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LETTERS

(+)-THIAZINOTRIENOMYCIN E: RELATIVE AND ABSOLUTE STEREOCHEMISTRY

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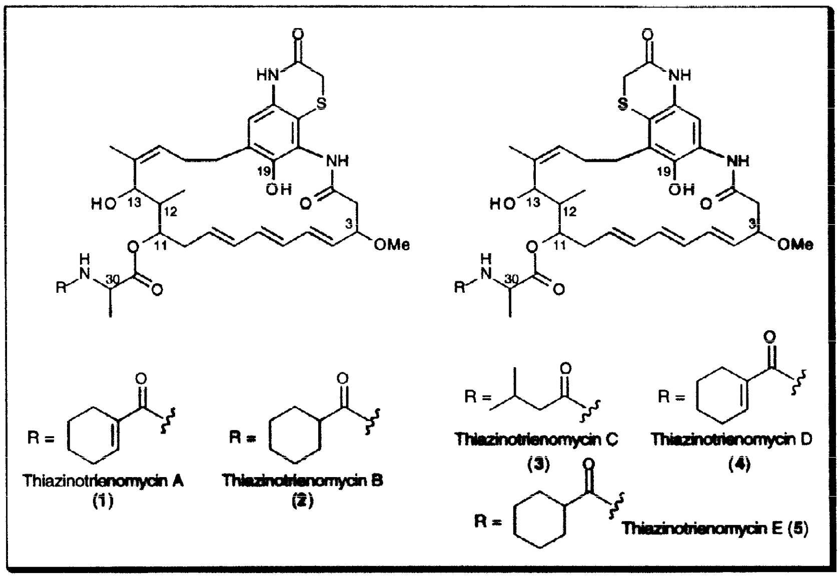
Abstract: The complete relative and absolute configurations of (+)-thiazinotrienomycin E, a potent new ansatrienin cancer cell growth inhibitory agent, have been determined via degradation and chemical correlation. © 1998 Elsevier Science Ltd. All rights reserved.

In 1995 Takeuchi and co-workers reported the isolation and planar structures of (+)-thiazinotrienomycins A-E, (**1-5**, Figure 1), novel ansatrienin antibiotics obtained from a culture broth of *Streptomyces* sp. MJ672-m3.[1] These compounds exhibit significant in vitro cytotoxicity against human cancer cell lines derived from the cervix (HeLa S_3: IC_{50} 1.5 - 200 ng/mL; C33A: IC_{50} 0.6 - 100 ng/mL), stomach (MKN28: IC_{50} 8.4 - 1330 ng/mL), colon (COLO201: IC_{50} 30 - 1200 ng/mL) and breast (MCF7: IC_{50} 40 - 1000 ng/mL).[1] Preliminary studies suggested that the thiazinotrienomycins act by inhibiting membrane transport of thymidine and uridine.[1]

Figure 1. Planar structures of thiazinotrienomycins A - E



The planar structures were elucidated via ^1H-^1H COSY, NOE, and HMBC NMR experiments; however, the relative and absolute stereochemistries remained undefined.[1] The thiazinotrienomycins proved to be heterocyclic congeners of the trienomycins and mycotrienins. Individual thiazinotrienomycins differ in the connectivity of the benzothiazine moiety and the structure of the acyl appendage at C(11).

We recently determined the complete stereochemistries of (+)-trienomycins A, B, C and F, (+)-mycotrienins I and II, and (+)-mycotrienols I and II (Figure 2), and we were confident that the degradation/chemical correlation strategy developed previously could be extended to the thiazinotrienomycins.[2] As prelude to total synthesis, we report here the relative and absolute configurations of (+)-thiazinotrienomycin E (**5**).

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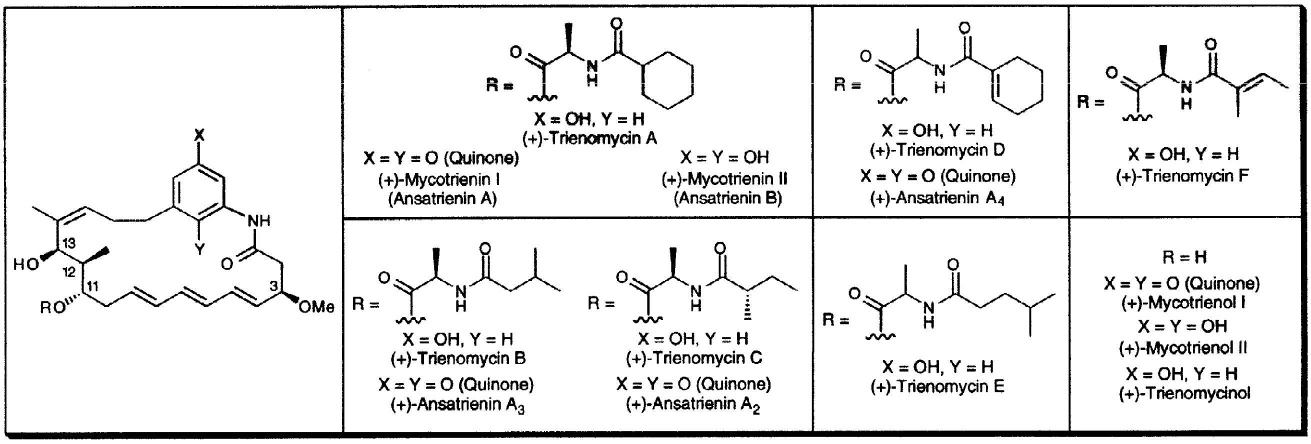
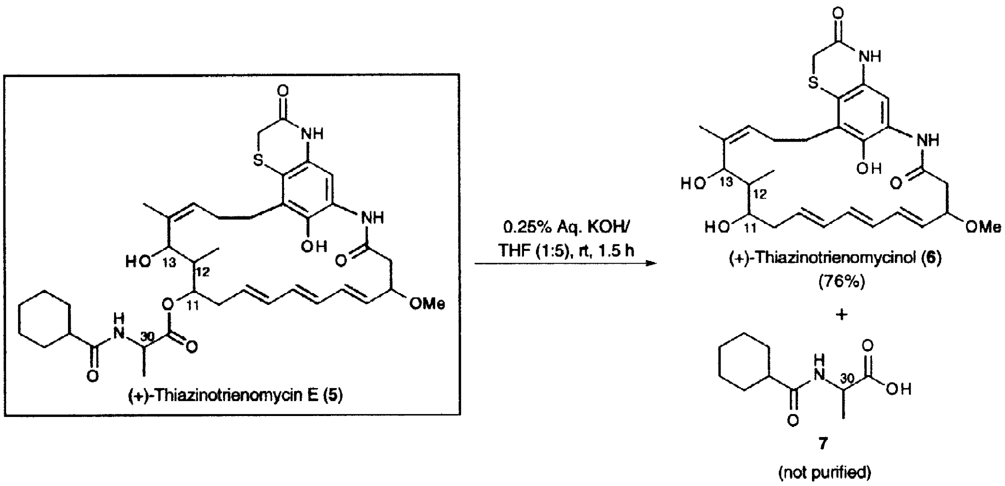
Figure 2. Stereochemistries of related ansatrienin antibiotics.

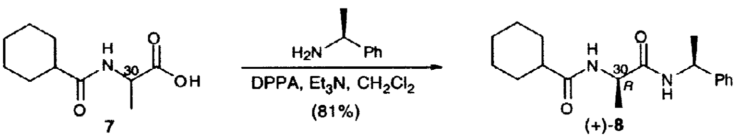


Removal of the side-chain of (+)-**5** with aqueous KOH provided the macrocycle, (+)-thiazinotrienomycinol (**6**),[3] in 76% yield after chromatography, as well as the crude acid **7** (Scheme 1). Without purification the acid was activated with diphenylphosphorylazide (DPPA)[4] and coupled with (*S*)-α-methylbenzylamine (MBA), furnishing diamide (+)-**8**[3] in 81% yield (Scheme 2). Comparison of (+)-**8** with authentic samples prepared from D- and L-alanine (^1H and ^{13}C NMR, optical rotation, melting point, and mixed melting point) established the *R* configuration at C(30).

Scheme 1

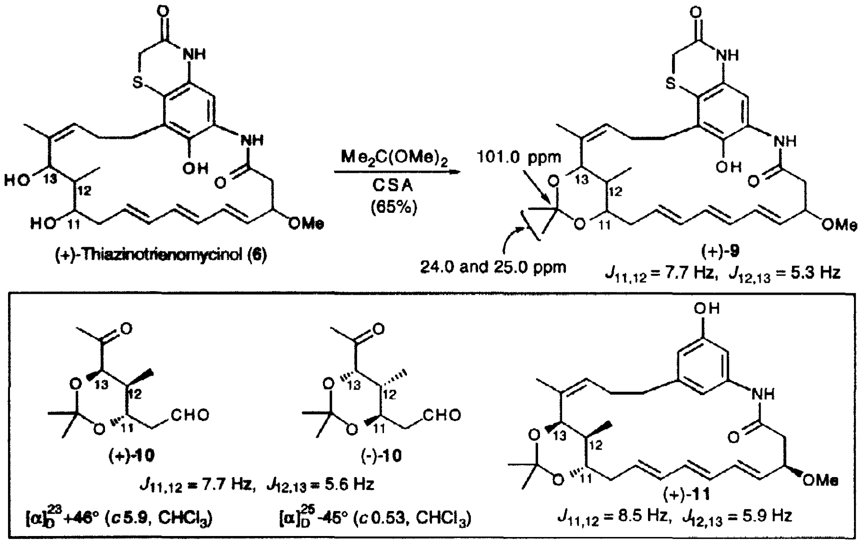


Scheme 2



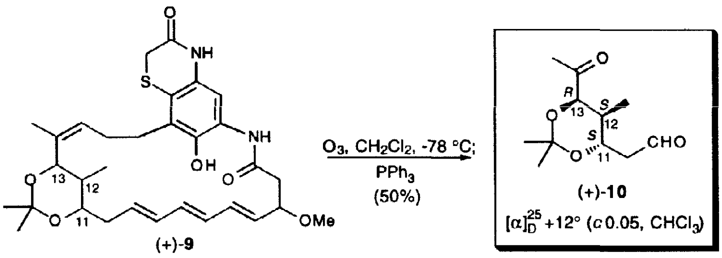
We turned next to the stereochemistry of (+)-thiazinotrienomycinol (**6**). Treatment of (+)-**6** with 2,2-dimethoxypropane and a catalytic amount of camphorsulfonic acid (CSA) furnished the corresponding 1,3-acetonide (+)-**9**[3] in 65% yield (Scheme 3). Comparison of the ^1H-^1H coupling constants $J_{11,12}$ and $J_{12,13}$ for (+)-**9** with the corresponding values previously predicted[2] for the four diastereomers of keto aldehyde **10**, in conjunction with the observed values of (+)- and (-)-**10**[2] and for (+)-trienomycinol acetonide (**11**)[2] defined the relative stereochemistry at the three contiguous centers as C(11,12) anti and C(12,13) syn. Carbon-13 NMR analysis of (+)-**9** employing the Rychnovsky-Evans empirical syn/anti correlation for 1,3-acetonides[5] provided further support for the anti relationship between C(11) and C(13).

Scheme 3

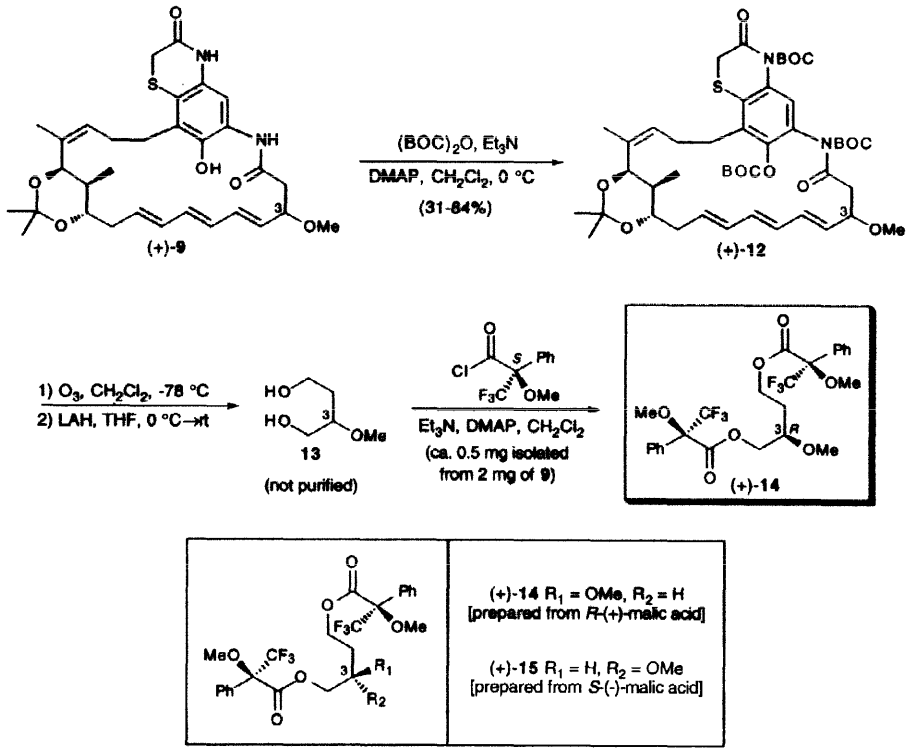


The determination of absolute stereochemistry began with ozonolysis of (+)-**9**; reductive work-up with triphenylphosphine furnished keto aldehyde (+)-**10** (50% yield, Scheme 4). Comparison (^1H and ^{13}C NMR, IR, MS, and optical rotation) with authentic samples of (+)- and (-)-**10**[2] revealed the *S*, *S*, and *R* absolute configurations at C(11), C(12), and C(13), respectively. The configuration at C(3) was then elucidated via the protocol devised earlier for the trienomycins. Conversion of (+)-**9** to the tris-Boc derivative (+)-**12**[3] (di-*tert*-butyldicarbonate, triethylamine, DMAP, CH_2Cl_2, 0 °C, 31-84% yield; Scheme 5) followed by ozonolysis and reduction with lithium aluminum hydride afforded 2-methoxy-1,4-butanediol (**13**); acylation with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride provided the bis Mosher ester (+)-**14**. Comparison of the latter with authentic samples prepared from *R*-(+)- and *S*-(-)-malic acid [i. e., (+)-**14** and (+)-**15**][2] defined the C(3) configuration as *R*.

Scheme 4



Scheme 5



In summary, we have unambiguously assigned the complete relative and absolute stereochemistry of (+)-thiazinotrienomycin E (**5**). The common absolute configuration found in **5**, the trienomycins, the mycotrienins, and the mycotrienols seems likely to prevail in the other thiazinotrienomycins and in the ansatrienins in general. Progress toward the total synthesis of these potent antitumor antibiotics will be reported in due course.

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3. All synthetic compounds were purified by flash chromatography on silica gel, except as otherwise indicated. The structure assigned to each new compound is in accord with its infrared, 500-MHz ^{1}H NMR, and 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry.
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