New approach to nonracemic 1-alkylamino-3-aryloxypropan-2-ols belonging to β-blockers via cyclic sulfites

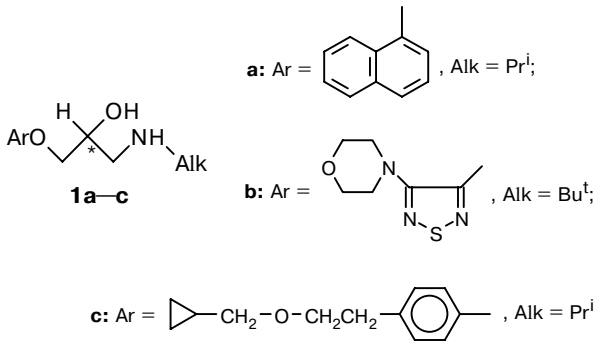
*Z. A. Bredikhina, A. V. Pashagin, D. V. Savel'ev, and A. A. Bredikhin**

A. E. Arbuzov Institute of Organic and Physical Chemistry Kazan Scientific Center of the Russian Academy of Sciences, 8 ul. Arbuzova, 420088 Kazan, Tatarstan, Russian Federation.
Fax: +7 (843 2) 75 2253. E-mail: baa@iopc.kcn.ru

Nonracemic β-blockers, *viz.*, (*S*)-propranolol and (*S*)-timolol, were prepared from (*S*)-glycidol in three steps consisting in the reaction with $SOCl_2$ followed by the reaction of the resulting (4*S*)-4-chloromethyl-2-oxo-1,3,2-dioxathiolanes with the corresponding phenol and the final cleavage of (4*R*)-aryloxymethyl sulfites under the action of amines in DMF.

Key words: cyclic sulfites, scalemic 1-amino-3-aryloxypropan-2-ols, (*S*)-propranolol, (*S*)-timolol, β-blockers.

Selective and nonselective β-adrenergic receptor blockers[1] (β-blockers, β-AB) belonging to the class of 1-alkylamino-3-aryloxypropan-2-ols (**1**), such as propranolol (**1a**), timolol (**1b**), betaxolol (**1c**), *etc.*, are widely used in therapy of vascular pathologies.

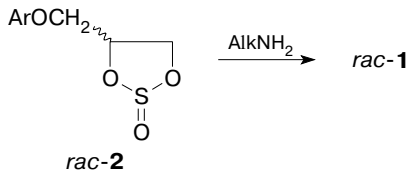


Of two enantiomers of compounds **1**, the (*S*)-isomers generally exhibit useful physiological activity. Since only a few of β-AB are now made commercially in the enantiomerically pure form (timolol (*S*)-**1b** and levobetaxolol (*S*)-**1c**), interest in the development of new procedures for the synthesis of scalemic (nonracemic) β-blocking agents still persists.

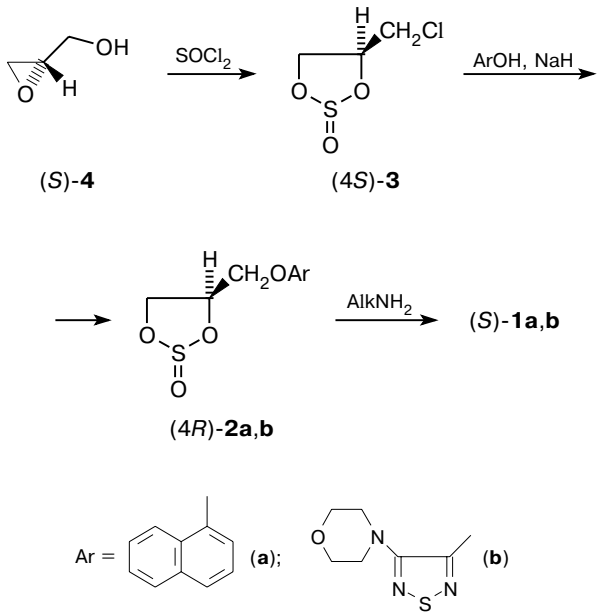
Recently, cyclic sulfites have attracted considerable attention in the preparative chemistry because they proved to be useful reagents in the synthesis of many classes of organic compounds.[2] In the synthesis of racemic β-AB and structurally related compounds, cyclic sulfites were used primarily at the stage of introduction of the amino group (Scheme 1).[3]

Racemic aryloxymethyl sulfites (**2**) were prepared from the corresponding 3-aryloxypropane-1,2-diols either by transesterificaion of dimethyl sulfite[3a] or by the reactions of $SOCl_2$ with glycols.[3b] In the synthesis of scalemic propranolol (*S*)-**1a**, a mixture of diastereomeric sulfites (4*R*)-**2a** was prepared in four steps from (*R*)-3-benzyloxypropane-1,2-diol[4] and then was treated with isopropylamine resulting in the ring opening.

Scheme 1



Scheme 2



In the present study, we examined the possibility of the synthesis of scalemic β-AB, *viz.*, (*S*)-propranolol and

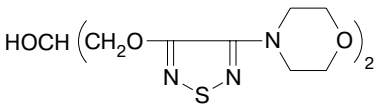
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 417—420, March, 2001.

(*S*)-timolol, from (*S*)-glycidol with the use of cyclic sulfites as the key intermediates.

Previously, we have developed a procedure for the preparation* of a diastereomeric mixture of 4-chloromethyl-2-oxo-1,3,2-dioxathiolane (**3**) by the direct reaction of $SOCl_2$ with glycidol (**4**).[5,6] In the cited studies, we have also demonstrated that the chiral center of glycidol retained its configuration in the final product and the enantiomeric purities of sulfites **3** were identical to that of the starting epoxyalcohol.

It was believed that the reactions of *rac*-**3** with aryl oxide anions proceed anomalously to give achiral symmetrical six-membered sulfites.[7,2] We demonstrated that this conclusion was based on the erroneous interpretation of the experimental results and that in aprotic solvents, the chlorine atom is replaced by the phenoxide anion with retention of the molecular skeleton.[8]

The reaction of a mixture of (2*RS*,4*S*)-**3** with the 1-naphthoxide anion, which was generated from 1-naphthol and NaH in toluene, proceeded smoothly according to Scheme 2 to form a mixture of isomers (2*R*,4*R*)-**2a** and (2*S*,4*R*)-**2a** in a ratio of 59 : 41 in ~80% yield. Both isomers were isolated and characterized in the individual form. In the synthesis with the use of 3-hydroxy-4-morpholino-1,2,5-thiadiazole as the aromatic component, the stage of conversion of chloromethyl sulfites (2*RS*,4*S*)-**3** into thiadiazolyloxymethyl sulfites was carried out in DMF because of the low solubility of the hydroxyl-containing heterocycle in toluene. When the reaction conditions were changed (DMF, 80—90 °C, 1 h), an undesirable product of double nucleophilic substitution, *viz.*, 1,3-bis[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (**5**), was isolated along with isomeric (2*R*,4*R*)-**2b** and (2*S*,4*R*)-**2b** formed as the major products.



5

Products **2b** and **5** were separated by column chromatography, diastereomeric (2*R*,4*R*)-**2b** and (2*S*,4*R*)-**2b**, which possess similar TLC mobilities, being eluted simultaneously. A mixture of sulfites **2b** partially crystallized upon storage, the crystalline portion being enriched with *cis*-diastereomer (2*S*,4*R*)-**2b**. The assignment of substituted cyclic sulfites to either *cis* or *trans* series was based on the ^1H NMR spectral data and, primarily, on the fact (see Ref. 6 and references cited therein) that the methine proton in *trans* isomers is manifested as an isolated signal with the chemical shift $\delta > 5$, whereas the analogous proton in *cis* isomers gives a signal at higher field with the chemical shift $\delta \leq 5$. The changes in the intensities associated with a change in the diastereomeric composition also helped in identifying the signals of individual isomers **2b** in the ^{13}C NMR spectra.

Prolonged refluxing of sulfites (2*RS*,4*R*)-**2a** with an excess of Pr^iNH_2 in MeCN under conditions described previously[4] did not afford the target product. Treatment of the reaction mixture involving washing with aqueous alkali gave rise to (*S*)-3-(1-naphthyloxy)propane-1,2-diol (**1a**) as the major product (m.p. 111—112 °C; *cf.* lit. data:[4] m.p. 110—112 °C; $[\alpha]_D^{20}$ +7.4 (*c* 1.0, MeOH); *cf.* lit. data:[4] $[\alpha]_D^{20}$ +7.6 (*c* 1.0, MeOH)). On the contrary, treatment of sulfites (4*R*)-**2a**,**b** with Pr^iNH_2 or Bu^tNH_2 in DMF at 60—80 °C allowed us to prepare the corresponding (*S*)-β-blockers (*S*)-**1a** and (*S*)-**1b** in approximately 80% yields. Their optical purities are of the same order of magnitude as that of the initial glycidol.

The procedure for the synthesis of aryloxypropanolamines **1** developed in the present study involves an ingenious stage of the preparation of chloromethyl sulfites **3**, whereas the subsequent stages are similar to those used in the conventional procedure for the commercial preparation[9] of racemic β-AB from epichlorohydrin (**6**).

Scheme 3

6 **7**

The reactions of epichlorohydrin with active nucleophiles are also accompanied by the formation of undesirable bis-adducts analogous to compound **5**.[10] However, it should be noted that the behavior of chloromethyl sulfites **3** as synthetic analogs of 1-chloro-2,3-epoxypropane (**6**) is substantially different.

It is known[11] that the reactions of activated 2,3-epoxypropanes with nucleophiles involve two directions of the attack, *viz.*, the attack at the C(1) atom and the attack at the C(3) atom with the opening of the oxirane ring followed by its regeneration. The final products formed by different mechanisms contain the chiral C(2) atom with opposite configurations. Consequently, simultaneous realization of both directions leads to partial racemization. In the case of the reaction of epichlorohydrin with the phenoxide anion, the major product (**7**, Ar = Ph; ~90%) was formed as a result of the attack at the C(3) atom.[11a] Taking into account that the mixture contained the minor product (~10%) formed through the attack at the C(1) atom and in view of the fact that procedures for blocking nucleophilic substitution at the C(1) atom are lacking, one should not expect that the reaction performed according to Scheme 3 even starting from enantiomerically pure compound **6** will afford the final products with high enantiomeric purities.

On the contrary, the nucleophilic replacement of the chlorine atom in chloromethyl sulfites **3** by the aryl oxide anion occurs predominantly (or even exclusively) through the attack of the exocyclic carbon atom. This is

* The scheme of the synthesis has been reported previously.[5]

evidenced by the configurations of the final 1-alkylamino-3-aryloxypropan-2-ols **1** as well as by the (*S*) configuration and by the high optical purity of the above-mentioned 3-(1-naphthyloxy)propane-1,2-diol. Therefore, the use of sulfite **3** instead of oxirane **6** in Scheme 3 leads to blocking of at least one of the existing channel for the racemization of the scalemic final products.

Experimental

The IR spectra of liquid and solid samples were recorded on a UR-20 spectrometer in thin films and in Nujol mulls, respectively. The NMR spectra were measured on Bruker WM-250 (250.13 MHz for ^{1}H) and Bruker MSL-400 (400.13 MHz for ^{1}H; 100.6 MHz for ^{13}C) spectrometers in $CDCl_3$ with Me_4Si as the internal standard. TLC was carried out on Silufol plates. The optical rotation was measured on a Polamat A polarimeter. The solvents were purified according to standard procedures.[14]

The starting (*S*)-glycidol (*S*)-**4** (*ee* = 90.1%) and the diastereomers of chloromethylsulfites (2*RS*,4*S*)-**3** (*ee* ≈ 90%) were prepared according to a known procedure.[6]

(2*RS*,4*R*)-4-(1-Naphthyloxy)methyl-2-oxo-1,3,2-dioxathiolanes (2a). A solution of freshly sublimed α-naphthol (1.53 g, 0.01 mol) in toluene (8 mL) was added to a suspension of NaH (0.26 g, 10 mmol) in toluene (2 mL). The reaction mixture was refluxed for 30 min and cooled to ~20 °C. Then a solution of a mixture of (2*S*,4*S*)- and (2*R*,4*S*)-2-oxo-4-chloromethyl-1,3,2-dioxathiolanes (1.66 g, 10 mmol), which were prepared according to a known procedure,[6] in toluene (5 mL) was added. The reaction mixture was refluxed for 1 h and then kept for 18 h. The precipitate that formed was filtered off and the solvent was removed *in vacuo*. A raw mixture of dioxathiolanes **2a** was obtained in a yield of 2.38 g (88%). The characteristics of the resulting mixture are in complete agreement with the published data.[4] Chromatography (silica gel L, 40/100 μm; 200×20 mm column; a heptane—CH_2Cl_2 mixture as the eluent) of the mixture (0.99 g) afforded (2*S*,4*R*)-**2a** in a yield of 0.16 g, R_f 0.42 (CH_2Cl_2), m.p. 97—99 °C, $[\alpha]_D^{20}$ −0.5 (*c* 0.43, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.46 (dd, 1 H, naphthyl—OC$\underline{H}_a$, *J* = 6.4 Hz, *J* = 10.0 Hz); 4.55 (dd, 1 H, naphthyl—OC$\underline{H}_b$, *J* = 4.8 Hz, *J* = 10.0 Hz); 4.72 (dd, 1 H, H_a(5), *J* = 6.8 Hz, *J* = 8.6 Hz); 4.82 (dd, 1 H, H_b(5), *J* = 8.1 Hz, *J* = 8.6 Hz); 5.01 (dddd, 1 H, H(4), *J* = 6.4 Hz, *J* = 4.8 Hz, *J* = 8.1 Hz, *J* = 6.8 Hz); 6.83, 7.38, 7.50, 7.82, and 8.26 (all m, 1 H, 1 H, 3 H, 1 H, and 1 H, respectively, naphthyl). ^{13}C NMR ($CDCl_3$), δ: 67.38 ($\underline{C}H_2O$—naphthyl); 68.83 (C(5)); 80.15 (C(4)); 105.02, 121.23, 121.77, 125.30, 125.56, 125.62, 126.64, 127.45, 134.43, and 153.50 (naphthyl).

Subsequent elution afforded (2*R*,4*R*)-**2a** as a viscous oil in a yield of 0.32 g, R_f 0.31 (CH_2Cl_2), $[\alpha]_D^{20}$ +24.2 (*c* 0.46, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.18 (d, 2 H, naphthyl—OC$\underline{H}_2$, *J* = 4.7 Hz); 4.56 (dd, 1 H, H_a(5), *J* = 4.4 Hz, *J* = 8.6 Hz); 4.86 (dd, 1 H, H_b(5), *J* = 6.6 Hz, *J* = 8.6 Hz); 5.34 (tdd, 1 H, H(4), *J* = 4.7 Hz, *J* = 4.4 Hz, *J* = 6.6 Hz); 6.75, 7.39, 7.54, 7.84, and 8.22 (all m, 1 H, 1 H, 3 H, 1 H, and 1 H, respectively, naphthyl). ^{13}C NMR ($CDCl_3$), δ: 66.65 ($\underline{C}H_2O$—naphthyl); 68.45 (C(5)); 78.11 (C(4)); 104.90, 121.27, 121.61, 125.24, 125.53, 125.57, 126.64, 127.49, 134.43, and 153.50 (naphthyl).

Reactions of (2*RS*,4*S*)-4-chloromethyl-2-oxo-1,3,2-dioxathiolanes ((2*RS*,4*S*)-3) with the sodium salt of 3-hydroxy-4-morpholino-1,2,5-thiadiazole. A solution of 3-hydroxy-4-morpholino-1,2,5-thiadiazole (1.12 g, 6 mmol), which was prepared according to a procedure reported previously,[15] in DMF (4 mL) was added with stirring to a suspension of NaH (0.15 g, 6 mmol) in DMF (2 mL) at 20 °C. The reaction mixture was heated to 70—80 °C, stirred at this temperature for 30 min, and cooled to ~20 °C. A solution of dioxathiolanes **3** (0.94 g, 6 mmol) in DMF (2 mL) was added to the reaction mixture. To terminate the reaction, the mixture was heated at 80—90 °C for 30 min and then stored for 18 h. The precipitate that formed was filtered off and washed on a filter with chloroform. The combined filtrates were concentrated *in vacuo*. The oily residue (1.4 g) was chromatographed on a 150×20-mm column (silica gel L, 40/100 μm; the heptane—Et_2O mixture as the eluent). A mixture of isomeric **(2*RS*,4*R*)-4-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxymethyl]-2-oxo-1,3,2-dioxathiolanes (2b)** was isolated in a yield of 0.62 g (47%); *cis* : *trans* = 3 : 2; the average R_f value was 0.44 (Et_2O). Found (%): C, 35.79; H, 4.07; N, 14.18. $C_9H_{13}N_3O_5S_2$. Calculated (%): C, 35.17; H, 4.26; N, 13.67. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 3.49 (distort.t, 4 H, NCH_2, *J* = 4.5 Hz); 3.79 (distort.t, 4 H, OC$\underline{H}_2$ of morpholine, *J* = 4.5 Hz); 3.55—3.77 and 4.36—4.76 (both m, 4 H, OCH_2), 4.18—4.31 (m, 0.6 H, CH *cis*-**2b**); 5.27—5.39 (m, 0.4 H, CH *trans*-**2b**). ^{13}C NMR ($CDCl_3$), δ: *trans* isomer (2*R*,4*R*)-**2b**, 48.00 (CH_2N); 66.49 (OCH_2 of morpholine); 68.26 and 69.08 (OCH_2); 77.77 (CH); 149.71 (N=C—N); 152.75 (N=C—O); *cis* isomer (2*S*,4*R*)-**2b**, 48.07 (CH_2N); 66.49 (OCH_2 of morpholine); 46.14 and 71.68 (OCH_2); 69.67 (CH); 149.89 (N=C—N); 153.54 (N=C—O). IR, ν/cm^{-1}: 960, 1120, 1220, 1240, and 1270 (C—O, S—O, S=O), 1500, 1540 (thiadiazole).

Subsequent elution afforded **1,3-bis[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (5)** in a yield of 0.24 g (24%), R_f 0.25 (Et_2O), m.p. 109—110 °C. Found (%): C, 41.72; H, 5.32; N, 19.27; S, 14.47. $C_{15}H_{22}N_6O_5S_2$. Calculated (%): C, 41.85; H, 5.15; N, 19.52; S, 14.89. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 3.40—3.61 (m, 9 H, NC$\underline{H}_2$, OH); 3.68—3.93 (m, 8 H, OC$\underline{H}_2$ of morpholine); 4.40—4.70 (m, 5 H, OC$\underline{H}_2$C$\underline{H}$(OH)C$\underline{H}_2$O). ^{13}C NMR ($CDCl_3$), δ: 48.02 (CH_2N); 66.48 (OCH_2 of morpholine); 68.27 (CH); 71.58 (CH_2O); 149.87 (N=C—N); 153.50 (N=C—O). IR, ν/cm^{-1}: 1520 and 1540 (thiadiazole); 3300 and 3350 (OH).

(*S*)-1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol ((*S*)-propranolol, (*S*)-1a). A solution of dioxathiolanes **2a** (0.4 g, 1.5 mmol) and Pr^iNH_2 (1.6 g, 27 mmol) in DMF (6 mL) was heated at 60—70 °C for ~45 h. After completion of the reaction, a 1 *M* aqueous solution of NaOH (20 mL) was added to the reaction mixture and the mixture was extracted with EtOAc (3×60 mL). The extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was dissolved in ether and dry HCl was passed through the solution until saturation was achieved. The precipitate that formed was filtered off and the hydrochloride was isolated in a yield of 0.35 g (80%). After recrystallization from the Pr^iOH—Et_2O mixture, **(*S*)-propranolol hydrochloride ((*S*)-1a · HCl)** was isolated in a yield of 0.3 g (68%), m.p. 190—192 °C, $[\alpha]_D^{20}$ −22.7 (*c* 1.1, EtOH) (*cf.* lit. data:[12] m.p. 194—196 °C, $[\alpha]_D^{20}$ −25.1 (*c* 1.05, EtOH)).

(*S*)-1-(*tert*-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol ((*S*)-timolol, (*S*)-1b). A solution of dioxathiolanes **2b** (0.2 g, 0.65 mmol) and Bu^tNH_2 (0.7 g, 9.8 mmol) in DMF (1.5 mL) was heated and kept at 70—80 °C for ~30 h. Then a 1 *M* aqueous solution of NaOH (10 mL) was added and the mixture was extracted with EtOAc (3×30 mL). The extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Timolol (*S*)-**1b** was obtained in a yield of 0.17 g (83%). The product was characterized as **hemimaleate**, m.p. 197—198 °C (EtOH), $[\alpha]_D^{20}$ −6.6 (*c* 5,

1 *M* HCl) (*cf.* lit. data:[13] m.p. 198—199 °C, $[\alpha]_D^{20}$ −7.5 (*c* 20, 1 *M* HCl)).

References

1. (a) B. G. Main, *β-Adrenergic Receptors,* in *Comprehensive Medicinal Chemistry*, Eds. C. Hansch, P. G. Sammer, and J. B. Taylor; Pergamon, Oxford, 1990, v. **3**, 187; (b) S. V. Yuzhakov, *Khim.-farm. Zh.*, 1995, **29**, 3 [*Pharm. Chem. J.*, 1995, **29** (Engl. Transl.)].
2. (a) B. B. Lohray, *Synthesis*, 1992, 1035; (b) B. B. Lohray and V. Bhushan, *Adv. Heterocycl. Chem.*, 1997, **68**, 89; (c) H.-S. Byun, L. He, and R. Bittman, *Tetrahedron*, 2000, **56**, 7051.
3. (a) Jpn. Pat. 81, 152, 461 (*Chem. Abstrs.*, 1982, **96**, 122634); Jpn. Pat. 58, 103, 380 (*Chem. Abstrs.*, 1983, **99**, 158232); (b) Span. ES Pat. 549, 138 (*Chem. Abstrs.*, 1987, **106**, 196052).
4. P. H. J. Carlsen and K. Aase, *Acta Chem. Scand.*, 1993, **47**, 737.
5. A. A. Bredikhin, S. N. Lazarev, A. V. Pashagin, and Z. A. Bredikhina, *Mendeleev Commun.*, 1999, **9**, 236.
6. A. A. Bredikhin, A. V. Pashagin, Z. A. Bredikhina, S. N. Lazarev, A. T. Gubaidullin, and I. A. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 1586 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 1575].
7. D. Ben-Ishay, *J. Org. Chem.*, 1958, **23**, 2013.
8. Z. A. Bredikhina, A. V. Pashagin, and A. A. Bredikhin, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 1774 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 1753].
9. *Pharmaceutical Manufacturing Encyclopedia*, Ed. M. Sittig, Noyes Publication: Park Ridge, 1988, V. **1**, 2.
10. V. Massonneau, X. Radisson, M. Mulhauser, N. Michel, A. Buforn, and B. Botannet, *New J. Chem.*, 1992, **16**, 107.
11. (a) D. E. McClure, B. H. Ariston, and J. J Baldwin, *J. Am. Chem. Soc.*, 1979, **101**, 3666; (b) J. J Baldwin, D. E. McClure, D. M. Gross, and M. Williams, *J. Med. Chem.*, 1982, **25**, 931.
12. H. S. Bevinakatti and A. A. Banerji, *J. Org. Chem.*, 1991, **56**, 5372.
13. NL Pat. 85 00, 939 (*Chem. Abstrs.*, 1986, **105**, 153065).
14. L. F. Tietze and T. Eicher, *Reaktionen und Synthesen im organisch-chemischen Practikum und Forschungslaboratorium*, Georg Thieme Verlag, Stuttgart—New York, 1991.
15. L. M. Weinstock, D. M. Mulvey, and R. Tull, *J. Org. Chem.*, 1976, **41**, 3121.

Received June 13, 2000;
in revised form October 6, 2000