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Stereoselective Total Synthesis of (±)-Antheridic Acid

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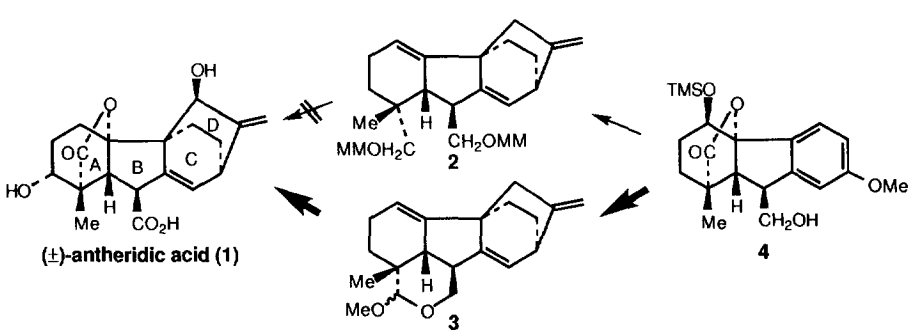
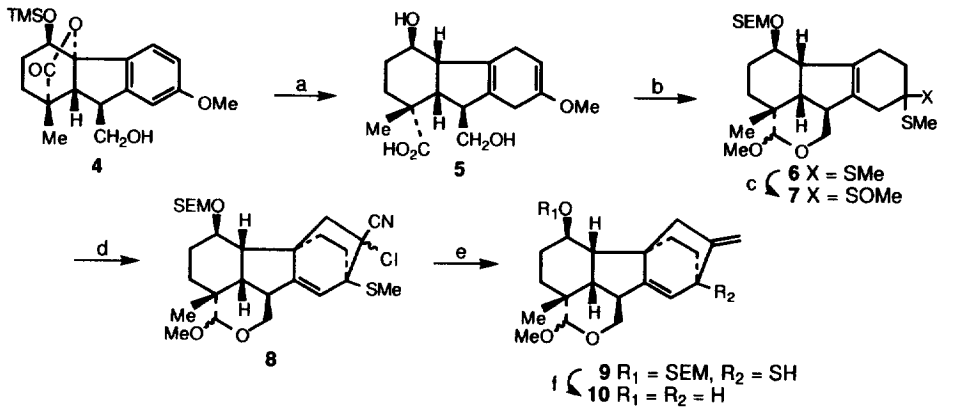
Abstract: A method for the total synthesis of (±)-antheridic acid was established.

Antheridic acid (antheridiogen An, **1**), possibly biogenetically derived from gibberellins, is structurally very congested, rigid and unique diterpenoid.[2] Functional groups are intricately situated among eight asymmetric centers. The unique structure of this compound and its interesting biological activity make its synthesis a challenging objective.[3,4] A stereoselective route from hydrofluorene derivative **4**[5] to tetracyclic compound **2** possessing an antheridic acid framework was previously reported.[6] Attempts to make dimethoxymethyl ether **2** into a more advanced intermediate for total synthesis were not successful[7] and consequently a new route to achieve this purpose was sought. This communication describes a new route through methylacetal **3** for the highly stereocontrolled total synthesis of (±)-antheridic acid (**1**).



Starting material **4**[5] was converted by hydrogenolysis followed by Birch reduction to carboxylic acid **5** having an A/B *cis* juncture, crucial for intermolecular Diels-Alder reaction in a later stage (Scheme I). Thioketalization and concomitant lactonization followed by the ordinary three step transformations gave thioketal **6**, whose selective oxidation by *m*CPBA gave sulfoxide **7**. The Diels-Alder reaction between 2-chloroacrylonitrile and the diene, formed by the thermolysis of sulfoxide **7**, was carried out diastereoselectively in one pot to afford adduct **8** in good yield.[8] The adduct **8** was then converted to intermediate **10** using the efficient seven step sequence, as previously reported.[6]

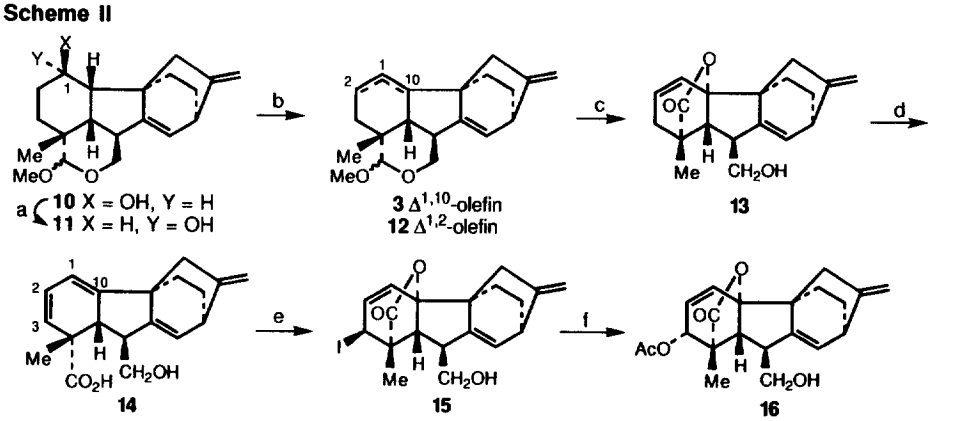
Scheme I



Reagents: a) i) aq. $HClO_4$, H_2, 10% Pd-C; ii) NaOH, EtOH then Na-NH_3, -34°C; b) i) MeSH, *p*-TsOH (cat.); ii) $Me_3SiCH_2CH_2OCH_2Cl$ (SEMCl), *i*-Pr_2NEt; iii) DIBAL, -78°C; iv) MeOH, $(MeO)_3CH$, *p*-TsOH (cat.),69% in 6 steps; c) *m*CPBA, -78°C; d) Et_3N, 130°C then $CH_2C(CN)Cl$, 110°C, 76% from **6**; e) i) DIBAL, -78°C; ii) $NaBH_4$, -5°C; iii) Ac_2O, Py; iv) Li-NH_3,-34°C; f) i) Ac_2O, Py; ii) c.HCl-MeOH, 8°C;iii) Li-NH_3, -34°C, 72% in 7 steps.

Functionalization of the A ring was then carried out starting from alcohol **10** as shown in Scheme II. The usual dehydration sequence (methanesulfonation followed by DBU treatment) on β-alcohol **10** gave an inseparable mixture of $\Delta^{1,10}$-olefin **3** and $\Delta^{1,2}$-olefin **12**, in a 29:71 ratio. Unfortunately, the major isomer **12** could not be transformed to a more advanced intermediate and then an alternative route for obtaining $\Delta^{1,10}$-olefin **3** in acceptable yield was investigated. By PCC oxidation followed by stereoselective reduction with Super-Hydride®,[9] the β-alcohol **10** was converted to α-alcohol **11**, which was dehydrated as above to give the $\Delta^{1,10}$-olefin **3** exclusively in excellent yield. The methylacetal moiety in **3** was transformed to the corresponding hydroxycarboxylic acid in two steps and the resulting product was lactonized by iodolactonization-dehydroiodination to give **13**. The introduction of an α-hydroxy group at the C-3 position was achieved regio- and stereoselectively by the following three simple steps:[10] 1) lactone **13** was converted to tetraenic acid **14** by the treatment with LDA in THF,[4] 2) iodolactonization of **14** with iodine-NaOH-Na_2CO_3

Scheme II

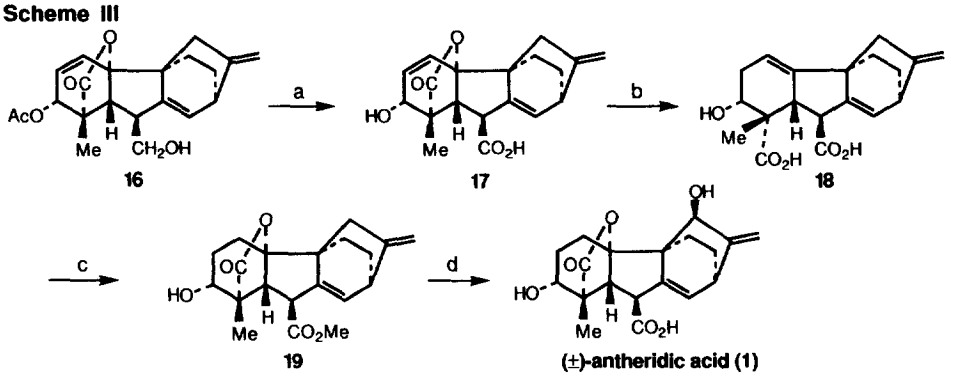


Reagents: a) i) PCC; ii) Super-Hydride®; b) i) MsCl, DMAP; ii) DBU, 110°C, 86% from **10**; c) i) 1NHCl-THF; ii) $NaClO_2$-NaH_2PO_4; iii) I_2, $NaHCO_3$ aq.; iv) DBU, 68°C,67% in 4 steps; d) LDA, -78°C, 100%; e) I_2, Na_2CO_3-NaOH aq.; f) AcONa, HMPA, 75°C, 92% in 2 steps.

aq. afforded **15**[11] as the sole product,[12] and 3) S_N2 substitution reaction of iodolactone **15** with NaOAc in HMPA afforded acetate **16**.[13,14]

The final stage of the synthesis of (±)-antheridic acid (**1**) was shown in Scheme III. The primary alcohol in **16** was oxidized to the carboxylic acid and the acetate was hydrolyzed to give hydroxy acid **17**. $\Delta^{1,2}$ -Double bond in **17** was selectively saturated by the procedure described previously,[15] to give (±)-methyl 15-deoxyantheridate (**19**) *via* dicarboxylic acid **18**. Finally, allylic oxidation of **19** with SeO_2 followed by hydrolysis of the methyl ester according to Mander's procedure[4a] completed the total synthesis of (±)-antheridic acid (**1**). The spectral properties were identical with those in the literature.[4a]

Scheme III



Reagents: a) i) PDC; ii) $NaClO_2$-NaH_2PO_4; iii) K_2CO_3, MeOH; b) LDA, Li, NH_3, -78°C; c) i) I_2, $NaHCO_3$ aq.; ii) CH_2N_2, 65% from **16**; iii) *n*-Bu_3SnH; d) i) SeO_2, *t*-BuOOH; ii) LiOH, MeOH aq.,73% in 3 steps.

The present study demonstrated a highly stereoselective synthesis of the antheridium inducing factor, (±)-antheridic acid.

References and Notes

1. Current address: *Department of Chemistry, Central Research Laboratories, Kaken Pharm. Co., Ltd. 14, Shinomiya Minami-kawara-cho Yamashina-ku Kyoto, 607, Japan*
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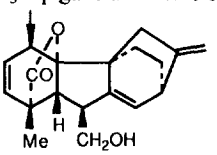
7. Owing to acid-labile of the three double bonds in intermediate **2**, the two methoxymethyl ether protecting groups could not be cleaved.

8. ΔE of two different transition states (dienophile approaching from β side to give the desired product and from α side to give undesired product) was about 2.9 kcal/mol calculated by the MacroModel Version 4.0.
9. It is of interest to note that $LiAlH_4$ reduction of ketone afforded α-alcohol **11** predominantly but that $NaBH_4$ reduction gave β-alcohol **10** as the major product.
10. Allylic oxidation at the C-3 position in **13** using a conventional reagent such as SeO_2, MnO_2, O_2-*hv*-sensitizer, and CrO_3-methylpyrazole was unsucceeded.
11. Compound **15**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.43 (1H, brd, *J* = 9.2 Hz), 1.51 (3H, s), 1.53~1.79 (4H, m), 1.83 (1H, dq, *J* = 15.6, 2.8 Hz), 2.31 (1H, brd, *J* = 15.5 Hz), 2.83 (1H, dq, *J* = 9.9, 3.3 Hz), 3.04 (1H, d, *J* = 9.9 Hz), 3.13 (1H, dt, *J* = 6.5, 2.6 Hz), 3.71 (1H, ddd, *J* = 11.8, 9.2, 3.9 Hz), 3.96 (1H, brd, *J* = 11.4 Hz), 4.63 (1H, q, *J* = 1.8 Hz), 4.85 (1H, brd, *J* = 1.3 Hz), 5.01 (1H, d, *J* = 3.9 Hz), 6.12 (1H, d, *J* = 9.4 Hz), 6.17 (1H, dd, *J* = 6.4, 2.6 Hz), 6.26 (1H, dd, *J* = 9.3, 3.9 Hz).; IR (KBr): 3416, 2944, 1780, 1649 cm^{-1}.; HRMS (EI) *m/z*: 424.0529 (M^+); Calcd for $C_{19}H_{21}O_3I$; 424.0535.
12. Treatment of **14** with iodine-$NaHCO_3$ aq. gave a mixture of **15** and **20**,[16] in 82:18 ratio.



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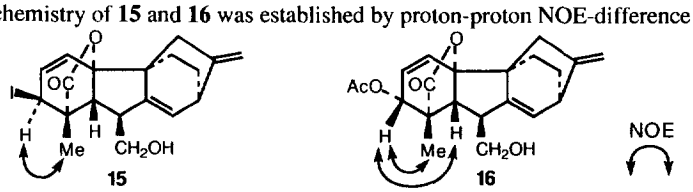
13. Compound **16**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, s), 1.39 (1H, dd, *J* = 9.9, 3.1 Hz), 1.54 (1H, m), 1.64 (1H, m), 1.70~1.83 (3H, m), 2.14 (3H, s), 2.34 (1H, brd, *J* = 15.3 Hz), 2.77 (1H, dq, *J* = 9.8, 2.9 Hz), 2.85 (1H, d, *J* = 9.8 Hz), 3.14 (1H, dt, *J* = 6.5, 2.6 Hz), 3.66 (1H, ddd, *J* = 11.7, 10.0, 3.4 Hz), 3.93 (1H, dt, *J* = 11.6, 3.0 Hz), 4.63 (1H, brd, *J* = 1.3 Hz), 4.85 (1H, brd, *J* = 1.2 Hz), 5.57 (1H, t, *J* = 2.2 Hz), 5.81 (1H, dd, *J* = 9.5, 2.6 Hz), 6.15 (1H, dd, *J* = 6.5, 2.5 Hz), 6.45 (1H, dd, *J* = 9.5, 1.8 Hz).; IR (KBr): 3424, 2927, 1777, 1729, 1650 cm^{-1}.; HRMS (EI) *m/z*: 328.1322 (M^+); Calcd for $C_{19}H_{20}O_5$; 328.1310.
14. The stereochemistry of **15** and **16** was established by proton-proton NOE-difference spectroscopy.



15 **16**

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16. Compound **20**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.39 (3H, s), 1.37~1.58 (2H, m), 1.76 (1H, m), 1.81~1.89 (2H, m), 2.16 (1H, ddd, *J* = 12.5, 10.2, 5.2 Hz), 2.53 (1H, brd, *J* = 14.7 Hz), 2.66 (1H, dq, *J* = 9.4, 2.9 Hz), 2.76 (1H, d, *J* = 9.5 Hz), 3.15 (1H, dt, *J* = 6.5, 2.8 Hz), 3.63 (1H, m), 3.92 (1H, brd, *J* = 11.3 Hz), 4.66 (1H, q, *J* = 1.4 Hz), 4.87 (1H, brd, *J* = 1.3 Hz), 5.10 (1H, dd, *J* = 2.8, 1.9 Hz), 5.62 (1H, dd, *J* = 9.2, 1.8 Hz), 6.05 (1H, dd, *J* = 9.2, 2.9 Hz), 6.12 (1H, dd, *J* = 6.5, 2.6 Hz).; IR (KBr): 3400, 2937, 1779, 1651 cm^{-1}.

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