

Stereoselective Osmylation of 5-Vinyl-4,5-dihydroisoxazoles

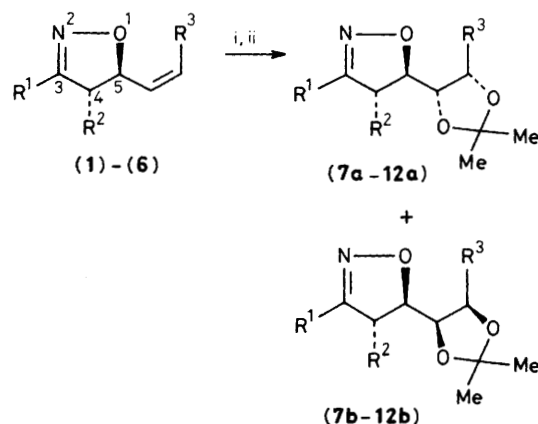
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Osmium tetroxide-catalysed *cis*-hydroxylation of 5-vinyl-4,5-dihydroisoxazoles proceeds stereoselectively affording the *anti*-products in fair to excellent diastereoisomeric excess; an entry to optically active compounds is also described.

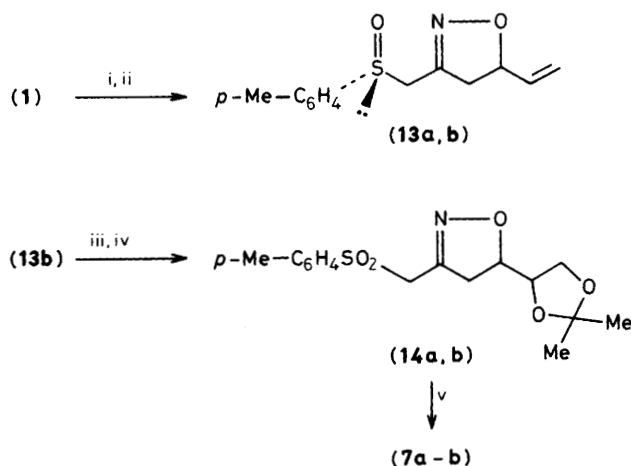
4,5-Dihydroisoxazoles (Δ^2 -isoxazolines) recently proved to be versatile building blocks for the stereocontrolled synthesis of a variety of functionalized acyclic carbon skeletons.^{1,2} While the control of both the relative¹ and absolute³ stereochemistry of the stereocentres, present or latent,^{1,2} in the heterocyclic ring is now well in hand, the stereoselective generation of

asymmetrically substituted carbon atoms outside the ring is still a challenging goal.⁴ In this respect a great deal of work has been devoted to stereoselective nitrile oxide cycloaddition to alkenes bearing an allylic oxygen substituent,^{2,5} since this reaction allows a straightforward entry to synthons of polyols and amino sugars.¹ We here report that osmium-catalysed⁶



- (1), (7) R¹ = Me; R² = R³ = H
 (2), (8) R¹ = CO₂Et; R² = R³ = H
 (3), (9) R¹ = Ph; R² = R³ = H
 (4), (10) R¹ = *p*-NO₂C₆H₄; R² = R³ = H
 (5), (11) R¹ = Me; R² = H; R³ = Me
 (6), (12) R¹ = Me; R² = Me; R³ = Me

Scheme 1. Reagents: i, OsO₄, Me₃N→O; ii, Me₂CO, *p*-MeC₆H₄SO₃H. Only one enantiomer is indicated for simplicity.



Scheme 2. Reagents: i, Lithium di-isopropylamide; ii, menthyl toluene-*p*-sulphinate; iii, OsO₄, Me₃N→O, room temp.; iv, Me₂CO, *p*-MeC₆H₄SO₃H; v, Na/Hg, NaH₂PO₄, MeOH.

cis-hydroxylation of the easily obtained 5-vinyl-Δ²-isoxazolines can provide an efficient alternative to the cycloaddition approach.

Reaction of a variety of nitrile oxides (generated *in situ* from nitroethane⁷ or from the appropriate hydroximoyl chloride^{2,8}) with commercially available 1,3-dienes⁹ afforded the isoxazolines (1)–(6) in high yields.† These were smoothly osmlyated to give a mixture of diastereoisomeric diols which were converted into the corresponding acetals (7)–(12) (Scheme 1). 200 MHz ¹H and ¹³C n.m.r. spectroscopy² allowed both structural assignment and evaluation of the diastereoisomeric

Table 1. Stereoselective synthesis of (7)–(12).^a

Entry	Compound	Yield, ^b %	Diastereoisomeric ratio ^c a : b
A	(7a, b)	80	78 : 22
B	(7a, b)	72 ^d	78 : 22
C	(8a, b)	83	77 : 23
D	(8a, b)	65 ^d	76 : 24
E	(9a, b)	74 ^e	75 : 25
F	(10a, b)	82 ^e	73 : 27
G	(11a, b)	80	86 : 14
H	(12a, b)	70 ^f	92 : 8

^a All reactions were carried out on a 1–5 mmol scale with 0.1 mol equiv. of OsO₄ (0.04 M in Bu^tOH) and with 2.0 mol equiv. of Me₃N→O·2H₂O in tetrahydrofuran–H₂O (10 : 1) at 0 °C for 5 h. Solid NaHSO₃ was added to quench the reaction. All new compounds gave analytical and spectral data in agreement with the proposed structures. ^b Overall yield of (7)–(12) from (1)–(6). ^c *anti*-Isomers always showed higher *R*_f values than their *syn*-counterparts (diethyl ether–hexane mixtures as eluant). ^d Reaction carried out at –20 °C. ^e Reaction time 15 h. ^f These products are impure and contain small traces of their isomers (see footnote†).

excesses.‡ Furthermore, the *anti*¹⁰ (7a–12a) and *syn* (7b–12b) products can be readily separated by flash chromatography to give diastereoisomerically pure compounds. Chemical yields and diastereoisomeric ratios are reported in Table 1.

As can be seen from the reported data the osmylation reaction is *anti* selective in agreement with the empirical rule proposed by Kishi for the OsO₄ oxidation of allylic alcohols and ethers.¹¹ The stereochemical outcome of the process seems to be almost insensitive to the nature of the R¹ group (entries A, C, E, and F) or to variation of the reaction temperature (entries A–D). The diastereoisomeric excesses observed in the case of products (7)–(10), *i.e.* when the double bond is mono-substituted, are similar to or lower than those obtained by cycloaddition of nitrile oxides to *O,O'*-isopropylidene-but-3-ene-1,2-diol,^{2,5} a reaction which gives (7)–(10) in *anti* : *syn* ratios ranging from 80 : 20 to 88 : 12.

However, a marked increase in stereoselectivity is achieved when the double bond bears a *cis*-substituent (entries A vs. G) in line with Kishi's model predictions.¹¹ This effect is further enhanced if the C-4 position of the heterocyclic ring becomes more sterically demanding (entry H), to the point that a 92 : 8 *anti* : *syn* ratio of isomers is observed for compound (12). Therefore in this case an almost complete control of the relative stereochemistry at four contiguous stereocentres can be secured by sequential cycloaddition and osmylation.

To obtain compounds such as (7), (11), and (12) in optically pure form we exploited our previously reported sulphoxide-mediated method.³

Indeed, *exo*-metallation of (1), chosen as a model compound, followed by reaction with commercially available (–)-(*S*)-menthyl toluene-*p*-sulphinate gave 3-sulphinylmethyl-5-vinyl-4,5-dihydroisoxazole (13a,b) as a *ca.* 1 : 1 mixture of epimers at C-5.³ These were separated by flash chromatography to afford sulphoxides (13a), [α]_D²³ +357.3° (*c* 0.2 in CHCl₃), m.p. 92–94 °C, and (13b), [α]_D²³ +187.0° (*c* 0.2 in CHCl₃), m.p. 45–47 °C (Scheme 2). Compound (13b)

† In the synthesis of compound (5) the cycloaddition reaction is completely regioselective, while in the synthesis of (6) a small amount (<5%) of the isomeric Δ²-isoxazoline was formed (see Table 1, footnote f).

‡ This can be done on the diols as well as on the acetals. However, the latter always gave larger chemical shift differences and were therefore preferred for the n.m.r. analysis. Results in full agreement with the literature² values were obtained.

was then converted by oxidation and acetalization into sulphones[§] (**14**) which was a 78:22 mixture of *anti* and *syn* isomers. This mixture was desulphurized³ to give (**7a,b**). Column chromatography afforded enantiomerically pure (**7a**), $[\alpha]_{\text{D}}^{23} -79.0^\circ$, m.p. 52–53 °C, and (**7b**), $[\alpha]_{\text{D}}^{23} -90.6^\circ$, m.p. 55–56 °C, in 51.5 and 14.5% overall yields from (**13b**), respectively.

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§ As expected the presence of the sulphur substituent at C-3 has no particular effect on the stereoselectivity of the osmylation, in contrast with results for an acyclic system.¹²