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Sequential Staudinger/Pictet–Spengler cyclization strategy for the construction of tetrahydroisoquinolines of the bioxalomycin and ecteinascidin family of alkaloids

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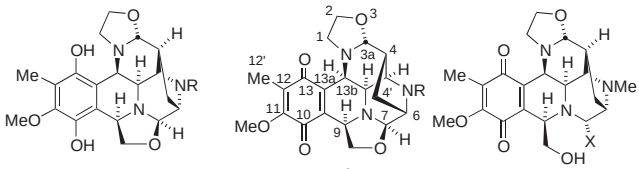
Abstract—The use of the Staudinger ketene–imine β-lactam-forming cycloaddition reaction and the Pictet–Spengler cyclization reaction in sequence, has been used to prepare highly functionalized tetrahydroisoquinolines relevant to the bioxalomycin and ecteinascidin family of antitumor alkaloids. © 2001 Published by Elsevier Science Ltd.

The bioxalomycins (**1**–**4**) are antitumor antibiotics isolated from *Streptomyces viridostaticus* subsp. '*litoralis*'.[1] Bioxalomycin α_2 (**2**), the main component of the mixture, possesses activity against Gram-positive and Gram-negative bacteria including potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[1] The structurally related saframycins[2] and the marine alkaloid ecteinascidin 743[3] are also potent antitumor antibiotics that contain densely functionalized tetrahydroisoquinoline ring systems. This family of natural alkaloids has attracted considerable synthetic attention due to their interesting profiles of biological activity and intriguing structures.[4,5] In addition, it has recently been demonstrated that bioxalomycin α_2 is a powerful DNA interstrand cross-linking agent and the oxidation state of the benzylic position (C13b) has been implicated as playing a functional role in this respect.[6]

As part of a program directed toward short, asymmetric total syntheses of these substances, we report here a potentially general method to construct densely functionalized tetrahydroisoquinolines that may be of potential use for the total synthesis of several members of this family of natural products and congeners. Our approach is based on the use of sequential Staudinger/Pictet–Spengler cyclization reactions that are readily adaptable to preparing optically pure tetrahydroisoquinolines.[7] Our retrosynthetic strategy for bioxalomycin α_2 is shown in Scheme 1.

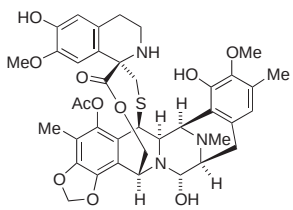
It was anticipated that the Staudinger reaction between an imine derived from aldehyde **13** and an *N*-protected ketene would afford the *cis*-relationship at C-13b and C-13c (bioxalomycin numbering).[7] After deprotection, amino phenol **12** could undergo a Pictet–Spengler reac-



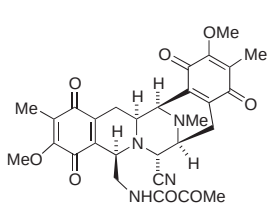
1, Bioxalomycin α_1, R = H
2, Bioxalomycin α_2, R = Me

3, Bioxalomycin β_1, R = H
4, Bioxalomycin β_2, R = Me

5, Naphthyridinomycin, X = OH
6, Cyanocycline A, X = CN



7, Ecteinascidin 743



8, Saframycin A

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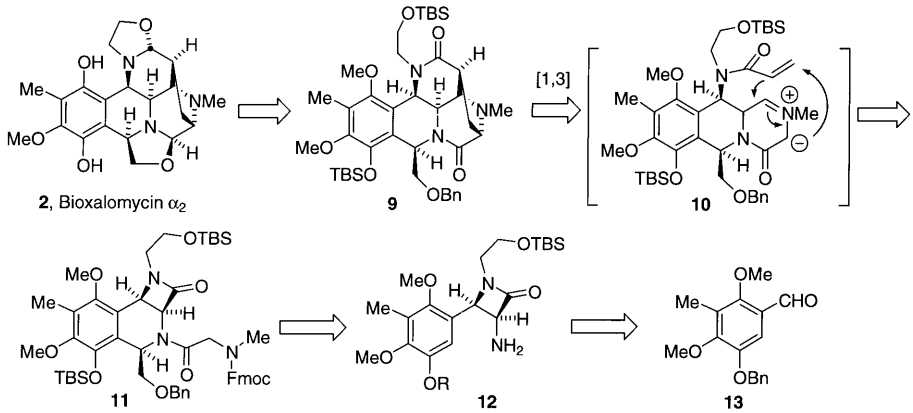
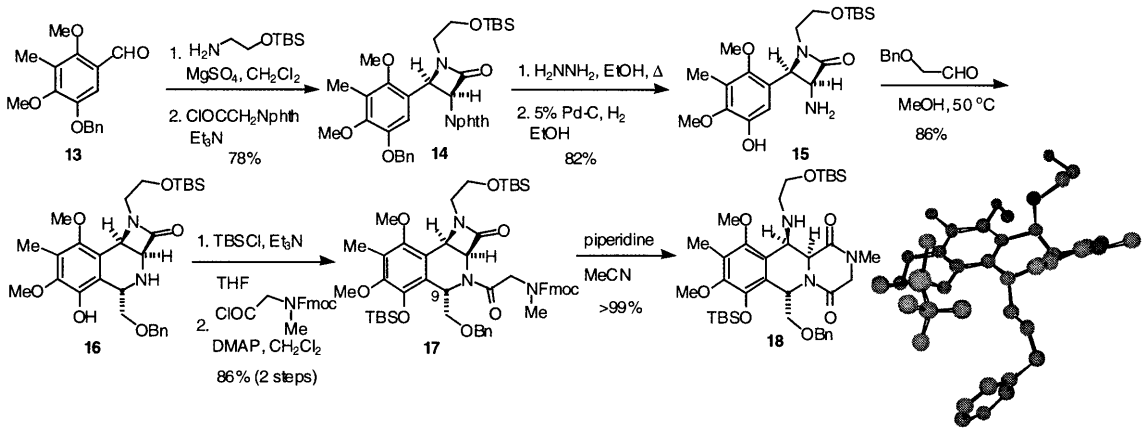
tion to form isoquinoline **11** that embodied all of the requisite functionality to tackle planned syntheses of bioxalomycin and ecteinascidin 743.

As shown in Scheme 2, aldehyde **13** was condensed with *O*-TBS-protected ethanolamine and $MgSO_4$ in CH_2Cl_2 to afford the incipient imine in excellent yield. The ketene of phthalimidoacetyl chloride was prepared at −78°C with the addition of NEt_3, the imine was added and the reaction warmed up to 0°C, which resulted in β-lactam **14** in 78% yield. The coupling constant between the β-lactam methines was 5.1 Hz, which is characteristic for the *syn* relationship and ^1H NMR nOe experiments confirmed the *syn* relationship. Removal of the phthalimide protecting group was achieved with hydrazine in refluxing ethanol, followed by hydrogenolysis of the benzyl ether to afford amino phenol **15**. Condensation of **15** with benzyloxyacetaldehyde in MeOH at 50°C resulted in **16** in 85% yield as a single diastereomer. The phenol of **16** was then protected using TBSCl and the amine acylated with Fmoc-sarcosine acid chloride to give **17**.

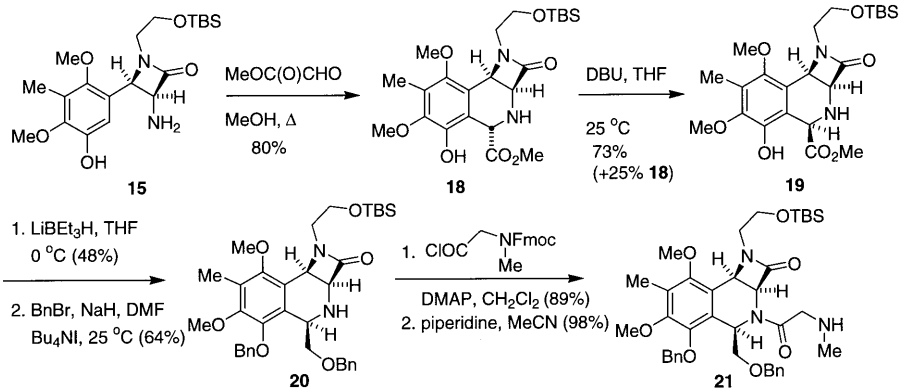
In order to secure the relative configuration of this product, a crystalline derivative was sought since ^1H NMR nOe studies proved ambiguous. Treatment of **17** with piperidine resulted in cyclization of the incipient secondary amine on the β-lactam to yield the crystalline



Scheme 1.



Scheme 2.

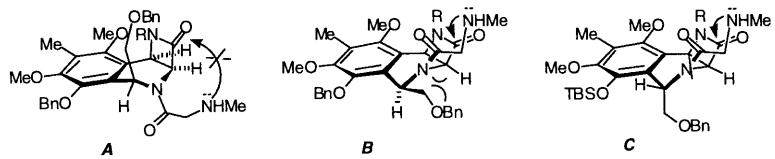


Scheme 3.

tricyclic substance **18** (95% yield) that was subjected to single-crystal X-ray analysis. The X-ray structure determination revealed that the relative stereochemistry at C-9 possessed the undesired *anti*-configuration.

In order to arrive at the correct relative configuration at C-9, we investigated the modification shown in Scheme 3. Pictet–Spengler reaction of **15** with methyl glyoxylate gave **18** in 80% yield as a single stereoisomer.[8] Epimerization of the *anti*-carbomethoxy group of **19** to the desired *syn*-isomer was accomplished by treatment of **18** with DBU in THF at room temperature affording 73% yield of **19** plus 25% unreacted **18**, which could be readily separated and recycled. Reduction of **19** to the corresponding alcohol was accomplished by treatment with $LiBEt_3H$; benzylation of both the phenolic and primary hydroxyl groups yielded **20**. Acylation of **20** as described above with Fmoc-sarcosine acid chloride followed by treatment with piperidine afforded **21** in high yield.

In stark contrast to **17**, the sarcosyl moiety of which cyclized spontaneously on the β-lactam upon removal of the Fmoc group to give the tricyclic product **18**, compound **21** was completely recalcitrant to a related cyclization even under more forcing conditions (2-OH-py, tol., Δ). The differences in reactivity between these two systems can be rationalized by considering that the conformation of **21** adopts a boat-like conformer (***A***) that disposes the β-lactam and benzyloxymethyl group in pseudo-axial orientations and the sarcosyl group pseudo-equatorial to obviate $A^{1,3}$ strain between the benzyloxymethyl and sarcosyl moieties in the alternative boat-like conformer (***B***). In the case of the secondary amide derived from the Fmoc deprotection of **17**, the *anti*-stereochemistry of the benzyloxymethyl group apparently secures access to a conformation (***C***) in which the sarcosyl moiety and the β-lactam are proximal in pseudo-equatorial orientations allowing for facile approach of the sarcosyl amino group on the β-lactam carbonyl.



Despite these interesting differences in reactivity, we have been able to effect the clean reductive ring-opening of the β-lactam of the Fmoc-protected derivative of **21** to the corresponding primary alcohol with $LiBEt_3H$ (6 equiv., THF, 56%, unoptimized). This species is presently being examined for the planned conversion to **10** and ultimately, bioxalomycin. The present approach to the densely functionalized tetrahdroisoquinoline core of the bioxalomycin/ecteinascidin family of alkaloids, may prove generally useful for accessing these and related tetrahydroisoquinolines in a rapid and efficient manner. In particular, it is significant that the Staudinger protocol exploited here, allows for the direct introduction of the correct oxidation state at the C13b position (bioxalomycin numbering). Studies along these lines are currently under investigation in these laboratories.[9]

Acknowledgements

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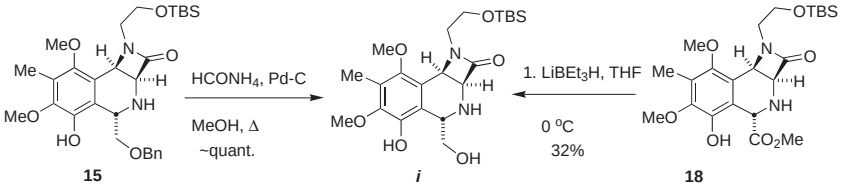
8. The relative stereochemistry of **18** was secured through correlation to ***i*** obtained from **15** as shown below:



15 ***i*** **18**

9. All new compounds gave satisfactory spectroscopic and analytical data consistent with the assigned structures.