A Highly Stereoselective One-Pot Tandem Consecutive 1,4-Addition−Intramolecular 1,3-Dipolar Cycloaddition Strategy for the Construction of Functionalized Five- and Six-Membered Carbocycles[†,1]

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Nitronates **3**, possessing a suitably located olefinic moiety and arising from conjugate addition of Grignard reagent **2** to nitro olefins **1**, are trapped as silyl nitronates **8** which undergo a facile intramolecular 1,3-dipolar cycloaddition. The resulting *N*-(silyloxy)isoxazolidines **9** are readily transformed into isoxazolines **6** and **7** upon treatment with acid, thus completing the entire sequence in one pot. While cycloaddition to the five-membered carbocycles, in general, proceeds smoothly at rt in a stereospecific manner, that to the six-membered ring is sluggish and less selective. The advantages of this strategy over the intramolecular nitrile oxide cycloaddition, namely greater stereoselectivity and adaptability to one-pot conditions, have been demonstrated. Extensive NMR investigations unravelled the stereochemistry unambiguously and underscored the inadequacy of coupling constants alone in determining the stereochemistry in cyclopentane systems. The explanation advanced to account for the selectivities, in terms of subtle differences among the putative transition state geometries, is in qualitative agreement with widely accepted assumptions pertaining to 1,3-dipolar cycloadditions.

Introduction

Tandem reactions have emerged in recent years as a powerful means for their operational simplicity and frequently observed selectivity, providing a fresh impetus to organic synthesis.[2] Prominent in this family are Michael initiated reactions, in which the enolate resulting from the initial 1,4-addition can subsequently undergo a legion of other transformations in the same reaction vessel, including a facile intramolecular cyclization.[2a,3] However, there are only sporadic reports of tandem reactions wherein Michael additions coupled with 1,3-dipolar cycloadditions are incorporated.[4]

Cyclopentanoids are precursors to prostaglandins and a plethora of other natural products.[5] While stereoselective synthesis of functionalized cyclopentanes is indeed a nontrivial task, there has been tremendous improvement in the efficiency of cyclizations with the advent of multiple bond forming [3 + 2] annulation processes.[5,6] However, since the [3 + 2] annulation strategy, by far, is largely dependent on trimethylenemethane (TMM) precursors and often requires transition metal catalysis,[5,6a,b] alternative avenues involving intramolecular thermal additions of oximes,[6e] nitrile oxides,[6f,7] and silyl nitronates[6f] providing cyclopentanes fused to an isoxazolidine or isoxazoline moiety are of considerable interest. The scope and effectiveness of the latter approaches are so striking in that they serve the twin purpose of generating a carbocycle and a heterocycle fused to each other in an essentially single operation. The isoxazolines themselves are versatile masked structural entities and lend easy access to γ-amino alcohols, β-hydroxy ketones, and the like, thereby opening up a convenient and useful entry into natural product synthesis.[8]

Nitro olefins are excellent Michael acceptors,[9] and the nitro group *per se* is amenable for further transformation to a host of reactive intermediates, including nitrile oxides[8,10] and silyl nitronates,[4c−d,6f,8a] which are of immediate concern to us. Furthermore, as part of our sustained interest in the chemistry of nitro olefins,[4cd,11] we have undertaken a scheme involving primarily the conjugate addition of carbon-centered nucleophiles (in the

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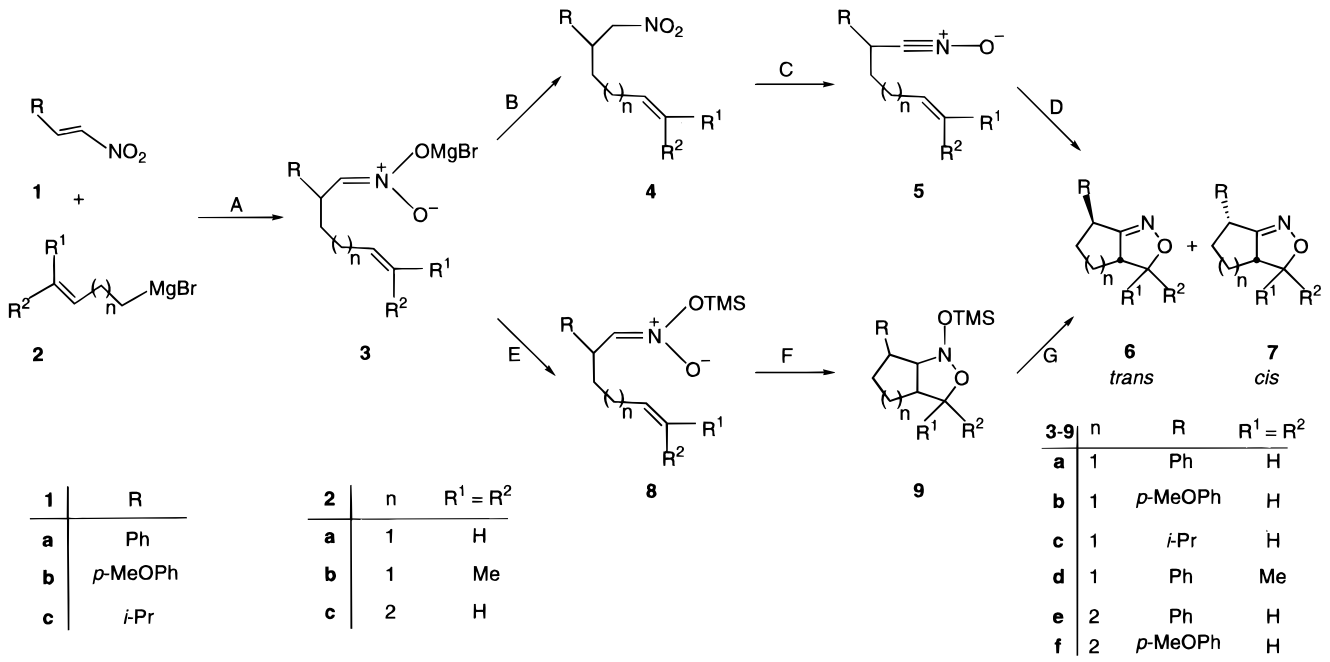
Scheme 1[a]



1	R
a	Ph
b	*p*-MeOPh
c	*i*-Pr

2	n	$R^1 = R^2$
a	1	H
b	1	Me
c	2	H

3-9	n	R	$R^1 = R^2$
a	1	Ph	H
b	1	*p*-MeOPh	H
c	1	*i*-Pr	H
d	1	Ph	Me
e	2	Ph	H
f	2	*p*-MeOPh	H

[a] (A) −90 °C, THF; (B) path 1, stepwise; (C) *t*-BOC_2O, DMAP (cat.), THF, rt, 72 h; (D) INOC; (E) path 2, tandem, one-pot, TMSCI, Et_3N, −90 to 0 °C, 2 h; (F) ISOC, HMPA, 0 °C−rt (a) rt, 15 h, when $n = 1$, $R^1 = R^2 = H$, (b) toluene, 60 °C (i) 48 h, when $n = 1$, $R^1 = R^2 = Me$, (ii) 15 h, when $n = 2$, $R^1 = R^2 = H$; (G) 10% HCl.

form of Grignard reagents) to nitro olefins and an intramolecular silyl nitronate−olefin cycloaddition (ISOC)[4cd,6f,8a,12] as the key steps. Recently ISOC has been demonstrated to be a stereoselective alternative[4c,d,6f] to analogous intramolecular nitrile oxide−olefin cycloaddition (INOC)[8,13] by adopting the ISOC strategy for the synthesis of oxygen-,[4d,6f] sulfur-, dimethoxycarbonyl carbon-[6f] and nitrogen-containing bicyclic isoxazolines.

The methodology reported here affords, in one pot, a five- or six-membered carbocycle fused to an isoxazoline moiety in a highly stereoselective manner from simple nitro olefins and suitably functionalized Grignard reagents.

Results and Discussion

Although addition of Grignard reagents to aliphatic nitro olefins gives rise to a complex mixture of products (arising from concomitant 1,4-addition, 1,2-addition, and diaddition),[14] similar additions to their aromatic counterparts (for instance, nitrostyrenes) proceed fairly smoothly,[11e,15] particularly at low temperatures.[11e] Stabilizing and solubilizing additives exert no influence on these practically instantaneous reactions.[11e] We, therefore, embarked on the idea of elaborating this procedure by employing a Grignard reagent, consisting of an appropriately placed olefinic moiety, as the nucleophile. This would enable one to perform an intramolecular cyclization between the nitro group and the unsaturated tether. The possibility of converting the nitronate resulting from the initial 1,4-addition to a more reactive nitrile oxide or silyl nitronate *in situ* appeared attractive for achieving a subsequent dipolar cycloaddition since this would obviate the cumbersome processes of quenching the nitronate using a proton source, isolating and purifying of the corresponding *ω*-nitroalkene, and subjecting the latter to a classical INOC or ISOC reaction. We also anticipated a probable enhancement in the diastereoselectivity under the one-pot conditions.

Our preliminary experiments aimed at performing the conjugate addition and INOC in one pot proved futile, presumably due to poor conversion of the nitronate **3a** to nitrile oxide **5a** in the presence of phenyl isocyanate and triethylamine[10a] under the conditions usually employed for nitroalkanes. Treatment of the nitronate **3a** with di-*tert*-butyl dicarbonate (*t*-BOC_2O) in the presence of catalytic amounts of DMAP[10b] led to the formation of the desired isoxazoline in 24% yield, *albeit* as a complex mixture. Later, we successfully carried out the INOC in a separate step *via* the isolated nitro olefin **4a** or **4b** (Scheme 1, path 1), and the product comprised a mixture of separable diastereomers **6a** and **7a** or **6b** and **7b** in a 3.5:1 (*trans*/*cis*) ratio (Table 1). It is instructive to note that the INOC reactions performed previously for the construction of oxygen-,[6f,11d] sulfur- and dimethoxycarbonyl carbon-containing[6f] five-membered rings fused

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Table 1. 1,4-Addition of Homoallylmagnesium Bromide 2a to Nitro olefins 1 and Subsequent INOC of Nitrile Oxide 5, Generated from ω-Nitroalkene 4 to Isoxazolines 6 and 7 in a Stepwise Sequence

entry	nitro-olefin **1**	1,4-adduct **4**	yield (%)	isoxazolines **6** and **7**	yield (%)	*trans*:*cis* **6**:**7**
1	**1a**	**4a**	78	**6a** + **7a**	80	3.5:1
2	**1b**	**4b**	76	**6b** + **7b**	88	3.5:1

to isoxazolines also afforded a mixture of diastereomers. Significantly, however, the *t*-BOC_2O/DMAP procedure[10b] turned out to be superior to the Mukaiyama−Hoshino procedure[10a] for the *in situ* generation of nitrile oxides from **4** since the diphenylurea, formed as a side product when the latter procedure was adopted, complicated the purification stage.

Subsequently, we set out to investigate the viability of conducting the 1,4-addition and the ISOC in one pot in a tandem consecutive protocol.[2b] This approach has at least one precedent in the literature, though with a nitrogen-centered nucleophile.[4c] This requires kinetically quenching the nitronate **3** using, for instance, TMSCl with generation of the silyl nitronate **8** and subjecting the latter to the ISOC reaction. Silyl nitronates (*e.g.* **8**) are regarded as synthetic equivalents of nitrile oxides (*e.g.* **5**) in their reactions with olefins[4c,d,6f,8a,12] since the resulting *N*-(silyloxy)isoxazolidines (*e.g.* **9**), upon treatment with acid or tetrabutylammonium fluoride (TBAF), undergo facile transformation to isoxazolines (*e.g.* **6** and **7**).

Indeed, we were pleased to observe the formation of the desired isoxazolines fused to a substituted carbocyclic five-membered ring under the following one-pot conditions (path 2, Scheme 1; see also the Experimental Section). The nitronate **3a** arising from conjugate addition of homoallylmagnesium bromide **2a** to nitrostyrene **1a** at low temperature was quenched with TMSCl. Subsequently, the reaction mixture was treated with Et_3N and warmed to 0 °C to ensure complete silylation. HMPA was then added and the mixture continued to stir at rt for 15 h, leading to complete cyclization of the silyl nitronate **8a** to *N*-(silyloxy)isoxazolidine **9a**. Treatment of **9a** with 10% aqueous HCl afforded the desilylated product **6a** in 66% overall yield (entry 1, Table 2). Similarly, other isoxazolines can be prepared in respectable overall yields from substituted nitrostyrenes as well (entry 2, Table 2). On the other hand, a substantial drop in the overall yield was encountered in the case of aliphatic nitro olefins (see entry 3, Table 2 for a representative example) which is quite understandable, given their behavior toward Grignard reagents as alluded to in the beginning of this section.

Et_3N and HMPA were found to have a profound influence on the cycloaddition. In the absence of either one or both of them, the reaction remained incomplete even after 72 h (footnote *a*, Table 2). While HMPA is a routinely used stabilizing and solubilizing additive, Et_3N is known to have specific stabilizing effect on silyl nitronates.[8a,12a]

However, the most remarkable feature of this ISOC reaction is the high degree of stereoselectivity observed, amounting to stereospecific formation of one diastereomer. So much so that the ISOC reaction proved superior to the INOC not only in terms of its adaptability to one-pot conditions but in terms of its stereoselectivity as well.

Table 2. 1,4-Addition of Grignard Reagent 2 to Nitro olefin 1, Silylation of the Nitronate 3, ISOC of the Silyl Nitronate 8, and Desilylation of *N*-(Silyloxy)isoxazolidine 9 to Isoxazolines 6 and 7 in a One-Pot Tandem Consecutive Protocol

entry	nitro-olefin **1**	Grignard reagent **2**	isoxazolines **6** and **7**	isolated overall yields (%)	*trans*:*cis* **6**:**7**
1	**1a**	**2a**	**6a** + **7a**	66[a]	>99:1
2	**1b**	**2a**	**6b** + **7b**	43	>99:1
3	**1c**	**2a**	**6c** + **7c**	18	>99:1
4	**1a**	**2b**	**6d** + **7d**	53	>95:5[b]
5	**1a**	**2c**	**6e** + **7e**	62	1:2.6
6	**1b**	**2c**	**6f** + **7f**	58	1:2.6

[a] 49% in the absence of HMPA and 41% in the absence of Et_3N. [b] The minor isomer **7d** could not be isolated in pure form.

Generality of the procedure described above was demonstrated by adapting it to the construction of six-membered carbocycles, but it required slight modifications. Cycloaddition to the six-membered ring was too sluggish at rt and addition of salts like $NaHCO_3$[2b] or *t*-BuOK[16] had only a marginal effect (<15% conversion). Heating the reaction mixture in THF provided only a complex mixture.

Recent investigations on nitrile oxide cycloadditions showed that polar solvents decrease the rate of cycloaddition, though marginally, indicating less charge buildup in the transition state of the cycloaddition as against that in the ground state.[17] This appeared to be the case in the silyl nitronate cycloaddition as well since we achieved complete cyclization to the six-membered ring by reducing the polarity of the medium by adding toluene and heating the reaction mixture at 60 °C for 15 h. But, in contrast to the stereospecificity observed during cyclization to the five-membered ring, the cyclization was less selective, furnishing a mixture of separable diastereomers in a 1:2.6 (*trans*/*cis*) ratio (entries 5 and 6, Table 2). Nevertheless, this is in concert with the observation made during the construction of oxygen- and sulfur-containing six-membered rings fused to isoxazolines.[6f]

The cycloadditions described so far encompass only monosubstituted unactivated alkenes as the dipolarophiles. However, dialkyl substitution at the terminal carbon does not affect the overall yield or selectivity (entry 4, Table 2), though drastic conditions (60 °C, 48 h) were necessary to circumvent the deceleration of the cycloaddition which could be rationalized in terms of the steric demand of one of the terminal methyl groups. As a matter of fact, this contravenes the observation made during the preparation of oxygen-containing bicyclic isoxazolines where dialkyl substitution at the terminal position was found to accelerate the cycloaddition which was attributed to superior frontier orbital overlap.[4d]

Stereochemistry. Structure and stereochemistry of isoxazolines **6** and **7** were unambiguously established using extensive NMR studies involving 2D-COSY and NOESY experiments, the results of which are summarized in Tables 3−7.[18] The ^1H NMR spectra recorded in $CDCl_3$ at 300 MHz for cyclopentane systems **6a**,**b**, **7a**,**b**, and **6d** were obscure due to overlapping of signals corresponding to H-3′ and H-3a in **6a**,**b**, H-3′, H-6, and

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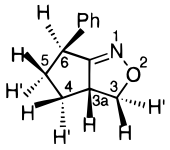
(18) The chemical shifts, multiplicities, coupling constants, and NOE data of representative examples are depicted in a concise fashion in Tables 3−6 for clarity and easy comparison.

Table 3. ^{1}H NMR (δ, C_6D_6, 600 MHz)[a] and NOESY[b] Data of Isoxazoline 6a

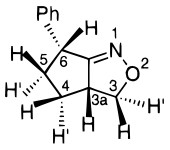


6a

no.	3	3′	3a	4	4′	5	5′	6	Ph
3	**4.10** (dd)	8.0	9.5						
3′	S	**3.49** (dd)	12.5						
3a	S	W	**3.13** (dddddd)	7.5	11.0	0.5		2.0	
4			M	**1.35** (ddddd)	12.0	1.5	7.0	1.0	
4′		M		S	**0.84** (dddd)	7.5	11.5		
5				W	M	**2.15** (ddddd)	13.0	8.5	
5′			W	M		S	**1.71** (dddd)	8.5	
6						M		**3.63** (tdd)	
Ph			W			W	W	M	**7.04−7.17** (m)

[a] Chemical shifts and multiplicities (in parentheses) are placed diagonally and *J* (Hz) off-diagonally (upper). [b] Placed off-diagonally (lower): S, strong; M, medium; W, weak.

Table 4. ^{1}H NMR (δ, C_6D_6, 600 MHz) and NOESY Data[a] of Isoxazoline 7a



7a

no.	3	3′	3a	4	4′	5	5′	6	Ph
3	**4.13** (dd)	8.0	9.5						
3′	S	**3.47** (dd)	12.5						
3a	M	W	**3.13** (ddtdd)	9.0	9.0		0.5	1.0	
4			M	**1.32** (dddd)	13.0	8.0	4.0		
4′		M		S	**1.04** (dqd)	8.5	9.0	0.5	
5			W	M		**1.98** (dddd)	13.5	10.0	
5′					M	S	**1.81** (ddddd)	6.5	
6			W			M		**3.40** (dddd)	
Ph		M			W		W	M	**7.15−7.29** (m)

[a] See footnotes, Table 3.

H-3a in **7a**,**b**, and H-4 and H-4′ in **6d**. However, upon changing the solvent to C_6D_6 and recording the spectra at 600 MHz, the signals became well-resolved. A detailed analysis of the ^{1}H NMR spectra of the cyclopentane systems disclosed that the coupling patterns, though duly confirmed by 2D-COSY experiments, do not shed much light into the stereochemistry. For instance, small ^4J couplings (of 2 and 1 Hz, respectively) are observed between the bridgehead hydrogen H-3a and benzylic hydrogen H-6 in both the isomers **6a** and **7a** (Tables 3 and 4). In fact, we have often seen *measurable coupling constants between hydrogens located on the two carbons* α *to an* sp^2 *center*. While we know of very few examples of this in the literature,[19] we think it is a general phenomenon. Vicinal coupling in **6a** between H-6 and H-5 or H-5′ are of equal magnitude (8.5 Hz, Table 3) and thus not diagnostic. Similarly, H-3a has identical couplings (9 Hz each) with its vicinal hydrogens H-4 and H-4′

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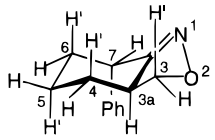
Table 5. ^{1}H NMR (δ, $CDCl_3$, 600 MHz) and NOESY Data[a] of Isoxazoline 6e

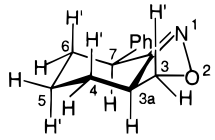


6e

no.	3	3′	$3a_{ax}$	4_{eq}	$4'_{ax}$	5_{eq}	$5'_{ax}$	6_{eq}	$6'_{ax}$	7_{eq}	Ph
3	**4.50** (dd)	8	10.5								
3′	S	**3.88** (dd)	9.5								
$3a_{ax}$	M	W	**3.21** (ddddd)	6.5	11.5					0.5	
4_{eq}			M	**2.10** (ddddd)	13.0	3.5	3.0	1.5			
$4'_{ax}$		W		S	**1.45** (dddd)	3.5	13.0				
5_{eq}					M	**1.71** (dquin)	14.0	3.5	3.5		
$5'_{ax}$			W	W		S	**1.58** (dddt)	3.0	13.5		
6_{eq}						W		**2.58** (dtt)	14.0	2.0	
$6'_{ax}$								S	**1.88** (dddd)	5.5	
7_{eq}								W	M	**4.25** (ddd)	
Ph			W				W	M		W	**7.23−7.37** (m)

[a] See Footnotes, Table 3.

Table 6. ^{1}H NMR (δ, $CDCl_3$, 600 MHz) and NOESY Data[a] of Isoxazoline 7e



7e

no.	3	3′	$3a_{ax}$	4_{eq}	$4'_{ax}$	5_{eq}	$5'_{ax}$	6_{eq}	$6'_{ax}$	7_{ax}	Ph
3	**4.56** (dd)	8	10.5								
3′	S	**3.85** (dd)	10.5								
$3a_{ax}$	M	W	**3.30** (dtdd)	6.0	13.0					1.0	
4_{eq}			M	**2.24** (ddtd)	12.0	3.0	3.0	2.0			
$4'_{ax}$		W		S	**1.50** (tdd)	3.5	13.0				
5_{eq}						**2.01** (ddq)	14.0	3.0	3.0		
$5'_{ax}$			W			S	**1.63** (dtt)	3.0	13.0		
6_{eq}							W	**2.16** (ddtd)	13.5	0.5	
$6'_{ax}$					W	W		S	**1.80** (dddd)	12.5	
7_{ax}			W				W	M		**3.52** (ddd)	
Ph									M	M	**7.30−7.35** (m)

[a] See footnotes, Table 3.

in **7a** (Table 4). ^{13}C NMR also did not provide much insight into the stereochemistry since no major difference was discernible between chemical shifts of the isomeric pairs **6a**, **7a** and **6b**, **7b** with the exception that, in the *cis* isomers **7a** and **7b**, the C-4 resonances were shielded by *ca.* 2 ppm in comparison with those of their *trans* counterparts **6a** and **6b**, respectively (26.4 and 26.2 *vs* 28.2 and 28.1, respectively). However, this does not constitute conclusive evidence *vis a vis* the stereochemistry. Subsequently, 2D-NOESY experiments provided incontrovertible proof for assigning the stereochemistry. A weak NOE interaction between H-3a and Ph (obviously due to the *ortho* hydrogens) taken together with the absence of any such interaction between H-3a and H-6

Table 7. ^{13}C NMR Chemical Shifts (δ, $CDCl_3$, 75.5 MHz) of Isoxazolines 6e, 7e, 6f, and 7f

entry	cmpd	C-1a	C-3	C-3a	C-4	C-5	C-6	C-7	C-1′	C-2′	C-3′	C-4′	others
1	**6e**	161.4	73.7	45.9	29.9	20.2	32.8	37.8	138.7	127.2	128.7	126.6	
2	**7e**	162.4	73.7	49.2	32.2	24.9	34.7	44.7	139.7	128.3	128.4	127.1	
3	**6f**	161.5	73.6	45.8	29.9	20.0	32.8	37.0	130.5	128.8	114.0	158.2	55.2
4	**7f**	162.6	73.5	49.0	32.1	24.7	34.7	43.6	131.7	129.0	113.6	158.3	55.0

suggests a *trans* stereochemisty for **6a** (Table 3). Conversely, the *cis* stereochemistry between H-3a and H-6 in **7a** is evident from a weak NOE interaction between them and the absence of any interaction between H-3a and Ph (Table 4).

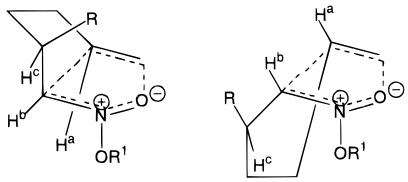
In view of the above, the stereochemistry of the analogs **6b**, **6c**, and **6d** could be assigned as *trans* and that of **7b** as *cis* based on their characteristic coupling patterns.

In stark contrast to the stereochemistry of cyclopentane systems **6a**−**d** and **7a**−**d** discussed so far, cyclohexane systems **6e**,**f** and **7e**,**f** displayed much more dependable ^{1}H and ^{13}C NMR characteristics, enabling a tentative stereochemical assignment at the outset. Strong diaxial couplings (11.5 and 13 Hz, respectively) were observed between bridgehead hydrogen H-3a and its vicinal axial hydrogen H-4′ in both of the isomers **6e** and **7e** (Tables 5 and 6). That the benzylic hydrogen H-7 in **6e** has only small couplings (2 and 5.5 Hz, respectively, *gauche*) with its vicinal hydrogens H-6 and H-6′ (Table 5) is diagnostic of its equatorial orientation and therefore of its *trans* relationship with H-3a. On the other hand, in **7e**, a 12.5 Hz coupling for H-7 (Table 6) could only arise from its *trans* diaxial relationship with one of its vicinal hydrogens (H-6′) which in turn is indicative of its *cis* diaxial relationship with H-3a. Results emanating from COSY and NOESY experiments confirmed these assignments. A weak NOE interaction between H-3a and Ph in conjunction with the absence of any NOE interaction between H-3a and H-7 reflects the *trans* stereochemistry of **6e** (Table 5), and the NOE interaction between H-3a and H-7 fits the *cis* isomer **7e** (Table 6).

^{13}C chemical shifts are also greatly influenced by the stereochemistry and conformation of the cyclohexane ring (Table 7). Interestingly enough, all the carbons in the cyclohexane ring are shielded by 1−7 ppm in the *trans* isomers **6e** and **6f** as opposed to those of their *cis* counterparts **7e** and **7f**, respectively, and the shielding is particularly pronounced for C-3a, C-5, and C-7. This is clearly attributable to the axial orientation of the aryl group in **6e** and **6f**.

In the light of the unimpeachable evidence obtained in favor of a *trans* stereochemistry in the major isomers of cyclopentanes fused to isoxazolines **6a**−**d** and **7a**−**d** and *cis* stereochemistry in the major isomers of cyclohexanes fused to isoxazolines **6e**,**f** and **7e**,**f**, it seemed appropriate to discuss factors influencing the stereochemical outcome. In fact, products closely resembling isoxazolines **6** and **7** in terms of substitution are obtained from analogous nitrone[13j,20] and nitrile oxide[6f,11d,13j,21] cycloadditions. In general, the stereochemistry between H-3a and H-6 in five-membered rings fused to isoxazoli(di)nes is predominantly *trans*, and that between H-3a and H-7 in six-membered rings fused to isoxazoli(di)nes is predominantly *cis*. These observations have often been supported by energy calculations.[13j,21]

The stereochemical course of the silyl nitronate cycloadditions is comparable with the analogous nitrone cycloadditions[22] in that in both cases the TSs leading to *N*-substituted isoxazolidines can be assumed to have identical geometries. Examination of molecular models reveals that the formation of cyclopentanes fused to *N*-(silyloxy)isoxazolidines (*e.g.* **9a**−**d**) could take place *via* an *exo* TS **10a**, arising from an *E*-nitronate, or *via* an *endo* TS **10b**, which results from a *Z*-nitronate, both



exo-E **10a** *endo-Z* **10b**

incidentally, leading to *cis* fused bicyclic isoxazolidines. Those TSs leading to *trans* fused systems, as products of kinetic control, appeared energetically destabilized or geometrically unattainable.[22,23]

Formation of *trans* isomers **6a**−**d** in overwhelming predominance in the intramolecular cycloaddition to five-membered rings is ascribable to the orientation of H_a, H_b, and R on the *exo* face of the TS **10b**, leading to *N*-(silyloxy)isoxazolidines. Since elimination of silanol involving H_b in no way interferes with the orientation of H_a and R, a *trans* relationship between H_a and H_c in the resulting isoxazolines is abundantly clear. This fully accords with the widely accepted view that approach of the dipole and dipolarophile takes place in two parallel planes[24] and that an *endo* TS is preferred in the absence of obvious steric effects.[25] Formation of *ca.* 5% *cis* isomer when the dipolarophile terminal is disubstituted is accountable in terms of the cycloaddition taking place *via* TS **10a**.

Insofar as the cycloaddition to the six-membered rings is concerned, model studies show that the stereochemistry is dictated by chairlike TSs, which is consistent with the NMR data. In principle, an *exo E*-TS **11a** or an *endo Z*-TS **11b** could lead to the *cis* isomers **7e**,**f** (H_a and H_c *cis* diaxial). However, the subtle difference is that while the transformation of **11b** to **7e**,**f** takes place *via cis* fused *N*-(silyloxy)isoxazolidines **9e**,**f** (products of thermodynamic control), the intermediate *N*-(silyloxy)isoxazolidines **9e**,**f** would be *trans* fused (products of kinetic control) if the TS is **11a**. TS **11b** seems preferred not only in terms of the superior FMO overlap but in terms

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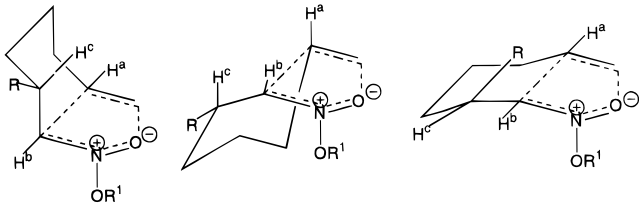
(23) Lebel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759.

(24) (a) Huisgen, R.; *J. Org. Chem.* **1976**, *41*, 403. (b) Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2043. (c) Leroy, G.; Nguyen, M. T.; Sana, M. *Tetrahedron* **1978**, *34*, 2459.

(25) (a) Tufariello, J. J.; Ali, Sk. A.; *Tetrahedron Lett.* **1978**, *19*, 4647. (b) Tufariello, J. J.; Puglis, J. M. *Ibid.* **1986**, *27*, 1265. (c) Burdisso, M.; Gandolfi, R.; Grunanger, P.; Rastelli, A. *J. Org. Chem.* **1990**, *55*, 3427. (d) Jung, M. E.; Gervay, J.; *Chemtracts* **1990**, *3*, 284.



exo-E *endo-Z* *exo-Z*

11a **11b** **11c**

of the reaction conditions employed (60 °C, 15 h). Formation of *trans* isomers **6e**,**f** (which is assumed to take place *via* an *exo Z*-TS **11c**) in considerable amounts (entries 5 and 6, Table 2) is in all probability the consequence of heating the reaction mixture which was inevitable in order to complete the cycloaddition. Prolonged heating is known to have a detrimental effect on the selectivity as equilibration of the cycloadducts,[25c,26] presumably *via* cycloreversions and readditions, takes place readily at higher temperatures.[27]

Conclusions

A convenient and stereoselective route to highly functionalized five- and six-membered carbocycles involving 1,4-addition of Grignard reagents, silylation of the resulting nitronate, subsequent intramolecular 1,3-dipolar silyl nitronate cycloaddition, and desilylation, all in one pot, has been described. While the intramolecular cycloaddition leading to five-membered rings fused to isoxazolines proceeds stereoselectively to provide preferentially *trans* isomers, such reactions leading to six-membered rings favor *cis* isomers.

Experimental Section

1. General.[11e] ^{1}H NMR, 2D-COSY, and NOESY experiments of isoxazolines **6** and **7** were performed on a Bruker DMX 600 FT spectrometer. Grignard reagents were freshly prepared in THF from activated Mg and appropriate alkyl bromide (Aldrich). DMAP (Reilly Industries Inc., IN) and *t*-BOC_2O (Sigma) were used without further purification. The following solvents and reagents were distilled from the indicated agent under argon: THF from sodium benzophenone ketyl, toluene from P_2O_5, and TMSCl, Et_3N, and HMPA from calcium hydride.

2. General Procedure for the Preparation of the Grignard Reagents 2. The reaction flask, fitted with a condenser and charged with Mg turnings (40 mg, 1.6 equiv), a crystal of iodine, and THF (2 mL), was immersed in a 70 °C oil bath. A portion of the alkyl bromide was then added while stirring. Once the reaction began, the oil bath was removed and the flask was cooled to 0 °C (ice bath). The remaining alkyl bromide (total 1.5 equiv) was then added as a solution in THF (1 mL) over a period of 1 h. Stirring continued at rt for an additional 1 h, if necessary, to complete the generation of the Grignard reagent.

3. General Procedure for the Stepwise Grignard Addition to Nitro olefins and INOC Reaction (*cf.* Table 1). 3.1. Preparation of *ω*-Nitroalkenes 4. To a stirred solution of the Grignard reagent **2**, cooled to −90 °C, was added nitro olefin **1** (1 mmol) in THF (1 mL). The reaction was quenched with saturated aqueous ammonium chloride (2 mL), brought to rt, stirred for 1 h, and extracted with ether. The ether extracts were washed with brine, dried (anhyd $MgSO_4$), and evaporated, and the residue was purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether as eluent.

3.2. INOC Reaction of *ω*-Nitroalkenes 4 to Isoxazolines 6+7. To a stirred solution of *ω*-nitroalkene **4** (0.5 mmol), in THF (3 mL) at rt, were added DMAP (6 mg, 10 mol%) in THF (0.5 mL) followed by *t*-BOC_2O (165 mg, 1.5 equiv) in THF (1 mL) in small instalments. Stirring was continued at rt for 72 h. The reaction mixture was then diluted with ether and washed with 5% aqueous HCl and brine. The ether solution was dried (anhyd $MgSO_4$) and evaporated, and the residue containing a mixture of isomers **6** and **7** was subjected to flash column chromatography on silica gel using ethyl acetate/petroleum ether (1:4 for entry 1 and 3:7 for entry 2) as eluent. The diastereomers differing marginally in mobility were separated; the more mobile component was identified as the *trans* isomer **6a** or **6b** (R_f 0.42 or 0.38) and the less mobile one as the *cis* isomer **7a** or **7b** (R_f 0.30 or 0.32).

4. General Procedure for the One-Pot Grignard Addition to Nitro olefins, Silylation, ISOC, and Desilylation Leading to Isoxazolines 6−7 (*cf.* Table 2). To a stirred solution of Grignard reagent **2** (1.5 equiv) in THF (3 mL), cooled to −90 °C, was added nitro olefin **1** (1 mmol) in THF (1 mL). After 5 min, TMSCl (0.24 mL, 3 equiv) and Et_3N (0.42 mL, 3 equiv) were added in succession, and the reaction mixture was allowed to warm to 0 °C over 2 h. HMPA (0.52 mL, 3 equiv) was then added, and the reaction mixture was (a) stirred for 15 h at rt (entries 1−3), (b) diluted with toluene (6 mL) and stirred at 60 °C (oil bath) for 48 h (entry 4), or (c) as in case b, but stirred for 15 h (entries 5,6). The reaction mixture was then cooled to 0 °C, treated with 10% aqueous HCl, stirred for 1 h at rt, poured into water, and extracted with ether; the ether extracts were washed with brine, dried (anhyd $MgSO_4$) and concentrated; and the residue was flash chromatographed on silica gel. Eluting system and R_f values are as follows. Ethyl acetate/petroleum ether: entry 1 1:4, 0.42; entry 2 3:7, 0.38; entry 3 1:19, 0.39; entry 4 1:4, 0.52 (**6d**) and 0.42 (**7d**); entry 5 1:9, 0.33 (**6e**) and 0.14 (**7e**); entry 6 3:7, 0.50 (**6f**) and 0.30 (**7f**).

6-Nitro-5-phenyl-1-hexene (4a): light yellow oil; ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 7.25 (m, 5H), 5.75 (ddt, J = 17, 13, 11 Hz, 1H), 4.95 (m, 2H), 4.56 and 4.53 (AB of ABX, J = 13, 8.5, 7.5 Hz, 2H), 3.47 (quint, J = 8 Hz, 1H), 1.94 (m, 2H), 1.79 (m, 2H); ^{13}C NMR (δ, $CDCl_3$, 75.5 MHz) 139.1 (s), 137.1 (d), 128.9 (d), 127.63 (d), 127.57 (d), 115.6 (t), 80.8 (t), 43.7 (d), 32.2 (t), 30.8 (t); MS *m*/*z* 205 (M^+, 3), 175 (14), 171 (23), 158 (100); HRMS calcd for $C_{12}H_{15}NO_2$ (M^+) 205.1103, found 205.1074.

6-Nitro-5-(4-methoxyphenyl)-1-hexene (4b): light yellow oil; ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 7.00 (m, 4H), 5.73 (ddt, J = 17, 13, 11 Hz, 1H), 4.97 (m, 2H), 4.53 and 4.48 (AB of ABX, J = 12.5, 8.5, 7.5 Hz, 2H), 3.43 (quint, J = 8 Hz, 1H), 1.93 (m, 2H), 1.79 (m, 2H); ^{13}C NMR (δ, $CDCl_3$, 75.5 MHz) 15.0 (s), 137.2 (d), 130.8 (s), 128.6 (d), 115.5 (t), 114.3 (d), 81.1 (t), 55.2 (q), 42.9 (d), 32.1 (t), 30.8 (t); MS *m*/*z* 236 (MH^+, 9), 235 (6), 189 (29), 175 (100); HRMS calcd for $C_{13}H_{18}NO_3$ (MH^+) 236.1287, found 236.1260.

***trans*-3a,4,5,6-Tetrahydro-6-phenyl-3*H*-cyclopenta[*c*]isoxazole (6a)**: colorless oil; ^{13}C NMR (δ, $CDCl_3$, 75.5 MHz) 172.9 (s), 140.6 (s), 128.7 (d), 126.9 (d), 126.8 (d), 74.8 (t), 55.6 (d), 39.6 (d), 38.5 (t), 28.2 (t); MS *m*/*z* 189 $(M + 2)^+$ (6), 173 (24), 159 (43), 119 (8), 91 (100); HRMS calcd for $C_{12}H_{15}NO$ $(M + 2)^+$ 189.1153, found 189.1220.

***cis*-3a,4,5,6-Tetrahydro-6-phenyl-3*H*-cyclopenta[*c*]isoxazole (7a)**: colorless oil; ^{13}C NMR (δ, $CDCl_3$, 75.5 MHz) 173.6 (s), 140.1 (s), 128.6 (d), 127.9 (d), 127.0 (d), 75.4 (t), 55.9 (d), 40.6 (d), 37.9 (t), 26.4 (t); MS *m*/*z* 188 (MH^+, 100), 187 (6), 170 (61); HRMS calcd for $C_{12}H_{14}NO$ (MH^+) 188.1075, found 188.1070.

***trans*-3a,4,5,6-Tetrahydro-6-(4-methoxyphenyl)-3*H*-cyclopenta[*c*]isoxazole (6b)**: colorless solid; mp 34−36 °C;

(26) (a) Lebel, N. A.; Banucci, E. G. *J. Org. Chem.* **1971**, *36*, 2440. (b) Burdisso, M.; Gandolfi, R.; Grunanger, P. *Tetrahedron* **1989**, *45*, 5579.

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^{1}H NMR[28] (δ, C_6D_6, 600 MHz) 7.10−6.75, 4.14, 3.66, 3.52, 3.32 (s, 3H), 3.21, 2.21, 1.77, 1.42, 0.90; ^{13}C NMR (δ, $CDCl_3$, 75.5 MHz) 173.2 (s), 158.4 (s), 132.6 (s), 127.9 (d), 114.1 (d), 74.7 (t), 55.5 (q), 55.2 (d), 38.8 (d), 38.6 (t), 28.1 (t); MS *m*/*z* 218 (MH^+, 100), 147 (11), 121 (6), 109 (13); HRMS calcd for $C_{13}H_{16}NO_2$ (MH^+) 218.1181, found 218.1185.

***cis*-3a,4,5,6-Tetrahydro-6-(4-methoxyphenyl)-3*H*-cyclopenta[*c*]isoxazole (7b)**: colorless oil; ^{1}H NMR[28] (δ, C_6D_6, 600 MHz) 7.22−6.80, 4.15, 3.50, 3.42, 3.32 (s, 3H), 3.15, 2.00, 1.84, 1.35, 1.07; ^{13}C NMR (δ, $CDCl_3$, 75.5 MHz) 173.8 (s), 158.5 (s), 132.1 (s), 128.9 (d), 114.0 (d), 75.5 (t), 55.3 (d), 54.7 (q), 39.9 (d), 37.9 (t), 26.2 (t); MS *m*/*z* 218 (MH^+, 100), 217 (29), 200 (6), 188 (7), 147 (19); HRMS calcd for $C_{13}H_{16}NO_2$ (MH^+) 218.1181, found 218.1180.

***trans*-3a,4,5,6-Tetrahydro-6-*iso*-propyl-3*H*-cyclopenta-[*c*]isoxazole (6c)**: colorless oil; ^{1}H NMR (δ, $CDCl_3$, 600 MHz)[29] 4.48 (dd, J = 9.5, 7.5 Hz, H-3), 3.77 (dd, J = 12.5, 7.5 Hz, H-3′), 3.69 (dddddd, J = 12.5, 11, 9.5, 7.5, 2, 0.5 Hz, H-3a), 2.45 (qdd, J = 8.5, 8, 8, 2, 1 Hz, H-6), 2.38 (ddddd, J = 13, 8, 7.5, 1.5, 0.5 Hz, H-5), 2.06 (ddddd, J = 12, 7.5, 7, 1.5, 1 Hz, H-4), 1.91 (ddddd, J = 13, 12, 8.5, 7, 0.5 Hz, H-5′), 1.71 (dsept d, J = 8, 6.5, 6.5, 0.5 Hz, 1H), 1.43 (tdd, J = 12, 12, 11, 7.5 Hz, H-4′), 1.01 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 6.5 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$, 75.5 MHz) 173.9 (s), 74.4 (t), 55.9 (d), 41.8 (d), 34.1 (t), 31.3 (d), 28.3 (t), 20.43 (q), 20.38 (q); MS *m*/*z* 154 (MH^+, 100), 136 (8), 124 (7); HRMS calcd for $C_9H_{16}NO$ (MH^+) 154.1232, found 154.1192.

***trans*-3a,4,5,6-Tetrahydro-3,3-dimethyl-6-phenyl-3*H*-cyclopenta[*c*]isoxazole (6d)**: colorless oil; ^{1}H NMR (δ, C_6D_6, 600 MHz)[29] 7.22−7.02 (m, 5H), 3.61 (tdd, J = 9, 8.5, 2, 1 Hz, H-6), 3.02 (dddd, J = 11, 7.5, 2, 0.5 Hz, H-3a), 2.18 (ddddd, J = 13, 8.5, 7, 2, 0.5 Hz, H-5), 1.74 (dddd, J = 13, 11.5, 9, 6.5 Hz, H-5′), 1.33 (s, 3H), 1.18 (ddddd, J = 12, 7.5, 6.5, 2, 1 Hz, H-4), 1.11 (dddd, J = 12, 11.5, 11, 7 Hz, H-4′), 1.06 (s, 3H); ^{13}C NMR (δ, $CDCl_3$, 75.5 MHz) 173.2 (s), 140.5 (s), 128.6 (d), 127.0 (d), 126.7 (d), 87.1 (s), 62.9 (d), 40.8 (d), 39.0 (t), 26.9 (q), 23.3 (t), 22.4 (q); MS *m*/*z* 216 (MH^+, 100), 158 (8), 138 (5), 117 (58); HRMS calcd for $C_{14}H_{18}NO$ (MH^+) 216.1388, found 216.1400.

***trans*-3,3a,4,5,6,7-Hexahydro-7-phenylcyclohexa[*c*]-isoxazole (6e)**: colorless solid; mp 71−73 °C; MS *m*/*z* 202 (MH^+, 100), 171 (10), 91 (19); HRMS calcd for $C_{13}H_{18}NO$ (MH^+) 202.1232, found 202.1220.

***cis*-3,3a,4,5,6,7-Hexahydro-7-phenylcyclohexa[*c*]-isoxazole (7e)**: colorless solid; mp 84−86 °C; MS *m*/*z* 202 (MH^+, 100), 171 (10), 85 (16), 83 (21); HRMS calcd for $C_{13}H_{16}NO$ (MH^+) 202.1232, found 202.1250.

***trans*-3,3a,4,5,6,7-Hexahydro-7-(4-methoxyphenyl)-cyclohexa[*c*]isoxazole (6f)**: colorless oil; ^{1}H NMR[28] (δ, $CDCl_3$, 600 MHz) 7.22−6.87, 4.49, 4.19, 3.86, 3.80 (s, 3H), 3.19, 2.53, 2.09, 1.86, 1.69, 1.57, 1.42; MS *m*/*z* 232 (MH^+, 100), 231 (64), 230 (12), 214 (7), 201 (10), 174 (8), 124 (7), 121 (12); HRMS calcd for $C_{14}H_{18}NO_2$ (MH^+) 232.1338, found 232.1280.

***cis*-3,3a,4,5,6,7-Hexahydro-7-(4-methoxyphenyl)cyclohexa[*c*]isoxazole (7f)**: colorless solid; mp 89−91 °C; ^{1}H NMR[28] (δ, $CDCl_3$, 600 MHz) 7.24−6.84, 4.51, 3.81, 3.77 (s, 3H), 3.44, 3.25, 2.19, 2.10, 1.95, 1.74, 1.59, 1.45; MS *m*/*z* 231 (M^+, 4), 230 (26), 202 (100), 184 (6), 171 (15), 91 (27), 84 (55); HRMS calcd for $C_{14}H_{16}NO_2$ $(M - H)^+$ 230.1181, found 230.1220.

Acknowledgment. Support of this research by a grant from the Israel Science Foundation is gratefully acknowledged.

Supporting Information Available: ^{13}C NMR spectra of compounds **4**, **6**, and **7** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961663V

(28) Multiplicities and coupling constants of *p*-anisyl-substituted isoxazolines **6b**, **7b**, **6f**, and **7f** are by and large identical to that of their phenyl analogs **6a**, **7a**, **6e**, and **7e**, respectively.

(29) Confirmed by COSY experiment.