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A Short Access to 3-Hydroxy-4-hydroxymethyltetrahydrofurans: Application to the Total Synthesis of Amphiasterin B4

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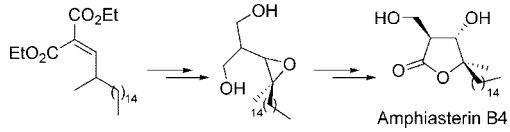


The first total synthesis of amphiasterin B4, a secondary metabolite previously isolated from *Plakortis quasiamphiaster* has been achieved. The core structure has been reached according to a highly stereoselective one-pot epoxidation/cyclization of an unsaturated diol. This substrate can be prepared from β,γ-unsaturated diesters readily available from the organocatalyzed protonation of a transient dienol generated by UV irradiation of corresponding α,β-unsaturated isomers.

Amphiasterins B and C have been isolated in 2001 from the marine sponge *Plakortis quasiamphiaster* growing in Indo-Pacific coral reefs.[1] As determined by MS and NMR, amphiasterins B (**1**; Figure 1) possess a common structure consisting of a 2-furanone subunit bearing respectively on position 3 a hydroxymethyl group and on position 4 a hydroxy group. As other butyrolactones found in this genus, they present also a quaternary center on position 5.[2−5]

Due to a low availability in Nature, only a few of these compounds have been tested to determine their biological activities. For example, amphiasterin B2 showed a moderate cytotoxicity against human cancer lines.[1] In connection with our interest in the total synthesis of marine natural products,[6−8] we have investigated the synthesis of amphiasterin B4 and some analogues.

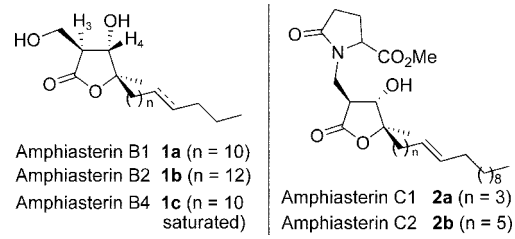
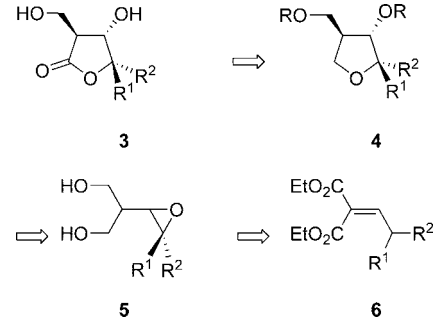


FIGURE 1. Amphiasterins B and C.

SCHEME 1. Retrosynthetic Pathway to Amphiasterins



To date, a large number of procedures already have been reported to prepare 5,5-disubstituted lactones[9] but none for compounds also possess the hydroxy and hydroxymethyl groups present on the five-membered ring of amphiasterins. We have first considered a general access to the core structure of amphiasterins and our strategy is depicted in Scheme 1. Butyrolactones **3** could result from the selective oxidation of the corresponding tetrahydrofurans **4** bearing both hydroxy and hydroxymethyl groups previously protected as ethers. The expected formation of the tetrahydrofuran was based on the ring-opening of an oxirane by one hydroxy group of the two free alcohols of precursors **5**. These diols could be prepared by a three-step sequence from esters **6** resulting themselves from the Knoevenagel condensation of diethyl malonate with an appropriate aldehyde. To avoid the possibility of *E*/*Z* selectivities, the starting materials were substituted at the γ-position by two similar alkyl substituents R^1 and R^2.

The condensation of diethyl malonate was first performed with isobutyraldehyde under conditions already mentioned in the literature.[10,11] The deconjugation of **6a** was next carried out under photochemical conditions. α,β-Unsaturated esters can be easily converted into their β,γ-unsaturated isomers according

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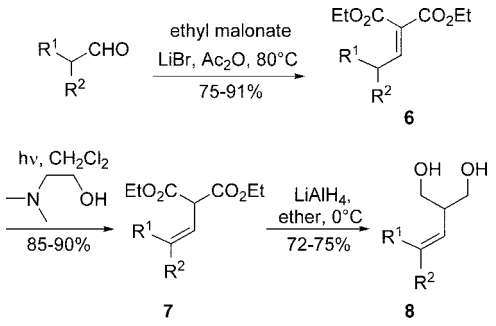
TABLE 1. Access to Unsaturated Diols 8



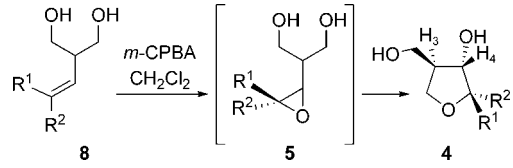
entry	R^1	R^2	**6**[a]	**7**[a]	**8**[a]
1	CH_3	CH_3	**6a** (75)	**7a** (90)	**8a** (72)
2	C_2H_5	C_2H_5	**6b** (85)	**7b** (85)	**8b** (74)
3	$-(CH_2)_5-$		**6c** (91)	**7c** (87)	**8c** (75)

[a] Yield of isolated compound.

to a 1,5-sigmatropic hydrogen migration leading to a photodienol species.[12] In the presence of a protic source like a β-amino alcohol, the transient species can deliver after protonation the resulting deconjugated ester.[13,14] This process has been widely studied in our group and applied to the synthesis of various natural products.[15] To our knowledge, this isomerization under UV activation had never been reported from diesters **6**. When a solution of **6a** was submitted to irradiation at a wavelength of 254 nm in the presence of *N*,*N*-dimethylaminoethanol at 0 °C, **7a** was isolated in fairly good yields and this compound was immediately reduced with $LiAlH_4$ in ether.[16] This efficient strategy was generalized to two other diesters **6b**,**c** and the results are given in Table 1.

The homoallylic diol **8a** was epoxidized with *m*-CPBA in dichloromethane[17] leading directly to a single regio- and diastereoisomer (Table 2, entry 1), which was characterized as tetrahydrofuran **4a** by NMR spectroscopy and mass spectrometry studies. According to Baldwin's rules, both 4-*exo*-tet and 5-*endo*-tet processes can be considered starting from epoxy alcohols like **5**.[18] For example, some disubstituted β,γ-epoxy alcohols have been reported to deliver oxetanes as the major adducts under basic conditions. In that case, the selectivity was explained by a better overlap between the orbitals of the nucleophile and the electrophile.[19] In our case, the formation of the five-membered ring from a trisubstituted epoxy alcohol took placed under acidic conditions and could be justified by a

TABLE 2. Tandem Epoxidation/Ring-Closing of Diols 8a−c into Tetrahydrofurans 4a−c



entry	R^1	R^2	**5**	**4**[a]
1	CH_3	CH_3	not det.	**4a** (60)
2	C_2H_5	C_2H_5	not det.	**4b** (79)
3	$-(CH_2)_5-$		not det.	**4c** (65)

[a] Yield of isolated compound.

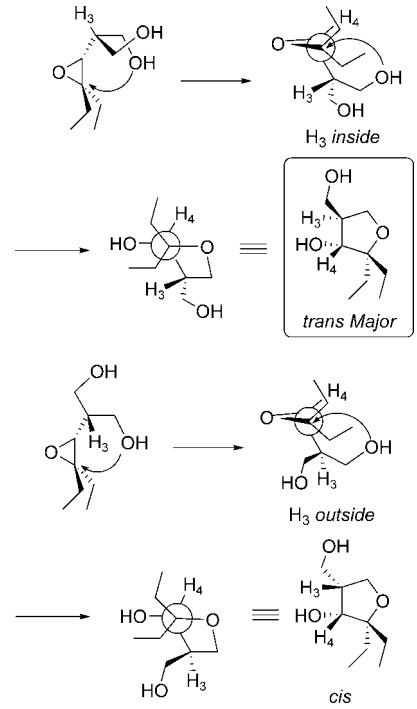


FIGURE 2. Desymmetrization of Epoxy-Diol **5b**.

better stabilization of a transient cationic species as already noticed with parent substrates.[20] The relative configuration of the two contiguous centers was established according to the value of the coupling constant between H_3 and H_4 (J = 9.0 Hz). By comparison with data reported for okaspirodiol, a natural product that disclosed a similar arrangement,[21] a trans relationship between the hydroxy and the hydroxymethyl substituents could be assigned. Similar regio- and stereoselectivities were noticed with the two γ-disubstituted diols **8b**,**c** tested (entries 2 and 3). This stereoselectivity could be related to a selective approach of one of the two hydroxymethyl pendants toward the epoxide moiety. To minimize steric interactions, the conformation for which the hydrogen atom appears inside seems much more favorable compared to the second one (Figure 2).

During the tandem epoxidation/cyclization process, a new stereocenter is created. Therefore, this efficient access to

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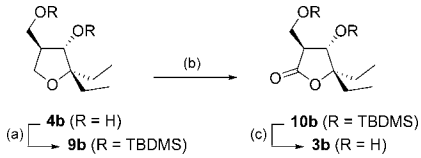
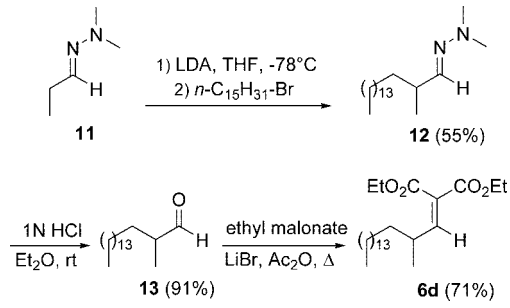
SCHEME 2. Oxidation of Tetrahydrofuran 4b into Furanone[a]



[a] Reagents and conditions: (a) TBDMS-Cl (4.2 equiv), imidazole (3 equiv), DMF, rt (80%). (b) PCC/Celite, Ph-H, Δ (70%). (c) HF·pyr, CH_3CN, rt, 12h (71%).

SCHEME 3. Formation of Malonate 6d



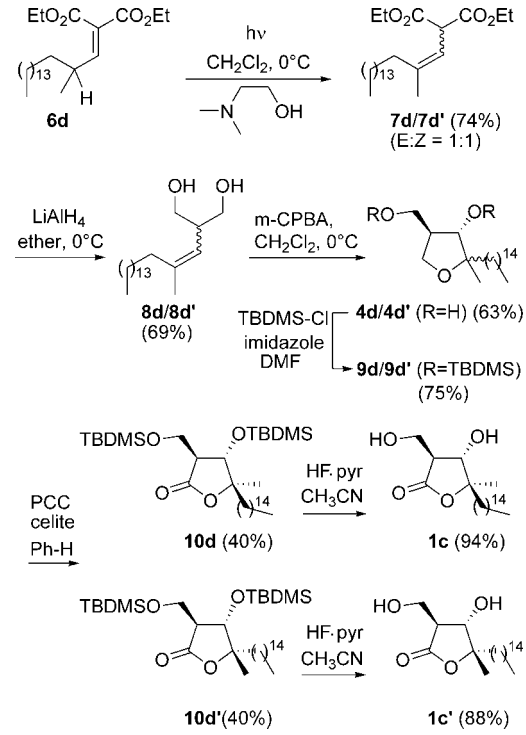
tetrahydrofurans represents a new example of desymmetrization of tris(hydroxymethyl)methane derivatives.[22]

To access the core structure of amphiasterins, the tetrahydrofuran subunit was selectively oxidized to 2-furanone. Compound **4b** was used as a model and the two hydroxy groups were first protected as TBDMS ether by using a well-established method.[23] A large number of oxidants already have been reported for the formation of butyrolactones from the parent cyclic ethers.[24−27] Among all of them, PCC adsorbed on Celite[25] led to the expected structure **10b** in 70% yield. Treated with an excess of HF·pyr in acetonitrile, the TBDMS ether was cleaved to furnish the fully deprotected structure **3b** in an acceptable yield (Scheme 2).

The above sequence was next applied to the first synthesis of amphiasterin B4. The α,β-unsaturated diester **6d** was prepared according to Scheme 3. Hydrazone **11** obtained by condensation of *N*,*N*-dimethylhydrazine with propionaldehyde was conveniently alkylated[28] with commercially available 1-bromopentadecane and hydrolyzed under acidic conditions into **13**.[29] This aldehyde reacted with diethylmalonate under conditions already used for **6a**−**c** to deliver the corresponding diester **6d**.

The irradiation of diester **6d** under conditions as described above furnished an unseparable 1:1 mixture of (*E*) and (*Z*)-β,γ-isomers **7d/7d′**. 1,3-Diols **8d**−**d′** were obtained by reduction with $LiAlH_4$ in ether. Epoxidation of the double bond was conveniently achieved by treatment with *m*-CPBA. The transient oxiranes led smoothly to an unseparable 1:1 mixture of the two tetrahydrofurans **4d** and **4d′** in 63% yield (Scheme 4). As mentioned before, the two hydroxy groups were etherified under standard conditions. By treatment with PCC on Celite, the two diastereoisomers **9d/9d′** were oxidized into the corresponding butyrolactones **10d** and **10d′**. Fortunately, these two substances

SCHEME 4. Synthesis of Amphiasterin B4 from 6d



were separated by chromatography on silica. Deprotection of the silyl ethers delivered amphiasterin **1c** and its epimer **1c′**.

In conclusion, we have achieved the first total synthesis of amphiasterin B4 in 10 steps from propionaldehyde and with a 3.3% overall yield. The strategy was based on a highly regio- and stereoselective cyclization of epoxydiols, the reaction proceeding with desymmetrization of the starting material. Work is now underway to complete the enantioselective synthesis of other members of this family of natural products.

Experimental Section

Formation of tetrahydrofurans 4d/4d′: To a solution of diols **8d/8d′** (0.052 g, 0.16 mmol) in dichloromethane (5 mL) was added at 0 °C *m*-CPBA (0.090 g, 0.51 mmol). After stirring overnight at rt, the resulting mixture was hydrolyzed and extracted with ethyl acetate. The organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed by concentration. After flash-chromatography on silica (eluent: methanol/dichloromethane 5/95), an unseparable 1:1 mixture of tetrahydrofurans **4d** and **4d′** (0.034 g, 0.10 mmol) was obtained. Yield = 63%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 6.7 Hz, H_{22}), 1.13 (1.5H, s, isomer **4d′**), 1.27 (1.5H, s, isomer **4d**), 1.28−1.59 (28H, m), 2.40−2.49 (1H, m), 3.45 (1H, dd, J = 8.6 and 19.5 Hz), 3.70−3.86 (3H, m), 3.97 (1H, dd, J = 8.6 et 17.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5 (CH_3), 19.3 (CH_3), 23.0, 27.3, 29.7−30.8, 32.3, 33.6 (CH_2, C_{20}), 40.4, 48.9, 64.8, 65.9, 81.4, 83.5; HRMS (CI) *m*/*z* calcd for $C_{21}H_{42}O_3$ + H 343.3212, found 343.3208.

Amphiasterin B (1c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 6.9 Hz), 1.17−1.34 (24H, m), 1.37 (3H, s), 1.40−1.50 (2H, m), 1.68−1.79 (2H, m), 2.85 (1H, dt, J = 9.9 and 4.9 Hz), 3.98 (1H, dd, J_{AB} = 11.3 Hz, J = 4.6 Hz), 4.06 (1H, dd, J_{AB} = 11.3 Hz, J = 5.0 Hz), 4.34 (1H, d, J = 9.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 19.4, 23.1, 23.9, 29.8−30.3 ($10CH_2$), 32.3, 40.3, 49.8, 59.7, 75.1, 87.4, 174.6; HRMS (ES) *m*/*z* calcd for $C_{21}H_{40}O_4$ + Na 379.2824, found 379.2820; IR ν 3377, 2914, 1759, 1469, 1265, 1099, 936, 739 cm^{-1}.

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Supporting Information Available: Experimental procedures and product characterization for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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