Tetrahedron Letters 53 (2012) 2114-2116

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet



Formal synthesis of (+)-crocacin C

Adele E. Pasqua^a, Frank D. Ferrari^a, James J. Crawford^b, Rodolfo Marquez^{a,*,†}

^a WestCHEM School of Chemistry, University of Glasgow, Glasgow G12 8QQ, UK ^b Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA

ARTICLE INFO

ABSTRACT

Article history: Received 21 December 2011 Revised 1 February 2012 Accepted 10 February 2012 Available online 18 February 2012

Keywords: Crocacins Formal synthesis Overman rearrangement The formal synthesis of (+)-crocacin C is reported. The approach described takes advantage of a highly regioselective epoxide cuprate addition and a diastereoselective Overman rearrangement. The synthesis is practical and amenable to scale up.

© 2012 Elsevier Ltd. All rights reserved.

The crocacins are a family of four antifungal and cytotoxic antibiotics isolated by Höfle and co-workers from two different strains of *Chondromyces* bacteria, which exhibit a wide range of biological activities.¹ Whilst crocacin A is only a moderate inhibitor of Gram positive bacteria, it has shown remarkable activity as a growth inhibitor of fungi and yeasts through inhibition of the electron flow within the cytochrome bc_1 segment (complex III) of the respiratory chain.¹ Additionally, crocacin D has shown a MIC of 1.4 ng/mL against *Saccharomyces cerevisiae* and an IC₅₀ of 60 µg/mL towards L929 mouse fibroblast cell cultures.



Structurally, crocacins A, B and D are unusual linear dipeptides incorporating glycine and a 6-aminohexenoic or 6-aminohexadie-

* Corresponding author. Tel.: +44 141 330 5953; fax: +44 141 330 4888.

E-mail addresses: rudi.marquez@glasgow.ac.uk, r.marquez@chem.gla.ac.uk

[†] Ian Sword Reader of Organic Chemistry.

0040-4039/\$ - see front matter \circledast 2012 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2012.02.049

noic acid, the nitrogen of which is protected by a complex polyketide derived acyl residue. Crocacin C is the free carboxamide common to all three of the other crocacins.

Crocacins A, B and D possess a highly reactive enamide unit, which is crucial for their biological activity. Mechanistically, it has been postulated that the enamide unit undergoes protonation and the resulting *N*-acyliminium ion is then subjected to nucleophilic attack to generate the enzyme conjugate required for activity.²

The promising biological activity of the crocacins together with their low natural abundance and interesting structural features, has made them attractive synthetic targets, and a number of formal and total syntheses have been reported.^{3–8}

As part of our efforts towards the synthesis of the crocacins, we envisioned accessing crocacin, A, B and D via crocacin C, using the imide olefination methodology recently developed in our group.⁹ In turn, crocacin C could be prepared using a modular approach in which the dienoate ester and the phenyl substituted alkene are incorporated by means of a Horner–Wadsworth–Emmons olefination and an Overman rearrangement, respectively (Scheme 1).

Our synthesis of (+)-crocacin C began with Roche ester **1**, which was silylated and the resulting ester **2** converted into the corresponding aldehyde **3** through a reduction-oxidation sequence. Olefination of aldehyde **3** yielded the desired *E*-ethyl enoate **4** as a single double bond isomer as determined by ¹H NMR analysis (Scheme 2).

Reduction of ester **4** afforded alkenol **5** which was then epoxidised under reagent-controlled conditions in excellent yield and with high diastereoselectivity to yield the *syn*-epoxy-alcohol **6** as an inseparable (95:5) mixture of diastereomers. Cuprate opening of the epoxy-alcohol mixture under Nakamura's conditions¹⁰ yielded the desired 1,3-diol **7** together with trace amounts of the 1,2-diol side product **8**. Treatment of the diastereomeric mixture



⁽R. Marquez).



Scheme 1. Crocacins' retrosyntheses.



Scheme 2. Synthesis of mono-protected triol 7.

with sodium periodate oxidised the 1,2-diol side product to the corresponding aldehyde which could be separated by flash column chromatography (Scheme 2).

The diastereomerically pure 1,3-diol **7** was selectively benzylated, and the resulting secondary alcohol **9** then methylated, to afford the differentially protected triol **10**. Desilylation of ether **10** yielded the free primary alcohol **11**, which was oxidised to produce aldehyde **12** in an excellent yield. Olefination of aldehyde **12** with the stabilised phosphorane **13**¹¹ gave the desired enone **14** as a single double bond isomer (Scheme 3).

With enone **14** in hand, the key Overman rearrangement was explored. Corey–Bakshi–Shibata reduction¹² of enone **14** afforded a 1.1:1 mixture of diastereoisomers that was separable by flash column chromatography. The desired allylic alcohol **15a** was acety-lated to afford the rearrangement precursor **16**, which upon treatment with PdCl₂(CH₃CN)₂ under Overman conditions¹³ cleanly transposed the acetate group to generate the *syn:anti:anti* adduct **17** in quantitative yield and as a single diastereomer. Removal of the acetate group followed by methylation of the resulting alcohol **18** afforded the core of (+)-crocacin C in an excellent yield (Scheme 4).

Selective hydrogenolysis of the benzyl group followed by oxidation of the resulting primary alcohol afforded the corresponding aldehyde intermediate. Stereoselective olefination under Horner– Wadsworth–Emmons conditions using phosphonoacetate **20**¹⁴ completed the formal synthesis of (+)-crocacin C. The spectral data and optical rotation of dienoate ester **21** matched those reported by Chakraborty and co-workers for the same advanced intermediate during their synthesis of (+)-crocacin C.⁴



Scheme 3. Synthesis of enone 14.



Scheme 4. Formal synthesis of (+)-crocacin C.

In conclusion, we have completed a formal synthesis of (+)crocacin C,¹⁵ taking advantage of a highly regioselective epoxide cuprate addition and of a diastereoselective Overman rearrangement. The synthesis is practical and amenable to scale up. We are currently in the process of expanding this approach to the synthesis of new crocacin analogues.

Acknowledgements

We would like to thank Dr. Ian Sword for postgraduate support (A.E.P.). The authors also thank Dr. Ian Sword and the EPSRC for funding.

References and notes

- 1. Kunze, B.; Jansen, R.; Höfle, G.; Reichenbach, H. J. Antibiot. 1994, 47, 881-886.
- (a) Crowley, P. J.; Berry, E. A.; Cromartie, T.; Daldal, F.; Godfrey, C. R. A.; Lee, D.-W.; Phillips, J. E.; Taylor, A.; Viner, R. *Bioorg. Med. Chem.* **2008**, *16*, 10345–10355; (b) Crowley, P. J.; Godfrey, C. R. A.; Viner, R. In ACS Symposium Series—Synthesis and Chemistry of Agrochemicals, 2007; Vol. 948, pp 93–103; c) Crowley, P. J.;

Aspinall, I. H.; Gillen, K.; Godfrey, C. R. A.; Devillers, I. M.; Munns, G. R.; Sageot, O. A.; Swanborough, J.; Worthington, P. A.; Williams, J. Chimia 2003, 57, 685–691;
(d) Nising, C. F.; Hillebrand, S.; Rodefeld, L. Chem. Commun. 2011, 47, 4062–4073.

- (a) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. Org. Lett. 2000, 2, 3365–3367; (b) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. Org. Lett. 2002, 4, 525–527; (c) Feutrill, J. T.; Rizzacasa, M. A. Aust. J. Chem. 2003, 56, 783–785; (d) Feutrill, J. T.; Lilly, M. J.; White, J. M.; Rizzacasa, M. A. Tetrahedron 2008, 64, 4880–4895.
- (a) Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett.* **2001**, 42, 497–499; (b) Chakraborty, T. K.; Jayaprakash, S.; Laxman, P. *Tetrahedron* **2001**, 57, 9461– 9467.
- (a) Dias, L. C.; de Oliveira, L. G. Org. Lett. 2001, 3, 3951–3954; (b) Dias, L. C.; de Oliveira, L. G.; Vilcachagua, J. D.; Nigsch, F. J. Org. Chem. 2005, 70, 2225–2234.
- (a) Sirasani, G.; Paul, T.; Andrade, R. B. J. Org. Chem. 2008, 73, 6386–6388; (b) Sirasani, G.; Paul, T.; Andrade, R. B. Bioorg. Med. Chem. 2010, 18, 3648–3655; (c) Andrade, R. B. Org. Prep. Proced. Int. 2009, 41, 359–383.
- Beşev, M.; Brehm, C.; Fürstner, A. Collect. Czech. Chem. Commun. 2005, 70, 1696– 1708.
- Candy, M.; Audran, G.; Bienayme, H.; Bressy, C.; Pons, J.-M. J. Org. Chem. 2010, 75, 1354–1359.
- (a) Villa, M. V. J.; Targett, S. M.; Barnes, J. C.; Whittingham, W. G.; Marquez, R. Org. Lett. 2007, 9, 1631–1633; (b) Mathieson, J. E.; Crawford, J. J.; Schmidtmann, M.; Marquez, R. Org. Biomol. Chem. 2009, 7, 2170–2175; (c) Pasqua, A. E.; Crawford, J. J.; Marquez, R. Tetrahedron 2011, 67, 7611–7617; (d) Sewell, A. L.; Villa, M. V. J.; Matheson, M.; Whittingham, W. G.; Marquez, R. Org. Lett. 2011, 13, 800–803.
- 10. Nakamura, R.; Tanino, K.; Masaaki, M. Org. Lett. 2003, 5, 3579-3582.
- Babu, K. S.; Li, X.-C.; Jacob, M. R.; Zhang, Q.; Khan, S. I.; Ferreira, D.; Clark, A. M. J. Med. Chem. 2006, 49, 7877-7886.
- 12. Kawai, N.; Mahadeo, S.; Uenishi, J. Tetrahedron 2007, 63, 9049–9056.
- (a) Anderson, C. E.; Overman, L. E.; Watson, M. P. Org. Synth. 2005, 82, 134; (b) Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. J. Am. Chem. Soc. 1980, 102, 7587–7588.
- 14. Mata, E. G.; Thomas, E. J. J. Chem. Soc., Perkin Trans. 1 1995, 785-799.
- Spectroscopic data for representative compounds: (4*S*,2*E*)-*Ethyl* 5-(*tert-butyldiphenylsilyloxy*)-4-*methylpent-2-enoate*, (4). ¹H NMR (400 MHz; CDCl₃): δ_H 7.66-7.56 (4H, m), 7.43-7.30 (6H, m), 6.91 (1H, dd, *J* = 15.8, 7.5 Hz), 5.80 (1H, dd, *J* = 15.8, 1.5 Hz), 4.17 (2H, q, *J* = 7.1 Hz), 3.60-3.53 (2H, m), 2.61-2.42 (1H, m), 1.29 (3H, t, *J* = 7.0 Hz), 1.12 (3H, d, *J* = 6.7 Hz), 1.01 (9H, s). ¹³C NMR

 $\begin{array}{l} (100 \text{ MHz; CDCl}_3): \delta_{C} \ 166.7, \ 152.8, \ 135.9, \ 133.6, \ 130.0, \ 127.9, \ 121.5, \ 67.6, \ 60.2, \\ 39.1, \ 26.9, \ 19.2, \ 16.6, \ 14.3, \ IR \ (neat): \ \nu \ 3416, \ 2961, \ 2859, \ 1717, \ 1653, \ 1472, \\ 1427, \ 1368, \ 1267, \ 1182, \ 1111, \ 1094, \ 1034, \ 982, \ 824, \ 802, \ 741, \ 700, \ 689, \\ 613 \ cm^{-1}, \ HRMS \ (isobutane, \ Cl+): \ found \ (M+H)^{*} \ 397.2203, \ C_{24}H_{33}O_{3}Si \ requires \\ 397.2190, \ [\alpha]_{D}^{24} - 10.40 \ (c \ 1.0, \ CHCl_{3}). \\ \begin{array}{c} ((2R,3R)-3-[(R)-1-(tert-Butyldiphenylsilyloxy)propan-2-yl]oxiran-2-yl]oxiran-2-yl]methanol, \\ \end{array}$

{(2R,3R)-3-{(R)-1-(tert-Butyldiphenylsilyloxy)propan-2-yl]methanol, (6). ¹H NMR (400 MHz; CDCl₃): δ_{H} 7.66–7.58 (4H, m), 7.42–7.28 (6H, m), 3.95 (1H, ddd, J = 17.8, 12.4, 5.3 Hz), 3.78–3.61 (3H, m), 3.19 (2H, d, J = 2.4 Hz), 1.81– 1.68 (2H, m), 1.10 (9H, s), 1.02 (3H, d, J = 6.0 Hz). ¹³C NMR (100 MHz; CDCl₃): δ_{C} 135.6, 133.6, 129.8, 127.8, 65.9, 61.9, 57.5, 56.9, 37.8, 26.9, 19.4, 12.9. IR (neat): ν 3429, 2961, 2858, 1472, 1427, 1111, 1007, 824, 739, 699, 690, 614 cm⁻¹. HRMS (isobutane, Cl+): found (M+H)^{*} 371.2052, C₂₂H₃₁O₃Si requires 371.2042. [$M_{12}^{25} - 9.60$ (c 0.125, CHCl₃).

(2R, 3R, 4S)-5-(Benzyloxy)-3-methoxy-2,4-dimethylpentan-1-ol, (**11**). ¹H NMR (400 MHz; CDCl₃): $\delta_{\rm H}$ 7.41–7.32 (5H, m), 4.50 (2H, s), 3.75 (1H, dd, *J* = 9.6, 4.4 Hz), 3.65–3.45 (4H, m), 3.38 (3H, s), 2.93 (1H, t, *J* = 6.4 Hz), 2.05–1.82 (2H, m), 0.80 (6H, m). ¹³C NMR (100 MHz; CDCl₃): $\delta_{\rm C}$ 138.6, 128.4, 127.9, 127.5, 89.1, 73.1, 72.2, 65.6, 61.1, 37.4, 36.4, 15.1, 14.6. IR (neat): ν 3433, 2924, 1458, 1366, 1088, 1026, 978, 903, 741, 694 cm⁻¹. HRMS (isobutane, Cl+): found (M+H)* 253.1805, C₁₅H₂₅O₃ requires 253.1804. [$\alpha_{\rm L}^{\rm 25}$ +3.20 (c 1.0, CHCl₃).

(25,35,4R,55,6E)-3,5-Dimethoxy-2,4-dimethyl-7-phenylhept-6-en-1-ol. ¹H NMR (500 MHz; CDCl₃): $\delta_{\rm H}$ 7.42–7.40 (2H, m), 7.36–7.31 (2H, m), 7.27–7.23 (1H, m), 6.58 (1H, d, *J* = 15.9 Hz), 6.19 (1H, dd, *J* = 16.0, 7.3 Hz), 4.07 (1H, ddd, *J* = 7.3, 2.7, 0.9 Hz), 3.87–3.82 (1H, m), 3.56–3.52 (1H, m), 3.54 (3H, s), 3.32 (3H, s), 3.29 (1H, dd, *J* = 2.3, 9.0 Hz), 2.89 (1H, dd, *J* = 7.4, 2.4 Hz), 1.91–1.84 (2H, m), 1.21 (3H, d, *J* = 7.3 Hz), 0.91 (3H, d, *J* = 7.3 Hz). ¹³C NMR (125 MHz; CDCl₃): $\delta_{\rm C}$ 136.9, 132.4, 129.5, 128.8, 127.8, 126.6, 88.6, 81.3, 64.7, 61.8, 56.5, 42.5, 35.9, 16.4, 10.5. IR (neat) v 3366, 2972, 2924, 2824, 1495, 1451, 1089 cm⁻¹. [α]²D⁰ –4.28 (c 1.0, CHCl₃).