Tetrahedron Letters 53 (2012) 4087–4089

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Stereoselective synthesis of the common polyketide fragment of hoiamides

M. Seenaiah, S. Chandrasekhar *

Division of Natural Products Chemistry, CSIR—Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 14 April 2012
Revised 21 May 2012
Accepted 23 May 2012
Available online 29 May 2012

Keywords:
Hoiamide
Polyketides
Crimmins aldol
Wittig olefination

ABSTRACT

Stereoselective synthesis of the polyketide fragment commonly present in hoiamide A, B, and C is described using iterative Crimmins aldol reaction as the key reaction.

Hoiamides, a new class of marine natural products which are isolated from cyanobacteria collected in Papua New Guinea and their structures were determined by spectral techniques.[1] This unusual structural complexity must have been derived from peptide–polyketide biogenetic pathway. The structure and stereochemical assignments were made by using extensive NMR studies, chemical degradation methods, and modified Mosher ester analysis (Fig. 1). Hoiamide A and B exhibited sodium influx with EC_{50} values of 1.7 and 3.9 μM, where as hoiamide C showed no significant pharmacological activity in these assays.

The natural products hoiamide A and B are cyclic depsipeptides, whereas hoiamide C is a linear compound. The structural complexity of these molecules includes 15 asymmetric carbons, peptide link, and three thiazole rings. The common structural feature in all three natural products is the polyketide fragment that is C_{30}–C_{40} of hoiamide A, C_{31}–C_{41} of hoiamide B, and C_{21}–C_{31} of hoiamide C. To date there is only one total synthesis of hoiamide C.[2]

In continuation of our work in the synthesis of marine cyclic peptides,[3] we were interested in the synthesis of hoiamides. Herein, we present the synthesis of polyketide fragment of hoiamides. The retrosynthetic analysis showed that the fragment **4** could be derived from thiazolidine system **5**, which in turn is envisioned from Crimmins aldol adduct **6**. The adduct **6** in turn could arise from known 1, -3-diol **7**, which can be obtained from propane-1, -3-diol **8** (Scheme 1).

Synthesis of the polyketide fragment **4** (Scheme 2) began from the known 1,3-diol **7**.[4] Next, the primary alcohol group in **7** was protected as *tert*-butyldimethylsilyl ether **9** (86%) by treating with TBS-Cl and Et_3N in CH_2Cl_2 and subsequent protection of the secondary alcohol using MeI and NaH in THF resulted in the methyl ether **10** (71%). In compound **10**, the silyl group was deprotected by treatment TBAF (1 M) in THF at 0 °C to afford the alcohol **11**. Alcohol **11** was efficiently oxidized with IBX in DMSO/THF at room temperature to provide the aldehyde **12**.

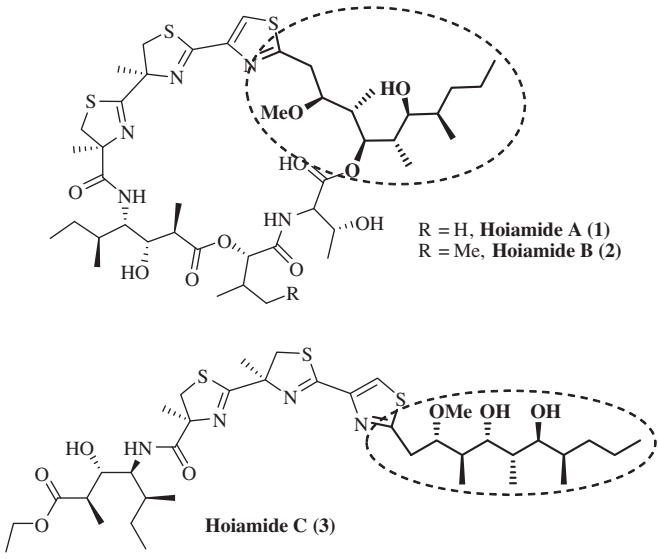

Figure 1. Structures of hoiamide A, B, and C.

* Corresponding author. Tel.: +91 040 27193210; fax: +91 040 27160512.
E-mail address: srivaric@iict.res.in (S. Chandrasekhar).

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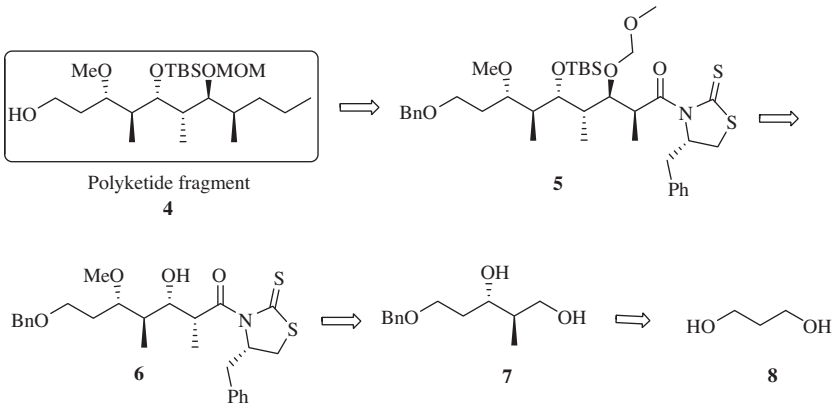
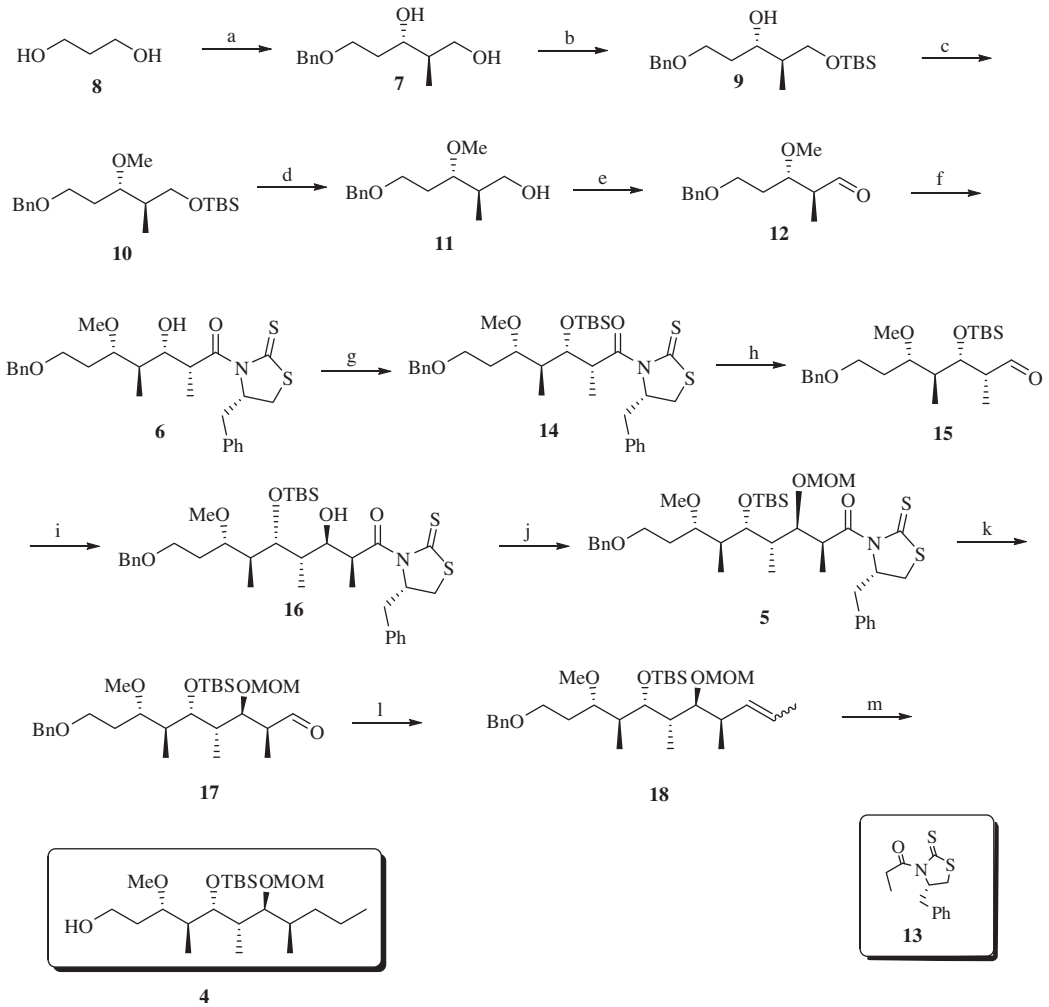
http://dx.doi.org/10.1016/j.tetlet.2012.05.103



Scheme 1. Retrosynthetic analysis of polyketide fragment.



Scheme 2. Reagents and conditions: (a) Ref. 4; (b) TBS-Cl, Et_3N, CH_2Cl_2, rt, 2 h, 86%; (c) NaH, MeI, THF, 0 °C, 3 h, 71%; (d) TBAF (1 M in THF), THF, 0 °C to rt, 2 h, 88%; (e) IBX, DMSO, THF, 0 °C to rt, 3 h, 85%; (f) **13**, $TiCl_4$ (1 M in CH_2Cl_2), DIPEA, CH_2Cl_2, 0 °C, 4 h, 70%, (95:5 dr); (g) TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 2 h, 88%; (h) DIBAL-H, CH_2Cl_2, −78 °C, 10 min, 90%; (i) **13**, $TiCl_4$ (−)-Sparteine (2 equiv), CH_2Cl_2, 0 °C, 12 h, 63%; (94:6 dr); (j) MOM-Cl, DIPEA, CH_2Cl_2, 0 °C, 3 h, 70%; (k) DIBAL-H, CH_2Cl_2, −78 °C, 10 min, 90%; (l) $PPh_3C_2H_5$, *n*-BuLi (1.6 M), THF, −78 °C, 2 h, 70%; (m) 10% Pd-C, H_2 (gas), EtOH, rt, 12 h, 80% .

According to the envisaged plan, the next task was a non-Evans *syn*-aldol reaction[5] of aldehyde **12** with the versatile Crimmins chiral auxiliary **13**. The chlorotitanium enolate of **13** was formed by addition of 1.05 equiv of $TiCl_4$, followed by 1.1 equiv of *i*-Pr_2NEt and subsequent addition of aldehyde **12** gave the alcohol **6** in 70% yield (95:5 dr).

Alcohol **6** was silylated by the action of TBSOTf and lutidine in CH_2Cl_2 at 0 °C to get compound **14** in 88% yield and 1, 2-*syn* stereo-

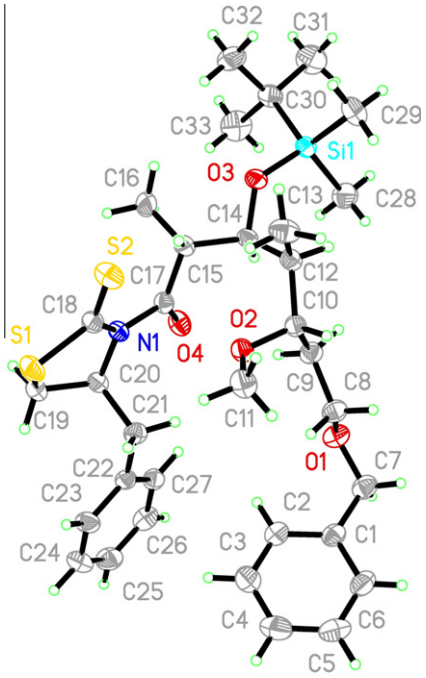


Figure 2. X-ray crystal structure of **14**.[6] Displacement ellipsoids are drawn at 30% probability level.

chemistry of the newly created asymmetric carbons was determined by X-ray crystallography.[6] Reduction of the imide with *i*-Bu_2AlH in CH_2Cl_2 at −78 °C provided the aldehyde **15** in 90% yield. Aldehyde **15** underwent a second Evans *syn*-aldol reaction[5] with propionylthiazolidinethione **13**, $TiCl_4$ (1.05 equiv), and (−)-Sparteine (2.2 equiv) in CH_2Cl_2 at 0 °C gave *syn* aldol product **16** in 63% yield (94:6 dr). Protection of secondary alcohol **16** by treatment with MOM-Cl and DIPEA in CH_2Cl_2 at 0 °C resulted in **5** (70% yield). Reductive removal of the chiral auxiliary of **5** with DIBAL-H in CH_2Cl_2 at −78 °C provided the corresponding aldehyde **17** in 90% yield.[7] Wittig reaction[8] of the aldehyde **17** with $PPh_3C_2H_5I$ and *n*-BuLi in THF at −78 °C led to olefin **18** as a mixture of *E*/*Z* isomers in 70% yield. The mixture of stereoisomers was converted into compound **4** in 80% yield by hydrogenation of the double bond and benzyl deprotection with 10% Pd-C in EtOH in one-pot. This constitutes the key polyketide fragment of hoiamides.

In summary, asymmetric aldol reaction has been utilized twice in a linear synthesis to generate all the required asymmetric carbons present in the polypropionate part of the target molecules.

Acknowledgments

M.S. thanks CSIR, New Delhi, for financial support in the form of a fellowship. The help of Balasubramanian Sridhar (the Laboratory of X-ray Crystallography, IICT) in X-ray crystal structure determination is acknowledged.

Supplementary data

Supplementary data (experimental procedures, characterization data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.103.

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6. Crystal data of compound (**14**): $C_{33}H_{49}NO_4S_2Si$, M = 277.35, monoclinic, space group $P2_1$, a = 13.3475(10) Å, b = 8.2602(6) Å, c = 16.6536(13) Å, β = 113.082(1), V = 1689.1(2) Å^3, Z = 2, D_{calcd} = 1.211 mg m^{-3}, T = 294(2) K, μ = 0.229 mm^{-1}, $F(000)$ = 664, λ = 0.71073Å. Data collection yielded 16,323 reflections resulting in 5935 unique, averaged reflection, 5804 with $I > 2\sigma$ (I). Full-matrix least-squares refinement led to a final R = 0.0263, wR = 0.0737, and GOF = 1.046. . CCDC 859873 contains supplementary Crystallographic data for the structure (Fig. 2). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.
7. The asymmetric aldol reaction which was performed twice in conversion of **12** into **6** and **5** into **17** is a matched pair as the existing chirality in aldehyde **12** and **5** and also the reaction conditions induced the chirality in an anti fashion, see Ref. 5c.
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