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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†

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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 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

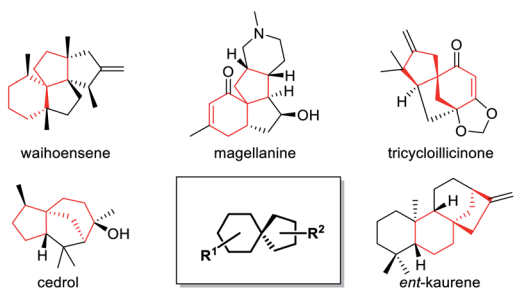

Fig. 1 Representative important natural products bearing the spirocyclo[4.5]decane core.

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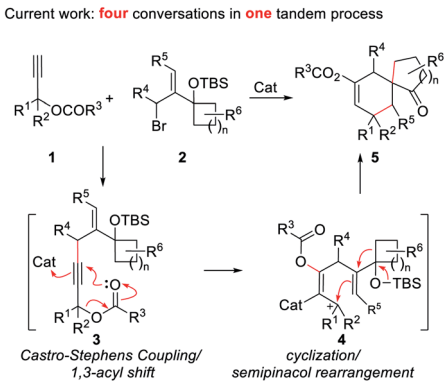


Scheme 1 Strategy design toward the spirocyclo[4.5]decane skeleton.

a spirocyclic quaternary carbon center through functional group migration or skeleton reorganization, has been used by us[6] and several other research groups[7] 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 shift/cyclizations,[8] we envisioned that a 1,3-acyloxy shift of the propargyl ester[9] intermediate **3** generated by a Castro–Stephens coupling[10] from propargyl ester **1** and allylic bromide **2** possessing a potential migration moiety might be viable to trigger a cyclization/semipinacol rearrangement of **4** affording multi-substituted spirocyclo[4.5]decane and related skeletons (Scheme 1). Based on the mechanism analysis of the above four transformations, it is highly likely to achieve them in a tandem manner. Additionally, since a series of substituent combinations can be used from the two substrates, this strategy, once feasible, will not only exhibit better transformation efficiency and product complexity and diversity, but also further enrich the content of semipinacol rearrangement. Herein, we present such a novel sequence and its application in the construction of the tetracyclic ring system of waihoensene, a new example of complex bioactive molecule-directed synthetic methodology development.

Discussion

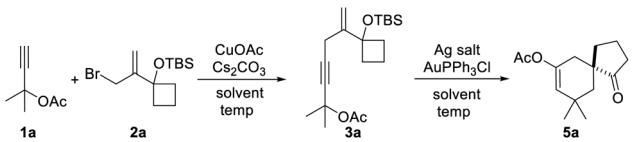
Optimization of reaction conditions

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.[12] Further screening of the base additive, solvent and reaction temperature 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 effect[13] 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.

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,

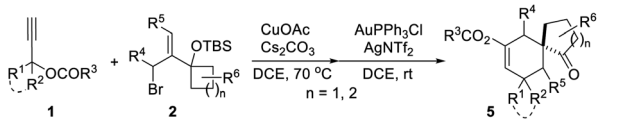
Table 1 Optimization of reaction conditions[a]

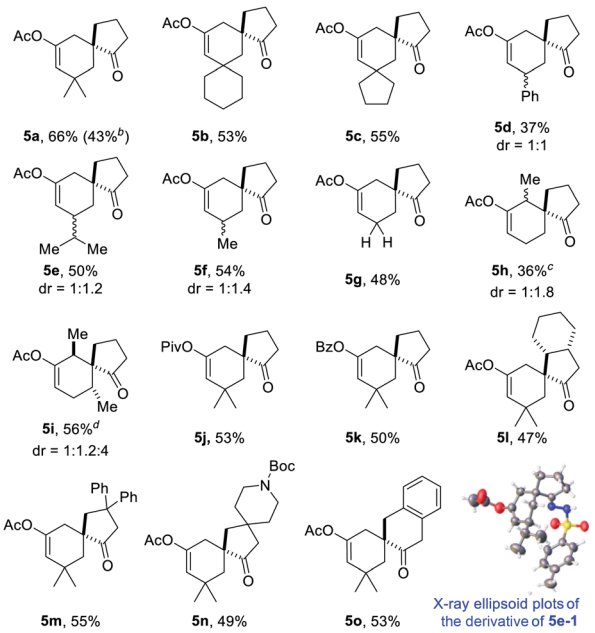


Entry	Solvent	Ag salt	Temp	Product	Yield
1	DCE[b]	—	70 °C[c]	**3a**	82%[d]
2	Benzene[b]	—	rt[c]	**3a**	40%[d]
3	THF[b]	—	rt[c]	**3a**	47%[d]
4	EtOH[b]	—	rt[c]	**3a**	55%[d]
5	CH_3CN[b]	—	rt[c]	**3a**	55%[d]
6	DMF[b]	—	rt[c]	**3a**	54%[d]
7	DCE	AgOTf	rt[e]	**5a**	57%[f]
8	DCE	$AgNTf_2$	rt[e]	**5a**	66%[f]
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_3CN[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

[a] Unless specified, all reactions were carried out using **1a** (0.5 mmol, 2.5 eq.), **2a** (0.2 mmol, 1.0 eq.), CuOAc (30 mol%), Cs_2CO_3 (50 mol%), $AuPPh_3Cl$ (10 mol%), and Ag salt (10 mol%) in a reaction tube in DCE (2 mL) at indicated temperature. [b] The solvent of Castro–Stephens coupling for **3a**. [c] Temperature for the first coupling reaction. [d] Isolated yield of **3a**. [e] The first coupling step was carried out at 70 °C. [f] Isolated yield of **5a** in a purification free manner. [g] After filtration, the filtrate was concentrated and diluted with the indicated solvent (4 mL) for the subsequent operation.

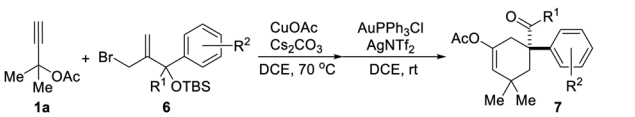
Table 2 Exploration of the generality of the tandem reaction of cyclic alkanes as migrating groups[a]

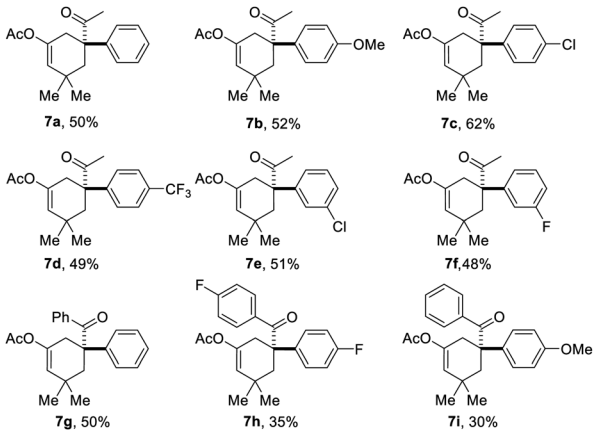




[a] Unless specified, all reactions were conducted using **1** (0.5 mmol, 2.5 eq.), **2** (0.2 mmol, 1.0 eq.), CuOAc (30 mol%), Cs_2CO_3 (50 mol%), $AuPPh_3Cl$ (10 mol%), and $AgNTf_2$ (10 mol%) in a reaction tube in DCE (2 mL) at indicated temperature. [b] 10 mmol of **1a** (1.26 g) and 4 mmol of **2a** (1.22 g) were used. [c] $CHCl_3$ was used as the solvent after Castro–Stephens coupling. [d] $AuCl_3$ (10 mol%) in 2 mL HFB (hexafluorobenzene) was used instead of the combination of $AuPPh_3Cl$ and $AgNTf_2$ after Castro–Stephens coupling; the structure shows the relative configuration of the major isomer.

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

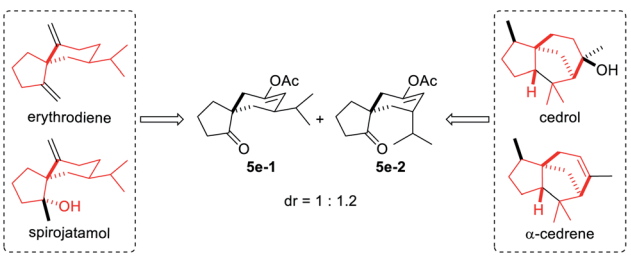




[a] All reactions were conducted using **1a** (0.5 mmol, 2.5 eq.), **6** (0.2 mmol, 1.0 eq.), CuOAc (30 mol%), Cs_2CO_3 (50 mol%), $AuPPh_3Cl$ (10 mol%), and $AgNTf_2$ (10 mol%) in a reaction tube in DCE (2 mL) at indicated temperature.

most of them could give the expected products in moderate to good yields. When R^1 and R^2 groups of propargyl ester formed a ring system (*i.e.*, cyclohexyl and cyclopentyl), the reaction with bromide **2a** (R^4, R^5, R^6 = H) proceeded smoothly providing tricyclic products **5b** and **5c** in 53% and 55% yield, respectively. Moreover, with the R^1 as H, R^2 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 **2** with different R^4/R^5 groups. In the case of substrate **2b** with R^4 and R^5 being Me and H, respectively, the expected product **5h** was obtained in 36% yield and 1/1 dr ratio. When both R^4 and R^5 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 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

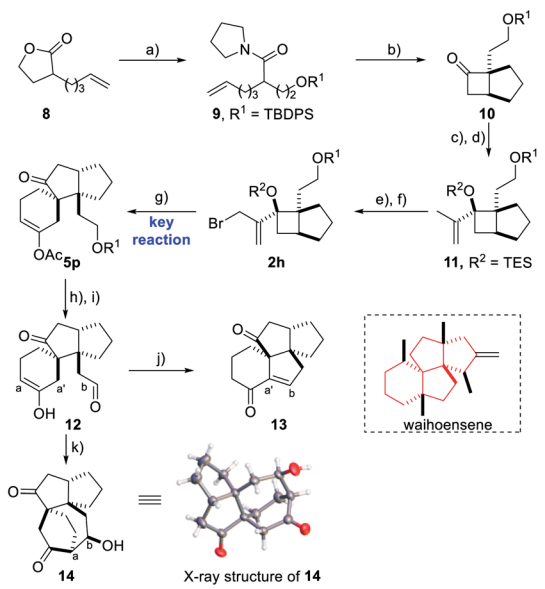


Scheme 2 New synthetic strategy design toward corresponding sesquiterpenes.

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 K_2CO_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.



Scheme 3 Synthetic utility of the tetracyclic skeleton of waihoensene. Reagents and conditions: (a) pyrrolidine, Et_3N, neat, 85 °C, then TBDPSCl, imidazole, CH_2Cl_2, 0 °C (98%); (b) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, DCE, reflux, then CCl_4/H_2O reflux (54%); (c) 2-bromopropene, *t*-BuLi, THF, −78 °C (85% brsm); (d) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (94%); (e) SeO_2, TBHP, CH_2Cl_2, 0 °C – rt (73% brsm); (f) CBr_4, PPh_3, imidazole, CH_2Cl_2, rt (90%); (g) prop-2-yn-1-yl acetate, CuOAc, Cs_2CO_3, DCE, 70 °C, then $AuCl_3$, PTS, HFB (hexafluorobenzene), rt (40%, dr = 3.2 : 1); (h) TBAF, THF, 0 °C (93%); (i) IBX, EtOAc, reflux (91%); (j) K_2CO_3, MeOH/H_2O = 100 : 1, 0 °C – rt (64%); (k) HCl, THF, rt (89%). TBDPSCl = *tert*-butyl diphenylchlorosilane, DCE = 1,2-dichloroethane, TESOTf = triethylsilyl trifluoromethanesulphonate, IBX = 2-iodoxybenzoic acid.

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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