Asymmetric Synthesis of the Benzoquinoid Ansamycin Antitumor Antibiotics: Total Synthesis of (+)-Macbecin

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A convergent asymmetric synthesis of the antitumor antibiotic macbecin I has been achieved. Six of the seven stereogenic centers within the target structure were controlled using asymmetric aldol methodology, while the final stereogenic center was established through internal asymmetric induction. Fragment coupling was accomplished using a mild, titanium tetrachloride mediated aldol reaction. The C-1-C-6 unsaturated dienic ester was stereoselectively incorporated through a kinetically controlled Horner-Emmons olefination. Macrolactamization and subsequent refunctionalization afforded macbecin I.

The benzoquinoid antibiotics, the macbecins, the herbimycins, and geldanamycin, are representative of an emerging class of ansa-bridged macrocyclic lactams possessing a significant range of antitumor activity.2 Macbecin I, along with its hydroquinone analog, macbecin II, were isolated in 1980.2 The structure and absolute stereochemistry of this natural product were subsequently determined by X-ray crystallography.3 An X-ray structure has also been obtained for herbimycin A (Figure 1),4 and although this study did not include an absolute configurational assignment, this issue has been resolved through a recently reported asymmetric synthesis.5 Finally, the stereochemical relationships in geldanamycin have not yet been reported despite the fact that this antibiotic was the first of the benzoquinoid ansamycins to have been isolated.6

Recent studies have indicated that the benzoquinoid ansamycins, specifically the herbimycins, have antitumor functions. In addition to reversing the characteristics of oncogene expression,7 herbimycin A has been shown to have potent antiangiogenic activity.8 This latter biological activity distinguishes the benzoquinoid ansamycins from their benzenoid9 and naphthoquinoid10 ansamycin relatives.

The numbering system appearing in the literature for the macbecin and herbimycin skeletons differs, with neither adhering to the accepted IUPAC rules. The numbering system chosen for the discussion is that corresponding to the numbering system for the secosteroid and identical to that used for herbimycin; however, the IUPAC names of macbecin derivatives reported in the Experimental Section are those derived from the 9-azabicyclo[3.3.1]nonane ring system.

Solid-State Structure.11 The Muroi X-ray structure of macbecin I lacking the C-7 urethane moiety is provided in Figure 2.3 By inspection, it is evident that nonbonding interactions, particularly in the C-8-C-10 region, along with ring unsaturation, significantly restrict the number of low-energy conformations of the macrocycle. In particular, the C-8 methyl group is the focal point of both an A(1,3) allylic strain interaction with the C-10 substituents and a potential gauche pentane interaction with the carbon substituents at C-6. In entertaining a synthesis of macbecin, we were aware of the fact that an unprotected C-7 hydroxyl substituent possessed the capacity to undergo an intramolecular conjugate addition to the dienic amide at C-3. However, the local conformational constraints in this region of the structure serve to orient the C-7 oxygen away from the interior of the macrocycle and the electrophilic C-9 center. It is also significant that the diene electrophilicity is probably further reduced by the constraints of

Figure 1. Representative benzoquinoid antibiotics.


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fragments required the use of some type of removable carbanion-stabilizing functional group, X. As an added constraint on the selection of this activating group, it was our desire to carry the aromatic nitrogen substituent through the assemblage of the seco acid as a nitro group, thus eliminating the necessity of protecting this heteroatom at intermediate points in the synthesis. In the following discussion we describe studies culminating in the successful asymmetric synthesis of (+)-macbecin 1,18

Results and Discussion

C13-C21 Aromatic Fragment. The synthesis plan for this macbecin fragment hinged on the identification of a removable carbanion-stabilizing “X” group to be employed for C13 activation and coupling. While a number of options were explored (X = –I, –SPh, –SO2Ph, –SO3Ph, –PPh3, –POPh3), that derivative wherein X was a carboxyl function was ultimately selected. It is noteworthy that, with the exception of the case where X = CO-R, all other activating groups required that the nitro group be sacrificed (i.e., reduced and protected) at some point during the fragment coupling sequence. Thus, the specific identity of the aromatic synthon was designated as 2.

The synthesis of 2 began with the construction of the illustrated aromatic aldehyde19 which was prepared in two high-yielding steps (Scheme II). Sequential nitration and methylation of 2-hydroxy-5-methoxybenzaldehyde proceeded in 71% overall yield to afford 2,5-dimethoxy-3-nitrobenzaldehyde as a yellow crystalline solid. Treatment of this aldehyde with the (Z) boron enolate derived from imide 1a20 according to the standard conditions27 then afforded the desired aldol adduct 3 (80%) as a single diastereomer.

Conversion of this aldol adduct to the completed aromatic acid required two necessary operations. In the first of these required transformations, conversion of the C13 hydroxyl moiety in 3 into the derived methyl ether 4 was carried out under sufficiently mild conditions (Me2OBF4, proton sponge21) so that the potential problem of retroaldolization was avoided. With this intermediate in hand, the one-carbon homologation via the Wolff rearrangement22 was addressed. Imide 4 was first treated with lithium hydrogen peroxide23 to provide the derived acid 5 (95%) which was transformed into the diazoketone with

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"Figure 2. Partial X-ray structure of macbecin 1".

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Total Synthesis of (+)-Macbecin

Scheme I

Scheme II*

*Key: (a) NaH, MeI; (b) Me3OBF4, Proton Sponge, CH2Cl2, 25 °C; (c) LiOOH, THF/H2O; (d) (CICO)2, DMF, CH2Cl2; (e) CH2N2, excess diazomethane via the intermediate acid chloride in 74% overall yield. The Wolff rearrangement was found to proceed very cleanly under the influence of silver nitrate in THF/H2O to afford the aromatic synthon 2 in 87% yield. In contrast, attempts to promote the Wolff rearrangement photochemically resulted in extensive decomposition with only trace amounts of the desired product being isolated.

With the aromatic synthon 2 in hand, its viability as a precursor to the quinoid nucleus was evaluated. Accordingly, the hydroquinone dimethyl ether 5 was transformed into a suitable aromatic amide model system for the completed macrocycle. The oxidation of this hydroquinone derivative with ceric ammonium nitrate provided a precedent for this transformation.

C9-C12 Fragment. The operational equivalent 7 for the C9-C12 dialdehyde synthon which was selected is illustrated below. Each aldehyde function, incorporated as an olefinic and amide equivalent, respectively, is accessible through oxidation or reduction of the desired terminus. As with the aromatic synthon, the construction of this fragment centered around the incorporation of the four stereocenters through the successive use of the chiral propionate imide 1a in the illustrated aldol reactions (Scheme III). Treatment of trans-cinnamaldehyde with the boron enolate derived from imide 1a according to the standard conditions afforded the aldol adduct 8 in 70% yield. Subsequent transamination of 8 with the aluminum amide reagent derived from N,N-dimethylhydroxylamine provided the N-methoxy-N-methylamide 9 which was methylated in high yield (MeI, NaH, THF/DMF, 0 °C) to provide the derived CII methyl ether 10 in 94% yield. As expected, DIBAL-H reduction afforded aldehyde 11 which was transformed into the homologated (E) trisubstituted olefinic ester 12 with (carbethoxymethylene)triphenylphosphorane in refluxing toluene. Capillary GLC analysis revealed the reaction produced a 94:6 mixture of olefin isomers from which the major (E) isomer 12 was isolated by chromatography in 78% yield. The second iteration of the chiral propionate aldol reaction to give 14 and its subsequent transamination to the assembled fragment 7a proceeded in good yield as did the protection of the C1 hydroxyl function.

The effectiveness of intermediate 7 in the synthesis scheme required the selective oxidation of the disubstituted olefin. This transformation was realized in the presence of the trisubstituted olefin with osmium tetroxide (20 mol %) using N-methylmorpholine N-oxide (1.1 equiv) as the reoxidant according to the conditions of VanRheenen and Kelly. 

(26) A similarly designed synthon was also employed in the synthesis of X-306: Evans, D. A.; Bender, S. L.; Morris, J. J. Am. Chem. Soc. 1986, 110, 2500-2506.


oxidation of the trisubstituted olefin had occurred. Cleavage of the diol with sodium periodate afforded the desired aldehyde 15 in 82% yield.

**Fragment Coupling.** Due to the constraints of the nitro function in the C13-C21 aromatic acid moiety, which precluded the use of strong bases for example, a mild aldol union of the two fragments was chosen. In the initial analysis of this reaction, it was concluded that the most desirable coupling would be the (E) enolate derived from the aromatic fragment 2 with the aldehyde 15. In this double stereodifferentiating aldol reaction both enolate and aldehyde face selectivity would be expected to operate in concert to afford the illustrated adduct having the desired hydroxyl stereochemistry at C12 (eq 4).30

![Scheme IV](image)

In the event that this option were to be pursued, a subsequent radical-mediated decarboxylation would complete the assemblage process (Scheme IV). In a variant of this strategy which postpones establishing the C12 hydroxyl center until the last step, decarboxylation might be achieved through the derived β-keto acid. A final chelate-controlled reduction of the C12 ketone would also complete the stereoselective coupling process.

Our initial plan was to form the bis-boryl enediolate derived from 2 (n-Bu₂BOTf, Et₂N, 0 °C) based on the precedent established in these laboratories some years ago.31 However, when these conditions failed to result in appreciable amounts of enolization in the face of apparent labilization of the C15 methoxyl moiety, 2 was transformed into its derived 2-mercaptotiazolinone32 derivative 16 with the intention of increasing the acidity of the substrate (Scheme V). When thiouamide 16 was transformed into its derived boron enolate (n-Bu₂BOTf, Et₂N, 0 °C), and subsequently treated with benzaldehyde, a 1:1:1 mixture of starting material, desired aldol adducts, and byproducts where the C15-methoxyl had been lost were obtained. Other Lewis acid/base enolization variants were evaluated with the hope of suppressing the side reaction at C15. Following

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30 This analysis presumes that nonchelate-controlled stereinduction imparted by the aldehyde coupling partner from the C11 methoxyl substituent would be dominant.
literature precedent,\(^{33}\) the Sn(II) triflate/N-ethylpiperidine (NEP) reagent pair was found to effectively mediate the coupling process to provide a 54% yield of aldo products, obtained as a mixture of diastereomers. It is interesting to note that at temperatures above -40 °C the Sn(II)-aldolate is unstable and readily undergoes cyclization to the corresponding β-lactone 18. Even better results were obtained using the titanium tetrachloride/triethylamine enolization procedure recently developed in these laboratories.\(^{34}\) Enolization of imide 16 (1.05 equiv of TiCl\(_4\), 1.10 equiv of Et\(_2\)N, CH\(_2\)Cl\(_2\), 0 °C, 1 h) followed by addition of aldehyde 15 (0 °C, 3.3 h) afforded 73% of aldol adduct 17 as a single diastereomer, along with 9% of recovered aldehyde and complete recovery of unreacted imide 16.

It is interesting that the titanium aldol reaction proceeds with complete stereocontrol. Although we have not definitively established the absolute stereochemical relationships at C\(_{12}\) and C\(_{13}\), we have confirmed that the reaction exhibits syn aldol diastereoselection from an analysis of the stereochemistry of the derived β-lactone 18 readily obtained from 17 (K\(_2\)CO\(_3\), THF, reflux, 88%). The trans stereochemical assignment in 18 is based on the characteristic vicinal coupling constants between the C\(_{12}\) and C\(_{13}\) protons (3.7 Hz).\(^{35}\)

After considerable experimentation, it was concluded that decarbonylation of carboxylic acid derivatives derived from hydroxylthioimide 17 via radical precursors (e.g., O-acyl thiodydroxamates,\(^{36}\) selenium ester\(^{37}\)) was not practical due to an intervention of β-lactone formation at the decarbonylation reaction temperatures (refluxing benzene) or to competitive reduction of the nitro group. At this point the alternative decarbonylation option was explored (Scheme VI). Aldol adduct 17 was readily oxidized to the β-keto imide 19 (90%) using the pyridine-buffered version of the Dess–Martin oxidation.\(^{38}\) It is interesting to note that one of the sulfur atoms in the thiolactamidethione moiety is replaced by oxygen during this transformation, presumably during the Na\(_2\)SO\(_4\) workup. Decarbonylation was then achieved by a simple lithium hydroxide hydrolysis (THF/H\(_2\)O, 25 °C) to afford, after acidification, the desired ketone 20 in 78% yield.

The last stereogenic center at C\(_{21}\) in the target structure was incorporated through the chelate-controlled reduction of ketone 20. Treatment of this ketone with Zn(BH\(_4\))\(_2\) (Et\(_2\)O, -78 °C -20 °C)\(^{39}\) afforded what was presumed to be the desired secondary alcohol 21 as a single isomer (>95:5 by \(^1\)H NMR analysis) in 85% yield. Although an unambiguous stereochemical assignment of the newly generated hydroxy center was not made at this point, it was felt that the high diastereoselectivity of the reaction reflected the anticipated, and well-precedented, high degree of chelate organization in the transition state. At this late stage in the synthesis it was concluded that the most expeditious proof of stereochemistry would be to carry forward to the natural product where a direct comparison could be made. Finally, methylation of the C\(_{21}\) alcohol with trimethylsulphonium tetrafluoroborate and proton sponge furnished 22 (83%), the completed C\(_{15}\)–C\(_{21}\) macrocyclic subunit lacking only the C\(_{1}-\)C\(_{4}\) dienic amide appendage.

**Stereoselective Diene Ester Formation.** Although ample precedent exists for the stepwise stereoselective synthesis of (2\(\E,4\Z\))-2-methylhexadienoates,\(^{41}\) it was our intention to attempt to incorporate the C\(_{15}\)–C\(_{21}\) diene ester stereoselectively in a single operation. In closely related transformations it has been demonstrated that the related vinyllogous phosphonate\(^{40}\) and phosphonate\(^{41}\) reagents undergo selective (\(\E,\E\)) olefination with aldehydes. Although the control elements of such reactions are still a matter of some debate,\(^{45}\) this outcome may be rationalized on either kinetic or thermodynamic grounds. In the present instance, the plan was to attempt to rely on kinetic control in the preferential generation of the (\(\E,\Z\)) transition state using activated,\(^{45}\) sterically demanding phosphonate enolates.\(^{44}\) The rationale for anticipating the desired olefination stereoselection is presented in Scheme VII.

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\(^{35}\) Mulser, J.; Zippel, M.; Bruntrup, G. Angew. Chem., Int. Ed. Engl. 1989, 19, 465-466. In addition, when 20 was thermally decarbonylated (150 °C, DMF, 6h) in low yield the E/C\(_{12}\)/C\(_{13}\) alkene was produced, corroborating the assignment based on the \(^1\)H NMR coupling constant (16.0 Hz).


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**Scheme VI**

![Scheme VI](image)

Key: (a) Dess–Martin periodinane, pyridine/CH\(_2\)Cl\(_2\), 25 °C; (b) LiOH, THF/H\(_2\)O, 26 °C; (c) Zn(BH\(_4\))\(_2\), cyclohexene, Et\(_2\)O, -75 to +20 °C; (d) Me\(_2\)OBF\(_4\), Proton Sponge, CH\(_2\)Cl\(_2\), 25 °C.

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**Scheme VII**

![Scheme VII](image)
Given the assumption that the aldehyde addition step can be rendered product-determining, steric congestion at the phosphorus center could destabilize the pseudo-equatorial unsaturated ester moiety in the (E,E) transition structure in favor of its (E,Z) counterpart. The phosphonates illustrated below (eq 5) were prepared from the parent dimethyl phosphonate 23a in analogy to the literature procedure. Treatment of phosphonate 23a with PCl₅ provided the derived dichloride which was esterified with a selection of alcohols to provide the phosphonates of interest. After screening phosphonates 23a-c under a range of olefination conditions with isobutyraldehyde, it was found that the lithium enolate wherein selectivities of ca. 2; showed the best ratio (3:2 = E,Z:E,E) of olefin isomers. The modest trend toward (Z) olefin diastereoselection documented by the three cases provides some support for the kinetic model presented above. With this data in hand, the analogous olefination was carried out with the macbecin fragment 24. The initial reactions of phosphonate 23c (1–4 equiv) with aldehyde 24 closely paralleled the reactions with isobutyraldehyde wherein selectivities of ca. 3:2 were observed; however, when the same transformation was conducted with 8 equiv of phosphonate, a surprising 73:27 mixture of diene esters was obtained from which the desired adduct 25(Z) was isolated in 70% yield (eq 6).

**Macebin I.** The completion of the synthesis of (+)-macebin I is summarized in Scheme VIII. After experiencing limited success with a number of reducing systems (SnCl₂, H₂/Pd/C; Al/Hg), catalytic hydrogenation with Lindlar’s catalyst afforded the anilinic ester 26(Z) in 94% yield along with 6% of unreacted starting material. Subsequent hydrolysis of the methyl ester (LiOH, THF/MeOH/H₂O) provided the aniline acid 27(Z) (100%) which was cyclized according to the conditions of Baker and Castro using N,N'-bis-[2-oxo-3-oxazolidinyl]phosphinic chloride (BOP-Cl) in the presence of Hünig’s base (0.001 M in toluene, 85 °C) to provide the intact macrocycle 28(Z) (67%). Oxidation of 28(Z) to the derived quinone 29a using the conditions developed for the model system (eq 3, CAN, MeCN) proceeded in 71% yield. Subsequent dehydrosilylation (TBAF, THF, 25 °C, 48 h) afforded decarbamoyl macebin 29b in 51% yield along with 10% recovered starting material. Finally, acylation of the C₂ hydroxyl using NaOAc, TFA provided synthetic (+)-macebin I which agreed in all respects with the data (1H NMR, 13C NMR, IR, [α]D, MS, TLC Rf in several solvent systems) reported in literature for the natural product. In addition, direct comparison with a sample of the natural product confirmed the assignment.

Unnatural Macbecin Isomers. In the event that the desired olefination reaction (eq 6) had not been successful, it was our intention to construct the unnatural trans Δ-4 olefinic macebin analog and then to attempt an isomerization of this macrocycle to the natural product. This plan was based on the assumption that the (E,Z) C–C diene configuration in the natural product was more stable than the (E,E) analog 28(E) and was fortified by molecular mechanics calculations which predicted that the desired (E,Z) macrocycle 28(Z) was more stable than the corre
sponding isomer 28(E). The validity of this postulate was
tested in the following set of experiments (Scheme IX).
Using chemistry analogous to that employed for the
synthesis (Scheme VIII), the anilino acid 27(E) was also
cyclized to macrocycle 28(E) with BOP-Cl in good yield.
It is testimony to the utility of this cyclization procedure
that these conditions were equally successful in affecting
macrocyclization of two substrates with significantly
different structural requirements.

When both 28(E) and 28(Z) were independently sub-
mitted to radical-mediated olefin equilibration (n-Bu-
SnH, AIBN, PhH, 75 °C,52 PhSSPh, PhH, 75 °C)53 the
same 2:1 mixture of 28(E) to 28(Z) was obtained along
with a third unidentified constituent of lower mass
(Scheme IX). It is thus concluded that this 2:1 mixture
represents the equilibrium mixture of macroyclic lactams.
Although the greater stability of the (E,E) macrocyclic lactam contradicts our prediction, these
experiments demonstrate that the undesired Δ-4 olefin
isomer can be transformed into the desired macbecin macrocycle 28(Z).

Conclusion

The preceding discussion describes our successful efforts
to synthesize (+)-macbecin. Chiral imide aldol method-
ology has been pivotal in the control of absolute stere-
oregular relationships in this and an earlier synthesis56
published in this laboratory. It is of some
pedagogical interest that the other syntheses of this
compound have been pivotal in the control of absolute stereochemical
issues of absolute stereoregular control.

Experimental Section

General Methods. Melting points are uncorrected. Infrared
spectra were recorded on a Perkin-Elmer 781 spectrophotometer.
1H, 13C, and 31P NMR spectra were recorded on Bruker AM-250
(250 MHz), AM-300 (300 MHz), AM-400 (400 MHz), or AM-600
(500 MHz) spectrometers. The numbering used in all assignments
is based on standard IUPAC rules unless otherwise indicated.
Optical rotations were recorded on a JASCO DIP-181 digital
polarimeter at 589 nm or other
Optical rotations were recorded on a JASCO DIP-181 digital
spectrophotometer.

Model

The numbering used for the assignemnts of the 1H NMR
resonances for this compound corresponds to that used in the discussion.

(52) For a review of olefin inversions see: Sonnet, P. E. Tetrahedron
1986, 36, 557-684.
(53) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. Synthesis 1990,
1123-1125.
(55) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J.
(56) The numbering used for the assignments of the 1H NMR
resonances for this compound corresponds to that used in the discussion.
(57) Inhoffen, H. H.; Isler, O.; von der Bey, G.; Raspe, G.; Zeller, P.;
washed successively with two 50-mL portions of 1 N HCl, 50 mL of H2O, and 50 mL of brine. The resulting yellow solution was dried over Na2SO4, filtered, and concentrated. Purification of the residue by chromatography (4 cm × 12 cm silica gel, solvent gradient: hex:ethyl acetate/hex:ethyl acetate/hex:acetone = 1:3:1, affording 491 mg (64%) of the desired 4 as a yellow oil in addition to 185 mg (25%) of recovered starting material: [α]D24 +105° (c 0.50, CH2Cl2); IR (thin film) 3700–3400, 3100, 2980, 2940, 2860, 1440, 1310, 770, 620, 580, 560, 555, 10.1.

(2R,3aR)-2-(2,5-Dimethoxy-3-nitrophényl)-3-methyl-2-propanol (3). To a stirred solution of 485 mg (1.06 mmol) of 3-cyano-2,5-dimethoxy-4-nitrophényl-3-methyl-2-propanol in 10 mL of anhydrous THF/H2O was added 1 mL of anhydrous CH2Cl2 is 6.72 mL (1.06 mmol) of anhydrous KHCO3, 8.75 mL of di-n-butylboron (100 mg, 0.50 mmol) of DMAP. The yellow solution was stirred for 2 h before being transferred into 200 mL of saturated sodium bisulfate solution. The layers were separated, and the aqueous layer was extracted with three 150-mL portions of CH2Cl2. The combined organic layers were washed successively with 150 mL of saturated NaHCO3 solution and 150 mL of brine, dried over Na2SO4, filtered, and concentrated. Purification by chromatography (4 cm × 14 cm silica gel, solvent gradient: 25% ethyl acetate/hexane to 35% ethyl acetate/hexane) afforded 1.23 g (87%) of the desired diastereomer 3 which required no further purification: [α]D24 +79.2° (c 1.1, CH2Cl2); IR (thin film) 3000–2100, 1410, 1355, 1310, 1290, 1060 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.27 (d, 1 H, J = 3.2 Hz, ArH), 7.14 (d, 1 H, J = 3.2 Hz, ArH), 4.51 (d, 1 H, J = 4.1 Hz, C2H3), 3.88 (s, 3 H, ArOCH3), 3.82 (s, 3 H, ArOCH3), 3.30 (s, 3 H, C2H5), 2.78 (m, 1 H, C2H5), 2.26 (m, 1 H, J = 7.2 Hz, C2H2); 13C NMR (CDCl3, 100 MHz) δ 179.8, 155.5, 145.0, 143.7, 136.8, 110.9, 108.9, 77.8, 62.7, 57.9, 56.0, 44.1, 9.5; exact mass calcd for C12H14O3N2: Na + requires m/z 228.0903, found m/z 228.0903 (FAB, m-nitrobenzyl alcohol, Na added).

(2E,3aR)-2-(2,5-Dimethoxy-3-nitrophényl)-3-methyl-2-butenyl Chloride. To a solution of 1.80 g (6.02 mmol) of acid 5 in 40 mL of CH2Cl2 at rt was added 680 mL (7.22 mmol) of oxalyl chloride followed by 46 μL (0.602 mmol) of DMF (caution: gas evolution). The resulting solution was stirred for 16 h at room temperature. Direct concentration of the mixture in vacuo afforded the acid chloride (pure by 1H and 13C NMR) as an oily residue which was used directly in the next reaction without further purification: 1H NMR (400 MHz, CDCl3) δ 7.31 (d, 1 H, J = 2.9 Hz, ArH), 7.14 (d, 1 H, J = 7.2 Hz, C2H2); 13C NMR (CDCl3, 100 MHz) δ 174.5, 155.4, 144.7, 143.7, 135.6, 119.1, 110.1, 77.5, 62.6, 58.2, 56.0, 55.5, 10.1.

(4R,5S)-1-Diazoo-(2,5-dimethoxy-3-nitrophényl)-4-methyl-5-phenyl-4-oxazolidinethione (4). To a cooled (−78 °C) solution of 21.8 g (93.0 mmol) of 1a in 200 mL of anhydrous CH2Cl2 were added 15.6 g (112 mmol) of anhydrous Et2N and 26.1 mL (103 mmol) of di-n-butylboron trifluoride. The resulting solution (25 mL) at −78 °C for 30 min and 0 °C for 15 min before the solution was recooled to −78 °C and 11.8 mL (93.0 mmol) of trans-cinnamaldehyde was added. The solution was stirred at −78 °C for 35 min and at 0 °C for 45 min before being quenched by the addition of 200 mL of a 1:1 mixture of pH 7 phosphate buffer/MeOH. Subsequently 250 mL of a 2.5% mixture of aqueous hydrogen peroxide/MeOH was added. The resulting mixture was concentrated and extracted with 200-mL portions of ethyl acetate. The combined organic phases were washed successively with 200-mL portions of saturated NaHCO3 solution and brine, dried over Na2SO4, filtered, and concentrated. Analysis of the 1H NMR spectrum of the unpurified mixture showed the product to be >95% one disastereomer. The product was purified by recrystallization from ethyl acetate–hexane to afford 23.8 g (70%)
were dried over Na$_2$SO$_4$, filtered, and concentrated. Purification of the residue by chromatography (4 cm $\times$ 12 cm silica gel, 20% ethyl acetate–hexane) afforded 1.25 g (85%) of the desired aldehyde 11 as a clear oil: [α]$_D$ +15.8$^\circ$ (c 4.50, CHCl$_3$); IR (CHCl$_3$) 3160–2800, 1725, 1695, 1650, 1540, 1480, 1440, 1430 cm$^{-1}$; 1H NMR (250 MHz, CDCl$_3$) $\delta$ 7.04–7.23 (m, 5 H, ArH), 6.69 (dd, 1 H, $J$ = 15.9, 8.0 Hz, C$_3$-H), 6.14 (dd, 1 H, $J$ = 15.9, 8.0 Hz, C$_3$-H), 3.81 (ppm) (50% ethyl acetate–hexane). Anal. Calcd for C$_9$H$_5$O$_2$: C, 76.36; H, 8.08.

To a cooled (−78 °C) solution of 1.5 g (5.2 mmol) of the starting ester 12 in 40 mL of anhydrous CH$_2$Cl$_2$ was added 13.8 g (20.8 mmol) of DIBAL. The solution was stirred for 1 h before 10 mL of acetone was added to quench the reaction. The solution was then warmed to rt, and 15 mL of 1 N aqueous solution of tartaric acid was added. The cloudy mixture was stirred for 30 min, and 20 mL of a concentrated aqueous solution of potassium hydroxide was added. The mixture was stirred for 30 min until a biphasic solution appeared. The aqueous phase was extracted three times with 40-mL portions of CH$_2$Cl$_2$, and the combined organic phases were dried over Na$_2$SO$_4$, filtered, and concentrated. Purification of the residue by chromatography (4 cm $\times$ 12 cm silica gel, 20% ethyl acetate–hexane) afforded 1.15 g (90%) of the desired alcohol 14 as a clear oil: [α]$_D$ +20.3$^\circ$ (c 2.88, CHCl$_3$); IR (CHCl$_3$) 3160–2800, 2750, 2400, 1725, 1630, 1600, 1580, 1540, 1510 cm$^{-1}$; 1H NMR (250 MHz, CDCl$_3$) $\delta$ 7.04–7.23 (m, 5 H, ArH), 6.69 (dd, 1 H, $J$ = 15.9, 8.0 Hz, C$_3$-H), 6.14 (dd, 1 H, $J$ = 15.9, 8.0 Hz, C$_3$-H), 3.81 (ppm) (50% ethyl acetate–hexane). Anal. Calcd for C$_9$H$_5$O$_2$: C, 76.36; H, 8.08.

To a cooled (−78 °C) solution of 1.5 g (5.2 mmol) of the starting ester 12 in 40 mL of anhydrous CH$_2$Cl$_2$ was added 13.8 g (20.8 mmol) of DIBAL. The solution was stirred for 1 h before 10 mL of acetone was added to quench the reaction. The solution was then warmed to rt, and 15 mL of 1 N aqueous solution of tartaric acid was added. The cloudy mixture was stirred for 30 min, and 20 mL of a concentrated aqueous solution of potassium hydroxide was added. The mixture was stirred for 30 min until a biphasic solution appeared. The aqueous phase was extracted three times with 40-mL portions of CH$_2$Cl$_2$, and the combined organic phases were dried over Na$_2$SO$_4$, filtered, and concentrated. Purification of the residue by chromatography (4 cm $\times$ 12 cm silica gel, 20% ethyl acetate–hexane) afforded 1.15 g (90%) of the desired alcohol as a colorless oil: [α]$_D$ +69.1$^\circ$ (c 1.30, CHCl$_3$); IR (CHCl$_3$) 3010–2920, 2400, 1700, 1650, 1560, 1530, 1380, 1360 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$) $\delta$ 7.41–7.27 (m, 10 H, ArH), 6.85 (dd, 1 H, $J$ = 15.9, 8.0 Hz, C$_3$-H), 6.13 (dd, 1 H, $J$ = 15.9, 8.0 Hz, C$_3$-H), 3.81 (ppm) (50% ethyl acetate–hexane). Anal. Calcd for C$_9$H$_5$O$_2$: C, 76.36; H, 8.08.

When the reaction mixture was then recooled to 0 °C and a solution of 23.6 mmol (30% ethyl acetate–hexane) was added. The mixture was then warmed to rt, and 12 mL of water was added to quench the reaction. The resulting mixture was partitioned between 70 mL of CH$_2$Cl$_2$ and 150 mL of brine. The aqueous layer was extracted with three 150-mL portions of CH$_2$Cl$_2$, and the combined organic phases were dried over Na$_2$SO$_4$, filtered, and concentrated. Purification of the residue by chromatography (4 cm $\times$ 12 cm silica gel, 20% ethyl acetate–hexane) afforded 1.15 g (90%) of the desired alcohol as a colorless oil: [α]$_D$ +20.3$^\circ$ (c 2.88, CHCl$_3$); IR (CHCl$_3$) 3160–2800, 1725, 1695, 1650, 1540, 1480, 1440, 1430 cm$^{-1}$; 1H NMR (250 MHz, CDCl$_3$) $\delta$ 7.04–7.23 (m, 5 H, ArH), 6.69 (dd, 1 H, $J$ = 15.9, 8.0 Hz, C$_3$-H), 6.14 (dd, 1 H, $J$ = 15.9, 8.0 Hz, C$_3$-H), 3.81 (ppm) (50% ethyl acetate–hexane). Anal. Calcd for C$_9$H$_5$O$_2$: C, 76.36; H, 8.08.
phases were washed with 20 mL portions of saturated NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. Purification of the residue by chromatography (3 cm × 15 cm silica gel, 25% ethyl acetate–hexane) afforded 1.41 g (77% yield) of the desired product 7b in 70 mL of a 10:3:1 mixture of ethyl acetate–hexane–tert-butyl methyl ether. The mixture was then dissolved in 40 mL of a 1:1 mixture of ethyl acetate–hexane. The solution was stirred for 18 h before being quenched by the addition of 50 mL of saturated aqueous sodium carbonate solution. The aqueous layer was then extracted three times with 50 mL of CH₂Cl₂ and the combined organic phases were dried over Na₂SO₄ and concentrated. Initial purification of the residue by chromatography (4 cm × 12 cm silica gel, 20% ethyl acetate–hexane) afforded a mixture of the desired product 7b and tert-butyldimethylsilanol (TBSOH). The mixture was then dissolved in 150 mL of saturated NaHCO₃ solution and the solution was stirred for 18 h before being quenched by the addition of 50 mL of saturated aqueous sodium carbonate solution. The aqueous layer was then extracted three times with 50 mL of CH₂Cl₂ and the combined organic phases were dried over Na₂SO₄ and concentrated. The residue was then purified by chromatography (3 cm × 15 cm silica gel, 25% ethyl acetate–hexane) to afford 0.77 g (95% yield) of the desired amide 8a as a yellow-orange heterogeneous solution.

Total Synthesis of (+)-Macbacin

540 mL (3.88 mmol) of anhydrous triethylamine was added to produce a deep brown solution which was stirred for 1 h. A solution of 1.27 g (3.17 mmol) of aldehyde 15 in 25 mL of CH2Cl2 was then transferred to the reaction mixture via cannula, and the mixture was cooled to 0 °C. The mixture was quenched by transferring the reaction mixture via cannula to a rapidly stirred 0 °C mixture of 250 mL of saturated aqueous sodium bicarbonate solution and 125 mL of CH2Cl2. The layers were separated, and the aqueous layer was extracted with an additional three 100-mL portions of EtOAc. The combined organic extracts were washed over Na2SO4, filtered, and concentrated. Purification of the residue by chromatography (5 cm × 12-cm silica gel, solvent gradient: 50% ethyl acetate–hexane to 70% ethyl acetate–hexane) afforded 1.49 g (81%) of the desired β-keto imide 19 as a yellow oil: [α]D +104° (c 1.00, CH2Cl2); IR (thin film) 3700–3200, 3090–2800, 1725, 1675, 1580, 1540, 1450, 1320, 1235 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.28 (d, 1 H, J = 3.2 Hz, ArH), 7.14 (d, 1 H, J = 3.2 Hz, ArH), 5.34 (d, 1 H, J = 10.2 Hz, C=H), 5.29 (d, 1 H, J = 5.9 Hz, C=H), 4.61 (d, 1 H, J = 2.5 Hz, C=H), 4.59 (d, 1 H, J = 4.7 Hz, C=H), 4.31 (d, 1 H, J = 4.7 Hz, C=H), 3.91 (s, 3 H, -OCH3), 3.83 (s, 3 H, -OCH3), 3.65 (s, 3 H, -OCH3), 3.33 (m, 2 H, C=H), 3.29 (s, 3 H, -OCH3), 2.97 (m, 1 H, C=H), 3.12 (s, 3 H, -OCH3), 3.12 (s, 3 H, -OCH3), 3.07 (s, 3 H, -NH2), 2.92 (m, 1 H, C=H), 2.67 (m, 1 H, C=H), 1.63 (m, 1 H, C=H), 1.16 (m, 3 H, J = 6.8 Hz, C5H5), 0.88 (observed d, 3 H, C(CH3)3), 0.88 (s, 9 H, C(CH3)3), 0.83 (d, 3 H, J = 6.8 Hz, C5H5), 0.83 (s, 9 H, C(CH3)3), 0.04 (s, 3 H, SiCH3), 0.04 (s, 3 H, SiCH3); 13C NMR (100 MHz, CDCl3) δ 203.7, 175.6, 171.4, 168.1, 154.8, 145.3, 137.5, 135.6, 127.9, 119.3, 108.5, 71.7, 62.8, 61.5, 60.3, 57.5, 57.0, 55.9, 47.6, 40.0, 38.3, 35.7, 31.8, 25.8, 24.4, 18.1, 14.9, 14.0, 12.1, 11.2, 4.6, -5.0; TLC Rf 0.25 (60% ethyl acetate–hexane).

To a cooled (0 °C) solution of 1.49 g (1.83 mmol) of the β-keto imide 19 in 80 mL of THF and 20 mL of H2O was added 2.19 g (91.6 mmol) of sodium lithium hydroxide. The reaction mixture was stirred at 0 °C for 5 min and then at rt for 3 h before being quenched by addition of 250 mL of pH = 4.5 NaHCO3 solution. The mixture was then accepted by three 150-mL portions of CH2Cl2. The combined organic layers were washed over Na2SO4, filtered, and concentrated. Purification of the residue by chromatography (5 cm × 12-cm silica gel, 35% ethyl acetate–hexane–2% acetic acid) afforded 870 mg (70%) of the desired ketone 20 as a yellow oil: [α]D +55° (c 0.88, CH2Cl2); IR (thin film) 3000–2800, 1720, 1670, 1540, 1435, 1350, 1255, 1235 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.28 (d, 1 H, J = 3.2 Hz, ArH), 7.16 (d, 1 H, J = 3.2 Hz, ArH), 5.03 (d, 1 H, J = 2.0 Hz, C5H5), 4.27 (m, 1 H, J = 2.0 Hz, C5H5), 4.16 (d, 1 H, J = 9.2 Hz, C5H5), 3.85 (s, 3 H, -OCH3), 3.84 (s, 3 H, -OCH3), 3.79 (d, 1 H, J = 3.7, 11.5 Hz, C5H5), 3.53 (s, 3 H, -OCH3), 3.47 (s, 3 H, -OCH3), 3.35 (s, 3 H, -OCH3), 3.24 (d, 1 H, J = 2.6, 8.8 Hz, C5H5), 2.97 (m, 1 H, C5H5), 2.93 (m, 1 H, C5H5), 2.25 (m, 1 H, C5H5), 1.50 (d, 3 H, J = 1.1 Hz, C5H5), 1.46 (m, 1 H, C5H5), 1.35 (d, 3 H, J = 6.9 Hz, C5H5), 1.03 (d, 3 H, J = 6.7 Hz, C5H5), 0.87 (s, 3 H, SiCH3), 0.61 (d, 3 H, J = 6.9 Hz, C5H5), 0.04 (s, 3 H, SiCH3), 0.04 (s, 3 H, SiCH3); 13C NMR (100 MHz, CDCl3) δ 175.4, 170.6, 154.9, 144.4, 144.3, 137.6, 133.2, 129.4, 118.5, 107.9, 94.2, 79.6, 77.1, 72.6, 51.8, 60.8, 57.7, 55.3, 35.8, 39.8, 37.4, 34.3, 31.4, 28.5, 17.6, 14.9, 11.2, -4.1, -7.4, -7.2, TLC Rf 0.66 (40% ethyl acetate–hexane); exact mass for C37H30O4N2S1+ requires m/z 820.3486, found m/z 820.3487 (FAB, m-nitrobenzyl alcohol, added Na).
of CH₂Cl₂; IR (thin film) 3650–3250, 3020–2820, 1650, 1540, 1470, 1370, 1260, 1240, cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.27 (d, 1 H, J = 8.2 Hz, ArH), 7.19 (d, 1 H, J = 3.2 Hz, ArH), 5.157, 5.149 (H, H₂-C₅H₁₁), 4.49 (d, 1 H, J = 4.5 Hz, CHO), 4.15 (d, 1 H, J = 9.0 Hz, C-H₃), 3.85 (s, 3 H, -OCH₃), 3.84 (s, 3 H, -OCH₃), 3.64 (s, 3 H, -OCH₃), 3.50 (m, 1 H, C-H₃), 3.44 (s, 3 H, -OCH₃), 3.26 (s, 3 H, -OCH₃), 3.08 (s, 3 H, -NCH₃), 2.98 (obscured m, 1 H, OCH₂), 2.77 (dd, 1 H, J = 5.1, 7.5 Hz, C-H₂), 2.48 (m, 1 H, C-H₃), 2.37 (d, 1 H, J = 5.0 Hz, -OH), 2.04 (m, 1 H, C-H₃), 1.56 (d, 3 H, J = 0.9 Hz, C₃-H₃), 1.49 (m, 2 H, C₂-H₂), 1.18 (d, 3 H, J = 6.3 Hz, C₃-H₃), 0.89 (s, 3 H, -CH₃), -0.01 (s, 3 H, -CH₃); ¹C NMR (100 MHz, CDCl₃): δ 203.9, 185.5, 145.5, 145.6, 139.0, 134.8, 130.6, 118.5, 108.5, 84.4, 61.8, 80.9, 77.8, 62.7, 60.8, 57.5, 56.9, 55.8, 51.1, 34.5, 33.8, 25.7, 17.9, 17.0, 13.1, 12.4, 9.4, -4.4, -5.1; TLC R₉ 0.50 (25% ethyl acetate–hexane); exact mass calcd for C₆H₅NO₂Si: Na + requires m/z 648.3544, found m/z 648.3528 (FAB, m-nitrobenzyl alcool, added Na)!

**Dimethyl 3-(Methoxycarbonyl)-3-methylprop-2-nylphosphonate (23a).** A mixture of 2.065 (10.6 mmol) of methyl (2E)-4-bromo-2-methyl-2-butenoate and 1.97 g (15.9 mmol) of trimethylphosphate was heated at 60 °C for 60 min. Distillation through a 5-cm Vigreux column (125 °C, 0.1 mm) afforded 1.73 g (73%) of the desired phosphonate 23a as a colorless oil (IR (CHCl₃) 2965, 1718, 1365, 1246 1506 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.73 (m, 1 H, C-H), 3.74 (d, 6 H, J = 11 Hz, POCH₃), 3.73 (s, 3 H, -OCH₃), 2.77 (dd, 2 H, J = 23, 8.3 Hz, C₃-H), 1.87 (br, 3 H, J = 4.4 Hz, C₃-H₃); ¹C NMR (100 MHz, CDCl₃) δ 167.1 (CO₂CH₃), 140.8 (J = 10 Hz, C₁₀), 129.5 (J = 11 Hz, C₁₀), 52.3 (J = 7 Hz, POCH₃), 51.4 (-OCH₃), 26.0 (J = 139 Hz, C₁₂), 12.0 (J = 3 Hz, C₃-H₃); exact mass calcd for C₇H₁₄O₆P: Na + requires m/z 245.0655, found m/z 245.0672 (FAB, m-nitrobenzyl alcohol, added Na)

**Bis(2,2-trifluoroethyl) 5-(Methoxycarbonyl)-3-methylprop-2-nylphosphonate (23e).** The neat phosphonate 23a (4.93 g, 22.2 mmol) was treated with 13.3 g (111 mg) of phosphorus pentachloride (PCl₅) to produce a colorless oil. Within 60 s the solid mass had become a free-flowing slurry which was stirred at rt for 2 h and then 75 °C for 6 h. The mixture was then cooled to room temperature, and the byproduct POCb and residual PCl₅ were removed in vacuo (POCl₅, 0.1 mm, rt; PCl₅, 0.1 mm, 75 °C). The unpurified dichloride was then dissolved in 30 mL of anhydrous benzene, and the resulting solution was cooled to 0 °C. In a separate flask, a solution of 19.3 mL (111 mmol) of Hunig's base in 30 mL of anhydrous benzene was treated with 8.10 mL (111 mg) of 2,2-trifluoroethyl bromide. There was then the transfer via cannula into 0 °C solution of the dichloride. The resulting deep orange solution was stirred at 0 °C for 30 min and then rt for 13 h before being concentrated and filtered through a plug of silica gel (5-cm × 12-cm silica gel, 60% ethyl acetate–hexane) to remove base-line material. The filtrate was concentrated, and the residue purified by chromatography (5-cm × 12-cm silica gel, solvent gradient: 25% ethyl acetate–hexane to 50% ethyl acetate–hexane) to afford 40% 6-ethyl 2-ethyl-3-(methylthio)-3-pentenoic acid, and 40% ethyl acetate–hexane; exact mass calcd for C₁₁H₂₀N₃O₅S: Na + requires m/z 707.3914, found m/z 707.3914 (FAB, m-nitrobenzyl alcohol, added Na).

**2-Ethyl-1-(2-methyl-3-pentynyl)ethanol (23b).** The title compound was prepared using a procedure exactly analogous to that described for the trifluoroethyl-derived phosphonate 23c: IR (CHCl₃) 3450, 3000–2800, 1705, 1650, 1450, 1380, 1350, 1260 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.66 (br, 1 H, J = 6.7 Hz, CH₃), 4.26 (m, 1 H, -OCH₂CH₃), 3.97 (m, 1 H, -CH₂CH₃), 3.72 (s, 3 H, -OCH₃), 2.93 (d, 2 H, J = 8.3, 5.6 Hz, C₃-H₃), 1.88 (br, d, 3 H, J = 5.1 Hz, C₃-H₃); ¹C NMR (100 MHz, CDCl₃) δ 170.7 (C₃=O), 165.9 (CH₂-C₃-H), 151.2 (J = 6.1 Hz, C₃), 137.2 (C₁₂), 125.0 (CH₃-Cl), 103.0 (CH₃); TLC R₉ 0.70 (60% ethyl acetate–hexane); exact mass calcd for C₇H₁₄O₂P: Na + requires m/z 277.0982, found m/z 277.0982 (FAB, m-nitrobenzyl alcohol, added Na)
Methyl (2E,4E,6Z,7E,8E,10S,11R,12S,14S,15R)-7-((tert-butyldimethylsiloxy)-15-((3,5-dimethoxy-3-nitrophenoxy)-11,12,15-trimethoxy-2,6,8,10,14-pentamethyl-2,4,4,8,8-pentadecatrienoate (28(Z)) and Methyl (2E,4E,6Z,7E,8E,10S,11R,12S,14S,15R)-7-((tert-butyldimethylsiloxy)-15-((3,5-dimethoxy-3-nitrophenoxy)-11,12,15-trimethoxy-2,6,8,10,14-pentamethyl-2,4,4,8,8-pentadecatrienoate (28(E)). To a cooled (-78 °C) solution of 706 mg (1.97 mmol) of phosphonate 23e in 10 mL of anhydrous Et2O was added 1.20 mL (1.97 mmol) of n-BuLi (1.64 M in hexane) to produce a peach solution. The solution was stirred at -78 °C for 15 min and then -20 °C for 15 min before being recooled to -78 °C. A cooled (-78 °C) solution of 154 mg (0.246 mmol) of aldehyde 24 in 3 mL of anhydrous Et2O was then transferred to the reaction mixture via cannula, and the resulting mixture was stirred for 4 h at -78 °C to -60 °C. The reaction mixture was then quenched with 50 mL of saturated ammonium chloride solution.

The layers were separated and the aqueous layer was extracted with three 50-mL portions of CH2Cl2. The combined organic layers were dried over Na2SO4, filtered, and concentrated. The 1H NMR (500-MHz, CDCl3) spectrum of the residue showed the reaction to have proceeded with ~3:1 selectivity (E/Z). Purification of the residue by chromatography (23: 6 cm × 12 cm, 6% ethyl acetate, CH2Cl2) afforded 83 mg of the undesired ester (25(E)) and some recovered phosphonate 23c, in addition to 139 mg (78%) of the desired E,Z unsaturated ester (25(Z)), contaminated with ~5% of recovered aldehyde 24. For the unsaturated ester (25(Z)) follow: [a]D +53.2° (c 0.70, CH2Cl2); IR (thin film) 2960–2980, 1795, 1735, 1700, 1600, 1530, 1500, 1280 cm−1; 1H NMR (500 MHz, CDCl3) δ 7.40 (d, 1 H, J = 10.7 Hz, C1-H), 6.78 (d, 1 H, J = 8.7 Hz, C15-H), 3.82 (t, 3 H, J = 8.0 Hz, C15-OCH3), 3.75 (d, 1 H, J = 5.0 Hz, C13-H), 3.62 (d, 1 H, J = 5.0 Hz, C13-CHO), 3.21 (s, 3 H, -OCH3), 3.18 (s, 3 H, -OCH3), 2.91 (s, 3 H, -OCH3), 2.85 (s, 3 H, -OCH3), 2.65 (s, 3 H, -OCH3), 2.03 (s, 3 H, -OCH3), 1.92 (s, 3 H, -OCH3), 1.49 (s, 3 H, C13-CH3), 1.35 (s, 3 H, -OCH3), 1.27 (s, 3 H, -OCH3), 1.20 (s, 9 H, (CH3)3Si).

To a solution of 74 mg (0.107 mmol) of BOP-C1. The solution was stirred at this point for 3 h. To this solution was added 7 mg (0.108 mmol) of anhydrous Ph2CH2Cl2 and the solution was then filtered through short column of anhydrous Et3N (CH2Cl2) afforded 72 mg (99%) of the desired unsaturated ester (27). The data for the unsaturated ester (27) follow: [α]D +53.2° (c 0.70, CH2Cl2); IR (thin film) 2960–2980, 1795, 1735, 1700, 1600, 1530, 1280 cm−1; 1H NMR (500 MHz, CDCl3) δ 7.40 (d, 1 H, J = 10.7 Hz, C1-H), 6.78 (d, 1 H, J = 8.7 Hz, C15-H), 3.82 (t, 3 H, J = 8.0 Hz, C15-OCH3), 3.75 (d, 1 H, J = 5.0 Hz, C13-H), 3.62 (d, 1 H, J = 5.0 Hz, C13-CHO), 3.21 (s, 3 H, -OCH3), 3.18 (s, 3 H, -OCH3), 2.91 (s, 3 H, -OCH3), 2.85 (s, 3 H, -OCH3), 2.65 (s, 3 H, -OCH3), 2.03 (s, 3 H, -OCH3), 1.92 (s, 3 H, -OCH3), 1.49 (s, 3 H, C13-CH3), 1.35 (s, 3 H, -OCH3), 1.27 (s, 3 H, -OCH3), 1.20 (s, 9 H, (CH3)3Si).
40% frequently show ions corresponding to quinone 29B in 2 mL of anhydrous CH$_2$Cl$_2$ was added 12.6 mg (194 µmol) of sodium cyanate and 15.0 mL (194 µmol) of trifluoroacetic acid. The mixture was stirred at 0 ºC for 5 min and at ambient temperature for 3 h before quenching with Na$_2$S$_2$O$_4$ solution. The solution was diluted with 10 mL of CH$_2$Cl$_2$ and the reaction quenched by addition of 10 mL of NaHCO$_3$ solution. The product was extracted with 20 mL portions of CH$_2$Cl$_2$ and dried over Na$_2$SO$_4$. Purification by preparative TLC (0.5 mm, EtOAc) afforded 1.2 mg (30 %) of recovered 29B and 1.8 mg (41%) of synthetic macbeein I: [α]$_D$ $^{+348}$ (c 0.11, CHCl$_3$). (lit. Muroi [α]$_D$ $^{+351}$ (c 0.10, CHCl$_3$), Baker [α]$_D$ $^{+362}$ (c 0.10, CHCl$_3$); IR (CHCl$_3$) 3480, 2920, 2930, 2930, 2930, 1740, 1655, 1655, 1650, 1565, 1540, 1375, 1325, 1240, 1085 cm$^{-1}$; $^{1}$H NMR (400 MHz, CDCl$_3$) δ 6.88 (br s, 1 H, NH), 7.23 (d, 1 H, J = 11.7 Hz, C$_8$H), 6.60 (dd, 1 H, J = 2.5, 1.5 Hz, QuH), 6.33 (dt, 1 H, J = 12.1, 1.8 Hz, C$_8$H), 5.60 (br s, 1 H, C$_8$H), 4.69 (br s, 1 H, NH), 4.57 (br s, 1 H, CH$_3$), 3.54 (br s, 1 H, C$_8$H), 3.32 (s, 3 H, C$_8$H), 3.29 (s, 3 H, C$_8$H), 2.50 (br s, 1 H, C$_8$H), 1.08 (s, 3 H, C$_8$H), 0.98 (s, 3 H, CH$_3$), 0.68 (s, 3 H, C$_8$H), 0.98 (s, 3 H, C$_8$H), 1.49 (m, 1 H, C$_8$H), 1.48 (s, 3 H, C$_8$H), 1.08 (d, 3 H, J = 6.5 Hz, C$_8$H), 1.02 (s, 3 H, C$_8$H), 0.79 (s, 3 H, C$_8$H), 0.79 (s, 3 H, C$_8$H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 187.7, 184.3, 168.8, 145.7, 144.8, 138.3, 136.6, 132.7, 132.5, 129.4, 128.9, 122.6, 112.9, 106.2, 83.3, 74.2, 73.4, 68.6, 68.3, 59.9, 58.5, 56.0, 36.7, 34.1, 25.1, 18.3, 15.6, 15.0, 13.4, 12.8, 12.3, 3.9, 4.6; TLC R$_f$ 0.96 (EtOAc); exact mass calcd for C$_{40}$H$_{46}$N$_{2}$O$_{4}$ Na $^{+}$ requires m/z 652.3684; found m/z 652.3682; exact mass$^{48}$ calcd for C$_{40}$H$_{46}$N$_{2}$O$_{4}$ Na $^{+}$ + Na $^{+}$ requires m/z 654.3592; found m/z 654.3592 (FAB, m-nitrobenzyl alcohol, Na$^{+}$ added).

Methyl (2E,4E,6E,7E,10E,12E,14E,16E,17E)-9-hydroxy-13,14,17-trimethoxy-4,8,10,12,15-pentamethyl-2-azabicyclo[16.3.1]docosa-4,6,10,13,17-pent~n~3JOJ2-triacetate (26E). The reduction was performed in direct analogy to the method used to produce 2(2Z) to afford 2(2E) in essentially quantitative yield. The product was immediately used in the next reaction without further purification. Purification by preparative TLC (0.5 mm plate, 20% ethyl acetate–hexane) afforded 1.0 mg (10%) of recovered 33 and 4.0 mg (51%) of the desired alcohol 29B as a yellow glass: [α]$_D$ $^{+208}$ (c 0.20, CHCl$_3$); IR (CHCl$_3$) 3385, 2970, 2930, 2800, 1700, 1660, 1605, 1575, 1250, 1050, 1030 cm$^{-1}$; $^{1}$H NMR (600 MHz, CDCl$_3$) δ 8.63 (br s, 1 H, NH), 7.32 (d, 1 H, J = 2.4 Hz, QuH), 7.13 (d, 1 H, J = 11.8 Hz, C$_8$H), 6.69 (apparent t, 1 H, J = 1.7 Hz, QuH), 6.38 (apparent t, 1 H, J = 11.9 Hz, C$_8$H), 5.86 (br t, 1 H, J = 7.2 Hz, QuH), 5.51 (d, 1 H, J = 9.3 Hz, C$_8$H), 4.61 (br s, 1 H, C$_8$H), 4.55 (s, 1 H, C$_8$H), 3.55 (s, 3 H, OCH$_3$), 3.52 (s, 1 H, C$_8$H), 3.35 (s, 3 H, OCH$_3$), 3.31 (s, 3 H, OCH$_3$), 3.26 (d, 1 H, J = 9.4 Hz, C$_8$H), 3.03 (m, 1 H, C$_8$H), 2.48 (m, 1 H, C$_8$H), 2.00 (m, 3 H, C$_8$H), 1.68 (m, 3 H, C$_8$H and C$_8$H).

(58) Mass spectra of molecules containing the quinone moiety frequently show isomeric molecular spectra in addition to that corresponding to the reduced hydquinone system. For details on the mass spectrometry of quinone-containing natural products, see: Ishihara, Y.; Shirahata, K.; Sano, H. J. Antibiot. 1989, 42, 49–55 and references therein.
Total Synthesis of (+)-Macbecin

H, Clr-H), 1.83 (s, 3 H, C7-CH3), 1.60 (m, 1 H, one of C12-H), 1.52 (s, 3 H, C9-CH3), 1.35 (m, 1 H, one of C12-H), 1.05 (d, 3 H, J = 6.6 Hz, C6-CH3), 0.95 (m, 3 H, J = 6.6 Hz, C6-CH3), 0.89 (s, 9 H, Si(CHO)3), 0.89 (d obscured, 3 H, C13-CH3), 0.01 (s, 3 H, SiCH3), -0.04 (s, 3 H, SiCH3).

(4E,6E,8S,9S,10E,12S,13R,14S,16S,17R)-9-(tert-Butylidimethylsililoxy)-13,14,17,20,22-pentamethoxy-4,8,10,12-pentamethyl-2-azabicyclo[6.1.0]nonan-3-one (28(2)) (identified by comparison of the corresponding 500-MHz 1H NMR spectra with those measured with authentic samples confirmed their identities.)

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Supplementary Material Available: 1H or 13C NMR spectra for those compounds which have been submitted to high-resolution mass spectral analysis in lieu of combustion analysis (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfiche version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.