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Facile Synthesis of @-Tide β-Strand Peptidomimetics: Improved Assembly in Solution and on Solid Phase

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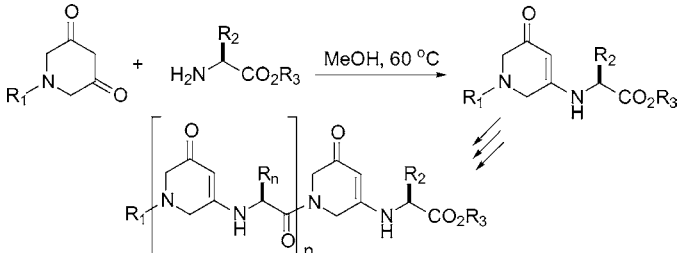
ABSTRACT



The synthesis of @-tide β-strand peptidomimetics has been improved such that oligomers now can be obtained from solution- and solid-phase synthesis protocols approaching the efficiency and flexibility of peptide chemistry. These methods enable the synthesis of @-tide oligomers with a variety of amino acids and with lengths up to 13 units.

The discovery of molecules that disrupt protein−protein interactions is a significant challenge and the subject of intense interest.[1] One strategy involves the design of analogues that mimic the peptide segments involved in the recognition interface.[1d,e] While a sequence excised from one protein partner may in principle be effective for this purpose, in practice short peptides adopt poorly defined structures and make undesirable candidates for drug discovery. As a consequence, a number of strategies have been pursued to develop nonpeptidic mimics of protein secondary structure, including the extended β-strand conformation appropriate for competing with protein−protein interactions that involve β-sheet-like interfaces.[2]

We recently reported the synthesis and association behavior of β-strand peptidomimetics called "@-tides".[3] @-Tides are composed of alternating amino acids and dihydropyridinones ("@-units"), which together predispose the oligomers to adopt the extended, β-strand conformation. As a consequence of this conformational control, @-tides readily associate in organic solvent as two-stranded antiparallel β-sheet-like homodimers. The @-unit is also effective at templating peptide β-sheet formation in water in the intramolecular context of a β-hairpin.[4] However, to explore the potential for @-tides to disrupt protein−protein interac-

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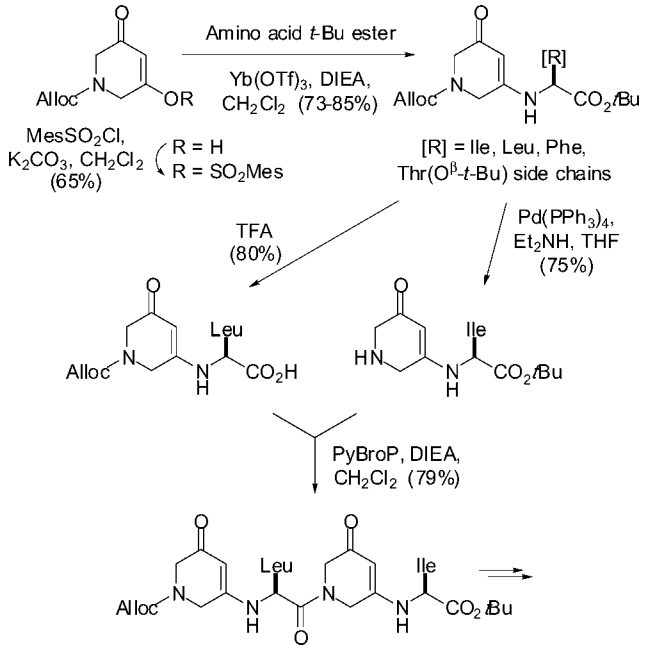
tions required significant improvement over the methods originally developed for their assembly (Scheme 1).[3] We now

Scheme 1. Original @-Tide Synthesis[a]



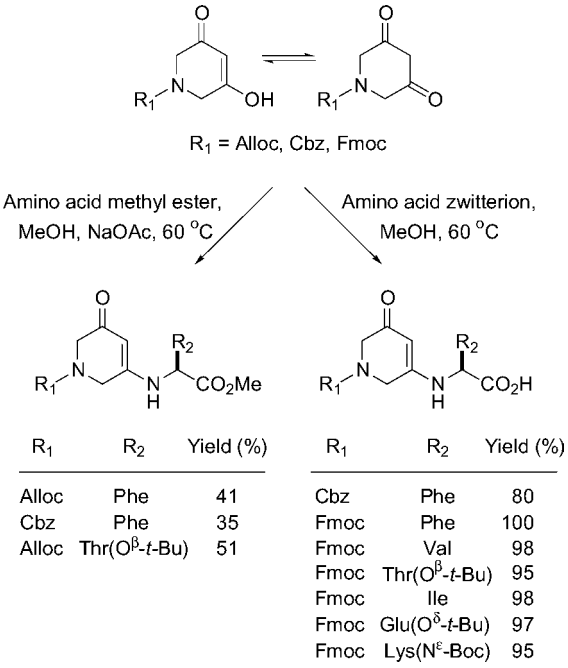
[a] Side chains [R] are indicated by the three-letter code of the amino acid itself, along with any side chain protecting group present.

describe @-tide chemistry that is nearly as flexible and efficient as peptide synthetic methods. Moreover, a variety of protection strategies are now available for formation of @-tide oligomers, facilitating the assembly of libraries incorporating both polar and nonpolar amino acids.

The di-@-tide building blocks were initially obtained from an ytterbium-catalyzed Michael addition−elimination reaction between an N-protected, C-activated dihydropyridinone unit and an amino acid protected as the *tert*-butyl ester.[3] While this combination generally affords good yields, amino acid methyl esters are noticeably less effective in this reaction (e.g., ca. 40−70% yields), often dimerizing to give the diketopiperazines. An alternative approach that provides access to orthogonally protected di-@-tides in fewer steps involves direct condensation of amino acids with the N-protected 3,5-piperazinedione (Scheme 2). This method is compatible with Fmoc, Alloc, and Cbz nitrogen protecting groups on the @-unit-, Boc-, and *t*-butyl-protected amino acid side chains and unprotected amino acids or their methyl esters. Moreover, the condensation products are often sufficiently pure after extraction that they can be used directly in subsequent steps. This route also eliminates the two chromatographic purifications that were necessary in preparation of the N-protected, C-activated @-unit and the di-@-tide products as shown in Scheme 1.[3]

With the ready availability of an assortment of differentially protected di-@-tides as building blocks, oligomers can be assembled in the same fashion as peptides. However, as

Scheme 2. Synthesis of Di-@-tide "Amino Acids"



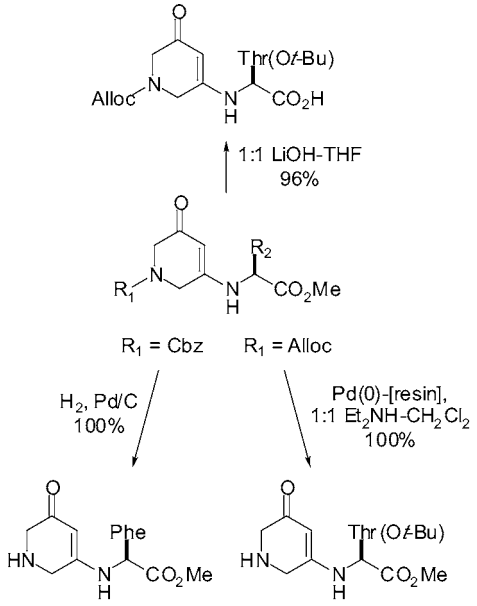
R_1	R_2	Yield (%)
Alloc	Phe	41
Cbz	Phe	35
Alloc	Thr(O^{β}-*t*-Bu)	51

R_1	R_2	Yield (%)
Cbz	Phe	80
Fmoc	Phe	100
Fmoc	Val	98
Fmoc	Thr(O^{β}-*t*-Bu)	95
Fmoc	Ile	98
Fmoc	Glu(O^{δ}-*t*-Bu)	97
Fmoc	Lys(N^{ε}-Boc)	95

in peptide synthesis, the efficiency of @-tide elongation depends on the ease with which both the deprotection and coupling reactions can be accomplished. Scheme 3 illustrates conditions and typical yields for removal of the N- and C-terminal protecting groups from representative di-@-tides. Standard conditions (1:1 TFA−CH_2Cl_2 for 2 h) were used for removal of Boc and *t*-Bu side chain protecting groups.

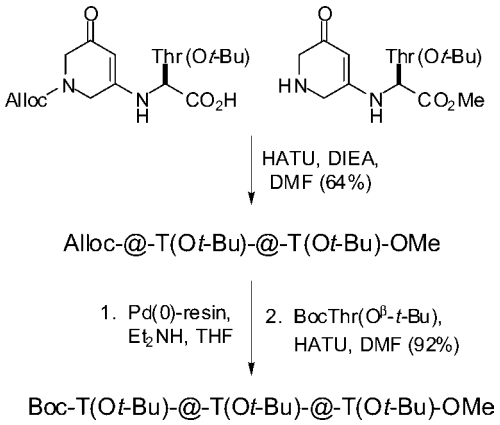
@-Tide elongation is accomplished by coupling two di-@-tides or a di-@-tide and an amino acid using HATU[5] as the activation reagent (Schemes 4 and 5). HATU is advanta-

Scheme 3. Deprotection Protocols



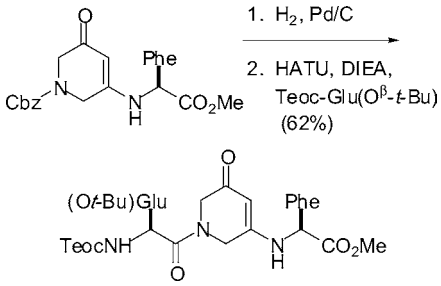
geous compared to the previously used PyBroP[5] because it is compatible with DMF, which is important for synthesis of the longer oligomers that associate more readily in solvents such as methylene chloride. Moreover, by deprotecting the Cbz group by hydrogenolysis or the Alloc group with a resin-bound Pd^0 species,[6] the triphenylphosphine oxide byproduct arising from $Pd(PPh_3)_4$ is avoided. Removal of this contaminant, as well as the phosphine oxide byproduct from PyBroP, had plagued the previous protocols and necessitated careful chromatographic purifications. With the protocols illustrated in Schemes 4 and 5, filtration through a short silica gel plug is all that is typically required after an extractive workup.

Scheme 4. @-Tide Elongation Using the Alloc Protecting Group

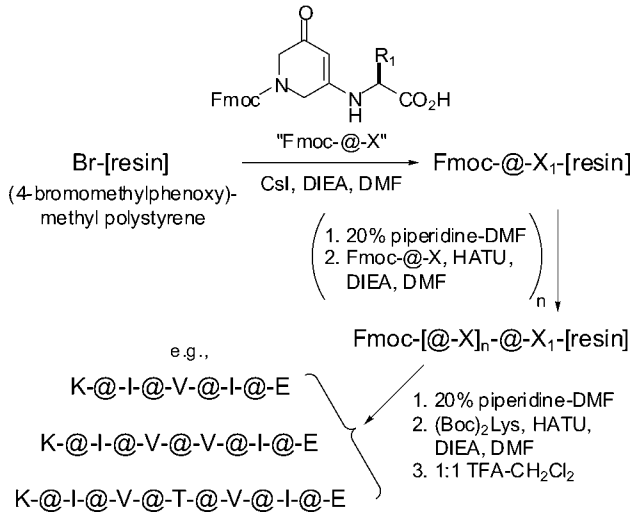


With the Fmoc protecting group, @-tide assembly on solid phase now mirrors the protocol used for solid-phase peptide synthesis. This strategy has been adapted to semiautomated

Scheme 5. @-Tide Elongation Using the Cbz Protecting Group



Scheme 6. Improved Solid-Phase Methods



synthesis and applied to the preparation of oligomers up to 13 units in length (Scheme 6). Isolated yields ranged from ca. 20−80%, depending on the hydrophobicity and length of the sequence: high yields were obtained for shorter nonpolar @-tides (penta- or hepta-@-tides), while lower yields were observed for polar and longer derivatives.

In summary, improved syntheses of @-tide peptidomimetics have been developed in solution and on solid phase. Ready access to the di-@-tide building blocks with different protecting groups brings @-tide and peptide chemistry into alignment and provides an opportunity to explore these β-strand mimics in a variety of applications.

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Supporting Information Available: Experimental procedures, characterization, and reference spectra for all compounds depicted (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; PyBroP = bromo-tris(pyrrolidino)phosphonium hexafluorophosphate

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