Acyliminium Cyclization of Chiral 5-(4-Alkenyl)-5-hydroxy-2-pyrrolidinone Derivatives

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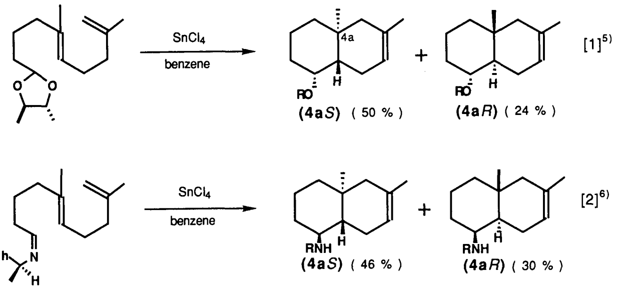
Synopsis. (3*R*,4*R*)-5-(4-Alkenyl)-3,4-bis(benzyloxy)-5-hydroxy-1-methyl-2-pyrrolidinones were cyclized with formic acid to give chiral carbocycles. The 6-membered carbocycle was predominantly formed from (*E*)-4-alkenyl, while the 5-membered carbocycle was formed from the (*Z*)-4-alkenyl side chain. One benzyl group was lost during the reaction, resulting in the formation of an ether bridge.

Acyliminium ions have been shown to exhibit high-selectivity in cyclization to an olefinic double bond;[1] the reaction has also been very effective to construct chiral organic molecules by starting from chiral acyliminiums.[2,3] Many natural products have been synthesized by this type of cyclization.[4] Most have been concentrated to nitrogen-containing targets.

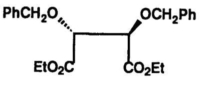
Terpenes are derived *in vivo* from cyclization of the acyclic polyene precursors, while several procedures to induce chiral cyclization *in vitro* have been developed. Examples concerning chiral acetal[5] and imine[6] are shown in Scheme 1. Although the cyclization yield was good, the chiral selectivity {e.g., [(**4a***S*)-(**4a***R*)]/[(**4a***S*)+(**4a***R*)]} was not very high in both cases. It is, thus, of interest to determine the chiral selectivity in constructing a carbocycle by acyliminium cyclization.



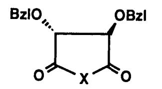
Scheme 1.

Several approaches have been reported concerning the cyclization of 5-(4-alkenyl)-5-alkoxy-2-pyrrolidinones[7] or 6-(4-alkenyl)-6-alkoxy-2-piperidinones.[8] Spirocyclic 6- and/or 5-membered carbocyclic products have been obtained in both cases. We wish to report here on our preliminary results concerning the formation of chiral carbocycles.

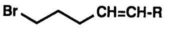
A chiral (3*R*,4*R*)-3,4-bis(benzyloxy)-1-methyl-2,5-pyrrolidinedione (**3**) was prepared from diethyl (2*R*,3*R*)-2,3-bis(benzyloxy) succinate (**1**)[9] via an acid anhydride **2** by similar procedures to those previously reported.[3,10] The imide **3** was treated with a Grignard reagent derived from bromide **4**, **5**, or **6** to give a diastereomeric mixture of **7a**/**7b**, **8a**/**8b**, or **9a**/**9b** in 78, 70, or 63% yield, respectively.



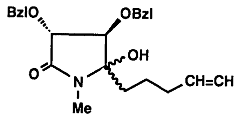
(1)



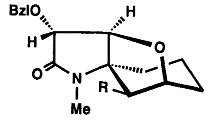
(2) X = O
(3) X = NMe



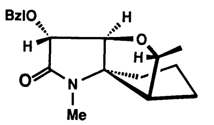
(4) R = Et, (*E*)
(5) R = Me, (*E*)
(6) R = Me, (*Z*)



(7) R = Et, (*E*)
(8) R = Me, (*E*)
(9) R = Me, (*Z*)



(10) R = Et
(11) R = Me



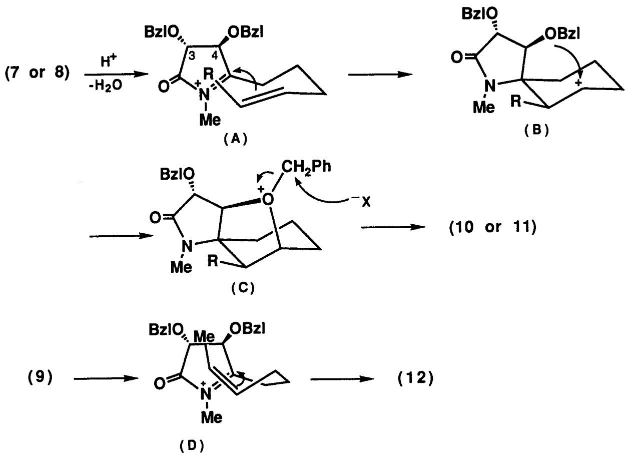
(12)

When **7a**/**7b** was subjected to acidic conditions (formic acid, room temperature for 24 h), spirocyclic cyclization products were obtained in 72% yield. The ^{1}H and ^{13}C NMR spectra of the mixture revealed that two isomeric products were present and that the major isomer was produced in yields over 90%. The structure of the major isomer was characterized as being **10**. The ^{1}H NMR spectrum of **10** shows that one benzyl group was lost during the reaction and that the partial structure of CH_3-CH_2-CH_A-$CH_B(O)$-CH_2- was present, though no coupling between H_A and H_B was observed. The latter evidence strongly suggests that those two protons are positioned at the bridge-head(C_5) and the bridge carbons(C_8) on the 6-oxabicyclo[3.2.1]octane framework. The stereochemistry was elucidated by the phase-sensitive NOESY spectrum (see Experimental). Though the structure of the minor isomer had not been clarified, it may be a 5-membered carbocycle (see vide infra).

In order to clarify the influence of the geometry of the double bond in the side chain, both **8a**/**8b** and **9a**/**9b** were subjected to similar conditions. In the case of (*E*)-olefin **8a**/**8b**, the product was again the 6-membered carbocycle **11**; for (*Z*)-olefin **9a**/**9b**, the 5-membered carbocycle **12** was produced exclusively. In every case, one benzyl group was lost during the reaction.

It is interest that the chiral selectivity is controlled to 100% and that the regiochemistry of the double bond on the side chain is almost completely related to the ring size of the formed carbocycle.

The formation of both carbocycles can be rationalized as follows (Scheme 2). In simple case when none of the substituents are present on the pyrrolidinone ring, the chair transition state has been shown to predominate over the boat type.[7] In the present case, the steric



Scheme 2.

repulsion between the substituent on (*E*)-olefin and the benzyloxyl group at C_3 on the pyrrolidine ring requires that the transition state is as shown in (**A**), and that the cationic center produced as cyclization proceeds is attacked by the benzyloxyl group at C_4 (**B**); the final nucleophilic removal of the benzyl group (**C**) gives the 6-membered carbocycle **10** or **11**. If (*Z*)-olefin is used a severe 1,3-steric repulsion between the *N*-methyl and the methyl group on the double bond arising in the chair form requires the transition state to be favored in the boat, as shown in (**D**).

The intramolecular participation of the benzyloxyl group was inevitable in the present cases, as was proved by the fact that the cyclization of **8a**/**8b** proceeded with either $BF_3\cdot(C_2H_5)_2O$ or DCC to afford the same spiro compound **11**.

Experimental

The melting points are uncorrected. IR spectra were taken on a JASCO IR Report-100 spectrophotometer. NMR spectra were measured in C_6D_6 except when otherwise stated, either on a JEOL FX90Q (90 MHz) or on a Brucker AM500 (500 MHz) spectrometer; the chemical shifts were recorded relative to the TMS as an internal standard. Column chromatographies were performed using a Merck Silica gel 60, while Flash chromatographies using a Wakogel C-300 with the stated solvent. Micro analyses were obtained at the Analytical Center, University of Tsukuba.

Diethyl (2*R*,3*R*)-2,3-Bis(benzyloxy)succinate (1).[9] **1** was conveniently prepared by treating diethyl (2*R*,3*R*)-2,3-dihydroxysuccinate with NaH (2 molar amounts) and benzyl bromide (4 molar amounts) in THF at room temperature for 30 min in 70% yield.

1: Oil; ^{1}H NMR ($CDCl_3$) δ=1.20 (t, 6H, *J*=7 Hz), 4.13 (br.q 4H, *J*=7 Hz), 4.38 (s, 2H), 4.46 and 4.88 (AB q, 4H, *J*=12.6 Hz), and 7.27 (s, 10H).

(3*R*,4*R*)-3,4-Bis(benzyloxy)-3,4-dihydro-2,5-furandione (2). According to the previously reported procedures,[3] acid anhydride **2** was prepared from **1**. Mp 95—96.5 °C (from benzene-hexane); ^{1}H NMR ($CDCl_3$) δ=4.61 (s, 2H), 4.73 and 4.93 (AB q, 4H, *J*=10.8 Hz), and 7.35 (s, 10H).

(3*R*,4*R*)-3,4-Bis(benzyloxy)-1-methyl-2,5-pyrrolidinedione (3). To a solution of 1.01 g (3.24 mmol) of **2** in 50 ml of dry ether was passed methylamine gas to give white precipitates. The whole was acidified with 1.5 M (1 M=1 mol dm^{-3}) hydrochloric acid and solids remained were collected and washed with cold water. The filtrate was extracted with dichloromethane to obtain an additional crop. The combined weight was 1.13 g (100%).

The solids were refluxed in 5 ml of acetyl chloride overnight. The mixture was diluted with toluene and evaporated (twice) to give a crude oil. The oil was purified by column chromatography (AcOEt) to give a pure imide **3** (952 mg, 90%).

3: Oil; ^{1}H NMR ($CDCl_3$) δ=2.99 (s, 3H), 4.36 (s, 2H), 4.75 and 4.97 (AB q, 4H, *J*=11.7 Hz), and 7.34 (s, 10H). $[\alpha]_D$=+177° (acetone, *c* 0.43). Found: C, 69.98; H, 5.90; N, 4.24%. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31%.

(3*R*,4*R*)-3,4-Bis(benzyloxy)-5-[(*E*)-4-heptenyl]-5-hydroxy-1-methyl-2-pyrrolidinone (7). To 26.8 mg (1.1 mmol) of magnesium in 0.3 ml of dry ether was added 9 µl of 1,2-dibromoethane, followed by 194.5 mg (1.1 mmol) of (*E*)-7-bromo-3-heptene (**4**) in 2 ml of ether. The mixture was stirred at room temperature for 3 h under an argon atmosphere. To the mixture was added 71.7 mg (0.44 mmol) of the imide **3** in 2 ml of ether; the mixture was stirred for 3 h. After aqueous NH_4Cl had been added, the ether was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated to give a crude oil, which was purified by column chromatography (hexane–AcOEt=3 : 2) to give a mixture of **7a** and **7b** (ca. 2 : 1) (72 mg, 78%).

7a+7b: Oil; ^{1}H NMR (500 MHz) δ=3.86 (d, 1H, *J*=4.8 Hz), 4.22 (d, 1H, *J*=4.8 Hz), 4.38 (d, 1H, *J*=11.8 Hz), 4.47 (d, 1H, *J*=11.8 Hz), 4.87 (d, 1H, *J*=11.5 Hz), and 5.31 (d, 1H, *J*=11.5 Hz) for **7a**; 4.07 (d, 1H, *J*=6.5 Hz), 4.19 (d, 1H, *J*=6.5 Hz), 4.59 (d, 1H, *J*=12.0 Hz), 4.64 (d, 1H, *J*=12.0 Hz), 4.80 (d, 1H, *J*=11.9 Hz), and 5.24 (d, 1H, *J*=11.9 Hz) for **7b**. Found: C, 73.53; H, 7.62; N, 3.25%. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31%.

(3*R*,4*R*)-3,4-Bis(benzyloxy)-5-[(*E*)-4-hexenyl]-5-hydroxy-1-methyl-2-pyrrolidinone (8). According to a similar procedure as that for **7**, a mixture of **8a** and **8b** (ca. 2.5 : 1) was prepared in 70% yield from the imide **3** and (*E*)-6-bromo-2-hexene (**5**). The products were purified by flash chromatography (hexane : AcOEt=6 : 4).

8a+8b: Oil; ^{1}H NMR (500 MHz) δ=3.86 (d, 1H, *J*=4.8 Hz), 4.22 (d, 1H, *J*=4.8 Hz), 4.38 (d, 1H, *J*=11.6 Hz), 4.47 (d, 1H, *J*=11.6 Hz), 4.88 (d, 1H, *J*=11.7 Hz), and 5.33 (d, 1H, *J*=11.7 Hz) for **8a**; 4.02 (d, 1H, *J*=6.3 Hz), 4.18 (d, 1H, *J*=6.3 Hz), 4.59 (d, 1H, *J*=11.9 Hz), 4.62 (d, 1H, *J*=11.9 Hz), and 4.82 (d, 1H, *J*=11.7 Hz) for **8b**.

(3*R*,4*R*)-3,4-Bis(benzyloxy)-5-[(*Z*)-4-hexenyl]-5-hydroxy-1-methyl-2-pyrrolidinone (9). According to a similar procedure as that for **7**, a mixture of **9a** and **9b** (ca. 4 : 1) was prepared in 63% yield from the imide **3** and (*Z*)-6-bromo-2-hexene (**6**). The products were purified by flash chromatography (hexane : AcOEt=4 : 1).

9a+9b: Oil; ^{1}H NMR (500 MHz) δ=4.19 (s, 2H), 4.58 (d, 1H, *J*=1.20 Hz), 4.67 (d, 1H, *J*=12.0 Hz), 4.79 (d, 1H, *J*=11.9 Hz), and 5.20 (d, 1H, *J*=11.9 Hz) for **9a**; 3.86 (d, 1H, *J*=4.7 Hz), 4.24 (d, 1H, *J*=4.7 Hz), 4.41 (d, 1H, *J*=11.8 Hz), 4.48 (d, 1H, *J*=11.8 Hz), 4.86 (d, 1H, *J*=11.6 Hz), and 5.29 (d, 1H, *J*=11.6 Hz) for **9b**.

Acid Cyclization[1] of 7. A solution of 49.7 mg of **7** in 5 ml of formic acid was stirred at room temperature for 24 h. After the addition of water, the products were extracted with dichloromethane. Column chromatography (hexane–AcOEt =2 : 1) gave a mixture of a spiro compound **10** and an unidentified isomer (29.3 mg, 72%).

10: Oil; ^{1}H NMR (500 MHz) δ=0.60 (t, 3H, *J*=7.2 Hz), 0.79—0.91 (m, 2H), 0.86 (m, 1H), 0.94 (dd, 1H, *J*=11.8 and 6.7 Hz), 0.96 (dd, 1H, *J*=10.5 and 3.4 Hz), 1.26 (td, 1H, *J*=11.8 and 6.1 Hz), 1.33 (m, 1H), 1.57 (m, 1H), 1.67 (ddd, 1H, *J*=13.6, 6.7, and 4.1 Hz), 2.47 (s, 3H), 4.12 (br.d, 1H, *J*=4.1

Hz), 4.32 (d, 1H, J=5.1 Hz), 4.37 (dd, 1H, J=5.1 Hz), 5.03 and 5.26 (AB q, ,2H, J=12.1 Hz), and 7.0—7.6 (m, 5H); ^{13}C NMR (125 MHz) δ=12.7 (q), 19.5 (t), 20.5 (t), 24.4 (t), 26.1 (q), 32.7 (t), 34.4 (t), 54.3 (d), 69.5 (s), 72.7 (t), 82.3 (d), 83.6 (d), 87.6 (d), and 171.3 (s); phase-sensitive NOESY: 0.79—0.91 ($\mathrm{CH_3C}H\mathrm{H}$-) vs. 4.32 ($\mathrm{PhCH_2}$-O-C$H$-). Found: C, 72.55; H, 8.14; N, 4.47%. Calcd for $\mathrm{C_{19}H_{25}NO_3}$: C, 72.35; H, 7.99; N, 4.44%.

Acid Cyclization[1] **of 8.** A) According to a similar procedure as that for **7**, a solution of 71 mg of **8** in 2 ml of formic acid was stirred at room temperature for 20 h. Flash chromatography (hexane : AcOEt=2 : 3) gave a spiro compound **11** (45 mg, 86%).

B) To a solution of 9.3 mg (0.023 mmol) of **8** in 2 ml of ether, 7 μl (0.024 mmol) of $\mathrm{BF_3\cdot(C_2H_5)_2O}$ was added; the mixture was stirred at room temperature for 16 h under an argon atmosphere. After the addition of saturated aqueous $\mathrm{NH_4Cl}$, the ether extract was evaporated and flash chromatographed (hexane : AcOEt=35 : 65) to afford 5.6 mg (81%) of **11**.

C) To a solution of 4.4 mg (0.011 mmol) of **8** in 0.2 ml of $\mathrm{CH_2Cl_2}$, 3.6 mg (0.017 mmol) of DCC was added; the mixture was stirred under argon for 19 h at room temperature. The TLC analysis clarified the formation of **11**.

11: Oil; ^{1}H NMR (500 MHz) δ=0.51 (d, 3H, J=7.0 Hz), 0.87 (ddd, 1H, J=13.0, 12.0, and 7.2 Hz), 0.93 (dd, 1H, J=12.0 and 6.5 Hz), 1.13 (q, 1H, J=7.0 Hz), 1.22 (dt, 1H, J=5.9 and 12.0 Hz), 1.30 (m, 1H), 1.54 (m, 1H), 1.61 (ddd, 1H, J=13.0, 7.0, and 3.9 Hz), 2.45 (s, 3H), 3.89 (br.d, 1H, J=3.9 Hz), 4.36 (s, 2H), 5.01 and 5.26 (AB q, 2H, J=12.0 Hz), and 7.1—7.6 (m, 5H); ^{13}C NMR (125 MHz), δ=13.6 (q), 19.5 (t), 26.0 (q), 32.5 (t), 34.3 (t), 46.3 (d), 69.7 (s), 72.8 (t), 82.4 (d), 86.6 (d), 86.7 (d), and 171.3 (s); phase-sensitive NOESY ($\mathrm{CDCl_3}$): 0.83 ($\mathrm{C}H_3$-CH-) vs. 4.24 ($\mathrm{PhCH_2}$-O-CH-); Found: C, 71.92; H, 7.72; N, 4.72%. Calcd for $\mathrm{C_{18}H_{23}NO_3}$: C, 71.73; H, 7.69; N, 4.65%.

Acid Cyclization[1] **of 9.** According to a similar procedure as that for **7**, a solution of 28.8 mg of **9** in 2.8 ml of formic acid was stirred at room temperature for 24 h. Column chromatography (hexane–AcOEt=1 : 1) gave a spiro compound **12** (21.4 mg, ca. 100%).

12: Oil; ^{1}H NMR (500 MHz) δ=0.99 (t, 3H, J=6.3 Hz), 1.10—1.19 (m, 1H), 1.19—1.25 (m, 1H), 1.26—1.34 (m, 1H), 1.35—1.41 (m, 2H), 1.48—1.55 (m, 1H), 1.61 (dt, 1H, J=8.5 and 5.3 Hz), 2.48 (s, 3H), 3.53 (dq, 1H, J=6.3 and 5.1 Hz), 4.13 (d, 1H, J=2.1 Hz), 4.17 (d, 1H, J=2.1 Hz), 4.95 and 5.20 (AB q, 2H, J=12.0 Hz), and 7.1—7.5 (m, 5H); ^{13}C NMR (125 MHz) δ=16.4 (q), 25.5 (t), 25.8 (t), 25.9 (q), 34.5 (t), 49.8 (d), 72.8 (t), 76.2 (d), 80.6 (s), 80.8 (d), 89.0 (d), and 171.0 (s); phase-sensitive NOESY 3.53(-O-CH-$\mathrm{CH_3}$) vs. 4.13 ($\mathrm{PhCH_2}$-O-CH-). Found: C, 71.56; H, 7.48; N, 4.65%. Calcd for $\mathrm{C_{18}H_{23}NO_3}$: C, 71.73; H, 7.69; N, 4.65%.

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