A New Synthesis of *N*-Alkyl 4-Methyl-1,4-dihydropyridines Utilizing *sec*-Aminodienyl Esters with Crotonaldehyde

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The reactions of *sec*-aminodienyl esters 3 with crotonaldehyde (4) afforded *N*-alkyl 3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridines 5, providing a new azaelectrocyclization reaction.

Key words aminodienyl ester; primary amine; crotonaldehyde; 1,4-dihydropyridine; azaelectrocyclization reaction

We are interested in the reactivities of the *sec*-aminodienyl esters **3**. The enaminic, dienic, and electronic "push pull" character of these molecules can lead to interesting cycloaddition and azaelectrocyclization reactions, as well as nitrodienamines and aminoacrylates synthons.[1—4] Previously,[1] we reported the cycloaddition reactions of methyl 5-(*N*,*N*-dimethylamino)-2,4-pentadienoate (*tert*-aminodienyl ester **1**) with α,β-unsaturated carbonyl compounds and quinones gave aromatic compounds.[1a] We also determined that the reactions of methyl 5-(*N*-alkylamino)-2,4-pentadienoates (*sec*-aminodienyl esters **3**) with acetaldehyde provided 2,3-dihydro-6*H*-1,3-oxazines, and the reactions of **3** in the presence of propargylaldehyde diethylacetal afforded self-condensation products, 1,4-dihydropyridines, as an unexpected reaction.[1b,d] Although several reactions using related aminodienyl esters have been reported, their utility and basic reactivity have not been well documented.[5]

Dihydropyridine derivatives are important for developing drugs and are relatively difficult to be synthesized. At this time, we firstly synthesized designed 1,4-dihydropyridine derivatives utilizing *sec*-aminodienyl esters **3** with crotonaldehyde (**4**), which produced the expected reaction. This reaction is a new synthetic method for obtaining 1,4-dihydropyridine derivatives, which is interesting in terms of organic chemistry research and also regarding the biological activity of drugs (hypotensive, anti-inflammatory and mutagenic effects).[6] The *sec*-aminodienyl esters **3** were prepared by reactions of the *tert*-aminodienyl ester **1** with primary amines **2**. The reactions of **3** with crotonaldehyde (**4**) afforded *N*-alkyl 3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridines **5**, providing a new azaelectrocyclization reaction.

The methyl 5-(*N*-alkylamino)-2,4-pentadienoate derivatives listed in Table 1, *sec*-aminodienyl esters **3a—f**, were selected for investigation (Chart 1). The *sec*-aminodienyl esters **3** were prepared by the reaction of the *tert*-aminodienyl ester **1** with the corresponding primary amines, namely, 3,4,5-trimethoxybenzylamine (**2a**), 4-chlorobenzylamine (**2b**), 2-(4-chlorophenyl)ethylamine (**2c**), 2-(2-chlorophenyl)ethylamine (**2d**), 2-(4-bromophenyl)ethylamine (**2e**), and 2,4-difluorobenzylamine (**2f**), respectively, under reflux in tetrahydrofuran (THF) (Table 1).

Previous syntheses of 1,4-dihydropyridines have been reported,[6,7] but synthetic methods using the related aminodienyl esters have barely been studied. On the basis of our earlier report on the formation of the product 2,3-dihydro-6*H*-1,3-oxazines[1b] by the reaction of *sec*-aminodienyl esters with acetaldehyde, we attempted to prepare the product 1-(3,4,5-trimethoxybenzyl)-3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridine (**5a**) by azaelectrocyclization reaction of the *sec*-aminodienyl ester **3a** with crotonaldehyde (**4**). As expected, the product **5a** was obtained in 53% yield by refluxing **3a** with crotonaldehyde (**4**) in xylene.

The structure of **5a** was proposed on the basis of the following spectroscopic analyses. The molecular formula of **5a** was found to be $C_{20}H_{25}NO_5$. The ^{1}H-NMR spectrum of **5a** showed the presence of aromatic protons at δ 6.40 (2H, s), methylene protons at δ 4.29 (2H, s), and three methoxy protons at δ 3.84 (3H, s) and 3.85 (6H, s) due to a 3,4,5-trimethoxybenzyl group, methoxy protons at δ 3.72 (3H, s), two olefinic protons at δ 5.62 (1H, d, J=15.3 Hz) and 7.25 (1H, d, J=15.3 Hz) due to (methoxycarbonyl)ethenyl group, methyl protons at δ 1.13 (3H, d, J=6.4 Hz), a methine proton at δ 3.40 (1H, q, J=6.4 Hz), and three olefinic protons at δ 4.84 (1H, dd, J=7.9, 4.9 Hz), 5.83 (1H, dd, J=7.9, 1.5 Hz) and at 6.35 (1H, d, J=0.9 Hz) due to a 1,4-dihydropyridine ring. The IR spectrum of **5a** indicated absorption bands at 1720 cm^{-1} (methoxycarbonyl group), and at 1690, 1680, 1670 cm^{-1} (three olefinic groups). The nuclear Overhauser effect correlation spectroscopy (NOESY) of **5a** revealed the presence of a cross-peak between the 4-methyl protons at δ

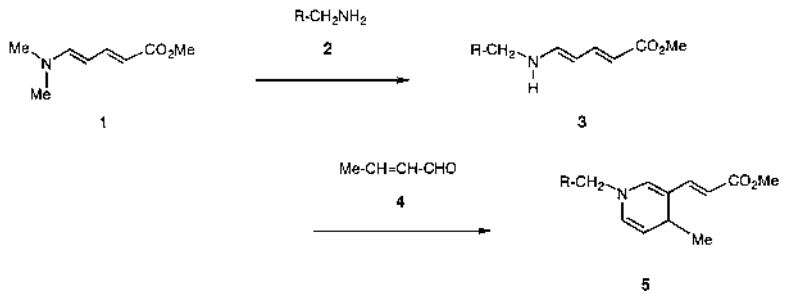

Chart 1

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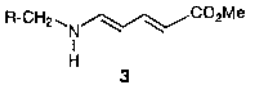
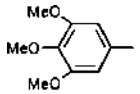
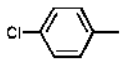
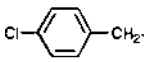
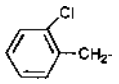
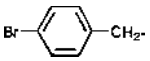
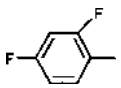
Table 1. The Reactions of *tert*-Aminodienyl Ester **1** with Primary Amines **2**[a)]

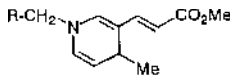


3

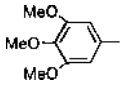
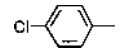
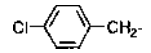
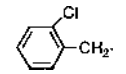
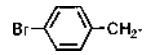
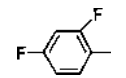
Starting amine	R	Reaction time (h)	Reaction product	Yield (%)	Appearance [solvent, mp (°C)]	^{1}H-NMR, δ (ppm)	IR (cm^{-1})
2a		90	**3a**	62	Light yellow oil	3.70 (3H, s, –Me), 3.84 (3H, s, –Me), 3.85 (3H, s, –Me), 3.86 (3H, s, –Me), 4.17 (2H, d, J=5.0 Hz, methylene H), 5.37 (1H, dd, J=13.1, 11.2 Hz, olefinic H), 5.50 (1H, d, J=14.9 Hz, olefinic H), 6.50 (2H, s, aromatic H), 6.80 (1H, dd, J=13.1, 7.5 Hz, olefinic H), 7.34 (1H, dd, J=14.9, 11.2 Hz, olefinic H), [$CDCl_3$]	3370, 1730, 1700, 1695, 1680, 1640, (neat)
2b		92	**3b**	72	Light yellow plates (ether–hexane, 83—84)	3.69 (3H, s, –Me), 4.22 (2H, d, J=5.5 Hz, methylene H), 5.31 (1H, dd, J=13.1, 11.6 Hz, olefinic H), 5.48 (1H, d, J=15.0 Hz, olefinic H), 6.78 (1H, dd, J=13.1, 7.6 Hz, olefinic H), 7.22 (2H, d, J=8.6 Hz, aromatic H), 7.31 (1H, dd, J=15.0, 11.6 Hz, olefinic H), 7.32 (2H, d, J=8.6 Hz, aromatic H), [$CDCl_3$]	3330, 1730, 1690, 1680, 1630, 1605, (KBr)
2c		76	**3c**	63	Light yellow oil	2.84 (2H, t, J=7.0 Hz, methylene H), 3.32 (2H, q, J=7.0 Hz, methylene H), 3.69 (3H, s, –Me), 5.32 (1H, dd, J=13.1, 11.6 Hz, olefinic H), 5.49 (1H, d, J=15.0 Hz, olefinic H), 6.67 (1H, dd, J=13.1, 7.6 Hz, olefinic H), 7.12 (2H, d, J=8.5 Hz, aromatic H), 7.29 (2H, d, J=8.5 Hz, aromatic H), 7.31 (1H, dd, J=15.0, 11.6 Hz, olefinic H), [$CDCl_3$]	3350, 1720, 1695, 1685, 1640, 1610, (neat)
2d		72	**3d**	84	Light yellow oil	3.00 (2H, t, J=7.0 Hz, methylene H), 3.35 (2H, q, J=7.0 Hz, methylene H), 3.68 (3H, s, –Me), 5.34 (1H, dd, J=13.1, 11.6 Hz, olefinic H), 5.47 (1H, d, J=14.7 Hz, olefinic H), 6.68 (1H, dd, J=13.1, 7.9 Hz, olefinic H), 7.23—7.17 (3H, m, aromatic H), 7.32 (1H, dd, J=14.7, 11.6 Hz, olefinic H), 7.38—7.36 (1H, m, aromatic H), [$CDCl_3$]	3350, 1730, 1690, 1620, 1595, 1540, (neat)
2e		71	**3e**	61	Light yellow oil	2.81 (2H, t, J=6.6 Hz, methylene H), 3.31 (2H, q, J=6.6 Hz, methylene H), 3.69 (3H, s, –Me), 5.30 (1H, dd, J=13.2, 11.4 Hz, olefinic H), 5.48 (1H, d, J=14.7 Hz, olefinic H), 6.66 (1H, dd, J=13.2, 7.7 Hz, olefinic H), 7.05 (2H, d, J=8.4 Hz, aromatic H), 7.31 (1H, dd, J=14.7, 11.4 Hz, olefinic H), 7.44 (2H, d, J=8.4 Hz, aromatic H), [$CDCl_3$]	3350, 1730, 1700, 1695, 1685, 1640, (neat)
2f		86	**3f**	69	Light yellow plates (ether–hexane, 89—91)	3.68 (3H, s, –Me), 4.25 (2H, d, J=5.3 Hz, methylene H), 5.32 (1H, dd, J=13.0, 11.4 Hz, olefinic H), 5.48 (1H, d, J=14.7 Hz, olefinic H), 7.45—6.63 (5H, m, aromatic H and olefinic H), [$CDCl_3$]	3330, 1720, 1690, 1650, 1620, 1595, (KBr)

a) All reactions were run in refluxing THF.

Table 2. The Reactions of *sec*-Aminodienyl Esters **3** with Crotonaldehyde (**4**)[a)]



5

Starting material	R	Reaction product	Yield (%)	^{1}H-NMR, δ (ppm)	IR (cm^{-1})	Formula, HR-MS *m/z* Calcd (Found)
3a		**5a**	53	1.13 (3H, d, *J*=6.4 Hz, –Me), 3.40 (1H, q, *J*=6.4 Hz, methine H), 3.72 (3H, s, –Me), 3.84 (3H, s, –Me), 3.85 (6H, s, –Me), 4.29 (2H, s, methylene H), 4.84 (1H, dd, *J*=7.9, 4.9 Hz, olefinic H), 5.62 (1H, d, *J*=15.3 Hz, olefinic H), 5.83 (1H, dd, *J*=7.9, 1.5 Hz, olefinic H), 6.35 (1H, d, *J*=0.9 Hz, olefinic H), 6.40 (2H, s, aromatic H), 7.25 (1H, d, *J*=15.3 Hz, olefinic H), [$CDCl_3$]	1720, 1690, 1680, 1670, 1610, 1590, (neat)	$C_{20}H_{25}NO_5$ 359.1730 (359.1702)
3b		**5b**	53	1.11 (3H, d, *J*=6.7 Hz, –Me), 3.38 (1H, q, *J*=6.7 Hz, methine H), 3.72 (3H, s, –Me), 4.31 (2H, s, methylene H), 4.82 (1H, dd, *J*=7.6, 4.9 Hz, olefinic H), 5.62 (1H, d, *J*=15.3 Hz, olefinic H), 5.78 (1H, dd, *J*=7.6, 1.2 Hz, olefinic H), 6.32 (1H, d, *J*=0.9 Hz, olefinic H), 7.14 (2H, d, *J*=8.2 Hz, aromatic H), 7.23 (1H, d, *J*=15.3 Hz, olefinic H), 7.33 (2H, d, *J*=8.5 Hz, aromatic H), [$CDCl_3$]	1720, 1700, 1690, 1670, 1605, 1580, (neat)	$C_{17}H_{18}ClNO_2$ 303.1026 (303.1056)
3c		**5c**	40	1.06 (3H, d, *J*=6.7 Hz, –Me), 2.80 (2H, t, *J*=7.0 Hz, methylene H), 3.35 (2H, t, *J*=7.0 Hz, methylene H), 3.35 (1H, q, *J*=6.7 Hz, methine H), 3.71 (3H, s, –Me), 4.75 (1H, dd, *J*=7.9, 4.9 Hz, olefinic H), 5.57 (1H, d, *J*=15.3 Hz, olefinic H), 5.68 (1H, dd, *J*=7.9, 1.5 Hz, olefinic H), 6.13 (1H, d, *J*=0.9 Hz, olefinic H), 7.09 (2H, d, *J*=8.2 Hz, aromatic H), 7.17 (1H, d, *J*=15.3 Hz, olefinic H), 7.27 (2H, d, *J*=8.2 Hz, aromatic H), [$CDCl_3$]	1720, 1690, 1680, 1670, 1605, 1580, (neat)	$C_{18}H_{20}ClNO_2$ 317.1180 (317.0850)
3d		**5d**	41	1.06 (3H, d, *J*=6.4 Hz, –Me), 2.97 (2H, t, *J*=7.0 Hz, methylene H), 3.34 (1H, q, *J*=6.4 Hz, methine H), 3.40 (2H, t, *J*=7.0 Hz, methylene H), 3.71 (3H, s, –Me), 4.75 (1H, dd, *J*=7.9, 4.9 Hz, olefinic H), 5.56 (1H, d, *J*=15.3 Hz, olefinic H), 5.74 (1H, dd, *J*=7.9, 1.5 Hz, olefinic H), 6.14 (1H, d, *J*=1.2 Hz, olefinic H), 7.17 (1H, d, *J*=15.3 Hz, olefinic H), 7.26—7.16 (3H, m, aromatic H), 7.38—7.36 (1H, m, aromatic H), [$CDCl_3$]	1715, 1695, 1680, 1670, 1605, 1580, (neat)	$C_{18}H_{20}ClNO_2$ 317.1180 (317.1165)
3e		**5e**	42	1.06 (3H, d, *J*=6.7 Hz, –Me), 2.78 (2H, t, *J*=7.0 Hz, methylene H), 3.34 (2H, t, *J*=7.0 Hz, methylene H), 3.34 (1H, q, *J*=6.7 Hz, methine H), 3.71 (3H, s, –Me), 4.75 (1H, dd, *J*=7.9, 4.9 Hz, olefinic H), 5.57 (1H, d, *J*=15.3 Hz, olefinic H), 5.68 (1H, dd, *J*=7.9, 1.5 Hz, olefinic H), 6.13 (1H, d, *J*=0.9 Hz, olefinic H), 7.03 (2H, d, *J*=8.5 Hz, aromatic H), 7.17 (1H, d, *J*=15.3 Hz, olefinic H), 7.42 (2H, d, *J*=8.5 Hz, aromatic H), [$CDCl_3$]	1720, 1690, 1680, 1670, 1610, 1580, (neat)	$C_{18}H_{20}BrNO_2$ 361.0676 (361.0752)
3f		**5f**	49	1.10 (3H, d, *J*=6.7 Hz, –Me), 3.36 (1H, q, *J*=6.7 Hz, methine H), 3.72 (3H, s, –Me), 4.34 (2H, s, methylene H), 4.82 (1H, dd, *J*=7.9, 4.9 Hz, olefinic H), 5.61 (1H, d, *J*=15.3 Hz, olefinic H), 5.82 (1H, dd, *J*=7.9, 1.5 Hz, olefinic H), 6.34 (1H, d, *J*=0.9 Hz, olefinic H), 6.90—6.82 (2H, m, aromatic H), 7.19 (1H, d, *J*=8.6 Hz, aromatic H), 7.23 (1H, d, *J*=15.3 Hz, olefinic H), [$CDCl_3$]	1720, 1695, 1685, 1670, 1605, 1580, (neat)	$C_{17}H_{17}F_2NO_2$ 305.1225 (305.1200)

a) All reactions were run in refuxing xylene for 2 h.

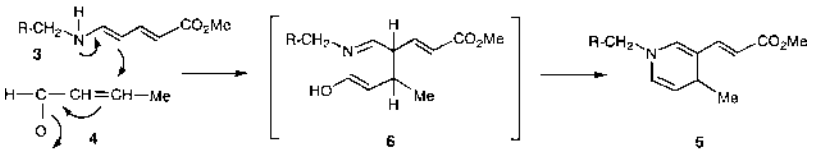


Chart 2

1.13 (3H) and the olefinic proton of a (methoxycarbonyl)-ethenyl group at δ 5.62 (1H), and a cross-peak between the methylene protons of a trimethoxybenzyl group at δ 4.29 (2H) and the 6-olefinic proton at δ 5.83 (1H). Therefore, it may be deduced that **5a** is a 4-methyl-1,4-dihydropyridine.

Regarding *sec*-dienylamine chemistry, we investigated the reactions of nitrodienamines with acetaldehyde gave 1,2-dihydropyridine derivatives,[4d] and the reactions of aminodienyl esters with crotonaldehyde in affording 1,4-dihydropyridine derivatives. These results have shown that their azaelectrocyclization reactions depend on the nature of the electron-withdrawing group at the terminal position of the *sec*-dienylamines, which result in changes in the reactive carbon site in the transition state. Their behavior suggests that we could make either 1,2- or 1,4-dihydropyridine derivatives as reaction products depending on the choice of *sec*-dienylamines. Namely, reagent treatment of *sec*-dienylamines which have a nitro group would provide 1,2-dihydropyridines, and reagent treatment of *sec*-dienylamines having a methoxycarbonyl group would yield 1,4-dihydropyridines.

1,4-Dihydropyridine compounds are a product of certain drugs. Drug derivatives containing halogen atoms (*ex*. Br, Cl, F) have often been known to show strong biological activity. Therefore, we synthesized 1,4-dihydropyridine derivatives having halogenated groups. In a similar manner, several other substituted 3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridines, **5b—f**, listed in Table 2, were prepared from the corresponding **3b—f** (Chart 1, Table 2).

The 6π-azaelectrocyclization reactions of *sec*-aminodienyl esters **3** with crotonaldehyde (**4**) may be explained as follows. Initially, the condensation reaction of **3** with crotonaldehyde (**4**) may generate the intermediate **6**, followed by intramolecular ring closure with dehydration, which could lead to 4-methyl-1,4-dihydropyridines **5**, as shown in Chart 2.

These results provide a new method of synthesizing *N*-alkyl 3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridines **5** utilizing *sec*-aminodienyl esters **3** with crotonaldehyde (**4**).

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO FT/IR-200 spectrometer, and ^{1}H- and ^{13}C-NMR spectra with a JEOL JNM-EX 90 or JEOL JNM-α500 spectrometer, with tetramethylsilane as an internal standard. MS were recorded with a JEOL JMS-D 300 spectrometer. Elemental analyses were recorded on a Yanaco CHN-corder MT-3. NH-DM 1020 (basic 100 Å type silica gel, Fuji Silysia Chemical, Ltd.) was used for column chromatography and thin layer chromatography (TLC). All runs were carried out under an argon atmosphere.

General Procedure for Reactions of *tert*-Aminodienyl Ester 1 with Primary Amines 2 A solution of the *tert*-aminodienyl ester **1** (233 mg, 1.5 mmol) and an amine **2** (0.5 mmol) in THF (4 ml) was refluxed for an appropriate period until the disappearance of the amine (checked by TLC). The reaction mixture was concentrated under a vacuum, then the residue was subjected to NH silica gel column chromatography with appropriate solvents. The isolated yield of **3** is based on **2**. The reaction conditions and properties of the prepared compounds **3** are shown in Table 1.

Methyl 5-(3,4,5-trimethoxybenzylamino)-2,4-pentadienoate (**3a**) was synthesized by the previously reported method.[1d]

Methyl 5-(4-Chlorobenzylamino)-2,4-pentadienoate (**3b**): Amine **2b**: 71 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product **3b**: 91 mg. High-resolution EI-MS *m/z*: Calcd for $C_{13}H_{14}ClNO_2$ (M^+): 251.0711. Found: 251.0505. *Anal*. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.57. Found: C, 61.20; H, 5.44; N, 5.48.

Methyl 5-[2-(4-Chlorophenyl)ethylamino]-2,4-pentadienoate (**3c**): Amine **2c**: 78 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product **3c**: 84 mg. High-resolution EI-MS *m/z*: Calcd for $C_{14}H_{16}ClNO_2$ (M^+): 265.0867. Found: 265.0677.

Methyl 5-[2-(2-Chlorophenyl)ethylamino]-2,4-pentadienoate (**3d**): Amine **2d**: 78 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product **3d**: 112 mg. High-resolution EI-MS *m/z*: Calcd for $C_{14}H_{16}ClNO_2$ (M^+): 265.0867. Found: 265.0864.

Methyl 5-[2-(4-Bromophenyl)ethylamino]-2,4-pentadienoate (**3e**): Amine **2e**: 100 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product **3e**: 95 mg. High-resolution EI-MS *m/z*: Calcd for $C_{14}H_{16}BrNO_2$ (M^+): 309.0360. Found: 309.0357.

Methyl 5-(2,4-Difluorobenzylamino)-2,4-pentadienoate (**3f**): Amine **2f**: 72 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product **3f**: 87 mg. High-resolution EI-MS *m/z*: Calcd for $C_{13}H_{13}F_2NO_2$ (M^+): 253.0915. Found: 253.0942. *Anal*. Calcd for $C_{13}H_{13}F_2NO_2$: C, 61.65; H, 5.17; N, 5.53. Found: C, 60.92; H, 5.06; N, 5.42.

General Procedure for Reactions of *sec*-Aminodienyl Esters 3 with Crotonaldehyde (4) A solution of *sec*-aminodienyl esters **3** (0.6035 mmol) and crotonaldehyde (10.0 μl, 0.1207 mmol) in xylene (3 ml) was refluxed for 20 h. The reaction mixture was subjected to NH silica gel column chromatography with appropriate solvents. The properties of the prepared compound **5** are shown in Table 2.

1-(3,4,5-Trimethoxybenzyl)-3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridine (**5a**): Substrate **3a**: 185 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product **5a**: 23 mg. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 23.4, 27.3, 51.1, 56.1, 57.5, 57.5, 60.9, 103.7, 103.7, 107.3, 108.6, 112.6, 127.6, 133.0, 137.5, 138.9, 146.2, 153.6, 153.6, 168.8.

1-(4-Chlorobenzyl)-3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridine (**5b**): Substrate **3b**: 152 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5b**: 20 mg.

1-[2-(4-Chlorophenyl)ethyl]-3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridine (**5c**): Substrate **3c**: 160 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5c**: 15 mg.

1-[2-(2-Chlorophenyl)ethyl]-3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridine (**5d**): Substrate **3d**: 160 mg. Solvent for chromatography: 25% ethyl acetate in hexane. Product **5d**: 16 mg.

1-[2-(4-Bromophenyl)ethyl]-3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridine (**5e**): Substrate **3e**: 187 mg. Solvent for chromatography: 25% ethyl acetate in hexane. Product **5e**: 18 mg.

1-(2,4-Difluorobenzyl)-3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridine (**5f**): Substrate **3f**: 153 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5f**: 18 mg.

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