Pergamon

Tetrahedron Letters 40 (1999) 3511–3514

TETRAHEDRON
LETTERS

A Pseudopeptide Platform with Side Chains Addressable for Combinatorial Applications

Palle H. Rasmussen and Julius Rebek, Jr.*

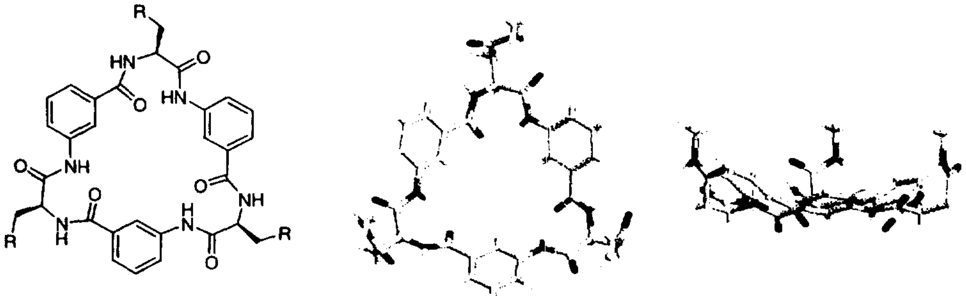
The Skaggs Institute for Chemical Biology and Department of Chemistry,
The Scripps Research Institute, La Jolla, CA 92037, USA.

Received 23 February 1999; revised 5 March 1999; accepted 8 March 1999

Abstract: A synthetic pathway is presented to new, functionalized, pseudopeptide molecular platforms with selectively removable protecting groups on their side chains. The platforms are available in gram quantities and are used as core molecules for combinatorial chemistry.

Keywords: Peptidomimetic; Platform; Combinatorial chemistry; Orthogonal protection.

Rigid molecules with C_3 symmetry that present functional groups on the same face of the structure can serve as core molecules for solution phase combinatorial chemistry,[1] and as templates for synthetic receptors.[2] Their advantage for the former application lies in the diversity available on a well-defined surface; for the latter application, their use as modules with spacers leads to cleft-like structures with convergent functional groups. For either use, gram-scale synthesis[3] and selectively removable blocking groups (orthogonal protection; addressability) are desirable. We report here such a structure[4] (Fig 1).



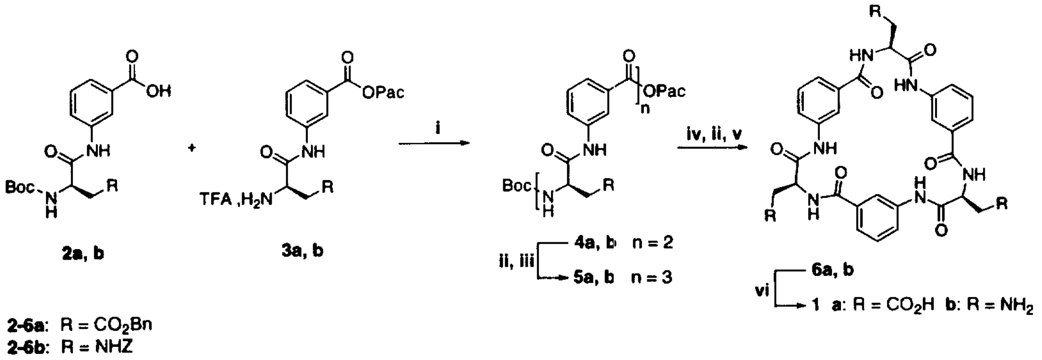
1a: R = COOH
1b: R = NH_2

Figure 1. General structure of the platforms (**1a**,**b**), and Monte Carlo minimized structure of **1a** functionalized as a tris(methylamide).

E-mail: jrebek@scripps.edu

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00544-4

A Monte Carlo conformational search using MacroModel v.5.5[5] and the MM2[6] force field reveal that these macrocyclics are stabilized by intramolecular hydrogen bonds (Fig 1) that rigidify their structures and enforce the presentation of the side chains on the same face of the molecule. The platforms have dimensions similar to those of ketals derived from triphenylene,[7] with approximately 1 nm distance between the side chains. This distance is almost twice that of other tripodal platforms[8] and is greater than those found in resorcinarenes,[9] calixarenes,[10] or tetraaryl porphyrins,[11] structures much-admired in supramolecular chemistry.

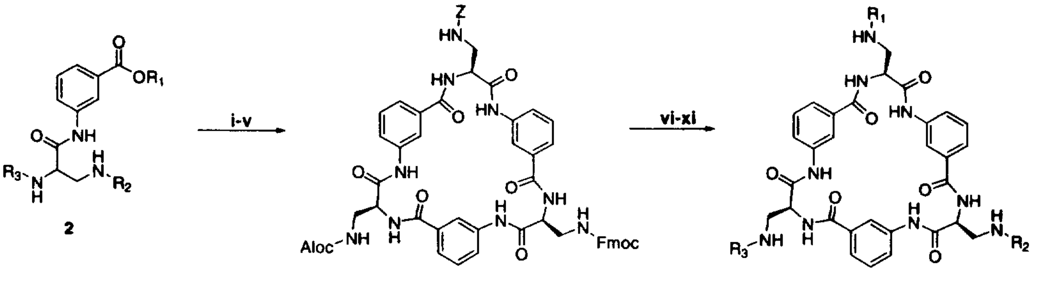


Scheme 1. i: HBTU, HOBt, DIEA, 81-87% ii: TFA, CHCl$_3$, r.t., 1h, >99% iii: 2a or 2b, HBTU, HOBt, DIEA, 59-65% iv: Zn, HOAc, 4 h, r.t., 64-92% v: DPPA, DIEA, DMF, 16 h, r.t., 55-60% vi: Pd/C, THF-DMF, 3h, 88-99%.

The platforms were synthesized in solution by a stepwise build-up of linear trimers (**5**, Scheme 1), followed by a macrolactamization. Specifically, **2a** and **2b** were coupled to **3a** and **3b**, respectively, using HBTU (2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) activation in combination with *in situ* neutralization to give the dimers (**4a**) and (**4b**) in 81-87% yield. Cleavage of the Boc groups gave the trifluoroacetates of **4a** and **4b** and their HBTU- activated coupling with **2a** and **2b**, respectively, was repeated to give the trimers (**5a**) and (**5b**) in 59-65% yield. Cleavage of the C-terminal phenacyl esters with zinc in acetic acid, followed by acidolytic cleavage of the N-terminal Boc groups, gave the respective deprotected linear trimers. These were cyclized with DPPA in DMF to afford **6a** and **6b** in 38-50% yield. Catalytic hydrogenolysis in the presence of Pd/C gave the deprotected core molecules **1a** and **1b** in 88-99% yields.

A version with the necessary selectively removable protecting groups (**7**, Scheme 2) was next synthesized, again starting with **2b**. Coupling to **2c** with HBTU was followed by C-terminal deprotection with zinc in acetic acid and coupling with **2d** afforded the linear trimer. The N-terminal Boc group and the C-terminal *tert*-butyl ester were removed simultaneously with TFA in chloroform and the resulting trimer was cyclized with DPPA in DMF giving the orthogonally protected platform (**7**) in 36% overall yield on a 1 g scale.

The synthesis of **8** illustrates the use of **7** for the synthesis of specific platforms with different side chains. The Fmoc group of **7** was removed with diethyl amine in DMF and the resulting free amine was acetylated in 96% yield. The Aloc group was then removed by palladium-catalyzed hydrostannolysis with tributyltin hydride[12] and the amine was reacted with phenylacetyl chloride to give the amide in 81% yield. Finally, catalytic hydrogenolysis of the Z group and reaction with 3,5-dichlorobenzoyl chloride gave **8** in 82% yield.



2

7

8

2b: R_1 = H, R_2 = Z, R_3 = Boc
2c: R_1 = Pac, R_2 = Fmoc, R_3 = H
2d: R_1 = ^{t}Bu, R_2 = Aloc, R_3 = H

R_1 = 3,5-dichlorobenzoyl, R_2 = acetyl,
R_3 = phenylacetyl

Scheme 2. **i**: **2b**, **2c**, HBTU, HOBt, DIEA, THF, r.t., 91% **ii**: Zn, HOAc, r.t., 2h, 83% **iii**: **2d**, HBTU, HOBt, DIEA, r.t., 74% **iv**: TFA, $CHCl_3$, r.t., 3h, >99% **v**: DPPA, DIEA, DMF, r.t., 16h, 65% **vi**: Et_2NH, DMF, r.t., 1h, 97% **vii**: AcCl, DIEA, THF-DMF, 99% **viii**: $[PPh_3]Pd(0)$, Bu_3SnH, AcOH, DMF, r.t., 1h, 82% **ix**: phenylacetyl chloride, DIEA, THF-DMF, r.t., 99% **x**: Pd/C, THF-DMF, r.t., 16h, >99% **xi**: 3,5-dichlorobenzoyl chloride, DIEA, THF-DMF, r.t., 2h, 83%.

The use of **1a** and **1b** as core molecules for solution phase combinatorial synthesis of mixtures[13] was established through small test libraries. Pre-activation of core molecule **1a** as its pentafluorophenyl ester led to succinimide formation,[14] but when **1a** was activated *in situ* as its mixed anhydride with isobutyl chloroformate at -30°C and coupled with a mixture of three amines,[15] a library containing 11 compounds was obtained. These were all identified by MALDI-TOF (HR-MS) and HPLC. Mixtures of three acid chlorides[16] or three sulfonyl chlorides[17] added to **1b** resulted in amide and sulfonamide libraries, respectively, each containing 11 compounds.

The building blocks (**2a-d**) were prepared by coupling of orthogonally protected amino acids to phenacyl or *tert*-butyl 3-aminobenzoate in in 77-93% yield, using isobutyl chloroformate activation. Orthogonally protected (2*S*)-2,3-diaminopropanoic acid derivatives were prepared by Hofmann rearrangement of the corresponding N-protected asparagine derivatives with iodobenzene diacetate[18] followed by protection of the resulting amine using standard procedures.[19]

In summary, an orthogonally protected platform (**7**) was synthesized on a gram scale and its use in the synthesis of combinatorial chemistry was demonstrated. Applications in molecular recognition are in progress and will be reported in due course.

Acknowledgements. The authors thank the Skaggs Research Foundation and The Danish Research Academy for financial support.

References and Notes

1 Kocis, P.; Issakova, O.; Sepetov, N. F.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*(37), 6623-6626.

2 a) Araki, K.; Inada, K.; Shinkai, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 72-74. b) Bisson, A.; Lynch, V.M.; Monahan M-K. C.; Anslyn E. V. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2340-2342. c) Pieters, R.J.; Cuntze, J.; Bonnet, M.; Diederich, F. *J. Chem. Soc., Perkin Trans. 2.* **1997**, 1891-1900.

3 Similar functionalized oxazole–based platforms are only available in 25 mg quantities. Mink, D.; Mecozzi, S.; Rebek, J., Jr. *Tetrahedron Lett.* **1998**, *39*, 5709-5712.

4 Ishida and coworkers have reported cyclic peptides with similar backbones but without functionalized side chains. a) Ishida, H.; Donowaki, K.; Suga, M.; Shimose, K.; Ohkubo, K. *Tetrahedron Lett.* **1995**, *36*(49), 8987-8990. b) Ishida, H.; Suga, M.; Donowaki, K.; Ohkubo, K. *J. Org. Chem.* **1995**, *60*, 5376-5375.

5 Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield , C.; Chang, G.; Hendrickson, T.; Still, C. W. *J. Comput. Chem.* **1990**, *11*, 440-467.

6 Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127-8134.

7 Waldvogel, S. R.; Wartini, A.; Rasmussen, P. H.; Rebek, J., Jr. *Tetrahedron Lett.* Submitted.

8 For recent examples see: a) Metzger, A.; Anslyn, E. V. *Angew. Chem. Int. Ed.* **1998**, *37*, 649-652. b) Cohen, S. M.; Meyer M.; Raymond K. M. *J. Am. Chem. Soc.* **1998**, *120*, 6277-6286.

9 For recent rewievs see: a) Timmerman, P.; Verbom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663-2704. b) Higler, I.; Timmerman, P.; Verbom, W.; Reinhoudt, D. N. Eur. *J. Org. Chem.* **1998**, 2689-2702.

10 Hamuro, Y.; Calama, M. C.; Park, H. S.; Hamilton, A. D. *Angew. Chem. Ed. Engl.* **1997**, *36*, 2680-2683.

11 For recent examples see: a) Jagessar, R.; Burns, D. H. *Chem. Commun.* **1997**, 1685-1686. b) Collman, J.P.; Wang, Z.; Straumanis, A. *J. Org. Chem.* **1998**, *63*, 2424-2425.

12 Dangles, O.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1987**, *52*, 4984-4993.

13 a) Carell, T.; Wintner J. M.; Bashir-Hashemi, A.; Rebek, J., Jr. *Angew. Chem. Ed. Engl.* **1994**, *33*, 2059-2061. b) Carell, T.; Wintner J. M.; Rebek, J., Jr. *Angew. Chem. Ed. Engl.* **1994**, *33*, 2061-2064. c) Carell, T. *et al.* Chem. Biol. **1995**, 2, 171-183. d) Shipps, G. W.; Jr., Spitz, U. P.; Rebek, J., Jr. *Bioorg. Med. Chem.* **1996**, *4*, 655-657. e) Pryor, K. E.; Shipps, G. W., Jr.; Skyler, D. A.; Rebek, J., Jr. *Tetrahedron* **1998**, *54*, 4107-4124.

14 Bodansky, M., Principles of Peptide Synthesis 2nd Edition. Springer, Berlin Heidelberg New York, p 202.

15 The amines used were: 4-Methoxybenzylamine, isobutylamine and H-Ala(OMe)•HCl.

16 The acid chlorides used were: Phenylacetyl chloride, acetyl chloride and 3,5-dichlorobenzoyl chloride.

17 The sulfonyl chlorides used were: Tosyl chloride, mesyl chloride and 4-nitrobenzenesulfonyl chloride.

18 Zhang, L.; Kauffmann, G. S.; Pesti, J. A.; Yin, J. *J. Org. Chem.* **1997**, *62*, 6918-6920.

19 a) Moore, S.; Patel, R. P.; Atherton, E.; Kondo, M.; Meienhofer, J. *J. Med. Chem.* **1976**, *19*(6), 766-772. b) Ruan, F.; Chen, Y.; Itoh, K.; Sasaki, T.; Hopkins, P. B. *J. Org. Chem.* **1991**, *56*, 4347-4354. c) Kunz, H.; Untervagt, C. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 436.