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First asymmetric total synthesis of aspinolide A

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ABSTRACT

The first total synthesis of aspinolide A has been achieved using ring-closing metathesis as a key step. The stereogenic centers were generated by means of hydrolytic kinetic resolution (HKR) of racemic epoxides.

Medium-sized-ring systems, those containing 8–11 atoms in the ring[1,2] are a subject of continuous interest to organic chemists, as they form the core of many bioactive natural products. Aspinolide A **1a**, a decanolide, was isolated in 1997 from the cultures of *Aspergillus ochraceus*[3] along with aspinolide B **1b** and aspinolide C **1c** (Fig. 1). The (*R*)-configuration of the secondary alcohol was assigned by applying the Helmchen method,[4] while the (*R*)-configuration of C-9 is assumed by analogy with aspinolide B.

As a part of our research program aimed at developing enantioselective synthesis of biologically active natural products based on hydrolytic kinetic resolution (HKR),[5] we became interested in devising a simple and concise route to aspinolide A. Herein, we report our successful endeavor toward the first total synthesis of **1a** employing HKR[6] and ring-closing metathesis (RCM)[7] as key steps.

The HKR method involves the readily accessible cobalt-based chiral salen complex as a catalyst and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and diol, which serve as a useful precursor in the synthesis of various compounds of biological importance.[8]

Our retrosynthetic analysis for the synthesis of aspinolide A **1a** is based on the convergent approach as outlined in Scheme 1. We envisioned that the ring-closing could be effected by ring-closing metathesis of diene **14**. Diene **14** could be prepared by EDCI coupling of the alcohol **4** and acid **12**. Alcohol **4** could be obtained from rac-propylene oxide **2** via HKR, while acid fragment could be prepared from 1,5-pentane diol **5**.

Thus, as shown in Scheme 2, commercially available propylene oxide **2** was subjected to Jacobsen's hydrolytic kinetic resolution using (*R*,*R*)-salen-Co-OAc catalyst to give (*R*)-propylene oxide (*R*)-**2** as a single isomer, which was easily isolated from the diol **3** by

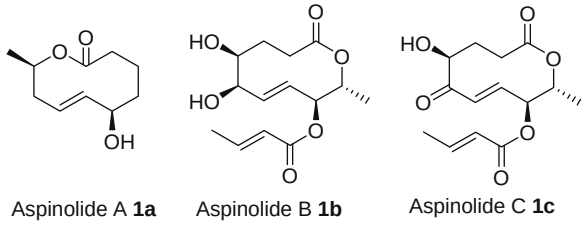
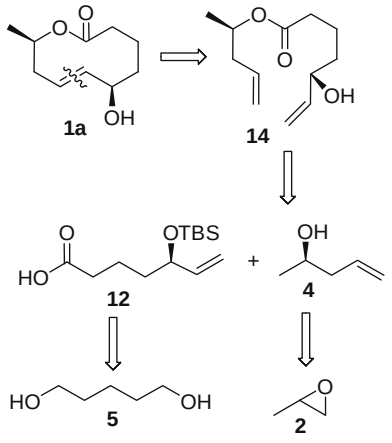


Figure 1. Aspinolides (A–C).



Scheme 1. Retrosynthetic analysis of aspinolide A.

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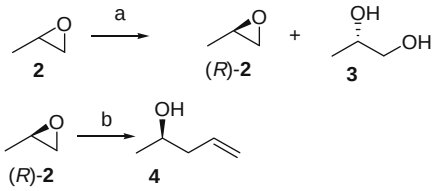
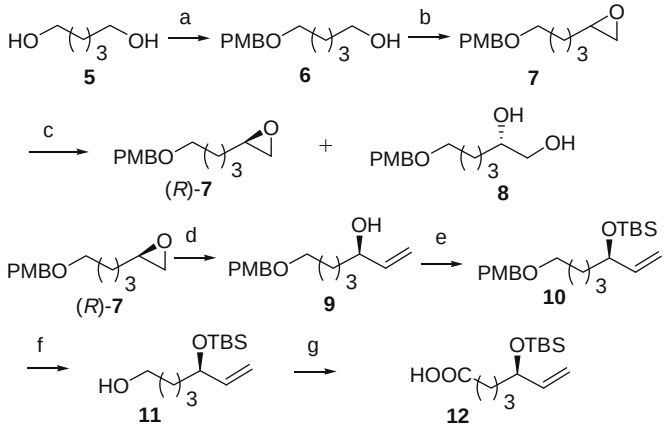


Scheme 2. Reagents and conditions: (a) (*R*,*R*)-salen-Co-(OAc) (0.5 mol %), distd H_2O (0.55 equiv), 0 °C, 14 h, (45% for (*R*)-**2**, 43% for **3**); and (b) vinylmagnesium bromide THF, CuI, −20 °C, 88%, 12 h.

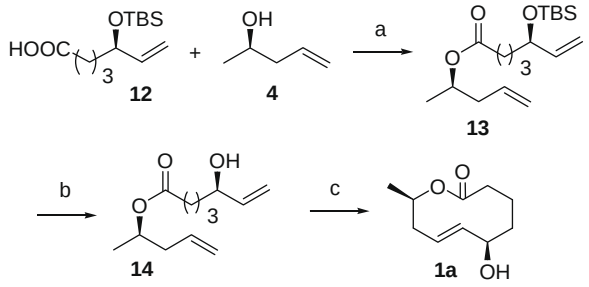
distillation.[6b] (*R*)-Propylene oxide was treated with vinylmagnesium bromide in the presence of cuprous iodide to give the required homoallylic alcohol **4** in 88% yield.[5e]

The synthesis of acid fragment **12** started from commercially available 1,5-pentanediol **5** as illustrated in Scheme 3. Thus selective monoprotection of **5** with *p*-methoxybenzyl bromide gave PMB ether **6**, which was subjected to Swern oxidation[9] followed by Corey–Chaykovsky reaction[10] with dimethylsulfoxonium methylide to afford the racemic epoxide **7** in 70% yield. Compound **7** was subjected to Jacobsen's hydrolytic kinetic resolution using (*R*,*R*)-salen-Co-OAc catalyst to give (*R*)-epoxide (*R*)-**7** in >99% ee,[11] which was easily separated from the (*S*)-diol **8** by column chromatography. Epoxide (*R*)-**7** on reaction with dimethylsulfonium methylide[12] afforded the required allylic alcohol **9** in 72% yield. Protection of hydroxy group of **9** as TBS ether followed by deprotection of PMB group[13] by DDQ gave the primary alcohol **11** in 92% yield. The alcohol **11** was oxidized to aldehyde using IBX followed by subsequent oxidation using $NaClO_2$ to give the required acid fragment **12**[14] in 76% yield.

With substantial amount of both the fragments in hand the coupling of alcohol **4** and acid **12** was achieved by using EDCI to afford diene **13**[15] in 86% yield. Ring-closing metathesis of **13** under various conditions using Grubbs' 1st and 2nd generation catalyst failed to provide the required 10-membered lactone. In order to circumvent the problem, we thought it appropriate to first deprotect the TBS group and then use the ring-closing metathesis for macrocyclization. Thus the TBS group of diene **13** was deprotected to get the alcohol **14**[16] which on ring-closing metathesis by using Grubb's first generation catalyst under high dilution conditions furnished a 10:1 (*E*/*Z*) mixture, which on chromatographic purification gave the target molecule **1a**[17] in 60% yield. The prepared synthetic aspi-



Scheme 3. Reagents and conditions: (a) PMBBr, NaH, THF, 0 °C to rt, 6 h, 92%; (b) (i) $(COCl)_2$, DMSO, −78 °C to −60 °C, Et_3N, CH_2Cl_2, (ii) $(CH_3)_3S(O)I$, NaH, DMSO, 60 °C, 1.5 h, 70%; (c) (*R*,*R*)-salen-Co-(OAc) (0.5 mol %), distd H_2O (0.55 equiv), 0 °C, 22 h, (44% for (*R*)-**7**, 45% for **8**); (d) $(CH_3)_3SI$, 2 h, *n*-BuLi, THF, 72%; (e) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 93%; (f) DDQ, CH_2Cl_2/H_2O (1:1), rt, 1 h, 92%; and (g) (i) IBX, EtOAc, reflux, and (ii) $NaClO_2$, NaH_2PO_4, DMSO, overnight, 76% from two steps.



Scheme 4. Reagents and conditions: (a) EDCI·HCl, DMAP, CH_2Cl_2, 0 °C, 5 h, 86%; (b) TBAF, THF, 7 h, 80%; and (c) $(PCy_3)_2$ $Ru(Cl)_2$=CH–Ph (20 mol %), CH_2Cl_2, reflux, 42 h, 60%.

nolide A is identical (IR, ^1H NMR, ^{13}C NMR) with the natural product and also has an optical rotation ($[\alpha]_D^{25}$ −41.6 (*c* 0.25, MeOH)) which is in good agreement with the literature value [$[\alpha]_D^{23}$ −43.8 (*c* 0.3, MeOH)].[3] Thus, the absolute stereochemistry of aspinolide **1a** was established as 5*R* and 9*R* (Scheme 4).

In conclusion, a convergent and efficient first total synthesis of aspinolide A, with high enantioselectivities has been accomplished and its absolute stereochemistry has been fixed. The stereocenters were generated by means of Jacobsen's hydrolytic kinetic resolution and cyclization was achieved by ring-closing metathesis. This approach could be used for the synthesis of other members of aspinolide family for structure–activity relationship. Currently work is in progress in this direction.

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14. *Spectral data of* **12**: $[\alpha]_D^{25}$ −6.56 (*c* 1.15, $CHCl_3$), IR ($CHCl_3$): *ν* 3442, 2930, 2858, 1713, 1463, 1254, 1087, 923 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 5.86–5.72 (m, 1H), 5.18–5.00 (m, 2H), 4.15–4.06 (m, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.76–1.63 (m, 2H), 1.60–1.46 (m, 2H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 179.9, 141.3, 114.0, 73.4, 37.2, 34.0, 29.7, 25.8, 20.3, 18.2, −4.4, −4.9; Anal. Calcd for $C_{13}H_{26}O_3Si$ (258.429): C, 60.42; H, 10.14. Found: C, 60.28; H, 10.31.
15. *Spectral data of* **13**: $[\alpha]_D^{25}$ −14.9 (*c* 0.50, $CHCl_3$), IR ($CHCl_3$): *ν* 2931, 2864, 1732, 1655, 1466, 1425, 1218, 1170, 781 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 5.83–5.70

(m, 2H), 5.17–5.02 (m, 4H), 5.0–4.93 (m, 1H), 4.12–4.08 (m, 1H), 2.28 (t, J = 7.5 Hz, 2H), 1.72–1.47 (m, 6H), 1.21 (d, J = 6.53 Hz, 3H), 0.09 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.1, 141.4, 133.7, 117.6, 113.8, 73.5, 69.7, 40.3, 37.3, 34.6, 25.9, 20.8, 19.5, 18.2, −4.4, −4.9; Anal. Calcd for $C_{18}H_{34}O_3Si$ (326.546): C, 66.21; H, 10.49. Found: C, 66.45; H, 10.22.

16. *Spectral data of* **14** : $[\alpha]_D^{25}$ −10.2 (c 0.3, $CHCl_3$), IR ($CHCl_3$): ν 3438, 2933, 1731, 1645, 1424, 1380, 1245, 1061; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.95–5.65 (m, 2H), 5.27–5.04 (m, 4H), 5.02–4.93 (m, 1H), 4.16–4.07 (m, 1H), 2.64–2.45 (m, 1H), 2.32 (t, J = 7.3 Hz, 2H), 2.27–2.17 (m, 1H), 1.78–1.67 (m, 2H), 1.61–1.5 (m, 2H), 1.20 (d, J = 6.31, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.1, 140.9, 136.1, 117.7, 116.9, 72.7, 69.9, 40.3, 36.2, 34.2, 20.7, 19.5; Anal. Calcd for $C_{12}H_{20}O_3$(212.285): C, 67.89; H, 9.5. Found: C, 67.77; H, 9.23.
17. *Spectral data of* **1a**: $[\alpha]_D^{25}$ −41.6 (c 0.25, MeOH), IR ($CHCl_3$): ν 3435, 2925, 2854, 1729, 1462, 1275, 1073, 971 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.5 (ddd, J = 15.6, 10.3, 4.5, 1H), 5.30 (dd, J = 15.6, 9.5, 1H), 5.05–4.8 (m, 1H), 4.03–3.98 (m, 1H), 2.46–2.41 (m, 2H), 2.30 (t, J = 7.2 Hz, 2H), 1.92–1.85 (m, 2H), 1.72–1.5 (m, 2H), 1.23 (d, J = 6.27, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 174.6, 137.23, 131.5, 74.4, 71.6, 42.0, 38.7, 35.5, 22.9, 19.1.