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An Intramolecular Acylnitroso Cycloaddition With a Cleavable Tether[1]

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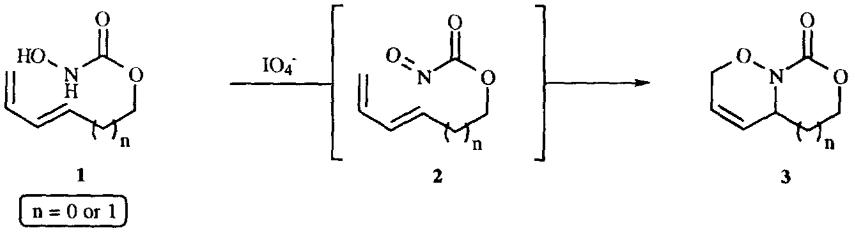
Abstract: An intramolecular acylnitroso cycloaddition with a cleavable tether is reported together with effective conditions for assembling the precursors and cleaving the tether. A possible application to the synthesis of AI-77-B is discussed.

The acylnitroso cycloaddition has a successful history in organic synthesis, being employed as a key step in a number of sophisticated total syntheses.[2] The intramolecular version, although of a more recent vintage has also proved to be of great value in natural products synthesis.[2] Herein we report a variant of the latter with a cleavable tether (scheme 1). Such a strategy offers the possibility of imposing control on the regiochemistry and in appropriate cases the stereochemistry of such cycloaddition reactions. It must, however, be recognised that on cleavage of the tether the product will be that of the corresponding intermolecular reaction and hence comparison will be made to these cases.



Scheme 1

N-hydroxycarbamates are usually prepared by condensation of a chloroformate or a similarly activated species with hydroxylamine. Initial experiments on the chloroformylation of sorbyl alcohol **4** showed a marked instabilty of this derivative and thus we opted to derivatise **4** with p-nitrophenylchloroformate. Thus on treatment of **4** with p-nitrophenylchloroformate (1.1 eq.) in the presence of pyridine a 91% yield of crystalline **5** was obtained. Displacement of p-nitrophenol was effected by treatment of **5** with a concentrated solution of hydroxylamine in pyridine at room temperature to afford **7** in up to 79% yield after chromatography. However, it proved difficult to obtain analytically pure samples of **7** by this method and the

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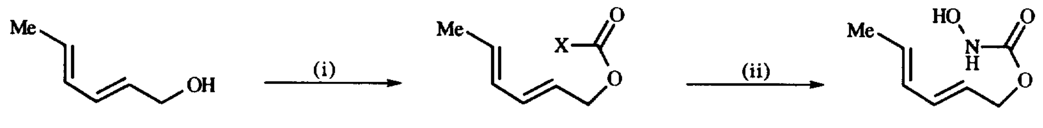
yields varied somewhat. Thus we reacted **4** with 1,1'-carbonyldiimidazole to deliver **6** in 97% yield[3] which was found to be essentially pure after an aqueous wash; subsequent treatment with hydroxylamine in pyridine afforded **7** in 84% yield (scheme 2).



4

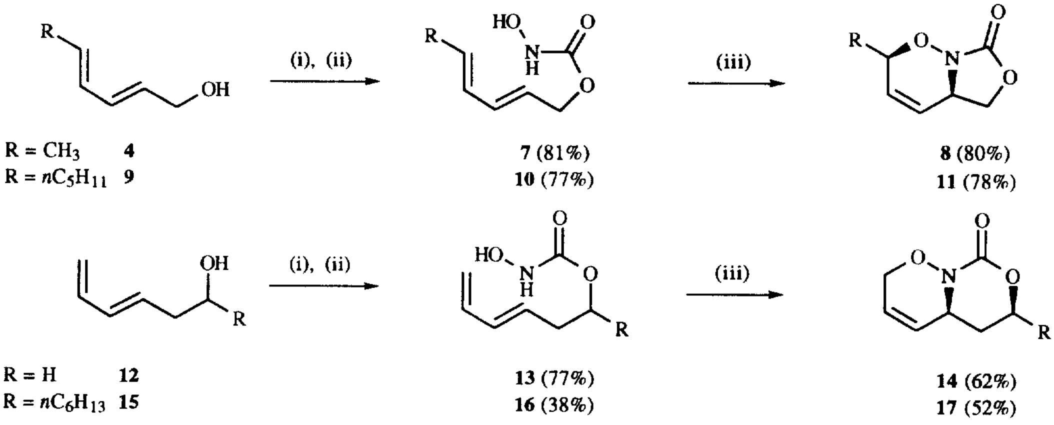
5 X = *p*-nitrophenoxy
6 X = imidazole

7

Reagents and Conditions:
(i) Either *p*-nitrophenylchloroformate, THF, pyridine or 1,1'-carbonyldiimidazole, CH_3CN (ii) $NH_2OH.HCl$, pyridine.

Scheme 2

With a satisfactory method for the synthesis of the cycloaddition precursors in place we prepared three further compounds with good to moderate overall yields (scheme 3).[4,5] Oxidation of the *N*-hydroxycarbamates to the corresponding nitroso species (Et_4NIO_4 at 0 °C)[6] with concomitant Diels-Alder cycloadditon afforded the bicyclic adducts **8**, **11**, **14** and **17**; slow addition of the *N*-hydroxycarbamate to the periodate solution giving the highest yields. For compound **17** only the diastereoisomer shown was detected by 300MHz ^1H NMR.



R = CH_3 **4**
R = nC_5H_{11} **9**

7 (81%)
10 (77%)

8 (80%)
11 (78%)

R = H **12**
R = nC_6H_{13} **15**

13 (77%)
16 (38%)

14 (62%)
17 (52%)

Reagents and Conditions:
(i) 1,1'-Carbonyldiimidazole (3eq.), CH_3CN; (ii) $NH_2OH.HCl$, Pyridine; (iii) NEt_4IO_4, $CHCl_3$, 0 °C.

Scheme 3

The stereoselectivity observed in the formation of **17** may be rationalised by the transition state model shown in fig. 1 which is in accord with that proposed for the equivalent acylimine cycloaddition reported by Weinreb *et al.*[7]

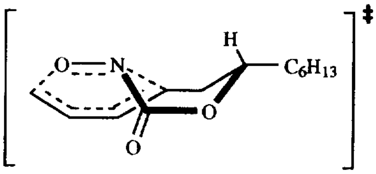
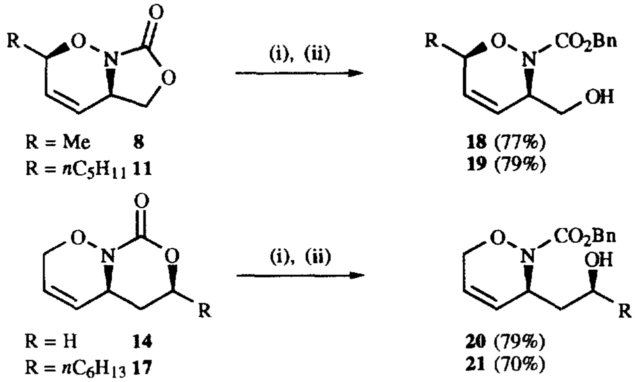


Figure 1

Hydrolysis of the tether occured smoothly in each case on treatment with alcoholic potassium hydroxide, the crude product being directly Z-protected to afford the corresponding carbamates in good overall yield (scheme 4).



R = Me **8**
R = nC$_5$H$_{11}$ **11**

18 (77%)
19 (79%)

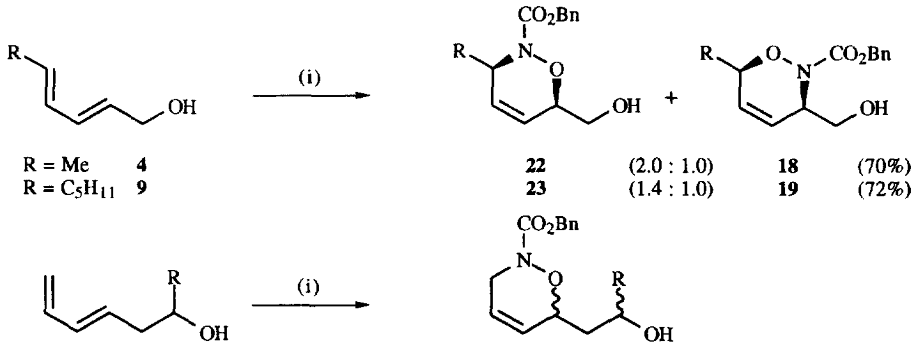
R = H **14**
R = nC$_6$H$_{13}$ **17**

20 (79%)
21 (70%)

Reagents and conditions: (i) KOH, EtOH; (ii) BnOCOCl, aq. NaHCO$_3$, CHCl$_3$.

Scheme 4

For the sake of comparison each of the dienes was reacted with benzyl nitrosoformate (scheme 5). In the case of the terminal dienes **12** and **15** the single regioisomer of cycloadduct obtained was of the opposite sense to the intramolecular case. The internal dienes **4** and **9** gave a mixture of regioisomers in the range 1.4-2.0 : 1.0, again favouring the opposite sense to the intramolecular case.



R = Me **4**
R = C$_5$H$_{11}$ **9**

22 (2.0 : 1.0) **18** (70%)
23 (1.4 : 1.0) **19** (72%)

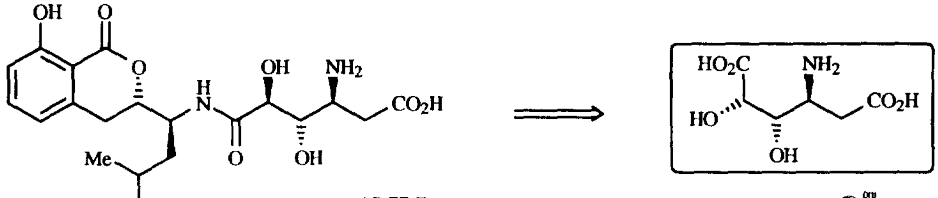
R = H **12**
R = C$_6$H$_{13}$ **15**

24 (79%)
25 (70%) ~7:1 mixture of diastereoisomers

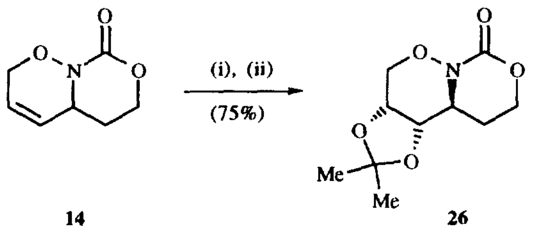
Reagents and conditions: (i) BnO(CO)NHOH, Et$_4$NIO$_4$, CHCl$_3$.

Scheme 5

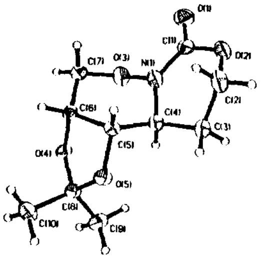
We are currently seeking to apply this methodology to a synthesis of the potent gastroprotective agent AI-77-B.[8] Pursuant to this objective we examined dihydroxylation of **14** and found that treatment with OsO$_4$ under the Upjohn conditions[9] followed by acetonide protection of the resultant diol[10] delivered **26** as a single diastereoisomer in 75% yield. The relative stereochemistry was established by X-ray crystallography (scheme 6).[11]



AI-77-B



14 26



ORTEP drawing of the X-ray structure of 26

Reagents and conditions: (i) OsO_4, NMO, acetone, H_2O; (ii) 2,2-dimethoxypropane, Amberlite 15.

Scheme 6

Acknowledgements

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References and Notes

1. This paper is dedicated to Prof. Sir Jack E. Baldwin F.R.S. on the occasion of his 60th birthday.
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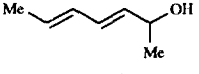

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11. Crystal data: monoclinic; $P2_1/c$; a = 10.619(1) Å, b = 14.300(1) Å, c = 7.364(1) Å, β = 103.952(9)°; Z = 4; goodness-of-fit on F^2 1.059; final R indices [$I > 2\sigma(I)$] R_1 = 0.0523, wR_2 = 0.1347; R indices (all data) R_1 = 0.0571, wR_2 = 0.1423. Complete supplementary material has been deposited at CCDC.