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

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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.

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 carbonyc 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
a spirocyclic quaternary carbon center through functional group migration or skeleton reorganization, has been used by us5 and several other research groups6 for the syntheses of a variety of bioactive molecules containing spirocyclo[4.5]decane and related skeletons. Accordingly, the development of more efficient semipinacol rearrangement involved reaction patterns is always a main research program of our group, especially, through ingenious design and realization of sequential chemical transformations in step economy. Inspired by the special chemical properties of propargyl ester in acyloxy sequential chemical transformations in step economy. Inspired especially, through ingenious design and realization of patterns is always a main research program of our group, more e

Discussion
Optimization of reaction conditions
Following the above assumption, we first tested the feasibility of the designed tandem reaction using propargyl ester 1a and allylic bromide 2a as the model substrates. As the copper catalyst has been successfully applied in Castro–Stephens coupling and the 1,3-acyloxy shift process to form an allene group,11 different copper catalysts were examined for promoting the expected reaction.12 Although none of them afforded the desired final product 5a, most could give the Castro–Stephens coupling product 3a, with a best yield of 68% using CuOAc.13 Further screening of the base additive, solvent and reaction temperature showed that the use of Cs2CO3 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% AuPPh3Cl and AgOTf could promote the desired reaction to give the product 5a in 57% yield (Table 1, entry 7). Furthermore, the counterion effect14 was also observed with this reaction, and the use of counterion NTf2− from AgNTf2 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 CH3CN 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 Cs2CO3 and the combination of AuPPh3Cl and AgNTf2 in DCE (Table 1, entry 8) was selected as the optimal reaction conditions.

Substrate scope investigation
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,
most of them could give the expected products in moderate to good yields. When R1 and R2 groups of propargyl ester formed into 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 5g in moderate to good yields, albeit with low diastereoselectivity for 5d to 5f. Additionally, the reaction was also compatible with substrate 2w with different R1/R2 groups. In the case of substrate 2b with R1 and R2 being Me and H, respectively, the expected product 5h was obtained in 36% yield and 1/1 dr ratio. When both R1 and R2 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 and cedrol, respectively, a new general synthetic strategy for these types of natural products might be developed based on propargyl ester with 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-1H-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).

### Table 2: Exploration of the generality of the tandem reaction of cyclic alkanes as migrating groups

| R1 | R2 | R3 | R4 | R5 | R6 | Product | Yield |
|----|----|----|----|----|----|---------|-------|
| Br | OTBS | Me | Me | Me | Me | 5a | 56% (43%) |
| Br | OTBS | Me | Me | Me | Me | 5b | 53% |
| Me | Me | Me | Me | Me | Me | 5c | 55% |
| Me | Me | Me | Me | Me | Me | 5d | 37% dr = 1:1 |
| Me | Me | Me | Me | Me | Me | 5e | 54% dr = 1:1.4 |
| Me | Me | Me | Me | Me | Me | 5f | 48% |
| Me | Me | Me | Me | Me | Me | 5g | 50% |
| Br | OTBS | Me | Me | Me | Me | 5h | 50% (5%) |
| Me | Me | Me | Me | Me | Me | 5i | 54% |
| Me | Me | Me | Me | Me | Me | 5j | 53% |
| Me | Me | Me | Me | Me | Me | 5k | 50% |

### Table 3: Exploration of the generality of the tandem reaction of aromatic rings as migrating groups

| R1 | R2 | R3 | R4 | R5 | R6 | Product | Yield |
|----|----|----|----|----|----|---------|-------|
| Me | Me | Me | Me | Me | Me | 7a | 50% |
| Me | Me | Me | Me | Me | Me | 7b | 52% |
| Me | Me | Me | Me | Me | Me | 7c | 53% |
| Me | Me | Me | Me | Me | Me | 7d | 49% dr = 1:1.2:4 |
| Me | Me | Me | Me | Me | Me | 7e | 53% |
| Me | Me | Me | Me | Me | Me | 7f | 54% |
| Me | Me | Me | Me | Me | Me | 7g | 50% |
| Me | Me | Me | Me | Me | Me | 7h | 51% |
| Me | Me | Me | Me | Me | Me | 7i | 50% |
| Me | Me | Me | Me | Me | Me | 7j | 50% |

### Scheme 2: New synthetic strategy design toward corresponding sesquiterpenes.

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moiety in a variety of natural products like limaspermidine\textsuperscript{15a} and strychnine,\textsuperscript{16a} 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, \textit{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,\textsuperscript{16a} 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 cycladdition reaction of an allene substrate prepared in 12 steps as the key step.\textsuperscript{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.\textsuperscript{18} The relative configuration of 5p and its diastereoisomer 5q was confirmed by the X-ray structure analysis of their derivatives.\textsuperscript{14} Next, the TBDPS protecting group of 5p was removed with TBAF followed by IBX oxidation providing dicarboxyl compound 12. A K$_2$CO$_3$-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\textsuperscript{16a} and geminal methyl groups,\textsuperscript{16b} 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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