Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5593–5595
Tetrahedron Letters

Stereoselective synthesis of the enantiomer of the key fragment of crocacin ☆

Sadagopan Raghavan* and S. Ramakrishna Reddy

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

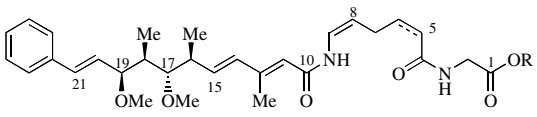
Received 21 April 2004; accepted 27 May 2004

Abstract—A novel, stereoselective synthesis of the enantiomer of alcohol **5** is disclosed. The key steps of the synthesis include mercuric trifluoroacetate promoted regio- and stereoselective hydration of an α,β-unsaturated ester, Frater-alkylation and use of morpholine derived amide for acylation.
© 2004 Elsevier Ltd. All rights reserved.

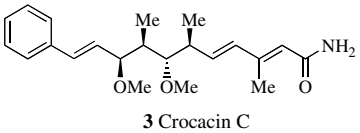
Crocacins A–D **1**–**4**, isolated from myxobacteria *Chondromyces crocatus* and *C. pediculatus*[1] possess antibacterial, antifungal and cytotoxic activity. Crocacins possess four contiguous chiral centres flanked by two *trans* double bonds in addition to a trisubstituted and *cis* double bonds. Their novel architecture and biological activity has attracted the attention of synthetic chemists and stereoselective routes to crocacin C,[2] crocacin D[3] and crocacin A[4] have been described. An advanced common intermediate for the synthesis of all the crocacins is the alcohol **5**, the synthesis of which was also disclosed recently.[5] We describe herein a stereoselective synthesis of the enantiomer **6** of alcohol **5** with the (2*R*,3*R*,4*S*,5*R*) configuration.

By a retrosynthetic analysis (Scheme 1) we envisaged alcohol **6** to be elaborated from the unsaturated ketone **7**, which in turn could be prepared from the amide **8** by acylation. The amide **8** could be traced back to the hydroxy ester **9**, which could be derived from the (*Z*)- or (*E*)-α,β-unsaturated ester **10** or **11**, respectively.

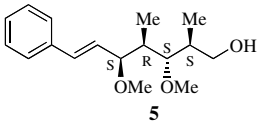
The aldehyde **12**[6] can be readily transformed into the (*Z*)-[6] and (*E*)-esters[7] in high yield. The hydroxy ester **9** can be prepared from **10** in two steps as described earlier.[6] This would warrant the use of toxic *n*-Bu_3SnH for debromination. To avoid the use of *n*-Bu_3SnH, reagents other than NBS were contemplated for the electrophile promoted functionalisation of esters **10** and **11**. In the event, treatment of ester **11** with mercuric trifluoroacetate in the presence of water in toluene, afforded the hydroxy ester **9** after demercuration of the organomercurial with $NaBH_4$.[8] This constitutes the first report on the heterofunctionalisation of an alkene mediated by



1 Crocacin A; R = Me; C5-C6 = double bond
2 Crocacin B; R = H; C5-C6 = double bond
4 Cocacin D; R = Me; C5-C6 = single bond



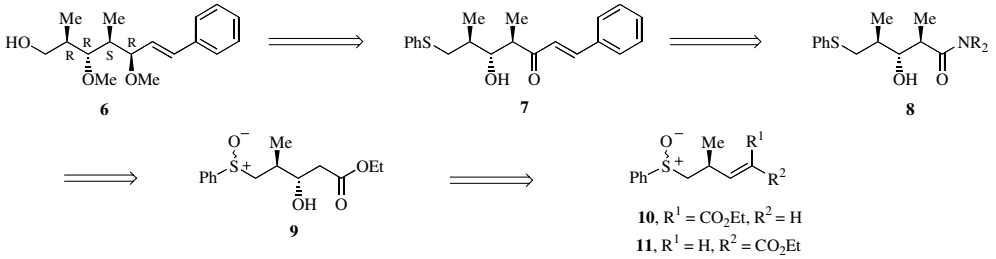
3 Crocacin C



5

Keywords: Crocacin; Mercuric trifluoroacetate; Frater-alkylation.
☆ IICT Communication No. 040321.
* Corresponding author. Tel.: +91-(0)-4027160123; fax: +91-(0)-4027160512; e-mail: purush101@yahoo.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.130

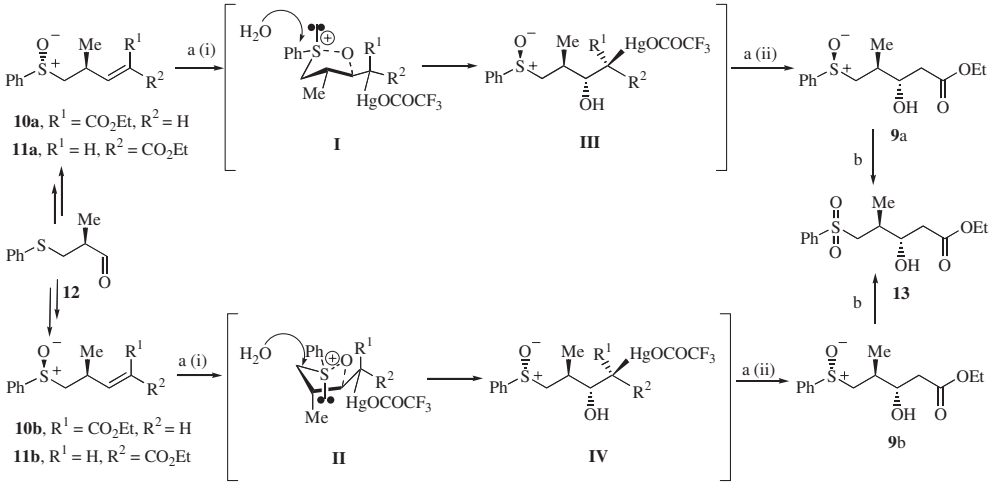


Scheme 1.

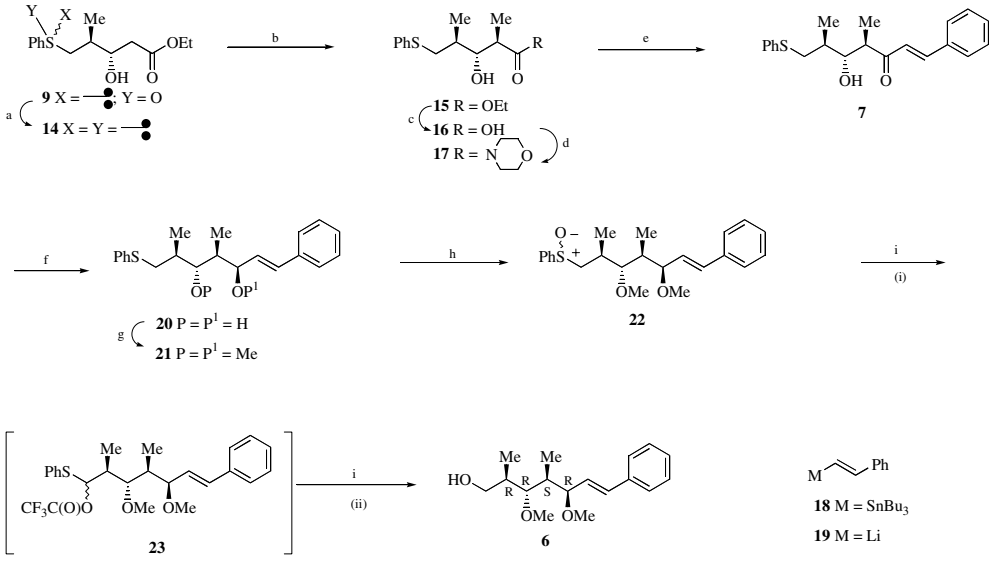
mercuric trifluoroacetate via intramolecular sulfinyl group participation. The inseparable mixture of epimeric sulfoxides **9** yielded sulfone **13** on oxidation with *m*-CPBA, the ^{1}H NMR spectrum of which revealed the presence of stereomers in a 18:1 ratio. The (*Z*)-ester **10** reacted under identical conditions to yield the products in the same ratio. The reaction can be envisaged to proceed via intermediates **I** and **II**[9] to afford the organomercurials **III** and **IV**, which on demercuration would yield the products (Scheme 2). The intermediate **II** with an axially disposed Me group would probably explain the erosion of stereoselectivity. The ester **11** was chosen as the starting material since it can be more readily prepared from aldehyde **12** than ester **10**.

The C4 methyl group of crocacin was envisaged to be introduced by Frater-alkylation.[10] To avoid alkylation at C1 the sulfinyl group in **9** was reduced by treatment with $TiCl_3$[11] to yield the sulfide **14**.[12] Treatment of the dianion of **14**, derived by treatment with LDA, with methyl iodide yielded compound **15** and its stereomer (not depicted) in a 4:1 ratio, respectively.[13] This mixture was taken ahead with the hope of removing the undesired stereomer at a later stage in the synthesis. Compound **15** on mild hydrolysis by treatment with aq LiOH yielded the acid **16**, which was converted to the amide **17** by treatment with morpholine and diisopropyl carbodiimide (DIC). Treatment of **17** with vinyl lithium **19** generated from the unsaturated stannane **18**,[14] yielded the unsaturated ketone **7**.[15] Hydroxy group directed reduction of **7** with $Me_4N(OAc)_3BH$[16] yielded the *anti* diol **20** cleanly.[17] The structure assigned to **20** was based on literature precedent and was proven by its elaboration to **6**. Thus treatment of **20** with NaHMDS and methyl iodide yielded the dimethoxy derivative **21**. Oxidation of sulfide **21** with $NaIO_4$[18] yielded an epimeric mixture of sulfoxides **22** in nearly equimolar amounts. Sulfoxide **22** on treatment with TFAA and Et_3N underwent Pummerer rearrangement to yield intermediate **23**, which without isolation was subjected to hydrolysis followed by reduction to yield the alcohol **6**, which had physical characteristics in excellent agreement to those reported in the literature for **5** except for the sign of rotation, $[\alpha]_D^{25}$ +6.0 (*c* 0.5, $CHCl_3$), literature[2c] $[\alpha]_D^{25}$ −6.5 (*c* 1, $CHCl_3$) (Scheme 3).

In summary we have described a novel, stereoselective synthesis of the advanced intermediate **6**, which can be elaborated into the enantiomer of crocacins by following earlier reports. The key steps of the synthesis include the use of mercuric trifluoroacetate as the electrophilic partner in the regio- and stereoselective hydration of the ester **11** via intramolecular nucleophilic assistance by the sulfinyl group, Frater-alkylation, use of the morpholine amide for acylation and the Pummerer reaction for the introduction of the hydroxy group. The strategy disclosed is flexible and would permit the preparation of derivatives for structure activity relationship studies by varying the electrophile in the Frater-alkylation step and the nucleophile used for the acylation.



Scheme 2. Reaction conditions: (a) i. $Hg(OCOCF_3)_2$, HgO, toluene, rt, ii. Et_3B, $NaBH_4$, −78 °C to rt, 75%; (b) *m*-CPBA, DCM, rt, 90%.

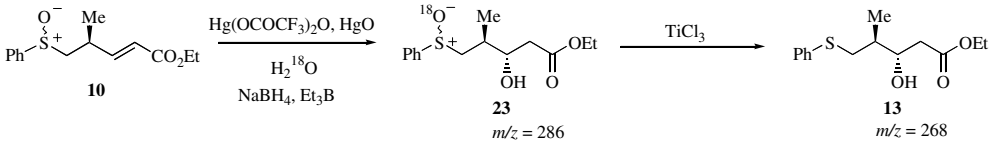


Scheme 3. Reaction conditions: (a) $TiCl_3$, EtOH, rt, 85%; (b) LDA, THF, −78 to −23 °C, MeI, HMPA, −78 to −23 °C, 75%; (c) LiOH, MeOH, THF, 0 °C, 90%; (d) morpholine, DIC, DMAP, DCM, rt, 70%; (e) **18**, *n*-BuLi, THF, −78 °C, 80%; (f) $Me_4NB(OAc)_3H$, CH_3CN, AcOH, rt, 85%; (g) NaHMDS, THF, 0 °C, MeI, 80%; (h) $NaIO_4$, MeOH, THF, rt, 80%; (i) i. TFAA, Et_3N, CH_3CN, rt, ii. aq $NaHCO_3$, $NaBH_4$, 0 °C, 75%.

Acknowledgements

S.R. is thankful to Dr. J. S. Yadav for constant support and encouragement, to Dr. A. C. Kunwar for NMR spectra and Dr. M. Vairamani for the mass spectra. S.R.R. is thankful to CSIR (New Delhi) for the senior research fellowship.

9. Treatment of ester **10** with mercuric trifluoroacetate in the presence of $H_2{}^{18}O$ yielded sulfoxide **23** with (*m*/*z* 286) two units higher than **9** (*m*/*z* 284). Subsequent reduction of the sulfinyl moiety yielded sulfide with the loss of 18 mass units conclusively proving intramolecular sulfinyl group participation.



References and notes

1. (a) Kunze, B.; Jansen, R.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 1075; (b) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **1999**, 1085.
2. (a) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2000**, *2*, 3365; (b) Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett.* **2000**, *42*, 497; (c) Chakraborty, T. K.; Jayaprakash, S.; Laxman, P. *Tetrahedron* **2001**, *57*, 9461; (d) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2001**, *32*, 3951.
3. Chakraborty, T. K.; Laxman, P. *Tetrahedron Lett.* **2003**, *44*, 4989.
4. (a) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2002**, *4*, 525; (b) Chakraborty, T. K.; Laxman, P. *Tetrahedron Lett.* **2002**, *43*, 2645.
5. Gurjar, M. K.; Khaladkar, T. P.; Borhade, R. G.; Murugan, A. *Tetrahedron Lett.* **2003**, *44*, 5183.
6. Raghavan, S.; Tony, K. A. *J. Org. Chem.* **2003**, *68*, 5002.
7. Raghavan, S.; Tony, K. A. *Tetrahedron Lett.* **2004**, *45*, 2639.
8. Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, *39*, 59.

Also while **9** showed a peak at 126 mass units corresponding to $[PhSOH]^+$ fragment in its mass spectrum, **23** showed a peak at 128 mass units.

10. (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825; (b) Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269.
11. Takahashi, T.; Iyobe, A.; Arai, Y.; Koizumi, T. *Synthesis* **1989**, 189.
12. After column chromatography of the crude product mixture, **13** was obtained pure without any trace of the stereoisomer.
13. The structure was assigned to the major product based on literature precedent, which was confirmed by the synthesis of **5**.
14. Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634.
15. Martin, R.; Romea, P.; Tey, C.; Urpi, F.; Vilarrasa, J. *Synlett* **1997**, 1414.
16. Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.
17. The minor stereomer from the Frater-alkylation reaction could be conveniently removed by purification by column chromatography.
18. Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282.