JOC Article

Highly Enantioselective Friedel−Crafts Reaction of Aromatic Amines with Ethyl Glyoxylate Catalyzed by Chiral Titanium(IV) Complexes: Practical Synthesis of Aminomandelic Acid Derivatives

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The asymmetric Friedel−Crafts reaction of a variety of *N*,*N*-dialkylanilines with ethyl glyoxylate has been achieved by the catalysis of titanium complexes of BINOL derivatives to give corresponding ethyl esters of *p*-*N*,*N*-dialkylaminomandelic acids in high yields (85−99%) and good to excellent enantioselectivities (80−96.6% ee) under the optimized reaction conditions, which has added a new catalyst for this class of reactions. The reaction could also be carried out at a reduced catalyst loading (1 mol %) in gram scale, which provided a practical synthesis of enantiopure aminomandelic acid derivatives.

Friedel−Crafts (F−C) reaction is one of the most fundamental C−C bond-forming reactions in organic synthesis.[1] The asymmetric F−C reaction of aromatic compounds with α-dicarbonyl compounds provided a simple procedure for the preparation of optically active mandelic acid derivatives with important biological properties. Although asymmetric F−C reactions using a chiral auxiliary or chiral substrates have been extensively studied,[2] the catalytic enantioselective version of this reaction has been less developed. The earlier work on catalytic enantioselective F−C reactions includes the reaction of anisole with chloral catalyzed by chiral alkoxyaluminum chloride and the addition of pyruvic esters to 1-naphthol using a chiral zirconium catalyst.[3] The real breakthrough of this research field was recently achieved by Mikami's group and Jørgensen's group independently.[4] Since their pioneering work, the research on the catalytic enantioselective F−C reaction has been an extensive interest in asymmetric catalysis.[5]

Recently, Jørgensen reported that F−C reaction of glyoxylate with *N*,*N*-dimethylanilines could be promoted by *tert*-butyl bisoxazoline-copper(II) complexes to give enantioenriched aminomandelic acid derivatives, a type of potential starting materials for many biologically active compounds, with high yield and enantioselectivity.[4c] Although titanium complexes of 1,1′-bi-2-naphthol (BINOL)[6] derivatives have been employed for F−C reacion of fluoral with anisole,[4a] the use of this type of catalysts for the F−C reaction of aromatic amine with activated carbonyl compound has not yet been reported. In the present work, we report our results on the first use of titanium complexes of BINOL derivatives (Scheme 1) for F−C reaction of *N*,*N*-dialkylamino aromatics with ethyl glyoxylate, which provided a highly efficient and enantioselective practical synthesis of aminomandelic acid derivatives.

The first trial on F−C reaction of *N*,*N*-dimethylaniline (**1a**) with ethyl glyoxylate (**2**) at room temperature in the presence of 10 mol % (*R*)-**4a**/Ti catalyst prepared in situ by mixing (*R*)-**4a** and Ti(O^{i}Pr)$_4$ in dichloromethane in a 2:1 molar ratio showed that the reaction proceeded smoothly to give (*R*)-**3a** in quantitative yield with 70.6% ee (entry 1, Table 1). The interesting point is that the catalytic activity of the BINOL−Ti complex was not reduced in the presence of an N-donor substrate that might coordinate with the Lewis acid center. The preferential activation of ethyl glyoxylate observed in this catalytic system may be attributed to the high oxophi-

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SCHEME 1. Chiral Ligands Employed for Asymmetric Induction

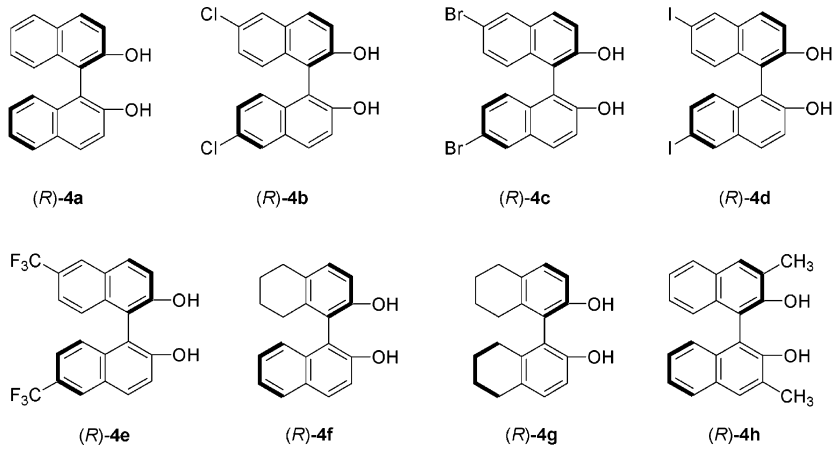
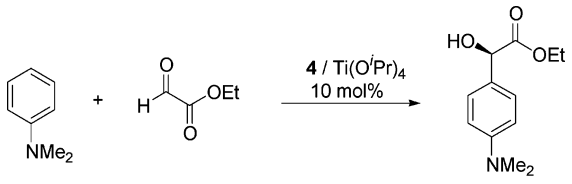


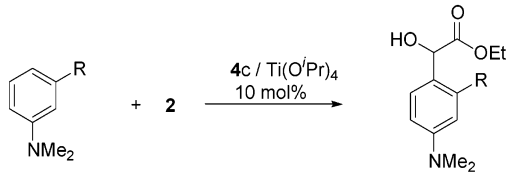
TABLE 1. Asymmetric Reaction of *N*,*N*-Dimethylaniline (1a−c) with Ethyl Glyoxylate (2) Catalyzed by Different BINOL−Ti Complexes under Various Conditions[a]



entry	ligand	solvent	temp (°C)	yield of **3a**[b] (%)	ee of **3a**[c] (%)
1	(*R*)-**4a**	CH_2Cl_2	rt	99	70.6
2	(*R*)-**4a**	toluene	rt	99	77.0
3	(*R*)-**4a**	THF	rt	99	48.0
4	(*R*)-**4b**	toluene	rt	99	91.6
5	(*R*)-**4c**	toluene	rt	99	90.6
6	(*R*)-**4d**	toluene	rt	99	85.9
7	(*R*)-**4e**	toluene	rt	99	54.0
8	(*R*)-**4f**	toluene	rt	61	74.9
9	(*R*)-**4g**	toluene	rt	66	69.4
10	(*R*)-**4h**	toluene	rt	50	7.0
11	(*R*)-**4b**	toluene	−10	99	89.6
12	(*R*)-**4c**	toluene	−10	99	96.2
13	(*R*)-**4c**	toluene	−20	95	95.8

[a] For a detailed procedure, see Experimental Section. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD column.

TABLE 2. Asymmetric F−C Reaction of Meta-Substituted *N*,*N*-Dimethylaniline (1c−h) with Ethyl Glyoxylate (2) Catalyzed by 4c/Ti Complex at 0 °C[a]



a: R = H; **b**: R = F; **c**: R = Me; **d**: R = OMe

a: R = H; **b**: R = F; **c**: R= Me; **d**: R = OMe

entry	substrate	temp (°C)	time (h)	product	yield[b] (%)	ee[c] (%)
1	**1a**	−10	24	(*R*)-**3a**	99	96.2
2	**1b**	−30	36	(−)-**3b**	85	87.7
3	**1c**	−30	36	(−)-**3c**	96	90.1
4	**1d**	−10	24	(−)-**3d**	99	80.0

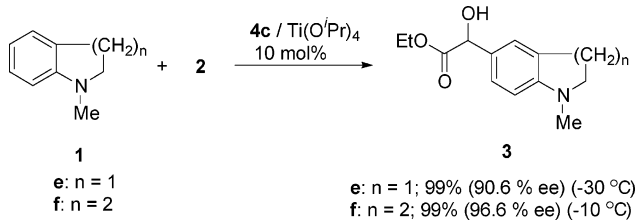
[a] For details, see Experimental Section. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD column.

licity of titanium ion and the relatively weak basicity of *N*,*N*-dimethylaniline. The solvent effect on the enantioselectivity of the reaction was evident (entries 1−3, Table 1). Toluene is superior to dichloromethane or THF.

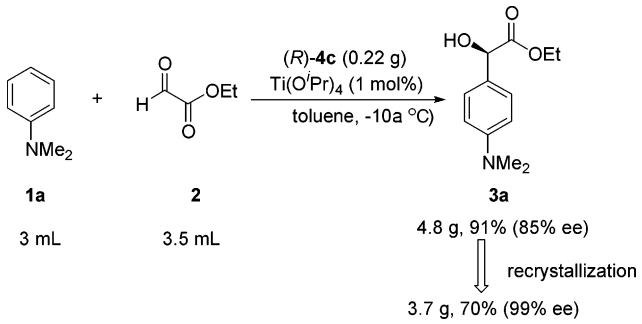
With these leading results in hand, we switched our effort to further improving the enantioselectivity of the reaction by tuning the steric and electronic modifications on the diol ligands. Accordingly, a series of chiral diol ligands, including commercially available or easily prepared BINOL derivatives (**4b**−**h**) shown in Scheme 1, were submitted to asymmetric catalysis. The results clearly demonstrated that the enantioselectivity and reactivity of the reaction were significantly influenced by both the electronic effect and the steric hindrance of the substituents at 6,6′-positions or 3,3′-positions of BINOL (entries 4−10, Table 1). Electron-withdrawing groups (such as Cl, Br, or I) at 6,6′-positions of BINOL are favorable for the improvement of the enantioselectivity of the reaction (85.9−91.6% ee) (entries 4−6) with the exception of 6,6′-CF_3-disubstituted BINOL (entry 7). The steric hindrance of methyl groups at 3,3′-positions of BINOL was proved to be disadvantageous for the reaction in terms of both reactivity and enantioselectivity (entry 2 vs 10). Using the ligands (*R*)-**4f**−**g** with a partially reduced backbone afforded the F−C product in much lower yield and slightly decreased enantioselectivities (entry 2 vs entries 8 and 9). Obviously, the lower catalytic activity of (*R*)-**4f**−**g**/Ti might be attributed to their relatively weak Lewis acidity because of electron-donating properties of the partially reduced backbone in ligands (*R*)-**4f**−**g**. Therefore, the correct assembly of the substituents and backbone of binaphthyl in the ligands is a key point for getting high reactivity and enantioselectivity of this asymmetric F−C reaction. Although the enantioselectivity of the reaction catalyzed by (*R*)-**4b**/Ti at a lower temperature (−10 °C) decreased slightly (entry 4 vs 11), up to 96.2% ee of F−C product has been achieved with the catalysis of (*R*)-**4c**/Ti at −10 °C without loss of the yields (>99%) (entry 12). Further decreasing the reaction temperature to −20 °C decreased the enantioselectivity of the reaction (entry 13).

The catalytic enantioselective F−C reaction of various meta-substituted *N*,*N*-dimethylanilines **1b**−**d** with ethyl glyoxylate (**2**) proceeded smoothly as well under the optimized reaction conditions to provide corresponding *p*-aminomandelic acid derivatives (**3b**−**d**) in high yields (85−99%) and enantioselectivities (80−90.1% ee) (Table 2). Both electron-donating (Me, MeO) and electron-

SCHEME 2. Asymmteric F−C Reaction of *N*-Methylindoline and *N*-Methyltetrahydroquiniline with Ethyl Glyoxylate (2) Catalyzed by 4c/Ti Complex



SCHEME 3. Practical Synthesis of Enantiopure Ethyl 4-*N*,*N*-Dimethylaminomandelate through Asymmteric F−C Reaction of 1a with 2



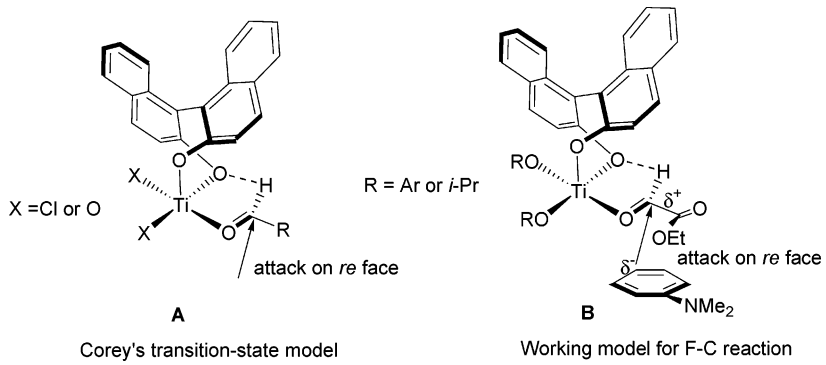
withdrawing substituents (F) were tolerated in the catalytic reaction. The substrates could be extended to heterocyclic aromatic amines as well (Scheme 2). The reactions of **1e**,**f** with **2** under the catalysis of (*R*)-**4c**/Ti led to the formation of **3e**,**f** as the only isomer in 99% yield with 90.6 and 96.6% ees, respectively. These results are comparable to or even better in certain cases than those obtained with the catalysis of bisoxazoline−copper(II) complexes.[4c]

To demonstrate the preparative utility of this methodology, the reaction of ethyl glyoxylate with *N*,*N*-dimethylaniline was conducted in a gram scale using only 1 mol % **4c**/Ti catalyst, affording the desired adduct **3a** in high yield (91%) and acceptable enantioselectivity (85% ee). Further recrystallization of the products from ethyl acetate and hexane gave enantiopure (*R*)-**3a** in 70% yield. Furthermore, the optimized best ligand **4c** could be easily obtained by simple bromination of commercially available (*R*)-BINOL in 96% yield.[7] Other starting materials such as titanium isoproxide and ethyl glyoxylate were cheap industrial products. Therefore, the present catalytic system has provided a practical and economical protocol to the synthesis of enantiopure aminomandelic acid derivatives.

As to the reaction pathway, the six-membered transition state involving a chiral Lewis acid, which has been reported to preferentially produce an ortho F−C product in the reaction of 1-naphthol,[3] could be excluded in the present catalytic system because of regiospecific formation of para-substituted dimethylaminomandelic acid derivatives in the reaction, although the *N*,*N*-dialkylamino group might coordinate with the center of Lewis acid. Mikami has proposed a transition state for titanium-catalyzed carbonyl ene reaction and heterocycloaddition of ethyl glyoxylate, in which the aldehyde is activated by the complexation with the chiral titanium catalyst via the formyl lone-pair electrons (monodentate) in syn form to formyl hydrogen.[8] Although the exact structure of the effective catalyst is unclear, Corey described a more detailed transition-state model for Mikami's enantioselective carbonyl-ene reaction, where formyl C−H···O hydrogen bonding occurs to the sterically favorable oxygen lone pair of the BINOL ligand to generate structure **A** as shown in Scheme 4.[9] On the basis of the observed absolute configuration of the F−C product in the present reaction system and Corey's transition-state model for carbonyl-ene reaction, we proposed a possible asymmetric induction pathway (**B**) for chiral titanium-catalyzed F−C reaction of *N*,*N*-dimethylaniline with ethyl glyoxylate, which is shown in Scheme 4. In this structure, the bottom (*re*) face of the formyl group is much more accessible to a nucleophile than the top (*si*) face since the latter is strongly shielded by the nearby naphthol subunit. The highly polarized C═O of formyl group with δ^+ at carbon atom will accept the attack of the most electron-abundant site (para position) of *N*,*N*-dimethylaniline ($\sigma_{meta} = -0.16$ vs $\sigma^+_{para} = -1.3$) from a less stereohindered direction (*re*) to give the product in (*R*)-configuration.

In summary, the asymmetric Friedel−Crafts reaction of a variety of *N*,*N*-dialkylanilines with ethyl glyoxylate has been achieved by the catalysis of titanium complexes of BINOL derivatives to give corresponding ethyl esters of *p*-*N*,*N*-dialkylaminomandelic acids in high yields and good to excellent enantioselectivities under the optimized reaction conditions, which has added a new catalyst for this class of reactions. The reaction could also be carried out at a reduced catalyst loading (1 mol %) in gram scale, which provided a practical synthesis of enantiopure aminomandelic acid derivatives.

SCHEME 4. Proposed Working Model for Asymmetric F−C Reaction



Experimental Section

General Methods. ^{1}H NMR spectra were recorded in $CDCl_3$ on a 300 MHz spectrometer at 25 °C. Chemical shifts were expressed in parts per million with TMS as an internal standard (δ = 0 ppm) for ^{1}H NMR. Optical rotation was measured with a 341 automatic polarimeter. EI mass spectra were obtained on a 5989A spectrometer. IR spectra were taken on a FTIR instrument and are reported in cm^{-1}. The enantiomeric excesses were determined by HPLC on a chiral column. All the experiments that were sensitive to moisture or air were carried out under an argon atmosphere using standard Schlenk techniques. Commercial reagents were used as received without further purification unless otherwise noted. Tetrahydrofuran (THF) and toluene were freshly distilled from sodium benzophenone ketyl and dichloromethane from calcium hydride before use.

Materials. (*R*)-BINOL (**4a**) was prepared by optical resolution with (*S*)-5-oxopyrrolidine-2-carboxanilide through molecular complexation.[10] Ligands (*R*)-**4b**−**h** were prepared following the literature procedures.[7,11−14] Ethyl glyoxylate was synthesized by the oxidation of diethyl tartrate with HIO_4 according to the literature method[15] or obtained by distillation of commercially available ethyl glyoxylate toluene solution.

General Procedure for Titanium-Catalyzed Enantioselective Friedel−Crafts Reaction of Aromatic Amines with Ethyl Glyoxylate. A 10 mL Schlenck tube was equipped with a magnetic stirrer. The air in the tube was replaced by argon. Ligand (*R*)-**4c** (22 mg, 0.05 mmol) was dissolved in 1 mL of toluene, and then Ti(O^{i}Pr)$_4$ (0.5 M in CH_2Cl_2, 50 μL, 0.025 mmol) was added to the solution. The mixture was stirred at room temperature for 2 h. The resulting orange solution was cooled to the specific temperature, and then aromatic amine **1** (0.25 mmol) and freshly distilled ethyl glyoxylate (40 μL, 0.5 mmol) were introduced into the reaction system. The reaction process was monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was submitted to flash chromatography separation on silica gel using hexanes−ethyl acetate (3:1) as an eluent to give the corresponding Friedel−Crafts reaction product **3a**−**f**.

2-(4-Dimethylaminophenyl)-2-hydroxyacetic Acid Ethyl Ester (3a):[4c] IR (KBr) ν_{max} 3451, 2999, 2961, 2890, 2808, 1730, 1616, 1525, 1357, 1190, 1079, 1014, 802, 572 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.22 (m, 2H), 6.70−6.68 (m, 2H), 5.05 (d, J = 4.8 Hz, 1H), 4.29−4.11 (m, 2H), 3.25 (d, J = 5.4 Hz, 1H), 2.94 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H); EIMS *m*/*z* (relative intensity) 223 (M$^+$, 13.61), 180 (5.68), 162 (19.35), 150 (100.00), 132 (8.68), 120 (5.22), 107 (8.91), 77 (7.48). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, t_{R1} = 17.675 min (major), t_{R2} = 25.933 min (minor).

2-(2-Fluoro-4-dimethylaminophenyl)-2-hydroxyacetic Acid Ethyl Ester (3b):[4c] IR (KBr) ν_{max} 3440, 2999, 2900, 1738, 1632, 1524, 1365, 1237, 1188, 1076, 1014, 977, 815, 802 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8.7 Hz, 1H), 6.45 (dd, J = 2.1 Hz, 8.4 Hz, 1H), 6.37 (dd, J = 2.1 Hz, 13.8 Hz, 1H), 5.27 (s, 1H), 4.30−4.21 (m, 2H), 2.96 (s, 6H), 1.27 (t, J = 7.2 Hz, 3H); EIMS *m*/*z* (relative intensity) 241 (M$^+$, 16.57), 168 (100.00), 152 (5.07), 138 (6.26), 125 (6.01), 97 (1.88), 77 (3.09). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, t_{R1} = 12.408 min (minor), t_{R2} = 14.658 min (major).

2-(2-Methyl-4-dimethylaminophenyl)-2-hydroxyacetic Acid Ethyl Ester (3c):[4c] IR (KBr) ν_{max} 3427, 2981, 2807, 1736, 1666, 1612, 1515, 1448, 1357, 1297, 1110, 1068, 968, 808 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.1 Hz, 1H), 6.56−6.54 (m, 2H), 5.27 (s, 1H), 4.27−4.16 (m, 2H), 3.30 (s, 1H), 2.94 (s, 6H), 2.40 (s, 3H), 1.24 (d, J = 7.2 Hz, 3H); EIMS *m*/*z* (relative intensity) 237 (M$^+$, 26.51), 220 (1.51), 184 (12.11), 164 (100.00), 148 (4.50), 134 (7.13), 121 (15.15), 77 (2.17). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, t_{R1} = 11.567 min (minor), t_{R2} = 15.925 min (major).

2-(2-Methoxy-4-dimethylaminophenyl)-2-hydroxyacetic Acid Ethyl Ester (d):[4c] IR (KBr) ν_{max} 3481, 2978, 1720, 1614, 1522, 1367, 1249, 1201, 1118, 1066, 1033, 980, 811 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 1H), 6.29 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 6.24 (d, J = 2.1 Hz, 1H), 5.17 (d, J = 2.4 Hz, 1H), 4.25−4.18 (m, 2H), 3.84 (s, 3H), 2.97 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H); EIMS *m*/*z* (relative intensity) 253 (M$^+$, 26.51), 180 (100.00), 164 (10.74), 150 (5.50), 121 (1.94), 77 (2.03). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, t_{R1} = 17.550 min (minor), t_{R2} = 20.175 min (major).

2-(1-Methyl-2,3-dihydro-1*H*-indol-5-yl)-2-hydroxyacetic Acid Ethyl Ester (3e):[4c] IR (KBr) ν_{max} 3460, 2979, 2927, 2854, 2811, 1733, 1617, 1498, 1369, 1276,1190, 1085, 1025, 809 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 9.6 Hz, 1H), 7.11 (d, J = 6.3 Hz, 1H), 6.46 (d, J = 8.7 Hz, 1H), 5.06 (s, 1H), 4.33−4.14 (m, 2H), 3.54 (s, 1H), 3.36 (t, J = 8.1 Hz, 2H), 2.78 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); EIMS *m*/*z* (relative intensity) 235 (M$^+$, 31.19), 205 (4.58), 180 (12.26), 162 (100.00), 132 (28.33), 117 (7.77), 91 (3.86), 77 (1.98). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, t_{R1} = 11.400 min (minor), t_{R2} = 14.692 min (major).

2-(1-Methyl-1,2,3,4-tetrahydroquinolin-6-yl)-2-hydroxyacetic Acid Ethyl Ester (3f):[4c] IR (KBr) ν_{max} 3435, 2980, 2935, 1732, 1614, 1514, 1323, 1201, 1095, 1024, 808 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (dd, J = 1.5 Hz, 8.5 Hz, 1H), 6.98 (d, J = 1.5 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 5.02 (s, 1H), 4.30−4.12 (m, 2H), 3.23 (t, J = 5.7 Hz, 2H), 2.88 (s, 3H), 2.76 (t, J = 6.3 Hz, 2H), 1.99−1.95 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H); EIMS *m*/*z* (relative intensity) 249 (M$^+$, 28.76), 233 (10.64), 205 (2.82), 176 (100.00), 160 (25.68), 146 (6.34), 120 (17.68), 91 (3.00), 77 (2.25). Enantiomeric excess was determined by HPLC on a Chiralcel OJ column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, t_{R1} = 21.050 min (major), t_{R2} = 24.975 min (minor).

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