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Use of the Diels−Alder Adduct of Pyrrole in Organic Synthesis. Formal Racemic Synthesis of Tamiflu

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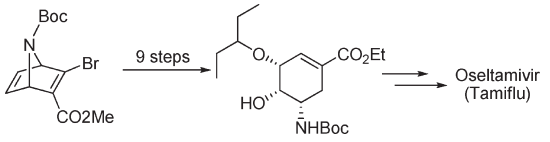
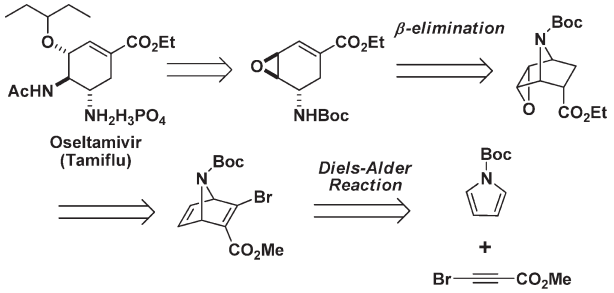


A new synthetic route to Tamiflu was developed via the Diels−Alder reaction of pyrrole and bromoacetylene.

Recently Tamiflu (oseltamivir phosphate) has been recognized as a key weapon in the combat of a new type of influenza and its importance and demand are now increasing. Tamiflu was first developed by Gilead Science, and is synthesized and marketed by Roche. Its production is performed starting from shikimic acid,[1] a natural product, so that development of a new synthesis from non-natural readily available chemical feedstock is required. The synthesis of Tamiflu has been investigated by many groups in the world and the total synthesis has been accomplished by Corey,[2] Shibasaki,[3] and other groups.[4]

Tamiflu contains ether and amino functional groups in a cyclohexene structure, so the proper and efficient installation of these groups is very important for the synthesis. Our synthetic strategy is illustrated in Scheme 1.

SCHEME 1



To construct such a polyfunctionalized cyclohexene unit, we were interested in the Diels−Alder adducts of pyrroles and acetylene.[5] This precursor may provide aminocyclohexene structure by elimination reaction of the bridged amine unit under the basic condition.[6] The adduct, 7-azabicyclo-[2.2.1]heptadiene, would be a potentially useful precursor for the installation of polyfunctionalities on the cyclohexane core. Pyrrole is an aromatic ring and it is not reactive toward the Diels−Alder reaction. However, pyrrole derivatives become good dienes in the Diels−Alder reaction with electron-deficient alkynes when an electron-withdrawing group is installed at the N1 position. In this paper, we report a formal synthesis of tamiflu from the Diels−Alder adduct of a pyrrole and an acetylene.

Our synthesis started from the Diels−Alder reaction of N-boc-pyrrole (Scheme 1). A solution of bromoacetylene carboxylate (**2**) in N-boc-pyrrole (**1**) was heated at 90 °C for 39 h and the Diels−Alder adduct, 7-*tert*-butyl 2-methyl 3-bromo-7-azabicyclo[2.2.1]hepta-2,5-diene-2,7-dicarboxylate (**3**), was isolated in 57% yield. An excess amount of **1**, which was used as the reaction solvent, was recovered by distillation after the reaction and reused for the preparation of

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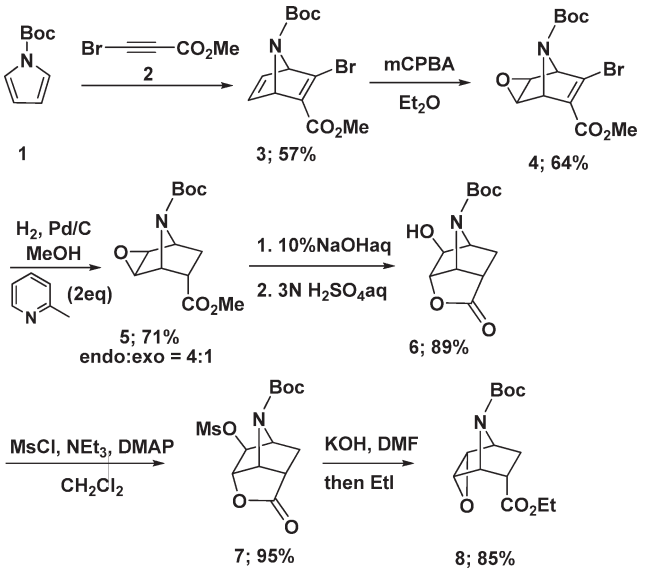
SCHEME 2

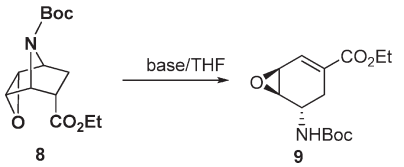


further batches of **3**. Treatment of **3** with mCPBA gave 5,6-epoxide **4** in 46% yield.[7] The oxidation took place in a stereoselective manner and *exo*-**4** was prepared as a single isomer. The use of oxone for the conversion resulted in the formation of a mixture of isomers. Stepwise formation of epoxide by using aqueous NBS followed by basic treatment also failed to provide the conversion to epoxide.[8] The reaction stopped after several hours and some starting material **3** was recovered even though a large excess of mCPBA was used—even after 24 h starting material was still present. Fortunately the recovered **3** was readily isolated from the reaction mixture by chromatographic treatment and reused. Finally we succeeded un improving the yield of **4** up to 64% by repeating the reaction procedure two times.

The reduction of **4** was carried out by the hydrogenation reaction catalyzed by Pd/C catalyst. Unfortunately the reaction was accompanied by the elimination of HBr, which induced the removal of the N-boc group after which decomposition of the azabicylic structure occurred. Addition of base effectively scavenged the HBr and desired **5** was isolated in more than 80% yield, although use of simple amine bases afforded a mixture of *endo*-**5** and *exo*-**5**. Finally we found that the use of 2 equiv of 2-methylpyridine as the base enhanced the endo/exo selectivity to 4:1 and compound **5** was isolated in 71% yield. Pure *endo*-**5** was isolated by further flash chromatography.

Basic hydrolysis of *endo*-**5** yielded the corresponding carboxylic acid, that then opened the epoxide to give tricyclic lactone alcohol **6** in 89% yield in one step.[9] The hydroxyl group in **6** was mesylated by treatment with MsCl to give **7** in 95% yield. Compound **7** was obtained as a crystalline form suitable for X-ray crystallographic analysis, which unambiguously showed the stereochemistry of **7** to be as shown in Scheme 2. Basic hydrolysis of **7** followed by esterification with EtI gave endoepoxide **8** in 85% yield.[10]

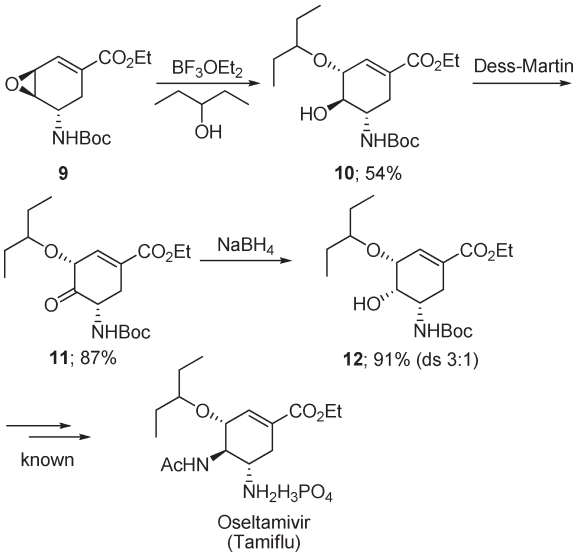
TABLE 1. Conversion of 8 to cyclohexene 9



entry	base (equiv)	additive (equiv)	time, h	temp, °C	yield of **9**,[a] %	recovery of **8**,[a] %
1	tBuOK (1.2)		40	−50	0	91
2	tBuOK (2.0)		26	reflux	0	86
3	tBuLi (1.3)		1	−50	20	8
4	LDA (1.3)		18	−50	24	38
5	LDA (1.3)	HMPA (1.5)	0.5	−78	62	2
6	LDA (1.3)	HMPA (3.0)	0.5	−78	60	21
7	LDA (1.3)	DMPU (1.5)	0.5	−78	22	0

[a]Isolated yield.

SCHEME 3



The next stage is the installation of the α,β-unsaturated ester in the cyclohexane ring. The results are summarized in Table 1. Exposure of **8** to tBuOK in THF at −50 °C resulted in total recovery of the starting material; thus the expected base-catalyzed elimination reaction did not take place (entry 1). The use of an excess amount of tBuOK or refluxing conditions was not effective to achieve the elimination either (entry 2). Use of tBuLi or LDA generated the desired **9** in low yield although some **8** was recovered (entry 3 and 4). The yield of **9** was greatly enhanced when HMPA was use as cosolvent of the reaction, resulting in an improved yield of **9** to 62% in the presence of 1.5 equiv of HMPA (entry 5).[11] An excess amount of HMPA was not effective in improving the conversion and the yield of **9** remained at a similar level (entry 6). Unfortunately, use of DMPU instead of HMPA did not afford **9** in good yield (entry 7).

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The final stage of the synthesis was performed in the following way (Scheme 3). Installation of the 3-pentyloxy group was achieved by treatment with 3-pentanol in the presence of BF_3OEt_2 to obtain compound **10** in 54% yield.[4j] The epimerization at the hydroxyl group of **10** was carried out by oxidation−reduction path way. Thus, the conversion of **10** to the corresponding ketone was achieved by treatment with the Dess−Martin periodinane to give **11** in 87% yield.[3] The reduction of **11** with $NaBH_4$ smoothly gave **12** in 91% yield. The diastereoselectivity was about 3:1. The major isomer of **12** showed an identical NMR spectrum to that of previously reported **12** prepared by Zutter.[4l] The conversion of **12** to Tamiflu has already been reported[4l] and thus concludes the formal synthesis of Tamiflu from readily available organic feedstock.

In conclusion, we have successfully achieved a new formal synthesis of Tamiflu in 9 steps from the Diels−Alder adduct of N-boc-pyrrole and an alkyne dienophile. Overall yield was 5.4%, and all of the steps proceeded in a sufficiently stereoselective manner. We are now trying to develop an asymmetric synthesis by using enzymatic optical resolution of compound **6**. The results will be reported in due course.

Experimental Section

Preparation of 3 via the Diels−Alder Reaction of *N*-Boc-pyrrole, 1. A mixture of **1** (48 mL, 288.8 mmol) and **2** (6.3 mL, 66.0 mmol) was heated at 90 °C for 39 h. After cooling, the mixture was subjected to flash chromatography (hexane−EtOAc 30:1, 20:1, then 15:1) to give **3** in 57% yield (12.42 g). Compound **1** was recovered in 99% (36.92 g), which was used for the reaction again. Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.03−7.18 (m, 2 H), 5.44−5.55 (m, 1 H), 5.07−5.20 (m, 1 H), 3.80 (s, 3 H), 1.41 (s, 9 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 162.4, 153.9, 147.4 (br), 143.5 (br), 141.0 (br), 140.4 (br), 81.1, 74.7 (br), 68.4 (br), 51.4, 27.7. Anal. Calcd for $C_{13}H_{16}BrNO_4$: C, 47.29; H, 4.88; N, 4.24. Found: C, 47.09; H, 4.66; N, 4.53.

Preparation of Epoxide 4. mCPBA (13.46 g, 77%, 60.1 mmol) was added to a solution of **3** (16.18 g, 49.0 mmol) in Et_2O (100 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h then at room temperature for 49 h. The mixture was concentrated and $NaHCO_3$(aq) was added. The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was combined, washed with $NaHCO_3$(aq) (20 mL) and brine (20 mL), and dried over Na_2SO_4. After being filtered, the crude product was concentrated and purified by flash chromatography (hexane−EtOAc 10:1) to give **4** in 46% yield (7.784 g) along with recovery of **3** in 5.836 g, which was subjected to a similar reaction conditions with use of mCPBA (5.942 g, 26.5 mmol) in CH_2Cl_2 (30 mL) to give **4** in 49% yield (3.011 g). The combined yield of the two manipulations was 64%. Compound **4** consisted of a stereoselective endoisomer, which contained two rotational isomers whose ratio was about 1:1. Oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.06 (s, 0.5 H), 4.91 (s, 0.5 H), 4.81 (s, 0.5 H), 4.67 (s, 0.5 H), 3.82 (s, 1.5 H), 3.81 (s, 1.5 H), 3.77−3.67 (m, 2 H), 1.56 (s, 4.5 H), 1.47 (s, 4.5); ^{13}C NMR (68 MHz, $CDCl_3$) δ 161.9, 161.8, 155.1, 155.0, 139.6, 139.3, 138.8, 138.6, 80.9, 80.8, 69.8, 69.3, 63.5, 62.7, 56.11, 55.9, 55.8, 55.5, 51.9, 27.8; HRMS (EI+ M) m/z 345.0217. Calcd for $C_{13}H_{16}NO_5Br$ 345.0212.

Hydrogenation of 4 To Prepare Compound 5. A sample of 10% Pd/C (16 mg) was added to a solution of **4** (0.160 g, 0.462 mmol) and 2-methylpyridine (0.086 g, 0.923 mmol) in MeOH (8 mL). Under hydrogen atmosphere, the mixture was stirred vigorously at room temperature for 50 h. Pd/C was removed over Celite pad and the filtrate was concentrated. The residue was purified by flash chromatography (hexane−EtOAc 4:1 then 2:1) to give *endo*-**5** in 56% yield (0.070 g) and *exo*-**5** in 14% yield (0.018 g). The *endo*-**5**/*exo*-**5** ratio was about 4:1. Compounds *endo*-**5** and *exo*-**5** contained two rotational isomers whose ratio was about 1:1. *endo*-**5**: white solid; mp 75.5−76 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.58 (d, J = 4.6 Hz, 0.5 H), 4.44 (d, J = 4.5 Hz, 0.5 H), 4.40 (d, J = 4.8 Hz, 0.5 H), 4.25 (d, J = 4.8 Hz, 0.5 H), 3.72 (s, 3 H), 3.39 (d, J = 3.3 Hz, 0.5 H), 3.36 (d, J = 3.3 Hz, 0.5 H), 3.32 (d, J = 3.4 Hz, 0.5 H), 3.30 (d, J = 3.4 Hz, 0.5 H), 3.20−3.06 (m, 1 H), 2.16 (dd, J = 4.8, 11.2 Hz, 0.5 H), 2.08 (dd, J = 4.5, 11.8 Hz, 0.5 H), 1.76 (dd, J = 3.3, 4.7 Hz, 0.5 H), 1.72 (dd, J = 3.5, 4.7 Hz, 0.5 H), 1.45 (s, 9 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 172.3, 157.5, 80.3, 58.6, 58.0, 57.4, 56.7, 52.1, 49.7, 49.3, 48.1, 45.5, 44.6, 29.1, 28.1. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.76; H, 6.98; N, 5.15. *exo*-**5**: white solid; mp 126.5−127 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.67 (s, 0.5 H), 4.53 (s, 0.5 H), 4.40 (d, J = 4.6 Hz, 0.5 H), 4.26 (d, J = 4.6 Hz, 0.5 H), 3.73 (s, 1.5 H), 3.72 (s, 1.5 H), 3.39−3.26 (m, 2 H), 2.53 (dd, J = 2.0, 4.4 Hz, 0.5 H), 2.49 (dd, J = 1.8, 4.5 Hz, 0.5 H), 2.20−2.41 (m, 1 H), 1.69 (d, J = 9.1 Hz, 0.5 H), 1.64 (d, J = 9.2 Hz, 0.5 H), 1.43 (s, 9 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 172.6, 172.5, 157.5, 157.3, 80.0, 60.0, 59.7, 56.9, 56.2, 52.1, 50.3, 49.8, 49.2, 43.8, 42.9, 29.8, 29.4, 28.0. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.95; H, 6.99; N, 5.19.

Preparation of Tricyclic Lactone 6. NaOH(aq) (10%, 6.5 mL) was added dropwise at 0 °C to a solution of *endo*-**5** (3.34 g, 12.45 mmol), and the resulting solution was stirred at 0 °C for 30 min and at room temperature for 40 h to neutralize the solution, then dilute H_2SO_4(aq) (3 M) was added. The solution was concentrated in vacuo. The pH of the remaining aqueous solution was adjusted to 2−3 by adding dilute H_2SO_4. The water solution was extracted with CH_2Cl_2 (5 × 50 mL) and the organic phase was dried over Na_2SO_4. Filtration and concentration of the filtrate gave a crude product of **6** in 89% yield (2.816 g), which was almost pure and ready to use for the next step. Mp 158−158.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.05 (t, J = 5.3 Hz, 1 H), 4.52 (d, J = 5.3 Hz, 1 H), 4.34 (d, J = 4.8 Hz, 1 H), 3.85 (d, J = 6.0 Hz, 1 H), 2.75 (dd, J = 4.8, 11.3 Hz, 1 H), 2.28−2.11 (m, 2 H), 1.84 (dd, J = 1.9, 13.6 Hz, 1 H), 1.47 (s, 9 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 177.2, 155.5, 84.5, 81.7, 77.4, 62.8, 61.7, 38.2, 32.4, 28.1; HRMS (FAB + M + 1) m/z 256.1186. Calcd for $C_{12}H_{18}NO_5$ 256.1179.

Preparation of Mesylate 7. MsCl (0.34 mL, 4.39 mmol) was added to a solution of **6** (1.01 g, 3.96 mmol) and Et_3N (0.66 mL, 4.77 mmol) at room temperature and the reaction mixture was stirred for 24 h. CH_2Cl_2 (10 mL) and $NaHCO_3$(aq) (8 mL) were added and the organic layer was separated. The water layer was extracted with CH_2Cl_2 (5 × 2 mL). The combined organic phase was washed with brine (5 mL) and dried over Na_2SO_4. After filtration, the filtrate was concentrated to give crude **7**, which was purified by recrystallization (acetone−hexane 1:3) in 95% (1.25 g) yield. White solid; mp 178.5−179 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.14 (t, J = 4.6 Hz, 1 H), 4.80 (d, J = 5.0 Hz, 1 H), 4.67 (d, J = 4.9 Hz, 1 H), 4.62 (s, 1 H), 3.10 (s, 3 H), 2.80 (dd, J = 4.8, 10.3 Hz, 1 H), 2.31 (ddd, J = 5.1, 11.3, 13.8 Hz, 1 H), 1.93 (dd, J = 1.9, 13.8 Hz, 1 H), 1.47 (s, 9 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 176.0, 154.0, 82.7, 82.5, 81.9, 61.4, 60.8, 38.8, 37.8, 32.6, 28.1. Anal. Calcd for $C_{13}H_{19}NO_7S$: C, 46.84; H, 5.74; N, 4.20. Found: C, 46.99; H, 5.75; N, 4.19.

Preparation of Endoepoxide 8. KOH (103.0 mg, 1.836 mmol) was added to a solution of **7** (103.0 mg, 0.309 mmol) in DMF (5 mL). The reaction mixture was stirred at room temperature for 30 h. EtI (0.2 mL, 2.49 mmol) was added to the solution and the reaction mixture was stirred for 24 h. A mixed solution of NH_4Cl(aq) and dilute HCl (5:1, 5 mL) was added and the aqueous phase was extracted with EtOAc (7 × 10 mL). The combined organic phase was washed with brine (2 × 5 mL) and dried over Na_2SO_4. Filtration followed by concentration of the filtrate in vacuo gave crude product, which was purified by flash chroma-

tography (hexane−EtOAc 4:1) to give **8** in 85% yield (74 mg) as a colorless oil. Compound **8** contained two rotational isomers whose ratio was about 1:1. ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.45−4.51 (m, 1 H), 4.28−4.10 (m, 3 H), 4.03−3.95 (m, 1 H), 3.91 (dd, J = 3.1, 4.4 Hz, 1 H), 2.91−2.79 (m, 1 H), 2.06−1.92 (m, 2 H), 1.57 (s, 4.5 H), 1.44 (s, 4.5 H), 1.28 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 172.0, 155.0, 80.7, 63.2, 63.0, 60.6, 60.1, 58.4, 44.2, 29.1, 28.2, 14.2. Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.49; H, 7.19; N, 4.78.

Conversion to Cyclohexene Epoxide 9. A solution of LDA was generated from a solution of iPr_2NH (0.31 mL, 2.2 mmol) in THF (10 mL) by adding HMPA (0.29 mL, 1.66 mmol) and tBuLi (1.58 M in pentane, 1.42 mmol). To the LDA solution was added a solution of **8** (309 mg, 1.09 mmol) in THF (5 mL) at −50 °C and the resulting solution was stirred for 16 h at the same temperature. The reaction mixture was warmed to 0 °C and NH_4Cl(aq) (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the organic phase was dried over Na_2SO_4. Filtration followed by concentration of the filtrate in vacuo gave crude product, which was purified by flash chromatography (hexane−EtOAc 8:1 then 4:1) to give **9** in 63% yield (194.0 mg). White solid; mp 58−58.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.12 (t, J = 3.3 Hz, 1 H), 4.64−4.51 (m, 1 H), 4.49−4.31 (m, 1 H), 4.21 (q, J = 7.0 Hz, 2 H), 3.63−3.53 (m, 1 H), 3.42 (t, J = 4.3 Hz, 1 H), 2.69 (d, J = 16.8 Hz, 1 H), 2.35 (d, J = 16.3 Hz, 1 H), 1.44 (s, 9 H), 1.30 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.9, 155.2, 133.6, 132.0, 100.7, 61.1, 55.8, 45.8, 43.1, 28.3, 26.8, 14.1. Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.04; H, 7.61; N, 5.03.

Installation of 3-Pentanyl Ether 10. Compound **9** (822 mg, 2.90 mmol) was dissolved in 3-pentanol (25 mL) and BF_3OEt_2 (1.0 mL, 3.2 mmol) was slowly added to the solution at −20 °C over 20 min. The solution was stirred for 1 h. $NaHCO_3$(aq) (30 mL) was added to the solution at 0 °C and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (hexane−EtOAc 5:1, 4:1 then 3:1) to give **10** in 54% yield (1.567 mmol). Pale yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.76 (s, 1 H), 4.85 (d, J = 7.6 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 4.06−3.98 (m, 1 H), 3.90−3.71 (m, 1 H), 3.60 (ddd, J = 3.6, 7.0, 10.2 Hz, 1 H), 3.48 (t, J = 4.9 Hz, 1 H), 2.88 (dd, J = 4.9, 18.6 Hz, 1 H), 2.70−2.59 (m, 1 H), 2.30−2.10 (m, 1 H), 1.58−1.47 (m, 4 H), 1.45 (s, 9 H), 1.28 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.4 Hz, 6 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 166.4, 156.6, 136.8, 129.4, 82.0, 80.0, 77.8, 73.9, 60.9, 50.2, 30.5, 28.4, 26.4, 26.1, 14.2, 9.5; HRMS (EI+ M) m/z 371.2324. Calcd for $C_{19}H_{33}NO_6$ 371.2308.

Oxidation to Ketone 11. A mixture of Dess−Martin periodate (88.7 mg, 0.209 mmol) and compound **10** (38.4 mg, 0.103 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 2 h. Filtration followed by flash chromatography (hexane−EtOAc 9:1) gave **11** in 87% yield (33.1 mg). Pale yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.79 (t, J = 2.9 Hz, 1 H), 5.50 (d, J = 7.1 Hz, 1 H), 4.82−4.59 (m, 2 H), 4.22 (q, J = 6.1 Hz, 2H), 3.52−3.35 (m, 2H), 2.46−2.22 (m, 1 H), 1.49−1.76 (m, 8 H), 1.44 (s, 9 H), 1.29 (t, J = 7.1 Hz, 3 H), 0.98 (t, J = 7.3 Hz, 3 H), 0.91 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 202.6, 165.4, 155.3, 138.0, 130.4, 83.7, 80.2, 76.5, 61.3, 55.2, 35.0, 28.3, 26.4, 25.4, 14.1, 9.5, 9.2.

Preparation of Ethyl 5-(*tert*-Butoxycarbonylamino)-4-hydroxy-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate, 12. $NaBH_4$ (14.0 mg, 0.37 mmol) was added to a solution of **11** (66.9 mg, 0.18 mmol) in MeOH at −50 °C and the reaction mixture was stirred for 30 min. $NaHCO_3$(aq) (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was washed with brine (10 mL) and dried over Na_2SO_4. Filtration followed by concentration gave crude product, which was purified by flash chromatography (hexane−EtOAc 8:1 then 4:1) to give **12** in 91% yield (61.1 mg). HPLC analysis revealed the diastereomeric ratio was 3:1. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (s, 1 H), 5.19 (d, J = 9.2 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.13−4.16 (m, 1H), 4.01−4.06 (m, 1 H), 3.85 (dt, J = 7.0, 10.5 Hz, 1 H), 3.48−3.35 (m, 1 H), 2.58 (dd, J = 5.6, 17.8 Hz, 1 H), 2.53−2.57 (br, 1 H), 2.32 (dd, J = 10.1, 17.3 Hz, 1 H), 1.66−1.51 (m, 4 H), 1.44 (s, 9 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 155.5, 135.7, 130.7, 81.7, 79.6, 73.9, 68.2, 60.9, 48.8, 28.5, 27.1, 26.4, 26.2, 14.3, 9.8, 9.4; HRMS (EI+ M) m/z 371.2309. Calcd for $C_{19}H_{33}NO_6$ 371.2308.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **3**, **4**, *endo*-**5**, *exo*-**5**, **6**, **7**, **8**, **9**, **10**, **11**, and **12** and X-ray crystallographic data for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.