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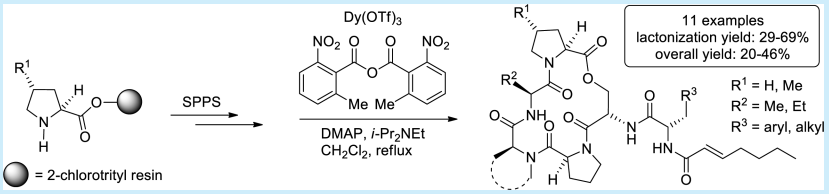
A Lanthanide(III) Triflate Mediated Macrolactonization/Solid-Phase Synthesis Approach for Depsipeptide Synthesis

Jordan D. Goodreid, Eduardo da Silveira dos Santos, and Robert A. Batey*

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON Canada, M5S 3H6

Supporting Information



ABSTRACT: The effect of dysprosium(III) triflate on macrolactonization reactions to form depsipeptides using MNBA (Shiina's reagent) is reported. Improved yields were obtained for the formation of 16-membered depsipeptides using lanthanide triflate additives. The use of a macrocyclization strategy permits the use of a semiautomated solid-phase synthesis approach for the rapid synthesis of analogues of the antibacterial A54556 acyldepsipeptides in only two physical operations, requiring only final product purification after cyclization.

Cyclic depsipeptides, which contain one or more ester bonds, are a privileged class of natural products which have provided several biologically active compounds that hold great promise as future antimicrobial and anticancer agents.[1] In addition to their broad range of biological activities, cyclic depsipeptides make challenging total synthesis targets, as they often feature nonproteinogenic amino acids and other structurally unique building blocks.[2] Remarkably there are few strategies for their synthesis and the key macrocyclization step is often problematic. Improved and general methods for their synthesis, particularly the development of new macrocyclization methods or improvements of existing protocols, are therefore of considerable interest. The most common strategy for the synthesis of cyclic depsipeptides involves macrolactamization of a linear depsipeptide, which is usually carried out in solution,[2] or in some cases directly on solid phase.[3] One potential problem to this approach is premature cleavage of the endoester bond during solid-phase synthesis of the linear precursor.[4] In principle macrolactonization of the corresponding seco acid[5] could provide a synthetically strategic alternative approach, owing to the ease by which these precursors are readily obtained using solid-phase chemistry. However, macrolactonization is often considerably more challenging and there are numerous examples of failed or extremely low yielding cyclization reactions in the synthesis of cyclic depsipeptides.[6]

Selecting the A54556 acyldepsipeptide (ADEP) family of natural products (**1**, Figure 1)[7] as a test case, we now report a new lanthanide(III) promoted macrolactonization approach to depsipeptide synthesis that also allows for the use of solid-phase synthesis techniques for the formation of the precursor seco acids. The 16-membered macrocyclic ring of the ADEP family is a typical depsipeptide core comprising 5 amino acid residues, including proline, alanine, *N*-methylalanine, and a serine, which forms the key depsi ester bond with a functionalized proline residue. Appended to the core is an exocyclic diamide unit attached to the serine residue. The ADEPs are an important new class of antibacterial agents that have received widespread attention due to their unique mechanism of action involving activation of caseinolytic protease (ClpP, a serine protease).[8] For example, the synthetic analog ADEP 4 (**2**, Figure 1) developed by Bayer has shown potent antibacterial activity against multidrug-resistant isolates of *S. aureus*, *S. pneumoniae*, and enterococci species *in vitro* as well as in mice.[9] To the best of our knowledge, Schmidt's macrolactamization of **4** (Scheme 1) represents the only known approach for the construction of the 16-membered core (**3**) and was used in the total synthesis of the structurally related enopeptin B.[10] Although this approach has provided access to the ADEP natural products[7] and related analogues (e.g., **2**, Figure 1),[9,11] it suffers inherent disadvantages from a practicality standpoint (e.g., 16 solution-phase synthesis steps, several intermediate purifications, and the use of many protecting groups). Conversely, a semiautomated approach using solid-phase peptide synthesis (SPPS) for assembly of the linear peptide (of general structure **5**) via Fmoc chemistry,

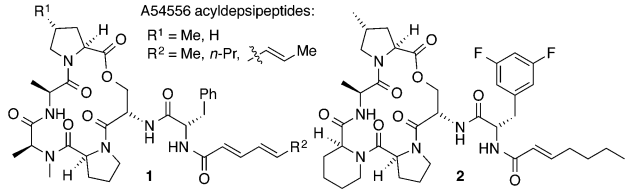


Figure 1. Structures of A54556 acyldepsipeptides (**1**) and a synthetic analogue, ADEP 4 (**2**).

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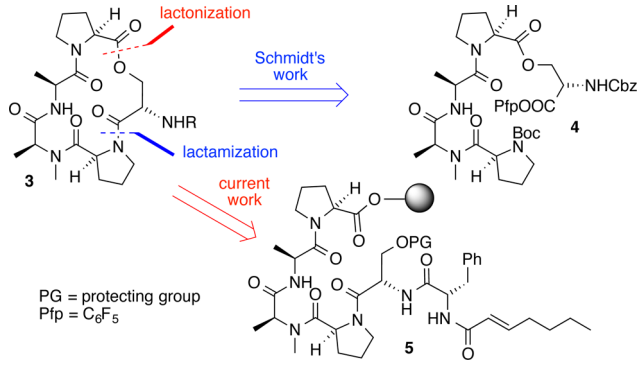
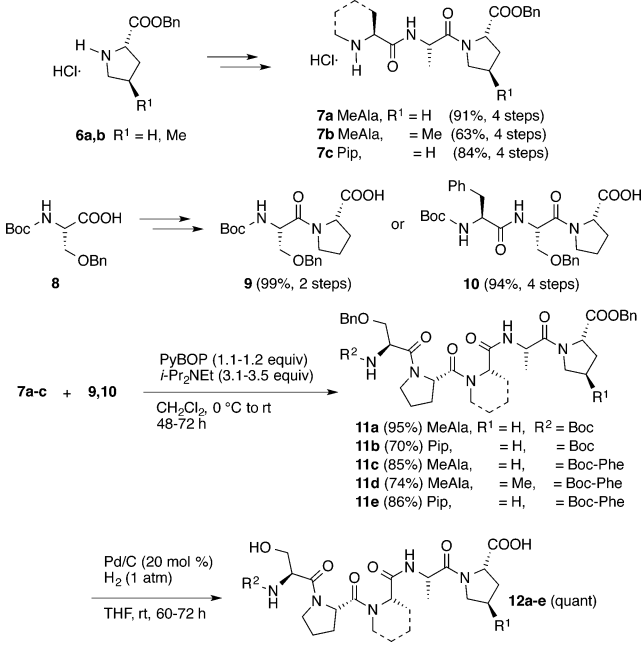
Scheme 1. Macrocyclization Strategies for ADEP Synthesis



followed by macrolactonization of the corresponding seco acid, would enable rapid access to analogues for future biological studies.

In order to test the feasibility of a macrolactonization closure, several model seco acid precursors (**12a–e**) were prepared using standard solution-phase peptide chemistry (Scheme 2).[12] Bis-

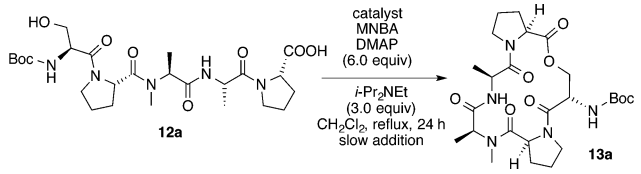
Scheme 2. Synthesis of Seco Acids 12a–e



benzyl-protected penta- and hexapeptides **11a–e** were obtained by the coupling of tripeptide hydrochloride salts **7a–c** with di- or tripeptide acid **9** or **10**, respectively, using the phosphonium reagent PyBOP. Seco acids **12a–e** were obtained via palladium-catalyzed hydrogenolysis of **11a–e**.

Due to the sensitive nature of cyclic depsipeptides and their propensity to undergo many side reactions during lactonization such as intermolecular coupling/diolide formation,[13] *O* → *N*-acyl transfer,[14] and C-terminal epimerization,[15] a mild lactonization procedure is preferred. Preliminary attempts to cyclize **12a** or **12b** using several known protocols, including Boden-Keck, Mukaiyama, Corey–Nicolaou, Yamaguchi, and PyBOP conditions, did not give synthetically useful quantities of the desired macrocycles (<10%). It is noteworthy that Mitsunobu conditions (DEAD, PPh_3) did yield the desired macrocycles derived from both **12a** and **12b**; however, complete separation of the macrocyclic products from the phosphine oxide byproduct proved tedious, and these conditions were not further pursued. After extensive screening using **12a**, Shiina's reagent MNBA (2-methyl-6-nitrobenzoic anhydride)[16] was found to be the most suitable reagent for further studies giving **13a** in 15% yield (Table 1, entry 1). Initial optimization of the substrate

Table 1. Optimization Studies for Macrolactonization of 12a[a]



no.	MNBA (equiv)	catalyst (mol %)	[**12a**] (mM)	yield (%)[b]
1	3.0	–	1.0	15
2	3.0	–	2.0	32
3	3.0	–	3.0	9
4	3.0	$Sc(OTf)_3$ (30)	2.0	48
5	3.0	$Hf(OTf)_4$ (30)	2.0	47
6	3.0	$La(OTf)_3$ (10)	2.0	71
7	3.0	$La(OTf)_3$ (20)	2.0	81
8	3.0	$La(OTf)_3$ (30)	2.0	87
9	3.0	$La(OTf)_3$ (30)	1.5	72
10	1.5	$La(OTf)_3$ (30)	2.0	56
11	3.0	$Dy(OTf)_3$ (30)	2.0	91
12[c]	3.0	$Dy(OTf)_3$ (30)	2.0	77
13	3.0	TfOH (30)	2.0	15
14[d]	3.0	$Dy(OTf)_3$ (30)	2.0	83

[a]All reactions performed on ≥100 mg scale (0.18 mmol) with respect to **12a**. [b]Isolated yield after column chromatography. [c]Reaction performed on a 1.0 g scale (1.83 mmol) over 48 h. [d]2,6-Di-*tert*-butyl-4-methyl-pyridine (DTBMP) (3.0 equiv) was used instead of Hünig's base.

concentration revealed 2.0 mM to give the highest yield of **13a** (Table 1, entry 2). In an effort to further improve the yield, the addition of various Lewis acid (LA) metal triflates was investigated. The use of transition metal LA catalysts such as titanium(IV) salts [e.g., $TiCl_2(ClO_4)_2$],[17] $Sc(OTf)_3$,[18] and $Hf(OTf)_4$[19,20] to promote the macrolactonization of mixed anhydrides has been reported. In our case, addition of 30 mol % $Sc(OTf)_3$ or $Hf(OTf)_4$ to the reaction gave only modest improvements in yield (Table 1, entries 4 and 5). However, the use of only 10 mol % $La(OTf)_3$, a lanthanide LA, gave a substantially higher yield of **13a** (71%) when compared with the corresponding transition metal salts (Table 1, entry 6).[21,22] Increasing the catalyst loading further to 20 and 30 mol % provided higher yields of **13a**, with the latter giving an 87% yield (Table 1, entry 8). Further attempts to improve the conditions by either lowering the concentration of **12a** or decreasing the number of equivalents of MNBA in the presence of 30 mol % $La(OTf)_3$ were both unsuccessful (Table 1, entries 9 and 10). $Dy(OTf)_3$ gave an even greater yield (91%) at 30 mol % loading (Table 1, entry 11).[23,24] Hence it was chosen as the LA additive for all further macrolactonizations. These conditions were found to be scalable, giving a 77% yield when performed on a 1.0 g scale (Table 1, entry 12). A control experiment showed that any residual triflic acid (from the metal salt) does not catalyze the reaction, as the direct addition of TfOH (30 mol %) gave a low yield of **13a** (Table 1, entry 13). Reaction in the presence of $Dy(OTf)_3$ (30 mol %) using a more sterically encumbered base

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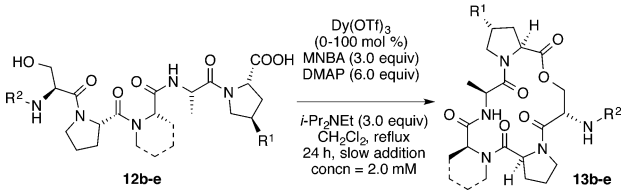
(e.g., DTBMP) resulted in a good yield of **13a** (Table 1, entry 14), confirming that the choice of base does not significantly effect the outcome of the reaction and that the yield increase is solely due to the LA.

To test the generality of this method with more complex precursors, seco acids **12b–e** (Scheme 2) were macrolactonized in the presence or absence of $Dy(OTf)_3$ (Table 2). In contrast to

Table 2. Macrolactonization of Seco Acids 12b–e[a]



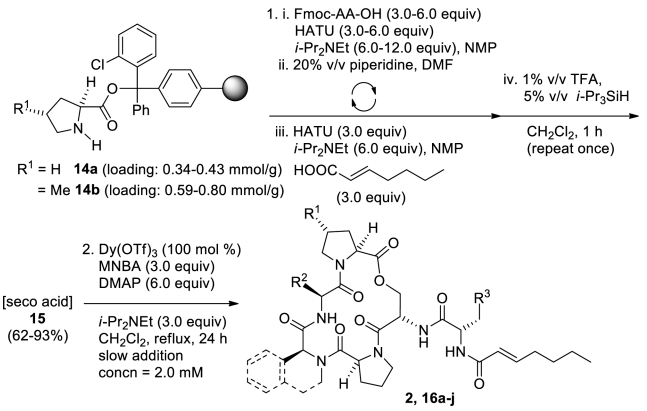
		$Dy(OTf)_3$ (mol %)			0	30	100
no.	residue	R^1	R^2	prod		yield (%)[b]	
1	Pip	H	Boc	**13b**	20	28	49 (62)[c]
2	MeAla	H	Boc-Phe	**13c**	20	53[d]	81
3	MeAla	Me	Boc-Phe	**13d**	23	53	93
4	Pip	H	Boc-Phe	**13e**	24	35	48

[a]All reactions performed on at least a 100 mg scale (0.14–0.18 mmol) with respect to **12b–e**. [b]Isolated yield after column chromatography. [c]MeCN was used at 45 °C. [d]Reaction performed on a 1.0 g scale of **12c** (1.45 mmol) over 48 h.

seco acid **12a** (Table 1), it was found that more rigid substrates bearing the pipecolic acid (Pip) residue (**12b**, **12e**) instead of the *N*-methylalanine (MeAla) were not as effectively cyclized using 30 mol % $Dy(OTf)_3$ (Table 2, entries 1 and 4). The same is true, albeit to a lesser extent, for substrates which incorporate an additional Phe residue (**12c–e**) (Table 2, entries 2–4). However, in all cases, the yields of **13b–d** could be improved by the addition of a stoichiometric amount of $Dy(OTf)_3$; this is more pronounced for **13c** and **13d** (Table 2, entries 2 and 3). Depsipeptides **13c** and **13d** are particularly noteworthy, as they are common intermediates in the synthesis of either the A54556[7] or enopeptin[10] natural products. Cyclization of seco acid **12b** occurred with a slightly improved yield of **13b** (62%) when stoichiometric $Dy(OTf)_3$ was used with acetonitrile as opposed to dichloromethane (Table 2, entry 1). This was likely due to solubility reasons and was not found to be the case for other substrates.

Using the optimized conditions the SPPS strategy was investigated (Table 3). Starting from H-Pro-2-ClTrt (**14a**), Fmoc protected amino acids Ala, MeAla, Pro, Ser(Trt), Phe, and (*E*)-hept-2-enoic acid were successively coupled using HATU/Hünig's base to generate the resin-bound hexapeptide **5** (Scheme 1). Cleavage from the solid support and concomitant deprotection using TFA/triisopropylsilane gave the linear seco acid precursor in 67% yield which was subsequently macrolactonized in its crude form to give **16a** in 69% yield and 46% overall yield (refers to the combined yield after both SPPS and macrolactonization operations) (Table 3, entry 1). Similarly, the corresponding Pip derivative was synthesized using SPPS and cyclized in 51% yield (33%, overall yield) to give **16b** (Table 3, entry 2). These encouraging preliminary results prompted the synthesis of other analogues (**16c–j**) including ADEP 4 (**2**, Figure 1 and Table 3, entry 4) starting from H-*trans*-4-Me-Pro-2-ClTrt **14b**. For these substrates, good cyclization yields (29–50%) and modest overall yields over both steps (20–41%) were

Table 3. Synthesis of ADEP Analogues 2 and 16a–j Using SPPS and a $Dy(OTf)_3$-Promoted Macrolactonization[a]



no.	residue	R^1	R^2	R^3	prod	yield (%)[b]
1	MeAla	H	Me	Ph	**16a**	69 (46)[c]
2	Pip	H	Me	Ph	**16b**	51 (33)
3	MeAla	Me	Me	3,5-F_2-C_6H_3	**16c**	50 (41)
4	Pip	Me	Me	3,5-F_2-C_6H_3	**2**	37 (31)
5	Pip	Me	Et	3,5-F_2-C_6H_3	**16d**	32 (25)
6	Tic	Me	Me	3,5-F_2-C_6H_3	**16e**	37 (27)
7	Pip	Me	Me	C_6F_5	**16f**	33 (27)
8	Pro	Me	Me	3,5-F_2-C_6H_3	**16g**	45 (42)
9	Pip	Me	Me	2-naphthyl	**16h**	33 (20)
10	Pip	Me	Me	3-benzothienyl	**16i**	29 (21)
11	Pip	Me	Me	*c*-Hex	**16j**	37 (27)

[a]All reactions performed on ≥0.20 mmol scale with respect to **14**. [b]Isolated macrolactonization yield after column chromatography. [c]Overall yield after both the SPPS and macrolactonization operations.

obtained (Table 3, entries 3–11). This SPPS approach allows for selective modification of the macrocyclic residues, which in contrast to previous methods must be done at an early stage. For example, the macrolactonization tolerates the replacement of the Ala residue with the 2-aminobutric acid moiety (Table 3, entry 5) or Pip residue with other rigidifying moieties such as Tic[25] or Pro (Table 3, entries 6 and 8). Several exocyclic Phe modifications were tolerated including 3,5-difluoroPhe, pentafluoroPhe, 3-(2-naphthyl)alanine, (3-benzothienyl)alanine, and cyclohexylalanine (Table 3 entries 3–11).[26,27]

In conclusion, the first examples of MNBA/lanthanide(III) salt-promoted macrolactonizations are demonstrated to give significantly higher product yields compared to the use of MNBA/DMAP alone. It seems plausible that the esterification/lactonization rate enhancement observed in the presence of lanthanide(III) triflate can be attributed to a substrate–metal complexation event prior to cyclization,[18] though the exact nature of this intermediate will require further study.[28] This simple protocol improves the efficiency of the challenging macrocyclization step required for the formation of medicinally relevant depsipeptide targets and provides significant practical benefits over standard macrolactamization based strategies. For ADEP analogues, quantities sufficient for medicinal chemistry studies can be readily synthesized in reasonable overall yields (20–46%) requiring only two physical operations and a single purification step. This is in contrast with Schmidt's approach, which requires numerous steps and purifications, and uses several different protecting groups. More generally a macrolactonization based strategy allows for the use of semiautomated SPPS for the assembly of linear precursors thus providing a more diversity-

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oriented and rapid approach for analogue synthesis than can be achieved through macrolactamization based strategies. Further investigations on the generality of this approach for the formation of other depsipeptide and macrocyclic natural products as well as mechanistic studies will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all compounds including copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rbatey@chem.utoronto.ca.

Notes

The authors declare no competing financial interest.

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(23) Initial attempts to macrolactonize the corresponding threonine and *allo*-threonine analogues of **12a** using these conditions were both unsuccessful, but alternative conditions are currently under investigation.

(24) THF and MeCN were also found to be suitable solvents for the macrolactonization of **12a** in the presence of 30 mol % $Dy(OTf)_3$, giving **13a** in 87% and 92% isolated yield, respectively.

(25) Tic = (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

(26) The antibacterial evaluation of these analogues is in progress and will be the subject of a full report.

(27) Attempts to replace the Pip moiety with other groups including azetidine-2-carboxylic acid, MeVal or MeLeu, or replacement of the adjacent Pro residue with *trans*-4-hydroxyproline(*t*-Bu) or Oic ((2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid) were not tolerated.

(28) NMR experiments in CD_2Cl_2 were carried out in order to establish the role of the lanthanide salt during ester formation. The mixed anhydride derived from Cbz-Pro-OH and MNBA was exposed to excess MeOH (~40 equiv) in the presence/absence of $La(OTf)_3$ (30 mol %). Methyl ester formation in the presence of $La(OTf)_3$ occurred cleanly and in less than 2 h, whereas in the absence of lanthanide salt required at least 12 h. Furthermore, the latter experiment results in an unselective ~1:1 mixture of the expected ester and starting material (Cbz-Pro-OH). For experimental details, see Supporting Information.

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