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A Convergent Synthesis of the Fully Elaborated Macrocyclic Core of TMC-95A

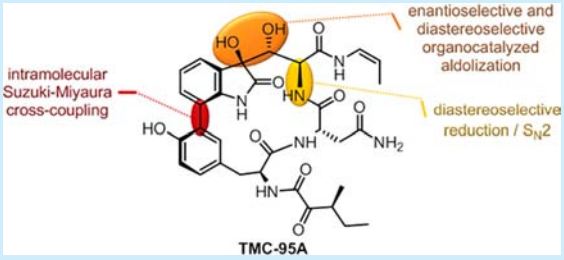
Alexis Coste,[†] Alexandre Bayle,[†] Jérome Marrot,[†] and Gwilherm Evano*[,‡]

[†]Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles Saint-Quentin-en-Yvelines, 45, avenue des Etats-Unis, 78035 Versailles Cedex, France

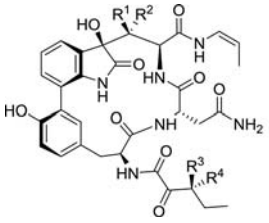
[‡]Laboratoire de Chimie Organique, Service de Chimie et PhysicoChimie Organiques, Université Libre de Bruxelles, Avenue F. D. Roosevelt 50, CP160/06, 1050 Brussels, Belgium

Supporting Information

ABSTRACT: A concise and straightforward synthesis of the fully elaborated macrocyclic core of TMC-95A is reported. A highly efficient organocatalyzed aldolization between isatin and dihydroxyacetone derivatives and formation of the biaryl subunit with concomitant macrocyclization are the characteristic features of this synthesis.



TMC-95A (**1a**) and its diastereoisomers TMC-95B–D (**1b–d**, Figure 1) were isolated in 2000 as fermentation



TMC-95	R^1	R^2	R^3	R^4
A (**1a**)	H	OH	Me	H
B (**1b**)	H	OH	H	Me
C (**1c**)	OH	H	Me	H
D (**1d**)	OH	H	H	Me

Figure 1. Structure of the TMC-95A–D.

products of *Apoispora montagnei* Sacc. TC 1093, a strain obtained from a soil sample from a bamboo forest in Kanagawa (Japan).[1,2] Common structural features of the TMC-95A–D include (*i*) a cyclic polypeptide containing a L-tyrosine, a L-asparagine, and a highly oxidized L-tryptophan bearing three contiguous stereocenters; (*ii*) a biaryl linkage between the tyrosine and tryptophan moieties; (*iii*) an appending *Z*-enamide; and (*iv*) a 3-methyl-2-oxopentanamide side chain.

Besides their complex and most interesting structure, biological evaluation of these macrocyclic peptides showed that TMC-95A inhibited the chymotrypsin-like, trypsin-like, and postglutamyl peptide hydrolytic activities of the proteasome with IC_{50} values of 5.4, 200, and 60 nM, respectively.[3] TMC-95B inhibited these activities to the same extent as TMC-95A, while TMC-95C and D were shown to be weaker inhibitors. TMC-95A also showed cytotoxic activities against human cancer HCT-116 and HL-60 cell lines and was shown to induce neurite outgrowth in PC12 cells.[4]

Unlike other synthetic or natural proteasome inhibitors, the binding mode of TMC-95A–D to the proteasome involves a dense network of hydrogen bonds in addition to perfectly fitting the active site of the latter.[5] This unique binding mode combined with their challenging structures have made them especially attractive targets for synthesis. Indeed, in addition to the development of simplified analogues of the TMC-95s[6] and to various synthetic studies,[7] three total syntheses have been reported since 2001 by the Danishefsky,[8] Hirama,[9] and Williams[10] groups. In all these syntheses, the macrocyclic core was formed by standard macrolactamization techniques and the biaryl subunit was installed in the middle stages of the syntheses by an intermolecular Suzuki–Miyaura cross-coupling. The *Z*-enamide side chain was introduced by a thermal rearrangement from an α-silylallyl amide in Danishefsky's synthesis while the strategy implemented in the Hirama's and Williams' syntheses relied on a decarboxylative elimination from an *allo*-threonine intermediate. Finally, a direct acylation with 3-methyl-2-oxopentanoic acid provided an epimeric mixture of TMC-95A and B in the Danishefsky and Williams approaches, a problem that was solved in Hirama's synthesis by using an α-hydroxy acid instead of the readily epimerizable α-oxo-derivative, which allowed for a selective preparation of TMC-95A. Examination of the number of steps involved in these syntheses (between 18 and 35) and overall yields (between 0.1 and 4%) revealed that the preparation of the oxidized tryptophan fragment was the most problematic part of all approaches, a problem that was partially addressed in Pearson's synthetic studies.[7f] Described herein is our approach to the fully elaborated macrocyclic core of TMC-95A, featuring an intramolecular Suzuki–Miyaura reaction for the key

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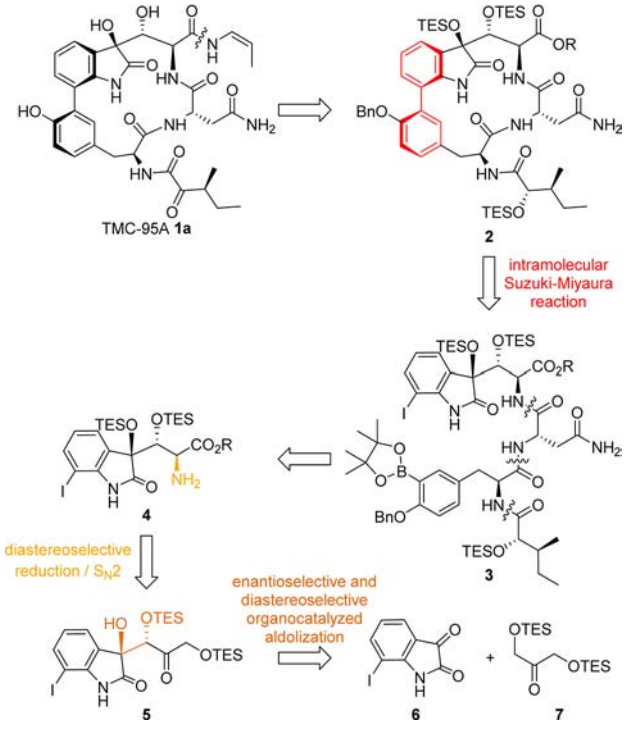
macrocyclization step and an enantioselective, organocatalyzed aldolization for the preparation of the oxidized tryptophan core.

From a retrosynthetic perspective, we envisioned installation of the enamide and oxopentanamide side chains using strategies developed in Hirama's synthesis from advanced and fully elaborated precursor **2** as depicted in Scheme 1. To install the

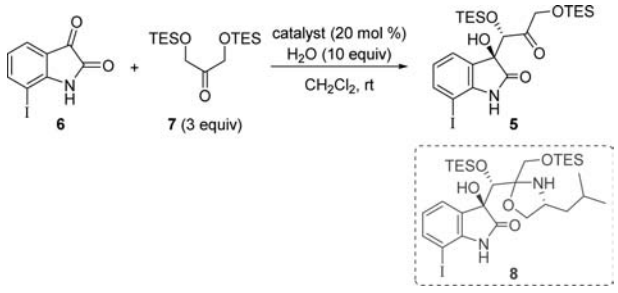
Scheme 1. Retrosynthetic Analysis of TMC-95A

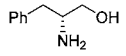
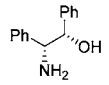
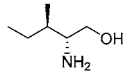
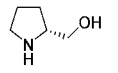
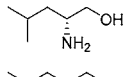
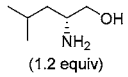
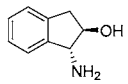


biaryl and simultaneously effect macrocyclization, we decided to employ an intramolecular Suzuki−Miyaura reaction from acyclic precursor **3**. Further analysis of **3** suggested that it could be disconnected at amide bonds to give simple amino acid precursors and the oxidized tryptophan fragment **4**. The amino acid moiety in **4** could finally be installed from the corresponding hydroxymethylketone in **5**, which could in turn be readily obtained in an enantioenriched form using an enantioselective organocatalyzed aldolization between isatin and dihydroxyacetone derivatives **6** and **7**.

To determine the feasibility of our approach, we started by examining the organocatalyzed aldolization between readily available 7-iodo-isatin **6** and TES-protected dihydroxyacetone **7**. While isatin and dihydroxyacetone derivatives had been extensively used in various organocatalytic processes, there was no report of a cross-aldolization between these carbonyl derivatives when we started this project, although an efficient organocatalyzed aldol reaction between isatins and acetal-protected dihydroxyacetone using a complex tetrazolyl-pseudo-peptide organocatalyst prepared in 9 steps from *N*-Boc-valine (with the ee in the 75−90% range and dr from 4:1 to 24:1) was reported by the Pearson group during the preparation of this manuscript.[7f] We initiated our studies by examining a set of standard organocatalysts for the aldolization between **6** and **7** (Table 1). While amino acids, diamines, and tetrazoles gave no conversion, aminoalcohols were found to be better promoters for this reaction since most of them gave good enantiomeric and diastereoisomeric ratios for the formation of **5**.[11] The conversion was however disappointingly low in all trials

Table 1. Optimization of the Organocatalyzed Aldolization



entry	organocatalyst	product(s) [a]	er(**5**) and dr(**5**)
1[b]		**5** (10%)	er: 91/9 dr: 95/5
2[b]		**5** (15%)	er: 85/15 dr: 80/20
3[b]		**5** (15%)	er: 95/5 dr >95/5
4[b]		**5** (16%)	er: 68/32 dr: 60/40
5[b]		**5** (19%)	er: 98/2 dr >95/5
6[b]	 (1.2 equiv)	**5** (51%) **8** (36%)	er: 98/2 dr >95/5
7[c]		**5** (73%)	er: 92/8 dr >95/5

[a]Yields of pure, isolated products. [b]Reaction time: 1 week. [c]Reaction time: 2 days.

(maximum 19% with 20 mol % of catalyst after one week) as shown with selected results collected in Table 1 (entries 1−5). The origin of the low conversion and slow kinetics of the reaction could be rationalized by performing a stoichiometric reaction in which D-leucinol was used in slight excess (Table 1, entry 6). A full conversion could be obtained under these conditions, and to our surprise, oxazolidine **8**, resulting from the condensation of the aminoalcohol to the aldolization product, was isolated in 36% yield, along with the aldol product **5** (51%). Capitalizing on this result, we hypothesized that it might be possible to avoid the formation of this oxazolidine byproduct, which results in the trapping of the catalyst, by slightly modifying the nature of the organocatalyst. Indeed, by using a cyclic *trans*-1,2-aminoalcohol, the resulting oxazolidine would be embedded in the 5,5 bicyclic core with a *trans* ring junction, which should be disfavored. Based on this hypothesis, we therefore evaluated the efficiency of *trans*-1-amino-2-indanol as the catalyst. To our delight, the reaction was greatly accelerated, oxazolidine could not be detected in the crude reaction mixture anymore, and the desired aldol product **5** could be obtained in 73% yield with good enantio- and diastereoselectivities (Table 1, entry 7).

With these results in hand, we next briefly evaluated the scope of the aldolization starting from 7-halo-isatins, protected or not, that could potentially be used for the preparation of the tryptophan fragment of TMC-95A. As shown by results collected in Scheme 2, the use of *trans*-1-amino-2-indanol was quite efficient and resulted in the formation of aldol products **5**,

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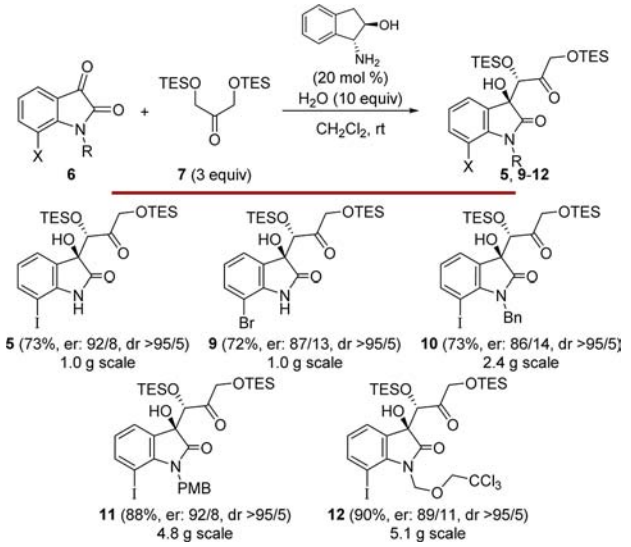
Scheme 2. *trans*-1-Amino-2-indanol Catalyzed Aldolization between Isatin and Dihydroxyacetone Derivatives



9–**12** in good yields, with total diastereocontrol, and with synthetically useful levels of enantioselectivity.

The optimization of the organocatalyzed aldol reaction set the stage for the completion of the synthesis of the tryptophan fragment of TMC-95A (Scheme 3). Gratefully, the aldolization could be conveniently performed on a multigram scale which allowed for an easy synthesis of **5** which was then protected as a TES ether to avoid problems associated with retro-aldolization. Further treatment with sodium borohydride in methanol at 0 °C allowed for a clean and diastereoselective reduction of the ketone in **13**. The configuration of the resulting alcohol in **14**, which is in agreement with results reported by the Overman group who rationalized the reduction of related β-keto-oxindoles by chelation between the carbonyl groups of the ketone and distal oxindole,[12] could be established by X-ray diffraction analysis of **16** obtained after selective deprotection of the primary alcohol with PPTS in a mixture of methanol and dichloromethane.

We next envisioned introducing the amino group required for the assembly of the tryptophan fragment at this stage of the synthesis by reacting alcohol **14** under Mitsunobu conditions in the presence of diphenylphosphoryl azide. To our surprise, an unexpected participation of the neighboring oxindole as an internal nucleophile occurred once the alcohol was activated, yielding, after addition of the azide to the intermediate iminium ion, the formation of tetrahydrofuroindole **15**.

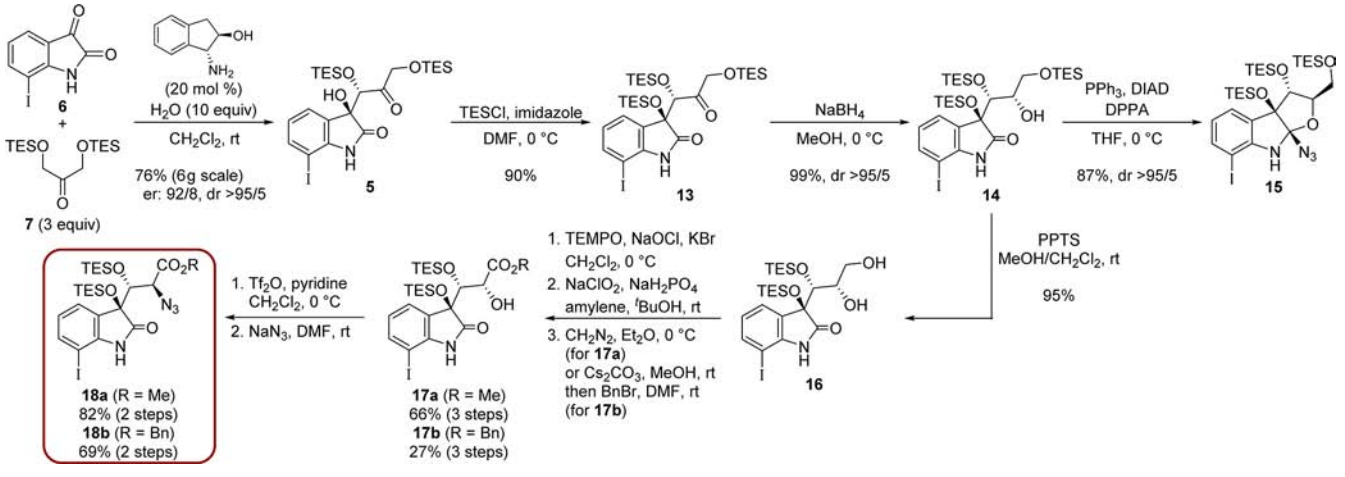
To avoid this participation of the oxindole, we slightly modified our strategy by transforming the protected primary alcohol in **14** to an ester prior to the nucleophilic substitution, in hopes that the greater reactivity of the activated alcohol would favor the intermolecular nucleophilic substitution. While this strategy bore some risk and even seemed counterintuitive, it turned out to be quite successful since the activation of the hydroxyl group in hydroxyesters **17a**,**b**, which were readily obtained by classical transformations from **16**, as a triflate followed by a displacement with sodium azide indeed provided the desired α-azido-esters **18a**,**b**, therefore completing the synthesis of the tryptophan fragment of TMC-95A in 9 steps (12−35% overall yield).

With these two differentially protected advanced intermediates **18a**,**b** in hand, we next proceeded to the final steps of the synthesis and to the key macrocyclization. The elaboration of the acyclic precursors and the end-game strategy are shown in Scheme 4.

The azide in **18a**,**b** was therefore reduced by a Staudinger reaction, and the resulting unstable amine, which is in equilibrium with the 4-(*o*-aminophenyl)pyroglutamate form resulting from opening of the oxindole by the amine, could be selectively acylated with Fmoc-protected asparagine, yielding dipeptides **19a**,**b**. Further deprotection of the Fmoc group followed by coupling with boronate **20** finally gave the acyclic precursors **3a**,**b**. This set the stage for the final macrocyclization step, which turned out to be quite challenging. After screening various palladium-based systems such as $PdCl_2(S\text{-}Phos)_2$, Pd_2dba_3/P^tBu_3, or Pd_2dba_3/S-Phos for the intramolecular Suzuki−Miyaura reaction enabling the formation of both the macrocycle and the biaryl subunit, we eventually evaluated the efficiency of a combination of $PdCl_2(dppf)$ and potassium carbonate in aqueous DME, conditions reported by the Zhu group in various total syntheses.[13] Gratifyingly, **3a**,**b** could be smoothly transformed to the corresponding macrocycles **2a**,**b**, in which the fully elaborated macrocyclic core of TMC-95A is installed.[14]

In conclusion, a concise and straightforward (14 steps) synthesis of the fully elaborated macrocyclic core of TMC-95A

Scheme 3. Synthesis of the Tryptophan Fragment of TMC-95A



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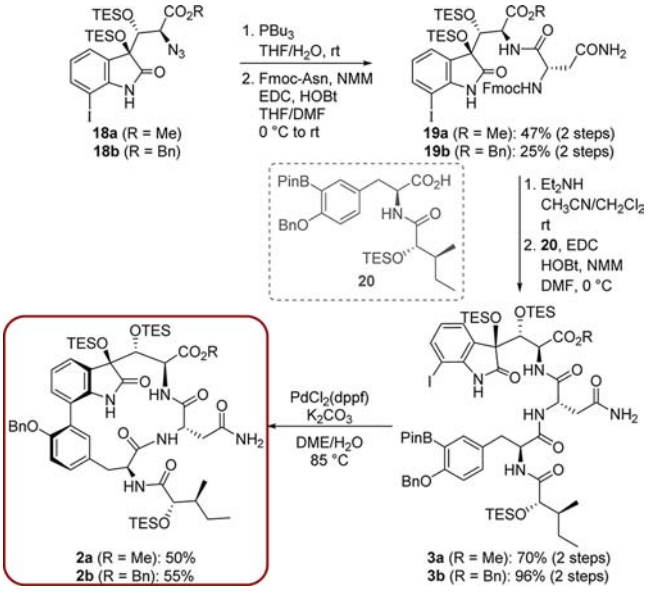
Scheme 4. Acyclic Precursors and Macrocyclization



is reported. A highly efficient organocatalyzed aldolization between isatin and dihydroxyacetone derivatives and the formation of the biaryl subunit with concomitant macrocyclization are the characteristic features of this synthesis. Further studies on TMC-95A–D and analogues will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and relevant HPLC traces and cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gevano@ulb.ac.be.

Notes

The authors declare no competing financial interest.

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(11) Diastereoisomeric and enantiomeric ratios were determined by ^{1}H NMR analyses of crude reaction mixtures and HPLC analyses. The relative and absolute configuration of **5** was established by X-ray analysis after derivatization: see Supporting Information for details.
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(14) It was previously shown that the macrocyclization would only provide the desired atropoisomer which follows the stereochemistry of the tertiary alcohol. See refs 1 and 8a, b.