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Synthetic studies directed toward amphidinol 2: elucidation of the relative configuration of the C1–C10 fragment

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ABSTRACT

Model compounds (**11** and **12**) for the C1–C10 tetrahydropyran fragment of amphidinol 2 were prepared from (2*S*)-benzyloxypropanal in 9 steps. The synthetic route relied on diastereoselective diene-aldehyde cycloaddition, stereoselective C-allylation, and reagent based enantioselective aldehyde allylation. Comparison of the NMR spectra for models **11** and **12** with that for amphidinol 2 indicated that the C1–C10 segment of the natural product possesses the 2*R**,4*R**,6*R**,7*S**,8*R**,10*S** *relative* configuration.

The amphidinols (AM) 1-15 are a series of polyene-polyol natural products isolated from cultured dinoflagellates *Amphidinium klebsii* and *Amphidinium carterae*.[1] The members of this family are characterized by a common bis-pyran polyol segment (highlighted in dashed box for **AM2**, Fig. 1); they differ with respect to the hydrophobic and hydrophilic chains connected to this common fragment. The amphidinols exhibit variable hemolytic activity as well as antifungal activity against *Aspergillus niger* (EC50 = 7.3 nM and 6 μg/disk, respectively, for **AM2**[1b]), and this activity is been attributed to the ability of the amphidinols to increase membrane permeability. It has recently been speculated that the common fragment adopts a 'hairpin' conformation and that the nature of the polyene chain affects the membrane affinity, while differences in the hydrophilic polyol segments of the AMs influence the pore size.[2] Amphidinol 3 is the only member of this family for which the complete relative and absolute configuration has been determined.[3] For this reason, amphidinol 3 has attracted the greatest synthetic interest, and numerous groups have prepared extended fragments of this target.[4]

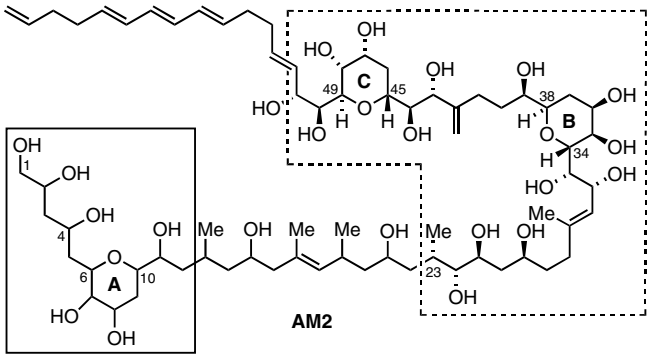

Figure 1. Skeletal structure of amphidinol 2 (**AM2**).

Amphidinol 2 (**AM2**) was isolated >10 years ago from cultures of *Amphidinium klebsii* by Tachibana's group.[1b] The atom connectivity indicated in Figure 1 was assigned on the basis of extensive ^{1}H and ^{13}C NMR spectroscopy. While these authors did not propose the stereochemistry of **AM2** at that time, it now seems likely that the C23–C51 segment of **AM2** has the same *relative* and *absolute* configurations as the C23–C51 segment of **AM3**, given the nearly identical nature of the ^{13}C NMR spectral data for these segments and their similar biological origin. We herein report on synthetic studies directed at elucidating the *relative* configuration of the C1–C10 segment of **AM2** (solid box, Fig. 1).

Tashibana and co-workers[1b] assigned the hydrogens at C6, C7, C8 and C10 of the tetrahydropyran ring A as equatorial, equatorial, axial and axial, respectively, on the basis of their $^{3}J_{H-H}$ couplings. For the purposes of identifying the *relative* configuration of the C1–C10 segment, we arbitrarily chose to prepare the tetrahydropyran ring with 6*R*,7*S*,8*R*,10*S* diastereomer. Diastereoselective Lewis acid-catalyzed cyclocondensation of 2(*S*)-benzyloxypropanal (prepared from readily available ethyl (*S*)-lactate) with 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene afforded the known[5] dihydropyranone **1** (Scheme 1). Reduction of **1** gave the pseudoglycal **2**. Oxidation of **2** with mCPBA in methanol[6] gave the α-methyl 5-deoxymannoside **3**, which was protected as its dibenzyl ether **4** using NaH/benzyl bromide. Ionization of the α-methoxy group with trimethylsilyl triflate and subsequent nucleophilic attack with allyltrimethylsilane proceeded to give the *trans* tetrahydropyran **5**.[7] Johnson-Lemieux[8] oxidation of **5** afforded aldehyde **6.**

Addition of allyl Grignard to **6** gave a mixture of two diastereomeric alcohols (**7**/**8**), which were difficult to completely separate (Scheme 2). Alternatively, reaction of **6** with allyl diisopinocampheylborane[9] (generated from (+)-$(IPC)_2$BOMe under salt-free conditions), followed by oxidative work-up, gave **7** as the exclusive

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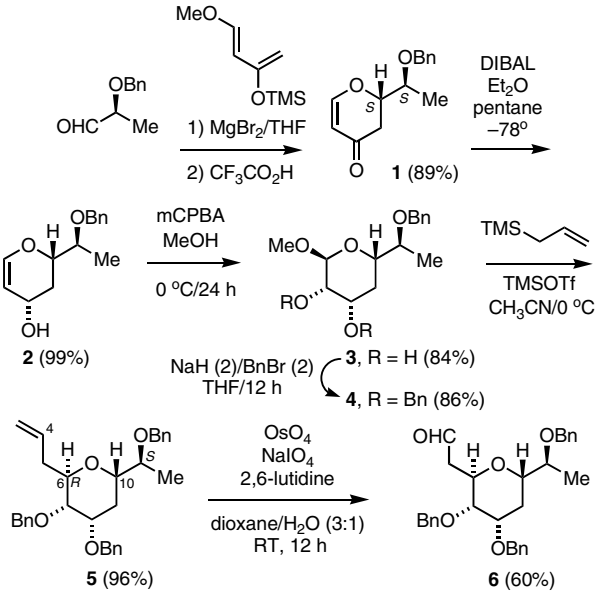
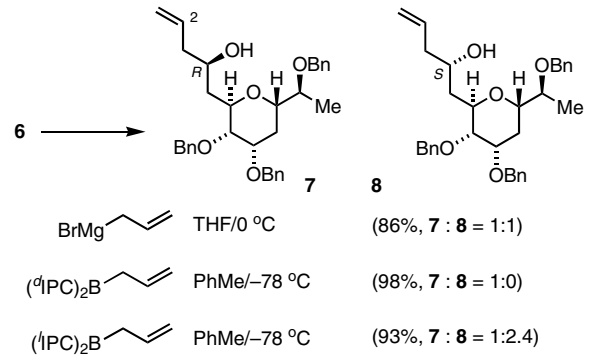


Scheme 1.

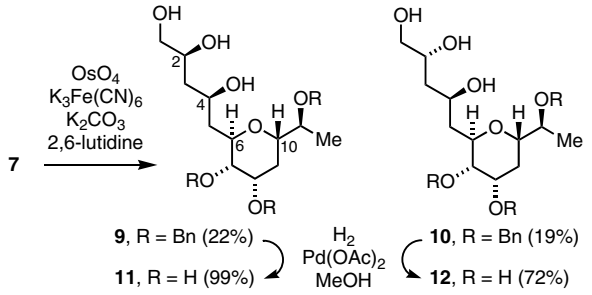


Scheme 2.

product.[10] Homoallylic alcohol **7** was assigned the 4(*R*) stereochemistry on the basis of the ^{1}H NMR spectral data of the corresponding (*S*)- and (*R*)- Mosher's esters. In particular, the H-2 signal for the (*S*)-MTPA ester appears at δ 5.62, while this signal for the (*R*)-MTPA ester appears upfield at δ 5.45 ppm.[11] In contrast, reaction of **6** with the chiral allylborane generated from (−)-(IPC)$_2$-BOMe, proceeded in a 'mismatched' double diastereoselective fashion to give a mixture of **7** and **8** (1:2.4). Pure **8**[10] could be prepared from pure **7** by Mitsunobu inversion[12] using *p*-nitrobenzoic acid, followed by hydrolysis.

The ^{13}C NMR spectra of these two diastereomers are relatively similar except for the signals for C4 and C6, which appear at δ 72.1 and 76.1 ppm for **7** and δ 68.0 and 71.7 ppm for **8,** respectively. The downfield shift for these signals in the *syn*- diastereomer (**7**) compared to the *anti*-diastereomer (**8**) has previously been observed in a number of diastereomeric tetrahydropyran structures bearing an axial (2-hydroxyalkyl)- or (2-hydroxyalkenyl) substituent.[13] Furthermore, the chemical shift for C6 of **7** (δ 76.1 ppm) is a closer match with that for C6 of amphidinol 2 (δ 77.3 ppm) than is the signal for C6 of **8** (δ 71.7 ppm).

With this insight, dihydroxylation of **7** with OsO_4 proceeded in a non-stereoselective fashion to afford a mixture of diols **9** and **10,** which were separable by preparative TLC (Scheme 3). The stereochemical assignments for **9** and **10** (*syn*- and *anti*-, respectively)



Scheme 3.

are based on their relative NMR spectral data.[10] In particular, the sum of the chemical shifts for C2 and C4 of **9** (δ 72.0 + 72.8 = 144.8 ppm) is greater than that for **10** (δ 69.7 + 70.0 = 139.7 ppm). Hoffmann observed that 'the sum of the chemical shifts of the two oxygen bearing carbon atoms ... should be numerically smaller for the *threo*-1,3-diols than for their *erythro*-counterparts'.[14] This difference was attributed to the presence of an axial substituent in the chair-like hydrogen bonded conformers of the *erythro*-diastereomer, and this empirical trend is documented in numerous cases.[15]

Reductive debenzylation of **9** gave **11**, while similar processing of **10** gave **12** (Scheme 3). Notably, while the chemical shifts for carbons C6–C12 of **11** and **12** are relatively similar, the chemical shifts for C2 and C4 of **11** (δ 72.0 and 69.7) are considerably different than those for **12** (δ 70.4 and 67.7 ppm). A comparison of the ^{13}C NMR signals of **11** and **12**, obtained in $CD_3OD/C_5D_5N/D_2O$, with the literature values[1b] for the corresponding atoms in amphidinol 2 is graphically presented in Figure 2.

From these comparisons, the chemical shifts of C1–C7 of **12** have a better match with **AM2**, than do those of **11**.[16] Thus, we propose that the *relative* configuration of **AM2** is 2*R**,4*R**,6*R**,7*S**,8*R**,10*S**.[17] The chemical shifts for C9 and C10 of both models **11** and **12** deviate from those of **AM2** by >1 ppm. From the present studies, it is not clear if these deviations are due to the differences in molecular structure at C12 [–CH_3 vs –$CH_2CH(Me)CH_2$ for **AM2**] or due to a difference in the relative stereochemistry at C11 or both. Further studies will be required to establish the relative configuration at C11 as well as other stereocenters in the polyol chain of **AM2**.

In summary, model compounds **11** and **12** for the C1–C12 segment of amphidinol 2 were prepared in 9 steps from (*S*)-2-benzyloxypropanal. Comparison of the ^{13}C NMR spectra of these models with that for the corresponding segment of **AM2** indicates that the *relative* configuration of **AM2** is 2*R**,4*R**,6*R**,7*S**,8*R**,10*S**.

Table 1
^{1}H NMR spectral data for **AM1**, **11** and **12** [chemical shift in δ, solvent $CD_3OD/C_5D_5N/D_2O$ (2:1:0.1)]

H	AM2[a]	11[b]	12[b]
1	3.57	3.55–3.63	3.57
1′	3.59	3.55–3.63	3.57
2	4.05	3.93–4.03	4.06
3	1.66	1.64–1.75	1.60–1.71
3′	1.67	1.64–1.75	1.60–1.72
4	4.14	4.08	4.15
5	1.68	1.64–1.75	1.60–1.71
5′	2.00	1.93	1.96
6	4.27	4.26	4.25
7	3.72	3.67	3.66
8	4.00	3.93–4.03	3.99

[a] Ref. 1b.
[b] Present work.

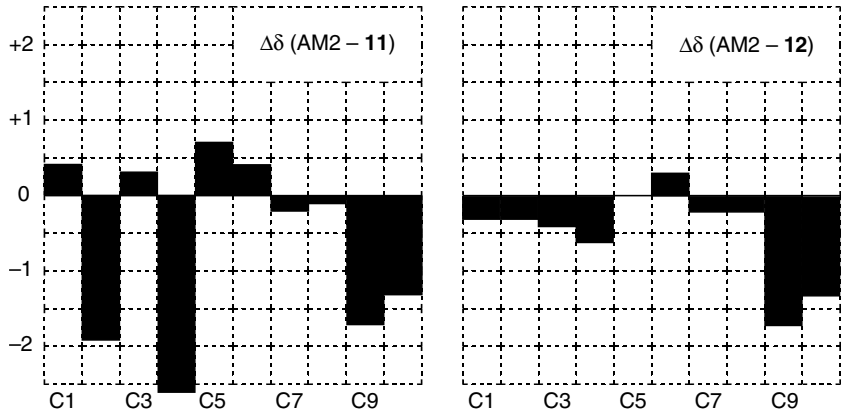


Figure 2. Difference between the chemical shifts of the carbon atoms of amphidinol 2 and those of models **11** and **12** ($CD_3OD/C_5D_5N/D_2O$).

Acknowledgments

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10. *Selected spectral data*: **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, J = 6.0 Hz, 3H), 1.49 (td, J = 2.1, 15.0 Hz, 1H), 1.64–1.81 (m, 2H), 1.99 (td, J = 9.3, 12.6 Hz, 1H), 2.10–2.32 (m, 2H), 3.43 (t, J = 3.0 Hz, 1H), 3.68–3.91 (m, 4H), 4.27 (td, J = 3.1, 11.7 Hz, 1H), 4.54 (m, 2H), 4.59 (s, 2H), 4.68 (ABq, J = 12.9 Hz, 2H), 5.04–5.10 (m, 2H), 5.82 (tdd, J = 7.2, 10.8, 16.8 Hz, 1H), 7.22–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 28.7, 35.3, 41.8, 68.0, 70.7, 71.68, 71.73, 71.79, 73.7, 74.1, 75.7, 76.1, 76.6, 117.7, 127.6, 127.7, 127.79, 127.83, 128.0, 128.1, 128.46, 128.5, 128.6, 135.3, 138.5, 138.7, 139.0. *Compound* **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J = 6.0 Hz, 3H), 1.31 (ddd, J = 3.8, 8.5, 14.6 Hz, 1H), 1.64–1.80 (m, 2H), 1.94 (td, J = 9.9, 12.8 Hz, 1H), 2.15 (t, J = 6.7 Hz, 2H), 3.39 (t, J = 3.0 Hz, 1H), 3.55 (ddd, J = 3.1, 6.7, 9.5 Hz, 1H), 3.64–3.77 (m, 3H), 4.32 (td, J = 3.5, 10.7 Hz, 1H), 4.44 (s, 2H), 4.48 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.59 (s, 2H), 4.96–5.04 (m, 2H), 5.66 (tdd, J = 7.2, 9.9, 17.2 Hz, 1H), 7.15–7.35 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 28.7, 35.3, 41.7, 68.0, 70.7, 71.68, 71.74, 71.8, 73.7, 74.1, 75.7, 76.5, 117.7, 127.6, 127.7, 127.8, 127.79, 127.88, 128.0, 128.45, 128.47, 128.48, 128.53, 135.1, 138.2, 138.7, 138.8. *Compound* **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, J = 6.3 Hz, 3H), 1.38–1.49 (m, 2H), 1.63 (td, J = 9.9, 14.4 Hz, 1H), 1.72–1.84 (m, 2H), 1.97 (td, J = 8.9, 13.0 Hz, 1H), 3.40 (t, J = 3.3 Hz, 1H), 3.43 (dd, J = 5.4, 11.1 Hz, 1H), 3.56 (dd, J = 3.7, 11.1 Hz, 1H), 3.68 (dt, J = 3.5, 8.4 Hz, 1H), 3.76 (td, J = 3.6, 8.7 Hz, 1H), 3.81–3.91 (m, 2H), 4.06 (br t, J = 9.9 Hz, 1H), 4.28 (br td, J = 3.0, 11.7 Hz, 1H), 4.49 (d, J = 11.1 Hz, 1H), 4.55 (s, 2H), 4.62 (d, J = 11.1 Hz, 1H), 4.66 (ABq, J = 12.3 Hz, 2H total), 7.23–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 28.7, 36.7, 39.7, 66.6, 70.9, 71.6, 72.0, 72.1, 72.8, 73.4, 74.2, 75.7, 75.9, 76.8, 127.61, 127.63, 127.79, 127.81, 128.0, 128.1, 128.42, 128.44, 128.46, 128.48, 128.5, 128.54, 138.17, 138.24, 138.3. *Compound* **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, J = 6.3 Hz, 3H), 1.42 (br d, J = 14.7 Hz, 1H), 1.49–1.66 (m, 2H), 1.74–1.87 (m, 2H), 1.97 (td, J = 9.3, 12.8 Hz, 1H), 3.40 (t, J = 3.6 Hz, 1H), 3.44 (dd, J = 6.9, 10.8 Hz, 1H), 3.53 (dd, J = 3.6, 10.8 Hz, 1H), 3.69 (dt, J = 3.3, 8.3 Hz, 1H), 3.74–3.92 (m, 3H), 4.09 (dt, J = 3.0, 8.3 Hz, 1H), 4.28 (br d, J = 12.0 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 4.55 (s, 2H), 4.61 (d, J = 11.7 Hz, 1H), 4.66 (ABq, J = 12.3 Hz, 2H total), 7.22–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 28.7, 36.2, 39.4, 66.8, 69.7, 70.0, 70.9, 71.7, 72.0, 73.5, 74.2, 75.85, 75.9, 127.6, 127.7, 127.8, 127.9, 128.1, 128.4, 128.5, 128.6, 138.3, 138.4. *Compound* **11**: ^{1}H NMR (400 MHz, $CD_3OD/C_5D_5N/D_2O$ = 2.0:1.0:0.1) δ 1.13 (d, J = 6.4 Hz, 3H), 1.64–1.75 (m, 3H), 1.80–1.97 (m, 3H), 3.51 (ddd, J = 3.2, 6.5, 9.6 Hz, 1H), 3.55–3.63 (m, 2H), 3.67 (br s, 1H), 3.83 (pent, J = 6.4 Hz, 1H), 3.93–4.03 (m, 2H), 4.05–4.12 (m, 1H), 4.23–4.29 (m, 1H); ^{13}C NMR (100 MHz, $CD_3OD/C_5D_5N/D_2O$ = 2.0:1.0:0.1) δ 19.6, 32.0, 37.9, 41.0, 67.3, 67.4, 69.7, 70.3, 71.8, 72.0, 75.5, 76.9. *Compound* **12**: ^{1}H NMR (400 MHz, $CD_3OD/C_5H_5N/D_2O$) δ 1.12 (d, J = 6.4 Hz, 3H), 1.60–1.71 (m, 4H), 1.82 (td, J = 10.0, 12.8 Hz, 1H), 1.96 (ddd, J = 7.4, 9.4, 14.2 Hz, 1H), 3.51 (ddd, J = 3.2, 6.5, 9.7 Hz, 1H), 3.57 (d, J = 6.0 Hz, 2H), 3.66 (t, J = 2.8 Hz, 1H), 3.83 (pent, J = 6.4 Hz, 1H), 3.96–4.06 (m, 2H), 4.15 (pent, J = 6.2 Hz, 1H), 4.22–4.27 (m, 1H); ^{13}C NMR (100 MHz, $CD_3OD/C_5D_5N/D_2O$ = 2.0:1.0:0.1) δ 19.5, 32.0, 38.5, 41.7, 67.4, 67.7, 68.0, 70.3, 70.4, 71.8, 75.5, 77.0.
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16. While the differences in the ^{1}H NMR spectral data for **11** and **12** (Table 1) are not as great as those for ^{13}C NMR spectra, there is also a closer match between **12** and **AM2** than between **11** and **AM2**, particularly for the alcohol methine hydrogens H2 and H4.
17. The solvent system [$CD_3OD/C_5D_5N/D_2O$ (2:1:0.1)] used in our work is the same as that used by Tachibana et al.[1b] for **AM2**. As a referee has noted, this solvent mixture would disrupt intramolecular hydrogen bonding within these polyol structures, and thus should be used with caution should be used when comparing the NMR spectral data in this solvent to those obtained in $CDCl_3$.