Supporting Informations

Enantioselective Michael Additions of Nitromethane by a Catalytic Double Activation Method (CDAM) Using Chiral Lewis Acid and Achiral Amine Catalysts

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Materials: 3,5-Dimethylpyrazole is commercially available. 4-Bromo-3,5-dimethylpyrazole and 4-iodo-3,5-dimethylpyrazole were prepared from 3,5-dimethylpyrazole by bromination and iodination, respectively. (*E*)-2-Alkenoyl chlorides and unsaturated amides of pyrazoles were prepared according to methods reported previously.^{1,2} 3-Crotonoyl-2-oxazolidinone **3** was prepared according to a reported procedure from crotonoyl chloride and 2-oxazolidinone which were purchased commercially.³ Raney nickel was purchased from Aldrich (Raney 2800 nickel, slurry in water, pore size is ca 50 micron, surface area is 80 - 100 m²/g).

Survey of Lewis acid catalysts: The anhydrous complex of (*R,R*)-DBFOX/Ph - nickel(II) hexafluoroantimonate was less reactive as a catalyst (48 hours, 19%, 31% ee) as compared as the aqua complex of (*R,R*)-DBFOX/Ph - nickel(II) perchlorate. Attempted use of several anhydrous (*R,R*)-DBFOX/Ph - Mtl(II) complex catalysts [Mtl = Ni(II), Zn(II), Cu(II), Mg(II)] did not mediate the reaction at all. The anhydrous (*R,R*)-DBFOX/Ph - Mtl(II) [Mtl = Ni(II), Zn(II), Cu(II), Mg(II)] complex catalysts were prepared according to the reported methods.⁴

Survey of Amine catalysts:

TMP gave the best balance for the catalytic activity and enantioselectivity (table shown below).

General procedure for the enantioselective Michael addition reactions catalyzed by the aqua complex of (*R,R*)-DBFOX/Ph - nickel(II) perchlorate:

The reaction of nitromethane with 1-crotonoyl-3,5-dimethylpyrazole (**1a**) is described as a typical example: A mixture of (*R,R*)-DBFOX/Ph (27.9 mg, 0.061 mmol) and nickel(II) perchlorate hexahydrate (22.3 mg, 0.061 mmol) in THF (3 ml) was stirred at room temperature for 5 min, and then 1-crotonoyl-3,5-dimethylpyrazole (**1a**, 100 mg, 0.61 mmol) was added. After stirring at -78 °C for an additional 5 min, a solution of nitromethane (3 ml) and TMP (10.3 µl, 0.061 mmol) was added. The mixture was warmed up to -20 °C and stirred for 96 h. The reaction mixture was poured into a saturated solution of ammonium chloride (5 ml) and extracted with ethyl acetate (8 ml x 3). The combined extracts were washed with brine, dried with magnesium sulfate, and evaporated in vacuo. The residue was passed through a flash silica gel column (eluted with hexane / diethyl ether (3:1 v/v)) to give analytically pure Michael adduct **2a** (117 mg, 85%).

Other aqua complexes were prepared according to a similar procedure by using Co(II), Zn(II), Cu(II) perchlorate hexahydrate and used for the reactions with **1a**.

3,5-Dimethyl-1-(3-methyl-4-nitrobutanoyl)pyrazole

(**2a**): Colorless oil; $[\alpha]_D^{25} = -8.69$ (93% ee estimated by chiral hplc analysis on Daicel Chiral Cell ADH, hexane / 2-propanol (99:1 v/v), 0.5 ml/min, t_r (minor) = 23.9 min, t_r (major) = 26.0 min, $c = 1.00$, CHCl₃); IR (neat) $\nu = 2970, 2930, 1724, 1585, 1553, 1458, 1435, 1412, 1379, 1335, 1312, 1246, 1140, 1001, 962, 804, \text{ and } 748 \text{ cm}^{-1}$; ¹H NMR (CDCl₃) $\delta = 1.08$ (3H, d, $J = 6.8$ Hz, CHCH₃), 2.23 (3H, s, 5'-CH₃), 2.54 (3H, d, $J = 0.7$ Hz, 3'-CH₃), 2.97 (1H, o, $J = 6.8$ Hz, H-3), 3.19 (1H, dd, $J_{2-3} = 6.3$ and $J_{\text{gem}} = 17.6$ Hz, one of H-2), 3.23 (1H, dd, $J_{2-3} = 7.1$ and $J_{\text{gem}} = 17.6$ Hz, the other of H-2), 4.39 (1H, dd, $J_{4-3} = 7.6$ and $J_{\text{gem}} = 12.2$ Hz, one of H-4), 4.56 (1H, dd, $J_{4-3} = 6.1$ and $J_{\text{gem}} = 12.2$ Hz, the other of H-4), and 5.98 (1H, s, 4'-CH₃); ¹³C NMR (CDCl₃) $\delta = 13.77$ (5'-CH₃), 14.49 (3'-CH₃), 17.58 (CH₃CH), 28.96 (C-3), 38.70 (C-2), 80.35 (C-4), 111.44 (C-4'), 144.17 (C-5'), 152.37 (C-3'), and 171.44 (C-1); Mass (75 eV, rel intensity, %) m/z 226 (base peak, $M^+ + 1$), 179 (21), 154 (14), 137 (18), and 97 (93). HRMS Calcd for C₁₀H₁₆N₃O₃ ($M^+ + 1$): 226.1192. Found: 226.1194.

Survey of Amine Catalysts

Amine	Time/h	Yield/%	ee/% ^a
TMP	5	97	84
DBU	5	97	72
Dicyclohexylamine	5	quant	74
1,1,3,3-Tetramethylguanidine	6	94	71
<i>N,N</i> -Diisopropylethylamine	6	79	74
1,8-Bis(dimethylamino)naphthalene	12	96	74
<i>N,N</i> -Diisopropylethylenediamine	48	78	69
Triton B	96	44	88
Piperidine	96	54	67
Pyrrolidine	96	31	70
Monoethanolamine	96	20	64
2,6-Lutidine	96	17	51
1,1,3,3-Hexamethyldisilazane	96	12	69
Tris(trimethylsilyl)amine	96	11	69
2,2,4,4,6,6-Hexamethylcyclotrisilazane	96	18	76

^aDetermined by chiral cell AD.

4-Bromo-3,5-dimethyl-1-(3-methyl-4-nitrobutanoyl)pyrazole (2b): Colorless prism (from ethyl acetate / hexane); mp 73 °C; $[\alpha]_D^{25} = -5.99$ (98% ee estimated by chiral hplc analysis on Daicel Chiral Cell ODH, hexane / 2-propanol (99:1 v/v), 0.5 ml/min, t_r (minor) = 29.1 min, t_r (major) = 31.0 min, $c = 1.00$, CHCl_3); IR (KBr) $\nu = 3433, 2990, 2972, 2924, 2889, 1722, 1686, 1576, 1547, 1493, 1468, 1437, 1375, 1335, 1288, 1279, 1204, 1163, 1138, 1123, 1101, 1074, 1034, 1015, 991, 953, 916, 889, 820, 754, \text{ and } 727 \text{ cm}^{-1}$; ^1H NMR (CDCl_3) $\delta = 1.17$ (3H, d, $J = 6.8 \text{ Hz}$, 3- CH_3), 2.23 (3H, s, 5'- CH_3), 2.25 (3H, s, 3'- CH_3), 2.96 (1H, o, $J = 6.8 \text{ Hz}$, H-3), 3.17 (1H, dd, $J_{2-3} = 6.5$ and $J_{\text{gem}} = 17.4 \text{ Hz}$, one of H-2), 3.23 (1H, dd, $J_{2-3} = 7.0$ and $J_{\text{gem}} = 17.4 \text{ Hz}$, the other of H-2), 4.40 (1H, dd, $J_{4-3} = 7.2$ and $J_{\text{gem}} = 12.1 \text{ Hz}$, one of H-4), and 4.54 (1H, dd, $J_{4-3} = 6.0$ and $J_{\text{gem}} = 12.2 \text{ Hz}$, the other of H-4); ^{13}C NMR (CDCl_3) $\delta = 12.70$ (5'- CH_3), 13.47 (3'- CH_3), 17.52 (3- CH_3), 28.98 (C-3), 38.12 (C-2), 80.23 (C-4), 102.60 (C-4'), 141.35 (C-5'), 151.01 (C-3'), and 170.89 (C-1); Mass (75 eV, rel intensity, %) m/z 305 (4), 303 (4, M^+), 177 (36), 176 (base peak), 175 (60), 174 (99), 173 (24), 102 (13), 96 (12), 95 (82), 83 (25), 69 (14), 66 (22), and 65 (33). Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{BrN}_3\text{O}_3$: C, 39.49; H, 4.64; N, 13.82. Found: C, 39.75; H, 4.64; N, 13.75.

4-Iodo-3,5-dimethyl-1-(3-methyl-4-nitrobutanoyl)pyrazole (2c): Colorless prism (from ethyl acetate / hexane); mp 80 °C; $[\alpha]_D^{25} = -5.00$ (98% ee estimated by chiral hplc analysis on Daicel Chiral Cell ODH, hexane / 2-propanol (99:1 v/v), 0.5 ml/min, t_r (minor) = 29.5 min, t_r (major) = 32.5 min, $c = 1.02$, CHCl_3); IR (KBr) $\nu = 2968, 2986, 2920, 1724, 1545, 1489, 1468, 1435, 1394, 1391, 1373, 1346, 1329, 1310, 1279, 1238, 1202, 1192, 1161, 1061, 989, 951, 912, 889, 754, 743, \text{ and } 729 \text{ cm}^{-1}$; ^1H NMR (CDCl_3) $\delta = 1.17$ (3H, d, $J = 6.8 \text{ Hz}$, 3- CH_3), 2.26 (3H, s, 5'- CH_3), 2.60 (3H, s, 3'- CH_3), 2.96 (1H, m, H-3), 3.18 (1H, dd, $J_{2-3} = 6.5$ and $J_{\text{gem}} = 17.6 \text{ Hz}$, one of H-2), 3.24 (1H, dd, $J_{2-3} = 7.2$ and $J_{\text{gem}} = 17.6 \text{ Hz}$, the other of H-2), 4.40 (1H, dd, $J_{4-3} = 7.2$ and $J_{\text{gem}} = 12.1 \text{ Hz}$, one of H-4), and 4.54 (1H, dd, $J_{4-3} = 6.0$ and $J_{\text{gem}} = 12.1 \text{ Hz}$, the other of H-4); ^{13}C NMR (CDCl_3) $\delta = 14.44$ (5'- CH_3), 15.47 (3'- CH_3), 17.48 (3- CH_3), 28.95 (C-3), 38.03 (C-2), 73.47 (C-4'), 80.20 (C-4), 145.02 (C-5'), 153.59 (C-3'), and 170.59 (C-1); Mass (75 eV, rel intensity, %) m/z 352 (12, $\text{M}^+ + 1$), 351 (2), 139 (12), 138 (31), 137 (61), and 120 (11). Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{IN}_3\text{O}_3$: C, 34.20; H, 4.03; N, 11.93. Found: C, 34.20; H, 4.03; N, 12.04.

1-(3-Ethyl-4-nitrobutanoyl)-3,5-dimethylpyrazole (2d): Colorless oil; $[\alpha]_D^{25} = +3.66$ (95% ee estimated by chiral hplc analysis on Daicel Chiral Cell ADH, hexane / 2-propanol (99:1 v/v), 0.3 ml/min, t_r (minor) = 29.8 min, t_r (major) = 31.6 min, $c = 1.20$, CHCl_3); IR (neat) $\nu = 2968, 2932, 2880, 1726, 1585, 1556, 1462, 1435, 1412, 1385, 1346, 1327, 1312, 1269, 1242, 1225, 1194, 1175, 1140, 1038, 1026, 1011, 986, 962, 806, \text{ and } 746 \text{ cm}^{-1}$; ^1H NMR (CDCl_3) $\delta = 1.01$ (3H, d, $J = 7.5 \text{ Hz}$, CH_3CH_2), 1.56 (2H, q, $J = 7.5 \text{ Hz}$, CH_3CH_2), 2.23 (3H, s, 5'- CH_3), 2.54 (3H, s, 3'- CH_3), 2.96 (1H, septet, $J = 6.5 \text{ Hz}$, H-3), 3.22 (1H, dd, $J_{2-3} = 7.7$ and $J_{\text{gem}} = 17.9 \text{ Hz}$, one of H-2), 3.28 (1H, dd, $J_{2-3} = 6.0$ and $J_{\text{gem}} = 17.9 \text{ Hz}$, the other of H-2), 4.50 (1H, dd, $J_{4-3} = 6.5$ and $J_{\text{gem}} = 12.1 \text{ Hz}$, one of H-4), 4.57 (1H, dd, $J_{4-3} = 6.3$ and $J_{\text{gem}} = 12.1 \text{ Hz}$, the other of H-4), and 5.98 (1H, s, H-4'); ^{13}C NMR (CDCl_3) $\delta = 10.88$ (C-5), 13.76 (5'- CH_3), 14.49 (3'- CH_3), 24.50 (CH_2CH_3), 35.14 (C-3), 36.32 (C-2), 78.32 (C-4), 111.39 (C-4'), 141.15 (C-5'), 152.32 (C-3'), and 171.82 (C-1); Mass (75 eV, rel intensity, %) m/z 240 (52, $\text{M}^+ + 1$), 155 (27), 139 (13), 138 (33), and 137 (65). HRMS Calcd for $\text{C}_{11}\text{H}_{18}\text{N}_3\text{O}_3$ ($\text{M}^+ + 1$): 240.1348. Found: 240.1347.

3,5-Dimethyl-1-(4-nitro-3-propylbutanoyl)pyrazole (2e): Colorless oil; $[\alpha]_D^{25} = +7.25$ (91% ee estimated by chiral hplc analysis on Daicel Chiral Cell ADH), hexane / 2-propanol (99:1 v/v), 0.3 ml/min, t_r (minor) = 28.1 min, t_r (major) = 30.6 min, $c = 1.20$, CHCl_3); IR (neat) $\nu = 2961, 2932, 2874, 1726, 1585, 1556, 1479, 1454, 1435, 1412, 1385, 1337, 1310, 1254, 1225, 1192, 1175, 1140, 1026, 993, 984, 962, 804, \text{ and } 748 \text{ cm}^{-1}$; ^1H NMR (CDCl_3) $\delta = 0.94$ (3H, t, $J = 7.0 \text{ Hz}$, $\text{CH}_3\text{C}_2\text{H}_4$), 1.39-1.51 (4H, m, $\text{CH}_3\text{C}_2\text{H}_4$), 2.23 (3H, s, 5'- CH_3), 2.54 (3H, d, $J = 0.7 \text{ Hz}$, 3'- CH_3), 2.83 (1H, septet, $J = 6.5 \text{ Hz}$, H-3), 3.21 (1H, dd, $J_{2-3} = 7.5$ and $J_{\text{gem}} = 17.9 \text{ Hz}$, one of H-2), 3.28 (1H, dd, $J_{2-3} = 6.0$ and $J_{\text{gem}} = 17.9 \text{ Hz}$, the other of H-2), 4.49 (1H, dd, $J_{4-3} = 6.5$ and $J_{\text{gem}} = 12.3 \text{ Hz}$, one of H-4), 4.54 (1H, dd, $J_{4-3} = 6.0$ and $J_{\text{gem}} = 12.3 \text{ Hz}$, the other of H-4), and 5.97 (1H, s, H-4'); ^{13}C NMR (CDCl_3) $\delta = 13.76$ ($\text{CH}_3\text{C}_2\text{H}_4$), 13.76 (5'- CH_3), 14.49 (3'- CH_3), 19.66 ($\text{CH}_3\text{CH}_2\text{CH}_2$), 33.45 ($\text{CH}_3\text{CH}_2\text{CH}_2$), 35.76 (C-3), 36.66 (C-2), 78.69 (C-4), 111.37 (C-4'), 144.14 (C-5'), 152.31 (C-3'), and 171.83 (C-1); Mass (75 eV, rel intensity, %) m/z 254 (46, $\text{M}^+ + 1$), 207 (13), 109 (13), 96 (13), 95 (18), 81 (13), and 69 (17). HRMS Calcd for $\text{C}_{12}\text{H}_{20}\text{N}_3\text{O}_3$ ($\text{M}^+ + 1$): 254.1505. Found: 254.1506.

3,5-Dimethyl-1-[4-nitro-3-(iso-propyl)butanoyl]pyrazole (2f): Colorless oil; $[\alpha]_D^{25} = +6.05$ (91% ee estimated by chiral hplc analysis on Daicel Chiral Cell ADH, hexane / 2-propanol (99:1 v/v), 0.3 ml/min, t_r (minor) = 27.2 min, t_r (major) = 28.7 min, $c = 1.07$, CHCl_3); IR (neat) $\nu = 2964, 2930, 1724, 1686, 1584, 1553, 1437, 1412, 1381, 1344, 1321, 1240, 1175, 1140, 1024, 962, 870, 806, \text{ and } 737 \text{ cm}^{-1}$; ^1H NMR (CDCl_3) $\delta = 0.99 - 1.01$ (6H, br d, $J = 6.8 \text{ Hz}$, $\text{CH}(\text{CH}_3)_2$), 1.87 - 1.95 (1H, m, H-5), 2.32 (3H, s, 5'- CH_3), 2.53 (3H, d, $J = 0.7 \text{ Hz}$, 3'- CH_3), 2.78 - 2.86 (1H, m, H-3), 3.12 (1H, dd, $J_{2-3} = 8.0$ and $J_{\text{gem}} = 17.6 \text{ Hz}$, one of H-2), 3.30 (1H, dd, $J_{2-3} = 5.1$ and $J_{\text{gem}} = 17.6 \text{ Hz}$, the other of H-2), 4.48 (1H, dd, $J_{4-3} = 6.8$ and $J_{\text{gem}} = 17.6 \text{ Hz}$, one of H-4), 4.54 (1H, dd, $J_{4-3} = 7.0$ and $J_{\text{gem}} = 17.6 \text{ Hz}$, the other of H-4), and 5.97 (1H, s, H-4'); ^{13}C NMR (CDCl_3) $\delta = 13.76$ ($\text{CH}_3\text{C}_2\text{H}_4$), 13.76 (5'- CH_3), 14.49 (3'- CH_3), 19.66 ($\text{CH}_3\text{CH}_2\text{CH}_2$), 33.45 ($\text{CH}_3\text{CH}_2\text{CH}_2$), 35.76 (C-3), 36.66 (C-2), 78.69 (C-4), 111.37 (C-4'), 144.14 (C-5'), 152.31 (C-3'), and 171.83 (C-1); Mass (75 eV, rel intensity, %) m/z 254 (46, $\text{M}^+ + 1$), 207 (13), 109 (13), 96 (13), 95 (18), 81 (13) and 69 (17). HRMS Calcd for $\text{C}_{12}\text{H}_{20}\text{N}_3\text{O}_3$ ($\text{M}^+ + 1$): 254.1505. Found: 254.1507.

1-(3-Cyclohexyl-4-nitrobutanoyl)-3,5-dimethylpyrazole (2g): Colorless oil; $[\alpha]_D^{25} = +13.69$ (91% ee estimated by chiral hplc analysis on Daicel Chiral Cell AD, hexane / 2-propanol (99:1 v/v), 0.5 ml/min, t_r (minor) = 16.1 min, t_r (major) = 18.1 min, $c = 1.00$, CHCl_3); IR (neat) $\nu = 2928, 2855, 1726, 1585, 1553, 1481, 1447, 1410, 1383, 1339, 1250, 1175, 1140, 962, 806, \text{ and } 750 \text{ cm}^{-1}$; ^1H NMR (CDCl_3) $\delta = 1.01 - 1.29$ (6H, m, C_6H_{11}), 1.48 - 1.76 (5H, m, C_6H_{11}), 2.23 (3H, s, 5'- CH_3), 2.53 (3H, d, $J = 0.7 \text{ Hz}$, 3'- CH_3), 2.76 - 2.84 (1H, m, H-3), 3.14 (1H, dd, $J_{2-3} = 7.7$ and $J_{\text{gem}} = 17.6 \text{ Hz}$, one of H-2), 3.33 (1H, dd, $J_{2-3} = 5.1$ and $J_{\text{gem}} = 17.6 \text{ Hz}$, the other of H-2), 4.52 (1H, d, $J_{4-3} = 6.5 \text{ Hz}$, H-4), and 5.97 (1H, $J = 0.7 \text{ Hz}$, H-4'); ^{13}C NMR (CDCl_3) $\delta = 13.79$ (5'- CH_3), 14.49 (3'- CH_3), 26.22, 26.28, 26.33, 29.33, 29.89 (each of C_6H_{11}), 34.38 (C-3), 38.70 (C_6H_{11}), 39.16 (C-2), 111.35 (C-4'), 144.18 (C-5'), 152.27 (C-3'), and 172.16 (C-1); Mass (75 eV, rel intensity, %) m/z 294 (24, $\text{M}^+ + 1$), 121 (11), 111 (11), 109 (24), 107 (14), 96 (11), 95 (31), 93 (14), 91 (12), 83 (24), 81 (29), 79 (12), 71 (15), 69 (29), and 67 (19). HRMS Calcd for $\text{C}_{15}\text{H}_{24}\text{N}_3\text{O}_3$ ($\text{M}^+ + 1$): 294.1818. Found: 294.1820.

1-[3-(tert-Butyl)-4-nitrobutanoyl]-3,5-dimethylpyrazole (2h): Colorless oil;

$[\alpha]_D^{25} = +10.32$ (95% ee estimated by chiral hplc analysis on Daicel Chiral Cell ODH and AD connected columns), hexane / 2-propanol (98:2 v/v), 0.5 ml/min, t_r (minor) = 30.7 min, t_r (major) = 32.5 min, $c = 1.01$, CHCl_3 ; IR (neat) $\nu = 2966, 2932, 2876, 1730, 1585, 1556, 1479, 1435, 1412, 1385, 1333, 1244, 1177, 1140, 1018, 995, 962, 893, 806, \text{ and } 748 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 1.00$ (9H, s, $\text{C}(\text{CH}_3)_3$), 2.34 (3H, s, $5'\text{-CH}_3$), 2.52 (3H, s, $3'\text{-CH}_3$), 2.91 (1H, m, H-3), 3.09 (1H, dd, $J_{2-3} = 7.7$ and $J_{\text{gem}} = 17.4$ Hz, one of H-2), 3.45 (1H, dd, $J_{2-3} = 4.3$ and $J_{\text{gem}} = 17.4$ Hz, the other of H-2), 4.37 (1H, dd, $J_{4-3} = 7.7$ and $J_{\text{gem}} = 13.0$ Hz, one of H-4), 4.59 (1H, dd, $J_{4-3} = 4.6$ and $J_{\text{gem}} = 13.0$ Hz, the other of H-4), and 5.97 (1H, s, H-4'); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 13.80$ ($5'\text{-CH}_3$), 14.48 ($3'\text{-CH}_3$), 33.38 (C-3), 34.65 (C-2), 42.59 ($\text{C}(\text{CH}_3)_3$), 77.28 (C-4), 111.30 (C-4'), 144.27 (C-5'), 152.18 (C-3'), and 172.37 (C-1); Mass (75 eV, rel intensity, %) m/z 268 (base peak, $\text{M}^+ + 1$), 221 (11), 155 (17), 138 (22), and 137 (47). HRMS Calcd for $\text{C}_{13}\text{H}_{22}\text{N}_3\text{O}_3$ ($\text{M}^+ + 1$): 268.1661. Found: 268.1661.

3,5-Dimethyl-1-[4-nitro-3-(1-propenyl)butanoyl]pyrazole (2i): Colorless oil; $[\alpha]_D^{25} = +24.89$ (75% ee estimated by chiral hplc analysis on Daicel Chiral Cell AD, hexane / 2-propanol (99:1 v/v), 0.5 ml/min, t_r (minor) = 21.2 min, t_r (major) = 23.0 min, $c = 1.14$, CHCl_3); IR (neat) $\nu = 2928, 1724, 1585, 1556, 1435, 1381, 1348, 962, 806 \text{ and } 748 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 1.65$ (3H, d, $J = 6.5$ Hz, $\text{CH}=\text{CHCH}_3$), 2.23 (3H, s, $5'\text{-CH}_3$), 2.53 (3H, s, $3'\text{-CH}_3$), 3.23 (1H, dd, $J_{2-3} = 7.0$ and $J_{\text{gem}} = 17.4$ Hz, one of H-2), 3.34 (1H, dd, $J_{2-3} = 6.5$ and $J_{\text{gem}} = 17.4$ Hz, the other of H-2), 3.45-3.54 (1H, m, H-3), 4.44 (1H, dd, $J_{4-3} = 8.5$ and $J_{\text{gem}} = 12.0$ Hz, one of H-4), 4.58 (1H, dd, $J_{4-3} = 6.0$ and $J_{\text{gem}} = 12.0$ Hz, the other of H-4), 5.40 (1H, dd, $J = 8.5$ and $J = 15.2$ Hz, $\text{CH}_3\text{CH}=\text{CH}$), 5.67 (1H, dq, $J = 6.5$ and $J = 15.2$ Hz, $\text{CH}_3\text{CH}=\text{CH}$), and 5.97 (1H, s, H-4'); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 13.67$ ($5'\text{-CH}_3$), 14.42 ($3'\text{-CH}_3$), 17.84 ($\text{CH}=\text{CHCH}_3$), 37.36 (C-2), 37.38 (C-3), 78.96 (C-4), 111.34 (C-4'), 127.68 ($\text{CH}=\text{CHCH}_3$), 129.73 ($\text{CH}=\text{CHCH}_3$), 144.10 (C-5'), 152.32 (C-3'), and 170.97 (C-1); Mass (75 eV, rel intensity, %) m/z 252 (86, $\text{M}^+ + 1$), 251 (11), 205 (17), 136 (16), 96 (11), and 95 (15). Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.36; H, 6.92; N, 16.12.

1-(3-Methoxycarbonyl-4-nitrobutanoyl)-3,5-dimethylpyrazole (2j): Colorless oil; $[\alpha]_D^{25} = -9.11$ (84% ee estimated by chiral hplc analysis on Daicel Chiral Cell ODH), hexane / 2-propanol (95:5 v/v), 1 ml/min, t_r (major) = 17.6 min, t_r (minor) = 20.4 min, $c = 1.01$, CHCl_3 ; IR (neat) $\nu = 2957, 2930, 1732, 1587, 1556, 1485, 1435, 1410, 1393, 1337, 1234, 1211, 1173, 1140, 1065, 984, 962, 883, 853, 814, 769, \text{ and } 741 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 2.23$ (3H, s, $5'\text{-CH}_3$), 2.52 (3H, s, $3'\text{-CH}_3$), 3.51 (1H, dd, $J_{2-3} = 6.3$ and $J_{\text{gem}} = 18.1$ Hz, one of H-2), 3.70 (1H, dd, $J_{2-3} = 5.6$ and $J_{\text{gem}} = 18.1$ Hz, the other of H-2), 3.71-3.84 (1H, m, H-3), 3.76 (3H, s, CO_2CH_3), 4.73 (1H, dd, $J_{4-3} = 5.1$ and $J_{\text{gem}} = 14.7$ Hz, one of H-4), 4.59 (1H, dd, $J_{4-3} = 6.8$ and $J_{\text{gem}} = 14.7$ Hz, the other of H-4), and 5.99 (1H, s, H-4'); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 13.58$ ($5'\text{-CH}_3$), 14.14 ($3'\text{-CH}_3$), 34.25 (C-3), 38.34 (C-2), 52.64 (CO_2CH_3), 74.35 (C-4), 111.46 (C-4'), 144.12 (C-5'), 152.70 (C-3'), 170.42 (C-1), and 171.04 (CO_2CH_3); Mass (75 eV, rel intensity, %) m/z 270 (base peak, $\text{M}^+ + 1$), 269 (3), 223 (10), 155 (12), 138 (19), 137 (36), 109 (13), 96 (13), 95 (19), 91 (10), 83 (11), and 81 (12). HRMS Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}_3$ ($\text{M}^+ + 1$): 252.1348. Found: 252.1348.

3,5-Dimethyl-1-(4-nitro-3-phenylbutanoyl)pyrazole (2k): Colorless solid; mp 92 °C; $[\alpha]_D^{25} = +58.79$ (74% ee estimated by chiral hplc analysis on Daicel Chiral Cell

AD, hexane / 2-propanol (99:1 v/v), 1 ml/min, t_r (major) = 18.4 min, t_r (minor) = 20.9 min, $c = 1.00$, CHCl_3 ; IR (KBr) $\nu = 3034, 2980, 2932, 1730, 1604, 1580, 1547, 1489, 1458, 1412, 1383, 1342, 1310, 1234, 1200, 1178, 1140, 1026, 989, 976, 959, 876, 818, 766, 745, 731, \text{ and } 704 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 2.22$ (3H, s, $5'\text{-CH}_3$), 2.47 (3H, d, $J = 0.7$ Hz, $3'\text{-CH}_3$), 3.51 (1H, dd, $J_{2-3} = 7.2$ and $J_{\text{gem}} = 17.6$ Hz, one of H-2), 3.66 (1H, dd, $J_{2-3} = 7.2$ and $J_{\text{gem}} = 17.6$ Hz, the other of H-2), 4.18 (1H, q, $J = 7.2$ Hz, H-3), 4.67 (1H, dd, $J_{4-3} = 8.2$ and $J_{\text{gem}} = 12.8$ Hz, one of H-4), 4.80 (1H, dd, $J_{4-3} = 6.8$ and $J_{\text{gem}} = 12.8$ Hz, the other of H-4), and 5.94 (1H, s, H-4'), 7.30 (5H, m, H-Ar); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 13.73$ ($5'\text{-CH}_3$), 14.35 ($3'\text{-CH}_3$), 38.51 (C-3), 39.54 (C-2), 79.52 (C-4), 111.38 (C-4'), 127.50, 127.83, 128.95 (each of CH, Ar), 138.71 (qC, Ar), 144.16 (C-5'), 152.42 (C-3'), and 170.67 (C-1); Mass (75 eV, rel intensity, %) m/z 288 (38, $\text{M}^+ + 1$), 155 (26), 139 (11), 138 (30), 137 (62), and 107 (16). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.46; H, 5.98; N, 14.47.

1-[3-(1,3-Benzodioxol-5-yl)-4-nitrobutanoyl]-3,5-dimethylpyrazole (2l): Colorless oil; $[\alpha]_D^{25} = +60.97$ (98% ee estimated by chiral hplc analysis on Daicel Chiral Cell AD, hexane / 2-propanol (98:2 v/v), 1 ml/min, t_r (major) = 24.9 min, t_r (minor) = 28.1 min, $c = 1.00$, CHCl_3); IR (KBr) $\nu = 2926, 1724, 1556, 1585, 1556, 1504, 1489, 1445, 1412, 1385, 1364, 1329, 1312, 1248, 1040, 962, 812, 762, \text{ and } 644 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 2.22$ (3H, s, $5'\text{-CH}_3$), 2.47 (3H, s, $3'\text{-CH}_3$), 3.44 (1H, dd, $J_{2-3} = 7.2$ and $J_{\text{gem}} = 17.6$ Hz, one of H-2), 3.62 (1H, dd, $J_{2-3} = 7.5$ and $J_{\text{gem}} = 17.6$ Hz, the other of H-2), 4.10 (1H, q, $J = 7.2$ Hz, H-3), 4.61 (1H, dd, $J_{4-3} = 8.7$ and $J_{\text{gem}} = 12.6$ Hz, one of H-4), 4.75 (1H, dd, $J_{4-3} = 6.5$ and $J_{\text{gem}} = 12.6$ Hz, the other of H-4), 5.91 (2H, s, OCH_2O), 5.95 (1H, s, H-4'), and 6.71 - 6.78 (5H, m, H-Ar); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 13.68$ ($5'\text{-CH}_3$), 14.29 ($3'\text{-CH}_3$), 38.38 (C-3), 39.38 (C-2), 79.70 (C-4), 101.12 (OCH_2O), 107.76, 108.56 (each Ar), 111.37 (C-4'), 120.83, 132.33 (each qC of Ar), 144.12 (C-5'), 147.11 (qC of Ar), 147.99 (qC of Ar), 152.40 (C-3'), and 170.59 (C-1); Mass (75 eV, rel intensity, %) m/z 332 (18, $\text{M}^+ + 1$), 285 (23), 189 (19), 154 (34), 148 (21), 123 (22), 111 (25), 109 (41), 111 (25), 109 (41), 107 (23), 105 (20), 95 (55), 93 (25), 91 (31), 85 (22), 83 (46), 81 (50), 79 (23), 77 (18), and 71 (29). HRMS Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_5$ ($\text{M}^+ + 1$): 332.1246. Found: 332.1241.

1-[3-(2-Furyl)-4-nitrobutanoyl]-3,5-dimethylpyrazole (2m): Colorless oil; $[\alpha]_D^{25} = +34.47$ (97% ee estimated by chiral hplc analysis on Daicel Chiral Cell AD, hexane / 2-propanol (99:1 v/v), 1 ml/min, t_r (major) = 19.0 min, t_r (minor) = 21.1 min, $c = 1.23$, CHCl_3); IR (neat) $\nu = 2924, 2853, 1724, 1556, 1433, 1379, 1333, 1240, 1146, 1015, 962, 916, 810, \text{ and } 741 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 2.15$ (3H, s, $5'\text{-CH}_3$), 2.43 (3H, s, $3'\text{-CH}_3$), 3.44 (1H, dd, $J_{2-3} = 7.5$ and $J_{\text{gem}} = 17.9$ Hz, one of H-2), 3.60 (1H, dd, $J_{2-3} = 6.8$ and $J_{\text{gem}} = 17.6$ Hz, the other of H-2), 4.21 (1H, q, $J = 7.0$ Hz, H-3), 4.66 (1H, dd, $J_{4-3} = 3.4$ and $J_{\text{gem}} = 13.3$ Hz, one of H-4), 4.71 (1H, dd, $J_{4-3} = 7.2$ and $J_{\text{gem}} = 13.3$ Hz, the other of H-4), 5.89 (1H, s, H-4'), 6.13 (1H, d, $J = 3.1$ Hz, Furyl), 6.21 (1H, app t, $J = 2.4$ Hz, Furyl), and 7.27 (1H, app t, $J = 0.9$ Hz, Furyl); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 13.74$ ($5'\text{-CH}_3$), 14.30 ($3'\text{-CH}_3$), 33.38 (C-3), 36.18 (C-2), 77.12 (C-4), 107.12 (C-4'), 110.43, 111.43, 142.26 (each of CH, Furyl), 144.18 (C-5'), 151.55 (C-3'), 152.56 (qC, Furyl), and 170.43 (C-1); Mass (75 eV, rel intensity, %) m/z 278 (38, $\text{M}^+ + 1$), 231 (26), 149 (12), 135 (19), 121 (11), 109 (15), 107 (11), 94 (13), 91 (11), 83 (15), 81 (18), 79 (10), 71 (11), and 69 (20). Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.58; H, 5.53; N, 14.95.

3,5-Dimethyl-1-[4-nitro-3-(2-

thienyl)butanoyl]pyrazole (2n): Pale-yellow oil; $[\alpha]_D^{25} = +63.11$ (97% ee estimated by chiral hplc analysis on Daicel Chiral Cell AD, hexane / 2-propanol (99:1 v/v), 1 ml/min, t_r (major) = 21.4 min, t_r (minor) = 33.4 min, $c = 1.00$, CHCl_3); IR (neat) $\nu = 3111, 2964, 2928, 2855, 1724, 1585, 1556, 1481, 1435, 1410, 1385, 1362, 1325, 1248, 1140, 1040, 982, 962, 851, 812, 758, \text{ and } 704\text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 2.23$ (3H, s, $5'\text{-CH}_3$), 2.50 (3H, d, $J = 0.7$ Hz, $3'\text{-CH}_3$), 3.57 (1H, dd, $J_{2-3} = 7.0$ and $J_{\text{gem}} = 17.6$ Hz, one of H-2), 3.71 (1H, dd, $J_{2-3} = 7.0$ and $J_{\text{gem}} = 17.6$ Hz, the other of H-2), 4.51 (1H, q, $J = 7.0$ Hz, H-3), 4.69 (1H, dd, $J_{4-3} = 7.7$ and $J_{\text{gem}} = 12.6$ Hz, one of H-4), 4.82 (1H, dd, $J_{4-3} = 6.5$ and $J_{\text{gem}} = 12.6$ Hz, the other of H-4), 5.96 (1H, d, $J = 0.7$ Hz, H-4'), 6.14 (1H, dd, $J = 3.6$ and $J = 5.1$ Hz, Thienyl), 6.98 (1H, m, Thienyl), and 7.27 (1H, dd, $J = 1.2$ and $J = 5.1$ Hz, Thienyl); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 13.77$ ($5'\text{-CH}_3$), 14.38 ($3'\text{-CH}_3$), 33.99 (C-3), 39.40 (C-2), 79.81 (C-4), 111.50 (C-4'), 124.77, 125.59, 127.08 (each Thienyl), 141.43 (qC of Thienyl), 144.23 (C-5'), 152.60 (C-3'), and 170.30 (C-1); Mass (75 eV, rel intensity, %) m/z 296 (3), 295 (7), 294 (38, $\text{M}^+ + 1$), 247 (25), 151 (19), 137 (13), 135 (10), 123 (10), and 110 (16). Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$: C, 53.23; H, 5.15; N, 14.32. Found: C, 53.56; H, 5.21; N, 14.21.

Synthetic application to total synthesis of (R)-(-)-Rolipram (5o):

3-Cyclopentyloxy-4-methoxybenzaldehyde: A mixture of 3-hydroxy-4-methoxybenzaldehyde (isovanillin) (5 g, 32.9 mmol), bromocyclopentane (17.7 ml, 165 mmol) and potassium carbonate (22.8 g, 165 mmol) in acetone (470 ml) was stirred vigorously for 96 h under reflux. After the mixture had been cooled down to room temperature, the insoluble solid was filtered off and the filtrate was evaporated in vacuo. The residue was treated with water (200 ml), and the aqueous solution was extracted with ethyl acetate (300 ml x 3). The combined extracts were washed with brine, dried over magnesium sulfate, and then evaporated in vacuo. The residue was dissolved in a small amount of ethyl acetate and the solution was chromatographed through a short silica gel column with hexane / ethyl acetate (1:3 v/v) to provide analytically pure 3-cyclopentyloxy-4-methoxybenzaldehyde (5.87 g, 81%): Pale reddish yellow oil; IR (neat) $\nu = 2961, 2872, 2839, 1688, 1585, 1510, 1434, 1265, 1238, 1161, 1132, \text{ and } 1022\text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 1.60 - 1.64$ (2H, m, C_5H_9), 1.82 - 2.02 (2H, m, C_5H_9), 3.93 (3H, s, OCH_3), 4.84 - 4.88 (1H, m, C_5H_9), 6.97 (1H, $J = 8.7$ Hz, Ar), 7.41 (1H, dd, $J = 8.2$ and $J = 2.0$ Hz, Ar), 7.45 (1H, d, $J = 2.0$ Hz, Ar), and 9.84 (1H, s, CHO); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 24.02$ (CH_2 of $c\text{-C}_5\text{H}_9$), 32.65 (CH_2 of $c\text{-C}_5\text{H}_9$), 56.06 (OCH_3), 80.36 (CH of $c\text{-C}_5\text{H}_9$), 110.66, 111.91, 126.29 (each Ar), 129.91, 148.16, 155.31 (each qC, Ar), and 191.05 (CHO); Mass (75 eV, rel intensity, %) m/z 221 (base peak, $\text{M}^+ + 1$), 220 (38), 219 (19), 153 (17), 152 (56), and 151 (16). Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$: C, 70.89; H, 7.32. Found: C, 70.76; H, 7.32.

3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-propanoic acid: Under dry nitrogen, sodium hydride (1.92 g, 80.1 ml) was added to a solution of ethyl phosphate (3.43 ml, 26.7 mmol) in anhydrous ethyleneglycol dimethyl ether (200 ml) and the resulting suspension was stirred at room temperature until the evolution of hydrogen ceased. A solution of bromoacetic acid (3.71 g, 26.7 mmol) in anhydrous ethyleneglycol dimethyl ether (67 ml) was added over 2 h. After stirring for 2 h, 3-cyclopentyloxy-4-methoxybenzaldehyde (5.87 g, 26.7 mmol) in ethyleneglycol dimethyl ether (10 ml) was added in one portion and stirring was continued at room temperature

for 24 h. The resulting suspension was warmed at reflux for 30 min. The reaction mixture was poured into ice water (200 ml) and extracted with diethyl ether (300 ml x 3). The combined aqueous extracts were acidified with hydrochloric acid (12 M) and extracted with ethyl acetate (300 ml x 3). The combined extracts were washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was recrystallized from ethyl acetate to provide analytically pure 3-(3-cyclopentyloxy-4-methoxyphenyl)-2-propanoic acid (6.37 g, 91%): Brownish solid; mp 191 °C; IR (KBr) $\nu = 2963, 2872, 2845, 2675, 2588, 2513, 1699, 1682, 1626, 1595, 1618, 1464, 1431, 1410, 1445, 1337, 1312, 1296, 1267, 1250, 1211, 1167, 1138, 1026, 995, 974, 847, \text{ and } 816\text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 1.62 - 1.69$ (2H, m, C_5H_9), 1.80 - 2.02 (2H, m, C_5H_9), 3.89 (3H, s, OCH_3), 4.78 - 4.82 (1H, m, C_5H_9), 6.30 (1H, d, $J_{2-3} = 15.7$ Hz, H-2), 6.87 (1H, $J = 8.5$ Hz, Ar), 7.09 (1H, d, $J = 1.9$ Hz, Ar), 7.12 (1H, dd, $J = 1.9$ and $J = 8.5$ Hz, Ar), and 7.72 (1H, d, $J_{3-2} = 15.7$ Hz, H-3); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 24.07$ (CH_2 of $c\text{-C}_5\text{H}_9$), 32.79 (CH_2 of $c\text{-C}_5\text{H}_9$), 56.03 (OCH_3), 80.55 (CH of $c\text{-C}_5\text{H}_9$), 111.53, 113.43, 114.55 (each of CH, Ar), 122.80 (C-2), 126.88, 147.19, 147.89 (each of qC, Ar), 152.54 (C-3), and 168.46 (C-1); Mass (75 eV, rel intensity, %) m/z 263 (27, $\text{M}^+ + 1$), 262 (28), 195 (11), 194 (30), 177 (12), 155 (26), 139 (129), 138 (30), 137 (57), and 120 (10). Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4$: C, 68.68; H, 6.92. Found: C, 68.60; H, 6.98.

(E)-1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-propenoyl]-3,5-dimethyl-pyrazole (1o): To a solution of (E)-3-(3-cyclopentyloxy-4-methoxyphenyl)-2-propanoic acid (2.00 g, 7.63 mmol) in anhydrous dichloromethane (15 ml) was added, dropwise at 0 °C under nitrogen, oxalyl chloride (0.99 ml, 11.4 mmol). The resulting yellow solution was allowed to warm up to room temperature and stirred for 6 h. The dichloromethane and oxalyl chloride were evaporated in vacuo to give a dark brown solid. The residue was dissolved in dry dichloromethane (15 ml) and, to this solution, a solution (15 ml) of 3,5-dimethylpyrazole (881 mg, 9.16 mmol) and pyridine (0.66 ml, 9.16 mmol) was added dropwise at 0 °C under nitrogen. After stirring at 0 °C for 12 h and at room temperature for 6 h, the reaction mixture was poured into water (20 ml) and extracted with dichloromethane (80 ml x 3). The combined extracts were washed with brine, dried with magnesium sulfate, and evaporated in vacuo. The residue was chromatographed through a short column of silica gel with hexane / diethyl ether (95:5 v/v) to give (E)-1-[3-(3-cyclopentyloxy-4-methoxyphenyl)-2-propenoyl]-3,5-dimethyl-pyrazole (1o) (7.21 g, 84%): Pale yellow solid; mp 94 °C; IR (KBr) $\nu = 2961, 2951, 2926, 1699, 1620, 1603, 1574, 1506, 1481, 1443, 1429, 1412, 1371, 1352, 1304, 1267, 1234, 1217, 1165, 1140, 1026, 1015, 997, 980, 856, \text{ and } 804\text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) $\delta = 1.59 - 1.68$ (2H, m, C_5H_9), 1.81 - 2.02 (6H, m, C_5H_9), 2.30 (3H, s, $5'\text{-CH}_3$), 2.62 (3H, d, $J = 0.7$ Hz, $3'\text{-CH}_3$), 3.88 (3H, s, OCH_3), 4.84 - 4.88 (1H, m, C_5H_9), 6.00 (1H, d, $J = 0.7$ Hz, H-4'), 6.87 (1H, $J = 8.5$ Hz, Ar), 7.19 (1H, d, $J = 1.9$ Hz, Ar), 7.25 (1H, dd, $J = 1.9$ and $J = 8.5$ Hz, Ar), 7.75 (1H, d, $J_{2-3} = 15.9$ Hz, H-2), and 7.85 (1H, d, $J_{3-2} = 15.9$ Hz, H-3); $^{13}\text{C NMR}$ (CDCl_3) $\delta = 13.78$ ($5'\text{-CH}_3$), 14.63 ($3'\text{-CH}_3$), 24.07 (CH_2 , C_5H_9), 32.75 (CH_2 , C_5H_9), 55.93 (OCH_3), 80.57 (CH, C_5H_9), 111.18, 111.45, 114.33, 115.12 (each Ar), 123.01 (C-2), 127.64 (qC, Ar), 144.28 (C-5'), 146.19, 147.69 (each qC, Ar), 151.62 (C-3), 152.47 (C-3'), 165.63 (C-1); Mass (75 eV, rel intensity, %) m/z 341 (37, $\text{M}^+ + 1$), 340 (44), 307 (24), 289 (12), 245 (37), 177 (69), 155 (26), 139 (11), 138 (28), 137 (53), 120 (10), and 79 (10). Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.65; H, 7.15; N, 8.29.

3,5-Dimethyl-1-[4-nitro-3-(3-cyclopentyloxy-4-methoxyphenyl)butanoyl]pyrazole (2o): A mixture of (*R,R*)-DBFOX/Ph (40.3 mg, 0.088 mmol) and nickel(II) perchlorate hexahydrate (32.2 mg, 0.088 mmol) in THF (4.4 ml) was stirred at room temperature for 5 min, and then (*E*)-1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-propenyl]-3,5-dimethyl-pyrazol (**1 o**, 300 mg, 0.88 mmol) was added. After stirring at -78°C for an additional 5 min, a solution of nitromethane (4.4 ml) and TMP (14.9 μl , 0.088 mmol) was added. The mixture was warmed up to -20°C and stirred for 168 h. The reaction mixture was poured into a saturated solution of ammonium chloride (5 ml) and extracted with ethyl acetate (10 ml $\times$ 3). The combined extracts were washed with brine, dried with magnesium sulfate, and evaporated in vacuo. The residue was passed through a flash silica gel column (eluted with hexane / diethyl ether (4:1 v/v)) to give analytically pure Michael adduct **2o** (321 mg, 91%): Colorless solid; mp 113°C ; $[\alpha]_{\text{D}}^{25} = +60.19$ (98% ee estimated by chiral hplc analysis of *N*-Boc derivative **6o**, $c = 1.00$, CHCl_3); IR (KBr) $\nu = 3437, 2951, 2924, 2874, 2841, 1726, 1593, 1555, 1516, 1448, 1437, 1423, 1376, 1348, 1335, 1258, 1236, 1209, 1167, 1144, 1022, 997, 982, 962, 877, 820, 808, 772, 737, 694$, and 650 cm^{-1} ; ^1H NMR (CDCl_3) $\delta = 1.59\text{--}1.61$ (2H, m, $H\text{-C}_5\text{H}_9$), $1.79\text{--}1.94$ (6H, m, $H\text{-C}_5\text{H}_9$), 2.22 (3H, s, $5'\text{-CH}_3$), 2.47 (3H, s, $3'\text{-CH}_3$), 3.43 (1H, dd, $J_{2-3} = 7.0$ and $J_{\text{gem}} = 17.4$ Hz, the other of H-2), 3.69 (1H, dd, $J_{2-3} = 7.7$ and $J_{\text{gem}} = 17.4$ Hz, the other of H-2), 3.81 (3H, s, OCH_3), 4.11 (1H, m, H-3), 4.64 (1H, dd, $J_{4-3} = 8.2$ and $J_{\text{gem}} = 12.3$ Hz, one of H-4), 4.75 (1H, m, OCH), 4.76 (1H, dd, $J_{4-3} = 6.5$ and $J_{\text{gem}} = 12.3$ Hz, the other of H-4), 5.95 (1H, s, H-4'), and 6.79 (3H, m, $H\text{-Ar}$); ^{13}C NMR (CDCl_3) $\delta = 13.75$ ($5'\text{-CH}_3$), 14.38 ($3'\text{-CH}_3$), $23.99, 32.70$ (each CH_2 of Cyclopentyl), 38.47 (C-3), 39.31 (C-2), 55.96 (OCH_3), 79.84 (C-4), 111.38 (C-4'), $112.23, 114.50, 119.42$ (each Ar), 130.86 (qC of Ar), 144.16 (C-5'), $147.73, 149.53$ (each qC of Ar), 152.35 (C-3'), and 170.79 (C-1); Mass (75 eV, rel intensity, %) m/z 402 (22, $\text{M}^+ + 1$), 401 (4), 355 (24), 191 (17), 177 (11), 155 (24), 150 (12), 139 (11), 138 (29), 137 (53), 120 (13), 107 (21), 91 (17), 90 (15), 89 (19), and 77 (18). Anal. Calcd for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.89; H, 6.78; N, 10.46.

(4*R*)-4-(3-Cyclopentyloxy-4-methoxy)-2-pyrrolidinone [(*R*)-(-)-Rolipram] (5o): A solution of **2o** (305 mg, 0.76 mmol) and Raney nickel (336 mg) in ethanol / dichloromethane (12.3 ml (3:2 v/v)) was stirred under a hydrogen atmosphere at room temperature for 96 h. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was subjected to column chromatography on silica gel with acetone / ethyl acetate (1:3 v/v) to provide analytically pure **5o** (150 mg, 72%): Colorless prism (from ethyl acetate / hexane); mp 130°C ; >99% ee, $[\alpha]_{\text{D}}^{25} = -29.99$ ($c = 0.10$, CH_3OH); $[\alpha]_{\text{D}}^{25} = -33.94$ ($c = 1.09$, CH_3OH); IR (KBr) $\nu = 3196, 3096, 2961, 2872, 1709, 1686, 1605, 1585, 1518, 1489, 1464, 1418, 1369, 1348, 1304, 1267, 1238, 1213, 1163, 1142, 1030, 1005, 972, 816, 799, 775$, and 691 cm^{-1} ; ^1H NMR (CDCl_3) $\delta = 1.52\text{--}1.54$ (2H, m, $c\text{-C}_5\text{H}_9$), $1.71\text{--}1.85$ (6H, m, $c\text{-C}_5\text{H}_9$), 2.39 (1H, dd, $J_{3-4} = 8.9$ and $J_{\text{gem}} = 16.9$ Hz, one of H-3), 2.63 (1H, dd, $J_{5-4} = 8.9$ and $J_{\text{gem}} = 16.9$ Hz, one of H-5), 3.31 (1H, dd, $J_{5-4} = 7.5$ and $J_{\text{gem}} = 9.2$ Hz, one of H-5), 3.54 (1H, q, $J = 8.5$ Hz, H-4), 3.68 (1H, t, $J_{5-4} = 8.7$ Hz, the other of H-5), $4.67\text{--}4.69$ (1H, m, OCH), $6.69\text{--}6.76$ (3H, m, Ar), and 7.05 (1H, br s, NH); ^{13}C NMR (CDCl_3) $\delta = 23.88$ (CH, C_6H_{11}), 32.67 (CH, C_6H_{11}), 38.18 (C-3), 39.81 (C-4), 49.76 (C-5), 56.00 (OCH_3), 80.45 (OCH), $112.10, 113.76, 118.68$ (each Ar), $134.52, 147.74, 149.03$ (each qC, Ar), and 177.95 (C-2); Mass (75 eV, rel intensity, %) m/z 275

(18, M^+), 208 (10), 207 (82), 151 (10), 150 (base peak), and 135 (14). Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$: C, 69.79; H, 7.68; N, 5.09. Found: C, 69.51; H, 7.75; N, 5.01.

(4*R*)-*N*-tert-Butoxycarbonyl-4-(3-cyclopentyloxy-4-methoxy)-2-pyrrolidinone (6o): To a solution of (*R*)-(-)-Rolipram **5o** (95.5 mg, 0.35 mmol) in CH_2Cl_2 (3.89 ml) were added, under nitrogen, triethylamine (0.05 mmol, 0.35 mmol) and 4-(dimethylamino)pyridine (85.5 mg, 0.7 mmol). The resulting solution was cooled to 0°C and then di-*tert*-butyl dicarbonate (0.16 ml, 0.7 mmol) was added by use of syringe and the solution was stirred for additional 15 min. The resulting yellowish solution was allowed to warm up to room temperature and stirred for 12 h. The reaction mixture was evaporated in vacuo and the residue was chromatographed through a short column packed with silica gel with hexane / ethyl acetate (1:1 v/v) as eluent to provide analytically pure **6o** (131 mg, 100%): Colorless solid; mp 78°C ; 98% ee, $[\alpha]_{\text{D}}^{25} = -4.59$ (98% ee estimated by chiral hplc analysis on Daicel Chiral Cell OD), hexane / 2-propanol (9:1 v/v), 0.8 ml/min, t_r (major) = 16.4 min, t_r (minor) = 22.1 min, $c = 1.00$, CHCl_3); IR (KBr) $\nu = 3003, 2964, 2936, 2872, 1794, 1769, 1695, 1520, 1464, 1454, 1379, 1367, 1354, 1300, 1261, 1238, 1159, 1140, 1105, 1026, 976, 826, 781, 752$, and 719 cm^{-1} ; ^1H NMR (CDCl_3) $\delta = 1.54$ (9H, s, $\text{OBu-}t$), $1.59\text{--}1.65$ (2H, m, $c\text{-C}_5\text{H}_9$), $1.79\text{--}1.98$ (6H, m, $c\text{-C}_5\text{H}_9$), 2.68 (1H, dd, $J_{3-4} = 9.7$ and $J_{\text{gem}} = 17.2$ Hz, one of H-3), 2.87 (1H, dd, $J_{3-4} = 8.5$ and $J_{\text{gem}} = 17.2$ Hz, the other of H-3), 3.47 (1H, q, H-4), 3.66 (1H, dd, $J_{5-4} = 8.5$ and $J_{\text{gem}} = 10.9$ Hz, one of H-5), 3.83 (3H, s, OCH_3), 4.13 (1H, dd, $J_{5-4} = 8.2$ and $J_{\text{gem}} = 10.9$ Hz, the other of H-5), $4.75\text{--}4.79$ (1H, m, OCH), and $6.75\text{--}6.85$ (3H, m, $H\text{-Ar}$); ^{13}C NMR (CDCl_3) $\delta = 23.97$ (CH, $c\text{-C}_5\text{H}_9$), 27.97 ($\text{OBu-}t$), 32.75 ($c\text{-C}_5\text{H}_9$), 36.03 (C-4), 40.51 (C-3), 56.08 (OCH_3), 80.54 (OCH), 82.93 ($\text{OBu-}t$), $112.20, 113.67, 118.73$ (each Ar), $132.94, 147.91$ (each qC of Ar), 149.33 (C=O, urethane), 149.88 (qC, Ar), and 173.11 (C=O, lactam); Mass (75 eV, rel intensity, %) m/z 376 ($\text{M}+1$, 23), 375 (46), 321 (17), 320 (91), 298 (24), 274 (10), 252 (37), 208 (31), 207 (60), 192 (20), 139 (11), 138 (29), 137 (55), and 120 (11). Anal. Calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 66.91; H, 7.80; N, 3.72.

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