Synthesis of a Peptidomimetic Analog of the Binding Domain of Rapamycin

Tushar K. Chakraborty* and Khaja Azhar Hussain
Indian Institute of Chemical Technology, Hyderabad - 500 007, India

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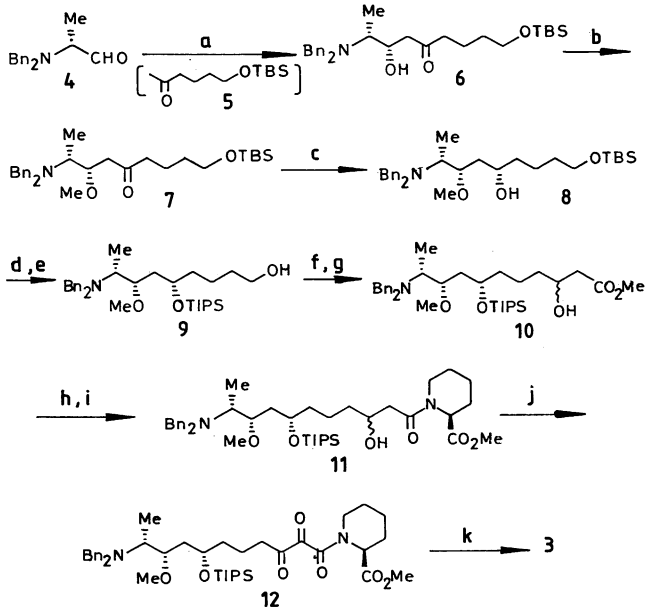
Stereoselective synthesis of a peptidomimetic analog of the binding domain of rapamycin starting from *N,N*-dibenzyl-*R*-alaninal is described.

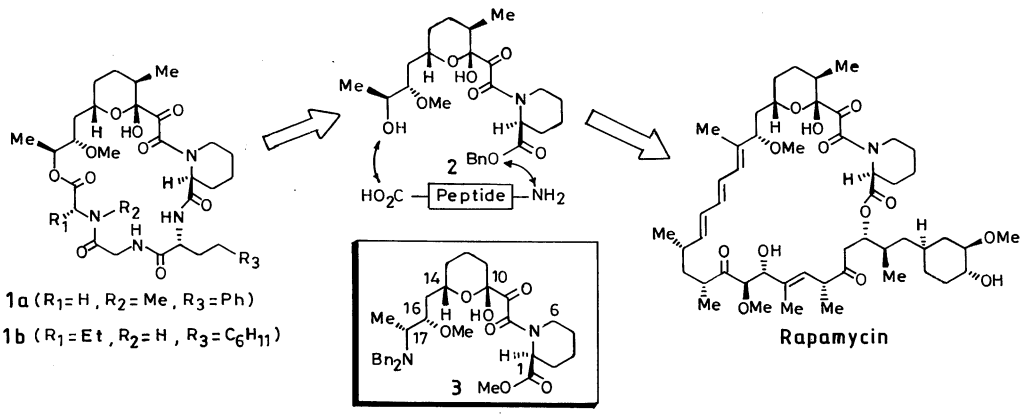
As part of our ongoing project on the development of peptide-based analogs of macrolide immunosuppressants we have recently reported the design, synthesis and biological evaluation of rapamycin-peptide hybrid molecules (**1**) which bind to FKBP12 with very high affinity.[1] In our synthesis, the FKBP12 binding domain **2**, obtained from rapamycin, was stitched, at two ends, with appropriate peptide tethers. In this communication, we report the synthesis of a peptidomimetic analog **3** of the binding domain which will obliterate the need to use rapamycin as starting material for making such compounds. This peptidomimetic analog, termed so by us because of its amino and carboxyl termini, will facilitate the subsequent stitching with the peptide tethers through two amide linkages and will lead to the development of fully synthetic and peptide-based analogs of these natural products.

Our synthesis started with *N,N*-dibenzyl-*R*-alaninal (**4**) (scheme 1). Diastereoselective non-chelate-controlled addition of lithium enolate, derived from the methylketo compound **5**, to **4** led to the exclusive formation of the desired *S*-alcohol **6**.[2,3] At this point it became necessary to methylate the hydroxyl group so that the other hydroxyl obtained by reduction of the keto could be subjected to necessary functional group manipulations. This was achieved using Ag_2O/MeI.[3] Reduction of the resulting β-methoxyketo compound **7** using Red-Al[4] gave the required *syn*-product **8** as the major compound (ca 3:2 *syn*:*anti* with total yield of 96%). The products were easily separated by standard silica gel-column chromatography. The *anti*-product was oxidized with PCC and subjected to reduction again to get an overall yield of 80% of the requisite *syn*-product **8**. The stereochemistry of the newly generated center was confirmed by desilylating **8**, followed by permethylation (NaH/MeI) and comparing the product (NMR, mass, optical rotation) with that obtained from the corresponding β-triethylsilyloxyketo compound following the same chemistry.[5]



Reagents and conditions: a) LDA (4.0 eq.), **5** (4.0 eq.), THF, - 78 °C to 25 °C, 1.5 h, 88%. b) Ag_2O (10.0 eq.), 4 A MS, MeI (10.0 eq.), ether, reflux, 48 h, 71%. c) Red-Al (2.0 eq.), ether, 0 °C, 15 min, 96% (58% isolated yield of the *syn*-product). d) TBDMSOTf (1.2 eq.), 2,6-lutidine (1.5 eq.), CH_2Cl_2, 0 °C, 15 min, 98%. e) HF. pyridine, THF, r.t., 1.5 h, 87%. f) $(COCl)_2$ (1.6 eq.), DMSO (3.2 eq.), CH_2Cl_2, - 78 °C, addition of **9**, 30 min, followed by Et_3N (5.0 eq.), - 78 °C to 0 °C, 1 h, 96%. g) LDA (4.0 eq.), $MeCO_2Me$ (4.0 eq.), THF, - 78 °C, 1.5 h, 87%. h) LiOH (4.0 eq.), THF: MeOH: H_2O (3:1:1), r.t., 1.5 h, 74%. i) EDCI (1.0 eq.), HOBt (1.0 eq.), *S*-pipecolic acid methyl ester (5.0 eq.), CH_2Cl_2, 0 °C to r.t., 12 h, 86%. j) DMP (6.0 eq.), pyridine (9.0 eq.), CH_2Cl_2, r.t., 30 min. k) aq. HF (48%): CH_3CN (1:9), r.t., 12 h, 58% (from **11**).

Scheme 1.



The *syn*-product **8**, thus obtained, was silylated with TIPSOTf/2,6-lutidine and selective removal of the primary TBS group gave the alcohol **9**.[3] Oxidation to aldehyde followed by nucleophilic addition of lithium enolate of methyl acetate gave the β-hydroxy ester **10**.[3] Saponification of **10** was followed by coupling with *S*-pipecolic acid methyl ester using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) to get **11**.[3] Oxidation of the β-hydroxyamide **11** with Dess-Martin periodinane (DMP)[6] gave the α,β-diketoamide **12** which on treatment with HF yielded the desired hemiketal protected compound **3**.[7]

The coupling of this peptidomimetic binding domain with peptide tethers is currently being persued. This practical protocol will allow to generate a large number of FKBP12 binding ligands with or without immunosuppressive activity. Such compounds may find useful application in biology as tools, or in medicine as improved immunosuppressants.

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References and Notes

1 a) T. K. Chakraborty and K. A. Hussain, *Tetrahedron*, **52**, 4053 (1996). b) T. K. Chakraborty, *Pure Appl. Chem.*, **68**, 565 (1996). c) T. K. Chakraborty, H. P. Weber, and K. C. Nicolaou, *Chem. & Biol.*, **2**, 157 (1995).

2 M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **30**, 1531 (1991), and the references cited therein.

3 Satisfactory NMR, mass and IR spectra were obtained for this compound.

4 a) D. A. Evans, J. L. Duffy, and M. J. Dart, *Tetrahedron Lett.*, **35**, 8537 (1994). b) D. A. Evans, M. J. Dart, and J. L. Duffy, *Tetrahedron Lett.*, **35**, 8541 (1994). c) Y. Mori and M. Suzuki, *Tetrahedron Lett.*, **30**, 4383 (1989).

5 The β-triethylsilyloxylketo compound showed better selectivity in reduction with hydride reagents (Ref. 4a and b). The major product was *syn* (ca. 9:1 ratio in favour of *syn* with Red-Al in ether at 0 °C) as determined by ^{13}C methyl shifts (19.79 and 30.19) of the acetonide prepared from the desilylated 1,3-diol (S. D. Rychnovsky and D. J. Skalitzky, *Tetrahedron Lett.*, **31**, 945 (1990) and D. A. Evans, D. L. Rieger, and J. R. Gage, *Tetrahedron Lett.*, **31**, 7099 (1990)

6 a) D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, **113**, 7277 (1991). b) M. J. Batchelor, R. J. Gillespie, J. M. C. Golec, and C. J. R. Hedgecock, *Tetrahedron Lett.*, **34**, 167 (1993).

7 **3**: ^1H NMR (200 MHz, $CDCl_3$): δ 7.32-7.15 (m, 10H, aromatic), 5.31 (d, J = 4.74 Hz, 1H, C2-H), 4.02-3.92 (m, 2H, C14-H, C16-H), 3.68 (s, 3H, CO_2CH_3), 3.61 and 3.25 (ABq, J = 13.57 Hz, 4H, NCH_2Ph) 3.3 (s, 3H, OCH_3), 3.32-3.28 (m, 1H, C6-H), 3.16 (dt, J = 12.9, 2.8 Hz, 1H, C3-H), 2.78 (dq, J = 6.5 Hz, 1H, C17-H), 2.48 (ddd, J = 16.0, 5.93, 4.74 Hz, 1H, C3-H), 2.34 (dd, J = 16.0, 9.5 Hz, 1H, C3-H), 2.24-1.14 (m, 12H, CH_2), 1.18 (d, J = 6.5 Hz, 3H, $-CH_3$). MS (LSIMS): m/z 569 (M^++Li-H_2O), 603 (M^++Na).