Total Synthesis of (±)-Arohynapene B

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The total synthesis of (±)-arohynapene B, an anticoccidial agent isolated from the fermentation broth of a fungal strain, has been achieved. The tetrahydronaphthalene ring was constructed by the Diels–Alder reaction between dimethyl acetylenedicarboxylate and the 1-(β-acetoxyvinyl)cyclohexene derivative, which was prepared from 3,5-dimethylcyclohexanone via the Ag^+-catalyzed rearrangement of the propargylic acetate derivative. The introduction of the dienylcarboxylic acid side chain was accomplished by the Horner–Wadsworth–Emmons olefination repeatedly utilizing ethyl diethylphosphonoacetate. Finally, careful removal of the protecting groups led to (±)-arohynapene B.

Arohynapenes are new anticoccidial agents, isolated from the fermentation broth of the *Penicillium* sp. FO-2295 strain, and their structures have been proposed as shown in Figure 1.[1] More recently, another natural product with a structure analogous to arohynapene B, tanzawaic acid A, has been isolated from *Penicillium citrinum* as an inhibitor of superoxide anion production,[2] of which the absolute structure has been elucidated as shown in Figure 1 by an asymmetric total synthesis.[3] Although the stereochemistry of the arohynapenes is still unclear, from a comparison between the reported spectral data of tanzawaic acid A and those of arohynapene B, we deduced that the relative stereochemistry of the two methyl substituents in arohynapene B will be a *cis* relationship. Herein, we report the first total synthesis of the racemic arohynapene B in a straightforward manner starting from *cis*-3,5-dimethylcyclohexanone, which also led to the assignment of its relative stereochemistry.

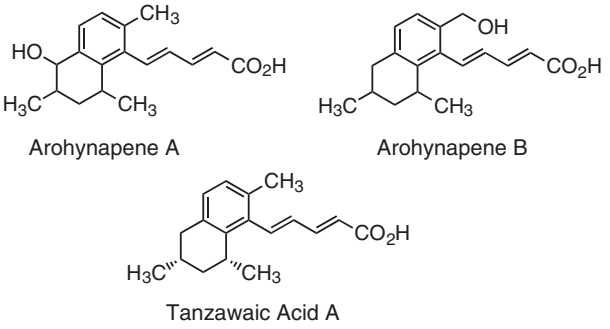
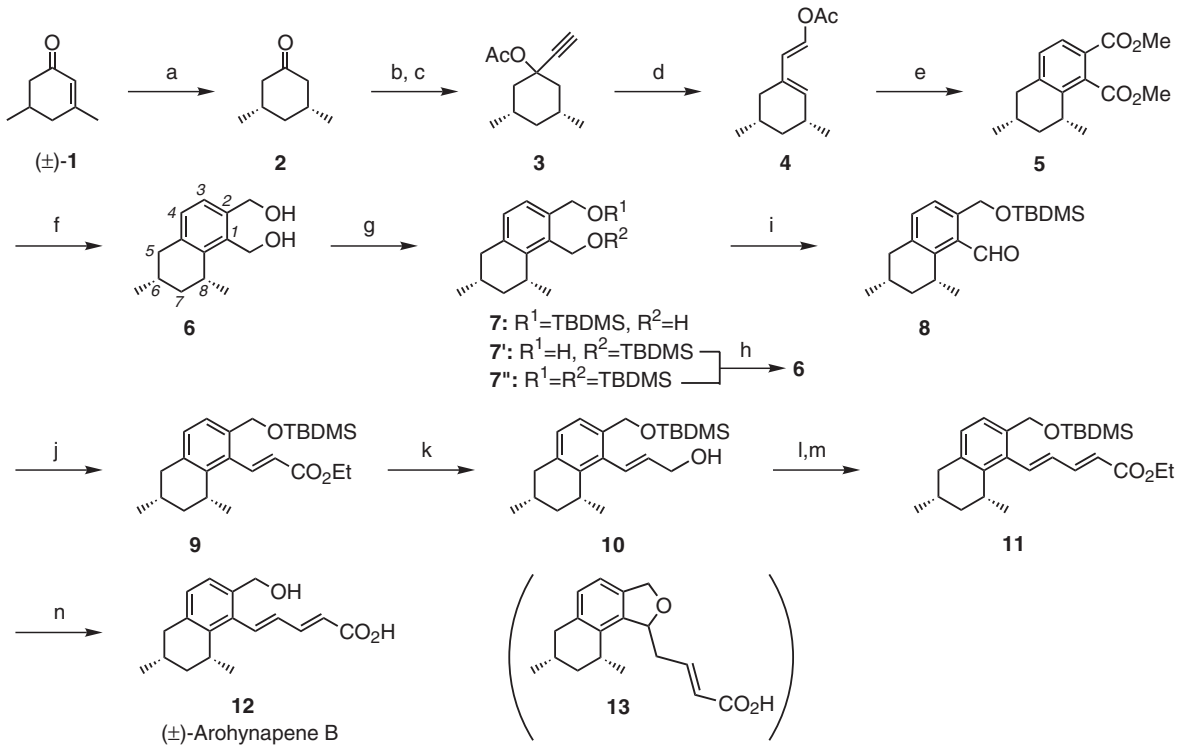


Figure 1.

Our approach to the tetrahydronaphthalene ring of arohynapene B involves a Diels–Alder reaction[4] between dimethyl acetylenedicarboxylate and 3,5-dimethyl-1-(β-acetoxyvinyl)cyclohexene, which could be prepared from the propargylic acetate derivative according to a literature procedure.[5] These results are summarized in Scheme 1. To start with, commercially available (±)-3,5-dimethyl-2-cyclohexen-1-one (**1**) was stereoselectively hydrogenated in the presence of 10% Pd/C under atmospheric H_2 in benzene to give *cis*-3,5-dimethylcyclohexanone **2**[6] (*cis:trans* = 19:1 estimated by ^{13}C NMR). The treatment of **2** with ethynylmagnesium bromide in THF, followed by acetylation, provided the propargyl acetate derivative **3** in 72% yield. The acetate **3** was converted to 1,3-dienyl acetate **4** by treatment with a catalytic amount of silver trifluoroacetate in refluxing benzene in 73% isolated yield after silica gel chromatography.[5] The Diels–Alder reaction of **4** was best accomplished using three equivalents of dimethyl acetylenedicarboxylate in toluene under reflux for four days, and then treating with DBN as a base for completion of the acetic acid elimination. Numerous reaction conditions were investigated in order to improve the product yield (solvent, Lewis acid catalyst, reaction temperature, base, etc.), but none proved to be better than the above conditions.

With the tetrahydronaphthalene skeleton in hand, we next focused on the introduction of the dienylcarboxylic acid side chain at the correct position. After reduction of the diester **5** with $LiAlH_4$, selective protection of the hydroxymethyl group at C-2 in the diol **6**[7] was investigated. When the diol **6** was treated with *t*-butyldimethylsilyl chloride (TBSCl) and triethylamine–DMAP(cat.) as base in dichloromethane, the desired TBS ether **7** was obtained in 47% yield along with the regioisomeric TBS ether **7′** (13%), bis-TBS ether **7″** (12%) and recovery of **6** (17%). In contrast, a similar reaction using two equivalents of imidazole as the base in DMF gave the TBS ether **7**, bis-TBS ether **7″** and the starting diol **6** in 48, 14 and 21% yields, respectively, without the production of the TBS ether **7′**. Although the yields of the desired product obtained from these two reactions are almost the same, the latter condition is more convenient because it can avoid difficulties in the separation of the regioisomeric by-product **7′** by column chromatography. The TBS-ether **7′** and bis-TBS ether **7″** were reused after converting to the diol **6** by treatment with tetrabutylammonium fluoride. Oxidation of the remaining hydroxyl group in **7** with PCC provided the aldehyde **8** in 79% yield. The attempt to introduce the dienylcarboxylate moiety directly to **8** using $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$/NaH failed because the reaction was very sluggish, and the yield of **11** was only 9%. Therefore, we next tried a stepwise approach for the installation of the side chain. The Horner–Wadsworth–Emmons olefination using $(EtO)_2P(O)CH_2CO_2Et$/NaH in dimethoxyethane gave the unsaturated ester **9** in 91% yield. The ester **9** was reduced to the allyl alcohol **10** by DIBAL in 97% yield. The oxidation of **10** with manganese dioxide afforded an unsaturated aldehyde, which was subsequently subjected to the second Horner–Wadsworth–Emmons olefination to provide the fully protected arohynapene B (**11**).

In the final steps, deprotection of the TBS ether and ethyl ester, the order of removal of the protecting groups is crucial for obtaining a high yield of the product **12**. If the TBS group is first removed and then the ethyl ester is hydrolyzed under basic con-



Scheme 1. Reagents and conditions: (a) H_2, 10% Pd/C, benzene, quant. (*cis:trans* = 19:1) (b) HC≡CMgBr, THF (c) Ac_2O, DMAP(cat.), pyridine, 72% from **2** (d) CF_3CO_2Ag(cat.), benzene, reflux, 73% (e) $MeO_2CC{\equiv}CCO_2Me$, toluene, reflux, then DBN, reflux, 42% (f) $LiAlH_4$, Et_2O, reflux, 59% (g) TBDMSCl, imidazole, DMF, 48% (h) Bu_4NF, THF (i) PCC, CH_2Cl_2, 79% (j) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, 91% (k) DIBAL, CH_2Cl_2, 97% (l) MnO_2, benzene (m) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, 84% from **10** (n) LiOH, THF–MeOH–H_2O, then Dowex 50W (H^+ form), 50 °C, quant.

ditions, the intramolecular conjugate addition of the hydroxyl group to the δ-position of the dienylcarboxylate side chain partially occurs to give the dihydroisobenzofuran derivative **13**, resulting in a decrease of the yield of **12**. This problem, however, could be solved by the following procedure: the ethyl ester was first hydrolyzed under basic conditions (LiOH/THF–MeOH–H_2O), and then the reaction mixture was neutralized with ion exchange resin (DOWEX 50W H^+-form). Furthermore, the addition of excess resin to the reaction mixture, followed by warming of the mixture to 50 °C led to (±)-arohynapene B **12** in quantitative yield. The ^1H and ^{13}C NMR data of the synthetic sample[8] were identical to those reported in the literature.[1] Hence, the relative stereochemistry of the two methyl groups in arohynapene B could be assigned to be *cis*.

In summary, we have achieved the total synthesis of (±)-arohynapene B (**12**) from the readily available *cis*-3,5-dimethylcyclohexanone (**2**) in 12 steps. This route is short and concise, featuring the direct construction of the tetrahydronaphthalene ring by the Diels–Alder reaction. The resolution of each enantiomer as well as the elucidation of the absolute configuration of the natural product is currently underway in our laboratory.

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7 For the *cis*-isomer of **6**: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.05 (d, 3H, J = 6.6 Hz, 6-CH_3), 1.24 (d, 3H, J = 7.3 Hz, 8-CH_3), 1.08–1.15 (m, 1H, H-7), 1.59–1.65 (m, 1H, H-6), 2.16–2.29 (m, 1H, H-7), 2.37 (dd, 1H, J = 11.9, 15.2 Hz, H-5), 2.63 (ddd, 1H, J = 2.6, 3.3, 15.2 Hz, H-5), 3.36 (dq, 1H, J = 6.6, 7.3 Hz, H-8), 4.64 (d, 1H, J = 11.9 Hz, 1-CH_2), 4.65 (d, 1H, J = 11.9 Hz, 1-CH_2), 4.72 (d, 1H, J = 11.9 Hz, 2-CH_2), 4.74 (d, 1H, J = 11.9 Hz, 2-CH_2), 6.99 (d, 1H, J = 7.9 Hz, H-4), 7.06 (d, 1H, J = 7.9 Hz, H-3).
8 Spectral data of the synthetic arohynapene B (**12**) ^1H NMR ($CDCl_3$, 270 MHz) δ 1.05 (d, 3H, J = 6.6 Hz), 1.13 (d, 3H, J = 6.6 Hz), 1.22–1.28 (m, 2H), 2.10–2.19 (m, 1H), 2.33–2.42 (m, 1H), 2.60–2.68 (m, 1H), 3.16–3.25 (m, 1H), 4.62 (s, 2H), 5.94 (d, 1H, J = 15.8 Hz), 6.56 (dd, 1H, J = 11.2, 15.8 Hz), 7.03 (d, 1H, J = 7.9 Hz), 7.13 (d, 1H, J = 15.8 Hz), 7.20–7.30 (m, 1H), 7.49 (dd, 1H, J = 11.2, 15.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 24.2, 29.6, 30.8, 39.6, 41.4, 63.1, 121.0, 125.8, 128.5, 131.5, 135.0, 136.2, 138.2, 139.0, 140.8, 145.5, 169.4.

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