

# Solid-phase synthesis of peptoids with structure-inducing tert-butyl side chains: A unique challenge finally met

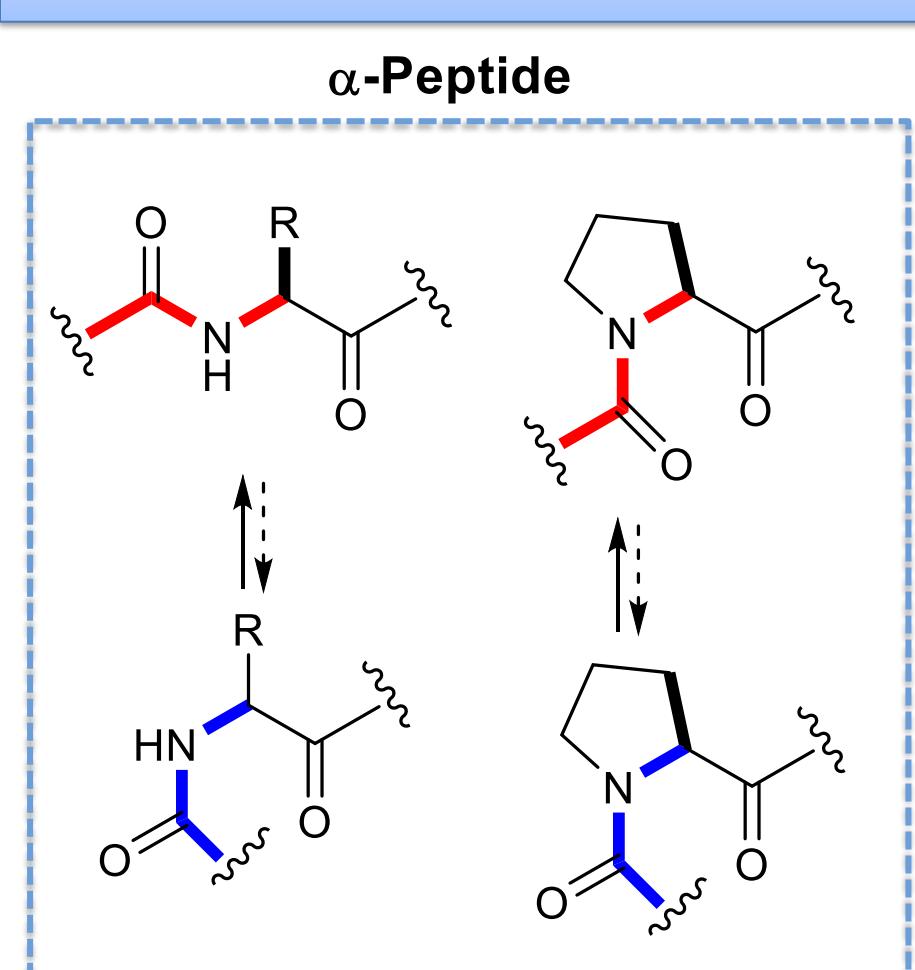
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<https://doi.org/10.17952/37EPS.2024.P1255>

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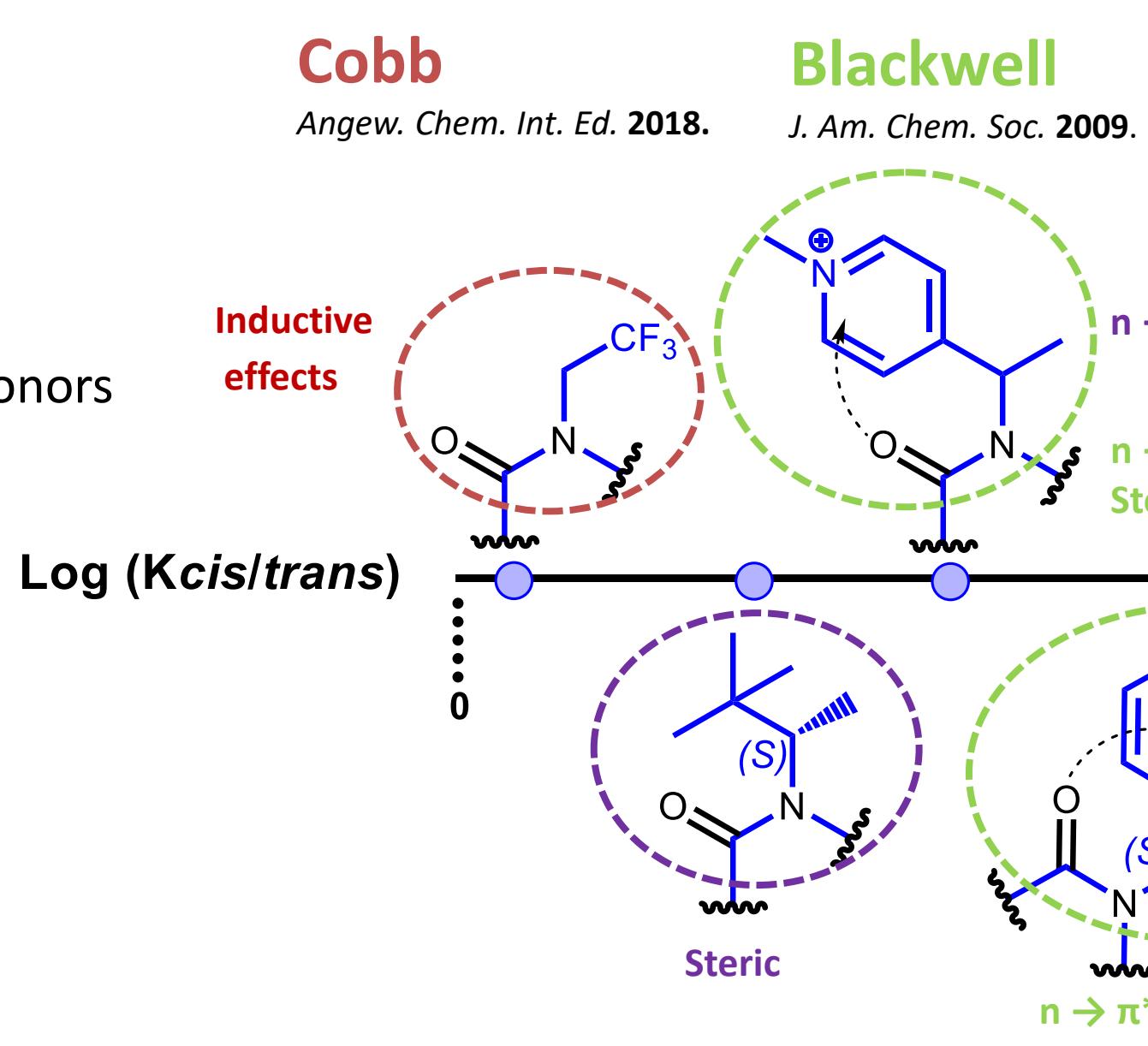
## Peptoids as peptidomimetic foldamers



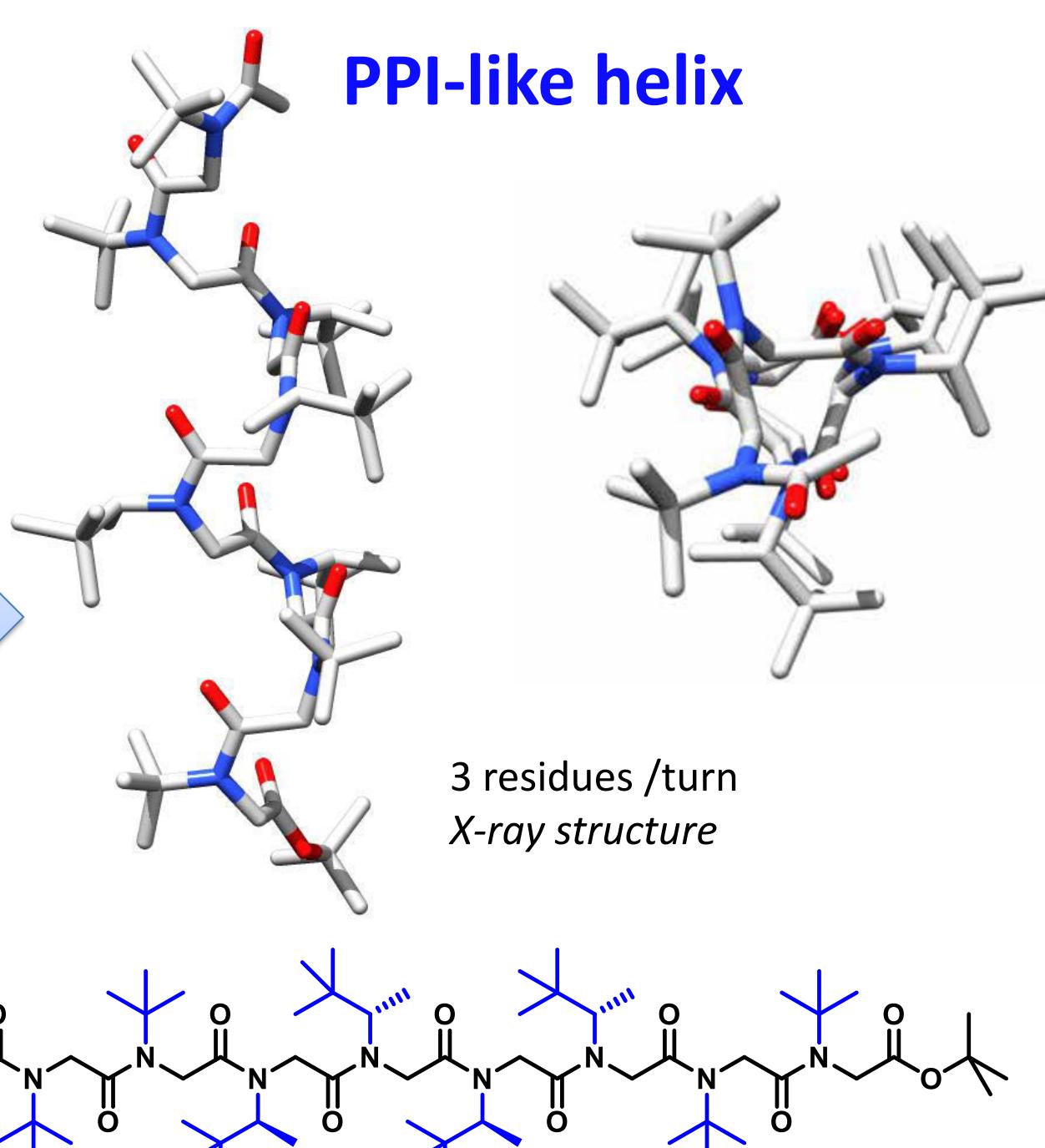
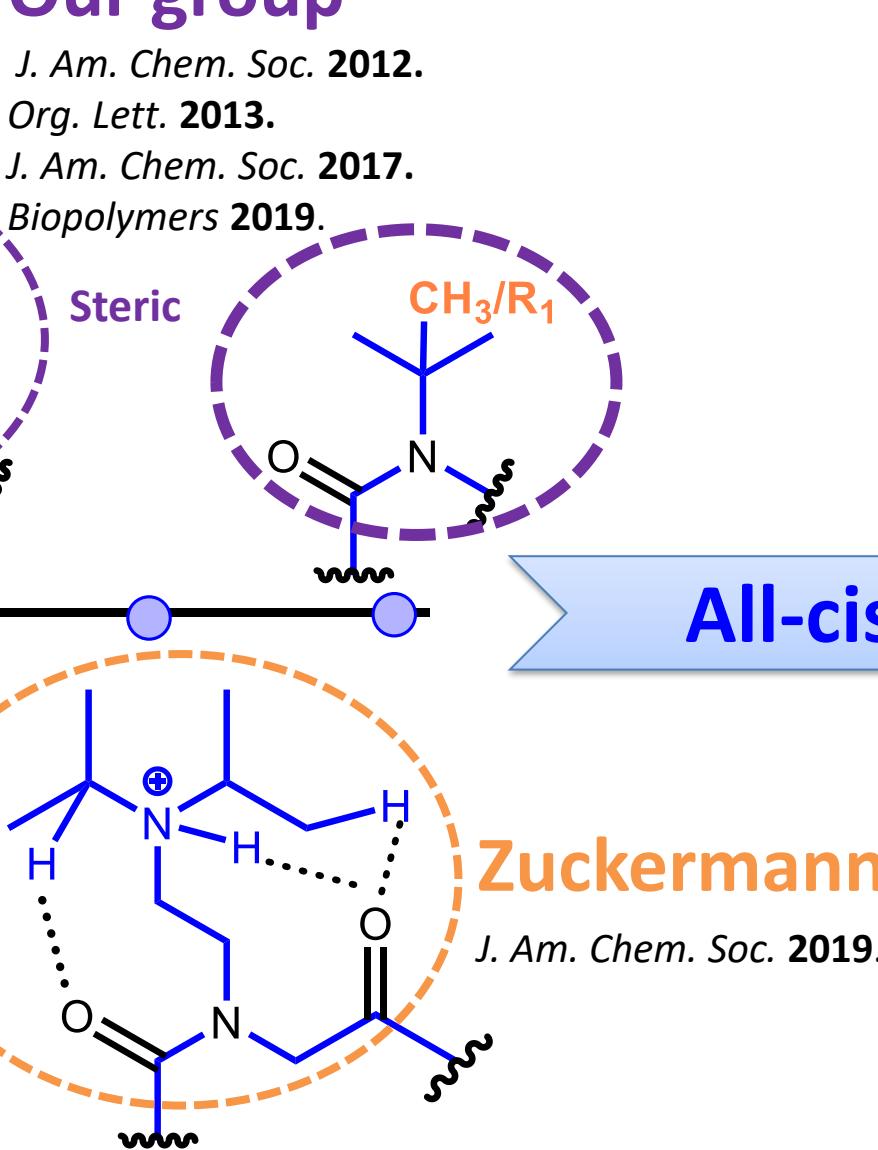
- No hydrogen bond donors
- Achiral backbone
- cis/trans isomerism

## Main side chains favoring cis peptoid amide bonds

Cobb  
Angew. Chem. Int. Ed. 2018.  
Blackwell  
J. Am. Chem. Soc. 2009.



Our group

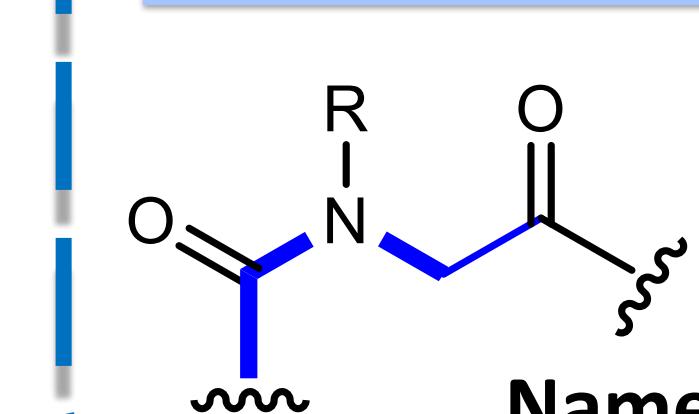


## Oligomers of N-substituted glycines

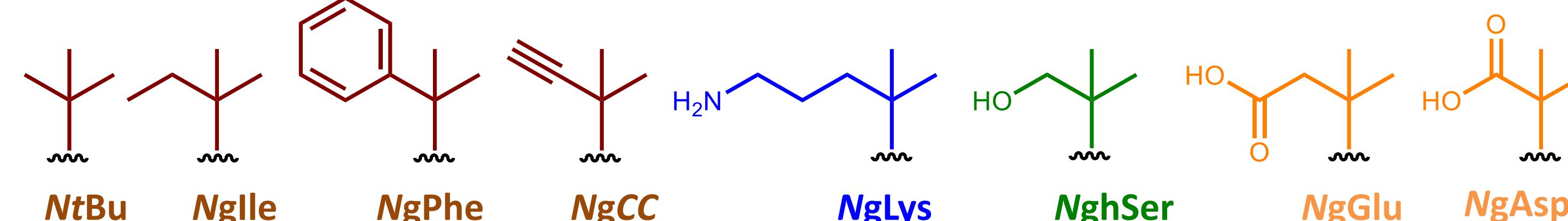
- Efficient and scalable submonomer synthesis
- Great potential for diversity
- Higher proteolytic stability than peptides
- Better biodisponibility

## Objectives

Rapid access to peptoid oligomers containing structure-inducing tert-butyl side chains



Name of peptoid unit :

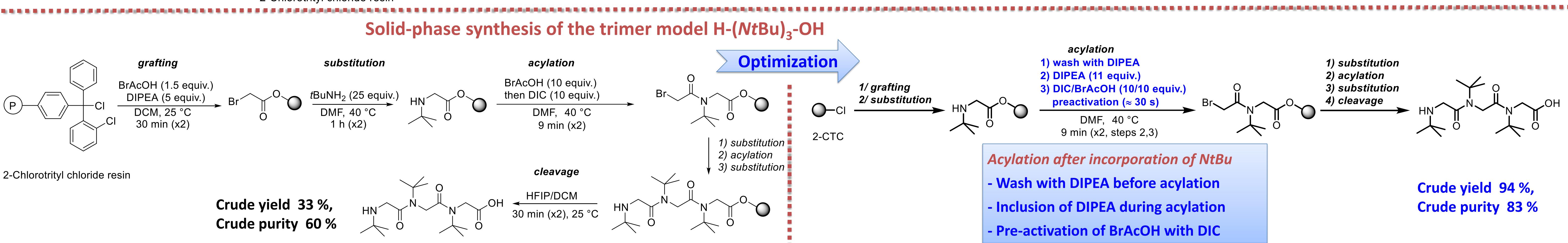
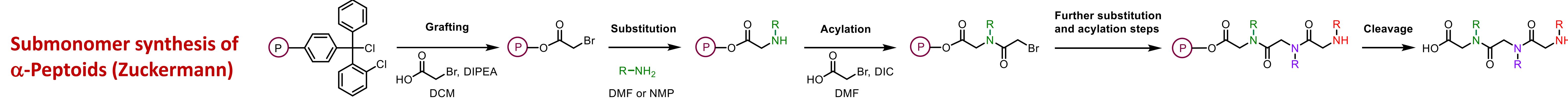


## Homogeneous and robust helix comprising only aliphatic residues

- Right-handed PPI-type helix
- Remarkable conformational regularity
- Longest solid-state structure for linear peptoids

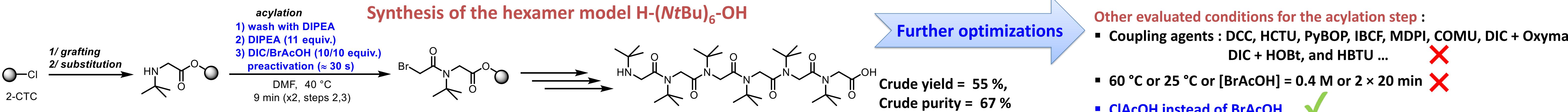
Roy, O.; Dumontel, G.; Faure, S.; Jouffret, L.; Kriznik, A.; Taillefumier, C. J. Am. Chem. Soc. 2017, 139, 13533–13540.

## Incorporation of peptoid units bearing these side chains by solid-phase synthesis ?

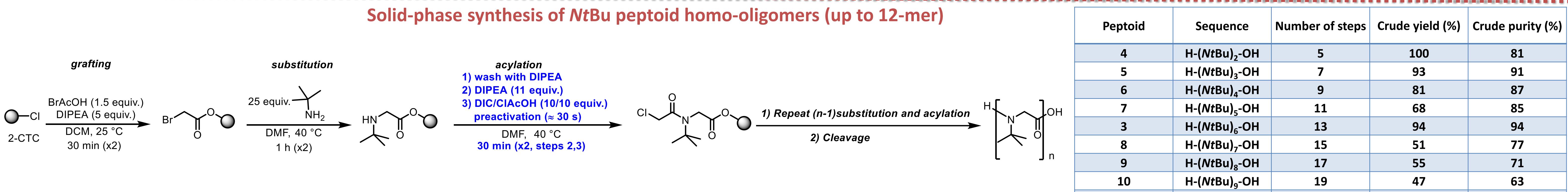


Acylation after incorporation of NtBu  
- Wash with DIPEA before acylation  
- Inclusion of DIPEA during acylation  
- Pre-activation of BrAcOH with DIC

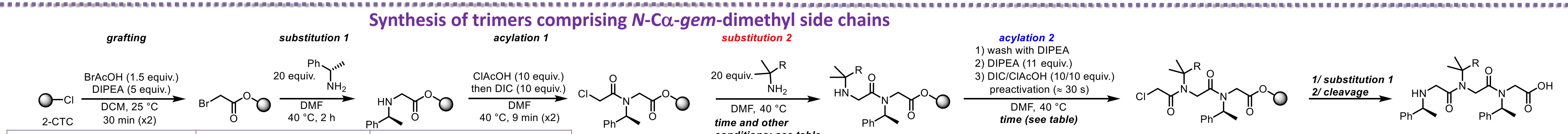
Crude yield 94%,  
Crude purity 83 %



Other evaluated conditions for the acylation step :  
▪ Coupling agents : DCC, HCTU, PyBOP, IBCF, MDPI, COMU, DIC + Oxyma, DIC + HOBT, and HBTU ... X  
▪ 60 °C or 25 °C or [BrAcOH] = 0.4 M or 2 × 20 min X  
▪ CIcOH instead of BrAcOH ✓



Peptoid	Sequence	Number of steps	Crude yield (%)	Crude purity (%)
4	H-(NtBu) <sub>2</sub> -OH	5	100	81
5	H-(NtBu) <sub>3</sub> -OH	7	93	91
6	H-(NtBu) <sub>4</sub> -OH	9	81	87
7	H-(NtBu) <sub>5</sub> -OH	11	68	85
3	H-(NtBu) <sub>6</sub> -OH	13	94	94
8	H-(NtBu) <sub>7</sub> -OH	15	51	77
9	H-(NtBu) <sub>8</sub> -OH	17	55	71
10	H-(NtBu) <sub>9</sub> -OH	19	47	63
11	H-(NtBu) <sub>12</sub> -OH	25	36	71



Monomer sequence	substitution 1 (time/other)	acylation 1 (time/other)	substitution 2 (time/other)	acylation 2 (time/other)	1/ substitution 1 /2/ cleavage
Ns1pe-NtBu-Ns1pe	2h	2x 30 min			
Ns1pe-NgIle-Ns1pe	2h	2x 30 min			
Ns1pe-NgPhe-Ns1pe	2h 5 equiv. KI + 5 equiv. DIPEA	22 equiv. DIPEA 20 equiv. DIC/ClAcOH			
Ns1pe-NgCC-Ns1pe	2x 2h 5 equiv. KI + 5 equiv. DIPEA	3x 30 min			
Ns1pe-NghSer(TBDMS)-Ns1pe	2h 5 equiv. KI + 5 equiv. DIPEA	3x 30 min			
Ns1pe-NgLys(Cbz)-Ns1pe	24h 5 equiv. KI + 5 equiv. DIPEA	2x 30 min			
Ns1pe-NgGlu(All)-Ns1pe	24h 5 equiv. KI + 5 equiv. DIPEA	3x 30 min			
Ns1pe-NgAsp(Bn)-Ns1pe	16 h 5 equiv. KI + 5 equiv. DIPEA	3x 30 min			