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ENANTIOSELECTIVE SYNTHESIS OF LYTHRACEAE ALKALOID LASUBINE II *VIA* OPTICALLY ACTIVE 2-ISOXAZOLINE[#]

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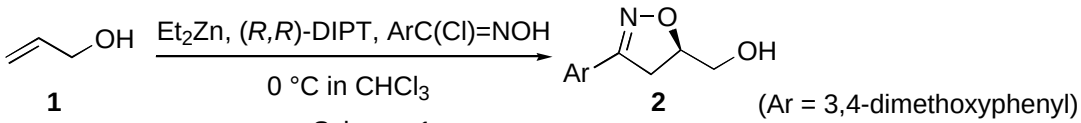
Abstract - Enantioselective synthesis of Lythraceae alkaloid lasubine II was achieved *via* optically active 2-isoxazoline, which was available by the asymmetric 1,3-dipolar cycloaddition of nitrile oxide to an achiral 2-propen-1-ol using diisopropyl (*R,R*)-tartrate as a chiral auxiliary.

The plants of Lythraceae family are widely distributed in different regions of the world and more than 40 alkaloids have been isolated from them. Most of these alkaloids possess a 2,4-disubstituted quinolizidine ring system.[1] Lasubine II, isolated from the leaves of *Lagerstroemia subcostata* Koehne,[2] consists of *trans*-quinolizidine framework. Racemic lasubine II has been synthesized by several methods, for example, Mannich reaction of isopelletierine with substituted benzaldehyde,[3a] nitrone cycloadditions,[3b,c] two successive cyclization of acyclic γ-amino alcohol,[3d] conjugate addition to *N*-acyldihydropyridone,[3e] addition of 2-siloxy-1,3-diene to *N*-acyliminium ion,[3f] cyclization of allylsilane on *N*-acyliminium ion.[3g] However, to the best of our knowledge, there was no report on the total synthesis of optically active form.

Recently, we reported an efficient enantioselective 1,3-dipolar cycloaddition of nitrile oxides to achiral allylic alcohols using diisopropyl (*R,R*)-tartrate [(*R,R*)-DIPT] as a chiral auxiliary to give the corresponding optically active 2-isoxazolines.[4] The utility of the present asymmetric 1,3-dipolar cycloaddition in the challenging arena of synthesis of lasubine II was explored. Herein, we describe the enantioselective synthesis of lasubine II starting from the optically active 2-isoxazoline *via* the sequential reduction and cyclization processes.

First the stoichiometric asymmetric 1,3-dipolar cycloaddition of 3,4-dimethoxybenzonitrile oxide to 2-propen-1-ol (**1**) was performed utilizing (*R,R*)-DIPT as a chiral auxiliary to give the corresponding 2-isoxazoline (**2**) with excellent enantioselectivity.[4a] The optically active 2-isoxazoline (**2**) was also prepared by our original catalytic method in 92% ee (Scheme 1).[4b] The absolute configuration of the ob-

[#]Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

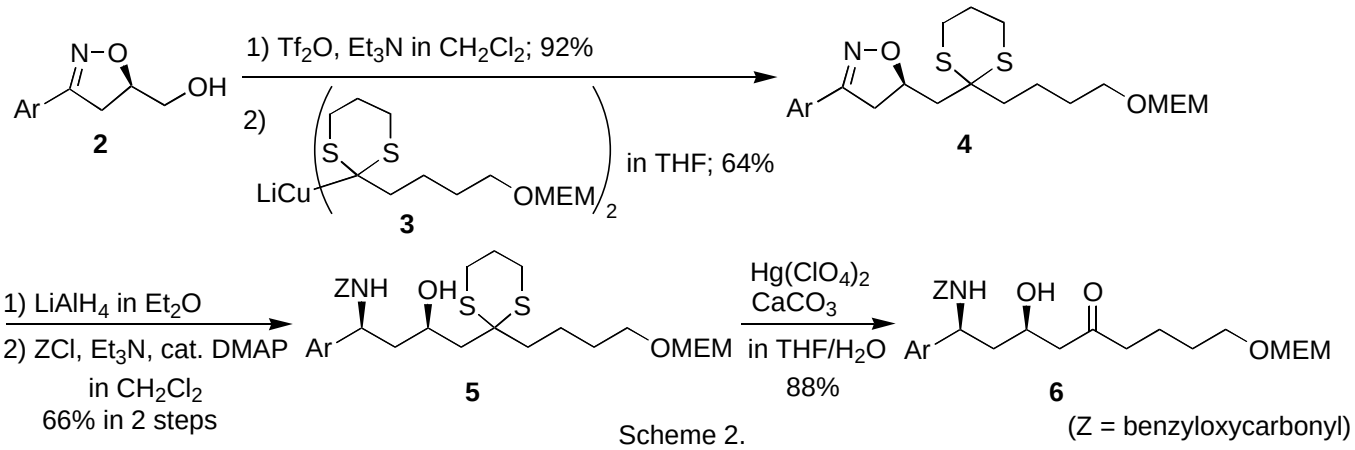


Scheme 1.

Stoichiometric Method: 1) Et_2Zn (1.0 eq.); 2) (*R,R*)-DIPT (1.0 eq.); 3) Et_2Zn (1.1 eq.); 4) ArC(Cl)=NOH (1.1 eq.); 83%, 92% ee.
Catalytic Method: 1) Et_2Zn (1.7 eq.); 2) (*R,R*)-DIPT (0.2 eq.); 3) ArC(Cl)=NOH (1.1 eq.), 1,4-dioxane (2.5 eq.); 85%, 92% ee.

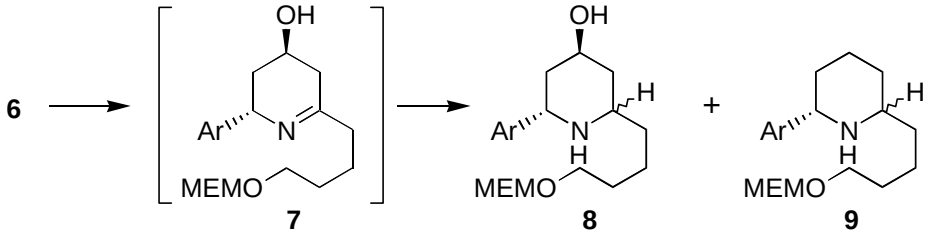
tained 2-isoxazoline (**2**) was determined to be *R*.[5,6]

The optically pure 2-isoxazoline (**2**), obtained by recrystallization from ethanol, was converted to its triflate,[7] followed by reaction with the cuprate (**3**)[8] to give the 2-isoxazoline (**4**).[6] At this stage, the whole carbon skeleton required for the synthesis of lasubine II was arranged. The reduction of the 2-isoxazoline (**4**) with $LiAlH_4$[9] followed by the protection of the resulting amino group with carbobenzoxy chloride (ZCl) afforded the *syn*-γ-amino alcohol derivative (**5**)[6] and its *anti*-isomer in 66% and 17% yields, respectively. The dithioacetal group of **5** was hydrolyzed by the treatment with mercury perchlorate in aqueous THF to give a β-hydroxy ketone (**6**)[6] (Scheme 2).



Scheme 2.

Next, the reductive deprotection of the amino group of **6** was examined (Scheme 3). The hydrogenolysis of Z group did not proceed on 10% Pd/C in EtOH. Even though 20% $Pd(OH)_2/C$ was used as a catalyst, Z group was inert under ordinary pressure of hydrogen (Entry1inTable1), but was deprotected under high pressure conditions. After the usual workup, the mixture of *cis*- and *trans*-2,6-disubstituted 4-piperidinols (**8**)[6] was obtained along with the deoxygenated 2,6-disubstituted piperidine (**9**) instead of the expected intermediate cyclic imine (**7**) (Entry 2). The deoxygenated product (**9**) might be derived from the dehydration of imine (**7**) or its tautomer enamine followed by the reduction. When reduction was carried out under acidic conditions in order to activate the imine for the reduction, the production of the deoxygenated piperidine (**9**) was rathe rincreased (Entry3) probably due to the acceleration of the dehydration step. To the contrary, the yield of desired piperidinol (**8**) was enhanced by the addition of amine. Among the amines examined, aqueous 25% NH_3 was found to be best to afford 2,6-*cis*-4-piperidinol [2,6-*cis*-**8**] in terms of not only the yield but also the diastereoselectivity (Entries 4-7). MEM group of 2,6-*cis*-**8** was hydrolyzed by the treatment with 3 M sulfuric acid to give **10**,[6] which was finally cyclized by Mitsunobu reaction to afford (-)-lasubine II ($[\alpha]_D^{25}$ -50°(c 0.37, MeOH); lit.,[2] $[\alpha]_D^{23}$ -34.7°(c 0.32, MeOH)) (Scheme 4). The spectra of ^1H NMR, IR, and MS of the synthetic lasubine II



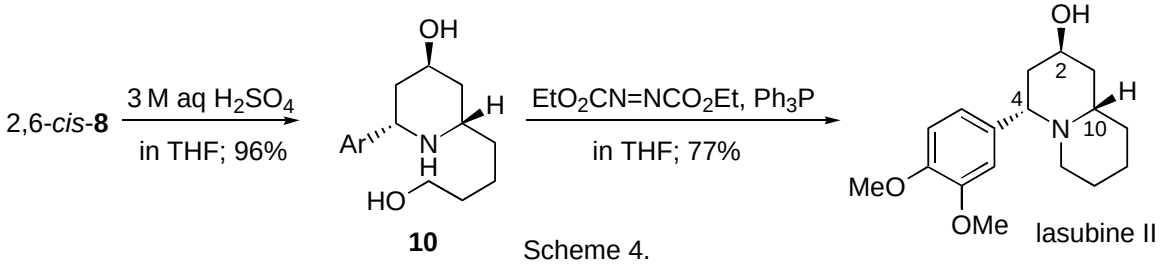
Scheme 3.

Table 1. Hydrogenolysis of **6** by the use of 20% $Pd(OH)_2/C$ catalyst[a)]

Entry	Pressure (atm)	additive[b)]	Time (h)	Yield (%) of **8**	*cis*/*trans*[c)]	Yield (%) of **9**
1	1	---	3.5	0	---	0
2	120	---	1.0	65	80/20	24
3	120	AcOH	1.0	39	89/11	47
4	120	Et_3N	1.0	79	78/22	19
5	120	$(i\text{-Pr})_2NEt$	1.0	78	78/22	17
6	120	piperidine	1.0	53	>99/<1	22
7	120	25% aq NH_3	1.0	85	>99/<1	trace

a) The reactions were carried out for 0.1 mmol of **6** in MeOH (5.5 mL) in the presence of 20% $Pd(OH)_2/C$ (50% w/w based on **6**) at rt. b) The ratio of additive/solvent was *ca.* 1/100 (v/v). c) Stereochemical relationship between the substituents at C-2 and C-6 of **8**.

were identical with those of the natural one.[2,10] The present work represents the first asymmetric synthesis of lasubine II from the optically active isoxazoline obtained by enantioselective 1,3-dipolar cycloaddition of nitrile oxide utilizing (*R*,*R*)-DIPT as a chiral auxiliary and established the absolute stereochemistry of (-)-lasubine II as 2*S*,4*S*,10*S*.[11]



Scheme 4.

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REFERENCES AND NOTES

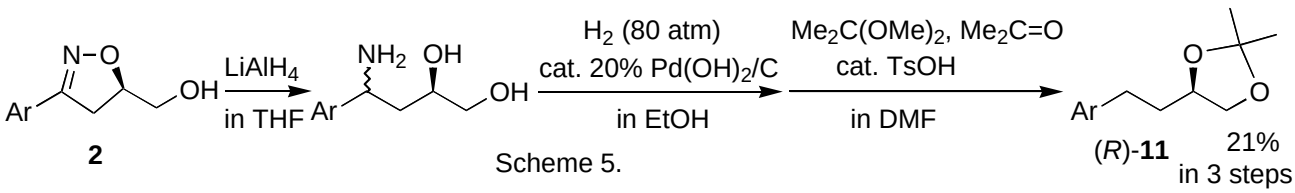
1 W. M. Golebiewski and J. T. Wróbel, "The Alkaloids," Vol. 18, ed. by R. G. A. Rodrigo, Academic Press, Inc., New York, 1981, Chap. 4.

2 K. Fuji, T. Yamada, E. Fujita, and H. Murata, *Chem. Pharm. Bull.*, 1978, **26**, 2515.

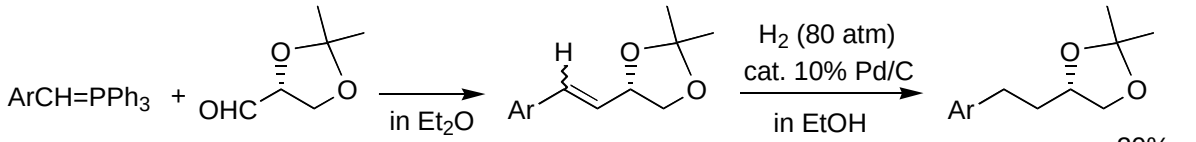
3 a) H. Iida, M. Tanaka, and C. Kibayashi, *J. Org. Chem.*, 1984, **49**, 1909; b) S. Takano and K. Shishido, *Chem. Pharm. Bull.*, 1984, **32**, 3892; c) R. W. Hoffmann and A. Endeshfelder, *Liebigs Ann. Chem.*, 1986, 1823; d) K. Narasaka, Y. Ukaji, and S. Yamazaki, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 525 ; e) J. D. Brown, M. A. Foley, and D. L. Comins, *J. Am. Chem. Soc*., 1988, **110**, 7445; f) R. A. Pilli, L. C. Dias, and A. O. Maldaner, *J. Org. Chem*., 1995, **60**, 717; g) V. Bardot, D. Gardette, Y. Gelas-Mialhe, J.-C. Gramain, and R. Remuson, *Heterocycles*, 1998, **48**, 507.

4 a) Y. Ukaji, K. Sada, and K. Inomata, *Chem. Lett*., 1993, 1847; b) M. Shimizu, Y. Ukaji, and K. Inomata, *Chem. Lett*., 1996, 455; c) Y. Yoshida, Y. Ukaji, S. Fujinami, and K. Inomata, *Chem. Lett.*, 1998, 1023.

5 The absolute configuration of the obtained 2-isoxazoline (**2**) was confirmed to be *R* by the chemical correlation between its derivative and the stereochemically unambiguous authentic compound; *i.e*., 2-isoxazoline (**2**) (100% ee) was transformed to (*R*)-**11** ($[\alpha]_D^{25}$ +4° (c 0.15, EtOH)) (Scheme 5), whose specific optical rotation was opposite to that of the authentic (*S*)-**11** ($[\alpha]_D^{25}$ -4° (c 0.24, EtOH)) derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (Scheme 6).



Scheme 5.

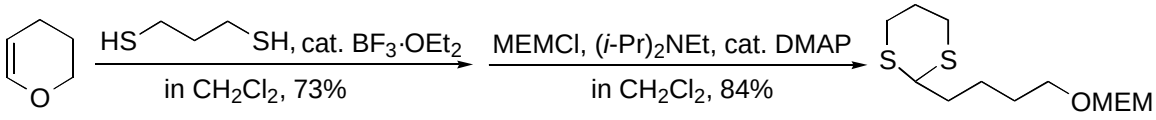


Scheme 6.

6 All new compounds were characterized by ^{1}H NMR spectra, IR spectra, and elemental analyses or MS spectra. $[\alpha]_D^{25}$ (MeOH): **2** (100% ee), -118° (c 0.11); **4**, -83° (c 0.56); **5**, -17° (c 0.51); **6**, -10° (c 0.25); 2,6-*cis*-**8**, -15° (c 0.31); **10**, -22° (c 0.07).

7 H. Kotsuki, *J. Syn. Org. Chem. Jpn*., 1999, **57**, 334.

8 1,3-Dithiane (**12**) was prepared as shown in Scheme 7. Cuprate (**3**) was prepared from 2 molar amounts of the dithianyl anion, derived from **12** and *n*-BuLi, and 1 molar amount of CuI in THF at -78 °C.[12]



Scheme 7.

9 V. Jäger and V. Buss, *Liebigs Ann. Chem*., 1980, 101; Y. Yamamoto, H. Kin, I. Suzuki, and N. Asao, *Tetrahedron Lett*., 1996, **37**, 1863.

10 K. Fuji and T. Yamada, private communication.

11 The absolute configuration of (-)-lasubine I was determined as 2*S*,4*S*,10*R*: D. L. Comins and D. H. LaMunyon, *J. Org. Chem*., 1992, **57**, 5807.

12 T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc*., 1972, **94**, 8641.