Transmission of Axial Chirality to Spiro Center Chirality, Enabling Enantiospecific Access to Erythrinan Alkaloids

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Abstract: Synthesis of *O*-methylerysodienone in enantiomerically pure form is described, where the axial chirality of the intermediate biphenyl is stereospecifically transmitted to the spiro center chirality of the erythrinan skeleton.

Key words: erythrinan alkaloid, biphenyl compound, axial chirality, spiro center chirality

The alkaloids, which share indolo[7a,1-*a*]isoquinoline skeleton (erythrinan skeleton), constitute a large group of plant metabolites called erythrinan alkaloids (Figure 1).[1–3]

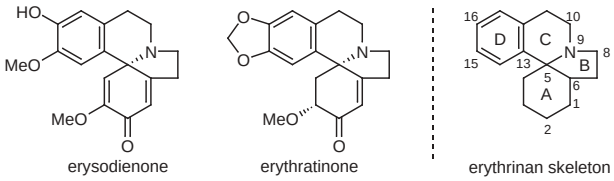
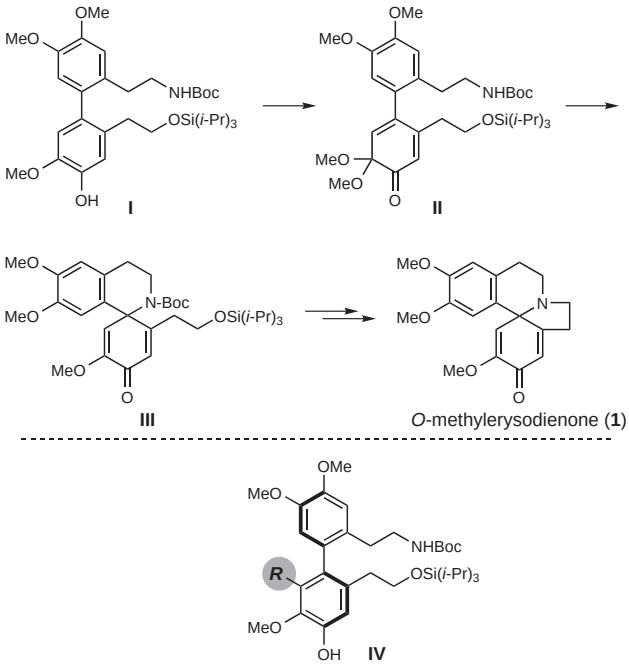


Figure 1 Natural erythrinan alkaloids.

In the preceding paper,[4] we described a novel approach to these alkaloids and its application to the total synthesis of *O*-methylerysodienone (**1**) in racemic form (Scheme 1). One of the key steps in this synthesis was the Lewis acid promoted spirocyclization of *ortho*-quinone monoacetal **II**, which was derived from appropriately substituted biphenyl **I**. In our effort to develop the enantioselective variant of this approach, we were interested in possibility of transmitting the axial chirality of the biphenyl intermediate to the spiro center chirality in the erythrinan product. If viable, it would provide a new opportunity for the enantioselective synthesis of erythrinan alkaloids,[2i–k] since various methods are becoming more available for the synthesis of axially chiral, non-racemic biphenyl compounds.[5] To test this possibility, we planned the asymmetric synthesis of *O*-methylerysodienone (**1**) starting from the non-racemic biphenyl **IV** possessing the additional *ortho* substituent *R*, which is removable after construction of the spiro center. Enantiospecific access to **1** would be possible if the substituent R could serve for restricting the axial bond rotation of **IV** to make the conformational isomers (enantiomers) isolable, and also



Scheme 1 Application of biphenyl with hindered rotation about the axial bond.

for preventing racemization in the subsequent synthetic process.

We hoped that trimethylsilyl group would be ideally suited for such purpose, and the trimethylsilylated biphenyl **9** was synthesized via bromobiphenyl **6** as shown in Scheme 2.[6]

Starting from aryl bromide **2** and arylboronic acid **3**, biphenyl alcohol **4** was obtained in three steps including Suzuki–Miyaura coupling,[7] Wittig methylenation, and hydroboration followed by oxidative workup in a similar manner as previously reported.[4] Alcohol **4** was further converted to compound **5** via acetylation followed by acid hydrolysis of the MOM group.[8] Selective bromination at the *ortho* position of the phenol in **5** was effected by pyridine·HBr_3 in pyridine in high yield. Other bromination agents, such as NBS and *N*-bromoacetamide, were less effective due to the competing formation of the corresponding *ortho*-quinone. The bromide, thus obtained, was deacetylated with K_2CO_3 in MeOH to give diol **6**.

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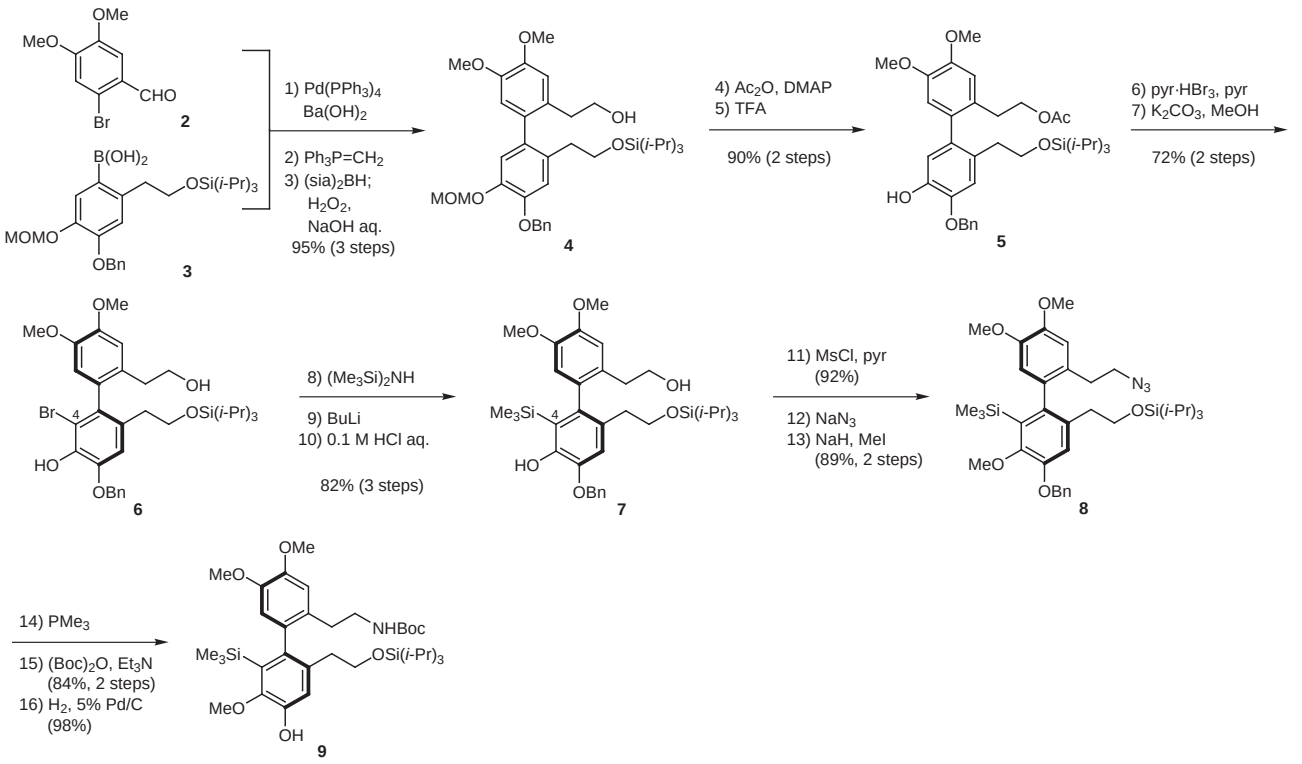
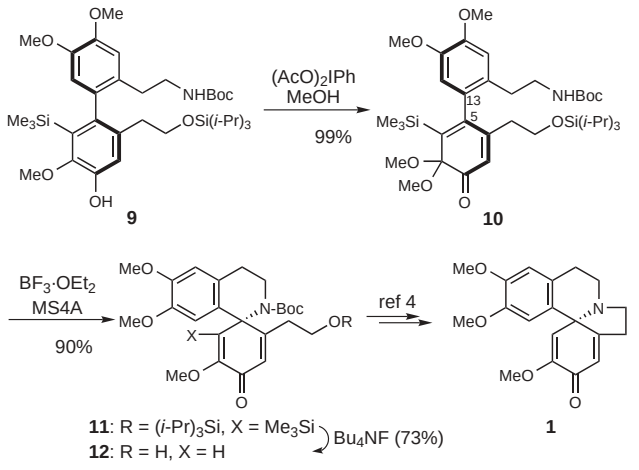


Scheme 2[9] *Conditions*: (1) DME, H_2O, 50 °C, 1 h; (2) THF, 25 °C, 1 h; (3) THF, 25 °C, 1 h; then 25 °C, 2 h; (4) pyridine, 25 °C, 15 min; (5) CH_2Cl_2, 25 °C, 1.5 h; (6) 0 °C, 10 min; (7) THF, 50 °C, 2.5 h; (8) THF, reflux, 3 h; (9) THF, –78 °C, 15 min; (10) THF, 0 °C, 10 min; (11) 25 °C, 30 min; (12) DMF, 60 °C, 5 h; (13) DMF, 0 °C, 10 min; (14) MeCN, H_2O, 25 °C, 5 h; (15) THF, 25 °C, 1 h; (16) EtOAc, MeOH, 25 °C, 1 h.

The axial bond rotation being hindered by three *ortho* substituents, diol **6** could be easily resolved by HPLC with chiral stationary phase [CHIRALPAK AD-H, hexane: *i*-PrOH = 85:15] into the enantiomers, which proved to be stable to racemization at room temperature.[9] The bromide in each isomer of **6** was substituted by a trimethylsilyl as in the following. Both of the two hydroxy groups in **6** were trimethylsilylated and the resulting bis(trimethylsilyl) ether was treated with BuLi in THF at –78 °C. Sequential halogen–metal exchange and migration of the lateral trimethylsilyl group rapidly proceeded at this temperature to give the C(4)-trimethylsilylated biphenyl.[3] Acid hydrolysis of the remaining trimethylsilyl ether gave biphenyl **7**. This compound **7** was further converted to phenol **9**, the precursor of *ortho*-quinone acetal, in six steps including selective mesylation of the alkanol, substitution by NaN_3, methylation of the phenol to give azide **8**, reduction of the azide, protection with a Boc group followed by cleavage of the benzyl group.



Scheme 3[9] Formation of *ortho*-quinone acetal **10** and its spirocyclization.

Phenol **9**, thus obtained, was subjected to oxidation with $(AcO)_2IPh$ in MeOH [25 °C, 15 min] to give *ortho*-quinone acetal **10** in high yield.[10] Notably, each enantiomer of **10** proved to be enantiomerically pure and stable to racemization at room temperature, showing the full stereochemical integrity during all these transformations.[11,12]

$BF_3{\cdot}OEt_2$ was an efficient catalyst for the spirocyclization of **10**.[4] With the catalyst load in 0.2 equivalents, the reaction completed in 30 minutes at –20 °C to give spiroisoquinoline **11** in 90% yield. To our delight, both isomers of **11** proved to be enantiomerically pure,[11] clearly showing that the reaction process was completely free from racemization.[12] Upon treatment of **11** with Bu_4NF (THF, 25 °C, 1.5 h), cleavage of trimethylsilyl and triisopropylsilyl groups proceeded at once to give **12**.

Finally, *O*-methylerysodienone (**1**)[13,14] was obtained from alcohol **12** in enantiomerically pure form in a same manner as previously reported for the racemate.[4] Thus, it was demonstrated that the axial chirality of biphenyl **6** could

be stereospecifically transmitted to the spiro center chirality in the erythrinan product **1**.

In summary, synthesis of *O*-methylerysodienone in enantiomerically pure form was described. Considering the increasing availability of axially chiral, non-racemic biphenyl compounds, the present conception, i.e. the transmission of axial chirality to spiro center chirality, will render a totally efficient and enantioselecive access to erythrinan alkaloids. The research in this direction is currently in progress and will be reported in due course.

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(6) All new compounds were fully characterized by ^{1}H and ^{13}C NMR, IR and combustion analysis. Data for the selected compounds follow. [*The specific rotation is shown for (+)-**6** and for each isomer derived from (+)-**6**. See ref. 9 and ref. 14] Compound **6**: $[\alpha]_D^{28}$ +20.5 (*c* 1.12, $CHCl_3$)*. ^{1}H NMR ($CDCl_3$): δ = 7.46–7.36 (m, 5 H), 6.97 (s, 1 H), 6.86 (s, 1 H), 6.54 (s, 1 H), 6.01 (s, 1 H), 5.15 (s, 2 H), 3.93 (s, 3 H), 3.82 (s, 3 H), 3.73–3.55 (m, 4 H), 2.60–2.45 (m, 4 H), 1.35 (br, 1 H), 0.97 (s, 21 H). ^{13}C NMR ($CDCl_3$): δ = 148.4, 147.3, 145.2, 141.8, 135.9, 134.2, 131.8, 130.0, 128.8, 128.5, 128.4, 127.9, 113.5, 113.2, 112.4, 111.5, 71.4, 63.8, 62.6, 55.8, 55.7, 37.6, 36.2, 17.9, 11.8. IR (NaCl): 3515, 2940, 2865, 1605, 1515, 1490, 1465, 1255, 1215, 1165, 1110, 1045, 755 cm^{-1}. Anal. Calcd for $C_{34}H_{47}BrO_6Si$: C, 61.90; H, 7.18. Found: C, 61.98; H, 7.45. HPLC (Daicel CHIRALPAK AD-H, ϕ0.46 × 250 mm × 2, hexane:*i*-PrOH = 85:15, 1.0 mL/min) retention time: 10.9 min for (+)-**6**, 12.8 min for (–)-**6**. Compound **9**: Colorless needles (hexane), mp 194.0–194.5 °C; $[\alpha]_D^{24}$ +16 (*c* 1.1, $CHCl_3$)*. ^{1}H NMR ($CDCl_3$): δ = 6.95 (s, 1 H), 6.78 (s, 1 H), 6.55 (s, 1 H), 5.48 (s, 1 H), 4.45 (s, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.60 (t, 2 H, *J* = 6.8 Hz), 3.30–3.18 (m, 2 H), 2.50–2.39 (m, 3 H), 2.34 (ddd, 1 H, $J_1 = J_2$ = 6.8 Hz, J_3 = 13.2 Hz), 1.42 (s, 9 H), 0.95 (s, 21 H), –0.1 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ = 155.8, 151.1, 148.2, 147.1, 146.6, 138.5, 134.1, 133.5, 132.0, 129.5, 119.1, 114.3, 111.4, 79.2, 64.1, 61.3, 55.9, 55.7, 40.1, 36.9, 33.1, 28.4, 17.9, 11.9, 1.7. IR (KBr): 3325, 2940, 2865, 1685, 1515, 1465, 1245, 1170, 1110, 880 cm^{-1}. Anal. Calcd for $C_{36}H_{61}NO_7Si_2$: C, 63.96; H, 9.09; N, 2.07. Found: C, 64.26; H, 9.38; N, 2.06. HPLC (Daicel CHIRALCEL OD-H, ϕ0.46 × 250 mm × 2, hexane:*i*-PrOH = 98:2, 1.0 mL/min) retention time: 20.5 min for (+)-**9**, 25.6 min for (–)-**9**. Compound **10**: $[\alpha]_D^{24}$ –24 (*c* 0.99, $CHCl_3$)*. ^{1}H NMR ($CDCl_3$): δ = 6.81 (s, 1 H), 6.61 (s, 1 H), 6.10 (s, 1 H), 4.59 (br, 1 H), 3.92 (s, 3 H), 3.85 (s, 3 H), 3.72–3.61 (m, 2 H), 3.42–3.33 (m, 2 H), 3.35 (s, 3 H), 3.24 (s, 3 H), 2.61 (t, 2 H, *J* = 7.7 Hz), 2.16 (ddd, 1 H, $J_1 = J_2$ = 7.2 Hz, J_3 = 14.5 Hz), 2.03 (ddd, 1 H, $J_1 = J_2$ = 5.6 Hz, J_3 = 14.5 Hz), 1.43 (s, 9 H), 0.99 (s, 21 H), –0.11 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ = 196.7, 155.7, 153.9, 153.2, 148.8, 148.3, 146.8, 130.1, 129.3, 125.2, 113.3, 111.3, 94.5, 79.3, 61.3, 55.9, 55.8, 50.3, 50.2, 39.8, 37.4, 33.2, 28.3, 17.9, 11.8, 1.6. IR (NaCl): 3385, 2945, 2865, 1715, 1665, 1510, 1465, 1250, 1165, 1090, 1070 cm^{-1}. Anal. Calcd for $C_{37}H_{63}NO_8Si_2$: C, 62.94; H, 8.99; N, 1.98. Found: C, 62.65; H, 9.18; N, 1.94. HPLC (Daicel CHIRALCEL OD-H, ϕ0.46 × 250 mm, hexane:*i*-PrOH = 98:2, 1.0 mL/min) retention time: 7.4 min for (–)-**10**, 12.6 min for (+)-**10**. Compound **11**: $[\alpha]_D^{27}$ +52.0 (*c* 1.73, $CHCl_3$)*. ^{1}H NMR ($CDCl_3$): δ = 6.56 (s, 1 H), 6.49 (s, 1 H), 6.05 (s, 1 H), 4.15 (ddd, 1 H, $J_1 = J_2$ = 5.1 Hz, J_3 = 13.2 Hz), 3.85 (s, 6 H), 3.76 (ddd, 1 H, J_1 = 5.1 Hz, J_2 = 8.9 Hz, J_3 = 13.2 Hz), 3.66 (s, 3 H), 3.63 (ddd, 1 H, J_1 = 6.2 Hz, J_2 = 8.1 Hz, J_3 = 9.7 Hz), 3.49 (ddd, 1 H, J_1 = 6.2 Hz, J_2 = 8.1 Hz, J_3 = 9.7 Hz), 3.03 (ddd, 1 H, J_1 = 5.1 Hz, J_2 = 8.9 Hz, J_3 = 16.1 Hz), 2.93 (ddd, 1 H, $J_1 = J_2$ = 5.1 Hz, J_3 = 16.1 Hz), 2.31 (ddd, 1 H, $J_1 = J_2$ = 6.2 Hz, J_3 = 12.3 Hz), 2.11 (ddd, 1 H, $J_1 = J_2$ = 8.1 Hz, J_3 = 12.3 Hz), 1.37 (s, 9 H), 0.94 (s, 21 H), 0.0 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ = 181.6, 167.4, 157.1, 154.9, 148.7, 148.5, 147.7, 126.3, 124.3, 123.5, 111.0, 109.8, 81.1, 66.3, 61.3, 59.8, 55.8, 55.7, 40.1, 34.7, 28.3, 27.9, 17.9, 11.7, 1.4. IR (NaCl): 2940, 2865, 1695, 1660, 1515, 1365, 1260, 1225, 1165, 1090, 860 cm^{-1}. Anal. Calcd for $C_{36}H_{59}NO_7Si_2$: C, 64.15; H, 8.82; N, 2.08. Found: C, 64.01; H, 9.02; N, 1.93. HPLC (Daicel CHIRALCEL OD-H, ϕ0.46 × 250 mm, hexane:*i*-PrOH = 99:1, 0.5 mL/min) retention time: 14.3 min for (+)-**11**, 17.1 min for (–)-**11**. Compound **1**: Pale yellow needles ($CHCl_3$), mp 90.5–91.0 °C; $[\alpha]_D^{24}$ +46 (*c* 0.86, $CHCl_3$)*. HPLC (Daicel CHIRALPAK AD-H, ϕ0.46 × 250 mm, hexane:*i*-PrOH = 80:20, 1.0 mL/min) retention time: 31.6 min for (+)-**1**, 25.3 min for (–)-**1**.

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(8) Attempts to remove the MOM group from alcohol **4** led to concomitant desilylation.

(9) We converted both isomers of **6** to *O*-methylerysodienone(**1**). The absolute configuration of each intermediate

was not determined. In Scheme 2 and Scheme 3, one of the enantiomers was tentatively drawn for convenience.

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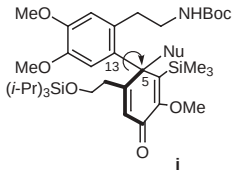
(11) The enantiomeric purity was determined by HPLC analysis. For the analytical conditions and retention times, see ref. 6.

(12) We were afraid of racemization in the oxidation of **9** and in the cyclization of **10**. If the reaction process involved dienone **i** as a transient intermediate, generated by the intermolecular attack of a nucleophile at the C(5), the change in the C(5) hybridization into sp^3 might have caused racemization due to the lowered rotational barrier about the C(5)-C(13) bond (Figure 2).



i

Figure 2

(13) (a) Ghosal, S.; Majumdar, S. K.; Chakraborti, A. *Aust. J. Chem.* **1971**, *24*, 2733. (b) Chou, C.-T.; Swenton, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 6898.

(14) The specific rotation of *O*-methylerysodienone has not been reported.