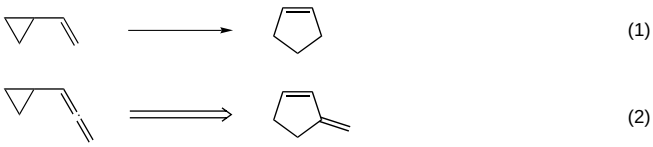
of the carbonyl groups and the alkylaluminum substituents are involved in the coordination. In a chelation complex, alkyl groups R are far removed from the carbonyl center due to the sp^3-like conformation of aluminum, so transfer of an R group from aluminum to the carbonyl center through an unfavorable four-membered transition state seems quite unlikely. See: T. Ooi, M. Takahashi, K. Maruoka, *J. Am. Chem. Soc.* **1996**, *118*, 11307; T. Ooi, E. Tayama, M. Takahashi, K. Maruoka, *Tetrahedron Lett.* **1997**, *38*, 7403. Other examples of bidentate Lewis acids: V. Sharma, M. Simard, J. D. Wuest, *J. Am. Chem. Soc.* **1992**, *114*, 7931; M. Reilly, T. Oh, *Tetrahedron Lett.* **1995**, *36*, 217; *ibid.* **1995**, *36*, 221.

[7] If the proposed mechanism is truly operative, it must be assumed that dilution would not affect the rate of alkylation with **1**, but would further retard reaction with **2**.

Rhodium(I)-Catalyzed Regioselective Ring-Expanding Rearrangement of Allenylcyclopropanes into Methylenecyclopentenes**

Minoru Hayashi, Tadashi Ohmatsu, Yun-Ping Meng, and Kazuhiko Saigo*

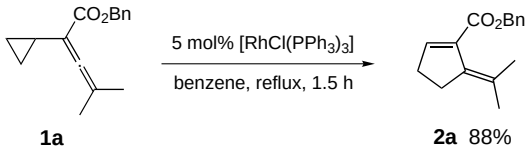
The vinylcyclopropane–cyclopentene rearrangement has attracted much attention owing to its potential synthetic utility.[1–3] The skeletal similarity between vinylcyclopropanes and allenylcyclopropanes led us to examine the rearrangement of allenylcyclopropanes into methylenecyclopentenes; the selective transformation has not yet been reported (Scheme 1).[3–5] Here we describe the first examples of the



Scheme 1. Similarity of the skeletal structures of vinylcyclopropanes and allenylcyclopropanes.

transition metal catalyzed selective transformation of allenylcyclopropanes into methylenecyclopentenes.

Our test of the hypothesis started with the allenylcyclopropane **1a**, which was easily prepared by palladium-catalyzed carbonylation of the benzyl carbonate of 2-methyl-4-cyclopropyl-3-butyn-2-ol. Heating allenylcyclopropane **1a** in refluxing benzene for 1.5 h in the presence of 5 mol% of $[RhCl(PPh_3)_3]$ gave the corresponding methylenecyclopentene **2a** in 88% yield (Scheme 2).



Scheme 2. Rhodium(I)-catalyzed rearrangement of cyclopropylallene **1a**.

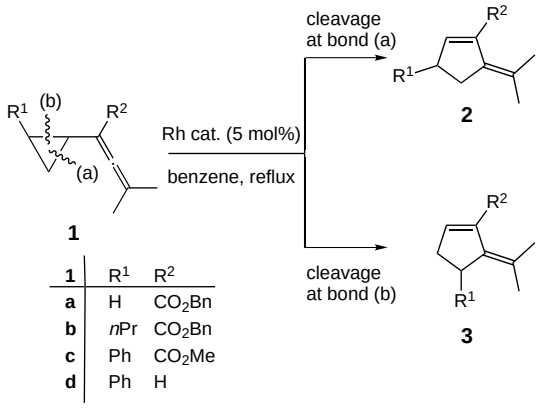
Wender and co-workers reported that a cationic rhodium(I) complex catalyzes the [5+2] cycloaddition of vinylcyclopropanes with alkynes faster than a neutral rhodium complex.[6] However, in our case, the cationic rhodium complex $[Rh(cod)_2]^+BF_4^-$ (cod = 1,5-cyclooctadiene) required a longer reaction time than $[RhCl(PPh_3)_3]$ to complete the rearrangement, although the initial reaction rate was faster (Table 1, entries 1 and 2). These reactions are the first examples of the selective rearrangement of an allenylcyclopropane into the corresponding methylenecyclopentene.

Table 1. Rhodium(I)-catalyzed rearrangement of allenylcyclopropanes

Entry	1	Cat.[a]	t [h]	Products[b]	Yield [%][c]	2:3[d]
1	**1a**	A	1.5	**2a**	88	–
2	**1a**	B	3	**2a**	88	–
3	**1b**	A	1	**2b/3b**	89	88:12
4	**1b**	C	3	**2b/3b**	98	>99:1
5	**1b**	B	10	**2b/3b**	89	>99:1
6	**1c**	A	3	**2c/3c**	99	69:31
7	**1c**	C	0.8	**2c/3c**	98	92:8
8	**1c**	B	14	**2c/3c**	95	5:95
9	**1d**	A	12	**2d/3d**	73	56:44
10	**1d**	D	12	**2d/3d**	79	15:85
11	**1d**	B	12	**2d/3d**	78	3:97

[a] Catalyst A: $[RhCl(PPh_3)_3]$, B: $[Rh(cod)_2]^+BF_4^-$, C: $[Rh(PPh_3)_3]^+BF_4^-$ (prepared in situ from an equimolar mixture of $[RhCl(PPh_3)_3]$ and $AgBF_4$), D: $[Rh(cod)(PPh_3)_2]^+BF_4^-$. [b] Satisfactory analytical and spectral data were obtained for all products listed here. [c] Yield of isolated product. [d] The isomer ratio was determined by ^1H NMR spectroscopy.

When the cyclopropane ring of the allenylcyclopropane bears a substituent, two isomers can be obtained on rearrangement, since there are two possibilities for carbon–carbon bond cleavage. Bond cleavage (a) gives methylenecyclopentene **2**, and cleavage (b) leads to the other regioisomer **3** (Scheme 3).



Scheme 3. Possible ring-opening reactions of the cyclopropane.

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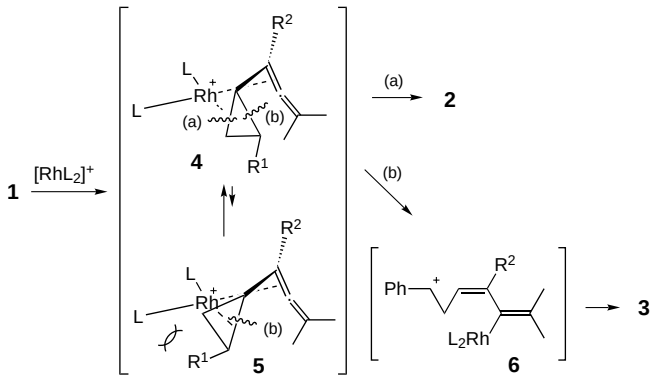
In our first trial with Wilkinson's complex as catalyst, allenylcyclopropane **1b**, which has a propyl group on the cyclopropane ring, gave the corresponding rearranged products in 89% yield as a mixture of two regioisomers **2b** and **3b** (Table 1, entry 3). In contrast, high regioselectivity for **2b** was achieved by using a cationic rhodium catalyst prepared in situ from Wilkinson's complex and silver tetrafluoroborate (entry 4). Another cationic rhodium complex without phosphane ligands also gave **2b** in excellent yield and selectivity (entry 5). These results indicate that the rearrangement of alkyl-substituted allenylcyclopropanes proceeds preferably by cleavage of bond (a) of the cyclopropane ring when a cationic rhodium catalyst is used.

A contrasting result was obtained for phenyl-substituted allenylcyclopropanes **1c** and **1d**. The rearrangement of **1c** in the presence of $[Rh(PPh_3)_3]^+BF_4^-$ gave the rearranged product **2c** with the same regioselectivity as observed for **1b** (entry 7). However, in a complete reversal of regioselectivity, methylenecyclopentene **3c** was selectively obtained when $[Rh(cod)_2]^+BF_4^-$ was used as catalyst (entry 8).[7] Cationic rhodium catalysts with or without phosphane ligands preferentially gave **3d** when allenylcyclopropane **1d** was used as substrate (entries 10 and 11). Therefore, the regioselectivity of the rearrangement of phenyl-substituted allenylcyclopropanes depends not only on the cationic character of the catalyst but also on the electron density of the allenyl group of the substrate.

Although we have no direct evidence for the mechanism of this rearrangement, the regioselectivity could be explained as follows (Scheme 4): The product **2** can be formed by cleavage



Scheme 4. Possible mechanism for the rhodium(I)-catalyzed rearrangement of cyclopropylallenes.

of bond (a) in **4**, which is overwhelmingly preferred to **5** because of steric repulsion between the substituent on the cyclopropane ring and the ligands of the catalyst (entries 4 and 5). The selective formation of **3** from the phenyl-substituted allenylcyclopropanes **1c** and **1d** could be ascribed to ionic ring opening with cleavage of bond (b) followed by oxidative insertion of the metal center to form the phenyl-stabilized cation **6** (entries 8, 10, and 11). Owing to the relatively low electron density of the allenyl group in **1c**, the cationic catalyst with phosphane ligands may not be sufficiently cationic to cleave bond (b) in **1c**, so that **2c** is preferentially formed for steric reasons (entry 7). The low regioselectivity of the reactions catalyzed by $[RhCl(PPh_3)_3]$ (entries 3, 6, and 9) can be explained by assuming the formation of a trigonal-bipyramidal intermediate[8] in which the interaction of both bonds (a) and (b) with rhodium leads to a mixture of **2** and **3**.

The transition metal mediated vinylcyclopropane–cyclopentene rearrangement is a well-established process,[2, 9] and simple vinylcyclopropanes are known to give conjugated dienes.[10, 11] In contrast, the present rearrangement of allenylcyclopropanes gave exclusively the ring-expanded products, and no conjugated diene was detected.

Since allenylcyclopropanes having one or more substituents on the cyclopropane ring and/or in the allenyl moiety can be easily prepared, the present rearrangement could be applied to the synthesis of multifunctional molecules. Moreover, the resulting methylenecyclopentenes have an exomethylene moiety, as well as other functional groups, and can be converted into methylenecyclopentane or cyclopentanone derivatives.

Experimental Section

The rearrangement reactions were performed on a 0.2–0.3 mmol scale. To a solution of the catalyst (5 mol%) in benzene (20 mL per mmol of substrate) was added **1**, and the resulting mixture was heated under reflux until the reaction was complete (monitoring by TLC). The reaction mixture was diluted with an approximately equal volume of hexane and filtered through a short silica gel column (eluent: AcOEt/hexane 10/90–30/70) to remove the catalyst. Purification by column chromatography or preparative TLC afforded **2** and/or **3**. The catalyst $[Rh(PPh_3)_3]^+BF_4^-$ was prepared in situ by mixing Wilkinson's complex and silver tetrafluoroborate (1:1) prior to adding the substrate.

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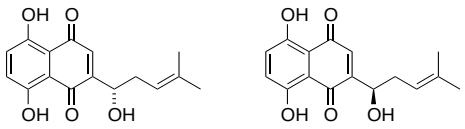
Concise and Efficient Total Syntheses of Alkannin and Shikonin**

K. C. Nicolaou* and David Hepworth

In ancient times extracts from the roots of *Alkanna tinctoria* in Europe and *Lithospermum erythrorhizon* in the Orient were used as natural purple dyes. More interestingly, Dioscorides recorded their use in ointments for the healing of wounds.[1] Early this century the enantiomeric naphthoquinones alkannin (**1**) and shikonin (**2**) (Scheme 1) were isolated[2] and identified[3] from these extracts. In fact, these natural products have been found in many species of Boraginaceae,[4] both as the free alcohols and ester derivatives—the ratio of enantiomers varies not only with species but also between the different derivatives.[5] More recently the wound-healing properties of these root extracts, which had drifted into folklore, were confirmed experimentally by Papageorgiou, and the active components identified as **1**, **2**, and closely related derivatives.[6] These natural products exhibit many other interesting biological effects including antibacterial,[7] antifungal,[8] anti-inflammatory,[9] antitumor,[10] analgesic,[9a,11] antipyretic,[12] and immunostimulatory[13] activities. In spite of the apparently simple molecular structures of **1** and **2**, short and efficient syntheses remained elusive. This, coupled with the extraordinary biological properties of these natural products, prompted us to investigate their total syntheses.

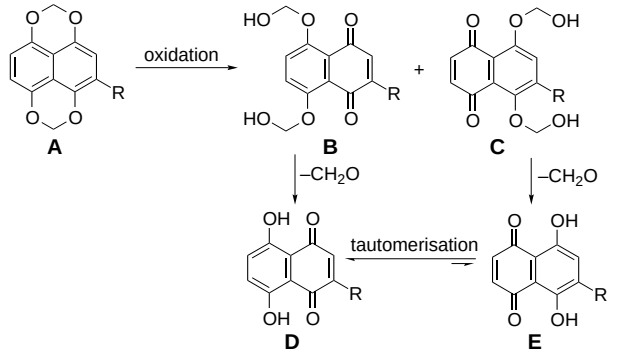


1 **2**

Scheme 1. Structures of alkannin (**1**) and shikonin (**2**).

Successful syntheses of **1** and **2** reported thus far have involved the use of 1,4,5,8-tetramethoxynaphthalene derivatives,[14] with only one exception.[15] While this protecting regime for the 5,8-dihydroxynaphthoquinone (naphthazarin) core has enabled the assembly of the side chain by several routes,[14] the final deprotection sequences to reveal the quinone system of the natural product are low-yielding and impractical. There are three major problems associated with the use of this protected system: a) initial oxidation using ceric ammonium nitrate (CAN) gives rise to two regioisomeric dimethoxynaphthoquinones with no or negligible selectivity.[14,16] Only one of these isomers can be converted into a naphthazarin in a single step;[14c,f,17] b) removal of the second pair of methyl protecting groups requires very harsh conditions ($Ag^{II}O$, HNO_3, dioxane) and gives only a poor yield of the naphthazarin derivative,[14a–f,18] and c) the drastic conditions for deprotection of the aromatic system make it prudent to protect the side-chain hydroxyl.[14e] The sensitivity of the natural products to acidic conditions[4a,14b] and to light and oxygen must also be addressed in designing efficient syntheses.[19]

We aimed to apply a novel protecting system for the naphthoquinone moiety, so that removal could be effected in one step (thus avoiding problems of regioselectivity of the oxidation) and under mild conditions compatible with an unprotected hydroxyl group. Furthermore, it was projected that this could be achieved through the use of the bismethyleneacetal derivatives of type **A** (Scheme 2). The isomers **D** and **E** should rapidly tautomerize in favor of the



A **B** **C** **D** **E**

Scheme 2. Strategy for the selective generation of **1** and **2** from bismethyleneacetal derivatives.

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