Organic & Biomolecular Chemistry

Cite this: Org. Biomol. Chem., 2011, 9, 3136

www.rsc.org/obc

COMMUNICATION

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

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Received 22nd January 2011, Accepted 15th February 2011 DOI: 10.1039/c1ob05124e

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.



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 InBr₃ 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 developed⁴ 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-



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 NEt₃ 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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[†] Electronic supplementary information (ESI) available: Experimental procedures, analytical data, ¹H and ¹³C spectra for compounds **11a–11e** and **13**. CCDC reference numbers 808006 (**11a**) and 808007 (**11b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05124e

Table 1 The vinylogous aldol-aza-Michael reaction between 2-aminobenzaldehydes and prenal D4

	$\begin{array}{c} R^{3} \\ R^{2} \\ R^{2} \\ R^{1} \end{array} \xrightarrow{\text{CHO}} \begin{array}{c} \text{prenal, iPr_2NH} \\ \text{dioxane/H_2O3.1} \\ \text{55 °C, 3 d} \end{array} \xrightarrow{R^{3}} \begin{array}{c} R^{3} \\ R^{2} \\ R^{2} \\ R^{1} \end{array} \xrightarrow{\text{CHO}} \begin{array}{c} R^{3} \\ R^{2} \\ R^{1} \\ R^{2} \\ R^{1} \end{array} \xrightarrow{\text{CHO}} \begin{array}{c} R^{3} \\ R^{2} \\ R^{1} \\ R^{2} \\ R^{1} \end{array} \xrightarrow{\text{CHO}} \begin{array}{c} R^{3} \\ R^{2} \\ R^{1} \\ R^{2} \\ R^{1} \\ R^{2} \\ R^{1} \end{array} \xrightarrow{\text{CHO}} \begin{array}{c} R^{3} \\ R^{2} \\ R^{1} \\ R^{2} \\ R^{2$				
		10	11 12		
Entry	Substrate 10	Product 11	Product 12	Yield 11 (%)	Yield 12 (%)
a	CHO NH ₂	H Me	CHO N H	46	23
b	CHO NH ₂ Me	H O OH N H Me	CHO Me	44	24
c	CI Me	CI Me	CI Me	61	8
d	CI NH2	CI N Me	CI NH CHO	45	11
e	O CHO NH ₂		CHO NH H	66	_

п4

п4



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

‡ Crystal structure determinations: The single-crystal X-ray diffraction study was carried out on a Bruker-Nonius Kappa-CCD diffractometer at 123(2) K using Mo-K α radiation ($\lambda = 0.71073$ Å). Direct methods (SHELXS-97)10 were used for structure solution and refinement was carried out using SHELXL-97¹⁰ (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(N,O) free).

11a: colourless, $C_{12}H_{15}NO_2$, M = 205.25, crystal size $0.30 \times 0.20 \times 0.10$ mm, monoclinic, space group $P2_1/c$ (No. 14): a = 10.838(1) Å, b = 7.683(1) Å, c = 12.432(1) Å, $\beta = 97.66(1)^{\circ}$, V = 1025.95(18) Å³, Z = 4, $\rho(\text{calc}) = 1.329$ Mg m⁻³, F(000) = 440, $\mu = 0.090$ mm⁻¹, 11513 reflections ($2\theta_{max} = 55^{\circ}$), 2334 unique [$R_{int} = 0.025$], 143 parameters, 2 restraints, $R1 (I > 2\sigma(I)) =$ 0.039, wR2 (all data) = 0.098, GOOF = 1.04, largest diff. peak and hole 0.315/-0.229 e Å⁻³

11b: colourless, $C_{13}H_{17}NO_2$, M = 219.28, crystal size $0.35 \times 0.25 \times 0.10$ mm, monoclinic, space group $P2_1/c$ (No. 14): a = 7.5344(6) Å, b = 22.2980(13) Å, c = 7.2117(7) Å, $\beta = 114.172(7)^\circ$, V = 1105.35(15) Å³, Z = 4, $\rho(\text{calc}) = 1.318$ Mg m⁻³, F(000) = 472, $\mu = 0.089$ mm⁻¹, 19255 reflections $(2\theta_{max} = 55^{\circ})$, 2532 unique [$R_{int} = 0.047$], 153 parameters, 2 restraints, R1 ($I > 2\sigma(I)$) = 0.040, wR2 (*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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