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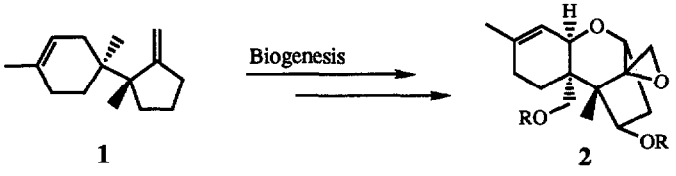
A Diastereoselective Synthesis of (±) Trichodiene[1]

John C. Gilbert* and Terence A. Kelly

Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712-1167 USA

Abstract: A route to the total synthesis of the title compound is described. The key step involves the [3,3] sigmatropic of the silyl keteneacetal derived from an allylic β-ketoester. The potential application of this protocol to the construction of the higher trichothecenes is also discussed.

A recent thrust of our research program has been the development of techniques to form the bond between adjacent quaternary carbon atoms. The outcome of this effort was a method that exploits the stereoselectivity of the [3,3] sigmatropic rearrangement of allylic β-ketoester derivatives and forms the desired connection in good yield and with excellent stereocontrol.[2] We now report the application of this method to the total synthesis of trichodiene (**1**),[3] the biogenetic precursor to the trichothecenes (*e.g.* **2**, equation 1).[4]

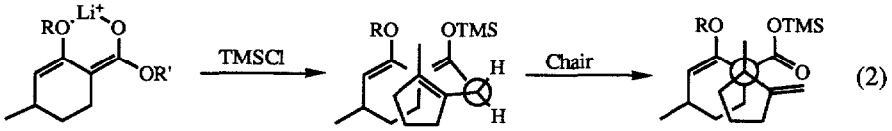


1 **2** (1)

The novel molecular architecture and interesting biogenetic role of trichodiene have made it a popular target for synthetic organic chemists. In fact, a number of syntheses of this molecule have already been reported.[5] However, only one of these efforts, an organometallic approach, converges through a diastereoselective (5:1) formation of the central carbon-carbon bond.[5j] A second convergent route, involving [3,3] sigmatropic rearrangements, has also been reported,[5f-i] but, thus far, all of the applications of this technique have required the separation of the desired carbon skeleton from its diastereomer. The current work demonstrates that a high degree of diastereoselectivity (92:8) can be instilled upon this latter process, an outcome which greatly increases its potential synthetic utility.

The origin of the stereoselectivity rests in two stages as illustrated in equation 2. The first step is the formation of a single silyl keteneacetal and the second step is the chair-boat selectivity of the isomerization. The specific implications of

each of these processes have been discussed in detail elsewhere.[2] A retrosynthetic analysis of the problem indicated that ester-enolate **3** was the desired target since trapping of this anion followed by a chair-like rearrangement (**4**) would produce a precursor to the trichodienyl skeleton (**5**).



(2)

3 **4** **5**

Initial attempts to trap anion **3** with trimethylsilyl chloride (TMSCl) were thwarted when R = trimethylsilyl (TMS), *t*-butyldimethylsilyl (TBS) or methoxymethyl (MOM). In the first case, the silyl groups were apparently cleaved under the conditions used to generate the anion. The TBS and the MOM protecting groups produced products derived from C-silylation, presumably due to steric interactions about the anionic oxygen center; the MOM group also has the potential to form a tightly chelated species with the cation. To avoid these problems, it was decided that a simple alkyl group would be most suited for the task and a method for the synthesis of R = Me was pursued. The results are shown in Scheme 1.

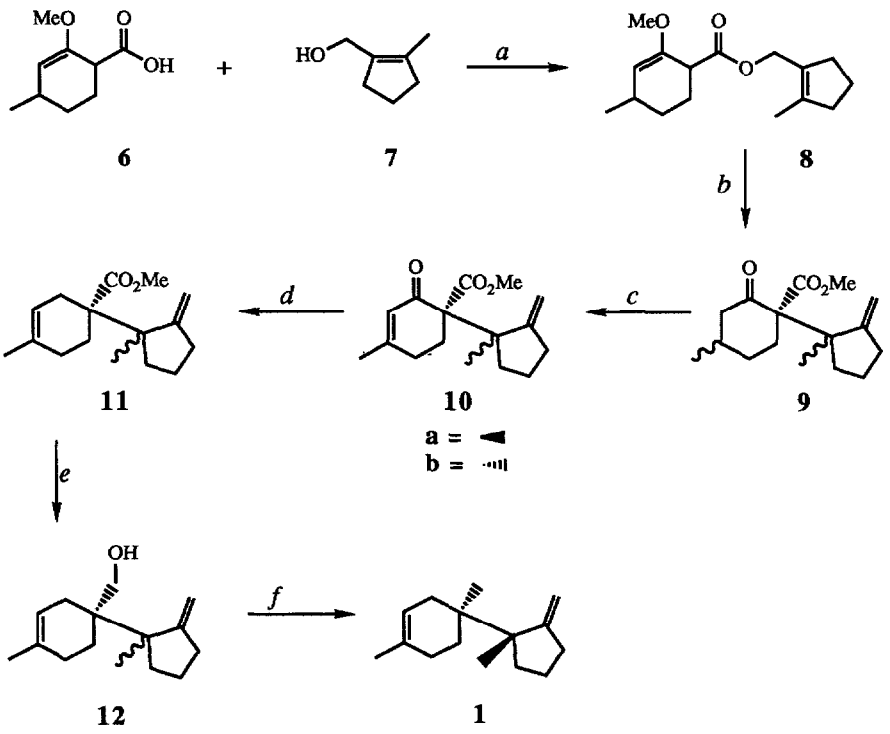
The carboxylic acid **6**[6] was esterified with alcohol **7**[5f,h,i] in 88% yield.[7] Treatment of this compound with lithium diisopropylamide (LDA) and TMSCl resulted in C-silylated material. This problem could be successfully avoided by using potassium hexamethyldisilazide (KHMDS) as the base[8] and by performing the silylation at -100 °C with *t*-butyldimethylsilyl chloride (*t*-BDMSCl) in hexamethylphosphoramide (HMPA) containing 18-crown-6.[9] Subsequent warming of the reaction mixture to 65 °C, and work-up with HF followed by CH_2N_2, generated compound **9** in 54% yield after flash chromatography.

At this point the extent of diastereoselectivity in the process was unclear. The ^{1}H-NMR spectrum indicated a mixture of diastereomers but it was impossible to determine their ratio or even how many there were. This was due to the fact that the rearrangement could produce up to four diastereomers of compound **9**, only two of which possessed the desired stereochemistry about the central carbon-carbon bond.

The first step in simplifying the problem was to destroy the superfluous chiral center by incorporating unsaturation into the cyclohexyl ring. This was accomplished by generating the lithium enolate of compound **9** and treating it with phenyl selenium bromide (PhSeBr). Careful oxidation of the resulting selenide to the selenoxide with *m*-chloroperbenzoic acid (*m*CPBA) at -78 °C[10] generated the α,β unsaturated esters **10** as a 92:8 mixture of diastereomers in 87% yield.

That the relative stereochemistry of the major isomer corresponded to **10a** was established by its conversion to trichodiene. First, the ketone was reduced to a methylene group by forming the tosylhydrazone in the presence of

Scheme 1



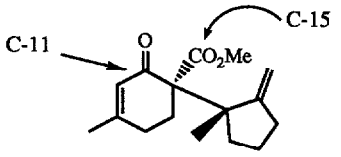
a. DCC, DMAP, Et_2O; *b*. (1)KHMDS, THF, -78 °C; (2) *t*-BDMSCl, HMPA, 18-C-6, -100 °C; (3) 65 °C; (4) HF, CH_3CN, 0 °C; (5) CH_2N_2; *c*. (1) LDA, THF, -78 °C; (2) PhSeBr; (3) *m*CPBA -78 °C; *d*. $TsNHNH_2$, $NaCNBH_3$, sulfolane, 120 °C; *e*. $LiAlH_4$, Et_2O; *f*. see text.

sodium cyanoborohydride ($NaCNBH_3$). The *in situ* reduction produced the esters **11** in 73% yield.[11] The esters were again a 92:8 mixture of diastereomers. The reduction of **11** with $LiAlH_4$ produced the alcohols **12**, the major (92:8) isomer of which was identical in all respects to a sample of **12a** which had been previously transformed into the natural product.[5h,i]

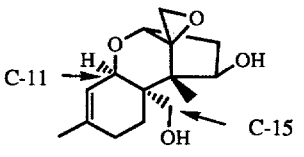
The sense of the diastereoselectivity is consistent with a chelation-controlled deprotonation step followed by rearrangement of the resulting silyl keteneacetal through a chair-like transition state. The stereochemical leakage presumably arises from a small amount of a boat-like structure during the rearrangement. While a rigorous test of this hypothesis has not been performed, it is entirely consistent with what is known about the transition states of [3,3] sigmatropic rearrangements in similar systems.[2,5f]

This completed the diastereoselective synthesis of trichodiene. The degree of stereoselectivity, 92:8, was excellent and the overall yield of the process (25% from known material) was quite reasonable. Furthermore, the residual carbonyl, ester and olefin moieties of intermediate **10a** allow for the potential elaboration to higher trichothecenes. This

relationship is demonstrated below by comparing the oxidation states of the carbon skeletons of **10a** and verrucarol **13**.[4] Application of this technique to the total synthesis of these compounds is currently being investigated.



10a



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