Synthesis of β,γ-Disubstituted α-Methylene-γ-butyrolactams Starting from the Baylis-Hillman Adducts

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α-Methylene-γ-butyrolactam derivatives are biologically important compounds.[1-3] They exhibit less cytotoxic activity than the corresponding α-methylene-γ-butyrolactone compounds in some cases.[1,2] However, the synthesis of these compounds was studied less extensively. In addition, many of the synthetic procedures showed the formation of undesired endocyclic unsaturated lactam during the synthesis of *exo*-methylene compounds.[4] Recently, Yus and co-workers reported the indium-promoted synthesis of α-methylene-γ-butyrolactams from the reaction of 2-(bromomethyl)acrylic acid and aldimine.[2a] In their paper they obtained γ-substituted-α-methylene-γ-butyrolactam derivatives in 18-49% yields as their *N*-substituted forms.[2a]

We and other groups reported a number of papers on the synthesis of a variety of heterocyclic compounds starting from the Baylis-Hillman adducts.[5] Basavaiah and co-workers published the synthesis of α-arylidene-γ-butyrolactam derivatives recently.[3a] However, they did not examined the synthesis of α-methylene-γ-butyrolactam derivatives.[3a] We presumed that we could synthesize α-methylene-γ-butyrolactams from the Baylis-Hillman adducts by following the Scheme 1.

Thus, we prepared starting material **3a** according to the method involving the DABCO salt concept, which was developed by us (Scheme 1).[6] The reaction of the Baylis-Hillman adduct **1a** and HBr gave the cinnamyl bromide **2a** in good yield.[7] The reaction of **2a** and DABCO in aqueous THF gave the corresponding DABCO salt, which reacted with nitroethane to afford **3a**. The compound **3a** was obtained as a diastereomeric *syn*/*anti* mixture, which could be separated by column chromatography.[6] However, it was impossible to assign their stereochemistry at the earliest stage. With the fast moving component (later it was found as **3a**-*anti*, *vide infra*) we obtained **4a**-*anti* in 78% yield under the reductive cyclization conditions of Fe/AcOH.[3a,8] Similarly, we obtained **4a**-*syn* in 77% yield under the same conditions from the slow moving **3a**-*syn* component.

The structures of **4a**-*syn* and **4a**-*anti* could be assigned by NOE experiments. As shown in Figure 1, when we irradi-

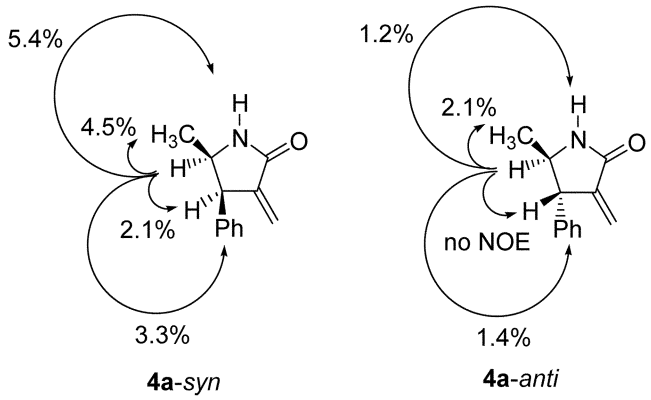
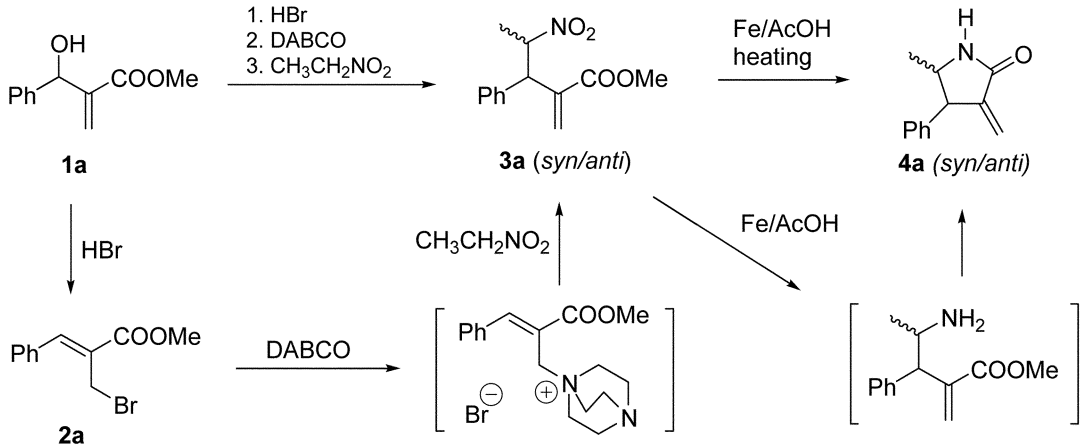


Figure 1



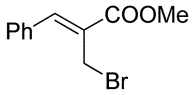
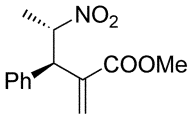
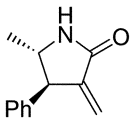
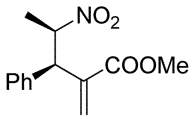
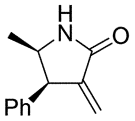
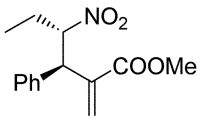
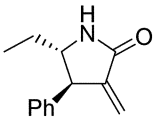
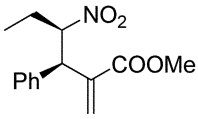
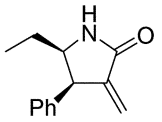
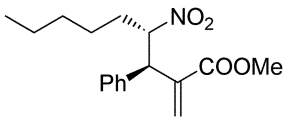
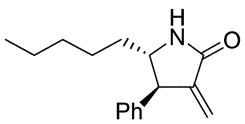
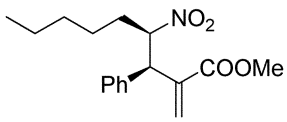
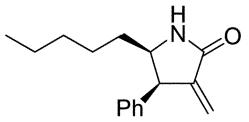
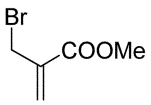
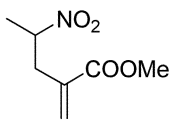
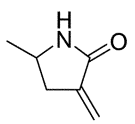
Scheme 1

ated the proton at γ-position we observed 2.1% NOE for the β-proton of **4a**-*syn*, whereas no increment for **4a**-*anti*. From the results we assigned the fast moving component of **3a** as *anti* form and the slow moving component as *syn* form (see also entries 1 and 2 in Table 1).

With these successful results we examined the generality of the reactions with other entries as summarized in Table 1. We obtained similar results when we changed nitroethane into nitropropane (entries 3 and 4) or nitrohexane (entries 5 and 6). However, the separation of **3c**-*anti* and **3c**-*syn* was impossible and we used the mixture for the synthesis of **4c**. Fortunately, we could isolate **4c**-*syn* in pure state in 62% yield. The corresponding **4c**-*anti* must be formed in the reaction mixture, but we did not obtain **4c**-*anti* in sufficient amount in analytically pure state. As shown in entry 7, use of **3d** afforded γ-mono-substituted lactam derivative **4d** in 81% yield.

In summary, we disclosed the efficient synthetic method for β,γ-disubstituted-α-methylene-γ-butyrolactams in moderate yields starting from the Baylis-Hillman adducts.

Table 1. Synthesis of α-methylene-γ-butyrolactams

Entry	Starting materials		Intermediates **3**[a]	Products **4**[b]
1	 **2a**	nitroethane	 **3a**-*anti* (33)	 **4a**-*anti* (78)
2			 **3a**-*syn* (49)	 **4a**-*syn* (77)
3	**2a**	nitropropane	 **3b**-*anti* (15)	 **4b**-*anti* (67)
4			 **3b**-*syn* (65)	 **4b**-*syn* (76)
5	**2a**	nitrohexane	 **3c**-*anti* (ca. 14)[c]	 **4c**-*anti* (-)[d]
6			 **3c**-*syn* (ca. 55)[c]	 **4c**-*syn* (62)[d]
7	 **2b**	nitroethane	 **3d** (79)[e]	 **4d** (81)

[a]Conditions: (i). **2a** (1.0 mmol), aq THF, DABCO (2.0 equiv), rt, 20 min, (ii). nitroalkane (1.5 equiv), rt, 2 days. [b]Conditions: 3 (1.0 equiv), Fe (10 equiv), AcOH, 90-100 °C, 12 h. [c]The two compounds **3c**-*anti* and **3c**-*syn* were isolated (69%) as a mixture and the ratio was 1 : 4 (*anti*/*syn*) based on ^{1}H NMR. We used the mixture for the next reaction. [d]We isolated **4c**-*syn* only in 62% yield in pure state. [e]Conditions: **2b** (1.0 equiv), DMF, nitroethane (1.5 equiv), K_2CO_3 (2.0 equiv), rt, 2 h.

Experimental Section

Typical procedure for the synthesis of 3a and 4a: A solution of **2a** (508 mg, 2.0 mmol) and DABCO (448 mg, 4.0 mmol) in aq THF (5 mL) was stirred 20 min at room temperature. To the reaction mixture nitroethane (225 mg, 3.0 mmol) was added and the reaction mixture was stirred at room temperature for 2 days. After the usual aqueous extractive workup with ether and flash column chromatographic purification process (hexanes/ether, 8 : 1) we obtained **3a**-*anti* (165 mg, 33%, R_f = 0.27) and **3a**-*syn* (245 mg, 49%, R_f = 0.22). The next reductive cyclization of **3a**-*anti* to **4a**-*anti* is typical. A mixture of **3a**-*anti* (125 mg, 0.5 mmol) and Fe (280 mg, 5.0 mmol) in acetic acid (2 mL) was heated to 90-100 °C for 12 h. After the usual aqueous extractive workup with ether and flash column chromatographic purification process with ether we obtained **4a**-*anti* (73 mg, 78%, R_f = 0.30). Spectroscopic data of synthesized compounds **3a**-**d** and **4a**-**d** are as follows.

Compound **3a**-*anti*: 33%; colorless oil; IR (film) 1722, 1551, 1265, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40 (d, J = 6.5 Hz, 3H), 3.67 (s, 3H), 4.46 (d, J = 11.5 Hz, 1H), 5.21-5.27 (m, 1H), 5.91 (s, 1H), 6.34 (s, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.01, 51.03, 52.04, 85.01, 124.72, 127.83, 128.63, 128.87, 136.57, 139.37, 165.84.

Compound **3a**-*syn*: 49%; colorless oil; IR (film) 1718, 1551, 1248, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.60 (d, J = 6.5 Hz, 3H), 3.71 (s, 3H), 4.39 (d, J = 11.0 Hz, 1H), 5.45-5.51 (m, 1H), 5.80 (s, 1H), 6.35 (s, 1H), 7.21-7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.84, 52.18, 52.22, 85.53, 127.48, 127.71, 127.90, 128.66, 137.36, 139.09, 166.14.

Compound **3b**-*anti*: 15%; colorless oil; IR (film) 1722, 1551, 1250, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.5 Hz, 3H), 1.55-1.62 (m, 1H), 1.74-1.82 (m, 1H), 3.67 (s, 3H), 4.48 (d, J = 12.0 Hz, 1H), 5.04-5.10 (m, 1H), 5.94 (s, 1H), 6.34 (s, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.12, 26.08, 50.17, 52.08, 91.62, 124.93, 127.83, 128.65, 128.91, 136.85, 139.35, 165.90.

Compound **3b**-*syn*: 65%; colorless oil; IR (film) 1720, 1552, 1252, 1151 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, J = 7.5 Hz, 3H), 1.89-1.95 (m, 2H), 3.69 (s, 3H), 4.40 (d, J = 11.5 Hz, 1H), 5.30-5.33 (m, 1H), 5.80 (s, 1H), 6.32 (s, 1H), 7.19-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.12, 25.95, 51.24, 52.06, 92.11, 127.27, 127.59, 127.89, 128.54, 137.35, 139.11, 166.05.

Compound **3c**-*anti*: 14%; colorless oil; IR (film) 2951, 1718, 1551, 1252, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, J = 6.6 Hz, 3H), 1.15-1.34 (m, 6H), 1.77-1.97 (m, 2H), 3.68 (s, 3H), 4.45 (d, J = 11.7 Hz, 1H), 5.10-5.19 (m, 1H), 5.93 (s, 1H), 6.32 (s, 1H), 7.18-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.79, 22.21, 25.31, 30.79, 32.60, 50.54, 52.11, 90.25, 125.07, 127.84, 128.67, 128.94, 136.93, 139.37, 165.92.

Compound **3c**-*syn*: 55%; colorless oil; IR (film) 2953, 1722, 1551, 1252, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.23-1.34 (m, 6H), 1.77-1.97 (m, 2H), 3.73 (s, 3H), 4.37 (d, J = 11.1 Hz, 1H), 5.37 (td, J = 11.1 and 3.0 Hz, 1H), 5.80 (s, 1H), 6.35 (s, 1H), 7.18-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.86, 22.30, 25.45, 30.92, 32.66, 51.68, 52.26, 90.89, 127.20, 127.79, 128.06, 128.71, 137.35, 139.42, 166.20.

Compound **3d**: 79%; colorless oil; IR (film) 2951, 1722, 1551, 1308, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56 (d, J = 6.9 Hz, 3H), 2.76 (dd, J = 14.1 and 5.1 Hz, 1H), 2.90 (dd, J = 14.1 and 9.0 Hz, 1H), 3.79 (s, 3H), 4.80-4.92 (m, 1H), 5.67 (s, 1H), 6.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.24, 37.93, 52.18, 82.36, 129.38, 134.63, 166.42.

Compound **4a**-*anti*: 78%; white solid, mp 112-113 °C; IR (film) 3219, 2964, 1701, 1659, 1427 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (d, J = 6.3 Hz, 3H), 3.55-3.60 (m, 1H), 3.67-3.76 (m, 1H), 5.11 (d, J = 3.0 Hz, 1H), 6.09 (d, J = 3.0 Hz, 1H), 7.20-7.39 (m, 5H), 7.62 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.00, 54.32, 56.43, 117.41, 127.29, 128.39, 128.80, 140.60, 145.12, 170.00; LCMS *m/z* 187 (M^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.89; H, 7.21; N, 7.35.

Compound **4a**-*syn*: 77%; white solid, mp 129-130 °C; IR (film) 3188, 2926, 1693, 1653, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (d, J = 6.3 Hz, 3H), 4.01-4.11 (m, 1H), 4.31-4.36 (m, 1H), 5.32 (d, J = 2.7 Hz, 1H), 6.23 (d, J = 2.7 Hz, 1H), 7.17-7.37 (m, 5H), 7.56 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.50, 49.12, 51.72, 118.56, 127.23, 128.40, 129.46, 138.51, 143.21, 170.61; LCMS *m/z* 187 (M^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.77; H, 7.13; N, 7.42.

Compound **4b**-*anti*: 67%; white solid, mp 122-123 °C; IR (film) 3198, 2922, 1697, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7.5 Hz, 3H), 1.54-1.79 (m, 2H), 3.52-3.59 (m, 1H), 3.65-3.70 (m, 1H), 5.13 (d, J = 3.0 Hz, 1H), 6.12 (d, J = 3.0 Hz, 1H), 6.57 (br s, 1H), 7.19-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.04, 28.79, 51.82, 61.85, 118.07, 127.24, 128.23, 128.86, 141.67, 144.72, 169.57; LCMS *m/z* 201 (M^+).

Compound **4b**-*syn*: 76%; white solid, mp 120-121 °C; IR (film) 3182, 2972, 1695, 1659, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J = 7.5 Hz, 3H), 0.96-1.16 (m, 2H), 3.74-3.82 (m, 1H), 4.31-4.36 (m, 1H), 5.30 (d, J = 2.7 Hz, 1H), 6.20 (d, J = 2.7 Hz, 1H), 7.19-7.36 (m, 5H), 8.32 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.67, 26.64, 49.01, 58.06, 117.87, 127.12, 128.28, 129.46, 138.62, 143.65, 171.00; LCMS *m/z* 201 (M^+). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.73; H, 7.70; N, 6.84.

Compound **4c**-*syn*: 62%; white solid, mp 118-119 °C; IR (film) 3203, 2930, 1701, 1655, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J = 7.2 Hz, 3H), 0.85-1.27 (m, 8H), 3.79-3.87 (m, 1H), 4.30-4.35 (m, 1H), 5.30 (d, J = 2.7 Hz, 1H), 6.20 (d, J = 2.7 Hz, 1H), 7.17-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.85, 22.36, 25.91, 31.48, 33.43, 49.21, 56.32, 118.17, 127.23, 128.37, 129.51, 138.59, 143.40, 170.59; LCMS *m/z* 243 (M^+).

Compound **4d**: 81%; white solid, mp 74-75 °C; IR (film) 3240, 2966, 1697, 1659, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (d, J = 6.3 Hz, 3H), 2.32-2.42 (m, 1H), 2.95-3.05 (m, 1H), 3.75-3.86 (m, 1H), 5.33 (t, J = 2.4 Hz, 1H),

5.96 (t, J = 2.4 Hz, 1H), 7.74 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.91, 34.78, 46.99, 115.61, 139.97, 170.75.

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References and Notes

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