Pergamon

Tetrahedron Vol. 51, No. 1, pp. 119-128, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)00873-6

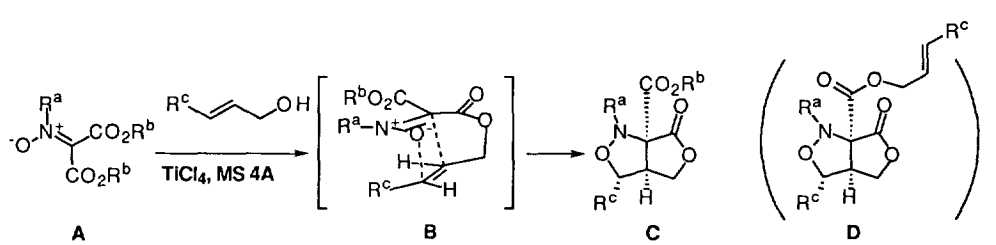
Studies on Tandem Transesterification and Intramolecular Cycloaddition of Nitrones. 2. Sequential Bicyclization of α,α-Dialkoxycarbonylnitrones with Allyl Alcohols

Osamu Tamura,* Toshiyuki Okabe, Tatsuya Yamaguchi, Junko Kotani, Kentoku Gotanda, and Masanori Sakamoto*

Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya, Tokyo 154, Japan

Abstract: Treatment of α,α-alkoxycarbonylnitrones with 1.5 equiv. of allyl alcohols in the presence of 0.1 equiv. of titanium tetrachloride and molecular sieves 4A causes tandem transesterification, *E,Z*-isomerization of the nitrone moieties, and intramolecular 1,3-dipolar cycloaddition to furnish bicyclic compound having ester group at the bridge head position. These reactions rarely give double transesterification product due to high reactivity of the intermediates as dipolars rather than transesterification reactivity.

Intramolecular cycloaddition of nitrones has been used for stereoselective construction of nitrogen containing carbon frameworks.[1] In the preceding paper,[2] we reported that treatment of α-methoxycarbonyl-nitrones with allyl alcohols in the presence of catalytic amounts of titanium tetrachloride and molecular sieves 4A (MS 4A) causes tandem[3] transesterification[4] and intramolecular 1,3-dipolar cycloaddition to give bicyclic compounds in one step. It was also reported[2] that the nitrones react selectively with (*Z*)-allyl alcohols of geometrical mixture of the allyl alcohols, namely, geometry differentiated cycloaddition.[2] If this tandem process can be applied to α,α-dialkoxycarbonylnitrones (**A**), it will give the corresponding intramolecular cycloadducts (**C**) *via* the intermediates (**B**). The cycloadducts (**C**) would be useful building blocks for various nitrogen containing compounds of biological interest such as α-substituted amino acids.[5] The crucial point of the sequential reaction would be whether the reaction can give **C** in place of further transesterification products (**D**), since **B** and **C** still have additional ester groups, which seem to be capable of further transesterification. We have now found that α,α-dialkoxycarbonylnitrones (**A**) react with allyl alcohols in the presence of catalytic amounts of titanium tetrachloride and MS 4A to afford bicyclic compounds (**C**) having ester group at the bridgehead position without double transesterification products (**D**).



A **B** **C** **D**

Results and Discussion

The starting α,α-dialkoxycarbonylnitrones (**1a-c**) were readily prepared by treatment of oxomalonic acid with alcoholic hydrogen chloride and heating with *N*-benzylhydroxylamine.[6] Tandem transesterification and intramolecular cycloaddition of **1a-c** with allyl alcohols (**2-6**) generally afforded bicyclic compounds (**7-11**) as shown in **Table 1**. In these reactions, the reaction of **1a** with **2** was the only one case which gave double transesterification product (**7'**) as a by-product. Thus, reaction of **1a** (1 equiv.) with **2** (1.5 equiv.) in the presence of titanium tetrachloride (0.1 equiv.) and MS 4A at room temperature smoothly proceeded to give **7a** accompanied by **7'** (entry 1). Although the reaction of **1b** with **2** required longer reaction time, it gave only **7b** in 74% yield (entry 2). When more bulky nitrone (**1c**) was used, the yield was remarkably decreased,

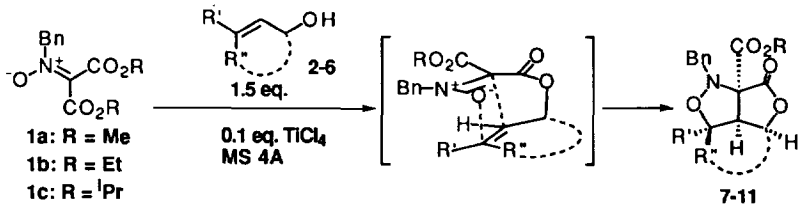
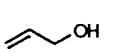
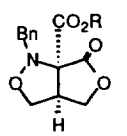
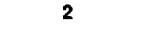
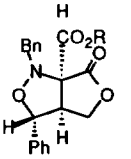
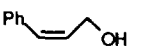
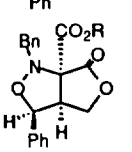
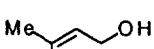
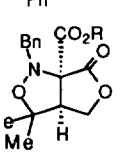
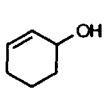
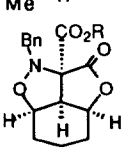


Table 1. Tandem transesterification and intramolecular cycloaddition of α,α-dialkoxycarbonylnitrones (**1a-c**) with allyl alcohols (**2-6**).[a]

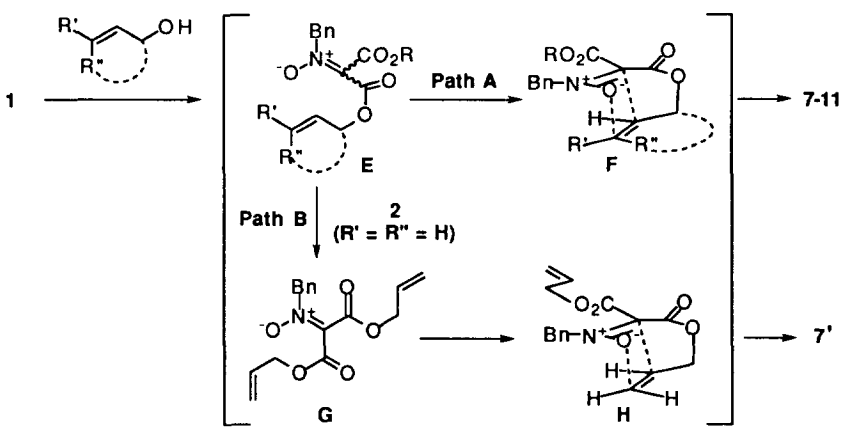
Entry	Nitrone	Allyl Alcohol	Conditions	Yield (%)[b]	Product
1	1a	 2	r.t., 1 h	44 26	 7a: R = Me 7': R = $CH_2CH{=}CH_2$
2	1b		r.t., 74 h	74	7b: R = Et
3	1c		r.t., 96 h	13	7c: R = iPr
4	1a	 3	r.t. 26 h; 50 °C, 5 h	65	 8a: R = Me
5	1b		r.t., 94 h	64	8b: R = Et
6	1a	 4	r.t., 48 h; 50 °C, 3 h	60	 9a: R = Me
7	1b		r.t., 42 h	84	9b: R = Et
8	1a	 5	r.t., 2 h	76	 10a: R = Me
9	1b		r.t., 42 h	73	10b: R = Et
10	1a	 6	r.t., 1 h	75	 11a: R = Me
11	1b		50 °C, 33 h	62	11b: R = Et

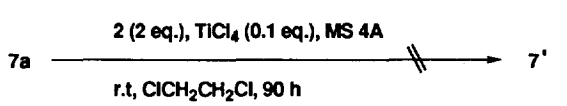
a) All the reactions were carried out in 1,2-dichloroethane by employing **1** (1 equiv.), allyl alcohol (1.5 equiv.), titanium tetrachloride (0.1 equiv.), and MS 4A (ca. 1 g/ mmol of **1**). b) Isolated yields.

presumably due to the steric hindrance (entry 3). Among these three types of nitrones, **1a** and **1b** were employed for the reactions using other allyl alcohols (**3**-**6**). This tandem process of α,α-dialkoxycarbonylnitrones (**1**) reflects the geometries of allyl alcohols similar to that of α-methoxycarbonylnitrone. While the reactions of **1a,b** with (*E*)-cinnamyl alcohol (**3**) exclusively afforded **8a,b** having 4,5-*trans*-stereochemistry on the isoxazolidine rings (entries 4,5), those of **1a,b** with (Z)-cinnamyl alcohol (**4**) gave **9a,b** bearing 4,5-*cis*-stereochemistry on the isoxzolidine rings (entries 6,7). 3,3-Disubstituted allyl alcohol (**5**) and cyclic allyl alcohol (**6**) also reacted with **1a,b** to afford corresponding cycloadducts **10a,b** and **11a,b**, respectively.

Formation of **7**-**11** may be explained as follows. Transesterification of **1** with **2**-**6** provides nitrone intermediate (**E**), which causes *E,Z*-isomerization of the nitrone moiety and intramolecular cycloaddition *via* transition state (**F**), giving **7**-**11** (path A) as shown in **Scheme 1**. The double transesterification product (**7'**) seems to be formed *via* intermediate (**G**) and transition state (**H**) (path B), since transesterification of **7a** with **2** (2 equiv.) to **7'** in the presence of titanium tetrachloride and MS 4A did not proceed at all. Electrophilicity of the nitrone moiety and substituent effect of the olefin moiety in E would play important roles in the selection of the reaction pathway (path A or B). Thus, the highly electrophilic nitrone moiety having ester group would cause rapid cycloaddition with the olefin moiety having any electron donating group such as alkyl or aryl groups before transesterification of the ester group with an allyl alcohol. Accordingly, reaction of **1a,b** with **3**-**6** bearing at least one electron donating group proceeded *via* path A to afford **8**-**11a,b** (entries 4-11), and reaction of **1a** with **2** having no electron donating group proceeded *via* both pathways to give **7a** and **7'**.[7]

Scheme 1





In the preceding paper, it was observed that reaction of α-methoxycarbonylnitrone (**1d**) with an excess of an 86 : 14 mixture of (*E*)- and (Z)-crotyl alcohols (**12**) showed reversal of selectivity to give a 13 : 87 mixture of the *trans*-**13d** and *cis*-**13d**. In contrast, the reaction of α,α-dialkoxycarbonylnitrone (**1a,b**) gave adducts in ratios which reflected the geometrical ratio of **12** to some extent (**Table 2**). Thus, in the case of **1a**, the reaction

afforded an 83 : 17 mixture of *trans*-**13a** and *cis*-**13a** in 87% yield (entry 1). The reaction of **1b** also gave *trans*-**13b** predominantly (entry 2).

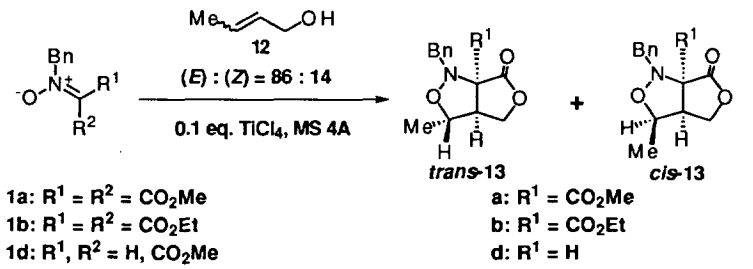


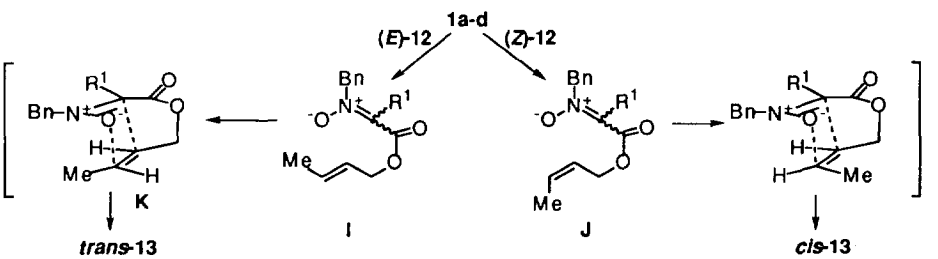
Table 2. Tandem transesterification and intramolecular cycloaddition of **1a,b** with geometrical mixture of crotyl alcohols (**12**).[a]

Entry	Nitrone	Conditions	Yield (%)	Product	Ratio[b] (*trans*-13 : *cis*-13)
1	1a	r.t., 67 h; 50 °C, 10 h	87	*trans*-13a *cis*-13a	83 : 17
2	1b	r.t., 23 h	81	*trans*-13b *cis*-13b	78 : 22

a) All the reactions were carried out in 1,2-dichloroethane using **1** (1 equiv.), **12** (10 equiv.). b) The ratios were estimated by integrations of their ^{1}H-NMR spectra.

Transesterification and reactivity of the intermediates again may play key roles in the difference between the reactions of **1a,b** and that of **1d** (**Scheme 2**). In the case of **1d**, intermediates (**I**) and (**J**) (R^1 = H) are equilibrated with each other *via* transesterification with (*Z*)-**12** and (*E*)-**12**, respectively. The selectivity (*trans*-**13d** : *cis*-**13d** = 13 : 87) is due to **I** having a steric hindrance between benzyl and methyl groups in the transition state (**K**). In the cases of **1a,b**, once transesterification occurs, resulting **I** and **J** (R^1 = CO_2R) have enough reactivities (electrophilicities) to cause rapid cycloaddition to afford *trans*-**13a,b** and *cis*-**13a,b**, respectively before further transesterification.[8] Accordingly, the reactions of **1a,b** with **12** gave the ratios of the products which reflected the geometrical ratio of **12**.

Scheme 2



Conclusion

As stated, we have found that treatment of α,α-alkoxycarbonylnitrones with 1.5 equiv. of allyl alcohols in the presence of 0.1 equiv. of titanium tetrachloride and molecular sieves 4A causes tandem transesterification, *E,Z*-isomerization of the nitrone moieties, and intramolecular 1,3-dipolar cycloaddition to furnish bicyclic compounds having ester group at the bridgehead position. The cycloadducts might be useful building blocks for various nitrogen containing compounds of biological interest such as α-substituted amino acids.

Experimental

General. All melting points were determined with a Yanagimoto MP-21 melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-30, and a Shimadzu FTIR-8100 spectrometer. ^{1}H-NMR spectra were measured with a JEOL JNM-EX270 (270 MHz) and a JEOL JNM-EX400 (400 MHz) spectrometer. The chemical shifts are expressed in ppm downfield from tetramethylsilane, using tetramethylsilane (δ = 0) and/or residual chloroform (δ = 7.25) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sept, septet; m, multiplet; br, broad signal. Mass spectra were taken with a JEOL JMS-DX302 mass spectrometer. Unless otherwise noted, all experiments were carried out under an atmosphere of dry argon using anhydrous solvents. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254, 0.25 mm, Art 5715) were used. The following abbreviations were used for solvents: diethyl ether (Et_2O), ethyl acetate (AcOEt), ethanol (EtOH), methanol (MeOH), and dichloromethane (CH_2Cl_2).

Dimethyl [(Phenylmethyl)imino]malonate *N*-Oxide (1a) Thionyl chloride (7.5 ml, 0.1 mol) and oxomalonic acid monohydrate (10.0 g, 74 mmol) were added to MeOH (400 ml) at room temperature. The mixture was heated at reflux for 0.5 h, and then concentrated *in vacuo* to give a residue. Toluene and N-benzylhydroxylamine[9] were added to the residue, and the mixture was refluxed 0.5 h employing a Dean-Stark trap. After cooling, the mixture was washed with a 5% solution of Na_2CO_3 and brine, and then dried over $MgSO_4$. Concentration of the mixture gave a residue, which was purified by column chromatography on silica gel (Et_2O : hexane = 1 : 1) to afford **1a** (8.71 g, 47%, two steps) as colorless crystals, mp 68-69 °C (recrystallized from hexane-Et_2O). IR ($CHCl_3$): 1740, 1541, 1233, 1111 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): δ 3.84 (3 H, s, CO_2Me), 3.88 (3 H, s, CO_2Me), 5.73 (2 H, s, PhC*H*$_2$), 7.52-7.34 (5 H, m, ArH). MS m/z: 251,(M^+, 2%), 234 (18), 221 (5), 175 (4), 91 (100). HRMS m/z: Calcd for $C_{12}H_{13}NO_5$: 251.0793. Found: 251.0793. Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.85. Found: C, 57.50; H, 5.32; N, 5.48.

Diethyl [(Phenylmethyl)imino]malonate *N*-Oxide (1b) a) This (20.8 mg, 50%) was prepared from thionyl chloride (15 μl, 0.21 mmol), oxomalonic acid monohydrate (20.0 mg, 0.15 mmol), EtOH (0.7 ml), N-benzylhydroxylamine (21.7 mg, 0.18 mmol), and toluene (1.5 ml) in the same manner as described for the preparation of **1a**. Colorless syrup. IR ($CHCl_3$): 1736, 1229, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): δ 1.30 (3 H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 1.33 (3 H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 4.29 (2 H, q, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 4.36 (2 H, q, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 5.72 (2 H, s, PhC*H*$_2$), 7.33-7.52 (5 H, m, ArH). MS m/z: 279 (M^+, 0.2%), 189 (3), 117, (4), 91 (100). HRMS m/z: Calcd for $C_{14}H_{17}NO_5$: 279.1107. Found: 279.1107.

b) Another lot of **1b** was prepared from diethyl oxomalonate[10]: A mixture of diethyl oxomalonate (1.50 g, 7.2 mmol), *N*-benzylhydroxylamine (0.884 g, 7.2 mmol), and camphor-10-sulfonic acid (50 mg) in xylenes (40 ml) was refluxed for 4 h. The mixture was diluted with a saturated solution of $NaHCO_3$, and then extracted with xylenes. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel (hexane : AcOEt = 3 : 1) to afford **1b** (1.49 g, 75%). The IR and ^{1}H-NMR spectra of this sample were identical with those in a).

Diisopropyl [(Phenylmethyl)imino]malonate *N*-Oxide (1c) This (0.77 g, 85%) was prepared from thionyl chloride (0.3 ml, 4.1 mmol), oxomalonic acid monohydrate (400 mg, 2.9 mmol), isopropanol (4 ml), *N*-benzylhydroxylamine (400 mg, 13 mmol), and toluene (16 ml) in the same manner as described for the preparation of **1a**. Colorless syrup. IR ($CHCl_3$): 1728, 1545, 1377, 1233, 1094 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): δ 1.21 (6 H, d, J = 6.3 Hz, CO_2CHMe_2), 1.24 (6 H, d, J = 6.3 Hz, CO_2CHMe_2), 5.06 (1 H, sept, J = 6.3 Hz, CO_2CHMe_2), 5.16 (1 H, sept, J = 6.3 Hz, CO_2CHMe_2), 5.63 (2 H, s, $PhCH_2$), 7.26-7.46 (5 H, m, ArH). MS m/z: 307 (M^+, 0.8%), 290 (2), 265 (8), 245 (5), 206 (3), 91 (100). HRMS m/z: Calcd for $C_{16}H_{21}NO_5$: 307.1420. Found: 307.1421.

General Procedure: Reactions of the Nitrones (1a-c) with Allyl Alcohols (2-6, 12) in the Presence of Titanium Tetrachloride and MS 4A (Table 1 and Table 2). To a stirred suspension of an allyl alcohol (0.15 mmol) and MS 4A (100-150 mg) in dry 1,2-dichloroethane (1 ml) was added titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 0.1 ml, 0.01 mmol) at room temperature. After 15 min, a solution of **1** (0.1 mmol) in 1,2-dichloroethane (0.5 ml) was added to the mixture under the same conditions. After stirring under conditions indicated in **Table 1** and **Table 2**, a small amount of water was added to the mixture, and the mixture was stirred for 1 h. The mixture was filtered through a pad of Celite, then the filtrate was diluted with water, extracted with dichloromethane, and dried over $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give a cyclized product.

(3a*R,6a*R**)-Tetrahydro-6a-methoxycarbonyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (7a) and (3a*R**,6a*R**)-Tetrahydro-6a-allyloxycarbonyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (7') (Table 1, entry 1).** Following General Procedure, **7a** (14.4 mg, 44%) and **7'** (8.8 mg, 26%) were prepared from **1a** (30.0 mg, 0.12 mmol), **2** (10.3 mg, 0.18 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 0.12 ml, 12 μmol), and MS 4A (210 mg) after column chromatography on silica gel (AcOEt-hexane, 3 : 2). **7a**, mp: 103-104 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$): 1779, 1757, 1221, 1217, 1190 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 3.71 (1 H, dddd, J = 7.9, 6.6, 3.0, 1.3 Hz, C_{3a}-H), 3.87 (3 H, s, CO_2Me), 3.88 (1 H, br d, J = 8.9 Hz, C3-*H*H), 3.98 (1 H, d, J = 14.9 Hz, PhC*H*H), 4.08 (1 H, ddd, J = 8.9, 6.6, 0.7 Hz, C3-H*H*), 4.30 (1 H, dd, J = 9.6, 3.0 Hz, C4-*H*H), 4.60 (1 H, d, J = 14.9 Hz, PhCH*H*), 4.66 (1 H, ddd, J = 9.6, 7.9, 0.7 Hz, C4-H*H*), 7.25-7.45 (5 H, m, ArH). MS m/z: 277 (M^+, 17%), 245 (2), 188 (5), 156 (4), 122 (8), 106 (7), 91 (100). HRMS m/z: Calcd for $C_{14}H_{15}NO_5$: 277.0950. Found: 277.0959. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.25; H, 5.43; N, 5.00. **7'**, a colorless syrup. IR ($CHCl_3$): 1779, 1732, 1649, 1285, 1188 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 3.73 (1 H, tdd, J = 6.6, 3.0, 1.0 Hz, C_{3a}-H), 3.89 (1 H, dd, J = 8.9, 1.0 Hz, C3-*H*H), 3.98 (1 H, d, J = 14.5 Hz, PhC*H*H), 4.09 (1 H, ddd, J = 8.9, 6.6, 0.7 Hz, C3-H*H*), 4.31 (1 H, dd, J = 9.6, 3.0 Hz, C4-*H*H), 4.62 (1 H, d, J = 14.5 Hz, PhCH*H*), 4.67 (1 H, ddd, J = 9.6, 6.6, 0.7 Hz, C4-H*H*), 4.76 (2 H, dq, J = 5.6, 1.3 Hz, CH_2=CHC*H*$_2$O), 5.32 (1 H, dq, J = 10.2, 1.3 Hz, Z-C*H*=CHCH$_2$O), 5.40 (1 H, dq, J = 17.2, 1.3 Hz, *E*-C*H*=CHCH$_2$O), 5.94 (1 H, ddt, J = 17.2, 10.2, 5.6 Hz, CH_2=C*H*CH$_2$O), 7.25-7.45 (5 H, m, ArH). MS m/z: 303 (M^+, 9%), 218 (4), 188 (5), 169 (5), 122 (8), 106 (7), 91 (100). HRMS m/z: Calcd for $C_{16}H_{17}NO_5$: 303.1107. Found: 303.1101.

(3a*R,6a*R**)-Tetrahydro-6a-ethoxycarbonyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (7b) (Table 1, entry 2).** Following General Procedure, **7b** (23.3 mg, 74%) was prepared from **1b** (30.0 mg, 0.11 mmol), **2** (11 μl, 0.16 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 0.11 μl, 11 μmol), and MS 4A (100 mg) after column chromatography on silica gel (AcOEt-hexane, 1 : 3). mp: 71-72 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$) : 1779, 1755, 1732, 1188 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ : 1.27 (3 H, t, J = 7.3 Hz, OCH_2CH_3), 3.64 (1 H, dddd, J = 7.9, 6.6, 2.6, 1.3

Hz, C_{3a}-H), 3.80 (1 H, dd, J = 8.9, 1.3 Hz, C_3-*H*H), 3.90 (1 H, d, J = 14.5 Hz, PhC*H*H), 4.01 (1 H, dd, J = 8.9, 6.6 Hz, C_3-H*H*), 4.18-4.34 (3 H, m, $CO_2CH_2CH_3$ and C_4-H), 4.54 (1 H, d, J = 14.5 Hz, PhCH*H*), 4.58 (1 H, m, C_4-H), 7.17-7.37 (5 H, m, ArH). MS m/z : 291 (M^+, 21 %), 188 (7), 122 (9), 92 (9), 91 (100). HRMS m/z : Calcd for $C_{15}H_{17}NO_5$: 291.1107. Found : 291.1102.

(3a*R,6a*S**)-Tetrahydro-6a-(isopropyloxycarbonyl)-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (7c) (Table 1, entry 3).** Following General Procedure, **7c** (2.0 mg, 13%) was prepared from **1c** (15.0 mg, 0.05 mmol), **2** (4.3 mg, 0.074 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 50 μl, 5.0 μmol), and MS 4A (136 mg) after column chromatography on silica gel (AcOEt-hexane, 2 : 3). IR ($CHCl_3$): 1778, 1749, 1603, 1509, 1456 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.33 (3 H, d, J = 6.0 Hz, CH*Me*Me), 1.34 (3 H, d, J = 6.0 Hz, CHMe*Me*), 3.68 (1 H, br t, J = 6.9 Hz, C_{3a}-H), 3.87 (1 H, br d, J = 9.0 Hz, C_3-*H*H), 3.96 (1 H, d, J = 14.5 Hz, PhC*H*H), 4.08 (1 H, dd, J = 9.0, 6.9 Hz, C_3-H*H*), 4.30 (1 H, dd, J = 9.2, 2.6 Hz, C_4-*H*H), 4.62 (1 H, d, J = 14.5 Hz, PhCH*H*), 4.65 (1 H, dd, J = 6.9, 2.6 Hz, C_4-H*H*), 5.19 (1 H, sept, J = 6.0 Hz, C*H*Me_2), 7.26-7.44 (5 H, m, ArH). MS m/z: 305 (M^+, 22%), 278 (2), 247 (3, 218 (7), 149 (4), 129 (5), 91 (100). HRMS m/z: Calcd for $C_{16}H_{19}NO_5$: 305.1263. Found: 305.1259.

(3*R,3a*R**,6a*S**)-Tetrahydro-6a-methoxycarbonyl-3-phenyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (8a) (Table 1, entry 4)** Following General Procedure, **8a** (36.0 mg, 65%) was prepared from **1a** (40.0 mg, 0.16 mmol), **3** (32.0 mg, 0.24 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 160 μl, 16 μmol), and MS 4A (370 mg) after column chromatography on silica gel (Et_2O-hexane, 1 : 2). mp: 109.5-110 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$): 1782, 1759, 1456, 1260, 1183 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 3.81 (1 H, ddd, J = 6.9, 3.3, 2.0 Hz, C_{3a}-H), 3.83 (3 H, s, CO_2Me), 4.54 (1 H, d, J = 14.8 Hz, PhC*H*H), 4.57 (1 H, dd, J = 9.6, 2.0 Hz, C_4-*H*H), 4.67 (1 H, d, J = 14.8 Hz, PhCH*H*), 4.73 (1 H, dd, J = 9.6, 6.9 Hz, C_4-H*H*), 4.98 (1 H, d, J = 3.3 Hz, C_3-H), 7.17-7.45 (10 H, m, ArH). MS m/z: 353 (M^+, 54%), 294 (7), 218 (7), 190 (6), 143 (17), 115 (12), 105 (8), 91 (100). HRMS m/z: Calcd for $C_{20}H_{19}NO_5$: 353.1263. Found: 353.1264.

(3*R,3a*R**,6a*S**)-Tetrahydro-6a-ethoxycarbonyl-3-phenyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (8b) (Table 1, entry 5)** Following General Procedure, **8b** (25.3 mg, 64%) was prepared from **1b** (30.0 mg, 0.11 mmol), **3** (21.6 mg, 0.16 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 110 μl, 11 μmol), and MS 4A (100 mg) after column chromatography on silica gel (CH_2Cl_2-hexane, 3 : 2). mp: 85-86 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$) : 1781, 1755, 1730, 1221 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.29 (3 H, t, J = 6.9 Hz, $CO_2CH_2CH_3$), 3.80 (1 H, ddd, J = 7.3, 3.3, 2.0 Hz, C_{3a}-H), 4.16 (1 H, d, J = 14.5 Hz, PhC*H*H), 4.29 (2 H, q, J = 6.9 Hz, $CO_2CH_2CH_3$), 4.56 (1 H, dd, J = 9.6, 2.0 Hz, C_4-*H*H), 4.69 (1 H, d, J = 14.5 Hz, PhCH*H*), 4.73 (1 H, dd, J = 9.6, 7.3 Hz, C_4-H*H*), 4.99 (1 H, d, J = 3.3 Hz, C_3-H), 7.27 (10 H, m, ArH). MS m/z : 367 (M^+, 55 %), 157 (18), 115 (11), 91 (100). HRMS m/z: Calcd for $C_{21}H_{21}NO_5$: 367.1420. Found : 367.1416.

(3*R,3a*S**,6a*R**)-Tetrahydro-6a-methoxycarbonyl-3-phenyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (9a) (Table 1, entry 6)** Following General Procedure, **9a** (34.0 mg, 60%) was prepared from **1a** (40.0 mg, 0.16 mmol), **4**[11] (32.0 mg, 0.24 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 160 μl, 16 μmol), and MS 4A (370 mg) after column chromatography on silica gel (AcOEt-hexane, 2 : 7). mp: 143.5-145 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$): 1779, 1757, 1497, 1456, 1383, 1250, 1186 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 3.81 (1 H, td, J = 7.3, 2.0 Hz, C_{3a}-H), 3.88 (3 H, s, CO_2Me), 3.89 (1 H, dd, J = 9.9, 2.0 Hz, C_4-*H*H), 4.15 (1 H, d, J = 14.9 Hz, PhC*H*H), 4.24 (1 H, dd, J = 9.9, 7.3 Hz, C_4-H*H*), 4.68 (1 H, d, J = 14.9 Hz, PhCH*H*), 5.29 (1 H, d, J = 7.3 Hz, C_3-H), 7.20-7.50 (10 H, m, ArH). MS m/z: 353

(M^+, 44%), 294 (7), 218 (4), 188 (5), 143 (31), 115 (9), 105 (7), 91 (100). HRMS m/z: Calcd for $C_{20}H_{19}NO_5$: 353.1263. Found: 353.1264. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.97. Found: C, 67.85; H, 5.44; N, 3.91.

(3*R,3a*S**,6a*R**)-Tetrahydro-6a-ethoxycarbonyl-3-phenyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (9b) (Table 1, entry 7)** Following General Procedure, **9b** (33.3 mg, 84%) was prepared from **1b** (30.0 mg, 0.11 mmol), **4** (21.6 mg, 0.16 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 110 µl, 11 µmol), and MS 4A (100 mg) after column chromatography on silica gel (CH_2Cl_2-hexane, 2 : 1). Colorless syrup. IR ($CHCl_3$) : 1754, 1732, 1186 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.35 (3 H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 3.80 (1 H, td, *J* = 7.6, 2.3 Hz, C_{3a}-H), 3.89 (1 H, dd, *J* = 9.9, 2.3 Hz, C_4-*H*H), 4.15 (1 H, d, *J* = 14.9 Hz, PhC*H*H), 4.23 (1 H, dd, *J* = 9.9, 7.6 Hz, C_4-H*H*), 4.29-4.43 (2 H, q, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 4.69 (1 H, d, *J* = 14.9 Hz, PhCH*H*), 5.28 (1 H, d, *J* = 7.3 Hz, C_3-H), 7.21-7.49 (10 H, m, ArH). MS m/z : 367 (M^+, 46 %), 188 (9), 157 (33), 115 (9), 91 (100). HRMS m/z: Calcd for $C_{21}H_{21}NO_5$: 367.1420. Found 367.1418.

(3a*R,6a*S**)-Tetrahydro-6a-methoxycarbonyl-3,3-dimethyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (10a) (Table 1, entry 8)** Following General Procedure, **10a** (18.4 mg, 76%) was prepared from **1a** (20.0 mg, 0.08 mmol), **5** (10.3 mg, 0.12 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 80 µl, 8 µmol), and MS 4A (170 mg) after column chromatography on silica gel (AcOEt-hexane, 2 : 3). Colorless syrup. IR ($CHCl_3$): 1779, 1757, 1258, 1175 1042 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.28 (3 H, s, C_3-Me), 1.40 (3 H, s, C_3-Me), 3.21 (1 H, dd, *J* = 5.6, 2.6 Hz, C_{3a}-H), 3.84 (3 H, s, CO_2Me), 4.06 (1 H, d, *J* = 15.5 Hz, PhC*H*H), 4.44 (1 H, dd, *J* = 10.6, 5.6 Hz, C_4-*H*H), 4.46 (1 H, dd, *J* = 10.6, 2.6 Hz, C_4-H*H*), 4.60 (1 H, d, *J* = 15.5 Hz, PhCH*H*), 7.20-7.47 (5 H, m, ArH). MS m/z: 305 (M^+, 29%), 246 (7), 232 (6), 190 (7), 104 (5), 91 (100). HRMS m/z: Calcd for $C_{16}H_{19}NO_5$: 305.1264. Found: 305.1268.

(3a*R,6a*S**)-Tetrahydro-6a-ethoxycarbonyl-3,3-dimethyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (10b) (Table 1, entry 9)** Following General Procedure, **10b** (20.9 mg, 73%) was prepared from **1b** (25.0 mg, 0.09 mmol), **5** (11.6 mg, 0.134 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 90 µl, 9 µmol), and MS 4A (190 mg) after column chromatography on silica gel (AcOEt-hexane, 1 : 3). Colorless syrup. IR ($CHCl_3$): 1778, 1751, 1370, 1256, 1227, 1119, 1042 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.27 (3 H, s, C_3-Me), 1.31 (3 H, t, *J* = 7.3 Hz, OCH_2CH_3), 1.39 (3 H, s, C_3-Me), 3.20 (1 H, dd, *J* = 5.6, 2.3 Hz, C_{3a}-H), 4.05 (1 H, d, *J* = 15.2 Hz, PhC*H*H), 4.30 (2 H, q, *J* = 7.3 Hz, OCH_2CH_3), 4.44 (1 H, dd, *J* = 9.6, 5.6 Hz, C_4-*H*H), 4.49 (1 H, dd, *J* = 9.6, 2.3 Hz, C_4-H*H*), 4.63 (1 H, d, *J* = 15.2 Hz, PhCH*H*), 7.18-7.72 (5 H, m, ArH). MS m/z: 319 (M^+, 13%), 246 (11), 204 (4), 188 (4), 157 (6), 91 (100). HRMS m/z: Calcd for $C_{17}H_{21}NO_5$: 319.1420. Found: 319.1428.

(3*R,3a*R**,4*S**,6a*S**)-Tetrahydro-6a-methoxycarbonyl-1-(phenylmethyl)-3,4-propano-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (11a) (Table 1, entry 10)** Following General Procedure, **11a** (14.2 mg, 75%) was prepared from **1a** (15.0 mg, 0.06 mmol), **6** (8.8 mg, 0.09 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 60 µl, 6 µmol), and MS 4A (120 mg) after column chromatography on silica gel (AcOEt-hexane, 1 : 1). mp: 148 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$): 1771, 1755, 1439, 1242, 1194, 1177 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.31-1.60 (4 H, m, C*H*H-CH_2-C*H*H), 1.98-2.03 (1 H, m, CH*H*-CH_2-CH_2), 2.21-2.26 (1 H, m, CH_2-CH_2-CH*H*), 3.26 (1 H, t, *J* = 6.6 Hz, C_{3a}-H), 3.77 (3 H, s, CO_2Me), 3.93 (1 H, d, *J* = 15.2 Hz, PhC*H*H), 4.08 (1 H, br t, *J* = 6.6 Hz, C_3-H), 4.53 (1 H, d, *J* = 15.2 Hz, PhCH*H*), 4.76 (1 H, br t, *J* = 6.6 Hz, C_4-H), 7.16-7.39 (5 H, m, ArH). MS m/z: 317 (M^+, 23%), 258 (12), 230 (10), 214 (4), 181 (5), 91 (100). HRMS m/z: Calcd for $C_{17}H_{19}NO_5$: 317.1264. Found: 317.1270. Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.22; H, 6.11; N, 4.39.

(3*R,3a*R**,4*S**,6a*S**)-Tetrahydro-6a-ethoxycarbonyl-1-(phenylmethyl)-3,4-propano-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (11b) (Table 1, entry 11)** Following General Procedure, **11b** (22.2 mg, 62%) was prepared from **1b** (30.0 mg, 0.11 mmol), **6** (16 μl, 0.16 mmol), and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 110 μl, 11 μmol), and MS 4A (100 mg) after column chromatography on silica gel (AcOEt-hexane, 1 : 3). mp: 99-100 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$): 1771, 1725, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.19-1.66 (4 H, m, methylene protons), 1.25 (3 H, t, *J* = 6.9 Hz, $CO_2CH_2CH_3$), 1.96-2.28 (2 H, m, methylene prorons), 3.25 (1 H, t, *J* = 6.9 Hz, C_{3a}-H), 3.93 (1 H, d, *J* = 14.9 Hz, PhC*H*H), 4.06-4.10 (1 H, m, C_{2a}-H), 4.15-4.33 (2 H, m, $CO_2CH_2CH_3$), 4.54 (1 H, d, *J* = 14.9 Hz, PhCH*H*), 4.80 (1 H, dt, *J* = 6.9, 2.6 Hz, C_4-H), 7.15-7.29 (5 H, m, ArH). MS m/z: 331 (M^+, 30 %), 258 (24), 230 (13), 91 (100). HRMS m/z: Calcd for $C_{18}H_{21}NO_5$: 331.1423. Found: 331.1423.

(3*R,3a*S**,6a*R**)-Tetrahydro-6a-methoxycarbonyl-3-methyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (*trans*-13a) and Its (3*S**,3a*S**,6a*R**)-Isomer (*cis*-13a) (Table 2, entry 1)** Following General Procedure, an 83 : 17 mixture of *trans*-**13a** and *cis*-**13a** (81.0 mg, 87%) was prepared from **1a** (80.0 mg, 0.318 mmol), **12** [(*E*) : (*Z*) = 86 : 14, 246 mg, 3.4 mmol], and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 320 μl, 32 μmol), and MS 4A (660 mg) after column chromatography on silica gel (Et_2O-hexane, 2 : 1). Further column chromatography on silica gel (Et_2O-hexane, 1 : 1) afforded pure *trans*-**13a** and *cis*-**13a**. *trans*-**13a**, colorless syrup. IR ($CHCl_3$): 1781, 1757, 1266, 1221, 1213 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.35 (3 H, d, *J* = 6.6 Hz, C_3-Me), 3.36 (1 H, dt, *J* = 7.6, 2.6 Hz, C_{3a}-H), 3.86 (3 H, s, CO_2Me), 4.04 (1 H, d, *J* = 14.8 Hz, PhC*H*H), 4.14 (1 H, br qd, *J* = 6.6, 2.6 Hz, C_3-H), 4.33 (1 H, dd, *J* = 9.6, 2.6 Hz, C_4-*H*H), 4.60 (1 H, d, *J* = 14.8 Hz, PhCH*H*), 4.62 (1 H, dd, *J* = 9.6, 7.6 Hz, C_4-H*H*), 7.45-7.73 (5 H, m, ArH). MS m/z: 291 (M^+, 34%), 205 (8), 188 (7), 143 (9), 91 (100). HRMS m/z: Calcd for $C_{15}H_{17}NO_5$: 291.1107. Found: 291.1110. *cis*-**13a**, mp: 161-162 °C (recrystallized from hexane-Et_2O). IR ($CHCl_3$): 1779, 1757, 1285, 1250, 1181 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.27 (3 H, d, *J* = 6.3 Hz, C_3-Me), 3.52 (1 H, td, *J* = 6.3, 2.6 Hz, C_{3a}-H), 3.85 (3 H, s, CO_2Me), 3.99 (1 H, d, *J* = 14.5 Hz, PhC*H*H), 4.28 (1 H, quin, *J* = 6.3 Hz, C_3-H), 4.44 (1 H, dd, *J* = 9.9, 6.3 Hz, C_4-*H*H), 4.50 (1 H, dd, *J* = 9.9, 2.6 Hz, C_4-H*H*), 4.57 (1 H, d, *J* = 14.5 Hz, PhCH*H*), 7.24-7.46 (5 H, m, ArH). MS m/z: 291 (M^+, 28%), 232 (5), 188 (5), 170 (4), 143 (14), 91 (100). HRMS m/z: Calcd for $C_{15}H_{17}NO_5$: 291.1107. Found: 291.1103. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.62; H, 5.88; N, 4.77.

(3*R,3a*S**,6a*R**)-Tetrahydro-6a-ethoxycarbonyl-3-methyl-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (*trans*-13b) and Its (3*S**,3a*S**,6a*R**)-Isomer (*cis*-13b) (Table 2, entry 2)** Following General Procedure, a 78 : 22 mixture of *trans*-**13b** and *cis*-**13b** (71.0 mg, 81%) was prepared from **1b** (80.0 mg, 0.29 mmol), **12** [(*E*) : (*Z*) = 86 : 14, 221 mg, 3.1 mmol], and titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 290 μl, 29 μmol), and MS 4A (820 mg) after column chromatography on silica gel (Et_2O-hexane, 1 : 1). Further column chromatography on silica gel (Et_2O-hexane, 1 : 2) afforded pure *trans*-**13b** and *cis*-**13b**. *trans*-**13b**, colorless syrup. IR ($CHCl_3$): 1779, 1754, 1302, 1279, 1224 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.33 (3 H, t, *J* = 7.3 Hz, OCH_2CH_3), 1.35 (3 H, d, *J* = 6.6 Hz, C_3-Me), 3.35 (1 H, dt, *J* = 7.6, 2.3 Hz, C_{3a}-H), 4.04 (1 H, d, *J* = 14.8 Hz, PhC*H*H), 4.13 (1 H, qd, *J* = 6.6, 2.3 Hz, C_3-H), 4.32 (2 H, q, *J* = 7.3 Hz, OCH_2CH_3), 4.33 (1 H, dd, *J* = 9.6, 2.3 Hz, C_4-*H*H), 4.62 (1 H, d, *J* = 14.8 Hz, PhCH*H*), 4.62 (1 H, dd, *J* = 9.6, 7.6 Hz, C_4-H*H*), 7.23-7.45 (5 H, m, ArH). MS m/z: 305 (M^+, 31%), 232 (10), 188 (7), 157 (8), 91 (100). HRMS m/z: Calcd for $C_{16}H_{19}NO_5$: 305.1263. Found: 305.1269. *cis*-**13a**, mp: 90.5-92 °C (recrystallized from hexane-Et_2O). IR ($CHCl_3$): 1779, 1754, 1246, 1211, 1179 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.27 (3 H, d, *J* = 6.9 Hz, C_3-Me), 1.33 (3 H, t, *J* = 7.3 Hz, OCH_2CH_3), 3.51 (1 H, td, *J* = 6.9, 2.6 Hz, C_{3a}-H), 3.98 (1 H, d, *J* = 14.9 Hz, PhC*H*H), 4.30 (1 H, quin, *J* = 6.9 Hz, C_3-H), 4.32 (2 H, q, *J* = 7.3 Hz, OCH_2CH_3), 4.43 (1 H, dd, *J* = 9.9,

6.9 Hz, C4-*H*H), 4.50 (1 H, dd, *J* = 9.9, 2.6 Hz, C4-H*H*), 4.58 (1 H, d, *J* = 14.9 Hz, PhCH*H*), 7.24-7.46 (5 H, m, ArH). MS m/z: 305 (M^+, 32%), 232 (10), 188 (8), 157 (14), 91 (100). HRMS m/z: Calcd for $C_{16}H_{19}NO_5$: 305.1264. Found: 305.1262.

ACKNOWLEDGMENTS: We are grateful to Miss Naka Mita, Mr. Hirohide Suzuki, and Mr. Ken-ichi Yamada for their technical assistance. This study was performed through Special Coordination Funds of the Science and Technology Agency of the Japanese Government.

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7. It is known that a less hindered ester undergoes transesterification more easily.[4] Accordingly, while reaction of **1a** with **2** gave the double transesterification product (**7'**), reactions of **1b,c** with **2** gave no **7'** type products.
8. If the further transesterification of **I** and **J** from **1a,b** were facilitated, **D** type compound should have been obtained similar to the discussion in **Scheme 1**. The reactions of **1a,b** with **12**, however, gave none of such compound. This observation also supports the speculation in **Scheme 2.**
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(*Received in Japan* 29 *August* 1994; *accepted* 7 *October* 1994)