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A general synthetic route towards bastadins. Part 1: Synthesis of the eastern part of bastadins 4–16

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Abstract

A general synthetic route for the construction of the eastern part of the macrocyclic bastadins 4–16 is presented. The brominated biaryl ethers are synthesized using the iodonium salt method. The synthesis is accomplished within 18 steps in 15.5% overall yield. © 1999 Elsevier Science Ltd. All rights reserved.

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Bastadins, natural products isolated from the marine sponges *Ianthella basta* and *Psammaplysilla purpurea*,[1] are a family of linear or macrocyclic bis-biaryl ether tetrapeptides possessing brominated aryl units and a unique α-oximino amide bond. In addition to their antibacterial, cytotoxic and anti-inflammatory activity, they constitute a new class of chemical probes for studying immunophilin/ryanodine-sensitive Ca^{2+} channel interactions in skeletal muscle.[2] More specifically, bastadin-5 enhances the FK506 induced release of FKBP12,[3] whereas FK506 promotes the dissociation of FKBP12 from the RyR-1 membrane complex. Notwithstanding the limited supply from natural sources and the significant biological activity of bastadins, the development of a general methodology leading to efficient preparation of all members of this class constitutes a synthetic challenge. Two successful total syntheses of macrocyclic bastadins have been reported to date.[4] However, they are restricted in the preparation of bastadin-6, which is symmetrically brominated on the aromatic rings (Fig. 1; Y^1,Y^3=Br).

Continuing our ongoing investigation in the area of biaryl ether natural products,[5] we would like to present a new synthetic approach, which may serve as a general route for the construction of all macrocyclic bastadins (excepting bastadin 13).

In order to ensure flexibility and general applicability, a synthetic strategy has to employ: (i) a general precursor capable of yielding all variations in the W–Z region; and (ii) a convenient and efficient method for the construction of heavily functionalized and asymmetrically brominated biaryl ethers. In order

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	Y^1	Y^2	Y^3	W–Z
Bastadin-4	H	Br	Br	
Bastadin-7	H	Br	H	
Bastadin-11	H	H	Br	
Bastadin-14	Br	Br	H	
Bastadin-8	H	Br	Br	
Bastadin-10	H	Br	H	
Bastadin-12	Br	Br	H	
Bastadin-17	H	H	Br	
Bastadin-5	H	Br	Br	
Bastadin-6	Br	Br	Br	
Bastadin-9	H	H	Br	
Bastadin-15	Br	Br	H	
Bastadin-16	Br	H	Br	

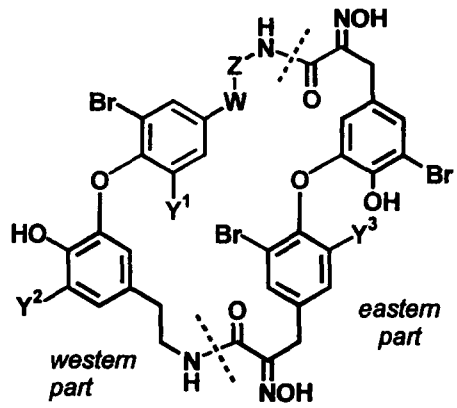
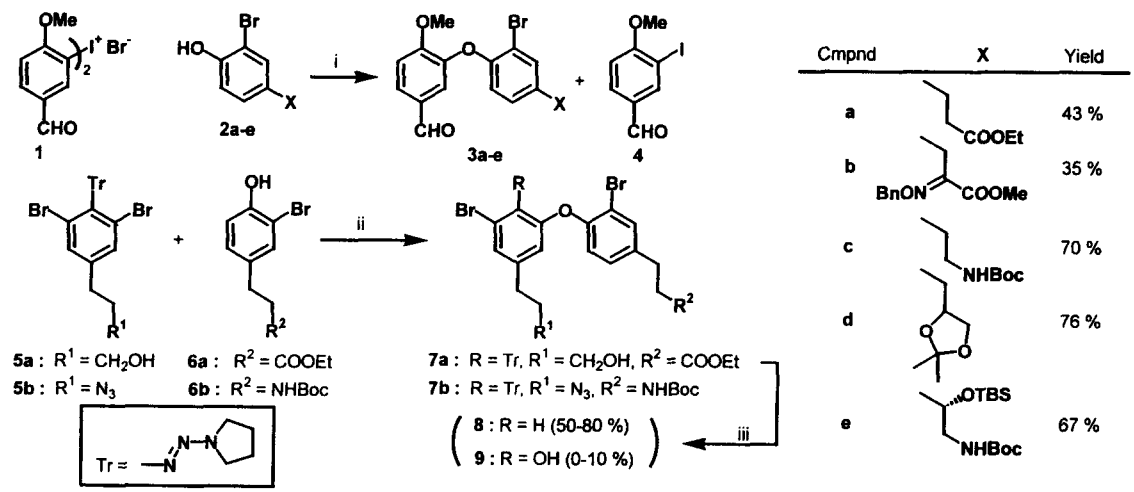
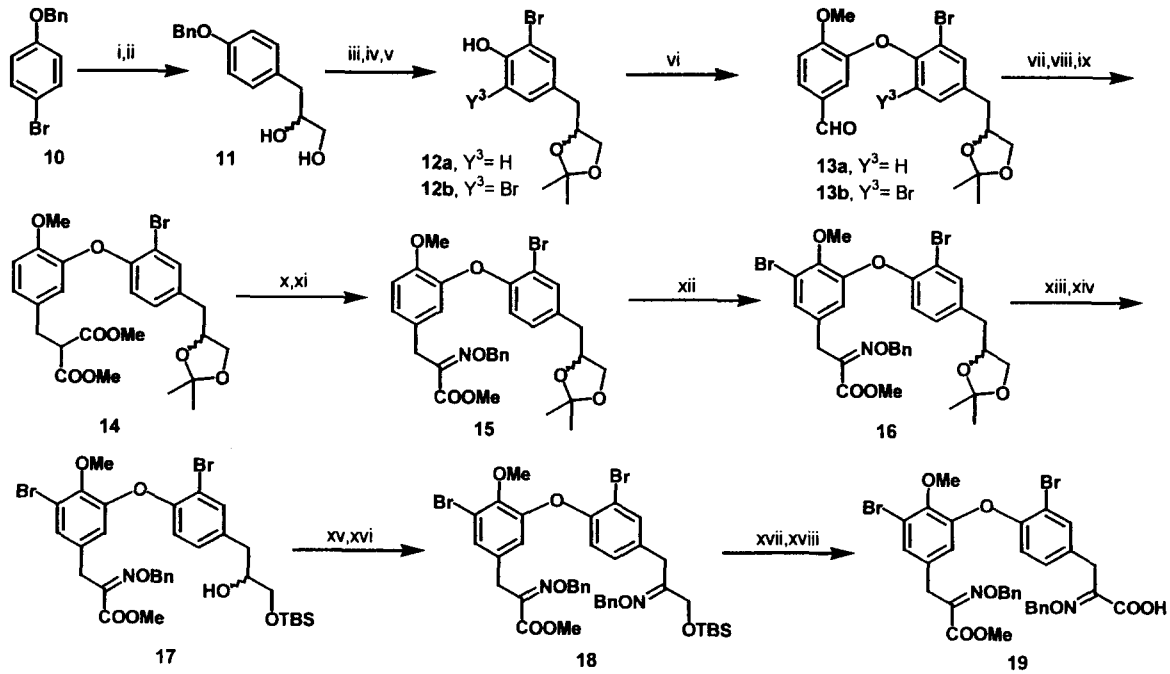


Figure 1. Bastadins found in *Ianthella basta*

to address the first issue, the hydroxy functionality was considered as a potentially suitable precursor. With regard to the coupling method, among the various procedures found in literature,[6] the Nicolaou approach,[7] which involves an efficient coupling of various triazenes with phenols (compounds **5a–6a** and **5b–6b**, Scheme 1), would lead to synthetic schemes of high convergence. However, the transformation of the triazene moiety to phenol was found to be problematic, since under several experimental conditions, substrate **7a** or several other model compounds, were mainly converted to the reduced product.[8] As a result, the task of removing two triazenes at the final stages would be 'prohibiting' for a highly efficient synthesis. Therefore, the iodonium salt method[9] was considered more appropriate, although less flexible. Satisfactory yields were only achieved when the aliphatic side chain of the phenol was deprived of acidic or enolizable protons (compare coupling yields of **2a–2e** with **1**, Scheme 1). In addition, variations on the substitution of the iodonium salt were greatly restricted, since strong mineral acids were necessary for its preparation.



Scheme 1. Model studies for the formation of brominated biaryl ethers. Reagents and conditions: (i) NaH, DMF, 90°C, **1**; (ii) K_2CO_3, CuBr·Me_2S, pyridine, CH_3CN, 80°C, 75–80%; (iii) THF/HCl 1N, or Dowex H^+ resin/CH_3CN/H_2O



Scheme 2. Synthesis of the eastern segment of bastadins 7, 10, 12, 14 and 15. Reagents and conditions: (i) Mg, THF, reflux, allyl bromide, 93%; (ii) $K_2OsO_2(OH)_2$, *tert*-BuOH/H_2O, $K_3Fe(CN)_6$, K_2CO_3, rt, 99%; (iii) 2,2-dimethoxypropane, acetone, PPTS, rt, 95%; (iv) H_2, AcOEt, 10% Pd/C, rt, 99%; (v) NBS (1 or 2.1 equiv.), DMF, rt, 87% for **12a**, 92% for **12b**; (vi) NaH, DMF, **1**, 90°C, 76% from **12a**, 78% from **12b**; (vii) $NaBH_4$, MeOH/THF 1/1 (v/v), rt, 95%; (viii) I_2, Ph_3P, imidazole, rt, 90%; (ix) $Na^+{}^-CH(COOMe)_2$, Et_2O, rt, 85%; (x) BuONO, MeONa, MeOH, 0°C, 85%; (xi) BnBr, NaH, DMF, rt, 87%; (xii) NBS, CH_3CN, 50°C, 85%; (xiii) HCl 1N, THF, rt, 100%; (xiv) TBSCl, imidazole, DMF, rt, 97%; (xv) TEMPO, NaOCl, acetone, KBr, $NaHCO_3$, 0°C, 85%; (xvi) $BnONH_2 \cdot HCl$, pyridine/EtOH 1/2 (v/v), 100°C, 92%; (xvii) TBAF, THF, rt, 100%; (xviii) TEMPO, NaOCl, acetone, KBr, $NaHCO_3$, 0°C, 78%. TBS=*tert*-Butyldimethylsilyl, NBS=*N*-bromosuccinimide, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy, TBAF=tetrabutylammonium fluoride, PPTS=pyridinium *p*-toluenesulfonate

Accordingly, the preparation of the eastern part of the bastadins was accomplished as follows (Scheme 2). Allylation of *p*-benzyloxybromobenzene **10**[10] and subsequent dihydroxylation with osmium tetroxide yielded diol **11**, which after acetonidation and phenol deprotection was subjected to NBS bromination. Depending on the equivalents of NBS used, mono- or di-*ortho*-brominated phenols **12a** or **12b** were synthesized. Intermediates **12a** or **12b** were readily subjected to coupling using the iodonium salt **1**,[7g] affording the desired biaryl ethers **13a** or **13b** in relatively high yield. At this point we decided to proceed with biaryl ether **13a**, which would provide an entry to asymmetrically brominated bastadins (Y^3=H). Thus, aldehyde **13a**, after reduction and subsequent iodination under Samuelsson[11] conditions, was condensed with the sodium salt of dimethyl malonate providing biaryl ether **14**. The carbanion of **14** attacked *n*-butylnitrite[12] yielding after benzylation the corresponding α-benzyloximino-methyl carboxylate **15**, as a single isomer. After several attempts, this was found to be the most appropriate stage to brominate the other aromatic ring. Thus, compound **15** after treatment with excess NBS in CH_3CN, was regiospecifically converted to brominated compound **16** in high yield. For the construction of the right part of the molecule, the acetonide moiety of compound **16** was acidically cleaved and after selective silylation of the primary hydroxyl group, alcohol **17** was obtained. Free radical oxidation with TEMPO[13] and subsequent benzyloximation of the resulting ketone afforded bis-benzyloxime **18**, as a mixture of *E* and *Z* isomers. The latter was smoothly converted to the desired eastern fragment (**19**) of bastadins 7, 10, 12, 14 and 15 after desilylation and free radical oxidation. The mixture could be separated

by column chromatography after the desilylation step. Although at the final stages of the synthesis both isomers could be in principle induced to adopt the more stable form observed in the natural product, in order to simplify the characterization of the intermediates, we opted to continue our synthesis using one of them. The eastern part of the remaining members (bastadins 4–6, 8–9, 11, 16–17) could be similarly synthesized using dibrominated intermediate **13b** as the starting material.

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