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Total Synthesis of Kadcoccinic Acid A Trimethyl Ester

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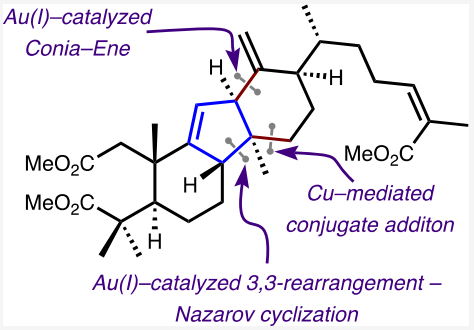
ABSTRACT: The first total synthesis of the trimethyl ester of kadcoccinic acid A is described. The central structural element of our synthesis is a cyclopentenone motif that allows the assembly of the natural product skeleton. A gold(I)-catalyzed cyclization of an enynyl acetate led to efficient construction of the cyclopentenone scaffold. In this step, optimization studies revealed that the stereochemistry of the enynyl acetate dictates regioisomeric cyclopentenone formation. The synthesis further highlights an efficient copper-mediated conjugate addition, merged with a gold(I)-catalyzed Conia-ene reaction to connect the two fragments, thereby forging the D-ring of the natural product. The synthetic strategy reported herein can provide a general platform to access the skeleton of other members of this family of natural products.



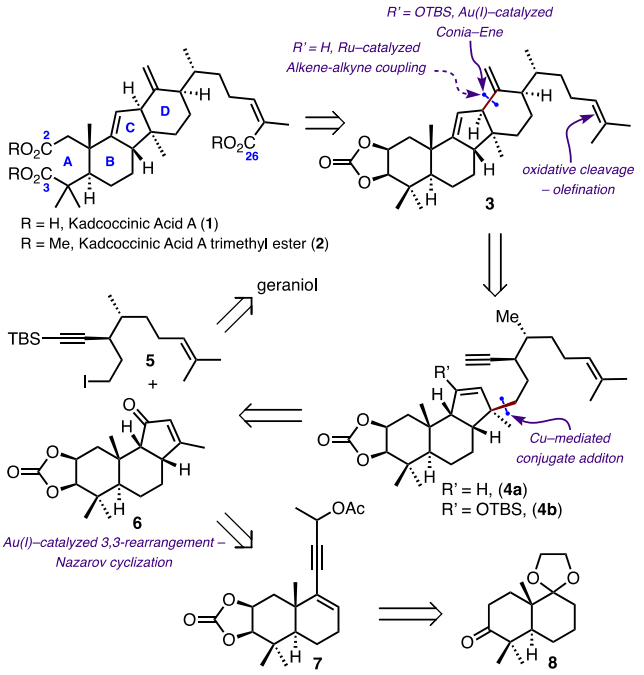
INTRODUCTION

The *Kadsura* species belong to the family of Schisandraceae, a rich source of complex polycyclic structures and triterpenoids.[1] These plants are commonly used as traditional Chinese herbal medicines for the treatment of a wide array of diseases such as gastroenteric disorders, duodenal ulcers, and gynecological problems to name a few.[2] Some of the compounds isolated from these plants were tested for their activities as antihepatitis, antitumor, anti-HIV activities, and so forth.[2] Kadcoccinic acids are a newly discovered subset of triterpenoid natural products isolated form *Kadsura coccinea*, also named as "Heilaohu", a climbing plant distributed in the southwestern provinces of China.[3] Due to the complex composition of these traditional medicines, little is known about the mechanism and pharmacological action of these compounds. Establishing a synthetic method to access the core structure of this family of natural products and their viable analogs would be impactful for future structural determination, as well as phytochemical and pharmacological research on *Kadsura coccinea*.

Structurally, kadcoccinic acids possess a rearranged lanostane structure, which is a very common natural product framework featuring a 6/6/5/6-fused tetracyclic ring system (named as rings A–D). Kadcoccinic acid A (**1**) in particular is one of the first isolated compounds of this family that features a 2,3-*seco*-6/6/5/6-fused tetracyclic triterpenoid skeleton. This triacid consists of a tricyclic core with a unique skipped diene motif and seven stereogenic centers. So far, the synthesis of kadcoccinic acids or any of their closely related analogues has not been achieved. Herein, we report a total synthesis of kadcoccinic acid A trimethyl ester (**2**), which could enable rapid access to this intriguing family of natural products.

In a retrosynthetic perspective, we envisioned a C2–C3 vicinal diol as a surrogate to install the dicarboxylic acid of the natural product at a late stage of synthesis (Scheme 1). This

Scheme 1. Kadcoccinic Acid A (1), Its Trimethyl Ester (2), and a Retrosynthetic Analysis



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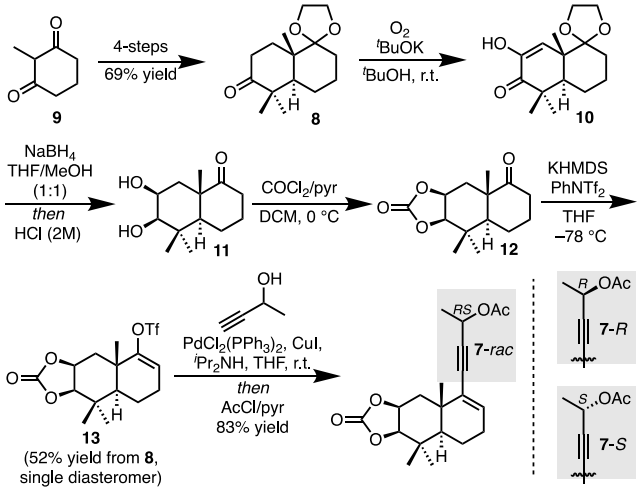
strategy would allow to selectively cleave the latter C−C bond and it would also add extra polarity to an otherwise very non-polar hydrocarbon skeleton throughout the synthetic route. One of the key features of kadcoccinic acid A that motivated us to pursue a synthetic endeavor was the skipped 1,4-diene. Stemming from our long-standing interest in the utilization of transition metal catalyzed alkene-alkyne coupling and cycloisomerization reactions, we envisioned to access the skipped diene of kadcoccinic acid A via an intramolecular Ru-catalyzed alkene-alkyne coupling reaction of the enyne compound **4a**.[4] Alternatively, the D ring can also be obtained through a gold(I)-catalyzed intramolecular Conia-ene reaction of a silyl enol ether moiety into the pendant terminal alkyne.[5] Intermediate **4b** could be obtained from a copper-mediated conjugate addition of an alkyl lithium reagent from alkyl iodide **5** into enone **6**. The cyclopentenone core in **6** could be accessed via a key gold(I)-catalyzed enynyl acetate [3,3]-rearrangement followed by a Nazarov cyclization.[6] Enynyl acetate 7 could be accessed from ketone **8**, and the side chain **5** could be synthesized from geraniol.

RESULTS AND DISCUSSION

Our synthesis commenced with the known ketone **8** that was prepared from 2-methyl-1,3-cyclohexadione (**9**) in four steps and 69% overall yield (Scheme 2).[7] With the well-defined

Scheme 2. Synthetic Route to Access Enynyl Acetate 7



geometry of the *trans*-decalin core in **8** to drive the following diastereoselective reactions, we set out to install a handle for late stage cleavage of C2−C3 bond in **8**. A highly efficient aerobic oxidation of the α-carbon to the carbonyl in **8** was carried out by using potassium *tert*-butoxide in *tert*-butanol under an atmosphere of oxygen.[8] The resulting α-diketone **10** (exists as keto−enol) was directly subjected to sodium borohydride reduction to deliver the *syn*-diol **11** after deprotection of the acetal group under the acidic workup conditions. The resulting diol was protected as a cyclic carbonate and the ketone group in **12** was elaborated to vinyl triflate **13** in 52% overall yield and as a single isolable diastereomer from ketone **8**. Sonogashira coupling of vinyl triflate **13** with the racemic 2-butyne-3-ol followed by acetylation of the resultant propargylic alcohol delivered the enynyl acetate 7-*rac* in 83% yield as a 1:1 diastereomeric mixture due to the newly added stereocenter.

With enynyl acetate 7-*rac* in hand, we set out to carry out the key cyclization reaction by following the reported procedure by the Zhang group.[6,9] Treatment of 7-*rac* with $AuCl(PPh_3)/AgSbF_6$ in wet CH_2Cl_2 led to complete conversion of the starting material and formation of the desired cyclopentenone **6** and its enol acetate **14** as well as the undesired cyclopentenone **15** (entry 1, Table 1). In contrast to the reported procedure by the Zhang group, the enol acetate **14** was not fully hydrolyzed to **6** under the gold-catalyzed conditions, presumably due to steric hindrance.[6] Nonetheless, treatment of reaction mixture with bis(trifluoromethanesulfonyl)amine (Tf_2NH) led to hydrolysis of the enol acetate and the desired product **6** was isolated in moderate yield of 38%. Less electrophilic NHC-based gold complex ($IPrAuNTf_2$) led to a slightly improved ratio of **14** to **15** since hydrolysis of **15** was not observed under the reaction condition and **6** was isolated after treatment of the mixture with Tf_2NH in 36% yield (entry 2). Screening of other solvents did not lead to further improvement of the reaction results. Using acetone as solvent resulted in completion of the reaction and **14** and **15** were isolated in nearly equal yields (entry 3). Other solvents such as toluene and THF only gave partial conversion of the starting material even after extended reaction times (entries 4 and 5). With acetone as solvent, in situ generation of the activated gold complexes did not improve the ratio of the desired product (entries 6 and 7). Interestingly, $[JohnPhosAu(CH_3CN)]SbF_6$ as catalyst, with its sterically demanding ligand, resulted in partial conversion of the starting material 7-*rac* in ∼2 h and more importantly, predominantly the desired enol acetate **14** was observed based on ^1H NMR analysis (entry 7). These results indicate the impact of the stereochemistry of the enynyl acetate center in 7-*rac* (1:1 *dr* at the propargylic acetate carbon), on the observed product distribution.

To further deconvolute this stereochemical effect, we prepared 7-*R* and 7-*S* by coupling the vinyl triflate **13** with enantiopure (*R*)-2-butyn-3-ol and (*S*)-2-butyn-3-ol to access 7-*R* and 7-*S* in 75% and 82% yields, respectively (Scheme 2). In agreement with our hypothesis, these two diastereomers led to complementary products upon treatment with catalytic $IPrAuNTf_2$ in acetone. Enynyl acetate 7-*R* predominantly led to the undesired regioisomeric cyclopentenone **15** (entry 9), while 7-*S* under the same reaction conditions, gave rise mainly to enol acetate **14** and cyclopentenone **6** was isolated in 57% yield after hydrolysis (entry 10). Carrying out the reaction of 7-*S* in CH_2Cl_2 as solvent gave a slightly improved ratio of the desired product **14** and 66% isolated yield of cyclopentenone **6** after hydrolysis (entry 11). Furthermore, performing the reaction of 7-*S* at 4 °C in CH_2Cl_2, instead of room temperature, led to exclusive formation of **14** and 91% isolated yield of this compound (Table 1, entry 12, see the Supporting Information (SI) for the stacked NMR spectra of 7-*rac*, 7-*S*, and 7-*R* under gold catalysis). Transfer of chirality from optically pure enynyl acetate to the ensuing cyclization product has been demonstrated and harnessed in total synthesis of natural products.[10] However, the current diastereodivergent phenomenon has not been disclosed before. Thus these findings could lead to applications in the stereoselective synthesis of regioisomeric cyclopentenones controlled by the stereochemistry of the enynyl acetate and add to the toolbox of total synthesis empowered by gold catalysis.[11]

With these results in hand, the enone **6** was obtained in 66% isolated yield from the enynyl acetate 7-*S* with 3 mol %

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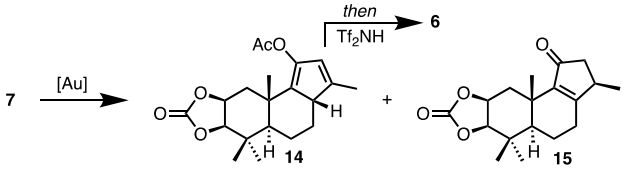
Table 1. Gold(I)-Catalyzed Nazarov Cyclization of 7[a]



entry[a]	7	[Au] (5 mol %)	solvent	conv.[b] (%)	14:15[b]	yield (%)[c] 14/15/6
1[d]	7-*rac*	$AuCl(PPh_3)_3/AgSbF_6$	CH_2Cl_2	>95	1:1.5[e]	−/−/38
2[d]	7-*rac*	$IPrAuNTf_2$	CH_2Cl_2	90	1.4:1	−/−/36
3	7-*rac*	$IPrAuNTf_2$	acetone	>95	1:1	46/43/−
4[f]	7-*rac*	$IPrAuNTf_2$	$PhCH_3$	20	1:1	−/−/−
5[f]	7-*rac*	$IPrAuNTf_2$	THF	40	1.5:1	−/−/−
6	7-*rac*	$AuCl(PPh_3)_3/AgSbF_6$	acetone	>95	1:1	41/46/−
7	7-*rac*	$IPrAuCl/AgSbF_6$	acetone	>95	1:1	44/52/−
8	7-*rac*	$[JohnPhosAu(CH_3CN)]SbF_6$	acetone	60	6:1	−/−/−
9	7-*R*	$IPrAuNTf_2$	acetone	>95	1:5	−/−/−
10	7-*S*	$IPrAuNTf_2$	acetone	>95	5:1	−/−/57
11	7-*S*	$IPrAuNTf_2$	CH_2Cl_2	>95	6:1	−/−/66
12[h]	7-*S*	$IPrAuNTf_2$	CH_2Cl_2	>95	>20:1	91/−/69

[a]Reactions were performed with **7** (0.1 mmol, 0.4 M conc.) at room temperature for 3−5 h; Cyclopentenone **6** is obtained by treatment of the reaction mixture with Tf_2NH solution (10 mol % in CH_2Cl_2). [b]Conversions of **7** and the ratios of **14**:**15** are estimated from ^{1}H-NMRs. [c]Yields of isolated products. [d]Wet dichloromethane was used. [e]A portion of **14** was hydrolyzed to **6** under the reaction conditions; ratio of **14**+**6** is nearly equal to **15**. [f]Reaction time was 18 h. [g]Conversion after 2 h. [h]Reaction was performed at 4 °C for 12 h.

$IPrAuNTf_2$ in CH_2C_2 as solvent followed by a mild acidic hydrolysis using a CH_2Cl_2 solution of Tf_2NH (Scheme 3a). The relative stereochemistry of enone **6** was established using *NOESY* spectroscopy. Some of the important *NOESY* correlations in **6** are shown in Scheme 3a (see the SI for additional details).

Analogous to the mechanism reported by the Zhang group,[6] and the work of Fensterbank and Malacria,[12,10b] we have proposed a simplified mechanism for the gold(I)-catalyzed [3,3]-rearrangement/Nazarov-type cyclization of enynyl acetate **7** with emphasis on the observed diastereodivergent phenomenon (Scheme 3b). The enynyl acetate moiety in **7** would undergo a [3,3]-rearrangement in the presence of the gold(I) catalyst leading to the allenoic acetates **16**-*S* and **16**-*R*. While **7**-*rac* would lead to *pseudo*-enantiomeric allenoic acetates (**16**-*S* and **16**-*R*) in an equal ratio, **7**-*S* and **7**-*R* would exclusively generate **16**-*S* and **16**-*R*, respectively. These intermediates would then coordinate to the gold(I) catalyst through the central carbon of allene, leading to the so-called "bent-allene"[12,10b] complexes **17a** and **17b**. On the basis of the reported studies, presence of bent-allene intermediates is fundamental to retain and transfer the chirality of the allenoic acetates to the ensuing intermediates. Intermediates **17a** and **18a** (also illustrated by their resonance forms **17b** and **18b**) are precursors for the cyclization reactions. Electrocyclic ring closure of **17b** and **18b** would give rise to **19** and **21**, respectively. Analogous to the precedent reports,[10b,e,f,9] transfer of chirality from bent-allenes **17a** and **18a** leads to the cyclized intermediates **19a** and **20a** with the illustrated stereochemistries. Au-carbenoids **19a** and **20a** would then undergo a facile 1,2-hydride shift, followed by the collapse of carbocations **19b** and **20b** to deliver the enol acetates **14** and **21**, respectively. Presumably, cyclopentadiene **21** undergoes a facile 1,5-hydride shift to alleviate the imposed strain on the B-ring due to the stereochemistry of the angular methylene group (with its hydrogen shown in blue). Conversely, the stereochemistry of the angular methylene group in **14** (with its hydrogen shown in red) would not create the same degree of strain in the B-ring, thus rendering the latter 1,5-hydride shift less likely to proceed. Indeed, energy minimized structures of **14** and **21** revealed that the B-ring adopts a more favorable chairlike conformation in **14** as opposed to a twisted boat conformation in **21** (**14** is more stable than **21** by 2.5 kcal/mol, Scheme 3c). It should be noted that enol acetate **22** is less sterically hindered than **14**, thus it can be hydrolyzed to cyclopentenone **15** under the reaction conditions, while the hydrolysis of **14** required addition of Tf_2NH to generate cyclopentenone **6**.

Preparation of the second fragment began with the preparation of known diol **24**,[13] which was obtained via a Sharpless asymmetric epoxidation of geraniol,[14] followed by a regio- and diastereoselective epoxide opening induced by sodium cyanoborohydride and BF_3-etherate conditions (Scheme 4).[13] The hydride addition to the epoxide proceeded from the *anti*-face of the epoxide, delivering the diol **24** in 79% yield from geraniol with >10:1 *d.r.* Treatment of diol **24** with sodium hydride/tosylimidazole gave access to the terminal epoxide **25** in 87% yield.[15] The epoxide was further elaborated to allylic alcohol **27** in 82% yield using *in situ* generated sulfur ylide of **26**.[16] The alcohol group was converted to allylic phosphate **28** using diethyl chlorophosphate in pyridine as solvent in 91% yield.[17] With this chiral secondary allylic phosphate **28** in hand, the stage was set to implement a copper catalyzed allylic alkynylation under the conditions reported by Sawamura and co-workers.[17b] They developed an allylic alkynylation of chiral secondary allylic phosphate in the presence of chiral NHC ligands (**L1**) that proceeded with the retention of stereochemistry on the allylic center. Upon treatment of **28** with TBS-protected acetylene in the presence of catalytic copper chloride and (*S*,*S*)-**L1** as the ligand, we were pleased to obtain **29** in 92% yield, with >20:1 branched/linear ratio and >12:1 *d.r.* It should be noted that, in line with the Sawamura's report,[17b] the chirality of the NHC ligand, employing (*S*,*S*)-**L1** or (*R*,*R*)-**L1**, had no impact on the

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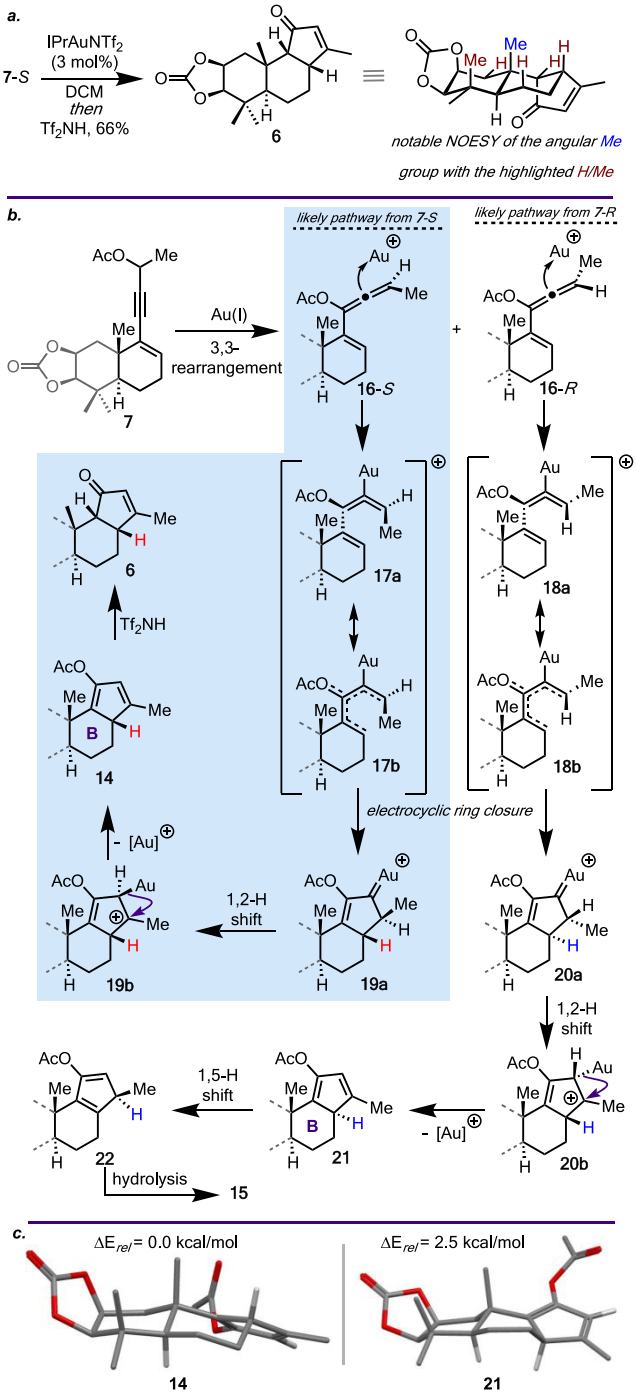
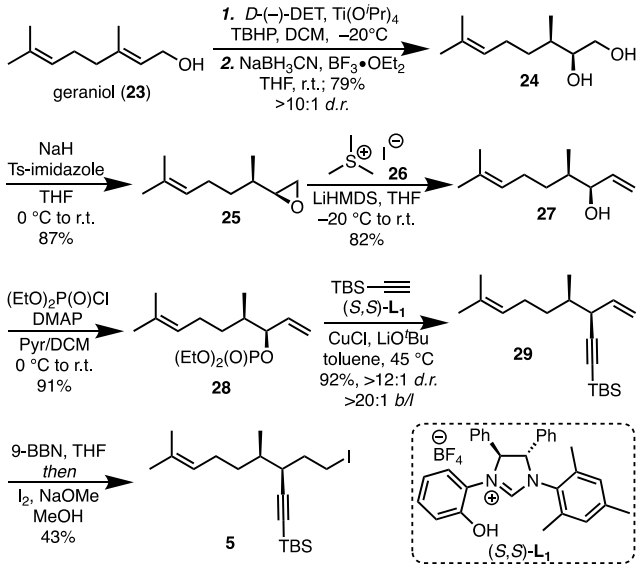
Scheme 3. (a) Access to enone 6. (b) A proposed mechanism of the gold(I)-catalyzed [3,3]-rearrangement/ Nazarov cyclization, and possible origin of the diastereodivergent event. (c) Geometries of 14 and 21 at B3LYP/6-31G* (most hydrogens are omitted for clarity)



diastereoselectivity or the yield of the allylic alkylated product **29**, and the reaction was fully substrate controlled. Nonetheless, performing the reaction in the absence of NHC ligands resulted only in the formation of the linear allylic alkynylated product. Lastly, the terminal double bond in **29** was converted to alkyl iodide **5** via a hydroboration/iodination reaction with a moderate yield.[18]

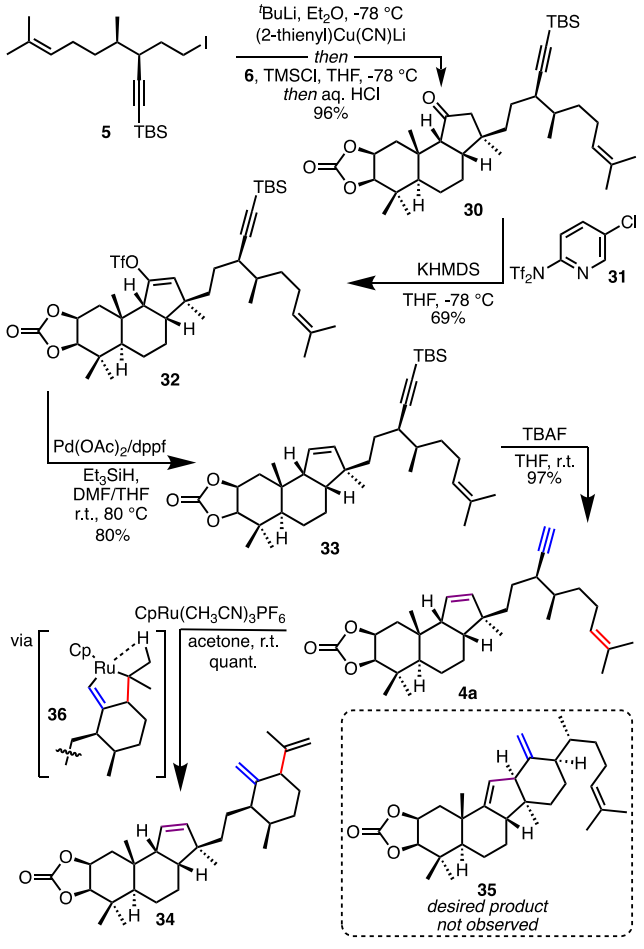
With the two fragments in hand, we envisioned a copper-mediated conjugate addition of the alkyl lithium reagent from

Scheme 4. Preparation of the Side Chain 5



5 to the cyclopentenone in **6** as a viable method to connect the two pieces (Scheme 5).[19] Sterically hindered cyclopentenones, similar to compound **6**, have been shown to be challenging in copper-mediated conjugate additions. The same challenge was

Scheme 5. Fusion of the Two Fragments and Attempts to Construct the Ring D



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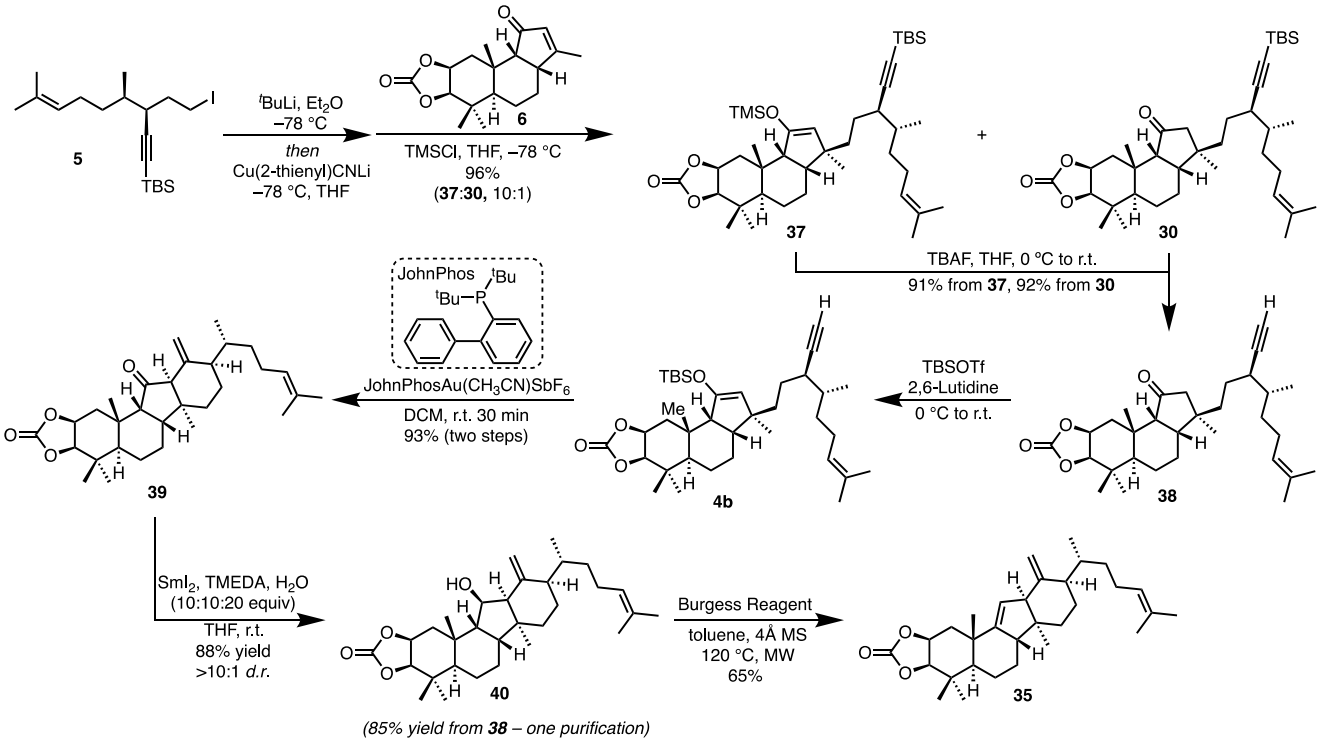
Scheme 6. Construction of Ring D via a Gold-Catalyzed Conia-ene Strategy, and Installation of the Skipped Diene



obvious in our synthesis as various conditions with different copper sources were unsuccessful in delivering the desired coupling product. Ultimately, lithium-halogen exchange[20] followed by the treatment with (2-thienyl)Cu(CN)Li[21] transformed the alkyl iodide **5** into a reactive organocuprate that resulted in efficient conjugate addition with the assistance of TMSCl leading to the corresponding TMS-enol ether.[22] The labile TMS group was then removed under acidic workup conditions to yield the cyclopentenone **30** in 96% yield. The ketone group in **30** was converted to vinyl triflate **32** using Comins' reagent (**31**) in 69% yield. Pd-catalyzed hydride reduction of the vinyl triflate gave access to cyclopentene **33** in 80% yield.[23] Desilylation of the terminal alkyne in **33** resulted in the tetracyclic structure **4a**, which was the precursor to carry out the envisioned Ru-catalyzed alkene-alkyne coupling. Treatment of **4a** with ruthenium catalyst resulted in clean conversion of the starting material. However, the product of this reaction was compound **34** and the desired product **35** was not formed. The undesired alkene-alkyne coupled product **34** is presumably formed via the ruthenium metallacycle **36**. The ruthenium-catalyzed alkene-alkyne coupling reactions are generally selective toward less substituted double bonds, thus providing a unique selectivity tool to construct C−C bonds. Unfortunately, in this particular case, the trisubstituted double bond was shown to be the much more reactive alkene, leading to coupling with the terminal alkyne as opposed to the disubstituted endocyclic double bond. Perhaps, the steric hindrance surrounding the endocyclic double bond renders the latter selectivity. We further converted the trisubstituted double bond in **4a** to an epoxide to eliminate the competing pathway. However, that strategy was not successful in forming the desired C−C bond using the ruthenium catalyst, and we observed complete decomposition of the starting material without any detectable product. It should be noted that engagement of the endocyclic double bond in an alkene−alkyne coupling requires formation of a ruthenacycle embedded in a fused multicyclic framework that appeared unlikely to be achieved.[24] Alternatively, palladium-catalyzed cycloisomerization reactions that obviate intermediacy of the latter metallacycle were pursed. Nonetheless, under various Pd-catalyzed cycloisomerization conditions using **4a**, formation of **35** was not observed. Additionally, multiple attempts to convert the terminal alkyne in **4a** to vinyl halides (bromide or iodide) for carrying out an intramolecular Heck-cyclization with the endocyclic double bond were not successful.[25] In most cases, we were not able to obtain the latter vinyl halides.

On the basis of these results, we turned our attention to an alternative approach to construct the desired C−C bond. A Conia-ene reaction was envisioned as a suitable manifold to form the D-ring of the natural product with the exocyclic double bond (Scheme 6).[5b] Through a similar operation as shown in Scheme 5, the copper-mediated conjugate addition of **5** to enone **6** proceeded smoothly and the coupled products were obtained in 96% yield with a 10:1 ratio of TMS-enol ether **37** to the ketone **30** without treatment by HCl. One of the early attempts to construct the D-ring was to carry out a Conia-ene reaction on the TMS-enol ether **37**. However, under various gold(I)-catalyzed conditions only hydrolysis of the TMS-enol ether to ketone **30** was observed.[5a,26,26d] In an alternative route, deprotected terminal alkyne **38** was accessed through desilylations of **37** and **30** with high yields. The ketone group in **38** was then converted to the corresponding TBS-enol ether **4b** using TBSOTf and 2,6-lutidine. With a short optimization, exposure of **4b** to catalytic [JohnPhosAu-(CH_3CN)]SbF_6 (5 mol %) in CH_2Cl_2 led to the desired product **39** in 93% yield and excellent diastereoselectivity.[26c,d] Of note, the standard gold(I)-catalyzed Conia-ene conditions developed by the Toste group[5a,26a] and utilized by others,[26b] mainly resulted in the hydrolysis of the TBS-enol ether, leading to ketone **38**.

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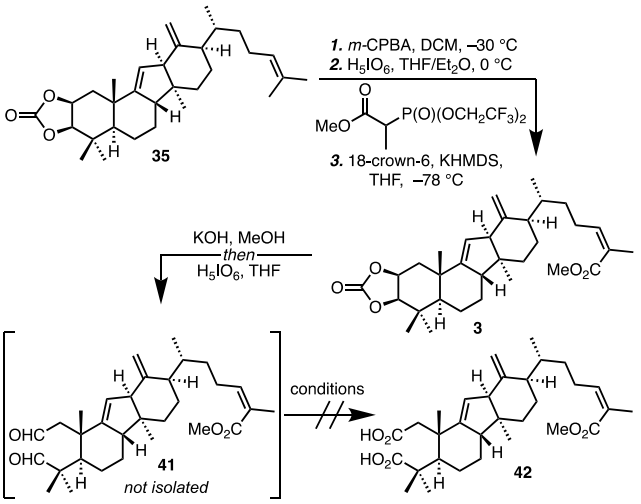
With the key C−C bond installed, elaboration of the ketone group to a double bond with the correct regiochemistry was the next key transformation (Scheme 6). Enolization of the ketone group in **39** to form a vinyl triflate, for a palladium hydride reduction, was not successful. Thus, we set out to reduce the ketone group to an alcohol for a dehydration reaction in order to access the desired double bond. Luche conditions to reduce the ketone group in **39** proved to be ineffective and only partial hydrolysis of the carbonate protecting group, without any reduction of the ketone group, was observed. Next, a samarium iodide (SmI_2) reduction of the ketone into secondary alcohol was pursued. Under excess SmI_2 (50 equiv) in THF, ketone **39** was reduced to the secondary alcohol **40** in ∼80% conversion. Complete conversion of the ketone could not be reached by further addition of SmI_2. The diastereoselectivity of the reduction was estimated to be ∼2.5:1 based on ^{1}H-NMR analysis. Reductions of ketones by SmI_2 are demonstrated to be influenced by various additives.[27] A survey of different additives revealed that tetramethylethylenediamine (TMEDA) could significantly improve the conversion as well as the diastereoselectivity of the reaction.[28] Thus, the reduction of **39** in the presence of TMEDA (10 equiv), SmI_2 (10 equiv), and water (20 equiv) was completed within 30 min, delivering the desired alcohol **40** in 88% isolated yield and with >10:1 *d.r.*. The stereochemistry of the carbinol carbon in **40** was established using *NOE* analysis (see the SI for additional details). Dehydration of alcohol **40** was achieved in 52% yield using Burgess reagent in refluxing toluene. The yield of this reaction was further improved to 65% by perfoming the reaction under microwave irradiation in the presence of 4 Å molecular sieves.[29] Judicious choice of the Burgess reagent for a *syn*-elimination resulted in the correct regioselectivity of the newly formed double bond, and the regioisomeric conjugated diene was not observed. The latter further signifies the stereochemistry of the secondary alcohol and highlights the impact of the diastereoselective reduction of the ketone **39**. It should be noted that the minor diastereomer of alcohol **40** did not undergo dehydration under various conditions.

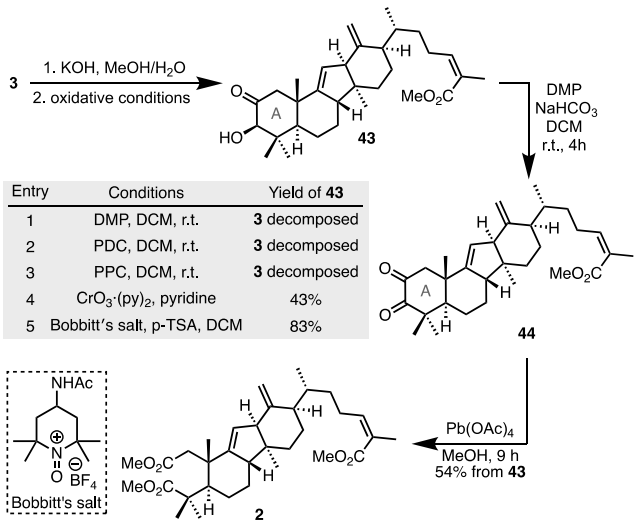
The trisubstituted double bond in **35** was converted to the *Z*-olefinic methyl ester **3** via a selective cleavage of this double bond followed by a Still-Gennari olefination in 66% overall yield (Scheme 7).[30] Deprotection of the carbonate protecting group under methanolic potassium hydroxide, followed by the treatment of the resulting diol with periodic acid gave access to dialdehyde **41**. Any attempts to further oxidize the dialdehyde intermediate under various oxidative conditions, such as Pinnick oxidation[31] and Tollens' oxidation,[32] failed to deliver the desired dicarboxylic acid **42**, and mainly led to decomposition of the dialdehyde **41**.

We then turned our attention to oxidative cleavage of the C2−C3 bond through an α-diketone[33] intermediate, generated from the oxidation of the diol intermediate (Scheme 8). After deprotection of the carbonate group in **3**, treatment of the resulting diol intermediate under various conditions was pursued. Typical oxidants such as DMP, PDC, and PPC, led to decomposition of the starting marterial. Fortunately, dipyridine chromium oxide in pyridine gave access to α-hydroxyl ketone **43** in 43% yield with high chemoselectivity for C3 oxidation.[34] Furthermore, a combination of Bobbitt's salt, 4-(acetylamino)-2,2,6,6-tetramethyl-1-oxo-piperidinium tetrafluoroborate, and *p*-toluenesulfonic acid improved the yield of this transformation to 83%.[35] Further oxidation of the

Scheme 7. Ring Opening of Ring A through Oxidative Cleavage of C2−C3 Diol



Scheme 8. Ring Opening of Ring A through Oxidative Cleavage of C2−C3 α-Diketone



Entry	Conditions	Yield of **43**
1	DMP, DCM, r.t.	**3** decomposed
2	PDC, DCM, r.t.	**3** decomposed
3	PPC, DCM, r.t.	**3** decomposed
4	$CrO_3{\cdot}(py)_2$, pyridine	43%
5	Bobbitt's salt, p-TSA, DCM	83%

generated α-hydroxyl ketone **43** by Dess-Martin periodinane led to 1,2-diketone **44**. Oxidative cleavage of **44** by lead tetraacetate in methanol gave rise to the corresponding trimethyl ester of kadcoccinic acid A (**2**) in 54% yield over two steps. Our successful synthesis of the trimethyl ester of kadcoccinic acid A provides an efficient and highly selective synthetic route to the 6/6/5/6-fused tetracyclic ring systems that is a common structural motif in this natural product family.

CONCLUSIONS

In summary, we report the first total synthesis of kadcoccinic acid A trimethyl ester. A cyclopentenone core was targeted as a strategic centerpiece of the synthesis which enabled assembly of the natural product skeleton. We utilized a gold-catalyzed Nazarov cyclization as an effecient methodology to access the cyclopentenone core. This reaction revealed a diastereodivergent process by which the stereochemistry of the enynyl acetate determined the regiochemistry of the cyclopentenone. Additionally, the synthesis evoked an efficient gold(I)-catalyzed Conia-ene reaction to construct the D ring of natural product with its characteristic exocyclic double bond. A

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highly efficient samarium iodide reduction of a sterically hindered cyclopentenone followed by a chemoselective dehydration gave rise to chemoselective formation of the skipped diene of the natural product. This modular and convergent synthesis presents a facile and unique strategy toward this family of triterpenoid natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05521.

Experimental procedures, analytical data (^{1}H-NMR, ^{13}C-NMR, HRMS, and $[\alpha]_D$) for all new compounds, additional details, *NOESY* analysis, and computational data (PDF)

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Notes

The authors declare no competing financial interest.

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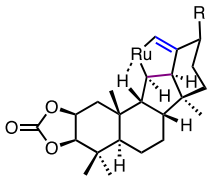
(24) Formation of **3** via the ruthenium catalyzed alkene-alkyne coupling necessitates formation of a ruthenacycle complex, embedded in a hexacyclic framework (shown below). Additionally, for the putative ruthenacycle to result in the formation of the desired products, interaction of ruthenium with the allylic proton for a terminating β-hydride elimination is needed. The latter constrains presumably forces the newly formed six-membered ring to adopt a twist-boat conformation that adds extra unfavorability to the ruthenacycle complex and thus renders formation of the desired product **3** unlikely to proceed..



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