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Synthesis of the β-hydroxydopa–γ-hydroxy-δ-sulfinylnorvaline component of ustiloxins A and B

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The dopa–sulfinylnorvaline component of ustiloxins A and B has been prepared using an Evans salen–Al-catalysed aldol reaction with a 6-mercaptoisovanillin derivative, followed by incorporation of the norvaline group and asymmetric oxidation of the resulting sulfide to give the corresponding sulfoxide.

The ustiloxins (Fig. 1) are a family of cyclic peptides isolated from the fungus *Ustilaginoidea virens*, which causes the growth of false smut balls on rice plants.[1] The ustiloxins possess a β-hydroxydopa residue as part of a 13-membered cyclic core, with ustiloxins A and B also possessing a γ-hydroxy-δ-sulfinylnorvaline moiety at the 6-position of the dopa aromatic ring. The ustiloxins are potent antimitotic agents and have been shown to bind to the rhizoxin site on tubulin.[2] Ustiloxins A and B are the most potent members of the family, being two-fold more active than the simplest member, ustiloxin D, which has no substituent at the 6-position of the dopa residue, suggesting that the sulfinylnorvaline moiety provides significant binding interactions with tubulin.

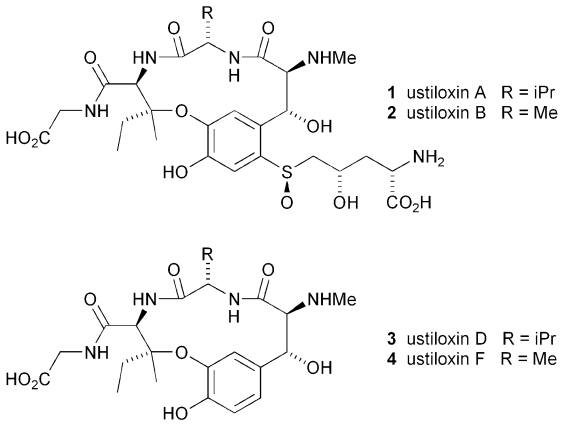
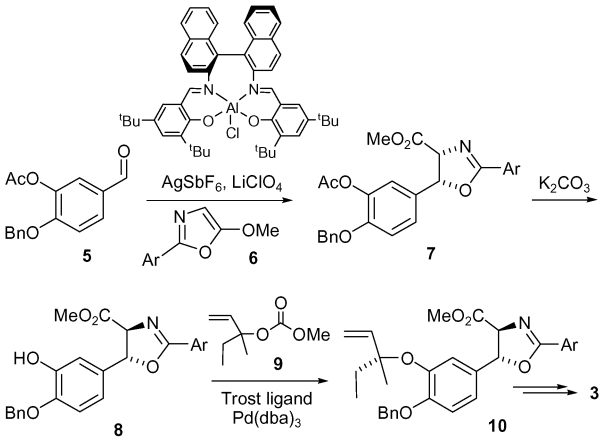


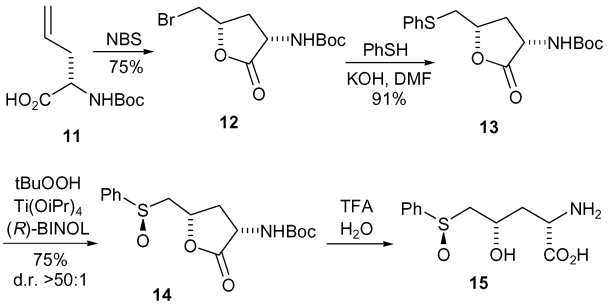
Fig. 1 Ustiloxins.

The total synthesis of ustiloxin D has been reported by the Joullié[3] and Wandless[4] groups. Of particular relevance to our current work is the approach employed by Wandless for the synthesis of the β-hydroxydopa component of ustiloxin D (Scheme 1). Wandless employed an Evans salen–Al-catalysed aldol reaction[5] of substituted benzaldehyde **5** and oxazole **6** to generate oxazoline **7**, which was epimerised to **8** then coupled to **9** to give β-hydroxydopa derivative **10** (Scheme 1).

We have previously reported a route to the sulfinylnorvaline moiety **15** present in ustiloxins A and B using thiophenol as a simple model for the dopa residue (Scheme 2).[7] Substitution of bromolactone **12** (prepared from Boc-allylglycine **11**) with thiophenolate generates sulfide **13**. Asymmetric oxidation of **13** to the sulfoxide **14** occurs with very high stereoselectivity, and global deprotection then gives the sulfinylnorvaline system **15** in which a phenyl group models the dopa residue of ustiloxin A



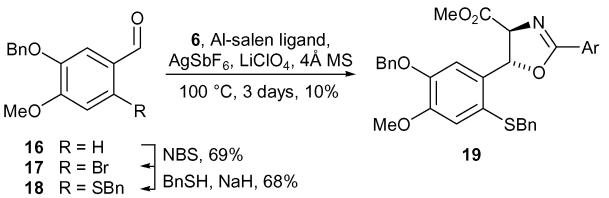
Scheme 1 Wandless' synthesis of ustiloxin D.[4,6]



Scheme 2 Model sulfinylnorvaline synthesis.[7]

and B. Herein we report elaboration of our model system to the preparation of a dopa–sulfinylnorvaline conjugate suitable for incorporation into a total synthesis of ustiloxins A and B.

Extension of the route developed by Wandless to the synthesis of the more complex ustiloxin A (or B) would require as the starting point a protected form of 4,5-dihydroxy-2-mercaptobenzaldehyde, such as **18** (Scheme 3), which we initially accessed by modification of the method of Schwartz.[8]



Scheme 3 Initial aldol substrate.

Isovanillin derivative **16** was treated with *N*-bromosuccinimide in DMF to generate aryl bromide **17** (Scheme 3).[9] Subsequent S_NAr reaction with benzyl mercaptan furnished the aldol substrate **18** in reasonable yield. However, **18** was

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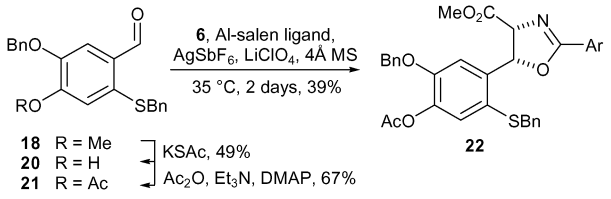
found to be reluctant to undergo aldol reaction with oxazole **6**, and the *trans*-oxazoline product **19** was obtained in only 10% yield after several days at elevated temperature (Scheme 3). Wandless reports that an increased catalyst loading of 10%, and strictly anhydrous conditions, were all that was required for the electron rich aldehyde **5** to undergo the aldol reaction effectively. However, the electron-donating nature and steric factors introduced by the additional *ortho*-sulfur substituent presumably limit the reactivity of **18**.

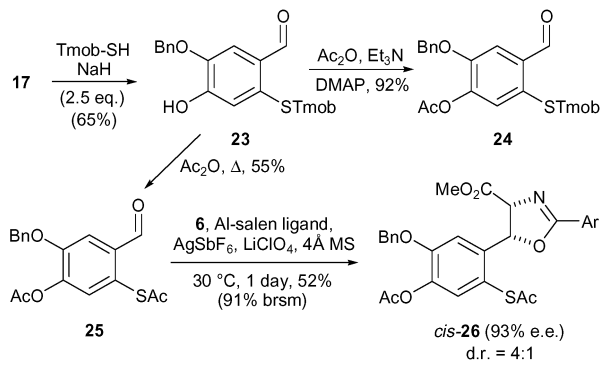
Accordingly, we sought to tune the electronic properties of the aldol substrate. The sulfide **18** was first converted to the corresponding sulfoxide in order to switch from an electron donating to an electron withdrawing group; however, no aldol adduct was produced at 35 °C.

We next sought to convert the methoxy group *para* to the aldehyde to a less electron-donating substituent. Selective demethylation of **18** by treatment with potassium thioacetate in DMSO, followed by treatment of the resulting phenol **20** with acetic anhydride, gave the acetate **21** (Scheme 4). A considerable improvement in the subsequent aldol reaction of **21** with oxazole **6** was observed, with the reaction proceeding at 35 °C to give the desired *cis*-oxazoline **22** in 39% yield. Despite this improvement, however, the still-modest yield and difficulties associated with *S*-benzyl deprotection led us to further modify the aldol substrate.



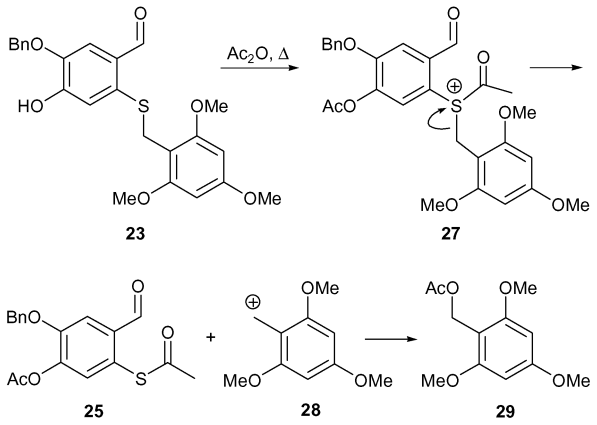
Scheme 4 Modified aldol substrate.

The 2,4,6-trimethoxybenzyl (Tmob) group has been employed as a thiol-protecting group and is removed under acidic conditions.[10] Accordingly, we prepared the *S*-Tmob protected analogue **23** (Scheme 5) using a similar route to that described for the *S*-benzyl compound **20**. However, in this case the route was significantly improved by employing two equivalents of the Tmob-thiol[11] such that the S_NAr and demethylation reactions occurred in the same pot to give **23** in a single step from **17**. Acetylation under mild conditions then furnished the substrate **24**. Unfortunately, **24** did not undergo the salen–Al-catalysed aldol reaction, even at elevated temperature and with increased catalyst loading. In retrospect, this substrate is significantly more sterically encumbered than **21**.



Scheme 5 Optimised aldol substrate.

Replacement of the Tmob group of **24** with an acetyl group was then investigated, in order to improve both the steric and electronic nature of the sulfur substituent. While the Tmob group is normally removed under acidic conditions, we envisaged an alternative procedure that would allow direct conversion of the *S*-Tmob group to the *S*-acetyl group. Acylative de-alkylation of tertiary amines upon treatment with acylating agents is a well-known process,[12] but very few examples of the corresponding reactions of sulfides are reported, and only involving intramolecular acylation.[13] We therefore investigated the feasibility of an *S*-acylation/dealkylation process for the removal of the *S*-Tmob group. Accordingly, the *S*-Tmob compound **24** was treated with acetic anhydride at reflux, and gratifyingly the *S*-Ac, *O*-Ac compound **25** was isolated in 55% yield (Scheme 5). Three transformations are in fact occurring in this one step: Tmob removal, *S*-acetylation, and *O*-acetylation. Presumably the transformation proceeds through bis-acylation of *S*-Tmob compound **23** to give *S*-acylsulfonium ion **27**, which would lose the stable trimethoxybenzyl cation **28** to give the *S*-acetyl product **25** (Scheme 6). Note that the lability of arylthiol esters renders an acylative dealkylation–thioester hydrolysis process a novel method for the deprotection of *S*-Tmob protected arylthiols (*vide infra*).

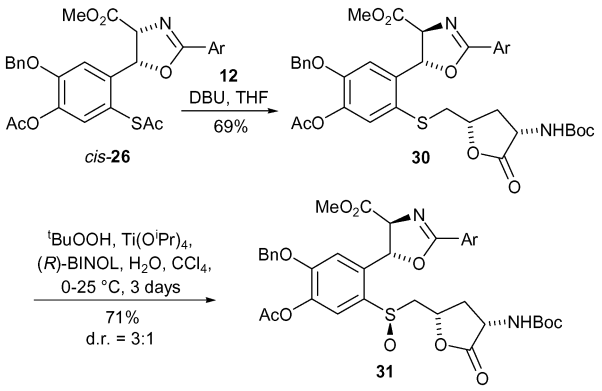


Scheme 6 Acylative de-alkylation of Tmob-protected arylthiol.

Compound **25** proved to be the best substrate for the salen–Al-catalysed aldol reaction to date. Treatment of the aldehyde **25** and oxazole **6** with 25 mol% Al-salen catalyst at 30 °C gave a 52% yield (91% based on recovered starting material) of the oxazoline **26**, as a separable 4 : 1 mixture of *cis*- and *trans*-isomers (Scheme 5). The *cis*-isomer was produced in 93% e.e., whereas the *trans*-isomer was produced in just 17% e.e., indicating the *trans*-isomer is produced in poor enantioselectivity directly from the aldol reaction, rather than by epimerisation of the *cis*-isomer. Attempts to drive the reaction to completion resulted in reduced stereoselectivity.

With the framework of the β-hydroxy-6-mercaptodopa residue in place, epimerization of the oxazoline, attachment of the norvaline moiety and asymmetric oxidation of the sulfur were next investigated. Treatment of aldol adduct *cis*-**26** with catalytic DBU effected epimerization to the corresponding *trans*-oxazoline, while the use of stoichiometric DBU was found to also effect removal of the *S*-acetyl group. Ultimately, we were again able to develop a one-pot procedure to effect several transformations: treatment of aldol adduct *cis*-**26** with 1.5 equiv. of DBU in the presence of bromolactone **12** gave the sulfide **30** directly in 69% yield (Scheme 7). Again, three transformations are conducted in one step: in this case epimerization of the oxazoline, selective *S*-deacetylation to give the corresponding thiophenolate, and subsequent substitution of the bromide **12**.

We next investigated the asymmetric oxidation of the sulfide **30** to the corresponding sulfoxide. Our model study (Scheme 2)[7] had shown that use of a catalytic amount of (*R*)-BINOL and $Ti(O^iPr)_4$ in the presence of ^tBuOOH gave the (*S*)-sulfoxide **14** as the only detectable isomer (d.r. > 50 : 1). However, when applying this oxidant system to the more complex substrate **30**, very low stereoselectivity was observed. After much experimentation, the optimal conditions developed were the use of a stoichiometric amount of (*R*)-BINOL and $Ti(O^iPr)_4$ and a large excess of



Scheme 7 Elaboration to dopa–sulfinylnorvaline conjugate.

water, which gave a 3 : 1 mixture of sulfoxide **31** and its epimer in 71% yield. The sulfoxide epimers were readily separable by flash chromatography. Sulfoxide **31** is a protected version of the complete dopa–sulfinylnorvaline component of ustiloxins A and B, and investigations toward incorporation of **31** into a total synthesis of ustiloxins A and B are currently under way in our laboratories.

In conclusion, we have achieved the synthesis of a β-hydroxydopa–γ-hydroxy-δ-sulfinylnorvaline component of ustiloxins A and B. Our method employs an Evans salen–Al-catalysed aldol reaction to generate the β-hydroxydopa portion, and alkylation/stereoselective sulfur oxidation to generate the sulfinylnorvaline portion. A novel deprotection of Tmob-protected arylthiols has been achieved and several one-pot, multi-step transformations have been developed which enable a highly efficient and succinct overall process.

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