JOC The Journal of Organic Chemistry

Note

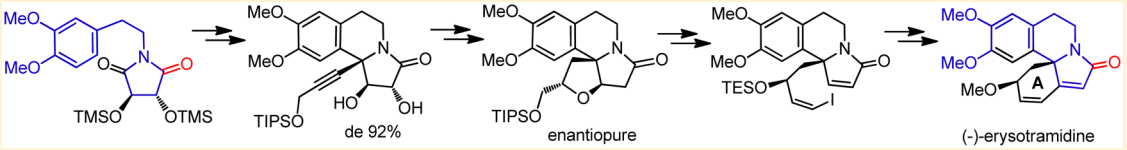
pubs.acs.org/joc

Heck Cyclization Strategy for Preparation of Erythrinan Alkaloids: Asymmetric Synthesis of Unnatural (−)-Erysotramidine from L-Tartaric Acid

Danuta Mostowicz, Mirosław Dygas, and Zbigniew Kałuża*

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

Supporting Information



ABSTRACT: With an imide derived from L-tartaric acid as the starting material, *ent*-erysotramidine was synthesized for the first time. The synthesis features the use of the enantiopure synthon, prepared in a set of highly stereoselective reactions, including N-acyliminium cyclization, dihydrofuranyl ring formation via silver-catalyzed intramolecular alcohol addition to acetylene, and vinyl ether catalytic hydrogen reduction. The crucial step of the synthesis, assembly of ring A, was achieved by using Heck cyclization of (*Z*)-iodoolefin.

The Erythrina alkaloids constitute a large group of natural products exhibiting diverse pharmacological effects[1] (Figure 1). Because of their unique bioactivity and challenges to construct the spirocyclic skeleton with a quaternary carbon stereogenic center, numerous approaches[2] for the preparation of racemic[3] and enantiopure[4] compounds with the erythrinian core have been developed.

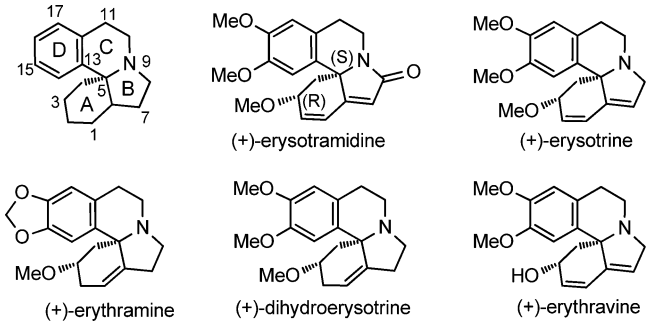


Figure 1. Erythrinan alkaloid skeleton and representative structures.

(+)-Erysotramidine and its deoxygenated derivative (+)-erysotrine are frequently selected as targets for total synthesis. However, only three research groups have succeeded with their preparation in a state of high enantiomeric purity. The first asymmetric synthesis of both alkaloids from (*S*)-3,4-dimethoxyphenylalanine methyl ester was reported by Tsuda two decades ago.[5] Another synthetic approach was announced by Simpkins et al.[4e] They accomplished a 13-step synthesis of (+)-erysotramidine (93% ee) using a chiral base imide desymmetrization, N-acyliminium addition, and radical cyclization as the key steps. The most recent formal synthesis of the discussed alkaloid was reported by Tietze et al.[4i] A crucial step of their elegant synthesis was a domino process: condensation of enantiopure keto ester with 3,4-dimethoxyphenethylamine, which led to spirocyclic silane with a complete erythrinan skeleton.

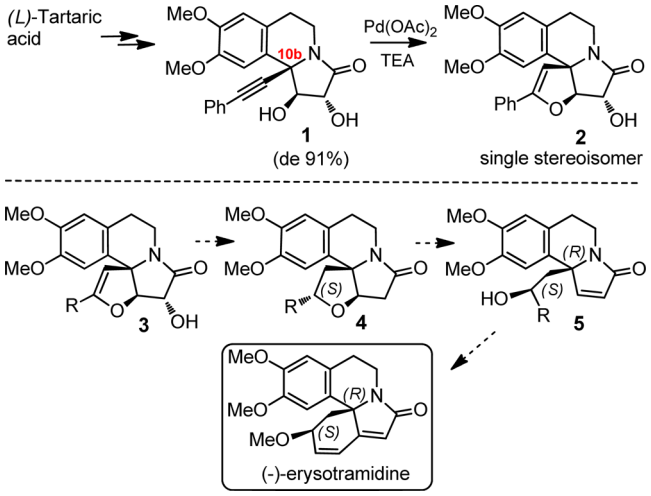
The existence of only three examples of asymmetric synthesis of natural (+)-erysotramidine indicate that the continuation of research in this field may lead to further development, including elaboration of a novel methodology for its preparation. Herein, we report the first total synthesis of unnatural (−)-erysotramidine from L-tartaric acid.

As part of a current project aimed at the preparation of isoquinoline alkaloids, we have developed a simple method for the synthesis of diacetoxyhexahydropyrroloisoquinolines[6] and their further transformation into highly functionalized enantiopure tetrahydroisoquinolines.[7] Throughout that study, the assignment of the configuration at the newly generated stereocenter within pyrroloisoquinolines was accomplished in all cases by NOE measurements, except for acetylene derivative **1**, lacking a diagnostic proton at the bridgehead carbon atom[6b] (Scheme 1). To overcome this difficulty, an epimeric mixture of **1** was subjected to palladium-catalyzed cyclization, furnishing dihydrofuranyl derivative **2** as a single stereoisomer. The formation of **2** has proven that the predominant epimer of **1** possesses an *S* configuration at C-10b. On close examination of the structure of **2**, we realized that an enantiomerically pure compound of this type (such as **3**) with a proper R substituent could be a suitable starting material for the synthesis of erysotramidine. We anticipated that reduction of an enol ether should proceed predominantly from the less hindered *Re* face to give furanyl derivative **4**, which on submission to elimination

Received: November 17, 2014
Published: January 8, 2015

DOI: 10.1021/jo5026157
J. Org. Chem. 2015, 80, 1957−1963

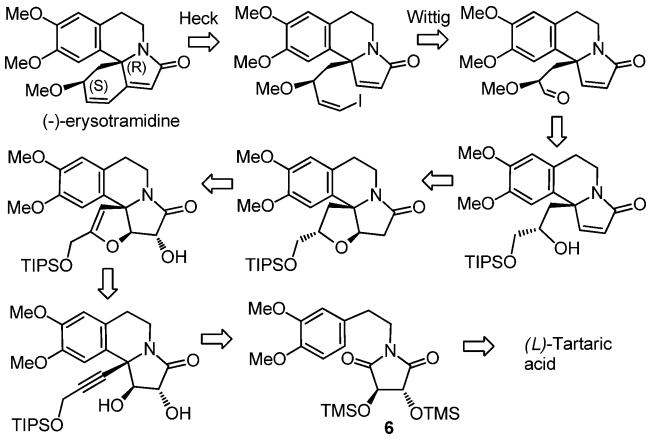
Scheme 1. New Concept of Erythrinan Alkaloid Synthesis Inspired by Earlier Work[6]



(retro-Michael reaction)[8] should lead to alcohol **5** with two stereogenic centers with the same configuration as unnatural (−)-erysotramidine.

The antipodes of biologically active compounds, synthetic as well as natural, often possess distinctly different biological functions.[9,10] To the best of our knowledge, (−)-erysotramidine was never previously synthesized. Therefore, we decided to undertake an effort to synthesize the antipode of the natural alkaloid, thereby facilitating the evaluation of its bioactivity. Our initial approach is outlined as a retrosynthesis in Scheme 2.

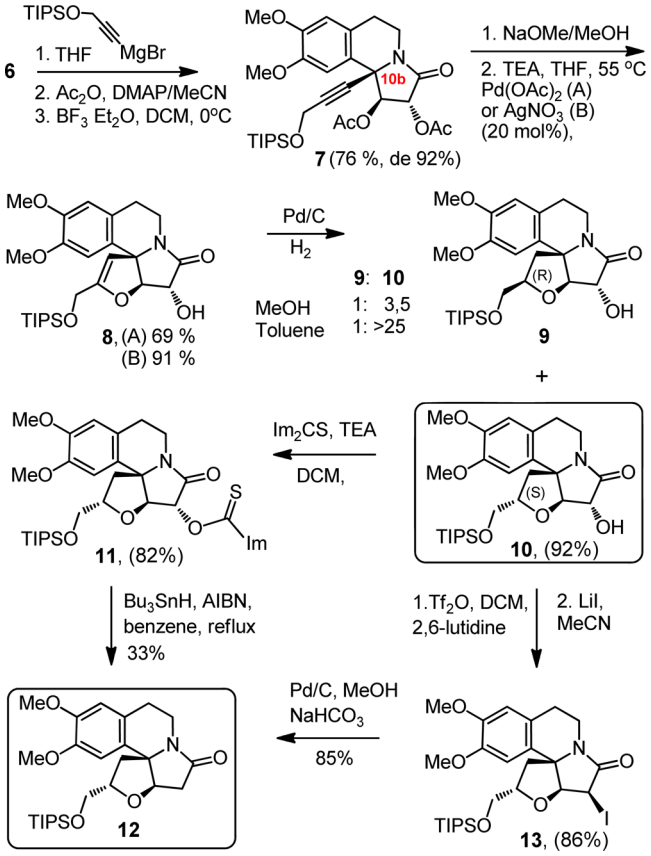
Scheme 2. Retrosynthesis of Unnatural (−)-Erysotramidine



The key step of a proposed synthesis is an intermolecular Heck reaction (IMH)[11] of (*Z*)-vinyl iodide, a product of Wittig olefination of α-methoxy aldehyde. Further disconnections lead to imide **6**, easily synthesized in two steps from L-tartaric acid.[4a,6b]

To verify our idea, we prepared pyrroloisoquinoline **7** using our three-step procedure:[6b] an addition of a Grignard reagent (derived from TIPS-protected propargyl alcohol) to imide **6**, acetylation, and BF_3−etherate induced cyclization (Scheme 3). The isolated epimeric mixture of diacetate **7** (76% yield, de 92%) was submitted to base hydrolysis followed by palladium diacetate cyclization, furnishing enantiopure dihydrofuranyl derivative **8**. The yield of **8** (69%) was acceptable, but the need to use an expensive palladium salt (20 mol %) and tedious

Scheme 3. Preparation of Enantiopure Intermediate 12



product purification on silica gel prompted us to examine a modified Hammond procedure[12] using silver nitrate in the presence of TEA. Under those conditions compound **8** was obtained in an excellent yield (91%).

The hydrogen reduction of **8** with Pd(C) catalyst in methanol led to a mixture of epimers **9** and **10**, isolated in about a 1:3.5 ratio, respectively. The relative configuration on the newly generated stereocenter in both epimers was assigned by NOE experiments. The observed proton interactions for isomers **9** and **10** provided unambiguous proof of their configuration (Figure 2).

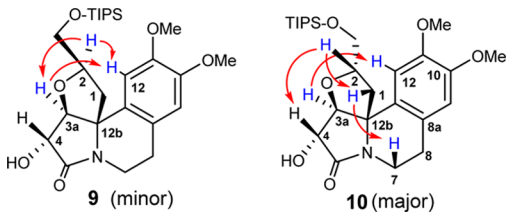


Figure 2. NOEs observed for diastereomers **9** and **10**.

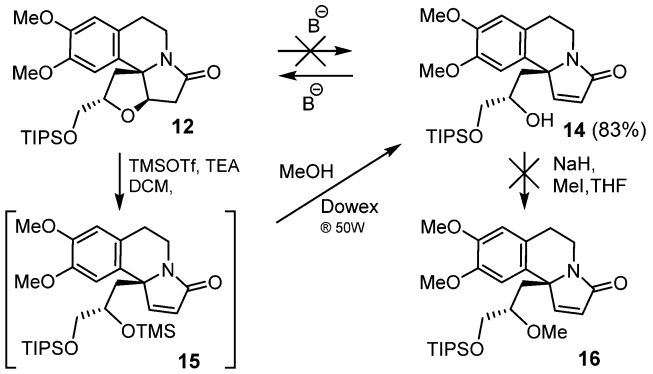
In agreement with our prediction, the required epimer **10** was prevalent; however, the stereoselectivity of the reduction was low. In order to improve the reaction selectivity in favor of epimer **10**, we tested several solvents and identified toluene as the solvent of choice. The hydrogen reduction of **8** in toluene resulted in excellent selectivity (**9**:**10** = 1:>25) to furnish, after flash chromatography and crystallization, enantiopure **10** in 92% yield. The alcohol **10** was submitted to thiocarbonyl imidazole ester formation and a Barton−McCombie deoxyge-

DOI: 10.1021/jo5026157
J. Org. Chem. 2015, 80, 1957−1963

nation[13] to give **12** in only 27% overall yield. The low yield prompted us to look for an alternative alcohol deoxygenation procedure. Alkyl iodides, easily available from alcohols,[14] can be conveniently reduced, e.g. by hydrogen with Pd(C) catalyst, into the dehalogenated derivatives.[15] Therefore, initially we attempted to prepare iodide **13** from alcohol **10** using PPh_3/I_2/imidazole, following the common procedure.[14] Unfortunately, only a fast decomposition of the substrate occurred. Further experimentation led to a simple two-step, one-pot procedure for the preparation of iodide **13**. Triflation of alcohol **10** in DCM, followed by the addition of LiI in MeCN solution, led to iodide **13** in 86% yield. Catalytic hydrogenolysis in the presence of sodium bicarbonate[15] furnished **12** in 85% yield (73% from **10**).

With enantiopure **12** in hand, we submitted it to a base-induced elimination (Scheme 4). Applying a variety of reaction

Scheme 4. Attempted Synthesis of Methyl Ether 16



conditions and bases (such as LDA,[8a] KOTMS,[8b] DBU,[8c] *t*-BuOK, HMDS-Na), we did not obtain the expected elimination product **14**. The use of a mixture of TMS-triflate and TEA[16] resulted in a fast reaction to give labile TMS-protected **15**, which was isolated as the alcohol **14**. Methylation of **14** with MeI in the presence of a base such as NaH or potassium *tert*-butoxide led back to **12** in a fast Michael addition. To avoid the use of a strong base, we examined several other commonly used methylation procedures, e.g. MeI/Ag_2O, CH_2N_2/HBF_4, and Meerwein's salt/lutidine, without any success, unfortunately.

Considering the above problems, we modified our initial plan by changing the order of the alcohol methylation–Heck cyclization reaction sequence. Standard deprotection of the hydroxyl group in silyl ether **12** furnished alcohol **17**, which was then submitted to Swern oxidation (Scheme 5).

The resulted crude aldehyde was promptly allowed to react with iodomethylene ylide using the Menche optimized procedure[17c] to give (*Z*)-iodoolefin **18** in 45% yield.[17] Finally, **18** was treated with a TESOTf/TEA mixture to afford elimination product **19** with the hydroxyl group protected as a relatively stable triethylsilyl ether.[18]

(*Z*)-Iodoolefin **19** was submitted to Heck cyclization using the Alibés procedure[11a] to give a mixture of the expected product **20** (4%), desilylated alcohol **21** (40%), and ketone **22** (40%) (Table 1, entry 1). Compound **22** is most likely a product of alcohol oxidation by the palladium(II) complex. To avoid this oxidation, we applied palladium(0) catalyst in DMF, and alcohol **21** was obtained in 62% yield as the sole product (entry 2). Cyclization with the same catalyst in toluene led to a mixture of silyl ether **20** (63%) and alcohol **21** (24%; entry 3).

Scheme 5. Preparation of (*Z*)-Vinyl Iodide 19

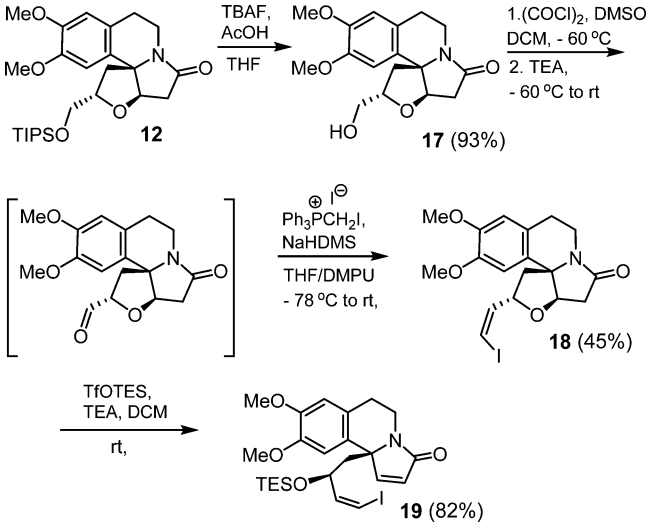
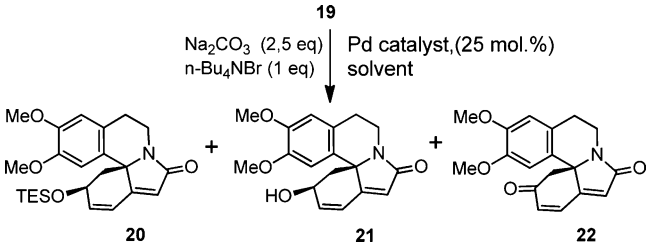


Table 1. Construction of the Erysotramidine A Ring: Optimization of Heck Cyclization Conditions[a]



entry	catalyst/additives	solvent/temp (°C)	time (h)	yield (%) 20	21	22
1	$PdCl_2(PPh_3)_2$ PPh_3 (1 equiv)	DMF/90	18	4	40	40
2	$Pd(PPh_3)_4$	DMF/80	24	0	62	0
3	$Pd(PPh_3)_4$	toluene/90	24	63	24	0
4[b]	$Pd(PPh_3)_4$	toluene/90	24	0	83	0

[a]Reactions were performed on 0.1 mmol scale in DMF or toluene (2.5 mL). [b]The crude product was dissolved in MeOH (5 mL), Dowex W40 resin (50 mg) was added, and the mixture was stirred for 15 min. Then workup and purification on silica gel were carried out.

Alternatively, to simplify the synthesis of alcohol **21**, the crude product of Heck cyclization was desilylated using acidic Dowex resin in methanol, and then the title compound was isolated in 83% yield. The final step of the synthesis, methylation of the alcohol **21** using the Tsuda procedure,[5] furnished (−)-erysotramidine in excellent yield (96%). The spectral data of the synthetic unnatural enantiomer was in full agreement with data reported previously for the natural product.[5] Furthermore, the absolute value of its optical rotation ($[\alpha]_D^{23} = -145.2°$ (*c* 1.57, $CHCl_3$)) was in good agreement with that reported for (+)-erysotramidine ($[\alpha]_D^{23} = +148.5°$ (*c* 1.2, $CHCl_3$)[5] and $[\alpha]_D^{23} = +121°$ (*c* 1.0, $CHCl_3$)[1e]).

In summary, a novel strategy for the asymmetric synthesis of erythrinan alkaloids has been developed. The effectiveness of our strategy was demonstrated by the completion of the first asymmetric synthesis of enantiopure unnatural (−)-erysotramidine from L-tartaric acid. Furthermore, starting from D-tartaric or L-malic acid, the presented methodology could be

DOI: 10.1021/jo5026157
J. Org. Chem. 2015, 80, 1957–1963

easily extended to the preparation of selected erythrinan alkaloids in their native configuration.

EXPERIMENTAL SECTION

Synthesis of (1*S*,2*R*,10b*S*)- and (1*S*,2*R*,10b*R*)-8,9-Dimethoxy-3-oxo-10b-(3-((triisopropylsilyl)oxy)prop-1-yn-1-yl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-1,2-diyl Diacetate (7). Our procedure was applied.[6] To a solution of triisopropylsilyl-protected propargyl alcohol[19] (45 mmol, 9.6 g) in THF (35 mL) was added methylmagnesium bromide (45 mmol, 15 mL, 3 M/Et_2O) dropwise at room temperature. The mixture was stirred for 1 h, and then the generated organomagnesium bromide was added slowly to a solution of imide **6**[4a,6b] (22.5 mmol, 9.9 g) in THF (35 mL) at 10 °C. The reaction mixture was stirred at 10 °C for 15 min and gradually warmed to room temperature, and stirring was continued until TLC indicated the disappearance of **6** (approximately 4−5 h). The reaction mixture was poured into an ice-cold saturated $NaHCO_3$ solution (200 mL) and extracted with MTBE (3 × 200 mL). The combined extracts were washed with ice-cold water and , brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude hydroxy lactam was dissolved in dry MeCN (150 mL), and after the solution was cooled to 0 °C, dimethylaminopyridine (5.5 g, 45 mmol) and Ac_2O (11.4 g, 10.6 mL, 112 mmol) were added. The cooling bath was removed, and stirring was continued at room temperature for 3 h. The reaction mixture was poured into ice-cold water (200 mL) and extracted with DCM (3 × 100 mL), and the collected extracts were washed with cold water (3 × 100 mL), saturated aqueous sodium bicarbonate (2 × 100 mL), and brine, dried ($MgSO_4$), and evaporated. Crude acetylated lactam was coevaporated with toluene (2×) and carefully dried at room temperature under high vacuum (<0.1 Torr, 2 h). The residue was dissolved in DCM (900 mL), the solution was cooled to 0 °C, and with vigorous stirring $BF_3{\cdot}Et_2O$ (12.7 g, 11.6 mL, 90 mmol, 4 equiv) was rapidly injected (syringe) in one portion. Stirring at 0 °C was continued for 15 min, and then the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL). Stirring was continued for 0.5 h, the layers were separated, and the aqueous layer was extracted with DCM (2 × 50 mL). The combined extracts were washed with water (2 × 200 mL) and , brine (100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The product was purified by flash column chromatography on silica gel using a diethyl ether/hexane (4/1, v/v) mixture as an eluent. Pyrroloisoquinoline **7** was isolated as a mixture of epimers (de 92%). Yield: 9.77 g, 76%, based on sequential three-step reaction from imide **6**. Yellowish oil. $[\alpha]_D^{23}$ = +106.8° (*c* 0.99, DCM). IR (DCM): 3509, 2942, 2866, 1757, 1730, 1519, 1227, 1069 cm^{-1}.

Selected Data for 23:1 Mixture of 1S,2R,10bS and 1S,2R,10bR Epimers. 1*S*,2*R*,10b*S* epimer of **7**: ^1H NMR (500 MHz) δ 6.75 (s, 1H), 6.57 (s, 1H), 5.72 (dd, 1H, *J* = 8.0, 1.0 Hz), 5.40 (d, 1H, *J* = 8.0), 4.44 (s, 2H), 4.35 (ddd, 1H, *J* = 13.1, 6.2, 1.6 Hz), 3.85 (s, 3H), 3.80 (s, 3H), 3.28−3.21 (m, 1H), 2.96−2.89 (m, 1H), 2.70 (dd, 1H, *J* = 16.2, 2.8 Hz), 2.23 (s, 3H), 2.12 (s, 3H), 1.07−1.02 (m, 21H); ^{13}C NMR (125 MHz) δ 170.2, 169.8, 164.6, 149.0, 148.3, 127.0, 124.6, 111.5, 107.9, 86.2, 80.8, 78.7, 74.2, 57.6, 55.9, 55.7, 52.0, 35.2, 27.5, 20.9, 20.7, 17.8, 12.0; MS (ES, HR) *m*/*z* (M + Na^+) calcd for $C_{30}H_{43}NO_8SiNa$ 596.2656, found 596.2649. 1*S*,2*R*,10b*R* epimer of **7**: ^1H NMR (500 MHz) δ 6.64 (s, 1H), 5.86 (s, 1H), 5.08 (s, 1H), 4.40 (s, 2H).

Synthesis of (3a*S*,4*R*,12b*S*)-4-Hydroxy-10,11-dimethoxy-2-(((triisopropylsilyl)oxy)methyl)-7,8-dihydro-3a*H*-furo[3′,2′:2,3]-pyrrolo[2,1-*a*]isoquinolin-5(4*H*)-one (8). Diacetate **7** (16 mmol, 9.17 g) was dissolved at room temperature in dry MeOH (160 mL) containing MeONa (600 mg, 11 mmol). The solution was stirred until TLC indicated the disappearance of the substrate (1 h), and then the reaction mixture was quenched by the addition of a small piece of dry ice and evaporated in vacuo. The residue was dissolved in DCM (160 mL), the precipitate was filtered off and washed with DCM, and the filtrate was evaporated. The residue was filtered through a pad of silica gel using an MTB/methanol (96/4) mixture. Yield: 7.3 g, 93%. This epimeric mixture of dihydroxypyrroloisoquinolines was used directly in the next step.

Cyclization Catalyzed with $Pd(OAc)_2$. The mixture of dihydroxypyrroloisoquinolines (0.48 g, 0.98 mmol) was dissolved in THF (6 mL), and $Pd(OAc)_2$ (44 mg, 0.20 mmol, 20 mol %) and triethylamine (60 μL, 0.40 mmol, 40 mol %) were added. The reaction mixture was stirred at room temperature until the disappearance of the substrate (TLC control), approximately 5 h. The mixture was poured into water and extracted with DCM (2 × 30 mL). The collected extracts were washed with water, saturated $NaHCO_3$ solution, and water again and then dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (gradient MTBE/hexane (7/3, v/v) to MTBE) to give **8** as a white amorphous solid. Yield: 0.33 g, 69%.

Cyclization Catalyzed with $AgNO_3$. The mixture of dihydroxypyrroloisoquinolines (2.45 g, 5.0 mmol) was dissolved in THF (30 mL), and $AgNO_3$ (170 mg, 1.0 mmol, 20 mol %) and triethylamine (140 μL, 1.0 mmol, 20 mol %) were added. The reaction mixture was heated at 55−60 °C for 6 h and then cooled to room temperature, filtered through a Celite pad, and evaporated in vacuo. The residue was purified as above to give **8** as a white amorphous solid: yield 2.23 g, 91%; white crystals; mp 142−144 °C (diethyl ether/hexane); $[\alpha]_D^{23}$ = +217.5° (*c* 0.97, DCM); IR (DCM) 3552, 3331, 2944, 2894, 2867, 1699, 1612, 1512, 1226, 1117 cm^{-1}; ^1H NMR (500 MHz) δ 6.60 (s, 1H), 6.54 (s, 1H), 5.31 (s, 1H), 4.87 (d, 1H, *J* = 3.9 Hz), 4.52 (t, 1H, *J* = 3.9 Hz), 4.38 (dd, 2H, *J* = 4.4, 1.3 Hz), 4.37−4.31 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.23 (d, 1H, *J* = 2.6 Hz), 3.09 (dt, 1H, *J* = 12.7, 3.8 Hz), 3.00−2.90 (m, 1H), 2.65 (dd, 1H, *J* = 16.2, 3.3 Hz), 1.19−1,10 (m, 3H), 1.08−1.04 (d, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 160.3, 148.6, 148.5, 129.8, 124.8, 111.1, 108.4, 102.7, 92.7, 77.6, 72.6, 59.0, 56.0, 55.9, 36.7, 27.6, 17.9, 11.9; MS (ES, HR) *m*/*z* (M + Na^+) calcd for $C_{26}H_{39}NO_6SiNa$ 512.2439, found 512.2461. Anal. Calcd for $C_{26}H_{39}NO_6Si$: C, 63.77; H, 8.03; N, 2.86. Found: C, 63.75; H, 8.08; N, 2.83.

Synthesis of (2*R*,3a*S*,4*R*,12b*R*)- and (2*R*,3a*S*,4*R*,12b*S*)-4-Hydroxy-10,11-dimethoxy-2-(((triisopropylsilyl)oxy)methyl)-3a,4,7,8-tetrahydro-1*H*-furo[3′,2′:2,3]pyrrolo[2,1-*a*]isoquinolin-5(2*H*)-one (9 and 10). *General Hydrogenation Procedure.* To a solution of **8** (0.49 g, 1.0 mmol) in solvent (30 mL) was added 10% Pd/C (0.17 g, Fluka 75990). The resulting suspension was stirred vigorously at 20 °C under an H_2 atmosphere (balloon) for 1 h. After purging with nitrogen, the catalyst was removed by filtration through a Celite pad and washed with DCM and the filtrate was concentrated.

Reduction in Methanol. The crude product was purified by flash column chromatography on silica gel using diethyl ether as eluent to give **9** (58 mg), **10** (230 mg), and a mixed fraction containing **9** and **10** (154 mg). This fraction was repurified on silica gel to give **9** (30 mg) and **10** (81 mg). The overall yield of **9** was 88 mg (18%) and of **10** was 310 mg (63%).

Reduction in Toluene. The crude product was purified by crystallization from an ethyl ether/hexane mixture, to give pure **10** (325 mg, 66%). The supernatant was evaporated in vacuo, and the residue was purified by flash column chromatography on silica gel using diethyl ether as eluent. The obtained solid was crystallized to give an additional amount of **10** (125 mg). The overall yield of **10** was 450 mg (92%).

*Data for **9**:* white crystals; mp 118 °C (methanol); $[\alpha]_D^{23}$ = +125.7° (*c* 1.0, DCM); IR (DCM) 3683, 3563, 2944, 2867, 1698 cm^{-1}; ^1H NMR (600 MHz) δ 6.73 (s, 1H), 6.58 (s, 1H), 4.58 (d, 1H, *J* = 3.5 Hz), 4.57−4.52 (m, 1H), 4.49 (s, 1H), 4.19 (dq, 1H, *J* = 6.5, 3.0 Hz), 3.88−3.73 (m, 7H), 3.79 (dd, 1H, *J* = 10.6, 4.1 Hz), 3.24−3.18 (m, 1H), 3.02 (d, 1H, *J* = 2.2 Hz), 3.01−2.94 (m, 1H), 2.73−2.68 (m, 1H), 2.37−2.28 (m, 2H), 1.15−1.05 (m, 21H); ^{13}C NMR (125 MHz) δ 171.4, 148.4, 148.3, 131.4, 124.8, 111.5, 106.8, 90.9, 83.1, 77.2, 70.0, 65.0, 56.1, 55.9, 44.0, 36.6, 27.1, 17.9, 11.9; MS (ES, HR) *m*/*z* (M + Na^+) calcd for $C_{26}H_{41}NO_6SiNa$ 514.2601, found 514.2596. Anal. Calcd for $C_{26}H_{41}NO_6Si$: C, 63.51; H, 8.40; N, 2.85. Found: C, 63.46; H, 8.38; N, 2.76.

*Data for **10**:* white crystals; mp 150 °C (ethyl acetate/hexane); $[\alpha]_D^{23}$ = +149.7° (*c* 1.0, DCM); IR (DCM) 3564, 3384, 2944, 2867, 1697, 1611, 1513, 1363, 1219, 1076 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 6.71 (s, 1H), 6.04 (s, 1H), 4.88 (d, 1H, *J* = 2.3 Hz), 4.83 (d, 1H, *J* =

DOI: 10.1021/jo5026157
J. Org. Chem. 2015, 80, 1957−1963

2.6 Hz), 4.60 (bs, 1H), 4.20 (dd, 1H, J = 12.9, 5.6 Hz), 3.84 (dd, 1H, J = 10.9, 3.7 Hz), 3.76−3.70 (m, 1H), 3.64 (dd, 1H, J = 10.9, 3.7 Hz), 3.39 (s, 1H), 3.31 (s, 1H), 2.71−2.64 (m, 1H), 2.54 (dt, 1H, J = 12.5, 4.3 Hz), 2.13 (dd, 1H, J = 13.3, 10.6 Hz), 1.99 (dd, 1H, J = 16.0, 4.1 Hz), 1.87 (dd, 1H, J = 13.3, 4.9 Hz), 1.08−1.00 (m, 21H); ^{13}C NMR (125 MHz) δ 172.9, 148.5, 148.4, 130.7, 125.3, 111.3, 107.4, 90.5, 79.8, 75.6, 70.9, 63.8, 56.1, 55.9, 44.0, 36.6, 27.2, 18.0, 11.9; MS (ES) m/z (M + Na)$^+$ found 514.26. Anal. Calcd for $C_{26}H_{41}NO_6Si$: C, 63.51; H, 8.40; N, 2.85. Found: C, 63.41; H, 8.44; N, 2.81.

Synthesis of *O*-((2*S*,3a*S*,4*R*,12b*S*)-10,11-Dimethoxy-5-oxo-2-(((triisopropylsilyl)oxy)methyl)-2,3a,4,5,7,8-hexahydro-1*H*-furo[3′,2′:2,3]pyrrolo[2,1-*a*]isoquinolin-4-yl) 1*H*-Imidazole-1-carbothioate (11). To a solution of **10** (98 mg, 0.20 mmol) in DCM (8 mL) were added thiocarbonyldiimidazole (178 mg, 1.0 mmol) and TEA (120 μL, 0.8 mmol). The mixture was heated at reflux for 24 h, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel using diethyl ether/ethyl acetate (7/3, v/v) as eluent: yield 98 mg (82%); yellowish crystals; mp 159 °C (diethyl ether/hexane); $[\alpha]_D^{23}$ = +120.7° (c 0.95, DCM); IR (DCM) 3134, 2944, 2867, 1712, 1611 cm^{-1}; ^{1}H NMR (500 MHz) δ 8.17 (s, 1H), 7.47 (s, 1H), 6.97 (s, 1H), 6.67 (s, 1H), 6.57 (s, 1H), 6.10 (s, 1H), 4.81 (d, 1H, J = 2.2 Hz), 4.50−4.40 (m, 1H), 4.26−4.18 (m, 1H), 4.04 (dd, 1H, J = 11.0, 3.9 Hz), 3.94 (dd, 1H, J = 11.0, 3.8 Hz), 3.87 (s, 3H), 3.83 (s, 3H), 3.23−3.15 (m, 1H), 3.14−3.02 (m, 1H), 2.70 (dd, 1H, J = 16.0, 3.9 Hz), 2.43 (dd, 1H, J = 13.5, 5.0 Hz), 2.32 (dd, 1H, J = 13.5, 10.8 Hz), 1.17−1.05 (m, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.6, 166.4, 148.8, 148.7, 136.4, 129.4, 129.3, 125.5, 118.5, 111.5, 107.2, 87.7, 83.2, 80.4, 71.4, 63.6, 56.1, 55.9, 43.7, 36.9, 27.1, 18.0, 12.0; MS (ES, HR) m/z (M + H$^+$) calcd for $C_{30}H_{44}N_3O_6SSi$ 602.2720, found 602.2711. Anal. Calcd for $C_{30}H_{43}N_3O_6SSi$: C, 59.87; H, 7.20; N, 6.98. Found: C, 59.66; H, 7.27; N, 6.94.

Synthesis of (2*S*,3a*S*,4*S*,12b*S*)-4-Iodo-10,11-dimethoxy-2-(((triisopropylsilyl)oxy)methyl)-3a,4,7,8-tetrahydro-1*H*-furo-[3′,2′:2,3]pyrrolo[2,1-*a*]isoquinolin-5(2*H*)-one (13). To a stirred solution of **10** (0.45 g, 0.90 mmol) and 2,6-lutidine (0.31 mL, 2.7 mmol) in DCM (20 mL) was added trifluoromethanesulfonic anhydride (0.22 mL, 1.4 mmol) dropwise at −10 °C. The solution was stirred at −10 °C for 1 h (TLC monitoring for substrate consumption). To the reaction mixture was added LiI (0.7 g, 5.2 mmol) suspended in CH_3CN (30 mL), and this mixture was stirred overnight at room temperature. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with DCM (3 × 50 mL). The combined organic extracts were washed with 10% aqueous citric acid solution, 10% aqueous sodium thiosulfate solution, and brine and then dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (gradient diethyl ether/hexane (8/2, v/v) to diethyl ether): yield 460 mg (86%); white crystals; mp 110 °C (hexane); $[\alpha]_D^{23}$ = +117.8° (c 0.89, DCM); IR (DCM) 3550, 2941, 2865, 1698 cm^{-1}; ^{1}H NMR (500 MHz) δ 6.71 (s, 1H), 6.53 (s, 1H), 4.80 (d, 1H, J = 7.8 Hz), 4.52 (d, 1H, J = 7.2 Hz), 4.42 (dd, 1H, J = 12.6, 6.6 Hz), 4.19−4.14 (m, 1H), 4.03 (dd, 1H, J = 10.8, 3.6 Hz), 3.90 (dd, 1H, J = 11.4, 3.6 Hz), 3.84 (s, 6H), 3.09 (dt, 1H, J = 12.6, 4.2 Hz), 3.02−2.94 (m, 1H), 2.61 (dd, 1H, J = 16.2, 3.6 Hz), 2.43 (dd, 1H, J = 13.2, 4.8 Hz), 2.32 (dd, 1H, J = 12.6, 10.8 Hz), 1.10−1.04 (m, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 148.7, 148.5, 128.7, 126.1, 111.5, 107.5, 81.5, 80.3, 72.8, 63.3, 56.1, 55.9, 43.7, 37.3, 27.3, 26.6, 18.0, 17.7, 12.3, 11.9; MS (ES, HR) m/z (M + Na$^+$) calcd for $C_{26}H_{40}NO_5ISiNa$ 624.1618, found 624.1614. Anal. Calcd for $C_{26}H_{40}INO_5Si$: C, 51.91; H, 6.70; N, 2.33. Found: C, 51,86; H, 6.71; N, 2.35.

Synthesis of (2*S*,3a*R*,12b*S*)-10,11-Dimethoxy-2-(((triisopropylsilyl)oxy)methyl)-3a,4,7,8-tetrahydro-1*H*-furo[3′,2′:2,3]-pyrrolo[2,1-*a*]isoquinolin-5(2*H*)-one (12). *Method A.* To a solution of thiocarbamate **11** (60 mg, 0.10 mmol) in benzene (10 mL) were added the tributyltin hydride (58 mg, 53 μL, 0.20 mmol) and α,α′-azoisobutyronitrile (4 mg, 0.025 mmol) successively. The reaction mixture was stirred under reflux for 6 h, additional tributyltin hydride (58 mg, 53 μL, 0.20 mmol) was added, and stirring and heating were continued overnight. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (gradient diethyl ether/hexane (1/9, v/v) to diethyl ether): yield 16 mg (33%).

Method B. To a solution of **13** (0.47 g, 0.78 mmol) in methanol (50 mL) were added solid $NaHCO_3$ (0.25 g, 3.0 mmol) and Pd/C 10% (0.15 g). The resulting suspension was stirred vigorously at 20 °C under an H_2 atmosphere (balloon) for 24 h. After purging with nitrogen, the catalyst was removed by filtration through a Celite pad and washed well with DCM and the collected filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using diethyl ether as eluent to give **12**: yield 0.31 g (85% yield); amorphous solid; $[\alpha]_D^{23}$ = +100.7° (c 1.00, DCM); IR (DCM) 3384, 2942, 2865, 1698, 1612 cm^{-1}; ^{1}H NMR (500 MHz) δ 6.73 (s, 1H), 6.54 (s, 1H), 4.78 (dd, 1H, J = 7.7, 1.9 Hz), 4.42 (dd, 1H, J = 13.0, 6.0 Hz), 4.18−4.12 (m, 1H), 3.98 (dd, 1H, J = 10.9, 3.9 Hz), 3.90−3.83 (m, 7H), 3.09 (dt, 1H, J = 12.6, 4.3 Hz), 3.01−2.92 (m, 1H), 2.72 (dd, 1H, J = 18.5, 7.8 Hz), 2.63−2.55 (m, 2H), 2.32 (dd, 1H, J = 13.2, 4.6 Hz), 2.23 (dd, 1H, J = 13.2, 10.8 Hz), 1.15−1.00 (m, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 148.4, 148.3, 129.7, 126.3, 111.5, 107.6, 82.6, 79.2, 73.2, 63.8, 56.1, 55.9, 44.1, 39.0, 36.1, 27.4, 18.0, 12.0; MS (EI, HR) m/z (M$^+$) calcd for $C_{26}H_{41}NO_5Si$ 475.2754, found 475.2745.

Synthesis of (*R*)-10b-((*S*)-2-Hydroxy-3-((triisopropylsilyl)-oxy)propyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]iso-quinolin-3(10b*H*)-one (14). To a stirred and precooled to −10 °C solution of TMS-OTf (417 μL, 2.3 mmol) in DCM (8 mL) was added TEA (403 μL, 2.9 mmol), followed by dropwise addition of a solution of **12** (554 mg, 1.2 mmol) in DCM (8 mL). Stirring was continued until disappearance of the substrate (TLC control), approximately 15 min, and then the reaction mixture was poured into ice-cold saturated $NaHCO_3$ solution and extracted with DCM (3 × 30 mL). The combined organic extracts were washed with brine and then dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was dissolved in methanol (10 mL), acidic Dowex 50W (300 mg) was added, and the mixture was stirred until TMS-ether was hydrolyzed (TLC control), approximately 15 min. The resin was filtered off and washed with methanol, and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (TBME/MeOH (97/3, v/v)): yield 460 mg, (83%); white crystals; mp 174−175 °C (ethyl acetate/hexane); $[\alpha]_D^{19}$ = +168.6° (c 1.02, DCM); IR (DCM) 3383, 2942, 2865, 1674 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.48 (d, 1H, J = 5.8 Hz), 6.74 (s, 1H), 6.59 (s, 1H), 6.11 (d, 1H, J = 5.8 Hz), 4.42 (dd, 1H, J = 13.3, 6.4 Hz), 3.88 (s, 3H), 3.84 (s, 3H), 3.54 (dd, 1H, J = 13.3, 7.9 Hz), 3.48−3.42 (m, 2H), 3.16−3.08 (m, 1H), 2.98−2.90 (m, 1H), 2.62 (dd, 1H, J = 16.0, 4.0 Hz), 2.16−2.05 (m, 2H), 1.13−1.01 (m, 21H); ^{13}C NMR (125 MHz) δ 171.7, 153.3, 148.2, 147.8, 129.1, 125.2, 124.6, 112.1, 109.4, 67.6, 67.5, 67.4, 56.2, 55.9, 42.3, 34.7, 28.9, 17.9, 11.9; MS (EI, HR) m/z (M$^+$) calcd for $C_{26}H_{41}NO_5Si$ 475.2754, found 475.2747. Anal. Calcd for $C_{26}H_{41}NO_5Si$: C, 65.65; H, 8.69; N, 2.94. Found: C, 65.43; H, 8.61; N, 2.96.

Synthesis of (*R*)-10b-((*S*)-2-Hydroxy-3-((triisopropylsilyl)-oxy)propyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]-isoquinolin-3(10b*H*)-one (17). To a solution of **12** (1.83 g, 3.9 mmol) in THF (40 mL) were added TBAF (1 M in THF, 6.2 mL, 6.2 mmol) and acetic acid (0.60 mL, 10 mmol). After the mixture was stirred for 24 h, the reaction was quenched with saturated NH_4Cl (150 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (MTBE/MeOH (9/1, v/v)) yielded the primary alcohol **17**: yield 1.14 g (93%); white crystals; mp 144 °C (ethyl acetate/hexane); $[\alpha]_D^{23}$ = +154.9° (c 1.04, DCM); IR (DCM) 3396, 2935, 2865, 1675, 1612 cm^{-1}; ^{1}H NMR (500 MHz) δ 6.73 (s, 1H), 6.55 (s, 1H), 4.81 (dd, 1H, J = 7.8, 2.0 Hz), 4.41 (dd, 1H, J = 13.1, 6.0 Hz), 4.26−4.20 (m, 1H), 3.94 (dd, 1H, J = 12.0, 2.9 Hz), 3.88 (s, 3H), 3.85 (s, 3H), 3.70 (dd, 1H, J = 12.0, 4.4 Hz), 3.08 (dt, 1H, J = 12.6, 4.2 Hz), 3.00−2.92 (m, 1H), 2.75 (dd, 1H, J = 18.5, 7.9 Hz), 2.65−2.57 (m, 2H), 2.32 (dd, 1H, J = 13.3, 4.7 Hz), 2.16 (dd, 1H, J = 13.3, 10.8 Hz), 1.90 (s, 1H); ^{13}C NMR (125 MHz) δ 172.7, 148.5,

DOI: 10.1021/jo5026157
J. Org. Chem. 2015, 80, 1957−1963

148.3, 129.3, 126.3, 111.5, 107.6, 82.9, 78.9, 73.4, 63.2, 56.2, 55.9, 43.6, 38.9, 36.1, 27.4; MS (EI) m/z (M^+) 319 (100%). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.74; H, 6.64; N, 4.35.

Synthesis of (2*S*,3a*R*,12b*S*)-2-((*Z*)-2-Iodovinyl)-10,11-dimethoxy-3a,4,7,8-tetrahydro-1*H*-furo[3′,2′:2,3]-pyrrolo[2,1-*a*]-isoquinolin-5(2*H*)-one (18). *Step 1: Alcohol Oxidation.* A solution of dimethyl sulfoxide (181 μL, 2.6 mmol) in DCM (5 mL) was added dropwise to a stirred solution of oxalyl chloride (111 μL, 1.3 mmol) in DCM (5 mL) at −60 °C. The mixture was stirred for 30 min, and then a solution of alcohol **17** (203 mg, 0.64 mmol) in DCM (5 mL) was added dropwise at −60 °C. After 0.5 h, TEA (520 μL, 4.0 mmol) was added dropwise and the resulting mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with DCM (2 × 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was used without purification in the next step.

Step 2: Wittig Olefination. The modified Menche procedure was applied.[17c] DMPU was used instead of the highly toxic HMPA. In the absence of light, to a THF (10 mL) solution of NaHMDS (1.0 M/THF, 0.96 mL, 0.96 mmol) was added a suspension of finely powdered phosphonium iodide (0.51 g, 0.96 mmol) in DMPU (4 mL) at 10 °C. The mixture was stirred for 1 min and cooled to −78 °C, and a solution of crude aldehyde (obtained in step 1, 0.64 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred at this temperature for 30 min, gradually warmed to 0 °C, and quenched with aqueous saturated NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Crude product was purified (in two passes) by flash chromatography on silica gel (first pass, using DCM/acetone/hexane (9/1/3, v/v/v) mixture as an eluent, and second pass, using hexane/MTBE/methanol (6/3/1, v/v/v) mixture) to give pure (*Z*)-vinyl iodide **18**: yield 127 mg (45%); amorphous solid; $[\alpha]_D^{23}$ = −1.9° (*c* 1.00, DCM); IR (DCM) 3499, 3064, 2927, 2854, 1691, 1672 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 6.56 (s, 1H), 6.20 (dd, 1H, *J* = 7.9, 6.7 Hz), 6.15 (s, 1H), 5.93 (dd, 1H, *J* = 7.9, 1.2 Hz), 4.86−4.80 (m, 1H), 4.49 (dd, 1H, *J* = 7.9, 2.1 Hz), 4.45 (dd, 1H, *J* = 12.9, 6.0 Hz), 3.39 (s, 3H), 3.33 (s, 3H), 2.79−2.69 (m, 1H), 2.68−2.60 (m, 1H), 2.52 (d, 1H, *J* = 18.3 Hz), 2.42 (dd, 1H, *J* = 13.2, 4.7 Hz), 2.36 (dd, 1H, *J* = 18.3, 8.0 Hz), 2.07−1.97 (m, 1H), 1.68 (dd, 1H, *J* = 13.2, 10.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 148.5, 148.4, 139.2, 129.1, 126.4, 111.5, 107.4, 84.1, 82.5, 80.7, 73.1, 56.3, 55.9, 47.1, 38.8, 36.2, 27.3; MS (EI, HR) m/z (M^+) calcd for $C_{18}H_{20}NO_4I$ 441.0437, found 441.0440.

Synthesis of (*R*)-10b-((*S*,*Z*)-4-Iodo-2-((triethylsilyl)oxy)but-3-en-1-yl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-(10b*H*)-one (19). To a stirred and precooled to −20 °C solution of TES-OTf (53 mg, 45 μL, 0.20 mmol) in DCM (1 mL) was added TEA (35 μL, 0.25 mmol), followed by dropwise addition of a solution of **18** (44 mg, 0.10 mmol) in DCM (1 mL). The reaction mixture was warmed to room temperature, and stirring was continued until TLC indicated the disappearance of **18** (approximately 2.5 h). The reaction mixture was poured into ice-cold saturated $NaHCO_3$ solution and extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (TBME/hexane (7/3, v/v)): yield 52 mg (93%); yellowish oil; $[\alpha]_D^{19}$ = +84.8° (*c* 1.01, DCM); IR (DCM) 3072, 2952, 2875, 1690 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.15 (d, 1H, *J* = 5.9 Hz), 6.48 (s, 1H), 6.17 (s, 1H), 5.98 (d, 1H, *J* = 5.9 Hz), 5.91 (t, 1H, *J* = 7.8 Hz), 5.70 (dd, 1H, *J* = 7.8, 1.0 Hz), 4.61 (dd, 1H, *J* = 13.2, 6.4 Hz), 4.46 (t, 1H, *J* = 8.3 Hz), 3.32 (s, 3H), 3.29 (s, 3H), 3.15 (dt, 1H, *J* = 12.2, 4.4 Hz), 2.84−2.74 (m, 1H), 2.20 (dd, 1H, *J* = 14.7, 8.8 Hz), 2.12 (dd, 1H, *J* = 16.1, 4.4 Hz), 1.88 (dd, 1H, *J* = 14.7, 2.0 Hz), 0.97 (t, 9H, *J* = 7.8 Hz), 0.58 (q, 6H, *J* = 7.8 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 171.5, 153.2, 149.3, 148.8, 144.1, 130.0, 125.8, 124.6, 113.3, 110.8, 80.3, 72.7, 67.1, 56.0, 55.5, 46.5, 35.6, 28.8, 7.2, 5.5; MS (EI, HR) m/z (M^+) calcd for $C_{24}H_{34}NO_4SiI$ 555.1302, found 555.1300.

Synthesis of 20−22. *General Procedure.* In a Schlenk flask containing vinyl iodide **19** (0.10 mmol, 55.5 mg), *n*-Bu_4NBr (0.1 mmol, 32.2 mg, 1 equiv), and Na_2CO_3 (0.25 mmol, 26.5 mg, 2.5 equiv) under an argon atmosphere were placed anhydrous DMF (or toluene) (2.5 mL) and Pd catalyst. The mixture was heated and stirred at the specified temperature and poured into saturated aqueous $NaHCO_3$ (10 mL), and the product was extracted with ethyl acetate (3 × 4 mL). The combined organic layers were washed with brine, dried on $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane/TEA (7/3/0.05, v/v/v) to isolate **20**, and/or ethyl acetate/methanol (98/2, v/v) to isolate compounds **21** and **22**. The reaction conditions, amount of catalyst, and product yield are given in Table 1.

(2S,13bR)-11,12-Dimethoxy-2-((triethylsilyl)oxy)-8,9-dihydro-1H-indolo[7a,1a]isoquinolin-6(2H)-one ***(20):*** yellowish oil; $[\alpha]_D^{22}$ = −13.5° (*c* 1.43, DCM); IR (DCM) 2953, 2875, 1686, 1664; ^1H NMR (C_6D_6, 500 MHz) δ 6.88 (s, 1H), 6.28 (s, 1H), 6.25 (dd, 1H, *J* = 10.1, 2.5 Hz), 5.95 (d, 1H, *J* = 10.1 Hz), 5.90 (s, 1H), 4.45−4.39 (m, 1H), 4.17−4.09 (m, 1H), 3.45 (s, 1H), 3.37−3.30 (m, 4H), 2.62 (dd, 1H, *J* = 11.8, 5.2 Hz), 2.55 (t, 2H, *J* = 6.9 Hz), 1.85 (dd, 1H, *J* = 11.3, 10.1 Hz), 0.86 (t, 9H, *J* = 7.9 Hz), 0.45 (q, 6H, *J* = 7.9 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 170.7, 157.0, 148.1, 139.5, 129.7, 127.1, 123.4, 121.0, 113.4, 109.8, 67.6, 66.2, 56.1, 55.4, 46.1, 37.6, 27.2, 6.9, 5.3, 4.9; MS (EI) m/z (M^+) 427.1 (100%); MS (ES, HR) m/z ($M + H^+$) calcd for $C_{24}H_{34}NO_4Si$ 428.2257, found 428.2261.

(2S,13bR)-2-Hydroxy-11,12-dimethoxy-8,9-dihydro-1H-indolo-[7a,1a]isoquinolin-6(2H)-one ***(21):*** colorless crystals, mp 85−86 °C (ethyl acetate) (lit.[5] mp for opposite enantiomer mp 86−87 °C); $[\alpha]_D^{22}$ = −180.5° (*c* 1.0, $CHCl_3$) (lit.[5] for opposite enantiomer +182.4° (*c* 0.25, $CHCl_3$)); ^1H NMR (500 MHz) δ 6.86 (dd, 1H, *J* = 10.0, 2.5 Hz), 6.79 (s, 1H), 6.70 (s, 1H), 6.29 (d, 1H, *J* = 10.0 Hz), 6.01 (s, 1H), 4.30 (m, 1H), 4.02−3.94 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.60 (ddd, 1H, *J* = 12.5, 6.8, 5.4 Hz), 3.11−2.93 (m, 2H). 2.80 (dd, 1H, *J* = 11.5, 5.1 Hz), 2.11 (brs, 1H), 1.69 (dd, 1H, *J* = 11.3, 10.3 Hz).

(R)-11,12-Dimethoxy-8,9-dihydro-1H-indolo[7a,1a]isoquinoline-2,6-dione ***(22):*** colorless solid; $[\alpha]_D^{22}$ = −187.4° (*c* 1.2, $CHCl_3$) (lit.[5] for opposite enantiomer +217° (*c* 0.26, $CHCl_3$)); IR (DCM film) 3484, 2935, 1677, 1513; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, 1H, *J* = 10.1 Hz), 6.85 (s, 1H), 6.66 (s,1H), 6.41 (d, 1H, *J* = 10.1 Hz), 6.37 (s, 1H), 4.26−4.17 (m, 1H), 3.84 (s, 3H), 3.72 (s, 1H), 3.45−3.35 (m, 1H), 3.27 (d, 1H, *J* = 15.1 Hz), 3.08−2.98 (m, 1H), 2.87−2.78 (m, 1H), 2.80 (d, 1H, *J* = 15.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.2, 169.7, 154.8, 148.9, 147.4, 138.5, 131.9, 128.1, 126.0, 125.5, 112.6, 108.0, 67.7, 56.0, 55.9, 52.5, 36.9, 27.6; MS (EI, HR) m/z (M^+) calcd for $C_{18}H_{17}NO_4$ 311.1158, found 311.1161.

Synthesis of (−)-Erysotramidine. The modified Tsuda procedure was used.[5] *n*-Bu_4NBr was used instead of Et_4NBr. A mixture of alcohol **21** (47 mg, 0.15 mmol), 85% KOH (100 mg, 1.5 mmol), *n*-Bu_4NBr (145 mg, 0.45 mmol), and MeI (3 mL) in THF (6 mL) was stirred at room temperature for 24 h. Workup and purification gave 47 mg (96%) of (−)-erysotramidine: yellowish oil; $[\alpha]_D^{23}$ = −145.2° (*c* 1.57, $CHCl_3$) (lit.[5] for opposite enantiomer $[\alpha]_D^{23}$ = +148.5° (*c* 1.2, $CHCl_3$)); ^1H NMR (500 MHz) δ 6.90 (dd, 1H, *J* = 10.2, 1.8 Hz), 6.80 (s, 1H), 6.72 (s, 1H), 6.33 (d, 1H, *J* = 10.1 Hz), 6.05 (s, 1H), 4.01 (dt, 1H, *J* = 12.9, 7.7 Hz), 3.86 (s, 4H), 3.76 (s, 3H), 3.66−3.58 (m, 1H), 3.34 (s, 3H), 3.13−2.95 (m, 2H), 2.81 (dd, 1H, *J* = 11.5, 5.0 Hz), 1.71 (t, 1H, *J* = 10.8 Hz); ^{13}C NMR (125 MHz) δ 170.9, 157.2, 148.6, 147.1, 136.4, 128.6, 126.5, 124.1, 120.2, 112.3, 108.3, 74.9, 66.5, 56.4, 56.2, 55.9, 41.4, 37.3, 27.1; MS (EI) m/z (M^+) 327 (100%).

■ ASSOCIATED CONTENT

Supporting Information

Text and figures giving general experimental methods as well as ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

DOI: 10.1021/jo5026157
J. Org. Chem. 2015, 80, 1957−1963

AUTHOR INFORMATION

Corresponding Author

*Z.K.: fax, (+48)-22-632-6681; e-mail, zbigniew.kaluza@icho.edu.pl.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to the National Science Centre (Grant NN 204 123437) for financial support.

REFERENCES

(1) (a) Hill, R. K. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, pp 483−515. (b) Dyke, S. F.; Quessy, S. N. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. *18*, pp 1−98. (c) Chawala, A. S.; Jackson, A. H. *Nat. Prod. Rep.* **1984**, *1*, 371−373. (d) Jackson, A. H. In *Chemistry and Biology of Isoquinoline Alkaloids*; Phillipson, J. D., Margaret, M. F., Zenk, M. H., Eds.; Springer: Berlin, Germany, 1985; pp 62−78. (e) Amer, M. A.; Shamma, M.; Freyer, A. J. *J. Nat. Prod.* **1991**, *54*, 329−363. (f) Flausino, O., Jr.; Santos, L. A.; Verli, H.; Pereira, A. M.; Bolzani, V. S.; Nunes-de-Souza, R. L. *J. Nat. Prod.* **2007**, *70*, 48−53.

(2) For a comprehensive review of synthetic approaches to Erythrina alkaloids, see: Reimann, E. Synthesis Pathways to Erythrina Alkaloids and Erythrina Type Compounds. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Eds.; Springer-Verlag: Wien, Austria, 2007; Vol. *88*, pp 1−62, and references citied therein.

(3) (a) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144−1155. (b) Hosoi, S.; Nagao, M.; Tsuda, Y.; Isobe, K.; Sano, T.; Ohta, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1505−1511. (c) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S.; Wang, Q. *J. Org. Chem.* **2002**, *67*, 5928−5937. (d) Lee, H. I.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 5067−5070. (e) El Bialy, S. A. A.; Braun, H.; Tietze, L. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 5391−5393. (f) Padwa, A.; Lee, H. I.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2004**, *69*, 8209−8218. (g) Padwa, A.; Wang, Q. *J. Org. Chem.* **2006**, *71*, 7391−7402. (h) Gao, S.; Tu, Y. Q.; Hu, X.; Wang, S.; Hua, R.; Jiang, Y.; Zhao, Y.; Fan, X.; Zhang, S. *Org. Lett.* **2006**, *8*, 2373−2376. (i) Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem.* **2006**, *71*, 2185−2187. (j) Tuan, L. A.; Kim, G. *Bull. Korean Chem. Soc.* **2010**, *31*, 1801−1802. (k) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Vassilikogiannakis, G. *Org. Lett.* **2013**, *15*, 3714−3717. (l) Heller, S. T.; Kiho, T.; Narayan, A. R. H.; Sarpong, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 11129−11133. (m) L'Homme, Ch.; Ménard, M.-A.; Canesi, S. *J. Org. Chem.* **2014**, *79*, 8481−8484.

(4) (a) Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449−2458. (b) Gill, C.; Greenhalgh, D. A.; Simpkins, N. S. *Tetrahedron Lett.* **2003**, *44*, 7803−7807. (c) Allin, S. M.; Streetley, G. B.; Slater, M.; Jamesa, S. L.; Martin, W. P. *Tetrahedron Lett.* **2004**, *45*, 5493−5496. (d) Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 619−622. (e) Blake, A. J.; Gill, C.; Greenhalgh, D. A.; Simpkins, N. S.; Zhang, F. *Synthesis* **2005**, 3287−3292. (f) Fukumoto, H.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2731−2734. (g) Zhang, F.; Simpkins, N. S.; Wilson, C. *Tetrahedron Lett.* **2007**, *48*, 5942−5947. (h) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Chem.—Asian J.* **2007**, *2*, 1127−1136. (i) Tietze, L. F.; Tölle, N.; Kratzert, D.; Stalke, D. *Org. Lett.* **2009**, *11*, 5230−5233. (j) Zhang, F.; Simpkins, N. S.; Blake, A. J. *Org. Biomol. Chem.* **2009**, *7*, 1963−1979.

(5) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Chikara, K.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087−2095.

(6) (a) Mostowicz, D.; Wójcik, R.; Dołęga, G.; Kałuża, Z. *Tetrahedron Lett.* **2004**, *45*, 6011−6015. (b) Kałuża, Z.; Mostowicz, D.; Dołęga, G.; Mroczko, K.; Wójcik, R. *Tetrahedron* **2006**, *62*, 943−953.

(7) Kałuża, Z.; Mostowicz, D.; Dołęga, G.; Wójcik, R. *Tetrahedron* **2008**, *64*, 2321−2328.

(8) For a retro-Michael reaction where alcohol is eliminated, see selected examples: (a) Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507−2509. (b) Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, *6*, 1535−1538. (c) Tinarelli, A.; Paolucci, C. *J. Org. Chem.* **2006**, *71*, 6630−6633.

(9) For a comprehensive review see: Brossi, A.; Pei, X.-F. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1998; Vol. *50*, pp 109−139.

(10) (a) Farmer, R. L.; Biddle, M. M.; Nibbs, A. E.; Huang, X.; Bergan, R. C.; Scheidt, K. A. *ACS Med. Chem. Lett.* **2010**, *1*, 400−405. (b) Kerr, D. J.; Flynn, B. L. *Org. Lett.* **2012**, *14*, 1740−1743. (c) Kerr, D. J.; Miletic, M.; Manchala, N.; White, J. M.; Flynn, B. L. *Org. Lett.* **2013**, *15*, 4118−4121.

(11) (a) Alibés, R.; Ballbé, M.; Busqué, F.; de March, P.; Elias, L.; Figueredo, M.; Font. *J. Org. Lett.* **2004**, *6*, 1813−1816. (b) Hua, D. H.; Zhao, H.; Battina, S. K.; Lou, K.; Jimenez, A. L.; Desper, J.; Perchellet, E. M.; Perchellet, J-P. H.; Chiang, P. K. *Bioorg. Med. Chem.* **2008**, *16*, 5232−5246. (c) Bennasar, M.-L.; Solé, D.; Zulaica, E.; Alonso, S. *Org. Lett.* **2011**, *13*, 2042−2045. (d) Bennasar, M.-L.; Solé, D.; Zulaica, E.; Alonso, S. *Tetrahedron* **2013**, *69*, 2534−2541. (e) Obase, A.; Kageyama, A.; Manabe, Y.; Ozawa, T.; Araki, T.; Yokoe, H.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Org. Lett.* **2013**, *15*, 3666−3669.

(12) Arimitsu, S.; Hammond, G. B. *J. Org. Chem.* **2007**, *72*, 8559−8561.

(13) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

(14) Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473−1479.

(15) (a) Pedersen, P. J.; Andresen, T. L.; Clausen, M. H. *Eur. J. Org. Chem.* **2012**, 6656−6661. (b) Wullschleger, C. W.; Gertsch, J.; Altmann, K.-H. *Chem. Eur. J.* **2013**, *19*, 13105−13111.

(16) Chi, S.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 3−5.

(17) Wittig olefination with iodomethylene triphenylphosphine ylide, due to the formation of side products, often leads to formation of the (*Z*)-iodovinyl derivative in moderate yield. Selected publications: (a) Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. M.; Davies, J. E.; Raithby, P. R.; Adams, J. P.; Forbes, I. T.; Press, N. J.; Thompsonc, M. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1494−1514. (b) Goundry, W. R. F.; Baldwin, J. E.; Lee, V. *Tetrahedron* **2003**, *59*, 1719−1729. (c) Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Org. Chem.* **2010**, *75*, 2429−2444.

(18) Reaction of **18** with TMS-triflate/TEA followed by standard workup gave an unstable alcohol, which, similarly to **14**, easily cyclizes in a presence of a base, restoring starting material. We anticipated that using a bulky silyl triflate, such as TBS or TIPS, we should obtain the elimination product with the hydroxyl group protected as a stable silyl ether. However, probably due to steric hindrance, reaction with these triflates did not proceed. Only with TES-triflate was the relatively stable TES-protected (*Z*)-iodoolefin **19** obtained.

(19) Oliveira, J. M.; Freitas, J. C.; Comasseto, J. V.; Menezes, P. H. *Tetrahedron* **2011**, *67*, 3003−3009.

DOI: 10.1021/jo5026157
J. Org. Chem. 2015, 80, 1957−1963