Cyclopeptide Synthesis

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Cyclative Cleavage through Dipolar Cycloaddition: Polymer-Bound Azidopeptidylphosphoranes Deliver Locked *cis*-Triazolylcyclopeptides as Privileged Protein Binders**

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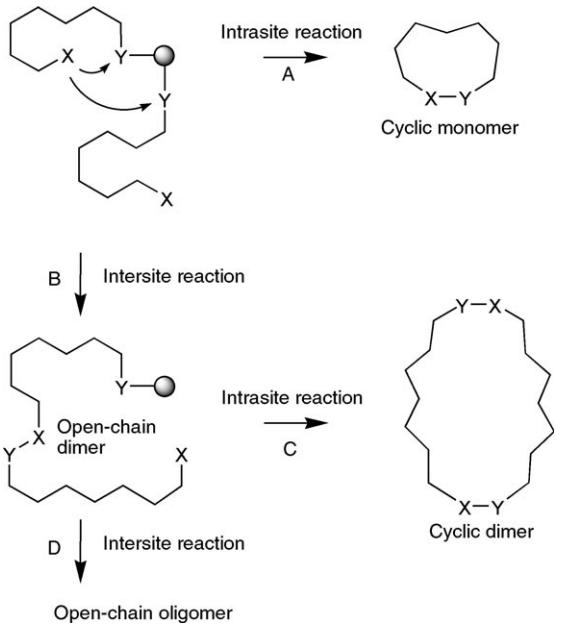
Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday

Cyclic peptides are important natural products displaying a broad range of biological effects including immunosuppression, antibacterial properties, and anticancer activity.[1] Many cyclopeptides act as potent inhibitors of protein–protein interactions and enzymatic activities as they display partially rigidified conformations and thus provide improved protein target recognition together with favorable pharmacokinetic properties and metabolic stability.[2] As a result several cyclopeptides have been used successfully as clinically approved drugs for decades, and cyclopeptides and pseudocyclopeptides continue to supply the pharmaceutical industry with novel drug candidates.[3,4]

Triazolylcyclopeptides have been introduced as pseudocyclopeptides with decreased flexibility as one peptide bond is replaced with the heterocycle locking it either in *trans*-peptide or in *cis*-peptide geometry.[5] For several biological targets, *cis*-locked cyclopeptides containing 1,5-disubstituted triazoles display significantly increased binding affinity and biological activity relative to the 1,4-disubstituted derivatives and native cyclopeptides.[5] Based on these observations triazolylcyclopeptides are considered as privileged protein binders.

Despite their broad biological significance, the synthesis of triazolylcyclopeptides and wild-type cyclopeptides still presents a major challenge and requires improved synthetic methods. Cyclization reactions in solution often deliver low yields and furnish mixtures of monomeric, oligomeric, cyclized, and open-chain products, when the intermolecular reaction competes with an intramolecular reaction path.[6] Attachment to a solid support can reduce oligomer formation considerably since the reaction sites are spatially separated (pseudo-dilution principle).[7] Nevertheless, intersite reactions are possible on highly swellable polymers, such as low-cross-linked polystyrene, and depend critically on the length and flexibility of the attached molecules.[8] If, however, cyclization and cleavage proceed in the same chemical reaction (referred to as cyclative cleavage), open-chain oligomeric by-products remain attached to the solid support and are easily removed by washing the resin, whereas cyclic monomers and cyclic oligomers are released in solution (Scheme 1).[9] Moreover, both the flexibility of the polymer support and the level of resin loading are parameters that can be exploited to favor intrasite versus intersite reactions.

In the light of these considerations, preparation of triazolylcyclopeptides employing cyclative cleavage appeared



Scheme 1. In cyclizations on solid supports intrasite reactions (A) compete with intersite reactions (B). In the special case of cyclative cleavage, path A yielding cyclic monomer competes with path B, providing the open-chain dimer still attached to the polymer. The latter can react either following path C to give the cyclic dimer (intrasite) or by path D leading to the attached open oligomer in an intersite reaction.

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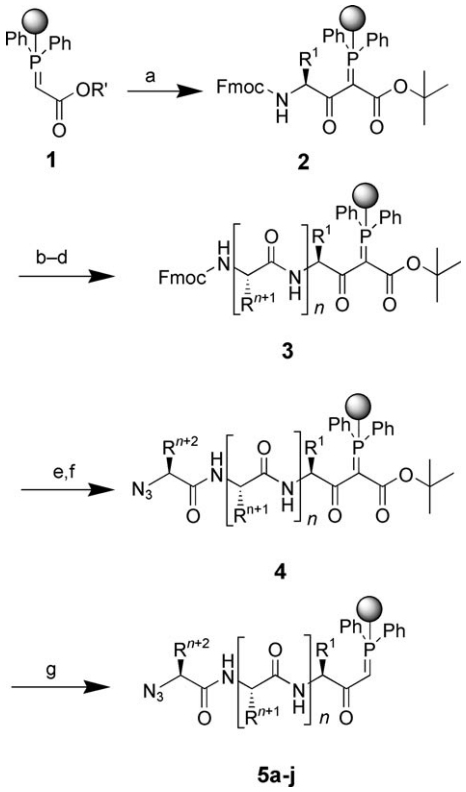
to be an attractive enterprise. Though 1,3-dipolar cycloadditions of azides and alkynes under Cu^{I} or Ru^{II} catalysis can be used to incorporate 1,4- and 1,5-disubstituted triazoles in peptides,[10] the efficacy of the Cu^{I}-catalyzed, 1,4-selective reactions dropped significantly for cyclizations[11] and the yields were even more disappointing on solid support.[12] Therefore, in most of these cases the 1,4-disubstituted triazole was introduced into cyclic peptides through the reaction of peptides with terminal azide and alkyne units in solution.[11–13] Alternatively, the 1,4-disubstituted triazole was prepared first in the linear peptide sequence and the cyclopeptide was obtained after a final lactamization step.[14]

Unfortunately, the synthesis of the biologically privileged 1,5-disubstituted triazolylcyclopeptides has proved to be especially difficult. No cyclizations of azidoalkynyl peptides to give 1,5-disubstituted triazoles either in solution or on solid support have been reported yet. As the ruthenium-catalyzed cycloaddition must be performed at high concentration (0.5–1.0 M), the reaction was not suitable at the higher dilutions required to reduce oligomer formation.[19] The only reported synthesis of 1,5-disubstituted triazolylcyclopeptides proceeded through a final lactamization reaction.[5a]

Recently, we have developed the synthesis of 1,5-peptidyltriazolyl peptides through metal-free, regioselective 1,3-dipolar cycloaddition reactions.[15] The method enabled preparation of triazolyl peptides starting from commercially available amino acid building blocks and yielded the products in high purity; a dipolar cycloaddition served as the cleavage reaction. As demonstrated by ROESY NMR analysis and a simulated annealing protocol, the obtained 1,5-disubstituted triazole acting as a *cis*-peptide-bond mimetic induces turn structures even in short peptide stretches. Moreover, using azidopeptidylphosphorane resins for cyclative cleavage should lead to the selective and exclusive formation of cyclized products as all open-chain monomers and oligomers are expected to remain attached to the polymer support (Scheme 1).

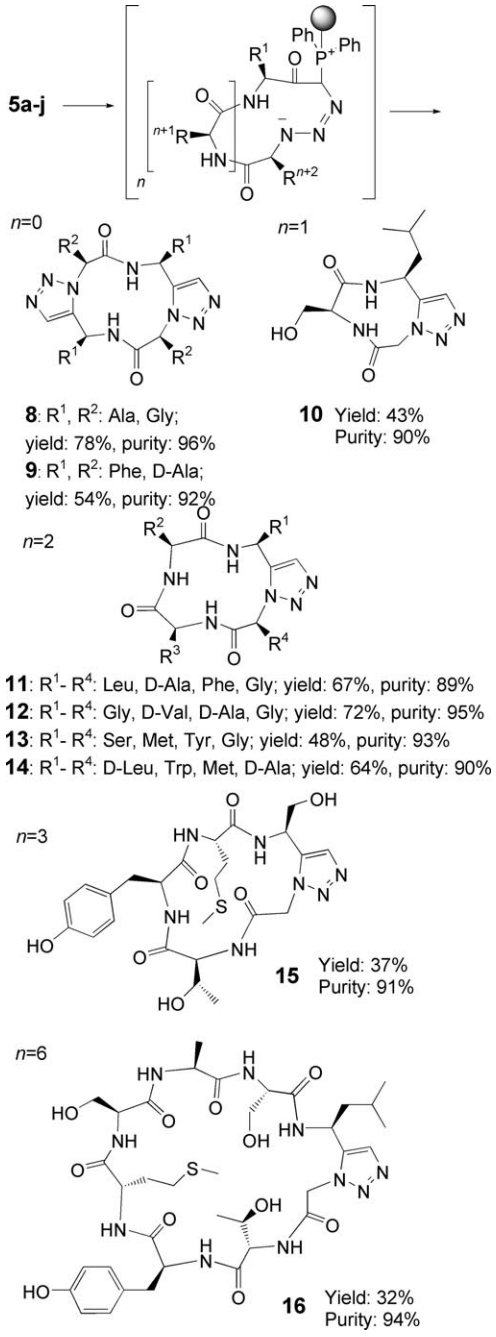
To test this hypothesis we prepared N-terminal azidopeptidylphosphoranes on a solid support (Scheme 2).[16] Starting from *tert*-butylphosphoranylidene acetate (**1**), amino acyl phosphorane **2** was obtained from a nonracemizing C-acylation employing an Fmoc-protected amino acid and BTFFH for activation; the products were obtained in 76–82% yield depending on the amino acid used in this step: glycine, leucine, phenylalanine, or *tert*-butylserine. Intermediate **2** was extended with further amino acids by employing standard couplings of Fmoc-protected amino acids (activation with diisopropylcarbodiimide/1-hydroxybenzotriazole) to furnish resin **3**. For the elongation steps various amino acids with and without side-chain protection were used including Pro, Leu, Val, Trp, Ser, Thr, Met, and Tyr. Following removal of the Fmoc groups from **3**, the resulting free amines were acylated with one of the 2-azido acids **6** or **7**, which were obtained by nucleophilic substitution of bromoacetic acid with sodium azide and by diazo transfer from freshly prepared triflyl azide, respectively.[17] The reaction furnished the azidopeptidylphosphoranylidene acetate **4**, which was treated with trifluoroacetic acid to remove all side-chain protecting groups. Cleavage of the C-terminal acetate ester led to instantaneous decarboxylation of the phosphoranylidene acetate, yielding azidopeptidylphosphoranes **5a–j**.



Scheme 2. Preparation of azidopeptidylphosphoranes **5a–i** on polystyrene support. Reaction conditions: a) Fmoc-AA-OH and BTFFH, DIPEA, DMF, 14 h; b) 20% piperidine/DMF; c) Fmoc-AA-OH, DIC, HOBt, DMF, 2 h; d) steps (b) and (c) are repeated *n* times; e) 20% piperidine/DMF; f) 2-azido acid (**6** or **7**), DIC, HOBt, DMF, 2 h; g) TFA/CH_2Cl_2 (95% v:v), 5 h followed by treatment with Et_3N. BTFFH = bis (tetramethylene)fluoroformamidinium hexafluorophosphate, DIPEA = *N*,*N*-diisopropylethylamine, DIC = diisopropylcarbodiimide, HOBt = 1-hydroxybenzotriazole, TFA = trifluoroacetic acid.

Cyclizations of **5a–j** were investigated with peptide chains of different lengths as well as varying amino acid sequences (Scheme 3, Table 1). A reaction temperature of 60–80 °C and polar solvents were sufficient for cyclative cleavage of azidopeptidylphosphoranes. DMF was the preferred solvent as it assured good solubility of those products which were only partially soluble in other polar solvents used to swell the polystyrene support. When the longer azidopenta-, and azidooctapeptidylphosphoranes **5i,j** ($n = 3$, 6) were heated in DMF exclusively the expected monomeric triazolyl cyclopeptides **15** and **16**, respectively, were formed. These results indicate that the solid support exerts a considerable degree of site separation.

When, however, the azidodipeptidylphosphoranes **5a,b** ($n = 0$) were treated under identical conditions, exclusively the dimeric bistriazolylcyclotetrapeptides **8** and **9** formed from intersite reactions (see Scheme 1). Azidotripeptidylphosphoranes **5c** ($n = 1$) delivered a 3:2 mixture of the monomeric triazolyl cyclotripeptide with the respective dimeric product. Azidotetrapeptidylphosphoranes **5e–h** ($n = 2$) were cyclized under identical conditions and provided the



Scheme 3. Products formed by cyclative cleavage of azidopeptidylphosphoranes **5a–j**. Yields and purities for **8**, **9**, **11**, **12**, and **14** are given for the crude products, data for compounds **10**, **13**, **15**, and **16** are reported after HPLC purification.

respective triazolyl cyclotetrapeptides as the major products. While azidotetrapeptidylphosphoranes **5g**,**h** furnished exclusively the cyclic monomers **13** and **14**, reactions of **5e** and **5f** yielded the monomeric triazolyl cyclopeptides **11** and **12** together with the corresponding dimeric products in minor amounts according to LC–MS analysis.

The formation of dimeric products indicates a significant degree of site interaction within the polymer support. As site separation depends strongly on the flexibility of the polymer

Table 1: Formation of monomeric and dimeric products by cyclative cleavage of phosphoranes **5a–j**.[a]

Phosphorane	Peptide sequence	*n* (chain length)	Prod.	Ring size[b]	Monomer [%][c]	Dimer [%][c]
5a,b	AG, Fa	0 (dipeptide)	**8**,**9**	12	0	100[b]
5c	LPG	1 (tri-)	[d]	9	60	40
5c	LPG	1 (tri-	[d]	9	80[c]	20[c]
5d	LSG	1 (tri-)	**10**	9	12	88
5d	LSG	1 (tri-)	**10**	9	75[c]	25[c]
5e	LaFG	2 (tetra-)	**11**	12	80	20
5f	GvaG	2 (tetra-)	**12**	12	85	15
5g	SMYG	2 (tetra-)	**13**	12	100	0
5h	lWMa	2 (tetra-)	**14**	12	100	0
5i	SMYTG	3 (penta-)	**15**	15	100	0
5j	LSASMYTG	6 (octa-)	**16**	24	100	0

[a] Peptide sequences are assigned with the one-letter code using capital letters for L-amino acids and small letters for D-amino acids. [b] Number of atoms in the ring. [c] The ratio of monomeric to dimeric products was determined based on the UV absorption signal at 220 nm in the LCMS chromatogram. If not noted specifically, the cleavage reactions were conducted from low-cross-linked microporous polystyrene (2% divinylbenzene, 1.6 mmol g^{-1}). [d] Product ratio for cleavage from low-cross-linked, microporous triphenylphosphane polystyrene (2% divinylbenzene, 1.6 mmol g^{-1}) and from highly cross-linked, macroporous polystyrene (>20% divinylbenzene, 1.62 mmol g^{-1}). [e] Product ratio for cleavage from highly cross-linked, macroporous triphenylphosphane polystyrene (>20% divinylbenzene, 1.62 mmol g^{-1}). [f] Not isolated; products precipitate during purification on column.

carrier, it should be enhanced in more rigid supports such as macroreticular (macroporous) polystyrene. Use of macroreticular polystyrene is supposed to affect the cyclization reaction and favor monomeric over dimeric cyclic products. To test this assumption, azidopeptidylphosphoranes **5a**,**c**,**d** were prepared using macroporous resin with >20% divinylbenzene (DVB) cross-linking, considerably more than the standard low-cross-linked, microporous polystyrene resins with only 2% DVB cross-linker. Both resins had an initial loading of approximately 1.6 mmol of triphenylphosphane per g. Cyclization of azidotripeptidylphosphorane **5c** on macroporous resin yielded the monomeric product in 80% yield, indicating a significant shift towards the intrasite reaction pathway. Unfortunately, the cyclization products derived from **5c** precipitated during purification and thus could not be isolated. Therefore, the tripeptide precursor **5d**, in which the proline residue of **5c** is replaced by serine to improve the product solubility, was synthesized both on micro- and macroporous resins. In this case, cyclization on the microporous resin delivered products in a 12:88 ratio in favor of the dimeric (intersite) cyclization product. Again the synthesis on the macroporous support yielded the monomeric (intrasite) reaction product **10** in excess (75:25); **10** was isolated and characterized spectroscopically. On the other hand, when the azidodipeptidylphosphorane **5a** on macroporous resin was heated in DMF, the dimeric product **8** was still delivered exclusively, albeit in significantly reduced yield (46% instead of 78%). Obviously, the intersite cyclization pathway is favored strongly in these cases so that formation of

the monomeric product was not detected even on the more rigid polymer.

These results are surprising at first glance if one considers a concerted mechanism of the dipolar cycloaddition reaction. Both experimental findings and calculations indicate, however, a stepwise reaction mechanism in the case of electron-rich dipolarophiles.[18] Considering phosphorus ylides as electron-rich dipolarophiles we can postulate a stepwise mechanism for their cycloadditions with azides as well. This stepwise mechanism, however, requires the attack of the ylide carbon at the terminal azide nitrogen (as depicted in Scheme 3) and thus must strongly disfavor intrasite reactions of shorter azidopeptidylphosphoranes over the concerted mechanism leading to the dimeric products **8** and **9**.

In summary, we have described the cyclative cleavage of azidopeptidylphosphoranes. Depending on the length of the starting material, the building block sequence, and the polymer rigidity the method delivered either monomeric or dimeric products. Pure dimers were obtained from azidodipeptidylphosphoranes ($n=0$). Tripeptidylphosphoranes ($n=1$) yielded mixtures of products, whereas longer starting materials provided monomeric products, either entirely pure ($n>3$) or with small dimeric impurities ($n=3$). The products of intrasite reactions were significantly favored by the use of a more rigid, highly cross-linked polymer support. All products were isolated in good to excellent yields which greatly exceeded previous results for comparable cyclizations in solution phase.[5a,19] The solubility of the products was critical for the yields obtained and for the feasibility of chromatographic purification. The NMR signals of all isolated products **8**–**16** were fully assigned in one- and two-dimensional ^{1}H and ^{13}C NMR spectra and the products were characterized by HRMS. The method completely avoids formation of soluble, noncyclized, oligomeric by-products and is therefore superior to solution protocols with respect to synthetic efficiency, yields, and purity.[19] This approach to *cis*-locked triazolyl cyclopeptides should considerably facilitate the systematic investigation of the structural and biological properties of these compounds, which are already known to have biological significance.

Experimental Section

Synthetic procedures and analytical data (HRMS, ^{1}H NMR, ^{13}C NMR) of all novel compounds are provided in the Supporting Information.

General synthesis of *cis*-triazolyl cyclopeptides **8**–**16**: Azidopeptidylphosphorane **5** (300 mg, 0.315 mmol) was swollen in anhydrous DMF (4 mL) and heated in a sealed glass vial at 80 °C for 14 h. After cooling to room temperature, the support was filtered off and washed with DMF (5 × 2 mL) with shaking. All the washing fractions were combined, and the solvent was removed under reduced pressure leaving the solid products. Compounds **8**, **9**, **11**, **12**, and **14** were pure enough in crude form to be characterized by NMR spectroscopy, while **10**, **13**, **15**, and **16** were purified by reversed-phase preparative HPLC prior to NMR analysis.

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[19] The difficulties in preparing this class of compounds through Ru^{II} catalysis were discussed in a recent PhD thesis: J. Springer, University of Amsterdam, **2008**, chap. 4, pp. 106–126, (*http://dare.uva.nl/document/116338*). To compare the efficiency of our new approach for the synthesis of *cis*-triazolyl cyclopeptides with the existing methods, compound **14** was prepared analogously to one example reported in reference [5a]. The yield of the cyclative cleavage was 64 %, while the yield of the lactamization procedure was 9 %.

