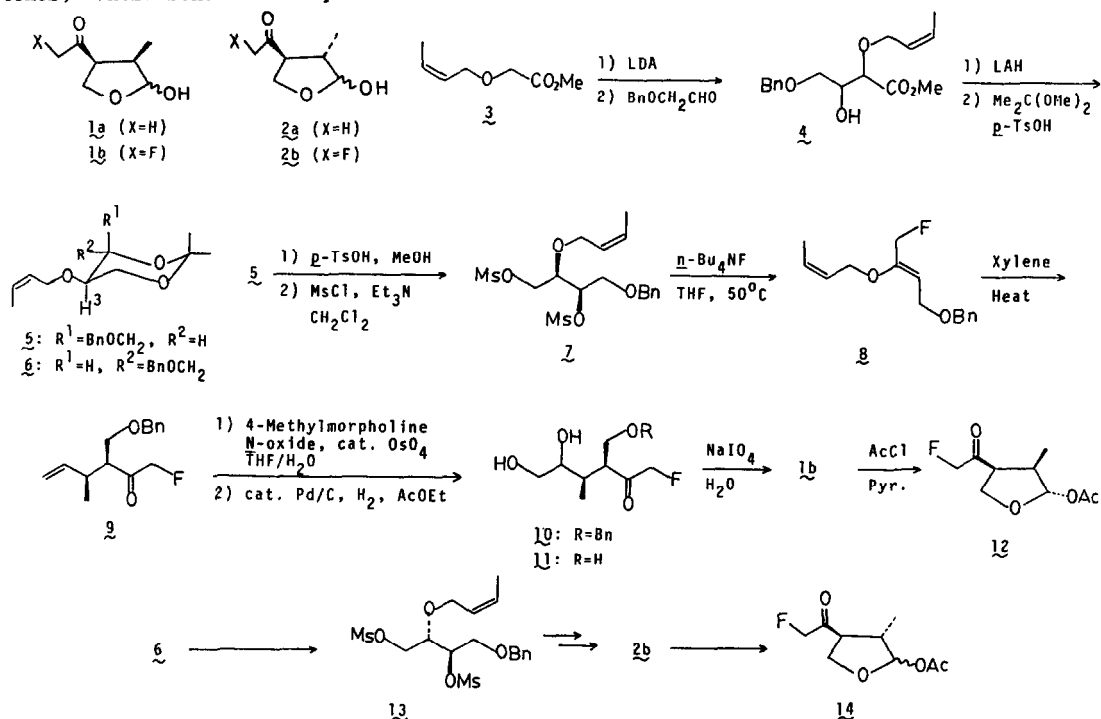


STEREOSPECIFIC SYNTHESIS OF (±)-FLUOROBOTRYODIPLODIN

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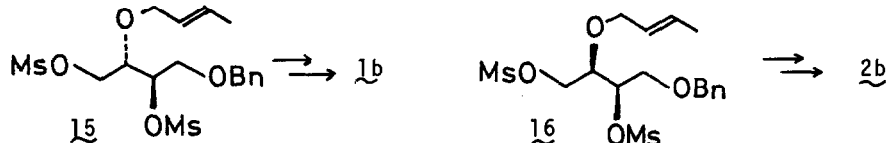
Summary: Stereospecific synthesis of (±)-fluorobotryodiplodin and its epimer is described, in which stereospecific fluoro-olefination and [3,3]-sigmatropic rearrangement were employed in the crucial steps.

Botryodiplodin 1a, isolated from *Botryodiplodia theobromae* Pat. is a mycotoxin with antibiotic and antileukemic properties,<sup>1</sup> and its syntheses were variously accomplished by several groups.<sup>2</sup> We now report the stereospecific synthesis of a fluoro analogue 1b of 1a and its epimer 2b utilizing a selective method for the synthesis of allylated fluoromethyl ketones,<sup>3</sup> whose schema are depicted as follows.



Aldol reaction of the crotyloxyacetate 3 with benzoyloxyacetaldehyde gave the adduct 4 in 95% yield as a mixture of *syn* and *anti*-isomers. LAH reduction followed by acetonide formation afforded a mixture of 5 and 6 in 76% yield in a 39 : 61 isomer ratio.<sup>4</sup> Separation of the isomers was readily attained by flash SiO<sub>2</sub> column chromatography, and 5 and 6 were respectively forwarded to the synthesis of 1b and 2b. The bis-mesylate 7 was prepared in 76% yield by hydrolysis of the acetonide 5 followed by mesylation.

The fluoro-olefination<sup>5</sup> of 7 was stereospecifically conducted to give the enol crotyl ether 8 in 70% yield. The thermal [3,3]-sigmatropic rearrangement also proceeded in a high stereoselectivity giving 9 in 92% as a chromatographically pure stereoisomer. 1, 2-Bis hydroxylation of 9 gave the diol 10 in 90% yield. The triol 11 obtained after debenzoylation of 10 (78%) underwent an oxidative cleavage-cyclization to give fluorobotryodiplodin 1b in 50% yield as a mixture of anomers.<sup>6</sup> Acetylation of 1b afforded the acetate 12 as a single isomer. Fluoroeipibotryodiplodin 2b was also synthesized stereospecifically from 6 via the same sequences and the structures of 1b and 2b were supported on comparison of their NMR spectra with those of 1a and 2a,<sup>2</sup> respectively.



1b and 2b could be similarly prepared from the bis-mesylates 15 and 16, respectively, but with a lower stereoselectivity in the [3,3]-sigmatropic rearrangement.

As shown, the fluoro-olefination and the [3,3]-sigmatropic rearrangement exercised as the key reactions in the present synthesis will offer a useful tool for the stereospecific synthesis of potential bioactive molecules containing a fluoromethyl ketone group. The biomedical aspects of the compounds 1b, 2b and related compounds will be published elsewhere.

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#### References and Notes

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4. The structures of 5 and 6 were determined on the basis of  $J_{R^2H^2}$  and  $J_{R^1H^2}$  values, respectively. (<sup>1</sup>H NMR spectra were taken on a JEOL GX400 spectrometer.) 5:  $J_{R^2H^2} = 2.14$  Hz. 6:  $J_{R^1H^2} = 9.16$  Hz.
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6. Fluorobotryodiplodin 1b(anomeric mixture): NMR (CDCl<sub>3</sub>) δ 0.89 (d, 3H x 19/31, J = 7.3 Hz), 1.08 (d, 3H x 12/31, J = 7.3 Hz), 2.2 (br s, 1H, disappeared on D<sub>2</sub>O exchange), 2.5 ~ 3.0 (m, 1H), 3.5 ~ 4.5 (m, 3H), 4.83 (dd, 2H x 19/31, J = 47.7, 0.7 Hz), 4.89 (d, 2H x 12/31, J = 47.5Hz), 5.20 (s, 1H); F NMR -231 and -228 ppm.

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