Natural Product Synthesis

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Total Synthesis of (+)-β-Erythroidine**

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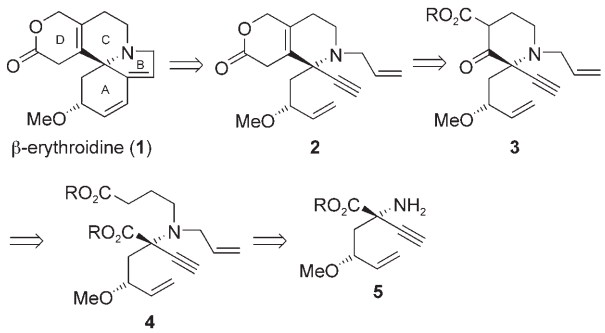
The *Erythrina* alkaloids[1] have received considerable attention over the past few decades owing to their intriguing biological activity[2] and characteristic polycondensed structures, which provide an opportunity to develop a new ring-forming methodology.[3] This family of alkaloids are classified into two groups according to their structural features: those whose D rings are aromatic, and those whose D rings contain an unsaturated lactone. Although a wide variety of methods have already been developed for the synthesis of the group containing an aromatic D ring,[1,3] the synthesis of their counterparts with non-aromatic D rings is limited to that of (±)-cocculolidine by Kitahara and co-workers.[3p] Herein, we describe the first total synthesis of (+)-β-erythroidine (**1**), a non-aromatic dienoid-type *Erythrina* alkaloid isolated from several species of the *Erythrina* genus together with α-erythroidine.[4,5]

Recently, we developed an efficient method[3j,6] for the construction of the erythrinan skeleton which relies on ring-closing metathesis[7,8] of a dienyne. On the basis of this methodology, we envisaged dienyne **2** as a precursor of **1** and postulated that this intermediate could be accessed from β-keto ester **3**, which would be available from **5** through **4** by N-alkylation followed by Dieckmann condensation (Scheme 1). In this synthetic plan, another key issue which must be addressed is the enantiocontrolled construction of ethynylated amino acid fragment **5**, which contains a quaternary center.



Scheme 1. Retrosynthetic analysis of β-erythroidine (**1**).

The required amino acid fragment was synthesized as **18** in enantiocontrolled manner by taking advantage of the method[9] that we previously developed for the construction of quaternary amino acids (Scheme 2). Thus, according to the procedure developed by Kotsuki et al.,[10] triflate **7**, which is readily available from 2,3-*O*-isopropylidene-D-threitol (**6**) through the corresponding monotosylate,[11] was treated with lithiated propargyl tetrahaydropyranyl ether to give tosylate **8**. Iodination of **8** followed by reductive cleavage of the resulting iodide gave alcohol **10**. Methylation of **10** and subsequent removal of the THP protecting group afforded propargyl alcohol **11**. Successive treatment[12] of **11** with $NaH_2Al(OCH_2CH_2OMe)_2$ and iodine allowed stereo- and regioselective formation of *Z*-iodoalkene **12**. Upon Sonogashira coupling[13] of **12** with trimethylsilylacetylene, the acetylene functionality was cleanly introduced and, after desilylation, *Z*-allylic alcohol **13** was obtained quantitatively. Although subsequent epoxidation of **13** proceeded with poor diastereoselectivity under Katsuki–Sharpless catalytic asym-

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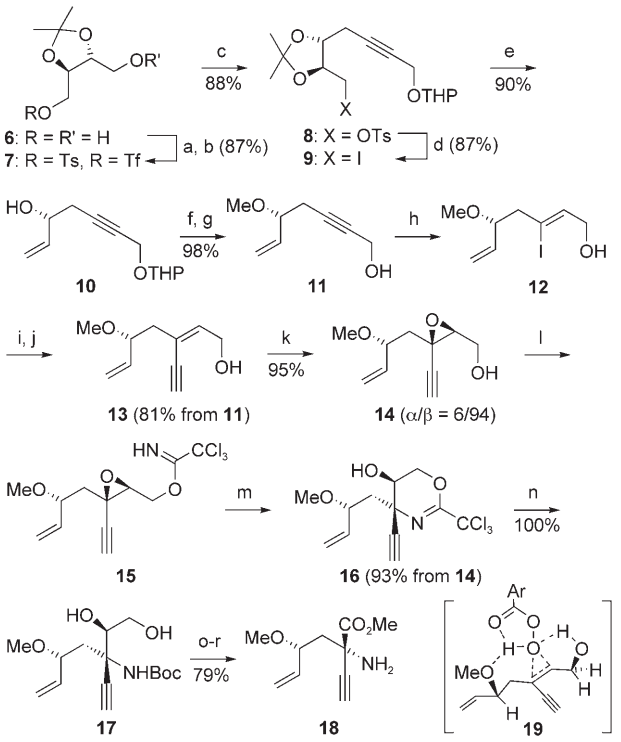
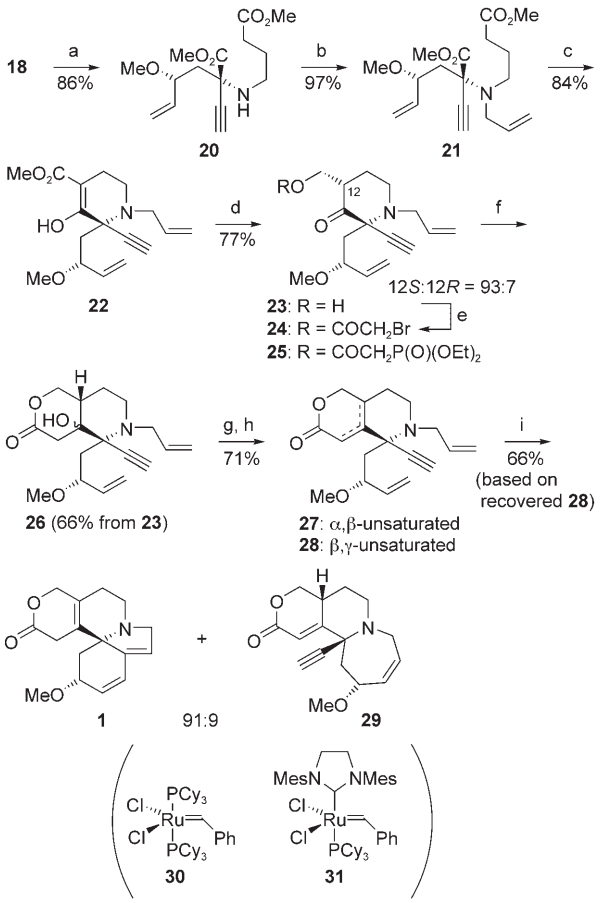


Scheme 2. Preparation of amino acid fragment **18**. Reagents and conditions: a) Ag_2O, TsCl, KI, CH_2Cl_2; b) Tf_2O, Et_3N, CH_2Cl_2, −15 °C; c) *n*BuLi, $CHCCH_2OTHP$, THF/DMPU, −20 °C; d) NaI, DMF, 70 °C; e) Zn, AcOH, EtOH, sonication; f) MeI, Ag_2O, Et_2O; g) PPTS, MeOH; h) $NaH_2Al(OCH_2CH_2OMe)_2$, Et_2O, 0 °C, then I_2; i) CHCTMS, [Pd-$(PPh_3)_2Cl_2$], CuI, iPr_2NH, THF, sonication; j) K_2CO_3, MeOH; k) *m*CPBA, $NaHCO_3$, CH_2Cl_2, −50 °C; l) Cl_3CCN, DBU, 4 Å M.S., CH_2Cl_2, 0 °C; m) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C; n) 1 M HCl, THF, then Boc_2O, $NaHCO_3$; o) $NaIO_4$, THF/H_2O; p) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O; q) CH_2N_2, MeOH; r) TFA, CH_2Cl_2. Ts = *p*-toluenesulfonyl; Tf = trifluoromethanesulfonyl; THP = tetrahydropyranyl; DMPU = *N,N′*-dimethyl-*N,N′*-propylene urea; DMF = *N,N*-dimethylformamide; PPTS = pyridinium *p*-toluenesulfonate; TMS = trimethylsilyl; *m*CPBA = *m*-chloroperoxybenzoic acid; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene; Boc = *tert*-butoxycarbonyl; TFA = trifluoroacetic acid.

metric epoxidation conditions,[14] we were pleased to find that the epoxidation using *m*CPBA occurred with excellent diastereoselectivity to give epoxide **14** as an inseparable mixture of α and β diastereoisomers (6:94 ratio, respectively). The observed high diastereoselectivity can be explained through transition state **19** where the approach of *m*CPBA is restricted to the β-face by hydrogen bonding (Scheme 2).[15]

At this stage, stereoselective introduction of a nitrogen atom at the quaternary center was achieved by Lewis acid promoted cyclization of an epoxy-trichloroacetimidate.[9] Thus, the epoxy alcohol **14** was converted into imidate **15** by reaction with trichloroacetonitrile in the presence of DBU. Upon treatment of **15** with 0.5 equivalents of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −20 °C, the cyclization took place selectively at the quaternary center of the epoxide with complete inversion of the stereochemistry to produce dihydrooxazine **16**. The stereochemical structure of **16** was unambiguously confirmed by X-ray analysis.[16] Acidic hydrolysis of **16** followed by *tert*-butoxycarbonylation afforded diol **17** quantitatively, which was successfully converted into the required ethynylated amino acid derivative **18** by a four-step sequence involving oxidation with $NaIO_4$, Pinnick oxidation,[17] esterification, and removal of the Boc protecting group.

Construction of the C,D ring system began with reductive alkylation of **18** (Scheme 3). Thus, reaction of **18** with methyl



Scheme 3. Completion of the total synthesis of (+)-β-erythroidine (**1**). Reagents and conditions: a) $MeO_2C(CH_2)_2CHO$, $NaBH(OAc)_3$, 4 Å M.S., THF, 0 °C; b) allyl bromide, K_2CO_3, DMF; c) NaH, MeOH, toluene, reflux; d) NaH, THF, 0 °C, then AlH_3, −10 °C; e) $BrCH_2COCl$, pyridine, CH_2Cl_2, 0 °C; f) SmI_2, THF; g) $SOCl_2$, pyridine; h) 10% NaOH, dioxane, reflux, then acidified with conc. HCl; i) **30** (0.1 equiv), CH_2Cl_2. Cy = cyclohexyl; Mes = mesityl.

3-formylpropanoate in the presence of $NaBH(OAc)_3$[18] and molecular sieves gave **20**, which was then allylated to afford amine **21** in good yield. Upon treatment of **21** with NaOMe in boiling toluene, Dieckmann condensation cleanly occurred to give condensation product **22**, which adopts almost exclusively the enol form. After conversion of **22** into the corresponding sodium enolate, its reduction in situ with AlH_3[19] gave a mixture (93:7) of aldol **23** and its C12 epimer, the stereochemistry of which was determined by NOE experiments (Figure 1).

To construct the D ring by an intramolecular Horner–Emmons reaction,[20] we attempted to prepare **25** from **23** by using either diethyl phosphonoacetic acid or its chloride under various conditions. However, this acylation proved

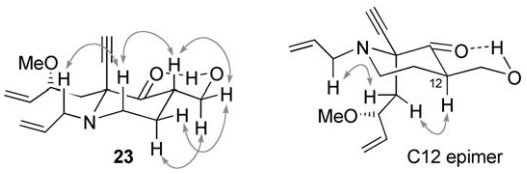


Figure 1. Significant NOE observed in the NOESY NMR spectra of aldol **23** and its C12 epimer.

troublesome because dehydration always took place predominantly. Therefore, we next investigated the approach based on an SmI_2-mediated intramolecular Reformatsky reaction.[21] In this case, acylation of **23** with bromoacetyl chloride in the presence of pyridine took place successfully to give bromoacetate **24** together with a small amount of the corresponding dehydrated product, although **24** was chromatographically unstable. Without purification, treatment of **24** with SmI_2 in THF at room temperature led to cyclization to give lactone **26** as a mixture of epimers (60:40). Treatment of **26** with thionyl chloride in pyridine caused dehydration to give an inseparable mixture of α,β-unsaturated lactone **27** and β,γ-unsaturated lactone **28** (74:26). Gratifyingly, in this particular case, saponification followed by acidification allowed highly selective production of the β,γ-lactone to give a mixture of **27** and **28** in a ratio of 6:94. Finally, treatment of this isomeric mixture with 0.1 equivalents of Grubbs' first-generation catalyst **30** in CH_2Cl_2 at room temperature for 6.5 h cleanly furnished (+)-β-erythroidine (**1**; $[\alpha]_D^{21} = +50.0°$ ($c = 0.21$, EtOH)),[22] in 42% yield together with **29** (4%), although an appreciable amount of unconverted **28** (31%) was recovered. In this particular case, Grubbs' second-generation catalyst **31** turned out to be less effective and gave **1** in less than 30% yield. The spectral data of **1** thus obtained show good agreement with those reported[4b,c] for the natural specimen.

In addition, we investigated the ring-closing metathesis of **20, 22, 26**, and **36** using catalysts **30** and **31** (Scheme 4). These results revealed that the mode of metathesis largely depends upon the structure of the substrate. Importantly, neither **32** nor **37** could be converted into **1** because of the extreme instability arising from their tetrahydroindole structures under basic conditions.

In conclusion, we have demosntrated the first total synthesis of (+)-β-erythroidine, a non-aromatic *Erythrina* alkaloid, in naturally occurring form by employing Lewis acid promoted cyclization of the epoxy-trichloroacetimidate and tandem ring-closing metathesis of the dienyne as key steps. The present work opens a new avenue for the enantioselective synthesis of *Erythrina* alkaloids.

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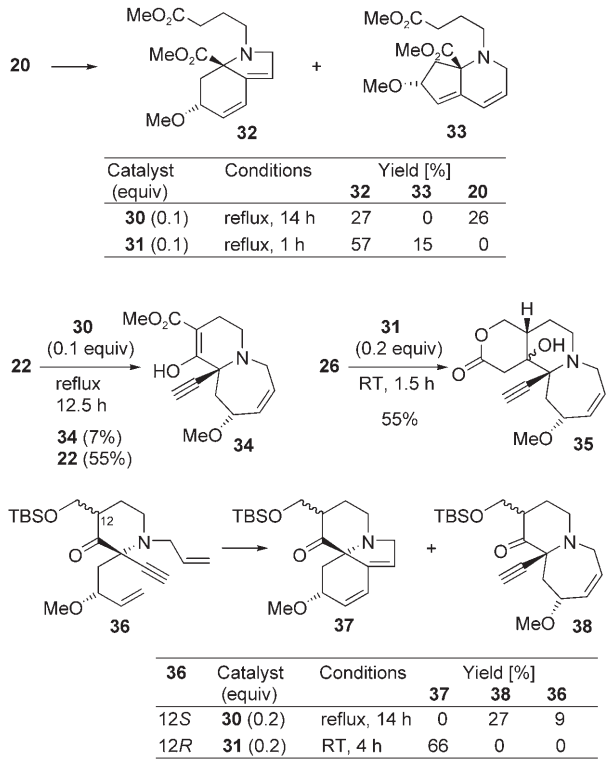

Catalyst (equiv)	Conditions	Yield [%] 32	33	20
30 (0.1)	reflux, 14 h	27	0	26
31 (0.1)	reflux, 1 h	57	15	0

36	Catalyst (equiv)	Conditions	Yield [%] 37	38	36
12*S*	**30** (0.2)	reflux, 14 h	0	27	9
12*R*	**31** (0.2)	RT, 4 h	66	0	0

Scheme 4. Ring-closing metathesis of dienynes. The reactions were carried out using Grubbs' catalysts **30** or **31** (0.1 or 0.2 equiv) in CH_2Cl_2 (0.05 M).

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