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Enantioselective synthesis of benzylbutyrolactones from 5-hydroxyfuran-2(5H)-one. New chiral synthons for dibenzylbutyrolactone lignans by a chemoenzymatic route

Jelle Brinksma, Hanneke van der Deen, Arjan van Oeveren and Ben L. Feringa *

Laboratory of Organic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

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A chemoenzymatic method is described for the asymmetric synthesis of benzylbutyrolactones. ($R$)-5-Acetoxyfuran-2(5H)-one (12) was obtained with ee > 99% in a multigram scale catalytic esterification using immobilized lipase PS. The addition of lithiated dithianes to chiral synthon 12 was followed by an effective multistep reduction to produce enantiomerically pure benzylbutyrolactones.

Introduction

Lignans are a class of natural compounds that can be found in almost any plant and an enormous variety of lignans are known today.1,2 The name lignan was introduced by Haworth in 1936.3 Numerous physiological properties are associated with lignans and the crude plant materials containing lignans have long been used in folk medicine. Typical examples of the biological responses observed are antitumor activity, anti-HIV activity and inhibitory effects on microsomal monoxygenases in insects.4 In general lignans are defined in four classes: dibenzylbutyrolactones (1) dioxabicyclo[3.3.0]octanes (2), 1-aryltetralins (3) and dibenzocyclooctadienes (4) (Fig. 1).

Fig. 1 Structures of lignans.

An impressive number of synthetic strategies to achieve the stereocontrolled formation of various structural classes of optically active dibenzylbutyrolactone lignans have been reported recently.5–11 In our laboratory short and flexible routes based on the readily available chiral synthon (5R)-(menthyloxy)furan-2(5H)-one (5) were developed (Scheme 1).2

The strategy was based on a tandem conjugate addition–alkylation using a benzylic nucleophile 6 and a benzylic electrophile 8 with full stereocontrol due to the presence of the chiral auxiliary group. After several reduction steps enantiomerically pure natural lignans were obtained.2 Using this strategy it is possible to achieve all naturally occurring structural classes of lignans. For example the stereocontrolled synthesis of enantiomerically pure (−)-hinokinin (10) was accomplished from (5R)-(menthyloxy)furan-2(5H)-one (5) in an overall yield of 37%. The conjugate addition of dithianes was used because, unfortunately, attempts to add organocuprates to 5-(menthyl oxy)furan-2(5H)-one were unsuccessful.12

Herewith we present full details of our new approach to lignan precursors avoiding stoichiometric use of chiral auxiliaries which is partly based on our previously reported strategy but exploiting ($R$)-5-acetoxyfuran-2(5H)-one (12) as a chiral starting material. Recently preliminary results on the resolution of 5-acetoxyfuran-2(5H)-one (12) in high yield and with ee’s > 98% were reported.13 It has been shown that lipase catalyzed transesterification of 5-acetoxyfuran-2(5H)-one is an attractive method to obtain the (S)-stereoisomers of furanones in enantiomerically pure form without the use of chiral auxiliaries.14 It is herewith disclosed that by reversal of the enzymatic protocol i.e. esterification instead of transesterification, enantiomerically pure ($R$)-12 is readily available in high...
yield. A chemoenzymatic route to benzyl butyrolactones by using (R)-5-acetoxyfuran-2(5H)-one (12) as chiral synthon has now been accomplished.

Results and discussion
The starting material for the enzymatic esterification is 5-hydroxyfuran-2(5H)-one (11). Vinyl acetate was used as the acyl donor for the enantioselective esterification of 11. Due to the spontaneous racemization, previously aldehyde 13a, of 5-hydroxyfuran-2(5H)-one (11) which contains a hemiacetal moiety, complete conversion to enantiomerically pure (R)-5-acetoxyfuran-2(5H)-one (12) can be achieved (Scheme 2).

![Scheme 2 Enzymatic esterification of 5-hydroxyfuran-2(5H)-one (11).](image)

The reaction was performed in diethyl ether in the presence of the enzyme Lipase R immobilized on Hyflo super cell. Lipase R is recommended in this esterification because it gives the enantiomerically pure R- enantiomer of 12 (ee > 98%). When enzyme PS, which gives the same enantiomer in a much faster reaction, was used a decreased ee was found (ee = 89%). For our application the reaction has been performed on a multigram scale (4 g). The progress of the reaction was monitored by 1H-NMR and the ee was determined by GC (see Experimental section). For a complete conversion extra enzyme was added during the reaction. After 10 d a conversion to 12 of 80% and an ee of >99% was found.

Although this procedure requires a long reaction time, major advantages are that the enzyme simply can be removed by filtration and reused, and after removal of the solvent by distillation, enantiomerically pure 12 is obtained. 5-Acetoxyfuran-2(5H)-one (12), obtained from the enzymatic esterification of 5-hydroxyfuran-2(5H)-one (11), was subsequently used as the chiral synthon in our new route to butyrolactones which are suitable precursors for a variety of lignans (Scheme 3).

![Scheme 3 Asymmetric 1,4-addition to (R)-5-acetoxyfuran-2(5H)-one (12).](image)

Introduction of the benzyl substituents involves stereoselective 1,4-addition of dithianes followed by reduction of the 5-acetoxy moiety. Therefore first the mono substituted furanones 17 were synthesized followed by removing the acetoxy and phenyl sulffide groups resulting in the benzylbutyrolactones which are suitable precursors for a variety of lignans (Scheme 3). The dithianes 15 were prepared by stirring a solution of the appropriate benzaldehyde with 2 equivalents of thiophenol and a catalytic amount of AlCl3 (Scheme 3).

The dithianes 15 were purified by crystallization and the results of the thioacetal formation are compiled in Table 1.

![Table 1 Dithianes 15 from benzaldehydes 14](image)

<table>
<thead>
<tr>
<th>Entry</th>
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<th>R1</th>
<th>R2</th>
<th>Dithiane</th>
<th>Yield (%)</th>
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<td>15a</td>
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<td></td>
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<td>2</td>
<td>H</td>
<td>15b</td>
<td></td>
<td></td>
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<td>3</td>
<td>OCH3</td>
<td>15c</td>
<td>CH3</td>
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<tr>
<td>4</td>
<td>OCH3</td>
<td>15d</td>
<td>OBn</td>
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<td>15f</td>
<td>H</td>
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</tbody>
</table>

* Yields of isolated pure products after crystallization. Product was available.

The dithianes 15 were prepared by stirring a solution of the appropriate benzaldehyde with 2 equivalents of thiophenol and a catalytic amount of AlCl3 (Scheme 3). The dithianes were purified by crystallization and the results of the thioacetal formation are compiled in Table 1.

Lithiated dithianes were generated by treatment of a solution of the dithianes 15 in THF with n-butyllithium (1.6 M in hexane) at −20 °C. This deprotonation step was followed by a conjugate addition of the lithiated dithianes to (R)-5-acetoxyfuran-2(5H)-one (12) at −80 °C. After 2 h the reaction was quenched with ammonium chloride and the 1,4-addition products 17 were obtained in 40–70% yield after column chromatography (Scheme 3). The results of the dithiane additions are summarized in Table 2.

The acetoxy moiety in 12 (Scheme 3) directs the lithiated dithianes to anti addition with respect to the acetoxy substituent. All benzylbutyrolactones 17 (Scheme 3) showed coupling constants JH4,5 < 2 Hz. The small coupling constants for the acetal proton (H4) in the 1H-NMR spectra are distinctive for the trans-relationship between the substituents at C4 and C5. For cis-4,5-disubstituted lactones coupling constants in the range of 3–6 Hz are found. Furthermore it should be emphasized that the acetoxy moiety in 12 is remarkably stable during the 1,4-addition reaction.
Optical rotations of the 4-substituted lactones were in agreement with those reported (see the Experimental section). Next the thioacetal and the 5-acetoxy groups have to be removed (Scheme 4). For the reductive desulfurization reactions of lactones 17 nickel boride was employed. Nickel boride was generated in situ from NiCl₂·6H₂O (5 equiv.) and NaBH₄ (20 equiv.) in MeOH in the presence of the 1,4-addition products 17. By using an excess of NiCl₂ complete desulfurization was achieved. The acetoxy substituted lactone intermediates 20 are further reduced by sequential addition of aqueous KOH, NaBH₄ and HCl in a one pot reduction procedure. The function of KOH is twofold: a) it reduces the catalytic activity of the nickel boride and therefore the additional NaBH₄ is not immediately decomposed to H₂ and boric acid and b) it opens the lactone 18 to the aldehyde 19, which is subsequently reduced with NaBH₄. The results with several substituted lactones are summarized in Table 3.

In conclusion it has been shown that (R)-5-acetoxyfuran-2(5H)-one 11 was synthesized following a literature procedure. Yield 80%; ¹H-NMR (200 MHz); 5.71 (br, 1H, OH), 6.18 (s, 1H, CH(OH)), 6.22 (d, δ = 6.0 Hz, 1H, CHCH), 7.31 (d, δ = 6.0 Hz, 1H, CHCH); ¹³C-NMR (200 MHz); 99.1 (CH), 124.3 (CH), 152.7 (CH), 172.2 (C).

Experimental

General remarks

¹H-NMR data were recorded on a Varian Gemini 200 or 300 MHz and CDCl₃ was used as solvent unless stated otherwise. Chemical shifts are denoted in δ units (in ppm) relative to the solvent and converted to the TMS scale using (CDCl₃) = 7.26 ppm. The chemical shifts (ppm) are positive in lowfield direction. Coupling constants are reported in hertz (Hz). The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and br (broad). ¹³C-NMR spectra were recorded on a Varian Gemini 200 (50.32 MHz) spectrometer. Chemical shifts are denoted in units (in ppm) relative to (CDCl₃) = 75.48 ppm. The ee’s of the products of enzymatic esterification were determined with a 50 m × 0.25 mm WCOT fused silica, CP cycloextrin B-2,3,6-M-19 column. The lipase R and lipase PS were obtained from Amano Enzyme Europa Ltd.

5-Hydroxyfuran-2(5H)-one 11

5-Hydroxyfuran-2(5H)-one 11 was synthesized following a literature procedure. Yield 80%; ¹H-NMR (200 MHz); 5.71 (br, 1H, OH), 6.18 (s, 1H, CH(OH)), 6.22 (d, δ = 6.0 Hz, 1H, CHCH), 7.31 (d, δ = 6.0 Hz, 1H, CHCH); ¹³C-NMR (200 MHz); 99.1 (CH), 124.3 (CH), 152.7 (CH), 172.2 (C).

Immobilization of lipase R

Lipase R (5.5 g) and Hylfo Super Cell [HSC, diatomaceous earth (SiO₂)] (18.3 g) were mixed. After adding 18.3 mL of a phosphate buffer of pH 7 the mixture was stirred well during 15 min. The enzyme mixture was spread on a Petri dish and allowed to dry in the air for 2 d and the immobilized lipase was collected.

Enzymatic esterification of 5-hydroxyfuran-2(5H)-one 11

5-Hydroxyfuran-2(5H)-one 11 (4.0 g, 40 mmol) was dissolved in 600 mL of diethyl ether. To this mixture 100 mL of vinyl acetate and immobilized lipase R (4 g) were added. The mixture was stirred at room temperature. At regular intervals samples were taken, filtered over Celite and the conversion was determined by ¹H-NMR spectroscopy. The enzyme was recovered by filtration, the solvent was evaporated under reduced pressure and the crude product purified by column chromatography (SiO₂, hexane–EtOAc 2:1), to give pure 12 as a yellow oil (4.00 g, 28.17 mmol, 70%). ¹H-NMR (200 MHz); 5.23 (1H, CHCH), 7.31 (d, δ = 6.0 Hz, 1H, CHCH);

General procedure for thioacetal formation: 5-[bis(phenylthio)-methyl]-1,3-benzodioxine 15a

The thioacetals were synthesized according to a literature procedure. Treatment of 7.5 g (50 mmol) of 14a and 12.0 g (109 mmol) thiophenol pure 15a (14.4 g, 41 mmol, 82%) was obtained after one crystallization from EtOH. ¹H-NMR (200 MHz); 5.36 (s, 1H, CH(SPh)), 5.95 (s, 2H, OCH₂(CH₃)), 6.63–6.99 (m, 3H, Ar), 7.23–7.38 (m, 10H, 2 × Ph); ¹³C-NMR (200 MHz); 60.0 (CH), 101.1 (CH), 107.7 (CH), 109.7 (CH), 121.4 (CH), 127.6 (CH), 128.7 (CH), 132.2 (CH), 132.8 (CH), 133.4 (CH).

Bis(phenylthio)methylbenzene 15b

The bis(phenylthio)methylbenzene 15b was synthesized according to the general procedure for the preparation of 15a, starting from 5.3 g (50 mmol) of 14b. Pure thioacetal 15b (12.3 g, 40 mmol, 80%) was obtained after one crystallization from EtOH. ¹H-NMR (200 MHz); 5.42 (s, 1H, CH(SPh)), 7.22–7.37 (m, 15H, 3 × Ph); ¹³C-NMR (200 MHz); 60.3 (CH), 127.7 (CH), 128.7 (CH), 132.2 (CH), 133.4 (CH).

Table 3 Lactones 21 via one-pot conversion of dithiane adducts

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Compound</th>
<th>Yield (%)*</th>
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<td>2</td>
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</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>H</td>
<td>21e</td>
<td>46</td>
</tr>
</tbody>
</table>

* Yields of pure isolated products after column chromatography (SiO₂, hexane–ethyl acetate).
127.8 (CH), 128.0 (CH), 128.4 (CH), 128.8 (CH), 132.5 (C), 134.5 (C), 138.0 (C).

4. [bis(phenylthio)methyl]-1,2-dimethoxybenzene 15c. Synthesized according to the general procedure for the preparation of 15a, starting from 10.0 g (60 mmol) of 14c. Pure thiacetal 15c (17.7 g, 48 mmol, 80%) was obtained after one crystallization from EtO–EtOAc. 1H-NMR (200 MHz): 3.81 (s, 3H, OCH3), 3.85 (s, 3H, OCH3), 5.42 (s, 1H, CH(SPh)), 6.71–6.90 (m, 3H, Ar), 7.23–7.39 (m, 10H, 2 × Ph); 13C-NMR (200 MHz): 23 56.6 (CH3), 59.8 (CH), 110.4 (CH), 121.0 (CH), 127.6 (CH), 128.7 (CH), 131.8 (C), 132.4 (CH), 148.7 (C).

4-Benzyloxy-1-[bis(phenylthio)methyl]-3-methoxybenzene 15d. Synthesized according to the general procedure for the preparation of 15a, starting from 12.4 g (50 mmol) of 14d. Pure thiacetal 15d (16.2 g, 39 mmol, 78%) was obtained after one crystallization from EtO–hexane. 1H-NMR (200 MHz): 3.81 (s, 3H, OCH3), 5.12 (s, 2H, OCH2Ph), 5.38 (s, 1H, CH(SPh)), 6.71–6.90 (m, 3H, Ar), 7.22–7.44 (m, 15H, 3 × Ph); 13C-NMR (200 MHz): 55.7 (CH3), 59.9 (CH), 70.8 (CH), 111.1 (CH), 113.2 (CH), 120.0 (CH), 127.2 (CH), 127.6 (CH), 127.7 (CH), 128.4 (CH), 128.7 (CH), 132.4 (CH), 132.5 (CH), 134.4 (C).

[4(RSR)]-4-[(3,4-Dimethoxyphenyl)bis(phenylthio)methyl]dihydrofuran-2(3H)-one 17e. Synthesized according to the procedure for the preparation of 17a, starting from 15e (2.59 g, 7.04 mmol) and (R)-5-acetoxyfuran-2(5H)-one (12, 1.00 g, 7.04 mmol). Pure 17e (oil) (1.73 g, 3.39 mmol, 48%) was obtained after purification by chromatography (SiO2, hexane–EtOAc 2:1); [α]D20 = -15 (c 1.13, CHCl3); 1H-NMR (300 MHz): 1.98 (s, 3H, OCH3), 2.71–3.03 (m, 3H, CH2CH3), 3.67 (s, 3H, OCH3), 3.78 (s, 3H, OCH3), 6.64 (d, J = 8.8 Hz, 1H, Ar), 7.11–7.29 (m, 11H, Ar); 13C-NMR (200 MHz): 23 20.6 (CH3), 31.2 (CH2), 48.9 (CH3), 55.6 (CH3), 55.7 (CH2), 70.5 (C), 95.9 (CH), 110.1 (CH), 113.0 (CH), 120.6 (CH), 128.7 (CH), 128.7 (CH), 129.1 (CH), 129.6 (C), 130.7 (C), 135.0 (CH), 143.8 (C), 148.9 (C), 164.8 (C), 174.0 (C). Elemental analysis requires for C23H20O2S2: C, 63.53, H, 5.10, S, 12.55. Found: C, 63.55, H, 5.23, S, 12.51%.

[4(RSR)]-4-[(3-Chlorobenzylidene)phenylthio)methyl]dihydrofuran-2(3H)-one 17f. Synthesized according to the procedure for the preparation of 17a, starting from 15f (3.50 g, 10.56 mmol) and (R)-5-acetoxyfuran-2(5H)-one (12, 1.50 g, 10.56 mmol). Pure 17f (2.10 g, 4.34 mmol, 41%) was obtained after purification by chromatography (SiO2, hexane–EtOAc 2:1); [α]D20 = -20 (c 0.71, CHCl3); 1H-NMR (300 MHz): 2.08 (s, 3H, OCH3), 2.89 (d, J = 6.59 Hz, 2H, CH2CH3), 3.20 (t, J = 1.47 Hz, 1H, CHCH3), 6.83 (d, J = 1.47 Hz, 1H, CHOCOAc), 7.22–7.55 (m, 14H, Ar); 13C-NMR (200 MHz): 23 20.6 (CH3), 31.3 (CH2), 48.5 (CH3), 69.2 (C), 95.8 (CH), 127.0 (C), 128.4 (CH), 128.8 (CH), 129.2 (CH), 129.5 (CH), 129.6 (CH), 132.8 (CH), 134.3 (C), 135.7 (CH), 135.8 (C), 146.8 (C), 147.6 (C), 148.1 (C), 168.4 (C), 174.0 (C). Elemental analysis requires for C24H17Cl2O2S: C, 61.98, H, 4.34, S, 13.22, Cl, 7.23. Found: C, 61.99, H, 4.46, S, 13.13, Cl, 7.43%.

General one pot procedure for thiacetal desulfurization, acetal hydrolysis, aldehyde reduction and ring closure: (3S)-4-(1,3-benzodioxol-5-yl)dimethyl]dihydrofuran-2(3H)-one 21a

A stirred solution of 17a (1.00 g, 2.02 mmol) and NiCl2·6H2O (2.32 g, 10 mmol) in 5 mL of THF and 50 mL of CH2OH was...
cooled to 0 °C. NaBH₄ (1.54 g, 40 mmol) was added in small portions in about 20 min at such a rate that the temperature was kept below 10 °C. Immediately after the last portion of NaBH₄ was added, 20 mL of a 2 M aqueous solution of KOH (40 mmol) was added at once, followed by additional NaBH₄ (0.38 g, 5 mmol) and the mixture was allowed to warm to room temperature while stirring for 2 h. The black precipitate was removed by filtration over Celite and the filtrate was acidified with 2 M aqueous HCl to pH = 1. Subsequently MeOH and THF were removed in vacuo. To the remaining suspension was added 40 mL of water and the mixture was extracted with CH₂Cl₂ (3 × 60 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The remaining oil was purified by chromatography (SiO₂, hexane–EtOAc 2:1) to give pure 21a (240 mg, 1.15 mmol, 56%) as a colorless viscous oil. [α]D₂⁰ = +5.8 (c 0.82, CHCl₃) [lit. 24 [α]D₂⁰ = +5.2 (c 1.14, CHCl₃)]; ¹H-NMR (200 MHz): 2.26 (dd, J = 17.6, 7.0 Hz, 1H, CH₂CH₂CH₃), 2.59 (dd, J = 17.4, 8.0 Hz, 1H, CH₂CH₂CH₃), 2.61–2.85 (m, 3H, CH₂CH₂CH₃), 4.01 (dd, J = 9.3, 6.2 Hz, 1H, CH₂Ar), 4.32 (dd, J = 9.2, 6.6 Hz, 1H, CH₂Ar), 5.94 (s, 2H, OCH₂O), 6.59 (dd, J = 7.8, 1.8 Hz, 1H, Ar), 6.63 (d, J = 1.5 Hz, 1H, Ar), 6.74 (d, J = 8.1 Hz, 1H, Ar); ¹³C-NMR (200 MHz): 33.9 (CH₂), 37.1 (CH), 38.4 (CH₂), 72.3 (CH₂), 100.9 (CH₂), 108.3 (CH), 108.7 (CH), 121.5 (CH₁), 131.8 (C₁), 146.3 (C), 147.8 (C), 176.8 (C). Elemental analysis calculated for C₂₁H₂₄O₂: C, 65.5; H, 5.5. Found: C, 64.90, H, 5.95.

(3S)-4-Benzylfuran-2(3H)-one 21b. Synthesized according to the procedure for the preparation of 21a, starting from 17b (0.42 g, 0.93 mmol), pure 21b (90 mg, 0.51 mmol, 55%) was obtained after purification by column chromatography (SiO₂, hexane–EtOAc 2:1) as a colorless viscous oil, [α]D₂⁰ = +6.3 (c 2.18, EtOH) [lit. 25 [α]D₂⁰ = +6.7 (c 0.57, EtOH)]; ¹H-NMR (200 MHz): 2.21 (dd, J = 17.4, 7.0 Hz, 1H, CH₂CH₂CH₃), 2.53 (dd, J = 17.6, 7.7 Hz, 1H, CH₂CH₂CH₃), 2.54–2.81 (m, 3H, CH₂CH₂CH₃), 3.96 (s, 3H, OCH₃), 4.28 (dd, J = 7.0, 9.2 Hz, 1H, Ar), 7.07–7.27 (m, 5H, Ph); ¹³C-NMR (200 MHz): 34.0 (CH₂), 36.9 (CH), 38.7 (CH₂), 72.5 (CH₂), 126.7 (CH₂), 128.5 (CH), 131.8 (C₁), 176.8 (C). Elemental analysis calculated for C₂₄H₂₂O₂: C, 75.0, H, 6.82. Found: C, 74.58, H, 6.87%. HRMS Caled. for C₂₄H₂₂O₂: 358.1604. Found: 358.1604.

(3S)-4-[3,4-Dimethoxyphenyl)methyl]dihydrofuran-2(3H)-one 21c. Synthesized according to the procedure for the preparation of 21a, starting from 17e (0.42 g, 0.87 mmol) pure 21c (80 mg, 0.38 mmol, 46%) was obtained after purification by column chromatography (SiO₂, hexane–EtOAc 2:1) as a colorless viscous oil, [α]D₀ = +5.1 (c 1.08, CHCl₃); ¹H-NMR (300 MHz): 2.13–2.80 (m, 5H, CH₂CH₂CH₃), 3.89–3.96 (m, 1H, CH₂Ar), 4.20–4.27 (m, 1H, CH₂Ar), 6.93–7.24 (m, 4H, Ar); ¹³C-NMR (200 MHz): 33.9 (CH₂), 36.9 (CH) 38.3 (CH₂), 38.7 (CH₇), 72.2 (CH₂), 72.5 (C), 126.7 (C), 126.9 (CH₂), 128.5 (CH), 128.6 (CH), 128.7 (CH), 130.0 (C), 134.4 (C), 138.1 (C), 140.1 (C), 176.5 (C). HRMS requires for C₂₄H₂₂O₂Cl: 210.045. Found: 210.04.

References
23 Not all signals were resolved due to overlap.

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