Synthesis of α-Methylene-β-Pyrrole Esters *via* Organocatalytic Regioselective Allylic Substitutions of Morita-Baylis-Hillman Acetates

Su-Hyun Kwon and Chang-Woo Cho*

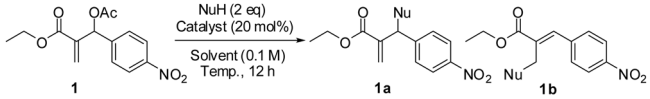
*Department of Chemistry, Kyungpook National University, Daegu 702-701, Korea. *E-mail: cwcho@knu.ac.kr*
Received July 15, 2008

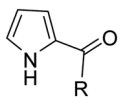
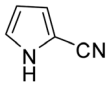
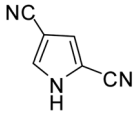
Key Words : Pyrrole, Organocatalytic allylic substitution, Morita-Baylis-Hillman acetate

The Morita-Baylis-Hillman (MBH) reaction is one of the most efficient methods for the synthesis of α-methylene-β-hydroxy carbonyl compounds as versatile intermediates for pharmaceuticals and biologically active natural products.[1] Considerable efforts have been devoted to the development of MBH reactions and their application to the synthesis of biologically potent compounds. Recently, stoichiometric[2] and organocatalytic[3,4] variants of allylic substitutions of MBH acetates *via* a tandem S_N2'-S_N2' mechanism have come to light. Different types of nucleophiles such as $TsNH_2$, phthalimides (*N*-based nucleophiles),[3,4a,c,d] dialkyl malonates, 2-silyloxyfuran (*C*-based nucleophiles),[3d,4b,d,e] and phenols (*O*-based nucleophiles)[3b,d] have been reported in the organocatalytic allylic substitutions of MBH acetates. However, to the best of our knowledge, there are no examples stating the use of pyrroles as nucleophiles in the organocatalytic allylic substitutions of MBH acetates, even though pyrroles are important moieties in many natural products,[5] pharmaceuticals,[6] and materials.[7] In this study, we report the first examples of organocatalytic allylic substitutions using pyrroles as nucleophiles for the synthesis of various α-methylene-β-pyrrole esters.

To explore the feasibility of pyrroles as nucleophiles in the organocatalytic allylic substitutions of MBH acetates, the allylic substitutions of MBH acetate **1** with a variety of pyrroles were performed in the presence of PPh_3 and DABCO as representative *P*- and *N*-based organocatalysts, respectively (Table 1). Neither of these catalysts provided the desired product **1a** when added to a THF solution of MBH acetate **1** and pyrrole at ambient temperature (Table 1, entries 1, 2). It was speculated that the leaving group was not sufficiently basic for the deprotonation of pyrrole as the pronucleophile. Therefore, in order to increase the acidity of pyrrole, electron-withdrawing groups were introduced into the 2-position of pyrrole. When an electron-withdrawing group such as a trichloromethylcarbonyl group or an ethyl ester group was introduced into the 2-position of pyrrole in the presence of PPh_3 or DABCO as the catalyst, respectively, the corresponding substitution products **1a** were not obtained (Table 1, entries 3, 4). Even 2-cyanopyrrole did not undergo allylic substitution with **1** in a THF solution in the presence of PPh_3 (Table 1, entry 5). In addition, in the case of PBu_3 as the catalyst, the allylic substitutions gave no desired allylic substitution product (Table 1, entry 6). On the contrary, when PPh_3 was replaced with DABCO with the other reaction conditions remaining the same, the allylic substitution product **1a** was obtained in 34% yield along with the regioisomeric by-product **1b** in 23% yield (Table 1, entry 7). However, under the same reaction conditions, the replacement of THF with toluene did not yield the desired allylic substitution product (Table 1. entry 8). Hence, it was concluded that DABCO is the appropriate catalyst to be used in the substitution reactions of **1** with pyrroles as the pronucleophiles (Table 1, entry 5, 6 *vs* 7). When 2,4-dicyanopyrrole, whose pK_a is lower than that of 2-cyanopyrrole, was used as the pronucleophile in the substitution reaction of **1** in the presence of DABCO in THF at ambient temperature, the yield of **1a** was marginally increased, *i.e.*, up to 49%, but **1b** was still generated in 25% yield (Table 1, entry 9). To

Table 1. Optimization of organocatalytic allylic substitutions of MBH acetates **1** with pyrrole nucleophiles[a]



Entry	NuH	Catalyst	Solvent	Temp. (°C)	Yield (%)	
					1a	**1b**
1		PPh_3	THF	rt	nd[b]	nd[b]
2		DABCO	THF	rt	nd[b]	nd[b]
3	 R = CCl_3, OEt	PPh_3	THF	rt	nd[b]	nd[b]
4		DABCO	THF	rt	nd[b]	nd[b]
5		PPh_3	THF	rt	nd[b]	nd[b]
6		PBu_3	THF	rt	nd[b]	17
7		DABCO	THF	rt	34	23
8		DABCO	Toluene	rt	nd[b]	nd[b]
9		DABCO	THF	rt	49	25
10		DABCO	Toluene	rt	26	nd[b]
11		**DABCO**	**Toluene**	**60**	**98**	**nd[b]**

[a]Procedure: To a reaction vessel charged with **1** (0.5 mmol, 100 mol%), NuH (1.0 mmol, 200 mol%), and catalyst (0.1 mmol, 20 mol%) was added solvent (5.0 mL, 0.1 M). The reaction was allowed to stir for 12 h, at which point the reaction mixture was evaporated onto silica gel and the product was isolated by silica gel chromatography. [b]Not detected.

prevent the formation of **1b**, the substitution reaction was tested under identical conditions in a series of solvents. Among the sovents screened, toluene proved to be superior to the rest. Hence, even though the allylic substitution of MBH acetate **1** with 2,4-dicyanopyrrole in toluene in the presence of DABCO at ambient temperature afforded **1a** in only 26% yield, fortunately, **1b** was not formed (Table 1, entry 10). By comparing the yields of the substitution reaction of **1** at various temperatures, 60 °C was identified as the ideal temperature that afforded **1a** in 98% yield as a single regioisomer (Table 1, entry 11).

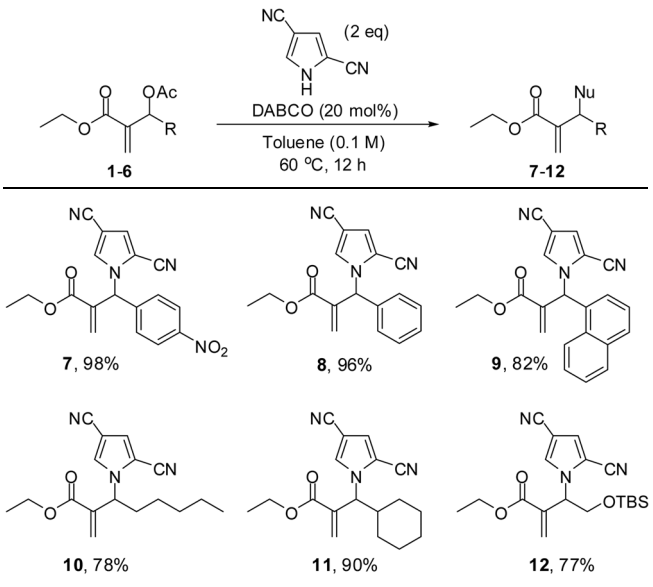
Under these optimized conditions, we explored the DABCO-catalyzed allylic substitutions of MBH acetates **1-6**, which bear aromatic, aliphatic, cyclohexyl, and TBS-protected hydroxymethyl substituents, with 2,4-dicyanopyrrole in toluene at 60 °C (Table 2). The corresponding allylic substitution products, which are α-methylene-β-pyrrole esters, **7-12** were obtained with good regioselectivity, as determined by ^{1}H NMR analysis, *via* a tandem S_N2'-S_N2' mechanism in good to excellent yields.

To expand the scope of pyrroles as nucleophiles in the DABCO-catalyzed regioretentive allylic substitutions of MBH acetates, the substitution reactions of the same with a series of pyrroles were explored under the optimized reaction conditions (Table 3). Among the pyrroles tested, 2-cyanopyrroles with 4,5-dibromo, 4-acetyl, and 4-phenylacetyl substituents underwent the catalytic allylic substitutions to provide the corresponding substitution products **13-15** as single regioisomers in good to excellent yields. However, under the same reaction conditions, 4-cyano-2-trichloroacetylpyrrole did not yield the desired substitution product **16**. Therefore, based on these results of the allylic substitutions using 2-trichloroacetylpyrrole, ethyl pyrrole-2-carboxylate (Table 1, entries 3, 4), and 4-cyano-2-trichloroacetylpyrrole (Table 3, **16**) as the nucleophile, it was speculated that the cyano group at the 2-position of the pyrroles used plays a crucial role in the substitution reactions.

To control the asymmetric induction of this transformation, (−)-8-phenylmenthol as a chiral auxiliary was used (Table 4). The DABCO-catalyzed allylic substitutions of the (−)-8-phenylmenthol ester **17** with various 4-substituted and 4,5-disubstituted 2-cyanopyrroles afforded the corresponding substitution products **18-21** as single regioisomers in good to excellent yields with a diastereomeric ratio of up to 7:1.

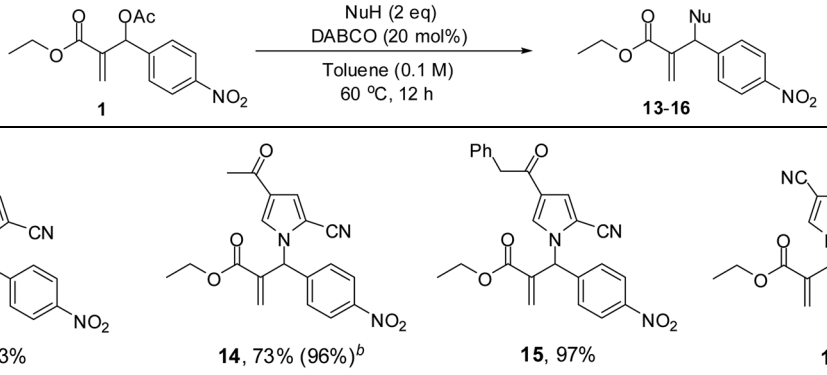
In conclusion, the regioselective allylic substitution of MBH acetates **1-6** with 4-substituted and 4,5-disubstituted 2-cyanopyrroles in the presence of DABCO catalyst afforded a series of α-methylene-β-pyrrole esters as the substitution products in good to excellent yields *via* a tandem S_N2'-S_N2' substitution mechanism. To the best of our knowledge, till date, pyrroles have never been used as nucleophiles in the organocatalytic allylic substitutions of MBH acetates. Therefore, this is the first example in which the pyrroles are used as nucleophiles in the substitution reactions. In addition, the asymmetric version of these transformations using (−)-8-phenylmenthol ester **17** afforded the corresponding substitution products **18-21** with a diastereomeric ratio of up to 7:1.

Table 2. DABCO-catalyzed allylic substitutions of MBH acetates **1-6** using 2,4-dicyanopyrrole as the nucleophile[a]



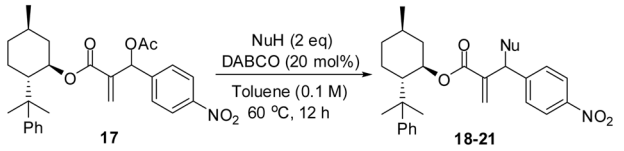
[a]Procedure: To a reaction vessel charged with substrate (0.5 mmol, 100 mol%), NuH (1.0 mmol, 200 mol%), and DABCO (0.1 mmol, 20 mol%) was added toluene (5.0 mL, 0.1 M). The reaction was allowed to stir at 60 °C for 12 h, at which point the reaction mixture was evaporated onto silica gel and the product was isolated by silica gel chromatography.

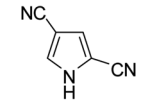
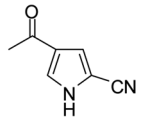
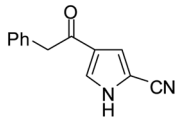
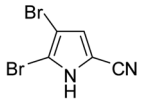
Table 3. Various pyrroles for DABCO-catalyzed allylic substitutions of MBH acetate **1**[a]



[a]Procedure: as described in Table 2. [b]Yield at 80 °C. [c]Not detected.

Table 4. Asymmetric allylic substitutions using (−)-8-phenylmenthol ester **17**[a]



Entry	NuH	Yield[b]	D.r.[c]
1		93% (**18**)	4:1
2		98% (**19**)	5:1
3		99% (**20**)	5:1
4		82% (**21**)	7:1

[a]Procedure: as described in Table 2. [b]Cited yields are of isolated material. In all cases, >95:5 regioselectivity is observed. [c]Diastereomeric ratio was determined by ^{1}H NMR analysis.

Experimental Section

Typical procedure for the allylic substitutions. To a reaction vessel charged with substrate (0.5 mmol, 100 mol%), NuH (1.0 mmol, 200 mol%), and DABCO (0.1 mmol, 20 mol%) was added toluene (5.0 mL, 0.1 M). The reaction was allowed to stir at 60 °C for 12 h, at which point the reaction mixture was evaporated onto silica gel and the product was isolated by silica gel chromatography.

The spectroscopic data of 7-15 and 17-21 are as follows.

Compound **7**: white solid, mp 87-88 °C; IR (neat) 2231, 1717, 1526, 1349, 913, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 1.7 Hz, 1H), 7.16 (d, J = 1.4 Hz, 1H), 6.76 (d, J = 0.7 Hz, 1H), 6.70 (s, 1H), 5.41 (d, J = 1.5 Hz, 1H), 4.25-4.22 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 148.4, 141.6, 137.5, 131.5, 130.3, 128.4, 124.6, 123.2, 113.4, 110.6, 106.9, 95.5, 62.2, 13.9; HRMS calcd for [M] $C_{18}H_{14}N_4O_4$ 350.3344, found 350.3351.

Compound **8**: colorless oil; IR (neat) 2229, 1717, 1543, 1455, 1371, 1262, 1143, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.42 (m, 3H), 7.15-7.12 (m, 3H), 7.10 (d, J = 1.5 Hz, 1H), 6.65 (s, 1H), 6.58 (s, 1H), 5.29 (d, J = 1.5 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 138.5, 134.4, 130.7, 129.9, 129.5, 129.4, 127.7, 122.8, 113.9, 110.9, 106.7, 94.6, 63.1, 61.7, 13.9; EIMS *m/z* 305 (M^+).

Compound **9**: colorless oil; IR (neat) 2228, 1716, 1540, 1330, 1249, 1147, 799 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.92 (m, 2H), 7.76-7.74 (m, 1H), 7.58-7.55 (m, 2H), 7.49-7.45 (m, 1H), 7.35 (s, 1H), 7.16 (d, J = 1.8 Hz, 1H), 7.09 (d, J = 7.0 Hz, 1H), 7.04 (d, J = 1.5 Hz, 1H), 6.67 (d, J = 0.7 Hz, 1H), 5.18 (d, J = 1.5 Hz, 1H), 4.21 (q, J = 7.0 Hz, 2H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 138.3, 134.0, 131.2, 130.5, 129.4, 129.1, 127.6, 126.5, 125.1, 124.9, 123.0, 121.9, 113.7, 110.7, 106.6, 94.5, 61.7, 59.6, 14.0; EIMS *m/z* 355 (M^+).

Compound **10**: colorless oil; IR (neat) 2932, 2229, 1717, 1543, 1375, 1260, 1158, 1025, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 1.5 Hz, 1H), 7.01 (d, J = 1.5 Hz, 1H), 6.55 (s, 1H), 5.92 (s, 1H), 5.20 (t, J = 8.5 Hz, 1H), 4.22-4.17 (m, 2H), 2.09-2.03 (m, 2H), 1.31-1.11 (m, 10H), 0.89-0.83 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 137.8, 130.2, 128.6, 122.2, 114.0, 111.4, 106.3, 94.6, 61.5, 59.9, 32.9, 31.0, 25.6, 22.2, 13.9, 13.7; EIMS *m/z* 299 (M^+).

Compound **11**: colorless oil; IR (neat) 2931, 2230, 1717, 1370, 1237, 1159, 1024, 981 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 1.5 Hz, 1H), 7.00 (d, J = 1.8 Hz, 1H), 6.59 (s, 1H), 6.07 (s, 1H), 4.80 (d, J = 11.2 Hz, 1H), 4.23-4.18 (m, 2H), 2.32-2.24 (m, 1H), 1.79-1.68 (m, 4H), 1.28 (t, J = 7.3 Hz, 3H), 1.31-1.14 (m, 4H), 1.00-0.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 136.2, 130.8, 125.7, 121.9, 114.1, 111.7, 106.6, 94.7, 66.1, 61.5, 60.8, 39.5, 30.6, 29.5, 25.8, 25.4, 14.0; EIMS *m/z* 311 (M^+).

Compound **12**: white solid, mp 82-83 °C; IR (neat) 2930, 2230, 1718, 1253, 1127, 838, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 1.5 Hz, 1H), 7.03 (d, J = 1.5 Hz, 1H), 6.56 (s, 1H), 5.77 (d, J = 1.2 Hz, 1H), 5.32 (t, J = 4.8 Hz, 1H), 4.19-4.16 (m, 2H), 4.15-4.04 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.80 (s, 9H), −0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 135.5, 131.1, 129.5, 122.1, 114.1, 111.2, 106.5, 94.4, 63.0, 61.6, 60.5, 25.5, 17.9, 13.9, −5.7, −5.8; HRMS calcd for [M] $C_{19}H_{27}N_3O_3Si$ 373.5286, found 373.5297.

Compound **13**: yellow oil, IR (neat) 2253, 1715, 1525, 1349, 913, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 6.97 (s, 1H), 6.90 (s, 1H), 6.80 (d, J = 1.0 Hz, 1H), 5.57 (d, J = 1.4 Hz, 1H), 4.26-4.23 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 148.0, 141.8, 135.9, 132.5, 129.2, 124.4, 124.1, 112.9, 111.6, 105.3, 101.1, 63.0, 61.9, 14.0; HRMS calcd for [M] $C_{17}H_{13}Br_2N_3O_4$ 483.1158, found 483.1204.

Compound **14**: yellow oil, IR (neat) 3122, 2984, 2225, 1717, 1675, 1525, 1349, 1211, 913, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 9.0 Hz, 2H), 7.32 (s, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 2.0 Hz, 1H), 5.39 (d, J = 1.5 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 2.39 (s, 3H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 163.8, 148.2, 142.2, 137.8, 131.2, 128.5, 127.5, 124.4, 120.9, 111.6, 106.5, 62.0, 61.7, 27.2, 13.9; HRMS calcd for [M] $C_{19}H_{17}N_3O_5$ 367.3620, found 367.3627.

Compound **15**: white solid, mp 107-108 °C; IR (neat) 2253, 1717, 1674, 1526, 1350, 913, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.8 Hz, 2H), 7.32-7.22 (m, 11H), 6.71 (d, J = 0.7 Hz, 1H), 6.65 (s, 1H), 5.32 (d, J = 1.4 Hz, 1H), 4.19 (q, J = 7.0 Hz, 2H), 4.01 (s, 2H), 1.22 (t, J =

7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 163.8, 142.2, 137.8, 134.1, 131.1, 130.1, 129.2, 128.8, 128.5, 128.3, 127.1, 125.4, 124.5, 123.9, 121.2, 111.6, 106.5, 62.0, 61.8, 47.1, 13.9; HRMS calcd for [M] $C_{25}H_{21}N_3O_5$ 443.4601, found 443.4609.

Compound **17** (mixture of two diastereomers, dr = 2:1): yellow oil; IR (neat) 2957, 1750, 1708, 1523, 1348, 1226, 1031, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.16 (m, 2H), 7.50-7.47 (m, 2H), 7.26-7.02 (m, 5H), 6.47 and 6.25 (minor: s, major: s, 1H), 5.74 and 5.67 (major: s, minor: s, 1H), 5.70 and 5.44 (major: d, *J* = 0.8 Hz, minor: d, *J* = 1.6 Hz, 1H), 4.89 and 4.80 (minor: dt, *J* = 10.4, 4.4 Hz, major: dt, *J* = 10.8, 4.4 Hz, 1H), 2.12-2.09 (minor: s, major: s, 3H), 2.08-2.01 (m, 1H), 1.76-1.68 (m, 7H), 1.23-1.15 (minor: d, *J* = 33.6 Hz, major: d, *J* = 20.0 Hz, 6H), 0.83 and 0.80 (minor: d, *J* = 6.3 Hz, major: d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 169.1, 163.7, 151.9, 147.8, 145.8, 138.4, 128.9, 128.3, 125.4, 125.2, 123.6, 75.6, 72.3, 50.5, 41.5, 39.6, 34.6, 31.4, 28.8, 26.6, 24.3, 21.1; EIMS *m/z* 479 (M^+).

Compound **18** (mixture of two diastereomers, dr = 4:1): colorless oil; IR (neat) 2253, 2127, 1651, 1026, 825, 763 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29-8.25 (minor: d, *J* = 8.5 Hz, major: d, *J* = 9.0 Hz, 2H), 7.35-7.27 (m, 4H), 7.20-7.04 (m, 5H), 6.03 (s, 1H), 5.97 (s, 1H), 5.02 and 4.96 (major: d, *J* = 1.5 Hz, minor: d, *J* = 1.5 Hz, 1H), 4.91-4.84 (m, 1H), 2.19-2.14 (m, 1H), 1.95-1.92 (m, 1H), 1.73-1.70 (m, 1H), 1.53-1.50 (m, 1H), 1.48-1.41 (m, 1H), 1.29 (s, 3H), 1.23-1.18 (m, 1H), 1.16 (s, 3H), 0.95-0.90 (m, 2H), 0.87 and 0.85 (minor: d, *J* = 6.5 Hz, major: d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) major: δ 162.7, 152.4, 148.2, 141.7, 137.1, 132.3, 130.0, 128.2, 125.3, 125.1, 124.4, 123.0, 113.4, 110.5, 106.7, 95.3, 76.2, 61.7, 49.7, 41.2, 39.2, 34.2, 31.1, 30.3, 26.0, 22.0, 21.6; EIMS *m/z* 536 (M^+).

Compound **19** (mixture of two diastereomers, dr = 5:1): colorless oil; IR (neat) 2923, 2223, 1675, 1525, 1348, 1210, 913, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.19 (m, 2H), 7.35-7.20 (m, 7H), 7.17-7.06 (m, 2H), 5.99 (s, 1H), 5.97 (s, 1H), 4.99 and 4.98 (major: d, *J* = 1.5 Hz, minor: d, *J* = 1.3 Hz, 1H), 4.90-4.83 (m, 1H), 2.38 (s, 3H), 2.19-2.13 (m, 1H), 1.93-1.88 (m, 1H), 1.71-1.68 (m, 1H), 1.50-1.45 (m, 1H), 1.43-1.39 (m, 1H), 1.26 (s, 3H), 1.16 (s, 3H), 0.95-0.88 (m, 2H), 0.84 and 0.79 (minor: d, *J* = 6.3 Hz, major: d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) major: δ 191.6, 163.0, 152.3, 148.1, 142.4, 137.5, 131.9, 128.3, 127.2, 125.4, 125.1, 124.3, 120.8, 111.6, 106.4, 76.0, 61.3, 49.9, 41.1, 39.3, 34.2, 31.0, 30.1, 29.6, 27.2, 26.1, 22.2, 21.6; EIMS *m/z* 553 (M^+).

Compound **20** (mixture of two diastereomers, dr = 5:1): white solid, mp 57-58 °C; IR (neat) 2923, 2223, 1709, 1674, 1525, 1348, 1244, 1155, 913, 744, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.19 (m, 2H), 7.35-7.11 (m, 12H), 7.08 (s, 1H), 7.05 (s, 1H), 5.98 (d, *J* = 0.7 Hz, 1H), 5.95 (s, 1H), 4.96 and 4.92 (major: d, *J* = 1.5 Hz, minor: d, *J* = 1.3 Hz, 1H), 4.87-4.81 (m, 1H), 3.99 (d, *J* = 2.5 Hz, 2H), 2.17-2.10 (m, 1H), 1.92-1.88 (m, 1H), 1.70-1.64 (m, 2H), 1.42-1.41 (m, 2H), 1.25 (s, 3H), 1.14 (s, 3H), 0.90-0.86 (m, 2H), 0.83 and 0.75 (minor: d, *J* = 6.3 Hz, major: d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) major: δ 152.3, 148.1, 137.5, 131.8, 129.2, 128.8, 128.3, 127.9, 127.1, 125.4, 125.1, 124.2, 120.0, 111.6, 106.3, 85.2, 76.0, 61.3, 49.9, 47.0, 41.0, 39.3, 34.2, 31.0, 30.2, 26.1, 22.2, 21.6; HRMS calcd for [M] $C_{39}H_{39}N_3O_5$ 629.7582, found 629.7590.

Compound **21** (mixture of two diastereomers, dr = 7:1): colorless oil; IR (neat) 2924, 2221, 1717, 1522, 1348, 1242, 1167, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (m, 2H), 7.32-7.24 (m, 10H), 7.16-7.12 (m, 1H), 6.94 (s, 1H), 6.24 (d, *J* = 1.3 Hz, 1H), 6.21 (s, 1H), 5.27 and 5.16 (major: d, *J* = 1.7 Hz, minor: d, *J* = 1.3 Hz, 1H), 4.97-4.91 (m, 1H), 2.16-2.09 (m, 1H), 1.89-1.80 (m, 1H), 1.75-1.65 (m, 1H), 1.50-1.38 (m, 2H), 1.32 (s, 3H), 1.27-1.24 (m, 1H), 1.18 (s, 3H), 1.17-1.09 (m, 1H), 0.98-0.94 (m, 1H), 0.85 and 0.84 (minor: d, *J* = 6.3 Hz, major: d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) major: δ 163.2, 151.7, 147.9, 141.7, 135.8, 132.7, 128.9, 128.0, 125.5, 125.0, 124.0, 112.6, 111.6, 105.0, 100.9, 75.7, 62.8, 50.2, 41.3, 39.4, 34.3, 31.2, 31.0, 29.3, 26.2, 23.2, 21.6; EIMS *m/z* 669 (M^+).

Acknowledgments. This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2007-331-C00157).

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