Trimethylsilyl Trifluoromethanesulfonate-Promoted Cycloaddition of Nitrones with Silyl Enol Ethers: Synthesis and Reactivity of 5-Siloxyisoxazolidines

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In the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), the reaction of nitrones with silyl enol ethers affords 5-siloxyisoxazolidines under mild conditions, in good to excellent yields. 5-Siloxyisoxazolidines can undergo chemoselective reductions to Mannich bases or N-hydroxy-1,3amino alcohols, and, in the presence of TMSOTf, react with silvlated carbon nucleophiles at the acetalic C-5 carbon to give, for example, 5-allyl- and 5-cyano-isoxazolidines.

The reaction of nitrones 1 with η^1 -allylic organometallic compounds can follow two alternative reaction pathways, depending on the nature of the metal involved (Scheme 1).



Scheme 1 Reagents: i, CH2=CHCH2MgCl; ii, CH2=CHCH2SiMe3

Allyl-magnesium and -zinc reagents, in analogy to the general behaviour displayed by organolithium and magnesium compounds,¹ give 1,3-addition to nitrones and lead to homoallylic hydroxylamines 2² (path A). Allyltrimethylsilane, on the other hand, undergoes a thermal, concerted 1,3-dipolar cycloaddition to give 5-(trimethylsilylmethyl)isoxazolidines 3³ (path B). We recently re-examined these reactions and worked out novel approaches to the isoxazolidine ring system. They are based on the formation of O-silylated hydroxylamines 4 and 5 carrying an electrophilic centre at the γ position relative to the nitrogen atom, which spontaneously undergoes ring closure to products 6 and 3, respectively (Scheme 2).



The iodo adduct 4 was generated by the addition of an iodinating agent (N-iodosuccinimide, ICl) to the homoallylic hydroxylamine 2, previously protected as its O-silyl derivative.²

Furthermore we found that the 1,3-dipolar cycloaddition of nitrones and allyltrimethylsilane can be catalysed by trimethylsilvl trifluoromethanesulfonate (TMSOTf).⁴ In the presence of this promoter the reaction takes place at 0-20 °C, while the thermal process requires a higher temperature $(T \ge 100 \text{ °C})^{3}$ Under these conditions the reaction was proposed to occur via the intermediate carbonium ion 5 which undergoes cyclisation to the isoxazolidine 3. As an extension of the latter work,⁵ we recently reported preliminary results obtained in the TMSOTfpromoted 1,3-dipolar cycloaddition of nitrones and silyl enol ethers 7, which, in analogy to allyltrimethylsilane, react under

mild conditions (T \leq 0 °C) and give 5-siloxyisoxazolidines 8 (Scheme 3).[†]



Scheme 3 Reagents and conditions: i, TMSOTf, 0 °C

We now report further results of this TMSOTf-promoted reaction, and consider also possible elaborations of the isoxazolidines 8.

Results and Discussion

We carried out a number of cycloadditions of simple (Z)aldonitrones with four model silvl enol ethers 7 lacking α substituents, in the presence of an equimolecular amount of TMSOTf in dichloromethane, at temperatures ranging from -20 to 20 °C. Besides isoxazolidines 8, 2,3-dihydroisoxazoles 9 are sometimes present as secondary products. The results are collected in Table 1.



When the steric demand of substituents is not severe, conversions into 5-siloxyisoxazolidines 8 are good to excellent and isolated yields range from 70 to 92%. Exceptions are found in run 5 ($\mathbf{R}^1 = \mathbf{Bu}^t$), run 7 ($\mathbf{R}^1 = \mathbf{Me}_2\mathbf{C}=\mathbf{CH}$), and run 8 ($\mathbf{R}^4 =$ SiBu'Ph₂).

It is possible to carry out the reactions using catalytic amounts of TMSOTf (runs 2, 3), but higher reaction times or temperatures are required to achieve acceptable conversions. A detrimental effect of either prolonging the reaction time or increasing the reaction temperature is given by the formation of appreciable amounts of 2,3-dihydroisoxazoles 9. It is worthy of note that there is an absence of 2,3-dihydroisoxazoles 9 when acetaldehyde silvl enol ethers are used under our standard conditions (1 mol equiv. of TMSOTf, 24 h, -10 to 0 °C), while they represent the major side-product when acetone and aceto-

t Ketene silyl acetals and Reformatsky reagents, more reactive than simple silyl enol ethers, do not require any activator for the addition to nitrones, which affords 5-isoxazolidinones at room temperature or below.6

Table 1 TMSOTf-promoted 1,3-dipolar cycloadditions*

	Run	1		7					
		R ¹	R ²	R ³	R ⁴	<i>T</i> (°C)	Product 8 (yield/%)	cis/trans	Product 9 (yield/%)
	1	Et	CH ₂ Ph	Н	SiBu'Me ₂	-10	8a (92)	70/30	9a (0)
	2	Et	CH,Ph	Н	SiBu'Me ₂	0	8a $(42)^{b,c}$	58/42	9a (17)
	3	Et	CH ₂ Ph	н	SiBu ^t Me ₂	20	8a (64) ^b	50/50	9a (32)
	4	Pr ⁱ	CH ₂ Ph	Н	SiBu ^t Me ₂	-10	8b (95)	38/62	9b (0)
	5	\mathbf{Bu}^{t}	CH ₂ Ph	Н	SiBu ^t Me ₂	-20	8c (52)	40/60	9c (0)
	6	Ph	Me	Н	SiBu ^t Me ₂	0	8d (87)	36/74	9d (0)
	7	Me ₂ C=CH	CH ₂ Ph	н	SiBu ^t Me ₂	20	8e (59)	22/78	9e (0)
	8	Et	CH ₂ Ph	Н	SiBu'Ph,	0	8 f (28)	80/20	9f (0)
	9	Et	CH ₂ Ph	Me	SiMe ₃	0	8g (91)	35/65	9g (6)
	10	Et	CH ₂ Ph	Me	SiMe ₃	20	8g (70) ^b	40/60	9 g (30)
	11	Pr ⁱ	CH ₂ Ph	Me	SiMe ₃	0	8h (88)	40/60	9h (8)
	12	Ph	Me	Me	SiMe ₃	0	8i (77)	40/60	9i (15)
	13	Et	CH,Ph	Ph	SiMe ₃	0	8 j (76) ^d	50/50	9 i (19)
	14	Pr ⁱ	CH_2Ph	Ph	SiMe ₃	0	8k (74) ^e	55/45	9k (21)

^{*a*} All reactions were carried out in the presence of 1.0 mol equiv. of TMSOTf in 24 h, unless otherwise stated. ^{*b*} 0.1 Mol equiv. of TMSOTf was used. ^{*c*} Reaction was run for 67 h. ^{*d*} Yields were determined by ¹H NMR analysis of the reaction mixture; an attempted separation by flash chromatography of *cis* and *trans* isomers gave high conversion of compound **8** into compound **9** i. ^{*c*} Yields were determined by GCMS analysis of the crude reaction mixture; flash chromatography gave almost complete conversion of compound **8** k into compound **9** k.

phenone silyl enol ethers are used (runs 9–14). Such observations can be accounted for by the greater stability of the C=C double bond in 5-substituted 2,3-dihydroisoxazoles, particularly when $R^3 = Ph$ (runs 13, 14). In this regard, attempts to purify isoxazolidines **8j**, **k** by flash-chromatography failed since they were almost quantitatively converted by silica gel into compounds **9j**, **k**.

cis-trans Diastereoselectivity is in general poor, the best results being obtained in the case of cis-isoxazolidines **8a** (d.e. 40%)* and **8f** (d.e. 60%) (runs 1, 8) and in the case of transisoxazolidines **8d** (d.e. 38%) and **8e** (d.e. 56%) (runs 6,7). cis- and trans-Isoxazolidines **8** are not configurationally stable; in fact, they are in general easily separated by flash chromatography but undergo partial cis-trans equilibration in a few hours in the presence of catalytic amounts of TMSOTf in CH₂Cl₂, as well as upon storage in the pure state at room temperature within a month. For example, cis-**8d** is converted into a 56/44 mixture of trans-**8d** and cis-**8d** after being stirred with 1 mol equiv. of TMSOTf in CHCl₃ at 0 °C for 3.5 h.

The assignment of the *cis* and *trans* stereochemistry to isoxazolidines **8** was made possible by the general observation that R_t -values of *cis* isomers are always higher than those of *trans* forms, and that multiplets relative to 4-H protons of *cis* isomers are broader in ¹H NMR spectra, better resolved, and well separated ²⁻⁴ (see Tables 2 and 3) compared with those for the *trans* isomers. In the case of 5-disubstituted isoxazolidines **8g–j**, NOE experiments confirmed the proposed stereochemical assignments.

We propose, for the TMSOTf-promoted cycloaddition process, the reaction mechanism depicted in Scheme 4. The first step involves the silylation of nitrone 1 by TMSOTf to give Osiloxyiminium ion 10. The evidence of the formation of intermediate 10 was obtained by recording the NMR spectra of Npropylidenebenzenemethanamine N-oxide in the presence of 1 mol equiv. of TMSOTf in CDCl₃. The comparison between δ values in the presence and in the absence of TMSOTf (Table 4) unambiguously confirmed that a strong complexation occurs. The subsequent 1,3-addition of silyl enol ether to intermediate 10 affords, in our opinion, the positively charged intermediate 11, which then cyclises to give oxonium species 12. Elimination of TMSOTf from intermediate 12 generates *cis*- and *trans*-8 as products. The last process is reversible; in fact, the ¹H NMR spectrum of pure isoxazolidine *trans*-8a treated with 1 mol



Scheme 4 Reagents: i, TMSOTf; ii, CH₂=CHOSiMe₂Bu^t

equiv. of TMSOTf shows, after 5 min, a general line-broadening and deshielding of all signals. In particular, 5-H is shifted downfield by 0.28 ppm, 3-H by 0.44 ppm, the two benzylic CH₂s by 0.37 and 0.32 ppm, respectively, and, finally, the multiplets of the two 4-H protons collapse to δ 2.41. These observations make us believe that oxonium ion 12 is actually in fast equilibrium with other species, namely 13 and 14 (Scheme 5).

Formation of hydroxylaminium ion 13 is supported by the observation that the strongest deshielding among the various protons is shown by 3-H and benzylic protons. This is consistent with the fact that the energy of a nitrogen lone pair is generally higher than that of an oxygen lone pair, the energy gap being amplified by the so-called α -effect when N–O bonds are involved. As concerns oxonium species 14, it is responsible for the partial silyl scrambling observed in runs 1–7. In fact, when acetaldehyde *tert*-butyldimethylsilyl enol ether was used, we always observed, besides 5-(*tert*-butyldimethylsiloxy)isoxazolines 8a–e, small amounts (generally limited to less than 5%) of 5-(trimethylsiloxy)isoxazolidines. These products have slightly lower $R_{\rm r}$ -values than do the corresponding *tert*-butyldimethyl-siloxyisoxazolidines and arise by detachment of *tert*-butyl-

^{*} Diastereoisomeric excess.

 Table 2
 ¹H NMR data for compounds 8 and 9 at 300 MHz

Compd.	3-Н	4-H	5-H	Others
cis- 8a	2.66–2.75 (m)	1.95 (ddd, J 2.4, 7.2, 12.6), 2.60 (ddd, J 6.0, 7.7, 12.6)	5.52 (dd, J2.4, 6.0)	0.01 (3 H, s, SiMe), 0.03 (3 H, s, SiMe), 0.86 (9 H, s, SiBu'), 0.91 (3 H, t, $J7.4$, CH_2Me), 1.45–1.75 (2 H, m, CH_2Me), 3.81 (1 H, d, $J13.8$, CH_2Ph), 4.03 (1 H, d, $J13.8$, CH_2Ph), 7.23–7.42 (5 H, m Ph)
trans- 8a	3.11–3.25 (m)	2.08 (ddd, J 4.8, 8.4, 12.3), 2.38 (ddd, J 1.0, 6.4, 12.3)	5.51 (dd, J 1.0, 4.8)	0.12 (3 H, s, SiMe), 0.14 (3 H, s, SiMe), 0.89 (3 H, t, J 7.5, CH ₂ Me), 0.94 (9 H, s, SiBu ^t), 1.34–1.45 (1 H, m, CH ₂ Me), 1.46– 1.59 (1 H, m, CH ₂ Me), 4.08 (1 H, d, J 13.2, CH ₂ Ph), 4.25 (1 H, d, J 13.2, CH ₂ Ph), 7.22–7.46 (5 H, m, Ph)
cis- 8b	2.61–2.72 (m)	2.06 (ddd, J 1.8, 6.3, 12.9), 2.37 (ddd, J 5.9, 8.7, 12.9)	5.52 (dd, J1.8, 5.9)	$(3 \text{ H}, s, \text{SiMe}), 0.02 (3 \text{ H}, s, \text{SiMe}), 0.85 (9 \text{ H}, s, \text{SiBu}), 0.91 (3 \text{ H}, d, J 6.8, \text{CH}Me_2), 0.94 (3 \text{ H}, d, J 6.8, \text{CH}Me_2), 1.90 (1 \text{ H}, octet, J 6.7, \text{C}HMe_2), 3.83 (1 \text{ H}, d, J 13.7, \text{C}H_2\text{Ph}), 3.98 (1 \text{ H}, d, J 13.7, \text{C}H_2\text{Ph}), 7.23-7.42 (5 \text{ H}, \text{ m}, \text{Ph})$
trans-8b⁴	3.02–3.12 (m)	2.11–2.17 (m, B), 2.17– 2.25 (m, A), 2.29 (ddd, J 1.4, 3.9, 7.2, A), 2.30– 2.36 (m, B)	5.49 (dd, J1.4, 4.7)	0.10 (1.2 H, s, SiMe, B), 0.13 (1.2 H, s, SiMe, B), 0.17 (3.6 H, s, SiMe, A), 0.87 (1.8 H, d, J 6.7, CH Me_2 , A), 0.88 (1.8 H, d, J 6.7, CH Me_2 , A), 0.91 (1.2 H, d, J 6.7, CH Me_2 , B), 0.92 (1.2 H, d, J 6.7, CH Me_2), 4.06 (1H, broad d, J 13.4, CH ₂ Ph), 4.28 (0.4 H, d, J 13.4, CH ₂ Ph, B), 4.30 (0.6 H, d, J 13.4, CH ₂ Ph, A), 7.21–7.43 (5 H m Ph)
cis- 8c	2.75 (dd, J 5.1, 10.2)	2.05 (ddd, J 2.7, 5.1, 13.1), 2.46 (ddd, J 5.9, 10.2, 13.1)	5.57 (dd, J2.7, 5.9)	(0.11, 11, 11, 11) (0.01 (3 H, s, SiMe), 0.02 (3 H, s, SiMe), 0.85 (9 H, s, Bu'), 0.93 $(9 H, s, SiBu'), 3.92 (1 H, d, J 13.7, CH_2Ph), 4.03 (1 H, d, J 13.7, CH_2Ph), 7.21-7.45 (5 H, m, Ph)$
trans-8c	3.10 (t, <i>J</i> 7.7)	2.20–2.35 (2 H, m)	5.47–5.53 (m)	$0.09 (3 \text{ H}, \text{s}, \text{SiMe}), 0.10 (3 \text{ H}, \text{s}, \text{SiMe}), 0.84 (9 \text{ H}, \text{s}, \text{Bu}'), 0.93 (9 \text{ H}, \text{s}, \text{SiBu'}), 4.05 (1 \text{ H}, \text{d}, J 13.6, CH_2\text{Ph}), 4.44 (1 \text{ H}, \text{d}, J 13.6, CH_2\text{Ph}), 4.44 (1 \text{ H}, \text{d}, J 13.6, CH_2\text{Ph}), 721-745 (5 \text{ H}, \text{m}, \text{Ph})$
cis- 8d	3.46 (m)	2.34 (ddd, J 2.6, 9.4, 13.1), 2.92 (ddd, J 6.1, 8 1 13.1)	5.57 (dd, J2.6, 6.1)	0.16 (3 H, s, SiMe), 0.20 (3 H, s, SiMe), 0.96 (9 H, s, SiBu'), 2.58 (3 H, s, NMe), 7.28–7.48 (5 H, m, Ph)
trans-8d	4.04 (br t, <i>J</i> ~ 8.6)	2.44–2.50 (2 H, m)	5.56 (m)	0.16 (3 H, s, SiMe), 0.19 (3 H, s, SiMe), 0.96 (9 H, s, SiBu ^t), 2.82 (3 H s NMe), 7, 28–7, 45 (5 H m Ph)
cis- 8e	3.37–3.48 (m)	2.02 (ddd, J 3.2, 9.7, 12.9), 2.60 (dt, J 6.4, 12.9)	5.45 (dd, J 3.2, 6.4)	$-0.06(3 \text{ H}, \text{s}, \text{SiMe}), -0.02(3 \text{ H}, \text{s}, \text{SiMe}), 0.81(9 \text{ H}, \text{s}, \text{SiBu}^{t}), 1.67(3 \text{ H}, \text{s}, \text{Me}), 1.72(3 \text{ H}, \text{s}, \text{Me}), 3.61(1 \text{ H}, \text{d}, J 14.1, CH_2Ph), 4.02(1 \text{ H}, \text{d}, J 14.1, CH_2Ph), 5.25(1 \text{ H}, \text{d}, J 9.1, CH=), 7.18-7.40$
trans- 8e	3.95–4.07 (m)	2.10–2.24 (2 H, m)	5.42–5.47 (m)	(3 H, m, H) 0.10 (3 H, s, SiMe), 0.14 (3 H, s, SiMe), 0.93 (9 H, s, SiBu'), 1.67 $(3 \text{ H}, \text{ s}, \text{Me}), 1.72 (3 \text{ H}, \text{ s}, \text{Me}), 3.95-4.07 (2 \text{ H}, \text{ m}, \text{CH}_2\text{Ph}), 5.16$ $(1 \text{ H}, \text{ H}, \text{ H}) = (1 \text{ CH}_2), 722, 730 (5 \text{ H}, \text{ m})$
cis- 8f	2.67–2.83 (m)	2.15 (ddd, J 2.4, 7.2, 12.7), 2.60 (ddd, J 6.1,	5.46(dd, J2.4, 6.1)	(111, 4, 3, 5, 1, C11-), 7.22-7.39 (311, 11, 11) $0.99 (3 H, t, J7.2, CH_2Me), 1.02 (9 H, s, SiBu'), 1.55-1.85 (2 H, m, CH_2Me), 3.80 (1 H, d, J 13.7, CH_2Ph), 4.03 (1 H, d, J 13.7, $
trans-8f	3.26-3.38 (m)	2.08 (ddd, J 4.7, 8.0, 13.1), 2.46–2.57 (m)	5.52 (d, J 4.7)	CH_2FH , $f.25-f.46$ (10 H, in, FH), $f.02-f.75$ (5 H, in, FH) 0.91 (3 H, t, $J7.2$, CH_2Me), 1.10 (9 H, s, SiBu'), 1.48-1.75 (2 H, m, CH_2Me), 4.21 (1 H, d, $J13.4$, CH_2Ph), 4.42 (1 H, d, $J13.4$, CH_2Ph), 7.28, 7.48 (10 H, m, Ph), 7.65, 7.76 (5 H, m, Ph)
cis- 8g	2.66–2.80 (m)	2.16 (dd, J9.4, 12.5), 2.40 (dd, J 7.4, 12.5)		Ch_{21} in, <i>i.e.</i> -1.46 (10 H, in, H), <i>i.e.</i> -1.76 (3 H, in, H) 0.01 (9 H, s, SiMe_3), 0.92 (3 H, t, $J7.4$, CH_2Me), 1.47 (3 H, s, 5- Me), 1.52–1.77 (2 H, m, CH_2Me), 3.75 (1 H, d, $J13.5$, CH_2Ph), $A O_3$ (1 H, d, $J13.5$, CH_2 Ph), 7.27 7.42 (5 H, m, Ph)
trans-8g	3.15–3.27 (m)	1.94 (dd, J9.4, 12.1), 2.49 (dd, J 6.4, 12.1)		4.05 (1 H, d, J 15.5, CH_2 H), $7.22-7.42$ (5 H, H, H) 0.21 (9 H, s, SiMe ₃), 0.86 (3 H, t, J 7.4, CH_2 Me), 1.54 (3 H, s, 5- Me), 1.61–1.75 (2 H, m, CH_2 Me), 4.07 (1 H, d, J 13.2, CH_2 Ph), 4.27 (1 H, d, J 13.2, CH_2 Ph), 7.21 (5 H, m, Ph)
<i>cis-</i> 8h	2.67–2.79 (m)	2.10–2.30 (2 H, m)		4.27 (1 H, d, J 15.2, CH_2 H), 7.21–7.42 (3 H, m, H) 0.01 (9 H, s, SiMe ₃), 0.91 (3 H, d, J 6.7, $CHMe_2$), 0.96 (3 H, d, J 6.7, $CHMe_2$), 1.47 (3 H, s, 5-Me), 1.81–1.96 (1 H, m, $CHMe_2$), 3.72 (1 H, d, J 13.5, CH_2 Ph), 4.02 (1 H, d, J 13.5, CH Ph) 7.25 7.46 (5 H m, Ph)
trans-8h	3.11 (dt, <i>J</i> 7.0, 9.4)	2.02 (dd, J9.4, 12.2), 2.41 (dd, J 7.0, 12.2)		CH_2 rin, $7.25-7.46$ (5 H, in, Fi) 0.21 (9 H, s, SiMe ₃), 0.89 (3 H, d, J 6.7, CHMe ₂), 0.92 (3 H, d, J 6.7, CHMe ₂), 1.54 (3 H, s, 5-Me), 1.62-1.75 (1 H, m, CHMe ₂), 4.06 (1 H, d, J 13.7, CH ₂ Ph), 4.36 (1 H, d, J 13.7, CHMe ₂) 7.21 7.46 (5 H, m, Ph)
<i>cis-</i> 8i	3.52 (dd, J 7.7, 10.0)	2.52 (dd, J 10.0, 12.8),		$C_{H_2}(n)$, $r_{2,1-7}(40 (5 H, m, FH))$ 0.26 (9 H, s, SiMe ₃), 1.56 (3 H, s, 5-Me), 2.54 (3 H, s, NMe), 7.25 7.47 (5 H m Ph)
trans-8i	4.04 (dd, J 5.8, 11.0)	2.32 (br t, $J \sim 11.5$), 2.58 (dd $J 5 8 12.0$)		0.25 (9 H, s, SiMe ₃), 1.61 (3 H, s, 5-Me), 2.76 (3 H, s, NMe), 7 23 $_{-7}$ 46 (5 H m Ph)
cis- 8j	2.83–2.95 (m)	(dd, <i>J</i> 5.6, 12.0) 2.46 (dd, <i>J</i> 8.9, 12.7), 2.56 (dd, <i>J</i> 7.5, 12.7)		-0.12 (6 H, s, SiMe ₃), 0.00 (3 H, s, SiMe ₃), 0.87 (3 H, t, J7.4, CH ₂ Me), 1.60-1.78 (2 H, m, CH ₂ Me), 3.98 (1 H, d, J 13.2, CH, Pb) 4.13 (1 H, d, J13.2, CH, Pb) 7.25-7.56 (10 H, m, Pb)
trans- 8j	3.29-3.40 (m)	2.14 (dd, J 10.2, 12.2), 2.81 (dd, J 5.6, 12.2)		$0.19(9 \text{ H}, \text{s}, \text{SiMe}_3), 0.90(3 \text{ H}, \text{t}, J7.4, \text{CH}_2Me), 1.51-1.68(2 \text{ H}, \text{m}, \text{CH}_2\text{Me}), 4.23(1 \text{ H}, \text{d}, J 13.6, \text{CH}_2\text{Ph}), 4.34(1 \text{ H}, \text{d}, J 13.6, \text{CH}_2\text{Ph}),$
trans- 8k	3.27 (dt, <i>J</i> 6.3, 10.0)	2.24 (dd, J 10.0, 12.2), 2.72 (dd, J 6.3, 12.2)		-0.02 (9 H, s, SiMe ₃), 0.86 (3 H, d, J 6.9, CHMe ₂), 0.92 (3, H, d, J 6.9, CHMe ₂), 1.65–1.75 (1 H, m, CHMe ₂), 4.23 (1 H, d, J 14.0, CH ₂ Ph), 4.39 (1 H, d, J 14.0, CH ₂ Ph), 7.25–7.57 (10 H, m Ph)
9g	3.62–3.73 (m)	4.53 (d, J 2.3)		1.81 (3 H, t, J 7.4, CH ₂ Me), 1.37–1.48 (2 H, m, CH ₂ Me), 1.85 (3 H, s, 5-Me), 3.84 (1 H, d, J 12.7, CH ₂ Ph), 4.19 (1 H, d, J 12.7, CH Ph) 7 25–7 46 (5 H m Ph)
9h	3.49 (dq, J 1.1, 6.6)	4.52 (q, J 1.1)		CH_2 , in, i.2-7, H_0 (1, ii, r) 0.82 (6 H, d, J 6.6, $CHMe_2$), 1.50–1.62 (1 H, octet, J 6.6, $CHMe_2$), 1.85 (3 H, t, J 1.1, Me), 3.81 (1 H, d, J 12.9, CH_2 Ph), 4.16 (1 H, d, J 12.9, CH_2 Ph), 7.25–7.46 (5 H, m, Ph)

Table 2 (continued)							
Compd.	3-Н	4-H	5-H	Others			
9i 9j	4.62–4.71 (m) 3.88 (dt, <i>J</i> 2.7, 6.9)	4.62–4.71 (m) 5.33 (d, <i>J</i> 2.7)		1.92 (3 H, s, 5-Me), 2.90 (3 H, s, NMe), 7.23–7.46 (5 H, m, Ph) 0.89 (3 H, t, J 7.4, CH ₂ Me), 1.49–1.63 (2 H, m, CH ₂ Me), 3.90 (1 H, d, J 12.6, CH ₂ Ph), 4.32 (1 H, d, J 12.6, CH ₂ Ph), 7.25– 7.58 (10 H, m, Ph)			
9k	3.69 (dd, J 2.8, 6.8)	5.32 (d, <i>J</i> 2.8)		$\begin{array}{l} 0.87 (3 \text{ H}, d, J6.8, \text{CH}Me_2), 0.90 (3 \text{ H}, d, J6.8, \text{CH}Me_2), 1.65 \\ 1.75 (1 \text{ H}, \text{octet}, J 6.8, \text{CH}Me_2), 3.87 (1 \text{ H}, d, J 12.6, \text{C}H_2\text{Ph}), \\ 4.29 (1 \text{ H}, d, J 12.6, \text{C}H_2\text{Ph}), 7.25 \\ -7.57 (10 \text{ H}, \text{m}, \text{Ph}) \end{array}$			

^a Two invertomers A and B were observed in the ratio 60:40.

Table 3 ¹³C NMR data for compounds 8 and 9 at 75 MHz

Compd.	C-3	C-4	C-5	CH ₂ Ph	Ph	NMe	Others
cis-8a	67.0	44.3	96.0	61.1	126.8, 127.9, 129.1, 137.7		-5.2 (MeSi), -4.4 (MeSi), 10.9 (MeCH ₂), 17.8 (Me ₃ C), 25.4 (MeCH ₃), 25.7 (Me ₃ C)
trans-8a	65.4	44.4	98.1	64.9	127.0, 128.2, 129.1, 138.3		-5.2 (MeSi), -4.1 (MeSi), 11.1 (<i>Me</i> CH ₂), 17.9 (Me ₃ C), 25.7 (<i>Me</i> ₃ C), 27.0 (MeCH ₃)
cis- 8b	70.3	39.9	96.4	61.8	126.9, 127.9, 129.2, 138.0		-5.2 (MeSi), -4.3 (MeSi), 17.5 (Me_2 CH), 17.8 (Me_3 C), 20.7 (Me_2 CH), 25.7 (Me_3 C), 29.3 (Me_2 CH)
trans-8b ^ª	69.5	41.5, 41.8	98.5, 98.7	65.5, 65.7	126.9, 128.1, 128.9, 138.7		-5.2 (MeSi), -4.1 (MeSi), 0.2 (2 × MeSi), 17.9 (Me ₃ C), 18.5 (Me ₂ CH), 18.6 (Me ₂ CH), 20.3 (2 × Me ₂ CH), 25.7 (Me ₃ C), 31.5 (Me ₂ CH), 31.6 (Me ₂ CH)
cis- 8c	73.1	40.1	97.0	64.4	126.8, 127.9, 129.1, 138.2		-5.4 (MeSi), -4.4 (MeSi), 17.8 (Me ₃ CSi), 25.7 (Me ₃ CSi), 27.2 (Me ₃ C), 33.8 (Me ₃ C)
trans-8c	72.5	40.5	99.9	66.7	126.8, 128.0, 128.9, 139.0		-5.4 (MeSi), -4.2 (MeSi), 17.8 (Me ₃ CSi), 25.7 (Me ₃ CSi), 26.5 (Me ₃ C), 33.5 (Me ₃ C)
cis-8d	73.6	50.1	95.8		127.8, 128.0, 128.5, 138.7	43.2	-4.9 (MeSi), -4.1 (MeSi), 18.0 (Me ₃ C), 25.8 (Me ₃ C)
trans-8d	70.2	48.9	97.0		127.4, 127.5, 128.4, 139.3	46.5	-5.1 (MeSi), -4.0 (MeSi), 17.8 (Me ₂ C), 25.7 (Me ₂ C)
cis-8e	59.9	46.3	95.9	65.2	126.7, 127.8, 128.8, 138.0		-5.1 (MeSi), -4.4 (MeSi), 17.9 (=CMe ₂), 18.4 (=CMe ₂), 18.4 (Me ₃ C), 25.9 (Me ₃ C), 122.4 (CH=), 136.7 (=CMe ₂)
trans- 8e	62.3	45.5	96.9	63.3	126.9, 128.1, 128.9, 138.3		-5.1 (MeSi), -4.0 (MeSi), 17.9 (= CMe_2), 18.2 (= CMe_2), 18.2 (Me_3C), 25.7 (Me_3C), 123.1 (CH=), 135.9 (= CMe_2)
cis- 8f	67.0	44.3	96.3	61.2	126.9, 127.3, 127.5, 127.7, 128.0, 129.1, 129.4, 129.5, 133.4, 133.9, 135.6, 135.9 137.8		10.9 (<i>Me</i> CH ₂), 19.1 (Me ₃ C), 25.5 (MeCH ₂), 26.6 (<i>Me</i> ₃ C)
trans-8f	65.4	44.4	98.6	65.5	127.6, 127.7, 128.2, 129.2, 129.6, 129.7, 134.8, 135.2, 135.5, 135.8		11.1 ($MeCH_2$), 19.0 (Me_3C), 26.6 (Me_3C), 26.9 ($MeCH_2$)
cis-8g	68.3	50.4	103.3	61.4	126.9, 127.8, 129.6, 137.7		1.5 (Me ₃ Si), 10.6 (<i>Me</i> CH ₂), 24.9 (5-Me), 29.0 (MeCH ₂)
trans-8g	67.0	49.5	105.4	64.2	126.9, 128.1, 128.9, 138.2		2.0 (Me ₃ Si), 11.0 ($MeCH_2$), 26.7 (5-Me), 30.1 (MeCH ₂)
cis-8h	72.0	45.0	103.7	62.1	127.0, 127.9, 129.7, 138.2		1.4 (Me_3Si), 17.3 (Me_2CH), 20.9 (Me_2CH), 24.5 (5-Me), 29.2 (Me_2CH)
trans-8h	71.2	46.8	105.9	65.2	126.8, 128.1, 128.8, 138.7		1.9 (Me ₃ Si), 18.3 (Me_2 CH), 20.5 (Me_2 CH), 26.2 (5-Me), 31.4 (Me ₂ CH)
cis -8i	74.4	55.6	103.4		127.8, 127.9, 128.5, 138.8	43.0	$1.8 (Me_3Si), 28.5 (5-Me)$
trans- 8i	71.7	53.8	104.6		127.5, 127.7, 128.1, 128.2, 139.9.	45.5	2.1 (Me_3Si), 29.7 (5- Me)
cis- 8j	68.1	53.1	104.2	61.5	125.6, 125.7, 127.1, 127.5, 127.9, 128.4, 128.8, 129.2 136.6, 145.4		1.1 (Me ₃ Si), 10.6 ($MeCH_2$), 25.0 (Me CH_2)
trans. 8 j	67.2	51.9	105.7	63.5	125.8, 127.0, 127.4, 127.8, 128.4, 129.6, 138.2, 144.0		$1.7 (Me_3Si), 11.0 (MeCH_2), 25.7 (MeCH_2)$
trans -8k	70.8	48.1	106.0	64.1	125.8, 126.8, 127.6, 127.7, 128.4, 129.0, 139.2		$1.7 (Me_3Si)$, 17.7 (Me), 20.6 (Me), 30.1 (Me ₂ CH)
9j	71.8	95.3	152.2	63.2	125.5, 127.0, 127.1, 127.3, 127.4, 127.6, 128.0, 128.3, 128.4, 128.5, 128.7, 129.8, 136.6		9.9 (CH ₂ <i>Me</i>), 29.2 (<i>C</i> H ₂ Me)
9k	76.4	93.5	152.4	63.8	125.5, 127.3, 128.1, 128.2, 128.3, 129.6, 136.7		18.2 (Me), 18.5 (Me), 33.7 (Me ₂ CH)

^a Two invertomers were observed in the ratio 60:40.

dimethylsilyl trifluoromethanesulfonate from oxonium intermediate 14. Moreover, intermediate 14 is probably responsible for the already mentioned TMSOTf-induced *cis-trans* equilibration of compounds 8.

5-Siloxyisoxazolidines 8 are versatile synthetic intermediates. First of all, acidic protodesilylation of compounds 8 occurs in good yield by the action of aqueous trifluoroacetic acid (TFA) at 20 °C. For example, diastereoisomeric mixtures of *cis*- and

trans-8a,-8d and -8i were converted into the corresponding 5hydroxyisoxazolidines 15a, 15d and 15i, which were isolated by flash chromatography. The same 5-hydroxyisoxazolidines 15 could be obtained by TFA-promoted hydration of 2,3dihydroisoxazoles 9 (Scheme 6).

cis- and trans-5-Hydroxyisoxazolidines 15 undergo fast equilibration (ring-chain tautomerism) and appear as single spots on TLC using different solvents (traces of open product are detected in the $v_{C=0}$ region of the IR spectrum of compound 15i). It is interesting to note that while isoxazolidines 15g-k, deriving from ketone silyl enol ethers, could be obtained, in principle, following a different route, namely the conjugate addition of *N*-alkylhydroxylamines to α , β -unsaturated ketones⁷ (the analogous reaction involving α , β -unsaturated esters is



Scheme 6 Reagents: i, aq. TFA

 Table 4
 NMR spectra
 of N-propylidene-N-trimethylsiloxybenzylammonium triflate 10a and the corresponding nitrone 1a

15

9

Ph N-OSiMe ₃ TfO ⁻			
1 2 10a			
δ			
8.60 (br s) ^a			
2.75 (dg, J 5.8, 7.7)			
1.28 (t, J 7.7)			
5.33 (s)			
7.45 (pseudo-s)			
0.48 (s)			
167.4			
22.6			
8.8			
66.0			
130.6, 130.2, 129.6			
1.9			

^{*a*} Upon irradiation at $\delta_{\rm H}$ 8.60, the signal at $\delta_{\rm H}$ 2.75 appears as a quartet (J 7.7 Hz).

known to lead to isoxazolidin-5-ones⁸), no reports are found in the literature about the analogous addition to α,β -unsaturated aldehydes, which should give access to isoxazolidines **15a**-f.* We demonstrated that the reaction of *N*-benzylhydroxylamine hydrochloride in aq. ethanol with 3-methylbut-2-enal in the presence of sodium acetate regioselectively affords, via 1,3addition, 3-methyl-but-2-enylidenebenzylamine *N*-oxide (used in run 7 of Table 1).

The second aspect of the chemistry of isoxazolidines we wish to discuss is the possibility of carrying out different chemoselective reductions to open-chain derivatives. An example is offered by the reaction of compound **15d** with NaBH₄ which affords hydroxylamino alcohol **16d** in high yield (Scheme 7).



Scheme 7 Solvent: i, MeOH

On the other hand, reduction of 5-siloxyisoxazolidines derived from ketone silyl enol ethers, such as compound 8g, with Zn/Cu couple in hot aq. acetic acid gives 4-(benzylamino)hexan-2one 17g via a chemoselective reduction of the N–O bond (Scheme 8). The two-step sequence involving nitrone silyl enol ether cycloaddition followed by Zn/Cu couple reduction represents a synthetic alternative to the Mannich reaction.



Scheme 8 Solvent: i, AcOH

The last topic we wish to discuss are the preliminary results on the most interesting reactions applied to isoxazolidines 8 from a synthetic point of view, since they construct a new carbon-carbon bond. The goal was to add silvlated carbon nucleophiles to isoxazolidines 8 in the presence of Lewis acids.¹⁰ Model isoxazolidine 8d was found to be less reactive than simple acetals, and cross-coupling reactions with allyltrimethylsilane and cyanotrimethylsilane could only be effected in the presence of TMSOTf at 50-75 °C (Scheme 9, Table 5), while other classical Lewis acids like BF3.OEt2, ZnI2, TiCl4 proved to be ineffective. Under these conditions cis- and trans-8 undergo a fast equilibration but, unfortunately, no good diastereoselectivity in the formation of the new stereogenic C-5 centre was achieved as a consequence of thermodynamic control. Since the most likely reactive intermediate involved in the coupling reaction corresponds to species 14, that is the product of the cycloaddition, it is possible to carry out the processes in one

* The formation of a 5-hydroxyisoxazolidine by the lithium enolate of acetaldehyde addition to nitrones has been recently reported,⁹ but the reaction seems to be limited to N,C-diaryl nitrones.

 Table 5
 TMSOTf-Promoted coupling of compound 8d with silylated carbon nucleophiles

Run	Nucleophile	Solvent	<i>T</i> (°C)	<i>t</i> (h)	Product	Yield(%) (cis/trans)	
1 2 3	allyltrimethylsilane allyltrimethylsilane cyanotrimethylsilane	CHCl ₃ toluene CHCl ₂	75 70 50	8 5 8	18d 18d 19d	60 (45/55) 44 (15/85) 53 (70/30)	



Scheme 9 Reagents: i, CH₂=CHCH₂SiMe₃, TMSOTf; ii, Me₃SiCN, TMSOTf

pot by exploiting the same TMSOTf to promote both the cycloaddition and the coupling reactions. So, after having stirred N-benzylidenemethylamine N-oxide with 1.4 mol equiv. of TMSOTf and 1.1 mol equiv. of tert-butyl(dimethyl)vinyloxy-silane in CHCl₃ at 0 °C for 23 h, it is sufficient to add allyltrimethylsilane (3 mol equiv.) and to heat at 60 °C for 7 h. cis- and trans-2-Methyl-3-phenyl-5-(prop-2-enyl)isoxazolidines (cis- and trans-18d) were formed in the ratio 55:45 and were isolated, after the usual work-up, in 44% overall yield.

Unfortunately, silyl enol ethers cannot be used in TMSOTfmediated cross-coupling reactions with isoxazolidines 8 since the reaction product is more reactive towards the nucleophile than is substance 8, and oligomerisation cannot be suppressed.

Conclusions

The cycloaddition of nitrones and silyl enol ethers, when promoted by TMSOTf, takes place at 0 °C or below through a stepwise mechanism which involves a series of silylated intermediates. The final 5-siloxyisoxazolidines, again in the presence of TMSOTf, undergo a further reaction with a different silylated carbon nucleophile at the acetalic C-5 carbon under more drastic conditions (50–70 °C). This makes possible a threecomponent one-pot coupling process where the same TMSOTf promotes first the 1,3-dipolar cycloaddition of the nitrone and the silyl enol ether, and then the nucleophilic substitution reaction with the second silylated compound.

Besides this interesting approach to a variety of synthetically flexible 3,5-disubstituted isoxazolidines, we have shown that chemoselective reductions of 5-siloxyisoxazolidines leading to Mannich products and *N*-hydroxy-1,3-amino alcohols are possible.

Experimental

¹H NMR and ¹³C NMR spectra of CDCl₃ solutions were recorded at 300 and 75 MHz, respectively with a VARIAN GEMINI 300 spectrometer. Chemical shifts are reported in ppm relative to internal standard Me₄Si (δ). NMR spectra of products 8 and 9 are reported in Tables 2 and 3, NMR spectra of isoxazolidines 15, 18 and 19 are collected in Tables 6 and 7. IR spectra were recorded on Perkin-Elmer PE 682 spectrophotometer. High-resolution mass spectra (HRMS) were obtained using a VG 7070 instrument at 70 eV. Gas chromatographic-mass spectrometric analyses (GCMS) were performed with an HP 5890 cross-linked methyl silicone glass capillary column (0.33 mm film thickness) connected to an HP 5970 quadrupole mass detector. The column temperature was programmed from 50 to 250 °C at 10 °C min⁻¹ and was then held at 250 °C for 10 min. The helium carrier gas flow rate was 1 cm³ min⁻¹. Analytical TLC was performed with Kieselgel 60 F₂₅₄ plates and mixed solvents [cyclohexane (C), diethyl ether (E), ethyl acetate (A)]. Kieselgel 60 (230-400 mesh) was used for flash chromatography. Reactions were performed in oven-dried

glassware under an atmosphere of dry argon. Dichloromethane and chloroform were purified before use (water content was 8 ± 1 ppm). All nitrones,¹¹ tert-butyl(dimethyl)vinyloxysilane,¹² tert-butyl(diphenyl)vinyloxysilane and trimethyl(1phenylvinyloxy)silane¹³ were prepared according to literature procedures; trimethyl-(1-methylvinyloxy)silane was purchased by Aldrich.

Reaction of N-Propylidenebenzylamine N-Oxide with tert-Butyl(dimethyl)vinyloxysilane. General Procedure.—To a stirred solution of nitrone **1a** (163 mg, 1 mmol) and silyl enol ether **7a** (0.24 g, 1.5 mmol) in dry dichloromethane (8 cm³) was added drop-by-drop (10 min) a solution of TMSOTf (0.21 cm³, 1.1 mmol) in dichloromethane (2 cm³) at -10 °C. After 24 h, the reaction mixture was quenched with saturated aq. NaHCO₃ (2 cm³); the two liquid layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 cm³). The combined organic layers were washed with brine (1 cm³), dried (Na₂SO₄), and evaporated to dryness. Flash chromatography (C-A 98:2) of the residue gave the products cis-**8a** (0.1 g, 28%) and trans-**8a** (0.2 g, 64%), as pale yellow oil.

cis-2-Benzyl-5-(tert-butyldimethylsiloxy)-3-ethylisoxazolidine cis-**8a** (Found: M⁺, 321.2128 C₁₈H₃₁NO₂Si requires M, 321.2124); TLC (C-E 85:15) $R_{\rm f}$ 0.71; m/z (%) 321 (M⁺, 22), 292 (M⁺ - Et, 10), 264 (M⁺ - Bu^t, 6), 199 (M⁺ - PhCH₂NOH, 100), 157 (27), 91 (CH₂Ph, 74) and 73 (53).

trans-2-*Benzyl*-5-(tert-*butyldimethylsiloxy*)-3-*ethylisoxazolidine* trans-**8a** (Found: M⁺, 321.2121); TLC (C–E 85:15) $R_{\rm f}$ 0.43; m/z (%) 321 (M⁺, 20), 292 (M⁺ – Et, 11), 264 (M⁺ – Bu^t, 7), 199 (M⁺ – PhCH₂NOH, 100), 157 (25), 91 (CH₂Ph, 72) and 73 (55).

cis-2-Benzyl-5-(tert-butyldimethylsiloxy)-3-isopropylisoxazolidine cis-**8b**. Purified by flash chromatography (C-E 96:4) as a clear oil (Found: M⁺, 335.2278. C₁₉H₃₃NO₂Si requires M, 335.2280); TLC (C-E 85:15) $R_{\rm f}$ 0.73; m/z (%) 335 (M⁺, 11), 292 (M⁺ - Prⁱ, 52), 278 (M⁺ - Bu^t, 8), 250 (18), 213 (M⁺ -PhCH₂NOH, 33), 171 (10), 91 (CH₂Ph, 100), 75 (18) and 73 (30).

trans-2-Benzyl-5-(tert-butyldimethylsiloxy)-3-isopropylisoxazolidine trans-**8b**. Purified by flash chromatography (C–E 96:4) as a clear oil (Found: M⁺, 335.2280); TLC (C–E 85:15) $R_{\rm f}$ 0.43; m/z (%) 335 (M⁺, 13), 292 (M⁺ – Prⁱ, 50), 278 (M⁺ – Bu^t, 10), 250 (17), 213 (M⁺ – PhCH₂NOH, 31), 171 (9), 91 (CH₂Ph, 100), 75 (18) and 73 (28).

cis-2-Benzyl-3-(tert-butyl)-5-(tert-butyldimethylsiloxy)isoxazolidine cis-8c. Purified by flash chromatography (C–E 99:1) as an oil (Found: M⁺, 349.2442. C₂₀H₃₅NO₂Si requires M, 349.2437); TLC (C–E 85:15) R_f 0.86; m/z (%) 349 (M⁺, 2), 292 (M⁺ – Bu^t, 94), 250 (8), 160 (10), 91 (CH₂Ph, 100), 75 (15) and 73 (19).

trans-2-*Benzyl*-3-(tert-*butyl*)-5-(tert-*butyldimethylsiloxy*)isoxazolidine trans-**8c**. Purified by flash chromatography (C–E 99:1) as an oil (Found: M⁺, 349.2439); TLC (C–E 85:15) $R_{\rm f}$ 0.76; m/z (%) 349 (M⁺, 2), 292 (M⁺ – Bu^t, 90), 250 (7), 160 (11), 91 (CH₂Ph, 100), 75 (14) and 73 (20).

cis-5-(tert-*Butyldimethylsiloxy*)-2-*methyl*-3-*phenylisoxazol-idine* cis-**8d**. Purified by flash chromatography (C–E 95:5) as a pale yellow oil (Found: M⁺, 293.1810. $C_{16}H_{27}NO_2Si$ requires M, 293.1811); TLC (C–E 85:15) R_f 0.67; m/z (%) 293 (M⁺, 7), 247 (M⁺ – CH₃NOH, 100), 205 (43), 135 [CH₃N(O)CHPh, 6], 134 [CH₃N(O)CPh, 18], 132 (16), 105 (18), 91 (CH₂Ph, 28), 75 (19), 73 (80) and 41 (7).

trans-5-(tert-*Butyldimethylsiloxy*)-2-*methyl*-3-*phenylisoxazolidine* trans-**8d**. Purified by flash chromatography (C–E 95:5) as a pale yellow oil (Found: M⁺, 293.1806); TLC (C–E 85:15) $R_{\rm f}$ 0.37; m/z (%) 293 (M⁺, 6), 247 (M⁺ – CH₃NOH, 100), 205 (45), 135 [CH₃N(O)CHPh, 4], 134 [CH₃N(O)CPh, 19], 132 (18), 105 (18), 91 (CH₂Ph, 30), 75 (17) and 73 (78).

cis-2-Benzyl-5-(tert-butyldimethylsiloxy)-3-(2-methylprop-1-

enyl)*isoxazolidine* cis-**8***e*. Purified by flash chromatography (C-E 95:5) as a pale yellow oil (Found: M⁺, 347.2283. C₂₀H₃₃NO₂Si requires M, 347.2280); TLC (C-E 80:20) R_f 0.85; *m/z* (%) 347 (M⁺, 6), 290 (M⁺ - Bu^t, 2), 226 (18), 225 (M⁺ - PhCH₂NOH, 92), 208 (17), 174 (22), 91 (CH₂Ph, 100), 75 (44) and 73 (68).

trans-2-*Benzyl*-5-(tert-*butyldimethylsiloxy*)-3-(2-*methylprop*-1-*enyl*)*isoxazolidine* trans-**8e**. Purified by flash chromatography (C-E 95:5) as a pale yellow oil (Found: M⁺, 347.2276); TLC (C-E 80:20) $R_{\rm f}$ 0.57; m/z (%) 347 (M⁺, 5), 226 (17), 225 (M⁺ – PhCH₂NOH, 90), 208 (16), 174 (23), 103 (11), 91 (CH₂Ph, 100), 75 (42) and 73 (70).

cis-2-Benzyl-5-(tert-butyldiphenylsiloxy)-3-ethylisoxazolidine cis-8f. Purified by flash chromatography (C–E 96:4) as a pale yellow oil (Found: M⁺, 445.2440. $C_{28}H_{35}NO_2Si$ requires M, 445.2437); TLC (C–E 90:10) $R_f 0.58$; m/z (%) 445 (M⁺, 11), 388 (M⁺ – Bu', 17), 323 (M⁺ – PhCH₂NOH, 65), 254 (14), 199 (100), 197 (26), 135 (64), 91 (CH₂Ph, 98), 77 (Ph, 23) and 75 (44). trans-2-Benzyl-5-(tert-butyldiphenylsiloxy)-3-ethylisoxazol-

idine trans-**8**f. Purified by flash chromatography (C–E 96:4) as a pale yellow oil (Found: M⁺, 445.2432); TLC (C–E 90:10) $R_{\rm f}$ 0.25; m/z (%) 445 (M⁺, 10), 338 (M⁺ – Bu^t, 18), 323 (M⁺ – PhCH₂NOH, 65), 254 (13), 199 (99), 197 (27), 137 (20), 135 (60), 91 (CH₂Ph, 100), 77 (Ph, 20) and 75 (42).

cis-2-*Benzyl*-3-*ethyl*-5-*methyl*-5-(*trimethylsiloxy*)*isoxazolidine* cis-**8g**. Purified by flash chromatography (C–E 98:2) as a pale yellow oil (Found: C, 65.4; H, 9.2; N, 4.7. $C_{16}H_{27}NO_2Si$ requires C, 65.5; H, 9.3; N, 4.8%); TLC (C–E 80:20) R_f 0.75; *m/z* (%) 293 (M⁺, 14), 171 (PhCH₂NOH, 100), 130 (7), 91 (CH₂Ph, 68), 82 (9), 75 (12), 73 (32) and 43 (8).

trans-2-*Benzyl-3-ethyl-5-methyl-5-(trimethylsiloxy)isoxazol-idine* trans-**8g**. Purified by flash chromatography (C–E 98 : 2) as a pale yellow oil (Found: C, 65.4; H, 9.2; N, 4.7 %); TLC (C–E 80 : 20) $R_{\rm f}$ 0.39; m/z (%) 293 (M⁺, 12), 171 (PhCH₂NOH, 100), 130 (4), 91 (CH₂Ph, 70), 82 (8), 75 (14), 73 (34) and 43 (7).

2-Benzyl-3-ethyl-5-methyl-2,3-dihydroisoxazole 9g. Purified by flash chromatography (C-E 98:2) as a pale yellow oil (Found: C, 76.8; H, 8.4; N, 7.0. $C_{13}H_{17}NO$ requires C, 76.8; H, 8.4; N, 6.9%); TLC (C-E 80:20) R_f 0.55; v_{max}/cm^{-1} 1670 (C=C). cis-2-Benzyl-3-isopropyl-5-methyl-5-(trimethylsiloxy)isox-

azolidine cis-**8h**. Purified by flash chromatography (C–E 99:1) as a pale yellow oil (Found: C, 66.3; H, 9.5; N, 4.6. C_{17} -H₂₉NO₂Si requires C, 66.4; H, 9.5; N, 4.6%); TLC (C–E 85:15) $R_f 0.68; m/z$ (%) 307 (M⁺, 3), 264 (M⁺ – Prⁱ, 11), 185 (M⁺ – PhCH₂NOH, 31), 174 (23), 91 (CH₂Ph, 100), 73 (11) and 43 (Prⁱ, 6).

trans-2-Benzyl-3-isopropyl-5-methyl-5-(trimethylsiloxy)isoxazolidine trans-**8h**. Purified by flash chromatography (C–E 99:1) as a pale yellow oil (Found: C, 66.5; H, 9.4; N, 4.6%); TLC (C–E 85:15) $R_{\rm f}$ 0.52; m/z (%) 307 (M⁺, 4), 264 (M⁺ – Prⁱ, 10), 185 (M⁺ – PhCH₂NOH, 33), 174 (21), 91 (CH₂Ph, 100), 73 (11) and 43 (Prⁱ, 4).

2-Benzyl-3-isopropyl-5-methyl-2,3-dihydroisoxazole **9h**. Purified by flash chromatography (C–E 99:1) as an oil (Found: C, 77.4; H, 8.7; N, 6.5. $C_{14}H_{19}NO$ requires C, 77.4; H, 8.8; N, 6.5%); TLC (C–E 85:15) R_f 0.85; ν_{max}/cm^{-1} 1670 (C=C).

cis-2,5-*Dimethyl*-3-*phenyl*-5-(*trimethylsiloxy*)*isoxazolidine* cis-**8i**. Purified by flash chromatography (C–E 98:2) as a pale yellow oil (Found: C, 63.4; H, 8.7; N, 5.3. C₁₄H₂₃NO₂Si requires C, 63.4; H, 8.7; N, 5.3%); TLC (C–E 85:15) $R_{\rm f}$ 0.78; *m/z* (%) 265 (M⁺, 4),219(M⁺ – CH₃NOH, 100), 146(11), 134(13),91(5),75 (18) and 73 (51).

trans-2,5-Dimethyl-3-phenyl-5-(trimethylsiloxy)isoxazolidine trans-**8i**. Purified by flash chromatography (C–E 98 : 2) as a pale yellow oil (Found: C, 63.3; H, 8.7; N, 5.3%); TLC (C–E 85:15) R_f 0.24; m/z (%) 265 (M⁺, 4), 219 (M⁺ – CH₃NOH, 100), 146 (15), 134 (11), 91 (4), 75 (14) and 73 (38).

2,5-Dimethyl-3-phenyl-2,3-dihydroisoxazole 9i Purified by

3163

flash chromatography (C-E 98:2) as a pale yellow oil (Found: C, 75.4; H, 7.5; N, 8.1. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.0%); TLC (C-E 85:15) $R_f 0.38$; v_{max}/cm^{-1} 1670 (C=C).

cis-2-Benzyl-3-ethyl-5-phenyl-5-(trimethylsiloxy)isoxazolidine cis-8j. Not isolated. TLC (C-E 85:15) R_f 0.80. NMR signals reported in Tables 1 and 2 are extracted from the spectra of a 2:1 mixture of *cis*-8j and 9j.

trans-2-Benzyl-3-ethyl-5-phenyl-5-(trimethylsiloxy)isoxazolidine trans-**8**j. Not isolated. TLC (C–E 85:15) R_f 0.61. NMR signals reported in Tables 1 and 2 are extracted from the spectra of a 3:2 mixture of trans-**8**j and **9**j.

2-Benzyl-3-ethyl-5-phenyl-2,3-dihydroisoxazole **9**j. Purified by flash chromatography (C–E 97:3) as a clear oil (Found: C, 81.4; H, 7.2; N, 5.3 C₁₈H₁₉NO requires C, 81.5; H, 7.2; N, 5.3%); TLC (C–E 85:15) $R_{\rm f}$ 0.66; $v_{\rm max}/{\rm cm}^{-1}$ 1650 (C=C); m/z (%) 265 (M⁺, 71), 248 (37), 188 (M⁺ – Ph, 6), 174 (M⁺ – CH₂Ph, 3), 160 (M⁺ – NCH₂Ph, 35), 105 (NCH₂Ph, 39), 91 (CH₂Ph, 100), 77 (Ph, 20), 65 (19) and 56 (17).

cis-2-Benzyl-3-isopropyl-5-phenyl-5-(trimethylsiloxy)isoxalidine cis-**8k**. Not isolated TLC (C–E 85:15) R_f 0.88; NMR signals could not be properly extracted from the spectra of the reaction mixture; m/z(%) 369 (M⁺, 1.5), 354 (M⁺ – Me, 2), 326 (M⁺ – Prⁱ, 55), 105 (26), 91 (100) and 77 (14).

trans-2-Benzyl-3-isopropyl-5-phenyl-5-(trimethylsiloxy)isoxazolidine trans-**8k**. Not isolated TLC (C-E 85:15) R_f 0.80; NMR signals reported in Tables 1 and 2 are extracted from the spectra of a 1:5 mixture of trans-**8k** and **9k**; m/z (%) 369 (M⁺, 2), 354 (M⁺ - CH₃, 2), 326 (M⁺ - Prⁱ, 58), 248 (M⁺ - PhCH₂NO, 3), 247 (11), 146 (5), 144 (5), 105 (23), 91 (PhCH₂, 100) and 77 (Ph, 12).

2-Benzyl-3-isopropyl-5-phenyl-2,3-dihydroisoxazole 9k. Purified by flash chromatography (C–E 99:1) as a pale yellow oil (Found: C, 81.8; H, 7.6; N, 5.0. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%); TLC (C–E 85:15) R_f 0.78; v_{max}/cm^{-1} 1655 (C=C).

Hydrolysis of 2-Benzyl-5-(tert-butyldimethylsiloxy)-3-ethylisoxazolidine cis-8a and trans-8a. General Procedure.—To a mixture of cis-8a and trans-8a (321 mg, 1 mmol, cis: trans 1:1) were added TFA (0.5 cm³, 6.7 mmol) and water (0.3 cm³) at room temperature. After 3 h the reaction mixture was neutralised with 5 mol dm⁻³ NaOH (1.34 cm³), then was extracted with CHCl₃ (3 × 20 cm³). The combined organic phases were dried (Na₂SO₄) and the solvent was evaporated off under reduced pressure. The residue was purified by flash chromatography C-E 1:1). 2-Benzyl-3-ethylisoxazolidin-5-ol 15a (115 mg, 55%, cis: trans 45:55) was isolated; TLC (C-E 1:1) R_f 0.41; v_{max}/cm^{-1} 3400br (OH).

2-Methyl-3-phenylisoxazolidin-5-ol **15d**. Hydrolysis of a mixture of cis-**8d** and trans-**8d** (293 mg, 1 mmol, cis:trans 6:4) under the same conditions as above gave compound **15d** (135 mg, 76%, cis:trans 2:1) purified by flash chromatography (C-E 1:1) as a clear oil; TLC (C-E 1:1) R_f 0.20; v_{max}/cm^{-1} 3400br (OH).

2,5-Dimethyl-3-phenylisoxazolidin-5-ol **15**i. Hydrolysis of cis-**8i** and trans-**8i** (235 mg, 1 mmol, cis: trans 55:45) under the same conditions as above afforded compound **15i** (150 mg, 77%, cis: trans 3:1), purified by flash chromatography (C-E 1:1) as an oil; TLC (C-E 1:1) R_f 0.36; ν_{max} /cm⁻¹ 3400br (OH) and 1730; m/z (%) 146 (M⁺ - CH₃NOH, 52), 131 (CH₃COCH=CHPh, 99), 115 (5), 103 (M⁺ - CH₃NOH - CH₃CO, 100), 91 (CH₂Ph, 3), 77 (Ph, 56), 74 (7) and 51 (38).

Hydration of 2,5-Dimethyl-3-phenyl-2,3-dihydroisoxazole 9i.—To a mixture of compound 9i (170 mg, 1 mmol) and water (0.3 cm³) was added TFA (0.5 cm³, 6.7 mmol) at room temperature. After 30 min the reaction mixture was neutralised with saturated aq. NaHCO₃ and extracted with diethyl ether (3 × 20 cm³). The combined organic phases were dried (MgSO₄) and the solvent was evaporated off under reduced

J. CHEM. SOC. PERKIN TRANS. 1 1993

Table 6 ¹H NMR data for compounds 15, 18 and 19 at 300 MHz

Compd.	3-H	4-H	5-H	Others
15a*	2.57-2.63 (m, cis), 3.16 (quin- tet, J 7.2, trans)	1.79–1.91 (m, <i>cis</i>), 2.03 (dd, J 5.0, 8.4, 12.9, <i>trans</i>), 2.38 (ddd, J 1.0, 6.6, 12.9, <i>trans</i>), 2.57– 2.63 (m, <i>cis</i>)	5.35 (dd, J 0.5, 5.8, cis), 5.44 (dd, J 1.0, 5.0, trans)	0.84 (3 H, t, J 7.4, CH ₂ Me trans), 0.88 (3 H, t, J 7.4, CH ₂ Me cis), 1.31–1.70 (4 H, m, CH ₂ Me cis + CH ₂ Me trans), 3.40 (2 H, br s, OH cis + OH trans), 3.73 (1 H, d, J 14.0, CH ₂ Ph cis), 4.06 (1 H, d, J 14.0, CH ₂ Ph cis), 4.08 (1 H, d, J 13.3, CH ₂ Ph trans), 4.17 (1 H, d, J 13.3, CH ₂ Ph trans), 7.18–7.38 (10 H, m, Ph cis + Ph trans)
15d <i>°</i>	3.49 (t, J 9.0, cis), 4.01–4.12 (m, trans)	2.33–2.40 (m, <i>cis</i>), 2.44– 2.60 (m, <i>trans</i>), 2.76– 2.85 (m, <i>trans</i>), 2.72– 3.03 (dt. <i>J</i> .71, 13.6, <i>cis</i>)	5.53–5.59 (m, cis), 5.61–5.66 (m, trans)	2.62 (6 H, s, NMe cis + NMe trans), 2.76–2.85 (2 H, m, OH trans + OH cis), 7.29–7.49 (5 H, m, Ph)
15i <i>°</i>	3.57 (br t, J 8.9, cis), 4.15 (dd, J 5.8, 12.1, trans)	2.28–2.44 (m, <i>trans</i>), 2.47 (dd, <i>J</i> 9.3, 13.2, <i>cis</i>), 2.50–2.70 (m, <i>trans</i>), 2.75 (dd, <i>J</i> 8.3, 13.2, <i>cis</i>)		1.58 (3 H, s, 5-Me cis), 1.62 (3 H, s, 5-Me trans), 2.61 (6 H, s, NMe cis + NMe trans), 2.79 (2 H, br s, OH cis + OH trans), 7.27-7.43 (10 H, m, Ph cis + Ph trans)
cis-18d	3.62 (br t, $J \sim 7.5$)	2.09 (ddd, J 6.9, 9.6, 12.4), 2.77 (dt, J 7.3, 12.4)	4.25–4.36 (1 H, m)	2.30–2.50 (1 H, m, 5-CH ₂), 2.53–2.68 (1 H, m, 5-CH ₂), 2.61 (3 H, s, NMe), $5.05-5.19$ (2 H, m, CH ₂ =), $5.78-5.93$ (1 H, m, =CH), $7.23-7.41$ (5 H, m, Ph)
trans-18d	3.42-3.54 (m)	2.29–2.53 (2 H, m)	4.28–4.39 (m)	2.29–2.53 (2 H, m, 5- CH_2), 2.59 (3 H, s, NMe), 5.06–5.20 (2 H, m, CH_{2}), 5.77–5.93 (1 H, m, = CH_{2}), 7.23–7.44 (5 H, m, Ph)
cis-19d	3.49 (br t, $J \sim 8.5$)	2.62 (ddd, J 3.8, 8.4, 13.0), 3.09 (dt, J 8.9, 13.0)	4.86 (dd, J 3.8, 8.9)	2.65 (3 H, s, NMe), 7.28–7.51 (5 H, m, Ph)
trans-19d	3.92-4.01 (m)	2.79 [°] (dt, J 8.0, 12.6), 2.98 (ddd, J 4.4, 6.9, 12.6)	4.81–4.94 (m)	2.74 (3 H, s, NMe), 7.28–7.53 (5 H, m, Ph)

^a cis- and trans-15 cannot be separated by flash chromatography. The reported data were obtained from spectra of fractions enriched in one isomer.

pressure. Flash chromatography (C–E 1:1) gave 2,5-dimethyl-3-phenylisoxazolidin-5-ol **15i** (160 mg, 82%, *cis:trans* 3:1) as an oil.

Reduction of 2-Methyl-3-phenylisoxazolidin-5-ol 15d.-To a solution of compound 15d (270 mg, 1.5 mmol) in methanol (0.8 cm³) was added NaBH₄ (42 mg, 1 mmol) at room temperature. After 2 h the solvent was evaporated off under reduced pressure, saturated aq. NaHCO₃ (1 cm³) was added, and the mixture was extracted with diethyl ether $(3 \times 10 \text{ cm}^3)$. The combined organic phases were evaporated to dryness and the residue was purified by flash chromatography (A-C 7:3) to give 3-(Nhydroxy-N-methylamino)-3-phenylpropan-1-ol 16d (250 mg, 92%); TLC (A–C 8:2) R_f 0.28; v_{max}/cm⁻¹ 3300br (OH); m/z (%) $181 (M^+, 3), 179 (M^+ - 2, 1), 163 (M - H_2O, 7), 136 (54), 121$ (10), 120 (36), 105 (100), 104 (30), 91 (CH₂Ph, 65), 77 (Ph, 32) and 51 (15); $\delta_{\rm H}$ 1.90–2.07 (1 H, m, 2-H), 2.07–2.20 (2 H, br s, NOH + OH), 2.34–2.48 (1 H, m, 2-H), 2.53 (3 H, s, NMe), 3.63– $3.82(3 \text{ H}, \text{m}, 1-\text{H}_2 + 3-\text{H})$ and $7.24-7.39(5 \text{ H}, \text{m}, \text{ArH}); \delta_c 35.2$ (C-2), 45.6 (MeN), 60.9 (C-3), 72.0 (C-1), 127.7, 128.2 and 128.9 (ArCH) and 138.5 (ArC).

Reduction of 2,5-Dimethyl-3-phenylisoxazolidin-5-ol 15i.-To a solution of compound 15i (290 mg, 1.5 mmol) in methanol (0.8 cm^3) was added NaBH₄ (42 mg, 1 mmol) at room temperature. After 30 min the solvent was evaporated off under reduced pressure, saturated aq. NaHCO₃ (1 cm³) was added, and the mixture was extracted with diethyl ether $(3 \times 10 \text{ cm}^3)$. The combined organic phases were evaporated to dryness and the residue was purified by flash chromatography (A-C 8:2) to give oily 4-(N-hydroxy-N-methyl)-4-phenylbutan-2-ol 16i (250 mg, 85%) as a 1:1 mixture of diastereoisomers on the basis of integrals of methyl signals in the ¹H NMR spectrum; v_{max}/cm^{-1} 3300br (OH); m/z (%) 193 (M⁺ - 2, 8), 146 (5), 134 (12), 131 (17), 121 (30), 120 (23), 118 (20), 105 (77), 104 (100), 78 (28) and 77 (52); $\delta_{\rm H}$ 1.20 ($\frac{3}{2}$ H, d, J 6.7, 1-H₃), 1.22 ($\frac{3}{2}$ H, d, J 6.3, 1-H₃), 1.65-1.75 (1 H, m, 3-H), 2.00-2.14 (2 H, br s, NOH + OH), 2.25-2.40 (1 H, m, 3-H), 2.51 (3 H, s, NMe), 2.54 (3 H, s, NMe), 3.80-3.90 (1 H, m, 4-H), 3.93-4.06 (1 H, m, 2-H) and 7.29-7.40 (5 H, m, ArH); δ_C 23.1 (C-1), 23.8 (C-1), 40.6 (C-3), 41.3 (C-3), 45.0 (MeN), 45.9 (MeN), 65.4 (C-4), 68.6 (C-4), 72.3 (C-2), 127.7, 127.9, 128.1, 128.5, 128.6 and 129.5 (ArCH) and 138.0 (ArC).

Reduction of 2-Benzyl-3-ethyl-5-methyl-5-(trimethylsiloxy)isoxazolidine cis-8g and trans-8g.-Copper(II) acetate (10 mg) and Zn dust (325 mg, 5 mmol) were poured into glacial acetic acid (0.8 cm³) and the solution was stirred for 10 min at room temperature until the blue colour disappeared. To this freshly prepared Zn/Cu couple was added a solution of isoxazolidines 8g (293 mg, 1 mmol; this reaction is often exothermic) in acetic acid (1.2 cm³)-water (0.3 cm³). After 1 h at 60-70 °C the reaction was worked up by addition of 6 mol dm⁻³ NaOH until pH 8 (glass electrode), and extraction with CHCl₃ (3×20 cm³). Flash chromatography (C-A 6:4) of the residue afforded 4-(benzylamino)hexan-2-one 17g (100 mg, 50%) as a yellow oil; TLC (C–A 1:1) $R_{\rm f}$ 0.20; $\nu_{\rm max}$ /cm⁻¹ 3700 (NH), 1710 (C=O), 1360 and 1180; $\delta_{\rm H}$ 0.93 (3 H, t, J 7.4, 6-H₃), 1.45–1.67 (2 H, m, 5-H₂), 1.90 (1 H, br s, NH), 2.16 (3 H, s, 1-H₃), 2.57 (2 H, d, J 6.3, 3-H₂), 3.05 (1 H, quint, J 6.3, 4-H), 3.74 (1 H, d, J 12.9, CH₂Ph), 3.87 (1 H, d, J 12.9, CH₂Ph) and 7.32–7.38 (5 H, m, ArH); $\delta_{\rm C}$ 9.7 (C-6), 26.4 (C-5), 30.6 (C-1), 47.9 (C-3), 50.9 (C-4), 54.6 (CH₂Ph), 126.8, 128.0 and 128.3 (ArCH), 140.4 (ArC) and 206.0 (C-2).

Coupling of Compound 8d with Allyltrimethylsilane (Table 5, Run 1).—To a solution of cis-8d and trans-8d (293 mg, 1.0 mmol) in CHCl₃ (13 cm³) were added allyltrimethylsilane (0.20 cm³, 1.3 mmol) and TMSOTf (0.212 cm³, 1.1 mmol) at room temperature. The mixture was stirred at 75 °C for 8 h and quenched with aq. NaHCO₃ (2 cm³); the two liquid layers were separated and the aqueous phase was extracted with diethyl ether (3 × 10 cm³). The combined organic layers were dried (MgSO₄), and evaporated to dryness. Flash chromatography (C-E 99:1) gave cis-and trans-2-methyl-3-phenyl-5-(prop-2enyl)isoxazolidine 18d as an oil (122 mg, 60%, cis:trans 1:1.3).

Alternatively (Table 5, run 2), to isoxazolidines *cis*-**8d** and *trans*-**8d** (293 mg, 1.0 mmol) dissolved in toluene (20 cm³) were added, at room temperature, allyltrimethylsilane (0.48 cm³, 3.0 mmol) and TMSOTF (0.212 cm³, 1.1 mmol). The mixture was stirred at 70 °C for 5 h and quenched with aq. NaHCO₃ (2 cm³);

Table 7 ¹³C NMR data for compounds 15, 18 and 19 at 75 MHz

Compd.	C-3	C-4	C-5	CH ₂ Ph Ph	NMe	Others
cis-15a ^a	65.4	43.5	95.4	64.6 127.1, 127.2, 128.1, 128.2,		10.8 (CH ₂ Me cis), 26.8 (CH ₂ Me cis)
trans-15a ª	67.2	42.3	97.6	60.6 (128.9, 129.1, 136.9, 137.8)		11.0 (CH ₂ Me trans), 25.0 (CH ₂ Me trans)
cis-15iª	74.2	52.8	102.0	127.4, 127.8, 128.0, 128.4,	42.6	25.9 (Me)
trans-15iª	74.2	51.2	103.3	128.6, 128.8, 137.6, 138.7	42.6	25.9 (Me)
cis-18d	73.3	40.4 ^b	76.2	127.5, 127.6, 128.6, 139.2	43.7	45.4 ^b (5-CH ₂), 117.2 (CH ₂ =), 134.6 (CH=)
trans-18d	73.0	38.9 ^b	76.1	127.7, 128.6, 129.0, 139.3	43.2	44.5 ^b (5-CH ₂), 117.4 (CH ₂ =), 133.9 (CH=)
cis-19d	63.7	44.1	72.0	127.8, 128.4, 128.7, 136.9	42.4	119.6 (CN)
trans-19d	63.5	43.8	71.9	127.3, 128.3, 128.8, 137.0	44.4	118.2 (CN)

^a cis- and trans-15 cannot be separated by flash chromatography. The reported data were collected from spectra of mixtures enriched in one isomer. Aromatic carbons of cis- and trans-15 are collected together.^b The assignments may have to be interchanged.

the two liquid layers were separated and the aqueous phase was extracted with diethyl ether $(3 \times 20 \text{ cm}^3)$. The combined organic layers were dried (MgSO₄), and evaporated to dryness. Flash chromatography of the oily residue gave the products 18d (90 mg, 44%, cis: trans 1:5).

One-pot Synthesis of Compound 18d.—To a stirred solution of isoxazolidine 8d [prepared from nitrone 1d (135 mg, 1 mmol) and silyl enol ether 7a (0.174 g, 1.1 mmol) in anhydrous chloroform (3 cm³)] was added drop-by-drop (10 min) a solution of TMSOTf (0.21 cm³, 1.4 mmol) in chloroform (2 cm³) at 0 °C. After 23 h was added allyltrimethylsilane (0.6 cm³, 3 mmol) and the reaction mixture was heated at 60 °C for 7 h before being quenched with saturated aq. NaHCO₃ (2 cm^3) ; the two liquid layers were separated and the aqueous phase was extracted with diethyl ether $(3 \times 20 \text{ cm}^3)$. The combined organic layers were dried (Na₂SO₄), and evaporated to dryness. The residue was chromatographed to give the products 18d (90 mg, 44%, cis: trans 55:45) as clear oil.

cis-2-Methyl-3-phenyl-5-(prop-2-enyl)isoxazolidine cis-18d (Found: C, 76.7; H, 8.4; N, 6.9. C₁₃H₁₇NO requires C, 76.8; H, 8.4; N, 6.9%); TLC (C-E 85:15) $R_{\rm f}$ 0.57; $v_{\rm max}/{\rm cm}^{-1}$ 1640 (C=C) and 990 (CH); m/z (%) 203 (M⁺, 26), 174 (56), 160 (46), 136 [PhCHN(CH₃)OH, 57], 135 (19), 134 [PhC=NO(CH₃), 100], 118 (43), 115 (31), 104 (28), 91 (PhCH₂, 63), 77 (Ph, 53) and 51 (26).

trans-2-Methyl-3-phenyl-5-(prop-2-enyl)isoxazolidine trans-18d (Found: C, 76.8; H, 8.4; N, 6.9%); TLC (C-E 85:15) R_f 0.46; $v_{\text{max}}/\text{cm}^{-1}$ 1640 (C=C) and 985 (CH); m/z (%) 203 (M⁺, 30), 174 (52), 160 (40), 136 [PhCHN(CH₃)OH, 50], 135 (18), 134 [PhC=NO(CH₃), 100], 118 (43), 115 (35), 104 (28), 91 (PhCH₂, 70), 77 (Ph, 45) and 51 (26).

Coupling of Compound 8d with Cyanotrimethylsilane.--- To a solution of cis-8d and trans-8d (293 mg, 1.0 mmol) in CHCl₃ (13 cm^3) were added cyanotrimethylsilane (0.173 cm³, 1.3 mmol) and TMSOTf (0.212 cm³, 1.1 mmol) at room temperature. The mixture was stirred for 8 h at 50 °C and quenched with saturated aq. NaHCO₃ (1 cm³); the two liquid layers were separated and the aqueous phase was extracted with diethyl ether $(3 \times 20 \text{ cm}^3)$. The combined organic layers were dried (Na₂SO₄), and evaporated to dryness. Flash chromatography (C-E 90:10) of the residue gave the cis- and trans-2-methyl-3phenylisoxazolidine-5-carbonitrile 19d (100 mg, 53%, cis: trans 2.4:1), as a yellow oil.

cis-2-Methyl-3-phenylisoxazolidine-5-carbonitrile cis-19d (Found: C, 70.3; H, 6.4; N, 14.9. C₁₁H₁₂N₂O requires C, 70.2; H, 6.4; N, 14.9%); TLC (C-E 65:35) $R_f 0.52$; $v_{max}/cm^{-1} 2230$ (CN); m/z (%) 188 (M⁺, 61), 143 (M - CH₃NO, 41), 142 (17), 135 [PhCHN(O)CH₃, 23], 134 (100), 115 (38), 91 (PhCH₂, 17), 77 (Ph, 30) and 51 H (22).

trans-2-Methyl-3-phenylisoxazolidine-5-carbonitrile trans-**19d** (Found: C, 70.2; H, 6.3; N, 14.9%); TLC (C-E 65:35) $R_{\rm f}$ 0.67; $\nu_{\rm max}/{\rm cm}^{-1}$ 2230 (CN); m/z (%) 188 (M⁺, 57), 143 (M -CH₃NO, 46), 142 (17), 135 [PhCHN(O)CH₃, 28], 134 (100), 116 (38), 115 (42), 91 (PhCH₂, 18), 77 (Ph, 37) and 51 (30).

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References

- 1 Z.-Y. Chang and R. M. Coates, J. Org. Chem., 1990, 55, 3464; 3475; A. Basha, J. D. Ratajczyk and D. W. Brooks, Tetrahedron Lett., 1991, 32. 3783.
- 2 F. Mancini, M. G. Piazza and C. Trombini, J. Org. Chem., 1991, 56, 4246; D. D. Dhavale, L. Gentilucci, M. G. Piazza and C. Trombini, Liebigs Ann. Chem., 1992, 1289.
- 3 S. Nawayama, S. Dan, Y. Inouye and H. Kakisawa, Chem. Lett., 1985, 957; P. DeShong, W. Li, J. W. Kennington, Jr., H. L. Ammon and J. M. Leginus, J. Org. Chem., 1991, 56, 1364.
- 4 D. D. Dhavale and C. Trombini, Heterocycles, 1992, 34, 2253.
- 5 D. D. Dhavale and C. Trombini, J. Chem. Soc., Chem. Commun., 1992, 1268.
- 6 H. Stamm and H. Steudle, Tetrahedron, 1979, 35, 647; S. Tomoda, Y. Takeuchi and Y. Nomura, Chem. Lett., 1982, 1787; Y. Kita, F. Itoh, O. Tamura, Y. Y. Ke and Y. Tamura, Tetrahedron Lett., 1987, 28, 1431; Y. Kita, O. Tamura, F. Itoh, H. Kishino, T. Miki, M. Kohno and Y. Tamura, J. Chem. Soc., Chem. Commun., 1988, 761.
- 7 B. Ly, F. Petrus, J. Verducci, D. Gombeau and G. Pfister-Guillouzo, Gazz. Chim. Ital., 1981, 111, 279.
- 8 J. E. Baldwin, L. M. Harwood and M. J. Lombard, *Tetrahedron*, 1984, 40, 4363; S. W. Baldwin and J. Aubé, *Tetrahedron Lett.*, 1987, 28, 179; I. Panfil, S. Maciejewski, C. Belzecki and M. Chmielewski, Tetrahedron Lett., 1989, 30, 1527; 1990, 31, 1901.
- 9 L. Ci Nunno and A. Scilimati, Tetrahedron, 1991, 47, 4121.
- 10 T. Mukaiyama and M. Murakami, *Synthesis*, 1987, 1043. 11 R. M. Coates and C. H. Cummins, *J. Org. Chem.*, 1986, **51**, 1383.
- 12 M. E. Jung and R. B. Blum, Tetrahedron Lett., 1977, 3791.
- 13 C. H. Heathcock, S. K. Davidsen, K. T. Hug and L. A. Flippin, J. Org. Chem., 1986, 51, 3027.

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