Total Synthesis and Structural Revision of a Harziane Diterpenoid

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ABSTRACT: The first total synthesis of nominal harziane diterpenoid 1 is disclosed, whose spectral characteristics did not match those of the reported natural product. Stereochemical analysis and subsequent synthesis of the epimeric tertiary alcohol led to reassignment of configuration of the natural product as shown for 2. At the heart of the synthesis is an enyne cycloisomerization that sets a key quaternary stereocenter within a cyclobutane with high diastereoselectivity. The route features strategies for the synthesis of the highly congested 6–5–7–4 carbon skeleton characteristic of the caged harziane diterpenoids.

Trichoderma fungi are widespread phytosymbionts, which protect host plants from fungal pathogens and enhance root growth as well as nutrient uptake.[1] These fungi find commercial application as biocontrol agents and serve as a rich source of natural products, including the unnamed harziane diterpenoid 1 (Scheme 1). [2a] Isolated in 2014, this secondary metabolite possesses an unprecedented carbon skeleton containing ring sizes from four to seven. It harbors six contiguous stereocenters, two of which are quaternary. These challenging structural features render harziane diterpenoid 1 a veritable target for study. In addition, our initial examination of the reported spectra led us to doubt the configurational assignment of the tertiary alcohol in 1 (see below). We disclose the first total synthesis of 1 and diastereomer 2 as well as the characterization of the latter as the revised structure for the natural product. The route features implementation of modern disconnections enabled by Au-catalysis to diastereoselectively install the cyclobutane core and the associated quaternary center.

Scheme 1. Nominal and revised Harziane diterpenoid.

Ten harziane diterpenoids have been isolated of which eight share the unique 6–5–7–4 carbon skeleton.[2] They possess antifungal[2c] and cytotoxic[2e,2f] activity against two human cancer cell lines; moreover, microbially-derived metabolites exhibit anti-HIV and anti-inflammatory activity.[3] Despite the promising biological profile, there are no reported synthetic studies, which would provide guidance in developing routes towards these complex targets.

In our retrosynthetic analysis, the bicyclo[3.2.1]octane core was retrodisconnected to tricyclic diene 3 (Scheme 2a). Inspired by reports on Au-catalyzed cycloisomerization of cyclopropylidenynes to methylenecyclobutanes by Gagné,[4,5] we envisioned accessing the target’s cyclobutane ring and quaternary stereocenter from alkynyl methylene substituted substrate 5. It should be noted that

Scheme 2. a) Retrosynthesis and b) prior work.

a) Retrosynthesis:

b) Prior work (Gagné, ref. 4):

Only example with terminal alkyn

50% Yield

“decomposes quite rapidly at rt”
prior methodological studies leave open the question of the suitability of enynes such as 5 in the cycloisomerization reaction because no cyclic substrates were reported and product diene (9) was reported as unstable. Moreover, no data was provided that would address whether the reaction would be diastereoselective. Enyne 5 was further retrodisconnected to diene 6, which was accessed from enyne ester 7.

The synthesis commenced with propargylation of readily available ester 10 to yield enyne 7, followed by Pd-catalyzed cycloisomerization[10] to give diene 6 (Scheme 3). The methyl ester was transformed into the corresponding methyl ketone, which was protected as dioxolane 11. Treatment with BH$_3$THF/alkaline H$_2$O$_2$ led to cyclopentane 12 with good diastereoselectivity (>4:1 dr) in favor of the desired all-cis isomer. Oxidation of the secondary alcohol and subsequent olefination using Petasis’ dicyclopentyl titanocene reagent[11] granted convenient access to the cyclopropylidene unit. The primary alcohol was subsequently transformed into alkyne 5 by oxidation and Ohira–Bestmann reaction, which was accompanied by quantitative epimerization of the intermediate aldehyde.


![Scheme 3 Diagram](image)

Reagents and conditions: a) LDA, THF, –40 °C, 97%; b) Pd(OAc)$_2$ (20 mol%), BBEDA (20 mol%), PhH, 65 °C, 79%; c) MeN-HOMe-HCl, MeMgBr, THF, –20 °C to –10 °C, 91%; d) ethylene glycol, (EtO)$_2$CH, PPTS (10 mol%), 78%; e) BH$_3$THF, THF, 0 °C, then NaOH, H$_2$O; 63%, >4:1 dr; f) Piv–Cl, pyridine, CH$_2$Cl$_2$, –78 °C, then MeOH, DMP, NaHCO$_3$, CH$_2$Cl$_2$, 76%; g) Cp$_2$Ti(C$_5$H$_5$)$_2$, NaHCO$_3$, PhMe, 55 °C, then LiAlH$_4$, PhMe, 0 °C, 52%; h) NMO, TPAP (5 mol%), 4 Å MS, CH$_2$Cl$_2$, 93%; i) K$_2$CO$_3$, MeOH, then Ohira–Bestmann reagent, 87%; j) Ph$_3$PdAuNTf$_2$ (3 mol%), CH$_2$Cl$_2$, –10 °C to 0 °C, 87%, >11:1 dr.

We next addressed the key Au-catalyzed cycloisomerization reaction. It should be noted that the single study of the rearrangement[12] deals exclusively with acyclic enynes that incorporate at least one phenyl group either on the alkyne or alkylidene cyclopropane (Scheme 2b). Moreover, the investigation discloses only a single terminal alkyne substrate (8 in Scheme 2b). When it was subjected to the reported conditions (cat. Ph$_3$PdAuNTf$_2$ in CH$_2$Cl$_2$, 9 was formed in 50% yield and described to “decompose[s] quite rapidly at rt”. Accordingly, it was uncertain whether cyclic enyne 5 would be a competent substrate, given that it bears a terminal alkyne and a methyl substituent on the cyclopropylidene. Beyond issues concerning reaction and product stability, it was unclear whether the newly formed quaternary stereocenter would be set diastereoselectively, with a preference for the desired configuration.

In light of the challenges, it is remarkable that treatment of enyne 6 with 3 mol% Ph$_3$PdAuNTf$_2$ at –10 °C furnished diene 3 in 87% yield and >1:1 dr ($^1$H NMR). Analysis of each diastereomer (NOE) unequivocally established that the newly formed quaternary stereocenter had the desired relative configuration.[8]

Regioselective hydroboration[9] of methylenecyclobutane 3 and oxidation[10] yielded enone 14, which proved recalcitrant to functionalization at C-6 under numerous conditions (Scheme 4). However, treatment of 14 with Nagata’s reagent[11] (Et$_2$AlCN) gave ketonitrile 15 (62%). Having set the second stereocontrolling center, ring expansion of cyclohexanone 15 was explored next. The use of traditional methods (e.g. TMSCHN$_2$/AlMe$_3$[12-13] or TMSC(Li)N$_2$[12-13]) gave products consistent with a preference for migration of the cyclobutane over the alternative methylene group.[14] This inherent preference prevailed even when employing alternative reaction conditions known to favor migration of the less substituted methylene end, such as TMSCHN$_2$/BF$_3$OEt$_2$[12-13] and EtO$_2$CCHN$_2$/BF$_3$OEt$_2$[12-13] or Et$_2$OBF$_3$[12-13]. Accordingly, ketone 15 was next converted into the corresponding trisubstituted olefin 16, which incorporates the necessary methyl group in the targeted natural product. The olefin would serve as a functional group handle to carry out ring enlargement at a later point in the sequence. The transformation 15 → 16 was achieved by enol triflate formation followed by cross coupling with Me$_2$Zn.

We next set out to forge the target’s bicyclo[3.2.1]octane ring. To this end, the protected ketone was unmasked and transformed into silyl enol ether 17. Reduction of the nitrile group in 17 (DIBAL–H) led to isolation of an aldime after aqueous workup and column chromatography. The fact that this aldime is isolable is unusual and underscores
Scheme 4. Elaboration of bicyclo[3.2.1]octane core.

![Diagram of bicyclo[3.2.1]octane core elaboration]

Reagents and conditions: a) thexylborane, THF, –10 °C, then NaOH, H₂O₂, 70%; b) TPAP (5 mol%), NMO, 4 Å MS, CH₂Cl₂, 83%; c) Et₂AlCN, PhMe, 0 °C to 10 °C, 61%; d) NaHMDMS, THF, –78 °C, then Comins’ reagent, THF, –78 °C to 0 °C, 74%; e) Pd(PPh₃)₃ (5 mol%), ZnMe₂, THF, 0 °C, 86%; f) PPTS, H₂O-acetone (1:9), 40 °C, 81%; g) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 80%; h) DIBAL–H, CH₂Cl₂, 0 °C to r.t., then aq. NaOH, silica gel, 0 °C to r.t., 71%; i) Cu, MeLi, BF₃·OEt₂, Et₂O, –78 °C to 10 °C, 89%; j) RuCl₃·xH₂O (20 mol%), NaIO₄, DCE–H₂O (5:4), 65%; k) LHMDS, THF, –78 °C to 0 °C; l) Ph₃PCH₂Br, KOt-Bu, THF, 0 °C to r.t., 79% (2 steps); m) DIBAL–H, CH₂Cl₂, 0 °C, 93%; n) KHMDS, Cs₂, THF, –78 °C to r.t., then MeI, 91%; o) AIBN (38 mol%), Bu₃SnH, PhH, 80 °C, 89%.

The severe steric hindrance of the constrained ring system. In this regard, it is important to note that all attempts at adding carbon nucleophiles to the tertiary nitrile to form the corresponding ketone proved futile under a wide range of conditions. Only exposure of the imine obtained from reduction of 17 to silica gel effected intramolecular aldol condensation to yield enone 18 in 71% yield. To the best of our knowledge, this represents a rare example of an enol ether adding to an unactivated N=C bond.[14]

Treatment of enone 18 under Yamamoto’s conditions[15] (MeLi, CuI, BF₃·OEt₂) effected conjugate addition in high yield and gave 19 as a single diastereomer (¹H NMR), whose structure was secured by X-ray crystallography. With the target’s bicyclo[3.2.1]octane core in hand, 19 was investigated as a substrate for the key ring expansion. Accordingly, oxidative cleavage of cyclohexene 19 gave the corresponding ketoaldehyde, which was treated with LHMDS to furnish ketoalcohol 20. Regioselective Wittig olefination, carbonyl reduction and deoxygenation under Barton–McCombie conditions[16] granted access to cycloheptene 21.

The exquisite diastereoselectivity in the conjugate addition to enone 18 reflects the strong inherent substrate bias towards addition from the Re face as a result of significant steric hindrance of the opposite Si face by the protruding methyl group at C-ε (Scheme 5). It should be noted that the susceptibility of enone 18 towards functionalization of the C-5 position proved instrumental and is likely the result of the stereoelectronic requirement for nucleophiles to approach the enone from an unhindered exocyclic trajectory (green arrow in 18).[17] In this respect, it is noteworthy that initial attempts at the functionalization of the C-5 position by 1,2-addition to closely related ketones as shown for 22 met with failure, as did attempted olefination. This resistance towards addition was attributed to severe steric hindrance by the protruding methyl groups at C-β and C-γ, which prevent nucleophiles from approaching the C-5 position along the endocyclic and exocyclic Bürgi–Dunitz trajectories.[18] This stands in stark contrast to the facile conjugate addition to enone 18 which allowed us to install the crucial methyl group and thus forge the target’s bicyclo[3.2.1]octane core in late-stage intermediate 21.

Scheme 5. Strategies for functionalization of C-5.

![Diagram of functionalization strategies]
In an initial end-game approach to the target, 21 was transformed into ketone 23 by ozonolysis (Scheme 6). Addition of MeMgBr led to formation of a tertiary alcohol in >19:1 dr and 87% yield. Molecular modelling suggests that additions to ketone 23 would be diastereoselective to give the configuration shown for 1. Unfortunately, the 'H and 13C NMR of synthetic material 1 failed to match that of the reported natural product. Specifically, the spectral discrepancies were largely relegated to the region surrounding the tertiary alcohol.

Our initial analysis of the reported spectral data had been cause for concern. In this respect, the isolation team had assigned the configuration at C-9 by NOE analysis that included the signals for the C-7 methylene group and the methyl groups at C-16, C-17, and C-19 as well as consideration of computational analysis (Scheme 7). Left without comment by the isolation team was the observation of a cross peak between the protons at δ 2.32 ppm and δ 1.43 ppm in the reported NOESY spectrum of the natural product. The former shift was assigned to the C-14 proton and the latter results from two overlapping singlets that correspond to the C-20 and C-19 methyl groups. This left unclear whether the observed NOE was due to the C-19 and/or the C-20 methyl group.

We proceeded to closely examine other members of the harziane diterpenoids. In this respect, the structure of 24 was confirmed by X-Ray crystallography, and, importantly, the NOESY spectrum does not possess a cross peak between the signals corresponding to H-14 and CH3-19. This data led us to hypothesize that the observed cross peak between 2.32 ppm and 1.43 ppm in the NOESY spectrum of the natural product indicates spatial proximity between H-14 and the methyl group at C-20. As such, the diastereomeric alcohol 2 was chosen as the most plausible alternative.

The epimeric tertiary alcohol (2) was accessed by hydration of alkene 21 (Scheme 6). Modelling suggested that the reaction would take place preferentially from the more exposed exocyclic face of the olefin, in accordance with the ketone addition previously executed (Scheme 6, 23 → 1). Accordingly, treatment of 21 under Mukaiyama hydration conditions led to formation of epimeric alcohol 2. Its configurational assignment was unequivocally secured by the observation of a NOESY cross peak between the CH3 group at C-20 and H-14 in C6D6 in which the methyl groups at C-19 and C-20 no longer overlap. To our delight, the spectral data of epimer 2 matched the reported data of the natural product ('H NMR, 13C NMR, IR, HRMS). Accordingly, the synthesis therefore constitutes a stereochemical revision of the harziane diterpenoid.
In conclusion, we achieved the first total synthesis of harziane diterpenoid tertiary alcohol and revised its configuration as shown for 2. The synthesis features application of a novel gold-catalyzed cycloisomerization reaction to install the target’s cyclobutane ring and associated quaternary stereocenter. Subsequent investigation of cyclization strategies led to the identification of an aldol addition strategy to forge the target’s tetracyclic core, followed by highly diastereoselective conjugate addition to install the challenging methyl group at C-5. These approaches provide strategic insight for the synthesis of the highly fused 6–5–7–4 ring system characteristic of the harziane diterpenoids.

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REFERENCES


(8) Later in the synthesis, crystal structures of advanced intermediates from each diene 4a and 4b further secured the configuration of the newly formed quaternary stereocenter (see SI). We ascribe the formation of the desired product (4) to the preferential formation of the more stable allyl cation 28 over allyl cation 29, which would lead to the undesired diastereomer:


For an example of a conjugate addition to a structurally related cyclohexenone, see: Liu, S.-A.; Trauner, D. Asymmetric Synthesis of the Antiviral Diterpene Wickerol J. Am. Chem. Soc. 2017, 139, 9491.
