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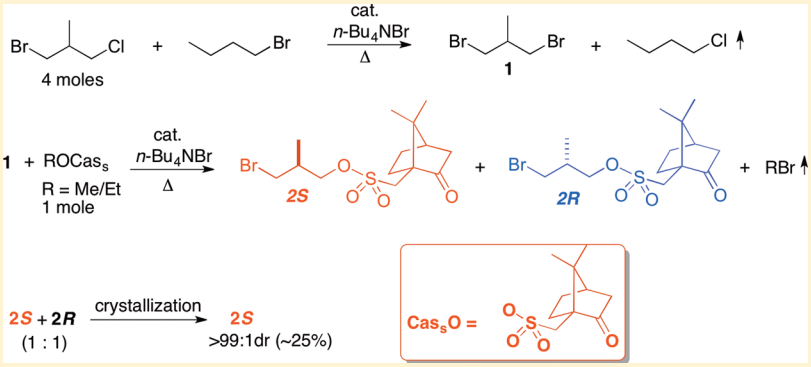
A Scalable, Nonenzymatic Synthesis of Highly Stereopure Difunctional C_4 Secondary Methyl Linchpin Synthons

Shekar Mekala and Roger C. Hahn*

Department of Chemistry, Syracuse University, Syracuse, New York 13244-4100, United States

Supporting Information



ABSTRACT: In response to the continuing widespread use of heterodifunctional C_4 secondary methyl building blocks in asymmetric synthesis, we have developed a mole-scale, two-step synthesis of a 1:1 mixture of the diastereomers of 3-bromo-2-methyl-1-propyl camphorsulfonate (casylate). One isomer (**2*S***) has been crystallized to >99:1 dr in ∼25% yield. Equilibration of the mother liquor (enriched in **2*R***) to a 1:1 mixture and recrystallization significantly raises the overall yield of **2*S***. Applications of **2*S*** include chemoselective Grignard coupling, enabling the very short synthesis of highly stereopure long-chain natural products containing remote, methyl-bearing stereogenic centers [e.g., (*R*)-tuberculostearic acid], with complete control of configuration. Also, Ag-mediated, completely chemoselective Br displacement from **2*S*** leads to a range of >99:1 er difunctional synthons. Both applications incorporate concurrent recovery of CasO. The *enantiomer* of **2*S*** can be made from commercial (1*R*)-10-CasOH.

INTRODUCTION

Much effort has focused on preparation and use of chiral secondary methyl synthons. Among the most versatile of these are difunctional C_4 secondary methyl building blocks (Figure 1). Roche esters (methyl 3-hydroxy-2-methylpropionates; non-crystallizable) have been widely applied to the synthesis of biologically active compounds. There are many routes to their preparation,[1−4] but none has achieved a greater ee than the products from microbe-mediated (formal) β-hydroxylation of isobutyric acid.[5] Other commonly used C_4 chiral synthons are products of desymmetrization of very cheap 2-methyl-1,3-propanediol or its diesters.[1] Many have sought convenient, scalable procedures to convert this diol to high er synthons. Trost et al.[6] have discussed advantages and disadvantages of enzymatic desymmetrizations and those mediated by nonenzymatic catalysts and chiral auxiliaries. Their chiral catalyst provided a desymmetrized 2-methyl-1,3-diol building block in 90% ee. However, large-scale preparation of >99% stereopure C_4 chiral building blocks of the type described here remains rare.[7,8]

Our approach to difunctional C_4 secondary methyl building blocks was inspired by the observation that many alkyl camphorsulfonates (casylates)[9] are crystalline. Crystallization remains a superior and often essential avenue to chiral building blocks at a very high level of stereoisomeric purity. In the context of the difunctional C_4 framework, 3-X-2-methyl-1-propyl casylates[10] (X = Cl/Br/I) were attractive because the two isomers are diastereomers, with different melting points and solubilities, making feasible separation by crystallization. Further, the nucleofugality of both halides and sulfonates could lead to chiral synthons conveniently usable for further elaboration. The bromalkyl casylate pair **2*R*** and **2*S***, with a critical similarity in Br/OCas nucleofugality (see below) and a 30° mp difference,[11] was chosen for further study. To obtain pure **2*R*** and **2*S*** for spectroscopic comparison and for seeding, commercially available (*R*)- and (*S*)-3-bromo-2-methyl-1-propanol were camphorsulfonated in standard fashion.

RESULTS AND DISCUSSION

The quest for a large-scale route to pure **2*S*** started with the scalable, quaternary salt-catalyzed bromide−chloride exchange[12] of commercially available racemic 1-bromo-2-methyl-3-chloropropane and 1-bromobutane, to provide dibromide **1** (Scheme 1, eq 1). This exchange and all others herein are thermoneutral and

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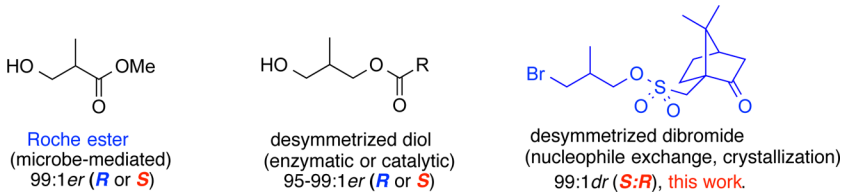
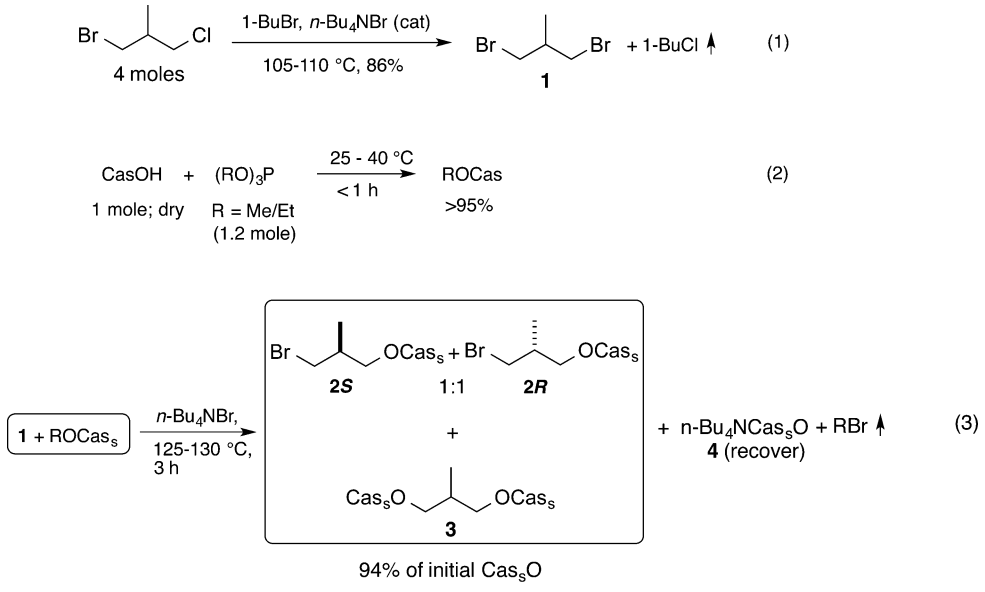


Figure 1. Some chiral C_4 difunctional building blocks.

Scheme 1. Preparation of 2*R* and 2*S*



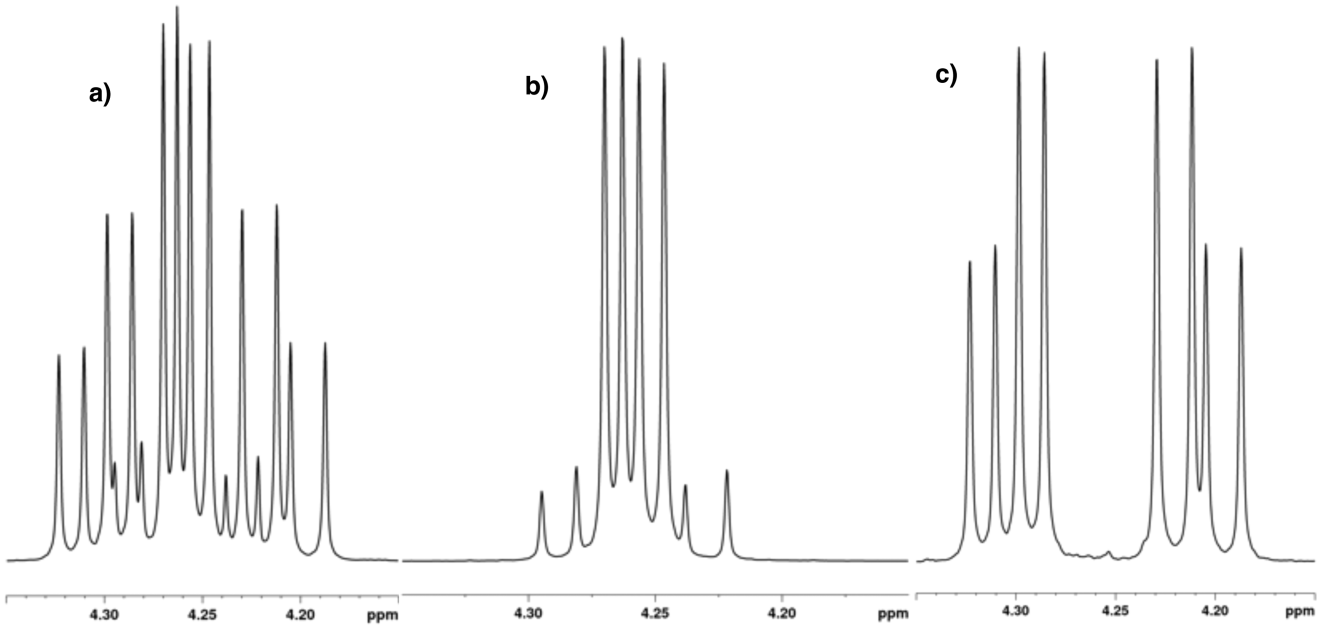


Figure 2. Partial spectra of (a) ~1:1 **2*S*/2*R***, (b) >99:1 **2*S*/2*R***, and (c) **2*R*** prepared from **2*S***.

scalable and need no solvent; the mixtures are homogeneous at exchange temperatures.

Me/EtOCas$_s$ was made directly from camphorsulfonic acid (conveniently on a one-mole scale) by modification of the reported Arbuzov reaction of TsOH with trialkyl phosphites (Scheme 1, eq 2).[13] Running the reaction neat shortened the time to 2 h and removed the need for solvent handling.

In the conversion of dibromide **1** to a **2*R*/2*S*** mixture by *n*-Bu$_4$NBr-catalyzed Br−OCas exchange (Scheme 1, eq 3), methyl or ethyl casylate (Me/EtOCas) was used as the covalent casylate source. Transfer of casylate to the C_4 manifold was driven to completion by distilling out low-boiling Me/EtBr. Casylate displaces bromide more readily than do the arenesulfonates previously studied;[14] this superiority has not been quantitated.

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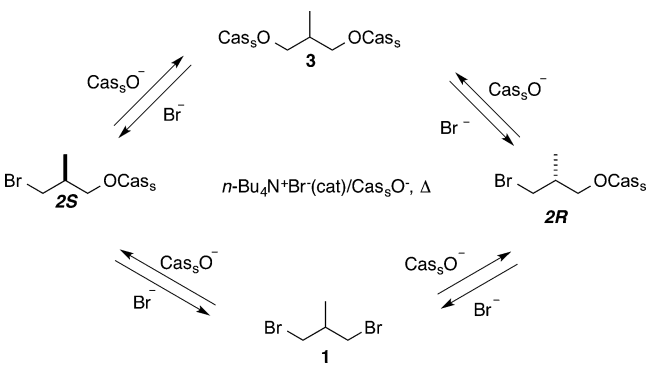
The exchange (eq 3) was performed with 3 equiv of **1** (6 equiv of Br vs OCas), to minimize the percentage of dicasylate **3** at equilibrium. The equilibrated product mixture, as determined by the disappearance of Me/EtBr (which removes 1 equiv of Br), included excess **1**, a 1:1 mixture of **2*R*** and **2*S***, and **3**; the mole ratio of total bromide to total casylate was approximately 5:1, thereby affording **1**, (**2*R*+2*S***), and **3** in the approximate (statistically predicted for Br (x) and OCas (y) by $x^2 + 2xy + y^2$) molar proportions 25:10:1. Unreacted dibromide **1** was distilled out at reduced pressure, to avoid increasing the proportion of dicasylate **3** by concurrent reversible CasO−Br exchange. The residue was taken up in Et_2O, and the catalyst, now n-Bu_4NOCas_s (**4**, reusable for the same reaction), was separated by H_2O extraction. The **2*R*** + **2*S*** mixture was easily separated from **3** by silica gel chromatography, but could be left in the mixture with minimal effect on subsequent crystallization.

Seeding a MeOH solution of the **2*R*** + **2*S*** mixture (and 1−2% residual dibromide **1**) with pure **2*S*** afforded ∼85:15 dr **2*S*** crystals; the mother liquor contained a 22:78 **2*S*/2*R*** mixture. Subsequent recrystallizations of the ∼85:15 dr material from Et_2O (preferably via evaporative concentration vs controlled cooling) afforded ∼25% of >99:1 dr **2*S***. In the range 95:5 **2*S*/2*R*** to 5:95 **2*S*/2*R***, ratios were assayed by 400-MHz ^{1}H NMR, by a resolved pair of doublets (δ 3.025 and 3.015, respectively) produced by the diastereogenic geminal protons at C10 of the camphor moiety; the other pair of doublets (δ 3.63) is unresolved. Above 95:5 **2*S*/2*R***, samples were assayed using the ddd's for the methylene protons adjacent to the OCas group. These are nearly identically centered in the two isomer spectra (δ 4.26), but the outside peaks for **2*R*** are baseline separated (δ 4.32 and 4.19) from all other peaks and discernible up to >99:1 dr. Spectroscopic comparisons of (a) ∼1:1 **2*S*/2*R***, (b) >99:1 dr **2*S*/2*R***, and (c) **2*R*** prepared from **2*S*** provide qualitative evidence of the high dr of **2*S*** (Figure 2).[15] The equally stereopure enantiomer of **2*S*** (**ent-2*S***) can be prepared via the same protocol, from commercially available (1*R*)-10-camphorsulfonic acid.

To improve the 25% yield, we used the *reversibility* of casylate−bromide exchange to obtain additional pure **2*S*** from **2*R*** and/or dicasylate **3**. A mixture of dibromide **1**, **2*S*/2*R*** mixture (∼25:75), **3**, and catalyst, under exchange conditions (Scheme 2), equilibrated (to nearly 1:1 diastereomers) in 4 h.

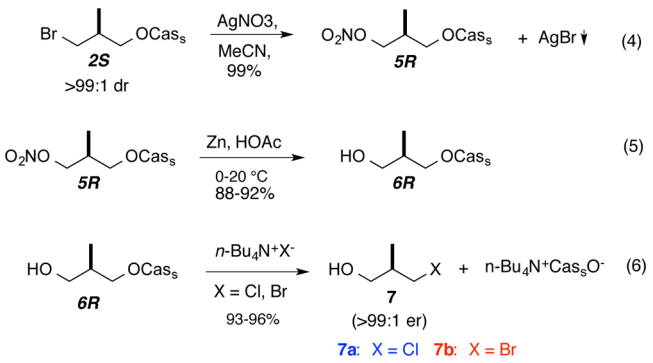
Recrystallization as before gave an improved (∼50%) yield of **2*S***, based on the overall amount of Et/$MeOCas_s$. Repetitions of the equilibration−crystallization cycle in this manner can further increase the yield, but efficiency increases will depend on improved separation in the crystallization steps. Equilibration−crystallization differs from a "crystallization-induced asymmetric transformation", in that isomer interconversion and crystallization are not concurrent.[16] The observed **2*S*/2*R*** equilibration appears to be the first example of diastereomer interconversion mediated by concurrent reversible S_N2 reactions at two *nonstereogenic* centers.

Scheme 2. Equilibration of 2*R* and 2*S*



With >100 g of >99:1 dr **2*S*** in hand, we turned to the critical question of chemoselectivity[17,18] in using this chiral synthon. Reaction of **2*S*** with a range of nucleophiles revealed a 9:1 or greater preference for bromide displacement, but direct OCas displacement by Nu^-, along with attack on OCas by in situ generated Br^-, appreciably degraded the chemical and optical purity of the products. A solution to this problem was found in the known halophilicity of Ag^+ and insolubility of AgBr, which enabled a nearly quantitative, completely selective silver-assisted[19,20] conversion of **2*S*** to the nitrate ester **5*R*** (Scheme 3, eq 4). Zinc in acetic acid[21,22] selectively reduced **5*R*** to alcohol

Scheme 3. Preparation of 5*R*, 6*R*, and 7a/7b



6*R* (Scheme 3, eq 5), which was reacted with n-Bu_4NCl/Br to give haloalkanol **7a** or **7b** and n-Bu_4NOCas_s (Scheme 3, eq 6).

The clean, high-yielding conversion of **2*S*** or **ent-2*S*** to **6*R*** or **ent-6*R*** opens access to other >99:1 er difunctional building blocks[1] by chemoselective nucleophilic displacement of OCas from **6*R*/ent-6*R*** by an array of nucleophiles (e.g., CN^-, $(RO_2C)_2CH^-$, I^-, N_3^-, ArS^-, $ArSO_2^-$. RNH_2). However, widely used **7b** and **ent-7b** (or their protected counterparts) and rarely used **7a** and **ent-7a** are considered keys, because their formation by reaction of **6*R*/ent-6*R*** with n-Bu_4NBr/Cl simultaneously puts OCas most efficiently into reusable form. The building blocks mentioned above often have been prepared from the corresponding Roche esters and desymmetrization products of 2-methyl-1,3-diol,[1] and **7b** and **ent-7b** are commercially available, but very expensive. The present method provides another avenue to these highly pure synthons, but differs from other methods in having the options of increasing the dr of **2*S*** (or its enantiomer) by recrystallization, and conveniently tracking the diastereomeric purity of **2*S*** to a very high level by ^{1}H NMR. The presence of the $OCas_s$ auxiliary in **5*R*** and **6*R*** similarly enables ^{1}H NMR confirmation of their very high dr's (isomer signals not detected). Alcohols **7**/**ent-7** (or protected derivatives) in which X = CN are of particular interest as one form of a heterodifunctional isoprenoid building block.[15,23,24] Also, many uses of alcohols **7**/**ent-7** in which X = I have been reported.[25,26]

The success of the **2*S*** to **7** sequence moved us to consider a second approach to increasing the yield of purified **2*S***. After converting very cheap 2-methyl-1,3-diol to racemic **7b** on a large scale,[27] we made a 1:1 mixture of **2*S*/2*R*** by direct camphorsulfonation of the alcohol, thus avoiding the presence

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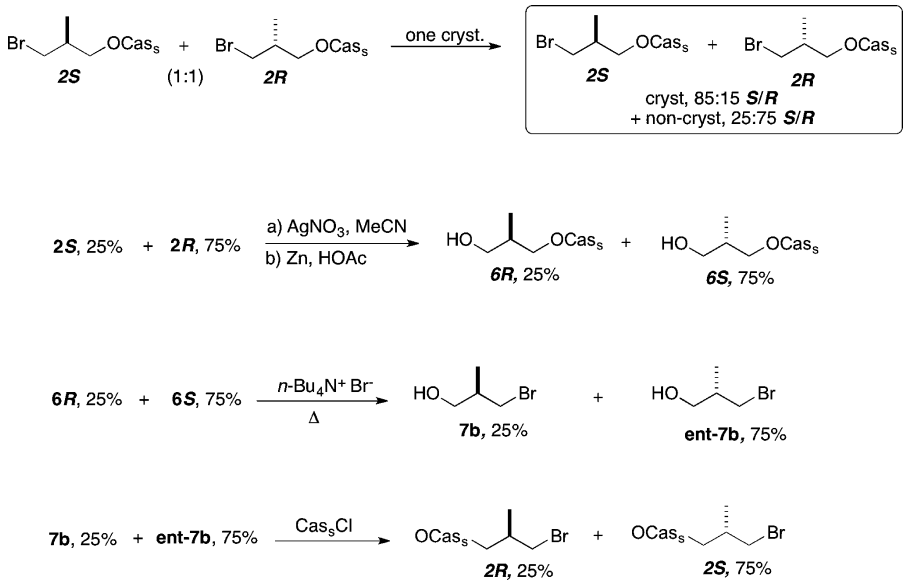
Scheme 4. Inversion of 2*R* and 2*S*

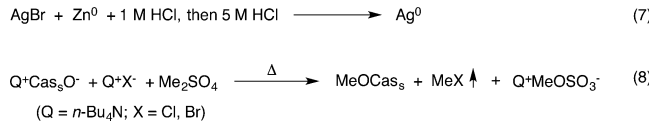


of dibromide **1**, Me/EtOCas, dicasylate **3**, and *n*-Bu$_4$NOCas (**4**). We planned to crystallize this mixture as before and subject the anticipated ~25:75 **2*S*/2*R*** mother liquor to the sequence seen in Scheme 3, eqs 4−6. The established chemoselectivity of this sequence would deliver 25:75 **7b/ent-7b**, which could be camphorsulfonated to 75:25 **2*S*/2*R***, thereby completing an overall *inversion* of **2*R*** and **2*S*** (Scheme 4).

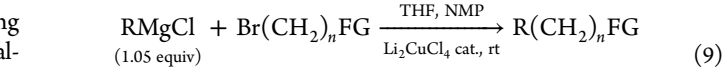
However, crystallization of the 1:1 **2*S*/2*R*** mixture, containing no dibromide **1**, dicasylate **3**, or *n*-Bu$_4$NOCas (**4**) gave a disappointing yield of 85:15 **2*S*/2*R*** crystals and a disappointing composition (36:64 **2*S*/2*R***) of the mother liquor (ML). ML crystallization (MeOH), seeding with **2*S***, gave crystals enriched in **2*R*** (30:70 **2*S*/2*R***) (see Experimental Section). Only after many more crystallizations was a 25% yield of >99:1 dr **2*S*** obtained. This experience and previous crystallization experiments raised the suspicion that the **2*S*/2*R*** system is susceptible to nucleation inhibition,[28] particularly of **2*R***, by the presence of one or more impurities. When another 36:64 **2*S*/2*R*** solution in MeOH with 2 mol % added dibromide was seeded with **2*S*** and cooled, crystallization was much slower, but gave 81:19 **2*S*/2*R*** material. The presence of "impurities" thus can account for the superior selectivity obtained in crystallization of 1:1 **2*S*/2*R*** mixtures obtained from Br−OCas exchange, which contain small amounts of dibromide. Although kinetic recrystallizations of <40:60 **2*S*/2*R*** mixtures (seeding with **2*R***) can afford <25:75 material suitable for inversion, the process is not efficient, making the inversion protocol less appealing. Also, repeated crystallizations from MeOH increase the appearance of substrate solvolysis products. On the other hand, recrystallizations of the initial 85:15 **2*S*/2*R*** crystals proceed well in Et$_2$O, with no substrate degradation. We compared the merits and drawbacks of the two protocols. Catalyzed equilibration avoids use of HBr, CasCl, and AgNO$_3$ and a reduction step, but incurs some loss/degradation of material and is limited to a 1:1 **2*S*/2*R*** mixture in starting the recycle process. The inversion protocol can provide >75:25 **2*S*/2*R*** to start the second crystallization sequence, but the recycle process, starting with the AgNO$_3$ reaction, is longer and lower yielding. Overall, optimized catalyzed equilibration is deemed the better protocol.

Recovery and reuse of expensive ingredients (Ag and OCas) in the conversion of **2*S*** to **7** reduces cost and waste. In the Ag$^+$-assisted displacement of Br, 1.5 equiv of AgNO$_3$ were used; the excess was completely recovered. AgBr also was quantitatively recovered and reduced by Zn^0 to Ag^0 (Scheme 5, eq 7).[29] The *n*-Bu$_4$NOCas$_s$ byproduct from conversion of **6*R*** to **7**, along with excess *n*-Bu$_4$NX, reacted with Me$_2$SO$_4$ to give MeX (distilled out) and recyclable MeOCas$_s$ (Scheme 5, eq 8).[30]

Scheme 5. Recycling Ag and OCas



A second chemoselective reaction of **2*S*/ent-2*S***, which does not require use of Ag$^+$, also has been uncovered. In 2000, Cahiez et al.[31] reported that bromoalkanes bearing other functional groups (Cl, ArSO$_3$, CN, OH, CO$_2$H, CO$_2$R, and CH$_2$COR), in the presence of catalytic Li$_2$CuCl$_4$ and additive NMP, chemoselectively couple with organomagnesium reagents at the Br site in excellent yields [85−90% except for the bromoalkyl arenesulfonate (55%)] (eq 9). These results, in which arenesulfonates were



less reactive than bromides, and ketones were tolerated, moved us to test the procedure with **2*S***. Indeed, coupling with CH$_3$(CH$_2$)$_6$MgBr (1.1 equiv) proceeded cleanly to give alkyl casylate **8** in 81% yield (unoptimized). With a high-yield conversion of alkyl casylate to alkyl bromide/chloride (and concurrent initiation of casylate reuse) already in hand, this chemoselective reaction further enhances the versatility of **2*S*/ent-2*S*** as a chiral linchpin,[32] as shown in a five-step formal synthesis of (*R*)-tuberculostearic acid (**11**) (Scheme 6), a component of a major phospholipid from *M. tuberculosis*, recently synthesized in five steps and 95:5 er.[33] Coupling of bromide **9** (made from **8** in >95% yield) with the Grignard of

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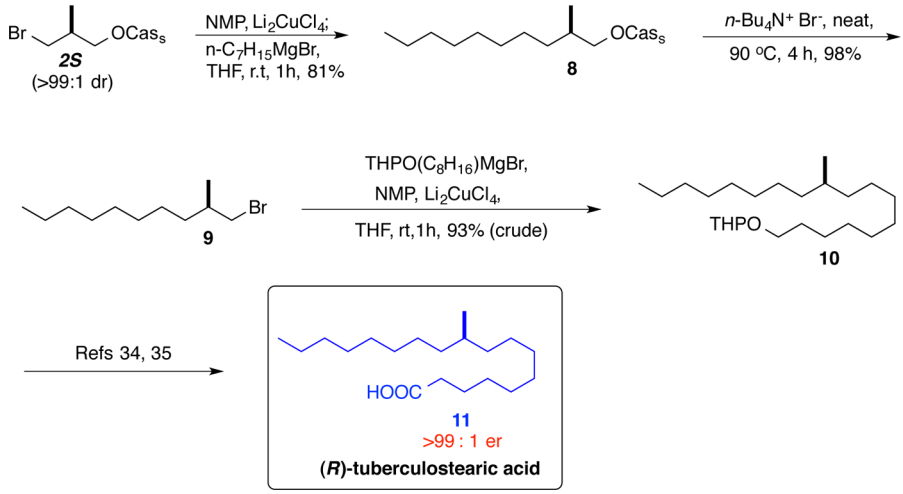
Scheme 6. Formal Synthesis of (*R*)-Tuberculostearic Acid (11)



THP-protected 8-bromo-1-octanol gave ether **10**, convertible in two known steps to **11**.[34,35] The demonstrated diastereomeric purity of **8** (^{1}H NMR) can be can be taken as evidence for the enantiomeric purity of **11**.

This sequence demonstrates that **2*S*** (or **ent-2*S***) can be conveniently and efficiently used in a scalable, nonenzymatic linchpin process to place a methyl branch, with either configuration in >99:1 er, at any desired position in a long-chain, sparsely functionalized hydrocarbon structure. Such compounds, many containing more than one methyl branch, abound in the world of insect (and other animal) communications. Because of the difficulty in determining the absolute configurations of such branches in biologically active substances, there is a need for simple ways to make all stereoisomers of these compounds.[36−38] Future work will explore those ways, as well as other uses of **7**.[39,40]

CONCLUSION

A protocol has been developed that converts racemic 1-bromo-3-chloro-2-methylpropane or racemic 3-bromo-2-methyl-1-propanol to a difunctional C_4 chiral building block (**2*S***) in >99:1 dr (or greater if desired). A bromide−casylate exchange process has been developed that, because of its reversibility and the C_s symmetry of the C_4 skeleton, also provides a way to increase the yield of **2*S*** at the expense of **2*R***. Chemoselective reactions of **2*S*** can afford a range of >99:1 er difunctional chiral synthons and concurrently release the casylate auxiliary for reuse. Chemoselective organometallic coupling of the bromide in **2*S*** has been shown to lead to highly efficient, enantioselective installation of remote, methyl-bearing secondary chiral centers in (e.g.) long-chain hydrocarbons, again with concurrent release of casylate. The concept introduced here, of placing an easily installed and easily removed chiral sulfonate into a chiral/prochiral manifold to create separable/crystallizable diastereomers, will be pursued further. Efforts will continue to improve crystallization efficiency and to remove silver from the process.

EXPERIMENTAL SECTION

General Experimental Methods. Melting points were measured on a standard apparatus and are uncorrected. Analytical TLC was performed on POLYGRAM Sil G/UV$_{254}$ and visualized under a 254 nm UV lamp and/or stained using alkaline aq KMnO$_4$ or 2,4-DNP in aq H$_2$SO$_4$−EtOH. Column chromatography was performed with silica gel, 60 Å, 40−63 μm. ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ at 300/400 MHz (^{1}H spectra) and 75/100 MHz (^{13}C spectra). Chemical shifts (δ, ppm) were referenced to the residual CHCl$_3$ signal (δ 7.26 ppm for ^{1}H NMR and δ 77.00 ppm for ^{13}C NMR). Each resonance was given with chemical shifts in ppm; multiplicities were given as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of a doublet), m (multiplet), b (broad) if signals were overlapped. Signals are assigned where significant. Elemental analyses were obtained on an elemental analyzer with a thermal conductivity detector and 2 M GC column at 50 °C. High resolution mass spectra were obtained using an FTICR-MS instrtument. Optical rotations were measured in a given solvent on a dual wavelength (589/546 nm) automatic polarimeter with a 1 dm cell. Values are reported as specific rotations: $[\alpha]_D$, T, concn c in solvent (g/100 mL). Anhydrous THF was obtained from a solvent purification system. Acetone and CH_2Cl_2 were dried (24 h) over activated 4 Å molecular sieves. Unless otherwise indicated, all reactions were conducted in oven- (140 °C) or flame-dried glassware, using distilled and degassed solvents under a positive pressure of dry Ar with standard Schlenk techniques. Air-sensitive reagents were stored in a glovebox containing dry Ar. Stainless steel syringes or cannulas (oven-dried at 140 °C and cooled under Ar) were used to transfer air- and moisture-sensitive liquids. Workups and purifications were carried out with reagent grade commercial solvents.

Warning: Many of these compounds are known or suspected to be toxic and/or carcinogenic.

1. Starting Materials for Bromide−Camphorsulfonate Exchange. *1.1. 1,3-Dibromo-2-methylpropane (1); Chloride−Bromide Exchange.* A mixture of 1-bromo-3-chloro-2-methylpropane (686 g, 4.00 mol), 1-bromobutane (1654 g, 12 mol), and *n*-Bu$_4$NBr (26.8 g, 0.08 mol, 0.5 mol %) was heated in a 2 L, three-neck flask with a magnetic stirrer, immersion thermometer, and 30 cm fractionating column (glass helices). Distillation of 1-chlorobutane (1 atm) was continued for 23 h. The pot solution was further fractionated at ∼100 mm; bromobutane (bp 60 °C) was removed until the pot reached 82 °C. The washed, dried, and filtered residue was fractionally distilled [bp 33 °C @ 3 mm (same column)] to give >99% pure **1** (745 g, 86%). ^{1}H NMR and ^{13}C NMR data matched literature values.[41] **^{1}H NMR** (400 MHz, CDCl$_3$): δ 3.53−3.43 (m, 4H), 2.23−2.12 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 37.6, 36.9, and 17.8.

*1.2. Ethyl (1S)-Camphor-10-sulfonate [Ethyl (1S) Casylate; EtOCas$_s$] (**12**).* (1S)-Camphor-10-sulfonic acid (116 g, 0.50 mol, predried at 80 °C *in vacuo*) and triethyl phosphite (97 g, 0.58 mol) were swirled together until homogeneous (moderate exotherm) and then heated for 2 h at 50 °C. ^{1}H NMR analysis indicated 100% conversion to EtOCas$_s$ (no CH$_3$ singlets for the acid at δ 1.06, 0.96). After kugelrohr removal of volatiles (76 °C/0.03 mmHg), the residue was crystallized (MeOH) to afford 126 g (96%) of **12**, mp 42.1−42.7 °C (lit[42] mp 46 °C). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 4.44−4.30 (m, 2H), 3.60 (d, J = 15.1 Hz, 1H), 2.98 (d, J = 15.1 Hz, 1H), 2.56−2.35 (m, 2H), 2.13 (t, J = 4.6 Hz, 1H), 1.96 (d, J = 18.5 Hz, 1H), 1.66 (m, 1H), 1.45 (m,

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1H), 1.41 (t, J = 7.0 Hz, 3H), 1.12 (s, 3H), 0.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.5, 66.8, 57.9, 47.9, 46.7, 42.7, 42.5, 26.8, 24.82, 19.8, 19.7, 15.0.

*1.3. Pure (2′R)- and (2′S)-1′-(3′-Bromo-2′-methylpropyl) (1S)-10-Camphorsulfonate (Casylates **2R** and **2S**).* Each of the precursor bromoalkanols was converted via the same general procedure to the corresponding (1*S*)-casylate as described for **2*S***: To a 0 °C solution of (*S*)-3-bromo-2-methyl-1-propanol (306 mg, 2.0 mmol) in pyridine (0.5 mL) was added a solution of freshly crystallized (1*S*)-casyl chloride (525 mg, 2.10 mmol) in pyridine (0.5 mL); crystals (pyr·HCl) formed within 5 min. After overnight refrigeration, CH_2Cl_2 (10 mL) was added, and the solution was washed with H_2O (1 × 25 mL), 2 N HCl (1 × 25 mL), and 10% aq $NaHCO_3$ (1 × 25 mL), dried (over $MgSO_4$), and filtered. The filtrate was stripped of solvent and heated to 90 °C at 1 mmHg to remove unreacted alcohol. The residue (573 mg, 78%), on addition of a few drops of MeOH, crystallized instantly to give pure **2*S***: mp 57−59 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.30−4.21 (m, 2H), 3.62 (d, J = 15 Hz, 1H), 3.52−3.42 (m, 2H), 3.025 (d, J = 15.1 Hz, 1H), 2.53−2.35 (m, 2H), 2.32−2.24 (m, 1H), 2.13 (t, J = 6.0 Hz, 1H), 2.10−2.00 (m, 1H), 1.96 (d, J = 18.5 Hz, 1H), 1.73−1.63 (m, 1H), 1.49−1.42 (m, 1H), 1.12 (s, 3H), 1.11 (d, J = 6.9 Hz, 3H), 0.89 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 213.5, 71.1, 57.1, 47.2, 46.0, 41.9, 41.7, 35.0, 34.2, 26.1, 24.1, 18.9, 18.9, and 14.6. Anal. Calcd for $C_{14}H_{23}BrO_4S$: C, 45.78; H, 6.31. Found: C, 46.11; H, 6.31; $[\alpha]^{25}_D$ +39.4 (c 5.2, $CHCl_3$).

A MeOH solution of **2*R*** crystallized on cooling (0 to −20 °C) and remained crystalline on cold filtration and rapid removal of residual solvent *in vacuo*: mp 27−31 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.32−4.19 (m, 2H), 3.62 (d, J = 15.1 Hz, 1H), 3.51−3.43 (m, 2H), 3.015 (d, J = 15.1 Hz, 1H), 2.53−2.35 (m, 2H), 2.32−2.24 (m, 1H), 2.13 (t, J = 6.0 Hz, 1H), 2.10−2.00 (m, 1H), 1.96 (d, J = 18.5 Hz, 1H), 1.73−1.65 (m, 1H), 1.49−1.42 (m, 1H), 1.11 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 0.88 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.3, 71.8, 57.8, 48.0, 46.7, 42.6, 42.4, 35.9, 34.9, 26.8, 24.8, 19.7, 19.6, 15.3. Anal. Calcd for $C_{14}H_{23}BrO_4S$: C, 45.78; H, 6.31. Found: C, 45.91; H, 6.18; $[\alpha]^{26}_D$ +25.8 (c 4.85, $CHCl_3$).

*1.4. Tetra-n-butylammonium Casylate (n-Bu$_4$N$^+$Cas$_s$O$^-$; **4**).* This salt, isolable from Br-OCas exchange reactions by H_2O extraction, was prepared independently: *n*-$Bu_4N^+Br^-$ (3.22 g, 10.0 mmol), $MeOCas_s$ (2.71 g, 11.0 mmol), and CH_2Cl_2 (a few drops) were mixed in a test tube and heated (oil bath, 77−80 °C) until gas evolution ceased (∼15 min). The mixture solidified on cooling; it was crushed in Et_2O, filtered, washed with Et_2O (2 × 15 mL), and dried to yield 4.62 g (97.5%) of **4** (crystals, mp 139−141 °C) containing no detectable $MeOCas_s$. **^{1}H NMR** (400 MHz, $CDCl_3$): (Many peak positions vary ±0.05 ppm in the presence of other compounds) δ 3.40 (d, J = 15.1 Hz, 1H), 3.26 (broad m, 8H), 2.91 (d, J = 15.1 Hz, 1H; diagnostic peak in bromide-casylate exchange mixtures), 2.71−2.62 (m, 1H), 2.32 (br dt, 1H), 2.03 (br t, 1H), 2.02−1.96 (m, 1H), 1.88 (d, 18.5 Hz, 1H), 1.70−1.60 (m, 9H), 1.44 (sext, 8H), 1.41−1.32 (m, 1H), 1.11 (s, 3H), 1.00 (t, 12H), 0.84 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 216.5, 58.3, 58.2, 47.6, 47.0, 42.6, 42.4, 26.7, 24.3, 23.6, 19.7, 19.5, 19.4, and 13.4. *n*-$Bu_4N^+Cas_sO^-$ is very soluble in H_2O, MeOH, EtOH, CH_2Cl_2, and $CHCl_3$; it is insoluble in ether, and can be recrystallized from dry EtOAc.

2.1. Conversion of Dibromide 1 to a 1:1 Mixture of Casylates 2*R* and 2*S*, and Dicasylate 3. $EtOCas_s$ (**12**; 260.4 g, 1.00 mol), dibromide **1** (648 g, 3.00 mol), and *n*-$Bu_4N^+Br^-$ (12.9 g, 0.04 mol, 1 mol %) were mixed in a 1L, 3-neck flask fitted with a N_2 bubbler insert, thermometer, and a vigreux column with a distillation head. At 90 °C (oil bath heating, N_2 bubbling), the mixture became homogeneous. At 126−127 °C (pot), EtBr distilled out steadily. After 2.5 h, ^{1}H NMR analysis indicated >95% disappearance of $EtOCas_s$; the collected distillate contained no dibromide. Kugelrohr removal of **1** (451 g) (oven 54−62 °C/7.5 to 0.05 mmHg) left 348 g (94.5% of the calculated weight) of clear, pale tan oil consisting of **2*R***, **2*S***, **3**, and *n*-$Bu_4N^+OCas_sO^-$ (**4**). The residue was taken up in sufficient Et_2O (∼300 mL) to make the solution less dense than H_2O, and extracted with H_2O (3 × 100 mL). Combined extracts were stripped of H_2O to give a near quantitative yield of **4**. The Et_2O phase was concentrated and taken up in Et_2O-hexanes (25:75 v/v). Silica gel flash column chromatography, eluting with 25:75 and then 50:50 Et_2O-hexanes, cleanly separated (1:1 **2*R*** + **2*S***) from dicasylate **3**. Crystallization of **3** afforded pure material, mp 89−91 °C; **^{1}H NMR** δ 4.32 (dd, J = 5.0, 9.9 Hz, 1H), 4.27 (overlapping dd's, 2H), 4.21 (dd, J = 6.6, 9.9 Hz, 1H), 3.61 (d, J = 15.1 Hz, 1H), 3.04 (d, J = 15.1 Hz, 1H), 1.10 (s, 3H), 1.09 (d, J = 8.0 Hz, 1H), 0.88 (s, 3H), + other camphor moiety signals. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.3, 70.3, 70.2, 57.9, 48.1, 46.9, 46.8, 42.8, 42.5, 33.4, 26.9, 24.9, 19.7, 19.6, and 13.1. Anal. Calcd for $C_{24}H_{32}O_8S_2$: C, 55.57; H, 7.38. Found: C, 55.79; H, 7.07.

2.2. Equilibration of a 2*R*-Enriched Mixture of 2*S* and 2*R*. A 36:64 mixture of **2*S*/2*R*** (77.85 g, 0.212 mol), dicasylate **3** (12.67 g, 0.0244 mol), and dibromide **1** (145 g, 0.67 mol) was heated with *n*-$Bu_4N^+Cas_sO^-$ (**4**, 28.1 g, 0.059 mol = ∼3 mol % of total functional groups). After 4 h @120 °C (bath temp), the mixture (now 49:51 **2*S*/2*R***) was cooled, and Et_2O (300 mL) and H_2O (150 mL) were added. The organic layer was washed with H_2O (3 × 50 mL; combined with the first aq layer) and satd aq NaCl (50 mL) and dried over Na_2SO_4−$MgSO_4$. Silica gel (15 g) was added, and the solution was pressure filtered through 1 in of SiO_2. Et_2O was distilled off, followed by kugelrohr distillation at reduced pressure to give 139 g (97%) of nearly pure **1**. The residue (82.5 g) was taken up in Et_2O−hexanes (50 mL 40:60) and chromatographed on silica gel. Elution with Et_2O−hexanes (25:75 v/v, then 100% Et_2O) in 21 500 mL fractions gave 73.4 g of colorless, ∼1:1 **2*S*** + **2*R*** (93% yield), followed by 9.0 g of dicasylate **3** (96% yield); overall recovery was 95%.

3. Crystallization of (1:1 2*R* + 2*S*). *3a. From a Mixture Containing Residual Dibromide.* A 1:1 mixture of **2*S*/2*R*** (166 g) containing residual C_4 dibromide was dissolved in MeOH (340 mL; ∼2:1 v/w). The cooled mixture (6 °C) was seeded with pure **2*S*** and left for 15 h and then cooled to −5 °C for 13 h. The mother liquor (ML) was removed; crystals were washed with cold Et_2O (50 mL) and air-dried to give 68.6 g of an 87:13 **2*S*/2*R*** mixture (^{1}H NMR analysis). Et_2O washings (44:56) weighed 6.0 g, and ML (25:75) weighed 91.3 g (calcd). The 87:13 crystals (68.6 g) were recrystallized from Et_2O (135 mL) as before to give 55.2 g of ∼96:4 **2*S*/2*R*** and 13.4 g of 45:55 **2*S*/2*R*** ML. The cooled 25:75 ML deposited 7.9 g of 70:30 crystals, leaving 83.4 g of 22:78 ML, which was saved for re-equilibration. Combined 44:56 washings (6.0 g) and 45:55 ML (13.4 g) were crystallized from MeOH (38 mL) as before to give 7.7 g of 73:27 crystals and 11.7 g of 24:76 ML (saved). Combined 70:30 crystals (7.9 g) and 73:27 crystals (7.7 g) were crystallized from Et_2O (25 mL) to give 10.3 g of 86:14 crystals and 5.3 g of 32:68 ML (saved). Crystallization of 10.3 g of 86:14 crystals from Et_2O (20 mL) gave 8.8 g of 95:5 crystals and 1.5 g of 66:34 ML. Combined 96:4 crystals (55.2 g) and 95:5 crystals (8.8 g) were crystallized from Et_2O (125 mL) to give 55.3 g of 99.7:0.3 dr crystals (calcd) and 8.7 g of ∼80:20 ML. Access to a 400 MHz NMR instrument later enabled an improved **2*S*/2*R*** dr assay, which showed the "99.7:0.3" dr to be closer to 99:1; one more crystallization (88% **2*S*** recovery) gave 48.7 g (29%) of >99:1 dr **2*S*/2*R***.

*3b. From a Mixture Containing No Dibromide **1**, Me/EtOCas, or C$_4$ Dicasylate **3**.* A 0 °C 1:1 mixture of **2*S*/2*R*** (168 g) in MeOH (340 mL) was seeded with pure **2*S***. After 15 h. the cold mixture was suction filtered, and the crystals were washed with cold Et_2O (50 mL) and air-dried to give 47.5 g of 85:15 **2*S*/2*R***. Mother liquor (120 g of 36:64 **2*S*/2*R***) recrystallization as above (240 mL of MeOH, seeding with **2*S***) gave 48 g of 30:70 **2*S*/2*R*** crystals and 72 g of 42:58 ML. Many recrystallizations gave a 25% yield of >99:1 dr **2*S***.

4. Preparation of 5*R*, 6*R*, and 7a/7b. *4.1. (2′R)-1′-(3′-Nitrato-2′-methylpropyl) (1S)-10-Camphorsulfonate (**5R**).*[19] To a solution of bromocasylate **2*S*** (8.0 g, 21.8 mmol) in dry CH_3CN (10 mL) was added $AgNO_3$ (5.53 g, 32.7 mmol, 1.5 equiv). After the solution refluxed for 5 h and cooled, the solid (AgBr, 4.0 g, 99%) was filtered off and washed with Et_2O (3 × 20 mL) and H_2O (3 × 20 mL). The separated aqueous layer was extracted with Et_2O, and the combined organic layers were dried over anhyd $MgSO_4$ and filtered, with subsequent removal of solvent *in vacuo* to give **5*R*** (7.5 g, 99%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.48−4.40 (m, 2H), 4.28−4.21 (m, 2H), 3.59 (d, J = 15.0 Hz, 1H), 3.00 (d, J = 15.0 Hz, 1H), 2.49−2.33 (m, 3H), 2.13 (t, J = 4.4 Hz, 1H), 2.11−2.00 (m, 1H), 1.96 (d, J = 18.5 Hz, 1H), 1.70−1.63 (m, 1H), 1.49−1.42 (m, 1H), 1.11 (d, J = 7.0 Hz, 3H), 1.10 (s, 3H), 0.87 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.4, 73.4, 70.5, 57.9, 48.1, 46.9, 42.7,

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42.5, 31.9, 26.9, 24.9, 19.7, 19.6, and 13.4. Anal. Calcd for $C_{14}H_{23}NO_7S$: C, 48.13; H, 6.63; N, 4.01. Found: C, 48.09; H, 6.87; N, 4.27; $[\alpha]_D^{24}$: +36.6 (*c* 5, $CHCl_3$).

*4.2. (2′R)-1′-(3′-Hydroxy-2′-methylpropyl) (1S)-10-Camphorsulfonate (**6R**).*[21] To a vigorously stirred, 10 °C (ice bath) solution of nitratoalkyl casylate **5R** (30.9 g, 88.4 mmol) and acetic acid (168 mL) was added Zn powder (17.4 g, 265 mmol, 1.6 equiv) at a rate to maintain the temperature. The stirred contents were allowed to warm to room temperature (8 h) and then diluted with EtOAc (250 mL), and the solid was filtered off. The two-phase filtrate was neutralized with saturated $NaHCO_3$, and the organic layer was washed with H_2O (3 × 150 mL) and saturated aq NaCl, dried over anhyd Na_2SO_4, and filtered; the solvent was then removed *in vacuo*. The residue was purified by silica gel flash chromatography (hexanes/Et_2O 3:1 v/v) to give hydroxyalkyl casylate **6R** (23.8 g, 88%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.32−4.27 (m, 2H), 3.67−3.51 (m, 2H), 3.59 (d, *J* = 15.1 Hz, 1H), 2.99 (d, *J* = 15.1 Hz, 1H), 2.51−2.32 (m, 2H), 2.11 (t, *J* = 2.4 Hz, 1H), 2.10−2.01 (m, 2H), 1.95 (d, *J* = 18.5 Hz, 1H), 1.95 (s, 1H (OH)), 1.7−1.65 (m, 1H), 1.47−1.41 (m, 1H), 1.10 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), and 0.87 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.9, 71.9, 63.5, 58.0, 48.1, 46.6, 42.7, 42.5, 35.7, 26.8, 24.9, 19.7, 19.7, and 13.1. HRMS (ESI) Calcd for $C_{14}H_{24}O_5S$ ([M + Na]$^+$): 327.123666. Found: 327.123670; $[\alpha]_D^{21}$ +4.0 (*c* 5.8, $CHCl_3$).

*4.3. (2R)-3-Chloro-2-methyl-1-propanol (**7a**).* To a 500 mL round bottom (rb) flask were added **6R** (23.5 g, 77.2 mmol), dry *n*-Bu_4NCl (32.2 g, 116 mmol; 1.5 equiv), and dry DCE (50 mL). After 16 h at reflux, DCE was distilled out. Et_2O (100 mL) was added to the cooled liquid and stirred for 15 min. The colorless solid precipitate (*n*-Bu_4NOCas_s + excess *n*-Bu_4NCl) was filtered off, and the filtrate was concentrated *in vacuo*. Kugelrohr distillation (20 °C/2 mmHg) gave **7a** (8.3 g, 93%) as a colorless oil. ^{1}H and ^{13}C NMR spectra matched literature data.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.66−3.54 (m, 4H), 2.11−2.00 (m, 1H), 1.47 (br s, 1H), 1.02 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 64.7, 47.6, 37.7, and 14.4; $[\alpha]_D^{22}$ −14.5 (*c* 0.65, $CHCl_3$) (lit.[43] $[\alpha]_D^{RT}$ −14.6 (*c* 4.13, EtOH).

*4.4. (2R)-3-Bromo-2-methyl-1-propanol (**7b**).* A mixture of **6R** (0.5 g, 1.64 mmol) and dry *n*-Bu_4NBr (0.795 g, 2.46 mmol; 1.5 equiv) was heated until it was liquid (10 min). Acetone (2 mL) was added, and the mixture was refluxed for 5 h. Acetone was evaporated, and Et_2O (10 mL) was added and stirred until a colorless solid formed (10 min). The ppt was filtered off, and the filtrate was concentrated *in vacuo*. The residue was chromatographed (silica gel) with Et_2O/hexanes (3:1) to give **7b** (0.24 g, 96%) as a colorless oil. ^{1}H and ^{13}C NMR spectra matched those of a commercial sample.[44] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.68−3.56 (m, 2H), 3.54−3.47 (m, 2H), 2.11−1.98 (m, 1H), 1.50 (br s, 1H), 1.05 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 65.4, 37.6, 37.3, and 15.4; $[\alpha]_D^{21}$ −6.2 (*c* 2.01, $CHCl_3$) (lit.[44] $[\alpha]_D^{25}$ −6.6 (*c* 2, $CHCl_3$).

5. Recycling Procedures. *5.1. Recovery of Silver.*[29] AgBr (88.5 g, 0.47 mol) and Zn powder (61.45 g, 0.94 mol) were thoroughly mixed in a 1 L beaker. Contents were cooled (ice/water), and 1 M aq HCl (500 mL) was added slowly, with stirring. The wet solid was transferred onto a filter funnel, and the liquid was drained off. Then 5 M aq HCl (4 × 250 mL) was added portionwise with stirring, until bubbling ceased. The gray solid was washed thoroughly with H_2O and vacuum-dried to give pure Ag^0 (~50.2 g, ~99%) as a gray-brown powder.

5.2. Recovery of Camphorsulfonate (as MeOCas$_s$).[30] Freshly distilled Me_2SO_4 (10.0 mL, ~25% excess) was slowly dripped into *n*-$Bu_4N^+Cas_sO^-$ (**4**, 38.6 g, 81.5 mmol, in a 500 mL, three-neck rb flask containing a magnetic stirring bar and fitted with a gas (N_2) inlet, a pressure-equalizing dropping funnel, and a takeoff condenser. The solid salt dissolved in the path of the liquid, and the bottom material liquefied sufficiently to allow the stirring bar to move. The bath (oil) was heated to 55 °C; the solid gradually dissolved and became a colorless, nearly homogeneous solution as the bath temperature reached 63 °C. After 2 h @68 °C (bath), ^{1}H NMR analysis showed singlets for Me_2SO_4, $MeOCas_s$, and $MeOSO_3^-$ at δ 3.98, 3.97, and 3.71, respectively; no signal was present for the $OCas_s$ ion. The colorless mixture remained liquid on cooling overnight. Et_2O (50 mL) and H_2O (100 mL) were added, and the whole was swirled until two clear phases appeared. NMR analysis of the Et_2O phase revealed mostly $MeOCas_s$, appreciable Me_2SO_4, and small amounts of *n*-Bu_4N^+ (δ 1.02 t) and $MeOSO_3^-$. Multiple Et_2O extractions of the aq phase afforded more $MeOCas_s$ and traces of the ionic impurities, but no Me_2SO_4. Aq $NaHCO_3$ (50 mL) was added to the initial Et_2O phase, and the mixture was stirred vigorously until Me_2SO_4 was gone. Combined Et_2O solutions were washed with H_2O and dried over $MgSO_4$. Filtration and solvent removal yielded 17.9 g (89%) of colorless crystals of $MeOCas_s$, mp 60−61 °C (lit[42] mp 61 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.95 (s, 3H), 3.60 (d, *J* = 15.1 Hz, 1H), 2.98 (d, *J* = 15.1 Hz, 1H), 2.51−2.36 (m, 2H), 2.12 (t, *J* = 4.4 Hz, 1H), 2.10−2.01 (m, 1H), 1.95 (d, *J* = 18.5 Hz, 1H), 1.70−1.63 (m, 1H), 1.47−1.41 (m, 1H), 1.11 (s, 1H), and 0.88 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.5, 57.8, 56.1, 48.0, 46.0, 42.7, 42.5, 26.8, 24.8, 19.7, and 19.6.

6. Direct Application of 2*S*: Formal Synthesis of (*R*)-Tuberculostearic Acid (11). *6.1. (2′R)-2′-Methyldecyl (1S)-10-Camphorsulfonate (**8**).*[31] To a stirred solution of **2S** (2.0 g, 5.44 mmol) and Li_2CuCl_4 [24 mg, 0.16 mmol (0.1 M in THF, 3 mol %)], THF (5 mL), and NMP (*N*-methyl-2-pyrrolidone, 2.2 g, 21.8 mmol) was added *n*-heptylmagnesium bromide (1.2 equiv of 1.3 M solution in THF, 6.53 mmol), dropwise at 20 °C. After being stirred for 1 h, the reaction mixture was cooled to −10 °C and quenched with 1 N HCl (25 mL). The aq layer was extracted with pentane (3 × 15 mL), and the combined organic layers were washed with 1 N HCl (15 mL) and H_2O (3 × 20 mL) and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave a colorless oil, which was purified by silica gel column chromatography, eluting with ether/pentane (0:1 and 1:10) to give alkyl casylate **8** (1.71 g, 81%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.17 (dd, *J* = 9.4, 5.6 Hz, 1H), 4.03 (dd, *J* = 9.4, 6.8 Hz, 1H), 3.60 (d, *J* = 15.0 Hz, 1H), 2.98 (d, *J* = 15.0 Hz, 1H), 2.55−2.36 (m, 2H), 2.12 (t, *J* = 4.4 Hz, 2H), 2.09−2.01 (m, 1H), 1.95 (d, *J* = 18.4 Hz, 1H), 1.89−1.81 (m, 1H), 1.68−1.61 (m, 1H), 1.47−1.25 (m, 16H), 1.12 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), and 0.89−0.86 (m, 6H). ^{1}H signals for the diastereomer of **11** (δ 4.17−4.03) were not detected. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.5, 75.0, 57.9, 47.9, 46.5, 42.7, 42.5, 33.1, 32.8, 31.8, 29.7, 29.5, 29.2, 26.8, 26.6, 24.9, 22.6, 19.8, 19.7, 16.5, and 14.1. HRMS (ESI) Calcd for $C_{21}H_{38}O_4S$ ([M + Na]$^+$): 409.2383. Found: 409.2382. $[\alpha]_D^{20}$ +30.85 (*c* 1.6, $CHCl_3$).

*6.2. (R)-1-Bromo-2-methyldecane (**9**).* A mixture of alkyl casylate **8** (1.50 g, 3.96 mmol) and *n*-$Bu_4N^+Br^-$ (1.91 g, 5.94 mmol) was heated to 90 °C for 4 h (neat; liquefied). Et_2O (20 mL) was added to the cooled mixture; stirring (10 min) caused formation of a white precipitate. This was filtered off, the solid was washed with Et_2O (10 mL), and the filtrate was concentrated *in vacuo* to give a colorless liquid, which was chromatographed on silica gel (pentane elution) to provide **9** (0.9 g, 98%) as a colorless liquid. ^{1}H and ^{13}C NMR spectral values matched literature data.[45] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.39 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.32 (dd, *J* = 9.8, 6.2 Hz, 1H), 1.82−1.74 (m, 1H), 1.46−1.26 (m, 13H), 1.0 (d, *J* = 6.6 Hz, 3H) and 0.88 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.6, 35.2, 34.9, 31.9, 29.7, 29.5, 29.3, 26.9, 22.7, 18.8, and 14.1. $[\alpha]_D^{20}$ −0.33 (*c* 0.9, $CHCl_3$) [lit.[46] $[\alpha]_D$ −0.31 (neat).

*6.3. (R)-10-Methyloctadecyl-1-tetrahydropyranyl Ether (**10**).*[34] The Grignard (8.0 mmol, 1.9 equiv by titration) freshly prepared from the THP ether of 8-bromo-1-octanol[34] was added dropwise, at 20 °C, to a stirred solution of bromoalkane **9** (1.0 g, 4.25 mmol), Li_2CuCl_4 (1.27 mL of 0.1 M solution in THF, 3 mol %), THF (5 mL), and NMP (2.05 mL, 21.3 mmol). After being stirred for 1 h more, the reaction mixture was cooled to 0−5 °C and quenched with ice cold aq NH_4Cl (25 mL). The separated aqueous layer was extracted with EtOAc (3 × 30 mL). Combined organic layers were washed with H_2O (3 × 30 mL) and brine (3 × 25 mL), dried over anhyd $MgSO_4$, filtered, and concentrated *in vacuo*. The colorless residue was purified by silica gel column chromatography, eluting with Et_2O/hexanes (0 → 5 → 10% Et_2O) to give ether **10** (1.46 g, 93%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.58−4.56 (m, 1H), 3.90−3.84 (m, 1H), 3.75−3.70 (m, 1H), 3.52−3.47 (m, 1H), 3.41−3.35 (m, 1H), 1.87−1.79 (m, 1H), 1.75−1.68 (m, 1H), 1.62−1.49 (m, 9H), 1.36−1.19 (m, 24H), 1.08−1.03 (m, 2H), and 0.89−0.82 (overlapped d and t, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 98.8, 67.7, 62.3, 37.1, 32.7, 31.9, 31.8, 30.8, 30.0, 30.0, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 27.0, 26.2, 25.5, 22.7, 22.6, 19.7, 19.7, 14.1,

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and 14.1. HRMS (ESI) Calcd for $C_{24}H_{48}O_2$([M + Na]$^+$): 391.3547. Found: 391.3546. $[\alpha]_D^{21}$ +4.48 (*c* 0.24 in $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rchahn@syr.edu.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Banfi, L.; Guanti, G. *Synthesis* **1993**, 1029−1056.

(2) Núñez-Rico, J. L.; Etayo, P.; Fernández-Pérez, H.; Vidal-Ferran, A. *Adv. Synth. Catal.* **2012**, *354*, 3025−3035.

(3) Qiu, M.; Wang, D.-Y.; Hu, X.-P.; Huang, J.-D.; Yu, S. B.; Deng, J.; Duan, Z.-C.; Zheng, Z. *Tetrahedron:Asymmetry* **2009**, *20*, 210−213.

(4) Asymmetric bioreduction of methyl 2-hydroxymethylacrylate and derivatives has been reported, but appears not to be easily scaled up: Stueckler, C.; Winkler, C. K.; Bonnekessel, B.; Faber, K. *Adv. Synth. Catal.* **2010**, *352*, 2663−2666.

(5) Goodhue, C. T.; Schaeffer, J. R. *Biotechnol. Bioeng.* **1971**, 203−214.

(6) Trost, B. M.; Malhotra, S.; Mino, T.; Rajapaksa, N. S. *Chem.—Eur. J.* **2008**, *14*, 7648−7657.

(7) Enzymatic synthesis of 5.9 g of >99% ee (*R*)-3-hydroxy-2-methylpropyl acetate has been reported: Bhuniya, R.; Nanda, S. *Tetrahedron* **2013**, *69*, 1153−1165. The % ee was based on an $[\alpha]_D$ comparison.

(8) Guduguntla, S.; Fañanás-Mastral, M.; Feringa, B. *J. Org. Chem.* **2013**, *78*, 8274−8280.

(9) McManus, S. P.; Roberts, F. E.; Lam, D. H.; Hovanes, B. *J. Org. Chem.* **1982**, *47*, 4386−4388. See also: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 389.

(10) Most of this work was done with (1*S*)-10-camphorsulfonates; in identifying compounds by number, the camphor chirality descriptor sometimes is omitted to minimize confusion.

(11) **2***R* has mp 27−31 °C; **2***S* has mp 57−59 °C. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981; p 342.

(12) Hahn, R. C. *J. Org. Chem.* **1988**, *53*, 1331−1333.

(13) (a) Nitta, Y.; Arakawa, Y.; Ueyama, N. *Chem. Pharm. Bull.* **1986**, *34*, 2710−2718. (b) A similar, less thorough, independent study appeared one year later: Karaman, R.; Leader, H.; Goldblum, A.; Breuer, E. *Chem. Ind. (London)* **1987**, *24*, 857−858.

(14) Hahn, R. C.; Tompkins, J. *J. Org. Chem.* **1988**, *53*, 5783−5785.

(15) Compare (e.g.): Cao, J.; Perlmutter, P. *Org. Lett.* **2013**, *15*, 4327−4329.

(16) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981; pp 369−377.

(17) Afagh, N. A.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 262−310 and references therein.

(18) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530−541.

(19) Ferris, A. F.; McLean, K. W.; Marks, I. G.; Emmons, W. D. *J. Am. Chem. Soc.* **1953**, *75*, 4078.

(20) Tertiary or benzylic bromides react with $AgNO_3$ in H_2O−acetone to give good yields of the corresponding alcohols: (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153−8156. (b) Easton, C. J.; Hutton, C. A.; Wui Tan, E.; Tiekink, E. R. T. *Tetrahedron Lett.* **1990**, *31*, 7059−7062. With **2***S*, in our hands, this method gave a mixture of alcohol and nitrate.

(21) Dewar, J.; Fort, G. *J. Chem. Soc.* **1944**, 496−499.

(22) High-yield catalytic hydrogenolysis of nitrate esters also has been reported: Kuhn, L. P. *J. Am. Chem. Soc.* **1946**, *68*, 1761−1762.

(23) Khumsubdee, S.; Zhou, H.; Burgess, K. *J. Org. Chem.* **2013**, *78*, 11948−11955.

(24) Marshall, J. A.; Andersen, M. W. *J. Org. Chem.* **1992**, *57*, 5851−5856.

(25) Liang, B.; Novak, T.; Tan, Z.; Negishi, E. *J. Am. Chem. Soc.* **2006**, *128*, 2770−2771.

(26) Xu, S.; Lee, C.-T.; Wang, G.; Negishi, E. *Chem.—Asian J.* **2013**, *8*, 1829−1835.

(27) Chong, J. M.; Heuft, M. A.; Rabbat, P. *J. Org. Chem.* **2000**, *65*, 5837−5838.

(28) Leeman, M.; Brasile, G.; Gelens, E.; Vries, T.; Kaptein, B.; Kellogg, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 1287−1290.

(29) Cucciolito, M. E.; Flores, G.; Vitagliano, A. *Organometallics* **2004**, *23*, 15−17.

(30) Brändström, A. *Preparative Ion Pair Extraction, an Introduction to Theory and Practice*, 2nd ed.; Apotekarsocieteten/Hässle Läkemedel: Stockholm, 1976, Ch. VIII, pp 143−144.

(31) Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733−2737.

(32) Chen, M. Z.; Gutierrez, O.; Smith, A. B., III. *Angew. Chem., Int. Ed.* **2014**, *53*, 1279−1282.

(33) Fodran, P.; Minnaard, A. J. *Org. Biomol. Chem.* **2013**, *11*, 6919−6928.

(34) Liu, X.; Stocker, B. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 3638−3648.

(35) Dyer, B. S.; Jones, J. D.; Ainge, G. D.; Denis, M.; Larsen, D. S.; Painter, G. F. *J. Org. Chem.* **2007**, *72*, 3282−3288.

(36) Bello, J. E.; Millar, J. C. *Tetrahedron: Asymmetry* **2013**, *24*, 822−826.

(37) Svensson, G. P.; Gündüz, E. A.; Sjöberg, N.; Hedenström, E.; Lassance, J.-M.; Wang, H.-L.; Löfstedt, C.; Anderbrant, O. *J. Chem. Ecol.* **2014**, *40*, 387−395.

(38) Wyatt, T. D. *J. Comp. Physiol. A* **2010**, *196*, 685−700.

(39) Cahiez, G.; Alexis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, *19*, 3013−3014.

(40) Najera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289−300.

(41) Westerbeek, A.; van Leeuwen, J. G. E.; Szymański, W.; Feringa, B. L.; Janssen, D. B. *Tetrahedron* **2012**, *68*, 7645−7650.

(42) Patterson, T. S.; Loudon, J. D. *J. Chem. Soc.* **1932**, 1725−1744.

(43) Gaucher, A.; Ollivier, J.; Marguerite, J.; Paugam, R.; Salaün, J. *Can. J. Chem.* **1994**, *72*, 1312−1327.

(44) *Aldrich Handbook of Fine Chemicals* 2012−2014; p 500.

(45) Maki, E. C.; Rodstein, J.; Millar, J. C.; Barbour, K. S.; Hanks, L. M.; Barbour, J. D. *J. Chem. Ecol.* **2011**, *37*, 714−716.

(46) Högberg, H.-E.; Hedenström, E.; Wassgren, A.-B.; Hjalmarsson, M.; Bergström, G.; Löfqvist, J.; Norin, T. *Tetrahedron* **1990**, *46*, 3007−3018.

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