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Prostanoids: LXXXI.* Synthesis of (±)-2-Decarboxy-2-ethyl-19,20-dinor-18-carboxyprostaglandin E_1**

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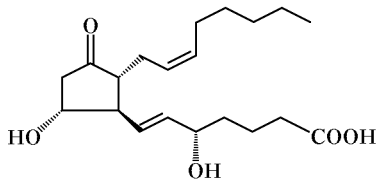
Abstract—2-Decarboxy-2-ethyl-19,20-dinor-18-carboxyprostaglandin E_1 was synthesized starting from (±)-7α-hydroxy-6β-hydroxymethyl-2-oxa-*cis*-bicyclo[3.3.0]octan-3-one.

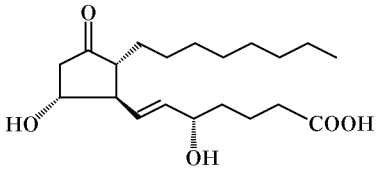
We previously developed a radically new procedure for modification of prostaglandins (PG) by designing structures isomeric to classical 9-LO prostanoids [2–5]. An important representative of the latter is 9-LO PGE_2 (**I**). The present communication reports on the synthesis of its α-dihydro derivative **II**. Compound **II** was selected as target product, taking into account its structural relation to 9-LO PGE_1 which can be regarded as alternative to natural prostaglandin E_1 (**III**) (Scheme 1). It is known that PGE_1 is a powerful vasodilator and antiaggregant; preparations based thereon are widely used in medicine [6, 7].

Scheme 2 illustrates the developed synthetic route to racemic analog of PGE_1 (**II**), starting from cyclopentane dihydroxy lactone **IV** [8] and utilizing phosphorus-containing building blocks. The hydroxy groups in **IV** were separately protected first with *tert*-butyldimethylsilyl (TBS) and then with tetrahydropyran-2-yl moieties under standard conditions [9]. The reduction of **VI** with $(i\text{-Bu})_2AlH$ gave compound **VII** which was brought into Wittig olefination using hexylidenetriphenylphosphorane. The free hydroxy group in **VIII** was converted into benzoyloxy, and hydrogenation of **IX** over Pd/C afforded saturated benzoate **X**. The subsequent stages included selective hydrolysis of the *tert*-butyldimethylsiloxy group in **X**, oxidation of alcohol **XI** with Collins' reagent, olefination of aldehyde **XII** according to Emmons–Horner (with the aid of phosphonate **XIII**), and reduction of enone **XIV** with sodium tetrahydridoborate. Diastereoisomeric products **XV** and **XVI** (with respect to C^{15}) were separated by column chromatography on silica gel. Protection of the 15-hydroxy group in 15α-isomer **XVI** with dihydropyran and alkaline hydrolysis of the ester groups in **XVII** gave hydroxy acid **XVIII**. The latter was oxidized with Jones' reagent, and protective groups were removed to obtain target product **II** in a satisfactory yield.

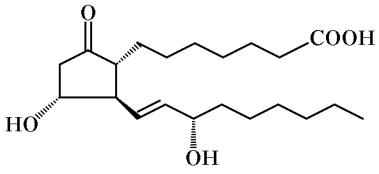
Scheme 1.



I, 9-LO PGE_2



II



III, PGE_1

* For communication LXXX, see [1].

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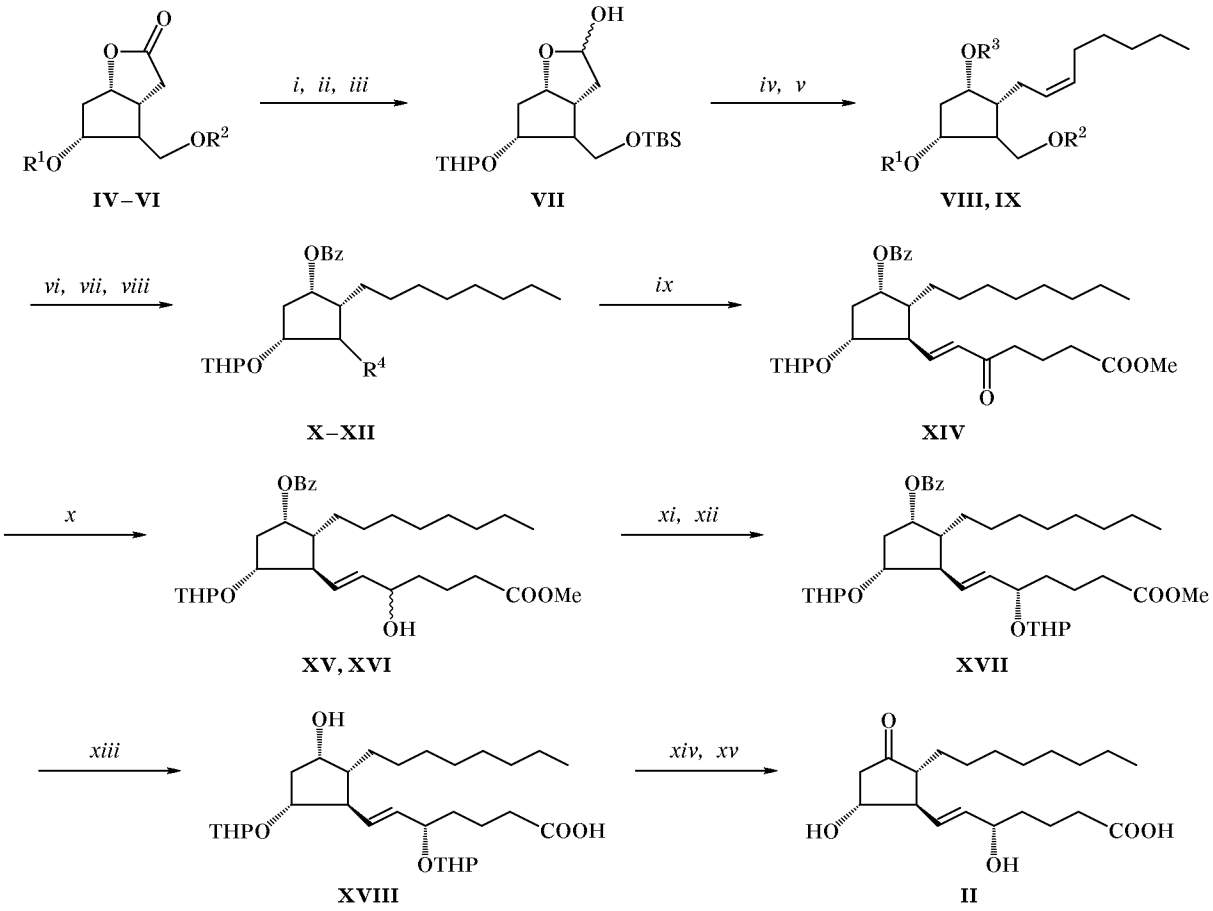
Scheme 2.



IV, $R^1 = R^2 = H$; **V**, $R^1 = H$, $R^2 = TBS$; **VI**, $R^1 = THP$, $R^2 = TBS$; **VIII**, $R^1 = THP$, $R^2 = TBS$, $R^3 = H$; **IX**, $R^1 = THP$, $R^2 = TBS$, $R^3 = Bz$; **X**, $R^4 = CH_2OTBS$; **XI**, $R^4 = CH_2OH$; **XII**, $R^4 = CHO$. Reagents and conditions: (*i*) 1.1 equiv of *t*-$BuMe_2SiCl$, imidazole, DMF, –78°C, 0°C, 1 h, 84%; (*ii*) 1.3 equiv of 2,3-dihydro-4*H*-pyran, CH_2Cl_2, 0°C, 92%; (*iii*) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, –78°C, 1 h; (*iv*) 1.4 equiv of $[Ph_3P{=}CHC_5H_{11}]$, benzene, 20°C, 3 h, 58%; (*v*) 1.5 equiv of BzCl, pyridine, 0°C, 45 min, 81%; (*vi*) 0.1 equiv of Pd/C, H_2, EtOH, 20°C, 2 h, 100%; (*vii*) 1 equiv of Bu_4NF, THF, 20°C, 2 h, 82%; (*viii*) $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2, 0°C, 15 min; (*ix*) 1.5 equiv of $(MeO)_2POCH_2CO(CH_2)_3CO_2Me$ (**XIII**), NaOH, CH_2Cl_2, 20°C, 20 min, 67%; (*x*) $NaBH_4$, EtOH, 0°C, 91%; (*xi*) SiO_2; (*xii*) 1.3 equiv of 2,3-dihydro-4*H*-pyran, CH_2Cl_2, 92%; (*xiii*) NaOH, MeOH, 20°C, 48 h; (*xiv*) H_2CrO_4, Me_2CO, –20°C, 30 min, 25%; (*xv*) AcOH–THF–H_2O, 2:3:1, 45°C, 2 h, 67%.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from thin films or suspensions in Nujol. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer operating at 300 and 75.47 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal reference.

Racemic compounds **V**–**IX** were synthesized from (±)-lactone **IV** by the procedures reported in [4] for the synthesis of optically active compounds **V**–**IX** from (–)-lactone **IV**. The spectral parameters of racemic compounds **V**–**IX** were consistent with those of the corresponding enantiomerically pure samples.

(±)-4α-Hydroxy-3β-[(3*S*)-hydroxy-6-carboxy-(1*E*)-hexenyl]-2α-octylcyclopentanone (II). To a solution of 0.23 g (0.41 mmol) of alcohol **XV** and a catalytic amount of *p*-toluenesulfonic acid in 3 ml of CH_2Cl_2 we added while stirring 0.08 g (0.9 mmol) of 2,3-dihydro-4*H*-pyran. The mixture was stirred for 30 min, 0.01 g of $NaHCO_3$ was added, the solvent was distilled off, and the residue was subjected to chromatography on silica gel using hexane–ethyl acetate (7:3) as eluent to obtain 0.18 g of ester **XVII**. A solution of 0.28 g of **XVII** and 0.56 g of NaOH in 10 ml of 50% aqueous methanol was stirred for 48 h at room temperature, acidified with 0.5 N hydrochloric acid to pH 6, and extracted with $CHCl_3$ (4 × 20 ml).

The extract was washed with a saturated aqueous solution of sodium chloride (2 × 10 ml), dried over magnesium sulfate, and evaporated. The residue was dissolved in 175 ml of acetone, the solution was cooled to –20°C under argon, and 29 ml of Jones's reagent (prepared from 6.5 g of CrO_3, 19 ml of H_2O, and 4.8 ml of H_2SO_4) was added. The mixture was stirred for 30 min, excess oxidant was decomposed by adding isopropyl alcohol, and a 5 N solution of NaOH was added while cooling until pH 5. The mixture was washed with 80 ml of a solution of sodium chloride and extracted with ether (6 × 50 ml), and the extract was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel. The purified keto acid was dissolved in a 10 ml of a mixture of acetic acid, tetrahydrofuran, and water at a ratio of 2:3:1, and the solution was stirred for 2 h at 45°C and evaporated. The residue was subjected to column chromatography on silica gel to obtain 0.05 g (27%) of compound **II** as an oily substance. IR spectrum, ν, cm^{-1}: 1670, 1750, 3600. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.89 t (3H, Me, J = 7 Hz), 1.15–2.93 m (22H, 11CH_2), 3.7–5.25 m (5H, 15-H, 11-H, 2O-H, COOH), 5.30–5.65 m (2H, CH=CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.94 ($C^{1'}$), 20.94 (C^{17}), 22.60 (C^1), 25.56 (C^6), 27.30 (C^7), 29.20 (C^5), 29.37 (C^4), 29.80 (C^3), 31.94 (C^2), 33.61 (C^{18}), 36.72 (C^{16}), 45.21 (C^{10}), 54.26 (C^8), 54.26 (C^{12}), 71.58 (C^{11}), 72.04 (C^{15}), 130.53 (C^{13}), 134.52 (C^{14}), 177.94 (COOH), 212.67 (CO).

(±)-1α-Benzoyloxy-3β-*tert*-butyldimethylsiloxymethyl-2α-octyl-4α-(2-tetrahydropyranyloxy)cyclopentane (X). To a solution of 1 g (1.83 mmol) of unsaturated ester **IX** in 30 ml of ethyl acetate we added 0.3 g of 10% Pd/C, and the mixture was stirred for 2 h under hydrogen, filtered, and evaporated to obtain 1 g (100%) of compound **X**. IR spectrum, ν, cm^{-1}: 1592, 1600, 1632, 1720, 3048, 3064. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.07 s (6H, 2Me), 0.85 t (3H, J = 7 Hz), 0.93 s (9H, 3CH_3), 5.41 m (1H, 1-H), 7.40–7.60 m and 8.05–8.10 m (5H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: –0.34 (2Me), 14.16 ($C^{8''}$), 18.35 (SiC), 19.45 and 19.65 ($C^{4'}$, THP), 22.68 ($C^{7''}$), 25.51 and 25.58 ($C^{1''}$), 25.97 (3Me), 27.85 ($C^{2''}$), 27.85 and 28.02 ($C^{5'}$, THP), 29.27 ($C^{3''}$), 29.44 ($C^{4''}$), 29.85 ($C^{5''}$), 30.97 and 31.18 ($C^{3'}$, THP), 31.9 ($C^{6''}$), 38.17 and 39.92 (C^5), 43.29 and 53.07 (C^2), 52.71 (C^3), 61.27 and 62.42 ($C^{6'}$, THP), 61.99 and 62.15 (CH_2O), 76.39 and 79.25 (C^4), 76.78 (C^1), 96.93 and 99.04 ($C^{2'}$, THP), 128.25 (C^m), 129.70 (C^o), 131.71 (C^i), 132.71 (C^p), 166.27 and 166.35 (CO_2).

(±)-1α-Benzoyloxy-3β-hydroxymethyl-2α-octyl-4α-(2-tetrahydropyranyloxy)cyclopentane (XI). A mixture of 4 g (7.3 mmol) of compound **X** and 2.32 g (7.35 mmol) of tetrabutylammonium fluoride in 7.5 ml of THF was stirred for 2 h at room temperature. It was then diluted with 200 ml of diethyl ether, washed in succession with 40 ml of an aqueous solution of $NaHCO_3$ and 80 ml of a saturated solution of NaCl, dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (4:1) as eluent to obtain 2.57 g (81%) of compound **XI** as a 3:2 (^1H NMR) mixture of diastereoisomers (R_f 0.11). Oily substance. IR spectrum, ν, cm^{-1}: 1680, 1740, 3450. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.83 t (3H, Me, J = 7 Hz), 4.60 m and 4.70 m (1H, 2′-H), 5.40 m (1H, 1-H), 7.40–7.60 m and 8.05–8.10 m (5H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.10 ($C^{8''}$), 19.41 and 20.22 ($C^{4'}$, THP), 22.61 ($C^{7''}$), 25.29 and 25.38 ($C^{2''}$), 27.70 and 27.78 ($C^{1''}$), 27.99 and 28.22 ($C^{5'}$, THP), 29.20 ($C^{3''}$), 29.37 ($C^{4''}$), 29.82 ($C^{5''}$), 30.94 and 31.19 ($C^{3'}$, THP), 31.82 ($C^{6''}$), 38.79 and 39.86 (C^5), 44.11 and 44.12 (C^2), 52.33 and 52.45 (C^3), 60.40 and 62.45 ($C^{6'}$, THP), 63.34 and 63.76 (CH_2OH), 75.65 and 75.74 (C^1), 79.58 and 80.23 (C^4), 98.00 and 99.57 ($C^{2'}$, THP), 128.25 and 128.30 (C^m), 128.30 and 129.63 (C^o), 130.73 and 130.85 (C^i), 132.76 and 132.84 (C^p), 166.18 and 166.22 (CO_2).

(±)-1α-Benzoyloxy-3β-[6-methoxycarbonyl-3-oxo-(1*E*)-hexenyl]-2α-octyl-4α-(2-tetrahydropyranyloxy)cyclopentane (XIV). A solution of 2 g of alcohol **XI** in 12 ml of methylene chloride was added with vigorous stirring at 0°C under argon to Collins' reagent prepared from 6.4 g of CrO_3 and 10.95 ml of pyridine in 80 ml of CH_2Cl_2. After 15 min (TLC), the mixture was filtered through a thin layer of silica gel, the filtrate was acidified to pH 6 with 2 N hydrochloric acid, and the organic phase was separated, washed with a saturated aqueous solution of NaCl (3 × 30 ml), dried over $MgSO_4$, and evaporated under reduced pressure to obtain 1.67 g of aldehyde **XII** (R_f 0.47; ethyl acetate–hexane, 3:7). IR spectrum, ν, cm^{-1}: 1500, 1590, 1610, 1720, 2740, 3020, 3040.

To a solution of 1.67 g of aldehyde **XII**, 1.29 g of phosphonate **XIII**, and 4.63 mg of benzyltriethylammonium chloride in 20 ml of methylene chloride we added under vigorous stirring at room temperature 0.37 ml of a 50% aqueous solution of NaOH. The mixture was diluted with 57 ml of CH_2Cl_2, acidified to pH 5 with 1 N hydrochloric acid, and the organic phase was separated, washed with a saturated aqueous solution of NaCl (3 × 15 ml), dried over $MgSO_4$, and

evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent ethyl acetate–hexane, 3:7; R_f 0.36) to isolate 1.7 g (67%) of enone **XIV** as a mixture of two diastereoisomers at a ratio of 3:2. IR spectrum, ν, cm^{-1}: 750, 1595, 1610, 1730, 3050, 3095. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.87 t (3H, Me, J = 7 Hz), 3.67 s (3H, OMe), 6.29 d and 6.26 d (1H, 2″-H, J = 16 Hz), 6.85, 6.85, 6.76, 6.73 d.d (1H, 1″-H, J = 16, 9 Hz), 7.40–7.60 m and 8.05–8.10 m (5H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.02 ($C^{8'''}$), 19.07 and 19.19 ($C^{5''}$), 19.19 and 19.37 ($C^{4'}$, THP), 22.61 and 22.63 ($C^{7'''}$), 25.29 and 25.35 ($C^{2'''}$), 27.50 ($C^{5'}$, THP), 29.10 ($C^{3'''}$), 29.24 ($C^{4'''}$), 29.64 ($C^{5'''}$), 30.66 ($C^{1'''}$), 31.73 and 31.87 ($C^{3'}$, THP), 33.03 ($C^{6''}$), 38.63 and 40.38 (C^5), 39.09 and 39.26 ($C^{4''}$), 47.83 (C^2), 51.47 (OMe), 53.82 and 54.34 (C^3), 61.82 and 62.41 ($C^{6'}$, THP), 74.82 and 75.07 (C^1), 79.23 and 81.26 (C^4), 96.78 and 98.91 ($C^{2'}$, THP), 128.31 (C^m), 129.55 (C^o), 130.51 and 130.82 (C^i), 131.20 and 131.35 ($C^{2''}$), 132.89 (C^p), 147.75 and 147.81 ($C^{1''}$), 165.92 and 166.00 (CO_2), 173.54 ($C^{7''}$), 199.02 and 199.16 ($C^{3''}$).

(±)-1α-Benzoyloxy-3β-[(3*R*- and 3*S*)-hydroxy-6-methoxycarbonyl-(1*E*)-hexenyl]-2α-octyl-4α-(2-tetrahydropyranyloxy)cyclopentanes XV and XVI. To a solution of 0.75 g of enone **XIV** in 10 ml of EtOH we added with stirring at 0°C a freshly prepared solution of 0.20 g of $NaBH_4$ in 10 ml of EtOH. The mixture was stirred for 30 min, 3 ml of MeOH was added, and the mixture was acidified to pH 5 with 3% hydrochloric acid and extracted with ethyl acetate (3 × 30 ml). The extract was washed with an aqueous solution of NaCl (2 × 15 ml), dried over $MgSO_4$, and evaporated under reduced pressure. The residue (yield 47%; a 3:2 mixture of diastereoisomers) was subjected to column chromatography on silica gel.

(±)-1α-Benzoyloxy-3β-[(3*R*)-hydroxy-6-methoxycarbonyl-(1*E*)-hexenyl]-2α-octyl-4α-(2-tetrahydropyranyloxy)cyclopentane (XV). IR spectrum, ν, cm^{-1}: 1740, 3450. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.87 t (3H, Me, J = 7 Hz), 3.63 s (3H, OMe), 4.50–4.70 m (1H, CH), 5.30–5.40 (1H, 4-H), 5.50–5.75 m (2H, CH=CH), 7.45–7.60 m and 8.00–8.10 m (5H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.96 ($C^{8'''}$), 18.84 and 19.30 ($C^{4'}$, THP), 20.77 ($C^{5''}$), 22.48 ($C^{7'''}$), 25.31 and 25.40 ($C^{2'''}$), 27.19 and 27.30 ($C^{5'}$, THP), 27.48 ($C^{1'''}$), 29.07 ($C^{3'''}$), 29.39 (C^4), 29.39 and 29.65 ($C^{5'''}$), 31.70 ($C^{6'''}$), 33.73 ($C^{6''}$), 36.58 ($C^{4''}$), 40.02 (C^5), 47.47 and 47.59 (C^2), 51.36 (OMe), 58.24 and 53.88 (C^3), 61.43 and 62.17 ($C^{6'}$, THP), 72.04 ($C^{3''}$), 74.82 and 75.11 (C^1), 81.57 (C^4), 96.14 and 98.71 ($C^{2'}$, THP), 128.19 (C^m), 129.47 (C^o), 130.63 (C^i), 132.19 and 132.39 ($C^{1''}$), 132.73 (C^p), 135.09 ($C^{2''}$), 165.99 (CO_2), 173.81 ($C^{7''}$).

(±)-1α-Benzoyloxy-3β-[(3*R*)-hydroxy-6-methoxycarbonyl-(1*E*)-hexenyl]-2α-octyl-4α-(2-tetrahydropyranyloxy)cyclopentane (XVI). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.04 ($C^{8'''}$), 19.23 and 19.35 ($C^{4'}$, THP), 20.94 and 21.03 ($C^{5''}$), 22.60 ($C^{7'''}$), 25.56 ($C^{2'''}$), 27.41 and 27.52 ($C^{5'}$, THP), 29.70 ($C^{1'''}$), 29.20 ($C^{3'''}$), 29.37 ($C^{4'''}$), 20.80 ($C^{5'''}$), 30.85 and 30.96 ($C^{3'}$, THP), 31.94 ($C^{6'''}$), 33.93 ($C^{6''}$), 36.73 ($C^{4''}$), 38.52 and 40.12 (C^5), 47.89 (C^2), 51.39 (OMe), 53.58 and 54.21 (C^3), 61.97 and 62.18 ($C^{6'}$, THP), 72.04 and 72.24 ($C^{3''}$), 75.39 and 75.15 (C^1), 79.94 and 81.46 (C^4), 96.41 and 96.87 ($C^{2'}$, THP), 128.33 (C^m), 129.63 (C^o), 130.87 (C^i), 132.57 and 132.84 ($C^{1''}$), 132.84 (C^p), 135.14 and 135.24 ($C^{2''}$), 166.16 (CO_2), 173.91 ($C^{7''}$).

REFERENCES

1. Akhmetvaleev, R.R., Baibulatova, G.M., Nuriev, I.F., Shitikova, O.V., and Miftakhov, M.S., *Russ. J. Org. Chem.*, 2001, vol. 37, no. 8, pp. 1085–1087.
2. Tolstikov, G.A., Akhmetvaleev, R.R., Zhurba, V.M., and Miftakhov, M.S., *Zh. Org. Khim.*, 1992, vol. 28, no. 9, pp. 1862–1869.
3. Miftakhov, M.S., Akhmetvaleev, R.R., Imaeva, L.R., Vostrikov, N.S., Saitova, M.Yu., Zarudii, F.S., and Tolstikov, G.A., *Khim.-Farm. Zh.*, 1996, vol. 30, no. 8, pp. 22–27.
4. Miftakhov, M.S., Imaeva, L.R., Fatykhov, A.A., and Akhmetvaleev, R.R., *Russ. J. Org. Chem.*, 1997, vol. 33, no. 1, pp. 47–54.
5. Imaeva, L.R., *Cand. Sci, (Chem.) Dissertation*, Ufa, 1998.
6. Nelson, N.A., Kelly, R.C., and Johnson, R.A., *Chem. Eng. News*, 1982, vol. 60, no. 22, pp. 30–44.
7. Collins, P.W. and Djnric, S.W., *Chem Rev.*, 1993, vol. 93, no. 4, pp. 1533–1564.
8. Tolstikov, G.A., Miftakhov, M.S., Valeev, F.A., Vostrikov, N.S., and Akhmetvaleev, R.R., *Zh. Org. Khim.*, 1984, vol. 20, no. 1, pp. 221–222.
9. Nicolson, R.C. and Verbruggen, H., *Tetrahedron Lett.*, 1983, vol. 24, no. 1, pp. 47–50.