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Application of the carbene cyclization–cycloaddition cascade in total synthesis*

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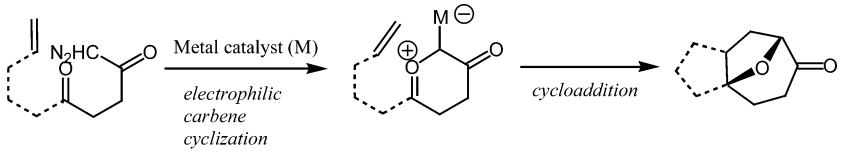
Abstract: The title reaction is a key transformation that has been applied to the synthetic studies of the antitumor and antifungal compounds, the pseudolaric acids.

Keywords: carbenes; dipolar cycloaddition; carbonyl ylides; pseudolaric acid; total synthesis.

INTRODUCTION

The cyclization of an electrophilic carbene with a tethered carbonyl group to furnish a carbonyl ylide, followed by cycloaddition with a dipolarophile, is a cascade reaction that constructs a bicyclic molecule bearing multiple stereocenters in one step (Scheme 1) [1]. This cascade reaction possesses the qualities of an ideal reaction because of its operational simplicity and atom economy, which pays exceptional dividends in terms of the increase in product molecular complexity. The intramolecular version of this reaction converts an acyclic diazoketone substrate into an oxatricyclic ketone bearing at least three new stereocenters.



Scheme 1 Carbene cyclization–cycloaddition cascade reaction.

The utility of this reaction is complemented by the fact that the resultant oxapolycyclic molecules are rigid and facially biased such that a variety of functional group transformations can be induced stereoselectively in a predictable fashion [2]. These substrates allow additional synthetic manipulations which increase the stereochemical complexities of the molecules for the synthesis of complex natural products.

This cascade reaction appeared to present an excellent opportunity for the expedient synthesis of a family of antitumor diterpenoid natural products, the pseudolaric acids (Scheme 2) [3]. The pseudolaric acids **1a–c** have been isolated from the root bark of a tree native to China, *Pseudolarix*

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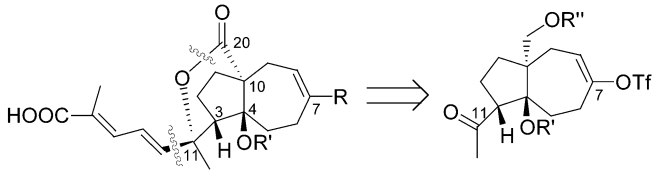
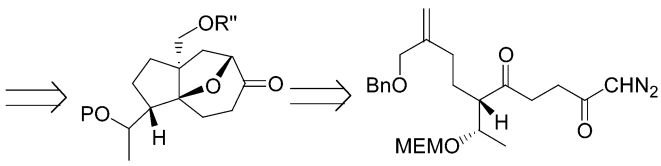
kaempferi Gordon (Pinaceae), which has been traditionally used to treat fungal infections as early as the 17th century [4]. Pseudolaric acid B **1b** has been determined to be the main antifungal constituent and has been evaluated to have activity comparable to that of amphotericin B against a number of strains of fungi [5]. In vitro tests of pseudolaric acids A, B, and C **1a–c** revealed their demonstrated cytotoxicity to several cancer cell lines at submicromolar levels with pseudolaric acids A and B being the more potent members of this family [6].



Pseudolaric acid A **1a** R= Me, R'= Ac
Pseudolaric acid B **1b** R= CO_2Me, R'= Ac
Pseudolaric acid C **1c** R= CO_2Me, R'= H

2



3 **4**

Scheme 2 Retrosynthetic analysis of the pseudolaric acids.

Structure of the pseudolaric acids and their retroanalyses

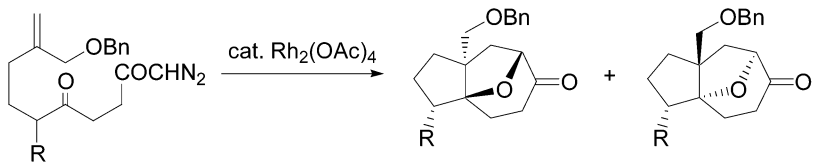
Pseudolaric acids A, B, and C all possess the same characteristic perhydroazulene skeleton with *trans*-fused acetoxy/hydroxy and lactone groups at the junctions, which is an unusual arrangement for naturally occurring hydroazulenes [7]. Embedded in the common structure are three tertiary and one quaternary stereocenters contiguously positioned in the tricyclic core. Owing to their intriguing molecular architectures and promising biological activities, the pseudolaric acids have been the targets of a number of synthetic efforts [8–12].

Our aim was to develop a convergent strategy to all of the members of the pseudolaric acid family **1** via the carbene cyclization–cycloaddition cascade reaction [12]. Thus, these target molecules were carried through retroanalysis via a cleavage of the lactone functionality, a disconnection of a vinyl nucleophile at C11, back to a common enol triflate precursor **2** (Scheme 2). From this intermediate, pseudolaric acid A bearing a methyl substituent and pseudolaric acids B and C with carbomethoxy groups at C7 are all accessible. Enol triflate **2** can be obtained via a reductive elimination of oxatricyclic ketone **3**, in which the acetate of the tertiary alcohol at C4 has been masked as an oxygen bridge. Oxatricyclic ketone **3** is envisioned as the key intermediate that could be constructed by carbene reaction cascade initiated by the decomposition of an appropriately functionalized acyclic diazoketone **4**.

In the context of this study in total synthesis, several aspects of this cascade reaction were explored. Although this reaction has been studied previously [1,13,14], the use of functionalized dipolarophiles have not been extensively examined in the intramolecular reaction. The successful application of this reaction requires the efficient and selective dipolar cycloaddition between the carbonyl ylide and a β,β-disubstituted unactivated olefin. The extent and direction of the diastereoselectivity with respect to pre-existing stereocenters were examined. Finally, the influence of the rhodium catalyst, in particular, chiral rhodium catalysts on the stereochemical outcome of this reaction, was also studied.

SYNTHETIC STUDIES

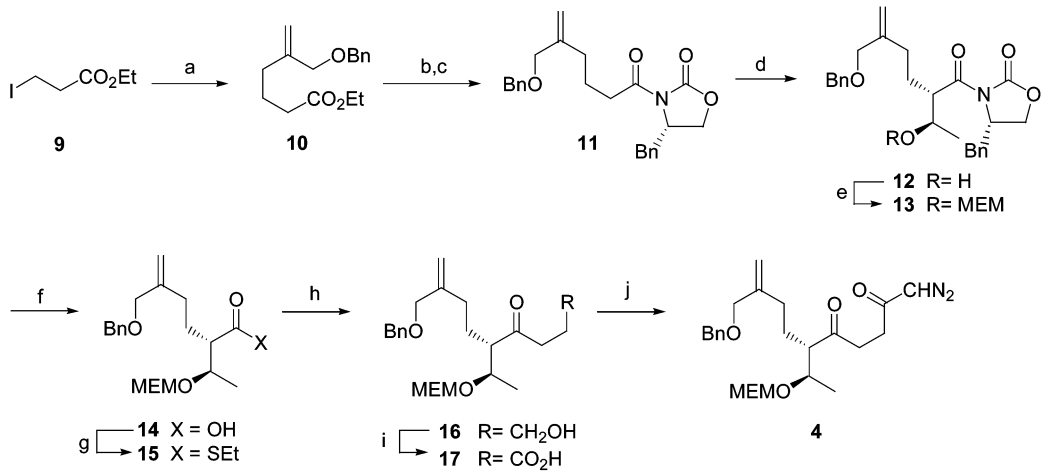
Two model studies provided the background for the synthetic studies. The carbene cyclization–cycloaddition cascade reaction of **5**, initiated with a catalytic amount of $Rh_2(OAc)_4$, smoothly yielded oxatricyclic ketone **6**, showing the viability of using a more hindered, benzyloxy-substituted olefin as the dipolarophile in the intramolecular cycloaddition (Scheme 3). In this sole cycloaddition product **6**, the oxygen bridge and the side chain at C10 were *trans* as required for the natural product, since the alternative *cis*-stereochemical arrangement was known to be much more strained [14].



Scheme 3 Model studies.

The diastereoselectivity with respect to pre-existing stereocenters was examined initially using **7**, bearing a methyl substituent at C3 where a more complex substituent would be required for the synthesis of pseudolaric acid (Scheme 3). The carbene cyclization–cycloaddition reaction of **7** produced two cycloadducts in 63 % yield in a ratio of 4:1. The major diastereomer was found to be **8a**, in which the C3 substituent and the benzyloxymethylene group were *syn* as required for pseudolaric acid, and substrate-based control yielded the desired isomeric cycloadduct. The relative stereochemistry in **8a** was determined by the observation of a nuclear Overhauser effect (NOE) between the methyl and the benzyloxymethylene protons, which showed that these groups were on the same side of the cyclopentane ring, and confirmed by the absence of this effect in isomer **8b**. This result was in contrast with previous studies of this reaction cascade for the construction of the tigliane system by Dauben et al. in which stereocenters on the tether had no bearing on the stereochemistry of the carbonyl ylide cycloaddition [3b], or related studies by Maier in which cycloadditions of isomünchnones gave products exclusively with the opposite diastereoselectivity [15].

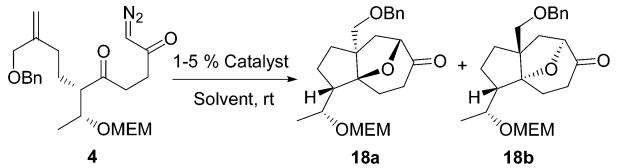
With these preliminary results in hand, the synthesis of the optically pure diazoketone precursor **4** was undertaken (Scheme 4). The zinc homoenolate of iodoester **9** was allylated with 2-benzyloxymethyl-3-bromopropene [16] to give ester **10** in 88 % yield. The absolute stereochemistry at C3 was installed using Evan's chiral auxiliary methodology [17]. Thus, ester **10** was hydrolyzed and activated to give the acylated oxazolidinone **11**. Aldol reaction via the boron enolate of **11** with acetaldehyde produced alcohol **12** as one diastereomer, which was subsequently protected to give ether **13**. Cleavage of the oxazolidone provided acid **14**, which was homologated by the addition of the cuprate derived from Normant's Grignard reagent, $ClMg(CH_2)_3OMgCl$, via thioester **15** [18]. Oxidation of the alcohol to acid **17**, activation and treatment with diazomethane, generated the requisite chiral diazoketone **4**.



Scheme 4 Synthesis of the chiral diazoketone **4**. Reagents and conditions: **a.** Zn, CuCN, 3-bromo-2-benzyloxymethylpropene, THF, DMA, rt, 88 %; **b.** NaOH, MeOH, 98 %; **c.** *t*-BuCOCl, Et_3N, DMAP, (*S*)-4-benzyl-2-oxazolidone, THF, –78 ºC to rt, 80 %; **d.** (i) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 ºC; (ii) CH_3CHO, –78 to 0ºC, 67 %, (92 % based on recovered substrate); **e.** MEMCl, DIPEA, CH_2Cl_2, rt, 93 %; **f.** (i) LiOH, H_2O_2, THF-H_2O, 0 ºC, (ii) Na_2SO_3, 86 %; **g.** EtSH, DCC, DMAP, CH_2Cl_2, rt, 91 %; **h.** $ClMg(CH_2)_3OMgCl$, CuI, THF, 77 %, (93 % based on recovered substrate); **i.** PDC, DMF, H_2O, 75 %; **j.** (i) *i*-BuOCOCl, Et_3N, THF, –20 ºC, (ii) CH_2N_2, Et_2O, 0 ºC to rt, 72 %.

Diazoketone **4** was subjected to treatment with a variety of rhodium catalysts; selected examples are shown in Table 1. Diazo decomposition with a catalytic amount of dirhodium acetate produced, in one step, the oxatricyclic adduct **3** in 61 % yield as two diastereomers **18a** and **18b** in a ratio of 1:1.3 (Table 1, entry 1). It was immediately apparent that the diastereoselectivity has diminished compared to the model studies of substrate **7**. Furthermore, the major diastereomer was **18b**, having the opposite stereochemistry required for the total synthesis. A screening of other commercially available rhodium catalysts did not lead to any increase for the desired isomer (Table 1, entry 2). Using a more polar solvent such as dichloromethane slightly disfavored the formation of desired isomer **18a**, while a less polar solvent such as benzotrifluoride tended to favor its formation [19,20] (Table 1, entry 3). However, the reaction appeared to be largely substrate-controlled.

Table 1 Carbene cyclization–cycloaddition cascade reaction of diazoketone **4**.



Entry	Catalyst	Solvent	Product Yield	18a : 18b
1	$Rh_2(OAc)_4$	CH_2Cl_2	61 %	1 : 1.3
2	$Rh_2(OCOCF_3)_4$	CH_2Cl_2	61 %	1 : 1.9
3	$Rh_2(OAc)_4$	CF_3Ph	45 %	1 : 1.2
4	Rh_2(R-DOSP)$_4$	CH_2Cl_2	53 %	1 : 1.3
5	Rh_2(S-DOSP)$_4$	CH_2Cl_2	62 %	1 : 1.7
6	Rh_2(S-DDBNP)$_4$	CH_2Cl_2	54 %	1 : 1.6
7	Rh_2(S-BPTV)$_4$	CH_2Cl_2	67 %	1.3 : 1
8	Rh_2(S-BPTV)$_4$	CF_3Ph	51 %	1.4 : 1

Although our preliminary results in the tandem cyclization–cycloaddition of substrate **7** gave the desired diastereomer **8a** with the C3 substituent *cis* with respect to the bridgehead substituent, the analogous reaction of substrate **4** generated the opposite diastereomer **18b** as the major product. In fact, the increase in the steric demand of the C3 substituent in compound **4** over **7** was initially expected to further enhance the factors that led to the predominance of **8a** over **8b**. The change in the diastereoselectivity from the case of model compound **7** appears to be due to the increase in the steric demands of the substituent at C3 in substrate **4**, which led to an undesirable steric interaction that was alleviated by cycloaddition in the opposite sense (Fig. 1). The effect of this through-space steric interaction is particularly acute in the present cycloaddition reaction with the benzyloxymethylene substituent in the β-position of dipolarophile.

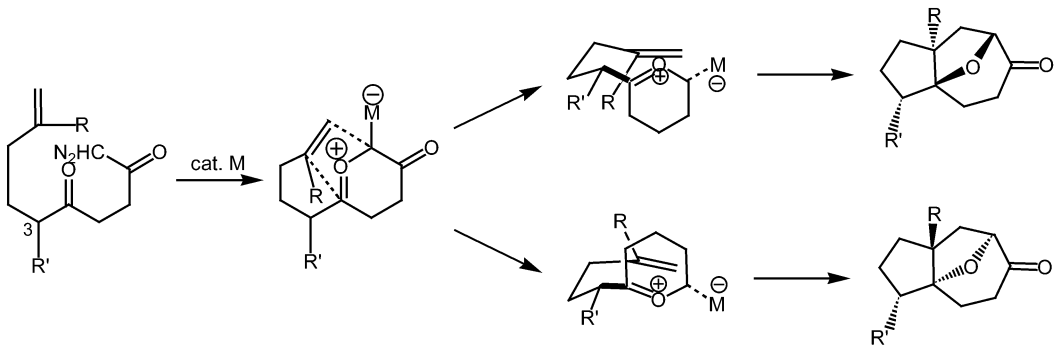


Fig. 1

The recent highly enantioselective carbene cyclization–cycloaddition reactions that have been realized strongly suggest that the rhodium complex remains associated to the carbonyl ylide during the cycloaddition [20,21]. Therefore, chiral rhodium catalysts were examined in this cascade reaction to see if reagent control could be exerted to overcome the substrate-based selectivity, to direct the formation of the desired isomer **18a** (Table 1, entries 4–8). The commercially available chiral rhodium catalysts based on *N*-arylsulfonylprolinate ligands $Rh_2(DOSP)_4$ led to good yields of the cycloadducts [22], but the stereochemical results of both the (*R*)- and (*S*)-enantiomeric catalysts remained in favor of the undesired diastereomer **18b** (entries 4–5). Although Hodgson's catalyst Rh_2(*R*-DDBNP)$_4$ was extremely successful in the enantioselective intramolecular cyclization–cycloaddition of a stabilized carbene, the diastereoselectivity of the reaction with substrate **4** was low (entry 6) [21]. Finally, Hashimoto's catalyst Rh_2(*S*-BPTV)$_4$, which induced highly enantioselective carbene cyclization intermolecular cycloadditions, generated diastereomers in which the ratio of cycloadducts was reversed in favor of the desired isomer **18a** for the first time (entry 7) [20]. Switching the solvent from dichloromethane to benzotrifluoride, the ratio in favor of **18a** was further increased to 1.4:1 (entry 8). This major diastereomer **18a** has the perhydroazulene nucleus of pseudolaric acid, and bears three of the four absolute stereocenters of the natural product. Further investigations to improve the diastereoselectivity for advanced intermediate **18a** are being conducted.

In summary, an approach toward the synthesis of the antifungal and cytotoxic pseudolaric acids based on the carbene cyclization–cycloaddition cascade reaction has been described. In this key reaction of diazoketone **4**, substrate-controlled diastereoselectivity was preferential for the undesired diastereomer, but reagent control through the use of Hashimoto's chiral rhodium catalyst Rh_2(*S*-BPTV)$_4$ reversed the selectivity in favor of **18a**. Thus, the synthesis of the key chiral intermediate **18a** containing three out of the four required stereocenters in the pseudolaric acids has been achieved. The transformation of **18a** to the target molecules, and the completion of the total synthesis following this strategy are being actively pursued.

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