6. C. Moller, and M. S. Plesset, *Phys. Rev.*, **46**, 618 (1934).
7. J. S. Binkley, M. Frisch, D. J. DeFrees, K. Raghavachari, R. A. Whiteside, H. B. Schlegel, G. Flueter, and J. A. Pople, Carnegie-Mellon Chem Pub Unit, Pittsburgh, PA, 1983.
8. (a) P. C. Hariharan, and J. A. Pople, *Theor. Chim. Acta*, **28**, 213 (1973); (b) M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees, and J. A. Pople, *J. Chem. Phys.*, **77**, 3654 (1982).
9. P. Pulay, *Mol. Phys.*, **17**, 197 (1969).
10. R. Fletcher, and M. J. D. Powell, *Comput. J.*, **6**, 163 (1963).
11. R. S. Mulliken, *J. Chem. Phys.*, **23**, 1833, 1841, 2338, 2343 (1963).
12. M. M. Szczesniak, and H. Ratajczak, *Chem. Phys. Lett.*, 44, 465 (1976).

Synthesis of Perhydroisoquinoline Ring Systems by *N*-Acyliminium Cyclization*

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Received December 28, 1987

The stereochemistry of *N*-acyliminium cyclizations to form decahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones was studied. Particular attention was paid to the stereocontrol by an acetoxy group present on pyrrolidone ring. Two of the three new chiral centers were formed stereospecifically, and the third was controlled by elimination-hydrogenation seqeunce.

Introduction

As part of a chemical program related to the synthesis of new pharmaceuticals, we became interested in the preparation of fused indolizidine ring systems. *N*-Acyliminium ion initiated olefin cyclizations have been recognized as a potent tool in the synthesis of nitrogen heterocycles mainly due to the effort of Speckamp group.[1] Although a number of stereochemical features of these reactions have been reported, the effect of asymmetric centers on their stereochemical course has received little attention.[2] Few earlier examples are shown in Figure 1. Speckamp has shown that the stereochemistry of cyclizations of *N*-acyliminium ion derived from tartarimide could be controlled.[3] Hart[4] and Chamberlain[5] have shown that the stereochemistry of cyclizations of *N*-acyliminium ions derived from maliimides were well controlled in their syntheses of pyrrolizidine alkaloids. Also it is known by Hart and Chamberlain that the regiochemistry of $NaBH_4$ reduction of maliimides is highly controllable. Herein are reported some results obtained during the course of studies.

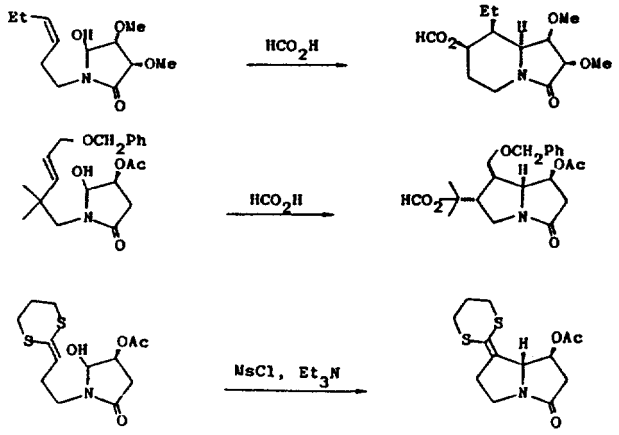
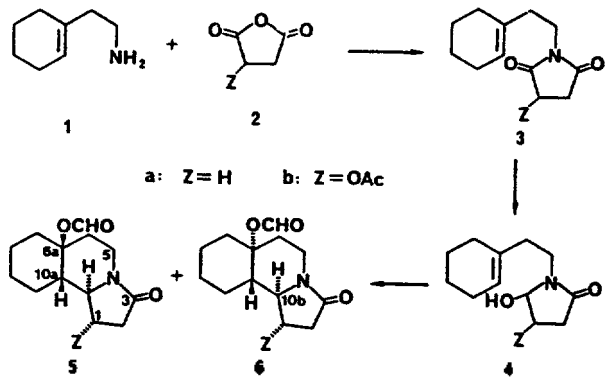


Figure 1. Examples of *N*-Acyliminium Cyclizations

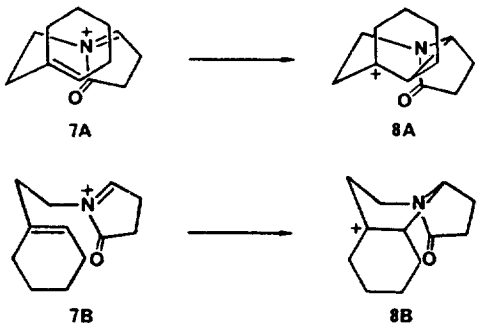
Results and Discussion

The study was begun with *N*-[2-(1-cyclohexenyl)ethyl] succinimide **3a**. The imide **3a** was prepared by reacting 2-(1-cyclohexenyl)ethylamine **1** and succinic anhydride **2a** followed by cyclization of the intermediate amide-acid with acetyl chloride[4] as shown in Scheme 1. This imide could be purified by column chromatography, but satisfactory result was obtained also by using crude product. The imide **3a** was reduced with $NaBH_4$ in methanol to give a hydroxylactam **4a** and it was treated with formic acid to give one major product. Although there were four possible isomers for cyclization product due to three asymmetric centers present in the structure (without considering optical isomers), the NMR spectrum of the major product showed only two formyl protons at δ 8.06 and 8.16. Two minor products were also detected.



Scheme 1

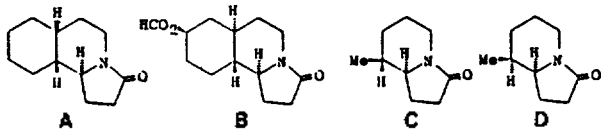
The reaction would proceed via two possible conformers as shown in Scheme 2. The conformer **7B** should proceed through boat form and the amount of the conformer itself



Scheme 2

would be unfavorable because of allylic strain.[6] Thus the stereochemistry of the major product is expected to be **5a** and **6a** which were derived from the conformer **7A.** Unfortunately, the stereochemistry at C_{6a} was epimeric as was evidenced by Speckamp in similar cases.[7,8] Speckamp has found that cyclization of hydroxylactam derived from glutarimide gave similar result.

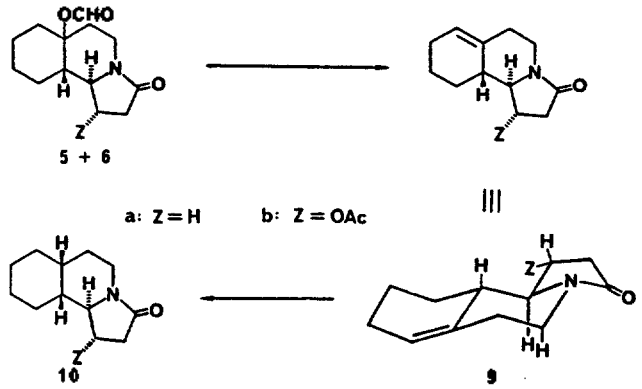
Table 1. Comparison of NMR Chemical Shifts



Compound	NCH_2	NCH	NCH_2
A	4.11	3.04	2.67
B	4.16	3.05	2.68
C	4.12	2.99	2.58
D	4.12	3.68	2.64

The NMR spectra showed subtle difference depending on relative stereochemistry at C_{10a} and C_{10b} in δ 2.6-4.3 region where C_5 and C_{10b} protons appeared.[7-9] Important characteristics of the formates 5a and 6a were (i) the signals of C_5 protons at δ 4.07 and 2.76; and (ii) the H_{10b} signal at δ 3.49 and 3.71 providing vital information on the ring junction and the stereochemistry of the adjacent substituent. The relative stereochemistry of C_{10a} proton was assigned also on the basis of analogy as shown in Table. For those four compounds, the chemical shifts of C_5 protons are very similar. But the chemical shift of C_{10b} proton shows obvious difference according to the relative stereochemistry of C_{10a} and C_{10b} protons. For compounds A, B and C, the two protons are trans and the chemical shifts of the C_{10b} protons are around 3. But for compound D, the two protons are cis and the chemical shift of the C_{10b} proton is much lower.

Thus two of the three new chiral centers were formed stereospecifically, but not the one with the oxygen functionality. The strereochemistry at C_{6a} was successfully controlled by the sequence of reactions as shown in Scheme 3. The formates **5a** and **6a** were hydrolyzed with potassium carbonate in methanol and the hydroxy compound thus obtained was dehydrated with methanesulfonyl chloride and triethylamine to give the unsaturated compound **9a.** Then the unsaturated compound **9a** was hydrogenated with palladium on charcoal to give one single lactam **10a** in over 90% purity as determined by high-field NMR. The structural assignment of formates **5a** and **6a** was also supported by this conversion. The yields were quantitative for these two steps. The notable feature of this sequence of reactions is the regiochemical control of dehydration and the stereochemical control of hydrogenation, although the stereochemical assignment at C_{6a} needs further study. The tentative assignment was based on molecular mechanics calculation on the unsaturated compound **9a.** As shown in Scheme 3, the hydrogenation should proceed from the top face of the most stable conformer thus giving cis junction between two six-membered rings.



Scheme 3

The conclusion which can be drawn here is that three asymmetric centers were formed stereoselectively from an achiral substrate by the series of reactions. Thus if a chiral group is placed at a suitable position where it can induce asymmetry for newly forming chiral centers, three new chiral centers can be constructed stereospecifically from one single chiral group.

An acyliminium ion with an asymmetric center was similarly prepared from *O*-acetyl-*d,l*-malic anhydride **2b**, which in turn was obtained by treatment of *d,l*-malic acid with acetyl chloride.[4] Acetoxy group was chosen as substituent because it showed good chiral induction.[4,5,10] The anhydride **2b** was reacted with amine **1** and acetyl chloride to give imide **3b** as shown in Scheme 1. The imide **3b** was reduced with $NaBH_4$ at -30°C in methanol to give regiochemically pure hydroxylactam **4b** and it was treated with formic acid. The crude product was chromatographed over silica gel and again only one formyl proton was identified by NMR at δ 8.03 and 8.18 from each of the two major products **5b** and **6b**, respectively.[11] Two minor products were also detected. Also the NMR spectra of **5b** and **6b** showed a significant resemblance upon comparision of the NMR spectrum of **5a** and **6a** in chemical shifts of C_5 and C_{10b} protons. Important characteristics of the compounds were (i) the signals of C_5 protons at δ 4.19 and 2.82; and (ii) the H_{10b} signals at δ 3.59 and 3.76. Thus the stereochemistry of cyclization was well controlled also by acetoxy group present on pyrrolidone ring, α to the reaction center. As depicted in Scheme 4, intermediate **11A** is preferred over **11B** because of steric hindrance.

Although the hydrolysis of the formates **5b** and **6b** to obtain hydroxy compounds was not very successful because of concomitant hydrolysis and/or elimination of the acetoxy group, they were obtained either directly from the hydroxylactam by base-catalyzed *N*-acyliminium cyclization[12] or by partial hydrolysis of **5b** and **6b** with ammonia water in

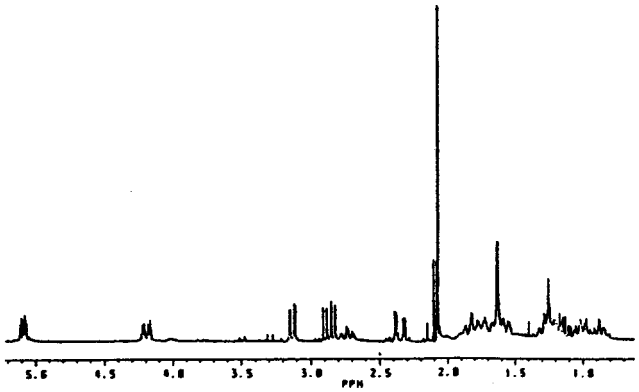
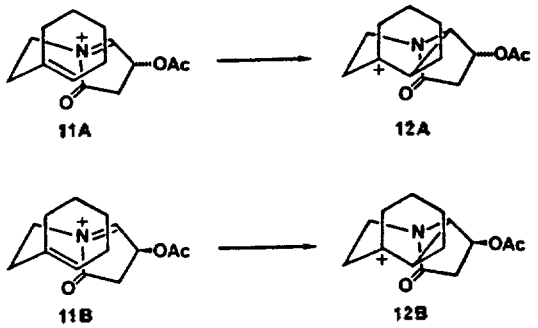


Figure 2. NMR Spectrum of 10b ($CDCl_3$, 300 MHz).



Scheme 4

methanol followed by treatment with methanesulfonyl chloride and triethylamine to give the same unsaturated compound **9b**. The NMR spectrum of the unsaturated compound showed that the chemical shifts of protons on C_5 and C_{10b} did not change much, except the appearance of vinyl proton at δ 5.66. This again confirms the regiospecificity of dehydration. The hydrogenation of the unsaturated compound was accomplished with palladium on charcoal and the lactam **10b** thus obtained was also over 90% pure as determined by high-field NMR (Figure II).

As a conclusion, the stereochemical outcome of *N*-acyliminium cyclizations to form a perhydroisoquinoline ring system, decahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one, via C-C bond formation between C_{10a} and C_{10b} was studied. Particular attention was paid to the asymmetric induction by substituents present on pyrrolidone ring. Two of the three new chiral centers were formed stereospecifically, and the stereochemistry of the other was controlled by elimination-hydrogenation sequence.

At present, a method to determine the stereochemistry of C_{6a} and application of this methodology in the synthesis of alkaloids are pursued in this laboratory.

Experimental

^{1}H NMR spectra were recorded on Varian Associates EM-360A and Bruker AM-300 spectrometers and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: Chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants, interpretation]. Infrared spectra were taken with a Shimadzu IR-435 instrument. Mass spectra were recorded on Shimadzu GCMS-QP 1000 spectrometer at an ionization energy of 70 eV. Samples on which molecular mass were measured exhibited no significant peaks at m/e greater than that of the parent. Analytical thin-layer chromatography was performed with Merck 0.25 mm thick precoated silica gel 60 F-254 plates. Column chromatography was performed over Merck silica gel (70-230 mesh).

N—[2-(1-cyclohexenyl)ethyl]succinimide (**3a**). To a suspension of 3.00 g of succinic anhydride **2a** in 45 m*l* of dichloromethane was added 4.18 m*l* of amine **1** with cooling in an ice-water bath. The resulting clear solution was heated under refulx for 1h followed by addition of 30 m*l* of dichloromethane and 15 m*l* of acetyl chloride. The resulting mixture was heated under reflux and concentrated in vacuo to give 7.05 g of crude imide **3a** as an oily residue. Analytical sample was obtained by column chromatography (silica gel, ethyl acetate: hexane = 1:1): IR(neat) 1700, 1770 cm^{-1}; NMR($CDCl_3$, 60 MHz) δ1.58(m, 4H, CH_2CH_2), 1.97(m, 4H, allylic CH_2), 2.16(t, 2H, J = 10.5 Hz, NCH_2CH_2), 2.63(s, 4H, imide CH_2), 3.55(t, 2H, J = 10.5 Hz, NCH_2), 5.30(s, 1H, = CH); mass spectrum *m/e* (relative intensity) 207(M^+, 7), 108(100).

rel-(6a*S*, 10a*S*, 10b*S*)-6a-Formyloxy-decahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one and *rel*-(6a*R*, 10a*S*, 10b*S*)-6a-Formyloxy-decahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**5a** + **6a**). To 3.62 g of crude **3a** in 135 m*l* of methanol was added 7.00 g of sodium borohydride over a 30-min period with cooling in an ice-water bath. The resulting mixture was diluted with 200 m*l* of water and extracted with five 100-m*l* portions of dichloromethane. The combined organic layer was dried ($NaSO_4$), filtered and concentrated in vacuo to give 2.85 g of crude hydroxylactam **4a** as an oily residue. The residue was dissolved in 50 m*l* of 90% formic acid. The resulting solution was stirred at room temperature for 2 h and concentrated in vacuo to give 3.26 g of an oily residue. The residue was chromatographed over silica gel to give 2.52 g of **5a** + **6a** as an oil: IR(neat) 1700, 1765 cm^{-1}; NMR($CDCl_3$, 300 MHz) δ1.09(dt, 0.5H J = 3.7, 7.2 Hz), 1.21-1.91(m, 10H), 2.23(m, 1H), 2.38(m, 2H), 2.50(d, 0.5H, J = 12.9 Hz), 2.76(q, 2H, J = 11.6 Hz), 3.49(dt, 0.5H, J = 7.7, 11.0 Hz), 3.71(dt, 0.5H, J = 7.2, 11.0 Hz), 4.07(m, 1H, NCH_2), 8.06(s, 0.5H, CHO), 8.16(s, 0.5H, CHO).

rel-(10a*R*, 10b*S*)-1,5,6,7,8,9,10,10b-Octahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**9a**). A mixture of 2.87 g of crude formates **5a** + **6a** and 1.28 g of sodium carbonate in 80 m*l* of methanol was stirred at room temperature for 45 h, and concentrated in vacuo. The residue was suspended in dichloromethane and filtered. The filtrate was concentrated in vacuo to give the hydroxy compound. To 20 mg of the above product in 5 m*l* of dichloromethane was added 0.15 m*l* of triethylamine and 0.15 m*l* of methanesulfonyl chloride at −5 °C and the resulting solution was stirred at room temperature for 1 h. The resulting solution was washed with water, dried ($NaSO_4$), filtered and concentrated in vacuo. The residue was chromatographed over silica gel to give **9a** as an oil: IR(neat) 1685 cm^{-1}; NMR($CDCl_3$, 300 MHz) δ1.87-2.30 (m, 2H), 2.40(m, 2H), 2.60(dt, 1H, J = 4.3, 12.4 Hz, NCH_2), 3.07(dt, 1H, J = 7.0, 9.9 Hz, NCH), 4.11(ddd, 1H, J = 1.8, 5.5, 12.6 Hz, NCH_2), 5.58(m, 1H, = CH); mass spectrum *m/e* (relative intensity) 191(M^+, 100), 176(11), 162(29).

rel-(6a*R*, 10a*R*, 10b*S*)-decahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**10a**). A solution of 20 mg of **9a** in 2 m*l* of ethanol

was hydrogenated in Paar apparatus at 40 psi for 2 h with catalytic amount of 10% palladium on charcoal. The resulting mixture was filtered and concentrated. The residue was chromatographed over silica gel to give **10a** in quantitative yield: IR(neat) 1685 cm^{-1}; NMR($CDCl_3$, 300 MHz) δ 0.76-1.87(m, 12H), 2.17(m, 2H, $COCH_2$), 2.36(m, 2H), 2.67(dt, 1H, J = 3.5, 12.3 Hz, NCH_2), 3.04(dt, 1H, J = 7.4, 9.6 Hz, NCH), 4.11(ddd, 1H, J = 1.8, 4.5, 13.2 Hz, NCH_2); mass spectrum *m/e* (relative intensity) 193(M^+, 66), 178(3.5), 98(100).

N-[2-(1-cyclohexenyl)ethyl]-*O*-acetyl-*d,l*-malimide (**3b**). The imide **3b** was similarly prepared from *O*-acetyl-*d,l*-malic anhydride[4] and amine **1**: IR(neat) 1705, 1745, 1785 cm^{-1}; NMR($CDCl_3$, 60 MHz) δ 1.57(m, 4H, $=CCH_2CH_2$), 1.95(m, 6H, $=CCH_2$), 2.13(s, 3H, $COCH_3$), 2.58(dd, 1H, J = 4.5, 18 Hz, $COCH_2$), 3.13(dd, 1H, J = 8, 18 Hz, $COCH_2$), 3.58(t, 2H, J = 7 Hz, NCH_2), 5.30(m, 1H, = CH), 5.37(dd, 1H, J = 4.5, 8 Hz, AcOCH); mass spectrum *m/e* (relative intensity) 265 (M^+, 10), 158(35), 108(76).

rel-(1*S*, 6a*S*, 10a*S*, 10b*R*)-1-Acetoxy-6a-formyloxy-decahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**5b**) and *rel*-(1*S*, 6a*R*, 10a*S*, 10b*R*)-1-Acetoxy-6a-formyloxy-decahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**6b**). **5b** and **6b** was similarly prepared as for **5a** and **6a**. From the crude product, two isomers were partially separable. **5b**: IR(neat) 1690(broad), 1735 cm^{-1}; NMR($CDCl_3$, 300 MHz) δ 1.17-1.64(m, 8H), 2.08 (s, 3H, $COCH_3$), 2.36(m, 3H), 2.81(m with dd, 3H, J = 8.0, 18.1 Hz, COCH, NCH_2, NCH), 3.76(dd, 1H, J = 2.7, 11.5 Hz, NCH), 4.19(ddd, 1H, J = 1.8, 6.9, 14.1 Hz, NCH_2), 5.10(ddd, 1H, J = 2.9, 3.1, 5.6 Hz, AcOCH), 8.03(s, 1H, CHO). **6b**: IR (neat) 1690(broad), 1735 cm^{-1}; NMR($CDCl_3$, 300 MHz) 1.15-1.94(m, 10H), 2.09(s, 3H), 2.41(ddd, 1H, J = 1.5, 4.3, 18.0 Hz, COCH), 2.82(m with dd, 3H, J = 8.2, 18.0 Hz, COCH, NCH_2, NCH), 3.59(dd, 1H, J = 3.4, 11.0 Hz, NCH), 4.19(m, 1H, NCH_2), 5.07(m, 1H, AcOCH), 8.18(s, 1H, CHO).

rel-(1*S*, 10a*R*, 10b*R*)-1-Acetoxy-1,5,6,7,8,9,10,10b-octahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**9b**). Method A: A solution of 260 mg of **5b** and **6b** in 1 m*l* of ammonia water and 20 m*l* of methanol was stirred for 5 h with cooling in an ice-water bath. When the reaction was partially progressed, the mixture was neutralized with 2*N* hydrochloric acid followed by addition of 20 m*l* of water. The resulting solution was extracted with five 20-m*l* portions of dichloromethane and the combined organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to given an oily residue. The residue was chromatographed over silica gel to give 60 mg of the hydroxy compound. To 20 mg of the hydroxy compound in 10 m*l* of dichloromethane was added 0.17 m*l* of triethylamine and 0.17 m*l* of methanesulfonyl chloride at −10 °C. The resulting mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was chromatographed over silica gel to give quantitative yield of **9b**. Method B: To 480 mg of **4b** in 25 m*l* of dichloromethane was added 1.90 m*l* of methanesulfonyl chloride and 1.06 m*l* of triethylamine with cooling in an ice-water bath. The mixture was stirred for 5 h at room temperature and concentrated in vacuo. The residue was chromatographed over silica gel to give quantitative yield of **9b**: IR(neat) 1690, 1740 cm^{-1}; NMR($CDCl_3$, 300 MHz) δ 0.83-2.19(m 9H), 2.08(s, 3H, $COCH_3$), 2.40(ddd, 1H, J = 1.6, 3.8, 18.1 Hz, COCH), 2.67(ddd, 1H, J = 1.7, 3.6, 12.7 Hz, NCH_2), 2.89(dd, 1H, J = 8.1, 18.1 Hz, COCH), 3.14(dd, 1H, J = 2.9, 10.5 Hz, NCH), 4.21(ddd, 1H, J = 1.7, 4.8, 13.3 Hz, NCH_2), 5.13(ddd, 1H, J = 3.1, 3.7, 8.0 Hz, AcOCH), 5.66(m, 1H, = CH); mass spectrum *m/e* (relative intensity) 249(M^+, 2.4), 189(66), 43(100).

rel-(1*S*, 6a*R*, 10a*R*, 10b*S*)-1-Acetoxy-decahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**10b**). A solution of 20 mg of **9b** in 2 m*l* of ethanol was hydrogenated in Paar apparatus at 50 psi for 30 min with catalytic amount of 10% palladium on charcoal. The resulting mixture was filtered and concentrated. The residue was chromatographed over silica gel to give quantitative yield of **10b**: IR(neat) 1740, 1690 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 0.76-2.13(m, 12H), 2.10(s, 3H, $COCH_3$), 2.41(ddd, 1H, J = 1.6, 6.8, 17.1 Hz, COCH), 2.87(dd, 1H, J = 1.6, 12.1 Hz, NCH_2), 2.92(dd, 1H, J = 8.2, 17.1 Hz, COCH), 4.23(m with dd, 2H, J = 6.0, 9.6 Hz, NCH, NCH_2), 5.05(ddd, 1H, J = 6.0, 6.8, 8.4 Hz, AcOCH); mass spectrum *m/e* (relative intensity) 251(M^+, 1.2), 208(2), 191(100).

References and Notes

Part of this work was presented at the 60th Meeting of the Korean Chemical Society (August, 1987), and at the 194th Meeting of the American Chemical Society (September, 1987).

1. W. N. Speckamp, H. Hiemstra, *Tetrahedron*, **41**, 4367 (1985).
2. (a) D. J. Hart, Y.-M. Tsai, *J. Org. Chem.*, **47**, 4403 (1982); (b) B. E. Maryanoff, D. F. McComsey, B. A. Duhl-Emswiler, *J. Org. Chem.*, **48**, 5062 (1983); (c) D. J. Hart, K.-I. Kanai, *J. Am. Chem. Soc.*, **105**, 1255 (1983).
3. B. P. Wijnberg, W. N. Speckamp, *Tetrahedron Lett.*, **21**, 1987 (1980).
4. D. J. Hart, T.-K. Yang, *J. Org. Chem.*, **50**, 235 (1985).
5. A. R. Chamberlain, J. Y. L. Chung, *J. Org. Chem.*, **50**, 4425 (1985).
6. D. J. Hart, *J. Am. Chem. Soc.*, **102**, 397 (1980).
7. H. E. Schoemaker, J. Dijkink, W. N. Speckamp, *Tetrahedron*, **34**, 163 (1978).
8. J. Dijkink, W. N. Speckamp, *Tetrahedron*, **34**, 173 (1978).
9. J. Dijkink, W. N. Speckamp, *Tetrahedron Lett.*, 935 (1977).
10. J.-K. Choi, D. J. Hart, *Tetrahedron* **41**, 3959 (1985).
11. The structures assigned for **5a/6a** and **5b/6b** can be interchanged.
12. A. R. Chamberlain, J. Y. L. Chung, *J. Am. Chem. Soc.*, **105**, 3653 (1983).