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$TiCl_4$-Promoted Cyclization Reactions of Aminoacetals and Ethenetricarboxylates Leading to Nitrogen-Containing Heterocycles

Shoko Yamazaki* and Masachika Takebayashi

Department of Chemistry, Nara University of Education, Takabatake-cho, Nara 630-8528, Japan

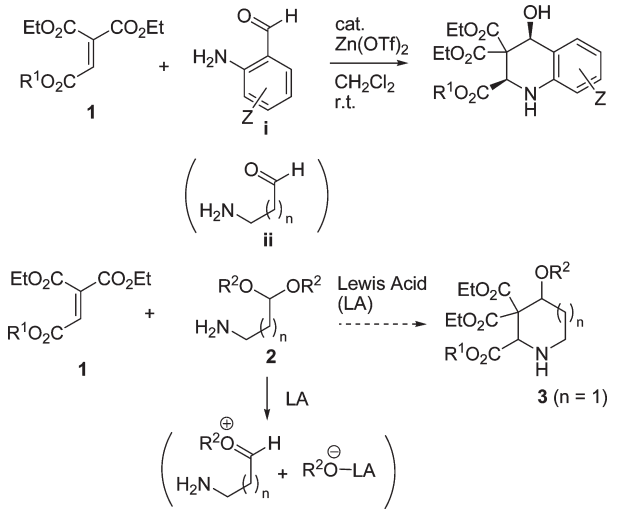
Supporting Information

ABSTRACT: Lewis acid-catalyzed cyclization of aminoacetals **2** and triethyl ethenetricarboxylate (**1a**) has been examined. The reaction of 3-aminopropionaldehyde diethyl acetal (**2a**) and **1a** in the presence of 1 equiv of $TiCl_4$ at room temperature gave 4-ethoxypiperidine-2,3,3-tricarboxylate **3a** in 92% yield with a 2,4-diastereomer ratio of 1:1. The reaction in the presence of 3 equiv of $TiCl_4$ gave 2,4-*trans*-piperidine derivative **3a** in 86% yield predominantly. The reaction of aminoacetaldehyde diethyl/dimethyl acetals **2c**, **d** and **1a** with 3 equiv of $TiCl_4$ gave 2,4-*trans*-4-pyrrolidine-2,3,3-tricarboxylates **5a**,**b** predominantly.

Nitrogen-containing six- and five-membered heterocyclic systems such as piperidines and pyrrolidines, including prolines and related amino acids, are important core structures in organic chemistry.[1] The development of new efficient synthetic strategies for the construction of piperidines and pyrrolidines is of considerable interest.

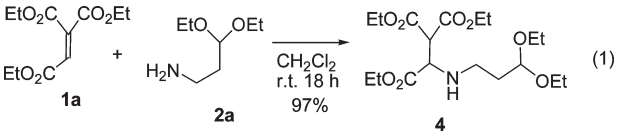
We have reported $Zn(OTf)_2$-catalyzed reactions of ethenetricarboxylates **1** with 2-aminobenzaldehydes **i** to afford tetrahydroquinoline derivatives (Scheme 1).[2] Ethenetricarboxylates **1** function as highly electrophilic Michael acceptors.[3] It is interesting

Scheme 1



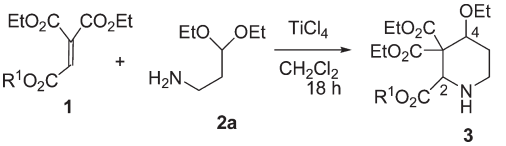
to develop the tandem aza-Michael-aldol reactions leading to nitrogen-containing heterocycles. Aminobenzaldehyde **i** contains both a nucleophile at nitrogen and an electrophile at the aldehyde moiety. Unprotected aliphatic aminoaldehydes **ii** undergo self-condensation.[4] Protected synthetic equivalents, for example, *N*-protected amino aldehydes, are effectively utilized in various organic syntheses.[5] Aminoacetals **2** are also considered to be protected aminoaldehydes and useful synthetic building blocks.[6] They serve as both a nucleophile at nitrogen and an electrophile at acetal with Lewis acid. Lewis acid-catalyzed cyclization of aminoacetals **2** and ethenetricarboxylates **1** leading to nitrogen-containing heterocycles such as **3** has been examined in this work.

At first, the reaction of 3-aminopropionaldehyde diethyl acetal (**2a**) and ethenetricarboxylate **1** without Lewis acid was carried out. The reaction of **2a** and triethyl ethenetricarboxylate (**1a**) in CH_2Cl_2 at room temperature gave an amine adduct, **4**, in 97% yield (eq 1).[7]



(1)

The reactions with 1 equiv of $SnCl_4$, $FeCl_3$, $AlCl_3$, $InCl_3$, $ZrCl_4$ or 0.2 equiv of $Zn(OTf)_2$ were examined next; however, these reactions also gave **4** as a major product. Among various Lewis acids, $TiCl_4$ has been used to activate acetal groups most effectively, owing to its Lewis acidity and its oxophilicity.[8] While the reaction of **2a** and **1a** in the presence of 0.2 equiv of $TiCl_4$ gave **4** as a major product, the reaction in the presence of 1 equiv of $TiCl_4$ at room temperature in CH_2Cl_2 gave 4-ethoxypiperidine-2,3,3-tricarboxylate **3a** in 92% yield with a 2,4-diastereomer ratio of 1:1 (eq 2, Table 1, entry 1). The reaction with 1 equiv of $TiBr_4$ also gave **3a** but in lower yield (46%) with a 2,4-diastereomer ratio of 1:1.



(2)

The reaction with $TiCl_4$ (1 equiv) at lower temperature reduced the yields, but gave 2,4-*cis* diastereomer preferentially

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Table 1. Reaction of 1a−f and 2a

entry	1	R^1	amt of $TiCl_4$ (equiv)	temp	3 (yield, %)	2,4-*trans*:*cis* ratio[c]
1	**1a**	Et	1	rt	**3a** (92)	1:1
2	**1a**	Et	1	−40 °C	**3a** (ca. 85)[a]	1:4
3	**1a**	Et	1	−78 °C	**3a** (ca. 46)[a]	1:9
4	**1a**	Et	1	80 °C	**3a** (63)[b]	1:1
5	**1a**	Et	2	rt	**3a** (93)	6:1
6	**1a**	Et	3	rt	**3a** (86)	>9:1
7	**1b**	^{i}Pr	3	rt	**3b** (78)	5:1
8	**1c**	allyl	3	rt	**3c** (57)	>9:1
9	**1d**	propargyl	3	rt	**3d** (77)	>9:1
10	**1e**	CH_2CF_3	3	rt	**3e** (41)	6:1
11	**1f**	^{t}Bu	1	rt	**3f** (19)	*cis*

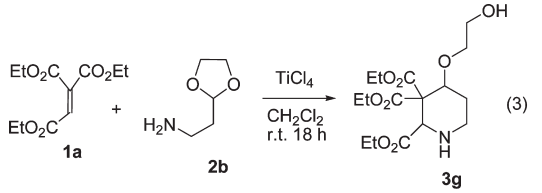
[a] Small amounts of impurity could not be removed. [b] In $ClCH_2CH_2Cl$. [c] The *trans*:*cis* ratio was determined by ^{1}H NMR (by the signals of H-6a,6b). For peak assignments and atom numbering, see the Experimental Section and Figure S1 in the Supporting Information.

(entries 2 and 3). The reaction with $TiCl_4$ (1 equiv) at 80 °C in $ClCH_2CH_2Cl$ gave **3a** in 63% yield with a 2,4-diastereomer ratio of 1:1. The reaction with 2 equiv of $TiCl_4$ at room temperature gave **3a** in 93% yield with a 2,4-*trans* stereochemistry preferentially (dr = 6:1, entry 5). When the reaction of **2a** and **1a** was carried out in the presence of 3 equiv of $TiCl_4$ at room temperature, 2,4-*trans*-piperidine derivative **3a** was obtained in 86% yield predominantly (dr > 9:1, entry 6).[9] 2,4-*trans* and *cis* stereochemistries were determined by NOESY spectra, such as the presence (for *cis*-**3**) of NOE peaks between H-2 and H-4 ring protons as shown in Figure S1 of the Supporting Information.

The reaction of ethenetricarboxylates **1b**−**e** and **2a** in the presence of 3 equiv of $TiCl_4$ gave **3b**−**e** *trans*-2,4-diastereomers preferentially. The reaction of **2a** and *tert*-butyl ester **1f** with 1 equiv of $TiCl_4$ gave *cis*-piperidine-2,3,3-tricarboxylate **3f** in low yield (19%). The reaction with 3 equiv of $TiCl_4$ led to decomposition, probably because of instability of the *tert*-butyl group in the reaction condition.

The reaction of diethyl benzylidenemalonate (PhCH=C$(CO_2Et)_2$) with **2a** in the presence of 1 or 3 equiv of $TiCl_4$ gave a complex mixture including the starting benzylidenemalonate and a small amount of benzaldehyde. Formation of benzaldehyde may arise from the reverse Knoevenagel reaction. The suitable reactivity of ethenetricarboxylate triesters **1** toward aminoacetal compared to benzylidenemalonate was shown by this efficient cyclization reaction.

The reaction of cyclic acetal 2-(2-aminoethyl)-1,3-dioxolane (**2b**) and **1a** with 1 or 3 equiv of $TiCl_4$ gave piperidine-2,3,3-tricarboxylate **3g** with a 2,4-diasteromer ratio of 1:1 in 98% and 64% yields, respectively (eq 3).



1 eq $TiCl_4$ 98% (dr 1:1)
3 eq $TiCl_4$ 64% (dr 1:1)
dr was determined by ^{1}H NMR signals of H-6a,6b.

Next five-membered-ring pyrrolidine formation was examined. The reaction of aminoacetaldehyde diethyl/dimethyl acetals **2c,d** and **1a** with 3 equiv of $TiCl_4$ gave 2,4-*trans*-pyrrolidine-2,3,3-tricarboxylates **5a,b** predominantly (eq 4,

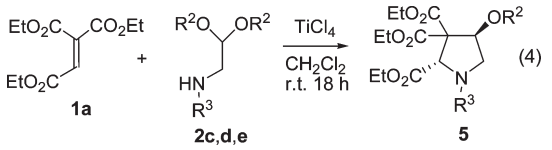


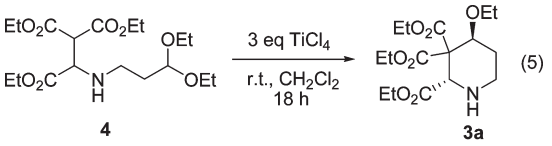
Table 2. Reaction of 1a and 2c−e

entry	2	R^2	R^3	amt of $TiCl_4$ (equiv)	5 (yield, %)	2,4-*trans*:*cis* ratio
1	**2c**	Et	H	1	**5a** (99)	3:1[b]
2	**2c**	Et	H	3	**5a** (95)	7:1[b]
3	**2d**	Me	H	1	**5b** (87)	3:1[c]
4	**2d**	Me	H	3	**5b** (91)	5:1[c]
5	**2e**	Me	Me	1	**5c** (64)	3:1[c]
6	**2e**	Me	Me	3	**5c** (89)	2:1[c]
7[a]	**2e**	Me	Me	3	**5c** (70)	2:1[c]

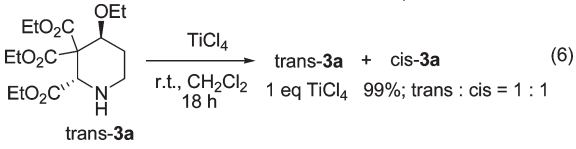
[a] The reaction was performed at −40 °C. The reaction with 1 equiv of $TiCl_4$ at −40 °C gave a mixture containing starting materials, an amine adduct, and a small amount of cyclized products. [b] The *trans*:*cis* ratio was determined by ^{1}H NMR (by the signals of H-2 (*trans*) and H-5a (*cis*)). For peak assignments and atom numbering, see the Experimental Section and Figure S2 in the Supporting Information. [c] Determined by the signals of H-5a,5b.

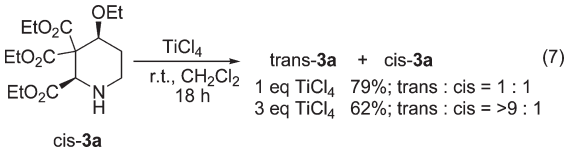
Table 2). The reaction of (methylamino)acetaldehyde dimethyl acetal (**2e**) gave the corresponding pyrrolidine with lower stereoselectivity. 2,4-*trans* and *cis* stereochemistries were determined by observed NOE peaks as shown in Figure S2 of the Supporting Information. Seven-membered-ring formation by the reaction of **1a** and 4-aminobutyraldehyde dimethyl acetal (**2** in Scheme 1; $n = 2$, R^2 = Me, R^3 = H) with 1 or 3 equiv of $TiCl_4$ was also examined. However, the reaction gave a complex mixture, probably because seven-membered-ring formation is not an efficient process and also the ring formation may compete with the intramolecular reaction of the acetal.

The reaction of **4** with 3 equiv of $TiCl_4$ at room temperature for 18 h gave 2,4-*trans*-piperidine derivative **3a** in 70% yield (eq 5). Treatment of the isolated 2,4-*trans*- or 2,4-*cis*-piperidine **3a** with 1 equiv of $TiCl_4$ led to a 1:1 diastereomer mixture (eqs 6 and 7). Treatment of 2,4-*cis*-piperidine **3a** with 3 equiv of $TiCl_4$ led to the 2,4-*trans* form. Thus, the *trans* and *cis* diastereomers are in equilibrium with the coordination of $TiCl_4$.



70%; trans : cis = >9 : 1





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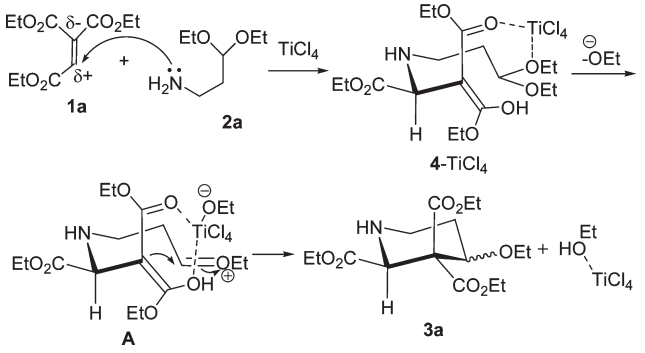
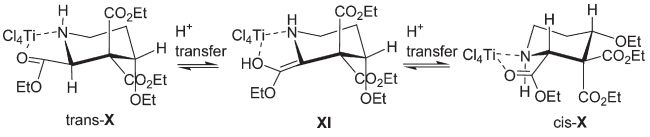
Scheme 2



Scheme 3



The probable mechanism for formation of the nitrogen-containing six-membered ring is shown in Scheme 2. Conjugate addition of nitrogen of **2a** to ethenetricaboxylate **1a** gives an adduct, **4**, which is coordinated with $TiCl_4$. $TiCl_4$-promoted abstraction of EtO^- from the acetal moiety gives an oxonium intermediate, **A**. The electrophilic oxonium moiety in the intermediate **A** reacts at the generated nucleophilic malonate carbon to give the cyclized product **3a**.

The stereochemistry of the nitrogen-containing ring is likely to be under thermodynamic control in the presence of $TiCl_4$ at room temperature. The $TiCl_4$ coordination diastereomers formed during complexation of the cyclized products may vary in stability by steric effects of multiple substituents and their $TiCl_4$ coordination. For six-membered-ring formation of **3a**−**e**, when 3 equiv of $TiCl_4$ was used, 2,4-*trans* diastereomer formation was preferred. This is probably because the *trans* isomer is more stable than the *cis* isomer in multiple $TiCl_4$-coordinated complex structures due to steric effects. The observed 2,4-*trans* selectivity of the six-membered ring using the calculations of model compounds is discussed in the Supporting Information.

Thus, efficient synthesis of highly substituted pyrrolidines was achieved. The stabilities by $TiCl_4$ substrate coordination (**3** + $n$$TiCl_4$ → **3**−$n$$TiCl_4$ (n = 1, 2)) and steric effects may vary depending on the sizes of the rings and substituents. The coordination of $TiCl_4$ with an opened cyclic acetal group in **3g** probably affects the stability.

The *trans*/*cis* isomerization occurs in the presence of $TiCl_4$. One possible pathway for the 2,4-*trans*/*cis* isomerization is the ester carbonyl/enol tautomerization that operates under Lewis acidic conditions (Scheme 3).[10] The other possible concomitant isomerization route is that the $TiCl_4$ coordination at the malonate moiety reproduces oxocarbenium ion intermediates, resulting in bond rotation and bond formation (see Scheme S1 in the Supporting Information).

In summary, the reaction of **2a** and **1a** in the presence of 1 equiv of $TiCl_4$ at room temperature in CH_2Cl_2 gave 4-ethoxypiperidine-2,3,3-tricarboxylate **3a** in high yield with a 2,4-diastereomer ratio of 1:1. On the other hand, the reaction in the presence of 3 equiv of $TiCl_4$ gave 2,4-*trans*-piperidine derivative **3a** predominantly. The reaction of aminoacetaldehyde diethyl/dimethyl acetals **2c,d** and **1a** with 3 equiv of $TiCl_4$ gave 2,4-*trans*-4- pyrrolidine-2,3,3-tricarboxylates **5a,b** predominantly.

This reaction demonstrates an efficient way to construct potentially useful amino acid-related nitrogen-containing heterocyclic compounds. Further study on the transformation of the products to biologically interesting compounds is under way.

EXPERIMENTAL SECTION

General Methods. ^1H chemical shifts are reported in parts per million relative to the peak for Me_4Si. ^{13}C chemical shifts are reported in parts per million relative to the peak for $CDCl_3$ (77.1 ppm). ^{19}F chemical shifts are reported in parts per million relative to the peak for $CFCl_3$. ^{13}C mutiplicities were determined by DEPT and HSQC. Peak assignments are made by 2D COSY, HSQC, NOESY, and HMBC spectra. Selected NOEs and HMBC correlations are shown in the Supporting Information.

Ethenetricarboxylates **1a**,[11a] **1b**,[11a] **1d**,[11b] and **1f**[11c] were prepared according to the literature. **1c** was prepared according to the literature procedure.[11a−c] **1e** was prepared by the reaction of 1,1-diethyl 2-hydrogen ethenetricaboxylate with 2,2,2-trifluoroethanol in the presence of PPh_3 and DEAD (diethyl azodicarboxylate), according to the literature procedure.[11d]

Data for ***1c****:* R_f = 0.5 (hexane:ether = 1:2); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 4.31 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.68 (ddd, J = 5.9, 1.4, 1.4 Hz, 2H), 5.28 (ddt, J = 10.4, 1.2, 1.2 Hz, 1H), 5.36 (ddt, J = 17.2, 1.5, 1.5 Hz, 1H), 5.92 (ddt, J = 17.2, 10.4, 5.9 Hz, 1H), 6.89 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.0 (CH_3), 62.1 (CH_2), 62.5 (CH_2), 66.3 (CH_2), 119.3 (CH_2), 129.7 (CH), 131.1 (CH), 139.2 (C), 162.2 (C), 163.2 (C), 164.2 (C); IR (neat) 2986, 1734, 1653, 1448, 1375, 1346, 1257, 1180, 1067, 1023 cm^{-1}; MS (EI) m/z 256 (M^+, 5.4), 211 (28), 200 (50), 154 (100); HRMS (FAB) m/z $(M + H)^+$ 257.1026 (calcd for $C_{12}H_{17}O_6$ 257.1025).

Data for ***1e****:* R_f = 0.5 (hexane:ether = 4:1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.33 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 4.32 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.56 (q, J = 8.2 Hz, 2H), 6.92 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.8 (CH_3), 13.9 (CH_3), 61.1 (CH_2, q, J_{CF} = 37 Hz), 62.4 (CH_2), 62.8 (CH_2), 122.6 (C, q, J_{CF} = 277 Hz), 127.4 (CH), 141.0 (C), 161.8 (C), 162.0 (C), 163.7 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −74.15 (t, J_{FH} = 8.4 Hz); IR (neat) 2987, 1735, 1653, 1376, 1286, 1255, 1170, 1071 cm^{-1}; MS (EI) m/z 299 ($(M + H)^+$), 298 (M^+); HRMS m/z M^+ 298.0663 (calcd for $C_{11}H_{13}F_3O_6$ 298.0664).

Experimental Procedure (Table 1, Entry 1). To a solution of **1** (244 mg, 1.0 mmol) in dichloromethane (2 mL) were added 3-aminopropionaldehyde diethyl acetal (**2a**) (147 mg, 1.0 mmol) and $TiCl_4$ (0.110 mL, 189 mg, 1.0 mmol) at 0 °C. The mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water. The mixture was diluted with dichloromethane, and then saturated aqueous $NaHCO_3$ was added. The organic phase was extracted with dichloromethane, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with dichloromethane−ether as the eluent to give **3a** (317 mg, 92%, *trans*:*cis* = 1:1 determined by ^1H NMR). *trans*-**3a** (113 mg) and *cis*-**3a** (84 mg) were isolated.

*Data for trans-****3a****:* R_f = 0.4 (CH_2Cl_2:ether = 1:1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.13 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.286 (t, J = 7.1 Hz, 3H), 1.288 (J = 7.1 Hz, 3H), 1.71 (dddd, J = 14.3, 3.2, 3.2, 3.2 Hz, 1H, H-5a), 2.01 (dddd, J = 14.3, 11.9,

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5.3, 2.6 Hz, 1H, H-5b), 2.10 (br s, 1H), 2.91 (ddd, J = 13.4, 5.3, 2.4 Hz, 1H, H-6a), 2.98 (ddd, J = 13.4, 11.9, 3.1 Hz, 1H, H-6b), 3.37 (dq, J = 9.0, 7.0 Hz, 1H), 3.58 (dq, J = 9.0, 7.0 Hz, 1H, OC*H*HCH$_3$), 4.12−4.29 (m, 8H, CO$_2$C*H*$_2$CH$_3$, H-4, H-2); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.9 (CH$_3$), 14.05 (CH$_3$), 14.08 (CH$_3$), 15.4 (CH$_3$), 26.0 (CH$_2$), 40.2 (CH$_2$, C-6), 58.8 (C, C-3), 59.3 (CH, C-2), 61.1 (CH$_2$), 61.2 (CH$_2$), 61.6 (CH$_2$), 65.3 (CH$_2$), 75.3 (CH, C-4), 168.6 (C), 169.2 (C), 171.5 (C); IR (neat) 3324. 2979, 2934, 1738, 1466, 1446, 1369, 1269, 1211, 1103, 1080, 1032 cm^{-1}; MS (EI) m/z 345 (M$^+$); HRMS m/z M$^+$ 345.1790 (calcd for $C_{16}H_{27}NO_7$ 345.1788). Anal. Calcd for $C_{16}H_{27}NO_7$: C, 55.64; H, 7.88; N, 4.06. Found: C, 55.38; H, 7.95; N, 4.25.

*Data for cis-**3a**:* R_f = 0.3 (CH$_2$Cl$_2$:ether = 1:1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.15 (t, J = 7.0 Hz, 3H), 1.258 (t, J = 7.1 Hz, 3H), 1.264 (t, J = 7.1 Hz, 3H), 1.31 (J = 7.1 Hz, 3H), 1.75 (dddd, J = 13.0, 10.8, 10.8, 4.6 Hz, 1H), 1.84 (dddd, J = 13.0, 3.8, 3.8, 3.8 Hz, 1H, H-5b), 2.11 (br s, 1H), 2.71 (ddd, J = 12.8, 10.8, 3.7 Hz, 1H, H-6a), 3.23 (ddd, J = 12.8, 4.1, 4.1 Hz, 1H), 3.46 (dq, J = 9.3, 7.0 Hz, 1H), 3.66 (dq, J = 9.3, 7.0 Hz, 1H), 3.76 (s, 1H, H-2), 3.85 (dd, J = 10.8, 4.0 Hz, 1H, H-4), 4.14−4.32 (m, 6H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.00 (CH$_3$), 14.01 (CH$_3$), 14.1 (CH$_3$), 15.5 (CH$_3$), 28.0 (CH$_2$), 42.7 (CH$_2$, C-6), 61.2 (CH$_2$), 61.3 (CH$_2$), 61.7 (CH$_2$), 63.0 (CH), 63.2 (C, C-3), 65.7 (CH$_2$), 80.8 (CH, C-4), 167.5 (C), 169.6 (C), 170.1 (C); IR (neat) 3364, 2979, 1739, 1466, 1445, 1369, 1301, 1260, 1104, 1063, 1037 cm^{-1}; MS (EI) m/z 345 (M$^+$); HRMS m/z M$^+$ 345.1790 (calcd for $C_{16}H_{27}NO_7$ 345.1788).

Experimental Procedure (Table 1, Entry 6). To a solution of **1** (244 mg, 1.0 mmol) in dichloromethane (2 mL) were added **2a** (147 mg, 1.0 mmol) and TiCl$_4$ (0.330 mL, 567 mg, 3.0 mmol) at 0 °C. The mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water. The mixture was diluted with dichloromethane, and then saturated aqueous NaHCO$_3$ was added. The organic phase was extracted with dichloromethane, dried (Na$_2$SO$_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with dichloromethane−ether as the eluent to give *trans*-**3a** (296 mg, 86%).

*Data for trans-**3b**:* R_f = 0.6 (CH$_2$Cl$_2$:ether = 1:1); colorless oil; for major isomer, ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.13 (t, J = 7.0 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.29 (J = 7.1 Hz, 3H), 1.71 (dddd, J = 14.3, 3.2, 3.2, 3.2 Hz, 1H, H-5a), 2.00 (dddd, J = 14.3, 11.8, 5.1, 2.6 Hz, 1H, H-5b), 2.15 (br s, 1H), 2.91 (ddd, J = 13.1, 5.1, 2.4 Hz, 1H, H-6a), 2.98 (ddd, J = 13.1, 13.1, 3.2 Hz, 1H, H-6b), 3.37 (dq, J = 9.1, 7.0 Hz, 1H), 3.58 (dq, J = 9.1, 7.0 Hz, 1H, OC*H*HCH$_3$), 4.13 (s, 1H, H-2), 4.14−4.30 (m, 5H, CO$_2$C*H*$_2$CH$_3$, H-4), 5.03 (septet, J = 6.2 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.9 (CH$_3$), 14.1 (CH$_3$), 15.4 (CH$_3$), 21.6 (CH$_3$), 21.7 (CH$_3$), 26.0 (CH$_2$), 40.1 (CH$_2$, C-6), 58.9 (C, C-3), 59.3 (CH, C-2), 61.1 (CH$_2$), 61.5 (CH$_2$), 65.3 (CH$_2$), 68.6 (CH), 75.3 (CH, C-4), 168.6 (C), 169.1 (C), 171.0 (C); IR (neat) 3321, 2979, 1734, 1466, 1446, 1374, 1267, 1212, 1106, 1081 cm^{-1}; MS (EI) m/z 359 (M$^+$, 15), 316 (64), 272 (85), 200 (92), 154 (100); HRMS m/z M$^+$ 359.1943 (calcd for $C_{17}H_{29}NO_7$ 359.1944).

*Data for trans-**3c**:* R_f = 0.5 (CH$_2$Cl$_2$:ether = 1:1); for major isomer, pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.13 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.28 (J = 7.1 Hz, 3H), 1.72 (dddd, J = 14.3, 3.1, 3.1, 3.1 Hz, 1H, H-5a), 2.01 (dddd, J = 14.3, 11.9, 5.2, 2.6 Hz, 1H, H-5b), 2.13 (br s, 1H), 2.91 (ddd, J = 13.1, 5.2, 2.2 Hz, 1H, H-6a), 2.98 (ddd, J = 13.1, 13.1, 3.2 Hz, 1H, H-6b), 3.38 (dq, J = 9.0, 7.1 Hz, 1H), 3.59 (dq, J = 9.0, 7.1 Hz, 1H, OC*H*HCH$_3$), 4.14 (dd, J = 2.6, 2.6 Hz, 1H, H-4), 4.15−4.29 (m, 4H), 4.21 (s, 1H, H-2), 4.58−4.68 (m, 2H), 5.23 (dddd, J = 10.4, 1.3, 1.3, 1.3 Hz, 1H), 5.35 (dddd, J = 17.2, 1.5, 1.5, 1.5 Hz, 1H), 5.93 (dddd, J = 17.2, 10.4, 5.8, 5.8 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.8 (CH$_3$), 14.0 (CH$_3$), 15.4 (CH$_3$), 25.9 (CH$_2$), 40.1 (CH$_2$, C-6), 58.7 (C, C-3), 59.2 (CH, C-2), 61.1 (CH$_2$), 61.5 (CH$_2$), 65.3 (CH$_2$), 65.8 (CH$_2$), 75.2 (CH, C-4), 118.5 (CH$_2$), 131.8 (CH), 168.5 (C), 169.1 (C), 171.2 (C); IR (neat) 3321, 2979, 2935, 1738, 1649, 1446, 1368, 1273, 1211, 1182, 1103, 1083 cm^{-1}; MS (EI) m/z 357 (M$^+$); HRMS m/z M$^+$ 357.1786 (calcd for $C_{17}H_{27}NO_7$ 357.1788). Anal. Calcd for $C_{17}H_{27}NO_7$: C, 57.13; H, 7.61; N, 3.92. Found: C, 56.77; H, 7.75; N, 3.87.

*Data for trans-**3d**:* R_f = 0.5 (CH$_2$Cl$_2$:ether = 1:1); colorless oil; for major isomer, ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.13 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.29 (J = 7.1 Hz, 3H), 1.72 (dddd, J = 14.3, 3.1, 3.1, 3.1 Hz, 1H, H-5a), 2.00 (dddd, J = 14.3, 12.0, 5.2, 2.6 Hz, 1H, H-5b), 2.07 (br s, 1H), 2.46 (t, J = 2.5 Hz, 3H), 2.91 (ddd, J = 13.1, 5.2, 2.3 Hz, 1H, H-6a), 2.98 (ddd, J = 13.1, 13.1, 3.2 Hz, 1H, H-6b), 3.38 (dq, J = 9.0, 7.1 Hz, 1H), 3.58 (dq, J = 9.0, 7.1 Hz, 1H, OC*H*HCH$_3$), 4.14 (dd, J = 3.0, 3.0 Hz, 1H, H-4), 4.15−4.29 (m, 5H, CO$_2$C*H*$_2$CH$_3$, H-2), 4.72 (d, J = 2.5 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.9 (CH$_3$), 14.1 (CH$_3$), 15.4 (CH$_3$), 26.0 (CH$_2$), 40.2 (CH$_2$, C-6), 52.6 (CH$_2$), 58.9 (C, C-3), 59.1 (CH, C-2), 61.3 (CH$_2$), 61.7 (CH$_2$), 65.4 (CH$_2$), 75.1 (CH), 75.2 (CH, C-4), 168.4 (C), 169.0 (C), 170.7 (C); IR (neat) 3270, 2979, 2936, 2129, 1743, 1445, 1369, 1269,1209, 1104, 1081 cm^{-1}; MS (EI) m/z 355 (M$^+$); HRMS m/z M$^+$ 355.1624 (calcd for $C_{17}H_{25}NO_7$ 355.1635).

*Data for trans-**3e**:* R_f = 0.5 (CH$_2$Cl$_2$:ether = 1:1); colorless oil; for major isomer, ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.14 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.28 (J = 7.1 Hz, 3H), 1.74 (dddd, J = 14.3, 3.0, 3.0, 3.0 Hz, 1H, H-5a), 1.96 (dddd, J = 14.3, 12.1, 5.1, 2.5 Hz, 1H, H-5b), 2.08 (br s, 1H), 2.92 (ddd, J = 13.0, 5.1, 2.2 Hz, 1H, H-6a), 3.00 (ddd, J = 13.0, 13.0, 3.1 Hz, 1H, H-6b), 3.38 (dq, J = 9.0, 7.0 Hz, 1H), 3.58 (dq, J = 9.0, 7.0 Hz, 1H, OC*H*HCH$_3$), 4.14−4.29 (m, 5H, CO$_2$C*H*$_2$CH$_3$, H-4), 4.30 (s, 1H, H-2), 4.41−4.57 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.8 (CH$_3$), 14.0 (CH$_3$), 15.40 (CH$_3$), 26.1 (CH$_2$), 40.1 (CH$_2$, C-6), 58.6 (CH, C-2), 59.2 (C, C-3), 60.9 (CH$_2$, q, J_{CF} = 37 Hz), 61.4 (CH$_2$), 61.8 (CH$_2$), 65.4 (CH$_2$), 75.3 (CH, C-4), 122.9 (C, q, J_{CF} = 277 Hz), 168.3 (C), 168.7 (C), 170.4 (C); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) −73.88 (t, J_{FH} = 8.4 Hz); IR (neat) 3322, 2979, 1741, 1446, 1414, 1369, 1281, 1164, 1105, 1082 cm^{-1}; MS (EI) m/z 399 (M$^+$); HRMS m/z M$^+$ 399.1502 (calcd for $C_{16}H_{24}F_3NO_7$ 399.1505). Anal. Calcd for $C_{16}H_{24}F_3NO_7$: C, 48.12; H, 6.06; N, 3.51. Found: C, 48.40; H, 6.17; N, 3.56.

*Data for cis-**3f**:* R_f = 0.3 (CH$_2$Cl$_2$:ether = 1:1); pale yellow crystals; mp 48−50 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.16 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.31 (J = 7.1 Hz, 3H), 1.46 (s, 9H), 1.76 (dddd, J = 12.8, 11.7, 11.7, 4.7 Hz, 1H), 1.86 (dddd, J = 12.8, 3.5, 3.5, 3.5 Hz, 1H, H-5b), 2.10 (br s, 1H), 2.67 (ddd, J = 12.5, 12.5, 3.5 Hz, 1H, H-6a), 3.20 (ddd, J = 12.6, 4.6, 2.7 Hz, 1H), 3.43 (dq, J = 9.5, 7.1 Hz, 1H), 3.56 (s, 1H, H-2), 3.67 (dq, J = 9.5, 7.1 Hz, 1H), 3.77 (dd, J = 11.4, 4.3 Hz, 1H, H-4), 4.17−4.35 (m, 4H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.0 (CH$_3$), 14.1 (CH$_3$), 15.4 (CH$_3$), 27.9 (CH$_3$), 28.0 (CH$_2$), 43.2 (CH$_2$, C-6), 60.9 (CH$_2$), 61.3 (CH$_2$), 63.4 (C, C-3), 63.9 (CH), 65.7 (CH$_2$), 81.8 (C), 81.9 (CH, C-4), 167.4 (C), 168.9 (C), 169.5 (C); IR (KBr) 3363, 2979, 1732, 1474, 1366, 1255, 1166, 1104, 1041 cm^{-1}; MS (EI) m/z 373 (M$^+$), 374 ((M + H)$^+$); HRMS m/z M$^+$ 373.2103 (calcd for $C_{18}H_{31}NO_7$ 373.2101). Anal. Calcd for $C_{18}H_{31}NO_7$: C, 57.89; H, 8.37; N, 3.75. Found: C, 57.93; H, 8.52; N, 3.61.

*Data for trans-**3g**:* R_f = 0.3 (ether:MeOH = 4:1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.285 (t, J = 7.1 Hz, 3H), 1.286 (t, J = 7.1 Hz, 3H), 1.74 (dddd, J = 14.1, 4.1, 4.1, 4.1 Hz, 1H, H-5a), 1.97 (dddd, J = 14.1, 10.9, 4.8, 3.0 Hz, 1H, H-5b), 2.30 (br s, 2H), 2.88 (ddd, J = 13.5, 4.3, 4.3 Hz, 1H, H-6a), 3.00 (ddd, J = 13.5, 10.8, 3.5 Hz, 1H, H-6b), 3.43−3.48 (m, 1H), 3.63−3.76 (m, 3H, OC*H*HC*H*$_2$OH), 4.13−4.30 (m, 8H, CO$_2$C*H*$_2$CH$_3$, H-2, H-4); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.8 (CH$_3$), 13.96 (CH$_3$), 14.02 (CH$_3$), 26.1 (CH$_2$), 39.9 (CH$_2$, C-6), 58.9 (C, C-3), 59.4 (CH, C-2), 61.4 (CH$_2$), 61.68 (CH$_2$), 61.71 (CH$_2$ × 2), 71.0 (CH$_2$), 75.3 (CH, C-4), 168.5 (C), 169.2 (C), 171.1 (C); IR (neat) 3368, 2981, 2938,

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1742, 1465, 1446, 1369, 1264, 1097, 1034 cm^{-1}; MS (EI) *m/z* 361 (M^+, 16), 288 (53), 242 (61), 154 (100); HRMS *m/z* M^+ 361.1736 (calcd for $C_{16}H_{27}NO_8$ 361.1737).

*Data for cis-**3g**:* R_f = 0.2 (ether:MeOH = 4:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.266 (t, *J* = 7.1 Hz, 3H), 1.271 (t, *J* = 7.1 Hz, 3H), 1.30 (*J* = 7.1 Hz, 3H), 1.74−1.79 (m, 2H), 2.28 (br s, 1H), 2.72 (ddd, *J* = 12.9, 6.4, 6.4 Hz, 1H, H-6a), 3.26 (ddd, *J* = 12.9, 5.2, 5.2 Hz, 1H, H-6b), 3.50 (ddd, *J* = 9.8, 4.9, 4.9 Hz, 1H), 3.67 (dd, *J* = 4.4, 4.4 Hz, 1H), 3.76 (ddd, *J* = 9.8, 3.8, 3.8 Hz, 1H), 3.95 (br s, 1H, H-2), 4.08 (dd, *J* = 6.1, 6.1 Hz, 1H, H-4), 4.11−4.33 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.0 (CH_3 × 2), 27.3 (CH_2), 40.7 (CH_2), 61.4 (CH_2 and CH, C-2), 61.5 (CH_2), 61.8 (CH_2 and C), 62.2 (CH_2), 70.9 (CH_2), 79.0 (CH, C-4) 167.7 (C), 169.3 (C), 170.2 (C); IR (neat) 3357, 2981, 2939, 1742, 1446, 1370, 1261, 1062 cm^{-1}; MS (EI) *m/z* 361 (M^+, 15), 288 (81), 242 (71), 154 (100); HRMS *m/z* M^+ 361.1739 (calcd for $C_{16}H_{27}NO_8$ 361.1737).

*Data for **4**:* colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.19 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.265 (t, *J* = 7.1 Hz, 3H), 1.273 (*J* = 7.1 Hz, 3H), 1.28 (*J* = 7.1 Hz, 3H), 1.74 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 2.00 (br s, 1H, N*H*), 2.59 (ddd, *J* = 11.6, 6.7, 6.7 Hz, 1H, NC*H*H), 2.86 (ddd, *J* = 11.6, 6.7, 6.7 Hz, 1H, NCH*H*), 3.44−3.53 (m, 2H, CH(OC*H*HCH$_3$)$_2$), 3.59−3.68 (m, 2H, CH(OCH*H*CH$_3$)$_2$), 3.83 (s, 2H, C*H*-N, C*H*(CO$_2$Et)$_2$), 4.16−4.26 (m, 6H), 4.56 (t, *J* = 5.7 Hz, 1H, C*H*(OEt)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.98 (CH_3), 14.02 (CH_3), 14.1 (CH_3), 15.30 (CH_3), 15.32 (CH_3), 34.1 (CH_2), 44.0 (CH_2, NCH_2), 55.1 (CH), 60.3 (CH, *C*H−N), 61.2 (CH_2, CH(O*C*H$_2$CH$_3$)$_2$), 61.3 (CH_2), 61.5 (CH_2), 61.6 (CH_2), 101.6 (CH, *C*H(OEt)$_2$), 167.4 (C), 167.5 (C), 172.4 (C); IR (neat) 3344, 1733, 1466, 1446, 1372, 1238, 1176, 1061, 1031 cm^{-1}; MS (ESI) *m/z* 414 ((M + Na)$^+$); HRMS *m/z* (M + Na)$^+$ 414.21039 (calcd for $C_{18}H_{33}NNaO_8$ 414.21039).

*Data for trans-**5a**:* R_f = 0.4 (CH_2Cl_2:ether = 1:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.12 (t, *J* = 7.0 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.279 (t, *J* = 7.1 Hz, 3H), 1.282 (*J* = 7.1 Hz, 3H), 2.31 (br s, 1H), 3.01 (dd, *J* = 12.4, 2.7 Hz, 1H, H-5a), 3.48 (dd, *J* = 12.4, 5.5 Hz, 1H, H-5b), 3.48−3.61 (m, 2H, OC*H*$_2$CH$_3$), 4.02−4.30 (m, 6H), 4.55 (s, 1H, H-2), 4.60 (dd, *J* = 5.5, 2.7 Hz, 1H, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.1 (CH_3 × 2), 15.2 (CH_3), 53.2 (CH_2, C-5), 61.4 (CH_2), 61.6 (CH_2), 61.8 (CH_2), 66.1 (CH, C-2), 66.3 (CH_2), 69.4 (C, C-3), 84.9 (CH_2, C-4), 167.2 (C), 168.4 (C), 171.3 (C); IR (neat) 3342, 2980, 1738, 1446, 1370, 1250, 1200, 1098, 1073, 1027 cm^{-1}; MS (EI) *m/z* 331 (M^+, 21), 258 (96), 212 (93), 171 (74), 140 (100); HRMS *m/z* M^+ 331.1632 (calcd for $C_{15}H_{25}NO_7$ 331.1631).

*Data for cis-**5a**:* R_f = 0.3 (CH_2Cl_2:ether = 1:1); obtained as a mixture with *trans*-**5a**; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.13 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.31 (*J* = 7.1 Hz, 3H), 2.29 (br s, 1H), 2.99 (dd, *J* = 11.8, 4.7 Hz, 1H, H-5b), 3.21 (dd, *J* = 11.8, 3.8 Hz, 1H, H-5a), 3.52−3.59 (m, 2H, OC*H*$_2$CH$_3$), 3.90 (br s, 1H, H-2), 4.10−4.33 (m, 6H), 4.53 (dd, *J* = 8.6, 4.3 Hz, 1H, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (CH_3), 14.1 (CH_3 × 2), 15.2 (CH_3), 51.6 (CH_2), 61.4 (CH_2), 61.6 (CH_2), 62.0 (CH_2), 66.3 (CH_2), 66.6 (CH, C-2), 68.3 (C, C-3), 84.9 (CH, C-4), 166.5 (C), 167.0 (C), 170.4 (C).

*Data for trans-**5b**:* R_f = 0.4 (CH_2Cl_2:ether = 1:1); colorless oil; for major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 6H), 2.22 (br s, 1H), 3.04 (dd, *J* = 12.5, 2.7 Hz, 1H, H-5a), 3.36 (s, 3H, OC*H*$_3$), 3.48 (dd, *J* = 12.5, 5.5 Hz, 1H, H-5b), 4.06 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.12−4.30 (m, 5H), 4.50 (dd, *J* = 5.5, 2.7 Hz, 1H, H-4), 4.54 (s, 1H, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.12 (CH_3), 14.14 (CH_3), 52.4 (CH_2, C-5), 58.4 (CH_3), 61.4 (CH_2), 61.7 (CH_2), 61.9 (CH_2), 66.0 (CH, C-2), 69.3 (C, C-3), 86.7 (CH, C-4), 167.1 (C), 168.3 (C), 171.2 (C); IR (neat) 3343, 2983, 1735, 1466, 1445, 1369, 1253, 1097, 1027 cm^{-1}; MS (EI) *m/z* 317 (M^+, 18), 244 (100); HRMS *m/z* M^+ 317.1472 (calcd for $C_{14}H_{23}NO_7$ 317.1475).

*Data for trans-**5c**:* R_f = 0.4 (CH_2Cl_2:ether = 1:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, *J* = 7.1 Hz, 3H), 1.277 (t, *J* = 7.1 Hz, 3H), 1.279 (t, *J* = 7.1 Hz, 3H), 2.43 (s, 3H, NC*H*$_3$), 2.61 (dd, *J* = 9.4, 6.1 Hz, 1H, H-5a), 3.42 (s, 3H), 3.44 (dd, *J* = 9.4, 6.0 Hz, 1H, H-5b), 4.03 (s, 1H, H-2), 4.05−4.29 (m, 6H), 4.64 (dd, *J* = 6.0, 6.0 Hz, 1H, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.8 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 40.6 (CH_3), 58.9 (CH_3), 59.0 (CH_2, C-5), 61.0 (CH_2), 61.82 (CH_2), 61.84 (CH_2), 67.5 (C, C-3), 72.1 (CH, C-2), 83.0 (CH, C-4), 167.4 (C), 168.3 (C), 170.6 (C); IR (neat) 2982, 2939, 1738, 1465, 1368, 1266, 1223, 1115, 1052 cm^{-1}; MS (EI) *m/z* 331 (M^+); HRMS *m/z* M^+ 331.1631 (calcd for $C_{15}H_{25}NO_7$ 331.1631).

*Data for cis-**5c**:* R_f = 0.3 (CH_2Cl_2:ether = 1:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.20 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 2.38 (s, 3H), 2.69 (dd, *J* = 9.9, 5.0 Hz, 1H, H-5b), 3.24 (dd, *J* = 9.9, 2.5 Hz, 1H, H-5a), 3.29 (s, 1H, H-2), 3.31 (s, 3H), 4.10−4.29 (m, 6H), 4.39 (dd, *J* = 5.0, 2.5 Hz, 1H, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 40.4 (CH_3), 58.8 (CH_3), 59.4 (CH_2), 60.9 (CH_2), 61.5 (CH_2), 62.2 (CH_2), 68.5 (C, C-3), 71.7 (CH, C-2), 83.1 (CH, C-4), 165.7 (C), 169.3 (C), 169.9 (C); IR (neat) 2981, 1735, 1465, 1369, 1263, 1215, 1108, 1047 cm^{-1}; MS (EI) *m/z* 331 (M^+); HRMS *m/z* M^+ 331.1628 (calcd for $C_{15}H_{25}NO_7$ 331.1631).

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectral data, selected NOEs and HMBC correlations, discussion on the observed 2,4-*trans* selectivity of the six-membered ring, scheme for the other possible isomerization route, Cartesian coordinates of the optimized geometries of model compounds, and copies of the 2D NOESY spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: yamazaks@nara-edu.ac.jp.

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