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Highly Stereoselective Asymmetric 6π-Azaelectrocyclization Utilizing the Novel 7-Alkyl Substituted *cis*-1-Amino-2-indanols: Formal Synthesis of 20-Epiuleine

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The thermal cyclization of 1-azatrienes to 1,2-dihydropyridines,[1] which is the so-called 6π-azaelectrocyclization, is one of the well-known concerted pericyclic reactions,[2−4] which proceed in a disrotatory mode.[5] Although a number of examples of the 6π-azaelectrocyclization have been reported,[1,6,7] the process required a high temperature and a long reaction time; therefore, the application of this reaction toward natural products synthesis is very limited in the literature. The recent pioneering work of Okamura and co-workers elucidated that the introduction of either an electron-donor or an -acceptor group at the 1-azatriene terminus moderately accelerated the rate of the electrocyclization.[5,8] Quite recently, we independently succeeded in significantly accelerating the aza-electrocyclization, based on the remarkable orbital interaction between the HOMO and LUMO of the 1-azatrienes by the combination of substituent effects, that is the C4-carbonyl and the C6-alkenyl or phenyl substituents.[9−11] Herein, we report the novel highly stereoselective asymmetric 6π-azaelectrocyclization based on the reactions between the (*E*)-3-carbonyl-2,4,6-trienal compounds and the chiral *cis*-1-amino-2-indanol derivatives using a remarkably simple operation under quite mild conditions (Figure 1).

After trials on almost 20 chiral amines which are effective in the imine-based asymmetric reactions,[12] we fortunately found that the reaction of **1**[9] containing a bulky 2,6,6-trimethylcyclohexene moiety with (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol **a**[13] quantitatively produced the pentacyclic piperidine derivative (−)-**1a**, $[\alpha]^{24}_{D}$ −45.4° (*c* 1.1, $CHCl_3$), as a single stereoisomer (Figure 1). The relative stereochemistry was unambiguously determined by the X-ray crystallographic analysis of the corresponding carboxylic acid derived from (−)-**1a**. The reaction may proceed via the isomerization of the dihydropyridine intermediary[14] toward the thermodynamically more stable aminoacetal (−)-**1a**.[15] To the best of our knowledge, this is the first achievement of the highly stereoselective 6π-azaelectrocyclization of the linear 1-azatrienes.[16]

Although we found the *cis*-aminoindanol (−)-**a** as an encouraging amine candidate, the reactions with the more general aldehydes **2** and **3**,[10] which contain linear alkenyl or phenyl substituents, only gave a 3:1 diastereomixture of the corresponding piperidines at the 2-position, as shown in Table 1 (entries 1 and 2). Fortunately, we found that the diastereoselectivity was significantly improved by introducing an alkyl substituent at the 7-position of (−)-**a**.[17] Thus, the highest selectivity was obtained by utilizing the isopropyl-substituted aminoindanol (−)-**d**, and the corresponding piperidine derivatives (−)-**2d** and (−)-**3d** were obtained in the ratio of 10:1 and 24:1 (entries 7 and 8), respectively. Moreover, (−)-**3d** was obtained as an almost single isomer at the lower temperature of 13 °C (entry 9). Thus, the highly stereoselective 6π-azaelectrocyclization was achieved by utilizing the novel 7-alkyl substituted *cis*-aminoindanol derivatives.

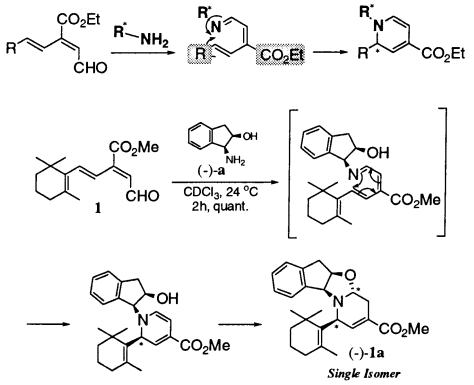
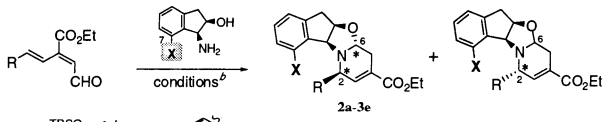


Figure 1.

Table 1. Selectivity of Azaelectrocyclization Using 7-Substituted Aminoindanols[a]



entry	aldehyde	amine	product (major isomer)	temp (°C)	dr (at the 2-position)[c]
1	2	(−)-**a**	**2a**	24	3:1[d]
2	3	(−)-**a**	(−)-**3a**	24	3:1
3	2	(−)-**b**	(−)-**2b**	24	5:1
4	3	(−)-**b**	(−)-**3b**	24	12:1
5[e]	2	**c**	**2c**	24	7:1
6[f]	3	**c**	**3c**	24	20:1
7	2	(−)-**d**	(−)-**2d**	24	10:1
8	3	(−)-**d**	(−)-**3d**	24	24:1
9	3	(−)-**d**	(−)-**3d**	13	>40:1
10[g]	2	**e**	**2e**	24	5:1
11[h]	3	**e**	**3e**	24	17:1

[a] Unless noted, all the reactions quantitatively provided a diastereomeric mixture of two piperidine derivatives, and the stereochemistry as shown. The relative stereochemistry of the products was determined based on their ^{1}H NMR and nOe experiments by comparing with that of **1a**. The stereochemistry of the 6-position of the minor isomers was not determined. [b] $CHCl_3$, 3 h. [c] Determined by ^{1}H NMR (400 MHz). [d] An inseparable mixture of four piperidine derivatives (15:5:3:1) was obtained. The diastereomeric ratio at the 2-position was determined after $LiAlH_4$ reduction of the crude products. [e−h] The racemic **c** and **e** were employed to examine the diastereoselectivity of the azaelectrocyclization.

The removal of the chiral indanol moiety in the obtained **1a**−**3d** was successfully achieved as shown in Table 2. Thus, **1a**−**3d** were reduced with lithium aluminum hydride to give the corre-

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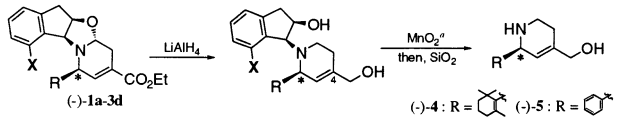
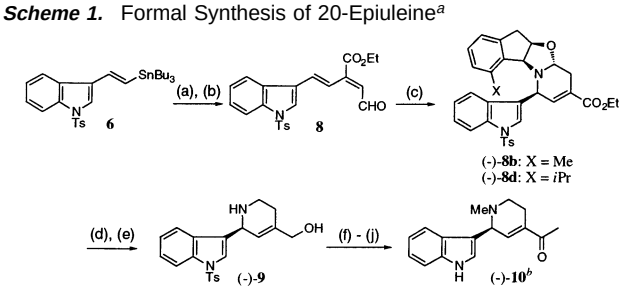
Table 2



entry	substrate	product	yield of diol (%)	yield of amino alcohol (%)
1	(−)-**1a**	(−)-**4**	100	69
2	(−)-**3a**	(−)-**5**	76[b]	55
3	(−)-**3b**	(−)-**5**	91	55
4	(−)-**3d**	(−)-**5**	91[c]	58

[a] The reaction was performed by treatment of the diols with manganese dioxide (10−20 w/w, chemicals treated, Wako) in ether for a few minutes at room temperature. [b,c] Total yield from aldehyde **3**.

Scheme 1. Formal Synthesis of 20-Epiuleine[a]



[a] Conditions: (a) ethyl (*Z*)-4-hydroxy-2-iodo-2-butenoate **7**, $Pd(PPh_3)_4$, LiCl, DMF, 115 °C, 64%; (b) MnO_2, CH_2Cl_2, 67%; (c) (−)-**b**, 96%, or (−)-**d**, 99%, $CHCl_3$, rt; (d) $LiAlH_4$, ether, 95% for (−)-**8b**, 83% for (−)-**8d**; (e) MnO_2, ether, rt, 3 min, then SiO_2 c.c., 73% for X = Me, 74% for X = *i*Pr; (f) 37% aq HCHO, $NaBH_3CN$, MeCN, rt, quant; (g) MnO_2, CH_2Cl_2; (h) MeLi, ether, THF, 55% for two steps; (i) NaOH aq, MeOH; (j) MnO_2, CH_2Cl_2, 40% for two steps. [b] (±)-**10** was reported to be converted into the racemic 20-epiuleine.[20a]

sponding diols in 76−100% yields,[18] which were then treated with manganese dioxide in ether at room temperature followed by silica gel chromatography to provide the corresponding amino alcohols (−)-**4** and (−)-**5** in 55−69% yields, respectively.[19]

Then, the method was successfully applied to the asymmetric synthesis of the ketone **10**, which is the key synthetic intermediate of the *Strychnos* indole alkaloid, (±)-20-epiuleine[20] by Husson and co-workers,[20a] as shown in Scheme 1. Thus, aldehyde **8**, which was prepared from the vinylstannane **6** and the vinyl iodide **7** according to our already established method,[10] was reacted with (−)-**b** or (−)-**d** to provide the corresponding piperidine derivatives (−)-**8b** or (−)-**8d** in an almost quantitative yield and with a 10:1 diastereoselectivity, respectively. After the minor isomers were separated, the compounds were reduced with lithium aluminum hydride followed by the treatment of the produced diols with manganese dioxide to afford the desired amino alcohol (−)-**9** in 73 and 74% yields, respectively. Finally, (−)-**9** was converted into (−)-**10**, whose spectral data were good agreement with those already reported,[20a] by the simple functional group manipulations as shown in Scheme 1. Thus, the asymmetric 6π-azaelectrocyclization established herein can be regarded as one of the new synthetic strategies. Further application of the method for natural products syntheses is now in progress in our laboratory.

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Supporting Information Available: Experimental details, characterization data, and copies of ^1H and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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