Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Syntheses of (*R*)- and (*S*)-enantiomeric 1,1,1-trifluoromethyl-2-alkanols with high enantiomeric purity controlled through derivatization with L-menthyl phthalate

Vadim Mikhailenko, Daria Yedamenko, Ganna Vlasenko, Alexander Krivoshey *, Valerii Vashchenko

State Scientific Institution 'Institute for Single Crystals', NAS of Ukraine, 60 Lenin Ave., Kharkov, Ukraine

ARTICLE INFO

Article history:
Received 20 May 2015
Revised 31 August 2015
Accepted 17 September 2015
Available online xxxx

Keywords:
Chromatography
Derivatizing agents
Enzymatic kinetic resolution
Trifluoromethyl-substituted alcohols

ABSTRACT

Readily available L-menthyl phthalate has been shown to be an effective derivatizing agent for determination of the enantiomeric purity of alkyl- and aryl-substituted 1,1,1-trifluoromethyl-2-alkanols using HPLC and GC. It has been shown that a previously described protocol for one-step enzymatic kinetic resolution results in the formation of the desired 1,1,1-trifluoromethyl-2-alkanols with 96–98% ee. Enrichment of the (R)-isomer of trifluoromethyl alkanols by repetition of the enzymatic hydrolysis procedure was found to increase the ee up to 99.9%. Furthermore, excessive conversion of the corresponding esters during enzymatic hydrolysis allowed enantiomerically pure (S)-1,1,1-trifluoromethyl-2-alkanols to be obtained.

Introduction

Chiral 1,1,1-trifluoromethyl-2-alkanols are useful synthons in modern medicinal and materials chemistry.[1–3] In particular, we have recently reported that esters of *p*-terphenyldicarboxylic acid and (*R*)-/(*S*)-enantiomeric 1,1,1-trifluoro-2-octanols possess promising properties as chiral components of liquid crystal materials for various practical applications.[4,5]

Such chiral alcohols do not occur in Nature and can be synthesized by reduction of the corresponding ketones using enantioselective catalysis, with enantiomeric excesses of up to 90%.[6] However, the most promising method for their synthesis is the lipase-catalyzed enzymatic hydrolysis of the corresponding esters, which have been reported to yield enantiomeric excesses exceeding 97%.[7,8] A common method to determine enantiomeric purity utilizes derivatization to give the corresponding diastereomeric mixtures for subsequent analysis using GC, HPLC, and NMR spectroscopy.[9] The well-known chiral derivatizing agent for alcohols α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, Mosher's acid; **1**, Fig. 1) has been successfully used for analyses of the enantiomeric purity of chiral alcohols by GC[7] and the determination of their absolute configuration by ^{1}H NMR spectroscopy.[8] (*S*)-Acetoxypropionyl chloride (**2**)[10] and (*S*)-trifluorolactic acid (**3**)[11] have also been proposed as derivatizing reagents for the determination of the enantiomeric purity of such compounds. It worth mentioning that derivatizing agents[7,10,11] are typically quite expensive synthetic chiral compounds, making them less cost-effective for routine analyses of the enantiomeric purity of chiral alcohols.

Thus, there is still a need for a more readily available chiral derivatizing agent with comparable performance to known derivatizing reagents under GC and/or HPLC analysis conditions. Taking into account the efficiency of readily available mono-phthalates as reagents for the enantiomeric resolution of alcohols[12] and amines,[13] we found it reasonable to examine L-menthyl phthalate (**4**, Fig. 1) as a derivatizing agent for 1,1,1-trifluoromethyl-2-alkanols and other secondary alcohols, as well as to compare it to MTPA.

Moreover, in view of practical applications (such as those above), it would be beneficial to have in hand a synthetic approach giving both (*R*)- and (*S*)-enantiomeric alcohols from a single racemic source. Herein, we describe such an approach and the control of the enantiomeric purity of (*R*)- and (*S*)-enantiomeric alcohols with the use of L-menthyl phthalate as a chiral derivatizing agent.

Results and discussion

Derivatization of racemic secondary alcohols *rac*-**5a–i** was achieved by esterification with an excess of L-menthyl phthalate (**4**) (obtained from L-menthol and phthalic anhydride in a manner similar to that as described in the literature[14]) using DCC/DMAP (Scheme 1).[15,16] The resulting mixture was filtered through silica to separate the diastereomeric esters (*R*)-**6** and (*S*)-**6** from unre-

* Corresponding author. Tel.: +380 57 3410128; fax: +380 57 3410273.
E-mail address: krivoshey@isc.kharkov.com (A. Krivoshey).

http://dx.doi.org/10.1016/j.tetlet.2015.09.073
0040-4039/

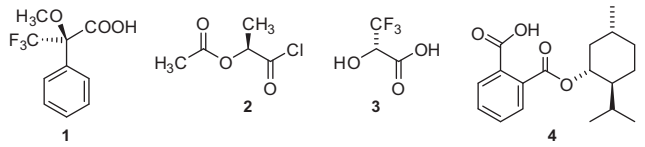


Figure 1. Structures of selected chiral derivatizing agents **1**–**4** for determining the enantiomeric purity of chiral secondary alcohols.

acted **4** and *N*,*N*′-dicyclohexylurea. The mixtures were analyzed by GC and HPLC (see ESI for details).

The (*R*)- or (*S*)-configurations in the mixtures of diastereomeric esters **6a**–**6d** and **7c** (see Scheme 2 and the discussion thereof) were assigned by comparison to their enantiomerically pure derivates, (*R*)-**6** and (*S*)-**6**, synthesized from the corresponding enantiomerically pure alcohols (*R*)-**5a**–**d** and (*S*)-**5a**–**c**, respectively (details regarding the synthesis and characterization of these standards, (*R*)-**6** and (*S*)-**6**, are given in ESI). Esters (*R*)-**6** and (*S*)-**6** showed equal absorbance at the wavelength (λ_{max}) 245 nm which was chosen as the analytical wavelength for HPLC analyses. The results of HPLC and GC analyses of derivates **6a**–**i** are given in Table 1.

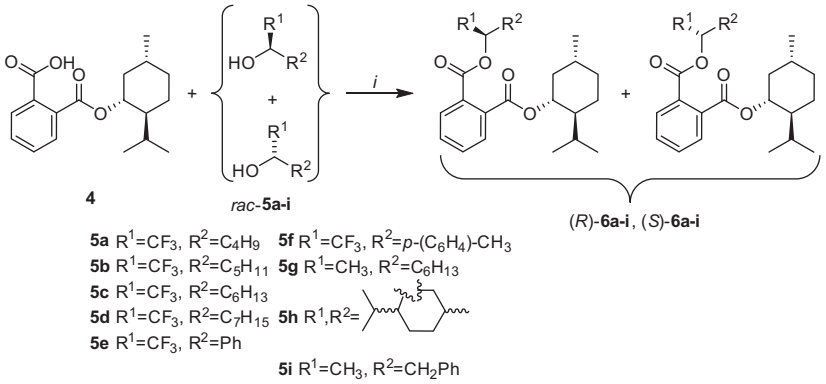
As can be seen from Table 1, using HPLC, the series of diastereomeric esters **6a**–**d** formed from the homologous 1,1,1-trifluoro-2-alkanols *rac*-**5a**–**d** (Table 1, entries 1–3 and 5) showed that resolution (R_S) increased with longer alkyl chain lengths. However, even in the case of the lowest R_S values (entry 1), it was high enough to separate the analytes almost to baseline, which allowed reliable determination of minor components at a level of less than 1%. Thus, such R_S values were considered to be sufficient for further applications. The effect of the alkyl chain was less pronounced in GC separations where modest resolution values were obtained. Moreover, R_S values reached a maximum for ester **6c** containing an intermediate terminal alkyl length (entry 3). Diastereomeric esters **6e**,**f** derived from aryl-substituted trifluoromethyl alkanols **5e**,**f** showed excellent separation using HPLC and modest to good separation when GC was employed (entries 6 and 7). In the case of compounds **6e**,**f**, the resolution was substantially increased when the benzene ring was substituted with a methyl group (compare entries 6 and 7). In comparison to the fluorine-containing compounds **5a**–**f** (Table 1, entries 1–3 and 5–7), L-menthyl phthalate (**4**) appeared to be a considerably less effective derivatizing agent for non-fluorinated alcohols *rac*-**5g**–**i**. In these cases, satisfactory separation was only achieved using HPLC for (±)-2-octanol derivatives **6g** (entry 8) while the derivatives of *rac*-menthol (**6h**) (entry 9) and 1-phenyl-2-propanol (**6i**) (entry 10) showed no noticeable separation. A similar tendency was also observed for the GC analyses of diastereomers **6g**–**i** (entries 8–10).

Diastereomeric ratios (dr) determined for derivates **6a**–**f** (around 50:50) showed good compliance to the equal amount of enantiomers expected in the starting racemic alcohols *rac*-**5a**–**f** (Table 1, entries 1–3 and 5–7). However, in the case of *rac*-**6g**–**i** (Table 1, entries 8–10), the dr value could not be accurately determined due to low separation of the corresponding chromatographic peaks.

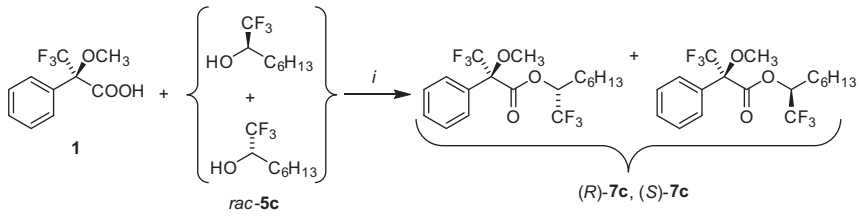
In order to compare our results to the known derivatizing agent MTPA (**1**),[7,8] we performed the derivatization of *rac*-**5c** with (*R*)-MTPA under the same reaction conditions[16] followed by GC analysis of the mixture of diastereomeric esters (*R*)-**7c** and (*S*)-**7c** (Scheme 2). The only difference was that centrifugation was used instead of filtration in order to exclude possible errors arising from different retention of the diastereomeric esters on silica. As shown in Table 1, use of (*R*)-MTPA (**1**) provided considerably higher resolution of the analytes under GC conditions than L-menthyl phthalate (**4**) (compare entries 3 and 4). Due to such high resolution, the diastereomeric esters (*R*)-**7c** and (*S*)-**7c** were fully separated by GC–MS and their individual mass-spectra confirmed the expected structures. However, in this case, the diastereomeric ratio (*R*)-**7c**/(*S*)-**7c** surprisingly indicated a prevalence for one of the diastereomers.

In order to assign the chromatographic peaks, 10% by weight of enantiomerically pure alcohol (*S*)-**5c** was added to (*R*)-**5c** (estimated ee 100%). Derivatization of this mixture with (*R*)-MTPA (**1**) gave a mixture of diastereomers (*R*)-**7c** and (*S*)-**7c** where 6.3% of (*S*)-**7c** was detected by GC. At the same time, using L-menthyl phthalate (**4**) for derivatization of the same mixture, gave diastereomers (*R*)-**6c** and (*S*)-**6c** with the expected ratio (10.3% by HPLC, 10.2% by GC). These results indicate that using (*R*)-MTPA (**1**) leads to an overestimation of the amount of the corresponding (*R*)-alcohol in a mixture of enantiomers. Thus, L-menthyl phthalate (**4**) is well suited as a derivatizing agent for the determination of enantiopurity for alkyl- and aryl-substituted trifluoromethyl alkanols under both HPLC and GC conditions. At the same time, the applicability of **4** for analysis of the enantiomeric purity for non-fluorinated alcohols **5g**–**i** should be considered as limited.

For the purpose of obtaining homologous (*R*)-enantiomeric 1,1,1-trifluoromethyl-2-alkanols (*R*)-**5a**–**d**, racemic alkanols *rac*-**5a**–**d** were first synthesized from ethyl trifluoroacetate by means of a Grignard addition/reduction sequence[17] followed by conversion to the corresponding chloroacetates *rac*-**8** (Scheme 3). Lipase-catalyzed enzymatic hydrolysis[8] proceeding with a conversion of less than 50% (according to GC–MS) gave a mixture of (*R*)-enantiomeric alcohol (*R*)-**5**, residual ester (*R*)-**8**, and unreacted ester (*S*)-**8**. The mixture could be separated by fractional distillation under reduced pressure to give alcohol and ester containing fractions.



Scheme 1. Derivatization of racemic secondary alcohols (*rac*-**5a**–**i**) with L-menthyl phthalate (**4**). Reagents and conditions: (i) DCC, DMAP, 1,2-dichloroethane, 0 °C–rt.



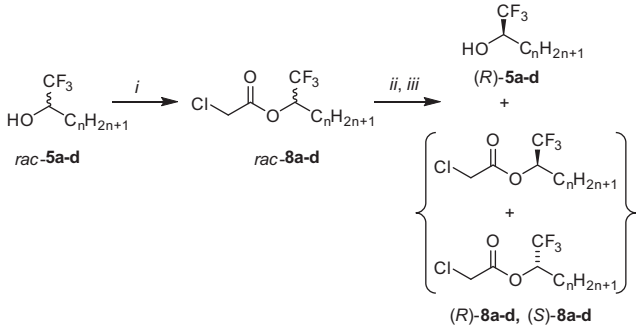
Scheme 2. Derivatization of racemic 1,1,1-trifluoromethyl-2-octanol (*rac*-**5c**) with (*R*)-MTPA (**1**). Reagents and conditions: (i) DCC, DMAP, 1,2-dichloroethane, 0 °C–rt.

Table 1
Separation of diastereomeric derivates **6a–i**, **7c** by HPLC- and GC

Entry	Derivate	HPLC		GC	
		R_S	dr	R_S	dr
1	**6a**	1.40	49:51	1.20	51:49
2	**6b**	1.84	51:49	1.29	49:51
3	**6c**	2.39	49:51	1.38	49:51
4	**7c**	—	—	2.30	72:28[a]
5	**6d**	2.53	50:50	1.32	50:50
6	**6e**	2.54	50:50	1.32	49:51
7	**6f**	3.18	50:50	1.81	50:50
8	**6g**	1.52	51:49	0.43	—[b]
9	**6h**	0	—	0	—
10	**6i**	0	—	0	—

[a] (*R*)-MTPA (**1**) was used as derivatizing agent (Scheme 2).
[b] Ratio could not be accurately determined due to the low R_S value.

The enantiomeric purity of alcohols (*R*)-**5a–d** was determined by derivatization with L-menthyl phthalate (**4**)[16] followed by HPLC and GC analyses of the diastereomeric mixtures (Table 2). As shown in Table 2 (entries 1, 3, 5 and 7), enzymatic hydrolysis of esters *rac*-**8a–d** (Scheme 3) gave alcohols (*R*)-**5a–d** in satisfactory yields. However, according to the specific rotation data, the enantiomeric purity of alcohols (*R*)-**5a**,**b**,**d** (entries 1, 3 and 7) appeared to be lower than described in the literature.[7] Quantitative estimation of the enantiomeric purity for (*R*)-**5a**,**b**,**d** by comparison to literature values does not give a good estimate due to the high uncertainty of optical rotation measurements (in our case, the uncertainty was ±1.8°). Moreover, the actual enantiomeric purity of compound (*R*)-**5c** (entry 5) could not be deduced from the literature since two different specific optical rotation values have been reported for a single declared ee value.[7] Therefore, the enantiomeric purity of alcohols (*R*)-**5a–d** (Table 2, entries 1, 3, 5 and 7) was determined by derivatization with L-menthyl phthalate (**4**). Obtained values for enantiomeric purity showed both good compliance with the values of specific optical rotation and good convergence of the HPLC and GC determinations.



Scheme 3. Synthesis of (*R*)-1,1,1-trifluoromethyl-2-alkanols ((*R*)-**5a–d**). Reagents and conditions: (i) chloroacetyl chloride, pyridine, CH_2Cl_2, 0 °C; (ii) *Lipase MY*, phosphate buffer (pH 7.28), 37 °C; (iii) in vacuo fractional distillation.

Table 2
Yield, specific rotation and enantiomeric purity of (*R*)-1,1,1-trifluoromethyl-2-alkanols ((*R*)-**5a–d**)

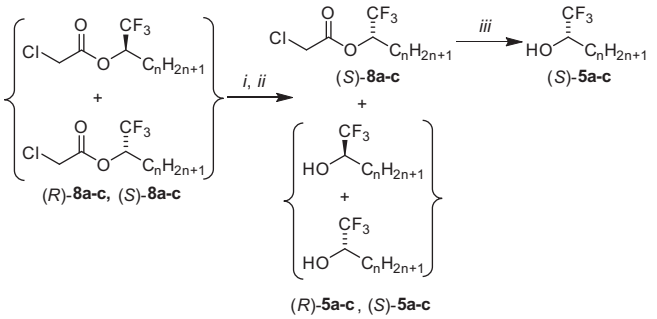
Entry	Compd	Yield (%)	Actual			Literature[7]	
			$[\alpha]_D^{25}$	Enantiomeric purity (ee) (%)		$[\alpha]_D^{25}$	ee (%)
				HPLC	GC		
1	(*R*)-**5a**	70[a]	+23.6	95.6 (91.2)	95.3 (90.6)	+29.5 +31.8	98 97
2	(*R*)-**5a**	75[b]	+27.0	99.9 (99.8)	>99.9[c]		
3	(*R*)-**5b**	68[a]	+24.0	95.5 (91.0)	95.8 (91.6)	+29.8 +28.0	97
4	(*R*)-**5b**	83[b]	+26.5	99.6 (99.2)	99.7 (99.4)		
5	(*R*)-**5c**	66[a]	+25.0	99.1 (98.2)	99.0 (98.0)	+24.0[d] +28.6[d]	97[d]
6	(*R*)-**5c**	78[b]	+25.0	>99.9[c]	>99.9[c]		
7	(*R*)-**5d**	60[a]	+25.1	98.1 (94.2)	98.0 (94.0)	+23.8	98

[a] Yield is calculated in relation to the theoretical yield of (*R*)-**5** from the enzymatic hydrolysis reaction according to Scheme 3.
[b] Yield is calculated in relation to 100% conversion of ester **8** during optical enhancement.
[c] Corresponding diastereomeric esters (*S*)-**6** were not detected.
[d] According to the literature,[7] two essentially different specific optical rotation values corresponding to a single ee value have been obtained through derivatization with (*R*)-MTPA (**1**).

Moreover, having in hand such accurate means for the determination of enantiomeric purity allows the detection of even small differences between enantiomeric purity values and can be effectively utilized during enantiomeric enhancement by repeated enzymatic hydrolysis. Indeed, conversion of alcohols (*R*)-**5a–c** which were initially obtained with low enantiomeric purity (Table 2, entries 1, 3 and 5) to the corresponding chloroacetates **8** followed by repetition of enzymatic hydrolysis (85% conversion of ester **8** according to GC–MS) and fractional distillation steps gave alcohols (*R*)-**5a–c** with markedly improved enantiomeric purity (compare entries 1, 3, 5 with 2, 4, 6, respectively).

The synthetic approach to (*S*)-enantiomers of 1,1,1-trifluoromethyl-2-alkanols (*S*)-**5a–c** consisted of three steps: (i) exhaustive lipase-catalyzed hydrolysis of a mixture of (*R*)-**8** and (*S*)-**8** formed after the isolation of (*R*)-**5** (see discussion with regard to Scheme 3), (ii) removal of the mixture of (*R*)-**5** and (*S*)-**5** alcohols by distillation, and (iii) saponification of the enantiomerically pure esters (*S*)-**8** thus obtained to yield the desired alcohols (*S*)-**5** (Scheme 4, Table 3).

Lipase-catalyzed hydrolysis of the residual (*R*)-**8a–c** proceeded slowly (4 days) and was stopped after 25–30% conversion of **8** was reached according to GC–MS. Presumably, the resultant mixtures contained ester (*S*)-**8** along with alcohols (*R*)-**5** and (*S*)-**5**. Fractional distillation of the mixture gave the corresponding ester and alcohol fractions of which the former was subjected to saponification leading to alcohol (*S*)-**5**. The enantiomeric purity of alcohols (*S*)-**5a–c** was determined by derivatization with L-menthyl



Scheme 4. Synthesis of (*S*)-1,1,1-trifluoromethyl-2-alkanols (*S*)-**5a**–**c**. Reagents and conditions: (i) *Lipase MY*, phosphate buffer (pH 7.28), 37 °C; (ii) in vacuo fractional distillation; (iii) KOH (aq), EtOH, Δ.

Table 3
Yields, specific rotation and enantiomeric purity of (*S*)-1,1,1-trifluoromethyl-2-alkanols ((*S*)-**5a**–**c**)

Entry	Compd	Yield[a] (%)	$[\alpha]_D^{25}$	Enantiomeric purity (ee) (%)	
				HPLC[b]	GC[b]
1	(*S*)-**5a**	19	−29.1	>99.9	>99.9
2	(*S*)-**5b**	25	−30.3	>99.9	>99.9
3	(*S*)-**5c**	27	−28.0	>99.9	>99.9

[a] Yield is calculated over five synthetic steps starting from racemic esters *rac*-**8** (Scheme 3 steps (ii) and (iii) and Scheme 4 steps (i) through (iii)); half-amounts of the esters *rac*-**8** were taken as 100%.
[b] Corresponding diastereomeric esters (*R*)-**8** were not detected.

phthalate (**4**)[16] followed by HPLC and GC analysis of the diastereomeric mixtures (Table 3, entries 1–3). No detectable amounts of the (*R*)-enantiomers were found, thus, alcohols (*S*)-**5a**–**c** obtained in this manner were enantiomerically pure.

In conclusion, readily available L-menthyl phthalate has been shown to be an effective derivatizing agent for alkyl- and aryl-substituted 1,1,1-trifluoromethyl-2-alkanols using HPLC and GC, while its applicability for certain non-fluorinated secondary alcohols is limited. In terms of resolution, better results were obtained using HPLC. It is worth mentioning that use of (*R*)-MTPA appears to lead to an overestimation of the amount of the (*R*)-isomer in mixtures of the enantiomeric 1,1,1-trifluoromethyl-2-alkanols. Using L-menthyl phthalate allows for careful control of the enantiomeric purity of enantiomeric 1,1,1-trifluoromethyl-2-alkanols obtained by enzymatic hydrolysis of their corresponding chloroacetates. In particular, enrichment of the (*R*)-isomeric trifluoromethyl alkanols by a repetition of the enzymatic hydrolysis procedure has been demonstrated. Furthermore, excessive conversion of the corresponding esters during enzymatic hydrolysis allows the production of enantiomerically pure (*S*)-1,1,1-trifluoromethyl-2-alkanols.

Acknowledgments

Financial support from National Academy of Sciences of Ukraine (project # 0112U002186) and National Foundation for Fundamental Sciences in Ukraine (Grant # dffd-Φ53.2/048) are gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.073.

References and notes

1. Hiyama, T. In *Organofluorine Compounds: Chemistry and Applications*; Yamamoto, H., Ed.; Springer: Berlin, 2000.
2. Pinard, E.; Alanine, A.; Alberati, D.; Bender, M.; Borroni, E.; Bourdeaux, P.; Brom, V.; Burner, S.; Fischer, H.; Hainzl, D.; Halm, R.; Hauser, N.; Jolidon, S.; Lengyel, J.; Marty, H.-P.; Meyer, T.; Moreau, J.-L.; Mory, R.; Narquizian, R.; Nettekoven, M.; Norcross, R. D.; Puellmann, B.; Schmid, P.; Schmitt, S.; Stalder, H.; Wermuth, R.; Wettstein, J. G.; Zimmerli, D. *J. Med. Chem.* **2012**, *53*, 4603.
3. Hayashi, H.; Wang, A.; Kawabata, K.; Goto, H. *Mater. Chem. Phys.* **2013**, *137*, 816.
4. Pozhidaev, E. P.; Torgova, S. I.; Minchenko, M. V.; Vashchenko, V. V.; Krivoshey, A. I.; Strigazzi, A. *Mol. Cryst. Liq. Cryst.* **2009**, *509*, 1042.
5. Pozhidaev, E. P.; Srivastava, A. K.; Kiselev, A. D.; Chigrinov, V. G.; Vashchenko, V. V.; Krivoshey, A. I.; Minchenko, M. V.; Kwok, H. S. *Opt. Lett.* **2014**, *39*, 2900.
6. Ramachandran, P. V.; Teodorovic, A. V.; Gong, B.; Brown, H. C. *Tetrahedron: Asymmetry* **1994**, *5*, 1075.
7. Yonezawa, T.; Sakamoto, Y.; Nogawa, K.; Yamazaki, T.; Kitazume, T. *Chem. Lett.* **1996**, 855.
8. Xiao, L.; Yamazaki, T.; Kitazume, T.; Yonezawa, T.; Sakamoto, Y.; Nogawa, K. *J. Fluorine Chem.* **1997**, *84*, 19.
9. Nógrádi, M. *Stereochemistry: Basic Concepts and Applications*; Pergamon Press: Oxford, 1981.
10. Ohtani, T.; Nakatsukasa, H.; Kamezawa, M.; Tachibana, H.; Naoshima, Y. *J. Mol. Catal. B: Enzym.* **1998**, *4*, 53.
11. Kubota, T.; Kanega, J.; Katagiri, T. *J. Fluorine Chem.* **1999**, *97*, 213.
12. Kurissery, A.; Darrin, D.; Li, J.; Diaz-Hernandez, M. D.; Jiménez-Barbero, J.; Mootoo, D. R. *J. Org. Chem.* **2009**, *74*, 7774.
13. Pallavicini, M.; Valoti, E.; Villa, L. *Tetrahedron: Asymmetry* **2001**, *12*, 1071.
14. Buck, R. T.; Coe, D. M.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, D.; Sanghera, B. *Tetrahedron: Asymmetry* **2003**, *14*, 791.
15. Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.
16. *General procedure for derivatization.* In a flask flushed with argon an accurately weighed quantity of an alcohol **5** (0.100 mmol), a derivatizing agent (L-menthyl phthalate (**4**) or (*R*)-MTPA (**1**), 0.140 mmol, 1.4 equiv), and *N*,*N*-dimethylaminopyridine (0.005 g, 0.044 mmol, 0.44 equiv) were dissolved in dry dichloroethane (1 ml) under an argon atmosphere with stirring. The flask was sealed with a rubber septum and cooled to 0 °C. A degassed solution of dicyclohexylcarbodiimide (0.030 g, 0.140 mmol, 1.4 equiv) in dry dichloroethane (2 ml) was added dropwise via syringe and the mixture was left overnight with stirring. The resultant suspension was worked up (filtered through a short pad of silica in the case of **4** or centrifuged in the case of **1**) and the obtained solution was analyzed by HPLC and GC–MS.
17. Cambell, K. N.; Knopbloch, J. O.; Cambell, B. K. *J. Am. Chem. Soc.* **1950**, *72*, 4380.