Available online at www.sciencedirect.com
ScienceDirect
Journal of Organometallic Chemistry 691 (2006) 5466–5475
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Total synthesis of (±)-erythrocarine using dienyne metathesis

Kazuya Shimizu [a], Masanori Takimoto [c], Yoshihiro Sato [a], Miwako Mori [b,*]

[a] Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan
[b] Health Sciences University of Hokkaido, Ishikari-tobetsu, Hokkaido 061-0293, Japan
[c] Organometallic Chemistry Laboratory, RIKEN, Hirosawa 2-1, Wako, Saitama 351-0198, Japan

Received 8 July 2006; received in revised form 28 July 2006; accepted 5 August 2006
Available online 17 August 2006

Abstract

Total Synthesis of (±)-erythrocarine was achieved using ruthenium-catalyzed dienyne metathesis as a key step. A tetrahydroisoquinoline skeleton having tetrasubstituted carbon center was constructed using our method, that is, carbon dioxide and an alkyl group were introduced onto an alkyne having a heteroatom in a tether using the nickel complex to produce α,β-unsaturated carboxylic acid and then isoquinoline skeleton was constructed by Michael reaction of the tethered nitrogen to the resultant α,β-unsaturated ester.

Keywords: Erythrocarine; Carboxylation; CO_2; Dienyne metathesis; Enyne metathesis; Alkylative carboxylation

1. Introduction

Erythrina alkaloids [1], which are widely distributed family, are structurally interesting and biologically active natural products [2]. The structural features of these alkaloids are that they possess a tetracyclic framework containing tetrahydroisoquinoline skeleton and have tetrasubstituted carbon center at the benzylic position of tetrahydroisoquinoline ring. The typical erythrina alkaloids are shown in Fig. 1. For the synthesis of erythrina alkaloids, how to construct this tetracyclic framework containing tetrasubstituted carbon center is important [3].

Carbon dioxide is a useful carbon 1-unit resource for synthetic organic chemistry. The Grignard reaction using carbon dioxide is an important method for conversion of an aryl or alkyl halide into the corresponding carboxylic acid. Transition metal-mediated or -catalyzed carboxylation is a promising reaction for utilization of carbon dioxide because the carbon–oxygen double bond of carbon dioxide coordinates to the transition metal to produce oxametalacyclopropane, which would react with the multiple bonds to form the new carbon-carbon bond. Recent reports of nickel-mediated [4] and -catalyzed [5] carboxylation reactions to alkyne are very interesting because the reaction proceeds under mild conditions. During the course of our study of nickel-mediated or catalyzed carboxylation to diene [6], allene [7], and alkyne [8], we developed the novel synthetic method of heterocycles [8b] using this method. Our procedure is shown in Scheme 1. If alkyne **1** having a hetero-atom in a tether is treated with an equimolar amount of Ni(0) and DBU under an atmosphere of carbon dioxide, oxanickelacycle **4** is formed. Transmetalation of an alkyl group of a zinc reagent to the nickel metal followed by reductive elimination gives trisubstituted alkene **6**, which was treated with CH_2N_2 after hydrolysis to give α,β-unsaturated ester **2**. Michael addition of a hetero-atom in a tether of **2** to an α,β-unsaturated ester gives heterocycle **3**. Using this method, we could synthesize various heterocycles **3a-d** in high yields, respectively.

The remarkable feature of this procedure is that the nitrogen or oxygen heterocycle having tetrasubstituted carbon center at the benzylic position can be synthesized. Thus, we decided to synthesize erythrocarine, which is one of the erythrina alkaloids and possesses the tetrasubstituted carbon center at the benzylic position. Erythrocarine

* Corresponding author. Fax: +81 11 706 4982.
E-mail address: mori@pharm.hokudai.ac.jp (M. Mori).

0022-328X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2006.08.013

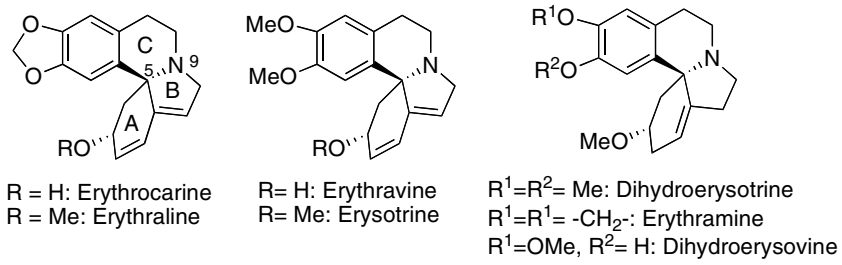
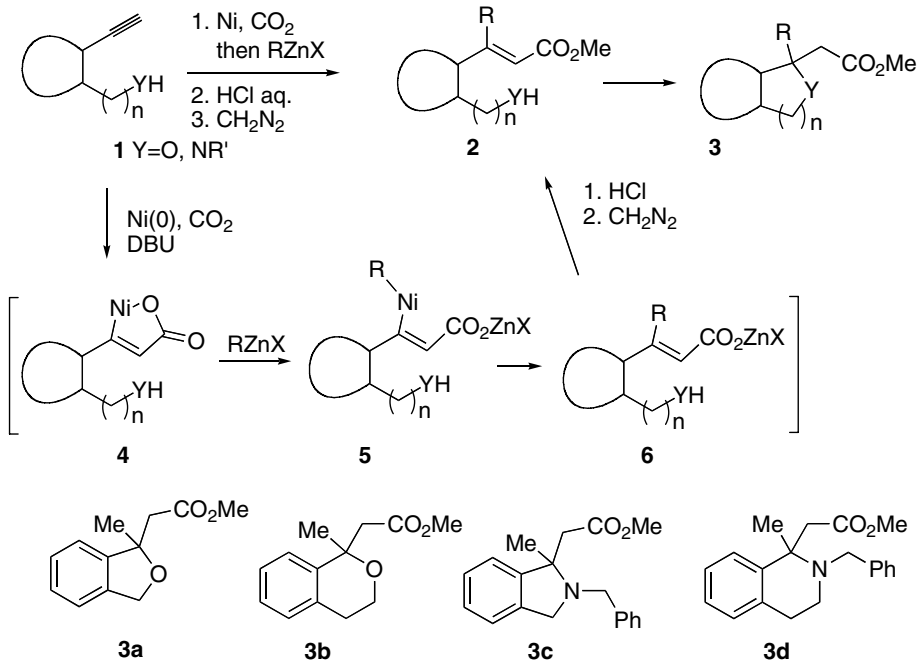
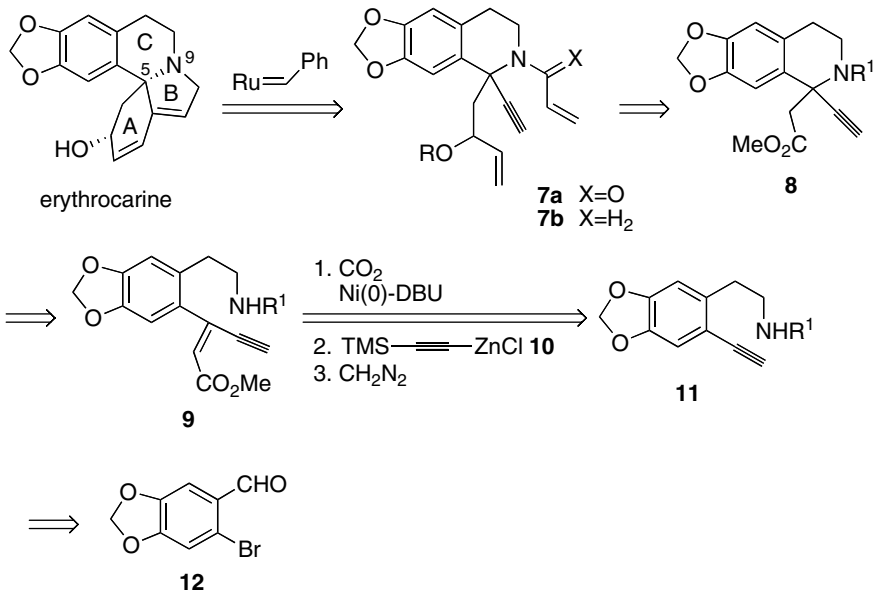


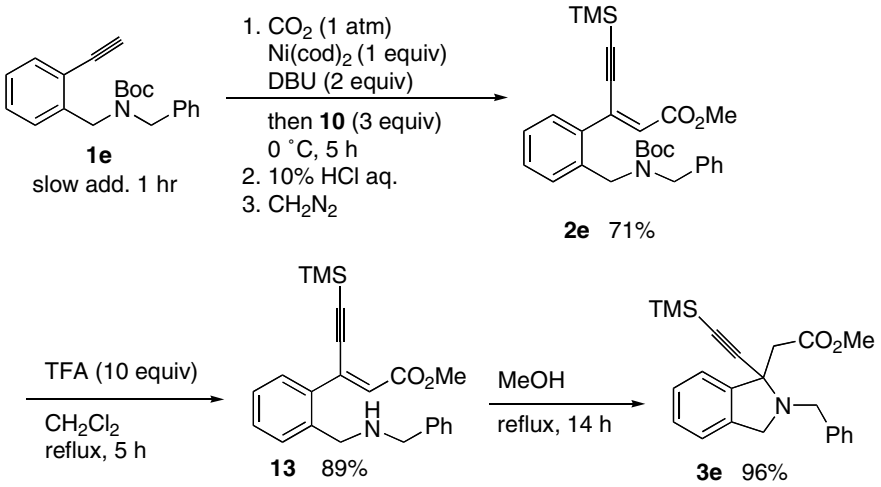
Fig. 1. Typical erythrina alkaloids.



Scheme 1. Novel synthesis of heterocycles using nickel-mediated alkylative carboxylation followed by Michael reaction.



Scheme 2. Retrosynthetic analysis of erythrocarine.



Scheme 3. Model study for construction of tetrasubstituted carbon center.

was isolated by Jackson in 1985 [9] and was not synthesized yet. Our retrosynthetic analysis is shown in Scheme 2. A framework of erythrocarine would be constructed from compound **7** having a dienyne moiety on isoquinoline ring using dienyne metathesis [10]. Compound **7** would be synthesized from **8**, whose tetrasubstituted carbon center would be constructed from alkyne **11** using our nickel-mediated alkylative carboxylation followed by Michael reaction. The starting alkyne **11** would be synthesized from commercially available *o*-bromopiperonal (**12**).

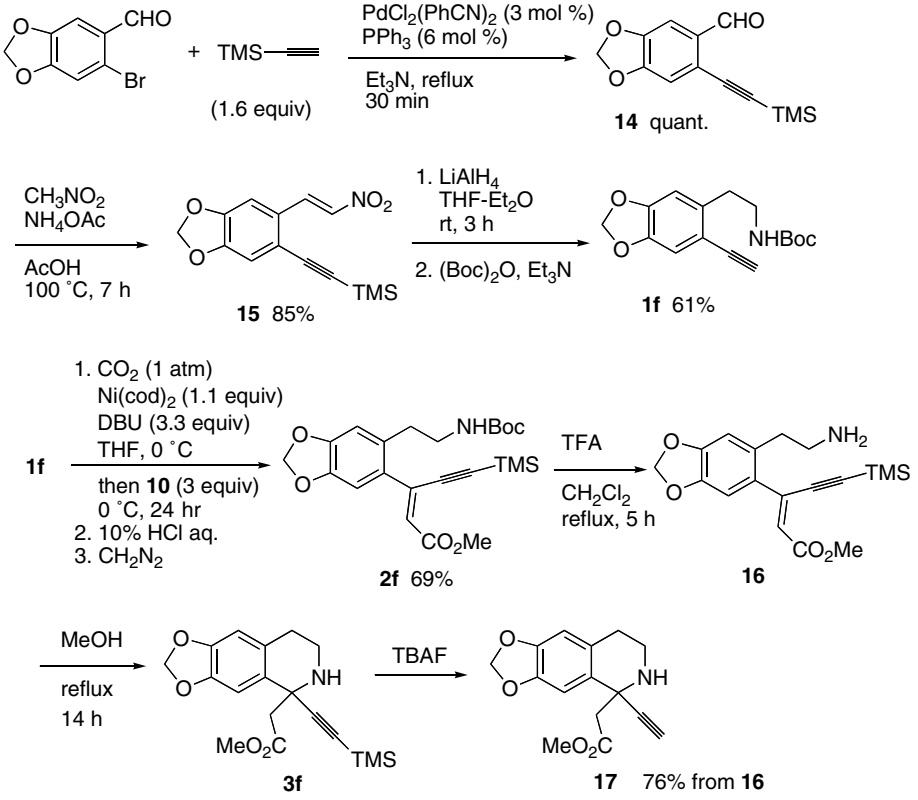
Initially, it was examined using a model compound whether a heterocycle having an alkynyl group at the benzylic position can be synthesized. To a THF solution of an equimolar amount of $Ni(cod)_2$ and 2 equivalents of DBU was added alkyne **1e** slowly under an atmosphere of carbon dioxide at 0 °C for 1 h. To this solution were added 3 equivalents of zinc reagent **10** and the whole solution was stirred at the same temperature for 5 h. The reaction mixture was hydrolyzed and the crude product was treated with CH_2N_2 to give α,β-unsaturated ester **2e** in 71% yield. Removal of the protecting group on nitrogen afforded secondary amine **13** in 89% yield, and a MeOH solution of **13** was refluxed for 14 h to give isoindoline **3e** in 96% yield (see Scheme 3).

Since the result indicates that the alkynyl group could be introduced at the benzylic position of isoindoline **3e**, synthesis of erythrocarine was started. Reaction of *o*-bromopiperonal with silylacetylene using $PdCl_2(PhCN)_2$ and PPh_3 smoothly proceeded to give **14** in quantitative yield. Condensation of aldehyde **14** with CH_3NO_2 afforded nitro compound **15** in 85% yield, which was reduced with $LiAlH_4$ followed by protection of the resultant primary amine to give **1f** in 61% yield. Introduction of a carboxyl group and an alkynyl group on the alkyne of compound **1f** was carried out in a similar manner for the synthesis of **2e** to give α,β-unsaturated ester **2f** in 69% yield. Deprotection of **2f** with TFA followed by Michael addition afforded isoquinoline derivative **3f**, whose silyl group was removed with TBAF to afford desired tetrahydroisoquinoline derivative **17** having tetrasubstituted carbon center at the benzylic position in 62% yield based on **16** (see Scheme 4).

Since it is known that the nitrogen of an amino group coordinates to the ruthenium catalyst and the catalytic activity of the ruthenium catalyst decreases [11], metathesis of dienyne **7a** was examined. Compound **17** was converted into **18** and olefin metathesis of **18** was first examined. When a CH_2Cl_2 solution of compound **18** and the first generation ruthenium carbene complex **i** [12] was stirred at room temperature under argon, none of the product was obtained and starting material **18** was recovered unchanged in 93% yield. However, the use of the second-generation ruthenium catalyst **ii** [13] gave a good result and desired compound **19** was obtained in 74% yield. Conversion of **19** into compound **20** having an alkene moiety was examined. The various attempts were made, for example, treatment of **19** with DIBAL, $LiAlH_4$, or vinyl lithium, or hydrolysis of **19** with NaOH and then treatment with vinyl lithium, but no desired compound was obtained. Presumably, the pyrrolidone moiety in compound **19** would react with these reagents (see Fig. 2; Scheme 5; Table 1).

Thus, dienyne metathesis of **7b** having the tertiary amine was examined. Treatment of **17** with allyl bromide gave **21**, which was reduced with $LiAlH_4$ to afford alcohol **22**. Swern oxidation followed by treatment with vinyl magnesium bromide gave a mixture of alcohol **7ba** and **7bb**, which was acetylated to give a mixture of diastereomers **23a** and **23b** (see Scheme 6).

Ruthenium catalyzed dienyne metathesis of **23** was carried out. When a CH_2Cl_2 solution of a mixture of dienyne **23a** and **23b** and the first generation ruthenium catalyst **i** was refluxed for 15 h, desired compound was not obtained and starting material **23** was recovered in 69% yield. Use of the second-generation ruthenium catalyst **ii** also did not give desired product. Since dienyne **23** has a tertiary amino group, it should coordinate to the ruthenium catalyst. Therefore, a mixture of **23** was converted into **23 · HCl**, which was treated with ruthenium catalyst **i** at room temperature in CH_2Cl_2 for 18 h [11]. We are pleased to find



Scheme 4. Synthesis of substrate.

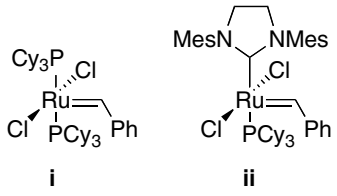


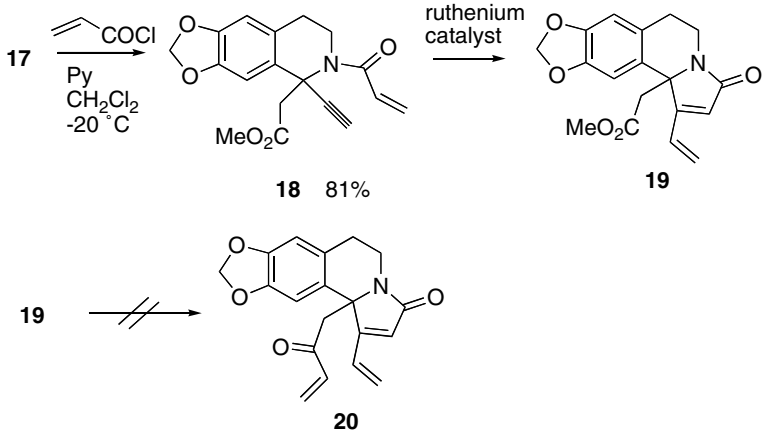
Fig. 2. Ruthenium catalyst.

Table 1
Olefin metathesis of **18**

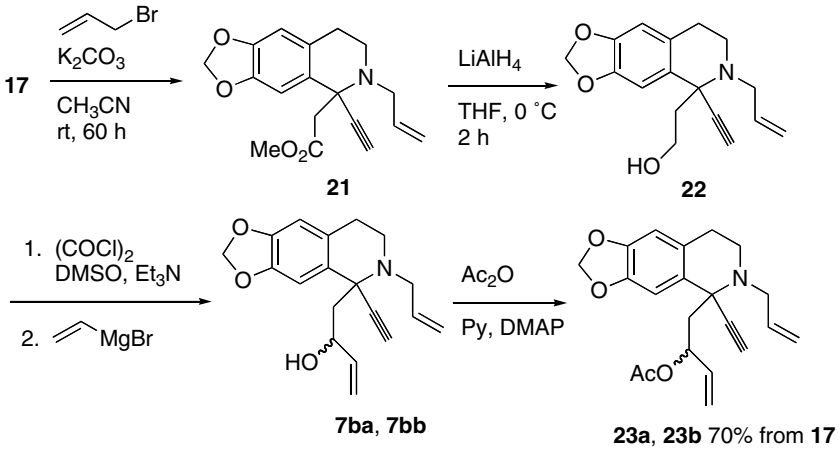
Entry	Catalyst	Conditions	Yield of **19** (%)
1	**i** (10 mol%)	CH_2Cl_2, rt, 1.5 h	0[a]
2	**ii** (8 mol%)	Toluene, 80 °C, 1 h	74

[a] **18** was recovered in 93% yield.

that a mixture of desired tetracyclic compounds **24a** and **24b** was obtained in a ratio of 1 to 1 in quantitative yield. Compound **25** was not formed in this reaction. To determine the stereochemistry of them, they were separated and each NOE experiment was carried out. An NOE of compound **24a**, which was found at the less polar position



Scheme 5. Examination of olefin metathesis.



Scheme 6. Synthesis of isoquinoline having triene.

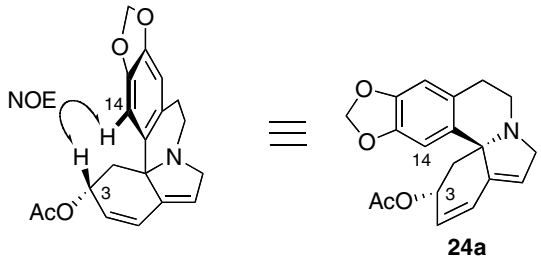


Fig. 3. Determination of the stereochemistry.

Table 2
Dienyene metathesis

Entry	Ru	Conditions	Product (%)	**23**
1	**i**	Reflux, 15 h	–	69
2	**ii**	Reflux, 1.5 h	–	42
3[a]	**i**	rt, 18 h	quant. (1:1)	–

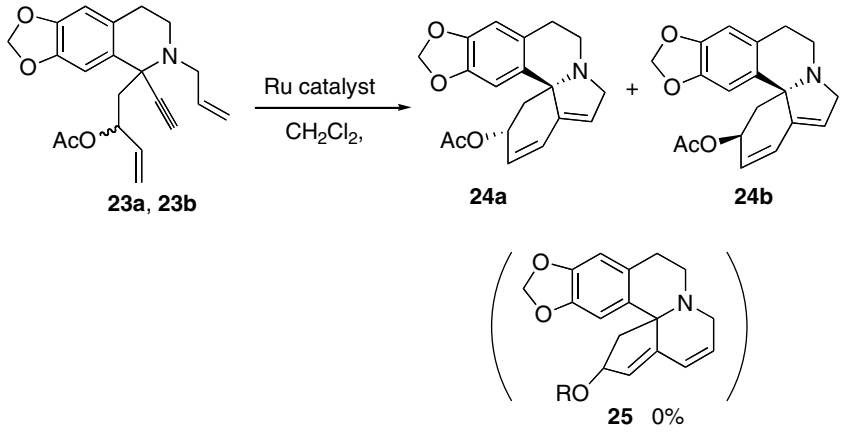
[a] **23 · HCl** was used as a substrate.

on TLC, was shown between the protons at the C3 position and at the C14 position on an aromatic ring. It means that an acetoxy group of **24a** is placed at the α-position of the cyclohexene ring and this is a same stereochemistry with that of erythrocarine (see Fig. 3; Scheme 7; Table 2).

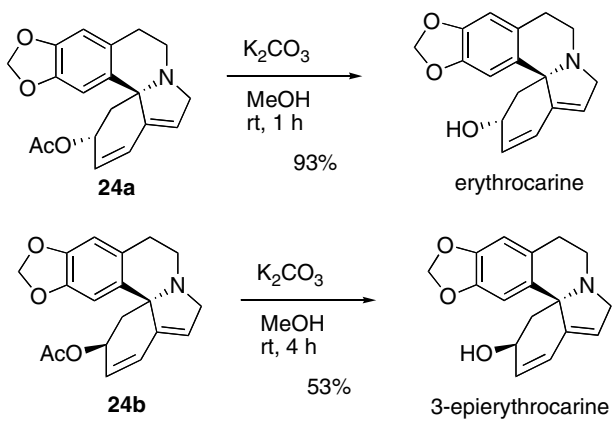
Compound **24a** was treated with K_2CO_3 in MeOH to give erythrocarine, whose spectral data agreed with those reported in the literature [9]. The other isomer **24b** was treated in a similar manner to give 3-epierythrocarine. Thus, the total synthesis of (±)-erythrocarine was achieved [14] (see Scheme 8).

The possible reaction course for formation of **24** was shown in Scheme 9. The fact that only compounds **24a** and **24b** were formed means that the ruthenium catalyst would react at first with the alkene at the allylic position of nitrogen to form ruthenium carbene complex **26**. This reacts with an alkyne part to produce complex **27**. Ring opening of ruthenacyclobutene of **27** gives ruthenium carbene **28**, which reacts with an alkene to give ruthenacyclobutane **29**. Ring opening of this gives desired tetracyclic compound **24 · HCl**.

A mixture of **7b** was separated into two isomers **7ba** and **7bb**. Compound **7ba** was converted to **23a · HCl**, which was treated with ruthenium catalyst **ii** in CH_2Cl_2 at room temperature for 20 h to afford **24a** in 62% yield along with starting material **23a** in 30% yield. To isomerize the hydroxyl group of **7bb** into **7ba** [15], Mitsunobu



Scheme 7. Dienyne metathesis.



Scheme 8. Synthesis of epierythrocarine.

reaction of **7bb** was carried out using DIPAD (diisopropylazodicarboxylate) and PPh_3 in the presence of AcOH, but starting material **7bb** was recovered in 74% yield along with acetylated compound **23b** in 21% yield. The reaction was carried out under various conditions but only starting material was recovered. Although the reason that conversion of **7bb** into **7ba** did not proceed is not clear, a hydrogen bond between the hydroxyl group and the amino nitrogen may prevent the reaction. Thus, Swern oxidation of **7bb** followed by treatment with $NaBH_4$ was carried out. As the result, compounds **7ba** and **7bb** were obtained in 44% yield and in a ratio of 1 to 0.8. Although the yield was not good, conversion of **7bb** to desired **7ba** was achieved (see Scheme 10).

In conclusion, erythrocarine was synthesized using dienyne metathesis as a key step and an overall yield is 9% via 15 steps from commercially available *o*-bromopiperonal. The tetrasubstituted carbon center at the benzylic position of tetrahydroisoquinoline skeleton was constructed using nickel mediated alkylative carboxylation followed by Michael reaction developed by our group.

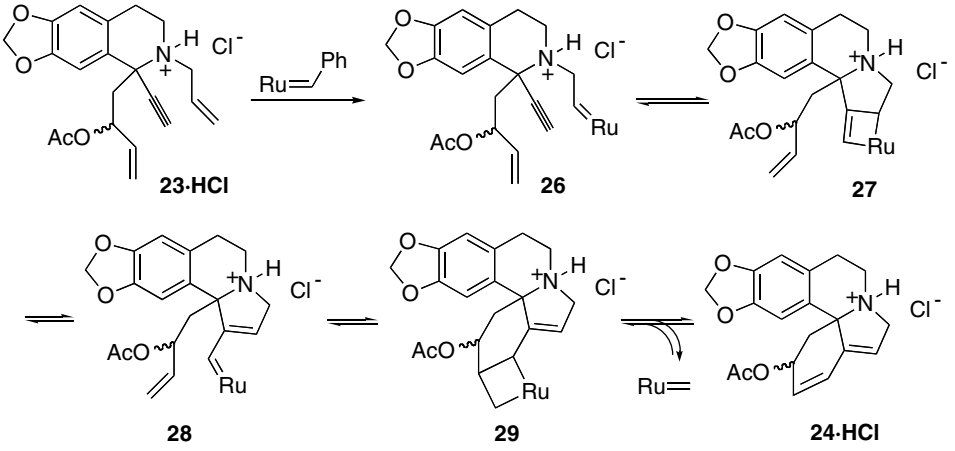
2. Experimental section

2.1. General information

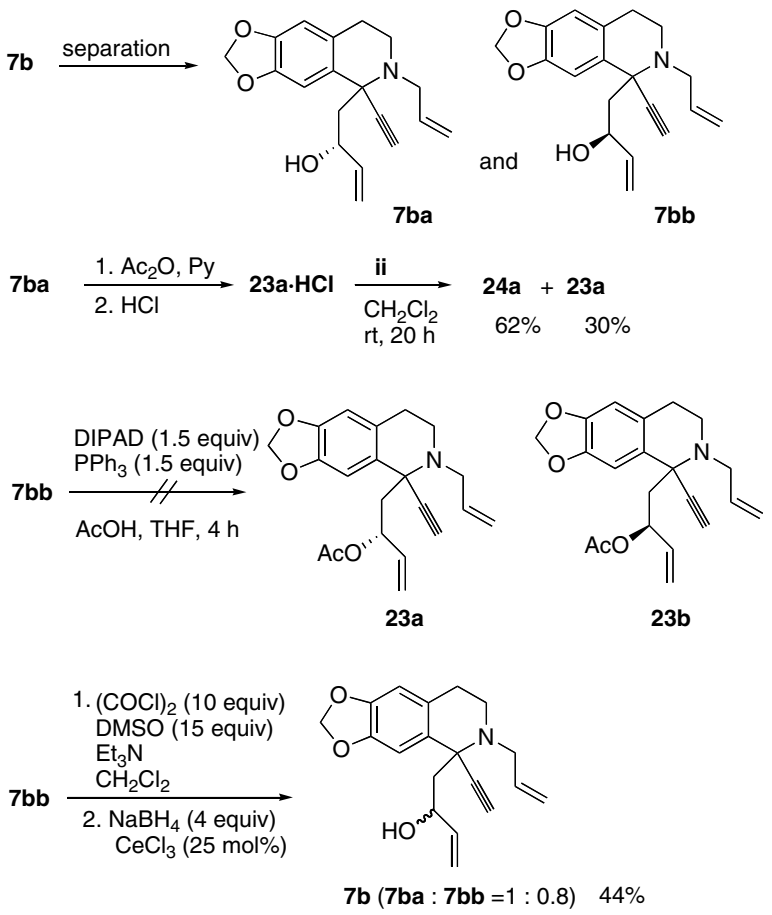
^1H NMR and ^{13}C NMR were recorded on a JEOL EX-270 (270 MHz for ^1H, 67.5 MHz for ^{13}C), or JEOL AL-400 (400 MHz for ^1H, 100 MHz, for ^{13}C) instrument in $CDCl_3$ with tetramethylsilane as an internal standard otherwise mentioned. Data are reported as follows: chemical shift in ppm (*d*), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration of protons (H). Infrared spectra (IR) were obtained on a Perkin Elmer 1605 FTIR spectrometer. Mass spectra were obtained on a JEOL JMS-FABmate (EI), a JEOL JMS-HX110 (FAB), or a JEOL JMS-700TZ (ESI). For column chromatography on silica gel, Merck Silica Gel 60 (70–230 or 230–400 mesh ATM) was used. For analytical or preparative TLC, Merck Silica Gel 60 PF_{254} was used. All solvents and reagents were purified when necessary using standard procedures. $Ni(cod)_2$ was prepared by a literature procedure [16] and handled under an argon atmosphere. All reactions were carried out under argon. Me_2Zn was purchased from Kanto Chemical Co. Inc.

3. Preparation of zinc reagent 10

To a solution of (trimethylsilyl)acetylene (3.1 mL, 22.0 mmol) in THF (12.1 mL) was added BuLi (1.62 M hexane solution, 15.4 mL, 22 mmol) at −78 °C and the solution was stirred at −78 °C for 40 min. To a suspension of $ZnCl_2$ (2.3 g, 17.0 mmol), which was dried at 130 °C for 12 h under vacuum, in THF (11. 0 mL) was added an above solution (THF solution, 0.74 M, 22.9 ml, 17.0 mmol) at 0 °C and the solution was stirred at the same temperature for 3 h. The solution was filtered and the filtrate was used as a zinc reagent of **10** (0.5 M THF/hexane solution).



Scheme 9. Possible reaction course.



Scheme 10. Conversion of β-hydroxyl group to α-form.

4. Typical procedure for the synthesis of α,β-unsaturated ester 2e

To a stirred suspension of $Ni(cod)_2$ [16] (99 mg, 0.36 mmol) and DBU (0.11 ml, 0.72 mmol) in degassed THF (2.9 mL) was slowly added **1e** (115 mg, 0.36 mmol) under an atmosphere of carbon dioxide at 0 °C for 1 h and the solution was stirred at the same temperature for 2 h. To this solution was added alkynyl zinc reagent (0.5 M THF/hexane solution, 2.2 mL, 1.1 mmol) at 0 °C and the solution was stirred at 0 °C for 24 h. To this solution was added 10% HCl and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was treated with CH_2N_2, whose product was purified by column chromatography (hexane/ethyl acetate, 10/1) on silica gel to give 3-{2-[(Benzyl-tert-butoxycarbonyl-amino)-methyl]-phenyl}-5-(trimethyl-silanyl)-pent-2-en-4-ynoic acid methyl ester (**2e**) (122 mg, 71%). IR (neat) 2966, 2147, 1732, 1699, 1602, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.37 and 1,44 (s and s, 4H and 5H), 3.75 (s, 3H), 4.28 and 4.44 (s and s, 0.9H, and 1.1H), 4.49 and 4.61(s and s, 1.1H and 0.9 H), 6.03 (s, 1H), 7.20-7.34 (m, 9 H);^{13}C NMR (100 MHz, $CDCl_3$) δ −0.41, 28.37, 39.56, 47.34, 49.41, 51.58, 79.99, 101.19, 110.50, 126.40, 127.08, 127.27, 127.78, 128.04, 128.37, 128.62, 128.84, 135.46, 136.09, 137.69, 155.86, 164.77; LR MS (EI) *m/z* 477 (M^+), 404, 377, 318, 286; HR MS (EI) calcd for $C_{28}H_{35}NO_4Si$ 477.2335, found 477.2342.

5. Typical procedure for synthesis of heterocycles using michael addition

A solution of **2e** (102 mg, 0.213 mmol) and TFA (0.16 mL, 2.13 mmol) in CH_2Cl_2 (2.5 mL) was refluxed for 5 h. To this solution was added sat. $NaHCO_3$ solution and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give secondary amine **13**. A solution of crude product **13** (5 mg, 0.013 mmol) in MeOH (3 mL) was refluxed for 14 h. Solvent was removed and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 4/1) to give [2-Benzyl-1-(trimethyl-silanylethynyl)-2,3-dihydro-1H-isoindol-1-yl]-acetic acid methyl ester (**3e**) (4.8 mg, 96%). IR (neat) 2952, 1928, 1734, 1456, 1248 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.16 (s, 9H), 3.13 (s, 2H), 3.56 (s, 3H), 3.63 (d,$J = 13.2$Hz, 1H), 3.68 (d,$J = 13.2$ Hz, 1H), 3.90 (d,$J = 13.2$ Hz, 1H), 4.18 (d,$J = 13.2$ Hz, 1H), 6.98-7.43 (m, 9 H); LR MS (EI) *m/z* 362 (M-Me), 318, 244, 226; HR MS (EI) calcd for $C_{23}H_{27}NO_2Si$ 377.1811, found 377.1819.

6. (*E*)-trimethyl(2-(6-(2-nitrovinyl)benzo[d][1,3]dioxol-5-yl)ethynyl)silane (15)

To a solution of 6-(trimethyl-silanylethynyl)-benzo[1,3]-dioxole-5-carbaldehyde (**14**) [17] (246 mg, 1.0 mmol) and NH_4OAc (64 mg, 0.83 mmol) in AcOH (2.5 ml) was added CH_3NO_2(0.27 ml, 5.0 mmol) and the solution was heated at 100 °C for 7 h. The solvent was removed and the residue was recrystalized from ether to give **15** (1.23 g, 85%). IR (film) 3104, 2955, 2149, 1610, 1330, 1253, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.28 (s, 9 H), 6.05 (s, 2H), 6.94 (s, 1H), 6.96 (s, 1H), 7.57 (d, $J = 13.6$ Hz, 1H), 8.46 (d,$J = 13.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.21, 101.35, 101.40, 101.90, 105.95, 112.34, 120.84, 126.62, 136.50, 136.92, 148.63, 150.50; LR MS (EI) *m*/*z* 289 (M^+), 243, 73; HR MS (EI) calcd for $C_{14}H_{15}NO_4Si$ 289.0770, found 289.0788; *Anal.* Calcd for $C_{14}H_{15}NO_4Si$: C, 58.11; H, 5.22; N, 4.84. Found: C, 58.06; H, 5.32; N, 4.82%.

7. [2-(6-Ethynyl-benzo[1,3]dioxol-5-yl)-ethyl]-carbamic acid *tert* -butyl ester (1f)

To a suspension of $LiAlH_4$ (885 mg, 23.3 mmol) in Et_2O (25 mL) was added **15** (2.25 g) in Et_2O (25 mL) at −78 °C and the solution was stirred at room temperature for 3 h. To this solution was added 15% aq. NaOH solution (0.9 mL) and the solution was stirred at room temperature for 14 h. Undissolved material was filtered off and the filtrate was concentrated. The residue was dissolved in MeOH (26 mL) and to this solution was added NEt_3(1.6 mL, 11.66 mmol) and $(Boc)_2O$ (2.7 mL, 11.66 mmol) and the solution was stirred at room temperature for 14 h. Solvent was removed and the residue was purified by column chromatography on silica gel (hexane/Et_2O, 10/1) to give **1f** (1.37 g, 61%). IR (neat) 3290, 2977, 2101, 1700, 1366, 1252, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.92 (t,$J = 6.8$ Hz, 2H), 3.17 (s, 1H), 3.37 (td,$J = 6.8$, 6.4 Hz, 2H), 4.57 (s, 1H), 5.96 (s, 2H), 6.68 (s, 1H), 6.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.43, 34.60, 41.08, 79.11, 79.53, 82.10, 101.32, 109.55, 112.14, 114.39, 136.72, 145.78, 148.29, 155.71; LR MS (EI) *m*/*z* 289 (M^+), 233, 216, 188, 172, 159, 57; HR MS (EI) calcd for $C_{16}H_{19}NO_4$ 289.1314, found 289.1315; *Anal*. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.23; H, 6.61; N, 4.74%.

8. 3-[6-(2-*tert*-Butoxycarbonylamino-ethyl)-benzo[1,3]dioxol-5-yl]-5-(trimethyl-silanyl)-pent-2-en-4-ynoic acid methyl ester (2f)

The crude product which was prepared according to the typical procedure for the synthesis of **2e** from $Ni(cod)_2$ (109 mg, 0.4 mmol) and DBU (0.18 mL, 1.2 mmol) in THF (2. 9 mL), **1f**(104 mg, 0.36 mmol) and **10** (2.2 mL, 1.1 mmol) in THF (5.8 mL) under carbon dioxide was purified by column chromatography on silica gel (hexane/ethyl acetate, 5/1) to give ester **2f** (111.2 mg, 69%). IR (film) 3445, 2977, 1710, 1595, 1167, 846, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 9 H), 1.40 (s, 9 H), 2.86 (t, $J = 7.2$ Hz, 2H), 3.30 (br, 2H), 3.77 (s, 3H), 4.51 (br, 1 H), 5.93 (s, 2H), 6.09 (s, 1H), 6.66 (s, 1H), 6.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.33, 28.41, 33.00, 41.40, 51.53, 101.30, 101.81, 109.11, 109.68, 109.90, 128.28, 130.49, 131.79, 136.78, 146.07, 148.06, 155.62, 164.96; LR MS (EI) *m*/*z* 445 (M^+), 389, 372, 344, 315; HR MS (EI) calcd for $C_{23}H_{31}NO_6Si$ 445.1920, found 445.1922.

9. Methyl 2-(5-ethynyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)acetate (17)

A solution of **2f** (933 mg, 3.1 mmol) and TFA (1.6 mL, 21 mmol, 10 equiv) in CH_2Cl_2 (8.4 mL) was stirred at room temperature for 3 h. Solvent was removed and the residue was dissolved in ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The residue was dissolved in THF (8 mL) and TBAF (THF solution, 1.0 M, 1.1 equiv, 2.3 mL) was added. The whole solution was stirred at 0 °C for 2 h. Water was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate) to give **17** (438 mg, 76% based on **16**). IR (film) 3286, 2952, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (br, 1H), 2.46 (s, 1H), 2.62 (ddd, $J = 16.0$, 4.0, 3.2 Hz, 1H), 2.84 (ddd,$J = 16.0$, 10.4, 5.6 Hz, 1H), 2.89 (d, $J = 16.0$ Hz, 1H), 3.12 (ddd,$J = 12.0$, 5.6, 3.2 Hz, 1H), 3.13 (d, $J =$ 16.0 Hz, 1H), 3.22 (ddd,$J = 12.0$, 10.4, 4.0 Hz, 1H), 3.70 (s, 3H), 5.90 (d, $J = 1.2$Hz, 1H), 5.92 (d, $J = 1.2$ Hz, 1H), 6.54 (s, 1H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.71, 39.57, 46.68, 51.77, 53.40, 71.61, 87.00, 100.89, 105.96, 108.84, 128.33, 130.29, 146.08, 146.55, 170.76; LR MS (EI) *m*/*z* 273 (M^+), 200, 185; HR MS (EI) calcd for $C_{15}H_{15}NO_4$ 273.1001, found 273.1009.

10. 1-(6-Allyl-5-ethynyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)but-3-en-2-ol (7ba,7bb)

To a solution of **17** (100 mg, 0.366 mmol) in CH_3CN (1.2 mL) was added K_2CO_3 (253 mg, 1.83 mmol) and allyl bromide (0.12 mL, 1.46 mmol) at 0 °C and the solution was stirred at room temperature for 60 h. Ethyl acetate was added and the organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue **21** was dissolved in THF (1 mL), and $LiAlH_4$ (36 mg, 0.95 mmol) was added at 0 °C. The suspension was stirred at 0 °C for 2 h. $Na_2SO_4 \cdot 10H_2O$ was added to the solution, and the solution was stirred at room temperature for 18 h. Undissolved material was filtered off and the filtrate was concentrated to give 2-(6-Allyl-5-ethynyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethanol **(22)**. To a solution of oxalyl chloride (0.1 mL, 1.1 mmol) in CH_2Cl_2 (1.5 mL)

was added DMSO (0.16 mL, 2.2 mmol) at −78 °C and the solution was stirred at the same temperature for 2 min. To this solution was added the above crude product **22** in CH_2Cl_2(1.5 mL) and the solution was stirred at −78 °C for 30 min. NEt_3(0.6 ml) was added to this solution at the same temperature and the solution was stirred at 0 °C for 30 min. Ethyl acetate was added and the organic layer was washed with aq. K_2CO_3 solution and brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (2 mL), and to this solution was added vinyl magnesium bromide (THF solution, 1.0 M, 1.1 mL, 1.1 mmol) at −78 °C and the solution was stirred at the same temperature for 2 h. Water was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give **7**, which was purified by column chromatography on silica gel (ethyl acetate/hexane, 4:1). **7ba**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (dd, $J = 14.8$, 2.0 Hz, 1H), 2.38 (dd, $J = 14.8$ 10.8 Hz, 1H), 2.46–2.55 (m, 2H), 2.53 (s, 1H), 2.91 (dd, $J = 14.0$, 8.8 Hz, 1H), 2.95–2.99 (m, 1H), 3.08 (ddd, $J = 11.4$, 5.2, 2.0 Hz, 1H), 3.74–3.80 (m,*2* H), 5.00 (ddd, $J = 10.4$, 1.6, 1.6 Hz, 1H), 5.15 (ddd, $J = 17.2$, 1.6, 1.6 Hz, 1H), 5.23 (d, $J = 10.4$ H, 1H), 5.27 (d, $J = 16.8$ Hz, 1H), 5.71 (ddd, $J = 17.2$, 10.4, 5.2 Hz, 1H), 5.85–5.95 (m, 1H), 5.91 (d, $J = 1.6$ Hz, 1H), 5.93 (d, $J = 1.6$ Hz, 1H) 6.21 (br, 1H), 6.53 (s, 1H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.70, 44.37, 44.81, 54.61, 61.62, 69.39, 74.02, 74.09, 83.10, 100.95, 106.75, 108.04, 113.74, 118.62, 129.00, 129.41, 134,65, 140.09, 146.56.

7bb: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (dd, $J = 15.2$, 2.8 Hz, 1H) 2.26 (dd, $J = 15.2$, 9.6 Hz, 1H), 2.48 (ddd, $J = 15.6$, 4.8, 4.8 Hz, 1H), 2.67 (s, 1H), 2.78 (ddd, $J = 15.6$, 10.0, 4.8 Hz, 1H), 2.95 (ddd, $J = 14.0$, 4.8, 4.8 Hz, 1H), 3.05 (dd, $J = 13.6$, 9.2 Hz, 1 H), 3.28 (ddd, $J = 14.0$, 9.6, 4.8 Hz, 1H), 4.03 (brd, $J = 13.6$ Hz, 1H), 4.75 (brs, 1H), 4.97 (ddd, $J = 10.0$, 1.6, 1.6 Hz, 1H), 5.17–5.26 (m, 3H), 5.72 (ddd, $J = 16.8$, 10.8, 4.8 Hz, 1H), 5.83–5.93 (m, 2H), 5.90 (s, 1H), 5.91 (s, 1H) 6.50 (s, 1 H), 6.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.47, 40.65, 46.80, 52.70, 62.46, 70.92, 76.04, 84.10, 100.85, 107.66, 108.14, 113.20, 117.75, 126.67, 130.43, 135.68, 140.20, 146.17, 146.65.

11. (R)-1-(6-allyl-5-ethynyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)but-3-en-2-yl acetate (23a) and (*S*)-1-(6-allyl-5-ethynyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)but-3-en-2-yl acetate (23b)

The crude product of **7** was dissolved in pyridine (1 mL) and Ac_2O (0.5 mL, 5.3 mmol) and DMAP (5 mg) and the solution was stirred at room temperature for 14 h. Ethyl acetate was added and the organic layer was washed with brine dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 4 : 1) to give **23** (90.2 mg, 5 steps 70%, 1 to 1 ratio of **23a** to **23b**). **23a**: IR (neat) 3287, 2900, 1738, 1642, 1487, 1235, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.29 (dd,$J = 15.4$, 5.4 Hz, 1H), 2.46 (s, 1H), 2.46–2.51 (m, 2H), 2.65 (dd,$J = 15.4$, 5.4 Hz, 1H), 2.77–2.97 (m, 3H), 3.64 (d,$J = 14.0$ Hz, 1H), 4.83 (d,$J = 10.4$ Hz, 1H), 4.92 (d,$J = 16.8$ Hz, 1H), 5.16 (d,$J = 10.4$ Hz, 1H), 5.23–5.27 (m, 2H), 5.39 (ddd,$J = 17.2$, 10.4, 6.2 Hz, 1H), 5.82–5.96 (m, 1H), 5.91 (d,$J = 11.6$ Hz, 2H), 6.49 (s, 1H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.51, 29.81, 43.96, 44.79, 53.91, 60.11, 71.47, 73.34, 84.44, 100.86, 107.28, 108.07, 114.93, 116.75, 129.81, 130.72, 136.40, 136.47, 146.11, 146.35, 169.61; LR MS (EI) *m*/*z* 353 (M^+), 328, 312, 294, 240; HR MS (EI) calcd for $C_{21}H_{23}NO_4$ 353.1627, found 353.1622. **23b**: IR (neat) 3282, 2900, 1736, 1642, 1484, 1236, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 3H), 2.35–2.57 (m, 3H), 2.46 (s, 1H), 2.53 (dd,$J = 11.2$, 11.2 Hz, 1H), 2.82–2.92 (m, 2H), 2.98 (d,$J = 11.2$ Hz, 1H), 3.51 (d,$J = 14.8$ Hz, 1H), 5.04 (d,$J = 10.0$ Hz, 1H), 5.08 (d,$J = 15.6$ Hz, 1H), 5.17 (d,$J = 10.0$ Hz, 1H), 5.32 (d,$J = 16.8$ Hz, 1H), 5.65 (d,$J = 6.4$ Hz, 1H), 5.73 (ddd,$J = 16.8$, 10.0, 5.6 Hz, 1H), 5.80–5.91 (m, 1H), 5.88 (s, 1H), 5.91 (s, 1H), 6.47 (s, 1 H) 6.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.46, 29.80, 44.51, 44.74, 54.03, 59.66, 70.00, 73.00, 84.84, 100.80, 107.91, 108.24, 114.92, 116.61, 129.08, 130.62, 136.14, 137.08, 145.74, 146.03, 169.35; LR MS (EI) *m*/*z* 353 (M^+), 312, 294, 240; HR MS (EI) calcd for $C_{21}H_{23}NO_4$ 353.1627, found 353.1601.

12. (3*R**, 5*R**)-3-Acetoxy-15,16-methylenedioxyerythrina-1,6-diene (24a) and (3*S**, 5*R**)-3-Acetoxy-15,16-methylenedioxyerythrina-1,6-diene (24b)

To a solution of a mixture of **23** (8.2 mg, 0.023 mmol) in Et_2O (1 mL) was added HCl in Et_2O solution (1.0 M, 0.05 mmol) at 0 °C and the solution was concentrated. To the solution of **23 · HCl** in degassed CH_2Cl_2 (0.5 mL) was added the second-generation ruthenium catalyst **ii** (2 mg, 0.002 mmol, 10 mol%) and the solution was stirred at room temperature for 16 h under argon gas. To this solution was added CH_2Cl_2 and aq. K_2CO_3 solution, and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/MeOH, 5:1) to give **24a** (4.5 mg, 50%) and **24b** (4.5 mg, 50%). **24a**: IR (neat) 2931, 1734, 1684, 1484, 1237, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (dd, $J = 11.2$, 11.2 Hz, 1H), 2.04 (s, 3H), 2.51 (dd, $J = 11.2$, 6.0 Hz, 1H), 2.60–2.67 (m, 1H), 2.82–2.91 (m, 2H), 3.42–3.51 (m, 2H), 3.73 (dd, $J = 14.8$, 2.8 Hz, 1H), 5.43 (ddd, $J = 8.4$, 6.0, 0.8 Hz, 1H), 5.77 (s, 1H), 5.82 (d, $J = 10.0$ Hz, 1H), 5.88 (s, 2 H), 6.59 (dd,$J = 10.0$, 2.8 Hz, 1H), 6.60 (s, 1H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.34, 25.11, 41.73, 44.46, 57.55, 67.08, 70.27, 100.64, 105.95, 108.65, 123.75, 126.17, 127.73, 129.58, 131.71, 141.42, 145.84, 146.09, 170.45; LR MS (EI) *m*/*z* 325 (M^+), 282, 266, 236; HR MS (EI) calcd for $C_{19}H_{19}NO_4$ 325.1314,

found 325.1313. **24b**: IR (film) 2926, 1727, 1682, 1482, 1236, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)*d* 1.70 (s, 3H), 2.39 (br, 1H), 2.55 (d, $J = 14.4$ Hz, 1H), 2.79–2.91 (m, 3H), 3.41 (d, $J = 14.4$ Hz, 1H), 3.62 (m, 1H), 3.86 (br, 1H), 5.38 (t, $J = 5.6$ Hz, 1H), 5.87 (s, 1H), 5.88 (s, 1H), 5.92 (s, 1H), 5.99–6.05 (m, 1H), 6.61 (s, 1H), 6.77 (d,$J = 10.0$ Hz, 1H), 6.88 (s, 1H); LR MS (EI) *m*/*z* 325 (M^+), 282, 266, 236; HR MS (EI) calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1289.

13. Erythrocarine

A solution of **24a** (4.5 mg, 0.015 mmol) and K_2CO_3(3.4 mg, 0.025 mmol) in MeOH (0.5 mL) was stirred at room temperature for 1 h. Ethyl acetate was added and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/MeOH, 5:1) to give erythrocarine (3.7 mg, 93%). IR (neat) 2931, 3104, 2860, 1479, 1228, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 1H), 1.83 (dd, $J = 11.2$, 11.2 Hz, 1H), 2.52 (dd, $J = 11.2$, 5.6 Hz, 1H), 2.71 (m, 1H), 2.83–2.91 (m, 2H), 3.51 (m, 2H), 3.79 (d, $J = 15.2$ Hz, 1H), 4.36 (m, 1H), 5.75 (br, 1H), 5.88 (s, 1H), 5.89 (s, 1H), 5.93 (d, $J = 9.6$ Hz, 1H), 6.51 (dd, $J = 9.6$, 2.0 Hz, 1H), 6.62 (s, 1H), 6.75 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 25.28, 44.65, 45.92, 57.71, 67.63, 67.69, 100.63, 106.01, 108.56, 122.95, 124.67, 127.82, 132.04, 134.12, 141.79, 145.74, 146.00; LR MS (EI) *m*/*z* 283 (M^+), 266, 254; HR MS (EI) calcd for $C_{17}H_{17}NO_3$ 283.1208, found 283.1220.

14. 3-Epierythrocarine

A solution of **24a** (4.5 mg, 0.015 mmol) and K_2CO_3 (3.4 mg, 0.025 mmol) in MeOH (0.5 mL) was stirred at room temperature for 4 h. Ethyl acetate was added and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Ethyl acetate/MeOH, 5:1) to give erythrocarine (2.0 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.55 (d, $J = 13.4$ Hz, 1H), 2.74 (ddd, $J = 15.6$, 4.8, 4.8 Hz, 1H), 2.93 (m, 1H), 3.21 (d, $J = 14.4$ Hz, 1H), 3.64–3.72 (m, 3H), 3.86 (d, $J = 13.4$ Hz, 1 H), 4.23 (m, 1H), 5.35 (m, 1H), 5.86 (br, 1H), 5.89 (s, 1H), 5.90 (s, 1H), 6.05 (dd, $J = 10.0$, 5.2 Hz, 1H), 6.66 (d, $J = 10.0$ Hz, 1H), 6.70 (s, 1H), 6.80 (s, 1H).

References

[1] (a) S.F. Dyke, S.N. Quessy, in: R.H.F. Manske (Ed.), The Alkaloids, Vol. 18, Academic Press, New York, 1981, p. 1;
(b) R.K. Hill, in: R.H.F. Manske (Ed.), The Alkaloids, Vol. 9, Academic Press, New York, 1967, p. 281;
(c) Y. Tsuda, T. Sano, in: G.A. Cordell (Ed.), The Alkaloids, Vol. 48, Academic Press, New York, 1996, p. 249.

[2] K. Folkers, R.T. Major, J. Am. Chem. Soc. 59 (1937) 1580.

[3] Synthesis of erythotrine (a) A. Mondon, H.J. Nestler, Angew. Chem. Int. Ed. 3 (1964) 588;
(b) Recent report for the synthesis of erythrina alkaloids and references are therein: A. Padwa, H.I. Lee, P. Rashatasakhon, M. Rose, J. Org. Chem. 69 (2004) 8209;
(c) S.M. Allin, G.B. Streetley, M. Slater, S.L. James, W.P. Martin, Tetrahedron Lett. 45 (2004) 5493;
(d) H. Fukumoto, T. Esumi, J. Ishihara, S. Hatakeyama, Tetrahedron Lett. 44 (2003) 8047.

[4] (a) G. Burkhart, H. Hoberg, Angew. Chem. Int. Ed. Engl. 21 (1982) 76;
(b) S. Saito, S. Nakagawa, T. Koizumi, K. Hirayama, Y. Yamamoto, J. Org. Chem. 64 (1999) 3975.

[5] (a) E. Dunãch, J. Périchon, J. Organomet. Chem. 352 (1988) 239;
(b) E. Dunãch, S. Dérien, J. Périchon, J. Organomet. Chem. 364 (1989) C33;
(c) S. Dérien, E. Dunãch, J. Périchon, J. Am. Chem. Soc. 113 (1991) 8447.

[6] (a) M. Takimoto, M. Mori, J. Am. Chem. Soc. 123 (2001) 2895;
(b) M. Takimoto, M. Mori, J. Am. Chem. Soc. 124 (2002) 10008;
(c) M. Takimoto, Y. Nakamura, K. Kimura, M. Mori, J. Am. Chem. Soc. 126 (2004) 5956.

[7] (a) M. Takimoto, M. Kawamura, M. Mori, Org. Lett. 5 (2003) 2599;
(b) M. Takimoto, M. Kawamura, M. Mori, Synthesis (2004) 791;
(c) M. Takimoto, M. Kawamura, M. Mori, Y. Sato, Synlett (2005) 2019.

[8] (a) M. Takimoto, K. Shimizu, M. Mori, Org. Lett. 3 (2001) 3345;
(b) K. Shimizu, M. Takimoto, M. Mori, Org. Lett. 5 (2003) 2323;
(c) M. Takimoto, T. Mizuno, Y. Sato, M. Mori, Tetrahedron Lett. 46 (2005) 5173.

[9] A.S. Chawla, F.M.J. Redha, A.H. Jackson, Phytochemistry 24 (1985) 1821.

[10] (a) S.-H. Kim, N. Bowden, R.H. Grubbs, J. Am. Chem. Soc. 116 (1994) 10801;
(b) S.-H. Kim, W.J. Zuercher, N.B. Bowden, R.H. Grubbs, J. Org. Chem. 61 (1996) 1073;
(c) T.-L. Choi, R.H. Grubbs, Chem. Commun. (2001) 2648;
(d) E.M. Codesido, L. Castedo, J.R. Granja, Org. Lett. 3 (2001) 1483;
(e) C.-J. Wu, R.J. Madhushaw, R.-S. Liu, J. Org. Chem. 68 (2003) 7889;
(f) F.-D. Boyer, I. Hanna, L. Ricard, Org. Lett. 3 (2001) 3095.

[11] G.C. Fu, S.T. Nguyen, R.H. Grubbs, J. Am. Chem. Soc. 115 (1993) 9856.

[12] P. Schwab, M.B. France, J.W. Ziller, R.H. Grubbs, Angew. Chem. Int. Ed. Engl. 34 (1995) 2039.

[13] M. Scholl, S. Ding, C.W. Lee, R.H. Grubbs, Org. Lett. 1 (1999) 953.

[14] Recently, Hatakeyama succeeded in a total synthesis of erythravine using dienyne metathesis. See Ref. [3d].

[15] Conversion of epierythrocarine to erythrocarine was carried out using Mitsunobu reaction, but no product was obtained due to the steric hindrance.

[16] R.A. Schunn, Inorg. Synth. 15 (1974) 5.

[17] D.B. Grotjahn, K.P.C. Vollhardt, Synthesis (1993) 579.