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Stereoselective synthesis of amphiasterin B4: assignment of absolute configuration

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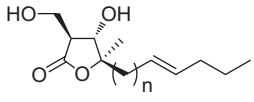
ABSTRACT

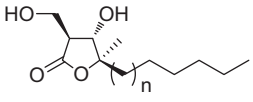
The first asymmetric synthesis of (+)-amphiasterin B4 was completed from a known *(S)*-β-benzyloxy-γ-lactone. Comparison with the spectroscopic properties reported for authentic material has given a clear indication as to the absolute stereochemistry of the natural amphiasterin B4.

Amphiasterins are a novel class of cytotoxic metabolites (IC_{50} <6 μM, NSCLC-N6 cancer cells) originally isolated from *Plakortis quasiamphiaster*, a marine sponge collected off both Caribbean and Indo–Pacific coral reefs.[1] From a structural point of view, amphiasterins can be classified into five groups (A–E series), whose components differ from each other in terms of the nature of the lateral chains. Accordingly, amphiasterins B, being comprised of five constituent members, share a common structural motif consisting of an α-hydroxymethyl-β-hydroxy-substituted γ-butyrolactone moiety and long carbon chains at the γ-position of the lactone ring (Fig. 1). Despite the obvious importance of this series of molecules, their biological activities have not been extensively studied due to a limited availability in nature, and their synthetic value is still underdeveloped.[2] Recently, Piva and Salim have reported the first total synthesis of amphiasterin B4, a noteworthy success based on regio- and stereoselective cyclization of racemic epoxydiols.[3] Unfortunately, however, the synthesis was performed non-enantioselectively, and the absolute stereochemistry of this natural product has remained unspecified, since only the relative configurations of the stereogenic centers have been defined by the same group. From this basis, we decided to explore an asymmetric approach employing a chiral pool strategy for the preparation of enantiomerically pure form of this compound. In this Letter, we report the success of our synthetic approach to (+)-amphiasterin B4, which allowed the definite assignment of the absolute configuration of the naturally occurring material.

Our approach to amphiasterin B4 started with the preparation of *(S)*-β-benzyloxy-γ-lactone **1** chosen as an appropriate chiral building block (Scheme 1). Conversion of dihydroxyacetone dimer into enantiomerically pure form of **1** was accomplished by an already published reaction protocol employing diastereomeric separation with *(S)*-(−)-α-methylbenzylamine.[4] As has been demonstrated for a similar system,[5] this chiral building block was readily transformed to *trans*-fused succinimide **2** in an overall yield of 16% through the six-step sequence involving the highly stereoselective hydroxylation with 2-phenylsulfonyl-3-phenyloxaziridine.[6,7] The reaction of **2** with methylmagnesium bromide resulted in a regioselective nucleophilic addition to the C2 carbonyl group to afford the corresponding γ-hydroxylactam.[8] This product could be reduced using sodium borohydride in methanol due to spontaneous equilibrium with the acyclic γ-ketoamide at ambient temperature, giving rise to acyclic γ-hydroxyamide **3** in 72% for two-steps.[9] From the synthetic viewpoint, our next objective was conversion of the secondary hydroxy group into ketone in order to install the long side chain via a nucleophilic addition at some stage of the synthesis. For this purpose, we first attempted replacement of the secondary amide group in **3** with an *N,N*-dialkylated amide group due to the fact that oxidation of this compound results in equilibrating reversion into the starting γ-hydroxylactam. Accordingly, THP-protected substrate **4**, which was prepared quantitatively from **3**, was converted into *N,N*-dimethyl amide derivative **5** through NaH deprotonation and subsequent reaction with methyl iodide. At this point it must be noted that introducing sterically demanding substituents adjacent to the putative carbonyl functionality can give significant improvements in stereoselectivity of nucleophilic addition to the carbonyl group.[10] Therefore, the benzyl protective groups of **5** were selectively



amphiasterin B1; n=10
B2; n=12
B3; n=16



amphiasterin B4; n=10
B5; n=12

Figure 1. Structures of constituent members of amphiasterins B1–B5.

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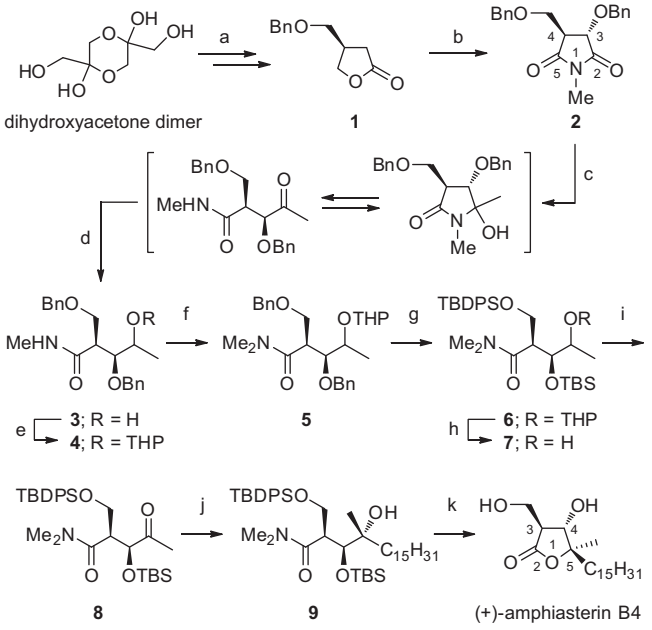

Scheme 1. Reagents and conditions: (a) see Ref. 4; (b) (i) LiHMDS, 2-phenylsulfonyl-3-phenyloxaziridine, THF, −78 °C; (ii) BnBr, Ag_2O, EtOAc; (iii) $MeNH_2$, THF–MeOH (2:1); 34% (three-steps); (iv) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2–THF (2:1), −78 to 0 °C; (v) $BF_3{\cdot}OEt_2$, THF, 0 °C; 80% (two-steps); (vi) PCC, MS4Å, CH_2Cl_2, 0 °C to rt; 58%; (c) MeMgBr, THF, −78 to 0 °C; (d) $NaBH_4$, MeOH, 72% (two-steps); (e) 2,3-DHP, PTSA, CH_2Cl_2, 0 °C; quant; (f) MeI, NaH, THF, 0 °C; (g) (i) H_2, Pd/C, EtOH; (ii) TBDPSCl, Et_3N, CH_2Cl_2; (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0 °C; 71% (four-steps); (h) PTSA, MeOH; 74%; (i) PDC, MS4Å, CH_2Cl_2; 78%; (j) *n*-$C_{15}H_{31}MgBr$, $CeCl_3$, THF, −40 to −20 °C; 72% (93:7); (k) (i) PTSA, toluene, 60 °C ; quant; (ii) 3% HCl–MeOH; 84%.

removed by hydrogenolysis (H_2, Pd/C) and the resulting primary and secondary hydroxy functionalities were then protected as the *tert*-butyldiphenylsilyl (TBDPS) and *tert*-butyldimethylsilyl (TBS) ethers, respectively, to give **6** in 71% yield for four-steps.[11]

Removal of the THP group of **6** using *p*-toluenesulfonic acid (PTSA) in methanol provided the corresponding alcohol **7** in 74% yield, which was then subjected to PDC oxidation in dichloromethane to afford the ketone **8** in 78% yield as a single stereoisomer.[12] As anticipated, the reaction of **8** with *n*-pentadecylmagnesium bromide proceeded with remarkably high stereoselectivity in the presence of $CeCl_3$ at −20 °C to give a 93:7 ratio of diastereomeric alcohols in 72% yield.[13] The major stereoisomer **9**, obtained through purification by column chromatography, underwent a PTSA-catalyzed cyclization at 60 °C to produce an almost quantitative yield of the fully protected lactone without racemization. Following deprotection of the silyl ethers by brief exposure to HCl in methanol, the fully synthetic amphiasterin B4 was obtained in 84% yield as an enantiomerically pure form. The structural identity of the synthetic and natural amphiasterin B4 was established by comparison of ^1H and ^{13}C NMR spectral data with literature data,[14] whereas the synthetic sample showed an approximately the same but opposite optical rotation, $[\alpha]_D$ +2.8 (*c* 0.8, $CHCl_3$), compared to the reported value, $[\alpha]_D$ −3.3 (*c* 0.3, $CHCl_3$).[1] From this, we are reasonably confident that the absolute configurations of the naturally occurring amphiasterin B4 should be assigned as *3R*, *4R*, and *5S*. Hence, it is obvious that the synthetic route developed could provide easy access to the optically active amphiasterin B family.

In conclusion, we have reported the success in achieving the synthesis of (+)-amphiasterin B4. The identity and stereochemistry of this product have been unequivocally established, with the most convincing evidence furnished by comparison with the properties reported for authentic material. To the best of our knowledge, this report represents the first example of asymmetric elaboration of amphiasterin B4 as well as the initial disclosure of the absolute stereochemistry of the natural amphiasterin B4.

Acknowledgment

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7. On the basis of simple ^1H NMR spectral data, **2** was isolated as a single enantiomer that has *(3S,4S)*-configuration, see Ref. 5
8. The high regioselectivity of the Grignard addition to the C2 carbonyl group could be attributed to the complex induced proximity effect, see: (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356–363; (b) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2669–2672; (c) Huang, P. Q.; Wang, S. L.; Ye, J. L.; Ruan, Y. P.; Huang, Y. Q.; Zheng, H.; Gao, J. X. *Tetrahedron* **1998**, *54*, 12547–12560.
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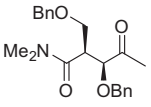
10. In fact, we observed that reaction of some Grignard reagents with dibenzyloxy-substituted ketone derived directly from **5** (see below) gave a decreased stereoselectivity (80:20) compared to those of structurally modified substrates bearing much bulkier silyl substituents as will be elaborated below.



11. An attempt to introduce the TBDPS group on the secondary hydroxy group failed presumably due to steric congestion. Therefore, the TBS group was used as an alternative to mask the hydroxy functionality.
12. High purity of the product was confirmed by the simplicity of the ^1H and ^{13}C NMR spectra that were consistent with the assigned structure, suggesting no racemization occurred in this oxidation step.
13. For example, the reaction of the dibenzyloxy-substituted ketone (see Ref. 10) in the absence of $CeCl_3$ resulted in a dramatic decrease of diastereoselectivity showing opposite preference (21:79). Therefore, the addition of $CeCl_3$ is necessary to obtain the desired isomer **9** with greater stereoselectivity, since this stereochemical course can be understood on the basis of a simple non-chelation model.
14. Characterization data for (+)-amphiasterin B4: IR (NaCl) ν_{max} 3436, 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.29 (dd, *J* = 9.9, 5.0 Hz, 1H, C*H*), 4.04 (m, 1H, CH_2), 3.92 (m, 1H, CH_2), 2.83 (dt, *J* = 9.9, 4.6 Hz, 1H, C*H*), 2.73 (d, *J* = 5.0 Hz, 1H, O*H*), 2.56 (br s, 1H, O*H*), 1.78–1.66 (m, 3H, CH_2), 1.45–1.21 (m, 30H, CH_2), 1.36 (s, 3H, CH_3), 0.88 (t, *J* = 6.6, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.1 (*C*), 87.0 (*C*), 74.6 (*C*H), 59.3 (CH_2), 49.4 (*C*H), 39.8 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.61 (CH_2), 29.57 (CH_2), 29.55 (CH_2), 29.48 (CH_2), 29.40 (CH_2), 29.3 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 18.9 (CH_3), 14.1 (CH_3). Anal. Calcd for $C_{21}H_{40}O_4$: C, 70.74; H, 11.31. Found: C, 70.61; H, 11.08.