Stereospecific Substitution of Enantiomerically Pure 1-(2-Pyridinyl)ethyl Methanesulfonate with β-Dicarbony Compounds

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Received January 7, 2002; accepted February 7, 2002

The alkylation of the sodium salt of the malonic acid diester with (*R*)-1-(2-pyridinyl)ethyl methanesulfonate (2) gave the dimethyl (*R*)-[1-(2-pyridinyl)ethyl]malonate (3a), stereospecifically. The alkylation reaction of methyl acetoacetate gave the methyl (2′*S*,2*R*/2*S*)-3-oxo-2-[1-(2-pyridinyl)ethyl]butanoate (3d) along with the methyl (*S*)-3-[1-(2-pyridinyl)ethoxy]-2-butenoate (4d). The acid hydrolysis and decarboxylation of 3d under acidic conditions gave (*R*)-4-(2-pyridinyl)pentan-2-one (6), and the alkylation of methyl (*R*)-[1-(2-pyridinyl)ethyl]acetoacetate with benzyl bromide gave a mixture of *C*-benzylated and *O*-benzylated products 7 and 8.

Key words stereospecific reaction; alkylation; chiral non-racemic pyridine

Heterocyclic compounds having a pyridine ring are important in organic chemistry.[1] A number of organic substances including in medicines, natural products, modern functional materials, ligands for catalysts, and so on, contain the pyridine unit. We have been interested in chiral compounds having a pyridine unit. Recently, we have reported the preparation of enantiomerically pure 1-(2-pyridinyl)ethanols,[2,3] and their stereospecific substitution reactions with *N*-, *S*-, and *O*-nucleophiles,[4—7] in which new enantiomerically pure pyridine derivatives having a tertiary chiral carbon center α to the pyridine ring have been synthesized (Chart 1). In this note, we report the substitution reaction of 1-(2-pyridinyl)-ethyl methanesulfonate with β-dicarbonyl compounds as a new *C*-nucleophile, and describe the synthesis of some new chiral pyridine derivatives.

The sodium salt of dimethyl malonate generated with NaH in tetrahydrofuran (THF) was reacted with the enantiomerically pure (*R*)-1-(2-pyridinyl)ethyl methanesulfonate (*R*)-**2**[8] in dimethyl sulfoxide (DMSO). The substitution reaction was completed within 2 h at 60 °C, and the dimethyl [1-(2-pyridinyl)ethyl]malonate (**3a**) possessing an (*R*)-chiral center was exclusively obtained in 82% yield (Chart 2). The enantiomeric purity was determined to be over 99% by chiral HPLC analysis using a chiral column.

The results with other β-dicarbonyl compounds are shown in Chart 3 and Table 1. Diethyl malonate and dimethyl methylmalonate were also alkylated with (*R*)-**2** to give **3b** and **3c** in 75 and 79% yields, respectively (entries 2, 3). However, the reaction with methyl acetoacetate gave **3d** as an 8 : 5 diastereomeric mixture in 54% yield along with the *O*-alkylated product **4d** in 10% yield (entry 4). The reaction of ethyl 2-methyl-3-oxo-butanoate gave the *C*-alkylation product **3e** in 42% yield and the *O*-alkylation product **4e** in 14% yield (entry 5). Although acetylacetone afforded an unseparable mixture of **3f** and **4f** in a 60% combined yield, cyclohexan-1,3-dione gave only the *O*-alkylated product **4g** in 40% yield.

Although the absolute stereochemistry has not yet been determined,[9] the substitutions can be assumed to occur with an inversion of the configuration based on the previous results for the substitution reactions with the *N*-, *S*-, and *O*-nucleophiles, and no exception has ever been observed in these series of the reactions.[4—7]

The substitution reaction with other *C*-nucleophiles were over reactive and did not provide the corresponding substituted product. For example, the reaction with a ketone enolate, Grignard reagent, and lithium acetylide gave complex mixtures. Only that with lithium phenylacetylide gave an allenic product **5** in 32% yield,[10] though none of the simple

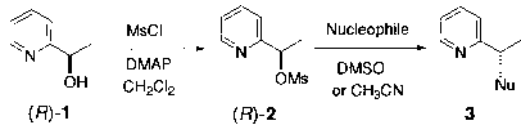

Chart 1

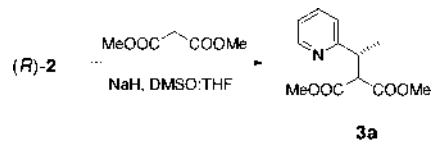

Chart 2

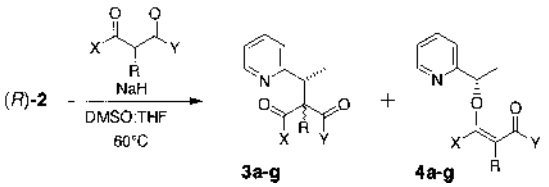

Chart 3

Table 1. Substitution Reaction of (*R*)-**2** with β-Dicarbonyl Compounds

Entry	R	X	Y	Time (h)	Product (yield)			
					3	(%)[a]	**4**	(%)[a]
1	H	OMe	OMe	2	**3a**	82	**4a**	—
2	H	OEt	OEt	2	**3b**	75	**4b**	—
3	Me	OMe	OMe	2	**3c**	79	**4c**	—
4	H	Me	OMe	7	**3d**	54[b]	**4d**	10
5	Me	Me	OEt	8	**3e**	42[c]	**4e**	14
6	H	Me	Me	8	**3f**[d]	50[e]	**4f**[d]	10[e]
7	H	–(CH_2)$_3$–		15	**3g**	—	**4g**	40

a) Isolated yields. *b*) An 8 : 5 diastereomeric mixture. *c*) A 3 : 2 diastereomeric mixture. *d*) Compounds **3f** and **4f** were unseparable. *e*) The yields were estimated based on their integration ratio of the proton NMR spectrum of the mixture.

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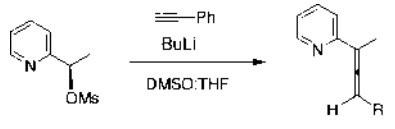

Chart 4

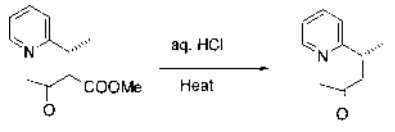

Chart 5

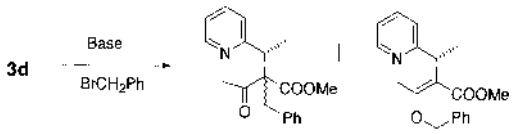

Chart 6

alkynylated product was obtained (Chart 4).

The alkylated product can further develop the synthesis of new chiral pyridines. For example, the hydrolysis of **3d** and successive decarbonylation in refluxing aq. HCl solution gave the chiral ketone **6** in 89% yield in an enantiomerically pure form.

On the other hand, the alkylation of **6** with benzyl bromide gave a mixture of *C*- and *O*-benzylated products. The reaction of the sodium salt of **3d** with benzyl bromide gave **7** in 32% yield as a mixture of diasteroisomers and **8** in 20% yield. The same benzylation reaction under phase transfer conditions gave **7** in 62% yield and **8** in 18% yield. However, the poor diastereofacial selectivity of the chiral enoate could be observed and a diastereomeric mixture of the benzylated products **7** was obtained as an almost equal ratio in both reactions (Chart 6).

In conclusion, several new pyridine derivatives were synthesized in an enantiomerically pure form by the stereospecific substitution reaction of the enantiomerically pure 1-(2-pyridinyl)ethyl methanesulfonate with β-dicarbonyl compounds.

Experimental

Melting points were taken on a Yanako MP-3 melting point apparatus and are not corrected. ^{1}H- and ^{13}C-NMR were recorded on a JEOL LA-300 spectrometer (300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR) in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were obtained on JASCO JMS-GC-mate (electron ionization (EI)) and JMS-SX 102A QQ (FAB and (chemical ionization (CI)) instruments. IR spectra were recorded on a JASCO FT/IR-410 instruments. Optical rotations were measured on a JASCO DIP-360 instrument. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an Ar atmosphere. THF was distilled freshly over sodium/benzophenone ketyl under a nitrogen atmosphere. DMSO was dried over CaH_2 and distilled before use. Thin layer chromatography (TLC) was performed with Merck 60F_{254} precoated silica gel plates. Flash chromatography was carried out using Merck Silica gel 60 (230—400 mesh).

Substitution Reaction of 2 with β-Dicarbonyl Compounds To a suspension of NaH (72 mg, 3.0 mmol) in THF (6.0 ml) was added the corresponding β-dicarbonyl compounds (**3**) (3.22 mmol) at 0 °C. After the hydrogen was ceased at room temperature, the mixture was added to a solution of 1-(2-pyridinyl)ethyl methanesulfonate (1.0 mmol) in DMSO (4.0 ml). The reaction mixture was warmed to 60 °C and stirred until the reaction was completed (see Table). After cooling, EtOAc and water were added. The organic phase was taken and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with water and brine, and dried over $MgSO_4$. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (eluent; EtOAc in hexane solution) to give the corresponding *C*- or *O*-alkylated products.

Dimethyl (*S*)-[1-(2-Pyridinyl)ethyl]malonate (**3a**): Yield 82%. Oil. *Rf*=0.48 (40% EtOAc in hexane). $[\alpha]_D^{25}$ +23° (*c*=1.29, $CHCl_3$). ^{1}H-NMR δ: 1.30 (3H, d, *J*=7.0 Hz), 3.54 (3H, s), 3.66 (1H, dq, *J*=10.6, 7.0 Hz), 3.77 (3H, s), 4.10 (1H, d, *J*=7.0 Hz), 7.10 (1H, ddd, *J*=7.3, 4.8, 1.1 Hz), 7.21 (1H, d, *J*=7.7 Hz), 7.59 (1H, td, *J*=7.7, 1.8 Hz), 8.49 (1H, d, *J*=4.0 Hz). ^{13}C-NMR δ: 19.2, 41.2, 52.3, 52.5, 56.7, 121.6, 122.8, 136.4, 149.1, 162.6, 169.4 (2C). IR (neat) cm^{-1}: 2954, 1736, 1593, 1570, 1435. Electron impact (EI)-MS (relative intensity, %) *m/z* 237 (M^+, 2), 222 (3), 206 (6), 178 (base), 146 (32), 106 (61). EI-high resolution (HR)-MS *m/z*: 237.0996 (Calcd for $C_{12}H_{15}NO_4$: 237.1001).

Diethyl (*S*)-[1-(2-Pyridinyl)ethyl]malonate (**3b**): Yield 75%. Oil. *Rf*=0.35 (20% EtOAc in hexane). $[\alpha]_D^{25}$ +20° (*c*=1.90, $CHCl_3$). ^{1}H-NMR δ: 1.02 (3H, t, *J*=7.2 Hz), 1.26 (3H, t, *J*=7.2 Hz), 1.28 (3H, d, *J*=6.8 Hz), 3.62 (1H, dq, *J*=10.5, 6.8 Hz), 3.96 (2H, d, *J*=7.2 Hz), 4.02 (1H, d, *J*=10.5 Hz), 4.21 (2H, q, *J*=7.2 Hz), 7.07 (1H, ddd, *J*=7.6, 4.5, 1.1 Hz), 7.19 (1H, d, *J*=7.6 Hz), 7.56 (1H, td, *J*=7.6, 1.8 Hz), 8.47 (1H, d, *J*=4.5 Hz). ^{13}C-NMR δ: 13.3, 13.6, 18.7, 40.7, 56.5, 60.6, 60.9, 121.1, 122.4, 135.9, 148.5, 162.3, 167.9, 168.4. IR (neat) cm^{-1}: 2979, 1738, 1593, 1570, 1473. EI-MS (relative intensity) *m/z* 265 (M^+, 5), 220 (22), 192 (97), 174 (40), 146 (76), 118 (32), 106 (base). EI-HR-MS (EI) *m/z*: 265.1311 (Calcd for $C_{14}H_{19}NO_4$: 265.1314).

Dimethyl (*S*)-Methyl[1-(2-pyridinyl)ethyl]malonate (**3c**): Yield 79%. Oil. *Rf*=0.52 (30% EtOAc in hexane). $[\alpha]_D^{24}$ −56° (*c*=1.68, $CHCl_3$); ^{1}H-NMR δ: 1.43 (3H, d, *J*=7.0 Hz), 1.47 (3H, s), 3.60 (3H, s), 3.76 (3H, s), 3.81 (1H, q, *J*=7.0 Hz), 7.10 (1H, ddd, *J*=7.3, 4.8, 0.7 Hz), 7.17 (1H, d, *J*=8.1 Hz), 7.57 (1H, td, *J*=7.7, 1.8 Hz), 8.50 (1H, dm, *J*=4.8 Hz). ^{13}C-NMR δ: 16.3, 17.2, 45.5, 52.3, 52.4, 57.9, 121.7, 123.6, 135.9, 148.8, 161.5, 171.9, 172.1. IR (neat) cm^{-1}: 2997, 2951, 1734, 1589, 1570, 1435. EI-MS (relative intensity, %) *m/z* 252 (M^+, 30), 220 (9), 160 (8), 107 (74), 57 (base). EI-HR-MS (EI) *m/z*: 252.1248 (Calcd for $C_{13}H_{18}NO_4$: 252.1236).

Methyl (2′*S*,2*R*/2*S*)-3-Oxo-2-[1-(2-pyridinyl)ethyl]butanoate (**3d**): Yield 54%. Solid (an 8 : 5 diasteromeric mixture), mp 62 °C (hexane). *Rf*=0.33 (50% EtOAc in hexane). ^{1}H-NMR δ: 1.25 (15/13H, d, *J*=7.0 Hz), 1.28 (24/13H, d, *J*=7.0 Hz), 2.15 (24/13H, s), 2.36 (15/13H, s), 3.71 (8/13H, dq, *J*=10.6, 7.0 Hz), 3.73 (5/13H, dq, *J*=10.6, 7.0 Hz), 3.78 (24/13H, s), 3.52 (15/13H, s), 4.27 (5/13H, d, *J*=10.6 Hz), 4.34 (8/13H, d, *J*=10.6 Hz), 7.09 (8/13H, ddd, *J*=7.8, 5.0, 1.2 Hz), 7.11 (5/13H, ddd, *J*=7.8, 5.0, 1.2 Hz), 7.20 (8/13H, d, *J*=7.8 Hz), 7.23 (5/13H, d, *J*=7.8 Hz), 7.59 (8/13H, td, *J*=7.8, 2.0 Hz), 7.62 (5/13H, td, *J*=7.8, 2.0 Hz), 8.45 (8/13H, dt, *J*=5.0, 2.0 Hz), 8.50 (5/13H, dt, *J*=5.0, 2.0 Hz). ^{13}C-NMR (major isomer) δ: 19.7, 30.4, 41.0, 52.4, 64.0, 121.5, 123.0, 136.5, 148.8, 162.7, 169.2, 202.6. ^{13}C-NMR (minor isomer) δ: 19.1, 30.8, 40.8, 52.1, 64.1, 121.5, 122.8, 136.5, 149.0, 162.9, 168.8, 203.0. IR (KBr) cm^{-1}: 2970, 1714, 1591, 1570, 1435. FAB-MS *m/z* 222 (M^++H). FAB-HR-MS *m/z*: 222.1136 (Calcd for $C_{12}H_{16}NO_3$: 222.1130). *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.96; H, 7.00; N, 6.35.

Methyl (*S*)-3-[1-(2-Pyridinyl)ethoxy]-2-butenoate (**4d**): Yield 10%. Oil. *Rf*=0.18 (20% EtOAc in hexane). $[\alpha]_D^{26}$ −70° (*c*=1.10, $CHCl_3$). ^{1}H-NMR δ: 1.60 (3H, d, *J*=6.6 Hz), 2.37 (3H, s), 3.58 (3H, s), 4.95 (1H, s), 5.24 (1H, q, *J*=6.6 Hz), 7.19 (1H, ddd, *J*=7.7, 5.0, 1.1 Hz), 7.29 (1H, d, *J*=7.7 Hz), 7.69 (1H, td, *J*=7.7, 1.7 Hz), 8.56 (1H, dm, *J*=5.0 Hz). ^{13}C-NMR δ: 19.2, 22.1, 50.6, 77.0, 93.3, 119.3, 122.6, 137.0, 149.1, 160.9, 168.2, 170.6. IR (neat) cm^{-1}: 2984, 2949, 1715, 1625, 1591, 1573, 1437. EI-MS (relative intensity, %) *m/z*: 221 (M^+, 9) , 206 (11), 192 (37), 178 (22), 162 (15), 148(9), 106 (base). EI-HR-MS *m/z*: 221.1041 (Calcd for $C_{12}H_{15}NO_3$: 221.1052).

Ethyl (2′*S*,2*R*/2*S*)-2-Methyl-3-oxo-2-[1-(2-pyridinyl)ethyl]butanoate (**3e**): Yield 42%. Oil (3 : 2 diasteromixture). *Rf*=0.31 and 0.19 (60% EtOAc in hexane). ^{1}H-NMR δ: 1.09 (3H, t, *J*=7.0 Hz), 1.30 (9/5H, q, *J*=7.0 Hz), 1.36 (9/5H, s), 1.39 (6/5H, d, *J*=7.3 Hz), 1.51 (6/5H, s), 2.14 (9/5H, s), 2.23 (6/5H, s), 3.90 (3/5H, q, *J*=7.0 Hz), 3.99 (2/5H, qd, *J*=7.0, 4.0 Hz), 4.24 (2H, q, *J*=7.0 Hz), 7.09 (1H, ddd, *J*=7.3, 4.8, 0.7 Hz), 7.18 (1H, d, *J*=7.7 Hz), 7.53—7.60 (1H, m), 8.47 (3/5H, d, *J*=4.8 Hz), 8.49 (2/5H, d, *J*=4.8 Hz). ^{13}C-NMR δ: (major isomer) 14.0, 15.5, 27.1, 45.2, 61.3, 63.8,

121.6, 123.4, 136.0, 148.6, 161.7, 172.1, 205.7. δ: (minor isomer) 13.8, 16.0, 26.9, 44.1, 61.1, 63.7, 121.6, 123.6, 135.9, 148.7, 162.1, 171.8, 205.0. IR (neat) cm^{-1}: 2983, 2941, 1739, 1714, 1589, 1435. EI-MS *m/z*: 249 (M^+), 206, 160, 134, 107. EI-HR-MS *m/z*: 249.1377 (Calcd for $C_{14}H_{19}NO_3$: 249.1365).

Ethyl (*S*)-2-Methyl-3-[1-(2-pyridinyl)ethoxy]-2-butenoate (**4e**): Yield 14%. Oil. *Rf*=0.60 (60% EtOAc in hexane). ^{1}H-NMR δ: 1.28 (3H, t, *J*=7.2 Hz), 1.58 (3H, d, *J*=6.6 Hz), 1.95 (3H, d, *J*=1.4 Hz), 2.27 (3H, d, *J*=1.4 Hz), 4.14 (2H, q, *J*=7.2 Hz), 5.14 (1H, q, *J*=6.6 Hz), 7.20 (1H, ddd, *J*=7.7, 5.0, 0.9 Hz), 7.37 (1H, d, *J*=7.7 Hz), 7.71 (1H, td, *J*=7.7, 1.8 Hz), 8.54 (1H, d, *J*=5.0 Hz). ^{13}C-NMR δ: 12.1, 14.3, 15.7, 22.5, 59.8, 76.1, 107.4, 119.5, 122.5, 137.2, 148.9, 162.4, 162.8, 169.5. IR (neat) cm^{-1}: 2981, 2935, 1732, 1699, 1626, 1593, 1574, 1437. FAB-MS *m/z* 250 (M^++H). FAB-HR-MS *m/z*: 250.1445 (Calcd for $C_{14}H_{20}NO_3$: 250.1443).

(*S*)-3-[1-(2-Pyridinyl)ethyl]-2,4-pentadione (**3f**) and (*S*)-3-[1-(2-Pyridinyl)ethyloxy]-3-penten-2-one (**4f**): Although **3f** and **4f** were obtained in 60% combined yield as an unseparable 5 : 1 diastereomeric mixture, pure **3f** was isolated by HPLC separation, partially. **3f**: Oil. *Rf*=0.40 (60% EtOAc in hexane). $[\alpha]_D^{25}$ +93° (*c*=1.02, $CHCl_3$). ^{1}H-NMR δ: 1.23 (3H, d, *J*=7.0 Hz), 2.05 (3H, s), 2.29 (3H, s), 3.78 (1H, dq, *J*=10.8, 7.0 Hz), 4.50 (1H, d, *J*=10.8 Hz), 7.11 (1H, dd, *J*=7.3, 5.0 Hz), 7.19 (1H, d, *J*=7.7 Hz), 7.60 (1H, td, *J*=7.7, 1.8 Hz), 8.47 (1H, d, *J*=5.0 Hz). ^{13}C-NMR δ: 19.5, 29.9, 30.2, 41.5, 73.7, 121.6, 122.8, 136.6, 149.0, 162.6, 203.3, 203.5. IR (neat) cm^{-1}: 2971, 2934, 1698, 1591, 1570, 1434. EI-MS (relative intensity, %) *m/z* 205 (M^+, 1), 190 (20), 187 (34), 172 (11), 162 (29), 146 (92), 120 (base). EI-HR-MS *m/z*: 205.1105 (Calcd for $C_{12}H_{15}NO_2$: 205.1103). **4f**: The following ^{1}H- and ^{13}C-NMR data of **4f** were picked up from the spectrum of the mixture: ^{1}H-NMR δ: 1.61 (3H, d, *J*=6.6 Hz), 2.00 (3H, s), 2.34 (3H, s), 5.27 (1H, q, *J*=6.6 Hz), 5.39 (1H, s), 7.21 (1H, ddd, *J*=7.5, 5.0, 1.1 Hz), 7.30 (1H, d, *J*=7.9 Hz), 7.70 (1H, td, *J*=7.7, 1.7 Hz), 8.57 (1H, d, *J*=4.8 Hz). ^{13}C-NMR δ: 19.8, 22.3, 32.0, 47.4, 77.1, 102.1, 119.3, 122.7, 137.2, 149.0, 161.2, 197.1.

(*S*)-3-[1-(2-Pyridinyl)ethyloxy]-2-cyclohexenone (**4g**): Yield 71%. Oil. *Rf*=0.18 (70% EtOAc in hexane). $[\alpha]_D^{25}$ −167° (*c*=1.75, $CHCl_3$). ^{1}H-NMR δ: 1.63 (3H, t, *J*=6.6 Hz), 1.92—2.05 (2H, m), 2.27—2.33 (2H, m), 2.51 (2H, t, *J*=6.3 Hz), 5.27 (1H, s), 5.29 (1H, q, *J*=6.6 Hz), 7.20 (1H, ddd, *J*=7.6, 5.0, 1.1 Hz), 7.29 (1H, d, *J*=7.9 Hz), 7.69 (1H, td, *J*=7.8, 1.8 Hz), 8.56 (1H, d, *J*=5.0 Hz). ^{13}C-NMR δ: 21.2, 21.8, 29.2, 36.6, 77.4, 104.8, 119.5, 122.8, 137.0, 149.4, 160.3, 176.3, 199.5. IR (neat) cm^{-1}: 2952, 1736, 1651, 1604, 1435. EI-MS (relative intensity, %) *m/z* 217 (M^+, 11), 200 (7), 188 (40), 174 (8), 161 (32), 147 (20), 106 (base). EI-HR-MS *m/z*: 217.1111 (Calcd for $C_{13}H_{15}NO_2$: 217.1103).

Reaction of Phenylacetylene To the mesylate (0.5 mmol) dissolved in DMSO (2 ml) was added a solution of lithium salt of phenylacetylene, generated from phenylacetylene (162 mg, 1.59 mmol, in 3 ml THF solution) and *n*-butyl lithium (1.49 mmol, 0.96 ml in 1.55 M hexane solution) at rt. It was stirred for 1 h at the same temperature, and quenched with water. The mixture was extracted with 40% EtOAc in hexane, washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography on silica gel eluted with 10% EtOAc in hexane to give 1-methyl-3-phenyl-1-(2-pyridinyl)allene (**5**) (33 mg) in 32% yield. Oil. *Rf*=0.42 (20% EtOAc in hexane). $[\alpha]_D^{23}$ +0.5° (*c*=1.21, $CHCl_3$). ^{1}H-NMR δ: 1.84 (3H, s), 5.63 (1H, br s), 7.22—7.27 (4H, m), 7.39—7.43 (2H, m), 7.65 (1H, d, *J*=7.7 Hz), 7.74 (1H, td, *J*=7.7, 1.5 Hz), 8.51 (1H, d, *J*=4.8 Hz). ^{13}C-NMR δ: 31.8, 68.4, 83.3, 91.7, 119.7, 122.1, 127.7 (2C), 127.9, 131.3 (2C), 137.0, 146.9, 161.4. IR (KBr) cm^{-1}: 3056, 2989, 2939, 2233, 1591, 1569, 1437. CI-MS (relative intensity, %) *m/z*: 208 ($M+1^+$, 72), 206 (40), 180 (22), 57 (base). CI-HR-MS *m/z* 208.1123 (Calcd for $C_{15}H_{14}N$: 208.1126).

Demethoxycarbonylation of 3d A 50% aqueous sulfuric acid solution (4 ml) of **3d** (11 mg) was refluxed for 15 h. After cooling, an excess of aq. $NaHCO_3$ was added carefully and the solution was made basic. The mixture was extracted with EtOAc, and the extract was washed with waster and brine, and dried over $MgSO_4$. After the solvent was removed, the residue was purified by flash chromatography on silica gel eluted with 30% EtOAc in hexane to give (*R*)-4-(2-pyridinyl)pentane-2-one (**6**) (72 mg) in 89% yield. Oil. *Rf*=0.38 (30% EtOAc in hexane). $[\alpha]_D^{25}$ −11° (*c*=1.14, $CHCl_3$). ^{1}H-NMR δ: 1.29 (3H, d, *J*=7.0 Hz), 2.11 (3H, s), 2.69 (1H, dd, *J*=16.9, 6.6 Hz), 3.10 (1H, dd, *J*=16.9, 7.3 Hz), 3.45 (1H, sext, *J*=7.0 Hz), 7.09 (1H, ddd, *J*=7.3, 4.8, 1.1 Hz), 7.19 (1H, d, *J*=7.7 Hz), 7.59 (1H, td, *J*=7.7, 1.8 Hz), 8.50 (1H, br d, *J*=4.8 Hz). ^{13}C-NMR δ: 21.0, 30.4, 37.0, 49.7, 121.2, 122.2, 136.3, 149.0, 164.7, 207.8. IR (neat) cm^{-1}: 2966, 2930, 1714, 1592, 1570, 1434. EI-MS (relative intensity, %) *m/z*: 163 (M^+, 1), 148 (61), 120 (base), 106 (36). EI-HR-MS *m/z*: 163.1002 (Calcd for $C_{10}H_{13}NO$: 163.0997).

Benzylation of 3d Method A: To a stirred THF solution (4.4 ml) of sodium salt of **3d** prepared from (100 mg, 0.46 mmol) and NaH (0.5 mmol, 1.1 eq) was added benzyl bromide (386 mg, 2.26 mmol) at 0 °C. The mixture was warmed up to room temperature and stirred for 30 min. Then, DMSO (4.4 ml) was added and the mixture was stirred for 9 h at room temperature. Water was added to the mixture and it was extracted with 30% EtOAc in hexane. The extract was washed with water and brine, and dried over $MgSO_4$. The crude oil was purified by silica gel flash chromatography. Elution with 15% EtOAc in hexane gave one of the diasteroisomers of **7** in 15% yield, that of 20% EtOAc gave **8** in 20% yield, and that of 30% EtOAc gave another polar diasteroisomer **7** in 17% yield.

Method B: A methylene chloride solution (0.72 ml) of **3d** (100 mg, 0.46 mmol), benzyl bromide (386 mg, 2.26 mmol), and Bu_4NHSO_4 (168 mg, 0.5 mmol), and a 5% aq. NaOH solution (0.72 ml) were stirred vigorously for 1 h at room temperature. The organic layer was separated and the aqueous layer was re-extracted with methylene chloride. The combined extracts were washed with water and brine, and dried over $MgSO_4$. The crude products were purified by the same procedure described above, giving less polar compound **7** in 26% yield, compound **8** in 18% yield and polar compound **7** in 36% yield, respectively.

Methyl (2′*R*,2*R*/2*S*)-2-Benzyl-3-oxo-2-[1-(2-pyridinyl)ethyl]-2-butenoate (**7**): Less polar isomer: Oil. *Rf*=0.61 (40% EtOAc in hexane). $[\alpha]_D^{24}$ +1.3° (*c*=0.6, $CHCl_3$). ^{1}H-NMR δ: 1.38 (3H, d, *J*=7.3 Hz), 1.87 (3H, s), 3.08 (2H, q, *J*=13.9 Hz), 3.69 (1H, q, *J*=7.0 Hz), 3.74 (3H, s), 7.05—7.21 (7H, m), 7.60 (1H, td, *J*=7.6, 1.9 Hz), 8.48 (1H, dm, *J*=4.8 Hz). ^{13}C-NMR δ: 17.6, 30.9, 41.0, 47.1, 51.6, 68.1, 121.7, 123.6, 126.7, 128.1 (2C), 130.3 (2C), 136.0, 136.6, 148.8, 161.8, 172.0, 206.1. IR (neat) cm^{-1}: 2947, 2879, 1705, 1589, 1570, 1434. EI-MS (relative intensity, %) *m/z*: 311 (M^+, 2), 296 (1), 280 (2), 269 (7), 268 (7), 236 (16), 178 (17), 146 (11), 107 (base). EI-HR-MS *m/z*: 311.1520 (Calcd for $C_{19}H_{21}NO_3$: 311.1521). Polar isomer: Oil. *Rf*=0.30 (40% EtOAc in hexane). $[\alpha]_D^{26}$ −26° (*c*=0.49, $CHCl_3$). ^{1}H-NMR δ: 1.50 (3H, d, *J*=7.0 Hz), 2.15 (3H, s), 3.18 (1H, d, *J*=13.6 Hz), 3.25 (1H, d, *J*=13.6 Hz), 3.58 (3H, s), 3.72 (1H, d, *J*=7.0 Hz), 7.03—7.24 (7H, m), 7.58 (1H, td, *J*=7.7, 1.8 Hz), 8.50 (1H, br d, *J*=4.8 Hz). ^{13}C-NMR δ: 17.8, 31.2, 40.1, 46.1, 51.7, 68.1, 121.6, 123.9, 126.7, 128.1 (2C), 130.0 (2C), 136.0, 136.8, 148.6, 161.8, 171.6, 207.3. IR (neat) cm^{-1}: 2949, 1737, 1708, 1589, 1570, 1434. EI-MS (relative intensity, %) *m/z*: 311 (M^+, 5), 296 (3), 280 (4), 269 (12), 268 (11), 236 (19), 178 (29), 146 (15), 107 (base). EI-HR-MS *m/z*: 311.1520 (Calcd for $C_{19}H_{21}NO_3$: 311.1521).

Methyl (*R*)-3-Benzyloxy-2-[1-(2-pyridinyl)ethyl]-2-butenoate (**8**): Oil. *Rf*=0.50 (40% EtOAc in hexane). $[\alpha]_D^{26}$ −64° (*c*=0.50, $CHCl_3$). ^{1}H-NMR δ: 1.54 (3H, d, *J*=7.3 Hz), 2.39 (3H, s), 3.50 (3H, s), 4.58 (1H, q, *J*=7.3 Hz), 4.90 (1H, d, *J*=12.5 Hz), 4.96 (1H, d, *J*=12.5 Hz), 7.01 (1H, dd, *J*=7.3, 4.8 Hz), 7.16—7.35 (6H, m), 7.50 (1H, td, *J*=7.7, 1.8 Hz), 8.49 (1H, dm, *J*=4.8 Hz). ^{13}C-NMR δ: 15.9, 17.1, 38.2, 50.8, 69.2, 120.2, 121.1, 127.1 (2C), 127.9, 128.5 (2C), 135.6, 136.8, 162.4, 164.9, 169.5. IR (neat) cm^{-1}: 2947, 1701, 1614, 1589, 1432. EI-MS (relative intensity, %) *m/z*: 311 (M^+, 1), 296 (2), 205 (29), 204 (29), 178 (9), 146 (61), 107 (20), 91 (base). EI-HR-MS *m/z*: 311.1527 (Calcd for $C_{19}H_{21}NO_3$: 311.1521).

Acknowledgments The authors are grateful to Ms. Satoko Fujisaki for the initial contribution of this project and also to Professors O. Yonemitsu and Y. Ito for their encouragement and valuable discussions. This work was financially supported by the Grant-in-Aid for Scientific Research on Priority Areas (A) from the Ministry of Education, Science, Sports and Culture, Japan, and a Special Grant for Cooperative Research administered by the Japan Private School Promotion Foundation.

References and Notes

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8) Preparation of the mesylate **2**, see in ref. 5.
9) Our efforts for making a single crystal of several salts for **3** and **4** with chiral non-racemic acids for X-ray analysis were fruitless due to the formation of inappropriate crystals.
10) The allene **5** was found to be 11% ee determined by HPLC analysis using a chiral column.