New General Asymmetric Synthesis of Versatile γ-Alkylated Butenolides and Its Application to Expeditious Synthesis of the Chiral Geissman–Waiss Lactones Useful for (+)-Retronecine Synthesis

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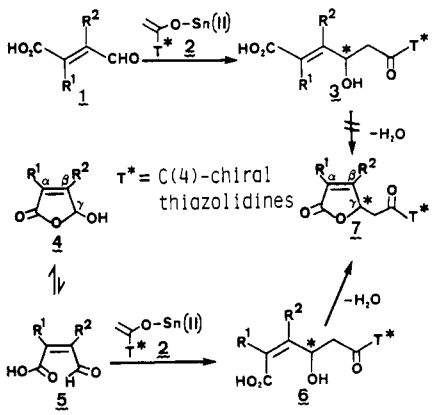
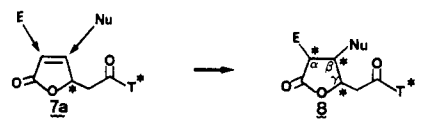
A new strategy for general asymmetric synthesis of chiral butenolides **7a–h** is established by utilizing excellent diastereocontrolled alkylation with chiral tin(II) enolate **10** at the γ-position of hydroxy butenolides **4a–h**. An efficient utility of the chiral butenolides is exemplified with the expeditious synthesis of the optically pure Geissman–Waiss lactone derivatives **23a** and **23b**.

Butenolides and saturated γ-lactones are encountered frequently in a large number of natural products, especially flavor components and insect sex pheromones.[2] Optically active γ-substituted butenolides should also be remarkably useful as the chiral synthons for syntheses of terpenoidal lactone pheromones [(+)- and (−)-eldanolide[3a,b]], antileukaemic lignans [(+)-*trans*-burseran,[3c] (−)-isostegane,[3c] and (+)- and (−)-steganacine[3d–e]], (−)-verrucarinolactone,[3f] prostacycline analogues,[4e–g] chrysanthemic acid,[3g] polyoxin J,[3h] (−)-ranunculin,[4b] lasalocid A,[4d] and other biologically active natural products.[3i–m] Due to the increasing interesting in the high versatility of butenolides as described above, there have been many reports on the preparation of optically active α,β-unsaturated γ-lactones. They have been obtained both from natural resources such as carbohydrates,[4a–k] ascorbic acids,[4l–n] tartaric acid,[4o] and L-glutamic acid[4p–r] and from synthetic compounds such as chiral α-acetylenic acids,[5a–c] chiral hydroxy sulfoxides,[5d–f] chiral epoxides,[5g–h] and other chiral materials.[5j–k] Among

Scheme I



Scheme II



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(2) (a) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449. (b) Cardellach, J.; Estopa, C.; Font, J.; Moreno-Mañas, M.; Ortuño, R. M.; Sanchez-Ferrando, F.; Valle, S.; Vilamajo, L. *Tetrahedron* **1982**, *38*, 2377. (c) Cardellach, J.; Font, J.; Ortuño, R. M. *J. Heterocycl. Chem.* **1984**, *21*, 327.

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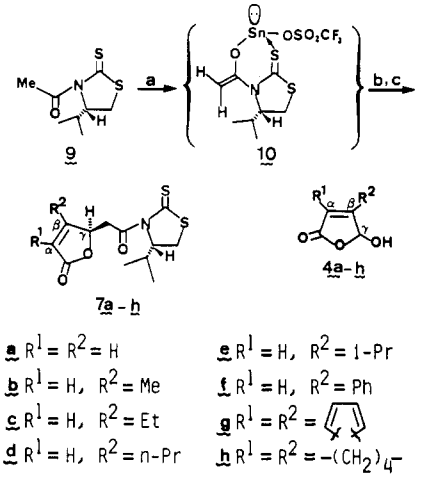
the previous methods, most of them take multisteps of reactions and/or it seemes to be difficult to gain a large amount of the material for practical use. We have disclosed a new and very simplified method for general synthesis of optically pure chiral butenolides **7** via highly diastereoselective alkylation with chiral tin(II) enolate **2** toward the *Z*-olefinic aldehydic acids **5** followed by lactonization of the resultant *Z*-olefinic hydroxy carboxylic acids **6** (Scheme I).

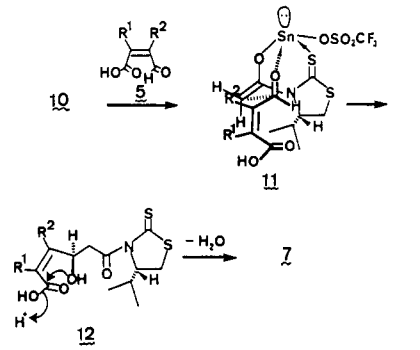
Ordinarily, *E*-olefinic hydroxy carboxylic acids **3** obtained by alkylation of *E*-olefinic aldehydic acids **1** with chiral tin(II) enolate **2** may not be converted to chiral butenolides **7** without manipulation like photoisomerization of the *E*-olefinic system toward the *Z*-olefinic system (Scheme I). However, *Z*-olefinic hydroxy carboxylic acids **6** obtained by the similar alkylation with chiral tin(II) enolate **2** from *Z*-olefinic aldehydic acids **5** can be readily lactonized under the usual acidic conditions, giving desired chiral γ-alkylated butenolides **7**. Although direct preparation of the *Z*-olefinic aldehydic acids **5** are remarkably difficult, these aldehydic acids **5** may be available under the equilibrium conditions with the corresponding stable γ-hydroxybutenolides **4** in solution (Scheme I). The important synthetic potential of compound **7a** (**7**, $R^1 = R^2 = H$) is considerable because it allows further chemical elaboration to give tris-substituted γ-lactone **8** with the asymmetric transformation from the chiral γ-carbon atom in compound **7a** (Scheme II).[6] As to our best knowledge, 5-hydroxy-2(5*H*)-furanone (**4a**)[7] has been reported to react with Witting-type reagents to generate *Z,E*-diene products[7,8] and with organometallic reagents to yield racemic γ-substituted butenolides.[9] Very recently, γ-(*l*-menthyloxy)butenolide obtained by acetalization of **4a** with *l*-menthol was efficiently utilized for the preparation of optically pure aminodiols.[10] However, there has been no report on the chiral butenolide synthesis by utilizing asymmetric alkylation at the γ-position of hydroxy butenolides **4**. Here we report a new highly diastereoselective synthesis of various γ-alkylated butenolides **7a-h** and its efficient application to the short synthesis of the chiral Geissman–Waiss lactone derivatives **23a** and **23b** useful for the synthesis of (+)-retronecine (**24**),[11] the constituted pyrrolizidine base of indicine *N*-oxide (**25**)[12] promising to be a new anticancer drug.

Scheme III[a]



[a] (a) $Sn(OSO_2CF_3)_2$ (1.3 equiv), *N*-ethylpiperidine (1.5 equiv), THF, −50 to −40 °C, 3 h; (b) **4a–h** (0.77 equiv), −5 to 0 °C, 2 h; (c) 5% HCl.

Scheme IV



Synthesis of Chiral γ-Alkylated Butenolides 7a–h. The chiral tin(II) enolate **10**[13] was, in situ, prepared by treatment of 3-acetyl-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (**9**)[13] with a THF solution of $Sn(OSO_2CF_3)_2$[14] and *N*-ethylpiperidine[14] at −50 to −40 °C for 3 h. After reaction of the enolate **10** with several γ-hydroxybutenolides **4a–h**[7,9d,15] at −5 to 0 °C for 2 h, treatment of the reaction mixture with 5% HCl afforded the chiral crystalline γ-alkylated butenolides **7a-h** in excellent chemical yields (81–93%) and in a highly diastereocontrolled manner [97.2–99.1% diastereomeric excess (de) by the HPLC analysis] (Scheme III and Table I). The absolute configuration of the newly formed chiral center in γ-alkylated butenolides **7a,b,g** was established to be the *R* configuration by their X-ray analyses.[16] The stereochemistry of the γ-position of other major butenolides **7c–f,h** was tenta-

(6) Alkylation of butenolide with stereocontrolled manner: Boeckman, R. K., Jr.; Heckendorn, D. K.; Chinn, R. L. *Tetrahedron Lett.* **1987**, *28*, 3551.

(7) Preparation of 5-hydroxy-2(5*H*)-furanone: White, J. D.; Carter, J. P.; Kezar, H. S. III *J. Org. Chem.* **1982**, *47*, 929.

(8) Wittig-type olefination of 5-hydroxy-2(5*H*)-furanone, see: (a) Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242. (b) Feliu, A. L.; Smith, K. J.; Seltzer, S. *J. Am. Chem. Soc.* **1984**, *106*, 3046. (c) Feliu, A. L.; Seltzer, S. *J. Org. Chem.* **1985**, *50*, 447. (d) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1983**, *48*, 758. (e) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 1772. (f) Al-Hakim, A. H.; Haines, A. H. *Tetrahedron Lett.* **1982**, *23*, 5295.

(9) Alkylation of 5-hydroxy-2(5*H*)-furanone with organometallic reagents, see: (a) Machado-Araujo, F. W.; Gore, J. *Tetrahedron Lett.* **1981**, *22*, 1969. (b) Roush, W. R.; Blizzard, T. A.; Basha, F. Z. *Tetrahedron Lett.* **1982**, *23*, 2331. (c) Canonne, P.; Akssira, M. *Tetrahedron Lett.* **1984**, *25*, 3453. (d) Canonne, P.; Plamondon, J.; Akssira,M. *Tetrahedron* **1988**, *44*, 2903.

(10) Feringa, B. L.; Lange, B. de. *Tetrahedron Lett.* **1988**, *29*, 1303.

(11) Chiral synthesis of (+)-retronecine, see: (a) Rüeger, H.; Benn, M. *Heterocycles* **1982**, *19*, 23. (b) Rüeger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331. (c) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (d) Chamberlin, A. R.; Chung, J. Y. *J. Org. Chem.* **1985**, *50*, 4425. (e) Buchanan, J. G.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1299. (f) Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans 1* **1987**, 2377. (g) Nishimura, Y.; Kondo, S.; Umezawa, H. *J. Org. Chem.* **1985**, *50*, 5210. (h) Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4605. (i) Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *J. Org. Chem.* **1987**, *52*, 2941. (j) Shishido, K.; Sukegawa, Y.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans 1*, **1987**, 993. (k) Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1988**, 685.

(12) Zalkow, L. H.; Glinski, J. A.; Gelbaum, L. T.; Fleischmann, T. J.; McGowan, L. S.; Gordon, M. M. *J. Med. Chem.* **1985**, *28*, 687 and references cited therein.

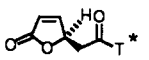
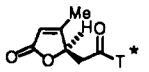
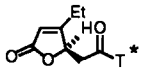
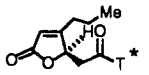
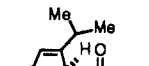
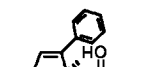
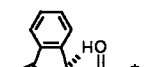
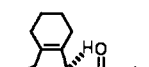
(13) Chiral tin(II) enolates, see: (a) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (b) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289. (c) Nagao, Y.; Kumagai, T.; Abe, T.; Ochiai, M.; Taga, T.; Machida, K.; Inoue, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 602. (d) Nagao, Y.; Dai, W.-M.; Ochiai, M. *Tetrahedron Lett.* **1988**, *29*, 6133. (e) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.

(14) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1983**, 297.

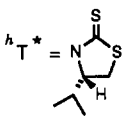
(15) Bourguignon, J. J.; Wermuth, C. G. *J. Org. Chem.* **1981**, *46*, 4889.

(16) Supplementary material is available.

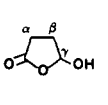
Table I. Synthesis of Chiral γ-Alkylated Butenolides 7a–h by Treatment of γ-Hydroxybutenolides 4a–h with Chiral Tin(II) Enolate 10

γ-hydroxy-butenolide	γ-alkylated butenolide[h]	diastrmer excess,[a] %	isolated yield, %	mp, °C	$[\alpha]^{25}_D$[f] (c in $CHCl_3$)
4a	 7a	99.1	86	88–88.5[b]	+222.5 (0.59)[g]
4b	 7b	98.4	85	117–119[b]	+347.9 (0.48)
4c	 7c	97.2	90	74.5–75[e]	+355.8 (0.65)
4d	 7d	99.0	85	102–104[c]	+357.4 (0.63)
4e	 7e	98.8	93	103–104.5[e]	+329.3 (0.72)
4f	 7f	98.7	81	171–172[d]	+264.3 (0.54)
4g	 7g	97.5	87	125–126.5[b]	+360.5 (0.65)
4h	 7h	98.4	90	136–137[e]	+360.1 (0.68)

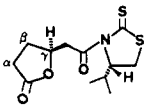
[a] Determined by HPLC analysis [column, Finepak sil φ 4.6 mm × 25 cm; eluent, EtOAc–hexane (20:80); flow rate, 1.0 mL/min; temperature, 33 °C; detection, UV 305 nm]. [b] Recrystallized from EtOAc–hexane. [c] Recrystallized from Et_2O. [d] Recrystallized from EtOAc. [e] Recrystallized from Et_2O–hexane. [f] $[\alpha]^{25}_D$ is measured in degrees. [g] Recorded at 21 °C.



tively assigned to be the *R* configuration on the basis of the similar mechanistic consideration of **11** to that for **7a**, **7b**, and **7g**. The same reaction of **13**[17] with chiral tin(II) enolate **10** gave γ-*S*-lactone **14** as a beautiful crystalline solid in 66% yield and in 97.6% de. Its stereochemistry was determined to be **14** by the X-ray crystallographic analysis.[16] It is noteworthy that this asymmetric alkylation followed by lactonization smoothly proceeds even in the cases of fairly sterically hindered γ-hydroxybutenolides such as **4e–4h**. The high *re*-face selectivity toward the formyl group of *Z*-olefinic aldehydic acids **5** by chiral tin(II) enolate **10** can be explained in terms of a six-membered transition state **11**[13e] where the α,β-unsaturated carboxylic acid moiety should be oriented at the less hindered equatorial position and would not affect on the Sn atom (see Scheme IV). The following acidic dehydration in **12** yielded the desired γ-alkylated butenolides **7**. Although an alternative mechanism involving asymmetric alkylation with chiral tin(II) enolate **10** onto an oxonium species **15** might be suggested, this speculation was excluded by the following fact. In spite of easy conversion of γ-acetoxybutenolide **16**[18] to the oxonium ion **15** in comparison with the case of **4a**, the reaction of the chiral tin(II) enolate **10** with **16** resulted in recovery (84%) of the starting compound **16**.



13



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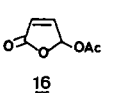


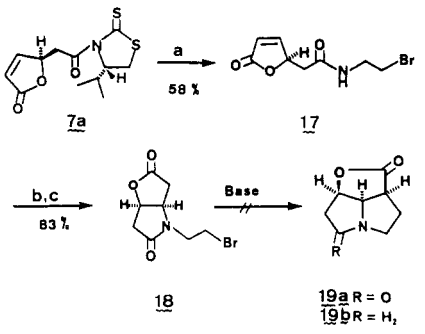
16

Thus, we established a new general simplified synthetic method for various chiral γ-alkylated butenolides **7** which should be useful as versatile functionalized synthons for the natural product and drug syntheses. This particular butenolide **7** possessing the thiazolidine amide moiety is

(17) Cf. Wermuth, C. G. *J. Org. Chem.* **1979**, *44*, 2406. We employed compound **13** freshly prepared by hydrogenation of **4a** (5% Pd/C, H_2, EtOAc) before use.

(18) (a) Yamamoto, M.; Izukawa, H.; Saiki, M.; Yamada, K. *J. Chem. Soc., Chem. Commun.* **1988**, 560. (b) Asaoka, M.; Yanagida, N.; Sugimura, N.; Takei, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1061.

Scheme V[a]

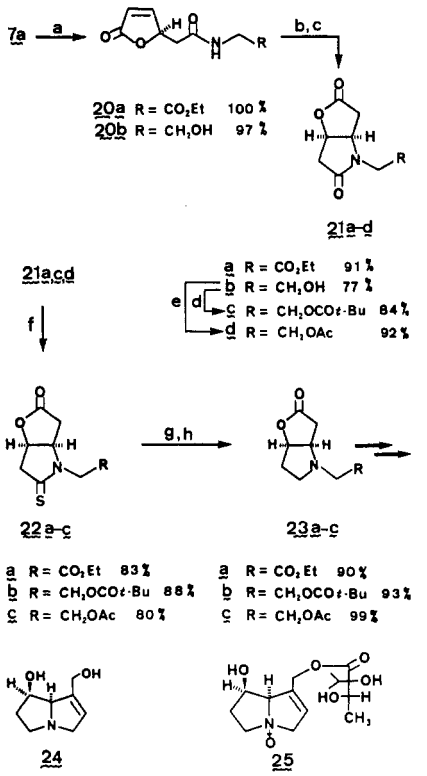


[a] (a) $HBr{\cdot}NH_2(CH_2)_2Br$, Et_3N, THF–H_2O (2:1), room temperature 2 h; (b) NaH, DMF, 10 °C, 5 h; (c) AcOH, −50 °C.

featured by the active amide structure exhibiting excellent reactivity toward various nucleophiles.

Stereocontrolled Synthesis of the Chiral Geissman–Waiss Lactone Derivatives 23a and 23b. Our initial effort was devoted to an expeditious synthesis of a tricyclic lactone–lactam derivative **19a** because an analogous compound **19b** has been already reported as an intermediate in the synthesis of (+)-retronecine (**24**).[11d] We anticipated that compound **19a** could be synthesized from the chiral γ-alkylated butenolide **7a**. Thus, **7a** was subjected to aminolysis with (2-bromoethyl)amine hydrobromide in the presence of triethylamine to give amide **17**. This amide **17** was expected to undergo tandem intramolecular Michael addition–alkylation reaction to afford the desired tricyclic lactone–lactam **19a** directly. However, treatment of **17** with sodium hydride (1 mol equiv) in DMF at 10 °C gave exclusively the stereoselective Michael addition product **18** instead of the product **19a** (Scheme V). The Michael addition reaction proceeded smoothly in the presence of a catalytic amount of the base. Quenching the reaction mixture with acetic acid at low temperature was found to be essential to obtain a high yield of the lactone–lactam product **18**. The optimum yield (83%) was gained when 0.5 mol equiv of sodium hydride was employed, and the reaction mixture was quenched with acetic acid at −50 °C. Treatment of **18** with lithium diisopropylamide in THF at −78 °C for 5 h and then at −22 °C for 13 h resulted in the decomposition of **18**. The failure in the production of **19a** may be due to the unfavorable geometric arrangement between the corresponding enolate of the lactone moiety and the side chain on nitrogen atom in **18** to render an S_N2 reaction. Hence, an alternative way was adopted to remove the lactam carbonyl oxygen atom in the analogues of **18** before subjecting to further cyclization (Scheme VI). The bicyclic lactone–lactam derivatives **21a** and **21b** were obtained from **7a** in excellent yields via aminolysis with ethyl glycinate and 2-aminoethanol followed by stereocontrolled intramolecular Michael addition of the resultant amide anion of **20a** and **20b**, respectively. Acylation of **21b** with trimethylacetyl chloride (pivaloyl chloride) and acetyl chloride in the presence of triethylamine gave **21c** and **21d** in 84% and 92% yields, respectively. Conversion of **21a,c,d** to the Geissman–Waiss lactone derivatives **23a–c** was achieved by following the known procedure. Compounds **21a,c,d** were treated with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphatane 2,4-disulfide (Lawesson's reagent)[19] under heating at 105 °C in toluene to give the corresponding thiolactams **22a–c** in good yields. Ethylation of these thiolactams **22a–c** with

Scheme VI[a]



[a] (a) NH_2CH_2R (R = CO_2Et or CH_2OH), THF, room temperature, 10 min; (b) NaH, DMF, 10 °C, 5 h; (c) AcOH, −50 °C; (d) *t*-BuCOCl, Et_3N, CH_3CN, room temperature, 9 h; (e) CH_3COCl, Et_3N, CH_3CN, room temperature, 3 h; (f) 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphatane 2,4-disulfide, toluene, 105 °C, 1 h; (g) Et_3OBF_4, CH_2Cl_2, room temperature, 3 h; (h) $NaBH_3CN$, MeOH–AcOH (92:8), room temperature, 3 h.

Et_3OBF_4 in CH_2Cl_2 followed by the selective reduction with $NaBH_3CN$ in MeOH–AcOH (92:8) afforded the desired bicyclic N-substituted pyrrolidine lactones **23a–c** in excellent yields, respectively.[11h,i] Compounds **23a** and **23b** synthesized independently from (−)-4-hydroxy-L-proline[11a,b] and (*R*)-malic acid,[11h,i] have been reported as the important intermediates in the asymmetric total synthesis of (+)-retronecine (**24**). Therefore, our present work constitutes a formal total synthesis of (+)-retronecine (**24**). In comparison with the previous asymmetric synthesis of **23a** and **23b**, our new procedure seemes to be superior in the view points on its expeditious chiral synthesis and optical purity.

Experimental Section

General Methods. Melting points were measured on a Yanagimoto apparatus and are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-202 spectrophotometer. Proton nuclear magnetic resonance spectra (^1H NMR) were obtained in the indicated solvents with a JEOL JMN-FX100 (100 MHz) or a JEOL JMN-GX400 (400 MHz) spectrometer; signals are given in ppm using $SiMe_4$ as internal standard. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a JEOL JMS-DX300 mass spectrometer. Combustion analyses were performed by Yanaco CHN corder MT-3. Optical rotations were recorded on a JASCO DIP-181 polarimeter in the indicated solvents. High-performance liquid chromatography (HPLC) was performed on a Shimadzu LC-4A instrument equipped with a SPD-2AS UV detector with use of a Finepak Sil 4.6 mm × 25 cm column.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light and 10% ethanolic phosphomolybdic acid–heat as developing agent. Preparative thin-layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates

(19) Scheibye, S.; Pederson, B. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* 1978, *87*, 229.

(60F-254). Flash column chromatographic separations were carried out on E. Merck silica gel (60, particle size 230–400 mesh). Workup means drying over anhydrous Na_2SO_4, filtration, and concentration in vacuo. THF and toluene were distilled from sodium benzophenone ketyl under N_2. Diisopropylamine, *N*-ethylpiperidine, Et_3N, pyridine, DMF, CH_2Cl_2, and CH_3CN were distilled from CaH_2. All other reagents were used as received. Phthalaldehydic acid **4g** was obtained from a commercial source. 5-Hydroxy-2(5*H*)-furanone (**4a**),[7] aldehydic acids **4b–f**,[15] and **4h**[9d] were prepared according to the literature procedures. Succinic semialdehyde **13** was freshly prepared by hydrogenation of 5-hydroxy-2(5*H*)-furanone (**4a**) over 5% Pd/C in EtOAc at room temperature under 1–2 atm of H_2 and used immediately.[17] 4-(*S*)-Isopropyl-1,3-thiazolidine-2-thione [4(*S*)-IPTT] was prepared according to our reported method.[13e] Tin(II) trifluoromethanesulfonate [tin(II) triflate] was prepared according to the literature procedures.[20]

3-Acetyl-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (9). To a suspension of 60% NaH (0.546 g, 13.64 mmol) in dry THF (10 mL) at 0 °C was added a solution of 4(*S*)-isopropyl-1,3-thiazolidine-2-thione (2.00 g, 12.40 mmol) in dry THF (10 mL). The mixture was stirred at 0 °C for 10 min, and acetyl chloride (0.98 mL, 13.64 mmol) was injected into the solution and stirred at 0 °C for 10 min and then at room temperature for 1 h. 5% Hydrochloric acid was added, and the mixture was extracted with EtOAc, washed with brine, and worked up. The crude product so obtained was purified by flash column chromatography (elution with 10% EtOAc in hexane), affording 2.363 g (94%) of **5** as a yellow oil: $[\alpha]^{22}_D$ +448.9° (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 1690, 1368, 1273, 1238, 1188, and 1072 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.06 and 1.18 (6 H, d, *J* = 6.8 Hz), 2.12–2.56 (1 H, m), 2.77 (3 H, s), 3.02 (1 H, dd, *J* = 1.5, 11.5 Hz), 3.52 (1 H, dd, *J* = 7.8, 11.5 Hz), 5.15 (1 H, ddd, *J* = 1.5, 6.3, 7.8 Hz); MS *m/z* 203 (M^+), 160, 118, 69; HRMS calcd for $C_8H_{13}NOS_2$ MW 203.0438, found *m/z* 203.0459 (M^+). Anal. Calcd for $C_8H_{13}NOS_2$: C, 47.26; H, 6.44; N, 6.89. Found: C, 47.51; H, 6.40; N, 7.10.

General Procedure for Preparation of Optically Pure C(5)-Alkylated Butenolides 7a–h and Saturated γ-Lactone 14. Tin(II) trifluoromethanesulfonate (1.20 g, 2.88 mmol) was dissolved in dry THF (6 mL) under an argon atmosphere at room temperature. To the solution cooled at −50 °C in a dry ice-acetonitrile bath was added successively *N*-ethylpiperidine (0.46 mL, 3.32 mmol) and 3-acetyl-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (**9**) (0.45 g, 2.22 mmol) in dry THF (3 mL), and then the mixture was stirred at −50 to −40 °C for 3 h to form the tin(II) enolate **10**. To the tin(II) enolate **10** was added the aldehydic acid **7a–h** (1.71 mmol) in dry THF (3 mL) or succinic semialdehyde **13** (1.71 mmol) in dry THF (3 mL) at −5 °C, and then the mixture was allowed to stir at −5 to 0 °C for 2 h. The reaction mixture was poured into a mixture of phosphate buffer solution (pH 7.0) (50 mL) and EtOAc (50 mL) with vigorous stirring, the precipitate was filtered off through Celite, and the residue was washed with EtOAc (3 × 50 mL). The combined filtrate was washed with 5% hydrochloric acid and brine and then submitted to workup to provide a crude product. A sample of the crude product was submitted to HPLC analysis under the indicated conditions to determine diastereomeric excess (see Table I). Flash column chromatography (elution with 25% EtOAc in hexane) of the crude product afforded the pure product **7a–h** or **14** (see Table I). Physical data for **7a–h** and **14** are reported as follows.

3-((2,5-Dihydro-5-oxo-2(*R*)-furanyl)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (7a): yellow prisms; IR ($CHCl_3$) 1782, 1755, 1688, 1362, 1170, 1160, 1080, 1038, 905, and 815 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.00 and 1.08 (6 H, d, *J* = 6.8 Hz), 2.20–2.60 (1 H, m), 3.09 (1 H, dd, *J* = 1.0, 11.2 Hz), 3.61 (1 H, dd, *J* = 7.5, 12.1 Hz), 3.67 (2 H, d, *J* = 6.9 Hz), 5.16 (1 H, br t, *J* = 6.9 Hz), 5.57 (1 H, ddt, *J* = 1.5, 2.0, 6.9 Hz), 6.17 (1 H, dd, *J* = 2.0, 5.9 Hz), 7.66 (1 H, dd, *J* = 1.5, 5.7 Hz); MS *m/z* 285 (M^+), 252, 202, 162 (100), 118, 83; HRMS calcd for $C_{12}H_{15}NO_3S_2$ MW 285.0488, found *m/z* 285.0487 (M^+). Anal. Calcd for $C_{12}H_{15}NO_3S_2$: C, 50.50; H, 5.30; N, 4.91. Found: C, 50.66; H, 5.29; N, 5.02.

3-((2,5-Dihydro-3-methyl-5-oxo-2(*R*)-furanyl)acetyl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (7b): yellow prisms; IR ($CHCl_3$) 1780 (shoulder), 1758, 1690, 1640, 1365, 1310, and 1170 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.00 (3 H, d, *J* = 7.8 Hz), 1.07 (3 H, d, *J* = 6.8 Hz), 2.11 (3 H, d, *J* = 1.5 Hz), 2.18–2.60 (1 H, m), 3.07 (1 H, dd, *J* = 1.0, 11.2 Hz), 3.34 (1 H, dd, *J* = 9.3, 17.6 Hz), 3.61 (1 H, dd, *J* = 7.8, 11.2 Hz), 3.75 (1 H, dd, *J* = 2.9, 17.6 Hz), 5.14 (1 H, ddd, *J* = 1.0, 6.4, 7.8 Hz), 5.40 and 5.49 (1 H, br s), 5.86 (1 H, m); MS *m/z* 299 (M^+), 283, 240, 162 (100), 139, 118, 97. Anal. Calcd for $C_{13}H_{17}NO_3S_2$: C, 52.15; H, 5.72; N, 4.68. Found: C, 52.07; H, 5.71; N, 4.76.

3-((2,5-Dihydro-3-ethyl-5-oxo-2(*R*)-furanyl)acetyl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (7c): yellow prisms; IR ($CHCl_3$) 1785 (shoulder), 1750, 1692, 1635, 1360, and 1168 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.01 and 1.08 (6 H, d, *J* = 7.3 Hz), 1.25 (3 H, t, *J* = 7.3 Hz), 2.20–2.60 (3 H, m), 3.07 (1 H, dd, *J* = 1.0, 11.7 Hz), 3.34 (1 H, dd, *J* = 9.8, 17.6 Hz), 3.62 (1 H, dd, *J* = 7.8, 11.7 Hz), 3.74 (1 H, dd, *J* = 3.4, 17.6 Hz), 5.14 (1 H, ddd, *J* = 1.0, 6.2, 7.8 Hz), 5.49 (1 H, ddd, *J* = 1.5, 3.4, 9.8 Hz), 5.85 (1 H, dd, *J* = 1.5, 3.4 Hz); MS *m/z* 313 (M^+), 162 (100), 118, 111. Anal. Calcd for $C_{14}H_{19}NO_3S_2$: C, 53.65; H, 6.11; N, 4.47. Found: C, 53.68; H, 6.16; N, 4.54.

3-((2,5-Dihydro-3-propyl-5-oxo-2(*R*)-furanyl)acetyl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (7d): yellow prisms; IR ($CHCl_3$) 1790 (shoulder), 1752, 1692, 1632, 1362, and 1168 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.00 and 1.08 (6 H, d, *J* = 6.8 Hz), 1.02 (3 H, t, *J* = 6.8 Hz), 1.48–1.86 (2 H, m), 2.22–2.60 (3 H, m), 3.08 (1 H, dd, *J* = 1.0, 11.7 Hz), 3.34 (1 H, dd, *J* = 9.8, 17.6 Hz), 3.61 (1 H, dd, *J* = 7.8, 11.7 Hz), 3.74 (1 H, dd, *J* = 2.9, 17.6 Hz), 5.15 (1 H, ddd, *J* = 1.0, 6.7, 7.8 Hz), 5.49 (1 H, ddd, *J* = 1.7, 2.9, 9.8 Hz), 5.85 (1 H, dd, *J* = 1.7, 3.4 Hz); MS *m/z* 327 (M^+), 161, 118 (100), 59. Anal. Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.02; H, 6.46; N, 4.28. Found: C, 54.82; H, 6.44; N, 4.31.

3-((2,5-Dihydro-3-isopropyl-5-oxo-2(*R*)-furanyl)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (7e): yellow prisms; IR ($CHCl_3$) 1785 (shoulder), 1750, 1690, 1628, 1360, 1277, and 1168 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.01 (3 H, d, *J* = 7.8 Hz), 1.08 (3 H, d, *J* = 6.8 Hz), 1.20 (3 H, d, *J* = 6.8 Hz), 1.27 (3 H, d, *J* = 6.4 Hz), 2.22–2.74 (2 H, m), 3.08 (1 H, dd, *J* = 1.0, 11.2 Hz), 3.34 (1 H, dd, *J* = 9.8, 17.6 Hz), 3.62 (1 H, dd, *J* = 7.8, 11.2 Hz), 3.73 (1 H, dd, *J* = 2.9, 17.6 Hz), 5.14 (1 H, ddd, *J* = 1.0, 6.0, 7.8 Hz), 5.48 (1 H, ddd, *J* = 1.5, 2.9, 9.8 Hz), 5.82 (1 H, dd, *J* = 1.5, 1.5 Hz); MS *m/z* 327 (M^+), 311, 162 (100), 125, 118. Anal. Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.02; H, 6.46; N, 4.28. Found: C, 54.94; H, 6.55; N, 4.33.

3-((2,5-Dihydro-3-phenyl-5-oxo-2(*R*)-furanyl)acetyl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (7f): yellow prisms; IR ($CHCl_3$) 1782 (shoulder), 1750, 1690, 1615, 1570, 1495, 1360, and 1165 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.01 (3 H, d, *J* = 6.8 Hz), 1.08 (3 H, d, *J* = 6.3 Hz), 2.20–2.62 (1 H, m), 3.08 (1 H, dd, *J* = 1.0, 11.2 Hz), 3.45 (1 H, dd, *J* = 8.2, 18.2 Hz), 3.62 (1 H, dd, *J* = 7.8, 11.2 Hz), 3.69 (1 H, dd, *J* = 4.0, 18.2 Hz), 5.14 (1 H, br t, *J* = 7.0 Hz), 6.14 (1 H, ddd, *J* = 1.7, 4.0, 8.2 Hz), 6.34 (1 H, d, *J* = 1.7 Hz), 7.50 (5 H, s); MS *m/z* 361 (M^+), 200, 172, 162 (100), 159, 118, 103. Anal. Calcd for $C_{18}H_{19}NO_3S_2$: C, 59.81; H, 5.30; N, 3.87. Found: C, 59.65; H, 5.25; N, 3.90.

3-((2,5-Dihydro-3,4-benzo-5-oxo-2(*R*)-furanyl)acetyl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (7g): yellow prisms; IR ($CHCl_3$) 1765, 1690, 1610, 1598, 1367, 1288, 1248, and 1170 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.03 and 1.10 (6 H, d, *J* = 6.8 Hz), 2.24–2.58 (1 H, m), 3.08 (1 H, dd, *J* = 1.0, 11.7 Hz), 3.57 (1 H, dd, *J* = 7.8, 11.7 Hz), 3.66 (1 H, dd, *J* = 7.8, 17.6 Hz), 3.95 (1 H, dd, *J* = 4.4, 17.6 Hz), 5.21 (1 H, ddd, *J* = 1.0, 6.5, 7.8 Hz), 6.08 (1 H, dd, *J* = 4.4, 7.8 Hz), 7.42–7.95 (4 H, m); MS *m/z* 335 (M^+), 302, 202, 175, 161, 146, 133 (100), 118, 77. Anal. Calcd for $C_{16}H_{17}NO_3S_2$: C, 57.29; H, 5.11; N, 4.18. Found: C, 57.53; H, 5.21; N, 4.19.

3-((2,5-Dihydro-3,4-tetramethylene-5-oxo-2(*R*)-furanyl)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (7h): yellow needles; IR ($CHCl_3$) 1780 (shoulder), 1750, 1690, 1365, 1285, and 1170 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.00 and 1.08 (6 H, d, *J* = 6.8 Hz), 1.50–1.96 (4 H, m), 2.08–2.60 (5 H, m), 3.07 (1 H, dd, *J* = 1.0, 11.2 Hz), 3.31 (1 H, dd, *J* = 9.3, 17.6 Hz), 3.60 (1 H, dd, *J* = 7.8, 11.2 Hz), 3.69 (1 H, dd, *J* = 3.9, 17.6 Hz), 5.14 (1 H, ddd, *J* = 1.0, 6.2, 7.8 Hz), 5.26–5.48 (1 H, m); MS *m/z* 339 (M^+), 323, 178, 162 (100), 151, 137, 118. Anal. Calcd for $C_{16}H_{21}NO_3S_2$:

(20) (a) Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.; Aubke, F. *Inorg. Chem.* **1977**, *16*, 1414. (b) Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353. (c) Iwasawa, N.; Mukaiyama, T. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 71.

C, 56.61; H, 6.24; N, 4.13. Found: C, 56.64; H, 6.28; N, 4.15.

3-((Tetrahydro-5-oxo-2(*S*)-furanyl)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (14): yellow needles; mp 79.5–80 °C (from EtOAc–hexane); IR ($CHCl_3$) 1770, 1690, 1250, and 1162 cm^{-1}; ^1H NMR (100 Hz, $CDCl_3$) δ 0.98 and 1.07 (6 H, d, J = 6.8 Hz), 1.78–2.70 (5 H, m), 3.05 (1 H, dd, J = 1.0, 11.2 Hz), 3.58 (1 H, dd, J = 7.8, 11.2 Hz), 3.66 (2 H, d, J = 6.8 Hz), 4.88–5.22 (2 H, m); MS m/z 287 (M^+), 254, 202, 161, 127, 118, 85 (100). Anal. Calcd for $C_{12}H_{17}NO_3S_2$: C, 50.15; H, 5.96; N, 4.87. Found: C, 49.92; H, 5.96; N, 4.72.

5-Acetoxy-2(5*H*)-furanone (16). To a solution of 5-hydroxy-2(5*H*)-furanone (**4a**) (0.47 g, 4.70 mmol) in dry THF (25 mL) at 0 °C was added acetyl chloride (0.50 mL, 7.0 mmol) and triethylamine (0.98 mL, 7.0 mmol). The mixture was allowed to stir for 46 h at room temperature, filtered through Celite, concentrated in vacuo, and flash column chromatographed (elution with 33% EtOAc–hexane) to afford 0.272 g (41%) of **16** as a pale-yellow oil: IR ($CHCl_3$) 1795, 1765, 1750 (shoulder), 1735 (shoulder), 1608, 1085, 1017, and 1000 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.17 (3 H, s), 6.32 (1 H, dd, J = 1.0, 5.9 Hz), 7.00 (1 H, dd, J = 1.0, 1.5 Hz), 7.35 (1 H, dd, J = 1.5, 5.9 Hz).

Reaction of 5-Acetoxy-2(5*H*)-furanone (16) with Chiral Tin(II) Enolate 10. To a THF solution of the tin(II) enolate **10** (prepared from 0.80 g of tin(II) trifluoromethanesulfonate, 0.30 g of 3-acetyl-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (**9**), and 0.31 mL of *N*-ethylpiperidine as described above) was added a solution of 5-acetoxy-2(5*H*)-furanone (**16**) (0.162 g, 1.14 mmol) in dry THF (2 mL) at −5 °C, and then the mixture was stirred at −5 to 0 °C for 2 h. Quenching the reaction with phosphate buffer solution (pH 7.0), filtration off the precipitate through Celite, extraction with EtOAc, and workup gave a crude mixture. Flash column chromatography (elution with 25% EtOAc in hexane) afforded 0.112 g (37% recovered) of **9**, 0.10 g (42%, generated by decomposition of **9**) of 4(*S*)-isopropyl-1,3-thiazolidine-2-thione, and 0.136 g (84% recovered) of **16**. No alkylation product between **16** and the enolate **10** was isolated.

***N*-(2-Bromoethyl)-2,5-dihydro-5-oxo-2(*S*)-furanacetamide (17).** A mixture of **7a** (1.0 g, 3.50 mmol), (bromoethyl)amine hydrobromide (0.79 g, 3.85 mmol), and triethylamine (0.56 mL, 4.00 mmol) in THF (12 mL) and water (6 mL) was stirred at room temperature for 2 h. The solvents were removed to dryness, and the residue was submitted to extraction with CH_2Cl_2 and workup. Flash column chromatographic separation (elution with 20% acetone in CH_2Cl_2) of the crude product afforded 0.503 g (58%) of **17** as colorless prisms: mp 89–91 °C (from acetone–EtOAc); $[\alpha]^{21}_D$ −47.4° (c 0.57, $CHCl_3$); IR ($CHCl_3$) 3430, 3340, 1785, 1752, 1672, 1522, 1160, 1095, and 815 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.69 (2 H, d, J = 6.8 Hz), 3.36–3.84 (4 H, m), 5.48 (1 H, ddt, J = 1.5, 2.0, 7.0 Hz), 6.16 (1 H, dd, J = 2.0, 5.9 Hz), 6.84 (1 H, br s), 7.68 (1 H, dd, J = 1.5, 5.4 Hz); MS m/z 247 (M^+), 168, 154, 97, 83 (100); HRMS calcd for $C_8H_{10}NO_3Br$ MW 246.9871, found m/z 246.9879 (M^+). Anal. Calcd for $C_8H_{10}NO_3Br$: C, 38.73; H, 4.06; N, 5.65. Found: C, 38.82; H, 4.10; N, 5.68.

(1*S*,5*S*)-2-Oxa-6-aza-6-(2-bromoethyl)bicyclo[3.3.0]octane-3,7-dione (18). To a suspension of 60% NaH (15.2 mg, 0.381 mmol) in DMF (1 mL) at 0 °C was added **17** (189 mg, 0.762 mmol) in DMF (1 mL), and then the mixture was stirred at 10 °C for 5 h. Acetic acid (24 μL in 0.5 mL of MeOH) was added at −50 °C, and then the mixture was warmed to 0 °C and stirred for 10 min. Removal of the solvents under vacuum below 35 °C (water bath) and flash column chromatographic purification (elution with 20% acetone in CH_2Cl_2) of the residue afforded 0.156 g (83%) of **18** as colorless needles: mp 137–139 °C (from acetone–hexane); $[\alpha]^{23}_D$ +61.0° (c 0.39, $CHCl_3$); IR ($CHCl_3$) 1785, 1700, 1400, 1348, 1320, 1165, and 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.75–2.87 (4 H, m), 3.29–3.36 (1 H, m), 3.49–3.54 (1 H, m), 3.60–3.66 (1 H, m), 4.07–4.14 (1 H, m), 4.67 (1 H, dt, J = 1.95, 5.62 Hz), 5.15 (1 H, dt, J = 1.47, 5.62 Hz); MS m/z 247 (M^+), 203, 168, 154 (100), 112. Anal. Calcd for $C_8H_{10}NO_3Br$: C, 38.73; H, 4.06; N, 5.65. Found: C, 38.91; H, 4.05; N, 5.67.

***N*-((Ethoxycarbonyl)methyl)-2,5-dihydro-5-oxo-2(*S*)-furanacetamide (20a).** To a solution of **7a** (0.50 g, 1.75 mmol) in dry THF (7 mL) cooled at 0 °C was added glycine ethyl ester (0.19 g, 1.84 mmol) in dry THF (1 mL), and then the mixture was stirred at room temperature for 10 min. Removal of the solvent and flash column chromatography (elution with 20% acetone in CH_2Cl_2) afforded 0.398 g (100%) of **20a** as colorless needles: mp 109–110 °C (from EtOAc–Et_2O); $[\alpha]^{23}_D$ −63.3° (c 0.52, $CHCl_3$); IR ($CHCl_3$) 3400, 1782, 1750, 1672, 1520, 1155, and 1093 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.29 (3 H, t, J = 7.3 Hz), 2.65 and 2.77 (2 H, AB qd, J = 14.7, 6.8 Hz), 3.98 and 4.08 (2 H, AB qd, J = 17.2, 5.4 Hz), 4.21 (2 H, q, J = 7.3 Hz), 5.46 (1 H, ddt, J = 1.5, 2.0, 6.8 Hz), 6.15 (1 H, dd, J = 2.0, 5.6 Hz), 6.50 (1 H, br s), 7.68 (1 H, dd, J = 1.5, 5.9 Hz); MS m/z 227 (M^+), 209, 181, 154, 125, 97, 83, 55. Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.65; H, 5.70; N, 6.13.

***N*-(2-Hydroxyethyl)-2,5-dihydro-5-oxo-2(*S*)-furanacetamide (20b).** To a solution of **7a** (1.0 g, 3.50 mmol) in dry THF (20 mL) cooled at 0 °C was added ethanolamine (0.212 mL, 3.50 mmol), and then the mixture was stirred at room temperature for 10 min. Removal of the solvent and flash column chromatography (elution with 50% acetone in CH_2Cl_2) of the residue afforded 0.63 g (97%) of **20b** as colorless needles: mp 86–88 °C (from acetone–EtOAc); $[\alpha]^{21}_D$ −60.2° (c 0.44, EtOH); IR (KBr) 3300, 1725, 1630, 1540, and 1055 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 2.54 and 2.71 (2 H, AB qd, J = 14.0, 4.9 Hz), 3.16–3.74 (4 H, m), 4.12 (1 H, br s, exchangeable by D_2O), 5.46 (1 H, ddt, J = 1.5, 2.0, 7.0 Hz), 6.12 (1 H, dd, J = 2.0, 6.0 Hz), 7.48 (1 H, br s), 7.69 (1 H, dd, J = 1.5, 6.0 Hz); MS m/z 185 (M^+), 167, 155, 125, 83. Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.56. Found: C, 51.93; H, 5.94; N, 7.58.

(1*S*,5*S*)-2-Oxa-6-aza-6-((ethoxycarbonyl)methyl)bicyclo[3.3.0]octane-3,7-dione (21a). To a suspension of 60% NaH (12.4 mg, 0.31 mmol) in DMF (1 mL) was added **20a** (141 mg, 0.62 mmol) in DMF (1.5 mL) at 0 °C, and then the mixture was stirred at 10 °C for 5 h. Acetic acid (26.7 μL, 0.46 mmol in 0.5 mL MeOH) was added at −50 °C, and then the mixture was warmed to 0 °C and stirred for 10 min. Removal of the solvents in vacuo below 35 °C (water bath) and flash column chromatography (elution with 50% EtOAc in CH_2Cl_2) of the residue afforded 129 mg (91%) of **21a** as a colorless oil: $[\alpha]^{23}_D$ +15.2° (c 1.22, $CHCl_3$) [lit.[11i] $[\alpha]^{11}_D$ +12.4° (c 1.28, $CHCl_3$)]; IR ($CHCl_3$) 1785, 1738, 1703, 1670, 1385, 1192, 1162, 1042, and 1015 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.28 (3 H, t, J = 7.3 Hz), 2.66–2.86 (4 H, m), 3.67 and 4.40 (2 H, AB q, J = 18.1 Hz), 4.20 (2 H, q, J = 7.3 Hz), 4.60 (1 H, dt, J = 2.9, 5.1 Hz), 5.16 (1 H, dt, J = 2.9, 5.0 Hz); MS m/z 227 (M^+), 209, 182, 154, 112; HRMS calcd for $C_{10}H_{13}NO_5$ MW 227.0797, found m/z 227.0798.

(1*S*,5*S*)-2-Oxa-6-aza-6-(2-hydroxyethyl)bicyclo[3.3.0]octane-3,7-dione (21b). To a suspension of 60% NaH (27.4 mg, 0.685 mmol) in DMF (1 mL) was added **20b** (105.7 mg, 0.571 mmol) in DMF (1 mL) at 0 °C, and then the mixture was stirred at 10 °C for 5 h. Acetic acid (43 μL in 0.5 mL MeOH) was added at −50 °C, and then the mixture was warmed to 0 °C and stirred for 10 min. Removal of the solvents in vacuo below 35 °C (water bath) and flash column chromatography (elution with 50% acetone in CH_2Cl_2) of the residue afforded 81.5 mg (77%) of **21b** as colorless prisms: mp 134–135 °C (from acetone–EtOAc); $[\alpha]^{21}_D$ +56.8° (c 0.23, EtOH); IR (KBr) 3260, 1770, 1630, 1165, and 1035 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 2.44–3.00 (4 H, m), 3.20 (1 H, s, exchangeable by D_2O), 3.44–3.78 (4 H, m), 4.50–4.76 (1 H, m), 5.14 (1 H, dt, J = 1.5, 6.0 Hz); MS m/z 185 (M^+), 167, 154, 142, 112 (100), 96. Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.56. Found: C, 51.78; H, 5.86; N, 7.66.

(1*S*,5*S*)-2-Oxa-6-aza-6-(2-(trimethylacetoxy)ethyl)bicyclo[3.3.0]octane-3,7-dione (21c). To a solution of **21b** (85 mg, 0.459 mmol) in CH_3CN (4 mL) was added trimethylacetyl chloride (0.17 mL, 1.378 mmol) and Et_3N (0.19 mL, 1.378 mmol) at 0 °C, and then the mixture was stirred at room temperature for 9 h. The reaction mixture was diluted with EtOAc, and the precipitate was filtered off through Celite. The filtrate was evaporated in vacuo to give a residue which was subjected to flash column chromatography (elution with 10% acetone in CH_2Cl_2) to afford 103.7 mg (84%) of **21c** as colorless crystals: mp 112–113 °C (from benzene–hexane) (lit.[11h,k] mp 109–110 °C, mp 112–113 °C); $[\alpha]^{23}_D$ +53.4° (c 0.61, $CHCl_3$) [lit.[11h,k] $[\alpha]^{17}_D$ +48.8° (c 0.53, $CHCl_3$), $[\alpha]^{26}_D$ +55.2° (c 0.69, $CHCl_3$)]; IR ($CHCl_3$) 1785, 1720, 1700, 1400, 1275, 1142, and 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (9 H, s), 2.75 (2 H, d, J = 4.9 Hz), 2.79 (2 H, d, J = 4.4 Hz), 3.08–3.15 (1 H, m), 4.01–4.11 (2 H, m), 4.32–4.39 (1 H, m), 4.54 (1 H, dt, J = 5.86, 3.91 Hz), 5.12 (1 H, dt, J = 2.44, 5.37 Hz); MS m/z 269 (M^+), 226, 184, 167 (100), 154 (100), 142, 125. Anal. Calcd for

$C_{13}H_{19}NO_6$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.83; H, 7.04; N, 5.19.

(1*S*,5*S*)-2-Oxa-6-aza-6-(2-acetoxyethyl)bicyclo[3.3.0]octane-3,7-dione (21d). To a solution of **21b** (25 mg, 0.189 mmol) in CH_3CN (3 mL) was added acetyl chloride (32 μL, 0.454 mmol) and Et_3N (64 μL, 0.454 mmol) at 0 °C, and then the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc, and the precipitate was filtered off through Celite. Removal of the solvent of the filtrate and flash column chromatographic purification (elution with 50% acetone in CH_2Cl_2) of the residue afforded 39.4 mg (92%) of **21d** as a colorless oil: $[\alpha]^{22}_D$ +39.7° (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 1785, 1732, 1695, 1210, and 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (3 H, s), 2.75–2.82 (4 H, m), 3.22–3.28 (1 H, m), 3.79–3.86 (1 H, m), 4.10–4.15 (1 H, m), 4.32–4.37 (1 H, m), 4.50 (1 H, dt, *J* = 1.95, 5.62 Hz), 5.12 (1 H, dt, *J* = 5.37, 3.91 Hz); MS *m/z* 227 (M^+), 184, 167, 154, 142, 125, 112, 55, 43 (100); HRMS calcd for $C_{10}H_{13}NO_5$ MW 227.0764, found *m/z* 227.0756 (M^+).

Preparation of Thiolactams. (1*S*,5*S*)-2-Oxa-6-aza-6-(2-acetoxyethyl)-3-oxobicyclo[3.3.0]octane-7-thione (22c): Representative Procedure. A solution of **21d** (0.334 g, 1.468 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphatane 2,4-disulfide (0.303 g, 0.749 mmol) in toluene (5 mL) was heated at 105 °C (oil bath temperature) for 1 h under argon. Removal of the solvent and flash column chromatography (elution with 50% EtOAc in CH_2Cl_2) of the residue afforded 0.2865 g (80%) of **22c** as colorless needles: mp 122–123 °C (from EtOAc–hexane); $[\alpha]^{25}_D$ +103.5° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 1790, 1740, 1465, 1215 (br), and 1040 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.08 (3 H, s), 2.86–2.98 (2 H, m), 3.32–3.42 (2 H, m), 3.50–3.80 (1 H, m), 4.16–4.44 (2 H, m), 4.44–4.66 (1 H, m), 4.80 (1 H, dt, *J* = 2.4, 5.4 Hz), 5.15 (1 H, dt, *J* = 2.4, 5.1 Hz); MS *m/z* 243 (M^+), 200, 182, 158, 112, 99, 71, 43 (100). Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76. Found: C, 49.31; H, 5.36; N, 5.68.

(1*S*,5*S*)-2-Oxa-6-aza-6-((ethoxycarbonyl)methyl)-3-oxobicyclo[3.3.0]octane-7-thione (22a): 83% yield; colorless crystals, mp 161–163 °C (from EtOAc) (lit.[11i] mp 157–158 °C); $[\alpha]^{25}_D$ +57.9° (*c* 0.57, $CHCl_3$) [lit.[11i] $[\alpha]^{12}_D$ +57.0° (*c* 0.44, $CHCl_3$)]; IR ($CHCl_3$) 1790, 1735, 1455, 1190, 1162, and 1135 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.30 (3 H, *J* = 7.3 Hz), 2.83 (2 H, d, *J* = 3.9 Hz), 3.36–3.46 (2 H, m), 4.10 and 4.85 (2 H, AB q, *J* = 17.1 Hz), 4.23 (2 H, q, *J* = 7.3 Hz), 4.80–4.88 (1 H, m), 5.19 (1 H, dt, *J* = 2.5, 4.8 Hz); MS *m/z* 243 (M^+), 210, 197, 171, 71. Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76. Found: C, 49.32; H, 5.31; N, 5.63.

(1*S*,5*S*)-2-Oza-6-aza-6-(2-(trimethylacetoxy)ethyl)-3-oxobicyclo[3.3.0]octane-7-thione (22b): 88% yield; colorless needles, mp 108–109 °C (from EtOAc–hexane); $[\alpha]^{26}_D$ +116.2° (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) 1783, 1720, 1458, 1275, and 1140 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.20 (9 H, s), 2.80–2.92 (2 H, m), 3.28–3.40 (2 H, m), 3.36–3.56 (1 H, m), 4.10–4.48 (2 H, m), 4.48–4.72 (1 H, m), 4.85 (1 H, dt, *J* = 3.4, 5.1 Hz), 5.16 (1 H, dt, *J* = 2.4, 5.1 Hz); MS *m/z* 285 (M^+), 200, 183, 158, 85, 57 (100). Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.38; H, 6.69; N, 4.84.

Reductive Desulfurization of Thiolactams. (1*S*,5*S*)-2-Oxa-6-aza-6-(2-acetoxyethyl)bicyclo[3.3.0]octan-3-one (23c): Representative Procedure. To a solution of triethyloxonium tetrafluoroborate (170 mg, 0.895 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of **22c** (167.5 mg, 0.688 mmol) in dry CH_2Cl_2 (5 mL) under ice cooling, and then the mixture was stirred at room temperature for 3 h. $NaBH_3CN$ (95%) (182 mg, 2.747 mmol) in MeOH (4.14 mL) and acetic acid (0.36 mL) were added to the mixture at 0 °C and stirred at 0 °C for 1 h and then at room temperature for 3 h. The solvent was removed, and saturated $NaHCO_3$ was added to the residue to reach pH 9.0. Extraction with $CHCl_3$ (10 mL × 5), drying over Na_2SO_4, concentration, and flash column chromatography (elution with 20% EtOAc in CH_2Cl_2) afforded 145 mg (99%) of **23c** as colorless prisms: mp 64–65 °C (from Et_2O); $[\alpha]^{25}_D$ −21.2° (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 1770, 1732, 1220 (br), 1168, and 1040 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.06 (3 H, s), 2.00–3.04 (7 H, m), 3.06–3.32 (2 H, m), 3.94–4.34 (2 H, m), 4.95 (1 H, dt, *J* = 3.9, 6.5 Hz); MS *m/z* 213 (M^+), 170, 153, 140 (100), 112, 70, 43. Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.21; H, 7.04; N, 6.51.

(1*S*,5*S*)-2-Oxa-6-aza-6-((ethoxycarbonyl)methyl)bicyclo[3.3.0]octan-3-one (23a): 90% yield; colorless needles, mp 50.5–51.5 °C (from Et_2O–hexane) [lit.[11i] mp 52–53 °C); $[\alpha]^{25}_D$ −36.9° (*c* 0.58, $CHCl_3$) [lit.[11i] $[\alpha]^{16}_D$ −35.2° (*c* 0.563, $CHCl_3$)]; IR ($CHCl_3$) 1772, 1735, 1185, and 1170 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.28 (3 H, t, *J* = 7.3 Hz), 1.90–2.50 (2 H, m), 2.54–2.62 (2 H, m), 2.62–2.90 (1 H, m), 3.10–3.34 (1 H, m), 3.34 and 3.50 (2 H, AB q, *J* = 16.6 Hz), 3.68 (1 H, dt, *J* = 3.4, 5.5 Hz), 4.18 (2 H, q, *J* = 7.3 Hz), 5.00 (1 H, dt, *J* = 3.4, 6.2 Hz); MS *m/z* 213 (M^+), 140 (100). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.02; H, 7.04; N, 6.64.

(1*S*,5*S*)-2-Oxa-6-aza-6-(2-(trimethylacetoxy)ethyl)bicyclo[3.3.0]octan-3-one (23b): 93% yield; a colorless oil; $[\alpha]^{26}_D$ −13.9° (*c* 0.92, $CHCl_3$) [lit.[11h] $[\alpha]^{11}_D$ −8.6° (*c* 0.78, $CHCl_3$)]; IR ($CHCl_3$) 1770, 1715, 1275, and 1150 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.20 (9 H, s), 1.90–3.06 (7 H, m), 3.10–3.36 (2 H, m), 3.92–4.36 (2 H, m), 4.94 (1 H, dt, *J* = 3.4, 6.4 Hz); MS *m/z* 255 (M^+), 240, 170, 153, 140 (100), 57; HRMS calcd for $C_{13}H_{21}NO_4$ MW 255.1468, found *m/z* 255.1467 (M^+).

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Supplementary Material Available: Details of the X-ray diffraction analysis of compounds **7a**, **7b**, **7g**, and **14** (18 pages). Ordering information is given on any current masthead page.