 resulted in both lower yields and lower (*E,Z*)-(*E,E*) ratios. The analogous reaction conducted with isobutyraldehyde affords a 60:40 mixture of (*E,Z*)-(*E,E*) isomers.

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