Synthesis of a Hydroxyethylene Dipeptide Isostere, a Core Unit of the HIV Protease Inhibitors Ritonavir and Lopinavir, and Its C-5 Epimer

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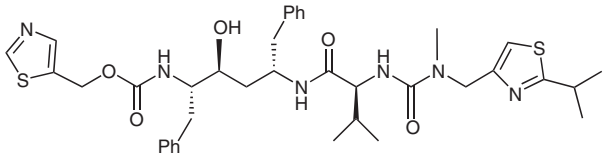
Abstract: A short synthesis of a hydroxyethylene dipeptide isostere, a core unit of the HIV protease inhibitors ritonavir and lopinavir, and its C-5 epimer is described.

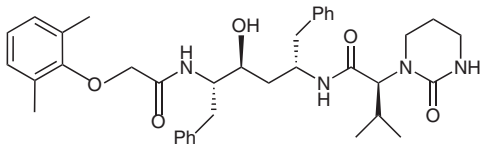
Key words: HIV–AIDS, peptidomimetic aspartyl protease inhibitors, regioselective epoxide opening

Acquired immunodeficiency syndrome (AIDS), a degenerative disease of the immune system, is one of the challenging problems in medicine. Among various strategies to combat this disease, therapeutic inhibition of the virally encoded HIV protease became an attractive target.[1] The treatment of HIV and AIDS was revolutionalised by the introduction of peptidomimetic aspartyl protease inhibitors.

Ritonavir[2] (**1**) (trade name 'Norvir', ABT-538) and lopinavir[3] (**2**) (trade name 'Aluviran', ABT-378) are FDA-approved, clinically effective peptidomimetic HIV protease inhibitors from Abbott Laboratories with high oral bioavailability (Figure 1). The structure of ritonavir (**1**) and lopinavir (**2**) was designed to target the enzyme's active site and is based on the hydroxyethylene dipeptide isostere.[2a]



ritonavir (**1**)



lopinavir (**2**)

Figure 1

Both ritonavir (**1**) and lopinavir (**2**) contain the same Phe-Phe hydroxyethylene isostere subunit **3** (Figure 2). Several syntheses of this core unit **3** and its C-3 epimer **4** are reported in the literature.[4] Compounds **3** and **4** are also known for their activity against HIV, with compound **3** being more active than compound **4**.[4i] To the best of our knowledge, the C-5 epimer of compound **3**, i.e. compound **5**, has not been reported in the literature. Therefore, it becomes a good synthetic target for exploring its anti-HIV activity. Herein, we describe a simple approach for the synthesis of Phe-Phe hydroxyethylene isostere core unit **3** and its C-5 epimer **5** from D-mannitol.

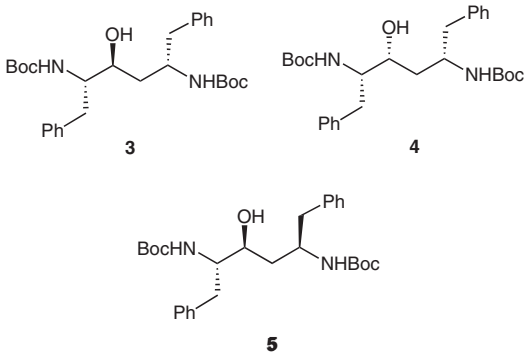


Figure 2

Commercially and inexpensively available D-mannitol was easily converted into (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**6**) using a well-known procedure.[5] Treatment of the aldehyde **6** with allyl bromide in the presence of zinc dust and aqueous ammonium chloride solution in tetrahydrofuran at 0 °C afforded the corresponding homoallyl alcohol **7** as a major diastereomer in favour of the *anti*-isomer[6] (*anti*/*syn* 96:4, from ^{1}H NMR spectroscopy), which was used as such for further reaction (Scheme 1). The free hydroxy functionality in compound **7** was protected as its benzyl ether using sodium hydride and benzyl bromide in tetrahydrofuran to give compound **8**. In this step, the two isomers were easily separated by column chromatography. Ketal cleavage of compound **8** using 60% aqueous acetic acid afforded diol **9**. The primary hydroxy group of the diol **9** was tosylated and then this compound was treated with base to give epoxide **10**. The alkene functionality in epoxide **10** was epoxidised using *m*-chloroperoxybenzoic acid to give the bis-epoxide **11** as an inseparable mixture of diastereomers, which was carried further as such.

Opening of the bis-epoxide **11** with phenylmagnesium bromide (5 equiv) in the presence of cuprous iodide (2 equiv) at –40 °C for four hours afforded the diol **12**

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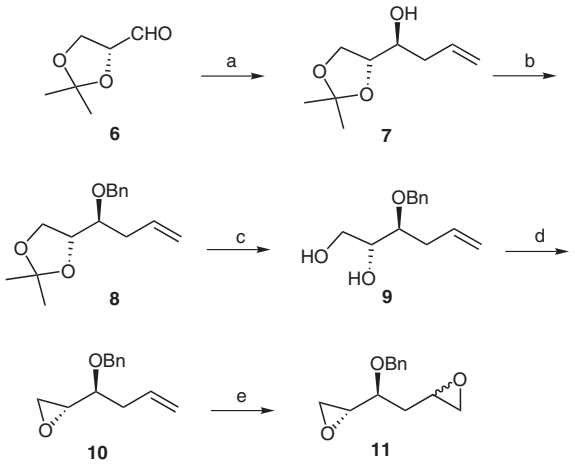
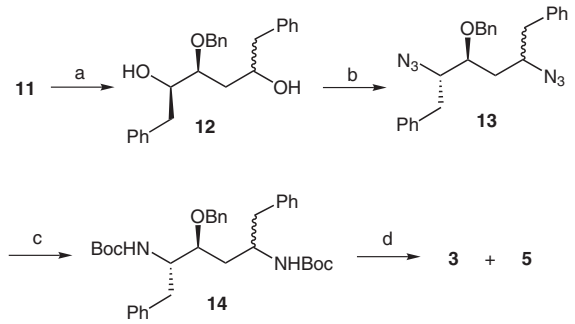


Scheme 1 *Reagents and conditions*: (a) CH_2=$CHCH_2Br$, Zn, NH_4Cl, 0 °C to r.t., 4 h, 91%; (b) BnBr, NaH, THF, 0 °C to r.t., 5 h, 94%; (c) 60% aq AcOH, r.t., 12 h, 89%; (d) TsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 24 h; then K_2CO_3, MeOH, 0 °C to r.t., 1 h, 76%; (e) MCPBA, CH_2Cl_2, r.t., 12 h, 83%.



Scheme 2 *Reagents and conditions*: (a) PhMgBr, CuI, THF, –40 °C to r.t., 4 h, 82%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 4 h; then NaN_3, DMF, 18-crown-6, 50 °C, 24 h, 71%; (c) $LiAlH_4$, THF, 0 °C to r.t., 1 h; then $(Boc)_2O$, 0 °C to r.t., 12 h, 89%; (d) $Pd(OH)_2/H_2$, MeOH, r.t., 4 h, compound **3**: 54%, compound **5**: 38%.

(Scheme 2). Conversion of diol **12** into the corresponding diazide **13** was achieved using sodium azide, via the dimesylate.[4a] The diazide **13** was reduced to diamine using lithium aluminum hydride, and in situ protection with $(Boc)_2O$ afforded compound **14**. Finally, the benzyl ether in compound **14** was deprotected using palladium(II) hydroxide/hydrogen in methanol to afford the target compound **3** and its C-5 epimer **5** in the ratio of 1.4:1. At this stage, these two epimers were separated by column chromatography, to give optically pure forms of **3** and **5**.

In conclusion, the above synthesis involves simple and standard steps starting from readily available (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (**6**). Activity study of compound **5** and preparation of its analogues are under progress.

TLC was performed on Merck Kieselgel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using EtOAc–petroleum ether (PE) as eluent. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 400 MHz or a Bruker Avance 300 MHz spectrometer. ^{1}H NMR data are expressed as chemical shifts in ppm, followed by multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) (*J* in Hz) and number of proton(s). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with a Horiba SEPA-300 digital polarimeter. Accurate mass measurement was performed on a QSTAR mass spectrometer (Applied Biosystems, USA).

(2*R*,3*S*)-3-Benzyloxy-1,2-*O*-isopropylidene-5-hexene-1,2-diol (8)

To a stirred soln of alcohol **7** (2.5 g, 14.53 mmol) in anhyd THF (40 mL) was added BnBr (2.6 mL, 21.80 mmol) under N_2 atmosphere. The reaction mixture was cooled to 0 °C, NaH (60% suspension in mineral oil; 0.87 g, 21.80 mmol) was added, then the reaction mixture was allowed to return to r.t., and stirred for 4 h. The reaction mixture was quenched by the addition of sat. aq NH_4Cl soln (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic fractions were collected and washed with H_2O (50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–PE, 1:49) to afford compound **8** (3.58 g, 94%) as a colourless oil.

$[\alpha]_D^{25}$ +33.68 (*c* 1.5, $CHCl_3$).

IR (KBr): 2986, 1370, 1213, 1073, 856, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.38 (s, 3 H), 2.26–2.47 (m, 2 H), 3.52 (q, *J* = 6.0 Hz, 1 H), 3.83 (dd, *J* = 6.0, 7.5 Hz, 1 H), 3.95–4.06 (m, 2 H), 4.59 (AB q, *J* = 12 Hz, 2 H), 5.07 (d, *J* = 10.5 Hz, 1 H), 5.12 (d, *J* = 15.8 Hz, 1 H), 5.86 (ddt, *J* = 6.8, 10.5, 15.8 Hz, 1 H), 7.21–7.33 (m, 5 H).

EIMS: *m*/*z* = 247 [M$^+$ – CH_3].

(2*R*,3*S*)-3-Benzyloxy-5-hexene-1,2-diol (9)

A soln of acetonide **8** (3 g, 11.45 mmol) in 60% aq AcOH (30 mL) was stirred at r.t. for 12 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), cooled to 0 °C and neutralised to pH 7 by adding sat. $NaHCO_3$ soln in small portions. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were collected and washed with H_2O (50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–PE, 1:1) to afford diol **9** (2.26 g, 89%) as a viscous liquid.

$[\alpha]_D^{25}$ +28.63 (*c* 1.2, $CHCl_3$).

IR (KBr): 3410, 2922, 1072, 735, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (br s, 1 H), 2.31–2.49 (m, 3 H), 3.56–3.76 (m, 4 H), 4.51 (d, *J* = 11.7 Hz, 1 H), 4.66 (d, *J* = 11.7 Hz, 1 H), 5.09 (d, *J* = 10.2 Hz, 1 H), 5.14 (d, *J* = 17.3 Hz, 1 H), 5.85 (ddt, *J* = 7.1, 10.2, 17.3 Hz, 1 H), 7.24–7.35 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.89, 63.32, 72.35, 72.50, 80.20, 117.52, 127.79, 128.41, 134.25, 138.02.

(4*S*,5*R*)-4-Benzyloxy-5,6-epoxy-1-hexene (10)

To an ice-cooled soln of diol **9** (1 g, 4.50 mmol) in anhyd CH_2Cl_2 (25 mL) were added Et_3N (1.9 mL, 13.50 mmol) and TsCl (0.86 g, 4.50 mmol). The reaction mixture was allowed to return to r.t., then stirred for 24 h, and extracted with CH_2Cl_2 (3 × 100 mL) and H_2O (50 mL). The combined organic fractions were collected and washed with H_2O (25 mL) and brine (25 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to afford tosylated compound, which was immediately used as such, without further purification, for the next reaction. To an ice-cooled soln of the primary tosylated diol (1.42 g, 3.78 mmol) in MeOH (15 mL), K_2CO_3 (1.57

g, 11.34 mmol) was added. The reaction mixture was allowed to return to r.t., and stirred for 1 h. The reaction mixture was filtered and the MeOH was removed on a Rotavapor® keeping the temperature of the water bath below 30 °C. The residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic fractions were collected and washed with H_2O (25 mL) and brine (25 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–PE, 1:19) to afford epoxide **10** (0.7 g, 91%) as a colourless oil.

$[\alpha]_D^{25}$ +5.44 (*c* 0.8, $CHCl_3$).

IR (KBr): 2923, 1102, 916, 741, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36–2.45 (m, 2 H), 2.65–2.74 (m, 2 H), 2.90 (m, 1 H), 3.29 (m, 1 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.61 (d, *J* = 12.1 Hz, 1 H), 5.08 (d, *J* = 10.5 Hz, 1 H), 5.12 (d, *J* = 17.3 Hz, 1 H), 5.88 (ddt, *J* = 6.8, 10.5, 17.3 Hz, 1 H), 7.23–7.32 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.22, 45.65, 53.12, 72.20, 77.76, 117.40, 127.62, 128.34, 134.00, 138.42.

EIMS: *m*/*z* = 204 [M^+].

(2*R*,3*S*,5*RS*)-3-Benzyloxy-1,2:5,6-diepoxyhexane (11)

To a stirred soln of epoxyalkene **10** (0.5 g, 2.45 mmol) in anhyd CH_2Cl_2 (15 mL), MCPBA (0.63 g, 3.67 mmol) was added at r.t., and stirring was continued for 12 h. The reaction mixture was brought to 0 °C and Na_2SO_3 soln was slowly added to quench excess MCPBA. The reaction mixture was washed with $NaHCO_3$ soln (30 mL) to remove *m*-chlorobenzoic acid and extracted with $CHCl_3$ (3 × 50 mL). The combined organic fractions were collected and washed with H_2O (20 mL) and brine (20 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–PE, 1:3) to afford bis-epoxide **11** (0.45 g, 83%) as a colourless oil, as a diastereomeric mixture.

$[\alpha]_D^{25}$ +18.95 (*c* 0.6, $CHCl_3$).

IR (KBr): 2923, 1722, 1453, 1260, 1094, 846, 748, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.94 (m, 2 H), 2.42–2.51 (m, 1 H), 2.65–2.80 (m, 4 H), 2.89–3.12 (m, 1 H), 3.37–3.54 (m, 1 H), 4.49–4.72 (mixture of d, 2 H), 7.21–7.36 (m, 5 H).

(2*R*,3*S*,5*RS*)-3-Benzyloxy-1,6-diphenylhexane-2,5-diol (12)

To a stirred suspension of Mg (0.31 g, 12.72 mmol) in anhyd THF (5 mL), PhBr (0.84 mL, 7.95 mmol) dissolved in THF (5 mL) was added at r.t. under N_2 atmosphere over a period of 15 min, and stirring was continued for 30 min. The reaction mixture was cooled to –40 °C, and to it CuI (0.61 g, 3.18 mmol) and bis-epoxide **11** (0.35 g, 1.59 mmol) dissolved in anhyd THF (5 mL) were added. After the addition was completed, the reaction mixture was warmed to r.t. and stirring was continued for another 4 h. The reaction mixture was quenched by the addition of aq NH_4Cl soln (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fractions were collected and washed with H_2O (20 mL) and brine (20 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–PE, 1:4) to afford compound **12** (0.49 g, 82%) as a thick syrup.

$[\alpha]_D^{25}$ –7.6 (*c* 0.9, $CHCl_3$).

IR (KBr): 3410, 2922, 2355, 1078, 1035, 755, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.99 (m, 4 H), 2.60–2.85 (m, 4 H), 3.46–3.68 (m, 1 H), 3.95–4.02 (m, 2 H), 4.38–4.61 (mixture of d, 2 H), 7.08–7.35 (m, 15 H).

FABMS: *m*/*z* = 377 [M^+ + 1].

(2*S*,3*S*,5*RS*)-2,5-Diazido-3-benzyloxy-1,6-diphenylhexane (13)

To an ice-cooled soln of diol **12** (0.3 g, 0.8 mmol) in anhyd CH_2Cl_2 (10 mL) were added Et_3N (0.67 mL, 4.8 mmol) and MsCl (0.18 mL, 2.4 mmol) under N_2 atmosphere. The reaction mixture was allowed to return to r.t., and stirred for 4 h. The reaction mixture was quenched by the addition of cold H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic fractions were collected and washed with H_2O (20 mL) and brine (20 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to afford dimesylated compound, which was immediately used as such, without further purification, for the next reaction. To a stirred soln of the dimesylate in anhyd DMF (6 mL) were added NaN_3 (0.31 g, 4.8 mmol) and 18-crown-6 (0.42 g, 1.6 mmol). The reaction was slowly heated to 50 °C, then heating was continued for 24 h. The reaction mixture was allowed to return to r.t., poured into cold H_2O (20 mL) and then extracted with EtOAc (3 × 75 mL). The combined organic fractions were collected and washed with H_2O (15 mL) and brine (15 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–PE, 1:19) to afford diazide **13** (0.24 g, 71%) as a colourless liquid.

$[\alpha]_D^{25}$ –4.87 (*c* 0.6, $CHCl_3$).

IR (KBr): 2100, 1250, 1090, 750, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.55–1.94 (m, 2 H), 2.63–2.98 (m, 4 H), 3.42–3.74 (m, 3 H), 4.44–4.71 (mixture of d, 2 H), 7.07–7.38 (m, 15 H).

(2*S*,3*S*,5*RS*)-3-Benzyloxy-2,5-bis[(*tert*-butoxycarbonyl)amino]-1,6-diphenylhexane (14)

Diazide **13** (0.2 g, 0.47 mmol) dissolved in anhyd THF (5 mL) was added to a stirred suspension of $LiAlH_4$ (53 mg, 1.41 mmol) in anhyd THF (5 mL) at 0 °C. The reaction mixture was allowed to reach 25 °C and stirring was continued for 1 h. The reaction mixture was cooled to 0 °C and quenched with 15% aq NaOH soln (0.1 mL) and H_2O (0.2 mL), then $(Boc)_2O$ (0.22 mL, 0.94 mmol) dissolved in anhyd THF (2 mL) was added. After being stirred for 12 h at r.t., the reaction mixture was filtered through a pad of Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–PE, 1:6) to afford compound **14** (0.24 g, 89%) as a thick syrup.

$[\alpha]_D^{25}$ –8.42 (*c* 1, $CHCl_3$).

IR (KBr): 3340, 2967, 1680, 1635, 1522, 1267, 1233, 1167, 645 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 1.39 (s, 9 H), 1.50–1.82 (m, 2 H), 2.54–2.86 (m, 4 H), 3.37–3.52 (m, 1 H), 3.72–4.10 (m, 2 H), 4.24–4.74 (mixture of d, 4 H), 7.02–7.36 (m, 15 H).

FABMS: *m*/*z* = 575 [M^+ + 1].

(2*S*,3*S*,5*S*)-2,5-Bis[(*tert*-butoxycarbonyl)amino]-1,6-diphenylhexan-3-ol (3) and (2*S*,3*S*,5*R*)-2,5-Bis[(*tert*-butoxycarbonyl)amino]-1,6-diphenylhexan-3-ol (5)

To a soln of compound **14** (0.18 g, 0.31 mmol) in anhyd MeOH (4 mL) was added a catalytic amount of $Pd(OH)_2$ and the mixture was stirred for 4 h under H_2 atmosphere, then filtered through Celite®. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (EtOAc–PE, 1:4) to afford compound **5** (58 mg, 38%) as a white solid; further elution (EtOAc–PE, 1:3) afforded compound **3** (82 mg, 54%) as a white solid.

Compound **3**:

Mp 194–196 °C; $[\alpha]_D^{25}$ –14.18 (*c* 1, $CHCl_3$).

IR (KBr): 3377, 2976, 1693, 1673, 1521, 1170, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (m, 1 H), 1.35 (s, 9 H), 1.41 (s, 9 H), 1.78 (m, 1 H), 2.71 (dd, *J* = 6.7, 14.1 Hz, 1 H), 2.78 (dd, *J* = 6.7, 14.1 Hz, 1 H), 2.89 (m, 2 H), 3.51 (m, 1 H), 3.65 (q, *J* = 8.2 Hz, 1 H), 4.05 (m, 1 H), 4.34 (d, *J* = 8.9 Hz, 1 H), 4.37 (m, 1 H), 5.03 (d, *J* = 8.9 Hz, 1 H), 7.12–7.30 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.26, 28.37, 39.09, 40.64, 41.58, 47.96, 55.79, 65.80, 78.98, 79.98, 126.04, 126.55, 128.32, 128.53, 129.16, 129.44, 137.35, 138.76, 155.96, 157.15.

FABMS: *m*/*z* = 485 [M^+ + 1].

Compound **5**:

Mp 140–142 °C; $[\alpha]_D^{25}$ –11.62 (*c* 1.2, $CHCl_3$).

IR (KBr): 3370, 2992, 1686, 1669, 1524, 1172, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 18 H), 1.61 (m, 2 H), 2.72–2.79 (m, 2 H), 2.83 (dd, *J* = 7.4, 13.4 Hz, 1 H), 2.88 (dd, *J* = 7.4, 13.4 Hz, 1 H), 3.41 (br s, 1 H), 3.59–3.71 (m, 2 H), 3.86 (m, 1 H), 4.56 (br d, 1 H), 4.81 (d, *J* = 8.9 Hz, 1 H), 7.08–7.30 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.32, 38.46, 39.73, 41.54, 50.09, 55.98, 69.90, 79.22, 79.63, 126.21, 126.42, 128.37, 129.30, 129.38, 137.56, 138.51, 155.89, 156.12.

FABMS: *m*/*z* = 485 [M^+ + 1].

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