

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

Angela F. Ku<sup>†</sup> and Gregory D. Cuny<sup>\*,‡</sup>

<sup>†</sup>Department of Chemistry and <sup>‡</sup>Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Science and Research Building 2, Rm 549A, Houston, Texas 77204, United States

## **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 synisomer **30**. Consequently, (-)-artabonatine E likely also has a syn-configuration (**31**).

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

However, only limited approaches to the preparation of 7oxygenated aporphines have been described.<sup>11</sup> 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.<sup>12</sup> 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

Received: January 2, 2015 Published: February 24, 2015

## Scheme 1. Retrosynthetic Analysis of Oxazoloaporphine A



use a palladium mediated ortho-arylation<sup>13</sup> with XPhos precatalyst, developed by Buchwald.<sup>14</sup>

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





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

In an one-pot reductive acid-mediated cyclization,<sup>17</sup> 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<sub>3</sub>·OEt<sub>2</sub>) 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 antiand 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  $Pd(OAc)_2/PCy_3 \cdot HBF_4$ .<sup>18</sup> 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 hydro-chloride (14), where the phenol could function as a directing group for *ortho*-phenol-arylation by making the reaction center more electron-rich.<sup>13</sup>

After the formation of amide **15** with EDC coupling, TBSprotection of the phenol gave **16**. Treatment of **16** with CDI followed by the one-pot three-step reductive cyclization and subsequent silvl 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.<sup>13c</sup> 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,<sup>20</sup> 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.<sup>21</sup> Subsequent reduction of the methyl ester to the intermediate aldehyde with DIBAL-H followed by acid-mediated cyclization with BF<sub>3</sub>·OEt<sub>2</sub> gave enantiomerically pure oxazolidinones 24a and 24b with moderate diastereoselectivity favoring the anticonfiguration (87:13 *dr*).<sup>22</sup> 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

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



98% yield.<sup>24</sup> Noteworthy, both acetylated aporphines **2** and **4** displayed rotational isomers in their <sup>1</sup>H NMR spectra due to steric hindrance caused by the *N*,*O*-diacetyl groups.<sup>25</sup> The ratio of the two rotamers varied in different deuterium solvents. For example, in CDCl<sub>3</sub> **2** showed a ratio of 7:3, while in CD<sub>3</sub>OD it was ~1:1.

Oxazoloaporphine 6 was previously reported to be the structure of (-)-artabonatine  $A^6$  However, the specific rotation and <sup>1</sup>H and <sup>13</sup>C NMR spectral data for this material indicated that the assigned structure was incorrect. However,  $(\pm)$ -syn-13b possessed the same <sup>1</sup>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<sub>3</sub>, formation of the methylenedioxy with CH2Br2, 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 <sup>1</sup>H NMR spectra and specific rotation,<sup>7</sup> we propose that (-)-artabonatine E also has a *syn*-configuration and is likely 31.

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



29 30: revised (-)-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 anticonfiguration. 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 <sup>1</sup>H and <sup>13</sup>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,

proposed to also have a syn-configuration (e.g., 31). Finally, this methodology will be useful for the preparation of other 7oxygenated 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.

## AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: gdcuny@central.uh.edu.

## Notes

The authors declare no competing financial interest.

### ACKNOWLEDGMENTS

We thank the University of Houston for financial support.

## REFERENCES

(1) (a) Shamma, M.; Slusarchyk, W. A. Chem. Rev. 1964, 64, 59–79.
 (b) Jackman, L. M.; Trewella, J. C.; Moniot, J. L.; Shamma, M.; Stephens, R. L.; Wenkert, E.; Leboeuf, M.; Cavé, A. J. Nat. Prod. 1979, 42, 437–449.
 (c) Israilov, I. A.; Karimova, S. U.; Yunusov, M. S.; Yunusov, S. Y. Chem. Nat. Compd. 1980, 16, 197–225.
 (d) Ríos, J. L.; Máñez, S.; Giner, R. M.; Recio, M. C. The Alkaloids; Cordell, G. A., Ed.; Academic: New York, 2000; Vol. 53, p 57.

(2) Rasamizafy, S.; Hocquemiller, R.; Cavé, A.; Fournet, A. J. Nat. Prod. 1987, 50, 674–679.

(3) Takatsu, H.; Yamadaya, T.; Furihata, K.; Ogata, M.; Endo, T.; Kojima, K.; Urano, S. J. Nat. Prod. **2005**, 68, 430–431.

(4) (a) Abu Zarga, M. H.; Shamma, M. J. Nat. Prod. **1982**, 45, 471–475. (b) Rasamizafy, S.; Hocquemiller, R.; Cavé, A.; Jacquemin, H. J. Nat. Prod. **1986**, 49, 1078–1085. (c) Wu, Y.-C.; Duh, C.-Y. J. Nat. Prod. **1990**, 53, 1327–1331.

(5) Hamonnière, M.; Leboeuf, M.; Cavé, A. *Phytochemistry* **1977**, *16*, 1029–1034.

(6) (a) Hsieh, T.-J.; Chen, C.-Y.; Kuo, R.-Y.; Chang, F.-R.; Wu, Y.-C. *J. Nat. Prod.* **1999**, *62*, 1192–1193. (b) Hsieh, T.-J. Ph.D. Thesis, Kaohsiung Medical College, Taiwan, 2003.

(7) Hsieh, T.-J.; Chang, F.-R.; Chia, Y.-C.; Chen, C.-Y.; Lin, H.-C.; Chiu, H.-F.; Wu, Y.-C. J. Nat. Prod. 2001, 64, 1157–1161.

(8) (a) Quevauviller, A.; Hamonnière, M. C. R. Acad. Sci. Hebd. Seances Acad. Sci. D 1977, 284, 93–96. (b) Oliver-Bever, B. Medicinal Plants of Tropical West Africa; Cambridge University Press: London, 1986; p 266.

(9) Brastianos, H. C.; Sturgeon, C. M.; Roberge, M.; Andersen, R. J. J. Nat. Prod. 2007, 70, 287–288.

(10) Naaz, H.; Singh, S.; Pandey, V. P.; Singh, P.; Dwivedi, U. N. Indian J. Biochem. Biophys. 2013, 50, 120–125.

(11) (a) Kessar, S. V.; Gupta, Y. P.; Yadav, V. S.; Narula, M.; Mohammad, T. Tetrahedron Lett. 1980, 21, 3307-3308. (b) Chackalamannil, S.; Dalton, D. R. Tetrahedron Lett. 1980, 21, 2029-2032.
(c) Kessar, S. V.; Gupta, Y. P.; Mohammad, T. Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem. 1981, 20, 984. (d) Kessar, S. V.; Mohammad, T.; Gupta, Y. P. Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem. 1983, 22, 321-324. (e) Seebach, D.; Huber, I. M. P.; Syfrig, M. A. Helv. Chim. Acta 1987, 70, 1357-1379. (f) Lenz, G. R. J. Org. Chem. 1988, 53, 4447-4452. (g) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. J. Org. Chem. 1999, 64, 6583-6596. (h) Bentley, K. W. Nat. Prod. Rep. 2006, 23, 444-463.

(12) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. A. J. Org. Chem. **1983**, 48, 3835–3837.

(13) (a) Cuny, G. D. Tetrahedron Lett. 2003, 44, 8149–8152.
(b) Cuny, G. D. Tetrahedron Lett. 2004, 68, 5167–5170. (c) Hellal, M.; Singh, S.; Cuny, G. D. Tetrahedron 2012, 68, 1674–1681.

(14) (a) Biscoe, M. R.; Brett, B. F.; Buchwald, S. L. J. Am. Chem. Soc. **2008**, 130, 6686–6687. (b) Biscoe, M. R.; Buchwald, S. L. Org. Lett. **2009**, 11, 1773–1775.

(15) Imanishi, M.; Tomishima, Y.; Itou, S.; Hamashima, H.; Nakajima, Y.; Washizuka, K.; Sakurai, M.; Matsui, S.; Imamura, E.; Ueshima, K.; Yamamoto, T.; Yamamoto, N.; Ishikawa, H.; Nakano, K.; Unami, N.; Hamada, K.; Matsumura, Y.; Takamura, F.; Hattori, K. *J. Med. Chem.* **2008**, *51*, 1925–1944.

(16) Lewis, R. T.; Macleod, A. M.; Merchant, K. J.; Kelleher, F.; Sanderson, I.; Herbert, R. H.; Cascieri, M. A.; Sadowski, S.; Ball, R. G.; Hoogsteen, K. J. Med. Chem. **1995**, 38, 923–933.

(17) Liu, X.-K.; Zheng, X.; Ruan, Y.-P.; Ma, J.; Huang, P.-Q. Org. Biomol. Chem. 2012, 10, 1275–1284.

(18) (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. J. Am. Chem. Soc. 2006, 128, 581–590. (b) Lafrance, M.; Blaquiere, N.; Fagnou, K. Eur. J. Org. Chem. 2007, 5, 811–825.

(19) Ikeuchi, M.; Ikeuchi, M.; Inoue, K.; Yamamoto, S.; Yamauchi, A.; Kihara, M. *Heterocycles* **2005**, *65*, 2925–2935.

(20) Huszthy, P.; Bradshaw, J. S.; Zhu, C. Y.; Izatt, R. M. J. Org. Chem. 1991, 56, 3330-3336.

(21) Wang, L.; Zhang, B.; Ji, J.; Li, B.; Yan, J.; Zhang, W.; Wu, Y.; Wang, X.; Hou, H. Synth. Commun. 2010, 40, 52–57.

(22) Kano, S.; Yuasa, Y.; Shibuya, S. *Heterocycles* 1985, 23, 395–398.
(23) Knaggs, S.; Malkin, H.; Osborn, H. M. I.; Williams, N. A. O.; Yaqoob, P. *Org. Biomol. Chem.* 2005, 3, 4002–4010.

(24) Butora, G.; Hudlicky, T.; Fearnley, S. P.; Stabile, M. R.; Gum, A. G.; Gonzalez, D. Synthesis **1998**, 665–681.

(25) (a) Pachaly, P.; Adnan, A. Z.; Will, G. *Planta Med.* **1992**, *58*, 184–187. (b) Chen, I.-S.; Chen, J.-J.; Tsai, I.-L. *Heterocycles* **1996**, *43*, 799–807. (c) Chen, J.-J.; Hung, H.-C.; Sung, P.-J.; Chen, I.-S.; Kuo, W.-L. Phytochemistry **2011**, *72*, 523–532.