Pure Appl. Chem., Vol. 79, No. 2, pp. 163–172, 2007. doi:10.1351/pac200779020163 © 2007 IUPAC

Recent results toward the stereoselective synthesis of biologically active natural products*

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Abstract: This paper describes the convergent and stereocontrolled asymmetric total synthesis of (+)-crocacins C and D, potent inhibitors of animal cell cultures and several yeasts and fungi, and (–)-callystatin A, a potent antitumor polyketide.

Keywords: natural product synthesis; antitumor compound; polyketides, diastereocontrol.

INTRODUCTION

Described herein are some examples of recent work from our laboratory that have led to the synthesis of bioactive molecules. In this paper, we will discuss our approaches to the total synthesis of (+)-crocacin D (1) [1], (+)-crocacin C (2) [2], and (-)-callystatin A (3) [3] (Fig. 1). We were attracted by their fascinating biological activities, molecular architectures, and low natural abundance, which makes their total synthesis extremely important. The synthetic routes were developed in order to be practical enough to allow the isolation of the desired targets in useful amounts as well as to provide access to new analogs with potential pharmacological activities.



Fig. 1

^{*}Paper based on a presentation at the 16th International Conference on Organic Synthesis (ICOS-16), 11–15 June 2006, Mérida, Yucatán, México. Other presentations are published in this issue, pp. 153–291.

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TOTAL SYNTHESIS OF (+)-CROCACINS C AND D

The crocacins D (1) and C (2) (Fig. 1) were isolated from *Chondromyces crocatus* and *Chondromyces pediculatus* strains as a second novel group of modified peptides [4,5]. These molecules inhibit the growth of a few *gram*-positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. Among the compounds of this series, (+)-crocacin D (1) shows higher biological activity against *Saccharomyces cerevisiae* as well as higher toxicity in L929 mouse fibroblast cell cultures, when compared to other crocacins. The relative configurations of crocacins were proposed by Jansen and coworkers by means of molecular modeling studies and nuclear Overhauser effect (NOE) experiments [4,5] and further confirmed by total synthesis [6–9]. The promising pharmacological activities of the crocacins, together with their structural complexity, have attracted the interest of synthetic organic chemists and the following groups have completed the total synthesis of these fascinating natural products: Rizzacasa [6–8], Chakraborty [6–8], and Dias [1,2]. In addition, there are several fragment syntheses and two formal total syntheses recently described by the research groups of Fürstner and Yadav [9c,9d].

To provide material for more extensive biological evaluation, along with access to novel analogs, we have undertaken the total synthesis of the polyketide (+)-crocacin D (1), the most active compound in this series. Crocacin D (1) is a dipeptide of glycine and 6-aminohexenoic acid showing four consecutive stereocenters, three (*E*)-double bonds, and a (*Z*)-enamide moiety, which represents the major synthetic challenge. In a retrosynthetic approach (Scheme 1), we could envisage the C9–N10 bond as being constructed from (*Z*)-vinyl iodide fragment (3) and crocacin C (2) using a Cu(I)-mediated cross-coupling. Fragment C1–C9, corresponding to (*Z*)-vinyl iodide fragment (3), is viewed as arising from methyl ester 4 and carboxylic acid 5. Fragments C11–C13 (*E*-vinyl stannane 6) and C14–C21 (*E*-vinyl iodide 7) in crocacin C could be joined employing a Stille cross-coupling reaction. Fragment C14–C21 (*E*-vinyl iodide 7) could be derived from epoxide 8.



Scheme 1 Retrosynthetic analysis.

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For the synthesis of (*E*)-vinyl iodide 7, we started from aldol adduct 9, easily prepared from a *syn*-aldol reaction (Scheme 2) [1,2]. Aldol 9 was converted to α,β -unsaturated ester 10 in good overall yields (Scheme 2). Reduction of ester 10 to the allylic alcohol and treatment with *m*-CPBA provided epoxide 8 [10]. The stereochemical outcome of this epoxidation reaction is well documented and is consistent with approach of *m*-CPBA from the side opposite to the OTBS at C19 [10]. The next steps involved epoxide opening and a sequence of deprotection and selective protection to provide diol 11. Methylation of the hydroxyl groups in 11 and removal of the *t*-butyldiphyenylsilyl (TBDPS) group gave alcohol 12. The last steps involved oxidation to the aldehyde and Takai olefination reaction to give (*E*)-vinyl iodide 7.



Scheme 2 Synthesis of (E)-vinyl iodide 7.

Fragment C11–C13 (*E*-vinylstannane **6**) was obtained from ethyl-2-butynoate in three steps (50 % overall yield and E/Z > 95:5) [1,2]. Finally, a Stille cross-coupling was the reaction of choice to connect fragments C11–C13 (**6**) and C14–C21 (**7**) providing (+)-crocacin C (**2**) in 84 % yield (Scheme 3). The route to crocacin C (**2**) involved 15 steps from *N*-propionyloxazolidinone in 21 % overall yield [1,2].



Scheme 3 Total synthesis of (+)-crocacin C (2).

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Our strategy to promote (Z)-enamide moiety formation in crocacin D is based on the elegant methodologies recently described by Buchwald [11] and Ma [12] and uses Cu(I) to mediate a cross-coupling between vinyl iodides and amides or carbamates. This methodology allowed us to obtain crocacin D (1) in a convergent way using an efficient copper-catalyzed cross-coupling reaction between crocacin C (2) and (Z)-vinyl iodide (3) to establish the challenging (Z)-enamide function (Scheme 4). It is interesting to point out that we were able to isolate small amounts of enecarbamate 13 as a by-product, originated from an intramolecular cyclization of 3.



Scheme 4 Total synthesis of crocacin D (1).

Our approach required required 16-steps from N-propionyl oxazolidinone and produced crocacin D in 14 % overall yield [1,2]. We believe the synthetic route described here to crocacin D should afford access to promising novel analogs with potential relevance to biological studies.

TOTAL SYNTHESIS OF (-)-CALLYSTATIN A

The potent antitumor polyketide (–)-callystatin A (**3**) was isolated in very small amounts (1 mg from 100 kg of sponge) by Kobayashi and coworkers in 1997 from the marine sponge *Callyspongia truncata* (Fig. 1) [13–15]. (–)-Callystatin A (**3**) shows remarkable high activity ($IC_{50} = 10 \text{ pg/mL}$) against KB tumor cell lines and 20 pg/mL against L1210 cells [13–15]. This fact, in addition to its structural complexity, has attracted the interest of synthetic organic chemists. The first total synthesis of (–)-callystatin A was reported in 1998 by the Kobayashi group [16a,17,18]. So far, the following groups have completed the total synthesis of this fascinating natural product: Kobayashi [16a], Crimmins [16b], Smith [16c], Kalesse [16d,h], Enders [16e], Marshall [16f], Lautens [16g], Panek [16i], and Dias [3].

Attracted by its potent cytotoxicity, and to provide material for more extensive biological evaluation, along with access to promising novel analogs, we have undertaken the total synthesis of callystatin A.

Our retrosynthetic analysis is illustrated in Scheme 5. A Suzuki-type coupling approach is viewed as being applied to join fragments C1–C11 (14) and C12–C22 (15) [19]. Fragment C1–C11 (14) arises from aldehyde 16 (C1–C6 fragment) and phosphonium salt 17 (C7–C11 fragment). Fragment C12–C22 (15) is viewed as being prepared from epoxide 18, available from Weinreb amide 19 [19]. This Weinreb amide could be derived from an Evans-type aldol reaction.



Scheme 5 Retrosynthetic analysis.

Our starting point was the synthesis of aldehyde **16**, which was easily prepared in few steps from L-malic acid in high yields [19]. The carbonyl group at C1 in aldehyde **16** needs to be masked as an acetal, which can be hydrolyzed under mild acidic conditions and oxidized to yield the α , β -unsaturated lactone at a later stage in the synthesis. Phosphonium salt **17** was prepared in excellent overall yield after a few steps from methyl 3-hydroxy-(*R*)-2-methyl propanoate [19].

The aldehyde **16** was then coupled with phosphonium salt **17** in the presence of $\text{LiCH}_2S(O)\text{CH}_3$ in toluene at -78 °C, leading to diene **20** in 82 % yield (Scheme 6). After removal of the silvl protecting group, the resulting primary alcohol was treated with I₂, PPh₃, and imidazole in CH₂Cl₂ to give alkyl iodide **14** (C1–C11 fragment of (–)-callystatin A) in 90 % yield (Scheme 6). This reaction sequence completed the synthesis of alkyl iodide **14** in 12 steps and 25 % overall yield [19].

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Scheme 6 Coupling between aldehyde 16 and phosphonium salt 17.

With efficient access to alkyl iodide 14, construction of the vinyl iodide 15 was initiated (Scheme 7). For the synthesis of vinyl iodide 15, an asymmetric aldol addition of the boron enolate derived from oxazolidinone 21 with 2-(*S*)-methylbutanal 22 gave aldol adduct 23 (89 %, ds > 95:5) (Scheme 7) [19,20]. This aldol adduct was transformed to allylic alcohol 24 in good overall yields. Epoxidation of allylic alcohol 24 with *m*-CPBA in CH_2Cl_2 at 0 °C gave epoxy alcohol 18 (96 % yield, >95:5 ds) [10].



Scheme 7 Preparation of epoxide 18.

Treatment of epoxide 18 with $Me_2CuCNLi_2$ in THF at -20 °C gave diol 25 (90 % yield) (Scheme 8) [21].

Treatment of the 1,3-diol **25** under Swern conditions promoted a selective oxidation of the primary alcohol to provide a β -hydroxy aldehyde, which after coupling with carboethoxyethylidene-triphenylphosphorane gave α,β -unsaturated ester **26** (89 %, *E*:*Z* > 95:5) (Scheme 8). Reduction of ester **26** to the allylic alcohol followed by oxidation with activated MnO₂ gave an intermediate aldehyde. At this point, it became necessary to protect the OH-function at C17 in the aldehyde as its TMS ether, in order to promote the Takai olefination reaction [22]. Under standard conditions, (*E*)-vinyl iodide **27** was obtained in 45 % overall yield after 4 steps (*E*:*Z* > 95:05). The TMS group was then easily removed by treatment of vinyl iodide **27** with EtOH in the presence of catalytic amounts of CSA (96 % yield) giving vinyl iodide **15**.



Scheme 8 Synthesis of vinyl iodide (15).

With the two fragments in hand, we were now poised to assemble the target molecule (Scheme 9). Gratifyingly, the coupling of fragments C1–C11 and C12–C22 was achieved through the use of a Pd-catalyzed coupling of an intermediate boronate derived from 14 with vinyl iodide 15 [16f,23]. Treatment of the boronate intermediate derived from alkyl iodide 14 with vinyl iodide 15 in the presence of Pd(dppf)Cl₂, AsPh₃, Cs₂CO₃, and water in dimethylformamide (DMF) gave lactol 28 in 67 % yield, together with α , β -unsaturated aldehyde 30 [16f,23].



Scheme 9 Suzuki coupling.

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The last steps in the synthesis proved to be challenging. Fortunately, it was found that when **28** was treated with AcOH:THF:H₂O (1:5:1) at ambient temperature for 72 h, hydrolysis of the C1 acetal took place smoothly to provide lactol **29** in 38 % overall yield, along with α , β -unsaturated aldehyde **30** (25 % yield) [3,16g].

The last steps in the synthesis involved oxidation of lactol **29** to hydroxy lactone **31** with MnO_2 in CH_2Cl_2 at ambient temperature (72 % yield), Dess–Martin [24] periodinane oxidation of the C17–hydroxyl function to the keto-lactone **32** (81 % yield), and TBS removal at C19 with HF-pyridine in THF/pyridine to provide (–)-callystatin A (77 %) (Scheme 10) [3].



Scheme 10 Total synthesis of (-)-callystatin A.

In summary, a convergent total synthesis of the marine natural product, (–)-callystatin A, was completed. The synthesis was accomplished in 19 steps over the longest linear sequence and provided the desired target in 3.5 % overall yield starting from readily available *N*-propionyl oxazolidinone **21**. We believe the methodology described here to (–)-callystatin A should afford access to promising novel analogs with potential relevance to biological evaluation.

ACKNOWLEDGMENTS

We are grateful to FAEP-UNICAMP, FAPESP, and CNPq (Brazil) for financial support. This work is a product of many talented and dedicated investigators whose names appear as coauthors and in the references provided.

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