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CONVERSION OF ISOXAZOLINES TO β-HYDROXY ESTERS. SYNTHESIS OF 2-DEOXY-D-RIBOSE

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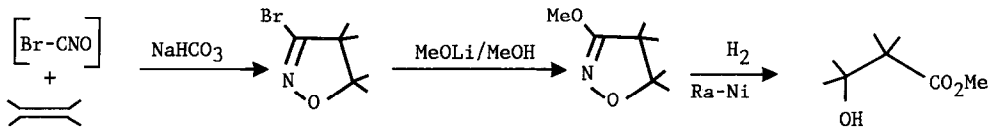
Summary: A simple and efficient preparation of β-hydroxy esters with a well-defined stereochemistry has been developed using 3-bromoisoxazolines as key-intermediates.A synthesis of 2-decxy-D-ribose is also reported.

Isoxazoles and Δ^2-isoxazolines have become a valuable tool for the synthesis of natural products[1-3]; we have undertaken recently a study which reveals their ability in the synthesis of biologically active compounds[4].
In continuing our efforts in this vein we now report the transformation of 3-bromoisoxazolines into β-hydroxy esters with a stereochemistry dictated by the structure of the starting alkene.
The overall process is quite straightforward and begins with the 1,3-dipolar cycloaddition of bromonitrile oxide[5], prepared "in situ" from dibromoformaldoxime and solid sodium bicarbonate, with the alkene of choice.

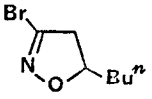
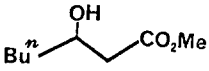
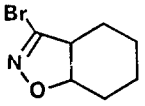
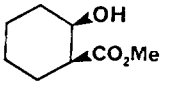
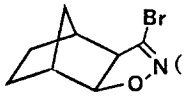
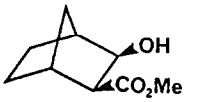
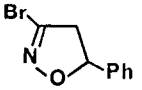
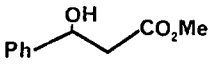
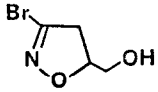
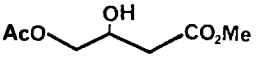
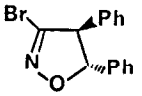
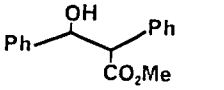
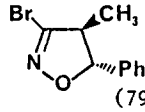
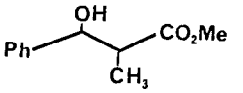
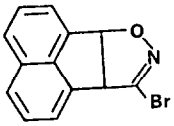
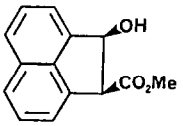
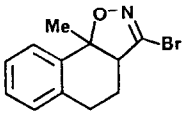
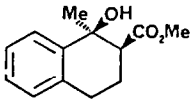
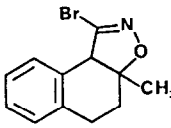
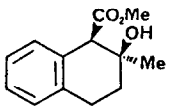
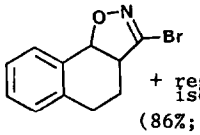
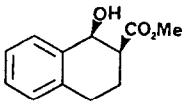
Scheme 1



1 2 3 4

Treatment of a methanolic solution of 2 with a base (MeOLi, $Ba(OH)_2$ or K_2CO_3) leads to the formation of 3-methoxyisoxazolines 3 which can be efficiently transformed into β-hydroxy esters 4 by a hydrogenolysis-hydrolysis procedure (H_2, Raney-Ni; $B(OH)_3$).
This methodology parallels that reported by Wade[6] based on benzenesulfonylnitrile oxide and

Table 1. Synthesis of β-Hydroxy Esters from 3-Bromoisoxazolines

Entry	Alkene	3-bromoisoxazoline (yield %)[a]	3-methoxyisoxazoline (yield %)[a]	β-hydroxy ester (yield %)[a]
a.	n-hexene	 (78)	(93)	 (47)
b.	cyclohexene	 (58)	(67)	 (32)
c.	norbornene	 (75)	(100)	 (78)
d.	styrene	 (75)	(100)	 (76)
e.	allyl alcohol	 (90)	(77)	 (84)[b]
f.	trans-stilbene	 (70)	(100)	 (88)
g.	trans-1-phenyl-propene	 + regio-isomer (79%; 73:27)	(83)	 (66)
h.	acenaphthylene	 (87)	(100)	 (88)
i.	1-methyl-3,4-dihydronaphthalene	 (85)	(100)	 (43)
l.	2-methyl-3,4-dihydronaphthalene	 + regio-isomer (77%; 74:26)	(67)	 (67)
m.	1,2-dihydronaphthalene	 + regio-isomer (86%; 79:21)	(96)	 (78)

[a]The yields were calculated after purification of the products by silica gel chromatography.
[b]The 3-methoxy-5-hydroxymethylisoxazoline was acylated before the hydrogenation step.

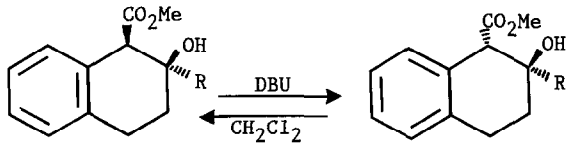
complements other routes[7], based on the chemistry of nitrile oxides, less flexible and difficult to apply to sensitive systems.

Several points of the present methodology are worthy of note. The efficacy of the cycloaddition step is mainly due to the generation of the nitrile oxide under a heterogeneous phase which limits the "in situ" concentration of the 1,3-dipole reducing the competing dimer formation. As a consequence, even sluggish dipolarophiles such as trisubstituted olefins (Entries i,l) enter the cycloaddition in excellent yields.

The preparation of 3-methoxyisoxazolines 3 has been carried out in methanol with a five fold excess of lithium methoxide but bases such as barium hydroxide or potassium carbonate are equally effective.

This treatment with bases does not epimerize the cycloadducts but entry g where a cis-trans isomerization occurs for both the regioisomers; a gas-chromatographic analysis reveals in fact that the cis-trans ratio is similar for the two regioisomers (22:78 and 21:79).This outcome can be attributed to the relative thermodinamic stability of the epimers.

As expected[8], the reduction step proceeds with a complete stereospecificity and this result was confirmed in two cases by the synthesis of the epimers as reported below:



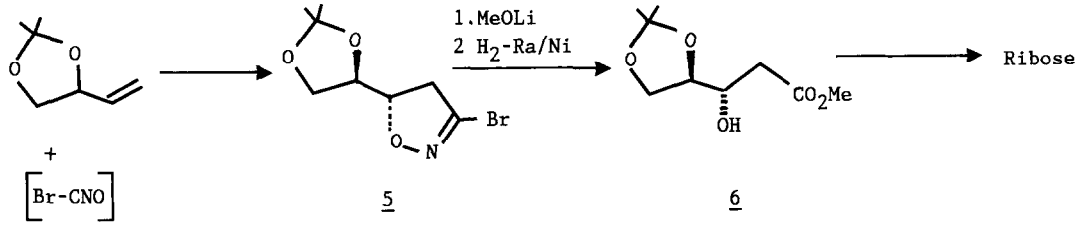
R =H	20%	80%
R =Me	48%	52%

To further illustrate the utility of the present methodology, we undertook a synthesis of 2-deoxy-D-ribose.

The cycloaddition of bromonitrile oxide to (+)-(S)-isopropylidene-3-buten-1,2-diol, prepared from D-glyceraldehyde by reaction with methylenetriphenylphosphorane[9], yielded a 86:14 mixture of diastereomeric cycloadducts (96% yield).

These products were separated by column chromatography, and the major isomer 5[10] was heated under reflux with an excess of lithium methoxide in methanol to prepare the corresponding 3-methoxy derivative in 87% yield which, in turn, was hydrogenated to give β-hydroxy ester 6[11] (79% yield). The overall yield of the reaction sequence is 69%.

6 was then transformed into 2-deoxy-D-ribose according to Kozikowski et al.[11].



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References and Notes

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5. Typical procedure: To a suspension of dibromoformaldoxime (2mmol) and $NaHCO_3$ (15mmol) in ethyl acetate(15ml),an excess of dipolarophile(10mmol) is added. The slurry is stirred overnight then poured into water and extracted with ether.The residue of the organic phase is column chromatographed, the cycloadducts separated from furoxan and excess dipolarophile.In Entry 1 a two fold excess of 1,3-dipole was used.
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10. The structure has been assigned in analogy to previosly reported results in this area[11]. 5: m.p.71-72°C(ligroin);α_D^{20} +75.52°(1.348,$CHCl_3$). 3-methoxy derivative: b.p.95-100°C/0.8mmHg;α_D^{20} +54.15°(1.278,$CHCl_3$).
11. A.P.Kozikowski and A.K.Ghosh, J.Org.Chem.,49,2762(1984).
12. The ^{1}H-NMR of 6 matches well with that previously reported whereas its specific rotation is slightly higher α_D^{24} -12.89°(c0.830,CH_2Cl_2) versus α_D^{24} -11.2°(c0.602,CH_2Cl_2). 6: b.p. 135-140°/0.4mmHg.

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