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A first convergent synthesis of the polyolic fragment of the antifungal pentaene macrolide strevertene A

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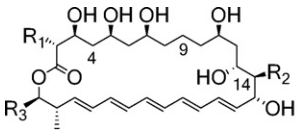
ABSTRACT

The C(4–14) polyolic segment of antifungal macrolide strevertenes has been synthesized for the first time in protected form, incorporating four stereogenic centers. The synthetic strategy developed is based on the connection of two subunits prepared starting from the same chiral building block.

Strevertenes A–G, architecturally interesting antifungal polyene macrolides, were isolated from fermentations with *Streptoverticillium* sp. LL-30F848 in 1999.[1] These natural products exhibit inhibitory activity against ergosterol production, and are a magnitude more potent than nystatin A, a clinically important drug. The major product of this new family of pentaene macrolides, strevertene A, as well as the complex, was determined to inhibit the growth of phytopathogenic fungi with MIC's between 5 and 25 μg/mL. However, the physicochemical liabilities of this class have precluded so far further studies and developments. The absolute and relative configuration of all the 10 stereogenic centers of strevertenes has been subsequently established,[2] and it is represented in the reported structures (see Fig. 1).

The intriguing structure, the low natural abundance, and their clinical potential prompted us to develop a synthesis of the major component, Strevertene A. Herein, we report a first convergent stereocontrolled synthesis of the C(4–14) polyol fragment for strevertene A (**1**), appropriately functionalized for future incorporation into the macrolide skeleton.

The synthetic strategy is based on our recently developed methodologies: (a) the intramolecular oxymercuration on α,β-unsaturated esters[3a] for δ-lactones syntheses and (b) the *one-pot* functionalization of alcohols to sulfides and subsequently to sulfones.[4]



Strevertenes
A R_1= Me, R_2= CO_2H, R_3= Me
B R_1= Et, R_2= CO_2H, R_3= Me
C R_1= Me, R_2= CO_2H, R_3= Et
D R_1= Et, R_2= CO_2H, R_3= Et
E R_1= Me, R_2= CO_2H, R_3= *i*-Pr
F R_1= Et, R_2= CO_2H, R_3= *i*-Pr
G R_1= Me, R_2= CH_2OH, R_3= Me

Figure 1. Strevertenes' A–G structures.

As shown in retrosynthetic analysis in Scheme 1, the key step involves the assembly of C(4–9) segment and C(10–14) segment by olefination reaction followed by chemoselective reduction of the newly formed double bond.

This final assembly to the advanced C(4–14) fragment **2**, a pseudo *meso* compound, was envisioned to involve coupling of aldehyde **3** with the anion derived from sulfone **4** or phosphonium salt **5**. Aldehyde **3**, sulfone **4**, and phosphonium salt **5**, each possessing two stereocenters, would arise from functional group transformation of the common parent compound **6**. Consequently **6** can be prepared from the homoallylic alcohol **7** readily available from commercial (*S*)-benzyl glycidyl ether (**8**) via cross-metathesis reaction.

Synthesis of compound **6** began with the addition of vinylmagnesium bromide to epoxide **8** to give the reported homoallylic

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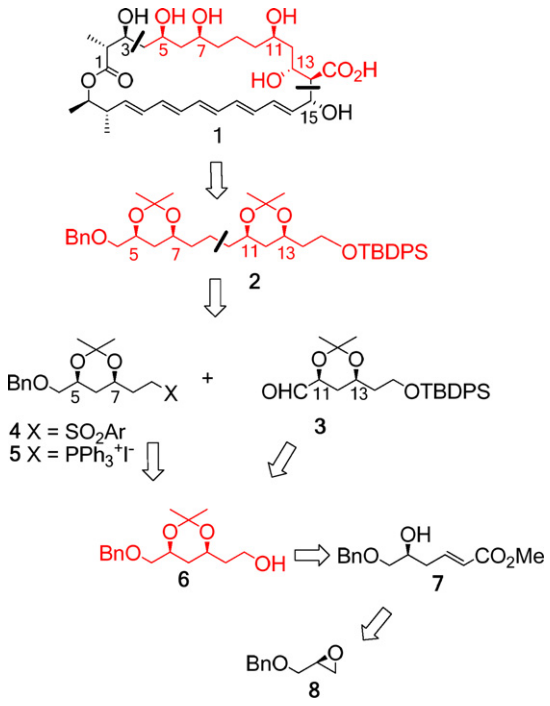
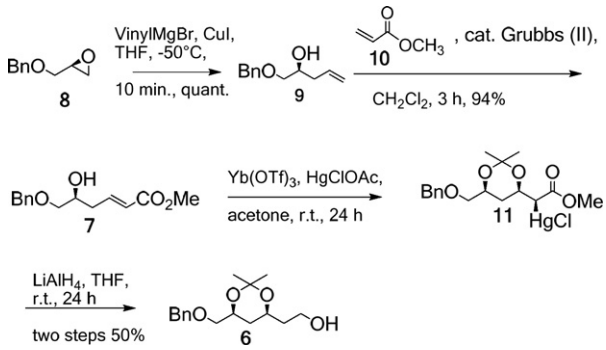


Scheme 1. Retrosynthetic analysis of strevertene A.

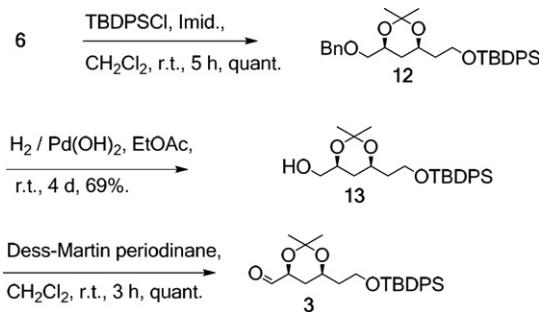


Scheme 2. Synthesis of tetrol **6**.

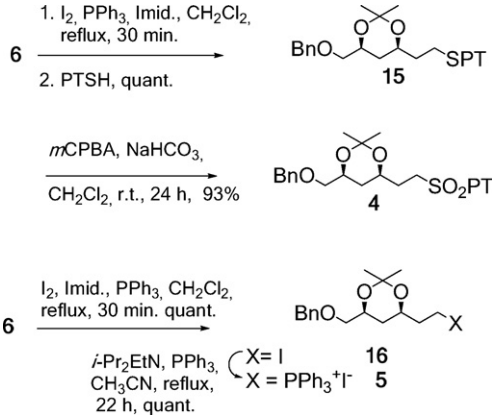
alcohol **9** in high yield (Scheme 2).[5] Treatment of **9** in a cross-metathesis reaction, with methyl acrylate **10** and second generation Grubbs catalyst, afforded the expected compound **7**[6] in high yield and stereoselectivity (94% yield, *E*/*Z* >99:1).[7] The 1,3-*syn* diol moiety of tetrol **6** was introduced by the oxymercuration reaction[3] on homoallylic alcohol **7**, generating the mercurium diol **11** with high diasteroselectivity. This adduct was subsequently reduced with $LiAlH_4$ in THF to afford alcohol **6** in 50% yield in two steps.[8]

The common tetrol **6** was converted into aldehyde **3** and sulfonyl derivative **4** and the phosphonium salt analog **5** as shown in Schemes 3 and 4. To this end, silylation of primary alcohol followed by debenzylation of **12**, using Pearlman's catalyst in EtOAc, provided alcohol **13** in 69% yield.[9] Aldehyde **3** was subsequently obtained from **13** in quantitative yield according to Dess–Martin oxidation conditions.[10]

The functionalization of compound **6** as sulfonyl or phosphonium salt was initiated with the *one-pot* iodination, and subsequent nucleophilic substitution with heteroarylthiol (phenyltriazolylthiol PT-SH) (Scheme 4) afforded sulphur derivative **15** in quantitative yield. Oxidation of the thioether with *m*-CPBA afforded sulfone **4** in very high yield (93% after column chromatography).[4] The alternative synthesis of the phosphonium salt **5** was



Scheme 3. Synthesis of aldehyde **3**.

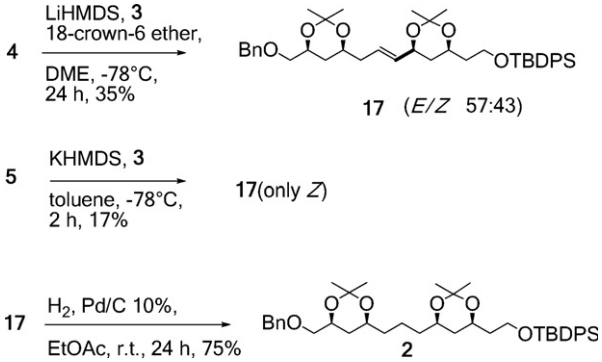


Scheme 4. Synthesis of sulfone **4** and phosphonium salt **5**.

accomplished by heating the iodide **16** with 10 equiv of triphenylphosphine (22 h, 85 °C) to afford, after crystallization, quantitative yield of the phosphonium salt in two steps.[11]

To obtain the key compound **2**, we tried firstly the *one-pot* Julia olefination[12] with sulfone **4** in order to generate the C(9–10) double bond (Scheme 5). The best conditions for obtaining compound **17** were found by using LiHMDS in DME at −78 °C in the presence of 18-crown-6-ether, in a 35% yield and a *E*/*Z* ratio of 57:43.

When the olefination was carried out under the Wittig conditions,[13] the coupling between the ylide of salt **5** and the aldehyde **3** afforded compound **17** in low yield but with excellent stereoselectivity (17% of yield and only *Z* isomer). Unfortunately, high sterical hindrance of precursors seems to limit this coupling efficiency.[14] However, finally chemoselective reduction of the C(9–10) double bond on compound **17**, performed with H_2 on Pd/C 10% in EtOAc in a good 75% yield, completed the synthesis of the target compound **2**.[15]



Scheme 5. Coupling reactions and synthesis of **2**.

Studies to improve the final coupling reactions to the C(4–14) polyol fragment **17** of strevertene A are ongoing in our laboratory.

In summary, we have achieved a convergent synthesis of compound **2**, an advanced C(4–14) polyol fragment toward the total synthesis of natural macrolide strevertene A (**1**). Highlights of the synthesis include the intramolecular oxymercuration–reduction sequence with the direct formation of the protected *syn* 1,3-diol and reductive demercuration to alcohol **6**. This important building block was prepared in only four steps in high yield and diastereoselectivity.

Progress toward the total synthesis of strevertene A will be reported in due course.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.022.

References and notes

1. Schlingmann, G.; Milne, L.; Borders, D. B.; Carter, G. T. *Tetrahedron* **1999**, *55*, 5977–5990.
2. Guo, J.; Schlingmann, G.; Carter, G. T.; Nakanishi, K.; Berova, N. *Chirality* **2000**, *12*, 43–51.
3. (a) Bonini, C.; Campaniello, M.; Chiummiento, L.; Videtta, V. *Tetrahedron*, in press, doi:10.1016/j.tet.2008.06.094.; (b) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 403–405; (c) Dreher, S. D.; Hornberger, K. R.; Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 3197–3199.
4. Bonini, C.; Chiummiento, L.; Videtta, V. *Synlett* **2005**, 3067–3070.
5. Bonini, C.; Chiummiento, L.; Lopardo, M. T.; Pullez, M.; Colobert, F.; Solladié, G. *Tetrahedron Lett.* **2003**, *44*, 2695–2697.
6. Pak, C. S.; Lee, E.; Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523–1530.
7. For recent reviews see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527; (b) Schmidt, B.; Hermanns, J. *Top. Organomet. Chem.* **2004**, *7*, 223–267; (c) Fuerstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043; (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.
8. For previous syntheses of alcohol **6** see: (a) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672–4685; (b) Mohr, P. *Tetrahedron Lett.* **1992**, *33*, 2455–2458; (c) Anderson, C. A.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3075–3078; For ***ent*-6** see: (d) Escudier, J. M.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1993**, *49*, 5253–5266; (e) Solladié, G.; Hutt, J. *Tetrahedron Lett.* **1987**, *28*, 797–800.
9. Hydrogenation of **12** with several protocols (Pd/C 5% and 10% in MeOH or in EtOAc, $PhSSiMe_3$ in CH_2Cl_2) gave always competitive deprotection of acetonide or degradation of the substrate.
10. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
11. Phosphonium salt was prepared as reported: Paquette, L. A.; Chang, S.-K. *Org. Lett.* **2005**, *7*, 3111–3114.
12. (a) Bonini, C.; Chiummiento, L.; Videtta, V. *Synlett* **2006**, 2079–2082; (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563; (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336.
13. Wittig reaction was performed as reported for a similar aldehyde: Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.
14. Several reaction conditions were tested for the olefination. When KHMDS, NaHMDS, and LiHMDS as bases in THF as solvent were used in Julia reaction, nearly no conversion was observed. Instead when BuLi and LiHMDS were used in THF for the Wittig reaction, only by-products were observed.
15. *Spectroscopic data of compound* **2**: $[\alpha]_D^{20}$ +1.4 (*c* 0.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (m, 5H), 7.40–7.34 (m, 10H), 4.62 (d, *J* = 12.5 Hz, 1H) 4.58 (d, *J* = 12.5 Hz, 1H), 4.14–4.04 (m, 2H), 3.88–3.76 (m, 2H), 3.72–3.60 (m, 2H), 3.54–3.46 (m, 1H), 3.42–3.34 (m, 1H), 1.73–1.67 (m, 4H), 1.46, 1.44, 1.43, 1.42 (4s, 12H), 1.05, 0.94–0.82 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 135.5, 134.0, 133.9, 129.7, 129.6, 128.4, 127.8, 127.6, 127.6, 125.5, 98.5, 98.4, 73.7, 73.5, 68.8, 68.6, 68.5, 65.7, 59.7, 39.3, 37.1, 36.3, 33.8, 31.9, 30.3, 29.7, 26.8, 22.7, 20.3, 19.8, 19.2. Anal. Calcd for $C_{41}H_{58}O_6Si$: C, 72.96; H, 8.66. Found: C, 72.98; H, 8.68.