in vacuo to yield 0.102 g (67%) of aldehyde **32** as a pale yellow oil: IR (film) 3060, 2975, 2860, 2720, 1710, 1680, 1610, 1590, 1560, 1480, 1445, 1400, 1365, 1320, 1250, 1050, 920, 780, 755, 700, 630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.79 (3 H, s), 6.15 (1 H, d, J = 0.7 Hz), 6.68 (1 H, dd, J = 11, 5.5 Hz), 7.21 (1 H, d, J = 7.5 Hz), 7.34–7.50 (2 H, m), 7.90–8.00 (4 H, m), 8.74 (1 H, s), 8.93 (1 H, d, J = 5.1 Hz), 10.17 (1 H, s); mass spectrum, m/z (relative intensity) 346 (16), 345 (M^+, 74), 316 (100), 299 (19), 298 (55), 237 (24), 209 (70), 181 (61), 127 (20); exact mass calcd for $C_{20}H_{15}O_3N_3$ 345.1113, found 345.1102.

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Registry No. 1, 86047-14-5; **10**, 26156-51-4; **11**, 123148-66-3; **12**, 72716-87-1; (±)-**13**, 123148-67-4; (±)-**13** *N*-nitroso deriv, 123148-65-2; (±)-**14**, 123148-68-5; (±)-**15**, 123148-69-6; **16**, 123148-70-9; **17**, 15121-84-3; **18**, 579-71-5; **19**, 1520-21-4; (±)-**20**, 123148-71-0; (±)-**21**, 123148-72-1; (±)-**22**, 123148-73-2; (±)-**29**, 123148-74-3; (±)-**30**, 123148-75-4; (±)-**31**, 123148-76-5; (±)-**32**, 123148-77-6.

1,3-Dipolar Cycloaddition of Nitrile Oxides with 1,4-Dihydropyridines and Conformational Analysis of Isoxazolo[5,4-*b*]pyridines

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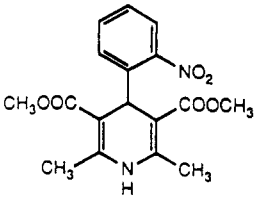
Cycloaddition reactions of nitrile oxides with 5-unsubstituted 1,4-dihydropyridine derivatives produced isoxazolo[5,4-*b*]pyridines in moderate to good yield. In each case examined, the reaction produced only a single isomer, the structure of which was assigned by NMR analysis and later confirmed by X-ray crystallography. Conformational analysis and comparison to known biologically active 1,4-dihydropyridines was carried out using molecular modeling and X-ray crystallographic data. Although overall the conformation of the pyridine ring of the isoxazolo[5,4-*b*]pyridines resembles that of the 1,4-dihydropyridines, molecular modeling predicted a higher degree of ring puckering for the bicyclic structure, which was quantitatively dependent on the hybridization of the ring nitrogen. The X-ray crystal structure revealed an even greater degree of puckering than predicted. An enantiospecific synthesis of the isoxazolo[5,4-*b*]pyridines employed intermediate diastereomeric esters. The isoxazolo[5,4-*b*]pyridines could be further elaborated by hydrolysis and decarboxylation to 5-cyano-1,4-dihydro-3-pyridinecarboxylic acids.

Recently, we have been seeking novel analogues of 1,4-dihydropyridine calcium channel blockers (CCB) that may have improved pharmacologic properties.[1] In this report we describe the synthesis and conformational analysis of some novel bicyclic analogues of the 1,4-dihydropyridine class of CCB, which includes nifedipine **1**. Bicyclic analogues are often useful for studying receptor–ligand interactions because they are rigid, geometrically defined derivatives that allow definition of spatial requirements for receptor binding. In the case of 1,4-dihydropyridines, bicyclic analogues have been reported that retain potent receptor affinity and either antagonist[2–4] or agonist[5] activity. A common feature of these derivatives is the retention of a 1,4-dihydropyridine ring as part of a relatively planar bicyclic ring system. Other conformationally restricted analogues of 1,4-dihydropyridines have been used to study the dihydropyridine receptor. The conformation of 1,4-dihydropyridines is an important factor for biological activity.[6,7] Therefore, to further define the role of ring conformation on activity, we prepared and then determined the conformation of a series of bicyclic compounds that resemble known, biologically active 1,4-dihydropyridines but lack the 1,4-dihydropyridine ring.

Previously reported bicyclic 1,4-dihydropyridine derivatives have been prepared by Hantzsch condensation of a cyclic aminoenone,[8] a diketone,[2,8,9] or a heterocyclic amine[10] or by manipulation of substituents on a preformed 1,4-dihydropyridine nucleus.[11] We chose to employ a cycloaddition approach to annelation because the resulting stereochemistry would be well defined. Most examples of cycloadditions involving dihydropyridines are the [2 + 2]-type.[12–14] Examples of 1,3-dipolar cycloaddition reac-



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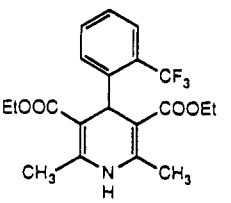

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† Universitē de Sherbrooke.

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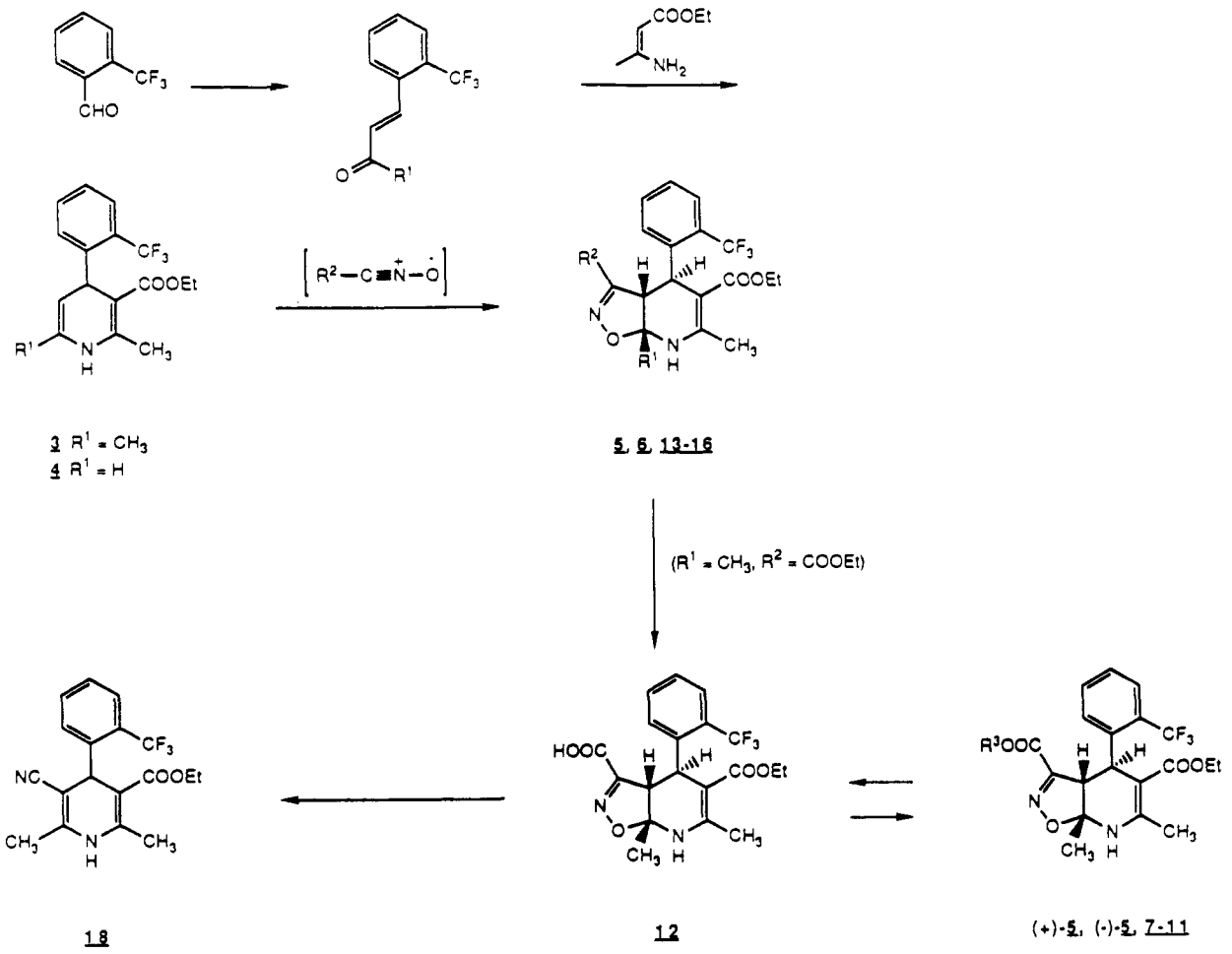
Scheme I



tions of 1,4-dihydropyridines are few,[15] although there are a number of examples of 1,3-dipolar cycloaddition involving 1,2-dihydropyridines.[14,16] We found no examples of dipolar cycloaddition reactions using highly substituted 1,4-dihydropyridines such as those associated with calcium channel blocking activity.

Nitrile oxides were employed as the 1,3-dipole because of their good reactivity with electron-rich double bonds and the ready availability of the substituted derivatives. In addition, evaluation of molecular models of the resulting isoxazolo[5,4-*b*]pyridines suggested that the conformation of the pyridine ring would be similar to that of the 1,4-dihydropyridine CCB, which have a relatively planar boat conformation.[17,18] The isoxazolo[5,4-*b*]pyridine ring system has not been prepared previously by 1,3-dipolar cycloaddition. A series of 4,7-dihydro derivatives was prepared by a Hantzsch-type cyclization of 5-amino-3-methylisoxazole.[10] A patent[19] reports the synthesis of two 3a,4,7,7a-tetrahydro derivatives, similar to the derivatives reported here, by cyclization of the corresponding 3-acetyl-1,4-dihydropyridine derivatives with hydroxylamine in poor yield. The stereochemistry of the cycloadduct was not reported.[20]

Results and Discussion

Cycloaddition. No reaction was observed between the 3,5-diester derivative **2** and carbethoxyformonitrile oxide (CEFNO).[21] The monoester derivative **3**, however, reacted with the nitrile oxide to produce the corresponding isoxazolo[5,4-*b*]pyridine, **5**, in 74% yield, as shown in Scheme I. The greater reactivity of **3** relative to **2** is likely due to a combination of reduced steric hindrance and increased electron density of the enamine-like double bond. In addition to the starting 1,4-dihydropyridine and the nitrile oxide dimer,[21] only a single product was detected. The cycloaddition of **4** similarly produced **6**. However, due to the instability of **4**, it was prepared and used without isolation. In general, yields of the cycloaddition from the requisite 5-unsubstituted and 5,6-diunsubstituted 1,4-di-

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(20) We have repeated the synthesis described in ref 19 and found that the cyclization reaction shown below gives the same stereochemistry as the 1,3-dipolar cycloaddition method described herein. Details may be found in the experimental section.

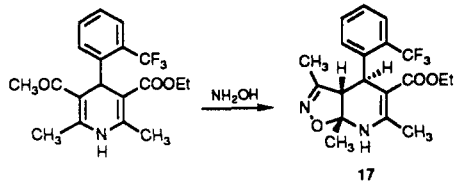

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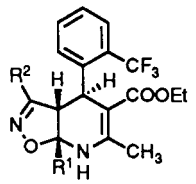
Table I. Isoxazolo[5,4-*b*]pyridine Derivatives



compd	R^1	R^2	yield, %	mp, °C	formula	anal.
5	CH_3	CO_2Et	74	158–9	$C_{21}H_{23}F_3N_2O_5$	C, H, N
(−)-**5**	CH_3	CO_2Et	32	156–8	$C_{21}H_{23}F_3N_2O_5$	C, H, N
(+)-**5**	CH_3	CO_2Et	61	156–7	$C_{21}H_{23}F_3N_2O_5$	C, H, N
6	H	CO_2Et	23	120–1	$C_{20}H_{21}F_3N_2O_5$	C, H, N
7	CH_3	CO_2Mn[b]	23	222–3	$C_{29}H_{37}F_3N_2O_5$	C, H, N
8	CH_3	CO_2Mn	18	114–6	$C_{29}H_{37}F_3N_2O_5$	C, H, N
9	CH_3	CO_2Pr	52	120–3	$C_{22}H_{25}F_3N_2O_5$	C, H, N, H_2O
10	CH_3	CO_2iPr	20	170–2	$C_{22}H_{25}F_3N_2O_5$	C, H, N
11	CH_3	CO_2Me	29	200–5	$C_{20}H_{21}F_3N_2O_5$	C, H, N
12	CH_3	CO_2H	97	174–5	$C_{19}H_{19}F_3N_2O_5$	C, H, N
13	CH_3	SO_2Ph	68	141–5	$C_{24}H_{23}F_3N_2O_5S$	C, H, N
14	CH_3	OEt	36	174–6	$C_{20}H_{23}F_3N_2O_4$	C, H, N
15	CH_3	CN	23	112–4	$C_{19}H_{18}F_3N_3O_3$	C, H, N
16	CH_3	COPh	40	197–8	$C_{25}H_{23}F_3N_2O_4$	C, H, N
17[a]	CH_3	CH_3	38	186–8	$C_{19}H_{21}F_3N_2O_3$	C, H, N

[a] See ref 20. [b] Mn = (−)-menthyl.

hydropyridines[22] with a variety of nitrile oxides were fair to excellent (Table I).

Nitrile oxide derivatives substituted with phenylsulfonyl, cyano, or phenylcarbonyl were used successfully to give **13**, **15**, and **16**, respectively. A variety of esters (**7**–**11**) were obtained by first saponifying the ethyl ester and reesterifying the resulting carboxylic acid with the appropriate alcohol and dicyclohexylcarbodiimide. The phenylsulfonyl derivative, **13**, is a useful intermediate in that it can be directly substituted with nucleophiles.[23] For example, treatment of **13** with lithium ethoxide produced the 3-ethoxy derivative **14**.

Structure Assignment. The regiochemistry of the cycloaddition was predicted to be [5,4-*b*] based on the complimentary dipoles of the nitrile oxide and the enamine double bond. Conversion of **5** by hydrolysis and decarboxylation[21] to the corresponding 5-cyano-1,4-dihydropyridine-3-carboxylic acid ester **18** (Scheme I) confirmed the assignment. The stereochemistry at C-3a,4 was assigned trans. This assignment is based on predicted steric hindrance by the pseudoaxial 4-phenyl group[17] to approach of the nitrile oxide. Supporting this assignment is the small coupling constant (1.7 Hz) observed in the NMR spectrum for the C-3a,4 protons, which is consistent with the trans stereochemistry.[1] In both of the two conformations possible for the cis isomer, a torsional angle of approximately 35° would exist, resulting in larger coupling constants. For the two trans conformations, the observed coupling constants are consistent with a conformation in which the phenyl group is pseudoaxial, similar to the conformation observed in 4-aryl-1,4-dihydropyridines.[17] The alternative equatorial conformation posesses a C-3a,4 H torsional angle of 180°, which is inconsistent with the observed small coupling constant. Finally, nuclear Overhauser enhancement difference spectra (NOEDS) show enhancement of C-3aH but not C-4H upon irradiation of the ring-junction methyl group, and a small (2%) enhancement of phenyl ring protons following irradiation of C-3aH. To make the assignment unambiguous and to provide precise conformational information, an X-ray crystal structure, Figure 1, was obtained that confirmed the structure assignment.

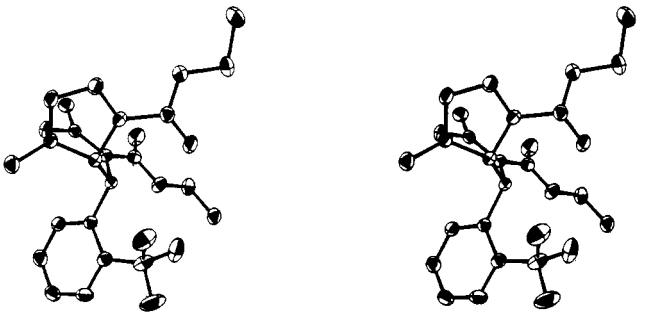


Figure 1. Stereoview of the X-ray crystal structure of (±)-**5**.

Stereospecific Synthesis. Since the 1,4-dihydropyridine receptor on the calcium channel is highly stereoselective,[24] we were interested in preparing pure enantiomers of one or more examples of the title compounds. The acid formed by saponification of **5** was reesterified with (−)-menthol. The resulting diastereomeric esters could be separated by flash chromatography.[25] Saponification and reesterification with ethanol produced the individual enantiomers of **5**. As mentioned above, the (ethoxycarbonyl)isoxazoles can be converted to **18**. Since the intermediate isoxazolo[5,4-*b*]pyridines have been resolved, this represents a stereospecific approach to 3-cyano-1,4-dihydropyridines.

Molecular Modeling and X-ray Crystallography. A correlation has been observed between the degree of puckering of the dihydropyridine ring and the calcium channel blocking activity.[6,7,17,18] Molecular modeling analyses were performed to compare the tetrahydropyridine ring conformation of **5** with the dihydropyridine ring of **2**, a potent calcium channel blocker.[6]

The structures of **2** and **5** were modeled using SYBYL.[26] Both structures were constructed starting with the crystal

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Table II. Quantification of ring puckering

compd	ring nitrogen hybridization	nitrogen torsion angles,[a] deg	sum of ring torsion angles, deg
5, modeled	N.3	126	158
5, modeled	N.pl3	174	61
5, crystal	-	163	156
2, modeled	N.pl3	175	49

[a] For planar geometry = 180°, for tetrahedral geometry = 120°.

coordinates of 1.[17] Each structure was optimized using Maximin2 with and without electrostatics. The sum of the ring torsion angles was used as an index of the degree of ring puckering.[17] The root mean square (RMS) fit of the ring to a plane defined by the atoms of the ring was also used to evaluate the extent of ring puckering.

A critical parameter for the calculation was the type of nitrogen defined for the dihydropyridine and tetrahydropyridine rings. For the dihydropyridine ring of **2**, the nitrogen was defined as N.pl3 with a planar geometry, based on the reported crystal data. For **5**, the compound was modeled twice, first with the nitrogen defined as N.pl3 and then as N.3 with an sp^3 configuration. Based on analogous structures extracted from the Cambridge crystallographic database, the nitrogen is probably intermediate between the two types, but likely closer to N.pl3 due to delocalization into the adjacent double bond. Thus the two calculations result in a range of potential degrees of pucker.

The degrees of puckering for **2** and **5** are listed in Table II. The results indicate that **5**, which contains the N.pl3-type nitrogen, is significantly more puckered than **2**. Using an N.3-type nitrogen produces an even larger difference. Inclusion of electrostatic parameters did not significantly affect the results.

The conformation of the crystal structure of **5** differs from the modeled structure in several respects. The 4-phenyl substituent does not bisect the tetrahydropyridine ring as is the general observation in 4-phenyl-1,4-dihydropyridines. Differences in the orientation of the ester groups is also apparent. As expected from the modeling study the geometry of the ring nitrogen is intermediate between planar and tetrahedral but closer to planar. The ring nitrogen is, however, less planar than the N.pl3 nitrogen in the model (Table II). The observed geometry reflects greater ring puckering than predicted by the model and substantially greater than is observed in 1,4-dihydropyridines. The fact that these compounds exhibit very weak affinity for the dihydropyridine receptor[27] is consistent with the hypothesis that planarity of the dihydropyridine ring is essential for good activity.

Experimental Section

General. Microanalyses were performed by the Parke-Davis Analytical Chemistry Section and were within ±0.4% of the calculated values for the specified elements, unless indicated. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$ solution on a Varian XL-200, EM-390, or IBM-100 spectrometer and are reported in δ units. IR spectra, reported in cm^{-1}, were recorded on a Nicolet FT IR spectrometer with KBr disks. Mass spectra were recorded on a VG 7070 E/HR mass spectrometer with an 11/250 data system. Silica gel 60 PF_{354} plates were used for thin-layer chromatography, and spots were visualized with UV light or iodine vapor. Flash chromatography refers to the method of Still et al.[25] Preparative MPLC employed Michel-Miller columns packed with 230-400 mesh silica gel. Organic extracts were dried over $MgSO_4$ unless indicated. Dry THF was obtained by distillation from potassium and benzophenone.

4-[2-(Trifluoromethyl)phenyl]-3-buten-2-one. To a mixture of 100 g (0.57 mol) of 2-(trifluoromethyl)benzaldehyde and 92.8 g (1.61 mol) of acetone was added 18 mL of freshly prepared aqueous 10% NaOH dropwise at a rate that maintained the reaction temperature between 25 and 31 °C. The reaction mixture was then stirred overnight at room temperature. The mixture was acidified with 1.0 N HCl and extracted with chloroform. The organic extracts were combined, dried (Na_2SO_4), and concentrated to an oil. Distillation in vacuo (103–105 °C, 2.0 mmHg) gave 83.8 g (69%): NMR ($CDCl_3$, 90 MHz) δ 7.95–7.20 (m, 5 H), 6.51 (d, J = 16.5 Hz, 1 H), 2.38 (s, 3 H).

3-[2-(Trifluoromethyl)phenyl]-2-propenal. A mixture of 2-(trifluoromethyl)benzaldehyde (7.4 g, 42 mmol) and acetaldehyde (5.0 g, 110 mmol) in 60 mL of ethanol and 300 mL water was cooled in an ice bath. A 10% sodium hydroxide solution (5.2 mL) was added dropwise at a rate that maintained the temperature between 10 and 20 °C. The reaction was maintained at 10–20 °C for 2 h and then allowed to warm gradually to room temperature overnight. After a total of 21 h, the mixture was acidified with 1.0 N HCl and extracted with chloroform. The organic layer was dried (sodium sulfate) and concentrated. The crude product was distilled (0.5 mmHg, 63–70 °C) to yield 2.9 g (34%) as an approximately equimolar mixture of *E* and *Z* isomers. The NMR (90 MHz) spectrum compared favorably with the corresponding spectrum of cinnamaldehyde.[28]

Ethyl 1,4-Dihydro-2,6-dimethyl-4-[2-(trifluoromethyl)-phenyl]pyridine-3-carboxylate (3). A solution containing 42.8 g (0.2 mol) of the butenone and 51.7 g (0.4 mol) of ethyl 3-amino-2-butenoate in 1 L of absolute ethanol was heated in a closed stainless steel vessel at 170 °C for 24 h. TLC of an aliquot of the reaction mixture showed only starting material and the 1,4-dihydropyridine product in the reaction mixture. The solution was concentrated, and the residue was dissolved in 150 mL of 1:1 hexanes–ethyl acetate and refrigerated for 72 h. Filtration produced 14.1 g of a yellow solid. The filtrate was concentrated, and the residue was redissolved in 50 mL of 1:1 hexanes–ethyl acetate and refrigerated for 5 h. A second crop of 10.7 g was collected. Total yield was 24.8 g (38%). The material was estimated to be about 90% pure by NMR and TLC. Attempts to further purify the compound by chromatography or recrystallization caused degradation and loss of material. Therefore the material was used quickly and without further purification: NMR ($CDCl_3$, 90 MHz) δ 7.65–6.90 (m, 4 H), 5.20 (b s, 1 H), 4.78 (d, J = 4.5 Hz, 1 H), 4.46 (d, J = 4.5 Hz, 1 H), 3.75 (q, J = 6.9 Hz, 2 H), 2.31 (s, 3 H), 1.58 (s, 3 H), 0.83 (t, J = 6.9 Hz).

Diethyl (3aα,4α,7aα)-3a,4,7,7a-Tetrahydro-6,7a-dimethyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]pyridine-3,5-dicarboxylate (5). The dihydropyridine, **3**, (10.0 g, 30.8 mmol) and ethyl chlorooximidoacetate[21] (7.0 g, 46.2 mmol) were dissolved in 250 mL of ether. Triethylamine (6.4 mL, 46.2 mmol) was added dropwise over 12 h using a syringe pump. The mixture was filtered and concentrated. The product was crystallized by trituration with ether. The solid was washed with several portions of ethyl acetate. The washings were combined and concentrated to yield an oil that was triturated with ether to yield a white solid, which was dried in vacuo to yield 10 g (74%): NMR (100 MHz, $CDCl_3$) δ 7.75 (dd, J = 10, 1.7 Hz, 1 H), 7.5–7.2 (m, 3 H), 5.67 (d, J = 1.7 Hz, 1 H), 4.52 (s, 1 H), 4.41 (q, J = 8.3 Hz, 2 H), 3.95 (qd, J = 8.3, 1.9 Hz, 2 H), 3.90 (s, 1 H), 2.50 (s, 3 H), 1.41 (t, J = 8.3 Hz, 3 H), 1.36 (s, 3 H), 1.08 (t, J = 8.3 Hz, 3 H).

Diethyl (+)-(3aα,4α,7aα)-3a,4,7,7a-Tetrahydro-6,7a-dimethyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]-pyridine-3,5-dicarboxylate [(+)-5]. To 4.50 g (8.18 mmol) of the low R_f product, **7**, was added 100 mL of Claisen's alkali followed by 50 mL of THF. The reaction mixture was stirred at room temperature for 5 h and concentrated. The residue was diluted with ice water, and concentrated hydrochloric acid was

(27) The compounds listed in Table I were evaluated for inhibition of [^{3}H]nitrendipine binding according to methods previously described.[1] None of the compounds exhibited significant inhibition (IC_{50} < 100 nM). Shih, Y. S.; Pugsley, T. A., unpublished results.

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added dropwise to pH 2. The precipitate was filtered, washed with water and ether, and then dried in vacuo overnight at 60 °C to yield 3.20 g (95%). The monoacid from the high R_f product, **8**, was similarly prepared except that this isomer was worked up via extraction of the aqueous acid layer with Et_2O. The NMR spectrum of each product were identical with that of the racemic acid, **12**. To a solution of 3.20 g (7.77 mmol) monoacid (prepared from low R_f product, **7**, with 0.095 g (0.777 mmol) of 4-(dimethylamino)-pyridine and 0.55 mL of ethanol in 70 mL of DMF) was added 1.68 g (8.16 mmol) dicyclohexylcarbodiimide. The reaction mixture was stirred at room temperature for 20 h, and the urea was filtered off. The filtrate was concentrated, and the residue was taken up in ethyl acetate. The organic layer was washed twice with water, dried, and concentrated. The crude product was purified by flash chromatography (10% diisopropyl ether in methylene chloride) to afford a white solid, which was recrystallized from diisopropyl ether and dried in vacuo at 80 °C to yield 2.10 g (61%). HPLC and 300-MHz NMR showed the diester to be 90% pure. The product was repurified by reverse-phase chromatography eluting with a gradient of 30–70% methanol in water to yield 350 mg, $[\alpha]_D = +392.5°$ (0.55, ethanol). HPLC indicates 97.5% purity and >99% enantiomerically pure.

Diethyl (−)-(3aα,4α,7aα)-3a,4,7,7a-Tetrahydro-6,7a-dimethyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]pyridine-3,5-dicarboxylate [(−)-5]. As for the enantiomer, to a solution of 1.73 g (4.20 mmol) of monoacid (prepared from the high R_f product, **8**, with 0.051 g (0.42 mmol) of (*N*,*N*-dimethylamino)pyridine and 0.30 mL of EtOH in 30 mL of DMF) was added 0.91 g (4.41 mmol) dicyclohexylcarbodiimide. The reaction mixture was stirred at room temperature for 14 h, and the precipitated urea was filtered off. The filtrate was concentrated, and the residue was taken up in ethyl acetate. The organic layer was washed twice with H_2O, dried, and concentrated. The crude product was recrystallized from diisopropyl ether: yield 600 mg (32%); $[\alpha]_D = -377.5°$ (0.56, ethanol), 97% pure by HPLC. NMR of both enantiomers were identical with the spectrum of racemic **5**.

Diethyl (3aα,4α,7aα)-3a,4,7,7a-Tetrahydro-6-methyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]pyridine-3,5-dicarboxylate (6). A mixture of 10.3 g (51.5 mmol) of [2-(trifluoromethyl)phenyl]-2-propenal and 7.32 g (56.6 mmol) of ethyl 3-amino-2-butenoate in 300 mL of ethanol was treated with 0.2 mL of piperidine and heated at reflux for 16 h. The mixture was cooled and concentrated to yield 12.5 g of the crude product as an oil. The mixture was used immediately without purification. Crude **4** (12.5 g, 51.5 mmol) was combined with ethyl chlorooximidoacetate[21] (11.7 g, 77.3 mmol) in 500 mL of ether. The reaction was placed under a nitrogen atmosphere, and triethylamine (10.7 mL, 77.3 mmol) was added over 12 h by syringe pump. The mixture was filtered and concentrated to 27 g of crude product. Flash chromatography (5% EtOAc in CH_2Cl_2) provided 1.3 g (23%) of the desired product as a white solid: NMR (200 MHz) δ 7.70 (d, J = 7.4 Hz, 1 H), 7.5–7.3 (m, 3 H), 5.48 (d, J = 6.8 Hz, 1 H), 4.55 (s, 1 H), 4.41 (q, J = 7.0 Hz, 2 H), 4.08 (dd, J = 6.8, 0.2 Hz), 4.05–3.80 (m, 2 H), 2.45 (s, 3 H), 1.35 (t, J = 7.0 Hz, 3 H), 1.08 (t, J = 7.5 Hz, 3 H).

5-Ethyl 3-[5-Methyl-2-(1-methylethyl)cyclohexyl] 3a,4,7,7a-Tetrahydro-6,7a-dimethyl-4-[2-(trifluoromethyl)-phenyl]isoxazolo[5,4-*b*]pyridine-3,5-dicarboxylate (7 and 8). The carboxylic acid, **12**, (8.7 g, 21 mmol) was dissolved in 100 mL of dimethylformamide, and dicyclohexylcarbodiimide (4.6 g, 22 mmol) and (*N*,*N*-dimethylamino)pyridine (0.27 g, 2.2 mmol) were added. The mixture was stirred for 30 min, and then (−)-menthol (3.6 g, 23 mmol) was added. The mixture was stirred overnight, concentrated, diluted with ethyl acetate, washed (4×) with water, dried, and concentrated. Two major products were observed on TLC (5% ethyl acetate in methylene chloride having R_f = 0.56 and 0.69. The low R_f product was crystallized from ethyl acetate. The supernatent was concentrated, and the residue was purified by flash chromatography (2% ethyl acetate in methylene chloride). The high R_f product was purified by crystallization from hexane (to remove menthol). Total yield was 2.7 g (23%) of low R_f product, **7**, and 2.1 g (18%) of the high R_f product, **8**. Combined yield was 41%. Low R_f product (**7**): mp 222–3 °C; $[\alpha]_D = 194°$ (0.051, methanol); NMR (200 MHz) δ 7.74 (d, J = 6.9 Hz, 1 H), 7.46–7.25 (m, 4 H), 5.54 (d, J = 1.4 Hz, 1 H), 5.00 (m, 1 H), 4.43 (s, 1 H), 4.0–3.9 (m, 3 H), 2.0–1.5 (m, 8 H), 1.3–0.7 (m, 18 H). High R_f product (**8**): mp 114–6 °C; NMR (200 MHz) δ 7.73 (d, J = 7.7 Hz, 1 H), 7.5–7.3 (m, 4 H), 5.59 (s, 1 H), 4.98 (m, 1 H), 4.44 (s, 1 H), 4.0–3.9 (m, 3 H), 2.48 (s, 3 H), 2.1–1.5 (m, 9 H), 1.4–0.8 (m, 14 H).

3-Propyl 5-Ethyl (3aα,4α,7aα)-3a,4,7,7a-Tetrahydro-6,7a-dimethyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]-pyridine-3,5-dicarboxylate (9). A mixture of carboxylic acid (700 mg, 1.70 mmol), 1-propanol (122 mg, 2.04 mmol), and 4-(dimethylamino)pyridine (21 mg, 0.17 mmol) was dissolved in 20 mL of DMF. Dicyclohexylcarbodiimide (368 mmol, 1.78 mmol) was added in a single portion. The mixture was stirred at room temperature for 18 h, filtered, and concentrated. The residue was dissolved in ethyl acetate, washed with aqueous saturated sodium bicarbonate, and dried. Evaporation of the solvent gave the crude product, which was recrystallized from isopropyl ether to yield 0.40 g (52%) as a white solid: NMR (200 MHz) δ 7.75 (d, J = 7.1 Hz, 1 H), 7.5–7.3 (m, 3 H), 5.64 (d, J = 1.5 Hz, 1 H), 4.64 (s, 1 H), 4.29 (t, J = 7.0, 2 H), 4.1–3.8 (m, 3 H), 2.47 (s, 3 H), 1.75 (m, 2 H), 1.35 (s, 3 H), 1.05 (t, J = 7.0 Hz, 3 H), 0.95 (t, J = 7.1, 3 H).

(3aα,4α,7aα)-3a,4,7,7a-Tetrahydro-6,7a-dimethyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]pyridine-3,5-dicarboxylic Acid 5-(Ethyl ester) (12). To a solution of **2** (9.9 g, 22.5 mmol) in 100 mL of THF was added 45 mL of 1 N sodium hydroxide solution. The solution was stirred for 2 h and evaporated to remove the THF. A white precipitate was collected and dried to yield 9.0 g (97%) of the desired product: NMR (200 MHz) δ 7.69 (d, J = 7.2 Hz, 1 H), 7.44–7.28 (m, 3 H), 6.37 (s, H), 5.68 (d, J = 1.3 Hz, 1 H), 3.90 (m, 2 H), 5.82 (d, J = 1.3 Hz, 1 H), 2.45 (s, 3 H), 1.04 (t, J = 7.0 Hz, 3 H).

Ethyl (3aα,4α,7aα)-3a,4,7,7a-Tetrahydro-6,7a-dimethyl-3-(phenylsulfonyl)-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]pyridine-5-carboxylate (13). (Phenylsulfonyl)-nitromethane (3.02 g, 15 mmol) in 10 mL of methylene chloride was treated with ethereal diazomethane (from Diazald) according to the method of Wade et al.[23] The excess diazomethane was blown off with a stream of nitrogen. A solution of **3** (2.34 g, 7.2 mmol) in 10 mL of methylene chloride was added followed by 6 mL of 1.0 N sodium hydroxide solution. The reaction mixture was stirred vigorously whereupon it warmed spontaneously. An ice bath was applied, and the product precipitated from the solution. After the mixture was stirred 30 min the precipitate was isolated by filtration and dried in vacuo at 60 °C to obtain 2.5 g (68%): NMR (200 MHz) δ 8.1–7.2 (m, 9 H), 5.43 (s, 1 H), 4.45 (s, 1 H), 4.04 (d, J = 1.6 Hz, 1 H), 4.0–3.8 (m, 2 H), 2.38 (s, 3 H), 1.34 (s, 3 H), 1.07 (t, J = 7.0 Hz, 3 H).

Ethyl (3aα,4α,7aα)-3-Ethoxy-3a,4,7,7a-tetrahydro-6,7a-dimethyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]-pyridine-5-carboxylate (14). Hexane-washed lithium metal (30 mg, 4.2 mmol) was added to 10 mL of ethanol. After dissolution was complete, 1.05 g (2.06 mmol) of the (phenylsulfonyl)isoxazole was added, and the mixture was heated at reflux for 1 h. The solution was concentrated, and the residue was partitioned between methylene chloride and water. The organic layer was filtered and concentrated. The solids obtained by filtration were combined with those obtained following evaporation, washed with 30% hexanes in methylene chloride, and then dried to yield 0.30 g (36%): NMR (200 MHz) δ 7.69 (d, J = 7.2 Hz, 1 H), 7.4–7.2 (m, 3 H), 4.87 (s, 1 H), 4.54 (s, 1 H), 4.20 (q, J = 7.0 Hz, 2 H), 4.1–3.8 (m, 2 H), 3.53 (s, 1 H), 2.48 (s, 3 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.03 (t, J = 7.1 Hz, 3 H).

Ethyl (3aα,4α,7aα)-3-Cyano-3a,4,7,7a-tetrahydro-6,7a-dimethyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]-pyridine-5-carboxylate (15). A solution of **3** (0.91 g, 2.8 mmol) and cyanoformohydroximic chloride[21] (0.58 g, 5.6 mmol) in 11 mL of ether was vigorously stirred under nitrogen. A 1 N aqueous solution of sodium carbonate (5.6 mL) was added via syringe pump over 2 h. The product, which precipitated, was collected by filtration and dried in vacuo: NMR (200 MHz) δ 7.75 (d, J = 7.2 Hz, 1 H), 7.5–7.2 (m, 3 H), 5.09 (s, 1 H), 4.58 (s, 1 H), 4.2–3.9 (m, 2 H), 3.77 (d, J = 1.3 Hz, 1 H), 2.51 (s, 3 H), 1.46 (s, 3 H), 1.09 (t, J = 7.1 Hz, 3 H).

Ethyl (3aα,4α,7aα)-3-Benzoyl-3a,4,7,7a-tetrahydro-6,7a-dimethyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]-pyridine-5-carboxylate (16). The dihydropyridine **3** (0.50 g,

Table III. Single-Crystal X-ray Crystallographic Analysis

formula	$C_{21}H_{23}F_3N_2O_5$
crystallization medium	acetonitrile
crystal size, mm	0.20 × 0.20 × 0.10
cell dimension	
a, Å	7.75120 (20)
b, Å	18.4817 (10)
c, Å	28.9320 (20)
space group	orthorhombic *Pbca*
Z	8
calcd density, g/cm^3	1.412
scan speed (2θ, deg min^{-1})	2
μ, mm^{-1}	0.98
$F(000)$ =	1840
T of data collection, °C	20
data range measured, deg	$2 < 2\theta < 144$
number of reflections measured	5976
number of unique reflections	4055
number of reflections with $I_{net} > 2.5\theta(I_{net})$	3261
number of parameters	373
final R factor	
R_f:	0.041
R_w:	0.024
max residual electron density, e/Å^3	0.240

1.6 mmol) and ethyl chlorooximidoacetate[21] (0.33 g, 1.8 mmol) were dissolved in 10 mL of ether, and a solution of triethylamine (0.25 mL, 1.8 mmol) in 10 mL ether was added via syringe pump over 12 h. The mixture was filtered, and the cake was washed with ether. The solid material was dissolved in chloroform, washed with water, dried, and concentrated to 0.33 g of crude product. Purification by flash chromatography (7:3, hexane–ethyl acetate) produced 0.30 g (40%) of a yellow solid: NMR (200 MHz) δ 8.00 (d, J = 7.0 Hz, 2 H), 7.8–7.3 (m, 7 H), 5.40 (d, J = 1.6 Hz, 1 H), 4.57 (s, 1 H), 4.16 (d, J = 2.1 Hz, 1 H), 3.9–3.7 (m, 2 H), 2.53 (s, 3 H), 1.41 (s, 3 H), 0.90 (t, J = 7.1 Hz, 3 H).

Ethyl (3aα,4α,7aα)-3a,4,7,7a-Tetrahydro-3,6,7a-trimethyl-4-[2-(trifluoromethyl)phenyl]isoxazolo[5,4-*b*]pyridine-5-carboxylate (17). Via the reported procedure,[19] 6.57 g (38 mmol) of 2-(trifluoromethyl)benzaldehyde, 3.8 g (38 mmol) of 2,4-pentanedione, and 5.0 g (38 mmol) of ethyl 3-amino-2-butenoate were combined in 200 mL of ethanol and heated at reflux for 2 days. The mixture was concentrated, and the residue was purified by flash chromatography using 20% ethyl acetate in hexane to obtain, after recrystallization from toluene, 1.5 g (11%) of ethyl 5-acetyl-1,4-dihydro-2,6-dimethyl-4-[2-(trifluoromethyl)phenyl]-pyridine-3-carboxylate: NMR (90 MHz) δ 7.4–7.0 (m, 4 H), 6.12 (br, 1 H), 5.48 (s, 1 H), 4.3–3.9 (m, 2 H), 2.28 (s, 3 H), 2.13 (s, 3 H), 2.09 (s, 3 H), 1.17 (t, J = 7 Hz, 3 H). A mixture of 1.3 g (3.5 mmol) of the product, 0.26 g (3.7 mmol) of hydroxylamine hydrochloride, and 0.5 mL of pyridine in 40 mL of ethanol was heated at reflux for 2 days. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with 0.5 N hydrochloric acid, dried, and concentrated. The residue was triturated with cold ethyl ether to yield a white solid, 0.5 g (38%): mp 186–8 °C; NMR (250 MHz) δ 7.70 (d, J = 7.6 Hz, 1 H), 7.45 (t, J = 7.2 Hz, 1 H), 7.34 (t, J = 7.4 Hz, 1 H), 7.28 (m, 1 H), 4.82 (s, 1 H), 4.49 (s, 1 H), 4.1–3.9 (m, 2 H), 3.46 (s, 1 H), 2.46 (s, 3 H), 1.96 (s, 3 H), 1.34 (s, 3 H), 1.06 (t, J = 7.1 Hz, 3 H).

Molecular Modeling. Studies were performed with the SYBYL operating system on a VAX 11/785 computer. The crystal coordinates of the dimethyl ester analogue of **2** were used as the starting point to build **2** and **5** by implementing BUILDING commands within SYBYL. Both **2** and **5** were built twice, once using a planar nitrogen and once using a tetrahedral nitrogen in the six-membered rings. The molecular geometries generated were further optimized with MAXIMIN2, employing the default options, both with and without electrostatics. The degrees of puckering of the ring were determined by calculating the RMS fit of the ring to a plane defined by the atoms of the ring and also by summing the torsion angles of the ring. The nitrogen torsion angles as defined by Andrews[29] were determined by measuring the C–N(–H)–C angles.

X-ray Structure Determination of 5. X-ray measurements were performed on a single-crystal diffractometer (Enraf-Nonius CAD4) using the $\omega - 2\theta$ scanning mode ($2\theta_{max}$ = 1440) and graphite-monochromated Cu Kα radiation (λ = 1.5418 Å). Crystal data and parameters are summarized in Table III. The unit cell parameters were determined by a least-squares fit of 2θ angles for 30 reflections in the range of $60° < 2\theta < 100°$. Two standard reflections were monitored at every 80 reflections intervals throughout the data collection and showed no significant fluctuation (within 3%). The observed intensities were corrected for Lorentz and polarization effects. No correction of the absorption effect was done. The structure was solved by direct methods. The positional parameters were refined by a full-matrix least-squares analysis. The hydrogen atoms were located in computed positions. For non-hydrogen atoms anisotropic thermal parameters were refined, and an isotropic refinement was applied to hydrogen atoms. No abnormally short contact distances were observed in the crystal packing. The function minimized was $\sum_n w(|F_o| - |F_c|)^2$. The weighting scheme used for refinement was based on counting statistics. At convergence, none of the positional and thermal parameters shifted more than 2% of their standard deviations. For all crystallographic computations, the NRCVAX[30] system of programs was used, and atomic scattering factors and the terms of the anomolous dispersion correction were taken from *International Tables for X-ray Crystallography*.[31]

Supplementary Material Available: Final atomic coordinates of non-hydrogen atoms with isotropic equivalent of the anisotropic thermal parameters, anisotropic thermal parameters of non-hydrogen atoms, coordinates of hydrogen atoms, and bond distances and angles between non-hydrogen atoms (9 pages). Ordering information is given on any current masthead page.

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