brine. After drying over $MgSO_4$, the solution was concentrated in vacuo to give an oil. The oil was purified using MPLC and 50% EtOAc to give 0.22 g (ca. 70%) of a mixture of 3-phenyl-*n*-propyl acetate and 3-(*o*-bromophenyl)-*n*-propyl acetate and 0.05 g (12%) of *N*-methyl-*o*-(3-acetoxypropyl)acetanilide (**12**) as a clear liquid: ^1H NMR (200 MHz, $CDCl_3$) δ 7.09-7.38 (m, 4 H, Ar*H*), 4.11 (t, 2 H, CH_2O, J = 6.3 Hz), 3.20 (s, 3 H, NCH_3), 2.64 (t, 2 H, $ArCH_2$, J = 7.3 Hz) 2.06 (s, 3 H, $COCH_3$), 1.86-2.05 (m, 2 H, $ArCCH_2$), 1.77 (s, 3 H, $COCH_3$); IR (neat, cm^{-1}) 2959 (m), 1738 (s), 1662 (s), 1601 (m), 1493 (s), 1453 (s), 1379 (s), 1034 (s), 775 (m); GLPC-MS (190 °C) t_R 2.88 min; m/e (relative height) 249 (M^+, 39), 192 (32), 174 (32), 148 (95), 146 (100), 91 (50).

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.41; H, 7.70; N, 5.62. Found: C, 67.23; H, 7.62; N, 5.59.

Double-Labeling Crossover Experiments with 24, 24-d_2,d_3. Run 1. To 1.90 mL (2.06 mmol) of methyllithium at -78 °C was added dropwise a precooled solution of 0.2441 g (0.988 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine and 0.2615 g (1.070 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine-d_2,d_3 in 10 mL of hexane. After addition, 3.6 mL (4.12 mmol) of *tert*-butyllithium was added. The solution was then stirred for 30 min at -78 °C. The solution was warmed to -15 °C, where it was allowed to stir for 3 h. The reaction was then quenched with water and cooled to -78 °C. To the solution was added 1.50 mL of acetyl chloride, and the reaction was allowed to warm to room temperature. After 48 h, the mixture was extracted twice with 10% HCl and 10% NaOH and once with brine. After being dried over $MgSO_4$, the solution was concentrated in vacuo to give an oil. The oil was then analyzed using capillary GLPC-MS: GLPC-MS (190 °C) t_R 2.87 min; m/e (relative height) 252 (67), 251 (100), 250 (74), 249 (85), 248 (50); calcd % d = 33% d_0, 19% d_1, 31% d_2, 17% d_3.

Run 2. To 0.68 mL (0.74 mmol) of methyllithium at -78 °C was added dropwise a precooled solution of 0.1061 g (0.435 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine and 0.0745 g (0.302 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine-d_2,d_3 in 3 mL of hexane. After addition, 1.29 mL (1.48 mmol) of *tert*-butyllithium was added. After this addition 8 mL of cooled hexane was added. The solution was then stirred for 30 min at -78 °C. The solution was warmed to -15 °C, where it was allowed to stir for 3 h. The reaction was then quenched with water and cooled to -78 °C. To the solution was added 1.50 mL of acetyl chloride, and the reaction was allowed to warm to room temperature. After 48 h, the mixture was extracted twice with 10% HCl and 10% NaOH and once with brine. After drying over $MgSO_4$, the solution was concentrated in vacuo to give an oil. The oil was then analyzed using capillary GLPC-MS: GLPC-MS (190 °C) t_R 2.87 min; m/e (relative height) 252 (43), 251 (82), 250 (56), 249 (100), 248 (0.4); calcd % d = 42% d_0, 16% d_1, 31% d_2, 12% d_3.

Run 3. To 0.99 mL (1.07 mmol) of methyllithium at -78 °C was added dropwise a precooled solution of 0.1555 g (0.637 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine and 0.1087 g (0.440 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine-d_2,d_3 in 6 mL of hexane. After addition, 1.9 mL (2.14 mmol) of *tert*-butyllithium was added. The solution was then stirred for 30 min at -78 °C. The solution was warmed to -15 °C, where it was allowed to stir for 1.5 h. The reaction was then quenched with water and cooled to -78 °C. To the solution was added 1.50 mL of acetyl chloride, and the reaction mixture was allowed to warm to room temperature. After 48 h, the mixture was extracted twice with 10% HCl and 10% NaOH and once with brine. After being dried over $MgSO_4$, the solution was concentrated in vacuo to give an oil. The oil was then analyzed using capillary GLPC-MS: GLPC-MS (190 °C) t_R 2.87 min, m/e (relative height) 252 (42), 251 (77), 250 (54), 249 (100), 248 (71); calcd % d = 43% d_0, 16% d_1, 29% d_2, 12% d_3.

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for support of this work and to Dr. Scott Wilson for assistance with the X-ray structure determination.

Supplementary Material Available: The preparations of methoxylamine, *N*-*n*-propylmethoxylamine, *N*-isopropylmethoxylamine, *N*-benzylmethoxylamine, *N*-[3-(*o*-bromophenyl)-*n*-propyl]methoxylamine (**11**), *N*-[4-(*o*-bromophenyl)-*n*-butyl]-methoxylamine, *N*-*n*-propyl-*O*-methyl-*p*-nitrobenzohydroxamic acid, *N*-isopropyl-*O*-methyl-*p*-nitrobenzohydroxamic acid, *N*-acetylbenzazepine (**3**), *N*-*n*-propyl-*N*-*n*-butylbenzamide, *N*-*sec*-butyl-*N*-benzylamine, the aryllithium reagents, the aminations in Schemes I-III, and the X-ray crystallographic data for *N*-acetylbenzoazetine (**1**) (30 pages). Ordering information is given on any current masthead page.

An Approach to Amphimedine and Related Marine Alkaloids Utilizing an Intramolecular Kondrat'eva Pyridine Synthesis[1]

Chakrapani Subramanyam, Michihiko Noguchi, and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received May 16, 1989

A strategy for the synthesis of the marine alkaloid amphimedine (**1**) and its congeners **2-5** has been investigated. The approach involves an intramolecular Diels-Alder reaction of a 4,5-disubstituted oxazole (Kondrat'eva reaction) to produce the ABC ring system of these natural products, followed by a photoenolization/electrocyclization to construct the D ring. The key oxazole olefin **30** was prepared in several steps starting from pyridine ester **10** and *o*-aminostyrene (**19**). The route to **30** utilized a Kozikowski modification of the Schollkopf oxazole synthesis as a key step. Thermolysis of oxazole **30** provided fused pyridine **31** via the desired [4 + 2] cycloaddition. Attempts to cyclize derived aldehyde **32** photochemically failed, affording primarily decarbonylation products.

Marine organisms have been the source of a wide variety of novel natural products. Although many terpenoids and related molecules are known, very few alkaloids have been isolated from marine sources. Amphimedine (**1**), a structurally unique pentacyclic aromatic alkaloid, was isolated in 1983 by Schmitz and co-workers from an *Amphimedon* species of sponge collected near Guam Island.[2] More recently, the closely related alkaloids cystodytin A (**2**), B

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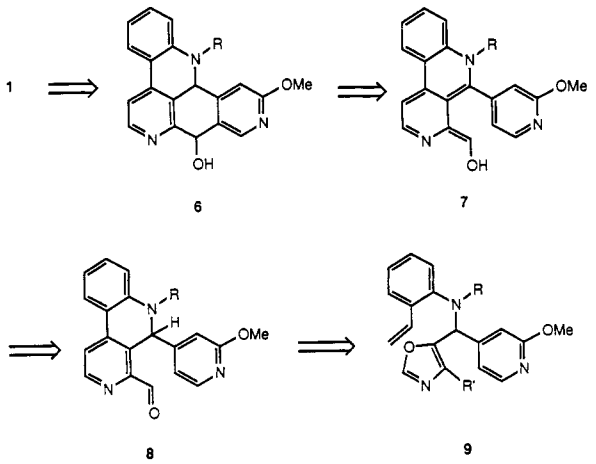
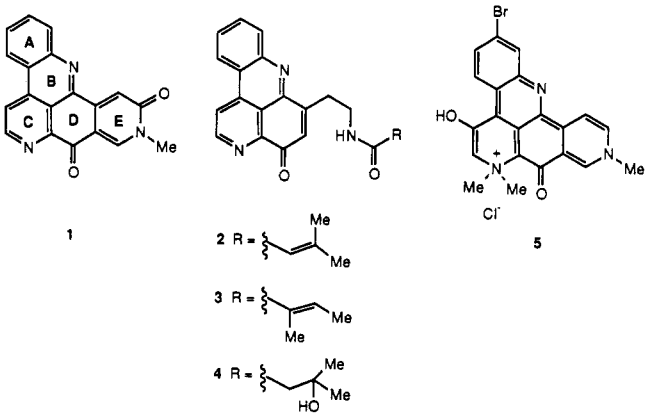
Scheme I



(3), and C (4) were isolated from Okinawan tunicate *Cystodytes dellechiajei*.[3] Amphimedine and the cystodytins all have antineoplastic activity. Another similar compound isolated from a marine sponge is petrosamine (5),[4,5] a pigment with interesting properties.

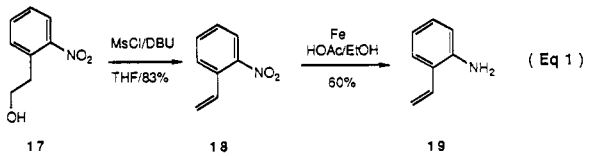


Four groups have reported synthetic studies in this area. Moody, Rees, and co-workers[6] described an approach to the ABCD tetracyclic framework of these alkaloids via a vinylnitrene cyclization. Recently Echavarren and Stille[7] completed an elegant total synthesis of amphimedine that featured an aryl–tin coupling and an intermolecular aza diene Diels–Alder reaction as pivotal steps. Two other groups have also described efficient syntheses of 1.[7b,c]

We have been interested in developing an efficient route to amphimedine (1) as shown in the brief retrosynthetic analysis in Scheme I.[1] It was our intention to prepare pentacyclic intermediate **6** via electrocyclization of **7**, which in turn would be generated by photoenolization of tetracyclic aldehyde **8**.[8] Such a process is precedented in simpler, nonheterocyclic systems.[9] We hoped to access **8** by an intramolecular Kondrat'eva pyridine synthesis of oxazole alkene **9**.[10,11] To date, only two reports of intramolecular Kondrat'eva pyridine syntheses have appeared,[12,13] one of which originated from these laboratories.

Our synthesis started with the known[14] methoxypyridine ester **10** (Scheme II), which was reduced with calcium borohydride[15] to alcohol **11** (80%). Oxidation of **11** with Collins reagent afforded aldehyde **12** in 94% yield. This aldehyde was next homologated by using a Passerini reaction[16] to afford *N*-methyl amide **13** (77%). Attempts to hydrolyze amide **13** directly proceeded in very poor yield. However, an alternative method was successfully used whereby amide **13** was first N-nitrosated and the resulting *N*-nitroso amide was rearranged to methyl ester **14**.[17] The acetyl group of **14** was removed to afford alcohol **15** (85% from **13**), which was oxidized with Collins reagent to α-keto ester **16** (95%).

o-Aminostyrene (**19**) was needed as the precursor for the A ring of **1**, but the known synthesis of **19** suffers from a poor overall yield and is not amenable to large-sc le preparations.[18] An alternate but more efficient approach to this compound was therefore devised (eq 1). Treatment



of commercially available *o*-nitrophenethyl alcohol (**17**) with methanesulfonyl chloride/DBU according to the method of McMurry[19] gave *o*-nitrostyrene (**18**) in good yield. Reduction of the nitro group with iron in acetic acid[20] afforded **19**.

Condensation of *o*-aminostyrene (**19**) with α-keto ester **16** afforded an intermediate imine that was reduced in situ with sodium cyanoborohydride[21] to afford α-amino ester **20** (78%) (Scheme III). It was our intention to construct the requisite oxazole ring (cf. **9**) using the carboxyl group of **20** via Schollkopf methodology.[22,23] Thus, attempts

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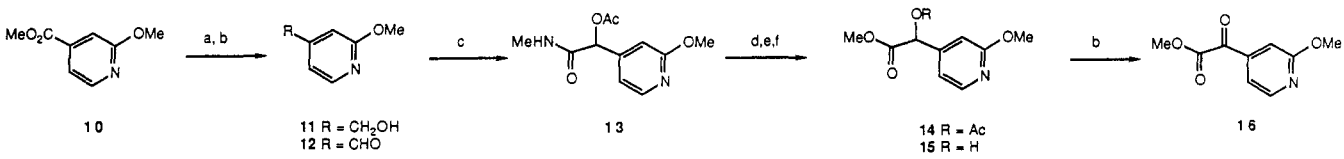
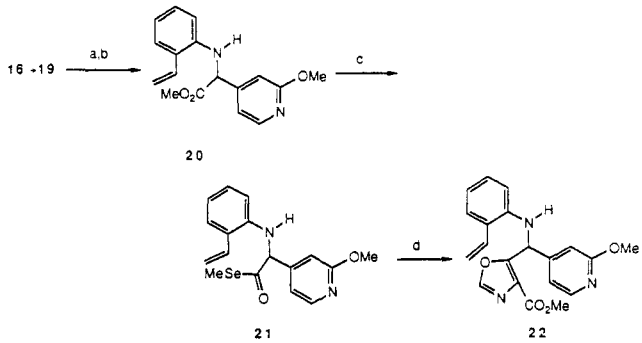
Scheme II[a]



10 | 11 R = CH_2OH, 12 R = CHO | 13 | 14 R = Ac, 15 R = H | 16

[a] (a) $Ca(BH_4)_2$, THF, room temperature; (b) CrO_3/pyr, CH_2Cl_2, room temperature; (c) MeNC, MeOH, AcOH, 60–65 °C; (d) $NaNO_2$, Ac_2O, AcOH, 0 °C; (e) Na_2CO_3, CCl_4, Δ; (f) NaOMe, MeOH, 0 °C.

Scheme III[a]



20 | 21 | 22

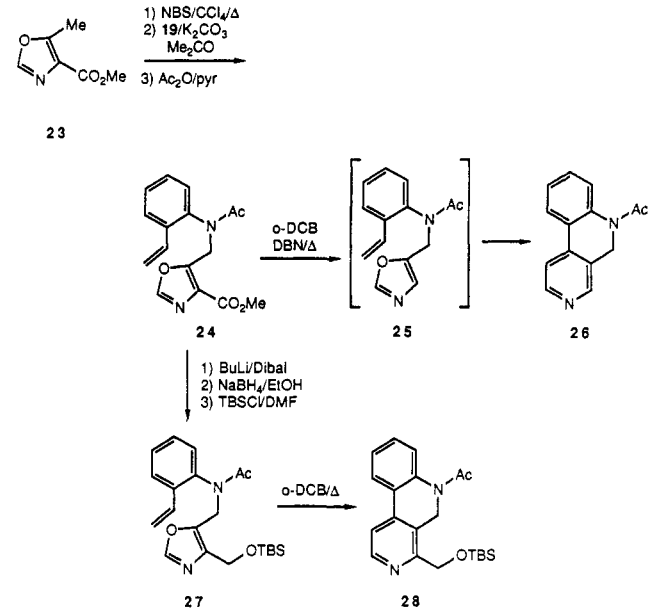
[a] (a) pTsOH, PhMe, 90 °C; (b) $NaCNBH_3$, MeOH, HOAc; (c) $Me_2AlSeMe$, PhMe; (d) $CNCH_2CO_2Me$, NEt_3, Cu_2O, THF.

were made to hydrolyze ester **20** to the corresponding carboxylic acid, which we hoped to subsequently activate. Unfortunately, this acid decarboxylated rapidly and quantitatively. Alternatively, it was possible to convert ester **20** directly to the selenol ester **21**,[24] and utilizing the Kozikowski modification[25] of the Schollkopf oxazole synthesis[22] we could prepare the desired intermediate **22** in good yield.

Before investigating the intramolecular cycloaddition of oxazole olefin **22**, some experiments were conducted on a simpler model system. Readily available oxazole ester **23**[26] was converted to **24** in good overall yield as shown in Scheme IV.[1] Thermolysis of **23** in a variety of solvents led only to recovered starting material. Since we had found in previous studies[12] of intramolecular Kondrat'eva cycloadditions that DBN was a beneficial additive, we conducted the reaction thermally in the presence of 1 equiv of this reagent. In fact, under these conditions cycloaddition did occur, but the undesired decarboxylated pyridine **26** was obtained. We believe that the DBN first dealkylates the ester **24** to give the corresponding acid,[27] which then thermally decarboxylates to oxazole **25**, followed by cyclization to **26**. We have independently synthesized **25** and found that it does smoothly cyclize to **26**.[1]

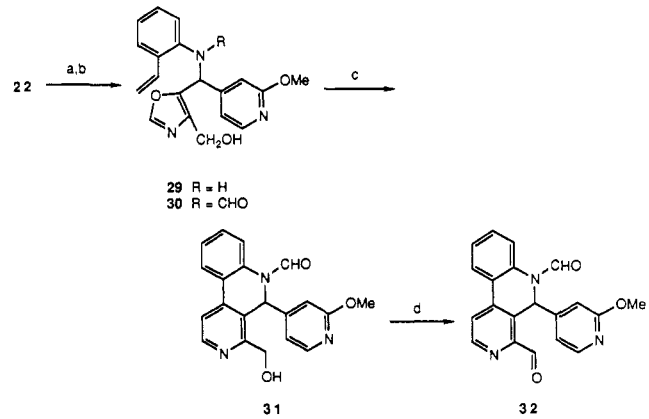
It is perhaps not surprising that oxazole ester **24** does not cyclize since it is known that oxazoles bearing an electron-withdrawing substituent at C-4 are unreactive in intermolecular cycloadditions.[28] We had hoped that the intramolecularity of our proposed cycloaddition would overcome this problem. In order to circumvent this difficulty, ester **24** was reduced to the alcohol[29] and protected as silyl ether **27**. Upon heating, oxazole **27** cyclized to the

Scheme IV



23 | 24 | 25 | 26 | 27 | 28

Scheme V[a]



31 | 32

[a] (a) $Ca(BH_4)_2$, THF, MeOH; (b) Ac_2O, HCO_2H, THF, room temperature; (c) *o*-DCB, DBN, 150 °C; (d) MnO_2, $CHCl_3$, room temperature.

desired α-substituted tricyclic pyridine **28**.

Returning to the amphimedine oxazole intermediate **22**, reduction of the ester group with calcium borohydride[15] gave alcohol **29** (82%), which was selectively N-acylated to yield formamide **30** (Scheme V). It turned out that it was not necessary to protect the hydroxyl group of **30** in order to perform the intramolecular Kontrat'eva reaction. Thus, heating oxazole **30** in *o*-dichlorobenzene containing DBN gave pyridine **31** in 71% yield. The aldehyde **32** required for the final cyclization step was prepared by activated manganese dioxide oxidation of alcohol **31** (67%).

Photochemical studies on aldehyde **32** were conducted with use of a high-pressure lamp through Pyrex in various solvents.[8,9] Irradiation of **32** in either acetone or benzene

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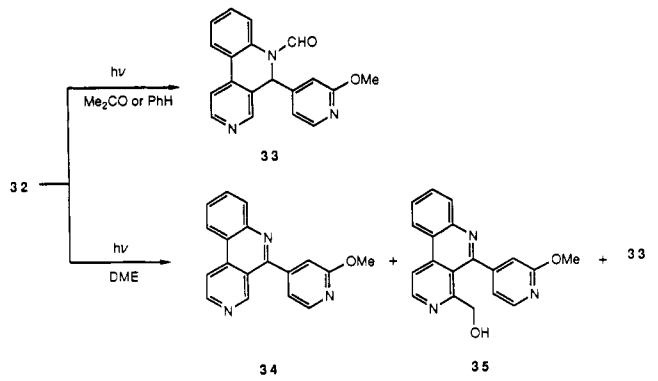
Scheme VI



unfortunately gave only decarbonylation product **33** (Scheme VI) along with recovered starting material and small amounts of uncharacterizable products. In dimethoxyethane compound **34** was formed, resulting from double decarbonylation and dehydrogenation, along with aldehyde photoreduction product **35** and decarbonylation product **33**. Thus, despite considerable effort, we have been unable to effect the photoenolization/electrocyclization strategy outlined in Scheme I. We are hopeful, however, that our general approach can be modified to allow construction of the final D ring of amphimedine (**1**) and the related alkaloids **2–5**.

Experimental Section

Infrared spectra (IR) were recorded on a Perkin-Elmer Model 197 or Perkin-Elmer Model 1310 spectrometer. Nuclear magnetic resonance spectra (^{1}H NMR) were obtained in the indicated solvents at 60 MHz on a Varian EM-360A NMR spectrometer, at 200 MHz on a Bruker WP-200 instrument, and at 360 MHz on a Bruker WP-360 spectrometer. Carbon-13 magnetic resonance spectra (^{13}C NMR) were recorded at 50 MHz on a Bruker WP-200 spectrometer. Mass spectra were obtained at 50–70 eV by electron impact (EI) on a KRATOS MS-9/50 double-focusing mass spectrometer. Analytical and preparative thin layer chromatography were performed on E.M. Merck silica gel PF-254. Column chromatography was done on 70–230-mesh silica gel 60 (E.M. Merck). Flash chromatography was performed with use of thick-walled glass columns on Baker silica gel (25–40 μm) as described by Still et al.[30] Anhydrous sodium sulfate was used to dry extracts unless otherwise noted.

2-Methoxy-4-(hydroxymethyl)pyridine (11). To a suspension of $NaBH_4$ (0.49 g, 12.9 mmol) in anhydrous THF (25 mL) was added powdered $CaCl_2$ (0.72 g, 6.5 mmol), and the mixture was stirred at room temperature for 1.5 h. A solution of ester **10**[14] (0.675 g, 4 mmol) in anhydrous THF (10 mL) was added. After being stirred at room temperature for 12 h, the reaction mixture was carefully diluted with 10% NaOH solution (10 mL) and extracted with $CHCl_3$ (3 × 100 mL). The extract was washed with water, dried, and concentrated in vacuo. The crude product was purified by flash chromatography (1:1 ethyl acetate/hexane) to afford 0.45 g (80%) of alcohol **11** as a pale yellow oil: IR (film) 3350, 2950, 1640, 1560, 1480, 1450, 1400, 1320, 1160, 1040, 980, 820, 760 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.8 (3 H, s), 4.6 (2 H, s), 5.3 (1 H, br s), 6.7–6.8 (2 H, m), 8.0 (1 H, d, J = 6.0 Hz); mass spectrum, m/z (relative intensity) 139 (M^+, 70), 138 (100), 110 (19), 109 (50), 108 (12), 80 (32), 51 (14), 39 (19), 28 (93).

2-Methoxy-4-formylpyridine (12). Collins reagent was prepared by the addition of CrO_3 (2.8 g, 0.028 mol) to a solution of pyridine (4.7 g, 0.059 mol) in CH_2Cl_2 (100 mL) and stirring the mixture for 25 min at room temperature. Alcohol **11** (0.65 g, 0.0047 mol) in CH_2Cl_2 (25 mL) was then added and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate and filtered through a pad of Florisil. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (25% ethyl acetate/hexane) to yield aldehyde **12** (0.6 g, 94%) as a pale yellow oil: IR (film) 3000, 2950, 2850, 2700, 1720, 1610, 1560, 1480, 1450, 1400, 1320, 1290, 1150, 1040, 980 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.0 (3 H, s), 7.1–7.3 (2 H, m), 8.3 (1 H, d, J = 6.0 Hz), 10.1 (1 H, s); mass spectrum, m/z (relative intensity) 137 (M^+, 100), 136 (90), 108 (33), 107 (65), 52 (33), 44 (51), 38 (28); exact mass calcd for $C_7H_7NO_2$ 137.0477, found 137.0477.

Preparation of α-Acetoxy Amide 13. To a solution of aldehyde **12** (1.2 g, 8.7 mmol) and methyl isocyanide (0.53 g, 12.9 mmol) in anhydrous methanol (20 mL) was added glacial acetic acid (0.74 g, 12.3 mmol). The mixture was refluxed under argon for 2.5 h and the solvent was removed in vacuo. Purification of the crude product by flash chromatography (ethyl acetate) yielded α-acetoxy amide **13** (1.6 g, 77%) as a colorless oil: IR (KBr) 3300, 2850, 1750, 1660, 1600, 1560, 1480, 1440, 1400, 1220, 1180, 1040 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.2 (3 H, s), 2.8 (3 H, d, J = 4.0 Hz), 3.9 (3 H, s), 6.0 (1 H, s), 6.8–7.2 (3 H, m), 8.1 (1 H, d, J = 6.0 Hz); mass spectrum, m/z (relative intensity) 238 (M^+, 18), 181 (37), 139 (94), 138 (100), 58 (38), 43 (82), 28 (57).

Conversion of α-Acetoxy Amide 13 to Ester 14. To a solution of α-acetoxy amide **13** (0.67 g, 2.8 mmol) in acetic anhydride (25 mL) and glacial acetic acid (10 mL) at 0 °C was added $NaNO_2$ (4.3 g, 62.3 mmol) over a period of 3 h. The mixture was stirred at 0 °C for 12 h and then at room temperature for 30 min. The reaction mixture was diluted with water and was extracted with ether (2 × 100 mL). The ether extract was washed carefully with 15% Na_2CO_3 solution (2 × 75 mL) and brine (1 × 50 mL) and dried. Removal of the solvent in vacuo gave 0.73 g (100%) of the N-nitroso amide as a pale yellow oil, which was used in the next step without further purification: IR (film) 3000, 2950, 1740, 1620, 1560, 1520, 1480, 1440, 1400, 1380, 1320, 1200, 1040, 1000, 980, 800 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.3 (3 H, s), 3.1 (3 H, s), 3.9 (3 H, s), 6.7–6.9 (2 H, m), 8.1 (1 H, d, J = 6.0 Hz); mass spectrum, m/z (relative intensity) 267 (M^+, 7), 208 (23), 180 (12), 138 (99), 117 (9), 43 (100), 28 (45).

Solid Na_2CO_3 (0.29 g, 2.73 mmol) was added to a solution of the above N-nitroso amide (0.73 g, 2.73 mmol) in CCl_4 (200 mL) and the mixture was refluxed under argon for 16 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was diluted with ethyl acetate and filtered. The filtrate was concentrated under reduced pressure to yield α-acetoxy ester **14** (0.62 g, 95%) of sufficient purity to be used in the next step: IR (film) 2950, 1750, 1620, 1560, 1480, 1440, 1400, 1380, 1280, 1220, 1160, 1040, 980, 810, 760 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.3 (3 H, s), 3.7 (3 H, s), 3.9 (3 H, s), 5.8 (1 H, s), 6.7–7.0 (2 H, s), 8.1 (1 H, d, J = 6.0 Hz); mass spectrum, m/z (relative intensity) 239 (M^+, 38), 238 (23), 138 (84), 43 (100).

Preparation of α-Hydroxy Ester 15. To a solution of α-acetoxy methyl ester **14** (0.62 g, 2.59 mmol) in anhydrous methanol (6 mL) at 0 °C was added a 2.5 M solution of freshly prepared NaOMe in methanol (3.1 mL, 7.8 mmol). The mixture was stirred at 0 °C for 10 min, diluted with glacial acetic acid (0.5 mL), and evaporated to dryness. The residue was diluted with water and extracted with ethyl acetate (2 × 100 mL). The extract was washed with brine, dried, and concentrated in vacuo. The crude product was purified by flash chromatography (40% ethyl acetae/hexane) to afford 0.45 g (85% from α-acetoxy amide **13**) of α-hydroxy ester **15** as an oil: IR (film) 3450, 2950, 1740, 1610, 1560, 1400, 1160, 1100, 1040 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.47 (1 H, d, J = 5.6 Hz), 3.80 (3 H, s), 3.94 (3 H, s), 5.15 (1 H, d, J= 5.5 Hz), 6.84 (1 H, dd, J = 0.6, 1.4 Hz), 6.94–6.98 (1 H, m), 8.14 (1 H, d, J = 5.4 Hz); mass spectrum, m/z (relative intensity) 197 (M^+, 77), 196 (59), 167 (11), 138 (100), 95 (11), 78 (40), 67 (13), 42 (15), 28 (51); exact mass calcd for $C_9H_{11}NO_4$ 197.0688, found 197.0681.

Oxidation of α-Hydroxy Ester 15. Collins reagent was prepared from pyridine (2.30 g, 29 mmol) and CrO_3 (1.48 g, 14.8 mmol) in anhydrous CH_2Cl_2 (75 mL). α-Hydroxy ester **15** (0.455 g, 2.3 mmol) in CH_2Cl_2 (20 mL) was then added and the mixture was stirred at room temperature for 40 min. The reaction mixture was dilued with ethyl acetate and filtered through a pad of Florisil. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (1:3 ethyl acetate/hexane) to provide α-keto ester **16** (0.43 g, 95%) as a pale yellow oil: IR (film) 3050, 2950, 2850, 1730, 1700, 1600, 1560, 1470, 1440, 1380, 1260, 1230,

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1150, 1000, 680 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 3.9 (6 H, s), 7.3 (2 H, m), 8.0 (1 H, d, J = 6.0 Hz); mass spectrum, m/z (relative intensity) 195 (M^+, 19), 136 (100), 108 (53), 81 (39), 66 (26), 38 (20), 28 (62); exact mass calcd for $C_9H_9NO_4$ 195.0532, found 195.0526.

1-(2-Nitrophenyl)ethylene (18). A solution of *o*-nitrophenethyl alcohol (17, 21.0 g, 0.126 mol) and DBU (91.62 g, 0.60 mol) in anhydrous THF (250 mL) was cooled to 0 °C. Methanesulfonyl chloride (29.6 g, 0.258 mol) was then added over a period of 30 min. The mixture was stirred at room temperature for 12 h and filtered, and the solids were washed with ether (750 mL). The combined filtrate was washed with 5% HCl (2 × 150 mL), water, and brine. The organic phase was dried and concentrated in vacuo. The residue was distilled [bp 58–60 °C (2 Torr)] to provide *o*-nitrostyrene (18, 15.5 g, 83%) as a pale yellow oil: ^1H NMR (60 MHz, $CDCl_3$) δ 5.3–5.8 (2 H, m), 6.9–7.9 (5 H, m).

1-(2-Aminophenyl)ethylene (19). Iron powder (30.5 g, 0.546 mol) was added to a solution of *o*-nitrostyrene (18, 20.0 g, 0.134 mol) in glacial acetic acid (150 mL) and absolute ethanol (150 mL). The mixture was refluxed under argon for 1 h and then cooled to room temperature. The reaction mixture was poured into water (1 L) and neutralized with solid Na_2CO_3. The resulting thick solution was extracted with ether (3 × 500 mL). The extract was dried and concentrated in vacuo. The residue was distilled [bp 47–49 °C (0.5 Torr)] from hydroquinone (0.5 g) to yield *o*-aminostyrene (19, 9.5 g, 60%) as a colorless oil: ^1H NMR (60 MHz, $CDCl_3$) δ 3.8 (2 H, br, s), 5.3–5.8 (2 H, m), 6.7–7.4 (5 H, m).

Synthesis of α-Amino Ester 20. A solution of *o*-aminostyrene (19, 0.98 g, 8.2 mmol), α-keto ester (1.07 g, 5.5 mmol), and *p*-tolunesulfonic acid monohydrate (0.052 g, 0.27 mmol) in anhydrous toluene (10 mL) was heated under argon at 90 °C for 2 h and then cooled to 0 °C. A solution of $NaCNBH_3$ (0.65 g, 10.2 mmol) in methanol (6 mL) was added followed by glacial acetic acid (0.5 mL). After being stirred at room temperature for 1 h, the reaction mixture was diluted with saturated $NaHCO_3$ solution and was extracted with ethyl acetate (2 × 75 mL). The extract was washed with water and brine and dried. Removal of the solvent under reduced pressure and purification of the crude product by flash chromatography (10% ethyl acetate/hexane) afforded 1.27 g (78%) of α-amino ester **20** as a pale yellow oil: IR (film) 3400, 3000, 2950, 1740, 1600, 1560, 1500, 1440, 1400, 1160, 1040, 990 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.77 (3 H, s), 3.93 (3 H, s), 5.05 (1 H, d, J = 5.3 Hz), 5.23 (1 H, d, J = 5.3 Hz), 5.45 (1 H, dd, J = 1.4, 11.0 Hz), 5.74 (1 H, dd, J = 1.4, 17.4 Hz), 6.29 (1 H, d, J = 8.1 Hz), 6.70–7.04 (5 H, m), 7.31 (1 H, d, J = 1.3 Hz), 8.16 (1 H, d, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$) δ 53.16, 53.48, 59.85, 109.34, 111.62, 115.34, 116.98, 118.46, 124.85, 127.65, 128.74, 132.52, 142.31, 147.41, 149.41, 164.69, 170.89; mass spectrum, m/z (relative intensity) 298 (M^+, 24), 239 (100), 118 (27), 77 (14), 28 (12); exact mass calcd for $C_{17}H_{18}N_2O_3$ 298.1317, found 298.1320.

Preparation of Selenol Ester 21. A 2.0 M solution of dimethylaluminum methaneselenolate (**22**) in toluene (3.2 mL, 6.4 mmol) was added to a solution of α-amino ester **20** (0.95 g, 3.2 mmol) in deoxygenated toluene (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then warmed to room temperature over 30 min. The yellow reaction mixture was treated with moist sodium sulfate and extracted with ether (3 × 75 mL). The extract was dried and concentrated in vacuo. The residue was purified by flash chromatography (10% ethyl acetate/hexane) to afford selenol ester **21** (0.9 g, 78%) as a pale yellow oil: IR (film) 3400, 2950, 1690, 1600, 1560, 1500, 1440, 1400, 1310, 1040, 740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.16 (3 H, s), 3.95 (3 H, s), 4.86 (1 H, d, J = 4.6 Hz), 4.98 (1 H, d, J = 4.9 Hz), 5.46 (1 H, dd, J = 1.5, 11.0 Hz), 5.74 (1 H, dd, J = 1.5, 17.4 Hz), 6.53 (1 H, d, J = 8.1 Hz), 6.79–7.33 (6 H, m), 8.20 (1 H, d, J = 5.2 Hz); mass spectrum, m/z (relative intensity) 361 (M^+, 0.1), 240 (18), 239 (100), 146 (7), 130 (15), 77 (12), 28 (7); exact mass calcd for $C_{17}H_{18}N_2O_2Se$ 362.0533, found 362.0546.

Preparation of Oxazole Ester 22. Anhydrous cuprous oxide (0.092 g, 0.62 mmol) was added to a mixture of selenol ester **21** (0.15 g, 0.41 mmol), triethylamine (0.063 g, 0.62 mmol), and methyl isocyanoacetate (0.12 g, 1.21 mmol) in anhydrous THF (5 mL). After being stirred at room temperature for 1 h, the reaction mixture was filtered through a pad of silica gel, which was eluted with ethyl acetate. The combined filtrate was concentrated in vacuo and the residue was purified by flash chromatography (1:3 ethyl acetate/hexane and then 2:3 ethyl acetate/hexane) to yield oxazole ester **22** (0.11 g, 73%) as a colorless oil: IR (film) 3350, 3130, 2950, 1720, 1600, 1560, 1510, 1450, 1400, 1320, 1200, 1040, 750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.92 (3 H, s), 3.96 (3 H, s), 4.96 (1 H, d, J = 8.7 Hz), 5.42 (1 H, dd, J = 1.4, 11.1 Hz), 5.69 (1 H, dd, J = 1.4, 17.3 Hz), 6.43 (1 H, d, J = 8.6 Hz), 6.64 (1 H, d, J = 7.9 Hz), 6.75–7.31 (5 H, m), 7.82 (1 H, s), 8.12 (1 H, dd, J = 0.4, 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 52.51, 53.52, 108.76, 111.99, 114.92, 117.25, 119.27, 125.54, 127.73, 128.14, 128.95, 132.40, 142.41, 147.61, 149.78, 150.06, 157.03, 162.05, 164.71; mass spectrum, m/z (relative intensity) 366 (9), 365 (M^+, 37), 306 (11), 225 (18), 188 (34), 130 (19), 118 (100), 117 (19), 91 (16), 28 (29); exact mass calcd for $C_{20}H_{19}N_3O_4$ 365.1375, found 365.1460.

Reduction of Oxazole Ester 22. Sodium borohydride (0.21 g, 5.5 mmol) and $CaCl_2$ (0.30 g, 2.7 mmol) were added in portions to a solution of oxazole ester **22** (0.607 g, 1.66 mmol) in anhydrous THF (20 mL) and methanol (5 mL) at 0 °C over 30 min. The reaction mixture was warmed to room temperature and stirred for 21.5 h. During this period $NaBH_4$ (0.17 g, 4.4 mmol) and $CaCl_2$ (0.24 g, 2.2 mmol) were added to the mixture. The reaction mixture was diluted with acetone and evaporated. The residue was treated with 5% NaOH and extracted with chloroform (4 × 50 mL). Removal of the solvent and purification of the crude product by flash chromatography (3:2 ethyl acetate/hexane) gave 0.457 g (82%) of alcohol **29** as a pale yellow oil: IR (film) 3350, 2950, 1600, 1560, 1500, 1490, 1310, 1040, 740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.92 (3 H, s), 4.62 (2 H, s), 5.40 (1 H, dd, J = 1.5, 11.0 Hz), 5.69 (1 H, dd, J = 1.5, 17.3 Hz), 5.81 (1 H, s), 6.53 (1 H, d, J = 7.7 Hz), 6.80–7.31 (6 H, m), 7.8 (1 H, s), 8.5 (1 H, dd, J = 0.3, 5.4 Hz); mass spectrum, m/z (relative intensity) 338 (8), 337 (M^+, 41), 251 (12), 225 (45), 220 (36), 219 (62), 191 (43), 190 (23), 174 (26), 146 (59), 130 (35), 118 (100), 91 (33); exact mass calcd for $C_{19}H_{19}N_3O_3$ 337.1426, found 337.1436.

Formylation of Amino Alcohol 29. To formic acetic anhydride [prepared from acetic anhydride (1 mL) and anhydrous formic acid (0.5 mL)] at 0 °C was added a solution of amino alcohol **29** (0.016 g, 0.047 mmol) in anhydrous THF (1.5 mL). The mixture was stirred at room temperature for 15 h. The solvent was removed in vacuo and the residue was dissolved in methanol (1 mL) and triethylamine (0.2 mL). The mixture was stirred at room temperature for 1 h and was concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate) to afford formamide **30** (0.014 g, 82%) as a pale yellow oil: IR (film) 3350, 2950, 1670, 1610, 1580, 1480, 1400, 1040, 920 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.90 (3 H, s), 4.6 (2 H, s), 5.20 (1 H, d, J = 11.0 Hz), 5.65 (1 H, d, J = 17.4 Hz), 6.28 (1 H, dd, J = 11.1, 17.4 Hz), 6.69 (1 H, s), 6.85 (1 H, J = 5.2 Hz), 7.01 (1 H, d, J = 7.6 Hz), 7.17–7.39 (3 H, m), 7.53 (1 H, d, J = 7.9 Hz), 7.7 (1 H, s), 8.10 (1 H, d, J = 5.2 Hz), 8.13 (1 H, s); mass spectrum, m/z (relative intensity) 365 (M^+, 10), 347 (16), 253 (38), 220 (23), 219 (100), 191 (32), 174 (20), 146 (43), 118 (22), 77 (23), 28 (74); exact mass calcd for $C_{20}H_{19}N_3O_4$ 365.1375, found 365.1404.

Diels–Alder Reaction of Oxazole Alcohol 30. A solution of oxazole alcohol **30** (0.15 g, 0.41 mmol) and DBN (0.05 g, 0.41 mmol) in anhydrous *o*-dichlorobenzene (60 mL) was deoxygenated with argon for 45 min. The mixture was heated at 150 °C under argon for 1.5 h and then cooled to room temperature. The solvent was removed in vacuo and the residue was purified by flash chromatography (2% methanol/ethyl acetate) to afford 0.10 g (71%) of pyridine alcohol **31** as a pale yellow oil: IR (film) 3350, 2950, 1680, 1600, 1560, 1480, 1390, 1320, 1040 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.80 (3 H, s), 4.54 (1 H, d, J = 15.3 Hz), 4.92 (1 H, d, J = 15.2 Hz), 6.22 (1 H, d, J = 0.6 Hz), 6.66 (1 H, dd, J = 1.2, 5.3 Hz), 6.91 (1 H, s), 7.18 (1 H, dd, J = 1.4, 7.4 Hz), 7.36–7.49 (2 H, m), 7.74 (1 H, d, J = 5.2 Hz), 7.95 (1 H, dd, J = 1.4, 7.3 Hz), 7.99 (1 H, d, J = 5.4 Hz), 8.70 (1 H, d, J = 5.3 Hz), 8.72 (1 H, s); mass spectrum, m/z (relative intensity) 347 (M^+, 34), 318 (21), 300 (24), 239 (42), 211 (56), 182, (41), 181 (100), 127 (28), 91 (38), 77 (24), 39 (25); exact mass calcd for $C_{20}H_{17}N_3O_3$ 347.1270, found 347.1271.

Preparation of Formamide Aldehyde 32. Activated MnO_2 (0.57 g, 6.56 mmol) was added to a solution of alcohol **31** (0.153 g, 0.441) in anhydrous $CHCl_3$ (10 mL), and the mixture was stirred at room temperature under argon for 20 h. The reaction mixture was filtered through a pad of silica gel, which was eluted with 50% ethyl acetate/hexane. The combined eluents were concentrated

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

Michael D. Taylor,* Richard J. Himmelsbach, Brian E. Kornberg, John Quin, III, Elizabeth Lunney, and Andrē Michel†

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Arbor, Michigan 48105, and Department of Chemistry, Universitē de Sherbrooke, Sherbrooke, Quebec J1K 2R1, Canada

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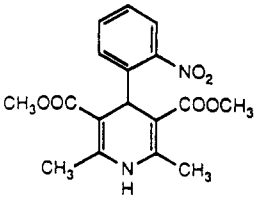
Cycloaddition reactions of nitrile oxides with 5-unsubstituted 1,4-dihydropyridine derivatives produced isoxazolo[5,4-*b*]pyridines in moderate to good yield. In each case examined, the reaction produced only a single isomer, the structure of which was assigned by NMR analysis and later confirmed by 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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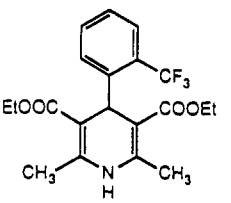

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† Universitē de Sherbrooke.

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