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Total Synthesis of Broussonetine F: The Orthoamide Overman Rearrangement of an Allylic Diol

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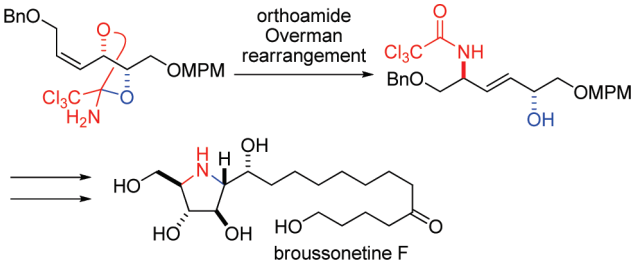
ABSTRACT



A first total synthesis of broussonetine F from diethyl L-tartrate was achieved. The cornerstone of our synthesis was an orthoamide Overman rearrangement, which provided an allylic amino alcohol with complete diastereoselectivity.

Our laboratory has been exploring new strategies to obtain biologically active natural products by using sigmatropic rearrangements of naturally occurring chiral polyols, such as carbohydrates and tartaric acid, with chirality transfer.[1] For example, we developed a sequential Overman rearrangement of allylic 1,2-bistrichloroimidate **2**, which was prepared from tartaric acid via allylic alcohol **1** to give bistrichloroacetamide **3** (Scheme 1).[2,3] The reaction proceeded with complete chirality transfer of two hydroxy groups and installed the diamino moiety in a single operation. This strategy was successfully applied to two enantioselective total syntheses of biologically active complex molecules, A-315675 and agelastatin A.[3c,d]

To expand the concept of chirality transfer from enantiopure polyols, we envisioned an orthoamide Overman rearrangement (Scheme 1, **4**→**5**→**6**).[4,5] If cyclic orthoamide **4** could be selectively formed from allylic 1,2-diol **1**, this compound would undergo the single rearrangement via α-hydroxy imidate **5**. Although the sequential Overman rearrangement can install two identical functional groups (**2**→**3**), the orthoamide Overman rearrangement could

(1) For selected reviews on chirality transfer through sigmatropic rearrangements, see: (a) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882. (b) Nubbemeyer, U. *Synthesis* **2003**, 961–1008. (c) Poulin, J.; Grisé- Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092–3101. (d) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 3133–3148.

(2) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597–599. For reviews on Overman rearrangement, see:(b) Overman, L. E.; Carpenter, N. E. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: New York, NY, 2005; Vol. 66, pp 1−107.

(3) For selected examples of sequential Overman/Overman rearrangements, see: (a) Banert, K.; Fendel, W.; Schlott, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 3289–3292. (b) Demay, S.; Kotschy, A.; Knochel, P. *Synthesis* **2001**, 863–866. (c) Momose, T.; Hama, N.; Higashino, C.; Sato, H.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 1376–1379. (d) Hama, N.; Matsuda, T.; Sato, T.; Chida, N. *Org. Lett.* **2009**, *11*, 2687–2690. We have also reported the formal total synthesis of (−)-morphine by the sequential Claisen rearrangement starting from D-glucal; see:Tanimoto, H.; Saito, R.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 358–362.

(4) We reported orthoamide-type Claisen rearrangements of allylic diols, which was successfully applied to the total synthesis of (−)-kainic acid; see: Kitamoto, K.; Sampei, M.; Nakayama, Y.; Sato, T.; Chida, N. *Org. Lett.* **2010**, *12*, 5756–5759.

(5) (a) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037–2039. (b) Danishefsky, S.; Lee., J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829–4837.

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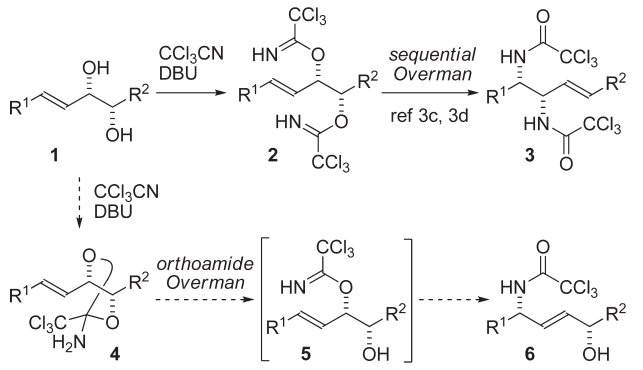
Scheme 1. Sequential and Orthoamide Overman Rearrangements



terminate the reaction after the first rearrangement. In contrast to the conventional Overman rearrangement, which requires protection of the homoallylic alcohol in allylic 1,2-diol **1**, the orthoamide-type reaction would enable us to perform the reaction with free 1,2-diols. The resulting allylic alcohol would undergo a variety of transformations. In spite of its utility, few orthoamide versions are documented.[5] Vyas reported that a rearrangement of the seven-membered cyclic orthoamide, prepared from *Z*-2-butene-1,4-diol, proceeded in 85% yield.[5a] Danishefsky disclosed in the total synthesis of (±)-pancratistatin that the orthoamide from an allylic 1,2-diol did not undergo the Overman rearrangement and also gave valuable mechanistic insight on this reaction.[5b]

To study the feasibility of the orthoamide Overman rearrangement in total synthesis, we have taken note of a new class of pyrrolidine alkaloids, broussonetines (Figure 1).[6] Isolated from the branches of *Broussonetia* kazinoki by Kusano and co-workers, broussonetines consist of a common pyrrolidine unit and a variable long hydrocarbon side chain. Most broussonetines have been shown to possess highly potent and selective glycosidase inhibitory activities. Interestingly, their inhibitory profile depends on the structure of the long hydrocarbon side chain. Because of their interesting structures and biological properties, a number of synthetic chemists have undertaken studies on the synthesis of broussonetines.[7,8] Yoda reported the first enantioselective total synthesis of broussonetine C (**7**) by Lewis acid

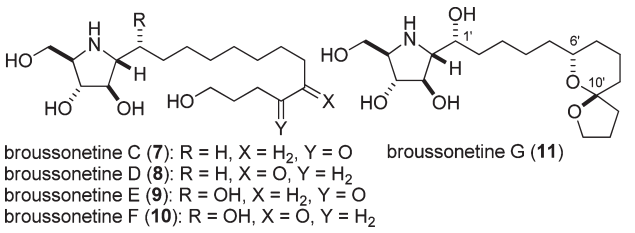
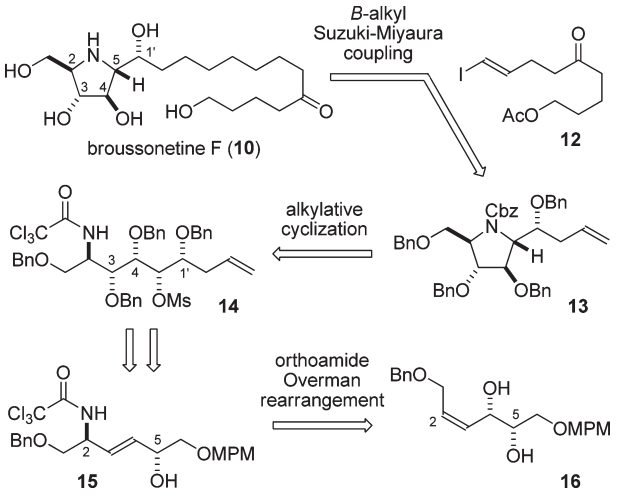


Figure 1. Representative broussonetines.

Scheme 2. Synthetic Plan for Broussonetine F



promoted deoxygenation of a C2-symmetrical imide as a key step.[7a] Perlmutter completed the second total synthesis of broussonetine C (**7**), using chiral-pool methodology from D-arabinose.[7b] Trost determined the stereochemistry of three carbon centers (C-1′, C-6′, C-10′) on the side chain in broussonetine G (**11**) and accomplished the total synthesis through a palladium-mediated dynamic kinetic asymmetric transformation.[7c,d] Very recently, Marco reported a convergent approach utilizing a cross-metathesis reaction, which culminated in the total synthesis of broussonetines D (**8**) and M.[7e] In this communication, we report the first total synthesis of broussonetine F (**10**) from L-tartrate employing the orthoamide Overman rearrangement.

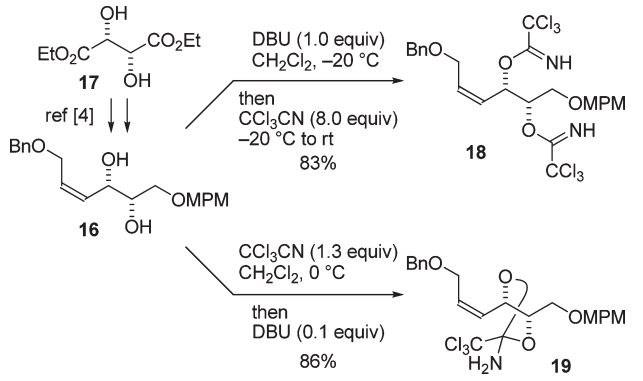
Our synthetic plan toward broussonetine F is outlined in Scheme 2. Considering a universal route toward the broussonetine family with its variety of side chains, it would be reasonable to adopt the late-stage coupling reaction between common pyrrolidine unit **13** and side chain unit **12** by a *B*-alkyl Suzuki−Miyaura coupling reaction.[9] Pyrrolidine **13** would be constructed by the alkylative cyclization of open chain intermediate **14**. This intermediate could be synthesized from allylic amino alcohol **15** through two diastereoselective reactions: (i) dihydroxylation (C3, C4) and (ii) allylation (C1′). As a defining feature of our synthesis, we envisioned that allylic amino alcohol **15** could

(6) For a review on isolation, biosynthesis, and biological activities of broussonetines, see: Shibano, M.; Tsukamoto, D.; Kusano, G. *Heterocycles* **2002**, *57*, 1539–1553. For selected reports on isolation of broussonetines, see:(a) Shibano, M.; Kitagawa, S.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 505–508. (b) Shibano, M.; Kitagawa, S.; Nakamura, S.; Akazawa, N.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 700–705. (c) Shibano, M.; Nakamura, S.; Akazawa, N.; Kusano, G. *Chem. Pharm. Bull.* **1998**, *46*, 1048–1050.

(7) For total syntheses of broussonetines, see: (a) Yoda, H.; Shimojo, T.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 1335–1336. (b) Perlmutter, P.; Vounatsos, F. *J. Carbohydr. Chem.* **2003**, *22*, 719–732. (c) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5987–5990. (d) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem.—Eur. J.* **2006**, *12*, 6607–6620. (e) Ribes, C.; Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Org. Biomol. Chem.* **2009**, *7*, 1355–1360.

(8) For a selected example of a synthetic study on broussonetines, see: Brimble, M. A.; Park, J. H.; Taylor, C. M. *Tetrahedron* **2003**, *59*, 5861–5868.

Scheme 3. Selective Formation of Cyclic Orthoamide **19**



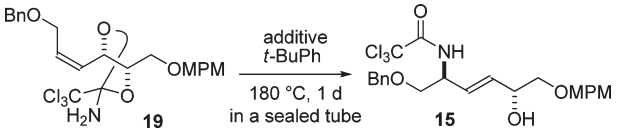
be stereoselectively synthesized by the orthoamide Overman rearrangement of *Z*-allylic 1,2-diol **16** derived from L-tartrate.[4]

The synthesis of broussonetine F began with selective formation of the cyclic orthoamide from allylic 1,2-diol **16**, which was prepared from diethyl L-tartrate (**17**) by a known procedure (Scheme 3).[4] To render our two novel sigmatropic rearrangements useful, flexible conditions to form either bisimidate **18** or cyclic orthoamide **19** from the common allylic 1,2-diol **16** are required. After an extensive survey, we found that the amount of DBU and CCl_3CN and the order of addition were crucial. When excess CCl_3CN (8 equiv) was added to a solution of **16**, DBU (1 equiv), and CH_2Cl_2, bisimidate **18** was selectively generated.[3c,d,10] On the other hand, addition of a catalytic amount of DBU (0.1 equiv) to a solution of **16**, CCl_3CN (1.3 equiv), and CH_2Cl_2 resulted in the selective formation of cyclic orthoamide **19** (dr = 1:1), along with a trace amount of bisimidate **18**.

With cyclic orthoamide **19** in hand, the stage was now set for the pivotal orthoamide Overman rearrangement (Table 1). A solution of cyclic orthoamide **19** and *tert*-butylbenzene was heated at 180 °C for 1 d in a sealed tube, giving allylic amino alcohol **15** in 17% yield (entry 1).[11] Because a prolonged reaction time caused severe decomposition, we next surveyed the effect of additives. Although K_2CO_3 did not improve the yield (entry 2),[12] we found that 2,6-di-*tert*-butylhydroxytoluene (BHT) suppressed the rate of decomposition to give **15** in 19% yield, together with recovery of 43% of **19** (entry 3).[13,14] The amount of BHT was critical, and 5 mol % of BHT gave the best results to afford **15** in 56% yield (77% yield brsm, entry 4). The reaction proceeded with complete chirality transfer probably through a chairlike transition state,[2] with **15** isolated as a single diastereomer.

(9) For selected reviews on *B*-alkyl Suzuki–Miyaura coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695. (d) Sasaki, M.; Fuwa, H. *Synlett* **2004**, *11*, 1851–1874. (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489. (f) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. (g) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013–2030.

Table 1. Orthoamide Overman Rearrangement of **19**[a]

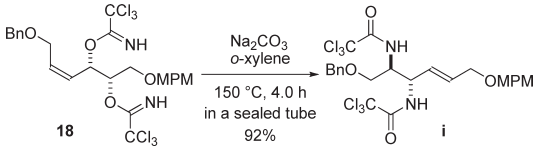


		yield (%)	
entry	additive	**15**	**19**
1	none	17	0
2	K_2CO_3	8	54
3	BHT (100 mol %)	19	43
4[b]	BHT (5 mol %)	56	27

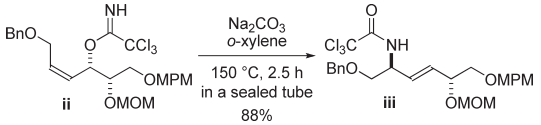
[a] Conditions: 50 μmol of **19**, *t*-BuPh, 180 °C in a sealed tube. [b] 406 μmol of **19** were used.

We then turned our attention to the construction of the polyhydroxy pyrrolidine unit (Scheme 4). Prior to the cyclization, we installed three secondary alcohols (C3, C4, C1′). The allylic alcohol in **15** was protected as a MOM ether to give **20**. Because the next dihydroxylation with achiral OsO_4 resulted in the undesired diasteroselectivity, **20** was treated under Sharpless' asymmetric conditions[15] (dr = 3:1), followed by recrystallization to furnish diol **21** in 61% isolated yield. After benzyl protection and MPM deprotection, the C1′ alcohol was stereoselectively established by chelation-controlled Hosomi–Sakurai allylation.[16] Namely, Swern oxidation of primary alcohol **22** provided the aldehyde, which was treated with allyl trimethylsilane and $MgBr_2 \cdot Et_2O$ to afford **23** as a single diastereomer. The resulting hydroxy group of **23** was protected as the benzyl

(10) The sequential Overman rearrangement of bistrichloroimidate **18** provided bistrichloroacetamide **i** in 92% yield.



(11) Overman rearrangement of MOM-protected trichloroacetoimidate **ii**, which was synthesized from **16** in four steps, proceeded at lower temperature and much faster than the orthoamide version. As Danishefsky reported in ref 5b, we also observed that two diastereomers of orthoamide **19** underwent equilibration at room temperature.



(12) Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188–192.

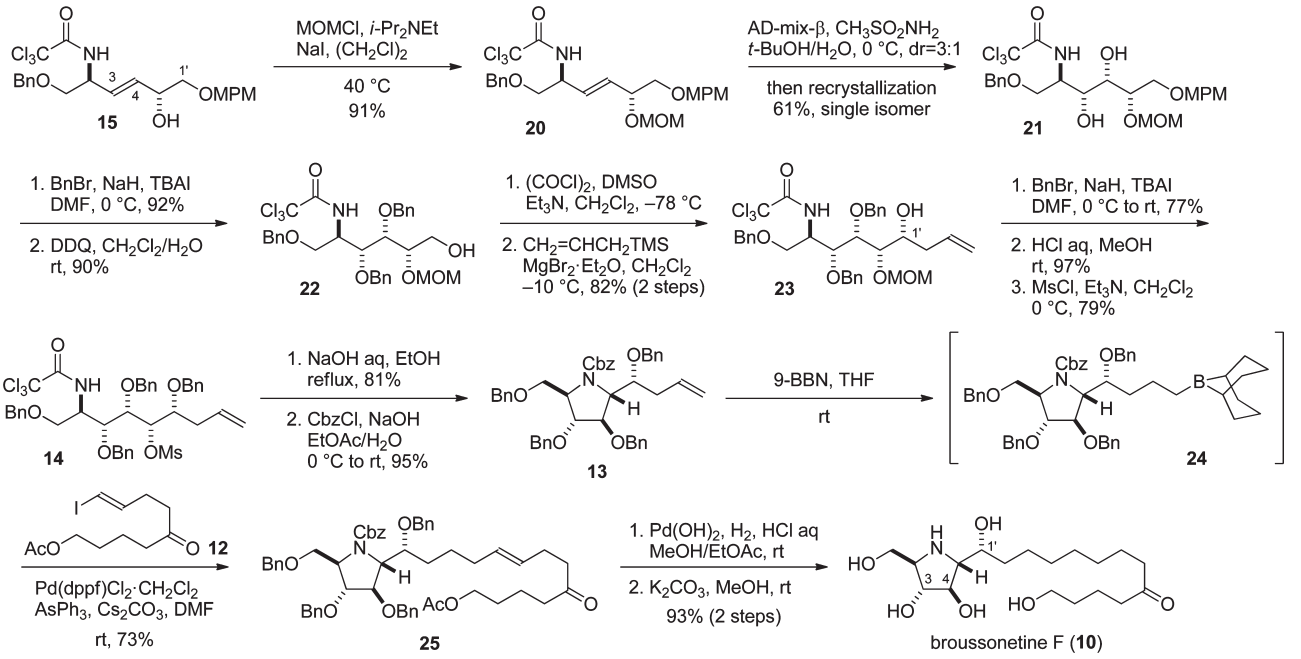
(13) Ammenn, J.; Altmann, K.-H.; Belluš, D. *Helv. Chim. Acta* **1997**, *80*, 1589–1606.

(14) We believe that BHT might suppress the decomposition pathway via a radical species.

(15) (a) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345–1376. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(16) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295–1298.

Scheme 4. Total Synthesis of Broussonetine F (**10**)



ether, followed by replacement of the MOM group with the mesyl group. The reaction of **14** with NaOH in refluxing EtOH resulted in cleavage of the trichloroacetyl group and concomitant alkylative cyclization. Subsequent protection of the secondary amine as a benzyl carbamate gave pyrrolidine **13** in 77% yield (2 steps).

To complete the total synthesis of broussonetine F, the remaining task was the coupling to the long hydrocarbon side chain (Scheme 4). Alkene **13** was treated with 9-BBN, and the subsequent palladium-catalyzed *B*-alkyl Suzuki−Miyaura coupling with vinyl iodide **12**[17] in the presence of $AsPh_3$ and Cs_2CO_3 furnished **25** in 73% yield.[18] Hydrogenation of the alkene and removal of the benzyl groups and the Cbz group in **25** were performed simultaneously. Finally, methanolysis of the acetate accomplished the total synthesis of broussonetine F (**10**). Our synthetic sample was indistinguishable from the authentic natural sample on the basis of ^{1}H NMR, ^{13}CNMR, HRMS, IR, and its optical rotation.

(17) Synthesis of vinyl iodide **12** is described in the Supporting Information.

(18) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015.

In summary, we have achieved a total synthesis of broussonetine F (**10**), whose key step was orthoamide Overman rearrangement of an allylic diol. This reaction is a useful transformation in total synthesis and complementary to our sequential Overman rearrangement. The flexible synthetic route using the late-stage Suzuki−Miyaura coupling to install a variety of side chain units is effective for future investigations of potent and selective glycosidase inhibitors.

Acknowledgment. We especially thank Professor M. Shibano (Osaka University of Pharmaceutical Sciences, Japan) for providing natural broussonetine F and copies of NMR spectra. Support from a Grant-in-Aid for Scientific Research, B20350021 from the Ministry of Education, Culture, Sports, Science and Technology, Japan is gratefully acknowledged.

Supporting Information Available. Experimental procedures; copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.