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Convergent synthesis of (+)-aspergillide B via a highly diastereoselective oxocarbenium allylation

Amanda J. Mueller Hendrix, Michael P. Jennings *

Department of Chemistry, 250 Hackberry Lane, The University of Alabama, Tuscaloosa, AL 35487-0336, United States

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ABSTRACT

The synthesis of (+)-aspergillide B is described by means of a highly diastereoselective oxocarbenium allylation followed by a cross-metathesis and final Yamaguchi macrolactonization.

Marine-derived natural products continue to provide medicinally relevant lead compounds for a variety of therapeutic areas.[1] One such family of biologically active compounds is the aspergillides as they were recently isolated in 2008 from the marine fungus *Aspergillus ostianus* strain 01F313 cultured within a bromine-modified medium by Kusumi and co-workers.[2] The aspergillides A (**1**), B (**2**), and C (**3**) are 14-membered lactones that contain either an α or a β-*C*-glycoside subunit and a *trans*-olefin as part of the macrocyclic structure. In addition to their intriguing structures, natural products **1–3** have shown cytotoxic properties against the L1210 murine leukemia cell line with LD_{50} values ranging from 2.0–71 μg/ml. However, the initial disclosure of Kusumi assigned the structures of aspergillides A and B incorrectly. The chemical synthesis of the presumed aspergillide A by Uenishi provided aspergillide B and shed light on a structural discrepancy between these two natural products.[3] Subsequent to this Letter, Kusumi and Ooi published structural revisions of both aspergillides A and B by means of X-ray crystallography.[4] The corrected structures of **1–3** are shown in Figure 1.

Based on the limited biological data and unique structural features of compounds **1–3**, there has been great synthetic interest in these natural products.[5–7] Herein, we disclose our synthesis of (+)-aspergillide B based on a stereoselective oxocarbenium allylation to forge the α-*C*-glycoside subunit.

Our synthetic blueprint to ***ent*-2** was envisioned to feature a Yamaguchi macrolactonization for the completion of the 14-membered ring as shown in Figure 2.[8] A diastereoselective cross-metathesis was reserved for the convergent coupling of two fragments and the α-*C*-glycoside segment would arise from a stereoselective oxocarbenium allylation process followed by a Ru-catalyzed terminal olefin isomerization protocol, vide infra.

Our synthetic outline to ***ent*-2** required the synthesis of the chiral alkenol **10** as delineated in Scheme 1. Hence, a copper-catalyzed Grignard addition of 3-butenyl magnesium bromide to (*R*)-propylene oxide (**9**) readily provided the desired secondary alkenol in 88% yield. Protection of the free hydroxyl group was achieved with the standard silylating reagents (TBSCl and imidazole) in DMF and furnished the TBS-protected alkenol **10** in 94% yield.

With the chiral alkenol segment **10** readily in hand and in multi-gram quantities, we next focused our effort on the completion of the α-*C*-glycoside portion of ***ent*-2** as delineated in Schemes 2 and 3. Thus, treatment of the TBS-protected aldehyde **11** with the chiral pinane *Z*-MEM-acetal crotyl borane reagent provided the MEM-protected diol **12** with a dr of >95:5 for the *syn* diastereomer and 94% ee with a 75% yield.[9] An ensuing ester formation of **12** with acryloyl chloride in the presence of Et_3N and DMAP afforded the acrylate ester **13** in 85% yield. With **13** in hand, we proceeded to form the α,β-unsaturated lactone via olefin metathesis. Hence, treatment of **13** with Grubbs' second generation carbene catalyst **14** under high dilution provided lactone **15** in a very good yield of 96%.[10] Subsequent reduction of the olefin resident in **15** with H_2 and Pd/C under atmospheric pressure furnished lactone **8**. With **8** in hand, partial reduction of the lactone moiety with DIBAL afforded the intermediate lactol and final capping of the hemiacetal with Ac_2O provided the oxocarbenium precursor **16** in 79% yield over two steps from **8**.

With acetate precursor **16** in hand, we proceeded to forge the α-*C*-glycoside subunit **7** by means of a stereoselective oxocarbenium allylation. Based on our previous synthetic ventures, we were hopeful that this approach would stereoselectively deliver the targeted α-*C*-glycoside with high levels of dr and in good to excellent

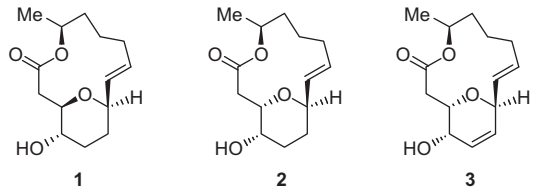

Figure 1. Corrected structures of aspergillides A (**1**), B (**2**), and C (**3**).

* Corresponding author. Tel.: +1 205 348 0351; fax: +1 205 348 9104.
E-mail address: jenningm@bama.ua.edu (M.P. Jennings).

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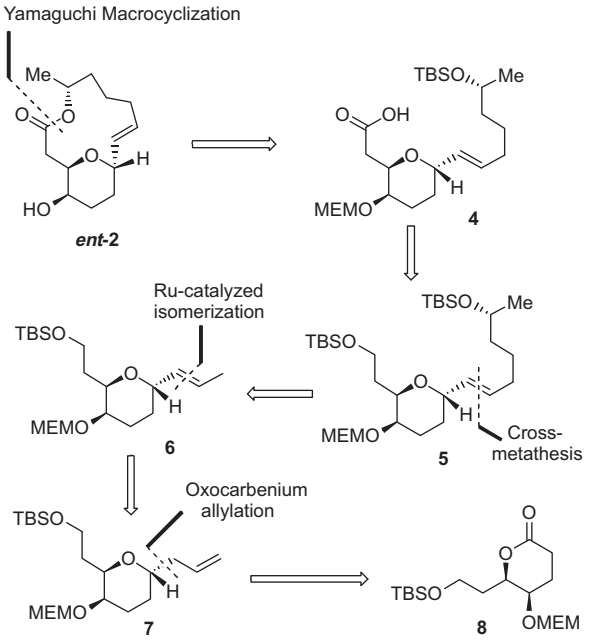
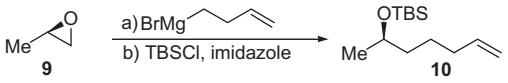
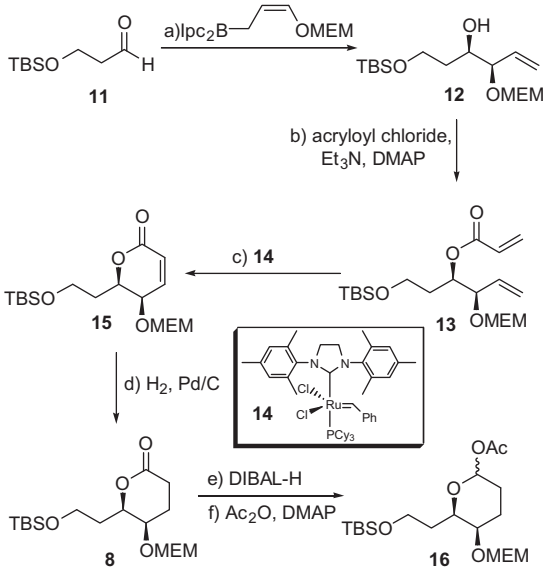


Figure 2. Retrosynthetic analysis of ***ent*-2**.

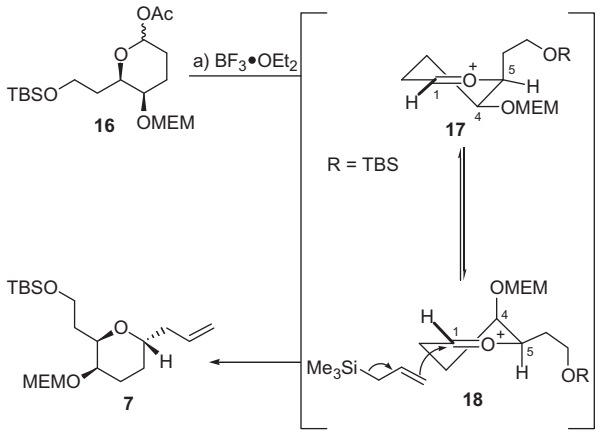


Scheme 1. Synthesis of intermediate **10**. Reagents and conditions: (a) 3-butenyl magnesium bromide (2.0 equiv), CuCN (10 mol %), THF, −78 °C, 12 h, 88%; (b) TBSCl (1.5 equiv), imidazole (3.0 equiv), DMF, 0 °C to rt, 12 h, 94%.



Scheme 2. Synthesis of intermediate **16**. Reagents and conditions: (a) BF_3/OEt_2 (1.3 equiv), (−)-$Ipc_2BCH_2CH{=}CHOMEM$ (1.1 equiv), THF, −78 °C, 3 h, 75%; (b) acryloyl chloride (2.0 equiv), NEt_3 (2.2 equiv), DMAP (5 mol %), CH_2Cl_2, 0 °C to rt, 12 h, 85%; (c) **14** (15 mol %), toluene, 80 °C, 24 h, 96%; (d) Pd/C (10%), EtOH, rt, 1.5 h, 99%; (e) DIBAL-H (2.5 equiv), CH_2Cl_2, −78 °C, 4 h, 99%; (f) Ac_2O (2.5 equiv), pyr (3.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, rt, 12 h, 80%.

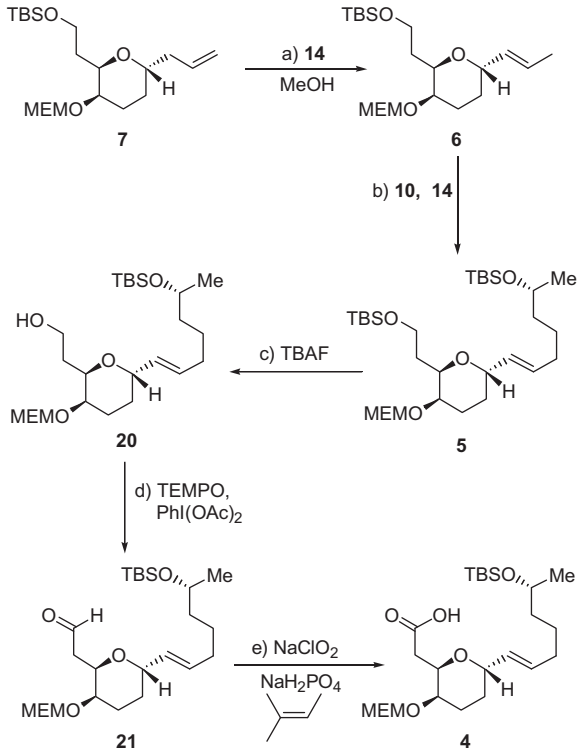
yield.[11] Hence, treatment of acetate **16** with $BF_3{\cdot}OEt_2$ at −78 °C led to the formation of an oxocarbenium cation which has two possible reactive conformers **17** and **18** as shown in Scheme 3. Conformer **17** should place the C5 substituent in the pseudo axial



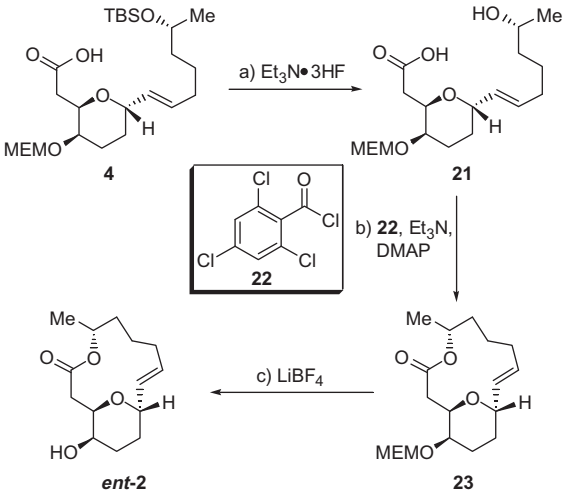
Scheme 3. Synthesis of intermediate **7**. Reagents and conditions: (a) BF_3/OEt_2 (1.5 equiv), allylTMS (2.5 equiv), CH_2Cl_2, −78 °C, 1 h, 85%.

position while the MEM acetal at C4 would be in the pseudo equatorial position. Contrary to **17**, conformer **18** would place the C5 side chain into the pseudo equatorial orientation while the MEM acetal is axial at C4. Based on our previous observations and in agreement with Woerpel's reports, we predicted that conformer **18** would be the reactive one and the allylTMS nucleophile would stereoselectively approach **18** from the axial position leading to the chair-like transition state via the stereoelectronic effect.[11–13] As expected, the α-*C*-glycoside **7** was isolated with a very high dr (>20:1) as a single stereoisomer in 85% yield.[14]

With the completion of the α-*C*-glycoside, an olefin isomerization of **7** prior to the convergent cross-metathesis was required. Inspired by Hanessian's Letter of terminal olefin isomerization



Scheme 4. Synthesis of intermediate **4**. Reagents and conditions: (a) **14** (10 mol %), MeOH, 60 °C, 6 h, 65%; (b) **10** (5.0 equiv), **14** (10 mol %), CH_2Cl_2, 45 °C, 8 h, 67%; (c) TBAF (3 equiv), THF, 0 °C to rt, 3 h, 65%; (d) TEMPO (10 mol %), $PhI(OAc)_2$ (1.1 equiv), CH_2Cl_2, rt, 12 h, 70%; (e) $NaClO_2$ (6 equiv), NaH_2PO_4 (6 equiv), 2-methyl-2-butene (8 equiv), *t*-BuOH/H_2O (3:1), rt, 95%.



Scheme 5. Synthesis of (+)-aspergillide B (***ent*-2**). Reagents and conditions: (a) $Et_3N/3HF$ (30 equiv), CH_3CN, 45 °C, 6 h, 63%; (b) **22** (3.9 equiv), NEt_3 (6.0 equiv), DMAP (30 equiv), toluene, 100 °C, 22 h, 75%; (c) $LiBF_4$ (30 equiv), CH_3CN/H_2O, 72 °C, 5 h, 85%.

utilizing Ru catalyst **14** in MeOH, we sought to utilize this procedure prior to the convergence of **6** and **10** as shown in Scheme 4.[15] Thus, treatment of **7** with catalyst **14** in MeOH readily afforded the isomerized olefin product **6** in 65% yield and as an 8/1: *E/Z* mixture. Subsequently, an *E* selective cross-metathesis of **6** and **10** with catalyst **14** was accomplished and provided compound **5** in 67% yield with an *E/Z* ratio of >20:1.[16] Selective deprotection of the primary TBS group with TBAF in the presence of a secondary one furnished the free primary alcohol **19** in 65% yield. An ensuing oxidation of the primary alcohol resident in **19** with TEMPO and $PhI(OAc)_2$ readily afforded aldehyde **20** in 70% yield.[17] Further oxidation of the aldehyde moiety to the carboxylic acid was accomplished in 95% yield under the Lindgren-Kraus-Pinnick conditions to provide acid **4**, and set the final stage of macrocyclization to provide ***ent*-2**.[18]

With the TBS-protected carboxylic acid **4** in hand, we focused our attention to the final macrocyclization and deprotection to afford ***ent*-2** as highlighted in Scheme 5. With this in mind, deprotection of the TBS group was accomplished with $Et_3N{\cdot}3HF$ and provided the free hydroxy-carboxylic acid compound **21** in 63% yield. An ensuing Yamaguchi macrocyclization of **21** under the reported standard conditions with **22**, Et_3N, and DMAP provided the MEM-protected macrolactone **23** in 75% yield.[8] Final deprotection of **23** with $LiBF_4$ furnished ***ent*-2** in 85% yield. The spectral data (^1H NMR, 500 MHz; ^{13}C NMR, 125 MHz) and HRMS data of synthetic ***ent*-2** were in agreement with the natural sample.[2,19] However, the optical rotation ($[\alpha]_D^{rt}$ +81.1, *c* = 0.0041 g/ml MeOH) confirmed that ***ent*-2** is the enantiomer of the natural aspergillide B.

In conclusion, the synthesis of (+)-aspergillide B has been accomplished by means of a highly diastereoselective oxocarbenium allylation and a Ru-catalyzed terminal olefin isomerization followed by a cross-metathesis and final Yamaguchi macrolactonization. The late stage convergence allows for the synthesis of a variety of analogues to examine the bioactivity of structurally diverse 'aspergillide-like' compounds against a collection of tumor cell lines and further develop the SAR of the aspergillide family of natural products.

Acknowledgments

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14. *Data for* **7**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.0 (m, 2H), 4.7 (dd, *J* = 15.9, 6.8 Hz, 2H), 4.0 (m, 1H), 3.7 (m, 6H), 3.5 (m, 2H), 3.3 (s, 3H), 2.2 (m, 2H), 1.9 (m, 1H), 1.8 (m, 2H), 1.7 (m, 2H), 1.3 (m, 1H), 0.09 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 116.5, 94.1, 72.9, 71.7, 70.3, 69.2, 67.0, 59.8, 58.9, 38.4, 29.7, 27.7, 25.9, 24.2, 18.3, −5.3. IR (CH_2Cl_2): 3100, 2932, 2874, 2359, 1640, 1463, 1250, 1092, 1046, 843, 780 cm^{-1}. R_f = 0.57, 30% EtOAc in hexanes. $[\alpha]_D^{24}$ +21.4 (*c* 0.013 g/mL, CH_2Cl_2). HRMS (EI) calcd for $C_{20}H_{40}O_5Si$ $[M]^+$: 389.2723; found: 334.2721.
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16. *Data for* **5**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.5 (m, 2H), 4.7 (dd, *J* = 15.9, 6.8 Hz, 2H), 4.2 (m, 1H), 3.9 (m, 1H), 3.7 (m, 6H), 3.5 (m, 2H), 3.4 (s, 3H), 1.9 (m, 4H), 1.7 (m, 4H), 1.4 (m, 4H), 1.1 (d, *J* = 6.1 Hz, 3H), 0.9 (s, 18H), 0.04 (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 129.7, 94.1, 72.7, 71.7, 70.8, 69.7, 68.4, 67.0, 59.7, 59.0, 39.2, 32.4, 25.9, 25.8, 25.3, 23.9, 23.7, 18.3, 18.1, −4.7. IR (CH_2Cl_2): 2930, 2858, 2356, 1466, 1362, 1260, 1089, 1039, 830, 766 cm^{-1}. R_f = 0.80, 30% EtOAc in hexanes. $[\alpha]_D^{24}$ +7.2 (*c* 0.013 g/mL, CH_2Cl_2). HRMS (EI) calcd for $C_{30}H_{62}O_6Si_2$ $[M]^+$: 575.4163; found: 575.4149.
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19. *Data for* ***ent*-2**: ^1H NMR (500 MHz, benzene-*d*) δ 6.1 (dddd, *J* = 15.6, 10.8, 4.8, 1.6 Hz, 1H), 5.3 (dd, *J* = 15.6, 4.4 Hz, 1H), 5.0 (m, 1H), 4.3 (m, 1H), 4.0 (d, *J* = 11.2 Hz, 1H), 3.2 (br s, 1H), 2.7 (dd, *J* = 13.6, 11.6 Hz, 1H), 2.1 (dd, *J* = 13.6, 2.0 Hz, 1H), 2.0 (dddd, *J* = 13.6, 10.8, 4.8, 2.4 Hz, 1H), 1.8 (br s, 1H), 1.7–1.8 (m, 2H), 1.5–1.6 (3H, m), 1.3–1.4 (m, 3H), 1.0 (d, *J* = 6.4 Hz, 3H), 0.9 (m, 1H). ^{13}C NMR (125 MHz, benzene-*d*) δ 169.8, 138.2, 129.1, 71.6, 69.9, 69.6, 67.3, 39.9, 32.1, 30.8, 27.8, 25.3, 22.6, 19.2. IR (CH_2Cl_2): 3381, 2926, 1717, 1267, 1187, 1086, 1017, 965 cm^{-1}. R_f = 0.33, 60% EtOAc in hexanes. $[\alpha]_D^{24}$ +81.1 (*c* 0.0041 g/mL, MeOH). HRMS (EI) calcd for $C_{14}H_{22}O_4$ $[M]^+$: 2547.1518; found 254.1513.