A Novel Asymmetric Synthesis of the Core Octadienoic Acid Unit of Cryptophycins from (*R*)-2,3-*O*-Cyclohexylideneglyceraldehyde

Dibakar Goswami, Payel Sur, Angshuman Chattopadhyay, Anubha Sharma, Subrata Chattopadhyay*

Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400 085, India
Fax +91(22)25505151; E-mail: schatt@barc.gov.in

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Abstract: A facile asymmetric synthesis of the octadienoic acid unit of cryptophycins was developed starting from (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde. The key steps of the synthesis are the stereocontrolled generation of the required asymmetric centers through (i) a gallium-mediated highly diastereoselective crotylation of the glyceraldehyde in [bmim][Br], (ii) a stereoselective allylation with allyltributylstannane, and (iii) an enantioselective Grignard addition to an α-oxygenated aldehyde.

Key words: asymmetric synthesis, chiral pool, cryptophycins, gallium, crotylation, allylation

Cryptophycins (Figure 1) are potent, tumor-selective tubulin-binding antimitotic agents[1] with excellent activity against multidrug-resistant (MDR) cancer cells.[2] Cryptophycin-A (**1**), initially isolated from the blue-green algae *Nostoc* sp. ATCC 53789[3a,b] and later from GSV 224,[3c] is an effective inhibitor of tubulin polymerization at substoichiometric concentrations[4] and inhibits vinblastine binding to tubulin.[4,5] A structurally related compound, arenastatin A (cryptophycin-24, **2**), isolated from the Okinawan marine sponge *Dysidea arenaria*[6a,b] and from *Nostoc* sp. GSV 224,[6c] is a potent inhibitor of tubulin polymerization[6d] and also shows excellent cytotoxicity against KB cells in vitro,[6a,b] but has a very short half-life. The metabolically stable synthetic analogue, cryptophycin-52 (**3**), shows exceptional in vivo potency and tumor-selective cytotoxicity, and is effective against drug-sensitive and drug-resistant tumor cells.[6c]

Structural variation within the subset of the macrocyclic cryptophycins is centered on three sites: (i) the styryl residue in **5**–**7** that is epoxidized in **1**–**4**, (ii) the β-alanine or α-methylated β-alanine residue as in **2** and **7**, and **1**, **3**–**6**, respectively, and (iii) the (*R*)-*O*-methyltyrosinyl residue of **2**, **4** and **6** that bears a *m*-chloro substituent in **1**, **3**, **5** and **7**. Essentially, the structure of the cryptophycins can be assembled in a convergent manner (Figure 1) from the protected octadienoic acid (**A** unit), D-tyrosine ester (**B** unit), the protected β-amino acid derivative (**C** unit) and the hydroxy acid (**D** unit). Amongst these, the presence of the epoxide unit in unit **A**, the methoxy and chloro substituents in unit **B** and certain substitution patterns in unit **C** contribute positively to the cytotoxic action of the cryptophycins.[6c] In view of their potent bioactivity, a large number of formal[7] and total[2a,8] syntheses of the cryptophycins have been reported. Given the units **B**–**D** are easily available, particular attention has been focused on the synthesis of the octadienamide fragment (**A** equivalent) of

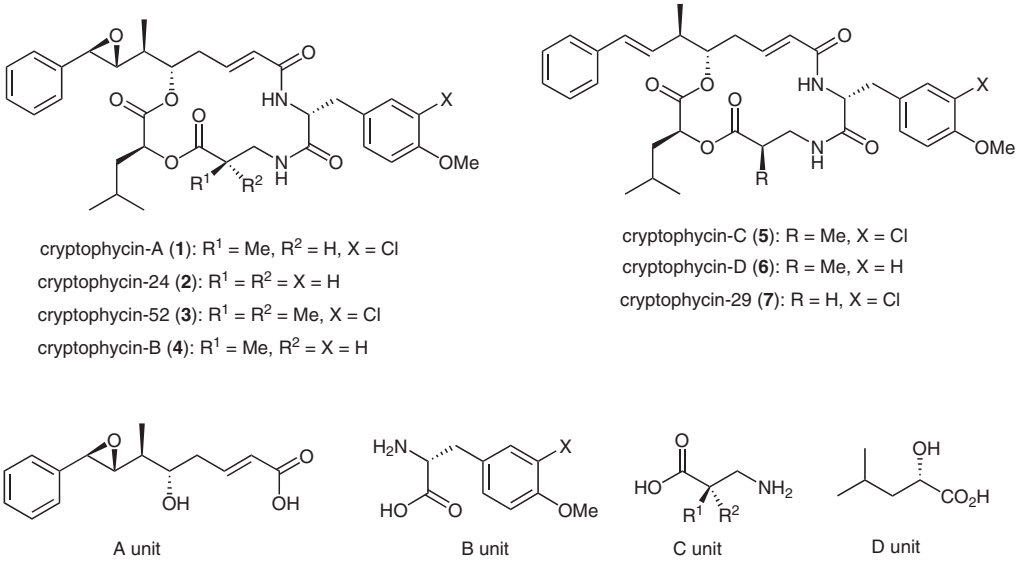

Figure 1 Chemical structures of the cryptophycins and units A–D

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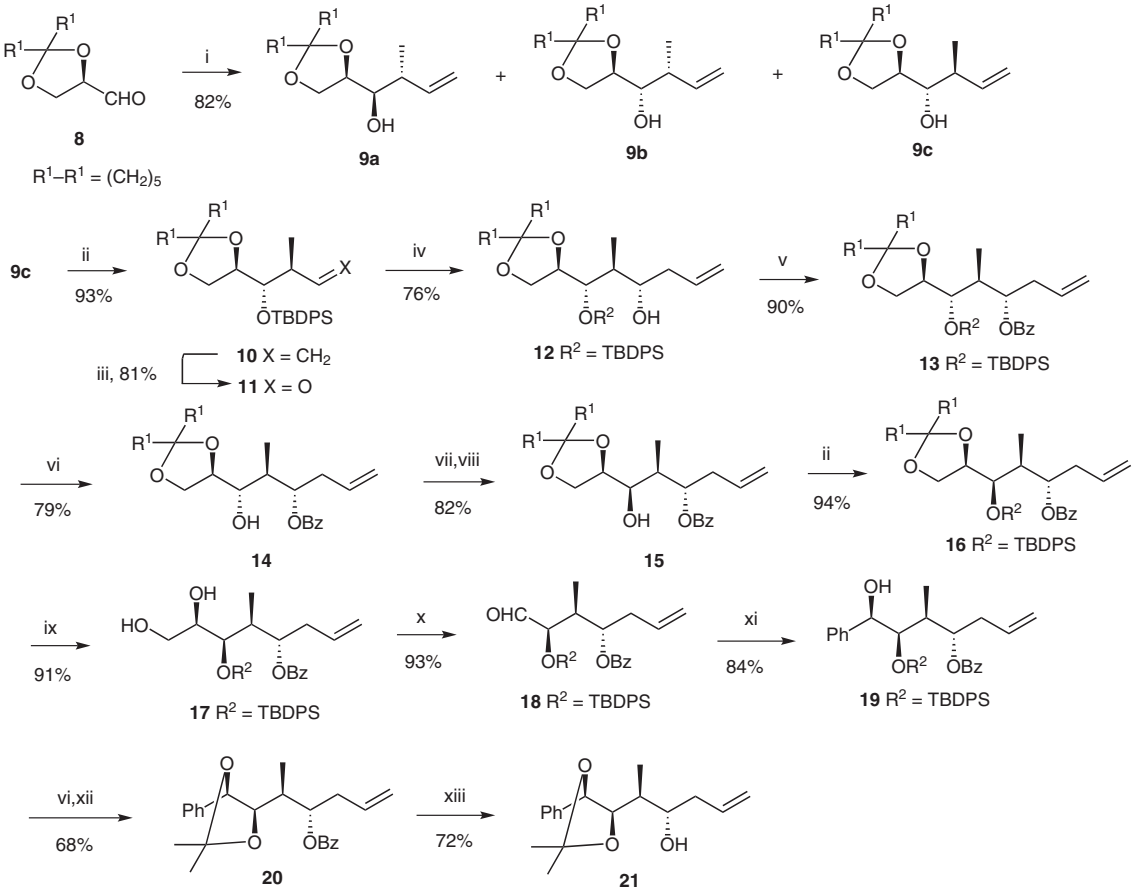
desoxycryptophycins, leading to a number of interesting methodologies.[7a,c,9] A strategic theme common to the majority of the syntheses of the epoxide-containing cryptophycins has been the introduction of the epoxide pharmacophore in a single late-stage operation through the use of *m*-chloroperoxybenzoic acid or dimethyldioxirane. The reported epoxidation methods proceed with a diastereoselectivity of 2–3:1, necessitating a chromatographic separation of the desired (major) β-isomer. In contrast, the more efficient protocols are based on prior introduction of the chiral diol unit at those centers.[8h,9] To this end, we have developed a novel asymmetric synthesis of **21** (**A** equivalent), bearing the chiral diol unit that can be elaborated to the cryptophycins.

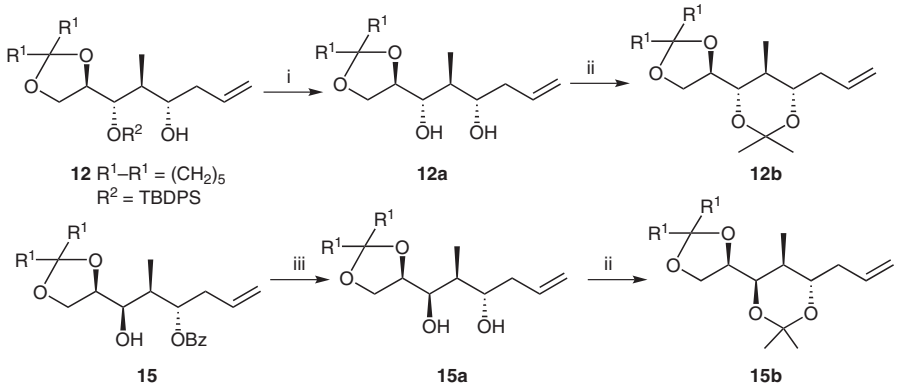
Earlier, we have found that the homoallylic alcohols **9a–c**, obtained by crotylation of 2,3-*O*-cyclohexylideneglyceraldehyde (**8**) (Scheme 1) are versatile intermediates for the syntheses of a variety of bioactive compounds.[10] It was envisaged that the alcohol stereomers **9a–c** are functionally sufficiently enriched and well-suited for elaboration to the target structural motif of the **A** unit of the cryptophycins. Further, following this strategy, it would be possible to introduce the required diol moiety in an enantioselective fashion, which would eventually produce the epoxide-containing cryptophycins.

The initial motivation for the present work stems from our previous observation that the stereochemistry of crotylation of the aldehyde **8** can be tuned by changing the metal and solvent. For example, while the zinc-mediated crotylation of **8** in wet tetrahydrofuran proceeds with modest *anti* selectivity to furnish the diastereomeric alcohols **9a–c** in a 2.4:33.1:64.5 ratio,[11a] when the reaction is carried out using indium in water, **9b** and **9c** are obtained in ~1:1 ratio.[11b] Very recently, we found that the gallium-mediated crotylation of **8** in [bmim][Br] proceeds with excellent diastereoselectivity to furnish **9a/9b/9c** in a 3:5:92 ratio and 82% overall yield.[12] It is worth mentioning that earlier, better stereocontrol in crotylation was accomplished with reagents such as crotyltrifluorosilane[13a,b] and crotyltrifluoroborates[13c] that need to be synthesized separately. In contrast, our approach,[12] using inexpensive and commercially available reagents such as crotyl bromide, [bmim][Br] and gallium, and the widely used chiral template **8**, provides a simple and convenient strategy for asymmetric crotylation.

For the synthesis of the cryptophycin segment (Scheme 1), compound **9c** was converted into the silyl derivative **10** by reaction with *tert*-butyldiphenylsilyl chloride in the presence of imidazole as the base. This, on reductive ozonolysis, gave the aldehyde **11**.



Scheme 1 *Reagents and conditions*: (i) MeCH=CHCH$_2$Br, Ga, [bmim][Br], 25 °C, 4 h; (ii) TBDPSCl, imidazole, CH_2Cl_2, 25 °C, 12 h; (iii) O_3, CH_2Cl_2, –78 °C, 1 h; Ph_3P, r.t., 16 h; (iv) allyltributylstannane, $InCl_3$, (*S*)-BINOL, CH_2Cl_2, r.t., 36 h; (v) BzCN, Et_3N, CH_2Cl_2, 0 °C to r.t., 18 h; (vi) TBAF, THF, 0 °C, 3 h; (vii) PCC, NaOAc, CH_2Cl_2, 0 °C, 3 h; (viii) K-Selectride®, THF, –78 °C, 3 h; (ix) TFA, H_2O, 0 °C, 3 h; (x) $NaIO_4$, MeCN, H_2O, r.t., 2 h; (xi) PhMgBr, THF, –30 °C, 3 h; (xii) 2,2-dimethoxypropane, PPTS, r.t., 1 h; (xiii) K_2CO_3, MeOH, r.t., 3 h.



Scheme 2 *Reagents and conditions*: (i) TBAF, THF, 0 °C, 2 h; (ii) 2,2-dimethoxypropane, PPTS, r.t., 1 h; (iii) K_2CO_3, MeOH, 0 °C, 2 h.

It was envisaged that a substrate-controlled Barbier-type allylation of the aldehyde **11** might provide an easy and economic route to the desired *syn*-alcohol **12**. For this purpose, we attempted the reaction between **11** and allyl bromide using different metal–solvent combinations (Zn, THF, sat. aq NH_4Cl; In, H_2O; In, [bmim][Br]; Ga, [bmim][Br]); however, the homoallylic alcohol **12** was obtained as a nonseparable diastereomeric mixture under all reactions conditions. Hence, the allylation of **11** was carried out[14] with allyltributylstannane in the presence of (*S*)-BINOL to obtain **12** with excellent (>30:1, *syn*/*anti*) diastereoselectivity. When the reaction was carried out with (*R*)-BINOL as the chiral auxiliary, the 3,5-*anti*-stereomer of **12** was obtained with >25:1 diastereoselectivity. This suggested that the stereochemistry of the reaction was dictated exclusively by that present in the reagent, without a significant contribution from the substrate chirality.

The 3,5-*syn*-alcohol **12** could be easily isolated by normal column chromatography. To confirm the 3,5-*syn* stereochemistry, **12** was converted into the acetonide derivative **12b** (Scheme 2). Thus, compound **12** was desilylated to the diol **12a** and subsequently converted into the cyclic acetal **12b** by reaction with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate. The 3,5-*syn* stereochemistry was confirmed from the ^{13}C NMR resonances.[15]

For the synthesis of the target compound (Scheme 1), the carbinol **12** was benzoylated to furnish compound **13**, which on desilylation gave the alcohol **14**. This was subsequently converted into the 3,5-*anti*-diol derivative **15** by oxidation of its carbinol function with pyridinium chlorochromate followed by reduction with K-Selectride®. As was done for compound **12**, the relative 3,5-*anti* stereochemistry of **15** was confirmed by analyzing the ^{13}C NMR resonances of the cyclic acetal **15b** (Scheme 2). Next, the alcohol **15** was silylated with *tert*-butyldiphenylsilyl chloride in the presence of imidazole to obtain compound **16**, which on deketalization with aqueous trifluoroacetic acid gave the diol **17** uneventfully (Scheme 1). Cleavage of the α-glycol of **17** with sodium periodate furnished the aldehyde **18**. Its reaction with phenylmagnesium bromide proceeded with excellent diastereoselectivity (dr >98:2) to furnish the target cryptophycin A unit **19** almost exclusively. For further confirmation of its structure, compound **19** was converted into the known compound **21**, that has been conceived as an advanced synthon for cryptophycin A.[9] Thus, compound **19** was desilylated and the resultant product was converted into the acetal **20** by acid-catalyzed condensation with 2,2-dimethoxypropane. Subsequent debenzoylation of **20** finally afforded the target synthon **21**, whose spectroscopic and optical data were in accordance with the reported values.[9]

In conclusion, an efficient asymmetric synthesis of the octadienoic acid unit (**A** unit) of cryptophycins from the easily available aldehyde **8** has been demonstrated. Amongst the existing syntheses of the **A** unit, the most recent route[9] is by far the best in terms of brevity (7/8 steps) and overall yield (~14%); however, it involves several reagents which need to be prepared separately and/or are suitable for synthesis on a very small scale. The formulation of simple and efficient asymmetric syntheses of bioactive target compounds remains one of the challenging goals in organic chemistry despite recent progresses.[16] Compared to the previous syntheses, all the steps in our synthesis can be carried out conveniently on a multigram scale. Also, despite requiring more steps, our synthesis provided the target compound in acceptable overall yield (18%). The present synthetic route is also amenable for the synthesis of other members of the cryptophycin family.

All chemicals (Fluka and Lancaster) were used as received. All solvents were dried following standard procedures. Other reagents were of AR grade. Unless otherwise mentioned, the organic extracts were dried over anhyd Na_2SO_4. IR spectra as thin films were scanned with a Jasco model A-202 FT-IR spectrophotometer. ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded with a Bruker AC-200 spectrometer using $CDCl_3$ as the solvent. The optical rotations were recorded with a Jasco DIP-360 digital polarimeter.

(3*S*,4*S*,5*R*)-4-*tert*-Butyldiphenylsilyloxy-5,6-cyclohexylidenedioxy-3-methylhex-1-ene (10)

To a soln of **9c** (1.44 g, 6.37 mmol) and imidazole (0.828 g, 12.18 mmol) in CH_2Cl_2 (30 mL) was added TBDPSCl (2.51 g, 9.15 mmol), and the mixture was stirred at 25 °C for 12 h. After completion of the reaction (cf. TLC), the mixture was poured into H_2O (20 mL) and extracted with $CHCl_3$ (3 × 15 mL). The organic extract

was washed with H_2O (2 × 5 mL) and brine (1 × 5 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc–hexane, 2:98) to give pure **10**.

Yield: 2.75 g (93%); colorless liquid; $[\alpha]_D^{23}$ +31.8 (*c* 2.31, $CHCl_3$).

IR (film): 1586, 998, 909 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.23–1.51 (m, 10 H), 2.28–2.37 (m, 1 H), 3.70–3.86 (m, 3 H), 4.01–4.10 (m, 1 H), 4.96–5.01 (m, 2 H), 5.81–5.98 (m, 1 H), 7.22–7.26 (m, 6 H), 7.68–7.77 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 19.6, 23.9, 24.0, 25.3, 26.9, 27.2, 34.7, 36.2, 40.9, 66.6, 76.1, 77.8, 108.9, 114.7, 127.5, 127.6, 129.7, 129.8, 133.8, 133.9, 135.6, 136.2, 140.4.

Anal. Calcd for $C_{29}H_{40}O_3Si$: C, 74.95; H, 8.68. Found: C, 75.10; H, 8.56.

(2*R*,3*S*,4*R*)-3-*tert*-Butyldiphenylsilyloxy-4,5-cyclohexylidenedioxy-2-methylpentanal (11)

Ozone was bubbled through a cooled (–78 °C) soln of **10** (2.55 g, 5.49 mmol) in CH_2Cl_2 (20 mL) until the solution turned blue. After 1 h, the excess O_3 was removed by purging with N_2 (gas), and the mixture was treated with Ph_3P (6.0 g, 22.89 mmol) and stirred at r.t. for 16 h. Most of the solvent was removed under reduced pressure, and the residue was dissolved in hexane (30 mL) and chromatographed (silica gel, 0–10% EtOAc–hexane) to furnish pure **11**.

Yield: 2.08 g (81%); colorless liquid; $[\alpha]_D^{22}$ +8.2 (*c* 1.00, $CHCl_3$).

IR (film): 1726 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 1.16–1.28 (m containing a d at δ 1.26, *J* = 7.0 Hz, 5 H), 1.41–1.48 (m, 8 H), 2.68–2.71 (m, 1 H), 3.42–3.48 (m, 1 H), 3.74–3.81 (m, 1 H), 4.12–4.22 (m, 2 H), 7.32–7.42 (m, 6 H), 7.56–7.71 (m, 4 H), 9.55 (d, *J* = 1.2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.4, 19.5, 23.8, 23.9, 25.1, 26.9, 34.6, 36.2, 49.9, 67.6, 73.9, 76.1, 109.6, 127.6, 127.9, 129.9, 130.2, 132.2, 133.4, 135.9, 136.2, 204.8.

Anal. Calcd for $C_{28}H_{38}O_4Si$: C, 72.06; H, 8.21. Found: C, 71.85; H, 8.45.

(4*S*,5*S*,6*S*,7*R*)-6-*tert*-Butyldiphenylsilyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-en-4-ol (12)

To a soln of azeotropically dried (with anhyd THF, 3 × 3 mL) $InCl_3$ (142 mg, 0.645 mmol) in CH_2Cl_2 (6.5 mL) was added (*S*)-BINOL (205 mg, 0.735 mmol) under argon. The mixture was stirred for 2 h, then allyltributylstannane (0.4 mL, 1.3 mmol) was added and the resulting mixture was stirred for 10 min, which was followed by the addition of H_2O (0.09 mL, 4.8 mmol) to afford a white suspension. This mixture was further treated with allyltributylstannane (0.950 mL, 3.0 mmol), stirred for 10 min and then **11** (1.0 g, 2.15 mmol) in CH_2Cl_2 (10 mL) was added. After the mixture was stirred at r.t. for 36 h, sat. aq $NaHCO_3$ (10 mL) was added. The organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (2 × 10 mL), and the combined organic extracts were washed with brine, dried and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 0–15% EtOAc–hexane) to furnish pure **12**.

Yield: 0.830 g (76%); colorless liquid; $[\alpha]_D^{22}$ +20.1 (*c* 1.20, $CHCl_3$).

IR (film): 3443 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.06 (overlapping s and d, *J* = 7.0 Hz, 12 H), 1.27–1.54 (m, 10 H), 1.77–1.82 (m, 1 H), 1.88–2.04 (m, 2 H), 2.75 (br s, 1 H), 3.55–3.63 (m, 2 H), 4.02–4.17 (m, 3 H), 4.92–4.99 (m, 2 H), 5.61–5.75 (m, 1 H), 7.34–7.44 (m, 6 H), 7.64–7.70 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.1, 19.4, 23.9, 25.0, 27.1, 35.0, 35.7, 39.6, 43.6, 68.5, 72.8, 74.2, 74.4, 110.1, 116.7, 127.6, 129.8, 129.9, 133.4, 133.6, 135.4, 136.1.

Anal. Calcd for $C_{31}H_{44}O_4Si$: C, 73.18; H, 8.72. Found: C, 72.95; H, 8.78.

(2*R*,3*S*,4*S*,5*S*)-1,2-Cyclohexylidenedioxy-4-methyloct-7-ene-3,5-diol (12a)

To a cooled (0 °C) and stirred soln of **12** (0.163 g, 0.32 mmol) in THF (10 mL) was added 1 M TBAF in THF (0.56 mL, 0.56 mmol), and the mixture was stirred for ~2 h (cf. TLC). It was poured into excess H_2O, and this mixture was extracted with EtOAc (3 × 5 mL). The combined organic extract was washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), and dried. Removal of the solvent under reduced pressure followed by column chromatography of the residue (silica gel, 0–10% EtOAc–hexane) furnished pure **12a**.

Yield: 0.068 g (78%); colorless liquid; $[\alpha]_D^{22}$ +15.2 (*c* 1.40, $CHCl_3$).

IR (film): 3437, 2933, 2858 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 3 H), 1.28–1.61 (m, 10 H), 2.09–2.21 (m, 2 H), 2.31–2.50 (m, 1 H), 3.09 (br s, 2 H), 3.71–4.03 (m, 4 H), 4.18–4.25 (m, 1 H), 5.09–5.16 (m, 2 H), 5.72–6.03 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.6, 23.7, 23.9, 25.1, 34.8, 36.0, 38.7, 40.5, 64.3, 74.1, 74.5, 76.4, 109.6, 117.7, 134.9.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.45; H, 9.75.

(4*S*,5*S*,6*S*,7*R*)-7,8-Cyclohexylidenedioxy-4,6-isopropylidenedioxy-5-methyloct-1-ene (12b)

A mixture of diol **12a** (0.050 g, 0.185 mmol), 2,2-dimethoxypropane (1 mL) and PPTS (cat.) was stirred for 1 h. Then, the mixture was treated with 10% aq $NaHCO_3$ and extracted with Et_2O (10 mL). The ether layer was washed with H_2O (1 × 2 mL) and brine (1 × 2 mL), dried and concentrated under reduced pressure to give a residue which was purified by column chromatography (silica gel, 0–10% EtOAc–hexane) to afford **12b**.

Yield: 0.048 g (84%); colorless liquid; $[\alpha]_D^{22}$ +23.4 (*c* 1.20, $CHCl_3$).

IR (film): 2935, 1107 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.6 Hz, 3 H), 1.24–1.42 (m overlapped with two s, 8 H), 1.55–1.59 (m, 8 H), 2.10–2.28 (m, 2 H), 2.32–2.49 (m, 1 H), 3.41–3.59 (m, 2 H), 3.85–3.90 (m, 1 H), 3.99–4.04 (m, 2 H), 5.01–5.09 (m, 2 H), 5.78–6.05 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.2, 19.6, 23.9, 25.2, 29.8, 35.3, 36.0, 37.1, 37.3, 66.8, 73.8, 75.0, 78.2, 97.7, 109.9, 116.4, 134.8.

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.75; H, 9.80.

(4*S*,5*S*,6*S*,7*R*)-4-Benzoyloxy-6-*tert*-butyldiphenylsilyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-ene (13)

To a cooled (0 °C) and stirred soln of the alcohol **12** (0.800 g, 1.58 mmol) and Et_3N (0.350 mL, 2.34 mmol) in CH_2Cl_2 (15 mL) was added BzCN (0.484 mL, 4.08 mmol). After the mixture was stirred at r.t. for 18 h, it was poured into H_2O (15 mL); the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 5 mL). The combined organic extracts were washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), and dried. Removal of the solvent under reduced pressure followed by column chromatography of the residue (silica gel, 0–10% EtOAc–hexane) furnished pure **13** as a mixture of rotamers.

Yield: 0.858 g (90%); light yellow liquid; $[\alpha]_D^{22}$ +13.5 (*c* 2.52, $CHCl_3$).

IR (film): 2935, 2857, 1638 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.16 (overlapping s and d, *J* = 7.0 Hz, 12 H), 1.23–1.54 (m, 10 H), 1.92–2.10 (m, 1 H), 2.23–2.31 (m, 2 H), 3.75–3.86 (m, 2 H), 3.89–3.99 (m, 1 H), 4.13–4.21 (m, 1 H), 4.87–5.01 (m, 2 H), 5.45–5.52 (m, 1 H), 5.56–5.77 (m, 1 H), 7.29–7.45 (m, 9 H), 7.66–7.92 (m, 5 H), 7.98–8.05 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.6, 11.0, 19.5, 23.7, 23.8, 25.1, 27.1, 34.7, 34.9, 35.7, 36.1, 36.8, 40.1, 40.5, 64.0, 67.8, 73.5, 73.8, 75.1, 75.5, 76.5, 109.4, 109.6, 116.9, 117.0, 127.4, 127.5, 128.3, 129.1, 129.4, 129.6, 129.7, 129.8, 130.2, 132.1, 132.9, 133.8, 133.9, 134.1, 135.8, 136.0, 136.1, 165.4, 165.5.

Anal. Calcd for $C_{38}H_{48}O_5Si$: C, 74.47; H, 7.89. Found: C, 74.28; H, 7.78.

(2*R*,3*S*,4*S*,5*S*)-5-Benzoyloxy-1,2-cyclohexylidenedioxy-4-methyloct-7-en-3-ol (14)

Desilylation of **13** (0.800 g, 1.33 mmol) with 1 M TBAF in THF (2.25 mL, 2.25 mmol) in THF (20 mL) at 0 °C for 3 h, followed by workup of the reaction mixture and purification of the residue by column chromatography (silica gel, 0–10% EtOAc–hexane) furnished pure **14**.

Yield: 0.390 g (79%); colorless liquid; $[\alpha]_D^{22}$ +18.7 (*c* 1.60, $CHCl_3$).

IR (film): 3437, 1720 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 7.4 Hz, 3 H), 1.20–1.36 (m, 2 H), 1.48–1.57 (m, 8 H), 2.01–2.13 (m, 1 H), 2.35–2.52 (m, 3 H), 3.72–3.89 (m, 3 H), 4.03–4.21 (m, 1 H), 4.97–5.13 (m, 2 H), 5.43–5.50 (m, 1 H), 5.72–5.93 (m, 1 H), 7.35–7.51 (m, 3 H), 7.92–8.08 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.4, 23.7, 23.9, 25.1, 34.4, 34.9, 36.0, 38.9, 64.1, 71.7, 74.7, 109.4, 117.5, 128.3, 129.5, 130.5, 132.8, 134.2, 165.9.

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.35; H, 7.96.

(2*R*,3*R*,4*S*,5*S*)-5-Benzoyloxy-1,2-cyclohexylidenedioxy-4-methyloct-7-en-3-ol (15)

To a cooled (0 °C) and stirred suspension of PCC (0.334 g, 1.52 mmol) and NaOAc (10 mol%) in CH_2Cl_2 (20 mL) was added the alcohol **14** (0.350 g, 0.95 mmol) in one portion. The reaction mixture was stirred for 3 h, then diluted with Et_2O (20 mL). The supernatant was passed through a pad of silica gel (2″ × 1″), which was washed with Et_2O (15 mL). Removal of the solvent under reduced pressure followed by column chromatography of the residue (silica gel, 0–10% EtOAc–hexane) furnished the corresponding ketone.

In view of its instability, the ketone was directly used for the next step. Thus, 1 M K-Selectride® in THF (1.30 mL, 1.30 mmol) was injected into a cooled (–78 °C) and stirred solution of the above ketone (0.290 g, 0.78 mmol) in THF (15 mL). The mixture was stirred at that same temperature until completion of the reaction (cf. TLC, ~3 h), then the excess hydride was decomposed with MeOH, and the supernatant was decanted and concentrated under reduced pressure. The residue was taken up in Et_2O (3 × 15 mL), and the organic extract was washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of the solvent under reduced pressure followed by column chromatography of the residue (silica gel, 0–10% EtOAc–hexane) furnished pure **15**.

Yield: 0.291 g (82%); colorless liquid; $[\alpha]_D^{22}$ +38.8 (*c* 1.06, $CHCl_3$).

IR (film): 3477, 1724 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 7.2 Hz, 3 H), 1.32–1.36 (m, 2 H), 1.37–1.57 (m, 8 H), 2.09–2.21 (m, 1 H), 2.26–2.34 (m, 2 H), 3.50–3.54 (m, 1 H), 3.87–3.94 (m, 2 H), 4.13–4.18 (m, 1 H), 4.34–4.45 (m, 1 H), 5.03–5.12 (m, 2 H), 5.25–5.32 (m, 1 H), 5.78–5.93 (m, 1 H), 7.39–7.53 (m, 3 H), 7.99–8.06 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.0, 23.7, 23.8, 25.0, 34.7, 36.1, 40.6, 64.4, 73.8, 76.2, 79.1, 109.1, 114.9, 129.4, 130.3, 133.2, 136.7, 140.4, 167.7.

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.71; H, 8.15.

(2*R*,3*R*,4*S*,5*S*)-1,2-Cyclohexylidenedioxy-4-methyloct-7-ene-3,5-diol (15a)

A mixture of **15** (0.100 g, 0.267 mmol) and anhyd K_2CO_3 (0.062 g, 0.454 mmol) in MeOH (10 mL) was stirred at 0 °C. After consumption of the starting material (cf. TLC, ~2 h), the mixture was concentrated under reduced pressure, the residue was taken up in Et_2O (10 mL), and the organic extract was washed with H_2O (2 × 5 mL) and brine (1 × 5 mL), and dried. Removal of the solvent under reduced pressure followed by preparative TLC of the residue (silica gel, 0–10% EtOAc–hexane) furnished pure **15a**.

Yield: 0.054 g (75%); colorless liquid; $[\alpha]_D^{22}$ +7.3 (*c* 2.3, $CHCl_3$).

IR (film): 3438, 2933, 2857 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.0 Hz, 3 H), 1.29–1.63 (m, 10 H), 2.34–2.37 (m, 1 H), 2.39–2.42 (m, 2 H), 3.02 (br s, 2 H), 3.37–3.42 (m, 1 H), 3.49–3.65 (m, 1 H), 3.79–3.83 (m, 1 H), 3.91–3.98 (m, 1 H), 4.05–4.12 (m, 1 H), 4.99–5.07 (m, 2 H), 5.70–5.84 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.4, 23.8, 23.9, 25.0, 35.2, 36.1, 38.0, 40.7, 65.9, 72.3, 76.9, 77.8, 110.0, 115.8, 139.4.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.42; H, 9.48.

(4*S*,5*S*,6*R*,7*R*)-7,8-Cyclohexylidenedioxy-4,6-isopropylidenedioxy-5-methyloct-1-ene (15b)

As described for **12a**, reaction of diol **15a** (0.030 g, 0.111 mmol) with 2,2-dimethoxypropane (1 mL) in the presence of PPTS afforded **15b** after workup of the reaction mixture and column chromatography of the residue (silica gel, 0–10% EtOAc–hexane).

Yield: 0.029 g (83%); colorless liquid; $[\alpha]_D^{22}$ +7.3 (*c* 2.32, $CHCl_3$).

IR (film): 2935, 2858, 1104 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.6 Hz, 3 H), 1.30 (s, 6 H), 1.33–1.59 (m, 10 H), 1.88–2.09 (m, 2 H), 2.21–2.39 (m, 1 H), 3.13–3.19 (m, 1 H), 3.56–3.68 (m, 1 H), 3.74–3.78 (m, 1 H), 3.95–4.05 (m, 2 H), 4.97–5.09 (m, 2 H), 5.71–5.95 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.1, 23.5, 23.9, 24.0, 25.2, 25.3, 34.7, 34.8, 36.7, 42.0, 67.8, 70.9, 73.5, 77.9, 100.3, 109.6, 114.4, 140.8.

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.72; H, 9.56.

(4*S*,5*S*,6*R*,7*R*)-4-Benzoyloxy-6-*tert*-butyldiphenylsilyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-ene (16)

Reaction of **15** (0.120 g, 0.321 mmol) with TBDPSCl (0.149 g, 0.543 mmol) in the presence of imidazole (0.044 g, 0.641 mmol) in CH_2Cl_2 (5 mL), and subsequent isolation, afforded a rotameric mixture of **16** after purification by column chromatography (silica gel, 0–10% Et_2O–hexane).

Yield: 0.189 g (94%); light yellow liquid; $[\alpha]_D^{22}$ +10.9 (*c* 1.41, $CHCl_3$).

IR (film): 1741 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.06–1.16 (merged s and d, *J* = 6.8 Hz, 12 H), 1.27–1.39 (m, 6 H), 1.44–1.56 (m, 4 H), 1.88–2.08 (m, 1 H), 2.18–2.32 (m, 2 H), 3.76–3.86 (m, 1 H), 3.89–3.99 (m, 1 H), 4.12–4.30 (m, 2 H), 4.79–4.99 (m, 2 H), 5.22–5.28 and 5.44–5.52 (two m, 1 H), 5.57–5.75 (m, 1 H), 7.25–7.48 (m, 9 H), 7.62–7.77 (m, 5 H), 7.89–8.05 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.6, 11.2, 19.5, 23.7, 23.8, 25.1, 27.1, 34.7, 34.9, 35.7, 36.1, 36.8, 40.1, 40.5, 64.0, 67.8, 73.5, 73.9, 75.1, 75.3, 75.5, 77.8, 109.4, 109.6, 117.0, 118.0, 127.4, 127.5, 128.3, 129.1, 129.4, 129.6, 129.7, 129.8, 130.2, 132.1, 132.9, 133.8, 133.9, 134.1, 135.8, 136.0, 136.1, 165.4, 165.5.

Anal. Calcd for $C_{38}H_{48}O_5Si$: C, 74.47; H, 7.89. Found: C, 74.55; H, 7.76.

(2*R*,3*R*,4*S*,5*S*)-5-Benzoyloxy-3-*tert*-butyldiphenylsilyloxy-4-methyloct-7-ene-1,2-diol (17)

A mixture of **16** (0.150 g, 0.244 mmol) and 80% aq TFA (10 mL) was stirred at 0 °C for 3 h. The mixture was diluted with H_2O (15 mL) and extracted with $CHCl_3$ (2 × 15 mL); the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 5 mL). The combined organic extracts were washed successively with 2% aq $NaHCO_3$ (1 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal under reduced pressure followed by column chromatography of the residue (silica gel, 0–40% EtOAc–hexane) furnished pure **17**.

Yield: 0.118 g (91%); colorless liquid; $[\alpha]_D^{22}$ +4.0 (*c* 1.34, $CHCl_3$).

IR (film): 3438, 1721 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09 (s, 9 H), 1.16 (d, *J* = 7.2 Hz, 3 H), 1.60 (br s, 2 H), 2.12–2.28 (m, 2 H), 2.32–2.51 (m, 1 H), 3.25–3.39 (m, 1 H), 3.54–3.75 (m, 3 H), 4.96–5.07 (m, 2 H), 5.32–5.39 (m, 1 H), 5.55–5.71 (m, 1 H), 7.12–7.41 (m, 8 H), 7.45–7.58 (m, 5 H), 7.80–7.84 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.2, 19.5, 27.1, 36.7, 41.9, 64.4, 72.2, 73.6, 77.8, 118.0, 127.5, 127.6, 128.3, 129.7, 133.1, 135.8, 136.0, 167.0.

Anal. Calcd for $C_{32}H_{40}O_5Si$: C, 72.14; H, 7.57. Found: C, 72.33; H, 7.36.

(2*R*,3*S*,4*S*)-4-Benzoyloxy-2-*tert*-butyldiphenylsilyloxy-3-methylhept-6-enal (18)

To a stirred soln of diol **17** (0.100 g, 0.188 mmol) in 60% aq MeCN (20 mL) at r.t. was added $NaIO_4$ (0.080 g, 0.376 mmol) in portions. The mixture was stirred for 2 h, then filtered, and the filtrate was extracted with $CHCl_3$ (2 × 10 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and concentrated under reduced pressure to give the aldehyde **18**.

Yield: 0.087 g (93%); colorless liquid; $[\alpha]_D^{23}$ +9.2 (*c* 1.22, $CHCl_3$).

IR (film): 2710, 1730, 1712 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.10 (overlapping s and d, *J* = 6.8 Hz, 12 H), 1.95–2.03 (m, 1 H), 2.21–2.29 (m, 2 H), 4.21 (dd, *J* = 1.8, 2.4 Hz, 1 H), 4.87–5.02 (m, 2 H), 5.23–5.29 (m, 1 H), 5.62–5.83 (m, 1 H), 7.15–7.47 (m, 9 H), 7.49–7.60 (m, 4 H), 7.78–7.82 (m, 2 H), 9.35 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.6, 19.5, 27.4, 36.7, 42.1, 74.5, 81.1, 116.9, 127.2, 127.5, 128.1, 129.2, 132.9, 136.0, 136.2, 140.8, 169.2, 203.4.

Anal. Calcd for $C_{31}H_{36}O_4Si$: C, 74.36; H, 7.25. Found: C, 74.24; H, 7.15.

(1*R*,2*R*,3*S*,4*S*)-4-Benzoyloxy-2-*tert*-butyldiphenylsilyloxy-3-methyl-1-phenylhept-6-en-1-ol (19)

To a cooled (–30 °C) and stirred soln of PhMgBr [prepared from 1-bromobenzene (0.056 g, 0.353 mmol) and Mg turnings (0.011 g, 0.441 mmol)] in THF (10 mL) was injected aldehyde **18** (0.089 g, 0.177 mmol) in THF (10 mL). The mixture was stirred for 3 h, then the reaction was quenched with sat. aq NH_4Cl (2 mL). The organic layer was separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with brine (1 × 5 mL) and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–15% EtOAc–hexane) afforded pure alcohol **19**.

Yield: 0.086 g (84%); white solid; $[\alpha]_D^{22}$ –5.2 (*c* 1.21, $CHCl_3$).

IR (film): 3478, 1721 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (s, 9 H), 1.12 (d, *J* = 7.4 Hz, 3 H), 1.86–2.12 (m, 3 H), 2.20–2.49 (m, 1 H), 4.18 (t, *J* = 3.4 Hz, 1 H), 4.75–4.84 (m, 2 H), 4.88–4.97 (m, 2 H), 5.37–5.54 (m, 1 H), 7.03–7.17 (m, 7 H), 7.25–7.43 (m, 9 H), 7.55–7.65 (m, 2 H), 7.74–7.78 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.6, 19.5, 27.1, 36.0, 38.9, 65.2, 74.2, 74.9, 117.3, 127.1, 128.3, 128.4, 128.6, 128.7, 129.7, 130.1, 132.9, 137.6, 139.9, 166.3.

Anal. Calcd for $C_{37}H_{42}O_4Si$: C, 76.78; H, 7.31. Found: C, 76.98; H, 7.42.

(4*S*,5*S*,6*R*,7*R*)-4-Benzoyloxy-6,7-isopropylidenedioxy-5-methyl-7-phenylhept-1-ene (20)

As described for **13**, treatment of **19** (0.150 g, 0.26 mmol) with 1 M TBAF in THF (0.30 mL, 0.30 mmol) in THF (10 mL), followed by workup of the reaction mixture and preparative TLC of the residue (silica gel, MeOH–$CHCl_3$, 1:19) furnished the pure desilylated product (0.071 g, 81%). This material (0.21 mmol) on stirring with PPTS (cat.) in 2,2-dimethoxypropane (1 mL) for 1 h, followed by isolation of the product and preparative TLC (silica gel, EtOAc–hexane, 1:9), afforded **20**.

Yield: 0.067 g (84%); colorless oil; $[\alpha]_D^{22}$ +11.2 (*c* 1.05, $CHCl_3$).

IR (film): 2923, 1718 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.2 Hz, 3 H), 1.28 (s, 3 H), 1.35 (s, 3 H), 1.82–1.89 (m, 1 H), 2.15–2.26 (m, 2 H), 4.15 (dd, *J* = 8.2, 3.6 Hz, 1 H), 4.72–4.85 (m, 2 H), 4.89–4.96 (m, 2 H), 5.28–5.52 (m, 1 H), 7.28–7.48 (m, 8 H), 7.95–8.10 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.2, 26.8, 27.0, 35.8, 40.1, 72.8, 79.5, 83.2, 108.6, 116.8, 127.2, 127.8, 128.5, 128.9, 133.0, 136.5, 168.1.

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.61; H, 7.25.

(4*S*,5*S*,6*R*,7*R*)-6,7-Isopropylidenedioxy-5-methyl-7-phenylhept-1-en-4-ol (21)

Hydrolysis of **20** (0.060 g, 0.16 mmol) with K_2CO_3 (0.048 g, 0.35 mmol) in MeOH (5 mL), followed by the usual workup of the reaction mixture and column chromatography of the residue (silica gel, 0–20% EtOAc–hexane), furnished pure **21**.

Yield: 0.031 g (72%); colorless liquid; $[\alpha]_D^{22}$ –3.4 (*c* 1.12, $CHCl_3$) [Lit.[9] $[\alpha]_D^{24}$ –3.34 (*c* 2.21, $CHCl_3$)].

IR (film): 3485, 2923 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 7.2 Hz, 3 H), 1.58 (s, 3 H), 1.62 (s, 3 H), 1.72–1.79 (m, 1 H), 2.07 (br s, 1 H), 2.12–2.28 (m, 2 H), 3.52–3.62 (m, 1 H), 4.12 (dd, *J* = 9.2, 2.4 Hz, 1 H), 4.72 (d, *J* = 9.2 Hz, 1 H), 4.99–5.16 (m, 2 H), 5.68–5.92 (m, 1 H), 7.26–7.42 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.5, 27.0, 27.2, 36.0, 39.5, 73.5, 79.9, 82.6, 108.7, 117.5, 126.8, 127.9, 128.5, 134.8, 137.5.

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.63; H, 8.61.

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