ASYMMETRIC [2+2] PHOTOCYCLOADDITION REACTION OF A CHIRAL DIOXOPYRROLINE TO 2-(TRIMETHYLSILOXY)BUTADIENE: CHIRAL SYNTHESIS OF *ERYTHRINA* ALKALOIDS¹⁾Takehiro SANO,^{*,a} Makiko KAMIKO,^a Jun TODA,^a Shinzo HOSOI,^b and Yoshisuke TSUDA^b*Showa College of Pharmaceutical Sciences,^a 3-3165 Higashi-tamagawagakuen, Machida-shi, Tokyo 194, Japan and Faculty of Pharmaceutical Sciences, Kanazawa University,^b 13-1 Takara-machi, Kanazawa 920, Japan*

The detailed stereochemical pathway of [2+2] photocycloaddition reaction of isoquinolinodioxopyrroline to 2-(trimethylsilyloxy)butadiene was clarified by using an enantiomerically pure substrate. The photoadducts were converted into the synthetic intermediates of *Erythrina* alkaloids, providing an efficient synthetic method in optically active forms.

KEYWORDS [2+2] photocycloaddition; face selectivity; chiral dioxopyrroline; photo-epimerization; cycloreversion; *Erythrina* alkaloid

[2+2] Photocycloaddition of dioxopyrroline to olefins has been intensively investigated to clarify factors controlling the stereochemical pathway of the reaction.²⁾ In this communication, we describe an asymmetric [2+2] photocycloaddition reaction of a chiral isoquinolinodioxopyrroline to 2-trimethylsilyloxybutadiene, which not only revealed the detailed stereochemical outcome of the above photocycloaddition reaction but also provided a new synthetic method of chiral *Erythrina* alkaloids.

The chiral dioxopyrroline (-)-1 of (5*S*)-configuration (mp 147–149°C, $[\alpha]_D^{22}$ -73.0°) was prepared from L-DOPA in a similar way as described in the synthesis of the corresponding methyl ester.³⁾

A solution of (-)-1 and 2-trimethylsilyloxybutadiene (2 mol eq) in dimethoxyethane (DME) was irradiated for 1 h at 0°C under a high-pressure mercury lamp with a Pyrex filter (≥ 300 nm) to give the two adducts 2⁴⁾ (56%) and 3⁴⁾ (11%). The adducts showed opposite Cotton effects ($[\theta]$ +1100° at 378 nm for 2 and $[\theta]$ -3600° at 375 nm for 3), suggesting that they are enantiomeric concerning the stereochemistry of the cyclobutane ring juncture (C2a and C11b). The stereochemistry of the vinyl and OTMS groups at C-1 was elucidated by the fact that adducts 2 and 3 showed similar chemical reactivities with that of the corresponding photoadduct⁵⁾ which lacks 6-ethoxycarbonyl group; thus the vinyl and OTMS group are in *exo*- and *endo*-configuration, respectively. The enantiomer excess (ee) of the adducts was determined as 20% for the major adduct (+)-2⁶⁾ and >99% for the minor adduct (-)-3⁶⁾ from the respective diastereomer excess (de) observed in the ¹H-NMR spectra of the derived (-)-(*R*)- α -methoxy- α -trifluoromethylphenylacetate 4 and 5 (Mosher's ester)⁷⁾ which were prepared by the route shown in Chart 1. Their absolute stereo-

Chart 1

chemistries were established by conversion into the known erythrinan derivatives⁸⁾ described below (Chart 4).

The low ee of (+)-2 suggested that this cycloaddition accompanied epimerization of C₆-COOEt group in one of the product (-)-3, which resulted in the enantiomer of (-)-2. In fact, the ee of 2 was found to largely depend on the reaction time. Short irradiation (30 min) of (-)-1 and the diene (2 mol eq) at 0°C gave (+)-2 of 78% ee^{9a)} and (-)-3 of >99% ee in 57% and 16% yields, respectively.

The more detailed pathway was evidenced from the following experiments. The dioxopyrroline (-)-1 was recovered without any loss of its optical activity by irradiation in DME for 1 h. Irradiation of (-)-3 of >99% ee in DME at 0°C for 3 h gave (±)-2^{9b)} in 18% yield. The formation of the racemate indicated that (-)-3 underwent not only the epimerization of the C₆-COOEt group but also cycloreversion of the cyclobutane ring and recombination of the formed (-)-1 with 2-trimethylsilyloxybutadiene. A similar irradiation of (-)-3 in the presence of the diene (10 mol excess) gave (+)-2 of 88% ee,^{9c)} though the chemical yield was low (25%), indicating that the cycloreversion-recombination process was accelerated in the presence of the excess diene.¹⁰⁾ Irradiation of (+)-2 of 70% ee under a similar condition slowly produced (-)-3 of 31% ee^{11a)} in 10% yield with recovery of (+)-2 in 78% yield without change of its ee. Similar irradiation of (+)-2 of 70% ee in the presence of the diene (10 mol excess) gave (-)-3 of 56% ee^{11b)} in 10% yield with recovery of (+)-2 in 69% yield without loss of its ee. The partial racemization of (-)-3 in these reactions must be due to the direct epimerization of (+)-2 to (+)-3, since, if (+)-3 were produced from (-)-2 through cycloreversion-recombination, the ee of the recovered (+)-2 should decrease.

From the above results, the whole reaction process is depicted as shown in Chart 2, where steps shown by bold arrows were observed in the photocycloaddition reaction of (-)-1 to the diene. Reaction rates of each step can be evaluated as $k_1 > k_2 > k_3 > k_4 > k_5 > k_6$: in these, cycloaddition is greatly accelerated by the presence of the excess diene, since the reaction is bimolecular.

Accepting the above scheme, the face selectivity (k_1/k_2) of the diene to (-)-1 in the photocycloaddition was estimated approximately as 2.5 (which is suggested by the early stage ratio of (+)-2 vs. (-)-3), indicating that the β -face addition is more favorable than the α -face addition, the result being in distinct contrast to Diels-Alder cycloaddition³⁾ of the diene to the same substrate, where the α -face addition was exclusively observed under high pressure conditions. Thus, the major path of the photochemical step may be explained by assuming that (-)-1 reacts to the diene by taking the COOEt equatorial conformation (A), where the aromatic ring is appreciably twisted from the average plane toward the α -face (dihedral angle of C1-C10b-C10a-C10 is *ca.* -31°), giving steric hindrance for approaching the diene from α -face (Chart 3). Although (-)-1 takes the COOEt axial conformation (B) (in which the corresponding dihedral angle is *ca.* +23°) at the ground state (X-ray analysis),³⁾ the calculated steric energy differ-

ence between A and B is small (0.6 kcal/mol).¹²) Preferentially the reaction from A gives (+)-2 and that from B gives (-)-3 with a ratio of 2.5:1.

Photoadducts (+)-2 and (-)-3 were converted into synthetic intermediates of *Erythrina* alkaloids without loss of their ee. A solution of (+)-2 of 20% ee in toluene was heated under reflux at 120°C for 2 h and the crude pyrolysate was treated with ethylene glycol in CH₂Cl₂ catalyzed by BF₃·Et₂O at room temperature to give the ketal **6**¹³ (71% from 2). Reduction of **6** with NaBH₄ in ethanol gave the alcohol **7**¹³ (100%), which afforded the ketone **8**¹³ (70%) by deacetalization. Similarly, (-)-3 of >99% ee was converted into the acetal **10**¹³ (86% from 3), the alcohol **11**¹³ (84%), and then the ketone **12**¹³ (95%). Erythrins **8** and **12** were identical with the authentic samples obtained by an intramolecular cyclization method⁸) in the spectral data and TLC behavior except for optical rotations. The derived Mosher's esters (**9** and **13**) were of 20% and >99% de, respectively. Thus the present synthesis provides a new method to synthesize *Erythrina* alkaloids in optically active forms.

Chart 4

REFERENCES AND NOTES

- 1) Part LIX of Dioxypyrrrolines. Part LVIII: J. Toda, M. Seki, K. Amano, T. Oyama, T. Sano, F. Kiuchi, Y. Tsuda, *Chem. Pharm. Bull.*, **42**, 739 (1994). This paper also constitutes Part XLIII of Synthesis of *Erythrina* and Related Alkaloids. Part XLII: Y. Tsuda, S. Hosoi, K. Ishida, M. Sangai, *Chem. Pharm. Bull.*, **42**, 204 (1994).
- 2) T. Sano, Y. Horiguchi, Y. Tsuda, *Chem. Pharm. Bull.*, **35**, 23 (1987); T. Sano, H. Enomoto, Y. Kurebayashi, Y. Tsuda, *ibid.*, **41**, 471 (1993) and references cited therein.
- 3) Y. Tsuda, S. Hosoi, N. Katagiri, C. Kaneko, T. Sano, *Heterocycles*, **33**, 497 (1992); Y. Tsuda, S. Hosoi, N. Katagiri, C. Kaneko, T. Sano, *Chem. Pharm. Bull.*, **41**, 2087 (1993).
- 4) **2**: mp 107-108°C, [α]_D²² -2.2° (c=0.45, CHCl₃), IR (KBr): 1769, 1727. ¹H-NMR: δ 0.04 (9H, s, SiMe₃), 0.71, 1.27 (each 3H, t, *J*=7 Hz, COOCH₂CH₃), 2.29, 3.40 (each 1H, d, *J*=13 Hz, H-2), 3.0-3.2 (2H, m, H-7), 3.78, 3.84 (each 3H, s, OMe), 3.77, 4.14 (each 2H, q, *J*=7 Hz, COOCH₂CH₃), 5.1-5.5 (3H, m, H-6, C=CH₂), 5.87 (1H, dd, *J*=9, 18 Hz, -CH=C), 6.60 (2H, s, ArH). **3**: mp 116-118°C, [α]_D²² -27.4° (c=0.44, CHCl₃), IR (KBr): 1773, 1754, 1725. ¹H-NMR: δ 0.07 (9H, s, SiMe₃), 1.08, 1.14 (each 3H, t, *J*=7 Hz, COOCH₂CH₃), 2.25, 3.32 (each 1H, d, *J*=13 Hz, H-2), 2.86 (1H, dd, *J*=7, 15 Hz, H-7), 3.22 (1H, dd, *J*=2, 15 Hz, H-7), 3.79, 3.86 (each 3H, s, OMe), 4.10 (2H, q, *J*=7 Hz, COOCH₂CH₃), 4.13 (2H, dq, *J*=2, 7 Hz, COOCH₂CH₃), 4.84 (1H, dd, *J*=2, 7 Hz, H-6), 4.9-5.6 (3H, m, CH=CH₂), 6.67, 6.70 (each 1H, s, ArH).
- 5) T. Sano, J. Toda, T. Ohshima, Y. Tsuda, *Chem. Pharm. Bull.*, **40**, 873 (1992).
- 6) Signs of (-) and (+) represent those at 375 nm, since their [α]_D values are very small.
- 7) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).
- 8) S. Hosoi, K. Ishida, M. Sangai, Y. Tsuda, *Chem. Pharm. Bull.*, **40**, 3115 (1992); Part XLII of ref. 1.
- 9) a) mp 111-112°C, [α]_D -6.3° (c=1.1, CHCl₃), CD (c=0.04, MeOH) [θ]_D²⁵ (nm): +4300 (378) (positive maximum), -1200 (320) (negative maximum); b) No Cotton effect; c) CD (c=0.05, MeOH) [θ]_D²⁵ (nm): +4800 (378), -1400 (320).
- 10) In these cases, **3** was not recovered from the reaction mixture, though its presence was suggested by an HPLC analysis.
- 11) a) CD (c=0.1, MeOH) [θ]_D²⁵ (nm): -1000 (375) (negative maximum), -1100 (365) (negative maximum); b) CD (c=0.1, MeOH) [θ]_D²⁵ (nm): -2000 (375), -2100 (365).
- 12) The least steric energies for A and B calculated by Chem 3D program (Quality =1) were 50.6 and 50.0 kcal/mol, respectively.
- 13) **6**: gum, [α]_D²² +1.6° (c=0.6, CHCl₃). **7**: gum, [α]_D²² +0.7° (c=1.0, CHCl₃). **8**: mp 211-213°C, [α]_D²² -0.7° (c=1.0, CHCl₃). **10**: mp 238-240°C, [α]_D²² -72.5° (c=1.0, CHCl₃). **11**: gum, [α]_D²² -69.4° (c=1.0, CHCl₃). **12**: gum, [α]_D²² -31.7° (c=1.0, CHCl₃).

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