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Enantioselective synthesis of sabina ketone

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Abstract—Both enantiomers of sabina ketone were efficiently prepared via an easy synthesis of 1-diazo-5-methylene-6-methylheptan-2-one, starting from succinic anhydride, followed by its highly enantioselective cyclization catalyzed by chiral dirhodium(II) compounds having *ortho*-metalated phosphines as ligands.

The bicyclo[3.1.0]hexane ring structure is present in a considerable number of natural monoterpenes and sesquiterpenes including the norterpene, sabina ketone **1**. This ketone is an intermediate in the synthesis of important chemicals such as sabinene and sabinene hydrates (Chart 1).[1] Partial syntheses of optically active sabina ketone have been reported starting from (+)-sabinene,[2] or through cyclopropanation of chiral ketals derived from 3-[(1-methyl)ethyl]-2-cyclopenten-1-one.[3] However, (+)-sabinene is both expensive and not readily available, and the two synthetic routes produce **1** with a low yield. Several total syntheses of this ketone, in the racemic form, have also been published.[1b,4,5] One of them starts from ethyl isopropylcyanoacetate and uses 1-diazo-5-methylene-6-methylheptan-2-one (**2**) as the key intermediate.[4] The proposed synthesis of the diazo **2** requires too many steps and its cyclization to sabina ketone, catalyzed by copper, occurs with moderate yield.

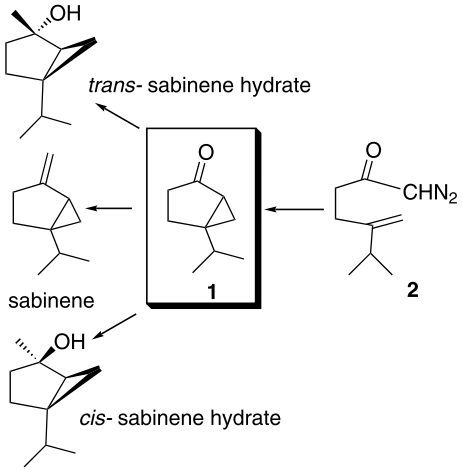

Chart 1. Structures of sabina ketone, sabinene hydrates and diazo compound **2**.

Previous studies, using simple model compounds, have shown the versatility of chiral dirhodium(II) compounds $Rh_2(O_2CF_3)_2(PC)_2$ [(**3**), PCH = triaryl phosphine], to accomplish enantioselective intramolecular cyclopropanation of 1-diazo-2-alkanones[6] (Fig. 1). It appeared of interest to extent this chemistry to the synthesis of natural sabina ketone and its enantiomer using a simple, straightforward total synthesis that could be upscaled for large production.

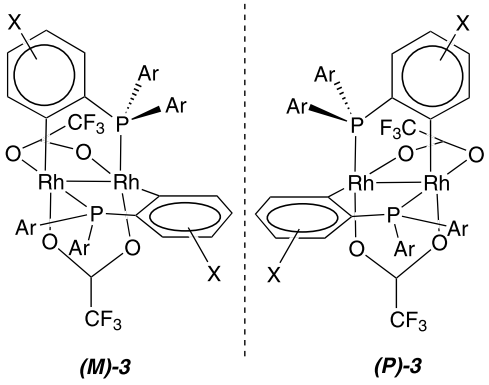

Figure 1. Structures of chiral dirhodium(II) compounds having metalated phosphines as ligands.

Keywords: sabina ketone; dirhodium(II) compounds; asymmetric synthesis.

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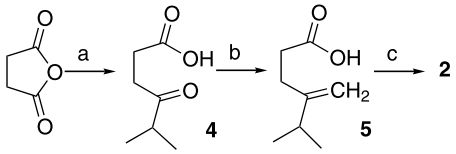
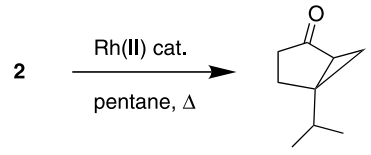


Scheme 1. Synthesis of 1-diazo-5-methylene-6-methylheptan-2-one (**2**). *Reagents and conditions*: (a) ^{i}PrMgCl, $Fe(acac)_3$, THF, 0°C; (b) Ph_3PCH_3Br, BuLi, DMSO, rt; (c) $ClCO_2Et$, CH_2N_2.

Table 1. Cyclopropanation of diazo compound **2** using dirhodium(II) complexes with *ortho*-metalated aryl phosphine ligands



PCH	Rh(II) chirality	Yield (%)	E.e.[a] (%)
$(C_6H_5)_3P$	(*M*)-**3a**	99	94 (1*S*,5*R*)
$(p\text{-}CH_3C_6H_4)_3P$	(*P*)-**3b**	99	89 (1*R*,5*S*)
$(m\text{-}CH_3C_6H_4)_3P$	(*M*)-**3c**	99	94 (1*S*,5*R*)

[a] E.e. values calculated in this report were based on GC analysis with a 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-β-CDX column.

The present work reports a short, efficient and practical synthesis of (+)- and (−)-**1** starting from the cheap and available succinic anhydride. Thus, isopropyl magnesium chloride was reacted with succinic anhydride in THF at 0°C in the presence of iron(III) acetylacetonate [$Fe(acac)_3$] leading to 5-methyl-4-oxohexanoic acid (**4**)[4,7] in a 50% yield. Reaction of **4** with methyltriphenylphosphonium bromide and butyllithium provided the 4-isopropylpent-4-enoic acid (**5**) which, upon reaction with methyl chloroformate followed by addition of freshly prepared diazomethane, led to diazo **2** in 65% yield over the two steps[9] (Scheme 1).

Next, cyclization of diazo **2** was performed in refluxing pentane using three different dirhodium(II) compounds[9] (Table 1). Sabina ketone was obtained with high yields in all the cases (99%) and the enantioselectivity values were high to excellent (between 89 and 94% e.e.). The configuration of the ketone depends on the chirality of the catalyst.

In view of the above results, this work constitutes an interesting strategy to the synthesis of both enantiomers of sabina ketone and therefore the entrance to provide several important chiral monoterpenes.

Acknowledgements

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9. **Synthesis of 5-methyl-4-oxohexanoic acid (4)**. To a solution of succinic anhydride (4.8 g, 48 mmol) and $Fe(acac)_3$ (0.51 g, 1.4 mmol) in THF (50 mL) a dropwise solution of isopropyl magnesium chloride (20 mL, 2 M in diethyl ether) was added, and the reaction mixture was stirred overnight at 0°C. The mixture was acidified with HCl 10%, extracted with dichloromethane (3×10 mL), and the organic layer was washed with NaOH 10% (3×10 mL). The aqueous solution was acidified with HCl 10% and extracted with dichloromethane. The extract was washed with water, dried ($MgSO_4$) and concentrated yielding compound **4**[4,7] (3 g, 50%) of: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (6H, d, $J=6.9$ Hz), 2.57 (3H, m), 2.69 (2H, m), 10.77 (1H, bs) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.6, 28.2, 34.9, 41.1, 179.3, 213.1 ppm. MS *m*/*z* (rel. int. %) 144 (M^+ 1), 102 (43), 73 (26), 71 (19). HRMS calcd for $C_7H_{12}O_2$: 144.0786. Found: 144.0785.
Synthesis of 4-isopropylpent-4-enoic acid (5). Butyllithium (11 mL, 1.6 M in hexane) was added to a solution of methyltriphenylphosphonium bromide (6.2 g, 17 mmol) in DMSO (40 mL), and the mixture was stirred for 1 h at room temperature. Then, a solution of the **4** (2.5 g, 17 mmol) and butyllithium (11 mL, 1.6 M in hexane) in THF (20 mL) was added, and the mixture was stirred overnight. The solution was quenched with water, acidified with HCl 10% and extracted with dichloromethane (3×10 mL), and the organic layer was washed with NaOH 10%. The aqueous solution was acidified with HCl 10% and extracted with dichloromethane. The extract was washed with water, dried ($MgSO_4$) and concentrated. The crude containing compound **5**[4] was employed for the next step without further purification.
Synthesis of 1-diazo-5-methylene-6-methylheptan-2-one (2). Diazo compound **2** was prepared from **5** by reaction with methyl chloroformate, followed by treatment with freshly prepared diazomethane.[8] The crude was chromatographed on silica gel with hexane/ethyl acetate (20:1) to give diazo ketone **2** (1.9, 65%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (6H, d, $J=6.8$ Hz), 2.04–2.28 (3H, m), 2.30–2.42 (2H, m), 4.52 (1H, s), 4.66 (1H, s), 5.15 (1H, bs) ppm.
Catalytic experiments. The catalytic reactions were performed dissolving the catalyst (1.5 mg, [substrate]/[Rh(II) complex] = 100) in dry refluxing pentane (30 mL) under an

argon atmosphere. The 1-diazo-5-isopropyl-4-penten-2-one (35 mg) was added to the solution and the mixture stirred for 1 h (the reaction, monitored by TLC, indicated completely transformation of the diazo compound). The reaction mixture was cooled to room temperature, the solvent evaporated and the crude product was filtered through a short chromatography column to eliminate the catalyst. The yield of the reaction was calculated by proton ^{1}H NMR and the cyclization product was purified by HPLC (hexane/ethyl acetate, 10: 1, $t_R = 12.37$), enantiomeric excesses were determined by GC analysis [oven temp. 100°C for 2 min, then 5°C/min to 180°C, $t_R = 9.99$ for (1*S*,5*R*) and $t_R = 10.66$ for (1*R*,5*S*)]. The configuration was determined by correlation of the sign of the rotation of polarized light with that of the known enantiomer.[3]