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New enantiomerically pure 1,2-dihydropyridine and its use for construction of optically active 2-azabicyclo[2.2.2]octane

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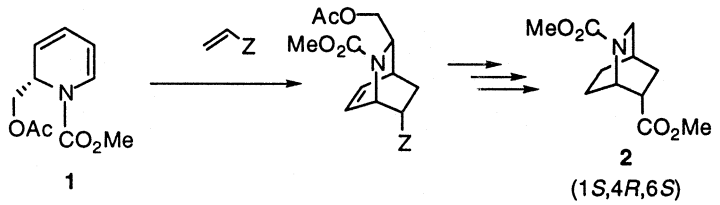
Abstract

An enantiomerically pure 1,2-dihydropyridine **1** was prepared from L-lysine utilizing anodic oxidation as a key step, and was utilized as a chiral diene synthon of the Diels–Alder reaction. Furthermore, a suitable condition for the Diels–Alder reaction between **1** and *N*-acryloyloxazolidinone (**8**) was exploited. That is, the presence of $AlCl_3$ efficiently promoted the Diels–Alder reaction to give a cycloadduct with high stereoselectivity, which was converted to an optically active 2-azabicyclo[2.2.2]octane derivative **2** (96.8% ee).

Keywords: Diels–Alder reactions; nitrogen heterocycles; amino acids and derivatives; asymmetric synthesis.

It is very worthwhile to exploit a new method for the synthesis of optically active 2-azabicyclo[2.2.2]octanes since such azabicyclic compounds are key synthetic intermediates of *iboga* alkaloides.[1] The Diels–Alder (D–A) reaction between chiral 1,2-dihydropyridines and olefins may be the most promising method for this purpose.[2,3] However, there have been few D–A reactions between chiral 1,2-dihydropyridines and olefins exploited so far. This may be due to the limited availability of chiral 1,2-dihydropyridines[2a,b] and dienophiles.[2c] This background prompted us to exploit new chiral 1,2-dihydropyridines usable for the D–A reaction.

In our continuing study on the utilization of easily available α-amino acids in organic synthesis,[4] we report herein a facile preparation of an enantiomerically pure 1,2-dihydropyridine **1**, which is a suitable diene for the synthesis of optically active 2,6-bis(methoxycarbonyl)-2-azabicyclo[2.2.2]octane (**2**), a precursor of muscarinic agonist,[5] with high ee (Eq. (1)).



(1)

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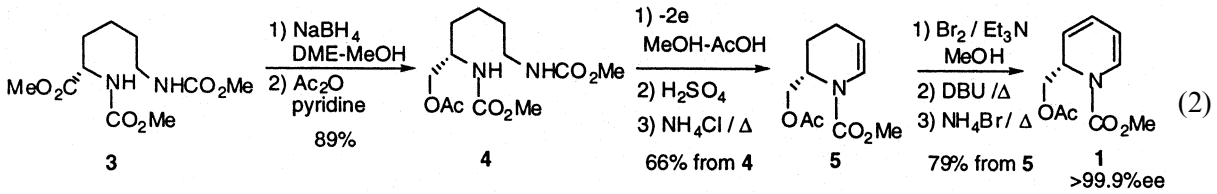
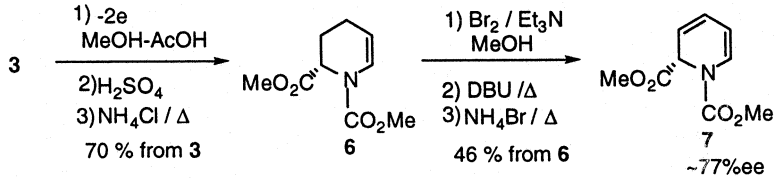
Enantiomerically pure (2*S*)-acetoxymethyl-1-methoxycarbonyl-1,2-dihydropyridine (**1**) could be prepared as follows (Eq. (2)). That is, the reduction of L-lysine derivative **3** with $NaBH_4$ followed by the acetylation yielded diamino acetate **4** in 89%. The electrochemical oxidation of **4** in methanol–AcOH[6] and the subsequent acid-catalyzed cyclization of ε-methoxylated product with a removal of methanol[7] gave 2-acetoxymethyl-1-methoxycarbonyl-1,2,3,4-tetrahydropyridine (**5**).

Then, β-bromo-α-methoxylation of **5**, dehydrobromination with DBU, and finally removal of methanol gave **1**.[4a]



(2)

The ee of thus obtained **1** was determined to be >99.9% by chiral stationary phase-HPLC analysis.[8] The extremely high ee of **1** was in contrast with that of optically active 1,2-bis-(methoxycarbonyl)-1,2-dihydropyridine (**7**), which was prepared according to procedures similar to the formation of **1** from **3** (Eq. (3)).[4a] The ee of **7** was ~77%.



(3)

As we had an enantiomerically pure **1** in hand, we tried the D–A reaction between **1** and *N*-acryloyloxazolidinone (**8**)[9] with an expectation that **1** might give higher ee in the D–A reaction than the previously reported 1,2-dihydropyridines **9**[2a,b] possessing a chiral auxiliary (X*) at the 1-position, since the chiral carbon-2 of **1** was positioned closer than X* of **9** to the reaction center in a transition state of the D–A reaction as shown in Figs. 1 and 2.[10]

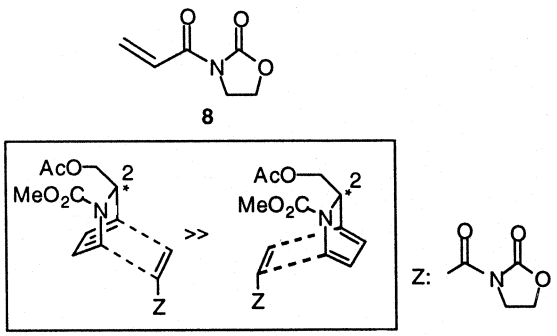


Figure 1. Plausible transition state in the D–A reaction between **1** and **8**

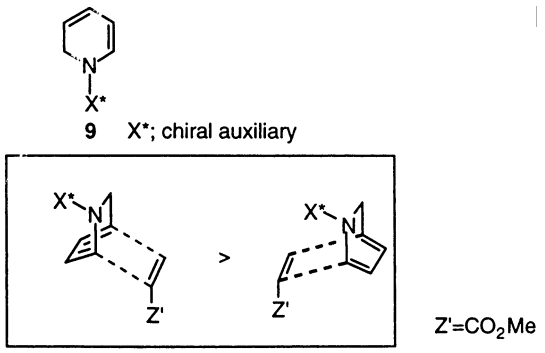
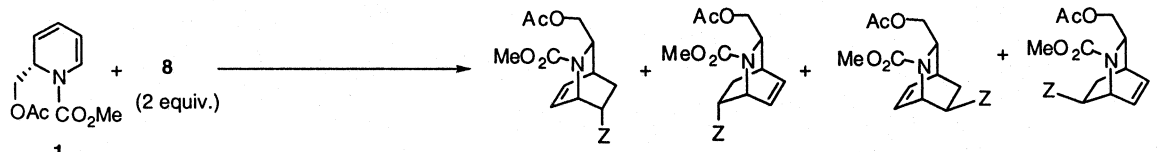


Figure 2. Plausible transition state in the D–A reaction between **9** and methyl acrylate

In fact, we obtained a high ee (96.8% de) as expected, which was much higher than the highest one (84% de)[2b] observed in the D–A reaction using **9**. The D–A reaction was carried out in the following way.

Heating a solution of **1** and **8** in xylene (130°C) for 12 h gave a mixture of D–A adduct (*anti*- and *syn-endo*-**10**, and *anti*- and *syn-exo*-**10**) in 60% yield (Eq. (4)),[11] while the reaction at 25°C resulted in a formation of a trace amount of the adducts (~2%). The *endo*:*exo* ratio of the adduct was found to be around 70:30 by means of ^{1}H NMR spectrum.[12] The *anti*:*syn* ratios of each isomer could not be determined at this stage because of the difficulty of their isolation on HPLC.

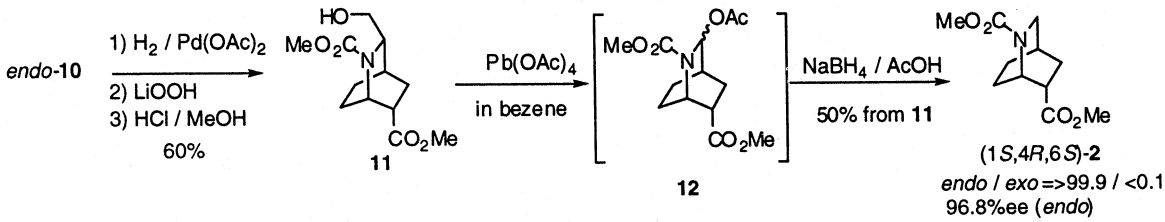
Noticeably, in contrast with the D–A reaction with heating, the D–A reaction carried out at below 25°C selectively gave *endo*-**10** in 77% yield when an equimolar amount of $AlCl_3$ was present,[13] while a catalytic amount of $AlCl_3$ almost failed to cause the D–A reaction.



(4)

in xylene at 130 °C, 12 h: 60%	68	:	5	:	22	:	5
or								
in CH_2Cl_2, $AlCl_3$ (1 equiv.), at 25 °C, 5 h: 77%	98.4	:	1.6	:	0	:	0

In order to make the *anti*:*syn* ratio of *endo*- and *exo*-**10** clear as well as to prepare a key synthetic intermediate for a muscarinic agonist, the cycloadduct (*endo*-**10**) obtained by the D–A reaction using $AlCl_3$ was converted to *endo*-**2** according to the procedures shown in Eq. (5). That is, the hydrogenation of *endo*-**10**, hydrolysis and esterification successively, afforded hydroxy ester **11**. Treatment of **11** with $Pb(OAc)_4$ in benzene followed by reduction with $NaBH_4$ in AcOH without purification of the oxidation product **12** gave *endo*-**2**, of which absolute configuration was determined to be (1*S*,4*R*,6*S*) by comparison with the reported data.[14] The ee of *endo*-**2** was 96.8%.[15]



(5)

Thus, the D–A reaction of **1** with **8** in the presence of $AlCl_3$ was found to proceed with a ratio of *anti-endo*-**10**:*syn-endo*-**10**:*anti-exo*-**10**:*syn-exo*-**10** = 98.4:1.6:0:0.[16] The high *anti*/*syn* selectivity might be explained in terms of the steric repulsion between **8** and 2-acetoxymethyl group of **1**. $AlCl_3$ associating with **8** may amplify the steric repulsion, which could also explain the high *endo*/*exo* selectivity.[17,18]

In summary a new enatiomerically pure 1,2-dihydropyridine **1** has been prepared from L-lysine. This has been used in an $AlCl_3$-promoted D–A reaction to form the 2-azabicyclo[2.2.2]octane **2** with excellent ee. We intend to use compound **1** as the starting material in the synthesis of a pharmaceutically useful compound.

Acknowledgements

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3. A more interesting method may be the Lewis acid-catalyzed asymmetric D–A reaction between achiral 1,2-dihydropyridines and olefins. The method, however, has not been developed at all presumably because of a strong interaction of Lewis acids with D–A products, which makes the catalytic cycle of the Lewis acids ineffective. See Ref. 2c.
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8. (*S*)-**1**: colorless oil: >99.9% ee {DAICEL HIRALCEL OJ (4.6 mmϕ, 25 cm) [*n*-hexane:2-propanol = 25:1 (v/v), 1.0 mL/min, detection at 210 nm, 14.3 min for (*S*)-**1**, 15.8 min for (*R*)-**1**]}; $[\alpha]_D^{25}$ −376 (*c* 0.7, methanol); ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.80 (s, 3H), 3.87–4.17 (m, 2H), 5.00–5.56 (m, 3H), 5.98–6.12 (m, 1H), 6.70 and 6.83 (2d, J = 8.0 and 8.0 Hz, 0.5H and 0.5H); anal. calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.79; H, 6.17; N, 6.60.
9. The D–A reaction between **1** and methyl acrylate in the presence of $AlCl_3$ almost failed to give the cycloadduct.
10. For examples of diastereoselective D–A reactions between racemic 2-alkyl-1,2-dihydropyridines and dienophiles, see: (a) Pavlov, A. V.; Mochalin, V. B. *Zh. Org. Khim*. **1983**, *19*, 234–235. (b) Augelmann, G.; Streith, J.; Fritz, H. *Helv. Chim. Acta* **1985**, *68*, 95–103.

11. Heating of *endo*-**10** at 130°C for 12 h did not cause any isomerization of *endo*-**10** into *exo*-**10**.
12. *endo*-**10**: δ 2.066 (s, 3H, $OCOCH_3$), 4.85–4.90 and 4.98–5.04 (2m, 0.5H and 0.5H, 1-methine H). *exo*-**10**: δ 2.073 (s, 3H, $OCOCH_3$), 4.83 and 4.96 (2d, $J=6.6$ and 6.6 Hz, 0.2H and 0.8H, 1-methine H).
13. Knaus, E. E.; Pasutto, F. M.; Giam, C. S.; Swinyard, E. A. *J. Hetreocycl. Chem.* **1976**, *13*, 481–486.
14. In Ref. 2a it is described that (1*S*,4*R*,6*S*)-**2** showed a dextrorotatory.
15. (1*S*,4*R*,6*S*)-**2**: colorless oil: 96.8% ee {DAICEL CHIRALCEL OJ (4.6 mmϕ, 25 cm×2) [*n*-hexane:ethanol = 100:1 (v/v), 0.5 mL/min, detection at 210 nm, 68 min for (1*S*,4*R*,6*R*)-**2**, 72 min for (1*R*,4*S*,6*S*)-**2**, 97 min for (1*R*,4*S*,6*R*)-**2**, 123 min for (1*S*,4*R*,6*S*)-**2**]}; $[\alpha]_D^{24}$ 81.5 (*c* 0.6, methanol); ^{1}H NMR ($CDCl_3$) δ 1.45–2.21 (m, 7H), 2.86–3.01 (m, 1H), 3.30–3.39 (m, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 4.25–4.31 (m, 0.5H), 4.39–4.45 (m, 0.5H); anal. calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.79; H, 7.47; N, 5.93.
16. The adducts **10** obtained by a thermal version of the D–A reaction of **1** with **8** (Eq. (4)) was converted to **2** in a similar way, and as the result, the ratio of the stereoisomers was found to be *anti-endo*-**10**:*syn-endo*-**10**:*anti-exo*-**10**:*syn-exo*-**10** = 68:5:22:5.
17. $Yb(OTf)_3$ instead of $AlCl_3$ gave a similar result, while $TiCl_4$, $Cu(OTf)_2$, and $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$ did not have any effect on the D–A reaction.
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