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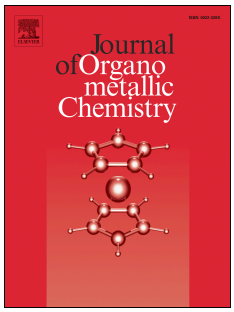

Catalytic cyclometallation of allylbenzenes by $EtAlCl_2$ and Mg as new route to synthesis of dibenzyl butane lignans

Lyudmila V. Parfenova, Tatyana V. Berestova, Pavel V. Kovyazin, Aydar R. Yakupov, Ekaterina S. Mesheryakova, Leonard M. Khalilov, Usein M. Dzhemilev

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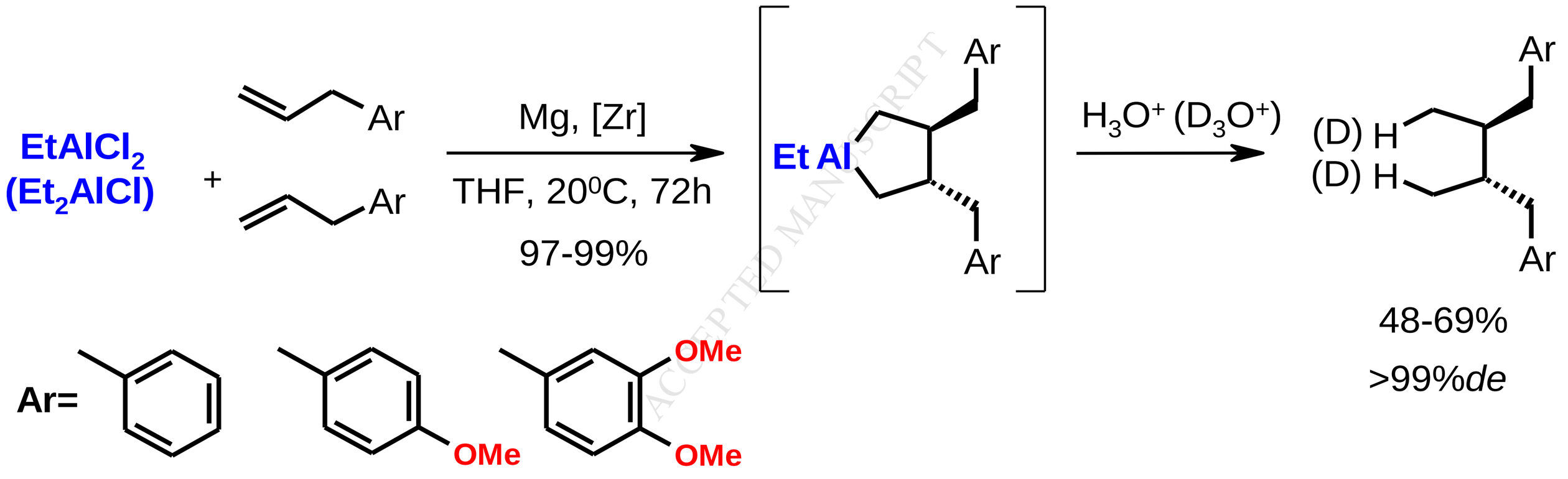

Catalytic cyclometallation of allylbenzenes by $EtAlCl_2$ and Mg as new route to synthesis of dibenzyl butane lignans

Lyudmila V. Parfenova,* Tatyana V. Berestova, Pavel V. Kovyazin, Aydar R. Yakupov, Ekaterina S. Mesheryakova, Leonard M. Khalilov, Usein M. Dzhemilev

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Abstract:

The cyclometallation of allylbenzenes (Ar= Ph, 4-MeO-Ph, 3,4-$(MeO)_2$-Ph) with $EtAlCl_2$ (Et_2AlCl) and Mg in the presence of Zr and Ti catalysts (Dzhemilev reaction) has been studied. The reaction run with high diastereoselectivity and gives cyclic organoaluminum compounds, which deuterolysis or hydrolysis gave 2*R*(*S*),3*R*(*S*)-dibenzyl butanes with yield of 48-69%. The study of catalyst structure effect on the substrate conversion, reaction chemo- and stereoselectivity showed that the best results were obtained in the case of Cp_2ZrCl_2 among the tested complexes. The enantioselectivity of neomenthylindenyl or neomenthyltetrahydroindenyl zirconium catalysts in the reaction did not exceed 20%ee. The *trans*-configuration of the substitutes in the metallacycles formed in the reaction has been proved by X-ray analysis of the hydrolysis product – 2*R*(*S*),3*R*(*S*)-dimethyl-1,4-bis[(4′- methoxyphenyl)methyl]-butane. The proposed method could be used for the one- pot diastereoselective synthesis of dibenzyl butane lignans from readily available allylbenzenes.

Keywords: cyclometallation, metallocenes, dibenzyl butanes, lignans, terameprocol, MTPA, (*R*)- 2- phenylselenopropanoic acid

1. Introduction

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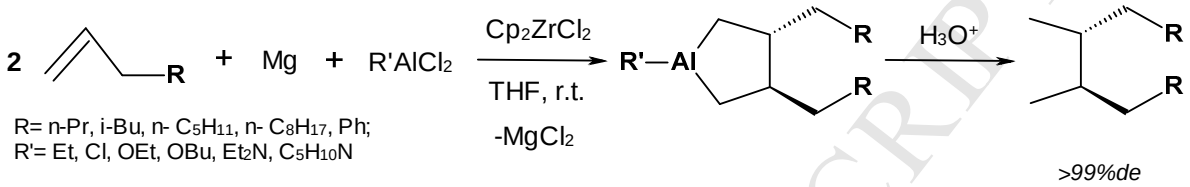
Catalytic alkene cycloalumination (Dzhemilev's reaction) is an effective and stereoselective method for the synthesis of a variety of organic compounds [1]. Thus, it was shown that a reaction of terminal alkenes with organoaluminum compounds (OAC) and Mg, catalyzed by Cp_2ZrCl_2, provides aluminacyclopentanes, which hydrolysis gives racemic 2,3- disubstituted butanes at high diastereselectivity [2].



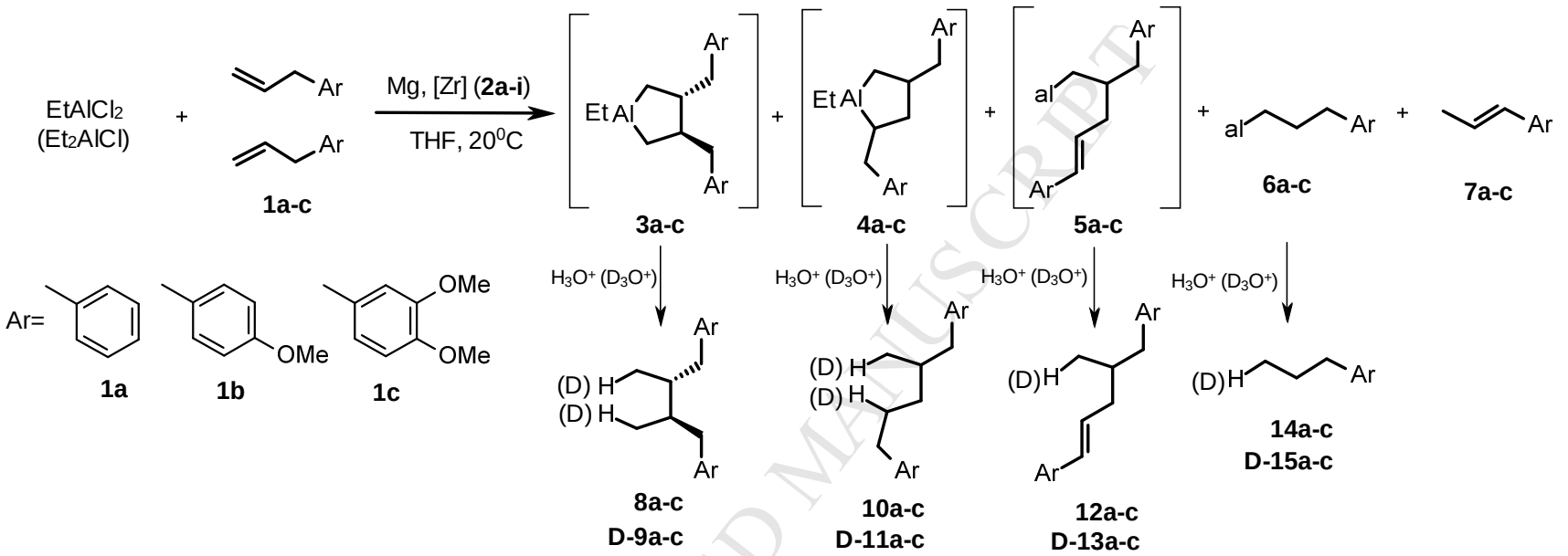
The use of methoxy-substituted allylbenzenes in the reaction opens a way to the one-pot diastereoselective synthesis of dibenzyl butane-type lignans [3] − a group of natural products, which are being considered as potential drugs due to a wide range of their biological activity. Thus, 2,3-dibenzylbutanes (for example, nordihydroguaiaretic acid (NDGA), dihydroguaiaretic acid (DGA), terameprocol and austrobailignan-5) show anti-tumor, antiviral, anti-inflammatory, antioxidant and other activity [4]. Despite the presence of numerous methods for their preparation in the literature [5,6], the development of new stereoselective synthetic routes is still of interest.

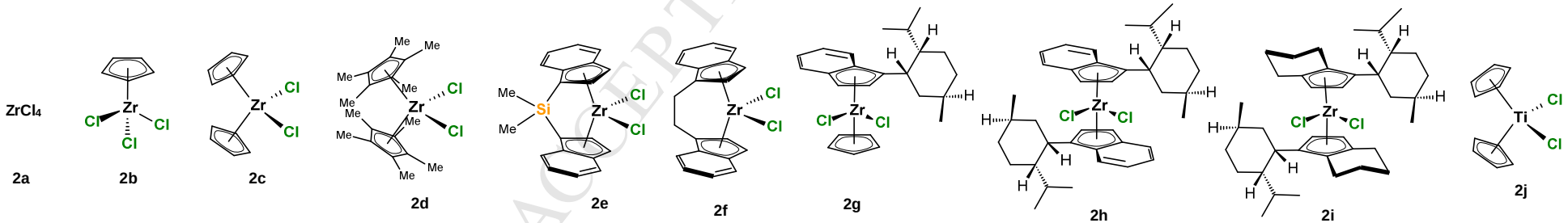
In order to find a novel approach to the synthesis of the dibenzyl butane lignans we have studied a reaction of methoxy-substituted allylbenzenes with $EtAlCl_2$ (Et_2AlCl) and Mg in the presence of Zr and Ti catalysts. The effect of the catalyst structure and the reaction conditions on the alkene conversion and reaction chemo-, regio- and enantioselectivity has been considered.

2. Results and discussion

We have studied the cyclometallation reaction of substituted allylbenzenes **1a-c** (Ar = Ph, 4-methoxyphenyl, 3,4-dimethoxyphenyl) by $EtAlCl_2$ (Et_2AlCl) and Mg in the presence of catalytic amounts of Zr and Ti complexes (**2a-i**) (Scheme 1) in ethereal solvents (THF, Et_2O) at a room temperature. The reaction runs with high diastereoselectivity (>99%*de*) and gives racemic 3*R*(*S*),4*R*(*S*)-dibenzylsubstituted

Scheme 1





aluminacyclopentanes **3a-c** as the major products**.** Moreover, we have identified regioisomers **4a-c**, acyclic organoaluminum compounds with double bond **5a-c**, hydroalumination products **6a-c** and alkenes with shifted double bond **7a-c**. The structure of the obtained organoaluminum compounds has been proved by the analysis of deuterolysis products **9a-c**, **11a-c**, **13a-c**, **15a-c**.

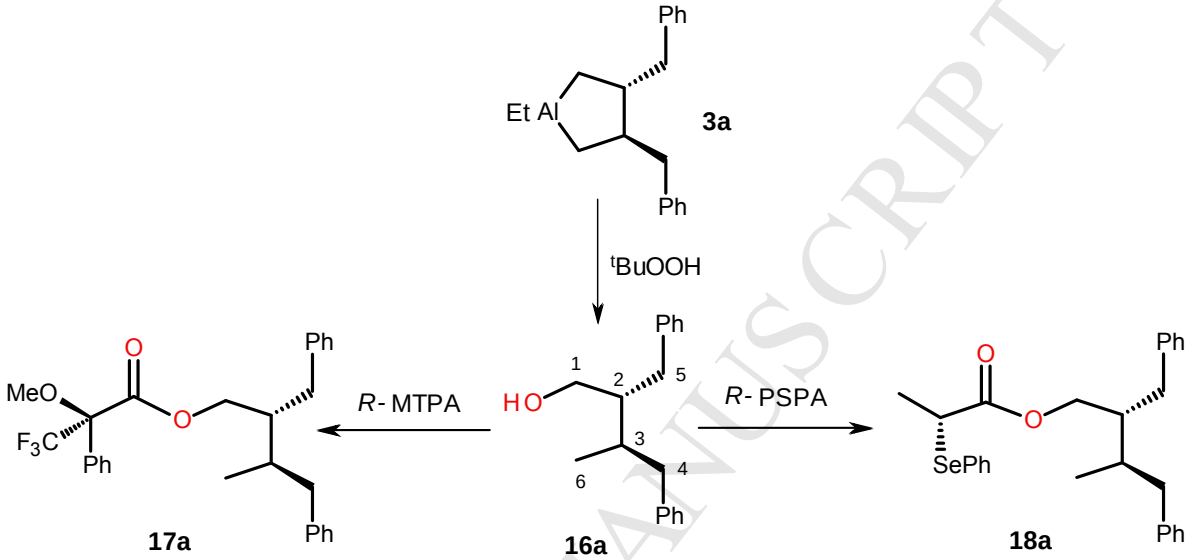
It has been found that the conversion of allylbenzenes **1a-c** in the reaction with $EtAlCl_2$ and Mg, catalyzed with Cp_2ZrCl_2 (**2c**), in THF at a room temperature for 72 h reaches 97-99%. The reaction gives expected cycloalumination products **3a-c** with yield of 48-69% according to GC analysis of deuterolysis products (Table 1, entries 4, 14, 23). Catalysts $ZrCl_4$ (**2a**) and $CpZrCl_3$ (**2b**) showed lower activity, chemo- and regioselectivity than complex **2c** in the reaction (Table 1, entries 1 and 2). Further, the application either of Et_2O solvent or of Et_2AlCl significantly reduces the conversion of the alkenes to 45-79% (see, for example, entries 3, 11, 13, 24 in Table 1). Increasing the reaction temperature accelerates the side hydroalumination reaction (Table 1, entries 5, 15, 22).

<Table 1>

Ansa-zirconocenes *rac*-**2e,f** show good activity in the reaction; however, they increase the relative content of regioisomer **4a-c** in the product mixture (Table 1, entries 7, 8, 17, 18, 25). Moreover, catalyst *rac*-**2f** speeds up the hydroalumination process.

It should be noted that the byproducts **5a-c** and **7a-c** are formed due to C-H activation in the reaction intermediates. Typically, in catalytic systems based on zirconocenes, the C-H activation process could be slowed down by an introduction of sterically hindered η^5- ligands into the metal complex [7]. This approach to the catalyst design could improve the reaction regioselectivity as well. Thus, for the further search for active, chemo- and stereoselective catalysts for allylbenzene cyclometallation reaction we have studied the catalytic effect of complexes containing bulky ligands, including enantiomerically pure: $Cp^*_2ZrCl_2$ (**2d**), $CpInd^*ZrCl_2$ (Ind*- 1-neomenthylindenyl) (**2g**), $Ind^*_2ZrCl_2$ (**2h**), Cp'_2ZrCl_2 (Cp′- 1-neomenthyl-4,5,6,7-tetrahydroindenyl) (**2i**). Unfortunately, the tested complexes

showed lower activity, chemo- and regioselectivity than **2c**. The enantiomeric excess was determined for oxidation product 2*R*(*S*),3*R*(*S*)-2-benzyl-3-methyl-4-phenyl-1-butanol (**16a**) using derivatization reagents *R*-MTPA (Mosher's reagent) [8] and (*R*) - 2 - phenylselenopropanoic acid (*R*-PSPA) [9]. The alcohol **16a** was isolated after the oxidation of the reaction mixture with ^{t}BuOOH for 24 h.



Thus, the enantioselectivity of complexes **2g-i** in the cyclometallation reaction did not exceed 20%ee. It should be noted that the increasing of steric hindrances in catalysts **2g-i** improved the reaction enantioselectivity, but dramatically decreased the alkene conversion.

Further, replacing of transition metal atom in the metallocene from Zr to Ti (Cp_2TiCl_2 (**2j**)) changed the reaction so that it resulted in C-H activation product **7** with a shifted double bond; this is generally characteristic to the Ti complexes.

During the isolation of the reaction products, we have obtained compound **8b** in the crystalline form suitable for the X-ray diffractometry analysis [10] (Table 2). Its ORTEP diagram is presented in Fig. 1. The geometric parameters of non-hydrogen bonds and angles observed in **8b** are summarized in Table 3. The torsion angle between the vicinal methyl groups of 169° proves their *trans*- configuration. The twist angle between the planes of the two phenyl groups is 78°. The distance between the centers of parallel phenyl groups of adjacent molecules in a crystal (Fig. 2) is 5.290 Å; this excludes the existence of $\pi - \pi$ interactions between the molecules.

<Figure 1>
<Figure 2>

<Table 2>
<Table 3>

Conclusions

Finally, the proposed method of catalytic cycloalumination of methoxy-substituted allylbenzenes by $EtAlCl_2$ and Mg provides an effective way to an one-pot synthesis of dibenzyl butane lignans. The study of catalyst structure effect on the activity and selectivity of the catalytic system showed that the best results were obtained in the case of zirconocene dichloride among the tested complexes. The asymmetric induction of enantiomerically pure neomenthylindenyl or neomenthyltetrahydroindenyl zirconium complexes did not exceed 20%ee.

The present work will be continued towards the search of new active and selective catalysts for these reactions, as well as the methods for the synthesis of dibenzylbutanediols, which could be obtained in the reaction via the oxidation of organoaluminum products.

Experimental

All operations with organometallic compounds were carried out under argon using Schlenk techniques. Solvents were dried and distilled under argon prior to use. THF, Et_2O was freshly distilled from sodium/benzophenone. Allylbenzenes (**1a-c**) were purchased from Aldrich. Commercially available $EtAlCl_2$ (85%) and Et_2AlCl (82%) were involved in the reactions. Tert-butyl hydroperoxide solution (5.5 M) in decane (Aldrich) was used for the oxidation of the reaction products.

Complex **2c** was prepared from $ZrCl_4$ (99.5%, Aldrich) [11]. Catalysts **2d-f** (98%, Strem) and **2i** (99.5%, Aldrich) were purchased and used as received. Catalysts **2g,h** were prepared from (+)-3-[(1'*S*,2'*S*,5'*R*)-2'-isopropyl-5'-methylcyclohexyl]indene (3-neomenthylindene) and $ZrCl_4$ (**2a**) (99.5%, Aldrich) [12] or $CpZrCl_3$ (**2b**) [13]. Complex **2i** was prepared from $TiCl_4$ (99.0%, Aldrich) [14].

The ^{1}H and ^{13}C NMR spectra were recorded on "Bruker AVANCE-400" spectrometer (400.13 MHz (^{1}H), 100.62 MHz (^{13}C)). The samples were prepared in standard tubes of 5 mm diameter. One and two-dimensional NMR spectra (COSY, HSQC, HMBC, NOESY) were measured using standard pulse sequences.

Elemental analyses of compounds **8**,**9b,c** were carried out on CHNO analyzer Carlo Erba-1106.

The hydrolysis and deuterolysis products of the reaction mixture were analyzed on Carlo Erba gas chromatograph (He, column 50,000 x 0.32 mm, fixed phase 'Ultra-1', flame ionization detector). GC-MS analysis was carried out on spectrometer QP 2010 Ultra (Shimadzu). The yields of reaction products and alkene conversion were determined using internal standard.

MTPA ester **17a** was synthesized as described in Ref. [8]. PSPA ester **18a** was prepared according to Ref. [9].

The single crystal of **8b** was prepared by slow evaporation of benzene solution at the room temperature. X-ray diffraction data was collected on a XCalibur Eos diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Collection and processing of data performed with using the program CrysAlis^{Pro} Oxford Diffraction Ltd., Version 1.171.33.66. The structure was refined by a full-matrix least-square technique using anisotropic thermal parameters for non-hydrogen atoms and a riding model for hydrogen atoms in the program SHELXS-97 [10]. Crystallographic data for the structure of **8b** have been deposited in the Cambridge Crystallographic Data Centre as a CIF deposition with file number CCDC 909400. Copies of these data can be obtained free of change on application to CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk) or from http://www.ccdc.cam.ac.uk/data_request/cif.

Reaction of allylbenzenes (1a-c) with $EtAlCl_2$ (Et_2AlCl) and Mg in the presence of complexes 2a-j.

A 10 ml flask equipped with a magnetic stirrer and filled with argon was loaded with 0.2 mmol of complexes (**2a-j**), 4 mmol of Mg (powder), 3 ml of a solvent (THF or Et_2O) and 4 mmol of allylbenzene (**1a-c**). The mixture was cooled to 0 ^oC and 5 mmol of $EtAlCl_2$ or Et_2AlCl was added dropwise. The reaction mixture was stirred for 72 h at 20–30^oC. Further, the mixture was decomposed with 10% HCl or DCl at 0^oC. The products were extracted with Et_2O; the organic layer was dried over Na_2SO_4 and analyzed by GC and GC–MS. The products **8,9a-c** were isolated by column chromatography on silica gel (hexane/Et_2O 5:1). NMR characteristics and mass-spectral data of **8a**, **9a** were identical to the literature data [2d].

The oxidation of the reaction mixture with ^tBuOOH for 24 h, subsequent hydrolysis with 10% HCl and extraction with Et_2O gave alcohol **16a**, which was isolated by column chromatography on silica gel (hexane/ethyl acetate 97:3).

2*R*(*S*),3*R*(*S*)-dimethyl-1,4-bis[(4′- methoxyphenyl)methyl]butane (8b). Isolated as white crystals with a purity of 98%, 324 mg (1.09 mmol, 54%); m/z (EI) 298 (M^+, %), 298 (9), 121 (75), 77 (9), 65 (10), 31 (100). Anal. Calcd. for $C_{20}H_{26}O_2$ (%): C, 80.50, H, 8.78, O, 10.72. Found (%): C, 80.53; H, 8.81; O, 10.66. ^1H NMR ($CDCl_3$) δ 0.87 (d, ^3J = 6.4 Hz, 6H, CH_3), 1.72-1.88 (m, 2H, CH), 2.45 (dd, ^2J = 13.6 Hz, ^3J = 8.4 Hz, 2H, CHCH*H*), 2.65 (dd, ^2J = 13.2 Hz, ^3J = 6.6 Hz, 2H, CHC*H*H); 3.83 (s, 6H, OCH_3) 6.85 (d, ^3J = 8.4 Hz, 4H, *m-H* (Ph)), 7.06 (d, ^3J = 8.4 Hz, 4H, *o*-H (Ph)). ^{13}C NMR ($CDCl_3$) δ 13.9 (C_1), 38.2 (C_2), 40.5 (C_3), 55.8 (OCH_3), 113.6 (C_6), 129.9 (C_5), 133.8 (C_4); 157.7 (C_7).

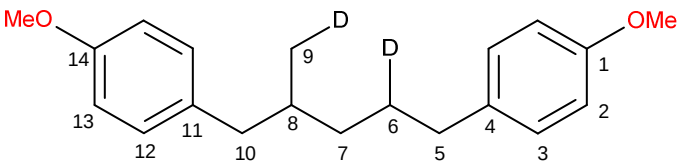
2*R*(*S*),3*R*(*S*)-2,3-bis[(4′-methoxyphenyl)methyl]butane-*1,4-d*$_2$ (9b): m/z (EI) 300 (M^+, %), 300 (4), 121 (100), 89 (2), 78 (11), 65 (3), 51 (2). Anal. Calcd. for $C_{20}H_{24}D_2O_2$ (%): C, 79.96; (H+D), 9.39; O, 10.65. Found (%): C, 81.01; (H+D), 9.47; O, 9.52. ^1H NMR ($CDCl_3$) δ 0.82-0.91 (4H, CH_2D), 1.77-1.87 (m, 2H, CH), 2.43 (dd, ^2J = 13.6 Hz, ^3J = 8.4 Hz, 2H, CHCH*H*), 2.65 (dd, ^2J = 13.6 Hz, ^3J = 5.8 Hz, 2H, CHC*H*H), 3.84 (s, 6H, OCH_3), 6.86 (d, ^3J = 8.4 Hz, 4H, *m-H* (Ph)), 7.07 (d, ^3J = 8.4 Hz, 4H, *o-H* (Ph)). ^{13}C NMR ($CDCl_3$) δ 13.6 (t, $J_{C\text{-}D}$ = 19.1

Hz, C_1), 38.2 (C_2), 40.5 (C_3), 55.3 (OCH_3), 113.6 (C_6), 129.9 (C_5), 133.8 (C_4), 157.7 (C_7).

2*R*(*S*),3*R*(*S*)-bis[(3′,4′-dimethoxyphenyl)methyl]butane ((±)-terameprocol) (8c). Isolated as colorless oil with a purity of 97%, 261 mg (0.73 mmol, 36%); m/z (EI) 358 (M^+, %), 358 (19), 179 (3), 165 (2), 151 (100), 137 (3), 135 (4), 121 (4), 107 (14), 91 (8), 78 (5), 77 (5), 73 (2), 65 (5), 40 (13). Anal. Calcd. for $C_{22}H_{30}O_4$ (%): C, 73.71, H, 8.44, O, 17.85. Found (%): C, 73.77; H, 8.49; O, 17.27. ^{1}H NMR ($CDCl_3$) δ 0.86 (d, ^3J = 6.4 Hz, 6H, CH_3), 1.72-1.82 (m, 2H, CH), 2.42 (dd, ^2J = 13.4 Hz, ^3J = 8.0 Hz, 2H, CHCH*H*), 2.58 (dd, ^2J = 13.6 Hz, ^3J = 6.8 Hz, 2H, CHC*H*H), 3.84 (s, 6H, OCH_3), 3.87 (s, 6H, OCH_3), 6.61 (s, 2H, CC*H*C (Ph)), 6.64 (d, ^3J = 8.0 Hz, 2H, CC*H*CH (Ph)), 6.78 (d, ^3J = 8.0 Hz, 2H, CCHC*H* (Ph)). ^{13}C NMR ($CDCl_3$) δ 13.9 (C_1), 37.6 (C_2), 41.0 (C_3), 55.77, 55.80 (OCH_3), 111.0 (C_8), 112.1 (C_5), 120.9 (C_9), 134.3 (C_4), 147.0 (C_7), 148.7 (C_6).

2*R*(*S*),3*R*(*S*)-bis[(3′,4′-dimethoxyphenyl)methyl]butane-*1,4-d*$_2$ (9c): m/z (EI) 360 (M^+, %), 360 (9), 180 (2), 151 (100), 107 (14), 78 (7), 77 (7), 73 (8), 65 (5). Anal. Calcd. for $C_{22}H_{28}D_2O_4$ (%): C, 73.30, (H+D), 8.95, O, 17.75. Found (%): C, 73.79; (H+D), 8.86; O, 17.35. ^{1}H NMR ($CDCl_3$) δ 0.82 (d, ^3J = 6.8 Hz, 4H, C*H*$_2$D), 1.71-1.80 (m, 2H, C*H*), 2.40 (dd, ^2J = 13.6 Hz, ^3J = 8.0 Hz, 2H, CHCH*H*), 2.56 (dd, ^2J = 13.6 Hz, ^3J = 6.8 Hz, 2H, CHC*H*H), 3.81 (s, 6H, OCH_3), 3.85 (s, 6H, OCH_3), 6.59 (s, 2H, CCHC (Ph)), 6.62 (d, ^3J = 8.2 Hz, 2H, CC*H*CH (Ph)), 6.75 (d, ^3J = 8.2 Hz, 2H, CCHC*H* (Ph)). ^{13}C NMR ($CDCl_3$) δ 13.6 (t, $J_{C\text{-}D}$ = 21.5 Hz, C_1), 37.5 (C_2), 41.0 (C_3), 55.73, 55.78 (OCH_3), 111.0 (C_8), 112.1 (C_5), 120.9 (C_9), 134.2 (C_4), 147.0 (C_7), 148.7 (C_6).

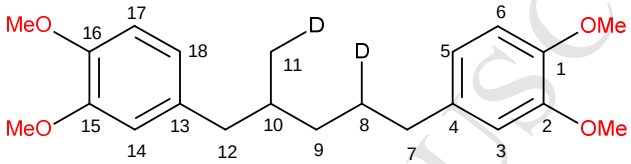
1-Methoxy-4-[5′-(4′′-methoxyphenyl)-2′-(methyl-*d*)-pentyl-4′-*d*]benzene (11b).



m/z (EI) 300 (M^+, %), 300 (8), 207 (3), 179 (2), 135 (2), 121 (100), 105 (2), 92 (2), 91 (5), 78 (4), 77 (6), 65 (7), 40 (29). ^{1}H NMR ($CDCl_3$) δ 0.93 (d, ^{3}J= 7.0 Hz, 2H,

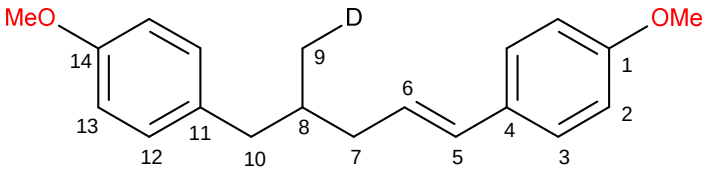
CH_2D), 1.20–1.32 (m, 1H, CHC*H*HCH), 1.41–1.52 (m, 1H, CHCH*H*CH), 1.60–1.80 (m, 1H, C*H*D), 1.72–1.81 (m, 1H, C*H*CH$_2$D), 2.39 (dd, ^2J = 13.4 Hz, ^3J = 7.8 Hz, 1H, CHC*H*HPh), 2.54–2.67 (m, 2H, CHDCH_2Ph), 2.59–2.68 (m, 1H, CHCH*H*Ph), 3.85 (s, 6H, OCH$_3$), 6.86- 6.94 (m, 4H, Ph(*m*-H)), 7.07- 7.10 (m, 4H, Ph(*o*-H)). ^{13}C NMR (CDCl$_3$) δ 19.2 (t, $J_{C\text{-}D}$ = 19.0 Hz, C$_9$), 29.0 (t, $J_{C\text{-}D}$ = 19.0 Hz, C$_6$), 35.1 (C$_8$), 35.3 (C$_5$), 36.2 (C$_7$), 42.9 (C$_{10}$), 55.2 (OMe), 113.6, 113.7 (C$_2$, C$_{13}$), 129.9, 130.0 (C$_3$, C$_{12}$), 133.6, 135.0 (C$_4$, C$_{11}$), 157.7 (C$_1$, C$_{14}$).

4-[5′-(3′′,4′′-Dimethoxyphenyl)-2′-(methyl-*d*)-pentyl-4′-*d*]-1,2-dimethoxy-benzene (11c).



m/z (EI) 360 (M$^+$, %), 360 (35), 165 (2), 151 (100), 152 (17), 135 (3), 136 (2), 137 (3), 121 (3), 107 (9), 91 (4), 78 (4), 77 (4), 65 (2), 40 (4). ^{1}H NMR (CDCl$_3$) δ 0.91–0.95 (m, 2H, CH_2D), 1.16–1.26 (m, 1H, CHC*H*HCH), 1.38–1.46 (m, 1H, CHCH*H*CH), 1.54–1.61 (m, 1H, C*H*D), 1.67–1.76 (m, 1H, C*H*CH$_2$D), 2.34 (dd, ^2J = 13.4 Hz, ^3J = 8.1 Hz, 1H, CHC*H*HPh), 2.48–2.61 (m, 2H, CHDCH_2Ph), 2.54–2.63 (m, 1H, CHCH*H*Ph), 3.85 (s, 6H, OCH$_3$), 3.88 (s, 6H, OCH$_3$), 6.52 – 6.95 (m, 6H, Ph). ^{13}C NMR (CDCl$_3$) δ 19.1 (t, $J_{C\text{-}D}$ = 19.0 Hz, C$_{11}$), 28.9 (t, $J_{C\text{-}D}$ = 19.0 Hz, C$_8$), 35.0 (C$_{10}$), 35.8 (C$_7$), 36.2 (C$_9$), 43.3 (C$_{12}$), 111.8, 111.9 (C$_6$, C$_{17}$), 112.3 (C$_{14}$), 115.5 (C$_3$), 121.2, 121.6 (C$_5$, C$_{18}$), 134.2 (C$_{13}$), 135.5 (C$_4$), 147.4 (C$_1$), 148.8 (C$_2$, C$_{16}$), 148.9 (C$_{15}$).

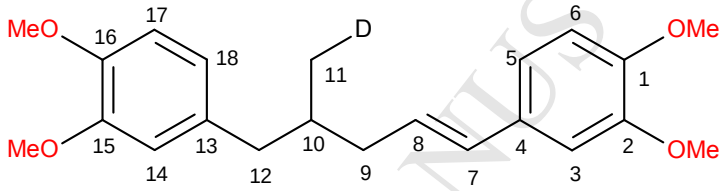
1-Methoxy-4-[(*E*)-5′-(4′′-methoxyphenyl)-4′-(methyl-*d*)-pent-1′-en-1′-yl]benzene (13b).



m/z (EI) 297 (M$^+$, %), 297 (42), 207 (15), 176 (11), 180 (2), 150 (18), 149 (11), 148 (16), 147 (100), 134 (60), 121 (99), 115 (19), 103 (8), 91 (38), 77 (19), 65 (8), 40 (99). ^{1}H NMR (CDCl$_3$) δ 0.95 (d, ^{3}J=6.8 Hz, 2H, CH_2D), 1.90 (sept, 1H, ^{3}J=6.4

Hz, CH), 2.04-2.14 (m, 1H, C*H*HCH=), 2.25-2.36 (m, 1H, CH*H*CH=), 2.45 (dd, ^{2}J= 13.4 Hz, ^{3}J= 6.2 Hz, 1H, C*H*HPh), 2.70 (dd, ^{2}J= 13.4 Hz, ^{3}J= 8.4 Hz, 1H, CH*H*Ph), 3.84 (s, 6H, OCH_3), 6.08-6.20 (m, 1H, C*H*=CHPh), 6.38 (d, 1H, ^{3}J= 16.0 Hz, CH=C*H*Ph), 6.78-6.93 (m, 4H, Ph(*m*-*H*)), 7.14 (d, 2H, ^{3}J=8.2 Hz, CH_2Ph(*o*-*H*)), 7.34 (d, 2H, ^{3}J= 8.6 Hz, CHPh(*o*-*H*)). ^{13}C NMR ($CDCl_3$) δ 19.1 (t, $J_{C\text{-}D}$ = 18.7 Hz, C_9), 35.6 (C_8), 40.1 (C_7), 42.3 (C_{10}), 55.2 (OMe), 113.7 (C_{13}), 113.9 (C_2), 127.1 (C_3), 127.2 (C_5), 129.3 (C_4), 130.1 (C_{12}), 130.6 (C_5), 133.4 (C_{11}), 157.8 (C_{14}), 158.7 (C_1).

1,2-Dimethoxy-4-[(*E*)-5′-(3′′,4′′-dimethoxyphenyl)-4′-(methyl-*d*)-pent-1′-en-1′-yl]benzene (13c).



m/z (EI) 357 (M^+, %), 357 (74), 219 (5), 207 (17), 206 (16), 193 (10), 180 (13), 179 (8), 177 (69), 164 (21), 159 (4), 151 (100), 152 (35), 147 (11), 146 (28), 137 (11), 131 (12), 121 (22), 115 (12), 107 (17), 103 (10), 91 (18), 90 (5), 77 (14), 73 (11), 65 (8), 40 (72). ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 2H, ^{3}J=6.8 Hz, CH_2D), 1.83–1.95 (m, 1H, CH), 1.99-2.11 (m, 1H,C*H*HCH=), 2.22-2.32 (m, 1H,CH*H*CH=), 2.42 (dd, ^{2}J= 13.6 Hz, ^{3}J=5.6 Hz, 1H, C*H*HPh), 2.65 (dd, ^{2}J= 13.6 Hz, ^{3}J=6.4 Hz, 1H, CH*H*Ph), 3.88 (s, 6H, OCH_3), 3.89 (s, 6H, OCH_3), 6.04-6.16 (m, 1H, C*H*=CHPh), 6.34 (d, 1H, ^{3}J= 15.6 Hz, CH=C*H*Ph), 6.61 (s, 1H, CH_2Ph(*o*-*H*)), 6.64 (d, 1H, ^{3}J= 8.0 Hz, CH_2Ph(*o*-*H*)), 6.78 (d, 1H, ^{3}J=8.0 Hz, CH_2Ph(*m*-*H*)), 6.82 (d, 1H, ^{3}J= 8.4 Hz, CHPh(*m*-*H*)), 6.90 (d, 1H, ^{3}J= 8.4 Hz, CHPh(*o*-*H*)), 6.92 (s, 1H, CHPh(*o*-*H*)). ^{13}C NMR ($CDCl_3$) δ 19.2 (t, $J_{C\text{-}D}$ = 18.7 Hz, C_{11}), 35.7 (C_{11}), 40.1 (C_9), 42.9 (C_{12}), 55.8, 56.0 (OMe), 108.7 (C_3), 111.1 (C_6), 111.2 (C_{17}), 112.5 (C_{14}), 118.9 (C_5), 121.1 (C_{18}), 127.4 (C_8), 130.9 (C_7), 131.0 (C_4), 133.9 (C_{13}), 147.2 (C_{16}), 148.4 (C_2), 148.7 (C_{15}), 149.1 (C_1).

2*R*(*S*),3*R*(*S*)-2-benzyl-3-methyl-4-phenyl-1-butanol (16a). Anal. Calcd. for $C_{20}H_{26}O_2$ (%): C, 84.99, H, 8.72, O, 6.29. Found (%): C, 84.88; H, 8.80; O, 6.32. ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3H, ^{3}J=6.8 Hz, CH_3), 1.84-1.94 (m, 1H, OCH_2C*H*),

1.97-2.09 (m, 1H, CH_3CH), 2.47 (dd, ^2J=13.2 Hz, ^3J=9.0 Hz, 1H, $CH_3CHCHHPh$), 2.73 (d, ^3J=7.6 Hz, 2H, CH_2Ph), 2.84 (dd, ^2J= 13.2 Hz, ^3J= 5.6 Hz, 1H, $CH_3CHCHHPh$), 3.64 (dd, ^2J= 10.8 Hz, ^3J= 6.0 Hz, 1H, $CHHOH$), 3.73 (dd, ^2J= 10.8 Hz, ^3J= 5.6 Hz, 1H, $CHHOH$), 7.12 (d, ^3J= 7.2 Hz, 2H, Ph(*o*-*H*)), 7.15-7.34 (m , 8H, Ph). ^{13}C NMR ($CDCl_3$) δ 15.8 (C_6), 35.2 (C_3), 35.4 (C_5), 40.7 (C_4), 46.7 (C_2), 62.9 (C_1), 125.8, 125.9, 128.2, 128.4, 129.0, 129.1, 141.1, 141.4 (Ph).

(*R*)-MTPA ester of 2*R*(*S*),3*R*(*S*)-2-benzyl-3-methyl-4-phenyl-1-butanol (17a). ^1H NMR ($CDCl_3$) δ 0.77 (d, ^3J= 6.8 Hz, 3H, CH_3CH); 1.78-1.95 (m, 1H, CH_3CH); 1.88-2.05 (m, 1H, OCH_2CH); 2.18-2.31 (m, 1H, $CH_3CHCHHPh$); 2.56-2.70 (m, 1H, $CH_3CHCHHPh$); 2.53, 2.58 (d, ^3J= 7.6 Hz, 2H, CH_2Ph); 3.495, 3.507 (s, 3H, OMe); 4.09 (dd, ^2J= 11.0 Hz, ^3J= 5.6 Hz, 1H, $CHHOH$), 4.27 (qd, ^2J= 11.2 Hz, ^3J=^3J= 5.7 Hz, 1H, CH_2OH), 4.41 (dd, ^2J= 11.0 Hz, ^3J= 5.2 Hz, 1H, $CHHOH$); 6.50-7.80 (m, 15H, Ph). ^{13}C NMR ($CDCl_3$) δ 15.20, 15.16 (C_6); 34.82, 35.01 (C_3); 35.2 (C_5); 40.5 (C_4); 42.83, 43.04 (C_2), 55.1 (OMe), 66.03, 66.07 (C_1), 84.9 (q, $^2J_{C\text{-}F}$= 27.5 Hz, CCF_3), 123.3 (q, $J_{C\text{-}F}$=288 Hz, CF_3), 125.9, 126.0, 126.1-129.1, 139.9, 140.7, 140.8 (Ph), 166.4 (C=O) .

(*R*)-PSPA ester of 2*R*(*S*),3*R*(*S*)-2-benzyl-3-methyl-4-phenyl-1-butanol (18a). ^1H NMR ($CDCl_3$) δ 0.87 (d, ^3J= 6.0 Hz, 3H, CH_3CH); 1.553, 1.557 (s, 3H, CH_3CHSe); 1.85-1.95 (m, 1H, CH_3CH); 1.91-1.99 (m, 1H, OCH_2CH); 2.37-2.47 (m, 1H, $CH_3CHCHHPh$); 2.54-2.72 (m, 2H, CH_2Ph); 2.71-2.80 (m, 1H, $CH_3CHCHHPh$); 3.75 (q, ^3J=7.2 Hz, CHSe), 3.78 (q, ^3J= 6.8 Hz, CHSe); 3.93-4.07 (m, 1H, $CHHOH$), 4.159 (dd, ^2J= 11.2 Hz, ^3J= 5.6 Hz, 1H, $CHHOH$), 4.168 (dd, ^2J= 11.2 Hz, ^3J= 6.00 Hz, 1H, $CHHOH$); 7.01-7.74 (m, 15H, Ph). ^{13}C NMR ($CDCl_3$) δ 15.4 (C_6); 17.7 (CH_3CHSe); 35.09, 35.21 (C_3); 35.34, 35.40 (C_5); 37.27, 37.52 (CHSe); 40.66, 40.69 (C_4); 43.1 (C_2); 65.1 (C_1); 125.7, 125.8, 127.9, 128.0, 128.2, 128.8, 129.1, 135.3, 135.4, 140.3, 140.9 (Ph); 173.54, 173.59 (C=O). ^{77}Se NMR ($CDCl_3$) δ 451.5, 453.2.

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References

1. (a) U.M. Dzhemilev, A.G. Ibragimov, Russ. Chem. Rev. 69 (2000) 121; (b) V.A. D'yakonov, Dzhemilev Reaction in Organic and Organometallic Synthesis (Chemistry Research and Applications), Nova Science Pub., New York, 2010.

2. (a) U.M. Dzhemilev, A.G. Ibragimov, A.B. Morozov, L.M. Khalilov, R.R. Muslukhov, G.A. Tolstikov, Russ. Chem. Bull. 40 (1991) 1022; (b) U.M. Dzhemilev, A.G. Ibragimov, A.B. Morozov, Mend. Comm. 1 (1992) 26; (c) U.M. Dzhemilev, A.G. Ibragimov, A.B. Morozov, R.R. Muslukhov, G.A. Tolstikov, Russ. Chem. Bull., 40 (1991) 1425; (d) U.M. Dzhemilev, A.G. Ibragimov, A.B. Morozov, R.R. Muslukhov, G.A. Tolstikov, Russ. Chem. Bull. 41 (1992) 1089; (i) U.M. Dzhemilev, A.G. Ibragimov, V.N. Azhgaliev, R.R. Muslukhov, Russ. Chem. Bull. 44 (1995) 1501; (f) A.G. Ibragimov, L.O. Khafizova, L.G. Yakovleva, E.V. Nikitina, K.G. Satenov, L.M. Khalilov, U.M. Dzhemilev, Russ. Chem. Bull. 48 (1999) 774.

3. (a) D.C. Ayres, J.D. Loike, Lignans: Chemical, biological and clinical properties, Cambridge University Press, Cambridge, 1990; (b) R.S. Ward, Nat. Prod. Rep. (1993) 1; (c) R.S. Ward, Nat. Prod. Rep. (1993) 183; (d) R.S. Ward, Nat. Prod. Rep. (1997) 43; (e) R.S. Ward, Nat. Prod. Rep. (1999) 75; (f) G.P. Moss, Pure Appl. Chem. 72 (2000) 1493.

4. (a) J.D. Lambert, R.T. Dorr, B.N. Timmermann, Pharm. Biol. 42 (2004) 149; (b) M. Saleem, H.J. Kim, M.S. Ali, Y.S. Lee, Nat. Prod. Rep. 22 (2005) 696.

5. (a) G. Schroeter, L. Lichtenstadt, D. Irineu, Ber. 51 (1918) 1587; (b) R.D. Haworth, C.R. Mavin, G. Sheldrick, J. Chem. Soc. (1934) 1423; (c) R.D. Haworth, T. Richardson, J. Chem. Soc. (1935) 120; (d) S.V. Lieberman, G.P. Mueller, E.T. Stiller, J. Am. Chem. Soc. 69 (1947) 1540; (e) Y. Sakakibara, Nippon kagaku zasshi 73 (1952) 235; (f) M.P. Gerchuk, V.M. Ivanova, Khim.

Nauka i Prom. 3 (1958) 685; (g) C.W. Perry, M.V. Kalnins, K.H. Deitcher, J. Org. Chem. 37 (1972) 4371; (h) T. Biftu, B.G. Hazra, R. Stevenson J. Chem. Soc., Perkin Trans. (1979) 2276; (i) A. Minato, K. Tamao, K. Suzuki, M. Kumada, Tetrahedron Lett. 21 (1980) 4017; (j) T. Takeya, T. Okubo, S. Nishida, S. Tobinaga, Chem. Pharm. Bull. 33 (1985) 3599; (k) K.V. Rao, S.K. Chattopadhyay, J. Org. Chem. 55 (1990) 1427; (l) A.R. Carroll, A.S. Krauss, W.C. Taylor, Aust. J. Chem. 46 (1993) 277; (m) R. Dhal, Y. Landais, A. Lebrun, J.-P. Robin, Tetrahedron 50 (1994) 1153; (n) A.R. Carroll, W.C. Taylor, Aust. J. Chem. 47 (1994) 937; (o) W.X. Gu, A.X. Wu, Q. Gao, X.F. Pan, Chin. Chem. Lett. 11 (2000) 15; (p) M.H. Gezginci, B.N. Timmermann, Tetrahedron Lett. 42 (2001) 6083; (q) Y.M. Xia, X.P. Cao, K. Peng, X.F. Ren, X.F. Pan, Chin. Chem. Lett. 4 (2003) 359; (r) J.-K. Son, S.H. Lee, L. Nagarapu, Y. Jahng, Bull. Korean Chem. Soc. 26 (2005) 1117; (s) Q. Wang, Y. Yang, Y. Li, W. Yu, Z. J. Hou, Tetrahedron 62 (2006) 6107; (t) Y.-M. Xia, Q. Wang, Y.-N. Din, F.-K. Yang, X.-P. Cao, Chin. J. Org. Chem. 28 (2008) 1040; (u) S. Yamauchi, T. Masuda T. Sugahara, Y. Kawaguchi, M. Ohuchi, T. Someya, J. Akiyama, Sh. Tominaga, M. Yamawaki, T. Kishida, K. Akiyama, M. Maruyama, Biosci., Biotechnol., Biochem. 72 (2008) 2981; (v) Y. Xia, Y. Zhang, W. Wang, Y. Ding, R. He, J. Serb. Chem. Soc. 75 (2010) 1325;

6. (a) G.P. Mueller, E.T. Stiller, S.V. Lieberman, U.S. Patent 2,456,443, 1948; (b) I.A. Pearl U.S. Patent 2,644,822, 1949; (c) C.V. Perry, U.S. Patent 3,906,004, 1975; (d) R.M. Parkhurst, R.S. Pardini, U.S. Patent 4,562,298, 1985; (e) Ch. Quingqi, J. A. Blomberg, WO 2010/014936, 2010.

7. (a) P.J. Chirik, M.W. Day, J.A. Labinger, J.E. Bercaw J. Am. Chem. Soc. 121 (1999) 10308; (b) P.J. Chirik, J.E. Bercaw, Organometallics 24 (2005) 5407.

8. (a) J.A. Dale, D.L. Dull, H.S. Mosher, J. Org. Chem. 34 (1969) 2543; (b) J.A. Dale, H.S. Mosher, J. Am. Chem. Soc. 95 (1973) 512.

9. N.V. Orlov, V.P. Ananikov, Chem. Commun. 46 (2010) 3212.

10. SHELXS, G.M. Sheldrick, Acta Cryst. A64 (2008) 112.

11. R.Kh. Freidlina, E.M. Brainina, A.N. Nesmeyanov, Dokl. Acad. Nauk SSSR 138 (1969) 1369.

12. G. Erker, M. Aulbach, M. Knickmeier, D. Wingbermuhle, C. Krueger, M. Nolte, S. Werner, J. Am. Chem. Soc. 115 (1993) 4590.

13. (a) L. Bell, R.J. Whitby, R.V.H. Jones, M.C.H. Standen, Tetrahedron Lett. 37 (1996) 7139; (b) L.V. Parfenova, T.V. Berestova, T.V. Tyumkina, P.V. Kovyazin, L.M. Khalilov, R.J. Whitby, U.M. Dzhemilev, Tetrahedron: Asymmetry 21 (2010) 299.

14. G. Wilkinson, J.M. Birmingham, J. Am. Chem. Soc. 76 (1954) 4281.

Table 1. Reaction of allylbenzenes **1a-c** with $EtAlCl_2$ ($ClAlEt_2$) and Mg, catalyzed by Zr and Ti complexes (**2a-j**) (mole ratio Cp_2ZrCl_2 : Mg : $EtAlCl_2$: allylbenzene = 1: 20:25:20, 22ºC, 72 h).

Entry	Substrate	[Zr]	OAC	Solvent	Alkene conversion, %	Product yield, % (*ee*%)[b]				
						9	**11**	**13**	**7**	**15**
1		**2a**	$EtAlCl_2$	THF	83	27	21	22	-	13
2		**2b**	$EtAlCl_2$	THF	85	21	16	10	29	9
3			Et_2AlCl	THF	66	29	2	9	10	14
4		**2c**	$EtAlCl_2$	THF	98	58	8	23	2	6
5			$EtAlCl_2$	THF (30º)	96	37	3	9	4	42
6	**1a**	**2d**	$EtAlCl_2$	THF	31	16	6	1	-	5
7		**2e**	$EtAlCl_2$	THF	70	47	13	5	2	1
8		**2f**	$EtAlCl_2$	THF	96	35	23	8	3	26
9		**2g**	$EtAlCl_2$	THF	83	21 (13)	14	7	24	18
10		**2h**	$EtAlCl_2$	THF	65	34 (16)	16	-	3	13
11			$EtAlCl_2$	Et_2O	79	30	45	-	2	2
12		**2i**	$EtAlCl_2$	THF	13	6 (20)	5	2	-	-
13			Et_2AlCl	THF	62	27	5	12	-	16
14		**2c**	$EtAlCl_2$	THF	99	69	9	14	3	2
15			$EtAlCl_2$	THF (30º)	99	26	1	7	20	44
16	**1b**	**2d**	$EtAlCl_2$	THF	27	19	7	-	-	-
17		**2e**	$EtAlCl_2$	THF	82	40	17	6	8	9
18		**2f**	$EtAlCl_2$	THF	99	34	21	8	4	30
19		**2g**	$EtAlCl_2$	THF	97	19	8	4	48	19
20		**2h**	$EtAlCl_2$	THF	51	12 (9)	11	-	27	-
21			$EtAlCl_2$	THF	96	31	8	17	11	27
22		**2c**	$EtAlCl_2$	THF (30º)	98	22	2	9	5	58
23			$EtAlCl_2$[a]	THF	97	48	8	19	18	3
24	**1c**		Et_2AlCl	THF	45	19	3	5	6	11
25		**2e**	$EtAlCl_2$	THF	99	50	23	5	2	17
26		**2f**	$EtAlCl_2$	THF	31	18	10	-	3	-
27		**2h**	$EtAlCl_2$	THF	43	25	12	-	6	-
28		**2j**	$EtAlCl_2$	THF	65	-	-	-	56	9

[a] Twofold excess of $EtAlCl_2$. [b] GC yield of deuterolysis products.

Table 2. Crystal data and structure refinement for **8b**

	8b
Empirical formula	$C_{20}H_{26}O_2$
Formula weight	298.41
Crystal system	monoclinic
Space group	I2/a
a/Å	13.1601(7)
b/Å	7.8740(4)
c/Å	16.9944(7)
α/°	90.00
β/°	107.993(5)
γ/°	90.00
Volume/Å3	1674.89(14)
Z	4
ρ_{calc}mg/mm3	1.183
μ/mm⁻1	0.074
2Θ range for data collection	5.04 to 62.26°
Data/restraints/parameters	2362/0/152
Goodness-of-fit on F^2	1.061
Final R indexes [I>=2σ (I)]	R1 = 0.0480, wR2 = 0.1260
Final R indexes [all data]	R1 = 0.0555, wR2 = 0.1327

Table 3. Bond lengths and angles in compound **8b**.

Label	Length(Å)	Label	Angle (˚)
O1–C3	1.3738(13)	C3–O1–C11	116.83(9)
O1–C11	1.4290(15)	C4–C2–C5	122.17(10)
C2–C4	1.3887(16)	O1–C3–C5	124.61(10)
C2–C5	1.3937(16)	O1–C3–C8	116.01(10)
C3–C5	1.3906(15)	C5–C3–C8	119.37(11)
C3–C8	1.3966(15)	C2–C4–C6	121.30(10)
C4–C6	1.5091(15)	C2–C4–C7	117.15(10)
C4–C7	1.4037(16)	C7–C4–C6	121.53(10)
C6–C10	1.5415(15)	C3–C5–C2	119.60(10)
C7–C8	1.3842(17)	C4–C6–C10	113.77(9)
C9–C10	1.5261(15)	C8–C7–C4	121.64(10)
C10–C101	1.544(2)	C7–C8–C3	120.06(10)
		C6–C10–C101	112.59(7)
		C9–C10–C6	110.27(9)
		C9–C10–C101	112.09(11)

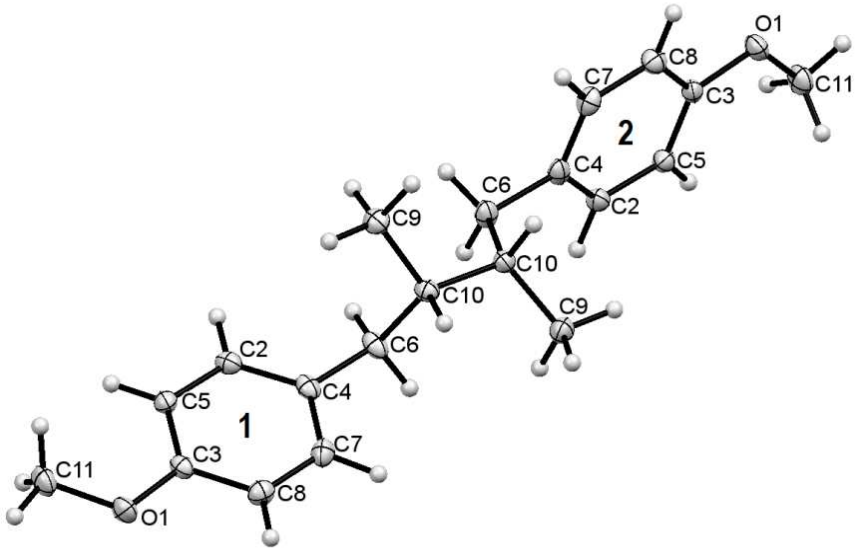

Fig. 1. ORTEP diagram of **8b.**

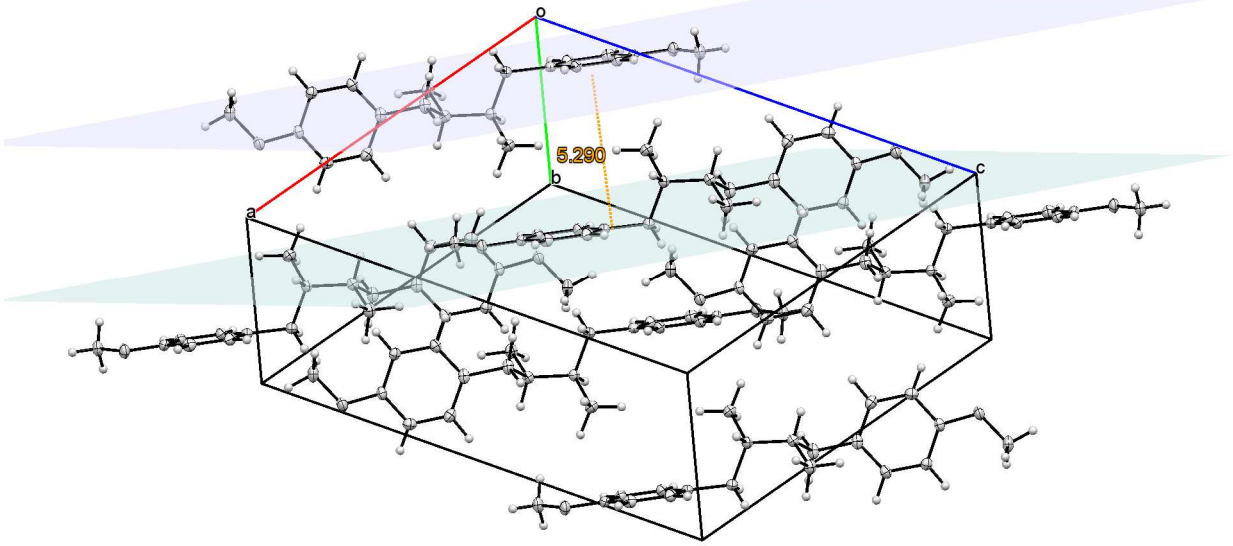

Fig. 2. ORTEP diagram: Crystal packing in compound **8b.**

Highlights

We studied catalytic cyclometallation of allylbenzenes with $EtAlCl_2$ (Et_2AlCl) and Mg

The one- pot diastereoselective synthesis of dibenzyl butane lignans is developed

The *trans*-configuration of the substitutes in the products is proved by X-ray analysis

Catalytic cyclometallation of allylbenzenes by $EtAlCl_2$ and Mg as new route to synthesis of dibenzyl butane lignans

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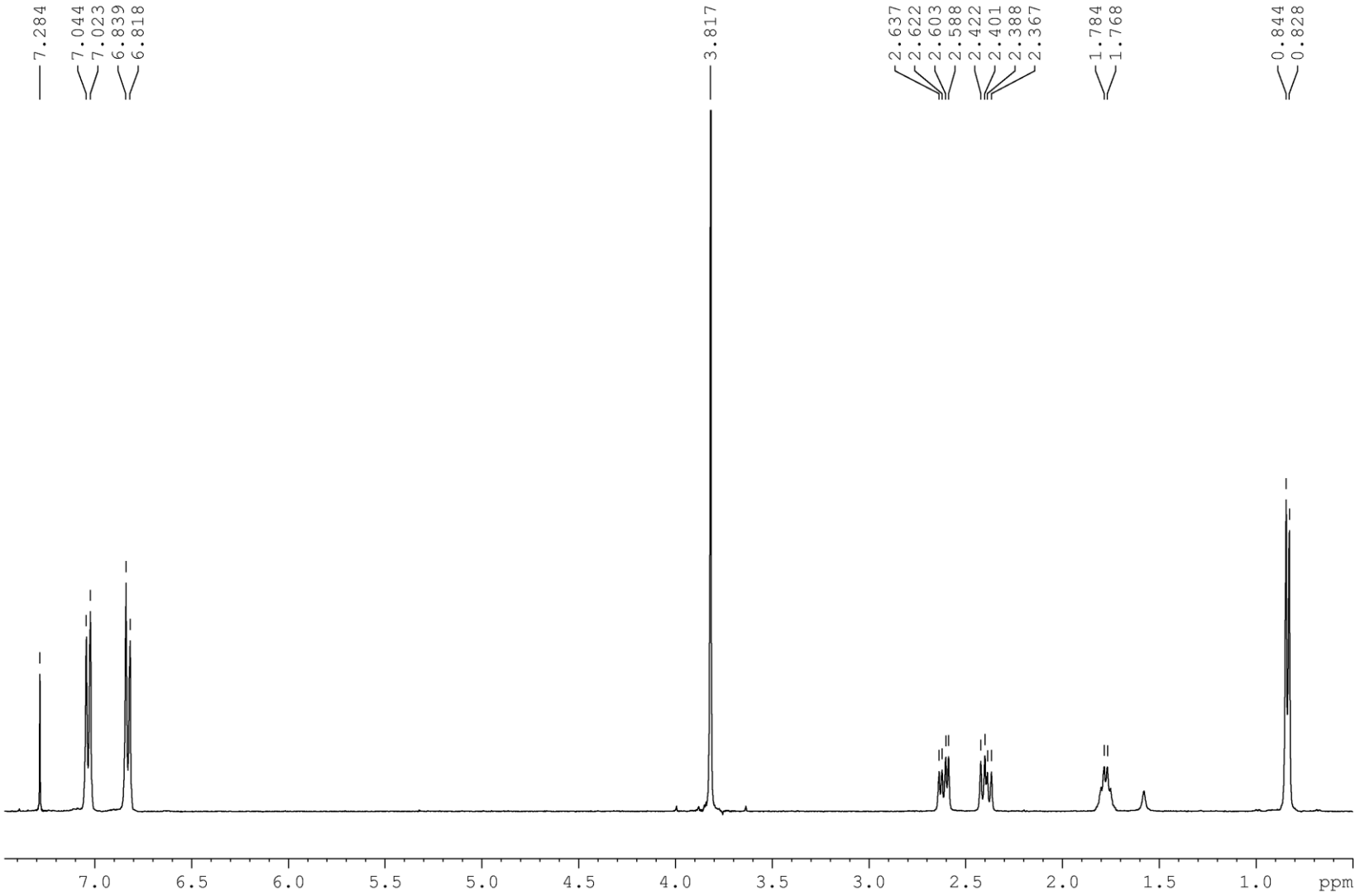
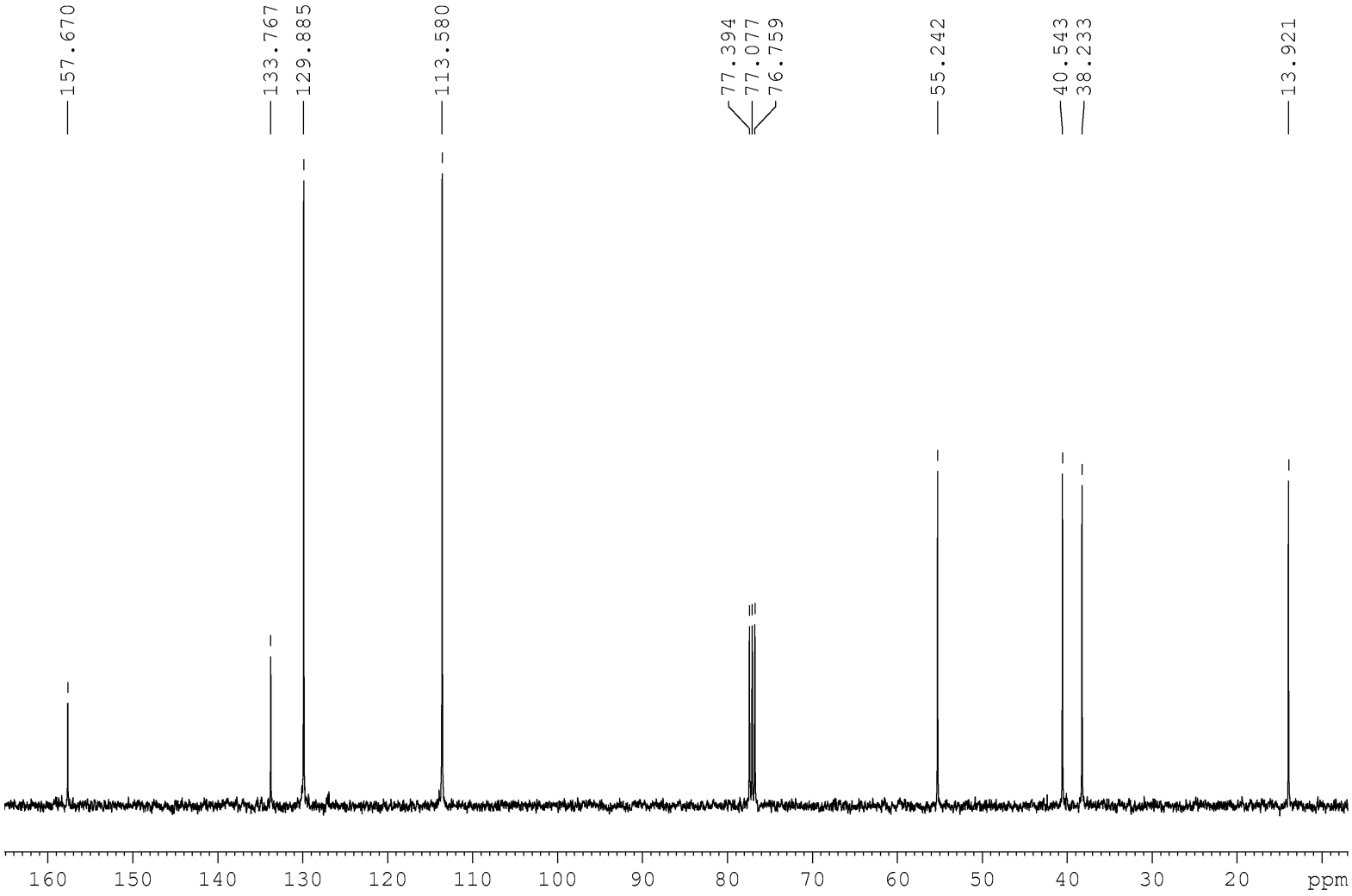
Supporting Information

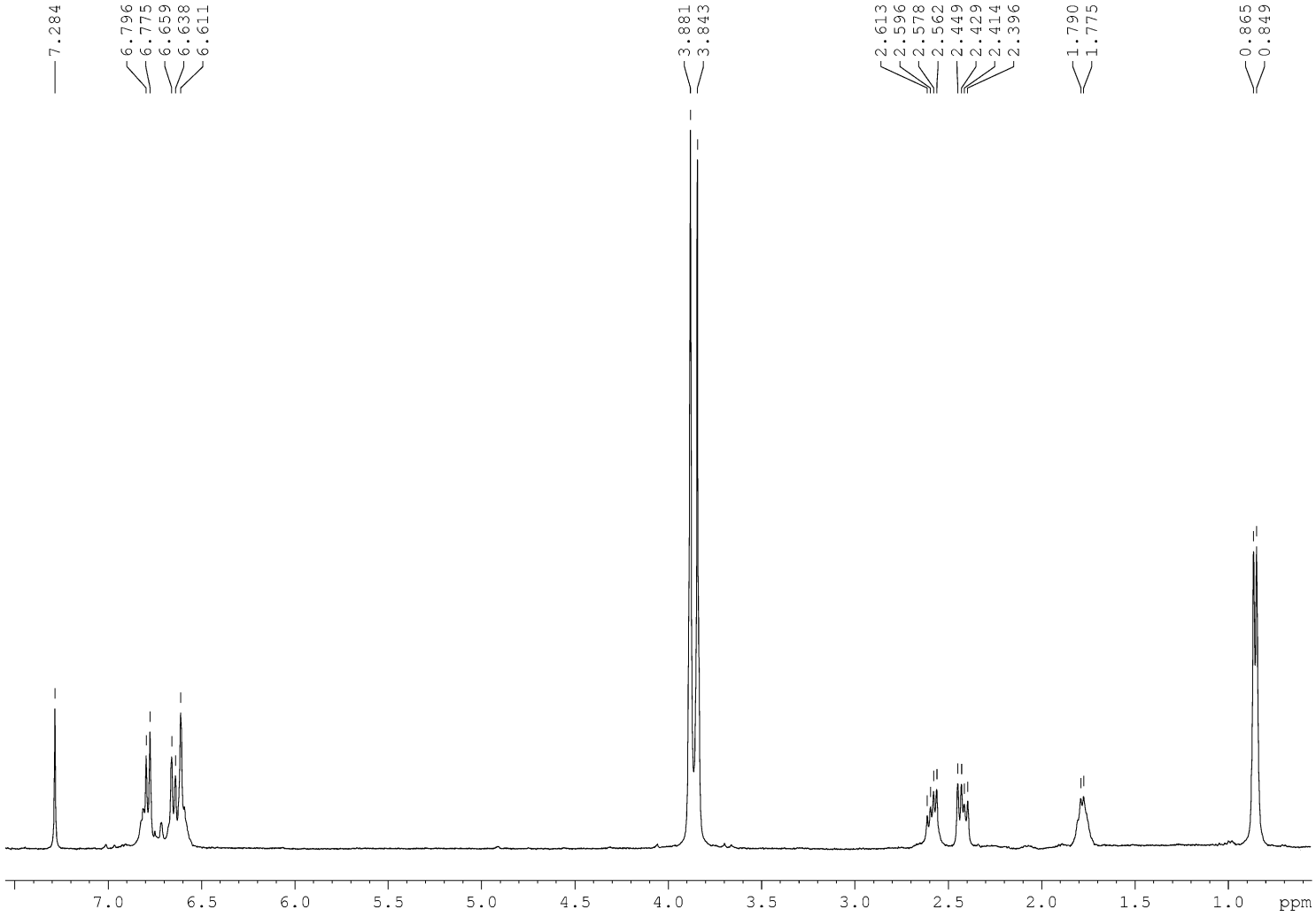
NMR ^{1}H of 2*R*(*S*),3*R*(*S*)-dimethyl-1,4-bis[(4′- methoxyphenyl)methyl]butane (**8b**).



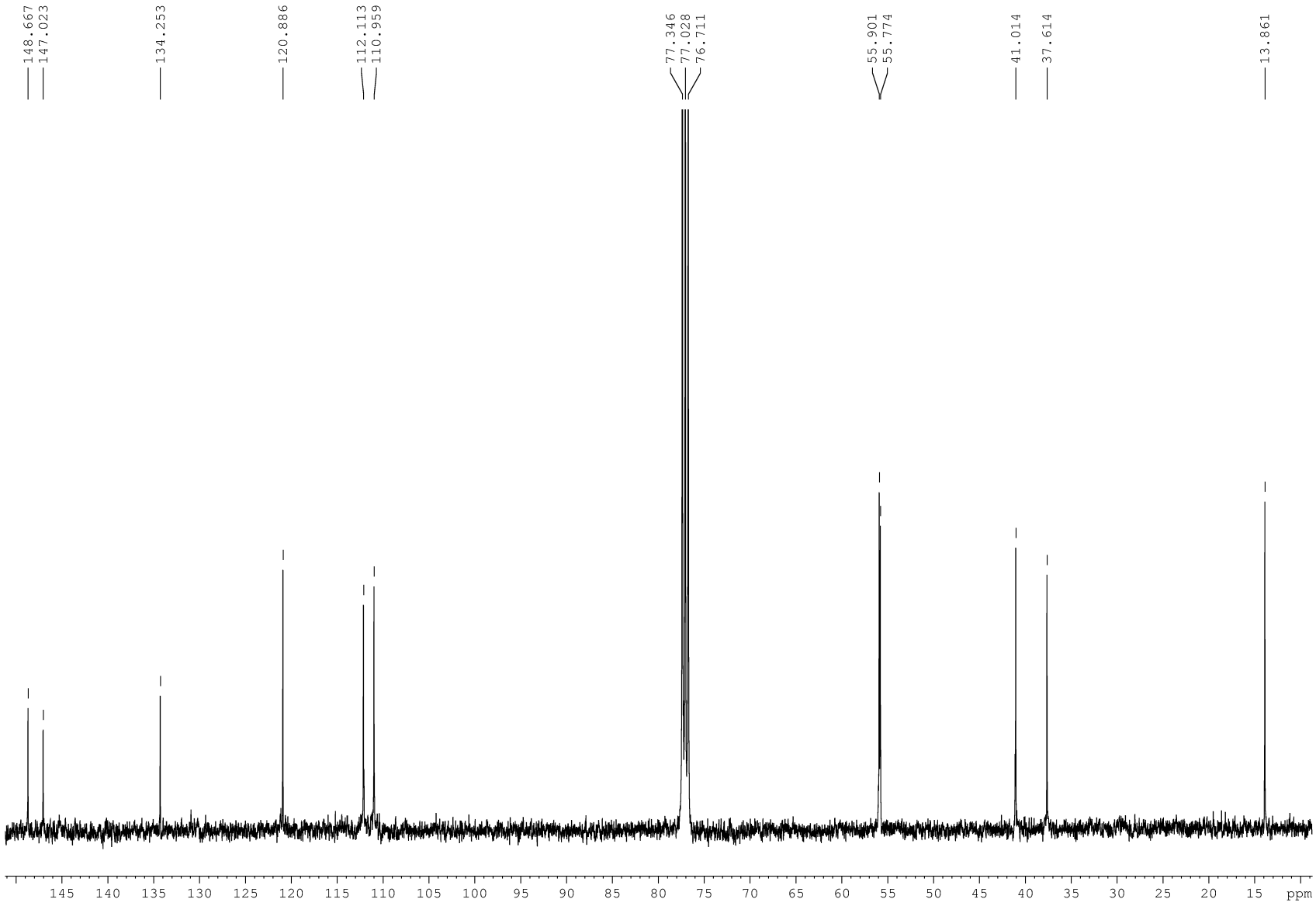
NMR ^{13}C of 2*R*(*S*),3*R*(*S*)-dimethyl-1,4-bis[(4′- methoxyphenyl)methyl]butane (**8b**).



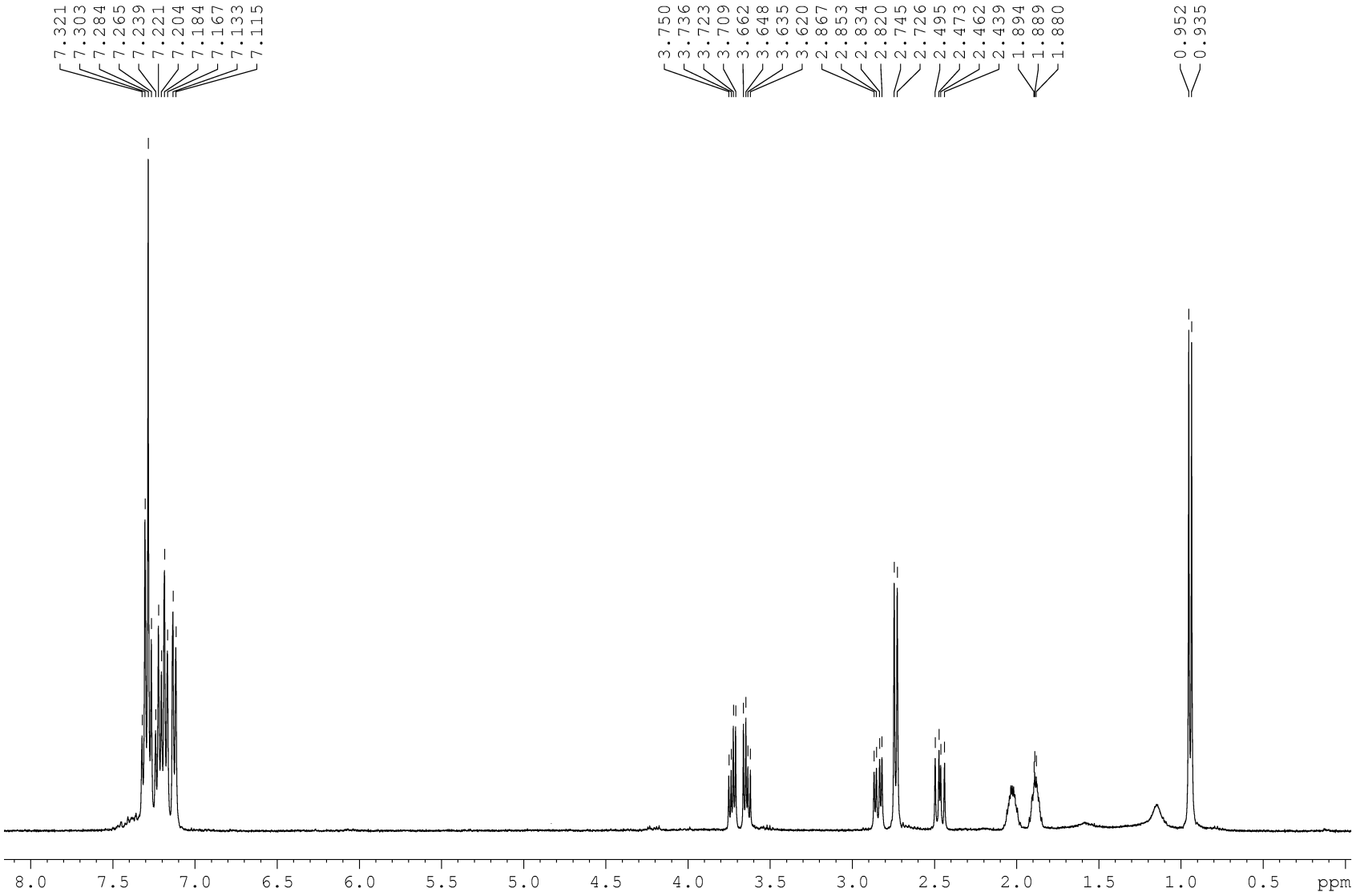
NMR ^{1}H of 2*R*(*S*),3*R*(*S*)-bis[(3′,4′-dimethoxyphenyl)methyl]butane ((±)-terameprocol) (**8c**).



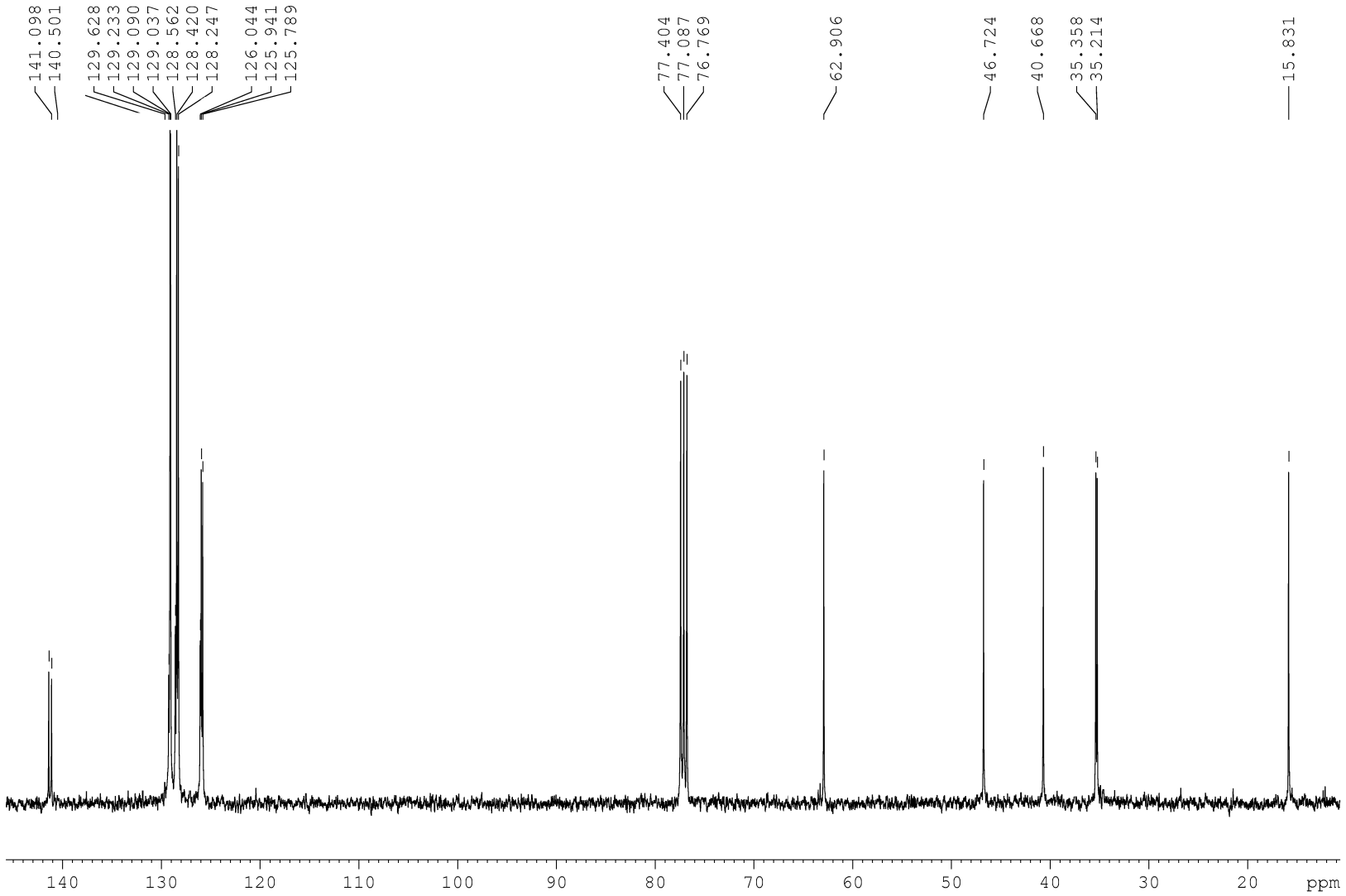
NMR ^{13}C of 2*R*(*S*),3*R*(*S*)-bis[(3′,4′-dimethoxyphenyl)methyl]butane ((±)-terameprocol) (**8c**).



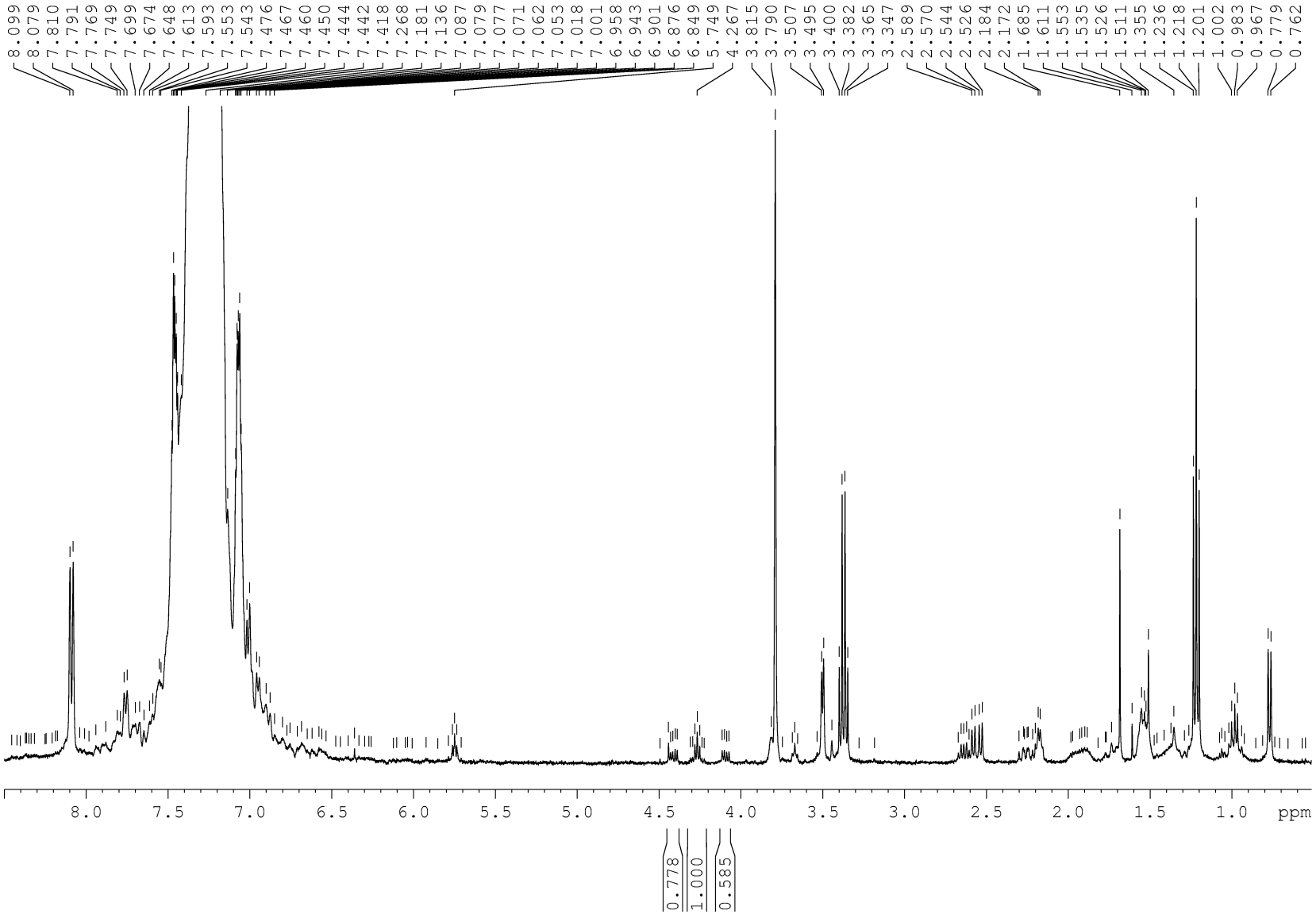
NMR ^{1}H of 2*R*(*S*),3*R*(*S*)-2-benzyl-3-methyl-4-phenyl-1-butanol (**16a**).



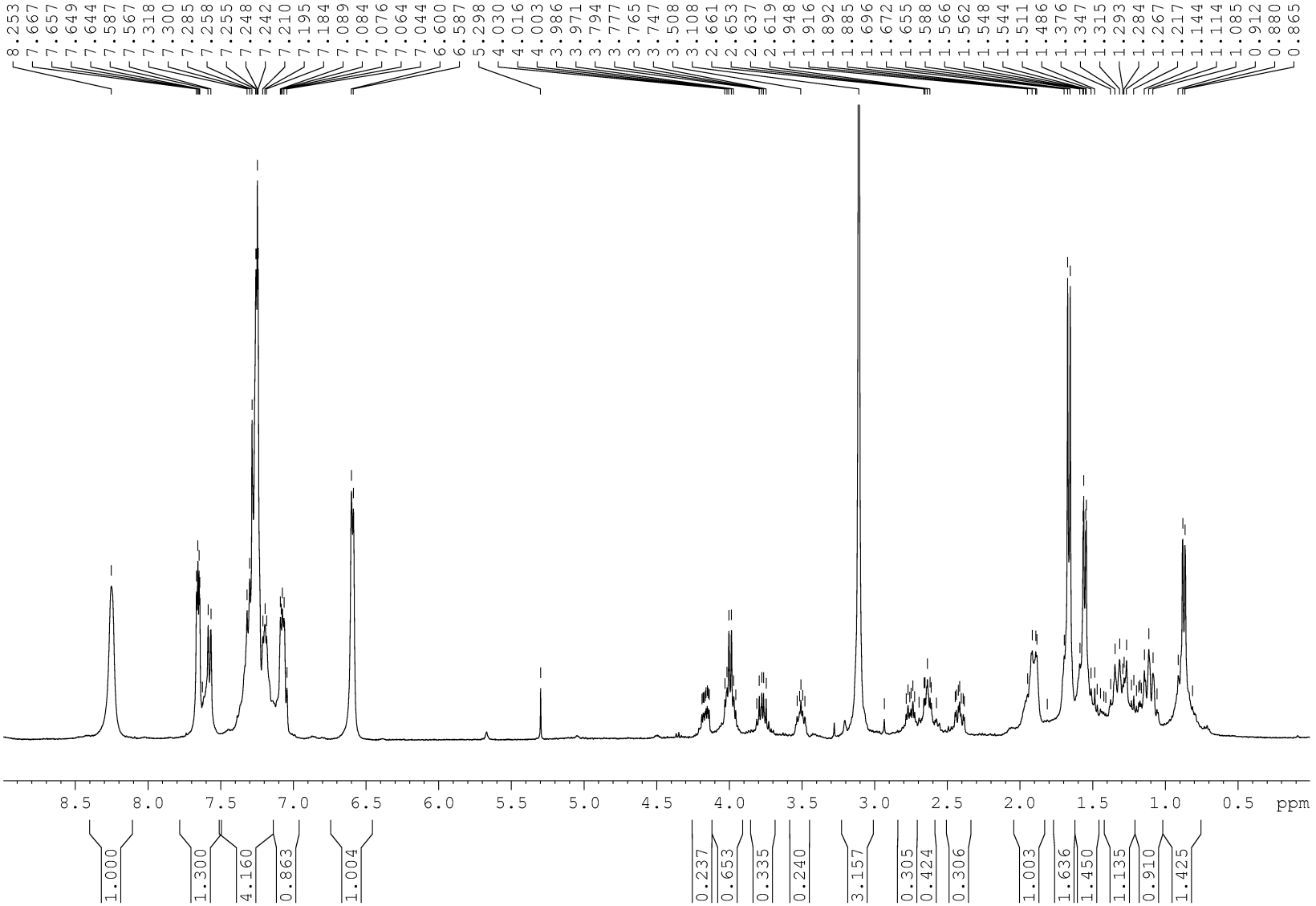
NMR ^{13}C of 2*R*(*S*),3*R*(*S*)-2-benzyl-3-methyl-4-phenyl-1-butanol (**16a**).



NMR ^{1}H of (*R*)-MTPA ester of 2*R*(*S*),3*R*(*S*)-2-benzyl-3-methyl-4-phenyl-1-butanol (**17a**).



NMR ^{1}H of (*R*)-PSPA ester of 2*R*(*S*),3*R*(*S*)-2-benzyl-3-methyl-4-phenyl-1-butanol (**18a**).



NMR ^{77}Se of (*R*)-PSPA ester of 2*R*(*S*),3*R*(*S*)-2-benzyl-3-methyl-4-phenyl-1-butanol (**18a**).