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A carbohydrate based approach towards the synthesis of aspercyclide C

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Abstract—A formal total synthesis of aspercyclide C (**3**) is described in which D-ribose is employed as a chiral pool material. The key step is a ring closing metathesis.

Bioassay guided fractionation and screening of *Aspergillus* sp. led to the isolation of three naturally occurring compounds named aspercyclide A (**1**), B (**2**) and C (**3**) as highly efficient binding inhibitors of the IgE receptor.[1] All are 11-membered macrolactones with an integrated biaryl ether moiety. The important biological activity, and interesting structural framework make the aspercyclides interesting targets for total synthesis. An expeditious synthesis of aspercyclide C was reported in 2005 by Fürstner and co-workers by taking advantage of an efficient ring closing metathesis to form the macrocycle.[2] As a part of our long standing interest in integrating RCM with chiron approaches and the synthesis of bioactive natural products, we have investigated the synthesis of aspercyclides.[3] Herein we report a formal synthesis of aspercyclide C using a chiral pool approach.

Employing RCM as the key macrocycle building reaction (Fig. 1),[4] **3** was disconnected to key intermediates **5** and **6**. D-Ribose acetonide **7** having the required two contiguous stereocenters was selected as a starting point for key coupling partner **5**. The Ullmann coupling[5] of *o*-vanillin with the known iodobenzoate **8** followed by

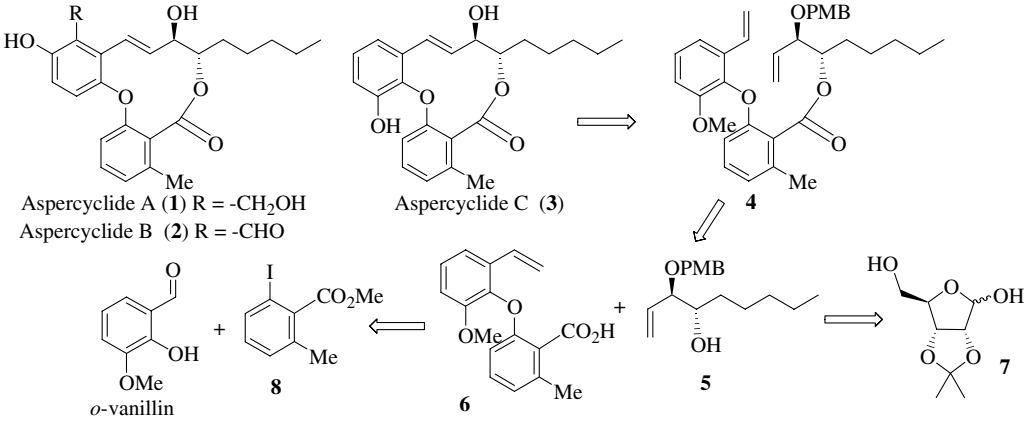

Figure 1. Aspercyclides A–C and a retrosynthetic strategy for aspercyclide C.

Keywords: Chiron approach; Ring closing metathesis (RCM); D-Ribose; Ullmann coupling; Mukaiyama reagent.
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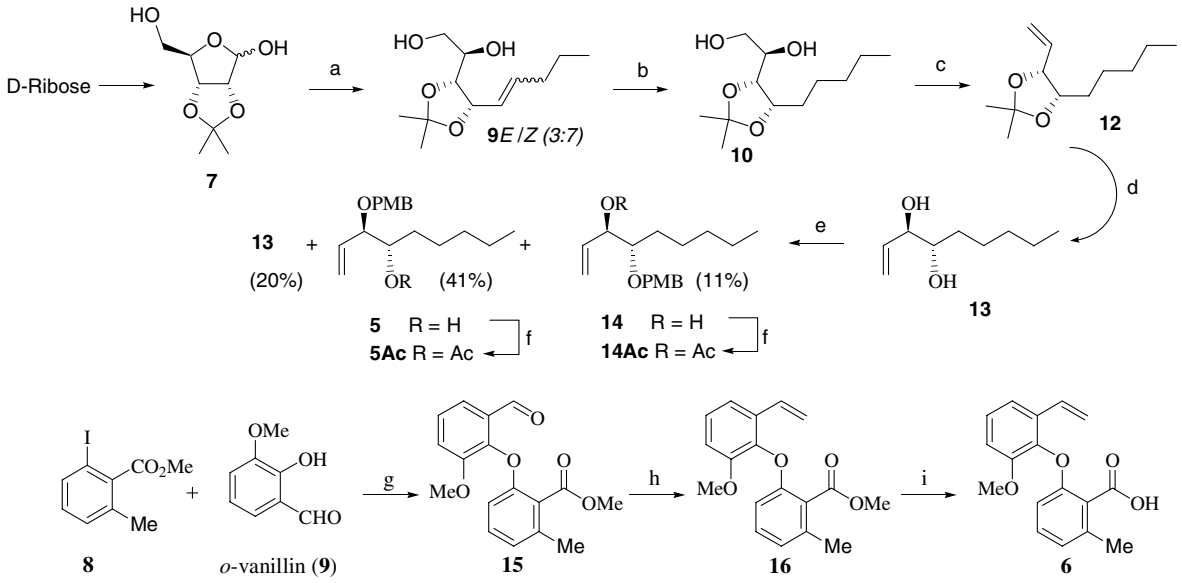


Scheme 1. Reagents and conditions: (a) $PPh_3C_4H_9Br$, *tert*-BuOK, THF, 0 °C → rt, 16 h, 63%; (b) Raney-Ni, H_2, ethanol, rt, 99%; (c) (i) MsCl, TEA, CH_2Cl_2, 0 °C, 3 h; (ii) Zn, NaI, DMF, 155 °C, 2 h, 66%; (d) *p*-TSA, MeOH, rt, 24 h, 99%; (e) NaH, PMBCl, 0 °C → rt, DMF, 10 h, **5** (41%), **14** (11%); (f) Ac_2O, cat. DMAP, pyridine, 0 °C → rt, **14Ac** (91%), **5Ac** (93%); (g) CuO, DMF, 140 °C, 50 h, 48%; (h) PPh_3CH_3I, *n*-BuLi, THF, 0 °C, 0.5 h, 82%; (i) NaOH, MeOH–H_2O (6:4), 48 h, 99%.

one carbon Wittig homologation and saponification should provide the requisite biaryl acid unit **6**.

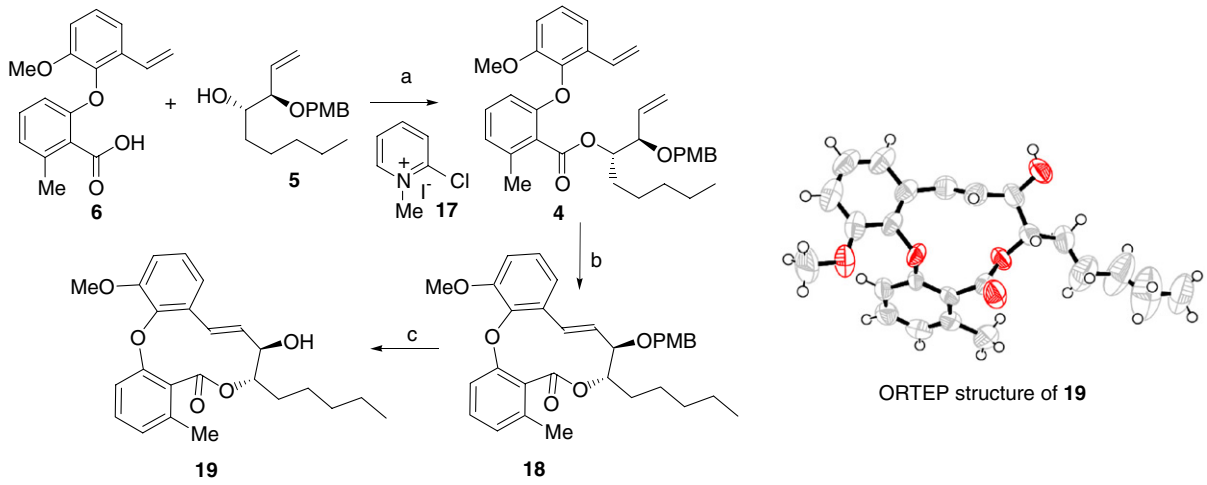
Scheme 1 summarizes our synthesis of key alcohol **5**. After substantial optimization using a variety of bases, the 4-carbon Wittig homologation of ribose acetonide **7**[6] was found to be facile with potassium *t*-butoxide and provided a 3:7 *E*/*Z*-mixture of olefins. Hydrogenation of the olefin using Raney-Ni in ethanol afforded diol **10**. Treatment of diol **10** with MsCl in the presence of Et_3N in dichloromethane followed by Zn-mediated elimination[7] of the resulting dimesylate gave olefin **12** , which was subjected to acid catalyzed hydrolysis to afford diol **13** in 61% over the three steps. Allylic-OH protection of diol **13** using PMBCl and NaH in DMF resulted in the preparation of key coupling partner **5** along with the other regiomer **14**. The structures of **5** and **14** were analysed with the help of spectral and analytical data of the corresponding acetates **5Ac** and **14Ac**, respectively.[8]

To prepare biaryl ether **6**, the Ullmann coupling of **8**[9] and *o*-vanillin was carried out in DMF in the presence of copper oxide to provide biaryl aldehyde **15**. One carbon homologation of **15** using triphenylmethylphosphonium iodide and *n*-BuLi in THF at −78 °C resulted in the formation of alkene **16** in 82% yield. Compound **16** was then subjected to the hydrolysis using NaOH in MeOH–H_2O to afford the second coupling partner, acid **6** in good yield.[10]

Having synthesized **5** and **6**, we proceeded further with their coupling and the ring closing metathesis. There are several observations regarding the coupling of **5** and **6** that deserve mention. Coupling using standard reagents such as DCC and EDCI met with failure.[11] In the case of the Yamaguchi reagent,[11c] we could only isolate the mixed anhydride in quantitative yields. Even our experiments to couple **5** and **6** under the conditions reported by Fürstner and co-workers using the Mukaiyama reagent[12] met with poor yields. Notably, when 1 equiv of NaH was added, after initial salt formation, the reaction proceeded smoothly and provided the key diene ester **4** in 71% yield. Reflecting upon the observations of Fürstner and co-workers,[2] the RCM of **4** was carried out in toluene at 120 °C by adding the catalyst using a syringe pump over 1 h to afford *E*-configured macrocyclic lactone **18**, exclusively.[13]

The *E*-configuration of the internal olefin was confirmed by the large coupling constant (16.0 Hz) between the olefinic protons in the ^1H NMR spectrum of **18**. Removal of the methyl and PMB protecting groups was attempted using excess BBr_3.[14] Our initial observation of the disappearance of compound **18** within 5 min after the addition of BBr_3 at −78 °C, prompted us to quench the reaction which gave macrolactone **19** in 91% yield as a result of selective PMB deprotection alone. The spectral and analytical data of compound **19** were in agreement with the assigned structure, and this was further substantiated by single crystal X-ray structural analysis (Scheme 2).[15–17] Attempted deprotections varying the temperatures, reaction time and the amount of BBr_3 resulted in the formation of aspercyclide C, however, its separation from the complex mixture could not be acheived.

In summary, we have reported a formal synthesis of aspercyclide C using a chiral pool approach and ring closing metathesis as the key reaction. Further application of the key intermediate-alcohol **5** towards the synthesis of other aspercyclides as well as analogues of aspercyclides for structure activity studies is in progress.



Scheme 2. Reagents and conditions: (a) **17**, TEA, toluene, 120 °C, 1 h, then NaH, 0 °C → rt, 2 h, 71%; (b) Grubbs' 2nd gen. catalyst, toluene, reflux, 3 h, 71%; (c) BBr_3, CH_2Cl_2, −78 °C, 5 min, 91%.

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8. (a) *Spectral data of* **5Ac**: $[\alpha]_D^{25}$ −51.2 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): *v* 758, 1036, 1070, 1247, 1514, 1374, 1514, 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ*: 0.87 (t, *J* = 6.2 Hz, 3H), 1.20–1.35 (m, 6H), 1.50–1.65 (m, 2H), 2.01 (s, 3H), 3.74 (dd, *J* = 5.0, 7.6 Hz, 1H), 3.80 (s, 3H), 4.30 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.94 (dt, *J* = 5.0, 7.6 Hz, 1H), 5.20–5.33 (m, 2H), 5.75 (ddd, *J* = 7.7, 10.6, 17.0 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) *δ*: 14.1 (q), 21.1 (q), 22.6 (t), 25.1 (t), 29.7 (t), 31.7 (t), 55.1 (q), 69.9 (t), 74.8 (d), 80.7 (d), 113.7 (d), 119.3 (t), 129.3 (d), 130.3 (s), 135.3 (d), 159.1 (s), 170.4 (s); ESI-MS: *m/z* = 321.3 (40%, $[M+H]^+$), 343.3 (100%, [M+Na]). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.31; H, 8.88; (b) *Spectral data of* **14Ac**: $[\alpha]_D^{25}$ −22.7 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): *v* 1035, 1244, 1465, 1514, 1613, 1741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ*: 0.91 (t, *J* = 6.2 Hz, 3H), 1.27–1.34 (m, 6H), 1.43–1.56 (m, 2H), 2.13 (s, 3H), 3.50 (dt, *J* = 3.3, 7.8 Hz, 1H), 3.84 (s, 3H), 4.47 (d, *J* = 11.1 Hz, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 5.28–5.37 (m, 2 H), 5.49 (dd, *J* = 2.7, 7.8 Hz, 1H), 5.91 (ddd, *J* = 6.4, 10.5, 17.1 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) *δ*: 14.1 (q), 21.2 (q), 22.6 (t), 25.4 (t), 30.5 (t), 31.7 (t), 55.2 (q), 72.0 (t), 75.8 (d), 79.7 (d), 113.7 (d), 118.3 (t), 129.6 (d), 130.5 (s), 133.1 (d), 159.2 (s), 170.0 (s) ppm. ESI-MS: *m/z* = 343.3 (100%, [M+Na]) Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.35; H, 8.66.
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10. *Spectral data of Compound* **6**: IR ($CHCl_3$): *v* 757, 1067, 1215, 1461, 1705, 1740, 3368 (br) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ*: 2.54 (s, 3H), 3.77 (s, 3H), 5.33 (d, *J* = 11.1 Hz, 1H), 5.83 (d, *J* = 17.5 Hz, 1H), 6.39 (d, *J* = 8.3 Hz, 1H), 6.83–6.97 (m, 3H), 7.08–7.29 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ*: 20.3 (q), 56.0 (q), 111.7 (d), 111.8 (d), 116.7 (t), 118.1 (d), 121.9 (s), 124.4 (d), 125.9 (d), 130.2 (d), 130.8 (d), 132.7 (s), 138.8 (s), 140.6 (s), 151.9 (s), 155.9 (s), 169.9 (s) ppm; ESI-MS: *m/z* = 285.1 (6%, [M+H]), 307.1 (100%, [M+Na]). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.69; H, 5.61.
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13. *Spectral data of Compound* **18**: $[\alpha]_D^{25}$ +148.6 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): *v* 757, 1081, 1251, 1460, 1514, 1585, 1610, 1735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 0.91 (t, *J* = 7 Hz, 3H), 1.29–1.54 (m, 6H), 1.55–1.62 (m, 1H),

1.99–2.05 (m, 1H), 2.33 (s, 3H), 3.74 (t, $J = 9.6$ Hz, 1H), 3.80 (s, 3H), 3.91 (s, 3H), 4.32 (d, $J = 11.5$ Hz, 1H), 4.58 (d, $J = 11.5$ Hz, 1H), 5.29 (dt, $J = 2.4$, 9.6 Hz, 1H), 5.95 (dd, $J = 9.6$, 16.0 Hz, 1H), 6.26 (d, $J = 16.0$ Hz, 1H), 6.55 (d, $J = 8.3$ Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.80 (d, $J = 7.6$ Hz, 1H), 6.84 (t, distorted, $J = 2$ Hz, 1H), 6.86 (t, distorted, $J = 2.5$ Hz, 1H), 6.93 (dd, $J = 1.2$, 8.3 Hz, 1H), 7.06 (t, $J = 7.9$ Hz, 1H), 7.12 (t, $J = 7.9$ Hz, 1H), 7.21 (t, distorted, $J = 2.2$ Hz, 1H), 7.23 (t, distorted, $J = 2.2$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1 (q), 19.3 (q), 22.6 (t), 25.3 (t), 31.7 (t), 32.0 (t), 55.2 (q), 56.1 (q), 70.5 (t), 75.7 (d), 82.9 (d), 111.7 (d), 113.8 (d), 114.3 (d), 121.7 (d), 123.7 (d), 125.4 (d), 126.8 (s), 129.4 (d), 129.6 (2d), 130.1 (s), 133.8 (s), 134.7 (s), 136.9 (d), 143.2 (s), 153.9 (s), 154.1 (s), 159.3 (s), 167.5 (s). ESI-MS: $m/z = 539.1$ (100%, [M+Na]). Anal. Calcd for $C_{32}H_{36}O_6$: C, 74.39; H, 7.02. Found: C, 74.13; H, 7.28.

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15. *Spectral data of Compound* **19**: $[\alpha]_D^{25}$ +330.5 (*c* 0.8, DCM); IR ($CHCl_3$): *v* 759, 1080, 1215, 1461, 1584, 1601,1722, 3445 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, $J = 6.6$ Hz, 3H), 1.26–1.45 (m, 4H), 1.50–1.60 (m, 1H), 1.63–1.73 (m, 2H), 2.03–2.10 (m, 1H), 2.35 (s, 3H), 3.90 (s, 3H), 4.03 (t, $J = 9.0$ Hz, 1H), 5.19 (t, 9.2 Hz, 1 H), 5.99 (dd, J= 9.2, 15.6 Hz, 1H), 6.27 (d, $J = 15.6$ Hz, 1H), 6.57 (d, $J = 8.3$ Hz, 1H), 6.73 (d, J= 7.53 Hz, 1H), 6.82 (d, $J = 7.5$ Hz, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 8.3$ Hz, 1H), 7.11 (d, $J = 8.3$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 (q), 19.4 (q), 22.6 (t), 25.4 (t), 31.7 (t), 31.8 (t), 56.1 (q), 76.9 (d), 77.2 (d), 111.8 (d), 114.4 (d), 121.6 (d), 123.7 (d), 125.5 (d), 126.7 (s), 127.9 (d), 129.7 (d), 133.6 (s), 134.7 (s), 137.8 (d), 143.2 (s), 153.8 (s), 154.1 (s), 167.7 (s) ppm. ESI-MS: $m/z = 397.3$ (5%, [M+H]), 419.2 (100%, [M+Na]). Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 72.82; H, 7.36.
16. (a) X-ray intensity data of compound **19** was collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, $\lambda_{MoK\alpha} = 0.71073$ Å at $T = 293$ (2) K. All the data were corrected for Lorentzian, polarisation and absorption effects using Bruker's SAINT and SADABS programs. The crystal structure was solved by direct methods using SHELXS-97 and the refinement was performed by full matrix least squares of F^2 using SHELXL-97. Hydrogen atoms were included in the refinement as per the riding model except for the hydroxyl group, which is located in the difference Fourier map. (b) G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997.
17. The crystallographic data of compound **19** has been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 656253. Copies of these data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk].