Total Synthesis and Structural Revision of a Harziane Diterpenoid

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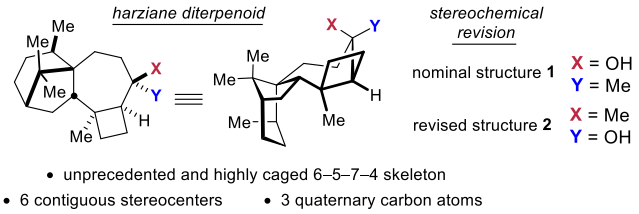
Abstract: The first total synthesis of nominal harziane diterpenoid **1** is disclosed, whose spectral characteristics did not match those of the reported natural product. Stereochemical analysis and subsequent synthesis of the epimeric tertiary alcohol led to reassignment of configuration of the natural 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 diastereocontrol. The route features strategies for the synthesis of the highly congested 6–5–7–4 carbon skeleton characteristic of the caged harziane diterpenoids.

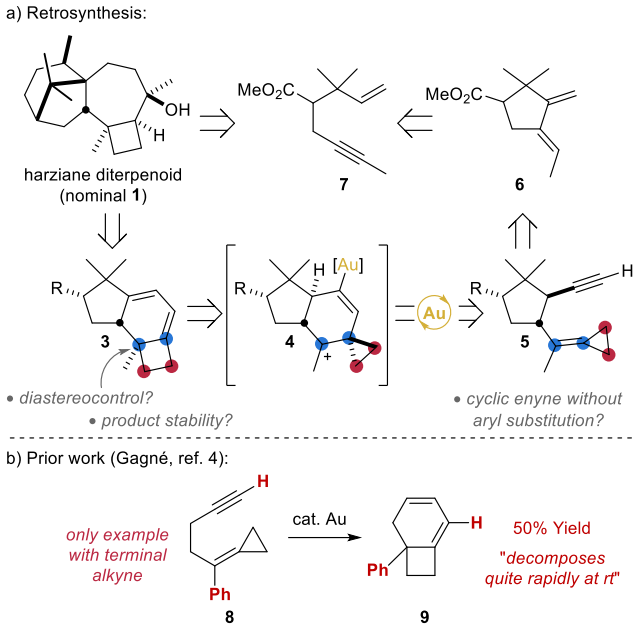
Trichoderma fungi are widespread phytosymbionts, which protect host plants from fungal pathogens and enhance root growth as well as nutrient uptake.[1] These fungi find commercial application as biocontrol agents and serve as a rich source of natural products, including the unnamed harziane diterpenoid **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 structural features render harziane diterpernoid **1** a challenging 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.

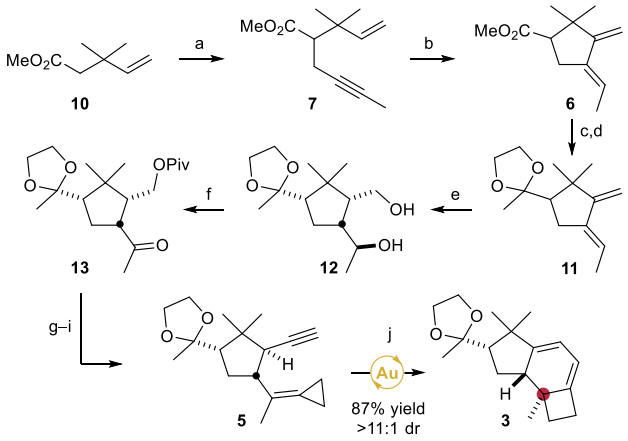
Ten harziane diterpenoids have been isolated of which eight share the unique 6–5–7–4 carbon skeleton.[2] They possess antifungal[2c] and cytotoxic[2e,2f] activity against two human cancer cell lines; moreover, microbially-derived metabolites exhibit anti-HIV and anti-inflammatory activity.[3] Despite 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 cyclopropylidenenynes 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 Gagné's seminal report[4] 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, the study did not include examples that would address whether the reaction would be diastereoselective. Enyne **5** was further retrodisconnected to diene **6**, which was accessed from enyne ester **7**.



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

The synthesis commenced with propargylation of readily available ester **10** to yield enyne **7**, followed by Pd-catalyzed cycloisomerization[6] 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_2O_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' dicyclopropyl titanocene reagent[7] 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.



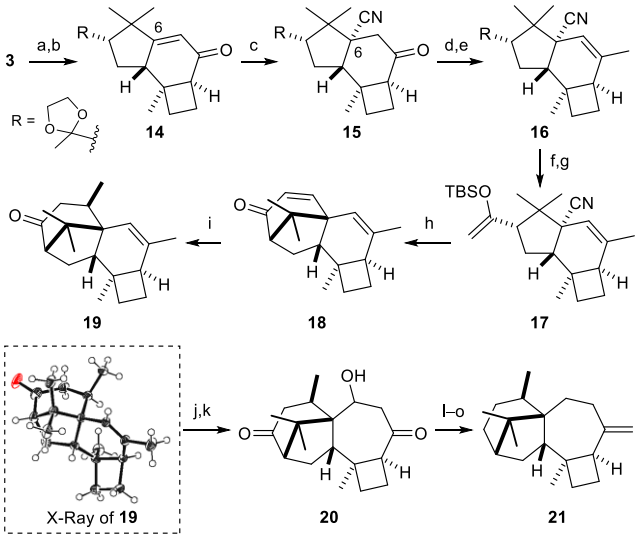
Scheme 3. Synthesis of diene **3**. Reagents and conditions: a) LDA, 1-bromobut-2-yne THF, –40 °C, 97%; b) $Pd(OAc)_2$ (20 mol%), BBEDA (20 mol%), PhH, 65 °C, 79%; c) MeNHOMe·HCl, MeMgBr, THF, –20 °C to –10 °C, 91%; d) ethylene glycol, $(EtO)_3CH$, PPTS (10 mol%), 78%; e) BH_3·THF, THF, 0 °C, then NaOH, H_2O_2, 63%, >4:1 dr; f) Piv–Cl, pyridine, CH_2Cl_2, –78 °C, then MeOH, DMP, $NaHCO_3$, CH_2Cl_2, 76%; g) $Cp_2Ti(C_3H_5)_2$, $NaHCO_3$, PhMe, 55 °C, then $LiAlH_4$, PhMe, 0 °C, 52%; h) NMO, TPAP (5 mol%), 4 Å MS, CH_2Cl_2, 93%; i) K_2CO_3, MeOH, then Ohira–Bestmann reagent, 87%; j) $Ph_3PAuNTf_2$ (3 mol%), CH_2Cl_2, –10 °C to 0 °C, 87%, >11:1 dr. THF=tetrahydrofuran, BBEDA=bis-benzylidene ethylenediamine, PPTS=pyridinium *p*-toluenesulfonate, DMP=Dess–Martin periodinane, NMO=4-methylmorpholine *N*-oxide, TPAP=tetrapropylammonium perruthenate.

We next addressed the key Au-catalyzed cycloisomerization reaction. It should be noted that the single study of the rearrangement[4] deals exclusively with acyclic enynes that incorporate at least one phenyl group either on the alkyne or alkylidenecyclopropane (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. $Ph_3PAuNTf_2$ in CH_2Cl_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 reactivity 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 **5** with 3 mol% $Ph_3PAuNTf_2$ at –10 °C furnished diene **3** in 87% yield and >11:1 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 (Et_2AlCN) gave ketonitrile **15** (62%).[11] Having set the second quaternary stereocenter, ring expansion of cyclohexanone **15** was explored next. The use of traditional methods (e.g. $TMSCHN_2/AlMe_3$[12a–c] or $TMSC(Li)N_2$[12d]) gave products consistent with a preference for migration of the cyclobutane over the alternative methylene group.[13] This inherent preference prevailed even when employing alternative reaction conditions known to favor migration of the less substituted methylene end, such as $TMSCHN_2/BF_3{\cdot}OEt_2$[12e–h] and $EtO_2CCHN_2/BF_3{\cdot}OEt_2$[12i] or Et_3OBF_4.[12j] 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_2Zn.

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 aldimine after aqueous workup and column chromatography. The fact that this aldimine is isolable is unusual and underscores 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



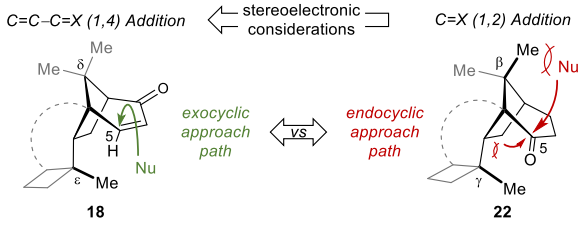
Scheme 4. Elaboration of bicyclo[3.2.1]octane core. Reagents and conditions: a) thexylborane, THF, –10 °C, then NaOH, H_2O_2, 70%; b) TPAP (5 mol%), NMO, 4 Å MS, CH_2Cl_2, 83%; c) Et_2AlCN, PhMe, 0 °C to 10 °C, 61% **15** + 24% 6-*epi*-**15**; d) NaHMDS, THF, –78 °C, then Comins' reagent, THF, –78 °C to 0 °C, 74%; e) $Pd(PPh_3)_4$ (5 mol%), $ZnMe_2$, THF, 0 °C, 86%; f) PPTS, H_2O–acetone (1:9), 40 °C, 81%; g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 80%; h) DIBAL–H, CH_2Cl_2, 0 °C to r.t., then aq. NaOH, silica gel, 0 °C to r.t., 71%; i) CuI, MeLi, $BF_3{\cdot}OEt_2$, Et_2O, –78 °C to 10 °C, 89%; j) $RuCl_3{\cdot}xH_2O$ (20 mol%), $NaIO_4$, DCE–H_2O (5:4), 65%; k) LHMDS, THF, –78 °C to 0 °C; l) Ph_3PCH_3Br, KO*t*-Bu, THF, 0 °C to r.t., 79% (2 steps); m) DIBAL–H, CH_2Cl_2, 0 °C, 93%; n) KHMDS, CS_2, THF, –78 °C to r.t., then MeI, 91%; o) AIBN (38 mol%), Bu_3SnH, PhH, 80 °C, 89%. TBSOTf=*tert*-butyldimethylsilyl trifluoromethanesulfonate, DIBAL–H=diisobutylaluminum hydride, DCE=1,2-dichloroethane, LHMDS=lithium bis(trimethylsilyl)amide, KHMDS=potassium bis(trimethylsilyl)amide, AIBN=2,2'-azobis(2-methylpropionitrile).

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.

Treatment of enone **18** under Yamamoto's conditions[14] (MeLi, CuI, $BF_3{\cdot}OEt_2$) effected conjugate addition in high yield and gave **19** as a single diastereomer (^{1}H 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[15] 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**).[16] 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

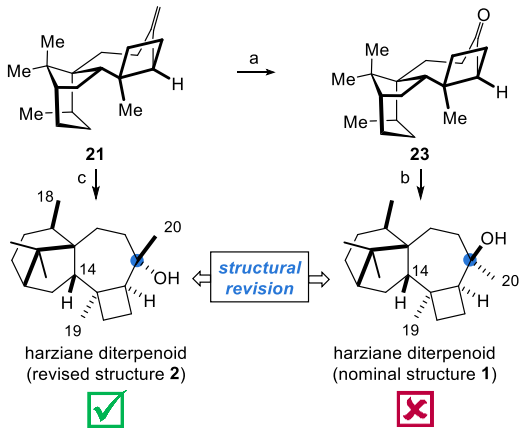
endocyclic and exocyclic Bürgi–Dunitz trajectories.[17] This stands in stark contrast to the facile conjugate addition to enone **18** which allowed us to install the crucial methyl group and thus forge the target's bicyclo[3.2.1]octane core in late-stage intermediate **21**.



Scheme 5. Strategies for functionalization of C-5.

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 ^{1}H and ^{13}C 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.

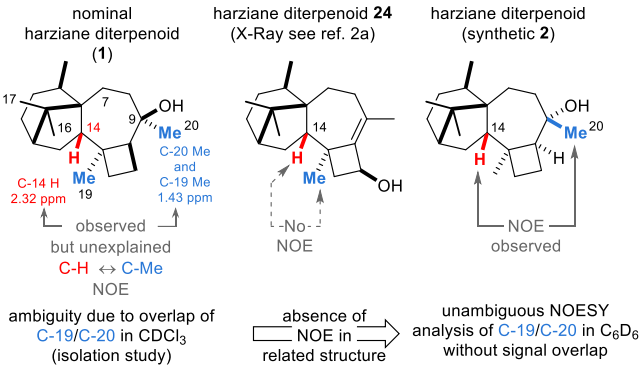
Our initial analysis of the reported spectral data had been cause for concern. In this respect, the isolation team had assigned the configuration at C-9 by NOE analysis that included the signals for the C-7 methylene group and the methyl groups at C-16, C-17, and C-19 as well as consideration of computational analysis (Scheme 7).[2a] 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.



Scheme 6. Completion and stereochemical revision. Reagents and conditions: a) O_3, MeOH–CH_2Cl_2 (3:2), –78 °C, then PPh_3, 78%; b) MeMgBr, Et_2O, 0 °C, 87%, >19:1 dr; c) $Co(acac)_2$ (18 mol%), O_2 (1 atm), $PhSiH_3$, THF, 83%.

We proceeded to closely examine other members of the harziane diterpenoids. In this respect, the structure of **24** was confirmed by X-Ray crystallography,[2a] and, importantly, the NOESY spectrum does not possess a cross peak between the signals corresponding to H-14 and CH_3-19. 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 spacial 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**.[18] Its configurational assignment was unequivocally secured by the observation of a NOESY cross peak between the CH_3-group at C-20 and H-14 in C_6D_6 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 (^{1}H NMR, ^{13}C NMR, IR, HRMS). Accordingly, the synthesis therefore constitutes a stereochemical revision of the harziane diterpenoid.



Scheme 7. Stereochemical reassignment of 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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Keywords: natural products • structural revision • gold catalysis • harziane diterpenoids • conjugate addition

[1] A. Schuster, M. Schmoll, *Appl. Microbiol. Biotechnol.* **2010**, *87*, 787-799.

[2] (a) E. Adelin, C. Servy, M.-T. Martin, G. Arcile; B. I. Iorga, P. Retailleau, M. Bonfill, J. Ouazzani, *Phytochemistry* **2014**, *97*, 55-61. (b) L. Barra, J. S. Dickschat, *ChemBioChem* **2017**, *18*, 2358-2365. (c) E. L. Ghisalberti, D. C. R. Hockless, C. Rowland, A. H. White, *J. Nat. Prod.* **1992**, *55*, 1690-1694. (d) L. Mannina, A. L. Segre, *Tetrahedron* **1997**, *53*, 3135-3144. (e) F.-P. Miao, X.-R. Liang, X.-L. Yin, W. Wang, N.-Y. Ji, *Org. Lett.* **2012**, *14*, 3815-3817. (f) M. Zhang, J.-M. Liu, J.-L. Zhao, N. Li, R.-D. Chen, K.-B. Xie, W.-J. Zhang, K.-P. Feng, Z. Yan, N. Wang,J.-G. Dai, *Chin. Chem. Lett.* **2016**, *27*, 957-960. (g) Y.-P. Song, S.-T. Fang, F.-P. Miao, X.-L. Yin, N.-Y. Ji, *J. Nat. Prod.* **2018**, *81*, 2553-2559; (h) Y.-P. Song, F.-P. Miao, X.-R. Liang, X.-L. Yin, N.-Y. Ji, *Phytochem. Lett.* **2019**, *32*, 38-41; (i) J.-X. Zou, Y.-P. Song, N.-Y. Ji, *Nat. Prod. Res.* **2019**, DOI: 10.1080/14786419.2019.1622110.

[3] (a) M. Zhang, J. Liu, R. Chen, J. Zhao, K. Xie, D. Chen, K. Feng, J. Dai, *Org. Lett.* **2017**, *19*, 1168-1171. (b) M. Zhang, J. Liu, R. Chen, J. Zhao, K. Xie, D. Chen, K. Feng, J. Dai, *Tetrahedron* **2017**, *73*, 7195-7199.

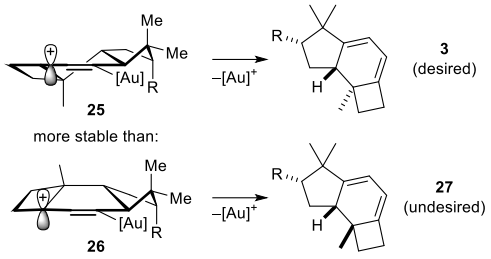
[4] H. Zheng, R. J. Felix, M. R. Gagné, *Org. Lett.* **2014**, *16*, 2272-2275.

[5] For other representative examples using Au catalysts for the synthesis of methylenecyclobutanes and related 4-membered rings, see: (a) S. G. Sethofer, S. T. Staben, O. Y. Hung, F. D. Toste, *Org. Lett.* **2008**, *10*, 4315-4318. (b) A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 4580-4583; (c) E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455; (d) J. P. Markham, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 9708-9709; (e) G. Li, X. Huang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 6944-6945; (f) F. Kleinbeck, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 9178-9179; for an example employing a Pt catalyst for the synthesis of cyclobutenes, see: (g) A. Fürstner, C. Aïssa, *J. Am. Chem. Soc.* **2006**, *128*, 6306-9307; (h) A. Masarwa; A. Fürstner; I. Marek, *Chem. Commun.* **2009**, *38*, 5760-5762; for further examples of applications of π-acid-catalyzed cycloisomerization reactions in total syntheses, see: (i) A. Fürstner, *Acc. Chem. Res.* **2014**, *47*, 925-938; (j) C. I. Stathakis, P. L. Gkizis, A. L. Zografos, *Nat. Prod. Rep.* **2016**, *33*, 1093-1117; (k) D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331-1367.

[6] (a) B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34-42. (b) B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan, C. T. MacPherson, *J. Am. Chem. Soc.* **1994**, *116*, 4255-4267.

[7] N. A. Petasis, E. I. Bzowej, *Tetrahedron Lett.* **1993**, *34*, 943-946.

[8] Later in the synthesis, crystal structures of advanced intermediates from diene **3** further secured the configuration of the newly formed quaternary stereocenter (see SI). We ascribe the formation of the desired product (**3**) to the preferential formation of the more stable allyl cation **25** over allyl cation **26**, which would lead to the undesired diastereoisomer:



[9] (a) H. C. Brown, E. Negishi, J.-J. Katz, *J. Am. Chem. Soc.* **1975**, *97*, 2791-2798. The observed regioselectivity is in accordance with reaction of the more strained double bond in **3**. The same regioselectivity was observed for the Birch reduction of a related diene: M. Kögl, L. Brecker, R. Warrass, J. Mulzer, *Angew. Chem. Int. Ed.* **2007**, *46*, 9320-9322.

[10] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, *21*, 1625-1627.

[11] W. Nagata, M. Yoshioka, *Tetrahedron Lett.* **1966**, *7*, 1913-1918. The relative configuration of the newly formed quaternary center was inferred from downstream products **18** and **19** using X-Ray crystallographic analysis (CCDC numbers 1963431 and 1963432).

[12] For a selection of examples, see: (a) S. Yang, B. Hungerhoff, P. Metz, *Tetrahedron Lett.* **1998**, *39*, 2097-2098. (b) A. K. Ghosh, B. D. Chapsal, A. Baldridge, M. P. Steffey, D. E. Walters, Y. Koh, M. Amano, H. Mitsuya, *J. Med. Chem.* **2011**, *54*, 622-634; (c) F. A. Macías, C. Carrera, N. Chinchilla, F. R. Fronczek, J. C. G. Galindo, *Tetrahedron* **2010**, *66*, 4125-4132; (d) H. Liu, C. Sun, N.-K. Lee, R. F. Henry, D. Lee, *Chem. Eur. J.* **2012**, *18*, 11889-11893; (e) N. Hashimoto, T. Aoyama, T. Shioiri, *Tetrahedron Lett.* **1980**, *21*, 4619-4622; (f) T. Sakai, S. Ito, H. Furuta, Y. Kawahara, Y. Mori, *Org. Lett.* **2012**, *14*, 4564-4567; (g) Y. Mori, K. Yaegashi, H. Furukawa, *J. Am. Chem. Soc.* **1997**, *119*, 4557-4558; (h) T. Kreuzer, P. Metz, *Eur. J. Org. Chem.* **2008**, 572-579; (i) H. J. Liu, S. P. Majumdar, *Synth. Commun.* **1975**, *5*, 125-130; (j) W. L. Mock, M. E. Hartman, *J. Org. Chem.* **1977**, *42*, 459-465.

[13] For reviews on the ring expansion reactions to form 7-membered rings, see (a) N. R. Candeias, R. Paterna, P. M. P. Gois, *Chem. Rev.* **2016**, *116*, 2937-2981; (b) E. J. Kantorowski, M. J. Kurth, *Tetrahedron* **2000**, *56*, 4317-4353; (c) P. Dowd, W. Zhang, *Chem. Rev.* **1993**, *93*, 2091-2115.

[14] Y. Yamamoto, K. Maruyama, *J. Am. Chem. Soc.* **1978**, *100*, 3240-3241.

[15] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, *16*, 1574-1585.

[16] For an example of a conjugate addition to a structurally related cyclohexenone, see: S.-A. Liu, D. Trauner, *J. Am. Chem. Soc.* **2017**, *139*, 9491-9494.

[17] H. B. Bürgi, J. D. Dunitz, E. Shefter, *J. Am. Chem. Soc.* **1973**, *95*, 5065-5067.

[18] S. Isayama, T. Mukaiyama, *Chem. Lett.* **1989**, *18*, 1071-1074. The observed diastereoselectivity (>5:1 dr) is consistent with attack on the more exposed face of the intermediate tertiary radical.