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TETRAHEDRON: *ASYMMETRY*

Synthetic studies toward ansatrienines: application of the Evans–Tishchenko reaction to chiral enones

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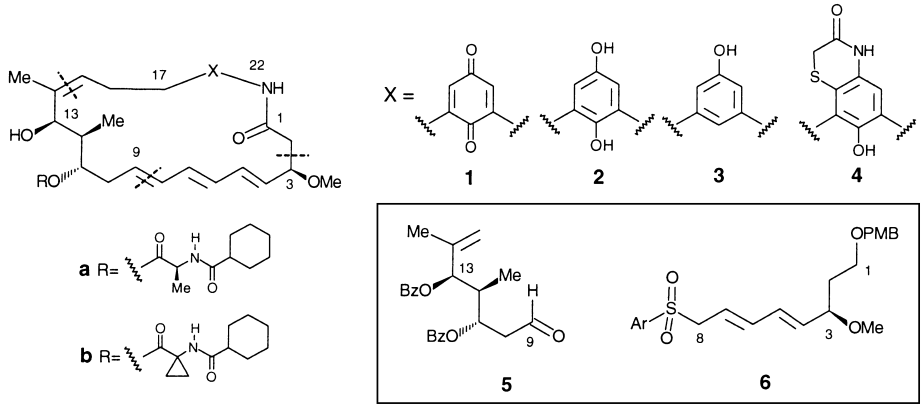
Abstract

Practical syntheses of the C9–C14 sterotriade **5** and the C1–C8 polyene unit **6** in ansatrienine A (mycotriene) (**1a**), and other ansamycin antibiotics is described. A key step for controlling the configuration of the stereogenic center at C13 involves the stereoselective reduction of enone **10** using the Evans–Tishchenko reaction.

The ansamycins comprise a growing class of complex macrolactam antibiotics from microbial sources.[1] They are characterized by a cyclic structure in which an aliphatic ansa chain forms a bridge between two non-adjacent positions of a cyclic π-system. Many of them exhibit antibacterial, antifungal or antitumor activity. A subgroup which has seen increasing interest lately is the benzenic ansamycins with 17 carbons and one nitrogen atom ansa chain.



In 1981, one of the first examples, the ansatrienines **1a** and **2a**, were isolated from the fermentation broth of *Streptomyces collinus* by Zähner, Zeeck and coworkers.[2] Independently, the groups of Natori,

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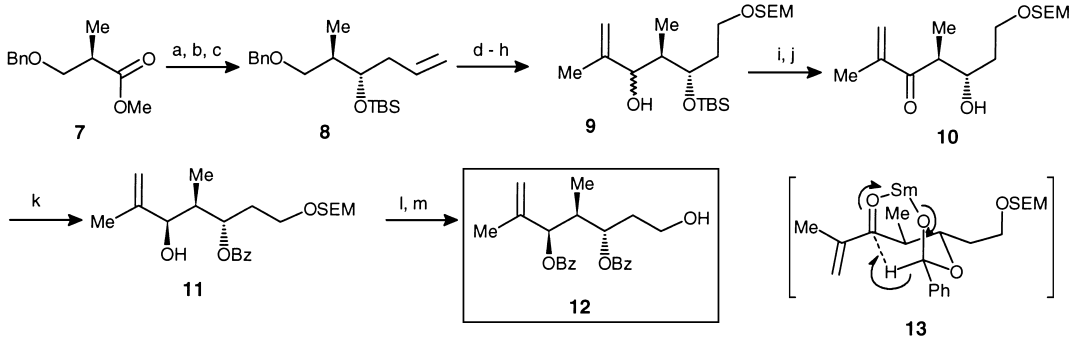
Sueda and Sasaki[3] described identical metabolites from *Streptomyces rishiriensis* which they named mycotrienes. Additionally, more potent members were found, namely the trienomycines **3a**[4] and the more recently discovered cytotrienes **1b**[5] as well as the highly active thiazinotrienomycines **4a**.[6] To date, only Smith and Panek have reported the total syntheses of mycotrienin and trienomycin[7] but this family of ansamycins still represents a significant challenge to the synthetic chemist.

In this paper we describe practical syntheses of the C1–C8 and C9–C14 units **5** and **6**. Methyl ester **7**[8] was the starting point for the synthesis of fragment **5** (Scheme 1). Reduction followed by Lewis acid mediated allylation of the intermediate aldehyde with 1-trimethylsilyl-2-propene gave rise to a 7.5:1 diastereomeric mixture of homoallyl alcohols which were protected as *tert*-butyldimethylsilyl (TBS) ethers **8**.[9] From this stage, it took five synthetic steps for efficiently preparing allylic alcohol **9**. The sequence was initiated by ozonolysis of the alkenic double bond followed by reductive work-up. At this stage, the diastereomers were separated by column chromatography. The primary alcohol was protected as 2-(trimethylsilyl)ethoxymethyl (SEM) ether, which enabled us to remove the benzyl protection. This was followed by periodinane oxidation[10] of the newly formed alcohol. Nucleophilic addition of the Grignard reagent derived from 2-bromo-1-propene furnished epimeric allyl alcohols **9** in a 2.5:1 ratio.



Scheme 1. Reagents and conditions: (a) dibal-*H*, CH_2Cl_2, −78°C, 1 h; (b) $TiCl_4$, −78°C, CH_2Cl_2, 15 min, then $H_2C{=}CH_2CH_2SiMe_3$, 15 min, 71% (for two steps), *syn*:*anti*=1:7.5; (c) TBSCl, imidazole, DMF, 35°C, 88%; (d) O_3, MeOH, −78°C, then 4–5 equiv. $NaBH_4$, 0°C, 95%; (e) SEMCl, $^{i}Pr_2EtN$, CH_2Cl_2, 40°C, 95%; (f) H_2, Pd/C, ethyl acetate, 98%; (g) Dess–Martin periodinane [lit.[10]], CH_2Cl_2, rt; (h) 2-bromo-1-propene, Mg, THF, then aldehyde, 0°C → rt, 72% (for two steps); (i) TBAF, ms 4 Å, THF, 83%; (j) DDQ, C_6H_6, 60°C, 2d, 82%; (k) SmI_2, PhCHO, THF, −10°C, 93%; (l) BzCl, pyr, −10°C → rt, 85% (+9% **11**); (m) 10 equiv. $MgBr_2 \cdot OEt_2$, 2.5 equiv. ^{i}BuSH, Et_2O, rt, 95%

At this stage it was uncertain which isomer prevailed. A Felkin–Ahn based transition state would preferentially lead to the *syn*,*anti*-isomer. However, under chelate-Cram conditions formation of the opposite *anti*,*anti*-stereoisomer would be favoured. Due to the low diastereoselectivity of the addition process and the stereochemical ambiguity related to the outcome of the reaction, we reckoned that applying the Evans–Tishchenko reduction[11] on β-hydroxy-ketone **10** would selectively furnish the desired stereotriade. The Evans–Tishchenko reaction requires a solution of SmI_2 in THF and the presence of an aldehyde and results in the directed reduction of a β-hydroxy ketone to afford an *anti* diol with selective formation of a monoester.[12] For this purpose, alcohols **9** were desilylated to the corresponding epimeric 1,3-diols which were converted to **10** {$[\alpha]_D^{25}$ +4.2 (*c*=1.3, $CHCl_3$)} either using DDQ or triphenylbismuth carbonate[13] as selective oxidants, the latter being too expensive for large scale oxidations. Treatment of **10** with an excess of samarium diiodide and benzaldehyde gave monobenzoate **11** {$[\alpha]_D^{24}$ −15.7 (*c*=1.27, $CHCl_3$)} as a single diastereomer in excellent yield. The stereochemical result of this reduction can be rationalized by assuming transition state **13** with all *C*-substituents occupying the equatorial positions. Final proof for the desired configurations of the three consecutive stereogenic centers came from an X-ray structural investigation of dibenzoate **14** (Fig. 1), which was obtained by

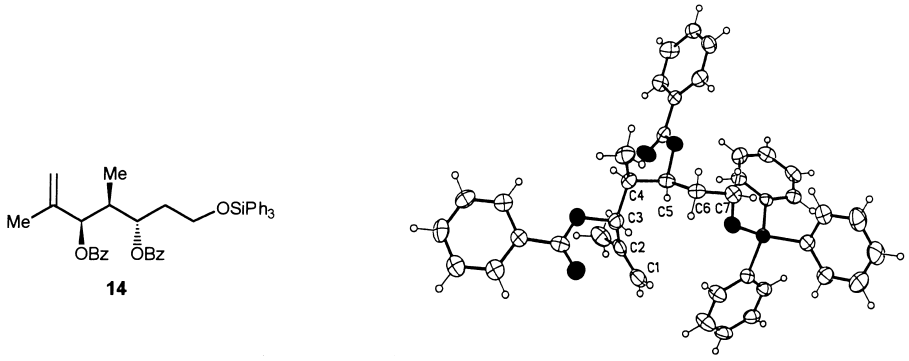
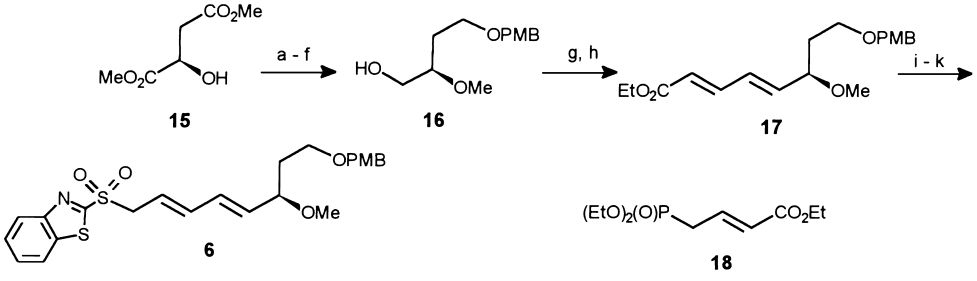


Figure 1. Thermal ellipsoid plot of **14** (ellipsoids are drawn in a 50% probability level)

benzoylation of the allylic alcohol group followed by removal of the SEM-protection using an alkyl thiol in the presence of $MgBr_2$ as the only feasable reagent system.[14] The resulting alcohol **12** {$[\alpha]_D^{24}$ +15.4 (*c*=1.18, $CHCl_3$)} is an ideal precursor for fragment **5** and in addition was employed for synthesizing **14** (TPSCl, imidazole, DMF, 50°C, 57%).[15]

The synthesis of fragment **6** commenced with a regioselective reduction of (*S*)-dimethyl malate **15** following a known procedure (Scheme 2).[16] Simple functional group manipulations led to alcohol **16** {$[\alpha]_D^{20}$ +11.9 (*c*=1.0, $CHCl_3$)} which was required for the alkenation step. Dess–Martin oxidation[10] followed by Horner–Emmons-olefination using phosphonate **18** afforded diene **17** {$[\alpha]_D^{20}$ +18.8 (*c*=1.0, $CHCl_3$)} which was converted into the target benzothiazole **6** in two steps which is required for the coupling of fragments **5** with **6** under Julia-alkenation conditions.[17]



Scheme 2. Reagents and conditions: (a) BH_3 SMe_2, $NaBH_4$, THF, rt; (b) TrCl, NEt_3, 4-DMAP, DMF, rt, 73%; (c) Ag_2O, MeI, CH_2Cl_2, Δ, 21d, 76%; (d) $LiAlH_4$, Et_2O, 0°C → rt, 95%; (e) 4-methoxybenzyl chloride (PMBCl), NaH, DMF, 0°C → rt, 97%; (f) Lewatit SP 1080, MeOH/$CHCl_3$, (7:1), 3–4d, 65%, (+12% starting trityl ether); (g) Dess–Martin periodinane [lit.[10]], CH_2Cl_2, rt, 1.5 h; (h) **18**, NaHMDS, THF, −70°C → −40°C, then addition of aldehyde, 67% (for two steps); (i) dibal-H, CH_2Cl_2, −70°C → rt, 81%; (j) PPh_3, DEAD, 2-mercapto-benzothiazole, THF, 32%; (k) H_2O_2, $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O$, EtOH, rt, 24 h, 85%

In summary, we developed highly stereoselective syntheses of the C1–C8 and C9–C14 units **6** (11 steps; 6.8% overall yield) and **5** (13 steps; 20% overall yield) of most members of the benzenic ansamycins. The Evans–Tishchenko reduction was efficiently applied for controlling the stereochemistry at C13.

Acknowledgements

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15. Selected physical and spectroscopic data for compound **14**: colorless crystals (needles), mp 129.5°C; $[\alpha]_D^{24}$ −8.8 (*c*=0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.04–7.83 (4H, m, Bz), 7.60–7.19 (21H, m, Bz, $SiPh_3$), 5.43 (1H, d, *J*=6.6, 3-H), 5.30 (1H, ddd, *J*=7.6, 5.0, 4.8, 5-H), 4.96 (1H, br s, 1-H_A), 4.91 (1H, br s, 1-H_B), 3.85 (2H, m, 7-H_A, 7-H_B), 2.48 (1H, ddq, *J*=7.6, 6.8, 6.6, 4-H), 2.01 (2H, 2d, *J*=6.2. 6-H_A, 6-H_B), 1.84 (3H, s, 2-CH_3), 1.04 (3H, d, *J*=6.8, 4-CH_3); ^{13}C NMR ($CDCl_3$) δ: 165.8, 165.4, 141.5, 133.9, 130.4, 130.3 (q, Ar), 135.3–127.7 (t, Ar), 77.9 (t, C-3), 72.3 (t, C-5), 60.2 (s, C-7), 37.7 (t, C-4), 32.7 (s, C-6), 18.4 (p, 2-Me), 10.3 (p, 4-Me). Crystallographic data (excluding structure factors) for **14** the structure reported have been deposited with the Cambridge Crystallographic Data Center (deposition number: CCDC 113503). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(0)1223-336033; e-mail: deposit@chemcrys.cam.ac.uk].
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