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A short route to the macrocyclic core of biaryl ether-based cyclopeptides

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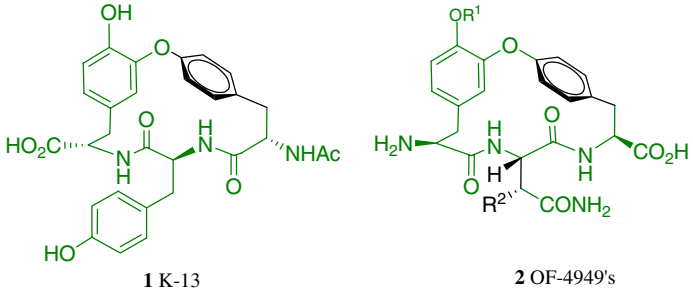
Abstract—A new route based on an intramolecular Horner–Wadsworth–Emmons type olefination of amidophosphonates has been developed for the construction of a 17-membered macrocyclic scaffold related to some biologically important biaryl ether-based cyclic peptides.

Members belonging to the family of naturally occurring biaryl ether-based cyclopeptides such as K-13 (**1**) and OF4949's (**2**) (Fig. 1) have proved to be exciting synthetic targets[1] over the past two decades, largely because of their good biological activities and structural complexity. Not surprisingly, non-natural biaryl ether-containing macrocycles have also been prepared[2] in the quest for potential therapeutic agents and/or compounds having altered bioactivity. Although a number of macrocyclisation methodologies for the construction of somewhat elusive biaryl ether-containing macrocyclic structures of varying ring sizes have emerged during these studies, newer methods for the construction of such compounds continue to be developed.[3] Of the various heterocyclisation routes, macrocyclisation through biaryl ether bond formation involving oxidative phenol coupling,[4] Ullmann cyclisation[5] or S_NAr reactions[6] has been widely used. An elegant C–C bond forming macrocyclisation protocol involving Pd-catalysed cyclisation of an organozinc derivative has recently been reported.[7] Macrocycle formation through intramolecular Horner–Wadsworth–Emmons (HWE) type olefination has proved to be highly effective in many demanding situations over the years.[8] Herein, we report a new route to the 17-membered ring system of some biaryl ether-containing cyclic peptides based on a HWE- type macroolefination of an amidophosphonate as the key step.

We envisioned that the macrocyclic model compound **3** (Scheme 1), related to the OF-4949 ring system, could



1 K-13 **2** OF-4949's

Figure 1.

Keywords: Olefination; Peptide; Biaryl; Macrocycle.
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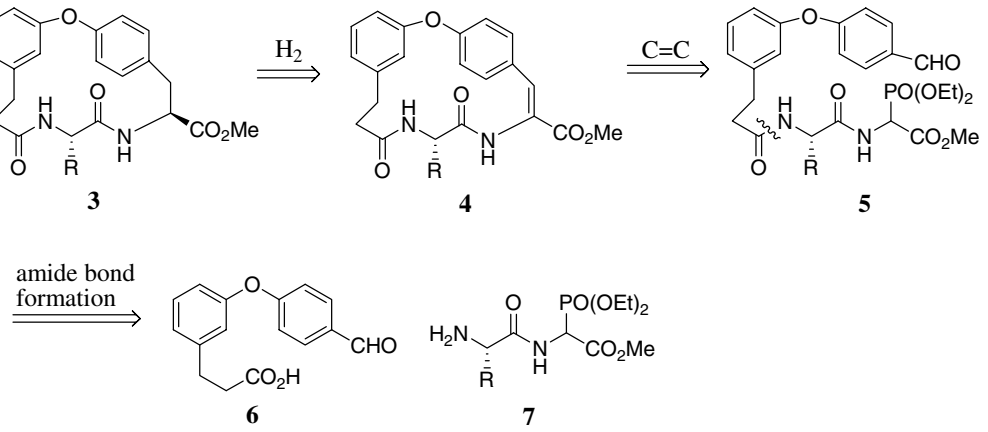


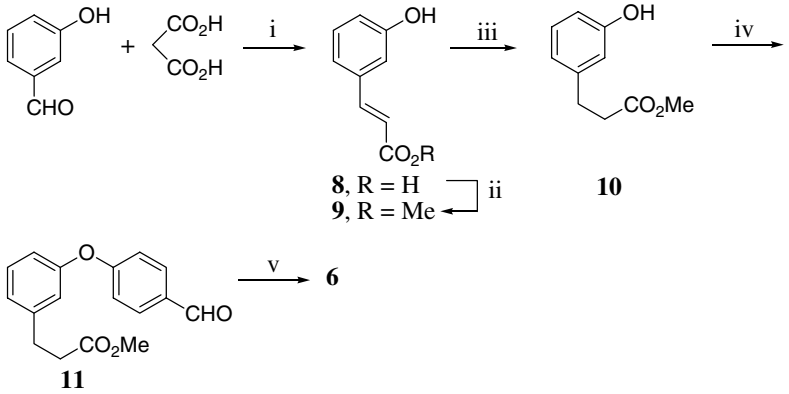
Scheme 1.

possibly be derived from either substrate or reagent controlled hydrogenation of the corresponding dehydropeptide **4** which, in turn, could be derived from amidophosphonate-aldehyde **5** if the crucial intramolecular olefination could be effected. Compound **5** was expected to be formed by condensation of the carboxylic acid **6** and amine **7** through amide bond formation.

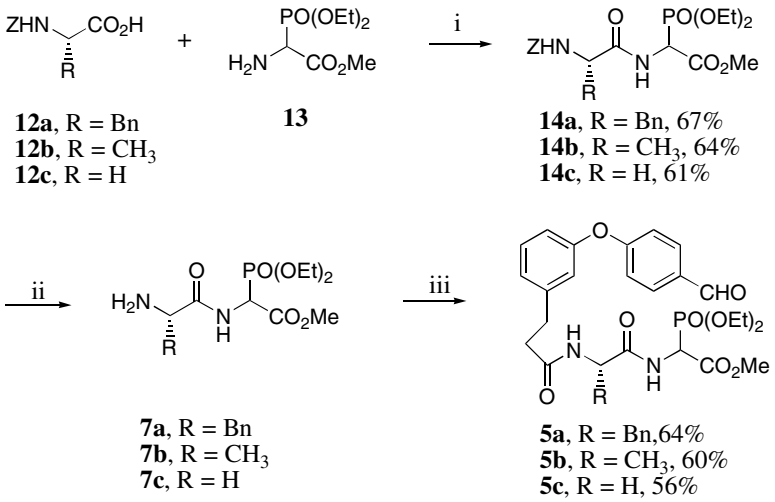
The synthetic sequence started from the known 3-hydroxybenzaldehyde which on treatment with malonic acid in refluxing pyridine afforded the known[3e] cinnamic acid derivative **8** (Scheme 2) in excellent yield (91%). The latter on esterification with acetyl chloride in methanol delivered unsaturated ester **9**, also in high yield. Catalytic hydrogenation of **9** with H_2 in the presence of Pd–C (10%) in ethanol/acetic acid (19:1) provided saturated ester **10** almost quantitatively. An Ullmann type coupling between phenol **10** and 4-iodobenzaldehyde proceeded well using 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD) as additive[9] in the presence of cesium carbonate and CuBr to afford biaryl ether **11** in high yield (89%). Hydrolysis of the ester functionality in the latter under conventional conditions using lithium hydroxide monohydrate in THF/water (5:1) liberated carboxylic acid **6**, uneventfully, in 94% yield.

Amide bond formation between Schmidt's aminophosphonate[10] **13** (Scheme 3) and the appropriate Z-protected amino acids **12a–c**, led to dipeptides **14a–c** in acceptable yields. Hydrogenolytic removal of the Z-group in the latter compounds provided access to the corresponding amines **7a–c** which were used without purification. Coupling of each of these amines with biaryl carboxylic acid **6** separately, led to macrocyclisation precursors **5a–c** in moderate to good yields.

With the key precursors in hand, we next focused on the macrocyclisation step. A number of bases have been used for intermolecular olefination of amidophosphonates with aromatic and aliphatic aldehydes. Notable among these are KOBu^t, NaH, DBU and 1,1,3,3-tetramethylguanidine (TMG). We opted to evaluate some of these conditions[11] but using higher dilution and/or elevated temperature. The results are summarised in Table 1. Initial experiments with substrate **5a** revealed that the reaction proceeded poorly with previously successful bases like DBU, KOBu^t or NaH under a range of conditions. Similarly, use of TMG as a base did not alter the fate of the reaction to any significant extent. In most of these cases, unchanged starting material was largely recovered. However, in some instances polar unidentified by-products were also formed. Following our earlier success[12] with the Nicolaou conditions[13] (K_2CO_3/18-crown-ether) in macrocycle construction, we opted to employ those conditions to the current effort.



Scheme 2. Reagents and conditions: (i) pyridine, morpholine (cat.), reflux, 2 h, 91%; (ii) AcCl, MeOH, reflux, 4 h, 96%; (iii) H_2, Pd–C, EtOH–AcOH (19:1), rt, 48 h, 97%; (iv) 4-IC$_6$H$_4$CHO, CuBr, Cs_2CO_3, TMHD, NMP, 75 °C, 16 h, 89%; (v) LiOH, THF–H_2O (5:1), rt, 4 h, 94%.



Scheme 3. Reagents and conditions: (i) DCC, CH_2Cl_2, −10 °C to rt, 6 h; (ii) H_2, Pd–C, MeOH, rt, 2 h; (iii) **6**, DCC, HOBt, CH_2Cl_2, −10 °C to rt, 12 h.

Table 1. Attempted macrocyclisation of **5a**

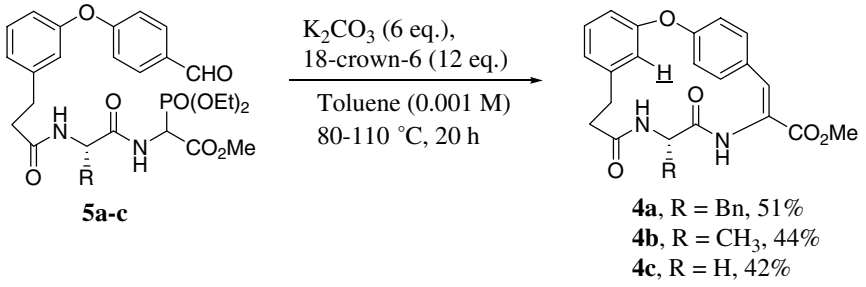
Entry	Base	Solvent	Concentration	Temperature	Time (h)	% **4a**
1	DBU	CH_2Cl_2	0.004	Reflux	12	8
2	$KOBu^t$	THF	0.004	rt to 50 °C	24	11
3	NaH	THF	0.004	rt to reflux	24	0
4	$Me_2NC(=NH)NMe_2$	THF	0.004	Reflux	24	14

Pleasingly, when a solution of amidophosphonate **5a** in toluene was slowly added (via a syringe pump) to a solution of K_2CO_3 (6 equiv) and 18-crown-6 (12 equiv) in toluene (0.001 M) at 80 °C and then heated to reflux for 20 h, conversion to the desired macrocycle **4a** (Scheme 4) took place in an acceptable 51% yield. Similarly, substrates **5b**–**c** were converted to cyclic dehydropeptides **4b**–**c**.

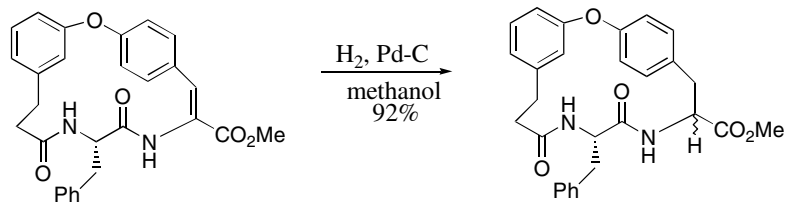
Macrocyclic compounds **4a**–**c** were obtained as colourless, amorphous, high melting solids.[14] The stereochemical integrity of the compound prepared was verified from HPLC studies in different solvents and using various columns including a chiral one, thereby indicating that negligible or no racemisation had taken place during macrocyclisation. The compounds displayed interesting ^1H NMR spectral properties in $CDCl_3$ where most of the peaks were obtained as broad singlets. Well resolved spectra were obtained in DMSO-d_6. A significant change of the chemical shift of the NH proton of the ΔPhe-residue was noticed when the solvent was changed from $CDCl_3$ (δ 6.30) to DMSO-d_6 (δ 9.40) indicating the formation of hydrogen bond in the latter solvent.[15] Moreover, the aromatic protons marked *H* in macrocyclic structures **4a**–**c** appeared around δ 6.2 which seemed to be diagnostic[16] of this kind of ring system. The other spectral parameters were consistent with the assigned structures.

Preliminary experiments revealed that dehydropeptide **4a** underwent rapid hydrogenation to the corresponding saturated compound **15** (Scheme 5) which was obtained as an inseparable mixture of two diastereomers (3:1, HPLC, ^1H NMR). However, elucidation of the stereoselectivity of the hydrogenation reaction was not established at this stage.

In conclusion, we have developed a concise convergent synthesis of the 17-membered macrocyclic scaffold of biologically important biaryl ether-based cyclic peptides



Scheme 4.



Scheme 5.

utilising intramolecular olefination of an amidophosphonate-aldehyde. The methodology described here may find application in the synthesis of other cyclic peptides containing a ΔPhe-residue. It is well known[17] that incorporation of a ΔPhe-residue in peptides confers resistance to enzymatic degradation. Moreover, ΔPhe-residues in cyclic peptides may introduce interesting conformational features relevant to drug design. Macrocyclic compounds **4a**–**c** may therefore find application in this regard. Their utility in the synthesis of biaryl ether-based natural products (and analogues thereof) through stereo-controlled hydrogenation seems to be a possibility as well. The scaffold[18] may also prove to provide opportunities for the preparation of derivatised biaryl ether-based cyclic peptides through well known transformation reactions on the unsaturated system.[19] Future work in these directions will be pursued in our laboratory.

Acknowledgements

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References and notes

1. For reviews, see: (a) Rao, A. V. R.; Gurjar, M. K.; Reddy, L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135; (b) Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096; (c) Zhu, J. *Synlett* **1997**, 133.
2. For a review, see: Fairlie, D. P.; Abbenante, G.; March, S. R. *Curr. Med. Chem.* **1995**, *2*, 654; For some recent reports, see: (a) Venkatraman, S.; Njoroge, F. G.; Girijavallabham, V. M.; Madison, V. S.; Yao, N. H.; Prongay, A. N.; Butkiewicz, N.; Pichardo, J. *J. Med. Chem.* **2005**, *48*, 5088; (b) Janetka, J. W.; Raman, P.; Stayshur, K.; Flentke, G. R.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 441.
3. (a) Cai, Q.; He, G.; Ma, D. *J. Org. Chem.* **2006**, *71*, 5268; (b) Decicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett.* **2001**, *3*, 1029; (c) Kohn, W. D.; Zhang, L.; Weigel, J. A. *Org. Lett.* **2001**, *3*, 971; (d) Arnusch, C. J.; Pieters, R. J. *Tetrahedron Lett.* **2004**, *45*, 4153; (e) Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079; (f) Cristau, P.; Vors, J.-P.; Zhu, J. *Tetrahedron Lett.* **2003**, *44*, 5575; (g) West, C. W.; Rich, D. E. *Org. Lett.* **1999**, *1*, 1819; (h) Pearson, A. J.; Zhang, P.; Bignan, G. *J. Org. Chem.* **1997**, *62*, 4536.
4. (a) Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912; (b) Suzuki, Y.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 4053.
5. Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc.* **1991**, *113*, 1427.
6. (a) Pearson, A. J.; Bignan, G.; Zhang, P.; Chelliah, M. *J. Org. Chem.* **1996**, *61*, 3940; (b) Janetka, J. W.; Rich, D. R. *J. Am. Chem. Soc.* **1997**, *119*, 6488; (c) Beugelmans, R.; Singh, G. P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1994**, *59*, 5535; (d) Bigot, A.; Tran Huu Dau, M. E.; Zhu, J. *J. Org. Chem.* **1999**, *64*, 6283; (e) Beugelmans, R.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 7391.
7. Perez-Gonzalez, M.; Jackson, R. F. W. *Chem. Commun.* **2000**, 2423.
8. For some recent applications, see: (a) Harvey, J. E.; Raw, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2003**, *44*, 7209; (b) Mulzer, J.; Ohler, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3842; (c) Gonzalez, M. A.; Pattenden, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1255; (d) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237; (e) O'Neil, G. W.; Philips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 5340; (f) Seo, S.-Y.; Jung, J.-K.; Paek, S.-M.; Lee, Y.-S.; Kim, S.-H.; Suh, Y.-G. *Tetrahedron Lett.* **2006**, *47*, 6527.
9. Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Riedes, P. J. *Org. Lett.* **2002**, *9*, 1623.
10. Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 33.
11. (a) Schmidt, U.; Griesser, H.; Leitenberger, V.; Leiberknecht, A.; Mangold, R.; Meyer, R.; Reidel, B. *Synthesis* **1992**, 487; (b) Geyer, A.; Gege, C.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3245; (c) Zhang, J. Y.; Xiong, C. Y.; Ying, J. F.; Wang, W.; Hruby, V. J. *Org. Lett.* **2003**, *5*, 3115; (d) Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. *Org. Lett.* **2001**, *3*, 3157.
12. Chattopadhyay, S. K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2429.
13. (a) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030; (b) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954.
14. *Typical procedure for the conversion* **5a** → **4a**: A solution of phosphonate-aldehyde **5a** (124 mg, 0.2 mmol) in dry toluene (40 ml) was added slowly over 4 h to a solution of K_2CO_3 (166 mg, 1.2 mmol) and 18-crown-6 (600 mg, 2.4 mmol) in dry toluene (160 ml) at 80 °C. The mixture was then heated to reflux for 16 h and then allowed to warm to rt. It was then sequentially washed with HCl (1 N, 2 × 25 ml), water (3 × 50 ml) and brine (25 ml) and then dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to leave a viscous mass which was purified by column chromatography over silica gel using a mixture of chloroform and methanol (19:1) as eluent to afford product **4a** as a colourless crystalline solid (48 mg, 51%).
Compound **4a**: Mp: 278–280 °C. $[\alpha]_D$ −42 (*c*, 0.5 in $CHCl_3$ + MeOH, 3:1). IR (KBr): 3283, 1718, 1643, 1497, 1244 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.56 (1H, s), 7.85 (1H, d, $J = 8.1$ Hz,), 7.69 (1H, s), 7.34–7.10 (9H, m), 6.96–6.84 (2H, m), 6.69 (1H, s), 6.24 (1H, s), 4.69 (1H, br s), 3.77 (3H, s), 3.02–2.91 (2H, m), 2.71–2.40 (3H, m),

2.12–2.05 (1H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5 (s), 168.5 (s), 164.7 (s), 157.1 (s), 155.4 (s), 142.6 (s), 136.9 (d), 136.4 (d), 129.8 (d), 128.9 (d), 128.8 (d), 127.6 (d), 127.4 (d), 125.7 (d), 124.8 (d), 122.8 (s), 118.9 (s), 115.0 (d), 113.6 (d), 52.5 (d), 51.8 (q), 39.2 (t), 31.9 (t), 27.5 (t). HRMS (TOF MS ES+): obsd 493.1715 (M+Na); calcd 493.1739 ($C_{28}H_{26}N_2O_5$+Na).

Compound **4b**: Mp: 284–286 °C. $[\alpha]_D$ −130 (*c*, 0.4 in $CHCl_3$ + MeOH, 3:1). IR (KBr): 3280, 1732, 1645, 1528, 1246 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.39 (1H, s), 7.82 (1H, d, $J = 6.7$ Hz), 7.66 (1H, s), 7.36–7.29 (3H, m), 7.10 (1H, s), 6.98–6.89 (2H, m), 6.69 (1H, s), 6.27 (1H, s), 4.48 (1H, br s), 3.77 (3H, s), 3.06 (1H, t, $J = 12.1$ Hz), 2.65–2.50 (2H, m), 2.25 (1H, br s), 1.16 (3H, d, $J = 5.5$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 169.9, 165.2, 157.7, 155.9, 143.1, 136.5, 130.4, 129.4, 128.4, 125.2, 123.3, 119.5, 115.5, 114.3, 52.3, 47.2, 32.6, 28.3, 19.2. HRMS (TOF MS ES+): obsd 417.1426 (M + Na); calcd 417.1426 ($C_{22}H_{22}N_2O_5$+Na).

Compound **4c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.94 (1H, s), 7.55 (1H, s), 7.48 (1H, s), 7.35 (2H, d, $J = 8.2$ Hz), 7.24 (1H, t, $J = 7.9$ Hz), 6.97–6.92 (3H, m), 6.86 (1H, d, $J = 7.8$ Hz), 6.22 (1H, s), 3.79 (3H, s), 3.76 (2H, d, $J = 5.7$ Hz), 2.84–2.81 (2H, m), 2.40–2.36 (2H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.5, 165.2, 157.1, 155.6, 142.1, 134.6, 130.8, 129.5, 129.1, 128.8, 123.9, 123.3, 120.7, 116.3, 115.0, 68.1, 52.7, 42.1, 38.7. HRMS (TOF MS ES+): obsd 381.1445 (M+H); calcd 381.1450 ($C_{21}H_{20}N_2O_5$+H).

15. Jain, R. M.; Rajashankar, K. R.; Ramakumar, S.; Chauhan, V. S. *J. Am. Chem. Soc.* **1997**, *119*, 3205.
16. Boger, D. L.; Nomoto, Y.; Teegarden, B. R. *J. Org. Chem.* **1993**, *58*, 1425–1433.
17. English, M. L.; Stammer, C. H. *Biochem. Biophys. Res. Commun.* **1978**, *83*, 1464.
18. For a recent review on amino acid derived macrocycles, see: Gibson, S. E.; Lecci, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1364; For our earlier studies on macrocyclic dehydropeptide-based scaffolds, see: Chattopadhyay, S. K.; Biswas, S. *Tetrahedron Lett.* **2006**, *47*, 7897.
19. For a recent review, see: Bonquer, C.; Walenzyk, T.; Konig, B. *Synthesis* **2006**, 1.