Synthesis of Potent CERT Inhibitor HPA-12 Featuring a Tandem Corey–Link and Intramolecular Nucleophilic Acyl Substitution Reaction

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Dedicated to Prof. Scott E. Denmark on the occasion of his 60th birthday

Abstract: A novel preparation of the potent CERT protein inhibitor (1*R*,3*S*)-HPA-12 is described. The synthesis is accomplished in five steps from (*S*)-Wynberg lactone and features a diastereoselective tandem Corey–Link and intramolecular nucleophilic acyl substitution reaction in a key step.

Key words: HPA-12, CERT protein, *gem*-dichloroepoxide, Corey–Link reaction, Wynberg lactone

CERT is an ATP-dependent trafficking protein that transports ceramides **1** (Figure 1) from the endoplasmic reticulum to the Golgi apparatus.[2] There, ceramides are converted enzymatically into sphingomyelin, which plays vital roles in cell signaling, apoptosis, and the formation of lipid rafts in biomembranes.[3] The amidodiol *N*-[(1*R*,3*S*)-3-hydroxy-1-(hydroxymethyl)-3-phenylpropyl]dodecamide (HPA-12, **2**) is a potent CERT inhibitor (IC_{50} = 50 nm) that was discovered and extensively studied by Kobayashi and Hanada.[4] Compound **2** has become an established tool for investigating sphingolipid metabolic pathways in cultured cells and animals. For example, it has recently been used to inhibit hepatitis C secretion from infected cells,[5] to study the function of CERT in UVB-irradiated keratinocytes,[6] and to help determine the mechanism of action of limonoid compounds in the inhibition of sphingomyelin biosynthesis.[7] In addition, modulation of sphingolipid metabolic pathways, including trafficking protein inhibition, is an emerging strategy for certain cancer and antiviral therapies.[8]

Several syntheses of HPA-12 have been published, including preparations by Kobayashi, involving transition-metal-mediated asymmetric Mannich-type reactions,[4b,9] Raghavan, featuring elaboration of a β-sulfonamido sulfoxide,[10] and Berkeš, highlighting a crystallization-induced asymmetric transformation approach.[11] Notably, the authors of this last report proposed a revised absolute configuration of the most potent HPA-12 stereoisomer from (*R*,*R*)-*anti*, as originally reported by Kobayashi,[4a,9a] to (*R*,*S*)-*syn* based upon a combination of synthesis, X-ray analysis, and comparative ^{1}H NMR data. A synthesis of a less potent isomer, (*S*,*R*)-HPA-12, was also reported in 2012.[12]

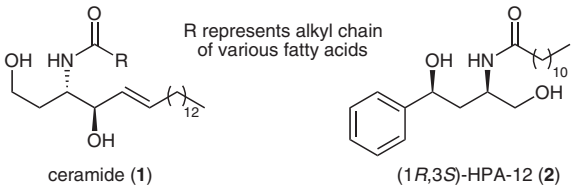

Figure 1

We intended to employ our recently published tandem Corey–Link[13] and intramolecular nucleophilic acyl substitution reaction (i.e., conversion of **6** into **9** via *gem*-dichloroepoxide **7** and substituted acid chloride **8**) as a featured step in the synthesis of **2** (Scheme 1).[14] One-pot reduction of the resulting lactone and the attached azide present in **9** using lithium aluminum hydride was expected to afford aminodiol **10**. N-Acylation of the amine in **10** would then furnish the target. This approach was designed to provide a concise path to (1*R*,3*S*)-HPA-12 (**2**) without the need for any protection/deprotection steps.

Friedel–Crafts acylation of (*S*)-Wynberg lactone **4**,[15] prepared in one step from chloral, acetyl chloride, *N*,*N*-diisopropylethylamine, and catalytic quinine, provided crystalline (*S*)-β-hydroxy ketone **5** in 89% yield (Scheme 1). It was important to conduct the Friedel–Crafts reaction at a 0.05 M substrate concentration to limit formation of the O-acylation byproduct **3** (Figure 2).[16] The use of granular aluminum trichloride, rather than finely powdered Lewis acid also resulted in significantly lower yields of **5**. Sonication of the powdered aluminum trichloride in benzene prior to addition of **4** created a fine suspension of the Lewis acid and furnished a modest increase in the yield of **5**. However, conducting the actual acylation reaction with ultrasound offered no noticeable increase in reaction rate or product yield.

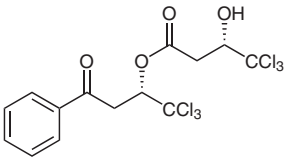

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Figure 2

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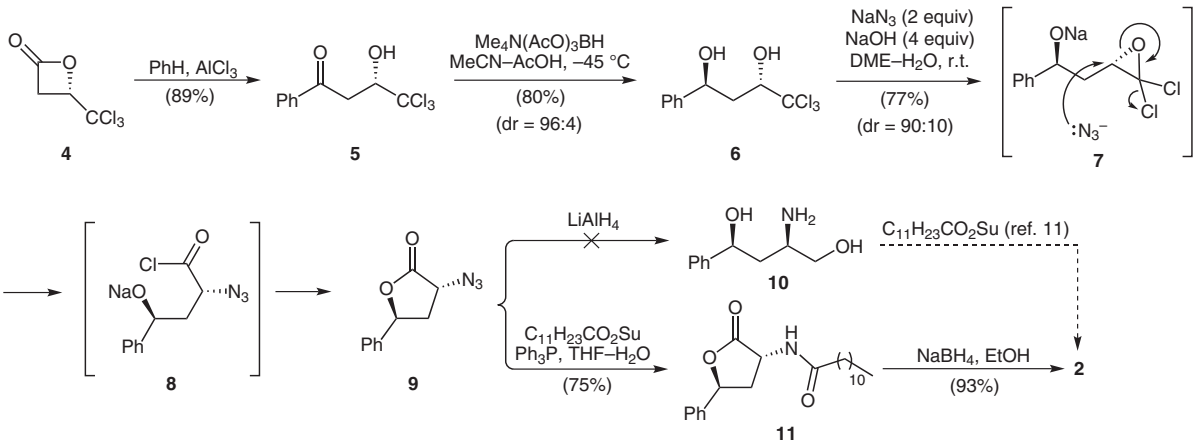


Scheme 1

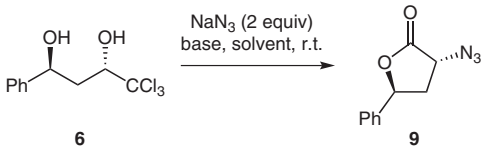
Directed 1,3-reduction of **5** using tetramethylammonium triacetoxyborohydride in acetonitrile–acetic acid[17] proceeded in 80% yield with a diastereomeric ratio (*anti*/*syn*) of 96:4[18] when the reaction temperature was held below –40 °C. Higher temperatures led to comparable yields of combined *anti*- and *syn*-1,3-diols; however, under such conditions, the *anti*/*syn* product ratios were severely eroded.

Diol **6**[19] was then treated with four equivalents of sodium hydroxide and two equivalents of sodium azide in 1,2-dimethoxyethane–water (1:4) to promote formation of a 2-azidocarboxylic acid chloride intermediate **8** by a Corey–Link reaction.[13] This intermediate underwent intramolecular O-acylation to generate substituted butyrolactone **9**.[20] As established previously, it was important to conduct the reaction at a 0.05 M substrate concentration to mitigate epimerization of **9**.[14] A portion of the lactone was hydrolyzed under the basic reaction conditions; however, mixing the crude reaction mixture in dilute aqueous hydrochloric acid for 2–3 hours prior to isolation provided a 90:10 mixture of *trans*/*cis* lactone epimers.[18] A simple separation of the diastereomers by chromatography furnished pure *trans*-disubstituted lactone **9** in 70% yield.

Despite the satisfactory outcome of the tandem Corey–Link and intramolecular acyl substitution reaction conducted under our previously reported conditions (Table 1, entry 1),[14] we screened other solvent systems and bases to ensure that the formation of **9** was fully optimized. Changes in the 1,2-dimethoxyethane–water solvent ratio (entry 2) did not improve the reaction, and employment of less sodium hydroxide severely limited conversion of **6** (entry 3). Substitution of sodium hydroxide with tetrabutylammonium hydroxide (entry 4)[21] or DBU and 18-crown-6 (entry 5),[22] conditions that have been employed successfully in other Jocic–Reeve or Corey–Link reactions,[23] also offered no benefit.

With *trans*-azidolactone **9** in hand, we attempted reduction of both the azide and lactone carbonyl in one pot using lithium aluminum hydride at temperatures ranging from 0–65 °C and with concentrations of the reductant ranging from 6–15 equivalents. In all cases, a complex

Table 1 Optimization Studies for the Conversion of **6** into **9**



Entry	Base (equiv)	Solvent	[**6**] (M)	Yield[a] (%)
1	NaOH (4)	DME–H_2O (1:4)	0.05	70
2	NaOH (4)	DME–H_2O (2:3)	0.05	45
3	NaOH (2.5)	DME–H_2O (1:4)	0.05	–[b]
4	TBAH (6.7)	CH_2Cl_2–TBAH (2:1)	0.05	–[c]
5	DBU (5), 18-crown-6 (cat.)	MeOH	0.05	40

[a] Isolated yield of pure *trans*-butyrolactone **9**.
[b] Reaction showed <5% conversion after 24 h.
[c] A complex mixture of products was formed.

mixture of products was formed, and the desired aminodiol **10** could not be obtained in satisfactory yield.

As a result, we slightly altered our approach to the preparation of **2** by attempting a tandem Staudinger reduction and N-acylation reaction adapted from the method reported by Bittmann and co-workers.[24] Treatment of **9** with triphenylphosphine and lauric acid *N*-hydroxysuccinimide ester in tetrahydrofuran–water (9:1) provided amidolactone **11** in 75% yield. The expected *trans* stereochemistry was supported by NOE difference and NOESY experiments. Subsequent reduction of **11** with sodium borohydride in ethanol furnished the target (1*R*,3*S*)-HPA-12 (**2**) in 93% yield and >98% ee[19] after column chromatography. All characterization data of **2** are consistent with those reported for the most potent HPA-12 stereoisomer,[4a] and the synthetic route and characterization data substantiate the revised absolute configuration proposed by Berkeš.[11,25]

In summary, a synthesis of potent CERT protein inhibitor (1*R*,3*S*)-HPA-12 (**2**) was accomplished in five steps and 33% overall yield from (*S*)-Wynberg lactone **4**. The outlined approach, which features a tandem Corey–Link and intramolecular nucleophilic acyl substitution step, rivals the most efficient preparations of the CERT trafficking protein inhibitor yet reported.

^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments at 360, 500, or 600 MHz and 90 or 125 MHz, respectively. ^{19}F NMR spectra were recorded at 338 MHz. Chemical shifts were referenced to acetone-d_6 (δ = 2.05 and 30.83) or $CDCl_3$ (δ = 7.26 and 77.0). Mass spectra were recorded on an AutoSpec-Ultima_NT mass spectrometer using electron ionization (EI) at 70 eV and an EBE sector mass analyzer. Melting points were determined with a Mel-Temp 1001D capillary melting point apparatus and are uncorrected. Ultrasonication was conducted with a Bransonic 2510R-DTH ultrasonic cleaner. IR spectra were recorded on a Jasco FT/IR-4100 instrument. Optical rotations were measured with a Rudolph AUTOPOL IV/6W polarimeter. TLC visualization was achieved by UV light (254 nm) or $KMnO_4$ staining. MeCN and benzene were dried over 4-Å molecular sieves prior to use. THF and Et_2O were distilled from Na/benzophenone ketyl radical. Chloral was purchased from Riedel-de Haën and distilled neat onto 4-Å molecular sieves. AcCl was distilled from $PhNMe_2$ (one-tenth volume). Anhyd AcOH was prepared by stirring AcOH–Ac_2O (1:1) for 1 h, and then AcOH was distilled onto 4-Å molecular sieves. All other reagents and solvents were used as received from commercial sources.

(*S*)-4-(Trichloromethyl)oxetan-2-one (4)

A dry 1-L, 3-neck round-bottom flask was fitted with two addition funnels and an argon supply. Quinine (406 mg, 1.25 mmol) and anhyd Et_2O (165 mL) were added to the round-bottom flask, then anhyd DIPEA (47.5 mL, 0.273 mol) was transferred to the flask by cannula. Chloral (24.5 mL, 0.251 mol) in anhyd Et_2O (115 mL) was added to one addition funnel. AcCl (17.8 mL, 0.250 mol) in anhyd Et_2O (115 mL) was added to the other addition funnel. While cooling to –15 °C, the chloral and AcCl were added dropwise to the mixture under argon at approximately equal rates over 1.5 h. After the addition was complete, the mixture was stirred at –15 °C for 2 h. Aq 1 M HCl (150 mL) was added and the mixture was warmed to r.t. and then filtered through Celite. The layers were separated, and the aqueous layer was extracted with Et_2O (5 × 30 mL). The combined organic layers were washed with 1 M HCl (3 × 25 mL), dried ($MgSO_4$), and concentrated by rotary evaporation yielding a light tan solid. The solid was placed under vacuum to remove excess volatile components then purified by bulb-to-bulb distillation (82 °C/0.27 mbar) to give **4** as a white solid (mixture of enantiomers). The solid was recrystallized (methylcyclohexane)[15] yielding pure (*S*)-**4** (23.4 g, 49%) as white, fluffy crystals; mp 52–53 °C.

$[\alpha]_D^{22}$ +15.6 (*c* 1.0, CH_2Cl_2) (corresponds to >98% ee[15]).

IR (KBr): 2972, 1644, 1101, 788 cm^{-1}.

^{1}H NMR (360 Hz, $CDCl_3$): δ = 5.01 (dd, *J* = 3.8, 5.7 Hz, 1 H), 3.74 (dd, *J* = 5.7, 17 Hz, 1 H), 3.60 (dd, *J* = 3.8, 17 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 96.6, 76.1, 42.5.

MS (EI): *m*/*z* = 71.0 [M – CCl_3].

HRMS (EI): *m*/*z* [M – CCl_3] calcd for $C_3H_3O_2$: 71.0133; found: 71.0130.

(*S*)-4,4,4-Trichloro-3-hydroxy-1-phenylbutan-1-one (5)

Powdered $AlCl_3$ (6.3 g, 47 mmol) in anhyd benzene (250 mL) was placed in a 1-L round-bottom flask. The system was sonicated for 1.5 h to create a fine suspension of the Lewis acid. The mixture was then cooled to 0 °C, and a soln of (*S*)-Wynberg lactone **4** (2.00 g, 12.5 mmol) in anhyd benzene (125 mL) was added dropwise. The reaction was warmed to r.t. and stirred until judged complete by TLC analysis (~12 h). The reaction was quenched by slow addition of aq sat. NH_4Cl (250 mL) and the aqueous layer was extracted with benzene (4 × 60 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (hexanes–EtOAc, 9:1) to give **5** (2.99 g, 89%) as white crystals; mp 62–63 °C.

$[\alpha]_D^{22}$ –35.6 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3448, 3061, 2924, 1683, 1449 cm^{-1}.

^{1}H NMR (360 Hz, $CDCl_3$): δ = 8.0 (d, *J* = 7.8 Hz, 2 H), 7.62 (t, *J* = 7.3 Hz, 1 H), 7.50 (t, *J* = 7.9 Hz, 2 H), 4.88 (ddd, *J* = 1.7, 4.5, 9.1 Hz, 1 H), 3.79 (d, *J* = 4.3 Hz, 1 H), 3.65 (dd, *J* = 0.7, 17.3 Hz, 1 H), 3.50 (dd, *J* = 9.1, 17.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.1, 136.4, 133.9, 128.8, 128.3, 102.6, 79.1, 40.8.

MS (EI): *m*/*z* = 249.0 [M – OH].

HRMS (EI): *m*/*z* [M – OH] calcd for $C_{10}H_8OCl_3$: 248.9641; found: 248.9638.

(1*S*,3*S*)-4,4,4-Trichloro-1-phenylbutane-1,3-diol (6)

A soln of tetramethylammonium triacetoxyborohydride (1.57 g, 5.98 mmol) in anhyd MeCN (3.4 mL) and anhyd AcOH (3.4 mL) under argon was stirred at r.t. for 1 h. The soln was then cooled to –50 °C. Hydroxy ketone **5** (200 mg, 0.75 mmol) in anhyd MeCN (1.1 mL) was added to the soln by syringe. The mixture stirred for 30 h at a bath temperature between –45 °C and –50 °C. The reaction was quenched with 0.5 M aq sodium potassium tartrate (8 mL) and warmed to r.t. The mixture was diluted with CH_2Cl_2 (6 mL) and the layers were separated. The organic phase was washed with aq sat. $NaHCO_3$ (10 mL). The aqueous phase was back extracted with CH_2Cl_2 (4 × 5 mL), and the combined organic layers were washed with aq sat. $NaHCO_3$ until the aqueous layer reached pH 7. The organic layers were then dried ($MgSO_4$) and concentrated. The crude product was evaluated by ^{1}H NMR spectroscopy to establish dr (*anti*/*syn*) = 96:4 and then purified by column chromatography (hexanes–EtOAc, 8:2) to obtain **6** (155 mg, 77%) as white crystals; mp 104–105 °C.

$[\alpha]_D^{22}$ –65.7 (*c* 2.0, CH_2Cl_2).

IR (KBr): 3419, 2906, 1641, 1427 cm^{-1}.

^{1}H NMR (360 Hz, $CDCl_3$): δ = 7.43–7.29 (m, 5 H), 5.12 (dt, *J* = 3.2, 9.5 Hz, 1 H), 4.44 (ddd, *J* = 1.9, 4.4, 10.0 Hz, 1 H), 3.25 (dd, *J* = 1.2, 4.7 Hz, 1 H), 2.45 (ddt, *J* = 1.4, 9.5, 14.3 Hz, 1 H), 2.27 (d, *J* = 3.9 Hz, 1 H), 2.07 (ddd, *J* = 2.6, 9.7, 14.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.7, 128.7, 127.9, 125.6, 103.8, 79.8, 70.8, 40.1.

MS (EI): *m*/*z* = 268.0 $[M]^+$.

HRMS (EI): *m*/*z* [M] calcd for $C_{10}H_{11}O_2Cl_3$: 267.9825; found: 267.9827.

(3*R*,5*S*)-3-Azido-5-phenyldihydrofuran-2(3*H*)-one (9)

Trichloromethyl carbinol **6** (100 mg, 0.37 mmol) in DME–H_2O (1.5 mL:6.0 mL) was placed in a sample vial with a magnetic stir bar. NaN_3 (48.2 mg, 0.74 mmol) (**CAUTION:** may explode if ground or contacted by metal surfaces) and freshly powdered NaOH (59.4 mg, 1.49 mmol) were added at once. The reaction was stirred rapidly at r.t. until judged complete by TLC analysis (12–24 h). The mixture was cooled to 0 °C, and the pH was adjusted to pH 2 with 0.5 M HCl. This mixture was stirred for 3 h to promote lactonization of any hydrolyzed product. The aqueous phase was extracted with EtOAc (5 × 15 mL), dried ($MgSO_4$), and concentrated. The crude product was evaluated by ^{1}H NMR spectroscopy to establish dr (*trans*/*cis*) = 90:10 and then purified by column chromatography (hexanes–EtOAc, 2:1) to obtain **9** (74.0 mg, 70%) as a clear, colorless oil.

$[\alpha]_D^{22}$ +175.4 (*c* 1.0, CH_2Cl_2).

IR (KBr): 2923, 2852, 1780, 1458 cm^{-1}.

^{1}H NMR (360 Hz, $CDCl_3$): δ = 7.45–7.34 (m, 3 H), 7.30–7.28 (m, 2 H), 5.65 (t, *J* = 6.6 Hz, 1 H), 4.36 (dd, *J* = 6.1, 7.9 Hz, 1 H), 2.60–2.44 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7, 138.0, 129.0, 128.8, 125.0, 79.2, 57.1, 36.8.

MS (EI): *m*/*z* = 203.1 $[M]^+$.

HRMS (EI): *m*/*z* [M] calcd for $C_{10}H_9N_3O_2$: 203.0695; found: 203.0691.

***N*-[(3*R*,5*S*)-2-Oxo-5-phenyltetrahydrofuran-3-yl]dodecanamide (11)**

To a soln of **9** (50 mg, 0.25 mmol) in THF–H_2O (6.6 mL:0.73 mL) were added lauric acid *N*-hydroxysuccinimide ester (183 mg, 0.62 mmol) and Ph_3P (78 mg, 0.30 mmol). The mixture was stirred at r.t. under argon for 48 h. The solvents were then removed by evaporation [*t*-BuOH (3–4 mL) was added to azeotropically remove residual H_2O], and the residue was dissolved in EtOAc (25 mL) and washed with ice cold 1% K_2CO_3 (4 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated. The crude material was purified by column chromatography (hexanes–EtOAc, 8:2) to afford **11** (66.2 mg, 75%) as a white solid; mp 96–97 °C.

$[\alpha]_D^{22}$ +38.2 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3303, 2918, 1648, 1164 cm^{-1}.

^{1}H NMR (360 Hz, $CDCl_3$): δ = 7.41–7.27 (m, 5 H), 6.52 (d, *J* = 6.7 Hz, 1 H), 5.73 (dd, *J* = 2.5, 8.5 Hz, 1 H), 4.61–4.54 (m, 1 H), 2.79 (ddd, *J* = 2.8, 9.3, 12.7 Hz, 1 H), 2.67–2.59 (m, 1 H), 2.23 (t, *J* = 7.8 Hz, 2 H), 1.66–1.58 (m, 2 H), 1.35–1.20 (m, 16 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4, 173.7, 138.9, 128.9, 128.5, 125.0, 78.6, 48.3, 36.9, 36.1, 31.9, 29.6, 29.6, 29.5, 29.3, 29.3, 29.2, 25.4, 22.7, 14.1.

MS (EI): *m*/*z* = 359.2 $[M]^+$.

HRMS (EI): *m*/*z* [M] calcd for $C_{22}H_{33}NO_3$: 359.2460; found: 359.2468.

***N*-[(1*R*,3*S*)-3-Hydroxy-1-(hydroxymethyl)-3-phenylpropyl]dodecamide (2)**

To a suspension of **11** (40.0 mg, 0.11 mmol) in abs EtOH (1.5 mL) was added $NaBH_4$ (21 mg, 0.55 mmol), and the mixture was stirred at r.t. for 20 h. The reaction was then quenched by the addition of 5% K_2CO_3 soln (2.4 mL), and the EtOH was removed by rotary evaporation. The aqueous phase was extracted with EtOAc (5 × 3 mL), and the resultant organic layers were combined, dried (Na_2SO_4), and concentrated. The product was purified by column chromatography (EtOAc–hexanes, 4:1) to obtain **2** (37.6 mg, 93%) as a white crystalline solid; mp 90–91 °C.

$[\alpha]_D^{22}$ –34.8 (*c* 1.0, $CHCl_3$).

IR (KBr): 3417, 3294, 1643 cm^{-1}.

^{1}H NMR (360 Hz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 6.43 (d, *J* = 6.6 Hz, 1 H), 4.80 (dd, *J* = 3.3, 8.9 Hz, 1 H), 4.08–4.01 (m, 1 H), 3.93 (s, 1 H), 3.70–3.62 (m, 2 H), 3.31 (s, 1 H), 2.15 (dd, *J* = 7.3, 8.0 Hz, 2 H), 2.04 (ddd, *J* = 3.5, 5.5, 14.6 Hz, 1 H), 1.92 (ddd, *J* = 7.0, 9.0, 15.8 Hz, 1 H), 1.64–1.55 (m, 2 H), 1.33–1.23 (m, 16 H), 0.88 (dd, *J* = 6.6, 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3, 144.3, 128.6, 127.7, 125.5, 71.9, 65.6, 50.5, 40.7, 36.8, 31.9, 29.6, 29.6, 29.5, 29.3, 29.3, 29.3, 25.7, 22.7, 14.1.

MS (EI): *m*/*z* = 363.3 $[M]^+$.

HRMS (EI): *m*/*z* [M] calcd for $C_{22}H_{37}NO_3$: 363.2773; found: 363.2766.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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