2007 Vol. 9, No. 17 3255-3257

Synthesis of Santiagonamine

Michael D. Markey, Ying Fu, and T. Ross Kelly*

E.F. Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467 ross.kelly@bc.edu

Received May 21, 2007

ABSTRACT

The first total synthesis of santiagonamine (1) is achieved in 12 steps from isovanillin. A palladium-catalyzed Ullmann cross-coupling reaction and a photocyclization are the key steps in the synthesis.

In 1984, Shamma and colleagues reported¹ the isolation and structure determination of santiagonamine (1). Santiagonamine, which was extracted from the stems and branches of the South American shrub *Berberis darwinii* Hook and shows wound-healing properties,² is the only known example—naturally occurring or otherwise—of the 10*H*-[1]benzopyrano[5,4,3-*hij*]isoquinoline ring system. Because of its structural novelty and the absence of any independent confirmation of the structure determination,³ the synthesis of this alkaloid was undertaken. Herein we report the first synthesis of 1 and the verification of the original structure assignment.

Retrosynthetic analysis (Figure 1) suggested that attachment of a side-chain equivalent (3) to intermediate 2 would lead to santiagonamine (1). Intermediate 2 was envisioned

to originate from manipulation of biaryl 4, with the latter being secured from an appropriate cross-coupling reaction

$$1 \Rightarrow \bigvee_{N=1}^{MeO} \bigvee_{X}^{X} \bigvee_{X}^{Z} \Rightarrow \bigvee_{R^{2}OC} \bigvee_{N}^{R^{1}O} \bigvee_{X}^{X} \bigcirc O$$

$$2 \qquad \qquad 4 \qquad \qquad R^{2}OC \bigvee_{N}^{X} \bigcirc O$$

$$6 \qquad \qquad 6$$

Figure 1. Retrosynthetic analysis of santiagonamine (1).

between functionalized monocycles **5** and **6**. Both **5** and **6** should be derivable from commercially available material.

The synthesis began (Scheme 1) with conversion of picolinic acid (7) into the secondary amide 8.4 Ortho-

Scheme 1

oxalyl chloride,
NEt3, DMF,
DCM, 0 °C;
aniine, 0 °C - rt
(74%)

7

NEt3, DMF,

⁽²⁾ Lewis, W. H.; Stonard, R. J.; Porras-Reyes, B.; Mustoe, T. A.; Thomas, A. Wound-healing composition. U.S. Patent 5,156,847, 1992.

⁽³⁾ For earlier synthetic studies stimulated by the structure of santiagonamine, see: (a) Castedo, L.; Cid, M. M.; Seijas, J. A.; Villaverde, M. C. *Tetrahedron Lett.* **1991**, *32*, 3871. (b) Pavé, G.; Chalard, P.; Viaud-Massuard, M.-C.; Troin, Y.; Guillaumet, G. *Synlett* **2003**, 987.

lithiation of **8** with *n*-butyllithium⁵ (*n*-BuLi) and subsequent quenching with iodine supplied the desired specific embodiment (**9**) of **6**.

Preparation of the unit (12) corresponding to 5 commenced (Scheme 2) with a previously described procedure⁶ for the

iodination of 3-hydroxy-4-methoxybenzaldehyde (isovanillin, **10**) to give iodide **11**. Protection of the hydroxyl group as its methoxymethyl (MOM) ether gave the known aldehyde **12**, which has also been prepared from **10** by a 3-step route.⁷

It was anticipated that a palladium-catalyzed Ullmann cross-coupling reaction⁸ would prove suitable for forming the hindered biaryl bond of **4**. Exposure of **9** and **12** on a 0.2 mmol scale to palladium and activated copper⁹ bronze at 145 °C gave the desired product **14**, albeit in only 7% yield (eq 1).^{10–12} Efforts to improve the yield of **14** were unsuccessful.

Consequently, we chose to convert aldehyde **12** into an imine, based on three considerations: imines (i) possess a history of success in Ullmann reactions, ¹³ (ii) contain a coordinating lone pair of electrons, ¹⁴ and (iii) preserve the benzylic carbon's oxidation state.

Condensation (Scheme 3) of 12 with cyclohexylamine gave imine 13. Without purification, 13 was coupled with 9 on a 10 mmol scale to afford, after an aqueous workup, biaryl 14 in 39% yield.

- (4) (a) Jóźwiak, A.; Brzeziński, J. Z.; Płotka, M. W.; Szcześniak, A. K.; Malinowski, Z.; Epsztajn, J. Eur. J. Org. Chem. 2004, 3254. (b) Brunner, H.; Nuber, B.; Prommesberger, M. J. Organomet. Chem. 1996, 523, 179. (5) Epsztajn, J.; Płotka, M. W.; Grabowska, A. Synth. Commun. 1997, 27, 1075.
- (6) Markovich, K. M.; Tantishaiyakul, V.; Hamada, A.; Miller, D. D.; Romstedt, K. J.; Shams, G.; Shin, Y.; Fraundorfer, P. F.; Doyle, K.; Feller, D. R. *J. Med. Chem.* **1992**, *35*, 466.
- (7) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. Org. Lett. 2006, 23, 5311 and references cited therein.
- (8) For leading references on the Ullmann reaction, see: (a) Kürti, L.; Czakó, B. Strategic Applications of Named Reactions in Organic Synthesis; Elsevier: Amsterdam, The Netherlands, 2005; p 466. (b) Nelson, T. D.; Crouch, R. D. Org. React. 2004, 63, 265. (c) Fanta, P. E. Synthesis 1974, 9. For examples of palladium-catalyzed Ullmann cross-coupling reactions, see: (d) Shimizu, N.; Kitamura, T.; Watanabe, K.; Yamaguchi, T.; Shigyo, H.; Ohta, T. Tetrahedron Lett. 1993, 34, 3421. (e) Thompson, W. J.; Gaudino, J. J. Org. Chem. 1984, 49, 5237. (f) Banwell, M. G.; Lupton, D. W.; Ma, X.; Renner, J.; Sydnes, M. O. Org. Lett. 2004, 6, 2741. (g) Some, S.; Dutta, B.; Ray, J. K. Tetrahedron Lett. 2006, 47, 1221.
 - (9) Kleiderer, E. C.; Adams, R. *J. Am. Chem. Soc.* **1933**, *55*, 4219. (10) When performed at 85 °C no biaryl **14** was isolated.

Scheme 3

To complete the ring system, **14** was transformed into styrene **22** by a Wittig reaction with methylenetriphenylphosphorane. Styrene **22** was then subjected to photocyclization, ¹⁵ but gave benzo[f]quinoline **23** instead of the desired benz[h]isoquinoline **24**. To overcome this unexpected result, ¹⁶ we hoped that by first forming the lactone we could alter the regioselectivity of the photocyclization.

(11) Although the yield to form 14 was poor, this approach served as an alternative to our first synthetic approach, where exposure of 9 and 25^{12} to palladium and activated copper bronze gave biaryl 26 (eq i) in 29% unopti-

$$\begin{array}{c} \text{MeO} \\ \text{MeO} \\ \text{MOMO} \\ \text{I} \\ \text{25} \\ \end{array} \begin{array}{c} \text{9 (1.6 equiv),} \\ \text{Cu}^0, \\ \text{Pd}_2(\text{dba})_3, \\ \text{DMF,} \\ \text{100 °C} \\ \text{(29\%)} \\ \end{array} \begin{array}{c} \text{MeO} \\ \text{MOMO} \\ \text{PhHNOC} \\ \text{PhHNOC} \\ \text{N} \\ \end{array} \begin{array}{c} \text{CONHPr} \\ \text{(i)} \\ \end{array}$$

mized yield on a 6 mmol scale. In an effort to complete the synthesis of 1 from 26, we were successful in forming the lactone and hydrolyzing the N-propyl amide to give carboxylic acid i. However, attempts to advance i (e.q., by selective reduction of the carboxylic acid with borane reagents) were unsuccessful. Possibly, the pyridine nitrogen directs the reduction to the lactone carbonyl in i.

(12) Iodoamide **25** was available in three steps from 3-hydroxy-4-methoxybenzoic acid (isovanillic acid). For a synthesis of **25**, see: Kelly, T. R.; Xie, R. L. *J. Org. Chem.* **1998**, *63*, 8045.

(13) (a) Sainsbury, M. Tetrahedron **1980**, 36, 3327. (b) Stark, L. M.; Lin, X.-F.; Flippin, L. A. J. Org. Chem. **2000**, 65, 3227.

(14) (a) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, 62, 2312. (b) Ziegler, F. E.; Chliwner, I.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790. (c) van Koten, G.; Leusink, A. J.; Noltes, J. G. *J. Chem. Soc. D* **1970**, 1107.

(15) For a leading reference on photocyclizations, see: (a) Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1. For related applications on similar ring systems, see ref 3a and: (b) Veeramani, K.; Paramasivam, K.; Ramakrishnasubramanian, S.; Shanmugam, P. *Synthesis* **1978**, 855. (c) Kende, A. S.; Curran, D. P. *J. Am. Chem. Soc.* **1979**, *101*, 1857. (d) McDonald, E.; Martin, R. T. *Tetrahedron Lett.* **1978**, *19*, 4723. (e) Padwa, A.; Doubleday, C.; Mazzu, A. *J. Org. Chem.* **1977**, *42*, 3271.

3256 Org. Lett., Vol. 9, No. 17, 2007

Accordingly (Scheme 4), 14 was deprotected with TMSBr to give phenol 15, which then underwent a Wittig reaction with methylenetriphenylphosphorane to afford styrene 16.

(16) The photocyclization of ii to a mixture of iii and iv has been re-

ported.3a We speculate that the failure of 22 to cyclize to 24 may be due to a repulsive steric interaction between the MOMO and PhHNOC groups that disfavors a conformation necessary to access the transition state leading to intermediate v.

Bromination of 16 at -78 °C with a mixture of triethylamine¹⁷ and bromine-1,4-dioxane¹⁸ gave bromide 17.¹⁹ Cyclization of 17 with trifluoracetic acid in THF gave styrene lactone 18. The latter, to our delight, underwent smooth and rapid photocyclization to give bromolactone 19.

Finally, the side-chain installation began with a Stille coupling between 19 and allytributyltin to give allyl lactone 20. Transformation of 20 into aldehyde 21 by the action of osmium tetroxide and sodium periodate²⁰ followed by reductive amination¹² of **21** with dimethylamine and sodium triacetoxyborohydride secured santiagonamine (1). The spectra of synthetic 1 are in excellent agreement with those reported for the natural product.²¹

In summary, we report the first total synthesis of santiagonamine. The synthesis, accomplished in 12 steps (2.6% overall yield) from commercially available isovanillin, affirms the original structure assignment.

Acknowledgment. We thank Dr. M. Shamma¹ (Pennsylvania State University) for helpful exchange of information. We are also grateful to Stepanie M. Ng (Boston College) for X-ray crystallographic studies.

Supporting Information Available: Experimental procedures and characterization data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0711974

Org. Lett., Vol. 9, No. 17, 2007 3257

⁽¹⁷⁾ When this reaction was performed at room temperature or in the absence of base there was competing addition of bromine to the vinyl group. We believe the triethylamine accelerates the rate of ring bromination by deprotonation of 16 to the corresponding phenoxide.

⁽¹⁸⁾ Finkelstein, B. L. In Encyclopedia of Reagents for Organic Synthesis; Paquette, L. A., Ed.; John Wiley: Chichester, UK, 1995; Vol. 1, p 686. (19) The regioselectivity of the bromination was later proven by an X-ray

crystallographic characterization of 19 (see the Supporting Information). (20) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. J. Org.

Chem. 1956, 21, 478.

⁽²¹⁾ Unfortunately, an authentic sample of natural 1 is no longer available.