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, oxygen being inserted chemoselectively into the electron rich C4-C5 bond. Sodium chromate\textsuperscript{24} achieved a similar result with accompanying with allylic oxidation to give the α-enone 17. Upon methanolyis the acylal function was cleaved leading to lactone 4 whose \(^1\)H NMR data were identical to those described by Ruveda\textsuperscript{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,\textsuperscript{1} herbimycins,\textsuperscript{2} and geldanamycin,\textsuperscript{3} are representatives of an emerging class of ansa-bridged macrocyclic lactams possessing a significant range of antitumor activity.\textsuperscript{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\textsuperscript{5} and one of herbimycin A have appeared.\textsuperscript{6}

The synthesis of I was initiated with the C\textsubscript{14}-C\textsubscript{15} aldol bond construction that establishes the two stereocenters resident in the fragment (Scheme II). Treatment of the (Z)-boron enolate of imide 4,\textsuperscript{7} derived from the (4R,5S)-norphephedrine-based oxazolidinone (X\textsubscript{1}H), with 2,5-dimethoxy-3-nitrobenzaldehyde\textsuperscript{8} according to the standard conditions\textsuperscript{9} afforded the desired aldol adduct 5 (90%, >97% diastereomeric purity).\textsuperscript{10} Methylation of the C\textsubscript{15} hydroxyl was accomplished by reaction of the aldol adduct with trimethylxonium tetrafluoroborate (Proton Sponge, CH\textsubscript{2}Cl\textsubscript{2}, 25 °C) to give methyloxazolidine 6 (89%).

oxidation afforded aldehyde derived from imide set up the final boron aldol reaction. Addition of the 4171-4174. (b) Levi, adduct NMR analysis). At this point, six of seven of the stereo-
substituted olefin was then stereoselectively incorporated DIBAL-H, CH2C12, -78 OC; (e) Ph3P=C(Me)C02Me, toluene, 28,6141-6144. (1) 87%
with the enolate derived from imide (1.1 equiv of (COCl)2, cat. DMB, 25 OC) and subsequent treatment with excess diazomethane (Et2O/CH2Cl2, 0-25 OC). Wolff rearrangement (AgNO3, THF/H2O, 25 OC, 24 h) then afforded the homoligated acid 9 in 88% yield. Finally, treatment of the acid with 2-mercaptopthiazolene (EDC, DMAP, CH2Cl2, 25 OC) furnished the completed synthon 1 in 84% yield.

With fragment 1 in hand, we addressed the C5-C12 synthons 2 (Scheme III). As with the aromatic synthons, 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 'H NMR analysis). Transamination of 10 according to the conditions of Weinreb,14 followed by methylation (MeI, NaH, THF/DMF, 0 OC), and DIBAL reduction furnished 13 in 87% yield for the three-step sequence. The C5-C6 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 (96% 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 'H 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 synthons 2 was then accomplished by successive transamination and subsequent silylation of the secondary alcohol (TBSCI, imidazole, DMB, 25 OC) to provide 18 in 87% overall yield. The C12 aldehyde moiety was then revealed by selective oxidation of the diastereomeric 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-Bu3BOTf 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 OC, 1 h) followed by addition of aldehyde 2 (0.9 equiv, 0 OC, 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-C12 synthon began with oxidation of 20 to the corresponding beta-ketoimide (90%) using the pyridine-buffered Dess–Martin oxidation.20 Subsequent lithium hydroxide hydrolysis and in situ thermal decarboxylation (THF/H2O, 25 OC) afforded the desired keto 21 in 73% yield. Chelate-controlled re-

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*Key: (a) n-Bu3BOTf, Et3N, trans-cinnamaldehyde; (b) AlMe3, MeONHMeHCl, CH2Cl2, -10 OC; (c) MeI, NaH, THF/DMF, 0 OC; (d) DIBAL-H, CH2Cl2, -78 OC; (e) Ph3P=C(Me)C02Me, toluene, 100 OC; (f) DIBAL-H, CH2Cl2, -78 OC; (g) (COCl)2, DMSO, CH2Cl2, Et3N, -60 OC; (h) 4, n-Bu3BOTf, Et3N; (i) AlMe3, MeONHMeHCl, CH2Cl2, -10 OC; (j) TBSCI, imidazole, DMB, 25 OC; (k) OsO4, NMO, t-BuOH/THF/H2O; NaI, NaHCO3, 25 OC; (l) I, TiCl4, Et3N, 0 OC; (m) Dess–Martin periodinane, pyridine/CH2Cl2, 25 OC; (n) LiOH, THF/H2O, 25 OC; (p) Zn(BH4)2, cyclohexane, Et3O, -78-20 OC; (q) Me30BF4, Proton Sponge, CH2Cl2, 25 OC.

19 See supplementary material for details.
neat trimethyl phosphite afforded the corresponding di-
methylphosphonate. Subsequent treatment with neat PCl₃
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 alde-
hyde 24 (prepared by Dibal reduction of 23 in 95% yield),
then provided a 73:27 mixture of (E,Z)-(E,E) unsat-
urated 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 catalyst)²⁷ to pro-
vide the anilinic ester 29 in 94% yield (6% recovered 28)
without any reduction of the diene moiety. Subsequent
hydrosylation of the methyl ester (LiOH, THF/MeOH/H₂O)
afforded the derived acid 30 in quantitative yield. Ma-
crocyclization according to the Baker conditions with
N₂,N₂-bis(2-oxo-3-oxaolidinyl)phosphinic chloride³⁰ in
the presence of Hunig’s base (0.001 M in PhCH₂, 85 °C, 67%)
provided the macrocycle 31. Oxidation of 31 to quinone
32 (CAN, CH₃CN/H₂O, 71%)³¹ and subsequent desilyla-
tion (TBAF, THF, 25 °C, 48 h, 51%, 10% recovered 32)
afforded decarbamoyl macbecin 33. Finally, acylation of
the C₁ hydroxy group (NaOCN, TFA, 71%)³² provided
synthetic macbecin I whose spectroscopic and physical
properties agreed in all respects with the data of the natu-
ral product.³³ In addition, direct comparison to a
natural sample (H NMR, ¹³C NMR, IR, [α]D, HR
FABMS) reported in the literature for the natural product.
³⁴

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Supplementary Material Available: Full experimental
details for all reactions, as well as analytical data for all in-
termediates 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 re-
resulted in both lower yields and lower (E,Z)-(E,E) ratios. The analogous
reaction conducted with isobutylaldehyde affords a 60:40 mixture of
(E,Z)-(E,E) isomers.

²⁷ For a related reduction of azides, see: Corey, E. J.; Nicolau, K.

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Perkin Trans. 1 1990, 47–65. Note that the ¹³C NMR spectral data
reported by Baker and Castro contains an error. The resonance at 15.26
ppm should be replaced by a resonance at 12.44 ppm (R. Baker, private
communication).

³¹ We gratefully acknowledge Professor Muroi (Takeda Chemical
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macbecin I for comparison purposes.