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

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Received: 15.10.2012; Accepted after revision: 05.11.2012

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-octahydropyridine 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 the tricyclic isoxazoline 5, constructed diastereoselectively through the INOC of the nitrile oxide 6, which could be derived from (−)-citronellal (7, Scheme 1).

Figure 1 Structures of aspermytin A and oblongolide C

Reduction of 8, prepared from 7 (3 steps, 89%) according to a published method, with lithium aluminum hydride gave the alcohol 9, which was converted to the cyanide 11 via the tosylate 10. Reduction with diisobutylaluminum hydride followed by reaction of the resulting aldehyde with hydroxylamine hydrochloride and sodium acetate provided the oxime 12. With the precursor of nitrile oxide 6 in hand, we then examined the key conversion. Treatment of 12 with a 7% aqueous solution of NaOCl in dichloromethane at room temperature for 24 hours provided, via the [3+2] cycloaddition of 6, the isoxazoline 5′ in 67% yield as a single product (method A). When the reaction was conducted in toluene, isoxazoline 5 was obtained in higher yield (81%) in a shorter period of time (6 h, method B). Alternatively, for the sake of comparison, the INOC using a nitroalkane was examined. Thus, Swern oxidation of 9 gave the aldehyde 13, which was converted into the one-carbon elongated nitroalkane 14 by a sequential addition of nitromethane, acetylation, and re-
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, with the aid of B3LYP-D(PCM)/6-311+G(d)//B3LYP/6-31G(d) calculations, the transition state 6-T1 leading to the formation of 5 was found to be more stable in Gibbs energy than 6-T2, which leads to the C4 epimer 5', by 20.9 kJ/mol. The forming B-ring in 6-T1 adopts a twist-chair conformation, while in 6-T2 it assumes a twist-boat conformation. The higher stability of 6-T1 is due to the more steric hindrance in 6-T2 [shorter distance between the two hydrogen atoms in 6-T2 (2.22 Å) than the sum of the van der Waals radii (2.4 Å), Figure 2].

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.

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).

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We next turned our attention to the synthesis of oblongolide C (2) starting from 3. For this synthesis, the construction of a quaternary carbon stereochemical center at C13 with the R configuration by a diastereoselective introduction of one extra carbon was necessary. Pinnick oxidation of 3 provided the carboxylic acid 17, which was treated with the benzylxoxymethyl anion,\(^2\) generated in situ from (benzylxoxymethyl)tri-\(n\)-butylstannane and \(n\)-butyllithium, in THF at \(-78^\circ\text{C}\) to give the hydroxyl carboxylic acid 19\(^22\) as a single diastereomer in 74% yield for the two steps. The configuration at the newly generated quaternary stereochemical 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 benzylxoxymethyl lithium would coordinate to the carboxylic acid and the C13 carbonyl oxygens. Finally, 19 was treated with lithium in liquid ammonia in THF at \(-40^\circ\text{C}\) to produce, via debenzylation followed by spontaneous lactonization, (\(-\))-oblongolide C (2),\(^3\) the spectroscopic properties and optical rotation of which are completely identical with those reported for the natural material (Scheme 4).\(^4\)

**Scheme 4** Synthesis of (\(-\))-oblongolide C

In summary, the second-generation enantiocontrolled total synthesis of (\(+\))-aspermytin A (1) has been achieved in a highly efficient manner in 15 steps from (\(-\))-citronellal (7) with an overall yield of 19% (in the oxime route; cf.\(^2\) in 9.7% overall for 24 steps from 7) employing a highly diastereoselective INOC for the construction of the C4 quaternary carbon stereogenic center as the key step. In addition, the first enantioselective total synthesis of oblongolide C (2) has been completed from the key intermediate 3 via the chelation-controlled, highly diastereoselective addition of benzylxoxymethyl lithium. The synthetic route developed here is general, efficient, and flexible and could be applied not only to the syntheses of other oblongolides\(^4\) but could also be used for assembling a library of compounds for biological evaluations.

**Acknowledgment**

This work was supported financially by a Grant-in-Aid for the Program for Promotion of Basic and Applied Research for Innovation in the Bio-oriented Industry (BRAIN). S. M. acknowledges financial support by a grant (No. 23105507; molecular activation) for Scientific Research on Priority Areas from MEXT of Japan. The generous allotment of computation time from the Research Center for Computational Science (RCCS), the National Institutes of Natural Sciences, Japan, is also gratefully acknowledged. We thank the Takasago International Co. for the generous gift of citronellal.

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

**References and Notes**


(7) **Analytical Data for 5**

Colorless needles, mp 94.5–94.8 °C (Et2O–hexane); [\(\alpha\)]\(_{D}\)^\(23\) = 22.6 (c 1.22, CHCl3). IR (KBr): 2920, 1713, 1494, 1455, 1377, 946, 846 cm\(^{-1}\). 1H NMR (400 MHz, CDCl3): \(\delta = 4.11\) (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 (ddd, \(J = 12.8, 5.6, 5.2, 1.6\) Hz, 1 H), 1.72–1.76 (m, 2 H), 1.28 (qq, \(J = 12.4, 3.2\) Hz, 1 H), 1.23–1.34 (m, 3 H), 1.13 (s, 3 H), 1.09–1.20 (m, 2 H), 0.87–0.96 (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, CDCl3): \(\delta = 164.4\) (C), 80.8 (CH), 54.2 (C), 51.3 (CH), 42.1 (CH3), 36.0 (CH3), 34.5 (CH3), 33.5 (CH2), 32.1 (CH), 27.7 (CH3), 22.3 (CH3), 21.9 (CH), 17.1 (CH2). ESI-HRMS: \(m/c\) calc'd for C13H21ONa\[M + Na\]^+ 230.1521; found: 230.1519.


The corresponding aldehyde was initially obtained by the
(a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.
(b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. Angew.

(15) For computational methodology, see Supporting
Information.


(17) The yields of the isoxazoline and 48% (4 steps), respectively.

(18) For theoretical studies on the intra- and intermolecular nitrile
oxide–alkene [3+2] cycloadditions, see: (a) Brown, F. K.;
2002, 67, 772. (c) Namboothiri, I. N. N.; Rastogi, N.;
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Lett. 2007, 9, 555.

(19) Analytical Data for 3

(20) Analytical Data for Aspermytin A (1)


(22) Analytical Data for 19

(23) Analytical Data for Oblongolide C (2)

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