

TETRAMATES AS ANTICANCER AND ANTIBACTERIAL CORE SCAFFOLDS

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BACKGROUND AND AIMS

Several natural products with a tetramic acid (pyrrolidine-2,4-dione) core have been proven to possess a wide range of biological activity including antibiotic, antiviral, antiulcerative and antitumours activity.¹ This project focuses on two examples of such natural products: **pramanicin**² and **equisetin**.³

The main objective is to develop chemical transformations of the common tetramate core to rapidly synthesise analogues, which mimic the natural product structures. Diversity will be introduced in the positions indicated in Figure 2, and the synthesised compounds will be assessed to examine their antibiotic and anticancer activities.

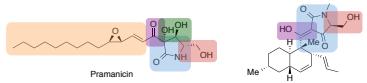


Figure 1. Structures of pramanicin and equisetin

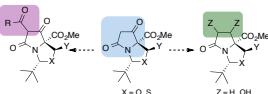


Figure 2. Aims of the project

PREPARATION OF THE TETRAMATE CORE

Oxazolidines **2a-c** were prepared from L-serine, L-cysteine and L-threonine methyl ester hydrochloride and trimethylacetaldehyde.⁴ N-Acylation with commercial ethyl hydrogen malonate under standard peptide coupling conditions gave the N-acyl compounds **3a-c**. Dieckmann cyclisation of **3a-c** with potassium *tert*-butoxide in THF gave tetramic acids **4a-c**.⁵

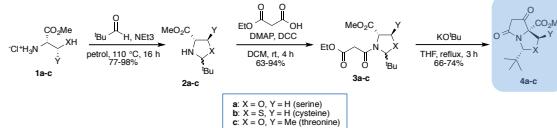


Figure 3. Synthesis of the tetramic acid for the three systems

ACYLATION OF THE TETRAMATE CORE

Acylation of oxazolidine **3a-c** followed by cyclisation with DBU gave Weinreb amides **6a-c**, which allows the introduction of any acyl group (alkyl, acyl, alkenyl and alkynyl) through a Grignard reaction.

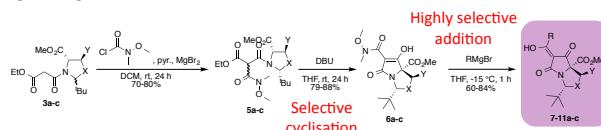


Figure 4. Synthesis of acylated compounds

Compound	R	Yield [%]		
		a (X=O, Y=H)	b (X=S, Y=H)	c (X=O, Y=Me)
7	Me	82	63	71
8	Ph	84	76	74
9	Ph-OMe	83	75	60
10	Ph	78	72	71
11	Ph	81	66	81

Table 1. Yields obtained for the synthesis of acylated compounds

Aiming to prepare a pramanicin-like acyl chain, alkyne **12** was prepared, which would then be isomerised to a dienone with palladium catalysis.⁶ However, alkyne **12** is unstable and quickly degrades to pyran **13**. Conversely, methylated alkyne **14** is stable and could be isomerised to **16**.

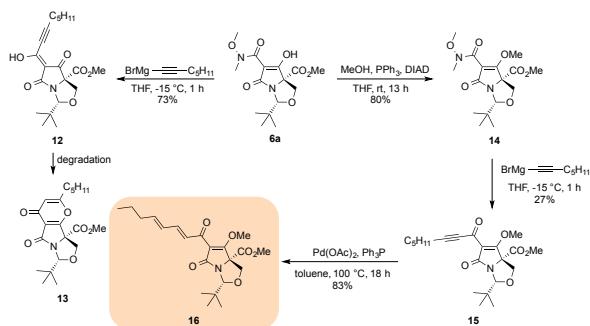


Figure 5. Introduction of a pramanicin-like acyl chain

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SUMMARY

This project aims to prepare simple mimics of two complex natural products, pramanicin and equisetin, that have anticancer and antibacterial properties.

Our goal is to exploit the structural information embedded in these natural products which have been optimised over many generations of natural selection for potent biological activity.

Rapid and efficient chemical synthesis of such small molecules has been achieved and assessment of their anticancer and antibacterial biological activity is currently in progress.

DEPROTECTION OF THE N,O-ACETAL

Deprotection of the N,O-acetal of the acylated compounds via a Corey-Richard procedure⁸ was unsuccessful, probably due to stabilisation of the lactam by intramolecular hydrogen bonding. Accordingly, deprotection of the methylated enol **18** gave the desired alcohol **17**.

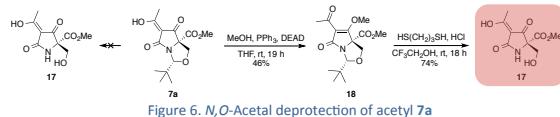


Figure 6. N,O-Acetal deprotection of acetyl 7a

REDUCTION OF THE TETRAMATE CORE

The ketone group of compounds **4a-c** can be reduced with NaBH4(OAc)3.⁷ The reaction takes place with high stereoselectivity due to hindering of the hydride attack from the nitrogen lone pair and the methyl ester.

As expected, reduction of the decarboxylated analogues **19a-c** occurred with lower stereoselectivity and was inverted for the cysteine and threonine systems, probably due to additional hindering from the bulky sulfur atom and methyl group respectively.

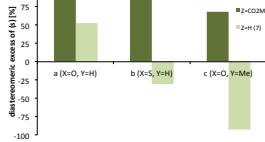


Chart 1. Diastereomeric excess of the (S) diastereomer for the reduction of **4a-c** and **19a-c**

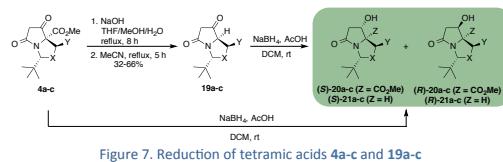


Figure 7. Reduction of tetramic acids **4a-c** and **19a-c**

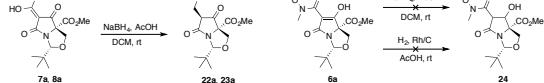


Figure 8. Unsuccessful reduction of the acylated compounds

CONCLUSIONS AND FUTURE WORK

1. The tetramate core of three systems has been prepared and functionalised by acylation, reduction and N,O-acetal deprotection. Highly selective synthetic routes have been designed to access libraries of compounds mimicking key features of the natural products pramanicin and equisetin.
2. Reduction of the tetramate core of the acylated compounds has been unsuccessful. Reduction of the Weinreb amide will be attempted by metal reduction and electrochemistry.
3. β-Lactonisation of the deprotected analogues will be studied.
4. All the synthesised compounds will be assayed for anticancer and antibacterial activity.

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