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Highly Convergent Enantioselective Route to Trichothecenes

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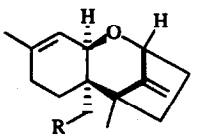
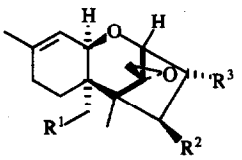
Key Words: Trichothecenes, enantioselective synthesis, ester enolate rearrangement.

Abstract: Total synthesis of (+)-15-hydroxytrichothec-9,12-diene (**4**) has been accomplished in 16 steps and in 5.5% overall yield from the optically active β-hydroxyester **9**. Creation of the vicinal quaternary centers resulted from a highly enantio- and diastereoselective Ireland-Claisen ester-enolate rearrangement.

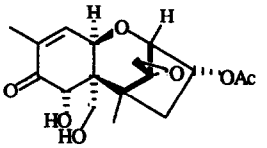
Trichothecenes are mevalonate-derived sesquiterpenes having a wide range of biological activities, most of which are adverse in nature.[1,2] However it has recently been shown that simple, non-toxic trichothecenes like **1** and **2a** serve as efficient inhibitors to the production of highly oxygenated toxic metabolites, *e.g.*, 3-acetyldeoxynivalenol (**3**), by *Fusarium culmorum*.[3] Continuing interest in the biological activity of the trichothecenes makes development of efficient routes to their synthesis in enantiomerically pure form of importance. Indeed, only two chemical syntheses of optically active trichothecenes have been reported to date,[4] although several of these compounds have been synthesized in racemic form.[5] We here report synthesis of (+)-15-hydroxytrichothec-9,12-diene (**4**, Scheme 4) *via* a convergent route that provides an intermediate suitably functionalized for elaboration to more highly oxygenated trichothecenes such as calonectrin (**2b**) and anguidine (**2c**).



1a R = F
1b R = H



2a R^1 = F, R^2 = R^3 = H
2b R^1 = R^3 = OAc, R^2 = H
2c R^1 = R^2 = OAc, R^3 = OH



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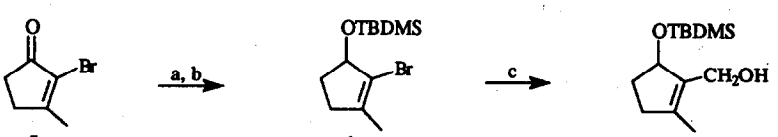
The linchpin of the synthesis is ester **11**[6] (Scheme 2). The requisite alcohol **7** was obtained in racemic form from bromoenone **5**[7a] following the protocol of Ziegler, et. al. (Scheme 1).[7b] The carboxylic acid **10** required to produce **11** was made as outlined in Scheme 2. Fermenting baker's yeast reduction[8] of racemic β-ketoester **8**[9] gave β-hydroxy ester **9** (45% ee). This compound, the source of chirality in the synthesis, was conveniently transformed to β-methoxycarboxylic acid **10** in two steps. Esterification of acid **10** with alcohol **7**

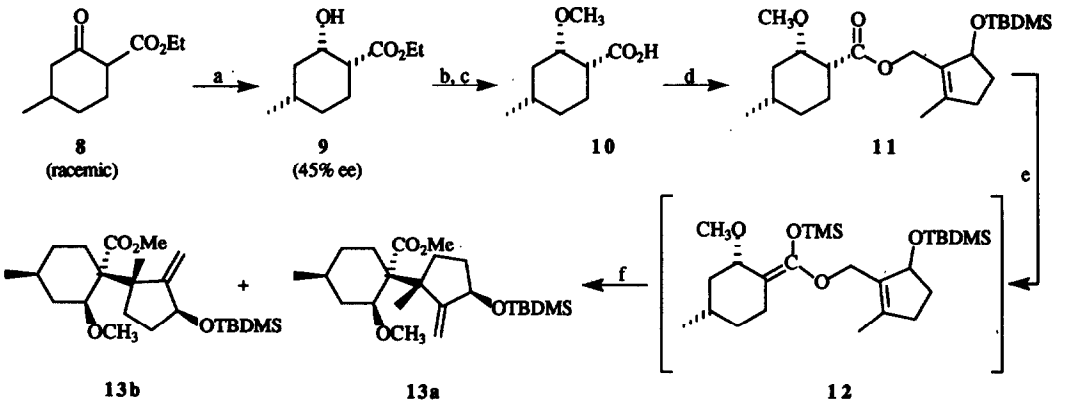
Scheme 1



5 **6** **7**

Reagents: a. DIBAL-H, CH_2Cl_2, 0 °C, 98%; b. TBDMSCl, TEA, DMAP, CH_2Cl_2, 95%;
c. t-BuLi, THF, -78 °C, then gaseous H_2CO, 98%.

Scheme 2



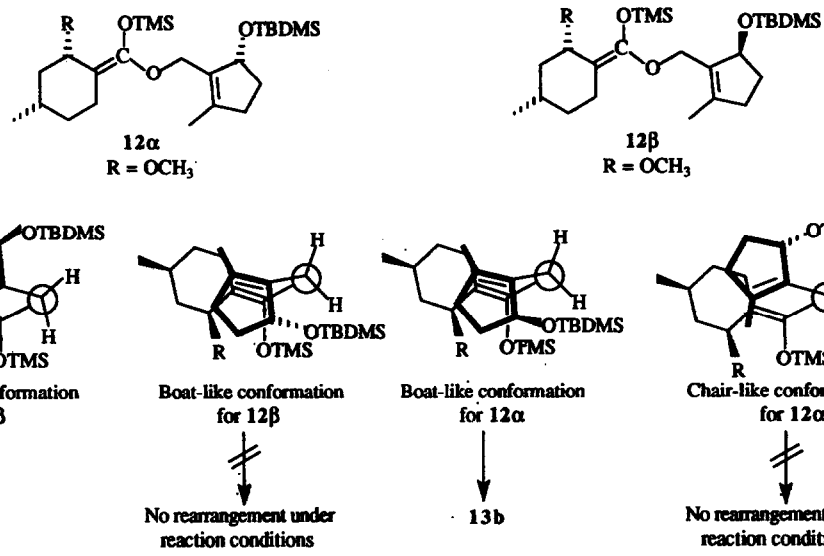
Reagents: a. Yeast, H_2O, sugar, 40%; b. KH, CH_3I, THF, -20 °C, 95%; c. 4*N* HCl, reflux, 6h, 85%; d. MsCl, TEA, CH_2Cl_2, then 7, DMAP, 77%; e. LDA, TMSCl, TEA, THF, -110 °C; f. (*i*) reflux, (*ii*) dil. HCl (*iii*) CH_2N_2/ether; 45% (combined yield).

gave the ester **11** as an equimolar mixture of two diastereomers, inseparable by chromatographic methods.

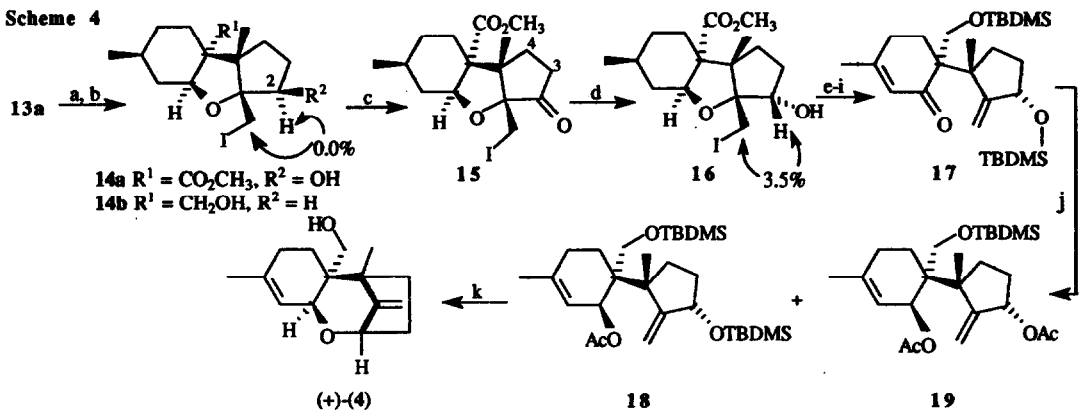
To effect the key Claisen rearrangement through the Ireland modification,[10] **11** was converted to silylketene acetal **12** through the lithium enolate, itself generated at -110 °C and trapped *in situ* with trimethylsilyl chloride (Scheme 2).[10b] The reaction mixture was warmed to room temperature and then heated at reflux to afford, after esterification, a mixture of only *two* diastereomeric esters in a ratio of 92:8.[11] In principle, [3,3]-sigmatropic rearrangement of **11** could afford *four* diastereomers, but the isomerization was anticipated[12] to occur exclusively from the *re* face of the silyl ketene acetal functionality; this indeed appears to be the case.[13] Analysis of molecular models, as summarized in Scheme 3, led us to conclude that the major isomer was **13a**, the product of a chair-like rearrangement of the diastereomeric ketene acetal **12**α, whereas the minor isomer, assigned as **13b**, resulted from a boat-like rearrangement of the other diastereomer, **12**β . Given the known proclivity of the Claisen rearrangement in these systems to favor reaction through the chair-like conformation,[14] it is not surprising that the isomerization of a presumably equimolar mixture of **12**α and **12**β would effect a kinetic stereoselection to afford mainly **13a**. If the structural assignment is correct, the isomer **13a** would then have the relative stereochemical disposition about the vicinal quaternary centers corresponding to that of the trichothecenes. This was ultimately confirmed by the successful conversion of **13a** to (+)-(**4**).

Ester **13a** was converted to the tricyclic ester **14a** (Scheme 4), which served as an excellent intermediate to invert the stereochemistry of the hydroxy group at C-2 (trichothecene numbering system). The relative stereochemistry of the hydroxy group in **14a** and **16** was easily proven by a nuclear Overhauser difference experiment, the results of which are shown in Scheme 4. The α-hydroxy compound **16** thus obtained was transformed efficiently to the cyclohexenone derivative **17**. Reduction of this enone with DIBAL-H and acetylation of the crude product gave the desired acetate **18**. Bis-acetate **19**, a by-product of this sequence of reactions, likely arises from desilylation under the conditions employed for acetylation. To complete the synthesis, the B-ring of the trichothecene was formed in a biomimetic fashion by treating the acetate **18** with HF·pyridine in CH_3CN, affording (+)-(**4**).[15] Critical to the assignment of the trichothecene skeleton to **4** were the chemical shifts and coupling constants of the protons at C-2 (4.27 ppm, J = 4.9 Hz) and C-11 (3.68 ppm, J = 5.4 Hz), as well as the ^{13}C chemical shifts; all these data correlated precisely with those expected for a trichothecene.[16]

Scheme 3



Scheme 4



Reagents: a. TBAF, THF, 82%; b. I_2, $NaHCO_3$, CH_3CN, 0 °C, 87%; c. Swern ox., 98%; d. $NaBH_4$, CH_3OH, 99%; e. TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 99%; f. DIBAL-H, toluene, 83%; g. 2,6-lutidine, TBDMSOTf, CH_2Cl_2, 99%; h.*(i)* Zn, pyridine, 95% EtOH, THF, reflux; *(ii)* Swern oxidation, 70% (two steps); i. *(i)* LDA, THF, -78 °C, PhSeBr; *(ii)* H_2O_2, pyridine, CH_2Cl_2, 85%; j. *(i)* DIBAL-H, toluene, 0 °C; *(ii)* Ac_2O, pyridine, anhy. K_2CO_3, 35% of **18** and 31% of **19** (two steps); k. **18**, HF.pyridine (excess), 0 °C to rt, CH_3CN, 85%.

The trichothecene thus formed is optically active and, based on the ee of **9** and the demonstrated complete transfer of chirality during the [3,3]-sigmatropic rearrangement,[12] is of 45% ee. Its absolute configuration, of course, is that of the unnatural antipodes.[17] This synthetic sequence provides a general route to the trichothecenes; specifically, hydroxy functions present at C-3 and C-4 in calonectrin (**2b**) and anguidine (**2c**) can be readily incorporated at the stage of the ketone **15**.[18]

References and Footnotes

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11. An inseparable mixture of esters, comprised of **11**, its C-2 epimer, and the β-elimination product from the enolate of **11**, was also isolated in 20-25% yield; the mass balance from the sequence involving formation and rearrangement reaction of **12** is some 65-70%.
12. The [3,3]-sigmatropic rearrangement of a silylketene acetal closely related to **12**, the only difference being replacement of OTBDMS with H, followed by steps (b) and (f) of Scheme 4, afforded **14b** as the major product; its stereochemistry was proven by x-ray crystallographic analysis: Gilbert, J. C.; Selliah, R. D. *in preparation.*
13. A rationale for the observed facial selectivity will be reported in a full paper.
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15. Data for (+)-(**4**): $[\alpha]_D^{23}$ 33.1° (c = 0.5, $CHCl_3$); IR (CCl_4) 3620 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.39 (m, 1H), 4.94 (s, 1H), 4.59 (s, 1H), 4.27 (d, *J* = 4.9 Hz, 1H), 3.70 (dd, *J* = 11.8, 4.3 Hz, 1H), 3.68 (d, *J* = 5.4 Hz, 1H), 3.46 (dd, *J* = 11.1, 4.0 Hz, 1H), 2.27 (ddd, *J* = 13.7, 9.3, 4.7 Hz, 1H), 2.05 (m, 2H), 1.88-1.72 (m, 4H), 1.67 (s, 3H), 1.60 (m, 1H), 1.39 (ddd, *J* = 13.0, 12.9, 5.1 Hz, 1H), 1.15 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 155.30, 140.51, 119.70, 102.95, 79.83, 66.83, 63.11, 47.74, 44.12, 32.66, 28.67, 27.32, 23.35, 19.90, 17.80; HRMS (CI) *m/z* calcd for $C_{15}H_{23}O_2$ (M+H), 235.1698, found 235.1707.
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17. The natural antipodes of trichothecenes can be obtained by starting with β-hydroxyester **9**, produced by the chemical reduction of β-ketoester **8** that has been prepared from (*R*)-3-methylcyclohexanone.

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