

(Z)-Dimethyl α -(Bromomethyl)fumarate, an Efficient Intermediate for the Selective Synthesis of Dimethyl 3-Alkyl Itaconates and 2-Alkyl 3-Carbomethoxy- γ -Lactams

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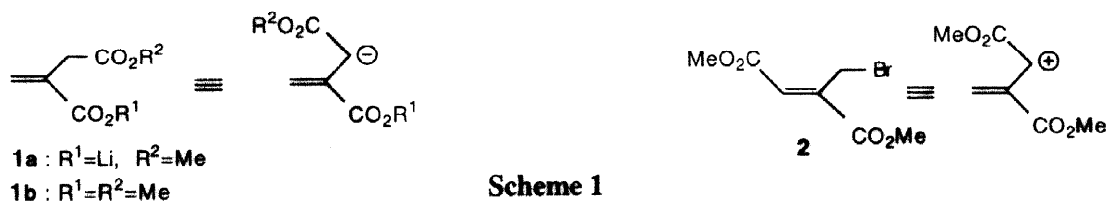
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Abstract: (Z)-Dimethyl α -(bromomethyl)fumarate **2** proved to be an efficient precursor of 3-substituted itaconic acid esters **3** via its reaction with magnesium dialkylcuprates. Some hindered esters **3** can be used for the diastereoselective synthesis of α -alkylated- β -methoxycarbonyl- γ -lactams **6**. © 1999 Elsevier Science Ltd. All rights reserved.

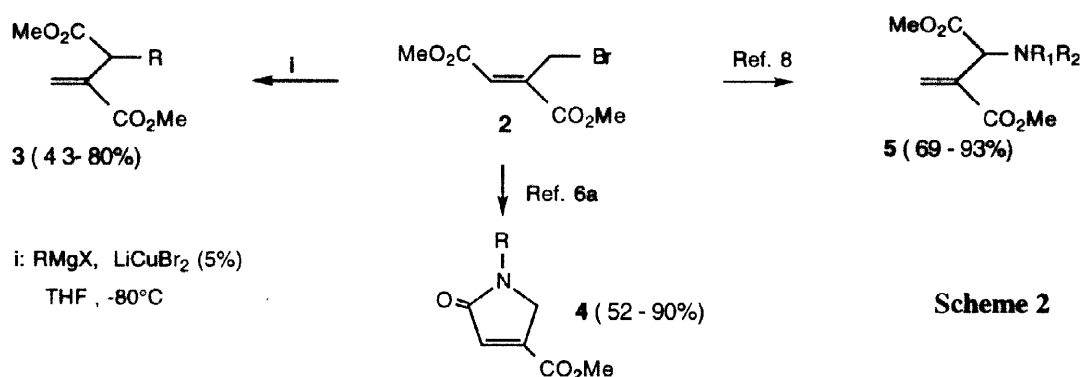
Carlson methods^{1a-c} for alkylation of anions of itaconic acid derivatives **1a,b** with aldehydes and ketones constitute the most common methods for the synthesis of natural products such as α -methylene- γ -butyrolactones^{2a,b} and some antitumor antibiotics like methylenolactocin^{3a,b}. To our knowledge, no general method for direct alkylation of itaconic esters **1b** has been described in the literature except the recently reported procedure using the cyclopentadiene-dimethyl itaconate adduct⁴. Generally, direct alkylation resulted in a complicated mixture of products probably arising from all possible carbanionic intermediates. The method⁵ requires the formation of dianions derived from monoesters of itaconic acid **1a**. In an ongoing project aimed at further illustrating the potentiality of readily available dimethyl α -(bromomethyl) fumarate **2**^{6a,b}, we have shown that **2** can be utilised as an electrophilic reagent for access to alkylated itaconic diesters **3**^{7a-c} (Scheme 1).



Scheme 1

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Bearing both an α,β -unsaturated methoxycarbonyl group (Michael acceptor) and a bromomethyl substituent (allylic bromide), dimethyl α -(bromomethyl)fumarate **2** can be regarded as a powerful electrophilic reagent and it reacts in clean S_N2' reactions with nucleophiles, giving, for example, pyrrolidin-2-ones **4**^{6a} and β -N,N-dialkylamino- α -methylene succinic acid esters **5**⁸ in high yields on reaction with primary and secondary amines respectively.



Now, we report its use as a key intermediate for the synthesis of β -alkylated itaconates **3** (Scheme 2) and α -alkyl β -carbomethoxy γ -butyrolactams **6** (Scheme 3). Preliminary experiments including the reaction of **2** with lithium or magnesium dialkylcuprates (R₂CuM: Li, MgX), give moderate yields in **3**. However, we have found that alkylmagnesium halide (*primary, secondary and tertiary aliphatic, vinylic and aromatic*, 1.2–1.7 equiv.) in the presence of a catalytic amount (5%) of LiCuBr₂, reacts spontaneously and regioselectively in THF at -80°C to give the corresponding 3-substituted dimethyl itaconates **3** with satisfactory yields as indicated in Table 1.

Table 1. Synthesis of 3-substituted dimethyl itaconates **3a–j**[†]

Entry	Reagent (equiv.) RMgX + 5% Cu(I)*	Adduct 3a–j	Yield (%)
1	CH ₃ MgI (1.2)	3 a	60
2	C ₂ H ₅ MgBr (1.2)	3 b	73
3	<i>n</i> -C ₃ H ₇ MgCl (1.3)	3 c	78
4	<i>i</i> -C ₃ H ₇ MgCl (1.3)	3 d	79
5	<i>i</i> -C ₃ H ₅ MgBr (1.7)	3 e	43
6	<i>n</i> -C ₄ H ₉ MgCl (1.2)	3 f	80
7	<i>t</i> -C ₄ H ₉ MgCl (1.4)	3 g	75
8	C ₆ H ₅ MgCl (1.2)	3 h	53
9	C ₆ H ₅ CH ₂ MgCl (1.4)	3 i	74
10	α -C ₆ H ₁₁ MgCl (1.3)	3 j	63

All reactions were carried out in 10 mmol scale of allylic bromide **2**. *Solution of LiCuBr₂ (1M) in THF was used. [†] Products **3a–i** were isolated as yellow liquids after column chromatography (10% AcOEt in hexane) except **3j** which was distilled.

Much attention has been given to a biologically active γ -lactams⁹ over the last years. We have applied the previously prepared itaconates **3** as intermediates in the synthesis of lactams. In fact, the reaction of primary amines (2 equiv.) with 3-alkylated itaconic esters **3** in a mixture of MeOH-H₂O (9:1) at room

temperature proceeds through a conjugate addition/lactamization (5-exo-trig process)¹⁰ sequence leading to the diastereoselective formation of α -alkyl β -carbomethoxy γ -lactams **6g** (Scheme 3) with moderate to good yields (Table 2).

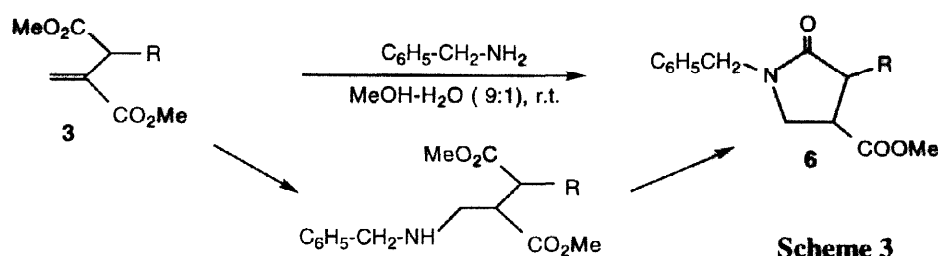
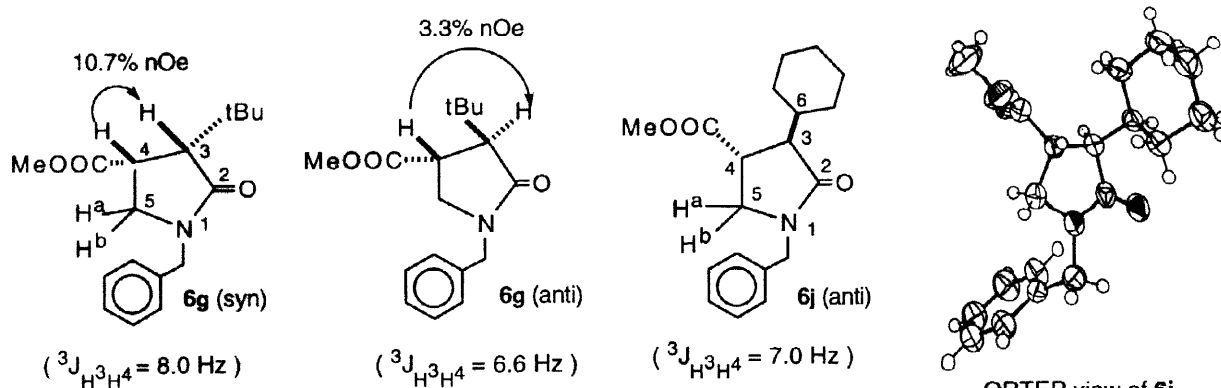


Table 2. Synthesis of α -alkyl- β -methoxycarbonyl- γ -lactams **6**

3-Alkylated itaconates 3	R	γ -Lactams 6b-j	% <i>Cis/trans</i>	Yield (%) [*]
3b	C ₂ H ₅	6b	23/77	60
3c	<i>n</i> -C ₃ H ₇	6c	13/87	54
3e	<i>i</i> -C ₃ H ₅	6e	0/100	37
3f	<i>n</i> -C ₄ H ₉	6f	22/78	83
3g	<i>t</i> -C ₄ H ₉	6g	47/53	50 [‡]
3i	C ₆ H ₅ CH ₂	6i	19/81	77
3j	<i>c</i> -C ₆ H ₁₁	6j	28/72	55

All reactions were carried out in 10 mmol scale of 3-alkyl itaconate **3**. ^{*}Yield of isolated lactams **6** after silica gel chromatography (30% AcOEt in hexane). [‡]The lactamization of **6g** was carried out in bromobenzene at reflux.

As shown in Table 2, lactams **6** were obtained as a mixture of *cis* and *trans* diastereoisomers which could be separated by further column chromatography. The stereochemistry of the major *trans* and the minor *cis* isomers was confirmed by ¹H-NMR and n.O.e experiments. These isomers could be differentiated by the chemical shifts of proton at C-4 which appeared further downfield (ca. 0.2–0.4 ppm) for the *trans* isomers, and by coupling patterns of vicinal protons at C-3 and C-4 (Scheme 4). The n.O.e spectra of separated diastereoisomers **6g** showed a 3.3% enhancement of C-3 proton for the *trans* isomer while this enhancement was 10.7% for the *cis* isomer. Finally, a crystal structure of the major isomer **6j** allowed the unambiguous establishment of the relative configuration *trans* of H³-C-C-H⁴ (³J_{H³H⁴} = 7.0 Hz) (Scheme 4).



ORTEP view of **6j**

In conclusion, we have demonstrated that dimethyl α -(bromomethyl) fumarate **2**, easily prepared from dimethyl itaconate **1b**, can be used as an electrophilic synthon for the synthesis of 3-alkylated itaconic esters and substituted γ -lactams.

EXPERIMENTAL SECTION

All reactions involving anhydrous conditions were conducted in dry glassware under a nitrogen atmosphere. Solvents were distilled under nitrogen immediately prior to use. Grignard reagents were prepared by the known procedures and stored under inert atmosphere. They were titrated prior to use¹¹, i.e. with 1M solution of benzyl alcohol in toluene and 2,2'-biquinoline as indicator. Reactions were monitored with an Intersmat 20M gas chromatograph using a 3m column packed with 10% SE 30 and by TLC on silica gel plates (Fluka Kieselgel 60 F254). For column chromatography, Fluka Kieselgel 70-230 mesh was used. The infrared (IR) spectra were determined on a Perkin Elmer Paragon 1000PC spectrophotometer. ¹H and ¹³C NMR (fully decoupled) and spectra were recorded on Bruker AMX 300 and ARX 400 spectrometers in CDCl₃ as solvent and TMS as the internal. GC-MS spectra were obtained using a HP 5890 chromatograph fitted with HP 1 (0.33 μ x 12m) and HP 5889A quadripolar spectrometer in Electronic Impact (70 eV) or in Chemical Ionization (500 eV) with NH₃ gas. The fragmentation peaks are given in relative intensity (%). Microanalyses were performed by the "Service Central d'analyses" of CNRS in Vernaison (France).

Synthesis of dimethyl β -alkyl- α -methylenesuccinate **3**

General procedure

To a stirred solution of dimethyl α -(bromomethyl)fumarate **2** (2.37 g, 10 mmol) and LiCuBr₂ (0.5 mL) in dry THF (50 mL) at -80 °C under N₂, was added slowly alkylmagnesium halide RMgX (1.2 to 1.7eq) via a syringe. After a few minutes (GC) at -80°C, the reaction mixture was quenched with a saturated NH₄Cl solution (50 mL), then allowed to warm to room temperature. The organic layer was separated and the aqueous phase was extracted with ether (3x15mL). The combined organic layers were washed with saturated Na₂S₂O₃ solution (25 mL) then with brine. After drying over MgSO₄, the solvents were removed under reduced pressure to give crude substituted itaconic ester **3** which was purified by column chromatography filled with silica gel upon elution with hexane-ethyl acetate (9:1).

Dimethyl β -methyl- α -methylenesuccinate (**3a**)

IR (neat) $\nu_{\max}$ / cm⁻¹: 1633 (C=C) ; 1714, 1735 (2 C=O). ¹H NMR (CDCl₃, δ ppm, *J* Hz): 1.35 (d, 3H, *J* =7, CH₃CH) ; 3.60 (q, 1H, *J* =7, CH₃CH) ; 3.66, 3.73 (2s, 6H, 2 CH₃O) ; 5.67, 6.27 (2s, 2H, CH₂=). ¹³C NMR (CDCl₃, δ ppm): 15.8 (CH₃CH) ; 40.9 (2 CHCH₃) ; 51.8 (2 CH₃O) ; 125.6 (CH₂=C) ; 139.4 (C=CH₂) ; 166.3, 174.0 (2 CO). *m/z*: 172 (M⁺, 5) ; 157 (87) ; 113 (97). Anal. Calcd for C₈H₁₂O₄ : C, 55.80 ; H, 7.02. Found : C, 55.78 ; H, 7.01.

Dimethyl β -ethyl- α -methylenesuccinate (3b)

IR (neat) $\nu_{\max}$ / cm^{-1} : 1631 (C=C) ; 1714, 1735 (2 C=O). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.9 (t, 3H, J = 7, CH_3CH_2) ; 1.62 (m, 2H, CH_3CH_2) ; 3.42 (t, 1H, J = 7, CH_2CH) ; 3.63, 3.73 (2s, 6H, 2 CH_3O) ; 5.70, 6.33 (2s, 2H, CH_2 =). ^{13}C NMR (CDCl_3 , δ ppm): 11.8 (CH_3CH_2) ; 24.1 (CH_2CH_3) ; 48.0 (CHCH_2) ; 51.7, 51.9 (2 CH_3O) ; 126.5 ($\text{CH}_2=\text{C}$) ; 137.9 ($\text{C}=\text{CH}_2$) ; 166.4, 173.4 (2 CO). m/z : 171 (1) ; 157 (100) ; 127 (22). Anal. Calcd for $\text{C}_9\text{H}_{14}\text{O}_4$: C, 58.06 ; H, 7.57. Found : C, 58.11 ; H, 7.55.

Dimethyl β -n-propyl- α -methylenesuccinate (3c)

IR (neat) $\nu_{\max}$ / cm^{-1} : 1631 (C=C) ; 1714, 1734 (2 C=O). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.93 (t, 3H, J = 7, CH_3CH_2) ; 1.61 (m, 4H, CH_2CH_2) ; 3.53 (t, 1H, J = 7, CH_2CH) ; 3.66, 3.76 (2s, 6H, 2 CH_3O), 5.76, 6.36 (2s, 2H, CH_2 =). ^{13}C NMR (CDCl_3 , δ ppm): 13.5 (CH_3CH_2) ; 20.4 (CH_2CH_3) ; 33.1 ($\text{CH}_2\text{CH}_2\text{CH}_3$) ; 46.1 (CHCH_2) ; 51.8, 51.9 (2 CH_3O) ; 126.5 ($\text{CH}_2=\text{C}$) ; 138.1 ($\text{C}=\text{CH}_2$) ; 166.4, 176.6 (2 CO). m/z : 200 (M^+ , 1) ; 171 (1) ; 169 (14) ; 157 (100) ; 141 (27). Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_4$: C, 59.98 ; H, 8.05. Found : C, 59.91 ; H, 8.08.

Dimethyl β -isopropyl- α -methylenesuccinate (3d)

IR (neat) $\nu_{\max}$ / cm^{-1} : 1625 (C=C) ; 1714, 1731 (2 C=O). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.88, 0.98 (2d, 6H, J = 6.9, $(\text{CH}_3)_2\text{CH}$) ; 2.17 (m, 1H, $(\text{CH}_3)_2\text{CH}$) ; 3.41 (d, 1H, J = 9.3, CHCO_2CH_3) ; 3.67, 3.78 (2s, 6H, 2 CH_3O), 5.93, 6.42 (2s, 2H, CH_2 =). ^{13}C NMR (CDCl_3 , δ ppm): 19.8, 20.8 ($(\text{CH}_3)_2\text{CH}$) ; 31.3 ($\text{CH}(\text{CH}_3)_2$) ; 51.6, 52.0 (2 CH_3O) ; 52.3 (CHCO_2CH_3) ; 127.2 ($\text{CH}_2=\text{C}$) ; 137.5 ($\text{C}=\text{CH}_2$) ; 166.9, 173.4 (2 CO). m/z : 200 (M^+ , 1) ; 169 (13) ; 157 (96) ; 141 (10) ; 126 (100).

Dimethyl β -isopropenyl- α -methylenesuccinate (3e)

IR (neat) $\nu_{\max}$ / cm^{-1} : 1644, 1630 (2 C=C) ; 1729 (2 C=O). ^1H NMR (CDCl_3 , δ ppm, J Hz): 1.8 (s, 3H, CH_3C) ; 3.70, 3.76 (2s, 6H, 2 CH_3O) ; 4.26 (s, 1H, CHCO_2CH_3) ; 4.88, 5.08 (2s, 2H, $\text{CH}_2=\text{CCH}_3$), 5.80, 6.20 (2s, 2H, $\text{CH}_2=\text{CCO}_2\text{CH}_3$). ^{13}C NMR (CDCl_3 , δ ppm): 22.3 ($\text{CH}_3\text{C}=\text{C}$) ; 52.6, 54.1 (2 CH_3O) ; 115.9 ($\text{CH}_2=\text{CCH}_3$) ; 127.8 ($\text{CH}_2=\text{CCO}_2\text{CH}_3$) ; 136.8 (CCH_3) ; 140.6 (CCO_2CH_3) ; 167.2, 172.2 (2 CO). m/z : 198 (M^+ , 2) ; 183 (6) ; 166 (86) ; 157 (1) ; 139 (26) ; 138 (42). Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_4$: C, 60.56 ; H, 7.11. Found : C, 60.51 ; H, 7.13.

Dimethyl β -n-butyl- α -methylenesuccinate (3f)

IR (neat) $\nu_{\max}$ / cm^{-1} : 1631 (C=C) ; 1715, 1731 (2 C=O). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.90 (t, 3H, J = 7, $\text{CH}_3\text{-CH}_2$) ; 1.10 - 2.00 (m, 6H, $(\text{CH}_2)_3$) ; 3.43 (t, 1H, J = 7, CH_2CH) ; 3.60, 3.70 (2s, 6H, 2 CH_3O) ; 5.66, 6.21 (2s, 2H, CH_2 =). ^{13}C NMR (CDCl_3 , δ ppm): 13.7 (CH_3CH_2) ; 22.2 (CH_2CH_3) ; 29.4, 30.8 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) ; 46.3 (CHCH_2CH_2) ; 51.8, 51.9 (2 CH_3O) ; 126.5 ($\text{CH}_2=\text{C}$) ; 138.3 ($\text{C}=\text{CH}_2$) ; 166.5, 173.6 (2 CO). m/z : 214 (M^+ , 1) ; 183 (14) ; 157 (100) ; 155 (70). Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4$: C, 61.66 ; H, 8.46. Found : C, 61.68 ; H, 8.51.

Dimethyl β -t-butyl- α -methylenesuccinate (3g)

IR (neat) $\nu_{\max}$ / cm^{-1} : 1621 (C=C) ; 1715, 1729 (2 C=O). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.97 (s, 9H, $(\text{CH}_3)_3\text{C}$) ; 3.64, 3.77 (2s, 6H, 2 CH_3O) ; 3.80 (s, 1H, $(\text{CH}_3)_3\text{CCCH}$) ; 6.13, 6.47 (2s, 2H, CH_2 =). ^{13}C NMR

(CDCl₃, δ ppm): 27.9 (3CH₃C) ; 34.4 (CCH₃) ; 51.2, 52.1 (2 CH₃O) ; 52.7 (CHC) ; 128.6 (CH₂=C) ; 135.5 (C=CH₂) ; 167.4, 172.9 (2 CO). m/z: 199 (1) ; 183 (70) ; 157 (70) ; 155 (22).

Dimethyl β -phenyl- α -methylenesuccinate (3h)

IR (neat) $\nu_{\max}$ / cm⁻¹: 1633 (C=C) ; 1714, 1738 ¹H NMR (CDCl₃, δ ppm, *J* Hz): 3.70, 3.78 (2s, 6H, 2CH₃O) ; 4.86 (s, 1H, CHCO₂CH₃) ; 5.45, 6.43 (2s, 2H, CH₂=) ; 7.30 (s, 5H, C₆H₅). ¹³C NMR (CDCl₃, δ ppm): 52.4, 52.6 (2 CH₃O) ; 53.2 (CHCO₂CH₃) ; 127.9, 128.3, 128.9, 129.1 (5 CH arom, CH₂=C) ; 135.9, 139.1 (C=CH₂, C arom) ; 166.9, 172.5 (2 CO). m/z: 234 (M⁺, 1) ; 202 (100) ; 175 (20), 157 (1), 115 (71). Anal. Calcd for C₁₃H₁₄O₄ : C, 66.65 ; H, 6.02. Found : C, 66.78 ; H, 6.11.

Dimethyl β -benzyl- α -methylenesuccinate (3i)

IR (neat) $\nu_{\max}$ / cm⁻¹: 1631 (C=C) ; 1729 (2 C=O). ¹H NMR (CDCl₃, δ ppm, *J* Hz): 3.08 (t, 1H, *J* = 7, CHCH₂) ; 3.60, 3.75 (2s, 6H, 2CH₃O) ; 3.76 (d, 2H, *J* = 7, CHCH₂) ; 5.65, 6.28 (2s, 2H, CH₂=), 7.16 (s, 5H, C₆H₅). ¹³C NMR (CDCl₃, δ ppm): 37.6 (CH₂C₆H₅) ; 48.9 (CHCH₂) ; 52.2, 52.3 (2 CH₃O) ; 126.6, 127.7, 128.5, 129.1 (5 CH arom, CH₂=C) ; 137.9, 138.9 (C=CH₂, C arom) ; 166.6, 173.2 (2 CO). m/z: 248 (M⁺, 3) ; 216 (11) ; 188 (35) ; 157 (23). Anal. Calcd for C₁₄H₁₆O₄ : C, 67.73 ; H, 6.49. Found : C, 67.74 ; H, 6.00.

Dimethyl β -cyclohexyl- α -methylenesuccinate (3j)

IR (neat) $\nu_{\max}$ / cm⁻¹: 1625 (C=C) ; 1722 (2 C=O). ¹H NMR (CDCl₃, δ ppm, *J* Hz): 1.16, 1.70 (2m, 11H, cC₆H₁₁) ; 3.46 (d, 1H, *J* = 9, CHCO₂CH₃) ; 3.63, 3.75 (2s, 6H, 2CH₃O) ; 5.91, 6.36 (2s, 2H, CH₂=). ¹³C NMR (CDCl₃, δ ppm): 26.4, 26.5, 26.6, 30.5, 31.9 (5CH₂ cyclohex) ; 41.4 (CH cyclohexyl) ; 51.8 (CHCO₂CH₃) ; 52.1, 52.5 (2CH₃O) ; 127.6 (CH₂=C) ; 137.7 (C=CH₂) ; 167.4, 173.9 (2CO). m/z: 240 (M⁺, 1) ; (181 (5) ; 157 (30) ; 126 (100). Anal. Calcd for C₁₃H₂₀O₄ : C, 64.98 ; H, 8.38. Found : C, 64.86 ; H, 8.36.

Synthesis of 3-Alkyl-1-benzyl-4-methoxycarbonyl pyrrolidin-2-ones (6)

Typical procedure

To a solution of dimethyl β -cyclohexyl- α -methylenesuccinate **3j** (2.4 g, 10 mmol) in methanol-water (10 mL: 9/1) was added dropwise benzylamine (2.1g, 21mmol). After stirring during 20 hours at room temperature, the reaction mixture was concentrated, the organic residue was purified on column chromatography by using silica gel (ethyl acetate/hexane 2:8). The *cis* and *trans* lactams diastereoisomers **6j** were separated.

Trans-1-Benzyl-3-ethyl-4-methoxycarbonyl pyrrolidin-2-one (6b)

IR (neat) $\nu_{\max}$ / cm⁻¹: 1681 (CON) ; 1735 (COO). ¹H NMR (CDCl₃, δ ppm, *J* Hz): 0.98 (t, 3H, *J* = 7.4, CH₃-CH₂) ; 1.68, 1.91 (2m, 2H, CH₂CH₃) ; 2.76 (m, 1H, H³) ; 2.91 (m, 1H, H⁴) ; 3.37 (m, 2H, H^{5a}, H^{5b}) ; 3.69 (s, 3H, CH₃O) ; 4.40, 4.52 (AB, 2H, *J* = 14.7, CH₂C₆H₅) ; 7.26 (m, 5H, C₆H₅). ¹³C NMR (CDCl₃, δ

ppm): 10.3 ($\underline{\text{CH}_3\text{CH}_2}$) ; 23.2 ($\underline{\text{CH}_2\text{CH}_3}$) ; 41.3 ($\underline{\text{NCH}_2\text{CH}}$) ; 46.3, 46.4 (2 $\underline{\text{CHCO}}$) ; 46.7 ($\underline{\text{CH}_3\text{O}}$) ; 52.1 ($\underline{\text{NCH}_2\text{C}_6\text{H}_5}$) ; 127.4, 127.8, 128.5 (5 $\underline{\text{CH}}$ arom) ; 135.8 ($\underline{\text{C}}$ arom) ; 173.2, 173.8 (2 $\underline{\text{CO}}$). m/z : 261 (M^+ , 41) ; 232 (11) ; 174 (78) ; 91 (100). Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$: C, 68.94 ; H, 7.32 ; N, 5.35. Found : C, 68.87 ; H, 7.33 ; N, 5.39.

Cis-1-Benzyl-3-ethyl-4-methoxycarbonyl pyrrolidin-2-one (6b)

IR (neat) ν_{max} / cm^{-1}): 1681 (CON) ; 1735 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 1.02 (t, 3H, $J=7.5$, $\underline{\text{CH}_3\text{CH}_2}$) ; 1.49, 1.82 (2m, 2H, $\underline{\text{CH}_2\text{CH}_3}$) ; 2.67 (m, 1H, H^3) ; 3.31 (m, 2H, H^4 , H^{5a}) ; 3.45 (m, 1H, H^{5b}) ; 3.67 (s, 3H, CH_3O) ; 4.41, 4.51 (AB, 2H, $J=14.7$, $\underline{\text{CH}_2\text{C}_6\text{H}_5}$) ; 7.29 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 11.7 ($\underline{\text{CH}_3\text{CH}_2}$) ; 20.7 ($\underline{\text{CH}_2\text{CH}_3}$) ; 41.0 ($\underline{\text{NCH}_2\text{CH}}$) ; 45.7, 46.4 (2 $\underline{\text{CHCO}}$) ; 46.8 ($\underline{\text{CH}_3\text{O}}$) ; 51.7 ($\underline{\text{NCH}_2\text{C}_6\text{H}_5}$) ; 127.5, 128.1, 128.5 (5 $\underline{\text{CH}}$ arom) ; 136.0 ($\underline{\text{C}}$ arom) ; 172.0, 174.0 (2 $\underline{\text{CO}}$). m/z : 261 (M^+ , 19) ; 232 (4) ; 174 (60) ; 91 (100).

Trans-1-Benzyl-3-n-propyl-4-methoxycarbonyl pyrrolidin-2-one (6c)

IR (neat) ν_{max} / cm^{-1}): 1681 (CON) ; 1735 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.95 (t, 3H, $J=7.2$, $\underline{\text{CH}_3\text{CH}_2}$) ; 1.42 (m, 2H, $\underline{\text{CH}_2\text{CH}_3}$) ; 1.54, 1.86 (2m, 2H, $\underline{\text{CHCH}_2\text{CH}_2}$) ; 2.82 (m, 1H, H^3) ; 2.89 (m, 1H, H^4) ; 3.36 (m, 2H, H^{5a} , H^{5b}) ; 3.69 (s, 3H, CH_3O) ; 4.40, 4.51 (AB, 2H, $J=14.7$, $\underline{\text{CH}_2\text{C}_6\text{H}_5}$) ; 7.26 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 13.8 ($\underline{\text{CH}_3\text{CH}_2}$) ; 19.5 ($\underline{\text{CH}_2\text{CH}_3}$) ; 32.7 ($\underline{\text{CH}_2\text{CH}_2\text{CH}}$) ; 42.1 ($\underline{\text{NCH}_2\text{CH}}$) ; 45.1, 46.4 (2 $\underline{\text{CHCO}}$) ; 46.9 ($\underline{\text{CH}_3\text{O}}$) ; 52.1 ($\underline{\text{NCH}_2\text{C}_6\text{H}_5}$) ; 127.5, 127.8, 128.5 (5 $\underline{\text{CH}}$ arom) ; 135.9 ($\underline{\text{C}}$ arom) ; 173.3, 174.2 (2 $\underline{\text{CO}}$). m/z : 275 (M^+ , 12) ; 233 (24) ; 174 (100) ; 91 (66). Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$: C, 69.79 ; H, 7.68 ; N, 5.08. Found : C, 69.66 ; H, 7.73 ; N, 5.09.

Cis-1-Benzyl-3-n-propyl-4-methoxycarbonyl pyrrolidin-2-one (6c)

IR (neat) ν_{max} / cm^{-1}): 1681 (CON) ; 1735 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.92 (t, 3H, $J=7.2$, $\underline{\text{CH}_3\text{CH}_2}$) ; 1.43, 1.75 (2m, 4H, $\underline{\text{CH}_2\text{CH}_2}$) ; 2.73 (m, 1H, H^3) ; 3.29 (m, 2H, H^4 , H^{5a}) ; 3.44 (m, 1H, H^{5b}) ; 3.66 (s, 3H, CH_3O) ; 4.43, 4.51 (AB, 2H, $J=14.7$, $\underline{\text{CH}_2\text{C}_6\text{H}_5}$) ; 7.29 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 14.0 ($\underline{\text{CH}_3\text{CH}_2}$) ; 20.4 ($\underline{\text{CH}_2\text{CH}_3}$) ; 29.4 ($\underline{\text{CH}_2\text{CH}_2\text{CH}}$) ; 41.1 ($\underline{\text{NCH}_2\text{CH}}$) ; 44.1, 46.4 (2 $\underline{\text{CHCO}}$) ; 46.7 ($\underline{\text{CH}_3\text{O}}$) ; 51.6 ($\underline{\text{NCH}_2\text{C}_6\text{H}_5}$) ; 127.5, 128.0, 128.5 (5 $\underline{\text{CH}}$ arom) ; 136.0 ($\underline{\text{C}}$ arom) ; 172.0, 174.1 (2 $\underline{\text{CO}}$). m/z : 275 (M^+ , 12) ; 233 (23) ; 174 (100) ; 91 (76).

Trans-1-Benzyl-3-i-propenyl-4-methoxycarbonyl pyrrolidin-2-one (6e)

IR (neat) ν_{max} / cm^{-1}): 1685 (CON) ; 1736 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 1.8 (s, 3H, $\text{CH}_3\text{C}=\text{}$) ; 3.12 (m, 1H, H^4) ; 3.41 (m, 2H, H^{5a} , H^{5b}) ; 3.50 (d, 1H, $J_{\text{H}^3\text{H}^4}=8.4$, H^3) ; 3.70 (s, 3H, CH_3O) ; 4.39, 4.57 (AB, 2H, $J=14.7$, $\underline{\text{CH}_2\text{C}_6\text{H}_5}$) ; 4.96, 5.02 (2s, 2H, $\text{CH}_2=\text{}$) ; 7.28 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 19.3 ($\underline{\text{CH}_3\text{C}=\text{}}$) ; 41.6 ($\underline{\text{CH}_2\text{CH}}$) ; 46.7 ($\underline{\text{CHCOOCH}_3}$) ; 46.8 ($\underline{\text{CH}_3\text{O}}$) ; 52.2 ($\underline{\text{NCH}_2\text{C}_6\text{H}_5}$) ; 53.3 ($\underline{\text{CHC}=\text{}}$) ; 115.6 ($\text{CH}_2=\text{}$) ; 127.6, 128.0, 128.6 (5 $\underline{\text{CH}}$ arom) ; 135.8 ($\underline{\text{C}}$ arom) ; 140.3 ($=\underline{\text{CCH}_3}$) ; 171.9, 172.6 (2 $\underline{\text{CO}}$). m/z : 273 (M^+ , 26) ; 214 (23) ; 190 (24) ; 118 (12) ; 91 (100). Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3$: C, 70.30 ; H, 7.00 ; N, 5.12. Found : C, 70.25 ; H, 7.03 ; N, 5.10.

Trans-1-Benzyl-3-n-butyl-4-methoxycarbonyl pyrrolidin-2-one (6f)

IR (neat) $\nu_{\max}$ / cm^{-1}): 1681 (CON) ; 1736(COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.91 (t, 3H, $J=7.0$, CH_3CH_2) ; 1.36 (m, H, $\text{CH}_2\text{CH}_2\text{CH}_3$) ; 1.59, 1.88 (2m, 2H, $\text{CH}_2\text{CH}_2\text{CH}$) ; 2.81 (m, 1H, H^3) ; 2.90 (m, 1H, H^4) ; 3.37 (m, 2H, H^{5a} , H^{5b}) ; 3.69 (s, 3H, CH_3O) ; 4.40, 4.50 (AB, 2H, $J=14.7$, $\text{CH}_2\text{C}_6\text{H}_5$) ; 7.26 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 13.7 (CH_3CH_2) ; 22.3 (CH_2CH_3) ; 28.3 ($\text{CH}_3\text{CH}_2\text{CH}_2$) ; 30.2 ($\text{CH}_2\text{CH}_2\text{CH}$) ; 42.0 (NCH_2CH) ; 45.1, 46.3 (2 CHCO) ; 46.8 (CH_3O) ; 52.0 ($\text{NCH}_2\text{C}_6\text{H}_5$) ; 127.4, 127.8, 128.5 (5 CH arom) ; 135.8 (C arom) ; 173.2, 174.1 (2 CO). m/z : 289 (M^+ , 14) ; 233 (27) ; 174 (100) ; 91 (73). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_3$: C, 70.56 ; H, 8.01 ; N, 4.84. Found : C, 70.47 ; H, 8.04 ; N, 4.79.

Cis-1-Benzyl-3-n-butyl-4-methoxycarbonyl pyrrolidin-2-one (6f)

IR (neat) $\nu_{\max}$ / cm^{-1}): 1681 (CON) ; 1736 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.89 (t, 3H, $J=7.1$, CH_3CH_2) ; 1.38, 1.80 (2m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$) ; 2.72 (m, 1H, H^3) ; 3.31 (m, 2H, H^4 , H^{5a}) ; 3.45 (m, 1H, H^{5b}) ; 3.66 (s, 3H, CH_3O) ; 4.43, 4.52 (AB, 2H, $J=14.7$, $\text{CH}_2\text{C}_6\text{H}_5$) ; 7.28 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 13.8 (CH_3CH_2) ; 22.6 (CH_2CH_3) ; 27.1 ($\text{CH}_3\text{CH}_2\text{CH}_2$) ; 29.3 ($\text{CH}_2\text{CH}_2\text{CH}$) ; 41.2 (NCH_2CH) ; 44.3, 46.5 (2 CHCO) ; 46.8 (CH_3O) ; 51.7 ($\text{NCH}_2\text{C}_6\text{H}_5$) ; 127.5, 128.1, 128.6 (5 CH arom) ; 136.0 (C arom) ; 172.1, 174.2 (2 CO). m/z : 289 (M^+ , 14) ; 233 (25) ; 174 (100) ; 91 (90).

Trans-1-Benzyl-3-t-butyl-4-methoxycarbonyl pyrrolidin-2-one (6g)

IR (neat) $\nu_{\max}$ / cm^{-1}): 1681 (CON) ; 1733 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 1.06 (s, 9H, 3 CH_3) ; 2.70 (d, 1H, $J_{\text{H}^3\text{H}^4}=6.6$, H^3) ; 3.00 (m, 1H, H^4) ; 3.31 (m, 2H, H^{5a} , H^{5b}) ; 3.68 (s, 3H, CH_3O) ; 4.34, 4.57 (AB, 2H, $J=14.7$, $\text{CH}_2\text{C}_6\text{H}_5$) ; 7.26 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 27.3 ($\text{C}(\text{CH}_3)_3$) ; 33.4 ($\text{C}(\text{CH}_3)_3$) ; 39.2 (NCH_2CH) ; 46.5, 47.1 (2 CHCO) ; 52.3 (CH_3O) ; 54.7 ($\text{NCH}_2\text{C}_6\text{H}_5$) ; 127.5, 128.0, 128.6 (5 CH arom) ; 136.1 (C arom) ; 173.1, 174.3 (2 CO). m/z : 289 (M^+ , 19) ; 232 (22) ; 174 (100) ; 91 (76).

Cis-1-Benzyl-3-t-butyl-4-methoxycarbonyl pyrrolidin-2-one (6g)

IR (neat) $\nu_{\max}$ / cm^{-1}): 1681 (CON) ; 1733 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 1.09 (s, 9H, (3 CH_3)) ; 2.59 (d, 1H, $J_{\text{H}^3\text{H}^4}=7.9$, H^3) ; 3.24 (m, 2H, H^4 , H^{5a}) ; 3.38 (m, 1H, H^{5b}) ; 3.62 (s, 3H, CH_3O) ; 4.45, 4.49 (AB, 2H, $J=14.7$, $\text{CH}_2\text{C}_6\text{H}_5$) ; 7.29 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 28.2 (3 CH_3) ; 32.8 ($\text{C}(\text{CH}_3)_3$) ; 41.4 (NCH_2CH) ; 46.6, 47.3 (2 CHCO) ; 51.6 (CH_3O) ; 55.1 ($\text{NCH}_2\text{C}_6\text{H}_5$) ; 127.5, 128.4, 128.5 (5 CH arom) ; 136.2 (C arom) ; 172.6, 173.2 (2 CO). m/z : 289 (M^+ , 17) ; 232 (23) ; 174 (100) ; 91 (81).

Trans-1-Benzyl-3-benzyl-4-methoxycarbonyl pyrrolidin-2-one (6i)

IR (neat) $\nu_{\max}$ / cm^{-1}): 1685 (CON) ; 1735 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 2.88 (m, 1H, H^3) ; 3.13 (m, 4H, H^{5a} , H^{5b} , $\text{C}_6\text{H}_5\text{CH}_2\text{CH}$) ; 3.28 (dd, 1H, H^4) ; 3.54 (s, 3H, CH_3O) ; 4.33, 4.52 (AB, 2H, $J=14.76$, $\text{NCH}_2\text{C}_6\text{H}_5$) ; 7.19 (m, 10H, 2 C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 35.2 ($\text{C}_6\text{H}_5\text{CH}_2\text{CH}$) ; 40.6 (NCH_2CH) ; 46.5, 46.7, 46.8 (2 CHCO , CH_3O) ; 52.1 ($\text{NCH}_2\text{C}_6\text{H}_5$) ; 126.5, 127.5, 127.9, 128.3, 128.6, 129.6 (10 CH arom) ; 135.7, 137.5 (2 C arom) ; 172.9, 173.2 (2 CO). m/z : 323 (M^+ , 45) ; 264 (19) ; 232 (81) ; 91 (100). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3$: C, 74.28 ; H, 6.54 ; N, 4.33. Found : C, 74.23 ; H, 6.48 ; N, 4.35.

Cis-1-Benzyl-3-benzyl-4-methoxycarbonyl pyrrolidin-2-one (6i)

IR (neat) $\nu_{\max}$ / cm^{-1}): 1685 (CON) ; 1735 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 2.80 (m, 1H, H^3) ; 3.08-3.28 (m, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}$, H^4 , H^{5a} , H^{5b}) ; 3.48 (s, 3H, CH_3O) ; 4.47 (s, 2H, $\text{NCH}_2\text{C}_6\text{H}_5$) ; 7.25 (m, 10H, 2 C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 32.8 ($\text{C}_6\text{H}_5\text{CH}_2\text{CH}$) ; 40.5 (NCH_2CH) ; 45.7, 46.6 (2 CHCO) ; 46.9 (CH_3O) ; 51.6 ($\text{NCH}_2\text{C}_6\text{H}_5$) ; 127.9, 128.1, 128.2, 128.3, 128.6, 129.8 (10 CH arom) ; 135.8, 138.5 (2 C arom) ; 173.2, 173.6 (2 CO). m/z : 323 (M^+ , 49) ; 264 (20) ; 232 (89) ; 91 (100).

Trans-1-Benzyl-3-cyclohexyl-4-methoxycarbonyl pyrrolidin-2-one (6j)

IR (neat) $\nu_{\max}$ / cm^{-1}): 1680 (CON) ; 1735 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 1.0-2.0 (m, 11H, C_6H_{11}) ; 2.80 (dd, 1H, $J_{\text{H}^3\text{H}^4}=7$, $J_{\text{H}^3\text{H}^6}=3.9$, H^3) ; 3.00 (m, 1H, H^4) ; 3.34 (m, 2H, H^{5a} , H^{5b}) ; 3.69 (s, 3H, CH_3O) ; 4.36, 4.57 (AB, 2H, $J=14.8$, $\text{CH}_2\text{C}_6\text{H}_5$) ; 7.27 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 26.1, 26.3, 28.1, 30.4 ; 38.6 (C_6H_{11}) ; 38.4 (CHCH_2N) ; 46.5, 47.5 (2 CHCO) ; 51.1 (CH_3O) ; 52.3 ($\text{CH}_2\text{C}_6\text{H}_{11}$) ; 127.6, 128.0, 128.6 (5 CH arom) ; 136.0 (C arom) ; 173.7, 174.1 (2 CO). m/z : 315 (M^+ , 6) ; 233 (35) ; 174 (99) ; 91 (100). Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_3$: C, 72.35 ; H, 7.98 ; N, 4.44. Found : C, 72.27 ; H, 7.89 ; N, 4.39.

Cis-1-Benzyl-3-cyclohexyl-4-methoxycarbonyl pyrrolidin-2-one (6j)

IR (neat) $\nu_{\max}$ / cm^{-1}): 1680 (CON) ; 1735 (COO). ^1H NMR (CDCl_3 , δ ppm, J Hz): 0.8-1.9 (m, 11H, C_6H_{11}) ; 2.61 (dd, 1H, $J_{\text{H}^3\text{H}^4}=8.96$, $J_{\text{H}^3\text{H}^6}=4.5$, H^3) ; 3.29 (m, 2H, H^4 , H^{5a}) ; 3.48 (m, 1H, H^{5b}) ; 3.68 (s, 3H, CH_3O) ; 4.46 (s, 2H, $\text{CH}_2\text{C}_6\text{H}_5$) ; 7.28 (m, 5H, C_6H_5). ^{13}C NMR (CDCl_3 , δ ppm): 25.9, 26.1, 26.6, 29.3, 31.5, 38.2 (C_6H_{11}) ; 41.2 (CHCH_2N) ; 46.3, 47.2 (2 CHCO) ; 49.3 (CH_3O) ; 51.7 ($\text{CH}_2\text{C}_6\text{H}_5$) ; 128.2, 128.5, 128.6 (5 CH arom) ; 136.1 (C arom) ; 171.8, 173.3 (2 CO). m/z : 315 (M^+ , 8) ; 233 (42) ; 174 (100) ; 91 (77).

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