(+)-Trienomycins A, B, and C: Relative and Absolute Stereochemistry

Amos B. Smith, III,* John L. Wood, Weichyun Wong, Alexandra E. Gould, and Carmelo J. Rizzo

Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania Philadelphia, Pennsylvania 19104

Shinji Funayama and Satoshi Ōmura*

School of Pharmaceutical Sciences, Kitasato University, and Kitasato Institute Minato-ku, Tokyo 108, Japan

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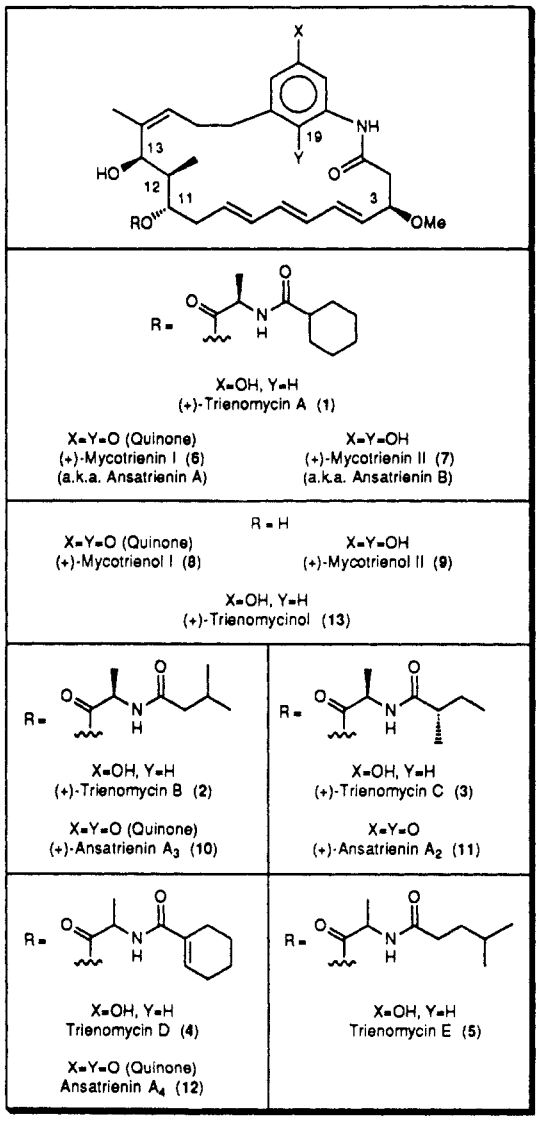
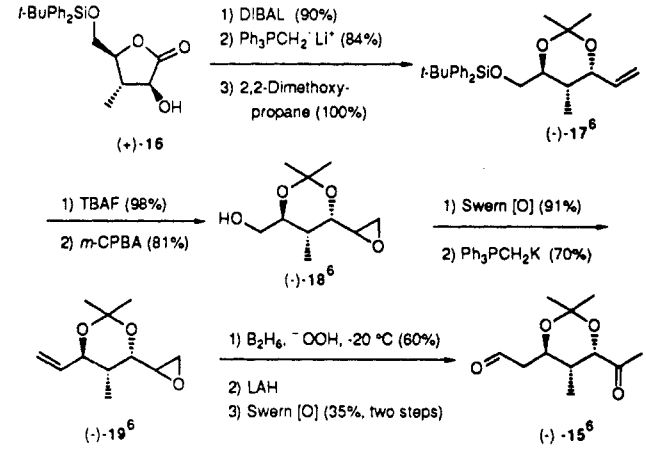
Umezawa and co-workers recently reported the isolation of five novel ansamycin antibiotics from the culture broth of *Streptomyces* sp. No. 83-16.[1] Termed trienomycins A-E (**1-5**), these compounds exhibited strong cytotoxicity in vitro against HeLa S_3 cells.[2]



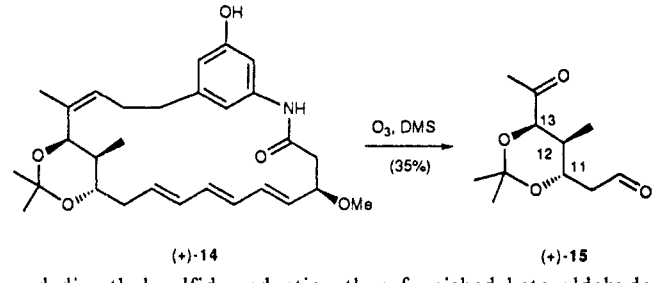
Scheme I



The most potent congener, (+)-trienomycin A [(+)-19-deoxymycotrienin II], along with (+)-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] Unlike the trienomycins, the mycotrienins displayed potent antifungal activity. Importantly, **6**, **7**, and several minor components (i.e., **10-12**) also were independently isolated from the culture broth of *Streptomyces collinus*[4] and designated the ansatrienins. Subsequent studies established the identity of the latter with the mycotrienins.[4c]

Surprisingly, the issues[5] of relative and absolute stereochemistry of the trienomycins and mycotrienins have not yet been addressed. As a prelude to total synthesis, we report here the complete relative and absolute configurations for (+)-trienomycins A, B, and C (**1-3**). These efforts should in turn facilitate biosynthetic studies underway elsewhere.[5]

As point of departure, deacylation of (+)-**1** [lithium aluminum hydride (LAH), -23 °C] to trienomycinol [(+)-**13**][2b] followed by acetonide formation [2,2-dimethoxypropane, camphorsulfonic acid (CSA)] provided (+)-**14**[6] (80% yield, two steps). Ozonolysis



and dimethyl sulfide reduction then furnished keto aldehyde (+)-**15**[6] as a colorless oil {$[\alpha]^{25}_D$ +45° (*c* 0.92, $CHCl_3$)}. The C(11,12) and C(12,13) proton coupling constants for (+)-**14** and (+)-**15** were determined to be 8.5 and 5.9 Hz and 7.7 and 5.6 Hz, respectively. Comparison with *J* values derived computationally for the four possible diastereomers of **15** revealed the C-(11,12)-trans, C(12,13)-cis relative stereochemistry and indicated that the dioxane rings in both (+)-**14** and (+)-**15** adopted twist-boat conformations.[7,8]

(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. *Ibid.* **1985**, *38*, 1677. (c) Nomoto, H.; Katsumata, S.; Takahashi, K.; Funayama, S.; Komiyama, K.; Umezawa, I.; Ōmura, S. *Ibid.* **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.; Shibata, K.; Komiyama, K.; Umezawa, I.; Ōmura, S. *Ibid.* **1988**, *41*, 1223.

(3) (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. *Ibid.* **1982**, *35*, 1467. (c) Sugita, M.; Natori, Y.; Sueda, N.; Furihata, K.; Seto, H.; Otake, N. *Ibid.* **1982**, *35*, 1474. (d) Sugita, M.; Furihata, K.; Seto, H.; Otake, N.; Sasaki, T. *Agric. Biol. Chem.* **1982**, *46*, 1111.

(4) (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. (c) See ref 3 in the following: Wu, T. S.; Duncan, J.; Tsao, S. W.; Chang, C. J.; Keller, P. J.; Floss, H. G. *J. Nat. Prod.* **1987**, *50*, 108.

(5) Casati, R.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1987**, *109*, 8102 and references cited therein.

(6) The structure assigned to each new compound is in accord with its infrared and high-field ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry.

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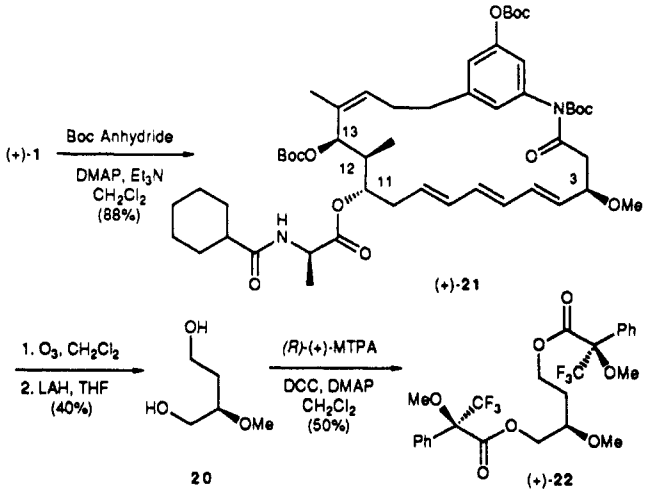
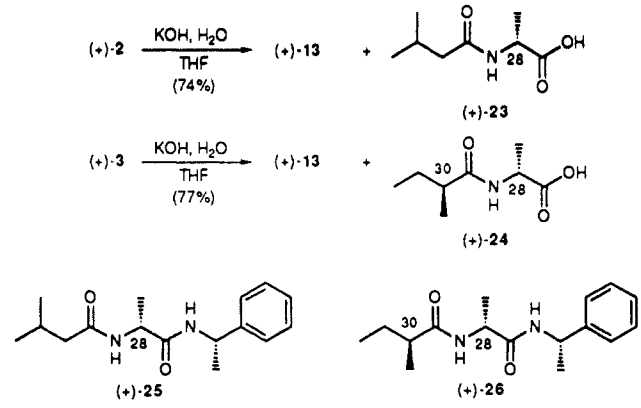
To elucidate the absolute configuration of the C(11,13) fragment, we embarked on an enantioselective synthesis of **15** (Scheme I) beginning with lactone (+)-**16**.[9] The resultant keto aldehyde [(−)-**15**][6] differed from the material obtained via degradation only in the sign of its optical rotation. This finding confirmed the relative configurations at C(11,13) and established the absolute stereochemistry of (+)-**15** as 11*S*,12*S*,13*R*.[10]

For investigation of the C(3) stereocenter of (+)-**1**, we envisioned 2-methoxy-1,4-butanediol (**20**)[11] as an attractive degradation target. Toward this end, protection of (+)-**1** as the tris-BOC derivative [(+)-**21**][6] followed by reductive ozonolysis (LAH) afforded diol **20** (40% yield),[12,13] which in turn was derivatized as the bis-Mosher ester (**22**).[6] Comparison with authentic samples of **22** and its C(3) diastereomer, prepared from (*S*)-(−)-, (*R*)-(+)-, and (±)-malic acid, permitted unambiguous assignment of the *R* absolute configuration at C(3).



We next elucidated the stereochemistry of trienomycins B and C via chemical correlation. Specifically, saponifications of (+)-**2** and (+)-**3** provided (+)-trienomycinol (**13**) and acids (+)-**23**[14] and (+)-**24**,[6] respectively. The latter furnished amides (+)-**25**[6] and (+)-**26**[6] [(*S*)-(−)-methylbenzylamine, diphenylphosphoryl azide (DPPA)], which in turn proved to be identical with authentic samples prepared from D-alanine.[15] Thus, the side chains in both (+)-**2** and (+)-**3** incorporate D-alanine moieties, and the additional C(30) stereocenter in (+)-**3** possesses the *S* configuration.

In summary, we have unambiguously assigned the complete relative and absolute configurations of trienomycins A, B, and C (**1-3**). The common absolute stereochemistry of **1-3** strongly suggests that similar features will prevail not only in trienomycins D and E but also in the closely related mycotrienins (**6** and **7**),



mycotrienols (**8** and **9**), and ansatrienins A_2-A_4 (**10-12**). Further stereochemical studies and progress toward the total synthesis of these potent antitumor/antifungal antibiotics will be reported in due course.

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Supplementary Material Available: Calculated coupling constant data for stereoisomers of compound **15** and spectroscopic data for compounds **14**, **15**, and **17-26** and stereoisomers of **22**, **25**, and **26** (12 pages). Ordering information is given on any current masthead page.

(7) Each isomer was subjected to a Monte Carlo conformational search: Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. The C(11,12) and C(12,13) ^{1}H coupling constants derived from the lowest energy conformations (i.e., those within 1.0 kcal/mol of the global minimum) were used for comparison.

(8) Further support for the cis-trans assignment emerged from the vicinal coupling constants reported for the twist-boat structure of *cis,trans*-2,2,4,5,6-pentamethyl-1,3-dioxane: $J_{4,5}$ = 5.3 Hz and $J_{5,6}$ = 7.9 Hz. See: Pihlaja, K.; Kellie, G. M.; Riddell, F. G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 252.

(9) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055.

(10) Following the CIP sequence rules, the corresponding configuration of (+)-**1** is 11*S*,12*R*,13*R*.

(11) Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1949**, *32*, 2003.

(12) Reduction of BOC-protected secondary amides to primary alcohols has been reported previously: 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.

(13) Compound **20** furnished high-field ^{1}H and ^{13}C (INEPT) NMR spectra and GC/MS data identical with those from a synthetic sample prepared by the method of Lardon.[11] Unfortunately, the low mass recovery of **20** precluded accurate measurement of the specific rotation.

(14) Schirlin, D.; Jung, M. Eur. Pat. Appl. EP 275,101, 1988; *Chem. Abstr.* **1989**, *110*, 173757v.

(15) The diastereomers of **25** derived from (±)- and L-alanine and three diastereomers of **26** were also prepared for comparison; see supplementary material.

Rate of Intramolecular Reduction of Ferryl Iron in Compound I of Cytochrome *c* Peroxidase

Ted Fox,[†] James T. Hazzard,[‡] Steven L. Edwards,[§] Ann M. English,*[,†] Thomas L. Poulos,*[,§,⊥] and Gordon Tollin*[,‡]

Department of Chemistry and Biochemistry
Concordia University
1455 de Maisonneuve Boulevard West
Montreal, Quebec, Canada H3G 1M8
Department of Biochemistry, University of Arizona
Tucson, Arizona 85721
Center for Advanced Research in Biotechnology of the
Maryland Biotechnology Institute and
Department of Chemistry and Biochemistry
University of Maryland, College Park
9600 Gudelsky Drive, Rockville, Maryland 20850

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Ferryl iron, Fe^{4+}, is the oxidation state of Fe in the enzyme intermediates of heme peroxidases[1] and possibly also heme monooxygenases[2] and cytochrome *c* oxidase.[3] However, the redox

* Authors to whom correspondence should be addressed.
† Concordia University.
‡ University of Arizona.
§ Center for Advanced Research in Biotechnology of the Maryland Biotechnology Institute.
⊥ Department of Chemistry and Biochemistry, University of Maryland.

(1) Reczek, C. M.; Sitter, A. J.; Terner, J. *J. Mol. Struct.* **1989**, *214*, 27. Penner-Hahn, J. E.; Eble, K. S.; McMurry, T. J.; Renner, M.; Balch, A. L.; Groves, J. T.; Dawson, J. H.; Hodgson, K. O. *J. Am. Chem. Soc.* **1986**, *108*, 7819.

(2) Ortiz de Montellano, P. R. *Acc. Chem. Res.* **1987**, *20*, 289. Marnett, L. J. *Cytochrome P-450: Structure, Mechanism and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1986; pp 29-76.

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