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Approaches to the Neurotrophically Active Natural Product 11-*O*-Debenzoyltashironin: A Chemoenzymatic Total Synthesis of the Structurally Related Sesquiterpene Khusiol

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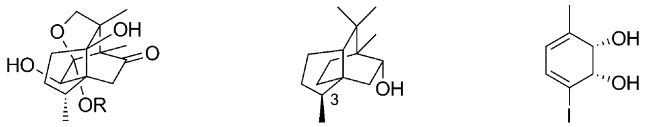
The sesquiterpenoid natural product 11-*O*-debenzoyltashironin (**1**, Scheme 1) and the corresponding benzoate ester tashironin (**2**) have been isolated from the pericaps of the eastern Asian plant *Illicium merrillianum*.[1] The structures of these compounds were determined using NMR spectroscopic techniques, and the former was shown to induce neurite outgrowth in fetal rat cortical neurons at concentrations as low as 0.1 μM.[1] As such and because of its compact and highly substituted tetracyclic structure, 11-*O*-debenzoyltashironin has attracted some attention as a synthetic target.[2] In 2006 Danishefsky and co-workers reported the first and thus far only total synthesis of (±)-**1**,[3] and two years later they described a modification of their elegant transannular Diels–Alder approach to the preparation of enantiomerically enriched variants of the intermediates associated with the original synthesis.[4] Starting in 2007 Mehta and Maity have reported a series of impressive studies[5] on the construction, in racemic form, of the tetracyclic core of compounds **1** and **2**. This work, which employs a tandem oxidative dearomatization — intramolecular Diels–Alder (IMDA) reaction — ring-closing metathesis (RCM) sequence, has recently culminated in a total synthesis of (±)-11-*O*-methyldebenzoyltashironin. No further work in the area has been described to date, and the lack of any reported structure–activity relationship studies is probably a reflection of the lengthy nature of the existing approaches to compound **1** and its congeners. In an effort to address this matter as well as the need to obtain the nonracemic forms of compound **1** and its congeners, we have begun exploring chemoenzymatic approaches to the tricyclic carbon framework of 11-*O*-benzoyltashironin. In this connection we now report the first enantioselective total synthesis of the sesquiterpenoid khusiol (**3**),[6,7] a system that embodies the same 3,6,7,7-tetramethyloctahydro-3a,6a-ethanoindene framework encountered in compound **1** although possessing the opposite stereochemistry at C3. The starting material used in the present work was the *cis*-1,2-dihydrocatechol **4**, which is readily obtained in approximately 80% *ee* through the enzymatic *cis* dihydroxylation of *p*-iodotoluene.[8]



1 R = H
2 R = Bz

3 **4**

Scheme 1. Structures of compounds **1**–**4**. Bz = benzoyl.

The assembly of the tricyclic core of khusiol (Scheme 2) followed a pathway established during a recently completed model study.[9] Thus, the readily derived acetonide derivative **5**[9,10] of diol **4** was converted, by metalation/*trans*-metalation protocols,[11] into the corresponding cuprate, which was treated with the dienone **6**,[9,12] thereby producing, through a selective conjugate addition process, the α,β-unsaturated ketone **7** (60%).[9] While compound **7** failed to engage in an IMDA reaction upon heating, one of the epimeric alcohols (**8**),[9] obtained by sodium borohydride mediated reduction of this enone, underwent the desired cycloaddition reaction on heating in mesitylene,[13] thereby producing the epimerically pure tricyclic alcohol **9**[9] (71% yield based on recovered *S*-**8**) that incorporates the two contiguous quaternary carbon centers associated with target **3**.

Compound **9**, the assigned structure of which is supported by single-crystal X-ray analyses of the corresponding 3,5-dinitrobenzoate[9] and ketone (see the Supporting Information for details of the X-ray analysis of the latter),[14] is presumably formed preferentially in the IMDA reaction because at the transition state for this process the hydroxy group associated with substrate *R*-**8** resides on the *exo*-face of the developing *cis*-perhydroindene substructure.

The next phase of the synthesis involved establishing a protocol for introducing the C3 methyl group. To these ends, compound **9** was oxidized to the corresponding ketone (99%) using a mixture of pyridinium dichromate (PDC) and acetic acid. The resulting reaction mixture was subjected to hydrogenation, thus affording the saturated system **10** (99%). Treatment of this compound with TMSOTf in the presence of triethylamine resulted in the formation of the kinetically favored silyl enol ether that was subjected to oxidation using a combination of IBX and MPO in DMSO.[15]

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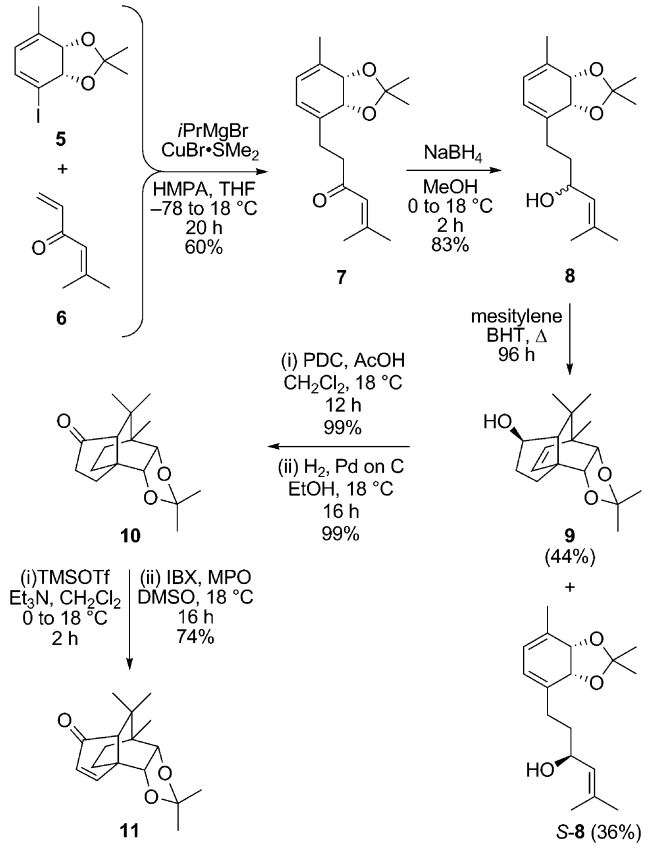
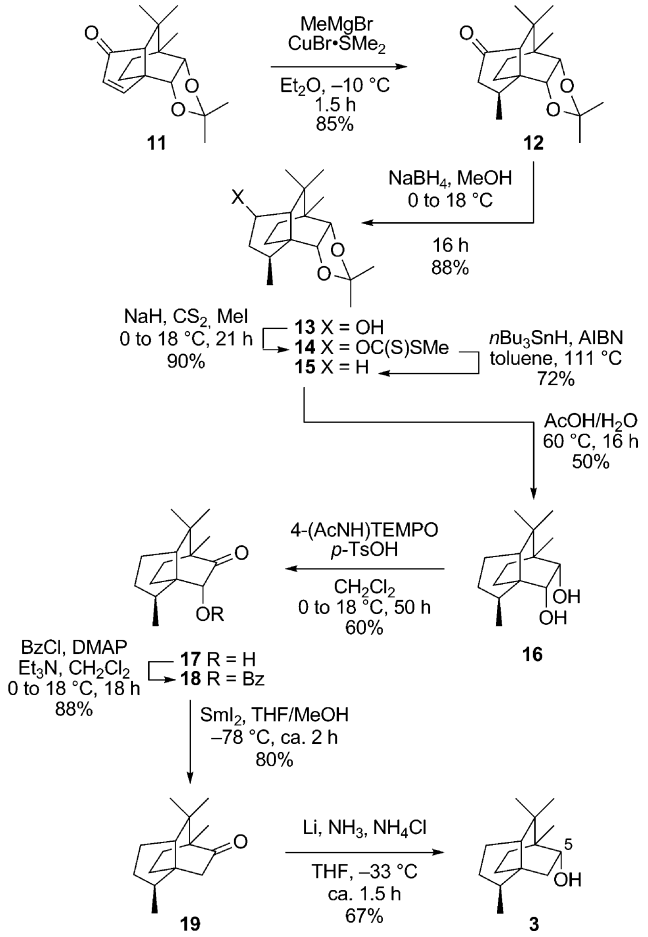


Scheme 2. Assembly of the khusiol framework. HMPA = hexamethylphosphoramide, BHT = butylhydroxytoluene, PDC = pyridinium dichromate, IBX = 2-iodoxybenzoic acid, MPO = 4-methoxypyridine-*N*-oxide, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

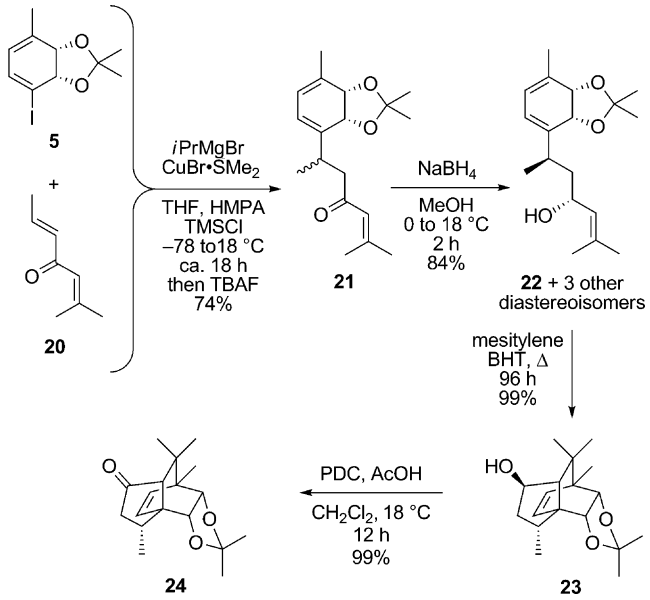


Scheme 3. Completion of the synthesis of khusiol (**3**). AIBN = azobisisobutyronitrile, TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl, *p*-TsOH = *p*-toluenesulfonic acid, DMAP = 4-(N,N-dimethylamino)pyridine.

By such means enone **11** was obtained in 74% yield (from **10**).

The completion of the synthesis of target **3** (Scheme 3) involved conjugate addition of the organocopper species generated in situ from methyl magnesium bromide and $CuBr{\cdot}SMe_2$ to enone **11**. As a result, the C3-methylated product **12** (85%) was obtained, the structure of which was determined by extensive 2D NMR spectroscopic studies. Treatment of compound **12** with $NaBH_4$ afforded a 4:1 mixture of the epimeric alcohols **13** (88% combined yield) that was converted (as a mixture) into the corresponding mixture of xanthate esters **14** (90%) under standard conditions. Subjection of these esters to the Barton–McCombie reduction protocol[16] using nBu$_3$SnH in the presence of AIBN then gave the deoxygenated compound **15** in 72% yield (from **14**). Acid-promoted hydrolysis of the acetonide unit within compound **15** was effected with acetic acid in water and the diol **16** (50% or 80% based on recovered **15**) so-formed was subjected to a Bobbitt-type oxidation using the oxammonium salt derived from the reaction of 4-(AcNH)TEMPO and *p*-TsOH.[17] In this way the acyloin **17** (60%) was formed in a remarkably selective manner. Compound **17** was converted into the corresponding benzoate **18** (88%) under standard conditions and the latter treated with samarium diiodide in THF/methanol,[18] thereby affording ketone **19**[19] in 80% yield. Following a procedure defined by Shanker and Subba Rao,[7] compound **19** was subjected to a dissolving metal reduction using Li in liquid ammonia and ammonium chloride as a proton source. In this way a chromatographically separable mixture of compound **3** (67%, ca. 85% *ee*) and its C5-epimer (5%) was obtained. The NMR and mass spectral data obtained for the former product were in complete accord with the assigned structure and matched those recorded in the literature for the racemic[7] as well as the enantiomerically pure modifications[6] of compound **3**. Final confirmation of the structure of our sample of khusiol followed from a single-crystal X-ray analysis of the derived 3,5-dinitrobenzoate.[20] Details are provided in the Supporting Information.

A method for establishing the *R* configuration at C3 in the 3,6,7,7-tetramethyloctahydro-3a,6a-ethanoindene framework, as required in developing a synthesis of the title compound **1**, is shown in Scheme 4. Thus, the cuprate derived from iododiene **5** was added to the trimethylated dienone **20**,[21] and the resulting approximately 2:1 mixture of the epimeric forms of compound **21** (74%) was treated with



Scheme 4. Assembly of the carbocyclic framework of 11-*O*-debenzoyltashironin. TBAF = tetra-*n*-butylammonium fluoride, TMSCl = trimethylsilyl chloride.

$NaBH_4$, thereby affording a 3:3:2:1 mixture of the four diastereoisomeric forms of allylic alcohol **22** in 84% combined yield. Heating this mixture in mesitylene at 165 °C for 96 h resulted in the exclusive formation of the IMDA adduct **23** (71% yield based on the diastereoisomer that reacts), which was readily oxidized to the corresponding ketone **24** (98%) using PDC in acetic acid.

The structure of compound **24** was confirmed by single-crystal X-ray analysis, and the derived ORTEP is shown in Figure 1.[22] Efforts to exploit this type of reaction sequence in the development of a total synthesis of the enantiomerically pure form of compound **1** are now underway. Results will be reported in due course.

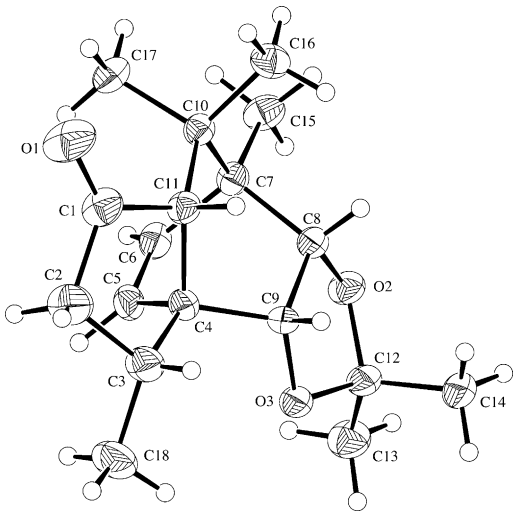


Figure 1. ORTEP derived from the single-crystal X-ray analysis of a mixture of compounds *ent*-**24** and **24** (compound **24** shown). Thermal ellipsoids are drawn at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

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Keywords: asymmetric synthesis · cycloaddition · synthetic methods · terpenoids

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[22] The crystal chosen for analysis contained a ca. 3:2 mixture of *ent*-**24** and **24**. This result arises from the starting material **4** containing ca. 10% of *ent*-**4**. The structure was solved and refined as an average structure in space group $P2_12_12$ with the two molecules occupying general positions in the asymmetric unit. Molecule 1 was ordered, but molecule 2 was 0.810(2):0.190 disordered. See the Supporting Information for further details. CCDC 795967 contains the supplementary crystallographic data for the compound mixture *ent*-**24**/**24**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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