JOC The Journal of Organic Chemistry

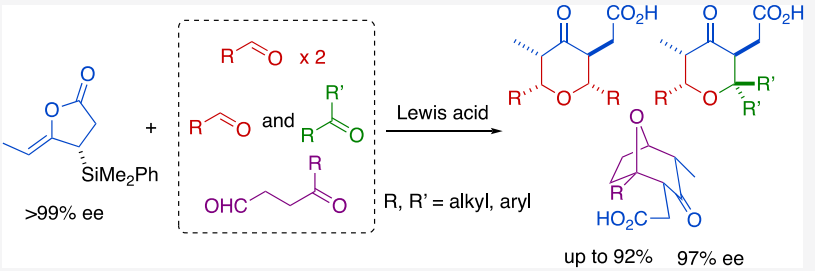
pubs.acs.org/joc Article

Stereoselective Synthesis of Polysubstituted Tetrahydropyranones via Acid-Promoted Cyclization of β-Silyl-γ-ethylidene-γ-butyrolactones with Aldehydes and Ketones

Shoma Ariyoshi, Kazuhiko Sakaguchi,* and Takahiro Nishimura

Cite This: https://doi.org/10.1021/acs.joc.1c01284 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

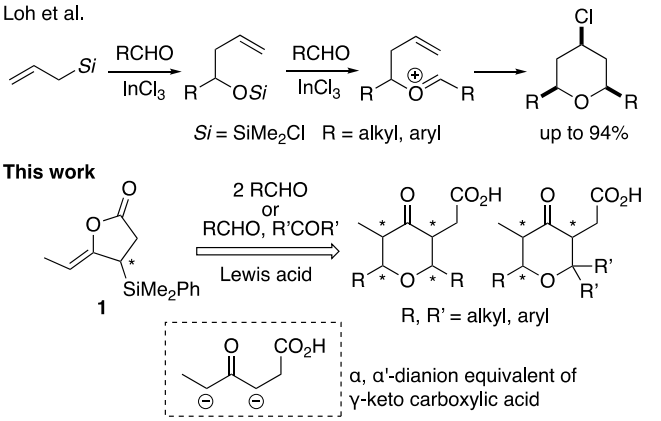


ABSTRACT: β-Silyl-γ-ethylidene-γ-butyrolactone upon one-pot treatment with aldehydes and ketones in the presence of Lewis acids underwent a tandem Hosomi−Sakurai/Prins cyclization to give polysubstituted tetrahydropyranones stereoselectively. Various aldehydes and ketones can be used in this reaction to produce the corresponding tetrahydropyranones. The optical purity of the starting γ-butyrolactone was substantially retained in the resulting tetrahydropyranones.

INTRODUCTION

Since substituted tetrahydropyranones are important components often found in biologically active natural/non-natural compounds, developing methods for synthesizing tetrahydropyranones is one of the important tasks in organic synthesis.[1−5] Although many methods for constructing substituted tetrahydropyran systems have been reported, developing stereoselective construction methods for polysubstituted tetrahydropyranones remains a challenging task.[1−5] Prins cyclization is a useful method for fabricating tetrahydropyran systems.[5] Chan and Loh synthesized 2,4,6-trisubstituted tetrahydropyrans from an allylsilane and two molecules of aldehydes through the Prins cyclization (Scheme 1).[5b] β-Silyl-γ-ethylidene-γ-butyrolactone **1** has a structure containing both an allylsilane and a vinyl ester. It is considered useful as an α,α′-dianion equivalent of γ-keto carboxylic acid. In this study, we report an efficient stereoselective one-pot synthesis of polysubstituted tetrahydropyranones by a three-component coupling of **1**, aldehydes, and ketones.

Scheme 1. Construction of Substituted Tetrahydropyran Systems by Prins Cyclization



RESULTS AND DISCUSSION

The reaction substrate β-silyl-γ-ethylidene-γ-butyrolactone **1** was synthesized from allenylsilane **2**[6] in two steps via gold-catalyzed cyclization (Scheme 2).[7] As the silyl group of **1**, we selected a dimethylphenylsilyl group, which is often used in the Hosomi−Sakurai reaction.[8] Treatment of **1** with benzaldehyde (3 equiv) in the presence of $BF_3{\cdot}OEt_2$ (2.5 equiv) in CH_2Cl_2 at −78 °C for 13 h produced tetrasubstituted tetrahydropyranone **3a** accompanied by its diastereomer **3a′** in 34% yield with high stereoselectivity (dr = 21:1, Table 1, entry 1). The yield of **3a** increased slightly at 0 °C (entry 2) and improved to 85% at

Received: June 2, 2021

https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Preparation of β-Silyl-γ-alkylidene-γ-butyrolactone 1

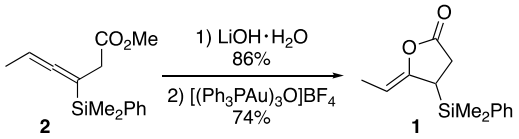
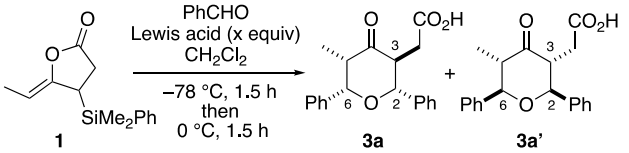


Table 1. Optimization of the Reaction Conditions for Acid-Promoted Cyclization of 1 with Aldehydes[a]



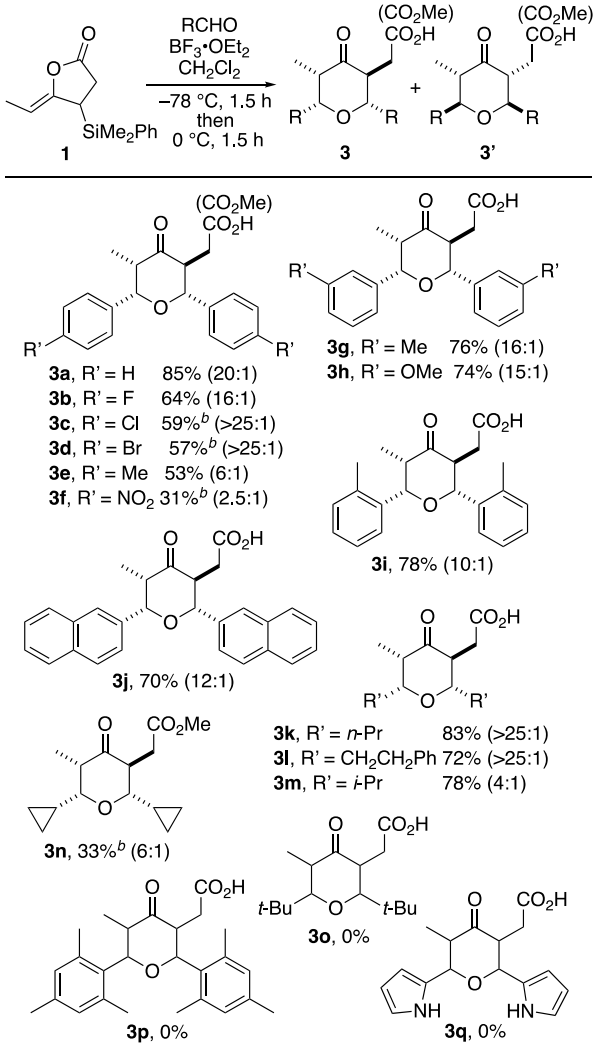
entry	Lewis acid	x (equiv)	yield of 3a + 3a′ (%)[b]	3a:3a′
1[c]	$BF_3·OEt_2$	2.5	34	21:1
2[d]		2.5	42	20:1
3		2.5	85[e]	20:1
4		0.2	25	13:1
5[f]		0.2	35	21:1
6	TMSOTf	2.5	80[e]	16:1
7	$FeCl_3$	2.5	71	3:1
8	$InCl_3$	2.5	73[e]	3:1
9	$Sc(OTf)_3$	2.5	58	6:1
10	$Cu(OTf)_2$	2.5	16	>25:1
11	$Zn(OTf)_2$	2.5	15	4:1
12	$TiCl_4$	2.5	11	2.3:1
13	TfOH	2.5	78	2.4:1
14	CF_3COOH	2.5	0	

[a]Reaction conditions: **1** (0.1 mmol), PhCHO (3 equiv), Lewis acid, CH_2Cl_2 (0.1 M), −78 °C, 1.5 h, followed by 0 °C, 1.5 h. [b]Yields were determined by ^1H NMR using triphenylmethane as an internal standard. [c]The reaction was performed at −78 °C, 13 h. [d]The reaction was performed at 0 °C, 1.5 h. [e]Isolated yield. [f]The reaction was performed at −78 °C, 4 h, followed by 0 °C, 4 h.

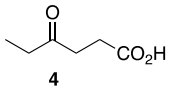
−78 °C for 1.5 h and at 0 °C for 1.5 h (entry 3). The reaction also proceeded with a catalytic amount of Lewis acid to give **3a** in 25% yield (entry 4), but no significant improvement in yield was observed when the reaction time was extended (entry 5). Trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a Lewis acid also promoted the reaction to give **3a** with good yield and high diastereoselectivity (80%, d*r* = 16:1, entry 6). When $FeCl_3$, $InCl_3$, and $Sc(OTf)_3$ were used as Lewis acids, the diastereoselectivity decreased (entries 7−9). The use of $Cu(OTf)_2$ reduced the yield (entry 10), and both the yield and diastereoselectivity decreased using $Zn(OTf)_2$ and $TiCl_4$ (entries 11 and 12). The reaction using trifluoromethanesulfonic acid (TfOH) as a Brønsted acid gave **3a** in 78% yield; however, the diastereoselectivity was low (entry 13). Trifluoroacetic acid did not promote the reaction (entry 14). The relative configurations of **3a** and **3a′** were determined by ^1H NMR spectral analysis.[9] The minor isomer **3a′** was a diastereomer at the C2, C3, and C6 positions of the major isomer **3a** (vide infra).

With the optimized reaction conditions in hand, the scope of aldehydes was explored (Table 2). A variety of electron-enriched and electron-deficient aromatic aldehydes with *para*-, *meta*-, or *ortho*-substituents can undergo this reaction to deliver the corresponding tetrasubstituted tetrahydropyranones in moderate to good yields with high diastereoselectivity (**3b**−**3j**). Among them, diastereoselectivity slightly decreased when *para*-Me- or NO_2-substituted benzaldehydes were employed (**3e**, **3f**). The use of 2-naphthaldehyde gave the corresponding tetrahydropyranone in 70% yield (d*r* = 12:1, **3j**). For aliphatic aldehydes with linear alkyl groups, the corresponding cyclization products were obtained in good yields with high diastereoselectivity (**3k**, **3l**). Aldehydes with branched alkyl groups decreased the diastereoselectivity (**3m**). The reaction with cyclopropanecarboxaldehyde gave the corresponding tetrahydropyranone (33%, **3n**) with a mixture of unknown byproducts. However, for sterically bulky pivalaldehyde and 2,4,6-trimethylbenzaldehyde, and for aromatic heterocycle-containing pyrrole-2-carboxaldehyde, the cyclization reaction did not occur, and γ-keto carboxylic acid **4**,[10] which was produced via hydrolysis of **1**, was obtained (**3o**, **3p**, and **3q**).

Table 2. Scope of Acid-Promoted Cyclization of 1 with Aldehydes[a]



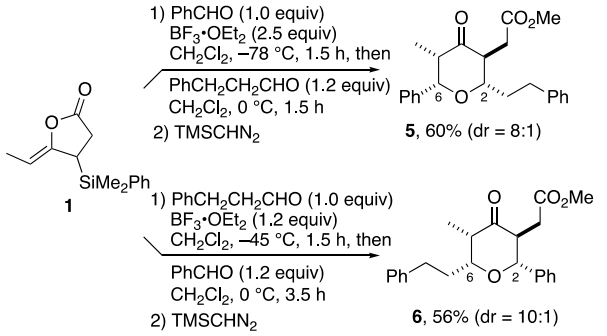
[a]Reaction conditions: **1** (0.1−0.2 mmol), aldehyde (3 equiv), $BF_3·OEt_2$ (2.5 equiv), CH_2Cl_2 (0.1 M), −78 °C, 1.5 h followed by 0 °C, 1.5 h. [b]Isolation yield of the corresponding methyl ester converted by reaction with trimethylsilyldiazomethane.



https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX

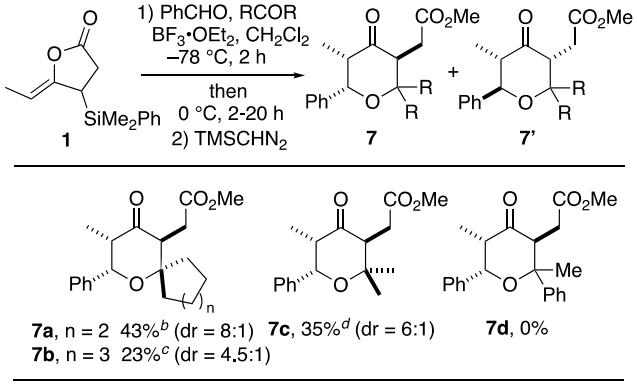
We then attempted the sequential introduction of two different aldehydes into the cyclization reaction. Treatment of **1** with $BF_3{\cdot}OEt_2$ and 1 equiv of benzaldehyde at −78 °C for 1.5 h followed by the reaction with 3-phenylpropanal at 0 °C for 1.5 h in a one-pot afforded tetrahydropyranone **5** with four different substituents in 60% yield (d*r* = 8:1, Scheme 3). By changing the order of introduction of these aldehydes, tetrahydropyranone **6**, where the substituents at the C2- and C6-positions were exchanged, could be synthesized.

Scheme 3. Acid-Promoted Cyclization of 1 with Two Different Aldehydes



We attempted the acid-promoted reaction of **1** using cyclohexanone instead of aldehydes. However, the desired cyclization did not occur, and γ-keto carboxylic acid **4** (83−84%) was obtained.[11] However, it was found that the cyclization involving **1**, aldehyde, and ketone occurred when the reaction was conducted in the presence of both aldehyde and ketone (Table 3). The acidic treatment of **1** with

Table 3. Acid-Promoted Cyclization of 1 with Aldehydes and Ketones[a]

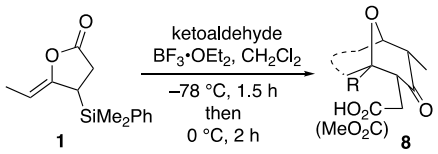


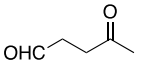
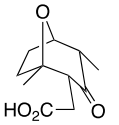
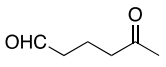
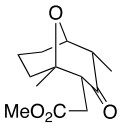
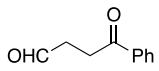
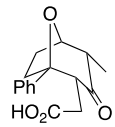
[a]Reaction conditions: **1** (0.1−0.2 mmol), PhCHO (1 equiv), ketone (1.3−4 equiv), $BF_3{\cdot}OEt_2$ (2.5 equiv), CH_2Cl_2 (0.1 M), −78 °C, 2 h, followed by 0 °C, 2−20 h (one-pot). [b]Cyclohexanone (1.3 equiv) was used, and the reaction time at 0 °C was 2 h. [c]Cycloheptanone (1.5 equiv) was used, and the reaction time at 0 °C was 20 h. [d]Acetone (4.0 equiv) was used, and the reaction time at 0 °C was 2.5 h.

benzaldehyde (1 equiv) and cyclohexanone (1.3 equiv) in the presence of $BF_3{\cdot}OEt_2$ (2.5 equiv) gave pentasubstituted tetrahydropyranone **7a** stereoselectively (43%, d*r* = 8:1).[9] Besides, cycloheptanone and acetone were used as ketone components to give the corresponding cyclization products **7b** and **7c**. These results suggested that ketones did not react with γ-butyrolactone **1**, and the introduction of ketones occurred after the reaction of **1** with 1 equiv of aldehydes to produce the corresponding tetrahydropyranones. In the case of using acetophenone, the corresponding **7d** was not formed.[12] This suggests that the cyclization was difficult with sterically bulky ketones, such as acetophenone.

We demonstrated that ketoaldehydes were successfully involved in this acid-promoted cyclization (Table 4). The

Table 4. Acid-Promoted Cyclization of 1 with Ketoaldehydes[a]



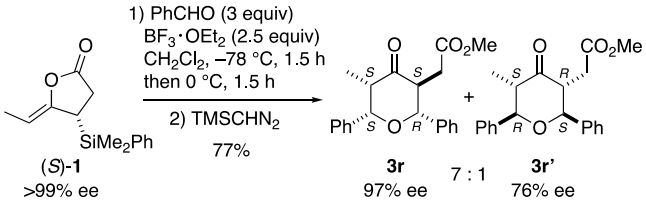
entry	ketoaldehyde	product	yield
1	 **9**	 **8a**	71%
2	 **10**	 **8b**	12%[b]
3	 **11**	 **8c**	92%

[a]Reaction conditions: **1** (0.1−0.2 mmol), ketoaldehyde (1.4 equiv), $BF_3{\cdot}OEt_2$ (2.5 equiv), CH_2Cl_2 (0.1 M), −78 °C, 1.5 h, followed by 0 °C, 2 h. [b]Isolation yield of the corresponding methyl ester converted by reaction with trimethylsilyldiazomethane.

treatment of **1** with γ-ketoaldehyde **9** (1.4 equiv) in the presence of $BF_3{\cdot}OEt_2$ (2.5 equiv) smoothly underwent cyclization to give the 8-oxabicyclo[3,2,1]octane derivative **8a** in 71% yield as a single diastereomer (entry 1).[9] A similar conversion using δ-ketoaldehyde **10** was rather messy, but the corresponding fused ring product could be obtained as an ester derivative (**8b**, entry 2). Notably, even when a sterically bulky phenyl ketone-containing aldehyde **11** was employed, the corresponding fused ring product **8c** was produced in excellent yield (92%, entry 3).

When the acid-promoted cyclization was conducted using enantiopure **1** (>99% ee)[13] and benzaldehyde, the optical purity of the obtained **3r** and **3r′** (methyl esters of **3a** and **3a′**, respectively) was 97% ee and 76% ee, respectively (Scheme 4).[14] The major product **3r** substantially retained the optical

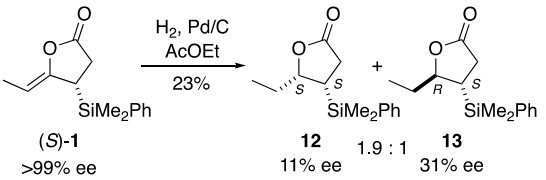
Scheme 4. Acid-Promoted Cyclization of Optically Active 1 with Aldehyde



https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX

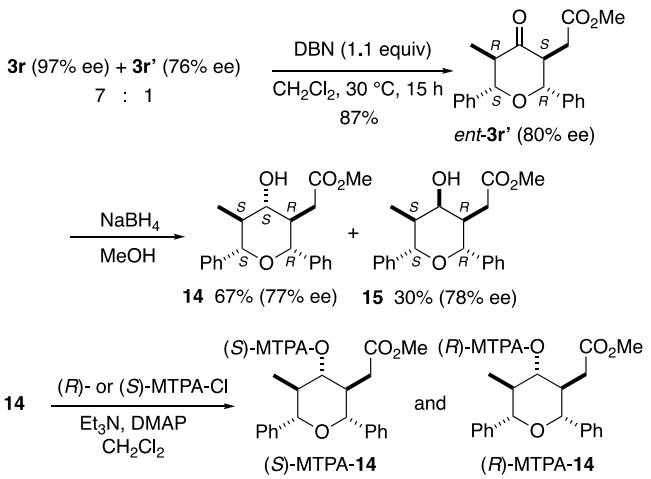
purity of the starting compound **1**. The absolute configuration of enantiopure **1** was confirmed to be *S* by conversion to the known γ-butyrolactone **13**[15] (Scheme 5). The low optical

Scheme 5. Determination of the Absolute Configuration of 1



purity of the obtained **12** (11% ee) and **13** (31% ee) suggested that the exo/endo isomerization of the olefin moiety of **1** occurred under hydrogenation conditions.[16] The absolute configuration of the obtained **3r** and **3r′** was determined (Scheme 6). The 7:1 mixture of **3r** (97% ee) and **3r′** (76% ee)

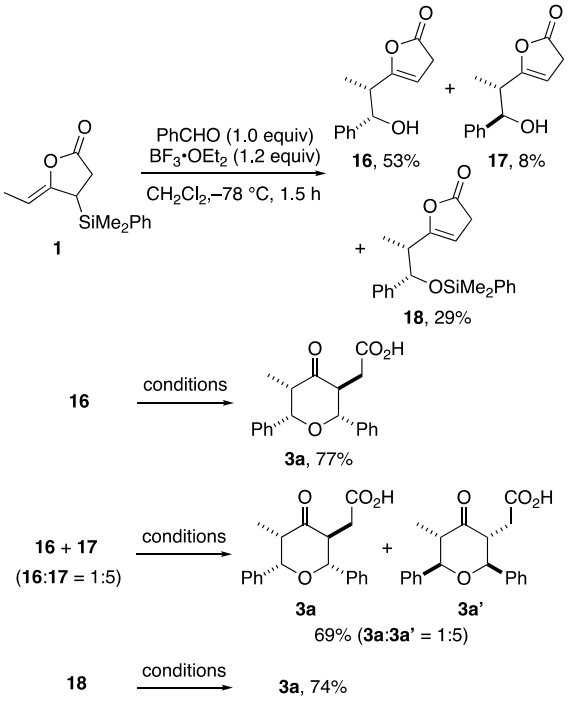
Scheme 6. Determination of the Absolute Configuration of 3r and 3r′



was subjected to isomerization with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) to give the enantiomer of **3r′** whose four substituents were in the equatorial conformation (87%, 80% ee). The resulting *ent*-**3r′** was reduced with $NaBH_4$ to give the secondary alcohols **14**[9] (67%, 77% ee) and **15** (30%, 78% ee). The obtained **14** was converted to its (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters, respectively. The absolute configuration of **14**, which reflects that of *ent*-**3r′**, was determined by the modified Mosher method (Supporting Information).[17]

To investigate the reaction pathway of this acid-promoted cyclization reaction, the stepwise conversion of **1** and aldehydes to tetrahydropyranones was examined. γ-Butyrolactone **1** was allowed to react with 1 equiv of benzaldehyde in the presence of $BF_3{\cdot}OEt_2$ at −78 °C to give the Hosomi−Sakurai reaction products, alcohol **16** (53%), its diastereomer **17** (8%), and silyl ether **18** (29%, Scheme 7). The reaction of the obtained **16** with 1.3 equiv of benzaldehyde at 0 °C gave **3a** (77%) as a single diastereomer. Under the same reaction conditions, a mixture of **16** and **17** (dr = 1:5) gave a mixture of **3a** and **3a′** (69%, dr = 1:5), and **18** gave **3a** (74%). The results of these stereospecific conversions suggested that the conversion from **1** with aldehydes to tetrahydropyranones **3**

Scheme 7. Stepwise Synthesis of Tetrahydropyranones from 1[a]

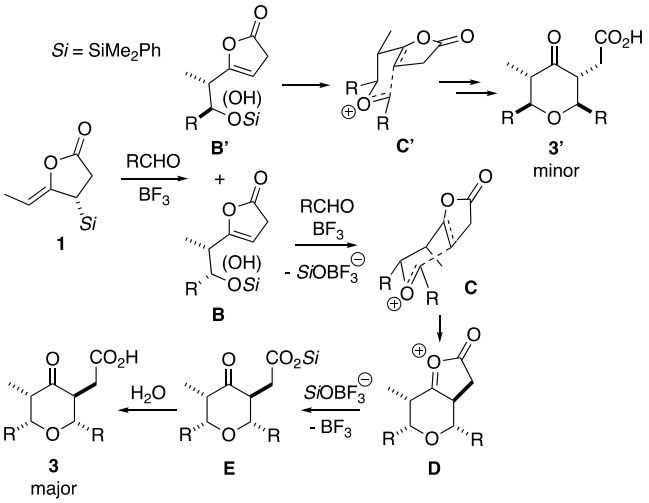


[a]Conditions: PhCHO (1.3 equiv), $BF_3{\cdot}OEt_2$ (1.3 equiv), CH_2Cl_2, 0 °C, 1.5 h.

occurred in a stepwise manner through the intermediates **16**, **17**, and/or **18**.

A plausible reaction pathway of the acid-promoted cyclization reaction of **1** with aldehydes is shown in Scheme 8. First, a nucleophilic attack of an allylsilane of **1** on the first

Scheme 8. Plausible Reaction Pathway of Acid-Promoted Cyclization of 1 with Aldehydes



aldehyde activated by Lewis acid produced the intermediate **B** (Hosomi−Sakurai reaction). Next, in the oxonium intermediate **C** obtained by reacting **B** with the second aldehyde molecule, the nucleophilic attack of an intramolecular alkene occurs through a chair-like transition state, producing cyclic intermediate **D** stereoselectively (Prins cyclization). Finally,

https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX

ring-opening of the resulting **D** followed by hydrolysis produces the substituted tetrahydropyranone **3**. The minor isomer **3′** is produced via the isomeric intermediate **B′**.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were purchased from Aldrich Chemical Company, Inc., Nacalai Tesque Co., Ltd., Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Ltd., and Wako Pure Chemical Industries, Ltd. and were used without further purification unless otherwise indicated. A Sartorius CPA224S was used as a balance. ^{1}H NMR spectra were recorded on a JEOL JNM-ECZ400S (400 MHz), a Bruker Biospin AVANCE III HD 400 (400 MHz), or a Bruker Biospin AVANCE III HD 600 (600 MHz). Chemical shifts of ^{1}H NMR spectra were reported in parts per million (ppm, δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$ or $(CH_3)_2O$ (δ = 2.04) in $(CD_3)_2O$. ^{13}C NMR spectra were recorded on a JEOL JNM-ECZ400S (100 MHz), a Bruker Biospin AVANCE III HD 400 (100 MHz), or a Bruker Biospin AVANCE III HD 600 (600 MHz). Chemical shifts of ^{13}C NMR spectra were reported in ppm (δ) relative to $CDCl_3$ (δ = 77.0) or $(CD_3)_2O$ (δ = 29.8). The following abbreviations were used; s, singlet: d, doublet: t, triplet: q, quartet: quint, quintet: sext, sextet: sept, septet: m, multiplet: br s, broad singlet. High-resolution mass spectra were obtained on a JEOL AccuTOF LC-Plus 4G JMS-T100LP spectrometer for electron spray ionization (ESI) or for direct analysis in real time (DART). All reactions were monitored by thin-layer chromatography (TLC), which was performed with precoated plates (silica gel 60 F-254, 0.25 mm layer thickness, manufactured by Merck). TLC visualization was accomplished using a UV lamp (254 nm) or a charring solution ($KMnO_4$ aq). Either Wakogel 60N (particle size, 38−100 μm) or Daisogel IR-60 1002W (particle size, 40−63 μm) was used for flash column chromatography on silica gel. Wakogel B-5F (particle size pass, 45 μm) was used for preparative TLC. Compounds **2**,[6] **9**,[18] **10**,[19] and **11**[20] were prepared according to the literature procedure.

Compound (1). To a solution of allenylsilane **2** (1.31 g, 5.03 mmol) in 3:1 MeOH/H_2O (25 mL) was added lithium hydroxide (1.06 g, 25.3 mmol), and the solution was stirred at room temperature for 18 h. The reaction was quenched with aq 2 N HCl. The reaction mixture was extracted with Et_2O (×3). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 5/1) to afford 3-(dimethyl(phenyl)silyl)hexa-3,4-dienoic acid (1.07 g, 86%) as a pale yellow oil. R_f: 0.2 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.52 (m, 2H), 7.36−7.33 (m, 3H), 4.96 (qt, J = 6.9, 2.1 Hz, 1H), 4.1−2.8 (br s, 1H), 2.95 (t, J = 2.1 Hz, 2H), 1.64 (d, J = 6.9 Hz, 3H), 0.39 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 209.6, 178.3, 137.2, 133.7, 129.1, 127.7, 88.0, 81.5, 35.9, 13.1, −2.9, −3.0; HRMS (ESI$^+$) m/z: calcd for $C_{14}H_{18}NaO_2Si$ $(M + Na)^+$, 269.0974; found, 269.0974. To a solution of 3-(dimethyl(phenyl)silyl)hexa-3,4-dienoic acid (2.58 g, 10.5 mmol) in anhydrous CH_2Cl_2 (53 mL) was added $[(Ph_3PAu)_3O]BF_4$ (151.9 mg, 0.103 mmol). The reaction mixture was stirred at room temperature for 3 h under a nitrogen atmosphere. The reaction mixture was filtered through silica gel. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 30/1) to give **1** (1.91 g, 74%) as a colorless oil and its endo isomer **1′** (244.3 mg, 9%) as a colorless oil.

Compound (1). $[\alpha]_D^{25}$: +97 (*c* 1.01, $CHCl_3$, >99% ee, *R*), $[\alpha]_D^{25}$: −98 (*c* 1.01, $CHCl_3$, >99% ee, *S*); R_f: 0.6 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, acetone-d_6): δ 7.58−7.56 (m, 2H), 7.43−7.35 (m, 3H), 4.30 (qd, J = 6.8, 1.7 Hz, 1H), 2.94 (dd, J = 18.2, 11.8 Hz, 1H), 2.83−2.78 (m, 1H), 2.45 (dd, J = 18.2, 4.2 Hz, 1H), 1.57 (dd, J = 6.8, 1.8 Hz, 3H), 0.38 (s, 3H), 0.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ 175.0, 151.9, 136.4, 134.8, 130.5, 128.8, 96.8, 30.6, 26.5, 10.6, −5.2, −5.3; HRMS (DART$^+$) m/z: calcd for $C_{14}H_{19}O_2Si$ $(M + H)^+$, 247.1154; found, 247.1148. Compound **1** was gradually isomerized to compound **1′** in $CDCl_3$. The stereochemistry of **1** was determined by nuclear Overhauser effect spectroscopy (NOESY).

Compound (1′). R_f: 0.5 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−7.48 (m, 2H), 7.41−7.37 (m, 3H), 3.13 (t, J = 1.6 Hz, 2H), 2.22 (qt, J = 7.6, 1.6 Hz, 2H), 1.05 (t, J = 7.6 Hz, 3H), 0.43 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 178.2, 163.6, 137.0, 133.5, 129.6, 128.1, 105.1, 37.7, 22.5, 11.8, −2.1; HRMS (DART$^+$) m/z: calcd for $C_{14}H_{19}O_2Si$ $(M + H)^+$, 247.1154; found, 247.1167.

General Procedure for the Synthesis of Tetrahydropyranones (Carboxylic Acids) Using Aldehydes (General Procedure A). To a solution of **1** (1 equiv) in anhydrous CH_2Cl_2 (0.1 M) was added aldehyde (3 equiv). The reaction mixture was stirred at −78 °C under a nitrogen atmosphere. $BF_3{\cdot}OEt_2$ (2.5 equiv, 1.2 M CH_2Cl_2 solution) was added slowly to the reaction mixture. The reaction mixture was stirred at −78 °C for 1.5 h and then stirred at 0 °C for 1.5 h. The reaction was quenched with brine at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography or preparative TLC on silica gel to give tetrahydropyranones (carboxylic acids) **3** and **3′**.

General Procedure for the Synthesis of Tetrahydropyranones (Methyl Esters) Using Aldehydes (General Procedure B). After performing general procedure A, to a solution of the resulting carboxylic acids in anhydrous toluene/methanol (4/1, 0.03 M) was added trimethylsilyldiazomethane (3.2 equiv, 2.0 M diethyl ether solution). The reaction mixture was stirred at room temperature for 1.5 h under a nitrogen atmosphere. The reaction was quenched with acetic acid at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography or preparative TLC on silica gel to give tetrahydropyranones (methyl esters) **3** and **3′**.

Compound (3a, Carboxylic Acid). According to general procedure A, the reaction of **1** (49.6 mg, 0.201 mmol) with benzaldehyde (65.4 mg, 0.616 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.42 mL, 0.504 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a mixture of **3a** and **3a′** (55.4 mg, 85%, **3a**:**3a′** = 20:1) as a colorless solid: mp. 156 °C (decomp); R_f: 0.1 (*n*-hexane/AcOEt = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.1−8.9 (br s, 1H), 7.49−7.24 (m, 10H), 5.02 (d, J = 2.8 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 3.34 (ddd, J = 11.5, 7.9, 3.6 Hz, 1H), 2.87 (qd, J = 7.2, 2.8 Hz, 1H), 2.56 (dd, J = 17.1, 7.9 Hz, 1H), 2.17 (dd, J = 17.1, 3.6 Hz, 1H), 1.10 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 209.9, 177.4, 139.0, 138.2, 128.9, 128.8, 128.3, 127.4, 127.1, 125.4, 83.7, 80.5, 51.0, 49.2, 29.5, 11.5; HRMS (ESI$^+$) m/z: calcd for $C_{20}H_{20}NaO_4$ $(M + Na)^+$, 347.1259; found, 347.1237. The relative configuration of **3a** was determined by NOESY.

Large-Scale Synthesis of 3a. According to general procedure A, the reaction was performed using **1** (615 mg, 2.50 mmol), benzaldehyde (797 mg, 7.50 mmol), and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 5.2 mL, 6.24 mmol) followed by purification by column chromatography on silica gel (*n*-hexane/AcOEt = 3/1−1/1) to give a mixture of **3a** and **3a′** (640 mg, 79%, **3a**:**3a′** = 15:1) as a colorless solid.

Compound (3r, Methyl Ester of 3a). According to general procedure B, the reaction was performed using (*S*)-**1** (24.0 mg, 0.0974 mmol), benzaldehyde (31.1 mg, 0.293 mmol), $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.20 mL, 0.240 mmol), and $TMSCHN_2$ (2.0 M diethyl ether solution, 0.16 mL, 0.320 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) to give a mixture of methyl-esterified **3r** and **3r′** (25.2 mg, 77%, **3r** (97% ee):**3r′** (76% ee) = 7:1) as a colorless solid. $[\alpha]_D^{25}$: +37 (*c* 0.72, $CHCl_3$, 7:1 mixture of **3r** (97% ee) and **3r′** (76% ee)); R_f: 0.4 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.24 (m, 10H), 5.04 (d, J = 2.8 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 3.58 (s, 3H), 3.39 (ddd, J = 11.6, 7.6, 3.8 Hz, 1H), 2.87 (qd, J = 7.1, 2.8 Hz, 1H), 2.57 (dd, J = 17.0, 7.6 Hz, 1H), 2.16 (dd, J = 17.0, 3.8 Hz, 1H), 1.12 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 210.1, 172.2, 139.1, 138.2, 128.7 (×2), 128.2, 127.3, 127.2, 125.4, 83.8, 80.5,

https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX

51.7, 51.1, 49.3, 29.4, 11.5; HRMS (DART$^+$) m/z: calcd for $C_{21}H_{23}O_4$ (M + H)$^+$, 339.1596; found, 339.1595.

*Compound (ent-**3r′**, Methyl Ester of **3a′**).* To a solution of a mixture of methyl-esterified **3r** (97% ee) and **3r′** (76% ee) (14.4 mg, 0.0426 mmol, **3r**:**3r′** = 7:1) in anhydrous CH_2Cl_2 (53 mL) was added 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (6.8 mg, 0.0548 mmol). The reaction mixture was stirred at room temperature for 16 h under a nitrogen atmosphere. The reaction mixture was filtered through silica gel. The filtrate was concentrated under reduced pressure to give methyl-esterified *ent*-**3r′** (12.5 mg, 87%, 80% ee, dr = 17:1) as a colorless solid: $[\alpha]_D^{20}$: +3 (*c* 0.63, $CHCl_3$, 80% ee); R_f: 0.4 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.26 (m, 10H), 4.57 (d, *J* = 10.2 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 3.59 (s, 3H), 3.38 (ddd, *J* = 11.5, 8.5, 3.0 Hz, 1H), 2.96 (dq, *J* = 10.2, 6.5 Hz, 1H), 2.59 (dd, *J* = 16.7, 8.5 Hz, 1H), 2.07 (dd, *J* = 16.7, 3.0 Hz, 1H), 0.88 (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 207.3, 172.3, 139.4, 138.7, 128.73, 128.71, 128.6, 128.5, 127.2, 127.1, 86.5, 84.2, 53.8, 51.82, 51.76, 29.9, 9.7; HRMS (ESI$^+$) m/z: calcd for $C_{21}H_{22}NaO_4$ (M + Na)$^+$, 361.1416; found, 361.1422.

*Compound (**3b**).* According to general procedure A, the reaction of **1** (49.2 mg, 0.200 mmol) with *p*-fluorobenzaldehyde (74.8 mg, 0.602 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.42 mL, 0.504 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 5/2) gave a mixture of **3b** and **3b′** (46.2 mg, 64%, **3b**:**3b′** = 16:1) as a colorless solid. R_f: 0.1 (*n*-hexane/AcOEt = 5/1); mp: 145 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.0−9.4 (br s, 1H), 7.45 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.29 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.12 (t, *J* = 8.8 Hz, 2H), 7.05 (t, *J* = 8.8 Hz, 2H), 4.99 (d, *J* = 2.6 Hz, 1H), 4.57 (d, *J* = 10.8 Hz, 1H), 3.28 (ddd, *J* = 10.8, 7.7, 3.8 Hz, 1H), 2.83 (qd, *J* = 6.9, 2.6 Hz, 1H), 2.55 (dd, *J* = 17.2, 7.7 Hz, 1H), 2.17 (dd, *J* = 17.2, 3.8 Hz, 1H), 1.08 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 209.3, 177.0, 162.9 (d, *J* = 246 Hz), 162.1 (d, *J* = 244 Hz), 134.7, 133.8, 128.9 (d, *J* = 8 Hz), 127.0 (d, *J* = 8 Hz), 115.9 (d, *J* = 21 Hz), 115.3 (d, *J* = 22 Hz), 83.0, 80.0, 50.9, 49.2, 29.4, 11.4; HRMS (ESI$^-$) m/z: calcd for $C_{20}H_{17}F_2O_4$ (M − H)$^-$, 359.1095; found, 359.1094.

*Compound (**3c**).* According to general procedure B, the reaction of **1** (23.3 mg, 0.0946 mmol) with *p*-chlorobenzaldehyde (40.2 mg, 0.286 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.20 mL, 0.240 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a diastereomeric mixture of carboxylic acids. Then, the reaction of the mixture with $TMSCHN_2$ (2.0 M diethyl ether solution, 0.16 mL, 0.320 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a mixture of **3c** and **3c′** (22.6 mg, 59%, **3c**:**3c′** = 25:1) as a colorless solid. R_f: 0.5 (*n*-hexane/AcOEt = 5/1); mp: 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.3 (m, 6H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.00 (d, *J* = 2.8 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 3.59 (s, 3H), 3.29 (ddd, *J* = 10.8, 7.4, 4.2 Hz, 1H), 2.83 (qd, *J* = 7.0, 2.8 Hz, 1H), 2.52 (dd, *J* = 17.2, 7.4 Hz, 1H), 2.16 (dd, *J* = 17.2, 4.2 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 209.2, 172.0, 137.4, 136.6, 134.7, 133.3, 129.0, 128.5 (×2), 126.8, 83.0, 79.9, 51.8, 50.7, 49.1, 29.3, 11.5; HRMS (ESI$^+$) m/z: calcd for $C_{21}H_{20}Cl_2NaO_4$ (M + Na)$^+$, 429.0636; found, 429.0616.

*Compound (**3d**).* According to general procedure B, the reaction of **1** (24.5 mg, 0.0994 mmol) with *p*-bromobenzaldehyde (55.2 mg, 0.298 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.21 mL, 0.252 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a diastereomeric mixture of carboxylic acids. Then, the reaction of the mixture with $TMSCHN_2$ (2.0 M diethyl ether solution, 0.16 mL, 0.320 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a mixture of **3d** and **3d′** (28.2 mg, 57%, **3d**:**3d′** = >25:1) as a colorless solid. R_f: 0.5 (*n*-hexane/AcOEt = 5/1); mp: 59−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.98 (d, *J* = 2.6 Hz, 1H), 4.58 (d, *J* = 10.8 Hz, 1H), 3.11 (s, 3H), 3.28 (ddd, *J* = 10.8, 7.5, 4.0 Hz, 1H), 2.83 (qd, *J* = 7.3, 2.6 Hz, 1H), 2.52 (dd, *J* = 16.9, 7.5 Hz, 1H), 2.16 (dd, *J* = 16.9, 4.0 Hz, 1H), 1.08 (d, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 209.1, 172.0, 137.9, 137.1, 132.0, 131.5, 128.8, 127.1, 122.9, 121.4, 83.1, 79.9, 51.9, 50.7, 49.1, 29.3, 11.5; HRMS (ESI$^+$) m/z: calcd for $C_{21}H_{20}Br_2NaO_4$ (M + Na)$^+$, 516.9626; found, 516.9646.

*Compound (**3e**).* According to general procedure A, the reaction of **1** (49.3 mg, 0.200 mmol) with *p*-tolualdehyde (73.1 mg, 0.608 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.42 mL, 0.504 mmol) followed by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a mixture of **3e** and **3e′** (40.1 mg, 53%, **3e**:**3e′** = 6:1) as a colorless solid. R_f: 0.1 (*n*-hexane/AcOEt = 3/1); mp: 161 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.3−9.5 (br s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.23−7.21 (m, 4H), 7.14 (d, *J* = 7.6 Hz, 2H), 4.97 (d, *J* = 2.5 Hz, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 3.33 (ddd, *J* = 11.3, 8.3, 3.4 Hz, 1H), 2.83 (qd, *J* = 7.1, 2.5 Hz, 1H), 2.54 (dd, *J* = 17.2, 8.3 Hz, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 2.15 (dd, *J* = 17.2, 3.4 Hz, 1H), 1.10 (d, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 210.2, 177.7, 138.6, 136.9, 136.1, 135.2, 129.4, 128.9, 127.0, 125.3, 83.5, 80.4, 51.1, 49.2, 29.6, 21.2, 21.1, 11.4; HRMS (ESI$^+$) m/z: calcd for $C_{22}H_{24}NaO_4$ (M + Na)$^+$, 375.1572; found, 375.1545.

*Compound (**3f**).* According to general procedure B, the reaction of **1** (24.5 mg, 0.0994 mmol) with *p*-nitrobenzaldehyde (90.0 mg, 0.596 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.42 mL, 0.504 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a diastereomeric mixture of carboxylic acids. Then, the reaction of the mixture with $TMSCHN_2$ (2.0 M diethyl ether solution, 0.15 mL, 0.300 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a mixture of **3f** and **3f′** (26.7 mg, 31%, **3f**:**3f′** = 2.5:1) as a colorless solid. R_f: 0.5 (*n*-hexane/AcOEt = 5/1); mp: 92−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.8 Hz, 2 H), 8.24 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 8.8 Hz, 2 H), 7.52 (d, *J* = 8.8 Hz, 2 H), 5.20 (d, *J* = 2.8 Hz, 1H), 4.88 (d, *J* = 10.9 Hz, 1H), 3.61 (s, 3H), 3.26 (ddd, *J* = 10.9, 6.9, 4.2 Hz, 1H), 2.96 (qd, *J* = 7.0, 2.8 Hz, 1H), 2.51 (dd, *J* = 17.0, 6.9 Hz, 1H), 2.29 (dd, *J* = 17.0, 4.2 Hz, 1H), 1.09 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 207.5, 171.7, 148.2, 147.4, 145.5, 145.0, 128.1, 126.2, 124.1, 123.7, 82.4, 79.7, 52.0, 50.1, 48.8, 29.1, 11.6; HRMS (ESI$^+$) m/z: calcd for $C_{21}H_{20}N_2NaO_8$ (M + Na)$^+$, 451.1117; found, 451.1125.

*Compound (**3g**).* According to general procedure A, the reaction of **1** (24.5 mg, 0.0994 mmol) with *m*-tolualdehyde (35.8 mg, 0.298 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.21 mL, 0.252 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a mixture of **3g** and **3g′** (26.6 mg, 76%, **3g**:**3g′** = 16:1) as a colorless solid. R_f: 0.1 (*n*-hexane/AcOEt = 3/1); mp: 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.0−8.1 (br s, 1H), 7.33−7.06 (m, 8H), 4.97 (d, *J* = 2.5 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 3.35 (ddd, *J* = 11.1, 8.1, 3.5 Hz, 1H), 2.85 (qd, *J* = 7.2, 2.5 Hz, 1H), 2.55 (dd, *J* = 17.2, 8.1 Hz, 1H), 2.41 (s, 3 H), 2.35 (s, 3 H), 2.16 (dd, *J* = 17.2, 3.5 Hz, 1H), 1.12 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 210.1, 177.5, 138.9, 138.6, 138.1, 137.8, 129.6, 128.7, 128.1 (×2), 127.8, 126.0, 124.3, 122.5, 83.8, 80.6, 51.1, 49.1, 29.6, 21.50, 21.48, 11.5; HRMS (ESI$^+$) m/z: calcd for $C_{22}H_{24}NaO_4$ (M + Na)$^+$, 375.1572; found, 375.1580.

*Compound (**3h**).* According to general procedure A, the reaction of **1** (49.7 mg, 0.202 mmol) with *m*-anisaldehyde (83.0 mg, 0.610 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.42 mL, 0.504 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a mixture of **3h** and **3h′** (59.2 mg, 74%, **3h**:**3h′** = 15:1) as a colorless solid. R_f: 0.1 (*n*-hexane/AcOEt = 3/1); mp: 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.8−8.9 (br s, 1H), 7.33 (t, *J* = 8.2 Hz, 2H), 7.26 (t, *J* = 8.2 Hz, 2H), 7.04−7.02 (m, 2H), 6.91−6.89 (m, 3H), 6.80 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.98 (d, *J* = 2.5 Hz, 1H), 4.53 (d, *J* = 10.8 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.31 (ddd, *J* = 10.8, 8.1, 3.6 Hz, 1H), 2.85 (qd, *J* = 7.2, 2.5 Hz, 1H), 2.55 (dd, *J* = 17.2, 8.1 Hz, 1H), 2.21 (dd, *J* = 17.2, 3.6 Hz, 1H), 1.10 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 209.9, 177.5, 159.8, 159.5, 140.4, 139.8, 129.8, 129.3, 119.4, 117.7, 113.7, 113.0, 112.3, 111.5, 83.4, 80.3, 55.3, 55.2, 50.9, 49.1, 29.5, 11.5; HRMS (ESI$^+$) m/z: calcd for $C_{22}H_{24}NaO_6$ (M + Na)$^+$, 407.1471; found, 407.1473.

https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX

*Compound (**3i**).* According to general procedure A, the reaction of **1** (49.6 mg, 0.201 mmol) with *o*-tolualdehyde (73.5 mg, 0.612 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.42 mL, 0.504 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a mixture of **3i** and **3i′** (55.2 mg, 78%, **3i**:**3i′** = 10:1) as a colorless solid. R_f: 0.1 (*n*-hexane/AcOEt = 3/1); mp: 143 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.1−8.9 (br s, 1H), 7.61−7.13 (m, 8H), 5.15 (d, *J* = 2.5 Hz, 1H), 4.85 (d, *J* = 10.9 Hz, 1H), 3.56 (ddd, *J* = 10.9, 8.7, 3.2 Hz, 1H), 2.87 (qd, *J* = 7.0, 2.5 Hz, 1H), 2.63 (dd, *J* = 17.0, 8.7 Hz, 1H), 2.42 (s, 3 H), 2.30 (s, 3 H), 2.11 (dd, *J* = 17.0, 3.2 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 210.3, 177.6, 136.1, 135.8, 133.0, 130.8, 130.3, 128.5, 127.3, 127.0, 126.9, 126.7, 125.8, 125.7, 78.6 (×2), 48.6 (×2), 29.3, 19.6, 19.0, 12.0; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{22}H_{24}NaO_4$ $(M + Na)^+$, 375.1572; found, 375.1592.

*Compound (**3j**).* According to general procedure A, the reaction of **1** (24.0 mg, 0.0974 mmol) with 2-naphthaldehyde (45.3 mg, 0.290 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.20 mL, 0.240 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a mixture of **3j** and **3j′** (29.1 mg, 70%, **3j**:**3j′** = 12:1) as a colorless solid. R_f: 0.1 (*n*-hexane/AcOEt = 3/1); mp: 176 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.5−9.6 (br s, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.91−7.82 (m, 6H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.53−7.41 (m, 6H), 5.24 (d, *J* = 2.2 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 1H), 3.50 (ddd, *J* = 11.0, 7.9, 3.5 Hz, 1H), 3.03 (qd, *J* = 7.1, 2.2 Hz, 1H), 2.60 (dd, *J* = 17.2, 7.9 Hz, 1H), 2.21 (dd, *J* = 17.2, 3.5 Hz, 1H), 1.17 (d, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.8, 176.9, 136.2, 135.6, 133.6, 133.1, 133.0, 132.7, 129.1, 128.1, 128.04, 128.01, 127.8, 127.6, 126.9, 126.5 (×2), 126.2, 125.9, 124.4, 124.3, 123.2, 84.0, 80.7, 51.0, 49.1, 29.6, 11.6; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{28}H_{24}NaO_4$ $(M + Na)^+$, 447.1572; found, 447.1537.

*Compound (**3k**).* According to general procedure A, the reaction of **1** (51.7 mg, 0.210 mmol) with butyraldehyde (44.9 mg, 0.623 mmol) and $BF_3{\cdot}OEt_2$ (71.5 mg, 0.503 mmol) followed by flash column chromatography on silica gel (*n*-hexane/AcOEt = 5/3) gave a mixture of **3k** and **3k′** (44.6 mg, 83%, **3k**:**3k′** = >25:1) as a pale yellow oil. R_f: 0.2 (*n*-hexane/AcOEt = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.0−8.4 (br s, 1H), 3.54 (ddd, *J* = 8.8, 4.1, 2.5 Hz, 1H), 3.32 (ddd, *J* = 11.0, 7.6, 3.2 Hz, 1H), 2.88 (ddd, *J* = 11.0, 7.6, 4.0 Hz, 1H), 2.67 (dd, *J* = 17.2, 7.6 Hz, 1H), 2.42 (qd, *J* = 7.0, 2.5 Hz, 1H), 2.31 (dd, *J* = 17.2, 4.0 Hz, 1H), 1.70−1.24 (m, 8H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 211.3, 178.0, 80.4, 78.9, 49.0, 47.9, 36.2, 33.8, 29.5, 19.0, 18.6, 13.9, 13.8, 10.7; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{14}H_{24}NaO_4$ $(M + Na)^+$, 279.1572; found, 279.1569.

*Compound (**3l**).* According to general procedure A, the reaction of **1** (26.7 mg, 0.108 mmol) with 3-phenylpropionaldehyde (46.0 mg, 0.343 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.23 mL, 0.276 mmol) followed by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a mixture of **3l** and **3l′** (29.5 mg, 72%, **3l**:**3l′** = >25:1) as a colorless solid. R_f: 0.1 (*n*-hexane/AcOEt = 3/1); mp: 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.0−8.2 (br s, 1H), 7.33−7.28 (m, 4H), 7.22 (d, *J* = 7.6 Hz, 6H), 3.57 (ddd, *J* = 9.4, 3.1, 2.6 Hz, 1H), 3.32 (ddd, *J* = 11.0, 7.9, 3.1 Hz, 1H), 3.05−2.86 (m, 3H), 2.81−2.62 (m, 3H), 2.44 (qd, *J* = 7.4, 2.6 Hz, 1H), 2.26 (dd, *J* = 17.6, 4.0 Hz, 1H), 2.07 (m, 1H), 1.97−1.92 (m, 2H), 1.66 (m, 1H), 1.21 (d, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 210.7, 177.6, 141.43, 141.39, 128.5 (×2), 128.4 (×2), 126.0 (×2), 79.6, 78.0, 49.0, 47.8, 35.9, 33.6, 32.1, 31.5, 29.4, 10.9; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{24}H_{28}NaO_4$ $(M + Na)^+$, 403.1885; found, 403.1864.

*Compound (**3m**).* According to general procedure A, the reaction of **1** (49.5 mg, 0.201 mmol) with isobutyraldehyde (44.0 mg, 0.610 mmol) and $BF_3{\cdot}OEt_2$ (71.5 mg, 0.503 mmol) followed by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a mixture of **3m** and **3m′** (40.1 mg, 78%, **3m**:**3m′** = 4:1) as a colorless solid. R_f: 0.2 (*n*-hexane/AcOEt = 3/1); mp: 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.4−10.4 (br s, 1H), 3.18 (*J* = 11.0, 1.2 Hz, 1H), 3.05 (ddd, *J* = 11.0, 7.8, 3.7 Hz, 1H), 2.99 (dd, *J* = 9.9, 2.1 Hz, 1H), 2.64 (dd, *J* = 17.0, 7.8 Hz, 1H), 2.59 (qd, *J* = 7.2, 2.1 Hz, 1H), 2.26 (dd, *J* = 17.0, 3.7 Hz, 1H), 1.89−1.82 (m, 1H), 1.79−1.73 (m, 1H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.08−0.94 (m, 9H), 0.79 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 212.2, 177.9, 84.9, 84.3, 47.2, 45.4, 29.8, 29.25, 29.15, 20.5, 20.0, 17.7, 14.0, 10.4; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{14}H_{24}NaO_4$ $(M + Na)^+$, 279.1572; found, 279.1567.

*Compound (**3n**).* According to general procedure B, the reaction of **1** (25.1 mg, 0.102 mmol) with cyclopropanecarboxaldehyde (21.3 mg, 0.304 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.21 mL, 0.252 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a diastereomeric mixture of carboxylic acids. Then, the reaction of the mixture with $TMSCHN_2$ (2.0 M diethyl ether solution, 0.16 mL, 0.320 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a mixture of **3n** and **3n′** (9.0 mg, 33%, **3n**:**3n′** = 6:1) as a yellow oil. R_f: 0.5 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s. 3H), 3.17 (ddd, *J* = 11.8, 7.0, 4.1 Hz, 1H), 2.73 (dd, *J* = 8.6, 2.6 Hz, 1H), 2.70 (dd, *J* = 17.0, 7.0 Hz, 1H), 2.60−2.50 (m, 3H), 1.33 (d, *J* = 7.6 Hz, 3H), 1.12−0.98 (m, 2H), 0.70−0.57 (m, 2H), 0.50 (m, 1H), 0.43−0.33 (m, 3H), 0.28 (sext, *J* = 4.5 Hz, 1H), 0.13 (sext, *J* = 5.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 211.0, 172.8, 85.4, 84.1, 51.8, 49.3, 49.2, 29.4, 15.4, 12.1, 11.7, 4.3 (×2), 2.2, 1.3; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{15}H_{22}NaO_4$ $(M + Na)^+$, 289.1416; found, 289.1403.

*Compound (**4**).*[10] According to general procedure A, the reaction of **1** (49.5 mg, 0.201 mmol) with cyclohexanone (59.0 mg, 0.601 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.42 mL, 0.504 mmol) followed by preparative TLC on silica gel (*n*-hexane/AcOEt = 2/1) gave **4** (21.7 mg, 83%) as a colorless oil. R_f: 0.1 (*n*-hexane/AcOEt = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.3−7.9 (br s, 1H), 2.71 (t, *J* = 6.3 Hz, 2H), 2.63 (t, *J* = 6.3 Hz, 2H), 2.47 (q, *J* = 7.4 Hz, 2H), 1.06 (t, *J* = 7.4 Hz, 3H).

*Compound (**5**).* To a solution of *β*-silyl-*γ*-ethylidene-*γ*-butyrolactone **1** (26.0 mg, 0.106 mmol) in anhydrous CH_2Cl_2 (1 mL) was added benzaldehyde (11.2 mg, 0.106 mmol). The reaction mixture was stirred at −78 °C under a nitrogen atmosphere. $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.22 mL, 0.264 mmol) was added slowly to the reaction mixture. The reaction mixture was stirred at −78 °C for 1.5 h. 3-Phenylpropionaldehyde (16.9 mg, 0.126 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C and stirred for 1.5 h. The reaction was quenched with brine at 0 °C and then extracted with CH_2Cl_2 (×3). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (*n*-hexane/AcOEt = 5/1) to give a diastereomeric mixture of carboxylic acids. Then, to a solution of the mixture in anhydrous toluene (2.8 mL) and methanol (0.7 mL) was added trimethylsilyldiazomethane (2.0 M diethyl ether solution, 0.16 mL, 0.320 mmol). The reaction mixture was stirred at room temperature for 1.5 h under a nitrogen atmosphere. The reaction was quenched with acetic acid at room temperature and then concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (*n*-hexane/AcOEt = 5/1) to give **5** (23.3 mg, 60%, d*r* = 8:1) as a colorless solid. R_f: 0.4 (*n*-hexane/AcOEt = 5/1); mp: 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4−7.1 (m, 10H), 4.83 (d, *J* = 2.6 Hz, 1H), 3.69 (s, 3H), 3.56 (ddd, *J* = 11.1, 8.1, 2.9 Hz, 1H), 3.11 (ddd, *J* = 11.1, 7.2, 4.2 Hz, 1H), 3.02 (ddd, *J* = 13.8, 8.6, 5.2 Hz, 1H), 2.84 (m, 1H), 2.78 (qd, *J* = 7.5, 2.6 Hz, 1H), 2.70 (dd, *J* = 17.0, 7.2 Hz, 1H), 2.32 (dd, *J* = 17.0, 4.2 Hz, 1H), 2.1−1.9 (m, 2H), 0.96 (d, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 210.7, 172.5, 141.5, 138.6, 128.43, 128.41, 128.3, 127.3, 125.9, 125.3, 79.7, 79.6, 51.9, 50.6, 47.4, 35.8, 31.4, 29.4, 11.3; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{23}H_{26}NaO_4$ $(M + Na)^+$, 389.1729; found, 389.1703.

*Compound (**6**).* To a solution of *β*-silyl-*γ*-ethylidene-*γ*-butyrolactone **1** (24.4 mg, 0.0990 mmol) in anhydrous CH_2Cl_2 (1 mL) was added 3-phenylpropionaldehyde (13.4 mg, 0.0990 mmol). The reaction mixture was stirred at −78 °C under a nitrogen atmosphere. $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.10 mL, 0.120 mmol) was added slowly to the reaction mixture. The reaction mixture was stirred at −45 °C for 1.5 h. Benzaldehyde (12.9 mg, 0.122 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C and stirred for 3.5 h. The reaction was quenched with brine at 0 °C and

https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX

then extracted with CH_2Cl_2 (×3). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) to give a diastereomeric mixture of carboxylic acids. Then, to a solution of mixture in anhydrous toluene (2.8 mL) and methanol (0.7 mL) was added trimethylsilyldiazomethane (2.0 M diethyl ether solution, 0.16 mL, 0.320 mmol). The reaction mixture was stirred at room temperature for 1.5 h under a nitrogen atmosphere. The reaction was quenched with acetic acid at room temperature and then concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) to give **6** (20.3 mg, 56%, d*r* = 10:1) as a colorless oil. R_f: 0.4 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.32 (m, 3H), 7.26−7.22 (m, 3H), 7.19−7.15 (m, 2H), 7.13−7.11 (m, 2H), 4.28 (d, *J* = 11.4 Hz, 1H), 3.71 (ddd, *J* = 8.2, 4.8, 2.4 Hz, 1H), 3.51 (s, 3H), 3.26 (ddd, *J* = 11.4, 7.6, 3.7 Hz, 1H), 2.72 (m, 1H), 2.60 (m, 1H), 2.52 (qd, *J* = 7.1, 2.4 Hz, 1H), 2.46 (dd, *J* = 16.8, 7.6 Hz, 1H), 2.06 (m, 1H), 2.00 (dd, *J* = 16.8, 3.7 Hz, 1H), 1.69 (m, 1H), 1.32 (d, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 210.3, 172.2, 141.5, 139.2, 128.71, 128.68, 128.5, 128.4, 127.2, 126.0, 84.0, 78.7, 51.7, 49.4, 49.1, 33.3, 31.8, 29.5, 11.0; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{23}H_{26}NaO_4$ (M + Na)$^+$, 389.1729; found, 389.1700.

General Procedure for the Synthesis of Tetrahydropyranones Using Ketones (General Procedure C). To a solution of *β*-silyl-*γ*-ethylidene-*γ*-butyrolactone **1** (1 equiv) in anhydrous CH_2Cl_2 (0.1 M) were added aldehyde (1.0 equiv) and ketone (1.3−4.0 equiv). The reaction mixture was stirred at −78 °C under a nitrogen atmosphere. $BF_3{\cdot}OEt_2$ (2.5 equiv, 1.2 M CH_2Cl_2 solution) was added carefully to the reaction mixture. The reaction mixture was stirred at −78 °C for 1.5 h and then the reaction mixture was stirred at 0 °C for 2−20 h. The reaction was quenched with brine at 0 °C and then extracted with CH_2Cl_2 (×3). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel to give a diastereomeric mixture of carboxylic acids. Then, to a solution of mixture in anhydrous 4:1 toluene/methanol (0.03 M) was added trimethylsilyldiazomethane (2.0 M diethyl ether solution, 3.2 equiv). The reaction mixture was stirred at room temperature for 1.5 h under a nitrogen atmosphere. The reaction was quenched with acetic acid at room temperature and then concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel to give tetrahydropyranone **7**.

*Compound (**7a**).* According to general procedure C, the reaction of **1** (26.7 mg, 0.108 mmol) with benzaldehyde (55.2 mg, 0.298 mmol), cyclohexane (13.5 mg, 0.138 mmol), and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.23 mL, 0.276 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a diastereomeric mixture of carboxylic acids. Then, the reaction of the mixture with $TMSCHN_2$ (2.0 M diethyl ether solution, 0.16 mL, 0.320 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 10/1) gave **7a** (15.5 mg, 43%, d*r* = 8:1) as a colorless solid. R_f: 0.6 (*n*-hexane/AcOEt = 5/1); mp: 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43−7.34 (m, 4H), 7.28 (m, 1H), 4.94 (d, *J* = 2.8 Hz, 1H), 3.69 (s, 3H), 3.30 (dd, *J* = 10.4, 2.9 Hz, 1H), 2.79−2.70 (m, 2H), 2.21 (dd, *J* = 16.7, 2.9 Hz, 1H), 2.01−1.05 (m, 10H), 0.95 (d, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 211.6, 172.8, 139.2, 128.2, 127.1, 125.4, 79.1, 72.3, 52.1, 51.9, 50.5, 37.1, 28.9, 26.8, 25.3, 21.7, 20.3, 11.6; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{20}H_{26}NaO_4$ (M + Na)$^+$, 353.1729; found, 353.1720. The relative configuration of **7a** was determined by NOESY and *J* values in ^{1}H NMR.

*Compound (**7b**).* According to general procedure C, the reaction of **1** (25.2 mg, 0.102 mmol) with benzaldehyde (10.2 mg, 0.0961 mmol), cycloheptanone (17.6 mg, 0.157 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.22 mL, 0.264 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a diastereomeric mixture of carboxylic acids. Then, the reaction of the mixture with $TMSCHN_2$ (2.0 M diethyl ether solution, 0.16 mL, 0.320 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 5/1) gave **7b** (8.2 mg, 23%, d*r* = 4.5:1) as a colorless oil. R_f: 0.6 (*n*-hexane/AcOEt = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.25 (m, 5H), 4.91 (d, *J* = 3.0 Hz, 1H), 3.69 (s, 3H), 3.33 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.75 (dd, *J* = 16.6, 10.8 Hz, 1H), 2.71 (qd, *J* = 7.0, 3.0 Hz, 1H), 2.25 (dd, *J* = 16.6, 2.8 Hz, 1H), 1.92−1.35 (m, 12H), 0.95 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 211.8, 172.8, 128.2, 127.3, 127.1, 125.5, 82.1, 72.9, 53.2, 51.9, 50.7, 42.4, 30.3, 29.0, 28.5, 28.1, 22.8, 21.0, 11.5; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{21}H_{28}NaO_4$ (M + Na)$^+$, 367.1885; found, 367.1862.

*Compound (**7c**).* According to general procedure C, the reaction of **1** (24.3 mg, 0.0986 mmol) with benzaldehyde (10.2 mg, 0.0961 mmol), acetone (23.7 mg, 0.408 mmol), and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.21 mL, 0.252 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave a diastereomeric mixture of carboxylic acids. Then, the reaction of the mixture with $TMSCHN_2$ (2.0 M diethyl ether solution, 0.16 mL, 0.320 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 4/1) gave **7c** (10.1 mg, 35%, d*r* = 6:1) as a colorless solid. R_f: 0.5 (*n*-hexane/AcOEt = 5/1); mp: 79−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.24 (m, 5H), 5.04 (d, *J* = 3.2 Hz, 1H), 3.70 (s, 3H), 3.39 (dd, *J* = 10.4, 3.2 Hz, 1H), 2.76 (dd, *J* = 16.6, 10.4 Hz, 1H), 2.68 (qd, *J* = 7.0, 3.2 Hz, 1H), 2.19 (dd, *J* = 16.6, 3.2 Hz, 1H), 1.51 (s, 3H), 1.14 (s, 3H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 211.6, 172.6, 138.9, 128.2, 127.2, 125.6, 78.3, 74.0, 51.9, 51.7, 50.7, 29.5, 29.2, 20.3, 11.5; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{17}H_{22}NaO_4$ (M + Na)$^+$, 313.1416; found, 313.1442.

General Procedure for the Synthesis of Tetrahydropyranones (Carboxylic Acids) Using Ketoaldehydes (General Procedure D). To a solution of *β*-silyl-*γ*-ethylidene-*γ*-butyrolactone **1** (1 equiv) in anhydrous CH_2Cl_2 (0.1 M) was added keto-containing aldehyde (1.4 equiv). The reaction mixture was stirred at −78 °C under a nitrogen atmosphere. $BF_3{\cdot}OEt_2$ (2.5 equiv, 1.2 M CH_2Cl_2 solution) was added slowly to the reaction mixture. The reaction mixture was stirred at −78 °C for 1.5 h and then stirred at 0 °C for 2 h. The reaction was quenched with brine at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel to give tetrahydropyranone **8**.

General Procedure for the Synthesis of Tetrahydropyranones (Methyl Esters) Using Ketoaldehydes (General Procedure E). After performing general procedure D, to a solution of the resulting carboxylic acids in anhydrous toluene/methanol (4/1, 0.03 M) was added trimethylsilyldiazomethane (3.2 equiv, 2.0 M diethyl ether solution). The reaction mixture was stirred at room temperature for 1.5 h under a nitrogen atmosphere. The reaction was quenched with acetic acid at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography or preparative TLC on silica gel to give tetrahydropyranone **8**.

*Compound (**8a**).* According to general procedure D, the reaction of **1** (25.2 mg, 0.102 mmol) with **9** (14.4 mg, 0.144 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.21 mL, 0.252 mmol) followed by purification by flash column chromatography on silica gel (*n*-hexane/AcOEt = 3/1) gave **8a** (15.3 mg, 71%) as a colorless solid. R_f: 0.1 (*n*-hexane/AcOEt = 3/1); mp: 51−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.8−9.0 (br s, 1H), 4.46 (dd, *J* = 6.7, 4.8 Hz, 1H), 3.09 (dd, *J* = 8.9, 4.3 Hz, 1H), 2.87 (dq, *J* = 6.5, 6.5 Hz, 1H), 2.77 (dd, *J* = 16.8, 8.9 Hz, 1H), 2.15 (dd, *J* = 16.8, 4.3 Hz, 1H), 1.95 (m, 1H), 1.70−1.59 (m, 2H), 1.50 (m, 1H), 1.44 (s, 3H), 0.94 (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 208.3, 177.7, 85.4, 80.5, 56.9, 50.0, 32.1, 29.9, 26.2, 24.5, 9.6; HRMS (ESI$^+$) *m*/*z*: calcd for $C_{11}H_{16}NaO_4$ (M + Na)$^+$, 235.0946; found, 235.0941. The relative configuration of **8a** was determined by NOESY.

*Compound (**8b**).* According to general procedure E, the reaction of **1** (28.1 mg, 0.114 mmol) with **10** (19.6 mg, 0.172 mmol) and $BF_3{\cdot}OEt_2$ (1.2 M CH_2Cl_2 solution, 0.23 mL, 0.276 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave a carboxylic acid. Then, the reaction of the mixture with $TMSCHN_2$ (2.0 M diethyl ether solution, 0.16 mL, 0.32 mmol)

https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX

followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave **8b** (3.5 mg, 12%) as a colorless oil. R_f: 0.5 (*n*-hexane/AcOEt = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 (ddd, J = 6.5, 4.5, 1.9 Hz, 1H), 3.72 (s, 3H), 3.03 (dd, J = 10.4, 1.8 Hz, 1H), 2.91 (quint, J = 6.5 Hz, 1H), 2.69 (dd, J = 16.1, 10.4 Hz, 1H), 2.10 (dd, J = 16.1, 1.8 Hz, 1H), 1.70−1.42 (m, 5H), 1.32 (s, 3H), 1.13 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 210.9, 172.9, 77.2, 75.3, 54.8, 52.0, 46.9, 32.7, 30.3, 29.4, 24.4, 16.3, 10.3; HRMS (ESI$^+$) m/z: calcd for $C_{13}H_{20}NaO_4$ $(M + Na)^+$, 263.1259; found, 263.1258.

*Compound (**8c**).* According to general procedure D, the reaction of **1** (26.3 mg, 0.107 mmol) with **11** (24.1 mg, 0.149 mmol) and BF_3·OEt_2 (1.2 M CH_2Cl_2 solution, 0.22 mL, 0.264 mmol) followed by purification by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) gave **8c** (26.9 mg, 92%) as a colorless solid. R_f: 0.1 (*n*-hexane/AcOEt = 3/1); mp: 118 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.0−9.0 (br s, 1H), 7.42−7.26 (m, 5H), 4.61 (t, J = 6.2 Hz, 1H), 3.21 (dd, J = 10.0, 3.6 Hz, 1H), 3.06 (quint, J = 6.2 Hz, 1H), 2.59 (dd, J = 16.8, 10.0 Hz, 1H), 2.11−1.97 (m, 3H), 1.84 (dd, J = 16.8, 3.6 Hz, 1H), 1.76 (m, 1H), 1.01 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 207.5, 177.2, 141.7, 128.4, 128.0, 126.2, 89.2, 80.3, 58.5, 50.4, 30.6, 29.9, 25.6, 9.5; HRMS (ESI$^+$) m/z: calcd for $C_{16}H_{18}NaO_4$ $(M + Na)^+$, 297.1103; found, 297.1099.

*Compounds (**12**) and (**13**).* A suspension of **1** (>99% ee, 18.7 mg, 0.0759 mmol) and 10% Pd/C (55% water, 9.8 mg, 0.00416 mmol) in AcOEt (3.4 mL) was stirred under H_2 for 20 h. The mixture was filtered on silica, and the filtrate was concentrated under reduced pressure to give a mixture of **12** and **13** [23%, **12**:**13** = 1.9:1 by NMR; R_f, 0.3 (*n*-hexane/AcOEt = 5/1)]. The formation of **13** was confirmed by comparing the ^{1}H NMR spectra of the obtained mixture with that of **13** described in the literature.[15] HPLC analysis with a chiral stationary phase column of the mixture showed that **12** and **13** were 11% ee and 31% ee, respectively. The absolute configuration of the obtained **13** was determined to be 4*S*,5*R* by comparison with the retention time of (4*R*,5*S*)-**13** (80% ee) described in the literature.[15] These results indicated that the absolute configuration of the starting **1** was *S*.

*Compounds (**14**) and (**15**).* To a solution of *ent*-**3a**′ (80% ee, 12.5 mg, 0.0369 mmol) in dry MeOH (0.9 mL) was added $NaBH_4$ (2.9 mg, 0.0763 mmol) at 0 °C, and the mixture was stirred at the same temperature for 0.5 h. The reaction was quenched by addition of water, and the mixture was concentrated under vacuum to remove methanol. The remained mixture was filtered through silica gel. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (*n*-hexane/AcOEt = 30/1) to give **14** (8.4 mg, 67%, 77% ee) as a pale yellow oil and **15** (3.8 mg, 30% 78% ee) as a pale yellow oil.

*Compound **14**.* $[\alpha]_D^{20}$: −12 (*c* 0.42, $CHCl_3$, 77% ee); R_f: 0.33 (*n*-hexane/AcOEt = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.26 (m, 10H), 4.35 (d, J = 9.6 Hz, 1H), 4.15 (d, J = 10.0 Hz, 1H), 3.54 (s, 3H), 3.44 (t, J = 9.0 Hz, 1H), 2.36 (m, J = 6.0 Hz, 1H), 2.31 (d, J = 6.0 Hz, 2H), 2.17 (br s, 1H), 1.88 (m, 1H), 0.85 (d, J = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.8, 140.2, 139.5, 128.4, 128.3 (×2), 127.9, 127.7, 127.4, 85.0, 82.8, 78.1, 51.7, 47.2, 45.7, 33.7, 13.4; HRMS (ESI$^+$) m/z: calcd for $C_{21}H_{24}NaO_4$ $(M + Na)^+$, 363.1572; found, 363.1567. The relative configuration of **14** was determined by NOESY.

*Compound **15**.* $[\alpha]_D^{25}$ +1 (*c* 0.38, $CHCl_3$, 78% ee); R_f: 0.36 (*n*-hexane/AcOEt = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.36 (m, 4H), 7.33−7.29 (m, 4H), 7.26−7.25 (m, 2H), 4.67 (d, J = 9.6 Hz, 1H), 4.59 (d, J = 10.8 Hz, 1H), 4.04 (s, 1H), 3.57 (s, 3H), 2.48−2.39 (m, 2H), 2.09−2.00 (m, 3H), 0.78 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.2, 140.9, 140.1, 128.4, 128.2, 128.1, 127.7, 127.5, 127.3, 80.1, 78.6, 70.9, 51.6, 44.7, 42.3, 33.0, 14.0; HRMS (ESI$^+$) m/z: calcd for $C_{21}H_{24}NaO_4$ $(M + Na)^+$, 363.1572; found, 363.1571.

*(S)-MTPA-**14**.* To a solution of **14** (1.9 mg, 0.0056 mmol), triethylamine (2.5 mg, 0.024 mmol) and *N*,*N*′-dimethylaminopyridine (DMAP, 0.8 mg, 0.0065 mmol) in anhydrous CH_2Cl_2 (0.9 mL) were added (*R*)-(−)-MTPA chloride (4.5 mg) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at 40 °C for 16 h. The reaction mixture was filtered through silica gel. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) to give (*S*)-MTPA-**14** (2.3 mg, 73%). R_f: 0.2 (*n*-hexane/AcOEt = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60−7.56 (m, 2H), 7.40−7.24 (m, 13H), 5.34 (t, J = 11.3 Hz, 1H), 4.74 (d, J = 10.2 Hz, 1H), 4.26 (d, J = 10.4 Hz, 1H), 3.54 (d, J = 1.6 Hz, 3H), 3.44 (s, 3H), 2.49 (dddd, J = 11.3, 10.2, 4.9, 1.6 Hz, 1H), 2.18 (dd, J = 17.0, 6.2 Hz, 1H), 2.12−2.03 (m, 2H), 0.60 (d, J = 6.4 Hz, 3H); HRMS (ESI$^+$) m/z: calcd for $C_{31}H_{31}F_3NaO_6$ $(M + Na)^+$, 579.1970; found, 579.1967.

*(R)-MTPA-**14**.* To a solution of **14** (2.3 mg. 0.0068 mmol), triethylamine (3.5 mg, 0.035 mmol) and DMAP (1.6 mg, 0.013 mmol) in anhydrous CH_2Cl_2 (0.9 mL) were added (*S*)-(−)-MTPA chloride (5.1 mg) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at 40 °C for 16 h. The reaction mixture was filtered through silica gel. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (*n*-hexane/AcOEt = 3/1) to give (*R*)-MTPA-**14** (2.3 mg, 61%). R_f: 0.2 (*n*-hexane/AcOEt = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60−7.58 (m, 2H), 7.43−7.22 (m, 13H), 5.41 (t, J = 11.3 Hz, 1H), 4.79 (d, J = 10.4 Hz, 1H), 4.28 (d, J = 10.0 Hz, 1H), 3.56 (d, J = 0.8 Hz, 3H), 3.48 (s, 3H), 2.39 (dddd, J = 11.3, 10.4, 4.2, 1.4 Hz, 1H), 2.15−2.06 (m, 2H), 1.91 (dd, J = 17.2, 2.8 Hz, 1H), 0.70 (d, J = 6.4 Hz, 3H); HRMS (ESI$^+$) m/z: calcd for $C_{31}H_{31}F_3NaO_6$ $(M + Na)^+$, 579.1970; found, 579.1959.

*Compounds (**16**), (**17**), and (**18**).* To a solution of β-silyl-γ-ethylidene-γ-butyrolactone **1** (252.4 mg, 1.02 mmol) in anhydrous CH_2Cl_2 (9 mL) was added benzaldehyde (110.4 mg, 1.04 mmol). The reaction mixture was stirred at −78 °C under a nitrogen atmosphere. BF_3·OEt_2 (1.2 M CH_2Cl_2 solution, 1.1 mL, 1.32 mmol) was added slowly to the reaction mixture. The reaction mixture was stirred at −78 °C for 1.5 h and then quenched with brine. The reaction mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 3/1) to give **16** (118.7 mg, 53%) as a colorless oil, **17** (16.7 mg, 8%, **16**:**17** = 1:5) as a colorless oil, and **18** (104.0 mg, 29%) as a pale yellow oil.

*Compound (**16**).* R_f: 0.1 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.26 (m, 5 H), 5.12 (dd, J = 3.2, 2.4 Hz, 1H), 5.03 (d, J = 4.8 Hz, 1H), 3.19 (dt, J = 24.4, 2.1 Hz, 1H), 3.13 (dt, J = 24.4, 2.4 Hz, 1H), 2.79 (m, 1H), 1.94 (br s, 1H), 1.14 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 176.5, 158.3, 142.1, 128.3, 127.6, 125.8, 99.7, 73.8, 41.3, 33.7, 10.7; HRMS (ESI$^+$) m/z: calcd for $C_{13}H_{14}NaO_3$ $(M + Na)^+$, 241.0841; found, 241.0826.

*Compound (**17**).* R_f: 0.1 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.28 (m, 5H), 5.25 (s, 1H), 4.74 (d, J = 7.5 Hz, 1H), 3.21 (d, J = 24.8 Hz, 1H), 3.18 (d, J =24.8 Hz, 1H), 2.83 (quint, J = 7.5 Hz, 1H), 2.36 (br s, 1H), 0.95 (d, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 176.6, 158.0, 141.5, 128.4, 128.1, 126.6, 100.0, 75.5, 41.5, 33.8, 14.0; HRMS (DART$^+$) m/z: calcd for $C_{13}H_{15}O_3$ $(M + H)^+$, 219.1021; found, 219.1032.

*Compound (**18**).* R_f: 0.5 (*n*-hexane/AcOEt = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−7.20 (m, 10 H), 5.01 (d, J = 4.4 Hz, 1H), 4.96−4.95 (m, 1H), 2.98 (dt, J = 24.2, 2.8 Hz, 1H), 2.88 (dt, J = 24.2, 2.0 Hz, 1H), 2.64 (m, 1H), 1.07 (d, J = 7.2 Hz, 3H), 0.25 (s, 3H), 0.23 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 176.6, 158.3, 142.9, 137.7, 133.4, 129.6, 128.0, 127.7, 127.2, 126.0, 99.5, 74.5, 42.3, 33.6, 10.5, −1.2, −1.9; HRMS (ESI$^+$) m/z: calcd for $C_{21}H_{24}NaO_3Si$ $(M + Na)^+$, 375.1392; found, 375.1365.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01284.

Spectral data for all new compounds and HPLC analyses with a chiral stationary phase (PDF)

https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX

AUTHOR INFORMATION

Corresponding Author

Kazuhiko Sakaguchi − *Division of Molecular Materials Science, Graduate School of Science, Osaka City University, Osaka 558-8585 Sumiyoshi, Japan*; orcid.org/0000-0002-2364-0970; Email: sakaguch@sci.osaka-cu.ac.jp

Authors

Shoma Ariyoshi − *Division of Molecular Materials Science, Graduate School of Science, Osaka City University, Osaka 558-8585 Sumiyoshi, Japan*

Takahiro Nishimura − *Division of Molecular Materials Science, Graduate School of Science, Osaka City University, Osaka 558-8585 Sumiyoshi, Japan*; orcid.org/0000-0002-7032-8613

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01284

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the Japan Society of the Promotion of Science (JSPS KAKENHI grant numbers 17K05935 and 20K05515) for supporting this work.

REFERENCES

(1) Construction of tetrahydropyran systems by oxa-Michael cyclization: (a) Reiter, M.; Turner, H.; Gouverneur, V. Intramolecular Hetero-Michael Addition of β-Hydroxyenones for the Preparation of Highly Substituted Tetrahydropyranones. *Chem. Eur. J.* **2006**, *12*, 7190−7203. (b) Nising, C. F.; Bräse, S. The oxa-Michael reaction: from recent developments to applications in natural product synthesis. *Chem. Soc. Rev.* **2008**, *37*, 1218−1228. (c) Fuwa, H.; Mizunuma, K.; Matsukida, S.; Sasaki, M. A new strategy for the synthesis of substituted dihydropyrones and tetrahydropyrones via palladium-catalyzed coupling of thioesters. *Tetrahedron* **2011**, *67*, 4995−5010. (d) Yao, H.; Ren, J.; Tong, R. A short and flexible route to tetrahydropyran-4-ones via conjugated nitrile oxides cycloaddition and oxa-Michael cyclization: a concise diastereoselective total synthesis of (±)-diospongin A. *Chem. Commun.* **2013**, *49*, 193−195. (e) Bosset, C.; Angibaud, P.; Stanfield, I.; Meerpoel, L.; Berthelot, D.; Guérinot, A.; Cossy, J. Iron-Catalyzed Synthesis of C2 Aryl- and N-Heteroaryl Substituted Tetrahydropyrans. *J. Org. Chem.* **2015**, *80*, 12509−12525.

(2) Construction of tetrahydropyran systems by Japp−Maitland reaction: (a) Clarke, P. A.; Martin, W. H. C. Diastereoselective Synthesis of Highly Substituted Tetrahydropyran-4-ones. *Org. Lett.* **2002**, *4*, 4527−4529. (b) Clarke, P. A.; Martin, W. H. C. Exploiting the Maitland−Japp reaction: a synthesis of (±)-centrolobine. *Tetrahedron* **2005**, *61*, 5433−5438. (c) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. Revisiting the Maitland−Japp reaction. Concise construction of highly functionalised tetrahydropyran-4-ones. *Chem. Commun.* **2005**, 1061−1063.

(3) Construction of tetrahydropyran systems by hetero-Diels−Alder cycloaddition: (a) Johannsen, M.; Joergensen, K. A. Asymmetric Hetero Diels-Alder Reactions and Ene Reactions Catalyzed by Chiral Copper(II) Complexes. *J. Org. Chem.* **1995**, *60*, 5757−5762. (b) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. Asymmetric Hetero-Diels-Alder Reactions Catalyzed by Chiral (Salen)Chromium(III) Complexes. *J. Org. Chem.* **1998**, *63*, 403−405. (c) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. Highly Enantio- and Diastereoselective Hetero-Diels−Alder Reactions Catalyzed by New Chiral Tridentate Chromium(III) Catalysts. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400. (d) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. FR901464: Total Synthesis, Proof of Structure, and Evaluation of Synthetic Analogues. *J. Am. Chem. Soc.* **2001**, *123*, 9974−9983. (e) Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. A New Dirhodium(II) Carboxamidate Complex as a Chiral Lewis Acid Catalyst for Enantioselective Hetero-Diels−Alder Reactions. *Angew. Chem., Int. Ed.* **2004**, *43*, 2665−2668.

(4) Construction of tetrahydropyran systems by Petasis−Ferrier rearrangement: Smith, A. B., III; Fox, R. J.; Razler, T. M. Evolution of the Petasis-Ferrier Union/Rearrangement Tactic: Construction of Architecturally Complex Natural Products Possessing the Ubiquitous cis-2,6-Substituted Tetrahydropyran Structural Element. *Acc. Chem. Res.* **2008**, *41*, 675−687.

(5) Construction of tetrahydropyran systems by Prins cyclization: (a) Cloninger, M. J.; Overman, L. E. Stereocontrolled Synthesis of Trisubstituted Tetrahydropyrans. *J. Am. Chem. Soc.* **1999**, *121*, 1092−1093. (b) Chan, K.-P.; Loh, T.-P. Lewis acid-catalyzed one-pot crossed Prins cyclizations using allylchlorosilane as allylating agent. *Tetrahedron Lett.* **2004**, *45*, 8387−8390. (c) Cossey, K. N.; Funk, R. L. Diastereoselective Synthesis of 2,3,6-Trisubstituted Tetrahydropyran-4-ones via Prins Cyclizations of Enecarbamates: A Formal Synthesis of (+)-Ratjadone A. *J. Am. Chem. Soc.* **2004**, *126*, 12216−12217. (d) Dalgard, J. E.; Rychnovsky, S. D. Oxonia-Cope Prins Cyclizations: A Facile Method for the Synthesis of Tetrahydropyranones Bearing Quaternary Centers. *J. Am. Chem. Soc.* **2004**, *126*, 15662−15663. (e) Tu, W.; Liu, L.; Floreancig, P. E. Diastereoselective Tetrahydropyrone Synthesis through Transition-Metal-Free Oxidative Carbon−Hydrogen Bond Activation. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184−4187. (f) Han, X.; Peh, G.; Floreancig, P. E. Prins-Type Cyclization Reactions in Natural Product Synthesis. *Eur. J. Org. Chem.* **2013**, *2013*, 1193−1208.

(6) Brawn, R. A.; Panek, J. S. Preparation and Use of Enantioenriched Allenylsilanes for the Stereoselective Synthesis of Homopropargylic Ethers. *Org. Lett.* **2007**, *9*, 2689−2692.

(7) (a) Okada, T.; Sakaguchi, K.; Shinada, T.; Ohfune, Y. Au-catalyzed cyclization of allenylsilanes. Regioselective conversion to 2-amino-4-silylmethylene γ-butyrolactone. *Tetrahedron Lett.* **2011**, *52*, 5740−5743. (b) Cadierno, V. Gold-Catalyzed Addition of Carboxylic Acids to Alkynes and Allenes: Valuable Tools for Organic Synthesis. *Catalysts* **2020**, *10*, 1206−1241.

(8) Masse, C. E.; Panek, J. S. Diastereoselective reactions of chiral allyl- and allenylsilanes with activated C=X π-bonds. *Chem. Rev.* **1995**, *95*, 1293−1316.

(9) The relative configuration of **3a**, **7a**, **8a**, and **14** was determined by NOESY and/or *J* values in ^{1}H NMR (Supporting Information).

(10) Paju, A.; Kanger, T.; Pehk, T.; Lindmaa, R.; Müürisepp, A.-M.; Lopp, M. Asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones. Part 2: Oxidative ring cleavage of 3-alkyl-1,2-cyclopentanediones: synthesis of 2-alkyl-γ-lactone acids. *Tetrahedron: Asymmetry* **2003**, *14*, 1565−1573.

(11) Markó, I. E.; Mekhalfia, A. Regiocontrol in the intramolecular silyl modified sakurai (ISMS) reaction. An efficient synthesis of a Dacus oleae fruit fly pheromone. *Tetrahedron Lett.* **1992**, *33*, 1799−1802.

(12) γ-Keto carboxylic acid **4**[10] (54%) and 3a (23%) were obtained.

(13) Enantiopure **1** (>99% ee) was prepared by the optical resolution of racemic **1** using HPLC with a chiral stationary phase column.

(14) The diastereoselectivity of **3r** (**3r**:**3r′** = 7:1) and the decrease in optical purity of **3r′** (76% ee) suggested that partial epimerization from **3r** to *ent*-**3r′** (or from **3a** to *ent*-**3a′**) occurred. It is unknown at what stage the epimerization occurred during the conversion.

(15) Pace, V.; Rae, J. P.; Harb, H. Y.; Procter, D. J. NHC−Cu(I) catalysed asymmetric conjugate silyltransfer to unsaturated lactones: application inkinetic resolution. *Chem. Commun.* **2013**, *49*, 5150−5152.

(16) Sakaguchi, K.; Kawamura, Y.; Saito, S.; Ohfune, Y. Pd-C Assisted Synthesis of *cis*-2,4-Disubstituted γ-Butyrolactones and their Properties for Ferroelectric Liquid Crystals. *Synlett* **1997**, *1997*, 624.

(17) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. High-field FT NMR application of Mosher's method. The absolute config-

urations of marine terpenoids. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.
(18) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; Gelder, R.; Maarseveen, J. H.; Hiemstra, H. Organocatalytic Enantioselective Total Synthesis of (−)-Arboricine. *Org. Lett.* **2009**, *11*, 2579−2581.
(19) Ghobril, C.; Sabot, C.; Mioskowski, C.; Baati, R. TBD-Catalyzed Direct 5- and 6-enolexo Aldolization of Ketoaldehydes. *Eur. J. Org. Chem.* **2008**, *2008*, 4104−4108.
(20) Uyeda, C.; Jacobsen, E. N. Enantioselective Claisen Rearrangements with a Hydrogen-Bond Donor Catalyst. *J. Am. Chem. Soc.* **2008**, *130*, 9228−9229.

https://doi.org/10.1021/acs.joc.1c01284
J. Org. Chem. XXXX, XXX, XXX−XXX