Preferential Intramolecular Ring Closure of Aminoalcohols with Diethyl Carbonate to Oxazolidinones

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The closure by cyclization with diethyl carbonate $(EtO)_2CO$ from aminoalcohols 1 as starting material can lead to the oxazolidinones 2a, b and 2c, respectively. In the reaction of *trans*-isomer (6) and $(EtO)_2CO$, isolated products were also only 5-membered oxazolidinone derivative (7), containing its dehydrated derivative 8. The preferential formation of the 5-membered oxazolidinone ring system apparently indicated that this process (5-Exo-Trig ring closure) is more favorable than that of 6- or 7-membered ring derivative (3 or 9) by 6- or 7-Exo-Trig ring closure.

Kew words ring closure; aminoalcohol; diethyl carbonate; β-aminoalanines; oxazolidinone; 5-Exo-Trig

In connection with our interest in the chemistry of β-aminoalanines,[1—4] we have reported the synthetic application of these materials as a synthon for the preparation of a 5-membered oxazolidinone ring system.[2] Some of the oxazolidinone derivatives have attracted much attention not only as a synthetic target but also because of the importance of the related compounds in the biological activities.[5,6]

This paper deals with the relative rates of ring closure by cyclization with diethyl carbonate $(EtO)_2CO$ from aminoalcohols as starting material. We report here two typical experimental results for the cyclization that has two possibilities as a function of the ring intramolecular cyclization by $(EtO)_2CO$.1

Results and Discussions

The objective of this report is to explore the orientation of ring closure of aminoalcohol by $(EtO)_2CO$. The compounds (**1**[7] and **6**[8]) are selected as the starting aminoalcohols, which have two hydroxy groups and a basic secondary amine in the molecules, so that the cyclization of these compounds employing $(EtO)_2CO$ can lead to the corresponding heterocycles (*e.g.* compounds **2** and **3**, respectively, in the case of aminoalcohol **1**).

Since the experiment using compound **1** under similar reaction conditions reported previously[2] resulted in a quite complex reaction mixture by TLC analysis, it is not used to determine conditions suitable for cyclization of this aminoalcohol (**1**). Then, we tried the cyclization of (**1**) under the conditions of this aminoalcohol (**1**) and $(EtO)_2CO$ in a 1/1.25 ratio. In this experiment, we isolated the majority of cyclized products (**2**) in 81% total yield [*cis* (**2a**, **2b**) : *trans* (**2c**) = *ca.* 3/1 determined by ^{1}H-NMR]. The relative ratio of *cis*/*trans* was based upon the signal at δ 3.67 and δ 3.72 for *cis* isomers (**2a**, **2b**). Because a diastereomeric mixture of aminoalcohol (**1**) (*cis* : *trans* = *ca.* 3/1) was used as the starting material (see Experimental), the 5-membered ring products (oxazolidinones) may generate the products **2** as a mixture of four diastereoisomers theoretically.

We were able to isolate two *cis*-isomers (**2a**, **b**, α or β-stereoisomers, respectively), and our repeated trials for separation of two pure *trans*-isomers were unsuccessful. However, NMR spectroscopic analysis showed the isolated sample **2c** was a mixture of two stereoisomers (see Experimental). In this case, the preferential formation of a 5-membered oxazolidinone ring system apparently indicated that this process (5-Exo-Trig[9] ring closure) is more favorable than that of 6-membered ring derivative **3** by 6-Exo-Trig ring closure. The fact that the 6-membered ring system can be isolated easily in the reaction of a noncompetitive cyclization system, *i.e.*, the formation of compound (**5**)[10] from the start-

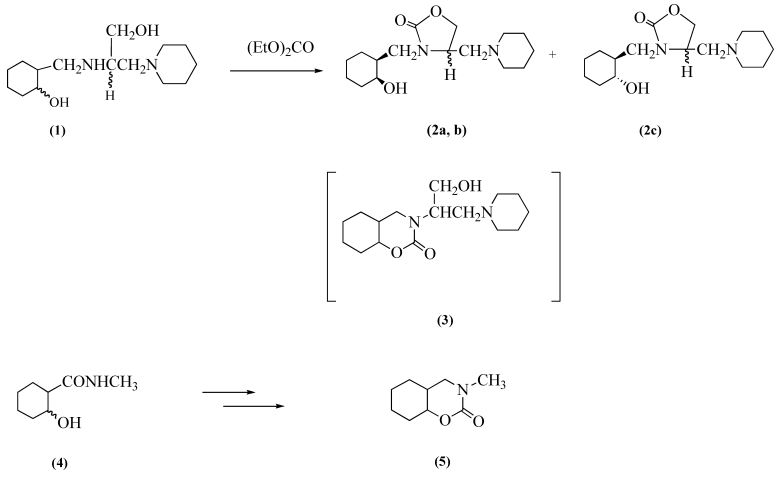

Chart 1

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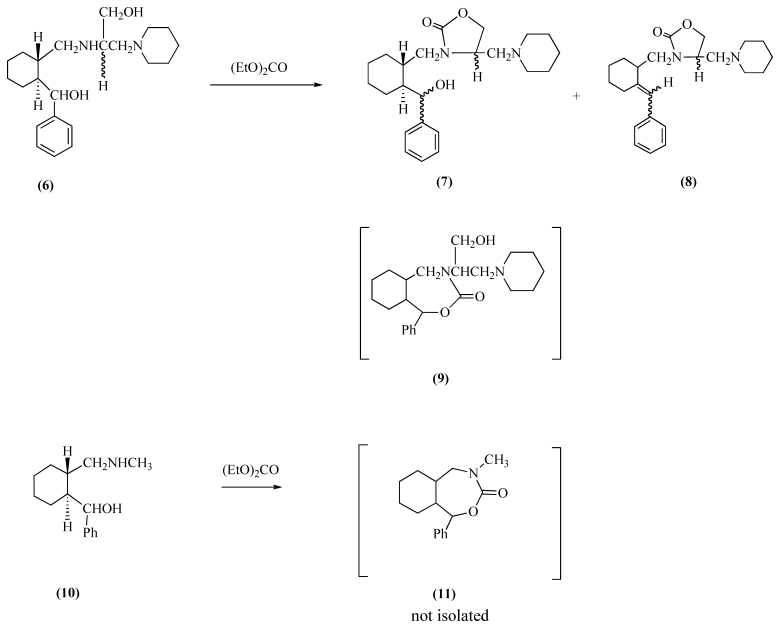

Chart 2

ing compound **4** is one piece of evidence in support of the above consideration (see Experimental).

In the reaction of *trans*-isomer (**6**)[8] and $(EtO)_2CO$, isolated products were also only 5-membered oxazolidinone derivatives (**7**), containing its dehydrated derivative **8**, in 53% total yield, and we could isolate none of the expectable 7-membered compound such as the structure **9** by 7-Exo-Trig ring closure. In addition to the above result, the reaction of aminoalcohol **10** with $(EtO)_2CO$ under similar conditions gave no expectable cyclized product **11**, and resulted in the recovery of the starting material.[11]

We are considering that the stereoelectronic requirement for the ring closure to 6 or 7-membered heterocyclic compounds may give rise to higher energies of both transition states rather than that of ring closure for 5-membered oxazolidinones (5-Exo-Trig ring closure).[9,12]

So far as we know, no previous report has dealt with these competitive ring closure tests as described above. We may emphasize that the reaction of β-aminoalcohol with $(EtO)_2CO$ under above limited reaction conditions at least, even in the presence of competitive hydroxy groups at the γ or δ-position, brings about cyclization to form preferentially the 5-membered oxazolidinones. Further synthetic applications of the above-mentioned information for related derivatives, particularly the quest for the biologically active lead compounds, are in progress.

Experimental

Melting points are uncorrected. IR spectra were measured with a Shimadzu FT/IR-8100 spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL JNM A-500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) at 35 °C unless otherwise noted. Chemical shifts are expressed as δ ppm downfield from an internal tetramethylsilane (TMS). The signal assignments were confirmed with ^{1}H–^{1}H two-dimensional (2D) correlation spectroscopy (COSY), ^{1}H–^{13}C heteronuclear multiple-quantum coherence (HMQC), ^{1}H–^{13}C heteronuclear multiple-bond connectivity (HMBC) spectra. The stereochemistry of the starting materials and products were also supported by NOEs experiment. FAB-MS were obtained with a JEOL JMS-HX110 mass spectrometer. The preparation of racemic β-aminoalanines as starting materials has already been described in our previous paper.[1—4] The following abbreviations in the brackets were used for the cyclohexane ring (Cyhx), the piperidine ring (Ppd), and for the oxazolidinone ring (Oxaz), respectively.

Reaction of Aminoalcohol (1) with (Et_2O)CO [Preparation of Oxazolidin-2-one (2)] A mixture of **1**[7] (0.34 g, 1.259 mmol) and freshly distillated diethyl carbonate (0.149 g, 1.590 mmol) in anhydrous benzene was refluxed for 10 min in the presence of a catalytic amount of sodium methoxide. After concentration of the solvent under reduced pressure, the residue was dissolved in Et_2O, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give an oily residue. The residue was simply chromatographed on silica gel with EtOH to afford a total amount of 0.30 g (81% yield) of an isomeric mixture of the cyclized oxazolidinone derivatives (**2a** : **2b** : **2c**=*ca.* 5/5/3 determinable by ^{1}H-NMR). This material was carefully chromatographed on silica gel (AcOEt→EtOH→MeOH as eluants) to afford pure isomers **2a** and **2b**, and an isomeric mixture of **2c**. In spite of careful analysis of 2D NMR data, we found no confirmable evidence regarding α- and β-isomers corresponding to the structure of **2a**, **2b**, and **2c** (a mixture of α- and β-isomers). The data of the products are shown below.

3-[*cis*-(2-Hydroxycyclohexyl)methyl]-4-(piperidin-1-ylmethyl)oxazolidin-2-one (Compound 2a) mp 101—103 °C. IR (KBr) cm^{-1}: 1728. ^{1}H-NMR (DMSO-d_6) δ: 1.16—1.78 (15H, m, Ppd H-3—H-5 and Cyhx H-2—H-6), 2.28 (1H, dd, J=13.0, 6.0 Hz, CHH-1-Ppd), 2.23—2.37 (4H, m, Ppd H-2, H-6), 2.54 (1H, dd, J=13.0, 6.5 Hz, CHH-1-Ppd), 3.06 (1H, dd, J=13.0, 7.0 Hz, Cyhx-CHH-Oxaz), 3.20 (1H, dd, J=13.0, 8.0 Hz, Cyhx-CHH-Oxaz), 3.67 (1H, br s, Cyhx H-1), 3.89 (1H, dd, J=8.0, 6.0 Hz, Oxaz-H_A-5), 3.93—3.96 (1H, m, Oxaz H-4), 4.14 (1H, br, OH), 4.30 (1H, dd, J=8.0, 8.0 Hz, Oxaz H_B-5). ^{13}C-NMR (DMSO-d_6) δ: 19.8, 24.1, 24.4, 24.9, and 25.5 (×2) (Cyhx C-3—C-5 and Ppd C-3—C-5), 32.5 (Cyhx C-6), 39.4 (Cyhx C-2), 45.1 (Cyhx-CH_2-Oxaz), 52.6 (Oxaz C-4), 54.4 (×2) (Ppd C-2 and C-6), 61.1 (CH_2-1-Ppd), 64.7 (Cyhx C-1), 66.0 (Oxaz C-5), 158.2 (CO). FAB-MS (positive) m/z: 197 ($C_{10}H_{17}N_2O_2^+$), 297 $(M+H)^+$. HR-FAB-MS(+) m/z: 297.2173 (Calcd for $C_{16}H_{29}N_2O_3$: 297.2178).

3-[*cis*-(2-Hydroxycyclohexyl)methyl]-4-(piperidin-1-ylmethyl)oxazolidin-2-one (Compound 2b) mp 111—112 °C. IR (KBr) cm^{-1}: 1717. ^{1}H-NMR (DMSO-d_6) δ: 1.18—1.68 (15H, m, Ppd H-3—H-5 and Cyhx H-2—H-6), 2.28 (1H, dd, J=13.0, 6.0 Hz, CHH-1-Ppd), 2.35—2.36 (4H, m, Ppd H-2, H-6), 2.49—2.52 (1H, m, CHH-1-Ppd), 3.08 (1H, dd, J=14.0, 6.5 Hz, Cyhx-CHH-Oxaz), 3.20—3.28 (1H, Cyhx-CHH-Oxaz), 3.72 (1H, br s, Cyhx H-1), 3.91 (1H, dd, J=8.0, 6.0 Hz, Oxaz H_A-5), 3.94—3.97 (1H, m, Oxaz H-4), 4.30 (1H, dd, J=8.0, 8.0 Hz, Oxaz H_B-5), 4.36 (1H, br, OH). ^{13}C-NMR (DMSO-d_6) δ: 20.0, 23.7, 23.8, 24.5, and 25.5 (×2) (Cyhx C-3—C-5 and Ppd C-3—C-5), 32.7 (Cyhx C-6), 39.0 (Cyhx C-2), 44.4 (Cyhx-CH_2-Oxaz), 51.8 (Oxaz C-4), 54.5 (×2) (Ppd C-2 and C-6), 60.8 (CH_2-1-Ppd), 65.5 (Cyhx C-1), 66.0 (Oxaz C-5), 157.9 (CO). FAB-MS (positive) m/z: 197 ($C_{10}H_{17}N_2O_2^+$), 297 $(M+H)^+$. HR-FAB-MS(+) m/z: 297.2178 (Calcd for $C_{16}H_{29}N_2O_3$: 297.2178).

3-[*trans*-(2-Hydroxycyclohexyl)methyl]-4-(piperidin-1-ylmethyl)oxa-

zolidin-2-one (Compound 2c) Obtained as oil. IR (KBr) cm^{-1}: 1744. ^{1}H-NMR (DMSO-d_6) δ: 0.82—1.82 (15H, m, Ppd H-3—H-5 and Cyhx H-2—H-6), 2.28 (1H, dd, J=12.5, 7.0 Hz, CHH-1-Ppd), 2.49—2.50 (4H, m, Ppd H-2, H-6), 2.53 (1H, dd, J=12.5, 5.5 Hz, CHH-1-Ppd), 3.04—3.28 (2H, m, Cyhx-CHH-Oxaz+Cyhx H-1), 3.44—3.50 (1H, m, Cyhx-CHH-1-Oxaz), 3.91 (1H, dd, J=8.0, 5.5 Hz, Oxaz H_A-5), 3.94—3.98 (1H, m, Oxaz H-4), 4.28 (1H, dd, J=8.0, 8.0 Hz, Oxaz H_B-5), 4.52 (1H, br, OH). ^{13}C-NMR (DMSO-d_6) δ: 23.8, 24.1, 24.2, 24.7, 24.8, 25.4 (×2), 25.5 (×2), 25.6, 28.0, and 28.4 (Cyhx C-3—C-5 and Ppd C-3—C-5), 35.2 (Cyhx C-6 for α- and β-isomers), 42.3 and 44.0 (Cyhx C-2), 44.5 and 45.6 (Cyhx-CH_2-Oxaz), 51.0 and 53.8 (Oxaz C-4), 54.0 and 54.6 (Ppd C-2 and C-6), 60.0 and 60.8 (CH_2-1-Ppd), 66.0 and 66.1 (Oxaz C-5), 71.2 and 73.9 (Cyhx C-1), 157.9 and 158.0 (CO). FAB-MS (positive) m/z: 197 ($C_{10}H_{17}N_2O_2^+$), 297 $(M+H)^+$. HR-FAB-MS(+) m/z: 297.2171 (Calcd for $C_{16}H_{29}N_2O_3$: 297.2178).

Reaction of Aminoalcohol (6) with (Et_2O)CO [Preparation of oxazolidin-2-ones (7, 8)] Freshly distillated diethyl carbonate (0.108 g, 0.915 mmol) and catalytic amounts of sodium methoxide were added to a solution of **6** (0.3 g, 0.833 mmol) in anhydrous benzene and the mixture was heated at 110°C for 10 min. The resulting mixture was dissolved in Et_2O and extracted with 1 N-HCl. The acidic aqueous layer was washed with Et_2O, neutralized with K_2CO_3, and then extracted with Et_2O. The ethereal extract was dried over anhydrous Na_2SO_4. Evaporation and purification by chromatography on silica gel (AcOEt) gave the free product **7** (170 mg, 53%), in which dehydrated compound **8** (*ca.* 18%) was detected by ^{1}H-NMR analysis. This material was carefully chromatographed on silica gel (AcOEt) to afford pure products **7** and **8** respectively. Both compounds α- and β-isomers and stereochemistry of the hydroxy group in compound **7** could not be specified. *E* and *Z* isomers for the compound **8** were not also determinable by careful spectroscopic analysis. The data of the products are shown below.

3-[*trans*-(2-(Hydroxy(phenyl)methyl)cyclohexyl)methyl]-4-(piperidin-1-ylmethyl)oxazolidin-2-one (Compound 7) Colorless very hygroscopic viscous oil**.** IR (KBr) cm^{-1}: 3453, 1752, 1743, 1727. ^{1}H-NMR (DMSO-d_6) δ: 1.13—1.62 (15H, m, Cyhx H-2—H-6 and Ppd H-3—H-5), 1.90—1.98 (1H, m, Cyhx H-1), 2.29—2.40 (5H, m, Ppd H-2, H-6 and CHH-Ppd), 2.55—2.59 (1H, m, CHH-Ppd), 3.21 (1H, dd, J=14.0, 11.0 Hz, CHH-Cyhx), 3.44 (1H, J=14.0, 4.5 Hz, CHH-Cyhx), 3.86—3.87 (1H, m, Oxaz H-4), 3.96—4.00 (1H, m, Oxaz H_A-5), 4.31 (1H, dd, J=8.5, 8.5 Hz, Oxaz H_B-5), 4.68 (1H, d, J=6.0 Hz, Ph-CHOH), 5.14 (1H, br s, OH), 7.21—7.34 (5H, m, ArH). ^{13}C-NMR (DMSO-d_6) δ: 23.2, 23.8 (×2), 25.5 (×2), 25.8 and 26.6 (Ppd C-3—C-5 and Cyhx C-3—C-6), 34.0 (Cyhx C-1), 44.9 (CH_2-Cyhx), 45.8 (Cyhx C-2), 51.1 (Oxaz C-4), 54.7 (×2) (Ppd C-2 and C-6), 60.1 (CH_2-1-Ppd), 66.2 (Oxaz C-5), 73.2 (Ph-CH-OH), 126.5 (×2), 126.6, and 127.7 (×2) (Ar C-2—C-6), 144.8 (Ar C-1), 157.8 (CO). HR-FAB-MS(−) m/z: 385.2491 ($C_{23}H_{33}N_2O_3$: 385.2475). *Anal.* Calcd for $C_{23}H_{34}N_2O_3 \cdot HCl \cdot 2.6H_2O$: C, 64.83; H, 9.52; N, 9.45. Found: C, 64.93; H, 9.56; N, 9.31.

3-[(2-Benzylidenecyclohexyl)methyl]-4-(piperidin-1-ylmethyl)oxazolidin-2-one (Compound 8) Colorless hygroscopic viscous oil. IR (KBr) cm^{-1}: 1752. ^{1}H-NMR (DMSO-d_6) δ: 1.16—2.56 (21H, Cyhx H-1, H-3—H-6, Ppd C-2—C-6, and CH_2-1-Ppd), 3.20—3.42 (2H, m, CH_2-Cyhx), 3.77—3.99 (2H, m, Oxaz H-4, H_A-5), 4.20—4.32 (1H, m, Oxaz H_B-5), 5.63—5.72 (1H, m, PhCH=), 7.20—7.36 (5H, m, ArH). ^{13}C-NMR (DMSO-d_6) δ: 22.1, 22.6, 23.0, 23.1, 23.5, 24.5, 25.1, 25.3 (×4), 25.5, 25.8 and 26.2 (Cyhx C-3—C-6 and Ppd C-3—C-5), 34.0 and 42.3 (Cyhx C-1), 44.9 and 45.6 (CH_2-Cyhx), 51.2 and 52.7 (Oxaz C-4), 54.3 (×2) and 54.4 (×2) (Ppd C-2 and C-6), 59.2 and 60.4 (CH_2-1-Ppd), 65.7 and 65.9 (Oxaz C-5), 80.2 and 80.3 (Ph-CH=), 126.1 (×2), 126.2 (×2), 126.4, 127.3, 127.8 (×2) and 127.9 (×2) (Ar C-2—C-6), 138.1 and 138.3 (Ar C-1), 153.0 and 153.1 (Cyhx C-2), 157.5 and 157.6 (CO). FAB-MS (positive) m/z: 369 $(M+H)^+$. *Anal.* Calcd for $C_{23}H_{32}N_2O_2 \cdot 1.3H_2O$: C, 70.48; H, 8.90; N, 7.15. Found: C, 70.51; H, 8.63; N, 6.99.

References and Notes

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7) This compound was prepared from 2-hydroxycyclohexanecarboxylic acid and β-piperidinoalanine according to the procedure reported previously.[1,2] For the preparation of 2-hydroxycyclohexanecarboxylic acid, see de Raadt A., Griengl H., Petsch M., Plachota P., Schoo N., Weber H., *Tetrahedron: Asymmetry*, **7**, 473—490 (1996). Compound (**1**): IR (KBr) cm^{-1}: 3410. ^{1}H-NMR (DMSO-d_6) δ: 1.05—1.64 (15H, m, Cyhx H-2—H-6 and Ppd H-3—H-5), 2.18—2.38 (6H, m, CH_2-1-Ppd and Ppd H-2, H-6), 2.42—2.52 (1H, m, Cyhx-CHH), 2.56—2.62 (1H, m, $NHCHCH_2N$=), 2.64—2.71 (1H, m, Cyhx-CHH), 3.0—3.3 (3H, br, OH ×2, and NH), 3.31—3.34 (2H, m, CH_2OH), 3.79—3.83 (1H, m, Cyhx H-1). FAB-MS (positive) m/z: 271 $(M+H)^+$. *Anal.* Calcd for $C_{15}H_{30}N_2O_2 \cdot 0.4H_2O$: C, 64.90; H, 11.18; N, 10.09. Found: C, 64.93; H, 11.17; N, 10.01.
8) This compound was prepared from *trans* 2-benzoylcyclohexanecarboxylic acid and β-piperidinoalanine by the same method described previously.[1,2] For the preparation of *trans* 2-benzoylcyclohexanecarboxylic acid, see Miyano S., Abe N., Fujisaki F., Sumoto K., *Heterocycles*, **26**, 1813—1826 (1987). Compound (**6**): IR (KBr) cm^{-1}: 3410, 3303. ^{1}H-NMR (DMSO-d_6, 70 °C) δ: 1.04—1.75 (16H, m, Cyhx H-1—H-6, and Ppd H-3—H-5), 2.24—2.82 (9H, m, Ppd H-2, H-6, CH_2-Ppd, Cyhx-$CH_2NHCHCH_2$ and $CH_2NHCHCH_2N$=), 3.37 (2H, dd, J=5.5, 4.0 Hz, CH_2OH), 3.8—4.8 (2H, br, OH and OH or NH), 4.59 (1H, dd, J=13.0, 6.5 Hz, PhCHOH), 5.0—6.0 (1H, br NH or OH), 7.25—7.28 (5H, m, ArH). FAB-MS (positive) m/z: 361 $(M+H)^+$. *Anal.* Calcd for $C_{22}H_{36}N_2O_2 \cdot 0.15H_2O$: C, 72.74; H, 10.07; N, 7.71. Found: C, 72.76; H, 10.16; N, 7.43.
9) Baldwin J. E., *J. Chem. Soc., Chem. Commun.*, **1976**, 734 (1976).
10) This compound was obtained from the reaction in the same manner described for (**2**). Starting 2-hydroxycyclohexanecarboxylic acid (*cis* : *trans*=*ca.* 3/1) was obtained by the method reported previously.[7] The product **5** obtained in this experiment was an oily material. IR (KBr) cm^{-1}: 3453 1691. ^{1}H-NMR (DMSO-d_6) δ: 1.21—1.81 (6H, m, Cyhx H-5, H_A-6, H-7 and H_A-8), 1.61—1.68 (1H, m, Cyhx H_B-6), 1.74—1.81 (1H, m, Cyhx H_B-8), 1.93—1.99 (1H, m, H-4a), 2.81 (3H, s, CH_3), 2.90 (1H, dd, J=12.0, 2.5 Hz, H-4), 3.44 (1H, dd J=12.0, 5.5 Hz, H-4), 4.39—4.41 (1H, m, H-8a). ^{13}C-NMR (DMSO-d_6) δ: 19.5, and 23.2 (C-7), 23.5, 23.9, 24.4, and 27.0 (C-5 and C-6), 29.2 and 30.8 (C-8), 31.4 and 35.8 (C-4a), 35.9 and 36.5 (CH_3), 51.3 and 51.9 (C-4), 74.1 and 78.2 (C-8a), 152.5 (×2) (CO). FAB-MS (positive) m/z: 170 $(M+H)^+$. *Anal.* Calcd for $C_9H_{15}NO_2 \cdot 0.15H_2O$: C, 62.88; H, 8.97; N, 8.15. Found: C, 62.85; H, 9.07; N, 7.87.
11) Other reaction conditions (including post-treatments of the reaction mixture) with the compound (**10**) provide a complex mixture including a few unknown unstable compounds, and our attempts to isolate the target 7-membered heterocycle (**11**) under a few different reaction conditions were unsuccessful. However, the observations of the formation of a product showed an IR absorption band at 1686 cm^{-1} and an ion peak of 258 in negative FAB-MS, though the product is still as a labile mixture, are strongly indicating the formation of the target 7-membered compound (**11**).
12) Both types of noncompetitive ring closures by 6-Exo-Trig and 7-Exo-Trig process are classified as allowed ring closure reactions in Baldwin's report.[9]