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TETRAHEDRON: *ASYMMETRY*

Intramolecular aminolysis of trichloroethyl esters: a mild macrocyclization protocol for the preparation of cryptophycin derivatives

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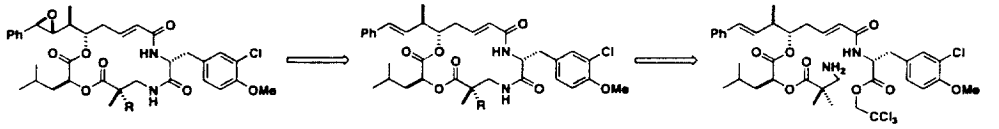
Abstract

The bifunctional catalyst 2-hydroxypyridine (2-pyridone) is shown to promote the intramolecular aminolysis of the polyfunctionalized long-chain amino trichloroethyl ester **8** to afford cryptophycin-51 (**4**). This process for the construction of the macrocyclic core of cryptophycin derivatives is noteworthy for its convenience, avoidance of expensive coupling reagents, and use of mild reaction conditions.

The cryptophycins are novel macrolides isolated from blue–green algae (*Nostoc* sp. strain GSV224) which have been shown by Moore and coworkers[1] to be potent tumor selective cytotoxins in vivo. Following the isolation and first total synthesis[2a] of cryptophycin A (**1**), there has been considerable interest in the development of novel synthetic routes to this class of compounds. Generally these efforts have been focused on the synthesis of the penultimate olefin intermediate **2**, followed by epoxidation of the olefin. In a similar fashion, Moore and Tius[2b] synthesized cryptophycin-52 (**3**), a synthetic analog of **1** bearing a 3-amino-2,2-dimethyl propionic acid subunit, through the intermediacy of olefin cryptophycin-51 (**4**). This sequence has been improved to support the multigram preparation of **3** and other analogs for preclinical and clinical evaluation. In the course of addressing the issues involved with forming the macrocyclic ring of **4**, I found that 2-hydroxypyridine significantly accelerated the macrolactamization of functionalized long-chain amino trichloroethyl esters like **8**. I therefore report here a mild, convenient process for the macrocyclization of key *seco*-derivatives for cryptophycin construction.



1: R=H, Cryptophycin A
3: R=Me, Cryptophycin-52

2: R=H
4: R=Me, Cryptophycin-51

8

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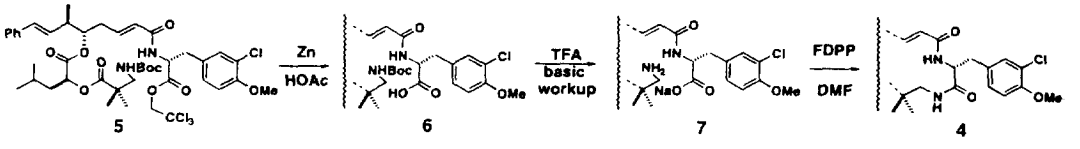
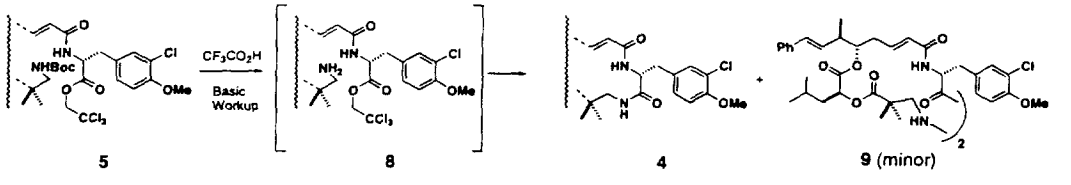
1. Results and discussion

Several synthetic strategies for the construction of the macrocyclic core of the cryptophycins[3] (and the structurally related arenastatins[4]) have predominantly involved ring-closure via formation of an amide linkage.[5] The literature describes simultaneous or sequential removal of C and N-terminus protecting groups to reveal an amino carboxylic acid, which is converted to the macrolactam via conventional peptide coupling reagents. A problematic issue associated with this sequence included the poor impurity profile of the crude product, which was due to the nature of the reagents and reaction conditions needed to remove the protecting groups and induce ring closure. These conditions usually require chromatographic purification of the macrocycle, which is expensive and difficult to implement on a large scale. These issues were encountered during the development of the original[2a] macrocyclization sequence shown in Scheme 1.



Scheme 1. Moore–Tius macrocyclization sequence

The three-step sequence commenced with the conversion of trichloroethyl ester **5** to the corresponding carboxylic acid **6** using zinc and acetic acid (HOAc). Conversion of crude **6** to the amino carboxylate **7** was accomplished with trifluoroacetic acid (TFA) followed by a basic workup. In the final step, ring closure was achieved in the presence of pentafluorophenyl diphenylphosphinate (FDPP) in DMF to provide **4** in 61% yield (overall from **5**) after chromatography. To reduce reagent expense, as well as minimize the effects of waste-stream issues associated with the use of zinc, DMF, and FDPP, we hypothesized that the trichloroethyl ester moiety might be sufficiently activated to allow a more direct route involving intramolecular aminolysis resulting in macrocyclic ring closure (Scheme 2).



Scheme 2. Macrolactamization via intramolecular aminolysis

The following reaction protocol gave encouraging results. Removal of the N-Boc group of **5** was accomplished within 15 min with neat TFA, followed by concentration and basic extractive work-up (0.5 N NaOH/EtOAc) to give nearly pure amino ester **8**. As summarized in Table 1, HPLC analyses of stirred room temperature solutions (0.02 M) of crude amino trichloroethyl ester **8** in DMF, CH_3CN and toluene indicated percent conversion of **8** to macrocycle **4** ranging from 13–22% over a period of 30 h (entries 1, 3, and 4). A heated solution of ester **8** in toluene exhibited an expected reaction rate increase and yield (entry 2). However, since we were anxious to maintain the lowest reaction temperature compatible with the chemical stability of the substrate (to minimize the production of impurities), the prospect of chemically promoting the macrolactamization reaction was explored.

The catalysis of ester aminolysis reactions has been extensively studied, although the intramolecular variants[6] are rare and have generally involved the formation of five- and six-membered rings. Very few aminolyses involving the formation of macrocycles[6e] have been reported. Examples of cat-

Table 1
Initial screening: percent Conversions (**8** to **4**), Rxn concentration: 0.02 M

Entry	Rxn Solvent	Rxn Temp.	Rxn Time	% Conversion
1	Toluene	20 °C	30 h	13%
2	Toluene	60 °C	25 h	52 %
3	CH_3CN	20 °C	30 h	22 %
4	DMF	20 °C	30 h	20 %

alysts for aminolysis reactions include amides,[7a] carboxylate anions,[7b] 2-hydroxypyridine,[7c–g] DMAP,[7h] imidazole[6d] and nucleosides.[7g]

Accordingly, potential candidates were tested for their ability to accelerate ring closure. Toluene was chosen as the reaction solvent based upon literature precedent of successful aminolyses accelerated by DMAP[7h] and benzoate[7b] in this non-polar medium. As summarized in Table 2, 2-hydroxypyridine (entry 7) and benzoate anion (entry 8) have been shown to significantly accelerate the macrolactamization process. In contrast, ring closure was very slow when the reaction was allowed to stir at room temperature without a promoter (entry 1) or in the presence of amine bases such as imidazole, *i*-Pr_2NEt, pyridine or DMAP (entries 3–6). Hydroxybenzotriazole (HOBt) exhibited a modest rate increase (entry 2), perhaps due to its structural similarity to 2-hydroxypyridine. TFA (1 equiv.) completely prevented ring closure (entry 9) as an expected consequence of increased protonation of the amino terminus of **8**.

Table 2
Catalyst screening in toluene, 0.02 M, 20°C. Percent conversions (**8** to **4**)

Entry	Catalyst	Equiv.	% Conv, t = 6h	% Conv, t=25 h
1	None	---	3.1	15
2	HOBt	0.5	---	36
3	Imidazole	0.5	---	22
4	*i*-Pr_2NEt	0.5	7.6	---
5	Pyridine	0.5	4.9	---
6	DMAP	0.5	4.8	---
7	2-Hydroxypyridine	0.5	42	>99
8	n-Bu_4N Benzoate	0.1	37	87
9	TFA	1.0	0.0	0.0

1.1. Origin of rate acceleration

Menger's[8a] seminal study of the bimolecular aminolysis of activated esters showed that, in a non-polar medium, the rate-limiting step is the breakdown of the tetrahedral intermediate to provide the amide product and an alcohol. Furthermore, Menger provided evidence[8b] that the aminolysis of aryl esters in aprotic solvents proceeds by a general base-catalyzed mechanism. Thus, benzoate anion, which is a 10 times[3] better proton acceptor than piperidine in toluene, functions to remove the ammonium proton of the tetrahedral intermediate and thereby enables its collapse to give the neutral amide (***TS-A***, Fig. 1). In contrast, 2-hydroxypyridine (***TS-B***) is thought to manifest its rate enhancing effect through a bifunctional[7d] mechanism. Thus, stabilization of the ionic aminolysis transition state occurs through simultaneous donation and acceptance of protons.

Having identified tetrabutylammonium benzoate and 2-hydroxypyridine as effective promoters for ring closure, the effect of each on yield and product quality of macrocycle **4** was evaluated. Freshly prepared 0.02 M solutions of amino ester **8** were allowed to stir in the presence of each reagent until complete consumption of **8** was observed. Each reagent was completely removed from the organic product solution

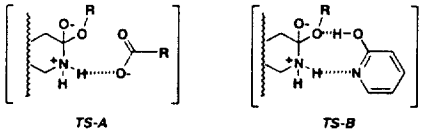


Fig. 1. Transition state structures depicting various modes of stabilization by catalysts

via extraction with aqueous $NaHCO_3$. Upon concentration, the crude oils were induced to crystallize (1:1 EtOAc:hexanes), to afford macrocycle **4** in 93–98% purity as a crystalline powder. ^1H NMR and mass spectral analysis of the filtrate revealed that the symmetrical dimer **9** (Scheme 2) was the principle impurity.

However, a limitation was noted during the evaluation of n-Bu_4N benzoate as a promoter. This reagent was prepared by the addition of 0.1 equiv. of n-Bu_4NHSO_4 to a toluene suspension of sodium benzoate (1 equiv.). When amino ester **8** was allowed to stir in this suspension, the reaction times for macrocyclization on a gram-scale became widely variable; reactions took 25–100 h to proceed to completion (Table 3, entry 1). The variability of the reaction times are not clearly understood, but appear to be related to the amount of adventitious water present in the reaction solution. The addition of 3 Å powdered molecular sieves appeared to inhibit macrocyclization.

Table 3
Isolated yields of macrocycle **4**. All reactions run at 0.02 M

Entry	Solvent	Promoter (eq)	Rxn Time	Temp.	*Seco*-5	Yields of 4
1	Toluene	n-Bu_4N Benzoate (0.1)	96 h	20 °C	1.7 g	57 %
2	Toluene	2-Hydroxypyridine (2.0)	16 h[9]	20 °C	575 g	80.4 %

Thus, 2-hydroxypyridine was found to be optimal for ring closure and facile workup. This reagent is inexpensive and is easily removed by aqueous extraction. Furthermore, on a large-scale, macrocycle **4** was afforded in 98.4% purity and in 80% yield (Table 3, entry 2).

In summary, a novel process for the construction of the macrocyclic core of cryptophycin derivatives is exemplified by the efficient, large-scale preparation of cryptophycin intermediate **4**. This process showcases a 2-hydroxypyridine-promoted, intramolecular aminolysis (macrolactamization) of trichloroethyl ester **8** and is noteworthy for its convenience, avoidance of expensive coupling reagents, and use of mild conditions. Details, generalization of the method, and studies directed towards dimer (**9**) reduction will be published in due course.

Acknowledgements

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