JOC The Journal of Organic Chemistry

ARTICLE

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Stereocontrolled Synthesis of Substituted Bicyclic Ethers through Oxy-Favorskii Rearrangement: Total Synthesis of (±)-Communiol E

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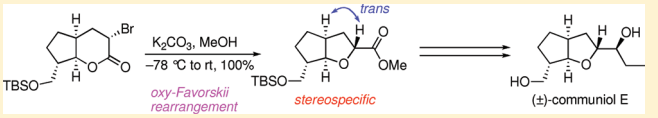
Supporting Information

ABSTRACT: The potential of the oxy-Favorskii rearrangement to form branched *cis*-fused bicyclic ethers was explored. Both tertiary and quaternary centers were constructed in highly stereospecific manners. Methanol and primary amines were effective nucleophiles for the rearrangement. The total synthesis of (±)-communiol E was achieved based on this method.



INTRODUCTION

Oxabicycles are important core structures of natural products and bioactive molecules. Communiol E (**1**),[1] laurenenyne A (**2**),[2] and dysiherbaine (**3**)[3] are representatives of this family (Figure 1). A key structure in these molecules is the *cis*-fused bicyclic ether that has an alkyl substituent *cis* to the bridgehead hydrogen at the carbon adjacent to the ring oxygen. Various synthetic approaches to such molecules have been described,[1b,4] but stereocontrolled routes to the substituted oxabicycles are still being researched.[5]

Base-induced ring contraction of α-halolactones, i.e., the oxy-Favorskii rearrangement, is a promising method for constructing branched oxacyclic systems.[6] Several synthetic applications have been reported;[7] however, the generality of substrates, scope of nucleophiles, and detailed stereospecificity remain unclear. We conducted a systematic study with sterically rigid bicyclic molecules not only to evaluate the potential of the oxy-Favorskii rearrangement but also to provide a new synthetic method for the construction of substituted oxabicyclic skeletons in the above natural products. Herein, we wish to report a highly convenient, stereocontrolled route to branched *cis*-fused bicyclic ethers based on halolactonization, α-bromination, and oxy-Favorskii rearrangement. It is important to note that both the tertiary and the quaternary centers were constructed in highly stereospecific manners. We also succeeded in the total synthesis of (±)-communiol E (**1**), a bicyclic polyketide isolated from *Podospora communis*, by the newly developed oxy-Favorskii methodology.

RESULTS AND DISCUSSION

Scheme 1 shows the general concept. The *cis* ring juncture in the oxabicycle would be established by halolactonization with carboxylic acid **4**. After reduction or functionalization of the resulting halide, halogenation at the α-position in **5** would be expected to occur from the convex face to give **6**. It is thought that oxy-Favorskii rearrangement takes place through the alkoxide intermediate **8** and intramolecular S_N2-type displacement delivers the *trans*-ester **9**. We envisioned that the entire synthetic process might be stereospecific and applicable to a variety of bicyclic lactones.

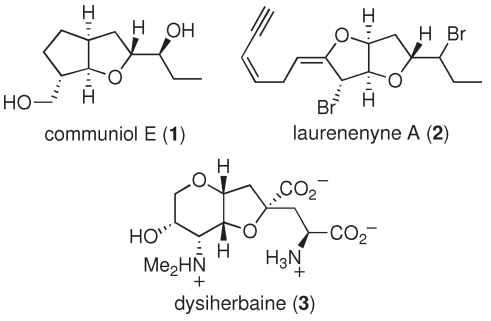


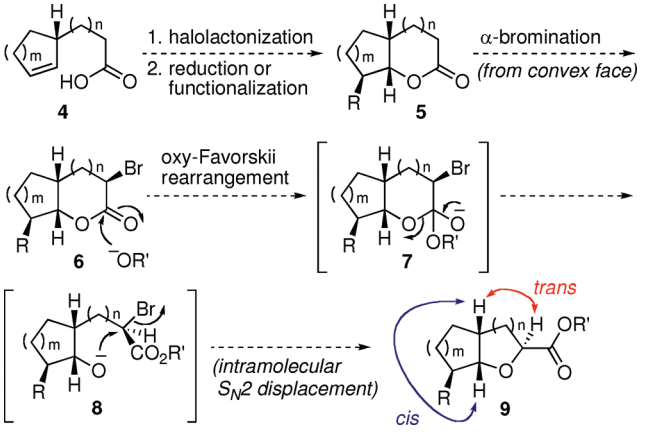
Figure 1. Structures of oxabicyclic natural products.

Thus, three kinds of racemic carboxylic acids, (±)-**4a**−**c**, which varied in ring size and length of carbon chain, were prepared[8] (Scheme 2). Iodolactonization of (±)-**4a**−**c** under the conventional conditions,[9] followed by radical reduction, afforded the *cis*-fused bicyclic lactones **5a**−**c** exclusively.[10] Subsequent α-bromination was best realized by treatment with $LiN(TMS)_2$/TMSCl followed by NBS.[11] In all cases, β-bromolactones **6a**−**c** predominated. The selectivity was clearly dependent on the ring size. For a small-ring compound like **5c**, the concave face is highly shielded such that the electrophile must approach from the less hindered convex face, thereby providing **6c** as a single isomer.

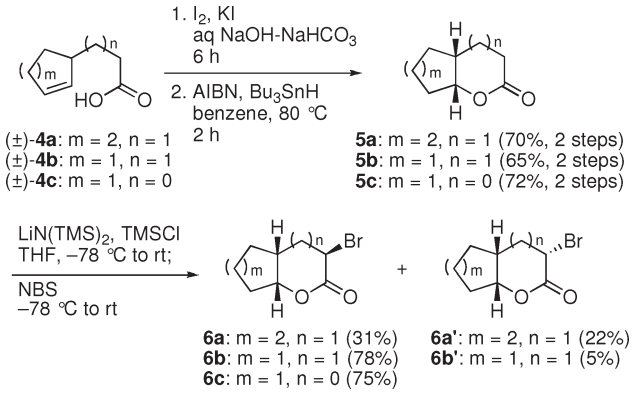
Received: May 25, 2011
Published: July 25, 2011

   dx.doi.org/10.1021/jo201064h | *J. Org. Chem.* 2011, 76, 7096–7103

Scheme 1. Concept of this Work



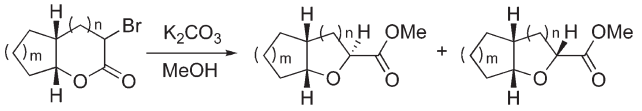
Scheme 2. Iodolactonization and α-Bromination

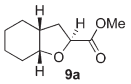
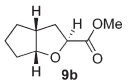
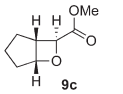
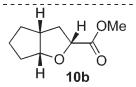


The stage was set for the oxy-Favorskii rearrangement. The stereochemically pure β-bromolactones **6a**–**c** were treated with K_2CO_3 in MeOH at room temperature (Table 1). The expected ring-contracted esters **9a**–**c** were obtained as the major products (entries 1, 3, and 5). Remarkably, formation of the five-membered ring was quite efficient, while the oxetane ring was inaccessible, probably due to ring strain. Contrary to our expectations, considerable amounts of epimeric esters **10a**–**c** were detected, which suggested that epimerization at the α-position took place. A comparative study with α-bromolactone **6b′**, the minor component in the α-bromination step, revealed that the reaction was stereospecific and there was no equilibrium between **9b** and **10b** (entry 7). In other words, partial racemization occurred before rearrangement, not after formation of the product. This led us to investigate the reaction under low temperature. Indeed, racemization was minimized when the temperature was first cooled to −78 °C and then warmed to room temperature (entries 2 and 4).

We next explored the generality of the oxy-Favorskii rearrangement by varying the nucleophiles (Table 2). Interestingly, neither a secondary alcohol (*i*PrOH) nor a tertiary alcohol (*t*BuOH) induced rearrangement (entry 2), while primary amines such as $MeNH_2$ and *i*PrNH$_2$ resulted in good yields and selectivities (entries 3 and 4). With a secondary amine (e.g., Et_2NH), E2-type elimination prevailed over

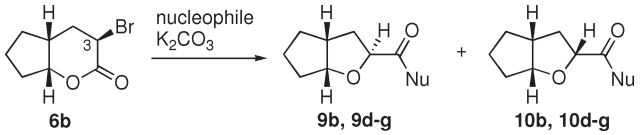
Table 1. Oxy-Favorskii Rearrangement[a]



entry	6	temp	major product	yield (%)[b] (9:10)[c]
1	6a	rt	 9a	82 (2:1)
2	6a	–78 °C to rt		78 (10:1)
3	6b	rt	 9b	78 (7:1)
4	6b	–78 °C to rt		79[d] (15:1)
5	6c	rt	 9c	15 (>20:1)
6	6c	–78 °C to rt		5 (>20:1)
7	6b'	–78 °C to rt	 10b	74 (1:4)

[a] The reactions were carried out in MeOH (0.1 M) in the presence of K_2CO_3 (1 equiv). [b] Isolated yield. [c] Determined by crude ^{1}H NMR. [d] NMR yield.

Table 2. Diversity of Nucleophiles



entry	nucleophile	temp	9 (Nu)	yield[a] (%) (9:10)[b]
1	MeOH	−78 °C to rt	**9b** (OMe)	78 (15:1)
2	*i*PrOH	rt	**9d** (O*i*Pr)	0[c]
3[d]	$MeNH_2$	rt	**9e** (NHMe)	100 (>20:1)
4[d]	*i*PrNH$_2$	rt	**9f** (NH*i*Pr)	74 (6:1)
5[d]	Et_2NH	rt	**9g** (NEt$_2$)	0[e]

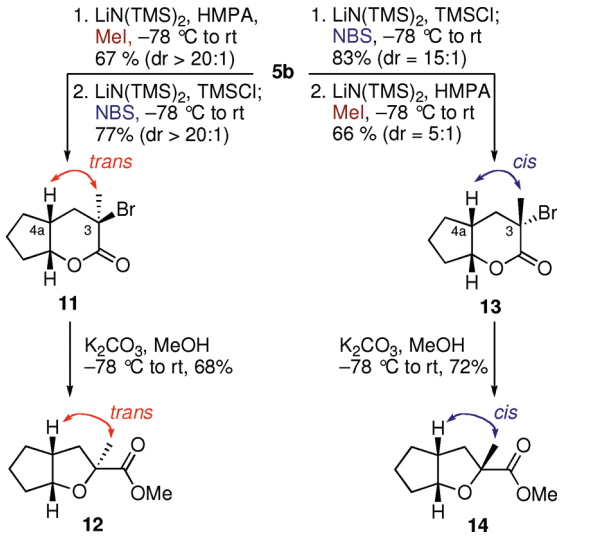
[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Racemization at C3 was observed. [d] The reaction was carried out in DMF. [e] α,β-Unsaturated lactone was exclusively obtained.

rearrangement (entry 5). The reaction was not applicable to thiol and selenol nucleophiles, where the S_N2 reaction occurred instead.[12]

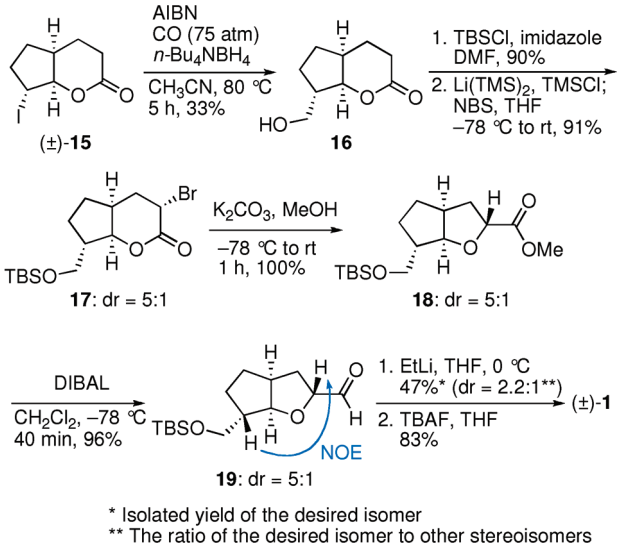
We next turned our attention to the formation of the quaternary center, which is found in natural products such as dysiherbaine (**3**). Owing to the highly stereospecific nature of the oxy-Favorskii reaction, it was expected that both stereoisomers could be accessed by conducting an alkylation–bromination sequence in the appropriate order. Thus, successive methylation–bromination with the bicyclic lactone **5b** furnished bromolactone **11**, in which the C3-methyl and C4a-H are in a *trans* relationship (Scheme 3). In contrast, a bromination–methylation sequence with **5b** afforded **13**, where the C3-methyl and C4a-H are *cis*, as the major product. These stereochemical outcomes are rationalized by the preferential addition of the electrophiles from the less hindered convex face. Subsequent rearrangements of **11** and **13** proceeded stereoselectively, providing esters **12** and **14**,

dx.doi.org/10.1021/jo201064h |*J. Org. Chem.* 2011, 76, 7096–7103

Scheme 3. Stereodivergent Formation of the Quaternary Center



Scheme 4. Total Synthesis of (±)-Communiol E



respectively, in reasonable yields. It should be noted that the intramolecular nucleophilic substitution onto the tertiary bromide proceeded smoothly without the influence of stereochemistry.

After identifying the generality of the oxy-Favorskii rearrangement for the bicyclic system, we undertook the total synthesis of communiol E (**1**) (Scheme 4). Iodolactone (±)-**15** was submitted to the recently developed tin-free radical/ionic hydroxymethylation conditions to afford hydroxylactone **16**.[13] It is noted that the highly susceptible lactone moiety survived under these reduction conditions, albeit in modest yield. After protection of the hydroxyl group as a TBS ether, bromination was effected to provide an inseparable mixture of bromolactones **17** in favor of the desired diastereomer. The crucial rearrangement was realized in a stereospecific manner and afforded ester **18** quantitatively.[14] DIBAL reduction of **18** at −78 °C gave aldehyde **19** without forming the alcohol, which was followed by ethylation and deprotection to furnish (±)-communiol E (**1**). We have explored a number of conditions in the ethylation step and found that treatment of **19** with EtLi in THF at 0 °C gave the best yield and selectivity.[15,16] The major drawback of the reaction was the recovery of starting material, which might be caused by enolization of the aldehyde. This problem was not resolved by using other organometallic reagents such as EtMgBr, EtMgBr/$CeCl_3$,[17] and EtLi/$CeCl_3$ or by using additives such as HMPA[18] and $ZnCl_2$. All spectral data of synthetic **1** were identical to those of the natural product.

CONCLUSION

We have shown the potential of the oxy-Favorskii rearrangement in the synthesis of substituted oxabicycles. All synthetic processes were stereospecific and useful for constructing branched *cis*-fused bicyclic hydrofurans. Methanol and primary amines were effective nucleophiles for the rearrangement. The quaternary center was also constructed stereospecifically by conducting an alkylation−bromination rearrangement sequence in the appropriate manner. Furthermore, total synthesis of (±)-communiol E was achieved. Further studies to synthesize other natural products including laurenenynes and dysiherbaine are currently underway in our laboratory.

EXPERIMENTAL SECTION

(±)-3-(Cyclohex-2-enyl)propanoic Acid (4a). To a suspension of magnesium turnings (166 mg, 6.83 mmol) in THF (5 mL) was added dropwise a solution of 2-(2-bromoethyl)-1,3-dioxolane (1.24 g, 6.83 mmol) in THF (5 mL). After dissolution of all of the magnesium, a solution of 3-bromocyclohexene (1.00 g, 6.21 mmol) in THF (5 mL) was slowly added to the Grignard reagent. The solution was stirred at room temperature for 1.5 h before addition of saturated aqueous NH_4Cl solution. The resulting mixture was extracted with Et_2O (2×), and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5) to give 2-(2-cyclohex-2-enylethyl)-1,3-dioxolane[19] (1.05 g, 5.76 mmol, 93%). To a solution of dioxolane (1.05 g, 5.76 mmol) in CH_3CN-H_2O (3:1, 57 mL) was added 1 M aqueous H_2SO_4 (19 mL). The mixture was stirred at room temperature for 19 h before addition of saturated $NaHCO_3$ solution. The resulting mixture was extracted with Et_2O (2×), and the combined organic layer was dried over anhydrous $MgSO_4$. Concentration of the ethereal solution gave the corresponding aldehyde (796 mg). To a solution of aldehyde (796 mg, 5.76 mmol) in *t*-BuOH-H_2O (4:1, 12 mL) were added 2-methyl-2-butene (3.05 mL, 28.8 mmol), KH_2PO_4 (784 mg, 5.76 mmol), and $NaClO_2$ (1.56 g, 17.3 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h before addition of $CHCl_3$ and 1 M aqueous HCl. The resulting mixture was extracted with $CHCl_3$ (2×), and the combined organic layer was washed with 1 M aqueous NaOH. The aqueous layer was acidified with 1 M aqueous HCl and extracted again with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give carboxylic acid **4a** (315 mg, 2.04 mmol, 35% for 2 steps). **4a**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddd, 1H, J = 10, 5.6, 2.8 Hz), 5.54 (br dd, 1H, J = 10, 2.0 Hz), 2.40 (t, 2H, J = 7.6 Hz), 2.15−2.06 (m, 1H), 2.02−1.94 (m, 2H), 1.83−1.46 (m, 5H), 1.26−1.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 130.9, 128.0, 34.6, 31.6, 31.0, 28.7, 25.4, 21.4; FT-IR (film) 3018, 2927, 2861, 2667, 1713, 1650, 1452, 1415, 1313, 1278, 1252, 1216, 1160, 1137, 1092, 1060 cm^{-1}.

(±)-(4a*R*,8a*R*)-Octahydro-2*H*-chromen-2-one (5a).[20] To a solution of carboxylic acid **4a** (102 mg, 0.660 mmol) in 0.5 M aqueous $NaHCO_3$ (3.7 mL, 1.85 mmol) were added 2.8 M aqueous NaOH

dx.doi.org/10.1021/jo201064h |*J. Org. Chem.* 2011, 76, 7096–7103

(59 μL, 0.165 mmol), KI (657 mg, 3.96 mmol), and iodine (335 mg, 1.32 mmol). The mixture was stirred at room temperature for 6 h and then diluted with $CHCl_3$ and saturated $Na_2S_2O_3$ solution. The resulting mixture was extracted with $CHCl_3$ (2×), and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated to give the corresponding iodolactone (147 mg, 0.525 mmol, 80%), which was used for the next reaction without further purification.

To a solution of iodolactone (147 mg, 0.525 mmol) in benzene (5 mL) were added Bu_3SnH (212 μL, 0.787 mmol) and AIBN (8.60 mg, 52.5 μmol). The mixture was stirred at 80 °C for 2 h and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 3) to give lactone **5a** (70.1 mg, 0.455 mmol, 87%). **5a**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49−4.46 (m, 1H), 2.50 (t, 2H, *J* = 7.6 Hz), 2.05−1.87 (m, 3H), 1.71−1.25 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 78.4, 32.7, 30.4, 27.0, 26.6, 24.5, 24.4, 20.2; FT-IR (film) 2933, 2860, 1734, 1448, 1350, 1296, 1244, 1196, 1161, 1138, 1107, 1065 cm^{-1}.

(±)-(4a*R*,7a*R*)-Hexahydrocyclopenta[*b*]pyran-2(3*H*)-one (5b).[21] To a solution of carboxylic acid **4b**[13] (100 mg, 0.713 mmol) in 0.5 M aqueous $NaHCO_3$ (4.0 mL, 2.00 mmol) were added 2.8 M aqueous NaOH (63.5 μL, 0.178 mmol), KI (711 mg, 4.28 mmol), and iodine (507 mg, 2.00 mmol). The mixture was stirred at room temperature for 3.5 h and then diluted with $CHCl_3$ and saturated $Na_2S_2O_3$ solution. The resulting mixture was extracted with $CHCl_3$ (3×), and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a corresponding iodolactone (158 mg, 0.594 mmol, 83%). Pale yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.91 (dd, 1H, *J* = 6.8, 2.0 Hz), 4.36−4.33 (m, 1H), 2.86−2.77 (m, 1H), 2.52−2.45 (ddd, 1H, *J* = 16.8, 6.4, 4.8 Hz), 2.38−2.30 (m, 1H), 2.27−2.18 (m, 1H), 2.12−2.04 (m, 1H), 1.67−1.59 (m, 1H), 1.58−1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 90.3, 36.0, 34.0, 30.1, 28.4, 27.9, 23.7; IR (neat) 2950, 2871, 1745 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_8H_{11}IO_2$ $[M]^+$ 265.9804, found 265.9806.

To a solution of iodolactone (123 mg, 0.464 mmol) in benzene (4 mL) were added Bu_3SnH (187 μL, 0.696 mmol) and AIBN (7.6 mg, 46 μmol). The mixture was stirred at 80 °C for 2 h and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 1) to give lactone **5b** (48.7 mg, 0.347 mmol, 75%). **5b**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (td, 1H, *J* = 6.0, 3.2 Hz), 2.51−2.45 (m, 1H), 2.39−2.25 (m, 2H), 2.21−2.13 (m, 1H), 2.03−1.76 (m, 4H), 1.63−1.54 (m, 2H), 1.50−1.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7, 83.4, 37.0, 33.7, 31.0, 28.8, 23.7, 23.1; IR (film) 2953, 2873, 1743, 1459, 1436, 1344, 1322, 1250, 1185, 1138, 1097, 1077, 1045, 1020 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_8H_{13}O_2$ $[M + H]^+$ 141.0916, found 141.0862.

(±)-(3a*R*,6a*R*)-Hexahydro-2*H*-cyclopenta[*b*]furan-2-one (5c).[22] To a solution of 2-(cyclopent-2-enyl)acetic acid (100 mg, 0.792 mmol) in 0.5 M aqueous $NaHCO_3$ (4.44 mL, 2.22 mmol) were added 2.8 M aqueous NaOH (70.7 μL, 0.178 mmol), KI (789 mg, 4.75 mmol), and iodine (401 mg, 1.58 mmol). The mixture was stirred at room temperature for 1.5 h and then diluted with $CHCl_3$ and saturated $Na_2S_2O_3$ solution. The resulting mixture was extracted with $CHCl_3$ (3×), and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a 4:1 inseparable mixture of 5-*exo*-cyclized iodolactone and 6-*endo*-cyclized iodolactone (196 mg, 0.778 mmol, 98%). To a solution of iodolactones (188 mg, 0.747 mmol) in benzene (7 mL) were added Bu_3SnH (301 μL, 1.12 mmol) and AIBN (12.3 mg, 74.7 μmol). The mixture was stirred at 80 °C for 2 h and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 3) to give lactone **5c** (69.8 mg, 0.553 mmol, 74%) and 2-oxabicyclo[3.2.1]octan-3-one (17.4 mg, 0.140 mmol, 18%). **5c**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (br t, 1H, *J* = 6.8 Hz), 2.91−2.83 (m, 1H), 2.82 (dd, 1H, *J* = 17, 1.0 Hz), 2.27 (dd, 1H, *J* = 17, 2.0 Hz), 2.06−2.02 (m, 1H), 1.89−1.80 (m, 1H), 1.78−1.64 (m, 3H), 1.55−1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 86.5, 38.0, 36.2, 33.7, 33.6, 23.5. 2-Oxabicyclo[3.2.1]octan-3-one: colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85−4.84 (m, 1H), 2.71 (ddd, 1H, *J* = 18.4, 5.2, 2.4 Hz), 2.55−2.52 (m, 1H), 2.57 (dt, 1H, *J* = 18.4, 2.0 Hz), 2.15 (td, 1H, *J* = 9.6, 2.4 Hz), 2.00−1.86 (m, 2H), 1.73−1.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 86.5, 38.0, 36.2, 33.7, 33.6, 23.5.

(±)-(3*R*,4a*R*,8a*R*)-3-Bromooctahydro-2*H*-chromen-2-one (6a). To a solution of lactone **5a** (49.9 mg, 0.324 mmol) in THF (1.6 mL) was added $LiN(TMS)_2$ (1.0 M solution in THF, 363 μL, 0.363 mmol) at −78 °C. The mixture was stirred at −78 °C for 1 h followed by the addition of TMSCl (51.0 μL, 0.405 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 0.5 h. The mixture was again cooled to −78 °C followed by the addition of NBS (86.5 mg, 0.486 mmol) in THF (1.5 mL). The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with H_2O and extracted with Et_2O (2×). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5) to give bromolactones **6a** (23.1 mg, 0.0991 mmol, 31%) and **6a′** (17.9 mg, 0.0768 mmol, 24%). **6a**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (quint, 1H, *J* = 3.2 Hz), 4.55 (dd, 1H, *J* = 6.4, 5.6 Hz), 2.45−2.29 (m, 2H), 2.24−2.16 (m, 1H), 1.97−1.90 (m, 1H), 1.71−1.30 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 79.0, 38.8, 35.5, 32.0, 30.0, 27.3, 23.7, 20.6; FT-IR (film) 2935, 2860, 1736, 1448, 1352, 1309, 1263, 1228, 1207, 1184, 1144, 1113, 1061, 1022 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_9H_{14}{}^{79}BrO_2$ $[M + H]^+$ 233.0177, found 233.0138. **6a′**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (dd, 1H, *J* = 11.2, 8.4 Hz), 4.59−4.54 (m, 1H), 2.78−2.70 (m, 1H), 2.18−2.09 (m, 1H), 2.03−1.95 (m, 2H), 1.71−1.24 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 77.8, 42.0, 36.8, 34.7, 29.6, 29.1, 23.8, 20.6.

(±)-(3*R*,4a*R*,7a*R*)-3-Bromohexahydrocyclopenta[*b*]pyran-2(3*H*)-one (6b). To a solution of lactone **5b** (557 mg, 3.97 mmol) in THF (14 mL) was added $LiN(TMS)_2$ (1.0 M solution in THF, 4.45 mL, 4.45 mmol) at −78 °C. The mixture was stirred at −78 °C for 1 h followed by the addition of TMSCl (630 μL, 4.96 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 0.5 h. The mixture was again cooled to −78 °C followed by the addition of NBS (1.06 g, 5.96 mmol) in THF (9 mL). The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with H_2O and extracted with Et_2O (2×). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5) to give bromolactones **6b** (680 mg, 3.10 mmol, 78%) and **6b′** (46.1 mg, 0.210 mmol, 5%). **6b**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (sextet, 1H, *J* = 3.2 Hz), 4.46 (t, 1H, *J* = 3.2 Hz), 2.57−2.47 (m, 2H), 2.12−1.92 (m, 3H), 1.85−1.75 (m, 1H), 1.65−1.54 (m, 1H), 1.50−1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 83.4, 39.4, 34.5, 33.9, 33.1, 32.3, 23.5; FT-IR (film) 2957, 2871, 1746, 1470, 1452, 1439, 1351, 1291, 1260, 1204, 1142, 1117, 1078, 1053, 1024 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_8H_{12}{}^{79}BrO_2$ $[M + H]^+$ 219.0021, found 218.9990. **6b′**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (td, 1H, *J* = 5.6, 3.6 Hz), 4.59 (dd, 1H, *J* = 13.2, 5.6 Hz), 2.80−2.73 (m, 1H), 2.48−2.37 (m, 1H), 2.08−1.81 (m, 5H), 1.63−1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 82.9, 43.2, 39.5, 36.6, 33.4, 32.4, 23.1; FT-IR (film) 2957, 2872, 1752, 1658, 1639, 1457, 1439, 1316, 1261, 1171, 1132, 1076, 1045 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_8H_{12}{}^{79}BrO_2$ $[M + H]^+$ 219.0021, found 219.0011.

(±)-(3*R*,3a*S*,6a*R*)-3-Bromohexahydro-2*H*-cyclopenta[*b*]furan-2-one (6c). To a solution of lactone **5c** (72.8 mg, 0.577 mmol) in THF (3 mL) was added $LiN(TMS)_2$ (1.0 M solution in THF, 646 μL, 0.646 mmol) at −78 °C. The mixture was stirred at −78 °C for 5 min followed by the addition of TMSCl (91.5 μL, 0.721 mmol). The reaction

mixture was warmed to 0 °C and stirred for 30 min. The mixture was again cooled to −78 °C followed by the addition of NBS (154 mg, 0.866 mmol) in THF (2 mL). The resulting mixture was warmed to room temperature and stirred for 1.5 h. The reaction mixture was quenched with water and extracted with EtOAc (2×). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10→3) to give bromolactone **6c** (89.3 mg, 0.436 mmol, 75%). **6c**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (br t, 1H, J = 5.2 Hz), 4.19 (br s, 1H), 3.03 (quint, 1H, J = 5.2 Hz), 2.16−2.11 (m, 1H), 2.07−1.97 (m, 1H), 1.86−1.72 (m, 3H), 1.61−1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 86.0, 50.4, 43.4, 32.3, 30.9, 23.9; FT-IR (film) 2966, 2875, 1778, 1470, 1451, 1437, 1349, 1330, 1319, 1286, 1260, 1236, 1186, 1134, 1087, 1039, 1026 cm^{-1}; HRMS (FAB) m/z calcd for $C_7H_{10}{}^{79}BrO_2$ $[M + H]^+$ 204.9864, found 204.9827.

(±)-(2*S*,3a*R*,7a*R*)-Methyl Octahydrobenzofuran-2-carboxylate (9a). To a solution of bromolactone **6a** (41.4 mg, 0.189 mmol) in MeOH (3.8 mL) was added K_2CO_3 (26.1 mg, 0.189 mmol) at −78 °C. The reaction mixture was allowed to warm to room temperature with stirring for 1 h. After concentration, the residue was purified by flash column chromatography (hexane/EtOAc = 3) to give a 10:1 inseparable mixture of esters **9a** and **10a** (27.2 mg, 0.148 mmol, 78%). The following data were selected from the spectra obtained by a mixture of **9a** and **10a**. Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, for **9a**) δ 4.59 (t, 1H, J = 7.2 Hz), 4.12 (dd, 1H, J = 6.3, 2.7 Hz), 3.74 (s, 3H, OMe), 2.11−1.99 (m, 5H), 1.67−1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, for **9a**) δ 174.9, 78.6, 75.2, 52.1, 37.7, 37.3, 27.9, 27.4, 24.2, 20.3; FT-IR (neat) 2930, 2857, 1758, 1738, 1458, 1436, 1368, 1270, 1230, 1155, 1110, 1082, 1050, 1023 cm^{-1}; HRMS (FAB) m/z calcd for $C_{10}H_{17}O_3$ $[M + H]^+$ 185.1178, found 185.1136.

(±)-(2*S*,3a*R*,6a*R*)-Methyl Hexahydro-2*H*-cyclopenta[*b*]furan-2-carboxylate (9b). To a solution of bromolactone **6b** (17.7 mg, 80.8 μmol) in MeOH (2 mL) was added K_2CO_3 (11.2 mg, 80.8 μmol). The reaction mixture was stirred for 2 h before addition of saturated NH_4Cl solution. The resulting mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5) to give a 7:1 inseparable mixture of esters **9b** and **10b** (10.7 mg, 62.9 μmol, 78%). The analytical samples were obtained by repeated flash column chromatography. **9b**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (br t, 1H, J = 5.2 Hz), 4.54 (dd, 1H, J = 7.6, 4.8 Hz), 3.73 (s, 3H), 2.74−2.66 (m, 1H), 2.31−2.24 (m, 1H), 1.94−1.82 (m, 2H), 1.73−1.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 86.7, 77.8, 52.1, 42.3, 37.9, 34.3, 32.8, 24.1; FT-IR (film) 2952, 2868, 1752, 1737, 1452, 1436, 1364, 1309, 1273, 1206, 1133, 1108, 1090, 1047, 1028 cm^{-1}; HRMS (FAB) m/z calcd for $C_9H_{15}O_3$ $[M + H]^+$ 171.1021, found 171.0977. **10b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (t, 1H, J = 5.4 Hz), 4.23 (dd, 1H, J = 9.6, 6.6 Hz), 3.74 (s, 3H), 2.73−2.64 (m, 1H), 2.46 (ddd, 1H, J = 12, 9.0, 6.3 Hz), 2.01−1.96 (m, 1H), 1.74−1.43 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 86.6, 77.9, 52.2, 42.6, 38.1, 33.7, 32.9, 23.5. HRMS (FAB) m/z calcd for $C_9H_{15}O_3$ $[M + H]^+$ 171.1021, found 171.0993.

(±)-(1*S*,5*R*,7*S*)-Methyl 6-Oxabicyclo[3.2.0]heptane-7-carboxylate (9c). To a solution of bromolactone **6c** (27.7 mg, 0.135 mmol) in MeOH (2.7 mL) was added K_2CO_3 (18.7 mg, 0.135 mmol). The reaction mixture was stirred at room temperature for 8 h before addition of saturated NH_4Cl solution. The resulting mixture was extracted with EtOAc (2×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 3) to give a 2.5:1 inseparable mixture of **9c** and 3-*epi*-**6c** (4.9 mg). Yields were calculated from the ^{1}H NMR spectrum and determined to be 15% for **9c** and 6% for 3-*epi*-**6c**. The following data were selected from the spectra obtained by a mixture of **9c** and 3-*epi*-**6c**. ^{1}H NMR (400 MHz, $CDCl_3$, for **9c**) δ 5.31 (t, 1H, J = 4.4 Hz), 4.50 (d, 1H, J = 4.4 Hz), 3.81 (s, 3H), 3.18−3.14 (m, 1H), 2.21−1.51 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, for **9c**) δ 173.3, 87.5, 81.0, 52.3, 43.3, 34.4, 30.4, 23.7; HRMS (EI) m/z calcd for $C_8H_{13}O_3$ $[M + H]^+$ 157.0865, found 157.0866.

(±)-(2*S*,3a*R*,6a*R*)-*N*-Methylhexahydro-2*H*-cyclopenta[*b*]furan-2-carboxamide (9e). To a solution of bromolactone **6b** (27.5 mg, 0.137 mmol) in DMF (456 μL) were added methylamine (40% in water, 30.4 μL, 0.348 μmol) and K_2CO_3 (18.9 mg, 0.137 mmol). The reaction mixture was stirred at room temperature for 2 h before addition of water. The resulting mixture was extracted with Et_2O (4×) and EtOAc (3×), and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated to give amide **9e** (23.2 mg, 0.137 mmol, 100%). **9e**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (br s, 1H), 4.57 (br t, 1H, J = 4.4 Hz), 4.37 (t, 1H, J = 7.2 Hz), 2.79 (d, 3H, J = 5.2 Hz), 2.68−2.60 (m, 1H), 2.22−2.15 (m, 1H), 2.05−1.99 (m, 1H), 1.81−1.40 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 86.6, 79.4, 42.7, 37.8, 34.7, 32.4, 25.7, 24.6; FT-IR (film) 3431, 3332, 2951, 2869, 2804, 1659, 1537, 1468, 1452, 1437, 1408, 1348, 1330, 1306, 1280, 1238, 1212, 1188, 1155, 1134, 1110, 1069, 1053, 1027 cm^{-1}; HRMS (FAB) m/z calcd for $C_9H_{16}NO_2$ $[M + H]^+$ 170.1181, found 170.1132.

(±)-(2*S*,3a*R*,6a*R*)-*N*-Isopropylhexahydro-2*H*-cyclopenta[*b*]furan-2-carboxamide (9f). To a solution of bromolactone **6b** (35.5 mg, 162 μmol) in DMF (456 μL) were added isopropylamine (58.8 μL, 685 μmol) and K_2CO_3 (22.4 mg, 162 μmol). The reaction mixture was stirred at room temperature for 15 h before addition of water. The resulting mixture was extracted with Et_2O (2×), and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a 6:1 inseparable mixture of amide **9f** and **10f** (23.6 mg, 120 μmol, 74%). The following data were selected from the spectra obtained by a mixture of **9f** and **10f**. Colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$, for **9f**) δ 6.43 (br s, 1H), 4.57 (br t, 1H, J = 5.2 Hz), 4.33 (t, 1H, J = 7.2 Hz), 4.14−3.98 (m, 1H), 2.67−2.61 (m, 1H), 2.17 (dt, 1H, J = 12.8, 7.6 Hz), 2.01 (ddd, 1H, J = 12.4, 6.8, 3.6 Hz), 1.82−1.40 (m, 6H), 1.14 (d, 3H, J = 6.4 Hz), 1.13 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, for **9f**) δ 172.0, 86.6, 79.3, 42.7, 40.7, 37.8, 34.7, 32.4, 24.7, 23.0, 22.8; FT-IR (film) 3279, 2971, 2954, 2934, 2894, 2863, 1646, 1541, 1467, 1456, 1447, 1380, 1362, 1339, 1327, 1307, 1290, 1251, 1207, 1168, 1157, 1128, 1109, 1070, 1052, 1019 cm^{-1}; HRMS (FAB) m/z calcd for $C_{11}H_{20}NO_2$ $[M + H]^+$ 198.1494, found 198.1498.

(±)-(3*R*,4a*R*,7a*R*)-3-Bromo-3-methylhexahydrocyclopenta[*b*]pyran-2(3*H*)-one (11). To a solution of lactone **5b** (50.2 mg, 0.358 mmol) in THF (4.3 mL) was added $LiN(TMS)_2$ (1.0 M solution in THF, 428 μL, 0.428 mmol) at −78 °C. The mixture was stirred at −78 °C for 1.5 h, followed by the addition of HMPA (186 μL, 1.07 mmol), and the stirring was continued for 30 min at −78 °C. After addition of CH_3I (133 μL, 2.14 mmol), the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was quenched with water and extracted with Et_2O (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5) to give the methylated lactone (36.9 mg, 0.239 mmol, 67%) and its C3-epimer (0.4 mg, 2.6 μmol, 0.7%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (dt, 1H, J = 6.6, 3.3 Hz), 2.62−2.50 (m, 1H), 2.39−2.29 (m, 1H), 2.03−1.75 (m, 6H), 1.63−1.53 (m, 2H), 1.27 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 84.6, 35.3, 35.1, 31.7, 31.4, 29.8, 23.3, 16.5; FT-IR (film) 2961, 2938, 2873, 1732, 1558, 1458, 1379, 1338, 1319, 1338, 1319, 1294, 1257, 1195, 1166, 1135, 1102, 1074, 1055 cm^{-1}; HRMS (FAB) m/z calcd for $C_9H_{15}O_2$ $[M + H]^+$ 155.1072, found 155.1048. **C3-epimer**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (td, 1H, J = 7.2, 4.2 Hz), 2.47−2.34 (m, 1H), 2.04−1.66 (m, 6H), 1.56−1.36 (m, 3H), 1.23 (d, 3H, J = 9.6 Hz); FT-IR (film) 2965, 2871, 1729, 1471, 1456, 1389, 1367, 1352, 1295, 1274, 1230, 1200, 1142, 1069, 1052, 1028, 1016, 1000 cm^{-1}.

To a solution of the methylated lactone (74.5 mg, 0.483 mmol) in THF (2 mL) was added $LiN(TMS)_2$ (1.0 M solution in THF, 1.74 mL, 1.74 mmol) at −78 °C. The mixture was stirred at −78 °C for 15 min followed by the addition of TMSCl (221 μL, 1.74 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 30 min. The mixture was again cooled to −78 °C followed by the addition of NBS (386 mg, 2.17 mmol) in THF (5 mL). The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with water and extracted with Et_2O (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10) to give bromolactone **11** (87.2 mg, 0.374 mmol, 77%). **11**: colorless needles; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (td, 1H, *J* = 6.6, 3.3 Hz), 2.61−2.47 (m, 2H), 2.07−1.86 (m, 3H), 1.96 (s, 3H), 1.81−1.63 (m, 2H), 1.61−1.52 (m, 1H), 1.49−1.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 83.4, 53.4, 41.7, 35.8, 34.8, 32.8, 29.7, 23.6; FT-IR (film) 2956, 2873, 1738, 1445, 1380, 1361, 1291, 1281, 1266, 1252, 1224, 1206, 1195, 1129, 1058, 1047, 1012, 1004 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_9H_{14}{}^{79}BrO_2$ $[M + H]^+$ 233.0177, found 233.0155.

(±)-(2*S*,3a*R*,6a*R*)-Methyl 2-Methylhexahydro-2*H*-cyclopenta[*b*]furan-2-carboxylate (12). To a solution of bromolactone **11** (42.3 mg, 0.181 mmol) in MeOH (3.6 mL) was added K_2CO_3 (25.0 mg, 0.181 mmol) at −78 °C. The reaction mixture was allowed to warm to room temperature with stirring for 1 h. The reaction was quenched with water and extracted with Et_2O (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10) to give ester **12** (22.7 mg, 0.123 mmol, 68%). **12**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (t, 1H, *J* = 6.0 Hz), 3.72 (s, 3H), 2.73−2.63 (m, 3H), 1.90−1.84 (m, 1H), 1.70−1.38 (m, 5H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 85.8, 84.8, 52.3, 44.7, 42.7, 34.0, 33.2, 24.1, 23.2; FT-IR (film) 2952, 2867, 1747, 1734, 1650, 1448, 1436, 1372, 1315, 1303, 1290, 1277, 1253, 1213, 1200, 1154, 1141, 1108, 1071, 1049, 1035, 1000 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{10}H_{17}O_3$ $[M + H]^+$ 185.1178, found 185.1123.

(±)-(3*S*,4a*R*,7a*R*)-3-Bromo-3-methylhexahydrocyclopenta[*b*]pyran-2(3*H*)-one (13). To a solution of lactone **6b** (50.0 mg, 0.227 mmol) in THF (2.3 mL) was added $LiN(TMS)_2$ (1.0 M solution in THF, 272 μL, 0.272 mmol) at −78 °C. The mixture was stirred at −78 °C for 1.5 h, followed by the addition of HMPA (118 μL, 0.681 mmol), and the stirring was continued for 30 min at −78 °C. After addition of CH_3I (846 μL, 1.36 mmol), the reaction mixture was allowed to warm to room temperature and stirred for 1.3 h. The reaction mixture was quenched with water and extracted with Et_2O (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10 → 1) to give lactone **13** (28.5 mg, 0.122 mmol, 54%) and its diastereomer **11** (6.6 mg, 0.028 mmol, 12%). **13**: colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (dt, 1H, *J* = 6.3, 4.2 Hz), 2.64−2.40 (m, 2H), 2.05−1.97 (m, 2H), 2.03 (s, 3H), 1.93−1.71 (m, 3H), 1.63−1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 84.0, 56.0, 43.3, 35.8, 34.5, 31.3, 28.9, 22.9; FT-IR (film) 2959, 2871, 1745, 1381, 1332, 1283, 1274, 1225, 1195, 1178, 1157, 1132, 1118, 1094, 1039, 1020 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_9H_{14}{}^{79}BrO_2$ $[M + H]^+$ 233.0177, found 233.0138.

(±)-(2*R*,3a*R*,6a*R*)-Methyl 2-Methylhexahydro-2*H*-cyclopenta[*b*]furan-2-carboxylate (14). To a solution of bromolactone **13** (88.8 mg, 0.381 mmol) in MeOH (7.6 mL) was added K_2CO_3 (52.7 mg, 0.381 mmol) at −78 °C. The mixture was allowed to warm to room temperature with stirring for 1 h. The reaction was quenched with water and extracted with Et_2O (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5 → 2) to give ester **14** (50.7 mg, 0.274 mmol, 72%). **14**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (t, 1H, *J* = 5.4 Hz), 3.73 (s, 3H), 2.80−2.70 (m, 1H), 2.13 (dd, 1H, *J* = 12.6, 9.0 Hz), 1.94 (dd, 1H, *J* = 12.6, 6.0 Hz), 1.95−1.85 (m, 1H), 1.67−1.40 (m, 5H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 85.5, 84.5, 52.4, 43.6, 42.6, 34.0, 32.6, 24.1, 23.8; FT-IR (film) 2952, 2869, 1752, 1436, 1371, 1275, 1242, 1131, 1105, 1031 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{10}H_{17}O_3$ $[M + H]^+$ 185.1178, found 185.1169.

(±)-(4a*S*,7*S*,7a*R*)-7-(Hydroxymethyl)hexahydrocyclopenta[*b*]pyran-2(3*H*)-one (16)[13]. Iodolactone **15** (133 mg, 0.500 mmol), *n*-Bu_4NBH_4 (158 mg, 0.62 mmol), AIBN (24 mg, 0.15 mmol), and CH_3CN (1 mL) were placed in a 30 mL stainless steel autoclave. The autoclave was closed, purged three times with CO, pressurized with 75 atm of CO, and then heated at 80 °C for 5 h. Exess CO was discharged at room temperature. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (hexane/EtOAc = 2 → 1) to give alcohol **16** (28.1 mg, 0.165 mmol, 33%). **16**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (dd, 1H, *J* = 7.3, 5.0 Hz), 3.74 (dd, 1H, *J* = 10.4, 5.6 Hz), 3.65 (dd, 1H, *J* = 10.4, 6.4 Hz), 2.50 (dt, 1H, *J* = 16.5, 4.4 Hz), 2.39−2.28 (m, 3H), 2.18−2.11 (m, 1H), 2.01−1.90 (m, 2H), 1.64−1.44 (m, 2H), 1.42−1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 84.6, 63.7, 49.1, 36.4, 30.7, 29.1, 26.2, 23.5; FT-IR (film) δ 3414, 2945, 2872, 1727 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 170 (M^+, 13), 114 (100), 96 (24), 80 (20), 67 (34), 55 (29); HRMS (EI) *m*/*z* calcd for $C_9H_{14}O_3$ $[M]^+$ 170.0943, found 170.0944.

(±)-(3*S*,4a*S*,7*S*,7a*R*)-3-Bromo-7-((*tert*-butyldimethylsilyloxy)methyl)hexahydrocyclopenta[*b*]pyran-2(3*H*)-one (17). To a solution of alcohol **16** (410 mg, 2.41 mmol) and imidazole (820 mg, 12.0 mmol) in DMF (12 mL) was added TBSCl (904 mg, 6.00 mmol). The mixture was stirred at room temperature for 2 h before addition of hexane and saturated NH_4Cl solution. The resulting mixture was extracted with hexane (3×), and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10) to give a corresponding TBS ether (618 mg, 2.17 mmol, 90%). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (dd, 1H, *J* = 7.0, 4.4 Hz), 3.69 (dd, 1H, *J* = 10, 4.8 Hz), 3.60 (dd, 1H, *J* = 10, 4.8 Hz), 2.48 (dt, 1H, *J* = 16, 5.2 Hz), 2.39−2.21 (m, 3H), 2.17−2.08 (m, 1H), 1.98−1.82 (m, 2H), 1.63−1.38 (m, 3H), 0.88 (s, 9H, TBS), 0.04 (s, 6H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 84.3, 63.2, 49.0, 36.6, 30.8, 29.0, 26.0, 25.8, 23.4, 18.2, −5.5, −5.4; FT-IR (film) 2952, 2930, 2858, 2710, 1746, 1471, 1463, 1434, 1388, 1361, 1321, 1251, 1177, 1067, 1017 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{15}H_{28}O_3Si$ $[M - t\text{Bu}]^+$ 227.1103, found 227.1123.

To a solution of TBS ether (204 mg, 0.717 mmol) in THF (3 mL) was added $LiN(TMS)_2$ (1.0 M solution in THF, 803 μL, 0.803 mmol) at −78 °C. The mixture was stirred at −78 °C for 5 min followed by the addition of TMSCl (114 μL, 0.896 mmol). The reaction mixture was warmed to 0 °C and stirred for 30 min. The mixture was again cooled to −78 °C followed by the addition of NBS (1.06 g, 5.96 mmol) in THF (9 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with water and extracted with Et_2O (2×). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10) to give a 5:1 inseparable diastereomeric mixture of bromolactone **17** (246 mg, 0.652 mmol, 91%). **17** (dr = 5:1): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, for major isomer) δ 4.97 (dd, 1H, *J* = 7.2, 4.8 Hz), 4.46 (t, 1H, *J* = 3.2 Hz), 3.74 (dd, 1H, *J* = 10, 5.2 Hz), 3.66 (dd, 1H, *J* = 10, 4.4 Hz), 2.54−2.43 (m, 2H), 2.36−2.26 (m, 1H), 2.08−1.99 (m, 2H), 1.94−1.82 (m, 1H), 1.56−1.40 (m, 2H), 0.89 (s, 9H, TBS), 0.06 (s, 3H, TBS), 0.05 (s, 3H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$, for major isomer) δ 167.9, 84.4, 63.0, 49.8, 39.3, 33.9, 33.0, 32.1, 26.6, 26.0, 18.4, −5.32, −5.30; FT-IR (film) 2952, 2928, 2857, 2738, 2710, 1743, 1471, 1463, 1440, 1388,

1361, 1299, 1254, 1201, 1146, 1103, 1078 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{15}H_{27}BrO_3Si$ [M − *t*Bu]$^+$ 307.0189, found 307.0157.

(±)-(2*R*,3a*S*,6*S*,6a*R*)-Methyl 6-((*tert*-Butyldimethylsilyloxy)methyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-carboxylate (18). To a solution of bromolactone **17** (227 mg, 0.601 mmol) in MeOH (12 mL) was added K_2CO_3 (83.1 mg, 0.601 mmol) at −78 °C. The mixture was allowed to warm to room temperature with stirring for 5 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10) to give a 5:1 inseparable diastereomeric mixture of ester **18** (189 mg, 0.601 mmol, 100%). **18** (dr = 5:1): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, for major isomer) δ 4.53 (t, 1H, *J* = 7.2 Hz), 4.49 (dd, 1H, *J* = 7.2, 2.8 Hz), 3.74 (s, 3H, OMe), 3.60 (dd, 1H, *J* = 10, 5.2 Hz), 3.52 (dd, 1H, *J* = 10, 6.4 Hz), 2.74−2.62 (m, 1H), 2.20−2.13 (m, 2H), 2.02−1.74 (m, 3H), 1.55−1.34 (m, 2H), 0.88 (s, 9H, TBS), 0.03 (s, 6H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$, for major isomer) δ 173.7, 88.9, 77.3, 64.2, 52.2, 49.0, 42.7, 37.5, 31.5, 28.0, 26.1, 18.5, −5.3; FT-IR (film) δ 2952, 2931, 2882, 2858, 2361, 1757, 1740, 1471, 1463, 1437, 1388, 1362, 1255, 1205, 1154, 1094, 1006 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{16}H_{30}O_4Si$ [M − *t*Bu]$^+$ 257.1209, found 257.1194.

(±)-(2*R*,3a*S*,6*S*,6a*R*)-6-((*tert*-Butyldimethylsilyloxy)methyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-carbaldehyde (19). To a solution of ester **18** (81.9 mg, 0.260 mmol) in CH_2Cl_2 (2.6 mL) was added DIBAL (1.04 M solution in hexane, 275 μL, 0.286 mmol) at −78 °C. After stirring for 40 min at −78 °C, the reaction mixture was treated with hexane and saturated Rochelle salt solution. The resulting mixture was stirred at room temperature for 3 h and extracted with Et_2O (2×). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10 → 3) to give a 5:1 inseparable diastereomeric mixture of aldehyde **19** (70.7 mg, 0.249 mmol, 96%). **19**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, for major isomer) δ 9.64 (d, 1H, *J* = 1.8 Hz), 4.43 (dd, 1H, *J* = 6.6, 2.7 Hz), 4.33 (td, 1H, *J* = 7.5, 1.8 Hz), 3.56 (d, 2H, *J* = 6.3 Hz), 2.72−2.61 (m, 1H), 2.21−2.16 (m, 1H), 2.08 (dt, 1H, *J* = 12.6, 8.1 Hz), 1.99−1.77 (m, 3H), 1.52−1.35 (m, 2H), 0.88 (s, 9H, TBS), 0.04 (s, 6H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$, for major isomer) δ 203.0, 89.6, 83.4, 64.6, 49.6, 43.2, 34.7, 31.9, 28.6, 26.4, 18.8, −4.95, −4.97; FT-IR (film) 3410, 2952, 2930, 2885, 2858, 2802, 2738, 2711, 1736, 1558, 1541, 1471, 1463, 1388, 1361, 1255, 1101, 1074, 1007 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{15}H_{28}O_3Si$ [M − *t*Bu]$^+$ 227.1103, found 227.1132.

(±)-Communiol E (1)[1]. To a solution of aldehyde **19** (21.9 mg, 0.0770 mmol) in THF (2 mL) was added EtLi (0.5 M solution in benzene and cyclohexane, 422 μL, 0.211 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with Et_2O (2×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was again dissolved in THF (2 mL) and treated with EtLi (0.5 M solution in benzene and cyclohexane, 703 μL, 0.352 mmol) at 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 20) to give the desired alcohol (11.3 mg, 0.0363 mmol, 47%) and a mixture of other stereoisomers (5.3 mg, 0.017 mmol, 22%). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (dd, 1H, *J* = 6.8, 3.6 Hz), 3.90 (ddd, 1H, *J* = 10.4, 5.2, 3.2 Hz), 3.78−3.72 (m, 1H), 3.61 (dd, 1H, *J* = 10, 5.6 Hz), 3.54 (dd, 1H, *J* = 10, 6.4 Hz), 2.64 (quint, 1H, *J* = 7.6 Hz), 2.10−2.01 (m, 2H), 1.98−1.89 (m, 2H), 1.83−1.74 (m, 1H), 1.57−1.25 (m, 4H), 0.99 (t, 3H, *J* = 7.2 Hz) 0.88 (s, 9H, TBS), 0.04 (s, 6H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.4, 80.8, 72.9, 64.6, 50.0, 43.1, 32.0, 31.6, 28.7, 26.1, 25.9, 18.5, 10.6, −5.2; FT-IR (film) 3451, 2955, 2930, 2859, 2738, 1471, 1463, 1388, 1361, 1254, 1101, 1070, 1032, 1005 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{35}O_3Si$ [M + H]$^+$ 315.2355, found 315.2310.

To a solution of alcohol (5.1 mg, 16 μmol) in THF (162 μL) was added TBAF (1.0 M solution in THF, 24 μL, 24 μmol). The mixture was stirred at room temperature for 17 h and quenched with saturated $NaHCO_3$ solution. The resulting mixture was extracted with Et_2O (2×) and EtOAc (3×), and the combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (EtOAc only) to give communiol E (**1**) (2.7 mg, 14 μmol, 83%). **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (dd, 1H, *J* = 7.6, 4.4 Hz), 3.93 (ddd, 1H, *J* = 10.4, 5.6, 3.6 Hz), 3.76 (td, 1H, *J* = 6.4, 3.2 Hz), 3.65 (dd, 1H, *J* = 10.8, 6.8 Hz), 3.60 (dd, 1H, *J* = 10.4, 7.6 Hz), 2.68 (quint, 1H, *J* = 8.0 Hz), 2.11−2.02 (m, 1H), 2.00−1.91 (m, 2H), 1.86−1.79 (m, 1H), 1.52 (br dd, 1H, *J* = 12.4, 5.6 Hz), 1.42 (quint, 2H, *J* = 7.6 Hz), 1.39−1.29 (m, 2H), 0.99 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.1, 80.9, 72.8, 65.2, 50.0, 43.1, 31.8, 31.3, 28.6, 25.9, 10.6; FT-IR (film) 3367, 2957, 2939, 2872, 1465, 1448, 1374, 1304, 1234, 1146, 1074, 1044, 1019 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{21}O_3$ [M + H]$^+$ 201.1491, found 201.1523.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for all new synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas (No. 2105) from MEXT and KAKENHI (22550115) from the JSPS.

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(8) In addition to compounds shown in Scheme 2, 4-(cyclopent-2-enyl)butanoic acid (m = 1, n = 2) was subjected to examination. However, we faced a serious problem in the iodolactonization step. The reaction proceeded in less than 17% yield even under Rousseau's conditions using bis(*sym*-collidine)iodine(I) hexafluorophosphate. Thus, we were unable to obtain sufficient quantities of bromolactone to test this methodology. For Rousseau's conditions, see: Simonot, B.; Rousseau, G. *J. Org. Chem.* **1993**, *58*, 4–5.

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(12) When bromolactone **6b** was reacted with PhSH in the presence of K_2CO_3 at −78 to −13 °C, α-phenylthiolactone was obtained in 91% yield (dr >20:1). Similarly, the reaction of **6b** with PhSeH at −78 °C provided α-phenylselenolactone in 85% yield (dr >20:1).

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(14) The relative stereochemistry was unambiguously confirmed by NOE after conversion to the aldehyde **19**.

(15) The crude NMR spectrum after ethylation indicated that three or four diastereomers were included in the mixture. The exact ratio was not assigned due to the complexity of the spectrum.

(16) The unwanted stereoisomeric mixtures were successfully converted to the desired isomer in the following steps: (i) Dess−Martin periodinane, pyridine, CH_2Cl_2, rt, 100%; (ii) DIBAL, $ZnCl_2$, CH_2Cl_2, −78 °C, 65% (for desired isomer).

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