

Reaction of 2-Isoxazolines with Organolithiums in the Presence of Boron Trifluoride

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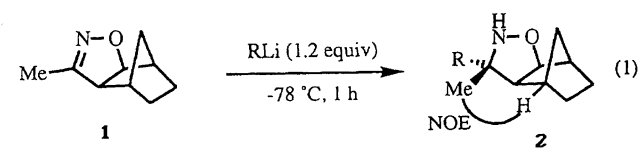
In the presence of boron trifluoride, 3,4,5-tri-, 3,5,5-tri and 3,5-disubstituted 2-isoxazolines underwent nucleophilic addition of alkyl- and aryllithiums to give 3,3,4,5-, 3,3,5,5-, and 3,3,5-substituted isoxazolidines in moderate to good yields. On the other hand, in the case of 3,4,5,5-tetrasubstituted isoxazolines, the addition did not proceed at all but proton abstraction took place to afford a "ate" complex of isoxazoline anions, formation of which was confirmed by deuteration and the aldol reaction with benzaldehyde.

2-Isoxazolines have often been used as key intermediates in a strategy to prepare heteroatom-substituted carbon chains of various natural products. The advantages of the isoxazoline strategy are well-documented in the work reported from various groups.¹⁾ 2-Isoxazolines are prepared by an intra- or an intermolecular cycloaddition of nitrile oxides and olefins in a highly stereoselective manner under mild conditions. The heterocyclic ring system is sufficiently robust to a range of transformations of other parts of the molecules before the isoxazoline is finally converted to the desired functionalities in high efficiency under specific and mild conditions. The isoxazoline ring can be transformed either into β -hydroxy carbonyl compounds without loss of stereochemistry of substituents by reductive cleavage of an oxygen–nitrogen bond or into γ -amino alcohols by reduction of a carbon–nitrogen double bond prior to the oxygen–nitrogen bond cleavage. In the latter case, stereochemical outcome of a newly formed stereogenic center can be successfully predicted based on the results of Jäger's systematic study on reduction of isoxazolines with hydride reagents.²⁾ Contrary to the successful hydride reduction, the carbon–nitrogen bond resists addition of other nucleophiles except when a C-3 substituent on the ring is a good leaving group.³⁾ Abstraction of C-4 ring protons and C-3 substituent protons usually takes place when the isoxazolines are treated with organolithium reagents.⁴⁾ During our study on Lewis acid-assisted reaction of weak and labile perfluoroalkyllithiums,⁵⁾ however, we have found that in the presence of boron trifluoride a certain kind of 2-isoxazolines undergo nucleophilic addition of organolithiums to give 3,3-disubstituted isoxazolines in moderate to good yields.⁶⁾ This reaction is considered as an attractive alternative to gain access to highly branched isoxazolidines and γ -amino alcohols. In this paper, we describe a detailed study on the behavior of 2-isoxazolines toward various organolithiums in the presence of boron trifluoride.

Results and Discussion

In order to find out the optimum reaction conditions as well as the scope and limitations for organolithiums, we first chose isoxazoline **1** as a substrate. The

isoxazoline **1** can easily be prepared from nitroethane and norbornene,⁷⁾ and high diastereoselectivity in the alkylation reaction is anticipated because one face of the isoxazoline ring is completely blocked by the substituent. The best results were obtained when 1.2 equivalents of an organolithium reagent was added to a mixture of the isoxazoline and 1.2 equivalents of boron trifluoride etherate in toluene at -78°C (Eq. 1 and Table 1). This addition order is crucial for success. When isoxazoline **1** was added to a mixture of phenyllithium and boron trifluoride etherate, the reaction occurred very sluggishly to lead mainly to recovery of the starting isoxazoline. All products were obtained as a single diastereomer as expected. The relative stereochemistry of isoxazolidines **2h** was confirmed by strong cross peaks between bridge head and methyl protons in its NOESY spectra. In other cases, we believed the relative stereochemistry as similar to **2h**. In ^{13}C NMR spectra of isoxazolidines **2**, some signals suffered line broadening due

Table 1. Nucleophilic Addition of Organolithiums to Isoxazoline **1**


Entry	RLi ^{a)}	Solvent	BF ₃ ·OEt ₂ /equiv	Yield/% ^{b)}
1	PhLi	Ether	1.2	2a 38
2	PhLi	CH ₂ Cl ₂	1.2	2a 92
3	PhLi	Toluene	1.2	2a 89
4	PhLi	Toluene	None	2a 70
5	MeLi	CH ₂ Cl ₂	1.2	2b 91
6	MeLi	CH ₂ Cl ₂	None	—
7	BuLi	CH ₂ Cl ₂	1.2	2c 14
8	<i>t</i> -BuLi	Toluene	1.2	—
9	CH ₂ =CHLi	Toluene	1.2	2d 76
10	CH ₂ =CHCH ₂ Li	Toluene	1.2	2e 82
11	2-Furyl-Li	Toluene	1.2	2f 99
12	2-Pyridyl-Li	Toluene	1.2	2g 20
13	C ₆ F ₁₃ Li	Ether	1.2	2h 91
14	PhC≡CLi	Toluene	1.2	—

a) As for preparation of organolithium, refer to the experimental. b) Isolated yield.

to the ring flipping.⁸⁾ As shown in Table 1, an increase in the basicity of organolithiums decreases the yields of isoxazolidines. In the case of phenyllithium, the addition occurred even in the absence of boron trifluoride etherate (Entry 4), although the yield was rather low. The reaction with *t*-butyllithium or lithium phenylacetylide did not take place and the isoxazoline was recovered (Entries 8 and 14). Other organometallic reagents such as phenylmagnesium bromide and lithium dimethylcuprate failed to react with **1** under the similar conditions.

Next, we conducted the reaction with variously substituted isoxazolines (Eq. 2 and Table 2). *cis*-4,5-Di-substituted isoxazolines **3** reacted smoothly with phenyllithium (Entries 1, 3, and 5). On the other hand, no formation of isoxazolidines was observed in the reaction of 3,4,5,5-tetrasubstituted isoxazolines (Entries 6 and 9), while the reaction of 3,5,5- and *trans*-3,4,5-trisubstituted isoxazolines with phenyllithium proceeded moderately (Entries 7 and 8). In the last case, the addition of a phenyl group took place from both π -faces to give a diastereomeric mixture of isoxazolidines (**4g/4g'**=73/27). These results suggest that there is a significant influence not only from a 4-substituent but also from a 5-substituent upon the facial selectivity. It should be noted that the isoxazolines **4a** and **2a** were diastereomeric to each other. This fact also supports the complete stereoselectivity in the reaction of **1** and **3a**.

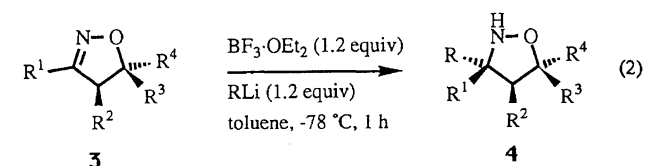
Diastereoselectivity of phenylation was then examined by using isoxazolines **5** with various substituents at

the ring 5 carbon (Eq. 3 and Table 3). When the 5-substituent has no oxygen atom, the addition occurred from the opposite side to the 5-substituents in high stereoselective manner (>90 : 10) irrespective of the presence of boron trifluoride etherate (Entries 1–5). Interesting results were obtained in the reaction of isoxazolines with ethoxymethyl and methoxyethoxymethyl group (**5e** and **5f**, Entries 6–12). In the presence of boron trifluoride etherate, phenylation of these compounds occurred almost nonstereoselectively, while in the absence of boron trifluoride, phenyllithium preferentially attacked from the opposite side of the 5-substituents, although the yields were very poor. The attack of phenyllithium from the same side as the 5-substituents reached a maximum in the presence of nearly one equivalent of boron trifluoride etherate.

The relative stereochemistry of the isoxazolidines of **6e** and **7e** was confirmed by transformation into cyclic urethanes **9** and **10** (Scheme 1). Clear correlation signals between the 4-methyl and H⁶ were observed only in the NOESY spectra of **10**. Moreover, H⁶ proton signals of **9** show a marked high field shift due to an anisotropic effect of the axial phenyl group. All H⁵ protons of isoxazolidines **6** appear at high field relative to the diastereomer **7**, which is very useful for determination of the relative stereochemistry.

Before discussing the transition states of this reaction, it is pertinent to mention what happened when the starting isoxazolines were recovered. When the reactions of **3d** with phenyllithium and of **1** with *t*-butyllithium were quenched with deuterium oxide, deuteration on the 3-methyl group took place. Interestingly,

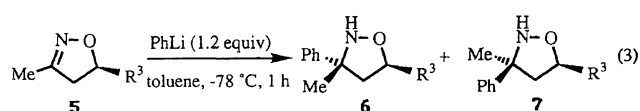
Table 2. Nucleophilic Addition of Organolithiums to Isoxazolines **3**



Entry	Isoxazoline 3				RLi ^{a)}	Yield ^{d)} %
	R ¹	R ²	R ³	R ⁴		
1	3a	Ph		H	PhLi	4a 80
2	3a				MeLi	4b 7
3 ^{c)}	3b	Me	–CH ₂ CH ₂ O–	H	PhLi	4c 94
4	3b				C ₆ F ₁₃ Li	4d 76
5	3c	Me	–CH ₂ OCH ₂ –	H	PhLi	4e 89
6	3d	Me		Me	PhLi	—
7	3e	Me	H	Me	PhLi	4f 31
8	3f	Me	Me	H	PhLi	4g/4g' 33 ^{d)}
9	3g	Me	Me	Me	PhLi	—

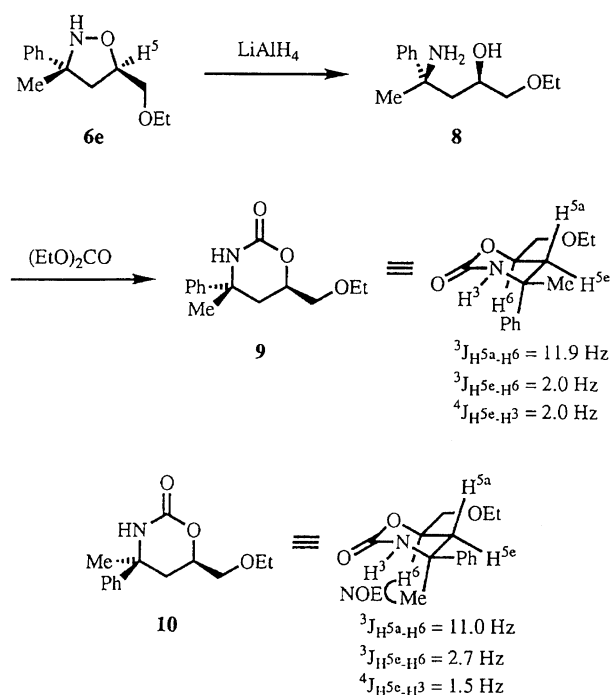
a) As for preparation of organolithiums, refer to the experimental. b) Isolated yield. c) The reaction was carried out in CH₂Cl₂. d) Diastereomer mixture (**4g** : **4g'**=73 : 27; determined by NMR).

Table 3. Nucleophilic Addition of Phenyllithium to 3,5-Disubstituted 2-Isoxazolines **5**



Entry	Isoxazoline		BF ₃ ·OEt ₂ equiv	Yield ^{a)} %	Ratio ^{b)} 6/7
	5	R ³			
1	5a	Ph	1.2	74	95/5
2	5b	CH ₂ Ph	1.2	70	90/10 ^{c)}
3	5c	CH ₂ SiMe ₂ Ph	1.2	74	>95/5 ^{c)}
4	5d	Bu	1.2	72	92/8 ^{c)}
5	5d		None	58	92/8 ^{c)}
6	5e	CH ₂ OEt	5	79	60/40
7	5e		1.2	72	55/45
8	5e		None	19	89/11
9	5f	CH ₂ OCH ₂ CH ₂ OMe	2.4	48	52/48
10	5f		1.2	41	41/59
11	5f		0.9	28	37/63
12	5f		None	4	61/39

a) Combined yield of **6** and **7**. b) The ratio was determined by GC analysis of the reaction mixture. c) The ratio was estimated by ¹H NMR analysis of the reaction mixture.



Scheme 1.

no deuteration of **3d** was observed in the absence of boron trifluoride etherate (Entry 4). Similarly, aldol adducts were obtained when the reaction was quenched with benzaldehyde, while no alkylation was observed by using either benzyl bromide or methyl iodide. Unfortunately, the relative stereochemistry of the aldol products could not be determined. This low reactivity toward electrophiles clearly show the formation of "ate" complexes.⁹⁾ The reaction of 3,5-disubstituted isoxazolines (**5d** and **5e**) with benzaldehyde is worthy of mention. In the reaction of **5d** with benzaldehyde using *t*-butyllithium, hydroxybenzylation of the 3-methyl group was preferred over that at the ring 4-position in the presence or absence of boron trifluoride etherate. On the other hand, the reaction preferentially took place at the ring 4-carbon of **5e** in the absence of boron trifluoride etherate, while poor regioselectivity was observed in the presence of boron trifluoride etherate (Table 4). These selectivities were not affected by elongation of the treatment period with the lithium reagent.

Mechanistic Consideration

We may think the reaction of **5e** with phenyllithium as a representative case (Scheme 2). Boron trifluoride is well-known to have only one coordination site. Thus, the Lewis acid can not chelate to both side chain oxygen atoms and isoxazoline ring heteroatoms of **5e**. However, the coordination of boron trifluoride to the isoxazoline heteroatoms from the same side of the 5-substituent would be favored because of spatial proximity. Then, phenyllithium would approach to the imino carbon from the same side as it forms a complex with boron trifluo-

ride. This proposal may be supported by the behavior of **5e** in treatment with *t*-butyllithium: In this case, boron trifluoride prevented the lithium reagent from coordinating to the side-chain oxygen atom and thus proton abstraction occurred at the 3-methyl group, preferentially.

Experimental

Distillation was carried out by using a Kugelrohr apparatus and the bath temperatures were reported as bp. Melting points are uncorrected. Unless otherwise specified, NMR spectra were obtained with a GSX-270 spectrometer at ambient temperature by using CDCl₃ as the solvent, tetramethylsilane as an internal standard for ¹H and ¹³C, and CFC1₃ as an internal standard for ¹⁹F. Mass spectra were measured with a Hitachi M80B-LCAPI spectrometer under the following ionizing conditions: EI (electron impact, 20 eV) and CI (chemical ionization, 70 eV, methane as CI gas). Column chromatography was carried out using Wakogel C-200. Ether and THF were distilled from sodium benzophenone ketyl. Other commercially available materials were used without further purification. All isoxazolines except for **3a** were prepared by the Mukaiyama-Hoshino method⁷⁾ using 1.2 to 10 equivalents of olefins in toluene. In the cases of **3e**, **3f**, and **3g**, the reaction was carried out in a stainless steel autoclave. Isoxazoline **3a** was prepared from benzaldehyde oxime by treatment with NCS followed by norbornene and triethylamine. All isoxazolines were purified by column chromatography on silica gel (hexane/CH₂Cl₂ or toluene) followed by either recrystallization or distillation. The regioisomeric purity of these isoxazolines was confirmed to be greater than 95% by NMR analysis. Butyllithium in hexane, *t*-butyllithium in pentane, methylolithium-lithium bromide in ether, and phenyllithium in ether-benzene were purchased from Aldrich Chem. Co. Other organolithiums were prepared according to the literature procedure.¹⁰⁾ All lithium reagents were titrated by the diphenylacetic acid¹¹⁾ or the 2,2'-biquinolyl¹²⁾ method prior to use.

General Procedure for the Reaction of Isoxazolines with Organolithiums: To a stirred solution of an isoxazoline (1 mmol) and BF₃·OEt₂ (0.15 ml, 1.2 mmol) in 10 ml of a solvent was added a titrated solution of organolithiums (1.2 mmol) at -78 °C over 5 min. After the mixture was stirred for 1 h at the same temperature, saturated aqueous NaHCO₃ (20 ml) and ether (20 ml) were added. In the case of D₂O or PhCHO quenching, 0.1 ml of D₂O or 0.12 ml of PhCHO (1.2 mmol) was added before the aqueous quenching. The organic phase was separated and the aqueous phase was extracted with ether (2×10 ml). The combined ethereal extracts were washed with brine (20 ml), dried over Na₂SO₄, and concentrated in vacuo. The residue was analyzed by GC (OV-1, 3 m) and ¹H NMR, and then was chromatographed on silica gel (hexane/CH₂Cl₂ or ether/CH₂Cl₂). In the case of perfluorohexyllithium, the reagent was generated in situ by adding 1.2 mmol of MeLi-LiBr in ether to a mixture of an isoxazoline (1 mmol), BF₃·OEt₂ (1.2 mmol), and perfluorohexyl iodide (535 mg, 1.2 mmol) at the same temperature.

(3*R, 3*aS**, 4*S**, 7*R**, 7*aS**)-3-Methyl-3-phenylperhydro-4,7-methano-1,2-benzisoxazole (2a):** Colorless oil, bp. 120 °C/0.3 mmHg (1 mmHg ≈ 133.322 Pa); ¹H NMR

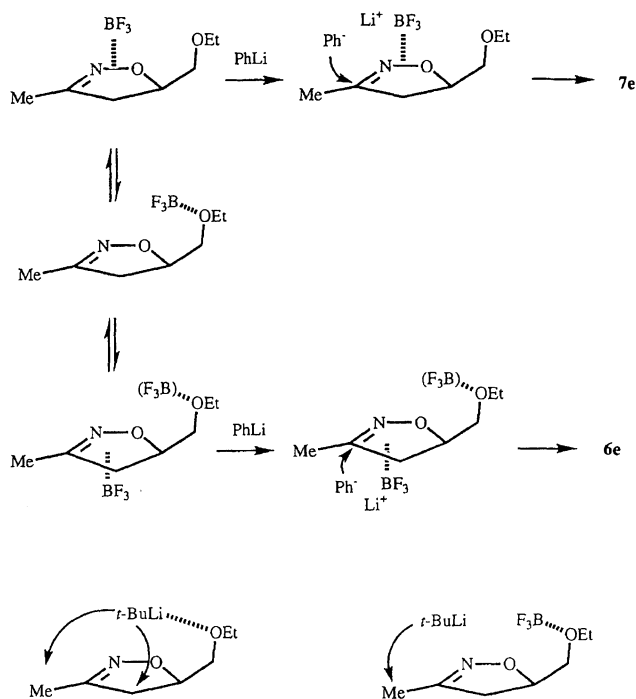
Table 4. Proton Abstraction from 2-Isoxazolines

1) $\text{BF}_3 \cdot \text{OEt}_2$, RLi , toluene, -78°C
 2) D_2O or PhCHO , $-78^\circ\text{C} \rightarrow \text{rt}$

11 $\text{R}' = \text{D}$ or Ph(HO)CH **12**

Entry	Isoxazoline	$\text{RLi}^{\text{a)}$	$\text{BF}_3 \cdot \text{OEt}_2$	Electrophile	Yield ^{b)}		Ratio ^{c)} 11/12
		equiv	equiv		%		
1	1	<i>t</i> -BuLi (1.2)	1.2	D_2O	11a+12a	53	>20/1
2	1	<i>t</i> -BuLi (1.2)	1.2	PhCHO	11b+12b	72	>50 ^{d)} /1
3	3d	PhLi (1.2)	1.2	D_2O	11c+12c	24	>20/1
4	3d	PhLi (1.2)	0	D_2O	11c+12c	0	—
5	3d	PhLi (1.2)	2.0	D_2O	11c+12c	14	>20/1
6	3d	PhLi (1.2)	2.0	D_2O	11c+12c	62	>20/1
7	3d	PhLi (1.2)	1.2	PhCHO	11d+12d	86	>50 ^{d)} /1
8	5d	<i>t</i> -BuLi (1.2)	1.2	PhCHO	11e+12e	68	79 ^{e)} /21 ^{f)}
9	5d	<i>t</i> -BuLi (1.2)	0	PhCHO	11e+12e	65	72 ^{e)} /28 ^{f)}
10	5e	<i>t</i> -BuLi (1.2)	1.2	PhCHO	11f+12f	65	56 ^{e)} /44 ^{f)}
11	5e	<i>t</i> -BuLi (1.2)	0	PhCHO	11f+12f	50	21 ^{e)} /79 ^{f)}

a) As for preparation of organolithiums, refer to the experimental. b) Isolated yield. The yield of deuteration was calculated by GC-MS analysis of the recovered isoxazoline. c) The ratio was estimated by NMR analysis of the reaction mixture. d) The diastereomer ratio was 7:3. e) The diastereomer ratio was 6:4. f) A mixture of two diastereomers (ratio=6:4).



Scheme 2.

$\delta=0.94$ (1H, m), 1.11 (1H, m), 1.21 (1H, m), 1.47 (3H, s), 1.50 (2H, m), 1.70 (1H, br d, $J=10.7$ Hz), 2.48 (3H, m), 3.99 (1H, d, $J=6.4$ Hz), 5.36 (1H, br), 7.22 (1H, m), 7.33 (2H, m), and 7.44 (2H, m); ^{13}C NMR $\delta=23.07$, 23.1 (br), 28.88, 34.80, 36.91, 40.81 (br), 62.46, 69.01 (br), 90.28 (br), 125.25, 126.46, 128.27, and 147.72; IR (neat) 3260m, 2960s, 2876s, 1602m, 1024s, 766s, and 702s cm^{-1} ; MS (CI) m/z (rel intensity) 230 (M^++1 , 88), 229 (M^+ , 61), 214 (43), 152 (63), and 135 (100). Found: C, 78.46; H, 8.63; N, 6.16%. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}$: C, 78.56; H, 8.35; N, 6.11%.

(3a^{S*}, 4S*, 7R*, 7aS*)-3,3-Dimethylperhydro-4,7-methano-1,2-benzisoxazole (2b): Colorless oil, bp 60 °C/0.3 mmHg; ^1H NMR $\delta=0.90$ —1.05 (2H, m), 1.12 (1H, m), 1.18 (3H, s), 1.21 (3H, m), 1.43 (2H, m), 1.55 (1H, d, $J=10.7$ Hz), 1.93 (1H, d, $J=6.4$ Hz), 2.26 (1H, m), 2.43 (1H, m), 4.06 (1H, d, $J=6.4$ Hz), and 4.66 (1H, br s); ^{13}C NMR $\delta=20.79$ (br), 22.97, 28.62 (br), 28.65, 34.19, 36.38, 40.66 (br), 61.59, 62.81, and 89.98 (br); IR (neat) 3196m, 2964vs, 2872s, and 982s cm^{-1} ; MS (CI) m/z (rel intensity) 168 (M^++1 , 38), 167 (M^+ , 17), 152 (42), 135 (10), 93 (25), and 74 (100). Found: C, 71.52; H, 10.49; N, 8.58%. Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}$: C, 71.81; H, 10.24; N, 8.37%.

(3S*, 3aS*, 4S*, 7R*, 7aS*)-3-Butyl-3-methylperhydro-4,7-methano-1,2-benzisoxazole (2c): Colorless oil, bp 100 °C/0.4 mmHg; ^1H NMR $\delta=0.91$ (3H, t, $J=6.7$ Hz), 0.90—1.15 (3H, m), 1.12 (3H, s), 1.2—1.6 (9H, m), 1.91 (1H, m), 2.19 (1H, m), 2.41 (1H, m), 3.98 (1H, d, $J=6.7$ Hz), and 4.30 (1H, br); ^{13}C NMR $\delta=13.99$, 19.10, 23.19, 23.24, 26.98, 28.83, 34.43, 36.88, 40.29, 41.27, 60.51, 66.04, and 90.49; IR (neat) 3202m, 2956vs, 2872s, 1466m, 1378m, and 1028 cm^{-1} ; MS (CI) m/z (rel intensity) 210 (M^++1 , 44), 208 (M^+-1 , 13), 194 (7), 152 (100), and 116 (70). Found m/z 210.1857. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}$: MH^+ , 210.1856.

(3S*, 3aS*, 4S*, 7R*, 7aS*)-3-Methyl-3-vinylperhydro-4,7-methano-1,2-benzisoxazole (2d): Colorless oil, bp 70 °C/0.5 mmHg; ^1H NMR $\delta=0.9$ —1.2 (3H, m), 1.26 (3H, s), 1.46 (2H, m), 1.62 (1H, br d, $J=10.4$ Hz), 2.12 (1H, m), 2.28 (1H, m), 2.44 (1H, m), 4.03 (2H, d, $J=6.4$ Hz), 5.00 (1H, br), 5.05 (1H, dd, $J=10.7$ and 0.9 Hz), 5.25 (1H, dd, $J=17.4$ and 0.9 Hz), and 5.87 (1H, dd, $J=17.4$ and 10.7 Hz); ^{13}C NMR $\delta=18.89$, 22.96, 28.75, 34.51, 36.25, 40.65, 60.57, 66.65, 90.02, 112.44, and 143.39; IR (neat) 3240m, 2960s, 2872s, 1640s, and 996s cm^{-1} ; MS (CI) m/z (rel intensity) 180 (M^++1 , 100), 179 (M^+ , 34), 164 (21), 152 (25), and 86 (96). Found: C, 73.39; H, 9.69; N, 7.71%. Calcd for $\text{C}_{11}\text{H}_{17}\text{NO}$: C, 73.70; H, 9.56; N, 7.81%.

(3R*, 3aS*, 4S*, 7R*, 7aS*)-3-Allyl-3-methylperhy-

dro-4,7-methano-1,2-benzisoxazole (2e): Colorless oil, bp 80 °C/0.5 mmHg; $^1\text{H NMR}$ δ =1.2–0.9 (3H, m), 1.14 (3H, s), 1.44 (2H, m), 1.56 (1H, br d, J =10.7 Hz), 2.00 (1H, br d, J =6.7 Hz), 2.1–2.3 (3H, m), 2.42 (1H, m), 4.00 (1H, d, J =6.7 Hz), 4.80 (1H, br s), 5.05–5.13 (2H, m), and 5.84 (1H, m); $^{13}\text{C NMR}$ δ =18.85, 22.98, 28.54, 34.42, 36.44, 40.67, 45.45, 59.42, 65.22, 89.80, 118.04, and 113.92; IR (neat) 3244m, 2960s, 2876s, and 1640m cm^{-1} ; MS (CI) m/z (rel intensity) 194 (M^+ +1, 36), 192 (M^+ -1, 6), 152 (100), and 100 (36). Found: C, 74.34; H, 9.95; N, 7.11%. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}$: C, 74.57; H, 9.91; N, 7.25%.

(3R*,3aS*,4S*,7R*,7aS*)-3-(2-Furyl)-3-methylperhydro-4,7-methano-1,2-benzisoxazole (2f): Colorless oil, bp 120 °C/0.3 mmHg; $^1\text{H NMR}$ δ =0.9–1.2 (3H, m), 1.47 (2H, m), 1.51 (3H, s), 1.71 (1H, m), 2.31 (1H, m), 2.46 (1H, m), 2.54 (1H, br d, J =6.4 Hz), 4.13 (1H, d, J =6.4 Hz), 5.48 (1H, br), 6.25 (1H, dd, J =3.4 and 0.9 Hz), 6.30 (1H, dd, J =3.4 and 1.8 Hz), and 7.34 (1H, dd, J =1.8 and 0.9 Hz); $^{13}\text{C NMR}$ δ =19.15 (br), 22.86, 28.66, 36.27, 37.78, 39.85 (br), 59.86, 65.53, 90.98 (br), 105.48 (br), 110.09, 141.52, and 157.46 (br); IR (neat) 3220m, 2960s, 2876s, and 1504 cm^{-1} ; MS (CI) m/z (rel intensity) 220 (M^+ +1, 3), 219 (M^+ , 17), 204 (31), and 125 (100). Found: C, 70.87; H, 7.81; N, 6.19%. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2$: C, 71.21; H, 7.81; N, 6.39%.

(3R*,3aS*,4S*,7R*,7aS*)-3-Methyl-3-(2-pyridyl)perhydro-4,7-methano-1,2-benzisoxazole (2g): Colorless oil, bp 120 °C/0.3 mmHg; $^1\text{H NMR}$ δ =0.9–1.5 (5H, m), 1.52 (3H, s), 1.50 (2H, m), 2.48 (3H, m), 2.71 (1H, m), 4.01 (1H, d, J =6.7 Hz), 5.80 (1H, br), 7.14 (1H, m), 7.64 (2H, m), and 8.55 (1H, m); $^{13}\text{C NMR}$ δ =20.21, 23.07, 28.71, 34.94, 36.60, 41.35 (br), 61.36 (br), 70.05, 89.80, 119.94, 121.61, 136.66, 148.63, and 165.28; IR (neat) 3260s, 2964vs, 1590s, 1472s, and 1436s cm^{-1} ; MS (EI) m/z (rel intensity) 230 (M^+ , 20), 215 (56), 152 (100), 136 (18), 133 (32), 80 (30), and 79 (37). Found: m/z 230.1421. Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}$: M^+ , 230.1418.

(3R*,3aS*,4S*,7R*,7aS*)-3-Methyl-3-(perfluorohexyl)perhydro-4,7-methano-1,2-benzisoxazole (2h): Colorless needles, mp 93–94 °C; $^1\text{H NMR}$ δ =1.03 (1H, m), 1.06 (1H, m), 1.10 (1H, m), 1.41 (3H, s), 1.52 (3H, m), 2.34 (1H, m), 2.50 (1H, m), 2.53 (1H, d, J =6.4 Hz), 4.08 (1H, d, J =6.4 Hz), and 5.33 (1H, br); $^{13}\text{C NMR}$ δ =22.81, 28.28, 34.61, 36.28, 40.69, 56.02, 70.52, (ddt, J =23, 19 and 2 Hz), 89.96, and 100–125 (6C); $^{19}\text{F NMR}$ δ =-81.29 (3F, tt, J =10 and 2 Hz), -117.35 (1F, dm, J =297 Hz), -118.2 (1F, m), -118.5 (1F, m), -119.47 (1F, dm, J =297 Hz), -122.31 (2F, m), -123.15 (2F, m), and -126.58 (2F, m); IR (KBr) 3264m, 2968m, 1244vs, 1200vs, and 1110vs cm^{-1} ; MS (CI) m/z (rel intensity) 472 (M^+ +1, 91), 452 (15), 406 (3), 378 (5), 364 (3), 342 (4), and 152 (100). Found: C, 38.15; H, 3.05; N, 2.98%. Calcd for $\text{C}_{15}\text{H}_{14}\text{F}_{13}\text{NO}$: C, 38.23; H, 2.99; N, 2.97%.

(3aS*,4S*,7R*,7aS*)-3,3-Diphenylperhydro-4,7-methano-1,2-benzisoxazole (4a): Colorless crystals, mp 161–163 °C; $^1\text{H NMR}$ δ =0.66 (1H, br d, J =9.9 Hz), 1.02 (2H, m), 1.18 (1H, m), 1.47 (2H, m), 2.19 (1H, m), 2.36 (1H, m), 2.99 (1H, d, J =6.7 Hz), 4.11 (1H, d, J =6.7 Hz), 5.44 (1H, br s), and 7.1–7.5 (10H, m); $^{13}\text{C NMR}$ δ =23.70, 28.71, 32.81 (br), 38.23, 38.69 (br), 76.00, 92.84 (br), 126.00, 127.01, 127.22, 127.37, 128.03, 128.46, 142.62 (br), and 144.92 (br) (One carbon around 20 ppm cannot be seen.); IR (KBr) 3196m, 2952s, 2908s, 1495s, 756s, and

708s cm^{-1} ; MS (CI) m/z (rel intensity) 292 (M^+ +1, 100), 214 (78), 197 (71), 182 (32), and 180 (37). Found: C, 82.44; H, 7.29; N, 4.61%. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}$: C, 82.44; H, 7.26; N, 4.81%.

(3S*,3aS*,4S*,7R*,7aS*)-3-Methyl-3-phenylperhydro-4,7-methano-1,2-benzisoxazole (4b): Colorless oil, bp 120 °C/0.3 mmHg; $^1\text{H NMR}$ δ =0.65 (1H, br d, J =10.4 Hz), 1.01 (3H, m), 1.38 (2H, m), 1.55 (3H, s), 1.99 (1H, m), 2.27 (1H, d, J =6.4 Hz), 2.34 (1H, m), 4.15 (1H, d, J =6.4 Hz), 5.19 (1H, br), 7.22 (1H, m), 7.32 (2H, m), and 7.42 (2H, m); $^{13}\text{C NMR}$ δ =23.46, 28.65, 29.24 (br), 32.86, 37.86, 39.75 (br), 63.50, 69.25, 91.26, 126.27, 126.81, 127.70, and 143.06; IR (neat) 3228s, 2976s, 2876s, 1602m, 1106s, 754s, and 704 cm^{-1} ; MS (CI) m/z (rel intensity) 230 (M^+ +1, 78), 229 (M^+ , 20), 214 (100), 197 (11), 195 (17), 152 (42), 136 (58), and 120 (51).

(3R*,3aS*,6aR*)-3-Methyl-3-phenylperhydrofuro[3,4-d]isoxazole (4c): Colorless needles, mp 127 °C; $^1\text{H NMR}$ δ =1.38 (3H, s), 2.14 (2H, m), 3.35 (1H, dt, J =8.2 and 5.2 Hz), 3.88 (1H, m), 4.04 (1H, m), 5.62 (1H, d, J =5.2 Hz), 5.72 (1H, br), 7.19 (1H, m), 7.31 (2H, m), and 7.53 (2H, m); $^{13}\text{C NMR}$ δ =21.68, 27.17, 57.14, 67.68, 69.65, 81.23, 125.34, 126.34, 127.98, and 146.23; IR (KBr) 3248s, 2976s, 2956s, 1494s, 1446s, 1376s, 1104s, 1066vs, 972vs, 766s, and 708s cm^{-1} ; MS (CI) m/z (rel intensity) 206 (M^+ +1, 14), 205 (M^+ , 5), 188 (11), 173 (48), 145 (95), and 136 (100). Found: C, 69.83; H, 7.32; N, 6.76%. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$: C, 70.22; H, 7.37; N, 6.82%.

(3R*,3aS*,6aR*)-3-Methyl-3-(perfluorohexyl)perhydrofuro[3,4-d]isoxazole (4d): Colorless needles, mp 76 °C; $^1\text{H NMR}$ δ =1.40 (3H, s), 2.14 (2H, m), 3.42 (1H, m), 3.90–4.07 (2H, m), 5.65 (1H, br), and 5.86 (1H, d, J =4.9 Hz); $^{13}\text{C NMR}$ δ =13.72 (m), 26.94, 51.51, 69.47, (ddt, J =23, 22, and 2 Hz), 69.83, 100–125 (6C), and 110.96; $^{19}\text{F NMR}$ δ =-81.38 (3F, tt, J =10 and 2 Hz), -116.50 (1F, dm, J =287 Hz), -117.24 (1F, dm, J =287 Hz), -118.41 (1F, dm, J =298 Hz), -120.29 (1F, dm, J =298 Hz), -122.21 (2F, m), -123.13 (2F, m), and -126.62 (2F, m); IR (KBr) 3232s, 2976m, 1246vs, 1202vs, 1178s, 1146vs, and 1090s cm^{-1} ; MS (CI) m/z (rel intensity) 448 (M^+ +1, 40), 406 (11), 378 (16), 128 (48), and 71 (100). Found: C, 32.10; H, 2.21; N, 3.25%. Calcd for $\text{C}_{12}\text{H}_{10}\text{F}_{13}\text{NO}_2$: C, 32.23; H, 2.25; N, 3.13%.

(3R*,3aR*,6aR*)-3-Methyl-3-phenylperhydrofuro[3,4-d]isoxazole (4e): Colorless needles, mp 159–160 °C; $^1\text{H NMR}$ δ =1.47 (3H, s), 3.37 (1H, td, J =6.7 and 1.8 Hz), 3.59 (1H, dd, J =10.7 and 4.0 Hz), 3.66 (1H, dd, J =10.4 and 6.7 Hz), 4.14 (1H, d, J =10.7 Hz), 4.30 (1H, dd, J =10.4 and 1.8 Hz), 4.70 (1H, dd, J =6.7 and 4.0 Hz), 5.72 (1H, br), 7.24 (1H, m), 7.34 (2H, m), and 7.47 (2H, m); $^{13}\text{C NMR}$ δ =21.85 (br), 58.04, 68.85 (br), 69.67, 76.02 (br), 86.11 (br), 125.40, 126.64, 128.28, and 145.90 (br); IR (KBr) 3224vs, 2976s, 2868s, 1498s, 1448vs, 1328s, 1116vs, 1084vs, 1068s, 916vs, and 706vs cm^{-1} ; MS (CI) m/z (rel intensity) 206 (M^+ +1, 72), 190 (10), 174 (6), 158 (7), 146 (100), 136 (42), 135 (29), 128 (32), and 120 (44). Found: C, 69.96; H, 7.43; N, 6.85%. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$: C, 70.22; H, 7.37; N, 6.82%.

3,5,5-Trimethyl-3-phenylisoxazolidine (4f): Colorless needles, mp 51–53 °C (bp 70 °C/0.15 mmHg); $^1\text{H NMR}$ δ =1.14 (3H, s), 1.41 (3H, s), 1.52 (3H, s), 2.20 (1H, d, J =12.2 Hz), 2.44 (1H, br d, J =12.2 Hz), 5.64 (1H, br) and 7.2–7.5 (5H, m); $^{13}\text{C NMR}$ δ =27.32, 27.85, 28.77, 55.56,

68.53, 84.93, 125.51, 126.69, 128.36, and 145.81; IR (neat) 3208s, 2972s, 1600s, 1492s, 1372s, 1296s, 1110s, 766s, and 700vs cm^{-1} ; MS (EI) m/z (rel intensity), 191 (M^+ , 43), 176 (80), 159 (22), 136 (45), 135 (57), 134 (100), and 117 (26). Found: m/z 191.1305. Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}$: M^+ , 191.1309.

(3*R,4*S**,5*R**)- and (3*S**,4*S**,5*R**)-3,4,5-Trimethyl-3-phenylisoxazolidine (4*g* and 4*g'*):** Colorless oil, bp 80 °C/0.2 mmHg; ^1H NMR 4*g*: δ =1.17 (3H, d, J =7.0 Hz), 1.25 (3H, d, J =6.1 Hz), 1.39 (3H, s), 2.24 (1H, dq, J =8.2 and 7.0 Hz), 3.74 (1H, m), 5.5 (1H br), and 7.2—7.5 (5H, m); 4*g'*: δ =0.76 (3H, d, J =7.0 Hz), 1.29 (3H, d, J =6.1 Hz), 1.55 (3H, s), 1.90 (1H, m), 3.55 (1H, dq, J =9.5 and 6.1 Hz), 5.5 (1H br), and 7.2—7.5 (5H, m); IR (neat) 3432vs, 3240s, 2972s, 766s and 704s cm^{-1} ; MS (EI) m/z (rel intensity) 191 (M^+ , 20), 176 (60), 135 (94), 134 (100), 117 (17), and 114 (14). Found: C, 75.02; H, 9.09; N, 7.22%. Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}$: C, 75.35; H, 8.96; N, 7.32%.

(3*R,5*R**)-3-Methyl-3,5-diphenylisoxazolidine (6*a*):** Colorless crystals, mp 63—35 °C; ^1H NMR δ =1.54 (3H, s), 2.26 (1H, dd, J =12.2 and 8.8 Hz), 3.03 (1H, dd, J =12.2 and 7.9 Hz), 4.91 (1H, br dd, J =8.8 and 7.9 Hz), 5.45 (1H br), and 7.2—7.6 (10H, m); ^{13}C NMR δ =27.51 (br), 51.42, 67.68, 83.45, 125.30, 125.66, 126.68, 127.33, 128.16, 128.22, 140.71, and 144.38; IR (KBr) 3210s, 3056s, 3024s, 2974s, 770vs, and 704vs cm^{-1} ; MS (CI) m/z (rel intensity) 240 (M^+ +1, 5), 238 (M^+ −1, 7), 223 (12), 207 (20), 136 (61), 135 (54), 134 (33), and 122 (100). Found: C, 80.38; H, 7.24; N, 5.88%. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}$: C, 80.30; H, 7.16; N, 5.84%.

(3*R,5*R**)- and (3*S**,5*R**)-5-Benzyl-3-methyl-3-phenylisoxazolidine (6*b* and 7*b*):** Colorless oil, bp 140 °C/0.5 mmHg; ^1H NMR 6*b*: δ =1.45 (3H, s), 2.00 (1H, dd, J =12.2 and 8.2 Hz), 2.66 (1H, dd, J =12.2 and 7.6 Hz), 2.89 (2H, m), 4.22 (1H, m), 5.04 (1H, br), and 7.1—7.5 (10H, m); 7*b* (typical signals): δ =1.47 (3H, s), 2.24 (1H, dd, J =12.2 and 7.3 Hz), 2.45 (1H, dd, J =12.2 and 7.6 Hz), and 4.47 (1H, m); ^{13}C NMR 6*b* δ =27.98 (br), 40.74, 48.27, 67.48, 83.00 (br), 125.47, 126.44, 126.83, 128.33, 128.40, 129.35, 137.69, and 144.69; 7*b* (typical signals): δ =27.70, 40.63, 67.38, 83.32, 125.50, 126.36, 128.35, 129.12, and 137.87; IR (neat) 3200s, 3060s, 3028s, 2972s, 2928s, 754vs, and 704vs cm^{-1} ; MS (CI) m/z (rel intensity) 254 (M^+ +1, 5), 253 (M^+ , 11), 238 (12), 176 (11), 145 (21), 136 (100), 134 (86), 120 (45). Found: C, 80.46; H, 7.48; N, 5.33%. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}$: C, 80.58; H, 7.56; N, 5.53%.

(3*R,5*R**)- and (3*S**,5*R**)-5-[(Dimethylphenylsilyl)methyl]-3-methyl-3-phenylisoxazolidine (6*c* and 7*c*):** Colorless oil, bp 165 °C/0.4 mmHg; ^1H NMR 6*c*: δ =0.33 (6H, s), 1.20 (1H, dd, J =14.1 and 8.9 Hz), 1.43 (1H, m), 1.47 (3H, s), 1.76 (1H, dd, J =11.9 and 7.9 Hz), 2.58 (1H, dd, J =11.9 and 7.6 Hz), 4.02 (1H, m), 5.0 (1H, br), and 7.1—7.5 (10H, m); 7*c* (typical signals): δ =0.30 (3H, s), 0.31 (3H, s), 1.00 (1H, dd, J =14.0 and 9.0 Hz), 1.25 (1H, dd, J =14.0 and 8.8 Hz), 1.43 (3H, s), 2.00 (1H, dd, J =12.2 and 7.9 Hz), 2.39 (1H, dd, J =12.2 and 7.3 Hz), and 4.26 (1H, m); ^{13}C NMR 6*c*: δ =−2.48, −2.27, 22.99, 29.30 (br), 50.81 (br), 68.07 (br), 81.36, 125.39, 126.84, 127.80, 128.37, 129.06, 133.44, 138.31, and 144.96; IR (neat) 3202s, 3064s, 2964s, 1250vs, 836vs, 764s, 730s, and 702s cm^{-1} ; MS (CI) m/z (rel intensity) 312 (M^+ +1, 3), 311 (M^+ , 1), 294 (4), 270 (6), 192 (26), 178 (25), 177 (17), 136 (64), 135 (76), 120 (86), and 116 (100). Found: C, 73.17; H, 7.86; N, 4.23%. Calcd for $\text{C}_{19}\text{H}_{25}\text{NOSi}$: C, 73.25; H, 8.09; N, 4.50%.

(3*R,5*S**)- and (3*S**,5*S**)-5-Butyl-3-methyl-3-phenylisoxazolidine (6*d* and 7*d*):** Colorless oil, bp 110 °C/0.5 mmHg; ^1H NMR 6*d*: δ =0.90 (3H, t, J =7.0 Hz), 1.2—1.45 (4H, m), 1.45—1.80 (2H, m), 1.52 (3H, s), 1.90 (1H, dd, J =12.2 and 8.3 Hz), 2.72 (1H, dd, J =12.2 and 7.9 Hz), 3.96 (1H, m), 5.23 (1H, br), 7.24 (1H, m), 7.34 (2H, m), and 7.45 (2H, m); 7*d* (typical signals): δ =2.08 (1H, dd, J =12.2 and 7.6 Hz), 2.52 (1H, dd, J =12.2 and 7.3 Hz), and 4.19 (1H, m); ^{13}C NMR 6*d*: δ =13.82, 22.47, 28.38, 34.52, 67.27, 82.81, 125.36, 126.62, 128.18, and 144.83; IR (neat) 3200s, 3060s, 3020s, 2960s, 2928s, 1448s, 764s, and 702s cm^{-1} ; MS (CI) m/z (rel intensity) 220 (M^+ +1, 27), 219 (M^+ , 14), 204 (29), 142 (19), 136 (48), 134 (100), 120 (49), and 102 (99). Found: C, 76.58; H, 9.87; N, 6.10%. Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}$: C, 76.67; H, 9.65; N, 6.39%.

(3*R,5*R**)- and (3*S**,5*R**)-5-Ethoxymethyl-3-methyl-3-phenylisoxazolidine (6*e* and 7*e*):** Colorless oil, bp 110 °C/0.4 mmHg; ^1H NMR 6*e* (less polar): δ =1.23 (3H, t, J =7.0 Hz), 1.52 (3H, s), 2.20 (1H, dd, J =12.2 and 7.3 Hz), 2.73 (1H, dd, J =12.2 and 8.5 Hz), 3.5—3.7 (4H, m), 4.18 (1H, m), 7.23 (1H, m), 7.34 (2H, m), and 7.51 (2H, m); 7*e* (polar): δ =1.13 (3H, t, J =7.0 Hz), 1.51 (3H, s), 2.34 (1H, dd, J =11.9 and 7.3 Hz), 2.52 (1H, dd, J =11.9 and 8.9 Hz), 3.35—3.5 (4H, m), 4.47 (1H, m), 7.26 (1H, m), 7.34 (2H, m), and 7.46 (2H, m); ^{13}C NMR 6*e* (less polar): δ =15.15, 26.86 (br), 45.64, 67.00, 67.46, 80.90, 125.60, 126.66, 128.28, and 145.40; 7*e* (polar): δ =15.03, 27.89, 44.99 (br), 66.92, 67.54, 72.45, 80.79 (br), 125.68, 127.00, 128.41, and 144.63 (br); IR 6*e* (neat): 3208m, 2976s, 2928s, 2872s, 1448s, 1380s, 1120vs, 766s, and 702s cm^{-1} ; 7*e* (neat): 3220m, 2976s, 2928s, 2872s, 1448s, 1378m, 1118vs, 768s, and 702s cm^{-1} ; MS (CI) m/z (rel intensity) 222 (M^+ +1, 21), 206 (12), 176 (15), 158 (25), 143 (100), 134 (35), and 120 (72). Found: C, 70.14; H, 8.44; N, 6.73%. Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_2$: C, 70.54; H, 8.65; N, 6.33%.

(3*R,5*R**)- and (3*S**,5*R**)-5-[(2-Methoxyethoxy)-methyl]-3-methyl-3-phenylisoxazolidine (6*f* and 7*f*):** Colorless oil, bp 105 °C/0.3 mmHg; ^1H NMR 6*f* (less polar): δ =1.52 (3H, s), 2.22 (1H, dd, J =12.2 and 7.3 Hz), 2.72 (1H, dd, J =12.2 and 8.2 Hz), 3.39 (3H, s), 3.5—3.75 (6H, m), 4.17 (1H, m), 7.22 (1H, m), 7.33 (2H, m), and 7.51 (2H, m); 7*f* (polar): δ =1.51 (3H, s), 2.37 (1H, dd, J =11.9 and 7.0 Hz), 2.51 (1H, dd, J =11.9 and 7.9 Hz), 3.28 (3H, s), 3.4—3.7 (6H, m), 4.48 (1H, m), 7.25 (1H, m), 7.34 (2H, m), and 7.44 (2H, m); ^{13}C NMR 6*f* (less polar): δ =26.67 (br), 45.45, 58.92, 67.31, 70.91, 71.87, 73.03, 125.54, 126.62, 128.22, and 145.25; 7*f* (polar): δ =27.79, 44.67 (br), 58.87, 67.50 (br), 70.86, 71.75, 72.93 (br), 80.86, (br), 125.66, 126.97, 128.36, and 144.42; IR 6*f* (neat): 3220m, 2876s, 1450s, 1118vs, 768m, and 704 cm^{-1} ; 7*f* (neat): 3208m, 2924s, 1450s, 1118vs, 766m, and 702m cm^{-1} ; MS (CI) m/z (rel intensity) 252 (M^+ +1, 20), 193 (20), 176 (10), 158 (19), 143 (100), 136 (31), 134 (30), and 120 (43). Found: m/z 252.1607. Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_3$: MH^+ , 252.1598.

(3*aS,4*S**,7*R**,7*aS**)-3-(2-Hydroxy-2-phenylethyl)-3*a*, 4, 5, 6, 7, 7*a*-hexahydro-4, 7- methano- 1, 2-benzisoxazole (11*b*):** Colorless oil, bp 180 °C/0.6 mmHg; ^1H NMR (major isomer): δ =1.0—1.2 (3H, m), 1.36 (1H, m), 1.4—1.5 (2H, m), 2.28 (1H, m), 2.48 (1H, m), 2.60 (2H, m), 2.97 (1H, br d, J =8.2 Hz), 3.50 (1H, br), 4.36 (1H, d, J =8.2 Hz), 5.01 (1H, dd, J =7.3 and 5.2 Hz), and 7.2—7.5 (5H, m); ^{13}C NMR (major isomer): δ =22.44,

26.94, 31.93, 36.34, 38.00, 42.60, 60.06, 71.29, 85.74, 125.49, 127.41, 128.21, 143.12, and 157.18; IR (neat) 3404s, 2960s, 2876s, and 700m cm^{-1} ; MS (CI) m/z (rel intensity) 258 ($M^+ + 1$, 7), 240 (100), 180 (9), 151 (36), 120 (23), and 107 (69). Found: C, 74.34; H, 7.57; N, 5.16%. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.68; H, 7.44; N, 5.44%.

(3aS*,5R*,7R*,7aR*)-3-(2-Hydroxy-2-phenylethyl)-6,6,7a-trimethyl-3a,4,5,6,7,7a-hexahydro-5,7-methano-1,2-benzisoxazole (11d): Colorless solid, mp 65–75 °C, bp 175 °C/0.5 mmHg; ^1H NMR (major isomer): δ =0.83 (3H, s), 0.99 (1H, d, J =10.4 Hz), 1.23 (3H, s), 1.24 (3H, s), 1.55 (1H, dt, J =13.7 and 3.4 Hz), 1.8–2.2 (4H, m), 2.55–2.85 (3H, m), 3.75 (1H, br), 5.02 (1H, m), 7.2–7.4 (5H, m); (minor isomer, typical signal): δ =5.01 (m); ^{13}C NMR (major isomer): δ =22.84, 26.18, 26.65, 26.92, 28.46, 35.65, 37.03, 39.08, 48.02, 49.54, 71.56, 89.36, 125.47, 127.31, 128.14, 143.12, and 159.73; IR (KBr) 3288vs, 2872s, 1038s, and 704s cm^{-1} ; MS (CI) m/z (rel intensity), 328 ($M^+ + \text{Et}$, 11), 300 ($M^+ + 1$, 9), 282 (100), 240 (20), 226 (18), 222 (11), 193 (37), 176 (24), 135 (26), and 107 (53). Found: C, 76.22; H, 8.56; N, 4.36%. Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_2$: C, 76.22; H, 8.42; N, 4.68%.

5-Butyl-3-(2-hydroxy-2-phenylethyl)-2-isoxazoline (11e) and 5-Butyl-4-(α -hydroxybenzyl)-3-methyl-2-isoxazoline (12e): Colorless oil; Found C, 72.72; H, 8.56; N, 5.40%. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2$: C, 72.84; H, 8.56; N, 5.66%.

11e (6:4 diastereomer mixture): Mp 43–48 °C; ^1H NMR (major isomer): δ =0.91 (3H, t, J =7.3 Hz), 1.3–1.4 (3H, m), 1.49 (1H, m), 1.6–1.75 (2H, m), 2.53 (1H, dd, J =17.1 and 8.2 Hz), 2.65–2.75 (2H, m), 3.00 (1H, m), 3.03 (1H, br), 4.51 (1H, m), 5.05 (1H, dd, J =8.2 and 4.3 Hz), and 7.25–7.4 (5H, m); ^{13}C NMR (major isomer): δ =13.93, 22.47, 27.61, 34.74, 37.74, 43.07, 71.41, 80.23, 125.62, 127.79, 128.53, 143.04, and 156.98; (minor isomer, typical signals): δ =27.58, 37.76, 71.37, and 143.01; IR (KBr) 3388vs, 2956s, 2928s, 1056m, 760m, and 700m cm^{-1} ; MS (CI) m/z (rel intensity) 248 ($M^+ + 1$, 3), 230 (100), 172 (6), 141 (34), 121 (8), and 107 (27).

12e (6:4 diastereomer mixture): ^1H NMR (major isomer): δ =0.76 (3H, m), 1.11 (4H, m), 1.34 (2H, m), 2.08 (3H, d, J =0.9 Hz), 2.19 (1H, br), 3.08 (1H, ddq, J =8.2, 5.8, and 0.9 Hz), 4.08 (1H, m), 4.76 (1H, d, J =8.2 Hz), and 7.25–7.45 (5H, m); ^{13}C NMR (major isomer): δ =13.80, 13.99, 22.18, 26.85, 34.25, 62.59, 75.33, 82.65, 126.44, 128.52, 128.79, 141.46, and 156.73; (minor isomer, typical signals): δ =13.95, 22.49, 27.63, 34.78, 37.78, 71.43, 80.27, 125.64, 127.84, 128.57, and 143.02; IR (KBr) 3264vs, 2965s, 1440s, 1058s, 926s, and 702vs cm^{-1} ; MS (CI) m/z (rel intensity) 248 ($M^+ + 1$, 18), 230 (9), 144 (100), 142 (50), and 107 (42).

5-Ethoxymethyl-3-(2-hydroxy-2-phenylethyl)-2-isoxazoline (11f) and 5-Ethoxymethyl-4-(α -hydroxybenzyl)-3-methyl-2-isoxazoline (12f): Colorless oil; Found: C, 67.29; H, 7.80; N, 5.32%. Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3$: C, 67.45; H, 7.68; N, 5.62%.

11f (6:4 diastereomer mixture): Mp 33–60 °C; ^1H NMR (major isomer): δ =1.18 (3H, t, J =7.0 Hz), 2.65–2.85 (3H, m), 2.97 (1H, m), 3.21 (1H, br), 3.35–3.6 (4H, m), 4.67 (1H, m), 5.01 (1H, m), and 7.2–7.45 (5H, m); ^{13}C NMR (major isomer): δ =14.90, 37.52, 39.74, 67.00, 71.15, 71.60, 78.47, 125.57, 127.67, 128.42, 142.94, and 156.73; (minor isomer): δ =14.92, 37.36, 40.23, 66.98, 71.47, 71.55, 78.47,

125.55, 127.67, 128.42, 142.98, and 156.93; IR (neat) 3636s, 2972s, 1114s, 1060s, 758m, and 702s cm^{-1} ; MS (CI) m/z (rel intensity) 250 ($M^+ + 1$, 7), 232 (66), 188 (13), 172 (16), 146 (18), 144 (39), 107 (100), and 105 (31).

12f (6:4 diastereomer mixture): ^1H NMR (major isomer): δ =1.09 (3H, t, J =7.0 Hz), 2.03 (3H, d, J =0.9 Hz), 2.6–3.5 (6H, m), 4.23 (1H, m), 4.80 (1H, m), and 7.2–7.4 (5H, m); (minor isomer): δ 1.06 (3H, t, J =7.0 Hz), 1.77 (3H, d, J =0.9 Hz), 2.6–3.5 (6H, m), 4.64 (1H, m), 4.97 (1H, m), and 7.2–7.4 (5H, m); IR (neat) 3416vs, 2976s, 2876s, 1454s, 1384s, 1118vs, 1060vs, and 704vs cm^{-1} ; MS (CI) m/z (rel intensity) 250 ($M^+ + 1$, 5), 232 (38), 202 (17), 188 (7), 172 (13), 144 (100), and 107 (70).

(2R*,4R*) and (2R*,4S*)-4-Animo-1-ethoxy-4-phenyl-2-pentanol (8 and 8'): To a suspension of LiAlH_4 (114 mg, 3 mmol) in 5 ml of ether was added a solution of **6e** (200 mg, 0.80 mmol) in 5 ml of ether at 0 °C. After the mixture was stirred overnight at room temperature, 10% aqueous NaOH (5 ml) was added. The mixture was extracted with ether (3 $\times$ 20 ml). The extracts were dried over Na_2SO_4 and concentrated in vacuo to leave a solid. Recrystallization of the solid from ether/hexane gave 190 mg (95%) of **8**: Colorless crystals, mp 50–52 °C; ^1H NMR δ =1.15 (3H, t, J =7.0 Hz), 1.58 (3H, s), 1.82 (2H, m), 2.8 (3H, br), 3.25 (2H, m), 3.44 (3H, m), and 7.2–7.5 (5H, m); IR (neat) 3368vs, 3280s, 3170s, 2976s, 2876vs, 1120s, 770s, and 702s cm^{-1} ; MS (EI) m/z (rel intensity) 224 (M^+ , 1), 208 (5), 143 (83), 120 (91), and 119 (100). Found: C, 69.92; H, 9.41; N, 6.12%. Calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_2$: C, 69.92; H, 9.48; N, 6.27%.

Alcohol **8'** was similarly obtained from **7e** in 85% crude yield. ^1H NMR δ =1.19 (3H, t, J =7.0 Hz), 1.56 (3H, s), 1.73 (1H, dd, J =14.3 and 10.4 Hz), 1.85 (1H, dd, J =14.3 and 2.4 Hz), 3.3 (3H, br), 3.37 (2H, m), 4.21 (1H, m), and 7.2–7.5 (5H, m).

(4R*,6R*)- and (4S*,6R*)-6-Ethoxymethyl-4-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-1,3-oxazin-2-one (9 and 10): A mixture of **8** (100 mg, 0.45 mmol), NaOMe (3 mmg), and diethyl carbonate (0.3 ml) was refluxed for 1 d. The mixture was diluted with ether (50 ml), washed with water and brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was chromatographed on silica gel (ether/ CH_2Cl_2) to give 25 mg (22%) of **9**: Colorless crystals, mp 128–129 °C; ^1H NMR δ =1.17 (3H, t, J =7.0 Hz), 1.72 (3H, s), 2.01 (1H, dd, J =14.0 and 11.0 Hz), 2.14 (1H, ddd, J =14.0, 2.7, and 1.5 Hz), 3.50 (2H, m), 3.62 (1H, dd, J =10.4 and 4.9 Hz), 4.60 (1H, dtd, J =11.0, 4.9, and 2.7 Hz), 6.35 (1H, br), and 7.2–7.5 (5H, m); ^{13}C NMR δ =14.97, 28.84, 38.80, 55.92, 67.09, 71.61, 73.67, 124.44, 127.47, 128.76, 145.98, and 154.08; IR (KBr) 3228s, 3108s, 1694vs, 1416vs, 1320vs, and 1100s cm^{-1} ; MS (CI) m/z (rel intensity) 250 ($M^+ + 1$, 30), 234 (7), 164 (5), 144 (18), 143 (100), and 119 (28). Found: C, 67.52; H, 7.65; N, 5.76%. Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3$: C, 67.45; H, 7.68; N, 5.62%.

Oxazinone **10** was similarly obtained from **8'** in 20% yield: Colorless crystals, mp 176–178 °C; ^1H NMR δ =1.51 (3H, t, J =7.0 Hz), 1.65 (3H, s), 2.05 (1H, dd, J =13.7 and 11.9 Hz), 2.30 (1H, dt, J =13.7 and 2.0 Hz), 3.49 (4H, m), 4.01 (1H, dtd, J =11.9, 4.9, and 2.0 Hz), 7.01 (1H, br), and 7.2–7.5 (5H, m); ^{13}C NMR δ =14.99, 31.14, 38.15, 56.77, 67.09, 71.69, 73.74, 125.09, 127.24, 128.71, 145.35, and 154.37; IR (KBr) 3352s, 3216s, 1692vs, 1416vs, 1320vs, 1118vs, and

1054s cm^{-1} ; MS (CI) m/z (rel intensity) 250 ($\text{M}^+ + 1$, 38), 234 (5), 164 (7), 144 (16), 143 (100), and 119 (19). Found: C, 67.06; H, 7.74; N, 5.50%. Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3$: C, 67.45; H, 7.68; N, 5.62%.

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