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A Chemoenzymatic and Enantioselective Route to the Tricyclic Frameworks Associated with the Protoilludane and Marasmane Classes of Sesquiterpene

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The enantiomerically pure *cis*-1,2-dihydrocatechol **3**, which is obtained in quantity by microbial dihydroxylation of toluene, has been converted over ten steps, including an initial Diels–Alder cycloaddition reaction, into the tricyclic ketone **12**. Direct irradiation of a benzene solution of the latter compound affords a mixture of compounds **13** and **14** which embody the tricyclic frameworks of the sesquiterpene natural products tsugicoline A (**1**) and isovelleral (**2**), respectively.

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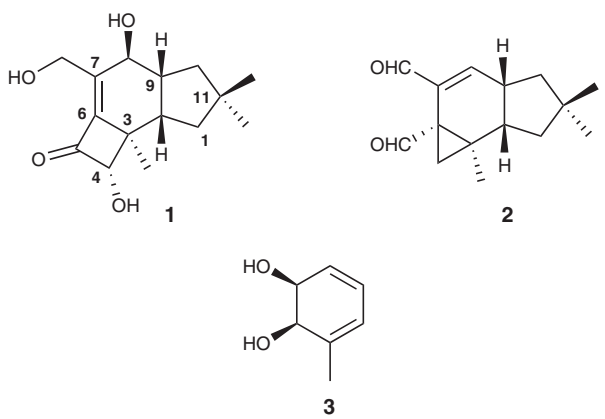
Tsugicoline A (**1**, Scheme 1) is a representative member of the Δ^6-protoilludane class of sesquiterpene natural product. The compound was first isolated, by an Italian group, from the fungus *Laurilia tsugicola* (*Echinodontium tsugicola*) in 1995.[1] While it is inactive against bacteria and fungi, tsugicoline A does inhibit the germination of the cress *Lepidium sativum*, a property which may be attributed to the presence of the strained enone moiety. The structurally related isovelleral (**2**), which belongs to the marasmane class of sesquiterpenes, was isolated from Basidiomycetes species belonging to the genus *Lactarius*[2] and displays antibacterial as well as antifeedant properties,[3] the latter feature likely important in the chemical defence mechanisms of the producing organisms.[4] In contrast to the situation with congener **1**, dialdehyde **2** has been the subject of several successful total synthesis studies.[5] Through such work it has been shown that the antimicrobial and cytotoxic activities of isovelleral and its non-natural enantiomer are comparable but the natural product is approximately ten times more mutagenic in an Ames test. Both enantiomers have the same affinity for the vanilloid receptor but significantly different affinities for the dopamine D1 receptor.[6]



Scheme 1.

As part of an ongoing program to exploit various fermentation products as starting materials in total synthesis,[7] we have recently described the conversion of the *cis*-1,2-dihydrocatechol **3** into both the triquinane-type sesquiterpene (–)-hirsutene[8] and the cyperene-type sesquiterpene (–)-patchoulenone.[9] Compound **3** is available in bulk quantities and enantiomerically pure form through microbial dihydroxylation of toluene using a genetically engineered form of *Escherichia coli* [JM109 (pDTG601)] that over-expresses the enzyme toluene dioxygenase (TDO).[10] As an extension of work in this area, we now outline simple protocols for the conversion of metabolite **3** into the tricyclic frameworks associated with tsugicoline A (**1**) and isovelleral (**2**). Since the enantiomeric form of compound **3** is also known,[11] then the work described here also provides access to the tricyclic frameworks associated with the non-natural enantiomers of compounds **1** and **2**.

The crucial elements of the present work are shown in Scheme 2 and the early stages are identical to those associated with our recently disclosed synthesis of (–)-hirsutene,[8] but they are repeated here for the sake of completeness. Thus, diene **3** engages in a high-pressure (19 kbar)-promoted reaction with cyclopenten-2-one (**4**) to give the *syn*-adduct **5** (70%) as the major product of reaction. Protection of the *cis*-diol within this adduct as the corresponding acetonide **6** (98%) was carried out under standard conditions

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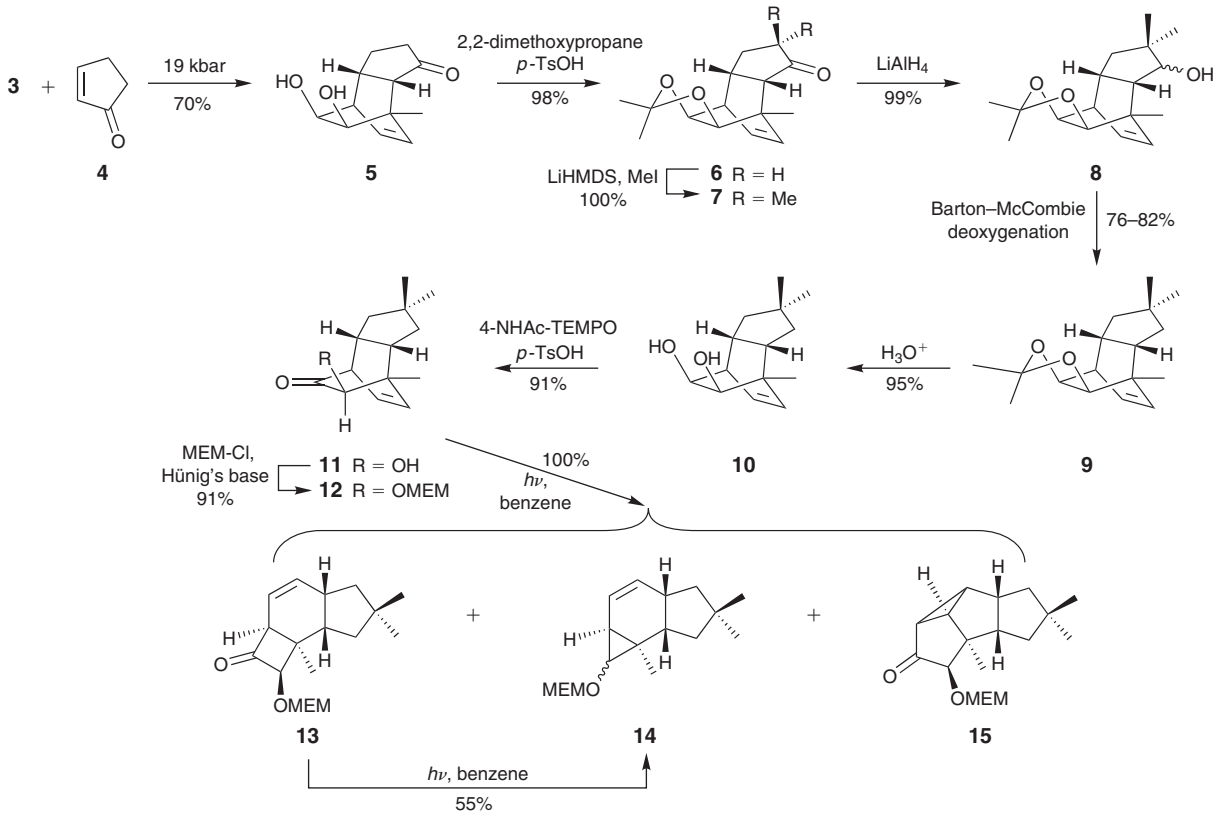
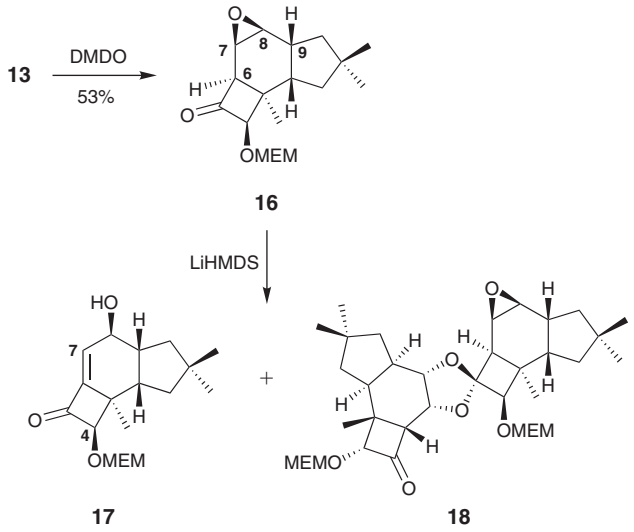


Scheme 2.

and thus enabled geminal dimethylation adjacent (α) to the carbonyl group. This was achieved using LiHMDS (lithium hexamethyldisilazide)/MeI and thereby afforded target **7** in quantitative yield. The now redundant ketone carbonyl group was removed by initial reduction of compound **7** to the corresponding alcohol **8** (99% of a 9 : 1 mixture of epimers) followed by Barton–McCombie reduction of the derived xanthate esters with Bu^n_3SnH, thereby affording acetonide **9** (76–82%). Acetal cleavage within the last compound proved rather difficult but could be achieved upon prolonged exposure of a THF solution of the substrate to acetic acid in water, thus affording diol **10** in 95% yield at 44% conversion. Selective oxidation of the hydroxyl group remote from the bridgehead methyl group within compound **10** was carried out using the sterically demanding oxoammonium salt derived from *p*-TsOH-promoted disproportionation of 4-acetamido-TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidinyl-1-oxy) and, in this manner, the acyloin **11** was obtained in 91% yield at 96% conversion. Compound **11** proved to be a rather sensitive material. It is prone to oligomerization, a process that can be stopped through its conversion into the corresponding MEM (2-methoxyethoxymethyl) ether **12** (91%) using MEM-Cl in the presence of Hünig's base.

In the pivotal step of the reaction sequence leading to the carbocyclic frameworks associated with compounds **1** and **2**, a benzene solution of ketone **12** was subject to direct irradiation with a high-pressure mercury lamp and in this manner a chromatographically separable mixture of photoproducts **13** (80% at 20% conversion), **14** (10% at 20% conversion of a 7 : 3 mixture of epimers), and the previously observed[8] triquinane **15** (10% at 20% conversion) was obtained. The structures of compounds **13** and **14** follow from comprehensive spectroscopic studies, including NOE experiments, of each of them. The tricyclic compound **13** is presumed to arise through a 1,3-acyl migration process,[12] while congener **14** is the product of a decarbonylation reaction that could occur directly from substrate **12** and/or after conversion of this last compound into isomer **13**. Certainly, resubjection of cyclobutanone **13** to the original photolysis reaction affords a 7 : 3 mixture of the epimeric forms of cyclopropane **14** (55%).

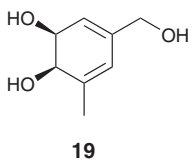
The reaction sequence outlined above would seem to offer very good prospects for achieving a total synthesis of tsugicoline A (**1**). For example, compound **13** reacts (Scheme 3) in a diastereofacially selective manner with dimethyldioxirane (DMDO)[13] to give the epoxide **16** (53%), the stereochemistry of which follows from NOESY experiments that reveal interactions between H6 and H8 but not H7 and H9. Treatment of compound **16** with LiHMDS affords the allylic alcohol **17** (55%) although the major product of reaction, at least when a large excess of base is used, is the fascinating 'hetero-dimer' **18** (49%). Compound **18** is presumed to arise through initial addition of the conjugate base of alcohol **17** to the cyclobutanone carbonyl of compound **16**. The hydroxyl group of the resulting hemiacetal, or its conjugate base, then engages in an intramolecular Michael addition reaction with the pendant enone residue to give the observed acetal **18**. Presumably formation of this dimer could be suppressed



Scheme 3.

through in situ trapping of the product of epoxide ring opening with TMS-Cl.

Exploiting the results detailed above in a total synthesis of tsugicoline A (**1**) requires, among other things, the development of methods for introducing the C7 hydroxymethyl group and inverting stereochemistry at C4 within a compound such as **17** or a precursor such as acyloin **11**. Attempts to effect the latter conversion on compound **11** using Mitsunobu protocols have been unsuccessful thus far. While chemical methods for introduction of the hydroxymethyl group could probably be devised, a more attractive approach would involve incorporating such a moiety from the beginning of the synthesis. In particular, it might be anticipated[11] that dihydroxylation of *m*-methylbenzyl alcohol (or some equivalent thereof) using TDO in a whole-cell biotransformation would deliver the *cis*-1,2-dihydrocatechol **19** (Scheme 4) which could be carried forward, in the manner described in Schemes 2 and 3, to give the C7-hydroxymethylated equivalent of compound **17**. Obviously, metabolite **19** would also be highly relevant to the development of a synthesis of isovelleral. Studies aimed at generating compound **19** by fermentation are now underway in these laboratories and will be reported upon in due course.



Scheme 4.

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