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A new carbohydrate-based synthetic approach to trichothecenes. Synthesis of a bicyclic BC core of verrucarol from D-galactose

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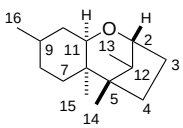
Abstract—An advanced bicyclic BC intermediate towards the total synthesis of verrucarol has been prepared from D-galactose via an intramolecular aldehyde–allylstannane reaction.

The trichothecenes constitute a large family of metabolites isolated from imperfect fungi and plants of the genus *Baccharis*.[1] They display a wide range of biological activity, including antiviral, antibacterial, antifungal, insecticidal and phytotoxic, and several members of this family are listed among the most cytotoxic agents known.[2] Control programs for mycotoxins, implicated in a number of serious threats to human and animal health, and search for biologically active natural products led to isolation of almost two hundred trichothecenes. With a few exceptions, the trichothecene sesquiterpenes share a common trichothecane skeleton (**1**), oxidized and esterified at different positions, with the verrucarol nucleus **2** being the most frequently found.



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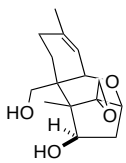
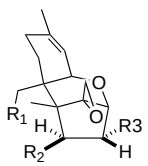
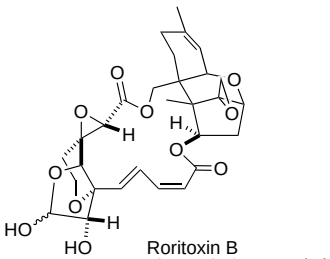


2 Verrucarol



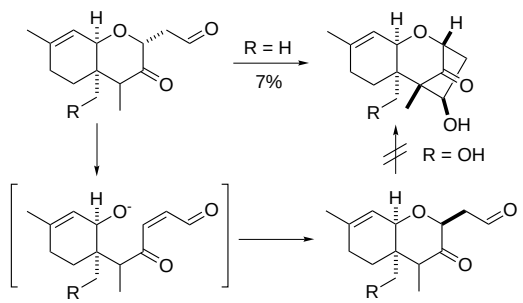
3 $R_1 = R_2 = R_3 = H$
4 $R_1 = R_3 = H$, $R_2 = OH$
5 $R_1 = R_3 = H$, $R_2 = OAc$
6 $R_2 = H$, $R_1 = R_3 = OAc$
7 $R_1 = R_2 = R_3 = OAc$



Roritoxin B
IG_{50} L1210 1.7 ng/ml

As potential anticancer agents, the trichothecenes have been the subject of intense studies on both structure modification[2a,2b,3] and total synthesis.[4] A large amount of synthetic approaches to trichothecenes has been disclosed so far, and several representative naturally occurring trichothecenes, trichodiene,[5] 12,13-epoxytrichotec-9-ene **3**,[6] trichodermol **4**,[7] trichodermin **5**,[8] verrucarol **2**,[9] calonectrin **6**,[10] anguidine **7**,[11] and sporol,[12] were synthesized, most of them in racemic form. In view of the functionality pattern present, the annelation of the C ring by an intramolecular aldol reaction seemed to be a rational way to the tricyclic skeleton of trichothecenes. Indeed, the first total synthesis of a trichothecene, trichodermin **5**, was accomplished, in very low yield, by this 'group 1 aldol' approach,[8a] but all attempts to extend this strategy to verrucarol **2** failed due to the easy isomerization of the required axial aldehyde intermediate to the equatorial one via a reversible Michael reaction under the basic reaction conditions (Scheme 1)[13,14]

As an alternative, an intramolecular aldehyde–allylstannane reaction under neutral conditions, by thermolysis,



Scheme 1.

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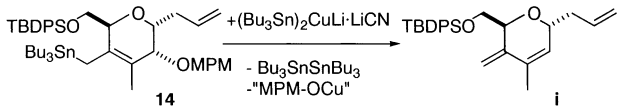
seemed plausible. This paper, inspired by some early results from Fraser–Reid's laboratory,[14] describes the first truly successful cyclization along the C4–C5 bond and the synthesis of an advanced bicyclic BC core of verrucarol from D-galactose.

C-Allyl galactopyranoside **8**, obtained as a mixture of α/β isomers (9:1) by the published procedure,[15] was deacetylated and then selectively silylated on the primary hydroxyl group to give **9**. Treatment of the latter with trimethyl *ortho*acetate set a temporary *ortho*ester protection onto the *cis* diol and then, after the alkylation of a free hydroxyl group with *para*-methoxybenzyl (MPM) chloride and hydrolysis during the usual aqueous acid workup, delivered the acetyl group to the axial hydroxyl[16] to give the selectively protected *C*-allyl galactopyranoside **10**, easily separable from the minor stereo- and regio-isomers by chromatography. Swern oxidation of **10** followed by the treatment with MeMgCl afforded the diol **11** with the required axial hydroxyl group at C5.† Oxidation of the secondary hydroxyl group in **11** with the Dess–Martin periodinane and protection of the tertiary one as the methoxymethyl (MOM) ether gave the ketone **12**. No other reagent allowed oxidation of **11** in good yield; however, the transformation of the diol **11** into the ketone **12** by a four-step sequence (1. Ac_2O/Py; 2. MOMCl, *i*-Pr_2NEt/CH_2Cl_2; 3. MeONa/MeOH; 4. Swern oxidation) was also efficient (overall yield 70%).

The Wittig methylenation of **12** to **13** was sluggish despite the fast consumption of the starting ketone. Under numerous conditions tried the yield of the alkene **13** did not exceed 60%, while some highly polar adduct persisted—presumably one of two Wittig betains, either restricted in attaining the reacting conformation or intercepted by the proximate silyl group. Under forcing conditions, the β-elimination of the TBDPS-OH became also a problem. In any event, the low efficiency of the reaction could definitely be attributed to basicity and size of the Wittig reagent. Indeed, the reaction of Me_3SiCH_2Li with the ketone **12** in the presence of $CeCl_3$ gave a mixture of two alcohols (45:55) which, upon treatment with KHMDS, afforded the desirable alkene **13** in much better overall yield. Careful preparation of anhydrous $CeCl_3$[17] is essential for success of the first step.

With the allyl ether **13** in hand, the elaboration of the allylstannane **14** was then addressed. The reaction of **13** with a higher order cuprate, $(Bu_3Sn)_2CuLi{\cdot}LiCN$, in THF was found to be extremely temperature-dependent rendering the usual process control methods (e.g. TLC) inefficient. Very slow at −78°C, this reaction went to completion within minutes at −20°C to give the allylstannane **14**, which underwent a consecutive ligand exchange[18] with the tin cuprate followed by an elimination to give the triene **i**‡ (Scheme 2). It was found that the allylic substitution reaction (**13→14**) is faster in diethyl ether, and upon dilution of the tin cuprate reagent, conveniently prepared from $Bu_2CuLi{\cdot}LiCN$ and Bu_3SnH in THT,[19] with ether the gratifying yield of the required allylstannane **14** (87% based upon recovered starting material (14%)) was obtained after 18 h at −78°C and the quenching of the reaction at the same temperature.



Scheme 2.

With the strategic allylstannane functionality in place, the delicate elaboration of a cyclization precursor, the acid- and base-sensitive aldehyde **16**,§ was next addressed. In accordance with expectations, steric constraints and electronic[20] factors prevailed over a conventional order of olefin reactivity,[21] and the ordinary OsO_4-catalyzed dihydroxylation of **14** in aqueous *t*-BuOH proceeded at the terminal double bond exclusively. Unfortunately, the reaction was very sluggish, and over-catalytic amounts of OsO_4 (0.2 equiv.) were required for complete conversion of the starting **14** to the diol **15** in a reasonable time (2 days). Because of the fragile functionality present, no attempts were made to liberate the diol from the residual osmate ester during workup at the end of reaction. All the above led to the significant loss of the valuable product during the chromatographic purification of the diol **15**¶ that was absolutely necessary before its periodate cleavage to the aldehyde **16**. Eventually, the reaction in the presence of quinuclidine[21b] (0.2 equiv.) allowed to circumvent this drawback by keeping the quantity of OsO_4 as low as 0.05 equiv. at 24 h reaction time with otherwise good yield of 86%. The pure diol **15** was then cleaved by $NaIO_4$ in aqueous MeOH, and the crude aldehyde **16** thus obtained was refluxed in xylene for 1 h to give the bicyclic product **17** in 72% overall yield from diol **15**.

In accordance with prediction from a cyclic transition state model,[22] the configuration of the newly created carbinol center in **17** proved to be unnatural and required inversion. The problem of inversion of configuration at C4 on the full-featured ABC tricyclic trichothecene intermediates has already been addressed in an early synthesis of verrucarol.

† The trichothecene numbering is used throughout the paper. For stereoelectronic reasons, the axial orientation of this hydroxyl is required for a later reaction **13→14**. The structure of **11** was solved by NMR, including NOE observed between the methyl group at C5 and the protons at C6 and C12.

‡ Hexabutylditin was also found in this reaction.

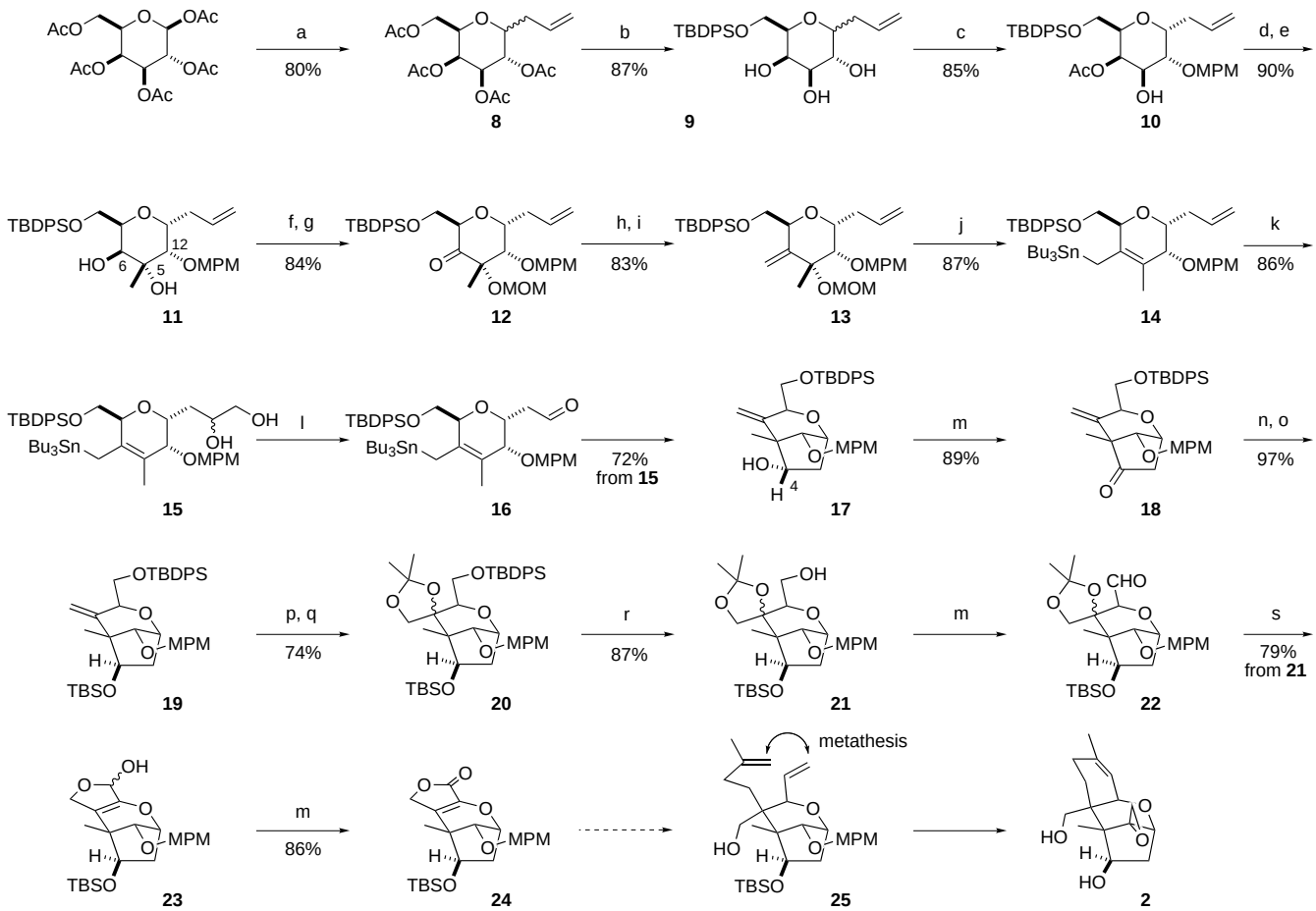
§ No acid treatments should be applied to any allylstannane intermediates of the scheme to avoid the elimination of tin and MPMO moieties (**→i**); besides, the aldehyde **16** undergo the fast isomerization to an equatorial dead-end isomer under the mild basic conditions, as mentioned above.

¶ Theoretically, up to 2 mole/mole of osmium used.

As a consequence of the quaternary center C6 present, the complex hydrides attack trichothec-9-en-4-ones from the β-face exclusively,[23] and the only solution to the problem was found, in rather low yield, by a nucleophilic substitution.[9c,d] On the contrary, the flattened B ring of the bicyclic system obtained permitted a beneficial α-side reagent approach. Indeed, the reduction of the 4-keto derivative **18** with $LiBHEt_3$ afforded the required isomeric alcohol as the sole product and in high overall yield. The characteristic NOE between the protons of the TBS and MPM groups in **19** proved its natural configuration at C4.

The enantiomerically pure bicyclic product **19**, obtained in 15 steps and overall yield of 17%, provides a plethora of possibilities for total synthesis of verrucarol **2** and related trichothecenes. A very attractive one consists of building the C ring of verrucarol by a ring-closing olefin metathesis reaction (→**25**→**2**). To explore this possibility, the alkene **19** was subjected to OsO_4-catalyzed dihydroxylation to give a mixture of diols (ca. 1:1) which were protected by isopropylidene group (**20**). Usually more robust, the TBDPS protection was selectively removed in the presence of TBS group by treatment with NaOH in aqueous DMPU,[24] and a separable mixture of alcohols **21** was oxidized to the aldehyde **22**. The latter smoothly eliminated acetone upon heating with $Ca(OH)_2$ in aqueous MeOH to give the lactol **23** with no open-chain γ-hydroxyaldehyde present, as evidenced by NMR spectra. Finally, oxidation of **23** afforded the α,β-unsaturated lactone **24**.[25] (Scheme 3).

The pursuit of the total synthesis of verrucarol **2** by the conjugate addition/ring-closing metathesis sequence from the lactone **24** and its open-chain derivatives, or by the cycloaddition onto **19**, **23** and **24** will be reported in due course.



Scheme 3. *Reagents and conditions*: (a) $CH_2{=}CHCH_2SiMe_3$ (3 equiv.), $BF_3{\cdot}Et_2O$ (5 equiv.)/CH_3CN, 4°C, 48 h (Ref. 15); (b) MeONa (cat)/MeOH, then TBDPSCl (1.2 equiv.), ImH (2.4 equiv.)/DMF; (c) $CH_3C(OMe)_3$ (2 equiv.), CSA (cat), rt; then Et_3N quench and concentration; then MPMCl (1.2 equiv.), NaH (2 equiv.), Bu_4NI (0.05 equiv.)/THF, rt; aqueous acid workup; (d) Swern oxidation; (e) MeMgCl (4 equiv.)/THF; −78°C to rt; (f) Dess–Martin periodinane (1.1 equiv.)/CH_2Cl_2, rt; (g) MOMCl (3 equiv.), *i*-Pr_2NEt (4 equiv.)/CH_2Cl_2, Δ; (h) **12**+$CeCl_3$ (2 equiv.)/THF, rt, 0.5 h; then add Me_3SiCH_2Li/pentane (2 equiv.), −10°C to rt; (i) $(Me_3Si)_2NK$ (1.1 equiv.)/THF, rt; (j) $(Bu_3Sn)_2CuLi{\cdot}LiCN$ (1.6 equiv.)/THF–Et_2O (1:4), −78°C, 18 h; (k) NMO (1.5 equiv.), OsO_4 (0.05 equiv.), quinuclidine (0.2 equiv.)/*t*-BuOH–H_2O (3:1), rt, 24 h; (l) $NaIO_4$/MeOH–H_2O (95:5), rt; then xylene, 140°C, 1 h; (m) NMO (1.5 equiv.), TPAP (0.05 equiv.), MS 4 Å/CH_3CN; (n) $LiBHEt_3$ (1.2 equiv.)/THF, −78°C; (o) TBSCl (1.2 equiv.), ImH (2.4 equiv.)/DMF, rt; (p) NMO (1.5 equiv.), OsO_4 (0.05 equiv.)/*t*-BuOH–H_2O (3:1), rt; (q) DMP, CSA (cat.)/CH_2Cl_2, rt; (r) 3 M NaOH–DMPU (1:9), 40°C, 3 h; (s) $Ca(OH)_2$/MeOH–H_2O, Δ.

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25. All new compounds were characterized by analytical and spectroscopic (including 2D NMR) methods. **24** had $[\alpha]_D$ +11.0 (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.27 and 6.86 (4H, ArH), 4.72 (1H, dd, $J=5.8$, 0.8 Hz, H-4), 4.72 and 4.65 (2H, 2d, $J=16.6$ Hz, 2×H-15), 4.61 and 4.51 (2H, 2d, $J=11.8$ Hz, OCH_2Ar), 4.10 (1H, dd, $J=6.9$, 2.5, H-2), 3.88 (1H, br.s, H-12), 3.81 (3H, s, $ArOCH_3$), 2.55 (1H, ddd, $J=15.7$, 6.9, 0.8 Hz, H-3 *exo*), 2.27 (1H, ddd, $J=15.8$, 5.8, 2.5 Hz, H-3 *endo*), 1.20 (3H, s, CH_3-14), 0.88 (9H, s, $SiC(CH_3)_3$), 0.047 and 0.041 (6H, 2d, $Si(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 166.3, 159.1, 138.7, 137.1, 130.3, 128.5, 113.8, 83.8, 80.6, 78.2, 71.8, 65.7, 55.1, 48.2, 45.2, 25.6, 18.0, 10.6, −4.6, −5.0.