A novel approach to the synthesis of benzoic and cinnamic acid derivatives with nor-isoprenoid substituents

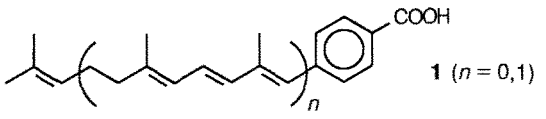
*G. V. Kryshtal', G. M. Zhdankina, and E. P. Serebryakov**

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

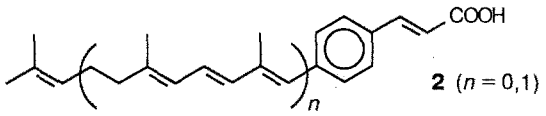
A novel strategy for the synthesis of 4-(nor-polyprenyl)-substituted benzoic acids and their esters of the general formula **1** as well as their vinylogs of the type **2**, based on the use of terephthalic aldehyde (**3**) and its tetramethyl acetal (**13**), is elaborated. The carbonyl groups in dialdehydes **3** and **12** can be selectively involved in the reaction sequences leading to the introduction of both aliphatic and functional substituents in positions 1 and 4 of the benzene ring.

Key words: terephthalic aldehyde; 1,4-bis(dimetoxymethyl)benzene; Wittig reaction; acetal condensation; regiocontrol.

The derivatives of 4-(nor-polyprenyl)-substituted benzoic acids of the general formula **1** as well as their vinyl analogs of the type **2** offer promise as compounds that possess multi-functional physiological activity (hypocholesterolemic, antitumor, antithrombotic, etc.) and do not cause hypervitaminosis and other side effects,[1] or as intermediates for the preparation of such compounds.



1 ($n = 0,1$)



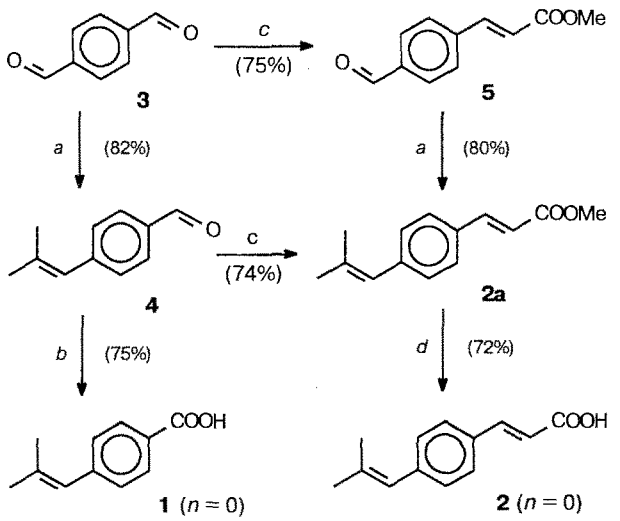
2 ($n = 0,1$)

The known schemes of the synthesis of these compounds[2–4] include transformations which require the use of alkali metal hydrides, organolithium reagents, or alkali metal alkoxides in anhydrous media.

In this paper we propose an alternative method for the preparation of type **1** 4-(nor-polyprenyl)-substituted benzoic acids and the corresponding type **2** vinyl analogs starting from terephthalic aldehyde (**3**). The method is based on the known ability of aromatic dialdehydes to undergo a selective Wittig reaction involving one of the aldehyde groups.[5,6]

For example, the interaction of **3** with 1.0 equiv. of isopropyltriphenylphosphonium iodide under the conditions of phase transfer catalysis (PTC) in the system $Cl_2C{=}CCl_2/K_2CO_3$ (solid) affords 4-(2-methyl-1-propenyl)benzaldehyde (**4**). Compound **4** is then converted by standard procedures to either 4-(2-methyl-1-propenyl)benzoic acid **1** ($n = 0$) or methyl ester of its vinyl analog (**2a**). Alkaline hydrolysis of the latter gives the corresponding acid **2** ($n = 0$) (Scheme 1). The sequence of the two Wittig reactions is reversible, that is, compound **3** can be converted initially to methyl 4-formylcinnamate (**5**) and compound **5** is converted thereafter to ester **2a**; the overall yield of compound **2a**, based on **3**, is practically equal (~60 %) in both cases.

Scheme 1



a. [*i*-PrPPh$_3$]$^+$I$^-$, K_2CO_3(solid)/$Cl_2C{=}CCl_2$, Δ; *b*. Ag_2O, NaOH—H_2O; *c*. $Ph_3P{=}CHCOOMe$, PhH, Δ; *d*. KOH, EtOH (aq.), Δ.

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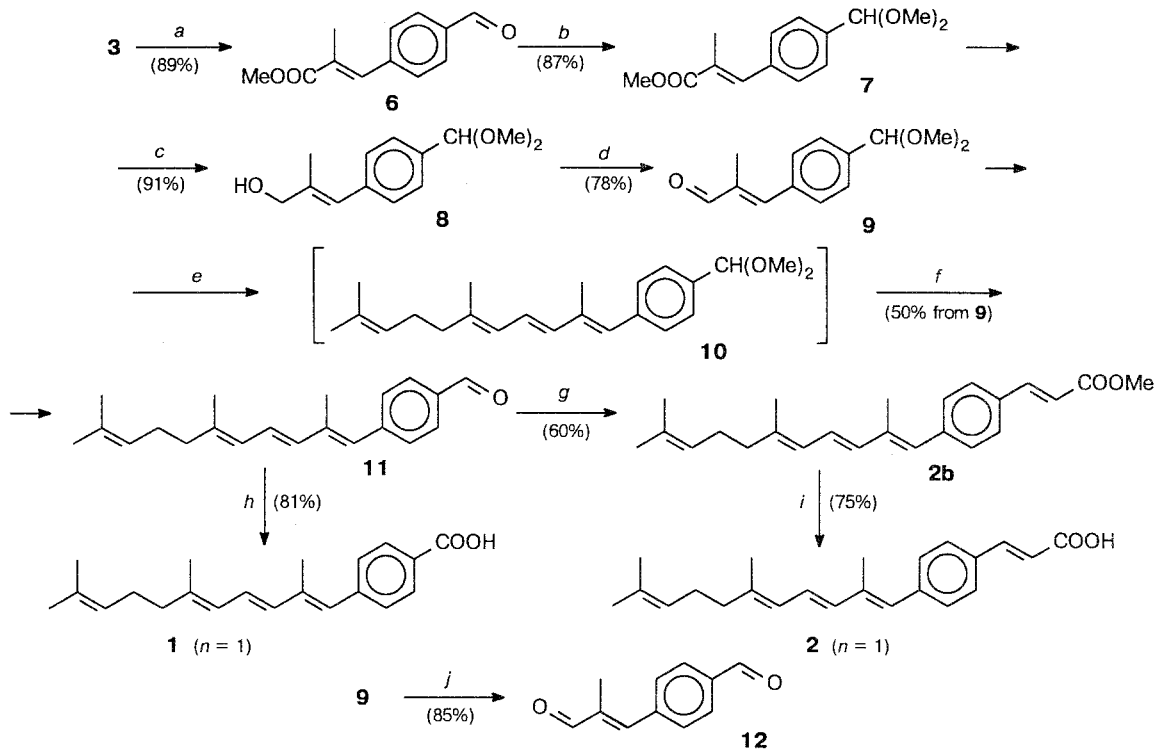
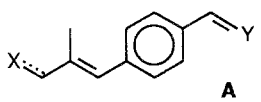
Scheme 2



a. $[Ph_3PCH(Me)COOMe]^+I^-$, $K_2CO_3/(CH_2CH_2O)_2$, Δ; *b*. $HC(OMe)_3$, $HClO_4$ (Cat.); *c*. $LiAlH_4$, ether; *d*. PCC, CH_2Cl_2; *e*. $[GerPPh_3]^+Br^-$, $K_2CO_3/(CH_2CH_2O)_2$, Δ; *f*. SiO_2, chromatography; *g*. $Ph_3P{=}CHCOOMe$, PhH, Δ; *h*. Ag_2O, NaOH—H_2O; *i*. KOH, EtOH (aq.), Δ; *j*. KU-2-8 cationite (H^+), H_2O.

The consecutive conversion of the aldehyde groups of compound **3** by various routes makes it possible to synthesize the 4-substituted acids **1** (n = 1) as well as acids **2** (n = 1) with a longer nor-polyprenoid chain (Scheme 2). In the first step of the synthesis aldehyde **3** was made to react with 1-methoxycarbonylmethylidenetriphenylphosphonium iodide under PTC to give the olefinic aldehydo ester **6**. The remaining free aldehyde group was protected by its conversion to dimethyl acetal (**7**). This made it possible to selectively reduce the ester group in **7** to an alcohol group with $LiAlH_4$ and to transform the resulting allylic alcohol **8** to the α,β-unsaturated aldehyde **9** by oxidation with pyridinium chlorochromate (PCC). Compounds **6**—**9** are synthetic equivalents of the bifunctional synthon **A**, which is a promising intermediate for the preparation of partly aromatic compounds with unsaturated side chains in positions 1 and 4 of the benzene ring.



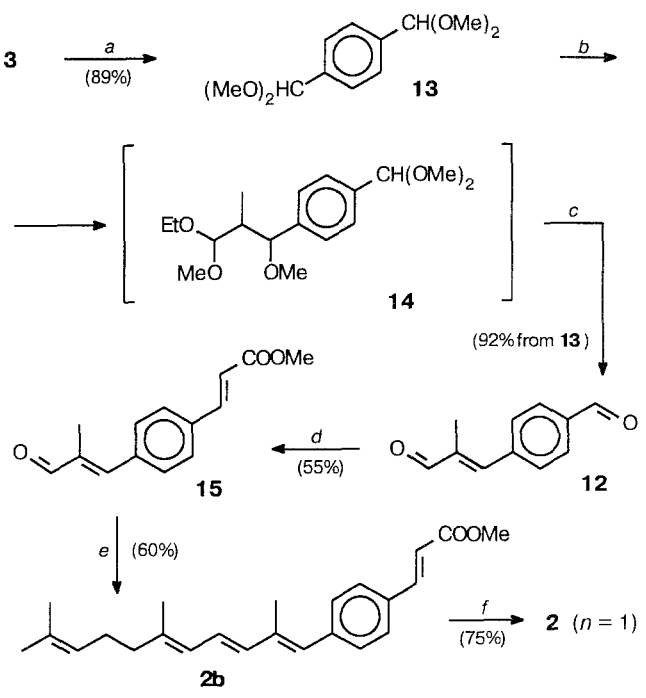
A

Thus, the reaction of enal **9** with geranyltriphenylphosphonium bromide (GTPB) under PTC conditions afforded the polyene acetal **10** which was hydrolized to give the corresponding aldehyde (**11**). Oxidation of the latter yielded 4-(2,6,10-trimethyl-1,3,5,9-undecatetraenyl)benzoic acid **1** (n = 1), while olefination of **11** according to Wittig led to methyl 4-(2,6,10-trimethyl-1,3,5,9-undecatetraenyl)cinnamate (**2b**) which was hydrolized to produce the corresponding acid **2** (n = 1) (Scheme 2).

Hydrolysis of aldehydoacetal **9** yielded the corresponding dialdehyde **12**. The same dialdehyde was also obtained using the «acetal» scheme, which is based on the condensation of acetals with vinyl esters by the controlled addition of terephthalic aldehyde tetramethyl acetal (**13**) to ethyl 1-propenyl ether to only one of the two acetal groups of **13** (Scheme 3). The exhaustive hydrolysis of the intermedate trialkoxyacetal **14** afforded dialdehyde **12**. Of the two carbonyl groups present in compound **12**, the CHO group attached to the benzene ring entered the Wittig reaction more easily. Interaction between equimolar amounts of dialdehyde **12** and carbomethoxymethylenetriphenylphosphorane gave the unsaturated aldehyde **15** as the main product with reasonable selectivity. The structure of this compound was confirmed by the ^1H NMR spectrum, in particular, by the signal at 9.5 ppm associated with an aliphatic aldehyde group, and by the absence of the signal at 10.0 ppm characteristic of an aromatic aldehyde.

The unaffected aldehyde group in compound **15** makes it possible to create a second side chain by selecting the appropriate Wittig reagent. The structure

Scheme 3



a. $HC(OMe)_3$, $HClO_4$ (Cat.); *b*. $CH_3CH{=}CHOEt$, $ZnCl_2$/AcOEt; *c*. AcOH—AcONa—H_2O, Δ; *d*. $Ph_3P{=}CHCOOMe$, PhH, Δ; *e*. $[GerPPh_3]^+Br^-$, $K_2CO_3/(CH_2CH_2O)_2$, Δ; *f*. KOH, EtOH (aq.), Δ.

of this side chain is determined only by the aliphatic substituent in the triphenylphosphonium salt used. For example, the reaction with GTPB under PTC conditions gave a homogeneous product identical to ester **2b** prepared according to Scheme 2 above.

The overall yield over eight steps of the synthesis of acid **2** (n = 1) from ester **2b** performed by the route outlined in Scheme 2 was ~16 %, while that obtained according to Scheme 3 was 27 % over six steps.

Experimental

The course of the reactions was monitored by TLC (Silufol plates) and GLC. The GLC analysis was carried out using an LKhM-80 instrument equipped with a flame ionization detector and a glass column (1.5 m×3 mm) packed with 5 % SE-30 or OV-17 on Chromaton N-AW-DMCS. The ^1H NMR spectra were recorded on Jeol FX-90Q (90 MHz) or Bruker WM-250 (250 MHz) spectrometers.

The reaction of aldehydes with triphenylphosphonium salts under PTC conditions (general procedure) (*cf.* ref. 1). A mixture of 1 mmol of an aldehyde, 1 mmol of a triphenylphosphonium salt, 2.0 g of K_2CO_3, and 0.1 mL of water in 10 mL of a solvent (tetrachloroethylene or dioxane) was stirred for several hours at 100—120 °C until the disappearence of the starting aldehyde according to GLC or TLC. The reaction mixture was cooled, the precipitate was separated by filtration and washed with ether, the filtrate was concentrated, and the residue was purified by chromatography on a column packed with SiO_2 (with 1:1 benzene—hexane as the eluent).

This procedure was used for preparation of compounds **4**, **6**, **10**, **2a**, and **2b**.

3.9 g of dialdehyde **3** and 13.0 g of isopropyltriphenylphosphonium iodide yielded 3.95 g (82 %) of compound **4** as a light-yellow oil; b.p. 92—95 °C (0.6 Torr); n_D^{20} 1.5910. ^1H NMR, δ: 1.9 and 2.0 (both s, 6 H, 2 CH_3); 6.3 (s, 1 H, CH=); 7.35 (m, 2 H, Ar); 7.8 (m, 2 H, Ar); 9.95 (s, 1 H, CHO).

0.85 g of compound **5** and 2.16 g of isopropyltriphenylphosphonium iodide gave 0.86 g (80 %) of ester **2a** as a light-yellow oil; b.p. 135—140 °C (0.6 Torr); n_D^{20} 1.5840. ^1H NMR, δ: 1.88 (s, 6 H, 2 CH_3); 3.76 (s, 3 H, OCH_3); 6.25 (s, 1 H, $CH{=}CMe_3$); 6.4 (d, 1 H, CH=, J = 16 Hz); 7.4 (m, 4 H, Ar); 7.7 (d, 1 H, CH=, J = 16 Hz).

6.2 g of dialdehyde **3** and 21.5 g of 1-(methoxycarbonyl)methylidenetriphenylphosphonium iodide gave 8.4 g (89 %) of compound **6** as a light-yellow oil; b.p. 118—120 °C (0.5 Torr); n_D^{20} 1.5910. ^1H NMR, δ: 2.1 (s, 3 H, CH_3); 3.8 (s, 3 H, OCH_3); 7.4—8.0 (m, 5 H, Ar, CH=); 10.0 (s, 1 H, CHO).

1.1 g of aldehyde **9** and 2.48 g of geranyltriphenylphosphonium bromide (prepared as disclosed in ref. 8) gave acetal **10** which was completely hydrolized in the course of column chromatography on SiO_2 to yield the corresponding aldehyde **11**. The latter was isolated as a light-yellow semi-crystalline mass in 50 % yield (over two steps). ^1H NMR, δ: 1.6—2.2 (m, 16 H, 4 CH_3, 2 CH_2); 4.8 and 5.1 (both s, 1 H, CH=); 6.0—6.5 (m, 3 H, 3 CH=); 7.0—7.6 (m 5 H, Ar, CH=); 9.5 (s, 1 H, CHO).

0.8 g of aldehyde **15** and 1.73 g of geranyltriphenylphosphonium bromide gave 0.6 g (60 %) of acid **2b** as a light-yellow viscous oil. ^1H NMR, δ: 1.6—2.2 (m, 16 h, 4 CH_3, 2 CH_2); 3.8 (s, 3 H, OCH_3); 5.1 (br. s, 1 H, CH=); 5.9—6.1 (m, 2 H, 2 CH=); 6.3—6.6 (m, 3 H, 3 CH=); 7.2—7.7 (m, 5 H, Ar, CH=).

The reaction of aldehydes with methoxycarbonylmethylenetriphenylphosphorane (general procedure). A mixture of 1 mmol of aldehyde and 1 mmol of methoxycarbonylmethylenetriphenylphosphorane in 30 mL of benzene was refluxed for several hours (the course of the reaction being monitored by GLC or TLC) until the starting aldehyde disappeared. After the removal of the solvent the product was purified on a column packed with Al_2O_3 (1:1 benzene—hexane as the eluent).

This procedure was used for preparation of **5**, **2a**, **2b**, and **15**.

2.7 g of dialdehyde **3** and 6.5 g of methoxycarbonylmethylenetriphenylphosphorane gave 2.8 g (75 %) of compound **5** as a light-yellow crystalline solid; m.p. 81—82 °C. ^1H NMR, δ: 3.8 (s, 3 H, OCH_3); 6.4 and 6.55 (both d, 1 H, CH=, J = 16 Hz); 7.5—7.9 (m, 5 H, Ar, CH=); 10.0 (s, 1 H, CHO).

1.6 g of aldehyde **4** and 3.24 g of methoxycarbonylmethylenetriphenylphosphorane gave 1.6 g (74 %) of ester **2a** identical to that described above.

0.47 g of aldehyde **11** and 0.53 g of methoxycarbonylmethylenetriphenylphosphorane gave 0.35 g (74 %) of ester **2b** identical to that described above.

1.5 g of dialdehyde **12** and 3.0 g of methoxycarbonylmethylenetriphenylphosphorane gave 1.1 g (55 %) of compound **5** as a light-yellow semi-crystalline mass. ^1H NMR, δ: 2.1 (d, 3 H, CH_3, J = 1.5 Hz); 3.8 (s, 3 H, OCH_3); 6.0—6.5 (m, 2 H, 2 CH—); 7.2—7.7 (m, 5 H, Ar, CH=); 9.5 (d, 1 H, CHO, J = 1.5 Hz).

Acids 1 (n = 0, 1) prepared by the oxidation of aldehyde **4** or **11** with silver oxide according to the procedure of ref. 9 proved to be identical to those described in ref. 4. Yield of **1** (n = 0) 75 %. ^{1}H NMR, δ: 1.85 and 1.9 (both s, 6 H, 2 CH_3); 6.3 (s, 1 H, CH=); 7.3 and 7.9 (both m, 4 H, Ar); 12.7 (br. s, 1 H, COOH). UV (hexane), λ_{max}/nm: 270 (ε 16650). Yield of **1** (n = 1) 81 %. ^{1}H NMR, δ: 1.5—2.1 (m, 16 H, 4 CH_3, 2 CH_2); 5.1 (br. s, 1 H, CH=); 5.9 (m, 1 H, CH=); 6.4—6.7 (m, 3 H, 3 CH=); 7.3 and 8.0 (both m, 4 H, Ar); 10.35 (br. s, 1 H, COOH).

Acids 2 (n = 0, 1), prepared by the alkaline hydrolysis of ester **2a** or **2b** according to the procedure of ref. 4, were identical to those described there[4]. Yield of **2** (n = 0) 72 %. ^{1}H NMR, δ: 1.88 (s, 6 H, 2 CH_3); 6.3 (br. s, 1 H, $CH=CMe_2$); 6.4 (d, 1 H, CH=, J = 16 Hz); 7.2—7.5 (m, 4 H, Ar); 7.7 (d, 1 H, CH=, J = 16 Hz); 12.1 (br. s, 1 H, COOH). UV (heptane), λ_{max}/nm: 300 (ε 21900). Yield of **2** (n = 1) 75 %. ^{1}H NMR, δ: 1.7—2.15 (m, 16 H, 4 CH_3, 2 CH_2); 5.1 (br. s, 1 H, CH=); 5.9 (m, 2 H, 2 CH=); 6.4—6.7 (m, 3 H, 3 CH=); 7.3—7.7 (m, 5 H, Ar, CH=); 11.8 (br. s, 1 H, COOH). UV (DMSO), λ_{max}/nm: 340 (ε 10050).

Acetals 7 and 3 were synthesized according to the known procedure.[10] The reaction of compound **6** (10.2 g) and $HC(OMe)_3$ (6.5 g) afforded 10.6 g (87 %) of acetal **7** as a colorless oil; b.p. 125—127 °C (0.5 Torr); n_D^{20} 1.5410. ^{1}H NMR, δ: 2.05 (d, 3 H, CH_3, J = 1.5 Hz); 3.27 (s, 6 H, 2 OCH_3); 3.75 (s, 3 H, OCH_3); 5.35 (s, 1 H, $CH(OMe)_2$); 7.3—7.7 (m, 5 H, Ar, CH=). 2.2 g of aldehyde **3** and 3.6 mL of $HC(OMe)_3$ produced 3.3 g (89 %) of acetal **13** as a colorless oil, b.p. 105—110 °C (1.0 Torr); n_D^{20} 1.4780, identical to that described in ref. 11.

Alcohol 8 was prepared from 7.5 g of acetal **7** and 0.9 g of $LiAlH_4$ in abs. ether according to the standard procedure. Yield 6.1 g (91 %); b.p. 130—145 °C (0.4 Torr); n_D^{20} 1.5948. ^{1}H NMR, δ: 1.9 (d, 3 H, CH_3, J = 1.5 Hz); 2.8 (s, 1 H, OH); 3.3 (s, 6 H, 2 OCH_3); 4.1 (s, 2 H, CH_2); 5.4 and 5.55 (both s, 1 H, $CH(OMe)_2$); 6.3 and 6.5 (both br.s, 1 H, CH=); 7.3—7.6 (m, 4 H, Ar).

Aldehyde 9 was produced by stirring alcohol **8** (6.0 g) with PCC (8.2 g) in dry CH_2Cl_2 (0.5 h, ~20 °C). The product was purified on a column packed with Al_2O_3. Yield 4.7 g (78 %); b.p. 115—120 °C (0.5 Torr); n_D^{20} 1.5845. ^{1}H NMR, δ: 2.09 (d, 3 H, CH_3, J = 1.5 Hz); 3.25 (s, 6 H, 2 OCH_3); 5.35 (s, 1 H, $CH(OMe)_2$); 7.15 (m, 1 H, CH=); 7.4—7.7 (m, 4 H, Ar); 9.5 (d, 1 H, CHO, J = 1.5 Hz).

Dialdehyde 12. ***a.*** Hydrolysis of acetal **9** (4.4 g) over a KU-2-8 cation exchanger (in the H^+-form) according to the procedure given in ref. 12 yielded 3.0 g (85 %) of dialdehyde **12** as a light-yellow semi-crystalline mass. ^{1}H NMR, δ: 2.1 (d, 3 H, CH_3, J = 1.5 Hz); 7.3—7.9 (m, 5 H, Ar, CH=); 9.5 (d, 1 H, CHO, J = 1.5 Hz); 10.0 (s, 1 H, CHO).

b. 1.15 mL of ethyl 1-propenyl ether was added with stirring to acetal **13** (2.26 g) mixed with 1.0 mL of a 10 % solution of $ZnCl_2$ in dry AcOEt, so that the temperature of the mixture did not exceed 42 °C. After ~12 h 15 mL of a solution prepared from AcOH (100 mL), AcONa (10 g), and H_2O (6.5 g) was added, and the reaction mixture was refluxed with stirring for 4 h. Then the mixture was cooled, poured onto ice, and the product of the hydrolysis was extracted with ether. The combined ethereal extracts were washed with water, saturated $NaHCO_3$ solution, and once again with water. The solution was dried with $MgSO_4$ and concentrated *in vacuo* to afford 1.6 g (92 %) of dialdehyde **12** as a semi-crystalline mass. The ^{1}H NMR spectrum of the compound was given above.

References

1. E. P. Serebryakov and A. G. Nigmatov, *Khim.-Farm. Zh.*, 1990, **24**, 104 [*Pharm. Chem. J.*, 1990, **24** (Engl. Transl.)].
2. Ger. Offen. DE 3320544, *Chem. Abstrs.*, 1984, **101**, 7482.
3. Eur. Pat. Appl. EP 110397, *Chem. Abstrs.*, 1985, **102**, 6874.
4. Eur. Pat. Appl. EP 194693, *Chem. Abstrs.*, 1989, **111**, 57300.
5. Y. Bigot, M. Delmas, and A. Gaset, *Synth. Commun.*, 1983, **13**, 177.
6. B. Morgan and D. Dolphin, *J. Org. Chem.*, 1987, **52**, 5364.
7. A. Kh. Khusid and B. G. Kovalev, *Zh. Org. Khim.*, 1987, **23**, 71 [*J. Org. Chem. USSR*, 1987, **23** (Engl. Transl.)].
8. O. Isler, H. Grutmann, H. Lindlar, M. Montavon, R. Ruegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, 1956, **39**, 463.
9. L. I. Zakharkhin, A. P. Pryanishnikov, and S. T. Ovseenko, *Zh. Org. Khim.*, 1989, **25**, 779 [*J. Org. Chem. USSR*, 1989, **25** (Engl. Transl.)].
10. G. V. Kryshtal', V. Dvorzhak, Z. Arnol'd, and L. A. Yanovskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 921 [*Bull. Acad. Sci USSR, Div. Chem. Sci*, 1986, **35**, 838 (Engl. Transl.)].
11. W. Erlichmann and K. Friedlich, *Chem. Ber.*, 1961, **94**, 2217.
12. A. Kh. Khusid and N. V. Chizhova, *Zh. Org. Khim.*, 1982, **18**, 2275 [*J. Org. Chem. USSR*, 1982, **18** (Engl. Transl.)].

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