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Clarification of the Stereochemical Course of Nucleophilic Substitution of Arylsulfonate-Based Nucleophile Assisting Leaving Groups

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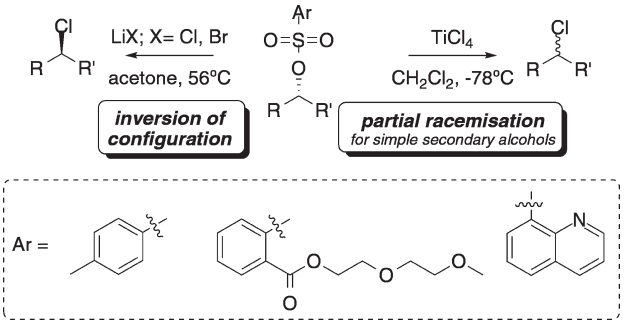

Secondary alcohols modified as tosylates, PEG-sulfonates, or quisylates undergo inversion of configuration at the reacting center when treated with lithium halide in acetone at reflux, where the PEG-sulfonates and quisylates are substantially more reactive. In sterically hindered cases, elimination is a competing process. In contrast, when treated with $TiCl_4$, simple secondary sulfonates give chloride products with partial inversion of configuration. Any observed retention of configuration in a given alkyl sulfonate substrate under these conditions is likely due to neighboring group participation or diastereoselective attack on a carbocation (or ion pair) rather than an S_Ni mechanism.

Introduction

Nucleophilic substitution at an sp^3 hybridized carbon bearing a leaving group represents a fundamental transformation in organic chemistry, where the stereochemical signatures of Walden inversion for the S_N2 mechanism or partial racemization via a planar carbocation and associated counterion in the S_N1 mechanism are fundamentally associated with each process.[1] The third possible stereochemical outcome for substitution is retention of configuration, where this mechanism is designated S_Ni.[2] It is clearly of the highest importance to be able to predict the stereochemical outcome of a given nucleophile−substrate pairing under any conditions employed. This is especially true when planning syntheses of complex targets where an inversion, (partial) racemization, or retention could dramatically alter the entire strategy for the synthesis. Accordingly, the development of new leaving groups for nucleophilic substitution processes with predictable stereochemical control remains an important research area.[3]

Recently, Lepore has shown that 2-(2-methoxyethoxy)ethyl 2-(alkoxysulfonyl)benzoates (PEG-sulfonates, ROPs) **1**, prepared in one step from an alcohol, ROH, undergo nucleophilic displacement at carbon with halide anion.[4] Notably,

(1) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; Wiley: New York, 2007.
(2) For a recent example, see: Moss, R, A.; Fu, X.; Tian, J.; Sauers, R.; Wipf, P. *Org. Lett.* **2005**, *7*, 1371–1374 and references therein.
(3) For an excellent recent review on "recent advances in heterolytic nucleofugal leaving groups", see: Lepore, S. D.; Mondal, D. *Tetrahedron* **2007**, *63*, 5103–5122 and references therein.
(4) Lepore, S. D.; Bhunia, A. K.; Cohn, P. *J. Org. Chem.* **2005**, *70*, 8117–8121.

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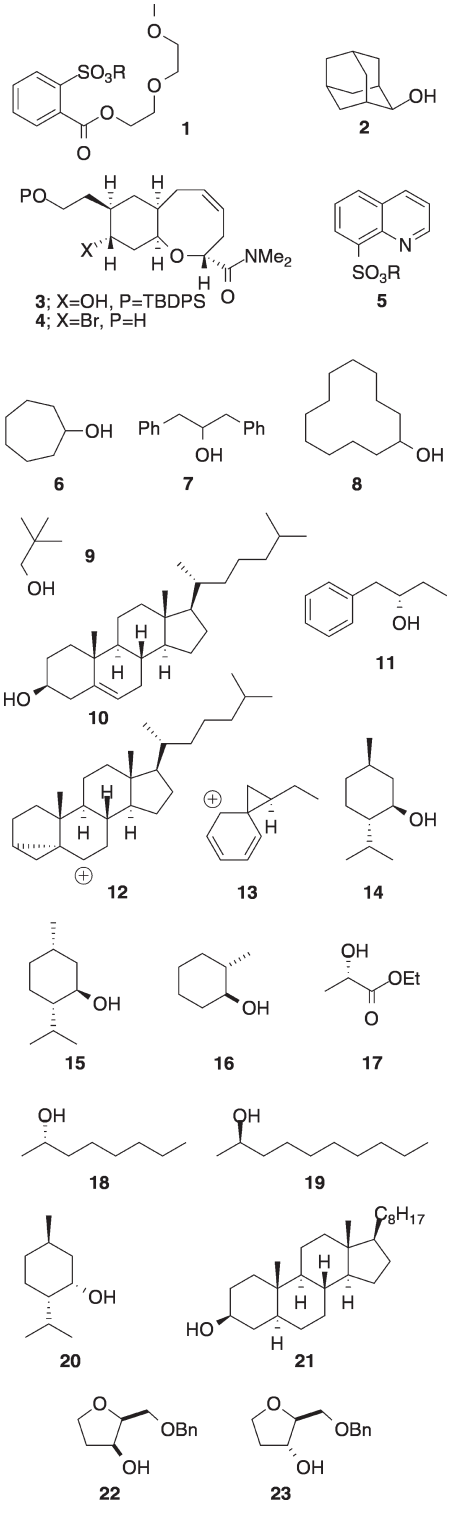
these PEG-sulfonates show acceleration of reaction rate compared to the electronically similar tosylates and show selectivity for lithium halides compared to sodium or potassium salts.



Lepore proposed that the polyether chain coordinates the metal cation, simultaneously stabilizing the negative charge on the leaving sulfonate and attracting the nucleophile to effect overall substitution. The finding that the corresponding PEG-sulfonate of 2-adamantanol (**2**) underwent reaction with lithium bromide to give 2-bromoadamantane but the 2-adamantyl tosylate did not react was taken as evidence of an S_Ni mechanism involving a macrocyclic transition state where the S_N2 pathway is "precluded due to steric shielding".[4] In further work, Lepore reported that selected PEG-sulfonates give secondary alkyl chlorides with retention of configuration on treatment with titanium tetrachloride and suggested that these reactions also proceed via an S_Ni mechanism.[5] Interestingly, under these conditions, a neopentyl PEG-sulfonate was found to give a rearranged product. This method has since been utilized by D. Kim et al.[6] as the key step to convert alcohol **3** to bromide **4** using titanium tetrabromide with observed retention of configuration in the total synthesis of (+)-microcladallene B. In 2008, Lepore reported that the use of selected PEG-sulfonates **1** or additionally alkyl quinoline-8-sulfonates (quisylates, ROQs) **5** also allowed for introduction of azide or bromide with retention of configuration using titanium(IV) salts via a proposed S_Ni mechanism.[7] Thus, the possible conclusion drawn from the current literature is that PEG-sulphonates and quisylates of any secondary alcohol should undergo substitution (by an S_Ni mechanism) with retention of configuration. In connection with both the London and Oxford groups' interest in the synthesis of complex halogenated natural products, we became interested in the use of these PEG-sulfonate groups for the potential introduction of chloride or bromide to access the obtusallene family of natural products[8] and elatenyne,[9] respectively. As a result of that interest, herein we clarify the stereochemical course of nucleophilic substitution of arylsulfonate-based nucleophile assisting leaving groups.

At the outset of our investigations, we considered that the two different types of reaction conditions reported by Lepore, metal halide in acetone[4] versus titanium(IV) salt in a chlorinated solvent,[5,7] could result in different stereochemical outcomes. In particular, it was notable that there were no reports on the use of PEG-sulfonates or quisylates of simple aliphatic enantiopure secondary alcohols under either of these conditions in the Boca Raton papers,[4,5,7] thereby defining the stereochemical outcomes for the simplest possible system with a single stereocenter. The finding that the PEG-sulfonate of 2-adamantanol (**2**) underwent reaction with lithium bromide in acetone to give the corresponding bromide[4] does not necessarily preclude inversion of configuration at the reacting center, since epimeric 4,4-dimethyl-2-adamantyl tosylates have been reported to yield products with a high degree of inversion on treatment with azide as the nucleophile.[10] When using titanium(IV) salts in conjunction

(5) Lepore, S. D.; Bhunia, A. K.; Mondal, D.; Cohn, P. C.; Lefkowitz, C. *J. Org. Chem.* **2006**, *71*, 3285–3286.

(6) Park, J.; Kim, B.; Kim, H.; Kim, S.; Kim, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4726–4728.

(7) Lepore, S. D.; Mondal, D.; Li, S. Y.; Bhunia, A. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7511–7514 and references therein.

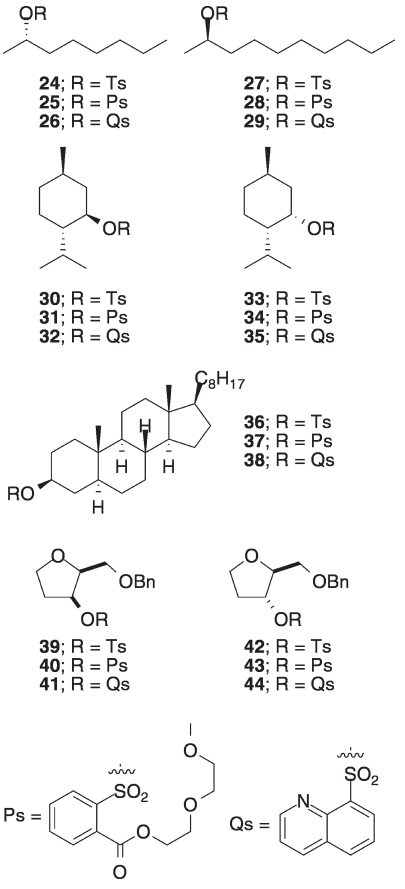
(8) For recent synthetic work on the obtusallenes, see: (a) Braddock, D. C.; Bhuva, R.; Millan, D. S.; Perez-Fuertes, Y.; Roberts, C. A.; Sheppard, R. N.; Solanki, S.; Stokes, E. S. E.; White, A. J. P. *Org. Lett.* **2007**, *9*, 445–448. (b) Braddock, D. C.; Millan, D. S.; Pérez-Fuertes, Y.; Pouwer, R.; Sheppard, R. N.; Solanki, S.; White, A. J. P. *J. Org. Chem.* **2009**, *74*, 1835–1841.

(9) For recent synthetic work directed towards the synthesis and structure determination of elatenyne, see: (a) Sheldrake, H. M.; Jamieson, C.; Burton, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 7199–7202. (b) Sheldrake, H. M.; Jamieson, C.; Pascu, S. I.; Burton, J. W. *Org. Biomol. Chem.* **2009**, *7*, 238–252.

(10) Banert, K.; Kurnianto, A. *Chem. Ber.* **1986**, *119*, 3826–3841.

with PEG-sulfonates,[5,7] no stereochemical information can be extracted from the employment of the reported PEG-sulfonates of achiral 2-adamantanol (**2**), 2-cycloheptanol (**6**), 1,3-diphenyl-2-propanol (**7**), and cyclododecanol (**8**) substrates. On the other hand, the PEG-sulfonate of neopentyl alcohol **9** was found to react with $TiCl_4$ to give a rearranged chloride,[5] implicating the intermediacy of a carbocation followed by a Meerwein−Wagner shift. It was also apparent that the reported PEG-sulfonates and quisylates derived from cholesterol (**10**)[11] and (*S*)-1-phenylbutan-2-ol (**11**) could possibly react by neighboring group participation under these conditions, via cation **12**[12] and phenonium ion **13**,[13] respectively, leading to the observed retention of configuration in these substrates by double inversion. The final group of reported PEG-sulfonate and quisylate modified substrates, menthol (**14**),[14] isomenthol (**15**),[14] and (±)-*trans*-2-methylcyclohexanol (**16**) (the corresponding neomenthol substrate was not reported), could all be subject to *diastereoselective* halogenation/aziridination under these conditions via carbocations (or ion pairs) and attack at the least hindered face leading also to the observed retention of configuration. The above considerations could also apply to the conversion of alcohol **3** into bromide **4** under the reported conditions. Interestingly, the PEG-sulfonate and quisylate of *S*-ethyl lactate **17** was found to undergo inversion of configuration when treated with titanium(IV) bromide, and it was noted that this suggests a change in mechanism.[7,15] Herein, we report on our investigations from London and Oxford where our first objective was to determine the stereochemical course of reaction under each of the different reaction conditions. Additionally, we desired to compare and contrast tosylates', PEG-sulfonates', and quisylates' behavior for a given alcohol substrate. Accordingly, we show that tosylates, PEG-sulfonates **1**, and quisylates **5** of enantiopure secondary alcohols (*S*)-octan-2-ol (**18**) and (*R*)-decan-2-ol (**19**) all undergo inversion of configuration at the reacting center when treated with lithium chloride to give their corresponding chlorides. The same chlorides are obtained from the same substrates when treated with titanium tetrachloride but with partial racemization. Alkenes and the products of hydride shifts are also obtained under these latter conditions. We also present our results of nucleophilic displacement of the tosylates, PEG-sulfonates, and quisylates of (1*R*,2*S*,5*R*)-menthol (**14**), (1*S*,2*S*,5*R*)-neomenthol (**20**), and 3β-chlolestanol (**21**) using LiCl or $TiCl_4$, and tosylates, PEG-sulfonates, and quisylates derived from the hydroxy tetrahydrofurans **22** and **23** on treatment with lithium bromide in acetone at reflux.

Results and Discussion



Tosylates **24**,[16] **27**, **30**,[17] **33**,[17] **36**,[18] **39**, and **42** were prepared by standard procedures from alcohols **18**, **19**, **14**, **20**, **21**, **22**, and **23**, respectively; the racemic *cis*-alcohol **22**[19] was prepared from *cis*-2-(benzyloxymethyl)-3-(methoxymethyl)oxirane according to a literature procedure[19] with the racemic *trans*-alcohol **23** being prepared from the *cis*-alcohol **22** by a Mitsunobu/hydrolysis sequence. PEG-sulfonates **25**, **28**, **31**,[5] **37**, **40**, and **43** were prepared from the same alcohols using the method of Lepore.[4] The corresponding quisylates **26**,[20] **32**,[20] **38**, **41**, and **44** were prepared by analogous procedures. Quisylate **35** was prepared by the method of

(11) In ref 4 cholesterol is shown incorrectly in Table 1 with a -C_6H_{12} side chain but is shown correctly with a -C_8H_{17} side chain in the structures in Supporting Information.

(12) For selected chlorinations of 3β-cholesterol with retention of configuration, see the following. (a) In two steps via the mesylate: Sun, Q.; Cai, S.; Peterson, B. R. *Org. Lett.* 2009, *11*, 567−570 and references therein. (b) With aluminium and titanium halides: Broome, J.; Brown, B. R.; Summers, G. H. R. *J. Chem. Soc.* **1957**, 2071–2073. (c) Via a xanthate and sulfuryl chloride: Kozikowki, A. P.; Lee, J. *Tetrahedron Lett.* **1988**, *29*, 3053–3056. (d) Directly with ferric chloride: Liu, F.-W.; Liu, H.-M.; Zhang, Y.-B.; Zhang, J.-Y.; Tian, L.-H. *Steroids* **2005**, *70*, 825–830.

(13) Cram, D. J. *J. Am. Chem. Soc.* **1964**, *86*, 3767–3772.

(14) In ref 4 (1*S*,2*R*,5*S*)-menthol is shown in Table 1. The PEG-sulfonate is shown as (1*R*,2*S*,5*R*), and the chloride product is shown as (1*R*,2*S*,5*R*) in Supporting Information. For isomenthol the (1*S*,2*R*,5*R*) enantiomer is shown in Table 1. The spectra shown on pages S4 and S10 of Supporting Information1 are annotated as derivatives of (1*S*,2*R*,5*S*)-menthol.

(15) The related 2-pyridylsulfonate group had already been reported to give inversion of configuration in nucleophilic bromination reactions using magnesium dibromide as the halide source: Hanessian, S.; Kagotani, M.; Komaglou, K. *Heterocycles* **1989**, *28*, 1115–1120.

(16) Juaristi, E.; Jiménez-Vázquez, H. A *J. Org. Chem.* **1991**, *56*, 1623–1630.

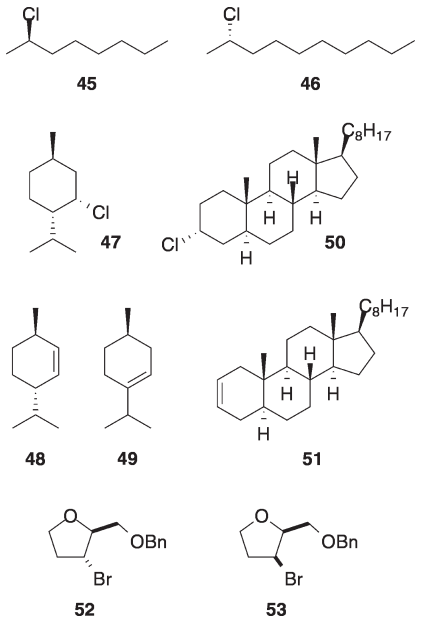
(17) Scianowski, J.; Rafinski, Z.; Wojtczak, A. *Eur. J. Org. Chem.* **2006**, 3216–3225.

(18) Naito, K.; Miura, A.; Azuma, M. *J. Am. Chem. Soc.* **1991**, *113*, 6386–6395.

(19) Schomaker, J. M.; Pulgam, V. R.; Borhan, B. *J. Am. Chem. Soc.* **2004**, *126*, 13600–13601.

(20) The quisylates of (±)-2-octanol, (±)-neomenthol, and (1*R*,2*S*,5*R*)-menthol have been reported: Corey, E. J.; Posner, G. H.; Atkinson, R. F.; Wingrad, A. K.; Halloran, D. J.; Radzik, D. M.; Nash, J. N. *J. Org. Chem.* **1989**, *54*, 389–393.

Corey.[20] This method was adapted for the preparation of quisylate **29** and PEG sulfonate **34**.



Substrates **24**−**38** were subjected to nucleophilic displacement using LiCl in acetone at reflux as per Lepore's original conditions (Table 1).[4] Tosylates *S*-**24** and *R*-**27** (entries 1 and 4) gave 2-chlorooctane **45** and 2-chlorodecane **46** in high isolated yield with inversion of configuration as judged by comparison of the optical rotation[21−23] with that of authentic (2*R*)-chlorooctane and (2*S*)-chlorodecane prepared by Appel chlorination[24] of (*S*)-octan-2-ol and (*R*)-decan-2-ol, respectively. PEG-sulfonates **25** and **28** (entries 2 and 5) and quisylates **26** and **29** (entries 3 and 6) also gave the chlorides with inversion of configuration, although some elimination products were also seen. Thus for simple secondary alcohols, under these conditions, tosylates, PEG-sulfonates, and quisylates all lead to the same stereochemical outcome: inversion of configuration.[25] However, by inspection of the reaction times, the PEG-sulfonate and quisylate groups are clearly superior leaving groups under these conditions. Evidently, the PEG-ether and quinoline nitrogen lone pair can both sequester lithium cation and activate the leaving group as previously postulated. This is also apparent from inspection of the results from menthol- and neomenthol-derived substrates **30**−**35** (entries 7−12). Tosylate **30** failed to react under the reaction conditions even after extended heating (entry 7). Presumably, the further steric encumbrance of the β-isopropyl group in this secondary alcohol is sufficient to prevent reaction under these conditions. However, the evidently more reactive PEG-sulfonate **31** underwent slow reaction to give neomenthyl chloride **47** as the major product, along with elimination products menth-2-ene **48** and menth-1-ene **49** (entry 8).[26] Notably, menthyl chloride was not observed. Quisylate **32** gave a similar product distribution (entry 9). In these cases the extra activation given by the coordinated metal is apparently sufficient to overcome any steric encumbrance. The stereochemical outcome from these reactions under these conditions is also inversion of configuration at the reacting center.[25] It is also apparent that additional activation for substitution for the PEG-sulfonates and quisylates goes hand-in-hand with additional propensity to eliminate (i.e., they are simply better leaving groups for either process). Thus, the neomenthyl tosylate **33**, which is perfectly set up for antiperiplanar elimination to give a trisubstituted olefin, did not undergo substitution but gave elimination product **49** and traces of regioisomer **48** (entry 10).[26,27] In line with previous relative reactivities, the PEG-sulfonate **34** and quisylate **35** reacted substantially more rapidly than the tosylate **33** but did not undergo substitution either, giving instead elimination products with essentially identical product distributions (entries 11 and 12). Finally, in cholestanol substrates **36**−**38**, where there is no possibility of

TABLE 1. Nucleophilic Displacement of Tosylates, PEG-Sulfonates, and Quisylates 24−38 Using LiCl in Refluxing Acetone

entry[a]	substrate[b]	product[c]	$[\alpha]_D$[d]
1	**24** (48; >90)	**45** (93)[e]	−28.3
2	**25** (3.5; >90)	**45** (92)[e]	−28.4
3	**26** (3.25; 80)	**45** (90)[f]	−28.1
4	**27** (36; >90)	**46** (100)	+28.3
5	**28** (4; >90)	**46** (85)[e]	+27.6
6	**29** (3.5; 70)	**46** (88)[e]	+26.3
7	**30** (72; <5)		
8	**31** (72; 60)	**47** (71); **48** (14); **49** (15)	
9	**32** (36; >90)	**47** (59); **48** (26); **49** (15)	
10	**33** (24; 89)	**48** (2); **49** (98)	
11	**34** (2.5; 92)	**48** (3); **49** (97)	
12	**35** (3.5; 65)	**48** (3); **49** (97)	
13	**36** (48; 30)	**50** (87); **51** (13)	
14	**37** (48; 82)	**50** (85); **51** (15)	
15	**38** (72; 64)	**50** (71); **51** (29)	

[a]All reactions performed at 0.2 M in acetone with 4 equivalents of LiCl; [b]Reaction time (h) followed by isolated yield in parentheses. Where yields are listed as >90 the reaction was essentially quantitative, but small quantities of the volatile chloride product were lost in the evaporative removal of acetone; [c]Product distribution in parentheses; [d]$[\alpha]_D$ values are based on mass of mixture, and are not corrected for any other components; [e]Traces of elimination products were observed by ^{1}H NMR. [f]Some unreacted alcohol (*ca.* 9%) was carried through from quisylate formation.

(21) (2*R*)-Chlorooctane has a negative optical rotation; as prepared by Appel chlorination: $[\alpha]_D$ −32.7 (CH_2Cl_2, *c* 0.32). (2*S*)-Chlorodecane has a positive optical rotation; as prepared by Appel chlorination: $[\alpha]_D$ +33.0 (CH_2Cl_2, *c* 0.97).

(22) A control experiment shows that (2*R*)-chlorooctane is configurationally stable to these reaction conditions (LiCl, refluxing acetone) at least up to 17 h. Recovered **45**: $[\alpha]_D$ −31.9 (CH_2Cl_2, *c* 0.29).

(23) There is some small disparity in the recorded optical rotations (Table 1, entries 1−6) with the expected rotations from 100% inversion of configuration for these products (see ref 21). Since we have shown that the products are configurationally stable under these conditions (see ref 22) *and* that the diastereomerically pure substrates **30**−**32** and **36**−**38** (Table 1) show *only* inverted chloride-containing products (as easily monitored by ^{1}H NMR; see Supporting Information), we surmise that these products are all enantiomerically pure and there is up to 10% error in the optical rotation readings. The source of error probably results from the volatility of the products and small amounts of alkene impurities from competing elimination. However, we were unable to separate the 2-chloroalkane enantiomers either by chiral HPLC or chiral GC at Imperial or Oxford, respectively, to determine exact ee's.

(24) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–811.

(25) This is the expected stereochemical outcome of an S_N2 mechanism (see ref 1), but this term has a strict kinetic relationship associated with it that has not been measured.

(26) All products were identified by comparison with an authentic sample.

(27) Halide anions in acetone have been previously noted to function as bases: Biale, G.; Parker, A. J.; Smith, S; Stevens, I. D. R.; Winstein, S. *J. Am. Chem. Soc.* **1970**, *92*, 115–122.

neighboring group participation (cf., cholesterol **10**), tosylate **36** reacted only sluggishly (entry 13). In contrast, the more reactive PEG-sulfonate **37** and quisylate **38** gave the inverted chloride **50**[25] as the major product, with some elimination product **51**.[26] It is manifest from the above results that under these conditions (LiCl, acetone) tosylate, PEG-sulfonate, and quisylate derivatives of secondary alcohols all undergo nucleophilic substitution with inversion of configuration at the reacting center.[25,28] In sterically hindered substrates, elimination is a competing process. Moreover, the PEG-sulfonates and quisylates are significantly more reactive than the corresponding tosylates under these conditions.

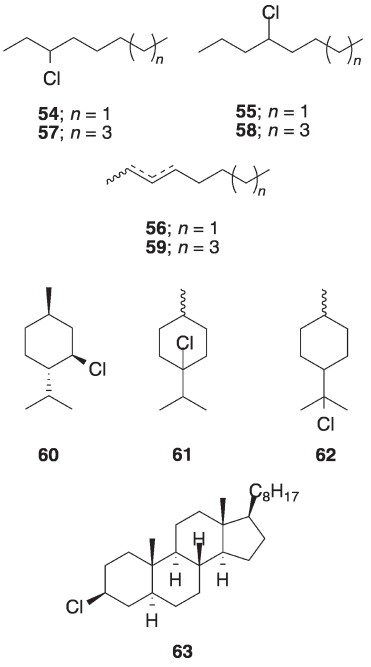
In connection with the Oxford's group work on the synthesis and structure determination of elatenyne,[9] we were interested in investigating the bromination of 3-hydroxy-tetrahydrofuan derivatives with the aim of converting a single 3-hydroxy-tetrahydrofuran into the corresponding bromide with either inversion or retention of configuration. As a model study, we elected to investigate the bromination of the tosylates, PEG-sulfonates, and quisylates derived from diastereomeric tetrahydrofurans **22** and **23**, which would allow us to determine the stereochemical course of the bromination reactions in these systems. The six sulfonate esters **39**−**44** were treated with lithium bromide in acetone at reflux using the conditions described by Lepore, and the crude reaction mixtures were analyzed by ^{1}H NMR after filtration through a silica plug (Table 2). The *cis*-sulfonate esters all gave the corresponding *trans*-bromide **52**, which was identical to material prepared by Appel bromination of the *cis*-alcohol **22**. Analysis of the ^{1}H NMR spectra from these three reactions indicated that the bromide derived from the *cis*-tosylate **39** contained a small amount of the *cis*-bromide **53**. Control experiments demonstrated that both the *cis*- and *trans*-bromides **53** and **52** were converted into one another under the reaction conditions, with the *cis*-bromide **53** reacting faster than the corresponding *trans*-bromide **52**. On extended reaction times (48 h) traces of the *cis*-bromide **53** were formed from both the reaction of the *cis*-PEG-sulfonate **40** and the *cis*-quisylate **41**. The *trans*-sulfonate esters (**42**-**44**) derived from the alcohol **23** reacted significantly more slowly than the corresponding *cis*-sulfonate esters, and none of the reactions had reached completion after 30 h. The PEG-sulfonate **43** and the quisylate **44** both gave the corresponding *cis*-bromide **53** as the major product, which was identical to material prepared by Appel bromination of the *trans*-alcohol **23**. Significant amounts of the *trans*-bromide **52** were also formed under the reaction conditions. The *trans*-tosylate **42** gave only a very small amount of the corresponding bromides as an approximate 6:1 mixture of **53**:**52**. The above results are entirely in accord with the mechanism of these reactions being nucleophilic substitution with inversion of configuration at the reacting center.[25] In keeping with this stereochemical scenario, the trans-sulfonates (**42**−**44**) and the *trans*-bromide (**52**) react more slowly as a result of the bromide anion having a more hindered trajectory in the *trans*-substrates then in the corresponding *cis*-substrates. This readily accounts for the formation

TABLE 2. Nucleophilic Displacement of Tosylates, PEG-Sulfonates, and Quisylates 39−44 Using LiBr in Refluxing Acetone

entry[a]	substrate[b]	product[c]	recovered substrate
1[d]	**39** (30; 59)	**52**:**53** (> 20:1)	30
2	**40** (8.5; 84)	**52** (100)	0
3	**41** (8.5; 81)	**52** (100)	0
4[d]	**42** (30; < 5)	**52**:**53** (ca. 1:6)	75
5[d]	**43** (30; 77)	**52**:**53** (ca. 1:7)	12
6[d]	**44** (30; 70)	**52**:**53** (ca. 1:8)	tr

[a]All reactions performed at 0.05 M in acetone with 4 equiv of LiBr. [b]Reaction time (h) followed by isolated yield in parentheses. [c]Product distribution in parentheses. [d]Reaction stopped after 30 h.

of significant amounts of the *trans*-bromide **52** in the reaction of the *trans*-sulfonates **42**−**44** with bromide anion. Moreover, as with the results reported in Table 1, the PEG-sulfonates and quisylates are significantly more reactive than the corresponding tosylates to lithium bromide in acetone.



Having established that tosylates, PEG-sulfonates, and quisylates all undergo substitution with inversion of configuration at the reacting center with lithium halides in refluxing acetone, substrates **24**−**38** were also subjected to nucleophilic displacement using $TiCl_4$ in dichloromethane at −78 °C as per Lepore's conditions (Table 3).[5] In our hands these reactions were not complete after 2 min as originally reported and were allowed to react for 1 h at this temperature before quenching.[29] The isolated products were analyzed by ^{1}H NMR and by polarimetry (Table 3). Inspection of the results for the sulfonate esters derived from simple secondary alcohols (Table 3, entries 1−6) shows that multiple products are formed. These include the expected 2-chloroadducts **45** (entries 1−3) and **46** (entries 4−6) as well as 3- and 4-chloroalkanes **54** and **55** (entries 1−3) and **57** and **58**

(28) Control experiments with 3-β- and 3-α-chlorocholestanes and menthyl chloride involving extended reflux (48 h) with LiCl (4 equiv) in acetone showed them to be configurationally stable, and they were recovered unchanged in quantitative yield.

(29) We found the tosylates to be comparably, if not more reactive than the corresponding quisylates and PEG-sulfonates to reaction with $TiCl_4$ by inspection of the evolution of the TLC profile for these reactions, although this was not quantified.

(entries 4−6).[26] Small quantities of the internal C_8 (**56**) (entries 1 and 2) and C_{10} (**59**) (entries 4 and 5) alkenes were also observed.[26] Thus, under these conditions, a different product profile is observed compared with that when employing lithium halide in refluxing acetone (vide supra, Table 1, entries 1−6). The products can all be postulated to be derived from a common secondary carbocation (or corresponding ion pair)[30] at the 2-position. Direct trapping of the carbocation yields 2-chloroalkanes **45** or **46**. Alternatively, 1,2-hydride shifts and subsequent trapping allow the formation of the 3- and 4-chloroalkanes **54** and **55**, or **57** and **58**.[26,31] Elimination under Saytzev orientation explains the presence of alkenes **56** or **59**. Analysis of the optical rotations of these mixtures reveals (Table 3) that substitution has proceeded with partial inversion of configuration.[32] Thus, the simplest model that can be formulated to account for all of these observations involves a $TiCl_4$-induced formation of a carbocation (or ion pair)[30] where the leaving group partially shields front side attack from a returning chloride nucleophile.[33,34] It also seems reasonable to suggest that other secondary sulfonate substrates (*vide infra*) will react via $TiCl_4$-induced carbocations (or ion pair) under these conditions.[30,34] Interestingly, the extent of racemization as judged from the optical rotations of the mixtures is significantly lower in the PEG-sulfonate and quisylate cases, indicating more tightly bound ion pairs.[35]

Thus, for simple secondary alcohols modified as tosylates, PEG-sulfonates, or quisylates, whereas reaction with LiCl in refluxing acetone leads to inversion of configuration[25] at the reacting center, the use of $TiCl_4$ leads to chlorides with partial inversion of configuration,[34] and retention of configuration is not observed. In contrast, the menthol-derived sulfonates **30**−**32** (entries 7−9), including the simple tosylate, all gave menthyl chloride **60**[26] with overall retention of configuration in good yield. A survey of the literature reveals that this is not a new phenomenon, and solvolysis of menthol tosylate with predominant retention of configuration has previously been reported.[36,37] In this case, on the basis of a significantly reduced β,β'-d_3 isotope effect, the authors proposed that a chairlike conformation persists in a rate-determining transition state and an intermediate ion pair, where the substituents at the 2- and 5-positions (relative to the reacting center) prevent the formation of a bent chair or half chair conformation where the "bottom-face" would become exposed. Nucleophilic capture then occurs on the exposed "top-face", leading to the observed retention of configuration. We suggest that the same effect is in operation with menthol sulfonates **30**−**32**, and under these conditions a $TiCl_4$-induced carbocation (or ion pair)[30,34] is formed where it is the conformation of the menthyl framework and not the leaving group that determines the resultant stereochemistry of the product. Notably Kim's substrate **3** also has this cyclohexyl substitution pattern, where the reaction proceeds with retention of configuration (vide supra). In further contrast, whereas neomenthol tosylate **33**, PEG-sulfonate **34**, and quisylate **35** all underwent elimination reactions with LiCl in refluxing acetone, on treatment with $TiCl_4$ tertiary chlorides **61** and **62** were isolated (entries 10−12).[26] Evidently, the incipient p-orbital forming from loss of any of the axially disposed sulfonates by $TiCl_4$-induced carbocation (or ion pair)[30] formation is perfectly aligned to induce an immediate 1,2-hydride shift from the neighboring axial hydrogen[38] at the 2-position leading to a tertiary carbocation and thence **61** after trapping by chloride. A second shift to give another tertiary carbocation can lead to chloride **62**.[39] Finally, the sulfonate derivatives of cholestanol **36**−**38** (entries 13−15) underwent reaction under these conditions to give epimeric chlorides **50** and **63**,[26] as well as elimination product **51** in some cases. Whereas with LiCl in refluxing acetone only chloride **50** with inversion of configuration was observed, the observation of both epimeric chlorides **50** and **63** under these conditions is consistent with $TiCl_4$-induced carbocation (or ion pair)[30] formation where the leaving group partially shields the top face. Unlike the menthol sulfonates, these sulfonates lack a 2-substituent on the cyclohexyl ring, which must allow sufficient conformational flexibility to accommodate bottom face attack. It is therefore apparent that under these conditions ($TiCl_4$, CH_2Cl_2,

TABLE 3. Nucleophilic Displacement of Tosylates, PEG-Sulfonates, and Quisylates 24−38 Using $TiCl_4$ in Dichloromethane

entry[a]	substrate[b]	product[c]	$[\alpha]_D$[d]
1	**24** (75)	**45** (40); **54** + **55** (56); **56** (4)	−4.7
2	**25** (>90)	**45** (62); **54** + **55** (35); **56** (3)	−13.6
3	**26** (>90)	**45** (43); **54** + **55** (57); **56** (0)	−7.5
4	**27** (88)	**46** (29); **57** + **58** (68); **59** (3)	+3.6
5	**28** (>90)	**46** (57); **57** + **58**; (42); **59** (1)	+11.7
6	**29** (>90)	**46** (42); **57** + **58**; (58); **59** (0)	+9.5
7	**30** (>90)	**60** (ca. 90)	
8	**31** (>90)	**60** (ca. 90)	
9	**32** (>90)	**60** (ca. 90)	
10	**33** (79)	**61** (47); **62** (53)	0.0
11	**34** (>90)	**61** (46); **62** (54)	0.0
12	**35** (>90)	**61** (46); **62** (54)	0.0
13	**36** (65)	**50** (42); **51** (40); **63** (18)	
14	**37** (82)	**50** (57); **51**(1); **63** (42)	
15	**38** (70)	**50** (66); **51** (8); **63** (26)	

[a]All reactions performed at 0.05 M in dichloromethane at −78 °C for 1 h with 2 equiv of $TiCl_4$. [b]Isolated yield in parentheses. [c]Product distribution in parentheses. [d]$[\alpha]_D$ values are based on mass of mixture and are not corrected for any other components.

(30) It is not our intention to become embroiled in the long-standing debate regarding precise mechanistic distinctions or the S_N1/S_N2 mechanistic borderline but simply to clarify the stereochemical outcomes using these leaving groups under given conditions such that other workers may make accurate predictions of the expected stereochemical outcomes.

(31) An authentic sample of 5-chlorodecane was prepared in anticipation of its observation. However, 5-chlorodecane was not observed in the product mixtures from reaction of **27**, **28**, and **29**.

(32) Assuming that all products arising from hydride shifts are racemic, the optical purities of the 2-chloroalkanes in Table 3, entries 1−6 are 36% (*R*), 67% (*R*), 53% (*R*), 37% (*S*), 61% (*S*), and 68% (*S*), respectively.

(33) One referee suggested that a mixed S_N1-S_N2 mechanism could be operating.

(34) This is the expected stereochemical outcome of an S_N1 mechanism (see ref 1), but this term has a strict kinetic relationship associated with it that has not been measured.

(35) A control experiment with (2*R*)-chlorooctane shows that it is configurationally stable under these conditions ($TiCl_4$, CH_2Cl_2, −78 °C, 1 h). Recovered **45**: $[\alpha]_D$ −32.5 (CH_2Cl_2, *c* 0.32).

(36) Hiral-Starcevic, S.; Majerski, Z.; Sunko, D. E. *J. Am. Chem. Soc.* **1974**, *96*, 3659–3661.

(37) The observation of menthyl chloride as a product (i.e., with retention of configuration) in the chlorination of menthol with PCl_5 and various additives has been long known: Smith, J. G.; Wright, G. F. *J. Org. Chem.* **1952**, *17*, 1116–1121 and references therein.

(38) Hiral-Starcevic, S.; Majerski, Z.; Sunko, D. E. *J. Org. Chem.* **1980**, *45*, 3388–3393.

(39) An authentic sample of these compounds was prepared as a mixture by treating menth-1-ene **49** with concentrated aqueous HCl. The identity of these compounds was also confirmed by readings of zero for their optical rotations reflecting the internal mirror plane that now exists in these compounds.

-78 °C), tosylate, PEG-sulfonate, and quisylate substrates all undergo nucleophilic substitutions consistent with $TiCl_4$-induced carbocation (or ion pair)[30] formation, leading to partial inversion of configuration[34] in simple secondary systems. In the case of menthol-derived sulfonates, the steric effect of the bulky isopropyl group dominates, and substrate-controlled retention of configuration is observed.[40]

Conclusion

We have clarified the stereochemical course of nucleophilic substitution of arylsulfonate-based leaving groups, showing that tosylates, PEG-sulfonates, and quisylates of secondary alcohols are all subject to inversion of configuration at the reacting center[25] when treated with lithium halides in refluxing acetone. The PEG-sulfonates and quisylates are considerably more reactive than the corresponding tosylates in their reactions with metal halide salts in acetone and are a significant addition to the armory of reagents available for the activation of hydroxy groups. The increased activity is consistent with the positively charged metal being chelated by the PEG group or coordinated by the quinoline lone pair and stabilizing the negative charge on the leaving sulfonate as originally proposed by Lepore. In contrast, $TiCl_4$-induced substitutions of tosylates, PEG-sulfonates, and quisylates leads to product distributions consistent with carbocation (or ion pair)[30] formation and in simple secondary substrates leads to partial inversion of configuration.[29,34] Any observed retention of configuration[5−7] is likely due to neighboring group participation[41] or diastereoselective attack on a carbocation (or ion pair) rather than an S_Ni mechanism.

Experimental Section

General. See Supporting Information.

General Procedure for Nucleophilic Substitution of Sulfonates 24−38 with LiCl. To a solution of sulfonate (1 equiv) in acetone (0.2 M) was added lithium chloride (4 equiv), and the reaction mixture was heated to reflux until no further reaction was evident by TLC. The mixture was allowed to cool, diluted with pentane, and filtered through a plug of silica. The solvent was evaporated to a minimum by atmospheric distillation and finally removed by Kugelrohr distillation. The resulting product mixtures were analyzed by ^{1}H NMR spectroscopy and polarimetry (Table 1). Products **45**−**51** were identified by the following characteristic ^{1}H and ^{13}C NMR shifts, and product ratios were obtained by integration of the same resonances in the ^{1}H NMR spectra (see Supporting Information). δ_H (**45**) 4.05 (m, 1H); (**46**) 4.06 (m, 1H); (**47**) 4.54[42] (br s, 1H); (**48**) 5.55[43] (br s, 2H); (**49**) 5.38[43] (br s, 1H); (**50**) 4.55[44] (br s, 1H); (**51**) 5.62[45] (br s, 2H) ppm. δ_c (**45**) 59.0; (**46**) 59.0; (**47**) 63.5 ppm. Authentic samples of simple aliphatic chlorides **45** and **46** were prepared by Appel chlorination of the corresponding secondary alcohol.

General Procedure for Appel Chlorination of Alcohols. To a solution of alcohol (1 equiv) in carbon tetrachloride (0.4 M) was added triphenylphosphine (2 equiv), and the reaction mixture was heated to reflux for 24 h. The reaction mixture was allowed to cool to rt, diluted with pentane, and filtered through a plug of silica, and the solvent was evaporated to a minimum by atmospheric distillation and finally removed by Kugelrohr distillation.

(*R*)-2-Chlorooctane 45. Prepared by Appel chlorination from (*S*)-octan-2-ol: $[\alpha]_D$ −32.7 (CH_2Cl_2, *c* 0.32); IR (thin film) υ_{max} 2928, 2959 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 4.10−4.01 (m, 1H), 1.77−1.69 (m, 2H), 1.53 (d, J = 6.7 Hz, 3H), 1.52−1.26 (m, 8H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 59.0, 40.4, 31.7, 28.8, 26.6, 25.4, 22.6, 14.1; GCMS 112 (13%, M − HCl), 83 (62), 70 (100), 55 (72).

General Procedure for Nucleophilic Substitution of Sulfonates 39−44 with LiBr. To a solution of sulfonate (1 equiv) in acetone (0.05 M) was added lithium bromide (4 equiv), and the reaction mixture was heated to reflux until no further reaction was evident by TLC (or for 30 h, whichever was the shorter time). The mixture was allowed to cool, diluted with light petroleum, and filtered through a plug of silica washing with ether. The solvent was removed in vauco, and the residue was analyzed by ^{1}H NMR. The residue was then purified by flash chromatography (4:1, light petroleum/ethyl acetate) (Table 2).

Bromide 52. To a stirred solution of (2*R**,3*R**)-2-(benzyloxymethyl)tetrahydrofuran-3-ol (50 mg, 0.24 mmol) in toluene (3 mL) were added triphenylphosphine (126 mg, 0.48 mmol) and carbon tetrabromide (159 mg, 0.48 mmol). The reaction mixture was heated to 80 °C for 1 h, cooled to rt, diluted with CH_2Cl_2 (10 mL), adsorbed onto silica, and purified by flash column chromatography (4:1, light petroleum/ethyl acetate) to give the title compound as a colorless oil (48 mg, 0.17 mmol, 74%); R_f 0.64 (1:1 petroleum ether 40−60°/ethyl acetate); IR ($CDCl_3$) ν_{max} 3030, 2983, 2944, 2858, 1497, 1451 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 4.61 (d, J = 12.1 Hz, 1H) 4.56 (d, J = 12.1 Hz, 1H), 4.31−4.24 (m, 2H), 4.08−3.98 (m, 2H), 3.61−3.55 (m, 2H), 2.56−2.48 (m, 1H), 2.25 (tdd, J = 4.3, 6.5, 13.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 128.4, 127.7, 127.6, 86.3, 73.5, 69.8, 67.3, 46.6, 36.8; MS (ES^+) *m*/*z* 288.0/290.0 $(M + NH_4)^+$ (100%), 293.0/295.0 $(M + Na)^+$, 563.0/565.0/567.0 $(2M + Na)^+$; HRMS (ES^+) *m*/*z* calcd for $C_{12}H_{15}{}^{79}BrNaO_2$ $(M + Na)^+$ 293.0148, $C_{12}H_{15}{}^{81}BrNaO_2$ $(M + Na)^+$ 295.0128, found 293.0145, 295.0128.

General Procedure for Nucleophilic Substitution of Sulfonates 24−38 with $TiCl_4$. To a solution of sulfonate (1 equiv) in dichloromethane (0.05 M) at −78 °C was added $TiCl_4$ (2 equiv) dropwise. The reaction mixture immediately became yellow and was stirred at −78 °C for 1 h. The mixture was then quenched with saturated sodium hydrogen carbonate solution and extracted with dichloromethane, and the combined organic phase was dried over magnesium sulfate and then passed through a plug of silica. The solvent was evaporated to a minimum by atmospheric distillation and finally removed by Kugelrohr distillation. The resulting product mixtures were analyzed by ^{1}H NMR spectroscopy and polarimetry (Table 3). Products **45**, **46**, **50**, **51**, and **54**−**63** were identified by the following characteristic ^{1}H and ^{13}C NMR shifts, and product ratios were obtained by integration of the same resonances in the ^{1}H NMR spectra (see Supporting Information). δ_H (**45**) 4.05 (m, 1H); (**46**) 4.06 (m, 1H); (**50**) 4.55[44] (br s, 1H); (**51**) 5.62[45] (br s, 2H); (**54**) 3.87 (m, 1H); (**55**) 3.93 (m, 1H); (**56**) 5.43 (m, 2H); (**57**) 3.88 (m, 1H); (**58**) 3.93; (**59**) 5.43[46] (m, 2H); (**60**) 3.80[4] (m, 1H); (**63**) 3.90 (m, 1H) ppm. δ_c (**45**) 59.0; (**46**) 59.0; (**54**) 65.9; (**55**) 64.0; (**57**) 66.0; (**58**) 64.1; (**60**) 63.9 ppm. Authentic samples of simple

(40) Control experiments with 3-β- and 3-α-chlorocholestanes and menthyl chloride show them to be configurationally stable under these conditions ($TiCl_4$, CH_2Cl_2, −78 °C, 1 h), and they were recovered unchanged in quantitative yield.

(41) For bromine as a NGP on a leaving PEG-sulfonate, see: Braddock, D. C.; Hermitage, S. A.; Kwok, L.; Pouwer, R.; Redmond, J. M.; White, A. J. P. *Chem. Commun.* **2009**, 1082–1084.

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aliphatic chlorides **54**, **55**, **57**, and **58** were prepared by Appel chlorination of the corresponding racemic alcohol (see Supporting Information). An authentic sample of **61** and **62** as a mixture was prepared by the action of concentrated aqueous HCl on menthene **49**. An authentic sample of chloride **63** was prepared by hydrogenation of the corresponding cholesterol chloride.

Chlorides 61 and 62. To 4-methyl 1-isopropylcyclohexene (8 mg, 0.06 mmol) was added 6 drops of conc aqueous HCl, and the mixture was allowed to stir for 24 h. The mixture was diluted with $CDCl_3$ (1.5 mL), and the resulting solution was washed with saturated $NaHCO_3$ solution and dried over magnesium sulfate. ^{1}H NMR showed complete conversion of the starting material to give **61** and **62** as an approximately 2:1 mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08−2.02 (m, 2H, **61**), 2.00−1.92 (m, 2H, **62**), 1.83−0.87 (m, 22H), 1.05 (d, J = 6.7 Hz, 6H, Cl-1), 0.95 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 80.1, 75.4, 50.2, 40.6, 37.2, 35.1, 32.5, 31.9, 30.7, 30.4, 29.7, 28.0, 22.5, 22.3, 17.6; GCMS (**61**) 138 (21%, M − HCl), 130 (19), 95 (100), 81 (19), 67 (17), 55 (17); GCMS (**62**) 138 (56%, M − HCl), 123 (42), 97 (75), 95 (84), 81 (100), 67 (39), 55 (76).

Chloride 63. To a stirred solution of 3β-cholesteryl chloride (150 mg) in diethyl ether (5 mL) was added Pd/C (15 mg). The reaction mixture was purged with hydrogen gas and allowed to stir for 4 h. The reaction mixture was then filtered through a plug of silica gel, and the solvent was removed in vacuo to give the title compound as a white powder (142 mg, 94% yield). Mp 110−114 °C; $[\alpha]_D$ + 5.0 (CH_2Cl_2, c 0.3); IR (thin film) υ_{max} 2933, 2865, 2850, 1467, 1373 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94−3.84 (m, 1H), 2.09−1.95 (m, 2H), 1.88−0.84 (m, 40H), 0.70−0.61 (m, 1H), 0.67 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 60.3, 56.4, 56.3, 54.2, 46.8, 42.6, 40.0, 39.6, 39.5, 38.7, 36.2, 35.8, 35.4, 35.3, 33.2, 32.0, 28.5, 28.2, 28.0, 24.2, 23.8, 22.8, 22.6, 21.1, 18.7, 12.2, 12.1; MS (EI$^+$) m/z 408 (M)$^+$, 406 (M$^+$); HRMS (EI$^+$) m/z calcd for $C_{27}H_{47}Cl$ (M)$^+$ 406.3366, found 406.3371.

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Supporting Information Available: General experimental procedures, synthetic procedures, and characterizing data for sulfonates **24**−**44** and bromide **53**; characterizing data for **46**, **54**, **55**, **57**, **58**, and 5-chlorodecane; copies of ^{1}H spectra and ^{13}C NMR spectra for **24**−**46**, **52**−**55**, **57**, **58**, 5-chlorodecane, and **63**; and copies of ^{1}H NMR spectra of the product mixtures for all substitution reactions recorded in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.