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Stereospecific access to α-haloalkyl esters *via* enol ester epoxides and synthesis of a C3–C21 fragment of bastimolide A†

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We report a 14-step synthesis of a C3–C21 fragment of bastimolides A and B, antimalarial macrocyclic polyketides. A crucial ring-opening reaction of an enol ester epoxide showed previously unexplored reactivity, leading to an asymmetric synthesis of α-haloalkyl esters. The α-haloalkyl ester synthesis was shown to be stereospecific, and provided access to a key α-silyloxyaldehyde to initiate application of configuration-encoded 1,5-polyol synthesis. This strategy established the C11/C15 and C15/C19 remote stereochemical relationships of the bastimolides. The potential of this C3–C21 fragment for coupling to C22–C41 was established using a Mukaiyama aldol reaction with a simple enolsilane.

Introduction

Malaria continues to have a significant global impact causing an estimated 249 million malaria cases in 2022,[1] and the threat of resistance emphasizes the continuing need for new treatment options. Marine cyanobacteria offer structurally interesting natural products that offer insights for drug discovery.[2] Among these are bastimolide A (**1**),[3] a 40-membered macrolide that has proven to exhibit potent antimalarial properties against four resistant strains of *Plasmodium falciparum* (IC_{50} = 80–270 nM), and its 24-membered macrolactone isomer, bastimolide B (**2**).[4] Both 1,3- and 1,5-polyol motifs are combined in its structure (Fig. 1), which bears little apparent resemblance to any clinical antimalarial drugs or preclinical candidates.[5] This suggests the possibility that biological evaluation of **1**, **2**, or analogs could uncover a new mode of action *via* a novel *Plasmodium* drug target.

Synthesis of the bastimolides is therefore a high priority, and various strategies to access structural subunits[6] and halogenated analogues[7] have appeared. Smith[8] and Aggarwal[9] have reported the first total syntheses of **1** and **2**, respectively, and Kirsch *et al.* reported a formal synthesis.[10] We recently reported asymmetric synthesis of a 1,5-polyol comprising the C22–C41 fragment of the bastimolides.[11]

Polyols bearing 1,5-relationships between hydroxyl groups often cause complications for configurational assignments,[12] stereocontrolled synthesis, and diastereomer separations.[13] This prompted our development of a *configuration-encoded* synthetic strategy[14] (Fig. 2) utilizing building blocks of defined hydroxyl configuration that are linked iteratively *via* Julia–Kocienski olefination.[15] Subjecting α-silyloxyaldehydes to Julia–Kocienski olefination with γ-sulfononitrile building blocks (*R*)-**3** or (*S*)-**3** establishes *syn*- or *anti*-1,5-diol relationships, and subsequent reduction of the nitrile regenerates α-silyloxyaldehyde functionality at the chain terminus for another iteration. The programmed assembly allows synthesis of all possible diastereomers of 1,5-polyols with equal facility, and obviates analytical or preparative separations of diastereomers. Here we disclose the configuration-encoded synthesis of the C3–C21 subunit of the bastimolides (**4**), aided by the discovery of mild conditions for stereospecific transformation of enol ester epoxides into 1-haloalkyl esters.

Results and discussion

Our retrosynthetic analysis (Fig. 2) involves two iterations of the configuration-encoded 1,5-polyol synthesis strategy. This

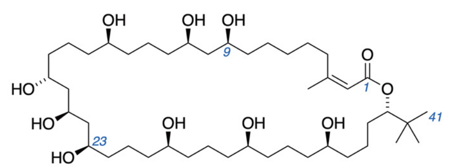

Fig. 1 Structures of bastimolides A (**1**) and B (**2**).

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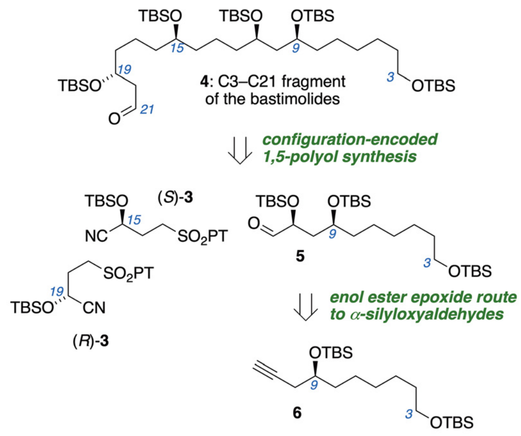
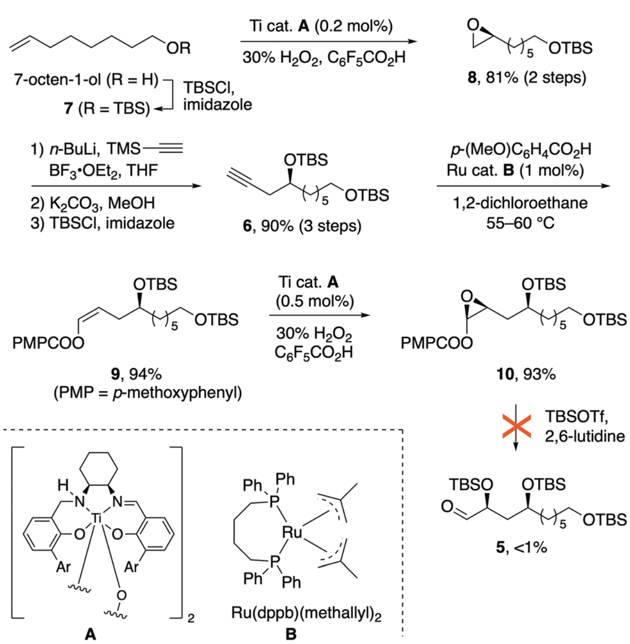


Fig. 2 Two iterations of configuration-encoded 1,5-polyol synthesis to access an *anti*,*syn*-1,5,9 triol stereotriad.

suggesting α-silyloxyaldehyde **5** as a key precursor, which would be coupled successively with (*S*)-**3** and (*R*)-**3** to unambiguously establish C15 and C19 configurations. Our earlier successes in three-step synthesis of α-silyloxyaldehydes from alkynes *via* enol ester epoxides[16] prompted a similar approach to **5** from alkyne **6**.

The synthetic sequence began with preparation of epoxide **8**[17] (Scheme 1), obtained in 92% ee by enantioselective Katsuki epoxidation of alkene **7** with the Berkessel Ti catalyst **A**.[18] Reaction of **8** with lithiated trimethylsilylacetylene, followed by alkyne desilylation and TBS protection of the 2° alcohol, furnished alkyne **6** in 72% yield over five steps, with only two column chromatography purifications.



Scheme 1 Synthesis of enol ester epoxide **10** and its anomalous reactivity.

The next task was to implement our three-step route from alkynes to α-silyloxyaldehydes. Ruthenium-catalyzed addition[19] of anisic acid to alkyne **6** (Scheme 1) gave (*Z*)-enol ester **9** in 90% yield, and another Berkessel–Katsuki epoxidation furnished enol ester epoxide **10** with excellent yield and selectivity (94%, 96 : 4 dr). The epoxide ring-opening, which had normally provided smooth access to α-silyloxyaldehydes upon treatment with silyl triflates and lutidine,[11,14c,16] failed in this case; only traces of the aldehyde **5** were observed. In an effort to understand this anomaly, simplified enol ester substrate **11a** (Fig. 3a) was subjected to the ring opening. Instead of α-silyloxyaldehyde **12a**, a dimeric hydroxyfuran structure **13** was obtained. This could be rationalized by an oxocarbenium ion (or its equivalent) undergoing nucleophilic attack by the nearby silyloxy substituent as implied by structure **C**, followed by some combination of silyl transfer events and dimerization. The dimerization finds precedent in a similar structure formed from furanoses.[20] Replacement of OTBS with less nucleophilic OBz would be expected to suppress the formation of dimer **13**, and indeed with substrate **11b** the expected ring-opening pathway to the α-silyloxyaldehyde **12b** was restored (64% yield).[11]

Further comment about unexpected structure **13** is warranted. The cis configuration at both ring junctions of **13** was assigned by its apparent C2 symmetry (4 signals in its ^{13}C NMR spectrum) and small coupling constants at the ring junction (J = 3.7 Hz observed at the anomeric C–H). A boatlike central ring would be accompanied by high torsional strain and lack of anomeric stabilization; we propose a chairlike conformation for the central ring of **13**, with pseudo-C2 symmetry attributed to a rapid chair–chair conformational equilibrium.

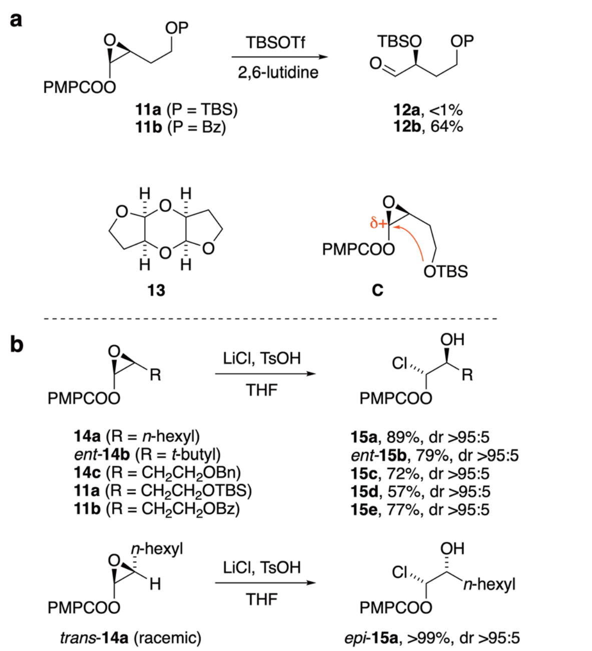
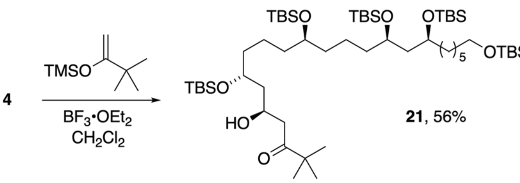


Fig. 3 (a) Simplified analogs **11a** and **11b** reveal the reason for anomalous reactivity of **10**. (b) Stereospecific enol ester epoxide ring-opening to 1-haloalkyl esters **15**.

Although changing to ester protection at the C9-OH could circumvent the anomalous reactivity of **10** and **11a**, we sought to address the problem head-on, with the hypothesis that a large concentration of an external nucleophile could suppress the offending cyclization. Indeed, upon treatment of enol ester epoxide **14a** with LiCl and TsOH, complete conversion to 1-haloalkyl ester **15a** was observed within 5 min. Similar results were observed with enol ester epoxides **14b**, **14c**, **11a**, and **11b**, producing 1-haloalkyl esters **15b**–**15e** respectively. All of these 1-haloalkyl esters were formed with complete stereospecificity despite the potential intermediacy of a planar oxocarbenium ion. Enol ester epoxide *trans*-**14a**, prepared *via* the corresponding *E*-enol ester, gave diastereomer *epi*-**15a**, providing further evidence of the stereospecific nature of the ring-opening. Crystallographic analysis of the 3,5-dinitrobenzoate derivative of **15b** (see ESI†) confirmed the structural assignment suggesting inversion of configuration by the chloride nucleophile. To our knowledge there is only one related example leading from an enol ester epoxide to a 1-haloalkyl ester ($SnCl_4$, 50% yield).[21] Here we provide for the first time (a) evidence of stereospecificity, (b) preliminary evaluation of scope, and (c) subsequent reactivity studies in application to target-oriented synthesis. Racemic 1-haloalkyl esters[22] have been used in various bond constructions,[23] and this access to enantiopure samples presents new opportunities for reaction development and mechanistic study.

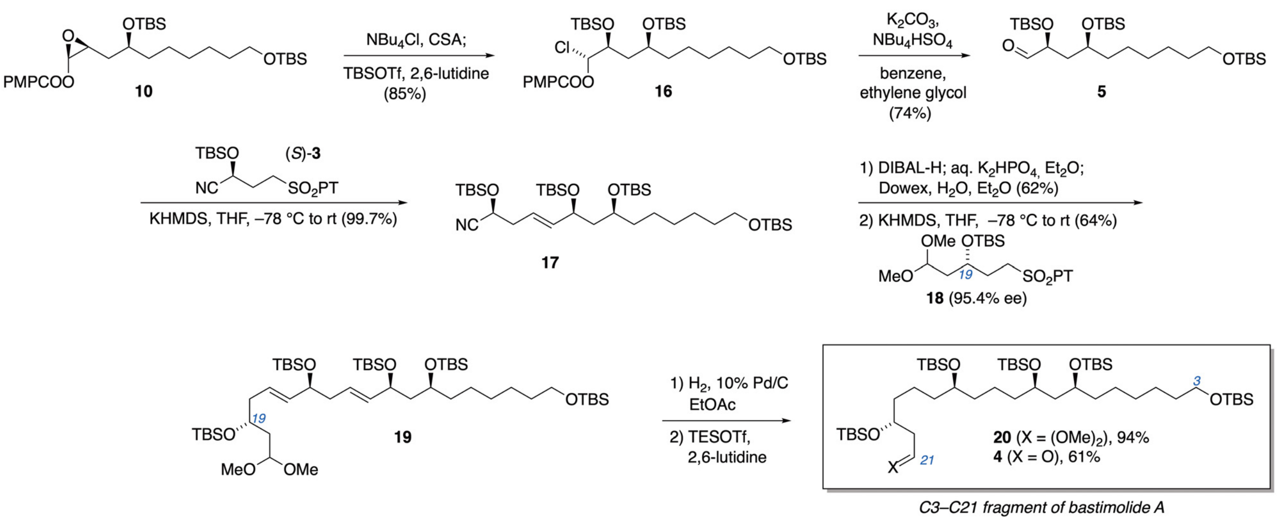
Turning our attention back to the synthetic route, we put the new method to the test in conversion of enol ester epoxide **10** to α-silyloxyaldehyde **5**. Treatment of **10** with a chloride source (NBu_4Cl was used for improved solubility) and camphorsulfonic acid, followed by *O*-silylation, cleanly furnished the α-haloalkyl ester **16** in 84.5% yield (Scheme 2). Transesterification with concomitant elimination of chloride then completed the alternative method for conversion of **10** to aldehyde **5**. While the typical K_2CO_3/MeOH was effective for this transesterification on microscale, scale-up was problematic. A more reliable modification employed phase-transfer catalysis: in an immiscible mixture of benzene (or toluene) and ethylene glycol, exposure to K_2CO_3 along with phase-transfer catalyst NBu_4HSO_4 furnished aldehyde **5** in 74% yield, along with recovered **10** (88% yield based on conversion).[24]

With aldehyde **5** in hand, we applied our configuration-encoded 1,5-polyol synthesis. Julia–Kocienski olefination with (*S*)-**3** smoothly established the *syn*-1,5-diol relationship between C11 and C15 with a quantitative yield of nitrile **17**. Reduction of the nitrile with DIBAL-H and a second iteration of the Julia–Kocienski reaction with alternative building block **18** then established the desired *anti*,*syn*-1,5,9-triol stereotriad in **19**, while placing masked aldehyde functionality at the terminus.[25] Sulfone **18** was prepared in 6 steps from acrolein (see ESI†), using Keck allylation (95% ee) to encode the desired configuration at the carbon destined to become C19 of the bastimolides. Hydrogenation of the alkenes of **19** afforded acetal **20**, which was converted to β-silyloxyaldehyde **4** through Fujioka–Kita acetal hydrolysis.[26] This aldehyde is the C3–C21 fragment of bastimolides, ready for Mukaiyama aldol coupling to the C22–C41 subunit.



(1)

An initial assessment of Mukaiyama aldol conditions for coupling to the C3–C21 subunit (**4**) employed the trimethylsilyl enol ether derived from pinacolone (eqn (1)). In the presence of $BF_3 \cdot OEt_2$, this enolsilane added smoothly to aldehyde **4** to afford aldol **21** (dr 88 : 12) with close correspondence to the 1,3-diastereocontrol we previously observed in similar polyacetate-type aldol adducts.[27] Diagnostic ^1H NMR data for several closely related aldol products in that prior report enabled



Scheme 2 Access to α-silyloxyaldehyde **5** and configuration-encoded assembly of the C3–C21 subunit of bastimolides.

assignment of *anti* configuration to the major diastereomer **21** and demonstrated the potential of **4** as a viable intermediate *en route* to bastimolides and analogs.

Conclusions

We have developed a synthesis of the C3–C21 fragment of bastimolides using the configuration-encoded approach to 1,5-polyol assembly. The synthetic sequence encountered an unexpected structural incompatibility of our previously established three-step conversion of alkynes to α-silyloxyaldehydes. Solving this problem led to the discovery of a stereospecific synthesis of enantiopure 1-haloalkyl esters; these are richly functionalized synthetic building blocks with further synthetic potential.

Data availability

Crystallographic data are available in CCDC 2403648. Preparative procedures and characterization data are provided in ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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