Acyliminium Cyclization of Several Chiral *N*-Alkenylsuccinimide Derivatives

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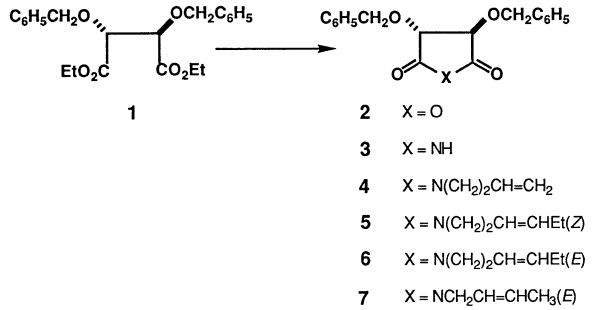
Synopsis. The acyliminium intermediate derived from (3*R*,4*R*)-*N*-(3-butenyl)-3,4-bis(benzyloxy)succinimide cyclized to give (8a*S*)- and (8a*R*)-hexahydro-3(2*H*)-indolidinone derivatives. On the other hand, those derived from *N*-3-hexenyl derivatives afforded (8a*S*)-hexahydro-3(2*H*)-indolidinone(s) exclusively. The geometry of the double bond reflected the stereochemistry of the products.

Biomimetic polyene-cyclization is one of the most challenging methods for synthesizing natural products, especially isoprenoid compounds.[1] However, a few cases have been reported regarding the introduction of a chiral environment during cyclization. Chiral acetal[2] or chiral imine[3] has been used for such purpose, but the chiral selectivity induced during the cyclization step was still not so good. For example, the selectivity of the ring juncture was 2:1 for the chiral acetal and 1.5:1 for the chiral imine.

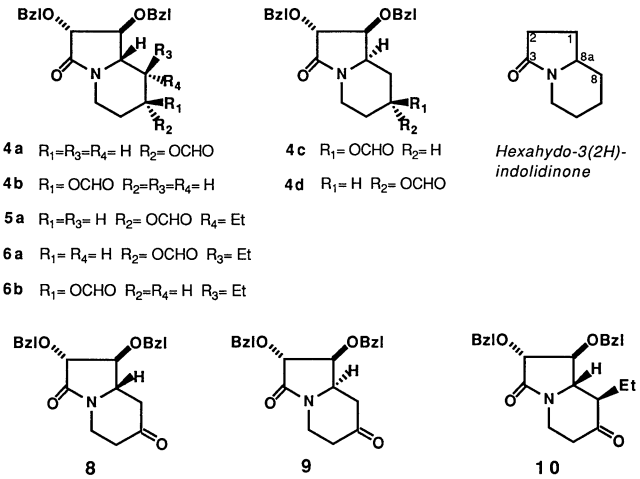
During the last decade, acyliminium intermediates have been successfully used for olefin cyclization and several nitrogen-containing natural products have been synthesized by this method.[4] In 1980, Wijnberg and Speckamp[5] reported on a reaction using chiral succinimide. We have been interested in the use of this chiral moiety to olefin-cyclization process and here wish to report our preliminary results.

(3*R*,4*R*)-3,4-Bis(benzyloxy)succinimide (**3**) was prepared according to similar methods[6,7] for the dimethoxy derivative. Condensation of the olefinic side chain on the N atom was achieved by the Mitsunobu conditions, giving *N*-alkenylsuccinimide derivatives **4**—**7**. After a reduction of one of the carbonyl groups, the resulting hydroxy lactams were treated with formic acid to promote cyclization.[5]

Four isomeric hexahydro-3(2*H*)-indolidinones (**4a**, **4b**, **4c**, and **4d**) were recognized in the relative yield of 4:2:2:1 during the cyclization from (3*R*,4*R*)-*N*-(3-butenyl)-3,4-bis(benzyloxy)succinimide (**4**). The relative yield was deduced by ^{1}H NMR . Since isomers **4a**—**4d** could not be separated from each component by the usual chromatographic technique, they were converted into two isomeric diketones, **8** and **9**, by oxidation of the corresponding alcohols. The structures and absolute stereochemistries of diketones **8** and **9** were easily characterized by ^{1}H NMR and CD spectra. The characteristic features of 90 MHz ^{1}H NMR spectra of the products are as follows: (1) One of the benzylic protons appears as an AB type while the other as a singlet. The chemical shifts of both benzylic protons are coincident in (8a*S*)-(**4a** and **4b**) and (8a*R*)-derivatives (**4c** and **4d**), respectively; (2) C_1–H appears as a triplet of J=ca. 5 Hz in (8a*S*)-series (**4a**, **4b**, and **8**) while as a double doublet of J=7 and 4 Hz in (8a*R*)-series (**4c**, **4d**, and **9**). Furthermore, in the (8a*S*)-series, a 5-bond long range coupling[8] (J=ca. 1.8 Hz) was observed between C_2–H and C_5–βH in every case when the spectra was measured at 500 MHz. The results were in contrast to those reported in an analogous 3,4-dimethoxy derivative (MeO– instead of $C_6H_5CH_2O$– in **4**);[5] only two products, corresponding to **4a** and **4c**, have been mentioned.



Scheme 1.



When ethyl gruop was introduced at the terminus of the double bond (**5** and **6**), the stereochemistry of the products could be perfectly controlled to give only (8a*S*)-indolidinones **5a**, as well as **6a** and **6b**, respectively. The stereochemistry at C_8 reflects the geometry of the starting olefinic double bond. The results can be explained if the cyclization proceeds through the chair-like transition state. The isomeric relationship between **6a** and **6b** was confirmed by converting them into the same diketone, **10**, the absolute configuration of which was also determined by its CD spectrum.

An attempted cyclization of **7**, which has an allylic double bond, did not proceed at all.

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were

measured in $CDCl_3$ either on a JEOL FX90Q (90 MHz) spectrometer or a Bruker AM500 (500 MHz) spectrometer; chemical shifts were recorded relative to the TMS as an internal standard. CD spectra were obtained on a JASCO J-20 spectrometer, while optical rotations were obtained on JASCO DIP-181 spectrometer. Flash-chromatographies were performed using Wakogel C-300. Micro analyses were performed at the Analytical Center, University of Tsukuba. High-resolution CI mass spectra were taken at Nippon Roche Research Center, Kamakura.

(3*R*,4*R*)-3,4-Bis(benzyloxy)succinic Anhydride (2). To an ice-water cooled solution of ethyl (*R*,*R*)-bis(benzyloxy)-succinate (**1**)[9] (11.6 g) in 70 ml of ethanol, 66 ml of 1 M (1 M=1 mol dm^{-3}) NaOH was added; the mixture was stirred at room temperature for 44 h. After the solution had been acidified with 3 M HCl, products were extracted with ether to give 9.11 g of a crude acid. This crude acid, without further purification, was refluxed in 50 ml of acetyl chloride for 15 h. After excess acetyl chloride had been removed under reduced pressure, the residue was dissolved in benzene–toluene and the solution was reevaporated to give crude crystals. Recrystallization from benzene–hexane afforded 5.8 g (62% from the ester) of **2**; hygroscopic, mp 101 °C; ^{1}H NMR δ=4.64 (s, 2H), 4.76 and 4.98 (AB, 4H, J=11.6 Hz), and 7.35 (s, 10H).

Found: C, 65.45; H, 5.51%. Calcd for $C_{18}H_{16}O_5 \cdot H_2O$: C, 65.44; H, 5.40%.

(3*R*,4*R*)-3,4-Bis(benzyloxy)succinimide (3). Ammonia gas was passed into a solution of 5.8 g of **2** in 150 ml of anhydrous ether. Water and hydrochloric acid were added and precipitates were collected by filtration to give 5.6 g (91%) of a succinamic acid, which was then refluxed in 200 ml of acetyl chloride for 49 h. A work-up similar to that mentioned before gave a quantitative yield of **3**. Recrystallization from ether–pentane afforded pure crystals; mp 58 °C; ^{1}H NMR δ=4.42 (s, 2H), 4.74 and 4.96 (AB, 4H, J=11.6 Hz), 7.34 (s, 10H), and 8.52 (br. s, 1H); $[\alpha]_D^{23}$ +143.9° (*c* 0.884, acetone).

Found: N, 4.46%. Calcd for $C_{18}H_{17}NO_4$: N, 4.49%.

Preparation of (3*R*,4*R*)-*N*-Alkenyl-3,4-bis(benzyloxy)succinimides (4—7). To a stirred mixture of the imide **3** (0.49 mmol), a given alcohol (0.54 mmol), and triphenylphosphine (0.54 mmol) in 10 ml of THF under argon, there was added drop by drop a solution of diethyl azodicaboxylate (0.54 mmol) in 10 ml of THF at 0 °C over a period of 1 h. Stirring was continued overnight at room temperature. The solvent was concentrated in vacuo and the residue was portioned between 15 ml of 1 M KOH and 20 ml of ether. The aqueous layer was extracted with two 20 ml portions of ether. The combined organic layers were washed with brine and dried over anhyd Na_2SO_4. After the solvent has been removed in vacuo, the residue was purified by column chromatography on silica gel (CH_2Cl_2) to give corresponding *N*-alkenylsuccinimides (**4—7**).

4: 96% yield; oil; ^{1}H NMR δ=2.34 (br. q, 2H, J=7.7 Hz), 3.58 (t, 2H, J=7.7 Hz), 4.35 (s, 2H), 4.64 and 4.97 (AB, 4H, J=11.6 Hz), 4.90—5.15 (m, 2H), 5.45—5.95 (m, 1H), and 7.33 (s, 10H).

Found: N, 3.75%. Calcd for $C_{22}H_{23}NO_4$; N, 3.83%.

5: 78%; oil; ^{1}H NMR δ=0.93 (t, 3H, J=7.2 Hz), 2.00 (quint, 2H, J=7.2 Hz), 2.35 (q, 2H, J=7.2 Hz), 3.54 (t, 2H, J=7.2 Hz), 4.34 (s, 2H), 4.75 and 4.98 (AB, 4H, J=11.6 Hz), 5.10—5.70 (m, 2H), and 7.35 (s, 10H).

Found: N, 3.56%. Calcd for $C_{24}H_{27}NO_4$: N, 3.56%.

6: 80%; oil; ^{1}H NMR δ=0.92 (t, 3H, J=7.5 Hz), 1.96 (br. quint, 2H), 2.28 (br. q, 2H, J=7.5 Hz), 3.54 (t, 2H, J=7.5 Hz), 4.34 (s, 2H), 4.75 and 4.97 (AB, 4H, J=11.6 Hz), 5.10—5.70 (m, 2H), and 7.35 (s, 10H).

Found: N, 3.40%. Calcd for $C_{24}H_{27}NO_5$: N, 3.56%.

7: 82%; mp 45—46.5 °C (from pentane); ^{1}H NMR δ=1.70 (d, 3H, J=6.0 Hz), 4.07 (d, 2H, J=6.0 Hz), 4.37 (s, 2H), 4.77 and 4.99 (AB, 4H, J=12.0 Hz), 5.3—6.0 (m, 2H), and 7.3 (s, 10H).

Found: N, 3.74%. Calcd for $C_{22}H_{23}NO_4$: N, 3.83%.

Cyclization Products from 4. According to a known method,[7] a solution of 0.13 ml of 12 M HCl in 10 ml of dry ethanol was added drop by drop at 0 °C to a mixture of (3*R*,4*R*)-*N*-(3-butenyl)-3,4-bis(benzyloxy)succinimide (**4**, 114 mg) and $NaBH_4$ (130 mg) over a period of 2 h. After the addition of water, the mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over anhyd Na_2SO_4. The crude hydroxy lactams (94 mg) obtained was stirred without further purification in 10 ml of formic acid for 18 h at room temperature. After concentrating in vacuo, the residue was dissolved in 30 ml of ether and washed with a saturated $NaHCO_3$ and brine. After removing the solvent, the residue was flash-chromatographed with hexane–EtOAc (1:1) to give a mixture of **4a**, **4b**, **4c**, and **4d** (66 mg, 53% yield from **4**): ^{1}H NMR δ=4.50 (br. s, 2H×1/3), 4.55 (br. s, 2H×2/3), 4.76 and 5.00 (AB, 2H×2/3, J=11.6 Hz), and 4.79 and 5.09 (AB, 2H×1/3, J=11.6 Hz), 7.98 (s, 1H×2/3), and 8.04 (s, 1H×1/3). The mixture (7 mg) could be separated by PTLC (hexane–EtOAc=1:1, 5 times) to give two sets of pairs—3.5 mg of (**4a**+**4c**; **4a**/**4c**=2:1): ^{1}H NMR δ=7.98 (s, 1H) and 1.9 mg of (**4b**+**4d**; **4b**/**4d**=2:1): ^{1}H NMR δ=8.04 (s, 1H).

Conversion of the Mixture (4a+4b+4c+4d) into Diketones 8 and 9. The mixture (**4a**+**4b**+**4c**+**4d**, 39 mg) in 5 ml of ethanol was stirred with 0.2 ml of 1 M KOH for 4 h at room temperature and the products were taken in ether to give 36 mg of a mixture of four alcohols. The alcohols (15 mg) were separated by PTLC (hexane–EtOAc=1:3, 6 times) to give two sets of pairs—10 mg of fraction A (two alcohols derived from **4a** and **4c**): ^{1}H NMR δ=5.08 and 4.79 (AB, J=11.7 Hz), 4.55 (s); 4.98 and 4.73 (AB, J=11.7 Hz), 4.50 (s) and 4 mg of fraction B (two alcohols derived from **4b** and **4d**): ^{1}H NMR δ=5.12 and 4.82 (AB, J=11.7 Hz), 4.55 (s); 5.01 and 4.77 (AB, J=11.7 Hz), 4.50 (s). Fraction A (10 mg) in 3 ml of dry CH_2Cl_2 was treated with pyridinium chlorochromate (9 mg) for 5 h at room temperature. Column chromatography with ether gave 7 mg of a mixture of diketones **8** and **9**. From fraction B (4 mg), a similar mixture of **8** and **9** (3 mg) was obtained. The major diketone **8** and the minor one **9** could be separated by PTLC (alumina, CH_2Cl_2–EtOAc=30:1, 5 times).

8: oil; ^{1}H NMR (500 MHz) δ=2.28 (dd, 1H, J=14.3 and 11.7 Hz), 2.37—2.43 (m, 2H), 2.65 (dd, 1H, J=14.4 and 4.1 Hz), 3.01 (ddd, 1H, J=12.6, 10.0, and 5.9 Hz), 3.60 (ddd, 1H, J=11.6, 4.8, and 4.1 Hz), 3.84 (t, 1H, J=4.8 Hz), 4.20 (br. d, 1H, J=4.8 Hz), 4.39 (ddd, 1H, J=13.2, 6.5, and 3.6 Hz), 4.49 and 4.55 (AB, 2H, J=11.8 Hz), 4.80 and 5.08 (AB, 2H, J=11.6 Hz), and 7.22—7.42 (m, 10H); CD (*c* 0.024, EtOH, 23 °C) $\Delta\varepsilon$(296 nm) −1.58.

Found: *m/z* 366.171. Calcd for $C_{22}H_{24}NO_4$: M+H, 366.170.

9: oil; ^{1}H NMR (500 MHz) δ=2.35—2.45 (m, 3H), 2.56 (dd, 1H, J=14.6 and 12.1 Hz), 2.96 (ddd, 1H, J=13.4, 11.0, and 5.4 Hz), 3.95 (ddd, 1H, J=11.8, 6.5, and 4.1 Hz), 4.10 (dd, 1H, J=6.6 and 4.2 Hz), 4.13 (d, 1H, J=4.2 Hz), 4.40 (ddd, 1H, J=13.5, 6.8, and 2.9 Hz), 4.44 and 4.52 (AB, 2H, J=11.8 Hz), 4.76 and 4.98 (AB, 2H, J=11.8 Hz), and 7.20—7.38 (m, 10H); CD (*c* 0.024, EtOH, 23 °C) $\Delta\varepsilon$(296 nm) +1.57.

Found: *m/z* 365.162. Calcd for $C_{22}H_{23}NO_4$: M, 365.162.

Cyclization products from Other *N*-Alkenylsuccinimides 5—7. According to conditions similar to the case of **4**, products were isolated and purified by column chromatography.

5a; 62% yield from **5**; oil; ^{1}H NMR (500 MHz) δ=0.82 (t, 3H, J=7.4 Hz), 1.22 (d, quint, 1H, J=14.5 and 7.4 Hz), 1.43 (ddq, 1H, J=14.5, 2.9, and 7.4 Hz), 1.64 (dt, 1H, J=12.5 and 5.6 Hz), 1.74 (dm, 1H, J=12.5 Hz), 1.99 (m, 1H, $w_{1/2}$=13 Hz), 2.70 (tdd, 1H, J=11.5, 5.4, and 1.5 Hz), 3.42 (dd, 1H, J=5.3 and 3.5 Hz), 3.98 (t, 1H, J=5.3 Hz), 4.08—4.14 (ddd, 1H, J=11.5, 5.9, and 1.5 Hz), 4.12 (dd, 1H, J=5.3 and 1.5 Hz), 4.43 and 4.53 (AB, 2H, J=11.8 Hz), 4.81 and 5.09 (AB, 2H, J=11.8 Hz), 4.98 (dt, 1H, J=11.8 and 4.1 Hz), 7.22—7.38 (m, 10H), and 8.01 (s, 1H).

Found: m/z 424.213. Calcd for $C_{25}H_{30}NO_5$: M+H, 424.212.

6a: 46% from **6**; oil; ^{1}H NMR (500 MHz) δ=0.88 (t, 3H, J=7.2 Hz), 1.48—1.60 (m, 4H), 2.09 (dm, 1H, J=13.0 Hz), 2.74 (tdd, 1H, J=12.8, 3.6, and 1.4 Hz), 3.26 (dd, 1H, J=10.4 and 5.4 Hz), 3.89 (t, 1H, J=5.4 Hz), 4.22 (dd, 1H, J=5.4 and 1.4 Hz), 4.24 (ddd, 1H, J=12.8, 5.4, and 3.6 Hz), 4.48 and 4.56 (AB, 2H, J=11.7 Hz), 4.94 (dt, 1H, J=10.3 and 5.2 Hz), 4.85 and 5.17 (AB, 2H, J=11.7 Hz), 7.22—7.40 (m, 10H), and 8.05 (s, 1H).

Found: m/z 424.212. Calcd for $C_{25}H_{30}NO_5$: M+H, 424.212.

6b: 14% from **6**; oil; ^{1}H NMR (500 MHz) δ=0.87 (t, 3H, J=6.3 Hz), 1.25—1.62 (m, 4H), 2.01 (ddd, 1H, J=14.0, 4.1, and 2.9 Hz), 2.88 (tdd, 1H, J=13.5, 5.4, and 1.4 Hz), 3.35 (dd, 1H, J=10.5 and 5.4 Hz), 3.83 (t, 1H, J=5.4 Hz), 4.09 (m, 1H, J=13.5and 5.4 Hz), 4.22 (dd, 1H, J=5.4 and 1.4 Hz), 4.48 and 4.56 (AB, 2H, J=11.7 Hz), 4.85 and 5.18 (AB, 2H, J=11.7 Hz), 5.42 (br. q, 1H, $w_{1/2}$=10 Hz), 7.23—7.40 (m, 10H), and 8.11 (s, 1H).

Found: m/z 424.213. Calcd for $C_{25}H_{30}NO_5$: M+H, 424.212.

Conversion of 6a or 6b into 10. According to the similar method to that mentioned above, **6a** or **6b** was converted into the same diketone, **10**.

10: oil; ^{1}H NMR δ=0.89 (t, 3H, J=7.3 Hz), 1.40—1.90 (m, 2H), 2.10—2.60 (m, 3H), 2.80—3.20 (m, 1H), 3.37 (dd, 1H, J=11.5 and 4.1 Hz), 3.94 (t, 1H, J=4.1 Hz), 4.22 (br. d, 1H, J=4.1 Hz), 4.30—4.60 (m, 1H), 4.53 (s, 2H), 4.87 and 5.18 (AB, 2H, J=11.7 Hz), and 7.10—7.60 (m, 10H); CD (c 0.328, EtOH, 23 °C) $\Delta\varepsilon$ (296 nm) −1.07.

Found: m/z 394.203. Calcd for $C_{24}H_{28}NO_4$: M+H, 394.202.

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