Pergamon

Tetrahedron Letters, Vol. 38, No. 19, pp. 3345-3348, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00654-0

Rapid and Efficient Solid Phase Syntheses of Cyclic Peptides with Endocyclic Biaryl Ether Bonds

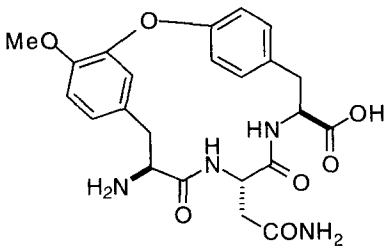
Kevin Burgess[a]* Dongyeol Lim,[a] Michele Bois-Choussy,[b] and Jieping Zhu[b]*

[a] Department of Chemistry, Texas A & M University, College Station, TX 77843 USA. burgess@chemvx.tamu.edu
[b] Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France. jieping.zhu@icsn.cnrs-gif.fr

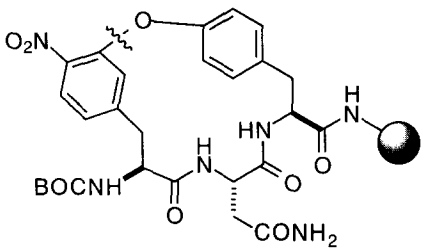
Key Words: vancomycin, OF4949, S_NAr, fluoronitroaryl, macrocyclization.

Abstract: Solid phase syntheses of the OF4949 derivatives **1** and **6 - 9** were performed via protection/deprotection of tyrosine side-chains on a support, and S_NAr macrocyclization reactions.

Solid phase synthesis techniques allow for rapid production of target molecules without the need for tedious and time consuming synthetic maneuvers to purify intermediates. The desirable features of preparations on supports have become topical with the recent emergence of combinatorial techniques, many of which require methods for solid phase syntheses, but they have been appreciated in peptide chemistry for decades. Solution phase peptide syntheses that take months or even years to perform can often be executed on the solid phase in a matter of days or weeks. It is therefore surprising that methods for solid phase syntheses have not been applied to heterodectic peptides with biaryl ether linkages like OF4949.[1] Reported here are solid phase syntheses of molecules related to OF4949 which we regard as a prelude to supported preparations of more complex targets in the vancomycin/teicoplanin series. The disconnection featured in this work will be macrocyclization via biaryl ether bond formation as implied below.



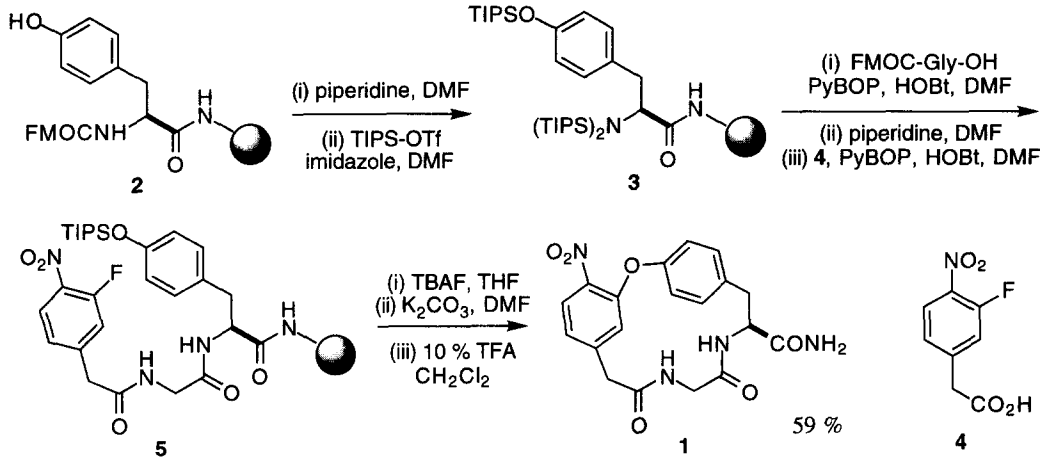
OF 4949 III



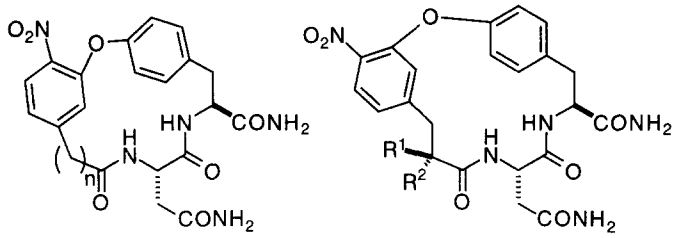
The anticipated strategy for this work was as follows. Supported linear peptidic substrates were to be constructed on a solid phase via standard techniques. Masking groups had to be found that would allow the phenolic hydroxyl of a tyrosine residue to be deprotected without cleaving the molecule from the support. Ring closure with concomitant formation of biaryl ether bonds was to be effected via S_NAr displacement reactions involving phenolate nucleophiles and fluoronitroaryl electrophiles.[2-17] The latter reaction has been

studied intensively by one of our research groups,[2-4,6-8,10,11,14,15] and by others.[5,9,12,13,16,18] We feel that it has significant advantages over alternatives like classical Ullman couplings,[19] oxidative procedures,[17,20,21] and activation of aromatic rings to nucleophilic attack by organometallics.[22-24]

The first target selected was the 16-membered ring macrocycle **1**. Attempts to construct the cyclization precursor with no tyrosine side-chain protection were complicated by acylation of the phenolic-OH group. Phenolic protection therefore was required but, unfortunately, the commercially available protected tyrosines seemed unsuitable because they are designed for the majority of consumers in the amino acid market, who desire simultaneous phenolic deprotection and cleavage from the resin. Syntheses of suitably protected tyrosine derivatives were contemplated but these hypothetical routes required several steps. Consequently, a method was developed to facilitate protection of the tyrosine side chain on the solid phase (Scheme 1). FMOC-Tyr was coupled to Rink's amide resin[25] until all the reactive amines were consumed (negative ninhydrin test)[26] giving the supported derivative **2**. This was treated with base to *N*-deprotect, then with an excess of triisopropylsilyl triflate (TIPS-OTf). Extensive silylation occurs (complete silylation was observed in less than 5 min in model solution phase experiments) to give an intermediate that probably has structure **3** although the amide bond may also be silylated. Subsequently, the supported cyclization precursor **5** was obtained via a sequence of standard coupling and deprotection steps. In preliminary experiments, the key intermediate **5** was treated with CsF/DMF to effect the ring closure.[15] Encouragingly, the product **1** was obtained in 25 % overall yield (yields quoted throughout this paper are based upon the available functional sites on the support, since the resin is the most expensive component in the synthesis). Later, it emerged that when **5** was instead treated with n-Bu4NF (TBAF) in THF, then with K_2CO_3 in DMF,[11] the overall yield increased to 59 % for this 10 step synthesis.



An approach which parallels that outlined in Scheme 1, but involving Asn(Tr) in place of Gly, was used to prepare the 16- and 17-membered macrocycles **6** and **7**. These compounds were isolated in 35 % and 25 % overall yields, respectively, after HPLC purification. These were the major products on the basis of HPLC analyses of the crude reaction mixtures; there was no evidence for significant epimerization of either the Asn or Tyr chiral centers in these cyclization reactions.



6 n = 1
7 n = 2

8 $R^1 = H_2N$, $R^2 = H$
9 $R^1 = H$, $R^2 = H_2N$

A problem arose in our initial attempts to prepare the OF4949[1] derivative **8** on a solid phase. Specifically, two isomeric compounds having the correct molecular mass (MS) and similar ^1H NMR spectra were isolated in 23 % and 20 % overall yields. These compounds did not interconvert at 150 °C, hence we concluded they were probably not atropisomers. Epimerization at the Asn or Tyr also seemed unlikely since the stereochemical integrity of both these residues was maintained in the syntheses of **6** and **7**. These observations led us to conclude that the two isomers were the desired material **8** and product **9** arising from epimerization at the *N*-terminal amino acid. Consequently, the final cyclization step was re-evaluated, and it was shown that treatment with TBAF alone was sufficient, *ie* reaction of the desilylated material with K_2CO_3 was redundant. When these milder conditions were applied but using the enantiomeric amino acid, *N*-BOC protected *(R)*-(3-fluoro-4-nitrophenyl)alanine, **9** was isolated in 36 % yield; HPLC analysis of the material cleaved from the resin indicated that less than 3 % epimerization had occurred. This experiment demonstrated the efficacy of the milder cyclization method, and proved our hypothesis concerning the identity of the two isomeric products **8** and **9**.

Throughout this work it was convenient to use gel phase ^{19}F NMR to follow the key cyclization step.[27,28] To do this, the resin bearing the cyclization precursors was immersed in an appropriate solvent (THF or DMF), and TBAF/THF was added. The supported substrates are sufficiently mobile to give interpretable ^{19}F NMR spectra using a machine set-up for solution phase experiments; magic angle spinning was not essential.[29] Figure 1 illustrates loss of an aromatic fluoride signal in the formation of a biaryl ether bond, corresponding to the key step in the synthesis of compound **1**.[30]

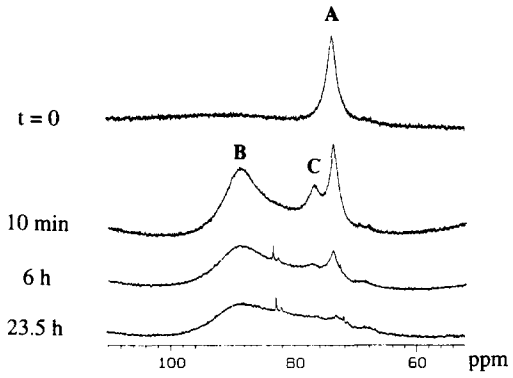


Figure 1. Decay of a ^{19}F NMR resonance corresponding to the cyclization in the solid phase synthesis of **1**. Peak **A** is the aromatic fluorine on the acyclic starting material; **B** and **C** are peaks arising from TBAF (probably an anhydrous and a hydrated form).

In conclusion, this work demonstrates how solid phase S_NAr reactions can be used to cyclize complex starting materials. These syntheses are extremely efficient (*eg* 59 % yield for 10 steps) and they can be repeated in relatively short times. For instance, any of the target molecules (**1**, **6**, **7**, and **9**) can be prepared in less than a week. We offer two predictions based on these observations. First, this type of reaction will be extremely valuable in combinatorial chemistry; indeed, other S_NAr reactions already have been used to prepare libraries.[31] Second, solid phase syntheses of molecules like vancomycin and teicoplanin are possible and will be faster and more convenient than solution phase methods. We are now attempting to prove that our predictions are well founded.

Acknowledgments. We thank The National Institutes of Health and The Robert A. Welch Foundation for support for this research, and K.B. thanks the NIH for a Research Career Development Award and the Alfred P. Sloan Foundation for a fellowship. NMR facilities were provided by the NSF via the chemical instrumentation program.

References and Note

1. Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063.
2. Beugelmans, R.; Zhu, J.; Husson, N.; Bois-Choussy, M.; Singh, G. P. *J. Chem. Soc., Chem. Commun.* **1994**, 439.
3. Beugelmans, R.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 7391.
4. Beugelmans, R.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 5649.
5. Rao, A. V. R.; Reddy, K. L.; Rao, A. S. *Tetrahedron Lett.* **1994**, *35*, 8465.
6. Beugelmans, R.; Singh, G. P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1994**, *59*, 5535.
7. Bois-Choussy, M.; Beugelmans, R.; Bouillon, J.-P.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 4781.
8. Beugelmans, R.; Neuville, L.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 8787.
9. Boger, D. L.; Borzilleri, R. M.; Nukui, S. *Biorg. Med. Chem. Lett.* **1995**, *5*, 3091.
10. Beugelmans, R.; Bourdet, S.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 1279.
11. Zhu, J.; Beugelmans, R.; Bourdet, S.; Chastanet, J.; Roussi, G. *J. Org. Chem.* **1995**, *60*, 6389.
12. Evans, D. A.; Watson, P. S. *Tetrahedron Lett.* **1996**, *19*, 3251.
13. Rao, A. V. R.; Reddy, K. L.; Rao, A. S.; Vittal, T. V. S. K.; Reddy, M. M.; Pathi, P. L. *Tetrahedron Lett.* **1996**, *37*, 3023.
14. Beugelmans, R.; Bigot, A.; Bois-Choussy, M.; Zhu, J. *J. Org. Chem.* **1996**, *61*, 771.
15. Beugelmans, R.; Bois-Choussy, M.; Vergne, C.; Bouillon, J.-P.; Zhu, J. *J. Chem. Soc., Chem. Commun.* **1996**, 1029.
16. Boger, D. L.; Zhou, J. *J. Org. Chem.* **1996**, *61*, 3938.
17. Inoue, T.; Sasaki, T.; Takayanagi, H.; Harigaya, Y.; Hoshino, O.; Hara, H.; Inaba, T. *J. Org. Chem.* **1996**, *61*, 3936.
18. Boger, D. L.; Borzilleri, R. M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1187.
19. Boger, D. L.; Nomoto, Y.; Teegarden, B. R. *J. Org. Chem.* **1993**, *58*, 1425.
20. Suzuki, Y.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6043.
21. Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912.
22. Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc.* **1995**, *117*, 10585.
23. Pearson, A. J.; Bignan, G.; Zhang, P.; Chelliah, M. *J. Org. Chem.* **1996**, *61*, 3940.
24. Pearson, A. J.; Shin, H. *J. Org. Chem.* **1994**, *59*, 2314.
25. Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787.
26. Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. BioChem.* **1970**, *34*, 595.
27. Shapiro, M. J.; Kumaravel, G.; Petter, R. C.; Beveridge, R. *Tetrahedron Lett.* **1996**, *37*, 4671.
28. Svensson, A.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1996**, *37*, 7649.
29. Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588.
30. The ^{19}F NMR were taken relative to C_6F_6 in DMF as an external reference. (29 ppm).
31. Dankwardt, S. M.; Newman, S. R.; Krstenansky, J. L. *Tetrahedron Lett.* **1995**, *36*, 4923.

(*Received in USA* 11 *March* 1997; *accepted* 27 *March* 1997)