ORGANIC LETTERS

2005
Vol. 7, No. 24
5465−5468

Short and Efficient Total Synthesis of Fraxinellone Limonoids Using the Stereoselective Oshima–Utimoto Reaction

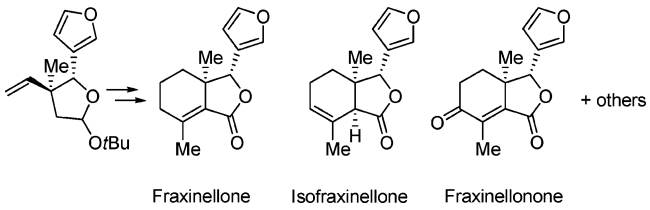
Stéphane Trudeau and James P. Morken*

Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

morken@unc.edu

Received September 19, 2005

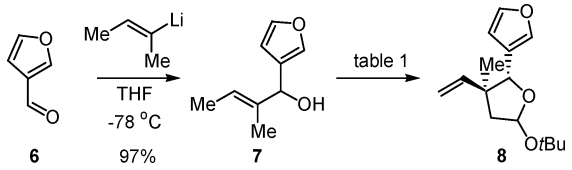
ABSTRACT



The catalytic diastereoselective Oshima–Utimoto reaction was employed for the construction of fraxinellone and related members of this limonoid family of natural products. After formation of the five-membered lactone, a stereoselective aldol reaction and olefin metathesis established the bicyclic ring system in the natural products.

Fraxinellone **1** and isofraxinellone **2** are the simplest examples of degraded limonoids and have been isolated from Rutaceae (*Dictamnus albus*,[1] *Dictamnus dasycarpus*,[2] and *Fagaropsis glabra*[3]) and Meliaceae (*Melia azedarach*[4]) plants (Scheme 1). While these compounds are known for their ichthyotoxic and insect antifeedant activities,[5] fraxinellone was also shown to have antiplatelet-aggregation and vascular relaxing activities,[6] whereas isofraxinellone has demonstrated antimutagenic activity.[7] We viewed these natural products as an opportunity to examine the utility of the Pd-catalyzed Oshima−Utimoto reaction for the assembly of sterically encumbered lactone targets.[8] This transformation brings about the coupling of simple vinyl ethers and allylic alcohols to afford cyclic five-membered acetals. Recently, we found that

Scheme 1



(1) (a) Thomas, H. *Ber. Dtsch. Pharm. Ges.* **1923**, *33*, 568. (b) Thomas, H.; Dambergis, C. *Arch. Pharm. Chem.* **1930**, *268*, 39.

(2) (a) Zhao, W.; Wolfender, J.-L.; Hostettmann, K.; Xu, R.; Qin, G. *Phytochemistry* **1998**, *47*, 7. (b) Liu, Z. L.; Xu, Y. J.; Wu, J.; Goh, S. H.; Ho, S. H. *J. Agric. Food Chem.* **2002**, *50*, 1447.

(3) Blaise, A. J.; Winternitz, F. *Phytochemistry* **1985**, *24*, 2379.

(4) (a) Nakatani, M.; Huang, R. C.; Okamura, H.; Iwagawa, T.; Tadera, K. *Phytochemistry* **1998**, *49*, 1773. (b) D'Ambrosio, M.; Guerriero, A. *Phytochemistry* **2002**, *60*, 419.

(5) Okamura, H.; Yamauchi, K.; Miyawaki, K.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **1997**, *38*, 263 and references cited therein.

(6) (a) Yu, S. M.; Ko, F. N.; Su, M. J.; Wu, T. S.; Wang, M. L.; Huang, T. F.; Teng, C. M. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1992**, *345*, 349. (b) Wu, T.-S.; Wang, M.-L.; Shyur, H.-J.; Leu, Y.-L.; Chan, Y.-Y.; Teng, C.-M.; Kuo, S.-C. *Chin. Pharm. J.* **1994**, *46*, 447.

(7) Miyazawa, M.; Shimamura, H.; Nakamura, S. I.; Kameoka, H. *J. Agric. Food Chem.* **1995**, *43*, 1428.

(8) (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809. (b) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050. For a related processes, see: (c) Hafner, W.; Prigge, H.; Smidt, J. *Liebigs Ann. Chem.* **1966**, 109. (d) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815. (e) Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1989**, *30*, 2767. (f) Kraus, G. A.; Thurston, J. *J. Am. Chem. Soc.* **1989**, *111*, 9203.

10.1021/ol0522687 CCC: $30.25
Published on Web 10/27/2005

this transformation can be accomplished in an efficient catalytic and stereoselective fashion with acyclic substrates, and that it can provide a useful tool for the synthesis of interesting natural products, such as (−)-11α,13-dihydroxanthatin.[9,10] To further probe the utility of this reaction, we have begun to focus our attention on the synthesis of more challenging targets such as those that bear quaternary centers and considered fraxinellone **1** and isofraxinellone **2**, as well as 9α- and 9β-hydroxyfraxinellone (**3** and **4**)[4b] and fraxinellonone **5**[2a,4a] (Figure 1).

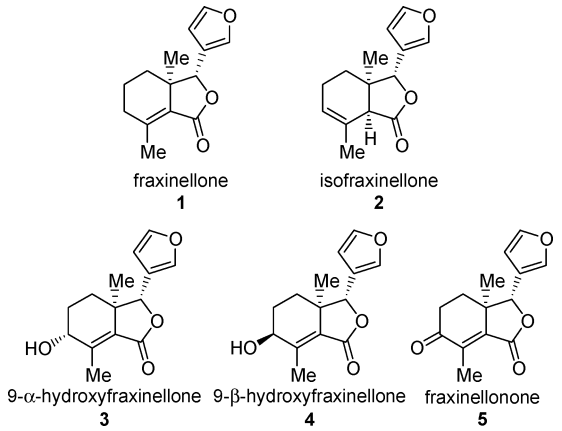


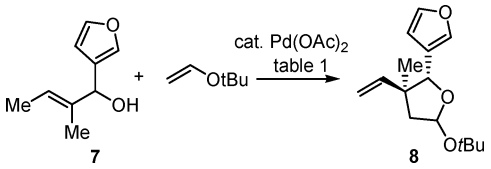
Figure 1.

While previous total syntheses of fraxinellone[11,12] and isofraxinellone[12] involved formation of the lactone moiety followed by late stage addition of the furan ring, we felt the Oshima−Utimoto reaction would enable an alternate retrosynthetic analysis. In this sense, we anticipated generating a key intermediate lactone, with the furan ring already in place, by executing a catalytic Oshima−Utimoto reaction followed by Jones oxidation.

Synthesis of fraxinellone **1** and isofraxinellone **2** began with the preparation of the secondary allylic alcohol **7** by treatment of (*E*)-2-bromo-2-butene with *t*-BuLi in THF at −78 °C followed by addition of 3-furaldehyde **6** (Scheme 1). Next, the Oshima−Utimoto reaction was examined using conditions established in our previous report.[9] Alcohol **7** was submitted to 10 mol % of $Pd(OAc)_2$, 2.5 equiv of $Cu(OAc)_2$ as the stoichiometric oxidant, and *n*-butyl vinyl ether in acetonitrile at 55 °C for 15 h. Unfortunately, the reaction was plagued with decomposition of starting material and low yield of desired product (12%). Furthermore, oxidation of the newly formed acetal to the lactone with Jones reagent was also inefficient (20% yield, data not shown).

To improve both the Oshima−Utimoto reaction with substrate **7** and the subsequent Jones oxidation, we investigated a series of reaction conditions with *tert*-butyl vinyl ether instead of *n*-butyl vinyl ether (Table 1). This strategy was adopted since we expected that, under acidic conditions of the Jones oxidation, cleavage of the *tert*-butyl group might facilitate oxidation. In an initial experiment, stoichiometric palladium(II) acetate was employed in neat *tert*-butyl vinyl ether at room temperature according to the original conditions set by Oshima and Utimoto, and acetal **8** was generated in 77% yield (entry 1). Using catalytic palladium (10 or 30 mol %) and copper(II) acetate as the reoxidant in acetonitrile at 55 °C, low yields of desired product were obtained (entries 2 and 3). When benzoquinone was used as the oxidant, the yield of product was slightly improved to 39% (entry 3). Addition of acetic acid was found to be inefficient at first (entry 4), but lowering the temperature of reaction and raising the amount of *tert*-butyl vinyl ether provided a cleaner higher yielding reaction (entries 6−10). The most efficient reaction was observed with 4 equiv of *tert*-butyl vinyl ether, 10 mol % of $Pd(OAc)_2$, 3 equiv of benzoquinone, and 1.1 equiv of acetic acid in acetonitrile at room temperature. Under these conditions, a 60% yield of desired acetal **8** was obtained after 16 h with >20:1 stereoinduction at the quaternary center and with a 2.6:1 ratio of anomers. It is noteworthy that performing the reaction in a microwave oven at 300 μW accelerated the reaction, giving acetal **8** in 55% yield after 2 h (entry 10).

Table 1. Survey of the Catalytic Oshima−Utimoto Reaction with Alcohol **7**[a]



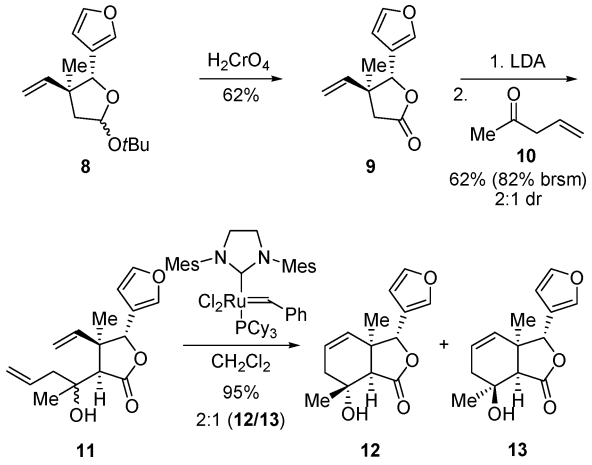
entry	equiv OtBu	oxidant	solvent	temp. (°C)	% **8**
1[b]	8	none	neat	25	77
2	2	$Cu(OAc)_2$	CH_3CN	55	25
3[c]	2	$Cu(OAc)_2$	CH_3CN	55	25
4	2	BQ	CH_3CN	55	39
5[d]	2	BQ/AcOH	CH_3CN	55	16
6	2	BQ/AcOH	CH_3CN	45	42
7	5	BQ/AcOH	CH_3CN	45	48
8	8	BQ/AcOH	neat	45	55
9	4	BQ/AcOH	CH_3CN	25	60
10[e]	4	BQ/AcOH	CH_3CN	25	55

[a] Reaction conditions: 10 mol % of $Pd(OAc)_2$, 2.5 equiv of $Cu(OAc)_2$ or 3 equiv of BQ, and 1.1 equiv of AcOH (if any); [**7**] = 1.0 M, 16 h of reaction time; BQ = benzoquinone. [b] 100 mol % of $Pd(OAc)_2$ was used. [c] 30 mol % of $Pd(OAc)_2$ was used. [d] [**7**] = 0.2 M in CH_3CN. [e] μW = 300 W, 2 h of reaction time.

Deprotection and oxidation of *tert*-butyl acetal **8** with Jones reagent afforded γ-butyrolactone **9** in good yield (Scheme 2). To prepare for construction of the six-membered ring, lactone **9** was deprotonated with LDA and the enolate trapped with 4-penten-2-one (**10**).[13] This aldol reaction furnished alcohol **11** with complete control of the relative configuration

(9) Evans, M. A.; Morken, J. P. Org. *Lett.* **2005**, *7*, 3367.
(10) Evans, M. A.; Morken, J. P. Org. *Lett.* **2005**, *7*, 3371.
(11) Tokoroyama, T.; Fukuyama, Y.; Kubota, T.; Yokotani, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1557.
(12) Okamura, H.; Yamauchi, K.; Miyawaki, K.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **1997**, *38*, 263.

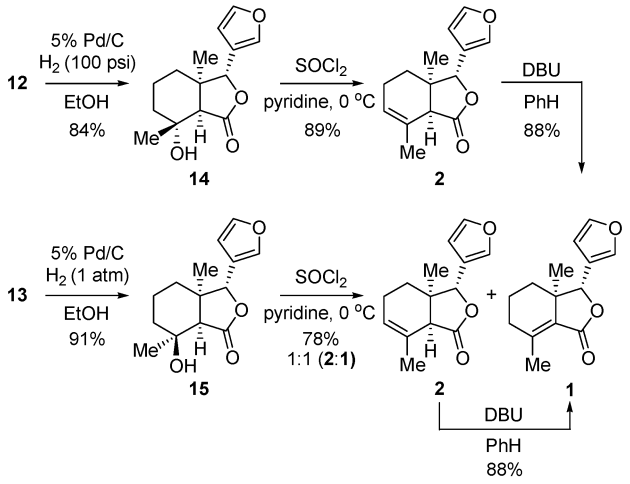
Scheme 2



at the α-carbon but little control of the newly formed hydroxyl stereocenter. While the relative stereochemistry at the newly formed tertiary alcohol was not controlled, both diastereomers could be separated following ring-closing metathesis with Grubbs' 2nd generation catalyst to provide tricycles **12** and **13** in 95% yield. Additionally, both diastereomers ultimately converge upon the natural product (vide infra).

Tricycles **12** and **13** were hydrogenated with 5% palladium on carbon to provide alcohols **14** and **15** in 84 and 91% yield, respectively (Scheme 3). The structure and relative config-

Scheme 3



uration of alcohol **15** was confirmed by single-crystal X-ray crystallography (Figure 2).[14] It is noteworthy that tricycle **12** required 100 psi of hydrogen pressure to perform hydrogenation of the double bond versus 1 atm for compound **13**. Completion of the synthesis was accomplished by dehydration of tertiary alcohol with thionyl chloride in pyridine. Alcohol **14** provided exclusively isofraxinellone **2** in 89% yield upon dehydration, while alcohol **15** afforded

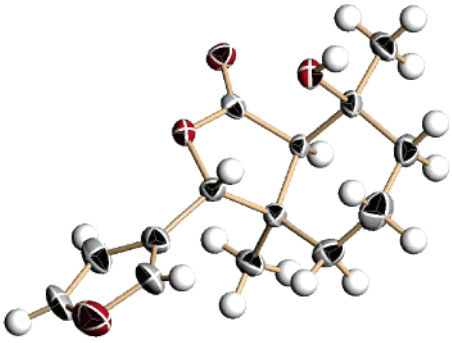
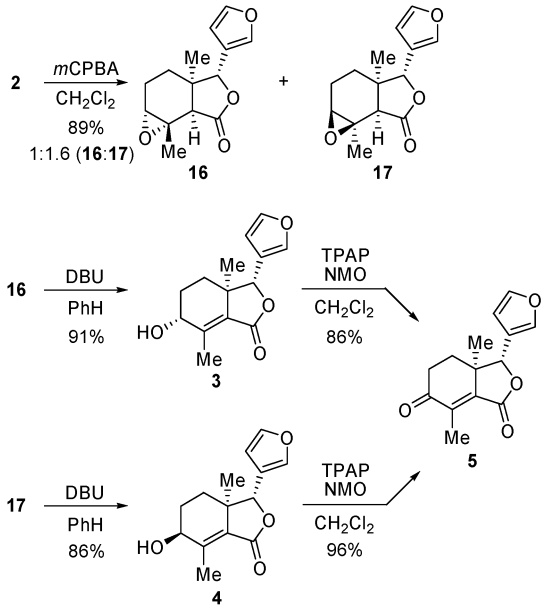


Figure 2. X-ray structure of **15**.

in a 1:1 ratio of fraxinellone **1** and isofraxinellone **2** in a combined yield of 79%. This difference in product distribution can be explained by the fact that the proton α to the lactone carbonyl in compound **15** is antiperiplanar with respect to the departing oxygen atom and can easily participate in dehydration to afford fraxinellone **1**. The methylene protons vicinal to the alcohol can also participate and afford isofraxinellone **2**. In contrast, the α-hydrogen in compound **14** is likely orthogonal to the alcohol, and elimination occurs to provide exclusively isofraxinellone **2** by loss of a methylene proton. Finally, migration of the double bond in isofraxinellone can be performed with DBU in benzene to give fraxinellone **1** in 88% yield.

To access natural products **3**−**5**, isofraxinellone **2** was treated with *m*-CPBA in dichloromethane. In this reaction, the electron-rich trisubstituted alkene reacts with the peracid faster than the furan ring to produce a 1:1.6 mixture of epoxides **16** and **17** in 65% yield (Scheme 4).[15] While the epoxidation reaction proceeded with poor stereocontrol, both

Scheme 4



9α-hydroxyfraxinellone (**3**) and 9β-hydroxyfraxinellone (**4**) could be isolated after DBU-induced epoxide opening. Compounds **16** and **17** yielded **3** in 91% yield and **4** in 86% yield, respectively. Fraxinellonone **5** was synthesized by oxidation with TPAP/NMO of either hydroxyfraxinellone **3** or **4** in 86 and 96% yield, respectively.

In summary, we have elaborated an efficient route for the synthesis of members of the family of fraxinellone using the catalytic diastereoselective Oshima−Utimoto reaction as the key step. We also surveyed a set of conditions for this key reaction in order to improve yield and ease of utilization, notably by performing the reaction with milder conditions at room temperature. Current efforts in our laboratories are now directed at the synthesis of other natural product targets. Developments regarding these efforts will be reported in due time.

Acknowledgment. This work was supported by the NIH (GM 64451). J.P.M. is a fellow of the Alfred P. Sloan foundation. The authors thank Dr. Peter White of the UNC X-ray analysis facility for assistance with crystallography.

Supporting Information Available: Characterization data, spectra, and experimental procedures (31 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0522687

(13) Schmieder-van de Vondervoort, L.; Bouttemy, S.; Padrón, J. M.; Le Bras, J.; Muzart, J.; Alsters, P. L. *Synlett* **2002**, 243.

(14) CCDC 283893 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) Similar selectivity in alkenyl furans has been noted: Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572.