

# Total Synthesis of (+)-Thiazinotrienomycin E

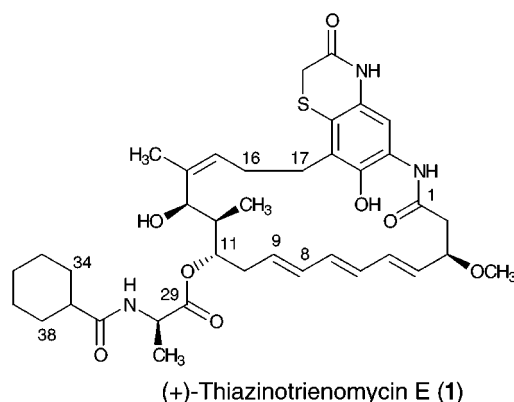
Amos B. Smith, III,\* and Zehong Wan

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

smithab@sas.upenn.edu

Received September 15, 1999

## ABSTRACT



The first total synthesis of (+)-thiazinotrienomycin E (1), member of a novel class of cytotoxic ansamycin antibiotics, has been achieved. The synthesis features a highly efficient construction of the aromatic fragment 3 incorporating TBS protection of the aniline, a significantly improved synthesis of (–)-19, an intermediate employed in our trienomycins A and F total syntheses, application of the Kocienski modified Julia protocol to elaborate the *E,E,E*-triene subunit, an efficient union of 3 and (+)-4, and Mukaiyama macrolactamization to access the thiazinotrienomycin macrolide.

In 1995 Hosokawa and co-workers reported the isolation and planar structures of the thiazinotrienomycins (A–E), a new family of ansamycin antibiotics produced by *Streptomyces* sp. MJ672-m3,<sup>1</sup> having significant in vitro cytotoxic activity

(1) Hosokawa, N.; Naganawa, H.; Inuma, H.; Hamada, M.; Takeuchi, T.; Kanbe, T.; Hori, M. *J. Antibiot.* **1995**, *48*, 471–478. Hosokawa, N.; Yamamoto, S.; Uehara, Y.; Hori, M.; Tsuchiya, K. S. *J. Antibiot.* **1999**, *52*, 485–490.

(2) Smith, A. B., III; Barbosa, J.; Hosokawa, N.; Naganawa, H.; Takeuchi, T. *Tetrahedron Lett.* **1998**, *39*, 2891–2894.

(3) Smith, A. B., III; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10777–10778. Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Barbosa, J.; Komiyama, K.; Omura, S. *J. Am. Chem. Soc.* **1996**, *118*, 8308–8315. Smith, A. B., III; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 8316–8328. For other synthetic approaches to the trienomycins and related mycotrienins, see: Masse, C. E.; Yang, M.; Solomon, J.; Panek, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4123–4134. Yadav, J. S.; Praveen Kumar, T. K.; Maniyan, P. P. *Tetrahedron Lett.* **1993**, *34*, 2965–2968. Fürstner, A.; Baumgartner, J. *Tetrahedron* **1993**, *49*, 8541–8560.

against a variety of human cancer cell lines.<sup>1</sup> As a prelude to total synthesis, we, in collaboration with Hosokawa and co-workers, assigned the complete relative and absolute stereochemistries of (+)-thiazinotrienomycin E (1) via degradation and chemical correlation.<sup>2</sup> We report here the first total synthesis of (+)-1.

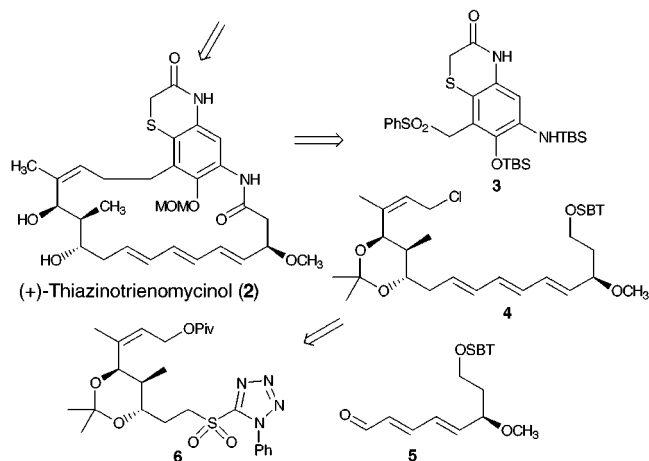
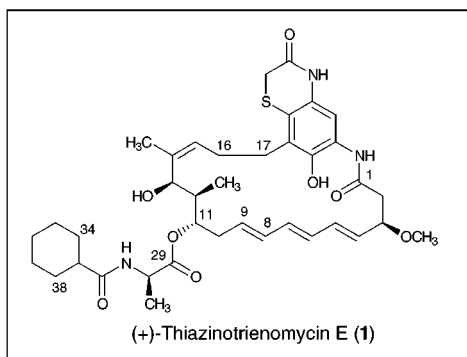
From the retrosynthetic perspective (Scheme 1), we planned to install the C(29–38) side chain at a late stage in the synthesis, thereby developing a unified strategy for the thiazinotrienomycins from (+)-thiazinotrienomycinol (2). A

(4) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *1*, 26–28. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178.

(5) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4571–4580.

(6) The structural assignment to each new compound is in accord with its IR, <sup>1</sup>H and <sup>13</sup>C NMR, and high-resolution mass spectra.

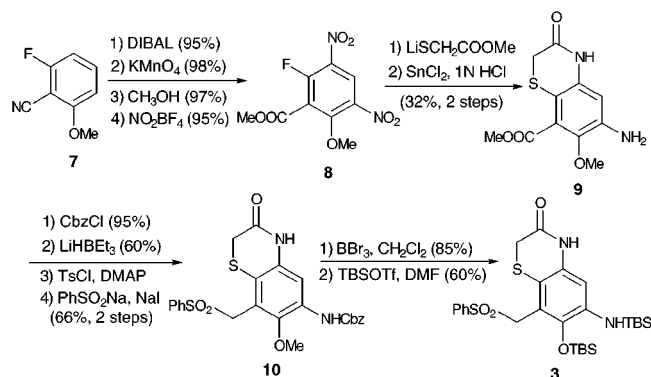
Scheme 1



similar tactic was employed for the trienomycins.<sup>3</sup> Continuing with this analysis, disconnection at the C(16–17) and C(1) linkages leads to subtargets **3** and **4**: assembly of the macrolide would entail sulfone alkylation and macrolactamization. Further disconnection at the C(8–9) olefin suggested a Kocienski-modified<sup>4a</sup> Julia olefination<sup>4b</sup> between **5** and **6** to construct the *E,E,E*-triene, a structural element that has proven problematic in the past.<sup>3</sup>

We began with the construction of subtarget **3**. DIBAL reduction of **7**, followed by oxidation, esterification, and dinitration<sup>5</sup> ( $\text{NO}_2\text{BF}_4$ ), furnished **8** in 86% yield for the four steps (Scheme 2). Substitution of fluorine with the lithium

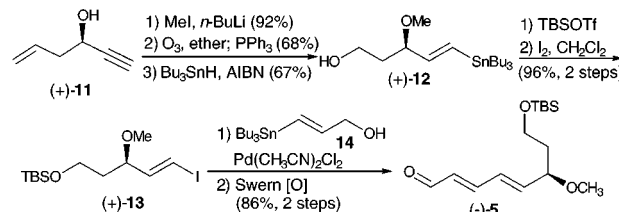
Scheme 2



salt of methyl thioglycolate<sup>7</sup> and reduction of the nitro groups with concomitant cyclization<sup>8</sup> then furnished benzolactam **9**<sup>6</sup> in modest overall yield. Protection of the aniline ( $\text{CbzCl}$ ), followed in turn by reduction of the ester ( $\text{LiHBEt}_3$ , 15-crown-5 ether, THF),<sup>9</sup> tosylation of the resultant alcohol, and displacement with sodium benzenesulfinate, provided **10**.<sup>6</sup> Both the methyl and Cbz groups were then removed ( $\text{BBR}_3$ ,  $\text{CH}_2\text{Cl}_2$ )<sup>10</sup> and the resultant intermediate *N*- and *O*-protected (TBSOTf, DMF).

Synthesis of subtarget **5** began with methylation of known alcohol (+)-**11**<sup>11</sup> (Scheme 3). Selective reductive ozonoly-

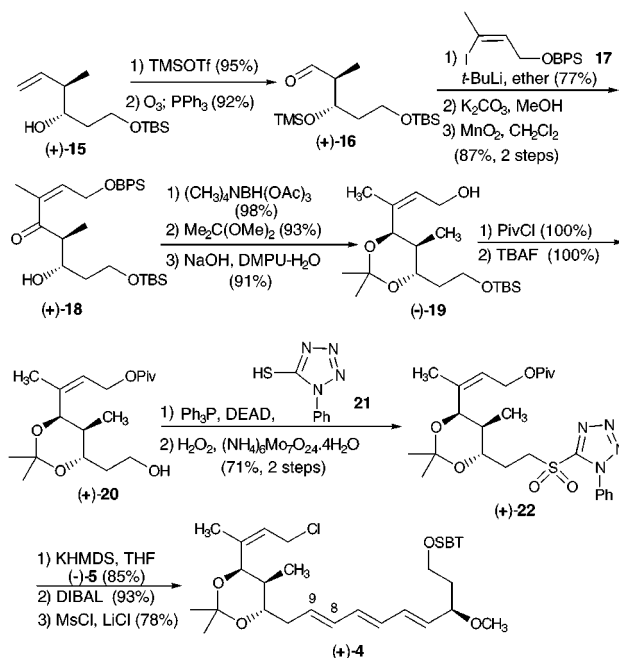
Scheme 3



sis,<sup>12</sup> followed by AIBN-promoted hydrostannylation, furnished *trans* vinyl stannane (+)-**12**,<sup>13</sup> contaminated with 6% of the *cis* isomer. Separation of the isomers via flash chromatography, protection of the primary hydroxyl (TBSOTf), and treatment with iodine afforded (+)-**13**.<sup>6</sup> Construction of (-)-**5** was then achieved via palladium-catalyzed Stille cross-coupling<sup>14</sup> with **14**<sup>15</sup> followed by Swern oxidation.<sup>16</sup>

For the synthesis of subtarget (+)-**4**, we required (-)-**19** (Scheme 4), first prepared in conjunction with our trieno-

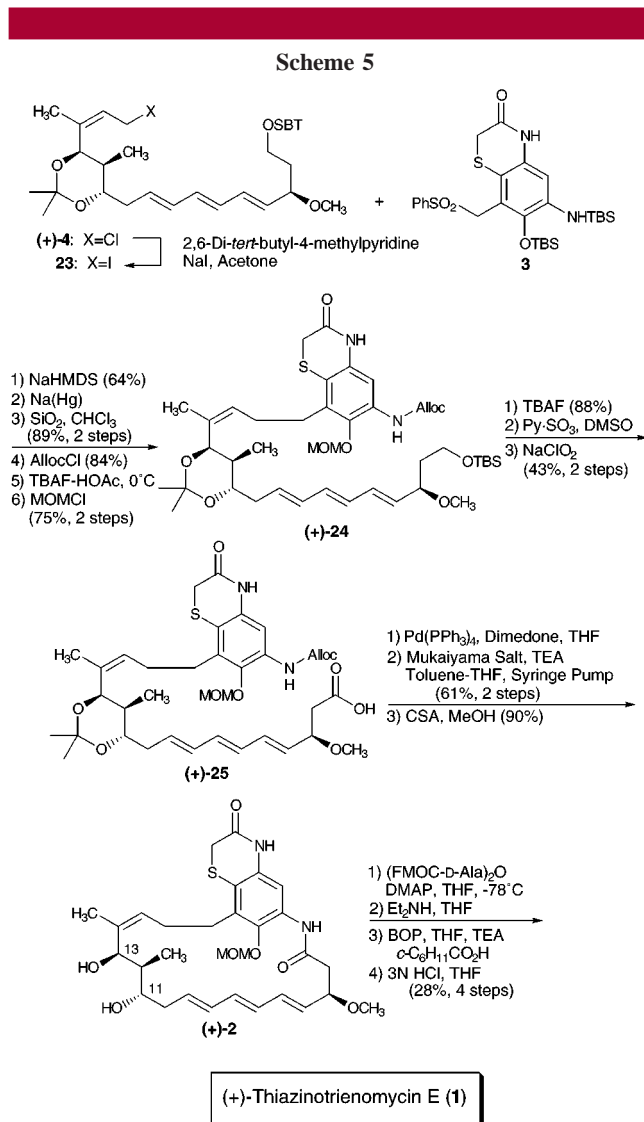
Scheme 4



mycin synthesis.<sup>3</sup> We report here a significant improvement in the construction of (–)-**19**. Protection of known alcohol (+)-**15**<sup>17</sup> followed by reductive ozonolysis furnished aldehyde (+)-**16**.<sup>6</sup> Addition of the vinyl anion derived from **17**, the latter available in two steps from 2-butyn-1-ol,<sup>18</sup> afforded a mixture of alcohols (ca. 2:1). After removal of the TMS group, selective oxidation of the allylic alcohol furnished (+)-**18**.<sup>6</sup> Completion of (–)-**19** entailed directed reduction of  $\beta$ -hydroxyl ketone with Me<sub>4</sub>NBH(OAc)<sub>3</sub> (95% de),<sup>19</sup> generation of the 1,3-acetonide, and selective removal of the primary BPS moiety.<sup>20</sup> Alcohol (–)-**19**, identical to that prepared previously,<sup>3</sup> was thus available in eight steps and 49% overall yield, compared to 15 steps and 25% overall yield.

Continuing with assembly of (+)-**4**, protection of the hydroxyl (PivCl), desilylation (TBAF), and Mitsunobu reaction<sup>21</sup> with 1-phenyl-1*H*-tetrazole-5-thiol (**21**), followed by oxidation (H<sub>2</sub>O<sub>2</sub>), furnished<sup>4a</sup> sulfone (+)-**22**.<sup>6</sup> Elaboration of the triene entailed addition of aldehyde (–)-**5** to the anion derived from (+)-**22** (KHMDs, THF, –78 °C); a mixture of the *E,E,E*- and *Z,E,E*-trienes (ca. 10:1) was obtained in 85% yield. Reductive removal of the pivaloate moiety (DIBAL) and conversion of the resultant allylic alcohol to the chloride furnished (+)-**4**.<sup>6</sup>

With fragments **3** and (+)-**4** in hand, we turned to assembly of the macrolide (Scheme 5). Allyl chloride (+)-**4** was converted to iodide **23**, and then without isolation added to the anion derived from **3** (NaHMDS, THF, –78 °C); a diastereomeric mixture of sulfones (ca. 2:1; 64%) resulted. Following reductive removal of the sulfone, the aniline was selectively liberated via treatment with silica gel in chloroform and subsequently protected as the Alloc carbamate. The phenolic TBS ether was then removed and the phenol protected as the MOM ether to furnish (+)-**24**.<sup>6</sup> A two-step



(7) Teulade, J. C.; Grassy, G.; Escalé, R.; Chapat, J. P. *J. Org. Chem.* **1981**, *46*, 1026–1030.

(8) Kelly, T. R.; Kim, M. H.; Curtis, A. D. M. *J. Org. Chem.* **1993**, *58*, 5855–5857.

(9) The reduction initially proved troublesome because the amide was unexpectedly more easily reduced than the ester under a variety of reducing conditions.

(10) Combes, S.; Finet, J.-P. *Synth. Commun.* **1997**, *27*, 3769–3778.

(11) Prepared in two steps from propargyl alcohol, see: Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095–13096.

(12) Chen, S.-Y.; Joullié, M. M. *Synth. Commun.* **1984**, *14*, 591–597.

(13) Interestingly, the aldehyde was also reduced under these conditions.

(14) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–817.

(15) Prepared from propargyl alcohol in one step, see: Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851–3854.

(16) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(17) Alcohol (+)-**15** is readily available in three steps from 3-buten-1-ol, see: Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318–333.

(18) Takemoto, T.; Sdeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477–8478.

(19) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

(20) To the best of our knowledge, this is the first example of such selectivity.

(21) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(22) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(23) Crimmins, M. T.; Al-awar, R. S.; Vallin, I. M.; Hollis, W. G., Jr.; O'Mahony, R.; Lever, J. G.; Bankaitis-Davis, D. M. *J. Am. Chem. Soc.* **1996**, *118*, 7513–7528.

oxidation protocol (Parikh–Doering<sup>22</sup> and NaClO<sub>2</sub><sup>23</sup>) after unmasking of the primary alcohol led to acid (+)-**25** as a mixture of rotamers (ca. 4:1). Palladium(0)-promoted removal of the Alloc group furnished the amino acid, precursor for macrocyclization. To our delight, slow addition of this acid via syringe pump to a mixture of 2-chloro-1-methylpyridinium iodide<sup>24</sup> and TEA in toluene effected macrolactamization (61%, two steps). Removal of the acetonide completed construction of (+)-thiazinotrienomycinol (**2**).<sup>6</sup>

All that remained to arrive at (+)-thiazinotrienomycin E (**1**) was installation of the amino acid side chain. To this end, C(11) acylation of (+)-**2** with the symmetrical anhydride of Fmoc-D-alanine,<sup>25</sup> liberation of the primary amine (Et<sub>2</sub>NH, THF), followed by BOP-mediated coupling with cyclohexanecarboxylic acid, and removal of the MOM group furnished (+)-thiazinotrienomycin E (**1**), identical in all respects with natural material (<sup>1</sup>H and <sup>13</sup>C NMR, IR, HRMS, optical rotation, and TLC in three solvent systems).

(24) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163–1166.

(25) The selectivity was 2:1 in favor of acylation at C(11). In addition, a small amount (<7%) of bis acylated material was isolated.

In summary, the first total synthesis of (+)-thiazinotrienomycin E has been achieved. The efficient assembly of the *E,E,E*-triene and the improved synthesis of advanced alcohol (–)-**19** are particularly noteworthy.

**Acknowledgment.** Financial support was provided by the National Institutes of Health (National Institute of General Medical Sciences) through Grant GM 29028. Z.W. gratefully

acknowledges a SAS dissertation fellowship from the University of Pennsylvania.

**Supporting Information Available:** Spectroscopic and analytical data for **1–6**, **8–10**, **12–13**, **16**, **18–20**, **22**, and **24–26** as well as representative experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL991049G