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Note

Synthesis and Absolute Configuration of MQ-A_3 [1-(14′-Methylhexadecanoyl) pyrrolidine], a Novel Aliphatic Pyrrolidine Amide from the Tropical Convolvulaceous Species

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A novel pyrrolidine amide (MQ-A_3) isolated from the tropical convolvulaceous species was synthesized in 5 steps by starting from commercially available 12-bromododecanol and (*S*)-2-methylbutylbromide. The absolute configuration of the natural product was confirmed by a comparison of the specific rotation values.

Key words: pyrrolidine amide; *Ipomoea aquatica*; *Merremia quinquefolia*; synthesis; absolute configuration

The Convolvulaceae comprise nearly two thousand predominantly tropical species. Some of them are very important because of their use for foods, the leaves of *Ipomoea aquatica*, for example, being used as a vegetable in Southeast Asia. Although a wide variety of low-molecular-weight secondary metabolites have been isolated,[1] their biological activities are hardly known. In 1999, Eich and his co-workers isolated MQ- A_1-A_5, B_2 and B_4 from the roots and aerial vegetative parts of two tropical convolvulaceous, *I. aquatica* and *Merremia quinquefolia* as well as from the seeds of *M. quinquefolia*.[1] The structures of the alkaloids were identified by an extensive spectroscopic analysis as pyrrolidine amides with branched or linear saturated aliphatic acyl moieties. This type of pyrrolidine amide with a branched saturated acyl group had not been described. In these alkaloids, only MQ-A_3 (**1**) was reported to be distributed in all the parts (roots, aerial parts and seeds) of *M. quinquefolia* and *I. aquatica*. In addition, MQ-A_3 (**1**) was reported to be optically active, but with no information available about its absolute configuration. We decided to synthesize a large amount of optically active MQ-A_3 (**1**) to determine its absolute configuration and to clarify its biological activity. This paper describes the synthesis of (+)-MQ-A_3 (**1**).

The synthetic procedure for MQ-A_3 (**1**) is shown in the scheme. We chose commercially available 12-bromododecanol (**2**) and (*S*)-2-methylbutylbromide (**3**) as starting materials. Protection of the hydroxy group of **2** as a tetrahydropyranyl (THP) ether gave bromide **4**. Bromide **4** was treated with the Grignard reagent derived from **3** (>99% ee, purchased from Aldrich) in the presence of dilithium tetrachlorocuprate[2] to give **5**. Deprotection of THP ether of **5** with concomitant oxidation of the resulting alcohol was executed with Jones' reagent in a single step to give acid **6**. The final step was the acylation of pyrrolidine with **6**. Accordingly, acid **6** was firstly converted to the corresponding acid chloride with thionyl chloride, and then treated with pyrrolidine in the presence of pyridine to give (+)-MQ-A_3 (**1**), $[\alpha]_D^{22} = +3.8°$ (*c* 0.68, $CHCl_3$); lit.[1] $[\alpha]_D^{20} = +5°$ (*c* 0.4, $CHCl_3$). The overall yield was 65% from **2** (5 steps). Since naturally occurring MQ-A_3 has been reported to show $[\alpha]_D^{20} = +5°$ (*c* 0.4, $CHCl_3$), the absolute configuration of natural MQ-A_3 (**1**) must be *S*. This synthesis was short and efficient to supply a large amount of **1**.

In conclusion, (+)-MQ-A_3 (**1**) was synthesized, and the absolute configuration of **1** was concluded to be *S*. The biological activity of **1** can now be clarified by using the synthetic sample.

Materials and Methods

^1H- and ^{13}C-NMR spectra were recorded by a Jeol JNM-400A spectrometer (in $CDCl_3$, $\delta = 7.26$ for ^1H, $\delta = 77.0$ for ^{13}C as the internal standard). IR spectra were recorded by a Shimadzu FTIR-8200A spectrometer, and MS data were recorded by a Jeol JMS-AX-505HA spectrometer. Optical rotation values were measured with a Jasco DIP-140 polarimeter, and Wakogel C-200 was used for column chromatography.

2-(12′-Bromododecyloxy)-tetrahydropyrane (**4**). To a stirred solution of **2** (1.46 g, 5.51 mmol) and dihydropyrane (DHP; 603 μl, 6.61 mmol) in CH_2Cl_2 (20 ml), a catalytic amount (*ca.* 10 mg) of *p*-TsOH was added at room temperature. After stirring for 2

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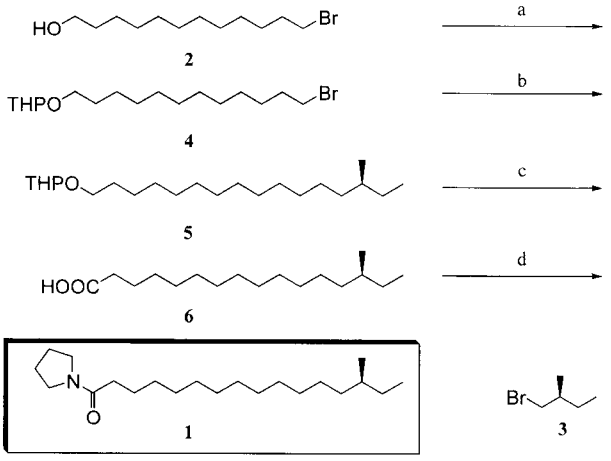

Scheme. Synthesis of MQ-A_3 (**1**).

(a) DHP, *p*-TsOH, CH_2Cl_2, r.t., 2 h (95% yield). (b) **3**, Mg, Et_2O, then Li_2CuCl_4, THF, −15°C-r.t., overnight (95% yield). (c) Jones' reagent, acetone, 0°C-r.t., 1 h (84% yield). (d) (1) $SOCl_2$, DMF, benzene, 100°C, 3 h; (2) pyrrolidine, pyridine, 0°C-r.t., 1 h (92% yield).

h, the mixture was poured into a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted several times with EtOAc, and the combined organic extracts were dried ($MgSO_4$). Concentration in vacuo followed by silica gel column chromatography (hexane/EtOAc = 100/1) gave 1.82 g (95%) of **4** as a colorless oil. NMR δ_H ($CDCl_3$): 1.25–1.86 (26H, m, 3,4,5,2′,3′,4′,5′,6′,7′,8′,9′,10′,11′-CH_2), 3.35 (1H, dt, J = 16.3, 7.1 Hz, 1′-C*H*H), 3.38 (2H, t, J = 6.8 Hz, 12′-CH_2), 3.49 (1H, m, 6-C*H*H), 3.71 (1H, dt, J = 16.3, 7.1 Hz, 1′-CH*H*), 3.85 (1H, ddd, J = 7.3, 7.8, 11.0 Hz, 6-CH*H*), 4.55 (1H, br.dd, J = 2.7, 4.4 Hz, 2-*H*). IR ν_{max} (film) cm^{-1}: 2925 (C-H), 2855 (C-H), 1455, 1440, 1350, 1200, 1135, 1120, 1080, 1035 (C-O), 995, 905, 870, 815, 720, 650. HRFABMS m/z ($M+H^+$): calcd. for $C_{17}H_{34}BrO_2$, 349.1743; found, 349.1742. *Anal.* Found; C, 58.32; H, 9.40%. Calcd. for $C_{17}H_{33}BrO_2$: C, 58.45; H, 9.52%.

(14′R)-2-(14′-Methylhexadecyloxy)-tetrahydropyrane (**5**). To a stirred solution of **4** (500 mg, 1.43 mmol) in dry THF (3 ml), the Grignard reagent [prepared from (*S*)-2-methylbutylbromide (**3**), >99% ee, purchased from Aldrich] (865 mg, 5.73 mmol) and magnesium (139 mg, 5.73 mmol) in dry Et_2O (10 ml)] were added dropwise at -15°C under argon. To the mixture, Li_2CuCl_4 in THF (0.50 M, 0.50 ml, 0.25 mmol) was added in one portion. The mixture was stirred overnight with gradual warming to room temperature, poured into water, and extracted several times with hexane. The combined organic extracts were washed with water and dried ($MgSO_4$). Concentration *in vacuo* followed by silica gel column chromatography (hexane/EtOAc = 150/1) gave 462 mg (95%) of **5** as a colorless oil. $[\alpha]_D^{22}$ +3.3° (*c* 0.97, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.84 (3H, d, J = 6.4 Hz, 14′-CH_3), 0.85 (3H, t, J = 7.1 Hz, 16′-CH_3), 1.11 (1H, m, 14′-*H*), 1.25–1.87 (32H, m, 3,4,5,2′,3′,4′,5′,6′,7′,8′,9′,10′,11′,12′,13′,15′-CH_2), 3.38 (1H, dt, J = 16.3, 7.1 Hz, 1′-C*H*H), 3.50 (1H, m, 6-C*H*H), 3.73 (1H, dt, J = 16.3, 7.1 Hz, 1′-CH*H*), 3.86 (1H, ddd, J = 7.3, 7.8, 11.0 Hz, 6-CH*H*), 4.58 (1H, br.dd, J = 2.7, 4.4 Hz, 2-*H*). IR ν_{max} (film) cm^{-1}: 2930 (C-H), 2855 (C-H), 1455, 1350, 1200, 1120, 1080, 1035 (C-O), 980, 905, 870, 815. HRFABMS m/z ($M+H^+$): calcd. for $C_{22}H_{45}O_2$, 341.3421; found, 341.3422. This compound was used in the next step without further purification.

(R)-14-Methylhexadecanoic acid (**6**). To a stirred solution of **5** (310 mg, 0.91 mmol) in acetone (3 ml), Jones' reagent (2.67 M, 1.37 ml, 3.65 mmol) was added dropwise at 0°C. The mixture was stirred for 1 h at room temperature, poured into water, and extracted several times with EtOAc. The combined organic extracts were washed with successively water and brine, and dried ($MgSO_4$). Concentration *in vacuo* followed by silica gel column chromatography (hexane/EtOAc = 15/1) gave 208 mg (84%) of **6** as colorless wax. Mp 30–31°C. $[\alpha]_D^{22}$ +4.1° (*c* 0.59, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.84 (3H, d, J = 6.4 Hz, 14-CH_3), 0.85 (3H, t, J = 7.1 Hz, 16-CH_3), 1.10 (1H, m, 14-*H*), 1.25 (22H, m, 4,5,6,7,8,9,10,11,12,13, 15-CH_2), 1.63 (2H, m, 3-CH_2), 2.17 (1H, s, *H*OOC), 2.34 (2H, t, J = 7.0 Hz, 2-*H*). IR ν_{max} (film) cm^{-1}: 2950 (*HO*-C=O), 1715 (O-C=*O*), 1470, 1430, 1410, 1375, 1275, 1250, 1230, 1205, 1190 (C-O), 1105, 1070, 915, 720, 680, 535. HRFABMS m/z ($M+H^+$): calcd. for $C_{17}H_{35}O_2$, 271.2638; found: 271.2598. *Anal.* Found; C, 75.55; H, 12.68%. Calcd. for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67%.

(+)-MQ-A_3 (**1**). To a stirred solution of **6** (208 mg, 0.77 mmol) in benzene (1 ml), $SOCl_2$ (1 ml) and 1 drop (*ca.* 10 mg) of DMF were added. After stirring for 3 h at 100°C, the mixture was concentrated *in vacuo*. The residue was cooled to 0°C and then dissolved in pyridine (1 ml). To the solution, pyrrolidine (193 μl, 2.31 mmol) was added. The mixture was stirred for 1 h at room temperature and then poured into diluted aqueous HCl. The aqueous layer was extracted several times with EtOAc. The combined organic extracts were washed with successively water and brine, and dried ($MgSO_4$). Concentration *in vacuo* followed by silica gel column chromatography (hexane/EtOAc = 10/1) gave 230 mg (92%) of **1** as a pale yellow oil. $[\alpha]_D^{22}$ +3.8° (*c* 0.65, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.83 (3H, d, J = 6.4 Hz, 14′-CH_3), 0.84 (3H, t, J = 7.1 Hz, 17′-CH_3), 1.10 (1H, m, 14′-*H*), 1.25 (22H, m, 4′,5′,6′,7′,8′,9′,10′,11′,13′,15′-CH_2), 1.64 (2H, m, 3′-CH_2), 1.84 (2H, m, 3-C*H*H, 4-C*H*H), 1.94 (2H, m, 3-CH*H*, 4-CH*H*), 2.24 (2H, t, J = 7.6 Hz, 2′-CH_2), 3.40 (2H, t, J = 6.8, 6.8 Hz, 2-C*H*H, 5-C*H*H), 3.46 (2H, t, J = 6.8, 6.8 Hz,

2-CH*H*, 5-CH*H*). NMR δ_C ($CDCl_3$): 11.4, 19.2, 24.4, 25.0, 26.1, 27.1, 29.45, 29.46, 29.50, 29.53, 29.61, 29.64, 29.66, 29.7, 30.0, 34.4, 34.9, 36.6, 45.5, 46.6, 171.9. IR ν_{max} (film) cm^{-1}: 2925 (C-H), 2850 (C-H), 1650 (N-*C*=*O*), 1430, 1375, 1340, 1225, 1195, 750, 720. HRFABMS *m/z* ($M+H^+$): calcd. for $C_{21}H_{42}NO$, 324.3268; found, 324.3302. *Anal.* Found; C, 77.94; H, 12.89; N, 4.23%. Calcd. for $C_{21}H_{41}NO$: C, 77.95; H, 12.77; N, 4.33%.

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References

1) Tofern, B., Mann, P., Kaloga, M., Jenett-Siems, K., Witte, L., and Eich, E., Aliphatic pyrrolidine amides from two tropical convolvulaceous species. *Phytochemistry*, **52**, 1437–1441, (1999).
2) Fouquet, G., and Schlosser, M., Improved carbon-carbon linking by controlled copper catalysis. *Angew. Chem. Int. Ed. Engl.*, **13**, 82–83, (1974).