Total Synthesis of (+)-Trienomycins A and F

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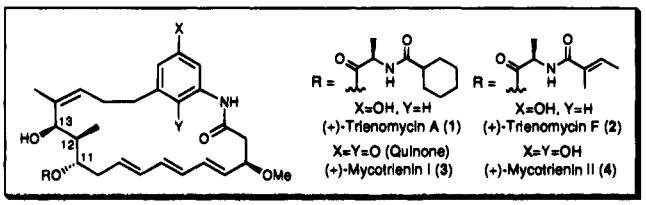
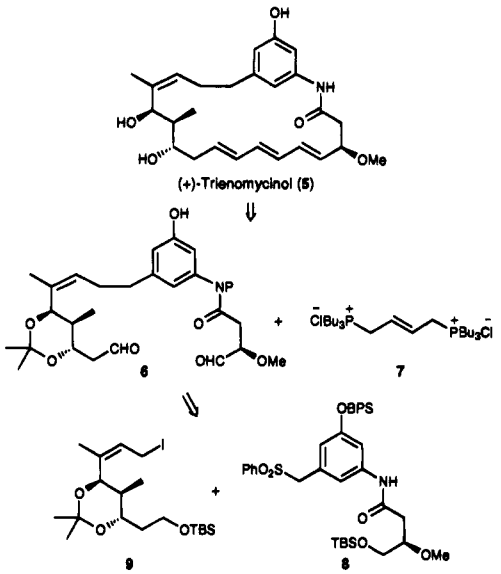
In 1985, Umezawa and co-workers at the Kitasato Institute (Tokyo) reported the isolation and planar structures of the trienomycins A−E, a new family of ansamycin antibiotics produced in the culture broth of *Streptomyces* sp. No. 83-16.[1] Bioassays revealed significant in vitro cytotoxicity against HeLa S_3 cells;[2] (+)-trienomycin A (**1**), the most potent congener, is also active against human PLC hepatoma (IC_{50} 0.01 μg/mL) and the L-5178Y murine leukemia cell line.[3] A sixth compound, (+)-trienomycin F (**2**), was discovered in our laboratories in 1990.[4,5]



As prelude to total synthesis, we determined the relative and absolute stereochemistries of the trienomycins via degradation to (+)-trienomycinol (**5**, Scheme 1), in conjunction with extensive ^1H and ^{13}C NMR studies and the partial syntheses of (+)-trienomycins A and F from **5**.[4,5] The trienomycin skeleton embodies an (*E,E,E*)-triene within a 21-membered lactam ring; functionalized C(11) side chains differentiate the individual structures. The closely related mycotrienins I and II (**3** and **4**) were isolated from the fermentation broth of *S. rishiriensis* T-23, which also produces (+)-trienomycin A (**1**) as a minor constituent.[6] We established the complete relative and absolute stereochemistries of the mycotrienins by chemical conversion of **1** to **3** and **4**.[7]

Retrosynthetically we envisioned (+)-trienomycinol (**5**), or a protected form thereof, as an advanced precursor to each of the trienomycins and in turn the mycotrienins (Scheme 1). A novel bis-olefination reaction of dialdehyde **6** with Wittig reagent **7** would install the (*E,E,E*)-triene unit of **5** and thereby effect macrolactamization.[8] Dialdehyde **6** would arise via

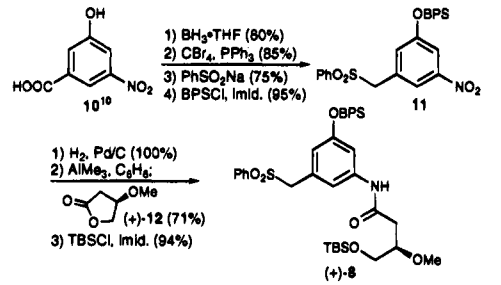
Scheme 1



alkylation of sulfone **8** with iodide **9**. A key consideration in this scenario was selection of an appropriate protecting group (P) for the secondary amide (vide infra). Herein we describe the first total syntheses of trienomycins A and F (**1** and **2**).[9]

Our point of departure for the phenolic subunit **8** was benzoic acid **10** (Scheme 2), readily available from 3,5-dinitrobenzoic acid in two steps.[10] Borane reduction, conversion to the benzylic bromide, displacement with sodium benzenesulfinate, and protection of the phenol as the *tert*-butyldiphenylsilyl (BPS) ether then provided sulfone **11**.[11] Reduction of the nitro group (H_2, Pd/C), acylation of the resultant amine with lactone (+)-**12**,[12] and masking of the primary hydroxyl as the *tert*-butyldimethylsilyl (TBS) ether completed construction of (+)-**8**.[11]

Scheme 2



Synthesis of allylic iodide **9** began with an Evans aldol addition of (+)-**13**[13] to methacrolein, affording exclusively the desired syn diastereomer (Scheme 3).[13,14] Silylation (TBS),

(1) Nomoto, H.; Katsumata, S.; Takahashi, K.; Funayama, S.; Komiyama, K.; Umezawa, I.; Ōmura, S. *J. Antibiot.* **1989**, *42*, 479 and references cited therein.

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

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(6) Sugita, M.; Natori, Y.; Sueda, N.; Furihata, K.; Seto, H.; Ōtake, N. *J. Antibiot.* **1982**, *35*, 1474 and references cited therein.

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

(8) The bis-Wittig macrocyclic ring construction was initially developed by John Wood in our laboratory: Wood, J. L. Ph.D. Thesis, University of Pennsylvania, 1991. For related reactions of bis-Wittig reagent **7** and substituted benzaldehydes and cinnamaldehydes leading to α,ω-diphenyl polyenes having the all (*E*)-configuration; see: Spangler, C. W.; McCoy, R. K.; Dembek, A. A.; Sapochak, L. S.; Gates, B. D. *J. Chem. Soc., Perkin Trans. 1* **1989**, 151. For an alternative strategy to a macrolide containing an (*E,E,E*)-triene unit, see: Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419.

(9) Other synthetic approaches to the trienomycins and mycotrienins: (a) Yadav, J. S.; Praveen Kumar, T. K.; Maniyan, P. P. *Tetrahedron Lett.* **1993**, *34*, 2965; 2969. (b) Panek, J. S.; Yang, M.; Solomon, J. *Tetrahedron Lett.* **1995**, *36*, 1003.

(10) Herlt, A. J.; Kibby, J. J.; Rickards, R. W. *Aust. J. Chem.* **1981**, *34*, 1319.

(11) All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 500-MHz ^1H NMR, and 62.8- or 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. In addition, compounds **8**, **11**, **16**, and **18** gave satisfactory combustion analyses.

(12) Preparation of the 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 the *O*-methyl derivative: Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1949**, *32*, 2003.

(13) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127 and references cited therein.

(14) The relative configurations at C(12) and C(13) were determined via X-ray analysis: unpublished results of Dr. Patrick J. Carroll, University of Pennsylvania.

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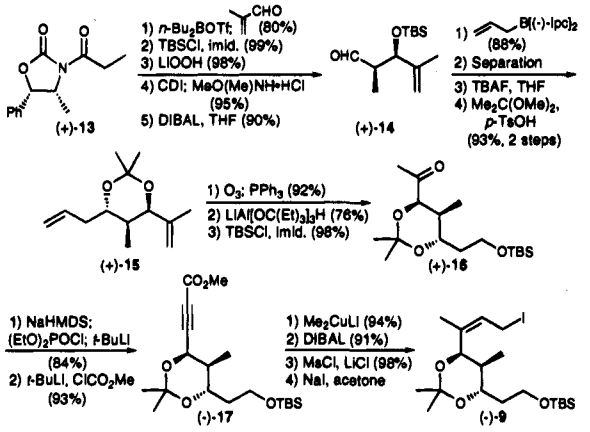
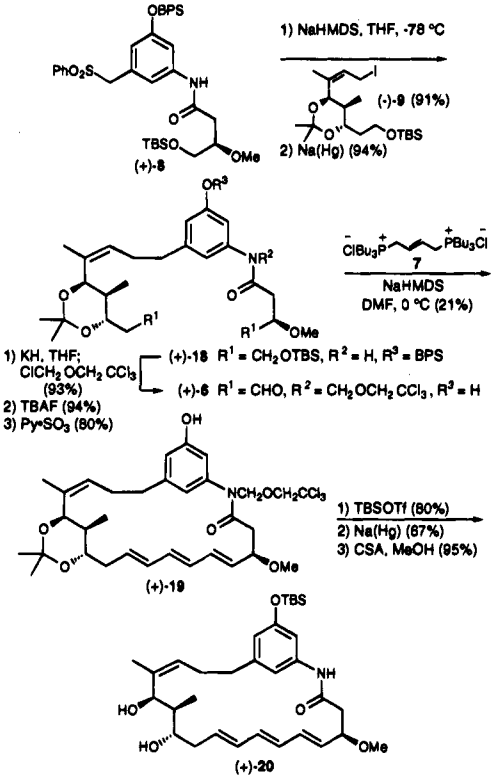
Scheme 3



hydrolysis (LiOOH, 3:1 THF/H_2O, 0 °C, 2 h)[15] to the acid (with full recovery of the chiral auxiliary), preparation of the Weinreb amide [1,1′-carbonyldiimidazole (CDI); *N,O*-dimethylhydoxylamine•HCl],[16] and DIBAL reduction[17] cleanly afforded aldehyde (+)-**14**[11] (66% yield, five steps). Allylboration via the Brown protocol[18] then yielded predominantly the requisite alcohol as a 12.5:1 mixture of diastereomers. Separation of the epimers, desilylation, and acetonide protection[19] furnished diene (+)-**15**.[11] Ozonolysis, chemoselective reduction of the derived aldehyde with lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride,[20] and silylation of the resultant alcohol smoothly generated ketone (+)-**16**.[11] Following conversion to the acetylene via the procedure of Negishi,[21] cuprate addition to the derived alkynyl ester (−)-**17**[11] provided exclusively the desired (*Z*) olefin.[22,23] DIBAL reduction then afforded the allylic alcohol, which was readily converted to the chloride and in turn to the unstable iodide (−)-**9**.

Without delay, iodide (−)-**9** was coupled with (+)-**8**; reductive desulfonylation then furnished adduct (+)-**18**[11] in excellent yield (86% over three steps from the allylic chloride) (Scheme 4). At this juncture, amide protection was required to block formation of the *N*-acyl hemiaminal, which did not undergo the bis-Wittig reaction. The choice of protecting group proved to be unexpectedly critical: attempted olefination of the Boc derivative led to β-elimination of methoxy, whereas *p*-methoxybenzyl and 2-(trimethylsilyl)ethoxymethyl (SEM) moieties could not be removed without extensive decomposition under oxidative (e.g., DDQ, CAN) or acidic conditions, respectively. Turning next to functionalities susceptible to reductive cleavage, we noted that Evans successfully utilized the 2,2,2-trichloroethoxymethyl unit for hydroxyl protection.[24] Moreover, Solladié established that (*E,E,E*)-trienes can survive exposure to Na(Hg),[25] the reagent Evans employed to fragment the β-chloroethyl acetal. Treatment of (+)-**18** with chloromethyl 2,2,2-trichloroethyl ether,[26] removal of the three silyl groups (TBAF), and oxidation with pyridine•SO_3 afforded dialdehyde (+)-**6**,[11] the key cyclization substrate. Addition of NaHMDS to a mixture of (+)-**6** and bis-Wittig salt **7** (DMF, 0 °C) led to the desired macrolactam (+)-**19**[11] in 21% yield, admixed with other triene isomers (34%).[27] Silylation of the phenol, liberation of the amide N−H with Na(Hg),[24] and acetonide removal provided the known TBS ether[5] of (+)-trienomycinol [(+)-**20**].[11] Installation of the side chains and desilylation, as we described previously,[5] gave (+)-trienomycins A (**1**) and F (**2**), identical in all respects with the corresponding natural products (^{1}H and ^{13}C NMR, IR, HRMS, optical rotation, and TLC in three solvent systems).

Scheme 4



In summary, we have completed the first total syntheses of representative trienomycin antibiotics [i.e., A and F (**1** and **2**)]. The route should likewise provide access to the remaining members of the family. The synthesis of (+)-**1** also constitutes a formal total synthesis of mycotrienins I and II (**3** and **4**).

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Supporting Information Available: Spectroscopic and analytical data for **6**, **8**, **9**, **11**, and **14**−**20**, as well as selected experimental procedures (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(16) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157.

(17) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(18) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 320 and references cited therein.

(19) The relative configuration at C(13) was deduced from the ^{13}C chemical shifts of the acetonide carbons of (+)-**19** via the method of Rychnovsky and Evans: (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

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(23) The olefin geometry was determined by NOE analysis of intermediates not described.

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(26) Chloromethyl 2,2,2-trichloroethyl ether was prepared via a method devised earlier for BOM-Cl: Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K., Jr.; Medwid, J. B. *Organic Syntheses*; Wiley: New York, 1988, Coll. Vol. VI, p 101. Also see: Salomaa, P.; Linnantie, R. *Acta. Chem. Scand.* **1960**, *14*, 777.

(27) The stereochemistries of the triene cogeners and their isomerization to (+)-**19** are under active investigation.