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CATALYTIC ENANTIOSELECTIVE SYNTHESIS OF (20*S*)-CAMPTOTHECIN INTERMEDIATES USING CYANOSILYLATION OF KETONES PROMOTED BY D-GLUCOSE-DERIVED LANTHANIDE CATALYST

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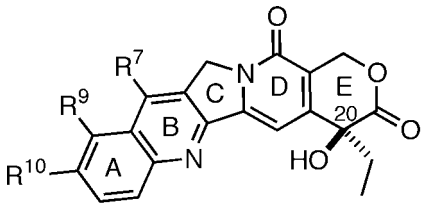
Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

Abstract – An efficient catalytic enantioselective synthetic route was developed for Curran's versatile camptothecin intermediate (**5**). The key step is the catalytic enantioselective cyanosilylation of ketone (**7**) using a chiral samarium (Sm) complex. The target ketone cyanohydrin (**6**) was obtained with 90% ee using 2 mol % of the catalyst. A gadolinium (Gd) complex derived from the same chiral ligand could also be used as an enantioselective catalyst to synthesize Corey's intermediate (**11**).

Introduction

Camptothecin (Figure 1, **1**) and its analogues are very important anti-cancer agents, especially for the treatment of solid tumors.[1] Topotecan (**2**) and irinotecan (**3**) have been approved as anti-cancer drugs, and several other derivatives are now in pre-clinical and clinical development. The mechanism of action of **1** is to interfere with the unwinding of supercoiled DNA by the cellular enzyme topoisomerase I.[2] Accumulated data on the structure–activity relationship of **1** indicate that, in general, substitution on C, D, and E rings is not well tolerated; however, substituents on A and B rings, especially at C7, C9, and C10, often have good biologic activity and improve physical or pharmacologic activity. Therefore, development of an efficient and flexible synthetic route to make various analogues is currently under intensive investigation.[3]



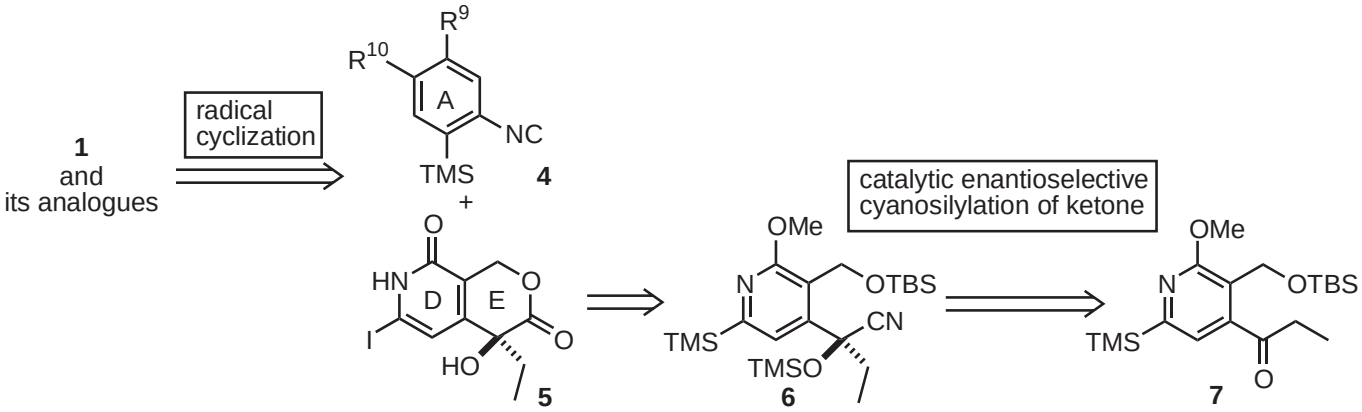
1: $R^7 = R^9 = R^{10} = H$ (camptothecin)
2: $R^7 = H$, $R^9 = CH_2NMe_2$, $R^{10} = OH$ (topotecan)
3: $R^7 = Et$, $R^9 = H$, $R^{10} =$ O-C(=O)-N⟨⟩-N⟨⟩ (irinotecan)

Figure 1

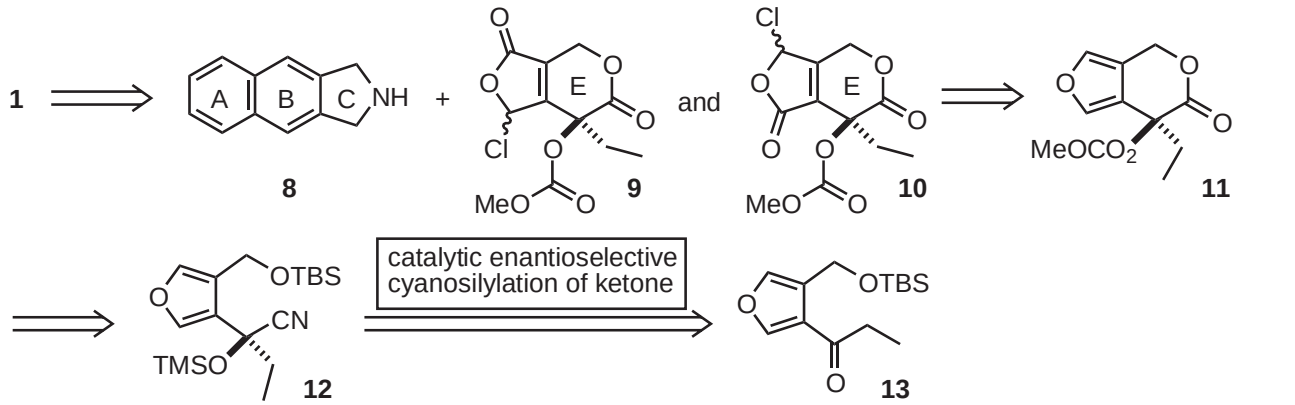
One of the authors' groups (Curran's group) developed a flexible synthetic route using radical cyclization to connect the A ring moiety and the DE ring moiety at the final stage of synthesis (Scheme 1).[3a] This route made it possible to introduce a fairly wide range of substituents on the A and B rings using substituted isocyanide (**4**). Therefore, the DE ring moiety (**5**) containing chiral α-hydroxy lactone is a common and versatile synthetic intermediate. Another flexible synthetic route was reported by Corey, connecting the ABC ring moiety (**8**) and E ring moieties (**9**) and (**10**) (Scheme 2).[4] In this case, the chiral α-hydroxy lactone derivative (**11**) is the versatile intermediate.

To synthesize these intermediates for camptothecin synthesis, we expected that our catalytic enantioselective cyanosilylation of ketones would be a powerful methodology.[5,6] We developed a catalytic enantioselective cyanosilylation of ketones using chiral ligand (**14**) derived from D-glucose.

Both (*R*)- and (*S*)-ketone cyanohydrins can be synthesized from a wide range of substrates using either the titanium complex or the lanthanide complex. Herein, we describe the details on the application of the (*S*)-selective catalytic cyanosilylation of ketones to synthesize two versatile synthetic intermediates for camptothecin.[7]



Scheme 1. Retrosynthesis based on Curran's route

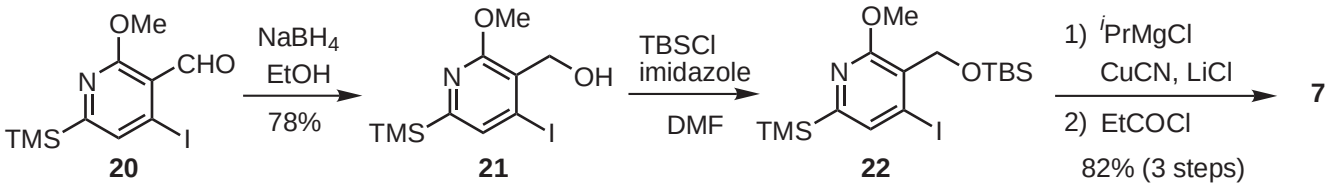


Scheme 2. Retrosynthesis based on Corey's route

Catalytic Enantioselective Synthesis of Curran's Intermediate

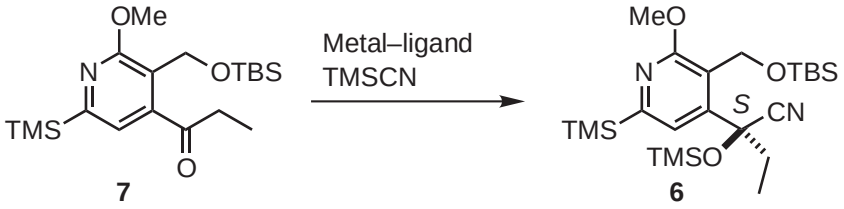
Ketone (**7**), the substrate for the catalytic enantioselective cyanosilylation, was synthesized from the known aldehyde (**20**),[3a] as shown in Scheme 3. The ethyl ketone was introduced to the pyridine ring using Knochel's procedure.[8]

When we started this project, we had only (*R*)-selective catalytic cyanosilylation of ketones using Ti-**14**. Therefore, we first used the Ti-**14** complex for the cyanosilylation of ketone (**7**). With 20 mol % of Ti-**14**, however, the reaction proceeded very slowly even at room temperature and the product, cyanohydrin (**6**), was obtained in 34% yield with only 18% ee (Table 1, entry 1). As expected, the major enantiomer was

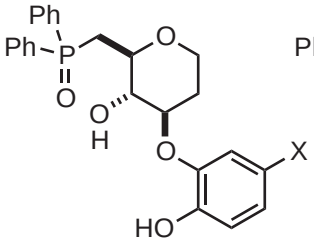


Scheme 3. Synthesis of ketone (**7**)

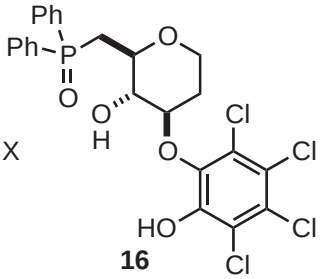
Table 1. Catalytic enantioselective cyanosilylation of ketone (**7**): synthesis of Curran's intermediate



entry	Metal (mol %)	ligand	ligand/Metal	solvent	°C	h	%	%ee	*S*/*R*
1	$Ti(O^iPr)_4$ (20)	**14**	1	THF	25	144	34	18	*R*
2	$Sm(O^iPr)_3$ (5)	**14**	1	THF	–40	24	88	20	*S*
3	$Sm(O^iPr)_3$ (5)	**14**	1.5	THF	–40	24	92	62	*S*
4	$Sm(O^iPr)_3$ (5)	**14**	1.8	THF	–40	24	92	72	*S*
5	$Sm(O^iPr)_3$ (5)	**14**	2	THF	–40	24	96	56	*S*
6	$La(O^iPr)_3$ (5)	**14**	1.8	THF	–40	44	95	26	*S*
7	$Gd(O^iPr)_3$ (5)	**14**	1.8	THF	–40	18	92	52	*S*
8	$Yb(O^iPr)_3$ (5)	**14**	1.8	THF	–40	44	84	21	*S*
9	$Sm(O^iPr)_3$ (5)	**14**	1.8	EtCN	–40	18	98	84	*S*
10	$Sm(O^iPr)_3$ (2)	**14**	1.8	EtCN	–40	44	100	82	*S*
11	$Sm(O^iPr)_3$ (5)	**15**	1.8	EtCN	–40	96	100	38	*S*
12	$Sm(O^iPr)_3$ (5)	**16**	1.8	EtCN	–40	65	90	42	*S*
13	$Sm(O^iPr)_3$ (5)	**17**	1.8	EtCN	–40	16	94	83	*S*
14	$Sm(O^iPr)_3$ (5)	**18**	1.8	EtCN	–40	14	100	91	*S*
15	$Sm(O^iPr)_3$ (2)	**18**	1.8	EtCN	–40	38	95	83	*S*
16	$Sm(O^iPr)_3$ (5)	**19**	1.8	EtCN	–40	12	94	90	*S*
17	$Sm(O^iPr)_3$ (2)	**19**	1.8	EtCN	–40	19	95	89	*S*
18	$Sm(O^iPr)_3$ (2)	**19**	1.8	EtCN–MeCN	–40	36	93	90	*S*



14: X = H
15: X = COPh



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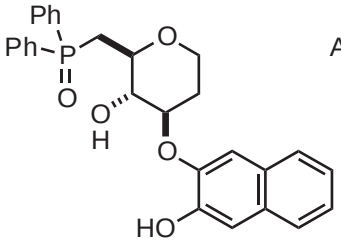

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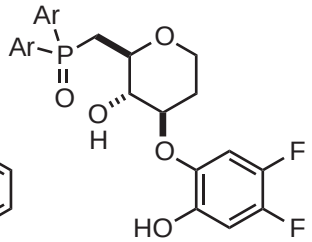
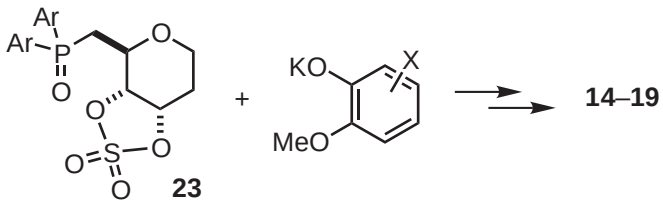


18: Ar = Ph
19: Ar = *p*-tol

the opposite of the desired one (*R*). After screening the Lewis acid metal, we found that the lanthanide

complex was more reactive than the titanium complex. Thus, when we used a samarium complex prepared from $Sm(O^iPr)_3$ and **14** in a 1:1 ratio in THF, the reaction was completed at –40 °C, and **6** was obtained in 88% yield with 20% ee (entry 2). Gratifyingly, the absolute configuration of the major product was switched to the desired one (*S*). There was an interesting dependency of the enantioselectivity on the ligand/metal ratio (entries 2–5). Increasing the ligand/metal ratio, improved the enantioselectivity to a maximum 72% ee at ligand/metal = 1.8 (entry 4). Other lanthanide metals gave less satisfactory results (entries 6–8).[9]

We next investigated the effect of the ligand structure (entries 9–18). Propionitrile was a better solvent than THF for this reaction with regard to enantioselectivity. Propionitrile improved the enantiomeric excess to 84% (entry 9) compared to 72% (entry 4) in THF. To quickly screen the ligand effect, development of a practical synthetic route of the ligands using a regioselective opening of the cyclic sulfate intermediate (**23**) by various catechols was essential (Scheme 4).[10] We synthesized a variety of ligands containing catechol of different electronic and steric demands using this route. The best ligand

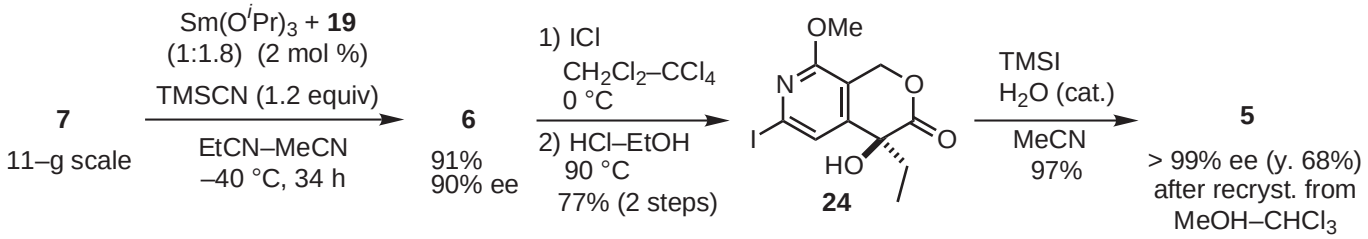


Scheme 4. Key step for the ligand synthesis

was determined to be **19**, containing a difluorocatechol moiety and a di-(*p*-tolyl)phosphine oxide. The increased Lewis acidity by the electron-withdrawing groups (the fluorine atoms) on the catechol, as well as the increased Lewis basicity by the electron-donating groups (the methyl groups) on the phosphine oxide might be key for the improved enantioselectivity of ligand (**19**) compared to the original ligand (**14**). The shortened reaction time was probably also due to this type of dual enhancement of the Lewis acidity and the Lewis basicity of the catalyst. Under the optimized conditions, the cyanohydrin product was obtained in 93% yield with 90% ee using 2 mol % of catalyst prepared from $Sm(O^iPr)_3$ and **19** in a 1:1.8

ratio (entry 18). This reaction could be conducted on an 11-g scale.

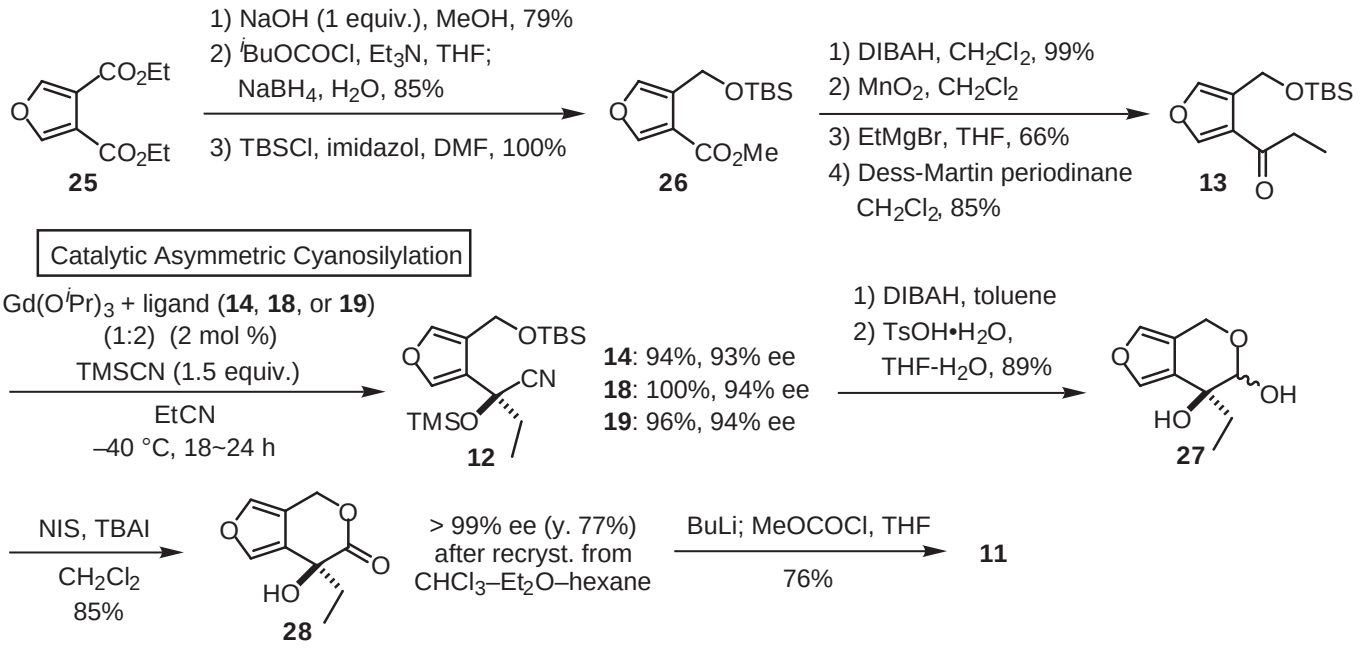
Conversion of the cyanohydrin to the enantiomerically pure Curran's intermediate (**5**) was achieved as shown in Scheme 5. Iododesilylation with ICl, direct lactone formation under acidic conditions, and demethylation gave **5** in high overall yield, which was then recrystallized from MeOH-$CHCl_3$ to give the enantiomerically pure **5**.



Scheme 5. Catalytic enantioselective synthesis of Curran's intermediate

Catalytic Enantioselective Synthesis of Corey's Intermediate

To demonstrate the usefulness of the catalytic enantioselective cyanosilylation of ketones, we applied the reaction to another convergent synthesis of camptothecin, previously reported by Corey.[4] In this first synthesis of naturally occurring (20*S*)-camptothecin, an optically pure synthetic intermediate was obtained through optical resolution. We first developed a convenient and reproducible route for the synthesis of ketone (**13**) (Scheme 6), modifying the original synthetic route. The results of catalytic enantioselective cyanosilylation of **13** using three selected ligands (**14**, **18**, and **19**) are summarized in Scheme 6. In this case, the Gd-catalyst gave better results than the Sm-catalyst,[11] and cyanohydrin (**12**) was obtained with up to 94% ee using 2 mol % of catalysts. From **12**, enantiomerically pure Corey's intermediate (**11**) was obtained in high overall yield as follows. Reduction of the cyanide with DIBAH followed by acidic desilylation gave lactol (**27**), which was then oxidized to lactone (**28**). Direct acid hydrolysis of **12** to **28** was not successful in this case. Enantiomerically pure **28** was obtained by recrystallization from a $CHCl_3$-Et_2O-hexane mixture. Methoxycarbonylation of the *tert*-alcohol through a lithium alkoxide gave enantiomerically pure Corey's intermediate (**11**).



Scheme 6. Catalytic enantioselective synthesis of Corey's intermediate

Conclusion

We developed two efficient catalytic enantioselective synthetic routes of camptothecin intermediates. The present work clearly demonstrates the power of our catalytic enantioselective cyanosilylation of ketones. Because camptothecin and its analogues are extremely important anti-cancer drugs, studies toward the development of a truly practical synthetic route are currently in progress in our laboratory.

EXPERIMENTAL

General: NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR, 125.65 MHz for ^{13}C NMR, and 202 MHz for ^{31}P NMR. Chemical shifts were reported downfield from TMS (= 0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. ^{31}P NMR were carried out with phosphoric acid (85%) as an external standard. Optical rotations were measured on a JASCO P-1010 Polarimeter. Column chromatographies were performed with silica gel Merck 60 (230-400 mesh ASTM). The enantiomeric excesses (ee's) were determined by HPLC analysis. HPLC analysis was performed on JASCO HPLC

systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 nm; column, DAICEL CHIRALPAK AS, AD, or DAICEL CHIRALCEL OJ, OD; mobile phase, hexane-2-propanol. In general, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Other reagents were purified by usual methods. Lanthanide alkoxide was purchased from Kojundo Chemical Laboratory Co., Ltd. (Fax: +81-492-84-1351).

[4-Iodo-2-methoxy-6-(trimethylsilyl)pyridin-3-yl]methanol (21): To a solution of $NaBH_4$ (1.1 g, 26.4 mmol) in EtOH (100 mL) at –40 °C was slowly added a solution of known aldehyde (**20**) (31.8 g, 94.9 mmol)[3a] in EtOH (50 mL). After stirring for 1 h, the reaction mixture was carefully quenched with brine and then extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (gradient hexane to hexane/AcOEt 91/9) to afford **21** (25.1 g, 78%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 2.52 (br s, 1H), 4.01 (s, 3H), 4.81 (s, 2H), 7.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –1.99, 53.78, 65.32, 11.65, 125.34, 133.19, 160.90, 165.81; IR (film, NaCl, cm^{-1}) 3485, 2960, 1580, 1450, 1039, 839; LRMS (70 eV, EI) m/z (rel int %) 337 (M^+), 322 (100), 306, 194, 180, 73. HRMS m/z calcd for $C_{10}H_{16}NO_2ISi$ (M^+) 336.9995, found 337.0002.

1-[3-(*tert*-Butyldimethylsilyloxymethyl)-2-methoxy-6-(trimethylsilanyl)pyridin-4-yl]propan-1-one (7): To a solution of **21** (2.2 g, 6.5 mmol) and imidazole (1.1 g, 16 mmol) in DMF (3.2 mL) at 0 °C was added TBDMSCl (1.34 g, 8.9 mmol). The mixture was then heated at 35 °C. After heating for 30 h, the reaction mixture was quenched with water and then extracted with hexane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 3.19 g of the crude product (**22**). The crude product was sufficiently pure for the subsequent reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 6H), 0.31 (s, 9H), 0.99 (s, 9H), 3.97 (s, 3H), 4.82 (s, 2H), 7.52 (s, 1H).

To a solution of crude **22** (6.5 mmol) in THF (25 mL) at –40 °C, ^{i}PrMgCl (7.0 mL, 2.0 M in THF) was added dropwise. The mixture was stirred at –40 °C for 1 h, and then CuCN•2LiCl [prepared from CuCN (1.2 g, 13.4 mmol) and LiCl (1.16 g, 27.4 mmol)] in THF (30 mL) was added. After 15 min, propionyl chloride (2.7 mL, 31.5 mmol) was added, and then the reaction was stirred for 1 h at –40 °C and 15 min at rt. The reaction was quenched with brine and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient hexane to hexane/Et_2O 95/5) to afford **7** (2.04 g, 82%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.29 (s, 9H). 0.91 (s, 9H), 1.18 (t *J* = 7.1 Hz, 3H), 2.85 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 3H), 4.78 (s, 2H), 6.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –1.95, 7.69, 18.59, 25.95, 36.52, 53.36, 57.62, 118.35, 118.97, 148.31, 160.23, 164.4, 207.17; IR (film, NaCl, cm^{-1}) 840.7, 1076.6, 1343.5, 1455.2, 1715.8, 2957.1; LRMS (70 eV, EI) m/z (rel int %) 392 (M^{+}-^{t}Bu), 324, 256, 192, 160, 128, 96, 64 (100). HRMS m/z calcd for $C_{15}H_{26}NO_3Si_2$ (M^{+}-^{t}Bu) 324.1451, found 324.1452.

(*S*)-1-[3-(*tert*-Butyldimethylsilyloxymethyl)-2-methoxy-6-(trimethylsilyl)pyridin-4-yl]-2-(trimethylsilyloxy)butyronitrile (6): $Sm(O^{i}Pr)_3$ (0.60 mmol, 0.2 M stock solution in THF) in THF (3.0 mL) was added to a solution of chiral ligand (**19**) (528 mg, 1.08 mmol) in THF (12 mL) in an ice bath and the mixture was stirred for 30 min at 45 °C. Cooling to rt, THF was evaporated and the residue was dried for 1.5 h under vacuum (5 mmHg). Dissolving the residue in propionitrile (5 mL) and acetonitrile (5 mL) mixture, TMSCN (4.8 mL, 36.0 mmol) was added at –40 °C. After 20 min, a solution of **7** (11.5 g, 30.0 mmol) in propionitrile (5 mL) and acetonitrile (5 mL) mixture was added slowly over 30 min and the mixture was stirred for 34 h at –40 °C. H_2O was added to quench the reaction (caution: HCN is generated.), and the product and the ligand were extracted with AcOEt. The combined organic layer was washed with sat. NaCl aq and dried over Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified by SiO_2 column chromatography (hexane/Et_2O = 400/1 to 200/1) to give pure **6** as colorless oil (13.2 g, 91%). Enantiomeric excess of **6** was determined by chiral HPLC after conversion to **24** (DAICEL

CHIRALPAK AS, hexane/2-propanol = 20/1, 1.0 mL/min, t_R 19.6 (minor) and 23.3 min (major)). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.11 (s, 3H), 0.12 (s, 3H), 0.17 (s, 9H), 0.29 (s, 9H), 0.89 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H), 2.25 (m, 2H), 3.98 (s, 3H), 4.85 (d, *J* = 11.0 Hz, 1H), 5.01 (d, *J* = 11.0 Hz, 1H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: -5.5, -5.4, -1.9, 0.9, 8.6, 18.5, 25.9, 37.3, 53.3, 55.6, 76.2, 118.5, 119.7, 120.4, 146.9, 153.0, 164.9; IR (neat) ν 2956, 1553, 1448, 1347, 1251, 1132, 1092, 840 cm^{-1}; MS m/z 480 (M^+), 423 (M^+–^{t}Bu); $[\alpha]^{24}_D$ –7.87° (c 6.10, $CHCl_3$) (72% ee); HRMS (M^+–^{t}Bu) Calcd for $C_{19}H_{35}N_2O_3Si_3$ 423.1956. Found 423.1942. The ligand and the silylated ligand were eluted from the column with MeOH/$CHCl_3$, treated with HCl aq in THF, extracted, and purified by SiO_2 column chromatography to recover pure ligand (**19**) in > 90% yield.

(*S*)-4-Ethyl-4-hydroxy-6-iodo-8-methoxy-1,4-dihydropyrano[3,4-*c*]pyridin-3-one (24): To a solution of **6** (9.13 g, 19.0 mmol) in CH_2Cl_2 (110 mL), ICl (3.81 mL, 76.0 mmol, 4 equiv) in CCl_4 (90 mL) was added dropwise at 0 °C. After 30 min, the reaction mixture was poured into 5% Na_2SO_3 aq. + satd. NaCl aq. (1 L:1 L) at 0 °C. The water layer was extracted with AcOEt and the organic layer was washed with satd. NaCl aq. The combined organic layer was dried over Na_2SO_4 and filtration followed by evaporation gave the crude mixture. This resulting iodide was not stable on silica gel and was used without further purification.

The crude mixture (10.5 g) was dissolved in half-saturated HCl (g) in EtOH (125 mL) and stirred at 60 °C for 30 min. Cooled to ambient temperature, the reaction mixture was poured into AcOEt + satd. NaCl aq. (1:1) at 0 °C. The water layer was extracted with AcOEt and the combined organic layer was dried over Na_2SO_4. Filtration, evaporation, followed by purification by silica gel column chromatography (hexane/AcOEt = 8/1~4/1) gave **24** in 77% yield (2 steps). For the spectroscopic data, see ref. 3a. $[\alpha]^{24}_D$ +25.2° (c 2.09, $CHCl_3$) (52% ee); HPLC (DAICEL CHIRALPAK AS, hexane/2-propanol = 20/1, 1.0 mL/min) t_R 19.6 (minor) and 23.3 (major) min.

(*S*)-4-Ethyl-4-hydroxy-6-iodo-3-oxo-1*H*-pyrano[3,4-*c*]-8-pyridone (5): The conversion of **24** to **5** was

originally reported in ref. 3a. To a solution of **24** (0.718 g, 2.06 mmol) in MeCN (7.5 mL), NaI (0.493 g, 3.29 mmol), TMSCl (0.42 mL, 3.29 mmol), and H_2O (18.5 μL, 1.03 mmol) were added at 0 °C. The mixture was stirred at 65 °C for 2 h and poured into 5% Na_2SO_3 aq. + brine (1:1). The water layer was extracted with AcOEt (x4) and the combined organic layers were dried over Na_2SO_4. Filtration, concentration, and purification by silica gel column chromatography gave **5** (0.593 g, 97%) as a white powder. Enantiomerically pure **5** was obtained by recrystallization from MeOH (4 mL) and $CHCl_3$ (0.5 mL) in 68% yield as colorless prisms. $[\alpha]^{29}_{D}$ +53.8° (c 1.01, MeOH) (> 99.5% ee); HPLC (DAICEL CHIRALCEL OJ-H, hexane/2-propanol = 4/1, 0.5 mL/min) t_R 22.0 (minor) and 23.7 (major) min.

4-(*tert*-Butyldimethylsilyloxymethyl)furan-3-carboxylic acid methyl ester (26): To a MeOH (60 mL) solution of commercially available **25** (5.25 g, 23.5 mmol), NaOH (0.94 g, 23.5 mmol) was added and the mixture was stirred at rt for 61 h.[12] Et_2O was added to the reaction mixture and precipitates were filtrated off. The filtrate was then neutralized by the addition of 1 N HCl at 0 °C and the water layer was extracted with AcOEt. The combined organic layer was dried over Na_2SO_4. Filtration, concentration, and purification though silica gel column chromatography (hexane/Et_2O = 4/1 to 1/1) gave the mono-ester in 78% yield (3.1 g). To the mono-ester (1.00 g, 5.88 mmol) solution in THF (10 mL), Et_3N (0.9 mL, 6.47 mmol) and ^{i}BuOCOCl (0.84 mL, 6.47 mmol) were added at –20 °C and the mixture was stirred for 15 min. Precipitates were filtrated off and the resulting filtrate was cooled to –20 °C. To the solution, a solution of $NaBH_4$ (0.334 g, 8.82 mmol) in H_2O (4 mL) was added. After 30 min, satd. NH_4Cl aq. was added to quench the reaction, and the water layer was extracted with AcOEt. Concentration and purification of the resulting crude mixture through silica gel column chromatography (hexane/Et_2O = 2/1) gave the mono-ol in 85% yield (0.782 g). To a solution of the mono-ol (2.56 g, 16.4 mmol) in DMF (7 mL), imidazole (3.35 g, 49.2 mmol) and TBSCl (3.71 g, 24.6 mmol) were added at 0 °C. After stirring for 1 h at rt, H_2O was added to quench the reaction and the water layer was extracted with AcOEt. Concentration and purification through silica gel column chromatography (hexane/Et_2O = 80/1 to 40/1)

gave **26** in 100% yield (4.43 g). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.11 (s, 6H), 0.93 (s, 9H), 3.81 (s, 3H), 4.84 (d, *J* = 1.6 Hz, 2H), 7.39 (dd, J = 1.5, 1.6 Hz, 1H), 7.95 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: -5.5, 18.3, 25.9, 51.4, 58.0, 116.7, 126.7, 141.3, 148.7, 163.8; IR (neat) ν 2954, 2858, 1731, 1541 cm^{-1}; MS m/z 239 (M^+–OMe), 213 (M^+–^{t}Bu); HRMS Calcd for $C_9H_{13}O_4Si$ (M^+–^{t}Bu) 213.0583. Found 213.0589.

1-[4-(*tert*-Butyldimethylsilyloxymethyl)furan-3-yl]propan-1-one (13): To a CH_2Cl_2 solution (35 mL) of **26** (3.34 g, 12.4 mmol), DIBAH (1.0 M in toluene, 37.1 mL, 37.1 mmol) was added dropwise for 30 min at –78 °C. After 30 min, H_2O was added at –78 °C, followed by the addition of satd. Rochelle salt aq. The water layer was extracted with AcOEt. The combined organic layer was concentrated and purification through silica gel column chromatography (hexane/Et_2O = 5/1) gave the mono-ol in 100% yield (3.14 g). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.12 (s, 6H), 0.91 (s, 9H), 3.17 (t, *J* = 6.1 Hz, 1H), 4.52 (d, *J* = 6.1 Hz, 2H), 4.64 (s, 3H), 7.31 (s, 1H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: -5.4, 18.3, 25.8, 55.2, 56.5, 124.2, 124.9, 140.2, 140.7; IR (neat) ν 3385, 2930, 2858, 1471 cm^{-1}; MS m/z 185 (M^+–^{t}Bu); HRMS Calcd for $C_8H_{13}O_3Si$ (M^+–^{t}Bu) 185.0634. Found 185.0625.

To the solution of this mono-ol (3.80 g, 15.7 mmol) in CH_2Cl_2 (60 mL), MnO_2 (20.4 g, 0.235 mol + 6.80 g, 0.078 mol + 2.72 g, 0.031 mmol) was added and the mixture was stirred at rt for 18 h. The reaction mixture was filtrated and concentrated to give the crude aldehyde, which was subjected to the next reaction without purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.10 (s, 6H), 0.93 (s, 9H), 4.85 (d, *J* = 1.9 Hz, 2H), 7.43 (dd *J* = 1.8, 1.9 Hz, 1H), 8.01 (d, *J* = 1.8 Hz, 1H), 9.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: -5.5, 18.3, 25.8, 57.8, 125.7, 126.4, 142.0, 152.7, 185.1.

To a solution of the aldehyde (crude, 3.35 g, 13.9 mmol) in THF (70 mL), EtMgBr (1.0 M in THF, 22.3 mL, 22.3 mmol) was added at –78 °C for 20 min. After 15 min, satd. NH_4Cl aq. was added and the water layer was extracted with AcOEt. The combined organic layer was washed with satd. NaCl aq., dried over $NaSO_4$, and concentrated. Purification through silica gel column chromatograohy (hexane/Et_2O = 20/1)

gave the alcohol in 66% yield (2.78 g) in two steps. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.12 (s, 6H), 0.91 (s, 9H), 0.99 (t, *J* = 7.3 Hz, 3 H), 1.83 (m, 2H), 3.56 (t, *J* = 5.5 Hz, 1H), 4.50 (dd, *J* = 5.5 Hz, 6.2 Hz 1H), 4.61 (d, *J* = 12.6 Hz, 1H), 4.64 (d, *J* = 12.6 Hz, 1H), 7.29 (s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: -5.4, 10.6, 18.3, 25.8, 29.3, 56.7, 67.6 123.6, 128.0, 140.0, 140.5; IR (neat) ν 3403, 2931, 2858, 1464 cm^{-1}; MS m/z 213 (M^+–^{t}Bu); HRMS Calcd for $C_{10}H_{17}O_3Si$ (M^+–^{t}Bu) 213.0947. Found 213.0943.

To a solution of the alcohol (2.73 g, 10.1 mmol) in CH_2Cl_2 (50 mL), Dess-Martin periodinane (5.57 g, 13.1 mmol) was added at 0 °C and the mixture was stirred for 40 min at rt. Then, satd. $NaHCO_3$ aq. was added to quench the reaction and precipitates were filtrated off through a celite pad. The water layer was extracted with CH_2Cl_2 and the combined organic layer was dried over Na_2SO_4. Concentration and purification through silica gel column chromatography (hexane/Et_2O =50/1 to 20/1) gave ketone (**13**) in 93% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.10 (s, 6H), 0.93 (s, 9H), 1.17 (t, *J* = 7.4 Hz, 3 H), 2.75 (q, *J* = 7.4 Hz, 2H), 4.87 (d, *J* = 1.6 Hz, 2H), 7.40 (dd, *J* = 1.6, 1.8 Hz, 1H), 7.98 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: -5.5, 8.1, 18.3, 25.9, 33.4, 58.6, 124.9, 126.9, 141.5, 148.2, 196.5; IR (neat) ν 2938, 1674, 1536, 1143 cm^{-1}; MS m/z 268 (M^+), 253 (M^+–Me), 211 (M^+–^{t}Bu, base peak); HRMS Calcd for $C_{10}H_{15}O_3Si$ (M^+–^{t}Bu) 211.0790. Found 211.0785.

(*S*)-2-[4-(*tert*-Butyldimethylsilyloxymethyl)furan-3-yl]-2-(trimethylsilyloxy)butyronitrile (12): $Gd(O^iPr)_3$ (0.015 mmol, 0.2 M stock solution in THF) in THF (75 μL) was added to a solution of chiral ligand (**19**) (15 mg, 0.030 mmol) in THF (0.3 mL) in an ice bath and the mixture was stirred for 30 min at 45 °C. Cooling to rt, THF was evaporated and the residue was dried for 1.5 h under vacuum (5 mmHg). Dissolving the residue in propionitrile (0.25 mL), TMSCN (0.15 mL, 1.13 mmol) was added at –40 °C. After 20 min, a propionitrile solution (0.38 mL) of **13** (0.201 g, 0.75 mmol) was added and the mixture was stirred for 24 h at –40 °C. Workup as described above and purification by column chromatography gave **12** as colorless oil (0.27 g, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.09 (s, 3H), 0.10 (s, 3H), 0.18 (s, 9H), 0.91 (s, 9H), 0.98 (t, *J* = 7.6 Hz, 3H), 1.98-2.15 (m, 2H), 4.62 (d, *J* = 1.2 Hz, 2H), 7.37 (dd, *J* = 1.2,

3.1 Hz, 1H), 7.49 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: -5.44, -5.40, 0.87, 8.7, 18.3, 25.8, 36.2, 56.7, 70.7, 120.2, 123.7, 124.6, 141.1, 142.5; IR (neat) ν 2956, 2858, 1464, 1255 cm^{-1}; MS m/z 310 (M^+–^{t}Bu); HRMS (FAB (PEG)) Calcd for $C_{18}H_{34}NO_3Si_2$ ($M+H^+$) 368.2077. Found 368.2082. $[\alpha]^{21}_D$ –22.8° (*c* 1.00, $CHCl_3$). Enantiomeric excess was determined after conversion to the corresponding benzoylamido alcohol (1. LAH, THF; 2. BzCl, Et_3N; 3. TBAF) by chiral HPLC (DAICEL CHIRALCEL OJ-H, hexane/2-propanol = 9/1, 1.0 mL/min, t_R 16.0 (minor) and 18.7 min (major)).

(*S*)-7-Ethyl-6,7-dihydro-4*H*-furo[3,4-*c*]pyran-6,7-diol (27): To a solution of **12** (41.7 mg, 0.113 mmol) in toluene (0.8 mL), DIBAH (1.0 M in toluene, 0.23 mL, 0.23 mmol) solution was added at –78 °C and the mixture was stirred for 1 h. Then, H_2O was added followed by the addition of 1 N HCl (3 mL). Extraction with AcOEt, drying over Na_2SO_4, and concentration gave crude aldehyde (41.2 mg), which was subjected to the following lactol formation. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.08 (s, 6H), 0.15 (s, 9H), 0.89 (t, *J* = 7.3 Hz, 3 H), 0.92 (s, 9H), 1.88-2.08 (m, 2H), 4.52 (dd, *J* = 1.2, 13.5 Hz, 1H), 4.58 (dd, *J* = 1.2, 13.5 Hz, 1H), 7.31 (d, *J* = 3.1 Hz, 1H), 7.35 (dd, *J* = 1.2, 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: -5.4, 2.0, 7.5, 18.3, 25.9, 28.6, 57.4, 82.3, 122.7, 125.0, 141.4, 141.7, 200.0.

To a solution of the crude oil in THF-H_2O (9:1, 0.8 mL), TsOH•H_2O (4.3 mg, 0.023 mmol) was added and the mixture was stirred for 13.5 h at rt. Satd. $NaHCO_3$ (3 mL) was added and the water layer was extracted with AcOEt (x 6). The combined organic layer was dried over Na_2SO_4 and concentrated. Purification through silica gel column chromatography (hexane/Et_2O = 4/1) gave lactol (**27**) in 89% yield (18.5 mg) in 2 steps. ^{1}H NMR ($CDCl_3$, 500 MHz, anomeric mixture, for major isomer) δ: 0.96 (t, *J* = 7.7 Hz, 3 H), 1.85 (m, 2H), 3.85 (d, *J* = 8.9 Hz, 1H), 4.67 (dd, *J* = 1.5, 14.3 Hz, 1H), 4.86 (dd, *J* = 1.5, 14.3 Hz, 1H), 4.87 (d, *J* = 8.9 Hz, 1H), 7.17 (m, 1H), 7.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 8.2, 29.8, 58.9, 70.0, 95.8, 118.8, 124.5, 134.8, 139.9.

(*S*)-7-Ethyl-7-hydroxy-4*H*,7*H*-furo[3,4-*c*]pyran-6-one (28): To a solution of **27** (0.344 g, 1.87 mmol) in CH_2Cl_2 (15 mL), tetrabutylammonium iodide (1.03 g, 2.80 mmol) and NIS (1.26 g, 5.60 mmol) were

added at 0 °C and the mixture was stirred at rt for 2.5 h. Then, satd. $Na_2S_2O_3$ aq. was added and the water layer was extracted with AcOEt. The combined organic layer was dried over Na_2SO_4 and concentrated. Purification through silica gel column chromatography (hexane/Et_2O = 4/1) gave pure lactone (**28**) in 85% yield (0.29 g). Enantiomerically pure compound was obtained by recrystallization from $CHCl_3$-Et_2O-hexane in 77% yield (0.224 g). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.01 (t, *J* = 7.3 Hz, 3 H), 1.85 (m, 2H), 3.41 (s, 1H), 5.35 (dd, *J* = 1.6, 13.9 Hz, 1H), 5.38 (d, *J* = 13.9 Hz, 1H), 7.35 (dd, *J* = 1.5, 1.6 Hz, 1H), 7.51 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 7.3, 32.4, 64.6, 72.6, 115.8, 123.8, 136.3, 138.6, 174.9; IR (KBr) ν 3398, 2971, 1718, 1558, 1381 cm^{-1}; MS m/z 182 (M^+), 164 (M^+–H_2O), 153; mp 61-66 °C; Anal. Calcd for $C_9H_{10}O_4$: C, 59.06; H, 5.49. Found: C, 59.34; H, 5.53. $[\alpha]^{21}_D$ +9.13° (*c* 1.01, MeOH); HPLC: DAICEL CHIRALCEL OD-H, hexane/2-propanol = 9/1, 1.0 mL/min, t_R 10.4 (minor) and 13.1 min (major).

(*S*)-2-Ethyl-2-methoxycarbonyloxy-3-oxo-4,8-dioxabicyclo[4.3.0]non-1(9),6-diene (11): To a solution of enantiomerically pure **28** (40 mg, 0.22 mmol) in THF (3 mL), BuLi (1.55 M in hexane, 0.16 mL, 0.25 mmol) was added at –78 °C and the mixture was stirred for 1 h. To this solution, MeOCOCl (67.9 μL, 0.878 mmol) was added, and after 10 min the reaction temperature was raised to 0 °C. After 30 min, satd. NaCl aq. was added and the organic layer was extracted with AcOEt. The combined organic layer was washed with satd. NaCl aq., dried over Na_2SO_4, and concentrated. Remained **28** was removed by filtration through a short-pad Al_2O_3 (neutral), and **11** was obtained by purification through silica gel column chromatography (hexane/Et_2O = 5:1) in 76% yield (40 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.90 (t, *J* = 7.4 Hz, 3 H), 2.07-2.27 (m, 2H), 3.73 (s, 3H), 5.40 (dd, *J* = 1.2, 14.5 Hz, 1H), 5.56 (dd, *J* = 1.2, 14.5 Hz, 1H), 7.34 (dd, *J* = 1.2, 1.5 Hz, 1H), 7.48 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 7.6, 33.1, 55.2, 65.2, 116.7, 121.6, 135.6, 138.9, 154.3, 169.1; IR (neat) ν 2979, 1747, 1556, 1443 cm^{-1}; MS m/z 240 (M^+); HRMS Calcd for $C_{11}H_{12}O_6$ (M^+) 240.0634. Found 240.0624. $[\alpha]^{21}_D$ –92.9° (*c* 1.99, MeOH)

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