Nucleophilic Additions to and Reductions of 5-Formyl- and 5-Acyl-2-isoxazolines (4,5-Dihydroisoxazoles): A Stereoselective Route to β,γ-Dihydroxy Ketones†

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Reductions of readily available 5-acyl-2-isoxazolines with L-Selectride follow the Felkin–Anh model and produce *syn*-5-hydroxyalkyl-2-isoxazolines with excellent (>95:5) selectivities. Swern oxidation of 5-hydroxymethyl-2-isoxazolines, followed by direct addition of a Grignard reagent to the intermediate 5-formyl-2-isoxazolines, also follows the Felkin–Anh model and produces *anti*-5-hydroxyalkyl-2-isoxazolines with modest (80:20) to excellent (>95:5) selectivity. In contrast, additions of Grignard reagents to 5-acyl-2-isoxazolines follow the chelation model, and give *syn* or *anti* products (depending on choice of acyl substituent and Grignard reagent) with good (90:10) to excellent selectivity. These selectivities are almost always far superior to those that can be obtained by direct nitrile oxide cycloaddition to a chiral allylic alcohol or ether. The resulting products are readily reduced to *syn*- or *anti*-β,γ-dihydroxy ketones. A speculative model to explain this surprising reversal in selectivity between formyl and acyl isoxazolines is proposed.

Over the past 10 years, the cycloadditive route to β-hydroxy carbonyl compounds has begun to emerge as the first strategic alternative to the ubiquitous aldol strategy.[1] The cycloadditive strategy, summarized in Scheme 1, involves alkene/nitrile oxide dipolar cycloaddition followed by reductive cleavage of the resulting 2-isoxazoline to a β-hydroxy carbonyl. In our laboratories, development of the 'first generation' cycloadditive strategy focused on finding good methods for conversion of isoxazolines into β-hydroxy carbonyls, on formation of *syn* and *anti* aldol adducts§ of β-hydroxy ketones, esters, and related derivatives, and on synthetic applications that illustrated the complementarity of the aldol strategy and the cycloadditive strategy.[1a]

Several years ago, the development of the cycloadditive strategy entered a second generation, where our goals were to imitate some of the more sophisticated features of the aldol strategy including the control of absolute stereochemistry, and the control of relative stereochemistry at stereocentres other than C-2 and C-3 (the sites directly controlled by the nitrile oxide cycloaddition). By controlling these aspects of relative and absolute stereochemistry, polyoxygenated chains with a number of stereocentres could be rapidly assembled. There are now good methods available to make optically pure 2-isoxazolines,[2] and several approaches to control relative stereochemistry at 'off-ring' sites of 2-isoxazolines (stereogenic centres in any of the R groups in Scheme 1) have been developed.[3]

One of the most valued aspects of the aldol reaction is the ability to construct β,γ-dihydroxy carbonyls,[4] as shown in Scheme 2. When R^2 or R^3 = H, choice of reaction conditions, protecting group (P), and enol or enolate partner can often be used to control *syn*/*anti* stereochemistry in the β,γ-dihydroxy carbonyl by favouring Felkin–Anh or chelation-controlled addition. However, when neither R^2 nor R^3 = H, control of *syn*/*anti* stereochemistry is more difficult. Cycloadditive strategy I is the direct analogy to the aldol strategy, and it has been extensively investigated by several groups.[5] Although these investigations have had important implications on our understanding of the effects of allylic stereocentres on cycloadditions,[6] relatively few types of 2-isoxazolines **3** can be prepared with acceptable levels of stereoselectivity. For secondary allylic alcohols **2** (R^2 = H), good selectivities for *anti* adducts have been obtained with very large R^3 groups (such as tertiary alkyl), but most R^2 groups (such as n-alkyl) give selectivities of *ca.* 70:30 in the dipolar cycloaddition. Good levels of *syn* selectivity with secondary allylic alcohols have not been observed, and selectivities for tertiary allylic alcohols (R^2,R^3 ≠ H) are not expected to be good either.[7]

Among the several possible alternatives to cycloadditive strategy,¶ we envisioned that cycloadditive strategy II had two especially attractive features. First, acrylates and related derivatives are reactive partners in nitrile oxide cycloadditions,[8] so isoxazolines **4** should be readily available. Indeed they can now be prepared in optically active form by cycloadditions with chiral acrylates.[2] Second, based on the large body of knowledge[9] about additions to α-oxy aldehydes and ketones, it seemed likely that all possible classes of β,γ-dihydroxy carbonyls **1** (*syn* or *anti* with R^2 or R^3 = H, *syn* or *anti* with R^2, R^3 ≠ H) could be prepared by varying the reaction conditions and the location of R^2 and R^3. This stereochemical correlation is illustrated in Scheme 3 in the context of the Felkin-Anh and chelation models.

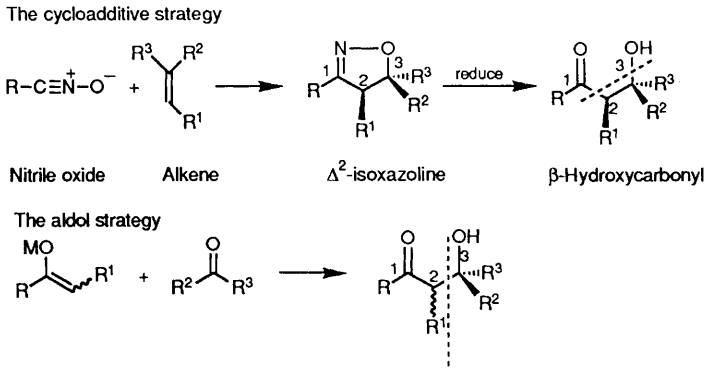
This paper reports complete details of our research on: (1) the synthesis of 5-acyl- and 5-formyl-2-isoxazolines; (2) reductions and nucleophilic additions to these intermediates; and (3) reductive cleavage of the so-formed 5-hydroxyalkyl-2-isoxazolines to β,γ-dihydroxy ketones. We can now prepare all four classes of β,γ-dihydroxy ketones with good (85:15) to excellent (>95:5) levels of stereoselectivity, and our studies have revealed an interesting dichotomy: nucleophilic additions to 5-formyl-2-isoxazolines and reductions of 5-acyl-2-isoxazolines proceed with (apparent) Felkin–Anh selectivity, but nucleophilic additions to 5-acyl-2-isoxazolines proceed with (apparent) chelation control.

Results

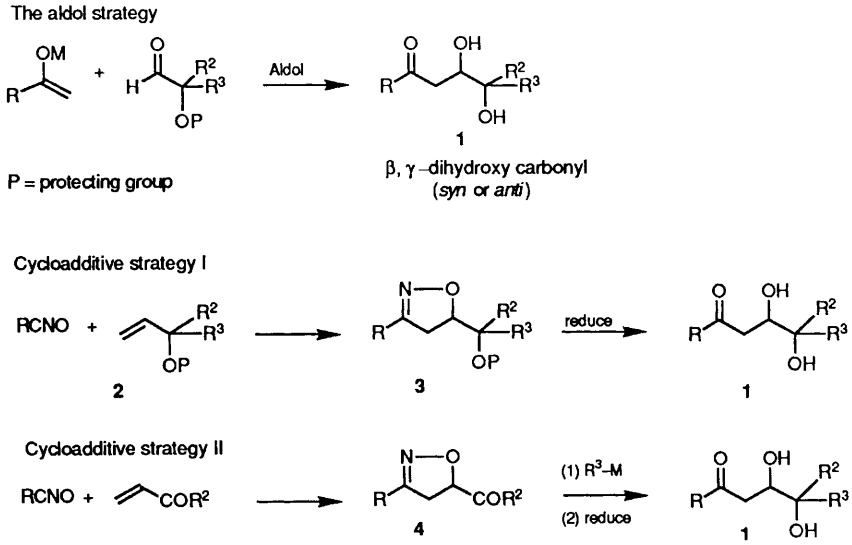
Reductions of 5-Acyl-2-isoxazolines.—We began our investigation by reducing readily available 2-isoxazolines **5a** and

† Submitted to commemorate the 150th anniversary of the Chemical Society/Royal Society of Chemistry.
‡ Dreyfus Teacher-Scholar (1986–91), National Institutes of Health Research Career Development Awardee (1987–92).
§ The prefixes *syn* and *anti* are used as defined by S. Masamune, Sk. A. Ali, D. L. Suitman and D. S. Garvey, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 557.

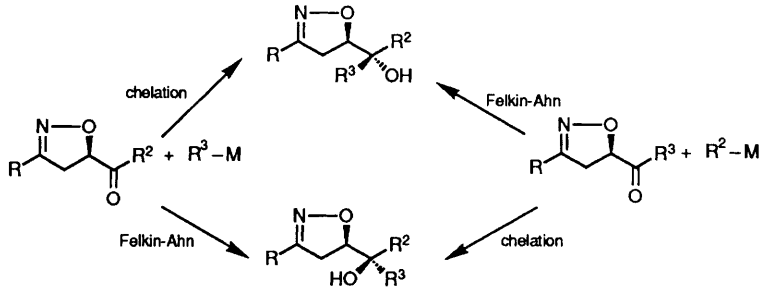
¶ Oxygenations of 5-vinyl-4,5-dihydroisoxazoles can give products like **3**, but such reactions have not shown high selectivity. See refs. 1*b* and 1*d*.



Scheme 1



Scheme 2



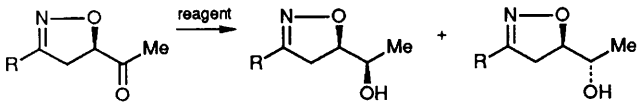
Scheme 3

7a with a collection of standard reagents.* Table 1 shows the results of this series of experiments. Crude reaction mixtures were generally very clean, although isolated yields were often not determined. Products **6a**-*syn* and **6a**-*anti* (or **8a**-*syn*/**8a**-*anti*) were identified by comparison with authentic samples, and *syn*/*anti* ratios were determined by GC. Most reagents provided the *syn* isomer (Felkin–Anh product) in excess, but the selectivity was low. In no case did the *anti* isomer predominate; even reagents chosen for chelation control (entries 7 and 8) provided low selectivity in favour of the *syn* isomer. In contrast, the bulky lithium tri-*sec*-butylborohydride (L-Selectride™) provided excellent selectivity in favour of the *syn* isomer.[11] Reduction of **5a** (entry 9) or **7a** (entry 14) with 1 equiv. of L-Selectride at −78 °C, followed by standard work-up, provided **6a**-*syn*/**6a**-*anti* (98:2) or **8a**-*syn*/**8a**-*anti* (97:3).

We then reduced several 5-acyl-2-isoxazolines with L-Selectride in order to test the generality of this procedure, and Table 2 summarizes the results of this series of experiments. Product ratios were determined by capillary GC, and structures for entries 1, 2 and 6 were assigned by preparing independent samples by dipolar cycloadditions of allylic *tert*-butyldimethylsilyl ethers (see below). Inherent in this assignment is the assumption that these cycloadditions follow precedent and favour *anti* isomers.[5,6] To confirm this assumption, the structure of the major product from entry 5 was determined by

* A few previous chemical reductions of 5-acyl-4,5 dihydroisoxazoles have not been stereoselective.[10a] For examples of enantioselective microbiol reductions, see ref. 10*b*.

Table 1 Survey of reduction of 5-acyl-2-isoxazolines



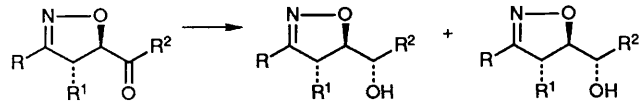
5a R = Ph
7a R = Bu^t

6a-*syn* R = Ph
8a-*syn* R = Bu^t

6a-*anti*
8a-*anti*

Entry	Isoxazoline	Reagent	Conditions	*syn*/*anti*
1	**5a**	$NaBH_4$	THF/EtOH/25 °C	57:43
2	**5a**	$LiAlH_4$	THF/−78 °C	80:20
3	**5a**	DIBAL	THF/−78 °C	75:25
4	**5a**	DIBAL	Hex./−78 °C	77:23
5	**5a**	$Li(Bu^tO)_3AlH$	THF/−78 °C	65:35
6	**5a**	$Li[Bu^i_2Bu^t]AlH$	THF−78 °C	77:23
7	**5a**	$Zn(BH_4)_2$	Ether/−78 °C	62:38
8	**5a**	$PhMe_2SiH/TiCl_4$	CH_2Cl_2/0 °C	58:42
9	**5a**	L-Selectride	THF/−78 °C	98:2
10	**7a**	$NaBH_4$	THF/EtOH/25 °C	53:47
11	**7a**	$LiAlH_4$	THF/−78 °C	56:44
12	**7a**	DIBAL	THF/−78 °C	60:40
13	**7a**	$Li(Bu^tO)_3AlH$	THF/25 °C	58:42
14	**7a**	L-Selectride	THF/−78 °C	97:3

Table 2 Reductions of 5-acyl-2-isoxazolines with L-Selectride



syn *anti*

5 R = Ph
7 R = Bu^t
9 R = Et

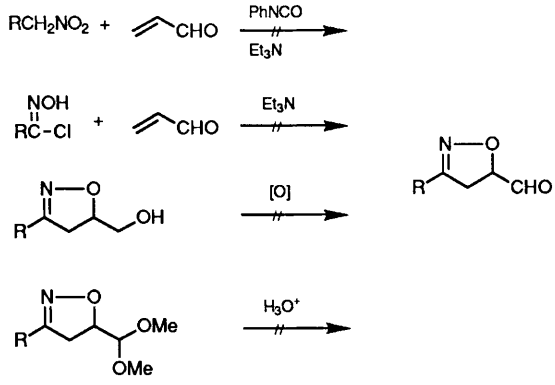
6 R = Ph
8 R = Bu^t
10 R = Et

Entry	Precursor	R^1	R^2	Yield	Products	*syn*/*anti* ratio
1	**5a**	H	Me	79%	**6a**	98:2
2	**7a**	H	Me	69%	**8a**	97:3
3	**9a**	H	Me	55%	**10a**	≥98:2
4	**5b**	H	Et	81%	**6b**	94:6
5	**7b**	H	Et	95%	**8b**	93:7
6	**5c**	H	c-C_6H_4	80%	**6c**	≥98:2
7	**5d**	Me	Me	84%	**6d**	≥98:2
8	**7d**	Me	Me	77%	**8d**	98:2

single crystal X-ray diffraction;* as expected, it was the *syn* isomer, **8b**-*syn*. Configurations for entries 7 and 8 were confirmed by an independent synthesis of **6d** from **6c**.†

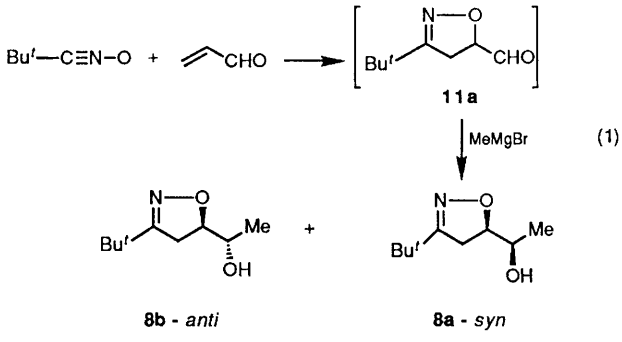
In each example, the *syn* selectivity was excellent (≥93:7), and isolated yields of purified products were good (69–95%). Two trends emerged from this series of reductions: (1) There was a slight decrease in selectivity on changing the acyl substituent from methyl to ethyl (compare entries 1/4, and 2/5), but the selectivity then increased (minor isomer no longer detected) on going to cyclohexyl (entry 6). (2) 3-*tert*-Butyl-2-isoxazolines gave marginally lower selectivity than 3-phenyl-2-isoxazolines (compare entries 1/2, 4/5, 7/8). This L-Selectride reduction of 5-acyl-2-isoxazolines is currently the only available method for preparation of *syn* alcohols like **6**, **8** and **10** with good stereoselectivity.

Nucleophilic Additions to 5-Formyl-2-isoxazolines.—Our next goal was to investigate the complementary reaction to the reduction of 5-acyl-2-isoxazolines: the nucleophilic addition to 5-formyl-2-isoxazolines. Although several 5-formyl-2-isoxazolines have been reported,[12] we encountered difficulties in preparing the compounds that we required. Scheme 4 summarizes a series of unsuccessful attempts to prepare some sample 5-formyl-2-isoxazolines (R = Et, Ph, Bu^t). Standard cycloadditions by the Mukaiyama[13] or Huisgen[14] methods, oxidation of a 5-hydroxymethyl-2-isoxazoline, or hydrolysis of a dimethyl acetal[15] all resulted in formation of a dark, uncharacterizable oil after standard work-up.



Scheme 4 Attempted formation of 5-formyl-2-isoxazolines

Eqn. (1) shows the results of a careful cycloaddition experiment that finally shed some light on the problem. We generated a benzene solution of pure *tert*-butyl nitrile oxide (free from triethylamine hydrochloride) by a procedure developed in our laboratories,[16] and then added this to a benzene solution of freshly distilled acrolein. After 6 h, the solution was *partially* concentrated, and a clean spectrum of the 5-formyl-2-isoxazoline **11a** was obtained, contaminated only by a large amount of benzene. Complete removal of the benzene gave the dark oil. Apparently, 5-formyl-2-isoxazoline **11a** can be formed by normal methods, but it is not stable as a neat liquid. Next we diluted the benzene solution containing **11a** with THF and then added an excess of methylmagnesium bromide. After standard work-up, we found that **8a**-*syn*/**8a**-*anti* formed in a ratio of 15:85. The major product is again predicted by the Felkin–Anh model.



8b - *anti* **8a** - *syn*

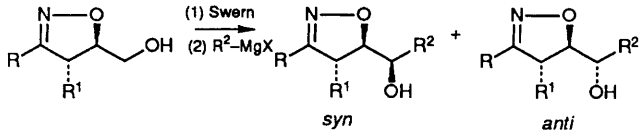
These experiments showed that 5-formyl-2-isoxazolines can be prepared by normal means, but that they can be difficult to isolate. However, the solution to the problem introduced in eqn. (1) is not very general because most nitrile oxides are not conveniently prepared in pure form in solution (they begin to dimerize). This led us to adopt a modified Swern oxidation[17] procedure introduced by Ireland and Norbek.[18] Eqn. (2) shows

* We thank Dr. J. Abola and Mr. K. Paris for solving the crystal structures. These compounds exhibit no unusual features, and full details of the structures will, in due course, be deposited with the Cambridge Crystallographic Database.

† Compound **6d** was correlated with **6c** by the following sequence of reactions (see Experimental section):

6a $\xrightarrow[(3)\ HF]{(1)TBDMSCl\ (2)\ LDA/MeI}$ **6d**

Table 3 Grignard additions to 5-formyl-2-isoxazolines

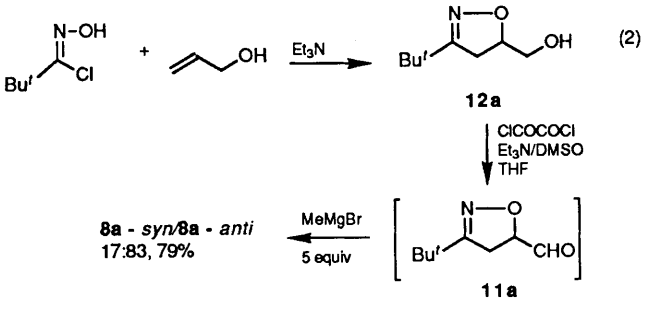


12 R = Bu^t **8** R = Bu^t
13 R = Ph **6** R = Ph

Entry	Starting material	R^1	R^2	Products	*syn*:*anti* ratio	Yield[a] (%)	Cycloaddition ratio[b] *syn*:*anti*
1	**13a**	H	Me	**6a**	17:83	60	22:78
2	**12a**	H	Me	**8a**	17:83	79	28:72
3	**13a**	H	Et	**6b**	17:83	58	—
4	**12a**	H	Et	**8b**	20:80	72	—
5	**13a**	H	c-C_6H_{11}	**6c**	11:89	40	7:93
6	**12a**	H	c-C_6H_{11}	**8c**	4:96	82	8:92
7	**13b**	Me	Me	**6d**	16:84	69	—
8	**12b**	Me	Me	**8d**	18:82	74	—
9	**13b**	Me	Et	**6e**	21:79	52	—
10	**12b**	Me	Et	**8e**	25:75	68	—
11	**13b**	Me	c-C_6H_{11}	**6f**	15:85	48	—
12	**12b**	Me	c-C_6H_{11}	**8f**	5:95	52	—

[a] The yields were not optimized and represent the overall yields from the starting alcohol. [b] The diastereoisomer ratios from cycloaddition of a nitrile oxide with an allylic silyl ether followed by desilylation. See eqn. (3).

the protocol. 5-Hydroxymethyl-2-isoxazoline **12a** was readily formed by a standard nitrile oxide cycloaddition. This was then oxidized under standard Swern conditions. After the oxidation was complete (but prior to the work-up), the mixture presumably containing **11a** was recooled to −78 °C, and then methylmagnesium bromide (5 equiv.) was added. After 4 h at −78 °C, the reaction was worked up, and we isolated **8a**-*syn*/**8a**-*anti* in a ratio of 17:83 in a combined yield of 79% (from **12a**). That the *syn*/*anti* ratio was nearly the same in the experiments in eqns. (1) and (2) shows that the remaining additives (DMSO, Et_3N) and side products from the Swern oxidation do not affect the stereochemistry of the nucleophilic addition.



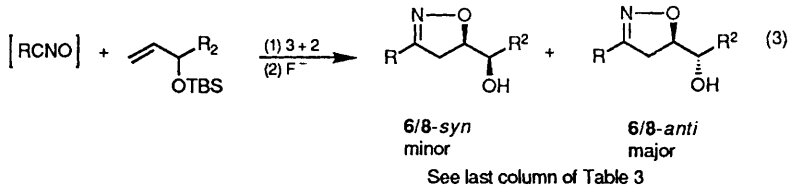
(2)

The Ireland–Norbeck procedure is especially attractive because the starting 5-hydroxyalkyl-2-isoxazolines are now readily available in optically active form.[3] Table 3 summarizes a series of experiments conducted with racemic precursors to test the generality of this method. Provided that the Swern procedure was followed carefully, good overall yields of products were obtained in all cases. *syn*/*anti* Ratios were determined by capillary GC. In each case, formation of the *anti* isomer (Felkin–Anh product) was favoured, although the *anti* selectivity for the nucleophilic additions in Table 3 is consistently lower than the *syn* selectivity for the reductions in Table 2. Authentic samples of many of the products were available either from dipolar cycloadditions with allylic silyl ethers [see eqn. (3)] or from the reductions in Table 2. Authentic samples of the products for entries 8–12 were not available, and the configurations of these products were assigned by analogy and similarities in spectra trends. The configuration of the products of entry 7 (closely related to entries 8–12) was proven by independent synthesis.

Comparing the 3-phenyl series **13** with the 3-*tert*-butyl series **12**, one sees that additions of methyl- and ethyl-magnesium bromide are marginally more selective in the 3-phenyl series (see entries 1/2, 3/4, 7/8, 9/10), but the additions of cyclohexylmagnesium chloride were more selective in the *tert*-butyl series (see entries 5/6, 11/12). We do not presently understand why additions of cyclohexylmagnesium chloride to **12a** and **12b** give such excellent selectivities. An unusual trend in the selectivity as a function of the nucleophile also appears; selectivity increases in the order Et ≤ Me < *c*-C_6H_{11} (compare entries 1/3/5, 2/4/6, 7/9,11, 8/10/12). This trend is reminiscent of the effects of size of acyl substituent that emerged from Table 2. Although we used methyl- and ethylmagnesium *bromide*, but cyclohexylmagnesium *chloride*, we did not investigate whether either of these trends was rooted in differences in the halide component of the Grignard reagent. Attempted additions of alkyllithium reagents in place of Grignard reagents gave complex mixtures of products. It seems likely that other classes of nucleophiles might give better selectivity than Grignard reagents, but research along these lines was not pursued.

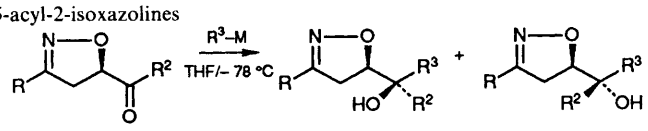
Cycloadditions of nitrile oxides to allylic silyl ethers [see eqn. (3)] also give modest to good *anti* selectivity,[5,6] so it is interesting to compare the selectivity in cycloaddition with the selectivity in nucleophilic addition. This is done in the last column of Table 3 for four representative substrates. In three of the four examples (entries 1,2,6), the nucleophilic addition gives better selectivity, while in one class (entry 5) the cycloaddition gives better selectivity. These observations can probably be generalized; with small R^2 groups, nucleophilic additions will give higher selectivities, but with large R^2 groups, both methods will give good selectivities (≥90:10).

Nucleophilic Additions to 5-Formyl-2-isoxazolines.—The last class of reactions is the nucleophilic additions to 5-acyl-2-isoxazolines, which should produce *syn* and *anti* β-2°, γ-3°-dihydroxy carbonyls. The results of this series of experiments are shown in Table 4. We started by adding methylmagnesium bromide, methyllithium, and lithium dimethylcuprate to ethyl ketone **5b** (entries 1–3). All the nucleophiles produced the same



See last column of Table 3

Table 4 Nucleophilic additions to 5-acyl-2-isoxazolines



5 R = Ph
7 R = Bu^t

8, 15, 16

Entry	Precursor	R	R^2	R^3-M	Yield	Products	*syn*/*anti*
1	**5b**	Ph	Et	MeMgBr	71%	**14**	10:90
2	**5b**	Ph	Et	MeLi	71%	**14**	33:67
3	**5b**	Ph	Et	Me_2CuLi	80%	**14**	20:80
4	**5a**	Ph	Me	EtMgBr	90%	**14**	90:10
5	**5a**	Ph	Me	c-C_6H_{11}MgCl	77%	**15**	>96: <4
6	**5c**	Ph	c-C_6H_{11}	MeMgBr	75%	**15**	<4: >96
7	**7a**	Bu^t	Me	c-C_6H_{11}MgCl	72%	**16**	>96: <4
8	**7c**	Bu^t	c-C_6H_{11}	MeMgBr	65%	**16**	<4: >96

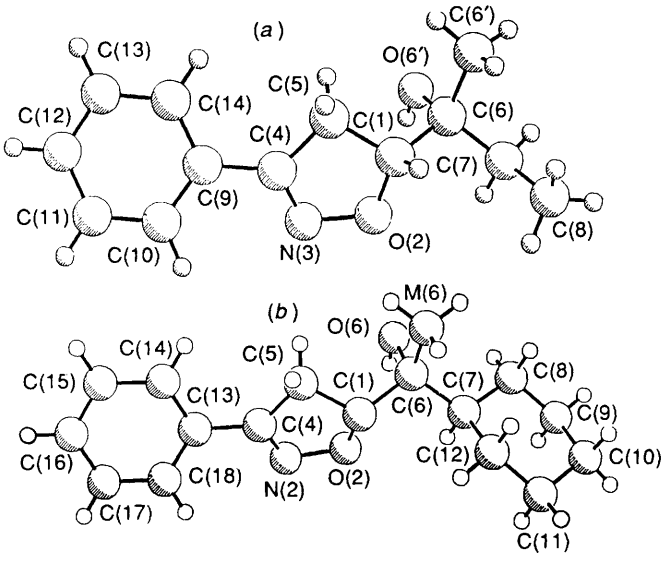


Fig. 1 ORTEP structures for (*a*) compound **14**-*anti* and (*b*) **15**-*syn*.

major product, but the best selectivity was observed with the Grignard reagent (entry 1, 10:90) so we conducted all subsequent additions with Grignard reagents. As expected, addition of ethylmagnesium bromide to methyl ketone (entry 4) produced the same two products, but in a reversed ratio (90:10).

The surprise came when we determined the structure of the major product from entry 1, and found that it corresponded to **14**-*anti*. The ORTEP plot of this structure is shown in Fig. 1. This is not the product predicted by the Felkin–Anh model, as had been observed in all previous additions and reductions. It is instead the (formal) product of chelation control.

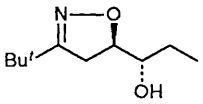
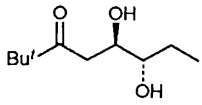
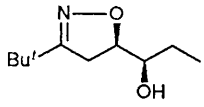
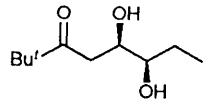
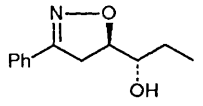
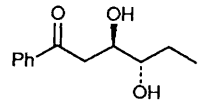
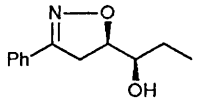
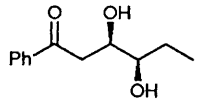
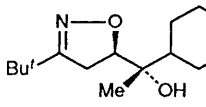
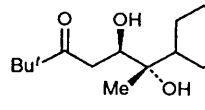
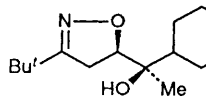
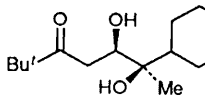
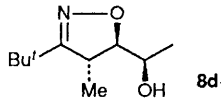
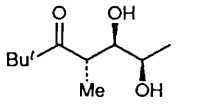
Several other additions with cyclohexyl and methyl alternating as ketone substituent and Grignard reagent showed high selectivity and the products again reversed when the substituent and the Grignard were interchanged (entries 5/6, 7/8). Since the chelation controlled product was not expected based on previous results, we conducted a second crystal structure determination on the major product from entry 5. An ORTEP plot of this structure is shown in Fig. 1(*b*). As before, the product **15**-*syn* is that predicted by the chelation model. Structures **16** were assigned by analogy to **15**.

Conversions into β,γ-*Dihydroxy Ketones*.—The last step in this cycloadditive route to β,γ-dihydroxy ketones is the reductive hydrolysis of the isoxazoline ring. To probe the efficiency of this step, several representative pairs of diastereoisomers were reduced under one of our standard conditions[19] [H_2 gas, Ra–Ni, 5:1 MeOH/H_2O, 5 equiv. $B(OH)_3$], and Table 5 summarizes the results of these reductions. In all cases, the β,γ-dihydroxy ketones were formed without detectable epimerization, and in modest isolated yields (52–65%). However, these yields are quite satisfactory since 3-phenyl and 3-*tert*-butyl-2-isoxazolines are among the most difficult classes to reduce cleanly (3-phenyl-2-isoxazolines often give amino alcohols,[19] and 3-*tert*-butyl-2-isoxazolines can give problems due to slow imine hydrolysis[20]). We believe that isoxazolines with other types of 3-substituents will given even better yields in the reduction step.

Discussion

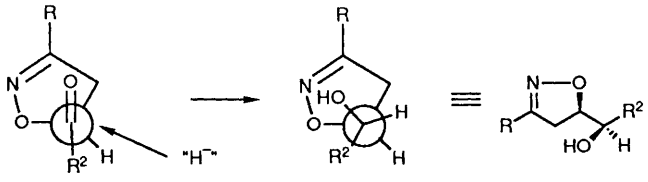
Our work on reductions of and nucleophilic additions to formyl- and acyl-isoxazolines shows that all the stereoisomers of secondary and tertiary 5-hydroxyalkyl-2-isoxazolines can be prepared with good selectivity by appropriate pairing of an isoxazoline with a nucleophile or reducing agent. The generality and selectivity of this strategy combine to make it a viable alternative to the aldol strategy. With a few possible exceptions, selectivities by this route (Cycloadditive route II, Scheme 2) will be significantly better than those expected from the direct nitrile oxide + allylic ether route (Cycloadditive route I, Scheme 2). Some of these attractive features are illustrated in the following paper[21] by the synthesis of two simple natural products: (±)-*exo*-brevicomin and (±)- and (−)-pestalotin.

Table 5 Reductive cleavage of isoxazoline rings

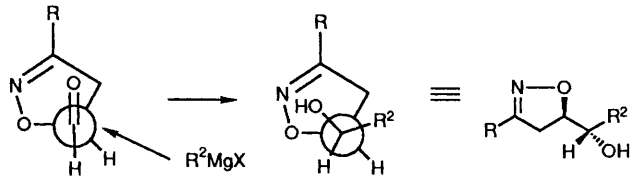
Substrates	Products	Yields (%)
 **8b**-*anti*	 **17b**-*anti*	53
 **8b**-*syn*	 **17b**-*syn*	56
 **6b**-*anti*	 **18a**-*anti*	62
 **6b**-*syn*	 **18a**-*syn*	65
 **16**-*anti*	 **19**-*anti*	52
 **16**-*syn*	 **19**-*syn*	54
 **8d**-*syn*	 **20d**-*syn*	54

The selectivities observed in the additions to, and reductions of, the carbonyl are interesting: reductions of 5-acyl-2-isoxazolines (Tables 1, 2) give Felkin–Anh selectivity (which is very high when L-Selectride is used), and the additions of Grignard reagents to 5-formyl-2-isoxazolines also give Felkin–Anh selectivity (Table 3), but the additions of Grignard reagents to 5-acyl-2-isoxazolines give products of chelation control (Table 4).

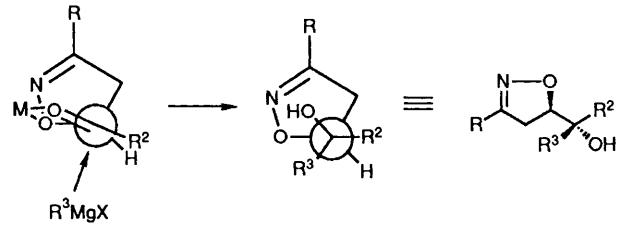
Of course, that Felkin–Anh or chelation model predicts the correct product is not of itself mechanistic information. Nonetheless, the Felkin–Anh model is widely supported both experimentally and theoretically,[9] and we believe that it is probably a good representation for the transition states (TSs) of the first two classes of reactions. These TS models are shown in Schemes 5a and b. Compared to a typical ether oxygen, the isoxazoline oxygen is a much weaker Lewis base (disfavouring a chelation TS), and it is more electronegative (favouring a Felkin–Anh TS). Indeed, the isoxazoline oxygen cannot even



Scheme 5a Reductions of 5-acyl-2-isoxazolines (Felkin–Anh model)



Scheme 5b Grignard additions to 5-formyl-2-isoxazolines (Felkin–Anh model)



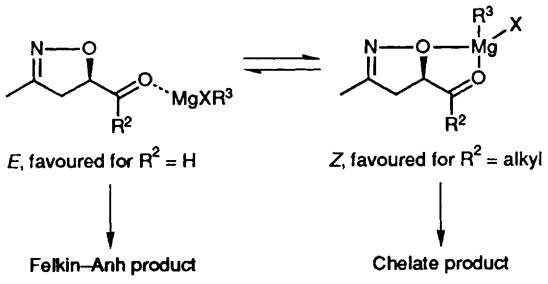
Scheme 5c Grignard additions to 5-acyl-2-isoxazolines (Chelate model)

muster up enough Lewis basicity to form an intramolecular hydrogen bond in the solid state of either of the crystal structures shown in Fig. 1.

Since it is well known that larger carbonyl substituents tend to give higher Felkin–Anh selectivities,[22] one is led to expect that Grignard additions to 5-acyl-2-isoxazolines should give

very good Felkin–Anh selectivities. Instead, precisely the reverse is observed: high selectivity for the apparent product of chelation control (see TS model in Scheme 5). Since there is no obvious reason why predictions of the Felkin–Anh model should be altered by changing from an aldehyde to a ketone, it seems possible that the products of Grignard additions to 5-acyl-2-isoxazolines really do proceed under chelation control. If so, then why do Grignard additions to aldehydes and ketones change from Felkin–Anh to chelation control?

Scheme 6 posits a speculative answer to this question. It seems likely that association of the carbonyl oxygen with a magnesium atom precedes these nucleophilic additions. For a 5-formyl complex (R^2 = H) and a Grignard reagent, an *E*-complex*[,23] should be highly favoured because the Lewis basicity of the isoxazoline oxygen is not sufficient to overcome unfavourable steric interactions in the *Z*-complex (the isoxazoline ring is much larger than H). This *E*-complex then reacts *via* a Felkin–Anh transition state. In contrast, *E*-complexes of acylisoxazolines have unfavourable steric interactions with the R^2 group, which is now an alkyl group rather than a small H. Similar interactions must be present in the *Z*-isomer, but now weak chelation provides some favourable interaction. In other words, a metal complex would rather be *cis* to a weakly chelating group than a non-chelating group if sizes of these groups are roughly equal, but *cis* to the non-chelating group if that group is significantly smaller than the weakly chelating one. The *Z*-complex is poised to go through a chelation TS. We assume that these ground state arguments will also translate to TS arguments.



Scheme 6 Model for Grignard additions

Given our decided absence of hard mechanistic information, we regard this model as highly speculative. We do not know with any certainty that chelation control is important in additions to 5-acyl-2-isoxazolines, and the model does not consider any of the mechanistic subtleties of the Grignard reaction. We only include this simple model because it makes two useful predictions: (1) selectivity reversals in additions to aldehydes and ketones may not be unique to isoxazolines, but may occur in many additions where weakly Lewis basic ethers are present and 'chelating' reagents are used or in additions where Lewis basic ethers are present and 'non-chelating' reagents are used (this has already been observed by Reetz and Hüllmann†[,23]), and (2) the selectivity reversal in the ketone should be suppressed if the *E*-chelate is favoured (for example by putting a good Lewis basic site in the R^2 group[24]). To date, we have not stringently tested either of these predictions, so we include the following disclaimer: the authors are not responsible for any results obtained by using their model.

* Several studies show that aldehydes often form E-complexes with metals.[23] (*a*) M. T. Reetz, H. Hüllmann and T. Seitz, *Angew. Chem., Int. Ed. Engl.* 1987, **26**, 477; (*b*) S. E. Denmark, B. R. Henke and E. Weber, *J. Am. Chem. Soc.*, 1987, **109**, 2512; (*c*) G. E. Keck and S. Castellino, *J. Am. Chem. Soc.*, 1986, **108**, 3847.

† Additions of methyl titanium triisopropoxide (a non-chelating reagent) to α-benzyloxy aldehydes give Felkin–Anh products, but additions to α-benzyloxy ketones give chelation products (see ref. 23).

Experimental

General.—All reactions were performed under a nitrogen atmosphere. Reagents and solvents were purified and dried as follows: triethylamine, DMSO, and DMF: distilled from CaH_2; benzene, THF, and ether: distilled from sodium/benzophenone. Medium pressure liquid chromatography (MPLC) was performed with (230–400 mesh ASTM) silica gel or on prepacked EM Lobar Li/Chroprep Si/60 columns. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 precoated plastic plates. Analytical gas chromatography was performed on a HP-5890 instrument equipped with a SPB-1 fused silica capillary column, 30 m, 0.25 mm, 0.32 mm i.d. column and a flame ionization detector (FID) using helium as a carrier gas. W-2 Raney nickel was prepared according to the standard procedure.[25] *J* Values are given in Hz.

General Procedure for the Formation of 5-Acyl-2-isoxazolines (5-Acyl-4,5-dihydroisoxazoles) by Huisgen's Method.[14]—*5-Acetyl-3-tert-butyl-4,5-dihydroisoxazole* **7a**.—A solution of triethylamine (1.30 ml, 9.30 mmol) in dry ether (6 ml) was added dropwise to a solution of methyl vinyl ketone (1.60 ml, 18.90 mmol) and pivalohydroximoyl chloride[26] (1.145 g, 8.45 mmol) in ether (20 ml) at −20 °C. The reaction mixture was warmed slowly to 25 °C and stirred for 6 h. The mixture was then filtered and washed with ether, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography with 17% EtOAc–hexane to give a colourless oil (1.21 g, 85%); $\delta_H(CDCl_3)$ 4.82 (1 H, dd, *J* 11.5, 6.0), 3.24 (1 H, dd, *J* 17.0, 6.0), 3.10 (1 H, dd, *J* 17.0, 11.5), 2.30 (3 H, s) and 1.20 (9 H, s); ν_{max}(thin film)/cm^{-1} 2984, 2975, 1694, 1469, 1336, 1298 and 1062; *m/z* 169 (M), 126, 105, 74, 59, 57, 45, 43 and 41 (Found: M$^+$, 169.1103. Calc. for $C_9H_{15}NO_2$: *M*, 169.1102).

3-tert-Butyl-5-propionyl-4,5-dihydroisoxazole **7b**. The reaction was performed with pivalohydroximoyl chloride (1.57 g, 11.6 mmol), ethyl vinyl ketone (2.31 ml, 23.2 mmol), and triethylamine (1.78 ml, 12.76 mmol) in ether. The product was purified by Kugelrohr distillation (aspirator pressure, 160 °C) to afford a clear oil (1.93 g, 90%); $\delta_H(CDCl_3)$ 4.86 (1 H, dd, *J* 11.6, 6.3), 3.40 (1 H, dd, *J* 17.4, 11.6), 3.25 (1 H, dd, *J* 17.4, 6.3), 2.89 (2 H, dq, *J* 14.1, 5.6), 1.19 (9 H, s) and 1.07 (3 H, t, *J* 7.5).

5-Acetyl-3-phenyl-4,5-dihydroisoxazole **5a**. The reaction was performed with benzohydroximoyl chloride (2.04 g, 13.12 mmol), methyl vinyl ketone (2.44 ml, 30.12 mmol), and triethylamine (2.31 ml, 16.57 mmol) in ether (26 ml). The product was purified by flash chromatography with 20% EtOAc–hexane to afford a white solid (2.335 g, 94%): m.p. 61.5–62.5 °C; $\delta_H(CDCl_3)$ 7.69 (2 H, m), 7.41 (3 H, m), 5.03 (1 H, dd, *J* 11.9, 6.2), 3.66 (1 H, dd, *J* 17.1, 6.3), 3.50 (1 H, dd, *J* 17.1, 11.8) and 2.37 (3 H, s); ν_{max}(thin film)/cm^{-1} 3009, 2980, 1732, 1497, 1420, 1350 and 1217; *m/z* 189 (M), 146, 118, 104, 91, 77 and 51 (Found: 189.0790. Calc. for $C_{11}H_{11}NO_2$: 189.0790).

3-Phenyl-5-propionylisoxazole **5b**. The cycloaddition was conducted with benzohydroximoyl chloride (0.903 g, 5.8 mmol), ethyl vinyl ketone (1.156 ml, 11.6 mmol), and triethylamine (0.890 ml, 6.38 mmol) in ether (12 ml). The product was purified by chromatography (20% EtOAc–hexane) to give a white solid (0.99 g, 83%); m.p. 39–41 °C; $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.40 (3 H, m), 5.06 (1 H, dd, *J* 11.9, 6.3 Hz), 3.65 (1 H, dd, *J* 17.1, 6.3), 3.50 (1 H, dd, *J* 17.0, 11.8), 2.77 (2 H, dq, *J* 7.3) and 1.09 (3 H, t, *J* 7.3); *m/z* 203 (M), 174, 118, 103, 91, 77 and 57 (Found: M$^+$, 203.0946. Calc. for $C_{12}H_{13}NO_2$: 203.0947).

5-Cyclohexylcarbonyl-3-phenyl-4,5-dihydroisoxazole **5c**. The reaction was performed with benzohydroximoyl chloride

(0.1270 g, 0.816 mmol), cyclohexyl vinyl ketone **23** (0.2238 g, 1.632 mmol) and triethylamine (0.125 ml, 0.897 mmol) in ether (2 ml). The product was purified by flash chromatography with 20% EtOAc–hexane to afford a white solid (0.188 g, 75%); m.p. 54.5–56.5 °C; $\delta_H(CDCl_3)$ 7.69 (2 H, m), 7.42 (3 H, m), 5.18 (1 H, dd, *J* 11.9, 6.4), 3.69 (1 H, dd, *J* 17.1, 6.4), 3.46 (1 H, dd, *J* 17.1, 12.0) and 1.3–1.8 (10 H).

trans-5-Acetyl-3-tert-butyl-4-methyl-4,5-dihydroisoxazole **7d**. The reaction was performed with pivalohydroximoyl chloride (0.9650 g, 7.12 mmol), (*E*)-pent-3-en-2-one (2.137 ml, 14.24 mmol), and triethylamine (1.092 ml, 7.83 mmol) in benzene (15 ml). The desired product was separated from its regioisomer by MPLC with 20% EtOAc–hexane to give a colourless oil (0.513 g, 40.8%); $\delta_H(CDCl_3)$ 4.34 (1 H, d, *J* 4.1), 3.45 (1 H, m), 2.25 (3 H, s), 1.33 (3 H, d, *J* 7.2) and 1.22 (9 H, s).

trans-5-Acetyl-4-methyl-3-phenyl-4,5-dihydroisoxazole **5d**. The cycloaddition was performed with (*E*)-pent-3-en-2-one, benzohydroximoyl chloride and triethylamine on the same scale as the preceding one. Compound **5d** was separated from its regioisomer by MPLC with 20% EtOAc–hexane in 42% yield: $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.41 (3 H, m), 4.60 (1 H, d, *J* 4.0), 3.95 (1 H, m), 2.32 (3 H, s) and 1.38 (3 H, d, *J* 7.2).

General Procedure for Formation of Isoxazolines by Mukaiyama's Method.[16]—*5-Acetyl-3-ethyl-4,5-dihydroisoxazole* **5c**.—To a solution of nitropropane (2.68 ml, 30 mmol) and methyl vinyl ketone (3.73 ml, 45 mmol) in benzene (30 ml) was added phenyl isocyanate (7.20 ml, 66 mmol) and a catalytic amount of triethylamine. The reaction mixture was stirred at 25 °C for 10 h after which water (1 ml) was added to destroy the excess of phenyl isocyanate and stirring was continued for 1 h. The reaction mixture was diluted with ether and filtered. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation to afford a colourless oil (4.60 g, 93%); $\delta_H(CDCl_3)$ 4.83 (1 H, dd, *J* 11.4, 6.5), 3.19 (1 H, dd, *J* 17.3, 6.3), 3.09 (1 H, dd, *J* 17.3, 11.4) 2.37 (2 H, q, *J* 7.6) and 1.17 (3 H, t, *J* 7.6).

Formation of 5-Hydroxymethyl-4,5-dihydroisoxazoles.—*5-Hydroxymethyl-3-phenyl-4,5-dihydroisoxazole* **13a**. Benzohydroximoyl chloride (1.3137 g, 8.45 mmol) and allyl alcohol (1.15 ml, 16.9 mmol) were dissolved in benzene (25 ml) and triethylamine (1.30 ml, 9.30 mmol) was added to the reaction mixture. The mixture was stirred for 12 h, filtered, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography with 50% EtOAc–hexane afforded a white solid (1.50 g, 87%): $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.40 (3 H, m), 3.91 (1 H, m), 3.71 (2 H, m), 3.40 (1 H, dd, *J* 16.6, 10.7), 3.28 (1 H, dd, *J* 16.6, 7.9) and 1.88 (1 H, t, *J* 6.2); ν_{max}(thin film)/cm^{-1} 3335, 3052, 2987, 2921, 1599, 1497, 1447, 1287, 1163, 1087 and 897; *m/z* 177 (M^+), 146, 118, 104, 91, 77, 63, 51 and 44.

3-tert-*Butyl-5-hydroxymethyl-4,5-dihydroisoxazole* **12a**. Pivalohydroximoyl chloride (1.183 g, 8.73 mmol) and allyl alcohol (1.19 ml, 17.5 mmol) were treated with triethylamine (1.34 ml, 9.6 mmol) in benzene (26 ml). The product was purified by flash chromatography with 50% EtOAc–hexane to give a colourless oil (1.20 g, 87.4%): $\delta_H(CDCl_3)$ 4.65 (1 H, m), 3.75 (1 H, m), 3.55 (1 H, m), 3.01 (1 H, dd, *J* 16.7, 10.7), 2.87 (1 H, dd, *J* 16.7, 7.4), 1.98 (1 H, t, *J* 6.5) and 1.20 (9 H, s); ν_{max}(thin film)/cm^{-1} 3406, 2966, 2872, 1612, 1497, 1462, 1396, 1336, 1219, 1122 and 879; *m/z* 157 (M), 142, 131, 126, 84, 69, 57, 51, 45, 43 and 41.

trans-5-*Hydroxymethyl-4-methyl-3-phenyl-4,5-dihydroisoxazole* **13b** *and* trans-4-*Hydroxymethyl-5-methyl-3-phenyl-4,5-dihydroisoxazole*.—To a solution of benzohydroximoyl chloride (1.83 g, 11.78 mmol) and (*E*)-but-2-en-1-ol (2.01 ml, 23.57 mmol) in benzene (30 ml) was added triethylamine (1.81 ml, 12.9 mmol). The reaction mixture was stirred for 16 h. Purification by MPLC with 33% EtOAc–hexane gave **13b** (oil) and its regioisomer (white solid) in a combined yield of 68%. Compound **13b**. $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.41 (3 H, m), 4.45 (1 H, m), 3.79 (1 H, m), 3.68 (2 H, m), 1.96 (1 H, t), 1.34 (3 H, d, *J* 7.2) ν_{max}(thin film)/cm^{-1} 3402, 3061, 2971, 2934, 1593, 1566, 1498, 1350, 1313, 1256 and 893; *m/z* 191 (M^+), 160, 149, 132, 117, 104, 91, 77, 57 and 51 (Found: M^+, 191.0947. Calc. for $C_{11}H_{13}NO_2$: *M*, 191.0946).

trans-3-tert-*Butyl-5-hydroxymethyl-4-methyl-4,5-dihydroisoxazole* **12b** *and* trans-3-tert-*Butyl-4-hydroxymethyl-5-methyl-4,5-dihydroisoxazole*.—The reaction was performed with pivalohydroximoyl chloride (1.400 g, 10.33 mmol), (*E*)-but-2-enol (1.76 ml, 20.66 mmol) and triethylamine (1.59 ml, 11.4 mmol) in benzene (30 ml). The products were purified by MPLC with 33% EtOAc–hexane to afford **12b** (0.714 g, 36.2%) and its regioisomer (0.703 g, 35.6%), both as clear oils. Compound **12b**: $\delta_H(CDCl_3)$ 4.19 (1 H, m), 3.65 (1 H, m), 3.54 (1 H, m), 3.12 (1 H, m), 1.88 (1 H, t), 1.43 (3 H, d) and 1.25 (9 H, s); ν_{max}(thin film/cm^{-1} 3407, 2969, 2869, 1479, 1464, 1366, 1242, 1047 and 891; *m/z* 171 (M), 140, 131, 84, 69, 57 and 41.

Generation of 5-Hydroxyalkyl-4,5-dihydroisoxazoles through Direct Cycloaddition.[5,6]—anti-5-(1-*Hydroxyethyl*)-3-*phenyl-4,5-dihydroisoxazole* **6a**-*anti*. The cycloaddition was performed with benzohydroximoyl chloride (0.143 g, 0.92 mmol) and 3-*tert*-butyldimethylsilyloxybut-1-ene (0.341 g, 1.84 mmol) in ether (2 ml). The reaction mixture was treated with triethylamine (0.14 ml, 1.01 mmol) and stirred at 25 °C for 12 h. The mixture was filtered, and GC analysis of the crude products showed a 78:22 diastereoisomer ratio. Desilylation was accomplished by treatment of the crude product with 5% HF–MeCN. Based on the GC analysis, a ratio of 78:22 in favour of the *anti* isomer was obtained. Purification by chromatography with 50% EtOAc–hexane afforded a white solid (0.143 g, 82%). See below for the spectroscopic data of **6a**.

anti-5-[*Cyclohexyl(hydroxy)methyl*]-3-*phenyl-4,5-dihydroisoxazole* **6c**-*anti*. To a solution of benzohydroximoyl chloride (67.0 mg, 0.433 mmol) and 1-*tert*-butyldimethylsilyloxycyclohex-1-enylprop-2-ene (0.220 mg, 0.867 mmol) in ether (1 ml) was added triethylamine (0.066 ml, 0.476 mmol). The reaction mixture was stirred at ambient temperature for 12 h. Desilylation of the crude product with 5% HF–MeCN showed a diastereoisomer ratio of 93:7 in favour of the *anti* product by GC analysis. The crude product was recrystallized from EtOAc–hexane to give a white solid (0.106 g, 66%): m.p., 159–162 °C; **6c**-*anti*: $\delta_H(CDCl_3)$ 7.68 (2 H, m), 7.41 (3 H, m), 4.84 (1 H, m), 3.74 (1 H, m), 3.44 (1 H, dd, *J* 16.6, 9.5), 3.22 (1 H, *J* 16.6, 10.1) and 1.3–1.8 (br m, 12 H); ν_{max}(thin film)/cm^{-1} 3663, 3020, 2930, 2875, 1641, 1601, 1572, 1490, 1358, 1223, 1207 and 1184; *m/z* 259 (M^+), 181, 148, 119, 104, 95, 77, 55 and 44 (Found: 259.1573. Calc. for $C_{16}H_{21}NO_2$: 259.1572).

anti-3-tert-*Butyl-5-(1-hydroxyethyl)-4,5-dihydroisoxazole* **5a**-*anti*. The reaction was performed with pivalohydroximoyl chloride (0.149 g, 1.1 mmol), 3-(*tert*-butyldimethylsilyloxy)but-1-ene (0.411 g, 2.2 mmol), and triethylamine (0.169 ml, 1.21 mmol). Desilylation was accomplished by treatment of the crude products with 5% HF–MeCN. A diastereoisomer ratio of 72:28 was given based on GC analysis. Purification of the crude products by chromatography afforded a clear oil (0.2132 g, 78%), and the spectroscopic data are provided below.

anti-3-tert-*Butyl-5-[cyclohexyl(hydroxy)methyl]-4,5-dihydroisoxazole* **13a**. Cycloaddition was undertaken with pivalohydroximoyl chloride (58.1 mg, 0.429 mmol) and 1-cyclohexyl-1-trimethylsilyloxyprop-2-ene (0.164 g, 0.644 mmol) in benzene (10 ml), and triethylamine (0.066 ml, 0.472 mmol) was added at

ambient temperature. Desilylation was conducted with 5% HF–MeCN. GC analysis showed a diastereoisomer ratio of 92:8. The crude product was purified by flash chromatography with 33% EtOAc–hexane and a white solid (62.7 mg, 61%) was obtained. See the following section for the data.

General Procedure for the Reduction of 5-Acyl-4,5-dihydroisoxazoles with L-Selectride.—syn-(1-*Hydroxyethyl*)-3-*phenyl*-4,5-*dihydroisoxazole* **6a**-*syn*. To a solution of 5-acyl-4,5-dihydroisoxazole **5a** (0.378 g, 2 mmol) in THF (7 ml) at −78 °C was slowly added a THF solution of L-Selectride (2.4 ml, 2.4 mmol). The reaction mixture was stirred for 6 h at −78 °C and then warmed to 25 °C. The reaction was quenched with water (1 ml), ethanol (4 ml) and 3M NaOH (4.5 ml), cooled to 0 °C, and 30% H_2O_2 (4 ml) was cautiously added. After the addition, the reaction mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was extracted with ether, and the extract was washed with water, brine and aqueous sodium hydrogencarbonate, dried ($MgSO_4$) and concentrated under reduced pressure. A ratio of 98:2 in favour of the *syn* isomer was given by GC analysis. After recrystallization, a white solid (0.197 g, 79%) was obtained: m.p. 77.5–78.5 °C; $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.41 (3 H, m), 3.79 (1 H, m), 3.40 (1 H, dd, *J* 16.7, 10.8), 3.18 (1 H, dd, *J* 16.7, 7.6), 2.17 (1 H, d, *J* 5.8) and 1.29 (3 H, d, *J* 6.4); $\delta_C(CDCl_3)$ 158.0, 131.8, 129.4, 128.8, 127.0, 85.0, 78.8, 37.6 and 19.3; ν_{max}(thin film)/cm^{-1} 3272, 3061, 2977, 2926, 1566, 1496, 1446, 1288, 1080 and 905; *m*/*z* 191 (M), 146, 118, 104, 91, 77, 51 and 45 (Found: C, 69.3; H, 7.05; M^+, 191.0947. Calc. for $C_{11}H_{13}H_{13}NO_2$: C, 69.09; H, 6.85%; *M*, 191.0946).

syn-5-(1-*Hydroxypropyl*)-3-*phenyl*-4,5-*dihydroisoxazole* **6b**-*syn*. The reduction was conducted with the 5-acyl-4,5-dihydroisoxazole **5b** (0.558 g, 2.75 mmol) in THF (11 ml). After addition of L-Selectride (3.30 ml, 3.30 mmol), the reaction mixture was stirred at −78 °C for 6 h to give a diastereoisomer ratio of 94:6 in favour of the *syn* isomer. A white solid (0.453 g, 80.4%) was obtained after the crude product was purified by flash chromatography with 33% EtOAc–hexane: m.p. 81.5–83.0 °C; $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.42 (3 H, m), 4.67 (1 H, m), 3.52 (1 H, m), 3.40 (1 H, dd, *J* 16.6, 10.7), 3.25 (1 H, dd, *J* 16.6, 8.1), 1.99 (1 H, d, *J* 7.1), 1.63 (2 H, m) and 1.06 (3 H, t, *J* 7.4); ν_{max}(thin film)/cm^{-1} 3574, 3021, 2963, 2930, 2855, 1641, 1602, 1572, 1499, 1358, 1223, 1207, 1072 and 955; *m*/*z* 205 (M), 176, 156, 146, 119, 104, 91, 77, 59, 55 and 51 (Found: C, 70.5; H, 7.45; M^+, 205.1103. Calc. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37%; *M*, 205.1103).

syn-5-[*Cyclohexyl*(*hydroxy*)*methyl*]-3-*phenyl*-4,5-*dihydroisoxazole* **6c**-*syn*. The reduction was performed with the 4,5-dihydroisoxazole **5c** (94.5 mg, 0.37 mmol) and L-Selectride solution (0.389 ml, 0.389 mmol) in THF (1.5 ml). After 8 h at −78 °C, the reaction mixture was worked up to give, on the basis of a GC analysis, a diastereoisomer ratio of >98:2. The crude product was purified by recrystallization to afford a white solid (75.4 mg, 79.5%): m.p. 159.5–160.5 °C; $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.40 (3 H, m), 4.86 (1 H, m), 3.31 (1 H, m), 1.99 (1 H, d, *J* 7.4), 1.1–1.8 (11 H); $\delta_C(CDCl_3)$ 130.2, 128.8, 126.6, 81.4, 41.4, 37.7, 29.7, 28.6, 26.4, 26.3 and 26.1; ν_{max}(thin film)/cm^{-1} 3416, 3056, 2920, 2847, 1598, 1568, 1498, 1361, 1325, 1072, 987, 949 and 933; *m*/*z* 259 (M), 148, 119, 104, 95, 91, 77, 67 and 45; (Found: C, 74.4; H, 8.2; M^+, 259.1573. Calc. for $C_{16}H_{21}NO_2$: C, 74.09; H, 8.16%; *M*, 259.1572).

4,5-anti-5,5′-syn-5-(1-*Hydroxyethyl*)-4-*methyl*-3-*phenyl*-4,5-*dihydroisoxazole* **6d**-*syn*. The reaction was conducted with the 4,5-dihydroisoxazole **5d** (50.8 mg, 0.25 mmol) and L-Selectride (0.30 ml, 0.30 mmol) in THF (1 ml) at −78 °C to give, on the basis of a GC analysis, in favour of the *syn* isomer. Purification of the crude product by flash chromatography with 25% EtOAc–hexane gave a white solid (43.1 mg, 84%): m.p. 69.5–70.5 °C; $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.38 (3 H, m), 4.13 (1 H, dd, *J* 6.1, 5.1), 3.76 (1 H, m), 3.54 (1 H, m), 2.22 (1 H, d, *J* 5.1), 1.35 (3 H, d, *J* 7.2) and 1.28 (3 H, d, *J* 6.4); $\delta_C(CDCl_3)$ 161.2, 130.1, 128.8, 128.7, 128.5, 127.6, 127.1, 92.4, 68.4, 44.1, 18.4 and 18.1; ν_{max}(thin film)/cm^{-1} 3411, 3059, 2973, 2877, 1498, 1455, 1378, 1310, 1147 and 909; *m*/*z* 205 (M), 160, 146, 132, 117, 104, 77, 58, 51 and 45 (Found: M^+, 205.1103. Calc. for $C_{12}H_{15}NO_2$: *M*, 205.1103).

syn-3-tert-*Butyl*-5-(1-*hydroxyethyl*)-4,5-*dihydroisoxazole* **8a**-*syn*. To a solution of **7a** (0.338 g, 2.00 mmol) in THF (7 ml) was added L-Selectride (2.1 ml, 2.1 mmol) at −78 °C, and the mixture was stirred for 8 h. Purification of the crude product by Kugelrohr distillation (aspirator pressure, 140 °C) gave a colourless oil (0.234 g, 69%) the diastereoisomer ratio of which was 97:3 on the basis of a GC analysis; $\delta_H(CDCl_3)$ 4.33 (1 H, m), 3.64 (1 H, m), 2.99 (1 H, dd, *J* 16.8, 6.2), 2.75 (1 H, dd, *J* 16.8, 7.1) and 1.18 (12 H, m); $\delta_C(CDCl_3)$ 166.5, 83.7, 69.2, 36.4, 33.1, 28.1 and 18.9; ν_{max}(thin film)/cm^{-1} 3416, 2967, 2933, 2906, 1461, 1394, 1336, 1255, 1134 and 877; *m*/*z* 171 (M), 142, 126, 74, 60, 57, 45 and 42 (Found: M^+, 171.1259. Calc. for $C_9H_{17}NO_2$: *M*, 171.1259).

syn-3-tert-*Butyl*-5-(1-*hydroxypropyl*)-4,5-*dihydroisoxazole* **8b**-*syn*. The reduction was performed with **7b** (0.952 g, 5.2 mmol) and L-Selectride (6.24 ml, 6.24 mmol) in THF (10 ml) at −78 °C to give, after a standard work-up, a diastereoisomer ratio of 93:7 (based on GC analysis). Kugelrohr distillation of the crude product gave a colourless oil (0.913 g, 95%); $\delta_H(CDCl_3)$ 4.44 (1 H, m), 3.38 (1 H, m), 3.01 (1 H, dd, *J* 16.7, 10.5), 2.83 (1 H, dd, *J* 16.7, 7.6), 1.98 (1 H, d, *J* 5.3), 1.55 (2 H, m), 1.20 (9 H, s) and 1.01 (3 H, t, *J* 7.6); ν_{max}(thin film)/cm^{-1} 3406, 2974, 2938, 1462, 1445, 1377, 1298, 1259, 1226, 1132, 1097 and 989; *m*/*z* 195, 170, 126, 112, 99, 84, 70 and 57 (Found: M^+, 185.1450. Calc. for $C_{10}H_{19}NO_2$: *M*, 185.1416).

(4,5)-anti-(5,5′)-syn-3-tert-*Butyl*-5-(1-*hydroxyethyl*)-4-*methyl*-4,5-*dihydroisoxazole* **8d**-*syn*. The reduction followed the standard procedure with *trans*-3-*tert*-butyl-4-methyl-5-acetyl-4,5-dihydroisoxazole **7d** (93.0 mg, 0.508 mmol) dissolved in THF (2 ml) at −78 °C, and addition of a THF solution of L-Selectride (0.61 ml, 0.61 mmol) to the stirred solution. Standard oxidative work-up gave a diastereoisomer ratio of >98:2 (by GC analysis). The product was obtained as a colourless oil (72.5 mg, 77%) after Kugelrohr distillation, $\delta_H(CDCl_3)$ 3.86 (1 H, dd, *J* 6.1, 5.1), 3.59 (1 H, m), 3.06 (1 H, m), 2.20 (1 H, d, *J* 5.0), 1.31 (3 H, d, *J* 7.1), 1.24 (9 H, s) and 1.19 (3 H, d, *J* 5.3); ν_{max}(thin film)/cm^{-1} 3416, 2970, 2934, 2874, 1479, 1466, 1365, 1244, 1110, 980 and 885; *m*/*z* 185, 170, 149, 140, 98, 84, 74, 57, 49 and 45 (Found: M^+, 185.1416. Calc. for $C_{10}H_{19}NO_2$: *M*, 185.1416).

syn-3-*Ethyl*-5-(1-*hydroxyethyl*)-4,5-*dihydroisoxazole* **10a**-*syn*. The reaction was conducted with **9a** (0.16 g, 1.86 mmol) and L-Selectride (2.24 ml, 2.24 mmol) in THF (8 ml) at −78 °C to give a diastereoisomer ratio of >98/2 (GC analysis of the crude products). Purification of the crude product by Kugelrohr distillation afforded a colourless oil (0.148 g, 55%); $\delta_H(CDCl_3)$ 4.36 (1 H, ddd, *J* 10.6, 7.1, 5.6), 3.66 (1 H, m), 2.98 (1 H, dd, *J* 17.0, 10.6), 2.73 (1 H, dd, *J* 17.0, 7.1), 2.35 (2 H, q, *J* 7.4), 2.20 (1 H, s) 1.21 (3 H, d, *J* 7.0) and 1.16 (3 H, t, *J* 7.4); ν_{max}(thin film)/cm^{-1} 3407, 2974, 2938, 1462, 1445, 1377, 1298, 1226, 1097, 1064, 989 and 939; *m*/*z* 143 (M^+), 126, 106, 98, 93, 70, 65, 56 and 45 (Found: M^+, 143.0946. Calc. for $C_7H_{13}NO_2$: *M*, 143.0946).

General Procedure for Nucleophilic Addition to 5-Formyl-4,5-dihydroisoxazoles.—anti-3-tert-*Butyl*-5-(1-*hydroxyethyl*)-4,5-*dihydroisoxazole* **8a**-*anti*. To a stirred solution of oxalyl chloride (0.067 ml, 0.77 mmol) in THF (2.0 ml) at −78 °C was added dimethyl sulphoxide (0.057 ml, 0.82 mmol). The solution was warmed to −35 °C for 5 min and then recooled to −78 °C. A solution of the 4,5-dihydroisoxazole **12a** in THF (1.0 ml) was added to the reaction mixture which was then warmed to −35 °C and, after 15 min, treated with triethylamine (0.51 ml,

3.7 mmol). The reaction mixture was warmed briefly to 25 °C and was then cooled to −78 °C. A THF solution of methylmagnesium bromide (1.28 ml, 3.7 mmol) was then added dropwise to the vigorously stirred reaction mixture. It was stirred at −78 °C for 3 h and then ethanol (1.0 ml) was added cautiously. The reaction mixture was warmed to room temperature and poured into saturated aqueous NH_4Cl (50 ml); the latter was then extracted with ether (100 ml × 2). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. GC analysis of the crude product established a 87:13 diastereoisomeric ratio in favour of the *anti* isomer. Chromatography of the residue afforded **8a**-*anti* (99.2 mg, 79%) as an oil: the major isomer showed $\delta_H(CDCl_3)$ 4.45 (1 H, m), 4.04 (1 H, m), 3.01 (1 H, dd, *J* 16.9, 8.5), 2.85 (1 H, dd, *J* 16.9, 10.7), 1.93 (1 H, d, *J* 3.2), 1.20 (9 H, s) and 1.14 (3 H, d, *J* 6.6); ν_{max}(thin film)/cm^{-1} 3405, 2973, 2928, 2496, 1599, 1570, 1358, 1253, 1067 and 904; *m/z* 171 (M^+), 148, 142, 126, 109, 84, 70, 57, 45 and 41 (Found: M^+, 171.1529. Calc. for $C_9H_{13}NO_2$: *M*, 171.1529).

anti-3-tert-*Butyl*-5-(1-*hydroxypropyl*)-4,5-*dihydroisoxazole* **8b**-*anti*. The reaction was performed with **12a** (0.244 g, 1.55 mmol) and ethylmagnesium bromide (2.67 ml, 7.75 mmol) following the standard procedure to give, on the basis of a GC analysis, a diastereoisomeric ratio of 80:20 in favour of the *anti* isomer. The crude product was purified by flash chromatography with 33% EtOAc–hexane to give a white solid (0.204 g, 77%): m.p. 44–45.5 °C; $\delta_H(CDCl_3)$ 4.48 (1 H, m), 3.80 (1 H, m), 3.01 (1 H, dd, *J* 16.8, 9.0), 2.83 (1 H, dd, *J* 16.8, 10.7), 1.90 (1 H, d, *J* 2.6), 1.44 (2 H, m), 1.20 (9 H, s) and 1.01 (3 H, t, *J* 7.4); ν_{max}(thin film)/cm^{-1} 3405, 2972, 2928, 1499, 1446, 1298, 1066, 862 and 760; *m/z* 185 (M^+), 170, 126, 112, 99, 84, 70 and 57 (Found: M^+, 185.1409. Calc. for $C_{10}H_{19}NO_2$: *M*, 185.1416).

anti-3-tert-*Butyl*-5-[*cyclohexyl*(*hydroxy*)*methyl*]-4,5-*dihydroisoxazole* **8c**-*anti*. The reaction was conducted with **12a** (65 mg, 0.414 mmol) and cyclohexylmagnesium chloride (1.04 ml, 2.07 mmol) was added upon the completion of the oxidation. A diastereoisomeric ratio of >96:4 was established in favour of the *anti* isomer (GC analysis). Purification of the crude product by chromatography with 25% EtOAc–hexane afforded a white solid (78.6 mg, 79%); m.p. 96–98 °C; $\delta_H(CDCl_3)$ 4.62 (1 H, m), 3.62 (1 H, m), 3.02 (1 H, dd, *J* 16.5, 9.4), 2.82 (1 H, dd, *J* 16.5, 10.6), 1.90 (1 H, d, *J* 2.7), 1.20 (9 H, s), 1.0–1.8 (11 H, br m); ν_{max}(thin film)/cm^{-1} 3422, 2924, 2853, 1601, 1497, 1450, 1365, 1242, 1028 and 891; *m/z* 239 (M^+), 224, 191, 182, 126, 113, 95, 84, 70 and 57 (Found: M^+, 239.1886. Calc. for $C_{14}H_{25}NO_2$: *M*, 239.1885).

anti-5-(1-*Hydroxyethyl*)-3-*phenyl*-4,5-*dihydroisoxazole* **6a**-*anti*. The reaction was performed with the 4,5-dihydroisoxazole **13a** (58.0 mg, 0.33 mmol) and methylmagnesium bromide (0.565 ml, 1.64 mmol) following the standard procedure. GC analysis established a 83:17 diastereoisomeric ratio in favour of the *anti* isomer. Purification by flash chromatography with 50% EtOAc–hexane gave a white solid (37.5 mg, 60%): m.p. 55–57 °C; for the major isomer **6a**: $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.40 (3 H, m), 4.66 (1 H, m), 4.13 (1 H, m), 3.42 (1 H, dd, *J* 16.6, 8.8), 3.22 (1 H, dd, *J* 16.6, 10.9), 2.12 (1 H, d, *J* 2.2) and 1.22 (3 H, d, *J* 6.5); ν_{max}(thin film)/cm^{-1} 3405, 3059, 2973, 2928, 1599, 1570, 1498, 1446, 1254, 1157, 1067 and 904; *m/z* 191 (M^+), 146, 119, 104, 91, 77, 69 and 45 (Found: M^+, 191.0947. Calc. for $C_{11}H_{13}NO_2$: *M*, 191.0946).

anti-5-(1-*Hydroxypropyl*)-3-*phenyl*-4,5-*dihydroisoxazole* **6b**-*anti*. The reaction was performed with the 4,5-dihydroisoxazole **13a** (0.109 g, 0.62 mmol) and slow addition of a THF solution of ethylmagnesium bromide (1.07 ml, 3.10 mmol). GC analysis showed a 83:17 diastereoisomeric ratio in favour of the *anti* isomer. Purification of the crude product by flash chromatography with 50% EtOAc–hexane yielded a thick oil (73.5 mg, 58%): for the major isomer $\delta_H(CDCl_3)$ 7.67 (2 H, m), 7.40 (3 H, m), 4.71 (1 H, m), 3.90 (1 H, m), 2.41 (1 H, dd, *J* 16.6, 9.1), 3.22 (1 H, dd, *J* 16.6, 11.0), 1.95 (1 H, d, *J* 3.1), 1.53 (2 H, m) and 1.05 (3 H, d, *J* 7.5); ν_{max}(thin film)/cm^{-1} 3405, 3059, 2973, 2928, 1599, 1570, 1498, 1446, 1253, 1157, 904 and 862; *m/z* 205 (M^+), 146, 119, 104, 83, 69, 59 and 45 (Found: M^+, 205.1103. Calc. for $C_{12}H_{15}NO_2$: *M*, 205.1103).

anti-5-[*Cyclohexyl*(*hydroxy*)*methyl*]-3-*phenyl*-4,5-*dihydroisoxazole* **6c**-*anti*. The reaction was performed with the 4,5-dihydroisoxazole **13a** (73.3 mg, 0.414 mmol) and cyclohexylmagnesium chloride (1.35 ml, 2.70 mmol) was added at −78 °C after the completion of the Swern oxidation. A 89:11 diastereoisomeric ratio was established on the basis of a GC analysis. The crude product was purified by recrystallization from EtOAc–hexane to give a white solid (34.7 mg, 40%). The major isomer was identical with the cycloaddition product described above on the basis of GC coinjection and ^1H NMR analyses.

(4,5)-anti-(5,5′)-anti-3-tert-*Butyl*-5-(1-*hydroxyethyl*)-4-*methyl*-4,5-*dihydroisoxazole* **8d**-*anti*. The reaction was performed with the oxidation of **12b** (59.9 mg, 0.35 mmol) and THF solution of methylmagnesium bromide (0.60 ml, 1.75 mmol) following the standard procedure. A diastereoisomeric ratio of 82:18 in favour of the *anti* isomer was established on the basis of a GC analysis. The product was purified by flash chromatography with 33% EtOAc–hexane to give a colourless oil (47.8 mg, 74%): for the major isomer **8d** $\delta(CDCl_3)$ 3.97 (1 H, dd, *J* 5.8, 4.1), 3.88 (1 H, m), 3.33 (1 H, m), 1.88 (1 H, s), 1.32 (3 H, d, *J* 7.1), 1.24 (9 H, s) and 1.17 (3 H, d, *J* 6.4); ν_{max}(thin film)/cm^{-1} 3412, 2971, 2943, 1497, 1464, 1366, 1244 and 908; *m/z* 185 (M), 140, 126, 98, 84, 69, 57 and 45 (Found: M^+, 185.1416. Calc. for $C_{10}H_{19}NO_2$: *M*, 185.1416).

(4,5)-anti-(5,5′)-anti-3-tert-*Butyl*-5-(1-*hydroxypropyl*)-4-*methyl*-4,5-*dihydroisoxazole* **8e**-*anti*. The reaction was conducted with **12b** (59.9 mg, 0.35 mmol), a THF solution of ethylmagnesium bromide (0.63 ml, 1.75 mmol) being added after completion of the oxidation. A 75:25 ratio in favour of the *anti* isomer **8e**-*anti* was established on the basis of a GC analysis. Purification by flash chromatography with 33% EtOAc–hexane afforded a white solid (46.9 mg, 68%): m.p. 53–55 °C; for the major isomer **8e**-*anti* $\delta_H(CDCl_3)$ 4.03 (1 H, dd, *J* 6.0, 4.1), 3.65 (1 H, m), 3.34 (1 H, m), 1.77 (1 H, d, *J* 3.7), 1.50 (2 H, m), 1.31 (3 H, d, *J* 7.2), 1.24 (9 H, s) and 1.01 (3 H, t, *J* 7.4); ν_{max}(thin film)/cm^{-1} 3416, 2967, 2934, 2876, 1601, 1464, 1366, 1242, 1092, 976 and 887; *m/z* 199 (M), 169, 163, 140, 126, 113, 98, 84, 57 and 45 (Found: M^+, 199.1571. Calc. for $C_{11}H_{21}NO_2$: *M*, 199.1572).

(4,5)-anti-(5,5′)-anti-3-tert-*Butyl*-5-[*cyclohexyl*(*hydroxy*)*methyl*]-4,5-*dihydroisoxazole* **8f**-*anti*. The nucleophilic addition was conducted with the 4,5-dihydroisoxazole **12b** (59.5 mg, 0.350 mmol) and a THF solution of cyclohexylmagnesium chloride (0.88 ml, 1.75 mmol) following the standard procedure. A diastereoisomeric ratio of >95:5 was established on the basis of a GC analysis. Purification of the crude product by recrystallization from EtOAc–hexane afforded a whtie solid (46.5 mg, 52%): m.p. 81–83 °C; $\delta_H(CDCl_3)$ 4.22 (1 H, m), 3.47 (1 H, m), 3.39 (1 H, m), 1.69 (1 H, d, *J* 3.6), 1.32 (3 H, d, *J* 7.2), 1.24 (9 H, s) and 1.3–1.8 (11 H, br m); ν_{max}(thin film)/cm^{-1} 3422, 2924, 2853, 1601, 1497, 1365, 1242, 1182, 1089 and 891; *m/z* 239 (M^+), 224, 220, 206, 191, 182, 178, 126, 113, 95, 84, 70 and 57 (Found: M^+, 239.1886. Calc. for $C_{14}H_{25}NO_2$: *M*, 239.1885).

(4,5)-anti-(5,5′)-anti-5-(1-*Hydroxyethyl*)-4-*methyl*-3-*phenyl*-4,5-*dihydroisoxazole* **6d**-*anti*. The reaction was performed with the 4,5-dihydroisoxazole **13b** (67.0 mg, 0.38 mmol). After the Swern oxidation, a THF solution of methylmagnesium bromide (0.65 ml, 1.90 mmol) was added to the reaction mixture. A diastereoisomeric ratio of 84:16 was established on the basis of a GC analysis. Chromatography of the crude product with 20% EtOAc–hexane yielded a white solid (40.1 mg, 69%): m.p. 74–76 °C; for the major isomer **6d**-*anti*: $\delta_H(CDCl_3)$ 7.67 (2 H, m),

7.41 (3 H, m), 4.23 (1 H, dd, *J* 6.0, 3.9), 4.05 (1 H, m), 3.81 (1 H, m), 1.90 (1 H, d, *J* 3.6), 1.34 (3 H, d, *J* 7.1) and 1.25 (3 H, d, *J* 6.5); ν_{max}(thin film)/cm^{-1} 3404, 3059, 2972, 2932, 1595, 1566, 1498, 1350, 1089 and 912 (Found: C, 70.35; H, 7.5. Calc. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37%).

(4,5)-anti-(5,5′)-anti-5-(1-*Hydroxypropyl*)-4-*methyl*-3-*phenyl*-4,5-*dihydroisoxazole* **6e**-*anti*. The reaction was performed with the 4,5-dihydroisoxazole **13b** (67.0 mg, 0.38 mmol) and a THF solution of ethylmagnesium bromide (0.65 ml, 1.90 mmol) following the standard procedure. GC analysis of the crude product established a 79:21 ratio in favour of **6e**-*anti*. Purification by flash chromatography with 33% EtOAc–hexane of the crude product afforded a white solid (40.4 mg, 52%): m.p. 60–62 °C; δ_H($CDCl_3$) 7.66 (2 H, m), 7.40 (3 H, m), 4.28 (1 H, dd, *J* 5.9, 4.2), 3.83 (1 H, m), 1.96 (1 H, s), 1.62 (2 H, m), 1.33 (3 H, d, *J* 7.2) and 1.05 (3 H, t, *J* 7.5); ν_{max}(thin film)/cm^{-1} 3399, 3058, 2924, 1595, 1566, 1499, 1350, 1312, 1103 and 891; *m*/*z* 219 (M^+), 160, 132, 117, 104, 77, 69, 58 and 51 (Found: M^+, 219.1259. Calc. for $C_{13}H_{17}NO_2$: *M*, 219.1259).

(4,5)-anti-(5,5′)-anti-5-[*Cyclohexyl*(*hydroxy*)*methyl*]-4-*methyl*-3-*phenyl*-4,5-*dihydroisoxazole* **6f**-*anti*. The reaction was performed with the 4,5-dihydroisoxazole **13b** (67.0 mg, 0.38 mmol) and a THF solution of cyclohexylmagnesium chloride (0.95 ml, 1.90 mmol) following the general procedure. GC analysis of the crude products established a 85:15 diastereoisomeric ratio. Purification of the crude product by chromatography with 25% EtOAc–hexane yielded a thick oil (47.8 mg, 48%): for the major isomer **6f**-*anti* δ_H($CDCl_3$) 7.66 (2 H, m), 7.39 (3 H, m), 4.46 (1 H, m), 3.87 (1 H, m), 3.58 (1 H, m), 2.02 (1 H, d, *J* 12.3) and 1.33 (3 H, d, *J* 7.2); ν_{max}(thin film)/cm^{-1} 3399, 3057, 2924, 2851, 1595, 1566, 1498, 1103 and 891; *m*/*z* 273 (M^+), 203, 186, 171, 160, 148, 132, 104, 95, 77, 55 and 51 (Found: M^+, 273.1728. Calc. for $C_{17}H_{23}NO_2$: *M*, 273.1729).

General Procedure for Nucleophilic Addition to 5-*Acyl*-4,5-*Dihydroisoxazoles*.—syn-5-(1-*Hydroxy*-1-*methylpropyl*)-3-*phenyl*-4,5-*dihydroisoxazole* **14**-*syn*. To a solution of **5a** (54 mg, 0.29 mmol) in THF (4 ml) was added a THF solution of ethylmagnesium bromide (0.122 ml, 0.342 mmol) at −78 °C. After 3 h, the reaction mixture was poured into saturated aqueous NH_4Cl (10 ml) and extracted with ether (15 ml × 3). The combined extracts were washed with water and brine and concentrated under reduced pressure: ^{1}H NMR and HPLC analyses established a diastereoisomeric ratio of 90:10. Purification by flash chromatography gave a white solid (66.7 mg, 90%): m.p. 77.5–78.5 °C; for the major isomer **14**-*syn* δ_H($CDCl_3$) 7.68 (2 H, m), 7.41 (3 H, m), 4.64 (1 H, dd, *J* 10.8, 5.7), 3.41 (1 H, dd, *J* 16.6, 9.5), 3.26 (1 H, dd, *J* 16.6, 11.0), 1.72 (2 H, m), 1.14 (3 H, s) and 1.00 (3 H, t, *J* 12.5); ν_{max}(thin film)/cm^{-1} 3381, 3035, 2984, 2972, 1580, 1469, 1406, 1337, 1298, 1207 and 1018; *m*/*z* 219 (M^+), 190, 172, 147, 119, 104, 91, 73 and 55 (Found: M^+, 219.1259. Calc. for $C_{13}H_{17}NO_2$: *M*, 219.1259).

anti-5-(1-*Hydroxy*-1-*methylpropyl*)-3-*phenyl*-4,5-*dihydroisoxazole* **14**-*anti*. The reaction was conducted with the 4,5-dihydroisoxazole **5b** (0.1015 g, 0.5 mmol) and methylmagnesium bromide (0.21 ml, 0.6 mmol) in THF (8 ml) at −78 °C. A diastereoisomeric ratio of 90:10 was established in favour of the *anti* isomer on the basis of ^{1}H NMR and HPLC analyses. The product was purified by chromatography with 25% EtOAc–hexane to give a white solid (0.769 g, 72%): m.p. 79.0–80.5 °C; δ_H($CDCl_3$) 7.67 (2 H, m), 7.41 (3 H, m), 4.61 (1 H, dd, *J* 10.8, 5.7), 3.41 (1 H, dd, *J* 16.6, 9.5), 3.26 (1 H, dd, *J* 16.6, 11.0), 1.72 (2 H, m), 1.14 (3 H, s), 1.00 (3 H, t, *J* 12.5); ν_{max}(thin film)/cm^{-1} 3381, 3035, 2984, 2972, 1580, 1469, 1406, 1336, 1298, 1207 and 1018; *m*/*z* 219 (M^+), 190, 172, 147, 119, 104, 91, 73 and 55 (Found: M^+, 219.1259. Calc. for $C_{13}H_{17}NO_2$: *M*, 219.1259).

anti-5-(1-*Cyclohexyl*-1-*hydroxyethyl*)-3-*phenyl*-4,5-*dihydroisoxazole* **15**-*anti*. The reaction was performed with the 4,5-dihydroisoxazole **5c** (54 mg, 0.29 mmol) and methylmagnesium bromide (0.17 ml, 0.342 mmol) in THF (4 ml) following the general procedure. HPLC analysis established a diastereoisomeric ratio of >96:4. The crude product was purified by chromatography with 20% EtOAc–hexane to give a white solid (54.6 mg, 72%); m.p. 103–105 °C; δ_H($CDCl_3$) 7.67 (2 H, m), 7.41 (3 H, m), 4.70 (1 H, t, *J* 10.2), 3.44 (1 H, dd, *J* 16.7, 10.1), 3.21 (1 H, dd, *J* 16.7, 10.7) and 1.9–1.3 (13 H, br m); ν_{max}(thin film)/cm^{-1} 3439, 3059, 2928, 2853, 1599, 1570, 1498, 1446, 1375, 1248, 1146, 1072, 902 and 860; *m*/*z* 273 (M^+), 190, 172, 148, 127, 119, 109, 83, 77, 67 and 55 (Found: M^+, 273.1729. Calc. for $C_{17}H_{23}NO_2$: *M*, 273.1729).

syn-5-(1-*Cyclohexyl*-1-*hydroxyethyl*)-3-*phenyl*-4,5-*dihydroisoxazole* **15**-*syn*. The reaction was performed with the 4,5-dihydroisoxazoline **5c** (64.0 mg, 0.25 mmol) and a THF solution of cyclohexylmagnesium bromide (0.11 ml, 0.303 mmol) at −78 °C following the general procedure. ^{1}H NMR and HPLC analyses established a diastereoisomeric ratio of >96:4. A white solid (60.0 mg, 75%) was obtained after purification of the crude product by chromatography with 20% EtOAc–hexane: m.p. 96–98 °C; δ_H($CDCl_3$) 7.67 (2 H, m), 7.41 (3 H, m), 4.22 (1 H, t, *J* 10.5), 3.48 (1 H, dd, *J* 16.8, 10.1), 3.21 (1 H, dd, *J* 16.8, 10.7) and 1.9–1.3 (13 H, br m); ν_{max}(thin film)/cm^{-1} 3434, 3059, 2928, 2853, 1599, 1570, 1498, 1446, 1358, 1244, 1151, 1074, 902 and 860; *m*/*z* 273 (M^+), 190, 172, 148, 127, 119, 109, 83, 77, 67 and 55 (Found: M^+, 273.1729. Calc. for $C_{17}H_{23}NO_2$; *M*, 273.1729).

syn-3-tert-*Butyl*-5-(1-*cyclohexyl*-1-*hydroxyethyl*)-4,5-*dihydroisoxazole* **16**-*syn*. The reaction was performed with the 4,5-dihydroisoxazole **7a** (0.261 g, 1.55 mmol) and a THF solution of cyclohexylmagnesium chloride (2.32 ml, 2.32 mmol) in THF (15 ml). Based on GC analysis, a diastereoisomeric ratio of >96:4 was established. After recrystallisation, the product was obtained as a white solid (0.273 g, 72%): m.p. 114–116 °C; δ_H($CDCl_3$) 4.59 (1 H, t, *J* 10.1), 3.06 (1 H, dd, *J* 16.6, 9.8), 2.83 (1 H, dd, *J* 16.6, 10.5), 1.19 (9 H, s) and 1.9–1.2 (12 H, br m); ν_{max}(thin film)/cm^{-1} 3431, 2973, 2936, 2882, 1498, 1446, 1358, 1205, 1134, 947, 910 and 864 cm^{-1}; *m*/*z* 238 (M − CH_3), 212, 170, 149, 127, 109, 99, 83, 67, 57 and 45 [Found: *m*/*z* 238.1806. Calc. for $C_{14}H_{24}NO_2$: (M − CH_3), 238.1807].

anti-3-tert-*Butyl*-5-(1-*cyclohexyl*-1-*hydroxyethyl*)-4,5-*dihydroisoxazole* **16**-*anti*. The reaction was performed with the 4,5-dihydroisoxazole **7c** (0.126 g, 0.53 mmol) and a THF solution of methylmagnesium bromide (0.91 ml, 2.64 mmol). Based on a GC analysis, a diastereoisomeric ratio of >96:4 was established. Recrystallisation of the crude product afforded a white solid (85.6 mg, 65%): m.p. 104–106 °C; δ_H($CDCl_3$) 4.48 (1 H, t, *J* 10.5), 3.06 (1 H, dd, *J* 16.7, 10.2), 2.83 (1 H, dd, *J* 16.7, 10.4), 1.74 (3 H, s), 1.20 (9 H, s)) and 1.9–1.2 (12 H, br m); ν_{max}(thin film)/cm^{-1} 3364, 2974, 2926, 2849, 1620, 1475, 1448, 1365, 1298, 1143 and 954; *m*/*z* 238 (M − CH_3), 210, 182, 170, 149, 139, 127, 109, 99, 95, 83, 67, 57 and 45 [Found: *m*/*z* 238.1806. Calc. for $C_{14}H_{24}NO_2$: (M − CH_3), 238.1807].

General Procedure for Reductive Cleavage of 4,5-*Dihydroisoxazoles*.[22] syn-5,6-*Dihydroxy*-2,2-*dimethyloctan*-3-*one* **17**-*syn*. To a solution of the dihydroisoxazole **8b**-*syn* (101.5 mg, 0.55 mmol) in 5:1 methanol–water (5 ml) was added boric acid (169.6 mg, 2.74 mmol) and a spatula tip of W-2 Raney nickel. The reaction was carried out under hydrogen by repeated evacuating and flushing with H_2 gas by means of a balloon attached to a three-way stopcock. The mixture was stirred vigorously for 2 h, and filtered through Celite into a separatory funnel containing water and CH_2Cl_2. After separation. the aqueous layer was extracted with CH_2Cl_2 several more times and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to yield the crude product (91.2 mg). Recrystallization of the crude product with EtOAc–hexane afforded the purified product as a white

solid (57.4 mg, 56%): m.p. 51–53 °C; $\delta_H(CDCl_3)$ 3.92 (1 H, m), 3.40 (1 H, d, *J* 3.5), 3.33 (1 H, m), 2.74 (2 H, m), 2.22 (1 H, d, *J* 6.5), 1.55 (2 H, m), 1.16 (9 H, s) and 0.99 (3 H, t, *J* 7.3); ν_{max}(thin film)/cm^{-1} 3385, 2967, 2936, 2876, 1703, 1464, 1360, 1240 and 1130; *m/z* 170, 159, 152, 137, 129, 113, 89, 85, 71 and 57 [Found: *m/z* 170.1307. Calc. for $C_{10}H_{18}O_2$: (M − H_2O), 170.1307].

anti-5,6-*Dihydroxy*-2,2-*dimethyloctan*-3-*one* **17**-*anti*. The reaction was conducted with the 4,5-dihydroisoxazole **8b**-*anti* (32.6 mg, 0.19 mmol) and boric acid (65.1 mg, 0.96 mmol) following the general procedure to give a white solid (18.3 mg, 53%) after recrystallization with EtOAc–hexane: $\delta_H(CDCl_3)$ 3.94 (1 H, m), 3.63 (1 H, m), 2.78 (1 H, dd, *J* 17.5, 3.0), 2.68 (1 H, dd, *J* 17.5, 9.0), 2.10 (1 H, d, *J* 3.9), 1.50 (2 H, m), 1.16 (9 H, s) and 1.00 (3 H, m); ν_{max}(thin film)/cm^{-1} 3382, 2984, 2926, 2872, 1693, 1406, 1365, 1298, 1207 and 1063; *m/z* 170 (M^+ − H_2O), 159, 152, 149, 137, 129, 113, 89, 85, 71 and 57 [Found: *m/z* 170.1307. Calc for $C_{10}H_{18}O_2$: (M − H_2O), 170.1307].

syn-3,4-*Dihydroxy*-1-*phenylhexan*-1-*one* **18**-*syn*. The reduction followed the hydrogenolysis procedure with the 4,5-dihydroisoxazole **6b**-*syn* (45.4 mg, 0.22 mmol) and boric acid (68.4 mg, 1.11 mmol) in 5:1 methanol–water solution (2 ml). After being stirred for 2 h at 25 °C, standard work-up of the mixture gave crude product (40.2 mg). This was purified by recrystallization from EtOAc–hexane to afford a white solid (30.1 mg, 65%): m.p. 105–107 °C; $\delta_H(CDCl_3)$ 7.98 (2 H, d, *J* 7.2), 7.59 (1 H, t, *J* 7.2), 7.49 (2 H, t, *J* 7.2), 4.15 (1 H, m), 3.50 (1 H, m), 3.42 (1 H, d, *J* 3.6), 3.29 (1 H, dd, *J* 17.8, 8.4), 3.20 (1 H, dd, *J* 17.8, 3.6), 2.28 (1 H, d, *J* 6.5), 1.66 (2 H, m) and 1.02 (3 H, t, *J* 7.5); ν_{max}(thin film)/cm^{-1} 3366, 2907, 1678, 1595, 1404, 1363, 1277, 1238 and 1140; *m/z* 190 (M^+ − H_2O), 172, 157, 150, 133, 120, 105, 77, 73 and 57 [Found: *m/z* 190.0994. Calc. for $C_{12}H_{14}O_2$: (M − H_2O), 190.0994].

anti-3,4-*Dihydroxy*-1-*phenylhexan*-1-*one* **18**-*anti*. The reduction and hydrolysis was conducted with the 4,5-dihydroisoxazole **6b**-*anti* (88.5 mg, 0.43 mmol) and boric acid (133.5 mg, 2.16 mmol) following the standard procedure to give a white solid (55.4 mg, 62%) after recrystallization of the crude product from EtOAc–hexane: m.p. 79–81 °C; $\delta_H(CDCl_3)$ 7.98 (2 H, d, *J* 7.3), 7.58 (1 H, t, *J* 7.3), 7.48 (2 H, t, *J* 7.3), 4.18 (1 H, m), 3.74 (1 H, m), 3.61 (1 H, d, *J* 3.1), 3.23 (2 H, m), 2.17 (1 H, d, *J* 3.6), 1.56 (2 H, m) and 1.03 (3 H, t, *J* 7.4); ν_{max}(thin film)/cm^{-1} 3418, 3063, 2978, 2938, 1687, 1599, 1563, 1491, 1364, 1272, 1180, 1099, 1001 and 756; *m/z* 190 (M − H_2O), 172, 157, 150, 133, 118, 105, 91, 84, 77, 57, 49 and 43 [Found: *m/z* 190.0994. Calc. for $C_{12}H_{14}O_2$: (M − H_2O), 190.0994].

anti-6-*Cyclohexyl*-5,6-*dihydroxy*-2,2-*dimethylheptan*-3-*one* **19**-*anti*. The reaction was conducted with the 4,5-dihydroisoxazole **16**-*anti* (43.4 mg, 0.17 mmol) and boric acid (53.0 mg, 0.58 mmol) following the described procedure. Purification of the crude product by recrystallization afforded a white solid (22.5 mg, 52%): m.p. 108–110.5 °C; $\delta_H(CDCl_3)$ 3.94 (1 H, m), 3.52 (1 H, d, *J* 3.2), 2.81 (1 H, dd, *J* 17.7, 2.1), 2.64 (1 H, dd, *J* 17.7, 9.9), 2.14 (1 H, s), 1.16 (9 H, s), 0.98 (3 H, s) and 1.0–2.0 (1 H, br m); ν_{max}(thin film)/cm^{-1} 3437, 2928, 2853, 1698, 1452, 1390, 1360, 1257, 1096 and 941; *m/z* 238 (M^+ − H_2O), 220, 205, 181, 173, 163, 155, 130, 127, 109, 83, 73, 71, 67, 57, 55, 45 and 43 [Found: *m/z* 238.1933. Calc. for $C_{15}H_{26}O_2$: (M − H_2O), 238.1933].

syn-6-*Cyclohexyl*-5,6-*dihydroxy*-2,2-*dimethylheptan*-3-*one* **19**-*syn*. The reaction was performed with the 4,5-dihydroisoxazole **16**-*syn* (58 mg, 0.23 mmol) and boric acid (70.9 mg, 1.15 mmol) under the standard hydrogenation reaction conditions. Purification of the crude product by recrystallization from EtOAc–hexane gave a white solid (31.5 mg, 54%): m.p. 111–113 °C; $\delta_H(CDCl_3)$ 4.04 (1 H, m), 3.57 (1 H, d, *J* 2.8), 2.71 (2 H, m), 2.05 (1 H, s), 1.0–1.9 (11 H, br m), 1.16 (9 H, s) and 0.97 (3 H, s); ν_{max}(thin film)/cm^{-1} 3360, 3127, 2959, 2932, 1603, 1481, 1390, 1223, 1261, 1118 and 996; *m/z* 238 (M − H_2O), 220, 205, 173, 155, 127, 109, 83, 73, 67, 57 and 43 [Found: *m/z* 238.1933. Calc. for $C_{15}H_{26}O_2$: (M − H_2O), 238.1933].

(4,5)-anti-(5,6)-syn-5,6-*Dihydroxy*-2,2-*dimethyl*-4-*methylheptan*-3-*one* **20**-*syn*. The reaction was performed with the 4,5-dihydroisoxazole **8d**-*syn* (26.5 mg, 0.143 mmol) and boric acid (44.3 mg, 0.716 mmol) under the standard hydrogenolysis reaction conditions. Purification of the crude product by recrystallization from EtOAc–hexane gave a white solid (14.3 mg, 54%): m.p. 92–94 °C; $\delta_H(CDCl_3)$ 4.19 (1 H, dd, *J* 13.0, 6.6), 3.65 (1 H, d, *J* 4.9), 2.35 (1 H, m), 1.15 (3 H, d, *J* 7.0), 1.12 (3 H, d, *J* 6.6) and 0.98 (9 H, s); ν_{max}(thin film)/cm^{-1} 3360, 3127, 2959, 2932, 1601, 1481, 1360, 1302, 1262, 1226, 1118, 1034, 981, 922 and 814; *m/z* 188 (M − H_2O), 188, 170, 152, 143, 137, 130, 113, 102, 98, 85, 69, 57 and 43 [Found: *m/z* 170.1306. Calc. for $C_{10}H_{18}O_2$: (M − H_2O), 170.1306].

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