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 chromate[24] achieved a similar result with accompanying with allylic oxidation to give the α-enone **17**. Upon methanolysis the acylal function was cleaved leading to lactone **4** whose ^{1}H 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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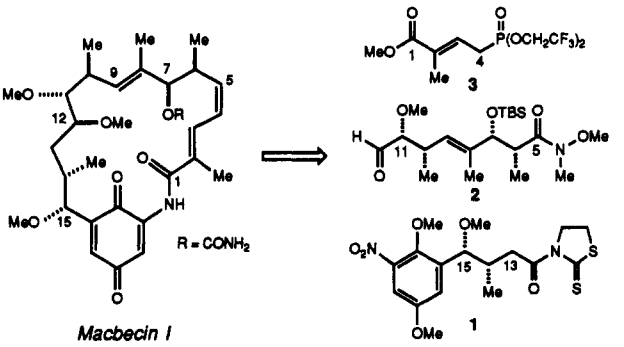
Summary: The asymmetric synthesis of macbecin I is described wherein the absolute stereochemical relationships were established through the use of chiral boron aldol bond constructions and internally directed α-methoxy ketone reduction, while the *E,Z* dienic amide moiety was installed in one step using a vinylogous phosphonate reagent.

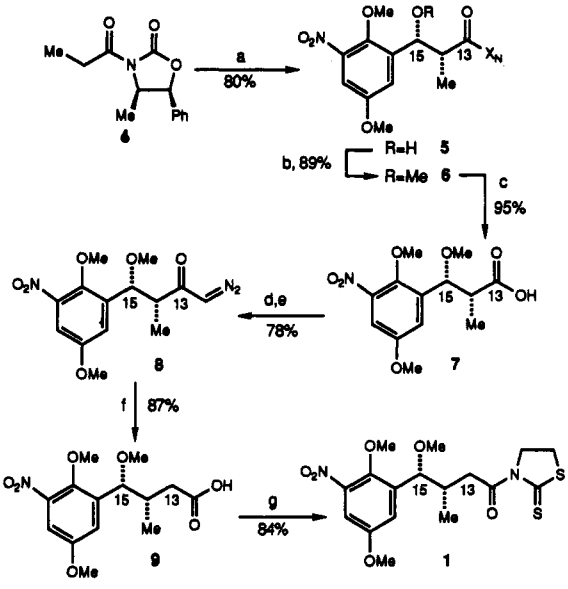
The benzoquinoid antibiotics, the macbecins,[1] herbimycins,[2] and geldanamycin,[3] are representatives of an emerging class of ansa-bridged macrocyclic lactams possessing a significant range of antitumor activity.[4] We describe in this paper our studies culminating in the successful total synthesis 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 I[5] and one of herbimycin A have appeared.[6]

The synthesis of **1** was initiated with the C_{14}–C_{15} 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-nitrobenzaldehyde[8] according to the standard conditions[9] afforded the desired aldol adduct **5** (80%, >97% diastereomeric purity).[10] Methylation of the C_{15}-hydroxyl was accomplished by reaction of the aldol adduct with trimethyloxonium tetrafluoroborate (Proton Sponge, CH_2Cl_2, 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-

Scheme I



Scheme II[a]



[a] Key: (a) *n*-Bu_2BOTf, Et_3N, 2,5-dimethoxy-3-nitrobenzaldehyde; (b) Me_3O BF_4, Proton Sponge, CH_2Cl_2, 25 °C; (c) LiOOH, THF/H_2O, 0 °C; (d) $(ClCO)_2$, DMF, CH_2Cl_2, 25 °C; (e) CH_2N_2, Et_2O/CH_2Cl_2, 0–25 °C; (f) $AgNO_3$, THF/H_2O, 25 °C; (g) 2-mercaptothiazoline, EDC, DMAP, CH_2Cl_2.

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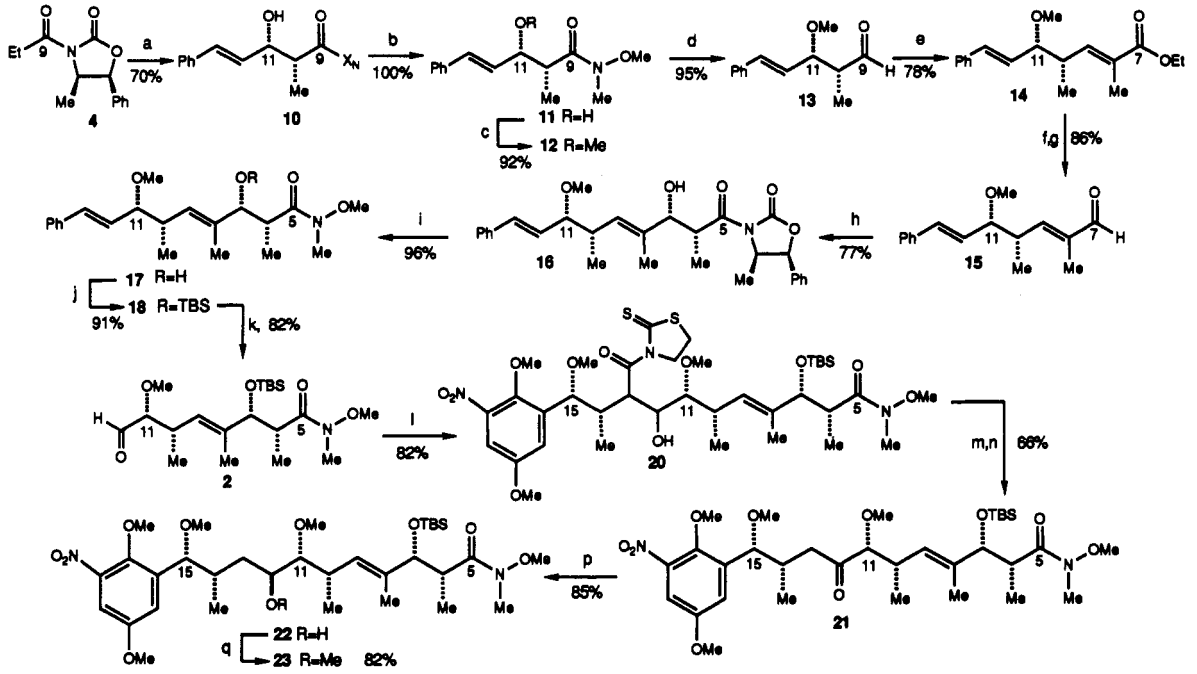
Scheme III[a]



[a] Key: (a) *n*-Bu_2BOTf, Et_3N, *trans*-cinnamaldehyde; (b) $AlMe_3$, MeONHMe·HCl, CH_2Cl_2, −10 °C; (c) MeI, NaH, THF/DMF, 0 °C; (d) DIBAL-H, CH_2Cl_2, −78 °C; (e) $Ph_3P{=}C(Me)CO_2Me$, toluene, 100 °C; (f) DIBAL-H, CH_2Cl_2, −78 °C; (g) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N, −60 °C; (h) **4**, *n*-Bu_2BOTf, Et_3N; (i) $AlMe_3$, MeONHMe·HCl, CH_2Cl_2, −10 °C; (j) TBSCl, imidazole, DMF, 25 °C; (k) OsO_4, NMO, *t*-BuOH/THF/H_2O; $NaIO_4$, $NaHCO_3$, 25 °C; (l) **1**, $TiCl_4$, Et_3N, 0 °C; (m) Dess–Martin periodinane, pyridine/CH_2Cl_2, 25 °C; (n) LiOH, THF/H_2O, 25 °C; (p) $Zn(BH_4)_2$, cyclohexane, Et_2O, −78–20 6C; (q) Me_3OBF_4, Proton Sponge, CH_2Cl_2, 25 °C.

drogen peroxide[13] 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 (Et_2O/CH_2Cl_2 0–25 °C). Wolff rearrangement ($AgNO_3$, THF/H_2O, 25 °C, 24 h) then afforded the homologated acid **9** in 88% yield. Finally, treatment of the acid with 2-mercaptothiazoline (EDC, DMAP, CH_2Cl_2, 25 °C) furnished the completed synthon **1** in 84% yield.

With fragment **1** in hand, we addressed the C_5–C_{12} 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 C_8–C_9 trisubstituted olefin was then stereoselectively incorporated (78%, 94:6 trans–cis by capillary GLC) by treatment of **13** with (carbethoxymethylene)triphenylphosphorane[15] in refluxing toluene. Sequential DIBAL reduction and Swern oxidation[16] (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 stereogenic centers resident in the macbecins had been established via the common imide precursor **4**.

Elaboration of **16** to the completed C_5–C_{12} 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 C_{12} aldehyde moiety was then revealed by selective oxidation of the disubstituted olefin with osmium tetroxide (20 mol %, NMO, *t*-BuOH/THF/H_2O).[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 $TiCl_4/Et_3N$ enolization procedure.[18] It is noteworthy that attempts to activate **1** toward enolization with other mild enolization reagents such as *n*-Bu_2BOTf resulted in loss of the C_{15}-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 $TiCl_4$, 1.10 equiv of Et_3N, CH_2Cl_2, 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 C_5–C_{15} 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/H_2O, 25 °C) afforded the desired ketone **21** in 73% yield. Chelate-controlled re-

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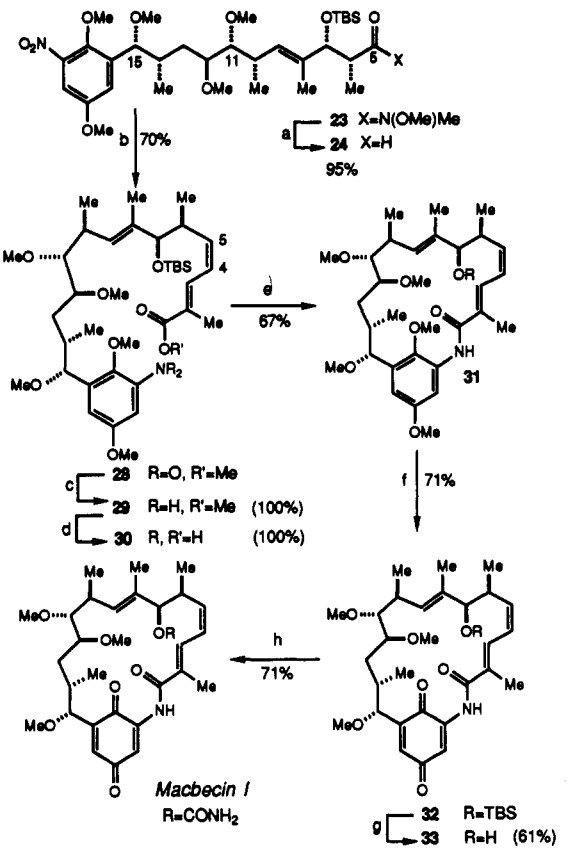
Scheme IV[a]



[a] Key: (a) DIBAL; (b) **3**, *n*-BuLi, Et_2O, −78 °C; (c) H_2, quinoline, $Pd(CaCO_3)$, PbO, EtOH; (d) LiOH, THF/MeOH/H_2O; (e) BOP-Cl, Hunig's base, $PhCH_3$, 85 °C; (f) CAN, H_2O/CH_3CN; (g) TBAF, THF, 25 °C, 48 h; (h) NaOCN, TFA, CH_2Cl_2.

duction of **21** with $Zn(BH_4)_2$[21] (4.0 equiv of cyclohexene, Et_2O, −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 C_{12}-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 C_{12}-alcohol using trimethyloxonium tetrafluoroborate and proton sponge (CH_2Cl_2, 25 °C) then afforded the completed C_5–C_{15} synthon **23** (83% yield).

The stereoselective incorporation of the C_1–C_4 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 tiglate[25] with neat trimethyl phosphite afforded the corresponding dimethylphosphonate. Subsequent treatment with neat PCl_5 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, Et_2O, −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 (H_2, Lindlar's catalyst[27]) 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/H_2O) afforded the derived acid **30** in quantitative yield. Macrocyclization according to the Baker conditions with *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride[28] in the presence of Hunig's base (0.001 M in $PhCH_3$, 85 °C, 67%) provided the macrocycle **31**. Oxidation of **31** to quinone **32** (CAN, CH_3CN/H_2O, 71%)[29] and subsequent desilylation (TBAF, THF, 25 °C, 48 h, 51%, 10% recovered **32**) afforded decarbamoyl macbecin **33**. Finally, acylation of the C_7 hydroxyl group (NaOCN, TFA, 71%) provided synthetic macbecin I whose spectroscopic and physical properties agreed in all respects with the data (^1H NMR, IR, $[\alpha]_D$, HR FABMS) reported in the literature for the natural product.[30] In addition, direct comparison to a natural sample (^1H NMR, ^{13}C NMR, IR, $[\alpha]_D$, 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.

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(31) We gratefully acknowledge Professor Muroi (Takeda Chemical Industries, Ltd., Osaka, Japan) for providing us with a natural sample of macbecin I for comparison purposes.