Aminodienyl Esters III: A New Synthesis of 1,4-Dihydropyridines by Self-Heterocyclic Annelation Reactions of *sec*-Aminodienyl Esters

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The reactions of *sec*-aminodienyl esters **3 in the presence of propargylaldehyde diethylacetal afforded 1,4-dihydropyridines. This provides a new self-heterocyclic annelation reaction.**

Key words aminodienyl ester; primary amine; 1,4-dihydropyridine; self-heterocyclic annelation reaction

We are interested in the reactivities of the *sec*-aminodienyl esters **3** containing enaminic, olefinic, and other attractive moieties as well as nitrodienamines and aminoenyl esters synthons, because of their electronic “push–pull” character which can lead to interesting cycloaddition reactions.^{1–4} Although several reactions using related aminodienyl esters have been reported, their utility and basic reactivity have not been well documented.⁵ Dihydropyridine chemistry is of interest from the point of view of pure research on heterocyclic compounds and also from the biological point of view (hypotensive, antiinflammatory and mutagenic effect).⁶ The *sec*-aminodienyl esters **3** were prepared by the reactions of *tert*-aminodienyl ester **1** and primary amines **2**. The reactions of **3** in the presence of propargylaldehyde diethylacetal afforded 1,4-dihydropyridines, which provides a new self-heterocyclic annelation reaction.

The following *sec*-aminodienyl esters, namely, methyl 5-(phenethylamino)-2,4-pentadienoate (**3a**), methyl 5-[2-(4-methoxyphenyl)ethylamino]-2,4-pentadienoate (**3b**), methyl 5-[2-(3,4-dimethoxyphenyl)ethylamino]-2,4-pentadienoate (**3c**), methyl 5-(2,3-dimethoxybenzylamino)-2,4-pentadienoate (**3d**), methyl 5-(3,5-dimethoxybenzylamino)-2,4-penta-

dienoate (**3e**), and methyl 5-(3,4,5-trimethoxybenzylamino)-2,4-pentadienoate (**3f**) 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, phenethylamine (**2a**), 4-methoxyphenethylamine (**2b**), 3,4-dimethoxyphenethylamine (**2c**), 2,3-dimethoxybenzylamine (**2d**), 3,5-dimethoxybenzylamine (**2e**), and 3,4,5-trimethoxybenzylamine (**2f**), respectively, under reflux in tetrahydrofuran (THF) (Table 1).

Many syntheses of 1,4-dihydropyridines have been reported,^{6,7} but synthetic methods using the related aminodienyl esters have been little studied. On the basis of our earlier report on the formation of the heterocyclic annelation product, 2,3-dihydro-6*H*-1,3-oxazines,^{1b} by the reaction of *sec*-aminodienyl esters with acetaldehyde, we attempted to prepare the heterocyclic annelation product, 4-ethoxy-3-[2-(methoxycarbonyl)ethenyl]-1-phenethyl-1,4-dihydropyridine (**5**), by cycloaddition reaction of the *sec*-aminodienyl esters **3** with propargylaldehyde diethylacetal. Unexpectedly, 3-[2-(methoxycarbonyl)ethenyl]-4-methoxycarbonylmethyl-1-phenethyl-1,4-dihydropyridine (**4a**) was obtained by the treatment of **3a** with propargylaldehyde diethylacetal in re-

Chart 1

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Table 1. The Reactions of *tert*-Aminodiethyl Ester **1** with Primary Amines **2**^{a)}

Initial compound	Reaction product	Reaction time (h)	Yield (%)	Appearance	IR (cm ⁻¹)
1a	3a	96	80	Light yellow oil	3380, 1734, 1687, 1620, 1597, 1520, (neat)
1b	3b	83	58	Light yellow oil	3360, 1730, 1690, 1610, 1595, 1510, (neat)
1c	3c	98	79	Light yellow oil	3380, 1730, 1700, 1690, 1680, 1640, (neat)
1d	3d	85	83	Light yellow oil	3360, 1730, 1700, 1690, 1680, 1630, (neat)
1e	3e	71	72	Light yellow oil	3380, 1730, 1700, 1695, 1680, 1640, (neat)
1f	3f	90	62	Light yellow oil	3370, 1730, 1700, 1695, 1680, 1640, (neat)

a) All reactions were run in refluxing THF.

Table 2. The Self-Heterocyclic Annelation Reactions of *sec*-Aminodiethyl Esters **3**^{a)}

Initial compound	Reaction product	Reaction time (h)	Yield (%)	Appearance	IR (cm ⁻¹)
3a	4a	3	32	Light yellow oil	1730, 1720, 1690, 1680, 1670, (neat)
3b	4b	1	33	Light yellow oil	1735, 1730, 1705, 1695, 1670, (neat)
3c	4c	3	37	Light yellow oil	1730, 1720, 1690, 1680, 1670, (neat)
3d	4d	3	35	Light yellow oil	1730, 1725, 1700, 1695, 1670, (neat)
3e	4e	3	36	Light yellow oil	1735, 1730, 1700, 1690, 1670, (neat)
3f	4f	2	25	Light yellow oil	1740, 1720, 1700, 1690, 1670, (neat)

a) All reactions were run in refluxing xylene.

Chart 2

fluxing xylene. Interestingly, the reaction did not proceed in the absence of propargylaldehyde diethylacetal. Although the reaction afforded **4a** by the treatment of **3a** with a catalytic amount of propargylaldehyde diethylacetal in low yield, the reaction proceeded smoothly with an excess amount of propargylaldehyde diethylacetal. The reaction was found to proceed with an acid catalyst such as zinc chloride. Thus, the active hydrogen of the acetylene moiety of propargylaldehyde diethylacetal seems to play the role of an acid catalyst.

The structure of the product **4a** was proposed on the basis of the following spectroscopic analyses. The molecular formula of the product **4a** was found to be the C₂₀H₂₃NO₄. The ¹H-NMR spectrum of **4a** showed the presence of aromatic protons at δ 7.32–7.14 (5H, m) and two methylene protons at δ 2.86–2.82 (2H, m) and 3.46–3.36 (2H, m) due to a phenethyl group, a methine proton at δ 3.79–3.76 (1H, m), methylene protons at δ 2.24 (1H, dd, *J*=15.3, 9.8 Hz) and 2.59 (1H, dd, *J*=15.3, 3.4 Hz), two methoxycarbonyl protons at δ 3.68 (3H, s) and 3.71 (3H, s), three olefinic protons at δ 4.86 (1H, dd, *J*=7.6, 5.2 Hz), 5.81 (1H, dd, *J*=7.6, 0.9 Hz)

and 6.18 (1H, s) due to a 1,4-dihydropyridine ring, two olefinic protons at δ 5.58 (1H, d, *J*=15.9 Hz) and 7.16 (1H, d, *J*=15.9 Hz). The IR spectrum of **4a** showed absorption bands at 1730, 1720, 1690, 1680, and 1670 cm⁻¹ due to two methoxycarbonyl groups and three olefinic groups, respectively. The nuclear Overhauser effect correlation spectroscopy (NOESY) of **4a** showed the presence of cross-peaks between the methylene protons of the phenethyl group at δ 3.46–3.36 (2H) and 2, 6-olefinic protons of 6.18 (1H) and 5.81 (1H) due to a 1,4-dihydropyridine ring, and a cross-peak between the methylene proton of 4-methoxycarbonylmethyl group at δ 2.59 (1H) and an olefinic proton of 2-(methoxycarbonyl)ethenyl group δ 5.58 (1H). Therefore, it may be deduced that **4a** is a 1,4-dihydropyridine.

Similarly, other substituted 1,4-dihydropyridines **4b–4f** were prepared from the corresponding **3b–3f** (Chart 1, Table 2).

The self-heterocyclic annelation reactions of *sec*-aminodiethyl esters **3** in the presence of propargylaldehyde diethylacetal may be explained to proceed as follows. Initially, the

self-condensation reaction of **3** with the active hydrogen of propargylaldehyde diethylacetal may generate the aminopronation intermediate **6**, followed by the elimination of the amino group in **6** and subsequent intramolecular ring closure could lead to 1,4-dihydropyridines **4** as shown in Chart 2.

These results provide a new method of synthesizing 1,4-dihydropyridines **4**.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-200 spectrometer, and ^1H -NMR and ^{13}C -NMR spectra on a JEOL JNM-AL300 or JEOL JNM- α 500 spectrometer, with tetramethylsilane as an internal standard. MS were recorded on a JEOL JMS-D 300 spectrometer. NH-DM 1020 (basic 100 Å type silica gel, Fuji Silysia Chemical Ltd.) were used for column chromatography and thin layer chromatography (TLC), respectively. All runs were carried out under argon.

General Procedure for Reactions of *tert*-Aminodienyl Ester **1 with Primary Amines **2**** A solution of the *tert*-aminodienyl ester **1** (1.5 mmol) and an amine (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 vacuum, and the residue was subjected to N-H silica gel column chromatography with appropriate solvents. The properties of the prepared compounds **3** are shown in Table 1. The isolated yield of **3** is based on the corresponding starting amines, and using 3 eq of *tert*-aminodienyl ester **1** to the corresponding starting amine instead of 1.5 eq increased the yield about 20–30 per cent.

Methyl 5-(Phenethylamino)-2,4-pentadienoate (3a**)^{1b}:** Solvent for chromatography: 30% ethyl acetate in hexane. Product: 92 mg. ^1H -NMR (500 MHz, CDCl_3) δ : 2.86 (2H, t, $J=6.8$ Hz, methylene H), 3.33 (2H, q, $J=6.8$ Hz, methylene H), 3.69 (3H, s, $-\text{CO}_2\text{Me}$), 4.18 (1H, br, NH), 5.31 (1H, dd, $J=13.1$, 11.6 Hz, olefinic H), 5.48 (1H, d, $J=14.7$ Hz, olefinic H), 6.67 (1H, dd, $J=13.1$, 7.9 Hz, olefinic H), 7.17–7.37 (6H, m, aromatic and olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: 231.1256. Found: 231.1253.

Methyl 5-[2-(4-Methoxyphenyl)ethylamino]-2,4-pentadienoate (3b**):** Solvent for chromatography: 40% ethyl acetate in hexane. Product: 76 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 2.81 (2H, t, $J=6.9$ Hz, methylene H), 3.30 (2H, q, $J=6.9$ Hz, methylene H), 3.69 (3H, s, $-\text{Me}$), 3.80 (3H, s, $-\text{Me}$), 5.31 (1H, t, $J=11.8$ Hz, olefinic H), 5.48 (1H, d, $J=14.9$ Hz, olefinic H), 6.68 (1H, dd, $J=13.1$, 8.1 Hz, olefinic H), 6.86 (2H, d, $J=8.7$ Hz, aromatic H), 7.10 (2H, d, $J=8.7$ Hz, aromatic H), 7.32 (1H, dd, $J=14.9$, 11.8 Hz, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$ (M^+): 261.1365. Found: 261.1386.

Methyl 5-[2-(3,4-Dimethoxyphenyl)ethylamino]-2,4-pentadienoate (3c**):** Solvent for chromatography: 50% ethyl acetate in hexane. Product: 115 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 2.81 (2H, t, $J=6.9$ Hz, methylene H), 3.31 (2H, q, $J=6.9$ Hz, methylene H), 3.69 (3H, s, $-\text{Me}$), 3.86 (3H, s, $-\text{Me}$), 3.87 (3H, s, $-\text{Me}$), 5.32 (1H, dd, $J=12.9$, 11.5 Hz, olefinic H), 5.48 (1H, d, $J=14.8$ Hz, olefinic H), 6.83–6.65 (4H, m, aromatic and olefinic H), 7.32 (1H, dd, $J=14.8$, 11.5 Hz, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$ (M^+): 291.1470. Found: 291.1636.

Methyl 5-(2,3-Dimethoxybenzylamino)-2,4-pentadienoate (3d**):** Solvent for chromatography: 40% ethyl acetate in hexane. Product: 115 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 3.68 (3H, s, $-\text{Me}$), 3.86 (3H, s, $-\text{Me}$), 3.87 (3H, s, $-\text{Me}$), 4.24 (2H, d, $J=5.8$ Hz, methylene H), 5.36 (1H, t, $J=11.5$ Hz, olefinic H), 5.47 (1H, d, $J=14.6$ Hz, olefinic H), 6.77 (1H, dd, $J=13.2$, 8.2 Hz, olefinic H), 6.89–6.82 (2H, m, aromatic H), 7.03 (1H, t, $J=8.0$ Hz, aromatic H), 7.33 (1H, dd, $J=14.6$, 11.5 Hz, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4$ (M^+): 277.1312. Found: 277.1307.

Methyl 5-(3,5-Dimethoxybenzylamino)-2,4-pentadienoate (3e**):** Solvent for chromatography: 50% ethyl acetate in hexane. Product: 100 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 3.69 (3H, s, $-\text{Me}$), 3.79 (3H, s, $-\text{Me}$), 3.80 (3H, s, $-\text{Me}$), 4.17 (2H, d, $J=5.5$ Hz, methylene H), 5.34 (1H, dd, $J=12.9$, 11.3 Hz, olefinic H), 5.49 (1H, d, $J=14.8$ Hz, olefinic H), 6.48–6.35 (3H, m, aromatic H), 6.79 (1H, dd, $J=12.9$, 7.7 Hz, olefinic H), 7.33 (1H, dd, $J=14.8$, 11.3 Hz, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4$ (M^+): 277.1314. Found: 277.1351.

Methyl 5-(3,4,5-Trimethoxybenzylamino)-2,4-pentadienoate (3f**):** Solvent for chromatography: 50% ethyl acetate in hexane. Product: 95 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 3.70 (3H, s, $-\text{Me}$), 3.84 (3H, s, $-\text{Me}$), 3.85 (3H, s, $-\text{Me}$), 3.86 (3H, s, $-\text{Me}$), 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). High-resolution EI-MS m/z : Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_5$ (M^+): 307.1420. Found: 307.1420.

General Procedure for Reactions of *sec*-Aminodienyl Esters **3 with Propargylaldehyde Diethylacetal** A solution of a *sec*-aminodienyl ester (0.5 mmol) and propargylaldehyde diethylacetal (2 mmol) in xylene (2 ml) was refluxed for an appropriate period. The reaction mixture was subjected to N-H silica gel column chromatography with appropriate solvents. The reaction conditions and properties of the prepared compounds **4** are shown in Table 2.

3-[2-(Methoxycarbonyl)ethenyl]-4-methoxycarbonylmethyl-1-phenethyl-1,4-dihydropyridine (4a**):** Solvent for chromatography: 30% ethyl acetate in hexane. Product: 27 mg. ^1H -NMR (500 MHz, CDCl_3) δ : 2.24 (1H, dd, $J=15.3$, 9.8 Hz, methylene H), 2.59 (1H, dd, $J=15.3$, 3.4 Hz, methylene H), 2.86–2.82 (2H, m, methylene H), 3.46–3.36 (2H, m, methylene H), 3.68 (3H, s, $-\text{Me}$), 3.71 (3H, s, $-\text{Me}$), 3.79–3.76 (1H, m, methine H), 4.86 (1H, dd, $J=7.6$, 5.2 Hz, olefinic H), 5.58 (1H, d, $J=15.9$ Hz, olefinic H), 5.81 (1H, dd, $J=7.6$, 0.9 Hz, olefinic H), 6.18 (1H, s, olefinic H), 7.16 (1H, d, $J=15.9$ Hz, olefinic H), 7.32–7.14 (5H, m, aromatic H). ^{13}C -NMR (125 MHz, CDCl_3) δ : 29.7, 29.7, 36.7, 41.2, 51.1, 51.5, 55.8, 104.8, 106.9, 108.6, 126.9, 128.5, 128.7, 128.7, 128.9, 128.9, 139.6, 145.6, 168.7, 172.2. High-resolution EI-MS m/z : Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4$ (M^+): 341.1625. Found: 341.1620.

3-[2-(Methoxycarbonyl)ethenyl]-4-methoxycarbonylmethyl-1-[2-(4-methoxyphenyl)ethyl]-1,4-dihydropyridine (4b**):** Solvent for chromatography: 30% ethyl acetate in hexane. Product: 31 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 2.24 (1H, dd, $J=14.9$, 10.0 Hz, methylene H), 2.60 (1H, dd, $J=14.9$, 3.1 Hz, methylene H), 2.77 (2H, t, $J=6.9$ Hz, methylene H), 3.37 (2H, t, $J=6.9$ Hz, methylene H), 3.66 (1H, m, methine H), 3.68 (3H, s, $-\text{Me}$), 3.71 (3H, s, $-\text{Me}$), 3.79 (3H, s, $-\text{Me}$), 4.85 (1H, dd, $J=7.5$, 5.0 Hz, olefinic H), 5.58 (1H, d, $J=15.6$ Hz, olefinic H), 5.79 (1H, d, $J=7.5$ Hz, olefinic H), 6.18 (1H, s, olefinic H), 6.84 (2H, d, $J=8.7$ Hz, aromatic H), 7.06 (2H, d, $J=8.7$ Hz, aromatic H), 7.17 (1H, d, $J=15.6$ Hz, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_5$ (M^+): 371.1733. Found: 371.1749.

3-[2-(Methoxycarbonyl)ethenyl]-4-methoxycarbonylmethyl-1-[2-(3,4-dimethoxyphenyl)ethyl]-1,4-dihydropyridine (4c**):** Solvent for chromatography: 50% ethyl acetate in hexane. Product: 38 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 2.24 (1H, dd, $J=15.7$, 9.9 Hz, methylene H), 2.61 (1H, d, $J=15.7$ Hz, methylene H), 2.78 (2H, t, $J=6.9$ Hz, methylene H), 3.39 (2H, t, $J=6.9$ Hz, methylene H), 3.67 (3H, s, $-\text{Me}$), 3.71 (3H, s, $-\text{Me}$), 3.75 (1H, m, methine H), 3.86 (6H, s, $-\text{Me}$), 4.86 (1H, dd, $J=7.7$, 4.9 Hz, olefinic H), 5.58 (1H, d, $J=15.4$ Hz, olefinic H), 5.80 (1H, d, $J=7.7$ Hz, olefinic H), 6.21 (1H, s, olefinic H), 6.82–6.65 (3H, m, aromatic H), 7.19 (1H, dd, $J=15.4$, 7.7 Hz, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_6$ (M^+): 401.1836. Found: 401.1816.

1-(2,3-Dimethoxybenzyl)-3-[2-(methoxycarbonyl)ethenyl]-4-methoxycarbonylmethyl-1,4-dihydropyridine (4d**):** Solvent for chromatography: 40% ethyl acetate in hexane. Product: 34 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 2.28 (1H, dd, $J=15.1$, 9.6 Hz, methylene H), 2.64 (1H, dd, $J=15.1$, 3.3 Hz, methylene H), 3.70 (3H, s, $-\text{Me}$), 3.71 (3H, s, $-\text{Me}$), 3.80 (1H, m, methine H), 3.82 (3H, s, $-\text{Me}$), 3.83 (3H, s, $-\text{Me}$), 4.36 (2H, s, methylene H), 4.88 (1H, dd, $J=7.7$, 5.2 Hz, olefinic H), 5.60 (1H, d, $J=15.4$ Hz, olefinic H), 5.95 (1H, d, $J=7.7$ Hz, olefinic H), 6.46 (1H, s, olefinic H), 6.75 (1H, d, $J=7.7$ Hz, aromatic H), 6.90 (1H, d, $J=8.0$ Hz, aromatic H), 7.04 (1H, t, $J=8.0$ Hz, aromatic H), 7.25 (1H, d, $J=15.4$ Hz, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_6$ (M^+): 387.1683. Found: 387.1696.

1-(3,5-Dimethoxybenzyl)-3-[2-(methoxycarbonyl)ethenyl]-4-methoxycarbonylmethyl-1,4-dihydropyridine (4e**):** Solvent for chromatography: 50% hexane in ethyl acetate. Product: 35 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 2.32 (1H, dd, $J=15.1$, 9.3 Hz, methylene H), 2.65 (1H, dd, $J=15.1$, 3.3 Hz, methylene H), 3.67 (3H, s, $-\text{Me}$), 3.72 (3H, s, $-\text{Me}$), 3.77 (3H, s, $-\text{Me}$), 3.79 (3H, s, $-\text{Me}$), 3.81 (1H, m, methine H), 4.30 (2H, s, methylene H), 4.92 (1H, dd, $J=7.7$, 4.9 Hz, olefinic H), 5.63 (1H, d, $J=15.4$ Hz, olefinic H), 5.91 (1H, d, $J=7.7$ Hz, olefinic H), 6.52–6.32 (3H, m, aromatic H), 7.25 (1H, d, $J=15.4$ Hz, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_6$ (M^+): 387.1680. Found: 387.1680.

1-(3,4,5-Trimethoxybenzyl)-3-[2-(methoxycarbonyl)ethenyl]-4-methoxycarbonylmethyl-1,4-dihydropyridine (4f**):** Solvent for chromatography: 50% hexane in ethyl acetate. Product: 26 mg. ^1H -NMR (300 MHz, CDCl_3) δ : 2.32 (1H, dd, $J=14.9$, 9.3 Hz, methylene H), 2.65 (1H, dd, $J=14.9$, 3.7 Hz, methylene H), 3.66 (3H, s, $-\text{Me}$), 3.72 (3H, s, $-\text{Me}$), 3.75 (1H, m, methine H), 3.84 (3H, s, $-\text{Me}$), 3.85 (3H, s, $-\text{Me}$), 3.86 (3H, s, $-\text{Me}$), 4.31 (2H, s, methylene H), 4.92 (1H, dd, $J=7.5$, 5.0 Hz, olefinic H), 5.63 (1H, d,

$J=15.6$ Hz, olefinic H), 5.92 (1H, dd, $J=7.5$, 1.9 Hz, olefinic H), 6.40 (2H, s, aromatic H), 6.42 (1H, s, olefinic H), 7.26 (1H, d, $J=15.6$ Hz, olefinic H). High-resolution EI-MS m/z : Calcd for $C_{22}H_{27}NO_7$ (M^+): 417.1784. Found: 417.1748.

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