Diastereoselectivity in the Lateral Metalation and Electrophilic Quenching of Isoxazolyloxazolines†

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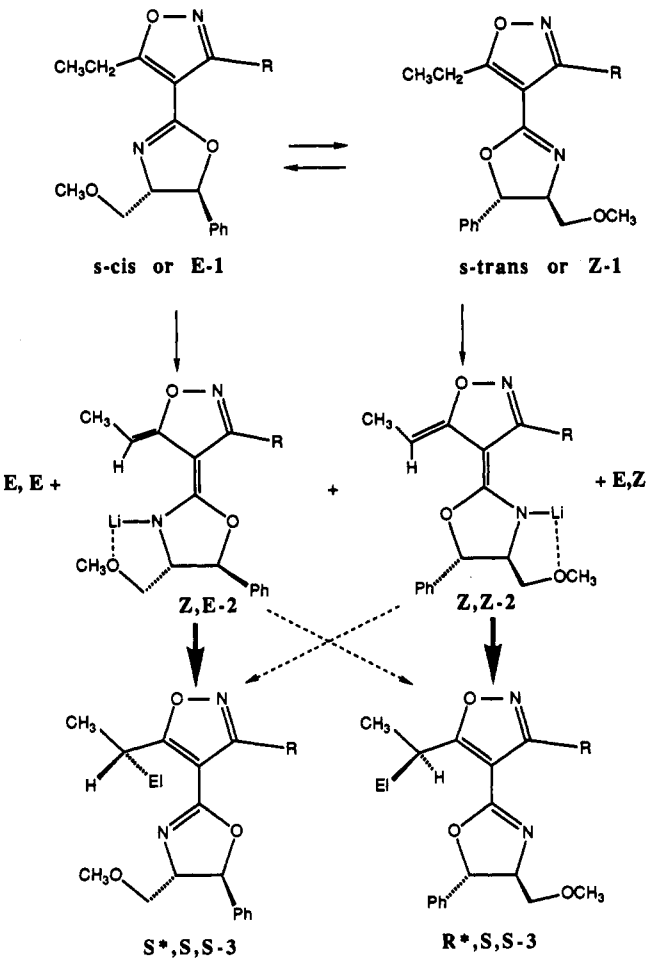
Metalation and electrophilic quenching of chiral isoxazolyloxazolines at the C-5 position of the isoxazole gives rise to modest diastereoselectivity in most cases. In general, the 4(*S*)-(methoxymethyl)-5(*S*)-phenyl-2-oxazoline auxilliary (Meyer's reagent) produces the *S* absolute configuration at the C-5 isoxazole position of the major diastereomer, for priorities isoxazole > El > R > H. The enantiomerically pure isoxazolyloxazolines **3** can be obtained by preparative HPLC. The isoxazolyloxazolines **3** can be deprotected selectively to produce isoxazolecarboxaldehyde **4**, and 4-isoxazolyl-1,4-dihydropyridine **5**. The solid-state conformation of **5** is O-endo with respect to the ring juncture between the heterocyclic rings and sp, sp with respect to the 3,5-diester groups. The (+) enantiomer of IDHP **5** proved to be 2 orders of magnitude more effective in the displacement of ^{3}H-labeled 1,4-dihydropyridine from Ca^{2+} channels in cardiac membranes.

4-Aryl-1,4-dihydropyridines (DHPs) are calcium channel antagonists.[1] Members of this class have significant clinical applications for antihypertension and angina and potential application for cerebrovascular vasospasm. Enantioselectivity of action is pronounced for DHPs; in the case of a chiral center at C-4 of the DHP one example demonstrated that biological activity differed by 3 orders of magnitude for the enantiomers.[2] We have found that bioisosteric replacement of the 4-aryl group with a 4-isoxazolyl moiety produces analogues, the 4-isoxazolyl-1,4-dihydropyridines (IDHPs) with robust calcium antagonist activity,[3] which in some cases lack the significant ionotropy associated with the DHPs.[4] Chirality plays an important role in biological activity, yet among the numerous reports concerning the biology of the isoxazoles,[5] only a few address this critical issue.[6] Given the importance of isoxazoles in many synthetic transformations, and our interest in the lateral metalation of isoxazoles,[7,8] we have initiated a study of the diastereoselectivity of the latter process.

Since the pioneering observations of useful asymmetric induction in carbon–carbon bond forming reactions by Meyers,[9] chiral enolate equivalents have developed into a standard tool for synthetic organic chemists. The success in asymmetric induction has been usually attributed to the formation of a geometrically defined enolate equivalent,[10] which incorporates some rigidity into the diastereotopic transition states, in turn resulting in meaningful differences in energy of activation between these transition states and thus translating into the diastereomeric selectivity observed. Often the rigidity involves a metal counterion; thus, the concept has been termed chelate-enforced intraannular chirality transfer.[10] Fewer examples exist of vinylogous systems. One notable example is the elegant vinylogous urethane work of Schlessinger,[11] which, consistent with the concept referenced above, fortuitously adopts a single geometric isomer. The major complicating factor encountered in the present study arises from the fact that a conformationally mobile ring juncture resides between the chiral auxilliary group and the site of lateral metalation and electrophilic quenching. The problem is illustrated in Scheme I. Rotation about the ring juncture between isoxazole and oxazoline moieties gives rise to an infinity of conformations, with the extremes being repre-

Scheme I. Rotation about the Ring Juncture Gives Rise to Two Possible *Z*-Lithiovinylogous Imidates



† Dedicated to Professor Albert I. Meyers on the occasion of his 60th birthday.

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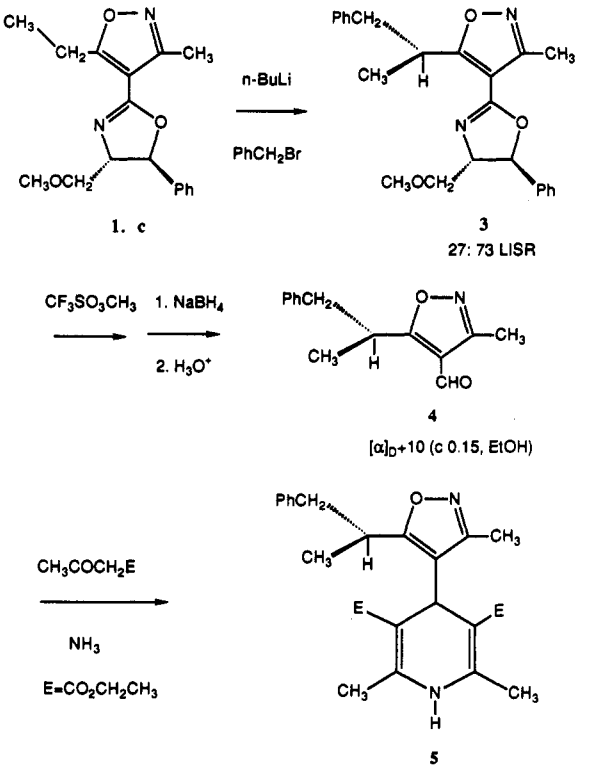
sented by the *E*-1 and *Z*-1 ring juncture conformations illustrated. Upon metalation both *Z* and *E* geometric isomers are possible for the lithiovinylogous imidate **2**, but the *E* conformations would appear to be excessively hindered and are not shown. In the electrophilic quenching step, available precedent would lead to the expectation that the *Z,E*-**2** would lead to *S,S,S*-**3** as the major product and that *Z,Z*-**2** would give rise to *R,S,S*-**3**.

In the event, excellent chemical yields are usually obtained upon metalation and electrophilic quenching with a variety of electrophiles. The diastereoselectivities obtained to date have been modest. We have attempted variation of temperature, base, order of addition, and counterion. Results are shown in Table I. Butyllithium as base produced de's comparable to those originally reported by Meyers for the simple enolate equivalent[12] (on the order of 46–48% de, entries 1 and 11); however, no significant improvement was observed for either LDA (entry 14) or LiHMDS (entries 3 and 15). No improvement was noted for NaHMDS (entry 4), Cp_2ZrCl_2 (entry 12),[13] and the de was actually lower for KHMDS (entry 5). Similarly, lowering the temperature during electrophilic quenching gave no corresponding rise in de (entry 13).

Scheme II. Deprotection of Isoxazolyloxazoline 3 and Synthesis of Isoxazolecarboxaldehyde 4 and IDHP 5



5-(Hydroxymethyl)isoxazoles are metabolites produced from the corresponding 5-methylisoxazoles oxacillin and isoxicam in vivo.[8g,23,24] Therefore, we were interested in the use of electrophilic oxygen sources. Toward this end, we used *N*-(phenylsulfonyl)-3-phenyloxaziridine (Davis reagent),[14] Table I (entries 9 and 21), which produced excellent chemical yields but modest diastereoselectivity. Isoxazoles containing nitrogen functional groups occur in nature and are useful agents for the study of central nervous system diseases.[8b] Using the method of Evans and Vederas,[15] reaction of **2** with diethyl azodicarboxylate (DEAD) produced excellent chemical yields of the hydrazinoisoxazolyloxazolines (Table I, entries 10 and 22). Quenching with benzoyl chloride, using the conditions of Evans,[17] produced the β-keto isoxazolyloxazoline diastereomers in essentially equal amounts (Table I, entries 8 and 20). Quenching with disulfides produced the ((thioalkyl)isoxazolyl)oxazolines (Table I, entries 23 and 27).[16] We also considered inverse addition (Table I, entries 24–6), which produced best results with added cerium trichloride. However, even these best results were only modest. The electrophiles used in Table I correspond to a Hansch five-member cluster congener set[18] and thus represent a potentially useful, general tool for systematic exploration of chiral substituent effects for isoxazoles with valuable agricultural and medicinal applications.

In most cases, the diastereomers are separable by preparative HPLC, and enantiomerically pure isoxazolyloxazolines can be obtained. The one exception, entry 11, could be readily transformed to the 4-isoxaolyl-1,4-dihydropyridine **5**, vide infra, which could be resolved by HPLC using a chiral stationary phase. Deprotection of the oxazoline in the presence of the isoxazole could be

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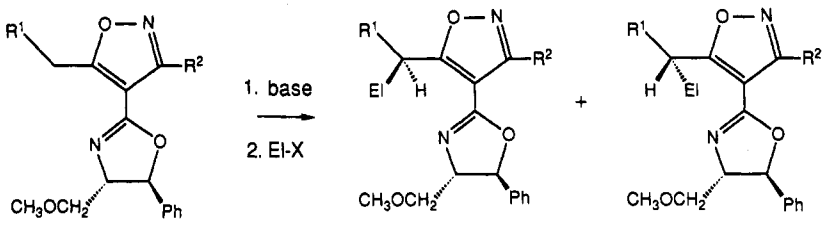
Table I. Diastereoselectivity in the Lateral Metalation and Electrophilic Quenching of Isoxazolyloxazolines



1. a. $R^1 = CH_3$, $R^2 = C_6H_5$
b. $R^1 = CH_2C_6H_5$, $R^2 = C_6H_5$
c. $R^1 = R^2 = CH_3$
d. $R^1 = CH_2C_6H_5$, $R^2 = CH_3$
e. $R^1 = SC_6H_5$, $R^2 = CH_3$

For R* priorities are in the order isoxazole > El > R^1.

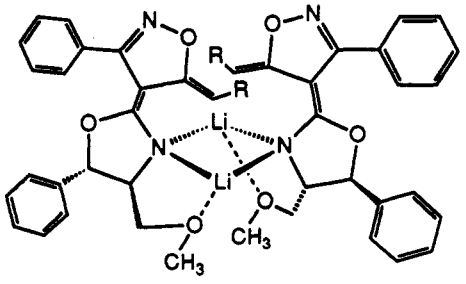
entry	base	R^1	El-X	R^2	ratio	empirical formula	mass spectrum[f] (rel int)	anal. found (calcd) C	H	N
1	BuLi	CH_3	$PhCH_2$-Br	Ph	33:67[a] 26:74[b]	$C_{29}H_{28}N_2O_3$	453 (56.6)	76.67 (76.96)	6.33 (6.24)	6.00 (6.19)
2	BuLi	$PhCH_2$	CH_3-I	Ph	62:37[b]	same as above				
3	LiHMDS	CH_3	$PhCH_2$-Br	Ph	25:75[b]	same as above				
4	NaHMDS	CH_3	$PhCH_2$-Br	Ph	23:77[b]	same as above				
5	KHMDS	CH_3	$PhCH_2$-Br	Ph	34:66[b]	same as above				
6	BuLi	CH_3	n-Bu-Br	Ph	39:61[b]	$C_{26}H_{30}N_2O_3$	419 (100)	74.51 (74.61)	7.20 (7.22)	6.77 (6.64)
7	BuLi	CH_3	CH_3OCH_2-Cl	Ph	37:63[b]	$C_{24}H_{26}N_2O_4$	407 (100)	70.84 (70.41)	6.30 (6.44)	6.82 (6.84)
8	BuLi	CH_3	PhCO-Cl	Ph	53:47[b]	$C_{29}H_{26}N_2O_4$	466[g] (10)	74.55 (74.64)	5.62 (5.61)	5.50[j] (6.00)
9	BuLi	CH_3	(HO)[h]	Ph	56:44[e] 40:60[b]	$C_{22}H_{22}N_2O_4$	379	69.71 (69.82)	5.87 (5.86)	7.25 (7.40)
10	BuLi	CH_3	(E-NH-N-E)[i]	Ph	46:54[b]	$C_{28}H_{32}N_4O_7$	537	63.02 (62.68)	5.87 (6.01)	10.25 (10.43)
11	BuLi −78 °C	CH_3	$PhCh_2$-Br	CH_3	27:73[d]	$C_{24}H_{26}N_2O_3$	391 (100)	73.60 (73.82)	6.66 (6.71)	7.45 (7.18)
12	BuLi Cp_2ZrCl_2	CH_3	$PhCH_2$-Br	CH_3	29:71[e]	same as above				
13	BuLi −100 °C	CH_3	$PhCH_2$-Br	CH_3	27:73[d]	same as above				
14	LDA	CH_3	$PhCH_2$-Br	CH_3	27:73[d]	same as above				
15	LiHMDS	CH_3	$PhCH_2$-Br	CH_3	27:73[d]	same as above				
16	BuLi	$PhCH_2$	CH_3-I	CH_3	63:37[d] 64:36[e]	same as above				
17	BuLi	CH_3	n-Pr-I	CH_3	34:66[d]	$C_{20}H_{26}N_2O_3$	343 (4.36)	69.96 (70.15)	7.72 (7.65)	8.11 (8.18)
18	BuLi	CH_3	n-Bu-I	CH_3	23:77[b]	$C_{21}H_{28}N_2O_3$	357 (100)	70.64 (70.76)	7.69 (7.92)	7.60 (7.86)
19	BuLi	CH_3	CH_3OCH_2-Cl	CH_3	25:75[b]	$C_{21}H_{28}N_2O_3$	347 (100)	66.37 (66.26)	6.90 (7.02)	7.87 (8.13)
20	BuLi	CH_3	PhCO-Cl	CH_3	53:47[d]	$C_{24}H_{24}N_2O_4$	404[g] (7.27)	70.69 (71.27)	6.04 (5.98)	6.30[k] (6.92)
21	BuLi	CH_3	(HO)[h]	CH_3	40:60[d] 38:61[b]	$C_{17}H_{20}N_2O_4$	317 (99.28)	64.43 (64.54)	6.31 (6.37)	8.92 (8.86)
22	BuLi	CH_3	(E-NH-N-E)[i]	CH_3	30:70[c]	$C_{23}H_{30}N_4O_7$	475 (100)	57.86 (58.21)	6.33 (6.37)	11.62 (11.81)
23	BuLi	CH_3	PhS-SPh	CH_3	47:53[e]	$C_{23}H_{24}N_2O_3S$	408 (100)	67.51 (67.62)	5.92 (5.92)	6.88 (6.86)
24	BuLi	PhS	CH_3-I	CH_3	59:41[e]	same as above				
25	LDA	PhS	CH_3-I	CH_3	52:48[e]	same as above				
26	BuLi $CeCl_3$	PhS	CH_3-I	CH_3	66:34[e]	same as above				
27	BuLi	CH_3	2-pyridyl-S–S-2-pyridyl	CH_3	44:56[e]	$C_{22}H_{23}N_3O_3S$	410 (100)	64.34 (64.53)	5.65 (5.66)	10.27 (10.26)

[a] Determined by integration of the oxazoline C-5 signal at 90 MHz, the diastereomer listed first is the signal furthest downfield from TMS. [b] Determined by HPLC, on a Chiracel OJ column, using hexane/ethanol, 98:2. The diastereomer listed first elutes first from the column. [c] HPLC, as above but the sample was dissolved in hexane/ethanol, 98:2, for injection, then eluted with 100% hexane. [d] Determined using LISR at 90 MHz, using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III). [e] Determined by integration at 300 MHz of the C-5 R group, unless otherwise noted. This typically represents a methyl signal (ca. δ 1, d, 3 H), see the Experimental Section for spectroscopic details. [f] Chemical ionization, corresponding to the protonated molecular ion $[M + 1]^+$, unless otherwise noted. [g] Electron impact, corresponding to the molecular ion $[M]^+$. [h] The electrophilic source of oxygen used was *N*-(phenylsulfonyl)-3-phenyloxaziridene, according to Davis, ref 14. [i] The electrophile was diethyl azodicarboxylate (DEAD), according to Evans, ref 15. [j] Exact mass calculated 466.1892, found 466.1890 (0.6 ppm). [k] Exact mass calculated 404.1736, found 404.1695 (4.8 ppm).

effected by N-methylation with methyl trifluoromethanesulfonate, followed by reduction with sodium tetrahydridoborate, shown in Scheme II.[19] The intermediate aminal was hydrolyzed to the isoxazolecarboxaldehyde 4 in excellent yield. The aldehyde 4 was then transformed via Hantzsch pyridine synthesis to the crystalline IDHP 5. The major isoxazolyloxazoline diastereomer (27:73 ratio by LIS) correlated with the slow moving (-)-IDHP, 27:73 by HPLC, $[\alpha]_D$ -22.9 (EtOH, c 7.42). Thus, no racemization occurred during the deprotection and Hantzsch pyridine synthesis sequence. There was good agreement between the enantiomeric purity of 5 as assessed by HPLC-CSP (46%) and polarimetry (52%), using $[\alpha]_D$ -43 (EtOH, c 1.1), for enantiomerically pure IDHP 5 obtained by chromatographic resolution.

The absolute configuration the (-)-IDHP 5 was assigned by chemical degradation. Optically pure (-)-IDHP 5, obtained by chromatographic resolution, was subjected to ring opening[20] and hydrolysis to (S)-(+)-2-methyl-3-phenylpropionic acid.[21] The structure of (-)-IDHP 5 was confirmed by single-crystal X-ray diffractometry; the crystallographic data is presented in the Supplementary Material. The conformation of IDHP 5 in the solid state is, surprisingly, O-endo with respect to the ring juncture between the heterocyclic rings. The conformations of the esters in the 3- and 5-position of the DHP are both sp. Molecular mechanics predicted that this conformation at the ring juncture represents the minimum energy conformer. In solution 2D NOESY spectroscopy indicated ready interconversion at both ring juncture and ester. The radioligand binding of the IDHP enantiomers of 5 was evaluated: the (+) enantiomer had $K_I = (3.7 \pm 0.58) \times 10^{-9}$, $n_H = 1.06$, while the (-) enantiomer of 5 had $K_I = (2.1 \pm 0.82) \times 10^{-7}$, $n_H = 1.1$. Thus, not only is (+)-5 a robust calcium antagonist which exhibits enantioselectivity of action, but it is also the most biologically active IDHP found to date.

We have considered several factors in explaining the modest diastereoselectivity observed for the isoxazoyloxazolines. A critical observation is that lowering the temperature during electrophilic quenching gave no corresponding rise in de (Table I, entry 13). This observation suggests the possibility that the isoxazole moiety is too large sterically to aggregate and form the dimeric lithioazaenolate 6 which appears to contribute to higher diastereoselectivity.[22]



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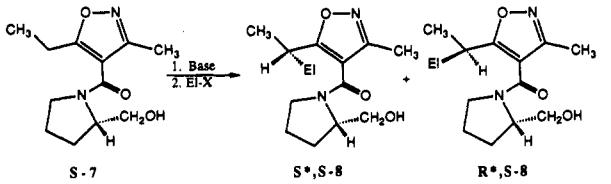
Another possibility for the modest ratios observed is the conformation at the ring juncture. Molecular mechanics calculations suggested that there is not a large intrinsic difference in energy between E and Z conformation about the single bond connecting the heterocyclic rings in 1. 2D NOESY spectroscopy provides evidence for an average Z conformation of 1 at room temperature, while at -78 °C both conformations are in evidence. A Z conformer of 1 would place the prochiral C-5 position of the isoxazole 5.2 Å from the C-4 position of the oxazoline (according to the molecular mechanics calculation coordinates), further than the distance between the latter chiral center in more successful applications of this auxilliary.

Table II. Diastereoselectivity Using Carboxamide Dianions of (S)-7



S-7 S*,S-8 R*,S-8

entry	ElX	yield, %	de	α
1	n-C_4H_9Br	42	13:87	1.224
2	$C_6H_5SSC_6H_5$	54	39:61	1.098
3	(E-NHN-E)	85	38:62	1.157

Finally, we have briefly examined an alternate chiral auxilliary group, the carboxamide of (S)-prolinol 7.

While the isoxazole-C-4-carboxamide of (S)-prolinol 7 gives rise to slightly higher de in the case of n-butyl iodide (compare Table I, entry 18, with Table II, entry 1) and diphenyl disulfide (compare Table I, entry 23, to Table II, entry 2), the process was complicated by lower chemical yield. For diazodicarboxylate the de was lower (compare Table I, entry 22, and Table II, entry 3) and the chemical yield comparable for the two methods.

Further optimization of reaction conditions for lateral metalation of these and other auxilliaries, as well as application of the enantiomerically pure isoxazoles, is being pursued in our laboratories and will be reported in due course.

Experimental Section

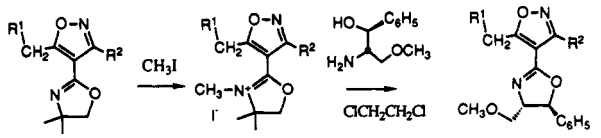
General Methods. The purity of all title compounds was determined to be greater than 95% by TLC, HPLC, ^1H NMR spectral analysis, and/or elemental analysis. ^1H NMR spectra were recorded at 300 MHz, unless otherwise specified, in $CDCl_3$ solution and are reported as ppm downfield from TMS. HPLC analysis were performed on a 25-cm × 0.46-cm-i.d. or 25-cm × 2.0-cm-i.d. Chiracel Daicel OJ column, using Rainin Rabbit-HP HPLC with a Beckman Model 153 UV detector. The mass spectra were obtained using chemical ionization unless otherwise noted and are reported as m/z (relative intensity). IR spectra were obtained as neat oils or KBr pellets. Combustion analyses were performed by Desert Analytics. Radical chromatography was performed on a Harrison Associated Chromatotron using silica gel unless otherwise specified. Nitrogen gas was passed over activated catalyst R3-11 followed by indicator Drierite for reactions which required an inert atmosphere. THF was distilled from sodium and benzophenone; reagent-grade hexane, methylene chloride, and ethyl acetate were purchased, dried over drying salts, and distilled from P_2O_5 for chromatography. n-Butyllithium (n-BuLi) was titrated with diphenylacetic acid.

Starting materials **1a** and **1c** were prepared from the isoxazolyloxazolines 9,[8c] by N-methylation with iodomethane to produce the quaternary salts 10 and oxazoline exchange with (1S,2S)-2-amino-1-phenyl-3-O-methyl-1,3-propanediol in 1,2-dichloroethane solvent. The yields of this oxazoline exchange reaction were improved by running the reaction more concentrated, results are shown in Table III.

Isoxazolyloxazolines **1b,d,e**[8a] were prepared by lateral metalation and electrophilic quenching from the corresponding C-5 methyl compounds. The following example serves as the general procedure for the electrophilic quenching at the C-5 position of isoxazolyloxazoline (Table I, entries 1-8, 11-20).

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-5-((*R*,*S*)-1′-phenyleth-2′-yl)-3-phenylisoxazole (Table I, Entry 2). Isoxazolyloxazoline **1b** (902.4 mg, 2.0578 mmol) was dissolved in freshly distilled THF (25 mL) and cooled to -78°C under N_2 for 30 min. n-BuLi (0.943 mL of 2.4 M in hexane) was added dropwise via syringe. The reaction was

Table III. Synthesis of Isoxazolyloxazolines 1a and 1c



9 10 1 a, and 1 c

entry	R^1	R^2	[10]	yield, %	conditions
1	H	CH_3	0.08	49	reflux (bp 83 °C)
2	H	CH_3	0.28	83	70 °C
3	CH_3	CH_3	0.12	42	reflux
4	CH_3	CH_3	0.38	65	reflux, 12 h
5	CH_3	C_6H_5	0.08	18	reflux[8g]
6	CH_3	C_6H_5	0.36	43	reflux, 24 h
7	CH_3	C_6H_5	0.45	50	reflux, 48 h

then stirred at −78 °C for 2 h. Methyl iodide was added dropwise (0.15 mL). The resulting mixture was stirred at −78 °C for 2 h. Concentration was followed by workup. The standard workup was as follows: The reaction mixture was dissolved in 30 mL of CH_2Cl_2, washed with 2 × 50 mL of 5% $NaHCO_3$ and 2 × 100 mL of H_2O, and the aqueous layers were washed with 2 × 35 mL of CH_2Cl_2. The combined organic layers were filtered through anhydrous Na_2SO_4 and concd in vacuo to produce an oil. Silica gel column chromatography using 1:4:4 EtOAc/CH_2Cl_2/hexane as eluant gave 875.7 mg (R_f = 0.63), 94%, of pure desired product: IR (neat, cm^{-1}) 3063, 3028, 2976, 2889, 1670, 1602, 1497; ^1H NMR δ 7.7–7.67 (2 H, Ar, m), 7.42–7.06 (13 H, Ar, m), 5.30 (1 H, d, J = 6 Hz), 4.24 (1 H, m), 3.94 (1 H, m), 3.64–3.47 (2 H, CH_2OCH_3, m), 3.41 (3 H, s, OCH_3), 3.19–3.06 (1 H, m) and 2.88–2.81 (1 H, m) [J = 11, 4, 6, 9 and J = 6, 9, CH_2Ph], 1.37 (2 d corresponding to two diastereomers, 3 H, CH_3, J = 3, 6); ^{13}C NMR δ 178.9, 178.8, 161.7, 161.6, 157.6, 157.5, 140.2, 139.2, 139.1, 129.6, 129.5, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 126.3, 126.2, 125.7, 125.6, 125.5, 104.3, 104.2, 83.1, 74.4, 74.2, 73.9, 59.2, 41.3, 34.5, 34.4, 17.7, 17.4; MS 452.23 (M^+, 20.56), 407 (32), 317 (43), 261 (16), 144 (13), 119 (32), 117 (12), 116 (13), 91 (100), 77 (36), 57 (19). Anal. Calcd for $C_{29}H_{28}N_2O_3$: C, 76.96; H, 6.24; N, 6.19. Found: C, 76.67; H, 6.08; N, 5.99.

HPLC separation of diastereomers was accomplished (Rainin Dynamax silica column 21.4-mm i.d. × 25-cm length) either using 6:94 EtOAc/CH_2Cl_2 as eluant (major diastereomer fast moving, t_R 6, mL/min, t_R = 16.225 for slow moving minor diastereomer, α = 1.068) or using Chiralcel Daicel OJ column (25 cm × 0.46 cm) using 98:2 hexane/EtOH, as eluant $t_R(1)$ = 9.965, $t_R(2)$ = 12.035, 0.87 mL/min, α = 1.21: ^1H NMR δ 7.76–7.62 (2 H, d, Ar protons), 7.35–7.06 (13 H, m, Ar protons), 5.29–5.27 (d, 1 H, J = 6 Hz), 4.22–4.18 (1 H, m, J = 6 Hz), 3.81 (1 H, sext), 3.62–3.48 (2 H, md, J = 27, 6, 3 Hz), 3.48 (3 H, s, CH_3O), 3.19–2.76 (2 H, md, J = 6, 9 Hz), 1.32–1.29 (3 H, d, J = 9 Hz, CH_3); ^{13}C NMR δ 178.1, 160.8, 156.8, 139.5, 138.4, 128.8, 128.3, 128.2, 127.9, 127.63, 127.5, 127.4, 127.2, 125.5, 124.8, 103.4, 82.2, 73.6, 73.2, 58.4, 40.5, 33.7, 14.3.

Table I, entry 3, same structural data as Table I, entry 2, except de. Silica column chromatography 1:4:4 EtOAc/CH_2Cl_2/hexane, R_f = 0.63, yield after chromatography 59.6%.

Table I, entry 4, same structural data as Table I, entry 2, except de, yield after purification 36%.

Table I, entry 5, same structural data as Table I, entry 2; yield after chromatography 42%.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-5-((*R*,*S*)-2′-hexyl)-3-phenylisoxazole (Table I, entry 6): colorless oil; yield 65%; preparative TLC (EtOAc/hexane/CH_2Cl_2, 1:4:2, R_f 0.415). HPLC separation of diastereomers was accomplished using Chiralcel OJ column (25 cm × 0.46 cm, flow rate = 0.87 mL/min $t_R(1)$ = 6.955, $t_R(2)$ = 7.83, α = 1.126) and 98:2 hexane/EtOH as eluant: IR (neat, cm^{-1}) 3063, 3032, 2954, 2932, 2874, 1670, 1660, 1458; ^1H NMR δ 7.74–7.68 (2 H, m, Ar protons), 7.42–7.22 (8 H, m, Ar protons), 5.40–5.36 (1 H, dd, J = 6 Hz), 4.31–4.25 (1 H, m), 3.70–3.59 (3 H, m), 3.45–3.43 (3 H, 2 s due to two diastereomers, OCH_3), 1.84–1.67 (2 H, 2 bs), 1.39–1.37 (3 H, dd, J = 6 Hz), 1.30 (4 H, bm), 0.87 (3 H, t); ^{13}C NMR δ 179.0, 178.8, 160.8, 160.7, 157.1, 156.98, 139.6, 139.5, 128.7, 128.7, 128.3, 128.2, 127.9, 127.4, 127.2, 127.2, 124.9, 124.7, 103.3, 103.2, 82.3, 73.7, 73.5, 73.3, 58.4, 34.0, 31.6, 28.7, 21.7, 17.8, 17.7, 13.1; MS 420 (27), 419 (100), 418 (27), 417 (26), 375 (17), 374 (25), 373 (82), 362 (10), 261 (19), 257 (22), 125 (12), 119 (13), 113 (14), 104 (14), 91 (27). Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.614; H, 7.224; N, 6.693. Found: C, 74.51; H, 7.20; N, 6.77.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-phenyl-5-((1*R*,*S*)-1′-(methoxymethyl)prop-2′-yl)isoxazole (Table I, entry 7): pale yellow oil, yield after purification 85%, TLC (2:3 EtOAc/hexane) R_f 0.34; HPLC separation was accomplished using preparative Daicel Chiralcel column (25 cm × 0.46 cm, flow rate = 1.76 mL/min, $t_R(1)$ = 9.575, $t_R(2)$ = 11.60, α = 1.21); IR (neat, cm^{-1}) 3065, 3031, 2981, 2930, 1669, 1604, 1455; ^1H NMR δ 7.73–7.68 (2 H, m, Ar protons), 7.42–7.22 (8 H, m, Ar protons), 5.39 (1 H, d, J = 6 Hz), 4.29–4.23 (1 H, m), 3.98–3.93 (1 H, m), 3.77–3.55 (4 H, m), 3.43 (3 H, 2 s, two diastereomeric OCH_3), 3.32 (3 H, 2 s, two diastereomeric OCH_3), 1.41–1.38 (3 H, dd, J = 6, 6 Hz); ^{13}C NMR δ 176.3, 176.2, 160.9, 160.7, 156.9, 156.8, 139.5, 139.4, 128.9, 128.8, 128.7, 128.3, 128.2, 127.8, 127.6, 127.5, 127.3, 127.2, 127.1, 126.9, 124.8, 124.7, 124.6, 104.2, 104.1, 82.5, 82.2, 74.1, 73.9, 73.6, 73.4, 73.1, 58.4, 57.9, 57.8, 32.2, 32.1, 14.2, 14.1; MS 408 (30), 407 (100), 405 (14), 391 (15), 376 (13), 375 (40), 363 (16), 362 (14), 361 (52), 317 (16), 261 (10), 244 (34), 200 (9), 172 (10), 144 (12), 119 (16), 104 (18), 101 (15), 91 (29), 77 (17), 73 (21), 69 (11). Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.44; N, 6.89. Found: C, 70.84; H, 6.30; N, 6.82.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-phenyl-5-((1*R*,*S*)-1′-phenyl-1′-oxoprop-2′-yl)isoxazole (Table I, entry 8): preparative TLC (hexane/EtOAc, 2:1), R_f 0.42; IR (neat, cm^{-1}) 3063, 3036, 2989, 2831, 1960, 1901, 1819, 1740, 1686, 1450; MS exact mass calculated for $C_{29}H_{28}N_2O_4$ m/e 466.18938, obsd m/e 466.18925. Anal. Calcd for $C_{29}H_{26}N_2O_4$: C, 74.64; H, 5.62; N, 6.00. Found: C, 74.55; H, 5.62; N, 5.50.

The following example serves as the general procedure for the introduction of oxygen electrophiles (Table I, entries 9 and 21).

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-phenyl-5-((*R*,*S*)-1′-hydroxyeth-1′-yl)-isoxazole (Table I, Entry 9). Isoxazolyloxazoline **1a** (558.4 mg, 1.5407 mmol) was dissolved in THF (ca. 15 mL) and cooled to −78 °C under N_2 for 30 min. n-BuLi (0.705 mL, 2.4 M in hexane) was added dropwise via syringe. This mixture was stirred at −78 °C for 2 h. The Davis's reagent, N-(phenylsulfonyl)-3-phenyloxaziridine (1.5 equiv, 603 mg), was dissolved in 3 mL of THF and precooled and then added via cannula. The resulting mixture was stirred at −78 °C for 2 h. The reaction was then quenched with saturated NH_4Cl (2 mL) and warmed to rt. After concentration in vacuo the off-white solid was diluted with CH_2Cl_2 (30 mL) and washed with $NaHCO_3$ 5% (2 × 30 mL). After separation and extraction of the aqueous layers with CH_2Cl_2(2 × 20 mL), the combined organic layers were washed with H_2O (2 × 50 mL) and dried over anhydrous Na_2SO_4. Filtration, concentration, and silica gel radial chromatography (1:1 EtOAc/hexane, R_f 0.19) gave a colorless oil (478.06 mg, 82% yield); HPLC separation of diastereomers was accomplished using Chiralcel Daicel OJ column (25 cm × 0.46 cm, flow rate = 0.87 mL/min, $t_R(1)$ = 50.98, $t_R(2)$ = 58.41, α = 1.146) with 98:2 hexane/EtOH as eluant: IR (neat, cm^{-1}) 3221, 3063, 3036, 2982, 2885, 1678, 1647, 1601, 1450; ^1H NMR δ 7.59–7.14 (10 H, m, Ar protons), 6.87 (1 H, bs, OH), 5.45–5.43 (1 H, d, J = 6 Hz), 5.19–5.09 (1 H, sext, CH), 4.34–4.25 (1 H, m), 3.69–3.41 (2 H, m), 3.33 (3 H, s, OCH_3), 1.72–1.67 (3 H, t at 300 MHz, dd at 90 MHz, J = 6.6, 6.6 Hz); ^{13}C NMR δ 179.5, 179.2, 162.0, 161.9, 159.6, 159.5, 139.4, 129.8, 129.7, 129.4, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 125.4, 104.9, 104.7, 84.3, 84.2, 73.8, 73.7, 72.8, 63.3, 63.1, 63.1, 59.3, 59.2, 19.7, 19.4; MS: 380 (11), 379 (41), 378 (7), 377 (16), 364 (18), 363 (65), 334 (25), 333 (100), 317 (12), 216 (16), 200 (15), 198 (16), 164 (29), 144 (32), 119 (33), 118 (21), 117 (19), 105 (25), 104 (30), 91 (58), 77 (48), 55 (30). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.71; H, 5.87; N, 7.25.

The following example serves as the general procedure for the synthesis of hydrazinoisoxazolyloxazoline.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-5-[(*R*,*S*)-1′-[*N*,*N*′-bis(ethoxycarbonyl)-hydrazino]eth-1′-yl]isoxazole (Table I, Entry 10). Isoxazolyloxazoline **1a** (258.4 mg, 7.1298×10^{-1} mmol) was dissolved in anhyd THF (ca. 8 mL, 0.9 M solution) and cooled to −78 °C under

N_2 for 30 min. *n*-BuLi (0.33 mL of 2.4 M in hexane) was added dropwise via syringe. This mixture was stirred at −78 °C for 2 h. The precooled solution of diethyl azodicarboxylate (DEAD) (0.13 mL in 2 mL of THF) was added via cannula. The mixture was stirred at −78 °C for 2 h, and was then quenched by the addition of 0.5 mL of glacial AcOH. Extractive workup and silica gel column chromatography (EtOAc/CH_2Cl_2/hexane; 1:1:1, R_f 0.38) gave a viscous yellow oil (300.6 mg, 81% yield). HPLC separation of diastereomers was accomplished using Chiralcel OJ column (25 cm × 0.46 cm) with 98:2 hexane/EtOH as eluant $t_R(1)$ = 43.64, $t_R(2)$ = 47.03, α = 1.08): IR (neat, cm^{-1}) 3291, 3063, 2986, 2936, 1724, 1678, 1609, 1493; ^1H NMR δ 7.43–7.18 (10 H, m, Ar protons), 5.80 (1 H, bs, NH), 5.40 (1 H, bs), 4.23–4.11 (5 H, m), 3.71 (2 H, dd), 3.48–3.46 (3 H, 2 s, OCH_3), 1.76 (3 H, bs, CH_3 at C-5 position of isoxazole), 1.28 (3 H, t), 1.43–1.14 (3 H, t); ^{13}C NMR δ, 171.5, 161.2, 156.7, 155.9, 138.2, 129.0, 128.1, 127.9, 127.5, 127.2, 127.0, 124.8, 124.2, 103.1, 102.3, 82.4, 77.4, 73.4, 72.8, 62.6, 62.4, 61.8, 61.1, 58.5 (OCH_3), 16.4, 15.9, 14.9, 13.5; MS 537 (63) (M + 1), 636 (13), 448 (29), 363 (28), 362 (100), 315 (12), 199 (14), 144 (11), 143 (15), 132 (12), 104 (16), 91 (16), 77 (16); EI^+ *m/z* (relative intensity) 536 (9), 448 (24), 363 (29), 362 (100), 317 (17), 315 (19), 199 (29), 143 (27), 131 (27), 103 (28), 91 (34), 77 (31), 55 (17). Anal. Calcd for $C_{28}H_{32}O_7N_4$: C, 62.77; H, 6.01; N, 10.44. Found: C, 63.02; H, 5.85; N, 10.25.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-5-((*R*,*S*)-1′-phenylprop-2′-yl)-3-methylisoxazole (Table I, entries 11 and 16): workup and silica gel column chromatography with 10:1 CH_2Cl_2/EtOAc as eluant, R_f 0.65, gave the desired product in 66% yield: IR (neat, cm^{-1}) 3100, 3070, 3040, 2980, 2940, 1670, 1595, 1485; ^1H NMR δ 7.37–7.03 (10 H, m, Ar protons), 5.39–5.32 (1 H, dd, J = 6, 6 Hz, CH), 4.24–4.21 (1 H, m), 4.01–3.96 (1 H, sextet, lateral CH), 3.71–3.50 (2 H, md, J = 3, 6 Hz), 3.42 (3 H, s, OCH_3), 3.14–2.80 (2 H, md, J = 6, 9 Hz), 2.46 (3 H, 2 s, two diastereomers), 1.31 (3 H, dd, J = 3, 3 Hz, two diastereomers); ^{13}C NMR δ 177.3, 177.2, 158.5, 158.4, 156.9, 156.8, 140.3, 138.3, 128.3, 128.1, 128.0, 127.9, 127.8, 127.2, 125.3, 124.7, 124.6, 103.8, 103.7, 81.9, 73.4, 73.4, 58.7, 40.4, 40.3, 33.5, 16.8, 16.7, 10.9; MS 419 (12), 392 (25), 391 (100), 390 (33), 346 (21), 345 (81), 269 (11), 256 (11), 243 (23), 228 (38), 119 (39), 117 (11), 91 (99), 77 (8), 65 (7). Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.60; H, 6.66; N, 7.45.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-methyl-5-((*R*,*S*)-2′-pentyl)isoxazole (Table I, entry 17): same procedure as (Table I, entry 2), preparative TLC separation, 1:4:1 EtOAc/hexane/CH_2Cl_2 as eluant, R_f 0.36; IR (neat, cm^{-1}) 3034, 2960, 2931, 2874, 2827, 1669, 1608; ^1H NMR ($CDCl_3$) δ 7.41–7.31 (5 H, Ar protons), 5.42–5.39 (1 H, d, J = 9 Hz), 4.28–4.22 (1 H, m), 3.73–3.68 and 3.58–3.52 (3 H, 2 series of m), 3.14 (3 H, 2 s, two diastereomers, OCH_3), 2.18 (3 H, 2 s, two diastereomers, C-3 CH_3 group of isoxazole), 1.77–1.70 and 1.63–1.52 (2 H, 2 series of m, CH_2), 1.31–1.29 (3 H, d, J = 6 Hz, CH_3), 1.26–1.21 (2 H, m, CH_2), 0.89–0.83 (3 H, m, CH_3); ^{13}C ($CDCl_3$) ppm 179.2, 179.1, 159.5, 158.2, 140.8, 128.8, 128.2, 125.5, 125.3, 104.5, 82.9, 74.5, 74.4, 59.4, 37.4, 37.1, 32.1, 20.5, 18.8, 18.5, 13.9, 13.8, 12.0; MS 344 (11), 343 (48), 313 (11), 297 (100), 180 (24), 164 (5), 150 (5), 119 (51), 91 (29). Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 69.96; H, 7.72; N, 8.11.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-methyl-5-((*R*,*S*)-2′-hexyl)isoxazole (Table I, entry 18); same procedure as Table I, entry 2, preparative TLC separation with 1:4:2 EtOAc/hexane/CH_2Cl_2 as eluant, R_f 0.46; HPLC separation of diastereomers was accomplished using a Daicel Chiralcel column (25 cm × 0.46 cm, flow rate = 0.87 mL/min, $t_R(1)$ = 10.15, $t_R(2)$ = 11.36, α = 1.12); IR (neat, cm^{-1}) 3090, 3066, 3032, 2957, 2874, 1670, 1607, 1497; ^1H NMR δ 7.37–7.26 (5 H, m, Ar protons), 5.42–5.40 (1 H, d, J = 6 Hz), 4.28–4.21 (1 H, m), 3.74–3.52 (2 H, md, J = 6.5, 6, 3), 3.44 (3 H, s, OCH_3), 2.49–2.48 (3 H, 2 s, two diastereomers, C-3 methyl group of isoxazole), 1.89–1.61 (2 H, 2 bs), 1.31–1.29 (3 H, d, J = 6 Hz, CH_3), 1.26 (4 H, m, 2 CH_2), 0.88–0.85 (3 H, q, CH_3); ^{13}C NMR δ 178.3, 178.2, 158.7, 157.3, 140.0, 139.9, 127.9, 127.9, 127.3, 127.2, 124.6, 124.5, 103.7, 82.0, 81.9, 73.6, 58.4, 34.1, 33.8, 31.5, 31.4, 28.7, 28.6, 21.6, 21.5, 17.8, 17.7, 12.9, 11.1, 11.0; MS 358 (23), 357 (100), 356 (12), 355 (13), 313 (10), 312 (20), 311 (80), 194 (25), 149 (7), 119 (47), 91 (31), 79 (6). Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.759; H, 7.92; N, 7.86. Found: C, 70.64; H, 7.69; N, 7.60.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-methyl-5-[(*R*,*S*)-1′-(methoxymethyl)-2′-propyl]isoxazole (Table I, entry 19): same procedure as Table I, entry 2, preparative TLC separation using 1:1 EtOAc/hexane (R_f 0.65) gave a colorless oil in 85% yield; HPLC separation of diastereomers was accomplished using a Daicel Chiralcel column (25 cm × 0.46 cm, flow rate 0.87 mL/min, $t_R(1)$ = 10.47, $t_R(2)$ = 11.18, α = 1.07) using 98:2 hexane/EtOH as eluant); IR (neat) cm^{-1} 3065, 3033, 2982, 2881, 1671, 1612, 1494; ^1H NMR δ 7.40–7.27 (5 H, m, Ar protons), 5.43–5.41 (1 H, d, C-5 oxazoline, J = 6 Hz), 4.27–4.23 (1 H, m), 4.07–4.00 (1 H, sext), 3.73–3.42 (4 H, md, J = 7 and 6 Hz), 3.43 (3 H, s, OCH_3 group of oxazoline), 3.11–3.08 (3 H, 2 s, two diastereomers, OCH_3 group of electrophile), 2.48 (3 H, 2 s, two diastereomers, C-3 methyl group of isoxazole), 1.33–1.30 (3 H, dd, C-5 methyl group of isoxazole, J = 6 and 6 Hz); ^{13}C NMR δ 175.6, 158.7, 157.1, 139.9, 127.9, 127.3, 124.5, 124.4, 104.5, 82.0, 74.2, 73.6, 73.4, 58.4, 57.9, 57.8, 32.2, 32.1, 14.4, 14.1, 11.0, 10.7; MS 346 (12), 345 (56), 314 (12), 313 (44), 301 (19), 300 (19), 267 (18), 255 (53), 182 (45), 149 (17), 138 (14), 119 (68), 105 (10), 91 (53); EI 345 (1), 344 (2.5), 313 (29), 300 (24), 299 (100), 267 (15), 150 (10), 119 (62), 105 (12), 77 (13), 55 (11). Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.37; H, 6.90; N, 7.87.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-methyl-5-((*R*,*S*)-1′-phenyl-1′-oxoprop-2′-yl)isoxazole (Table I, entry 20): same procedure as Table I, entry 2, preparative TLC separation with 2:1 hexane/EtOAc (R_f 0.31) gave a yellow oil; IR (neat, cm^{-1}) 3063, 3034, 2985, 2891, 1677, 1660, 1612, 1450; ^1H NMR δ 7.5–7.2 (10 H, m, Ar protons), 5.7–5.5 (1 H, dt), 5.4–5.3 (1 H, dd), 4.3–4.2 (1 H, m), 3.8–3.44 (3 H, m), 3.38 and 3.41 (3 H, 2 s, two diastereomers), 2.475–2.471 (3 H, 2 s, two diastereomers), 1.64–1.61 (3 H, 2 d, two diastereomers); ^{13}C NMR δ 196.6, 175.7, 173.3, 173.2, 159.5, 158.1, 157.6, 140.4, 140.3, 135.7, 135.6, 133.2, 128.8, 128.7, 128.54, 128.50, 128.3, 128.2, 125.5, 105.4, 105.3, 83.1, 74.4, 74.2, 74.1, 59.3, 41.3, 41.2, 22.0, 20.1, 14.9, 11.9, 11.2, 4.8, 4.1; MS 406 (17), 405 (64), 404 (24), 360 (15), 359 (53), 242 (31), 164 (16), 119 (12), 105 (100), 91 (18), 77 (24); EI 405 (1.7), 404 (7), 360 (5), 359 (21), 137 (3), 119 (9), 115 (20, 106 (8), 105 (100), 91 (14), 58 (3), 55 (4); Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.92. Found: C, 70.69; H, 6.04; N, 6.30.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-methyl-5-((*R*,*S*)-1′-hydroxyeth-2′-yl)-isoxazole (Table I, entry 21): same procedure as Table I, entry 9, silica gel column separation with 3:7 EtOAc/hexane (R_f 0.33) as eluant gave an oil in 63% yield; IR (neat, cm^{-1}) 3383 (max), 3248 (max), 3090, 3066, 3032, 2985, 2932, 2898, 1655, 1607, 1454; ^1H NMR δ 7.41–7.27 (5 H, m, Ar protons), 7.15 (1 H, bs, OH), 5.57–5.55 (1 H, d, J = 6 Hz), 5.11–5.05 (1 H, q), 4.30–4.25 (1 H, m), 3.72–3.53 (2 H, m, CH_2 of CH_2OCH_3 group), 3.43 (3 H, s, OCH_3), 2.46 (3 H, s, C-3 methyl group of isoxazole), 1.64–1.61 (3 H, 2 d, two diastereomers, C-5 lateral CH_3, J = 6 and 6 Hz); ^{13}C NMR δ 178.4, 178.1, 159.0, 158.3, 131.0, 130.9, 128.0, 127.6, 124.5, 124.4, 104.1, 83.4, 72.9, 72.8, 72.5, 62.5, 62.4, 58.5, 19.1, 19.0, 10.9; MS 318 (19), 317 (99), 302 (10), 301 (56), 299 (22), 272 (17), 271 (100), 267 (22), 255 (10), 182 (6), 164 (33), 154 (11), 136 (30), 132 (21), 119 (23), 91 (37), 82 (15). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.43; H, 6.31; N, 8.92.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-methyl-5-[(*R*,*S*)-1′-[*N*,*N*′-bis(ethoxycarbonyl)hydrazino]-1′-ethyl]isoxazole (Table I, entry 22): same procedure as Table I, entry 10, silica gel column separation using 4:2:0.4 EtOAc/CH_2Cl_2/hexane (R_f 0.24) as eluant gave a viscous amber oil in 66% yield; IR (neat, cm^{-1}) 3290 (s), 2985, 2832, 1721, 1674, 1613, 1458. ^1H NMR δ 7.43–7.18 (5 H, m, Ar protons), 5.85 (1 H, bs, NH), 5.39–5.37 (1 H, d, J = 6 Hz), 4.33–4.29 (1 H, m), 4.27–4.13 (4 H, m), 3.68–3.58 (2 H, m), 3.45 (3 H, 2 s, two diastereomers, OCH_3), 2.46 (3 H, s, C-3 methyl group of isoxazole), 1.61 (3 H, bs), 1.31–1.24 (3 H, t), 1.19 (3 H, bs); ^{13}C NMR δ 173.3, 158.8, 156.6, 155.7, 154.4, 139.3, 128.0, 127.5, 124.6, 103.9, 82.4, 73.5, 73.3, 61.8, 61.1, 58.4, 51.0, 15.1, 13.6, 13.5, 11.0; MS 476 (22), 475 (91), 429 (17), 386 (38), 312 (15), 300 (100), 253 (21), 240 (14), 164 (12), 137 (14), 91 (19). Anal. Calcd for $C_{23}H_{30}N_4O_7$: C, 58.22; H, 6.37; N, 11.81. Found: C, 57.86; H, 6.37; N, 11.62.

The following example serves as the general procedure for the

synthesis of sulfur-containing isoxazolyloxazolines (Table I, entries 23–25 and 27).

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-methyl-5-[(*R*,*S*)-1′-(phenylthio)-1′-ethyl]isoxazole (Table I, Entry 23). Compound **2** (541.3 mg, 1.8022 mmol) was dissolved in freshly distilled THF (ca. 18 mL, 1 M solution) and cooled to −78 °C under N_2 for 30 min. *n*-BuLi (0.826 mL of 2.40 M in hexane) was added dropwise via syringe, and the mixture was stirred for 2 h at −78 °C. The precooled solution of diphenyl disulfide (805.4 mg, in 3 mL of THF) was added via cannula. The reaction mixture was stirred for 2 h at −78 °C and was then quenched with glacial acetic acid (1 mL) at −78 °C. Silica gel column chromatography using 2:1 hexane/EtOAc (R_f 0.32) as eluant gave a pale yellow oil (459.5 mg, 62% yield): IR (neat, cm^{-1}) 3063, 3032, 2978, 2880, 1676, 1608, 1458; ^1H NMR δ 7.37–7.18 (10 H, m, Ar protons), 5.38–5.36 (1 H, 2 d, J = 7.33 and 7.08 Hz, 90-MHz NMR), 5.25–5.20 (1 H, q, lateral C-5 CH), 4.23–4.09 (1 H, 2 m), 3.69–3.62 (1 H, m), 3.53–3.45 (1 H, m), 3.41 (3 H, 2 s, two diastereomers), 2.46–2.44 (3 H, d), 1.69–1.64 (3 H, t, with 300 MHz but at 90 MHz dd, J = 7.33 and 7.07 Hz); ^{13}C NMR δ 173.5, 173.4, 158.4, 158.3, 156.5, 156.3, 139.4, 133.3, 132.8, 131.9, 131.8, 127.8, 127.7, 127.4, 127.3, 127.2, 124.8, 124.6, 124.0, 82.2, 82.1, 73.5, 73.4, 73.3, 58.3, 58.2, 37.9, 37.7, 17.7, 17.4, 10.95; MS 410 (28), 409 (91), 408 (100), 299 (21), 267 (27), 255 (27), 246 (45), 231 (41), 164 (23), 136 (42), 132 (22), 119 (26), 111 (49), 110 (68), 109 (31), 91 (58), 77 (21), 66 (14). Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found: C, 67.51; H, 5.92; N, 6.88.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-3-methyl-5-[(*R*,*S*)-1′-(phenylthio)-1′-ethyl]isoxazole (Table I, Entry 26). Compound **5** (109.4 mg, 0.3 mmol) was dissolved in freshly distilled THF (ca. 10 mL) and cooled to −78 °C under N_2 for 1 h. *n*-BuLi was added dropwise via syringe. $CeCl_3$ was added (82.04 mg, predried at 140–150 °C, 0.08 mmHg for 2 h), and the mixture was stirred for 160 min at −78 °C. Methyl iodide (0.02 mL) was added dropwise, and the reaction mixture was allowed to warm to rt overnight. Quenching (5 mL of saturated NH_4Cl), extractive workup, and silica gel column chromatography (1:3:3 EtOAc/hexane/CH_2Cl_2, R_f 0.54) gave the desired product (21.9 mg, 19% yield). Structural data same as Table I, entry 23, except de.

4-[4,5-Dihydro-4(*S*)-*trans*-(methoxymethyl)-5(*S*)-phenyl-2-oxazolyl]-5-[(*R*,*S*)-1′-(2-pyridylthio)-1′-ethyl]-isoxazole (Table I, entry 27): same procedure as Table I, entry 23, preparative TLC separation using 3:1 hexane/EtOAc (R_f 0.70) gave a pale yellow oil in 63% yield; IR (neat, cm^{-1}) 3063, 3044, 2982, 2892, 1676, 1612, 1578; ^1H NMR δ 8.31–8.26 (1 H, dd, J = 6 and 3 Hz), 7.46–7.09 (5 H, m, Ar protons), 7.26–7.23 (1 H, dd, J = 3 and 3 Hz), 7.15–7.09 (1 H, dd, J = 6 and 9 Hz), 6.96–6.88 (1 H, md, J = 6, 3, 3, and 6 Hz), 6.02–5.95 (1 H, sextet), 5.45–5.36 (1 H, 2 d, J = 21 and 18 Hz), 4.25 (1 H, m), 3.73–3.50 (2 H, md, J = 3, 9, 6 and 3, 6 Hz), 3.44–3.43 (3 H, 2 s, two diastereomers, OCH_3), 2.48–2.47 (3 H, 2 s, two diastereomers), 1.81–1.77 (3 H, 2 d, two diastereomers, J = 9 and 9 Hz); ^{13}C NMR δ 173.8, 173.6, 158.8, 158.7, 156.7, 156.6, 156.3, 148.6, 148.5, 136.7, 135.1, 135.0, 127.9, 127.8, 127.7, 127.5, 127.3, 127.0, 124.7, 124.5, 124.4, 121.6, 121.3, 119.0, 118.9, 103.9, 103.8, 82.2, 73.7, 73.6, 73.5, 73.4, 58.4, 33.8, 33.7, 18.8, 10.9; MS 411 (27), 410 (100), 409 (37), 301 (20), 299 (15), 273 (9), 267 (9), 255 (19), 253 (18), 247 (39), 138 (15), 119 (13), 112 (59), 111 (23), 91 (16), 78 (15), 67 (10). Anal. Calcd for $C_{22}H_{23}N_3O_3S$: C, 64.52; H, 5.66; N, 10.26. Found: C, 64.34; H, 5.65; N, 10.27.

4-[*N*-(2-Hydroxy-3-methoxy-1-phenylpropyl)carbamoyl]-3-phenyl-5-((*R*,*S*)-1′-phenylprop-2′-yl)isoxazole. The compound in Table I, entry 2, (69.7 mg, 0.15 mmol) was refluxed for 17 h with 3 N HCl (12 mL), cooled to rt, diluted (100 mL H_2O), extracted (3 × 20 mL $CHCl_3$), and dried (Na_2SO_4). Filtration and concentration, followed by silica gel column chromatography using 1:3:1 EtOAc/CH_2Cl_2/hexane (R_f 0.6) as eluant, gave the amide as an oil (36.5 mg, 50% yield). HPLC separation of diastereomers was accomplished using a Daicel Chiralcel OJ column (25 cm × 0.46 cm, flow rate 0.87 mL/min, $t_R(1)$ = 52.88, $t_R(2)$ = 59.20, ratio of diastereomers 69:31) and 98:2 hexane/EtOH as eluant and shows no racemization: ^1H NMR δ 7.54–7.09 (15 H, m, Ar protons), 5.88–5.83 (1 H, t, J = 9 and 6 Hz), 4.85–4.81 (1 H, 2 d, J = 3 and 3 Hz), 4.23–4.15 (1 H, m), 3.84–3.79 (1 H, m), 3.84–3.79 (1 H, quint), 3.69–3.62 (1 H, m), 3.40–3.34 (2 H, dd, J = 3 and 3 Hz), 3.22–3.18 (3 H, 2 s), 3.15–2.82 (2 H, md, J = 3, 6, and 9), 1.33–1.30 (3 H, 2 d, two diastereomers, J = 3 and 3 Hz); ^{13}C NMR δ 178.0, 177.7, 161.4, 159.1, 140.1, 138.2, 129.3, 128.2, 128.0, 127.9, 127.5, 127.4, 127.3, 126.8, 125.6, 125.0, 109.8, 73.6, 73.5, 71.9, 58.2, 54.3, 54.12, 40.4, 33.5, 17.1, 16.9; MS 472 (9), 471 (33), 454 (23), 453 (79), 364 (12), 363 (33), 333 (14), 332 (43), 292 (14), 291 (15), 290 (65), 200 (10), 164 (11), 147 (17), 146 (11), 144 (12), 119 (52), 118 (14), 117 (15), 107 (22), 104 (24), 91 (100), 77 (17), 57 (18), 55 (19). Anal. Calcd for $C_{29}H_{30}N_2O_4$: C, 74.02; H, 6.43; N, 5.95. Found: C, 74.29; H, 6.42; N, 5.82.

[(3-Methyl-5-ethylisoxazol-4-yl)carbonyl]-2(*S*)-pyrrolidinemethanol (7). Thionyl chloride (24 mL) was added to freshly sublimed 3-methyl-5-ethylisoxazole-4-carboxylic acid (2.97 g, 0.019 mol, 50–55 °C, 0.25 mmHg) and stirred overnight. Concentration in vacuo and Kugelrohr distilation (40–42 °C, 0.06 mmHg) gave the isoxazole acid chloride as a colorless oil (3.32 g, 94.6% yield) which was transferred to an addition funnel, and dry $CHCl_3$ ($CaCl_2$, 10 mL) was added. A flask was charged with $CHCl_3$ (35 mL), (*S*)-(+)-pyrrolidinemethanol (1.1 equiv), 1.96 mL), and triethylamine (5.0 mL) and cooled to 0 °C under N_2, and to this solution was added dropwise the solution of isoxazole acid chloride in $CHCl_3$ at 0 °C, and the reaction mixture was allowed to come to rt overnight. The clear solution was washed with aqueous 2 N HCl (2 × 60 mL), 2 N NaOH (2 × 60 mL), and water (250 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, concd in vacuo, and chromatographed on silica gel to produce the product **7** as a yellow oil (3.83 g, 89% yield): IR (neat, cm^{-1}) 3403, 2976, 2934, 2880, 1609, 1435; ^1H NMR δ 4.39–4.29 (br m, 1 H), 3.81–3.63 (md, 2 H), 3.4–3.2 (m, 3 H), 2.8–2.7 (q, 2 H, isoxazole C-5 lateral CH_2), 2.27 (s, 3 H, isoxazole C-3 CH_3), 2.23–2.12 (m, 1 H), 1.93–1.61 (m, 3 H), 1.33–1.26 (t, 3 H, isoxazole C-5 lateral CH_3); ^{13}C NMR δ 167.5, 164.7, 158.1, 113.7, 65.8, 60.9, 49.7, 28.3, 24.7, 18.1, 13.8, 10.4; MS 239 (40.75, M + 1), 221 (9, M − H_2O), 208 (9), 207 (56), 138 (100), 84 (14), 82 (14), 70 (10), 57 (27).

Control: Authentic Racemic 8. 3-Methyl-5-((*R*,*S*)-2′-hexyl)isoxazole-4-carboxylic Acid. Freshly distilled (70–90 °C, 0.07 mmHg) 4,4-dimethyl-2-(3-methyl-5-(2′-hexyl)isoxazolyl)oxazoline[8a] (450 mg, 1.7021 mmol) was refluxed with 3 N HCl (35 mL) for 15 h. Extractive workup and radial silica gel chromatography (1:11 EtOAc/CH_2Cl_2) gave the desired isoxazole-carboxylic acid as a white-creamy solid (315.4 mg, 87.7% yield): MS 212 (9.9, M + 1), 211 (15.5), 169 (20), 168 (10), 155 (100), 150 (15), 83 (31), 82 (21), 69 (14), 57 (27), 55.032 (18.33), 54.997 (27.82); EI 211 (21.41, M^+), 169 (13), 168 (11), 155 (100), 150 (15), 83 (20), 82 (15), 58 (99), 57 (15), 55 (20). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.53; H, 7.99; N, 6.71.

***r*-3-Methyl-5-((*RS*)-2′-hexyl)-4-[[(*S*)-2′-(hydroxymethyl)-*N*-pyrrolidino]carbonyl]isoxazole (8).** The 3-methyl-5-((*R*,*S*)-2′-hexyl)isoxazole-4-carboxylic acid from above (429.8 mg, 2.0343 mmol) was treated with $SOCl_2$ (8 mL) and stirred overnight. Concentration and Kugelrohr distillation (70 °C, 0.1 mmHg) gave the corresponding isoxazole acid chloride as a colorless oil (328.5 mg, 70.3% yield), which was diluted with dry $CHCl_3$ (ca. 10 mL) and transferred to an addition funnel. A round-bottom flask was charged with dry $CHCl_3$ (10 mL), (*S*)-(+)-2-pyrrolidinemethanol, and Et_3N (0.4 mL) and cooled to 0 °C. To this solution was added the solution of isoxazole acid chloride, dropwise under N_2. The reaction was allowed to warm to rt overnight. Extractive workup (washing with 2 × 30 mL of 2 N HCl, 2 × 30 mL of 2 N NaOH, back-extraction of aqueous layer with 3 × 20 mL of $CHCl_3$). The combined $CHCl_3$ layers were dried over anhyd Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 EtOAc/hexane, R_f 0.75) gave the desired product **7** as yellow oil (406.8 mg, 96% yield): IR (neat) cm^{-1} 3410 (OH), 2956, 2934, 2838, 1703, 1613, 1433; ^1H NMR δ 4.50 (br s, 1 H), 4.4 (br s, 1 H), 3.54–3.49 (m, 2 H), 3.2 (br t, 3 H), 2.83 (br s, 2 H), 2.55–2.4 (m, 3 H), 2.09–2.08 (2 s, 3 H, two diastereomers, isoxazole lateral C-5 CH_3), 2.01 (br s, 1 H), 1.77 (br s, 1 H), 1.59–1.42 (m, 2 H), 1.15–1.08 (t, 3 H), 0.69–0.64 (t, 3 H); ^{13}C NMR δ 174.5, 174.4, 164.7, 157.1, 156.9, 112.8, 66.5, 60.9, 60.8, 49.7, 49.6, 35.2, 34.4, 32.5, 32.4, 29.4, 29.3, 28.4, 28.3, 24.5, 24.4, 22.5, 22.4, 18.6, 18.5, 18.1, 13.8, 13.6, 10.4; MS 295 (37.33, M + 1), 195 (13), 194 (100), 85 (11), 84 (11), 70 (20), 57 (20), 55 (19); EI 294 (0.5, M^+), 263 (17), 195 (13), 194 (100), 85 (11), 70

(9). Anal. Calcd for $C_{16}H_{28}N_2O_3$: C, 65.27; H, 8.90; N, 9.51. Found: C, 65.03; H, 8.93; N, 9.52. A LIS study indicated a 48:52 ratio of diastereomers.

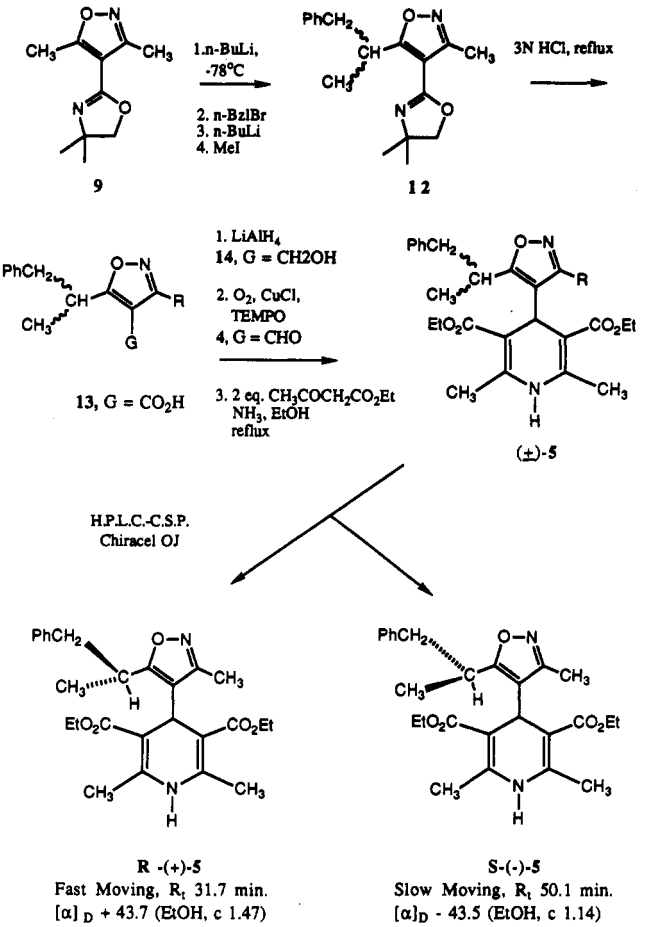
3-Methyl-5-((*R*,*S*)-2′-hexyl)-4-[[(*S*)-2′-(hydroxymethyl)-*N*-pyrrolidino]carbonyl]isoxazole (Table II, Entry 1). Isoxazole 7 (129.9 mg, 0.545 mmol) was added to dry THF (10 mL), and the solution was cooled to −78 °C for 30 min. To this solution was added a precooled solution of *n*-BuLi/TMEDA (3 mL of 0 °C THF, 0.36 mL of TMEDA, and 1.05 mL of 2.29 M *n*-BuLi in hexane) dropwise under an inert atmosphere, and the mixture was stirred at −78 °C for 2 h. *n*-Butyl bromide (0.062 mL) was added slowly, and reaction mixture was allowed to warm to rt overnight. Quenching, extractive workup, and preparative TLC chromatography (2:1 EtOAc/hexane, R_f 0.75) gave the desired compound 8 as yellow oil. (68.01 mg, 42% yield); HPLC separation of diastereomers was accomplished using a Daicel Chiralcel OJ column (25 cm × 0.46 cm, flow rate = 1.76 mL/min, $t_R(1)$ = 9.85, $t_R(2)$ = 12.06, α = 1.224) and using 98:2 hexane/EtOH as eluant. Structural data was the same as for authentic diastereomeric mixture described above, with the exception that LIS indicated a 13:87 ratio.

3-Methyl-5-[(*R*,*S*)-1′-(phenylthio)-1′-ethyl]-4-[[(*S*)-2′-(hydroxymethyl)-*N*-pyrrolidino]carbonyl]isoxazole, 8 (Table II, Entry 2). Isoxazolecarboxamide 7 (581.5 mg, 2.4403 mmol) in THF (ca. 15 mL) under N_2 was cooled to −78 °C. *n*-BuLi was added dropwise by syringe (4.75 mL of 2.26 M in hexane) at −78 °C and stirred for 2 h. Diphenyl disulfide was added via cannula (1.094 g dissolved in 3 mL of THF and precooled) and stirred for 2 h, after which time the reaction was quenched (1.5 mL of glacial AcOH). Short silica gel chromatography and then preparative TLC (2:1:1 hexane/EtOAc/MeOH, R_f 0.5) gave the desired compound as a yellow oil (457 mg, 54% yield); HPLC separation of diastereomers was accomplished using a Daicel Chiralcel column (25 cm × 0.46 cm, flow rate 0.87 mL/min, $t_R(1)$ = 43.67, $t_R(2)$ = 47.93, α = 1.098, diasteromeric ratio 39:61): IR (neat, cm^{-1}) 3415, 3062, 2974, 2880, 1621, 1470; ^1H NMR δ 7.38–7.27 (m, 5 H, Ar-H), 4.55–4.49 (m, 1 H), 4.29 (br s, 1 H), 3.77–3.66 (dm, 2 H), 3.16 (dm, 2 H), 2.27–2.25 (ds, 3 H, diastereomers), 2.15–1.85 (d br s, 2 H), 1.78–1.52 (m, 6 H); diastereomeric ratio 42:58 (dd, 3 H, J = 7.33, 7.33, for isoxazole C-5 lateral CH_3, 90 MHz); ^{13}C NMR δ 169.8, 169.6, 163.2, 163.0, 156.4, 132.3, 132.0, 131.8, 128.3, 128.0, 127.4, 127.2, 112.8, 112.7, 65.8, 65.4, 60.4, 60.2, 48.7, 48.5, 38.2, 27.6, 27.4, 23.8, 23.6, 18.4, 17.6, 9.7; MS 347 (88, M + 1), 346 (28), 251 (13), 247 (17), 246 (100), 245 (33), 239 (28), 237 (40), 207 (14), 205 (14), 138 (33), 137 (25), 136 (28), 111 (73), 110 (43), 109 (14), 102 (15), 100 (10), 84 (34), 82 (11), 70 (39), 57 (12), 55 (13); exact mass calcd for $C_{18}H_{22}N_2O_3S$ 346.13526, observed 346.1383820.

3-Methyl-5-[(*R*,*S*)-1′-[*N*,*N*′-bis(ethoxycarbonyl)-hydrazino]-1′-ethyl]-4-[[(*S*)-2′-(hydroxymethyl)-*N*-pyrrolidino]carbonyl]isoxazole (Table II, Entry 3). Isoxazole 7 (452.5 mg, 1.899 mmol) was dissolved in THF (ca. 15 mL) under N_2 and cooled to −78 °C for 30 min. *n*-BuLi was added (1.86 mL, 2.26 M in hexane) dropwise with stirring. The reaction was run for 2 h at −78 °C. Diethyl azodicarboxylate solution in THF (0.36 mL in 3 mL of THF and precooled) was added via cannula and stirred for 2 h. Quenching (5 mL of aqueous NH_4Cl), extractive workup, and preparative TLC separation (6:2:1 hexane/EtOAc/EtOH, R_f 0.23) gave the desired compound as a viscous red oil (664.2 mg, 85% yield); HPLC separation of diastereomers was accomplished using a Daicel Chiralcel column (25 cm × 0.46 cm, $t_R(1)$ = 30.15, $t_R(2)$ = 34.88, α = 1.157, diasteromeric ratio 38:62): IR (neat, cm^{-1}) 3433, 3283, 2981, 2947, 2861, 1713, 1616, 1435; ^1H NMR δ 7.68 (br s, 1 H), 5.57 (br s, 1 H), 4.22 (br s, 2 H), 4.17 (br s, 4 H), 3.85 (br s, 1 H), 3.70 (br s, 1 H), 3.34 (br s, 2 H), 2.28 (s, 3 H, isoxazole C-3 CH_3), 2.12–1.81 (3 br s, 4 H), 1.63–1.61 (d, 3 H, J = 6 Hz, isoxazole C-5 CH_3), 1.31–1.25 (t, 6 H, CH_3's of $CO_2CH_2CH_3$ group); ^{13}C NMR δ 166.8, 162.6, 156.2, 155.4, 154.7, 112.5, 63.9, 63.0, 62.0, 61.8, 60.9, 59.4, 59.3, 49.9, 48.4, 45.4, 27.1, 27.0, 23.6, 23.4, 19.1, 13.8, 13.4, 9.2, 9.1; MS 414 (24), 413 (100, M + 1), 381 (28), 367 (23), 324 (13), 312 (27), 267 (10), 253 (11), 251 (11), 240 (22), 239 (46), 237 (20), 221 (14), 207 (25), 152 (16), 138 (59), 128 (17), 105 (11), 102 (13), 100 (15), 84 (46), 82 (12), 70 (44), 62 (15), 57 (16). Anal. Calcd for $C_{18}H_{29}O_7$: C, 52.42; H, 6.84; N, 13.58. Found: C, 52.59; H, 6.80; N, 13.36.

Control: Preparation and Chromatographic Resolution of IDHP 5. The racemic IDHP 5 was prepared as outlined in Scheme III. Isoxazolyloxazoline 9 was prepared and metalated as previously described.[8g]

Scheme III. Preparation and Chromatographic Resolution of IDHP 5



3-Methyl-5-(1′-phenylprop-2′-yl)isoxazole-4-carboxylic acid (13): ^1H NMR δ 10.05 (br s, 1 H), 6.8–7.2 (m, 5 H), 3.83 (m, 2 H), 2.99 (m, 1 H), 2.72 (m, 1 H), 2.26 (s, 3 H), 1.12 (d, 3 H, J = 6 Hz); ^{13}C NMR 181.8, 170.0, 159.7, 138.5, 128.7, 128.3, 126.5, 108.5, 40.5, 34.5, 17.6, 11.4; MS 246 (24.6, M + 1), 91 (100, tropylium); EI 245 (12, M^+), 91 (100). An analytical sample was obtained by preparatiuve TLC (SiO_2, hexane/ethanol, 4:1) R_f 0.33. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.52; H, 6.23; N, 5.68.

3-Methyl-5-(1′-phenylprop-2′-yl)isoxazole-4-carbinol (14): ^1H NMR δ 7.15–7.27 (m, 3 H), 7.0 (d, 2 H), 3.99 (s, 2 H), 3.2 (m, 1 H), 2.85–2.99 (m, 2 H), 2.2 (s, 3 H), 1.425 (d, 3 H, J = 9 Hz); ^{13}C NMR δ 171.6, 159.4, 139.7, 128.9, 128.4, 126.5, 113.8, 53.3, 42.3, 34.6, 18.7, 9.8; IR 3387, 3027, 2982, 1627, 1012; MS 232 (46, M + 1), 214 (37, M − H_2O), 91 (100). An analytical sample was obtained by preparative TLC (SiO_2, hexane/ethanol/methylene chloride, 3:1:1) R_f 0.72. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.05. Found: C, 72.68; H, 7.47; N, 5.73.

(±)-3-Methyl-5-(1′-phenylprop-2′-yl)isoxazole-4-carbaldehyde (4): ^1H NMR δ 9.59 (s, 1 H), 7.2–7.3 (m, 3 H), 7.0–7.1 (m, 2 H), 3.66 (m, 1 H), 3.04 (m, 2 H), 2.41 (s, 3 H), 1.45 (d, 3 H, J = 6 Hz). ^{13}C NMR δ 183.2, 181, 158.7, 138.3, 128.7, 128.5, 126.8, 115.7, 41.6, 31.7, 18.2, 10.8. IR: 3027, 2974, 2931, 1687.7 ($\nu_{C=O}$), 1592; MS 230 (37, M + 1), 229 (12, M^+), 228 (5, M − 1, isoxazolylacylium), 91 (100). An analytical sample was obtained by preparative TLC (SiO_2, hexane/ethyl acetate, 5:1) R_f 0.27. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.1. Found: C, 73.08; H, 6.63; N, 6.02.

(±)-Diethyl 2,6-dimethyl-4-[5-(1′-phenylprop-2′-yl)-3-methylisoxazol-4-yl]-1,4-dihydropyridine-3,5-dicarboxylate (5): mp 146–7 °C; ^1H NMR δ 7.1–7.2 (m, 3 H), 6.9 (m, 2 H), 5.99 (br s, 1 H), 4.8 (s, 1 H), 4–4.2 (m, 4 H), 3.16 (m, 1 H), 3.09 (m, 1 H), 2.74 (dd, 1 H), 3.24 (s, 3 H), 2.23 (s, 3 H), 2.17 (s, 3 H), 1.1–1.3 (m, 9 H); ^{13}C NMR δ 172.8, 167.4, 166.9, 159.7, 143.3, 142.6, 140.1,

128.7, 128.2, 125.9, 120.7, 102.4, 102.2, 59.8, 59.7, 40.8, 33.6, 28.9, 19.5, 19.3, 19.0, 14.3, 13.3, 10.1; IR 3391, 3064, 2978, 2933, 1732, 1682, 1625, 1495, 1210; MS 453 (35, M + 1), 379 (16.2), 338 (11), 301 (35), 252 (100), 91 (17). An analytical sample was obtained by preparative TLC (SiO_2, hexane/ethyl acetate, 4:1), R_f 0.16. Anal. Calcd for $C_{26}H_{32}N_2O_5$: C, 69.01; H, 7.13; N, 6.19. Found: C, 68.75; H, 7.21; N, 6.33.

The racemic mixture was separated on a Daicel CHIRALCEL OJ column using 2% ethanol in hexane solvent with a flow rate of 1 mL/min. The enantiomers eluted approximately at 32 and 50 min, at ca. 50 °C. Enantiomeric purity was checked by reinjection after fraction collection. Within the limits of detection, the fractions were single enantiomers.

The procedures for X-ray crystallography[4,25,26] and radioligand binding[3,27] have been described previously, and are detailed in the supplementary material.

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Supplementary Material Available: 2D NOESY spectrum of 1, molecular mechanics calculations (including Cartesian coordinates) of *Z*- and *E*-1, tables of X-ray data for IDHP 5 (atomic coordinates and isotropic thermal parameters, bond lengths, bond angles, and anisotropic thermal parameters, H atom coordinates), molecular mechanics calculation for 5, and NOESY spectrum of 5 (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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A New Approach to Kainoids through Tandem Michael Reaction Methodology: Application to the Enantioselective Synthesis of (+)- and (−)-α-Allokainic Acid and to the Formal Synthesis of (−)-α-Kainic Acid†

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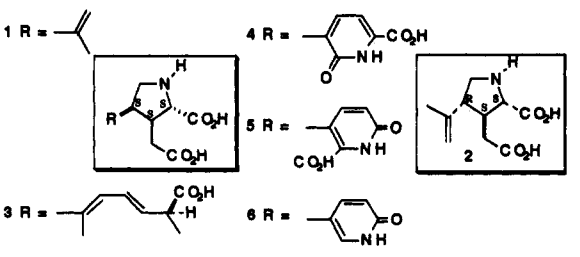
A convergent, one-pot construction of functionalized pyrrolidine ring systems has been developed. The method is based on a tandem Michael reaction initiated by an intermolecular conjugate addition of a nitrogen nucleophile to an electrophilic olefin followed by trapping of the generated enolate by a built-in α,β-unsaturated acceptor. After model studies verified the feasibility of the process and gave information about its stereochemical outcome, the strategy was successfully applied to kainoid synthesis. The construction of the basic pyrrolidine skeleton of all the members of the family requires coupling of a suitable electrophilic subunit with a common donor–acceptor fragment containing the nitrogen nucleophile. Thus, the enantioselective synthesis of (+)-α-allokainic acid (2) and the formal synthesis of its C-4 epimer (−)-α-kainic acid (1), have been accomplished using methyl vinyl ketone and 2-nitro-3-methyl-1,3-butadiene, respectively, as electrophilic partners of (*S*)-4-(benzylamino)-5-hydroxy-2-pentenoic acid ethyl ester (17), easily derived in six steps from D-serine. Although the acetyl group of methyl vinyl ketone is a logical precursor to the isopropenyl moiety of 2, the use of the nitrobutadiene is more appropriate for the synthesis of 1 because of the startling degree of control of the cyclization stereochemistry exerted by the nitro group.

Introduction

The term kainoid refers to a group of naturally occurring, nonproteinogenic amino acids possessing a pyrrolidine dicarboxylic acids nucleus as a common structural feature.[1] Certain members of this family (Chart I), such as α-kainic acid (1) and its C-4 epimer α-allokainic acid (2),[2] domoic acid (3),[3] and acromelic acids A (4), B (5),[4] and C (6),[5] are of considerable interest since they have been found to exhibit powerful biological properties, principally neuroexcitatory, which can be ascribed to their acting as conformationally restricted analogues of glutamic acid.

Chart I



From a synthetic viewpoint, these compounds present a considerable challenge,[6] most notably because the pyr-

† Taken in part from the thesis of "Dottorato di Ricerca in Scienze Chimiche" of G. Spalluto, Parma, Modena and Ferrara Universities, 1989–1991.

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