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Total synthesis of (+)-aspermytin A

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ABSTRACT

The first enantioselective total synthesis of aspermytin A, a new neurotrophic polyketide isolated from a cultured marine fungus of the genus *Aspergillus* sp., has been accomplished in 24 steps with an overall yield of 9.7% from *S*-(−)-citronellal.

Aspermytin A[1] has been isolated from a marine-derived fungus of the genus *Aspergillus* sp. by Tsukamoto et al. The structure of this polyketide was elucidated as **1** on the basis of spectral data and its absolute configuration was assigned by its CD spectrum. The key structural features of the molecule are the functionalized *trans*-octahydronaphthalene skeleton and the four contiguous stereogenic centers, two of which are quaternary carbons, on the ring. Aspermytin A (**1**) showed a significant neurotrophic effect on rat pheochromocytoma (PC-12) cells at concentration of 50 μM. The intriguing chemical structure, combined with its promising biological profile, has made aspermytin A an attractive target for total synthesis. During the course of our synthetic investigations, we have reported the total synthesis of equisetin (**2**),[2] an enantiomeric analog of **1**, in which an efficient and stereoselective strategy for the construction of the *trans*-octahydronaphthalene with four contiguous stereogenic centers has been developed by using the $AlMe_3$-mediated intramolecular Diels–Alder (IMDA) reaction[3] as the key step. We report here the first total synthesis of (+)-aspermytin A (**1**) employing a similar IMDA reaction for the construction of the octahydronaphthalene core and the diastereoselective creation of the C13 quaternary stereogenic center as the key reaction steps (Fig. 1).

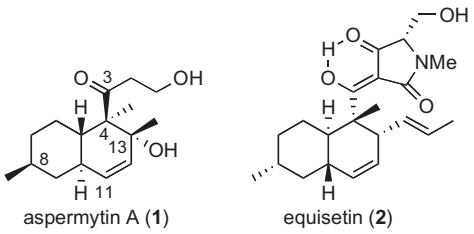
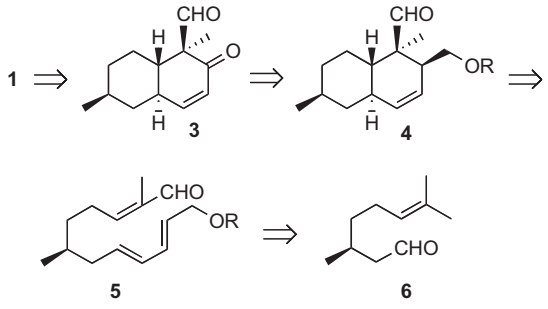


Figure 1.

Our retrosynthetic analysis of aspermytin A is shown in Scheme 1. We envisaged the diastereoselective constructions of the C13 quaternary stereogenic center and the β-hydroxy ketone moiety at C4 being achieved from **3** in the last stage of the synthesis. The keto aldehyde **3** might be derived from **4**, the IMDA adduct of the triene **5** which can be prepared from *S*-(−)-citronellal (**6**), via an oxidative cleavage of the C–C bond of the oxymethyl functionality at the future C13 (Scheme 1).

The substrate **13** for the IMDA reaction was synthesized as shown in Scheme 2. The aldehyde **7**, prepared from *S*-(−)-citronellal (**6**) via a four-step sequence, was treated with 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, $CrCl_2$, Mn, LiI, and TMSCl in THF[4] to give the (*E*)-vinyl boronate **8** selectively. The Suzuki–Miyaura coupling[5] of **8** with (*E*)-(3-bromoallyloxy)(*tert*-butyl)diphenylsilane[6] provided the (*E*,*E*)-diene **9**, which was exposed to acidic conditions to give the monosilylated alcohol **10** selectively in 83% yield from **7**. Sequential Swern oxidation, Wittig reaction, DIBAH reduction, and MnO_2 oxidation provided the triene aldehyde **13** in 84% yield for the four steps (Scheme 2).

The key IMDA reaction of **13** was examined and the results are shown in Table 1. After a solution of **13** in toluene was heated at 150 °C for 48 h in the presence of catalytic methylene blue[7] in a sealed tube, the cycloadduct was obtained as an inseparable 2:1



Scheme 1. Retrosynthetic analysis of aspermytin A.

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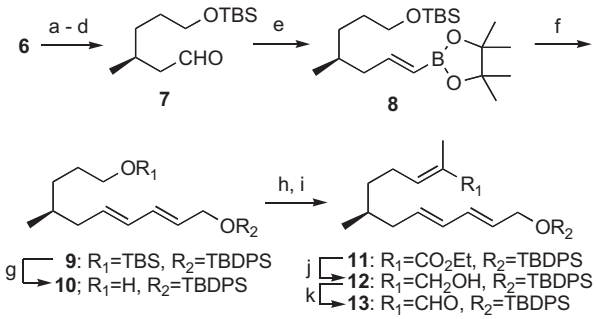
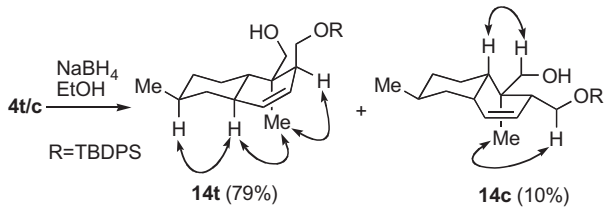
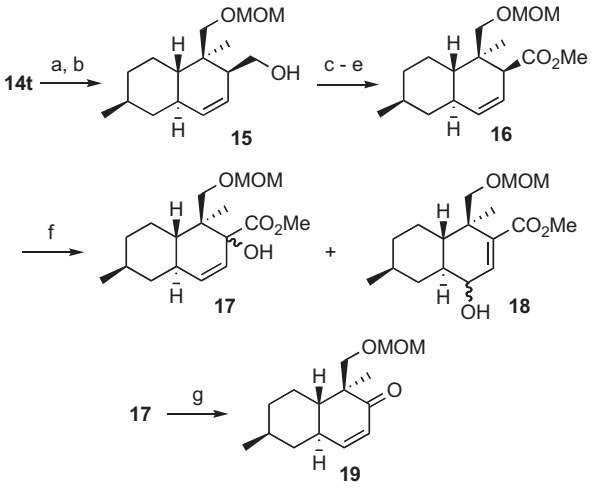


Scheme 2. Synthesis of triene **13**. Reagents and conditions: (a) $HO(CH_2)_2OH$, *p*-TsOH·H_2O, benzene; (b) O_3 then $NaBH_4$, MeOH, CH_2Cl_2; (c) 0.5 N HCl, THF; (d) TBSCl, imidazole, 4-DMAP, CH_2Cl_2, 43% from **6**; (e) 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, $CrCl_2$ (0.6 equiv), Mn (6 equiv), LiI (4 equiv), TMSCl (6 equiv), THF; (f) (*E*)-(3-bromoallyloxy)(*tert*-butyl) diphenylsilane, $Pd_2(dba)_3$·$CHCl_3$, Ph_3P, 1 N NaOH, THF; (g) 0.5 N HCl, THF, 83% from **7**; (h) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, 86%; (i) $Ph_3PC(Me)CO_2Et$, benzene, 99%; (j) DIBAH, THF, 99%; (k) MnO_2, CH_2Cl_2, quant.



Scheme 3. Separation of diastereomers and the stereochemistries.



Scheme 4. Reagents and conditions: (a) MOMCl, $^iPr_2NEt$, CH_2Cl_2, quant.; (b) TBAF, THF, 93%; (c) DMP, $NaHCO_3$, CH_2Cl_2, 94%; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH/THF (3/1); (e) CH_2N_2, Et_2O, 98% (2 steps); (f) KHMDS, O_2, $(EtO)_3P$, THF, 27% for **17**, 35% for **18**; (g) $LiBH_4$ then $NaIO_4$, 5% H_3PO_4 (aq), THF, 52%.

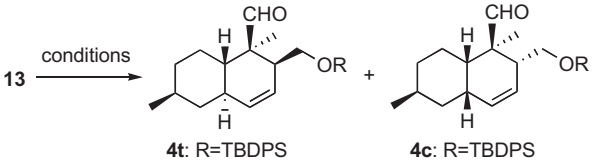
mixture of the trans-isomer **4t** and the cis-isomer **4c** in 36% yield (entry 1). When the reaction was conducted in the presence of aluminum-based Lewis acids,[8] good results were obtained (entries 2–5). The best result was achieved by using Me_2AlCl to give an inseparable 8:1 mixture of **4t**/**c** in 92% yield (entry 5) (Table 1).

Separation of the diastereoisomers and structure determination were accomplished in the next stage. Thus, reduction of the **4t**/**c** mixture with $NaBH_4$ provided the chromatographically separable **14t** and **14c** in 79% and 10% yield, respectively. The stereochemistries were determined by NOE experiments as shown in Scheme 3.

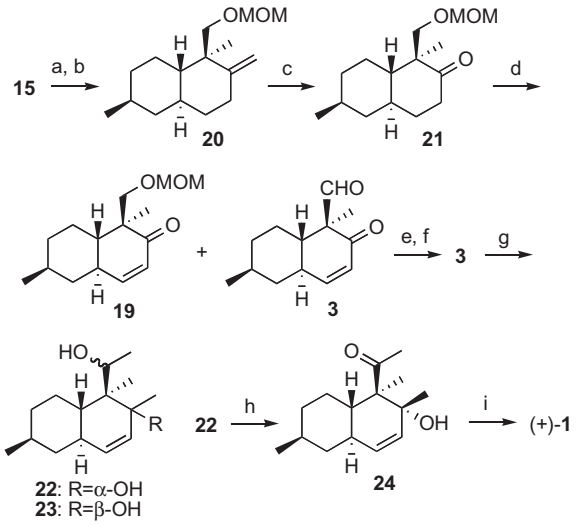
With the desired octahydronaphthalene **14t** in hand, we next examined its conversion to the enone **19**. MOM protection of the primary alcohol moiety in **14t** followed by desilylation gave **15** which was converted to the methyl ester **16** in good overall yield. Treatment of **16** with KHMDS, O_2, and triethylphosphite in THF[9] produced a separable mixture of the α-hydroxy ester **17**[10] and the γ-isomer **18**[10] in 27% and 35% yield, respectively. The desired α-isomer **17** was reduced with $LiBH_4$ and the resulting diol was oxidatively cleaved by $NaIO_4$ to give the enone **19** in 52% yield. To improve the yield of **19** from the methyl ester **16**, we examined several reaction conditions for the oxidative cleavage; however, we were unable to effect a conversion in greater than 14% yield (the overall yield of **19** from **15** was 13% for five steps). These unsuccessful results therefore led us to explore another synthetic route for obtaining the key enone **3** efficiently. (Scheme 4).

Since it was thought that the presence of a double bond would cause a side reaction(s) and lower yields, the double bond in **15** was reduced, and the resulting primary alcohol was dehydrated by employing the Nishizawa-Grieco protocol[11] to give **20** with an exocyclic olefin moiety. Ozonolysis followed by reductive work-up produced the ketone **21**, which was treated with IBX[12] in DMSO/toluene to provide a mixture of the two enones, **19** and **3** (11:1 from ^{1}H NMR). The crude mixture was then subjected to acidic hydrolysis (of the MOM ether in **19**) and oxidation with Dess–Martin periodinane (DMP) to produce the key intermediate **3** in 63% overall yield from **15** in 6 steps. Introduction of the two methyl groups onto the C3 aldehyde and the C13 ketone carbonyls in **3** was achieved by treatment with MeLi to give a separable mixture of **22** (1:1 inseparable mixture at C3) and **23** (3:1 inseparable mixture at C3) in 80% and 11% yield, respectively. As for the stereochemical outcome at C13, the preferential introduction of the methyl group from the *si*-face would be attributed to the presence of α-methyl at C4, which would prevent an approach of the methyl from the *re*-face. Thus, another key step for the construction of the

Table 1
Intramolecular Diels–Alder reaction of **13**



Entry	Solvent	Additive (equiv)	Temp (°C)	Time (h)	Yield (%)	**4t**:**4c**
1	Toluene	Methylene blue	150	48	36	2:1
2	CH_2Cl_2	Me_3Al (1.5)	−78 to 0	1.5	52	13.5:1
3	CH_2Cl_2	Et_2AlCl (0.5)	−78 to 0	2	78	10:1
4	CH_2Cl_2	$EtAlCl_2$ (0.5)	−78 to −15	18	69	9:1
5	CH_2Cl_2	Me_2AlCl (1.5)	−78 to 0	8.5	92	8:1



Scheme 5. Reagents and conditions: (a) H_2, Pd–C, EtOH, 96%; (b) $^nBu_3P$, *o*-nitrophenyl selenocyanate then 30% H_2O_2 (aq), $NaHCO_3$, THF, quant.; (c) O_3, Me_2S, MeOH, CH_2Cl_2, 87%; (d) IBX, DMSO, toluene; (e) 6 N HCl, THF; (f) DMP, CH_2Cl_2, 75% from **21**; (g) MeLi, THF, 80% for **22**, 11% for **23**; (h) TPAP, NMO, 4 Å MS, CH_2Cl_2, 92%; (i) LDA, (1*H*-benzo[*d*][1,2,3]triazol-1-yl)methanol, THF, 95%.

C13 quaternary stereogenic center was realized. Oxidation of **22** with TPAP and NMO in the presence of 4 Å MS provided the hydroxy ketone **24** as a single product in 92% yield. Finally, the aldol condensation using LDA and (1*H*-benzo[*d*][1,2,3]triazol-1-yl)methanol[13] proceeded cleanly to give aspermytin A (**1**) in 95% yield. The spectral data of synthetic aspermytin A were fully consistent with those of the natural product. We attribute the difference in the magnitude of the optical rotation data {$[\alpha]_D^{28}$ +7.6 (*c* 0.97, $CHCl_3$); lit. $[\alpha]_D^{25}$ +1.2 (*c* 0.102, $CHCl_3$)} to that of the synthetic material having a much higher level of purity[14] (Scheme 5).

In summary, we have completed the first total synthesis of optically pure (+)-aspermytin A (**1**) using a diastereoselective Me_2AlCl-mediated IMDA reaction and a substrate-controlled construction of an allylic quaternary stereogenic center as the key steps. In addition, the absolute structure of aspermytin A was unambiguously established by total synthesis. Our synthetic studies described here may contribute to the development of a new type of anti-Alzheimer agents.

Acknowledgments

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