An Efficient Access to Aspermytin A and Oblongolide C through an Intramolecular Nitrile Oxide–Alkene [3+2] Cycloaddition

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Abstract: The second generation synthesis of (+)-aspermytin A and the first total synthesis of (–)-oblongolide C have been accomplished employing an intramolecular nitrile oxide–alkene [3+2] cycloaddition as the key step.

Key words: total synthesis, enantioselectivity, cycloaddition, aspermytin A, nitrile oxide

Aspermytin A (1) has been isolated from a marine-derived fungus of the genus Aspergillus sp. by Tsukamoto et al. The key structural features of the molecule are the functionalized trans-octahydronaphthalene skeleton and the four contiguous stereogenic centers on the ring, two of which are quaternary carbons. Aspermytin A showed significant neurotrophic effects on rat pheochromocytoma (PC-12) cells at a concentration of 50 μM and could be a potential lead for the development of anti-Alzheimer chemotherapeutic agents. In our previous paper, we reported the first enantioselective total synthesis of (+)-aspermytin A (1) via an intramolecular Diels–Alder reaction as the key step, in which the synthesis was accomplished in 9.7% overall yield for 24 steps. However, further evaluation of the biological activities of the natural product and its congeners necessitated the development of a much more efficient synthetic route. Herein we describe the second generation synthesis of (+)-1, which has been achieved efficiently, employing as the key step a highly diastereoselective intramolecular nitrile oxide–alkene [3+2] cycloaddition reaction (INOC) for the construction of the C4 quaternary carbon stereogenic center. In addition, the first enantioselective total synthesis of oblongolide C (2), which was isolated from the endophytic fungus Phomopsis sp. and shown to exhibit antimicrobial activities against some kinds of bacteria and fungi, has been accomplished, starting from an intermediate used in the synthesis of 1 (Figure 1).

Our synthetic strategy is outlined in Scheme 1. Since aspermytin A (1) has been synthesized uneventfully from the aldehyde 3 via a three-step sequence, we decided to prepare 3. Our idea was to prepare the quaternary stereogenic center at C4 and the enone moiety in 3 from 4 by oxidation. The β-hydroxyketone 4 would be derived from

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duction with sodium borohydride. Upon exposure to phenyl isocyanate and triethylamine in benzene at room temperature to reflux, the starting 14 was recovered completely whereas when p-chlorophenyl isocyanate and triethylamine in benzene at room temperature were used, the isoxazoline 5 was produced in 84% yield diastereoselectively (method C). The reaction using ethyl chloroformate, triethylamine, and 4-DMAP in chloroform at room temperature provided 5 in a comparable yield of 81% (method D, Scheme 2).

The stereochemistry of 5 was confirmed by NOE experiments as shown in Scheme 2, and the preferential formation was supported by theoretical calculations of the transition-state energy for the two conformers shown in Figure 2. Thus, treatment of 4 with TMSOTf and triethylamine in dichloromethane at 0 °C gave the silyl enol ether 15, which was sequentially reacted with IBX·MPO and IBX in a mixture of DMSO and dichloromethane at room temperature to give the key intermediate 3 in 58% yield for the two steps. The synthetic 3 was spectroscopically identical to the authentic material which has been synthesized in our laboratories. Finally, it was converted, via the keto alcohol 16, into (+)-aspermytin A (1) in three steps thereby completing the second-generation total synthesis (Scheme 3).

The isoxazoline 5 was then treated with trimethyl borate and Raney nickel (W2) in aqueous methanol under an atmosphere of hydrogen to give the β-hydroxy ketone 4 in 87% yield. Attempted direct conversion of 4 to 3 employing IBX (at 80 °C, 48 h) resulted in decomposition. When the reaction was conducted with the IBX-MPO (4-methoxyxypyrindine-N-oxide) complex, the corresponding keto aldehyde was obtained quantitatively; however, oxidation to the enone did not occur. Therefore, we decided to try a stepwise conversion. 16

**Scheme 2**

Reagents and conditions: (a) LiAlH4, Et2O, r.t., 2 h; (b) p-TsCl, Et3N, 4-DMAP, CH2Cl2, r.t., 1 h; (c) KCN, KI, DMSO, H2O, 60 °C, 12 h, 89% (3 steps); (d) DIBAL-H, CH2Cl2, –78 °C, 2 h; (e) NH2OH·HCl, NaOAc, MeOH, r.t., 15 min, quant. (2 steps); (f) method A: 7% NaOCl (aq), CH2Cl2, r.t., 24 h, 67%; method B: 7% NaOCl (aq), toluene, r.t., 6 h, 81%; (g) (COCl)2, DMSO, Et3N, CH2Cl2, –78 °C to 0 °C, 1 h; (h) MeNO2, KF, 18-crown-6 then Ac2O, 4-DMAP then NaBH4, THF, r.t., 14 h, 57% (3 steps from 8); (i) method A: 7% NaOCl (aq), CH2Cl2, r.t., 24 h, 67%; method B: 7% NaOCl (aq), toluene, r.t., 6 h, 81%; (j) CICO2Et, Et3N, CHCl3, r.t., 16 h, 81%.

**Figure 2**

Two transition structures for INOC; atomic distances (underlined) at the B3LYP/6-31G(d) level

Thus, treatment of 4 with TMSOTf and triethylamine in dichloromethane at 0 °C gave the silyl enol ether 15, which was sequentially reacted with IBX-MPO and IBX in a mixture of DMSO and dichloromethane at room temperature to give the key intermediate 3 in 58% yield for the two steps. The synthetic 3 was spectroscopically identical to the authentic material which has been synthesized in our laboratories. Finally, it was converted, via the keto alcohol 16, into (+)-aspermytin A (1) in three steps thereby completing the second-generation total synthesis (Scheme 3).

**Scheme 3**

Reagents and conditions: (a) H2, Raney Ni (W2), MeOH, CH2Cl2, H2O, r.t., 1 h, 87%; (b) TMSOTf, Et3N, CH2Cl2, 0 °C, 0.5 h; (c) IBX-MPO then IBX, DMSO, CH2Cl2, r.t., 10 h, 58% (2 steps); (d) MeLi, THF, –78 °C, 1 h, 80%; (e) TPAP, NMO, 4 Å MS, CH2Cl2, r.t., 1 h, 92%; (f) LDA, {1H-benzo[d][1,2,3]triazol-1-yl}methanol, THF, –78 °C, 2 h, 95%.
We next turned our attention to the synthesis of oblongolide C (2) starting from 3. For this synthesis, the construction of a quaternary stereogenic center at C13 with the $\alpha$ configuration by a diastereoselective introduction of one extra carbon was necessary. Pinck oxidation of 3 provided the carboxylic acid 17, which was treated with the benzlyoxymethyl anion,21 generated in situ from (benzlyoxymethyl)trimethylstannane and n-butyllithium, in THF at $-78^\circ$C, to give the hydroxyl carboxylic acid 19 as a single diastereomer in 74% yield for the two steps. The configuration at the newly generated quaternary stereogenic center was established by NOE experiments as shown in Scheme 4. The highly diastereoselective formation of the requisite 19 can be explained by taking into account the chelated transition state 18, in which the benzlyoxymethyl lithium would coordinate to the carboxylic acid and the C13 carbonyl oxygens. Finally, 19 was treated with lithium in liquid ammonia in THF at $-40^\circ$C to produce, via debenzylation followed by spontaneous lactonization, ($-$)-oblongolide C (2),23 the spectroscopic properties and optical rotation of which are completely identical with those reported for the natural material (Scheme 4).4

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(7) Analytical Data for 5
Colorless needles, mp 94.5–94.8 $^\circ$C (Et,O–hexane); [α]$_D^{23}$ +22.6 (c 1.22, CHCl$_3$). IR (KBr): 2920, 1713, 1494, 1455, 1377, 946, 846 cm$^{-1}$. 1H NMR (400 MHz, CDCl$_3$): δ = 4.41 (d, J = 7.6 Hz, 1 H), 3.91 (d, J = 7.6 Hz, 1 H), 2.62 (ddd, J = 14.8, 4.8, 2.0 Hz, 1 H), 2.21 (dt, J = 14.0, 5.6 Hz, 1 H), 1.82–1.88 (dddd, J = 12.8, 5.6, 5.2, 1.6 Hz, 1 H), 1.72–1.76 (m, 2 H), 1.28 (dq, J = 12.4, 3.2 Hz, 1 H), 1.23–1.34 (m, 3 H), 1.13 (s, 3 H), 1.09–1.20 (m, 2 H), 0.78–0.96 (m, 1 H), 0.89 (d, J = 6.4 Hz, 3 H), 0.67 (q, J = 12.4 Hz, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 164.4 (C), 91.8 (CH$_2$), 54.2 (C), 51.3 (CH$_2$), 42.1 (CH$_3$), 36.0 (CH), 34.5 (CH$_2$), 33.5 (CH$_2$), 32.1 (CH), 27.7 (CH$_2$), 22.3 (CH$_2$), 21.9 (CH), 17.1 (CH$_3$). ESI-HRMS: m/z calcld for C$_{12}$H$_8$NO$_2$ [M + Na]$^+$: 230.1521; found: 230.1519.


(13) The yields of the isoxazoline 5 from the literature known 8 via the oxime 12 and the nitroalkane 13 were 72% (6 steps) and 48% (4 steps), respectively.


(15) For computational methodology, see Supporting Information.


(a) The corresponding aldehyde was initially obtained by the reaction with IBX-MPO and the requisite enone 3 was generated by the subsequent addition of IBX in a one-pot process.

(19) **Analytical Data for 3**

Colorless needles, mp 62.5–63.3 °C (hexane) (lit.2 62.3–62.6 °C). [α]_D^20 ~107 (c 1.74, CHCl_3); [α]_D^10 –103 (c 0.91, CHCl_3). IR (KBr): 2934, 2839, 2734, 1733, 1660 cm⁻¹. ¹H NMR (400 MHz, CDCl_3): δ = 9.52 (s, 1 H), 6.75 (dd, J = 10.0, 1.6 Hz, 1 H), 5.97 (dd, J = 10.0, 2.8 Hz, 1 H), 2.27 (qd, J = 11.2, 2.8, 2.8 Hz, 1 H), 2.09 (dd, J = 11.6, 10.8, 3.2 Hz, 1 H), 2.01 (ddd, J = 13.2, 3.2, 3.2 Hz, 1 H), 1.75–1.82 (m, 1 H), 1.47–1.64 (m, 1 H), 1.35 (dq, J = 13.2, 4.0 Hz, 1 H), 1.27 (dd, J = 12.4, 12.0, 3.6 Hz, 1 H), 1.19 (s, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.94–0.97 (m, 2 H). ¹³C NMR (100 MHz, CDCl_3): δ = 200.5 (CH), 200.4 (C), 155.1 (CH), 127.1 (CH), 80.5 (C), 43.3 (CH), 40.2 (CH), 37.1 (CH), 34.0 (CH_2), 32.9 (CH), 26.0 (CH_2), 22.2 (CH_2), 11.0 (CH_3). ESIMS-HRMS: m/z calcd for C_13H_18O_2Na [M + Na]^+: 229.1204; found: 229.1198. 259.1310; found: 259.1304.

(20) **Analytical Data for Aspermytin A (1)**

Colorless needles, mp 122–123 °C (hexane). [α]_D^23 –194 (c 1.11, CHCl_3); [α]_D^25 –184 (c 0.20, CHCl_3). IR (KBr): 3398, 2950, 2921, 1740, 1237, 1122, 1021, 767, 733 cm⁻¹. ¹H NMR (400 MHz, CDCl_3): δ = 5.65 (d, J = 10.0 Hz, 1 H), 5.55 (dd, J = 10.0, 2.4 Hz, 1 H), 4.26 (s, 2 H), 2.00 (q, J = 10.8 Hz, 1 H), 1.76 (s, OH, D_2O exchangeable, 1 H), 1.66–1.68 (m, 3 H), 1.42–1.50 (m, 2 m, 2 H), 1.26–1.36 (m, 1 H), 1.14 (s, 3 H), 0.91 (d, J = 6.4 Hz, 3 H), 0.85–0.95 (m, 1 H), 0.77 (q, J = 12.0 Hz, 1 H). ¹³C NMR (100 MHz, CDCl_3): δ = 178.9 (C), 135.7 (CH), 125.6 (CH), 78.8 (C), 76.9 (CH_2), 49.4 (C), 43.8 (CH), 41.1 (CH_3), 36.3 (CH), 34.7 (CH_2), 32.8 (CH_2), 25.8 (CH_3), 22.2 (CH_2), 8.9 (CH_3). ESIMS-HRMS: m/z calcd for C_21H_29O_4[M + Na]^+: 345.2066; found: 345.2070.