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Asymmetric Induction of the Iodolactonization Reaction of α-Sulfurated γ-Unsaturated Amides

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The 1,3-asymmetric iodolactonization reaction of enantiopure α-sulfurated γ-unsaturated amides has been investigated. With sulfinyl and sulfonyl groups, a poorly stereoselective reaction was observed, whereas with a sulfanyl moiety, the diastereoselectivity can be high as 96:4. The role of the oxygen atom on the sulfur moiety is discussed.

Introduction

The iodolactonization is a useful reaction[1] to prepare cyclic compounds from γ-unsaturated carboxylic acids,[2] esters,[3] or amides.[4] When these compounds are substituted in the α position, a high 1,3-asymmetric induction is usually observed: trans selectivity with amides in contrast with cis selectivity with acids. Various substituents have been studied: alkyl,[5] oxygenated,[3] and halogenated[6] functions, amino groups,[7] and phosphonate.[8] Surprisingly, the cyclization of sulfurated amides (with an unsubstituted double bond) has not been studied.[9] The stereocontrolled iodocyclization has been successfully investigated using an amide bearing a chiral auxiliary on the nitrogen atom[10] or a chiral primary amine as a ligand.[11]

Here, we report a novel example of the 1,3-asymmetric iodolactonization of α-sulfurated γ-unsaturated amides: enantiopure sulfinyl **4b**, sulfanyl **4a**, and sulfonyl **4c**.

Results and Discussion

Recently, we have disclosed an efficient asymmetric synthesis of α-sulfinyl γ-unsaturated amide **4b** (or its enantiomer) from cyclohexyl thiol and a very cheap chiral auxiliary: diacetone-D-glucose (Scheme 1).[12] This synthesis was carried out in five steps and 40% overall yield. The thioamide **3** was obtained by an asymmetric thio-Claisen rearrangement of the (*Z*)-ketene aminothioacetal **2** directed by the cyclohexylsulfinyl group with both absolute and relative stereocontrol (Scheme 1). The substrate for the rearrangement was easily obtained by deprotonation of (*R*)-**1** with *t*-BuLi and subsequent allylation of the resulting enethiolate at the sulfur atom by allyl bromide. The rearrangement of this compound[13] into (*SS*,2*S*)-**3** was improved using $CeCl_3$ as a catalyst at room temperature: an excellent diastereomeric ratio of 97:3 (99:1 after recrystallization), an enantiomeric excess of 96%, and a yield of 83% were obtained.[14] Then, this thioamide **3** was selectively converted to the corresponding amide **4b** with an oxidizing agent, dimethyldioxirane,[15] formed in situ from oxone, acetone, and $NaHCO_3$. The oxidation of the sulfoxide and the double bond can be avoided by slow addition of oxone and by monitoring the conversion of **3** by ^1H NMR.

The iodolactonization[16] was tested first on the enantiopure sulfoxide **4b** (Scheme 2 and Table 1).

Using standard conditions, THF−H_2O−iodine (entry 1, Table 1), a mixture of two products was isolated: 3-(*R*)-cyclohexane-sulfinyl-5-iodomethylfuran-2(5*H*)-one **6b** and iodohydrin **7b** in 60 and 38% yields, respectively.

* Corresponding author.

(1) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681−13736.

(2) For a recent example: Wang, M.-X.; Zhao, S.-M. *Tetrahedron: Asymmetry* **2002**, *13*, 1695−1702.

(3) For a recent example: Macritchie, J. A.; Peakman, T. M.; Silcock, A.; Willis, C. L. *Tetrahedron Lett.* **1998**, *39*, 7415−7418.

(4) For a recent example: Rozner, E.; Liu, Y. *Org. Lett.* **2003**, *5*, 181−184.

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(8) (a) Lee, C. W.; Gil, J. M.; Oh, D. Y. *Heterocycles* **1997**, *45*, 943−948. (b) Zhao, Y.; Pei, C.; Wong, Z.; Xi, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *66*, 115−125.

(9) An example with a phenylsulfonyl group has been described, but the stereochemistry of the lactone was not mentioned: Lee, J. W.; Oh, D. Y. *Heterocycles* **1990**, *31*, 1417−1421. Lee, J. W.; Jung, J. H.; Oh, D. Y. *Bull. Korean Chem. Soc.* **1994**, *15*, 842−845.

(10) Moon, H.-S.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 6504−6505.

(11) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297−300.

(12) Nowaczyk, S.; Alayrac, C.; Reboul, V.; Metzner, P.; Averbuch-Pouchot, M.-T. *J. Org. Chem.* **2001**, *66*, 7841−7848.

(13) It is also possible to carry out this reaction without isolation of **2**.

(14) On a large scale and in the absence of $CeCl_3$: 80% yield and 90:10 dr.

(15) Mukaiyama, T.; Uchiro, H.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1990**, 1019−1022.

(16) Dr was measured before purification, as epimerization on the asymmetric center in position 3 easily takes place on silica gel.

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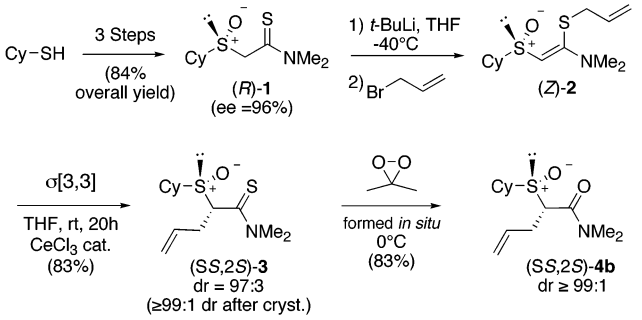
TABLE 1. Results of the Iodolactonization Reaction of Amides 4a, 4b and 4c

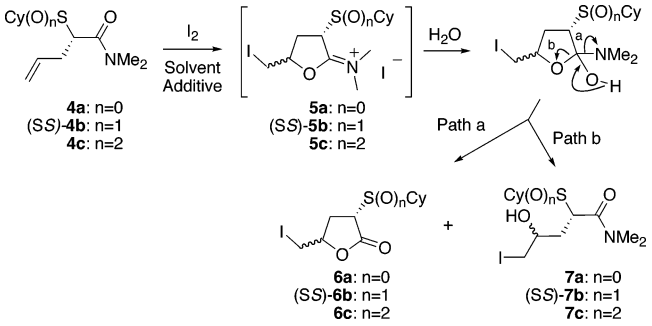
entry	amide	solvents/additive	temp, time	lactone **6** % yield[e] (trans:cis[f])		iodohydrin **7** % yield[e] (dr[f])	
1	**4b**	THF:H_2O[a]/none	rt, 1 h	**6b**	60 (72:28)	**7b**	38 (79:21)
2		CH_3CN:H_2O[a]/none	rt, 4 h		60 (81:19)		36 (81:19)
3		DME:H_2O[a]/none	rt, 1 h		62 (76:24)		36 (76:24)
4		THF:H_2O[a]/$NaHCO_3$	rt, 24 h		39 (79:21)		61 (60:40)
5		THF:H_2O[a]/HCl	rt, 1 h		66 (82:18)		31 (72:28)
6		THF:H_2O:MeOH[b]/none	rt, 1 h		53 (75:25)		34 (78:22)
7		THF:H_2O:MeOH[b]/HCl[c]	rt, 1 h		66 (84:16)		19 (68:32)
8		THF:H_2O:MeOH[b]/HCl[c]	−23 °C, 20 h		69 (85:15)		25 (76:24)
9		THF:H_2O[a]/$CuCl_2$[d]	rt, 1 h		60 (77:23)		37 (77:23)
10		THF:H_2O[a]/$CuCl_2$[d]	rt, 1 h		65 (72:28)		21 (73:27)
11	**4a**	THF:H_2O[a]/none	rt, 0.75 h	**6a**	96 (94:06)		
12		CH_3CN:H_2O[a]/none	rt, 24 h		78 (95:05)		
13		DME:H_2O[a]/none	rt, 0.75 h		89 (94:06)		
14		THF:H_2O[a]/none	−23 °C, 2 h		98 (95:05)		
15		THF:H_2O[a]/$NaHCO_3$	rt, 0.75 h		82 (94:06)		
16		THF:H_2O:MeOH[b]/HCl[c]	−23 °C, 17 h		93 (94:06)		
17	**4c**	THF:H_2O[a]/none	rt, 0.75 h	**6c**	80 (62:38)		

[a] Solvent/water = 8:1. [b] THF/water/MeOH = 8:1:1. [c] HCl: 2.5 equiv. [d] $CuCl_2$: 0.5 or 1 equiv. [e] Isolated yield. [f] Determined by ^1H NMR on the crude product.

SCHEME 1. Thio-Claisen Transposition



SCHEME 2. Iodolactonization



Moreover, these two compounds were formed in a mixture of trans and cis isomers in the respective ratios of 72:28 and 79:21. These results were similar in DME−H_2O and CH_3CN−H_2O (entries 2 and 3). As these ratios were similar, these two compounds should have the same precursor, the imidate **5b**, which can be hydrolyzed according to two different pathways (Scheme 2: pathway a or b).

We have been surprised by the low diastereoselectivity and the formation of the iodohydrin **7b**. This compound was usually obtained during the hydrolysis of the supposed iodoimidate salt **5b** under basic conditions.[17] However, the reaction performed with $NaHCO_3$ (entry 4) was not selective and a mixture of **6b** and **7b** was still obtained.[18] On the other hand, the hydrolysis of the iodoimidate at pH < 7 is known to facilitate the lactone formation. Thus, in the presence of 2.5 equiv of HCl (entry 5), the yield of lactone **6b** (66%) and the diastereoselectivity (82:18) were improved but the iodohydrin was still present.[18] To facilitate the hydrolysis of imidate[19] **5b**, the reaction was performed in the presence of MeOH (entry 6). Again, a similar result was obtained. However, the combination of MeOH and HCl (entries 7 and 8) afforded the best result in terms of yield and diastereoselectivity: 69% and 85:15 dr at low temperature (−23 °C).[18]

It is interesting to note that the sulfinyl group enhances the reaction rate: only 1 h instead of more than 24 h is required in most cases.

To confirm the absolute configuration of the new stereogenic center of **6b**, the mixture of *trans*- and *cis*-lactone was desulfinylated by mild reduction[20] in the presence of SmI_2−THF−HMPA. The resulting lactone was analyzed by enantioselective HPLC (Daicel AD column). By comparison with an enantiopure sample of the (*R*)-lactone,[21] we were able to assign the (*R*) configuration to the major trans isomer of **6b**.

According to the literature, whatever the substituent in α position of the amide is, the 1,3-chirality transfer has been always very efficient due to a favored transition state, avoiding $A_{1,3}$ interactions between the 2-substituent and the imidate function (Scheme 3).[22] Thus, the

(17) (a) Maligres, P. E.; Weissman, S. A.; Upadhyay, V.; Cianciosi, S. J.; Reamar, R. A.; Purick, R. M.; Sager, J.; Rossen, K.; Eng, K. K.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1996**, *52*, 3327−3338. (b) LeBlond, C. R.; Rossen, K.; Gortsema, F. P.; Zavialov, I. A.; Cianciosi, S. J.; Andrews, A. T.; Sun, Y. *Tetrahedron Lett.* **2001**, *42*, 8603−8606.

(18) In these conditions, some variation of dr between the lactone and the iodohydrin was observed (Table 1; entries 4, 5, 7, and 8) without any rational explanation.

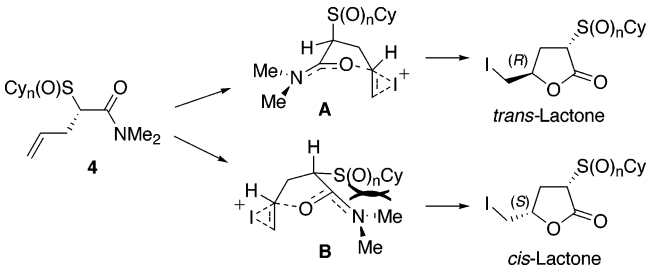
(19) Kantlehner, W.; Gutbrod, H.-D. *Liebigs Ann. Chem.* **1980**, 1677−1688.

(20) Handa, Y.; Inanaga, J.; Yamaguchi-ku, M. *J. Chem. Soc., Chem. Commun.* **1989**, 298−299.

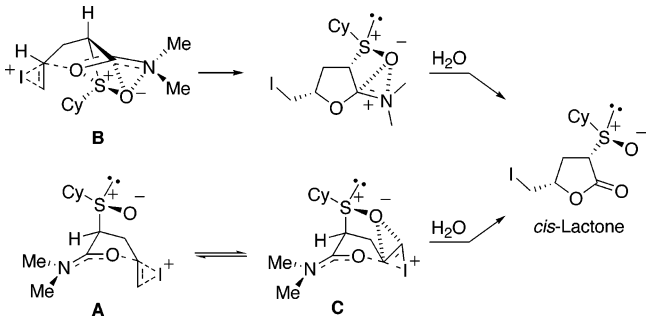
(21) Prepared from (*R*)-dihydro-5-(hydroxymethyl)-2(*3H*)-furanone by iodation: Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456−2466.

(22) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079−1085.

SCHEME 3. Origin of Diastereoselectivity



SCHEME 4. Interactions with Sulfinyl Amide Derivative



model **A**, where the substituent is located at the pseudoaxial position, is sterically favored in comparison to the model **B**, where the substituent is oriented at the pseudoequatorial position. Consequently, the *trans*-lactone is often the only isolated product.

To explain the moderate selectivity that we have observed in the sulfinyl series, we suggest a strong electrostatic attraction between the polarized S−O bond and the amide dipole (N^+=C−O^-) stabilizing the transition state **B** (Scheme 4). A similar observation has already been made with a α-phosphorylated amide.[23]

A stabilization between the oxygen atom of the sulfinyl group and the iodonium could also be proposed,[24] as suggested in a similar case with an α-amino[25] or an α-hydroxylated[26] starting material. Thus, the model **C**, a conformer of model **A**, could also explain the formation of the *cis*-lactone.

To decrease this interaction, we tried to use copper salts, which are known to complex the oxygen atom of the sulfinyl group.[27] Unfortunately, with $CuCl_2$ or other salts[28] (entries 9 and 10), comparable results were obtained.

We have also investigated steric effects of the amide function. The *N*,*N*-diethyl and *N*,*N*-diisopropyl derivatives (**8b** and **9b**) have been synthesized using the same strategy as in Scheme 1 (Figure 1). However, with **8b** as starting material, the diastereoselectivity and the chemoselectivity were not improved. Surprisingly, neither lactone **6b** nor the corresponding iodohydrin was observed with the amide **9b**, which was not recovered in the crude.

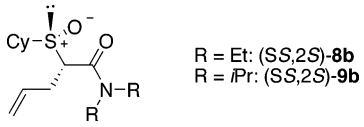
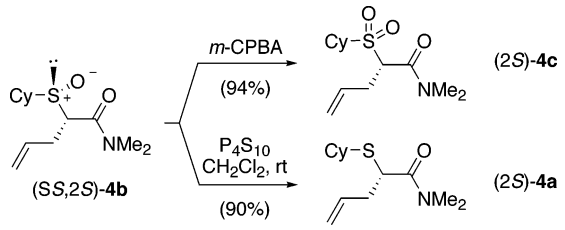


FIGURE 1. Amides **8b** and **9b**.

SCHEME 5. Synthesis of Amides 4a and 4c



To remove the presumed interactions (models **B** and **C**), we modified the sulfur moiety. We performed the iodolactonization reaction with the α-sulfanyl γ-unsaturated amide **4a** and the α-sulfonyl γ-unsaturated amide **4c**.

The amide **4a** was selectively obtained by reduction of **4b** in the presence[29] of P_4S_{10} in 90% yield, and the oxidation of **4b** by *m*-CPBA gave access to amide **4c** (Scheme 5).

Whatever the solvent used (THF, CH_3CN, or DME), without additive, the iodolactonization of **4a** at room temperature afforded the desired lactone **6a** (entries 11−13) in almost quantitative yield and, as expected, with an excellent diastereomeric ratio of 94:6.[30] This ratio was not dependent upon the temperature reaction (entry 14). Addition of $NaHCO_3$ or HCl to the reaction (entries 15−16) did not either affect this ratio. The two diastereisomers were easily separated by chromatography on silica gel. Moreover, as this reaction was highly selective, we decided to characterize the intermediate, the cyclic imidate salt **5a**, by ^1H and ^{13}C NMR analysis. For this purpose, the reaction was performed in an aprotic solvent, $CDCl_3$, in the NMR tube.[31]

When the amide **4c** was used (entry 17) and under standard conditions, a mixture of trans and cis isomers of 3-cyclohexanesulfonyl-5-iodomethylfuran-2(5*H*)-one **6c** was obtained in a modest ratio of 62:38 and in 80% yield. As expected, the interaction described above (between the oxygen atom of the sulfone and the iodonium or the imidate functions) could also explain this modest selectivity.

On the other hand, surprisingly, the iodohydrins **7a** and **7c** were not detected in the crude product. Although we have not been able to obtain clear evidence for the high selectivity so far, we suggest a competition of the two reactions when the sulfinyl amide **4b** was used: the classical iodolactonization reaction between the amide

(23) In this case, the imidate salt was not hydrolyzed by water. See ref 8b.

(24) This model was suggested by one of the three reviewers.

(25) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1985**, *26*, 5307−5308. See also ref 7a.

(26) Chamberlin, A. R.; Dezube, M.; Dussault, P., McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819−5825. Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672−677.

(27) Kagan, H. B.; Ronan, B. *Rev. Heteroatom Chem.* **1992**, *7*, 92−116.

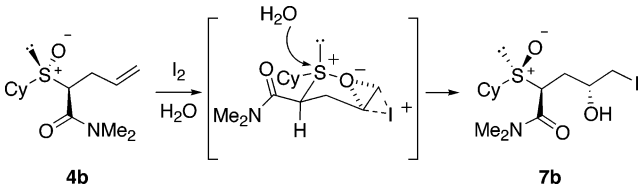
(28) Other copper salts have been studied without noticeable improvement: $CuSO_4$, $Cu(OAc)_2$, or $Cu(NO_3)_2$.

(29) Still, I. W. J.; Hasan, S. K.; Turnbull, K. *Synthesis* **1977**, 468−469.

(30) Trans:cis assignments were determined by comparison of ^1H NMR spectra of lactone **6a**, obtained by lactonization of **4a**, and **6a** obtained by reduction (P_4S_{10}) of **6b**.

(31) Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, *33*, 1299−1302.

SCHEME 6. Iodohydrin Formation with Inversion of Configuration on Sulfur



function and the double bond, but also the intramolecular nucleophilic attack by the sulfinyl group of iodonium ion followed by hydrolysis through attack of water on sulfur atom (Scheme 6).[32] Moreover, the postulated intermediate could be also stabilized by the above-mentioned interaction between the oxygen atom of the sulfinyl and the iodonium.

Conclusion

In conclusion, the influence of a sulfur substituent on the selectivity of the iodolactonization is demonstrated. Whereas the sulfinyl and sulfonyl groups were not efficient, an excellent 1,3-induction has been obtained with an α-sulfanylamide function (dr up to 96:4). We now envisage applying this methodology to the total synthesis of natural lactones bis-lactones such as iso-avenaciolide or ethisolide[33] from lactone **6b**.

Experimental Section

(*S*)-2-Cyclohexylsulfinyl-1-(*N*,*N*-dimethylamino)-1-(prop-2-enylsulfanyl)-(*Z*)-ethene (2). To a solution of thioamide (*R*)-**1** (11 g, 47 mmol) in THF (140 mL) was slowly added a 1.6 M solution of *t*-BuLi in pentane (32.5 mL, 52 mmol) at −40 °C. The reaction mixture was stirred at −40 °C for 1 h, and then allyl bromide (5.3 mL, 61.1 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 1.5 h. Then, the reaction mixture was cooled before the hydrolysis (50 mL). The aqueous layer was acidified with diluted sulfuric acid (5%) and extracted with dichloromethane (3 x 150 mL); the combined organic layers were washed with saturated aqueous NaCl (150 mL), dried over $MgSO_4$, and then concentrated to obtain keteneaminothioacetal **2** as a colorless oil, $R_f = 0.03$ (EtOAc). ^{1}H NMR characteristic signals ($CDCl_3$, 250 MHz) δ 2.99 (s, 6H), 5.17 (s, 1H). This compound was immediadely used for the next step without any purification.

(S*S*,2*S*)-2-Cyclohexylsulfinyl-*N*,*N*-dimethylpent-4-enethioamide (3). $CeCl_3$ (1.17 g, 4.7 mmol) was added to a stirred solution of (*Z*)-**2** (12.83 g, 47 mmol) in THF (350 mL) at room temperature. The reaction was monitored by TLC. After 17 h, the reaction mixture was hydrolyzed with a solution of saturated $NaHCO_3$ (200 mL) and extracted with dichloromethane (3 x 150 mL). Then, the organic layers were washed with a solution of saturated $NaHCO_3$ (2 x 200 mL) and saturated aqueous NaCl (200 mL), dried over $MgSO_4$, and concentrated to dryness to afford the crude thioamide. The diastereomeric ratio was determined by ^{1}H NMR analysis: (S*S*,2*S*):(S*S*,2*R*) = 97:3. Chromatography on silica gel (EtOAc; $R_f = 0.29$) afforded **3** (10.7 g, 39 mmol) in 83% yield. After crystallization from EtOAc−petroleum ether 9:1, (S*S*,2*S*)-**3** (8.5 g, 31 mmol) in 66% yield was isolated. Yellow solid: mp 76 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15−1.99 (m, 10H), 2.83 (tt, $J = 3.9$ Hz, $J = 12.1$ Hz, 1H), 3.06−3.12 (m, 2H), 3.37 (s, 3H), 3.49 (s, 3H), 4.13 (dd, $J = 5.7$ Hz, $J = 9.1$ Hz, 1H), 5.08−5.27 (m, 2H), 5.71−5.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.4, 25.3, 25.4, 26.0, 28.5, 36.6, 42.1, 44.0, 54.4, 68, 119.4, 132.7, 196.6; IR (KBr) ν 3072, 2930−2854, 1518, 1450−1434, 1394, 1266, 1140, 1036, 916 cm^{-1}; MS (70 eV, EI) *m*/*z* (%) 274 (MH^+, 1), 247 (2), 190 (1), 108 (21), 83 (56), 55 (100), 45 (42); Anal. Calcd for $C_{13}H_{23}NOS_2$: C, 57.12; H, 8.49; N, 5.13; O, 5.86; S, 23.41. Found: C, 56.99; H, 8.55; N, 5.18; O, 6.03; S, 23.35.

(*S*)-2-Cyclohexylsulfanyl-*N*,*N*-dimethylpent-4-enamide (4a). P_4S_{10} (2.65 g, 5.06 mmol) was added slowly to a stirred solution of (S*S*,2*S*)-**4b** (dr 99:1, 3.04 g, 11.80 mmol) in dichloromethane (95 mL) at room temperature. The reaction was monitored by TLC. After 45 min, the dichloromethane layer was filtered through a pad of Celite; the crude was washed with dichloromethane, and then the filtrate was placed in a separatory funnel. The organic layer was washed with water 2x and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2; $R_f = 0.37$) to afford **4a** (2.52 g, 10.46 mmol) as a yellow oil in 90% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10−2.20 (m, 10H), 2.41−2.54 (m, 1H), 2.89−2.78 (m, 2H), 2.99 (s, 3H), 3.13 (s, 3H), 3.57 (dd, $J = 6.1$ Hz, $J = 8.8$ Hz, 1H), 5.03−5.15 (m, 2H), 5.78−5.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 25.6, 26.0, 34.5, 34.7, 36.1, 37.4, 42.2, 42.8, 117.0, 135.6, 170.9; IR (NaCl) ν 2928, 2852, 1646, 1490, 1448, 1396, 1338, 1264, 1206, 1140, 1104, 1056, 914, 818 cm^{-1}; MS *m*/*z* (%) 242 (MH^+, 22), 127 (100), 112 (26), 98 (26), 87 (18), 72 (61), 55 (26). $C_{13}H_{23}NOS$. Exact mass: calcd 242.1578; found 242.1570.

(S*S*,2*S*)-2-Cyclohexylsulfinyl-*N*,*N*-dimethylpent-4-enamide (4b). To a solution of (S*S*,2*S*)-**3** (dr 99:1, 2.00 g, 7.3 mmol) in acetone (100 mL) were added sodium bicarbonate (2.33 g, 27.7 mmol) and water (10 mL). This suspension was cooled at 0 °C. Then, 0.25 equiv of oxone (1.12 g) was first added. After 10 min of stirring, 0.25 equiv of oxone was added every 10 min (5 × 1.12 g). The reaction was monitored by TLC (EtOAc) and ^{1}H NMR. Water (200 mL) was then added. The aqueous layer was extracted with ethyl acetate (4 x 200 mL). The combined organic phases were dried over $MgSO_4$ and then evaporated to dryness. Chromatography on silica gel (EtOAc; $R_f = 0.23$) afforded **4b** (1.55 g, 6.0 mmol) in 83% yield. White solid: mp 73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98−1.81 (m, 10H), 2.45 (tt, $J = 3.8$ Hz, $J = 11.9$ Hz, 1H), 2.62−2.68 (m, 2H), 2.81 (s, 3H), 2.92 (s, 3H), 3.69−3.75 (m, 1H), 4.91−5.08 (m, 2H), 5.57−5.71 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 22.6, 24.9, 25.0, 25.4, 27.7, 32.3, 35.3, 37.5, 55.5, 60.6, 118.5, 132.6, 167.7; IR (KBr) ν 3072, 2930, 2854, 1518, 1450−1434, 1394, 1266, 1140, 1036, 916 cm^{-1}; MS (70 eV, EI) *m*/*z* (%) 257 (M^+, 0.71), 175 (73), 149 (13), 134 (60), 128 (46), 98 (15), 83 (98), 55 (59), 53 (100), 44 (69). Anal. Calcd for $C_{13}H_{23}NO_2S$: C, 60.7; H, 9.0; N, 5.4; S, 12.5. Found: C, 60.6; H, 9.0; N, 5.8; S, 12.6.

(*S*)-2-Cyclohexylsulfonyl-*N*,*N*-dimethylpent-4-enamide (4c). To a cooled (0 °C) solution of (S*S*,2*S*)-**4b** (dr 99:1, 100 mg, 0.39 mmol) in dichloromethane (6 mL) was added *m*-CPBA (130 mg). The reaction was monitored by TLC. The dichloromethane layer was washed with a solution of saturated $NaHCO_3$ (3 x 15 mL) and then treated with saturated aqueous NaCl (15 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed on silica gel (petroleum ether−EtOAc, 1:1; $R_f = 0.38$) to afford **4c** (100 mg, 0.37 mmol) in 94% yield. White solid: mp 52 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.10−2.28 (m, 10H), 2.72−2.85 (m, 1H), 2.94−3.09 (m, 1H), 3.04 (s, 3H), 3.17 (s, 3H), 3.38 (tt, $J = 3.6$ Hz et $J = 11.9$ Hz, 1H), 4.22 (dd, $J = 3.3$ Hz, $J = 11.2$ Hz, 1H), 5.05−5.22 (m, 2H), 5.59−5.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 25.1, 25.2, 25.2, 25.3, 26.5, 32,9, 36.6, 38.4, 60.2, 65.3, 118.8, 132.7, 165.0; IR (KBr) ν 3074, 2932, 2860, 1656, 1490, 1454, 1432, 1398, 1268, 1204, 1186, 1122, 1054, 996, 936 cm^{-1}; GC/MS *m*/*z* (%) 274 (MH^+, 7), 127 (100), 112 (21), 98 (24), 83 (16), 72 (69), 55 (41), 44 (14). $C_{13}H_{23}NO_3S$. Exact mass: calcd 273.1398; found 273.1397.

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Imidate (5a). To a solution of (2*S*)-**4a** (10 mg, 0.04 mmol) in $CDCl_3$ (0.5 mL) was added iodine (31 mg, 0.12 mmol) at room temperature. After 5 min, the mixture was analyzed by ^1H NMR and ^{13}C NMR. Signals of the (3*S*,5*R*)-major isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24−2.26 (m, 10H), 2.88 (dd, J = 5.2 Hz, J = 13.7 Hz, 1H), 3.05 (ddd, J = 7.2 Hz, J = 10.5 Hz, J = 13.8 Hz, 1H), 3.12 (m, 1H), 3.51 (s, 3H), 3.67 (s, 3H), 3.64−3.70 (m, 1H), 3.75 (dd, J = 6.1 Hz, J = 10.6 Hz, 1H), 4.6 (d, J = 7.0 Hz, 1H), 5.48−5.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 2.1, 25.4, 26.1, 26.2, 33.7, 33.8, 40.6, 42.1, 43.4, 44.9, 47.1, 91.4, 178.5.

General Procedure for the Synthesis of Lactones (6) and Iodohydrin (7) by Iodolactonization. Amide **4** was diluted in solvent (THF, DME, or CH_3CN)−H_2O (8:1 v/v, 0.06 M) or THF−H_2O−MeOH (8:1:1 v/v, 0.05 M). Iodine (3 equiv) was added at the temperature indicated in Table 1. The reaction was monitored by TLC. After the time indicated in the Table 1, the mixture was diluted with dichloromethane and treated twice with $Na_2S_2O_3$ aqueous solution. The organic layers were washed with a saturated solution of $NaHCO_3$ and with saturated aqueous NaCl. After drying over $MgSO_4$, the organic phase was evaporated to dryness. The crude mixture was analyzed by ^1H NMR to determine the diastereoisomeric ratio. The crude was chromatographed on silica gel.

4,5-Dihydro-3-cyclohexylsulfanyl-5-iodomethyl-2(3*H*)-furanone (6a). Obtained from (2*S*)-**4a** (2.50 g, 10.3 mmol) according to entry 11. Chromatography on silica gel (CH_2Cl_2−petroleum ether, 7:3) afforded **6a** (3.33 g, 9.8 mmol) in 95% yield. White solid: mp 58 °C. R_f = 0.45 (minor) and 0.57 (major) (CH_2Cl_2−petroleum ether, 7:3). Signals of the (3*S*,5*R*)-major isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21−2.18 (m, 10H), 2.27−2.43 (m, 2H), 3.05−3.17 (m, 1H), 3.32 (dd, J = 7.1 Hz, J = 10.5 Hz, 1H), 3.43 (dd, J = 4.4 Hz, J = 10.5 Hz, 1H), 3.73 (dd, J = 2.9 Hz, J = 8.0 Hz, 1H), 4.62−4.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 6.9, 25.6, 25.7, 25.9, 32.6, 33.4, 36.8, 39.0, 43.3, 77.0, 174.3. Signals of the (3*S*,5*S*)-minor isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20−2.14 (m, 10H), 2.02 (ddd, J = 6.6 Hz, J = 7.7 Hz, J = 13.8 Hz, 1H), 2.89 (ddd, J = 7.0 Hz, J = 9.2 Hz, J = 13.8 Hz, 1H), 3.09−3.18 (m, 1H), 3.37 (dd, J = 8.5 Hz, J = 10.1 Hz, 1H), 3.50 (dd, J = 4.9 Hz, J = 10.1 Hz, 1H), 3.72 (dd, J = 9.2 Hz, J = 7.7 Hz, 1H), 4.53−4.63 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 6.3, 25.8, 25.9, 26.0, 33.2, 33.6, 36.2, 39.4, 44.0, 77.4, 175.2; IR (KBr) ν 2926, 2848, 1754, 1446, 1366, 1336, 1306, 1264, 968, 920 cm^{-1}; GC/MS *m*/*z* (%): 340 (M^+, 13), 226 (30), 213 (15), 115 (100), 99 (5), 81 (50), 55 (33). Anal. Calcd for $C_{11}H_{17}IO_2S$: C, 38.83; H, 5.04; S, 9.43. Found: C, 39.05; H, 5.07; S, 9.02.

4,5-Dihydro-3-cyclohexylsulfinyl-5-iodomethyl-2(3*H*)-furanone (6b) and Iodohydrin (7b). Obtained from (2*S*,S*S*)-**4b** (2.60 g, 10.12 mmol) according to entry 8. Chromatography on silica gel (CH_2Cl_2−MeOH, 98:2) afforded **6b** (2.40 g, 6.74 mmol) in 67% yield and **7b** (1.00 g, 2.49 mmol) in 25% yield. **6b** is a white solid: mp 81 °C. R_f = 0.6 (EtOAc). Signals of (3*S*,S*S*,5*R*)-**6b**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25−2.12 (m, 10H), 2.29 (ddd, J = 6.2 Hz, J = 10.0 Hz, J = 14.3 Hz, 1H), 2.77 (tt, J = 3.6 Hz, J = 11.6 Hz, 1H), 3.12 (ddd, J = 5.0 Hz, J = 7.8 Hz, J = 14.3 Hz, 1H), 3.38−3.43 (m, 2H), 3.91 (dd, J = 5.0 Hz, J = 10.0 Hz, 1H), 4.58−4.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 8.9, 24.4, 24.9, 25.1, 26.2, 26.4, 25.9, 56.9, 58.8, 77.6, 172.1. Signals of (3*S*,S*S*,5*S*)-**6b**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25−2.12 (m, 10H), 2.60−2.71 (m, 3H), 3.29 (dd, J = 8.4 Hz, J = 10.0 Hz, 1H), 3.38−3.56 (m, 1H), 3.90 (dd, J = 8.5 Hz, J = 13.0 Hz, 1H), 4.74−4.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 5.7, 24.6, 25.1, 25.2, 25.7, 24.8, 56.9, 58.6, 78.2, 172.1. Signals of the (3*R*,S*S*,5*R*)- **6b**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25−2.12 (m, 10H), 2.60−2.71 (m, 1H), 3.04−3.09 (m, 1H), 3.38−3.56 (m, 2H), 3.61−3.69 (m, 1H), 3.76 (dd, J = 5.9 Hz, J = 11.1 Hz, 1H), 4.58−4.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 5.9, 24.6, 24.7, 25.8, 26.4, 30.4, 53.8, 56.0, 77.9, 169.5. Signals of (3*R*,S*S*,5*S*)-**6b**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25−2.12 (m, 10H), 2.63 (ddd, J = 8.5 Hz, J = 10.2 Hz, J = 14.3 Hz, 1H), 2.98 (ddd, J = 2.6 Hz, J = 6.8 Hz, J = 14.3 Hz, 1H), 3.4 (dd, J = 6.5 Hz, J = 10.7 Hz, 1H), 3.46 (dd, J = 3.9 Hz, J = 10.7 Hz, 1H), 3.52 (tt, J = 3.9 Hz, J = 11.2 Hz, 1H), 3.70 (dd, J = 2.6 Hz, J = 10.2 Hz, 1H), 4.69−4.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 8.1, 24.8, 25.1, 25.3, 26.2, 33.2, 54.9, 57.2, 77.7, 169.5; IR (KBr) ν 2920, 2852, 1760, 1446, 1336, 1178, 1040 cm^{-1}; MS (70 eV, EI) *m*/*z* (%) 357 (MH^+, 37), 274 (26), 147 (14), 97 (22), 83 (63), 55 (100). Anal. Calcd for $C_{11}H_{17}IO_3S$: C, 37.08; H, 4.81. Found: C, 37.26; H, 4.79. **7b** is colorless oil: R_f = 0.1 (EtOAc). Signals of the major isomer: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.20−2.05 (m, 10H), 2.31 (dt, J = 3.7 Hz, J = 14.3 Hz, 1H), 2.39−2.47 (m, 1H), 2.92 (tt, J = 4.0 Hz, J = 11.3 Hz, 1H), 3.01 (s, 3H), 3.22 (s, 3H), 3.27−3.30 (m, 1H), 3.36 (dd, J = 4.9 Hz, J = 10.3 Hz, 1H), 3.62−3.75 (m, 1H), 4.32 (dd, J = 3.9 Hz, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.6, 23.5, 24.0, 25.1, 25.4, 27.8, 31.6, 36.5, 38.1, 54.9, 56.5, 69.3, 167.6. Signals of the minor isomer: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.20−2.05 (m, 11H), 2.39−2.47 (m, 1H), 2.85 (tt, J = 3.7 Hz, J = 11.7 Hz, 1H), 3.03 (s, 3H), 3.21 (s, 3H), 3.27−3.30 (m, 1H), 3.34−3.40 (m, 1H), 3.41−3.63 (m, 1H), 4.54 (dd, J = 3.7 Hz, J = 9.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.6, 23.0, 25.0, 25.1, 25.5, 27.8, 32.2, 36.5, 38.1, 55.0, 56.0, 67.4, 167.2; IR (NaCl) ν 3344, 2932, 2856, 1764, 1700, 1684, 1636, 1560, 1540, 1496, 1400, 1344, 1258, 1180, 1138, 1024 cm^{-1}; MS (eV, EI) *m*/*z* (%) 402 (MH^+, 0.13), 319 (1), 274 (5), 97 (22), 83 (43), 55 (100). $C_{18}H_{24}INO_3S$. Exact mass: calcd 402.0599; found 402.0623.

(4,5)-Dihydro-3-cyclohexylsulfonyl-5-iodomethyl-2(3*H*)-furanone (6c). Obtained from (2*S*)-**4c** (54 mg, 0.2 mmol) according to entry 17. Chromatography on silica gel (*n*-pentane−EtOAc, 7:3; R_f = 0.41) afforded **6c** (59 mg, 0.16 mmol) in 80% yield. White solid: mp 147 °C. Signals of the (3*S*,5*R*)-major isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18−2.30 (m, 10H), 2.41 (ddd, J = 7.6 Hz, J = 10.6 Hz, J = 14.7 Hz, 1H), 3.13 (ddd, J = 3.6 Hz, J = 7.3 Hz, J = 14.7 Hz, 1H), 3.37−3.52 (m, 2H), 3.56 (tt, J = 3.5 Hz, J = 12.1 Hz, 1H), 4.27 (dd, J = 3.6 Hz, J = 10.6 Hz, 1H), 4.23−4.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 7.9, 22.6, 24.8, 25.0, 25.1, 26.8, 28.8, 59.0, 59.5, 77.8, 168.3. Signals of the (3*S*,5*S*)-minor isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18−2.30 (m, 10H), 2.72 (ddd, J = 6.8 Hz, J = 7.5 Hz, J = 14.5 Hz, 1H), 2.89 (ddd, J = 7.6 Hz, J = 10.6 Hz, J = 14.5 Hz, 1H), 3.37−3.52 (m, 2H), 3.68 (tt, J = 3.5 Hz, J = 12.1 Hz, 1H), 4.31 (dd, J = 7.5 Hz, J = 10.6 Hz, 1H), 4.23−4.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 4.8, 22.6, 24.8, 25.1, 26.8, 27.1, 58.2, 59.3, 78.3, 168.2; IR (KBr) ν 2932, 2854, 1752, 1448, 1412, 1312, 1274, 1212, 994 cm^{-1}; GC/MS *m*/*z* (%) 373 (M^+, 3), 226 (100), 99 (49), 71 (16), 55 (34). Anal. Calcd for $C_{15}H_{27}O_2S$: C, 63.12; H, 9.53; N, 4.91. Found: C, 62.90; H, 10.11; N, 4.89.

(S*S*,2*S*)-2-Cyclohexylsulfinyl-*N*,*N*-ethylpent-4-enamide (8b). Amide **8b** was synthesized using the procedure described for amide **4b**. White solid: mp 114 °C. R_f = 0.4 (EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93−1.89 (m, 10H), 1.01 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H), 2.58 (tt, J = 3.7 Hz, J = 11.9 Hz, 1H, CH−Cy), 2.66−2.81 (m, 2H), 3.14−3.36 (m, 4H), 3.69 (dd, J = 4.9 Hz, J = 9.0 Hz, 1H), 4.98−5.13 (m, 2H), 5.63−5.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.0, 14.6, 23.4, 23.5, 25.4, 25.8, 26.0, 33.2, 40.2, 42.6, 55.9, 61.6, 119.1, 133.1, 167.2; IR (KBr) ν 3078, 2974, 2856, 1616, 1456, 1358, 1264, 1216, 1138, 1042, 912 cm^{-1}. Anal. Calcd for $C_{11}H_{17}IO_4S$: C, 35.49; H, 4.60; S, 8.61. Found: C, 35.48; H, 4.62; S, 8.88.

(S*S*,2*S*)-2-Cyclohexylsulfonyl-*N*,*N*-ethylpent-4-enamide (9b). Amide **9b** was synthesized using the procedure described for amide **4b**. White solid: mp 125 °C; R_f = 0.51 (EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17−2.03 (m, 10H), 1.20 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H), 1.38 (d, J = 6.6 Hz, 3H), 1.40 (d, J = 6.6 Hz, 3H), 2.70 (tt, J = 3,6 Hz, J = 12,1 Hz, 1H), 2.78−2.92 (m, 2H), 3.40 (sept, J = 6,6 Hz, 1H), 3.78 (dd, J = 4.8 Hz, J = 8.7 Hz, 1H), 4.04 (sept, J = 6.6 Hz, 1H), 5.11−5.25 (m, 2H), 5.77−5.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.5, 20.6, 21.0, 21.3, 22.9, 25.5, 26.1, 28.5, 33.4, 46.7, 49.7, 55.5, 63.0, 118.9, 133.3, 167.2; IR (KBr) ν 2928,

2856, 1616, 1452, 1374, 1270, 1208, 1120, 1040, 912 cm^{-1}. Anal. Calcd for $C_{17}H_{31}O_2S$: C, 65.13; H, 9.97; N, 4.47. Found: C, 64.98; H, 10.21; S, 4.37.

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Supporting Information Available: General procedure and NMR spectra for various compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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