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

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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 vibsanetype diterpene family.<sup>1-4</sup> A unique feature of this polyoxygenated compact molecule is the bicvclo[3.3.1]nonane spiro- $\gamma$ -lactone, to which we were attracted due to our familiarity with this system (i.e., 2).<sup>5</sup>

Later work by Fukuyama<sup>2</sup> divulged the related natural products 15-O-methylneovibsanin F (3) and 14-epi-15-Omethylneovibsanin F (4)<sup>6</sup> 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

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(4) Fukuyama, Y.; Kubo, M.; Fujii, T.; Matsuo, A.; Minoshima, Y.; Minami, H.; Morisaki, M. Tetrahedron 2002, 58, 10033.

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(6) Synthetic studies towards 15-O-methylneovibsanin F (3) and 14-epi-15-O-methylneovibsanin F (4) will be reported in due course.

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diastereomer. Regioselective conversion of 7 into hydroxyketone 8, via DMDO oxidation of the silvl enol ether,



14-epi-15-O-Methylneovibsanin F (4)

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

<sup>(1)</sup> Kubo, M.; Fujii, T.; Hioki, H.; Tanaka, M.; Kawazu, K.; Fukuyama, Y. Tetrahedron Lett. 2001, 42, 1081.

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).



Conjugate addition of commercial (1,3-dioxolan-2-ylmethyl)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 ( $\beta$ ) *C*-allylated diastereomer. This unavoidable





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  $\alpha$  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





trifluoromethanesulfonate<sup>10</sup> affording aldehyde **16** in 50% yield over two steps. Modifying the procedure of Davies,<sup>11</sup> 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,<sup>12</sup> a one-pot microwave<sup>13</sup>mediated Finkelstein/elimination reaction gave the *exo*-cyclic

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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<sup>14</sup> for this type of transformation as have the use of palladium (0) catalysts.<sup>15</sup> 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  $(\pm)$ -5,14-bis-*epi*-spirovibsanin A (22) was warranted. Comparison of <sup>1</sup>H NMR and <sup>13</sup>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  $\alpha$  stereochemistry at position 14, for example, 15-*O*-methylneovibsanin F (3).<sup>6</sup>

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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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