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T3P-Promoted, Mild, One-Pot Syntheses of Constrained Polycyclic Lactam Dipeptide Analogues via Stereoselective Pictet−Spengler and Meyers Lactamization Reactions

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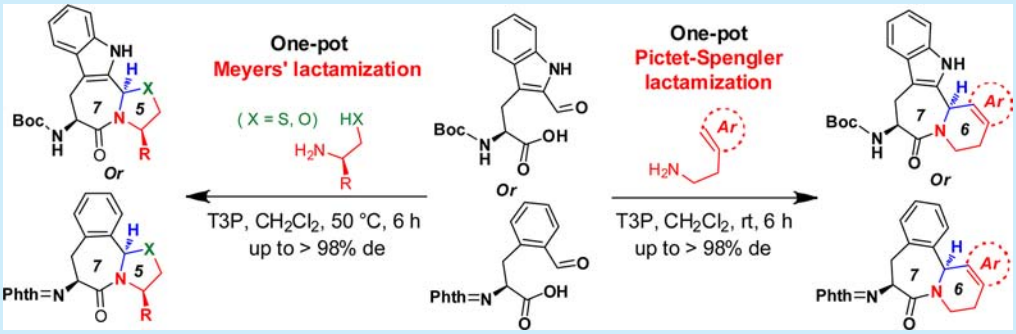
Supporting Information



ABSTRACT: A new convenient, mild, one-pot procedure is described for the diastereoselective synthesis of constrained 7,5- and 7,6-fused azabicycloalkanes. Using 2-formyl-L-tryptophan and 2-formyl-L-phenylalanine as bielectrophilic building blocks, T3P-mediated Pictet−Spengler and Meyers lactamization reactions were developed to present chiral and polycyclic aminoindolo- and aminobenzazepinone compounds in excellent yields. The conformationally constrained compounds can serve as templates for peptidomimetic research or polyheterocyclic privileged scaffolds.

Fused bicyclic lactam azabicyclo[*x.y.z*]alkane scaffolds are found in many natural products[1] and serve as intermediates in the preparation of molecules possessing interesting biological activities.[2] Additionally, peptide derivatives incorporating cyclic or bicyclic lactams are widely used for constraining main chain dihedral angles. These lactams can potentially force a peptide chain to adopt reverse-turn conformations[3] as was demonstrated for the "bicyclic turned dipeptide" (BTD) azabicyclo[*x.y.*0]alkane amino acids **1** (Figure 1).[4] These fused bi- or polycyclic lactams of different ring size (5,4- to 7,6-fused bicyclic lactams) have been used with success in the field of peptide mimicry.[5,6] Hence, the design and synthesis of new constrained polycyclic lactams for peptidomimetic purposes is a topic of considerable interest in medicinal chemistry. Unfortunately, most of the reported methods for the synthesis of these privileged templates suffer from poor diastereoselectivity, which requires chromatographic separation, and a multistep synthetic strategy.

Previously, our group reported that tetrahydro-4-amino-azepinones, derived from amino acids such as phenylalanine and tryptophan, could also serve as "privileged scaffolds" since their use resulted in a range of highly potent G protein-coupled receptor ligands.[7] The corresponding 7,5- and 7,6-fused indolo- and benzoazepinones **2** and **3** (Figure 1, X = CH_2) have also been reported in various medicinal chemistry applications.[8−11] Therefore, it was highly desirable to develop short, efficient, and diastereoselective procedures toward novel 7,5-fused indolo- and benzazepinone amino acids **2** and **3** (X = S, O). In addition, mild conditions that could accommodate substrates

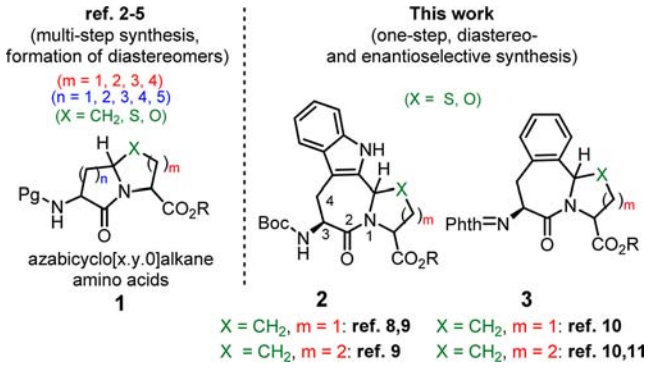


Figure 1. Azabicyclo[*x.y.*0]alkane amino acids **1**−**3**.

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bearing acid- and base-sensitive functional groups are important (Figure 1).

Pictet–Spengler[12] reactions and Meyers lactamizations[13] are typical bielectrophile–binucleophile reactions that produce new stereogenic centers. Recently, we reported several modifications to common synthetic protocols of the Meyers[14] and Pictet–Spengler lactamizations[15] for the diastereoselective formation of 5,5-, 6,5-, and 6,6-fused bicyclic lactams under milder conditions via solvent- and catalyst-free microwave-assisted condensation by using enantiopure amino alcohols or amino-indoles and γ- or δ- keto acids.

Levacher independently developed a one-pot Meyers lactamization, promoted by pivalic acid under microwave irradiation (150 °C, 2–10 h), leading to axially chiral 7,5-fused lactams from biaryl precursors with moderate to good yields and high diastereomeric excesses.[16] Unfortunately, these acidic conditions are not compatible with acid-labile functionalities.

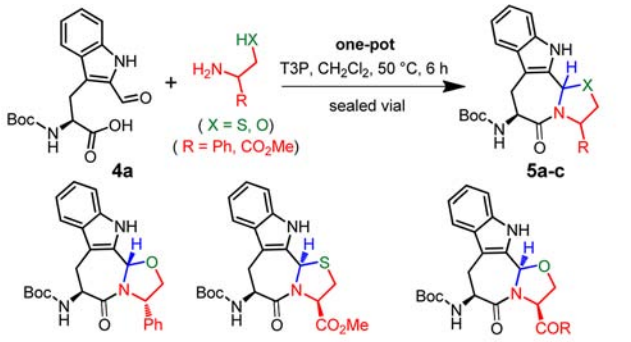
As a continuation of our efforts in peptidomimetic design, it was proposed that the 7,5- and 7,6-fused bicyclic lactam scaffolds **2** and **3** (X = S, O) could be synthesized via Meyers lactamizations using *N*-Boc-2-formyl-L-Trp-OH[17] (**4a**) and *N*-Phth-2-formyl-L-Phe-OH[18] (**4b**) as bielectrophiles.

In order to find the best reaction conditions for the synthesis of fused oxazoloindoloazepinone derivatives **5a–c** as a prototype of the Meyers reaction (Scheme 1), *N*-Boc-2-formyl-L-Trp-OH (**4a**) and (*S*)-phenylglycinol were chosen as model substrates. In our initial investigations, classic dehydrating conditions were applied by conventional heating in toluene for 24 h, with azeotropic removal of water, and in the presence or absence of an acid catalyst (AcOH, TFA, PTSA). Unfortunately, this mainly led to substrate degradation. Moreover, under mild microwave irradiation no conversion of the model keto acid **4a** in the presence of (*S*)-phenylglycinol was observed at 110 °C (5–120 min). In search of milder lactamization conditions, the reaction was performed with 1–2 equiv of commercially available propylphosphonic anhydride[19] (T3P, 50 wt % solution in EtOAc) in CH_2Cl_2 at room temperature for 18 h. T3P is used as a reactive coupling and dehydrating reagent, presents low toxicity, low epimerization tendency, and high functional group compatibility, and its byproducts are water soluble.[20] Under these conditions, only weak conversion (ca. 28%) was detected by LC–MS. To our satisfaction, a full conversion to the desired Meyers' bicyclic lactam **5a** was obtained by stirring the mixture for 6 h at 50 °C (full conversion, 87% isolated yield, > 98% de) in a sealed vial which was placed in an oil bath (Scheme 1). Only a single diastereomer was observed, isolated, and characterized as the isomer having a (*S*)-configuration of the newly formed stereogenic center by 2D ^{1}H NOESY studies. This result is consistent with those reported by Amat[21] and Allin[22] for the stereoselective Meyers lactamization in the case of δ-oxo acids as bielectrophilic starting material.

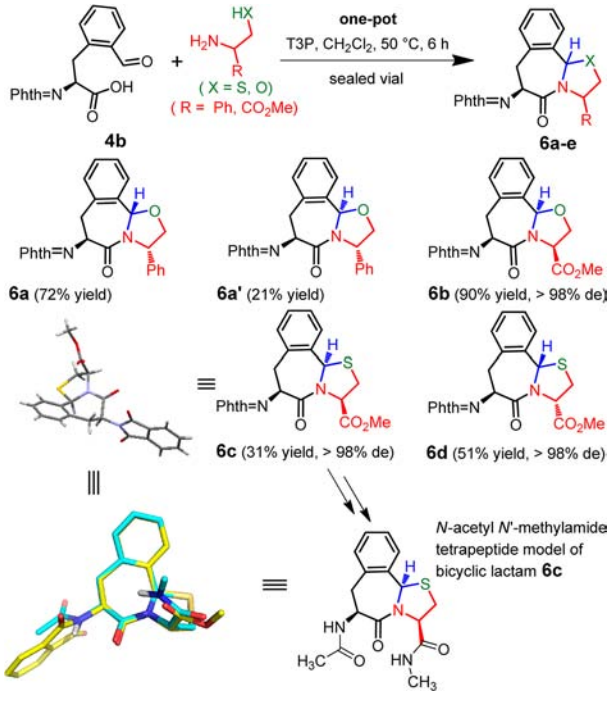
To explore the substituent scope of this methodology, **4a** was condensed with L-cysteine methyl ester to give **5b** in good yield and high diastereomeric excesses (81% isolated yield, > 98% de). Furthermore, oxazololactam **5c** was prepared as a mixture of diastereoisomers (34% de) in excellent yield (91%) by cyclodehydration of a chiral L-serine methyl ester with **4a**. Whereas **5c** could not be separated from its epimer **5c′**, the corresponding methylamides **5d** and **5d′** were isolated by column chromatography and used for a NMR study (vide infra).

For the synthesis of fused oxazolo- and thiazolobenzazepinones **6a–d**, the stereoselective Meyers' cyclocondensation reaction of *N*-Phth-2-formyl-L-Phe-OH (**4b**) with (*S*)-phenylglycinol, under the optimized conditions, gave access to a mixture of separable diastereoisomers **6a** (72% isolated yield, > 98% de) and **6a′** (21% isolated yield, > 98% de), respectively (Scheme 2). The relative stereochemistry of the major isomer **6a**, was determined by NOE studies. Similarly, constrained dipeptides **6b**, **6c**, and **6d** could be accessed starting from **4b** and the methyl ester of L-Ser, L-Cys, and D-Cys, respectively. After purification, the desired products **6b–d** were obtained in excellent to moderate yields and high diastereoselectivity (Scheme 2; 31–90% isolated yield, > 98% de). Both reactions

Scheme 1. Synthesis of 7,5-Fused Oxazolo- and Thiazoloindoloazepinones 5a–c



Scheme 2. Synthesis of 7,5-Fused Oxazolo- and Thiazolobenzazepinones 6a–d[a]



[a]Overlay of the X-ray structure of **6c** (yellow) and the predicted lowest energy conformer of its *N*-acetyl *N*′-methylamide tetrapeptide model (cyan) is shown.

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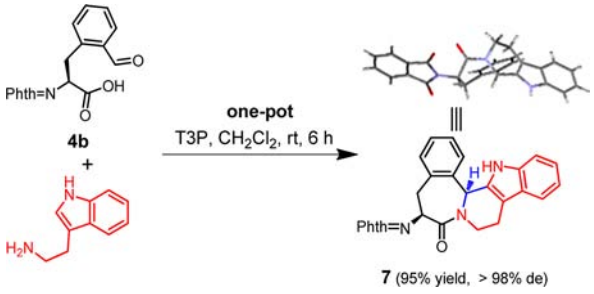
of keto acid **4b** with L-Cys methyl ester and D-Cys methyl ester resulted in the formation of two diastereomers (HPLC dr 80:20 and dr 95:5, respectively). Since bicyclic lactams **6c** and **6d** were difficult to separate using silica gel chromatography, they were purified via diastereoselective precipitation in EtOH. The stereochemistry at the ring fusion in **6c** and **6d** was assigned from the NOESY spectra and that of **6c** was confirmed by X-ray crystallography. In order to study the turn-inducing ability of the obtained dipeptidic scaffolds **6b–d**, similar to previous studies in our group,[23] the conformational preferences for the respective *N*-acetyl *N*′-methylamide tetrapeptide models were investigated by molecular modeling (Scheme 2 and the Supporting Information). Belvisi reported that 7,5-fused bicyclic lactams of type **1** which lack the aromatic phenyl ring (m = 1, n = 3, X = CH_2, Figure 1) can stabilize (inverse) γ-turn conformations in short peptides.[24] In contrast to these results, the lowest energy conformers of all three *N*-acetyl-*N*′-methylamide tetrapeptide models of dipeptidic bicyclic lactams **6b–d** were not consistent with β- and γ-turn formations. A NMR study of **5d** and **5d**′ confirmed the absence of an intramolecular hydrogen bond (see the Supporting Information).

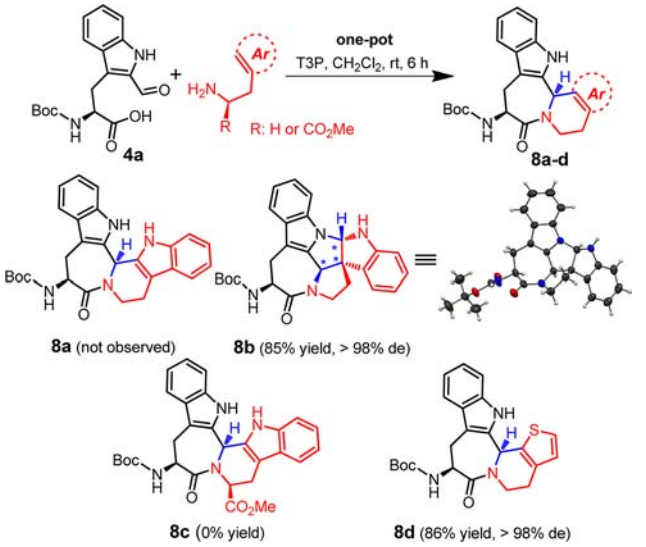
Next, the synthesis of polycyclic lactam **7**, which contains a skeleton that was previously used to prepare dopamine receptor ligands,[25] was attempted. The stereocontrolled Pictet–Spengler reaction, which proceeds via an *N*-acyliminium ion cyclization, was carried out by mixing *N*-Phth-2-formyl-L-Phe-OH (**4b**) and tryptamine followed by addition of 1 equiv of T3P and stirring at room temperature for 6 h in CH_2Cl_2 to give the desired product **7** as a single *trans* diastereomer in good yield and excellent diastereomeric excess (Scheme 3; 72% isolated yield, >98% de). The relative stereochemistry of product **7** was determined by X-ray diffraction analysis.

Scheme 3. Stereocontrolled Pictet–Spengler Reaction into Polycyclic Lactam 7



Surprisingly, in the case of *N*-Boc-2-formyl-L-Trp-OH (**4a**) and tryptamine, the expected product **8a** was not obtained by a one-pot procedure. Instead, the polycyclic spirolactam **8b** was isolated as a single diastereomer as determined by X-ray diffraction analysis (Scheme 4). The synthesis of compound **8c** by cyclocondensation reaction of keto acid **4a** with L-tryptophan methyl ester proved to be unsuccessful, leading mainly to the degradation of starting material **4a**. No polycylic lactam formation was observed either. This problem could potentially be related to the low solubility of the substrates and the reaction intermediates. In contrast, under the optimized Pictet–Spengler conditions, an excellent yield and diastereselectivity (86% isolated yield, >98% de) was obtained for thiophene derivative **8d**, a scaffold related to the reported benzo[*a*]thieno[3,2-*h*]quinolizidine.[26]

Scheme 4. Pictet–Spengler Reactions of *N*-Boc-2-formyl-L-Trp-OH 4a



In conclusion, a convenient and efficient one-pot synthesis has been developed for new 7,5- and 7,6-fused bicyclic lactams via a stereoselective Meyers and Pictet–Spengler lactamization with propylphosphonic anhydride (T3P) as a neutral catalyst. This one-pot procedure tolerates acid-sensitive groups such as the Boc group and offers a simple and very efficient route to a new class of optically pure aminoindolo- and -benzazepinone derivatives (i.e., 7,5- and 7,6-fused bicyclic lactams) in high yields, starting from *N*-Boc-2-formyl-L-tryptophan (**4a**) and *N*-Phth-2-formyl-L-Phe-OH (**4b**) as a chiral formylcarboxylic acid. These azabicyclo[5.3.0]alkane amino acid building blocks of types **5b**, **5c**, and **6b–d** could serve as constrained dipeptide scaffolds in diverse bioactive peptide chains. In analogy, the synthesis of constrained 7,6-fused bicyclic lactams via use of homoserine and–cysteine amino acids could be envisaged as well. The structural complexity and the variation in substitution patterns present in these scaffolds could be suitable for the preparation of a wide library of compounds, enabling their use in various biological and medicinal applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02145.

Complete experimental procedures, product characterization, full spectroscopic data for all new compounds, and conformational analysis via molecular modeling (PDF)

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Notes

The authors declare no competing financial interest.

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