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Peptidomimetic Synthesis by Way of Diastereoselective Iodoacetoxylation and Transannular Amidation of 7−9-Membered Lactams

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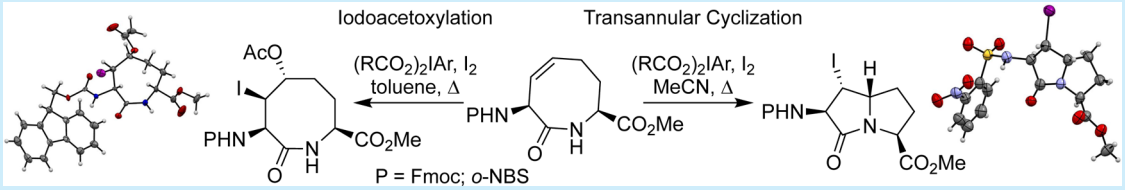
Supporting Information



ABSTRACT: Azacyclo- and azabicycloalkanone peptidomimetics were synthesized regio- and diastereoselectively by iodoacetoxylation and transannular amidation reactions on unsaturated lactam precursors contingent on ring size, olefin position, solvent, and hypervalent iodine(III) reagent. 4-Iodopyrrolizidinone **1**, 7-iodoindolizidinone **2**, and 4-iodo-5-acetoxylactams (e.g., **6** and **7**) were made stereospecifically from 7−9-membered olefins **16**, iodine, and hypervalent iodine(III) in acetonitrile or toluene, respectively. X-ray crystallography demonstrated potential for mimicry of natural peptide turn side chain and backbone conformations.

Stereoselective synthesis and functionalization of ring systems are fundamental goals in organic and medicinal chemistry.[1] In peptide mimicry, stereocontrolled ring synthesis is desired to replicate precisely the side chain and backbone orientations responsible for biological activity.[2] Constrained dipeptide lactam and azabicyclo[X.Y.0]alkanone rings have shown great utility for the mimicry of biologically active peptide secondary structures.[3,4] Although the stereoselective synthesis and functionalization of small ring lactams have been effectively accomplished, their introduction into bicyclic motifs and the construction and modification of their larger 7−9-member ring counterparts remain two relatively unmet challenges.[5] Employing unsaturated 7−9-membered lactams, stereocontrolled means have now been conceived for their conversion to fused bicycles composed of small ring systems (fused 5,5-, 5,6-, and 6,4-bicycles **1**−**5**) as well as their functionalization (e.g., **6**−**8**, Figure 1). Exploring the scope and limitations of this method, a set of turn mimics bearing ring substituents has been made for replicating peptide geometry.

Recently,[6,7] a ring-closure metathesis (RCM)−transannular lactam cyclization strategy was disclosed for the synthesis of iodo substituted azabicyclo[X.Y.0]alkanone amino acid derivatives, e.g. fused 5,5-, 6,5-, 6,6-, and 7,5-bicycles (**1**, **9**−**11**, Scheme 1, Figure 1). Iodolactamization using iodine gave effectively 6,5-, 6,6-, and 7,5-bicycles respectively from 9- and 10-membered lactams; yet, similar conditions (i.e., I_2, THF, 80 °C or I_2, $NaHCO_3$, rt) failed to induce cyclization of 7- and 8-membered lactams **15** and **16**, as well as 9-membered lactam isomers **15c** and **16c**.

A breakthrough in the transannular iodolactamization occurred on addition of diacetoxy iodobenzene (DIB) to the I_2 mixture, which converted **16b** diastereoselectively to pyrrolizidinone **1**.[6]

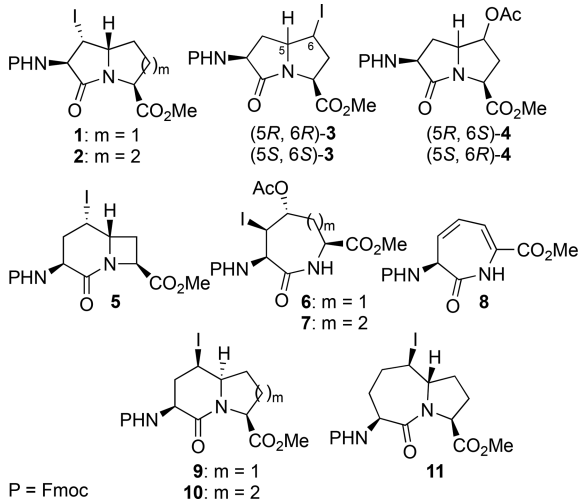


Figure 1. Novel bicycles (**2**−**5**) and lactams (**6**−**8**) and previously synthesized bicycles (**1** and **9**−**11**) from transannular lactamization and iodoacetoxylation reactions.

Previously, DIB had been used in oxidative cyclization of *o*-hydroxystyrenes to benzofurans,[8] and *in situ* generation of hypervalent iodine species from DIB and I_2 has been employed in aromatic ring,[9] olefin,[10] and alkyne[11] functionalization using halogen, oxygen, and carbon nucleophiles. The nature of the hypervalent iodine reagent has, to our knowledge, yet to be

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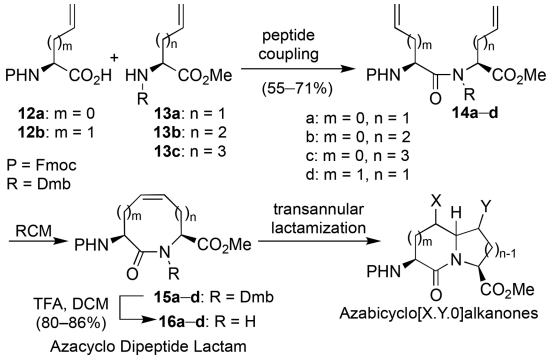
Scheme 1. Synthetic Strategy to Azacyclo- and Azabicycloalkanones of Different Ring Sizes



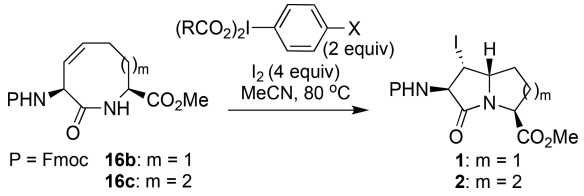
examined in such chemistry, particularly with nitrogen nucleophiles. By studying the influence of sterically hindered carboxylate and aromatic ligands with varying electron densities, effective transannular iodolactamization as well as iodoacetoxylation of unsaturated lactams has now been achieved to provide stereoselectively novel 5,5-, 5,6-, and 6,4-fused and 7- and 8-membered ring systems **2**–**8** (Figure 1).

Unsaturated lactams of 7- to 9-atoms were made by coupling 4–7-carbon chain length ω-olefin amino carboxylates[12] **12a,b** and **13a–c**, followed by RCM on the resulting dipeptides **14a–d** (Scheme 1).[6] *N*-(Fmoc)Vinylglycine **12a** was coupled as its acid chloride to 2-*N*-(Dmb)aminopent-4-enoate **13a**, hex-5-enoate **13b**, and hept-6-enoate **13c** to afford dipeptides **14a–c** in 55%, 46%, and 57% yields, respectively.[6] Dipeptide **14d** was prepared in 71% yield by coupling of *N*-(Fmoc)allylglycine (**12b**) and 2-*N*-(Dmb)aminohex-5-enoate (**13b**) using HATU and *N*-ethylmorpholine in DCM. For RCM, less (10–12 mol % vs 30–35 mol %) second generation Grubbs' catalyst in 1,2-dichloroethane at reflux gave higher yields in shorter reaction times (24 h vs 72 h) than first generation Grubbs' catalyst in dichloromethane at reflux, e.g., 80% vs 68% yield of lactam **15c**. Lactams **15a–d** were converted to **16a–d** in 70–80% yields by Dmb group removal using 50% TFA in DCM. Attempts at transannular iodolactamization of 7–9-membered lactams failed using iodine in THF, MeCN, or toluene at rt to reflux resulting in loss of the Dmb group in the case of **15a–d** and recovered starting material from **16a–d**. The cyclization of **15b** was also unsuccessful using I_2 and DIB.

In acetonitrile, pyrrolizidinone **1** was prepared from 8-membered lactam **16b**, DIB, and I_2 at reflux in 62% yield.[6] Also, iodoindolizidin-9-one **2** was prepared diastereoselectively in 52% yield using the same conditions on 9-membered lactam **16c** (entry 1, Table 1). The ligands on the hypervalent iodine were examined in the cyclization of lactams **16b** and **16c** using a set of iodonium reagents,[13] possessing different aryl substituents and carboxylates,[14] in MeCN at 80 °C (Table 1). Notably higher yields were typically obtained employing electron-rich aromatic substituents and bulky carboxylates. The highest yields (78% and 75%) of pyrrolizidinone and indolizidinone **1** and **2** were obtained using 4-methoxy-iodosobenzene di(adamantane-1-carboxylate) (MIDAd, entry 10, Table 1). Concurrent iodination of the Fmoc group using bis(trifluoroacetoxy)iodobenzene gave the corresponding bicycles as 2,7-diiodo-Fmoc derivatives **1a** and **2a** (entry 11, Table 1), which were characterized by X-ray crystallography and NMR spectroscopy.

Using DIB and I_2 in MeCN at 80 °C, 8-membered lactam **16d** gave a mixture of 6-iodo- and 6-acetoxy pyrrolizidinones **3** and **4** and azetidinylpiperidine **5** (entry 1, Table 2). Yet, 7-membered

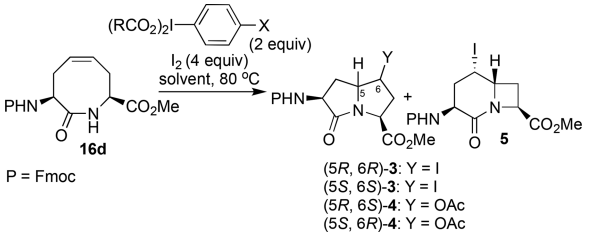
Table 1. Influence of Hypervalent Iodine(III) on Transannular Iodolactamization



entry	X	R	% yield **1** (m = 1)	% yield **2** (m = 2)
1	H	Me	62[6]	52
2	F	Me	51	52
3	Me	Me	52	60
4	OMe	Me	62	68
5	H	*t*-Bu	61	62
6	Me	*t*-Bu	59	61
7	OMe	*t*-Bu	71	70
8	CF_3	Ad[a]	61	57
9	H	Ad[b]	65	62
10	OMe	Ad[c]	78	75
11	H	CF_3	51[d]	35[d]

[a]8 equiv of hypervalent iodine and 16 equiv of I_2 employed. [b]6 equiv of hypervalent iodine and 12 equiv of I_2 employed. [c]3 equiv of hypervalent iodine and 6 equiv of I_2 employed. [d]Isolated as 2,7-diiodo-Fmoc derivatives **1a** and **2a**. Ad = 1-Adamantane.

Table 2. Synthesis of Azabicyclo[3.3.0]- and [4.2.0]Alkanone Amino Esters 3–5[a]



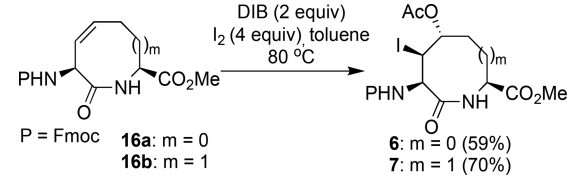
			isolated yield (%)				
	X	R	(5*R*,6*R*)-**3**	(5*S*,6*S*)-**3**	(5*R*,6*S*)-**4**	(5*S*,6*R*)-**4**	**5**
1	H	Me	20	18	5	–	4
2	OMe	Ad	21	19	–	–	8
3	H	Me	15	16	–	4	–

[a]Solvent = MeCN (entries 1 and 2); toluene (entry 3).

lactam **16a** failed to react. Application of the MIDAd conditions on lactam **16d** increased slightly the yields of iodopyrrolizidinones **3** and azetidine **5** (entry 2, Table 2). On lactam **16a**, the MIDAd conditions caused dehydration yielding 35% of azepinone **8** (Figure 1), as ascertained by X-ray crystallography.

In toluene, 7- and 8-membered lactams **16a** and **16b** reacted with DIB and I_2 to give iodoacetoxylation products **6** and **7** in 59% and 70% yields, respectively (Scheme 2). On the other hand, lactam **16c** gave a 45% yield of indolizidin-9-one **2** along with

Scheme 2. Synthesis of Iodoacetoxy Lactams



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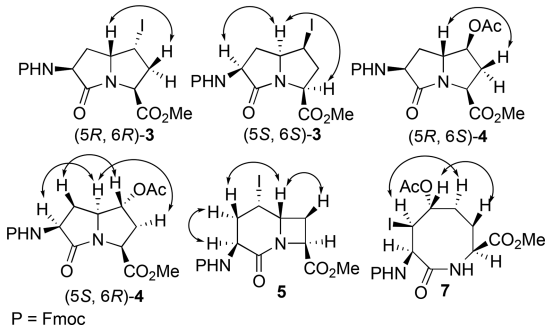

Figure 2. Representative NOESY correlations used to assign the relative configurations of ring systems **3**−**5** and **7**.

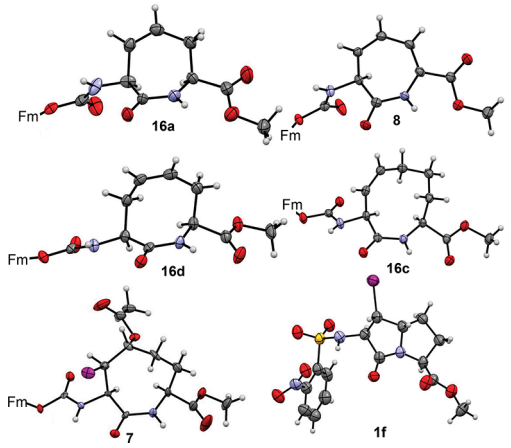

Figure 3. X-ray structures of lactams **7**, **8**, **16a,c,d** and bicycle **1f** (fluorenylmethyl group removed and represented as Fm for clarity; C, gray; H, off-white; N, blue; O, red; I, magenta).

trace amounts of iodoacetoxylation product. Lactam **16d** gave (*S*,*S*)- and (*R*,*R*)-6-iodopyrrolizidinones **3** (15% and 16%) along with (*S*,*R*)-6-acetoxypyrrolizidinone **4** (4%) and trace amounts of iodoacetoxylation product (Table 2).

Stereochemical assignments for the ring systems were made based on a combination of NMR spectroscopy and X-ray crystallography [Supporting Information (SI)]. The configurations of iodo acetates **6** and **7** were assigned based on analysis of dihedral angle coupling constants, which correlated with the X-ray structure of the latter. After through-bond correlations were made using COSY experiments to assign all protons in the bicycle, through-space nuclear Overhauser effects were measured to correlate the stereochemistry of the amino acid derived α-carbons with the newly generated ring fusion and iodide or acetate bearing carbons (Figure 2). The trans relationship of the ring fusion and iodide carbon bearing protons was in certain cases inferred based on the reaction mechanism. In addition, in bicycles (5*R*, 6*R*)-**3**, (5*R*, 6*S*)-**4**, and **5**, upfield shifting of the β-proton was observed due to anisotropy from the neighboring carboxylate.[15]

Type VI β-turn mimicry by 7−9-membered lactams was established using X-ray crystallography of **16a**, **16c**, and **16d**, as well as 8-membered iodo acetate **7** (Figure 3, Table 3).[16] The dihedral angles of 8- and 9-membered lactams matched closely those of the central residues of an ideal type VI β-turn (except for ϕ^{i+2}); those of 7-membered lactam **16a** reflected values of an ideal type VI2 β-turn.

The literature offers two lines of thought on the reaction mechanism using DIB and I_2. Their combination has been suggested to rapidly provide iodobenzene and two equivalents of

Table 3. Comparison of Dihedral Angles of Lactams with Ideal Secondary Structures

Type of β-turn	ϕ^{i+1}	ψ^{i+1}	ϕ^{i+2}	ψ^{i+2}
Ideal type VIb β-turn	−135°	135°	−75°	160°
Ideal type VI2 β-turn	−120°	120°	−60°	0°
7-membered lactam **16a**	−120°	178°	−158°	10°
7-membered lactam **8**	−89°	174°	−143°	0°
8-membered lactam **7**	−158°	155°	−146°	154°
8-membered lactam **16d**	−156°	176°	−154°	168°
9-membered lactam **16c**	−157°	160°	−151°	175°

acetyl hypoiodite, which serves as iodinating agent.[10,17,18] On the other hand, exchange of iodide for one acetoxy group has been suggested to provide acetyl hypoiodite and an acetoxy iodobenzene iodide salt, which reacts with the olefin.[19] In our NMR experiments, DIB and I_2 reacted in CD_3CN to give rapidly iodobenzene and AcOI.[10b] Preparation of AcOI *in situ* from silver acetate (500 mol %) and I_2 (500 mol %) in MeCN and reaction with lactam **16c** gave indolizidinone **2** in 45% yield; moreover, addition of 4-iodoanisole (300 mol %) to the reaction mixture increased the yield of **2** to 54%. Analysis by LCMS demonstrated that lactam **16b** reacted with AcOAg and I_2 to give pyrrolizidinone **1** and iodoacetate **7** in a 2:1 ratio, which reduced to 1.3:1 on addition of AgI (500 mol %) to the DIB condition indicating that the silver salt may interfere with lactamization, perhaps by amide coordination. Mixing AgOAc with I_2 in CD_3CN gave AcOI, the acetate carbonyl, and methyl group ^{13}C NMR signals of which were respectively up- and downfield shifted on addition of anisole (50 mol %), which also caused an upfield shift of the methyl singlet in the ^1H NMR spectrum, indicating coordination between AcOI and the electron-rich aromatic ring (SI).[20,21] Iodination of the Fmoc group using ditrifluoroacetoxyiodobenzene and I_2 may also be explained by *in situ* formation of the iodinating reagent CF_3CO_2I.[22,23]

The influences of hypoiodite, solvent, and ring size on the products from iodoacetoxylation and transannular cyclization may be explained using RCO_2I as an active reagent. The selectivity of facial attack of olefins **16a**−**c** by RCO_2I is directed by the allylic amine which may hydrogen bond with solvent or acyl hypoiodite reagent respectively in MeCN and toluene (Figure 4). Iodonium ion formation is likely reversible.[24] In toluene, subsequent attack of the iodonium ion by acetate occurs from the opposite face to give **6** or **7**. In MeCN, the iodonium ion is opened by intramolecular attack of the amide to give bicycles **1** and **2**. The influences of the allylic amine and hydrogen bonding were further demonstrated by the synthesis and reactivity of *o*-nitrobenzenesulfonamides (*o*-NBS, Supporting Information) **16e** and **16f** (Figure 4). *N*-Methyl sulfonamide **16e** cannot hydrogen bond and gave predominantly bicycle **1e** in both solvents; sulfonamide **16f** behaved like carbamate **16b** and gave mainly bicycle **1f** and iodoacetate **7f** contingent on solvent. Stereochemical assignments for **1e**, **1f**, and **7f** were based on NMR spectroscopy, X-ray analysis (**1f**) and analogy with their Fmoc counterparts. Favored formation of iodoacetate in the smaller ring systems may correlate with distance between the allylic amine and olefin, because a linear relationship between ring size and the acuteness of the allylic bond dihedral angle about the α- and vinyl-carbon C−C bond (**16a**, 175°; **16b**, −154°;[6] **16c**, −134°) was observed in the X-ray structures of 7−9-membered lactams.

In conclusion, we have shown that diastereoselective transannular iodolactamization and iodoacetoxylation of 7−9-membered lactams can be effectively achieved using the

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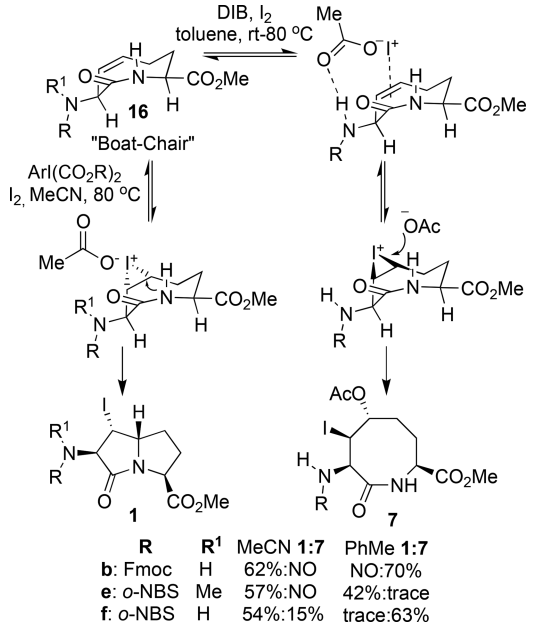

Figure 4. Proposed mechanisms for iodoacetoxylation and transannular lactamization (NO = Not Observed).

combination of iodine and hypervalent iodine(III). Contingent on solvent, an allylic carbamate appeared to serve as a key directing group for iodonium ion formation. In acetonitrile, subsequent intramolecular transannular cyclization provided stereoselectivity 4-iodopyrrolizidinone **1** and 4-iodoindolizidinone **2**. In toluene, intermolecular attack of acetate provided 7- and 8-membered iodoacetates **6** and **7**. Bulky carboxylates and electron-rich aromatic ligands on the hypervalent iodine improved yields in the formation of bicycles. X-ray crystallographic analysis has also shown the potential of 7−9-membered lactams to serve as β-turn mimics with complementary structures to those previously reported for azabicyclo[X.Y.0]alkanones. The fundamental findings and novel peptidomimetics from this study offer thus rich potential for the synthesis and functionalization of lactam ring systems for exploring peptide conformation−activity relationships.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02275.

Experimental procedures; characterization data (^{1}H, ^{13}C, 2D NMR, HRMS, IR, mp, and specific rotation) (PDF)
X-ray data for **1a** (CIF)
X-ray data for **7** (CIF)
X-ray data for **8** (CIF)
X-ray data for **16a** (CIF)
X-ray data for **16c** (CIF)
X-ray data for **16d** (CIF)
X-ray data for **1f** (CIF)

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Notes

The authors declare no competing financial interest.

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