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Synthesis of bastadin analogs through an S_NAr coupling strategy

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Abstract—The synthesis of a bastadin-5 analog was achieved in 16% overall yield (16 steps, longest linear sequence) using a strategy of intermolecular S_NAr coupling to create diphenyl ether bonds and sequential amide couplings to close the ring. Noteworthy elements include assembly of all four substituted aryl rings from two simple benzaldehydes, strict regiocontrol of *meta*- versus *para*-aryl ether bonds and management of the reductively-sensitive aryl bromine substituents. © 2002 Elsevier Science Ltd. All rights reserved.

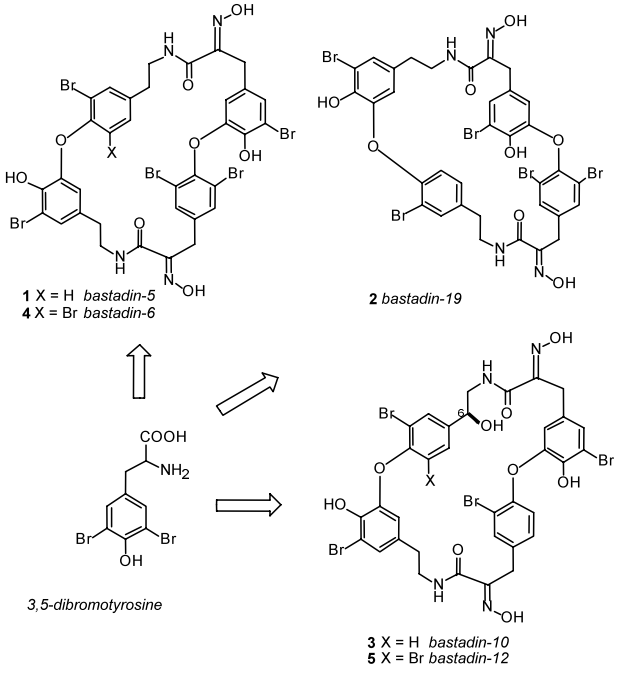
The bastadins comprise a unique family of polybrominated compounds obtained from the marine sponges *Ianthella basta* (Pallas),[1] *I. quadrangulata*[2] and *Psammaplysilla purpurea*.[3] Bastadins are biosynthesized from brominated tyrosine or tyramine units, a feature that is common to metabolites from sponges of the order Verongida. The cyclic members of the series (e.g. bastadin-5, **1**, Scheme 1) are 28-membered macrolactams based on the hypothetical parent ring, *bastarane*, that embodies two amide bonds, two diphenyl ethers linkages produced by phenolic coupling and up to six aryl Br substitutents. An alternate phenolic coupling gives rise to isomeric compounds based on an *isobastarane* skeleton and exemplified by bastadin-19 (**2**).[1g]

Bastadin-5 (**1**) is a potent agonist of the RyR-1/FKBP12 Ca^{2+} channel complex in skeletal muscle (**1**) that mobilizes Ca^{2+} from sarcoplasmic reticulum (SR) stores by altering channel gating kinetics of the tetrameric channel protein ($EC_{50}=2.3$ μM).[1g] Although both the mechanism of channel gating and the binding locus of **1** are unknown it is known that the bastadin binding site is distinct from those of known Ca^{2+} agonists, such as ryanodine and caffeine.[1g]

The activity is very structure-specific. Bastadin-10 (**3**),[1c] a C-6 hydroxylated analog of **1**, also induces Ca^{2+} release through a mechanism that obviates the need for micromolar Ca^{2+}. In contrast, **2**, the *isobastarane* isomer of **1**, is essentially inert (EC_{50} >100 μM).

The Ca^{2+} channel activity of **1** and related bastadins make them excellent tools for exploring Ca^{2+} mobilization in striated muscle, the gating mechanism and possibly the role of FKBP12 in channel activity.[4]

Two reports have appeared on the total syntheses of macrocyclic bastadins.[5,6] Both exploit biomimetic oxidative phenolic coupling: bastadin-6 (**4**) (thallium(III) nitrate)[5] and bastadin-12 (**5**) (horseradish peroxidase).[6]



Scheme 1.

Keywords: bastadins; nucleophilic aromatic substitution; Horner–Emmons; Ca^{2+} channel; RyR-1.

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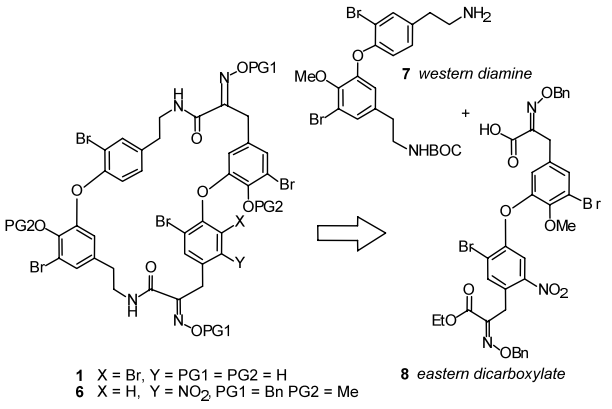
The latter approaches suffer from either lack of regiocontrol of the diaryl ether bond, low yield or limitation to 'symmetrical' cases.

New strategies for construction of diphenyl ethers include tandem coupling of diamines with Erlenmeyer-type bis-azlactones,[7] triazene-modified Cu(I) Ullmann-ether synthesis type coupling[8] and an approach based on phenoxide addition to π-aryl $[RuCp]^+$ complexes.[9] Ring closure of the 28-membered macrolactam has been achieved by Sih and co-workers[6] in their recent synthesis of **4**, and by Couladouros et al. in construction of a derivative of bastadin-12 (**5**).[8b]

Although in the past we have assembled a simple substituted bastarane in as few as five steps from two simple benzaldehydes,[7] control of *bastarane* versus *isobastarane*, was not possible. We chose to pursue a synthesis of the unsymmetrical analog **6** using an *intermolecular* S_NAr strategy in order to gain control of the regiochemistry and direct the formation of the *bastarane*-ring (Scheme 2).[10] The $ArNO_2$ group in **6** serves as a useful 'handle' for introduction of Br or photoaffinity labels (ArN_3) through reduction-diazonium salt displacement. Fusion of the two halves of the macrocycle (the 'western' diamine, **7** and the 'eastern' dicarboxylate **8**) would be brought about by sequential amide bond couplings. We now report the successful execution of this plan and the synthesis of **6** in a highly convergent manner and installation of all four aryl rings from two aldehydes—3,4-dihydroxybenzaldehyde (**9**) and 3-bromo-4-fluorobenzaldehyde (**10**).

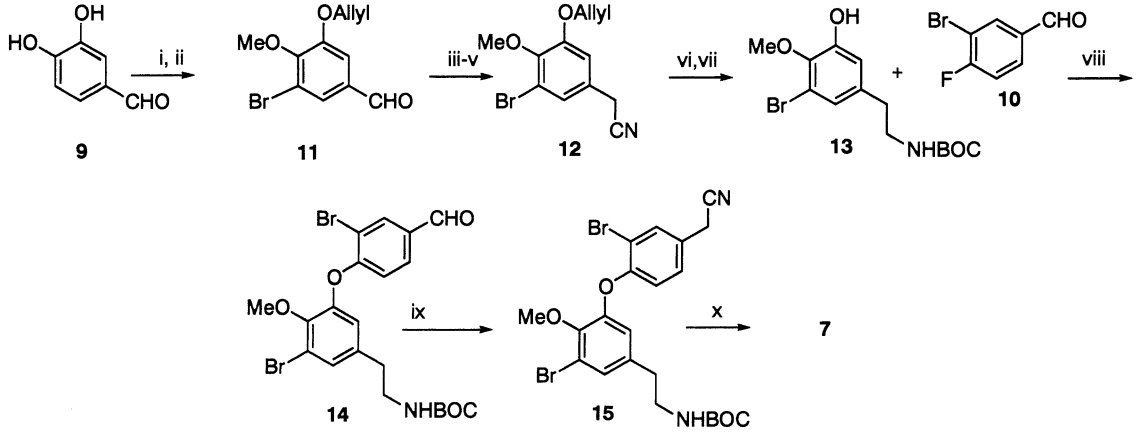


Scheme 2. Retrosynthetic analysis of bastadin-5 analog **6**.

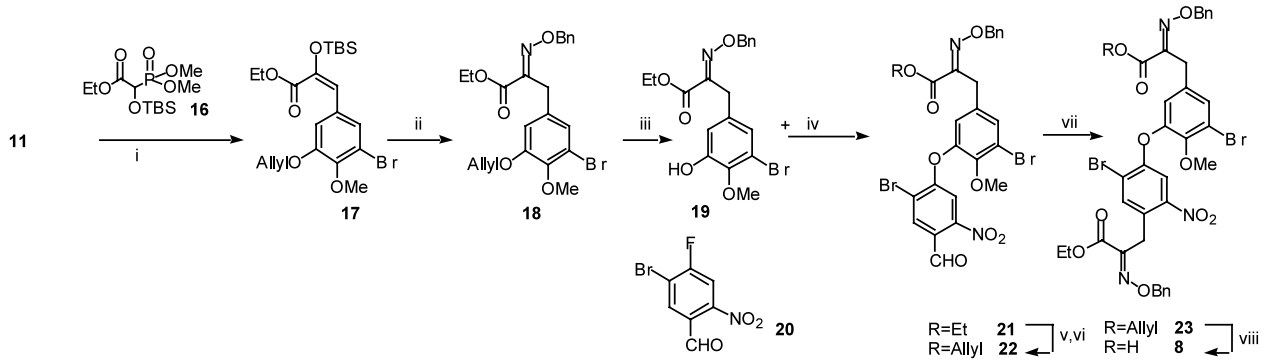
Bromination of catechol **9**[11] (Scheme 3) followed by two sequential directed alkylations gave the differentially protected benzaldehyde **11**[12] which was converted into phenylacetonitrile **12** in three steps as follows. Reduction with $NaBH_4$ and conversion of the product benzyl alcohol to the corresponding chloride was followed by cyanide displacement under phase-transfer conditions to afford **12** (89%).

Reduction of **12** and simultaneous removal of the *O*-allyl protecting group was achieved in one step (BH_3·THF)[13] to give the expected phenethylamine, which was immediately protected as the *N*-BOC compound **13** (78%, two steps). Intermolecular S_NAr substitution of **13** with 3-bromo-4-fluorobenzaldehyde (**10**) afforded aldehyde **14** in high yield (88%). Repetition of the homologation sequence on **14** (reduction-halide displacement-cyanide displacement) gave **15** (89%, two steps) followed by nitrile reduction (BH_3·THF, 98%) to give the monoprotected diamine **7** (55% yield from **10**).

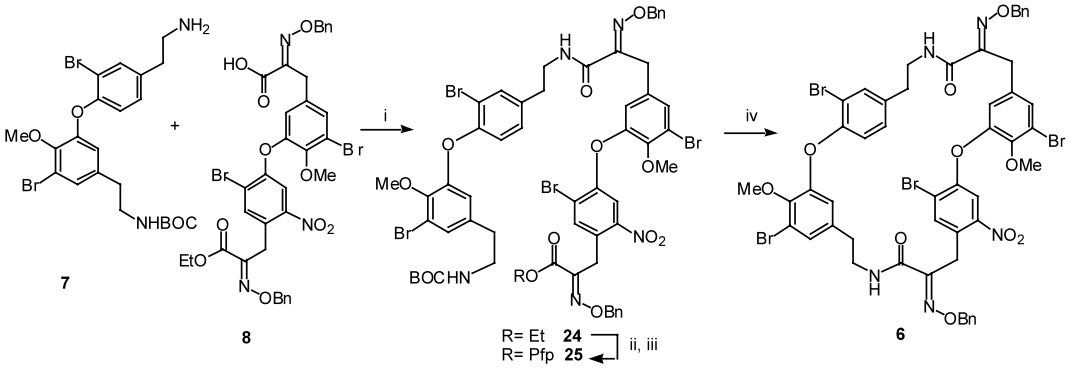
The 'eastern' hemisphere intermediate **8** was also prepared from **11**, this time using a Horner–Emmons strategy for step-wise extension of each carboxaldehyde group to the corresponding α-ketoxime (Scheme 4). Condensation of the aldehyde **11** with phosphonate **16**[14] (NaHMDS, −78°C) yielded the *O*-TBS enol ether **17** (1:1 *E*/*Z*). Treatment of **17** with HF-pyridine in the presence of $BnONH_2$–HCl resulted in simultaneous removal of the TBS group and in situ formation of the *O*-benzyl oxime **18** as single isomer (*E*, 89%, two steps).[15] Selective removal of the allyl protecting group without reductive cleavage of the aryl bromide was conveniently carried out with $RhCl_3·2H_2O$ in hot



Scheme 3. *Reagents and conditions*: (i) Br_2, HOAc, 92%; (ii) MeI, Li_2CO_3, DMF, 4 h, then AllylBr, K_2CO_3, 2 h (82% overall); (iii) $NaBH_4$, MeOH, 0°C, 30 min; (iv) *n*-Bu_3P, CCl_4, 0°C; (v) Bu_4NCl, NaCN, CH_2Cl_2:H_2O (10:1 v/v), 89% (two steps); (vi) BH_3·THF, THF, reflux, 6 h then HCl/MeOH, reflux, 2 h; (vii) Et_3N, pH 8, $(BOC)_2O$, MeCN, 4 h, 78% (two steps); (viii) K_2CO_3, DMF, 5 h, 88%; (ix) repeat (iii), (iv), (v) 91% (three steps); (x) BH_3·THF, THF, 0°C, 10 h, 98%.



Scheme 4. *Reagents and conditions*: (i) NaHMDS, phosphonate, **16**, 78°C, then **11**, −78°C to rt, 30 min, 82% (1:1 *E*/*Z*); (ii) HF-pyr, HCl·H_2NOBn, rt, 10 h, 89% (two steps); (iii) $RhCl_3 \cdot 3H_2O$ (4% w/v), EtOH, reflux, 12 h, 76%; (iv) K_2CO_3, DMF, 4 h, 91%; (v) LiOH, THF:MeOH:H_2O (4:1:1 v/v/v); (vi) AllylBr, K_2CO_3, 83% (two steps); (vii) repeat (i) and (ii) 73% (two steps; (viii) $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, THF, 3 h, 90%.



Scheme 5. *Reagents and conditions*: (i) DCC, HOBT, CH_2Cl_2, 10 h, 78%; (ii) LiOH, THF:MeOH:H_2O (4:1:1 v/v/v); (iii) C_6F_5OH, DCC, CH_2Cl_2, 10 h, 81% (two steps); (iv) HCl, CH_2Cl_2, pH 2, 4 h, then dilute to 0.005 M in CH_2Cl_2, Et_3N, pH 8, rt 3 days, 60%.

EtOH[16] to give the phenol **19** (76%). S_NAr coupling of **19** with 3-bromo-4-fluoro-6-nitro-benzaldehyde (**20**, prepared from **10**[17]) proceeded in 91% to give the nitro diphenyl ether **21**.[18]

Transesterification of **21** was required to differentiate the two carboxylate groups after the second Horner–Emmons reaction. Alkylation of the carboxylic acid liberated by saponification of **21** (LiOH, MeOH–THF–H_2O) gave allyl ester **22** which was immediately transformed by Horner–Emmons reaction and desilylation–oximation, as before, to provide **23** (61%, four steps). Catalytic deprotection of the allyl ester **23** under mild reducing conditions ($Pd(OAc)_2$, PPh_3, Et_3N, HCOOH,[19] THF, 3 h, 90%) gave the *E*,*E*-bis-oximino carboxylic acid **8**[15] and set the stage for the macrocycle closure (Scheme 5).

Coupling of *N*-BOC diamine **7** with acid **8** (DCC, HOBt, CH_2Cl_2) gave the protected tetracycle **24** in 78% yield. We chose to employ the activated pentafluorophenol (Pfp) ester **25** that would undergo macrolactamization upon removal of the *N*-BOC group in the western hemisphere. Saponification of **24** and re-esterification of the resultant carboxylic acid with C_6F_5OH (DCC) gave **25** (81%). Removal of the *N*-BOC group in **25** (HCl, CH_2Cl_2) was followed by dilution to 5 mM with CH_2Cl_2 and basification with Et_3N (pH ~8). After 3 days, cyclized product **6**[20] was obtained in a reproducible yield of 60% (three trials). The overall yield for the synthesis of **6** from **9** was 16% (16 steps, longest linear sequence). Efforts are underway to prepare related photoaffinity analogs of **6** and evaluate their activity in Ca^{2+} channel modulation.[21]

In conclusion, we have demonstrated a highly-convergent strategy to the intact bastarane carbon skeleton and the synthesis of the tetrabromo bastadin analog **6**. The method can be applied generally to other bastadins and demonstrates the utility of S_NAr susbtitutions to provide control *meta*- versus *para*-diaryl ethers in highly substituted bastadin macrocycles.[22]

Acknowledgements

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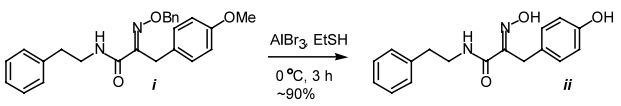
References

1. (a) Kazlauskas, R.; Lidgard, R. O.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett*. **1980**, *21*, 2277–2280; (b) Kazlauskas, R.; Lidgard, R. O.; Murphy, P. T.; Wells, R. J.; Blount, J. F. *Aust. J. Chem*. **1981**, *34*, 765–786; (c) Miao, S.; Andersen, R. J. *J. Nat. Prod*. **1990**, *53*, 1441–1446; (d) Pordesimo, E. O.; Schmitz, F. J. *J. Org. Chem*. **1990**, *55*, 4704–4709; (e) Dexter, A. F.; Garson, M. J.; Hemling, M. E. *J. Nat. Prod*. **1993**, *56*, 782–786; (f) Gulavita, N. K.; Wright, A. E.; McCarthy, P. J.; Pomponi, S. A.; Kelly-Borges, M.; Chin, M.; Sills, M. A. *J. Nat. Prod*. **1993**, *56*, 1613–1617; (g) Jaspars, M.; Rali, T.; Laney, M.; Schatzman, R. C.; Diaz, M. C.; Schmitz, F. J.; Pordesimo, E. O.; Crews, P. *Tetrahedron* **1994**, *50*, 7367–7374; (h) Mack, M.; Molinski, T. F.; Buck, E. D.; Pessah, I. N. *J. Biol. Chem*. **1994**, *269*, 23236–23349; (i) Park, S. K.; Jurek, J.; Carney, J. R.; Scheuer, P. J. *J. Nat. Prod*. **1994**, *57*, 407–410; (j) Franklin, M. A.; Penn, S. G.; Lebrilla, C. B.; Lam, T. H.; Pessah, I. N.; Molinski, T. F. *J. Nat. Prod*. **1996**, *59*, 1121–1127.
2. Coll, J. C.; Kearns, P. S.; Rideout, J. A.; Sankar, V. *J. Nat. Prod*. **2002**, *65*, 753–756.
3. Carney, J. R.; Scheuer, P. J.; Kelly-Borges, M. *J. Nat. Prod*. **1993**, *56*, 153–157.
4. Pessah, I. N.; Molinski, T. F.; Meloy, T. D.; Wong, P.; Buck, E. D.; Allen, P. D.; Mohr, F. C.; Mack, M. M. *Am. J. Physiol*. **1997**, *41*, C601.
5. (a) Nishiyama, S.; Suzuki, T.; Yamamura, S. *Chem. Lett*. **1982**, 1851; (b) Nishiyama, S.; Yamamura, S. *Tetrahedron Lett*. **1982**, *23*, 1281.
6. Guo, Z. W.; Machiya, K.; Salamonczyk, G. M.; Sih, C. J. *J. Org. Chem*. **1998**, *63*, 4269.
7. For a discussion on regioisomers produced from tandem macrolactamization of pairs of bis-azlactone-diamines, see: Bailey, K. L.; Molinski, T. F. *J. Org. Chem*. **1999**, *64*, 2501.
8. (a) Couladouros, E. A.; Moutsos, V. I. *Tetrahedron Lett*. **1999**, 7027; (b) Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T. Y.; Li, H.; Bräse, S.; Ramanjulu, J. M. *J. Am. Chem. Soc*. **1997**, *119*, 3421. For an example of triazene meditated coupling applied to bastadin-12, see: Couladouros, E. A.; Moutsos, V. I. *Tetrahedron Lett*. **1999**, *40*, 7023.
9. Leone-Stumpf, D.; Lindel, T. *Chem. Eur. J*. **2001**, *7*, 3961.
10. For recent examples of *intramolecular* S_NAr ring closure in natural products synthesis, see: (a) Evans, D. A.; Wood, M. R.; Watson, P. S.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed*. **1998**, *37*, 2700–2704; (b) Mori, Y.; McAtee, J. J.; Rogel, O.; Boger, D. L. *Tetrahedron Lett*. **2001**, *42*, 6061–6064; (c) Boger, D. L. *Med. Res. Rev*. **2001**, *21*, 356–381; (c) Boger, D. L.; Kim, S. H.; Mori, Y.; Weng, J. H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc*. **2001**, *123*, 1862–1871; (d) Boger, D. L.; Weng, J. H.; Miyazaki, S.; McAtee, J. J.; Castle, S. L.; Kim, S. H.; Mori, Y.; Rogel, O.; Strittmatter, H.; Jin, Q. *J. Am. Chem. Soc*. **2000**, *122*, 10047–10055; (e) Boger, D. L.; Kim, S. H.; Miyazaki, S.; Strittmatter, H.; Weng, J. H.; Mori, Y.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc*. **2000**, *122*, 7416–7417.
11. Pschoor, R. *Justus Liebigs Anal. Chem*. **1912**, 29.
12. Wymann, W. E.; Davis, R.; Patterson, J. W., Jr.; Pfister, J. R. *Synth. Commun*. **1988**, *18*, 1379–1384.
13. Thomas, R. M.; Mohan, G. H.; Iyengar, D. S. *Tetrahedron Lett*. **1997**, *38*, 4721.
14. Phosphonate **14** was made in 79% from ethyl glyoxylate (two steps). For phosphonate preparation, see: Nakamura, E. *Tetrahedron Lett*. **1981**, *22*, 663; for TBS protection, see: Plantier-Royon, R.; Anker, D.; Robert-Baudouy, J. *J. Carbohydr. Chem*. **1991**, *10*, 239.
15. The *E*-oxime configuration in **18** assigned by ^{13}C NMR which correlates with an upfield shift (δ 30.9 ppm) caused by steric compression of the α-CH_2 carbon in *E*-ketoximines, as seen in all bastadins ($\delta \sim 28$–29 ppm, see Ref. 1), compared to the corresponding signal in *Z*-ketoximes ($\delta \sim 35$ ppm), cf. Arabshahi, L.; Schmitz, F. J. *J. Org. Chem*. **1987**, *52*, 3584.
16. (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem*. **1973**, *38*, 3224; (b) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. *J. Am. Chem. Soc*. **1976**, *98*, 7102.
17. Aldehyde **20** was prepared in 98% yield by nitration of **10**, cf.: Michael, F. J.; Noffz, D. *Chem. Ber*. **1957**, *90*, 1586.
18. Use of the *meta*-nitrobenzaldehyde **20**, rather than the *ortho*-nitro isomer, could provide analogs of **1** that locate a photoaffinity label at a site removed from steric congestion next to the diaryl ether bond. Model studies (Bailey, K. B. Ph.D. thesis, 2002, University of California, Davis) show that 3-bromo-4-fluorobenzaldehyde is sufficiently activated to participate in similar S_NAr displacements. Therefore, the *meta*-NO_2 group in **20** imparts little or no activation, as expected.
19. Corey, E. J.; Choi, S. *Tetrahedron Lett*. **1993**, *34*, 6969.
20. Pfp ester **24** (50.0 mg, 0.03 mmol) was stirred in CH_2Cl_2 saturated with $HCl_{(g)}$ (2 mL) at pH 2 for 5 h. Additional CH_2Cl_2 was added to a dilution of 0.005 M, and reaction mixture adjusted to pH 8 with TEA. The macrolactamization proceeded at ambient temperature for 3 days. The mixture was concentrated and purified over SiO_2 to give **24** as a tan oil (21.3 mg, 60%); ^1H NMR (400 MHz, $CDCl_3$) δ 2.57 (t, $J=6.0$ Hz), 2.76 (t, $J=6.0$ Hz, 2H), 3.28 (dd, $J=6.0$, 6.0 Hz, 2H), 3.49 (dd, $J=6.0$, 6.0 Hz, 2H), 3.80 (s, 3H), 3.87 (s, 2H), 3.95 (s, 3H), 4.11 (s, 2H), 5.11 (s, 2H), 5.16 (s, 2H), 6.43 (d, $J=2.0$ Hz, 1H), 6.59 (t, $J=6.0$ Hz, 1H), 6.81 (d, $J=8.4$ Hz, 1H), 6.85 (t, $J=6.0$ Hz, 1H), 6.95 (d, $J=2.0$ Hz, 1H), 7.00 (s, 1H), 7.05 (dd, $J=2.0$, 8.4 Hz, 1H), 7.20 (dd, $J=2.0$, 8.4 Hz, 1H), 7.28 (m, 10H), 7.35 (d, $J=8.4$ Hz, 1H), 7.38 (d, $J=8.4$ Hz, 1H), 7.42 (dd, $J=2.0$, 8.4 Hz, 1H), 7.56 (s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 26.7 (CH_3), 28.7 (CH_2), 34.8 (CH_2), 34.9 (CH_2), 40.2 (CH_2), 40.7 (CH_2), 61.1 (CH_3), 61.3 (CH_3), 77.6 (CH_2), 77.7 (CH_2), 112.2 (CH), 114.7 (C), 117.3 (CH), 117.5 (C), 118.0 (C), 118.3 (C), 118.8 (C), 120.8.5 (CH), 121.7 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.5 (CH), 131.4 (CH), 133.9 (C), 134.0 (CH), 135.8 (C), 136.2 (C), 136.5 (CH), 136.7 (C), 146.0 (C), 147.5 (C), 147.6 (C), 148.6

(C), 150.3 (C), 150.7 (C), 151.1 (C), 151.3 (C), 153.0 (C), 161.7 (C), 162.0 (C); MALDI MS found m/z 1211.9778 $[M+Na]^+$, $C_{50}H_{43}N_5O_{10}Br_4Na$ requires 1211.9641.

21. Model studies were carried out on deprotection of the final products. For example, exposure of the model compound ***i*** to selective ether cleavage conditions gave ***ii*** in excellent yield (Bailey, K. L.; Molinski, T. F., unpublished; Boger, D. L.; Weng, J. H.; Miyazaki, S.; McAtee, J. J.; Castle, S. L.; Kim, S. H.; Mori, Y.; Rogel, O.; Strittmatter, H.; Jin, Q. *J. Am. Chem. Soc.* **2000**, *122*, 10047–10055).



22. The alternative approach to construction of the macrolactam—formation of the amide bonds first then *macrocyclization* by intramolecular S_NAr substitution—is the subject of current investigation in our lab.