A carbohydrate approach for the formal total synthesis of (−)-aspergillide C

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Abstract
An enantioselective formal total synthesis of aspergillide C is accomplished using commercially available tri- O-acetyl- D-galactal employing a Ferrier-type C-glycosylation, utilizing a Trost hydrosilylation and protodesilylation as key reactions.

Introduction
Aspergillides A, B and C (Figure 1) (three, novel, bicyclic, 14-membered macrolides with 2,6-cis or trans-fused di- or tetrahydropyan rings) are unexpected, novel, secondary metabolites, isolated from the marine-derived fungus Aspergillus ostianus strain 01F313 in bromine-modified 1/2PD culture medium [1-4]. Interestingly, these compounds show cytotoxicity against mouse lymphocytic leukemia cells (L1210) with LD50 values of 2.1, 71.0, and 2.0 μg/mL, respectively [5,6]. The striking structural architecture and interesting biological properties have attracted significant attention from synthetic chemists with respect to their total synthesis [7-26] and have inspired medicinal chemists to synthesize diverse analogues in search for better potential molecules [27]. We have recently developed the total synthesis of these 14-membered macrolides and have accomplished the total syntheses of aspergillide B [15] and both enantiomers of aspergillide C [21]. The chiron approach has been a conventional strategy to achieve the total synthesis of complex, natural products with known handedness.

Figure 1: Structures of aspergillides.
Herein we disclose our strategy for the formal total synthesis of (−)-aspergillide C in a concise manner following the chiron approach.

**Retrosynthetic Analysis**

Through a retrosynthetic analysis, we envisaged that the macrolide 3 could be prepared from the seco acid 4 which can be easily accessed from 5 in five steps (Scheme 1). Compound 5, in turn, can be synthesized from commercially available tri-O-acetyl-D-galactal (6) and alkyne 7 through a Ferrier-type C-glycosylation reaction followed by the reduction of the triple bond to the trans double bond. Alkyne 7 can be synthesized from alkyne 8 involving an isomerization reaction. Alkyne 8 was easily accessible from (R)-propylene oxide (9) through an epoxide opening reaction with 1-butyne.

![Scheme 1: Retrosynthetic analysis for (−)-aspergillide C.](image)

**Results and Discussion**

In recent work on aspergillides, Achmatowicz adducts were utilized as the key source for the construction of the dihydropyran moiety and the side arm was synthesized using a Zipper rearrangement as a key reaction after an epoxide ring opening reaction of (R)-propylene oxide (9) as shown in Scheme 2. We proceeded further by utilizing it for masking the functionalities. Compound 10 was disilylated using TMSCl in the presence of n-BuLi and later treated with 1 N HCl to get the free secondary alcohol which was further treated with benzoyl chloride in the presence of pyridine to produce the corresponding benzoyl ester 7 as a side chain fragment to be utilized for a Ferrier-type C-glycosylation reaction with the sugar tri-O-acetyl-D-galactal (6). Compound 6 was treated with silylated alkyne 7 in the presence of SnCl₄ to afford alkynylated dihydropyran 11 as the only isomer, resulting in an 85% yield. The resulting dihydropyran ring was found to have a 2,6-trans configuration, owing to the attack of the alkyne from the opposite face of the acetyl-protected carbinol present in C6 position [28-31]. The geometry of the compound was also characterized by 2D NMR studies wherein significant NOESY correlations were observed for the C2 proton and the methylene protons of the carbinol moiety present on C6. Also, the NOESY correlation was absent between the C2 proton and the C6 proton (Figure 2).

![Scheme 2: Synthesis of 11. Reaction conditions: (a) n-BuLi, THF/ HMPA (5:1), −78 °C to rt, 12 h, 95%; (b) Li, t-BuOK, H₂N(CH₂)₃NH₂, rt, 4 h, 92%; (c) i. n-BuLi, TMSCl, THF, −78 °C, 92%; ii. pyridine, C₆H₅COCl, CH₂Cl₂, 0 °C to rt, 1 h, 98%; (d) SnCl₄, CH₂Cl₂, 0 °C to rt, 1 h, 85%.](image)

![Figure 2: Key NOESY correlations observed in compound 11.](image)
After the alkynylation reaction, the stage was set to proceed further for the partial reduction of the alkyne moiety to obtain the trans-configured olefin. Based on our previous experience with this transformation, we proceeded directly with Trost’s hydrosilylation–protodesilylation protocol [32], where alkyne 11 was treated with excess triethoxysilane in the presence of a catalytic amount of [Cp*Ru(MeCN)3]PF6 to afford vinyl triethoxysilane 12 (Scheme 3). Compound 12 was then protodesilylated upon exposure to HF/pyridine to yield the desired trans-olefin 5. Compound 5 possessed the required stereochemical configuration including the desired trans-olefin geometry, but required a one-carbon homologation to access the matched seco acid 4. To achieve the one-carbon homologation with appropriate functionality, it was necessary to perform sequential chemoselective transformations. In this regard, we proceeded by selectively deprotecting the acetyl groups (without affecting the benzoate functionality) by employing acetyl chloride in anhydrous methanol to afford diol 13 [33]. A two-fold silylation and selective mono desilylation afforded primary alcohol 14 which was converted to its corresponding nitrile via the triflate. The nitrile functionality was hydrolysed with 8 N NaOH in ethanol to yield the seco acid 4. The seco acid 4 was already utilized for the total synthesis of (−)-aspergillide C through macrolactonization and TBS deprotection as reported earlier by Kuwahara (Table 1) [23]. Thus, by

Table 1: Comparison of 1H and 13C NMR data of seco acid 4 with earlier data.

| Position | Kuwahara data [23] | Our data |
|----------|---------------------|----------|
|          | 1H                  | 13C NMR | 1H                  | 13C NMR |
|          | δ mult [J (Hz)]     | CDCl3, 500 MHz | δ mult [J (Hz)]     | CDCl3, 125 MHz |       | δ mult [J (Hz)]     | CDCl3, 300 MHz | 13C NMR |
|          | 13C NMR CDCl3,125 MHz |          |          | CDCl3, 75 MHz |
| 1        | 174.9 (COOH)        |          |          | 175.0       |
| 1        | 2.72 (dd, J = 16.1, 8.8, 1H) | 37.7 | CH2 | 2.71 (dd, J = 15.9, 9.1) | 37.8 |
| 2        | 2.53 (dd, J = 16.1, 3.9, 1H) | 68.1 | CH2 | 3.93–3.98 (m) | 68.1 |
| 3        | 3.93–3.96 (m, 1H)   | 68.1     | CH   | 68.1 |
| 4        | 4.18 (dt, J = 8.8, 3.2, 1H) | 126.7 | CH2 | 68.1 |
| 5        | 5.85–5.91 (m, 1H, 2H) | 127.5 (CH) |          | 127.5       |
| 6        | 127.5 (CH)          |          |          | 127.5       |
| 7        | 4.69 (d, J = 5.9, 1H) | 72.5 (CH) |          | 4.68 (d, J = 5.3) | 72.4 |
| 8        | 5.51 (dd, J = 15.6, 5.9, 1H) | 130.7 (CH) |          | 5.51 (dd, J = 15.8, 6.0) | 130.7 |
| 9        | 5.66 (dt, J = 15.6, 6.6, 1H) | 124 (CH) |          | 5.77–5.60 (m) | 134.6 |
| 10       | 2.00–2.08 (m, 1H)   | 36.0 (CH2) |          | 1.96–2.20 (m) | 35.9 |
| 11       | 2.08–2.16 (m, 1H)   | 24.4 (CH2) |          | 24.5       |
| 12       | 1.34–1.52 (m, 1H)   | 31.7 (CH2) |          | 31.7       |
| 13       | 3.82 (sex, J = 6.3, 1H) | 64.4 (CH) |          | 64.4       |
| 14       | 1.18 (d, J = 6.3, 3H) | 22.8 (CH3) |          | 22.9       |
| 15       | 0.093 (s, 3H)       | –4.6 (Si-CH3) |          | –4.6       |
| 16       | 0.086 (s, 3H)       | –4.1 (Si-CH3) |          | –4.1       |
| 17       | –                   | 18.2 (C) |          | 18.2       |
| 18       | 0.90 (s, 9H)        | 25.9 (C(CH3)3) |          | 25.9       |
| OH       | 1.25 (s, 1H)        | –1.25 (s) |          | –          |

Scheme 3: Synthesis of 4 and formal total synthesis of (−)-aspergillide C (3). Reaction conditions: (a) [Cp*(MeCN)3Ru](PF6)3SiH, CH2Cl2, 0 °C to rt, 1 h, 95%; (b) HF/pyridine, pyridine, THF, 0 °C, 5 min, 90%; (c) cat. AcCl, MeOH, rt, 12 h, 90%; (d) (i) TBSCI, imidazole, DMAP, CH2Cl2, rt, 12 h, 95%; (ii) 70% HF in pyridine, THF, 0 °C, 12 h, 90%; (e) (i) Tf2O, 2,6-lutidine, −78 °C, 10 min; (ii) NaCN, DMF/DMSO, 18-crown-6, 90 °C, 30 min 88% overall for two steps; (f) 8 N NaOH, EtOH, 90 °C, 3 h, 75%.
synthesizing 4, we have achieved the formal total synthesis of \((-\)-aspergillicid C).

Conclusion

In conclusion, a formal total synthesis of \((-\)-aspergillicid C has been achieved through a concise, stereocontrolled synthesis of the known key intermediate 4 in 8 steps with an overall yield of 36.9% starting from commercially available tri-O-acetyl-D-galactal. A C-glycosidation, Trost’s hydrolylation and protodesilylation protocol have been used as the key steps for achieving the formal total synthesis.

Supporting Information

Supporting Information File 1
Experimental details and analytical data. [http://www.beilstein-journals.org/bjoc/content/ supplementary/1860-5397-10-329-S1.pdf]

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