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Synthesis of an advanced intermediate enroute to thiomarinol antibiotics

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ABSTRACT

A stereoselective synthesis of the C1-C14 fragment of thiomarinols is disclosed. The key steps include the stereoselective preparation of an allylic sulfide via a chloro sulfide by 1,2-asymmetric induction, ring-closing metathesis reaction, Kirmse-Doyle reaction for the preparation of a γ,δ-unsaturated ester, Nozaki-Hiyama-Kishi coupling and Julia-Kocienski olefination reaction. Substrate controlled asymmetric induction has been advantageously employed for the creation of stereogenic centers. Noyori transfer hydrogenation and asymmetric hydrogenation reactions have been utilized for the creation of carbinol stereocenters.

1. Introduction

Thiomarinols A, B, E and H (Fig. 1) rare natural products, isolated from the marine bacterium *Pseudoalteromonas sp.* SANK73390,[1–3] possess a pyrrothine moiety linked through an amide to marinolic acids that are related to clinically potent antibiotic pseudomonic acid A.[4,6] Thiomarinol H, possessing an anhydroornithine moiety was isolated from *Alteromonas* sp.[5] The thiomarinols display potent activity against Gram-positive and Gram-negative bacteria including MRSA strain (MIC <0.01μgmL^{-1}). Thiomarinols A, B, E and H differ structurally from pseudomonic acid by the presence of a C4-hydroxyl, a shorter C1-alkoxy chain and an *E*-alkene instead of the C10-C11 epoxide and is more potent possessing wider spectrum of activity.

Thiomarinols like pseudomonic acid A inhibit the bacterial isoleucinyl tRNA synthetase enzyme responsible for loading the amino acid isoleucine onto its associated tRNA required for ribosomal protein synthesis. The impressive bioactivity and intriguing structure with five contiguous stereocenters (C4-C8) have attracted considerable attention from synthetic and medicinal chemists.[7] Herein, we describe a stereoselective route to the advanced intermediate **6**, constituting the C1-C14 subunit of thiomarinols by application of an α-chloro sulfide for the stereoselective preparation of an allylic sulfide, ring-closing metathesis reaction and Kirmse-Doyle rearrangement as the crucial steps.

2. Results and discussion

The retrosynthesis is depicted in Scheme 1. Thiomarinol can be obtained from the unsaturated acid **6** and alcohol **7**. The acid **6** can be obtained from the reaction of a suitable nucleophile derived from the iodo alkene **9** with aldehyde **8**. Aldehyde **8** can be derived from aldehyde **10** by Julia-Kocienski olefination with sulfone **11**. Aldehyde **10** was envisaged to be obtained from the unsaturated ester **12** which in turn can be traced to allyl sulfide **13**. Sulfide **13** can readily be obtained from chloro diol **14**.

The synthesis began with the chloro diol **14** (>95 ee), obtained by hydrolytic kinetic resolution of epichlorohydrin,[8] which on treatment with thiophenol in the presence of DBU furnished the diol sulfide **15**. Selective mono protection of the primary hydroxyl as its silyl ether **16** followed by allylation of the secondary hydroxyl furnished compound **17**. Reaction of **17** with *N*-chlorosuccinimide yielded α-chloro sulfide **18** which without isolation was treated with vinylzinc bromide to afford allylic sulfide **19** (>95 dr).[9] Ring-closing metathesis using Grubbs' II generation catalyst[10] **20**, furnished sulfide **13**, Scheme 2.

Syringe pump addition of ethyl diazoacetate to the solution of sulfide **13** in the presence of catalytic rhodium acetate resulted

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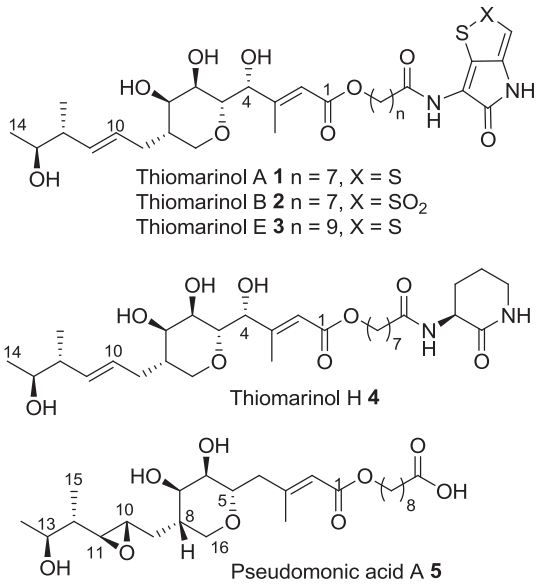


Fig. 1. Structures of thiomarinols and pseudomonic acid A.

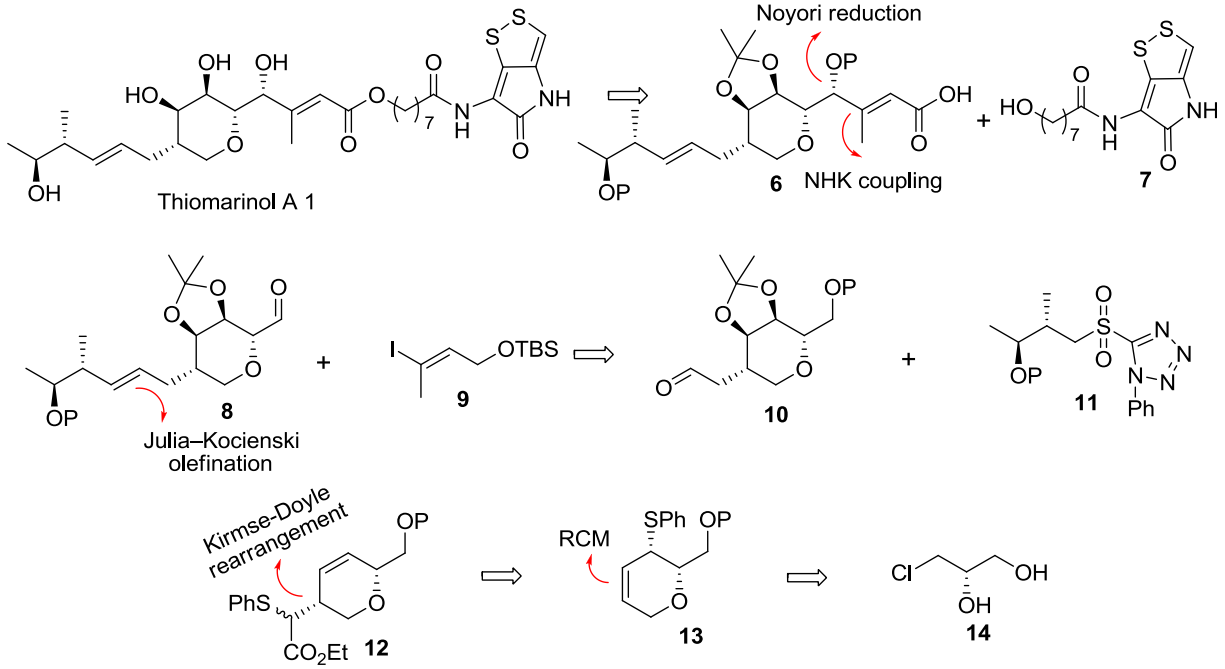
sequentially in ylide formation and Kirmse-Doyle rearrangement[11] to afford an inseparable epimeric mixture of esters **12**. Catalytic dihydroxylation employing the Upjohn process[12] led to substrate-controlled stereoselective introduction of the hydroxyl groups with concomitant oxidation of the sulfide to furnish epimeric sulfones **21**. Protection of the diol as the acetonide **22** followed by reductive desulfonylation[13] using Na-Hg yielded methyl ester **23** via transesterification. Partial reduction of the ester using DIBAL-H yielded aldehyde **10**, Scheme 3.

The sulfone partner for Julia olefination was readily prepared from ethyl acetoacetate **24**. BINAP-Ru(II)-catalyzed Noyori asymmetric hydrogenation[14] furnished β-hydroxy ester **25** (93:7 er).[15] The enantiomeric excess was determined from its mandelate ester derivative. Frater-Seebach alkylation[16] of the dianion derived from **25** with MeI afforded the ester **26** (95:5 dr). Protection of the hydroxy group as its MOM-ether **27** followed by reduction of the ester with LAH afforded alcohol **28**. Treatment with *N*-phenyltetrazole thiol **29** under Mitsunobu conditions[17] cleanly afforded sulfide **30** that was oxidized using *m*CPBA to furnish sulfone **11**, Scheme 4.

Treatment of sulfone[18] **11** with KHMDS followed by addition of aldehyde **10** and stirring while gradually allowing it to attain rt overnight furnished alkene **31** (*E*:*Z* = 88:12). Deprotection of the silyl ether using TBAF afforded alcohol **32**. It is to be noted that alcohol **32** has been employed as the key intermediate in the synthesis of pseudomonic acid.[19] Selective oxidation of the primary alcohol using $PhI(OAc)_2$ and TEMPO[20] yielded aldehyde **8** which was subjected to NHK coupling[21] with iodo alkene **9**[22] to furnish an inseparable mixture of allylic alcohols **33** (dr 45:55). Oxidation of the epimeric alcohols to the ketone **34** using Dess-Martin periodinane[23] followed by stereoselective reduction using Noyori's catalyst[24] afforded alcohol **36** (dr 92:8). Protection of the secondary alcohol as the TBS ether **37** followed by selective removal of the primary TBS ether afforded alcohol **38**. Oxidation using $PhI(OAc)_2$ and TEMPO in aq acetonitrile[25] furnished the advanced intermediate **6**, corresponding to the C1-C14 subunit of thiomarinol, Scheme 5.

3. Conclusions

In conclusion, a stereoselective route to the advanced intermediate of thiomarinol antibiotics is described. The key steps include the preparation of an allylic sulfide by reaction of vinylzinc bromide with chloro sulfide, ring-closing metathesis reaction, Kirmse-Doyle rearrangement, Julia-kocienski olefination and Nozaki-Hiyama-Kishi coupling for the successful introduction of the C4-hydroxyl group. Also Noyori transfer hydrogenation and asymmetric hydrogenation reactions have been used to introduce carbinol



Scheme 1. Retrosynthetic Disconnection of Thiomarinol.