Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 19, pp. 2299-2300, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00414-3

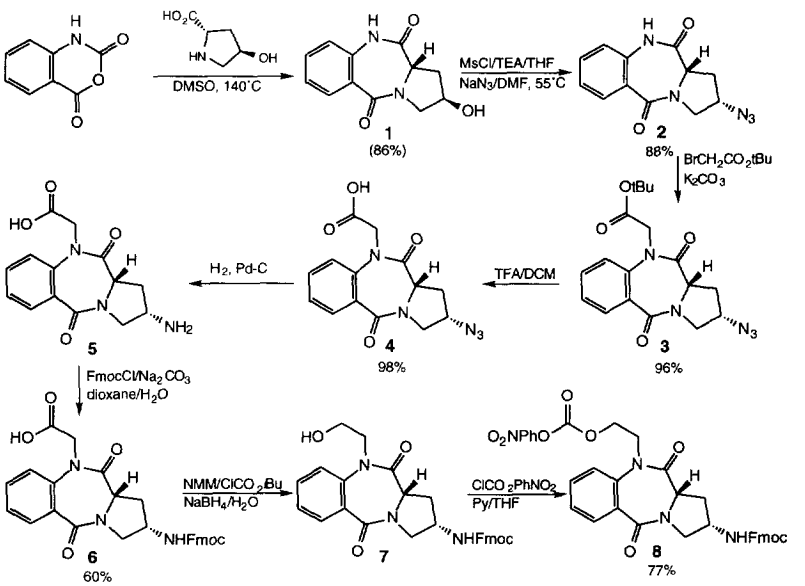
BUILDING BLOCKS FOR PEPTIDE AND CARBAMATE LIBRARIES

Yingzhi Bi and Peter G. Schultz*

Department of Chemistry, University of California, Berkeley, CA 94720

Abstract: A building block containing the 1,4-benzodiazepine-2,5-diazepine pharmacophore has been synthesized for use in constructing both peptide and carbamate combinatorial libraries. Copyright © 1996 Elsevier Science Ltd

Unnatural amino acids have found considerable use as building blocks in medicinal, peptide and protein chemistry,[1] and more recently, in the generation of combinatorial libraries for drug discovery.[2] These include conformationally constrained amino acids, amino acids bearing biophysical probes and photoaffinity labels, and amino acids containing side chain groups with novel steric or electronic properties. Amino acids that incorporate pharmacophores are particularly attractive for the synthesis of combinatorial libraries.[3] The benzodiazepine skeleton has been found in a wide range of biologically active molecules[4,5] and has itself been synthesized in a combinatorial format.[5] We report here the synthesis of Fmoc protected amino acid **6** and amino carbonate **8** building blocks containing the benzodiazepine pharmacophore for use in the synthesis of peptide and carbamate combinatorial libraries.



The dilactam alcohol **1** was chosen as a key intermediate for further elaboration. Amongst the different methods[6-8] reported in the literature for the preparation of 1,4-benzodiazepin-2,5-diones, Kim's

method[6] is the simplest. Thus with a slight modification of the Stille procedure[6b] the desired core skeleton **1** was obtained in 86% yield by reacting isatoic anhydride with *t*-4-hydroxylproline in DMSO at 140 °C. The hydroxyl function was then converted into an azido group in 88% overall yield by mesylation of the hydroxyl group in THF in the presence of TEA followed by azide displacement in DMF at 55 °C. The displacement went exclusively with conversion of the configuration as indicated by the isolation of a single product and confirmed by the splitting pattern and coupling constants of the protons on the adjacent carbons. Alkylation of the amide nitrogen with *t*-butyl bromoacetate followed by removal of the *t*-butyl group with 50% TFA in methylene chloride introduced the acid functionality. Reduction of the azide under hydrogen in the presence of Pd/C catalyst afforded the amino group which was directly protected with Fmoc according to the literature method.[9] Reversal of the above sequence, i.e., reduction of the azide followed by protection of the amino group with Fmoc then the removal of the *t*-butyl group, is also a viable approach. However, the current sequence is more versatile and could be used to generate the Boc amino analogues or any other protected amino analogues. Finally the Fmoc amino acid was converted into the desired carbamate building block in 77% overall yield.[10]

Acknowledgement: This work was supported by the Director, Office of Health Effects Research, of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098. PGS is a Howard Hughes Medical Institute Investigator.

References and Notes:

1. (a) DeGrado, W. F. *Adv. Prot. Chem.* **1988**, *39*, 51. (b) Chorev, M.; Goodman, M. *Acc. Chem. Res.* **1993**, *26*, 266. c) Cornish, V. W.; Mendel, D.; Schultz, P. G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 621.
2. (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.
3. Wang, G. T.; Li, S.; Wideburg, N.; Kraffe, G. A.; Kempf, D. J. *J. Med. Chem.* **1995**, *38*, 2995.
4. (a) Thurston, D. E. Advances in the study of Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Antitumor antibiotics in *Molecular Aspects of Anticancer Drug-DNA Interactions*. (b) Hurley, L. H. *J. Antibiot.* **1977**, *30*, 349, and references therein.
5. (a) For combinatorial synthesis of 1,4-benzodiazepin-2-ones see Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997. (b) For combinatorial synthesis of 1,4-benzodiazepin-2,5-diones see Boojamara, C. L.; Brow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742; Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 574.
6. (a) Kim, D. H. *J. Heterocycl. Chem.* **1975**, *12*, 1323. (b) Pena, M. R., Stille, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 5417.
7. Akssira, M., Boumzebra, M., Kasmi, H., Dahdouh, A. *Teteahedron* **1994**, *50*, 9051.
8. Molina, P., Diaz, I., Tarraga, A. *Tetrahedron* **1995**, *51*, 5617.
9. Bodansky, M.; Bodansky, A. *The Practice of Peptide Synthesis* , 2nd Ed, Springer-Verlag: Berlin **1994**, p20. **6**: ^{1}H NMR, (300 MHz, DMSO-d_6) δ 2.29 (m, 1 H), 2.56 (m, 1 H), 3.15 (dd, 1 H, J = 6.3, 11.6), 3.79 (dd, 1 H, J = 6.7, 11.4), 4.11 (q, 1 H, J = 6.8), 4.28 (m, 4 H), 4.52 (ABq, 2 H, J = 17.4), 7.30-7.50 (m, 6 H), 7.62 (t, 1 H, J = 8.2), 7.70 (d, 2 H, J = 7.6), 7.78 (d, 1 H, J = 8.2), 7.90 (d, 2 H, J = 7.7); ^{13}C (75 MHz, DMSO-d_6) δ 31.18, 46.67, 48.65, 50.62, 50.78, 55.44, 65.55, 120.10, 122.44, 125.19, 125.67, 127.06, 127.61, 128.85, 129.72, 132.27, 139.30, 140.70, 143.82, 155.56, 164.52, 169.16, 170.02; MS (ESI) *m/z* 512 (MH^+).
10. Cho, C. Y.; Moran, E. J.; Cherry, S.; Stephans, J.; Fodor, S. P. A.; Adams, C.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, 261 1303. **8**: ^{1}H NMR, (300 MHz, $CDCl_3$) δ 2.38 (m, 1 H), 2.72 (d, 1 H, J = 14.3), 3.75 (dd, 1 H, J = 5.1, 13.0), 3.91 (d, 1 H, 12.7), 4.00-4.50 (m, 7 H), 4.62 (m, 2 H), 6.46 (d, 1 H, J = 6.6), 7.18-7.41 (m, 8 H), 7.58 (m, 3 H), 7.73 (d, 2 H, J = 6.8), 7.93 (d, 1 H, J = 7.4), 8.11 (d, 2 H, J = 7.7); ^{13}C (75 MHz, $CDCl_3$) δ 31.33, 46.96, 48.00, 49.61, 54.08, 57.23, 65.41, 66.75, 119.74, 121.76, 122.92, 124.94, 125.02, 125.12, 126.72, 126.80, 127.50, 130.47, 132.44, 138.62, 140.98, 143.69, 143.79, 145.17, 152.09, 155.01, 155.54, 164.73; MS (ESI) *m/z* 663 (MH^+).

(*Received in USA* 13 *August* 1996; *accepted* 30 *August* 1996)