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A Concise and Modular Three-Step Synthesis of (*S*)-Verapamil using an Enantioselective Rhodium-Catalyzed Allylic Alkylation Reaction

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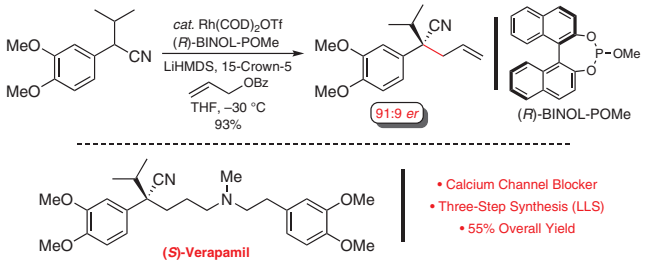

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Abstract A concise and modular asymmetric synthesis of the calcium channel blocker (*S*)-verapamil is described. This approach employs an enantioselective rhodium-catalyzed allylic alkylation reaction between an α-isopropyl-substituted benzylic nitrile and allyl benzoate to construct the challenging acyclic quaternary stereocenter. The terminal olefin then serves as a convenient synthetic handle for a hydroamination to introduce the phenethylamine moiety, furnishing (*S*)-verapamil in three steps and 55% overall yield, thus providing the most efficient synthesis of this important pharmaceutical reported to date. Furthermore, given the modular nature of the synthesis, it can be readily modified to prepare structurally related bioactive agents.

Key words allylic alkylation, enantioselective, nitrile anion, rhodium catalysis, (*S*)-verapamil

The development of pharmacologically active agents that improve the quality and longevity of human life has had an enormous societal impact. Nevertheless, the increasing cost of drug discovery and the low success rate of clinical candidates prompted a recent examination of the characteristics present in successful drug candidates. Interestingly, while the physical properties of a clinical candidate are explicitly considered, the molecular complexity has been largely ignored.[1] Notably, molecules that contain more sp^3 stereogenic centers and less aromatic rings traverse the stages of drug discovery with significantly fewer problems. Indeed, there is now a major departure from the so-called 'flatland' approach of medicinal chemistry. Nonetheless, the introduction of stereogenic carbon centers can pose problems due to the different biological properties of both enantiomers, which has driven the development of modern asymmetric methods. In this regard, the construction of ternary benzylic stereocenters can be problematic, since they are often prone to epimerization and oxidation, which negatively impacts their suitability for drug development. Hence, the installation of quaternary stereogenic centers circumvents these issues, albeit the asymmetric synthesis of this motif remains an ongoing challenge for modern synthetic organic chemistry.[2,3] A particularly important class of quaternary stereocenters are tertiary benzylic nitriles, which are present in several important pharmaceuticals and agrochemicals. For example, the calcium channel blocker verapamil (**1**), a commonly prescribed drug that is on the World Health Organization's Model List of Essential Medicines for the treatment of hypertension, angina and heart rhythm disorders, contains this structural entity (Scheme 1A). Although this agent is administered as the racemate, the two enantiomers exhibit different biological effects, which nicely exemplifies the importance of being able to prepare both stereoisomers selectively.[4] For example, the *S*-enantiomer exhibits higher efficacy and reduced side effects for the treatment of hypertension and cardiac arrhythmia, which is ascribed to specific transmembrane calcium channel antagonist activity. In contrast, the *R*-enantiomer is optimal for the treatment of angina, since it affects a broader range of cell pump actions. Hence, the ability to selectively prepare the enantiomers of verapamil is important given their respective biological properties.

Consequently, several synthetic approaches have been devised to prepare enantiomerically enriched verapamil (**1**), albeit they generally rely on chiral pool and resolution-based strategies.[5] Nevertheless, two catalytic asymmetric syntheses of verapamil have been independently reported (Scheme 1B).[6,7] In 2005, Mermerian and Fu described the first enantioselective synthesis of (*S*)-verapamil (**1**) using an eight-step longest linear sequence (LLS).[6] The key quaternary stereocenter was introduced *via* acylation of the silyl ketene imine **2**, in the presence of the chiral DMAP catalyst **4**, which furnished **3** in 72% yield and with a 90.5:9.5 enantiomeric ratio *en route* to (*S*)-verapamil (**1**) in an

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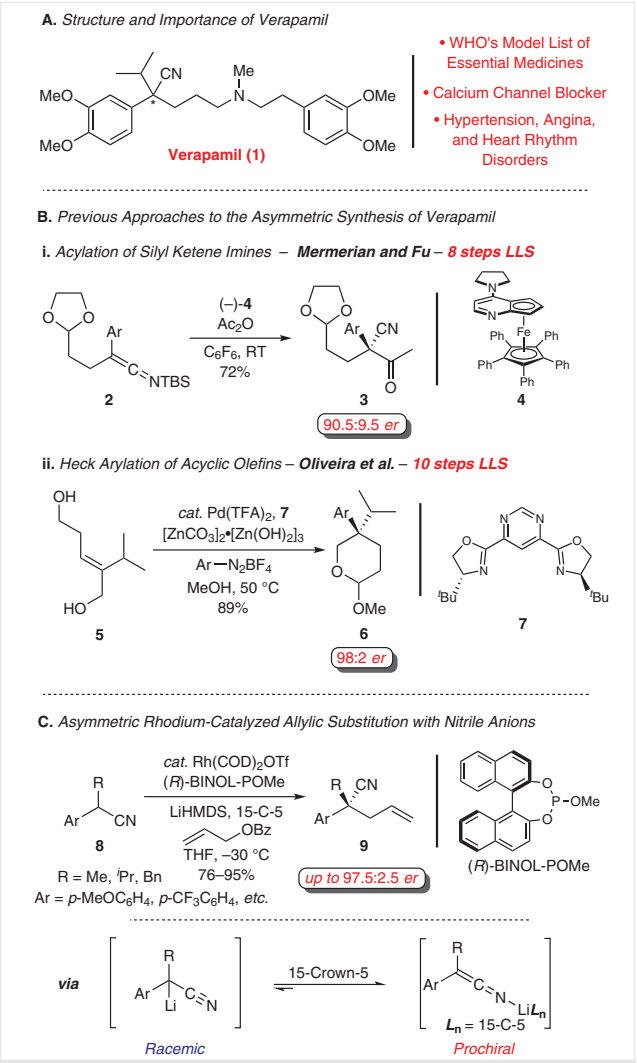
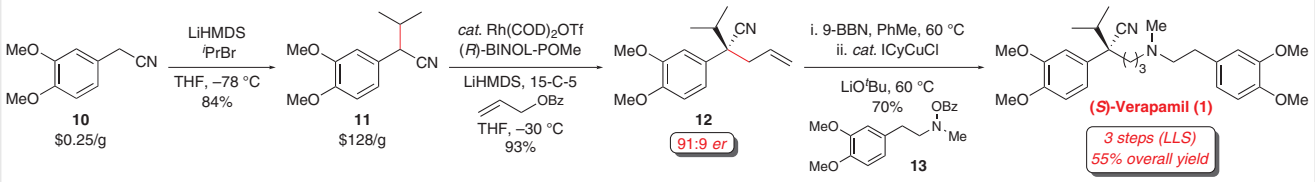


Scheme 1 Previous asymmetric approaches to verapamil (**1**) and the background for the enantioselective rhodium-catalyzed allylic substitution with nitrile anions

additional five steps (Scheme 1B, i). In 2015, Oliveira *et al.* reported a ten-step synthesis of the (*R*)-enantiomer of **1** from a commercially available starting material, which employed an enantioselective Heck arylation to prepare the key quaternary stereocenter.[7] Treatment of the diol **5** with an aryldiazonium salt and a *bis*-oxazoline containing palladium catalyst afforded the *O*-methyl lactol **6** in 89% yield and with a 98:2 enantiomeric ratio, which was readily transformed to (*R*)-verapamil (**1**) in an additional five steps (Scheme 1B, ii). In recent work, Kobayashi and co-workers have reported a formal synthesis of the (*S*)-enantiomer of **1** using an asymmetric copper-mediated S_N2' reaction to construct the quaternary stereocenter using a twelve-step sequence.[8] Nevertheless, the key intermediate requires an additional six-steps to deliver (*S*)-verapamil (**1**). Herein, we now report a concise three-step asymmetric synthesis of (*S*)-verapamil (**1**) using an enantioselective rhodium-catalyzed allylic alkylation reaction between an α-substituted benzylic nitrile and allyl benzoate to construct the challenging acyclic quaternary stereocenter (Scheme 2).

In a program directed toward the development of novel rhodium-catalyzed allylic substitution reactions,[9–11] we recently described the first enantioselective rhodium-catalyzed alkylation of α-substituted benzyl nitrile anions for the construction of *acyclic* quaternary carbon stereogenic centers (Scheme 1C).[12,13] A key and striking feature with this approach was the discovery that deaggregating additives, such as 15-crown-5 (15-C-5), significantly improve the level of asymmetric induction, which was attributed to the selective generation of a prochiral *N*-metalated species that enables π-facial discrimination by the chiral rhodium catalyst. The presence of this putative intermediate is supported by density functional theory (DFT)[14] and X-ray crystallography,[15] which indicate that crown ethers stabilize the *N*-metalated keteniminate structure of lithiated phenyl acetonitrile as opposed to the sp^3-hybridized *C*-metalated derivative. For instance, treatment of lithiated α-substituted benzylic nitriles **8** with allyl benzoate, in the presence of a cationic rhodium complex and (*R*)-BINOL-POMe, affords the tertiary benzylic nitriles **9** in excellent yields and high enantiomeric ratios. Hence, given the expedient access to enantioenriched tertiary benzylic nitriles afforded by this approach, we envisaged it would provide the basis for a concise synthesis of (*S*)-verapamil (**1**).

The synthesis commences with the deprotonation of the commercially available homoveratronitrile (**10**) with LiHMDS followed by an electrophilic quench with 2-bromopropane to afford the requisite α-isopropyl-substituted benzyl nitrile **11** in 84% yield (Scheme 2). Although intermediate **11** is commercially available, we deemed it to be too expensive to justify as a starting point for the synthesis, and it also reduces the modularity of the approach. Enantioselective rhodium-catalyzed allylic alkylation of **11** using



Scheme 2 Synthesis of (*S*)-verapamil (**1**) *via* enantioselective rhodium-catalyzed allylic alkylation

the aforementioned reaction conditions furnished the tertiary homoallylic nitrile **12** in 93% yield with a 91:9 enantiomeric ratio. Although the selectivity is consistent with our earlier studies, we had envisioned that the electron-withdrawing *m*-methoxy group would temper the impact of the *p*-methoxy group and thereby improve enantiocontrol.[12] Following several unsuccessful attempts at the direct hydroamination of the terminal olefin, the installation of the required amine was accomplished by the application of the copper-catalyzed amination of alkyl boranes developed by Lalic and co-workers.[16] Hydroboration of the terminal olefin with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by *in situ* treatment with ICyCuCl and the *O*-benozyl hydroxylamine **13** furnished (*S*)-verapamil (**1**) in 70% yield (Scheme 2), in which the spectroscopic data and optical rotation were consistent with the reported values.[7]

A particularly attractive feature with this approach is the ability to modify all the components and access either enantiomer to optimize for a specific biological property. Additionally, the allyl group represents a versatile synthon that can tailor the distance between the nitrile and the amine through oxidative cleavage and homologation. Thus, the approach lends itself to the preparation of related analogues (devapamil, emopamil, gallopamil, and norverapamil),[5e,17] which would have proven challenging to prepare *via* more conventional approaches. *Overall, the modular three-step sequence provides access to enantiomerically enriched (S)-verapamil (**1**) in 55% yield, which constitutes the most concise synthesis of this target reported to date*.

In conclusion, we have described a three-step synthesis of the calcium channel blocker (*S*)-verapamil (**1**) from a commodity chemical. A key feature of this approach is the ability to employ an enantioselective rhodium-catalyzed allylic alkylation of a nitrile anion with allyl benzoate to install the challenging *acyclic* quaternary stereocenter. Importantly, the terminal olefin introduced in this step can be employed as a synthetic handle for the introduction of the phenethylamine fragment to complete the synthesis. Finally, given the modular nature of the synthesis, we envision that this approach could find significant utility in the target-directed synthesis of the benzylic tertiary nitrile motif present in other important pharmaceuticals and agrochemicals.

All reactions were carried out in anhydrous solvent using commercially available reagents that were purchased and used as received. (*R*)-BINOL-POMe was prepared according to the previous reported procedure.[11a] THF was freshly distilled from sodium benzophenone ketyl. Analytical TLC was performed on pre-coated 0.2 mm thick silica gel 60-F_{254} plates (Merck); visualized using UV light and by treatment with a $KMnO_4$ stain, followed by heating. All compounds were purified by flash chromatography using silica gel 60 (40–63 μm, Silicycle) and gave spectroscopic data consistent with being ≥95% the assigned structure. Melting points (uncorrected) were obtained from a Büchi M560 melting point instrument. Optical rotations [α] were measured on a Anton Parr MCP 200 polarimeter with a tungsten halogen lamp (589 nm) at the stated temperature (indicated in °C as a superscript) using a 0.7 mL quartz cell of 100 mm length; solution concentrations (*c*) are given in g/100 mL. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer in either $CDCl_3$ or CD_3OD at ambient temperature; chemical shifts (δ) are given in ppm and calibrated using the signal of residual undeuterated solvent as internal reference (δ_H = 7.26 and δ_C = 77.16 for $CDCl_3$; δ_H = 3.31 and δ_C = 49.00 for CD_3OD). ^{1}H NMR data are reported as follows: chemical shift (multiplicity, 1st order spin system if available, coupling constant, integration). Coupling constants (*J*) are reported in hertz (Hz) and apparent splitting patterns are designated using the standard abbreviations. ^{13}C NMR spectra with complete proton decoupling were described with the aid of an APT sequence, separating methylene and quaternary carbons (e, even), from methyl and methine carbons (o, odd). IR spectra were recorded on an Agilent Technologies Cary 630 FT-IR (ATR) spectrometer; wavenumbers are given in cm^{-1}; and the abbreviations w (weak, <33%), m (medium, 33–66%), s (strong, 67–95%), and vs (very strong, >95%) are used to describe the relative intensities of the IR absorbance bands. Mass spectra were obtained through the Chemistry Department Mass Spectrometry Service at Queen's University.

2-(3,4-Dimethoxyphenyl)-3-methylbutanenitrile (11)[18]

LiHMDS (9.00 mL, 9.00 mmol; 1 M solution in THF) was added dropwise to a stirred solution of 2-(3,4-dimethoxyphenyl)acetonitrile (**10**; 1.329 g, 7.5 mmol) in THF (30 mL) at –78 °C under an atmosphere of argon. The anion was allowed to form over *ca.* 30 min, then 2-bromopropane (0.845 mL, 9.00 mmol) was added dropwise and the reaction mixture allowed to stir for *ca.* 1 h before being slowly warmed to RT and stirred until completion (TLC control). The reaction mixture was then quenched by addition of sat. aq NH_4Cl and extracted with Et_2O. The organic phases were combined, dried (anhyd $MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product. Purification by flash column chromatography (silica gel, eluting with 20–30% EtOAc/hexane) afforded the α-isopropyl benzyl nitrile **11** as a white solid; yield: 1.381 g (84%); mp 52–53 °C.

IR (Neat): 3078 (w), 2959 (m), 2935 (w), 2876 (w), 2838 (w), 2232 (w), 1595 (m), 1507 (s), 1453 (m), 1423 (m), 1249 (s), 1226 (s) 1159 (s), 1145 (s), 1021 (s), 866 (m), 824 (s), 743 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.86–6.83 (m, 2 H), 6.79 (s, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.59 (d, *J* = 6.3 Hz, 1 H), 2.10 (oct, *J* = 6.7 Hz, 1 H), 1.05 (d, *J* = 6.7 Hz, 6 H).

(*S*)-2-(3,4-Dimethoxyphenyl)-2-isopropylpent-4-enenitrile (12)

$Rh(COD)_2OTf$ (0.012 g, 0.025 mmol) and (*R*)-BINOL-POMe (0.035 g, 0.100 mmol) were dissolved in THF (5 mL) at RT under an atmosphere of argon. 2-(3,4-Dimethoxyphenyl)-3-methylbutanenitrile (**11**; 0.110 g, 0.500 mmol) and 15-crown-5 (0.094 mL, 0.475 mmol) were added and the mixture cooled to –30 °C with stirring. LiHMDS (0.475 mL, 0.475 mmol; 1 M solution in THF) was added dropwise and the anion allowed to form over *ca.* 15 min. Allyl benzoate (0.041 g, 0.25 mmol) was added *via* tared gastight syringe and the mixture was allowed to stir at –30 °C for *ca.* 16 h. The reaction was quenched by the addition of sat. aq NH_4Cl and extracted with Et_2O. The organic phases were combined, dried (anhyd $MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product. Purification by flash column chromatography (silica gel, eluting with 20–30% Et_2O/hexane) afforded the α-quaternary nitrile **12** as a pale yellow oil; yield: 0.060 g (93%); $[\alpha]_D^{20}$ +12.4 (*c* = 0.6, $CHCl_3$).

Chiral HPLC analysis (CHIRALPAK AD-H column): 97:3 hexane/*i*-PrOH at 1.0 mL/min flow rate; t_R *S*-enantiomer (major) = 9.2 min, t_R *R*-enantiomer (minor) = 10.4 min; 91:9 *er*.

IR (Neat): 3080 (w), 2966 (w), 2936 (w), 2876 (w), 2838 (w), 2235 (w), 1642 (w), 1591 (w), 1517 (s), 1465 (m), 1443 (m), 1260 (vs), 1237 (s), 1148 (s), 1026 (s), 922 (m), 805 (m), 767 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 6.92 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.85 (d, *J* = 1.9 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 5.50 (ddt, *J* = 17.1, 10.0, 7.1 Hz, 1 H), 5.09 (dd, *J* = 17.1, 1.1 Hz, 1 H), 5.04 (d, *J* = 10.2 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 2.83 (dd, A of ABX, J_{AB} = 13.9 Hz, J_{AX} = 7.6 Hz, 1 H), 2.60 (dd, B of ABX, J_{AB} = 14.2 Hz, J_{BX} = 6.6 Hz, 1 H), 2.13 (sept, *J* = 6.7 Hz, 1 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.98 (e), 148.40 (e), 132.41 (o), 130.09 (e), 121.15 (e), 119.43 (e), 119.13 (o), 111.05 (o), 110.09 (o), 56.08 (o), 55.94 (o), 53.39 (e), 42.22 (e), 37.27 (o), 18.87 (o), 18.62 (o).

HRMS (EI): *m*/*z* (M^+) calcd for $C_{16}H_{21}NO_2$: 259.1572; found: 259.1575.

O-Benzoyl-*N*-(3,4-dimethoxyphenethyl)-*N*-methylhydroxylamine (13)

2-(3,4-Dimethoxyphenyl)-*N*-methylethanamine (1.11 mL, 6.0 mmol) was added in one portion to a stirred suspension of benzoic peroxyanhydride (1.73 g, 5 mmol) and K_2HPO_4 (1.31 g, 7.5 mmol) in DMF (12.5 mL) at RT under an atmosphere of argon. The solution was allowed to stir for *ca.* 1 h (TLC control). The reaction mixture was quenched by the addition of deionized H_2O and stirred for several minutes until all solids dissolved. The resulting mixture was partitioned between EtOAc and sat. aq $NaHCO_3$. The combined organic phases were washed with H_2O and brine, dried (anhyd $MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product. Purification by flash column chromatography (silica gel, eluting with 30–50% EtOAc/hexanes) afforded **13** as a yellow oil; yield: 1.47 g (93%).

IR (Neat): 3060 (w), 2995 (w), 2934 (w), 2833 (w), 1733 (s), 1589 (w), 1513 (s), 1449 (m), 1252 (s), 1236 (s), 1140 (s), 1058 (s), 1023 (s), 803 (m), 763 (m), 707 cm^{-1} (vs).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.99–7.98 (m, 2 H), 7.58–7.55 (m, 1 H), 7.46–7.42 (m, 2 H), 6.77–6.73 (m, 3 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.22 (t, *J* = 7.5 Hz, 2 H), 2.93 (s, 3 H), 2.89 (t, *J* = 7.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.28 (e), 149.04 (e), 147.63 (e), 133.18 (o), 132.04 (e), 129.52 (o), 129.35 (e), 128.49 (o), 120.64 (o), 112.27 (o), 111.49 (o), 62.83 (e), 56.00 (o), 55.93 (o), 47.24 (o), 33.55 (e).

HRMS (EI): *m*/*z* (M^+) calcd for $C_{18}H_{21}NO_4$: 315.1471; found: 315.1476.

(*S*)-Verapamil (1)[5–7,19]

(*S*)-2-(3,4-Dimethoxyphenyl)-2-isopropylpent-4-enenitrile (**12**; 0.052 g, 0.2 mmol) and 9-BBN (0.024 g, 0.100 mmol) were dissolved in toluene (0.5 mL) and heated to 60 °C for *ca.* 16 h under an atmosphere of argon. The solution was cooled to RT and LiO*t*-Bu (0.018 g, 0.220 mmol), ICyCuCl (3.31 mg, 10.00 μmol), and toluene (3.3 mL) were added. The flask was evacuated and backfilled with argon and the mixture was heated again to 60 °C. A solution of *O*-benzoyl-*N*-(3,4-dimethoxyphenethyl)-*N*-methylhydroxylamine (**13**; 0.069 g, 0.220 mmol) in toluene (0.2 mL) was added dropwise *via* a syringe pump over 4 h and the resulting mixture was stirred until completion (TLC control). The solution was then cooled to RT and diluted with Et_2O and washed with sat. aq $NaHCO_3$. The aqueous layer was extracted with Et_2O and the combined organic layers were extracted with 3 M aq HCl. The combined aqueous phases were adjusted to pH 10 with 3 M aq NaOH and then extracted with CH_2Cl_2. The organic phases were combined and then washed with brine, dried (anhyd $MgSO_4$), filtered, and concentrated *in vacuo* to give a crude yellow oil. Purification by flash chromatography (silica gel, eluting with 2–6% MeOH/CH_2Cl_2) afforded (*S*)-verapamil (**1**) as a colorless oil; yield: 0.064 g (70%); $[\alpha]_D^{20}$ –5.0 (*c* = 0.31, EtOH) {Lit.[7] $[\alpha]_D^{20}$ –10 (*c* = 0.31, EtOH)}.

IR (Neat): 3057 (w), 2954 (m), 2932 (m), 2872 (w), 2835 (w), 2788 (w), 2232 (w), 1604 (w), 1589 (w), 1513 (s), 1461 (m), 1414 (m), 1257 (s), 1234 (s), 1144 (s), 1026 (s), 805 (m), 765 cm^{-1} (m).

^1H NMR (500 MHz, CD_3OD): δ = 7.00 (dd, *J* = 8.3, 2.0 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.94 (d, *J* = 1.8 Hz, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 6.76 (d, *J* = 1.7 Hz, 1 H), 6.67 (dd, *J* = 8.1, 1.7 Hz, 1 H), 3.83 (s, 6 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 2.68–2.64 (m, 2 H), 2.59–2.55 (m, 2 H), 2.53–2.40 (m, 2 H), 2.27 (s, 3 H), 2.18 (sept, *J* = 6.7 Hz, 1 H), 2.13 (ddd, A of ABXY, J_{AB} = 13.4 Hz, J_{AX} = 11.6 Hz, J_{AY} = 4.6 Hz, 1 H), 1.94 (app td, B of ABXY, J_{AB} = J_{BX} = 12.7 Hz, J_{BY} = 4.5 Hz, 1 H), 1.58–1.50 (m, 1 H), 1.23–1.14 (m, 1 H), 1.19 (d, *J* = 6.6 Hz, 3 H), 0.77 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 150.84 (e), 150.48 (e), 150.15 (e), 149.03 (e), 133.59 (e), 132.01 (e), 122.47 (e), 121.99 (o), 120.47 (o), 113.72 (o), 113.27 (o), 112.82 (o), 111.09 (o), 59.72 (e), 57.38 (e), 56.67 (o), 56.55 (o), 56.46 (o), 54.79 (e), 42.15 (o), 38.72 (o), 36.33 (e), 32.89 (e), 23.97 (e), 19.37 (o), 18.91 (o).[20]

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{39}N_2O_4$: 455.2904; found: 455.2889.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707390.

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