Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 29–36

TETRAHEDRON: *ASYMMETRY*

# Lithiated camphor-derived oxazolidinone *S,N*-acetals as chiral formyl anion synthons in additions to aldehydes. Asymmetric synthesis of α-hydroxy aldehydes and α-hydroxy acids

Robert E. Gawley,* Silvio A. Campagna, Marcelina Santiago and Tong Ren†

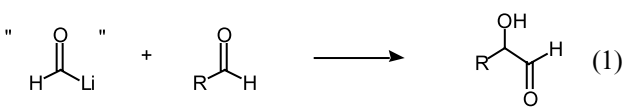
*Department of Chemistry, University of Miami, Coral Gables, FL 33124, USA*

Received 7 December 2001; accepted 22 January 2002

**Abstract**—*N*-(Phenylthiomethyl)oxazolidinones derived from camphor can be lithiated and added to aldehydes in good yields and stereoselectivities. The adducts are crystalline, which simplifies isolation of the major diastereomer from the product mixture. Hydrolysis affords enantiopure α-hydroxy aldehydes, which can be oxidized to α-hydroxy acids in good yields. The steric course of the reaction is analyzed in detail and a mechanistic model is presented. 

## 1. Introduction

Recent years have seen a surge of interest in the chemistry of functionalized organometallic reagents such as α-aminoorganolithiums, especially those where the metal-bearing carbon is stereogenic. Because these organometallic reagents are chiral, they may be used in stereoselective additions to prochiral aldehydes. This general area has been the subject of several recent publications, including two reviews.[1,2] Herein we report a study on the use of chiral organolithium compounds as chiral acyl anion synthons, an asymmetric version of the venerable Corey–Seebach reaction (Eq. (1)).[3] This synthetic transformation produces α-hydroxy acids after oxidation, which have considerable utility in enantioselective synthesis.[4] Both we[5] and others[6–8] have investigated this problem. The stereoselectivities achieved in the previously reported systems range from very low to very high, but the structural components in the chiral anion that influence stereoselectivitity have only recently begun to come into focus.[8]



(1)

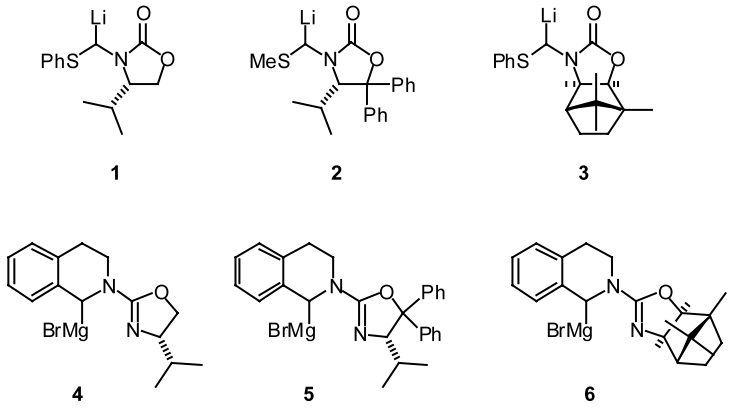
Our initial efforts in this area from some years ago involved deprotonation of *N*-(phenylthiomethyl)-oxazolidinone **1**, derived from valine. Addition to benzaldehyde in THF at −78°C proceeded with 66% ds, but the diastereomeric products could not be separated. More recently, Seebach's group showed that *N*-(methylthiomethyl)oxazolidinone **2**, also derived from valine, showed very good diastereoselectivities in additions to aldehydes (typically 70–90% ds), unsymmetrical ketones, chalcone, and imines.[7] The improved diastereoselectivity in moving from **1** to **2** is probably due to the *gem*-diphenyl groups, which restrict the motion of the isopropyl group, such that it 'appears' to anything near the lithiated carbon, similar to a *tert*-butyl group.[8]

Several years ago, we used a similar rationale to improve a chiral auxiliary for tetrahydroisoquinoline Grignard reagents, which we used as chiral nucleophiles for additions to prochiral aldehydes in the synthesis of some phthalideisoquinoline alkaloids. Specifically, in additions of the Grignard reagent **4** to benzaldehyde, we had observed 71% ds,[9] but when *gem*-diphenyl groups were introduced, as in **5**, the selectivity improved to 80%.[10] In the same study, we found that camphor-derived oxazoline **6** also afforded 80% ds, and produced adducts that were highly crystalline, in some cases obviating the need for a chromatographic separation of diastereomeric products. For this reason, we chose to evaluate a camphor-derived chiral acyl anion synthon, **3**, in additions to aldehydes, in the hope of improving the stereoselectivity over the results obtained

* Corresponding author. Tel.: 305-284-3279; fax: 305-668-3313; e-mail: rgawley@miami.edu

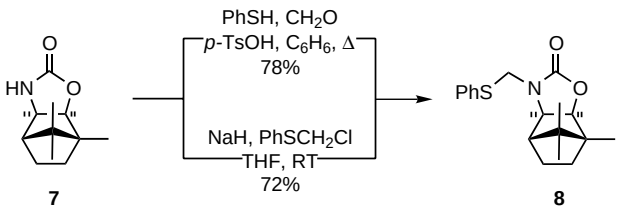
† Author to whom inquiries regarding the X-ray structures should be addressed. Tel.: 305-284-6617; fax: 305-284-1880; e-mail: tren@miami.edu

0957-4166/02/$ - see front matter 
PII: S0957-4166(02)00043-5




with **1** and/or the crystallinity of the addition products. This has resulted in the present study, in which **3** is used to prepare enantiopure α-hydroxy aldehydes and α-hydroxy acids.

There is a large amount of literature on the additions of chiral organolithium[1] and organomagnesium compounds[2] to prochiral aldehydes, but the observed diastereoselectivities are highly variable, and only rarely are they outstanding. One of the more elusive goals has been to gain insight into the reasons for the variable stereoselectivity of additions of these chiral nucleophiles to prochiral aldehydes. The adducts from addition of **3** to aldehydes proved to be highly crystalline, and X-ray analysis of two of the products established the relative and absolute configurations of the two new stereogenic centers. Interestingly, the steric course of the addition reaction changes for the sterically demanding pivaldehyde. In combination with recent results on **2** and related systems from the Seebach group,[8] knowledge of the steric course permits a mechanistic rationale to be constructed, and a subtle structural variable to be identified.




**Scheme 1.**

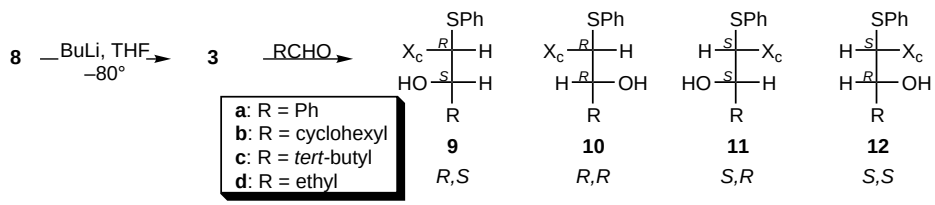
## 2. Oxazolidinone synthesis

In 1991, Bonner and Thornton[11] reported the synthesis of oxazolidinone **7** in three steps from camphor quinone, which we followed with a slight modification. As shown in Scheme 1, *S*,*N*-acetal **8** can be made either by condensation of **7** with paraformaldehyde and thiophenol (78% yield) or by alkylation of the sodium salt with (phenylthio)methyl chloride (72% yield).

## 3. Lithiation of 8 and additions to aldehydes

The stereoselectivity of addition of aldehydes to lithiated oxazolidinone *S*,*N*-acetal **3** was evaluated. Scheme 2 illustrates the four possible diastereomeric addition products in general form. The deprotonation of *S*,*N*-acetal **8** with *n*-butyllithium in THF at –78°C, generates the α-aminoorganolithium intermediate **3** that was added to four representative aldehydes to afford addition products **9**–**12** in moderate to excellent yield, as summarized in Table 1.

SFC and/or HPLC analysis of the product mixture revealed that, of the four possible stereoisomeric products, two predominated in each case. Recrystallization of the product mixture afforded a single diastereomer in useful yields. X-Ray crystallographic analysis revealed that the major product in the addition of **3** to benzaldehyde was **10a**, with diastereoselectivities of 79–86%, depending on the temperature (entry 1). The configuration of the minor diastereomer was established as **9a** by oxidation of (*R*,*R*)-alcohol **10a** to a ketone, and sodium borohydride reduction to a mixture of (*R*,*S*)-**9a** and (*R*,*R*)-**10a** (see Section 7 for details). This mixture was shown by SFC and HPLC to be the same two compounds produced in the addition reaction.




**Scheme 2.**

**Table 1.** Yield and diastereomer ratio for Scheme 2

| Entry | R | d.r. at −78°C **9**:**10** | Yield (%)[a] | d.r. at −100°C **9**:**10** | Yield (%)[a] | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Ph | 21:79 | 83 | 14:86 | 77 | 72 **10a** |
| 2 | $C_6H_{11}$ | 31:61 | 81 | 24:76 | 74 | 63 **10b** |
| 3 | *t*-Bu | 56:44 | 52 | 64:34 | 59 | 51 **9c** |
| 4 | Et | 35:65 | 80 | 24:76 | 71 | 38 **10d** |

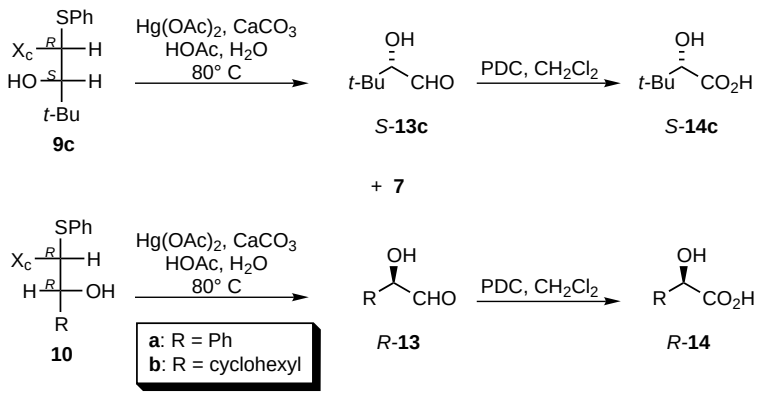
[a] Diastereomeric mixture.
[b] Single diastereomer after recrystallization (ethyl acetate/hexane).

Interestingly, X-ray analysis of the major addition product to pivaldehyde revealed it to be the (*R*,*S*)-diastereomer **9c**. An oxidation–reduction sequence further revealed that the minor diastereomer was (*R*,*R*)-**10c**. As described below, mercury-assisted hydrolysis of **10a** and **10b** and **9c** to the corresponding α-hydroxy aldehydes followed by oxidation to known α-hydroxy acids confirmed the absolute configuration at the carbinol carbon for all three adducts. The propanal adduct **10d** was not hydrolyzed because of anticipated solubility problems. The configuration at the carbon bearing the auxiliary is *R* in **9c** and **10a**, so is assigned *R* by analogy with **10b** and **10d**.

## 4. Conversion to α-hydroxy aldehydes and α-hydroxy acids

Enantiomerically enriched α-hydroxy carboxaldehydes were prepared by mercuric acetate oxidative-hydrolysis of the isolated major diastereomers **9c**, **10a** and **10b**. Scheme 3 shows this hydrolysis reaction as well as the recovery of the chiral auxiliary **7** in 72–80% yield. Yields of α-hydroxy carboxaldehydes **13a–c**, recovered **7**, and optical rotations are summarized in Table 2.

As shown in Scheme 3, α-hydroxy aldehydes **13a–c** could be oxidized with pyridinium dichromate (PDC)




**Scheme 3.**

**Table 2.** Yield and rotation data for auxiliary hydrolysis (Scheme 3)

| Entry | Carbinol | R | α-Hydroxy carboxaldehyde | Yield (%)[a] | $[\alpha]_D^{25}$ (MeOH)[b] | Recovered **7** (%) |
|---|---|---|---|---|---|---|
| 1 | **10a** | Ph | (*R*)-**13a** | 78 | −112 | 80 |
| 2 | **10b** | $C_6H_{11}$ | (*R*)-**13b** | 75 | −12 | 78 |
| 3 | **9c** | *t*-Bu | (*S*)-**13c** | 67 | −5 | 72 |

[a] Yields after purification by silica gel chromatography.
[b] Values obtained with $c=1.0$ except for **13c** for which $c=0.7$.

**Table 3.** Rotation data for α-hydroxy acids (Scheme 3), and literature comparisons

| Entry | α-Hydroxy carboxaldehyde | R | $[\alpha]_D^{25}$ ($H_2O$) **14** | $[\alpha]_D^{25}$ ($H_2O$) (Aldrich catalog) | O.p. **14** (%) | Configuration **14** |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**13a** | Ph | −151 | +154 (*S*) | 98 | *R* |
| 2 | (*R*)-**13b** | $C_6H_{11}$ | −23 | −23 (*R*) | 100 | *R* |
| 3 | (*S*)-**13c** | *t*-Bu | −60 | −62 (*S*) | 97 | *S* |

to the corresponding α-hydroxy acids **14a**–**c** in 47–68% yield. Rotation data and literature comparisons, summarized in Table 3, confirm the configurations established by X-ray analysis for precursors to **13a** and **13c**, and establish the configuration for **14b**, and by extrapolation, of **13b** and **10b**.

## 5. Discussion

Addition of **3** to benzaldehyde, cyclohexane carboxaldehyde, and presumably propanal, occurred predominantly to the *Si* face of the aldehyde. In contrast, addition to pivaldehyde occurred with lower selectivity, adding to the *Re* face of the aldehyde. Analysis of X-ray crystal structures of adducts **9** and **10** revealed that they had the same absolute configuration at the former metal-bearing carbon, differing only at the carbinol carbon. Diastereomers **11** and **12** were only present in trace amounts at most, and could not be detected at all in several experiments.

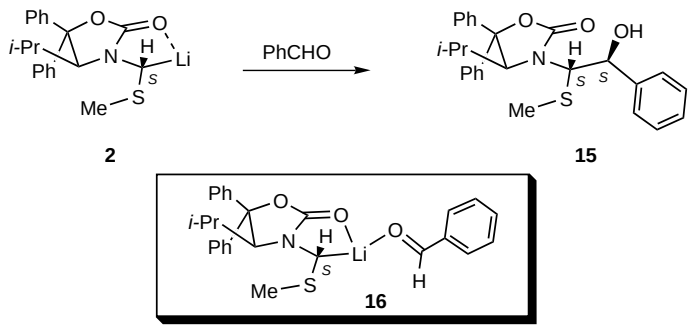
Analysis of the steric course of this reaction can only begin if the configuration of the lithium-bearing carbon of **3** is known. Although we have no direct evidence for the configuration of this stereocenter in **3**, there is enough precedent in related systems to allow a reasonable prediction. In particular, detailed spectroscopic studies of **2** by the Seebach group, along with Bauer and ourselves,[8] revealed several structural features that are likely to be present in **3** as well. Specifically (Scheme 4), IR studies showed that the lithium in **2** is chelated by the carbonyl oxygen, calculations showed that the *S*-methyl group prefers a position antiperiplanar to the C–Li bond and NMR studies established the configuration of the carbanionic carbon as *S*.[8] Even though the barrier to inversion in a related achiral system is only 11 kcal/mol, the diastereomeric bias created by the isopropyl substituent at position 4 of the oxazolidinone ring is such that none of the minor epimer is present between −105 and −20°C.[8] Similar features apparently operate in other α-aminoorganolithium reagents employing an oxazolidinone chiral auxiliary.[12]

The addition products, typified by **15**, result from addition of the (*S*)-organolithium to the *Re* face of the aldehyde to give (*S*,*S*)-**15**.[7,8] A possible coordination complex between **2** and an aldehyde (e.g. **16**) has several structural features that are relevant (possible coordinating solvent molecules are deleted for clarity). The Lewis-acidic lithium ion should coordinate to the aldehyde oxygen *trans* to the aldehyde's phenyl ring. If the aldehyde oxygen is *trans* to the SMe group (on the five-membered chelate ring), the correct (*Re*) face is presented to the carbanionic carbon. Addition with retention of configuration at the metal-bearing carbon ($S_E2ret$[13]) then gives the observed major product.

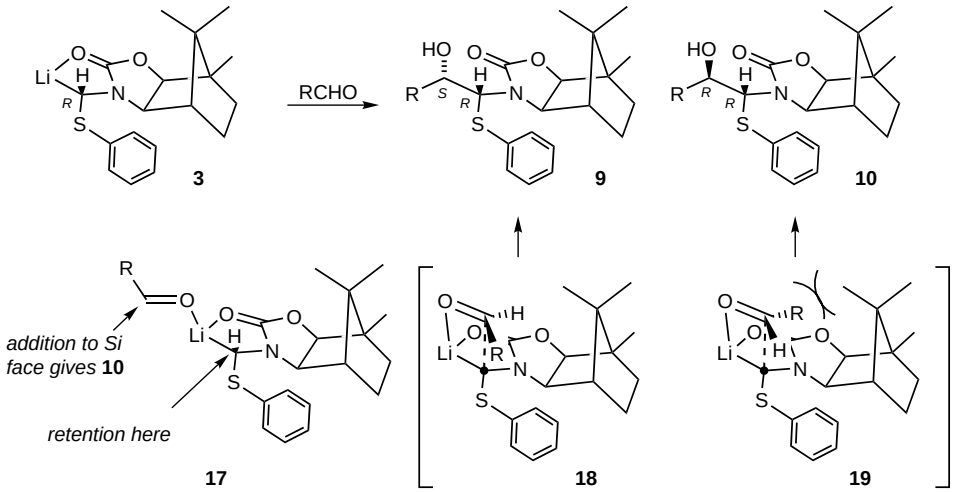
The addition of **3** to aldehydes produces a mixture of **9** and **10**, with the latter predominating except when R = *tert*-butyl. Extrapolation of the structural features of **2** to **3** suggest the structure for **3** shown in Scheme 5. Specifically, the lithium ion is chelated by the carbonyl oxygen, the lithium-bearing carbon is *R*, so as to place the *S*-phenyl on the opposite side of the oxazolidinone ring relative to the camphor moiety, and the *S*-phenyl bond is antiperiplanar to the C–Li bond. Coordination of the aldehyde as in **16** gives **17**, in which the *Si* face is presented to the carbanionic carbon. Addition to the *Si* face, with retention at the carbanionic carbon ($S_E2ret$[13]), gives **10**, the major product in three of the four examples studied. We speculate that the reason for the reversal of steric course, may be as follows.

In structures **16** and **17**, the lithium ion is in the nodal plane of the aldehyde π bond. In order for the carbanion to add to the carbonyl carbon, the aldehyde must rotate to give a structure such as **18** or **19**. Such a reaction trajectory has been predicted in a theoretical investigations of the addition of methyllithium aggregates to formaldehyde and acetaldehyde.[14] Note, however, that as this rotation occurs, the aldehyde substituent may encounter one of the geminal methyls in the camphor moiety in TS **19**, which leads to **10**. Such an encounter may destabilize **19** relative to **18** when R is an extremely bulky *tert*-butyl group, leading to a reversal in topicity and **9** as the major product. Confirmation of this hypothesis will require computer modeling studies that are beyond the scope of this paper.

Because of the close similarity of **2** and **3**, it is instructive to compare the selectivities in asymmetric additions to the same, or very similar aldehydes. For benzaldehyde, the *Re*/*Si* facial selectivity of **2** is 90:10 at −78°C and 93:7 at −100°C. This compares with 79:21 at −78°C and 86:14 at −100°C for addition of **3** to benzaldehyde. At −78°C, the difference in transition state energies is therefore 340 cal/mol, and 260 cal/mole at −100°C. At




**Scheme 4.**




**Scheme 5.**

−100°C, **2** gave a 70:30 d.r. when added to butanal, whereas **3** gave a 76:24 ratio when added to propanal, corresponding to differences in transition state energies of only 100 cal/mol. These energy differences are less than half the energy difference between the synclinal and antiperiplanar conformations of butane (900 cal/mol). In other words, very subtle structural differences in either the chiral auxiliary or the electrophile can change the diastereoselectivity, or even the steric course, of an electrophilic substitution to a significant degree. Fig. 1 shows a comparison between probable solution structures of **17** and *ent*-**16**, highlighting the space in *ent*-**16** that is occupied by a methyl group in **17**, and which may account for the observed selectivity differences, as well as the change in steric course observed with **17**, when R is *tert*-butyl.

## 6. Summary

In conclusion, the Bonner–Thornton oxazolidinone, **7**, is a very good chiral auxiliary for generating chiral acyl anion synthons via *S*,*N*-acetal **8**, which may be used in an asymmetric version of the Corey–Seebach reaction. Enantiopure α-hydroxyaldehydes and α-hydroxy acids can be prepared readily, and the auxiliary recovered in excellent yield. A particular advantage of this system is that the initially formed addition products are highly crystalline, simplifying purification and diastereomeric enrichment.

## 7. Experimental

Proton NMR spectra were recorded at 400 MHz, whereas carbon spectra were recorded at either 100 MHz or 23 MHz. Electrospray ionization mass spectrometry (ESI-MS) were obtained on an orthogonal acceleration time-of-flight (oa-TOF-MS), at duPont Pharmaceutical company, courtesy of Dr. J. Castoro. The samples were analyzed using a $MeOH/H_2O$ eluent without an HPLC column, and a 2 μL injection volume. The eluent was flowing at 0.2 mL/min and an internal standard was added at 5 μL/min. Elemental analysis was performed by Atlantic Microlabs. High Performance Liquid Chromatography (HPLC) separations used a chiral phase (*R*)-DNBPG (covalent) Pirkle column with isocratic conditions using isopropanol/hexane. Modifier for supercritical fluid chromatographic (SFC) separations was methanol, with either an OD or AD Chiralcel column. Diode array detection was used for both techniques. Gas chromatography was performed with a 15 m 5% phenyl methyl silicone vitreous silica gel capillary column. All reactions involving air- or moisture-sensitive reagents were conducted under an atmosphere of nitrogen (balloon) in septum-stoppered flasks. Transfer of reagents was accomplished using standard syringe techniques.

All glassware was oven dried (120°C) and cooled under a nitrogen atmosphere. Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium benzo-

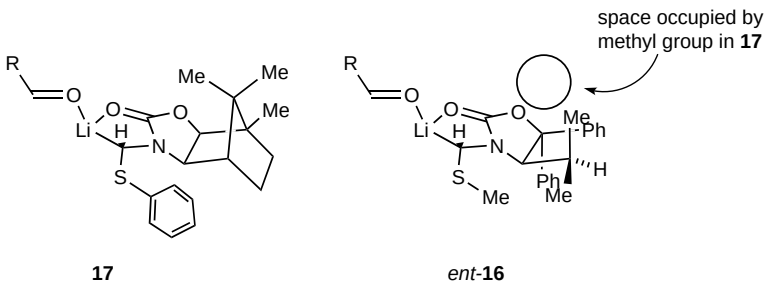



**Figure 1.**

phenone ketyl immediately prior to use. Triethylamine and tetramethylethylenediamine (TMEDA) were distilled under nitrogen from calcium hydride. Commercial solutions of *n*-butyllithium in hexanes and *sec*-butyllithium in cyclohexane were titrated prior to use with *sec*-butanol using 1,10-phenanthroline (monohydrate) as an indicator.

### 7.1. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-5-phenylsulfanylmethyl-3-oxa-5-azatricyclo-[5.2.1.0$^{2,6}$]-decane-4-one 8

**Procedure A**: To a stirred solution of oxazolidinone **7**[11] (2.0 g, 10.2 mmol) in benzene (25 mL) was added *p*-toluenesulfonic acid (catalytic amount, 0.1 equiv.) and paraformaldehyde (0.45 g, 10.2 mmol) at 25°C in one portion. After stirring for 30 min at 25°C, thiophenol (1.06 mL, 10.2 mmol) was added. The reaction mixture was heated under reflux using a Dean–Stark azeotropic separation apparatus until no more water was collected (approximately 8 h). Benzene was removed by rotary evaporation and the crude product purified by column chromatography (ethyl acetate/hexane, 1:4 v/v) to afford **8** as a white solid (2.51 g, 78%). Mp = 74–75°C; IR (KBr): 3080, 2985, 2944, 1760, 1580, 1485, 1420, 1320, 1290, 1240, 1090, 1050, 1030, 980, 900 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.4–7.2 (m, 5H), 5.6 (d, $J$ = 8 Hz, 1Ha), 4.4 (d, $J$ = 8 Hz, 1Hb), 4.2 (d, $J$ = 6 Hz, 1H), 3.8 (d, $J$ = 6 Hz, 1H), 1.90 (m, 1H), 1.7 (m, 2H), 1.5 (m, 2H), 1.1 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H). $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ 4.0, 5.3, 11.2, 27.9, 29.2, 33.3, 34.6, 38.2, 48.6, 88.3, 92.0, 129.9, 130.2, 134.3, 134.8, 184.2. ESI-MS calcd for $C_{18}H_{24}NO_2S$ (MH$^+$): 318.1528; found 318.1519. Anal. calcd for $C_{18}H_{23}NO_2S$: C, 68.10%, H, 7.30%, N, 4.41%; found: C, 67.99%, H, 7.30%, N, 4.36%.

**Procedure B**: To stirred solution of oxazolidinone **7** (6.60 g, 37.0 mmol) in THF (25 mL) was added sodium hydride (60% dispersion in mineral oil, 1.78 g, 44.4 mmol) at 0°C. After stirring the suspension for 30 min, $Bu_4NI$ (catalytic amount) and phenylthiomethyl chloride (4.90 mL, 37.0 mmol) were added. The reaction mixture was heated under reflux for 6 h, cooled to room temperature and carefully quenched with brine (10 mL). The mixture was extracted with diethyl ether (3×25 mL). The organic layers were combined and dried over $MgSO_4$. After filtration and concentration by rotary evaporation, the product was purified by column chromatography (ethyl acetate/hexane, 1:4 v/v) to yield **8** (8.5 g, 72%).

### 7.2. General procedure for deprotonation of (1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-5-phenylsulfanylmethyl-3-oxa-5-aza-tricyclo-[5.2.1.0$^{2,6}$]-decane-4-one 8 and its addition reaction to aldehydes

To a stirred solution of **8** (0.1 M) in THF at −78°C ($CO_2$/acetone) was added *n*-BuLi (1.1 equiv., 1.6 M in hexanes) dropwise over 5 min. The color of solution changed to dark orange–red after the addition of *n*-BuLi. The reaction mixture was stirred at −78°C for 30 min and then the corresponding aldehyde (1.2 equiv.) was added dropwise. In the case of −100°C addition, the solution was stirred for 30 min at −78°C, then transferred to a liquid nitrogen/methanol slush bath. After equilibrating for 10 min, the aldehyde was added dropwise. In either case, the reaction was stirred for an additional hour and then quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ether (three times). The combined organic phases were washed with brine and dried over $MgSO_4$. After vacuum filtration and concentration, the residue was dried under high vacuum for 24 h. The products were purified by chromatography for characterization only, but otherwise were sufficiently pure for further reactions.

#### 7.2.1. (1*R*,2*S*,6*R*,7*S*)-5-((1*R*,2*R*)-2-Hydroxy-2-phenyl-1-phenylsulfanylethyl)-1,10,10-trimethyl-3-oxo-5-azatricyclo-[5.2.1.0$^{2,6}$]-decane-4-one 10a (from addition of 3 to benzaldehyde)

Mp: 81–83°C; IR (KBr): (br) 3420, 3010, 2980, 1950, 1700, 1590, 1410, 1360, 1340, 1270, 1220, 1100, 1040, 980, 820 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.5–7.2 (m, 10H), 5.4 (d, $J$ = 6 Hz, 1H), 5.1 (m, 1H), 4.1 (d, $J$ = 8 Hz, 1H), 3.8 (br, s, 1H), 3.6 (d, $J$ = 8 Hz, 1H), 2.7–2.2 (m, 4H), 2.1 (m, 1H), 0.90 (s, 3H), 0.77 (s, 3H), 0.68 (s, 3H). $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ 4.0, 5.3, 11.2, 27.9, 29.2, 33.3, 34.6, 38.2, 38.6, 48.6, 88.2, 92.0, 127.2, 128.2, 128.8, 129.9, 130.2, 132.4, 134.8, 135.2, 184.2. ESI-MS calcd for $C_{25}H_{30}NO_3S$ (MH$^+$): 424.1946; found 424.1946. Anal. calcd for $C_{25}H_{29}NO_3S$: C, 70.89%, H, 6.90%; found: C, 70.91%, H, 7.07%. *Crystal data*: $C_{25}H_{29}NO_3S$, $M$ = 423.6, monoclinic, space group $P2_1$, $a$ = 10.028(1), $b$ = 11.080(1), $c$ = 11.003(1) Å, $\beta$ = 115.360(1)°, $V$ = 1104.7(1) Å$^3$, $Z$ = 2; Data were collected on a Bruker SMART1000 CCD diffractometer at 27°C with MoK$\alpha$ radiation ($\lambda$ = 0.71073 Å). $R_1$ = 0.0305, $wR_2$ = 0.0778, absolute structure (Flack) parameter = 0.04(6). Further details have been deposited with the Cambridge Crystallographic Data Centre (CCDC 175200, UM168).

#### 7.2.2. (1*R*,2*S*,6*R*,7*S*)-5-((1*R*,2*R*)-2-Hydroxy-2-cyclohexyl-1-phenylsulfanylethyl)-1,10,10-trimethyl-3-oxo-5-aza-tricyclo-[5.2.1.0$^{2,6}$]-decane-4-one 10b (from addition of 3 to cyclohexanecarboxaldehyde)

Mp: 164–165°C; IR (KBr): (br) 3430, 3100, 3010, 2980, 1695, 1480, 1410, 1340, 1270, 1220, 1100, 1030, 970, 930, 820 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.6–7.2 (m, 5H), 5.3 (d, $J$ = 8 Hz, 1H), 5.1 (d, $J$ = 8 Hz, 1H), 4.2 (d, $J$ = 8 Hz, 1H), 3.8 (m, 1H), 3.7 (m, 1H), 3.6 (br, s, 1H), 2.2 (m, 1H), 1.8–1.6 (m, 3H), 1.3–0.92 (m, 11H), 1.0 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H). $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ 3.9, 4.2, 4.5, 4.8, 4.9, 5.0, 5.3, 11.2, 27.9, 29.2, 33.3, 34.6, 38.2, 48.6, 88.2, 92.0, 127.2, 128.2, 128.8, 129.8, 185.2. ESI-MS calcd for $C_{25}H_{36}NO_3S$ (MH$^+$): 430.2416; found 430.2430. Anal. calcd for $C_{25}H_{35}NO_3S$: C, 69.89%, H, 8.21%; found: C, 69.62%, H, 8.26%.

**7.2.3. (1*R*,2*S*,6*R*,7*S*)-5-((1*R*,2*R*)-2-Hydroxy-1-phenylsulfanylbutyl)-1,10,10-trimethyl-3-oxo-5-aza-tricyclo-[5.2.1.0$^{2,6}$]-decane-4-one 10d (from addition of 3 to propanal)**. Mp: 67–69°C; IR (KBr): (br) 3450, 3010, 2990, 1700, 1490, 1410, 1360, 1340, 1270, 1220, 1100, 1030, 970, 930, 820 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.6–7.2 (m, 5H), 5.1 (d, $J=6$ Hz, 1H), 4.2 (d, $J=6$ Hz, 1H), 4.1 (m, 1H), 3.9 (m, 2H), 3.8 (br, s, 1H), 3.6 (m, 2H), 2.0 (m, 1H), 1.8–1.7 (m, 3H), 1.5 (t, 3H), 1.0 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H). $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ 3.9, 4.6, 5.3, 11.2, 27.9, 28.0, 29.2, 33.3, 34.6, 38.2, 48.6, 88.3, 92.0, 127.2, 128.2, 128.8, 129.8, 132.4, 184.2. ESI-MS calcd for $C_{21}H_{30}NO_3S$ ($MH^+$): 376.1946; found 376.1953. Anal. calcd for $C_{21}H_{29}NO_3S$: C, 67.17%, H, 7.78%. Found: C, 67.32%, H, 7.94%.

**7.2.4. (1*R*,2*S*,6*R*,7*S*)-5-((1*R*,2*S*)-2-Hydroxy-3,3-dimethyl-1-phenylsulfanylbutyl)-1,10,10-trimethyl-3-oxo-5-aza-tricyclo-[5.2.1.0$^{2,6}$]-decane-4-one 9c (from addition of 3 to pivaldehyde)**. Mp: 135–136°C; IR: (br) 3450, 3010, 2990, 1700, 1490, 1410, 1340, 1270, 1220, 1100, 1030, 970, 930, 820 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.6–7.2 (m, 5H), 4.2 (d, $J=6$ Hz, 1H), 4.0 (m, 1H), 3.7 (m, 2H), 3.2 (br, s, 1H), 1.8 (m, 2H), 1.7–1.6 (m, 3H), 1.1 (s, 3H), 0.90 (s, 3H), 0.80 (d, $J=6$ Hz, 9H), 0.76 (s, 3H). $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ 3.98 (3C), 4.6, 5.3, 5.4, 11.2, 27.1, 28.3, 28.5, 29.2, 33.3, 34.6, 38.2, 48.6, 52.2, 88.3, 92.0, 127.8, 128.2, 128.8, 129.8, 185.2. ESI-MS calcd for $C_{25}H_{34}NO_3S$ ($MH^+$): 404.2259; found 404.2258. Anal. calcd for $C_{23}H_{33}NO_3S$: C, 68.45%, H, 8.24%; found: C, 68.61%, H, 8.23%. *Crystal data*: $C_{23}H_{33}NO_3S$, $M=403.6$, orthorhombic, space group $P2_12_12_1$, $a=6.8616(5)$, $b=12.011(1)$, $c=27.465(2)$ Å, $V=2263.4(3)$ Å$^3$, $Z=4$; Data were collected on a Bruker SMART1000 CCD diffractometer at 27°C with MoK$\alpha$ radiation ($\lambda=0.71073$ Å). $R_1=0.0325$, $wR_2=0.0727$, absolute structure (Flack) parameter $=-0.04(6)$. Further details have been deposited with the Cambridge Crystallographic Data Centre (CCDC 175201, UM169).

### 7.3. General procedure for the oxidation of carbinol products 9/10 with pyridinium chlorochromate (PCC)

To a stirred suspension of pyridinium chlorochromate (23.3 g, 0.15 mol) in anhydrous dichloromethane (150 mL) at 25°C was added the corresponding carbinols **9**/**10** (0.1 mol) dissolved in dichloromethane (20 mL) in one portion. After stirring the mixture for 1.5 h, dry diethyl ether (200 mL) was added and the supernatant liquid decanted from a black gum. The insoluble residue was washed with ether (3×30 mL) until it became a granular black solid. The combined ether solution was passed through a short pad of florisil under vacuum. The solvent was removed by rotary evaporation, affording the ketone product in 85–95% yield. The ketones were purified by recrystallization (diethyl ether/hexane, 3:2) for characterization.

**7.3.1. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-5-((1*R*)-*2*-oxo-2-phenyl-1-phenylsulfanyl-ethyl)-3-oxa-5-aza-tricyclo-[5.2.1.0$^{2,6}$]-decane-4-one (from 9a/10a)**. Mp: 96–98°C; IR (KBr): 3020, 2980, 1950, 1720, 1695, 1590, 1410, 1360, 1340, 1270, 1220, 1100, 1040, 980, 820 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.7–7.2 (m, 10H), 5.1 (s, 1H), 4.8 (m, 1H), 3.8 (m, 1H), 2.7–2.2 (m, 3H), 2.1 (m, 2H), 0.90 (s, 3H), 0.77 (s, 3H), 0.68 (s, 3H). $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ 4.0, 5.3, 11.2, 27.7, 29.2, 33.3, 34.6, 38.2, 48.6, 88.2, 92.0, 127.2, 128.8, 129.9, 130.2, 132.4, 134.8, 134.3, 134.8, 179.4, 184.2. ESI-MS calcd for $C_{25}H_{28}NO_3S$ ($MH^+$): 422.1790; found 422.1798. Anal. calcd for $C_{25}H_{27}NO_3S$: C, 71.23%, H, 6.46%; found: C, 71.16%, H, 6.54%.

**7.3.2. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-5-((1*R*)-2-oxo-2-cyclohexyl-1-phenylsulfanyl-ethyl)-3-oxa-5-aza-tricyclo-[5.2.1.0$^{2,6}$]decane-4-one (from 9b/10b)**. Mp: 158–160°C; IR (KBr): 3100, 3010, 2980, 1720, 1695, 1480, 1410, 1340, 1270, 1220, 1100, 1030, 970, 930, 820 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.6–7.2 (m, 5H), 3.8 (m, 1H), 3.7 (m, 2H), 2.2 (m, 2H), 1.8–1.6 (m, 3H), 1.3–0.92 (m, 11H), 1.0 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H). $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ 3.90, 4.2, 4.4, 4.8, 5.0, 5.2, 11.2, 27.9, 29.2, 33.3, 34.6, 38.2, 48.6, 88.3, 92.0, 127.2, 128.2, 129.8, 132.4, 178.4, 185.2. ESI-MS calcd for $C_{25}H_{34}NO_3S$ ($MH^+$): 428.2259; found 428.2271. Anal. calcd for $C_{25}H_{33}NO_3S$: C, 70.22%, H, 7.78%, N, 3.28%; found: C, 70.53%, H, 8.08%, N, 3.14%.

**7.3.3. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-5-((1*R*)-2-oxo-3,3-dimethyl-1-phenylsulfanyl-butyl)-3-oxa-5-aza-tricyclo-[5.2.1.0$^{2,6}$]-decane-4-one (from 9c/10c)**. Mp: 66–68°C; IR (KBr): 3010, 2990, 1700, 1690, 1490, 1410, 1340, 1270, 1220, 1100, 1030, 970, 930, 820 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.6–7.2 (m, 5H), 4.0 (m, 1H), 3.7 (m, 2H), 1.8 (m, 2H), 1.7–1.6 (m, 3H), 1.1 (s, 3H), 0.90 (s, 3H), 0.80 (s, 9H), 0.76 (s, 3H). $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$, 3.98 (3C), 4.6, 5.2, 5.7, 11.2, 28.0, 29.2, 33.3, 34.6, 38.2, 48.6, 88.2, 127.8, 128.2, 128.8, 129.8, 132.4, 178.8, 185.2. Anal. calcd for $C_{23}H_{31}NO_3S$: C, 68.79%, H, 7.78%. Found: C, 68.94%, H, 7.91%.

**7.3.4. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-5-((1*R*)-2-oxo-1-phenylsulfanyl-butyl)-3-oxa-5-aza-tricyclo-[5.2.1.0$^{2,6}$]-decane-4-one (from 9d/10d)**. Mp: 82°–84°C; IR (KBr): 3010, 2990, 1710, 1690, 1490, 1410, 1360, 1340, 1270, 1220, 1100, 1030, 970, 930, 820 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.6–7.2 (m, 5H), 4.1 (m, 1H), 3.9 (q, 2H), 3.6 (m, 2H), 2.0 (m, 2H), 1.8–1.7 (m, 3H), 1.4 (t, 3H), 1.0 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H). $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ 3.9, 4.6, 5.3, 5.7, 11.2, 28.0, 29.2, 33.2, 34.6, 38.2, 48.6, 88.2, 92.0, 128.8, 129.8, 132.4, 134.8, 180.2, 184.2. ESI-MS calcd for $C_{21}H_{28}NO_3S$ 374.1790 ($MH^+$): found 374.1785. Anal. calcd for $C_{21}H_{27}NO_3S$: C, 67.53%, H, 7.29%. Found: C, 67.90%, H, 7.54%.

### 7.4. General procedure for the reduction of above ketones to 9/10 epimeric carbinol mixture with sodium borohydride

To a stirred solution of the ketone (1 mmol) in methanol (15 mL) at 25°C was added a solution of $NaBH_4$ (2 mmol) in water/methanol (1:1 v/v) in one

portion. The reaction mixture was stirred for 1 h and then quenched with dilute aqueous acetic acid (3 mL). The mixture was extracted with diethyl ether (3×20 mL), washed with brine and dried over $MgSO_4$. After filtration and concentration by rotary evaporation the corresponding mixture of carbinol epimers was obtained in 67–73% yield. No further purification was needed for these compounds.

### 7.5. General procedure for the oxidative hydrolysis of carbinols 10a, 10b and 9c to α-hydroxy carboxaldehydes 13a, 13b and 13c, respectively

To a stirred solution of the corresponding carbinol **10a**, **10b** and **9c** (1.0 mmol) in aqueous 80% acetic acid (10 mL) at 25°C was added a solution of mercuric acetate (2.2 mmol) in acetic acid (10 mL). Powdered calcium carbonate (2.2 mmol) was added to buffer the reaction mixture near pH 7. The stirred mixture was heated to 80°C under nitrogen for 4–6 h. After this period of time, the reaction was complete as indicated by TLC ($CH_2Cl_2$/MeOH, 1:1). The mixture was allowed to cool to room temperature and filtered through a Celite bed. The filter cake was washed with hexane/dichloromethane (1:1). The organic phase was separated from the filtrate and washed with aqueous ammonium acetate (5 M, 5 mL), water (5 mL) and brine (5 mL). After drying the organic solution over $MgSO_4$, filtration and concentration by rotary evaporation, crude α-hydroxy aldehyde **13a**–**28** was obtained in 72–80% yields. Purification of **13a**–**c** was accomplished by silica chromatography (hexane/ethyl acetate, 1:9).

### 7.6. General procedure for the oxidation of α-hydroxy aldehydes 13a, 13b and 13c to α-hydroxy carboxylic acids 14a, 14b and 14c, respectively

To a stirred suspension of $(C_5H_5N)_2Cr_2O_7$ (1.2 mmol) in dichloromethane (20 mL) at 25°C was added a solution of the correspond α-hydroxy aldehydes **13a**–**c** (1.0 mmol) in dichloromethane (10 mL) in one portion. The mixture was stirred for 2 h at room temperature. At that time, no starting material was observed by TLC (dichloromethane/methanol, 1:1). Phosphoric acid (1 mL) was added and the insoluble residue was filtered through a short pad of Florisil. The cake was washed with dichloromethane (5 mL). The dark filtrate was filtered through a silica gel plug and washed with dichloromethane (~5 mL). After concentration, the crude α-hydroxy carboxylic acid was obtained in 47–68% yield. Purification of the α-hydroxy carboxylic acid was achieved by preparative TLC (dichloromethane/methanol, 1:1). Characterization of α-hydroxy carboxylic acids **13a**–**c** were made by comparison of $^1H$ and $^{13}C$ NMR, and specific rotation, with commercially available (*R*)-(+)-mandelic acid **14a**, (*S*)-(+)-hexahydromandelic acid **14b** and (*S*)-(−)-2-hydroxy-3,3-dimethylbutyric acid **14c**.

## Acknowledgements

This work was generously supported by the National Institutes of Health (GM 56271). We thank the University of Miami for the purchase of the CCD diffractometer used in this work.

## References

1. Gawley, R. E. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed. Stereoselective addition of chiral α-aminoorganometallics to aldehydes; JAI: Greenwich, CT, 1998; Vol. 3, pp. 77–111.
2. Gawley, R. E. In *Grignard Reagents*: *New Developments*; Richey, H. G., Ed. Stereoselective additions of chiral Grignard reagents to aldehydes: stereochemical and mechanistic principles, with examples using α-amino Grignard reagents; John Wiley and Sons: New York, 2000; pp. 139–164.
3. (a) Seebach, D. *Synthesis* **1969**, 17–36; (b) Kolb, M. In *Encylopedia of Reagents for Organic Synthesis*; Paquette, L., Ed. 2-Lithio-1,3-dithiane; John Wiley and Sons: Chichester, 1995; Vol. 5, pp. 2983–2989.
4. Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Synthesis*; VCH: Weinheim, 1997.
5. Gawley, R. E.; Zhang, Q.; McPhail, A. T. *Tetrahedron: Asymmetry* **2000**, *11*, 2093–2106.
6. (a) Colombo, L.; Di Giacomo, M.; Brusotti, G.; Delogu, G. *Tetrahedron Lett*. **1994**, *35*, 2063–2066; (b) Colombo, L.; Di Giacomo, M.; Brusotti, G.; Milano, E. *Tetrahedron Lett*. **1995**, *36*, 2863–2866; (c) Kise, N.; Urai, T.; Yoshida, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3125–3128.
7. (a) Gaul, C.; Seebach, D. *Org. Lett*. **2000**, *2*, 1501–1504; (b) Gaul, C.; Schärer, K.; Seebach, D. *J. Org. Chem*. **2001**, *66*, 3059–3073.
8. Gaul, C.; Arvidsson, P. I.; Bauer, W.; Gawley, R. E.; Seebach, D. *Chem. Eur. J*. **2001**, *7*, 4117–4125.
9. (a) Rein, K. S.; Gawley, R. E. *Tetrahedron Lett*. **1990**, *31*, 3711–3714; (b) Rein, K. S.; Gawley, R. E. *J. Org. Chem*. **1991**, *56*, 1564–1569.
10. (a) Zhang, P.; Gawley, R. E. *Tetrahedron Lett*. **1992**, *33*, 2945–2948; (b) Gawley, R. E.; Zhang, P. *J. Org. Chem*. **1996**, *61*, 8103–8112.
11. Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc*. **1991**, *113*, 1299–1308.
12. (a) Gawley, R. E.; Rein, K.; Chemburkar, S. *J. Org. Chem*. **1989**, *54*, 3002–3004; (b) Pearson, W. H.; Lindbeck, A. C. *J. Org. Chem*. **1989**, *54*, 5651–5654; (c) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc*. **1993**, *1993*, 2622–2636; (d) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc*. **1991**, *113*, 8546–8548.
13. Gawley, R. E. *Tetrahedron Lett*. **1999**, *40*, 4297–4300.
14. (a) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc*. **1993**, *115*, 11016–11017; (b) Haeffrier, F.; Sun, C.; Williard, P. G. *J. Am. Chem. Soc*. **2000**, *122*, 12542–12546.