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Synthesis of Spirotetramates via a Diels–Alder Approach

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ABSTRACT

A study toward the unusual spirotetramate core of the pyrroindomycin antibiotics employing an intermolecular Diels–Alder reaction of an *exo*-methylene tetramic acid dienophile is described. The *exo*-methylene tetramate is readily synthesized from *S*-methylcysteine, and its reactivity as a dienophile is compared with that of related dehydroalanine derivatives. An alternative approach to spirotetramates using a nitroalkene dienophile is also reported.

Tetramic acids (pyrrolidine-2,4-diones) occur widely in Nature as secondary metabolites produced by a wide range of terrestrial and marine organisms.[1−3] A large number of these natural products carry acyl substituents at C-3, and these 3-acyltetramates often have more pronounced biological activity, a fact ascribed to their potential ability to act as ligands for metal ions and to mimic phosphate.[2] 3-Acyltetramates, which originate by mixed biosynthetic routes involving nonribosomal peptide and polyketide pathways, range in structural complexity from tenuazonic acid **1**,[4−7] to equisetin **2**,[8−11] to cylindramide A **3**[12−14] (Figure 1).

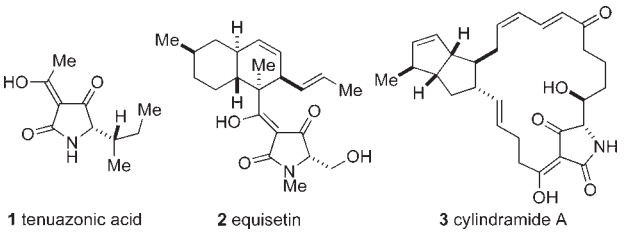

Figure 1. Some naturally occurring 3-acyltetramic acids.

However, it was the reports on the structurally unique antibiotics, the pyrroindomycins **4**,[15,16] that captured our attention. These compounds, isolated from fermentation of culture LL42D005, a strain of *Streptomyces rugosporus*,

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during the screening for molecules active against Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE), not only contain the unusual 1,8-dihydropyrroloindole heterocycle[17] but also differ from other 3-acyltetramic acid natural products in that they contain a spirotetramate core (Figure 2). The pyrroindomycins represent the first spirotetramates isolated from Nature, although closely related spirotetronic acids such as chlorothricin **5b** are known (Figure 2).[18] Although the stereochemistry of the pyrroindomycins remains unknown their unusual architecture and structural complexity make them interesting and challenging targets for synthesis. We now report the first efforts in this direction with an approach to the spirotetramate core utilizing the Diels–Alder reaction.

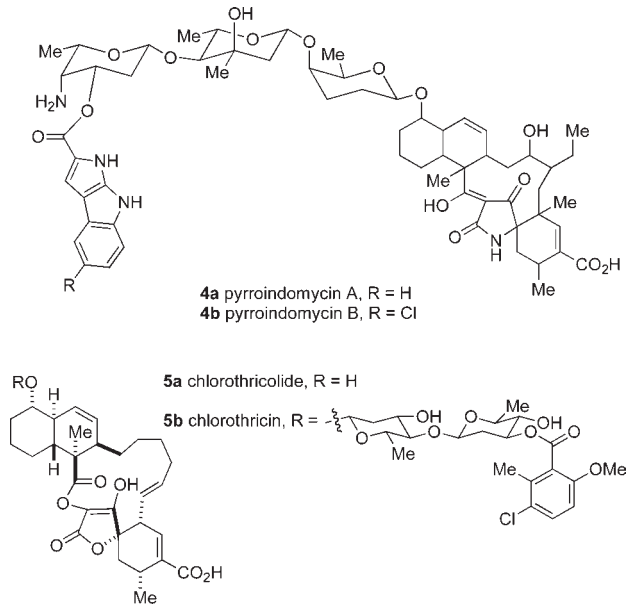
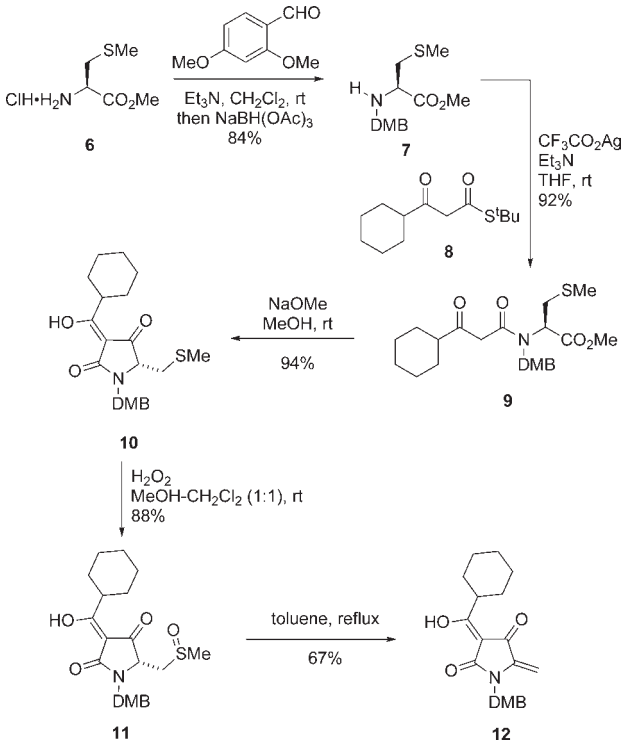


Figure 2. Structures of the spirotetramate pyrroindomycins and related spirotetronates, chlorothricolide and chlorothricin.

Several methods have been employed to synthesize tetramic acids in general,[1] but the most common method used for 3-acyltetramic acids is the Lacey–Dieckmann cyclization of a β-ketoamide.[19] However none of these methods involve the synthesis of 3-acylspirotetramates, and therefore we have developed a new approach to these spiro compounds utilizing the *exo*-methylene 3-acyltetramic acid **12** (containing a cyclohexyl group as a model for the complex octalin system of the pyrroindomycins) as a dienophile in an intermolecular Diels–Alder reaction. This strategy not only complements similar strategies used for spirotetronic acids[18] but also continues our use of dehydroalanine type dienophiles in the synthesis of complex natural products.[20]

The synthesis of the tetramic acid dienophile **12** started from readily available *S*-methyl cysteine methyl ester **6** (Scheme 1). Protection of the amine functionality *via* reductive amination with 2,4-dimethoxybenzaldehyde and $NaBH(OAc)_3$ gave amine **7** in excellent yield. The 2,4-dimethoxybenzyl (DMB) group was chosen for its capacity to tolerate conditions used further in the synthesis and its proven ability to be readily removed from complex tetramic acids.[14] Formation of β-ketoamide **9** was achieved in excellent yield by reaction of the protected amine **7** with thioester **8** (prepared from cyclohexane carboxylic acid and the lithium enolate of *tert*-butyl thioacetate) using the Ley protocol of triethylamine and silver trifluoroacetate.[11] Lacey–Dieckmann cyclization using standard conditions gave the desired 3-acyltetramic acid **10**. Sulfoxide **11** was readily prepared *via* oxidation using hydrogen peroxide, and the final step was achieved by a thermal elimination of the sulfoxide to give the methylene tetramic acid **12** in good yield (Scheme 1). Long reaction times and promotion of the elimination using basic conditions led to the degradation of starting material. Tetramic acid **12** was obtained as a yellow oil and exists as a mixture of enol forms at room temperature as observed in its proton and carbon NMR spectra, presumably the dominant species being the 2,4-diketo form with an

Scheme 1. Synthesis of the *exo*-Methylene Tetramate Dienophile **12**



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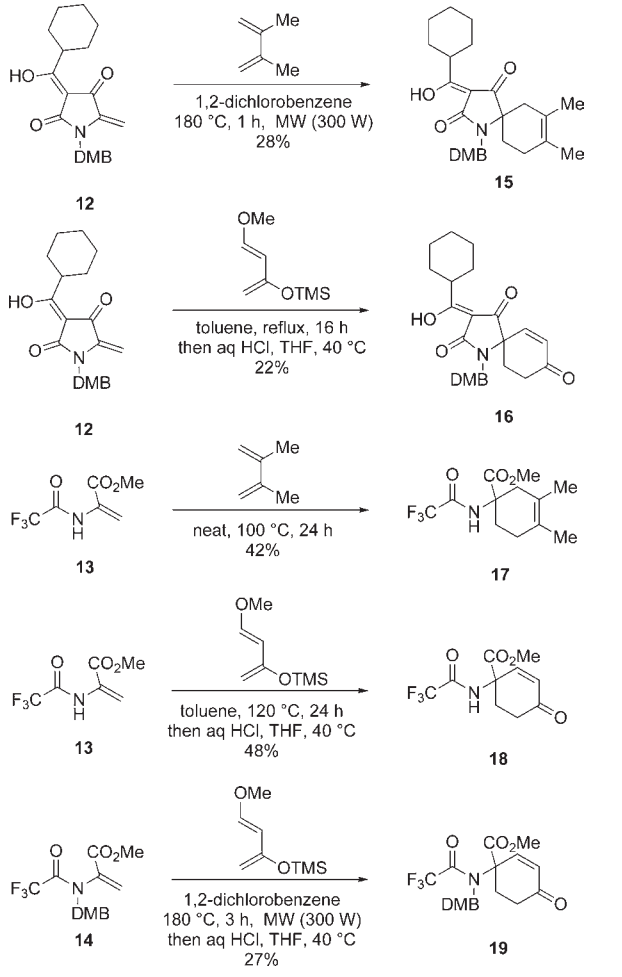
exocyclic enol in accord with previous observations on 3-acyltetramic acids.[21]

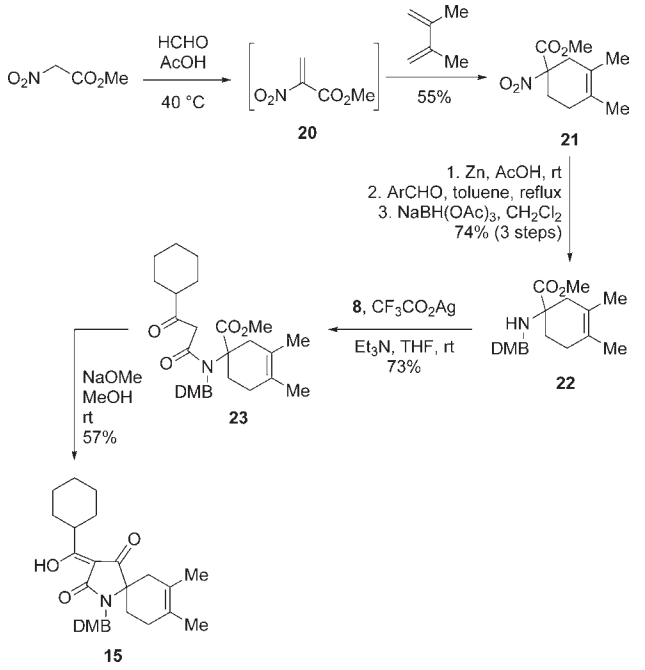
With the desired dienophile **12** in hand, its ability to undergo a Diels–Alder reaction with simple electron-rich dienes was investigated and compared to that of the structurally related known dehydroalanine **13**,[22] and the corresponding DMB-derivative **14**. Tetramic acid **12** proved a relatively modest dienophile but nevertheless reacted with 2,3-dimethyl-1,3-butadiene and with Danishefsky's diene to give the desired spirotetramates **15** and **16** in moderate yields (Scheme 2), as predominantly

Scheme 2. Diels–Alder Reactins of *exo*-Methylene Tetramate **12** and Related Dehydroalanine Derivatives **13** and **14**



single enol tautomers. In the Diels–Alder reaction with Danishefsky's diene, the initial adduct was not isolated but converted into enone **16** under acidic conditions, and the regiochemical outcome was confirmed by HMBC spectroscopy (no correlation was observed between the ketone carbon of the enone and the spirocenter) and is in accord with literature precedent for dehydroalanine derivatives.[23] Attempts to improve the yield of the Diels–Alder reactions using Lewis acids and higher temperatures were unsuccessful, resulting in degradation of the tetramic acid dienophile. As expected, *N*-trifluoroacetyl dehydroalanine **13** underwent the corresponding Diels–Alder reactions satisfactorily to give the cyclohexenes **17** and **18** (Scheme 2). However, in contrast to **13**, the *N*-protected dehydroalanine **14** showed reduced activity and only underwent a Diels–Alder reaction with Danishefsky's diene to give **19** (after enone formation under acidic conditions) in poor yield. Dehydroalanine derivatives such as **7** are known to undergo a Diels–Alder reaction with a range of dienes,[23–25] but it appears that the steric and/or electronic effects of the *N*-2,4-dimethoxybenzyl group are detrimental to reactivity. The *exo*-methylene tetramate **12** shows similar dienophilic reactivity to the *N*-2,4-dimethoxybenzyl dehydroalanine **14**; attempts to remove the DMB-protecting group from tetramate **12** to enhance reactivity were not successful.

Scheme 3. Alternative Synthesis of Spirotetramate **15**



In view of the poor reactivity of the methylene tetramate **12** in the direct Diels–Alder route to spirotetramates, we also investigated an alternative route in which the cycloaddition was effected *before* formation of the pyrrolidine-2,4-dione, exemplified for the case of spirotetramate **15** (Scheme 3). At the same time, we also elected to increase the reactivity of the dienophile by employing the highly

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reactive nitroalkene ester **20**, generated *in situ*. Thus following a literature procedure,[26] methyl nitroacetate was condensed with formalin in acetic acid in the presence of 2,3-dimethyl-1,3-butadiene at 40 °C to give the cyclohexene nitro ester **21** in 55% yield. Reduction of the nitro group with zinc in acetic acid, followed by reductive amination with 2,4-dimethoxybenzaldehyde using an analogous procedure to that described previously, gave the aminoester **22**. Silver trifluoroacetate mediated reaction of **22** with thioester **8** proceeded smoothly and gave the β-ketoamide **23**, subsequently subjected to Lacey–Dieckmann cyclization to give the desired spirotetramate **15** (Scheme 3), identical to the sample prepared by the Diels–Alder reaction of tetramate **12**. This method for preparing spirotetramates has the advantage of being able to use less reactive dienes for the Diels–Alder reaction, provided they are stable to acidic conditions, and will enable the preparation of a range of 3-acylspirotetramates.

In conclusion we have developed new methodology for the short and efficient syntheses of spirotetramates from inexpensive starting materials, which will be directly applicable to spirotetramate containing natural products.

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Supporting Information Available. Full experimental details and characterization data, copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.