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

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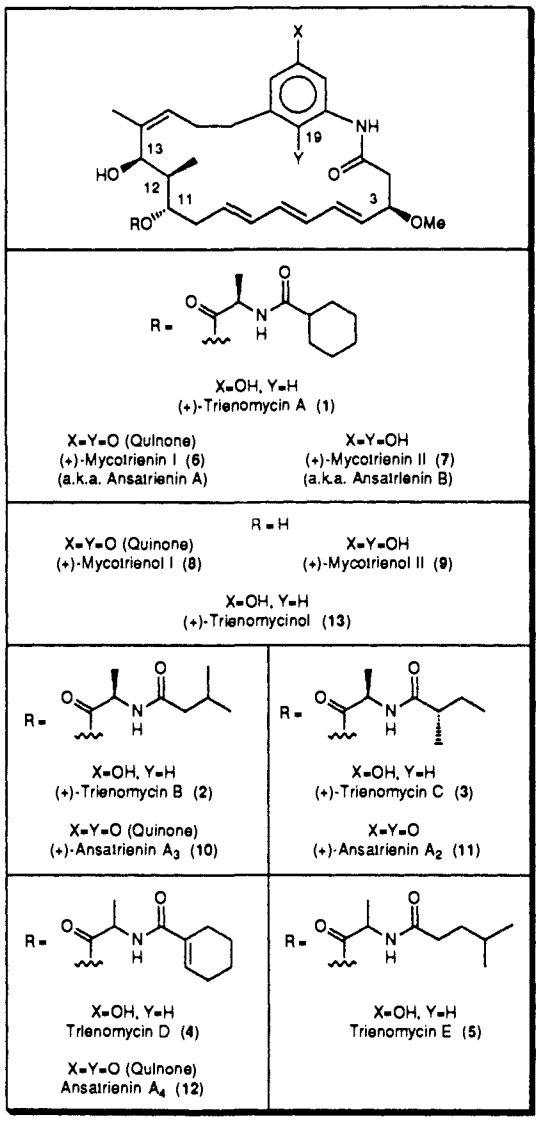
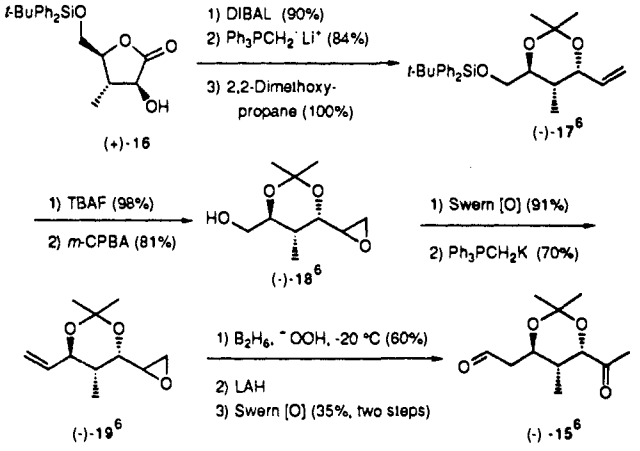
Umezawa and co-workers recently reported the isolation of five novel ansamycin antibiotics from the culture broth of *Streptomyces* sp. No. 83-16.[1] Termed trienomycins A-E (**1-5**), these compounds exhibited strong cytotoxicity in vitro against HeLa S_3 cells.[2]



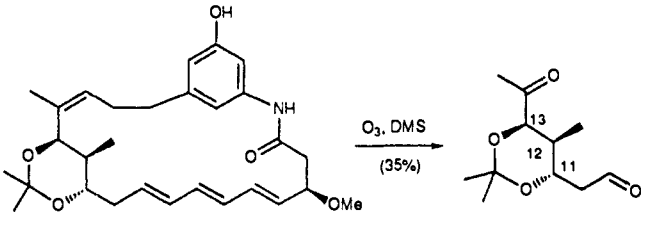
Scheme I



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.; Ōtake, N. *J. Antibiot.* **1982**, *35*, 1460. (b) Sugita, M.; Sasaki, T.; Furihata, K.; Seto, H.; Ōtake, N. *Ibid.* **1982**, *35*, 1467. (c) Sugita, M.; Natori, Y.; Sueda, N.; Furihata, K.; Seto, H.; Ōtake, N. *Ibid.* **1982**, *35*, 1474. (d) Sugita, M.; Furihata, K.; Seto, H.; Ōtake, 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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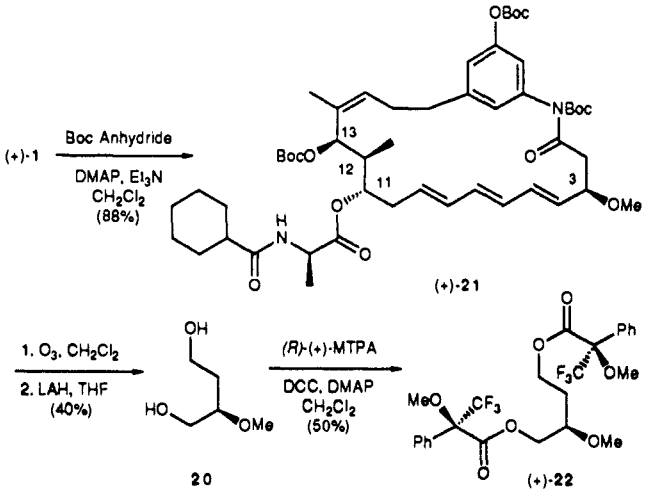
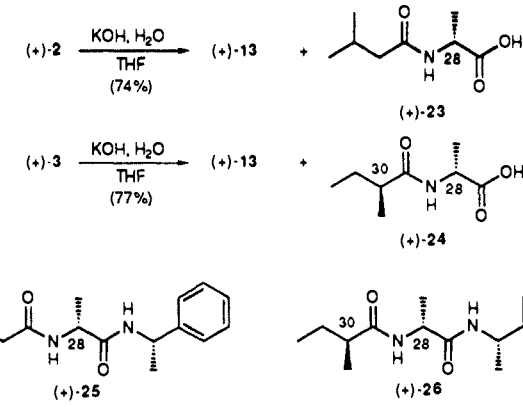
To elucidate the absolute configuration of the C(11,13) fragment, we embarked on an enantioselective synthesis of **15** (Scheme I) beginning with lactone (+)-**16**.[9] The resultant keto aldehyde [(−)-**15**][6] differed from the material obtained via degradation only in the sign of its optical rotation. 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

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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

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(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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