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An approach towards C12 oxo analogues of the side chain of pumiliotoxin B/allopumiliotoxin 339A and B†

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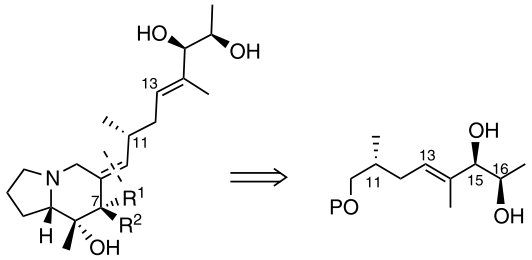
Abstract—A route towards the synthesis of analogues of pumiliotoxin and allopumiliotoxin side-chain is described. The C15,C16 diol was introduced by asymmetric dihydroxylation using AD-mix β of C10,C17 enynone intermediate **14**, or of C13,C17 precursor **17**, or by using a chiron-based route from **24**. The trisubstituted alkene functionality was established using arylthio conjugate addition to ynones **16** and **27**, followed by a copper-catalyzed stereoretentive reaction with methylmagnesium bromide. The approach enables access to C12 oxo systems and offers an approach towards new C14 analogues.

The venomous skin secretions of Dendrobatid frogs have proven a rich source of structurally complex bioactive alkaloids (several hundred), with a wide variety of potent biological activities,[2] including potent neurotoxins such as histrionicotoxins, batrachotoxin and gephrotoxin. Pumiliotoxin and the closely related rarer allopumiliotoxin alkaloids were first isolated over 30 years ago from this source.[3] The architecture of the structurally unusual pumiliotoxins A and B, and the allopumiliotoxins (sharing the basic heterocyclic core of pumiliotoxins A and B, differing only in possessing a 7-OH group) was established some years later (Fig. 1).[4] Since then there has been much interest in these compounds, spurred by their dramatic activity on cardiac functions. The class of compounds is particularly interesting, as some other members, *differing only in side-chain functionality or hydroxyl group protection*, are mild cardiodepressants.[5] The cardiac activities displayed by pumiliotoxins, and the effects of changes in side-chain functionality, indicates the importance of the side chain to the mechanism of action of different congeners. The mechanism of action of these agents involves binding to voltage dependent sodium channels and thereby modulating sodium flux through these channels.[5d,6]

The allopumiliotoxins and pumiliotoxins have been the subject of a number of synthetic efforts since the early 1980s. Total syntheses of the allopumiliotoxins 339A **2** and 339B **3** have been described by Trost,[7] Overman[8] and Kibayashi,[9] and of pumiliotoxin B **1**,[10] along with a number of approaches to the ring system. The Overman and Kibayashi syntheses proceed via an acetylenic precursor of the side chain, or through a C10 aldehyde precursor, essentially derivatives of **4**.

Our objective was to develop a synthetic route which would allow for additional structural variability at C12, specifically including oxygenation, and to evaluate alternatives to Wittig/Horner–Emmons methods to introduce the C13,C14 alkene which could facilitate



1 $R^1 = R^2 = H$ pumiliotoxin B

2 $R^1 = OH$, $R^2 = H$ allopumiliotoxin 339A

3 $R^1 = H$, $R^2 = OH$ allopumiliotoxin 339B

4

Figure 1. Pumiliotoxins and allopumiliotoxins: side-chain target.

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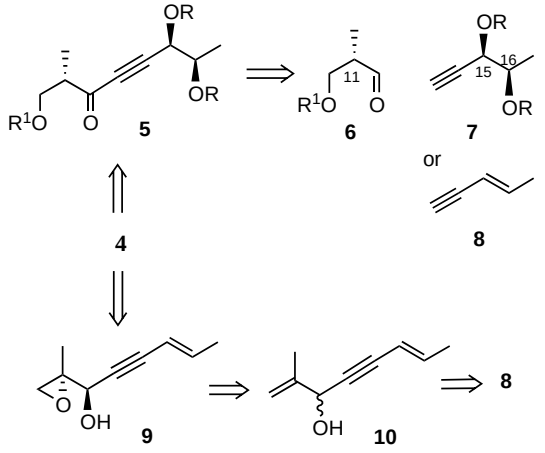
divergent introduction of groups other than the C14 methyl substituent. These were variations not addressed in previous syntheses, but of interest given the significance of side-chain structure to variations in biological activity (all natural analogues are C12 methylene, and syntheses to date do not readily allow variation here).

Our approach is based on disconnection at the exocyclic alkene yielding **4** since our potential approaches to the ring system and analogues all involve late formation of that bond, or its immediate precursor. A C10 aldehyde could also be a precursor of a homologated acetylene and we reasoned that our syntheses should proceed through such an intermediate, thus allowing both for the option to intercept either of the Kibayashi or Overman routes, as well as being applicable to new strategies towards the bicyclic ring system and analogues.[11]

Retrosynthetic analysis of the side-chain backbone envisages disconnections at C12,C13, with two alternatives for introduction of the C11 stereochemistry and terminal (C10) alkoxy group (Scheme 1). As an alternative to addition of **7** we also considered coupling of a vinyl metal-derived via Negishi zircomethylation of acetylene **7**—to introduce the C13,C14 substituted alkene directly. One strategy aimed to introduce C11 chirality and C10 hydroxylation from a commercial chiron starting material; the second approach sought to evaluate asymmetric resolution of (*R*,*S*)-**10**. Both approaches ultimately aimed to utilize overall *trans* addition of H-Me across keto acetylenes of type **5**, via thermodynamically controlled cuprate addition,[12] or phenylthio conjugate addition and copper catalyzed Grignard substitution of the phenylthio group.[13] Both routes potentially offered relatively short access to the fully functionalized side chain with C12 oxygenation, and to C14 analogues.

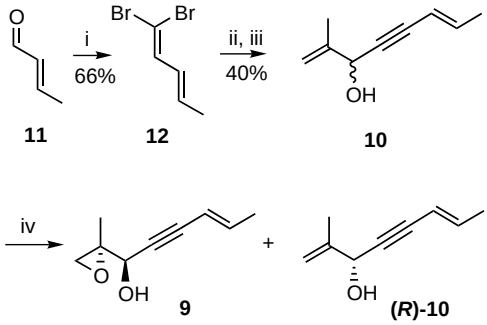
The route via (*R*,*S*)-**10** proposed addition of the acetylide anion from **8** to methacrolein, followed by kinetic resolution using Sharpless asymmetric epoxidation to generate **9**. We reasoned that directed epoxide ring opening would then provide the C11 stereochemistry and the terminal hydroxyl present in **5**. This was attractive given the low cost of methacrolein (compared to the precursor of **6**) and the potential to recycle the unreactive allylic alcohol enantiomer (oxidation, re-reduction).



Scheme 1. Retrosynthesis of side-chain analogue targets (R,R^1-protecting groups).

Thus, crotonaldehyde **11** was subjected to a modified Corey–Fuchs procedure[14] to give the dibromoolefin **12** in 65–70% yield. This was converted to the lithium acetylide of **8** which was reacted in situ by addition of methacrolein to give (*R*,*S*)-**10** directly in ca. 40% yield over these steps after purification by distillation (Scheme 2). Sharpless AE kinetic resolution[15] led to **9** in 51% yield, 63% e.e. and the slower reacting enantiomer (*R*)-**10** in 30% yield, 80% e.e. The conditions were not optimized, but indicated that obtaining **9** with high e.e. would require considerably lower isolated yields. The anticipated regiocontrolled epoxide opening with Red-Al (which has good precedent on comparable systems),[16] which would invert at C11 as required, was evaluated before pursuing optimization of the kinetic resolution. The continually low yields for the ring opening led us to abandon this approach, and consequently we did not further optimize the AE kinetic resolution.

We therefore turned to routes utilizing **6** as the C10–C12 unit, with either attachment of the complete C13–C17 unit of type **7**, already containing the two hydroxy chiral centres, or of the achiral enyne **8** (subsequently introducing the C15,C16 functionality). With the synthesis of the acetylide of **8** already established, and the chiral aldehyde **6** [R^1 = TBDMS][17] conveniently derived from methyl (2*S*)-3-hydroxy-2-methylpropionate (silylation, then DIBAL-H semi-reduction or by complete reduction with lithium borohydride and Swern or Dess–Martin reoxidation), this connectivity was evaluated. Thus, direct reaction of **6** with the acetylide anion of **8** generated in situ gave the desired enyne **13**.[18] Yields after purification were variable (25–50%), with diastereoselectivity (from crude NMR analysis) of the order of 4:1. The diastereomeric mixture was oxidized under Swern conditions to give the ketone **14** in 70% purified yield. Asymmetric dihydroxylation of **14** using AD mix-β generated the diol **15**, which was then protected as its isopropylidene acetal giving **16** under stan-

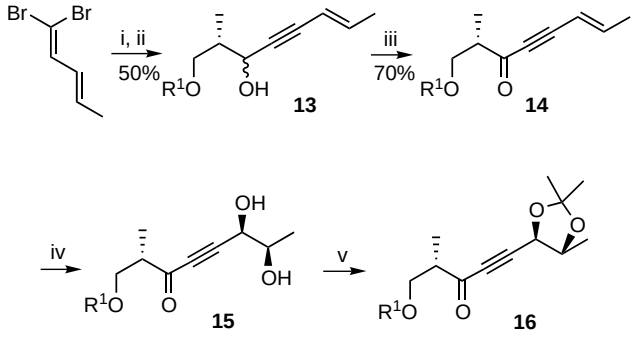


Scheme 2. *Reagents and conditions*: (i) CBr_4, Ph_3P, Et_3N, 0°C 2.5 h→20°C 1.5 h; (ii) BuLi, HMPA, −78°C; (iii) add methacrolein→20°C; (iv) Ti(O*i*-Pr)$_4$, (+)-DIPT, TBHP, CH_2Cl_2, −20°C, 11 h.

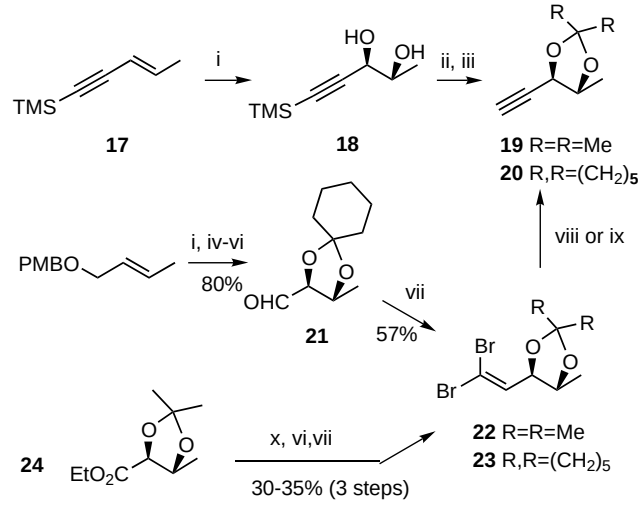
dard conditions (Scheme 3). This provided one route to the key intermediate type (cf. **5**) desired.

Three routes to building blocks of type **7** were evaluated (Scheme 4). The first is analogous to the route in Scheme 3, but carrying out the asymmetric dihydroxylation prior to introduction of the C12–C13 bond, through asymmetric dihydroxylation of the TMS derivative **17**[19] of enyne **8**. Reaction of **17** with AD mix-β yielded the novel (*R*,*R*)-diol **18** in 80% yield and >90% e.e.[20] The diol was protected as its isopropylidene acetal, and desilylated (both steps >90% yields) to afford **19**.

The same basic unit was also prepared (as cyclohexanone-derived acetal **20**) by a slightly different route from PMB-protected crotyl alcohol, elaborated to the chiral aldehyde **21**[21] and thence to the novel dibromoolefin **22**.[22] Intriguingly, this gave poor reproducibility in a single-step conversion to acetylene **20**, and thus a two-step route via the *E*-vinyl bromide was used (conditions ix). Another approach to **19** via dibromoalkene **22** was from the commercially available ethyl (4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate **24**. Reduction then reoxidation (Dess–Martin periodinane was also effective) proved more reliable than DIBAL-H reduction to generate the intermediate aldehyde. Although the route from commercial **24** is a step shorter than that from crotonaldehyde (via asymmetric synthesis from **17**), **24** is comparatively expensive and so particularly on a larger scale, the route from crotonaldehyde is cost-effective.



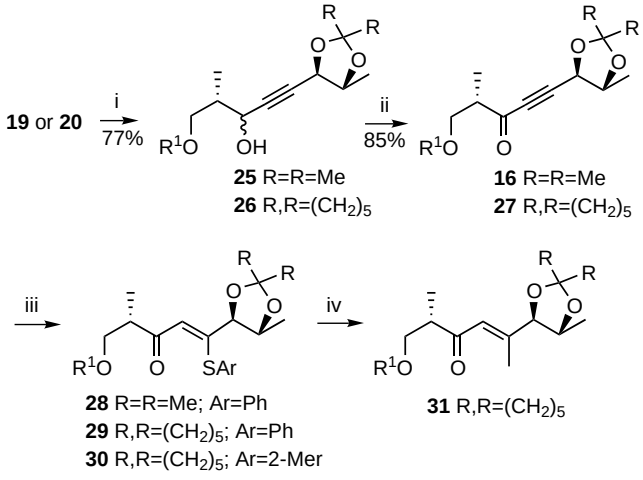
Scheme 3. [R[1] = TBDMS] *Reagents and conditions*: (i) *n*-BuLi, −78°C, 6 h then HMPA; (ii) **6**; (iii) $(COCl)_2$, DMSO, Et_3N, −78°C; (iv) AD mix-β, *t*-BuOH, H_2O, 0°C→rt, 20 h; (v) CSA, $(MeO)_2CMe_2$, Me_2CO, 12 h.



Scheme 4. *Reagents and conditions:* (i) AD mix-β, *t*-BuOH, H_2O, 0°C→rt, 20 h; (ii) CSA, $(MeO)_2CMe_2$, Me_2CO, 12 h; (iii) TBAF; (iv) $C_6H_{10}O$, CSA, THF, rt, 14 h; (v) DDQ, CH_2Cl_2, rt, 1 h; (vi) $(COCl)_2$, DMSO, Et_3N, −78°C; (vii) CBr_4, Ph_3P, Et_3N, −20°C, 20 min→20°C, 30 min; (viii) *n*-BuLi, 2 equiv., −78°C; (ix) *n*-BuLi, 1 equiv., −78°C, 10 min, isolation of vinyl bromide, then KO*t*-Bu, THF, 2 h; (x) $LiBH_4$.

Addition of the lithium acetylide of **19** or **20** to aldehyde **6** proceeded to give the adducts **25** and **26**, the best yield (77%) being obtained in the latter case (Scheme 5). The diastereomers of **26** could be chromatographically separated to provide a 6.7:1 diastereomeric ratio. Swern oxidation afforded the target ketones **16** and **27** in ca. 85% purified yield.

There are few methods for the overall *trans*-addition of carbon nucleophile-H to either alkynoate or alkynone conjugate acceptors. Mukaiyama reported overall *trans*-addition to alkynoates via a two-step methodology employing *Z*-stereospecific conjugate addition of sodium thiophenolate to alkynoates, and copper-catalyzed Grignard addition–elimination of the intermediate vinyl sulfide.[13] We had previously evaluated this, along with thermodynamic cuprate addition to simplified (achiral) analogues of **16** and **27**, and ascertained that use of thiophenol or 2-mercaptothiazole were successful in the latter general approach.[23] Application of these conditions to **16** and **27** provided *E* (**28**–**30**) and *Z* mixtures in 65–82% total yield, with *E*:*Z* ratios around 2:1 and 1:1, respectively. These could be separated chromatographically most easily for the cyclohexanone-



Scheme 5. [R[1] = TBDMS; 2-Mer = 2-mercaptothiazole] *Reagents and conditions*: (i) *n*-BuLi, −78°C, 2 h then **6**→20°C; (ii) $(COCl)_2$, DMSO, Et_3N, −78°C; (iii) ArSH, THF, MeOH, 2 h, rt (for **28**/**29**) or 7 h, Δ (for **30**); (iv) MeMgBr, CuI, −78°C, 5 h, then −20°C, 13 h→0°C, 1 h.

derived acetals **29** and **30**. Copper catalyzed Grignard addition–elimination to **29** gave the target **31** in 60% purified yield.

This thus provides a new route to C12 oxo precursors to C10–C17 side-chain analogues. C12 is a site of modification unavailable from natural sources, or prior chemical syntheses. Reductive ketone removal would directly afford the natural product side chain, but the ketone can also be a precursor to reduction to C12-hydroxy analogues of the side chain. In addition, the use of a Grignard source for introduction of the C13,C14 trisubstituted alkene offers the prospect of future analogue diversification by employing other alkyl Grignard reagents to access what would constitute a new class of C14 side-chain analogues.

Acknowledgements

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