# Stereocontrolled Preparation of the C1-C14 Polyene Fragment of Benzenic Ansamycin Antibiotics Ansatrienin A and B

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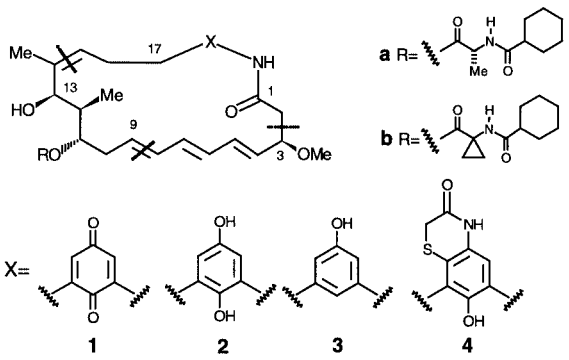
*Received 1 July 1999*

*Dedicated to Professor Axel Zeeck on the occasion of his 60th birthday*

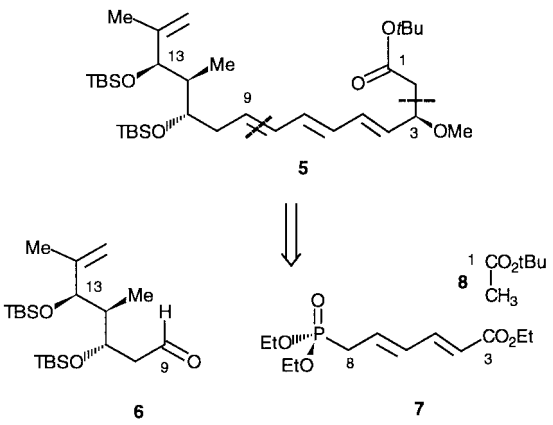
**Abstract**: A practical synthesis of the C1-C14 polyene unit **5** in ansatrienin A (mycotrien I), **1a**, and other ansamycin antibiotics is described which involves elaboration of the chiral unsaturated aldehyde **6** and phosphonate **7**, followed by coupling of the building blocks by Horner-Emmons-olefination and Duthaler´s aldolation. The synthesis of **6** successfully applies two consecutive Evans-aldol reactions for constructing the carbon backbone.

**Key words:** Evans-aldolation, Horner-Emmons olefination, macrolactam antibiotic

The ansamycins are an important class of complex macrolactam antibiotics from microbial sources.[1] Typically they consist of a cyclic structure in which an aliphatic ansa chain forms a bridge between two non-adjacent positions of a cyclic π-system. Many of the ansamycins exhibit antibacterial, antifungal or antitumor activity. *E. g.*, rifamycin, the most prominent example of ansamycin antibiotics, is in clinical use and is one of the most potent drugs against tuberculosis. One ansamycin subgroup, has seen increasing interest lately. They are benzenic members with a 17 carbons and one nitrogen atom containing ansa chain. In 1981, the first examples, the ansatrienins A and B **1a** and **2a**, were isolated from the fermentation broth of *Streptomyces collinus* by Zähner, Zeeck and coworkers.[2] Independently, the groups of Natori, Sueda and Sasaki[3] described identical metabolites from *Streptomyces rishirensis* which they named mycotrienins I and II. Additionally, more potent members were found, namely the trienomycins **3a**[4] and the recently discovered cytotriens **1b**[5] as well as the highly active thiazinotrienomycins **4a**.[6]




Typical structural features for all these natural products are a stereotriad from C-13 to C-11,[7] an all *trans* triene unit as well as a trisubstituted *(Z)*-alkene. As this ansa bridge is identical for all derivatives listed, the development of a short and highly efficient synthesis represents the entrance for all members, including those that were discovered recently. To date, only the groups of Smith and Panek have reported the total syntheses of mycotrienin and trienomycin.[8] In both cases the aromatic portion was introduced at an earlier stage and ring closure was achieved in the triene unit.




**Scheme 1**

In this paper[9] we describe a practical synthesis of the C1-C14 unit **5** which is uniformly present in benzenic ansamycin antibiotics **1** - **4**. We decided to assemble fragment **5** from aldehyde **6** and phosphonate **7** and acetate **8** (Scheme 1). For the preparation of the stereotriad in **6**, we developed an efficient aldol-based strategy utilizing Evans oxazolidinones as chiral auxiliaries.[10,11] Thus, the boron enolate derived from acylated oxazolidinone derivative **9** reacted with methacrolein to afford the (2´*R*, 3´*R*)-adduct **10** as a single isomer. Transamidation and silylation generated the Weinreb amide **11** which was reduced to the corresponding aldehyde **12**.[12]

Compound **12** then served as the aldehyde component in the aldol reaction with the boron enolate generated from (4*S*)-3-(methylthioacetyl)-4-benzyl-1,3-oxazolidin-2-one **14**.[13] The coupling reaction led to the β-hydroxy amide **13** in a >20:1 diastereomeric ratio. The methylthio substitu-



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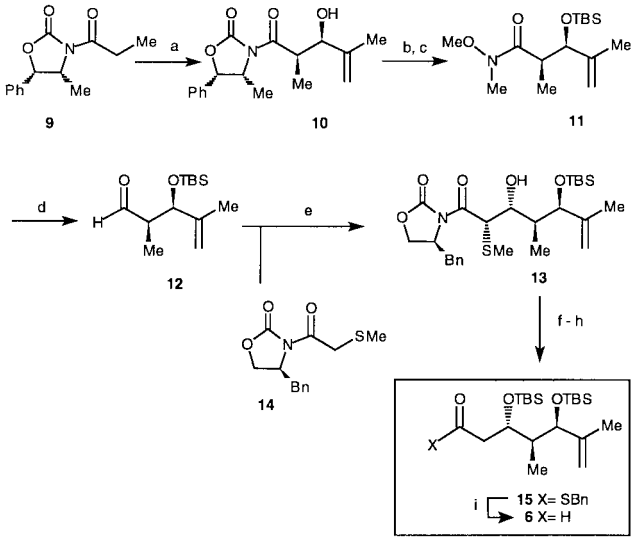
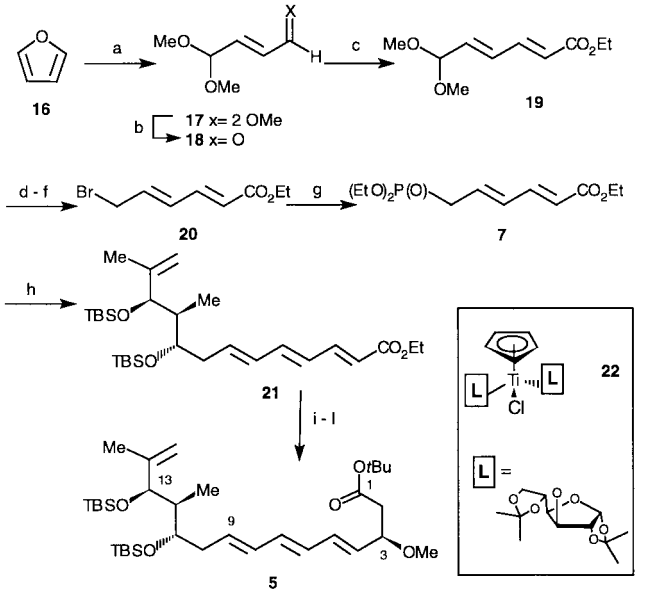


Reagents and Conditions:
a) $Bu_2BOTf$, $Et_3N$, $CH_2Cl_2$, -78 °C, $CH_2$ = $C(CH_3)CHO$, 87%; b) Me-ONHMe•HCl, $AlMe_3$, THF, -20 °C→ rt; c) $^tBuMe_2SiCl$, imidazole, DMF, 50 °C, 79% (for two steps); d) 1.15 eq. DIBALH, $CH_2Cl_2$, -78 °C; e) **14**, $Bu_2BOTf$, $^iPr_2EtN$, $CH_2Cl_2$, -78 °C, then addition of **12**, -78 °C→ rt, 66% (for two steps); f) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 50 °C, 12h, 95%; g) *Raney*-Ni, $THF_{abs}$, Δ, 1.5h. 90%; h) BnSH, $^nBu$-Li, THF, 0 °C, then addition to oxazolidinone, 20 min, 85%; i) 1.25 eq. DIBALH, $CH_2Cl_2$, -78 °C, 90% crude.

**Scheme 2**



Reagents and Conditions:
a) $Br_2$, MeOH, -40 °C, 39%; b) 6% $H_3PO_4$, 100 °C, 1h; c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, -10 °C, 83% (for two steps); d) HOAc, $H_2O$, NaOAc, 100 °C, 2.5h; e) $NaBH_4$, EtOH, 87% (for two steps); f) $PBr_3$, $Et_2O$, Δ, 1h; g) $P(OEt)_3$, 120 °C,1h, 82% (for two steps); h) 4 eq. **7**, 3 eq. LiHMDS, THF, -78 °C→ rt, 1h, -78 °C, then **6**, -70 °C→ rt, 77%; i) 2 eq. DIBALH, $CH_2Cl_2$, -78 °C; j) $MnO_2$ (90% crude for two steps); k) **8**, LDA, -78 °C, then addition of **22**, -30 °C, then addition of aldehyde at -78 °C, 69%; l) MeI, $Ag_2O$, 72%.

**Scheme 3**

ent induced the desired configuration in the β-position with high stereoselectivity. Silylation followed by reductive removal of the methylthio group with Raney-Ni under anhydrous conditions[14] and subsequent cleavage of the oxazolidinone ring, using lithiated benzyl mercaptan afforded thiolester **15** in satisfactory yield.[15] It should be noted that all other attempts to transamidate, reduce or hydrolyse the amide group met with total failure. Finally, DIBALH promoted reduction of the thiolester group in **15** provided the aldehyde **6** in 9 steps and about 28% overall yield.

The second building block, phosphonate **7**, required for olefination with aldehyde **6** was readily prepared from furan **16** (Scheme 3). According to Makin and Telegina[16] oxidative cleavage with bromine in methanol led to the acid labile tetramethoxybutene **17** which was selectively transformed into aldehyde **18**.[17] Horner-Emmons olefination afforded diene **19** which was converted into phosphonate **7** in four straightforward steps,[18] starting with acetal hydrolysis and reduction of the intermediate aldehyde to the corresponding alcohol, followed by bromination to give **20** and subsequently phosphonation under Michaelis-Arbuzov conditions. The Horner-Emmons-olefination between phosphonate **7** and aldehyde **6** was accomplished in the presence of lithium hexamethyldisilazide in THF at -78 °C, and gave rise to triene **21** (all-*trans*/other diastereomers ≅ 10:1).[19] A two-step reduction/oxidation sequence led to the corresponding aldehyde which was subjected to Duthaler´s aldolation conditions.[20] The asymmetric aldol reaction afforded the elongated product in 69% isolated yield with high stereoselectivity. The other diastereoisomer was not formed, as judged from the $^1H$ NMR spectrum.[21] Finally, the target C1-C14 fragment **5** was obtained after methylation of the alcohol at C-3 under neutral conditions using $MeI/Ag_2O$.

Work is now in progress to synthesise the top aromatic portions and to link it to **5** and hence achieve the total syntheses of the benzenic ansamycin antibiotics **1a** and **4a**.

## Acknowledgement

We thank the Fonds der Chemischen Industrie and the Bayer AG (Germany) for financial support.

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(19) All compounds showed satisfactory spectroscopic data as well as microanalytical and/or mass spectrometry data. Diastereomeric ratios were established by $^1$H NMR. Selected physical and spectroscopic data for compounds **21** and **5**: **21**: colourless oil; $^1$H NMR (200 MHz, $CDCl_3$) δ:7.28 (1H, dd, *J* = 15.0, 11.2, 6-H), 6.50 (1H, dd, *J* = 14.8, 10.4, 4-H), 6.19 (1H, dd, *J* = 14.8, 11.2, 5-H), 6.09 (1H, dd, *J* = 15.0, 10.4, 3-H), 5.85 (1H, ddd, *J* = 15.0, 6.8, 6.8, 7-H), 5.84 (1H, d, *J* = 15.0, 2-H), 4.85 (1H, m, 13-$H_A$), 4.81 (1H, m, 13-$H_B$), 4.20 (2H, q, *J* = 7.0, $OCH_2CH_3$), 3.76 (1H, d, *J* = 6.0, 11-H), 3.53 (1H, m, 9-H), 2.15 (2H br t, *J* = 6.8, 8- $H_A$, 8-$H_B$), 1.79 (1H, m, 10-H), 1.69 (3H, s, 12-$CH_3$), 1.29 (3H, t, *J* = 7.0, $OCH_2CH_3$), 0.94 (3H, d, *J* = 6.8, 10-$CH_3$), 0.89, 0.86 (18H, 2s, 2 $^t$Bu), 0.04, 0.01, -0.01 and -0.05 (12H, 4s, 2 $SiMe_2$); $^{13}$C NMR (50 MHz, $CDCl_3$) δ:167.2 ($CO_2$Et), 146.5 (C-12), 144.8, 141.0, 138.5, 131.5, 127.9, 120.1 (C-2 - C-7), 112.8 (C-13), 79.5 (C-11), 72.5 (C-9), 60.2 ($OCH_2CH_3$), 43.5 (C-10), 35.2 (C-8), 25.8 (2 x $^t$Bu), 18.2, 18.0 (2 x $^t$Bu), 16.7 (12-$CH_3$), 14.3 ($OCH_2CH_3$), 10.0 (10-$CH_3$), -4.3, -4.5, -4.6, -5.0 (2 x $SiMe_2$). **5**: colourless oil; $[\alpha]^{24}_D$ = -23.2 (*c* 0.77, $CHCl_3$); IR ($cm^{-1}$) ν: 2956(s), 2930(s), 2858(s), 1732(m), 1463(m), 1368(m), 1254(s), 1055(s), 836(s); $^1$H NMR (400 MHz, $CDCl_3$) δ:6.28-5.92 (m, 4H, 5-H, 6-H, 7-H, 8-H), 5.67 (1H, m, 9-H), 5.48 (1H, dd, *J* = 15.0, 8.0, 4-H), 4.84 (1H, m, 15-$H_A$), 4.81 (1H, m, 15-$H_B$), 4.01 (1H, ddd, *J* = 8.0, 7.6, 6.1, 3-H), 3.77 (1H, d, *J* = 9.0, 13-H), 3.51 (1H, m, 11-H), 3.27 (3H, s, $OCH_3$), 2.54 (1H, dd, *J* = 14.8, 7.6, 2-$H_A$), 2.63 (1H, dd, *J* = 14.8, 6.1, 2-$H_B$), 2.10 (2H br t, *J* = 6.6, 10-H), 1.78 (1H, m, 12-H), 1.70 (3H, br s, 14-$CH_3$), 1.43 (9H, s, O$^t$Bu), 0.93 (3H, d, *J* = 6.8, 12-$CH_3$), 0.88, 0.86 (18H, 2s, 2x $^t$Bu), 0.04, 0.0, -0.02 -0.04 (12H, 4s, 2 x $SiMe_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ:170.1 (C-1), 146.5 (C-15), 134.1, 134.0, 133.5, 131.8, 131.1, 129.4 (C-4 - C-9), 112.7 (C-14), 80.6 (O$^t$Bu), 79.5 (C-3), 78.9 (C-13), 72.7 (C-11), 56.4 ($OCH_3$), 43.5 (C-12), 42.4 (C-2), 35.0 (C-10), 28.1 (O$^t$Bu), 25.8 (2 x Si$^t$Bu), 18.2, 18.0 (2x Si$^t$Bu), 16.7 (14-$CH_3$), 10.0 (12-$CH_3$), -4.3, -4.5, -4.6 and -5.0 (2 x $SiMe_2$).

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