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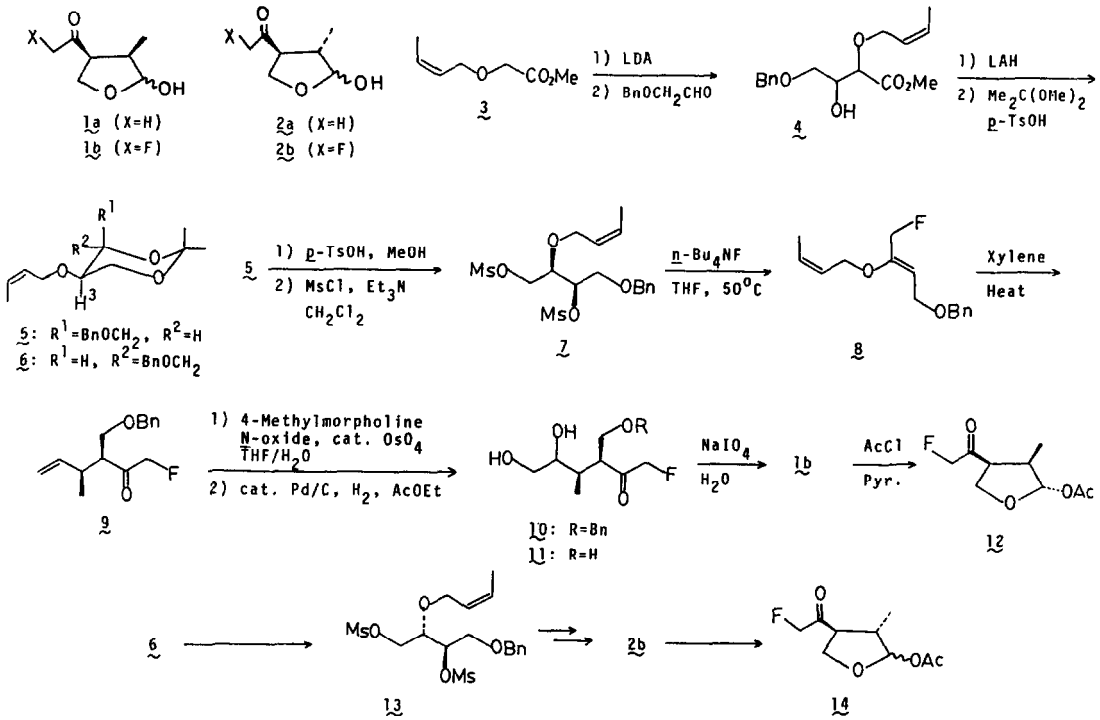
STEREOSPECIFIC SYNTHESIS OF (±)-FLUOROBOTRYODIPLODIN

Yuko Nakahara, Makoto Shimizu, and Hirosuke Yoshioka
The Institute of Physical and Chemical Research (RIKEN)
Wako, Saitama, 351-01 Japan

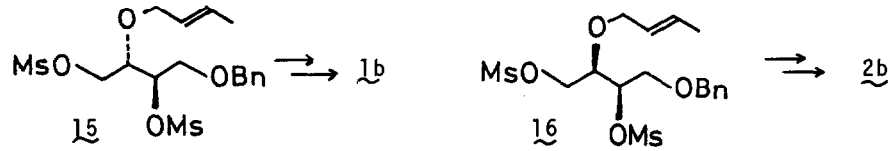
Summary: Stereospecific synthesis of (±)-fluorobotryodiplodin and its epimer is described, in which stereospecific fluoro-olefination and [3,3]-sigmatropic rearrangement were employed in the crucial steps.

Botryodiplodin **1a**, isolated from *Botryodiplodia theobromae Pat.* is a mycotoxin with antibiotic and antileukemic properties,[1] and its syntheses were variously accomplished by several groups.[2] 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,[3] whose schema are depicted as follows.



Aldol reaction of the crotyloxyacetate **3** with benzyloxyacetaldehyde 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.[4] Separation of the isomers was readily attained by flash SiO_2 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[5] of 7 was stereospecifically conducted to give the enol crotyl ether 8 in 70% yield. The thermal [3,3]-sigmatropic rearrangment 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 debenzylation of 10 (78%) underwent an oxidative cleavage-cyclization to give fluorobotryodiplodin 1b in 50% yield as a mixture of anomers.[6] Acetylation of 1b afforded the acetate 12 as a single isomer. Fluoroepibotryodiplodin 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 specta with those of 1a and 2a,[2] 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 rearrangment 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 elesewhere.

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References and Notes

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4. The structures of 5 and 6 were determined on the basis of $J_{R^2H^\beta}$ and $J_{R^1H^\beta}$ values, respectively. (^{1}H NMR spectra were taken on a JEOL GX400 spectrometer.) 5: $J_{R^2H^\beta}$ = 2.14 Hz. 6: $J_{R^1H^\beta}$ = 9.16 Hz.
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6. Fluorobotryodiprodin 1b(anomeric mixture): NMR ($CDCl_3$) 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_2O 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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