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The thiopyran route to polypropionates. Asymmetric synthesis of the building blocks by enantioselective protonation

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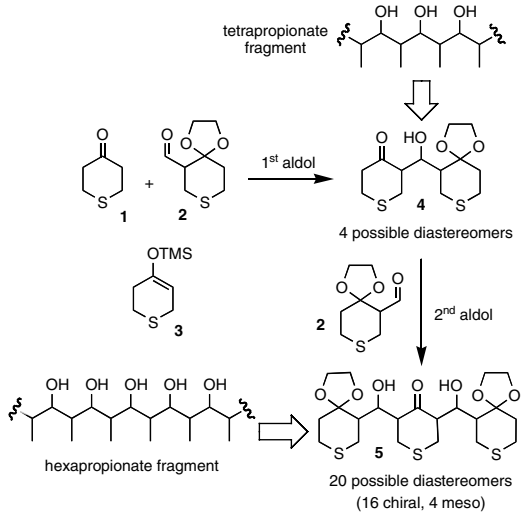
Abstract—Enantioselective protonation of the *s*-BuLi derived lithium enolate of (*S*)-phenyl 1,4-dioxa-8-thia-spiro[4.5]decane-6-carbothioate **14** with *N*-isopropylephedrine **15** gives **14** as a 10:1 mixture of enantiomers. Recrystallization of nonracemic **14** gives a highly enantioenriched material (>90% ee), which can be converted into 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde **2** without racemization. Diastereoselective aldol reactions of tetrahydro-4*H*-thiopyran-4-one with nonracemic **2** proceed with negligible racemization to give adducts that are useful building blocks for polypropionate synthesis.

1. Introduction

We have been investigating the stereoselectivities of sequential aldol reactions of **1** and **2** as the foundation of a thiopyran-based synthetic route to polypropionates (Scheme 1).[1–3] The diastereoselectivity of the first aldol reaction is easily modulated. Three of the four possible diastereomers from the reaction of **2** with **3** can be produced stereoselectively simply by varying the mediator (**4as** with MeLi, **4ss** with $TiCl_4$, **4sa** with $MgBr_2{\cdot}OEt_2$)[1] while the fourth diastereomer can be obtained in good overall yield by isomerization (**4sa** → **4aa**).[3] The second aldol reaction is also highly diastereoselective. Using racemic components, reactions of the Ti(IV) enolates of **4** with **2** occur with considerable mutual kinetic enantioselection† (MKE)[4,5] and, in each case, give one of the eight possible diastereomers‡ of **5** with high stereoselectivity.[2] To gain access to nonracemic diastereomers of **4** and **5** and as a prelude to an investigation of double stereodifferentiation[6,7] in the aldol reactions of **4** with **2**, we required enantioenriched aldehyde **2**. Herein we report a simple and efficient synthesis of (+)-**2** and (−)-**2** via enantioselective protonation[8,9] and demonstrate that their conversion into the tetrapropionate synthons **4** occurs without racemization.



Scheme 1.

2. Results and discussion

Initial attempts to obtain enantioenriched **2** focused on the resolution of carboxylic acid **7** (Scheme 2). Ketal

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† Also known as mutual kinetic resolution. See Ref. 4 for a discussion of the relative merits of the terminology.

‡ There are 20 possible diastereomers of **5** (16 chiral and 4 meso). Assuming no isomerization of the ketone, an aldol reaction of any one racemic diastereomer of **4** with racemic **2** can give eight possible diastereomers.

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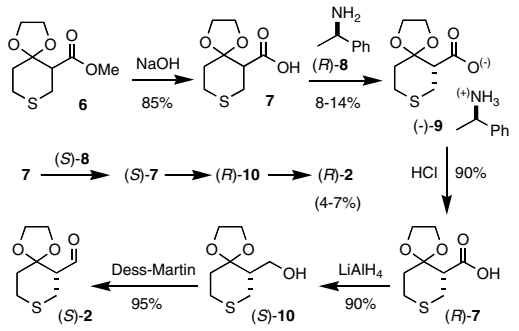


Scheme 2.

ester (±)-**6** was easily prepared in two steps from commercially available dimethyl 3,3′-thiobispropanoate (>80% yield on 100 g scale).[1] Hydrolysis of (±)-**6** gave the desired acid (±)-**7** in 89% yield. Crystallization of the salt prepared from (±)-**7** and (*R*)-(+)-**8** (1 equiv) from methanol/ether yielded a 3.5–4:1 mixture of diastereomers (by ^{1}H NMR) in 30–35% yield. Recrystallization of this salt gave (−)-**9** as a 25:1 mixture of diastereomers in 8–14% overall yield. The relative configuration of **9** was established by X-ray crystallographic analysis thereby confirming that (−)-**9** was derived from (*R*)-**7**.[§] Extraction of an acidified (pH = 1) solution of (−)-**9** (de = 91%) gave (*R*)-(−)-**7** in good yield. Similar treatment of the combined mother liquors from the above crystallizations gave the acid **7** slightly enriched in the (*S*)-enantiomer (65% yield, 10–20% ee). The rather poor yield of recovered **7** stems from the instability of the mother liquors, which darken considerably on standing. Resolution of the recovered **7** as carried out above but using (*S*)-(−)-**8** gave (*S*)-(+)-**7** (91% ee) in 7–12% yield (5–8% overall). Reduction of (*R*)-(−)-**7** with $LiAlH_4$ gave (*S*)-(−)-**10** (90%) with enantiomeric purity (determined by ^{1}H NMR of the derived Mosher's ester) matching the de of precursor **9**. Oxidation of (*S*)-(−)-**10** with the Dess–Martin periodinane[10] gave (*S*)-(−)-**2** in excellent yield and with enantiomeric purity (determined by ^{1}H NMR in presence of Eu(tfc)$_3$ as a chiral shift reagent) consistent with that of precursor **10**. Using the same route, (*R*)-(+)-**2** was prepared from (*S*)-(+)-**7**.

Despite considerable effort, we were unable to improve on the efficiency of the resolution of **7**. Although this route provided usable amounts of the desired **2** with reasonable enantiomeric purity, the low overall yields prompted the investigation of alternative strategies. Enantioselective protonation of enol derivatives has recently emerged as a simple and attractive method to obtain nonracemic carbonyl derivatives.[8,9] Inspired by the impressive results reported by Fehr et al.[11] for enantioselective protonation of enolates of α-cyclogeranic acid (2,6,6-trimethyl-2-cyclohexene-1-carboxylic acid) esters using **15** as the chiral proton source (easily prepared from ephedrine;[12,13] both enantiomers commercially available), we applied this method to various derivatives of **6** (Table 1). In each case, enolate formation was confirmed by quenching a control experiment with D_2O to obtain the starting material (>90% yield) with >90% deuterium incorporation with complete proton transfer from **15** (5–10 equiv) confirmed by adding D_2O prior to work-up to obtain starting material (>90% yield) with <10% deuterium incorporation.

Table 1. Enantioselective protonation of enolates from **6**, **7**, and **13** with (+)-**15**[a]

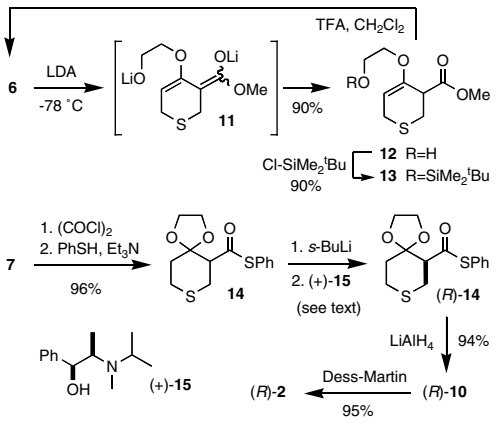
Entry	Starting ester	Base (equiv)	Product % ee
1	**6**	LDA (3)	5[b]
2	**6**	*s*-BuLi (2)[c]	20
3	**13**	LDA (2)	9
4		*s*-BuLi (2)	20
5		LDA (2)/*n*-BuLi (2)[d]	33
6		LDA (2)/*n*-BuLi (2)[d,e]	60
7	**7**	LDA (2)	50
8		*s*-BuLi (2)	60
9		*s*-BuLi (2)[e]	71
10		*s*-BuLi (2)[f]	82

[a] Reactions (ca. 0.1 mmol scale) at −78 °C with enolate formation for 30 min (LDA, inverse addition) or 5 min (*s*-BuLi) followed by addition of (+)-**15** (5 equiv) and after 1 h, addition of D_2O and work up (>90% yield).
[b] Workup included exposure of the crude product **12** to TFA in CH_2Cl_2 to obtain **6**.
[c] Enolate formation and protonation at −100 °C (bath).
[d] *n*-BuLi added after enolate formation with LDA; 10 equiv of (+)-**15** was used.
[e] Addition of (+)-**15** over 2 h.
[f] Addition of (+)-**15** at −100 °C followed by warming to −78 °C over 1 h.

The lithium enolate from reaction of **6** with LDA at −78 °C was unstable and underwent elimination and deprotonation to give the putative alkoxide dienolate dianion **11** and by using excess LDA **12** could be isolated in 90% yield (Scheme 3).[14] Brief exposure of **12** to acid regenerated **6** in excellent yield. Quenching the reaction of **6** and excess LDA (3 equiv) with (+)-**15** followed by treatment with acid gave **6** with <10% ee.[¶] The lithium enolate from reaction of **6** with *s*-BuLi (2 equiv) was stable at −100 °C; however, **6** was obtained with only 20% ee after quenching the enolate at this temperature with (+)-**15**. The TDBMS ether derivative **13** was obtained with <10% ee[¶] on quenching its LDA generated lithium enolate with (+)-**15**. In this case, quenching the enolate with D_2O returned the product with only ca. 70% deuterium incorporation suggesting the possibility of 'internal proton return'.[15] Treatment of the enolate with *n*-BuLi prior to addition of D_2O gave complete deuterium incorporation while the addition of (+)-**15** (10 equiv) in place of D_2O gave **13** with 33% ee (2:1 er). A 60% ee (4:1 er) could be obtained by slow addition of (+)-**15** to the enolate at −78 °C but further improvements could not be

[§] Crystallographic data (excluding structure factors) for (+)-**9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 236943. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

[¶] Measured by ^{1}H NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) as a chiral solvating agent. The absolute configuration of the major enantiomer was not determined.

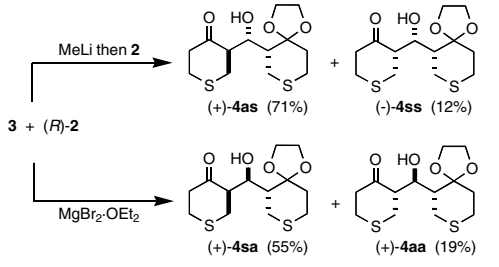


Scheme 3.

realized despite considerable experimentation (varying temperature, stoichiometry, concentration).

In contrast to **6**, the LDA derived lithium enolate of **14** was stable at −78 °C while protonation with (+)-**15** at that temperature gave (−)-**14** as a 3:1 mixture of enantiomers (50% ee). The lithium enolate from reaction of **14** with *s*-BuLi (substantial addition to the ester occurred with *n*-BuLi) was more convenient to prepare and gave slightly better results on protonation with (+)-**15** (4:1 er, 60% ee). A 6:1 er (71% ee) could be obtained by slow addition (2 h) of (+)-**15** to the lithium enolate of **14** at −78 °C. Control experiments established that protonation of the lithium enolate of **14** with (+)-**15** was very slow at −100 °C and that **14** slowly racemized (ca. 5%/h) in the presence of the lithium alkoxide of (+)-**15** at −78 °C. Under optimized conditions, (+)-**15** was added at once to the lithium enolate of **14** at −100 °C and the solution slowly warmed to −78 °C to give (−)-**14** as a 10:1 mixture of enantiomers (82% ee).[¶] This procedure can be easily performed on a gram scale and, most importantly, the enantioenriched **14** could be purified to high ee by recrystallization (50% yield, >95% ee). The process is very efficient overall considering that the mother liquors and the easily recovered (+)-**15** can be reused directly. Reduction of (−)-**14** with $LiAlH_4$ gave the previously characterized (+)-**10** establishing that (−)-**14** has an (*R*)-configuration.

With efficient synthetic routes to (+)-**2** and (−)-**2** secured, we turned our attention to the preparation of dipropionate building blocks **4** (Scheme 4). Reactions of **3** with (*R*)-**2** (91% ee) using the procedures previously described with (±)-**2**,[1] gave the expected aldol products **4**.



Scheme 4.

The individual diastereomers **4as**, **4ss**, **4sa**, and **4aa** had ee's of 90–91% (by ^{1}H NMR of the corresponding MOM ether derivatives in the presence of (−)-TFAE as a chiral solvating agent) establishing that the aldol reactions occurred with negligible racemization of (*R*)-**2**. Analogous results were obtained using (*S*)-**2**.

3. Conclusion

In summary, highly enantiomerically enriched **14** can be efficiently obtained by protonation of its *s*-BuLi derived lithium enolate with **15**. Sequential $LiAlH_4$ reduction and DMP oxidation of **14** gives the corresponding aldehyde **2** without racemization. Diastereoselective aldol reactions of **1** with nonracemic **2** similarly proceeded with negligible racemization. The aldol adducts **4** are useful tetrapropionate synthons. We have previously reported the stereoselective reduction[1] of individual isomers of **4** to give *syn*- or *anti*-1,3-diols that can be desulfurized[16] without loss of stereochemical integrity. Bisaldols **5** have been prepared by diastereoselective aldol reactions of **4** with **2**.[2] Enantiomerically pure and synthetically useful hexapropionate synthons **5** should now be available from nonracemic building blocks **2** and **4**. Our progress towards this objective will be reported in due course.

4. Experimental

4.1. 1,4-Dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde 2

A solution of alcohol (*S*)-(−)-**10** (92% ee; 207 mg, 1.09 mmol) and water (19 μL, 1.06 mmol)[17] in CH_2Cl_2 (10.5 mL) was added to a stirred solution of Dess–Martin periodinane (DMP)[18] (675 mg 1.59 mmol) under argon. After 10 min, Et_2O (15 mL) was added and a white precipitate formed after 10 min. A solution made up of saturated aqueous $NaHCO_3$ (5.9 mL) and $Na_2S_2O_3$ (1.5 g) diluted to 15 mL with water was added to the stirred reaction mixture resulting in two clear layers. The aqueous phase was extracted with Et_2O and the combined organic layers dried over Na_2SO_4 and concentrated to give (*S*)-(−)-**2** as a light yellow oil {198 mg, 97%; $[\alpha]_D^{24} = -130$, (*c* 1.0, C_6H_6); 91% ee} that was homogeneous by ^{1}H NMR. Spectral data for (*S*)-(−)-**2** was in accord with that previously reported for (±)-**2**.[1] Using the same procedure, (*R*)-(+)-**10** (91% ee; 205 mg, 1.08 mmol) gave (*R*)-(+)-**2** as a light yellow oil {188 mg, 93%; $[\alpha]_D^{24} = +130$, (*c* 1.0, C_6H_6); 91% ee}. The enantiomeric ratio (er) of **2** (ca. 0.07 M in $CDCl_3$) was determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$ (ca. 0.2 equiv) by integration of the peaks at δ 10.36 [1H, br s, HC-7, (*S*)-**2**] and δ 10.33 [1H, br s, HC-7, (*R*)-**2**]. The absolute configuration of **2** was assigned based on the absolute configuration of precursor **10**.

4.2. 1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-tetrahydro-4*H*-thiopyran-4-one 4

Reaction of (*R*)-**2** (91% ee; 82 mg, 0.44 mmol) with the lithium enolate of **1** prepared from **3** (330 mg,

1.76 mmol) and MeLi following the reported procedure[1] (but using 4 equiv of enolate to maximize the conversion), gave (+)-**4as** {94 mg, 71%; $[\alpha]_D^{24} = +39$, (*c* 1.0, $CHCl_3$)} and (−)-**4ss** 17 mg, 13%; $[\alpha]_D^{24} = -48$, (*c* 1.3, $CHCl_3$). Reaction of (*R*)-**2** (91% ee; 68 mg, 0.36 mmol) with **3** (135 mg, 0.72 mmol) in the presence of $MgBr{\cdot}OEt_2$ following the published procedure[1] gave (+)-**4sa** {60 mg, 55%; $[\alpha]_D^{24} = +44$, (*c* 1.0, $CHCl_3$)} and (+)-**4aa** 21 mg, 19%; $[\alpha]_D^{24} = +22$, (*c* 1.0, $CHCl_3$). NMR data for (+)-**4as**, (−)-**4ss**, (+)-**4sa**, and (+)-**4aa** were in accord with that previously reported for the racemic analogues.[1] Ee's for the major diastereomers (**4as** and **4sa**) were determined to be ca. 90% by ^1H NMR of the corresponding MOM ether derivatives (prepared in ca. 95% yield by reaction with MOM-Cl, *i*-Pr_2EtN and Bu_4NI)[3] in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE, 5–10 equiv) as a chiral solvating agent. In each case, signals for one of the protons from the MOM methylene group and or methyl group were adequately separated for the two enantiomers. Analogous results were obtained from the aldol reactions of (*S*)-(−)-**2**.

4.3. 1,4-Dioxa-8-thia-spiro[4.5]decane-6-carboxylic acid 7

From **6**. Aqueous NaOH (0.75 M; 150 mL, 0.11 mol) was added to a stirred solution of **6** (16.01 g, 0.073 mol) in MeOH (40 mL) at ambient temperature (exothermic). After 1.5 h, the mixture was cooled to 0 °C, acidified to pH 1 by addition of conc. HCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give (±)-**7** as a white solid (14.55 g, 97%) that was homogeneous by ^1H NMR. Recrystallization (CH_2Cl_2/hexane; 1:15) yielded (±)-**7** as white needles (13.35 g, 89%; mp 101–102 °C. Anal. Calcd for $C_8H_{12}O_4S$: C, 47.04; H, 5.92. Found: C, 47.03; H, 5.95).

From **9**. A solution of (−)-**9** (1.6 g, 4.9 mmol; 92% de) in CH_2Cl_2 (25 mL) was extracted with 1 M HCl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers dried over Na_2SO_4 and concentrated to give (*R*)-(−)-**7** as a white solid {902 mg, 90%; mp 92–93 °C; $[\alpha]_D^{24} = -54$, (*c* 1.0, $CHCl_3$); 92% ee)}. The aqueous layer was made basic (pH >12) by addition of solid NaOH (exothermic) and then extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 concentrated to give (*R*)-(+)-**8** as a light yellow liquid (591 mg, 99%). Using the above procedure, (+)-**9** (820 mg, 2.5 mmol; 92% de) gave (*S*)-(+)-**7** as a white solid {424 mg, 82%; mp 93–94 °C; $[\alpha]_D^{24} = +54$, (*c* 1.0, $CHCl_3$); 92% ee}. A sample of (*S*)-(+)-**7** obtained from (+)-**9** (>98% de) had $[\alpha]_D^{24} = +60$ (*c* 1.0, $CHCl_3$): IR ν_{max} 3197 (br), 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.04–3.99 (4H, m, $H_2CO\times2$), 3.11 (1H, ap dd, *J* = 9, 14 Hz, HC-7), 3.02–2.96 (2H, m, HC-6, HC-7), 2.79 (1H, *J* = 3.5, 9, 13 Hz, HC-9), 2.71 (1H, dddd, *J* = 1, 3.5, 7, 13 Hz, HC-9), 2.22 (1H, ddd, *J* = 3.5, 7, 13.5 Hz, HC-10), 1.86 (1H, ddd, *J* = 3.5, 9, 13.5 Hz, HC-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1 (s), 107.4 (s), 65.3 (t), 64.8 (t), 51.0 (d), 35.8 (t), 29.6 (t), 26.9 (t); LRMS (EI), *m/z* (relative intensity): 204 ($[M]^+$, 50), 176 (43), 159 (19), 132 (62), 113 (17), 99 (100), 86 (45); HRMS *m/z* calcd for $C_8H_{12}O_4S$ 204.0457, found 204.0456 (EI). The enantiomeric ratio (er) of **7** was determined by ^1H NMR (0.2 M in $CDCl_3$; resolution is concentration dependent) in the presence of (*R*)-**8** (1 equiv) by integration of the peaks at δ 2.87 (1H, dd, *J* = 4, 11 Hz, HC-7, (*R*)-**7**) and δ 2.80 (1H, dd, *J* = 4, 11 Hz, HC-7, (*S*)-**7**). Ratios >35:1 were confirmed by comparison of the minor peak to the ^{13}C satellite (0.55% assumed) of the major peak. The (*S*,*S*) relative configuration within (+)-**9** was established by X-ray crystallographic analysis; the absolute configuration of (+)-**7** follows because (+)-**9** is prepared from (−)-**8**, which is known to be of an (*S*)-configuration.

4.4. 1-Phenylethylammonium 1,4-dioxa-8-thia-spiro[4.5] decane-6-carboxylate 9

(±)-**7** (9.6 g, 47 mmol) was added to a solution of (*R*)-(+)-**8** (5.7 g, 47 mmol) in MeOH (15.4 mL). The solution was diluted with Et_2O (123 mL) and the well-stoppered vessel allowed to stand at ambient temperature (crystallization could be accelerated by addition of 1–2 mg of seed crystals of (−)-**9** of >25:1 dr). After crystals had begun to precipitate (generally within 1 h with seeding), the mixture was stored at 4 °C for 24 h. Filtration yielded (−)-**9** (4.9 g, 32%; 3.7:1 dr by ^1H NMR). Recrystallization as above but using a 4:1 (v/v) ratio of Et_2O and MeOH, respectively, gave (−)-**9** (1.6 g, 10%, 25:1 dr). The combined mother liquors were diluted with aqueous HCl (1 M) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give (*S*)-(+)-**7** (6.0 g, 63%; ca. 20% ee). Resolution as above but using (*S*)-(−)-**8** gave (+)-**9** (0.82 g, 8.6%, 5.3% overall; 23:1 dr). Repeated recrystallization of (+)-**9** gave a sample with >100:1 dr {mp 148–149 °C; $[\alpha]_D^{24} = +34$, (*c* 1.0, $CHCl_3$)}: ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.35 (5H, m, Ph), 6.65 (3H, br s, H_3N), 4.25 (1H, q, *J* = 6.5 Hz, HCN), 3.88–3.80 (4H, m, $H_2CO\times2$), 2.97 (1H, dd, *J* = 8, 13.5 Hz, HC-7), 2.91 (1H, dd, *J* = 3, 13, 5 Hz, HC-7), 2.66–2.63 (3H, m, HC-6, H_2C-9), 2.25–2.22 (1H, m, HC-10), 1.70–1.67 (1H, m, HC-10), 1.50 (3H, m, *J* = 6.5 Hz, H_3C); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0 (s, C=O), 143.3 (s, Ph), 129.1 (d×2, Ph), 128.1 (d, Ph), 126.7 (d×2, Ph), 108.4 (s, C-5), 65.3 (t, C-2/3), 64.7 (t, C-2/3), 52.7 (d, C-6), 51.5 (d, CHN), 36.0 (t, C-10), 30.6 (t, C-7), 27.3 (t, C-9), 23.4 (q, CH_3). The diastereoisomeric ratio (dr) of **9** was determined by ^1H NMR (0.2 M in $CDCl_3$; resolution is concentration dependent) by integration of the peaks at δ 2.87 (1H, dd, *J* = 4, 11 Hz, HC-7, *R***R**-diastereomer) and δ 2.80 (1H, dd, *J* = 4, 11 Hz, HC-7, *R***S**-diastereomer). Ratios >35:1 were confirmed by comparison of the minor peak to the ^{13}C satellite (0.55% assumed) of the major peak. The (*S*,*S*) relative configuration within (+)-**9** was established by X-ray crystallographic analysis (CCDC 236493); the absolute configuration follows because (+)-**9** is prepared from the known (*S*)-(−)-**8**.

4.5. 1,4-Dioxa-8-thia-spiro[4.5]dec-6-ylmethanol 10

From **7**. A solution of (*R*)-(−)-**7** (91% ee; 719 mg, 3.5 mmol) in THF (2 mL) was added dropwise via

syringe over 10 min to a stirred suspension of $LiAlH_4$ (200 mg, 5.3 mmol) in THF (15 mL) at 0 °C. The solution was removed from the ice bath and, after 1 h, heated under reflux for 45 min. After the mixture had cooled to room temperature, ether (15 mL), water (0.2 mL), 15% aqueous NaOH (0.2 mL), and water (0.6 mL) were added sequentially. The resulting mixture was stirred for 1 h, during which time a white precipitate formed. The mixture was filtered through Celite® and the combined filtrate and ether washings dried over Na_2SO_4, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to give (*S*)-(−)-**10** as a colorless oil {618 mg, 92%; $[\alpha]_D = -22$, (*c* 1.0, $CHCl_3$)}. This material was determined to be 90% ee by analysis of the derived Mosher's ester. Spectral data for (*S*)-(−)-**10** was in accord with that previously reported for (±)-**10**.[1] Following the same procedure (*S*)-(+)-**7** (91% ee; 408 mg, 3.5 mmol) was converted into (*R*)-(+)-**10** {346 mg, 91%; $[\alpha]_D = +23$, (*c* 1.0, $CHCl_3$); 91% ee}.

From **14**. A solution of (*R*)-(−)-**14** (355 mg, 1.20 mmol) in THF (5 mL) was added dropwise via syringe over 5 min to a stirred suspension of $LiAlH_4$ (90 mg, 2.4 mmol) in THF (30 mL) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and after 1.5 h, was quenched by addition of 15% aqueous NaOH (ca. 0.5 mL). After 30 min, the mixture was filtered through a short pad of Celite®, Al_2O_3, and Na_2SO_4 (in three layers, top to bottom) and the combined filtrate and DCM washings concentrated to give (*R*)-(+)-**10** as a colorless oil that was homogeneous by TLC and ^1H NMR {215 mg, 94%; $[\alpha]_D = +24$, (*c* 1.0, $CHCl_3$); 95% ee}. The ee of **10** was determined by reaction of a small sample (5–10 mg) with the acid chloride prepared from (*R*)-Mosher's acid (1.5 equiv) in the presence of Et_3N and DMAP as previously described[19] gave the crude Mosher's ester;[20] the absence of **10** was confirmed by ^1H NMR. The de of the Mosher's ester (and by implication the ee of the starting **10**) was determined by integration of the peaks at δ 4.64 (1H, dd, $J=4$, 11 Hz, HCO-MTPA, *S*,*R*-diastereomer) and δ 4.58 (1H, dd, $J=4$, 11 Hz, HCO-MTPA, *R*,*R*-diastereomer). Ratios >35:1 were confirmed by comparison of the minor peak to the ^{13}C satellite (0.55% assumed) of the major peak. (+)-**10** is assigned the (*R*)-configuration because $LiAlH_4$ reduction of (+)-**7** gave (+)-**10** and the absolute configuration of (*S*)-(+)-**7** was established by X-ray crystallographic analysis of its ammonium salt with (*S*)-(−)-**8** [i.e. (+)-**9**].

4.6. Methyl 3,6-dihydro-4-(2-hydroxyethoxy)-2*H*-thiopyran-3-carboxylate 12

LDA was prepared by addition of BuLi (2.5 M in hexanes; 8.4 mL, 21 mmol) to a stirred solution of *i*-Pr_2NH (2.33 g, 23 mmol) in THF (65 mL) at 0 °C under argon. The mixture was cooled to −78 °C and a solution of the ketal ester **6** (1.46 g, 6.72 mmol) in THF (2 mL) added dropwise via syringe. After 30 min, the reaction was quenched by addition of H_2O (10 mL) and the mixture diluted with brine and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (50% EtOAc in hexane) to yield the titled compound as a light yellow oil (1.37 g, 94%): IR ν_{max} 3435, 1731, 1666 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.42 (1H, dd, $J=3.5$, 4.5 Hz, HC-5), 3.68–3.42 (4H, m, $H_2CO\times2$), 3.25 (3H, s, H_3CO), 3.16 (1H, dd, $J=4.5$, 5 Hz, HC-3), 2.94 (1H, dd, $J=5$, 13.5 Hz, HC-2), 2.90 (1H, br d, $J=16.5$ Hz, HC-6), 2.75 (1H, dd, $J=4.5$, 16.5 Hz, HC-6), 2.50 (1H, dd, $J=4.5$, 13.5 Hz, HC-2); ^{13}C NMR (125 MHz, C_6D_6) δ 172.2, 152.7, 96.4, 68.9, 60.9, 52.3, 45.9, 28.5, 25.1; LRMS (EI), *m*/*z* (relative intensity): 218 ($[M]^+$, 13), 190 (10), 173 (100), 158 (19), 140 (46), 115 (37), 99 (31), 86 (9); HRMS *m*/*z* calcd for $C_9H_{14}O_4S$ 218.0613, found 218.0611.

4.7. Methyl 3,6-dihydro-4-[2-(dimethyl(1,1-dimethylethyl) silyloxy)ethoxy]-2*H*-thiopyran-3-carboxylate 13

t-$BuMe_2SiCl$ (802 mg, 5.17 mmol), Et_3N (1.4 mL, 10 mmol), and DMAP (29 mg, 0.24 mmol) were sequentially added to a stirred solution of the hydroxy ester **12** (1.02 g, 4.70 mmol) in CH_2Cl_2 (20 mL) under argon. After 18 h, MeOH (5 mL) was added and the mixture washed with brine. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers dried over Na_2SO_4, concentrated, and the residue passed through a short silica pad eluting with 30% EtOAc in hexane to afford the titled compound as a light yellow oil (1.46 g, 94%): IR ν_{max} 1743, 1671 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.53 (1H, dd, $J=4$, 4 Hz, HC-5), 3.73–3.63 (2H, m, H_2CO), 3.56–3.50 (2H, m, H_2CO), 3.39 (3H, s, H_3CO), 3.34 (1H, dd, $J=4.5$, 5.5 Hz, HC-3), 2.98 (1H, dd, $J=5.5$, 13.5 Hz, HC-2), 2.92–2.84 (2H, m, HC-6), 2.58 (1H, dd, $J=4.5$, 13.5 Hz, HC-2); ^{13}C NMR (125 MHz, C_6D_6) δ 171.58 (s, CO), 153.63 (s, C-4), 95.51 (d, C-5), 68.90 (t, C-3′), 62.35 (t, C-2′), 52.02 (q, CH_3O), 46.31 (d, C-3), 29.02 (t, C-2), 26.44 (q×3, $(CH_3)3C$), 25.20 (t, C-6), 18.88 (s, $C(CH_3)_3$), −4.79 (q, CH_3Si), −4.84 (q, CH_3Si); LRMS (EI), *m*/*z* (relative intensity): 317 ($[M-CH_3]^+$, 3), 275 ($[M-C_4H_9]^+$, 19), 257 (19), 229 (22), 213 (11), 173 (33), 89 (33), 73 (100); HRMS *m*/*z* calcd for $C_{15}H_{28}O_4SSi$ 332.1478 (275.0773 for $M-C_4H_9$), found 275.0767 ($M-C_4H_9$).

4.8. (*S*)-Phenyl 1,4-Dioxa-8-thia-spiro[4.5]decane-6-carbothioate 14

From (±)-**7**: Oxalyl chloride (5.4 mL, 62 mmol) was added dropwise to a stirred solution of (±)-**7** (8.42 g, 41.2 mmol) in benzene (80 mL) at room temperature under argon. After 3 h, the mixture was concentrated and thiophenol (4.50 mL, 43.7 mmol) and Et_3N (11.5 mL, 83.7 mmol) added sequentially to a stirred solution of the residue in THF (130 mL) (a white precipitate formed). After 15 min, the mixture was filtered through a mixture of basic Al_2O_3 and Celite and the combined filtrate and washings concentrated to give (±)-**14** as a white solid (11.8 g, 96%) that was homogeneous by ^1H NMR. Recrystallization from ether gave analytically pure (±)-**14** (10.5 g, 86%; mp 80–82 °C. Anal. Calcd for $C_{14}H_{16}O_3S_2$: C, 56.73; H, 5.44. Found: C, 56.79; H, 5.59): IR ν_{max} 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)

δ 7.40 (5H, s, Ph), 4.03–3.93 (4H, m, $H_2CO\times2$), 3.28–3.22 (2H, m, HC-6, HC-7), 2.93–2.86 (2H, m, HC-7, HC-9), 2.63 (1H, dddd, $J=2$, 3.5, 5.5, 13.5 Hz, HC-9), 2.15 (1H, ddd, $J=3$, 5.5, 13.5 Hz, HC-10), 1.87 (1H, ddd, $J=3.5$, 11.5, 13.5 Hz, HC-10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6 (s), 134.5 (d×2), 129.5 (d), 129.3 (d×2), 127.9 (s), 107.7 (s), 65.4 (t), 65.2 (t), 59.7 (d), 37.4 (t), 30.1 (t), 26.8 (t); LRMS (EI), *m/z* (relative intensity): 296 (13), 187 (68), 159 (20), 109 (12), 99 (100), 55 (25); HRMS *m/z* calcd for $C_{14}H_{16}O_3S_2$ 296.0541, found 296.0543.

Enantioselective protonation: *s*-BuLi (1.1 M in hexanes; 6.2 mL, 6.8 mmol) was added dropwise via syringe over 5 min to a stirred solution of (±)-**14** (1.02 g, 3.44 mmol) in THF (165 mL) at −78 °C under argon. After 15 min, the mixture was cooled to −100 °C and after 15 min, a solution of (1*S*,2*R*)-(+)-*N*-isopropylephedrine (+)-**15**[11,12] (3.4 g, 18.9 mmol) in THF (5 mL) was added at once via syringe. The mixture was allowed to warm slowly to −78 °C over 40 min and after 2 h at that temperature, the reaction quenched by addition of water (5 mL). The cooling bath was removed and after 15 min, the mixture was diluted with aqueous HCl (2 M) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (50% EtOAc in hexane) to give (−)-**14** as a white solid {1.01 g, 99%; $[\alpha]_D^{24}=-14$, (*c* 1.0, $CHCl_3$); 82% ee}. Recrystallization (2×) of this sample from ether gave (−)-**14** {0.516 mg, 51%; mp 76–78 °C; $[\alpha]_D^{24}=-18$, (*c* 1.0, $CHCl_3$); 95% ee}. A sample of (−)-**14** with >98% ee was obtained by further crystallization {mp 78–79 °C; $[\alpha]_D^{24}=-19$, (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{16}O_3S_2$: C, 56.73; H, 5.44. Found: C, 56.73; H, 5.64}. The mother liquors from above were combined and concentrated to give (−)-**14** (0.490 g, 48%; ca. 65% ee). To recover (+)-**15**, the aqueous phase was made basic (pH ca. 12) by addition of 30% aqueous NaOH and then extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and the reddish-brown residue subjected to bulb-to-bulb distillation (150 °C, 0.4 mbar) to afford (+)-**15** as a pale yellow oil {3.2 g, 94%; $[\alpha]_D^{24}=+2.5$, (*c* 6.0, $CHCl_3$)}. Reduction of **14** gave **10** whose ee was determined by ^1H NMR of the derived Mosher's ester (see above under **10**). (−)-**14** is assigned the (*R*)-configuration because $LiAlH_4$ reduction of (−)-**14** gave (*R*)-(+)-**10** of established absolute configuration (see above under **10**).

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