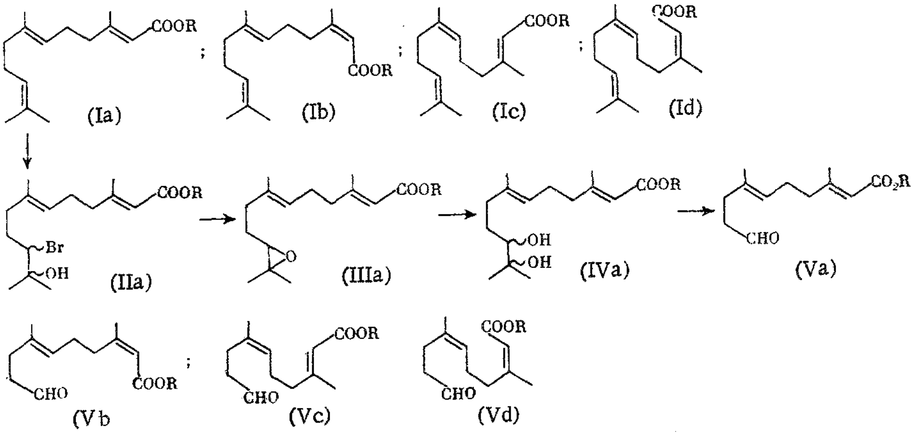
4. B. K. Nefedov and R. V. Dzhaparidze, Izv. Akad. Nauk GSSR, 3, No. 2, 129 (1977).
5. R. Y. Schultz and P. D. Montgomery, J. Catal., 13, 105 (1969).
6. K. K. Robinson, A. Hershman, J. H. Craddok, and J. F. Roth, J. Catal., 27, 389 (1972).
7. M. S. Jarrell and B. C. Gates, J. Catal., 40, 255 (1975).

BUILDING BLOCKS FOR ACYCLIC POLYISOPRENOID SYNTHESIS BASED ON ISOMERIC FARNESENATE ESTERS

N. Ya. Grigor'eva, I. M. Avrutov,
A. V. Semenovskii, V. N. Odinokov,
V. R. Akhunova, and G. A. Tolstikov

UDC 542.91:547.481:547.913.3

The simplest route to the synthesis of acyclic polyisoprenoids, especially polyprenols [1], comprises successively linking together blocks of 2-3 isoprenoid units having terminal functional groups which are capable of providing selective protection and undergoing various reactions. In this case, it is necessary that the geometry of the double bonds in such blocks should make it possible to construct polyisoprenoid chains in which the bonds have a given (E or Z) configuration and are in a given position. Blocks which satisfy these requirements can be obtained on the basis of four isomeric farnesenate esters (Ia-Id)



R=H, C_2H_5

One promising approach might be to react (Ia) with N-bromosuccinimide [2-4] to form the bromohydrin (IIa), and to convert this via the epoxide (IIIa) and diol (IVa) into the aldehyde ester (Va), which is obtained in an overall yield of 40-45%. When this sequence of reactions is applied to esters (Ib-Id) however, the yield of the corresponding aldehyde esters (Vb-Vd) is approximately halved. The yields cannot be increased by carrying out the same reactions starting from the tetrahydrofuran ethers of the corresponding isomeric farnesols.

In searching for a better route to the synthesis of aldehyde esters (V) we have undertaken a comparative study of other methods of converting the isopropylidene group in farnesenate esters (Ia-Id) into an aldehyde group. Oxidation of (Ia-Id) with OsO_4 in the presence of $NaIO_4$ [5] is evidently nonselective, attacking all of the double bonds, and the aldehyde esters (Va-Vd) are formed in insignificant amounts. The recently proposed method of oxidizing with OsO_4 in the presence of N-methylmorpholine oxide [6] followed by cleavage of the diols (IVa-IVd) with $NaIO_4$ was somewhat more successful, but the overall yields of (Vb-Vd) were still not more than 15-18% based on the corresponding (I). Approximately the same yields of (Va-Vd) are obtained by oxidizing (I) with p-methoxycarbonyl-perbenzoic acid [7] followed by conversion of the epoxides (III) via the diols (IV) into the aldehyde esters (V).

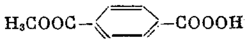
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Institute of Chemistry, Bashkir Branch of the Academy of Sciences of the USSR, Ufa. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 382-387, February, 1979. Original article submitted September 12, 1977.

0568-5230/79/2802-0353$07.50

TABLE 1. PMR, IR, and UV Spectra of Aldehyde Esters (V) and (VI) and Their Dimethyl Acetals (DMA)

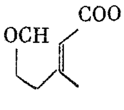
Compound	PMR spectrum δ, ppm (J, Hz)											IR spectrum, ν, cm^{-1} stretching vibrations			UV spectrum, λ, nm (log ε)
	$COOCH_2\underline{CH_3}$, t 3H (7)	$^7CCH_3$, s, 3H	$^3CCH_3$, s, 3H	$^9CH_2$, s, 2H	CH_2, m, 6H	OCH_3, s, 6H	$COOCH_2$, q, 2H (7)	OCHO, t, 1H (5)	^6CH, m, 1H	^2CH, s, 1H	CHO, unres. t, 1H	C=C, m	C=O, s	C—H (CHO group), m	
(Va)	1,17	1,55	2,05	2,05	2,1–2,6		4,0		5,06	5,5	9,6	1655	1730	2735	205 (3,8865), 208 (3,8865), 218 (3,8692)
(DMA)	1,15	1,51	2,04	2,04	2,1–2,5	3,1	3,97	4,12	5,10	5,5		1655	1725		
(Vb)	1,17	1,55	1,8	2,0–2,8			4,0		5,10	5,5	9,6	1655	1730	2735	205 (4,1614), 208 (4,1553), 217 (4,1139)
(DMA)	1,19	1,55	1,81	1,83	2,0–2,6	3,2	4,0	4,23	5,10	5,5		1650	1720		
(Vc)	1,20	1,65	2,08	2,08	2,1–2,5		4,0		5,03	5,5	9,62	1655	1730	2735	206 (3,7160), 208 (3,7243), 218 (3,7243)
(DMA)	1,21	1,65	2,10	2,10	2,2–2,6	3,2	4,0	4,16	5,00	5,51		1655	1725		
(Vd)	1,20	1,65	1,84	2,0–2,8			4,0		5,10	5,5	9,62	1655	1730	2735	205 (3,8993), 218 (3,9395)
(DMA)	1,19	1,62	1,83	2,1–2,8		3,18	4,0	4,24	5,10	5,5					
(VIa)	1,16		2,06		2,4–3,0		3,96			5,54	9,65	1650	1725	2740	219 (3,740)
(DMA)	1,20		2,04		2,4–3,0	3,19	4,0	4,2		5,52		1660	1725		
(IVb)	1,20		1,85		2,4–3,0		4,0			5,55	9,64	1655	1720	2740	220 (3,686)
(DMA)	1,20		1,85		2,4–3,0	3,18	4,0	4,2		5,51		1650	1725		

TABLE 2. Comparison of Yields of (Va-Vd), %, in Studied Synthesis Methods

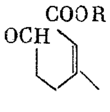
Initial farnesenate ester (Ia-Id)	Synthesis method (oxidizing agent)			
	O_3*	NBS	OsO_4	
(Ia)	48	44	–	–
(Ib)	44	16	–	–
(Ic)	56	15	16	18
(Id)	60	18	15	15

*Yields are based on (I) reacted.

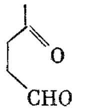
Isoprenoid aldehydes may also be obtained by preparative ozonolysis [8,9]. In the case of esters (Ia-Id), reduction of the corresponding ozonides as described in [9] and evaporation of the solvent gives a mixture of the initial ester (Ia-Id) and the corresponding aldehyde esters (Va-Vd) and either (VIa), in the case of (Ia) and (Ic), or (VIb), in the case of (Ib) and (Id)



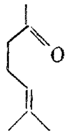
(VIa)



(VIb)



(VII)



(VIII)

Aldehyde esters (VIa) and (VIb) are evidently formed by the reaction of esters (Ia-Id) with 2 moles of ozone. This is indicated by the material balance with respect to ozone and by the detection of levulaldehyde (VII) in the reaction mixture before evaporation. Ketone (VIII), a product of the oxidative cleavage of (I) through the Δ^6 double bond, is not detected among the reaction products.

Aldehydes (Va-Vd) can be recovered from the reaction mixtures in yields of 50-60% based on (I) reacted. Their spectral characteristics, as well as those of aldehyde esters (VIa-VIb) and the dimethyl acetals of (V) and (VI), are given in Table 1.* The effect of the ozonolysis conditions on the ratio of reaction products has been discussed in detail in [10]. We need only note here that the amount of aldehyde esters (VIa) and (VIb) formed from esters (Ic) and (Id) with a Z^6 double bond is appreciably less than from isomers (Ia) and (Ib) with an E^6 double bond [the (Vc):(VIa) and (Vd):(VIb) ratio is 1.3-1.5, while the (Va):(VIa) and (Vb):(VIb) ratio is not more than 0.8]. This difference is evidently due to the fact that the Z^6 double bond is less reactive than the E^6 double bond with respect to the ozonolysis of (I).

Thus, comparison of the yields of aldehyde esters (Va-Vd) obtained by the four studied methods of synthesizing them from isomeric farnesenate esters (Table 2) shows that partial ozonolysis is the best method. Only in the case of the E,E aldehyde ester (Va) can synthesis via the bromohydrin (IIa) compete with this method.

The COOR group in the aldehyde esters may not participate in a number of carbonyl-group reactions, especially in the Wittig reaction. In this case, when it is necessary to react the "tail" end of the molecule, the carbonyl group of the aldehyde esters (V) can be protected and the COOR group subjected to chemical conversion, for example

$$\underset{(Ia)}{RCOOC_2H_5} \rightarrow \underset{(IXa)}{RCH_2OH} \rightarrow \underset{(Xa)}{RCH_2Hal}$$

These reactions have already been used in isoprenoid chemistry. A number of general methods for preparing allylic bromides from the corresponding alcohols have been used to convert E,E-farnesol (IXa), geraniol, and nerol into their bromides [11-13]. On investigating various methods for synthesizing (IXa-IXd) from (Ia-Id), we discovered that reduction of (Ia-Id) with $LiAlH_4$ at –30°C, notwithstanding the data in [14], proceeds with partial reduction

---

*The mass spectra of aldehyde esters (V) and (VI) and their dimethyl acetals have also been obtained and will be discussed separately.

of the conjugated double bond. This side reaction can be avoided by using $LiAlH_4(OEt)$ instead of $LiAlH_4$. We also found that it is not necessary to use hygroscopic complex bromides for preparing bromides (Xa-Xd) from the allylic alcohols (IXa-IXd). The reaction goes smoothly when PBr_3 is used at –15°C.

Under the conditions described, the reaction sequences (Ia-Id) → (IXa-IXd) → (Xa-Xd) proceed with complete retention of the configuration of the double bonds, as shown by ^{13}C NMR. The considerable difference in the chemical shifts of the signals from the isomeric compounds makes this method much more convenient for determining the configuration of the double bonds in the individual isomers than PMR. In addition, ^{13}C NMR spectroscopy can be used to analyze the composition of isomer mixtures; this can be illustrated in the case of the isomeric farnesyl bromides (Xa) and (Xb), which decompose under the conditions of GLC analysis. A complete assignment of the signals in the ^{13}C NMR spectra of (Ia-Id), (IXa-IXd), and (Xa-Xd) is given in [15].

EXPERIMENTAL

Esters (Ia-Id) were prepared by reacting pure E- and Z-geranylacetones with ethoxyacetylene [16] and distilling the mixture of isomers in a rectification column.

Gas–liquid chromatography was carried out using an LKhM-8MD chromatograph with a 2 m × 3 mm column containing 2.5% Apiezon L on Chromosorb W, with a flame-ionization detector and N_2 as carrier gas, and also (for ozonolysis products) using a Tsvet 102 chromatograph with a 2 m × 3 mm column containing 15% Apiezon L on Chromaton N-AW-DMCS with a flame-ionization detector and He as carrier gas.

Thin-layer chromatography was effected on Silufol R with an ether:hexane (1:2) solvent. Preparative column chromatography was effected on silica gel L (40-100 μ).

The PMR spectra were obtained with a Tesla BS-487B spectrometer, using CCl_4 as solvent and HMDS as internal standard; the chemical shifts are given on the δ scale. The IR spectra were recorded with a UR-20 instrument using thin-layer samples. The UV spectra were recorded with a Specord UV-VIS spectrometer using ethanol solutions.

Ozonolysis of Esters (Ia-Id). An ozone–oxygen mixture was passed at a rate of 30 liters/h (ozonizer output 50 mmole O_3 per hour) through a solution of 10 g (38 mmole) of (Ib) in 150 ml of n-octane containing 1.6 ml (38 mmole) of methanol at 0°C until 1.64 g (34 mmole) of O_3 has been absorbed. The solution was flushed with N_2 and a sample taken. The sample was reduced on a Lindlar catalyst and analyzed by GLC. The bulk of the reaction mixture was cooled to –60°C and decanted to isolate the ozonide. The latter was dissolved in acetone, treated with 0.1 g of Lindlar catalyst, and hydrogenated at ∿20°C until all peroxide compounds were reduced. The catalyst was filtered off and the acetone distilled off to give 4 g of a mixture comprising 7% of (Ib), 31% of (Vb), and 62% of (VIb).

Chromatography of this mixture on 100 g of silica gel (ether:hexane = 1:2) gave 1.2 g of aldehyde ester (Vb) and 2.2 g of aldehyde ester (VIb). Similar treatment of the n-octane solution* (see above) gave 6 g of a mixture containing 73% of (Ib), 18% of (Vb), and 9% of (VIb). Chromatography of this mixture gave 4.2 g of the initial (Ib), 0.9 g of (Vb), and 0.3 g of (VIb). The total yield of (Vb) was 2.1 g [23% based on initial (Ib) and 44% based on (Ib) reacted]; $n_D^{20} = 1.4875$. Found: C 69.96; H 9.01; C = C 19.55%. $C_{14}H_{22}O_3$. Calculated: C 70.55; H 9.31; C = C 20.1%.

Dimethyl Acetal of (Vb). This was prepared, like the dimethyl acetals of the other isomers (V) and aldehyde esters (VIa-VIb), by treatment with excess methanol in the presence of NH_4Cl as described in [9]; bp 67-69°C/1 mm; $n_D^{20} = 1.4567$.

The following were prepared analogously. 1) (Va), yield 48%†; $n_D^{20} = 1.4895$. Found: C 70.21; H 9.35; C = C 19.62%. $C_{14}H_{22}O_3$. Calculated: C 70.55; H 9.31; C = C 20.1%. Dimethyl acetal, bp 65-67°C/1 mm; $n_D^{20} = 1.4565$. 2) (Vc), yield 56%†; $n_D^{20} = 1.4890$. Found: C 70.09; H 9.28; C = C 19.58%. $C_{14}H_{22}O_3$. Calculated: C 70.55; H 9.31; C = C 20.10%. Dimethyl acetal, bp 64-66°C/1 mm; $n_D^{20} = 1.4572$. 3) (Vd), yield 60%†; $n_D^{20} = 1.4870$. Found: C 70.04; H 9.21; C = C 19.63%. $C_{14}H_{22}O_3$. Calculated: C 70.55; H 9.31; C = C 20.1%. Dimethyl acetal, bp 63°C/1 mm; $n_D^{20} = 1.4570$.

---

*This solution can also be used as solvent for the ozonolysis of a fresh portion of (Ib).

†Yields are based on (I) reacted.

Reaction of Esters (Ia-Id) with N-Bromosuccinimide and Conversion of Bromohydrins (II) to Aldehyde Esters (V) via Epoxides (III) and Diols (IV). A solution of 1.7 g of (Id) in 8 ml of t-C_4H_9OH and 2.3 ml of water was treated at 2-4°C with 1.4 g of N-bromosuccinimide, stirred at 2-4°C for 2.5 h, evaporated, and the residue dissolved in 10 ml of saturated Na_2SO_4 solution and extracted with ether. Conventional working up gave 2.3 g of crude (IId).

Bromohydrin (IId) was dissolved in 33 ml of abs. methanol, treated with 4.13 g of K_2CO_3 and stirred for 0.5 h, the reaction being monitored by TLC. The reaction mixture was filtered and the filtrate poured into saturated Na_2SO_4 solution and extracted with ether. Conventional working up gave 1.22 g of crude (IIId).

Epoxide (IIId) was treated with 10 ml of THF, 5 ml of water and 0.34 g of 8% $HClO_4$, and stirred at 20°C, the reaction being monitored by TLC. After 0.5 h, the mixture was diluted with saturated Na_2SO_4 solution and extracted with ether. The extract was successively washed with $NaHCO_3$ and Na_2SO_4 solutions and evaporated. The residue was dissolved in hexane and extracted with 40% aqueous methanol. The aqueous methanol fraction was evaporated to leave an aqueous residue, which was extracted with ether. Conventional working up gave 0.8 g of (IVd), which was pure according to TLC.

A solution of diol (IVd) in 7 ml THF was stirred under argon while adding a solution of 0.8 g $NaIO_4$ in 10 ml water, and then stirred for 20 h. On completion of the reaction (TLC), the mixture was diluted with 10 ml of saturated Na_2SO_4 solution and extracted with ether. Conventional working up gave 0.62 g of crude (Vd) with a purity of 60% according to GLC and PMR. Chromatography of the product on 20 g of silica gel under N_2 pressure (hexane:ether, 9:1) gave 0.33 g [18% based on (Id)] of pure (Vd).

Analogously, (Va) was prepared from (Ia) in a yield of 44% based on (Ia), (Vb) was prepared from (Ib) in a yield of 16% based on (Ib), and (Vc) was prepared from (Ic) in a yield of 15% based on (Ic). When the same reactions were carried out starting from the tetrahydrofuran ether of farnesol, the yield was 14%.

Reaction of (Id) with OsO_4 and N-Methylmorpholine N-oxide Followed by Cleavage of Diol (IVd) with $NaIO_4$ to Form Aldehyde Ester (Vd). A solution of 2.64 g of (Id) in 3 ml THF was added dropwise at ∼20°C to a mixture of 0.1 g OsO_4, 1.33 g N-methylmorpholine N-oxide, 20 ml t-C_4H_9OH, 6 ml THF, and 2 ml water. The dark-violet reaction mixture was stirred for 40 h, then treated with 1 g of $Na_2S_2O_4$ and 12 g of silica gel, stirred for 0.25 h, and filtered. The filtrate was adjusted to pH 7 with 1 N H_2SO_4 and evaporated. The residue was treated with 8 ml of saturated NaCl solution and extracted with ethyl acetate. Conventional working up gave 1.74 g of crude diol (IVd). The latter was treated with $NaIO_4$ as described above. Chromatography gave 0.35 g [15% based on (Id)] of (Vd). Analogously, (Vc) was obtained from (Ic) in 16% yield.

Reaction of (Id) with p-Methoxycarbonylperbenzoic Acid Followed by Conversion of Epoxide (IIId) to Aldehyde Ester (Vd). A solution of 6.4 g of (Id) in 110 ml of CH_2Cl_2 was added rapidly at 0-5°C to a suspension of 8 g of 75% p-methoxycarbonylperbenzoic acid in 50 ml CH_2Cl_2. The mixture was stirred at 0-5°C for 4.5 h, the reaction being monitored by GLC. The reaction mixture was neutralized with a 5% Na_2CO_3 solution. Conventional working up gave 6.5 g of crude epoxide (IIId). Conversion of (IIId) to (Vd) was effected as described above. Chromatography gave 0.9 g [15% based on (Id)] of aldehyde ester (Vd). Analogously, (Vc) was prepared from (Ic) in 18% yield.

Preparation of Isomeric Farnesols (IXa-IXd). A solution of 40.4 g of (Ia) in 150 ml of abs. ether was treated at ∼20°C with a solution of $LiAlH_3(OEt)$ prepared by adding a mixture of 13 ml abs. ethanol and 85 ml abs. ether to 228 ml of a 1 M solution of $LiAlH_4$ in ether at −10°C. The mixture was stirred for 2 h and then carefully treated with 30 ml of saturated NH_4Cl solution while cooling. After conventional working up, the product was distilled in vacuo, giving 17.7 g (71%) of (IXa). According to GLC, PMR, and ^{13}C NMR, the product contained no 2,3-dihydrofarnesol or isomeric farnesols.

Pure farnesols (IXb-IXd) were prepared analogously.

Preparation of Isomeric Farnesyl Bromides (X). A solution of 2.6 ml PBr_3 in 20 ml abs. ether was added over 0.5 h at −15°C to a solution of 15 g of (IXd) and 1.5 ml of pyridine in 75 ml abs. ether, the solution being carefully shielded from light. The mixture was stirred for 0.3 h, warmed to ∼20°C, stirred for 3 h, and poured into a mixture of ice and Na_2CO_3. Conventional working up gave 15.8 g (82%) of bromide (Xd), which was purified by chromatography under N_2 pressure (hexane). Found: Br 27.84%. $C_{15}H_{25}Br$. Calculated: Br 28.07%.

According to ^{13}C NMR data, the product was not contaminated with isomeric farnesyl bromides. PMR spectrum: 1.54-1.70 m (12H, $CH_3C=$), 1.91-2.05 m (8H, $CH_2C=$), 3.88 d (2H, CH_2Br, J = 8.5 Hz), 4.99 m (2H, $\underline{HC}=$), 5.44 t. m (1H, $=C\underline{H}CH_2Br$, J = 8.5 Hz). The following were obtained analogously. 1) (IXb), yield 85%; PMR spectrum 1.53-1.71 m (12H, $CH_3C=$), 1.92-2.08 m (8H, $CH_2C=$), 3.85 d (2H, CH_2Br, J = 8.5 Hz), 5.00 m (2H, $HC=$), 5.42 t.m. (1H, $C\underline{H}CH_2Br$, J = 8.5 Hz). 2) (IXc), yield 83%; PMR spectrum 1.55-1.71 m (12H, $CH_3C=$), 1.96-2.11 m (8H, $CH_2C=$), 3.83 d (2H, CH_2Br, J = 8.5 Hz), 5.05 m (2H, $HC=$), 5.45 t.m. (1H, $=C\underline{H}CH_2Br$, J = 8.5 Hz). 3) (IXd), yield 82%; PMR spectrum 1.53-1.73 m (12H, $CH_3C=$), 1.93-2.09 (8H, $CH_2C=$), 3.87 d (2H, CH_2Br, J = 8.5 Hz)., 5.03 m (2H, $HC=$), 5.45 t.m. (1H, $=C\underline{H}CH_2Br$, J = 8.5 Hz).

The authors wish to thank A. S. Shashkov for recording and helping to interpret the ^{13}C NMR spectra.

CONCLUSIONS

1. Four oxidative methods of converting E,E-, Z,E-, E,Z- and Z,Z-farnesenate esters into the corresponding isomeric ethyl 10-oxo-3,7-dimethyl-2,6-decadienoate esters have been investigated with the object of synthesizing a set of stereoisomeric blocks for building up acyclic isoprenoids. The best method is preparative ozonolysis, giving yields of ∿50% based on the farnesenate ester reacted.

2. Differences are observed in the reactivity of the isomeric farnesenate esters containing Z^6 and E^6 double bonds.

LITERATURE CITED

1. V. N. Shibaev, Usp. Biol. Khim., 17, 187 (1976).
2. E. E. van Tamelen and T. J. Curphey, Tetrahedron Lett., 121 (1962).
3. R. J. Anderson, C. A. Henrick, J. B. Siddal, and R. Zurflüh, J. Am. Chem. Soc., 94, 5379 (1972).
4. V. L. Mizyuk and A. V. Semenovskii, Izv. Akad. Nauk SSSR, Ser. Khim., 2074 (1976).
5. R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, J. Org. Chem., 21, 478 (1956).
6. V. van Rheenen, R.C. Kelly, and D. J. Cha, Tetrahedron Lett., 1973 (1976).
7. G. S. Bylina, U. M. Dzhemilev, N. S. Vostrikov, G. A. Tolstikov, A. M. Moiseenkov, A. V. Semenovskii, and S. S. Shavanov, Izv. Akad. Nauk SSSR, Ser. Khim., 447 (1978).
8. G. Stork, M. Gregson, and P. A. Grieko, Tetrahedron Lett., 1391 (1969).
9. V. N. Odinokov, V. R. Akhunova, R. S. Bakeeva, R. I. Galeeva, A. V. Semenovskii, A. M. Moiseenkov, and G. A. Tolstikov, Zh. Org. Khim., 13, 532 (1977).
10. V. N. Odinokov, V. R. Akhunova, G. A. Tolstikov, A. V. Semenovskii, and V. L. Mizyuk, Zh. Org. Khim., 14, 1851 (1978).
11. E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, J. Am. Chem. Soc., 92, 2139 (1970).
12. E. J. Corey, C. U. Kim, and M. Takeda, Tetrahedron Lett., 4339 (1972).
13. G. Stork, P. A. Grieko, and M. Gregson, Tetrahedron Lett., 1393 (1969).
14. J. W. K. Burrell, R. F. Garwood, L. M. Jackman, E. Oskay, and B. C. L. Weedon, J. Chem. Soc. C., 2144 (1966).
15. A. S. Shashkov, N. Ya. Grigor'eva, I. M. Avrutov, A. V. Semenovskii, V. N. Odinokov, V. K. Ignatyuk, and G. A. Tolstikov, Izv. Akad. Nauk SSSR, Ser. Khim., 388 (1979).
16. A. V. Semenovskii, V. A. Smit, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 1424 (1965).