JOC The Journal of Organic Chemistry

Note

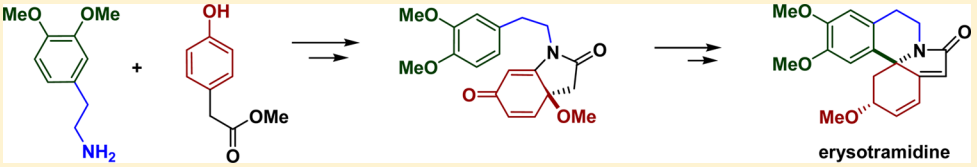
pubs.acs.org/joc

Synthesis of the Erythrina Alkaloid Erysotramidine

Chloé L'Homme, Marc-André Ménard, and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produits Naturels, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, H3C 3P8 Québec, Canada

Supporting Information



ABSTRACT: A concise synthesis of erysotramidine (an alkaloid belonging to the erythrina family) was achieved starting with an inexpensive phenol and amine derivative. The synthesis is based on oxidative phenol dearomatizations mediated by a hypervalent iodine reagent and includes a novel route to a key indolinone moiety.

Erythrina alkaloids[1] are natural tetracyclic compounds **1** isolated from wide variety of tropical plants (Figure 1). The

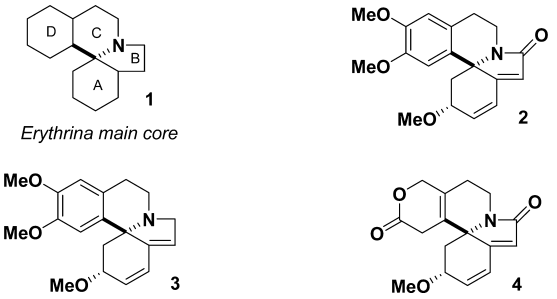


Figure 1. Erythrina alkaloid members.

structures contain an aza-spiran ring and exhibit hypotensive, sedative, and anticonvulsive properties as well as curare-like effects.[2] The compounds may be divided into aromatic structures such as erysotramidine[3] **2** and erysotrine[2c] **3** and nonaromatic structures such as β-erythroidine **4**.[4] The publication of several elegant syntheses has generated widespread interest in these compounds in the scientific community.[5,6]

In this note, we describe a concise preparation of erysotramidine, an alkaloid belonging to the aromatic erythrina family, in eight steps.

Our approach employed a hypervalent iodine reagent[7] to promote dearomatization of phenol subunits into advanced functionalized intermediates. Hypervalent iodine reagents are often used in synthetic procedures because these environmentally benign and inexpensive reagents reduce the need for toxic heavy metals. Transformations involving hypervalent iodine have already demonstrated their remarkable synthetic utility, as described in the pioneering work of Kita and coworkers.[8] Our synthesis involved two oxidative dearomatizations, a new tandem aza-Michael-rearomatization process to produce a key indolinone moiety, a Pictet–Spengler cyclization,[9] a stereoselective reduction, and an etherification. One objective of this note is to illustrate the effectiveness of hypervalent iodine reagents in total synthesis of natural products, Figure 2.

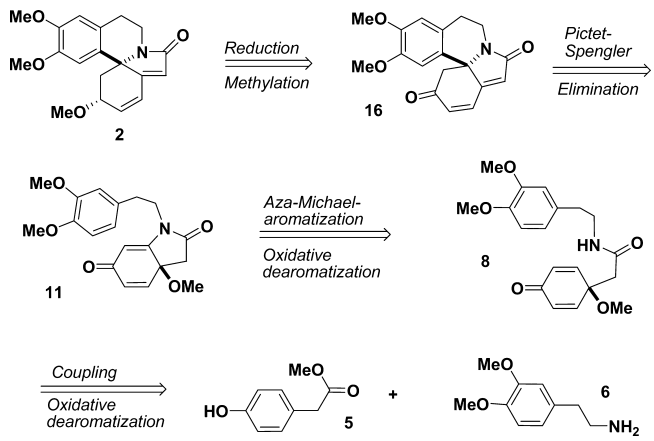


Figure 2. Retrosynthesis of erysotramidine.

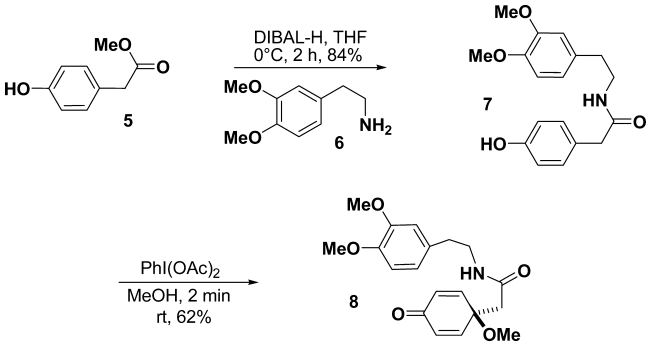
The synthesis began with commercially available phenol **5** and amine **6**, which were joined through an amide linkage to produce **7** in 84% yield using a reaction promoted by an aluminum salt.[10] Amide **7** was treated in methanol with (diacetoxyiodo)-benzene (DIB) to induce the first oxidative dearomatization, resulting in the functionalized prochiral dienone **8** in 62% yield. An interesting aspect of this transformation is its ability to reconfigure the inert unsaturations of the phenol moiety **7** into the oxidized intermediate **8**, in which the unsaturated bonds are readily functionalized, Scheme 1.

Treatment of dienone **8** with TMS-OTf followed by $BF_3{\cdot}Et_2O$ led directly to indolinone **10**. This transformation took place through silyl activation of the enone functionality, enabling a 1,4

Received: July 15, 2014
Published: August 20, 2014

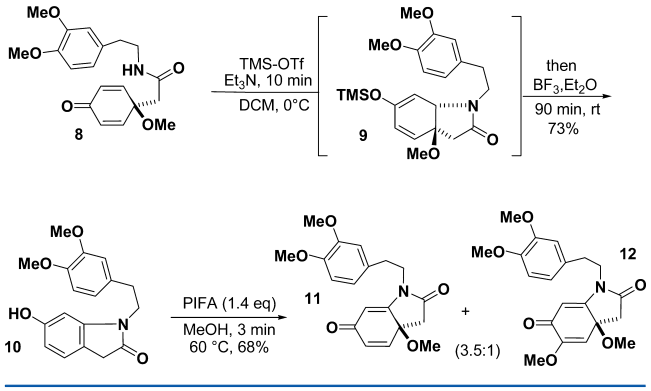
   dx.doi.org/10.1021/jo501583c | J. Org. Chem. 2014, 79, 8481–8485

Scheme 1. First Oxidative Dearomatization Process



attack via a Michael process to afford the bicyclic intermediate **9**, which was subsequently transformed into the aromatic compound **10** through further Lewis acid activation of the methoxy group. The transformation of compound **7** into **10** represents a new two-step route to indolinone derivatives through the equivalent of a C−H activation mediated by a hypervalent iodine reagent,[11] Scheme 2. The first step of this

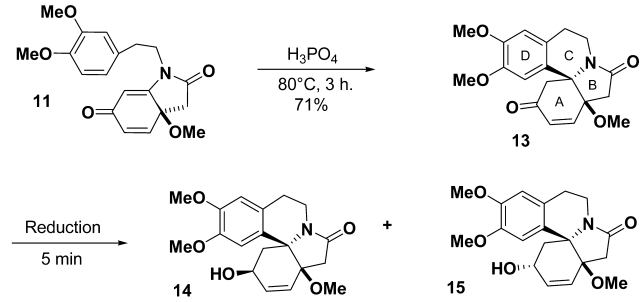
Scheme 2. Second Oxidative Dearomatization Process



sequence is related to the noteworthy stereoselective process developed by Wipf and Kim to produce hydroindole cores.[12] It should be noted that the prochiral dienone **8** obtained during the first activation could be used in an enantioselective synthesis of the erythrina alkaloids if the first aza-Michael process was enantioselectively controlled.[13] Unfortunately, in our hands, all asymmetric 1,4-addition attempts failed. At this stage, a second aromatic activation mediated by bis(trifluoroacetoxy)-iodobenzene (PIFA) led to a separable mixture of the desired dienone **11** and a similar byproduct **12** bearing one more methoxy group in 68% yield, in a favorable ratio (3.5:1) of compound **11**. Formation of compound **12** could be explained by a first methanol addition, during the oxidative activation, in *ortho* position instead of the required *para* position followed by a rearomatization process that would lead to an *ortho*-methoxy analogue of compound **10** that would be then oxidized into byproduct **12**, Scheme 2.

The main tetracyclic core **13** was obtained under acidic conditions in 71% yield. The transformation resembled a Pictet−Spengler rearrangement, which is a popular method of producing the aza-spiran moiety of the erythrina alkaloids.[9] The ketone functionality may be selectively reduced at this point using a hydride reagent. We had supposed that the bowl-shape generated by rings A and B would control the stereoselectivity, but unfortunately hydride reduction using $LiBH_4$, Red-Al, or L-Selectride primarily produced the undesired diastereomer **14** (9:1 by NMR). Interestingly, and for reasons that are unclear, only Luche's conditions resulted in a favorable ratio (2.4:1 by NMR) of the desired diastereomer **15**,[14] Scheme 3.

Scheme 3. Formation of the Main Tetracyclic System

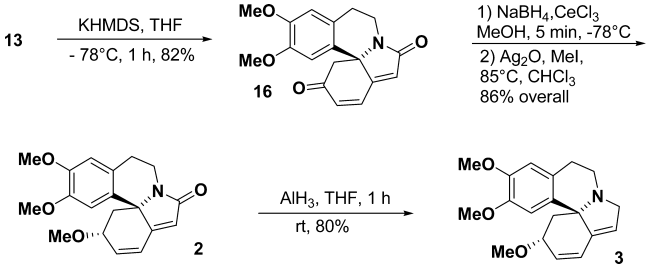


Reagent	Solvent	Temp.	14:15	yield (%)
$LiBH_4$	THF	-78°C	9:1	63
$NaBH_4$-$CeCl_3$	TFE	0°C	1:2.4	82

If compound **15** represented a potential precursor of erysotramidine **2**, then the stereoselectivity observed during the reduction process was not good and required optimization. Consequently, the transformation of compound **13** into the desired target was improved by delaying the ketone reduction in order to produce the desired alcohol stereocenter with greater stereoselectivity at the end of the synthesis. Consequently, the polyconjugated system appearing in the structure of **2** was first obtained by treatment of compound **13** with KHMDS, leading to the flattened structure **16** through an E1cB mechanism in 82% yield. It should be noted that the conformation of the polyconjugated scaffold **16** is more conducive to the desired stereochemistry than its precursor **13**, and treatment of **16** with a hydride provided the desired alcohol with a diastereoselectivity of 9:1 by NMR. The synthesis of erysotramidine **2** was concluded with a mild and quantitative methylation in the presence of Ag_2O and iodomethane in 86% yield overall from compound **16**. The NMR and mass spectrometry data obtained were identical with the data reported in the literature.[6i] It should be noted that erysotrine **3**, a relative alkaloid of the same family, may be obtained by further treatment of erysotramidine **2** with AlH_3 in 80% yield, as previously reported in the literature,[15] Scheme 4.

A natural product belonging to the erythrina family was synthesized from inexpensive starting materials. The synthesis demonstrated the power and utility of hypervalent iodine chemistry in total synthesis and highlighted the development of a novel method for producing indolinone cores.

Scheme 4. Syntheses of Erysotramidine and Erysotrine



dx.doi.org/10.1021/jo501583c | J. Org. Chem. 2014, 79, 8481−8485

EXPERIMENTAL SECTION

Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), quin (quintuplet), m (multiplet), and further qualified as app (apparent), br (broad). Coupling constants, *J*, are reported in Hz. HRMS were measured in the electrospray (ESI) mode on a LC-MSD TOF mass analyzer.

***N*-(3,4-Dimethoxyphenethyl)-2-(4-hydroxyphenyl)-acetamide (7).** To a mixture of 2-(3,4-dimethoxyphenyl)ethanamine **6** (6.16 mmol, 1.04 mL, 2.8 equiv) in anhydrous THF (17 mL, 0.1 M) at 0 °C was added dropwise DIBAL-H in hexane (1.0 M, 6.65 mmol, 6.65 mL, 3.0 equiv). The solution was stirred for 10 min at 0 °C and then was allowed to warm to room temperature. The mixture was stirred for 1.5 h, a solution of methyl 2-(4-hydroxyphenyl)acetate **5** (2.2 mmol, 368.2 mg, 1.0 equiv) in THF (5 mL) was added, and the mixture was stirred overnight. The reaction was quenched by addition of 1.0 M HCl, and the organic layer was washed with brine and ethyl acetate and dried over sodium sulfate. The crude was purified by flash silica gel chromatography (65 → 90% ethyl acetate/hexane) to give 579.5 mg of product 7 (84% yield) as a white solid. mp 156 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.25 (br, 1H), 7.97 (br, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 3H), 3.74 (s, 6H), 3.41 (s, 2H, rotamer), 3.27 (t, *J* = 6.9 Hz, 2H), 2.66 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.4, 155.7, 148.4, 147.1, 131.8, 129.7, 126.4, 120.3, 114.8, 112.4, 111.7, 55.4, 55.2, 41.5, 40.3, 34.5; HRMS (ESI) *m*/*z*: calcd for $C_{18}H_{22}NO_4$ $(M + H)^+$, 316.1543; found, 316.1536.

***N*-(3,4-Dimethoxyphenethyl)-2-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)acetamide (8).** To a solution of compound 7 (0.944 mmol, 297.7 mg, 1.0 equiv) in methanol (7.4 mL) at 0 °C was added a solution of DIB (1.322 mmol, 425.6 mg, 1.4 equiv) in methanol (2.0 mL). The reaction was stirred for 5 min and was filtered in silica gel with 20% MeOH in DCM. The crude was purified by flash silica gel chromatography (80% ethyl acetate/hexane) to provide a yellow oil (201.2 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.6 Hz, 1H), 6.72 (c, 2H), 6.67 (d, *J* = 10.2 Hz, 2H), 6.40 (t, *J* = 6.6 Hz, 1H), 6.29 (d, *J* = 10.2 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.52 (q, *J* = 6.6 Hz, 2H), 3.08 (s, 3H), 2.76 (t, *J* = 6.6 Hz, 1H), 2.45 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 167.7, 148.9, 148.3, 147.6, 131.4, 131.0, 120.5, 111.7, 111.1, 72.9, 55.7, 52.9, 49.8, 46.4, 40.3, 34.9; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{24}NO_5$ $(M + H)^+$, 346.1649; found, 346.1650.

1-(3,4-Dimethoxyphenethyl)-6-hydroxyindolin-2-one (10). Dienone **8** (0.037 mmol, 12.8 mg, 1.0 equiv) and anhydrous triethylamine (0.11 mmol, 15.4 μL, 3.0 equiv) were dissolved in anhydrous DCM (7.0 mL, 0.2 M). TMSOTf (0.092 mmol, 16.8 μL, 2.5 equiv) was added at 0 °C, and the reaction mixture was allowed to warm to room temperature. The reaction was followed by TLC until the starting material disappeared (10 min), and $BF_3{\cdot}Et_2O$ was then added (0.11 mmol, 14.0 μL, 3.0 equiv) during 90 min. An aqueous solution of ammonium chloride was added, and the organic layer was washed with brine and dried over sodium sulfate. The product was purified by flash column chromatography (60% ethyl acetate/hexane) to provide a yellow oil **10** (7.6 mg, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.8 Hz, 1H), 6.78 (s, 1H), 6.76 (d, *J* = 14.6 Hz, 1H), 6.38 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.47 (d, *J* = 2.1 Hz, 1H), 3.86 (t, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.43 (s, 3H), 2.89 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 156.1, 148.9, 147.7, 145.6, 130.6, 125.0, 120.7, 116.0, 112.0, 111.3, 108.3, 97.1, 55.9, 55.8, 41.6, 35.1, 33.1; HRMS (ESI) *m*/*z*: calcd for $C_{18}H_{20}NO_4$ $(M + H)^+$, 314.1387; found, 314.1379.

1-(3,4-Dimethoxyphenethyl)-3a-methoxy-3,3a-dihydro-1*H*-indole-2,6-dione (11). To a solution of compound **10** (0.056 mmol, 17.6 mg, 1.0 equiv) in methanol (0.4 mL) at 60 °C was added a solution of PIFA (0.078 mmol, 33.7 mg, 1.4 equiv) in methanol (0.4 mL). The reaction was stirred for 5 min and was filtered on silica gel with 20% MeOH in DCM. The crude was purified by flash silica gel chromatography (40% ethyl acetate/hexane) to provide a brown oil (11.2 mg, 58% yield) of compound **11** and a dark yellow oil (2.0 mg, 10% yield) of compound **12**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.0 Hz, 4H), 6.70 (d, *J* = 10.0 Hz, 1H), 6.68 (s, 1H), 6.53 (d, *J* = 10.0 Hz, 1H), 6.34 (dd, *J* = 10.0, 1.4 Hz, 1H), 5.78 (d, *J* = 1.4 Hz, 1H), 3.90 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.52 (m, 1H), 3.35 (dd, *J* = 8.7, 5.1 Hz, 1H), 2.91 (s, 3H), 2.80 (t, 7.6 Hz, 2H), 2.72 (d, 16.2 Hz, 1H), 2.56 (d, 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 173.1, 158.0, 148.8, 147.7, 136.9, 133.5, 129.5, 120.5, 111.6, 111.1, 103.9, 72.7, 55.7, 50.9, 42.1, 41.3, 32.6; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{22}NO_5$ $(M + H)^+$:344.1492; found: 344.1484.

1-(3,4-Dimethoxyphenethyl)-3,3a-dihydro-3a,5-dimethoxy-1*H*-indole-2,6-dione (12). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.0 Hz, 4H), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 6.37 (t, *J* = 2.1 Hz, 1H), 5.52 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.78 (t, *J* = 8.0 Hz, 2H), 3.39 (s, 6H), 3.30 (d, *J* = 2.1 Hz, 2H), 2.82 (t, 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 172.7, 154.6, 149.0, 148.0, 129.6, 129.3, 128.5, 120.7, 111.8, 111.4, 97.2, 91.9, 55.9, 55.8, 50.2 (*2), 42.0, 32.4, 32.1,; HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{23}NNaO_6$ $(M + Na)^+$, 396.1418; found, 396.1419.

(4a*S*,13b*R*)-4a,11,12-Trimethoxy-4a,5,8,9-tetrahydro-1*H*-indolo[7a,1-a]isoquinoline-2,6-dione (13). The compound **11** (0.088 mmol, 30.0 mg, 1.0 equiv) and phosphoric acid 85% (11.1 mL) were stirred at reflux for 3 h. The mixture was poured into a 2 M NaOH solution, extracted with DCM, washed with water, and dried with Na_2SO_4. The residue was then purified by silica gel chromatography with 100% ethyl acetate to give enone **13** (21.2 mg, 71%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 10.5 Hz, 1H), 6.59 (d, *J* = 10.5 Hz, 1H), 6.27 (d, *J* = 10.6 Hz, 1H), 4.31 (ddd, *J* = 13.0, 8.0, 2.2 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.12 (d, *J* = 16.2 Hz, 1H), 3.11 (m, 1H), 3.03 (s, 3H), 2.96 (d, *J* = 17.2 Hz, 1H), 2.91 (m, 1H), 2.81 (d, *J* = 17.2 Hz, 1H), 2.70 (d, *J* = 16.2 Hz, 1H), 2.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 168.6, 148.2, 148.1, 147.3, 128.5, 126.8, 125.8, 111.7, 108.6, 78.8, 68.5, 55.6, 51.6, 51.4, 41.3, 35.1, 28.0; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{22}NO_5$ $(M + H)^+$:344.1492; found: 344.1487.

(2*S*,4a*S*,13b*R*)-2-Hydroxy-4a,11,12-trimethoxy-4a,5,8,9-tetrahydro-1*H*-indolo[7a,1-a]isoquinolin-6(2*H*)-one (14). To a solution of **13** (9 mg, 0.026 mmol, 1.0 equiv) in trifluoroethanol (0.26 mL) at 0 °C was added $CeCl_3{\cdot}7H_2O$ (0.11 mmol, 20 mg, 4.1 equiv) and then $NaBH_4$ (0.110 mmol, 2.1 mg, 4.1 equiv). The solution was allowed to room temperature, and the reaction was followed by TLC. The reaction was quenched by a solution of NH_4Cl, and the organic layer was washed with brine and DCM and dried over sodium sulfate. The residue was then purified by silica gel chromatography (2% MeOH in DCM) to give the compound **14** (5.2 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.58 (s, 1H), 6.06 (s, 2H), 4.28 (t, *J* = 6.0 Hz, 1H), 4.13 (ddd, *J* = 13.1, 6.5, 3.3 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.26 (m, 1H), 3.18 (s, 3H), 3.05 (m, 1H), 2.69 (d, *J* = 16.9 Hz, 1H), 2.68 (m, 1H), 2.49 (d, *J* = 16.9 Hz, 1H), 2.34 (dd, *J* = 14.3, 5.6 Hz, 1H), 2.19 (dd, *J* = 14.3, 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 147.9, 146.7, 132.6, 130.0, 129.0, 126.5, 111.4, 77.8, 65.1, 64.2, 55.8, 55.6, 51.5, 43.0, 41.8, 35.9, 27.3; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{24}NO_5$ $(M + H)^+$, 346.1649; found, 346.1642.

(2*R*,4a*S*,13b*R*)-2-Hydroxy-4a,11,12-trimethoxy-4a,5,8,9-tetrahydro-1*H*-indolo[7a,1-a]isoquinolin-6(2*H*)-one (15). Pale yellow oil: 2.2 mg, 24%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.64 (s, 1H), 6.11 (dd, *J* = 10.4, 1.9 Hz, 1H), 6.02 (dt, *J* = 10.4, 1.9 Hz, 1H),4.39 (br, 1H), 4.13 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.40 (m, 1H), 2.98 (s, 3H), 2.90 (m, 2H), 2.85 (d, *J* = 16.9 Hz, 1H), 2.72 (dd, *J* = 16.9, 1.2 Hz, 1H), 2.57 (ddd, *J* = 12.4, 5.1, 1.2 Hz, 1H), 1.73 (dd, *J* = 12.4, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 148.1, 146.8, 132.1, 130.7, 127.1, 125.6, 111.5, 109.9, 77.7, 66.4, 65.2, 55.9, 55.7, 51.1, 45.1, 41.7, 34.9, 27.4; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{24}NO_5$ $(M + H)^+$, 346.1649; found, 346.1653.

(*S*)-11,12-Dimethoxy-8,9-dihydro-1*H*-indolo[7a,1-a]-isoquinoline-2,6-dione (16). To a solution of **15** (0.0273 mmol, 9.4 mg, 1.0 equiv) in anhydrous THF (0.4 mL) at −78 °C was added KHMDS (0.5 M in toluene, 0.06 mmol, 0.12 mL, 2.2 equiv) dropwise. The reaction was followed by TLC, and after completion, a solution of NH_4Cl was added. The organic layer was washed with brine and AcOEt and dried with Na_2SO_4. The product was purified by silica gel chromatography (5% MeOH in DCM) to give the compound **16** (7.0 mg, 82%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 10.1

dx.doi.org/10.1021/jo501583c | *J. Org. Chem.* 2014, 79, 8481−8485

Hz, 1H), 6.84 (s, 1H), 6.65 (s, 1H), 6.41 (d, J = 10.1 Hz, 1H), 6.38 (s, 1H), 4.21 (ddd, J = 11.6, 4.9, 1.7 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.39 (m, 1H), 3.27 (d, J = 15.1 Hz, 1H), 3.02 (m, 1H), 2.82 (m, 1H), 2.79 (d, J = 15.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 169.7, 154.7, 148.7, 147.2, 138.4, 131.8, 128.0, 125.9, 125.5, 112.4, 107.8, 67.7, 55.9, 55.8, 52.4, 36.9, 27.6; HRMS (ESI) m/z: calcd for $C_{18}H_{18}NO_4$ $(M + H)^+$, 312.1230; found, 312.1235.

(2*R*,13b*S*)-2-Hydroxy-11,12-dimethoxy-8,9-dihydro-1*H*-indolo[7a,1-a]isoquinolin-6(2*H*)-one (17). To a solution of **16** (0.0112 mmol, 3.5 mg, 1.0 equiv) in methanol (0.12 mL) at −78 °C was added $CeCl_3{\cdot}7H_2O$ (0.046 mmol, 17.1 mg, 4.1 equiv) and then $NaBH_4$ (0.045 mmol, 1.7 mg, 4.0 equiv). After 5 min, the reaction was quenched by aqueous NH_4Cl, and the organic layer was washed with brine and DCM and dried over sodium sulfate. The residue may be purified by silica gel chromatography (2% MeOH in chloroform) to afford compound **17** (3.1 mg, 90%). However, this intermediate was air-sensitive and was rapidly used for the further transformation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (dd, J = 10.1, 2.4 Hz, 1H), 6.79, (s, 1H), 6.71 (s, 1H), 6.30 (d, J = 10.2 Hz, 1H), 6.03 (s, 1H), 4.30 (br, 1H), 3.97 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.60 (m, 1H), 3.07 (m, 1H), 2.96 (dd, J = 15.9, 1.9 Hz, 1H), 2.81 (dd, J = 11.2, 4.4 Hz, 1H), 1.70 (dd, J = 11.2, 10.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 156.9, 148.5, 147.0, 138.9, 128.4, 126.4, 123.7, 120.3, 112.1, 108.0, 66.5, 55.9, 45.0, 37.4, 27.0; HRMS (ESI) m/z: calcd for $C_{18}H_{20}NO_4$ $(M + H)^+$, 314.1387; found, 314.1392.

Erysotramidine (2). To a degassed solution of **17** (0.01 mmol, 3.1 mg, 1.0 equiv) in anhydrous acetonitrile (0.2 mL) were added Ag_2O (0.05 mmol, 11.6 mg, 5.0 equiv) and MeI (0.05 mmol, 3 μL, 5.0 equiv). The solution was stirred in a sealed tube overnight at reflux in the dark. The reaction was quenched with water, and the organic layer was washed with brine and AcOEt and dried with Na_2SO_4. The residue was purified by flash column chromatography (5% MeOH in DCM) to provide erysotramidine **2** (3.4 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (dd, J = 10.1, 2.2 Hz, 1H), 6.80 (s, 1H), 6.72 (s, 1H), 6.33 (d, J = 10.1 Hz, 1H), 6.04, (s, 1H), 4.00 (dt, J = 13.2, 7.5 Hz, 1H), 3.86 (s + m, 4H), 3.76 (s, 3H), 3.62 (m, 1H), 3.34 (s, 3H), 3.04 (m, 2H), 2.81 (dd, J = 11.0, 5.0 Hz, 1H), 1.71 (dd, J = 11.0, 10.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 157.0, 148.6, 147.0, 136.3, 128.7, 126.5, 124.1, 120.3, 112.2, 108.2, 74.9, 66.3, 56.4, 56.1, 55.9, 41.4, 37.3, 27.0; HRMS (ESI) m/z: calcd for $C_{19}H_{22}NO_4$ $(M + H)^+$, 328.1541; found, 328.1543.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures and ^{1}H and ^{13}C NMR characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: canesi.sylvain@uqam.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are very grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), and the provincial government of Quebec (FQRNT and CCVC) for their financial support of this research.

■ REFERENCES

(1) Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1996; Vol. *48*, pp 249.

(2) (a) Boekelheide, V. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1960; Vol. *7*, pp 201. (b) Hill, R. K. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. *9*, pp 483. (c) Dyke, S. F.; Quessy, S. N. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. *18*, pp 1. (d) Chawala, A. S.; Jackson, A. H. *Nat. Prod. Rep.* **1984**, *1*, 371.

(3) (a) Ito, K.; Furukawa, H.; Haruna, M. *Yakugaku Zasshi* **1973**, *93*, 1611. (b) Mantle, P. G.; Laws, I.; Widdowson, D. A. *Phytochemistry* **1984**, *23*, 1336.

(4) Aguilar, M. I.; Giral, F.; Espejo, O. *Phytochemistry* **1981**, *20*, 2061.

(5) (a) Joo, J. M.; David, R. A.; Yuan, Y.; Lee, C. *Org. Lett.* **2010**, *12*, 5704. (b) Tuan, L. A.; Kim, G. *Bull. Korean Chem. Soc.* **2010**, *31*, 1800. (c) Liang, J.; Chen, J.; Liu, J.; Li, L.; Zhang, H. *Chem. Commun.* **2010**, *46*, 3666. (d) Onoda, T.; Takikawa, Y.; Fujimoto, T.; Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2009**, 1041. (e) Yoshida, Y.; Mohri, K.; Isobe, K.; Itoh, T.; Yamamoto, K. *J. Org. Chem.* **2009**, *74*, 6010. (f) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Chem.—Asian J.* **2007**, *2*, 1127. (g) Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *J. Organomet. Chem.* **2006**, *691*, 5466. (h) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143. (i) Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem.* **2006**, *71*, 2185. (j) Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 619. (k) Fukumoto, H.; Esumi, T.; Ishihara, J.; Hatakeyama, S. *Tetrahedron Lett.* **2003**, *44*, 8047. (l) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323. (m) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Vassilikogiannakis, G. *Org. Lett.* **2013**, *15*, 3714. (n) Isobe, K.; Mohri, K.; Takeda, N.; Suzuki, K.; Hosoi, S.; Tsuda, Y. *Chem. Pharm. Bull.* **1994**, *42*, 197. (o) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087. (p) Tsuda, Y.; Hosoi, S.; Sano, T.; Suzuki, H.; Toda, J. *Heterocycles* **1993**, *36*, 655. (q) Isobe, K.; Mohri, K.; Suzuki, K.; Haruna, M.; Ito, K.; Hosoi, S.; Tsuda, Y. *Chem. Pharm. Bull.* **1991**, *32*, 1195. (r) Tsuda, Y.; Hosoi, S.; Nakai, A.; Sakai, Y.; Abe, T.; Ishi, Y.; Kiuchi, F.; Sano, T. *Chem. Pharm. Bull.* **1991**, *39*, 1365. (s) Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 479. (t) Ito, K.; Suzuki, F.; Haruna, M. *J. Chem. Soc., Chem. Commun.* **1978**, 733.

(6) (a) Ogawa, S.; Iida, N.; Tokunaga, E.; Shiro, M.; Shibata, N. *Chem.—Eur. J.* **2010**, *16*, 7090. (b) Juma, B.; Adeel, M.; Villinger, A.; Reinke, H.; Spannenberg, A.; Fischer, C.; Langer, P. *Adv. Synth. Catal.* **2009**, *351*, 1073. (c) Tietze, L. F.; Tolle, N.; Kratzert, D.; Stalke, D. *Org. Lett.* **2009**, *11*, 5230. (d) Zhang, F.; Simpkins, N. S.; Blake, A. J. *Org. Biomol. Chem.* **2009**, *7*, 1963. (e) Padwa, A.; Wang, Q. *J. Org. Chem.* **2006**, *71*, 7391. (f) Wang, Q.; Padwa, A. *Org. Lett.* **2006**, *8*, 601. (g) Gao, S.; Tu, Y. Q.; Hu, X.; Wang, S.; Hua, R.; Jiang, Y.; Zhao, Y.; Fan, X.; Zhang, S. *Org. Lett.* **2006**, *8*, 2373. (h) El Bialy, S. A. A.; Braun, H.; Tietze, L. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 5391. (i) Padwa, A.; Lee, H. I.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2004**, *69*, 8209. (j) Lee, H. I.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 5067. (k) Chikaoka, S.; Toyao, A.; Ogasawara, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 312. (l) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144. (m) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Heterocycles* **1992**, *33*, 497. (n) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975. (o) Tsuda, Y.; Hosoi, S.; Nakai, A.; Ohshima, T.; Sakai, Y.; Kiuchi, F. *J. Chem. Soc., Chem. Commun.* **1984**, 1216. (p) Sano, T.; Toda, J. *Heterocycles* **1982**, *18*, 229. (q) Mondon, A.; Nestler, H. J. *Chem. Ber.* **1979**, *112*, 1329. (r) Haruna, M.; Ito, K. *J. Chem. Soc., Chem. Commun.* **1976**, 345. (s) Mondon, A.; Nestler, H. J. *Angew. Chem.* **1964**, *76*, 651.

(7) (a) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (b) Traoré, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y. S. *Tetrahedron* **2010**, *66*, 5863. (c) Andrez, J. A.; Giroux, M. A.; Lucien, J.; Canesi, S. *Org. Lett.* **2010**, *12*, 4368. (d) Liang, H.; Ciufolini, M. A. *Tetrahedron* **2010**, *66*, 5884. (e) Pouységu, L.; Sylla, T.; Garnier, T.; Rojas, L. B.; Charris, J.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 5908. (f) Guérard, K. C.; Sabot, C.; Beaulieu, M. A.; Giroux, M. A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893. (g) Jen, T.; Mendelsohn, B. A.; Ciufolini, M. A. *J. Org. Chem.* **2011**, *76*, 728. (h) Beaulieu, M. A.; Sabot, C.; Achache, N.; Guérard, K. C.; Canesi, S. *Chem.—Eur. J.* **2010**, *16*, 11224. (i) Beaulieu, M. A.; Guérard, K. C.; Maertens, G.; Sabot, C.; Canesi, S. *J. Org. Chem.* **2011**, *76*, 9460. (j) Guérard, K. C.; Guerinot, A.; Bouchard-Aubin, C.; Ménard, M. A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121. (k) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (l) Traoré, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y. S. *J. Org. Chem.* **2011**, *76*, 1409. (m) Pouységu,

L.; Marguerit, M.; Gagnepain, J.; Lyvinec, G.; Eatherton, A. J.; Quideau, S. *Org. Lett.* **2008**, *10*, 5211. (n) Jacquemot, G.; Menard, M. A.; L'Homme, C.; Canesi, S. *Chem. Sci.* **2013**, *4*, 1287. (o) Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7065. (p) Desjardins, S.; Andrez, J. A.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406. (q) Jaquemot, G.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 7588. (r) Yoshimura, A.; Middleton, K. R.; Luedtke, M. W.; Zhu, C.; Zhdankin, V. V. *J. Org. Chem.* **2012**, *77*, 11399. (s) Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.; Maskaev, A. V.; Zhdankin, V. V. *Org. Lett.* **2013**, *15*, 4010. (t) Beaulieu, M. A.; Ottenwaelder, X.; Canesi, S. *Chem.—Eur. J.* **2014**, *20*, 7581.

(8) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (c) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787. (d) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (e) Dohi, T.; Itob, M.; Yamaokaa, N.; Morimotoa, K.; Fujiokab, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797. (f) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

(9) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(10) Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* **2001**, *42*, 9039.

(11) Giroux, M. A.; Guérard, K. C.; Beaulieu, M. A.; Sabot, C.; Canesi, S. *Eur. J. Org. Chem.* **2009**, 3871.

(12) (a) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5457. (b) Wipf, P.; Kim, Y.; Goldstein, D. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576. (d) Wipf, P.; Mareska, D. A. *Tetrahedron Lett.* **2000**, *41*, 4723. (e) Methot, J. L.; Wipf, P. *Org. Lett.* **2000**, *2*, 4213.

(13) Maertens, G.; Menard, M. A.; Canesi, S. *Synthesis* **2014**, 1573 and articles cited therein.

(14) Structures of compounds **14** and **15** have been assigned by NMR NOE. In addition, these compounds have been treated in the presence of KHMDS and subsequently O-methylated (Ag_2O, CH_3I) to produce the known natural product erysotramidine **2**, which was obtained from diastereoisomer **15**.

(15) (a) Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 479. (b) Sano, T.; Toda, J.; Maehara, N.; Tsuda, Y. *Can. J. Chem.* **1987**, *65*, 94.

dx.doi.org/10.1021/jo501583c | *J. Org. Chem.* 2014, 79, 8481−8485