Total Synthesis and Structural Revision of a Harziane Diterpenoid

Moritz Hönig and Erick M. Carreira*

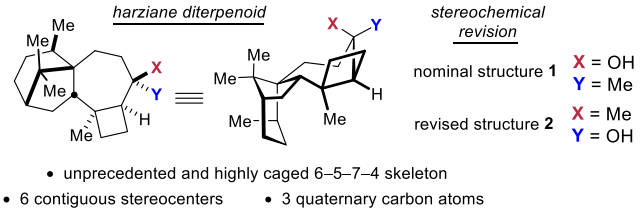
ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland.

* E-mail: erickm.carreira@org.chem.ethz.ch

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 challenging structural features render harziane diterpernoid **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.

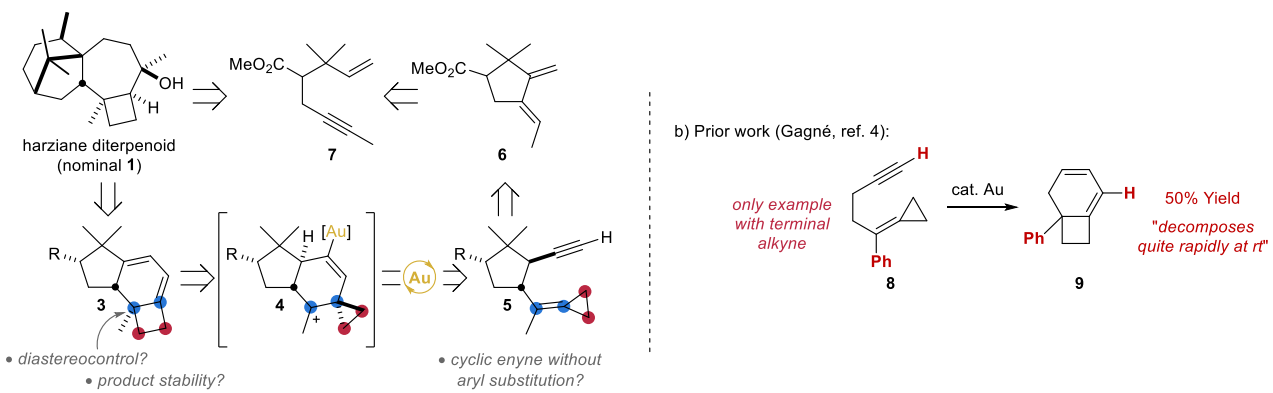
Scheme 1. Nominal and revised Harziane diterpenoid.



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 cyclopropylidenenynes to methylenecyclobutanes by Gagné,[4,5] we envisioned accessing the target's cyclobutane ring and quaternary stereocenter from alkynyl methelene substituted substrate **5**. It should be noted that

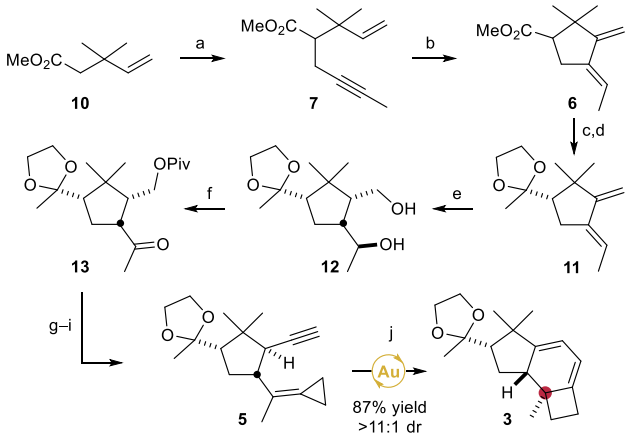
Scheme 2. a) Retrosynthesis and b) prior work.



prior methodological studies[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, 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[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[8] 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.



[a]Reagents and conditions: a) LDA, 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.

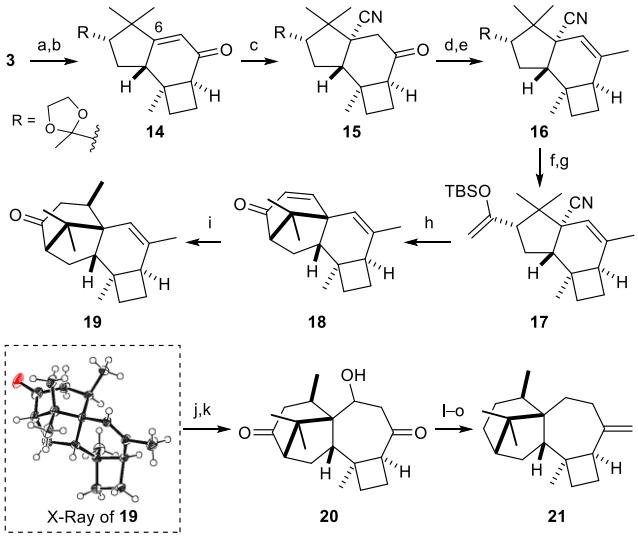
We next addressed the key Au-catalyzed cycloisomerization reaction. It should be noted that the single study of the rearrangement[4] deals exclusively with acyclic enynes that incorporate at least one phenyl group either on the alkyne or alkylidenecyclopropane (Scheme 2b). Moreover, the investigation 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 **6** 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[11] (Et_2AlCN) gave ketonitrile **15** (62%). 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

Scheme 4. Elaboration of bicyclo[3.2.1]octane core.[a]



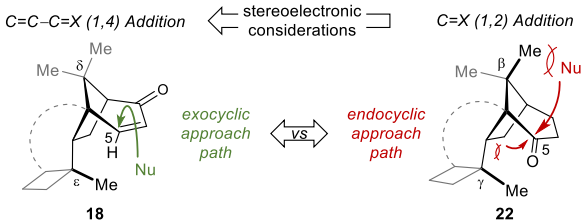
[a]Reagents and conditions: a) thexylborane, THF, –10 °C, then NaOH, H_2O_2, 70%; b) TPAP (5 mol%), NMO, 4 Å MS, CH_2Cl_2, 83%; c) Et_2AlCN, PhMe, 0 °C to 10 °C, 61%; d) NaHMDS, THF, –78 °C, then Comins' reagent, THF, –78 °C to 0 °C, 74%; e) $Pd(PPh_3)_4$ (5 mol%), $ZnMe_2$, THF, 0 °C, 86%; f) PPTS, 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%.

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-H imine.[14]

Treatment of enone **18** under Yamamoto's conditions[15] (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[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**.

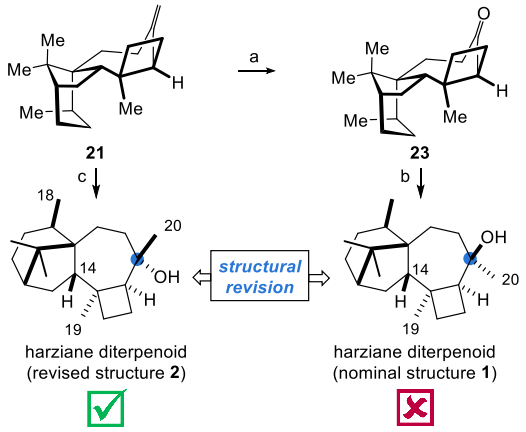
Scheme 5. Strategies for functionalization of C-5.



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.

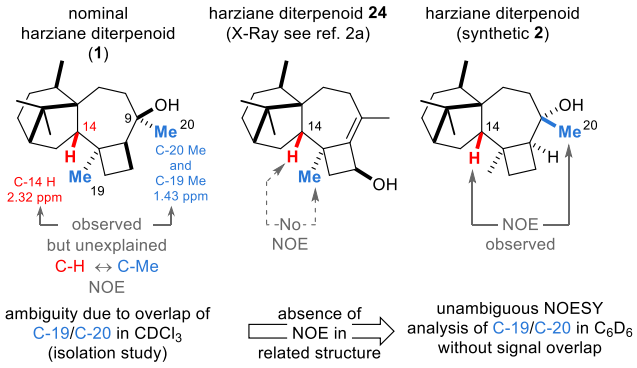
Our initial analysis of the reported spectral data had been cause for concern. In this respect, the isolation team had assigned the configuration at C-9 by NOE analysis that included the signals for the C-7 methylene group and the methyl groups at C-16, C-17, and C-19 as well as consideration of computa-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



[a]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%.

Scheme 7. Stereochemical reassignment of harziane diterpenoid.[a]



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[19] led to formation of epimeric alcohol **2**. 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.

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.

ACKNOWLEDGMENT

We acknowledge Dr. Jamal Ouazzani and Dr. Géraldine Le Goff of CNRS, France, for providing a ^{13}C-NMR spectrum of the isolated natural product. We are grateful to Dr. N. Trapp and M. Solar for X-ray crystallographic analysis. M.H. acknowledges a fellowship of the Stipendienfonds Schweizerische Chemische Industrie (SSCI). We thank Julia Reisenbauer for conducting synthetic studies towards derivatives of **3** and Lukas Lüthy for conducting synthetic studies towards derivatives of **14**.

REFERENCES

(1) Schuster, A.; Schmoll, M. Biology and biotechnology of *Trichoderma Appl. Microbiol. Biotechnol.* **2010**, *87*, 787.

(2) (a) Adelin, E.; Servy, C.; Martin, M.-T., Arcile, G.; Iorga, B. I.; Retailleau, P.; Bonfill, M.; Ouazzani, J. Bicyclic and tetracyclic diterpenes from a *Trichoderma* symbiont of *Taxus baccata Phytochemistry* **2014**, *97*, 55. (b) Barra, L.; Dickschat, J. S. Harzianone Biosynthesis by the Biocontrol Fungus *Trichoderma ChemBioChem* **2017**, *18*, 2358. (c) Ghisalberti, E. L.; Hockless, D. C. R.; Rowland, C.; White, A. H. Harziandione, a New Class of Diterpene from *Trichoderma Harzianum J. Nat. Prod.* **1992**, *55*, 1690. (d) Mannina, L.; Segre, A. L. A New Fungal Growth Inhibitor from *Trichoderma viride Tetrahedron* **1997**, *53*, 3135. (e) Miao, F.-P.; Liang, X.-R.; Yin, X.-L.; Wang, W.; Ji, N.-Y. Absolute Configurations of Unique Harziane Diterpenes from *Trichoderma* Species *Org. Lett.* **2012**, *14*, 3815. (f) Zhang, M.; Liu, J.-M.; Zhao, J.-L.; Li, N.; Chen, R.-D.; Xie, K.-B.; Zhang, W.-J.; Feng, K.-P.; Yan, Z.; Wang, N.; Dai, J.-G. Two new diterpenoids from the endophytic fungus *Trichoderma* sp. Xy24 isolated from mangrove plant *Xylocarpus granatum Chin. Chem. Lett.* **2016**, *27*, 957. (g) Song, Y.-P.; Fang, S.-T.; Miao, F.-P.; Yin, X.-L.; Ji, N.-Y. Diterpenes and Sesquiterpenes from the Marine Algicolous Fungus *Trichoderma harzianum* X-5 *J. Nat. Prod.* **2018**, *81*, 2553; (h) Song, Y.-P.; Miao, F.-P.; Liang, X.-R.; Yin, X.-L.; Ji, N.-Y. Harziane and cadinene terpenoids from the alga-endophytic fungus *Trichoderma asperellum* A-YMD-9-2 *Phytochem. Lett.* **2019**, *32*, 38; (i) Zou, J.-X.; Song, Y.-P.; Ji, N.-Y. Deoxytrichodermaerin, a harziane lactone from the marine algicolous fungus *Trichoderma longibrachiatum* A-WH-20-2 *Nat. Prod. Res.* **2019**, DOI: 10.1080/14786419.2019.1622110.

(3) (a) Zhang, M.; Liu, J.; Chen, R.; Zhao, J.; Xie, K.; Chen, D.; Feng, K.; Dai, J. Two Furanharzianones with 4/7/5/6/5 Ring System from Microbial Transformation of Harzianone *Org. Lett.* **2017**, *19*, 1168. (b) Zhang, M.; Liu, J.; Chen, R.; Zhao, J.; Xie, K.; Chen, D.; Feng, K.; Dai, J. Microbial oxidation of harzianone by *Bacillus* sp. IMM-006 *Tetrahedron* **2017**, *73*, 7195.

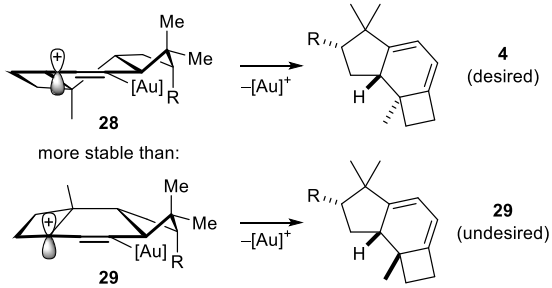
(4) Zheng, H.; Felix, R. J.; Gagné, M. R. Gold-Catalyzed Enantioselective Ring-Expanding Cycloisomerization of Cyclopropylidene Bearing 1,5-Enynes *Org. Lett.* **2014**, *16*, 2272.

(5) For other representative examples using Au catalysts for the synthesis of methylenecyclobutanes and related 4-membered rings, see: (a) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. Au(I)-Catalyzed Ring Expanding Cycloisomerizations: Total Synthesis of Ventricosene *Org. Lett.* **2008**, *10*, 4315. (b) Pitaval, A.; Leboeuf, D.; Ceccon, J.; Echavarren, A. M. Access to the Protoilludane Core by Gold-Catalyzed Allene-vinylcyclopropane Cycloisomerization *Org. Lett.* **2013**, *15*, 4580; (c) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. Prins Cyclizations in Au-Catalyzed Reactions of Enynes *Angew. Chem. Int. Ed.* **2006**, *45*, 5452; (d) Markham, J. P.; Staben, S. T.; Toste, F. D. Gold(I)-Catalyzed Ring Expansion of Cyclopropanols and Cyclobutanols *J. Am. Chem. Soc.* **2005**, *127*, 9708; (e) Li, G.; Huang, X.; Zhang, L. Au(I)-Catalyzed Efficient Synthesis of Functionalized Bicyclo[3.2.0]heptanes *J. Am. Chem. Soc.* **2008**, *130*, 6944; (f) Kleinbeck, F.; Toste, F. D. Gold(I)-Catalyzed Enantioselective Ring Expansion of Allenylcyclopropanols *J. Am. Chem. Soc.* **2009**, *131*, 9178; for an example employing a Pt catalyst for the synthesis of cyclobutenes, see: (g) Fürstner, A.; Aïssa, C. $PtCl_2$-Catalyzed Rearrangement of Methylenecyclopropanes *J. Am. Chem. Soc.* **2006**, *128*, 6306.

(6) (a) Trost, B. M. Palladium-catalyzed cycloisomerizations of enynes and related reactions *Acc. Chem. Res.* **1990**, *23*, 34. (b) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, C. T. Pd-Catalyzed Cycloisomerization to 1,2-Dialkylidenecycloalkanes. 1 *J. Am. Chem. Soc.* **1994**, *116*, 4255.

(7) Petasis, N. A.; Bzowej, E. I. Biscyclopropyl Titanocene: A Novel Reagent for the Synthesis of Alkylidene and Vinyl Cyclopropanes *Tetrahedron Lett.* **1993**, *34*, 943.

(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 diasteroisomer:



(9) Brown, H. C.; Negishi, E.; Katz, J.-J. Hydroboration. XXXVII. Structural study of the hydroboration of olefins with thexylborane in the molar ratio of 1:1. Convenient synthesis of thexylmonoalkylboranes and their ready conversion to monoalkylboranes *J. Am. Chem. Soc.* **1975**, *97*, 2791.

(10) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. Preparation and Use of Tetra-n-butylammonium Per-ruthenate (TBAP) and Tetra-n-propylammonium Per-ruthenate (TPAP reagent) as New Catalytic Oxidants for Alcohols *J. Chem. Soc. Chem. Commun.* **1987**, *21*, 1625.

(11) Nagata, W.; Yoshioka, M. Alkylaluminum cyanides as potent reagents for hydrocyanation *Tetrahedron Lett.* **1966**, *7*, 1913.

(12) For a selection of examples, see: (a) Yang, S.; Hungerhoff, B.; Metz, P. A Short Conversion of Cyclohexanones to Cycloheptenones *Tetrahedron Lett.* **1998**, *39*, 2097. (b) Ghosh, A. K.; Chapsal, B. D.; Baldridge, A.; Steffey, M. P.; Walters, D. E.; Koh, Y.; Amano, M.; Mitsuya, H. Design and Synthesis of Potent HIV-1 Protease Inhibitors Incorporating Hexahydrofuropyranol-Derived High Affinity P_2 Ligands: Structure–Activity Studies and Biological Evaluation *J. Med. Chem.* **2011**, *54*, 622; (c) Macías, F. A.; Carrera, C.; Chinchilla, N.; Fronczek, F. R.; Galindo, J. C. G. Synthesis of the western half of breviones C, D, F and G *Tetrahedron* **2010**, *66*, 4125; (d) Liu, H.; Sun, C.; Lee, N.-K.; Henry, R. F.; Lee, D. New Methylene Homologation Method for Cyclic Ketones *Chem. Eur. J.* **2012**, *18*, 11889; (e) Hashimoto, N.; Aoyama, T.; Shioiri, T. New Methods and Reagents in Organic Synthesis. 10. Trimethylsilyldiazomethane($TMSCHN_2$). A new, stable, and safe Reagent for the Homologation of Ketones *Tetraedron Lett.* **1980**, *21*, 4619; (f) Sakai, T.; Ito, S.; Furuta, H.; Kawahara, Y.; Mori, Y. Mechanism of the Regio- and Diastereoselective Ring Expansion Reaction Using Trimethylsilylyldiazomethane *Org. Lett.* **2012**, *14*, 4564; (g) Mori, Y.; Yaegashi, K.; Furukawa, H. Oxiranyl Anions in Organic Synthesis: Application tot he Synthesis of Hemibrevetoxin B *J. Am. Chem. Soc.* **1997**, *119*, 4557; (h) Kreuzer, T.; Metz, P. Enantioselective Synthesis oft he Hydroazulene Core of 3α-Hydroxy-15-rippertene *Eur. J. Org. Chem.* **2008**, 572; (i) Liu, H. J.; Majumdar, S. P. On the Regioselectivity of Boron Trifluoride Catalyzed Ring Expansion of Cycloalkanones with Ethyl Diazoacetate *Synth. Commun.* **1975**, *5*, 125; (j) Mock. W. L., Hartman, M. E. Synthetic Scope of the Triethyloxonium Ion catalyzed Homologation of Ketones with Diazoacetic Esters *J. Org. Chem.* **1977**, *42*, 459.

(13) For reviews on the ring expansion reactions to form 7-membered rings, see (a) Candeias, N. R.; Paterna, R.; Gois, P. M. P. Homologation Reaction of Ketones with Diazo Compounds *Chem. Rev.* **2016**, *116*, 2937; (b) Kantorowski, E. J.; Kurth, M. J. Expansion to Seven-Membered Rings *Tetrahedron* **2000**, *56*, 4317; (c) Dowd, P.; Zhang, W. Free Radical-Mediated Ring Expansion and Related Annulations *Chem. Rev.* **1993**, *93*, 2091.

(14) Examples for the addition of silyl enol ethers to *N*-tosyl imines include: (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. Catalytic, Enantioselective Alkylation of α-Imino Esters Using Late Transition Metal Phosphine Complexes as Catalysts *J. Am. Chem. Soc.* **1998**, *120*, 4548; (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. Catalytic, Enantioselective Alkylation of α-Imino Esters: The Synthesis of Nonnatural α-Amino Acid Derivatives *J. Am. Chem. Soc.* **2002**, *124*, 67; Examples for the addition of ketones to NH imines include: (c) Sawa, M.; Morisaki, K.; Kondo, Y.; Morimoto, H.; Ohshima, T. Direct Access to N-Unprotected α- and/or β-Tetrasubstituted Amino Acid Esters via Direct Catalytic Mannich-Type Reactions Using N-Unprotected Trifluoromethyl Ketimines *Chem. Eur. J.* **2017**, *23*, 17022; (d) Sawa, M.; Miyazaki, S.; Yonesaki, R.; Morimoto, H.; Ohshima, T. Catalytic Enantioselective Decarboxylative Mannich-Type Reaction of *N*-Unprotected Isatin-Derived Ketimines *Org. Lett.* **2018**, *20*, 5393; (e) Gale, D. M.; Krespan, C. G. Fluoroalkylamines *J. Org. Chem.* **1968**, *33*, 1002; (f) Hara, N.; Tamura, R.; Funahashi, Y.; Nakamura, S. *N*-(Heteroarenesulfonyl)prolinamides-Catalyzed Aldol Reaction between Acetone and Aryl Trihalomethyl Ketones *Org. Lett.* **2011**, *13*, 1662.

(15) Yamamoto, Y.; Maruyama, K. $RCu{\cdot}BF_3$. 3. Conjugate Addition to Previously Unreactive Substituted Enoate Esters and Enoic Acids *J. Am. Chem. Soc.* **1978**, *100*, 3240.

(16) Barton, D. H. R.; McCombie, S. W. A New Method for the Deoxygenation of Secondary Alcohols *J. Chem. Soc. Perkin Trans. 1* **1975**, *16*, 1574.

(17) 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 A *J. Am. Chem. Soc.* **2017**, *139*, 9491.

(18) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group. *J. Am. Chem. Soc.* **1973**, *95*, 5065.

(19) Isayama, S.; Mukaiyama, T. A New Method for Preparation of Alcohols from Olefins with Molecular Oxygen and Phenylsilane by the Use of Bis(acetylacetonate)cobalt(II) *Chem. Lett.* **1989**, *18*, 1071.