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TOTAL SYNTHESIS OF BASTADINS

Shigeru Nishiyama and Shosuke Yamamura
Department of Chemistry, Faculty of Science and Technology, Keio University
Hiyoshi, Yokohama, Japan

Summary: Bastadins-1, -2 and -3, the novel metabolites originated from four bromotyrosine units, were synthesized, and each geometry at the oxime C=N double bonds was unambiguously determined to be *anti*.

In connection with the novel metabolites derived from brominated tyrosine [bastadins -1 (1), -2 (2) and -3 (3)],[1] biomimetic oxidation of methyl 3,5-dibromo-4-hydroxyphenylpyruvate oxime (4) was carried out using thallium (III) nitrate (TTN) to afford a dimeric spiroisoxazol (5) in *ca.*44% yield, from which the corresponding biphenyl ether (6) was obtained in almost quantitative yield, as a key intermediate for bastadin-2 synthesis.[2,3]

Similarly, on oxidation with thallium (III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA) containing small amount of CH_2Cl_2 (room temp., 20 h), methyl 3-bromo-4-hydroxyphenylpyruvate oxime (7)[4] was converted into three spiroisoxazols [8 (7%), 9 (6%) and 10 (5%)][5] and a plausible compound (11) which was directly reduced with Zn powder in THF containing small amount of AcOH (0°, 35 min) to afford a biphenyl-type compound (12)[6] in 8% overall yield. Under the same condition as that of 5, Zn reduction of 9 afforded the corresponding biphenyl ether (13)[7] in 48% yield.

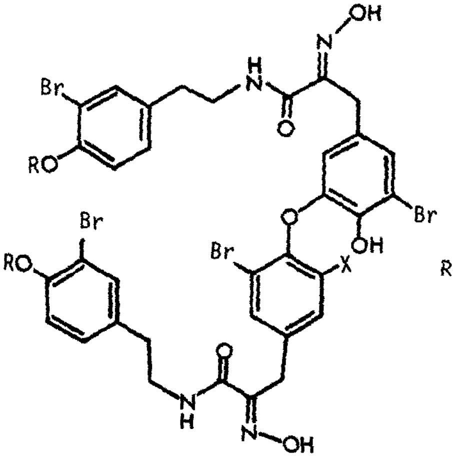
The bromotyramine moiety of bastadins was also synthesized, as follows. 3-Bromo-4-hydroxybenzaldehyde was treated with *p*-methoxybenzyl chloride - K_2CO_3 in DMF (room temp., 14 h) and then with nitromethane in THF - K_2CO_3 (room temp., 18 h) to give a nitro compound (14) in 71% overall yield, which was directly dehydrated with Ac_2O - pyridine to the corresponding α,β-unsaturated nitro compound (15)[8] in 79% yield. 15 was further reduced with $NaBH_4$ in diglyme (0°, 1 h) to a saturated nitro compound (16)[9] in 65% yield, which was finally converted into 3-bromotyramine *p*-methoxybenzyl ether (17),[10] in almost quantitative yield, on treatment with Zn powder in dioxane containing AcOH (0 - 5°, 40 min).

Synthesis of bastadin-1

The dibromobiphenyl ether (13) reacted with excess amounts of 3-bromotyramine *p*-methoxybenzyl ether (17) (60°, 41 h) to give the desirable diamide (18) in 34% yield.[11] Finally, 18 was subjected to deprotection with TFA - CH_2Cl_2 (room temp., 20 min) to give bastadin-1 (1) [ν_{max}(film) 1650, 1620sh., 1570 and 1530 cm^{-1}] in 63% yield, whose ^1H NMR spectrum was identical with that of an authentic sample.[1,12]

Synthesis of bastadin-2

Similarly, amidation of the tribromobiphenyl ether (6) with 17 was also carried out (65°, 36 h) to afford the desirable diamide (19) in 36% yield.[13] Furthermore, under the same condition

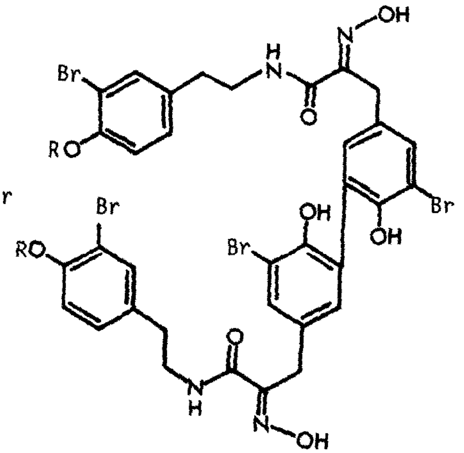


1 R = H, X = H

2 R = H, X = Br

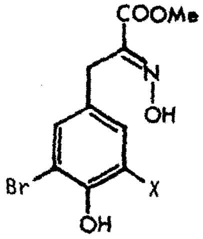
18 R = $CH_2C_6H_4OMe$-*p*, X = H

19 R = $CH_2C_6H_4OMe$-*p*, X = Br



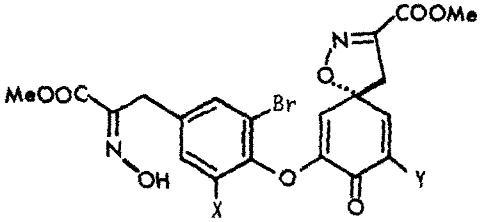
3 R = H

20 R = $CH_2C_6H_4OMe$-*p*



4 X = Br

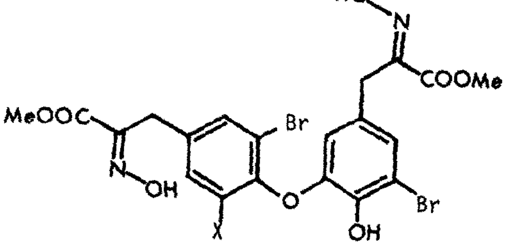
7 X = H



5 X = Br, Y = Br

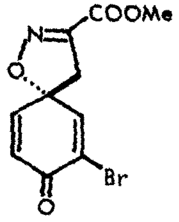
9 X = H, Y = Br

10 X = H, Y = H



6 X = Br

13 X = H



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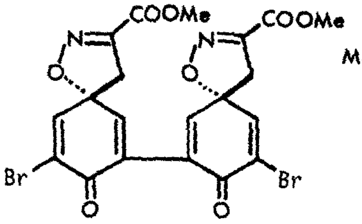

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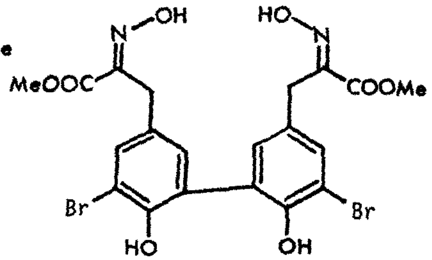

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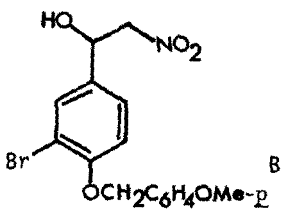

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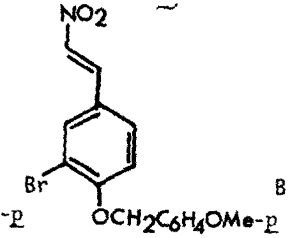

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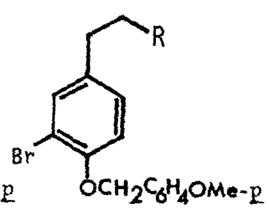

16 R = NO_2

17 R = NH_2

as that of **18**, **19** was readily converted into bastadin-2 (**2**) [ν_{max}(film) 1655, 1580 and 1530 cm^{-1}] in 82% yield, whose ^1H NMR spectrum was identical with that of an authentic sample.[1,12]

Synthesis of bastadin-3

Amidation of the biphenyl dimer (**12**) with excess amounts of **17** was carried out (60°, 4 days) to afford the corresponding diamide (**20**)[14] in 17% yield, which was further submitted to demethoxybenzylation with TFA - CH_2Cl_2 (room temp., 20 min) to give bastadin-3 (**3**) [ν_{max}(film) 1650, 1570, 1530 and 1510 cm^{-1}] in 56% yield, whose ^1H NMR spectrum was identical with that of an authentic sample.[1,12]

The present study indicates that each geometry at the oxime C=N double bonds is anti in bastadins-1, -2 and -3. Further synthetic study of macrocyclic bastadins[1] is in progress.

The authors wish to thank Dr. R. Kazlauskas (Roche Research Institute of Marine Parmacology) for providing them with ^1H NMR spectra of bastadins and their methyl ethers. They are also indebted to Dr. M. Toda (Ono Central Research Institute) and Mr. S. Kidokoro (Ohmori Research Institute, Tobishi Pharmaceutical Co. Ltd.) for measurements of high resolution mass spectra.

References and Notes

1. R. Kazlauskas, R. O. Lidgard, P. T. Murphy, and R. J. Wells, Tetrahedron Lett., 21, 2277 (1980); R. Kazlauskas, R. O. Lidgard, P. T. Murphy, R. J. Wells, and J. F. Blount, Aust. J. Chem., 34, 765 (1981).
2. H. Noda, M. Niwa, and S. Yamamura, Tetrahedron Lett., 22, 3247 (1981).
3. The yield of **6** was improved by using a mixed solvent [THF - AcOH (50 : 1)].
4. The oxime (**7**) has been synthesized from 3-bromo-4-hydroxybenzaldehyde in 4 steps [1) N-acetylglycine - AcONa in Ac_2O 2) AcOH - 6N HCl 3) $NH_2OH{\cdot}HCl$ - $NaHCO_3$ in H_2O 4) MeOH - conc.HCl]; **7**: mp 157 - 158°; $C_{10}H_{10}NO_4{}^{79}Br$ (m/e 287(M^+)); ν_{max}(Nujol) 1695, 1605 and 1580 cm^{-1}; δ(pyridine-d_5) 3.60(3H, s), 4.07(2H, s), 7.05(1H, d, J= 9Hz), 7.37(1H, dd, J= 2.5, 9Hz) and 7.88(1H, d, J= 2.5Hz).
5. **8**: mp 132 - 133°; $C_{10}H_8NO_4{}^{79}Br$ (m/e 285(M^+)); ν_{max}(film) 1725, 1670, 1635 and 1600 cm^{-1}; δ($CDCl_3$) 3.37(2H, s), 3.83(3H, s), 6.39(1H, d, J= 10.5Hz), 6.93(1H, dd, J= 2.5, 10.5Hz) and 7.35(1H, d, J= 2.5Hz). **9** as a syrup: $C_{20}H_{16}N_2O_8{}^{79}Br_2$ (m/e 570(M^+)); ν_{max}(film) 1720, 1690, 1650sh. and 1595 cm^{-1}; δ($CDCl_3$) 3.30(2H, AB-q)*, 3.78(3H, s), 3.80(3H, s), 3.7-3.9(2H, superimposed on MeO signals), 5.62(1H, d, J= 2.5Hz), 7.01(1H, d, J= 7Hz), 6.9-7.2(1H, superimposed on 1H doublet), 7.3-7.4(1H, superimposed on solvent signal) and 7.62(1H, d, J= 2.5Hz). **10** as a syrup: $C_{20}H_{17}N_2O_8{}^{79}Br$ (m/e 492(M^+)); ν_{max}(film) 1720, 1675, 1645 and 1590 cm^{-1}; δ($CDCl_3$) 3.30(2H, s), 3.82(6H, s), 3.7-3.9(2H, superimposed on MeO signal), 5.58(1H, d, J= 2.5Hz), 6.36(1H, d, J= 10.5Hz), 6.8-7.1(3H, complex) and 7.63(1H, d, J= 2.5Hz).
   * J-value could not be measured accurately.
6. **12**: mp 243° (dec); $C_{20}H_{18}N_2O_8{}^{79}Br_2$ (m/e 572(M^+)); ν_{max}(Nujol) 1730, 1690sh. and 1570 cm^{-1}; δ(pyridine-d_5) 3.71(6H, s), 4.14(4H, s), 7.57(2H, d, J= 2.5Hz) and 7.74(2H, d, J= 2.5Hz).
7. **13** as a syrup: $C_{20}H_{18}N_2O_8{}^{79}Br_2$ (m/e 572(M^+)); ν_{max}(film) 1725 and 1575 cm^{-1}; δ(pyridine-d_5) 3.67(3H, s), 3.71(3H, s), 4.10(4H, s), 6.83(1H, d, J= 9Hz), 7.2-7.3(1H, superimposed on solvent signal), 7.36(1H, dd, J= 2.5, 9Hz) and 7.7-7.9(2H, complex).

8. 15: mp 129 - 130°; $C_{16}H_{14}NO_4{}^{79}Br$ (m/e 363(M^+)); ν_{max}(Nujol) 1620, 1605, 1580, 1545 and 1505sh. cm^{-1}; δ($CDCl_3$) 3.72(3H, s), 5.07(2H, s), 6.8-7.1(3H, complex), 7.2-7.5(4H, complex), 7.73 (1H, d, J= 2.5Hz) and 7.86(1H, d, J= 13.5Hz).
9. 16: mp 74 - 75°; $C_{16}H_{16}NO_4{}^{79}Br$ (m/e 365(M^+)); ν_{max}(film) 1605, 1580, 1540, 1510sh. and 1375 cm^{-1}; δ($CDCl_3$) 3.12(2H, t, J= 7.5Hz), 3.70(3H, s), 4.40(2H, t, J= 7.5Hz), 4.95(2H, s), 6.7-7.1(4H, complex) and 7.2-7.4(3H, complex).
10. This compound (17) was used for the next amidation without further purification, and this amine was characterized as its acetamide: mp 110 - 112°; $C_{18}H_{20}NO_3{}^{79}Br$ (m/e 377(M^+)); ν_{max} (Nujol) 1635, 1610, 1580, 1540 and 1510 cm^{-1}; δ(pyridine-d_5) 1.98(3H, s), 2.78(2H, t, J= 7.5 7.5Hz), 3.58(3H, s), 3.4-3.7(2H, superimposed on MeO signal), 5.00(2H, s), 6.9-7.3(4H, complex), 7.4-7.6(3H, complex) and 8.4-8.7(1H, br).
11. 18 as a syrup: ν_{max}(film) 1655, 1610, 1580, 1530sh. and 1510 cm^{-1}.
12. The molecular formulae of the synthetic bastadins were characterized as the corresponding permethyl ethers [$C_{39}H_{40}N_4O_8{}^{79}Br_4$ (m/e 1008 (M^+)) for bastadin-1 pentamethyl ether; $C_{39}H_{39}N_4O_8{}^{79}Br_5$ (m/e 1086(M^+)) for bastadin-2 pentamethyl ether; $C_{40}H_{42}N_4O_8{}^{79}Br_4$(m/e 1022 ($M^+$)) for bastadin-3 hexamethyl ether].
13. 19 as a syrup: ν_{max}(film) 1660, 1600, 1575 and 1510 cm^{-1}.
14. 20 as a syrup: ν_{max}(film) 1660, 1605, 1580 and 1510 cm^{-1}.

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