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Total Synthesis of (±)-5,14-bis-*epi*-Spirovibsanin A

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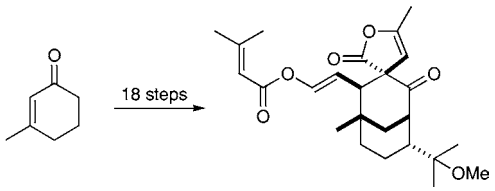
ABSTRACT



The total synthesis of (±)-5,14-bis-*epi*-spirovibsanin A was achieved in 18 steps. Physical data obtained from (±)-5,14-bis-*epi*-spirovibsanin A lends strong support to the proposed connectivity and relative stereochemistry of spirovibsanin A.

Spirovibsanin A[1] (**1**) (Figure 1), isolated by Fukuyama from *Viburnum awabuki*, is an unusual member of the vibsane-type diterpene family.[1−4] A unique feature of this polyoxygenated compact molecule is the bicyclo[3.3.1]nonane spiro-γ-lactone, to which we were attracted due to our familiarity with this system (i.e., **2**).[5]

Later work by Fukuyama[2] divulged the related natural products 15-*O*-methylneovibsanin F (**3**) and 14-*epi*-15-*O*-methylneovibsanin F (**4**),[6] which surprisingly differ only in configuration at position 14. From our perspective this fact casts doubt over the stereochemical assignment at position 14 of **1**, and considering bicyclo[3.3.1]nonanes of type **2** (albeit epimeric at positon 6) were in hand, we embarked on a total synthesis campaign in the racemic series.

Key to this endeavor was intermediate **10**, which was succinctly accessed via a novel keto transposition/carbonylation sequence. Treating *rac*-enone **6**, obtained from **5**,[7−9] with HCl in methanol gave bicyclic ketone **7** as the sole diastereomer. Regioselective conversion of **7** into hydroxyketone **8**, via DMDO oxidation of the silyl enol ether,

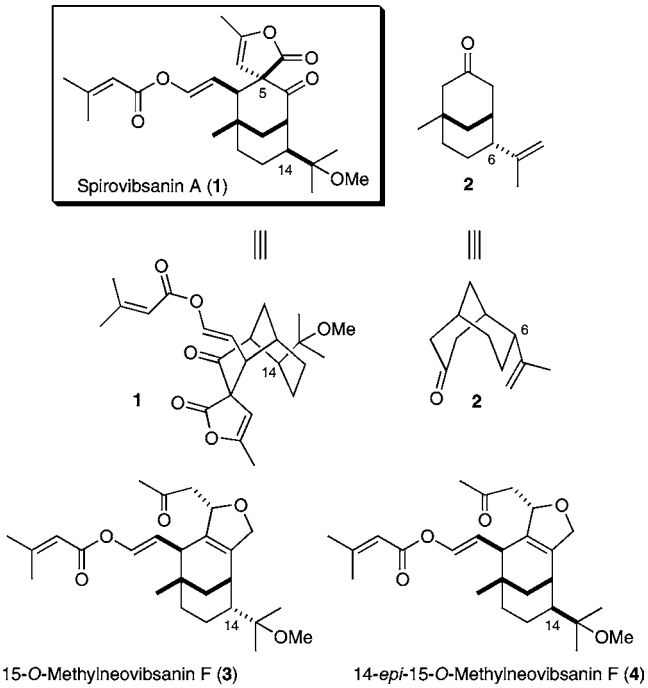


Figure 1. Spirovibsanin A (**1**) and related family members.

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(2) Fukuyama, Y.; Kubo, M.; Minami, H.; Yuasa, H.; Matsuo, A.; Fujii, T.; Morisaki, M.; Harada, K. *Chem. Pharm. Bull.* **2005**, *53*, 72.
(3) Fukuyama, Y.; Minami, H.; Matsuo, A.; Kitamura, K.; Akizuki, M.; Kubo, M.; Kodama, M. *Chem. Pharm. Bull.* **2002**, *50*, 368.
(4) Fukuyama, Y.; Kubo, M.; Fujii, T.; Matsuo, A.; Minoshima, Y.; Minami, H.; Morisaki, M. *Tetrahedron* **2002**, *58*, 10033.
(5) Gallen, M. J.; Goumont, R.; Clark, T.; Terrier, F.; Williams, C. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 2929.
(6) Synthetic studies towards 15-*O*-methylneovibsanin F (**3**) and 14-*epi*-15-*O*-methylneovibsanin F (**4**) will be reported in due course.
(7) Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*, 1327.

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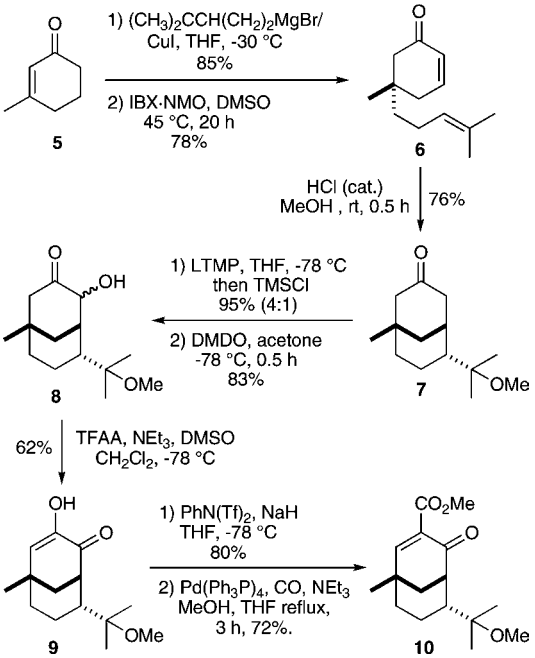
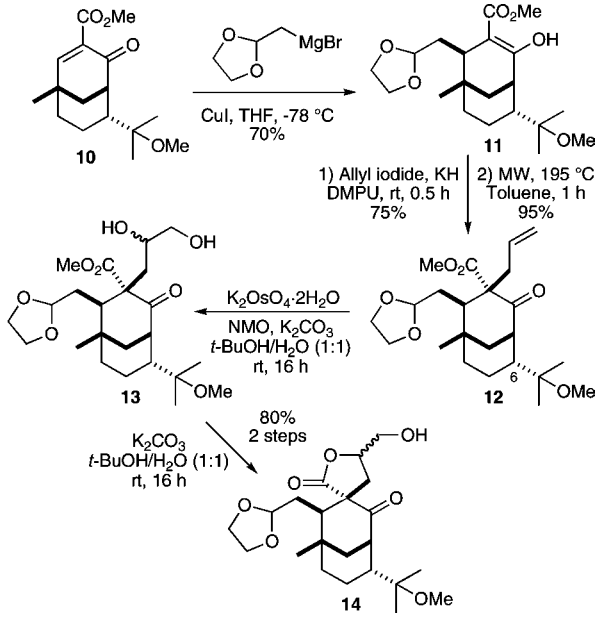
proceeded smoothly. Moffatt−Swern oxidation gave the keto transposed diosphenol **9**. Palladium-catalyzed carbonylation of the corresponding triflate then gave rise to ester **10** in 14% overall yield from **5** (eight steps) (Scheme 1).

Scheme 1. Preparation of Intermediate **10**.



Conjugate addition of commercial (1,3-dioxolan-2-yl-methyl)magnesium bromide to ester **10** occurred stereoselectively affording enol **11** in 70% yield. *O*-Allylation of **11** followed by a Claisen rearrangement afforded only the undesired (*β*) *C*-allylated diastereomer. This unavoidable

Scheme 2. Preparation of Intermediate **14**.



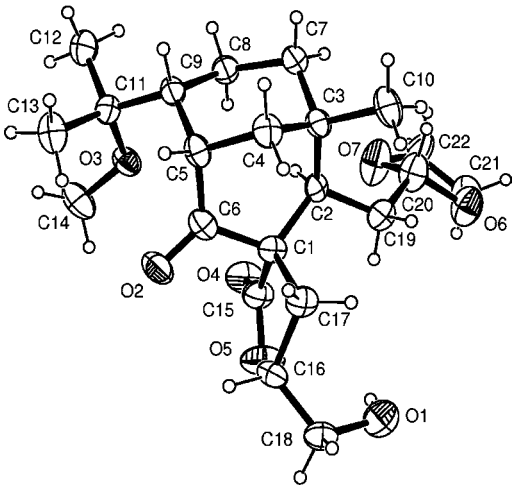
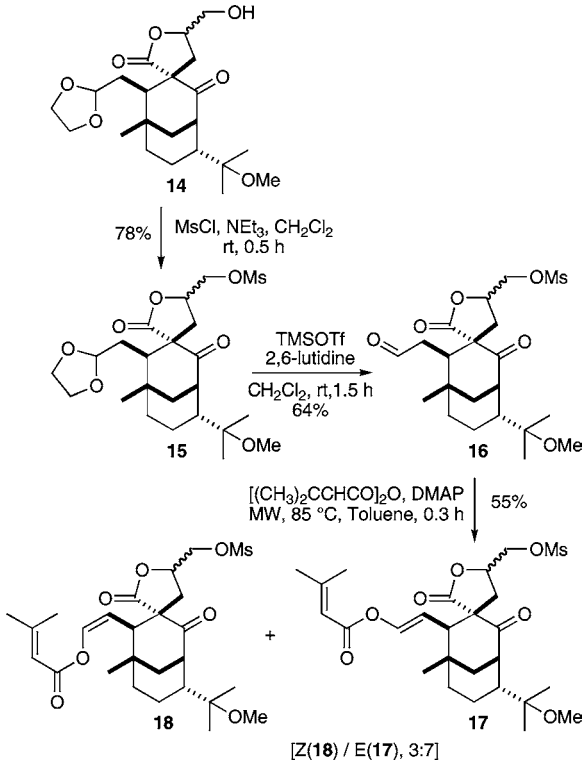


Figure 2. X-ray crystal structure of lactone **14** at the 30% ellipsoid probability.

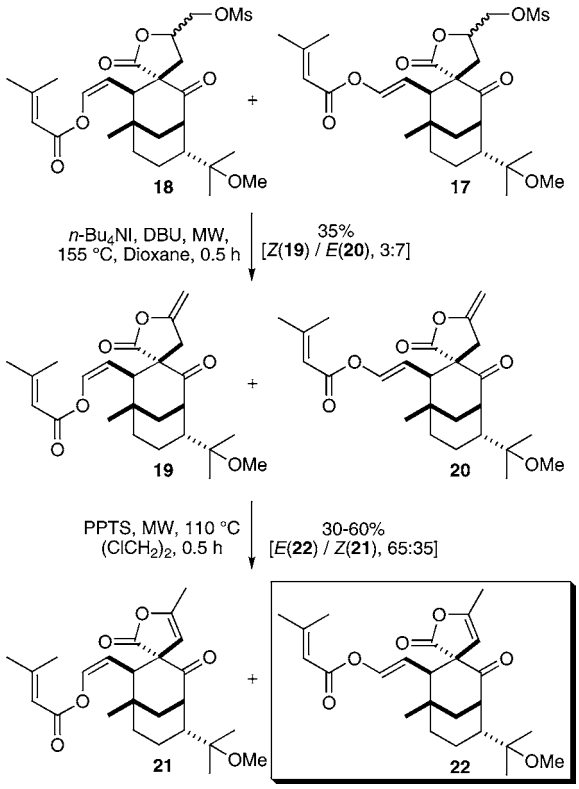
specificity is most likely a result of large steric shielding of the α face by the dimethylmethoxy substituent at position 6. Dihydroxylation of **12** afforded diol **13**, which underwent intramolecular transesterification on treatment with base giving lactone **14** in 80% yield over two steps (Scheme 2). The X-ray crystal structure of **14** elaborated the connectivity of the newly formed spirolactone and confirmed the undesired diastereomer of **12** (see Figure 2).

Lactone **14** was converted into the corresponding mesylate **15**, which was subsequently deprotected with trimethylsilyl

Scheme 3. Preparation of Advanced Intermediate **17**.



Scheme 4. Total Synthesis of (±)-5,14-bis-*epi*-spirovibsanin A **22**



trifluoromethanesulfonate[10] affording aldehyde **16** in 50% yield over two steps. Modifying the procedure of Davies,[11] the crotonate side chain was installed as a mixture of *E*- and *Z*-isomers in a ratio of 7:3 (55%) (Scheme 3).

Based in part on the work of Jäger,[12] a one-pot microwave[13]-mediated Finkelstein/elimination reaction gave the *exo*-cyclic enlactones **19** and **20**. All attempts to directly eliminate the mesylate function (i.e., **17** and **18**) failed. The final step required an *exo*- to *endo*-cyclic double bond isomerization. An acid-catalyzed (i.e., TsOH) process has been reported by Jäger[14] for this type of transformation as have the use of palladium (0) catalysts.[15] To our satisfaction, however, slight modification of the Jäger protocol (i.e., PPTS rather than TsOH) unveiled the desired material as a mixture of isomers [i.e., **21** (*Z*)/**22** (*E*)], separable by HPLC (Scheme 4).

In conclusion, considering the stereochemical incertitude over spirovibsanin A (**1**), a total synthesis campaign arriving at (±)-5,14-bis-*epi*-spirovibsanin A (**22**) was warranted. Comparison of ^{1}H NMR and ^{13}C NMR data of both **1** and **22** gives strong support to Fukuyama's proposed connectivity and relative stereochemistry. This work identifies an efficient route to vibsane type family members containing α stereochemistry at position 14, for example, 15-*O*-methylneovibsanin F (**3**).[6]

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

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