(+)-Trienomycins A, B, C, and F and (+)-Mycotrienins I and II: Relative and Absolute Stereochemistry

Amos B. Smith, III,*,† John L. Wood,† Weichyun Wong,† Alexandra E. Gould,† Carmelo J. Rizzo,† Joseph Barbosa,† Kanki Komiyama,‡ and Satoshi Ōmura*,‡

Contribution from the Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104, and The Kitasato Institute and School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo 108, Japan

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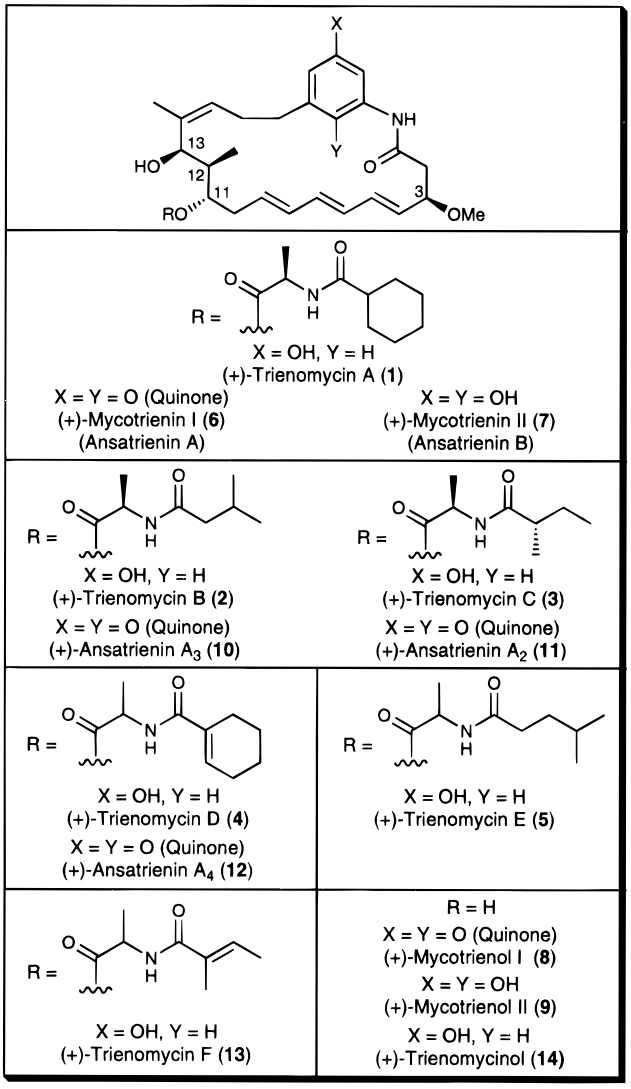
Abstract: The complete relative and absolute stereochemistries have been elucidated for the ansamycin antibiotics (+)-trienomycins A, B, and C and their potent antifungal congeners, the (+)-mycotrienins I and II. A new species, (+)-trienomycin F, has also been isolated and characterized. In addition, an end-game synthetic strategy for the trienomycins and mycotrienins has been developed.

In 1985 Umezawa and co-workers at the Kitasato Institute (Tokyo) disclosed the isolation and planar structures of five new ansamycin antibiotics produced by *Streptomyces* sp. No. 83-16.[1] These compounds, designated the (+)-trienomycins A−E (**1**−**5**), exhibited strong in vitro cytotoxicity against HeLa S_3 cells;[2] (+)-trienomycin A (**1**), the most potent congener, was also active against the L-5178Y murine leukemia cell line as well as human PLC hepatoma cells (IC_{50} 0.01 μg/mL).[3]

(+)-Mycotrienins I and II (**6** and **7**) and (+)-mycotrienols I and II (**8** and **9**) had previously been obtained from the fermentation broth of *Streptomyces rishiriensis* T-23,[3,4] accompanied by (+)-trienomycin A as a minor component. In contrast with the trienomycins, the mycotrienins displayed potent antifungal activity. The ansatrienins A and B and three minor components, (+)-ansatrienins A_2, A_3 and A_4 (**10**−**12**), were independently isolated from the culture broth of *Streptomyces collinus.*[5] Subsequent studies established that ansatrienins A and B were identical to mycotrienins I and II.[6]

The N-acylated alanine side chains of the (+)-trienomycins and (+)-mycotrienins were identified via degradation (vide infra). Extensive ^{1}H and ^{13}C NMR analyses, augmented by chemical interconversions, revealed the planar structures of the macrolactam rings, which differ only in the oxidation state of the aryl moiety.[1,3,4] However, neither these initial efforts nor



† University of Pennsylvania.
‡ Kitasato University.
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(1) (a) Funayama, S.; Okada, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1107. (b) Funayama, S.; Okada, K.; Iwasaki, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1677. (c) Nomoto, H.; Katsumata, S.; Takahashi, K.; Funayama, S.; Komiyama, K.; Umezawa, I.; Ōmura, S. *J. Antibiot.* **1989**, *42*, 479.

(2) (a) Umezawa, I.; Funayama, S.; Okada, K.; Iwasaki, K.; Satoh, J.; Masuda, K.; Komiyama, K. *J. Antibiot.* **1985**, *38*, 699. (b) Funayama, S.; Anraku, Y.; Mita, A.; Yang, Z.-B.; Shibata, K.; Komiyama, K.; Umezawa, I.; Ōmura, S. *J. Antibiot.* **1988**, *41*, 1223.

(3) Hiramoto, S.; Sugita, M.; Andō, C.; Sasaki, T.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 1103.

(4) (a) Sugita, M.; Natori, Y.; Sasaki, T.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1460. (b) Sugita, M.; Sasaki, T.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1467. (c) Sugita, M.; Natori, Y.; Sueda, N.; Furihata, K.; Seto, H.; Ōtake, N. *J. Antibiot.* **1982**, *35*, 1474. (d) Sugita, M.; Furihata, K.; Seto, H.; Ōtake, N.; Sasaki, T. *Agric. Biol. Chem.* **1982**, *46*, 1111.

(5) (a) Damberg, M.; Russ, P.; Zeeck, A. *Tetrahedron Lett.* **1982**, *23*, 59. (b) Lazar, G.; Zähner, H.; Damberg, M.; Zeeck, A. *J. Antibiot.* **1983**, *36*, 187.

(6) (a) Wu, T. S.; Duncan, J.; Tsao, S. W.; Chang, C. J.; Keller, P. J.; Floss, H. G. *J. Nat. Prod.* **1987**, *50*, 108. (b) Casati, R.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1987**, *109*, 8102, and references cited therein.

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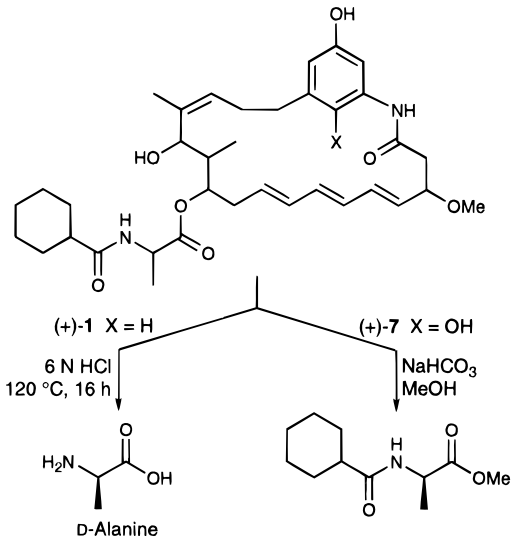
extensive biosynthetic investigations[6] have addressed the stereochemistry of the macrocyclic skeleton.

As a prelude to total synthesis,[7] we have elucidated the complete relative and absolute configurations for (+)-trienomycins A−C (**1**−**3**)[8] and (+)-mycotrienins I and II (**6** and **7**).[9] These studies also led to the discovery and characterization of a new congener, (+)-trienomycin F (**13**),[10] as well as the development of an end-game synthetic strategy for elaboration of the trienomycins from a common advanced intermediate, (+)-trienomycinol (**14**).[10] Herein we provide a full account of this venture.

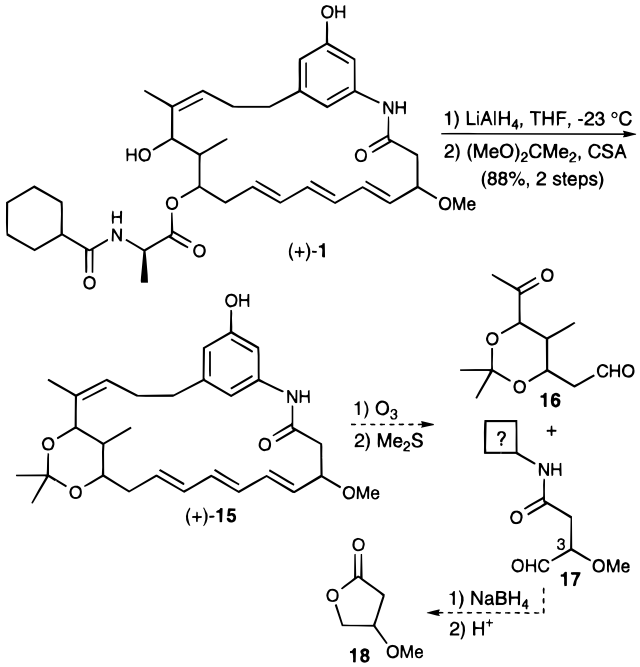
A Degradation Strategy for (+)-Trienomycin A. With ample quantities of the trienomycins available, we envisioned the development of a degradation scheme beginning with trienomycinol (**14**) and focusing on the three contiguous stereogenic centers at C(11−13) and the isolated methoxy center at C(3). Side-chain cleavages of individual trienomycins and mycotrienins have been described previously (Scheme 1). Umezawa isolated D-alanine upon acidic hydrolysis of (+)-trienomycin A (**1**) (6 N HCl, 120 °C, 16 h).[1b] Earlier, Seto liberated an intact *N*-acyl alanine moiety as its methyl ester via alkaline methanolysis ($NaHCO_3$, MeOH) of (+)-mycotrienin II.[4b] Comparison of the latter with an authentic sample prepared from L-alanine and cyclohexanecarbonyl chloride led to unambiguous assignment of the D configuration for the alanine subunit.

Scheme 1



Our point of departure (Scheme 2) was the known deacylation of (+)-trienomycin A (**1**) to (+)-trienomycinol (**14**) with $LiAlH_4$,[2b] followed by acetonide formation to give (+)-**15**. Initially we envisioned that a reductive ozonolysis sequence would then provide the C(11−13) keto aldehyde **16** as well as a mixture of products containing the C(3) stereocenter (i.e., **17**). Reduction of the aldehyde moiety in **17** and acid-promoted cyclization were then expected to provide γ-lactone **18**.

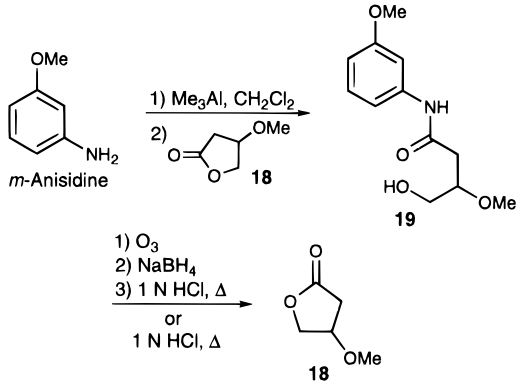
Scheme 2



In a model study, we explored the viability of our proposed sequence for isolation of γ-lactone **18**. Both enantiomers of lactone **18**[11] were prepared via known methods from (+)- and

(−)-malic acid.[12] The model aromatic amide **19** was obtained by coupling of lactone **18** with the Weinreb aluminum amide derived from *m*-anisidine (Scheme 3).[13] As expected, either ozonolysis of **19** followed by reduction and acidification or simple acidification furnished the desired lactone **18**.

Scheme 3



Turning next to the degradation of **1**, ozonolysis[14] of the acetonide of trienomycinol (+)-**15** and reductive workup with

(7) Smith, A. B., III; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10777.

(8) Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Funayama, S.; Ōmura, S. *J. Am. Chem. Soc.* **1990**, *112*, 7425.

(9) Smith, A. B., III; Wood, J. L.; Ōmura, S. *Tetrahedron Lett.* **1991**, *32*, 841.

(10) Smith, A. B., III; Wood, J. L.; Gould, A. E.; Ōmura, S.; Komiyama, K. *Tetrahedron Lett.* **1991**, *32*, 1627.

(11) Doyle, M. P.; Van Oeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982.

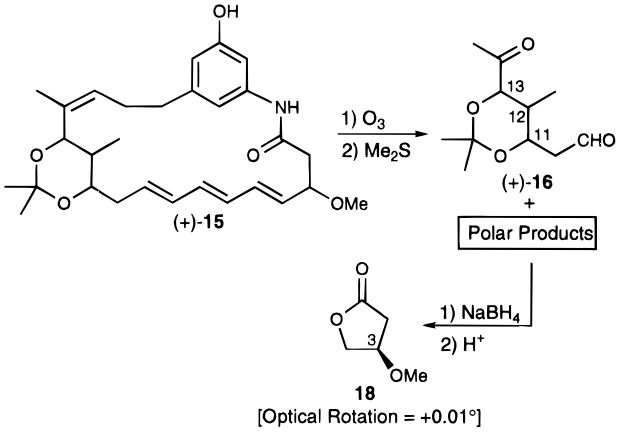
(12) Preparation of hydroxy γ-lactone: (a) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389. (b) Tanaka, A.; Yamashita, K. *Synthesis* **1987**, 570. Conversion to *O*-methyl derivative: (c) Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1949**, *32*, 2003.

(13) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (b) Basha, A.; Lipton, M. F.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. (c) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49.

(14) For a review of ozonolysis, see: Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1, Chapter 4, p 15.

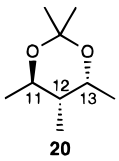
Me_2S afforded keto aldehyde (+)-**16** [$[\alpha]_D^{25}$ +45° (*c* 0.53, $CHCl_3$)] in 35% yield along with a mixture of more polar materials (Scheme 4). Reduction of the mixture with excess $NaBH_4$ followed by exposure to strong acid provided only a trace (<1 mg) of γ-lactone **18**. Moreover, the optical rotation was only +0.01°, providing at best a tentative assignment of the *R* configuration at C(3).

Scheme 4



Relative and Absolute Stereochemistry of Fragment 16: Molecular Modeling and Asymmetric Synthesis. Given a viable degradation route to keto aldehyde (+)-**16** we focused on determination of the relative and absolute configurations of C(11), C(12), and C(13). We first analyzed the relative stereochemistry via ^{1}H NMR, anticipating that the initial assignments would ultimately be secured by asymmetric synthesis. Importantly, the C(11,12) and C(12,13) coupling constants for both (+)-**15** and (+)-**16** were quite similar to those reported for the pentamethyl-1,3-dioxane **20**[15] (Table 1).

Table 1. Observed $J_{11,12}$ and $J_{12,13}$ Values (Trienomycin Numbering) for (+)-**15**, (+)-**16**, and **20**

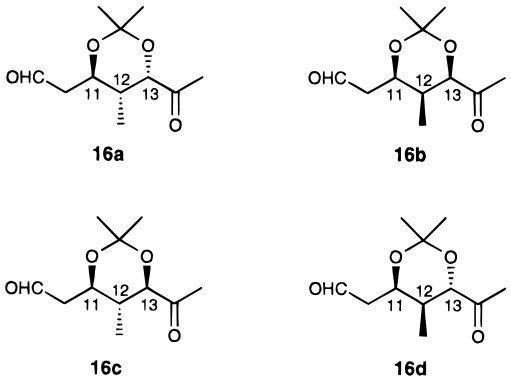


20

compound	$J_{11,12}$ (Hz)	$J_{12,13}$ (Hz)
(+)-**15**	8.5	5.9
(+)-**16**	7.7	5.6
20	7.9	5.3

The relative stereochemistry was further evaluated by subjecting the four diastereomers of keto aldehyde (+)-**16** (**a**−**d**, Table 2) to a Monte Carlo conformational search.[16] MacroModel[17] was then employed to predict C(11,12) and C(12,13) coupling constants (Table 2) for all conformations within 1.0 kcal/mol of the global minima. By far the best correlation with the experimental couplings was obtained for a twist−boat conformer of the C(11,12)-anti, C(12,13)-syn isomer **16a** [$J_{C(11,12)}$ = 8.7 Hz, $J_{C(12,13)}$ = 5.3 Hz], providing further support for our tentative assignment.

Table 2. Calculated Energies and Coupling Constants for the Favored Monte Carlo Conformations of **16a**−**d**



16a **16b** **16c** **16d**

isomer	MM2 energy (kcal/mol)	$J_{11,12}$ (Hz)	$J_{12,13}$ (Hz)	ring conformation
16a	−7.96	10.7	5.3	chair
	−7.89	10.7	5.3	chair
	−7.82	10.7	5.3	chair
	−7.61	10.7	5.3	chair
	−7.05	*8.7*	*5.3*	*twist boat*
16b	−9.95	2.7	2.1	chair
	−9.70	2.7	2.8	chair
	−9.13	2.7	2.8	chair
	−9.04	2.7	2.7	chair
16c	−11.05	10.6	11.0	chair
	−11.14	10.6	11.1	chair
	−10.98	10.7	11.1	chair
16d	−8.43	2.6	0.6	chair
	−8.29	2.7	0.6	chair
	−7.89	2.6	0.6	chair
	−7.78	5.3	9.5	twist boat
	−7.49	5.4	9.5	twist boat
exptl: 15,16		*8.5, 7.7*	*5.9, 5.6*	

Reasonably confident of the relative stereochemistry, we embarked on an asymmetric synthesis of **16a**, the C(11,12)-anti, C(12,13)-syn diastereomers (Scheme 5).[18] DIBAL reduction of the known butenolide (+)-**21**[19] afforded a 1:1 mixture of epimeric lactols **22** (99% yield). Wittig methylenation (*n*-BuLi, Ph_3PCH_3Br, THF, 0 °C; 83%), protection of the resultant diol (+)-**23** as the acetonide (98%), and desilylation (TBAF, THF; quantitative) provided alcohol (−)-**25**. Treatment of (−)-**25** with excess *m*-CPBA and $NaHCO_3$ (CH_2Cl_2 at reflux) then furnished epoxide **26** as a 3:1 diastereomeric mixture in 81% yield. To facilitate characterization of more advanced intermediates, the isomers were separated chromatographically and the major epimer [(−)-**26**] was subjected to Swern oxidation, affording aldehyde (−)-**27** in 97% yield. Standard Wittig olefination (*n*-BuLi, Ph_3PCH_3Br, THF) proved unsatisfactory, but a salt-free protocol (KH, Ph_3PCH_3Br)[20] delivered the requisite olefin (−)-**28** in 70% yield. Hydroboration and oxidative workup afforded alcohol (−)-**29** (48%). Finally, LAH-mediated epoxide opening followed by Swern oxidation of the resultant alcohol gave keto aldehyde (−)-**16a** [$[\alpha]_D^{25}$ −44.6° (*c* 0.53, $CHCl_3$)] in 35% yield for the two steps. This

(15) Pihlaja, K.; Kellie, G. M.; Riddell, F. G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 252.

(16) (a) MacroModel V2.5: Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. Department of Chemistry, Columbia University, New York, NY 10027. (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

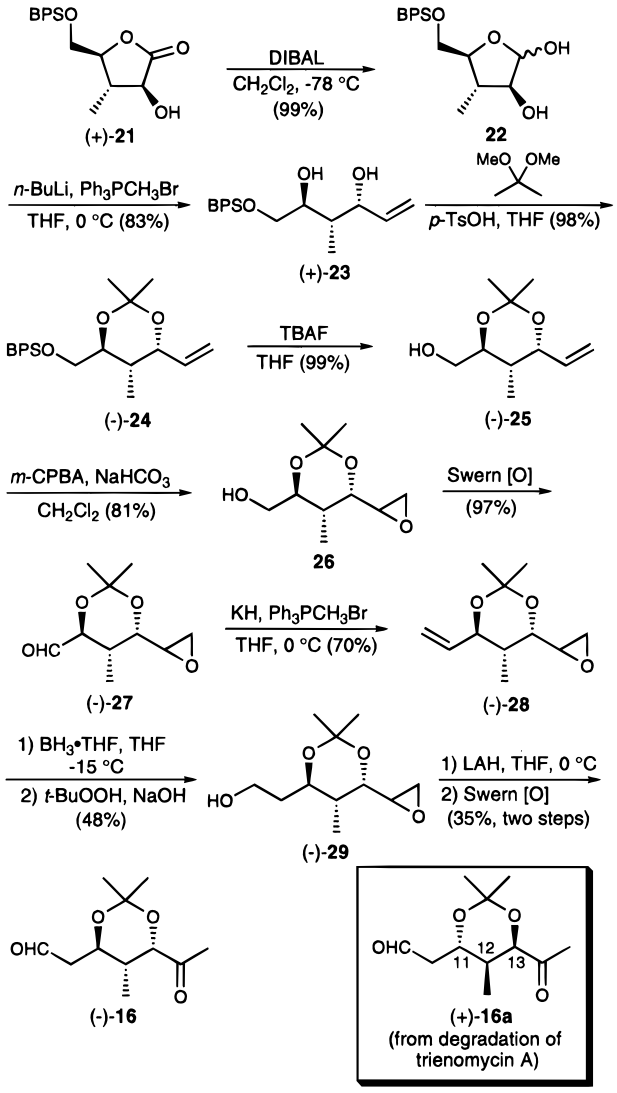
(17) Coupling constants were determined in the NMR submode of MacroModel.

(18) Wong, W. Ph.D. Thesis, University of Pennsylvania, Philadelphia, PA, 1993.

(19) (a) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055. (b) Hanessian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170.

(20) Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1978**, *43*, 1031.

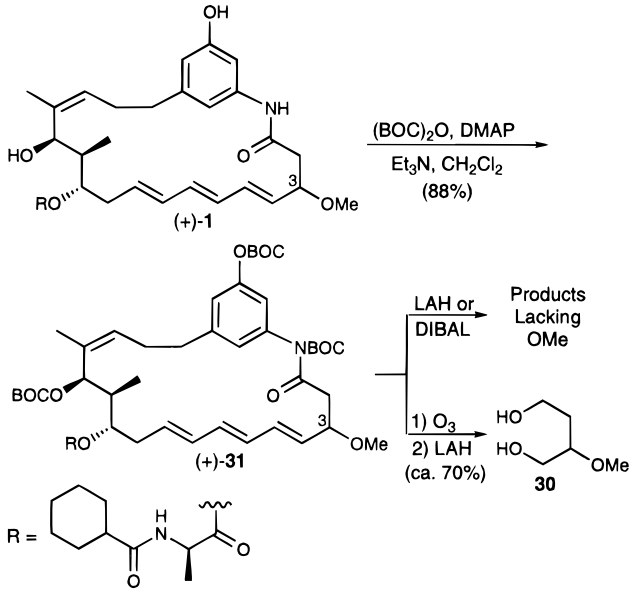
Scheme 5



material proved identical to **16** obtained via degradation of (+)-**1** in all respects except for the sign of optical rotation. Thus, the relative stereochemistry was confirmed and the absolute stereochemistry established as 11*S*, 12*S*, 13*R*. As described in the accompanying paper,[21] we have also prepared the enantiomer (+)-**16** as a key intermediate in a total synthesis of (+)-trienomycins A and F.

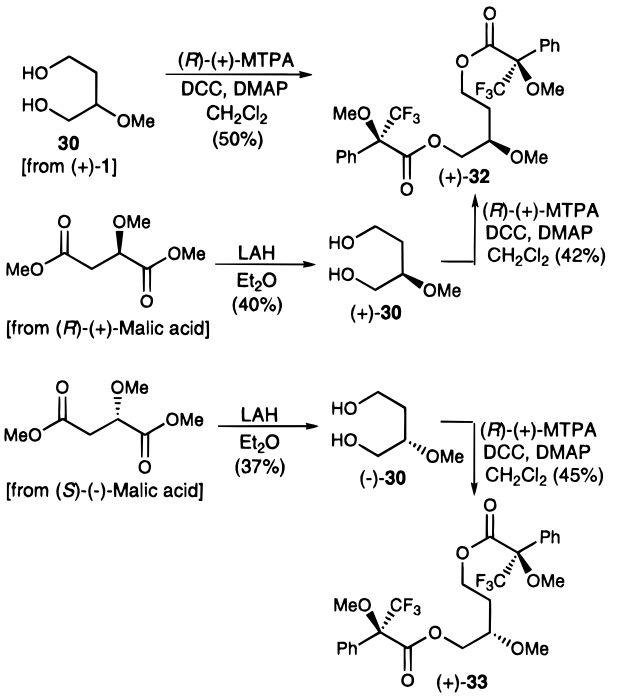
An Effective Tactic for Determination of the C(3) Absolute Configuration. Although our initial degradation scheme succeeded admirably in elucidation of the C(11−13) configurations, the stereochemistry at C(3), the final stereocenter within the trienomycin A macrocyclic skeleton, remained uncertain. We envisioned that 2-methoxy-1,4-butanediol (**30**), an alternative degradation target, could be generated via Fukuyama reduction of the BOC-protected secondary amide **31**, followed by ozonolysis and reduction of the derived hydroxy aldehyde. To this end, (+)-**1** was converted to the tris-BOC derivative (+)-**31** (Scheme 6).[22] Direct reduction of the amide with DIBAL or LAH afforded products devoid of the C(3) methoxy group, which presumably underwent β-elimination. However, treatment of (+)-**31** with ozone prior to LAH reduction provided the desired diol **30** in 70% yield.

Scheme 6



Following derivatization of **30** as the bis(Mosher ester) (+)-**32**, careful comparison (i.e., GC/MS, HRMS, ^{1}H and ^{13}C INEPT NMR) with authentic samples of the diastereomers (+)-**32** and (+)-**33** unambiguously verified the *R* configuration at C(3) (Scheme 7), in accord with our tentative earlier assignment. The relative and absolute stereochemistry of the (+)-trienomycin A skeleton thus proved to be 3*R*, 11*S*, 12*R*, 13*R*,[23] completely defining the structure of the natural product in conjunction with the side-chain degradation studies of Umezawa.

Scheme 7



Relative and Absolute Configurations of (+)-Trienomycins B and C. We next sought to elucidate the stereochemistries of (+)-trienomycins B (**2**) and C (**3**) via chemical correlation. All three congeners were believed to embody a common macrolactam, but in contrast with (+)-trienomycin A [(+)-**1**], the absolute configurations of the alanine side chains in (+)-**2** and (+)-**3** were not assigned in the initial structure work.[1b]

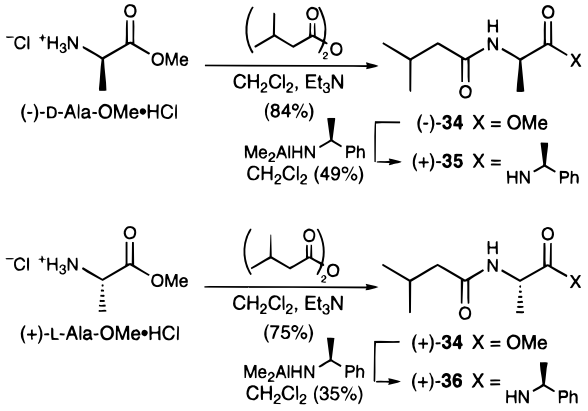
(21) See following article in this issue: Smith, A. B., III; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 8316.

(22) Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 5196. Also see: Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

(23) Following the CIP sequence rules, the analogous configuration of (+)-**16** is designated 11*S*, 12*S*, 13*R*.

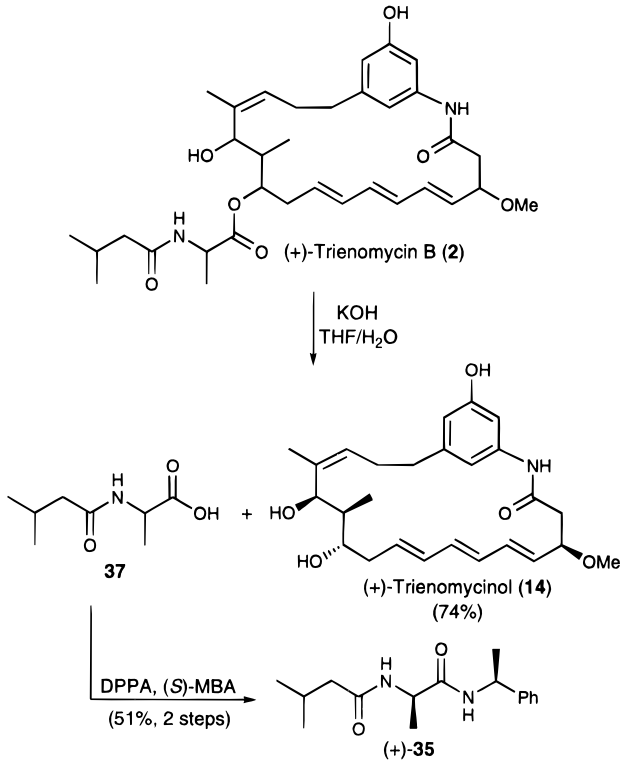
Reverse-phase HPLC afforded pure samples of (+)-**2** and (+)-**3**.[24] Before undertaking the degradative cleavage of the side chains, we prepared authentic derivatives containing the *N*-acylalanine moiety in **2**. Acylation of D- and L-alanine methyl ester hydrochlorides with the symmetrical anhydride[25] of isovaleric acid furnished (−)-**34** and (+)-**34** (Scheme 8). Unfortunately, the specific rotations of these enantiomers were quite low, and we were reluctant to pursue a degradation strategy that would rely solely upon this analytical technique. Instead, we chose to employ the chiral auxiliary (*S*)-α-methylbenzylamine (MBA), anticipating that the resultant diastereomers could be differentiated either spectroscopically or chromatographically. In addition, this group could be readily incorporated into the requisite authentic samples by acylation of the derived dimethylaluminum amide[13] with the alanine methyl esters (−)- and (+)-**34**, providing amides (+)-**35** and (+)-**36**, respectively (Scheme 8).

Scheme 8



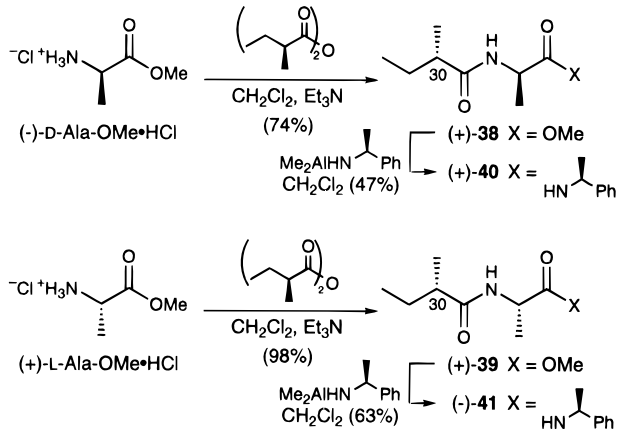
With these materials in hand, we attempted to liberate the intact side chain of (+)-trienomycin B (**2**). Following saponification of (+)-**2** with KOH (Scheme 9), the organic phase contained (+)-trienomycinol (**14**), identical in all respects with the compound obtained via degradation of (+)-**1**. Acidification of the aqueous phase afforded carboxylic acid **37**, which without purification was subjected to diphenylphosphoryl azide (DPPA)-mediated coupling[26,27]with (*S*)-MBA. The formation of amide (+)-**35** established the D configuration of the alanine residue in (+)-**2**.

Scheme 9



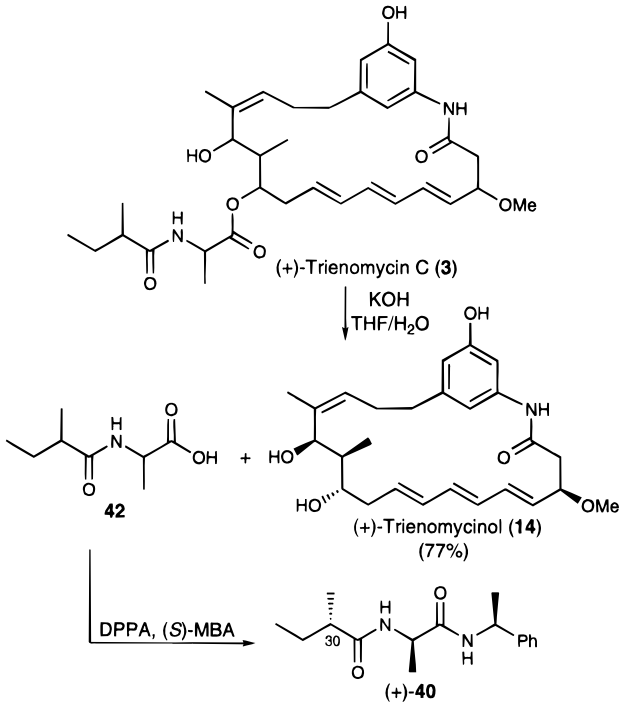
For the synthesis of the side-chain moities of (+)-trienomycin C, only the *S* enantiomer of 2-methylbutyric acid was available. Further exploiting the successful strategy devised for **2**, the D- and L-alanine methyl ester hydrochlorides were first acylated with the symmetrical anhydride[25] of (*S*)-2-methylbutyric acid (Scheme 10). Coupling of the resultant methyl esters [(+)-**38** and (+)-**39**] with the dimethylaluminum amide[13] of (*S*)-MBA then afforded (+)-**40** and (−)-**41**, respectively.

Scheme 10



By analogy with the degradation of **2**, saponification of (+)-trienomycin C (**3**) with KOH generated (+)-trienomycinol (**14**), again identical with the macrocycle derived from (+)-**1**, as well as the crude acid **42** (Scheme 11). Coupling of **42** with (*S*)-MBA (DPPA)[26,27] afforded amide (+)-**40**, revealing both the D configuration of the side-chain alanine moiety and the *S* configuration at C(30).

Scheme 11



Isolation and Characterization of a New Congener, (+)-Trienomycin F. In the course of our stereochemical investiga-

tions, we discovered that mixtures of (+)-trienomycins B and C also contained small amounts of a new congener, which we designated (+)-trienomycin F (**13**). After HPLC separation, comparison with **1**−**3** via 500-MHz ^{1}H NMR suggested that **13** contained a different acyl fragment attached to the D-alanine residue. Three distinct resonances were attributable to this moiety: a quartet of doublets (δ 6.53, J = 1.4 and 6.9 Hz, 1 H), an apparent triplet (δ 1.83, J_{app} =1.1 Hz, 3 H), and a doublet of doublets (δ 1.75, J =1.0 and 6.9 Hz, 3 H).[28] In conjunction with homonuclear decoupling experiments, which verified the 6.9-Hz coupling between the resonances at δ 1.75 and 6.53, these data were indicative of a 2-methyl-2-butenamide unit. Comparison of the chemical shift for the C(31) vinylic proton in (+)-**13** with the corresponding resonances for methyl tiglate (**43a**), methyl angelate (**44a**), and the derived *N*-acyl-D-alanine methyl esters **43b** and **44b**[29] then established the *E* geometry of the C(30,31) olefin (Table 3).

Table 3. Vinylic ^{1}H NMR Chemical Shifts for (+)-**13** and Four Model 2-Methyl-2-butenamides

a R = OMe
b R = D-Ala-OMe

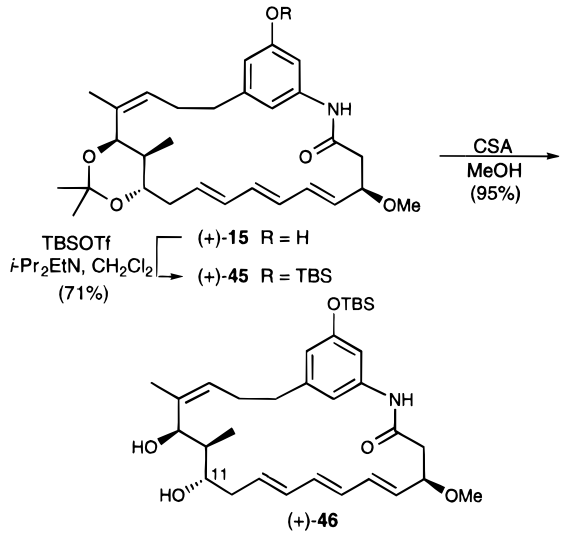
compound	R	δ (ppm)
43a	OMe	6.97
44a	OMe	6.18
43b	D-Ala-OMe	6.48
44b	D-Ala-OMe	5.57
(+)-**13**	D-Ala-OR	6.53

Partial Synthesis of (+)-Trienomycins A and F: A Flexible End-Game Synthetic Strategy. To confirm the structure of (+)-trienomycin F (**13**), we designed a partial synthesis from (+)-trienomycinol (**14**), available in adequate quantities from our degradation work. We anticipated that an end-game strategy for a unified synthetic approach to the trienomycins would also emerge from this effort.

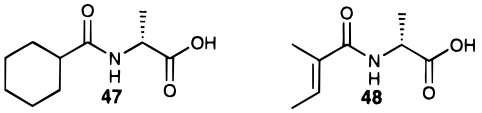
Our first concern *a priori* was chemoselective functionalization of the C(11) hydroxyl. Importantly, Zeeck and co-workers employed DCC to achieve the selective C(11) acylation of (+)-mycotrienol I (**8**).[5b] Extension of this tactic to our system would entail protection of the phenolic hydroxyl in acetonide (+)-**15** and liberation of the anti diol prior to the critical acylation step.

In the event, the phenol was readily converted to the methyl ether (MeI, Ag_2O, Δ, 31% yield)[12c] and MEM ether (MEM Cl, *i*-Pr_2EtN, CH_2Cl_2, 77%),[30] but attempts to remove these groups met with limited success. Turning next to a silyl protecting group, reaction of **15** with *tert*-butyldimethylsilyl (TBS) triflate[31] gave the ether in 71% yield (Scheme 12). In this case, the TBS group could be removed with TBAF[32] in CH_2Cl_2. Methanolysis of the acetonide (camphorsulfonic acid, MeOH) then provided diol (+)-**46** (95%).

Scheme 12

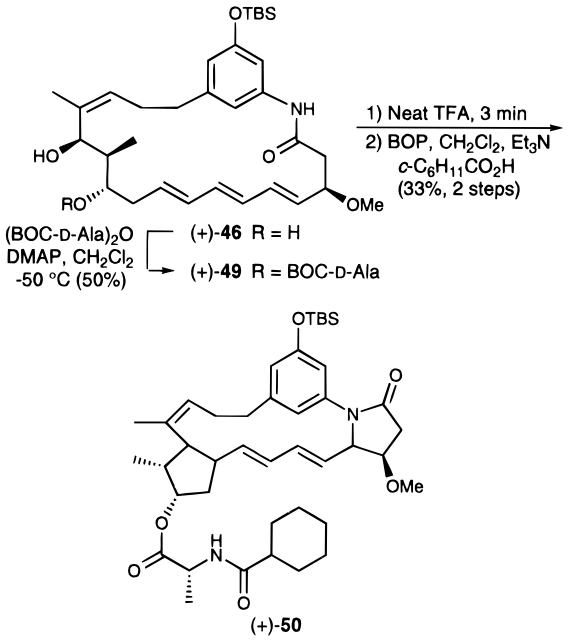


In principle, the selective C(11) acylation could be effected with either the complete side chain or an N-protected alanine derivative. The latter approach would require subsequent deprotection and N-acylation, whereas the former would rely upon the DPPA method[26,27] described earlier to suppress epimerization of the *N*-acylamino acid. This issue was resolved when DPPA failed to promote coupling of (+)-**46** with either **47** or **48**,[33] the side chains of (+)-trienomycins A and F, respectively.



At this juncture, we turned to the stepwise route, whereby initial acylation of the C(11) hydroxyl in (+)-**46** with the symmetrical anhydride[25] of BOC-D-alanine[34] (DMAP, CH_2Cl_2, −50 °C) afforded (+)-**49** in 50% yield (Scheme 13). Subsequent unmasking of the amine with neat TFA[35] resulted in

Scheme 13



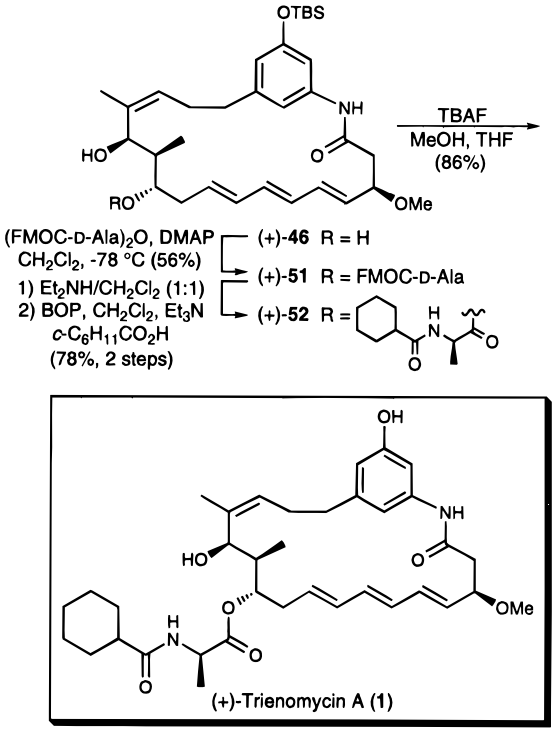
skeletal rearrangement; acylation with cyclohexane carboxylic acid and benzotriazol-1-yloxytris(dimethylamino) phosphonium

(24) From ca. 100 mg of a mixture believed to contain only (+)-trienomycins B and C, we isolated ca. 3 mg of (+)-trienomycin F.
(25) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: New York, 1984; p 101.
(26) The Weinreb aluminum amide couplings were accompanied by partial (ca. 10−22%) epimerization at C(28).
(27) (a) See ref. 25, p 247. (b) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(28) Chemical shift data are reported in ppm relative to internal TMS.
(29) Nair, M. D.; Adams, R. *J. Am. Chem. Soc.* **1961**, *83*, 922.
(30) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
(31) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(32) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

hexafluorophosphate (BOP)[36] then furnished a compound spectroscopically in accord with the structure (+)-**50**.[37]

To circumvent the acid-promoted rearrangement, we employed the base-labile FMOC protecting group. Selective C(11) acylation of (+)-**46** with the symmetrical anhydride[25] of FMOC-D-alanine[38] gave (+)-**51** in 56% yield (Scheme 14) along with

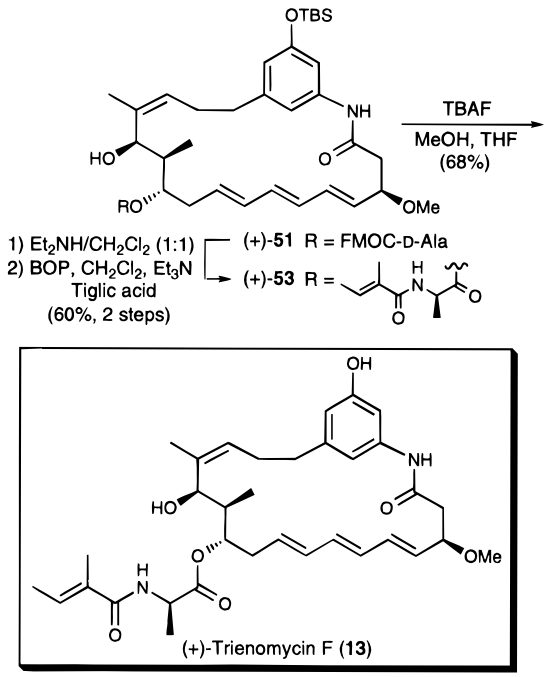
Scheme 14



a 28% combined yield of the C(13)-*O*-acyl and bis-acyl products. Liberation of the primary amine by exposure to diethylamine in CH_2Cl_2 (1:1, 25 °C, 30 min)[38] followed directly by BOP-mediated coupling with cyclohexanecarboxylic acid afforded (+)-**52** (78% yield, two steps). Desilylation with TBAF[32] then furnished (+)-trienomycin A (**1**), identical with the natural material in all respects [500-MHz ^{1}H NMR, 125-MHz ^{13}C (INEPT) NMR, IR, UV, HRMS, optical rotation, TLC (three solvent systems), melting point, and mixed melting point].

Having established the viability of our end-game synthetic strategy, we next confirmed the structure of (+)-trienomycin F (**13**) via an analogous sequence (Scheme 15). Specifically, the FMOC group in (+)-**51** was removed with diethylamine as

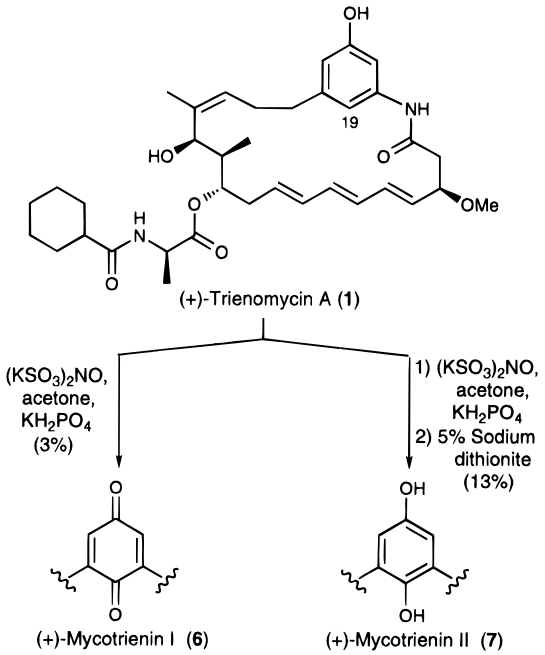
Scheme 15



before, followed by acylation with tiglic acid and BOP to give (+)-**53**. Cleavage of the TBS group provided semisynthetic (+)-**13** in 68% yield, identical with natural (+)-trienomycin F. The 3*R*, 11*S*, 12*R*, 13*R*, 28*R* configurations we elucidated for (+)-trienomycins A−C were conserved in the new congener.

Stereochemistry of (+)-Mycotrienins I and II. As in the trienomycin series, the relative and absolute stereochemistries of the mycotrienins have remained unknown apart from the D-alanine side-chain configuration. In an effort to extend the (+)-trienomycin assignments to the (+)-mycotrienins, we explored the possibility of chemical correlation via selective C(19) oxidation of (+)-trienomycin A (**1**) (Scheme 16).

Scheme 16



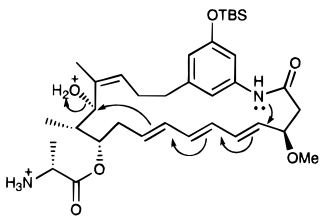
(33) Acids **47** and **48** were prepared via coupling of D-alanine methyl ester with the symmetrical anhydrides of cyclohexanecarboxylic and tiglic acids, respectively, followed by ester hydrolysis.

(34) BOC-D-alanine was purchased from Schweizerhall, Inc. (South Plainfield, NJ).

(35) See ref 25, p 170.

(36) (a) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219. (b) Castro, B.; Dormoy, J. R.; Dourtoglou, B.; Evin, G.; Selve, C.; Ziegler, J.-C. *Synthesis* **1976**, 751. (c) Castro, B.; Evin, G.; Selve, C.; Seyer, R. *Synthesis* **1977**, 413.

(37) A plausible pathway for the formation of (+)-**50** under acidic conditions is illustrated below. The propensity of related model systems to form γ-lactams has also been observed in our laboratory (Wood, J. L., unpublished results).



(38) Chang, C. D.; Waki, M.; Ahmad, M.; Meienhofer, J.; Lundell, E. O.; Haug, J. D. *Int. J. Peptide Protein Res.* **1980**, *15*, 59.

Oxidation of (+)-**1** with Fremy's salt [$(KSO_3)_2NO$][39] furnished (+)-mycotrienin I (**6**) in 3% yield. Despite partial decomposition upon exposure to silica, the identity of semisynthetic **6** was unambiguously established by comparison [500-MHz ^1H and 125-MHz ^{13}C (INEPT) NMR, IR, HRMS, optical rotation, and TLC (three solvent systems)] with a sample of natural (+)-mycotrienin I.[40] A second sample of (+)-**1** was likewise treated with Fremy's salt and then washed with 5% aqueous sodium dithionite to reduce the resultant quinone to the hydroquinone. Semisynthetic (+)-mycotrienin II (**7**), isolated in 13% yield, proved indistinguishable from natural material as well. These results revealed that the (+)-mycotrienins share the chiral architecture of the (+)-trienomycins, differing only in the oxidation state of the aromatic nucleus.

Summary. The complete relative and absolute stereochemistries of (+)-trienomycins A, B, and C (**1**−**3**) have now been elucidated. These investigations also led to the discovery and characterization of a new congener, (+)-trienomycin F (**13**). The partial synthesis of (+)-**1** and (+)-**13** established the viability of (+)-trienomycinol (**14**) as an advanced intermediate in a unified synthetic approach to the trienomycins. In addition, the trienomycin stereochemical assignments were extended to (+)-mycotrienin I and II (**6** and **7**) and hence to (+)-mycotrienols I and II (**8** and **9**).[41]

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Supporting Information Available: Complete experimental details for compounds **1**, **6**, **7**, **13**, **15**, **16**, **19**, **23**−**26a**, **26b**, **27**−**36**, **38**−**41**, **43b**, **44b**, **45**, **46**, **49**, and **50**−**53** (21 pages). See any current masthead page for ordering and Internet access instructions.

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(39) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229.

(40) We gratefully acknowledge a generous gift of (+)-mycotrienins I and II from Professor H. Seto (University of Tokyo).

(41) Mycotrienin II has been converted to mycotrienols I and II: (a) ref 4c. (b) Sugita, M.; Hiramoto, S.; Andō, C.; Sasaki, T.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 799.