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# SYNTHESIS OF $^{13}$C-LABELED VERAPAMIL COMPOUNDS

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## SUMMARY

Two $^{13}$C-labeled verapamil compounds were prepared. 2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-[2-(3,4-dimethoxyphenyl-1-[$^{13}$C]-ethyl)methylamino]-valeronitrile was synthesized from 2-(3,4-dimethoxyphenyl)-1-[$^{13}$C]-ethylamine, which was prepared from 3,4-dimethoxybenzyl chloride by displacement with $^{13}$C-labeled KCN followed by diborane reduction. 2-(3,4-Di-[$^{13}$C]-methoxyphenyl)-2-isopropyl-5-[2-(3,4-di-[$^{13}$C]-methoxyphenethyl)methylamino]-valeronitrile containing 50% incorporation of $^{13}$C in the N-methyl group was prepared *via* demethylation of verapamil and subsequent re-methylation with $^{13}$C-labeled $CH_3I$.

## INTRODUCTION

Verapamil (1), 2-(3,4-dimethoxyphenyl)-2-isopropyl-5-[2-(3,4-dimethoxyphenethyl)methylamino]valeronitrile, is a slow calcium channel antagonist used in the treatment of angina, hypertension, and paroxysmal superventricular tachycardia.[1-3] Its pharmacologic, metabolic and pharmacokinetic properties have attracted considerable interest.[4-8] Enantiomeric differences in pharmacological effects[9-14] and different rates of metabolism of its enantiomers have been reported.[10-16] We sought heavy isotope labeled 1 which would be suitable for thorough analysis of metabolites arising from N- and O-dealkylation, and for mechanistic work concerning formation of some of these metabolites. Although $^{13}$C- and deuterium-labeled compounds have been

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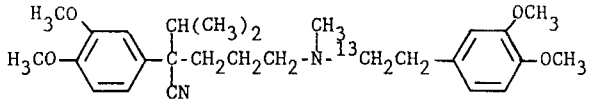
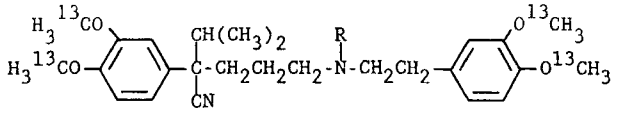
reported,[17-22] none had labels in these positions. In this paper, we report the synthesis of verapamil labeled with $^{13}C$ in the 1-position of the phenethyl side chain (2) and with $^{13}C$-labels in all four O-methyl groups (3). Compound 3 also had 50% incorporation of $^{13}C$ in the N-methyl group.



2



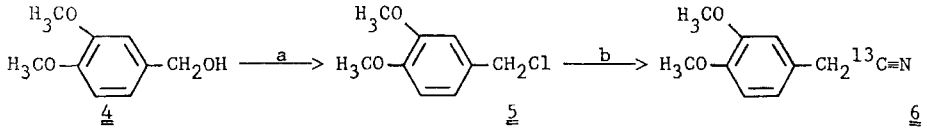
3 R = $^{12}CH_3$ and $^{13}CH_3$

## RESULTS AND DISCUSSION

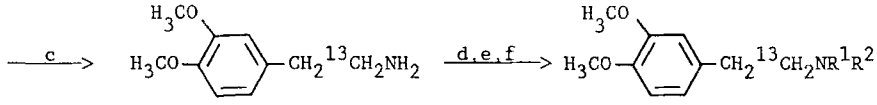
The α-$^{13}C$-phenethyl-labeled verapamil (2) was prepared by displacement of mesylate 12 with N-methyl-2-(3,4-dimethoxyphenyl)-1-[$^{13}C$]-ethyl]amine (9) (Scheme 1). Synthesis of this labeled secondary amine was initiated from 3,4-dimethoxybenzyl alcohol (4) which, when allowed to react with methanesulfonyl chloride for 20 hours at room temperature, gave 3,4-dimethoxybenzyl chloride (5) in 71% yield. Displacement of the chloride with $K^{13}CN$ in DMF gave $^{13}C$-labeled nitrile 6 in 81% yield. Reduction of the nitrile with borane in THF afforded $^{13}C$-labeled primary amine 7 (96%).

Final elaboration of 7 to secondary amine 10 was carried out via a variation of Johnstone's procedure.[23,24] Thus, treatment of 7 with trifluoroacetic anhydride gave 8 which, after conversion to its sodium salt using NaH in THF, was alkylated with $CH_3I$ to afford tertiary trifluoroacetamide 9. Hydrolysis of the amide in 7:1 MeOH/5 N aqueous NaOH resulted in formation of labeled secondary amine 10 in 74% yield from 7. Displacement of mesylate 12 with 10 in DME gave 2 in 44% yield.

Synthesis of tetra-O-$^{13}C$-methyl-verapamil (3) commenced from verapamil hydrochloride (1) which was O-demethylated by heating in aqueous 48% HBr (Scheme 2).[25] Despite numerous attempts, selective methylation of the four



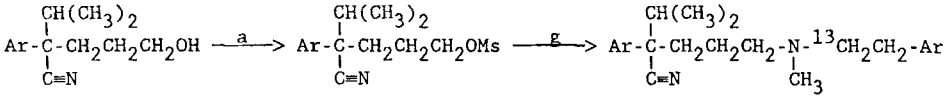
4 5 6



7 8 $R^1$ = H $R^2$ = $COCF_3$

9 $R^1$ = $CH_3$ $R^2$ = $COCF_3$

10 $R^1$ = $CH_3$ $R^2$ = H



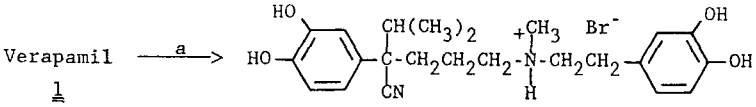
11 12 2

Ar = 3,4-$(CH_3O)_2$-Ph

Reagents: a, MsCl, $Et_3N$, $CH_2Cl_2$; b, $K^{13}C{\equiv}N$, DMF; c, $BH_3$, THF; d, $(CF_3CO)_2O$, $Et_3N$, $CH_2Cl_2$; e, NaH, $CH_3I$, THF; f, aq NaOH, $CH_3OH$; g, $Et_3N$, 9, DME.

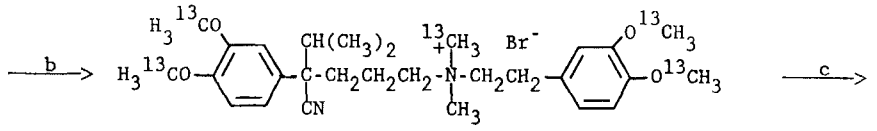
SCHEME 1.

phenolic hydroxyl groups of 12 without concurrent methylation of the tertiary amine was unsuccessful. We, however, found that quaternary ammonium salt 14, prepared by reaction of 13 with a large excess of $^{13}$C-iodomethane and potassium carbonate in acetone, could be successfully demethylated using sodium ethanethiolate in HMPA[26] to afford a 1:1 mixture of tetra-$^{13}$C-verapamil (O-[$^{13}$C]$_4$) and penta-$^{13}$C-verapamil (O-[$^{13}$C]$_4$ and N-[$^{13}$C]) (3) in 50% overall yield from 13.

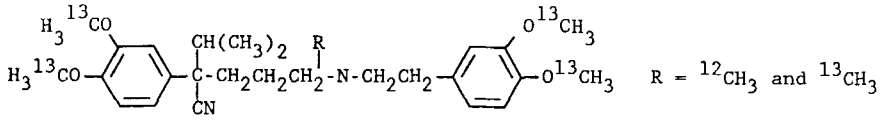


Verapamil 1

13



14



3

Reagents: a, 48% HBr; b, $^{13}CH_3I$, $K_2CO_3$, acetone; c, EtSH, HMPA.

SCHEME 2.

In the NMR spectrum of quaternary ammonium salt 14, two different N-methyl groups ($\delta$ 3.19 and 3.14) are observed due to the presence of a mixture of two diastereoisomers. Separate signals are observed for the N-$^{13}$C-methyl groups, $J_{CH}$ = 144 Hz and the N-$^{12}$C-methyl groups, $J_{C\text{-}CH}$ = 2.7 Hz. After conversion to $^{13}$C-labeled compound 3 two signals for the N-methyl group were also observed in its proton NMR spectrum because $J_{CH}$ = 133 Hz for the N-labeled isotopomer. Though isotopically pure penta-$^{13}$C-verapamil could obviously be prepared via this procedure by starting from N-$^{13}$C-methyl-verapamil,[22] we did not repeat the synthesis of this latter substrate because 3 as a mixture of isotopomers, was adequate as a substrate for the planned metabolic experiments.

The mass spectrum (CI-methane) of 3 showed ions at m/z 459, 460, 461, and 462 (38[$^{13}$C]$_4$:49[$^{13}$C]$_5$:12[$^{13}$C]$_6$:2[$^{13}$C]$_7$) vs. verapamil (1) 455, 456, and 457 (76:21[$^{13}$C]$_1$:3[$^{13}$C]$_2$) (Figure 1). In addition, protonated M-2 ions at m/z 457 and 458 in 3 and at 453 in 1 respectively, were observed in each spectrum. Significant EI fragmentation also occurred as shown by ions at m/z 305, 306 and 307 (79:100:18) and at 236 and 237 (10:12) for 3. The m/z 305 and 306 ions arise by loss of the 3,4-dimethoxybenzyl group affording a mixture of [$^{13}$C]$_2$ and [$^{13}$C]$_3$ ions, compared to verapamil, m/z 303 and 304 (100:23). The ratio of [$^{13}$C]$_4$ to [$^{13}$C]$_5$ incorporation was estimated to be ca. 50:50 based on the m/z 305/306 ratio (47:53 after correction for natural abundance $^{13}$C) or the m/z 459/460 ratio (48:52 after correction for natural abundance $^{13}$C).

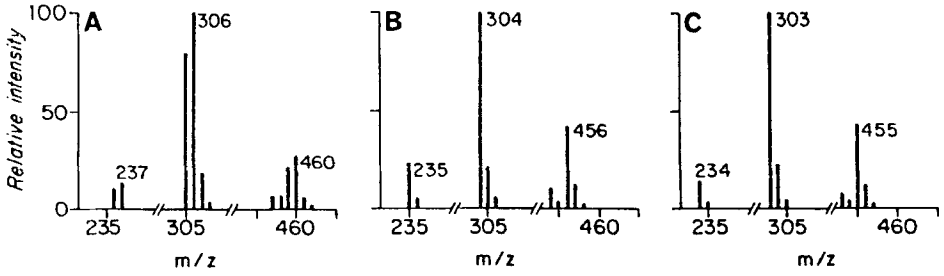



FIGURE 1. Partial CI-mass spectrum of A, compound 3; B, compound 2; C, verapamil (1).

The mass spectrum (CI-methane) of 2 showed expected ions at m/z 456, 304 and 235 vs. verapamil (1) m/z 455, 303 and 234 indicative of a single $^{13}$C atom being incorporated (Figure 1).

Metabolic studies using these $^{13}$C-labeled compounds are currently in progress.

## EXPERIMENTAL

High field proton and carbon NMR spectra were obtained at 300 and 75 MHz, on a Varian VXR-300 spectrometer. Chemical shifts are expressed in parts per million ($\sigma$) downfield from internal tetramethylsilane ($\sigma$ 0.0). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained on a VG-7070 mass spectrometer by direct insert probe. Infrared spectra were recorded on a Perkin-Elmer 283 infrared spectrometer. Analytical thin layer chromatography (TLC) was carried out on Analtech silica gel HLF TLC plates (0.25 mm thickness) and the spots were detected by a UV lamp (254 nm). Merck Silica Gel 60 (230-400 mesh ASTM) was used for flash column chromatography.[27] Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Unless otherwise specified, concentration of reaction mixtures or extracts was carried out (after drying with $MgSO_4$) on a Buchi rotary evaporator at aspirator pressure.

Tetrahydrofuran (THF) was distilled under argon from sodium metal with benzophenone as an indicator. Methylene chloride was distilled from phosphorous pentoxide. Triethylamine, hexamethylphosphoric triamide (HMPA),

and dimethoxyethane (DME) were distilled under argon from powdered NaH. All solvents used for extraction were reagent grade. Unless otherwise indicated, all other reagents or solvents were used without further purification. Prepurified argon was dried by passing through a two foot column packed with indicating Drierite™ and KOH. All glassware was either oven dried for a minimum of 2 hours at 140°C and then purged with argon or flame dried under a continuous flow of argon. All reactions were carried out under an argon atmosphere.

3,4-Dimethoxybenzyl chloride (5). To a stirred solution of 7.25 g (71.65 mmol, 1.20 equiv) of $Et_3N$ and 7.85 g (68.53 mmol, 1.15 equiv) of methanesulfonyl chloride in 100 mL of dry $CH_2Cl_2$ was added 10.01 g (59.5 mmol) of 3,4-dimethoxybenzyl alcohol (4) at 0°C. The mixture was warmed to room temperature and stirred for 20 h. The mixture was then washed with 5% v/v aq HCl (2 x 75 mL). The organic phase was dried, filtered and concentrated. The residue was chromatographed on 150 g of silica gel, eluting with 25% EtOAc/hexanes, to afford 7.83 g of the product (5) as a pale yellow oil (71%): TLC (25% EtOAc/hexanes) $R_f$ 0.56; $^1H$ NMR ($CDCl_3$) 6.95 (1H, dd, J = 8.1, 2.1 Hz), 6.92 (1H, d, J = 2.1 Hz), 6.83 (1H, d, J = 8.1 Hz), 4.59 (2H, s), 3.92(3H, s) and 3.90 ppm (3H, s).

1-[$^{13}C$]-2-(3,4-Dimethoxyphenyl)acetonitrile (6). To a solution of 900 mg (13.6 mmol) of $K^{13}CN$ (Merck, 99% $^{13}C$) in 5 mL of dry DMF, was added 3.00 g (16.07 mmol, 1.18 equiv) of 3,4-dimethoxybenzyl chloride (5). After stirring the mixture at 50°C for 16 h, it was transferred to a separatory funnel, diluted with 75 mL of EtOAc, and washed with $H_2O$ (3 x 75 mL). The organic phase was dried, filtered and concentrated. The residue was chromatographed on 75 g of silica gel, eluting with 25% EtOAc/hexanes, to afford 1.96 g of the product (6) as a yellowish-white crystalline solid (81%): TLC (25% EtOAc/hexanes) $R_f$ 0.24; mp 61-62°C; $^1H$ NMR ($CDCl_3$) 6.86-6.80 (3H, m), 3.90 (3H, s), 3.88 (3H, s) and 3.70 ppm (2H, d, $J_{C-CH}$ = 10.5 Hz); $^{13}C$ NMR ($CDCl_3$-enriched carbon only) 118.2 ppm.

1-[$^{13}C$]-2-(3,4-Dimethoxyphenyl)ethylamine (7). To a solution of 1.80 g

(10.1 mmol) of nitrile 6 in 20 mL of dry THF, was added 20 mL of 1 M borane in THF (20 mmol, 1.98 equiv). The solution was warmed to 55°C and stirred for 20 h. The solution was then cooled to 0°C, and the excess borane was destroyed by careful addition of $H_2O$ (2 mL). The mixture was concentrated, and the residue was diluted with 30 mL of concentrated HCl and stirred for 8 h at 60°C. After cooling to 0°C, the mixture was diluted with 50 mL of $H_2O$, made alkaline by addition of 15.0 g of NaOH and extracted with $CH_2Cl_2$ (3 x 50 mL). The organic extracts were combined, dried, filtered and concentrated to afford 1.76 g of 7 as a yellow oil (96%): $^1$H NMR ($CDCl_3$) 6.86-6.70 (3H, m), 3.92 (3H, s), 3.90 (3H, s), 2.94 (2H, d of m, $J_{CH}$ = 135 Hz), 2.73 (2H, m) and 1.83 ppm (2H, m).

[1-[$^{13}$C]-2-(3,4-Dimethoxyphenyl)ethyl]methylamine (10). To a stirred solution of 1.76 g (9.66 mmol) of the primary amine (7) and 1.47 g (14.5 mmol) of $Et_3N$ in 30 mL of $CH_2Cl_2$ was added 4.06 g (19.3 mmol, 2.0 equiv) of trifluoroacetic anhydride at 0°C. The mixture was stirred at 0°C for 1 h and then concentrated to remove unreacted anhydride. The residue was diluted with 50 mL of $CH_2Cl_2$ and then washed with 50 mL of 5% v/v aq HCl followed by saturated aq $NaHCO_3$ (2 x 50 mL). The organic phase was dried, filtered, and concentrated. The residue was dissolved in 50 mL of THF and treated with 2.75 g (19.4 mmol, 2.0 equiv) of iodomethane followed by slow addition of 450 mg (18.75 mmol) of NaH. The mixture was stirred at room temperature for 3 h, diluted with 100 mL of $CH_2Cl_2$ and then filtered through celite. The filtrate was concentrated, diluted with 75 mL of EtOAc, and washed with 50 mL of 5% v/v aq HCl. The organic phase was dried, filtered, and concentrated. The residue was chromatographed on silica gel, eluting with 50% EtOAc/hexanes, to afford the intermediate tertiary trifluoroacetamide which was dissolved in 35 mL of methanol and treated with 5 mL of 5 N aq NaOH. The mixture was stirred at room temperature for 2 h and then concentrated. The residue was diluted with 30 mL of $H_2O$ and extracted with $CH_2Cl_2$ (2 x 50 mL). The organic extracts were dried, filtered and concentrated to afford 1.41 g of the product (10) as a yellow oil (74%): $^1$H NMR 6.82-6.70 (3H, m), 3.89 (3H, s), 3.87 (3H, s), 2.82 (2H, dt, $J_{CH}$ = 135 Hz and J = 6.9 Hz), 2.75 (2H, q, J = 6.9 Hz) and 2.43 ppm

(3H, d, J = 5.7 Hz, collapsing to a singlet on addition of $D_2O$); $^{13}C$ NMR

1-[(Methanesulfonyl)oxy]-4-cyano-4-(3,4-dimethoxyphenyl)-5-methylhexane (12). To a stirred solution of 2.50 g (9.01 mmol) of alcohol 11[23] and 1.37 g (13.5 mmol, 1.50 equiv) of $Et_3N$ in 75 mL $CH_2Cl_2$ was added 1.14 g (9.95 mmol, 1.10 equiv) of methanesulfonyl chloride at 0°C. The mixture was stirred at 0°C for 1 h and then washed with 5% v/v aq HCl (2 x 50 mL). The organic phase was dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 50% EtOAc/hexanes, to afford 3.05 g of the product (12) as a pale yellow oil (96%): TLC (50% EtOAc/hexanes) $R_f$ 0.46; $^1H$ NMR ($CDCl_3$) 6.93 (1H, dd, J = 8.4, 2.3 Hz), 6.86 (1H, d, J = 8.4 Hz), 6.84 (1H, d, J = 2.3 Hz), 4.18 (2H, t, J = 6.0 Hz), 3.91 (3H, s), 3.89 (3H, s), 2.98 (3H, s), 2.25 (1H, m), 2.10 (1H, septet, J = 6.7 Hz), 1.98 (1H, m), 1.80 (1H, m), 1.47 (1H, m), 1.22 (3H, d, J = 6.7 Hz) and 0.82 ppm (3H, d, J = 6.7 Hz).

2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-[2-(3,4-dimethoxyphenyl-1-[$^{13}C$]-ethyl)methylamino]valeronitrile (2). A solution of 611 mg (3.11 mmol) of secondary amine 10, 1.30 g (3.16 mmol, 1.17 equiv) of mesylate 12, and 350 mg of $Et_3N$ (3.46 mmol, 1.11 equiv) in 5 mL of dry DME was stirred at 85°C for 24 h. The mixture was then cooled to room temperature and concentrated. The residue was diluted with 50 mL of EtOAc and washed with 50 mL of saturated aqueous $NaHCO_3$. The organic phase was dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10% MeOH/EtOAc, to afford 625 mg of the product (2) as a pale yellow oil (44%): $^1H$ NMR ($CDCl_3$) 6.91 (1H, dd, J = 8.3, 2.2 Hz), 6.85 (1H, d, J = 2.2 Hz), 6.82 (1H, d, J = 8.3 Hz), 6.78 (1H, d, J = 8.7 Hz), 6.70 (1H, d, J = 1.9 Hz), 6.68 (1H, dd, J = 8.7, 1.9 Hz), 3.89 (3H, s), 3.88 (3H, s), 3.86 (3H, s), 3.85 (3H, s), 2.66 (3H, m), 2.32 (3H, m), 2.18 (3H, d, J = 5.0 Hz), 2.07 (2H, m), 1.82 (1H, m), 1.54 (1H, m), 1.18 (4H, d on a multiplet, J = 6.7 Hz) and 0.78 ppm (3H, d, J = 6.7 Hz); $^{13}C$ NMR ($CDCl_3$-enriched carbon only) 60.1 ppm; MS (CI-methane) m/z 458, 457, 456, 455, 454 (3, 12, 42, 3, 9), 306, 304, 305, 303 (4, 20, 100, 2), 236, 235, 234 (4, 22, 1).

2-(3,4-Di-[$^{13}$C]-methoxyphenyl)-2-isopropyl-5-[2-(3,4-di-[$^{13}$C]-methoxyphenethyl)methylamino]valeronitrile (3). A solution of 500 mg of verapamil HCl (1) in 25 mL of aq 48% HBr was heated to 120°C for 16 h under argon. The mixture was then concentrated under full vacuum pump pressure (<0.1 mm Hg) at 80°C. After the solvent had been evaporated, the residue was heated for an additional 4 h at 80°C under vacuum to afford 495 mg of phenol 13 as an off-white foamy solid. To a solution of 41 mg (0.085 mmol) of this solid (13) in 1.5 mL of acetone was added 1.0 g (7.0 mmol, 82 equiv) of [$^{13}$C]-iodomethane (Merck, 99% $^{13}$C) followed by 200 mg (1.45 mmol) of $K_2CO_3$. The mixture was stirred at room temperature for 12 h, diluted with 10 mL of acetone and then filtered. The filtrate was concentrated, taken up in 10 mL of dry THF and refiltered. The second filtrate was concentrated and the residue (14) was used immediately in the ensuing step without further purification: $^1$H NMR ($CDCl_3$) 6.95 (1H, dd, J = 8.6, 2.0 Hz), 6.88 (1H, d, J = 2.0 Hz), 6.83 (1H, d, J = 2.0 Hz), 6.82 (1H, d, J = 8.6 Hz), 6.71 (1H, d, J = 8.5 Hz), 6.62 (1H, dd, J = 8.5, 2.0 Hz), 3.89 (3H, d, $J_{CH}$ = 145 Hz), 3.87 (3H, d, $J_{CH}$ = 145 Hz), 3.81 (3H, d, $J_{CH}$ = 145 Hz), 3.77 (3H, d, $J_{CH}$ = 145 Hz), 3.19 (0.75 H, d, $J_{CH}$ = 144 Hz), 3.19 (0.75 H, d, $J_{C-CH}$ = 2.7 Hz), 3.14 (0.75 H, d, $J_{CH}$ = 144 Hz), 3.14 (0.75 H, d, $J_{C-CH}$ = 2.7 Hz). The crude quaternary ammonium salt (14) was dissolved in 1.5 mL of dry HMPA. Then, 251 mg (4.04 mmol) of ethanethiol was added followed by 51 mg (2.1 mmol) of NaH (added slowly to maintain controlled bubbling) at 0°C. The mixture was stirred at 0°C for 5 minutes and then at 50°C for 2 h. The mixture was then cooled, diluted with 30 mL of 1 N aq NaOH, and extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with 1 N aq NaOH (5 x 25 mL). The organic phase was dried, filtered and concentrated. The residue was chromato-graphed on 20 g of silica gel, eluting with 10% MeOH/EtOAc, to afford 19.7 mg of 3 as a colorless oil (50% based on 41 mg of 13): $^1$H NMR ($CDCl_3$) 6.91 (1H, dd, J = 8.4, 2.0 Hz), 6.86 (1H, d, J = 2.0 Hz), 6.83 (1H, d, J = 8.4), 6.79 (1H, d, J = 8.7 Hz), 6.70 (1H, d, J = 2.0 Hz), 6.69 (1H, dd, J = 8.7, 2.0 Hz), 3.89 (3H, d, $J_{CH}$ = 144.3 Hz), 3.88 (3H, d, $J_{CH}$ = 144.4 Hz), 3.87 (3H, d, $J_{CH}$ = 144.3 Hz), 3.85 (3H, d, $J_{CH}$ = 144.3 Hz), 2.67 (2H, m), 2.51 (2H, m), 2.35 (2H, m), 2.20 (1.5 H, s),

2.20 (1.5 H, d, $J_{CH}$ = 133.1 Hz), 2.12 (1 H, m), 2.07 (1H, septet, J = 6.6 Hz), 1.84 (1H, m), 1.55 (1H, m), 1.18 (4H, d on m, J = 6.6 Hz), 0.79 (3H, d, J = 6.6 Hz); $^{13}C$ NMR ($CDCl_3$-enriched carbons only) 56.58, 56.51, 56.48, 54.44 (O-$^{13}C$) and 42.60 ppm (N-$^{13}C$); MS (CI-methane) m/z 462, 461, 460, 459, 458, 457 (1, 6, 27, 21, 6, 6), 308, 307, 306, 305 (3, 18, 100, 79), 237, 236 (12, 10).

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