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Supporting Information

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Direct Organocatalytic Highly Enantio- and Diastereoselective Mannich Reaction of α-Substituted α-Cyanoacetates - A Novel Approach

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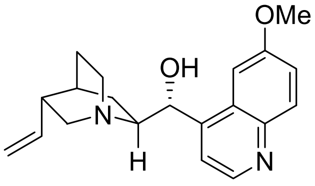
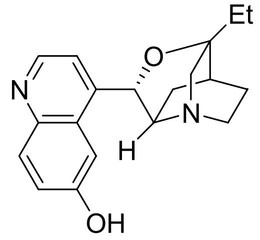
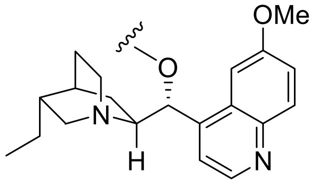
Structures of the catalysts.



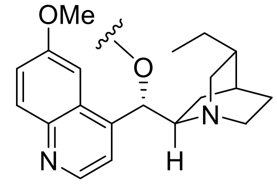
quinine



β-isocupreidine



DHQ



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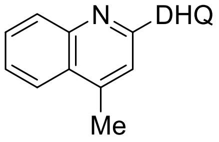

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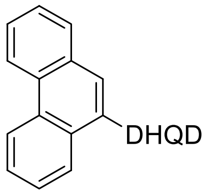
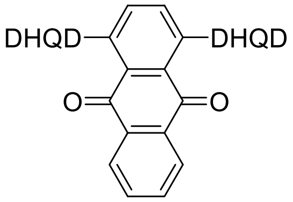
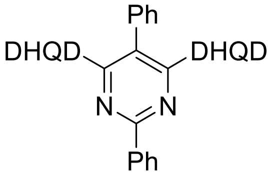


DHQD-PHN



$(DHQD)_2AQN$



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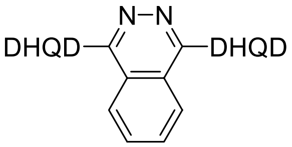


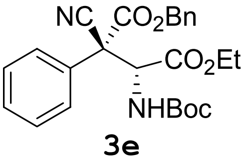
$(DHQD)_2PHAL$

General Methods. NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 MHz (^1H) or 100 MHz (^{13}C), respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals. ^{13}C spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a Micromass LCT spectrometer using electrospray (ES^+) ionization techniques. Flash chromatography (FC) was carried out using the FlashMaster II from

Jones chromatography with columns containing Merck silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed using precoated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ stain. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel ChiralPak AD or Daicel Chiralcel OD columns).

Materials. Solvents were distilled prior to use according to standard techniques. The catalysts are all commercially available and were used as received. The α–iminoesters **2** were prepared according to the procedure by Kobayashi et al.[1] The α-aryl-α-cyanoesters **1** were prepared by deprotonation of the corresponding benzylic nitriles with LDA followed by reaction with chloroformates according to a literature procedure.[2] The β-ketoester **5** was prepared in the same manner starting from 1-indanone.

General Procedure for the Mannich reaction of α-aryl-α-cyanoacetates with imines: To an oven dried Schlenk tube was added $(DHQD)_2PYR$ (0.005 mmol, 4.8 mg), 1.0 mL of CH_2Cl_2, and nucleophile (0.10 mmol). The solution was cooled to -78 °C and a CH_2Cl_2 solution (1.5 mL) of the imine (0.12-0.15 mmol) was added dropwise over a period of 1 h. The mixture was stirred for additional 1-4 h (see below) at -78 °C and was then allowed to warm to room temperature (approx. 10 min). The product was then purified by FC.



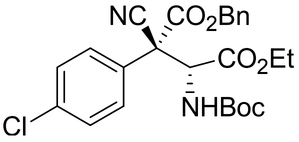
3e

The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (87:13)]; flow rate 1.0 mL/min; *u*-diastereomer: τ_{minor} = 11.3 min, τ_{major} = 14.7 min; *l*-diastereomer: τ_{minor} = 13.3 min, τ_{major} = 23.9 min. Relative areas (*u*/*l*): 89/11 (215 nm).

3e: Reaction time 2.5 h.

u-diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.42-7.46 (m, 2H), 7.28–7.38 (m, 8H), 5.53 (br d, 1H, *J* 10.1 Hz), 5.31 (d, 1H, *J* 12.2 Hz), 5.26 (d, 1H, *J* 12.2 Hz), 5.22 (br d, 1H, *J* 10.0 Hz), 4.06 (m, 2H), 1.28 (s, 9H), 1.06 (t, 3H, *J* 6.9 Hz). ^{13}C NMR δ ($CDCl_3$) 168.2, 166.2, 154.4, 134.1, 130.5, 129.3, 128.9 (2C), 128.6, 128.6 (2C), 128.2 (2C), 127.3 (2C), 116.6, 80.7, 77.2, 69.0, 62.3, 58.7, 28.0 (3C), 13.7. HRMS calc.: $C_{25}H_{28}N_2NaO_6$ 475.1845; found: 475.1855.

The diastereomeric ratio (89/11) was determined by integration of multiplet at 7.42-7.46 (*u*-diastereomer) and multiplet at 7.60-7.64 (*l*-diastereomer).



3f

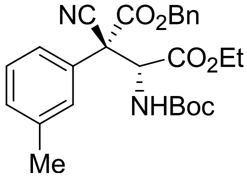
The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*-PrOH (89:11)]; flow rate 1.0 mL/min; *u*-diastereomer: τ_{minor} = 13.5 min, τ_{major} = 20.3 min; *l*-diastereomer: τ_{minor} = 14.6 min, τ_{major} = 18.9 min. Relative areas (*u*/*l*): 80/20 (225 nm).

3f: Reaction time 4.0 h.

u-diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.29-7.39 (m, 9H), 5.50 (br d, 1H, *J* 10.1 Hz), 5.29 (d, 1H, *J* 12.3 Hz), 5.26 (d, 1H, *J* 12.2 Hz), 5.18

(br d, 1H, *J* 10.0 Hz), 4.09 (m, 2H), 1.29 (s, 9H), 1.11 (t, 3H, *J* 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 168.0, 166.0, 154.3, 135.7, 133.9, 129.1, 128.8, 128.9 (2C), 128.8 (2C), 128.6 (2C), 128.3 (2C), 116.4, 80.9, 77.3, 69.2, 62.5, 58.7, 27.9 (3C), 13.7. HRMS calc.: $C_{25}H_{27}ClN_2NaO_6$ 509.1455; found: 509.1458.

The diastereomeric ratio (80/20) was determined by integration of multiplet at 4.09 (*u*-diastereomer) and multiplet at 4.21 (*l*-diastereomer).



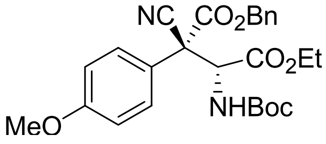
3g

The ee was determined by HPLC using a Chiralpak OD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; *u*-diastereomer: τ_{minor} = 17.3 min, τ_{major} = 13.5 min; *l*-diastereomer: τ_{minor} = 16.0 min, τ_{major} = 12.6 min. Relative areas (*u*/*l*): 86/14 (224 nm).

3g: Reaction time 2.2 h.

u-diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.30-7.35 (m, 5H), 7.27 (s, 1H), 7.25 (d, 1H, *J* 7.6 Hz), 7.22 (t, 1H, *J* 7.6 Hz), 7.15 (d, 1H, *J* 7.4 Hz), 5.52 (br d, 1H, *J* 10.1 Hz), 5.30 (d, 1H, *J* 12.2 Hz), 5.28 (d, 1H, *J* 12.0 Hz), 5.23 (br d, 1H, *J* 10.2 Hz), 4.06 (m, 2H), 2.29 (s, 3H), 1.28 (s, 9H), 1.07 (t, 3H, *J* 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 168.6, 166.5, 154.6, 139.0, 130.6, 134.5, 130.3, 129.0, 128.9, 128.8, 128.5 (2C), 128.0 (2C), 124.6, 117.0, 80.9, 77.5, 69.2, 62.5, 58.9, 28.3 (3C), 21.6, 13.9. HRMS calc.: $C_{26}H_{30}N_2NaO_6$ 489.2002; found: 489.2004.

The diastereomeric ratio (86/14) was determined by integration of singlet at 2.29 (*u*-diastereomer) and singlet at 2.34 (*l*-diastereomer).



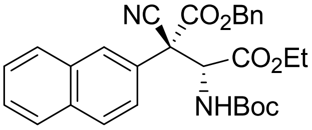
3h

The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; *u*-diastereomer: τ_{minor} = 11.4 min, τ_{major} = 14.2 min; *l*-diastereomer: τ_{minor} = 15.9 min, τ_{major} = 13.0 min. Relative areas (*u*/*l*): 86/14 (217 nm).

3h: Reaction time 2.4 h.

u-diastereomer: ^{1}H NMR (CDCl$_3$) δ 7.34 (d, 2H, *J* 8.9 Hz), 7.28-7.38 (m, 5H), 6.85 (d, 2H, *J* 8.9 Hz), 5.52 (br d, 1H, *J* 10.5 Hz), 5.29 (d, 1H, *J* 12.2 Hz), 5.24 (d, 1H, *J* 12.2 Hz), 5.18 (br d, 1H, *J* 10.5 Hz), 4.06 (m, 2H), 3.78 (s, 3H), 1.29 (s, 9H), 1.08 (t, 3H, *J* 7.0 Hz). ^{13}C NMR (CDCl$_3$) δ 168.2, 166.3, 160.2, 154.4, 134.2, 128.7, 128.6 (2C), 128.6 (2C), 128.1 (2C), 122.2, 116.8, 114.1 (2C), 80.7, 77.3, 68.9, 62.3, 58.7, 55.3, 28.0 (3C), 13.7. HRMS calc.: $C_{26}H_{30}N_2NaO_7$ 505.1951; found: 505.1949.

The diastereomeric ratio (85/15) was determined by integration of multiplet at 4.06 (*u*-diastereomer) and multiplet at 4.19 (*l*-diastereomer).



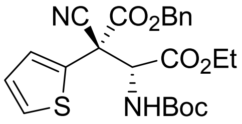
3i

The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; *u*-diastereomer: τ_{minor} = 10.4 min, τ_{major} = 14.6 min; *l*-diastereomer: τ_{minor} = 13.5 min, τ_{major} = 18.4 min. Relative areas (*u*/*l*): 88/12 (240 nm).

3i: Reaction time 3.0 h.

u-diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 1H, *J* 1.9 Hz), 7.77–7.83 (m, 2H), 7.72–7.76 (m, 1H), 7.59 (dd, 1H, *J* 8.7 Hz, 2.0 Hz), 7.48-7.54 (m, 2H), 7.31–7.34 (m, 5H), 5.58 (br d, 1H, *J* 10.5 Hz), 5.34 (br d, 1H, *J* 10.6 Hz), 5.32 (br s, 2H), 4.05 (m, 2H), 1.14 (s, 9H), 1.00 (t, 3H, *J* 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 168.2, 166.2, 154.3, 134.1, 133.2, 132.7, 128.7, 128.7, 128.6 (2C), 128.3, 128.2 (2C), 127.7, 127.4, 127.2, 127.2, 126.8, 124.1, 116.7, 80.6, 77.3, 69.1, 62.3, 58.7, 27.8 (3C), 13.6. HRMS calc.: $C_{29}H_{30}N_2NaO_6$ 525.2002; found: 525.2004.

The diastereomeric ratio (88/12) was determined by integration of doublet at 5.58 (*u*-diastereomer) and doublet at 5.74 (*l*-diastereomer).



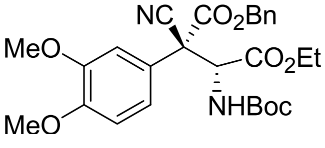
3j

The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; *u*-diastereomer: τ_{minor} = 10.1 min, τ_{major} = 14.5 min; *l*-diastereomer: τ_{minor} = 12.1 min, τ_{major} = 25.8 min. Relative areas (*u*/*l*): 82/18 (217 nm).

3j: Reaction time 2.5 h.

u-diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.30–7.40 (m, 6H), 7.25 (d, 1H, *J* 2.8 Hz), 6.97 (dd, 1H, *J* 5.1 Hz, 3.8 Hz), 5.61 (br d, 1H, *J* 9.9 Hz), 5.31 (d, 1H, *J* 12.2 Hz), 5.27 (d, 1H, *J* 12.2 Hz), 5.21 (br d, 1H, *J* 9.7 Hz), 4.08 (m, 2H), 1.37 (s, 9H), 1.12 (t, 3H, *J* 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 167.7, 165.4, 154.4, 133.9, 131.9, 128.7 (2C), 128.7, 128.6 (2C), 128.2, 128.0, 126.7, 115.7, 80.9, 77.3, 69.4, 62.5, 59.8, 28.0 (3C), 13.7. HRMS calc.: $C_{23}H_{26}N_2NaO_6S$ 481.1409; found: 481.1410.

The diastereomeric ratio (82/18) was determined by integration of doublet at 5.61 (*u*-diastereomer) and doublet at 5.42 (*l*-diastereomer).



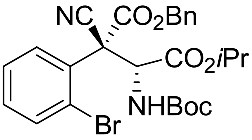
3k

The ee was determined by HPLC using a Chiralpak OD column [hexane/*i*PrOH (97:3)]; flow rate 0.7 mL/min; *u*-diastereomer: τ_{minor} = 30.1 min, τ_{major} = 24.9 min; *l*-diastereomer: τ_{minor} = 21.1 min, τ_{major} = 23.0 min. Relative areas (*u*/*l*): 84/16 (219 nm).

3k: Reaction time 2.1 h.

u-diastereomer: ^{1}H NMR (CDCl$_3$) δ 7.31–7.34 (m, 5H), 7.03 (dd, 1H, *J* 8.5 Hz, 2.3 Hz), 6.84 (d, 1H, *J* 2.2 Hz), 6.80 (d, 1H, *J* 8.5 Hz), 5.53 (br d, 1H, *J* 10.2 Hz), 5.27 (s, 2H), 5.21 (br d, 1H, *J* 10.5 Hz), 4.07 (m, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 1.30 (s, 9H), 1.08 (t, 3H, *J* 7.0 Hz). ^{13}C NMR (CDCl$_3$) δ 168.2, 166.3, 154.4, 149.7, 148.9, 134.2, 128.7, 128.6 (2C), 128.3 (2C), 122.4, 120.0, 116.6, 110.8, 110.0, 80.8, 77.3, 69.0, 62.2, 58.7, 55.9, 55.7, 28.0 (3C), 13.7. HRMS calc.: $C_{27}H_{32}N_2NaO_8$ 535.2056; found: 535.2053.

The diastereomeric ratio (85/15) was determined by integration of double doublet at 7.03 (*u*-diastereomer) and double doublet at 7.19 (*l*-diastereomer).



3m

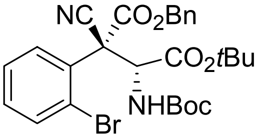
The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; *u*-diastereomer: τ_{minor}

= 8.3 min, τ$_{major}$ = 12.6 min; *l*-diastereomer: τ$_{minor}$ = 15.1 min, τ$_{major}$ = 11.6 min. Relative areas (*u*/*l*): 85/15 (216 nm).

3m: Reaction time 3.0 h.

u-diastereomer: ^{1}H NMR (CDCl$_3$) δ 7.60 (d, 1H, *J* 7.0 Hz), 7.25–7.40 (m, 5H), 7.10–7.25 (m, 3H), 5.71 (br d, 1H, *J* 10.4 Hz), 5.53 (br d, 1H, *J* 10.4 Hz), 5.32 (s, 2H), 4.93 (h, 1H, *J* 6.1 Hz), 1.28 (s, 9H), 1.22 (d, 3H, *J* 6.3 Hz), 1.02 (d, 3H, *J* 6.1 Hz). ^{13}C NMR (CDCl$_3$) δ 167.7, 165.8, 154.5, 135.5, 135.0, 134.0, 130.8, 130.5, 128.7, 128.6 (2C), 128.5 (2C), 127.6, 123.1, 115.3, 80.5, 77.3, 70.6, 69.4, 55.9, 28.1 (3C), 21.4, 21.2. HRMS calc.: $C_{26}H_{29}BrN_2NaO_6$ 567.1107; found: 567.1125.

The diastereomeric ratio (85/15) was determined by integration of doublet at 7.60 (*u*-diastereomer) and doublet at 7.56 (*l*-diastereomer).



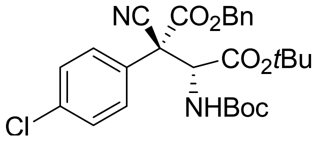
3n

The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (85:15)]; flow rate 1.0 mL/min; *u*-diastereomer: τ$_{minor}$ = 9.7 min, τ$_{major}$ = 12.7 min; *l*-diastereomer: τ$_{minor}$ = 15.5 min, τ$_{major}$ = 15.5 min. Relative areas (*u*/*l*): 98/2 (218 nm).

3n: Reaction time 4.3 h.

u-diastereomer: ^{1}H NMR (CDCl$_3$) δ 7.61 (dd, 1H, *J* 9.0 Hz, 1.9 Hz), 7.33–7.40 (m, 5H), 7.16–7.28 (m, 3H), 5.50 (br d, 1H, *J* 10.4 Hz), 5.48 (br d, 1H, *J* 10.4 Hz), 5.32 (br s, 2H), 1.33 (s, 9H), 1.28 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 167.1, 165.6, 154.2, 135.1, 133.8, 130.9, 130.7 (2C), 130.5, 128.7, 128.6 (2C), 128.5, 127.5, 123.5, 115.6,

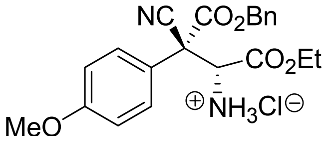
84.0, 80.3, 77.3, 69.3, 55.7, 28.0 (3C), 27.5 (3C). HRMS calc.: $C_{27}H_{31}BrN_2NaO_6$ 581.1263; found: 581.1260.
In the ^1H NMR spectrum only the *u*-diastereomer was observed.



3o

The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; *u*-diastereomer: τ_{minor} = 8.4 min, τ_{major} = 8.7 min; *l*-diastereomer: τ_{minor} = 15.5 min, τ_{major} = 17.1 min.

3o: Reaction time 3.1 h.
u-diastereomer: ^1H NMR ($CDCl_3$) δ 7.39 (d, 2H, *J* 8.7 Hz), 7.27-7.36 (m, 7H), 5.44 (br d, 1H, *J* 10.2 Hz), 5.28 (d, 1H, *J* 13.0 Hz), 5.23 (d, 1H, *J* 12.0 Hz), 5.08 (br d, 1H, *J* 10.3 Hz), 1.30 (s, 9H), 1.29 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 166.6, 166.0, 154.5, 135.6, 134.0, 129.4, 129.0 (2C), 128.9 (2C), 128.8, 128.7 (2C), 128.3 (2C), 116.5, 84.3, 80.8, 77.2, 69.2, 59.0, 28.0 (3C), 27.6 (3C). HRMS calc.: $C_{27}H_{31}ClN_2NaO_6$ 537.1768; found: 537.1754.

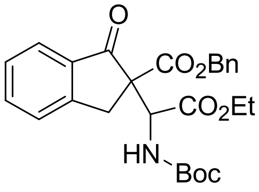


4

Compound **3h** (96 mg, 0.199 mmol) was placed in a dried flask equipped with a magnetic stirrer under argon. Then, 1.2 mL of a 4M solution of HCl in 1,4-dioxane was added by syringe. The mixture was stirred at ambient temperature until TLC showed complete disappearance of the starting material (5 h). The solvent was removed in vacuo. Dry THF was added and the mixture was reevaporated to yield the HCl-salt of the amine as an off-white solid. Yield: 97%.

The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (85:15)]; flow rate 1.0 mL/min; *u*-diastereomer: τ_{minor} = 35.6 min, τ_{major} = 27.7 min; *l*-diastereomer: τ_{minor} = 33.5 min, τ_{major} = 41.8 min. Relative areas (*u*/*l*): 83/17 (242 nm).

4: *u*-diastereomer: ^{1}H NMR (CDCl$_3$) δ 8.05–8.82 (br s, 3H), 7.42 (d, 2H, *J* 8.1 Hz), 7.22–7.35 (m, 5H), 6.88 (d, 2H, *J* 8.2 Hz), 5.42 (d, 1H, *J* 12.3 Hz), 5.37 (d, 1H, *J* 12.3 Hz), 5.02 (s 1H), 3.89-4.06 (m, 2H), 3.79 (s, 3H), 0.92 (t, 3H, *J* 6.8 Hz). ^{13}C NMR (CDCl$_3$) δ 165.1, 164.6, 160.7, 134.2, 128.4 (2C), 128.4, 128.3 (2C), 128.2 (2C), 120.1, 115.5, 114.8 (2C), 70.0, 63.3, 57.1, 55.4, 54.7, 13.4. HRMS calc.: $C_{21}H_{22}N_2HO_5$ 383.1601; Found: 383.1595.
The diastereomeric ratio (85/15) was determined by integration of doublet at 6.88 (*u*-diastereomer) and doublet at 6.97 (*l*-diastereomer).



6

The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; major diastereomer: τ_{minor} = 13.2 min, τ_{major} = 16.5 min; minor diastereomer: τ_{minor} = 14.7 min, τ_{major} = 25.0 min. Relative areas (major/minor): 98/2 (257 nm).

6: Reaction time: 24 h.
Major diastereomer: ^{1}H NMR (CDCl$_3$) δ 7.69 (d, 1H, *J* 7.7 Hz), 7.54 (td, 1H, *J* 7.4 Hz, 0.9 Hz), 7.37 (d, 1H, *J* 7.7 Hz), 7.31 (t, 1H, *J* 7.4 Hz), 7.19-7.27 (m, 5H), 5.56 (br d, 1H, *J* 8.7 Hz), 5.16 (d,

1H, *J* 9.5 Hz), 5.10 (d, 1H, *J* 12.4 Hz), 5.06 (d, 1H, *J* 12.6 Hz), 3.87-4.03 (m, 2H), 3.65 (d, 1H, *J* 17.8 Hz), 3.38 (d, 1H, *J* 17.7 Hz), 1.30 (s, 9H), 1.00 (t, 3H, *J* 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 199.7, 169.5, 168.5, 155.0, 152.6, 135.5, 135.1, 135.0, 135.3, 128.3 (2C), 128.1, 127.8 (2C), 126.1, 124.6, 80.1, 67.5, 61.6, 61.6, 56.6, 34.7, 28.0 (3C), 13.7. HRMS calc.: $C_{26}H_{29}NNaO_7$ 490.1842; found: 490.1841. $[\alpha]_D^{20}$ +47 (*c* 1.0, CH_2Cl_2).

The diastereomeric ratio (98/2) was determined by integration of doublet at 5.16 (major-diastereomer) and doublet at 4.87 (minor-diastereomer).

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