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Communication

Synthesis of Cyclopentenones with C4-Quaternary Stereocenters via Stereospecific [3,3]-Sigmatropic Rearrangement and Applications in Total Synthesis of Sesquiterpenoids

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ABSTRACT: A cationic gold(I)-catalyzed asymmetric [3,3]-sigmatropic rearrangement of sulfonium leads after cyclization to cyclopentenones with a C4-quaternary stereocenter. Starting with simple vinyl sulfoxides and propargyl silane, numerous compounds were isolated with moderate to good yields and excellent enantiomeric excesses (26 examples). The application of this simple methodology allowed the efficient total synthesis of five natural sesquiterpenoids, including enokipodin A and B, hitoyopodin A, lagopodin A, and isocuparene-3,4-diol.

Stereoselective formation of quaternary carbon centers remains one of the biggest challenges in organic chemistry. The presence of four different carbon substituents on the same atom implies an important steric hindrance around the stereocenter, and this may partially explain the limited number of methodologies developed.[1] On the other hand, more and more natural products and active pharmaceutical ingredients (APIs) with at least one quaternary center are isolated and possess intrinsic biological properties of interest.[2] Among them, C4-chiral cyclopentenone scaffolds deserve to be emphasized. Indeed, this motif is present in numerous natural products and can be seen as a platform for more complex molecules (Scheme 1a).[3] In addition to the inherent reactivity of the α,β-unsaturated ketone for 1,2- and 1,4-additions, the acidic α-position to carbonyl group allows easy selective functionalizations. However, the state-of-the-art methods for the synthesis of chiral C4-quaternary cyclopentenones are quite limited (Scheme 1b). For instance, cyclopentanones were formed through asymmetric metal-catalyzed conjugate additions[1,4] to β-substituted cyclopentenones followed by an oxidative dehydrogenation step to recover the enone function.[5] On the other hand, Nazarov cyclization and Wagner−Meerwein rearrangement of acyclic dienones furnish cyclopentenones with C4 and C5 stereogenic centers,[6a,b] and Pauson−Khand reaction could deliver the same functionalized chiral products in an efficient way but with a narrow substrate scope.[6c,d] We propose here to use a gold-catalyzed asymmetric [3,3]-sigmatropic rearrangement starting from enantioenriched vinyl sulfoxide **1** and propargyl silane to yield chiral 4-oxopentanal derivatives **2** with transfer of the chirality from the sulfur atom to the quaternary carbon center (Scheme 1c). In the past decade, numerous studies have demonstrated the synthetic interest in [3,3]-sigmatropic rearrangement for the synthesis of quaternary stereocenters,[7] specifically with sulfur-containing substrates.[8] Indeed, after the development of gold-catalyzed processes,[9a−d] charge-accelerated [3,3]-rearrangements were developed via interrupted Pummerer reaction/sigmatropic rearrangements.[9f−p]

Our participation in this field was to use electron-rich arylalkynes and vinyl sulfoxides as partners, for the synthesis of 1,4-dicarbonyl derivatives.[9e] In the present study, we demonstrated that after the sigmatropic rearrangement, ketoaldehydes **2** could be easily converted to C4-chiral cyclopentenones **3** and applied this methodology to the fast and efficient total syntheses of five sesquiterpenoids.

For the optimization of this reaction, we first screened different gold(I) catalysts to produce **2a**, starting from vinyl sulfoxide[10] (*R*)-**1a** and tri-isopropyl(prop-2-yn-1-yl)silane in a 1/2 ratio (Table 1, entries 1−3). Commercially available cationic JohnPhosAu(MeCN)SbF_6 catalyst (L_1AuSbF_6) proved to be the most efficient catalyst (entry 3). Decreasing the relative stoichiometry to a 1/1.5 ratio, 16 h at 30 °C, allowed us to isolate product **2a** in 63% yield (entries 3−5). The use of 5 mol % gold catalyst or triflimide decreased the conversion (entries 6 and 7, see SI for the full optimization table). It is important to note the perfect chirality transfer from sulfur to carbon atom in all cases. The same reaction was then performed using optimized conditions (entry 4, Table 1), and the solvent was removed after completion (Scheme 2). Potassium carbonate and *tert*-butanol were added to the crude mixture to perform the intramolecular aldol condensation/elimination reaction to afford **3a** in 94% yield. Overall, compound (*S*)-**3a** was isolated in a one pot transformation in 59% yield and 97% ee. That confirms that this Au(I)-catalyzed rearrangement, combined with an aldolization reaction, is a very efficient process to yield highly enantioenriched cyclopentenones.

With these optimized reaction conditions, we studied the scope of the reaction. Importantly, starting from the *E*-vinyl

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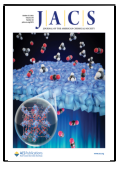

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Scheme 1. Strategies Toward the Synthesis of Cyclopentenones with C4-Quaternary Stereocenters

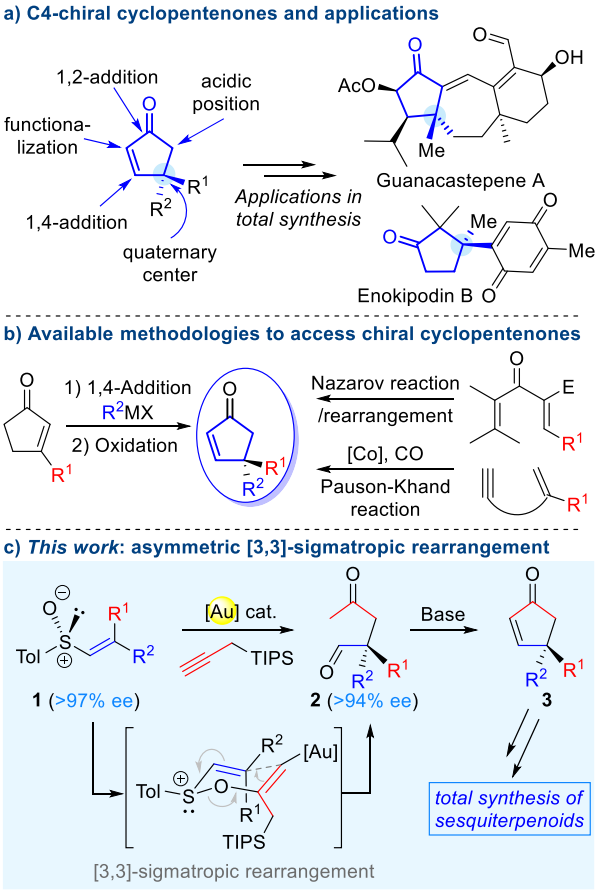
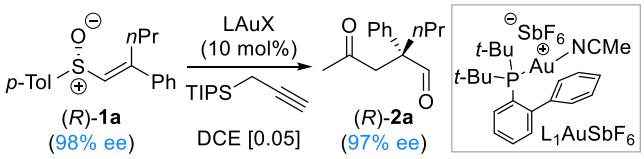


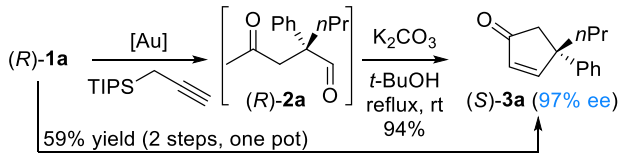
Table 1. Optimization of the Reaction Conditions



entry	LAuX	substrate ratio	T (°C)	t (h)	yield 2a[a] (%)
1	PPh_3AuNTf_2	1/2	20	60	59
2	$PPh_3AuCl/AgSbF_6$	1/2	20	60	62
3	L_1AuSbF_6	1/2	20	60	70
4	L_1AuSbF_6	1/1.5	30	16	68(63)[b]
5	L_1AuSbF_6	1/1	30	16	36
6[c]	L_1AuSbF_6	1/1.5	30	60	60(56)[b]
7	$HNTf_2$	1/1.5	30	16	40

[a]NMR yield, with the use of dibromomethane as internal standard. [b]Isolated yield. [c]5 mol % catalyst at 1 mmol scale.

Scheme 2. Cyclization Step for the Formation of 3



sulfoxides, compounds (*S*)-**3** were isolated, while *Z*-isomers of **1** produce (*R*)-**3** products, with the same excellent conservation of the enantiomeric excesses. Due to their occurrence in natural products, we first applied this method to the synthesis of 4-aryl-4-methylcyclopentenone products **3b**−**3g** (Scheme 3). Starting with diversely substituted aromatic groups, the chirality transfer was always excellent, furnishing compounds **3b**−**g** in up to 70% yield and 96−99% ee. Functionalized substrates such as *p*-bromo-aryl or *p*-ester-aryl derivatives smoothly gave the rearrangement products (*S*)-**3h,i** (up to 98% ee). Tolylsulfonate, alkylester, and benzyl ether-functionalized substrates were also well tolerated in this transformation (compounds **3j**−**l**). The latter examples highlight the wide tolerance of diversely functionalized substrates in our mild reaction conditions. More sterically hindered naphthyls and heteroaryls, such as thiophene and benzofuran groups, delivered the corresponding chiral cyclopentenones **3m**−**p** in up to 58% yield and 95−99% ee. Finally, this methodology was efficiently extended to the use of *β*,*β*-dialkyl-vinyl sulfoxides **1q**−**s**, for the formation of **3q**−**s**, in 63−65% yield (94−97% ee).

Concerning the mechanism of this transformation, the reaction started with the gold activation of propargyl silane (Scheme 4a). The presence of silicon is very important for the success of this transformation, due to the well-known properties of silicon to stabilize *β*-positive charge (intermediate **I′**).[11a−c] This substrate has already been used successfully in organic synthesis and in [3,3]-sigmatropic rearrangements.[11d−g] Subsequent addition of vinyl sulfoxide **1** to Au(I)-activated alkyne (**I**) furnished sulfonium intermediate (**II**). After [3,3]-sigmatropic rearrangement through a chairlike transition state, thionium ion (**III**) could be formed. Hydrolysis and protodemetalation steps gave chiral 1,4-dicarbonyls **2**. Moreover, this transformation with the traceless chiral sulfoxide auxiliary allowed a stereospecific reaction: the double bond geometry of vinyl sulfoxide determines the absolute configuration of the carbon stereogenic center (Scheme 4b and SI for details on substrate syntheses[10]).

Starting from suitably decorated substrates, this methodology could easily be applied in the total synthesis of a number of naturally occurring secondary metabolite sesquiterpenes such as cuparenes, herbertenes, and others.[12] We decided to focus our attention on the synthesis of natural products whose total syntheses are rarely reported or are laborious using the established methodologies (Scheme 5). We first applied the newly developed methodology to the total synthesis of lagopodin A and hitoyopodin A, isolated from the mushroom *Coprinopsis cinerea* (Scheme 5a, left).[13a,b] Starting with (*S*)-**3e**, easily obtained from the corresponding vinyl sulfoxide (*E*)-**1e**, compound **4** was isolated in a three step sequence including a copper 1,4-addition of a methyl group, a Pd-mediated oxidation,[5] and a nickel-catalyzed addition of trimethylaluminum. Final CAN (ceric ammonium nitrate) oxidation furnished lagopodin A (18% overall yield, 7 steps). From the same intermediate **4**, a sequence combining the demethylation of aryl methoxy groups and cyclization promoted by BBr_3 delivered hitoyopodin A in 15% overall yield in 7 steps.

This contrasts with the sole total synthesis previously described with moderate overall yields (<5%) and using a rather long synthetic pathway (16−17 steps).[13b]

We then synthesized enokipodin A and B (Scheme 5a, right), isolated from a culture broth of a mushroom "enokidake" (*Flammulina velutipes*) and possessing antimicrobial activities.[14a,b] Since both enantiomers of compound **3** could be isolated starting from either pure *E*- or pure *Z*-isomers of vinyl sulfoxide **1**, we investigated the isomerization of substrate *E*-**1e** to *Z*-**1e**, to

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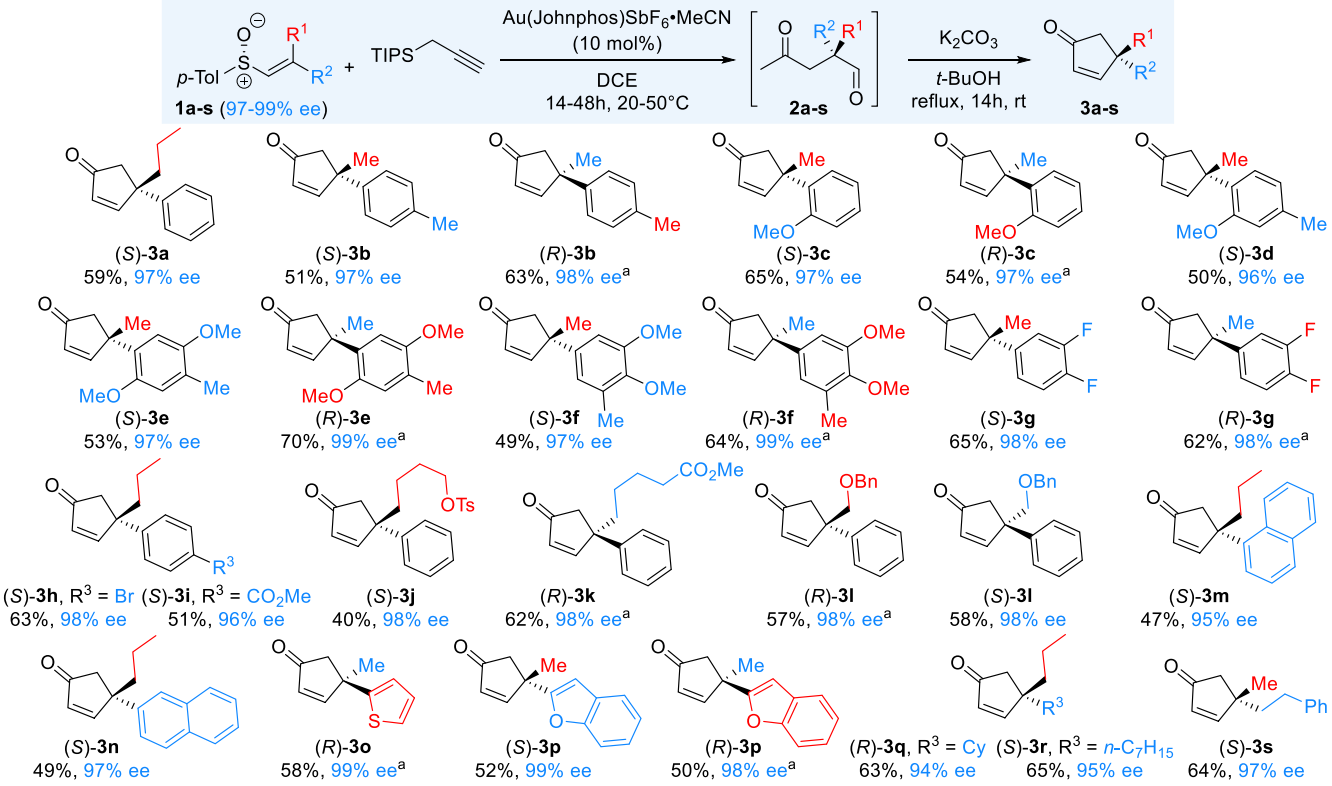
Scheme 3. Reaction Scope of the Catalytic Transformation for the Formation of C4-Chiral Cyclopentenones[b]



[a]Starting from (*Z*)-isomer of **1**. [b]Isolated yield after purification by column chromatography on silica gel.

have straightforward access to both enantiomers of **3e** from the same olefin. This was realized under UV lamp irradiation (365 nm) over 15 min in acetonitrile (10/90 *E*/*Z* ratio, 60% yield of enantiopure compound *Z*-**1e**[15] after recrystallization, see SI for the optimization table). After formation of (*R*)-**3e**, subsequent dimethylation and palladium-catalyzed hydrogenation of the double bond delivered **5** in 71% yield. Then, boron tribromide deprotection or CAN oxidation steps furnished enokipodin A and enokipodin B in 24% and 32% overall yield, respectively, over 6 steps. The asymmetric syntheses of these natural products are the shortest in terms of number of steps, with the highest overall yields described so far.[14c−f] These total syntheses emphasize the importance of easy access to both enantiomers of **3** and the versatile functionalization of this small molecular "Swiss army knife".

Finally, the sterically congested 1-aryl-1,2,2-trimethylcyclopentane natural product called isocuparene-3,4-diol[16] was synthesized for the first time (Scheme 5b). With compound (*R*)-**3f** in hand, dimethylation, sulfuration, and hydrogenation steps and then deprotection of the phenols delivered the desired compound in 11% overall yield over 7 steps. The ^{1}H and ^{13}C NMR spectra and $[\alpha]_D^{20}$ were in accordance with those of natural product {$[\alpha]_D^{20}$ −73.4 (*c* 0.25, $CHCl_3$); lit.:[16] $[\alpha]_D^{20}$ −73.6 (*c* 0.35, $CHCl_3$)}.

To examine the practicability of this newly developed gold-catalyzed methodology, we performed further investigations. Indeed, some divergent transformations on **2a** provided in one step three different chiral structures of interest (Scheme 6). Aldolization performed under mild conditions, at 40 °C, formed alcohol **7** in 75% yield without further elimination reaction. Cyclobutane **8**, possessing three contiguous stereogenic centers, was isolated via McMurry coupling[17] (74% yield, 3:1 dr). Finally, chiral 1,4-dihydropyridazine[18] **9** was isolated in 88% yield by reaction of **2a** with hydrazine.

In conclusion, we have developed a new stereospecific transformation for the straightforward synthesis of cyclopentenones with C4-quaternary stereogenic centers. Enantioenriched products were easily obtained in two steps from cheap reagents and possess all the required functionalities for applications to short and efficient total syntheses of natural products, as illustrated by the total synthesis of five natural products. In the future, we plan to use this reaction as a key step in the synthesis of more complex molecular targets.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07966.

Experimental procedures, additional experimental details, and full spectroscopic data for all new compounds (PDF)

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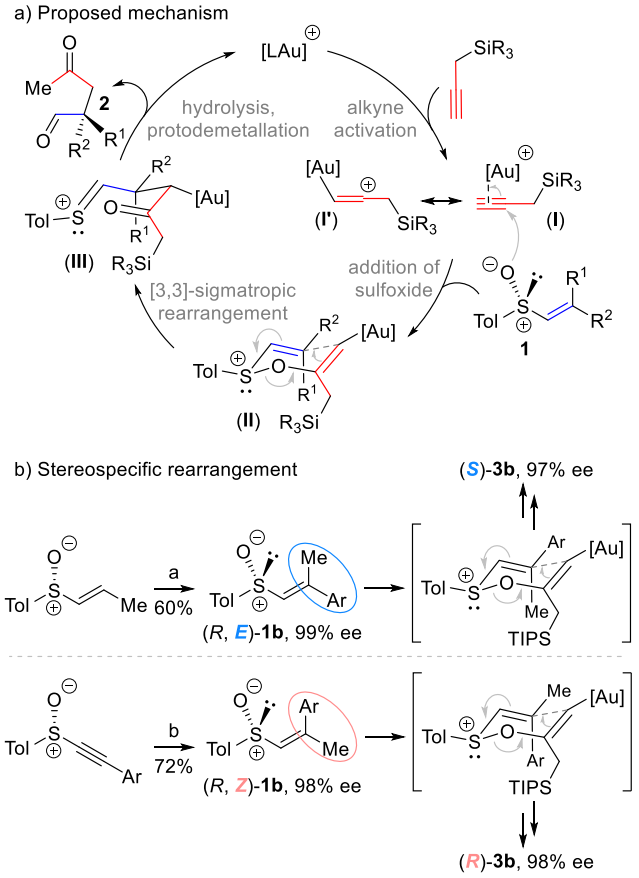
Scheme 4. Mechanism and Proposed Transition State[a]



[a]Reagents and conditions: (a) ArI, $Pd(OAc)_2$(10 mol %), dppp (10 mol %), Ag_2CO_3, DMF, 100 °C, 36 h; (b) $CuOTf_2$ (2 mol %), $ZnMe_2$, THF, −78 °C to rt, 12 h; dppp = 1,3-bis-(diphenylphosphanyl)propane; Ar = *p*-Me-C_6H_4.

https://pubs.acs.org/10.1021/jacs.1c07966

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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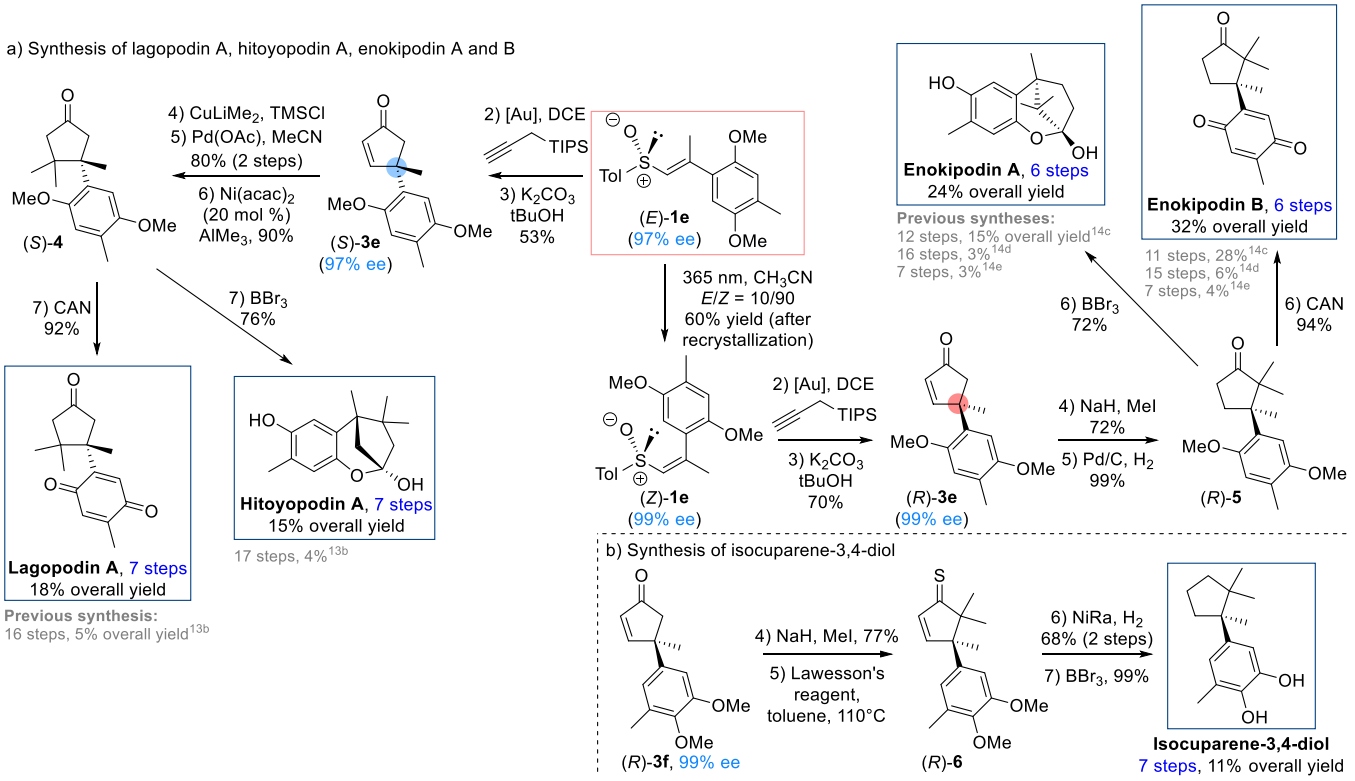
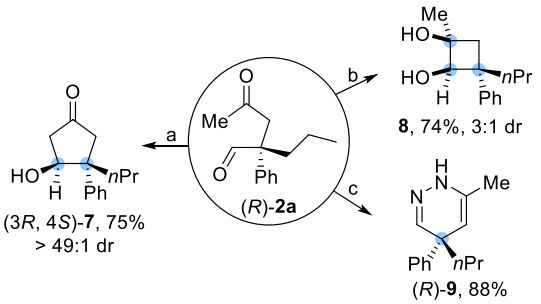
Scheme 5. Total Synthesis of Five Sesquiterpenoids



Scheme 6. Follow-up Transformations of 2a[a]



[a]Reagents and conditions: (a) K_2CO_3 (2.0 equiv), *t*-BuOH, 40 °C, 96 h; (b) $TiCl_4$/zinc dust (1/1), dry THF, 0 °C, 15 min and then reflux, 2.5 h; (c) NH_2NH_2, MeOH, reflux, 2 h.

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