Direct Asymmetric Synthesis of Quaternary Carbon Centers via Addition-Elimination Process: Nitroolefination of α-Substituted δ-Lactones[1,†]

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Abstract: The reactions of chiral nitro enamines **2a-c** with zinc enolates **4-6** of α-substituted δ-lactones afforded α,α-disubstituted δ-lactones with a high ee through an addition-elimination process. The best results were obtained with the reaction of **2c** with **5**. Michael-type addition of the enolate onto the nitro enamine is kinetically controlled and decides the absolute stereochemistry of the product. A cyclic transition model is proposed to rationalize the *S*-selectivity.

Many natural biologically active complex organic molecules possess quaternary carbon centers. The chiral construction of those molecules has been a stimulating subject, and a plethora of methods for the asymmetric synthesis of quaternary carbon centers have appeared in recent years[3,4] since the pioneering work of Yamada and his co-worker[5] from the late 1960s through the mid-1970s. Among the most striking are the extensive studies of Meyers' group[6] utilizing chiral bicyclic lactam and the studies on alkylation of chiral enamine prepared from β-keto ester and (*S*)-valine *tert*-butyl ester by Koga's group.[7] These approaches are indirect asymmetric syntheses involving a diastereoselective reaction in the asymmetric induction step followed by the removal of a chiral auxiliary at the later stage. Many other papers on the chiral construction of a quaternary carbon center fall in this category.[4-7] A rather unexplored field is the direct asymmetric synthesis of quaternary carbons involving an enantioselective reaction. This led us to develop a new method for direct chiral construction of quaternary carbon centers through an addition-elimination process using (*S*)-(+)-2-(methoxymethyl)pyrrolidine (SMP) as a chiral leaving group.

In general, use of chiral leaving groups is not a sophisticated method for asymmetric induction. Consider an S_N2 reaction with a chiral leaving group as a typical case. The influence of a chiral environment will decrease on going from the ground state to the transition state, because the bond between carbon and a chiral leaving group becomes longer in the transition state than the ground state. Moreover, the nucleophile to become chiral should approach from the opposite side of the leaving group. In fact, enantiomeric excess (ee) of the internal alkylation utilizing a chiral leaving group, reported by Duggan and Murphy[8] for the first time, was not remarkable. In spite of these shortcomings, this type of asymmetric induction has lately received much attention from both mechanistic[9] and synthetic[10-12] points of view. Three strategems, (i) increasing the bulkiness of the chiral leaving group,[10] (ii) designing a reaction involving a cyclic transition state,[11] and (iii) inserting another step before the leaving group is eliminated, have been employed to overcome the inherent disadvantage of asymmetric synthesis with chiral leaving groups. The last approach involving syntheses of chiral binaphthyls by nucleophilic aromatic substitution reported by Wilson and Cram[12] is very interesting, because a high degree of ee was obtained for many binaphthyls. The high % ee is ascribed to the initial ipso addition of aryl metal reagents before elimination of the chiral group takes place. This was the first successful chiral induction with the last approach through a one-pot addition-elimination sequence. Another example of the same type of chiral induction in aliphatic systems will be presented here. Chiral nitro enamines[13] **2a-c** were selected because the nitro group is strongly electron withdrawing enough to undergo the Michael addition in the presence of the basic nitrogen moiety at the β-position.[14] The synthetic utility of

† This paper is dedicated to Professor H. Yajima, on his retirement from Kyoto University.

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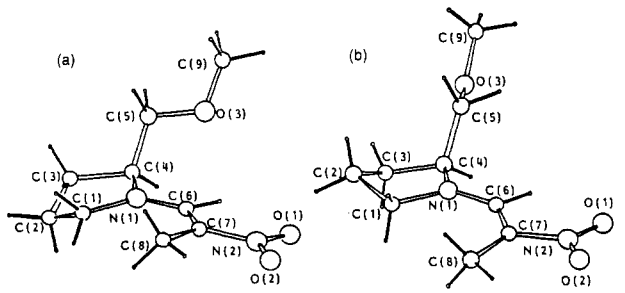


Figure 1. Crystal structure of (*S*)-1-[2-(methoxymethyl)pyrrolidino]-2-nitropropene (**2b**) in two conformations A (a) and B (b), showing the atom-labeling scheme.

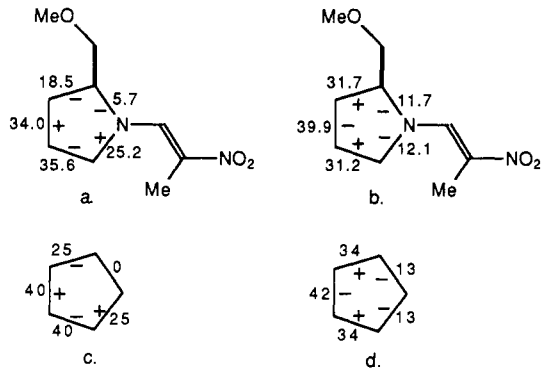
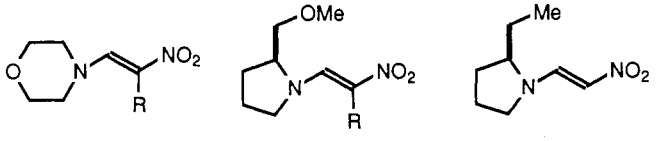


Figure 2. Torsion angles of the pyrrolidine ring of **2b** in conformations A (a) and B (b) determined by the X-ray analysis and of cyclopentane in the envelope (c) and the half-chair (d) conformations taken from ref 20.

nitroolefins[15] was another reason for the choice of nitro enamines **2a–c**.

Results

Synthesis and Structure of Nitro Enamines 2a–c. One-pot synthesis of morpholino enamine **1a** has been reported by Royer



1a, R = H
1b, R = CH_3
1c, R = C_2H_5

2a, R = H
2b, R = CH_3
2c, R = C_2H_5

3

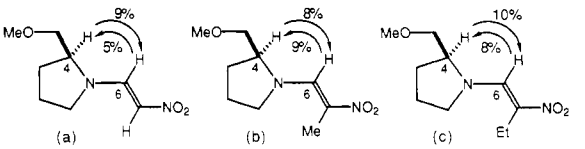


Figure 3. NOE experiments on **2a** (a), **2b** (b), and **2c** (c).

et al.[16] Other morpholino enamines **1b** and **1c** were prepared by the same method in high yields.[17] Amine interchange reaction[18] of morpholino enamines **1a–c** with SMP afforded the desired chiral nitro enamines **2a–c** in excellent yield, respectively. *E*-Configuration of the double bond in **2b** was determined unambiguously[19] by X-ray crystallographic analysis.

(*S*)-1-[2-(Methoxymethyl)pyrrolidino]-2-nitropropene (**2b**) exists in two individual conformations A and B in the crystalline state (Figure 1). The sign and torsion angle values of the pyrrolidine ring in each form are given in Figure 2, which includes values for the envelope form with C_S symmetry and the half-chair form with C_2 symmetry, of cyclopentane.[20] Comparison of those values and signs leads to the conclusion that, in conformation A, the pyrrolidine ring exists in a flattened envelope form most puckered at C2, while it takes a flattened half-chair form in conformation B. An important characteristic feature involving the nearly planar sp^2-hybridized nitrogen (N1) is preserved in both conformations. Table I (supplementary material) lists bond lengths, bond angles, and torsion angles. The double-bond character of the N1–C6 bond is clearly seen from the shortening of this bond in both conformation A and B. Two torsion angles around the nitrogen (N1), C1–N1–C6–C7 (−14.2°) and C4–N1–C6–C7 (174.9°) in conformation A, indicate the sp^2 nature of the nitrogen (N1) with a p-orbital slightly developed above the *si* face. On the other hand, the nitrogen (N1) in conformation B is totally sp^2-hybridized becuase the sum of the same torsion angles reaches nearly 180° (−178.8°). Further support for the sp^2 character of the nitrogen (N1) is provided by the sum (359.5° for conformation A and 359.3° for conformation B) of valence angles around N1. It is noteworthy that almost all non-hydrogen atoms, except for C2, C3, and the methoxymethyl group, are located approximately on the same plane in conformation B in spite of severe $A_{1,3}$ strain (torsion angles of 4.8° for N1–C6–C7–C8 and of −175.0° for N1–C6–C7–N2). The pyrrolidine ring in conformation A is similar to that in conformation B, but C1 is slightly out of the plane.

The *s*-*E*-conformation[21] about the N1–C6 bond in the chiral nitro enamine **2b** is preserved in solution. Thus, the 3.88 ppm H4 proton and the 8.54 ppm H6 proton exhibit a considerable nuclear Overhauser effect (NOE) on each other (Figure 3b). IR absorption at 1628 cm^{-1} indicates the presence of a C=N^+ bond. This further suggests that a flat arrangement of all non-hydrogen atoms, except for C2, C3, and the methoxymethyl group, in **2b** is kept in solution. Chiral enamines **2a** and **2c** proved to be of the same geometry at the double bond as that of **2b** from the olefinic proton resonances (8.38 ppm for **2a** and 8.48 ppm for **2c**). The NOE shown in parts a and c of Figure 3 supports the *s*-*E*-structures for **2a** and **2c** in solution, respectively.

(*R*)-1-[2-Ethylpyrrolidino]-2-nitroethylene (**3**) was prepared by the amino exchange reaction of **1a** with (*R*)-2-ethylpyrrolidine, obtained from (*S*)-(−)-1-(*tert*-butoxycarbonyl)-2-[[[4-(methylphenyl)sulfonyl]oxy]methyl]pyrrolidine[22] with the Gilmann reagent followed by removal of the amino-protecting group.

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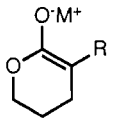
Table II. Asymmetric Nitroolefination of Lactone Enolates via Addition–Elimination Sequence

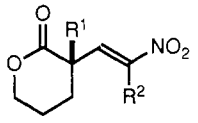
run	nitro enamine	enolate[a]	countercation	reaction temp, °C	condition time, h	product	yield,[b] %	$[\alpha]^{20}_D$ ($CHCl_3$)	% ee[c]	quenching method
1	**2a**	**4**	Li^+	−78 to RT	5	**7a**	81[e]	−4.0	30	B
2	**2a**	**4**	Cu^+	−78	0.5	**7a**	76	−9.7	70	B
3	**2a**	**4**	Zn^{2+}	−78 to −40	3	**7a**	99	−12.3	86	B
4	**2a**	**5**	Li^+	−78	1	**8a**	56	+8.3[f]	35	B
5	**2a**	**5**[g]	Li^+	−20	0.3	**8a**	22[e]			B
6	**2a**	**5**[h]	Li^+	−20	2	**8a**	43[e]		46	B
7	**2a**	**5**	Cu^+	−78	0.5	**8a**	42	+0.7	82	B
8	**2a**	**5**	Zn^{2+}	−78	2	**8a**	94	+20.2[f]	82	A
9	**2a**	**5**[g]	Zn^{2+}	−20	2	**8a**	39[e]			B
10	**2a**	**5**[h]	Zn^{2+}	−20	2	**8a**	70[e]		90	B
11	**2a**	**6**	Zn^{2+}	−78 to −40	1	**9a**	86	−25.8	87	A
12	**2b**	**4**	Zn^{2+}	−78	0.3	**7b**	69	−50.8	93	A
13	**2b**	**5**	Zn^{2+}	−78	1	**8b**	65	−25.7	90	B
14	**2b**	**6**	Zn^{2+}	−78	1	**9b**	54	−54.3	92	A
15	**2c**	**4**	Zn^{2+}	−78	1.5	**7c**	87	−46.1	85	B
16	**2c**	**5**[i]	Zn^{2+}	−78	2	**8c**	89	−37.2	96	A
17	**2c**	**6**	Zn^{2+}	−78 to −50	1.7	**9c**	69	−67.8	96	A
18	**3**	**5**[g]	Zn^{2+}	−40 to −20	2	**8a**	55[e]			B
19	**3**	**5**[h]	Zn^{2+}	−40 to −20	1	**8a**	91[e]		74	B
20	**2a**	**10**	Cu^+	−78 to −10	4.5	**12**	82	−21.3	56	A
21	**2a**	**11**	Zn^{2+}	−78 to −40	2.5	**13**	72	−22.6	63	A

[a] 3 equiv of enolate was used unless otherwise stated. [b] Isolated yield. [c] Determined by 400-MHz ^1H NMR with $Eu(hfc)_3$. [d] Method A: with 0.5% HCl. Method B: with *p*-TsOH in CH_2Cl_2. [e] Determined by HPLC analysis with phenanthrene as an internal standard. [f] Determined at 435 nm. [g] 1 equiv of enolate was used. [h] 2 equiv of enolate was used. [i] 6 equiv of enolate was used.

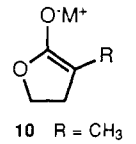
Nitroolefination of α-Substituted δ-Lactones. The reactions of nitro enamines **2a–c** with enolates **4–6** of α-substituted δ-lactones



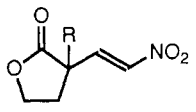
4 R = CH_3
5 R = C_2H_5
6 R = $CH_2CH{=}CH_2$



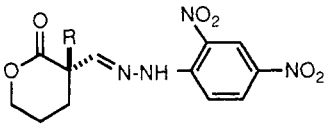
7a R^1 = CH_3, R^2 = H
7b R^1 = CH_3, R^2 = CH_3
7c R^1 = CH_3, R^2 = C_2H_5
8a R^1 = C_2H_5, R^2 = H
8b R^1 = C_2H_5, R^2 = CH_3
8c R^1 = C_2H_5, R^2 = C_2H_5
9a R^1 = $CH_2CH{=}CH_2$, R^2 = H
9b R^1 = $CH_2CH{=}CH_2$, R^2 = CH_3,
9c R^1 = $CH_2CH{=}CH_2$, R^2 = C_2H_5



10 R = CH_3
11 R = C_2H_5



12 R = CH_3
13 R = C_2H_5



14 R = C_2H_5
15 R = CH_3

are listed in Table II. The results on the reaction of nitro enamine **2a** with the enolate **4** indicate that Zn^{2+} is among the most satisfactory as a countercation in terms of both chemical yield and % ee (runs 1–3). A similar trend was observed in the reaction of **2a** with **5** (runs 4, 7, and 8). Thus, Zn^{2+} was chosen as a countercation in runs 9–19. 2-Substituted nitro enamines **2b** and **2c** gave better ee than the parent nitro enamine **2a**. The ee's of the reaction of γ-lactone enolates **10** and **11** were less satisfactory than the corresponding δ-lactones, even when Cu^+ (run 20) or Zn^{2+} (run 21) was used as a countercation.

The *S*-configuration at the induced quaternary center of **8a** was determined through the conversion into (+)-quebrachamine.[23] Ozonolysis of optically active **8a** afforded the aldehyde, characterized as 2,4-dinitrophenylhydrazone **14** with a negative optical rotation. The same hydrazone **14**, with the same optical rotation, was obtained from **8b** and **8c**, proving the *S*-configuration at the quaternary carbon of **8b** and **8c**. The *S*-configuration of **7a** was confirmed by its conversion into (+)-podocarpic acid.[24] The same chiral hydrazone **15** was obtained from **7a–c**, supporting the *S*-configuration of the latter two. The CD data for lactones are compiled in Table III (supplementary material). With the exception of **7a** and **8a**, a common feature is a negative Cotton effect observed around 330–350 nm. Thus, **9a–c** may have the same absolute configuration at the center of chirality.

Table IV. Variation of the Yield of **8a** from the Reaction of **2a** and **5** (M = Li) by Quenching Conditions

entry	conditions	yield[a] of **8a**, %	recovery[a] of **2a**, %
1	0.5 N HCl–CH_2Cl_2	78.0	1.4
2	*p*-TsOH in CH_2Cl_2	79.0	4.0
3	H_2O–CH_2Cl_2	65.0	15.0

[a] Determined by HPLC with phenanthrene as an internal standard.

Table V. Crossover Experiments[a,b] between **4** and **5**

run[c]	M^+	1st enolate (mol equiv)	2nd enolate (mol equiv)	reaction time, h	yield,[d] % **2a**	**7a**	**8a**
1	Li^+	**4** (5)		2	0	75	
		4 (5)	**5** (5)	2	0	76	0
2	Li^+	**5** (5)		2	4		79
		5 (5)	**4** (5)	3.5	0	0	78
3	Li^+	**5** (2)		5	15		74
		5 (2)	**4** (10)	7	0	15	76
4	Zn^{2+}	**4** (5)		2	0	89	
		4 (5)	**5** (5)	4	0	88	0
5	Zn^{2+}	**5** (5)		3	7		85
		5 (5)	**4** (5)	4	0	5	78
6	Zn^{2+}	**5** (2)		7	46		41
		5 (2)	**4** (10)	8	0	50	46

[a] Reaction temp; from −78 to −20 °C. [b] Nitro enamine **2a** was used in all runs. [c] The upper row in each run includes the results obtained just before the addition of the second enolate indicated at the lower in the same run. [d] Determined by HPLC with phenanthrene as an internal standard.

Mechanism of Asymmetric Induction. Kinetic or Thermodynamic Control? Quenching conditions have a remarkable effect on the yield of the reaction. The nitro enamine **2a** was treated with 5 equiv of **5** (M = Li) in dimethoxyethane (DME) at −78 to −20 °C for 1.5 h, and the reaction mixture was quenched under

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different conditions (Table IV). Quenching under acidic conditions afforded a reasonable yield of product **8a** with a small amount of recovered starting material **2a** (entries 1 and 2), while a considerable amount of **2a** was obtained under basic conditions (entry 3). This indicates that the reaction stays at the intermediate adduct **16** in the reaction medium[25] and elimination of either the prolinol or lactone moiety occurs depending upon the workup procedure when lithium is employed as a countercation. The difference in the yield due to the workup procedure was not observed in the case of zinc enolate.

The question to be answered at this point is whether the addition step is reversible or not.[26,27] Results of detailed crossover experiments[28] are given in Table V. In each run, 5 mol equiv of the first enolate was added to a solution of nitro enamine **2a**, and the yield of the corresponding product was determined by HPLC just before the second enolate was added. The product from the second enolate was not observed in runs 1, 2, and 4, because only a negligible amount of the starting nitro enamine **2a** remained in the reaction mixture. Note the results of runs 3 and 6 in which approximately the same amount of product arising from the second enolate was obtained even though a large excess of this enolate had been used. These findings clearly show that the addition of enolates onto the nitro enamine **2a** is not reversible regardless of the countercation. Thus, the observed asymmetric induction is controlled kinetically, when the addition of the enolate decides the absolute stereochemistry of the product.

Face Differentiations. The extent of this reaction increases as the molar equivalent of enolate increases. The reaction of enolate **5** (M = Zn) with nitro enamine **2a** was not completed until 3 mol equiv of **5** (M = Zn) were employed (runs 8–10 in Table II). A total of 2 mol equiv of enolate **5** (M = Zn) was sufficient to complete the reaction with nitro enamine **3** in which the methoxyl group in **2a** was replaced by a methyl group (runs 18 and 19 in Table II). Thus, the methoxyl group in **2a** is responsible for the chelation with enolate **5** (M = Zn) to consume an extra mole of enolate.

The *re*-face of the starting enolate is preferentially selected in the transition state of the rate-determining addition step of this reaction, because the product with the *S*-configuration is always provided regardless of the starting enolates and nitro enamines. Another face differentiation includes the nitro enamine, which is important for providing some insight into the mechanism of this asymmetric induction. There are two possibilities for the mode of attack of an enolate onto the face of chiral nitro enamines **2a–c**: (1) approach of the enolate from the *si*-face of the nitro enamine keeping the coordination with the methoxyl group and (2) attack of the *re*-face of the nitro enamine, whereby the chelating enolate acts as a bulky group to block the *si*-face. The former can be eliminated because both **2a** and **3** gave the *s*-product. Thus, the methoxyl group in **2a–c** functions as a chelating site with the metal cation to make the *si*-face bulkier. This may account for the higher ee with **2a** than with **3** though the methoxyl group is less bulky than the methyl group.[29]

As seen in Table II, the ee is deeply affected by the metal cation. Clearly, chelation in the transition state plays an important role in deciding the enantioselectivity. The reason for the selection

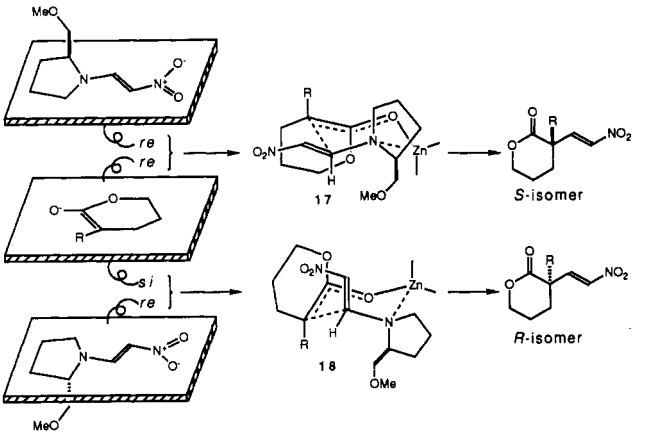
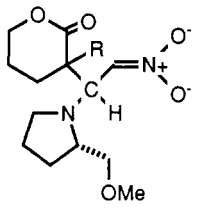


Figure 4. Possible cyclic transition states **17** and **18** leading to the *S*-isomer and the *R*-isomer, respectively.

of the *re*-face of the lactone is shown in Figure 4. The combination of the *re*/*re*-faces affords the cyclic transition state **17** leading to the observed *S*-isomer, provided the original *s*-*E*-conformation about the N1–C6 bond in the nitro enamine is preserved. The *si*/*re*-combination gives the transition state **18**, which results in the formation of the *R*-isomer. The transition state **17** should be more stable than **18** because the nitroalkyl group is disposed equatorially in **17**. Thus, of the four possible combinations, the *re*-face of both the enolate and the nitro enamine was selected to provide the *S*-isomer preferentially.



16

Experimental Section

(*S*)-1-[2-(Methoxymethyl)pyrrolidino]-2-nitroethylene (2a). General Procedure. To a methanolic solution (60 mL) of morpholino nitro enamine **1a** (1.7 g, 11 mmol) was added dropwise a solution of SMP (2.0 g, 17 mmol) in MeOH (12 mL), and the mixture was stirred at 45 °C under N_2 for 3 h. The solvent was removed, and the residue was purified by short-column chromatography over silica gel (AcOEt:hexane = 3:1) followed by Kugelrohr distillation (170 °C, 0.3 mm) to give a yellow oil of analytically pure **2a** (1.86 g, 91%): MS *m*/*e* 186 (M^+); IR ($CHCl_3$) ν 1612, 1464, 1300, 1250 cm^{-1}; UV (EtOH) λ_{max} 354 (ϵ 39 000), 204 nm (ϵ 68 000); ^1H NMR ($CDCl_3$) δ 1.83 (m, 1 H), 1.99–2.24 (m, 3 H), 3.17–3.31 (m, 2 H), 3.38 (s, 3 H), 3.48 (m, 1 H), 3.88 (m, 1 H), 6.59, 8.42 (ABq, 2 H, J = 10.7 Hz); $[\alpha]^{22}_D$ −140.1° (*c* 1.59, $CHCl_3$). Anal. Calcd for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.31; H, 7.44; N, 15.02.

(*R*)-1-[2-Ethylpyrrolidino]-2-nitroethylene (3). To a solution of CuI (571 mg, 3 mmol) in dry ether (13 mL) was added 6 mL (6 mmol) of a 1.0 M solution of MeLi in ether at 0 °C under N_2. To the solution was added a solution of (*S*)-(−)-1-(*tert*-butoxycarbonyl)-2-[[4-[(methylphenyl)sulfonyl]oxy]methyl]pyrrolidine[22] (356 mg, 1 mmol) in CH_2Cl_2. Then, the mixture was stirred for 3 h at 0 °C and quenched with saturated NH_4Cl. Extractive workup with CH_2Cl_2 gave a brown oil, which was treated with CF_3COOH (1 mL) at 0 °C for 30 min and poured into dilute HCl and ether. The ethereal layer was washed successively with aqueous KOH and brine, dried with $MgSO_4$, and evaporated to give crude (*R*)-2-ethylpyrrolidine (68 mg, 69%). An amine interchange reaction of this brown oil (42 mg, 0.42 mmol) with nitro enamine **1a** (134 mg, 0.84 mmol) in MeOH (4.5 mL) gave a yellow oil, **3** (22 mg, 31%): bp 190 °C (0.04 mm); MS *m*/*e* 170 (M^+); IR ($CHCl_3$) ν 1621, 1310, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29, 6.60 (ABq, 2 H, J = 10.5 Hz), 3.00–3.80 (m, 3 H), 1.18–2.24 (m, 6 H), 0.96 (t, 3 H, J = 7.3 Hz); $[\alpha]^{22}_D$ −49.0° (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.77; H, 8.45; N, 16.64.

General Procedure for Asymmetric Nitroolefination. (See Table II for conditions and results.) Lithium diisopropylamide (LDA) was prepared by adding a 1.6 M solution of *n*-BuLi in hexane (1.9 mL, 3 mmol) to a

(25) The adduct of an active methylene compound with a nitro enamine was detected by ^1H NMR. See: Lerche, H.; König, D.; Severin, T. *Chem. Ber.* **1974**, *107*, 1509.

(26) Bergmann, E. D.; Ginsberg, D.; Pappo, R. *Org. React.* (*N.Y.*) **1959**, *10*, 179.

(27) It is well-known that the Michael-type addition of enamines onto nitroolefins is readily reversible. See: Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162.

(28) There was some confusion on the crossover experiments between lithium enolates **4** (M = Li) and **5** (M = Li) at the early stage of this work.[1] We did not notice that increasing the reaction temperature up to −30 °C dramatically decreased the reaction time required for the addition of the enolate onto the nitro enamine. The progress of the reaction was conveniently monitored by TLC. The reaction proceeded further in a capillary tube before quenching, because the temperature was raised while taking up the reaction mixture. This has led to the wrong conclusion that the addition of the lithium enolates onto the nitro enamine is readily reversible.

(29) Hirsch, J. A. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; John Wiley & Sons: New York, 1967; Vol. 1, pp 199–222.

solution of diisopropylamine (0.43 mL, mmol) in dry DME (4 mL) at −78 °C under N_2 followed by stirring for 30 min at 0 °C. A solution of the lactone (3.5 mmol) in DME (7 mL) was added dropwise to the solution of LDA at −78 °C. After being stirred for 30 min at −78 °C, the mixture was added dropwise to a stirred solution of the nitro enamine (1 mmol) in DME (3 mL) at −78 °C. The reaction was performed under the condition shown in Table II, and then the resulting mixture was quenched by the method A or B and purified by flash column chromatography (silica gel, AcOEt–hexane) to give the desired nitroolefins. Results are given in Table II. The % ee was determined by chiral shift 400-MHz ^1H NMR analysis ($CDCl_3$, $Eu(hfc)_3$).

The zinc enolates were prepared from lithium enolate by adding an equimolar amount of $ZnCl_2$ (0.69 M solution in ether) at −78 °C and stirring at −20 °C for 30 min. The copper enolates were prepared by adding the powdered CuI to a lithium enolate at −78 °C and stirring at 0 °C for 30 min.

Quenching Method A. The reaction mixture was poured into cold 0.5 N HCl through a bridge slowly.

Quenching Method B. The reaction mixture was poured into a stirred suspension of *p*-TsOH (5–10 equiv of base) in CH_2Cl_2 through a tube. The CH_2Cl_2 layer was washed with water twice, dried ($MgSO_4$), and evaporated.

Examination of Quenching Conditions (Table IV). To a solution of nitro enamine **2a** (22.3 mg, 0.12 mmol) in DME (1 mL) was added lithium enolate **5** (0.6 mmol) in DME (2 mL) with phenanthrene as an internal standard at −78 °C under N_2, and the mixture was stirred at −78 to −20 °C for 2 h. Part of the resulting mixture was transferred through a tube into 0.5 N HCl–CH_2Cl_2 and a suspension of *p*-TsOH (ca. 5 equiv of base) in CH_2Cl_2 or water–CH_2Cl_2, and each was extracted with CH_2Cl_2 using Extrelut 3 column. The residue obtained after evaporation was analyzed by HPLC (column, Jasco fine-pack SIL (25 × 0.46); hexane–isopropanol (2:1); flow rate, 3 mL/min; detector, 25 nm).

Crossover Experiments between 4 and 5 (Table V). To a solution of nitro enamine **2a** in DME was added lithium enolate **4** or **5** prepared in DME with phenanthrene as an internal standard at −78 °C, and the mixture was stirred under the reaction conditions in Table V. Part of the resulting mixture was transferred through a tube into a suspension of *p*-TsOH (ca. 5 equiv of base) in CH_2Cl_2 and extracted by means of Extrelut 3 column. The remaining reaction mixture was cooled to −78 °C again, and the enolate **5** or **4** was added. After the reaction was performed under the conditions in Table V, the products were analyzed by HPLC.

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Supplementary Material Available: General experimental details, spectral data on **2b,c**, **7a–c**, **8a–c**, **9a–c**, **12**, and **13**, procedures and data on **14** and **15**, Table I, Table III, and tables of crystal data, bond lengths, bond angles, atomic coordinates, and thermal parameters for **2b** (13 pages). Ordering information is given on any current masthead page.

Synthesis and Evaluation of Hypothetical Intermediates in the Biosynthetic Conversion of Protoberberine to Benzo[*c*]phenanthridine Alkaloids. Evidence for Oxidative C–N Bond Fission Followed by Intramolecular Recyclization in Cell Cultures of *Corydalis incisa*

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Abstract: In order to clarify the nitrogen–carbon cleavage process in the biosynthetic conversion of protoberberine to benzo[*c*]phenanthridine alkaloids, the novel, deuterated, 6-hydroxylated protoberberines **19** and **26** have been synthesized as hypothetical intermediates and studied in *Corydalis incisa* callus cell cultures. The syntheses relied on the in situ conversion of the unstable amino aldehydes **17** and **23** to the acetals **18** and **24**, which afforded the desired products **19** and **26** under acidic conditions. The structure of **26c** was confirmed by X-ray analysis. In solution, both **19** and **26** were found to exist as an equilibrium mixture of at least two carbinol ammonium species and one amino aldehyde form. Of these two novel diastereomeric carbinol ammonium compounds **19** and **26**, only the 13,14-cis isomer **26** was transformed into the labeled benzo[*c*]phenanthridines corynoline (**11**) and corynoloxine (**12**). However, corycavine (**8**) was incorporated more effectively into **11** and **12** than **26**. Both **19** and **26** were bioconverted via the corresponding amino alcohols **30** and **25** to the dehydro derivative **29**. Mass spectral analysis of the biosynthetic products indicated that unexpectedly, some H–D exchange at C-8 had occurred.

The benzophenanthridine alkaloids (±)- and (+)-corynoline (**11**), as well as (±)- and (+)-corynoloxine (**12**), have been isolated from *Corydalis incisa* Pers. (Scheme I).[1,9] A number of studies involving the incorporation of labeled precursors[2-11] have confirmed the earlier suggestion that the benzophenanthridines arise biosynthetically from the protoberberines (e.g., **1–3**)[12,13] via the protopines (e.g., **7** and **8**).[14] The commonly postulated intermediate is compound **9**. Nucleophilic addition of the enamine to the aldehyde in **9** would give an iminium ion, which could then

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