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Two Asymmetric Syntheses of AMG 221, an Inhibitor of 11β-Hydroxysteroid Dehydrogenase Type 1

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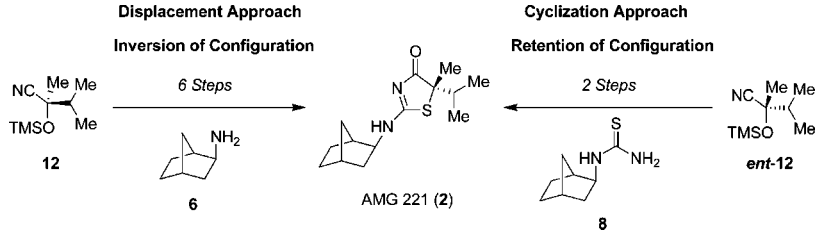

Two asymmetric syntheses of AMG 221 (**2**), an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) discovered in our laboratories, are reported. One of the syntheses utilizes chiral trimethylsilyl cyanohydrin **12** as starting material and the other utilizes its enantiomer *ent*-**12**. The displacement approach involves the conversion of **12** to **2** via a six-step sequence, occurs with net inversion of configuration, and employs amine **6** as starting material. This route features a novel approach toward chiral dialkylsubstituted α-mercaptoacids. The cyclization approach entails the synthesis of **2** from *ent*-**12** in 2 steps, takes place with net retention of configuration, and uses thiourea **8** as starting material. The final step of this route exemplifies a novel synthesis of chiral C-5 dialkylsubstituted 2-aminothiazolones from chiral α-hydroxyacids and thioureas. Insights into the mechanism of this transformation and study of the effect of the medium on the stereochemical outcome of the reaction are presented.

Introduction

The 2-aminothiazolone core structure represents a widely exploited pharmacophore in the pharmaceutical industry.[1] While the majority of biologically active 2-aminothiazolones display a C-5 alkylidene,[2] some C-5 dialkylsubstituted 2-aminothiazolones are also biologically relevant. An example of the former group of substances is 5-(2,4-dihydroxybenzylidene)-2-(phenylimino)-1,3-thiazolidin (DBPT),[3] a potential therapeutic agent for colorectal cancer (Figure 1). Herbicidal agent **1**[4] is a representative of the latter ensemble of compounds. During the course of a recent development program, we became interested in elaborating strategies for the synthesis of AMG 221 (**2**), an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) discovered in our laboratories.[5] Inhibitors of 11β-HSD1 are potential therapeutic agents for the treatment of type 2 diabetes.[6]

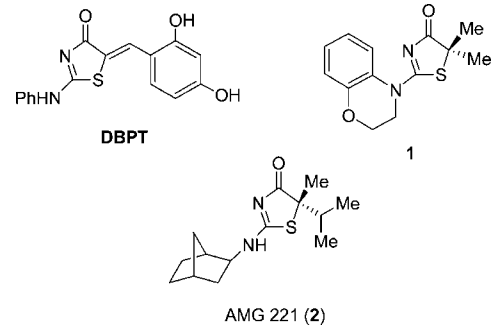

FIGURE 1. Examples of 2-aminothiazolones.

While several methods for the assembly of achiral C-5 dialkylsubstituted 2-aminothiazolones have been described, the synthesis of their chiral counterparts has received little attention. The alkylation of anions of C-5 monoalkylsubstituted 2-aminothiazolones constitutes a commonly used approach to generate C-5 dialkylsubstituted 2-aminothiazolones.[4,7] The addition of

(1) Pulici, M.; Quartieri, F. *Tetrahedron Lett.* **2005**, *46*, 2387–2391.
(2) Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175–203, and references cited therein.
(3) Teraishi, F.; Wu, S.; Zhang, L.; Guo, W.; Davis, J. J.; Dong, F.; Fang, B. *Cancer Res.* **2005**, *65*, 6380–6387.
(4) Suzuki, M.; Morita, K.; Yukioka, H.; Miki, N.; Mizutani, A. *J. Pesticide Sci.* **2003**, *28*, 37–43.
(5) Henriksson, M.; Homan, E.; Johansson, L.; Vallgarda, J.; Williams, M.; Bercot, E.; Fotsch, C. H.; Li, A.; Cai, G.; Hungate, R. W.; Yuan, C.; Tegley, C.; St. Jean, D.; Han, N.; Huang, Q.; Liu, Q.; Bartberger, M. D.; Moniz, G. A.; Frizzle, M. J. Patent WO 2005116002.
(6) Kershaw, E. E.; Morton, N. M.; Dhillon, H.; Ramage, L.; Seckl, J. R.; Flier, J. S. *Diabetes* **2005**, *54*, 1023–1031.

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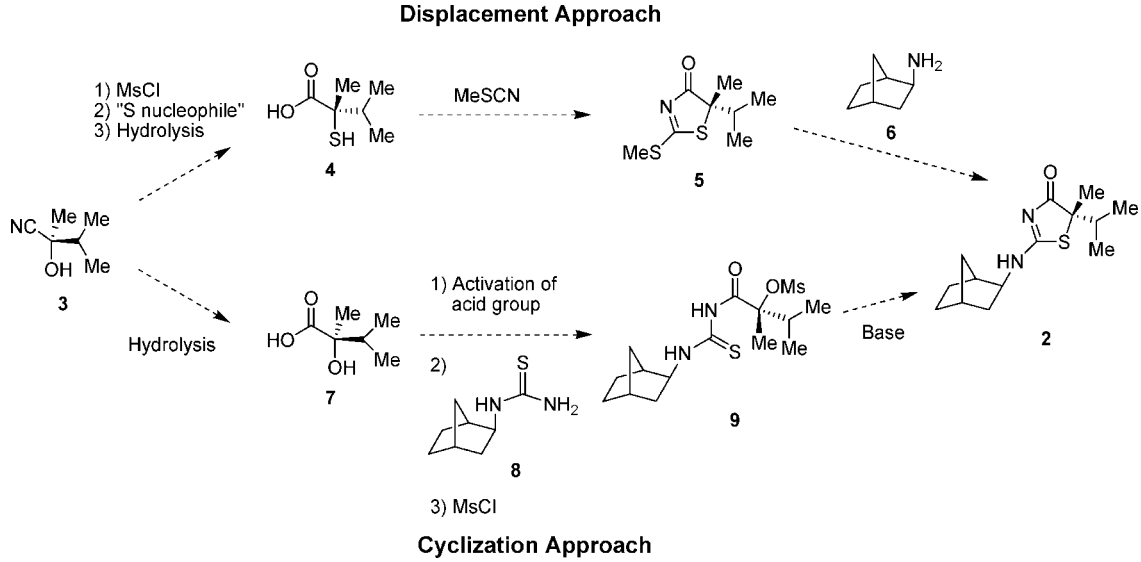
SCHEME 1. Synthetic Strategies Toward 2-Aminothiazolone 2



amines to 2-thiothiazolones has also been exploited to obtain these molecules.[8] Another method described to synthesize these compounds is the condensation of thioureas and α-haloacids or esters, though the transformation has a limited substrate scope in the case of tertiary halides.[9] Tertiary α-bromoacid bromides have been used to circumvent this problem by rendering the halogen displacement an intramolecular process.[4,10]

A flexible strategy for the synthesis of **2** in which simple chiral cyanohydrin **3** and either amine **6**[11] or thiourea **8**[11] could be utilized as starting material was contemplated (Scheme 1). In the displacement approach, the simple chiral building block **4** was expected to be obtained from chiral cyanohydrin **3** via a three-step sequence involving activation of the hydroxy group of **3** as a mesylate, S_N2 displacement using a nucleophilic sulfur reagent,[12] and hydrolysis of the nitrile function to yield the corresponding carboxylic acid **4**. 2-Thiothiazolone **5** would be generated from **4** by condensation with MeSCN.[13] Finally, AMG 221 (**2**) was proposed to be synthesized from **5** by treatment with *S*-(*exo*)-2-aminonorbornane (**6**).[8,14] In the cyclization approach, acid **7** would be produced by hydrolysis of the nitrile function of **3**. Acylthiourea **9** was projected to be generated by reaction of thiourea **8** with the acid chloride formed from **7** followed by mesylation of the tertiary alcohol group. The synthesis of **2** from **9** was predicted to have a reasonable chance of success due to the intramolecular nature of the proposed S_N2 displacement.[10]

Results

Displacement Approach. The enantioselective preparation of trimethylsilyl cyanohydrin **12** catalyzed by the aluminum chiral Salen complex **11** and *N*,*N*-dimethylaniline *N*-oxide has been reported by Feng and co-workers.[15] We elected to utilize this efficient and reliable transformation for the generation of **12** (85−92% ee, Scheme 2).[16] Unfortunately, hydrolysis of the trimethylsilylether group of **12** utilizing HCl (1 M in MeOH) or NaOH (1 M in MeOH) resulted in complete racemization and recovery of (±)-**3**. Alternatively, the treatment of **12** with 0.05 equiv of CSA in 2-methyltetrahydrofuran (2-MeTHF) permitted trimethylsilyl ether hydrolysis while maintaining configurational stability. Mesylation of the crude material (**3**) proceeded smoothly and **13** was isolated in 92% yield over the last two transformations.

Several nucleophilic sulfur reagents were surveyed to effect the S_N2 displacement of the mesylate group of **13**. The use of KSAc, *t*-BuSNa, and $EtOCS_2K$ was unsuccessful. In these cases, elimination to form the corresponding α,β-unsaturated nitrile was the dominant reaction pathway. Thioacetic acid has been reported to bring about such a transformation for a related example in the presence of 2,4,6-collidine.[17] Although these experimental conditions (AcSH, 2,4,6-collidine, toluene, 50 °C,

(7) For additional examples see: (a) St. Jean, D. J.; Yuan, C.; Bercot, E. A.; Cupples, R.; Chen, M.; Fretland, J.; Hale, C.; Hungate, R. W.; Komorowski, R.; Veniant, M.; Wang, M.; Zhang, X.; Fotsch, C. *J. Med. Chem.* **2007**, *50*, 429–432. (b) Chande, M. S.; Suryanarayan, V. *Tetrahedron Lett.* **2002**, *43*, 5173–5175.

(8) Caille, S.; Bercot, E. A.; Cui, S.; Faul, M. M. *J. Org. Chem.* **2008**, *73*, 2003–2006.

(9) The majority of examples reported involve the reaction of α-bromomalonates with thioureas. For examples see: (a) Kochikyan, T. *Synth. Commun.* **2004**, *34*, 4219–4225. (b) Hurst, D. T.; Stacey, A. D.; Nethercleft, M.; Rahim, A.; Harnden, M. R. *Aust. J. Chem.* **1988**, *41*, 1221–1229.

(10) For an additional example see: Skinner, G. S.; Elmslie, J. S.; Gabbert, J. D. *J. Am. Chem. Soc.* **1959**, *81*, 3756–3759.

(11) For synthesis of **6**, see: Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. J. *Tetrahedron Lett.* **2005**, *46*, 7831–7834. For synthesis of **8**, see ref 5. A manuscript describing the syntheses of **6** and **8** in >99% ee and >100 Kg scale is in preparation.

(12) This displacement represents a considerable synthetic challenge due to the sterically hindered nature of the stereogenic center of **3** (and of the corresponding mesylate). A suitable nucleophilic sulfur reagent for this transformation would hopefully be identified.

(13) Analogous cyclizations utilizing α-mercaptoacid derivatives and cyanamides to generate 2-aminothiazolones have been reported. For examples see: (a) Kretov, A. E.; Bespalyi, A. S. *Zh. Obshch. Khim.* **1963**, *33*, 3323–3325. (b) D'Angeli, F.; Santinello, I. *Farmaco, Ed. Sci.* **1957**, *12*, 960–968.

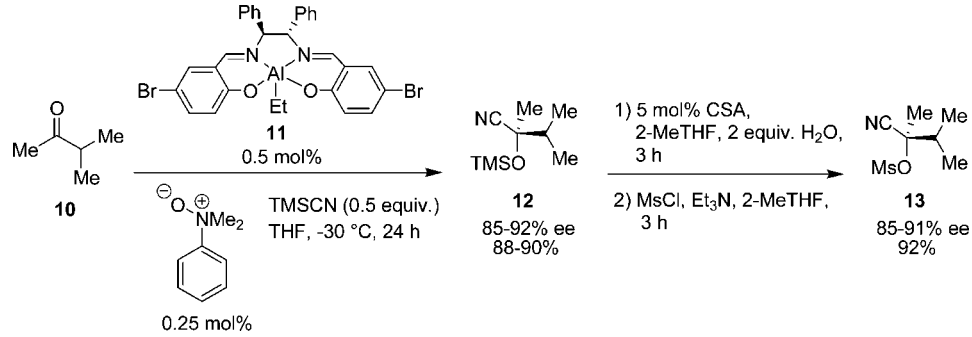
(14) Couplings of 2-thiothiazolones and amines to generate C-5 dialkylsubstituted 2-aminothiazolones are reported in ref 6. For general examples (not dialkylsubstituted substrates) see: (a) Unangst, P. C.; Connor, D. T.; Cetenko, W. A.; Sorenson, R. J.; Kostlan, C. R.; Sircar, J. C.; Wright, C. D.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1994**, *37*, 322–328. (b) Khodair, A. I. *J. Heterocycl. Chem.* **2002**, *39*, 1153–1160.

(15) Chen, F.-X.; Zhou, H.; Liu, X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. *Chem. Eur. J.* **2004**, *10*, 4790–4797.

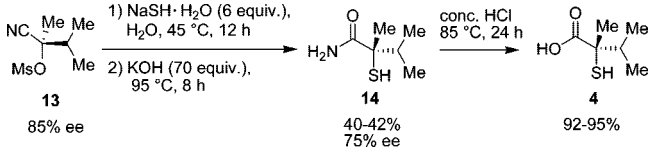
(16) Feng and co-workers utilized the chiral Salen ligand and Et_3Al as separate reagents in the reaction to generate the complex **11** in situ. We have found that complex **11** can be prepared and isolated for convenient use as a preformed catalyst.

(17) Effenberger, F.; Gaupp, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1765–1775.

SCHEME 2. Synthesis of Mesylate 13



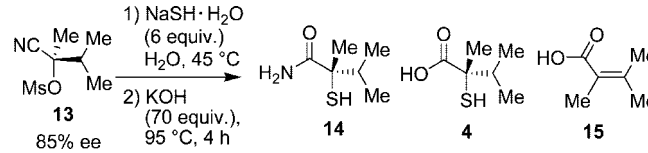
SCHEME 3. Introduction of Thiol Moiety



24 h) gave the desired thioacetate product in 35% yield (>50% of **13** unreacted), the reaction rate was too low to be practical. The desired S_N2 displacement was conducted with NaSH·H_2O[18] (6 equiv) in H_2O at 45 °C and the transformation was complete after 12 h (Scheme 3). However, the resultant thiocyanohydrin had poor stability[19] after acidification of the aqueous reaction medium (pH ∼2). Moreover, this intermediate was unstable to the acidic conditions necessary for hydrolysis of the nitrile function (concentrated HCl, 80−95 °C). These obstacles were circumvented by a stepwise hydrolysis of the nitrile group. Thus, addition of KOH (70 equiv) to the aqueous reaction mixture after completion of the displacement step (NaSH·H_2O, H_2O, 45 °C, 12 h) and aging at 95 °C for 8 h afforded amide **14** (40−42% yield, 75% ee).[20] This intermediate was isolated and treated with aqueous concentrated HCl at 85 °C for 24 h to provide carboxylic acid **4** (92−95% from **14**). It should be noted that direct hydrolysis of **14** to generate **4** under basic conditions (KOH, 95 °C) was feasible. However, this process required 72 h and produced a lower yield (20%), due to the formation of elimination product **15** (Table 1).

The erosion of chirality observed in the displacement step (85% ee to 75% ee) was studied in further detail. Toward this end the displacement step was run for 48 h. It was determined that the NaSH displacement was incomplete after 4 h at 45 °C (32% of **13** not consumed by GC) but reached completion after 10 h. The mixture was sampled at different time intervals during the experiment and the aliquots were treated with KOH at 95 °C for 4 h[21] (entries 1−6, Table 1). The percent ee values of **14** (after KOH treatment) increased during the course of the

TABLE 1. Stereoselectivity of NaSH Displacement in Buffered Reaction Media[a]



entry	time for step 1 (h)	additive for step 1	**14** (% Y)	**14** (% ee)	**4** (% Y)	**15** (% Y)
1	1	none	11	51	2	69
2	2	none	25	70	4	49
3	4	none	44	75	4	29
4	10	none	54	75	2	11
5	24	none	52	75	4	12
6	48	none	48	75	5	14
7	18	HCl	53	81	3	11
8	18	AcOH/NaOAc	51	81	3	13

[a] Reaction conditions: 20 mL of H_2O per g of **13** utilized. Assay yields determined by GC versus an authentic standard are reported.

NaSH step from 51% ee (entry 1, 1 h) to 75% ee (entry 3, 4 h and entry 4, 10 h). Moreover, the thiocyanohydrin intermediate was determined to be configurationally stable under the reaction conditions as demonstrated by the unchanged percent ee value of **14** (75%) for additional cycling times of 12 h (entry 5) or 36 h (entry 6). The pH of the NaSH aqueous solution was measured throughout the course of the reaction and determined to change from ∼11 to ∼8.5 in the first 2 h of the transformation and be constant for the remaining 10 h of the NaSH treatment. This finding led to the hypothesis that the displacement reaction was less stereoselective at higher pH (11) than at lower pH (8.5). Thus, the NaSH step was performed with either HCl (entry 7) or a AcOH/NaOAc buffer (entry 8) as additives to maintain aqueous solutions of pH ∼8.5 throughout the course of the reactions. As a result, the percent ee values of **14** were significantly improved (entry 7, 81% ee and entry 8, 81% ee).

AMG 221 (**2**) was synthesized by reaction of α-mercaptoacid **4** with MeSCN[13] (3.0 equiv) in the presence of 3 Å molecular sieves at 110 °C followed by treatment of the resultant 2-thiothiazolone **5** (Scheme 1) with *S*-(*exo*)-2-aminonorbornane (**6**, 99% ee) in MeOH (overall yield 45−47%, Scheme 4).[14,22] The absolute configuration of **2** was established using a series of single-crystal X-ray analyses[23] and consequently the absolute configurations of **4**, **12**, and **13** were determined to be as drawn.

(18) For synthesis of tertiary α-mercaptoesters from tertiary α-haloesters with NaSH·H_2O see: Itsuda, H.; Kawamura, M.; Kato, K.; Kimura, S. Patent JP 63010755.

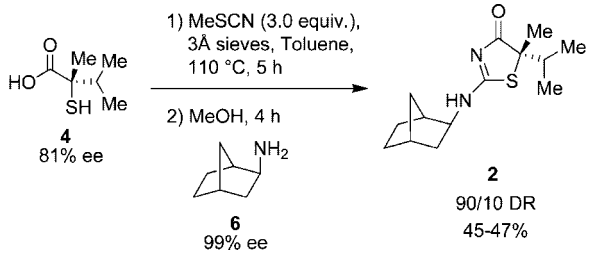
(19) Thioacetonitrile has been reported to be an unstable species, see: Gaumont, A. C.; Wazneh, L.; Denis, J. M. *Tetrahedron* **1991**, *47*, 4927–4940.

(20) A baseline separated chiral GC assay was developed for **14**. No such assay was available for **4**. It was assumed that no important change in % ee occurred going from **14** to **4**. This assumption was proven correct after synthesis of **2** from **4**. The reported yield of **14** (40−42%) includes 4−6% of **4** (if **4** is excluded the isolated yield of **14** is 34−38%) generated in the KOH step and separated by chromatography. One plausible reason for the low isolated yield of **14** is the difficulty in extracting this species from water (high water solubility, see the Experimental Section, ref 38).

(21) The aliquots were treated with KOH to generate **14** and allow for quantitative achiral and chiral analyses (GC). The assay yields of **14** were typically 10−20% higher than the corresponding isolated yields.

(22) Mixtures of **2** and its diastereomer (having the opposite absolute configuration at C-5 on the 2-aminothiazolone ring, compound **16**) of >85/15 DR could be upgraded to >99.5/0.5 DR through a single recrystallization of a mixture of the corresponding salts (made with a simple achiral acid). The complete details associated with this upgrade will be included in a separate paper, which is currently in preparation. Alternatively, the same two compounds could be separated by chiral chromatography.

SCHEME 4. Synthesis of 2 from Carboxylic Acid 4

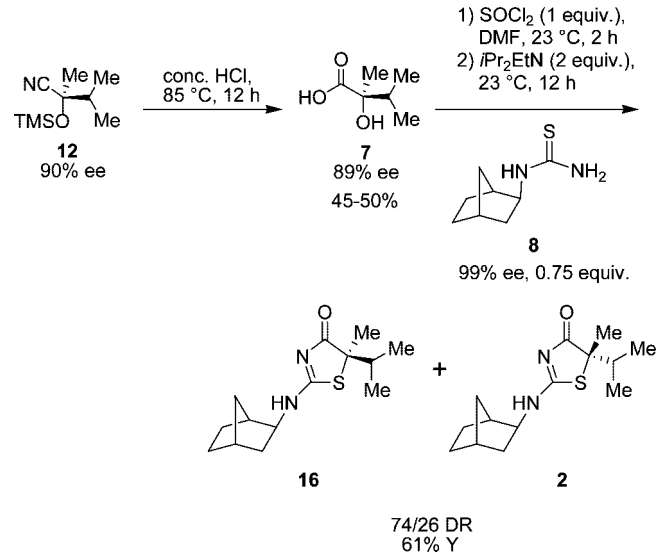


Cyclization Approach. Our study of the second proposed asymmetric approach to **2** commenced with the hydrolysis of trimethylsilyl cyanohydrin **12** utilizing aqueous concentrated HCl at 85 °C to provide **7** in a moderate 45−50% yield (Scheme 5). The absolute configuration of **7** was ascertained by single-crystal X-ray analysis of the salt produced from **7** and (*R*)-(+)-α-methylbenzylamine.[24] The synthesis of an acylthiourea product via the coupling of acid **7** and thiourea **8** (99% ee) was planned.[25,26] To achieve this purpose, **7** was treated with $SOCl_2$ in DMF for 2 h, **8** and *i*-Pr_2EtN (2 equiv) were added, and the resultant reaction mixture was aged for 12 h. Unexpectedly, this experiment directly provided 2-aminothiazolones **16** and **2** in a 61% isolated yield for both isomers and a 74/26 DR (**16/2**), along with 18% unreacted **8**. Some loss of chiral information was observed in this cyclization as the percent ee of starting material **7** was 89% (95/5 ER). Moreover, the stereochemical outcome for the major diastereomer resulted from a net retention of configuration.

The effect of the solvent utilized on the newly discovered ring formation process was examined using racemic **7**. The transformation was successful in DMF and DMAC and afforded **2/16** mixtures of 50/50 DR (entries 1 and 2, Table 2). These results excluded the possibility that the stereochemical outcome of the ring formation process is controlled by the chirality of thiourea **8** (99% ee). The reaction was unsuccessful with THF, CH_3CN, or DMSO as solvents (entries 3, 4, and 5). An experiment conducted in DMSO afforded a complex mixture of products (no **2/16** or **8**).

The transformation was explored utilizing *ent*-**7** (87% ee) as starting material while changing the α-hydroxyacid activator and tertiary amine base employed. Thionyl chloride (entry 1, 62%, Table 3) was successfully replaced with $PO(OMe)Cl_2$ (entry 3, 59%) to effect the desired transformation while the use of $SOBr_2$ (entry 2, 16%) afforded a lower assay yield of

SCHEME 5. Single Step Formation of 2-Aminothiazolones 16/2 from Acid 7

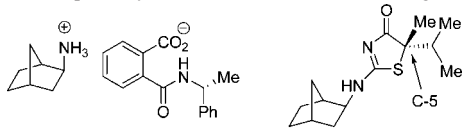


2/16 along with a complex mixture of unidentified products. Other tertiary amine bases were successfully utilized in the process to provide **2/16** in assay yields of 62% (*N*-methylmorpholine, entry 4) and 66% (Et_3N, entry 5). In these experiments, the major diastereomer produced was **2** as could be predicted from the result obtained with **7** (Scheme 5). Furthermore, the **2/16** DR range was relatively narrow (from 73/27 to 81/19) and again represented a significant loss of stereochemical information relative to *ent*-**7** (87% ee, 94/6 ER). Reaction in the absence of base led to the recovery of starting material **8** (entry 6).

In these early studies, DMF and DMAC had been the only effective solvents for the cyclization process (Table 2, vide supra). In an effort to probe the transformation in less polar media, mixtures of solvents were utilized. DMF was employed as a minor component along with THF or 2-MeTHF (Table 4). Gratifyingly, these combinations of solvents afforded **2/16** mixtures with DR values ranging from 88/12 to 91/9,[22] which represented losses of 2−5% relative to *ent*-**7** (87% ee, 94/6 ER) and constituted a marked improvement with regard to earlier results (Table 3, vide supra). The assay yields were lower than those of the same experiments performed in DMF (Table 3, entries 1 and 3). The preeminent result of this series was obtained using $PO(OMe)Cl_2$ in 25% DMF/2-MeTHF (v/v) (entry 3, 49%).

The study of the effect of the reaction medium on this transformation was further pursued. The data presented in Table 5 reflect the results of a single experiment separated into three different aliquots after the first part of the reaction (treatment of *ent*-**7** with $PO(OMe)Cl_2$ in DMF for 2 h). The aliquots were charged with the appropriate solvent, **8**, and *i*-Pr_2EtN, and stirred for an additional 12 h. The measured erosion of chirality correlated well with the polarity of the solvent utilized in the second part of the experiment; the more polar solvent (DMSO, entry 3) afforded a 68/32 mixture of stereoisomers and the least polar solvent (2-MeTHF, entry 1) provided a 84/16 mixture of stereoisomers. From these results it can be concluded that the erosion of chirality in the first part of the experiment is minimal (no greater than 88/12 ER (77% ee) *ent*-**7** to 84/16 DR **2/16**) and that the polarity of the medium in the second part of the experiment influences the stereochemical outcome of the reaction in a significant manner. The reaction conditions

(23) The absolute configuration of amine **6** was ascertained using single-crystal X-ray analysis of the phthalamic acid salt presented below, prepared from **6** and a phthalamic acid derivative of known absolute configuration (*R*). **2** was synthesized from **6** and the absolute configuration of **2** at C-5 was thus determined by single-crystal X-ray analysis of **2**. For this last analysis, although the angles refine to 90°, the data show that the crystal is truly monoclinic, with the *R*(int) for the orthorhombic system of 0.47 and that of the other two monoclinic systems 0.509 and 0.519, respectively, with the correct monoclinic setting value of 0.020.



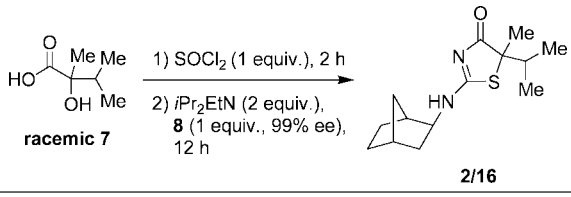
2

(24) This salt has been synthesized before (Mori, K.; Ebata, T.; Takechi, S. *Tetrahedron* **1984**, *40*, 1761–1766.) but no single-crystal X-ray analysis was performed. The DR of the salt was upgraded to 98.3/1.7 by recrystallization (twice hexanes/IPA and once THF) prior to single-crystal X-ray analysis.

(25) For an example of such a coupling, see: Sun, C.; Zhang, X.; Huang, H.; Zhou, P. *Bioorg. Med. Chem.* **2006**, *14*, 8574–8581.

(26) **8** was generated from **6**, thus establishing its absolute configuration.

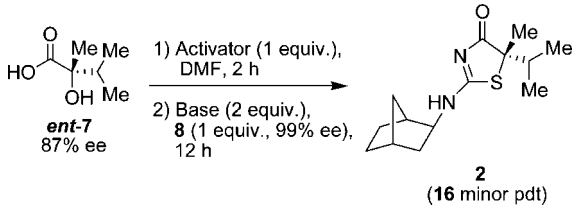
TABLE 2. Solvent Screen in Formation of 2/16 from Racemic 7[a]



entry	solvent	**8** (%)	**2/16** (%)	DR
1	DMF	15	62[b]	50/50
2	DMAC	21	55[c]	50/50
3	THF	88	0	NA
4	CH_3CN	91	0	NA
5	DMSO	0	0	NA

[a] Reaction conditions: 10 mL of solvent per g of **7** utilized. Both parts of the experiments ran at 23 °C. [b] Isolated yield. [c] Assay yield determined by HPLC versus an authentic standard.

TABLE 3. Activator and Base Screen in Formation of 2/16 from *ent*-7[a]



entry	activator	base	**2/16** (%)	DR
1	$SOCl_2$	iPr_2EtN	62[b]	80/20
2	$SOBr_2$	iPr_2EtN	16[c]	73/27
3	$PO(OMe)Cl_2$	iPr_2EtN	59[b]	79/21
4	$SOCl_2$	*N*-methylmorpholine	62[c]	79/21
5	$SOCl_2$	Et_3N	66[c]	81/19
6	$SOCl_2$	none	0	NA

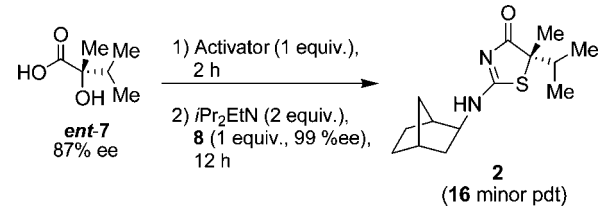
[a] Reaction conditions: 10 mL of DMF per g of *ent*-**7** utilized. Both parts of the experiments ran at 23 °C. [b] Isolated yield. [c] Assay yield determined by HPLC versus an authentic standard.

described in entry 1 represent the optimized procedure to synthesize **2** from *ent*-**7**.

Efforts were directed at clarifying the mechanism of the 2-aminothiazolone formation process. Toward this end, racemic **7**[27] was treated with $SOCl_2$ [or $PO(OMe)Cl_2$][28] in DMF at 23 °C. Addition of excess 2-MeTHF to the reaction mixture resulted in the precipitation of intermediate **17**,[29] as depicted in Scheme 6. The white solid (**17**) was also produced by addition of racemic **7** to a pre-stirred solution of $SOCl_2$ in DMF (23 °C, 2 h), aging of the resultant mixture for 2.5 h, and addition of antisolvent (2-MeTHF). The structure of **17** was determined utilizing a series of NMR experiments (^{13}C, COSY, HSQC, HMBC, $^{1}H-^{15}N$ HMBC).[30] The chloride content of the salt was measured to be 13 wt % by $AgNO_3$ titration (theoretical 15 wt %). Racemic salt **17** was subjected to the reaction conditions employed in the second part of the cyclization transformation [iPr_2EtN (2 equiv), HCl (1 M solution in Et_2O, 1 equiv), **8** (0.5 equiv, 99% ee) in DMF] and 2-aminothiazolones **2** and **16** were obtained as major products albeit in moderate yield (46% for both isomers).

The observed stereochemical outcome of the cyclization (see Tables 4 and 5, vide supra) was of net retention of configuration. We intended to probe this result further by performing the cyclization with a different leaving group than that employed thus far. To this end, mesylate **18** was synthesized via the route detailed in Scheme 7. The carboxylic acid function of *ent*-**7**

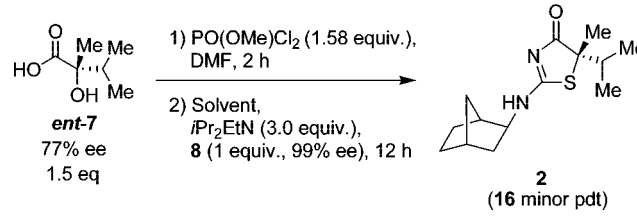
TABLE 4. Solvent Mixture Screen in Formation of 2/16 from *ent*-7[a]



entry	reagent	solvents (v/v)	**2/16** (%)	DR
1	$SOCl_2$	25% DMF/2-MeTHF	31	88/12
2	$PO(OMe)Cl_2$	25% DMF/THF	47	89/11
3	$PO(OMe)Cl_2$	25% DMF/2-MeTHF	49	91/9

[a] Reaction conditions: 10 mL of solvent per g of *ent*-**7** utilized. Both parts of the experiments ran at 23 °C. Assay yields determined by HPLC versus an authentic standard are reported.

TABLE 5. Effect of Solvent Polarity in Formation of 2/16 from *ent*-7[a]



entry	solvent	dielectric constant (ε_r)	**2/16** (%)	DR
1	2-MeTHF	7.0	73[b]	84/16
2	acetone	21.0	63[c]	77/23
3	DMSO	47.2	78[c]	68/32

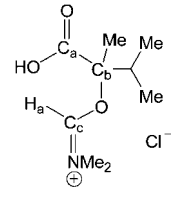
[a] Reaction conditions: 7.5 mL of DMF and 22.5 mL of other solvent used per g of *ent*-**7**. Both parts of the experiments ran at 23 °C. [b] Isolated yield. [c] Assay yield determined by HPLC versus an authentic standard.

(27) Racemic **7** was employed for this mechanistic study due to the availability of the starting material.

(28) Intermediate **17** was generated and observed by ^{1}H NMR in DMF-d_7 by treatment of **7** with both $SOCl_2$ and $PO(OMe)Cl_2$. However, when $PO(OMe)Cl_2$ was utilized the isolation of **17** as a solid from the reaction mixture was complicated by the presence of an additional phosphorus species [PO(OMe)O-HCl] and the solid obtained could not be filtered easily.

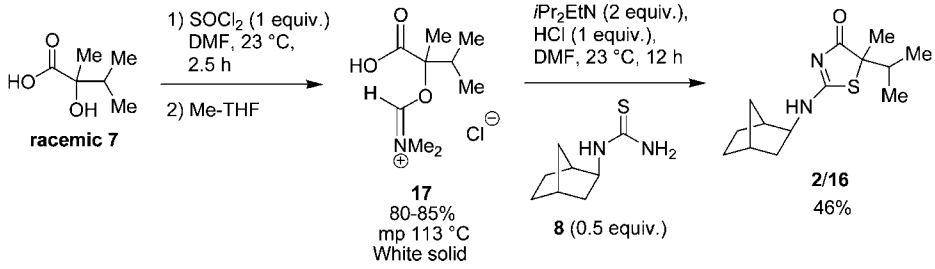
(29) Alkoxyiminium ions have been synthesized from DMF. For examples see: Barluenga, J.; Campos, P. J.; Gonzalez-Nunez, E.; Asensio, G. *Synthesis* **1985**, 426–428. Sforza, S.; Dossena, A.; Corradini, R.; Virgili, E.; Marchelli, R. *Tetrahedron Lett.* **1998**, *39*, 711–714. Dimethyl substituted alkoxyiminium ions have been utilized as leaving groups. For examples see: Hanessian, S.; Plessas, N. R. *Chem. Commun.* **1967**, *22*, 1152–1155. Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Koike, N.; Procopiou, P. A. *J. Org. Chem.* **1998**, *63*, 6273–6280.

(30) The $^{1}H-^{13}C$ HMBC displays a 3-bond correlation between H_a and C_b but not between H_a and C_a. The chemical shift of H_a is 9.08 ppm and that of C_c is 167.5 ppm. These NMR experiments were performed with a 600 MHz instrument equipped with a cryoprobe. Additionally, an HRMS was obtained for salt **17** (organic portion) and the salt was acidic on litmus test (MeOH solution).

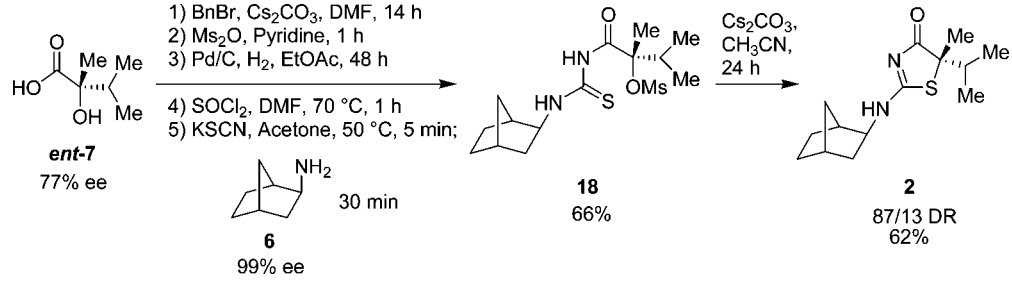


17

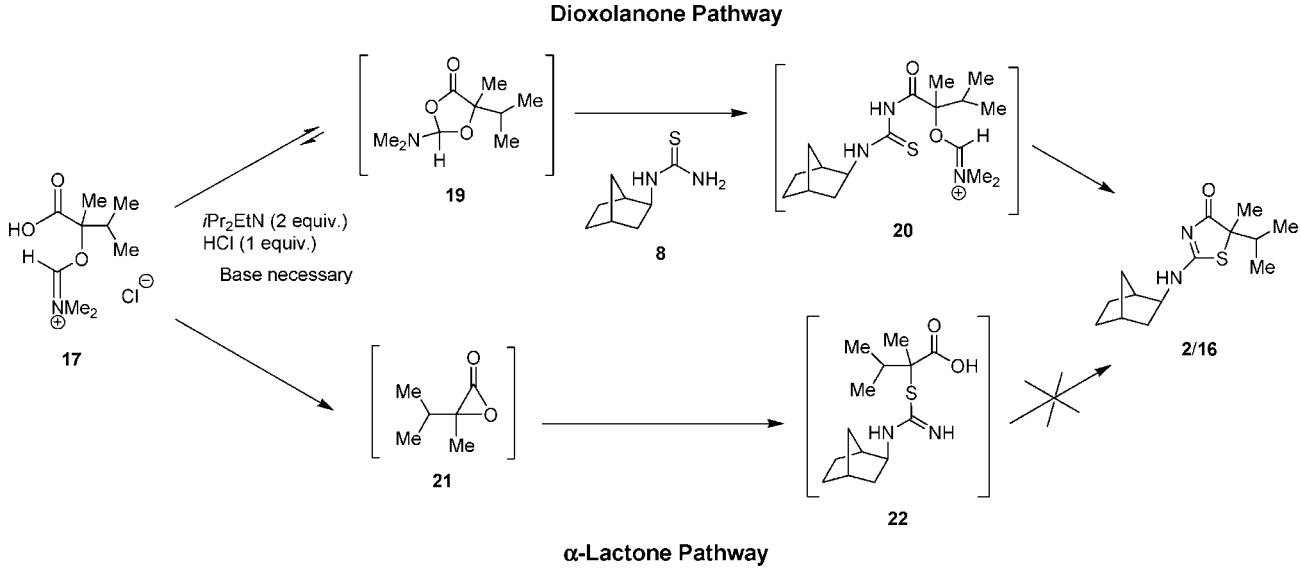
SCHEME 6. Formation of 2/16 from Racemic 7 via Chloride Salt 17



SCHEME 7. Synthesis of 2/16 via Mesylate 18



SCHEME 8. Mechanistic Proposal for Conversion of Salt 17 to 2/16

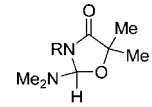


was benzylated (BnBr, Cs_2CO_3) and the tertiary alcohol was derivatized as a mesylate utilizing Ms_2O and pyridine. Following hydrogenolysis of the benzyl ester linkage, acyl thiourea **18** was obtained by sequential treatment of the resultant carboxylic acid with $SOCl_2$, KSCN, and **6** (66% yield from *ent*-**7**). This isolated intermediate (**18**) was reacted with Cs_2CO_3 to afford **2** (62%). The loss of stereochemical information observed in this series of reactions was minimal [77% ee (89/11 ER) *ent*-**7** to 87/13 DR **2/16**] and a net retention of configuration was observed.

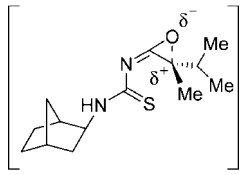
Discussion

A mechanistic proposal for the transformation of racemic salt **17** into **2/16** is presented in Scheme 8 (dioxolanone pathway). In this mechanism, dioxolanone **19**[31] is produced by deprotonation of the carboxylic acid function of **17** with *i*Pr_2EtN followed by 5-membered ring formation. As described in Table 3, in the absence of a tertiary amine base the reaction did not proceed and **8** remained unreacted. This result may be explained by the failure of **19** to form without base. The carbonyl group of **19** is susceptible to nucleophilic attack by **8** to give rise to intermediate **20**. A species having the molecular weight (340) of intermediate **20** was observed by mass spectroscopy (chemical ionization) upon reaction of **17** with **8** in the presence of *i*Pr_2EtN (2 equiv) but in the absence of HCl, thereby lending further evidence for this mechanistic explanation.[32] One possible alternative mechanism to explain the conversion of **17** to **2/16**

(31) Aza analogues of proposed intermediate **19** have been generated employing DMF and isolated, see: (a) Cavicchioni, G.; D'Angeli, F.; Casolari, A.; Orlandini, P. *Synthesis* **1988**, *94*, 7–950. (b) Scrimin, P.; D'angeli, F.; Veronese, A. C.; Baioni, V. *Tetrahedron Lett.* **1983**, *24*, 4473–4476.



R = Me, Bn, *t*Bu



23

FIGURE 2. Proposed epoxy-imine intermediate **23**.

is also depicted in Scheme 8 (α-lactone pathway) and involves the intermediacy of α-lactone[33] **21**. Although it is conceivable that carboxylic acid **22** would be generated via this mechanism, the condensation reaction necessary to produce **2/16** typically occurs at 80−90 °C and not 23 °C.[34] Moreover, this mechanism does not account for the observation of a 340 amu intermediate by mass spectroscopy. Therefore, this second mechanism is not considered to be a likely pathway to generate **2/16** from **17**.

Considering the data presented in Table 4 (vide supra) and Scheme 7, a common stereochemical outcome for these transformations was observed. This result was independent of the nature of the leaving group utilized for these two examples. A single intermediate is put forward in Figure 2 to account for these results. The observed stereochemical outcome of net retention can be rationalized by a double inversion mechanism proceeding via epoxy-imine intermediate **23**,[35] which is disposed toward internal attack of the pendant thiourea moiety. The covalent character of the epoxide C−O bond in **23** may depend on the polarity of the medium employed (Tables 4 and 5). More polar solvents are expected to better solvate the C^+ and O^- charges and cause **23** to possess a less covalent C−O bond. This weaker C−O bond would facilitate rotation around the epoxide C−C bond before the cyclization of **23** to form **2** and result in greater loss of stereochemical information.

Both routes to AMG 221 (**2**) described here exemplify novel approaches to chiral C-5 dialkylsubstituted 2-aminothiazolones. Clearly, the linear sequence from ketone **10** to 2-aminothiazolone **2** is shorter in the case of the cyclization approach (3 steps) than in the case of the displacement approach (7 steps), which represents a substantial advantage for application on large scale.

Summary

Asymmetric strategies to synthesize AMG 221 (**2**) from either amine *S*-**6** or thiourea *S*-**8** have been described. In the displacement approach, trimethylsilyl cyanohydrin **12** and amine **6** were utilized as chiral starting materials and **2** was generated in six linear steps with a net inversion of configuration relative to building block **12**. This route features a novel approach toward chiral dialkylsubstituted α-mercaptoacids. The enantiomer of **12** (*ent*-**12**) as well as thiourea **8** were employed as chiral starting materials in the cyclization approach. Two linear steps were necessary to synthesize **2** from *ent*-**12** and a net retention of configuration was observed. The final reaction of this sequence represents a novel one-step synthesis of a chiral C-5 dialkyl-substituted 2-aminothiazolone from a chiral dialkylsubstituted α-hydroxyacid and a thiourea occurring with minimal loss of stereochemical information when an adequate reaction medium is utilized. Insights into the mechanism of this transformation, including the structure determination of intermediate **17**, were also provided.

Experimental Section

Aluminum Complex 11.[36] $AlEt_3$ (2.0 M in hexanes, 2.5 mL, 0.005 mol) was slowly added via syringe to a solution of 2-((*E*)-((1*S*,2*S*)-2-((*E*)-5-bromo-2-hydroxybenzylideneamino)-1,2-diphenylethylimino)methyl)-4-bromophenol (2.9 g, 0.005 mol) in THF (10 mL) under an atmosphere of nitrogen. Gas evolution was observed, a yellow precipitate formed, and the reaction was exothermic. The mixture was cooled to 23 °C and heptane was added (20 mL). The suspension was stirred for 15 min, filtered, and the solid was washed with hexanes (15 mL) to afford 2.75 g (87%) of **11** as a yellow powder. Decomposition temperature ∼280 °C. ^{1}H NMR [400 MHz, $(CD_3)_2NCDO$)] δ 8.43 (s, 1 H), 8.08 (s, 1 H), 7.30−7.65 (m, 14 H), 6.80−6.88 (m, 2 H), 5.49 (d, 1 H, J = 12 Hz), 5.40 (d, 1H, J = 12 Hz), 0.87 (s, 3 H, J = 8 Hz), −0.05−0.20 (m, 2H); ^{13}C NMR [100 MHz, $(CD_3)_2NCDO$] δ 172.0, 165.9, 165.7, 165.1, 162.5, 138.9, 138.9, 138.1, 136.2, 136.1, 134.4, 130.5, 129.6, 129.5, 129.4, 128.8, 123.9, 123.7, 121.4, 121.1, 107.0, 106.4, 72.0, 70.8, 10.1, 3.8 (br signal); IR (neat) 2850, 1625, 1535, 1462, 1378, 1311, 1183, 829, 780, 697 cm^{-1}; exact mass $[C_{30}H_{25}AlBr_2N_2O_2 + H]^+$ calcd 631.0176, measured 631.0157.

(*R*)-2,3-Dimethyl-2-(trimethylsilyloxy)butanenitrile (12). TMSCN (28.8 g, 0.29 mol) and *N*,*N*-dimethylaniline oxide (0.2 g, 0.0015 mol) were dissolved in THF (75 mL) and the resultant solution was stirred for 1 h at 23 °C under an atmosphere of nitrogen. 3-Methylbutan-2-one (50.0 g, 0.58 mol) was added via syringe and the mixture was cooled to −30 °C. Complex **11** (1.82 g, 0.0029 mol) was added and the reaction mixture was stirred for 24 h. The mixture was warmed to 23 °C and filtered. The filtrate was concentrated (30 mmHg) and the residue was distilled under reduced pressure (30 mmHg, 80 °C) to yield 47.2 g (88%) of **12** (85% ee) as an oil. Chiral GC analysis: Cyclosil-B, 30 m × 250 μm × 0.25 μm, 1 μL injection, 2.2 mL/min, 21.5 psi, 50 to 51 °C over 25 min, FID detector, **12** at 23.6 min, *ent*-**12** at 23.9 min. $[\alpha]^{23}_D$ +12.2 (*c* 2.10, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (septet, 1 H, J = 4 Hz), 1.53 (s, 3 H), 1.04 (d, 3 H, J = 4 Hz), 1.02 (d, 3 H, J = 4 Hz), 0.25 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.5, 73.4, 39.1, 26.0, 17.1, 16.9, 1.15; IR (neat) 2969, 1375, 1254, 1160, 991, 841, 755 cm^{-1}; exact mass $[C_9H_{19}NOSi + Na]^+$ calcd 208.1128, measured 208.1130.

(*R*)-2-Cyano-3-methylbutan-2-ylmethanesulfonate (13). 12 (11.0 g, 0.059 mol, 85% ee) was dissolved in 2-MeTHF (110 mL) under an atmosphere of nitrogen at 23 °C. Water (4.4 mL) and CSA (0.68 g, 0.00295 mol) were added and the solution was stirred for 3 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (100 mL), the phases were separated, and the aqueous phase was extracted with 2-MeTHF (2 × 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and

(32) This species was converted to **2** and **16** by chromatography on silica gel or treatment with 1 M HCl in THF.

(33) For evidence of an α-lactone intermediate, see: Pirrung, M. C.; Brown, W. L. *J. Am. Chem. Soc.* **1990**, *112*, 6388–6389. For addition of a nucleophile to an α-lactone intermediate, see: Adam, W.; Alzerreca, A.; Liu, J.-C.; Yany, F. *J. Am. Chem. Soc.* **1977**, *99*, 5768–5773.

(34) For examples see: (a) St. Jean, D. J.; Yuan, C.; Bercot, E. A.; Cupples, R.; Chen, M.; Fretland, J.; Hale, C.; Hungate, R. W.; Komorowski, R.; Veniant, M.; Wang, M.; Zhang, X.; Fotsch, C. *J. Med. Chem.* **2007**, *50*, 429–432. (b) Leite, A. C. L.; Lima, R. S.; Moreira, D. R.; Cardoso, M. V.; Brito, A. C. G.; Santos, L. M. F.; Hernandes, M. Z.; Kiperstok, A. C.; Lima, R. S.; Soares, M. B. P. *Bioorg. Med. Chem.* **2006**, *14*, 3749–3757.

(35) For a proposed epoxy-imine intermediate, see: Cohen, A. D.; Showalter, B. M.; Toscano, J. P. *Org. Lett.* **2004**, *6*, 401–403. For an isolated epoxy-imine intermediate, see: Ziegler, E.; Kollenz, G.; Ott, W. *Justus Liebigs Ann. Chem.* **1976**, *11*, 2071–2082.

(36) Complex *ent*-**11** was synthesized utilizing an identical procedure and the opposite enantiomer of the chiral Salen ligand.

(37) We have encountered difficulties with regard to the completion of the subsequent mesylation reaction when the residue did not remain under high vacuum (∼1 mmHg) for the described amount of time (12 h). If any problem is encountered with completion of the mesylation, the cyanohydrin intermediate can be distilled (20 mmHg, 110 °C). We have utilized this alternative procedure and it resolved any issues observed with completion of the mesylation reaction.

concentrated under reduced pressure (~1 mmHg for 12 h).[37] The residue was dissolved in 2-MeTHF (100 mL) under an atmosphere of nitrogen at 23 °C. Et_3N (12.34 mL, 0.088 mol) and MsCl (6.78 mL, 0.088 mol) were added via syringes and the reaction mixture was stirred for 3 h. The reaction was exothermic and precipitates were formed. The mixture was treated with saturated aqueous $NaHCO_3$ (100 mL), the phases were separated, and the aqueous phase was extracted with 2-MeTHF (3 × 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatographic purification (70 g silica gel, 10−30% EtOAc/hexanes) of the residual material yielded 10.36 g (92%) of **13** (85% ee) as an oil. Chiral GC analysis: Cyclosil-B, 30 m × 250 μm × 0.25 μm, 1 μL injection, 2.2 mL/min, 29.3 psi, 150 to 180 °C over 20 min, FID detector, **13** at 11.5 min, enantiomer of **13** at 11.8 min. $[\alpha]^{23}_D$ +15.0 (*c* 1.25, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 3 H), 2.24 (septet, 1 H, *J* = 8 Hz), 1.89 (s, 3 H), 1.14 (t, 6 H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.7, 82.6, 39.7, 37.8, 23.1, 16.7, 16.6; IR (neat) 2979, 1466, 1358, 1180, 1048, 901, 805 cm^{-1}; exact mass $[C_7H_{13}NO_3S + Na]^+$ calcd 214.0508, measured 214.0510.

(*S*)-2-Mercapto-2,3-dimethylbutanoic Acid (4). $NaSH \cdot H_2O$ (23.2 g, 0.314 mol) was dissolved in water (200 mL) and the solution was warmed to 45 °C under an atmosphere of nitrogen. The pH of the aqueous solution was adjusted to 8.7 by addition of 1.2 mL of aqueous concentrated HCl. **13** (10.0 g, 0.052 mol, 85% ee) was added via pipet and the reaction mixture was stirred for 24 h. To the resultant solution was added KOH (200 g, 3.57 mol) as a solid and the mixture was warmed to 95 °C. The solution was stirred for 10 h and cooled to 23 °C. The mixture was chilled (0 °C) and aqueous concentrated HCl (~400 mL) was added via pipet until the pH of the aqueous mixture was ~2. The internal temperature of the aqueous mixture during this process was kept under 40 °C. The heterogeneous mixture was diluted with 200 mL of water (all salts were solubilized) and extracted using IPAC (3 × 500 mL).[38] The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatographic purification (40 g silica gel, 5−60% EtOAc/hexanes) of the residue yielded 2.54 g (33%) of **14** (81% ee) and 0.38 g (5%) of **4**.[39] Chiral GC analysis of **14**: Cyclosil-B, 30 m × 250 μm × 0.25 μm, 1 μL injection, 2.2 mL/min, 29.3 psi, 150 to 180 °C over 20 min, FID detector, **14** at 12.3 min, enantiomer of **14** at 12.5 min. Amide **14** (2.5 g, 0.017 mol) was dissolved in aqueous concentrated HCl (36 mL) and the resultant mixture was warmed to 85 °C under an atmosphere of nitrogen. The mixture was stirred for 24 h, cooled to 23 °C, and extracted using IPAC (3 × 100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatographic purification (15 g silica gel, 10−20% EtOAc/hexanes) of the residual material yielded 2.32 g (92% from **14**) of **4** as a solid. Mp 78−80 °C; $[\alpha]^{23}_D$ +3.2 (*c* 2.60, $CDCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (septet, 1 H, *J* = 4 Hz), 2.22 (s, 1 H), 1.43 (s, 3 H), 1.09 (d, 3 H, *J* = 4 Hz), 0.98 (d, 3 H, *J* = 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 53.9, 36.4, 20.2, 18.2, 17.3; IR (neat) 2968, 2877, 1693, 1404, 1276, 1110, 925 cm^{-1}; exact mass $[C_6H_{12}O_2S + Na]^+$ calcd 171.0450, measured 171.0449.

2-Aminothiazolones 2/16. 4 (1.1 g, 0.0073 mol, 81% ee) was dissolved in toluene (11 mL) under an atmosphere of nitrogen. Activated 3A sieves (5.5 g) and MeSCN (1.5 mL, 0.022 mol) were added and the resultant mixture was warmed to 110 °C. The mixture was stirred for 5 h and cooled to 23 °C. The mixture was treated with saturated aqueous $NaHCO_3$ (20 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatographic purification (10 g silica gel, 10−20% EtOAc/hexanes) of the residual material yielded **5**. This material was dissolved in MeOH (11 mL) and **6** (1.22 g, 0.011 mol, 99% ee) was added under an atmosphere of nitrogen. The solution was stirred for 4 h at 23 °C and concentrated. Chromatographic purification (10 g silica gel, 10−40% EtOAc/hexanes) of the residue yielded 0.87 g (45%) of a **2/16** mixture (90.1/9.9) as a solid. Chiral HPLC analysis: OD-H column, 250 mm × 4.6 mm, 5 μm; 1.5 mL/min; 5 μL; 25 °C; 0.025% diethylamine/6% ethanol/94% hexane, isocratic; **16** at 4.34 min, **2** at 6.85 min. ^{1}H NMR (400 MHz, $CDCl_3$, 90.15/9.85 mixture of diastereomers, signals for the major diastereomer) δ 3.33−3.40 (m, 1 H), 2.36−2.45 (m, 2 H), 2.21 (septet, 1 H, *J* = 8 Hz), 1.84−1.91 (m, 1 H), 1.60−1.83 (m, 1 H), 1.42−1.68 (m, 3 H), 1.62 (s, 3 H), 1.13−1.30 (m, 4 H), 1.05 (d, 3 H, *J* = 8 Hz), 0.90 (d, 3 H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 90.15/9.85 mixture of diastereomers, signals for the major diastereomer) δ 191.1, 180.9, 70.9, 59.5, 43.0, 38.5, 35.9, 35.7, 35.6, 28.2, 26.6, 25.6, 19.0, 18.4; IR (neat) 3168, 2959, 2869, 1696, 1585, 1440, 1327, 1256, 1090, 1017, 829 cm^{-1}; exact mass $[C_{14}H_{22}N_2OS + H]^+$ calcd 267.1526, measured 267.1525.

(*S*)-2,3-Dimethyl-2-(trimethylsilyloxy)butanenitrile (*ent*-12). The procedure is identical with that used for the synthesis of **12** except that catalyst *ent*-**11** was utilized. Chiral GC analysis for *ent*-**12** (87% ee): Cyclosil-B, 30 m × 250 μm × 0.25 μm, 1 μL injection, 2.2 mL/min, 21.5 psi, 50 to 51 °C over 25 min, FID detector, **12** at 23.4 min, *ent*-**12** at 24.0 min. $[\alpha]^{23}_D$ −12.13 (*c* 1.70, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (septet, 1 H, *J* = 4 Hz), 1.53 (s, 3 H), 1.04 (d, 3 H, *J* = 4 Hz), 1.02 (d, 3 H, *J* = 4 Hz), 0.25 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.5, 73.4, 39.1, 26.0, 17.1, 16.9, 1.15; IR (neat) 2969, 1375, 1254, 1160, 992, 841, 755 cm^{-1}; exact mass $[C_9H_{19}NOSi + Na]^+$ calcd 208.1128, measured 208.1129.

(*S*)-2-Hydroxy-2,3-dimethylbutanoic Acid (*ent*-7). Aqueous concentrated HCl (60 mL) was warmed to 85 °C under an atmosphere of nitrogen. *ent*-**12** (5.0 g, 0.027 mol, 87% ee) was added and the mixture was stirred for 16 h. The solution was cooled to 23 °C and extracted using IPAC (3 × 75 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatographic purification (30 g silica gel, 10−50% EtOAc/hexanes) of the residual material yielded 1.61 g (45%) of *ent*-**7** (87% ee) as a solid. The chiral GC analysis was performed using the corresponding ethyl ester:[40] Cyclosil-B, 30 m × 250 μm × 0.25 μm, 1 μL injection, 2.8 mL/min, 28.2 psi, 80 to 105 °C over 17 min, FID detector, ethyl ester of **7** at 6.52 min, ethyl ester of *ent*-**7** at 6.60 min. Mp 47−49 °C; $[\alpha]^{23}_D$ +5.70 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (septet, 1 H, *J* = 8 Hz), 1.44 (s, 3 H), 1.00 (d, 3 H, *J* = 8 Hz), 0.93 (d, 3 H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 77.1, 35.5, 23.3, 17.2, 15.8; IR (neat) 3433, 2973, 2882, 1725, 1460, 1377, 1247, 1164, 1120, 1045, 948, 855, 737 cm^{-1}; exact mass $[C_6H_{12}O_3 + Na]^+$ calcd 155.0678, measured 155.0679.

2-Aminothiazolones 2/16. *ent*-**7** (1.0 g, 0.0076 mol, 77% ee)[41] was dissolved in DMF (7.5 mL) under an atmosphere of nitrogen. $PO(OMe)Cl_2$ (0.96 mL, 0.0081 mol, 85% pure) was added via syringe and the solution was stirred at 23 °C for 2 h. The reaction mixture was divided into three equal portions (~2.5 mL) and one of the portions was diluted with 2-MeTHF (7.5 mL) under an atmosphere of nitrogen. **8** (0.29 g, 0.0017 mol, 99% ee) and *i*Pr_2EtN (0.87 mL, 0.005 mol) were immediately added (**8** as a solid and *i*Pr_2EtN via syringe) and the resultant mixture was stirred for 12 h at 23 °C. The mixture was treated with saturated aqueous $NaHCO_3$ (15 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under

(38) A fourth extraction with IPAC still yielded ~4% of **14**. This finding supports the hypothesis that the low isolated yield in this step is in part due to the water solubility of **14**.

(39) The yield of **4** was calculated using ^{1}H NMR integration ratios obtained from a mixture of **4** and **15**. The chromatographic separation of **4** and acid **15** is very challenging.

(40) This ester was synthesized from **7** utilizing the following reaction conditions: EtI, K_2CO_3, DMF.

(41) This lot of *ent*-**7** was of 77% ee. The difference in % ee relative with the previous lot (87% ee) arose in the formation of *ent*-**12**.

reduced pressure. Chromatographic purification (5 g silica gel, 10−30% EtOAc/hexanes) of the residual material yielded 0.33 g (73%) of a **2/16** mixture (84/16) as a solid. Chiral HPLC analysis: OD-H column, 250 mm × 4.6 mm, 5 μm; 1.5 mL/min; 5 μL; 25 °C; 0.025% diethylamine/6% ethanol/94% hexane, isocratic; **16** at 4.45 min, **2** at 5.99 min.[42] ^{1}H NMR (400 MHz, $CDCl_3$, 84/16 mixture of diastereomers, signals for the major diastereomer) δ 3.33−3.40 (m, 1 H), 2.36−2.45 (m, 2 H), 2.21 (septet, 1 H, J = 8 Hz), 1.84−1.91 (m, 1 H), 1.60−1.83 (m, 1 H), 1.42−1.68 (m, 3 H), 1.62 (s, 3 H), 1.13−1.30 (m, 4 H), 1.05 (d, 3 H, J = 8 Hz), 0.90 (d, 3 H, J = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 84/16 mixture of diastereomers, signals for the major diastereomer) δ 191.1, 180.9, 70.9, 59.5, 43.0, 38.5, 35.9, 35.7, 35.6, 28.2, 26.6, 25.6, 19.0, 18.4; IR (neat) 3168, 2957, 1696, 1587, 1440, 1327, 1256, 1090, 1017, 834 cm^{-1}; exact mass $[C_{14}H_{22}N_2OS + H]^+$ calcd 267.1526, measured 267.1524.

Racemic Alkoxyiminium Salt 17. Racemic **7**[43] (0.5 g, 0.0037 mol) was dissolved in DMF (5 mL) under an atmosphere of nitrogen. $SOCl_2$ (0.28 mL, 0.0039 mol) was added via syringe and the solution was stirred at 23 °C for 2.5 h. 2-MeTHF (50 mL) was added and the suspension was filtered. The solid was rinsed with 2-MeTHF (10 mL) and dried on the filter cake for 2 h to afford 0.66−0.70 g (80−85%) of racemic **17** as a white solid. Mp 112−114 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 9.08 (s, 1 H), 3.42 (br s, 6 H), 2.34 (septet, 1 H, J = 8 Hz), 1.83 (s, 3 H), 1.13 (d, 3 H, J = 8 Hz), 1.06 (d, 3 H, J = 8 Hz); ^{13}C NMR (150 MHz, CD_3OD) δ 173.6, 167.5, 95.0, 39.3 (broad signal), 36.7, 21.4, 17.8, 16.2. As detailed in footnote 25, the ^{1}H−^{13}C HMBC displays a 3-bond correlation between H_a and C_b but not between H_a and C_a. IR (neat) 2974, 2353, 1690, 1245, 1123 cm^{-1}; exact mass (organic portion) $[C_9H_{18}NO_3]^+$ calcd 188.1281, measured 188.1282. **17** was acidic when tested on litmus as a MeOH solution. Chloride content of **17** (theory 15 wt %) was measured by $AgNO_3$ titration in MeOH/H_2O (Titroline instrument): 13 wt %.

2-Aminothiazolones 2/16. Racemic **17** (0.6 g, 0.0027 mol) was dissolved in DMF (7.0 mL) under an atmosphere of nitrogen. **8** (0.23 g, 0.00135 mol, 99% ee), *i*Pr_2EtN (0.94 mL, 0.0054 mol), and HCl (2.7 mL, 0.0027 mol, 1 M solution in Et_2O) were added (**8** as a solid, *i*Pr_2EtN and HCl via syringes) and the solution was stirred at 23 °C for 12 h. The mixture was treated with saturated aqueous $NaHCO_3$ (20 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatographic purification (10 g silica gel, 10−40% EtOAc/hexanes) of the residual material yielded 0.17 g (46%) of a **2/16** mixture (50/50) as a solid. Chiral HPLC analysis: OD-H column, 250 mm × 4.6 mm, 5 μm; 1.5 mL/min; 5 μL; 25 °C; 0.025% diethylamine/6% ethanol/94% hexane, isocratic; **16** at 4.34 min, **2** at 6.85 min. ^{1}H NMR (400 MHz, $CDCl_3$, 50/50 mixture of diastereomers, signals for both diastereomers) δ 9.60−10.03 (br s, 1 H), 3.33−3.39 (m, 1 H), 2.32−2.48 (m, 2 H), 2.18−2.24 (m, 1 H), 1.86−1.97 (m, 1 H), 1.73−1.82 (m, 1 H), 1.45−1.68 (m, 6 H), 1.10−1.29 (m, 3 H), 1.00−1.07 (m, 3 H), 0.85−0.94 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 50/50 mixture of diastereomers, signals for both diastereomers) δ 191.0, 190.9, 181.0, 70.7, 70.6, 59.6, 59.5, 42.9, 42.7, 38.4, 38.3, 35.9, 35.9, 35.7, 35.6, 35.6, 35.5, 28.2, 26.6, 26.5, 25.6, 18.9, 18.3.

Mesylate 18. *ent*-**7** (1.98 g, 0.015 mol, 77% ee)[41] was dissolved in MeOH (28 mL) and water (5.6 mL) under an atmosphere of nitrogen. Cs_2CO_3 (2.44 g, 0.0075 mol) was added as a solid, the reaction mixture was stirred for 0.5 h at 23 °C, and the solvents were evaporated under reduced pressure. The residue was dissolved in DMF (22.5 mL) and BnBr (1.9 mL, 0.0158 mol) was added via syringe. The reaction mixture was stirred for 14 h at 23 °C. EtOAc (80 mL) and water (50 mL) were added and the phases were separated. The organic phase was washed with brine (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residual material was dissolved in pyridine (15 mL) and the resultant solution was cooled to 0 °C under an atmosphere of nitrogen. DMAP (185 mg, 0.0015 mol) was added as a solid. A CH_2Cl_2 (20 mL) solution of Ms_2O (4.0 g, 0.023 mol) was added via syringe over a period of 20 min. The mixture was warmed to 23 °C and stirred for 1 h. CH_2Cl_2 (100 mL) and water (50 mL) were added and the phases were separated. The organic phase was washed with aqueous 1 M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in 200 mL of 30% EtOAc/hexanes, the resultant solution was filtered through 20 g of silica gel, and the solvents were evaporated under reduced pressure. The residual material was dissolved in EtOAc (50 mL) and Pd/C (237 mg, 10 wt %, 0.00023 mol) was added as a solid. The reaction mixture was stirred under 1 atm of H_2 at 23 °C for 48 h. The mixture was filtered through Celite and the Celite pad was rinsed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure to afford 2.6 g of the crude carboxylic acid−mesylate intermediate as a white solid. An analytically pure sample of this material was obtained by recrystallization from hexanes. Mp 45−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 1 H), 3.14 (s, 3 H), 2.17 (m, 1 H), 1.80 (s, 3 H), 1.04 (d, 3 H, J = 4 Hz), 1.00 (d, 3 H, J = 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.92, 91.19, 40.36, 36.75, 19.45, 16.83, 15.59; IR (neat) 2974, 2884, 2556, 1707, 1330, 1173, 905, 552 cm^{-1}; exact mass $[C_7H_{14}O_5S - CH_4O_3S]^+$ calcd 114.0681, measured 114.0682. $SOCl_2$ (3.6 mL, 0.049 mol) and DMF (0.1 mL) were added via syringes to the crude carboxylic acid−mesylate under an atmosphere of nitrogen. The reaction mixture was warmed to 70 °C, stirred for 1 h at that temperature, cooled to 23 °C, and concentrated under reduced pressure. The residual material was dissolved in acetone (25 mL) and the resultant solution was cooled to 0 °C under an atmosphere of nitrogen. KSCN (1.31 g, 0.0135 mol) was added as a solid. The mixture was warmed to 50 °C and stirred for 5 min at that temperature. The reaction mixture was cooled to 23 °C and a solution of **6** (1.36 g, 0.0123 mol, 99% ee) in acetone (9 mL) was added via syringe over a period of 20 min. The mixture was warmed to 50 °C and stirred at that temperature for 30 min. The suspension was cooled to 23 °C, filtered through Celite, and the Celite pad was rinsed with EtOAc (20 mL). The filtrate was concentrated under reduced pressure. Flash chromatography (20 g silica gel, 0−40% EtOAc/hexanes) of the residue afforded 3.64 g (66% from *ent*-**7**) of **18** (mixture of diastereomers) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 10.17 (br s, 1 H), 8.78 (br s, 1 H), 4.08 (m, 1 H), 3.19 (s, 3 H), 2.45 (m, 1 H), 2.35 (m, 1 H), 2.20 (m, 1 H), 1.92 (m, 1 H), 1.83 (s, 3 H), 1.57 (m, 1 H), 1.53 (m, 1 H), 1.40 (m, 2 H), 1.29 (m, 2 H), 1.20 (m, 1 H), 1.05 (d, 3 H, J = 4 Hz), 0.98 (d, 3 H, J = 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 177.32, 171.19, 93.31, 59.15, 41.78, 40.86, 39.95, 36.71, 36.02, 35.93, 28.16, 26.35, 17.79, 16.99, 16.64; IR (neat) 3318, 2960, 1685, 1525, 1352, 1209, 897, 521 cm^{-1}; exact mass $[C_{15}H_{26}N_2O_4S_2 + H]^+$ calcd 363.1412, measured 363.1407.

2-Aminothiazolones 2/16. 18 (73 mg, 0.0002 mol) was dissolved in MeCN (1 mL) under an atmosphere of nitrogen and Cs_2CO_3 (98 mg, 0.0003 mol) was added as a solid. The mixture was stirred at 23 °C for 24 h, filtered through Celite, and the Celite pad was rinsed with EtOAc (5 mL). The filtrate was concentrated under reduced pressure. Flash chromatography (4 g silica gel, 5−30% acetone/hexanes) yielded 33 mg (62% from **18**) of a **2/16** mixture (87/13) as a solid. Chiral HPLC analysis: OD-H column, 250 mm × 4.6 mm, 5 μm; 1.5 mL/min; 5 μL; 25 °C; 0.025% diethylamine/6% ethanol/94% hexane, isocratic; **16** at 4.35 min, **2** at 6.84 min. ^{1}H NMR (400 MHz, $CDCl_3$, 90.15/9.85 mixture of diastereomers,

(42) The retention times of **2** and **16** were slightly shifted in this trace relative to other data. The identity of the peaks was confirmed employing a 50/50 mixture of **2/16**.

(43) Racemic **7** was prepared according to the procedure described in the following report: Mori, K.; Ebata, T.; Takechi, S. *Tetrahedron* **1984**, *40*, 1761–1766.

signals for the major diastereomer) δ 3.33−3.40 (m, 1 H), 2.36−2.45 (m, 2 H), 2.21 (septet, 1 H, $J = 8$ Hz), 1.84−1.91 (m, 1 H), 1.60−1.83 (m, 1 H), 1.42−1.68 (m, 3 H), 1.62 (s, 3 H), 1.13−1.30 (m, 4 H), 1.05 (d, 3 H, $J = 8$ Hz), 0.90 (d, 3 H, $J = 8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 90.15/9.85 mixture of diastereomers, signals for the major diastereomer) δ 191.1, 180.9, 70.9, 59.5, 43.0, 38.5, 35.9, 35.7, 35.6, 28.2, 26.6, 25.6, 19.0, 18.4; IR (neat) 3168, 2959, 2869, 1696, 1585, 1440, 1327, 1256, 1090, 1017, 829 cm^{-1}; exact mass $[C_{14}H_{22}N_2OS + H]^+$ calcd 267.1526, measured 267.1525.

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Supporting Information Available: Copies of ^{1}H, ^{13}C, COSY, HMQC, HMBC, and ^{1}H−^{15}N HMBC NMR spectra along with crystallographic information files (CIFs). This material is available free of charge via the Internet at http://pubs.acs.org.

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