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Synthetic Studies of 7-Oxygenated Aporphine Alkaloids: Preparation of (−)-Oliveroline, (−)-Nornuciferidine, and Derivatives

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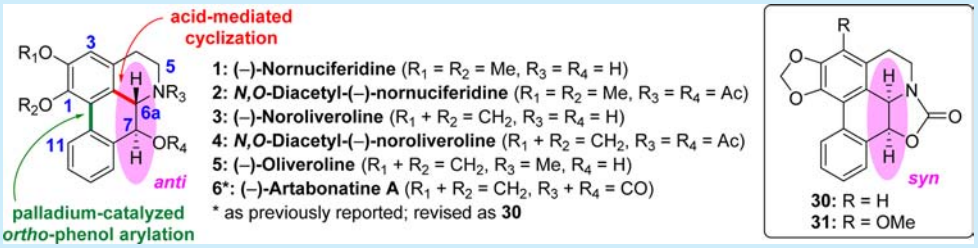
Supporting Information



ABSTRACT: 7-Oxygenated aporphines **1**−**6** possessing anti-configurations have previously been reported. In order to explore their bioactivities, a synthesis was established by utilizing a diastereoselective reductive acid-mediated cyclization followed by palladium-catalyzed ortho-arylations. Moderate XPhos precatalyst loading (10 mol %) and short reaction times (30 min) were sufficient to mediate the arylations. Alkaloids **1**−**5** were successfully prepared, while (−)-artabonatine A was revised to syn-isomer **30**. Consequently, (−)-artabonatine E likely also has a syn-configuration (**31**).

Aporphine alkaloids are a class of natural products that share a characteristic tetracyclic nucleus containing a tetrahydroisoquinoline substructure.[1] A series of 7-oxygenated aporphine alkaloids that possess an anti-configuration between protons 6a and 7 have been reported (Figure 1): (−)-nornuciferidine (**1**),[2] *N*,*O*-diacetyl-(−)-nornuciferidine (**2**),[3] (−)-noroliveroline (**3**),[4] *N*,*O*-diacetyl-(−)-noroliveroline (**4**),[3] (−)-oliveroline (**5**),[5] (−)-artabonatine A (**6**; as previously reported),[6] and (−)-artabonatine E (**7**; as previously reported).[7] Some of these compounds have also exhibited interesting biological activities. For example, **5**, first isolated from *Polyalthiaoliveri* (family: *Annonaceae*),[5] demonstrated anti-Parkinsonian activity in a mice model,[8] antiproliferation via cell cycle arrest by inhibiting G_2 DNA damage checkpoint,[9] and in silico prediction of anticholinergic activity by targeting acetylcholinesterase (AChE).[10]

However, only limited approaches to the preparation of 7-oxygenated aporphines have been described.[11] Herein, we report an efficient diastereoselective synthesis of 7-oxygenated aporphines bearing an anti-configuration between protons 6a and 7 utilizing mandelic acids. In addition, this work has resulted in the structure reassignment of (−)-artabonatine A and a proposed reassignment for (−)-artabonatine E.

A retrosynthetic analysis for 7-oxygenated aporphines is outlined in Scheme 1. Oxazoloaporphine **A** was proposed as the precursor of the desired alkaloids, which would be assembled by arylation of aryl halide **B**. This material would be obtained by cyclization of hydroxylcarbamate **C**, which would be derived from phenethylamines **D** and mandelic acids **E**.

The first crucial step in the strategy is C−C bond formation between C-6a and the aromatic ring, which could be mediated by cyclization via the formation of an acyl iminium ion under acidic conditions. Incorporation of this intermediate into a cyclic carbamate has been reported to facilitate diastereoselective ring closure with an anti-configuration between protons 6a and 7.[12] As a result, the chirality of C-6a could be controlled by an established stereocenter at C-7. The second key C−C bond formation creating the biaryl linkage was envisioned to

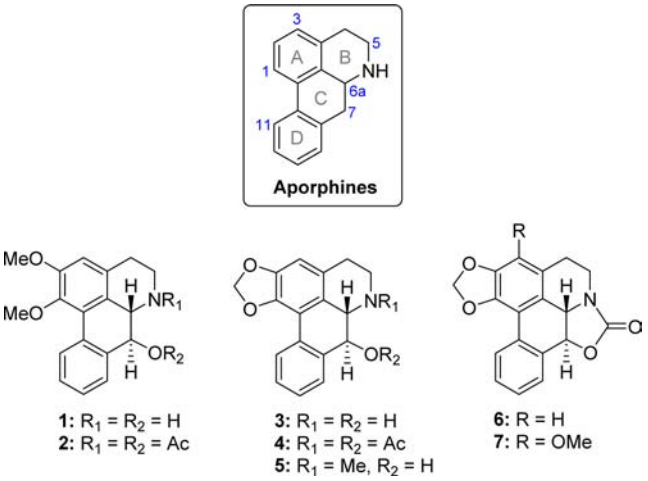


Figure 1. Aporphine scaffold and the reported structures of 7-oxygenated aporphine alkaloids **1**−**7**.

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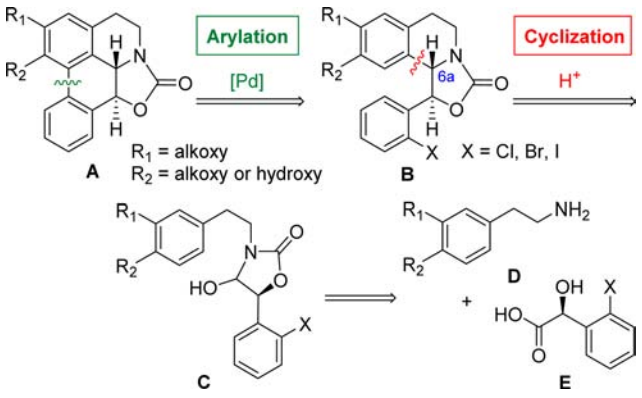
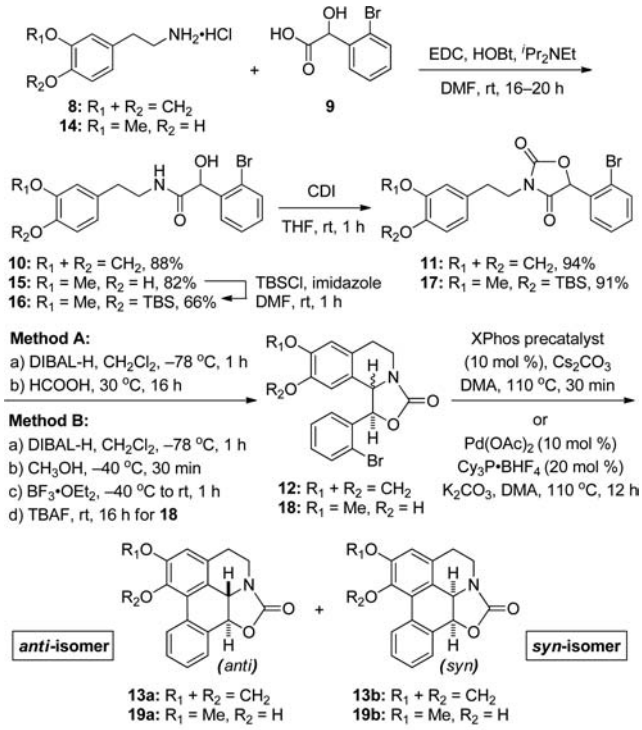
Scheme 1. Retrosynthetic Analysis of Oxazoloaporphine A



use a palladium mediated ortho-arylation[13] with XPhos precatalyst, developed by Buchwald.[14]

To examine the feasibility of this approach, a racemic synthesis (Scheme 2) was commenced by coupling two

Scheme 2. Racemic Synthesis



cyclization	product	*dr* (*anti*/*syn*)	arylation	*anti*	*syn*
Method A	**12** (66%)	**12a**/**12b** = 85:15	$Pd(OAc)_2/Cy_3P•BHF_4$	**13a** (0%)	**13b** (6%)
Method B	**12** (79%)	**12a** (exclusively)	XPhos precatalyst	**13a** (0%)	
Method B	**18** (67%)	**18a**/**18b** = 67:33	XPhos precatalyst	**19a** (46%)	**19b** (31%)

fragments, 3,4-methylenedioxyphenethylamine hydrochloride (**8**) and 2-bromomandelic acid (**9**), with EDC in 88% yield.[15] Amide **10** was treated with carbonyldiimidazole (CDI) to form *N*-acylcarbamate **11** in 94% yield.[16]

In an one-pot reductive acid-mediated cyclization,[17] **11** was selectively reduced at the more electron-deficient amide carbonyl with DIBAL-H at −78 °C. Addition of methanol quenched the reaction and released the corresponding hemiaminal intermediate. The mixture was then treated with a Lewis acid (e.g., $BF_3·OEt_2$) triggering ring closure of the in situ generated *N*-acyliminium ion. As expected, the cyclic carbamate restricted the orientation so that the electron-rich aromatic ring attacked the iminium ion from the less hindered side facilitating ring closure with excellent diastereoselectivity generating the anti-isomer **12** in 79% yield. For comparison, formic acid resulted in a lower diastereomeric ratio (*dr*) of anti- and syn-isomers (**12a**/**12b** = 85:15). Since diastereomers **12a** and **12b** could not be easily separated, this mixture was carried directly to the biaryl linkage step.

To our disappointment, no desired anti-product **13a** was observed with XPhos precatalyst or $Pd(OAc)_2/PCy_3·HBF_4$.[18] However, syn-product **13b** was obtained from the syn-isomer **12b**. In order to resolve the lack of reactivity of the anti-isomer, we modified our strategy by replacing the initial starting material **8** with 4-hydroxy-3-methoxyphenethylamine hydrochloride (**14**), where the phenol could function as a directing group for *ortho*-phenol-arylation by making the reaction center more electron-rich.[13]

After the formation of amide **15** with EDC coupling, TBS-protection of the phenol gave **16**. Treatment of **16** with CDI followed by the one-pot three-step reductive cyclization and subsequent silyl group removal with TBAF generated cyclized product **18**, as a mixture of anti-isomer **18a** and syn-isomer **18b** with moderate diastereoselectivity (67:33 *dr*). To our delight, *ortho*-phenol-arylation was successfully achieved after treating the mixture with XPhos precatalyst at 110 °C for only 30 min. Purification by column chromatography gave aporphines **19a** (46%) and **19b** (31%) in a combined yield of 77%.

The relative stereochemistry of the products was confirmed by two-dimensional nuclear magnetic resonance (2D NMR). Interestingly, the rigid conformation induced by the cyclic carbamate resulted in a smaller coupling constant of 4.6 Hz (dihedral angle ∼135° between H-6a and H-7) for anti-isomer **18a** and 8.6 Hz (dihedral angle ∼0°) for syn-isomer **18b**. After arylation, the coupling constant of *anti*-isomer **19a** increased to 13.2 Hz (∼180°), and that of syn-isomer **19b** had a relatively smaller value of 7.5 Hz (∼15°).

Inspired by the success of this approach, we attempted to use commercially available (*S*)-(+)-chloromandelic acid (**20**) for the synthesis of enantiopure aporphine alkaloids, although it was unclear if the chloride might prove challenging in the *ortho*-phenol-arylation.[13c] However, racemerization occurred when the amide was converted to the desired cyclic carbamate starting material with CDI. Therefore, an alternative method was devised as outlined in Scheme 3.

Starting materials **14** and **20** were transformed into **21**[19] and **22**,[20] respectively. Amine **21** was then treated with triphosgene at 100 °C to form the corresponding isocyanate intermediate, which upon addition of **22** generated the open carbamate **23**.[21] Subsequent reduction of the methyl ester to the intermediate aldehyde with DIBAL-H followed by acid-mediated cyclization with $BF_3·OEt_2$ gave enantiomerically pure oxazolidinones **24a** and **24b** with moderate diastereoselectivity favoring the anti-configuration (87:13 *dr*).[22] These two isomers were separated after several recrystallizations. *ortho*-Phenol-arylation of aryl chloride **24a** was carried out with the XPhos precatalyst, furnishing **25** in high yield (90%). This material was then used as the precursor of aporphines **1**−**5**.

Derived from precursor **25** via methylation followed by hydrolysis and acetylation gave alkaloids **1** and **2**, respectively. Oxazoloaporphine **6** was obtained by demethylation of **25** with BBr_3[23] and formation of the methylenedioxy with CH_2Br_2. Hydrolysis and subsequent acetylation generated alkaloids **3** and **4**. Reduction of **6** with DIBAL-H furnished alkaloid **5** in

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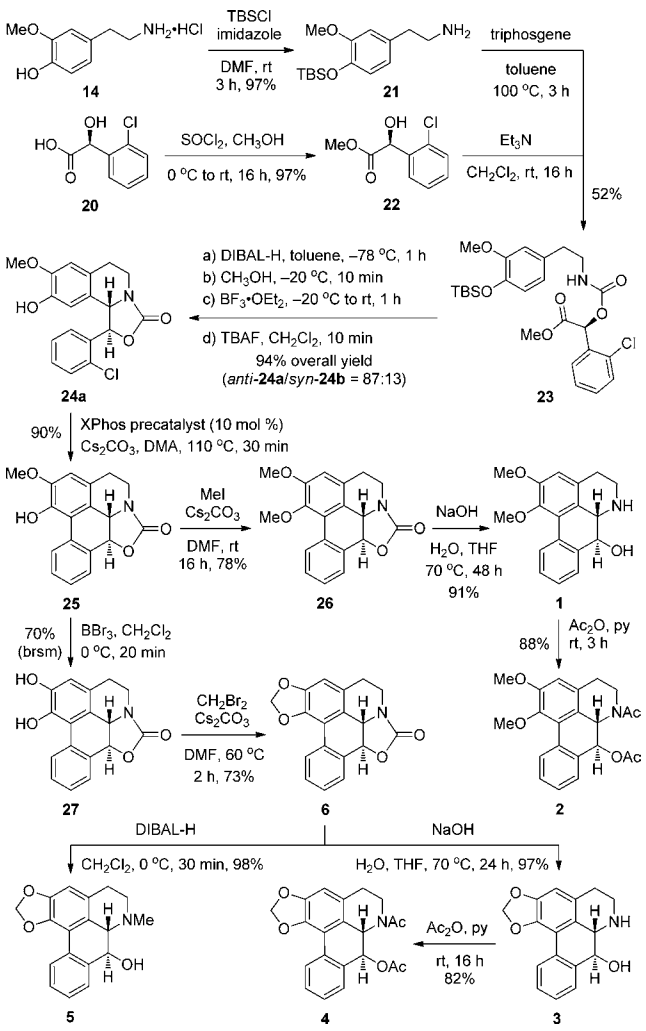
Scheme 3. Enantioselective Synthesis of Alkaloids 1−5 via Formation of Open Carbamate 23

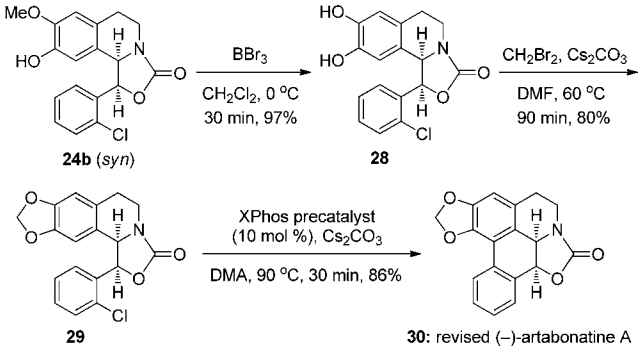


98% yield.[24] Noteworthy, both acetylated aporphines **2** and **4** displayed rotational isomers in their ^{1}H NMR spectra due to steric hindrance caused by the *N*,*O*-diacetyl groups.[25] The ratio of the two rotamers varied in different deuterium solvents. For example, in $CDCl_3$ **2** showed a ratio of 7:3, while in CD_3OD it was ∼1:1.

Oxazoloaporphine **6** was previously reported to be the structure of (−)-artabonatine A.[6] However, the specific rotation and ^{1}H and ^{13}C NMR spectral data for this material indicated that the assigned structure was incorrect. However, (±)-*syn*-**13b** possessed the same ^{1}H NMR spectral data as reported for (−)-artabonatine A, indicating that the reported natural product has a syn-configuration. In order to confirm the absolute stereochemistry of the natural product, syn-isomer **24b** was converted to the alkaloid by demethylation with BBr_3, formation of the methylenedioxy with CH_2Br_2, and direct arylation with XPhos precatalyst (Scheme 4). Since both the specific rotation and the spectral data of **30** were in agreement with those reported for (−)-artabonatine A, the structure of this natural product is reassigned as **30**. On the basis of the reported ^{1}H NMR spectra and specific rotation,[7] we propose that (−)-artabonatine E also has a *syn*-configuration and is likely **31**.

In summary, a convenient synthesis of naturally occurring 7-oxygenated aporphine alkaloids **1−5** with an overall yield of

Scheme 4. Synthesis of (−)-Artabonatine A



15−28% in ≤8 steps from chiral mandelic acid **20** has been developed by utilizing a one-pot reductive acid-mediated cyclization followed by palladium-catalyzed ortho-arylation. The presence of the cyclic carbamate facilitated ring closure with moderate to excellent diastereoselectivities for the anti-configuration. The XPhos precatalyst proved useful for mediating both *ortho*-phenol and direct arylations of chloride substrates **24a** and **29** with excellent yields of 90% and 86%, respectively. In addition, the structure of (−)-artabonatine **A** was revised from **6** to **30** based on comparison of the specific rotation and ^{1}H and ^{13}C NMR for the synthetic material with the reported values. The structure of (−)-artabonatine **E** was proposed to also have a syn-configuration (e.g., **31**). Finally, this methodology will be useful for the preparation of other 7-oxygenated aporphine alkaloids and non-natural derivatives that can be explored for pharmacological utility.

■ ASSOCIATED CONTENT

Supporting Information

Description of the detailed experimental procedures and NMR spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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