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Application of Rh-catalyzed cyclization for the construction of three consecutive chiral carbons in 4,9-dimethylspiro[4.4]nonane-2,7-dione

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Abstract

Asymmetric cyclization using Rh-complexes has been applied to the synthesis of 4,9-dimethylspiro[4.4]nonane-2,7-diones. The spiro[4.4]nonane skeleton bearing three consecutive chiral carbons could be stepwisely constructed from an identical starting material by the combination of a cationic Rh[(*S*)-BINAP]ClO_4 and a neutral $RhCl(PPh_3)_3$. The relationship between the stereochemistry of the spirodiketones and the Rh-complex was also discussed.

Keywords: cyclization; spiro compounds; rhodium; asymmetric reactions.

Some spiro compounds, found as biologically active products from natural sources,[1] have been designed as chiral ligands for asymmetric syntheses,[2] and prepared as new materials. Construction of the chiral quaternary carbon in spirane skeletons continues to be a fascinating challenge to organic chemists.[3] We have previously reported the construction of spiro compounds using enzymatic methods[4] and stereoselective methods using cycloalkane-1,2-diols as a chiral auxiliary.[5] Here, we wish to describe the asymmetric synthesis of 4,9-dimethylspiro[4.4]nonane-2,7-dione using Rh-catalyzed cyclization twice.[6,7] We planned the stepwise route using the Rh-catalyzed cyclization twice to construct 4,9-dimethylspiro[4.4]nonane-2,7-dione. It was expected that the selection between a neutral or a cationic Rh-complex, and the choice of proper phosphin ligands would afford the desired optically active spiro compounds stereoselectively.

The 4-pentenal substrate **6** for the first Rh-catalyzed cyclization was prepared as follows. Acetylacetone **1** was converted into diester **2** by dialkylation with methyl bromoacetate in 84%

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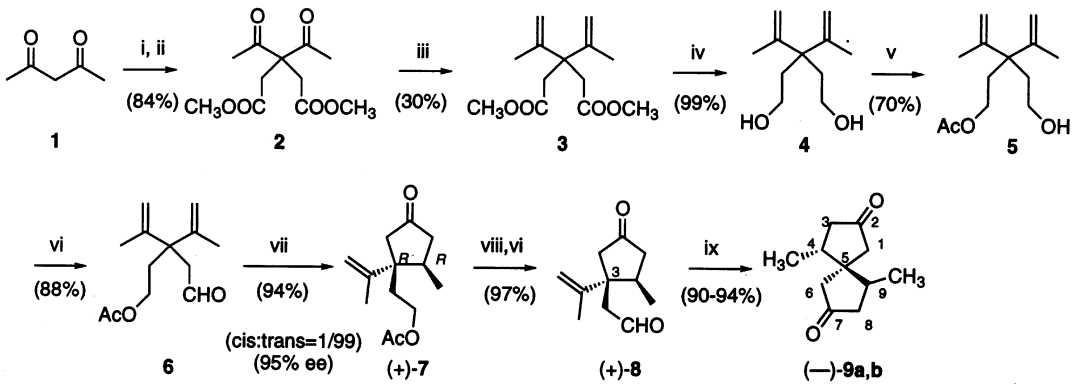
yield. Olefination of the 1,3-dicarbonyl function in **2** with Nysted reagent {cyclodibromodi-μ-methylene[μ-(tetrahydrofuran)]trizinc}[8] afforded diene **3** in 30% yield. The diester **3** was reduced to diol **4** (99%), and the diol **4** was converted to the 4-pentenal **6** by monoacetylation and subsequent oxidation with PCC in 62% overall yield.

The cyclization by the cationic Rh[(*S*)-BINAP]ClO_4† (0.05 equiv.) in CH_2Cl_2 at room temperature afforded cyclopentanone (+)-**7** in 94% yield. The ratio of *cis* and *trans* in the obtained (+)-**7** was 1 (*cis*) to 99 (*trans*). The relative stereochemistry of product (+)-**7** was unambiguously determined by the NOESY ^1H–^1H NMR spectrum. Correlation between the methyl proton signals δ 1.06 (d, $J=7.3$ Hz, 3H) and the methylene signals δ 2.41–2.50 (m, 2H) was observed. The enantiomeric excess of (+)-**7** was determined to be 95% ee by the ^1H and ^{13}C NMR spectra, after conversion of (+)-**7** into the (*R*,*R*)-butane-2,3-diol acetal. Furthermore, the relative and absolute stereochemistries of (+)-**7** were correlated with those of (3*R*,4*R*)-3,4-dimethyl-3-isopropenylcyclopentanone (−)-**10** which was obtained by the Rh[(*S*)-BINAP]ClO_4-catalyzed cyclization.[7] Therefore, the absolute stereochemistry of (+)-**7** cyclized by the cationic Rh[(*S*)-BINAP]ClO_4 should be 3*R*,4*R*. Cyclization by the neutral Rh[(*S*)-BINAP]Cl did not proceed at all, due to the low catalytic activity of the neutral Rh-complex and the bulkiness of the BINAP ligand. The obtained cyclopentanone (+)-**7** was converted into 4-pentenal (+)-**8** by solvolysis of the acetyl function and subsequent oxidation of primary alcohol in 98% overall yield, as shown in Scheme 1.

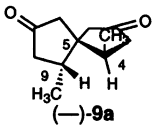
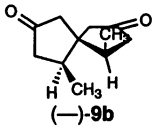


Scheme 1. *Reagents and conditions*: (i) $BrCH_2COOCH_3$, NaH; (ii) $BrCH_2COOCH_3$, *t*-BuOK; (iii) Nysted reagent, $TiCl_4$; (iv) $LiAlH_4$; (v) Ac_2O, 4-DMAP, pyridine; (vi) PCC; (vii) Rh[(*S*)-BINAP]ClO_4; (viii) K_2CO_3, MeOH; (ix) Rh-complexes

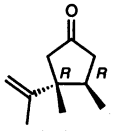
The results of the second cyclization by the Rh-complexes are summarized in Table 1. The cyclization of (+)-**8** by the neutral Rh[(*R*)- or (*S*)-BINAP]Cl did not proceed at all (entries 3, 4) because of the bulky quaternary carbon at the C(3)-position and the low reactivity of the neutral Rh[(*R*)- or (*S*)-BINAP]Cl complex. The cyclization by the cationic Rh[(*R*)-BINAP]ClO_4 did not proceed (entry 1), but the cyclization by the cationic Rh[(*S*)-BINAP]ClO_4 proceeded to afford spirodiketone (−)-**9a** in 94% yield (entry 2). The cyclization of (+)-**8** by the achiral $RhCl(PPh_3)_3$ afforded (−)-**9b** in 90% yield. The spectroscopic data of (−)-**9a** and (−)-**9b** were apparently different.

† Rh[(*S*)-BINAP]ClO_4 was prepared in situ from Rh[(NBD)(*S*)-BINAP]ClO_4 by hydrogenation.

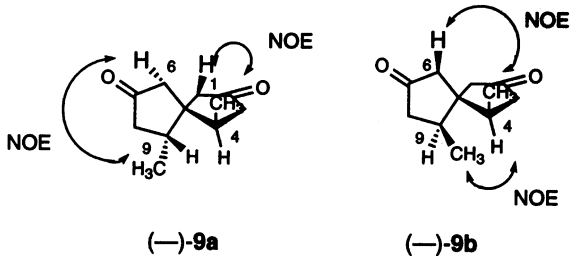
Table 1
The second cyclization of (+)-**8** by the Rh-complexes[a)]

Entry	Rh-complex	Product: Yield (%)	Product:	Product: Ratio of **9a** : **9b**
1	Rh[(*R*)-BINAP]ClO_4	0	 (—)-**9a**	-
2	Rh[(*S*)-BINAP]ClO_4	94		97 : 3
3	Rh[(*R*)-BINAP]Cl[b)]	0		-
4	Rh[(*S*)-BINAP]Cl	0	 (—)-**9b**	-
5	$RhCl(PPh_3)_3$	90		5 : 95

a) Cyclizations were carried out in CH_2Cl_2 using 0.05 eq. of the cationic Rh-complex or 0.50 eq. of the neutral Rh-complex at room temperature.
b) Spirodiketone was not isolated, but decarbonylated product (—)-**10** was obtained.


(—)-**10**

The spirodiketones **9** contain three consecutive chiral carbons, and the *C2*-axis at the quaternary carbon C(5) exists in some spirodiketones; therefore, three pairs of enantiomers exist. The ^{13}C NMR spectrum of (–)-**9a** showed six peaks, while those of (–)-**9b** showed eleven peaks. These results indicate that the *C2*-symmetry exists in the structures **9a** but not in **9b**. In the NOESY H–^{1}H NMR spectrum of (–)-**9a**, correlation between the methyl proton signals δ 1.08 (d, $J=6.9$ Hz, 6H) at the C(4 and 9)-position and the methylene signals δ 2.31 (d, $J=17.6$ Hz, 2H) at the C(1 and 6)-position was observed. In the spectrum of (–)-**9b**, the correlation between the methyl proton signals δ 1.14 (d, $J=6.9$ Hz, 3H) at the C(9)-positon and the methine signals δ 2.34 (m, 1H) at the C(4)-position and also the methyl signals δ 1.03 (d, $J=6.9$ Hz, 3H) at the C(4)-position and the methylene signals δ 2.50 (d, $J=18.0$ Hz, 1H) at the C(6)-position were observed (Fig. 1). Moreover, it is already reported that the stereochemistry of 3,4-substituted cyclopentanones cyclized from 4-pentenal by the $RhCl(PPh_3)_3$ is 3,4-*cis*. Based on these results, we concluded the stereochemistry of (–)-**9a** as 4*R*,5*S*,9*R*, and (–)-**9b** as 4*R*,5*S*,9*S*.[9]



(—)-**9a** (—)-**9b**

Figure 1. Correlations observed in the NOESY ^{1}H–^{1}H NMR spectra (only relevant correlations were depicted)

The diastereomeric ratio of spirodiketones **9** in entry 2 was determined to be 97 (**9a**) to 3 (**9b**) by the ratio of methyl proton signals of **9a** at δ 1.08 (d, 6H), and the signal of **9b** at δ 1.14, 1.03 (each d, total 6H), in the ^{1}H NMR spectrum, and that in entry 5 was 5 (**9a**) to 95 (**9b**).

The stereoselectivity for the first cyclization was consistent with the previous experiments.[6,7] The outcome in the stereochemistry of spirodiketones **9** could be explained as follows: First, the stereochemistry of C(4)- and C(5)-carbons in the spirodiketones was derived from the C(4)- and C(3)-carbons of cyclopentanone **7** with retention of its chirality, respectively. Thus, the stereochemistry of the C(9)-carbon in spirodiketones **9** was newly constructed by the second Rh-catalyzed cyclization.

The second cyclization by the neutral $RhCl(PPh_3)_3$ would be explained by considering the plausible acyl-rhodium intermediates. Intermediate (a) would be less stable than intermediate (b) because the repulsion between the methyl function at the C(4)-position and the rhodium metal exists in the intermediate (a). Consequently, the spirodiketone (−)-**9b** (Table 1, entry 5) was obtained as a major product by way of the stable intermediate (b), as shown in Fig. 2. The relative stereochemistry of (−)-**9b** was *cis* between the methyl function at the C(9)-position and the C(4)-carbon of the spirane skeleton. The second cyclization by the cationic Rh-complex gave the opposite stereochemistry at the C(9)-position to that by the neutral Rh-complex. This phenomenon has already been observed in the Rh-catalyzed cyclization of 4-pentenals.[7] The cyclization of (+)-**8** by Rh[(*S*)-BINAP]ClO_4 proceeded to afford (−)-**9a**, but use of Rh[(*R*)-BINAP]ClO_4 was not effective. This result would be attributed to the fact that the absolute stereochemistry of (3*R*,4*R*)-(+)-**8** accorded with that of Rh[(*S*)-BINAP]ClO_4.

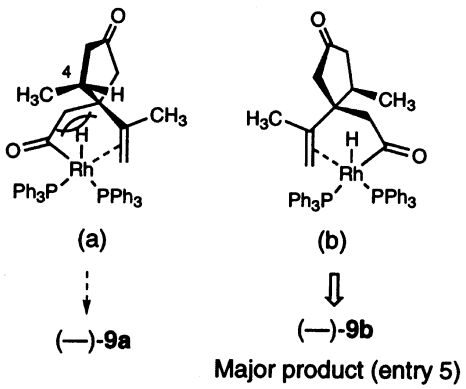


Figure 2. Plausible mechanism for the stereoselection of the second cyclization by the $RhCl(PPh_3)_3$

The Rh-catalyzed cyclization was applied to construct the optically active spiro[4.4]nonane-2,7-dione skeleton. Spiro[4.4]nonanes (−)-**9a**,**b** bearing a chiral quaternary carbon, could be constructed in diastereoselective and enantioselective manners by using the Rh-complex twice. The strategy described here would be useful for the construction of spirane skeletons.

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