Efficient Syntheses of the Polyene Fragments Present in Amphidinols

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Received 6 May 2007

Abstract: The C53–C67 and C53–C65 polyene fragments of amphidinols have been synthesized in an efficient and convergent fashion from sorbic acid in good overall yields (30–31%) by employing a chemoselective cross-metathesis of a Weinreb amide and a Julia–Kocienski olefination as the key steps.

Key words: cross-metathesis, Julia–Kocienski olefination, amphidinols, polyenes

Unique structures and powerful bioactivities of polyketide metabolites have often attracted attention of synthetic chemists. Amphidinols (AMs) are a small class of such polyketides isolated from the genus *Amphidinium*. Amphidinol 1 was first reported by Satake et al. in 1991,[1] and fourteen more congeners have been reported since.[2] The amphidinols, all of which display varying degrees of antifungal and hemolytic activities, have common structural features including two highly substituted tetrahydropyran rings and a long carbon chain encompassing multiple hydroxyl groups. They are also characterized by their skipped polyene chain starting at C52 and ending either at C65 as a terminal olefin (AMs 2, 4, 6, 8, 9 and 10) or at C67 as a terminal *E*-diene (AMs 1, 3, 5, 7 and 11), exemplified here as AM4 and AM3 (Figure 1).

Amphidinol 3 has shown a particularly potent biological activity among the other amphidinols,[2e] and Paquette,[3] Roush,[4] and Rychnovsky[5] have already been engaged in the polyene-fragment synthesis. As we recently developed a chemoselective cross-metathesis with sorbamides,[6] and as Weinreb amides are versatile compounds, we envisaged that we could use this type of reaction for the synthesis of the polyene unit present in amphidinols.

A convergent approach to synthesize the C53–C65 and C53–C67 fragments (compounds **8** and **10**) of AMs was considered. A Julia–Kocienski olefination between sulfones **7a** or **7b** and aldehyde **5** would provide the polyenes in an efficient and stereoselective manner. The aldehyde, in turn, would be derived from sorbic acid **1** via sorbamide **2** by using the cross-metathesis reaction we reported previously (Scheme 1).[6]

The syntheses of polyenes **8** and **10** started from sorbic acid **1** which was converted into the Weinreb amide **2** [1,1′-carbonyldiimidazole (CDI), *N*,*O*-dimethyl-hydroxylamine hydrochloride, CH_2Cl_2].[7] A cross-metathesis between amide **2** and the TBS-protected pent-1-en-5-ol **3** in the presence of Hoveyda–Grubbs catalyst [**Ru-I** (5 mol%), CH_2Cl_2, r.t., 2 h] yielded diene **4** in 57%. An *E*/*Z* ratio of 20:1 was established by examining the ^{1}H NMR

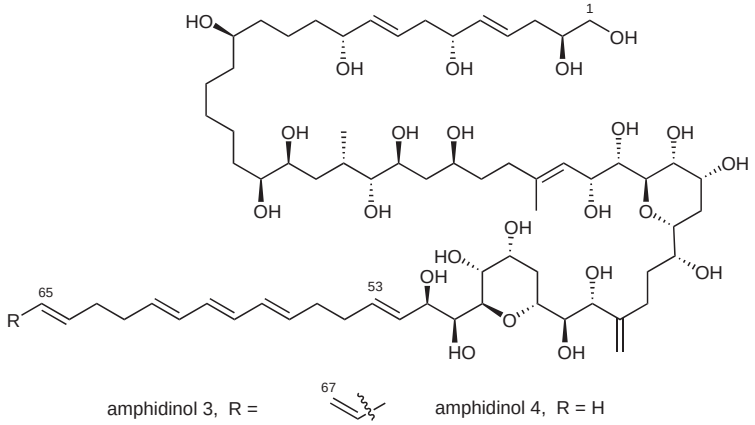
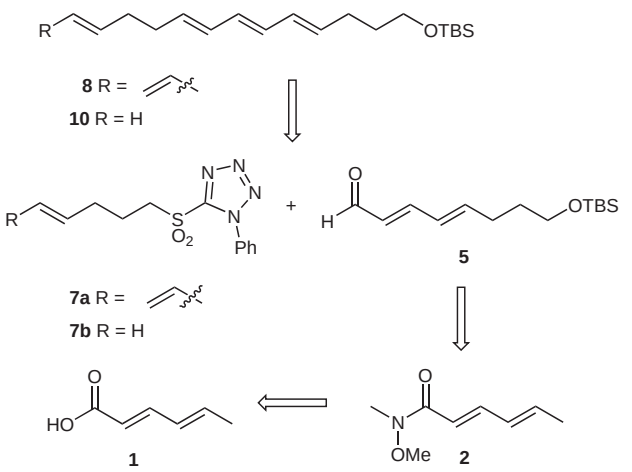


Figure 1 Structure of amphidinols 3 and 4

SYNLETT 2007, No. 14, pp 2286–2288
Advanced online publication: 20.07.2007
DOI: 10.1055/s-2007-984910; Art ID: G10507ST

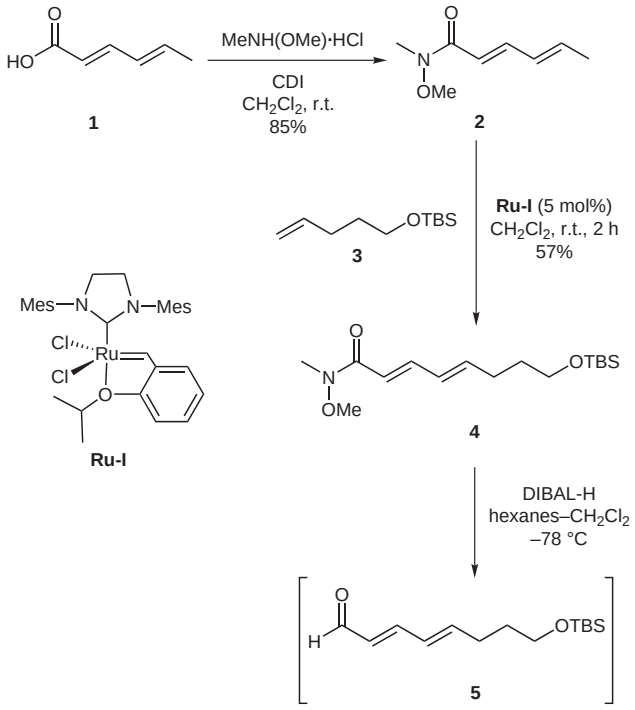


Scheme 1 Retrosynthesis of polyenes **8** and **10**

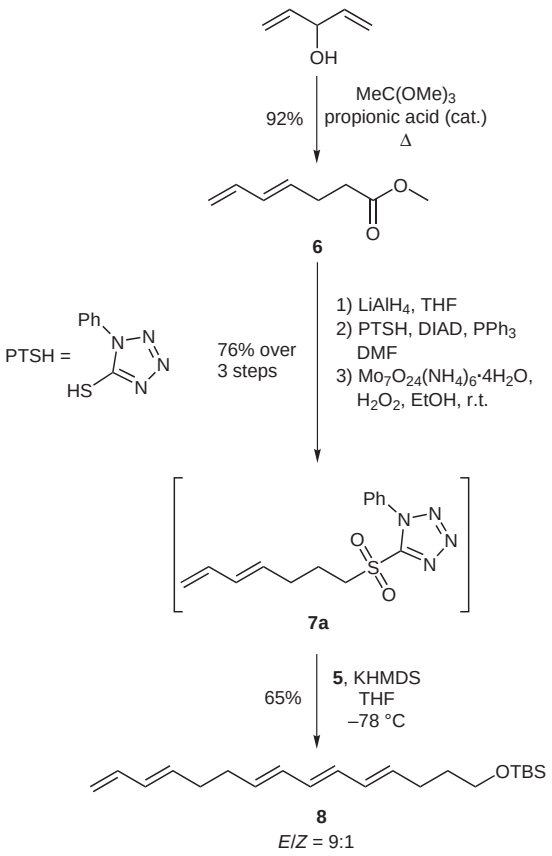
spectrum. After reduction of **4** by DIBAL-H (–78 °C, hexanes–CH_2Cl_2), the unstable aldehyde **5** was immediately used without purification in the subsequent Julia–Kocienski olefination with sulfones **7a** and **7b** (Scheme 2).

Sulfone **7a** was prepared from penta-1,4-dien-3-ol in 5 steps (Scheme 3). The starting alcohol was subjected to the Johnson–Claisen rearrangement [$MeC(OMe)_3$, propionic acid, reflux][8] to produce dienic ester **6** in 92% yield.

This ester was reduced ($LiAlH_4$, THF) to the corresponding alcohol,[9] which was then transformed to a thioether by using a Mitsunobu reaction (PTSH, DIAD, PPh_3, DMF).[10] Without purification, the thioether was subjected to a mild



Scheme 2 Synthesis of aldehyde **5**



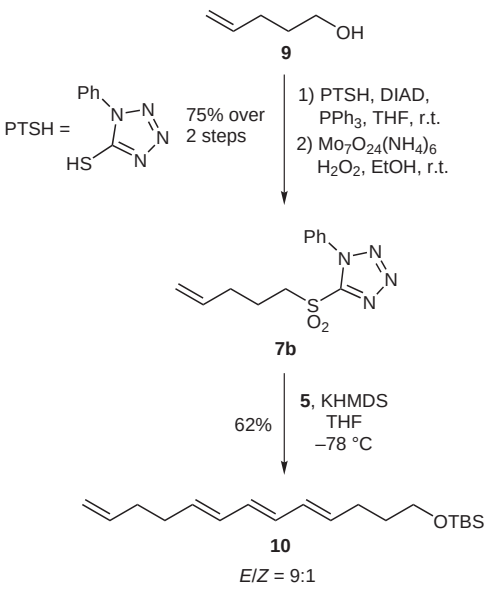
Scheme 3 Synthesis of polyene **8**

oxidation [$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (13 mol%), H_2O_2, EtOH, r.t.][10] and converted into the desired sulfone **7a** in 76% yield over the 3 steps.

Compound **7a** and aldehyde **5** were coupled under the Barbier-type conditions with KHMDS (1.3 equiv, THF, –78 °C)[11] to generate the desired polyene **8** in a 65% yield. The *E*/*Z* ratio for the newly created double bond was evaluated to be 9:1 by both GC-MS and ^{1}H NMR analyses (Scheme 3).[12]

By using the same methodology as described above, but by condensing aldehyde **5** with sulfone **7b**, the synthesis of the skipped polyene fragment C53–C65 of AM4 (compound **10**) was also accomplished (Scheme 4). Sulfone **7b** was obtained in two steps and in 75% yield from pent-4-en-1-ol (**9**) by using a Mitsunobu reaction (PTSH, DIAD, PPh_3, THF, r.t.), followed by an oxidation step [$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (13 mol%), H_2O_2, EtOH, r.t.]. The obtained sulfone **7b** was immediately condensed with the freshly prepared aldehyde **5** (KHMDS, THF, –78 °C) to afford the desired polyene **10** in 62% yield. An *E*/*Z* ratio of 9:1 was determined by GC-MS and ^{1}H NMR analyses.[13]

To conclude, by using a cross-metathesis of a sorbamide derivative and a Julia–Kocienski olefination as the key steps, the polyene fragments (C53–C65 and C53–C67) of the AMs were assembled. Starting from sorbic acid, polyenes **8** and **10** were synthesized efficiently in 31% and 30% yield, respectively, over 4 steps.



Scheme 4 Synthesis of polyene **10**

In addition, the general synthetic route presented here could provide a rapid access to a wide range of skipped polyenes with a conjugated triene moiety. Efforts towards the total synthesis of amphidinol 3 are ongoing, and further results will be reported in due course.

Acknowledgment

We are grateful to Prof. J. Y. Lallemand (ICSN/CNRS) for financial support.

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(12) ***tert*-Butyl-dimethyl-{[(4*E*,6*E*,8*E*,12*E*)-pentadeca-4,6,8,12,14-pentaenyl]oxy}-silane (8)**
A 9:1 mixture of inseparable *E*- and *Z*-isomers; R_f = 0.63 (PE–Et_2O, 9:1). IR (neat): 3012, 2927, 2855, 1651, 1603, 1253, 1100 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 6.29 (dtd, *J* = 17.0, 10.2, 0.7 Hz, 1 H), 6.18–5.97 (m, 5 H), 5.62 (m, 1 H), 5.54 (dt, *J* = 14.5, 6.7 Hz, 2 H), 5.06 (d, *J* = 17.0 Hz, 1 H), 4.93 (d, *J* = 10.1 Hz, 1 H), 3.51 (t, *J* = 6.2 Hz, 2 H), 2.14 (td, *J* = 7.4, 7.1 Hz, 2 H), 2.05–1.99 (m, 4 H), 1.56 (tt, *J* = 7.6, 6.3 Hz, 2 H), 1.00–0.96 (m, 9 H), 0.06–0.03 (m, 6 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 137.6 (d), 134.4 (d), 134.0 (d), 133.2 (d), 132.0 (d), 131.7 (d), 131.6 (d), 131.5 (d), 131.4 (d), 115.2 (t), 62.5 (t), 32.5 (t), 32.8 (t), 32.7 (t), 29.5 (t), 26.1 (q), 18.5 (s), -5.2 (q). MS (EI): *m/z* = 322 (7) [M^+], 275 (20), 265 (20), 133 (100), 67 (37). ESI-HRMS: *m/z* calcd for $C_{21}H_{36}OSi + Na^+$: 355.2428; found: 355.2429.

(13) ***tert*-Butyl-dimethyl-{[(4*E*,6*E*,8*E*)-tetradeca-4,6,8,12-tetraenyl]oxy}-silane (10)**
R_f = 0.53 (PE–Et_2O, 98:2). IR (neat): 3013, 2928, 2856, 1641, 1101, 993 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.12–6.01 (m, 4 H), 5.81 (ddt, *J* = 17.1, 10.3, 6.4 Hz, 1 H), 5.72–5.61 (m, 2 H), 5.02 (ddd, *J* = 17.1, 3.4, 1.5 Hz, 1 H), 4.97 (m, 1 H), 3.61 (t, *J* = 6.4 Hz, 2 H), 2.21–2.11 (m, 6 H), 1.64–1.54 (m, 2 H), 0.91–0.87 (m, 9 H), 0.06–0.02 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (d), 134.0(d), 133.4 (d), 131.4 (d), 131.1 (d), 130.9 (d), 130.8 (d), 114.8 (t), 62.5 (t), 33.5 (t), 32.4 (t), 32.2 (t), 29.1 (t), 26.0 (q), 18.4 (s), –5.3 (q). MS (EI): *m/z* = 306 (6) [M^+], 249 (74), 175 (10), 133 (87), 131 (46), 91 (100), 81 (11), 75 (96), 55 (14). ESI-HRMS: *m/z* calcd for $C_{19}H_{34}OSi + Na^+$: 329.2271; found: 329.2271.