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A new approach toward the bicyclo[3.2.1]octenes via a carbocation-based cyclization from unusually functionalized seven-membered ring precursors

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Dedicated to Professor Feng-Peng Wang on the occasion of his 70th birthday

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ABSTRACT

A base-promoted 1,5-ester shifting rearrangement reaction has been developed to access unusually functionalized seven-membered ring precursors, which could be further successfully transformed into bicyclo[3.2.1]octenes by directly closing one-carbon bridge via a key carbocation-based cyclization, providing a new and efficient route to the core of many natural products and their analogs.

1. Introduction

The functionalized bicyclo[3.2.1]octane cores are commonly found in nature as structurally basic frameworks of numerous biologically interesting and synthetically challenging natural products.[1] Most of these compounds bear quaternary carbon centers adjacent to the bridged methylene (Fig. 1). Such compounds comprise many bioactive sesqui- and diterpenes, for example, the tricyclic cedane-type sesquiterpenes: α-cedene (**1**),[2] α-funebrene (**2**)[3] and 8, 14-cedranediol (**3**),[4] and the tetracyclic stemodane-type diterpenes: martimol (**4**)[5] and aphidicolin (**5**).[6]

Owing to the significance of this scaffold both from theoretical and synthetic points of view, tremendous progress has been achieved in this field during the past decades, providing many useful synthetic methodologies that have proved particularly well adapted in some elegant total syntheses of complex natural products.[1] Currently, the most popular approaches to this carbon skeleton predominately rely on cyclization of properly functionalized six-membered ring or five-membered ring precursor to form the two carbon or three carbon bridge of the bicyclo[3.2.1] core.[1] It is of surprising that the relatively straightforward approach by closing the one-carbon bridge of the bicyclo[3.2.1] skeleton from seven-membered ring has not been broadly developed,[7] probably due to the difficulties in the preparation of the seven-membered ring precursors.

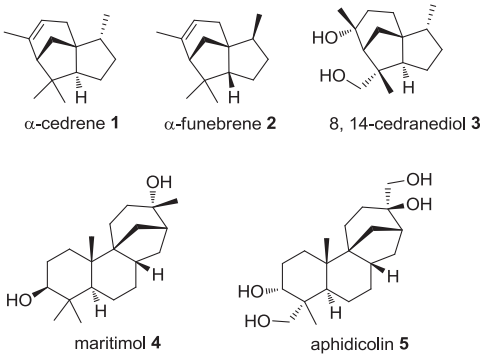

Fig. 1. Structures of the representative sequiterpenes and diterpenens bearing bicyclo[3.2.1]octane moieties.

Herein, we wish to report an rapid construction of a functionalized bicyclo[3.2.1]octene unit bearing a methylene bridge from the properly functionalized seven-membered unsaturated

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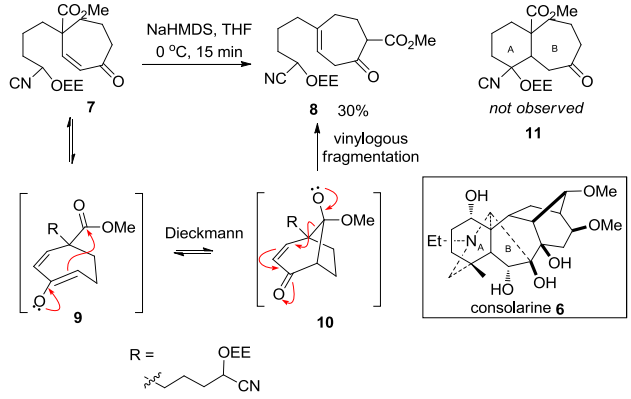
carbocycles, generated by an unusual transannular migration of ester group on the easily accessible seven-membered rings.

2. Result and discussion

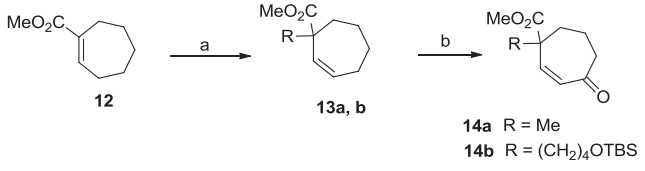
During recent work within our group focusing on the synthesis of consolarine (**6**),[8] we unexpectedly observed a migrated rearrangement of ester group on seven-membered ring (Scheme 1). When attempting to perform intramolecular Michael addition of conjugated enone **7** to close the ring A using sodium bis(-trimethylsily)amide (NaHMDS) as base, we observed the generation of β-keto ester **8** in 30% yield without isolation of any expected intramolecular Michael addition product **11**.



Scheme 1. Unexpected observation of the formation of **8** and proposed mechanistic pathway.

This β-ketoester compound was tentatively thought to result from a base promoted Dieckmann-type reaction of the enol form of the cyclic enone onto the ester group to form a plausible bicyclo [3.2.1]enone monohemiketal intermediate **10**, followed by a vinylogous retro-Dieckmann-type fragmentation[9] of the C–C bond of the one-carbon bridge linking to the quaternary carbon and a double bond migration. We conceived that this unusual 1,5-ester shift[10] might provide an alternative strategy to access functionalized seven-membered carbocycles, which would be useful as building blocks in synthesis of more complex ring systems compatible with some natural products.

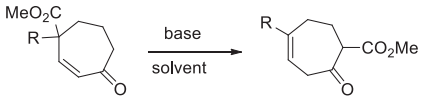
To probe and develop this interesting process we chose the readily accessible model substrate **14a** bearing a simple methyl group for an optimization study (Scheme 2). Following a modified Kuwajima and Urabe's deconjugative alkylation procedure reported by Trost and co-workers,[11,12] the commercially available methyl cyclohept-1-enecarboxylate could be smoothly transformed into **13a** in good yield by treatment with LDA and iodomethane in THF in the presence of HMPA. Subsequent allylic oxidation was performed with PDC and *tert*-butyl hydroperoxide in benzene at rt,[13] delivering the desired conjugated enone **14a** as migration substrate in 79% yield. By applying the same procedure the four-carbon alkyl substituted derivative **14b** was afforded in 49% yield for the two steps.



Scheme 2. Preparation of the model substrates. Reagents and conditions: (a) LDA, HMPA, RI, THF, −78 °C, 60% for **13a**, 65% for **13b**; (b) *t*-BuOOH (70%), PDC, Celite, benzene, rt, 79% for **14a**, 75% for **14b**.

With the model substrate in place, the development of optimum migration conditions was addressed by testing various reaction parameters (Table 1). Initial treatment of **14a** with NaHMDS in THF at 0 °C gave an encouraging 40% yield of **15a** (entry 1). Screening of the bases discovered that the KHMDS proved to be relatively more favorable, giving a slightly elevated 47% yield (entry 3). Other bases such as LiHMDS, *t*-BuOK and NaH all gave decreased yields (entry 2, 10, and 11) and the LDA only resulted in decomposition of substrate (entry 12). Lowering the temperature has little influence on the reaction (entry 4 and 7). By changing the solvent to toluene, the yield could be further improved to 60%. Increasing the concentration was found to be beneficial to this transformation. Ultimately, it was found that the optimal reaction being performed at 0.2 M in toluene could give a highest yield of 77% (entry 8 and 9). By employing this optimal reaction condition ketoester **8** and **15b** could also be efficiently prepared in good yield, indicating a potentially general substrate tolerance of this conversion (entry 13 and 14).

Table 1
Optimization of the base-promoted tansannular rearrangement of ester group on **14a**[a]



Entry	Substrate	Base	Solvent	Temp (°C)	Yield (%)[b]
1	**14a**	NaHMDS	THF	0	40
2		LiHMDS	THF	0	30
3		KHMDS	THF	0	47
4		KHMDS	THF	−78→0	45
5		KHMDS	Ether	0	45
6		KHMDS	Toluene	0	60
7		KHMDS	Toluene	−78→0	58
8		KHMDS	Toluene	0	77[c]
9		KHMDS	Toluene	0	53[d]
10		*t*-BuOK	THF	0	35
11		NaH	THF	0	5
12		LDA	THF	0	0
13	**14b**	KHMDS	THF	0	80
14	**7**	KHMDS	THF	0	60

[a] Reactions were conducted with 1.2 equiv base at 0.05 M concentration unless noted.
[b] Isolated yields.
[c] Performed at 0.2 M concentration.
[d] Performed at 0.5 M concentration.

This uncommon rearrangement reaction prompted us to further investigate the mechanism of the reaction. We reasoned that if the mechanic pathway was as shown in Scheme 1, the bicyclo[3.2.1] enone **10** should be a crucial intermediate in this transformation. Nevertheless, no such a bicycle compound was isolated in the reaction mixture under above basic conditions. Recently, Dixon and co-workers[7e] reported an acid-catalyzed Dieckmann-type condensation to access bicyclo[3.2.1]- octenediones. Thus, following the same acidic condition, **14a** was firstly converted to the expected bridged bicycle **16** in a reasonable yield of 50%. Subsequently, treatment of **16** with sodium methoxide or sodium ethoxide in toluene led to smooth vinylogous fragmentation, successfully delivering the vinyl ketoester **15a** and **17** in 80% and 70% yield, respectively (Scheme 3). This stepwise reaction process apparently demonstrates the rationality of the transformation pathway proposed in Scheme 1. Interestingly, when diketone **16** was submitted to the action of methanolic potassium hydroxide followed by methylation with CH_2N_2, it was found that compound **16** was completely transformed back to the starting material **14a** in almost quantitative yield via a common retro-Dieckmann-type cleavage.[14]