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Synthesis of (+)-agelasine D from (+)-manool

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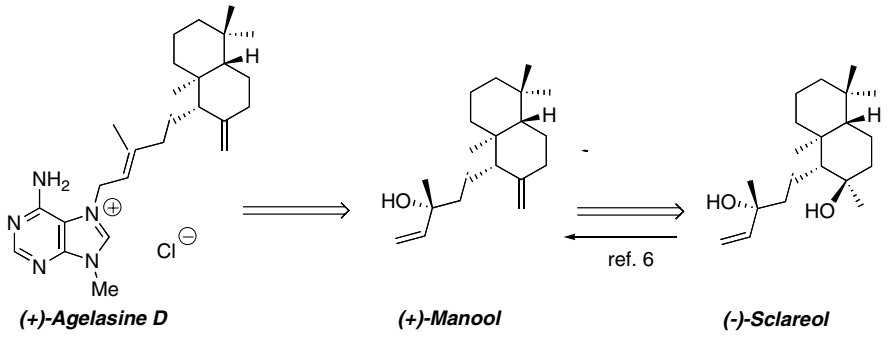
Abstract—(+)-Agelasine D, originally isolated from the marine sponge *Agelas nakamurai*, is synthesized for the first time. The terpenoid side chain was readily available from the diterpene alcohol (+)-manool.

Agelasines are 7,9-dialkylpurinium salts isolated from marine sponges. At the present a total of 11 9-methyladeninium salts, agelasine A-I, epiagelasine C, and agelin B, has been isolated from *Agelas* species.[1] All compounds carry a diterpenoid side chain in the adenine 7-position. Until now, only (−)-agelasine A,[2] (−)-agelasine B,[3] and (±)-agelasine F,[4] have been synthesized. The agelasines are associated with bioactivities such as antimicrobial and cytotoxic effects as well as contractive responses of smooth muscles and inhibition of Na, K-ATPase.[1,5] We herein report the first synthesis of (+)-agelasine D.[1a,d] The starting material for the terpenoid side chain is the readily available (+)-manool, and, at least formally, also the less expensive (−)-sclareol[6] (Scheme 1).

Synthesis of agelasines requires regioselective alkylation of an adenine derivative to give a 7,9-dialkylated purinium salt. However, alkylation on 9-substituted adenine gives mainly 1,9-dialkyl derivatives, and when 7-alkyladenines are reacted with alkyl halides, the second *N*-substituent is preferably introduced on *N*-3.[7] Treatment of *N*-alkoxy-9-methyl-9*H*-purin-6-amines[8,9] with alkylating agents results, on the other hand, in the desired alkylating pattern.[7]

The alkyl halide necessary for the introduction of the *N*-7 terpenoid substituent in agelasine D was generated by bromination of (+)-manool employing phosphorus tribromide (Scheme 2).[10] The best *E*/*Z*-selectivity obtained was 85:15 and the crude bromide **1** was used directly for alkylation of the purine derivative **2**. Attempts to generate the pure *E* allylic bromide **1** by treatment of manoyl acetate with TMS–bromide and zinc iodide[11] gave less satisfactory results.



Scheme 1.

Keywords: Allylation; Halogenation; Marine metabolites; Purines; Terpenes and terpenoids.
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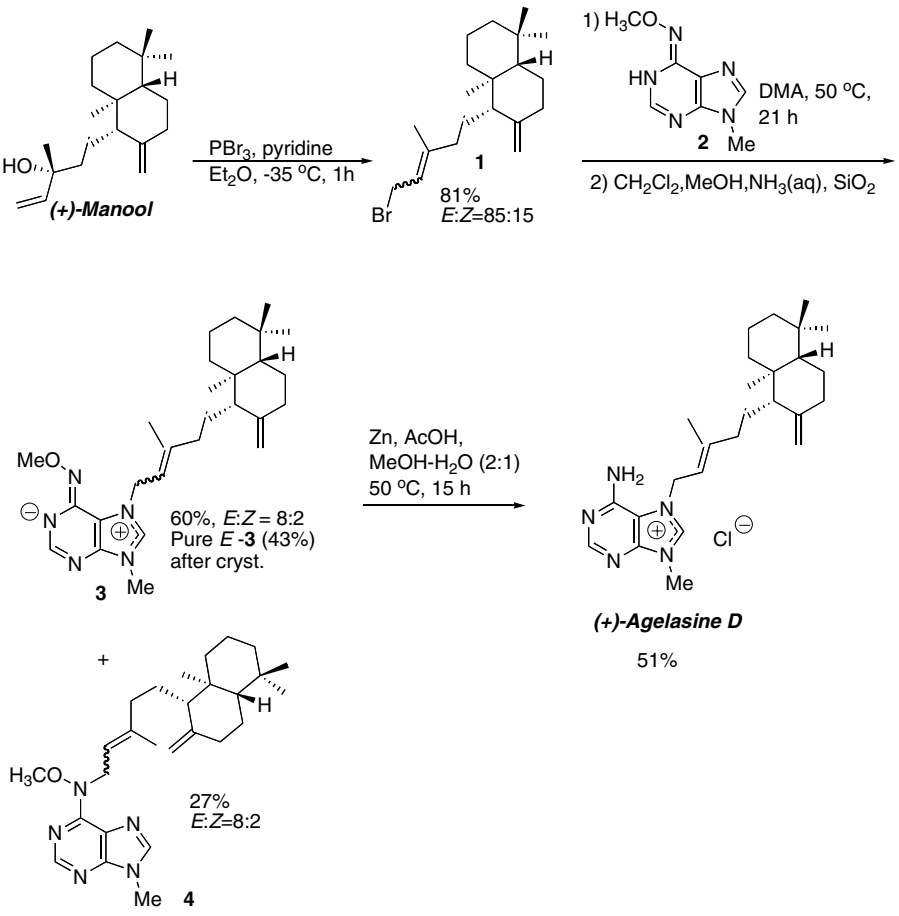

Scheme 2.

As in the previously reported syntheses of agelasines,[2–4] alkylation of the methoxyadenine **2** gave a mixture of the desired product **3** as well as the N^6 alkylated isomer **4**[12] (Scheme 2). After separation of the products by flash chromatography employing an eluent mixture containing ammonia, the major product was isolated as an *E*/*Z* mixture of the betaine **3**. The pure *E*-**3** was obtained after crystallization from EtOAc. Finally the *N*-methoxy group was removed reductively to give the target compound, (+)-agelasine D.[13]

Agelasine D is currently under testing for antimycobacterial activity. Both agelasine F[5d] as well as sclareol[14] (structure, see Scheme 1) are previously reported to be active against *Mycobacterium tuberculosis*.

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9. In solution, compound **1** mainly exists as the tautomer shown in Scheme 2.
10. Synthesis of the bromide **1**: A solution of PBr_3 (0.33 mL, 3.5 mmol) in dry diethyl ether (5 mL) was added dropwise to a stirred solution of (+)-manool (1.02 g, 3.5 mmol) and pyridine (0.28 mL, 3.5 mmol) in dry diethyl ether (5 mL) at −35 °C. After stirring for 1 h at −35 °C, the mixture was diluted with diethyl ether (10 mL), extracted with 10% aq HCl (5 mL) and satd aq $NaHCO_3$ (2×5 mL), dried ($MgSO_4$), and evaporated in vacuo at ambient temperature to give the crude bromide **1**; yield 1.06 g (85%) oil, *E*/*Z* ratio: 85:15. *E*-**1**: ^{1}H NMR ($CHCl_3$, 300 MHz): δ 0.66 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 1.1–2.4 (m, 16H), 1.70 (s, 3H, CH_3), 4.00 (d, 2H, *J* 8.4 Hz, CH_2), 4.47 (br s, 1H, CH_2=), 4.81 (br s, 1H, CH_2=), 5.48 (br t, 1H, CH=, *J* 8.4 Hz); *Z*-**1**: ^{1}H NMR ($CHCl_3$, 300 MHz): δ 0.66 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 1.08–2.4 (m, 16H), 1.75 (s, 3H, CH_3), 3.94 (d, 2H, *J* 8.4 Hz, CH_2), 4.56 (br s, 1H, CH_2=), 4.86 (br s, 1H, CH_2=), 5.48 (br t, 1H, CH=, *J* 8.4 Hz); HRMS found 355.1838, calcd for $C_{20}H_{34}{}^{81}Br$ [$(M+H)^+$] 355.1823.
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12. Synthesis of the compounds **3** and **4**: A mixture of compound **1** (405 mg, 2.26 mmol) and the allylic bromide **2** (1.038 g, 2.94 mmol) in dry DMA (7 mL) was stirred at 50 °C under argon for 21 h. The reaction mixture was evaporated and the products were separated by flash chromatography on silica gel eluting with CH_2Cl_2, followed by EtOAc–EtOH–NH_3 (aq) (160:5:2), EtOAc–EtOH–NH_3 (aq) (40:10:1), and CH_2Cl_2–MeOH–NH_3 (aq) (35:5:1). Compound **3**: Yield 636 mg (60%) as an *E*/*Z* mixture. Crystallization from EtOAc afforded 436 mg (43%) pure *E*-**3**, mp 195–197 °C, $[\alpha]_D^{20}$ +23.8 (*c* 2, $CHCl_3$). ^{1}H NMR ($CHCl_3$, 300 MHz): δ 0.64 (s, 3H, CH_3), 0.76 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.93–2.38 (m, 16H), 1.76 (s, 3H, CH_3), 3.72 (s, 3H, NCH_3), 3.81 (s, 3H, OCH_3), 4.44 (br s, 1H, CH_2=), 4.79 (br s, 1H, CH_2=), 5.03 (br d, 2H, *J* 7.3 Hz, CH_2), 5.36 (br t, 1H, *J* 7.3 Hz, CH=), 7.68 (s, 1H), 7.76 (s, 1H); HRMS: found 452.3402, calcd for $C_{27}H_{42}N_5O^+$ 452.3383. Compound **4**: Yield 278 mg (27%) oil, as an 8:2 *E*/*Z* mixture. ^{1}H NMR ($CHCl_3$, 300 MHz, *E*-**4** shown): δ 0.57 (s, 3H, CH_3), 0.71 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.80–2.28 (m, 16H), 1.71 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.87 (s, 3H, NCH_3), 4.41 (br s, 1H, CH_2=), 4.65–4.71 (m, 3H), 5.34 (br t, 1H, *J* 5.8 Hz, CH=), 7.75 (s, 1H, H-8), 8.41 (s, 1H, H-2); HRMS: found 452.3360, calcd for $C_{27}H_{41}N_5O$ 452.3383.
13. Synthesis of (+)-agelasine D: A mixture of the betaine **3** (138 mg, 0.31 mmol) and Zn powder (186 mg, 2.84 mmol) in MeOH (5 mL), water (1 mL), and concd acetic acid (0.2 mL) was stirred under argon at 60 °C for 15 h. After cooling, the mixture was filtered and the solid washed with 25 mL MeOH. The filtrate was mixed with MeOH (10 mL), satd aq NaCl (1.5 mL), and water (10 mL) and stirred for 1 h before evaporation. The residue was dissolved in satd aq NaCl (5 mL) and water (5 mL), extracted with CH_2Cl_2 (5×25 mL), dried ($MgSO_4$), and evaporated. The product was purified by flash chromatography on silica gel eluting with CH_2Cl_2 followed by CH_2Cl_2–MeOH (100:1), CH_2Cl_2–MeOH (40:1), and CH_2Cl_2–MeOH (4:1); yield 69 mg (51%), mp 128–130 °C, colorless crystals; $[\alpha]_D$ +9.4 (*c* 1.0, CH_3OH); (lit.[1a] $[\alpha]_D^{20}$ +10.4 (*c* 1.1, CH_3OH). ^{1}H NMR ($CHCl_3$, 300 MHz): δ 0.60 (s, 3H, Me), 0.74 (s, 3H, Me), 0.82 (s, 3H, Me), 0.7–2.3 (m, 16H), 1.81 (s, 3H, Me), 4.05 (br s, 3H, NMe), 4.38 (br s, 1H), 4.74 (br s, 1H), 5.36 (br t, 1H, CH=, *J* 6.3 Hz), 5.66 (br d, 2H, CH_2, *J* 6.3 Hz), 7.09 (br s, 2H, NH_2), 8.43 (s, 1H), 10.62 (s, 1H). HRMS: found 422.3263, calcd for $C_{26}H_{40}N_5{}^+$ 422.3278. ^{13}C NMR data were also in good agreement with those reported before.[1a]
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