First Total Synthesis of (+)-11-Hydroxyerythratidine

Toshio Onoda, Yosuke Takikawa, Takashi Fujimoto, Yoshizumi Yasui, Keisuke Suzuki, Takashi Matsumoto*

Department of Chemistry, Tokyo Institute of Technology and SORST-JST Agency, 2-12-1, O-okayama, Meguro-ku, Tokyo 152-8551, Japan
Fax +81(3)57343531; E-mail: tmatsumo@chem.titech.ac.jp

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Abstract: The first total synthesis of (+)-11-hydroxyerythratidine is described. The strategy is featured by a highly stereoselective construction of the C(5) spiro center via the Lewis acid promoted cyclization of *ortho*-quinone acetal, derived from di-*ortho*-substituted biphenyl **9** with a chiral center at the side chain.

Key words: asymmetric synthesis, biphenyls, erythrinan alkaloids, natural product, spirocenter chirality

Erythrinan alkaloids constitute a class of natural products, sharing indolo[7a,1-*a*]isoquinoline skeleton (Figure 1).[1,2] These compounds have been popular synthetic targets by the challenges posed by the unique tetracyclic amino structures, and also by the physiological significance, exhibiting curare-like, sedative, hypotensive, and central nerve system depressant activities.[1,3,4] Indeed, many synthetic approaches have been developed, though the enantioselective ones are still limited.[4]

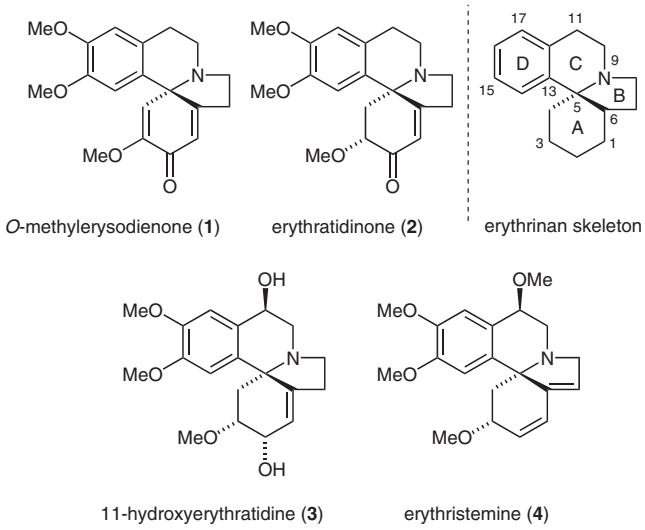
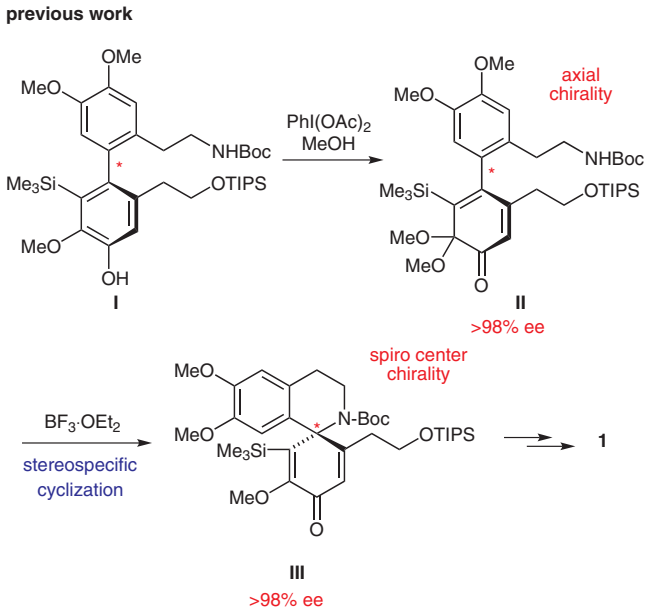


Figure 1 Natural erythrinan alkaloids

We recently reported an enantioselective approach to these alkaloids via the chiral transmission, and its viability was demonstrated by the total synthesis of (+)-*O*-methylerysodienone (**1**, Scheme 1).[5] By installing a TMS group for retarding the atropisomerization (enantiomerization), the axial chirality of *ortho*-'*tri*'-substituted biphenyl **I** is nicely transmitted into the chirality of spirocycle **III** via the Lewis acid promoted cyclization of *ortho*-quinone acetal **II**.

In further study, we focused on a class of minor erythrinan alkaloids with additional oxy function at C(11), such as **3** and **4**. By an adrenaline-like substructure at the N(9)–C(17) framework, intriguing biological profiles may be expectable. However, the synthesis of such C(11)-oxy compounds has been virtually unexplored; only one racemic synthesis has been recorded to date.[6,7]



Scheme 1 Stereospecific spirocyclization strategy

We became interested, however, in the possibility that the chiral center at the side chain in biphenyl **IV** may direct the mode of cyclization of *ortho*-quinone acetal **V**, allowing the stereocontrolled formation of the C(5) spiro center (Scheme 2). The key to such a plan was the behavior of two *ortho*-quinone acetal rotamers **Va** and **Vb**; given they are rapidly interconverting because of a *ortho*-'*di*'-substituted biphenyl-like structure, an optimistic assumption was either the cyclization rate or the equilibrium preference of **Va** and **Vb** was somehow different enough, enabling the diastereoselective cyclization to occur.

In this communication, we describe the realization of this scenario, albeit not straightforward, and application to the first total synthesis of (+)-11-hydroxyerythratidine (**3**).[8]

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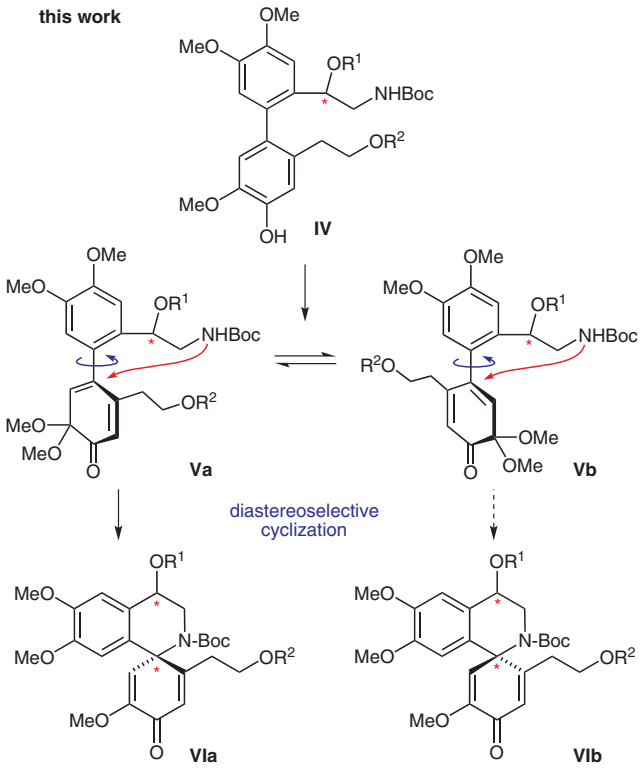
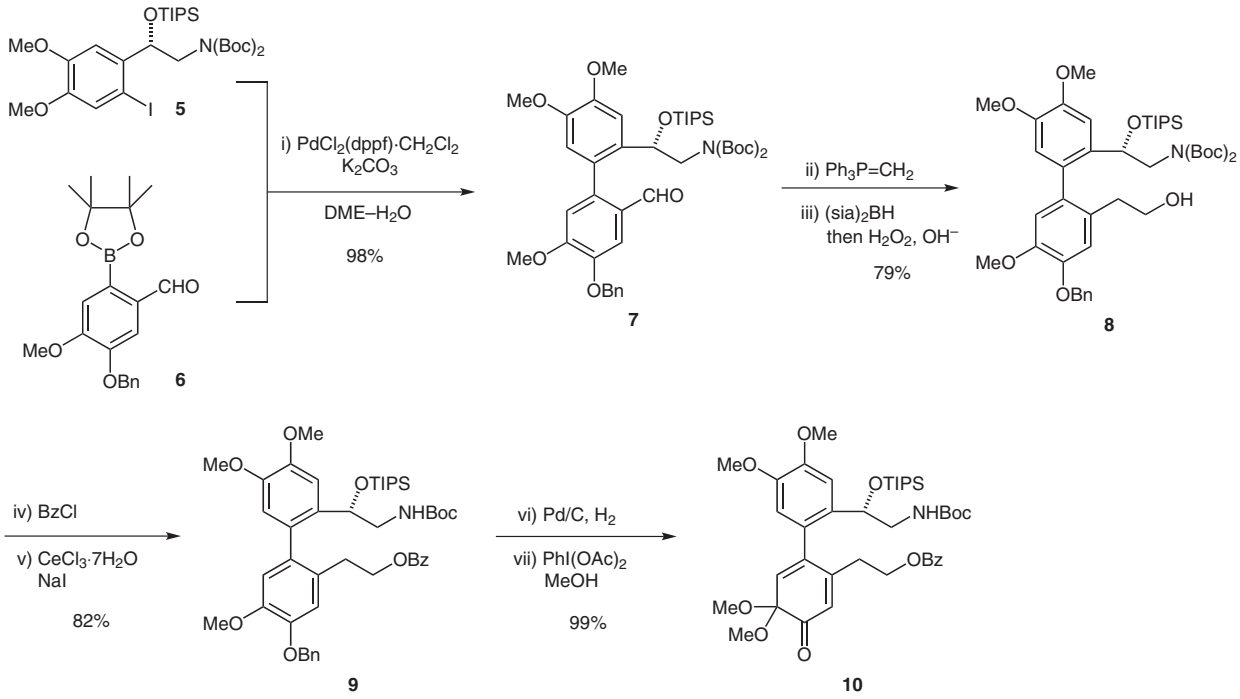


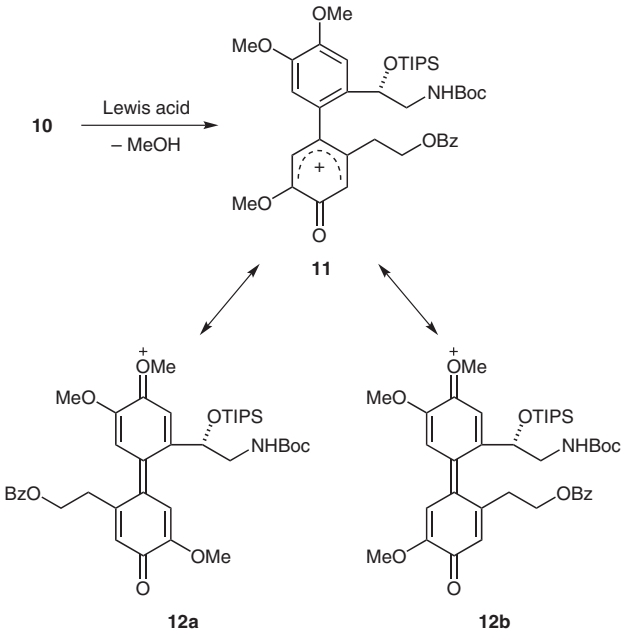
Scheme 2 Diastereoselective spirocyclization strategy

As the enantiomerically pure spirocyclization precursor, *ortho*-quinone acetal **10** was prepared starting from aryl iodide **5** {$[\alpha]_D^{26}$ –11 (*c* 0.92, $CHCl_3$), >99.5% ee},[9,10] which was coupled with boronic ester **6**[11] by Suzuki–Miyaura reaction[12] (Scheme 3). The reaction with 10 mol% of $PdCl_2(dppf)\cdot CH_2Cl_2$ (K_2CO_3, DME–H_2O, 60 °C) cleanly afforded biphenyl aldehyde **7** in 98% yield. The Wittig methylenation of the formyl group ($Ph_3P{=}CH_2$, THF), and hydroboration of the resulting olefin [$(Me_2CHCHMe)_2BH$, THF, 0 °C] followed by oxidative workup (H_2O_2, aq NaOH) afforded alcohol **8**. After protection of the primary alcohol by a benzoyl (BzCl, DMAP, pyridine, CH_2Cl_2), one of the Boc groups on the nitrogen was removed by treatment with $CeCl_3\cdot 7H_2O$ and NaI in MeCN (23–25 °C).[13] Final removal of the benzyl group (H_2, 10% Pd/C, MeOH) and selective oxidation of one of the aromatic rings by $PhI(OAc)_2$ (MeOH, 0 °C) gave the desired *ortho*-quinone acetal **10** in high yield.[14]

At the stage that *ortho*-quinone acetal **10** was obtained, NMR analyses ($CDCl_3$ and $C_6D_5CD_3$) showed us a pessimistic data;[15] two rotamers are present in roughly 1:1 ratio, which are interconverting only slowly. Variable-temperature NMR showed that the rotamer peaks did not coalesce even at 70 °C ($C_6D_5CD_3$), and further warming led to decomposition. The estimated rotational barrier was >18 kcal/mol, albeit not that high to allow rotamer separation. Nevertheless, we proceeded to examine the spirocyclization with a hope that the relevant bond rotation would become dynamic at the key cyclization stage, because the oxophenonium species **11** would help by the enforced planarity from contribution of the extended quinone-type resonances as **12a** and **12b** (Scheme 4).



Scheme 3 *Reagents and conditions*: i) 60 °C, 6 h; ii) THF, r.t., 1 h (80%); iii) THF, 0 °C, 2 h (99%); iv) DMAP, pyridine, CH_2Cl_2, r.t., 40 min (99%); v) MeCN, 23–25 °C, 37 h (83%); vi) MeOH, r.t., 2 h (quant.); vii) 0 °C, 1.5 h (99%).

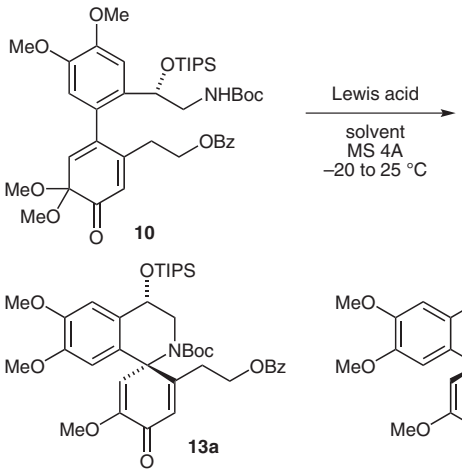


Scheme 4

Based on our previous experiences in related cyclizations,[5] we first examined $BF_3{\cdot}OEt_2$, TMSOTf and some other metal triflates (CH_2Cl_2, MS4A, –20 °C to 25 °C). Selected results are shown in Table 1. The reaction proceeded reasonably well with $BF_3{\cdot}OEt_2$, TMSOTf, $Yb(OTf)_3$, or $Cu(OTf)_2$, though the stereoselectivity was not spectacular so long as CH_2Cl_2 was used as the solvent (entries 1–4). However, we found a remarkable solvent effect; $Cu(OTf)_2$ in toluene specifically led to the excellent result — the desired spirocycle **13** was obtained in 96% yield in favor of **13a** in a 14:1 ratio (entry 8).[16]

The stereostructure of the major isomer **13a** was determined by X-ray crystallography after derivatization to diol **14** [(1) *n*-Bu_4NF, THF, –78 °C to 0 °C; (2) K_2CO_3, MeOH, –20 °C to r.t.],[17] thereby showing the *S*-configuration of the spiro stereogenic center, needed for the erythrinan alkaloids (Scheme 5).[1]

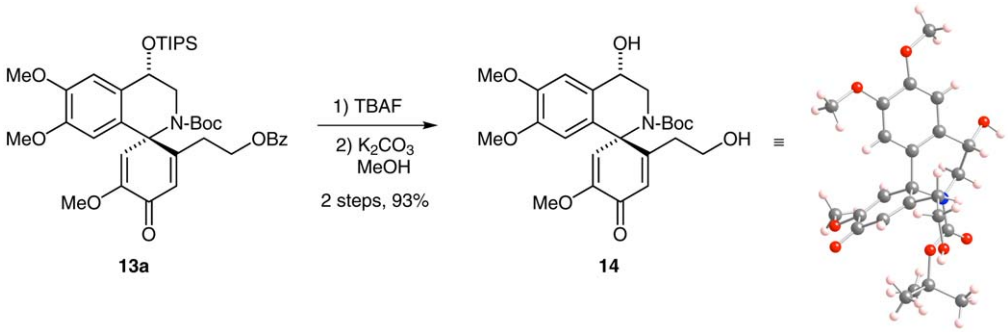
Table 1 Spirocyclization of *ortho*-Quinone Acetal **10**



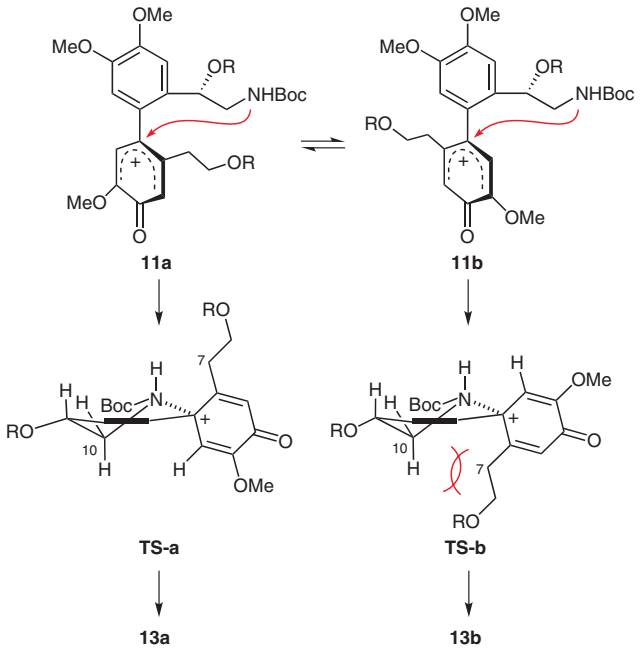
Entry	Lewis acid	(equiv)	Solvent	Yield (%)	**13a/13b**
1	$BF_3{\cdot}OEt_2$	0.5	CH_2Cl_2	76	1:1
2	TMSOTf	0.3	CH_2Cl_2	55	1:1.2
3	$Yb(OTf)_3$	0.3	CH_2Cl_2	75	1.3:1
4	$Cu(OTf)_2$	0.3	CH_2Cl_2	55	2.4:1
5	$BF_3{\cdot}OEt_2$	0.5	toluene	65	1:1.5
6	TMSOTf	0.3	toluene	55	1:1.2
7	$Yb(OTf)_3$	0.3	toluene	35	14:1
8	$Cu(OTf)_2$	0.4	toluene	95	14:1

The predominance of **13a** could be explained as follows (Scheme 6): If one assume the *pseudo*-equatorial placement of the bulky (triisopropylsilyl)oxy group in the transition state with half-chair-like conformation, two possible transition structures are **TS-a** (leading to **13a**) and **TS-b** (leading to **13b**). Among these, **TS-b** is less favored by steric repulsion as shown, letting aside the specific role of $Cu(OTf)_2$ and the solvent effect.

Having secured the key spiro center, our focus was shifted to the synthesis of 11-hydroxyerythratidine (**3**),[8] one of the C(11)-oxygenated erythrinan alkaloids.



Scheme 5 Conversion of spirocycle **13a** into diol **14** and the X-ray crystal structure of **14**. *Reagents and conditions*: i) THF, –78 °C to 0 °C, 3 h (quant.); ii) –20 °C to r.t., 6 h (93%).



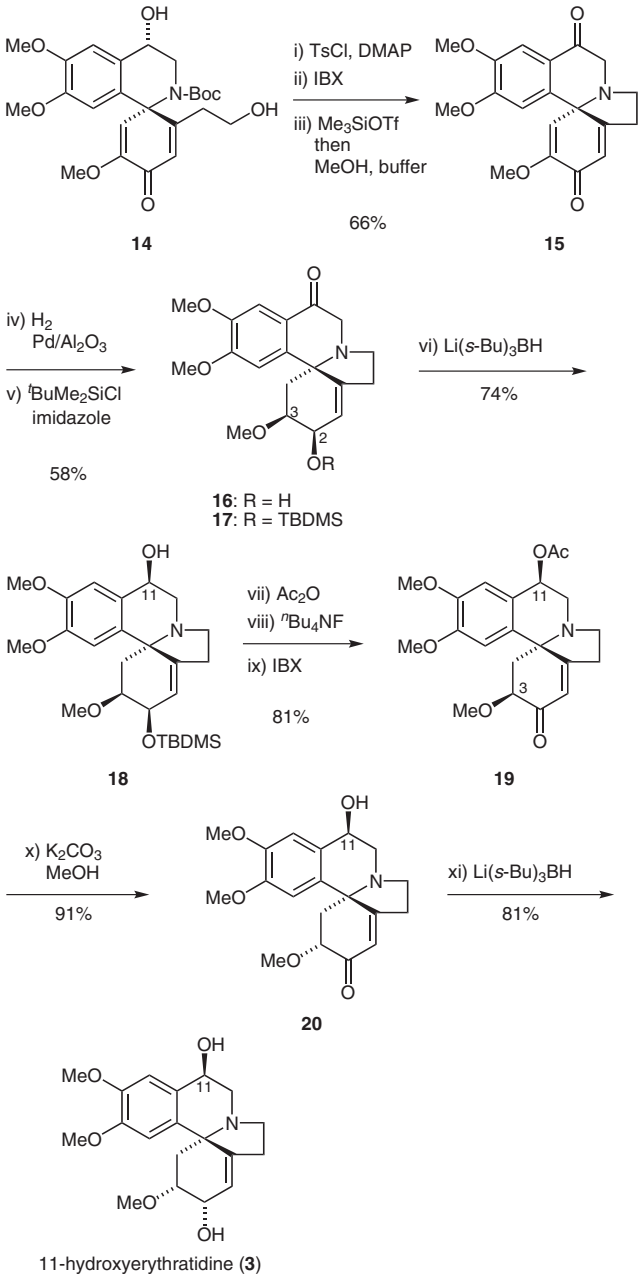
Scheme 6 Proposed transition-state structures for the spirocyclization [the bold lines in **TS-a** and **TS-b** represent the side view of the aromatic ring (the ring D)]

For the B-ring cyclization, the primary alcohol in diol **14** {$[\alpha]_D^{28}$ –1.5 (*c* 1.2, $CHCl_3$), >99.5% ee} was selectively tosylated (TsCl, pyridine, CH_2Cl_2, 0 °C) and the remaining alcohol was oxidized [*o*-iodoxybenzoic acid (IBX), DMSO].[18,19] Upon removal of the Boc group via formation of the trimethylsilyl carbamate (TMSOTf, CH_2Cl_2, 0 °C)[20] and subsequent hydrolysis (MeOH, pH 7 phosphate buffer), the desired B-ring cyclization spontaneously proceeded to give tetracycle **15** (Scheme 7), with a complete erythrinan skeleton as well as the functionalities ready for further transformations.

Selective hydrogenation of the C(3)–C(4) double bond necessitated considerable trials, but was finally effected by using 5% Pd on alumina as the catalyst [H_2 (1 atm), H_2O–EtOH (1:5)]. Simultaneously the C(2) carbonyl underwent reduction, presumably via hydrogenation of the enol tautomer from the less hindered α-face to give 2,3-*cis*-alcohol **16** exclusively.[21,22] Alcohol **16**, thus obtained, was protected by a *tert*-butyldimethylsilyl (TBDMS) group (TBDMSCl, imidazole, DMF, 0 °C).

Reduction of the C(11) carbonyl in **17** with Li(*s*-Bu)$_3$BH (THF, –78 °C to 0 °C) gave the corresponding 11β-alcohol **18** exclusively,[23,24] which was then converted into ketone **19** in three steps including acetylation of the C(11) hydroxy (Ac_2O, DMAP, pyridine, 0 °C), removal of the TBDMS group (*n*-Bu_4NF, THF), and oxidation of the resulting C(2) hydroxy group by IBX (DMSO).

Upon treatment with K_2CO_3 in MeOH, ketone **19** cleanly underwent epimerization at C(3) and deacetylation to give alcohol **20** in 91% yield, whose stereostructure was unambiguously determined by X-ray crystal structure analysis (Figure 2).[17,22]



Scheme 7 Synthesis of (+)-11-hydroxyerythratidine (**3**). *Reagents and conditions*: i) pyridine, 0 °C, 1.5 h (74%); ii) DMSO, r.t., 2.5 h (93%); iii) CH_2Cl_2, 0 °C, 3 h (96%); iv) H_2O–EtOH (1:5), r.t., 4.5 h; v) DMF, 0 °C, 1 h (58%, 2 steps); vi) THF, –78 °C to 0 °C, 2 h (74%); vii) DMAP, pyridine, 0 °C, 1 h (93%); viii) THF, r.t., 2 d (92%); ix) DMSO, r.t., 1 h (95%); x) r.t., 1.5 h (91%); xi) THF, –78 °C to 0 °C, 1 h (81%).

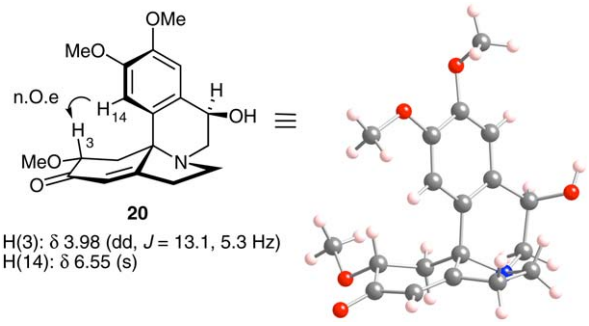


Figure 2 The X-ray crystal structure of **20** and the observed NOE

Finally, reduction of the C(2) carbonyl with Li(*s*-Bu)$_3$BH (THF, –78 °C to 0 °C) proceeded exclusively in an α-selective manner to complete the first synthesis of 11-hydroxyerythratidine (**3**) {$[\alpha]_D^{24}$ +203 (*c* 1.1, $CHCl_3$), >99.5% ee}.[25,26]

In summary, we have accomplished the first total synthesis of 11-hydroxyerythratidine (**3**). The key step was the Lewis acid promoted cyclization of *ortho*-quinone acetal **10** to effect the construction of the chiral spiro center at C(5) in highly diastereoselective manner. This synthesis demonstrates a new application of biphenyl derivative as a scaffold for stereocontrolled and convenient assembly of polycyclic structures in natural product synthesis. Further application of this methodology is now under investigation in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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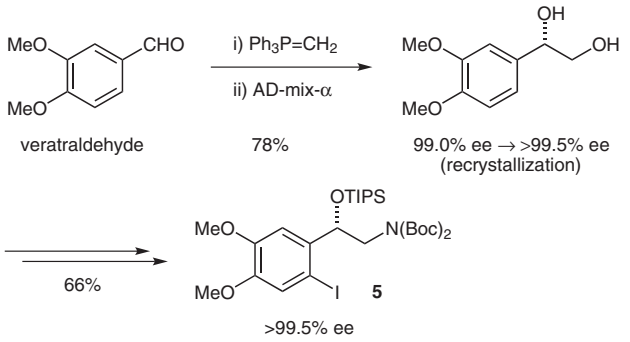
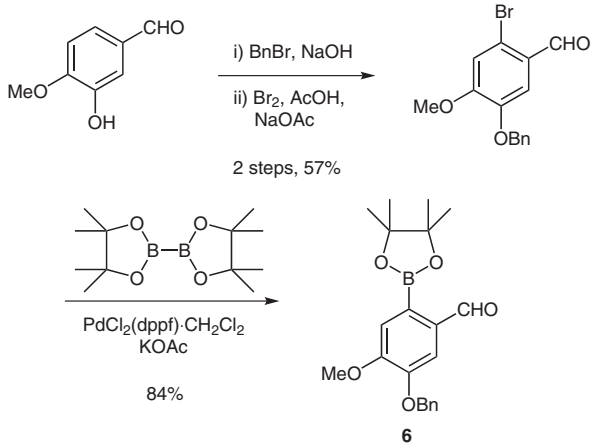
(9) Iodide **5** (>99.5% ee) was prepared from varatraldehyde via the Sharpless asymmetric dihydroxylation (Scheme 8). See Supporting Information.



Scheme 8

(10) The reaction with the corresponding mono-Boc derivative was not fruitful.

(11) Boronic ester **6** was synthesized in three steps from isovanillin (Scheme 9). For the palladium-catalyzed boronic ester formation with bis(pinacolato)diboron, see: (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813.



Scheme 9

(12) (a) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447. (b) For a review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

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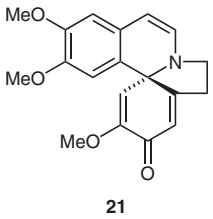
(15) (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
(16) **Experimental Procedure**
To a suspension of 4 Å MS (3.05 g) and $Cu(OTf)_2$ (1.06 g, 2.09 mmol) in toluene (13 mL) was added dropwise *ortho*-quinone acetal **10** (4.36 g, 5.78 mmol) in toluene (25 mL) at –20 °C, and the mixture was allowed to warm to 25 °C. After stirring for 13 h, the reaction was quenched by adding sat. aq $NaHCO_3$. The mixture was filtered through a Celite pad and the products were extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 3:2) to afford spirocycle **13a** (3.75 g, 90%) and **13b** (261 mg, 6%).
(17) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 712628 (for compound **14**) and 712629 (for compound **20**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax:+44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk]; http://www.ccdc.cam.ac.uk/products/csd/deposit/.
(18) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
(19) Attempted cyclizations of the derivatives possessing hydroxy or protected hydroxy at C(11) resulted in affording tetracyle **21** (Figure 3) with C(10)–C(11) double bond in various yields.



21

Figure 3

(20) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870; and references cited therein.
(21) α-Orientation of the C(2)hydrogen in **16**–**18** was deduced as follows:(1) The assumed ketone intermediate, though not detected, was supposed to be prone to enolization at the C(2) carbonyl to be hydrogenated [*cf.* epimerization of ketone **19** at C(3)];(2) in compounds **16**–**18**, the NOE was not observed between the hydrogens at C(2) and C(14) while observed in compound **3** with 2β-hydrogen (see ref. 26).
(22) Acetylation of **20** [Ac_2O, DMAP, pyridine] gave the stereoisomer of ketone **19**, which obviously shows that the conversion of **19** into **20** was the two-step process including the deacetylation and the epimerization at C(3). Because α-orientation of the C(3) methoxy in **20** was confirmed by X-ray crystal structure analysis, it leads to β-orientation of the C(3) methoxy in compound **19** as well as **16**–**18**.
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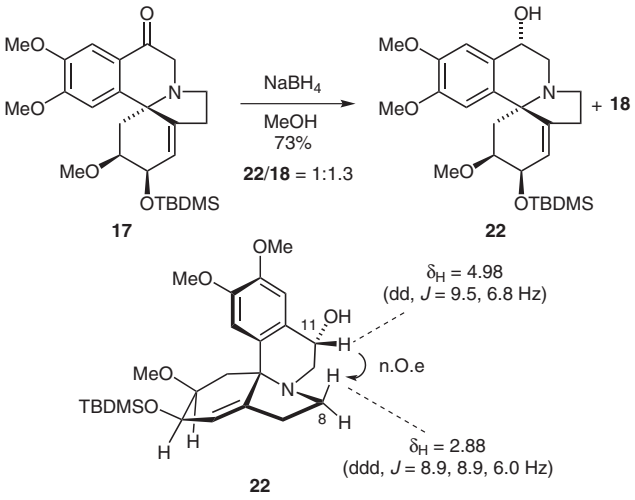
(24) The 11β-configuration of **18** was confirmed by employing its C(11) epimer **22** (Scheme 10), obtained as the minor isomer by the reduction with $NaBH_4$ (MeOH, r.t.), in which the NOE was observed between the hydrogens at C(8) and C(11).



Scheme 10

(25) The preference of the hydride attack from the β-face could be ascribed to the steric hindrance to the α-attack by the axial hydrogen at C(4).
(26) **(+)-11-Hydroxyerythratidine (3)**
Mp 188.5–190.3 °C (hexane–$CHCl_3$); $[\alpha]_D^{24}$ +203 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.82 (dd, 1 H, J_1 = 12.5 Hz, J_2 = 11.6 Hz), 1.93 (dd, 1 H, J_1 = 11.6 Hz, J_2 = 4.1 Hz), 2.00–2.25 (br, 2 H), 2.20–2.30 (m, 1 H), 2.40–2.60 (m, 1 H), 3.02 (ddd, 1 H, $J_1 = J_2$ = 9.3 Hz, J_3 = 6.8 Hz), 3.14 (ddd, 1 H, $J_1 = J_2$ = 9.3 Hz, J_3 = 3.0 Hz), 3.29 (dd, 1 H, J_1 = 15.4 Hz, J_2 = 1.2 Hz), 3.35 (s, 3 H), 3.62 (ddd, 1 H, J_1 = 12.5 Hz, $J_2 = J_3$ = 4.1 Hz), 3.73 (dd, 1 H, J_1 = 15.4 Hz, J_2 = 5.7 Hz), 3.83 (s, 3 H), 3.91 (s, 3 H), 4.44–4.54 (br, 1 H), 4.56–4.66 (br, 1 H), 5.86–5.94 (br, 1 H), 6.50 (s, 1 H), 7.06 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5, 35.5, 48.8, 50.5, 55.9, 56.1, 56.5, 62.9, 63.3, 64.7, 76.2, 109.8, 111.8, 120.8, 128.2, 128.3, 145.6, 148.0, 148.7. IR (ATR): 3393, 2926, 2866, 2852, 1509, 1462, 1255, 1101, 1057, 981, 873, 778, 750 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.48; H, 7.55; N, 3.83. HPLC [CHIRALCEL® OD-H (Daicel), Ø 0.46 × 25 cm (2×), hexane–2-PrOH (4:1), 1.0 mL/min, 30 °C, 254 nm] t_R = 12.6 min for **3** (15.4 min for *ent*-**3**). NOE was observed between the hydrogens at C(2) and C(14) (Figure 4).

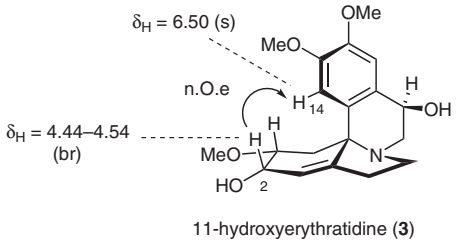


Figure 4