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Stereoselective cycloadditions of chiral acyl-nitroso compounds; selective reactions of ring-cleaved cycloadducts leading to a new approach to polyoxamic acid

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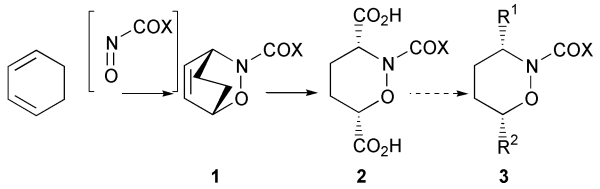
Diesters obtained from diacids produced by oxidative ring cleavage of cycloadducts derived from acyl-nitroso compounds and cyclic 1,3-dienes undergo highly regioselective hydrolysis on reaction with lithium hydroperoxide, which allows for easy differentiation of the carboxyl groups leading to a new approach to polyoxamic acid.

The stereoselective cycloaddition of acyl-nitroso compounds to cyclic dienes can provide a powerful approach to the synthesis of a range of natural products.[1] We are interested in extending our previous studies[2] in this area to their application in natural product synthesis. A strategy common to several of these synthetic endeavours involves oxidative cleavage of the double bond of the cycloadduct **1**, followed by differentiation of the resulting diacid **2**, to give an intermediate **3** in which the groups R^1 and R^2 can be selectively modified in the subsequent synthetic scheme (Scheme 1).

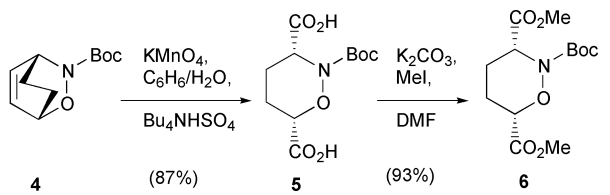


1 **2** **3**

Scheme 1

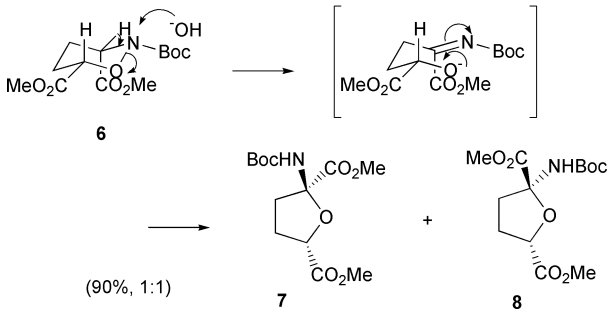
One of the most convenient methods for the oxidative cleavage (**1** to **2**) uses potassium permanganate under phase transfer conditions. The resulting diacids are often rather insoluble solids and so for convenience in subsequent reactions they are converted to the corresponding diesters (Scheme 2).

One of the simplest approaches to the differentiation of diesters derived from diacids such as **2** would be by selective hydrolysis. To investigate this, the racemic *tert*-butoxycarbonyl (Boc) cycloadduct **4** was converted into the diester **6** in high yield (Scheme 2) and its reaction with aqueous base investigated. Initial attempts to carry out such selective hydrolysis of **6** led to either decomposition, or to a rearrangement. For example, exposure of the diester **6** to barium hydroxide octahydrate in methanol resulted in the isolation of an inseparable mixture of two compounds, isomeric with starting material, which have been tentatively assigned as the epimeric



4 (87%) **5** (93%) **6**

Scheme 2



6 **7** **8**

Scheme 3

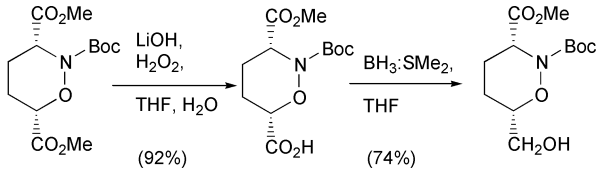
tetrahydrofurans **7** and **8** (Scheme 3). The physical data (MS, IR, ^{1}H NMR and ^{13}C NMR spectra) are consistent with the proposed structures, and it is possible that these products arise *via* an elimination process (Scheme 3).[3]

The chemoselectivity might then be a consequence of the conformation of diester **6**. The ^{1}H NMR spectrum of **6** shows a low-field proton with a large *trans*-diaxial coupling constant (12 Hz) assigned to H-6, implying that the C-6 ester group is equatorial. Consequently H-3 should be equatorial, and well aligned for a *trans* elimination. Molecular modelling[4] using the MM2 force field predicts that the lowest energy conformation of the diester corresponds to that suggested from analysis of the ^{1}H NMR spectrum (Scheme 3).

Selective hydrolysis could however be achieved using lithium hydroxide and hydrogen peroxide[5] to produce the mono-ester **9** in high yield. The structure of this mono-ester was provisionally assigned as **9**, confirmed by its subsequent reactions. This difference in reactivity towards nucleophilic attack was also evident in the reaction of diester **6** with sodium borohydride. Reaction of **6** with sodium borohydride supported on alumina[6] ($NaBH_4$–Al_2O_3) gave selectively the alcohol, **10**. Although the reduction of diester **6** into **10** is direct and experimentally simple, the yield is moderate (45%), and in our hands the reaction did not scale up well. Reduction of acid **9** with borane–methyl sulfide (Scheme 4) is both clean and high yielding, and this two step process represents a better route to alcohol **10**.

The highly regioselective hydrolysis of **6** is also consistent with the above conformation (Scheme 3), as it corresponds to preferential attack on the equatorial, rather than the axial ester group, known to be the case in cyclohexane systems.[7]

As might be expected for nucleophilic attack on the more reactive ester group, both hydrolysis and reduction of diester **6**



6 (92%) **9** (74%) **10**

Scheme 4

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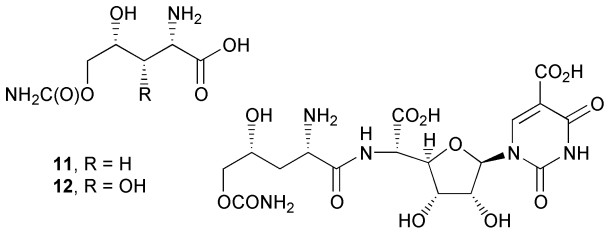
take place at the same carbonyl group. That this corresponded to attack at the C-6 ester rather than C-3 was demonstrated by carrying out the cleavage of the N–O bond of alcohol **10** by the action of anhydrous SmI_2 in THF, and careful analysis of the ^1H NMR spectra of the product. From these spectra, and other NMR measurements, it was clear that the proton next to the ester group was adjacent to the NH, and that a $CH(OH)CH_2OH$ fragment was present, thereby confirming the structure of **10** as illustrated (Scheme 4).

At this stage we realised this strategy could open up a new approach towards the polyoxamic acid, **11**. This amino acid is a



Polyoxin E, **13**

fragment of a number of natural products known as the polyoxins, which form a class of peptidyl nucleoside antibiotics, isolated from cultures of *Streptomyces cacaoi var. asoensis*.[8] A number of polyoxins have been isolated, including polyoxin E, **13**. These natural products are known to inhibit chitin synthesis and are active against the phytopathogenic fungus *Pellicularia filamentosa f. sasakii*, which causes sheath blight disease of rice plants. The polyoxins were found to be excellent agricultural fungicides and have been widely used as such in Japan since 1966.

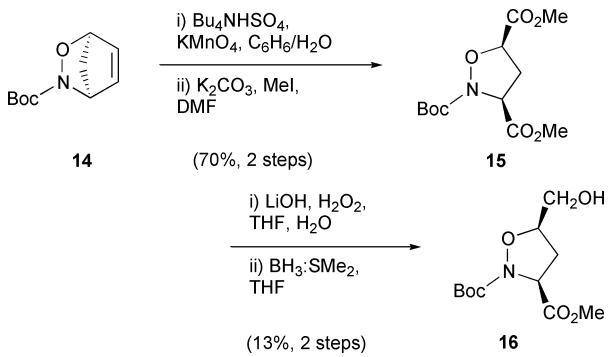
No synthesis of the amino acid portion **11** of polyoxin E has been uncovered, although there are a number of syntheses that have been reported for various polyoxins,[9] as well as for the other amino acid, **12**,[10] commonly found in the polyoxin series.

Our initial studies involved the acyl-nitroso cycloaddition with cyclopentadiene, producing the racemic cycloadduct **14**. This was converted to the diacid by oxidative double bond cleavage under phase transfer conditions, followed by a simple esterification procedure to produce the desired diester **15** in satisfactory yield (Scheme 5).

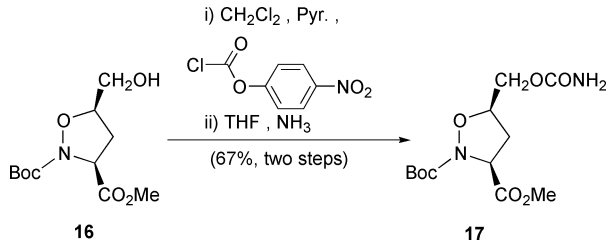
Regioselective transformation of the diester **15** to the desired alcohol ester **16** was carried out by selective hydrolysis to the acid ester, followed by chemoselective reduction of the carboxylic acid moiety (Scheme 5).

A moderate drop in overall yield was observed on going from the six-ring system to this five-ring system, however the regioselectivity of the hydrolysis step was complete with only a single isomer being isolated from the reaction mixture, albeit it in a modest yield of 43%.

At this point the *O*-carbamoyl group was attached by standard chemistry[11] in good yield, as illustrated in Scheme 6 to give compound **17** a fully protected analogue of the desired



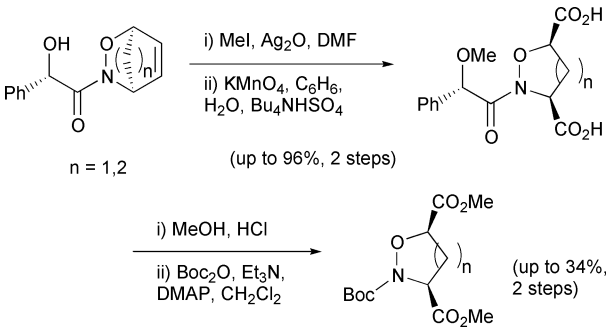
Scheme 5



Scheme 6

polyoxamic acid, which to date has not been unmasked to polyoxamic acid itself.

All the chemistry described above was carried out using racemic cycloadducts. This chemistry is easily transferred to either enantiomeric series by use of the acyl-nitroso intermediate derived from either enantiomer of mandelic acid, as outlined in Scheme 7 for *S*-mandelohydroxamic acid.[12]



Scheme 7

In conclusion we have demonstrated a facile approach for the differentiation of diesters derived from cycloadducts of acyl-nitroso species with cyclic dienes and have a useful route to functionalised oxazines and isoxazolines, as well as applying this methodology to develop a new approach to the synthesis of polyoxamic acid. We are currently extending these studies, and investigating the application of this approach to the synthesis of other nitrogen containing natural products.

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