Pergamon

Tetrahedron Letters 40 (1999) 7027–7030

TETRAHEDRON LETTERS

A general synthetic route towards bastadins. Part 2: Synthesis of the western part of bastadins 4–16, and fully functionalized macrocycle of bastadin 12

Elias A. Couladouros [a,b,*] and Vassilios I. Moutsos [a,b]

[a] *Department of Chemistry, Agricultural University of Athens, Iera Odos 75, Athens 118.55, Greece*

[b] *Organic and Bioorganic Chemistry Laboratory, NCSR Demokritos 153.10 Ag. Paraskevi, Attikis, PO Box 60228, Athens, Greece*

Received 1 July 1999; accepted 21 July 1999

Abstract

A general synthetic route for the construction of the western part of the macrocyclic bastadins 4–16 is presented. The western and the eastern segments were coupled using the imidazolide of the corresponding acid. The bromine at position Y^2 may be added at this advanced step regiospecifically, strengthening the convergence of the presented approach. Finally, the fully functionalized α,ω-aminoacid is cyclized with EDC affording the macrocyclic ring of bastadin-12 in 72% yield (3.5% overall yield). © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: bastadins; iodonium salt; synthesis; natural products; aromatic bromination.

Aiming towards a general method for the synthesis of the title compounds we have shown an efficient route for the construction of the eastern part, utilizing iodonium salt methodology for the formation of the biaryl ether.[1] This present report elaborates a similar approach for the synthesis of the western part of bastadins (Fig. 1).

As was noted in the preceding article, the necessary hydroxyl functionality of the W–Z region was introduced with the desired stereochemistry in the early stages of the synthesis using the Sharpless protocol[2] for the dihydroxylation of terminal alkene **2** (Scheme 1). Subsequent selective tosylation and displacement with azide anion afforded azide **3**. Silylation of the secondary hydroxyl group, reduction of the azide moiety,[3] concomitant one-pot Boc-protection of the resulting amine and subsequent hydrogenolysis of the benzyl ether, provided phenol **4**. At this point, *ortho*-, mono-, or dibromination could be performed with satisfactory selectivity. However, the differentiation at Y^1 position was thought to be more appropriate at a later stage, thus proceeding with the dibromide intermediate only. The newly formed dibromo-phenol **6** was converted to the corresponding sodium salt and coupled with iodonium salt **1** affording biaryl ether **7**. The latter, after sodium borohydride reduction, displacement by iodine and one carbon elongation using cyanide anion provided nitrile **8**. Luckily, nitrile **8** could be transformed to

* Corresponding author. Tel: +30-1 6503 679; fax: +30-1 677 7849; e-mail: ecoula@mail.demokritos.gr

PII: S0040-4039(99)01430-6

	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	

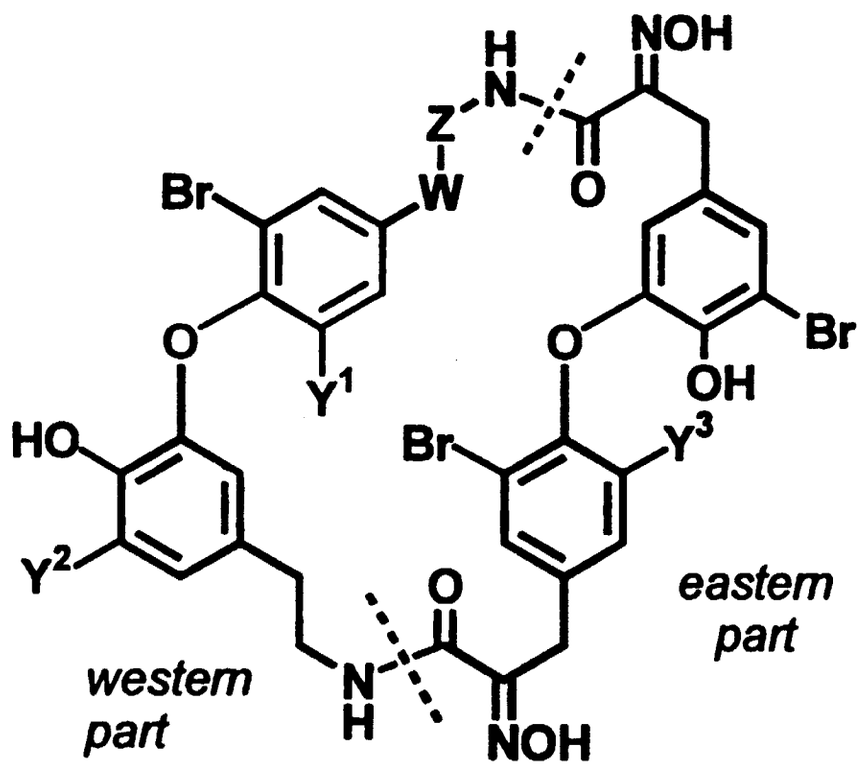
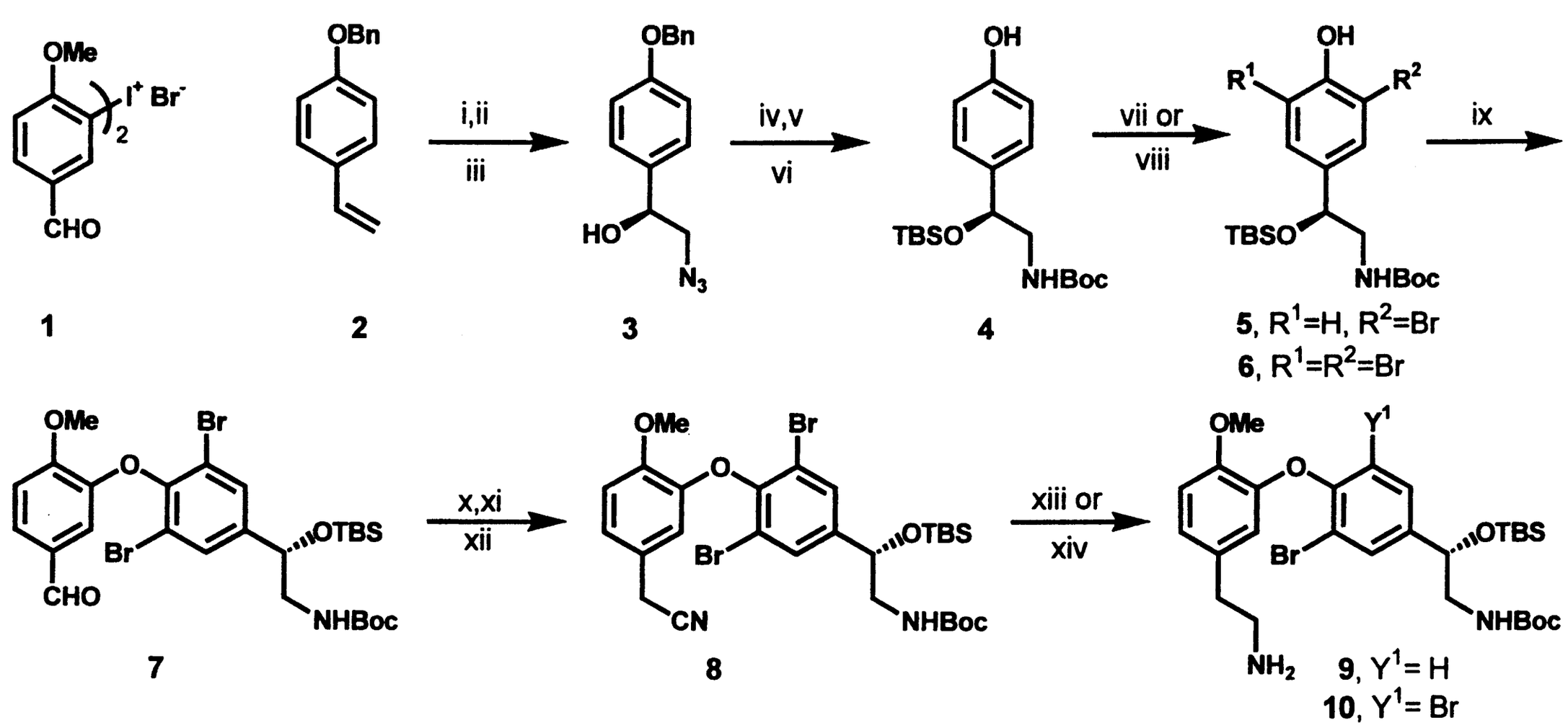


Figure 1. Bastadins found in *Ianthella basta*

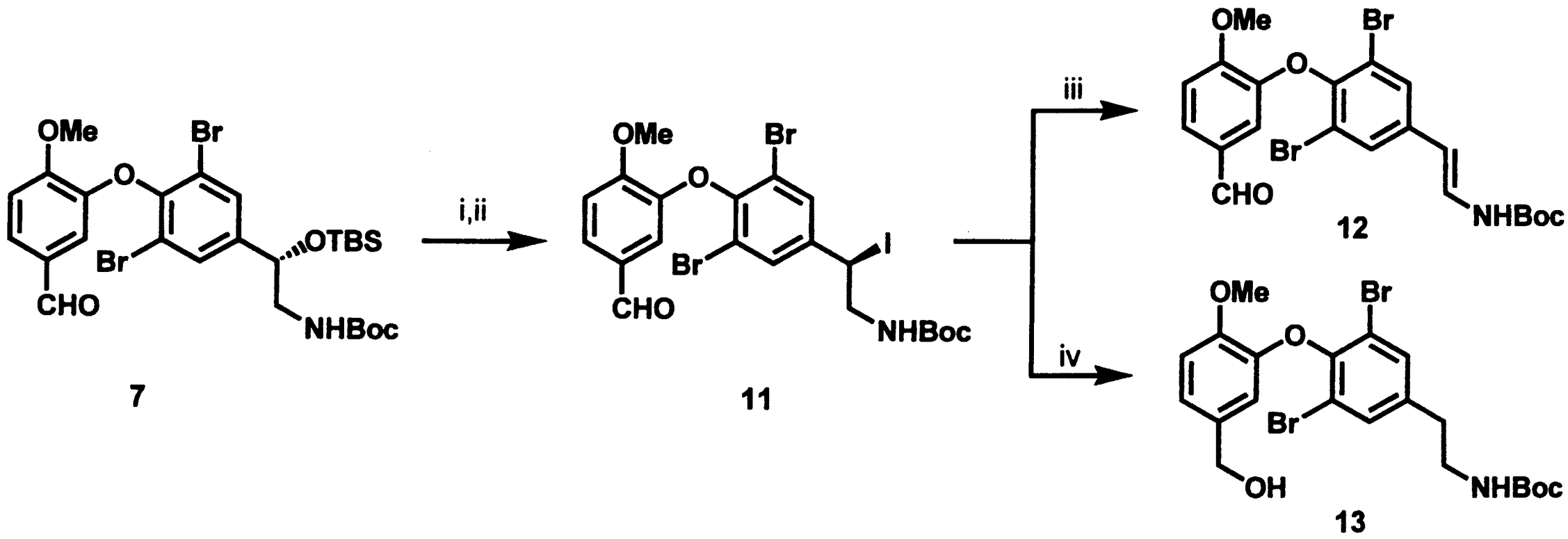
mono- or dibromo-amine intermediates **9** or **10** by simply altering the metal during the reduction process[4] as described in Scheme 1. The mono-bromide **9** was selectively synthesized using $NiCl_2$, whereas the dibromide **10** was prepared as an 8:2 mixture with monobromide **9**, utilizing $CoCl_2$. Hence, the synthesis of the western part of bastadins 9, 11, 16 and 17 was accomplished in high overall yield and convergence.



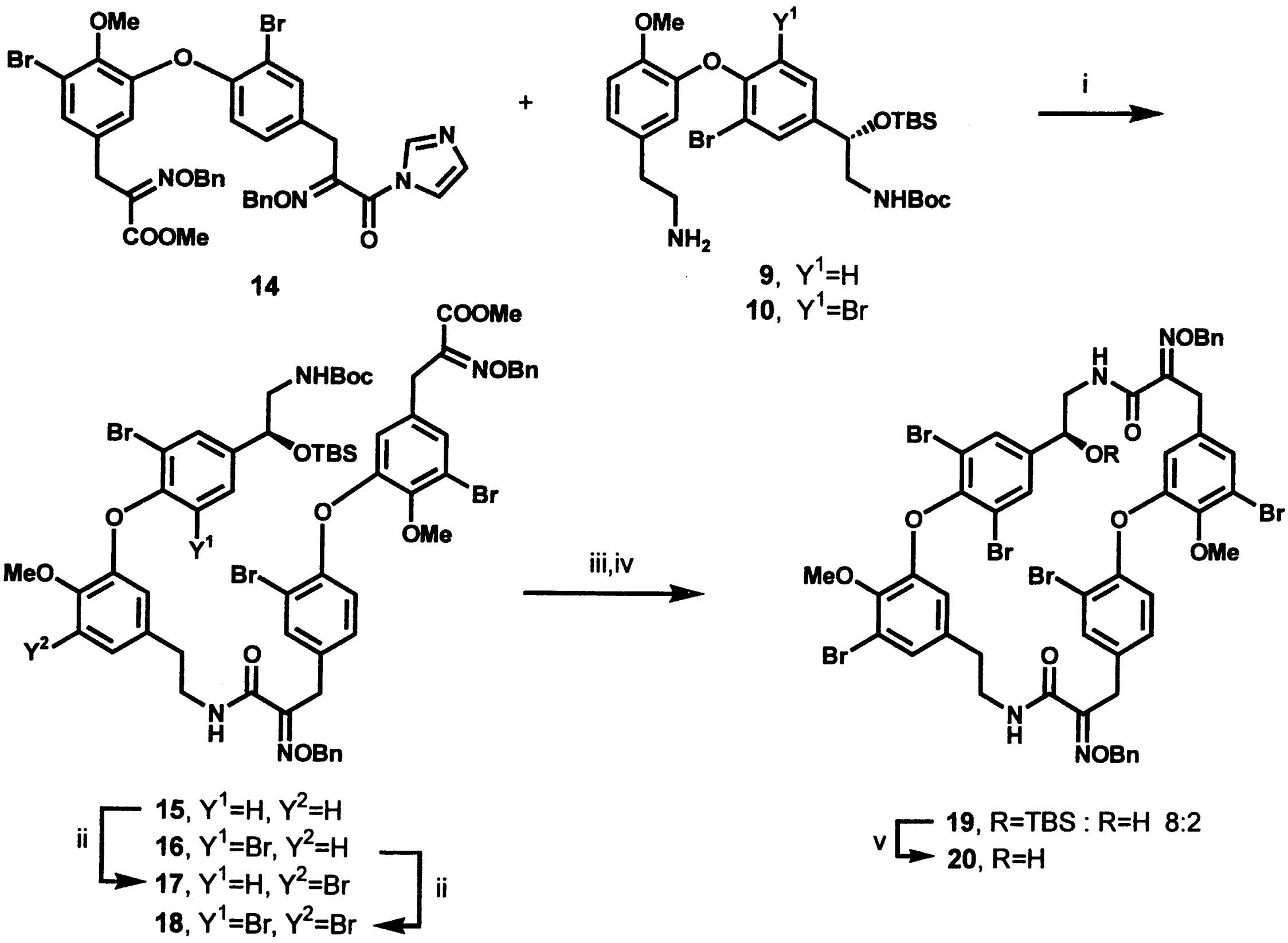
Scheme 1. Synthesis of the western segment of bastadins 9, 11, 16, 17. Reagents and conditions: (i) Sharpless AD-mix-α, 96%, 97% ee; (ii) TsCl, pyridine/CH_2Cl_2, 0°C, 93%; (iii) NaN_3, DMF, 50°C, 87%; (iv) TBSCl, imidazole, DMF, rt, 97%; (v) PPh_3, H_2O, THF, $(Boc)_2O$, rt, 95%; (vi) H_2, AcOEt, 10% Pd/C, rt, 98%; (vii) NBS (1 equiv.), DMF, rt, 88%; (viii) NBS (2 equiv.), DMF, rt, 82%; (ix) NaH, DMF, 90°C, **1**, 68%; (x) $NaBH_4$, THF/MeOH 1/1 (v/v), rt, 95%; (xi) I_2, Ph_3P, imidazole, THF, rt, 92%; (xii) KCN, DMF, 40°C, 98%; (xiii) $NaBH_4$, $NiCl_2$, MeOH, 0°C, 75% (compound **9**); (xiv) $CoCl_2$, $NaBH_4$, MeOH, 0°C, 70% (8:2 mixture, **10**:**9**). TBS=*tert*-Butyldimethylsilyl, NBS=*N*-bromosuccinimide, Ts=*p*-toluenesulfonyl, $(Boc)_2O$=di-*tert*-butyl dicarbonate

In order to explore the utilization of the hydroxyl group as a general precursor for all functionalities present at the W–Z region of bastadins, compound **7** (Scheme 2) was transformed after desilylation to the corresponding iodide **11**. The latter was smoothly converted either to alkene **12** or alkane **13** using DBU

or $NaBH_4$, respectively, providing the necessary intermediates for the construction of bastadins 4–7, 9, 11 and 14–16.



Scheme 2. Chemistry on the W–Z region. Reagents and conditions: (i) TBAF, THF, rt, 98%; (ii) I_2, Ph_3P, imidazole, THF, rt, 90%; (iii) DBU, THF, rt, 85%; (iv) $NaBH_4$, THF/MeOH 1/1 (v/v), rt, 62%. DBU=1,8-Diazabicyclo[5.4.0]undec-7-ene, TBAF=tetrabutylammonium fluoride



Scheme 3. Synthesis of fully protected bastadin-12. Reagents and conditions: (i) THF, **9** (yield 65%) or **10** (yield 67%); (ii) excess NBS, CH_3CN, 80°C, **15** to **17**, 75%, **16** to **18**, 78%; (iii) LiOH 3N/MeOH/THF 1/1/1 (v/v/v), rt, 95%; (iv) TFA/CH_2Cl_2 1/1 (v/v), rt, 30 min then EDC, HOBt, DMF, 67%; (v) TBAF, THF, rt, 98%. HOBt=*N*-Hydroxybenzotriazole, EDC=1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, TFA=trifluoroacetic acid

Having both parts of the molecule available, the synthesis of the cyclic skeleton of bastadins was attempted. In order to study the efficiency of macrolactamization (Scheme 3), four protected aminoacids (**15**, **16**, **17** and **18**) were used as advanced intermediates. Several experiments revealed that these aminoacids could be synthesized in good yields through coupling of imidazolide **14** with primary amines **9** or **10**. Subsequently, these open bastadin precursors could be selectively brominated at Y^2 position with NBS.[5] It is worth mentioning, that this was a regiospecific bromination due to the heavy substitution of the other aromatic rings with relatively bulky alkyl or aryloxy substituents. The only available activated position for addition was the one *ortho*- to the methoxy group. The terminal amino and carboxylic acid functionalities were unmasked via saponification and trifluoroacetic acid treatment and the resulting amino acid underwent in situ cyclization using EDC and *N*-hydroxybenzotriazole to afford a mixture of bastadin precursor **19** and its desilylated analog **20**, in satisfactory yield. This mixture was treated with TBAF providing compound **20** in 67% overall yield from precursor **18**.

In conclusion, we have developed an efficient strategy for the synthesis of all possible variations of the bastadin framework. Using these fragments we have synthesized for the first time the macrocyclic skeleton of bastadin-12 possessing the 'unsymmetrical' bromination pattern and an asymmetric hydroxyl group. We are currently working on the assembly of all other members of this family of natural products and the completion of their total synthesis.

Acknowledgements

We would like to thank ALCHIMICA and UNIPHARMA S.A. for their financial support. V.I.M. would like to thank the National Scholarship Foundation of Greece for a scholarship.

References

1. Couladouros, E. A.; Moutsos, V. I. *Tetrahedron Lett.* **1999**, *40*, 7023–7026.
2. (a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585–4588; (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.
3. (a) Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763–764; (b) Knouzi, N.; Vaultier, M.; Carrié, R. *Bull. Soc. Chim. Fr.* **1985**, 815–819.
4. Satoh, T.; Suzuki, S. *Tetrahedron Lett.* **1969**, 4555–4558.
5. Carreño, M. C.; Ruano, J. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328–5331.