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Improved Synthesis of Racemate and Enantiomers of Taniguchi Lactone and Conversion of Their C–C Double Bonds into Triple Bonds

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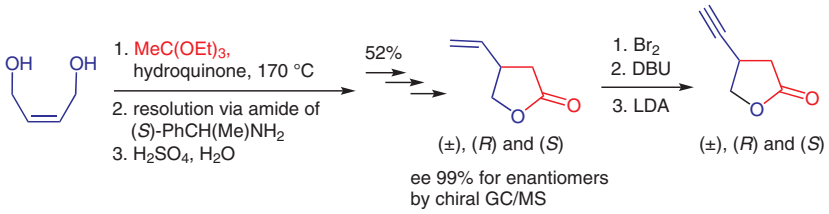

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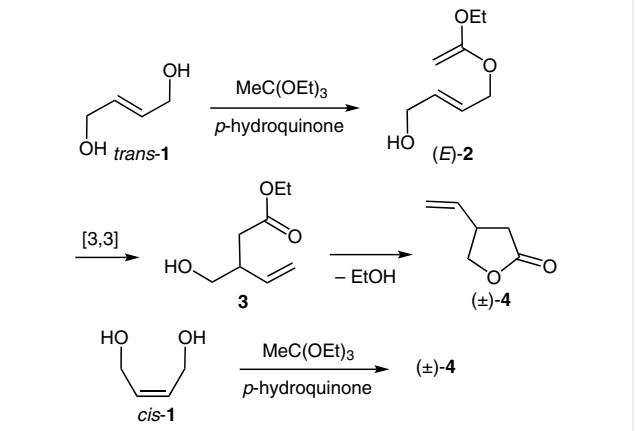
Abstract *cis*-2-Butene-1,4-diol was heated with triethyl orthoacetate and *p*-hydroquinone as catalyst at 170 °C to give racemic Taniguchi lactone. It was converted into diastereomeric amides with (*S*)-1-phenylethylamine for stereoisomer resolution. The double bonds of (±)-, (*R*)- and (*S*)-Taniguchi lactones were brominated and dehydrobrominated in two steps, using at first DBU and then LDA, to deliver the triple bonds.

Key words alkynes, chiral resolution, electrocyclic reaction, halogenation, acetals, lactones

Enantiomerically pure building blocks derived either from natural products or easily prepared by a few steps, are useful starting materials for syntheses. The enantiomers of the Taniguchi lactone [4-vinyldihydrofuran-2(3*H*)-one (**4**)] were first used by Ishibashi and Taniguchi,[1] but initially prepared by Kondo and Mori[2] in 89% from *trans*-2-butene-1,4-diol (*trans*-**1**) and triethyl orthoacetate using *p*-hydroquinone as catalyst (Scheme 1). The enantiomers were accessed by resolution using (*S*)-1-phenylethylamine,[1] 1-(1-naphthyl)ethylamine,[3] or by enantioselective syntheses, which delivered only small[4] quantities. Recently, von Kieseritzky et al.[5] prepared the racemate on a large scale from *trans*-**1** (40 kg) in 86% yield and performed a chiral resolution with (*S*)-1-phenylethylamine, which yielded 8.4 kg of the (*S*)-enantiomer [(*S*)-**4**, ee >99%], but did not yield any (*R*)-**4**. Various syntheses were based on the Taniguchi lactones. The racemate was used as a starting material for the synthesis of 2′-methylcarbovir analogues,[6] and the (*S*)-enantiomer for the synthesis of plant natural products phrymarolin I,[1] (+)-haedoxan,[3] and finally natural quinine.[7]

In connection with a click chemistry project,[8] we became interested in structural analogues of racemic and enantiomerically pure Taniguchi lactones containing a triple bond instead of the double bond. We envisaged using the Taniguchi lactones as starting materials for their preparation. The literature procedure for the racemic lactone builds on the [3,3]-sigmatropic rearrangement of ketene acetal (*E*)-**2** generated from *trans*-2-butene-1,4-diol (*trans*-**1**) and triethyl orthoacetate catalyzed by *p*-hydroquinone (Scheme 1). The hydroxy ester **3** immediately cyclized to give racemic Taniguchi lactone (±)-**4**.

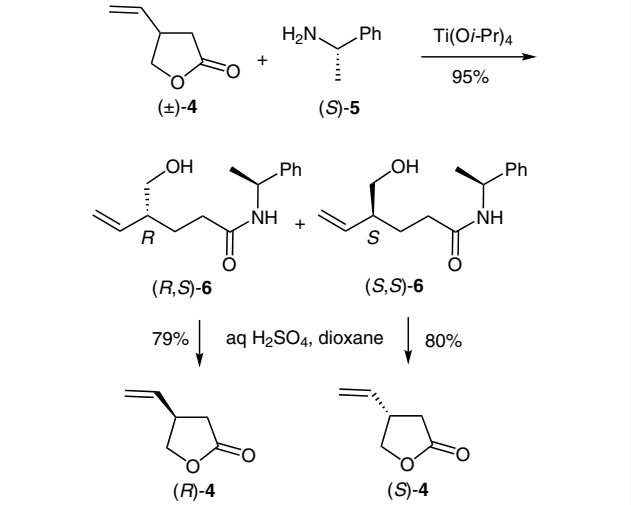
As the price for commercial *trans*-**1** is up to ten times higher than that for *cis*-**1**, we decided to try the cheaper diol as starting material and embarked on the detailed investigation of the reaction once we had prepared (±)-, (*S*)- and (*R*)-**4**. When a mixture of *cis*-diol (375 mmol), triethyl orthoacetate (540 mmol), and *p*-hydroquinone (21 mol%) was heated for 5 hours at 130 °C and 20 hours at 160 °C, ethanol was distilled off and collected. Evolution of ethanol was rapid during heating the first hour at 130 °C but slowed at 160 °C. The mixture was fractionally distilled at 20 mmHg and furnished 59% of (±)-**4** in admixture with an impurity, whose structure was tentatively assigned as *p*-diethoxybenzene. While diol *trans*-**1** reacted at 140–150 °C, the *cis*-



Scheme 1 Conversion of *trans*-**1** and *cis*-**1** into racemic Taniguchi lactone (±)-**4**

isomer needed the somewhat higher temperature of 160–170 °C. Although the yield was lower with *cis*-**1** compared to the 89% of the literature[2] for the *trans*-**1**, the price of the cheaper starting material easily outweighs the lower yield.

In order to obtain the enantiomers (*R*)-**4** and (*S*)-**4**, we opted for an indirect resolution concept by combining literature procedures[1,5] and improving them. The racemic lactone was converted into diastereomeric amides by reacting it with (*S*)-1-phenylethylamine (ee 99%) catalyzed by Ti(O*i*-Pr)$_4$ at 75 °C (Scheme 2).

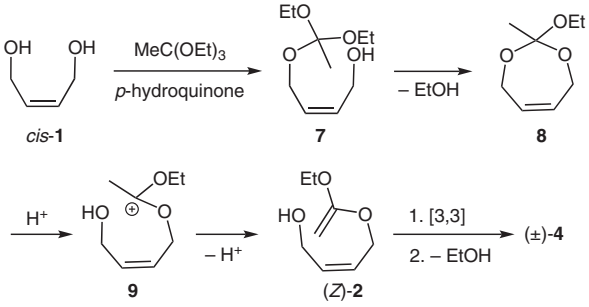


Scheme 2 Resolution of racemic Taniguchi lactone via diastereomeric amides with (*S*)-1-phenylethylamine and conversion of amides into their respective enantiomers **4**

The mixture of crude diastereomeric amides was dissolved in *tert*-butyl methyl ether. After the addition of seeding crystals prepared separately, this solution was very slowly cooled from 30 °C to 4 °C in the refrigerator. The crystals were collected and recrystallized twice to get diastereomerically pure amide (*S*,*S*)-**6** as proven by the conversion into (*S*)-Taniguchi lactone delineated later. The mother liquor was subjected to flash chromatography on silica gel to obtain the less polar diastereomer (*R*,*S*)-**6**, which was crystallized from diisopropyl ether/1,2-dichloroethane. The two spectroscopically fully characterized diastereoisomers were converted by the method of von Kieseritzky et al.[5] into the respective lactones (*R*)-**4** and (*S*)-**4**. Their ee was determined by enantioselective GC/MS and found to be >99% for (*R*)-**4** and 99% for (*S*)-**4**. In order to confirm these data, an enantioselective HPLC method was employed (data not shown).

The distilled Taniguchi lactone prepared from *cis*-2-butene-1,4-diol (*cis*-**1**) contained evidently 1,4-diethoxybenzene formed by ethylation of 1,4-hydroquinone by triethyl orthoacetate and some minor impurities. As these products could not be removed by fractional distillation, a chemical approach for purification was studied. The reaction mixture was first treated with aqueous HCl in THF to hydrolyze acid-labile compounds. After 30 minutes, excess aqueous solution of KOH was slowly added to hydrolyze the lactone. Extraction with diethyl ether removed insoluble compounds. Flash chromatography allowed to isolate 1,4-diethoxybenzene (10 mol% of *p*-hydroquinone used as catalyst) whose melting point and spectroscopic data were identical to those of the literature.[9] The alkaline solution was acidified with H_2SO_4 and the regenerated lactone was isolated by extraction with diethyl ether. Bulb to bulb distillation gave homogeneous Taniguchi lactone in 70% yield.

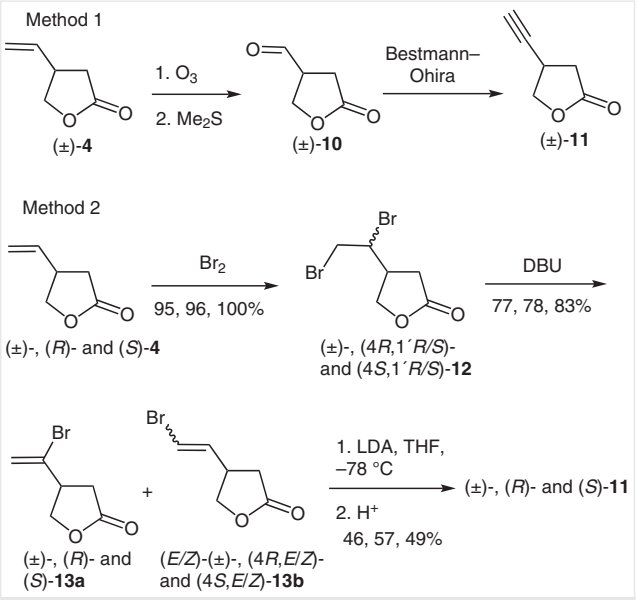
Next, simple experiments were performed to be able to propose a reaction mechanism for the formation of racemic Taniguchi lactone from *cis*-2-butene-1,4-diol (*cis*-**1**) by following the quantity of collected ethanol (Scheme 3). When a mixture of *cis*-**1** (118 mmol), triethyl orthoacetate (105 mmol), and *p*-hydroquinone (10 mol%) was heated at 120 °C for 1 hour and at 170 °C for 15 minutes, a total of 220 mmol of ethanol was collected (for details, see experimental part). Afterwards, ethanol was formed very slowly. The orthoacetate was used in a substoichiometric quantity not to interfere with the purification of the formed product because of a potentially similar boiling point. Fractional distillation under reduced pressure furnished a homogeneous colorless liquid in 86% yield. The spectroscopic data and the combustion analysis proved that the product was the cyclic orthoacetate **8**, first mentioned by Kondo and Mori as a side product without providing data. When **8** was heated with *p*-hydroquinone (10 mol%) at 170 °C for 30 hours and purified by chemical means and bulb-to-bulb-distillation, the Taniguchi lactone was isolated in 52% yield. We assume that at the reaction temperature of 170 °C, the 4,7-dihydro-1,3-dioxepine (**8**) was ring opened by protonation followed by elimination of ethanol to generate ketene acetal (*Z*)-**2** as intermediate. It underwent the [3,3]-sigmatropic rearrangement less easily (two axial substituents in the six-membered transition state) than (*E*)-**2** (one axial substituent in the six-membered transition state), necessitating the higher reaction temperature of 170 °C. The resulting γ-hydroxy ester lactonized by elimination of ethanol.



Scheme 3 Reaction mechanism for racemic Taniguchi lactone from *cis*-2-butene-1,4-diol (*cis*-**1**)

We also tested catalysts other than *p*-hydroquinone by heating mixtures of *cis*-2-butene-1,4-diol/orthoacetate for 18 hours at 170 °C with continuous removal of ethanol. A sample of the crude reaction mixtures was analyzed by ^{1}H NMR spectroscopy. Propionic acid[10] (20 mol%) furnished a mixture of Taniguchi lactone and 4,7-dihydro-1,3-dioxepine (**8**) (78:22), 2,4,6-triisopropylbenzoic acid (5 mol%) (65:35), 2,4-dichlorophenol (5 mol%) (24:76), and 2,4,6-trichlorobenzoic acid (8 mol%) (88:12). Interestingly, none of these catalysts was more effective than *p*-hydroquinone.

For the conversion of the double bond into a triple bond in the Taniguchi lactones, we envisaged a combination of ozonolysis and Bestmann–Ohira protocol[11] (Scheme 4, Method 1). Ozonolysis of racemic Taniguchi lactone (±)-**4** in CH_2Cl_2/MeOH at –78 °C delivered a mixture of products, which contained also labile aldehyde (±)-**10** as evidenced by ^{1}H NMR spectroscopy. As it could neither be purified by flash chromatography nor used in the Bestmann–Ohira reaction without purification, this approach had to be abandoned in favor of Method 2.

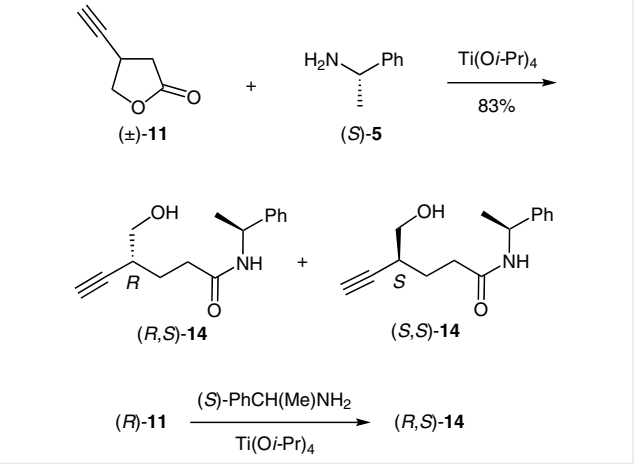


Scheme 4 Conversion of double bond into triple bond in (±)-, (*R*)- and (*S*)-Taniguchi lactone

This access was optimized in the racemic series (Scheme 4). It was based on the bromination of the double bond at 0 °C in CH_2Cl_2, which gave virtually a 1:1 mixture of diastereomeric dibromides (±)-**12**. Initially, we hoped to eliminate both bromines in one step. However, neither *t*-BuOK in THF, MeONa/MeOH nor LDA in THF produced alkyne (±)-**11**. Therefore, a two-step sequence was developed. When the mixture of diastereomeric dibromides was treated with DBU[12] (2 equiv) in acetonitrile at 0 °C for 30 minutes and 1 hour at room temperature, one equivalent of HBr was eliminated to give a mixture of three monobromides (±)-**13a**/(*E*/*Z*)-(±)-**13b** (77%) in a ratio of 77:15:8. The elimination of the second equivalent HBr had to be effected with excess LDA[13] (4 equiv). It was necessary to allow the reaction mixture to warm from –78 °C to –20 °C in the cooling bath and keep it there for 15 to 30 minutes to completely convert (±)-**13a** into the alkyne. Workup, flash chromatography, and bulb-to-bulb distillation furnished alkyne (±)-**11** in 46% yield. Similarly, the vinyl bromides derived from (*R*)- and (*S*)-Taniguchi lactones were converted into (*R*)- and (*S*)-alkyne, respectively, in yields of 57% and 49%. Their ee was determined by enantioselective GC/MS and found to be >99% and 99%, respectively. The alkynes crystallized after bulb-to-bulb distillation and were compounds with low melting points (about 35 °C).

In principle, there are two approaches to alkynes (*R*)-**11** and (*S*)-**11**. The first one, delineated in Schemes 2 and 4, starts with stereoselective resolution of racemic Taniguchi lactone followed by conversion of the double bonds of the enantiomers of the Taniguchi lactone into triple bonds. The second one starts with the racemic Taniguchi lactone, which is transformed into alkyne (±)-**11** which then gets resolved as diastereoisomeric derivatives (Scheme 5). The two diastereomeric amides are obtained from alkyne (±)-**11** by Ti(O*i*-Pr)$_4$-catalyzed ring opening with (*S*)-1-phenylethylamine in the same way as the racemic Taniguchi lactone. The diastereomeric amides (*R*,*S*)-**14** and (*S*,*S*)-**14** were separated by flash chromatography on silica gel. Similarly, alkyne (*R*)-**11** gave the less polar amide (*R*,*S*)-**14**. In analogy, the more polar amide will have (*S*,*S*)-configuration. We assume that these amides can be converted into alkynes (*R*)-**11** and (*S*)-**11** by the method used for amides (*R*,*S*)-**6** and (*S*,*S*)-**6** to (*R*)-**4** and (*S*)-**4**, respectively.

In summary, we have prepared racemic Taniguchi lactone from *cis*-2-butene-1,4-diol and triethyl orthoacetate in the presence of an acidic catalyst at 170 °C. We postulate the formation of a cyclic orthoacetate, 2-ethoxy-2-methyl-



Scheme 5 Conversion of alkynes (±)-**11** and (*R*)-**11** into amides of (*S*)-1-phenylethylamine

4,7-dihydro-1,3-dioxepine as an intermediate. Resolution via fractional crystallization of the diastereomeric amides or via flash chromatography on silica gel or liquid chromatography on chiral stationary phases (data not shown) derived from (*S*)-1-phenylethylamine followed by acidic hydrolysis and cyclization delivered the enantiomers of the Taniguchi lactone. Their double bonds were transformed into the respective alkynes via their dibromides and vinyl bromides. The chiral center at C-4 remained stable throughout all synthesis steps.

^{1}H and ^{13}C NMR spectra (*J*-modulated) were obtained from compounds dissolved in $CDCl_3$ at 300 K using a Bruker AV 400 (^{1}H: 400.13 MHz and ^{13}C: 100.61 MHz), AV III 400 (^{1}H: 400.27 MHz and ^{13}C: 100.65 MHz), AV III 600 (^{1}H: 600.25 MHz), and AV III HD 700 (^{1}H: 700.40 MHz) spectrometer, respectively. Chemical shifts were referenced to internal residual $CHCl_3$ (δ_H = 7.24) and $CDCl_3$ (δ_C = 77.00). IR spectra were recorded on a Bruker VERTEX 70 IR spectrometer in ATR mode. High-resolution mass spectra (HRMS) were obtained using a Finnigan MAT, Bremen, MAT 95S mass spectrometer (EI). Optical rotations were measured at 20 °C on a PerkinElmer 351 polarimeter in a 1 dm cell. TLC was carried out on 0.25 mm thick Merck plates, coated with silica gel 60 F_{254}. Flash (column) chromatography was performed with Merck silica gel 60 (230–400 mesh). Spots were visualized by UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (23.0 g) and of $Ce(SO_4)_2{\cdot}4H_2O$ (1.0 g) in 10% aq H_2SO_4 (500 mL), followed by heating with a heat gun. Melting points were determined on a Reichert Thermovar instrument and are uncorrected.

Determination of ee of (*R*)-**4** and (*S*)-**4** was carried out by using an enantioselective GC/MS method [MEGA-DEX DMP Beta (dimethyl pentyl-β-cyclodextrin), 0.25 µm film, 25 m × 0.25 mm i.d., He flow (1 mL/min), 70 °C, 2 min, +0.1 °C/min to 75 °C]: (*R*)-**4**: t_R = 42.4 min; (*S*)-**4**: t_R = 40.7 min. For determination of ee of (*R*)- and (*S*)-**11**: 70 °C, 2 min, +0.1 °C/min to 76 °C: (*R*)-**11**: t_R = 52.3 min, (*S*)-**11**: t_R = 44.0 min.

Analytical separation of (*R*,*S*)-**6** and (*S*,*S*)-**6** was carried out by HPLC [Chiralpak IC column, 4.6 × 250 mm, 5 µm, *i*-PrOH/heptanes (1:4), diode array, 1 mL/min]: t_R = 4.80 min for (*R*,*S*)-**6**, t_R = 6.12 min for (*S*,*S*)-**6**. Analytical separation of (*R*,*S*)-**14** and (*S*,*S*)-**14** was carried out by HPLC [Chiralpak ID column, 5 µm, 4.6 × 250 mm, *i*-PrOH/heptanes (15:85), diode array, 1 mL/min]: t_R = 9.37 min for (*R*,*S*)-**14**, t_R = 11.96 min for (*S*,*S*)-**6**.

Racemic Taniguchi Lactone (±)-4 from *cis*-2-Butene-1,4-diol [(*cis*)-1] by a Modified Literature Procedure

A mixture of *cis*-2-butene-1,4-diol (33.03 g, 375 mmol, 30.81 mL), triethyl orthoacetate (87.61 g, 540 mmol, 99 mL), and *p*-hydroquinone (8.58 g, 78.03 mmol, 20.8 mol%) was stirred for 5 h at 130 °C and for 20 h at 160 °C. EtOH was removed by distillation at atmospheric pressure. Fractional distillation at reduced pressure (20 mmHg) gave three fractions of colorless oils; 1st fraction: 85–94 °C, 4.71 g, mixture of Taniguchi lactone and side products; 2nd fraction: 94–100 °C, 6.60 g, mixture of Taniguchi lactone and side products; 3rd fraction: 100 °C, 29.39 g, mixture of Taniguchi lactone and 12 mol% of a product tentatively assigned as *p*-diethoxybenzene on the basis of NMR spectra (see later), 59% yield.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 5.73 (ddd, *J* = 17.6, 10.2, 7.5 Hz, 1 H), 5.17–5.09 (m, 2 H), 4.38 (dd, *J* = 8.8, 7.7 Hz, 1 H), 3.96 (dd, *J* = 8.8, 7.9 Hz, 1 H), 3.24–3.12 (m, 1 H), 2.61 (dd, *J* = 17.4, 8.4 Hz, 1 H), 2.33 (dd, *J* = 17.4, 8.9 Hz, 1 H).

^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 176.3, 135.7, 117.3, 72.1, 39.6, 34.0.

Diastereomeric Amides (*R*,*S*)- and (*S*,*S*)-6

A mixture of racemic Taniguchi lactone (±)-**4** (27.49 g, 245 mmol), (*S*)-1-phenylethylamine (29.69 g, 245 mmol, 31.60 mL, ee 99%), and $Ti(Oi\text{-}Pr)_4$ (104.59 g, 368 mmol, 108.79 mL) in anhyd THF (75 mL) was stirred at 75 °C for 2 d. After cooling to r.t., aq HCl (90 mL, 2 M) was added and stirring was continued for 1 h. The mixture was centrifuged to remove TiO_2. The pellet was twice suspended in EtOAc and centrifuged. The supernatant aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to yield the crude mixture of amides (*R*,*S*)-**6** and (*S*,*S*)-**6** (54.2 g, 95%) as a crystalline solid in admixture with side products.

The mixture was dissolved in warm (29–30 °C) *tert*-butyl methyl ether (TBME). The solution was allowed to cool very slowly to 4 °C (flask was placed into a Dewar partly filled with warm water of 29–30 °C after the addition of seeding crystals obtained by flash chromatography as given below; Dewar was covered with a Styropor plate and placed into a refrigerator of 4 °C). These first crystals of (*S*,*S*)-**6** were collected, washed with cold TBME, and combined with crystals of (*S*,*S*)-**6**, which were obtained from the mixture of (*R*,*S*)-**6** and (*S*,*S*)-**6** in the mother liquor by flash chromatography. The combined crystals were recrystallized twice as before {purity monitored by TLC after each crystallization, hexanes/EtOAc (1:2), plate developed twice: R_f [(*R*,*S*)-**6**] = 0.60, R_f [(*S*,*S*)-**6**] = 0.43}.

The first mother liquor was concentrated under reduced pressure and the residue was flash chromatographed (hexanes/EtOAc, 1:1). This chromatography furnished homogeneous, less polar diastereomer (*R*,*S*)-**6**, which was recrystallized from *i*-Pr_2O/1,2-$C_2H_4Cl_2$ (slow cooling to +4 °C) and only a small amount of the more polar amide (*S*,*S*)-**6** was obtained. The fractions containing mixtures of amides and the residues from the mother liquors from the recrystallizations of (*S*,*S*)-**6** were dissolved in warm TBME and very slowly cooled to +4 °C as before to obtain again impure (*S*,*S*)-**6**, which was recrystallized with the first crystals directly obtained from the crude product.

Less Polar Amide (*R*,*S*)-6

Colorless crystals; mp 55 °C (*i*-Pr_2O/1,2-$C_2H_4Cl_2$) (Lit.[1,5] mp not given); $[\alpha]_D^{27}$ –77.3 (*c* 2.2, $CHCl_3$) {not given in Lit.[5], but in Lit.:[1] $[\alpha]_D^{25}$ –78.2 (*c* 2.2, $CHCl_3$)}.

IR (ATR): 3296, 2976, 1693, 1526, 1364, 1237, 1213, 1160, 1103, 988 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 5 H), 5.79 (br s, 1 H), 5.77–5.67 (m, 1 H), 5.16–5.06 (m, 3 H), 3.58 (AB-part of ABX-system, *J* = 10.9, 6.2, 5.5 Hz, 2 H), 2.73 (sext, *J* = 6.6 Hz, 1 H), 2.46 (br s, 1 H), 2.33 (AB-part of ABX-system, *J* = 14.4, 7.2, 6.3 Hz, 2 H), 1.47 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 171.0, 143.0, 138.1, 128.7 (2 C), 127.5, 126.2 (2 C), 116.8, 65.5, 49.0, 42.8, 39.0, 21.7.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.20; H, 8.10; N, 6.10.

More Polar Amide (*S*,*S*)-6

Colorless crystals; mp 98–100 °C (TBME) [not given in Lit.[5], but in Lit.[1] mp 97–99 °C (TBME)]; $[\alpha]_D^{27}$ –87.3 (*c* 2.17, $CHCl_3$), $[\alpha]_D^{25}$ –75.5 (*c* 2.2, acetone) {Lit.[5] $[\alpha]_D^{25}$ –75.5 (*c* 2.2, $CHCl_3$); Lit.[1] $[\alpha]_D^{25}$ –100.0 (*c* 2.3, $CHCl_3$)}.

IR (ATR): 3306, 2978, 2932, 1639, 1531, 1494, 1418, 1252, 1038 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.35–7.19 (m, 5 H), 6.10 (br d, *J* = 7.1 Hz, 1 H), 5.76–5.65 (m, 1 H), 5.13–5.02 (m, 3 H), 3.65–3.49 (m, 2 H), 2.97 (br s, 1 H), 2.69 (sext, *J* = 6.5 Hz, 1 H), 2.32 (AB-part of ABX-system, *J* = 14.3, 7.2, 6.2 Hz, 2 H), 1.45 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 171.2, 142.9, 138.0, 128.6 (2 C), 127.4, 126.1 (2 C), 116.7, 65.3, 48.8, 42.7, 38.8, 21.6.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.06; H, 7.71; N, 5.98.

Conversion of Amides (*R*,*S*)-6 and (*S*,*S*)-6 into Taniguchi Lactones (*R*)-4 and (*S*)-4

Amide (*R*,*S*)-**6** (13.57 g, 58.15 mmol), H_2O (43 mL), concd H_2SO_4 (8.76 mL), and 1,4-dioxane (22 mL) were stirred for 19 h at 80 °C (monitored by TLC). H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were washed with brine (60 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by bulb-to-bulb distillation [90–110 °C/20 mmHg; Lit.[1] bp 170 °C (bath)/2666 Pa] to yield Taniguchi lactone (*R*)-**4** (5.13 g, 79%) as a colorless oil; $[\alpha]_D^{20}$ –3.6 (*c* 1.05, $CHCl_3$) {Lit.[1] $[\alpha]_D^{22}$ –5.2 (*c* 2.3, EtOH); Lit.[3] $[\alpha]_D^{19}$ –5.6 (*c* 1.60, EtOH)}; ee >99%. The spectroscopic data were identical to those of (±)-**4**.

Similarly, amide (*S*,*S*)-**6** (15.65 g, 67.08 mmol) was converted into the colorless Taniguchi lactone (*S*)-**4** (6.024 g, 80%); ee 99%; $[\alpha]_D^{20}$ +4.3 (*c* 0.94, $CHCl_3$) {Lit.[5] $[\alpha]_D^{25}$ +7.1 (*c* 1.0, $CHCl_3$); Lit.[1] $[\alpha]_D^{19}$ +4.9 (*c* 4.3, EtOH); Lit.[3] $[\alpha]_D^{19}$ +6.0 (*c* 1.68, EtOH)}.

Conversion of *cis*-2-Butene-1,4-diol into Taniguchi Lactone (±)-4, Using *p*-Hydroquinone as Catalyst

A mixture of *cis*-2-butene-1,4-diol (6.70 g, 76 mmol), triethyl orthoacetate (13.56 g, 83.6 mmol, 1.1 equiv), and *p*-hydroquinone (0.937 g, 7.6 mmol, 10 mol%) was heated for 1 h at 120 °C (4.6 g of EtOH was collected) and 24 h at 170 °C (after heating for 15 min the temperature of 170 °C was reached and a total of 6.77 g EtOH was obtained; after 24 h, 10.56 g). A few percentage (^{1}H NMR) of 4,7-dihydro-1,3-dioxepine might have been present in the crude reaction mixture. THF (4 mL), H_2O (2 mL) and HCl (0.5 mL, 12 M) were added to the cooled reaction mixture at r.t. After stirring vigorously for 30 min, a cold solution of KOH (5.415 g) in H_2O (40 mL) was added slowly (exothermic!). After 1 h, the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was flash chromatographed (heptanes/CH_2Cl_2, 2:1, R_f = 0.31) to give 1,4-diethoxybenzene (0.128 g) as colorless crystals; mp 69–70 °C (heptanes) (Lit.[9] mp 71–72 °C). The NMR spectroscopic data were identical to those reported in the literature.

The alkaline aqueous layer containing the potassium salt of the organic acid was acidified by slow addition of concd H_2SO_4 (9.6 mL) at 0 °C. After vigorously stirring for 1 h, a separate organic phase had formed. The mixture was extracted with Et_2O (4 × 20 mL). The combined organic layers were washed with brine and sat. aq $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (95–100 °C/5 mmHg) to furnish homogeneous racemic Taniguchi lactone (±)-**4** (6.004 g, 70%) as a colorless oil.

2-Ethoxy-2-methyl-4,7-dihydro-1,3-dioxepine (8)

A mixture of *cis*-2-butene-1,4-diol (10.356 g, 118 mmol), triethyl orthoacetate (17.034 g, 19.25 mL, 105 mmol), and *p*-hydroquinone (1.299 g, 11.8 mmol, 10 mol%) was heated at 120 °C. EtOH (6.978 g, 151 mmol) was collected during the first 30 min. After another 30 min, the amount had increased (7.582 g, 165 mmol). Then, the temperature was increased to 170 °C and reached that temperature within 15 min and was kept there for 15 min. A total of 10.122 g (220 mmol) of EtOH had formed. Further formation of EtOH was very slow. Fractional distillation (58 °C/3 mbar) yielded 4,7-dihydro-1,3-dioxepine (**8**)[2] (13.578 g, 82%) as a colorless liquid.

IR (ATR): 2977, 2941, 1379, 1158, 1072, 1035, 950 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 5.63 (AB-part of ABX-system, J_{AB} = 11.4 Hz, *J* = 1.6 Hz, 2 H), 4.26 (br AB-system, *J* = 15.7 Hz, 4 H), 3.56 (q, *J* = 7.1 Hz, 2 H), 1.51 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 128.9 (2 C), 116.0, 61.4 (2 C), 58.8, 19.0, 15.4.

HRMS-EI: *m*/*z* calcd for $C_8H_{14}O_3^+$: 158.0943; found: 158.0935 ± 5 ppm.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.56; H, 9.54.

Conversion of 4,7-Dihydro-1,3-dioxepine (8) into Taniguchi Lactone (±)-4

A mixture of 4,7-dihydro-1,3-dioxepine (**8**; 11.697 g, 73.9 mmol) and *p*-hydroquinone (0.813 g, 7.39 mmol, 10 mol%) was heated at 170 °C for 30 h. EtOH (2.762 g, 60 mmol) was collected. The reaction mixture contained Taniguchi lactone and 4,7-dihydro-1,3-dioxepine in a molar ratio of 10:1 admixed with impurities. The mixture was chemically purified and subjected to bulb-to-bulb distillation (90–100 °C/5 mmHg) to give lactone (±)-**4** (4.324 g, 52%) as a colorless liquid, which was homogeneous as determined by NMR spectroscopy.

(±)-, (4*R*,1′*R*/*S*)- and (4*S*,1′*R*/*S*)-4-(1,2-Dibromoethyl)dihydrofuran-2(3*H*)-one [(±)-12, (4*R*,1′*R*/*S*)-12 and (4*S*,1′*R*/*S*)-12]

A solution of Br_2 in CH_2Cl_2 (29.72 mmol, 1.05 equiv, 12.38 mL of a 2.4 M solution in CH_2Cl_2) was added dropwise to a stirred solution of (±)-Taniguchi lactone (3.176 g, 28.3 mmol) in anhyd CH_2Cl_2 (56 mL) at 0 °C. The solvent and excess Br_2 were removed under reduced pressure to give a mixture of dibromides (±)-**12** (quantitative yield) as an orange oil. The crude dibromides were pure enough for the next step. Flash chromatography (heptanes/EtOAc, 3:1, R_f = 0.30) furnished a mixture of colorless dibromides in 95% yield.

Similarly, lactone (*R*)-**4** (2.243 g, 20 mmol) was converted into (–)-dibromides (4*R*,1′*RS*)-**12**. Flash chromatography yielded the mixture of (–)-dibromides (5.226 g, 96%) as a colorless oil; ratio of diastereomers 1.00:1.08; $[\alpha]_D^{18}$ –6.7 (*c* 1.0, acetone).

Similarly, lactone (*S*)-**4** (2.70 g, 24.1 mmol) was converted into a mixture of (+)-dibromides (4*S*,1′*RS*)-**12** in quantitative yield. The analytical sample was purified by flash chromatography; ratio of colorless diastereomers 1.0:1.1; $[\alpha]_D^{18}$ +7.5 (*c* 2.1, acetone).

IR (ATR): 3527, 2971, 2911, 1766, 1414, 1172, 1025 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ [A (major dibromide):B (minor dibromide) = 52:48] = 4.49 (dd, *J* = 9.2, 8.4 Hz, 1 H, B), 4.45 (dd, *J* = 9.3, 8.1 Hz, 1 H, A), 4.31–4.24 (m, 2 H, A and B), 4.18 (dd, *J* = 9.2, 7.2 Hz, 1 H, B), 4.17 (dd, *J* = 9.3, 7.4 Hz, 1 H, A), 3.86 (dd, *J* = 10.7, 4.5 Hz, 1 H, B), 3.84 (dd, *J* = 11.1, 4.5 Hz, 1 H, A), 3.59 (dd, *J* = 11.1, 9.1 Hz, 1 H, A), 3.53 (t, *J* = 10.6 Hz, 1 H, B), 3.39–3.22 (m, 2 H, A and B), 2.73 (dd, *J* = 17.6, 9.1 Hz, 1 H, A), 2.58 (AB-part of ABX-system, J_{AB} = 17.6 Hz, *J* = 8.9, 8.7 Hz, 2 H, B). 2.50 (dd, *J* = 17.6, 8.9 Hz, 1 H, A).

^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 175.1, 174.9, 70.9, 69.6, 52.9, 52.7, 38.8, 38.2, 33.8, 33.32, 33.3, 30.0.

Anal. Calcd for $C_6H_8Br_2O_2$: C, 26.50; H, 2.97. Found: C, 26.75; H, 3.07.

(±)-, (4*R*)- and (4*S*)-4-(1-Bromoethenyl)- and (±)-, (4*R*)- and (4*S*)-4-[(*E*/*Z*)-2-Bromoethenyl)]dihydrofuran-2(3*H*)-one [(±)-13a, (4*R*)-13a and (4*S*)-13a, and (*E*/*Z*)-(±)-13b, (4*R*,*E*/*Z*)-13b, and (4*S*,*E*/*Z*)-13b]

A solution of DBU (999 mg, 6.56 mmol, 2 equiv) in anhyd MeCN (6.6 mL) was added dropwise to a stirred solution of dibromides (±)-**12** (892 mg, 3.28 mmol, crude product) in anhyd MeCN (6.5 mL) at 0 °C (ice bath). Stirring was continued for 30 min at 0 °C and 1 h at 25 °C (water bath) before the solution was concentrated at reduced pressure. CH_2Cl_2 (20 mL) and aq HCl (7.0 mL, 1 M) were added. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (100–110 °C/0.7 mbar) to yield a mixture of monobromides (±)-**13a** and (*E*/*Z*)-(±)-**13b** (483 mg, 77%) as a colorless oil; ratio of monobromides 77:15:8. An analytical sample was obtained by flash chromatography (heptanes/EtOAc, 3:1, R_f = 0.31) and bulb-to-bulb distillation.

Similarly, a mixture of (–)-dibromides (4*R*,1′*R*/*S*)-**12** (5.136 g, 18.87 mmol, not purified by flash chromatography) derived from (*R*)-Taniguchi lactone was converted into a mixture of vinyl bromides (*R*)-**13a** and (4*R*,*E*/*Z*)-**13b**. The crude product was purified by bulb-to-bulb distillation (2.821 g, 78%; ratio of colorless bromides: 77:15:8). An analytical sample was obtained by flash chromatography before bulb-to-bulb distillation; $[\alpha]_D^{18}$ –28.4 (*c* 1.65, acetone).

Similarly, a mixture of (+)-dibromides (4*S*,1′*R*/*S*)-**12** (1.36 g, 5 mmol, not purified by flash chromatography) derived from (*S*)-Taniguchi lactone was converted into a mixture of vinyl bromides (*S*)-**13a** and (4*S*,*E*/*Z*)-**13b**. The crude product was purified by bulb-to-bulb distillation (790 mg, 83%; ratio of colorless bromides: 82:13:5). An analytical sample was obtained by flash chromatography before bulb-to-bulb distillation; $[\alpha]_D^{18}$ +28.2 (*c* 2.3, acetone).

IR (ATR) of vinyl bromides derived from (*S*)-lactone: 2910, 1769, 1626, 1415, 1374, 1166, 1025, 997 cm^{-1}.

^1H NMR, 700.40 MHz, $CDCl_3$): δ [vinyl bromides in the ratio 82:13:5 derived from (*S*)-lactone] = 6.34 (br d, *J* = 7.1 Hz, 1 H, *Z*), 6.27 (d, *J* = 13.6 Hz, 1 H, *E*), 6.13 (dd, *J* = 13.4, 8.6 Hz, 1 H, *E*), 6.11 (dd, *J* = 8.3, 7.1 Hz, 1 H, *Z*), 5.78 (d, *J* = 2.3 Hz, 1 H), 5.55 (d, *J* = 2.3 Hz, 1 H), 4.49 (t, *J* = 8.9 Hz, 1 H, *Z*), 4.41 (dd, *J* = 9.1, 8,1 Hz, 1 H), 4.39 (1 H, *E*), 4.20 (dd, *J* = 9.2, 7.6 Hz, 1 H), 4.02–3.97 (m, 2 H, *E* and *Z*), 3.72–3.65 (m, 1 H, *Z*), 3.49 (quint, *J* = 8.1 Hz, 1 H), 3.29–3.21 (m, 1 H, *E*), 2.76 (dd, *J* = 17.5, 8.7 Hz, 1 H, *Z*), 2.66 (AB-part of ABX-system, J_{AB} = 17.6 Hz, *J* = 8.8, 8.4 Hz, 2 H, overlapping with 1 H of *E*), 2.37 (dd, *J* = 17.4, 9.0 Hz, 1 H, *E*), 2.33 (dd, *J* = 17.5, 8.4 Hz, 1 H, *Z*).

^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 175.9, 175.4, 175.1, 134.9, 132.8, 131.5, 119.2, 111.4, 108.4, 71.26, 71.254, 71.0, 45.0, 39.5, 36.5, 33.7, 33.6, 33.4.

Anal. Calcd for $C_6H_7BrO_2$: C, 37.73; H, 3.69; O, 16.75. Found: C, 37.62; H, 3.82; O, 16.80.

(±)-, (*R*)- and (*S*)-4-(Ethynyl)dihydrofuran-2(3*H*)-one [(±)-11, (*R*)-11 and (*S*)-11]

n-BuLi (11 mL, 27.55 mmol, 4.2 equiv, 2.5 M solution in hexanes) was added dropwise to a solution of *i*-Pr_2NH (26.24 mmol, 2.655 g, 3.71 mL, 4 equiv) in anhyd THF (10 mL) under an argon atmosphere at –30 °C. After stirring for 30 min at that temperature, the solution was cooled to –78 °C and a mixture of vinyl bromides (±)-**13a** and (*E*/*Z*)-(±)-**13b** (1.253 g, 6.56 mmol) dissolved in anhyd THF (3 mL) was added dropwise. The dry ice was removed from the cooling bath, which was allowed to warm slowly to –20 °C. The temperature of the bath was kept there for 15–30 min and then cooled to –78 °C. A cold mixture of concd HCl (4.5 mL, 37%) and MeOH (4.5 mL) was added in one portion and the cooling bath was removed. CH_2Cl_2 (25 mL) and H_2O (21 mL) were added while the flask was cooled with ice. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with H_2O (20 mL) and sat. aq $NaHCO_3$ (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was flash chromatographed (CH_2Cl_2, R_f = 0.37), and then purified by bulb-to-bulb distillation (50–60 °C/0.7 mbar) to give racemic alkyne (±)-**11** (332 mg, 46%) as a colorless oil, which crystallized (mp 35 °C).

When a sample of the reaction mixture was withdrawn at –40 °C (or after stirring for 15 min at –20 °C), quenched with HCl (2 M), und worked up extractively, the mixture contained the alkyne and only vinyl bromide **13a** (molar ratio: 1:0.02 at –20 °C) by ^1H NMR analysis.

Similarly, a mixture of (–)-vinyl bromides (*R*)-**13a** and (4*R*,*E*/*Z*)-**13b** (1.253 g, 6.56 mmol) derived from (*R*)-Taniguchi lactone was converted into (–)-alkyne (*R*)-**11** (410 mg, 57%) as a colorless oil, which crystallized (mp about 35 °C) after bulb-to-bulb distillation; $[\alpha]_D^{19}$ –45.8 (*c* 1.5, acetone); ee >99% by chiral GC/MS

HRMS-EI: *m*/*z* calcd for $C_6H_7O_2^+$: 111.0441; found: 111.0436 ± 5 ppm.

Similarly, a mixture of vinyl bromides (*S*)-**13a** and (4*S*,*E*/*Z*)-**13b** (1.448 g, 7.58 mmol) derived from (*S*)-Taniguchi lactone was converted into alkyne (*S*)-**11** (413 mg, 49%) as a colorless crystalline product after bulb-to-bulb distillation; $[\alpha]_D^{25}$ +45.4 (*c* 1.55, acetone); ee 99% by chiral GC/MS.

IR (ATR) of oily racemate: 3281, 2915, 1769, 1374, 1329, 1161, 1078, 1043, 1015 cm^{-1}.

^1H NMR (400.27 MHz, $CDCl_3$): δ = 4.47 (dd, *J* = 8.8, 7.7 Hz, 1 H), 4.19 (dd, *J* = 8.8, 7.5 Hz, 1 H), 3.41–3.30 (m, 1 H), 2.61 (AB-part of ABX-system, J_{AB} = 17.4 Hz, *J* = 8.7, 8.5 Hz 2 H), 2.22 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 174.8, 81.2, 71.8, 71.6, 34.6, 26.8.

Anal. Calcd for $C_6H_6O_2$: C, 65.45; H, 5.49; O, 29.06. Found: C, 65.08; H, 5.71; O, 28.70.

(*R*)- and (*S*)-3-(Hydroxymethyl)-*N*-[(*S*)-1-phenylethyl]pent-4-ynamide [(*R*,*S*)- and (*S*,*S*)-14]

A mixture of alkyne (±)-**11** (105 mg (0.955 mmol), (*S*)-1-phenylethylamine (242 mg, 2 mmol, 98% ee), Ti(O*i*-Pr)$_4$ (80 mg, 2.28 mmol) and THF (0.29 mL) was kept at 75 °C for 9 h. After cooling to r.t., aq HCl (1 mL, 2 M), H_2O (2 mL), and EtOAc (6 mL) were added. The organic phase was separated and the aqueous layer extracted with EtOAc (2 × 6 mL). The combined organic phases were washed with H_2O (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (heptanes/EtOAc, 1:2, R_f = 0.28 and 0.19) furnished the less polar amide (*R*,*S*)-**14** (80 mg, 36%), a mixture of amides (16 mg, 7%), and the more polar amide (*S*,*S*)-**14** (87 mg, 40%). Both amides were crystallized from CH_2Cl_2/heptanes to give colorless crystals.

(*R*,*S*)-14

Mp 78–79 °C; $[\alpha]_D^{20}$ –59.0 (*c* 0.9, acetone).

(*S*,*S*)-14

Mp 92–93 °C; $[\alpha]_D^{20}$ –69.8 (*c* 0.9, acetone).

Similarly, alkyne (*R*)-**11** (36 mg, 0.33 mmol) was converted into colorless amide (*R*,*S*)-**14** [59 mg, 78%; R_f = 0.28 (heptanes/EtOAc, 1:2)]; mp 78–79 °C; $[\alpha]_D^{20}$ –59.9 (*c* 1.0, acetone).

(*R*,*S*)-14

IR (ATR): 3273, 2877, 1635, 1539, 1498, 1450, 1372, 1243, 1067, 1028 cm^{-1}.

^1H NMR (600.25 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 5 H), 6.07 (br d, *J* = 6.8 Hz, 1 H), 5.10 (quint, *J* = 7.0 Hz, 1 H), 3.63 (AB-part of ABX-system, J_{AB} = 11.0 Hz, *J* = 6.1, 5.2 Hz, 2 H), 3.06–3.00 (m, 1 H), 2.80 (br s, 1 H), 2.46 (d, *J* = 6.7 Hz, 2 H), 2.14 (d, *J* = 2.5 Hz, 1 H), 1.48 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 169.8, 142.8, 128.7 (2 C), 127.4, 126.1 (2 C), 71.6, 64.6, 49.1, 38.7, 31.6, 31.5, 21.7.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; O, 13.83. Found: C, 72.26; H, 7.37; N, 6.01; O, 14.22.

(*S*,*S*)-14

IR (ATR): 3278, 2931, 1629, 1537, 1424, 1372, 1233, 1050 cm^{-1}.

^1H NMR (600.25 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H), 6.03 (br d, *J* = 6.6 Hz, 1 H), 5.11 (quint, *J* = 6.9 Hz, 1 H), 3.69 (AB-part of ABX-system, J_{AB} = 10.9 Hz, *J* = 6.1, 5.2 Hz, 2 H), 3.07–3.00 (m, 1 H), 2.81 (br s, 1 H), 2.47 (AB-part of ABX-system, J_{AB} = 14.8 Hz, *J* = 6.7, 6.6 Hz, 2 H), 2.13 (d, *J* = 2.4 Hz, 1 H), 1.48 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (150.93 MHz, CDCl): δ = 169.8, 142.8, 128.6 (2 C), 127.5, 126.2 (2 C), 71.6, 64.6, 49.1, 38.7, 31.4, 21.6.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; O; 13.83. Found: C, 72.34; H, 7.45; N, 6.07; O, 14.25.

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Supporting Information

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