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Total synthesis of (±)-erythravine based on ring closing dienyne metathesis☆

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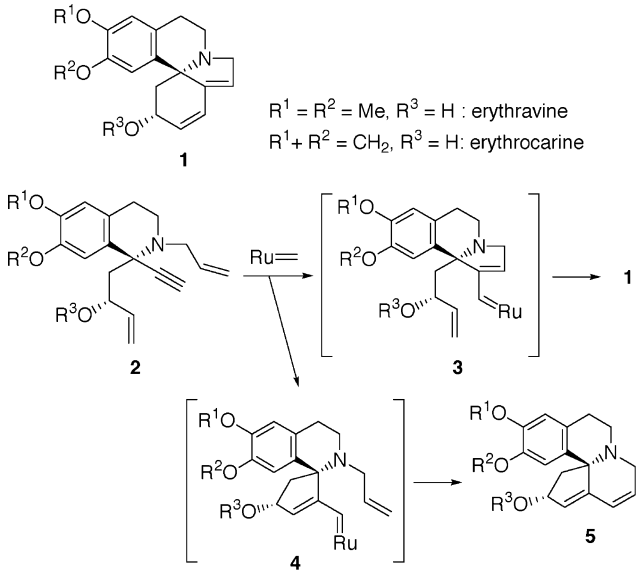
Abstract—The first total synthesis of (±)-erythravine was achieved in thirteen steps from 3,4-dimethoxyphenethylamine using ring closing dienyne metathesis as the key step.

Dienoid-type erythrinan alkaloids **1** comprise a major group of the Erythrina family of natural products. These compounds have received considerable attention over the past few decades due to their various intriguing biological activity and unique erythrinane skeleton.[1] Although a wide variety of methods have already been developed for the synthesis of this family of alkaloids,[1,2] we were interested in a new approach which relies on ring closing metathesis (RCM) of dienyne **2** on the basis of the Grubbs' protocol (Scheme 1).[3,4]

We postulated that the initial RCM reaction would lead to preferential formation of complex **3** producing **1**, rather than **4** giving **5**, due to the difference in the steric hindrance of two olefinic double bonds. Recently, Mori et al. reported the synthesis of (±)-erythrocarine based on the same strategy.[5] Their report prompted us to disclose herein the first total synthesis[6] of (±)-erythravine which we have independently achieved.[7]

3,4-Dimethoxyphenethylamine (**6**) was first converted to compound **7**, which was then reacted with diethyl propiolate in boiling trifluoroacetic acid to give diester **9** via Pictet–Spengler type reaction[8] of **8**. Reduction of **9** with $LiAlH_4$ followed by selective silylation gave TBDPS–ether **10**. Swern oxidation of **10** and reaction of the resulting aldehyde with Bestmann's reagent[9] afforded enyne **11**. Upon sequential desilylation, Swern oxidation, and Grignard reaction using vinylmagnesium bromide, **11** yielded dienyne **12** as a 1:1 epimeric mixture. For the next RCM reaction, acetate **13** and TES–ether **14** were also prepared each as a 1:1 epimeric mixture from **12**.

The crucial tandem RCM process was examined using Grubbs' catalysts **15**[10] and **16**[11] under various conditions. When alcohol **12** was treated with 10–20 mol% of either Grubbs' catalyst in CH_2Cl_2 or toluene, no reaction occurred at room temperature and only partial decomposition of **12** was observed at elevated temperature. On the other hand, upon treatment of acetate **13**



Scheme 1.

Keywords: ring closing dienyne metathesis; erythrina alkaloid; erythravine; total synthesis.

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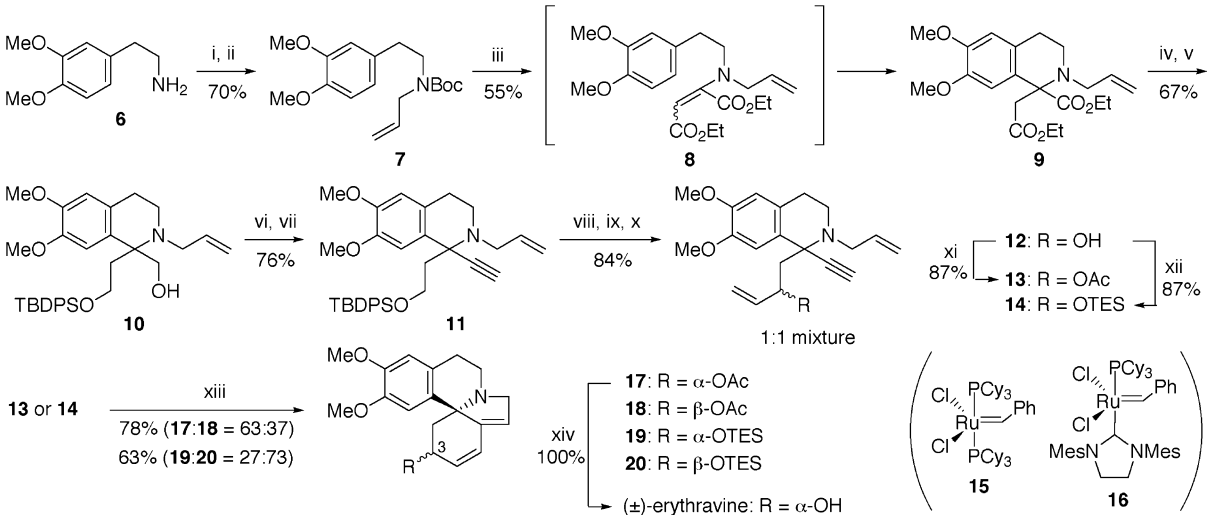

Scheme 2. *Reagents and conditions*: (i) Boc_2O, CH_2Cl_2; (ii) NaH, CH_2=$CHCH_2Br$, THF, reflux; (iii) $EtO_2CC{\equiv}CCO_2Et$, CF_3CO_2H, reflux; (iv) $LiAlH_4$, THF; (v) *t*-$BuPh_2SiCl$, Et_3N–DMAP (cat.), CH_2Cl_2; (vi) $(COCl)_2$, DMSO, CH_2Cl_2 at −78°C then Et_3N, 0°C; (vii) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH; (viii) $(n\text{-}Bu)_4NF$, THF; (ix) $(COCl)_2$, DMSO, CH_2Cl_2, at −78°C then Et_3N, 0°C; (x) CH_2=$CHMgBr$, THF; (xi) Ac_2O, Et_3N–DMAP (cat.), CH_2Cl_2; (xii) Et_3SiCl, Et_3N–DMAP (cat.), CH_2Cl_2; (xiii) **15** (10 mol%), CH_2Cl_2 (0.04 M), reflux; (xiv) K_2CO_3, MeOH.

with 10 mol% of **15** in CH_2Cl_2 (0.04 M) at reflux, the reaction completed after 8 h and tetracyclic compounds **17** and **18** were obtained in a ratio of 63:37 in 78% yield. In this particular case, the reaction turned out to be very sluggish at room temperature, possibly because of the coordination of the free tertiary amine to the ruthenium catalyst.[12,13] After separation of **17** and **18**, H–H COSY and NOE experiments allowed us to determine their stereostructures unambiguously. Similarly, reaction of **14** with **15** gave **19** and **20** in a ratio of 27:73 in 63% yield. We were pleased to find that the tetetracyclic compounds corresponding to **5** were not produced at all in these reactions. It is therefore apparent that the RCM reactions of **13** and **14** initially occurred between the *N*-allyl group and the acetylene (Scheme 2).

Interestingly, in each reaction, the two epimeric products were not equally produced even though a 1:1 epimeric mixture was used as the starting material. In addition, in the reaction of **13**, α-isomer **17** was preferentially formed, while β-isomer **20** was favored in the reaction of **14**. These results may have arisen from the difference between the epimers in the rate of cyclization or the rate of decomposition. The steric and electronic nature of the C3-substituent is thought to affect these rates. Finally, treatment of **17** with K_2CO_3 in methanol furnished (±)-erythravine. The synthetic substance exhibited spectral properties[14] in accord with those reported[15] for natural erythravine. (±)-3-Epierythravine was also synthesized by methanolysis of **18**, quantitatively.

In conclusion, we have achieved a concise thirteen-step synthesis of (±)-erythravine from 3,4-dimethoxyphenethylamine based on tandem RCM reaction of a dienyne for the first time. The synthetic method used is of general value in approaches to related erythrina alkaloids.

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14. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.62 (s, 1H), 6.55 (dd, $J=2.0$, 10.0 Hz, 1H), 5.97 (d, $J=10.0$ Hz, 1H), 5.75 (brs, 1H), 4.50–4.49 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.69 (dd, $J=3.0$, 14.5 Hz, 1H), 3.57 (d, $J=14.5$ Hz, 1H), 3.51–3.46 (m, 1H), 3.02–2.92 (m, 2H), 2.65–2.59 (m, 1H), 2.56 (dd, $J=5.5$, 11.5 Hz, 1H), 1.82 (dd, $J=10.5$, 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 147.3, 141.8, 134.3, 130.4, 126.0, 124.9, 122.7, 111.5, 109.2, 67.8, 67.3, 56.5, 55.8, 55.8, 45.3, 43.5, 23.8; HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1517, found: 299.1521.
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