Tetrahedron Letters,Vol.23,No.36,pp 3699-3702,1982 0040-4039/82/363699-04$03.00/0
Printed in Great Britain

SYNTHESIS OF BASTADIN-6 TRIMETHYL ETHER, A NOVEL 28-MEMBERED RING LACTAM

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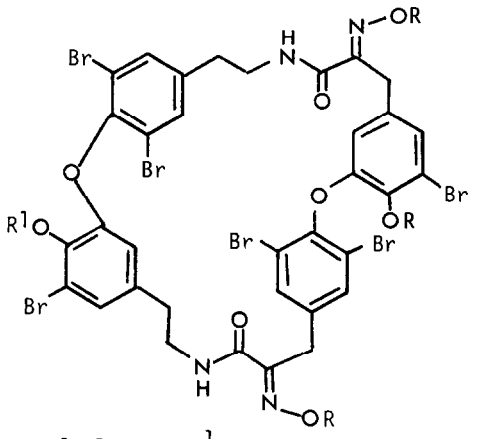
Summary Bastadin-6 trimethyl ether, a 28-membered ring lactam, was synthesized by means of phenolic oxidation of dibromobastadin-2 trimethyl ether with thallium (III) nitrate (TTN) leading to the formation of the corresponding macrocyclic biphenyl ether as a key step From bastadin-2 trimethyl ether, a 26-membered ring compound was also synthesized

In connection with the novel metabolites derived from brominated tyrosine, we have synthesized bastadins-1, -2 and -3 [1] The first two metabolites are acyclic biphenyl ethers having two amide bonds From view points of biological and physiological activities, particularly, bastadins-5 and -6, macrocyclic metabolites produced by Ianthella basta, are quite interesting [2] In the present paper, we wish to describe the synthesis of bastadin-6 trimethyl ether (1) on the basis of a biogenetic consideration of bastadin-6 (2), in which the macrocyclic 28-membered ring formation must be carried out by means of phenolic oxidation of the corresponding acyclic precursor, as follows

When treated with excess 3-bromotyramine p-methoxybenzyl ether[1] (60 °C, 13 h), the permethylated biphenyl ether (3)[3] was readily converted into the corresponding diamide (4),[4,5] which was further treated with trifluoroacetic acid (TFA) in CH_2Cl_2 (room temp , 40 min) to afford bastadin-2 trimethyl ether (5)[6] in 46% overall yield This ether was directly oxidized with thallium (III) trifluoroacetate (TTFA) in TFA at room temperature for 15 h to give a 26-membered ring compound (6) in 22% yield, which was characterized as its diacetate (7) [7] In this case, any product with a bastarane skeleton has not yet been detected However, this experiment strongly suggests that such a 26-membered ring substance (8) as 6 may co-occur together with bastadins-5 and -6 in the Verongid sponge Ianthella basta, although it has not yet been found Accordingly, as seen in the case of methyl 3,5-dibromo-4-hydroxyphenylpyruvate oxime methyl ether,[8] dibromobastadin-2 trimethyl ether (9)[9] seems to be more favorable as a substrate, which has been obtained in quantitative yield on bromination of 5 using 0 2M bromine in $CHCl_3$ (room temp , 2 h) Thus, an oxidative cyclization reaction of 9 was successfully carried out, as shown below

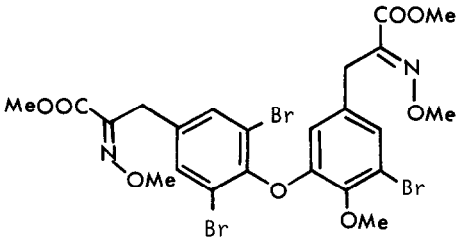
To a solution of TTN (0 14 mmol) in MeOH (2 ml) was added dibromobastadin-2 trimethyl ether (0 05 mmol) in AcOEt (0 5 ml) and the mixture was stirred at 4 °C for 20 h, and then partitioned between $CHCl_3$ and water The $CHCl_3$ extract was separated by preparative TLC [Kieselgel PF_{254}, hexane - AcOEt (1 1)] to afford two macrocyclic dienones (10 and 11)[10] in 20 and 11% yields, respectively The former (10) was reduced with Zn - AcOH in THF (water-bath temp , 1 5 h) to afford the corresponding phenol (1), bastadin-6 trimethyl ether,[11] which was further methylated with MeI - K_2CO_3 in DMF (room temp , 19 h) to afford bastadin-6 tetramethyl ether (12)[2,12] in



1 R = Me, R^1 = H

2 R = R^1 = H

12 R = R^1 = Me



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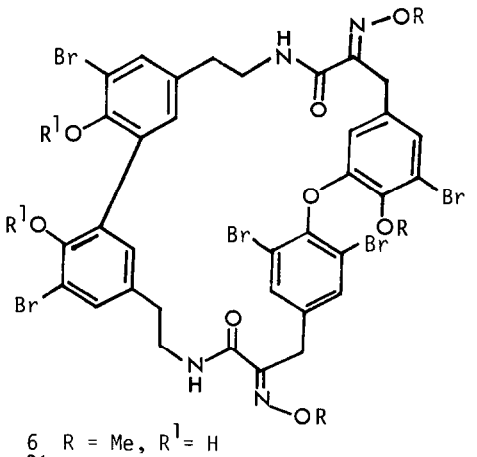
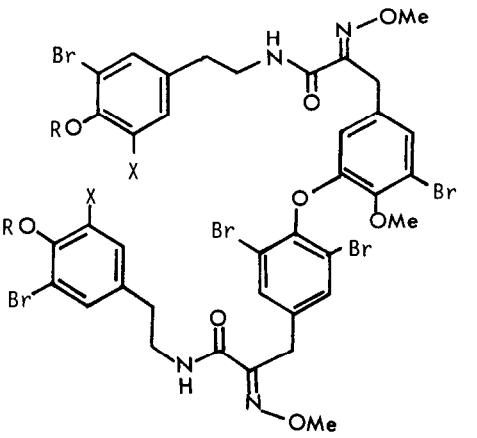


6 R = Me, R^1 = H

7 R = Me, R^1 = Ac

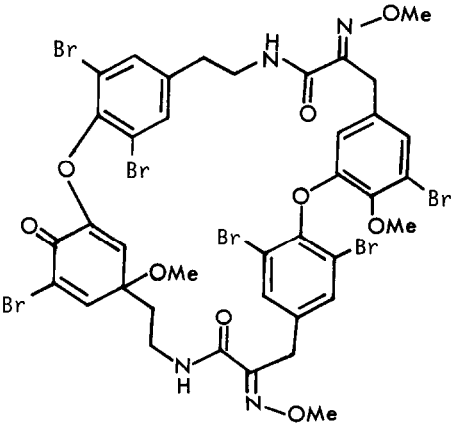
8 R = R^1 = H



4 R = $CH_2C_6H_4OMe$-p, X = H

5 R = X = H

9 R = H, X = Br



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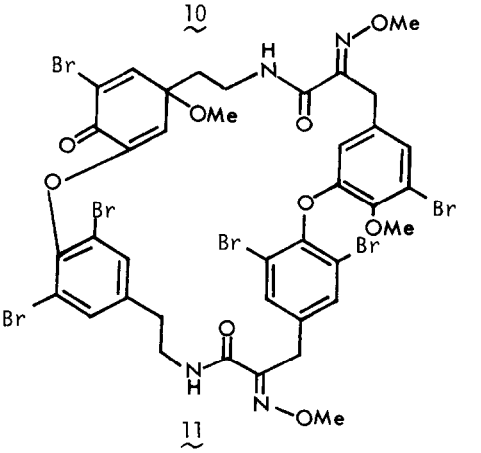

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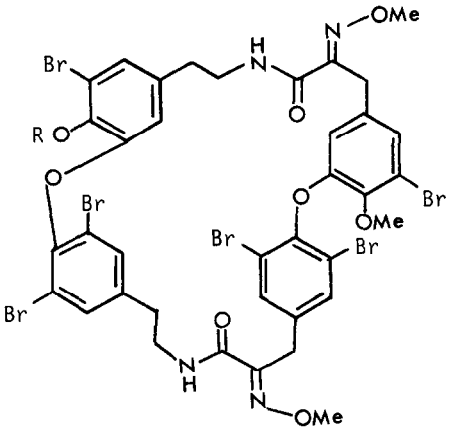
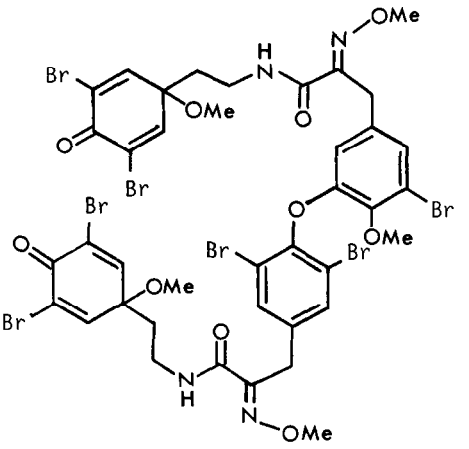


13 R = Me
14 R = H



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58% overall yield According to essentially the same procedure as described above, the macrocyclic dienone (11) was also subjected to zinc reduction followed by methylation to afford the corresponding tetramethyl ether (13)[13] via a trimethyl ether (14)[14] in 33% overall yield

As expected, of two cyclization pathways leading to the formation of the macrocyclic dienones (10 and 11), it should be noted that the oxidative cyclization reaction of 9 related to natural bastadins-5 and -6 is more favorable and takes place regioselectively even in such a flexible 28-membered ring formation Furthermore, conformations of 12 and 13 seem to be pretty different to each other, as judged from their ^{1}H NMR spectra one of the four MeO signals in the former is observed in high magnetic field (δ 3 61) as compared with the others (δ 4 02, 4 03 and 4 06),[15] while 13 has no MeO signal in such a high magnetic field (δ 3 92, 4 02, 4 04 and 4 08)

Finally, instead of TTN oxidation, anodic oxidation of 9 in MeOH - THF (4 1) containing $LiClO_4$ was carried out at a controlled potential (+1300 mV vs SCE) to afford an acyclic dienone (15)[16] in ca 9% yield [17] Synthetic studies on bastadins-5, -6 and -7 are in progress

The authors wish to thank Dr R Kazlauskas (Roche Research Institute of Marine Pharmacology) for providing them with the spectral data of bastadins They are also indebted to Dr Y Terada (Meijo University) and Mr S Kidokoro (Ohmori Research Institute, Tobishi Pharmaceutical Co Ltd) for measurements of ^{1}H NMR and high resolution mass spectra

References and Notes

1 S Nishiyama and S Yamamura, Tetrahedron Lett , 23, 1281 (1982)
2 R Kazlauskas, R O Lidgard, P T Murphy, R J Wells, and J F Blount, Aust J Chem , 34, 765 (1981)
3 This compound was readily produced from 3,5-dibromo-4-hydroxyphenylpyruvate oxime in three steps [1) TTN in MeOH, 2) Zn - AcOH in THF, 3) MeI - K_2CO_3 in DMF]
4 The molecular ion peak has not been observed in its mass spectrum, but the structure of 4 is supported by its spectral data ν_{max} (film) 3400, 1660, 1600, 1575, 1555, 1540 and 1510 cm^{-1}, δ($CDCl_3$) 2 5-2 8(4H, complex), 3 2-3 6(4H, complex), 3 57(2H, s), 3 72(9H, br s), 3 83(2H, s), 3 95(6H, br s), 5 00(4H, s), 6 22(1H, d, J= 1 5Hz), 6 6-7 0(9H, complex), 7 10(1H, d, J= 1 5Hz), 7 3-7 5(5H, complex) and 7 57(2H, s)
5 This compound(4) was also characterized as its demethoxybenzylation product

6 5 as a syrup $C_{37}H_{35}{}^{79}Br_3{}^{81}Br_2N_4O_8$ (m/e 1062(M^+)), ν_{max} (film) 3350br , 1655, 1605, 1575sh , 1560sh , 1530 and 1510 cm^{-1}, δ ($CDCl_3$) 2 73(2H, t, J= 8Hz), 2 79(2H, t, J= 6Hz), 3 47(2H, q*), 3 53(2H, q*), 3 68(2H, s), 3 77(3H, s), 3 89(2H, s), 4 01(3H, s), 4 02(3H, s), 6 24 (1H, d, J= 2Hz), 6 6-7 0(4H, complex), 7 12(1H, d, J= 2Hz), 7 2-7 3(2H, overlapped with solvent signal) and 7 54(2H, s)
* J-value could not be measured accurately

7 Acetylation of 6 with Ac_2O - pyridine afforded the corresponding diacetate (7) in 88% yield $C_{41}H_{37}{}^{79}Br_3{}^{81}Br_2N_4O_{10}$ (m/e 1144(M^+)), ν_{max} (film) 3400, 1765, 1670, 1605, 1595sh , 1590sh , 1560, 1545sh and 1525 cm^{-1}, δ ($CDCl_3$) 2 07(3H, s), 2 08(3H, s), 2 6-2 9(4H, complex), 3 65 (3H, s), 4 02(3H, s), 4 05(3H, s), 3 5-4 0(8H, overlapped with MeO signals), 6 12(1H, d, J= 1 5Hz), 6 97(2H, br s), 7 15(1H, d, J= 1 5Hz), 7 47(2H, br s) and 7 57(2H, s)

8 H Noda, M Niwa, and S Yamamura, Tetrahedron Lett , 22, 3247 (1981)

9 9 as a syrup m/e 863 [M^+($C_{37}H_{33}{}^{79}Br_7N_4O_8$) - 351 ($C_{10}H_{11}{}^{79}Br_2NO_3$)], ν_{max} (film) 3430, 1665, 1610, 1585, 1565sh , 1550 and 1535 cm^{-1}, δ (acetone-d_6) 2 7-3 0(4H, complex), 3.4-3 8(4H, complex), 3 77(2H, s), 3 87(3H, s), 4 07(3H, s), 4 12(3H, s), 4 0-4 2(2H, overlapped with two MeO signals), 6 50(1H, d, J= 1 5Hz), 7 37(1H, d, J= 1 5Hz), 7 58(4H, s) and 7 87(2H, s)

10 10 as a powder $C_{38}H_{34}{}^{79}Br_3{}^{81}Br_3N_4O_9$ (m/e 1170(M^+)), ν_{max} (film) 3400, 1670, 1600, 1580, 1560sh , 1540sh and 1520 cm^{-1}, δ (acetone-d_6) 3 26, 3 52, 3 99 and 4 05(each 3H, s) 11 as a syrup $C_{38}H_{34}{}^{79}Br_3{}^{81}Br_3N_4O_9$ (m/e 1170(M^+)), ν_{max} (film) 3400, 1670, 1600, 1580, 1560sh , 1540sh and 1520 cm^{-1}, δ (acetone-d_6) 3 31, 3 86, 3 97 and 4 02(each 3H, s)

11 1 mp (dec) >250 °C, $C_{37}H_{32}{}^{79}Br_3{}^{81}Br_3N_4O_8$ (m/e 1140(M^+)), ν_{max} (Nujol) 3250, 1670, 1640, 1600, 1580sh , 1570sh , 1560 and 1535 cm^{-1}, δ (pyridine-d_5) 2 7-3 0(4H, complex), 3 4-3 7 (4H, complex), 3 70(3H, s), 3 76(3H, s), 3 90(2H, s), 4 00(2H, s), 4 08(3H, s), 6 73(1H, d, J= 1 5Hz), 6 80(1H, d, J= 1 5Hz), 7 27(1H, d, J= 1 5Hz), 7 43(1H, d, J= 1 5Hz), 7 63 (2H, s) and 7 87(2H, s)

12 12 as a syrup $C_{38}H_{34}{}^{79}Br_3{}^{81}Br_3N_4O_8$ (m/e 1154(M^+)), ν_{max} (film) 3425, 1670, 1610, 1585, 1560, 1550 and 1525 cm^{-1}, δ ($CDCl_3$) 2 6-3 0(4H, complex), 3 3-3 6(4H, complex), 3 61(3H, s), 3 72(2H, s), 3 85(2H, s), 4 02(3H, s), 4 03(3H, s), 4 06(3H, s), 6 2-6 24(2H, complex), 7 07 (1H, d, J= 2Hz), 7 17(1H, d, J= 2Hz), 7 46(2H, s) and 7 53(2H, s)

13 13 as a syrup $C_{38}H_{34}{}^{79}Br_3{}^{81}Br_3N_4O_8$ (m/e 1154(M^+)), ν_{max} (film) 3425, 1665, 1600sh , 1585, 1560, 1550 and 1515 cm^{-1}, δ ($CDCl_3$) 2 5-2 8(4H, complex), 3 3-3 6(4H, complex), 3 92(5H, s), 4 02(3H, s), 4 04(3H, s), 4 08(3H, s), 4 0-4 1(2H, overlapped with MeO signals), 5 90(1H, br s), 6 10(1H, br s), 7 10(2H, br s), 7 40(2H, s) and 7 50(2H, s)

14 14 mp (dec) ca 195 °C, $C_{37}H_{32}{}^{79}Br_3{}^{81}Br_3N_4O_8$ (m/e 1140(M^+)), ν_{max} (Nujol) 3400, 1670, 1610sh , 1580sh , 1565sh , 1550 and 1520 cm^{-1}, δ (pyridine-d_6) 2 6-2 9(4H, complex), 3 4-3 7 (4H, complex), 3 78(5H, s), 3 87(3H, s), 4 08(5H, s), 6 45(1H, d, J= 1 5Hz), 6 55(1H, d, J= 1 5Hz), 7 28(1H, d, J= 1 5Hz), 7 47(1H, d, J= 1 5Hz), 7 58(2H, s, overlapped with solvent signal) and 7 75(2H, s)

15 The ^1H NMR spectrum of bastadin-5 tetramethyl ether is quite similar to that of bastadin-6 tetramethyl ether (see ref 2)

16 15 as a syrup m/e 1220 [M^+($C_{39}H_{32}{}^{79}Br_4{}^{81}Br_3N_4O_{10}$) - 62 (2 x MeO)], ν_{max} (film) 3400, 1670, 1590, 1560sh , 1540sh and 1520 cm^{-1}, δ (acetone-d_6) 3 28(6H, s), 3 60(2H, s), 3 80(3H, s), 3 95(2H, s), 3 97(3H, s), 4 04(3H, s), 6 32(1H, d, J= 2Hz), 7 18(1H, d, J= 2Hz), 7 50(2H, s), 7 51(2H, s) and 7 67(2H, s)

17 Further study on anodic oxidation of this compound is in progress

(Received in Japan 29 May 1982)