ORGANIC LETTERS

2007
Vol. 9, No. 17
3255−3257

Synthesis of Santiagonamine

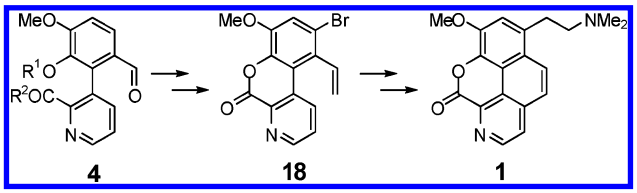
Michael D. Markey, Ying Fu, and T. Ross Kelly*

E.F. Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

ross.kelly@bc.edu

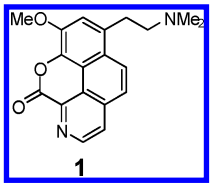
Received May 21, 2007

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 reported[1] 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

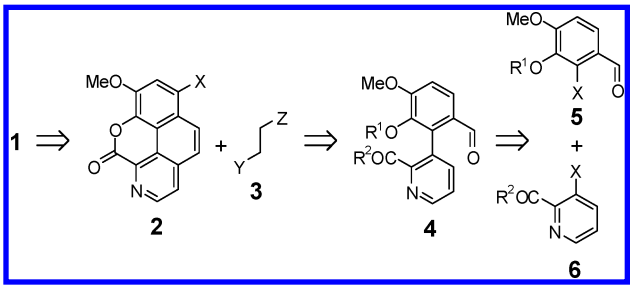
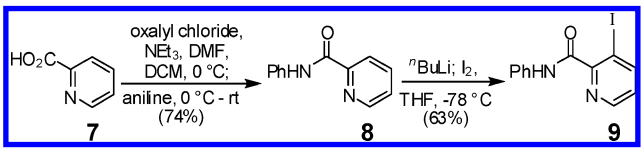


Figure 1. Retrosynthetic analysis of santiagonamine (**1**).

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

The synthesis began (Scheme 1) with conversion of picolinic acid (**7**) into the secondary amide **8**.[4] Ortho-

Scheme 1



(1) Valencia, E.; Patra, A.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 3163.

(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.

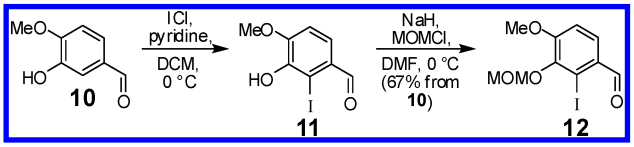
(3) For earlier synthetic studies stimulated by the structure of santiagonamine, see: (a) Castedo, L.; Cid, M. M.; Seijas, J. A.; Villaverde, M. C. *Tetrahedron Lett.* **1991**, *32*, 3871. (b) Pavé, G.; Chalard, P.; Viaud-Massuard, M.-C.; Troin, Y.; Guillaumet, G. *Synlett* **2003**, 987.

10.1021/ol0711974 CCC: $37.00
Published on Web 07/21/2007

lithiation of **8** with *n*-butyllithium[5] (*n*-BuLi) and subsequent quenching with iodine supplied the desired specific embodiment (**9**) of **6**.

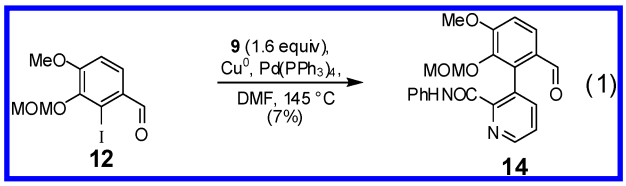
Preparation of the unit (**12**) corresponding to **5** commenced (Scheme 2) with a previously described procedure[6] for the

Scheme 2



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]

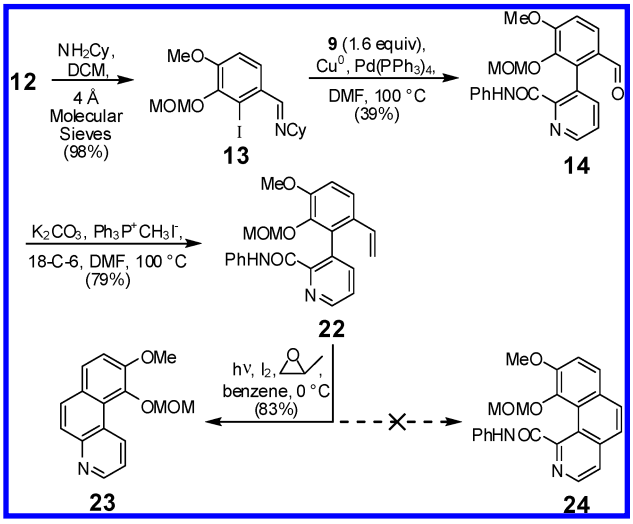
It was anticipated that a palladium-catalyzed Ullmann cross-coupling reaction[8] would prove suitable for forming the hindered biaryl bond of **4**. Exposure of **9** and **12** on a 0.2 mmol scale to palladium and activated copper[9] bronze at 145 °C gave the desired product **14**, albeit in only 7% 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.

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.

(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.

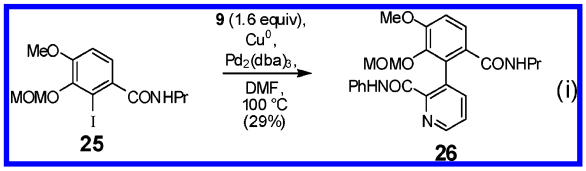
(7) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* **2006**, *23*, 5311 and references cited therein.

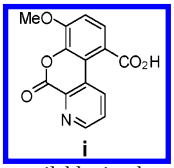
(8) For leading references on the Ullmann reaction, see: (a) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Amsterdam, The Netherlands, 2005; p 466. (b) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265. (c) Fanta, P. E. *Synthesis* **1974**, 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.

(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% unoptimized 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.g., 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**.





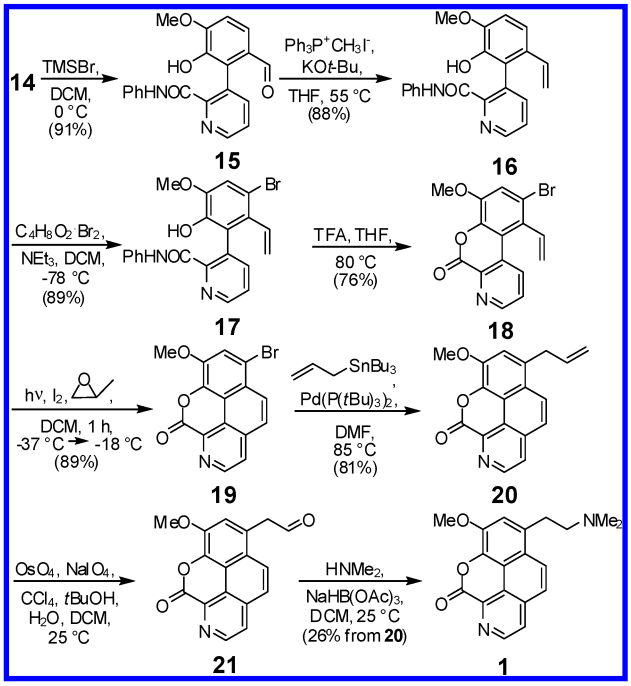
(12) Iodoamide **25** was available in three steps from 3-hydroxy-4-methoxybenzoic acid (isovanillic acid). For a synthesis of **25**, see: Kelly, T. R.; Xie, R. L. *J. Org. Chem.* **1998**, *63*, 8045.

(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.

Scheme 4



Accordingly (Scheme 4), **14** was deprotected with TMSBr to give phenol **15**, which then underwent a Wittig reaction with methylenetriphenylphosphorane to afford styrene **16**. Bromination of **16** at −78 °C with a mixture of triethylamine[17] and bromine−1,4-dioxane[18] 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 periodate[20] followed by reductive amination[12] 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]

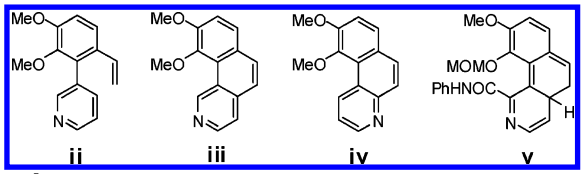
In summary, we report the first total synthesis of santiagonamine. The synthesis, accomplished in 12 steps (2.6% overall yield) from commercially available isovanillin, affirms the original structure assignment.

Acknowledgment. We thank Dr. M. Shamma[1] (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

(16) The photocyclization of **ii** to a mixture of **iii** and **iv** has been reported.[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**.



(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.