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Chemoenzymatic Synthesis of the Enantiomer of 4,12-Dihydroxysterpurene, the Structure Assigned to a Metabolite Isolated from the Culture Broth of *Stereum purpureum*

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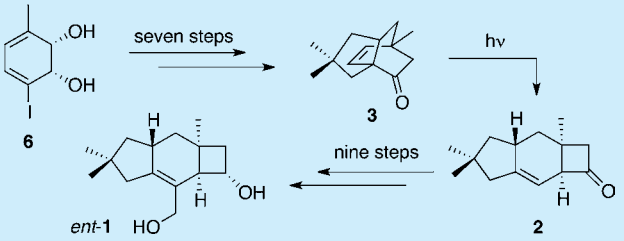
Supporting Information

ABSTRACT: Compound *ent*-**1** has been prepared by engaging a derivative of the enantiomerically enriched and microbially derived *cis*-1,2-dihydrocatechol **6** in an intramolecular Diels–Alder reaction, elaboration of the adduct so-formed to the cyclopentannulated bicyclo[2.2.2]octenone **3**, and photochemical rearrangement of this to the cyclobutanone **2**. By such means it has been established that 4,12-dihydroxysterpurene (**1**) is not the structure of the natural product isolated by Xie and co-workers from a culture broth of *Stereum purpureum*.



The sterpurene class of sesquiterpenoid embodies the polyhydro-1*H*-cyclobuta[*f*]indene framework that is isomeric, therefore, with that present in the more commonly encountered and biogenetically related protoilludane group of natural products wherein the associated four- and five-membered rings are angularly, rather than linearly, fused to the central six-membered ring.[1] To date most sterpurenes have been isolated from fungal sources, notably *Stereum purpureum* that causes silver-leaf disease.[2] The structures of these compounds have been established through the application of the usual range of spectroscopic techniques, and their absolute configurations were determined using exciton chirality methods and Mosher ester analyses.[2c] Details of the biosynthetic pathway leading to the sterpurenes have been elucidated through ^{13}C-labeled acetate incorporation studies.[1,3]

While the precise biological roles of these metabolites remain unclear, their distinctive molecular architectures have prompted an array of synthetic studies.[4] Various protocols have been established for the assembly of the sterpurene framework including those involving cationic/biomimetic rearrangements,[4a,n] electroreductive cyclizations,[4b] intermolecular [4 + 2]- and/or [2 + 2]-cycloadditions,[4c,j] intramolecular cycloadditions of various types,[4d,f,g,m] [4 + 3]-cycloaddition/quasi-Favorskii rearrangement sequences,[4k] intramolecular and iron(I)-mediated C–H insertions,[4e,i] and photochemically induced 1,3-acyl migration reactions.[4h,l] A significant fraction of these have culminated in the synthesis of sterpurenes, although generally of the nonoxygenated, parent member of the class (viz. sterpurene) and, with one exception,[4d] always in racemic form. Interestingly, it has been reported[2h,i] that the protoilludane tsugicoline A can be converted into a sterpurene derivative under biocatalytic conditions.

In 1992 Xie and co-workers reported[2f] the isolation of a new sterpurene from a culture broth of *Stereum purpureum* that caused "silvering" of mountain ash seedlings. On the basis of one- and two-dimensional ^{1}H NMR spectroscopic studies alone they assigned structure **1** (Figure 1) to this compound and so

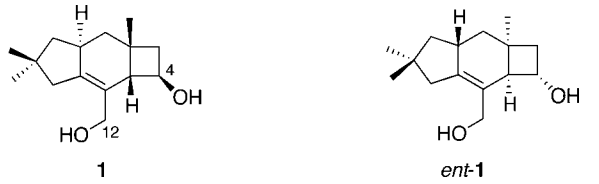


Figure 1. Structures of compounds **1** and *ent*-**1**.

naming it 4,12-dihydroxysterpurene. Herein we report a chemoenzymatic total synthesis of the enantiomer, *ent*-**1**, of 4,12-dihydroxysterpurene and thereby establishing that the structure assigned to the natural product is incorrect.

The strategy used to prepare target *ent*-**1** is shown in retrosynthetic form in Figure 2. Thus, we anticipated that this could be obtained using standard functional group interconversions (FGIs) from cyclobutanone **2** that itself would be formed through the photochemically promoted 1,3-acyl rearrangement[4h,l,5,6] of the cyclopentannulated bicyclo[2.2.2]-octenone **3**. This last compound was to be generated from congener **4**, the anticipated product of a Type-I intramolecular Diels–Alder (IMDA) reaction of triene **5**.[7] It was expected that compound **5** could be obtained by engaging the acetonide derivative of diol **6** in a cross-coupling reaction with an organometallic that embodies the required, olefin-containing side chain. *cis*-1,2-Dihydroactechol **6** is readily available in ca. 80% ee through the whole-cell biotransformation of *p*-iodotoluene.[8,9]

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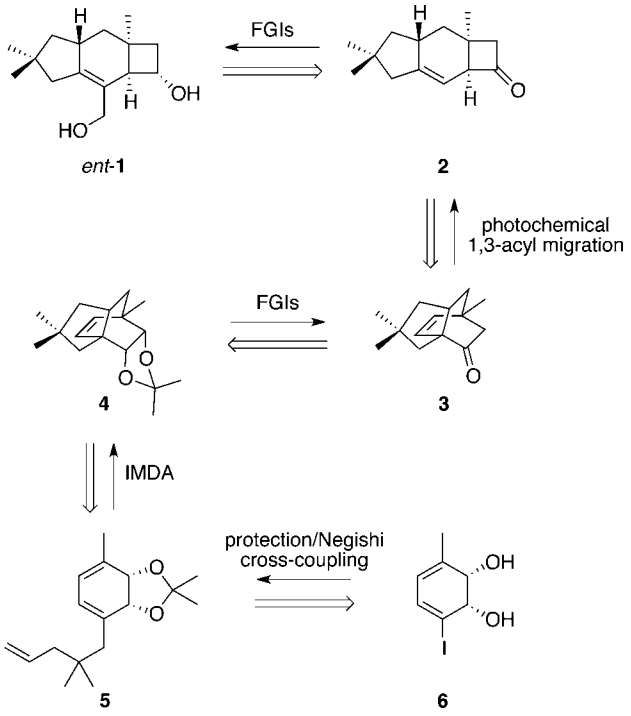
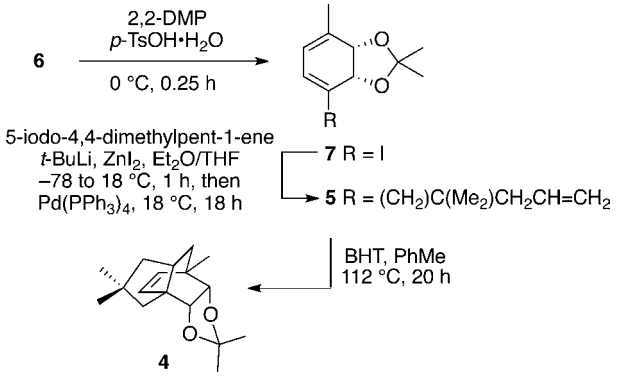


Figure 2. Retrosynthetic analysis of target *ent*-**1**.

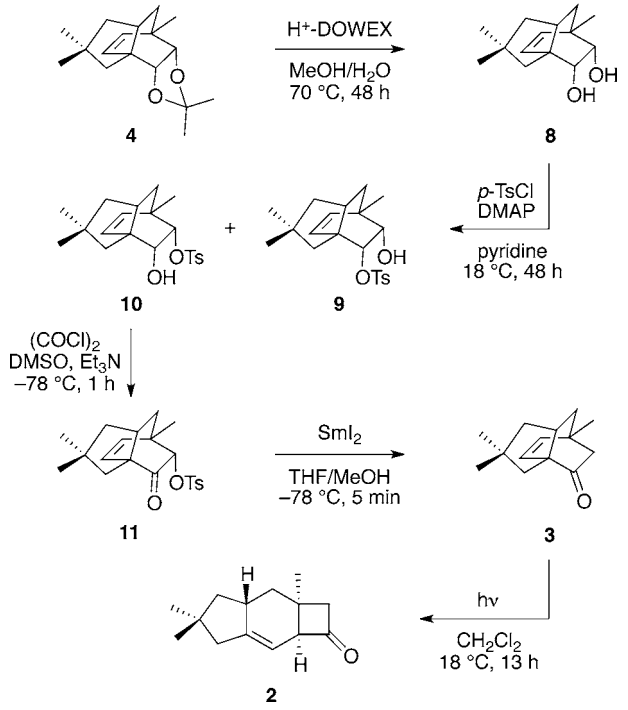
The opening stages of the implementation of this plan are shown in Scheme 1 and started with the Negishi cross-coupling of the known[10] acetonide derivative, **7**, of compound **6** with the organozinc species obtained by sequential treatment of 5-iodo-4,4-dimethylpent-1-ene[11] with *tert*-butyllithium and zinc iodide. When a toluene solution of the product triene **5** (97%) containing the free-radical inhibitor butylated hydroxytoluene (BHT) was heated at reflux for 20 h, then the anticipated IMDA reaction took place and thereby affording adduct **4** in 88% yield.

Scheme 1. Reaction Sequence Leading to the IMDA Adduct 4



The elaboration of the cyclopentannulated bicyclo[2.2.2]-octane **4** into the corresponding ketone **3**, the substrate required for exploring the pivotal photochemical isomerization step, involved the reaction sequence outlined in Scheme 2. Specifically, then, acetonide **4** was hydrolyzed to corresponding diol **8** (80% brsm) using acidified DOWEX-50WX8 resin and the latter was subjected to a reaction with 3 mol equiv of *p*-toluenesulfonyl chloride (*p*-TsCl) in the presence of 4-(*N*,*N*-

Scheme 2. Synthesis of Ketone 3 and Its Photochemical Rearrangement to Cyclobutanone 2



dimethylamino)pyridine (DMAP) and pyridine to give a chromatographically separable mixture of monotosylates **9** (29%) and **10** (52%). The structure of product **9** was confirmed by single-crystal X-ray analysis.[12] Oxidation of alcohol **10** using Swern protocols afforded the corresponding ketone **11** (90%) that upon treatment with samarium iodide was reduced to the sought-after congener **3** (87%).[13] Gratifyingly, when a dichloromethane solution of this last compound was subject to direct irradiation with a high-pressure mercury vapor lamp the desired 1,3-acyl migration reaction took place to produce the cyclobutenone **2** (85% brsm) that embodies the "5−6−4" ring system[4m] of the sterpurenes. All the spectroscopic data derived from compound **2** were in accord with the assigned structure, the signature component of these being a cyclobutanone carbonyl absorption band appearing at 1778 cm^{-1} in the infrared spectrum.[14]

The elaboration of compound **2** to target *ent*-**1** was achieved using the chemistry shown in Scheme 3 and involved an initial, $LiAlH_4$-mediated and completely stereoselective reduction of the former compound to alcohol **12** (85%) that was then subjected to a Mitsunobu reaction using benzoic acid as a nucleophile.[15] The resulting unsaturated ester **13** (80%) was treated with osmium tetraoxide under the Upjohn conditions and so producing the crystalline diol **14** (73%),[16] the structure of which was confirmed by single-crystal X-ray analysis.[12] Swern oxidation of compound **14** provided the expected acyloin **15** (97%) that could not itself be methylenated using the Wittig reagent. However, the readily derived trimethylsilyl ether **16** (94%) could, providing, after cleavage of the silyl ether using tetra-*n*-butylammonium fluoride (TBAF), the allylic alcohol **17** (44% over two steps). On treatment with pyridinium chlorochromate (PCC) this last compound underwent a Dauben−Michno oxidative rearrangement reaction[17] to give the *α*,*β*-unsaturated aldehyde **18**, and on exposure to DIBAl-H this was reduced to the target diol *ent*-**1** (54% from **17**).

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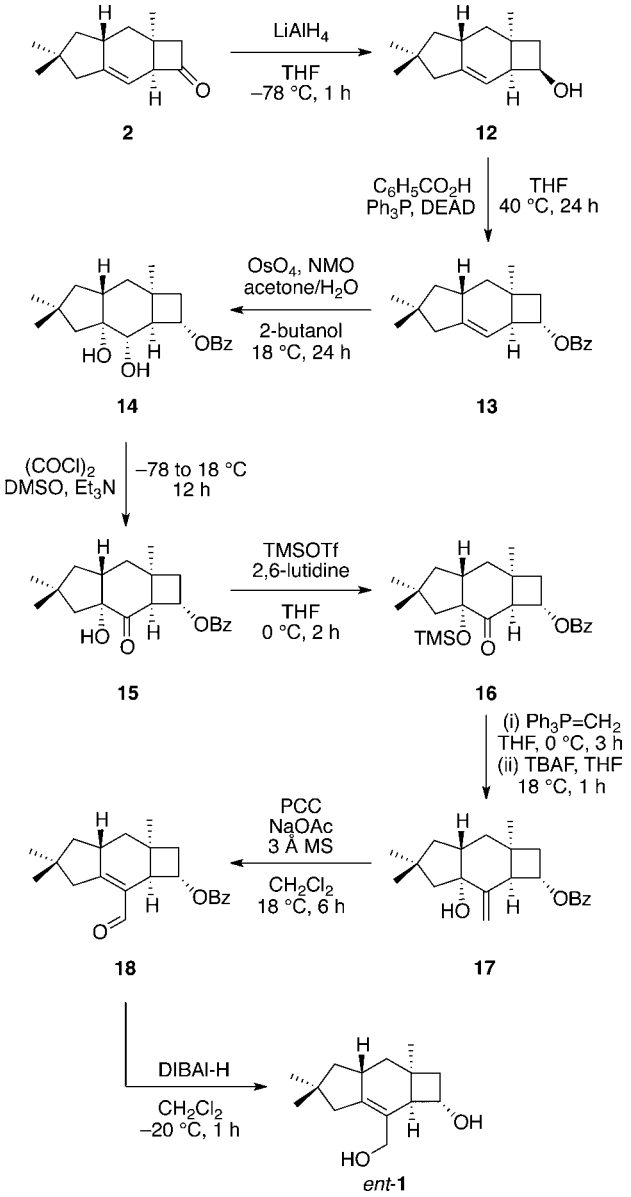
Scheme 3. Completion of the Synthesis of Target *ent*-1



The spectral data derived from product *ent*-**1** were in complete accord with the assigned structure but did not match those reported[2f] for the natural product isolated by Xie and co-workers. As revealed in Table 1, among the many notable differences in the ^{1}H NMR spectral data sets recorded for compound *ent*-**1** and the natural product, the resonances due the diastereotopic oxymethylene protons at C12 in the former compound appear as a pair of mutually coupled one-proton doublets (J = 11.6 Hz) at δ 4.08 and 3.91 while the analogous signals in the natural product appear at δ 4.52 and 4.40 (J = 8.8 Hz). Similar comparison of the ^{13}C NMR data sets was not possible because the relevant spectrum has not been reported for the natural product and nor has the specific rotation. The absence of such data means that the true structure of this natural product will be difficult to establish without obtaining additional samples and, thereby, securing further spectroscopic data.

The present work defines a useful strategy for the synthesis of various oxygenated forms of the sterpurene framework and should, therefore, provide an effective means for the preparation of various enantiomeric forms of members of this family of sesquiterpenoid natural product. Interestingly, the IMDA cycloaddition reaction leading to the formation of adduct **4** also affords ca. 7% of that isomer arising from addition of the dienophile to the same face (α-face) of the diene as occupied by the acetonide group. In principle this minor adduct, which is pseudoenantiomerically related to the major one, could be elaborated to ketone *ent*-**3** using the same transformations as shown in Scheme 2 and thence provide access to photoproduct *ent*-**2** that possesses the same absolute configuration as the naturally occurring sterpurenes.[18]

Table 1. Comparison of the ^{1}H NMR Data (δ_H) Recorded for Synthetically Derived Compound *ent*-1 with Those Reported for the Natural Product Isolated by Xie et al. and Designated 4,12-Dihydroxysterpurene

ent-1[a]	Xie's natural product[b]
4.08, d, J = 11.6 Hz, 1H	4.52, d, J = 8.8 Hz, 1H
3.91, d, J = 11.6 Hz, 1H	4.40, d, J = 8.8 Hz, 1H
3.66, dt, J = 8.6 and 4.6 Hz, 1H	4.33, m, 1H
2.42, m, 1H	2.75, broad m, 1H
2.29, m, 1H	2.46, broad d, J = 16.3 Hz, 1H
2.17–2.22, complex m, 1H	2.29, broad d, J = 14.4 Hz, 1H
2.06–2.02, complex m, 1H	2.27, m, 1H
1.89, broad s, 2H[c]	2.20, broad d, J = 11.4 Hz, 1H
1.67–1.63, complex m, 1H	1.76, m, 1H
1.60, t, J = 4.8 Hz, 1H	1.74, dd, J = 12.8 and 5.2 Hz, 1H
1.57, t, J = 4.8 Hz, 1H	1.68, dd, J = 12.8 and 5.1 Hz, 1H
1.16, s, 3H	1.25, s, 3H
1.04, t, J = 11.3 Hz, 1H	1.15, dd, J = 12.8 and 5.2 Hz, 1H
0.99, s, 3H	1.07, s, 3H
0.93, s, 3H	1.03, s, 3H
0.55, t, J = 12.1 Hz, 1H[d]	0.69, dd, J = 12.8 and 11.1 Hz, 1H[e]

[a]Data recorded in CD_2Cl_2 at 400 MHz. [b]Data obtained from ref 2f and recorded in CD_2Cl_2 at 400 MHz. [c]Includes signal due to OH group proton. [d]Signal due to the second OH group proton not observed. [e]Signals due to OH group protons not reported.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures; data derived from the single-crystal X-ray analyses and CIFs of compounds **9** and **14** (CCDC Nos. 1036580 and 1036581, respectively); and ^{1}H and ^{13}C NMR spectra of compounds *ent*-**1**, **2**–**5**, and **8**–**17** as well as certain isomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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