Direct Trifluoroacetylation Across a Trimethylsilyloxy System as a Stereospecific, Chemo- and Regioselective Approach to C3-Vicinal Halohydrins

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Abstract: Trifluoroacetylation across the silyloxy system of 1-acyl-2-*O*-trimethylsilyl-3-haloglycerols with trifluoroacetic anhydride (TFAA) in the presence of a halide anion (e.g. Bu_4NX; X = Cl, Br or I), followed by removal of the trifluoroacetyl transient protection, provides a new, efficient entry to configurationally pure C3-vicinal halohydrins.

Key words: trimethylsilyl ethers, trifluoroacetic anhydride, tetra-*n*-butylammonium halides, C3-vicinal halohydrins, 1-acyl-3-halo-*sn*-glycerols

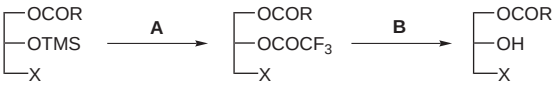
Despite the increasing need for configurationally pure vicinal halohydrins as valuable precursors to diverse functional groups manipulation in natural product synthesis,[1–3] access to these compounds is still limited as direct methods for their preparation (e.g. addition of hypohalous acids and hypohalites to olefins,[4] the ring opening of epoxides by means of metal halides,[5,6] ammonium halides,[7] hydrohalides,[8] elemental halogens,[9] etc.) often suffer from low to moderate regioselectivity,[4,10] substrate incompatibility,[11] excessive expense[12] or poor availability[13,14] of the reagents employed, or afford mixtures of stereoisomers.[6]

An alternative two-step approach, involving insertions of organosilicon halides into oxiranes[15] with a subsequent deprotection of thus produced O-silylated derivatives of vicinal halohydrins,[14] is not only incapable of circumventing the aforementioned shortcomings but also introduces additional synthetic problems since cleavage of even relatively labile silyl ethers (e.g. trimethylsilyl- or *tert*-butyldimethylsilyl derivatives) require conditions that either preclude presence of acid,[14] base,[16] or oxidation–reduction sensitive functionalities[17] in the molecule or are known to trigger prohibitive structural rearrangements of the molecular skeleton (e.g. acyl migration, racemization, etc.) after exposure of a free hydroxyl group.[16,18] For cyclic halohydrins, a method based on the catalytic transfer hydrogenation of α-haloketones via dynamic kinetic resolution has also been reported.[19]

Recently, 2-O-silylated glycerol derivatives have become easily accessible in high yields and under mild conditions from glycidyl precursors;[2] thus, we were interested in the development of an efficient protocol for their transformation, preferably via a direct conversion to avoid drawbacks of stepwise deprotection–protection procedures, into the corresponding trifluoroacetyl esters.

The important point of having a trifluoroacetyl functionality in a molecule is that it confers stability to glycerol derivatives (e.g. prevents migration of fatty acid residues within the glycerol skeleton) and thus such compounds can be considered as storage forms for labile, biologically important mono- or diacyl glycerols.[20] The added value of the trifluoroacetyl protection is that this group can be removed practically quantitatively under mild conditions, and the produced mono- or diglycerides usually do not require chromatographic purification.[20]

So far, examples of direct transformation of various silyloxy systems (e.g. trimethylsilyl-, *tert*-butyldimethylsilyl-, triisopropylsilyl-, *tert*-butyldiphenylsilyl ethers, etc.) into either acetyl group (e.g. using $FeCl_3$–acetic anhydride,[21] pyridine–acetic anhydride–acetic acid or methanol–acetic acid,[22] $ZnCl_2$–acetyl chloride,[23] $SnBr_2$–acetyl bromide[24]) or higher carboxylates,[20] are known from the literature. These methods, however, are (i) incompatible with trifluoroacetyl derivatives due to harsh reaction conditions; (ii) virtually not selective towards any of the commonly employed silyl transient protections; and (iii) inapplicable if C3-vicinal halohydrins bearing a terminal acid chain are needed.



1–4 **5–8** **9–12**

yields: 91–95% yields: 100%

1, **5**, **9** = 3-halo-*sn*, R = $C_{17}H_{33}$, X = Cl
2, **6**, **10** = 3-halo-*sn*, R = $C_{17}H_{33}$, X = Br
3, **7**, **11** = 3-halo-*sn*, R = $C_{17}H_{33}$, X = I
4, **8**, **12** = *rac*, R = Ph, X = Br

Scheme 1 *Reagents and conditions*: step (A): $(F_3CCO)_2O$ (2 equiv), Bu_4NX (2.0 equiv), $CHCl_3$, r.t., 5 h; step (B): pyridine (10 equiv), MeOH (250 equiv), CH_2Cl_2–pentane, r.t., 20 min.

In this letter, we report on a simple and efficient protocol for the replacement of trimethylsilyl group with a trifluoroacetyl function under mild conditions using tri-

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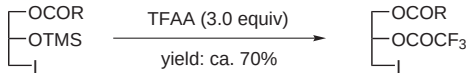
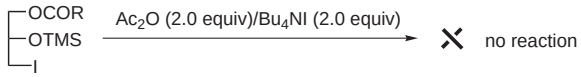
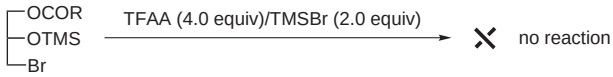
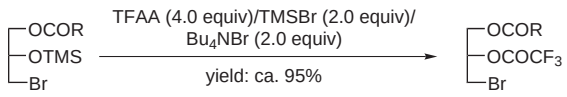
Table 1 Mechanistic Studies

Entry	Reaction conditions (in $CHCl_3$)[a]	Temp	Time
1		r.t.	7 d
2		80 °C	1 h
3		r.t.	8 h
4		r.t.	4 h

[a] RCO = oleoyl; Bu_4N = tetra-*n*-butylammonium; TFAA = $(CF_3CO)_2O$; TMS = trimethylsilyl.

fluoroacetyl anhydride (TFAA) in chloroform in the presence of halide ions (Bu_4NX, X = Cl, Br or I). To avoid side-product formation in a possible halogen-exchange process, the halide anion used was matched to that present in halohydrins **1**–**4**.

The reaction conditions for a direct trifluoroacetylation of 2-O-trimethylsilylated haloglycerides bearing representative aliphatic (compounds **1**–**3**) or aromatic acyl groups (compound **4**) with TFAA in the presence of a halide ion (step A in Scheme 1), were investigated under various experimental conditions (type of solvents, ratio of reactants, etc.).

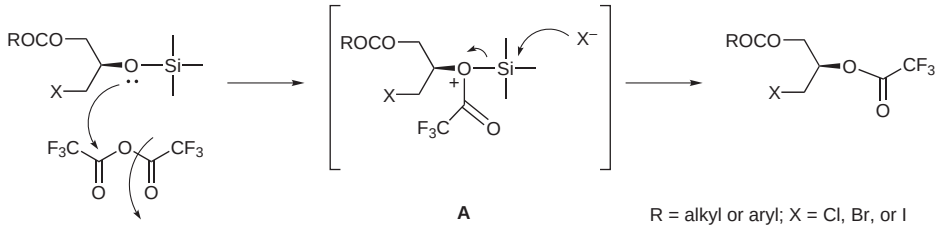
It was found that when TFAA (2.0 equiv) was added to **1**–**4** and Bu_4NX (2.0 equiv, X = Cl, Br or I) in chloroform and the reaction mixture was left at room temperature for four to five hours, this produced quantitatively and in a highly chemo- and regiospecific fashion (>99%, by ^1H NMR and ^{13}C NMR spectroscopy) trifluoroacetates **5**–**8**, which were isolated in 91–95% yields after filtration through a short pad of silica gel.[26]

The rates of the above reactions were not appreciably affected by electronic features or the type of the functional groups present in **1**–**4** (e.g. aliphatic vs. aromatic acyl group, or chloride vs. bromide vs. iodide) or the kind of the halide ion used. Other trimethylsilyl-protected primary, secondary or sterically hindered alcohols (e.g. 1,3-propanediol, cholesterol, 1-*O*-hexadecyl-3-bromoglycerol, α-tocopherol, etc.) also underwent quantitative trifluoroacetylation, with a notable exception of triisopropylsilyl- and *tert*-butyldiphenylsilyl ethers which turned out to be completely stable under the reaction conditions.

Mechanistic studies using ^1H NMR and ^{13}C NMR spectroscopy (Table 1) showed that TFAA alone (entry 1) effected trifluoroacetylation across the trimethylsilyloxy system of compound **3** to produce trifluoroacetate **7**, but the reaction was sluggish and did not go to completion at room temperature for one week.

Other carboxylic acid anhydrides (e.g. acetic anhydride), when used either alone or in combination with Bu_4NX (X = Cl, Br or I), remained essentially unreactive even at elevated temperature (entry 2). As shown in entry 3, TFAA in the presence of TMSX (X = Cl, Br or I) was also inefficient in replacing the trimethylsilyl group in the model substrate by trifluoroacetyl, although it is known that this system generates highly electrophilic species, trifluoroacetyl halides.[25] The latter reactions, however, could be rescued by the addition of the corresponding Bu_4NX (entry 4).

The above observations suggest a mechanism (Scheme 2), which involves initial coordination of a trifluoroacetyl group to the oxygen atom of the siloxy system, followed by nucleophilic attack of a halide ion on the silicon center in intermediate **A** to produce the ester bond. The combination of nucleophile and electrophile catalysis rationalizes the fact that under the reaction conditions the replacement of the TMS protection by the trifluoroacetyl group occurs without scrambling of the terminal acyl moiety as apparently no free hydroxy group of the glycerol skeleton is exposed. In addition, since no C–O bond scission takes place at the stereogenic carbon center, the transformation should be stereospecific and occur with retention of configuration. Fair independence of the rate



Scheme 2

of trifluoroacetylation on the nature of the external halide used, as well as the formation of only 2-O-trifluoroacetylated halohydrins **5**–**8** (Scheme 1, route A) with defined stereochemistry, and the lack of an intramolecular acyl rearrangement, are in agreement with this mechanism.

An alternative scenario that would invoke a nucleophilic attack by a trifluoroacetate anion on silicon seems less plausible, as halide ions are apparently more effective as a nucleophile for silicon than trifluoroacetate. This is also consistent with the experimental data that trifluoroacetylation was significantly faster in the presence of external halides.

Finally, to demonstrate feasibility of the removal of trifluoroacetyl groups from halohydrins **5**–**8** under mild conditions, these compounds were treated in CH_2Cl_2–pentane with pyridine (10 equiv) and methanol (250 equiv) at room temperature. The reactions were quantitative (completion within 20 min) and, after removal of volatile products, afforded positional homogenous vicinal haloalkanols **9**–**12** (purity >99%, by ^{1}H NMR and ^{13}C NMR spectroscopy) without any supplementary purification (route B, Scheme 1).[27]

In conclusion, we have developed a general, simple and efficient synthetic strategy for a direct conversion of trimethylsilylated halohydrins **1**–**4** to 2-O-trifluoroacetylated derivatives **5**–**8**, from which the corresponding C3-vicinal haloalkanols (**9**–**12**), that bear acyl residues sensitive to migration, can be retrieved directly and without recourse to additional work-up or purification steps.

The reactions are clean, entirely chemo- and regiospecific, and afford the target products under mild conditions in practically quantitative yields. The method makes use of commercially available reagents and is potentially tolerant toward the presence of other, more stable silyl groups.

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References and Notes

(1) (a) Momose, D.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 2669. (b) Ueda, Y.; Maynard, S. C. *Tetrahedron Lett.* **1988**, *29*, 5197. (c) Konopelski, J. P.; Boehler, M. A.; Tarasow, T. M. *J. Org. Chem.* **1989**, *54*, 4966. (d) Venturello, C.; D'Aloisio, R. *Synthesis* **1985**, 33. (e) Righi, G.; Bonini, C. *Recent Res. Dev. Org. Chem.* **1999**, *3*, 343. (f) Righi, G.; Chionne, A.; D'Achille, R.; Bonini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 903. (g) Ciaccio, J. A.; Heller, E.; Talbot, A. *Synlett* **1991**, 248. (h) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248. (i) Bird, P. R.; Chadha, J. S. *Tetrahedron Lett.* **1966**, *38*, 4541. (j) Martin, J. D.; Palazon, J. M.; Perez, C.; Ravelo, J. L. *Pure Appl. Chem.* **1986**, *58*, 395. (k) Martin, J. D.; Perez, C.; Ravelo, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 7801.

(2) Stamatov, S. D.; Stawinski, J. *Tetrahedron Lett.* **2006**, *47*, 2543.

(3) de Haas, G. H.; van Deenen, L. L. M. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 951.

(4) Boguslavskaya, L. S. *Russ. Chem. Rev.* **1972**, *41*, 740.

(5) (a) Azzena, F.; Calvani, F.; Crotti, P.; Gardelli, C.; Macchia, F.; Pineschi, M. *Tetrahedron* **1995**, *51*, 10601. (b) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021. (c) Righi, G.; Pescatore, G.; Bonadies, F.; Bonini, C. *Tetrahedron* **2001**, *57*, 5649. (d) Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Tetrahedron* **1998**, *54*, 2709.

(6) Bartas-Yacoubou, J.-M.; Maduike, N.; Kyere, S.; Doan, L.; Whalen, D. L. *Tetrahedron Lett.* **2002**, *43*, 3781.

(7) (a) Onaka, M.; Sugita, K.; Takeuchi, H.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1173. (b) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1992**, *48*, 3805.

(8) (a) Gao, L.-X.; Murai, A. *Chem. Lett.* **1989**, 357. (b) Gao, L.-X.; Murai, A. *Chem. Lett.* **1991**, 1503.

(9) (a) Konaklieva, M. I.; Dahl, M. L.; Turos, E. *Tetrahedron Lett.* **1992**, *33*, 7093. (b) Sharghi, H.; Eskandari, M. M. *Tetrahedron* **2003**, *59*, 8509. (c) Sharghi, H.; Eskandari, M. M.; Ghavami, R. *J. Mol. Catal. A: Chem.* **2004**, *215*, 55. (d) Sharghi, H.; Eskandari, M. M. *Synthesis* **2002**, 1519.

(10) Bonini, C.; Righi, G. *Synthesis* **1994**, 225.

(11) (a) Soroka, M.; Goldeman, W.; Malysa, P.; Stochaj, M. *Synthesis* **2003**, 2341. (b) Solladie-Cavallo, A.; Lupattelli, P.; Marsol, C.; Isarno, T.; Bonini, C.; Caruso, L.; Maiorella, A. *Eur. J. Org. Chem.* **2002**, 1439.

(12) (a) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2001**, *42*, 3955. (b) Kwon, D. W.; Cho, M. S.; Kim, Y. H. *Synlett* **2003**, 959.

(13) (a) Tamami, B.; Mahdavi, H. *React. Funct. Polym.* **2002**, *51*, 7. (b) Niknam, K.; Nasehi, T. *Tetrahedron* **2002**, *58*, 10259. (c) Hara, S.; Hoshio, T.; Kameoka, M.; Sawaguchi, M.; Fukuhara, T.; Yoneda, N. *Tetrahedron* **1999**, *55*, 4947. (d) Sharghi, H.; Naeimi, H. *Synlett* **1998**, 1343.

(14) Leung, W.-H.; Wong, T. K. T.; Tran, J. C. H.; Yeung, L.-L. *Synlett* **2000**, 677.

(15) (a) Kricheldorf, H. R.; Morber, G.; Regel, W. *Synthesis* **1981**, 383. (b) Andrews, G. C.; Crawford, T. C.; Contillo, L. G. *Tetrahedron Lett.* **1981**, *22*, 3803. (c) Detty, M. R.; Seidler, M. D. *Tetrahedron Lett.* **1982**, *23*, 2543. (d) Iqbal, J.; Amin Khan, M.; Ahmad, S. *Synth. Commun.* **1989**, *19*, 641.

(16) Dodd, G. H.; Golding, B. T.; Ioannou, P. V. *J. Chem. Soc., Chem. Commun.* **1975**, 249.

(17) (a) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817. (b) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177. (c) Bajwa, J. S.; Vivelo, J.; Slade, J.; Repic, O.; Blacklock, T. *Tetrahedron Lett.* **2000**, *41*, 6021.

(18) (a) Paltauf, F.; Hermetter, A. *Prog. Lipid Res.* **1994**, *33*, 239. (b) Serdarevich, B. *J. Am. Oil Chem. Soc.* **1967**, *44*, 381. (c) Sjursnes, B. J.; Anthonsen, B. *Biocatalysis* **1994**, *9*, 285.

(19) Ros, A.; Magriz, A.; Dietrich, H.; Fernandez, R.; Alvarez, E.; Lassaletta, J. M. *Org. Lett.* **2006**, *8*, 127.

(20) Stamatov, S. D.; Stawinski, J. *Tetrahedron Lett.* **2002**, *43*, 1759.

(21) (a) Ganem, B.; Small, V. R. *J. Org. Chem.* **1974**, *39*, 3728. (b) Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129.

(22) Fuchs, E.-F.; Lehmann, J. *Chem. Ber.* **1974**, *107*, 721.

(23) Kim, S.; Lee, W. J. *Synth. Commun.* **1986**, *16*, 659.

(24) Oriyama, T.; Oda, M.; Gono, J.; Koga, G. *Tetrahedron Lett.* **1994**, *35*, 2027.

(25) Stamatov, S. D.; Stawinski, J. *Synlett* **2005**, 2587.

(26) **Typical Procedure for the Conversion of the Silyl Ethers 1–4 into the Corresponding Trifluoroacetate Derivatives 5–8 (Step A)**

To a solution of silyl ether **1**–**4** (1.00 mmol) and tetra-*n*-butylammonium halide (2.00 mmol) in alcohol-free CH_3Cl (5.0 mL), TFAA (0.278 mL, 2.00 mmol) was added and the reaction system was kept under argon at r.t. for 4–5 h. CH_3Cl and volatile reaction components were evaporated in vacuo, the residue was taken in toluene (5.0 mL) and passed through a pad of silica gel (ca. 5 g) prepared in the same solvent. The support was washed with toluene (ca. 100 mL), fractions containing the target compounds were combined, the eluent was removed under reduced pressure, and the residue was kept under high vacuum at r.t. for 2–3 h to afford trifluoroacetate **5**–**8** in >90% yields (purity >99% by ^{1}H NMR).

1-Oleoyl-2-trifluoroacetyl-3-chloro-*sn*-glycerol (**5**): obtained from **1** (0.447 g, 1.00 mmol) and Bu_4NCl (0.556 g, 2.00 mmol) for 5 h. Yield 0.429 g (91%, colorless oil); R_f = 0.66 (pentane–toluene–EtOAc, 40:50:10); $[\alpha]_D^{20}$ +0.28 (*c* 9.65, $CHCl_3$). Anal. Calcd (%) for $C_{23}H_{38}ClF_3O_4$ (470.99): C, 58.65; H, 8.13; Cl, 7.53. Found: C, 58.61; H, 8.10; Cl, 7.53%.

1-Oleoyl-2-trifluoroacetyl-3-bromo-*sn*-glycerol (**6**): obtained from **2** (0.492 g, 1.00 mmol) and Bu_4NBr (0.645 g, 2.00 mmol) for 4 h. Yield 0.490 g (95%, colorless oil); R_f = 0.69 (pentane–toluene–EtOAc, 40:50:10); $[\alpha]_D^{20}$ +3.47 (*c* 8.05, $CHCl_3$). Anal. Calcd (%) for $C_{23}H_{38}BrF_3O_4$ (515.44): C, 53.59; H, 7.43; Br, 15.50. Found: C, 53.62; H, 7.37; Br, 15.55.

1-Oleoyl-2-trifluoroacetyl-3-iodo-*sn*-glycerol (**7**): obtained from **3** (0.539 g, 1.00 mmol) and Bu_4NI (0.739 g, 2.00 mmol) for 4 h. Yield 0.529 g (94%, colorless oil); R_f = 0.70 (pentane–toluene–EtOAc, 40:50:10); $[\alpha]_D^{20}$ +6.40 (*c* 10.01, $CHCl_3$). Anal. Calcd (%) for $C_{23}H_{38}IF_3O_4$ (562.44): C, 49.11; H, 6.81; I, 22.56%. Found: C, 49.10; H, 6.80; I, 22.59.

1-Benzoyl-2-trifluoroacetyl-3-bromo-*rac*-glycerol (**8**): obtained from **4** (0.331 g, 1.00 mmol) and Bu_4NBr (0.645 g, 2.00 mmol) for 4 h. Yield 0.334 g (94%, colorless oil); R_f = 0.59 (pentane–toluene–EtOAc, 40:50:10). Anal. Calcd (%) for $C_{12}H_{10}BrF_3O_4$ (355.10): C, 40.59; H, 2.84; Br, 22.50. Found: C, 40.57; H, 2.80; Br, 22.50.

(27) **Typical Procedure for the Conversion of Trifluoroacetates 5–8 into the Corresponding Halohydrin Derivatives 9–12 (Step B)**

To a solution of trifluoroacetyl halohydrin **5**–**8** (1.00 mmol) in pentane–CH_2Cl_2 (3:1, v/v, 5.0 mL), a mixture of pyridine (0.8 mL, 10 mmol) and MeOH (10.1 mL, 250 mmol) in the same solvents (5.0 mL) was added at 0 °C and the reaction system was left at r.t. for 20 min. Solvents were evaporated under reduced pressure (bath temp. 50 °C) and the residue was kept under high vacuum at r.t. for 2–3 h to afford the deprotected haloalkanols **9**–**12** practically quantitatively (purity >99% by ^{1}H NMR).

1-Oleoyl-3-chloro-*sn*-glycerol (**9**): obtained from **5** (0.471 g, 1.00 mmol). Yield 0.375 g (100%, colorless oil); R_f = 0.32 (pentane–toluene–EtOAc, 40:50:10); $[\alpha]_D^{20}$ +3.00 (*c* 5.66, $CHCl_3$). Anal. Calcd (%) for $C_{21}H_{39}ClO_3$ (374.98): C, 67.26; H, 10.48; Cl, 9.45. Found: C, 67.30; H, 10.42; Cl, 9.42.

1-Oleoyl-3-bromo-*sn*-glycerol (**10**): obtained from **6** (0.515 g, 1.00 mmol). Yield 0.418 g (100%, colorless oil); R_f = 0.33 (pentane–toluene–EtOAc, 40:50:10); $[\alpha]_D^{20}$ +2.45 (*c* 8.53, $CHCl_3$). Anal. Calcd (%) for $C_{21}H_{39}BrO_3$ (419.44): C, 60.13; H, 9.37; Br, 19.05. Found: C, 60.13; H, 9.42; Br, 19.10.

1-Oleoyl-3-iodo-*sn*-glycerol (**11**): obtained from **7** (0.562 g, 1.00 mmol). Yield 0.466 g (100%, white solid); R_f = 0.36 (pentane–toluene–EtOAc, 40:50:10); $[\alpha]_D^{20}$ +2.39 (*c* 8.37, $CHCl_3$); mp 33.0–33.6 °C; lit.[3] $[\alpha]_D^{20}$ +1.9 (*c* 10, $CHCl_3$); mp 33.4 °C. Anal. Calcd (%) for $C_{21}H_{39}IO_3$ (466.44): C, 54.07; H, 8.43; I, 27.21. Found: C, 54.15; H, 8.40; I, 27.27.

1-Benzoyl-3-bromo-*rac*-glycerol (**12**): obtained from **8** (0.355 g, 1.00 mmol). Yield 0.259 g (100%, colorless oil); R_f = 0.32 (pentane–toluene–EtOAc, 40:50:10). Anal. Calcd (%) for $C_{10}H_{11}BrO_3$ (259.10): C, 46.36; H, 4.28; Br, 30.84. Found: C, 46.42; H, 4.24; Br, 30.80.