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Synthesis and reactivity of a putative biogenetic precursor to tricholomenyns B, C, D and E

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Dedicated to Professor Harry Wassermann on the occasion of his 90th birthday and in recognition of his profound and wide-ranging contributions to the discipline of organic chemistry

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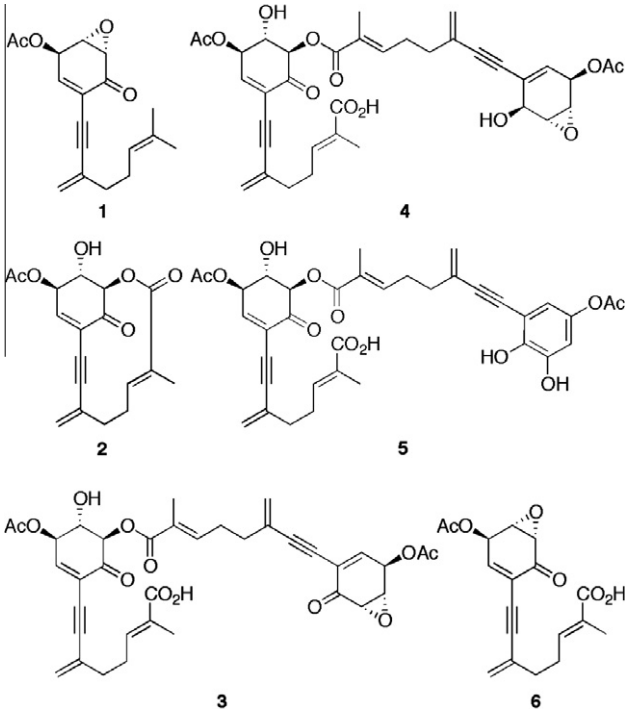
ABSTRACT

A chemoenzymatic synthesis of the putative biogenetic precursor, **6**, to the epoxy-quinol type natural products, tricholomenyns B, C, D and E (**2**–**5**, respectively), has been achieved. However, treatment of compound **6** under a variety of conditions failed to effect its conversion into any of the natural products **2**–**5**. In contrast, the simple model system **22** reacts with acetic acid in the presence of stoichiometric quantities of Ti(OPr-*i*)$_4$ to give the diacetate **23**.

Studies carried out in the mid-1990s by Vidari and co-workers[1,2] resulted in the isolation of the highly oxygenated cyclohexanoid natural products, tricholomenyns A–E (**1**–**5**, respectively), from the fruiting bodies of the Basidiomycetes species *Tricholoma acerbum* (Bull.: Fr) Quel collected in the Italian Apennines. Their structures were elucidated using NMR spectroscopic and mass spectrometric techniques. Compounds **1** and **2** were found to act as anti-mitotic agents and proved more potent in this respect than Colcemid™ (deacetyl *N*-methylcolchicine), a clinically effective cytotoxic agent.[1] It has been suggested[2] that the biosynthesis of tricholomenyns C–E 'proceeds via a not yet isolated intermediate arising from the regiospecific oxidation of congener **1** at the C-14 methyl group.' Presumably, the monomeric tricholomenyn B (**2**) could also arise via cyclization of the same intermediate, the most obvious form of which is carboxylic acid **6**.

As part of an ongoing program directed towards the synthesis of epoxyquinol-type natural products,[3,4] we have recently completed an enantioselective synthesis of tricholomenyn A.[3b] As an extension of these efforts we are pursuing the synthesis of tricholomenyn B (**2**), the first example of a natural cyclohexenoid containing an acetylenic ansa bridge. To this end we now describe the preparation, in enantiomerically pure form, of its potential biogenetic (and synthetic) precursor, acid **6**, and report on the chemical reactivity of this compound.



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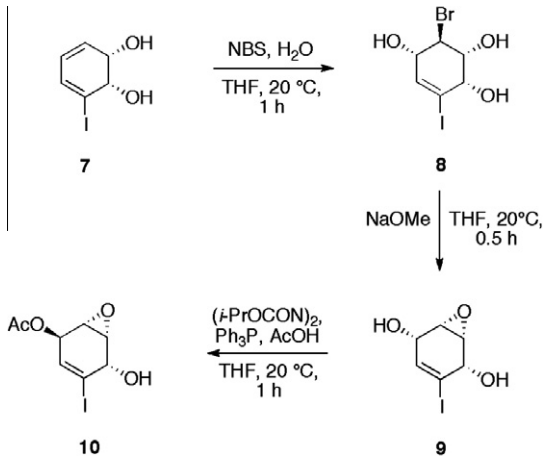
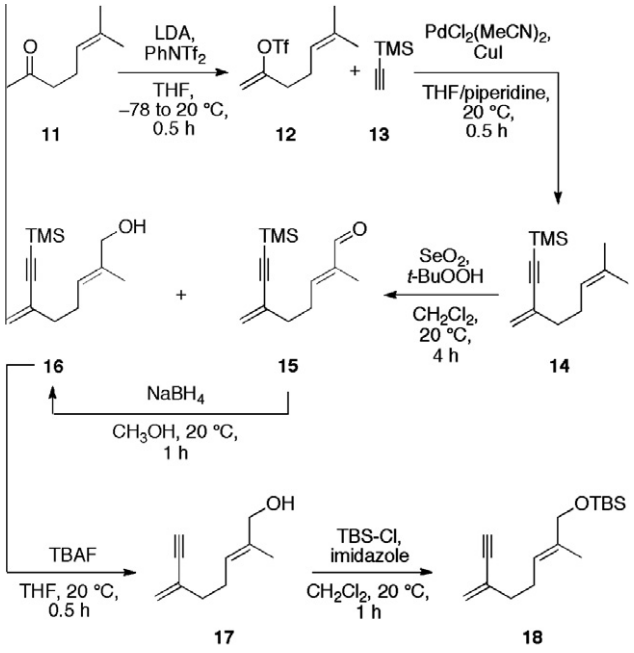


Scheme 1.

The preparation of target **6** involved three distinct stages, namely the synthesis of the core and the side-chain and then, in the final stage, the linking of these two units followed by some simple functional group interconversions. The first stage is shown in Scheme 1 and starts with the conversion of the readily available and enantiomerically pure *cis*-1,2-dihydrocatechol **7**[5] into bromohydrin **8**[3a] (68%) through reaction with *N*-bromosuccinimide in wet THF. Treatment of compound **8** with sodium methoxide resulted in the regioselective formation of epoxide **9**[3a] (85%) that was subjected to Mitsunobu reaction[6] with di-*iso*-propyl diazoacetate (DIAD)/Ph_3P using acetic acid as the nucleophile[6] and thus producing, in a completely regioselective manner, acetate **10** in 64% yield.

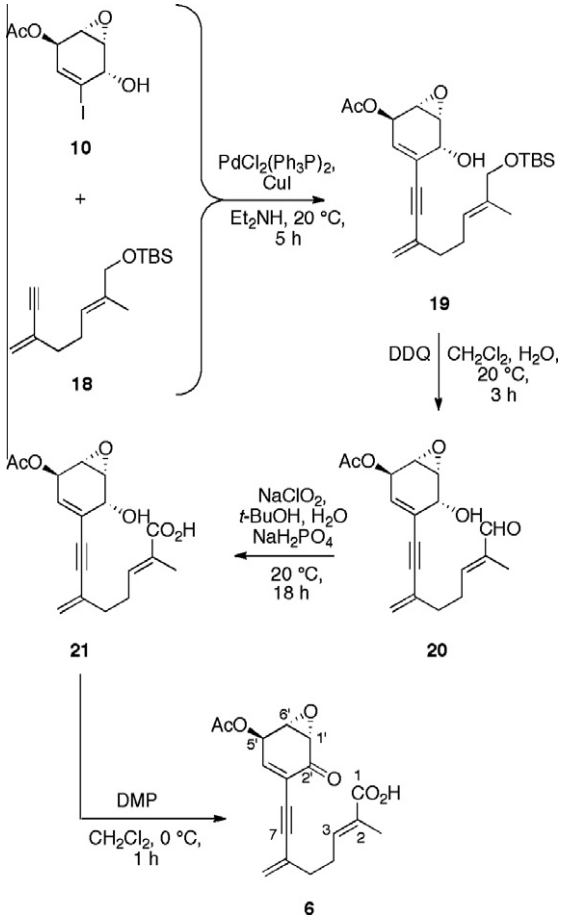
The acetylene-containing side-chain associated with target **6** was synthesized from the commercially available ketone **11** using the reaction sequence shown in Scheme 2. Thus, compound **11** was converted, under standard conditions, into the corresponding enol triflate **12**[3b,7] (88%) that was subjected to Sonogashira cross-coupling[8] with trimethylsilylacetylene (**13**) to give the dienyne **14**[7a,b] (87%). Treatment of compound **14** with *tert*-butyl hydroperoxide in the presence of 0.5 mol equiv of selenium dioxide[9] afforded a chromatographically separable mixture of aldehyde **15** (18%) and alcohol **16** (32%). The former product could be converted into the latter (97%) using sodium borohydride in methanol. Treatment of compound **16** with tetra-*n*-butylammonium fluoride (TBAF) then afforded the terminal acetylene **17** (99%) which was converted, under standard conditions, into the corresponding TBS ether **18** (94%) ready for coupling to the core molecule **10**.



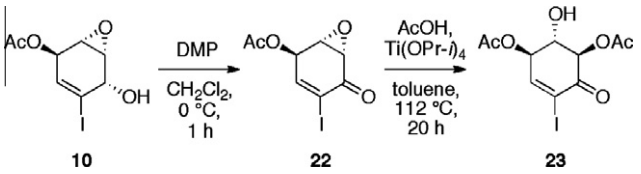
Scheme 2.

In the final stage (Scheme 3) of the synthesis of target acid **6**, compounds **10** and **18** were subjected to a Sonogashira cross-coupling reaction and the product **19** (85%) thereby obtained was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to afford aldehyde **20** in 72% yield. Pinnick oxidation[10] of compound **20** gave acid **21** (89%) that was then subjected to reaction with Dess–Martin periodinane (DMP)[11] so as to effect oxidation of the remaining free hydroxy group and complete the synthesis of acid **6**[12] (55%). The $\{^1H\}^{13}C$ NMR spectrum of compound **6** displayed the expected eighteen signals including nine due to sp^2-hybridized and two due to sp-hybridized carbons. The illustrated *E*-configuration about the $\Delta^{2,3}$-double bond in target **6**, which is that expected based on the selectivity rules for such SeO_2-mediated hydroxylation reactions,[13] and the likely mechanism of this process,[14] was confirmed through the observation of an NOE of the C-4 methylene protons (resonating at δ_H 2.47) upon irradiation of the C-2 methyl group protons (which resonate at δ_H 1.86). The chemical shift of the resonance due to H-3 (δ_H 6.87) is also consistent with the geometry assigned to the $\Delta^{2,3}$-double bond.[9]

Acid **6** proved to be a remarkably stable species and thus far we have been unable to engage it in any productive thermal-, acid- or



Scheme 3.



Scheme 4.

base-promoted isomerization or dimerization processes regardless of the concentration of the substrate used. In contrast, the model system **22**, which is readily obtained in 95% yield by oxidation of alcohol **10** with DMP (Scheme 4), reacted with acetic acid in the presence of 1.1 mol equiv of $Ti(OPr\text{-}i)_4$ to give the diacetate **23**[15] (26%) as the only characterizable product of reaction. Under the same conditions, compound **6** was consumed but no identifiable products could be isolated from the reaction mixture.

The origin of the divergent reactivities of compounds **6** and **22** remains unclear at the present time. There are various explanations for our failure to observe the conversion of the former compound into any of tricholomenyns B–E. Thus, for example, it is possible that epoxy-acid **6** is not a biogenetic precursor to these natural products or that the relevant conversions (of **6**) are enzyme-mediated processes unable to be mimicked under strictly chemical (i.e., non-biological) conditions.

Acknowledgements

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Supplementary data

Supplementary data (including experimental procedures and product characterization for compounds **6**, **10** and **15**–**23**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.139.

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12. Selected spectral data for compound **6**: $[\alpha]_D = -213.4$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.87 (m, 1H), 6.77 (dd, *J* = 5.5 and 2.5 Hz, 1H), 5.82 (m, 1H), 5.47 (d, *J* = 1.0 Hz, 1H), 5.38 (d, *J* = 1.0 Hz, 1H), 3.75 (m, 1H) 3.59 (dd, *J* = 4.0 and 1.5 Hz, 1H), 2.47 (dd, *J* = 14.0 and 7.0 Hz, 2H), 2.35 (br t, *J* = 7.0 Hz, 2H), 2.13 (s, 3H), 1.86 (d, *J* = 1.0 Hz, 3H) (signal due to carboxylic acid proton not observed); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.5 (C), 173.5 (C), 169.8 (C), 143.5 (CH), 140.8 (CH), 129.6 (CH_2 or C), 128.1 (C), 124.9 (C), 124.4 (CH_2 or C), 95.2 (C), 82.7 (C), 64.2 (CH), 54.9 (CH), 53.0 (CH), 35.7 (CH_2), 27.5 (CH_2), 20.7 (CH_3), 12.2 (CH_3); IR ν_{max} 2928, 2204, 1757, 1740, 1698, 1643, 1422, 1371, 1289, 1218, 1024, 910 cm^{-1}; MS *m*/*z* (ESI, −ve ionization) 329 [$(M-H^+)^-$, 19%], 287 (99), 243 (100), 225 (27); HRMS Found: $(M-H^+)^-$, 329.1021. $C_{18}H_{17}O_6$ requires $(M-H^+)^-$, 329.1025.
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15. Selected spectral data for compound **23**: $[\alpha]_D = -51.0$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49 (d, *J* = 2.5 Hz, 1H), 5.66 (dd, *J* = 8.5 and 2.5 Hz, 1H), 5.44 (d, *J* = 8.5 Hz, 1H), 4.20 (m, 1H), 2.72 (br s, 1H), 2.24 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.2 (C), 170.5 (C), 170.0 (C), 153.6 (CH), 102.1 (C), 75.0 (CH), 74.5 (CH), 73.0 (CH), 20.9 (CH_3), 20.7 (CH_3); IR ν_{max} 3468, 2923, 2852, 1752, 1710, 1373, 1223, 1071, 1036, 800, 737 cm^{-1}; MS *m*/*z* (EI, 70 eV) 354 ($M^{+\cdot}$, 5%), 312 (20), 252 (100), 223 (16), 210 (32); HRMS Found: $M^{+\cdot}$, 353.9597. $C_{10}H_{11}IO_6$ requires $M^{+\cdot}$, 353.9600.