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A Concise Synthesis of Storniamide A Nonamethyl Ether [1]

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Abstract: (E,E)-Storniamide A nonamethyl ether is obtained from 3-(3,4,5-trimethoxyphenyl)pyruvic acid and 2-(4-hydroxyphenyl)ethylamine in three steps with an overall yield of 19%. © 1998 Elsevier Science Ltd. All rights reserved.

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Recently, the storniamides A-D (1-4) were isolated as a new group of pyrrole alkaloids from marine sponges of the genus *Cliona* [2]. They showed antibiotic activity against several Gram-positive bacteria.



We have previously reported on a biomimetic synthesis of 3,4-bisaryl-pyrrole-2,5-dicarboxylic acids by oxidative coupling of two molecules of arylpyruvic acid and reaction of the resulting 1,4-diketone with ammonia or a suitable amine [3,4,5]. This methodology can also be applied for the synthesis of storniamide A nonamethyl ether (8) as depicted in Scheme 1.

The synthesis of the pyrroledicarboxylic acid 6 [6] from 3-(3,4,5-trimethoxyphenyl)pyruvic acid (5) was carried out in one pot in THF at -78°C by conversion of 5 into its dianion with *n*-BuLi, followed by consecutive addition of iodine and 2-(4-methoxyphenyl)ethylamine. The product 6 was obtained in 56% yield and converted into the corresponding diamide 7 by treatment with *N*-(3-dimethylaminopropyl)-*N*^{*}-ethyl carbodiimide hydrochloride/*N*-hydroxybenzotriazole (EDCI/HOBt) and concentrated aqueous ammonia in 83% yield. The enamide side chains were attached by heating amide 7 with a large excess of (4-methoxyphenyl)acetaldehyde [7] to 200 °C [8]. Storniamide A nonamethyl ether (8) [6] was obtained as a mixture of the (*E*,*E*)-, (*E*,*Z*)- and (*Z*,*Z*)-isomers in a ratio of 3:4:1. Isomerization of the mixture with iodine in CHCl₃ at 25 °C enriched the (*E*,*E*)-isomer giving a ratio of 6:5:1. The three isomers could be separated by chromatography on a silica gel column (EtOAc/petroleum ether 2:3) to yield the desired (*E*,*E*)-isomer of 8 [6] in 19% overall yield. Experiments to convert (*E*,*E*)-8 into the natural product 1 were as yet unsuccessful.

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Scheme 1. Reagents and conditions: (a) (i) THF, n-BuLi (2.2 equiv), -78 °C; (ii) I₂ (0.5 equiv), -78 °C \rightarrow 25 °C; (iii) p-H₃COC₆H₄CH₂CH₂NH₂(1.7 equiv), 4 Å molecular sieves, reflux; 1 h; (b) CH₃CN, HOBt (4.2 equiv), EDCI (5.5 equiv), NH₄OH, reflux; 1 h; (c) p-H₃COC₆H₄CH₂CHO (12 equiv), 200°C (melt), 4 h.

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References and Notes

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- [6] Selected spectroscopic data: 6: mp 204-205°C. UV (MeOH): λ_{max} (ϵ) = 252.28 nm (26532). IR (KBr): $\tilde{\nu}$ = 3565 (m), 3420 (br., m), 2959 (s), 2835 (m), 1715 (s), 1669 (m), 1586 (s), 1513 (s), 1464 (s), 1425 (s), 1414 (m), 1375 (m), 1351 (m), 1300 (w), 1281 (w), 1241 (s), 1190 (m), 1174 (m), 1127 (s), 1068 (w), 1026 (w), 1003 (m), 925 (w), 904 (w), 883 (w), 824 (w), 784 (w), 754 (w), 718 (w), 699 (w), 667 cm⁻¹ (w). ¹H NMR ([D₆]acetone, 300 MHz): δ 7.22 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 6.41 (s, 4 H), 4.92 (t, J = 7.9 Hz, 2 H), 3.76 (s, 3 H), 3.67 (s, 6 H), 3.64 (s, 12 H), 3.11 (t, J = 7.9 Hz, 2 H). ¹³C NMR ([D₆]acetone, 75 MHz): δ 162.43, 158.96, 152.79, 137.54 (C-O), 131.08, 130.80, 130.60, 130.19 (CH), 124.34, 114.20 (CH), 109.05 (CH), 60.00 (OCH₃), 55.85 (OCH₃), 54.94 (OCH₃), 48.82 (NCH₂), 37.56 (CH₂). EI MS (170°C): *m/z* (rel. intensity) = 621 (1) [M⁺], 577 (6) [M⁺ CO₂], 533 (100) [M⁺ 2 CO₂]. HR EI MS calcd. for C₃₃H₃₅NO₁₁ [M⁺] 621.2210, found 621.2230.

 $(E,E)-8: yellow oil. - UV (CH_3CN): \lambda_{max} (\epsilon) = 223.12 (sh, 43412), 268.41 (23485), 334.52 nm (26986). - IR (KBr): \tilde{\nu} = 3379 (m), 3002 (s), 2936 (s), 2835 (m), 1667 (s), 1651 (s), 1607 (s), 1581 (s), 1504 (s), 1463 (s), 1410 (s), 1340 (s), 1302 (s), 1243 (s), 1177 (s), 1126 (s), 1033 (s), 1005 (s), 944 (s), 843 (s), 757 (s), 666 (m), 528 cm⁻¹ (m). - ¹H NMR (CDCI₃, 300 MHz): <math>\delta$ 7.37 (dd, J = 10.8, 14.6 Hz, 2 H), 7.16 (d, J = 8.6 Hz, 4 H), 7.13 (d, J = 8.4 Hz, 2 H), 7.01 (d, J = 10.9 Hz, 2 H), 6.81 (d, J = 8.8 Hz, 4 H), 6.79 (d, J = 8.7 Hz, 2 H), 6.37 (s, 4 H), 5.46 (d, J = 14.6 Hz, 2 H), 5.01 (t, J = 7.2 Hz, 2 H), 3.85 (s, 6 H), 3.79 (s, 6 H), 3.68 (s, 12 H), 3.68 (s, 3 H), 3.16 (t, J = 7.1 Hz, 2 H). - ¹³C NMR (CDCI₃, 75 MHz): δ 158.68, 158.29, 157.97, 153.40, 137.80 (C-O), 130.62, 130.46, 128.36, 128.28, 126.64, 126.30, 126.06, 120.18, 114.18, 113.70, 113.08, 107.87, 61.01 (OCH₃), 55.27 (OCH₃), 55.14 (OCH₃), 48.67 (NCH₂), 37.55 (CH₂). - ESI MS: *m/z* (rel. intensity) = 1768 (1) [2 M⁺ + H], 922 (28) [M⁺ + K], 906 (72) [M⁺ + Na], 884 (36) [M⁺ + H], 883 (1) [M⁺]. - HR ESI MS: calcd. for C₅₁H₅₃N₃O₁₁ + Na [M⁺ + Na] 906.3578, found 906.3596.

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