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Total synthesis of (+)-crocacin D

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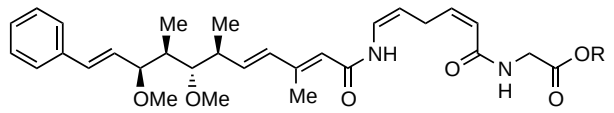
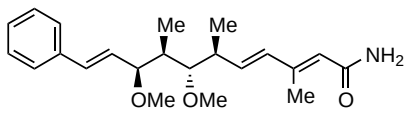
Abstract—The first total synthesis of the potent antifungal and cytotoxic agent (+)-crocacin D in optically pure form following a convergent strategy is described here. The regioselective ring opening of a silyl-substituted epoxide with an azide ion, based on a method developed by us earlier, and subsequent subjection of the resulting α-azido-β-hydroxyalkylsilane intermediate to a Peterson elimination reaction at an appropriate stage during the synthesis constituted the key steps for the stereoselective construction of the crucial *cis* enamide moiety of the molecule. © 2002 Published by Elsevier Science Ltd.

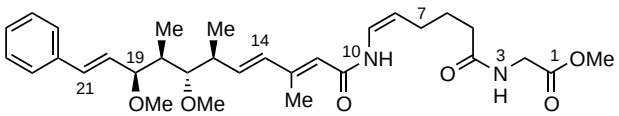
Crocacins A–D (**1**–**4**), isolated from the myxobacterial strains of *Chondromyces crocatus* (crocacins A–C) and *C. pediculatus* (crocacin D),[1,2] possess wide ranging biological activities. The major component crocacin A (**1**) inhibits the growth of Gram-positive bacteria moderately, but exhibits very effective growth inhibition of fungi and yeasts, caused by the inhibition of electron flow within the cytochrome bc_1 segment (complex III) of the respiratory chain.[3] Crocacin D (**4**) shows a distinctly higher biological activity against *Saccharomyces cerevisiae* and higher toxicity in L929 mouse fibroblast cell culture compared to other crocacins.



1: crocacin A (R = Me)
2: crocacin B (R = H)



3: crocacin C



4: crocacin D

The crocacins represent a second novel group of modified peptides from *C. crocatus*. However, unlike the chondramides isolated earlier,[4] crocacins are linear dipeptides. The main structural features of crocacin molecules are polyketide derived four consecutive stereocenters, unusual dipeptides of glycine and a 6-aminohexenoic (in crocacin D) or hexadienoic acid (in crocacins A and B) and a large number of double bonds with their respective geometric constraints. While the relative configurations of these molecules were deduced using 2D NMR experiments and molecular modeling studies,[2] their absolute configurations were established by the total synthesis of crocacin C.[5]

One of the major problems encountered in the much-awaited total synthesis of the other members of the family is the presence of a unique *cis* enamide moiety in these molecules, construction of which remained a challenging task. In this paper, we describe a novel strategy for the stereoselective synthesis of this crucial structural moiety[6] based on two key reactions, (a) the regioselective opening of a silyl-substituted epoxide with an azide ion, based on work carried out by us and others earlier[7] and (b) subjection of the resulting α-azido-β-hydroxyalkylsilane intermediate to a Peterson elimination reaction[8] at an appropriate stage, leading to a successful first total synthesis of (+)-crocacin D (**4**).

The synthesis started with the monosilyl-protected pentane-1,5-diol **5** (Scheme 1), which was transformed into the silylated-acetylenic product **6** in three steps in 68% overall yield: (a) the Swern oxidation of the free hydroxyl group to an aldehyde; (b) olefination of the aldehyde using Ph_3P and CBr_4 to give a dibromoolefin; and finally (c) treatment of the Li–acetylide, generated

Keywords: antifungals; cytotoxins; aldol reactions; Peterson olefination; enamide.

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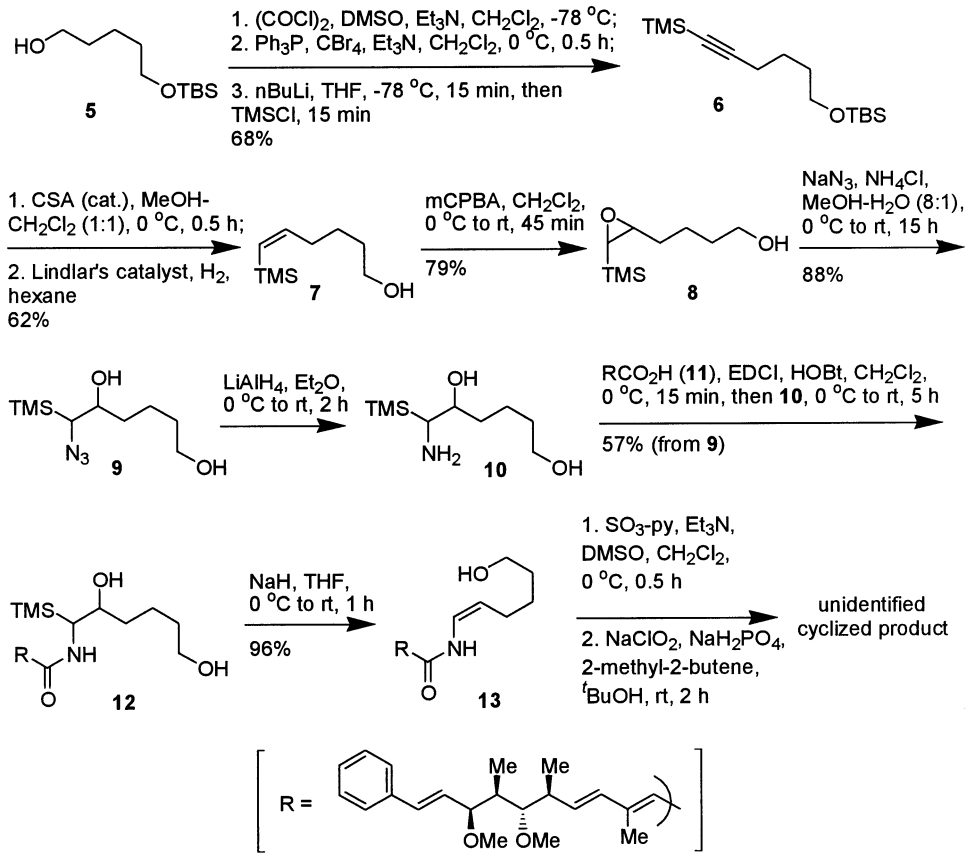
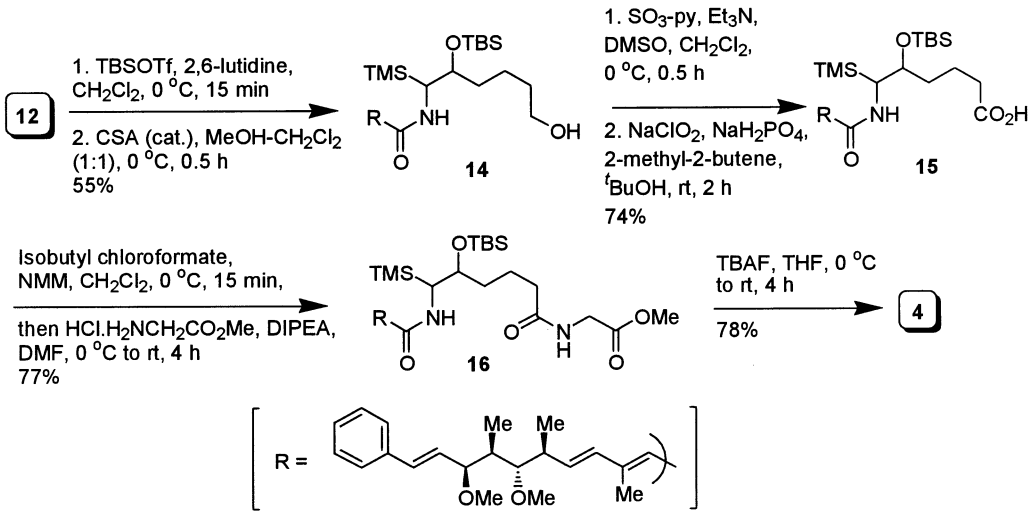


Scheme 1. Stereoselective synthesis of **13**.

by adding *n*-BuLi to the dibromoolefin intermediate, with trimethylsilyl chloride (TMSCl). Deprotection of the TBS group of **6** using a catalytic amount of camphorsulfonic acid (CSA) was followed by hydrogenation of the acetylenic moiety using Lindlar's catalyst to give the *cis* vinylsilane **7** in 62% yield. Epoxidation of **7** using *m*CPBA furnished the *cis* epoxysilane **8**. As expected, treatment of **8** with NaN_3 in the presence of NH_4Cl led to a very facile opening of the epoxide ring with complete regioselectivity at the silyl-substituted center to provide the α-azido-β-hydroxyalkylsilane intermediate **9** in 88% yield.[7a,b] The azido group of **9** was selectively reduced to the requisite amine **10** using $LiAlH_4$[7d] and after aqueous work-up, the product was used directly to couple with the known acid **11** that was earlier prepared by us during the synthesis of crocacin C.[5a,c] To a solution of **11** in CH_2Cl_2, 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-(dimethylamino)-propyl)carbodiimide hydrochloride (EDCI) were added sequentially at 0°C and the reaction mixture was stirred at that temperature for 15 min, followed by the addition of a solution of **10** in CH_2Cl_2. The reaction was complete in 5 h. After the usual aqueous work-up, chromatographic purification gave the amide **12** in 57% yield (from **9**). The stage was now set to carry out the Peterson reaction on compound **12**. Treatment of **12** with NaH in THF at 0°C led to the formation of the enamide **13** in quantitative yield (>96%). The formation of the *cis* olefin as the sole product was confirmed by the ^1H NMR spectrum of **13** which did not show any trace of the *trans* isomer. To complete the synthesis of our target molecule, the primary hydroxyl group of **13** was next subjected to a two-step oxidation protocol to prepare the corresponding acid. Unfortunately, the product isolated was not the expected acid. That an aldehyde was formed in the first step during the oxidation was confirmed. However, the product after the second step did not have the C8–C9 double bond as indicated by its ^1H NMR spectrum. Although its structure is yet to be established fully, preliminary investigations of the spectroscopic data suggest that it is an intramolecularly cyclized lactone.

Having failed to proceed any further with the enamide compound **13**, it was decided to carry out the Peterson elimination reaction in the last step of our synthesis after incorporating the glycine unit as shown in Scheme 2. Thus, the diol **12** was subjected to a routine two-step reaction sequence involving di-TBS protection followed by a selective primary deprotection, to prepare the secondary-hydroxyl protected intermediate **14** in 55% yield. A two-step oxidation process, identical to that described in Scheme 1, transformed **14** into the acid **15** in 74% yield. Attempted coupling of **15**, following the conditions outlined in Scheme 1 for **10**→**11**, did not provide the expected product in good yield and the major product showed the disappearance of the N10-amide proton. However, treatment of **15** with isobutyl chloroformate in the presence of *N*-methylmorpholine



Scheme 2. Final steps in the synthesis of (+)-crocacin D (**4**).

(NMM) led to a mixed anhydride which reacted successfully with glycine methyl ester to furnish **16** in 77% yield. Finally, deprotection of the TBS group of **16** using tetra-*n*-butylammonium fluoride (TBAF) in THF led to the formation of an oxy anion intermediate that underwent a smooth in situ Peterson elimination process, in 78% yield, to install the final and most important *cis* enamide moiety in the framework with complete stereoselectivity resulting in the successful completion of the first total synthesis of crocacin D (**4**). Our synthetic crocacin D (**4**) showed rotation $[\alpha]_D^{20}$ +100.3 (*c* 0.13, MeOH); lit. value: $[\alpha]_D^{22}$ +109.6 (*c* 0.56, MeOH)[2] and was identical in all respects with the naturally occurring crocacin D having all spectroscopic data[9] matching with those reported for the natural product.[2]

In conclusion, a mild method for the synthesis of a *cis* enamide starting from an epoxysilane following two simple steps, silyl-directed epoxide opening with an azide ion and a Peterson elimination, has been developed leading to the first total synthesis of (+)-crocacin D. Although a similar approach using epoxysilanes as substrates for the synthesis of simple enamides has very recently been reported,[6a] its efficacy in the synthesis of a complex natural product containing this very challenging structural moiety is realized here for the first time. This will help us to achieve the total synthesis of the other members of the family. Further work is currently in progress.

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9. Selected physical data for **4**. $R_f = 0.4$ (silica, 60% EtOAc in petroleum ether); $[\alpha]_D^{20}$ +100.3 (*c* 0.13, MeOH); IR (neat): ν_{max} 3309, 2917, 1742, 1647, 1360, 1176, 1082 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz, TMS as reference): δ 9.10 (d, $J = 10$ Hz, 1H, N10-*H*), 7.55 (br m, 1H, N3-*H*), 7.45 (d, $J = 8.0$ Hz, 2H, aromatic *ortho*-protons), 7.31 (dd, $J = 8.0$, 7.4 Hz, 2H, aromatic *meta*-protons), 7.22 (t, $J = 7.4$ Hz, 1H, aromatic *para*-proton), 6.77 (ddt, $J = 10$, 9, 1.5 Hz, 1H, C9-*H*), 6.58 (d, $J = 16.1$ Hz, 1H, C21-*H*), 6.24 (dd, $J = 16.1$, 7.24 Hz, 1H, C20-*H*), 6.12 (d, $J = 15.7$ Hz, 1H, C14-*H*), 6.10 (dd, $J = 15.7$, 8.1 Hz, 1H, C15-*H*), 5.9 (d, $J = 1.0$ Hz, 1H, C12-*H*), 4.66 (dt, $J = 9$, 7.4 Hz, 1H, C8-*H*), 4.07 (ddd, $J = 7.24$, 2.4, 1.0 Hz, 1H, C19-*H*), 3.96 (d, $J = 5.8$ Hz, 2H, C2-H_2), 3.67 (s, 3H, C1-OCH_3), 3.51 (s, 3H, C17-OCH_3), 3.29 (s, 3H, C19-OCH_3), 3.18 (dd, $J = 9.5$, 2.3 Hz, 1H, C17-*H*), 2.62 (m, 1H, C16-*H*), 2.26 (m, 2H, C5-H_2), 2.26 (d, $J = 0.7$ Hz, 3H, C13-CH_3), 2.12 (m, 2H, C7-H_2), 1.67 (m, 2H, C6-H_2), 1.57 (m, 1H, C18-*H*), 1.17 (d, $J = 7.1$ Hz, 3H, C16-CH_3), 0.84 (d, $J = 6.8$ Hz, 3H, C18-CH_3); MS (LSIMS): *m*/*z* (%): 509 (23) [M++H–CH_3OH], 563 (12) [M++Na].