COMMUNICATION

Synthetic studies towards marmycins A and B: development of the vinylogous aldol–aza-Michael domino reaction†

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The vinylogous aldol–aza-Michael domino reaction between 2-aminobenzaldehydes and prenal was developed to build up the core of natural products marmycin A and B without the need of protective groups.
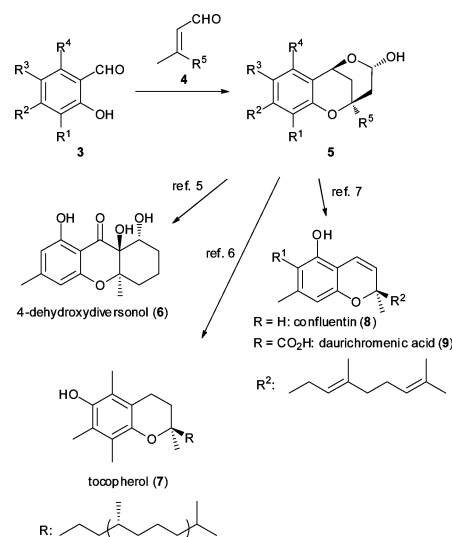
The natural products marmycin A (**1**) and B (**2**) are cytotoxic quinones isolated from a marine sediment-derived actinomycete bacterium related to the genus *Streptomyces*.[1] Their cytotoxicities against several cancer cell lines as well as their unique pentacyclic structure makes it an interesting target for synthesis.

R = H: marmycin A (**1**)
R = Cl: marmycin B (**2**)
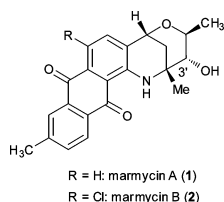
To date, no total synthesis of these products has been reported and only approaches to build up the core structure have been published. Yao and Zhang synthesized 3′-demethyl analogues using an InBr$_3$ catalyzed aminoglycosidation, but only low diastereomeric excesses were obtained using by this strategy.[2] Independently and shortly after this publication, Snider used a related strategy with a preformed building block.[3]

In our group, the vinylogous aldol–oxa-Michael domino reaction between salicylaldehydes **3** and methyl substituted α,β-unsaturated aldehydes **4** for the synthesis of tricyclic lactols **5** has been developed[4] and applied to the synthesis of dehydroxydiversonol (**6**).[5] Woggon *et al.* used the same reaction for the asymmetric synthesis of α-tocopherol (**7**),[6] confluentin (**8**) and daurichromenic acid (**9**)[7] (Scheme 1). The analogeous aza-variant of this reaction, however, is unknown.[8,9]

As lactols **5** are useful building blocks for natural product synthesis, we decided to transfer the reaction to 2-

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Scheme 1 The vinylogous aldol–oxa-Michael domino reaction in natural product synthesis.

aminobenzaldehydes as substrates. With this strategy, the construction of the marmycin core could be realized in a very short and efficient manner. We first investigated the feasibility of such a domino process with protected 2-aminobenzaldehyde (NTs and NBoc). However, no reaction took place and only starting materials were recovered. We then focused our interest on the reaction between unprotected 2-aminobenzaldehyde (**10a**) and prenal using the optimized conditions for the oxa-variant with NEt$_3$ as base. To our delight, we could isolate the desired product **11a** as a single diastereomer, albeit in low yield (12%), along with 58% of the aza-Michael–aldol product **12a**. An intensive screening of bases revealed that diisopropylamine gave the best results concerning yield and chemoselectivity (46% of **11a** and 23% of **12a**). The relatively long reaction time of 3 days is comparable to the oxa-Michael cascade.

With these optimized conditions we screened some substituted 2-aminobenzaldehydes (Table 1).

The relative configuration of the products were proven by crystal structure analyses of compounds **11a** and **11b** (Fig. 1 and 2).‡

To the best of our knowledge, this is the first reported method to build up the marmycin core structure including the bridgehead 3′-methyl group. Moreover, the lactol can be easily eliminated to give
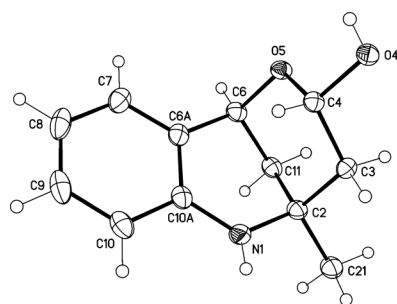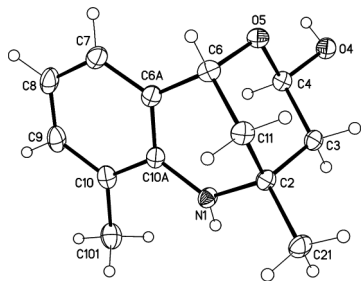
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Table 1 The vinylogous aldol–aza-Michael reaction between 2-aminobenzaldehydes and prenal

Entry	Substrate **10**	Product **11**	Product **12**	Yield **11** (%)	Yield **12** (%)
a				46	23
b				44	24
c				61	8
d				45	11
e				66	—

Fig. 1 Molecular structure of **11a** (displacement parameters are drawn at 50% probability level).

Fig. 2 Molecular structure of **11b** (displacement parameters are drawn at 50% probability level).

the 3,4-dihydropyran **13**, a useful intermediate for the synthesis of various analogues of marmycin (Scheme 2).
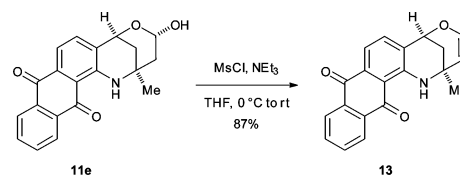
Scheme 2 Elimination to the 3,4-dihydropyran **13** as precursor for marmycin analogues.

The application of this strategy to the total synthesis of marmycins A and B is currently under investigation

Notes and references

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Mg m^{-3}, $F(000) = 472$, $\mu = 0.089$ mm^{-1}, 19255 reflections ($2\theta_{max} = 55°$), 2532 unique [$R_{int} = 0.047$], 153 parameters, 2 restraints, $R1$ ($I > 2\sigma(I)$) = 0.040, w$R2$ (*all data*) = 0.103, GOOF = 1.08, largest diff. peak and hole 0.347/−0.203 e Å^{-3}.

CCDC 808006 (**11a**) and CCDC 808007 (**11b**).

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