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OZONOLYTIC TRANSFORMATIONS OF OLEFINIC DERIVATIVES OF L-MENTHOL AND RICINOLIC ACID

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Ozonolysis and reduction of olefinic derivatives of ricinolic acid and L-menthol were studied using hydroxylamine hydrochloride and sodium trisacetoxyborohydride to reduce the peroxide products.

Key words: ozonolysis and reduction, olefinic derivatives of L-menthol and ricinolic acid, hydroxylamine hydrochloride, sodium trisacetoxyborohydride.

L-Menthol and ricinolic acid are promising substrates for chiral polyfunctional compounds owing to their high optical activities and availability from mint and castor oils. The polyfunctional compounds can then be used as convenient building blocks to synthesize organic compounds with more complicated structures.

Herein we report experimental results on expanding the synthetic potential of the title compounds using ozonolytic transformations of their olefinic derivatives such as castor oil (**1a**) and its acetate (**1b**), a secondary homoallylic alcohol (**6**) obtained from **1a** [1], and the regiospecific dehydration product of L-(-)-menthol (**10**) [2], (*R*)-menth-3-ene (**11**) and its 3-substituted analogs (**16**, **18**, **20**, **21**). The last compounds were prepared by acid dehydration (TsOH, PhH, Δ, 24 h) of previously reported [3] tertiary alcohols (**13-15**). 3-Methylmenthol (**13**) formed a single cycloolefin (**16**), like when oxalic acid is used (100°, 24 h) [4]. Dehydration of 3-ethylmenthol (**14**) produced in 87% a mixture (94:3:3) of all possible isomers at the double bond with the thermodynamically most stable 3-ethyl-*p*-menth-3-ene (**18**) dominating. The same situation was observed upon dehydration of phenyl-substituted menthol (**15**). The ratio of the thermodynamic (**20**) and kinetic (**21**) products was 7:3.

We used hydroxylamine hydrochloride as one of the reductants of the peroxide products. It has been used only in a few instances for these purposes and always in methanol solution. Depending on the nature of the substrates, aldehydes [5], aldoximes [6, 7], and methyl esters were formed [8].

It seemed logical to assume that hydroxylamine hydrochloride would react with the ozonolysis products in methanol to form at first aldehydes that would then convert to aldoximes and undergo Beckmann rearrangement to the corresponding nitriles, the nitrile groups of which would convert to carboxymethyls to form the methyl esters. We confirmed this hypothesis using the conversion of the ozonolysis peroxide products into a whole series of disubstituted (**1a**, **1b**), trisubstituted (**11**), and tetrasubstituted (**16**) olefins using hydroxylamine hydrochloride.

Oxidation of castor oil (**1a**, 85% ricinolic acid) and its acetate (**1b**) by ozone (3 mol) in methanol followed by work up with hydroxylamine hydrochloride produced mixtures (1.6:4.9:1 and 1:4.6:2.4) of hydroxyester **2**, C-9 diester **3**, and its mononitrile derivative **4**, respectively. Oxidation of homoallylic alcohol **7**, which is available from castor oil (**1a**) [1], with an equimolar amount of ozone and work up with hydroxylamine hydrochloride produced a mixture (1:1:1.6) of the same hydroxyester **2**, nitrile **8**, and methyl ester **9** of nonanoic acid. Work up of the peroxide products from ozonolysis of olefins **11** and **16** confirmed that their ketones are relatively unreactive compared with the aldehyde toward hydroxylamine hydrochloride. These cycloolefins were converted in high yields and sleectively into the previously described ketoester (**12**) [9, 10] and diketone **17** [4]. The products were identified using NMR spectroscopy and mass spectrometry in combination with chromatographic separation of the components.

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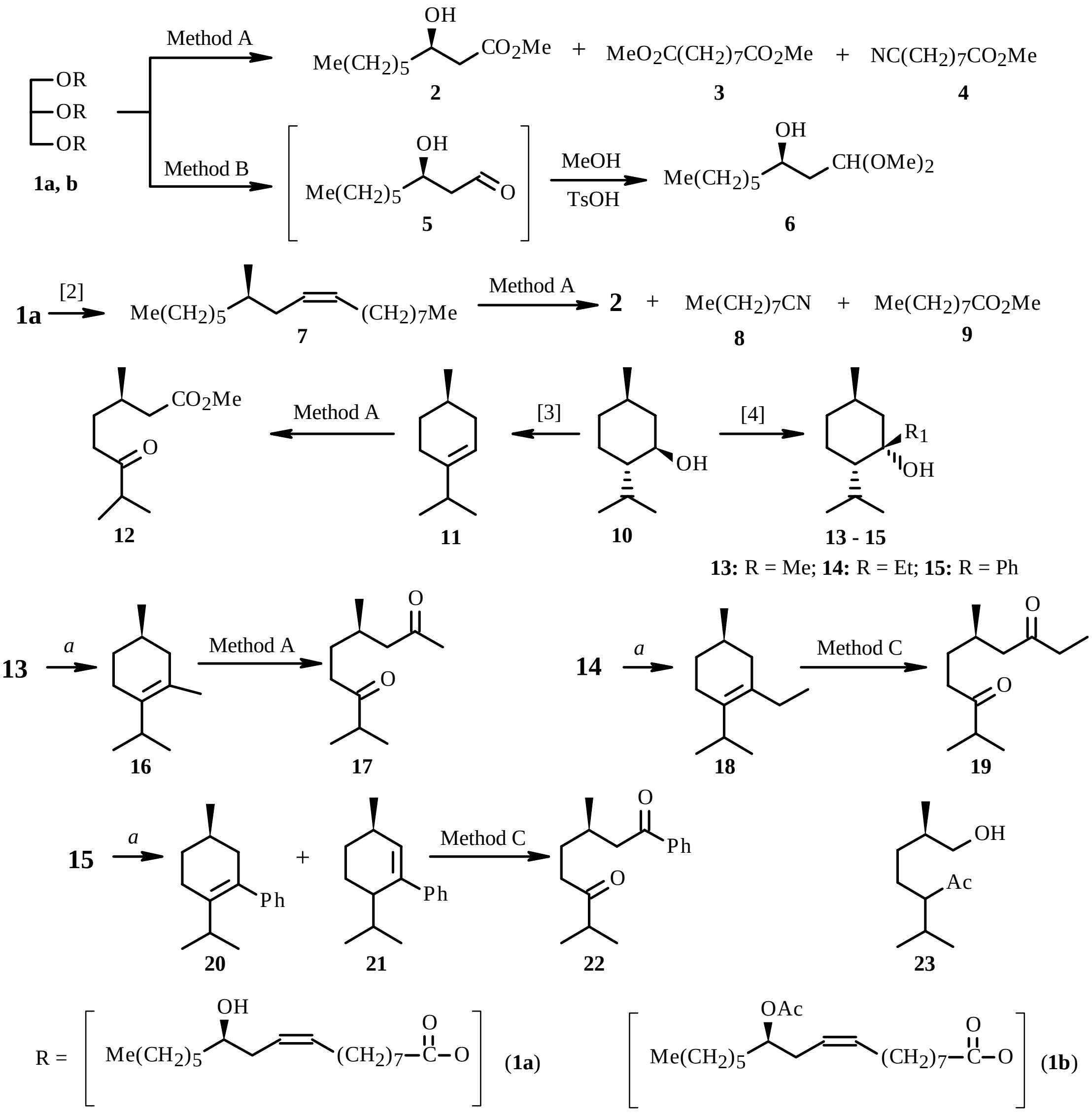

a. TsOH/PhH/Δ

Method A: 1. O_3/MeOH, 2. $NH_2OH \cdot HCl$, MeOH; Method B: O_3/CH_2Cl_2, 2. $NH_2OH \cdot HCl$, CH_2Cl_2;
Method C: 1. O_3/MeOH, 2. $NaBH(OAc)_3$

Interesting results were obtained for the ozonolysis of castor oil (**1a**) in methylenechloride. Successive work up with hydroxylamine hydrochloride (boiling, 10 h) and methanol in the presence of *p*-TsOH (boiling, 6 h) produced a single low-molecular-weight product, hydroxyacetal **6**. Therefore, hydroxylamine hydrochloride acted only as a reductant of the ozonides formed most probably under these conditions to give the precursor of **6**, (3*R*)-hydroxynonanal **5**.

Thus, previous results [5-8] and those presented herein indicate that hydroxylamine hydrochloride is an effective reductant of the peroxide products from ozonolysis of olefins to give carbonyl compounds. Depending on the nature of the substrate, solvent [11], and work up conditions, the resulting aldehydes undergo subsequent transformations by the route aldehyde → aldoxime → nitrile → ester, forming pure compounds or their mixtures, or the corresponding acetal.

Because dehydration of alcohols **14** and **15** produced mixtures enriched in one cycloolefin or another, we used sodium trisacetoxyborohydride, which can selectively reduce an aldehyde without affecting a ketone [12, 13], to convert their peroxide products from ozonolysis.

Ozonolysis and reduction of a mixture enriched in 3-ethyl-*p*-menth-3-ene (**18**) under the aforementioned conditions led to facile chromatographic separation of the corresponding diketone **19** from the other minor products. Reduction of the ozonolysis products of a mixture (7:3) of 3-phenylsubstituted menthenes **20** and **21** formed in 65% purity (according to GC and

NMR) diketone **22**. Another probable product of ozonolytic transformation of **21**, hydroxyketone **23**, was not observed, like the substrate itself (**21**). We explained this observation by the possible preferential polymerization of the styrene derivative (**21**) under the ozonolysis conditions.

EXPERIMENTAL

IR spectra of thin layers were recorded on a Specord M-82 instrument. NMR spectra were recorded on a Bruker AMX-300 spectrometer (300.13 MHz working frequency for ^{1}H and 75.47 for ^{13}C) in $CDCl_3$ and acetone-d_6 relative to TMS. Chromatography was performed on Chrom-5 [1.2-m column, silicone SE-30 stationary phase (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm), working temperature 50-300°C], Chrom-41 [2.4-m column, PEG-6000 stationary phase, working temperature 50-200°C], and Shimadzu GC-9A instruments [25-m quartz capillary column, OV-101 stationary phase, working temperature 80-260°C] with He carrier gas. Mass spectra were recorded in a computerized GC—MS consisting of an HP 5890 chromatograph with an HP 5972A mass-selective detector, a HP 5MS chromatography column (25 m × 0.25 mm), 40°C column temperature, 5-min isotherm, heating at 8°C/min to 250°C, injector temperature 260°C, mass spectral scanning of 28-300 amu in 1 s. Optical rotation was measured on a Perkin—Elmer 241-MC polarimeter. TLC used Sorbfil (Russia) SiO_2. Column chromatography used SiO_2 (70-230, Lancaster, England). The ozonator produced 40 mmol O_3 per hour. Isolation and chromatography used *t*-butylmethylether (TBME).

General Method of Dehydrating Methyl- (13), Ethyl- (14), and Phenyl- (15) *p*-Menthols. A mixture of the appropriate alcohol (20.0 mmol), which was prepared as before [3], and *p*-TsOH (1.15 g, 6.7 mmol) in benzene (20 mL) was boiled for 24 h, cooled, diluted with hexane (20 mL), washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried over $MgSO_4$, and evaporated.

(4*R*)-2,4-Dimethyl-1-(1-methylethyl)cyclohex-1-ene (16). Yield 2.74 g (90%), $[\alpha]_D^{20}$ +9.0 (*c* 2.5, $CHCl_3$). IR, PMR, and ^{13}C NMR data were practically identical to those previously reported [4].

(4*R*)-4-Methyl-2-ethyl-1-(1-methylethyl)cyclohex-1-ene (18). Yield 2.88 g (87%). IR spectrum (KBr, ν, cm^{-1}): 1645 (C=C). PMR spectrum ($CDCl_3$, δ, ppm): 0.75-1.00 [12H, m, CH_3C-4, $(CH_3)_2C$, $\underline{CH_3}CH_2$), 1.48-1.70 (2H, m, H_a-3, H_a-5), 1.84-2.08 (2H, m, H_e-3, H_e-5), 1.85-2.05 (3H, m, H-4, H-6), 2.05-2.10 (2H, m, $C\underline{H_2}CH_3$). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.43 (q, $\underline{C}H_3CH_2$), 21.91 [q, $CH(\underline{C}H_3)_2$], 22.32 (q, CH_3C-4), 22.95 (t, $CH_3\underline{C}H_2$), 25.76 (t, C-6), 25.82 [d, $\underline{C}H(CH_3)_2$], 28.6 (d, C-4), 34.55 (t, C-5), 38.32 (t, C-3), 129.79 (s, C-1), 134.0 (s, C-2).

(4*R*)-4-Methyl-2-phenyl-1-(1-methylethyl)cyclohex-1-ene (20) and (4*R*)-4-Methyl-2-phenyl-1-(1-methylethyl)cyclohex-2-ene (21). Yield 3.77 g (88%) of a mixture (7:3) of olefins **20** and **21**.

(4*R*)-4-Methyl-2-phenyl-1-(1-methylethyl)cyclohex-1-ene (20). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 20.72 (q, CH_3C-4), 21.34 and 21.58 [q, $CH(\underline{C}H_3)_2$], 22.49 (t, C-6), 29.18 [d, $\underline{C}H(CH_3)_2$], 30.26 (d, C-4), 31.23 (t, C-5), 41.49 (t, C-3), 126.09 (d, C-4′), 128.18 (d, C-3′, C-5′), 128.38 (d, C-2′, C-6′), 134.94 (s, C-2), 137.48 (s, C-1′), 143.87 (s, C-1).

(4*R*)-4-Methyl-2-phenyl-1-(1-methylethyl)cyclohex-2-ene (21). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 20.72 (q, CH_3C-4), 21.26 and 21.62 [q, $CH(\underline{C}H_3)_2$], 21.77 (t, C-6), 28.84 (d, C-4), 31.04 (t, C-5), 31.36 [d, $\underline{C}H(CH_3)_2$], 41.57 (d, C-1), 125.15 (d, C-4′), 125.76 (d, C-3), 126.76 (d, C-3′, C-5′), 128.75 (d, C-2′, C-6′), 131.20 (s, C-2), 141.70 (s, C-1′).

General Ozonolysis Method of Olefins (1a, 1b, 7, 11, 16). Method A. An O_3/O_2 mixture (calc. 1 mol O_3 per 1 mol double bond) was bubbled through a solution of olefin (10.0 mmol) in absolute MeOH (50 mL) at 0°C. The reaction mixture was purged with Ar, stirred at 0°C, treated over 0.5 h with $NH_2OH\cdot HCl$ (2.4 g, 35.0 mmol, per one double bond), boiled until the peroxide disappeared (10 h), evaporated, diluted with CH_2Cl_2 (100 mL), and washed with H_2O. The organic layer was dried over Na_2SO_4 and evaporated.

Ozonolysis of Castor Oil (1a). Yield 10.1 g containing the methyl ester of 3*R*-hydroxynonanoic acid (**2**), dimethylester of nonanedioic acid (**3**), and methyl ester of 8-cyanooctanoic acid (**4**) in a 1.6:4.9:1 ratio according to GC.

Ozonolysis of Castor Oil Acetate (1b). Yield 9.2 g containing the methyl ester of 3*R*-hydroxynonanoic acid (**2**), dimethyl ester of nonanedioic acid (**3**), and methyl ester of 8-cyanooctanoic acid (**4**) in a 1:4.6:2.4 ratio according to GC.

Ozonolysis of *R*-Octadec-9*Z*-en-7-ol (7). Yield 2.6 g of product containing the methyl ester of 3*R*-hydroxynonanoic acid (**2**), nonanenitrile (**8**), and methyl ester of nonanoic acid (**9**) in a 1:1:1.6 ratio according to GC.

Methyl Ester of 3*R*-Hydroxynonanoic Acid (2). $[\alpha]_D^{20}$ -198.7° (*c* 0.08, CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 3420 (OH), 1740 (C=O), 1140 (C–O). PMR spectrum (acetone-d_6, δ, ppm, J/Hz): 0.93 (3H, t, ^3J = 7.0, H-9), 1.35 (8H, m, H-5—H-8), 1.52 (2H, m, H-4), 2.41 (1H, dd, ^2J = 15.1, ^3J = 8.1, H_a-2), 2.50 (1H, dd, ^2J = 15.1, ^3J = 4.8, H_b-2), 3.67 (3H, s, CO_2CH_3), 3.98-

4.03 (1H, m, H-3). ^{13}C NMR spectrum (acetone-d_6, δ, ppm): 13.32 (q, C-9), 22.24 (t, C-8), 25.51 (t, C-5), 28.97 (t, C-6), 31.56 (t, C-7), 36.90 (t, C-4), 41.96 (t, C-2), 50.50 (q, $CO_2\underline{C}H_3$), 67.54 (d, C-3), 171.89 (s, C-1). Mass spectrum (*m/z*, I_{rel}, %): 188 (0.3) $[M]^+$, 170 (1), 139 (8), 138 (8), 111 (0.6), 115 (1), 113 (8), 103 (100), 97 (8), 96 (10), 87 (8), 74 (100), 59 (8), 45 (7), 31 (10).

Methyl Ester of 8-Cyanooctanoic Acid (4). IR spectrum (KBr, ν, cm^{-1}): 2220 (C≡N), 1745 (C=O). PMR spectrum (acetone-d_6, δ, ppm, J/Hz): 1.35 (6H, m, H-4—H-6), 1.40-1.50 (2H, m, H-7), 1.55-1.65 (2H, m, H-3), 2.30 (2H, t, J = 7.2, H-2), 2.46 (2H, t, J = 7.0, H-8), 3.61 (3H, s, CO_2CH_3). ^{13}C NMR spectrum (acetone-d_6, δ, ppm): 16.04 (t, C-8), 24.47 (t, C-3), 25.08 (t, C-7), 28.57 (t, C-4—C-6), 34.85 (t, C-2), 50.42 (q, $CO_2\underline{C}H_3$), 120.00 (s, C-9), 173.03 (s, C-1). Mass spectrum (*m/z*, I_{rel}, %): 183 (0.2) $[M]^+$, 152 (39), 124 (21), 123 (20), 110 (19), 111 (7), 98 (9), 97 (32), 96 (9), 83 (32), 82 (25), 74 (100), 69 (11), 68 (7), 59 (39), 54 (8), 41 (25), 40 (8).

Nonanenitrile (8). IR spectrum (KBr, ν, cm^{-1}): 2230 (C≡N). PMR spectrum (acetone-d_6, δ, ppm, J/Hz): 0.94 (3H, t, ^3J = 7.0, H-9), 1.3-1.5 (10H, m, H-4—H-8), 1.68 (2H, q, J = 7.0, H-3), 2.50 (2H, t, J = 7.0, H-2). ^{13}C NMR spectrum (acetone-d_6, δ, ppm): 13.39 (q, C-9), 16.09 (t, C-2), 22.32 (t, C-8), 25.17 (t, C-3), 29.06 (q, C-4—C-6), 31.46 (q, C-7), 92.41 (s, C-1).

Ozonolysis of (*R*)-Menth-3-ene (11). 3-Menthene (**11**) isolated as before [2] afforded after chromatography [SiO_2, PE:MTBE (50:1), R_f 0.34] the methyl ester of 5*R*,7-dimethyl-6-oxooctanoic acid (**12**, 1.30 g, 65%), $[\alpha]_D^{23}$ +9.5° (*c* 5.27, $CHCl_3$). IR and NMR spectra were practically identical to those reported previously [9, 10].

Ozonolysis of (*R*)-3-Methyl-*p*-menth-3-ene (16). 3-Methylmenthene (**16**) isolated as before [2] afforded (4*R*)-4,8-dimethyl-2,7-nonanedione (**17**, 1.59 g, 86%), $[\alpha]_D^{20}$ +8.9° (*c* 2.5, $CHCl_3$). IR and NMR spectra were practically identical to those reported previously [4].

(3*R*)-1,1-Dimethoxy-3-nonanol (6). Method B. An O_3/O_2 mixture (calc. 3 mol O_3 per 1 mol castor oil) was bubbled through a solution of castor oil (**1a**, 1.0 g, 1.1 mmol) in CH_2Cl_2 (10 mL) at 0°C. The reaction mixture was purged with Ar, diluted with CH_2Cl_2 (6 mL), stirred at 0°C, treated over 0.5 h with $NH_2OH\cdot HCl$ (0.8 g, 11.55 mmol), boiled until the peroxide disappeared (10 h), diluted with CH_2Cl_2 (100 mL), and washed with H_2O. The organic layer was dried over Na_2SO_4 and evaporated. The solid (0.94 g) was boiled for 6 h with MeOH (5 mL) in the presence of a catalytic amount of *p*-TsOH. The solvent was evaporated. The remainder was diluted with MTBE (100 mL) and washed with H_2O. The organic layer was dried over Na_2SO_4 and evaporated. The solid was chromatographed (SiO_2, CH_2Cl_2, R_f 0.45) to afford **6** (0.42 g, 98%). The IR and NMR spectra were practically identical to those reported previously [14].

General Ozonolysis Method of 3-Ethyl- (18) and 3-Phenyl- (20, 21) *p*-menth-3-enes. Method B. An O_3/O_2 mixture was bubbled through a stirred solution of olefin (10.0 mmol) and glacial AcOH (1.20 g, 20.0 mmol) in CH_2Cl_2 (28 mL) at -4 to -2°C until 10.3 mmol of O_3 was absorbed. The reaction mixture was purged with Ar, diluted with CH_2Cl_2 (14 mL), stirred at 10°C, and treated with a previously prepared suspension of $NaBH(OAc)_3$ [prepared by adding a solution of glacial AcOH (8.22 g, 137.0 mmol) in CH_2Cl_2 (14 mL) to a suspension of $NaBH_4$ (1.74 g, 45.8 mmol) in CH_2Cl_2 (69 mL) with subsequent stirring for 2 h]. The reaction mixture was warmed to room temperature, stirred for 3 h, cooled to 10°C, and treated with a solution of NaOH (3.12 g) in water (69 mL). The organic layer was separated, washed successively with saturated NH_4Cl solution and water, dried over Na_2SO_4, and evaporated.

2,6*R*-Dimethyl-3,8-decanedione (19). Yield 1.44 g (73%), $[\alpha]_D^{20}$ +7.3° (*c* 1.5, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1712 (C=O). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.88 (3H, d, J = 2.0, CH_3C-6), 1.08 (6H, d, J = 2.0, CH_3C-2, C-1), 2.11 (3H, s, H-10), 0.93-1.00 (2H, m, H-5), 1.15-1.65 (1H, m, H-6), 2.15-2.65 (6H, m, H-4, H-7, H-9). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 18.33 (q, H-1, CH_3-2), 19.71 (d, CH_3C-6), 28.36 (q, C-10), 31.95 (t, C-5), 36.52 (t, C-7), 37.99 (t, C-9), 40.65 (d, C-2), 49.74 (t, C-4), 211.21 (s, C-8), 214.66 (s, C-3).

3*R*,7-Dimethyl-1-phenyl-1,6-octanedione (22). Yield 1.60 g (65%), $[\alpha]_D^{20}$ -14.9° (*c* 2.5, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1708 (C=O), 1594 (Ar). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.02 (3H, d, ^3J = 6.6, CH_3C-4), 1.09 (6H, d, CH_3C-9, H-10), 1.40-1.60 and 1.62-1.75 (2H, m, H-5), 2.10-2.25 (1H, m, H-4), 2.45-2.60 (2H, m, H-6), 2.63 (1H, septet, ^3J = 6.7, H-8), 2.71 (1H, dd, ^2J = 14.1, ^3J = 7.8, H-3), 2.95 (1H, dd, ^2J = 14.1, ^3J = 5.7, H-3), 7.47 (2H, t, ^3J = 7.2, H-3, H-5), 7.58 (1H, t, ^3J = 7.2, H-4), 7.95 (2H, d, ^3J = 7.2, H-2, H-6). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 18.30 (q, CH_3C-8, C-9), 19.84 (q, CH_3C-4), 29.34 (d, C-4), 30.82 (t, C-5), 38.08 (t, C-6), 40.81 (d, C-8), 45.78 (t, C-3), 128.04 (d, C-3′, C-5′), 128.56 (d, C-2′, C-6′), 132.95 (d, C-4′), 137.28 (s, C-1′), 199.87 (s, C-2), 214.62 (s, C-7).

REFERENCES

1. G. Yu. Ishmuratov, R. Ya. Kharisov, A. Kh. Shayakhmetova, L. P. Botsman, O. V. Shitikova, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 529 (2005).
2. R. Appel and H.-D. Wihler, *Chem. Ber.*, **109**, 3446 (1976).
3. S. Panev and V. Dimitrov, *Tetrahedron: Asymmetry*, **11**, 1517 (2000).
4. G. Yu. Ishmuratov, M. P. Yakovleva, G. V. Zaripova, L. P. Botsman, R. R. Muslukhov, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 451 (2004).
5. A. G. Mustafin, D. I. D′yachenko, R. R. Gataullin, G. Yu. Ishmuratov, R. Ya. Kharisov, I. B. Abdrakhmanov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 937 (2003).
6. USSR Pat. No. 1622366; *Byull. Izobret.*, No. 3 (1991).
7. V. N. Odinokov, G. Yu. Ishmuratov, O. S. Kukovinets, R. Ya. Kharisov, E. A. Lozhkina, A. G. Mustafin, I. B. Abdrakhmanov, and G. A. Tolstikov, *Zh. Org. Khim.*, **34**, 229 (1998).
8. R. R. Gataullin, Author's Abstract of a Doctoral Dissertation in Chemical Sciences, Ufa (2004).
9. V. N. Odinokov, G. Yu. Ishmuratov, M. P. Yakovleva, R. L. Safiullin, A. N. Volgarev, V. D. Komissarov, R. R. Muslukhov, and G. A. Tolstikov, *Dokl. Akad. Nauk*, **326**, 842 (1992).
10. V. N. Odinokov, G. Yu. Ishmuratov, M. P. Yakovleva, R. L. Safiullin, V. D. Komissarov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1301 (1993).
11. G. Hilgetag and A. Martin, eds., *Weygand—Hilgetag Preparative Organic Chemistry*, Wiley-Interscience, Chichester, Engl. (1979).
12. G. Yu. Ishmuratov, R. Ya. Kharisov, M. P. Yakovleva, O. V. Botsman, R. R. Muslukhov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 198 (1999).
13. G. Yu. Ishmuratov, R. Ya. Kharisov, M. P. Yakovleva, O. V. Botsman, R. R. Muslukhov, and G. A. Tolstikov, *Zh. Org. Khim.*, **37**, 49 (2001).
14. J. Kula, T. B. Quang, and M. Sikora, *Tetrahedron: Asymmetry*, **11**, 943 (2000).