used as an internal lock. Residual protio CH_2Cl_2 solvent absorbances were used as internal secondary references (relative to tetramethylsilane). The internal reference in D_2O solutions was 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt.

Diastereomeric ratio determinations in CD_2Cl_2 solutions were performed by integration of the externally diastereotopic ^1H NMR N-CH_3 signals. An indication of the diastereomeric ratio in D_2O solutions was obtained by integration of the externally diastereotopic ^{13}C NMR N-CH_3 signals.

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An Unusual Stereochemical Outcome of a Peroxyacid Epoxidation Reaction: Stereospecific Synthesis of (4′*R*)-Spiro[oxirane-2,4′-5′α-cholestan-3′β-ol]

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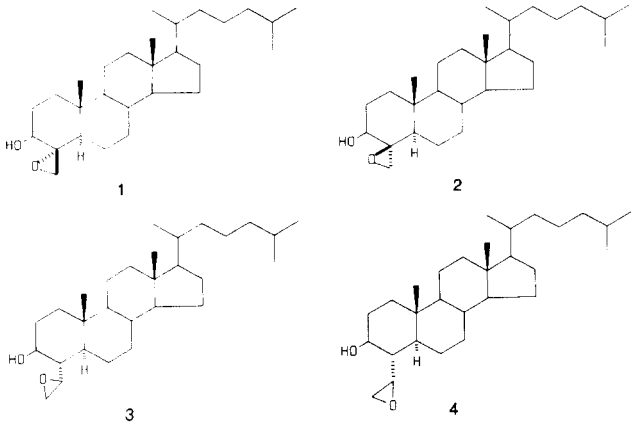
The epoxidation of 4-methylene-5α-cholestan-3β-ol (**10**) with *m*-chloroperoxybenzoic acid or with (+)- or (−)-diethyl tartrate/*tert*-butyl hydroperoxide–titanium tetraisopropoxide leads stereospecifically to (4′*R*)-spiro[oxirane-2,4′-5′α-cholestan-3′β-ol] (**1**). The relative stereochemistry of **1** has been established by X-ray crystallography. The lack of directional effect by the hydroxyl group in the epoxidation of the allylic alcohol **10** is unusual.

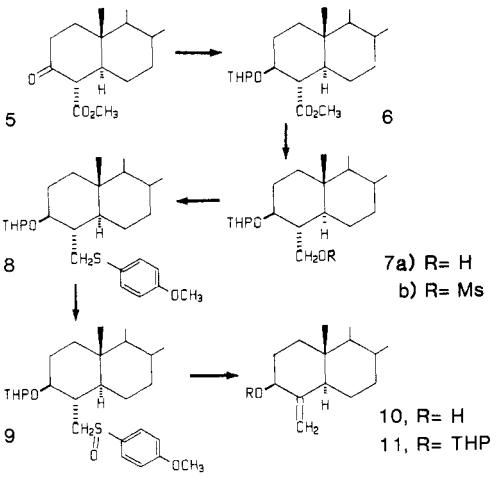
As part of a program aimed at the development of inhibitors of the cholesterol biosynthetic enzyme 4-methyl sterol oxidase[1] we required (4′*R*)- and (4′*S*)-spiro[oxirane-2,4′-5′α-cholestan-3′β-ol (**1** and **2**). We have shown[2]



previously that the homologous 4′α-(2(*S*)-oxiranyl)- and 4′α-(2(*R*)-oxiranyl)-3′β-hydroxy-5′α-cholestanes (**3** and **4**) are potent inhibitors of this enzyme system. This report describes the stereospecific synthesis of (4′*R*)-spiro[oxirane-2,4′-5′α-cholestan-3′β-ol] (**1**) and the assignment of its relative stereochemistry by X-ray crystallography.

The allylic alcohol **10** (Chart I) was chosen as the most convenient precursor of the spiro epoxides **1** and **2**. Alternative precursors such as 4-methylene-5α-cholestan-3-one[3] or 4-oxo-5α-cholestan-3β-ol are labile or difficult to homologate. It was intended to generate the epoxides **1** and **2** from the allylic alcohol **10** by appropriate asymmetric epoxidation procedures.[4] There is ample precedent for hydroxy-assisted organic peroxyacid epoxidation of allylic alcohols to furnish epoxides in which the stereochemistry of the epoxide is determined by the configuration of the hydroxy group.[5] Peroxyacid oxidation of 4-methylene-5α-cholestan-3β-ol (**10**) might therefore be expected to furnish predominantly the (4′*S*)-spiro epoxide

Chart I



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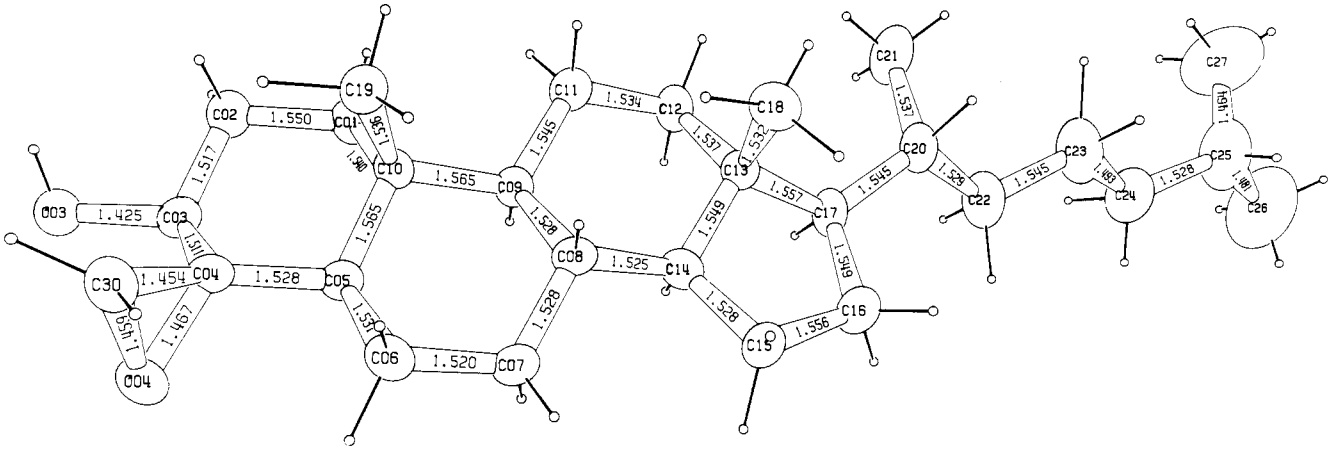

Figure 1. ORTEP[8] drawing showing crystal conformation and bond lengths. Esd's of bond lengths are in the range 0.008–0.012 Å for the steroid nucleus but become as large as 0.022 Å at the end of the side chain.

2. We also planned to apply the Sharpless asymmetric epoxidation method[6] utilizing (−)-diethyl tartrate and *tert*-butyl hydroperoxide.

A method for making 4-methylene-5α-cholestan-3β-ol, described by Djerassi et al.,[7] involves lithium diisopropylamide rearrangement of 3β,4β-epoxy-4α-methylcholestane, but the latter compound is not readily accessible, and the route was not pursued. Instead we developed a very high yield reaction sequence leading to the allylic alcohol **10** (Chart I). The key step in the sequence involves the thermal elimination of sulfinic acid from a steroidal sulfoxide. Thus, sodium borohydride reduction of 4α-carbomethoxy-5α-cholestan-3-one (**5**) and chromatographic separation of the resulting 3α- and 3β-alcohols were followed by conversion of the pure 3β-hydroxy compound to the 3β-tetrahydropyranyl (THP) ether (**6**) and then reduction with lithium aluminum hydride to give 4α-(hydroxymethyl)-5α-cholestan-3β-ol 3-THP ether (**7a**). To ensure the survival of the THP protecting group, the reduction product was isolated under strictly neutral conditions. Compound **7a** was converted to the corresponding mesylate **7b** and then, by a displacement reaction with the sodium salt of 4-methoxybenzenethiol, to the thioether **8**. Oxidation of the thioether **8** with *m*-chloroperoxybenzoic acid gave the sulfoxide **9**, which without purification was heated in xylene under reflux to furnish a mixture comprising mainly the desired allylic alcohol **10**, with the THP-protected derivative **11** as a minor component. The nearly complete loss of the THP ether group was presumably due to the sulfinic acid produced in the reaction. When the sulfoxide was refluxed in xylene containing anhydrous potassium carbonate, only 4-methylene-5α-cholestan-3β-ol THP ether (**11**) was obtained. Furthermore, chromatographic separation was now unnecessary, and removal of xylene followed by crystallization gave directly compound **11**, in excellent yield.

The *m*-chloroperoxybenzoic acid epoxidation of the free 3β-hydroxy-4-methylene steroid **10** was thought likely to furnish (4'S)-spiro[oxirane-2,4'-5'α-cholestan-3'β-ol] (**2**) as the major stereoisomer. On the other hand, protection of the 3β-hydroxy group followed by peroxyacid oxidation was expected to result in decreased diastereoselectivity. On this basis we epoxidized both the THP-protected and the free allylic alcohol, **11** and **10**, respectively, with *m*-chloroperoxybenzoic acid. The corresponding epoxides were obtained in very good yield and proved to be identical after the removal of the THP protecting group from the epoxide derived from **11**. Exactly the same result was obtained by *m*-chloroperoxybenzoic acid oxidation of 4-methylene-5α-cholestanyl 3β-acetate followed by hydrolysis of the 3β-acetoxy group. In each case, the epoxidation gave exclusively the (4'R)-spiro isomer (**1**), a rather surprising outcome based on the expected directive effect of the 3β-hydroxy group.

By the use of either (+)- or (−)-diethyl tartrate in the *tert*-butyl hydroperoxide and titanium tetraisopropoxide epoxidation of allylic alcohols, selective diastereofacial oxidation was achieved by Sharpless et al.[6] We applied this procedure to compound **10** and obtained the (4'R)-spiro epoxide **1** as the only oxidation product from reaction with either (+)- or (−)-diethyl tartrate. The reaction with (−)-diethyl tartrate was noticeably slower and gave only about 40% conversion during the reaction period.

Stereochemistry

The constitution of spiro epoxide **1** was readily established by routine spectroscopic methods (IR, MS, and ^{1}H NMR). The hydroxyl group at C-3 was known to be in the β-configuration but the configuration of the epoxide group at C-4 had to be unambiguously assigned. Extensive NMR investigations, which included NOESY, failed to yield results that could permit unequivocal assignment of stereochemistry. The stereochemistry was then investigated by X-ray crystallography.

Crystallographic Results

The crystal conformation of **1**, assuming the known steroid absolute conformation, is shown in the ORTEP[8] drawing in Figure 1, and it may be seen that the configuration of the spiro ring is 4α. All ring junctions are trans and the whole molecule is fairly flat; apart from the methyl and the epoxy ring atoms, all heavy atoms are within 0.6 Å of a least-squares plane. An alternative description is that the two planes consisting of the ring atoms and the side-chain atoms are at about 25° to each other. These two planes have individual maximum deviations of 0.6 and 0.3 Å, respectively. The D ring is fairly close to being in the half-chair conformation and has Altona–Geise–Romers parameters[9] $\phi_m = 46.6°$ and $\Delta = 6.7°$. The magnitude of ϕ_m is quite usual in steroids.[10] A drawing of the molecule

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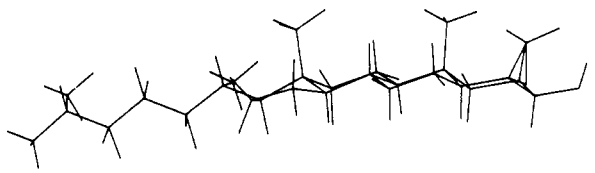

Figure 2. Line drawing of the molecule perpendicular to steroid nucleus showing the near planarity of this part of the molecule.

from the side showing the near planarity is given as Figure 2.

The elongated molecules, approximately 18 × 5.5 × 4 Å, are linked by reasonably strong intermolecular O3–H···O4 hydrogen bonds along the screw axis. The dimensions of the hydrogen bond are O···O = 2.847 (9) Å, H···O = 2.04 (6) Å, and O–H···O = 154 (5)°. A packing diagram is given as Figure 3 (Supplementary Material), which shows some hydrogen bonds and which also indicates the fairly tight packing of the rings in contrast to the very loose packing of the side chain. The lack of strong nonbonded interactions among the chain atoms may explain the large thermal parameters observed.

Summary

The usual directive effect of the hydroxyl group in allylic alcohol epoxidation by peracid is not observed in the *m*-chloroperbenzoic acid epoxidation of the 3β-hydroxy-4-methylene compound **10**. Unexpectedly, oxygen was delivered to the double bond exclusively from the α-face of the steroid. Presumably the unfavorable steric interactions of a β-face peracid complex with the 19-methyl group and with the 2β- and 6β-hydrogen atoms provide the basis for this outcome.

Experimental Section

General Methods. Melting points were obtained on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 462 spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ solution using either an IBM FT80 or a Varian XL-200 spectrometer. Mass spectra were obtained on an LKB-9000 instrument. HPLC separations were performed on a Waters 6000 instrument using a Whatman semipreparative column. Column chromatography was performed on silica gel according to Still's method.[11]

(4*R*)-(Hydroxymethyl)-5α-cholestan-3β-ol 3-Tetrahydropyranyl Ether (7). To a solution of 4α-carbomethoxy-5α-cholestan-3β-ol (**5**, 17.6 g, obtained via $NaBH_4$ reduction of the corresponding 3-ketone) in dry THF (250 mL) were added dihydropyran (16.20 mL) and pyridinium *p*-toluenesulfonate (2.03 g). The mixture was stirred for 25 h and the solvent was removed in vacuo. The oily crude product was dissolved in ether (800 mL), washed with saturated $NaHCO_3$ (2 × 400 mL) and then with an equal volume of brine, and dried (Na_2SO_4). After the solvent was removed in vacuo, the crude solid product (**6**) was dried (high vacuum, 4 h). It was redissolved in anhydrous ether (350 mL), treated with lithium aluminum hydride (3.5 g) at 0 °C in one portion, and then stirred at room temperature. After 2 h it was cooled (ice-water bath) and excess lithium aluminum hydride was destroyed by the dropwise addition of ethyl acetate, followed by dropwise addition of saturated Na_2SO_4 to coagulate the aluminate. The mixture was dried (Na_2SO_4), filtered, and evaporated in vacuo. Crystallization from acetone gave 4α-(hydroxymethyl)-5α-cholestan-3β-ol 3-THP ester (**7**, 19.7 g): mp 104–106 °C; NMR (200 MHz) δ 4.76 and 4.66 (THP-H), 4.05–3.34 (m, 1, 3α-H); MS *m/z* 502 (M$^+$), 484, 430, 418, 402, 384, 370.

4-Methylene-5α-cholestan-3β-ol (10). 4α-(Hydroxymethyl)-5α-cholestan-3β-ol 3-THP ether (**7**, 4.0 g) in CH_2Cl_2 (120 mL) was converted to the corresponding mesylate by reaction with Et_3N (1.44 mL) and methanesulfonyl chloride (0.71 mL) at 0 °C followed by stirring at room temperature for 1 h. The crude mesylate in dry THF (30 mL) was added to the sodium salt of 4-methoxybenzenethiol generated from NaH (0.53 g, 50% dispersion in oil) and 4-methoxybenzenethiol (1.18 mL) in THF (15 mL). Anhydrous DMF (60 mL) was added and the solution was refluxed for 3 h, cooled to room temperature, and poured into a large excess of 5% aqueous NaOH. It was extracted with ether (3 × 200 mL), and the organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford the crude steroidal thioether **8**. A solution of this crude thioether **8** in dry CH_2Cl_2 (200 mL) at −20 °C was treated with *m*-chloroperoxybenzoic acid (82%, 1.42 g). After 5 min the solution was diluted with CH_2Cl_2 (300 mL), washed several times with saturated $NaHCO_3$ and then with brine, and dried (K_2CO_3). The solvent was removed in vacuo and the crude sulfoxide (**9**, 4.3 g) was refluxed for 2 days in *o*-xylene (100 mL) containing anhydrous K_2CO_3 (6.0 g). The *o*-xylene was removed in vacuo and dichloromethane (300 mL) was added. The mixture was filtered and evaporated, and the residue was recrystallized from acetone to give 4-methylene-5α-cholestan-3β-ol THP ether (**11**, 3.12 g, 79%): mp 120–122 °C; ^{1}H NMR δ 5.25 (br s, 1), 4.92 (br s, 1), 4.82 (t), 4.60 and 4.55 (br s), 3.94 and 3.45 (m); MS *m/z* 484 (M$^+$) 469, 429, 400, 384.

Removal of the THP ether group from **11** using 10% aqueous HCl (10 mL) in THF (50 mL) at reflux for 45 min followed by crystallization from acetone afforded 4-methylene-5α-cholestan-3β-ol (**10**): mp 134–136 °C; IR (KBr) 3600, 1645 cm^{-1}; ^{1}H NMR (80 MHz) δ 5.03 (br s, 1), 4.61 (br s, 1); MS *m/z* 400 (M$^+$). Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.87; H, 12.25.

When anhydrous K_2CO_3 was left out during the reflux of the sulfoxide in xylene, 4-methylene-5α-cholestan-3β-ol (**10**) and the corresponding THP-protected derivative (**11**) were obtained after chromatographic separation in yields of 50% and 12%, respectively.

(4′*R*)-Spiro[oxirane-2,4′-5′α-cholestan-3′β-ol] (1). To a solution of 4-methylene-5α-cholestan-3β-ol (**10**, 0.14 g) in dry CH_2Cl_2 (10 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (82%, 0.16 g). The solution was allowed to warm to room temperature and after 1.5 h of stirring, ether (50 mL) was added. The ether extract, after being washed several times with 10% aqueous $NaHCO_3$ and then with brine, was dried (anhydrous K_2CO_3) and evaporated in vacuo. The product was crystallized from acetone to afford (4′*R*)-spiro[oxirane-2,4′-5′α-cholestan-3′β-ol] (1, 0.124 g, 85%): mp 152–153 °C; IR (KBr) 3430 cm^{-1}; ^{1}H NMR (80 MHz) 3.72 (q, 1, *J* = 5.4, 11.2 Hz, 3α-H), 3.00 (d, 1, *J* = 4.8 Hz), 2.65 (d, 1, *J* = 4.8 MHz); MS *m/z* 416 (M$^+$) 386, 262. Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.62; H, 11.49.

Crystallography: colorless monoclinic prisms; $P2_1$; reduced cell: *a* = 7.7849 (6) Å, *b* = 6.5800 (4) Å, *c* = 25.5989 (16) Å, β = 97.392 (5)° (from least-squares refinement of 17 reflections; ±θ; θ = 20–25°; Cu Kα X-radiation; λ = 1.5418 Å). The phase problem was highly intractable; programs of MITHRIL[12] in practically every combination and level of difficulty allowed by the system, including MAGEX, RANTAN, and YZARC, with and without active and passive quartet inequalities, gave *E* maps showing "chicken wire" with apparently up to nine fused rings. Finally, 300 sets of random phases were generated for the 117 planes occurring most often in negative quartets with *B* values greater than 0.3, and the sets were used as input for the tangent formula to generate 500 phases. The best solutions, giving most weight to NQEST,[13] showed chicken-wire *E* maps again but there was sufficient lack of symmetry to allow the choice of 22 atomic positions for a trial model, which was expanded by Fourier methods to include the entire molecule. Refinement was carried out with the intensity data divided into two groups corresponding to the two crystals used. Indications of all H atoms were found in a difference map although it proved expedient to hold the thermal parameters of chain H atoms and the positional parameters of the terminal methyl H atoms constant. The H atom on O3 was found on the line con-

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necting it to an O4 atom in a symmetry-related molecule. The O···O distance is 2.847 (9) Å and this fact further confirms the assignment of atomic labels to the epoxide atoms, which was first based on the heights of peaks in the E map, then on the fact that the assignment produced very similar thermal factors for the external atoms O4 and C30, and finally on the detection of peaks attributable to H atoms at the calculated positions for C30 (full-matrix least-squares refinement, heavy atoms anisotropic, XTAL[14] refinement program, final R factor = 0.07). Fuller experimental data, tables of observed and calculated structure factors, and refinement parameters are available as Supplementary Material.

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Supplementary Material Available: A packing diagram, full refinement parameters, and a table of molecular dimensions (5 pages); observed and calculated structure factors (13 pages). Ordering information is given on any current masthead page.

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Larreantin, a Novel, Cytotoxic Naphthoquinone from *Larrea tridentata*

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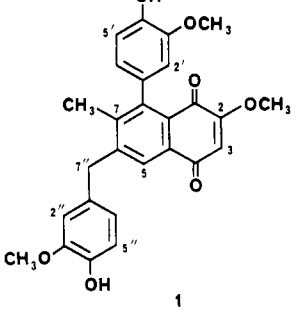
The structure of larreantin (1), a novel, cytotoxic naphthoquinone derivative from the roots of *Larrea tridentata* (Zygophyllaceae), has been deduced through a combination of spectroscopic techniques, with particular use being made of the NOE difference and CSCM 1D and selective INEPT techniques. Larreantin represents a new class of natural products in which the naphthoquinone ring may be formed through oxidative cyclization of two phenylpropene units with a preformed benzoquinone.

In previous work we have described the isolation of several new triterpenes[1] and lignans[2,3] from the stems and leaves of the creosote bush *Larrea tridentata* (DC) Coville (Zygophyllaceae), a plant under investigation for its fertility regulating principles. With a view to isolating additional quantities of nor-3′-demethoxyisoguaiacin, the active antifertility principle[3] from the above ground parts, a phytochemical investigation of this material was initiated. At the same time we also examined the methanol extract of the root of this plant for its cytotoxic potential in both the KB and P-388 assays.[4,5] The methanol extract of the plant was subjected to flash chromatography on Celite, eluting with $CHCl_3$/MeOH (98:2) and a portion of the resulting cytotoxic (P-388, ED_{50} 0.57 μg/mL) fraction was chromatographed on silica gel to afford nine fractions, all of which displayed cytotoxic activity in the P-388 test system. Further chromatography of one of these fractions (ED_{50} 0.62 μg/mL) by LPLC on silica gel afforded 16 fractions, the most polar of which gave larreantin on crystallization.

Larreantin, mp 204–206 °C, displayed a molecular ion at m/z 460, analyzing for $C_{27}H_{24}O_7$, and only the fragment ions at m/z 429 ($M^+ - 31$) and 137 were of any significance in the EIMS. The UV spectrum displayed maxima at



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241.5, 259, 286, and 348 nm, and the IR spectrum showed strong hydroxyl group absorption at 3400 cm^{-1}, together with carbonyl bands at 1687 and 1649 cm^{-1}. Other strong absorption bands were observed at 1619, 1514, 1340, 1284, 1255, 1239, 1212, and 1088 cm^{-1}.

The ^1H NMR spectrum indicated the presence of an aromatic methyl group (δ 2.024), a benzylic methylene (δ 4.057), three aromatic methoxy groups at δ 3.792, 3.818, and 3.837, and eight aromatic protons. Six of these protons were observed in two 1,2,4-(or 1,3,4-)trisubstituted aromatic systems, with two singlet aromatic protons at δ 6.083 and 7.983. The final two protons were observed as exchangeable phenolic protons at δ 5.697 and 5.781. The interrelationships of the aromatic protons were determined through a homonuclear COSY experiment. Thus the ortho-coupled doublet at δ 6.954 was coupled to a doublet of doublets (J = 2.1, 7.7 Hz) at δ 6.499, which was itself coupled to a doublet (J =2.1 Hz) at δ 6.539. The corresponding coupled protons in the second aromatic unit

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