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Facile access to diverse all-carbon quaternary center containing spirobicycles by exploring a tandem Castro–Stephens coupling/acyloxy shift/cyclization/semipinacol rearrangement sequence†

Ye Zhang,^a Tian-Lu Zheng,^a Fu Cheng,^a Kun-Long Dai,^a Kun Zhang,^b Ai-Jun Ma,^b Fu-Min Zhang,^a Xiao-Ming Zhang,^a Shao-Hua Wang^{a,b} and Yong-Qiang Tu^{a,c}

Efficient combination of two or more reactions into a practically useful purification free sequence is of great significance for the achievement of structural complexity and diversity, and an important approach for the development of new synthetic strategies that are industrially step-economic and environmentally friendly. In this work, a facile and efficient method for the construction of highly functionalized spirocyclo[4.5]decane derivatives containing a synthetically challenging quaternary carbon center has been successfully developed through the realization of a tandem Castro–Stephens coupling/1,3-acyloxy shift/cyclization/semipinacol rearrangement sequence. Thus a series of multi-substituted spirocyclo[4.5]decane and functionalized cyclohexane skeletons with a phenyl-substituted quaternary carbon center have been constructed using this method as illustrated by 24 examples in moderate to good yields. The major advantages of this method over the known strategies are better transformation efficiency (four consecutive transformations in one tandem reaction), product complexity and diversity. As a support of its potential application, a quick construction of the key tetracyclic diterpene skeleton of waihoensene has been achieved.

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Introduction

Spiro bicyclic scaffolds incorporating all-carbon quaternary stereocenters, as a big number of key structural moieties, broadly exist in bioactive natural products and pharmaceutical molecules, and often play essential roles in their characteristic bioactivity.¹ Because of the highly steric repulsion caused by its four carbonic substituents,² however, the construction of this type of moiety is a long-standing challenging topic.³ Taking the spirocyclo[4.5]decane skeleton as a typical example, a lot of bioactive natural products as well as synthetic intermediates contain this key unit (Fig. 1).⁴ Therefore, in order to synthesize these target molecules and facilitate corresponding molecular function studies, how to efficiently construct this unit has

become a crucial and difficult step. Although several strategies based on different intermolecular or intramolecular cycloaddition patterns of relatively complex substrates have been developed during the past decade,⁵ it is still highly desirable to further explore alternative approaches for pursuing transformation efficiency, and product diversity as well as extensibility.

Results

Design plan

Besides the above strategies, it is particularly noticeable that the semipinacol rearrangement reaction, which can generate

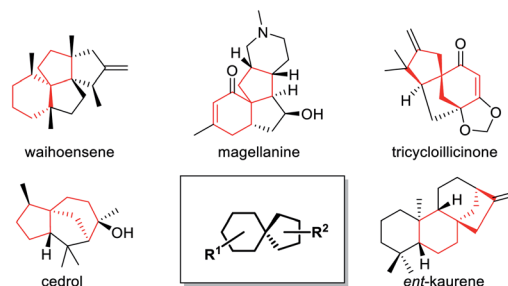


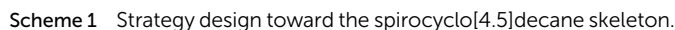
Fig. 1 Representative important natural products bearing the spirocyclo[4.5]decane core.

^aState Key Laboratory of Applied Organic Chemistry, School of Pharmacy, Lanzhou University, Lanzhou 730000, P. R. China. E-mail: tuyq@lzu.edu.cn; wangshh@lzu.edu.cn

^bSchool of Biotechnology and Health Science, Wuyi University, Jiangmen 529020, P. R. China

^cSchool of Chemistry and Chemical Engineering, Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, Shanghai Jiao Tong University, Shanghai 200240, P. R. China

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Optimization of reaction conditions

showed that the use of Cs_2CO_3 in DCE at 70°C could produce **3a** in the best yield of 82% (Table 1, entry 1). Subsequently, the realization of the initial tandem reaction in a purification free manner was then investigated. Fortunately, after a quick removal of the solid from the reaction mixture through Celite pad filtration following the Castro–Stephens coupling reaction, a first attempt using the combination of 10 mol% AuPPh_3Cl and AgOTf could promote the desired reaction to give the product **5a** in 57% yield (Table 1, entry 7). Furthermore, the counterion effect¹³ was also observed with this reaction, and the use of counterion NTf_2^- from AgNTf_2 exhibited the best result of 66% yield for **5a** (Table 1, entry 8). Next, several different solvents were applied to this tandem reaction. Among them, benzene, THF and CH_3CN could give the desired product in low yield (Table 1, entries 11–16). Other solvents were not compatible with this transformation. Finally, the use of CuOAc along with Cs_2CO_3 and the combination of AuPPh_3Cl and AgNTf_2 in DCE (Table 1, entry 8) was selected as the optimal reaction conditions.

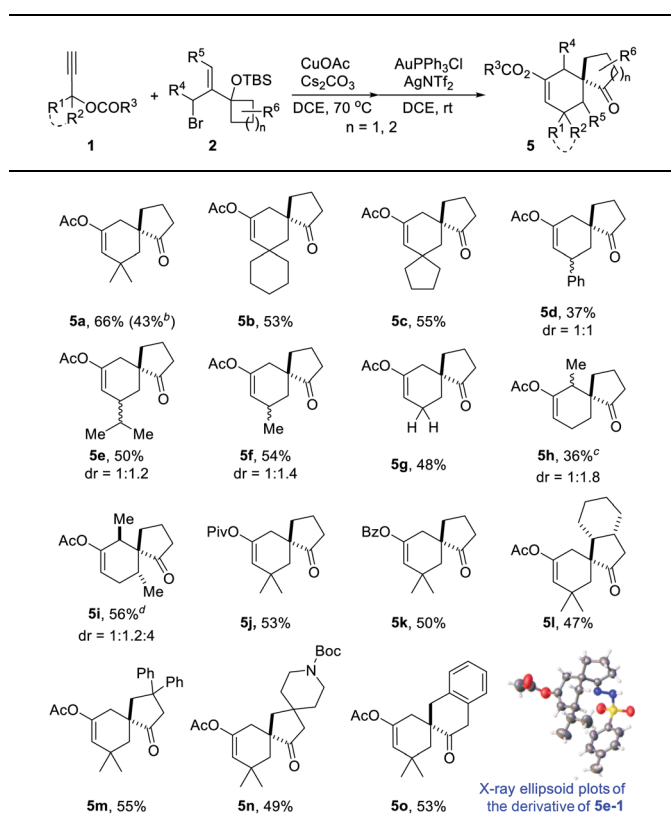
With the optimal reaction conditions in hand (Table 1, entry 8), we began to explore the generality of this reaction, and the results are summarized in Tables 2 and 3. Among the substrates tested,

Reaction scheme showing the synthesis of 5a:

1a + 2a $\xrightarrow[\text{solvent temp}]{\text{CuOAc, Cs}_2\text{CO}_3}$ 3a $\xrightarrow[\text{solvent temp}]{\text{Ag salt, AuPPh}_3\text{Cl}}$ 5a

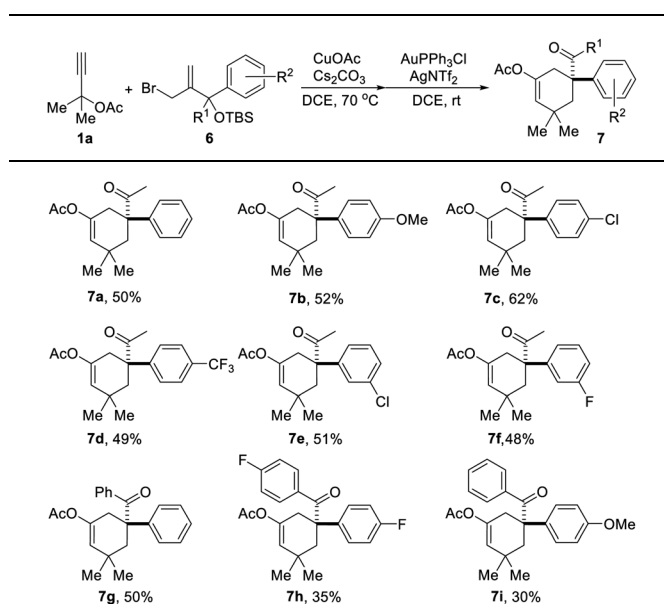
Entry	Solvent	Ag salt	Temp	Product	Yield
1	DCE ^b	—	70 °C ^c	3a	82% ^d
2	Benzene ^b	—	rt ^c	3a	40% ^d
3	THF ^b	—	rt ^c	3a	47% ^d
4	EtOH ^b	—	rt ^c	3a	55% ^d
5	CH ₃ CN ^b	—	rt ^c	3a	55% ^d
6	DMF ^b	—	rt ^c	3a	54% ^d
7	DCE	AgOTf	rt ^e	5a	57% ^f
8	DCE	AgNTf ₂	rt ^e	5a	66% ^f
9	DCE	AgSbF ₆	rt ^e	5a	53% ^f
10	DCE	AgBF ₄	rt ^e	5a	49% ^f
11	Benzene ^g	AgNTf ₂	rt ^e	5a	11% ^f
12	THF ^g	AgNTf ₂	rt ^e	5a	27% ^f
13	EtOH ^g	AgNTf ₂	rt ^e	5a	nd
14	CH ₃ CN ^g	AgNTf ₂	rt ^e	5a	53% ^f
15	DMF ^g	AgNTf ₂	rt ^e	5a	nd
16	DMSO ^g	AgNTf ₂	rt ^e	5a	nd

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Table 2 Exploration of the generality of the tandem reaction of cyclic alkanes as migrating groups^a

^a Unless specified, all reactions were conducted using **1** (0.5 mmol, 2.5 eq.), **2** (0.2 mmol, 1.0 eq.), CuOAc (30 mol%), Cs₂CO₃ (50 mol%), AuPPh₃Cl (10 mol%), and AgNTf₂ (10 mol%) in a reaction tube in DCE (2 mL) at indicated temperature. ^b 10 mmol of **1a** (1.26 g) and 4 mmol of **2a** (1.22 g) were used. ^c CHCl₃ was used as the solvent after Castro–Stephens coupling. ^d AuCl₃ (10 mol%) in 2 mL HFB (hexafluorobenzene) was used instead of the combination of AuPPh₃Cl and AgNTf₂ after Castro–Stephens coupling; the structure shows the relative configuration of the major isomer.

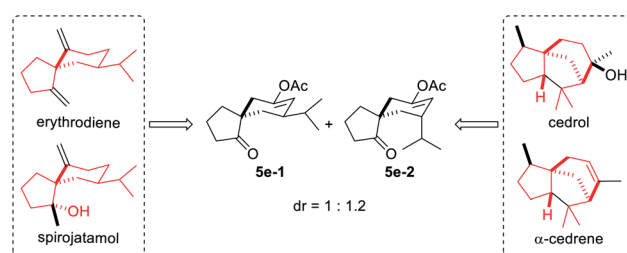
most of them could give the expected products in moderate to good yields. When R¹ and R² groups of propargyl ester formed a ring system (*i.e.*, cyclohexyl and cyclopentyl), the reaction with bromide **2a** (R⁴, R⁵, R⁶ = H) proceeded smoothly providing tricyclic products **5b** and **5c** in 53% and 55% yield, respectively. Moreover, with the R¹ as H, R² could be H, Ph, isopropyl, or methyl, and all reactions could give the desired products **5d** to **5f** in moderate to good yields, albeit with low diastereoselectivity for **5d** to **5f**. Additionally, the reaction was also compatible with substrate **2** with different R⁴/R⁵ groups. In the case of substrate **2b** with R⁴ and R⁵ being Me and H, respectively, the expected product **5h** was obtained in 36% yield and 1/1 dr ratio. When both R⁴ and R⁵ were Me (**2c**), the desired product **5i** was produced with good diastereoselectivity and yield. It should be noted that a series of natural product skeletons might be obtained by our protocol. For example, since the relative configuration of the two diastereoisomers of ketone **5e** (ref. 14) (**5e-1** and **5e-2**) is consistent with natural products erythrodiene^{4c,d} and cedrol,^{4g,h} respectively, a new general synthetic strategy for these types of natural products might be developed based on propargyl ester with

Table 3 Exploration of the generality of the tandem reaction of aromatic rings as migrating groups^a

^a All reactions were conducted using **1a** (0.5 mmol, 2.5 eq.), **6** (0.2 mmol, 1.0 eq.), CuOAc (30 mol%), Cs₂CO₃ (50 mol%), AuPPh₃Cl (10 mol%), and AgNTf₂ (10 mol%) in a reaction tube in DCE (2 mL) at indicated temperature.

pivaloyl, and benzoyl was successful to give the corresponding products **5j** and **5k** in 53% and 50% yield, respectively. In order to prove the efficiency of this method in the rapid construction of product complexity, other four allylic bromides **2d–2g** were applied to the reaction, which produced four spirocyclic products in good yields. Among them, products **5l** and **5m** confirmed the feasibility of adding additional substituents on the cyclobutanol moiety, while product **5n** showed that the amine group is amenable to this reaction. It was noteworthy that substrate **2g** with a 2,3-dihydro-1*H*-inden-2-ol motif could go through the reaction through a five-membered ring to a six-membered ring expansion affording product **5o**. In order to demonstrate the potential utility of such a reaction, the transformation between **1a** and **2a** was attempted on the gram scale giving **5a** in a moderate yield of 43% (Scheme 2).

Based on the above results, the application of this method in the construction of a functionalized cyclohexane skeleton with a phenyl-substituted quaternary carbon center, a common

**Scheme 2** New synthetic strategy design toward corresponding sesquiterpenes.

moiety in a variety of natural products like limaspermidine^{15a} and strychnine,^{15b} was further investigated. Accordingly, a series of allylic bromides with an aryl substituted tertiary alcohol moiety were applied to this reaction with substrate **1a**. All of the tested substrates afforded the expected products, and the regioselectivity of this reaction during the migration step agrees well with the common semipinacol rearrangement pattern, *i.e.*, aryl groups and aryl groups with an electron-donating substituent are more preferred than alkyl groups and aryl groups with an electron-withdrawing substituent, respectively. For example, substrates **6a–6f** all gave the aryl group migrated products, and substrate **6i** led to ketone **7i** as the sole product. Besides, the steric hindrance effect of the substituent on the aromatic ring has also been clearly observed. When the substituent on the phenyl ring was chloro, product **7c** with the substituent at the *para*-position was obtained in higher yield than the one with it at the *meta*-position (**7e**).

Synthetic application

In order to demonstrate the efficiency of this method in constructing a highly complex structural skeleton, a quick assembly of the key tetracyclic skeleton of waihoensene,¹⁶ a unique diterpene molecule isolated from the New Zealand podocarp, featuring fused and strained tetracyclic rings and four

consecutive congested all-carbon quaternary centers, was attempted using this reaction as the key step (Scheme 3). Due to the great difficulty in constructing such a tetracyclic framework with vicinal quaternary carbon centers, only one synthetic strategy toward waihoensene has been reported in 2017 using a tandem cycloaddition reaction of an allene substrate prepared in 12 steps as the key step.¹⁷ Herein, based on the method we developed, starting from prop-2-yn-1-yl acetate **1g** and **2h** synthesized from the known reagent **8** in 6 steps, a facile access to a tricyclic skeleton was accomplished affording **5p** in 40% yield and a dr ratio of 3.2/1 using hexafluorobenzene as the solvent.¹⁸ The relative configuration of **5p** and its diastereoisomer **5q** was confirmed by the X-ray structure analysis of their derivatives.¹⁴ Next, the TBDPS protecting group of **5p** was removed with TBAF followed by IBX oxidation providing dicarbonyl compound **12**. A K₂CO₃-induced tandem hydrolysis/intramolecular aldol cyclization/elimination reaction would give compound **13**. Thus a quick construction of the tetracyclic skeleton core of waihoensene with vicinal all-carbon centers was realized through the use of this key methodology. Additionally, an unprecedented [3.2.2] bridged motif **14** could be obtained through a different cyclization model in the presence of HCl.

Conclusions

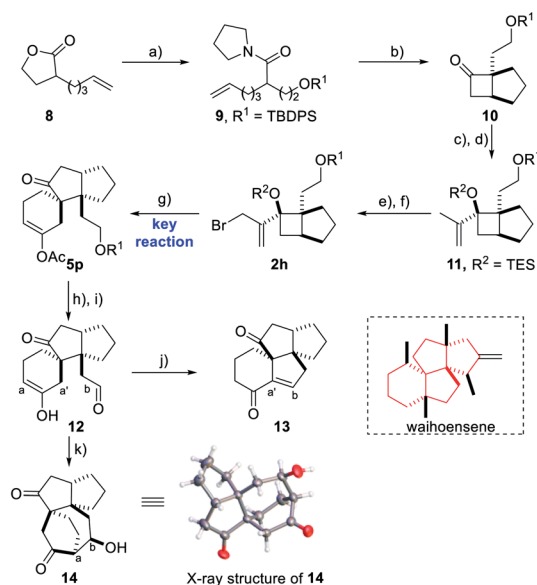
In summary, targeting a highly functionalized spirocyclo[4.5]decane skeleton, a purification free tandem Castro–Stephens coupling/1,3-acyloxy shift/cyclization/semipinacol rearrangement reaction of propargyl esters with allylic bromide has been successfully developed. This method not only features a highly efficient chemical conversion into complex spirobicyclic compounds from simple readily available substrates, but also exhibits a wide substrate scope. Especially, compared with our previous work on semipinacol rearrangement related synthetic methodology, some characteristic functional groups that are necessary for the corresponding bioactive natural products, such as isopropyl^{4g,h} and geminal methyl groups,^{4a} can be readily installed. Moreover, the generation of a vinyl ester moiety by this transformation provides an important hinge for subsequent transformation enabling a quick construction of the key 6/5/5/5-fused tetracyclic skeleton of waihoensene. Further application of this method for the total synthesis of related bioactive natural products is ongoing in the same lab.

Conflicts of interest

The authors declare no competing interests.

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Scheme 3 Synthetic utility of the tetracyclic skeleton of waihoensene. Reagents and conditions: (a) pyrrolidine, Et₃N, neat, 85 °C, then TBDPSCl, imidazole, CH₂Cl₂, 0 °C (98%); (b) Tf₂O, 2,6-di-*tert*-butyl-4-methylpyridine, DCE, reflux, then CCl₄/H₂O reflux (54%); (c) 2-bromopropene, *t*-BuLi, THF, −78 °C (85% brsm); (d) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C (94%); (e) SeO₂, TBHP, CH₂Cl₂, 0 °C – rt (73% brsm); (f) CBr₄, PPh₃, imidazole, CH₂Cl₂, rt (90%); (g) prop-2-yn-1-yl acetate, CuOAc, Cs₂CO₃, DCE, 70 °C, then AuCl₃, PTS, HFB (hexafluorobenzene), rt (40%, dr = 3.2 : 1); (h) TBAF, THF, 0 °C (93%); (i) IBX, EtOAc, reflux (91%); (j) K₂CO₃, MeOH/H₂O = 100 : 1, 0 °C – rt (64%); (k) HCl, THF, rt (89%). TBDPSCl = *tert*-butyl diphenylchlorosilane, DCE = 1,2-dichloroethane, TESOTf = triethylsilyl tri-fluoromethanesulphonate, IBX = 2-iodoxybenzoic acid.



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