Chiral Crotylsilane-Based Approach to Benzoquinoid Ansamycins: Total Synthesis of (+)-Macbecin I

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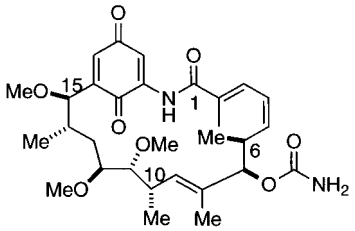
Abstract: A highly convergent total synthesis of the antitumor antibiotic (+)-macbecin I (**1**) has been achieved through the homologation of the aldehyde **3** (C5−C21 aromatic fragment) to the *E,Z*-dienoate **2** by employing a sequential olefination strategy. Subsequent macrolactonization and a final two-step oxidation sequence were the principle steps used to complete the synthesis. Six of the seven syn-stereochemical relationships (C6−C7, C10−C11, and C14−C15) were introduced using our asymmetric crotylation bond construction methodology. The C12 stereocenter was introduced by an alkoxy-directed hydroboration reaction. An alternative strategy for introducing the C10 stereo center via a diastereoselective hydroboration reaction of 1,1-disubstituted olefin **6b** provided a more atom efficient approach to intermediate **7**.

Introduction

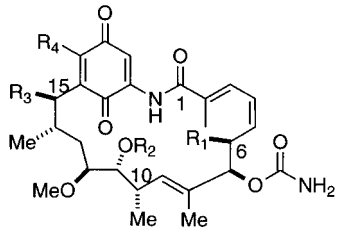
(+)-Macbecin I (**1**) is a member of the class of biologically active ansamycin antibiotics (Figure 1). Structurally, these natural products can be divided into two broad classes, naphthalenic ansamycins and benzenic ansamycins.[1] The naphthalenic ansamycins also include the rifamycins, streptovaricins, tolypomycin, and naphthomycin; the benzenic ansamycins include maytansine, geldanamycin, colubrinol, herbimycin, and macbecin (Figure 2). The well-known maytansines were once advocated as promising antitumor agents, and rifamycin is used clinically as an antitubercular and antibacterial drug.[2]

Macbecin I (**1**) and its hydroquinone analogue macbecin II were isolated in 1980.[3] The structures and absolute stereochemistry of these natural products were determined by X-ray crystallography.[4] A stereoview of a minimized conformation of (+)-macbecin I illustrates its topological characteristics (Figure 3). An X-ray structure was also obtained for herbimycin A,[5] and the absolute configurational assignment was confirmed by total synthesis.[6] The stereochemistry of geldanamycin has not yet been published, although circumstantial evidence suggests that there is a common biosynthetic pathway, and hence is analogous to those of herbimycin A and macbecin I. The antibiotics possess a 19-membered ring lactam in which the ansa chain is linked to a substituted benzoquinone ring at the meta position. The complex ansa chain contains seven stereogenic centers, an isolated trisubstituted double bond, and a (*Z,E*)-diene (Figure 1).



1 (+)-Macbecin I

Figure 1. (+)-Macbecin I (**1**).



Compound	R_1	R_2	R_3	R_4
Herbimycin A	OMe	H	OMe	H
Herbimycin B	OMe	H	OMe	H
Herbimycin C	OMe	Me	H	H
Geldanamycin*	OMe	H	H	OMe

*stereochemistry not assigned

Figure 2. Representative structures of related ansamycins.

The biological activities and the structural complexity exhibited by the benzoquinoid ansamycins make them attractive molecules for synthesis. Over the past few years, two total syntheses of (+)-macbecin I (**1**) have been reported by Baker[7]

(1) (a) Lüttringhaüs, A.; Gralheer, H. *Justus Liebigs Ann. Chem.* **1942**, *67*, 550−552. (b) Prelog, V.; Oppolzer, W. *Helv. Chim. Acta* **1973**, *56*, 2279−2285.

(2) (a) Burfani, M.; Kluepfel, D.; Lancini, G.; Leitish, J.; Mesentser, A. S.; Prelog, V.; Schook, F. P.; Sensi, P. *Helv. Chim. Acta* **1973**, *56*, 2315−2318. (b) White, R. J.; Martinelli, E.; Gallo, G. G.; Lancini, G. *Nature* **1973**, *243*, 273−275. (c) Karlsson, A.; Sartori, G.; White, R. J. *Eur. J. Biochem.* **1974**, *47*, 251−253. (d) Johnson, R. D.; Haber, A.; Rinehart, K. L. *J. Am. Chem. Soc.* **1974**, *96*, 3316−3318. (f) Haber, A.; Johnson, R. D.; Rinehart, K. L.; *J. Am. Chem. Soc.* **1977**, *99*, 3541−3342.

(3) (a) Yamakim, H.; Iguchi-Ariga, S.; Ariga, H. *J. Antibiot.* **1989**, *42*, 604−610. (b) Tanida, S.; Hasegawa, T.; Higashide, E. *J. Antibiot.* **1980**, *33*, 199−204.

(4) Muroi, M.; Haibara, K.; Asai, M.; Kamiya, K.; Kishi, T. *Tetrahedron* **1981**, *37*, 1123−1130.

(5) Furusaki, A.; Matsumoto, T.; Nakagawa, A.; Omura, S. *J. Antibiot.* **1980**, *33*, 781−785.

(6) Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 6015−6018.

(7) (a) Baker, R.; Castro, J. *J. Chem. Soc., Chem. Commun.* **1989**, 378−381. (b) Baker, R.; Castro, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47−65.

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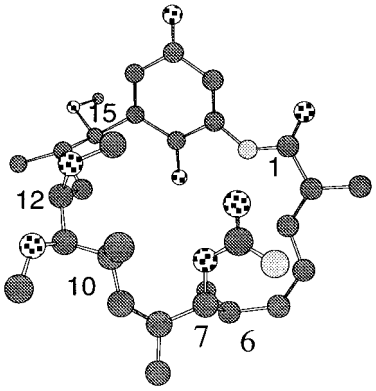


Figure 3. (+)-Macbecin I 3-D view (calculated with Chem3D Pro using MM2 minimization techniques).

and Evans[8] and formal syntheses have been reported by Martin[9] and Kallmerten.[10] Our first approach to the total synthesis of **1** was published in 1995.[11]

Synthetic Analysis

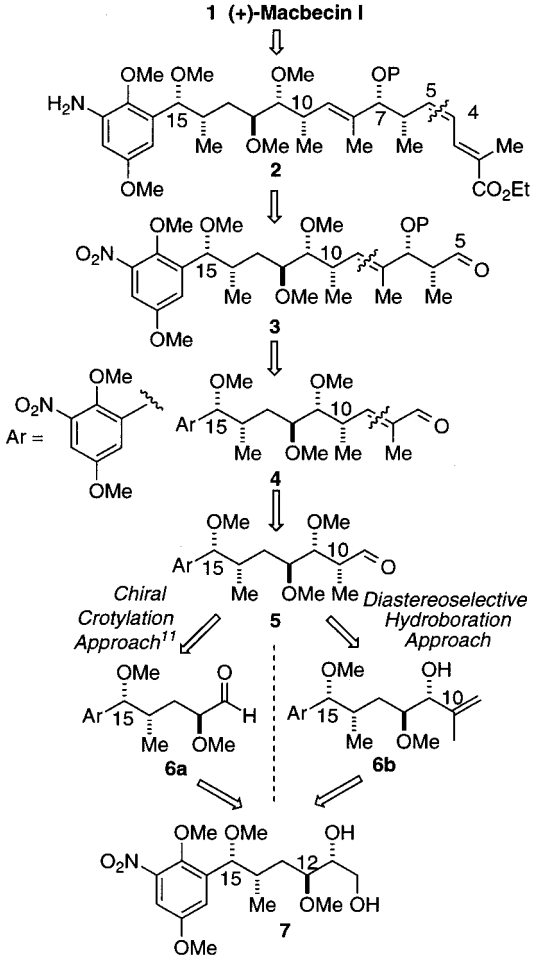
It was our intention to design a pathway that could address the stereoselective installation of the stereogenic centers utilizing our chiral (*E*)-crotylsilane methodology. The use of these silane reagents bearing C-centered chirality represents a fundamentally different approach from chiral enolate based bond construction commonly used in the preparation of stereochemically complex molecules. A retrosynthetic analysis of **1** suggested that a first disconnection at the amide bond would provide an acyclic precursor seco acid **2** (Scheme 1). The macrolactonization of such an intermediate is well-precedented in the syntheses of benzenoid ansamycins maytansine and (−)-*N*-methylmaytansine,[12] as well as in the previous two syntheses of (+)-macbecin I.[7,8] Further disconnection of the diene moiety resulted in the advanced intermediate **3**, which contains all seven resident stereogenic centers of the target. The C6−C7 syn relationship of the hydroxy and methyl groups was established by addition of chiral crotylsilane **9c** to advanced α,*β*-unsaturated aldehyde **4** under Lewis acid-catalyzed conditions. Disconnection at the double bond simplified the structure to intermediate **5** that was synthesized using two distinct approaches. The first route involved the 1,2-diol cleavage of intermediate **7** and addition of crotylsilane **9b** to the resulting aldehyde **6a**.[11] The second approach relied on a diastereoselective hydroboration of the allylic alcohol **6b**, which was also derived from diol **7**, introducing the syn relationship between C10 and C11. Intermediate **7** was prepared from adduct **8,** which was obtained through a Lewis acid-promoted diastereoselective addition reaction between chiral crotylsilane **9a** and dimethyl acetal **10**, followed by a heteroatom-directed hydroboration (Figure 4).[13]

Results and Discussion

Construction of C11−C21 Aromatic Fragment. The synthesis of (+)-macbecin I (**1**) was initiated with the assemblage of the C11−C21 aromatic fragment which relied on our chiral crotylsilane bond construction methodology.[14] The Lewis acid-promoted addition **9a** to dimethyl aryl acetal **10** allowed the assemblage of a highly functionalized intermediate **8**, which included three stereogenic centers of the original target molecule. Our design thoughts in this area were as follows: the 2,5-dimethoxy-5-nitro core of this intermediate should be easily converted into the aminobenzoquinone moiety of the natural product after macrolactonization. The α-benzyloxy ester functionality facilitates the alkoxy-directed hydroboration reaction to introduce the C12 stereocenter with high stereoselectivity (vide infra).[13] This benzyloxy substituent not only played a crucial role during the installation of C12 but also was necessary to access intermediate **7**, allowing the successful introduction of C10 (vide infra). The synthesis of **8** was initiated by construction of the dimethoxy aryl acetal **10**, which is derived from *p*-methoxyphenol.[15] The desired 2,5-dimethoxy-3-nitrobenzyl dimethyl acetal **10** was obtained as a yellow oil in four steps and in 52% overall yield. In accordance with our previous reports,[16] combining acetal **10** and chiral crotylsilane **9a** in CH_2Cl_2, in the presence of a catalytic amount of TMSOTf (0.5 equiv) at −78 °C for 16 h, afforded the desired adduct **8** as a single diastereomer (>30:1 syn/anti) in 89% yield.

Introduction of the C12 Stereocenter. At this point, we were faced with the task of devising a regio- and stereoselective oxygenation reaction of the isolated trans double bond of the

Scheme 1



(8) (a) Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, *57*, 1067−1069. (b) Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471−485.

(9) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Hartmann, M. *J. Org. Chem.* **1992**, *57*, 1070−1072.

(10) Kallmerten, J.; Eshelman, J. E.; Epps, J. L. *Tetrahedron Lett.* **1993**, *34*, 749−752.

(11) Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587−10588.

(12) (a) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, C.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6612−6615. (b) Corey, E. J.; Weihel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439−1441.

(13) Panek, J. S.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5288−5290.

(14) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.

(15) Rubenstein, L. *J. Chem. Soc.* **1925**, *127*, 1998−2004.

(16) Panek, J. S.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5790−5792.

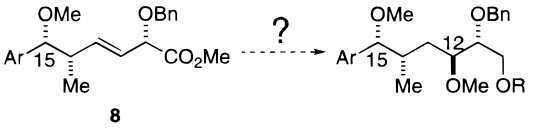
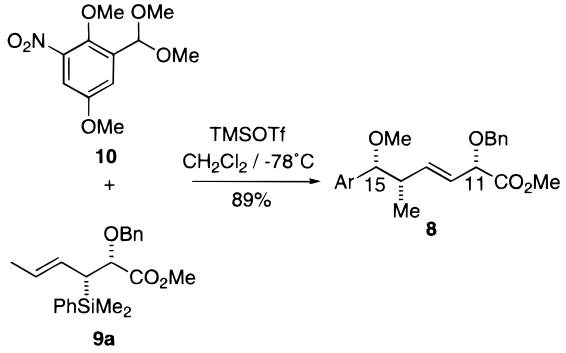
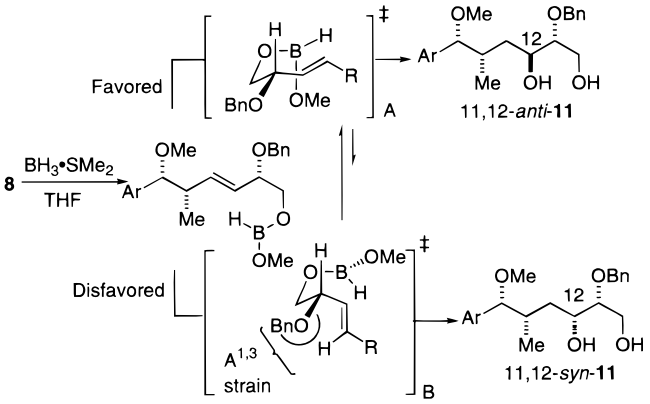


Figure 4. Required stereoselective oxygenation of **8**.

Scheme 2



Scheme 3

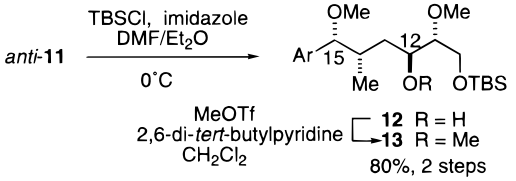


C11−C15 aromatic subunit **8**. Figure 3 illustrates the required transformation, given the fact that we had an efficient route to install three of the seven stereocenters in compound **8** through the use of asymmetric crotylation chemistry.

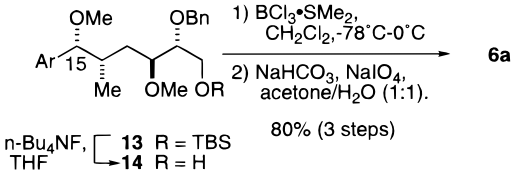
We envisioned the possibility of oxygenating the *E* double bond of the α-alkoxy-*β*,*γ*-unsaturated methyl ester **8** by a borane methyl sulfide hydroboration reaction. Gratifyingly, we encountered what seemed to be an intramolecular process, wherein the directing alkoxy group is produced from a selective borohydride reduction of the methyl ester, resulting in good levels of regio- and diastereoselection (Scheme 3).[13] Methyl ester **8** was treated with BH_3•SMe_2 (1.05 equiv) in THF at 0 °C for 2 h, before it was allowed to warm to room temperature (rt) for 16 h. The reaction mixture was then oxidized by alkaline hydrogen peroxide (4−5 equiv) at 0 °C. The desired 1,3-diol **11** was obtained with 8.5−11:1 anti/syn (C11/C12) diastereoselection in 85% isolated yield. The stereochemical course of this reaction is consistent with an intramolecular mechanism and suggests that the α-alkoxy group adjacent to the carbonyl plays a crucial role in this process. It appears to be responsible for polarizing the adjacent double bond, thereby reinforcing the positional and olefin face selectivity of the hydroboration pathway. It also enhances the rate of carbonyl reduction, so that it competes favorably with the intermolecular olefin hydroboration pathway, achieving the selective formation of the boronate-like intermediate.[13,17]

Selective protection of the primary alcohol of **11** using TBSCl (1.05 equiv) and imidazole (4−5 equiv) in anhydrous DMF/Et_2O at 0 °C, followed by methylation of the secondary alcohol

Scheme 4



Scheme 5



under mild conditions (2,6-di-*tert*-butylpyridine, MeOTf, CH_2Cl_2, rt), afforded intermediate **13** in approximately 80% overall yield (Scheme 4). When a stronger base (NaH) was employed to generate the C12 alkoxide in the methylation, an S_N-Ar-type (IPSO) intramolecular substitution at the *o*-methoxy group by the alkoxide led to formation of a cyclic aryl ether.[18]

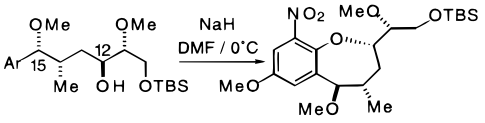
At this stage, four of the seven stereocenters (C11, C12, C14, and C15) have been assembled in only two steps (asymmetric crotylation and heteroatom-directed hydroboration) with two subsequent steps for primary alcohol protection and methyl ether formation. With intermediate **13** in hand, introduction of C10 stereogenic center was pursued.

Installation of the C10 Stereogenic Center. A closer examination of adduct **5**, revealed that the C10−C11 bond could be constructed by a double stereodifferentiating aldol condensation or perhaps a crotylation reaction. This was especially suitable for an in situ-generated oxocarbenium addition between crotylsilane **9b** and aldehyde **6a**. By employing this three-component reaction system, we can establish a syn relationship between the methoxy and the methyl groups in a single step with high levels of diastereoselection. The strategy began with the cleavage of the primary silyl ether **13** to afford the intermediate alcohol **14** in quantitative yield (Scheme 5).

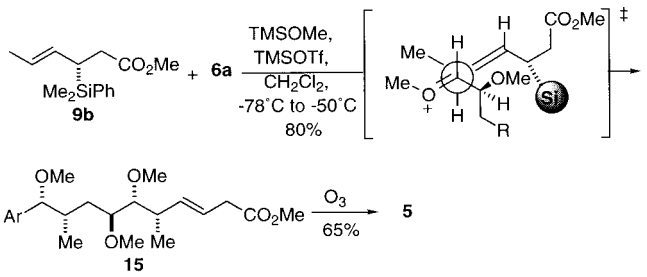
The crucial debenzylation was first carried out with BCl_3 (1.5 equiv) in CH_2Cl_2 at −78 °C. It is important to note that with more equivalents of BCl_3 or a higher reaction temperature, the aromatic fragment was also cleaved from the main acyclic chain. However, if the same transformation was performed with BCl_3•SMe_2 (2.0 equiv) in CH_2Cl_2 from −78 to 0 °C, the desired 1,2-diol was obtained in 95% isolated yield. The 1,2-diol bond cleavage was accomplished by $NaIO_4$ and $NaHCO_3$ in acetone/H_2O at room temperature to provide aldehyde **6a** in 80% yield (three steps from **13**). After obtaining the α-methoxy aldehyde **6a**, we then addressed the critical double-stereodifferentiating crotylation reaction for the introduction of the C10/C11 stereocenters. Aldehyde **6a** was combined with TMSOMe and crotylsilane **9b** in CH_2Cl_2 and subsequently treated with TMSOTf (2 equiv) from −78 to −50 °C for 48 h. This three-component reaction system afforded the desired crotylation

(17) The selective reduction of α-hydroxy esters with BH_3•SMe_2 in combination with $NaBH_4$ has been reported. See: (a) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fuji, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389−1392. (b) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067−4086.

(18) Spectral data are consistent with the following structure:



Scheme 6



adduct **15** in 80% isolated yield, with a diastereoselection of 12:1 favoring the syn homoallylic ether (Scheme 6). This syn bond construction reinstalled the C11 stereocenter and introduced the C10 methyl group. Unfortunately, the reaction did not go to completion when the temperature was maintained below −50 °C or when less than 2 equiv of TMSOTf was used to promote the reaction. The lower reactivity and diastereoselection of this process may result from a mismatched transition state between chiral aldehyde **6a** and chiral silane reagent **9b**, with the C11−C12 stereocenters emerging with an anti-Felkin stereochemical relationship, as the crotylation is illustrated with the antiperiplanar transition state (Scheme 6).[19] Although the selectivity of this reaction did not reach the levels obtained in the acetal additions previously described, the chiral silane reagent is still capable of overriding the chirality of aldehyde **6a**, determining the stereochemistry of this double-stereodifferentiating reaction.

The C8/C9 trisubstituted double bond was elaborated through ozonolysis of olefin **15** to obtain aldehyde **5**, which was also synthesized by means of an uncatalyzed hydroboration of the terminal allylic alcohol **6b** (vide infra). Even though C10 was successfully installed using a crotylation reaction, a more atom economical approach that would preserve the C11 stereocenter installed in the first addition of aryl acetal **10** and crotylsilane **9a**, giving us an alternative route with higher efficiency, was then undertaken. In 1992, Evans and co-workers[20] reported that 1,1-disubstituted olefins can be converted to terminal alcohols with high levels of syn diastereoselection between the newly formed stereocenter C2 and a preexisting C3 stereocenter by using catechol borane and $RhCl(Ph_3P)_3$ (Wilkinson's catalyst). This catalyzed hydroboration provided the complimentary stereochemistry of the uncatalyzed hydroboration of 1,1-disubstituted olefins using bulky dialkylboranes (Figure 5). Although the mechanism of the stereochemical-determining step of this reaction is not fully understood,[20] a sufficient number of examples were documented to make this a viable option. However, treatment of the intermediate **19** with $RhCl(Ph_3P)_3$ and freshly distilled catechol borane in THF at room temperature for 16 h followed by neutral oxidation with H_2O_2 and KH_2PO_4−NaOH buffer (pH = 7) afforded a mixture of 6:1 primary alcohols in 66% yield. Unfortunately, this transformation favored the formation of the incorrect C10 isomer, which was confirmed by analysis of the ^{1}H NMR of the corresponding acetonides.

As an alternative route to install C10/C11 using the proposed hydroboration of the 1,1-disubstituted terminal olefin, treatment of allylic alcohol **6b** under uncatalyzed hydroboration conditions

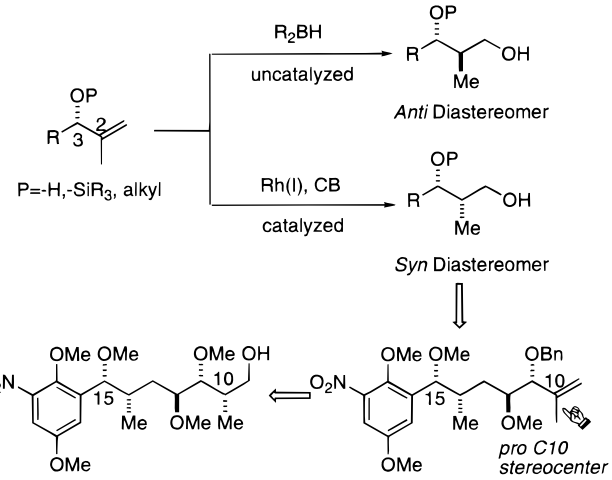
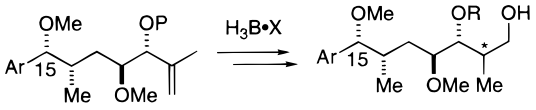
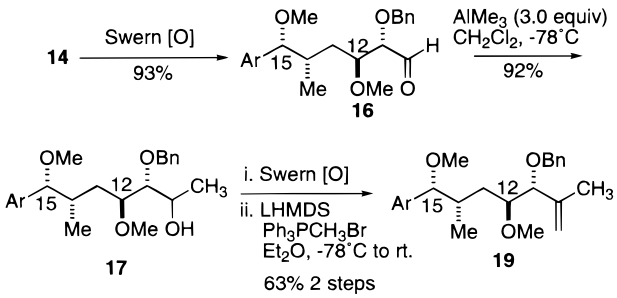


Figure 5. Comparison of Rh(I)-catalyzed and uncatalyzed hydroboration.

Scheme 7



Scheme 8



appeared to be a feasible approach based on a similar transformation reported by Tatsuta[6] and co-workers in the total synthesis of herbimycin A (Scheme 7). Similar findings were also reported by Paterson and Channon.[21]

The synthesis of the 1,1-disubstituted olefin intermediate **19** was initiated by a Swern oxidation of **14**, which afforded the α-benzyloxy aldehyde **16** in 93% yield (Scheme 8). Treating aldehyde **16** with Me_3Al in CH_2Cl_2 at −78 °C for 15 min afforded the desired secondary alcohol **17** in 92% yield with good levels of diastereoselection (>12:1).[22] The final construction of the intermediate terminal olefin **19** from **17** was accomplished by a stepwise Swern oxidation and Wittig homologation (LHMDS, Ph_3PCH_3Br, Et_2O, −78 °C to rt) sequence in 63% overall yield. The solvent employed had a significant impact on the outcome of the Wittig reaction. When THF was used as the solvent, a dramatic drop in the yield (∼40%) of the reaction was observed.

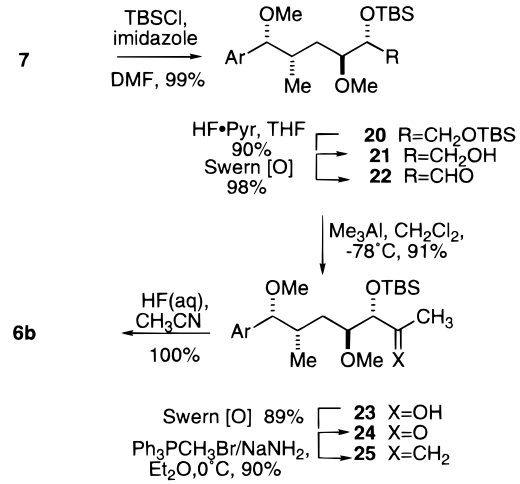
(19) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−76.

(20) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671−6679. (b) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679−6685. (c) Burgess, K.; Donk, W. A.; Westcott, S. A.; Marder, T. B.; Baker, R. T.; Calabrese, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 9350−9359.

(21) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797−800.

(22) Nucleophilic additions to aldehyde **16** under alkaline conditions (CH_3MgBr, MeLi, $(CH_3)_2CuLi$) did not provide useful yields of desired alcohol. When CH_3MgBr was used in the reaction at −100 °C in Et_2O or THF, no desired product could be isolated and the starting aldehyde had decomposed extensively. The cuprate reagent gave low yields (∼20%) in Et_2O, while the MeLi provided a mixture (∼3:1) of desired secondary alcohols in about 40−50% yield in Et_2O and 20−30% yield in THF at −100 °C. The poor results from these reactions may be due to the electron-withdrawing effect of the aromatic nitro group, as it is capable of activating the adjacent methyl group to nucleophilic substitution. Methyl nucleophiles, therefore, attack the aromatic methyl, resulting in demethylation of the benzenic ring.

Scheme 9



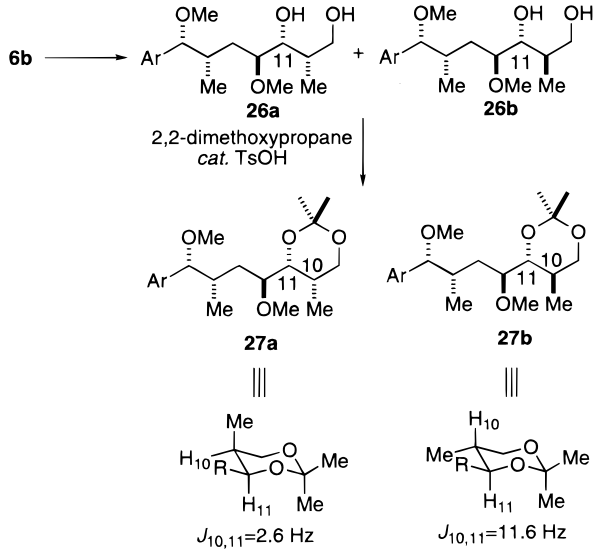
Hydroboration of olefin **19** with BH_3·THF in THF afforded a mixture of primary alcohols in a 1.5:1 diastereomeric ratio favoring the syn isomer (desired product). Alkylboranes (catechol borane, 9-BBN, or (+)-IPC_2BH) all favored formation of the anti product. The chiral borane reagents had no significant effect on the diastereomeric outcome of this reaction.

Attempts to remove the benzyl group from intermediate **19** and perform the hydroboration with the free hydroxy group failed to provide the required alcohol **6b**. Deprotection attempts with $TiCl_4$, BCl_3, BBr_3, BCl_3·SMe_2, and lithium naphthalenide were among the different conditions that were surveyed. A more labile protecting group was then necessary. Taking into account that the benzyloxy group was a crucial unit for the heteroatom-directed hydroboration, the new protective group had to be introduced at a later stage. A silicon-based protecting group strategy at C10 was envisioned to be sufficiently stable to the reaction sequence yet easily removed under acidic conditions to achieve intermediate **6b**. Therefore, a TBS-protected ether was introduced at the 1,2-diol **7**. Protection of both hydroxyl groups using TBSCl (2.5 equiv) and imidazole (6 equiv) in DMF at 0 °C, followed by selective deprotection of the primary TBS ether under HF·pyridine conditions, afforded the corresponding alcohol **21** in excellent yield (89%, two steps). Following the same synthetic sequence as described in Scheme 8, to construct the terminal double bond, the desired intermediate **25** was obtained in six steps 64% overall yield. Removal of the silyl protecting group using 48% aqueous HF in CH_3CN at room temperature proceeded in quantitative yield, affording pure allylic alcohol **6b** (Scheme 9).

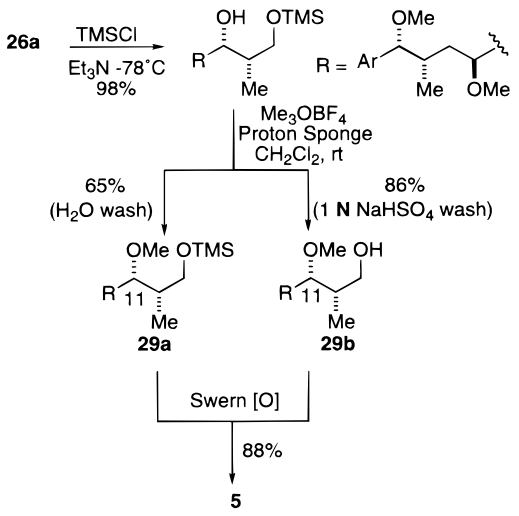
Hydroboration of terminal allylic alcohol **6b** gave low selectivities when BH_3·SMe_2 was used as the hydroborating agent. However, in the presence of BH_3·THF, the 1,3-diols were obtained in excellent yield (98%) as a 5−7:1 syn/anti diastereomeric mixture favoring the desired intermediate **26a**. The relative configuration was determined by acetonide formation and measurements of the ^{1}H NMR ^3J-bond coupling constants analysis (Scheme 10).

With useful amounts of intermediate **26a** obtainable, we needed a relatively labile protecting group for the primary hydroxyl that would allow us to obtain the methyl ether of C11. A trimethylsilyl ether appeared as the group of choice, since it could be easily removed under mild acidic conditions during the workup procedure to obtain precursor **29a** or be directly deprotected and oxidized to aldehyde **30** under Swern conditions.[23] Treatment of 1,3-diol **26a** with TMSCl (1.1 equiv) and Et_3N (2 equiv) in THF at −78 °C for 15 min cleanly afforded

Scheme 10



Scheme 11



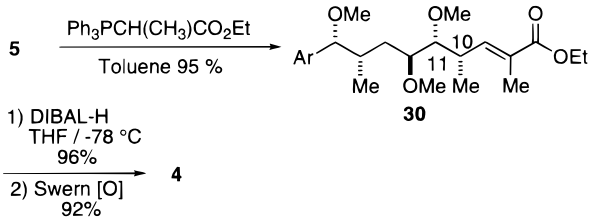
the primary trimethylsilyl ether **28** in 98% yield. Methylation of the C11 secondary alcohol was carried out using trimethyloxonium tetrafluoroborate (10 equiv) and proton sponge (10 equiv) in CH_2Cl_2 at room temperature for 2 h. When the reaction mixture was washed with H_2O, 65% of the methylated product **29a** with the TMS group still attached to the primary position could be isolated. On the other hand, when a 1 N $NaHSO_4$ solution was used to wash the crude mixture, 86% of the methylated product **29b** with a free primary hydroxyl group was isolated as the major product. Both intermediates could be converted, with comparable yields, to the corresponding aldehyde **5** by means of a Swern oxidation (Scheme 11).

Subsequent treatment of **5** with (carbethoxymethylene)-triphenylphosphorane[24] in refluxing toluene afforded the α,β-unsaturated ester **30**, which was conveniently converted into α,β-unsaturated aldehyde **4** by sequential DIBAL-H reduction and Swern oxidation (Scheme 12).

At this stage of the synthesis, an advanced intermediate bearing five of the seven stereogenic centers and one trisubstituted double bond had been assembled. The five stereocenters were introduced through two asymmetric crotylation and one

(23) Maycock, C.; Barros, T.; Afonso, C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1221−1223.
(24) Kishi, Y.; Johnson, M. R. *Tetrahedron Lett.* **1979**, *20*, 4347−4750.

Scheme 12



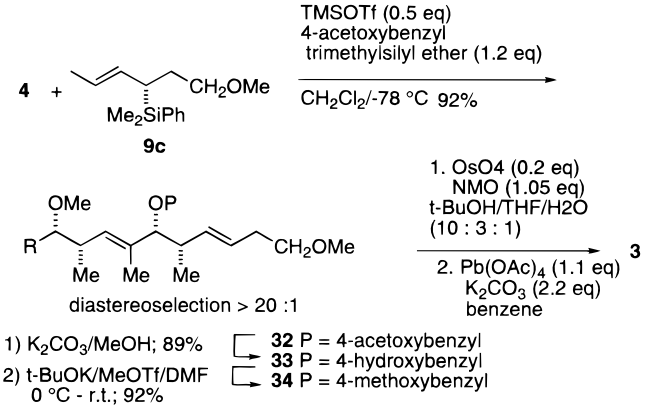
heteroatom-directed hydroboration or, alternatively, through one asymmetric crotylation, one heteroatom-directed hydroboration, and one diastereoselective hydroboration. Thus, we have established a convergent route to an advanced intermediate that was elaborated to the seco acid precursor (**2**) of the macbecin I macrocycle.

Introduction of the C6/C7 Stereogenic Centers. It was our intention to introduce the C6/C7 stereocenters with our crotylation methodology. The successful use of this methodology will require the introduction of a oxygen protective group other than benzyl group. Considering the chemical compatibility of the various functional groups to strong Lewis acids and catalytic hydrogenolysis conditions (i.e., competing double-bond reduction), removal of the C7 benzyl group would be problematic. To circumvent these functional groups compatibility problems, a protecting group that could be removed under relatively mild oxidation conditions was investigated. It is well-precedented that the substituted methoxybenzyl group can be easily removed by oxidative cleavage [dichlorodicyanobenzoquinone (DDQ) or cerium(IV) ammonium nitrate (CAN)];[25] the oxidation potentials of related substituted benzyl alcohols have been measured by E. A. Mayeda.[26] The reactivities of various substituted benzyl ethers and alcohols toward DDQ and CAN have also been reported.[27]

With this information, an investigation of several oxygen substituted benzyl ethers as possible protecting groups was undertaken. There were three essential concerns in this study: (i) an efficient condensation had to be achieved in the three-component crotylation reaction, (ii) a substituted benzyl functionality with lowest oxidation potential was necessary to employ the mildest, and most efficient, oxidizing agent, and (iii) the deprotected allylic alcohol should not be overoxidized to the ketone.[28] Two advantages in using a substituted benzyl group as a protecting group are (1) protection of the incipient C7 hydroxy group occurs in the course of crotylation with the three component system which also installs the C6/C7 stereogenic centers and (2) the potential to simultaneously oxidize the ansamycin aromatic unit to the benzoquinone and remove the C7-substituted benzyl ether protecting group in a single operation. Therefore, three candidates were chosen for this study on the basis of their oxidation potentials. They were *m*-methoxybenzyl (1.4 V), 2,3-dimethoxybenzyl (between 1.3 and 1.4 V), and 4-acetoxybenzyl group (∼1.9 V), which can be easily converted into the 4-methoxybenzyl group (1.3 V).

With the appropriate conditions in hand, the 4-methoxybenzyl group was chosen for C7 hydroxy protection. The last pair of stereocenters (C6/C7) was then constructed by an in situ-

Scheme 13



generated oxocarbenium ion addition reaction among intermediate **4**, chiral crotylsilane **9c,** and 4-acetoxybenzyl trimethylsilyl ether in CH_2Cl_2 at −78 °C for 16−18 h. The adduct **32** was isolated with a diastereoselection of greater than 20:1 syn/anti in 92% yield. Subsequent hydrolysis with K_2CO_3 (2 equiv) in MeOH, followed by treatment with ^{t}BuOK and MeOTf in DMF at 0 °C to room temperature for 5 h afforded the *p*-methoxybenzyl (PMB)-protected ether in 82% yield over two steps. Selective cleavage of the *trans*-disubstituted double bond was accomplished by OsO_4-promoted dihydroxylation reaction with NMO in ^{t}BuOH/THF/H_2O (10:3:1) at room temperature for 4−5 h, followed by treatment of the crude diol with K_2CO_3 (2 equiv) and $Pb(OAc)_4$ (1.1 equiv) in anhydrous benzene at room temperature for 5 min, produced the α-methyl aldehyde **3** in 67% yield over two steps (Scheme 13).

Thus far, the C5−C21 macbecin subunit including all seven stereogenic centers, leaving only the installation of the C1−C4 dienic amide unit has been assembled.

Formation of C1−C4 Diene Fragment. Completion of the *Z,E*-dienoate system was carried out by a sequential olefination reaction. A *Z*-selective Horner−Emmons olefination was carried out between aldehyde **3** and trifluoroethyl phosphonate reagent developed by Still and co-workers.[29] Treatment of the phosphonate with $KN(TMS)_2$ and 5 equiv of 18-crown-6 in anhydrous THF followed by addition of aldehyde **3** in THF afforded an inseparable mixture of α,β-unsaturated esters **36** (*Z/E* = 15:1) in 82% yield. Treatment of the purified esters **36** with DIBAL-H (THF, −78 °C) followed by Swern oxidation afforded aldehydes **38**. The completion of the macbecin framework was accomplished by treating aldehydes **38** with (carbethoxymethylene)triphenylphosphorane in refluxing toluene for 12 h. The *E,Z*-dienoate **39** was isolated in 97% yield with an *E/Z* ratio of 12:1 (Scheme 14).

Nitro Group Reduction. The goal of utilizing the aryl nitro group, as the masked amine, throughout the entire reaction sequence was successfully achieved, albeit with some degree of difficulty. It was now required to reduce this function in the presence of an α,β,γ,δ-unsaturated ester, a trisubstituted double bond, a benzylic methyl ether, and a 4-methoxybenzyl group. In earlier published syntheses of macbecin, the use of $SnCl_2$,[30] aluminum amalgam,[31] and palladium on carbon,[32] resulted in either low yields or extensive decomposition of the starting material. The only successful reduction of such aryl nitro group was accomplished by catalytic hydrogenation with

(25) (a) Yonemitsu, O.; Abe, R.; Nakajima, N. *Chem. Pharm. Bull.* **1988**, 4244−4247. (b) Oikawa, Y.; Tanaka, T.; Horita. K.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5393−5396. (c) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron lett.* **1985**, *26*, 6291−6292.

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(28) Trost, B. M.; Chung, J. Y. L. J. *Am. Chem. Soc.* **1985**, *107*, 4586−4588.

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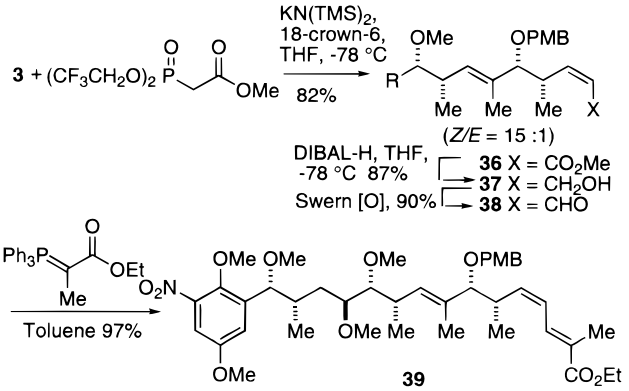
(30) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839−842.

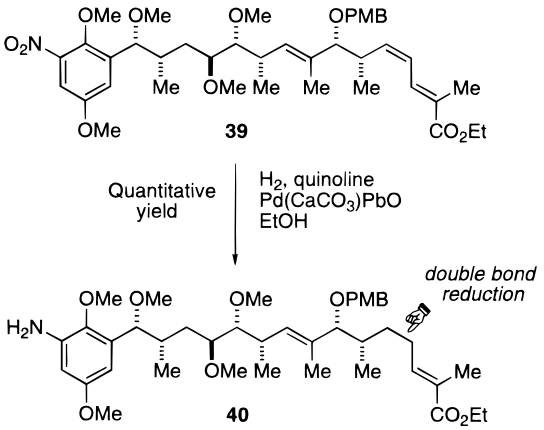
(31) Corey, E. J.; Vlattas, I.; Anderson, N. H.; Harding, K. *J. Am. Chem. Soc.* **1968**, *90*, 3247−3248.

(32) Nakano, M.; Sato, Y. *J. Org. Chem.* **1987**, *52*, 1844−1847.

Scheme 14



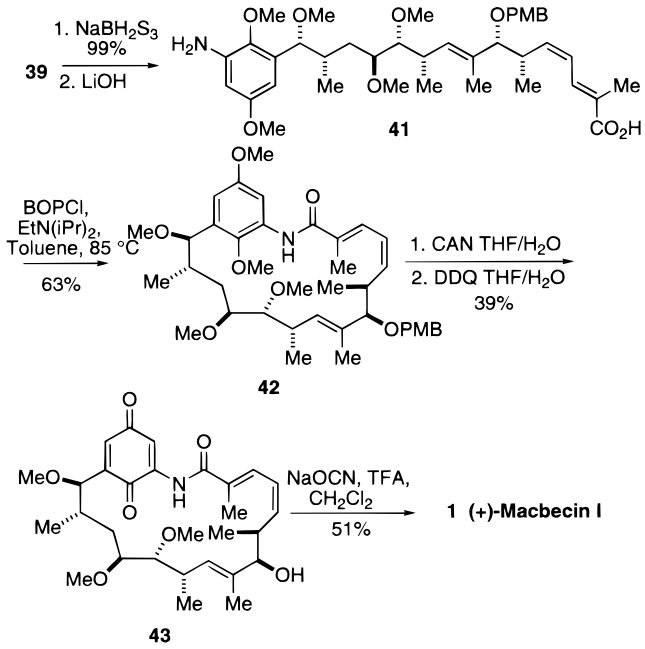
Scheme 15



Lindlar's catalyst[33] which afforded the anilinic ester in 94% yield along with 6% of starting material. However, extensive hydrogenation of the γ,δ-*Z* double bond was often observed when the same procedure was applied to ester **39** (Scheme 15).

(+)-Macbecin I. The crucial reduction of the aryl nitro group was finally accomplished by $NaBH_4$ and elemental sulfur according to the procedures of Lalancette.[34] After the mixture was stirred in refluxing THF for 5 h, the desired anilinic ester **2** was obtained in 99% yield. The steps remaining for the completion of the synthesis of macbecin are depicted in Scheme 16. The required hydrolysis of the ethyl ester of **2** (LiOH, THF/MeOH/H_2O) provided the amino acid **41** in 92% crude yield. Macrocyclization according to the conditions of Baker and Castro using *N*,*N*′-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[35] in the presence of diisopropylethylamine (0.001 M in toluene, 85 °C) provided the fully protected macrocyclic lactone **42** in 63% yield over two steps. The crucial oxidation and deprotection step of macrocycle **42** was carried out using the conditions previously evaluated on the model systems. Oxidation of macrocycle **42** by CAN (7.5 equiv) in MeCN/H_2O (10:1) at −10 °C for 30 min led to extensive decomposition of the starting material, and only a trace amount of decarbamoyl (+)-macbecin **43** could be observed. Oxidation of the macrocycle by CAN (5 equiv) in THF/H_2O (10:1) at −10 °C provided a reasonably clean benzoquinone product with only trace

Scheme 16



amounts of decarbamoyl macbecin **43**. Treatment of this crude benzoquinone with DDQ (1.5 equiv) in THF/H_2O (20:1) provided decarbamoyl macbecin **43** in 39% yield over two steps. Finally, acylation of the C7 hydroxyl (NaOCN, TFA) provided synthetic (+)-macbecin I (**1**), which agreed in all respects with the data (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]^{23}_D$, MS, and TLC R_f) reported in the literature for the natural product [synthetic, $[\alpha]^{23}_D = +341°$ (*c* 0.14, $CHCl_3$); natural, Muroi[4] $[\alpha]_D = +351°$ (*c* 0.10, $CHCl_3$)].

Conclusions

In the course of this work, the successful total synthesis of (+)-macbecin I has been achieved in 33 steps with 0.64% overall yield beginning with crotylsilane **9a** and acetal **10**. Chiral (*E*)-crotylsilane methodology has been pivotal in the control of five of the seven stereogenic centers within the target (+)-macbecin I. A diastereoselective hydroboration of the 1,1-disubstituted terminal allylic alcohol **6b** was successfully employed to install the C10 stereogenic center, and a heteroatom-directed hydroboration of adduct **8** provided the C12 stereocenter. Therefore, this report represents the first total synthesis of (+)-macbecin I without the use of metal enolate-based methodology for the construction of the stereochemical relationships.

Experimental Section

Methyl (2*S*,3*E*,5*S*,6*R*)-2-(Benzyloxy)-6-(2,5-dimethoxy-3-nitrophenyl)-6-methoxy-5-methyl-3-hexenoate (8). A cooled (−78 °C) solution of 7.20 g (27.7 mmol) of the 2,5-dimethoxy-3-nitrobenzyl dimethyl acetal **10** and 10.18 g (27.6 mmol) of (2*R*,3*R*,4*E*)-2-(benzyloxy)-3-(dimethylphenylsilyl)hexenoate **9a** in 60 mL of anhydrous CH_2Cl_2 was treated with 2.5 mL (13.5 mmol) of (trimethylsilyl)-trifluoromethanesulfonate (TMSOTf) dropwise. The resulting deep red solution was stirred at −78 °C for 16 h, before it was diluted with 60 mL of saturated $NaHCO_3$ solution and stirred for 15 min at rt. The layers were separated, and the aqueous layer was extracted with two portions of 30 mL of CH_2Cl_2. The combined yellow organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (solvent gradient: 10% EtOAc/PE to 40% EtOAc/PE) afforded 11.0 g (89%) of pure desired adduct **8** (de > 96%) as a yellow solid: $[\alpha]^{23}_D = +77.6°$ (*c* 1.91, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (m, 6H), 7.14 (d, 1H, $J = 3.6$ Hz), 5.79−5.74 (dd, 1H, $J = 8.0, 15.6$ Hz), 5.43−

(33) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590−591.

(34) (a) Lalancette, J. M.; Freche, A.; Brindle, J. R.; Laliberte, M. *Synthesis*, **1972**, 527−532. (b) Lalancettte, J. M.; Freche, A.; Monteux, R. *Can. J. Chem.* **1968**, *46*, 2754−2757.

(35) (a) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R. *Synthesis* **1980**, 547−551. (b) Van Der Auwera, C.; Anteunis, M. J. O. *Int. J. Peptide Protein Res.* **1987**, *29*, 574−588.

5.37 (dd, 1H, $J = 6.8, 15.6$ Hz), 4.51 (d, 2H, $J = 3.2$ Hz), 4.40 (d, 1H, $J = 6.8$ Hz), 4.30 (d, 1H, $J = 6.8$ Hz), 3.82 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 3.24 (s, 3H), 2.55−2.53 (m, 1H), 1.10 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.1, 155.2, 145.5, 143.5, 138.2, 137.2, 137.1, 128.3,127.9, 127.8, 125.4, 118.6, 109.0, 80.5, 78.2, 70.9, 62.7, 57.3, 55.9, 52.0, 43.0, 15.5; IR (neat) ν_{max} 3100, 2995, 1750, 1620, 1580, 1530, 1490, 1430; CIHRMS M + NH_4^+ 477.2267 ($C_{24}H_{33}N_2O_8$ requires 477.2237).

(2*R*,3*S*,5*S*,6*R*)-2-(Benzyloxy)-6-(2,5-dimethoxy-3-nitrophenyl)-6-methoxy-5-methylhexa-1,3-diol (11). A cooled (0 °C) solution of 11.0 g (24.7 mmol) of **8** in 300 mL of anhydrous THF was treated with 2.6 mL of BH_3·SMe_2 (10 M, 26.0 mmol) dropwise over 10 min. The resulting reaction mixture was allowed to warm to rt over 2 h and stirred for 16 h at rt, before it was cooled to 0 °C. The solution was then diluted with 10 mL of MeOH followed by NaOOH (4 equiv, 20 mL, 5 M NaOH aqueous solution; 11.3 mL, 30% H_2O_2) oxidation. The reaction mixture was stirred at 0 °C for 30 min and 90 min at rt, before it was diluted with 30 mL of 5% aqueous HCl solution. The layers were separated, and the aqueous layer was extracted with four portions of 50 mL of EtOAc. The combined organic phases were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (solvent gradient: 30% EtOAc/PE to 100% EtOAc) afforded 8.1 g of pure *anti*-1,3-diol **11** along with 1.01 g of *syn*-1,3-diol in 85% as a viscous yellow oil: $[\alpha]^{23}_D = +27.0°$ (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 7.27 (d, 1H, $J = 2.8$ Hz), 7.14 (d, 1H, $J = 2.8$ Hz), 4.62 (ABq, 2H, $J = 11.6$ Hz), 4.52 (d, 1H, $J = 4.8$ Hz), 3.84−3.82 (m, 1H), 3.81 (s, 6H), 3.81−3.77 (m, 2H), 3.33−3.25 (m, 1H), 3.25 (s, 3H), 2.46 (d, 1H, $J = 4.0$ Hz), 2.21−2.18 (t, 1H, $J = 5.6$ Hz), 2.05−2.02 (m, 1H), 1.55−1.46 (m, 2H), 0.84 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 154.8, 145.1, 143.3, 138.2, 137.8, 128.1,127.5, 127.4, 118.5, 108.4, 81.8, 81.1, 71.6, 69.2, 62.4, 60.7, 57.08, 55.5, 36.5, 35.4, 13.5; IR (neat) ν_{max} 3450, 2970, 1540, 1480, 1430; CIHRMS M + NH_4^+ 467.2400 ($C_{23}H_{35}N_2O_8$ requires 467.2393).

(2*S*,4*S*,5*R*)-5-(2,5-Dimethoxy-3-nitrophenyl)-2,5-dimethoxy-4-methylpentanal (6a). A solution of 2.20 g (6.13 mmol) of 1,2-diol **7** in 60 mL of acetone/H_2O (1:1) was treated with 1.54 g of $NaHCO_3$ (18.33 mmol) and 2.0 g of $NaIO_4$ (9.35 mmol). The resulting solution was stirred at ambient temperature for 100 min before it was diluted with 50 mL of H_2O. The aqueous layer was extracted three times with 50 mL of Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue (5% EtOAc/PE to 20% EtOAc/PE) afforded 1.69 g (84%) of desired aldehyde **6a** as a yellow oil: $[\alpha]^{23}_D = +7.3°$ (*c* 0.85, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, 1H, $J = 2.0$ Hz), 7.26 (d, 1H, $J = 3.2$ Hz), 7.12 (d, 1H, $J = 3.2$ Hz), 4.43 (d, 1H, $J = 4.8$ Hz), 3.82 (s, 3H), 3.81 (s, 3H), 3.64−3.59 (m, 1H), 3.41 (s, 3H), 3.22 (s, 3H), 2.06−2.02 (m, 1H), 1.71−1.64 (m, 1H), 1.59−1.54 (m, 1H), 0.86 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 203.5, 155.0, 145.2, 143.5, 138.2, 118.7, 108.6, 84.0, 80.7, 62.6, 58.2, 57.4, 55.9, 34.9, 33.2, 13.3; IR (neat) ν_{max} 3000, 2860, 1750, 1650, 1550, 1500, 1450; CIHRMS M + NH_4^+ 359.1829 ($C_{16}H_{27}N_2O_7$ requires 359.1818).

Methyl (3*E*,5*S*,6*R*,7*S*,9*S*,10*R*)-10-(2,5-Dimethoxy-3-nitrophenyl)-6,7,10-trimethoxy-5,9-dimethyl-3-decenoate (15). To a cooled (−78 °C) solution of 1.69 g (5.15 mmol) aldehyde **6a**, 1.07 g (10.27 mmol) of TMSOMe, and (4*E*,3*S*)-3-(dimethylphenylsilyl)hexenoate **9b** in 10 mL of anhydrous CH_2Cl_2 was added 1.9 mL (10.3 mmol) of TMSOTf. The resulting solution was stirred at −78 °C for 18 h and then allowed to warm to −50 °C. After being stirred for 24 h at −50 °C, the reaction solution was diluted with 20 mL of saturated $NaHCO_3$ aqueous solution. The aqueous phase was extracted three times with 30 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue (solvent gradient: 10% EtOAc/PE to 30% EtOAc/PE) afforded 2.05 g (80%) of adducts **15** (∼15:1 syn/anti at C_{10}/C_{11}) as a yellow oil: $[\alpha]^{23}_D = +38.5°$ (*c* 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 1H, $J = 3.2$ Hz), 7.15 (d, 1H, $J = 3.2$ Hz), 5.54−5.49 (m, 1H), 5.44−5.38 (m, 1H), 4.43 (d, 1H, $J = 4.4$ Hz), 3.82 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H), 3.44 (s, 3H), 3.29 (s, 3H), 3.25−3.21 (m, 1H), 3.21 (s, 3H), 3.12−3.07 (dd, 1H, $J = 7.6, 14.4$ Hz), 3.00 (d, 2H, $J = 7.2$ Hz) 2.30−2.25 (m, 1H), 2.01−1.94 (m, 1H), 1.66−1.63 (m, 1H), 1.45−1.39 (m, 1H), 1.06 (d, 3H, $J = 6.4$ Hz), 0.76 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.9, 154.9, 145.4, 143.5, 138.8, 136.8, 121.8, 118.7, 108.4, 84.1, 81.6, 80.6, 62.6, 60.5, 57.4, 56.9, 55.8, 51.6, 39.3, 37.7, 35.1, 33.2, 16.9, 13.1; IR (neat) ν_{max} 2990, 2860, 1750, 1650, 1550, 1500, 1450; CIHRMS M + NH_4^+ 501.2833 ($C_{24}HN_2O_7$ requires 501.2812).

(2*R*,3*R*,4*S*,6*S*,7*R*)-7-(2,5-Dimethoxy-3-nitrophenyl)-3,4,7-trimethoxy-2,6-dimethylheptanal (5). Into a cooled (−78 °C) solution of 1.37 g (2.75 mmol) of olefin **15** and 0.2 mL (2.5 mmol) of pyridine in methanol was bubbled ozone gas until the solution turned blue in color (ca. 15 min). The reaction mixture was then quenched with 1.6 mL (21.8 mmol) of Me_2S and allowed to warm to rt. After being stirred at ambient temperature for 14 h, the reaction mixture was concentrated. Purification of the remaining residue (solvent gradient: 10% EtOAc/PE to 30% EtOAc/PE) afforded 0.73 g (65%) of desired aldehyde **5** as a yellow oil: $[\alpha]^{23}_D = +47.7°$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, 1H, $J = 1.2$ Hz), 7.30 (d, 1H, $J = 3.2$ Hz), 7.18 (d, 1H, $J = 3.2$ Hz), 4.46 (d, 1H, $J = 4.8$ Hz), 3.87 (s, 3H), 3.86 (s, 3H), 3.61−3.58 (dd, 1H, $J = 4.8, 6.0$ Hz), 3.35 (s, 6H), 3.33−3.29 (obscured m, 1H), 3.28 (s, 3H), 2.66−2.64 (m, 1H), 2.03−2.00 (m, 1H), 1.63−1.55 (m, 2H), 1.19 (d, 3H, $J = 7.2$ Hz), 0.91 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 203.4, 155.0, 145.4, 143.5, 138.6, 118.7, 108.6, 81.7, 81.3, 79.5, 62.6, 59.2, 57.7, 57.5, 55.9, 48.3, 35.5, 35.1, 13.9, 8.7; IR (neat) ν_{max} 2910, 2800, 1710, 1620, 1570, 1510, 1470, 1420; CIHRMS M + NH_4^+ 431.2401 ($C_{20}H_{35}N_2O_8$ requires 431.2393).

(2*S*,3*E*,5*S*,6*R*)-7-(2,5-Dimethoxy-3-nitrophenyl)-4,7-dimethoxy-2,6-dimethyl-1-ene-3-heptanol (6b). To a solution of **25** (2.50 g, 5.0 mmol, 1.0 equiv) in 25.1 mL of CH_3CN was added 5.1 mL of 48% aqueous HF. The reaction was stirred at room temperature for 1 h before it was diluted with 50 mL of saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 20 mL), washed with BRINE (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (30% EtOAc/PE) afforded 1.92 g (100%) of allylic alcohol **6b** as a bright yellow oil: $[\alpha]^{23}_D = +72.4°$ (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 1H, $J = 3.2$ Hz), 7.13 (d, 1H, $J = 3.2$ Hz), 5.07 (bs, 1H), 4.90 (bs, 1H), 4.42 (d, 1H, $J = 4.8$), 4.33 (bs, 1H), 3.81 (s, 6H), 3.37 (s, 3H), 3.33−3.29 (m, 1H), 3.21 (s, 3H), 2.21 (d, 1H, $J = 2.3$ Hz), 2.0−1.92 (m, 1H), 1.68 (s, 3H), 1.61−1.54 (m, 1H), 1.31−1.23 (m, 1H), 0.80 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 155.0, 145.5, 143.6, 143.0, 138.8, 118.8, 111.6, 108.7, 81.4, 80.3, 73.1, 62.7, 57.5, 57.3, 55.9, 35.1, 31.8, 19.5, 13.6; IR (neat) ν_{max} 3854, 3744, 3019, 1734, 1700, 1685, 1653, 1617, 1576, 1480, 1457; CIHRMS M + NH_4^+ (calcd for $C_{19}H_{33}N_2O_7$) 401.2289, found 401.2298.

(2*R*,3*R*,4*S*,6*S*,7*R*)-7-(2,5-Dimethoxy-3-nitrophenyl)-4,7-dimethoxy-2,6-dimethylhepta-1,3-diol (26a). A cooled (−5 °C) solution of 1.92 g (5.0 mmol) of **8g** in 50.1 mL of anhydrous THF was treated with 20 mL of BH_3·THF (1.0 M, 20.0 mmol, 4.0 equiv) dropwise over 10 min. The resulting reaction mixture was kept at −5 °C for 45 min. The solution was then diluted with 5 mL of MeOH followed by NaOOH (1.5 equiv, 2.50 mL, 3 M NaOH aqueous solution; 0.83 mL of 30% H_2O_2) oxidation. The reaction mixture was stirred at 0 °C for 30 min and 90 min at rt, before it was diluted with 20 mL of H_2O. The layers were separated, the aqueous layer was extracted with four portions of 50 mL of EtOAc. The combined organic phases were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (solvent gradient: 30% EtOAc/PE to 100% EtOAc) afforded 1.76 g of pure 1,3-diol **26a** along with 0.25 g of the diastereomer 1,3-diol **26b** as a viscous yellow oil: $[\alpha]^{23}_D = +71.9°$ (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 1H, $J = 3.6$ Hz), 7.15 (d, 1H, $J = 3.6$ Hz), 4.46 (d, 1H, $J = 4.6$ Hz), 3.83 (s, 3H), 3.82 (s, 3H), 3.78−3.73 (m, 1H), 3.67−3.62 (m, 2H), 3.33 (s, 3H), 3.32−3.29 (obscured m, 1H), 3.24 (s, 3H), 2.46 (d, 1H, $J = 3.2$ Hz), 2.04−2.01 (m, 1H), 1.87−1.84 (m, 1H), 1.73−1.63 (m, 2H), 1.52−1.48 (m, 1H), 1.02 (d, 3H, $J = 6.9$ Hz), 0.85 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 155.1, 145.5, 143.6, 138.5, 118.9, 108.6, 81.5, 79.9, 73.7, 66.8, 62.7, 57.5, 57.4, 55.9, 36.1, 34.9, 33.2, 14.2, 11.5; IR (neat) ν_{max} 3425, 2937, 2829, 1653, 1576, 1533, 1481; CIHRMS M + H^+ (calcd for $C_{19}H_{32}NO_8$) 402.2128, found 402.2126.

(2*R*,3*R*,4*S*,6*S*,7*R*)-7-(2,5-Dimethoxy-3-nitrophenyl)-4,7-dimethoxy-2,6-dimethyl-1-((trimethylsilyl)oxy)-3-heptanol (28). To a stirred

solution of diol **26a** (1.76 g, 4.4 mmol) in 21.9 mL of anhydrous THF (0.2 M) at −78 °C was added Et_3N (1.22 mL, 8.8 mmol, 2.0 equiv) followed by addition of TMSCl (0.91 mL, 4.8 mmol, 1.1 equiv). The reaction was kept at −78 °C for 15 min before it was diluted with 20 mL of H_2O. The reaction mixture was extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification on SiO_2 (20% EtOAc/PE) afforded 2.03 g (98%) of the pure silyl ether **28** as a yellow oil: $[\alpha]^{23}_D = +55.9°$ (*c* 0.71, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 1H, J = 3.3 Hz), 7.16 (d, 1H, J = 3.3 Hz), 4.44 (d, 1H, J = 4.6 Hz), 3.83 (s, 3H), 3.81 (s, 3H), 3.73−3.70 (m, 1H), 3.61 (ABq, 2H, J_{AB}=4.0 Hz), 3.32 (s, 3H), 3.29−3.25 (obscured m, 1H), 3.23 (s, 3H), 2.84 (bs, 1H), 2.06−2.01 (m, 1H), 1.86−1.83 (m, 1H), 1.61−1.52 (m, 2H), 0.99 (d, 3H, J = 6.9 Hz), 0.88 (d, 3H, J = 6.6 Hz), 0.09 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 155.1, 145.6, 143.6, 138.9, 118.9, 108.6, 81.6, 79.7, 77.4, 76.6, 74.6, 67.4, 62.7, 57.5, 57.4, 55.9, 35.4, 35.1, 34.1, 33.8, 22.3, 14.1, 14.0, 11.5, −0.7; IR (neat) ν_{max} 3688, 3468, 3020, 2400, 1710, 1533, 1479, 1427; CIHRMS M + H^+ (calcd for $C_{22}H_{40}NSiO_8$) 474.2523, found 401.2518.

(3*E*,5*S*,6*R*,7*E*,9*S*,10*R*,11*S*,13*S*,14*R*)-6-(4′-Acetoxybenzyl)-14-(2,5-dimethoxy-3-nitrophenyl)-1,10,11,14-tetramethoxy-5,7,9,13-tetramethyl-3,7-tetradecadiene (32). A cooled (−78 °C) solution of 0.27 g (0.904 mmol) of 4-acetoxybenzyl trimethylsilyl ether, 0.212 g (0.906 mmol) of (2*E*,4*S*)-4-(dimethylphenylsilyl)-6-methoxyhexene **9c,** and 0.342 g (0.755 mmol) of aldehyde **4** in 2 mL of anhydrous CH_2Cl_2 was treated with 0.07 mL (0.38 mmol) of TMSOTf dropwise. The resulting solution was stirred for 18 h before it was quenched by 5 mL of saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted three times with 10 mL of CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue (solvent gradient: 10% EtOAc/PE to 30% EtOAc/PE) afforded 0.5 g (92%) of desired addition product **32** (de > 20:1) as a yellow oil: $[\alpha]^{23}_D = +42.5°$ (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 1H, J = 8.4 Hz, 2H), 7.25 (d, 1H, J = 3.2 Hz), 7.16 (d, 1H, J = 3.2 Hz), 7.01 (d, 2H, J = 8.4 Hz,), 5.37−5.33 (m, 2H), 5.20 (d, 1H, J = 9.6), 4.45 (d, 1H, J = 4.4 Hz), 4.31 (ABq, 2H, J = 12.4 Hz), 3.82 (s, 3H), 3.81 (s, 3H), 3.43 (s, 3H), 3.32−3.27 (m, 3H), 3.26 (s, 3H), 3.25 (s, 3H), 3.22 (s, 3H), 3.19−3.16 (m, 1H), 3.10−3.08 (dd, 1H, J = 2.1, 8.0 Hz), 2.57−2.51 (m, 1H), 2.38−2.28 (m, 1H), 2.27 (s, 3H), 2.18−2.11 (m, 2H), 2.05−1.96 (m, 1H), 1.74−1.65 (m, 1H), 1.55 (d, 3H, J = 1.2 Hz), 1.44−1.38 (m, 1H), 1.05 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.8 Hz), 0.77 (d, 3H, J = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.5, 154.9, 149.8, 145.5, 143.6, 138.9, 136.4, 134.5, 132.8, 132.6, 128.5, 125.7, 121.3, 118.8, 108.5, 88.4, 84.6, 81.8, 80.9, 72.5, 69.0, 62.7, 60.7, 58.4, 57.5, 56.9, 55.9, 39.7, 35.1, 34.7, 33.6, 33.1, 21.1, 17.4, 16.6, 13.4, 12.5; IR (neat) ν_{max} 2970, 1760, 1530, 1480, 1460, 1430; CIHRMS M + NH_4^+ 734.4301 ($C_{39}H_{62}N_2O_{11}$ requires 734.4353).

Methyl (2*Z*,4*S*,5*R*,6*E*,8*S*,9*R*,10*S*,12*S*,13*R*)-5-(4′-Methoxybenzyl)-13-(2,5-dimethoxy-3-nitrophenyl)-9,10,13-trimethoxy-4,6,8,12-tetramethyl-2,6-tridecadienoate (36). To a cooled (−78 °C) solution of 450 mg (1.7 mmol) of 18-crown-6 ether and 160 mg (0.5 mmol) of bis(2,2,2-trifluoroethyl)phosphonoacetate in 5 mL of anhydrous THF was added 1.1 mL (0.55 mmol) of $KN(TMS)_2$ (0.5 M in toluene). The resulting solution was stirred for 5 min, before 211.4 mg (0.343 mmol) of starting aldehyde **3** in 1.5 mL of anhydrous THF (0.5 mL rinse) was added. The reaction mixture was stirred for 3 h at −78 °C, before it was quenched with saturated NH_4Cl aqueous solution. The aqueous layer was extracted three times with 10 mL of Et_2O, dried over $MgSO_4$, filtered, and concentrated to provide a mixture of 15:1 *Z*/*E* olefin products. Purification of the residue (solvent gradient: 15%−30% EtOAc/PE) afforded 192.5 mg (82%) of desired *Z* olefin **36** as a yellow oil: $[\alpha]^{23}_D = +75.0°$ (*c* 1.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 1H, J = 3.6 Hz), 7.19 (d, 2H, J = 8.8 Hz), 7.15 (d, 1H, J = 3.6 Hz), 6.83 (d, 2H, J = 8.8 Hz), 5.97−5.92 (dd, 1H, J = 10.4, 11.6 Hz), 5.60 (d, 1H, J = 11.6 Hz), 5.19 (d, 1H, J = 10.4 Hz), 4.44 (d, 1H, J = 4.0 Hz), 4.40 (ABq, 2H, J = 11.2 Hz), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.59 (s, 3H), 3.43 (s, 3H), 3.41−4.39 (obscured m, 1H), 3.23 (s, 3H), 3.20 (s, 3H), 3.19−3.09 (m, 2H), 2.53−2.45 (m, 2H), 2.02−1.95 (m, 1H), 1.73−1.65 (m, 1H), 1.53 (d, 3H, J = 0.8 Hz), 1.40−1.32 (m, 1H), 1.05 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.8 Hz), 0.69 (d, 3H, J = 7.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 166.3, 158.9, 154.9, 152.3, 145.4, 143.6, 138.9, 133.1, 131.9, 130.5, 129.0, 128.5, 118.8, 113.6, 108.5, 87.1, 84.3, 81.7, 81.3, 69.4, 62.6, 60.7, 57.5, 56.8, 55.9, 55.2, 50.9, 35.5, 35.2, 34.8, 33.1, 17.7, 15.9, 13.2, 12.2; IR (neat) ν_{max} 2970, 1720, 1650, 1620, 1580, 1530, 1450; CIHRMS M + NH_4^+ 705.3991 ($C_{37}H_{57}N_2O_{11}$ requires 705.3962).

Ethyl (2*E*,4*Z*,6*S*,7*R*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-7-(4′-Methoxybenzyl)-15-(3-amino-2,5-dimethoxyphenyl)-11,12,15-trimethoxy-2,6,8,-10,14-pentamethyl-2,4,8-pentadecatrinoate (2). To a mixture of 15 mg (0.4 mmol) of solid $NaBH_4$ and 45 mg (1.4 mmol) of sulfur was added 3 mL of anhydrous THF dropwise. After the mixture was stirred for 5 min (most of the solid has dissolved), 48 mg (0.065 mmol) of starting nitro compound **39** was added in 1 mL of THF (followed by 0.5-mL rinse twice). After refluing for 5 h, the reaction mixture was cooled to rt and diluted with 2 mL of NaOH (2 M) aqueous solution and 5 mL of H_2O. The aqueous layer was extracted three times with 10 mL of Et_2O and two times with 10 mL of EtOAc, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue (solvent gradient: 20% to 50% EtOAc/PE) afforded 46 mg (99%) of desired anilinic ester **2** as a light yellow oil: $[\alpha]^{23}_D = +73.7°$ (*c* 0.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, J = 11.6 Hz), 7.21 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 6.38 (br s, 2H), 6.11 (t, 1H, J = 11.6 Hz), 5.48 (t, 1H, J = 10.4 Hz), 5.21 (d, 1H, J = 9.6 Hz), 4.31 (ABq, 2H, J = 11.2 Hz), 4.32 (d, 1H, J = 4.8 Hz), 4.19−4.11 (m, 3H), 3.80 (obscured m, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.43 (s, 3H), 3.37 (d, 1H, J = 8.8 Hz), 3.26 (s, 3H), 3.21 (s, 3He), 3.19−3.17 (m, 1H), 3.15−3.08 (dd, 1H, J = 2.4, 8.0 Hz), 3.06−2.97 (m, 1H), 2.53−2.49 (m, 1H), 2.02−1.91 (m, 1H), 1.81 (d, 3H, J = 1.6 Hz), 1.76−1.64 (m, 1H), 1.50 (s, 3H), 1.36−1.29 (m, 1H), 1.27 (t, 3H, J = 6.8 Hz), 1.06 (d, 3H, J = 6.8 Hz), 1.05 (d, 3H, J = 6.8 Hz), 0.75 (d, 3H, J = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.4, 159.0, 156.2, 140.9, 140.0, 139.9, 134.9, 133.6, 132.9, 132.2, 130.5, 129.3, 127.9, 123.2, 113.7, 101.6, 101.1, 88.2, 84.8, 82.2, 81.1, 69.3, 60.6, 60.5, 59.8, 57.2, 56.8, 55.3, 55.2, 35.8, 35.5, 34.6, 33.3, 18.0, 17.5, 14.3, 14.0, 12.3, 11.8; CIHRMS M^+ 711.4313 ($C_{41}H_{61}NO_9$ requires 711.4346).

(2*E*,4*Z*,6*S*,7*R*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-7-(4′-Methoxybenzyl)-15-(2,5-dimethoxy-3-nitrophenyl)-11,12,15-trimethoxy-2,6,8,10,14-pentamethyl-2,4,8-pentadecatrienoic Acid (41). To a solution of 35 mg (0.049 mmol) of anilinic ester **2** in 10 mL of 2:2:1 MeOH/THF/H_2O was added 41 mg (0.98 mmol) of solid $LiOH·H_2O$. The reaction mixture was stirred at ambient temperature for 48 h. The mixture was concentrated to remove the MeOH and THF and then dissolved in 30 mL of pH 4.5 NaH_2PO_4 solution. The mixture was extracted with five 30-mL portions of CH_2Cl_2, with the aqueous layer being saturated with solid NaCl between each extraction. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 31 mg (92%) of crude desired aniline acid **41** as a pale yellow glass. This material was used in the next step without further purification.

(4*E*,6*Z*,8*S*,9*R*,10*E*,12*S*,13*R*,14*S*,16*S*,17*R*)-9-(4′-Methoxybenzyl)-13,14,17,20,22-pentamethoxy-4,8,10,12,16-pentamethyl-2-azabicyclo-[16.3.1]docosa-1(22),4,6,10,18,20-hexaen-3-one (42). To a heated solution (85 °C) of 31 mg (0.045 mmol) of crude amino acid **41** and 160 μL (0.92 mmol) of Hünig's base in 55 mL of anhydrous $PhCH_3$ was added 92 mg (0.36 mmol) of BOP-Cl. The solution was stirred at this temperature for 12 h before it was cooled to rt and poured into 50 mL of pH 4.5 NaH_2PO_4 solution. The layers were separated, and the aqueous layer was extracted with three 30-mL portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (solvent gradient: 20% to 40% EtOAc/PE) afforded 20 mg (63%) of desired macrocycle **42** as a clear glass: ^{1}H NMR (400 MHz, DMSO) δ 9.30 (s, 1H), 7.15 (d, 2H, J = 8.0 Hz), 6.88 (d, 2H, J = 8.0 Hz), 6.61 (d, 1H, J = 3.2 Hz,H), 6.44 (d, 1H, J = 3.2 Hz), 5.93 (d, 1H, J = 12.0 Hz), 5.78 (t, 1H, J = 11.2 Hz), 5.03 (t, 1H, J = 10.4 Hz), 4.92 (d, 1H, J = 10.0 Hz), 4.35 (d, 1H, J = 5.2 Hz), 4.10 (ABq, 2H, J = 11.6 Hz), 3.73 (s, 3H), 3.68 (s, 3H), 3.42 (s, 3H), 3.40 (s, 3H), 3.21 (s, 3H), 3.17 (obscured d, 1H, J = 9.6 Hz), 3.16 (s, 3H), 3.15−3.08 (m, 1H), 2.85 (m, 1H), 2.52−2.49 (m, 1H), 2.15−2.12 (m, 2H), 1.79 (s, 3H), 1.51−1.48 (m, 1H), 1.00 (d, 3H, J = 6.8 Hz), 0.94 (s, 3H), 0.85 (d, 3H, J = 6.8 Hz), 0.58 (d, 3H, J = 6.8 Hz); CIHRMS M + H^+ 666.4002 ($C_{39}H_{56}NO_8$ requires 666.4006).

Decarbamoyl Macbecin (43). To a cooled (−10 °C) solution of 22 mg (0.033 mmol) starting macrocycle **42** in 10 mL of 10:1 THF/H_2O was added 170 μL of 1 N ceric ammonium nitrate (CAN) aqueous solution. The resulting solution was stirred at −10 °C for 30 min, before it was poured onto 50 mL of H_2O. The aqueous layer was extracted two times with 15 mL of Et_2O and three times with 15 mL of CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was dissolved in 10 mL of 20:1 THF/H_2O at 0 °C and treated with 11 mg (0.048 mmol) of DDQ. The resulting solution was stirred at 0 °C for 40 min, before it was diluted with 10 mL of H_2O. The aqueous layer was extracted two times with 15 mL of Et_2O and three times with 15 mL of CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by preparative TLC (Et_2O) afford 4.9 mg (39%) of desired decarbamoyl macbecin **43** as a yellow glass: $[\alpha]^{23}_D = +198°$ (*c* 0.12 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (br s, 1H,), 7.32 (d, 1H, $J = 2.4$ Hz), 7.13 (d, 1H, $J = 11.6$ Hz), 6.63 (t, 1H, $J = 1.7$ Hz), 6.38 (t, 1H, $J = 11.9$ Hz), 5.86 (t, 1H, $J = 7.2$ Hz), 5.51(d, 1H, $J = 9.3$ Hz), 4.61 (br s, 1H), 4.55 (s, 1H), 3.53(s, 3H), 3.52 (obscured s, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 3.26 (d, 1H, $J = 9.4$ Hz), 3.03 (m, 1H), 2.48 (m, 1H), 2.00 (s, 3H), 1.68 (m, 3H), 1.47 (s, 3H), 1.09 (d, 3H, $J = 6.4$ Hz), 0.97 (d, 3H, $J = 7.0$ Hz), 0.78 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 187.6, 184.3, 168.7, 144.9, 143.7, 138.1, 134.9, 133.1, 132.4, 129.3, 127.9, 123.5, 112.9, 83.7, 83.3, 78.0, 76.8, 60.6, 58.4, 55.5, 38.1, 35.0, 34.0, 29.7, 17.8, 15.1, 13.1, 12.3, 11.9; CIHRMS M^+ 516.2977 ($C_{29}H_{42}NO_7$ requires 516.2961).

(+)-Macbecin I (1). To a cooled (0 °C) solution of 4.9 mg (9.5 μmol) of quinone **43** in anhydrous CH_2Cl_2 were added 15.4 mg (237 μmol) of sodium cyanate and 18 μL (234 μmol) of trifluoroacetic acid. The mixture was stirred at 0 °C for 15 min and at ambident temperature for 4.5 h before the solution was diluted with 15 mL of CH_2Cl_2 and the reaction quenched by addition of 10 mL of 5% $NaHCO_3$ solution. The product was extracted with 3 × 20 mL of CH_2Cl_2, and combined organic phases were dried over $MgSO_4$ and filtered. Purification by preparative TLC (Et_2O) affored 2.8 mg (51%) of synthetic (+)-macbecin I: $[\alpha]^{23}_D = +341°$ (*c* 0.14, $CHCl_3$); lit.[4] $[\alpha]_D = +351°$ (*c* 0.10, $CHCl_3$); lit.[7] $[\alpha]_D = +377°$ (*c* 0.10, $CHCl_3$); lit.[8a] $[\alpha]_D = +348°$ (*c* 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 7.33 (d, 1H, $J = 2.5$ Hz), 7.12 (d, 1H, $J = 11.7$ Hz), 6.60 (dd, 1H, $J = 1.5, 2.5$ Hz), 6.33 (dd, 1H, $J = 1.8, 12.1$ Hz), 5.80 (br s, 1H), 5.66 (dd, 1H, $J = 6.8, 10.7$ Hz), 5.25 (br s, 1H), 4.69 (br s, 2H), 4.57 (s, 1H), 3.54 (br s, 1H), 3.52 (s, 3H), 3.32 (s, 3H), 3.29 (s, 3H), 3.25 (m, 1H), 3.08 (m, 1H), 2.48 (m, 1H), 1.98 (s, 3H), 1.68 (m, 2H), 1.49 (m, 1H), 1.48 (s, 3H), 1.08 (d, 3H, $J = 6.5$ Hz), 1.02 (d, 3H, $J = 7.0$ Hz), 0.79 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8, 184.0, 169.1, 155.7, 144.8, 141.1, 138.2, 133.2, 132.2, 131.6, 128.9, 124.1, 112.8, 83.6, 79.2, 77.1 (obscured), 60.1, 58.2, 55.6, 34.7 (br), 33.9, 33.5 (br), 17.3 (br), 14.9, 13.3, 13.1, 12.3; IR ($CHCl_3$) 3690, 3540, 3420, 3360, 2990, 2930, 1740, 1690, 1665, 1650, 1610, 1585, 1505, 1460, 1375, 1325, 1240, 1210, 1175, 1155, 1095, 1070, 1030; CIHRMS M^+ 576.3265 ($C_{30}H_{46}N_3O_8$ requires 576.3285).

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Supporting Information Available: ^{1}H and ^{13}C spectral data for all intermediates as well as full spectral data for all compounds not listed in the Experimental Section (95 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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