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TOTAL SYNTHESIS OF BASTADIN-6, A BROMINATED TYROSINE-DERIVED METABOLITE FROM THE SPONGE *IANTHELLA BASTA*

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Bastadin-6, a 28-membered ring lactam, was synthesized from the known bis-*p*-methoxybenzyl bastadin-2 in 6 steps.

Recently, several novel metabolites (bastadins -1~-7) have been isolated from the sponge *Ianthella basta*.[1] In the present paper, we wish to describe total synthesis of bastadin-6 (**1**) on the basis of biogenetic consideration of macrocyclic bastadins, all of which seem to be produced on phenolic oxidation of the corresponding acyclic precursors.

On treatment with benzyl chloride (5.6 eq.) - K_2CO_3 (3 eq.) in DMF (room temp., 2 days) followed by deprotection with CF_3COOH - CH_2Cl_2 (room temp., 10 min), bis-*p*-methoxybenzyl bastadin-2 (**2**)[2] (1 eq.) was readily converted into tribenzyl bastadin-2 (**3**)[3] in *ca.* 82% overall yield, which was further treated with Br_2 (2 eq.) - $CHCl_3$ (room temp., 25 min) to afford dibromobastadin-2 tribenzyl ether (**4**)[4] in 82% yield. According to the same procedure as described in the previous paper,[5] oxidation of **4** (1 eq.) with TTN (2.5 eq.) in MeOH (4 °C, 200 min) afforded two macrocyclic dienones (**5** and **6**)[6] in 13 and 10% yields, respectively. The former (1 eq.) was reduced with Zn (160 eq.) - AcOH in THF (*ca.* 25 °C, 50 min) to give the corresponding tribenzyl ether (**7**)[7] in 61% yield. Finally, **7** (1 eq.) was subjected to hydrogenolysis using Pd black (*ca.* 10 eq.) - AcOH in dioxane (room temp., 30 min) to afford bastadin-6 (**1**) in 74% yield,[8] whose IR and ^1H NMR spectra are completely identical with those of natural one.[1] The synthetic compound was further characterized as the known tetramethyl ether.[1, 5] According to the similar procedure to that of **5**, **6** has also been converted into the corresponding known tetramethyl ether.[5]

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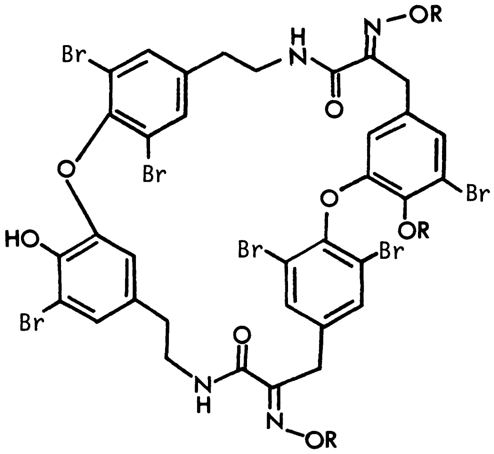
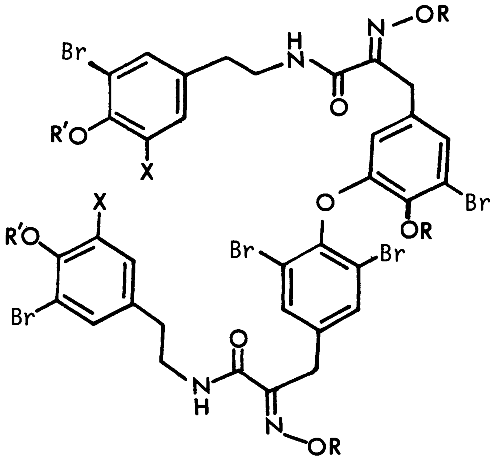
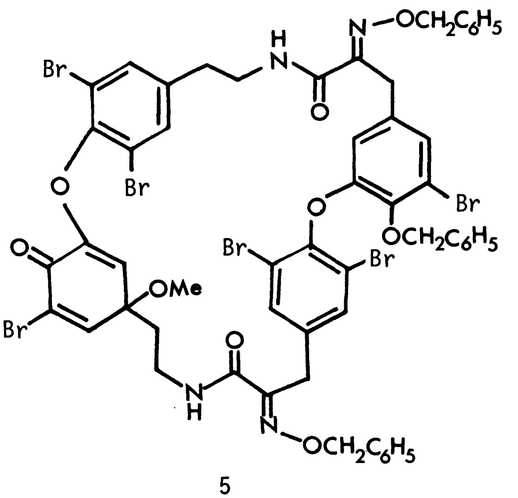


1 R = H
7 R = $CH_2C_6H_5$



2 R = H, R'= $CH_2C_6H_4OMe$-*p*, X = H
3 R = $CH_2C_6H_5$, R'= X = H
4 R = $CH_2C_6H_5$, R'= H, X = Br



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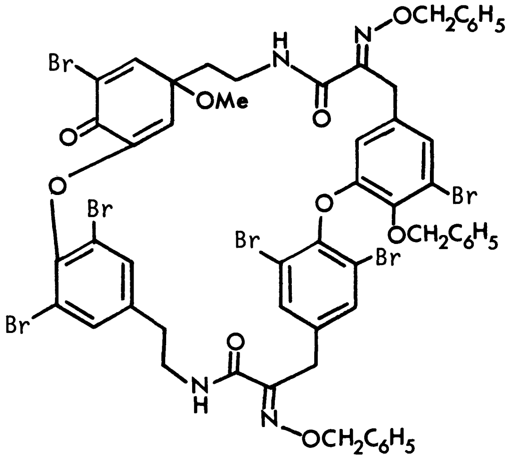

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References

1. R. Kazlauskas, R. O. Lidgard, P. T. Murphy, R. J. Wells, and J. F. Blount, Aust. J. Chem., 34, 765 (1981).
2. S. Nishiyama and S. Yamamura, Tetrahedron Lett., 23, 1281 (1982).
3. 3 as a syrup: $C_{55}H_{47}N_4O_8{}^{79}Br_3{}^{81}Br_2$ [m/e 1290(M^+)]; ν_{max} (film) 3400, 3200, 1660, 1605, 1565, 1550sh., 1530 and 1510 cm^{-1}; $\delta(CDCl_3)$ 2.68(4H, complex), 3.43(4H, complex), 3.72(2H, s), 3.83(2H, s), 4.98(2H, s), 5.15(2H, s), 5.20(2H, s), 6.28(1H, d, J= 1.5Hz) and 6.5 - 7.6(28H, overlapped with solvent signal, complex).
4. 4 as a syrup: $C_{55}H_{45}N_4O_8{}^{79}Br_3{}^{81}Br_4$ [m/e 1450(M^+)]; ν_{max} (film) 3400, 3350, 1665, 1605, 1580, 1560sh. and 1525 cm^{-1}; $\delta(CDCl_3)$ 2.67(4H, complex), 3.43(4H, complex), 3.72(2H, s), 3.83(2H, s), 5.02(2H, s), 5.18(4H, s), 6.30(1H, d, J= 1.5Hz) and 6.5 - 7.7(26H, overlapped with solvent signal, complex).
5. S. Nishiyama, T. Suzuki, and S. Yamamura, Tetrahedron Lett., 23, 3699 (1982).
6. 5 as a syrup: $C_{56}H_{46}N_4O_9{}^{79}Br_3{}^{81}Br_3$ [m/e 1398(M^+)]; ν_{max} (film) 3420, 1670, 1600, 1585, 1560, 1550 and 1520 cm^{-1}; $\delta(CDCl_3)$ 2.78(4H, complex), 3.17(3H, s), 3.37(4H, complex), 3.77(2H, s), 3.82(2H, s), 4.97(2H, s), 5.12(2H, s), 5.27(2H, s), 5.67(1H, d, J= 1.5Hz), 6.27(1H, d, J= 1.5 Hz), 6.7 - 7.0(2H, complex), 7.47(2H, s), 7.52(2H, s) and 7.1 - 7.7(17H, overlapped with solvent signal, complex). 6 as a syrup: $C_{56}H_{46}N_4O_9{}^{79}Br_3{}^{81}Br_3$ [m/e 1398(M^+)]; ν_{max} (film) 3400, 1670, 1600, 1580, 1560, 1550 and 1520 cm^{-1}; $\delta(CDCl_3)$ 2.70(4H, complex), 3.17(3H, s), 3.3 - 3.6(4H, complex), 3.70(2H, s), 3.78(2H, s), 5.07(2H, s), 5.22(4H, s), 5.47(1H, d, J= 1.5Hz), 5.97(1H, d, J= 1.5Hz), 6.8 - 7.0(2H, complex) and 7.1 - 7.7(21H, overlapped with solvent signal, complex).
7. 7 as a syrup: $C_{55}H_{44}N_4O_8{}^{79}Br_3{}^{81}Br_3$ [m/e 1368(M^+)]; ν_{max} (film) 3400, 3350sh., 1665, 1600, 1580, 1560, 1540sh. and 1520 cm^{-1}; $\delta(CDCl_3)$ 2.70(4H, complex), 3.45(4H, complex), 3.75(4H, s), 4.92 (2H, s), 5.15(2H, s), 5.22(2H, s), 6.27(1H, d, J= 1.5Hz), 6.40(1H, d, J= 1.5Hz), 6.7 - 7.4 (20H, overlapped with solvent signal, complex), 7.45(2H, s) and 7.53(2H, s).
8. The benzyl group was proved to be a good protecting one for the two oxime groups.

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