Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 4989–4992

TETRAHEDRON LETTERS

Total synthesis of (+)-crocacin A

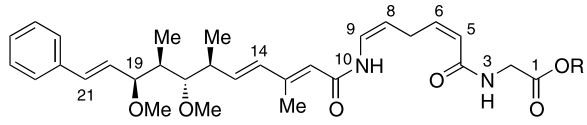
Tushar K. Chakraborty* and Pasunoori Laxman

Indian Institute of Chemical Technology, Hyderabad 500 007, India

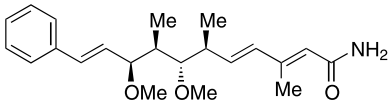
Received 31 March 2003; revised 1 May 2003; accepted 9 May 2003

Abstract—Total synthesis of the potent antifungal and cytotoxic agent (+)-crocacin A is described. The crucial (*Z*)-5,6-enoic amide moiety in this molecule was built by stereoselective partial reduction of a skipped diyne precursor. The diene, thus obtained, was transformed into a silyl epoxide that was regioselectively opened with an azide ion to furnish an α-azido-β-hydroxyalkylsilane intermediate. Peterson elimination of this β-hydroxysilane component in the final step resulted in the formation of the (*Z*)-8,9-enamide moiety of the molecule leading to a successful completion of its total synthesis.

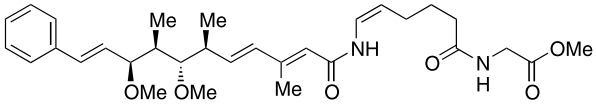
Crocacins A–D (**1**–**4**) were isolated from the myxobacterial strains of *Chondromyces crocatus* (crocacins A–C) and *Chondromyces pediculatus* (crocacin D).[1,2] The wide ranging biological activities of crocacins[1–3] have attracted the attention of synthetic chemists.[4] While the synthesis of crocacins C **3** and D **4** have already been achieved by us and others,[4] the much awaited total synthesis of the other members of the family, namely crocacins A **1** and B **2**, remained elusive due to the presence of a synthetically challenging 6-aminohexadienoic acid with a skipped (*Z*,*Z*)-'1,4-diene' moiety in these molecules. The 'right half' of this diene is composed of a conjugated (*Z*)-enoic amide unit, while the 'left half' carries an equally challenging (*Z*)-enamide fragment. In this paper, we describe a novel strategy for the stereoselective construction of this crucial diene segment based on the following key reactions: (a) a P-2 Ni-assisted stereoselective partial reduction[5] of an appropriate skipped diyne precursor[6] to build the corresponding (*Z*,*Z*)-diene intermediate that eventually led to the synthesis of the desired (*Z*)-5,6-enoic amide moiety; (b) selective epoxidation of the (*Z*)-vinylsilane in the 'left' terminal of the aforesaid diene intermediate using *m*CPBA; (c) regioselective opening of the silyl-substituted epoxide with an azide ion, based on work carried out by us and others earlier;[7] and (d) subjection of the resulting β-hydroxysilane to a Peterson elimination reaction[8] in the final stage to furnish selectively the crucial (*Z*)-8,9-enamide moiety,[9] culminating in the total syntheses of (+)-crocacin A **1**.



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



3: crocacin C



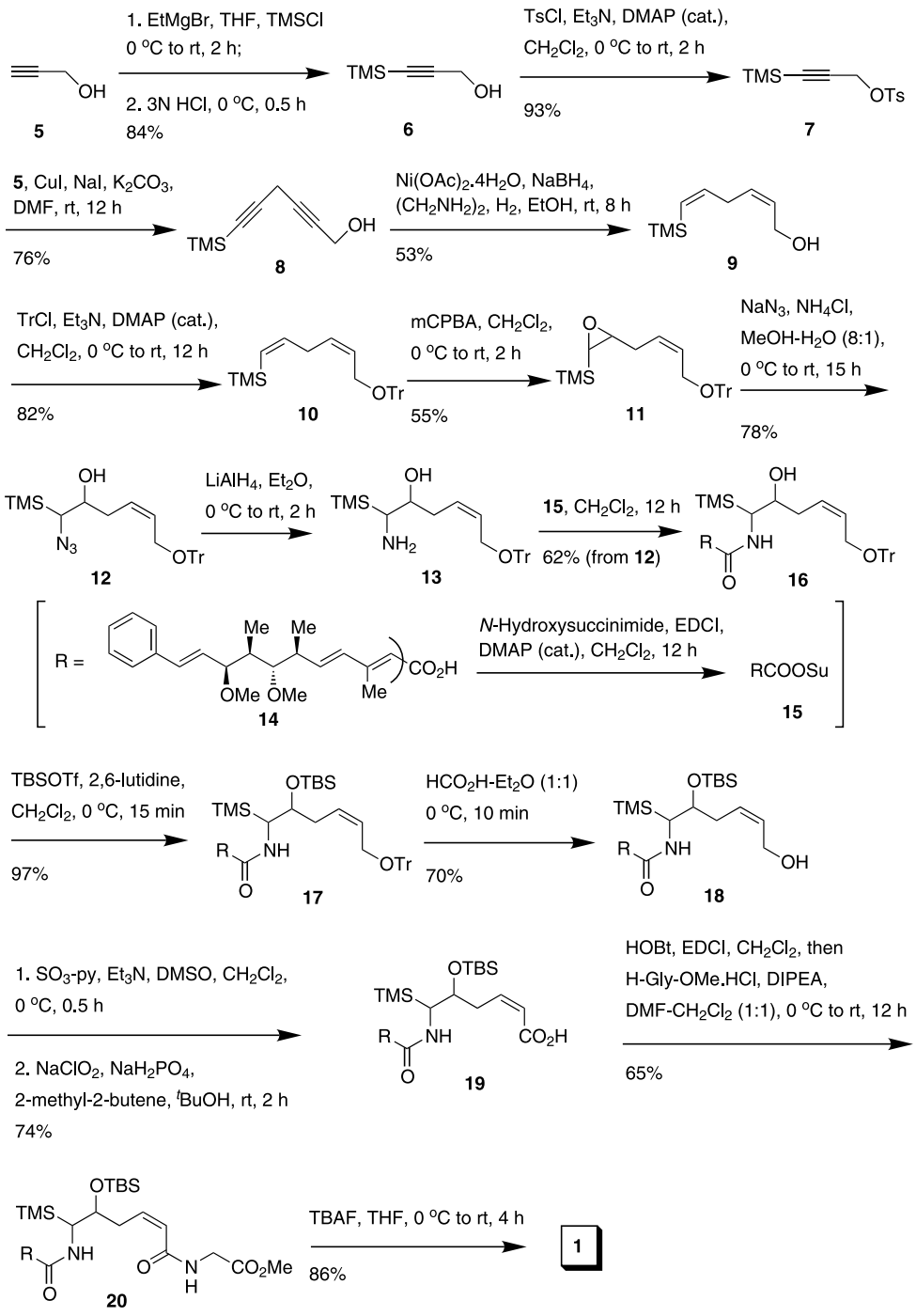
4: crocacin D

The synthesis was started from propargyl alcohol **5** (Scheme 1) which was transformed into a silylated-acetylenic product **6** in two steps in 84% overall yield, (a) reaction of the dianion of **5**, prepared by using the Grignard reagent EtMgBr, with trimethylsilyl chloride (TMSCl) to give a disilylated intermediate, and (b) selective deprotection of the *O*-silyl group under acid-catalyzed conditions to furnish **6**. The primary hydroxyl group of **6** was protected as the tosylate to give **7** in 93% yield. Next, the propargylic tosylate **7** was coupled with the 1-alkyne unit **5** in a copper-mediated reaction[6] that provided the requisite skipped diyne **8** in 76% yield. Stereoselective partial reduction of the diyne **8** using P-2 Ni[5,6] led to the formation of the skipped diene **9** as the major product in 53% yield. As the reduction of the silyl-acetylenic moiety was slower in

Keywords: antifungal; cytotoxin; aldol reaction; Peterson olefination; enamide; crocacin.

* Corresponding author. Fax: +91-40-27160387, 27160757; e-mail: chakraborty@iict.ap.nic.in

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01171-7



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

comparison to that of the propargylic alcohol end, complete reduction of the latter to a single bond, to some extent, could not be avoided. However, this minor side-product was easily separated chromatographically.

With the skipped diene **9** in hand, attempts were made to selectively epoxidize the vinyl silane moiety of the molecule. However, reaction of **9** with *m*CPBA resulted in epoxidation of the allyl alcohol with almost no trace of the required silyl epoxide. After many trials and errors, it was found that increasing steric hindrance at one end of the molecule could enhance the extent of epoxidation at the other terminal. Thus, protection of the allylic hydroxyl with a bulky protecting group forced the *m*CPBA to react preferentially at the other end giving the required silyl epoxide as the major product. The trityl group emerged as the best choice for protecting the hydroxyl function of **9** to facilitate this preferential epoxidation of the silyl-substituted olefin. Reaction of **9** with TrCl in the presence of Et_3N as base and a catalytic amount of DMAP in CH_2Cl_2 furnished the trityl ether **10** in 82% yield. Compound **10** was epoxidized with *m*CPBA to give **11** as the major product in 55% yield after separating the minor side-

products which included the di-epoxide and also a small amount of the other epoxide by chromatography.

As expected, treatment of **11** 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 **12** in 78% yield.[7a,b] Attempted elongation of the allyl alcohol terminal at this stage by trityl deprotection, oxidation of the primary hydroxyl group to the acid via an aldehyde and coupling with H-Gly-OMe, resulted in an intramolecular 1,3-dipolar cycloaddition reaction between the azido group and the 'activated ene' at the aldehyde stage to give an unwanted triazoline compound. It was, therefore, decided first to functionalize the azido terminal of **12** to attach the C11–C27 residue, leaving the extension of the right hand side to be carried out at a later stage.

Accordingly, the azido group of **12** was selectively reduced to the amine **13** using $LiAlH_4$[7d] and after aqueous work-up, the product was coupled directly with the known acid **14** that was earlier prepared by us during the synthesis of crocacin C.[4c,e] Treatment of **14** with *N*-hydroxysuccinimide using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI) and a catalytic amount of DMAP furnished an active ester **15**, which was reacted with the amine **13** in CH_2Cl_2 for 12 h. After the usual aqueous work-up, chromatographic purification gave the expected amide **16** in 62% yield (from **12**). Protection of the secondary hydroxyl as the *tert*-butyldimethylsilyl (TBS) ether furnished compound **17** in 97% yield. This was followed by deprotection of the trityl-protected primary hydroxyl to give the (*Z*)-allylic alcohol **18** in 70% yield.

A two-step oxidation process transformed **18** into the acid **19** in 74% yield. The acid **19** was reacted successfully with glycine methyl ester using 1-hydroxybenzotriazole (HOBt) and EDCI as coupling reagents to furnish the expected product **20** in 65% yield. Finally, deprotection of the TBS group of **20** 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 86% 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 our target molecule, crocacin A **1**. Our synthetic crocacin A **1** showed rotation $[\alpha]_D^{20} = +106.3$ (*c* 0.08, MeOH); lit. value: $[\alpha]_D^{22} = +109.6$ (*c* 1, MeOH).[2] It was identical in all respects with naturally occurring crocacin A having all spectroscopic data[10] matching those reported for the natural product.[2] Further work is in progress.[11]

Acknowledgements

The authors wish to thank Drs. A. C. Kunwar and M. Vairamani for NMR and mass spectroscopic assistance, respectively and CSIR, New Delhi for a research fellowship (P.L.).

References

1. Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot*. **1998**, *51*, 1075–1080.
2. Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem*. **1999**, 1085–1089.
3. Kunze, B.; Jansen, R.; Höfle, G.; Reichenbach, H. *J. Antibiot*. **1994**, *47*, 881–886.
4. (a) Chakraborty, T. K.; Laxman, P. *Tetrahedron Lett*. **2002**, *43*, 2645–2648; (b) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett*. **2002**, *4*, 525–527; (c) Chakraborty, T. K.; Jayaprakash, S.; Laxman, P. *Tetrahedron* **2001**, *57*, 9461–9467; (d) Dias, L. C.; de Oliveira, L. G. *Org. Lett*. **2001**, *3*, 3951–3954; (e) Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett*. **2001**, *42*, 497–499; (f) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett*. **2000**, *2*, 3365–3367.
5. (a) Brown, C. A.; Ahuja, V. K. *J. Org. Chem*. **1973**, *38*, 2226; (b) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun*. **1973**, 553.
6. For some useful references on skipped diynes and dienes, see: (a) Guiard, S.; Santelli, M.; Parrain, J.-L. *Tetrahedron Lett*. **2002**, *43*, 8099–8101. (b) Durand, S.; Parrain, J.-L.; Santelli, M. *Synthesis* **1998**, 1015–1018. (c) Jeffery, T.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron Lett*. **1992**, *22*, 5757–5760.
7. (a) Chakraborty, T. K.; Reddy, G. V. *Tetrahedron Lett*. **1991**, *32*, 679–682; (b) Chakraborty, T. K.; Reddy, G. V. *Tetrahedron Lett*. **1990**, *31*, 1335–1338; (c) Tomoda, S.; Matsumoto, Y.; Takeuchi, Y.; Nomura, Y. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 3283–3284; (d) Tomoda, S.; Matsumoto, Y.; Takeuchi, Y.; Nomura, Y. *Chem. Lett*. **1986**, 1193–1196.
8. (a) Ager, D. J. *Org. React*. **1990**, *38*, 1–223; (b) Ager, D. J. *Synthesis* **1984**, 384–398; (c) Hudrlick, P. F.; Peterson, D.; Rona, R. *J. Org. Chem*. **1975**, *40*, 2263–2264; (d) Hudrlick, P. F.; Peterson, D. *J. Am. Chem. Soc*. **1975**, *97*, 1464–1468.
9. For earlier work on the synthesis of enamides, see: (a) Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett*. **2001**, *3*, 3955–3957; (b) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett*. **2001**, *42*, 1217–1220; (c) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett*. **2000**, *41*, 3735–3738; (d) Shen, R.; Porco, J. A., Jr. *Org. Lett*. **2000**, *2*, 1333–1336; (e) Snider, B. B.; Song, F. *Org. Lett*. **2000**, *2*, 407–408; (f) Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397–399; (g) Brettle, R.; Mosedal, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2185–2195; (h) Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc*. **1977**, *99*, 1993–1996.
10. Selected physical data for **1**. $R_f = 0.4$ (silica, 50% EtOAc in petroleum ether); $[\alpha]_D^{20} = +106.3$ (*c* 0.08, MeOH); IR (neat): ν_{max} 3255, 2933, 2831, 1757, 1655, 1521, 1451, 1263, 1121, 980 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz, TMS as reference): δ 10.03 (d, $J = 10.75$ Hz, 1H, N10-*H*), 7.95 (t, $J = 5.5$ Hz, 1H, N3-*H*), 7.45 (d, $J = 8.0$ Hz, 2H, aromatic *ortho*-protons), 7.30 (dd, $J = 8.0$, 7.4 Hz, 2H, aromatic *meta*-protons), 7.22 (t, $J = 7.4$ Hz, 1H, aromatic *para*-proton), 6.82 (ddt, $J = 10.75$, 8.6, 1.5 Hz, 1H, C9-*H*), 6.58 (d, $J = 16.1$ Hz, 1H, C21-*H*), 6.24 (dd, $J = 16.1$, 6.8 Hz, 1H, C20-*H*), 6.18 (d, $J = 16.1$ Hz, 1H, C14-*H*), 6.13 (dd, $J = 16.1$, 8.3 Hz, 1H, C15-*H*), 6.05 (dt, $J = 11.2$,

8.3 Hz, 1H, C6-*H*), 5.95 (d, $J=11.2$ Hz, 1H, C5-*H*), 5.82 (br d, $J=1.0$ Hz, 1H, C12-*H*), 4.77 (q, $J=8.6$ Hz, 1H, C8-*H*), 4.07 (m, 3H, C2-H_2, C19-*H*), 3.68 (s, 3H, C1-OCH_3), 3.52 (s, 3H, C17-OCH_3), 3.32 (m, 2H, C7-H_2), 3.29 (s, 3H, C19-OCH_3), 3.19 (dd, $J=9.5$, 2.3 Hz, 1H, C17-*H*), 2.62 (m, 1H, C16-*H*), 2.26 (d, $J=1.0$ Hz, 3H, C13-CH_3), 1.57 (m, 1H, C18-*H*), 1.18 (d, $J=7.1$ Hz, 3H, C16-CH_3), 0.84 (d, $J=6.8$ Hz, 3H, C18-CH_3); MS (LSIMS): m/z: 507 [M^++H−CH_3OH], 539 [M^++H].

11. Attempted synthesis of crocacin B **2** from crocacin A **1**, an apparently trivial step, by saponification using LiOH in THF–MeOH–H_2O system gave an unexpected cyclized product. The product, which is yet to be characterized fully, was possibly formed by an intramolecular nucleophilic attack on the 8,9-enamide moiety by the carboxylate anion as the signals of the 8,9-olefin protons were missing in its ^{1}H NMR spectrum along with a large shift in the 10-NH chemical shift. This necessitated devising an alternate strategy to synthesize crocacin B **2**, which will be reported in due course.