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Tandem Ring Expansion and Insertion Reaction of Alkenic Cyclobutanols Mediated by Palladium——A Novel Approach to Bicyclo[4.3.0]nonane Systems

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Abstract: A new method for the synthesis of hydrindans was developed by the palladium mediated tandem ring expansion and insertion reaction of alkenic cyclobutanol **5** to give the hydrindan **17** as a key step.

Many types of polycyclic compounds possessing a hydrindan skeleton are found in nature[1a,b] and also have been important synthons[1c-e] for a variety of natural products. Several halogenated terpenes having such ring system such as, oppositol **1**,[2] iriediol **2**,[3] irieol A **3**[3] and a diterpene hydroperoxide **4**,[4] have also been isolated from marine sources and attracted much attention (Figure 1).

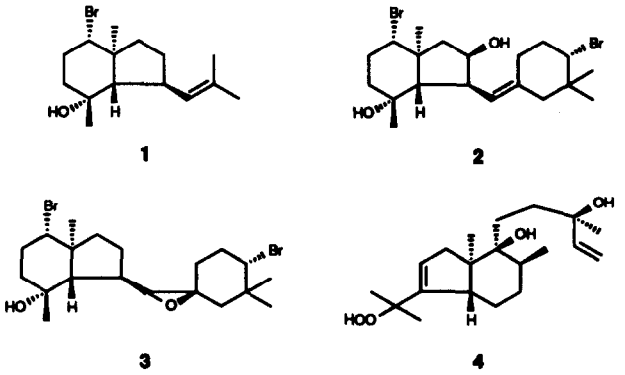
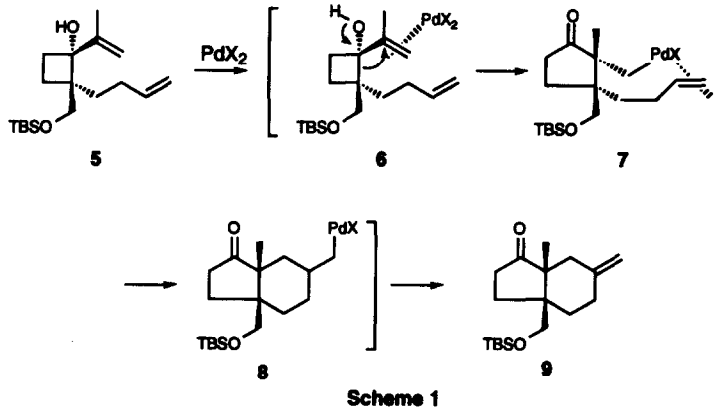


Figure 1

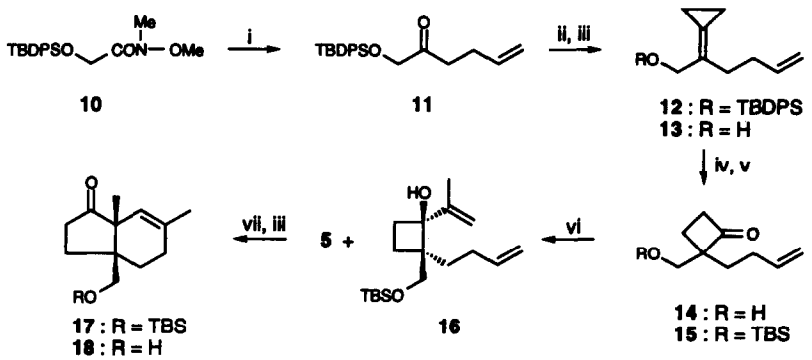
As an extension of our study of cyclobutanes,[5,6] we have developed a new route to hydrindan ring system which relies on palladium mediated ring expansion[7] of alkenic cyclobutanol **5** *via* **6** to form palladium complex **7** at the first stage, then insertion reaction at the second stage giving **8** and β elimination to afford **9** (Scheme 1). Herein, we describe the results with full details.



5 6 7 8 9

Scheme 1

The synthesis of the alkenic cyclobutanol **5** was straightforward and as follows (Scheme 2).



10 **11** **12** : R = TBDPS, **13** : R = H

14 : R = H, **15** : R = TBS

16

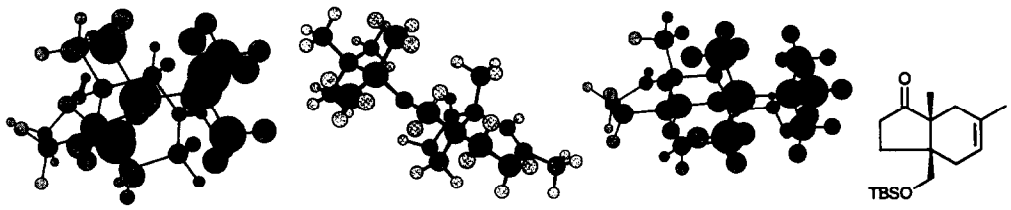
17 : R = TBS, **18** : R = H

Scheme 2: *Reagents and Conditions*: i $BrMg(CH_2)_2CH{=}CH_2$, THF, 0 °C, 1.5 h; ii cyclopropyltriphenylphosphonium bromide, NaH, THF, 62 °C, 4 h; iii Bu^n_4NF, THF, room temp., 3.5 h; iv MCPBA, CH_2Cl_2, room temp., 1 h; v TBSCl, imidazole, DMAP, DMF, room temp., 1.5 h; vi isopropenylmagnesium bromide, $CeCl_3$, THF, room temp., 3 h; vii $PdCl_2(MeCN)_2$, DME, 85 °C, 18 h.

Grignard reaction (95%) of the hydroxamate **10**[6] with 3-butenylmagnesium bromide afforded the ketone **11** which was then converted into the cyclopropylideneethanol **13** in 95% overall yield by Wittig reaction with cyclopropylidenetriphenylphosphorane followed by desilylation of the resulted silyl ether **12** with tetra-*n*-butylammonium fluoride (Bu^n_4NF). Selective epoxidation[8] (53%) of the cyclopropylideneethanol **13** with *m*-chloroperbenzoic acid (MCPBA) followed by silylation (94%) of the resulted cyclobutanone alcohol **14** afforded the *t*-butyldimethylsilyl (TBS) ether **15** which on the reaction with isopropenylcerium reagent afforded the alkenic cyclobutanol **5**[9] (76%) together with its diastereomer **16** (19%). The cyclobutanol **5** thus obtained was then subjected to the tandem ring expansion and insertion reaction using bis(acetonitrile)palladium chloride [$PdCl_2(MeCN)_2$] to give the hydrindan silyl ether **17** (29%).

In this reaction, the initially expected product **9** isomerized to the thermodynamically most stable isomer **17** of the plausible three isomers **9**, **17** and **19**. This was supported by the evaluation of the total strain energies

of **9**, **17** and **19** by means of the GMMX 1.0 program[10] showing the isomer **17** to be the most stable isomer (Figure 2).



9 ΔE strain 25.01 Kcal/mol

17 ΔE strain 20.50 Kcal/mol

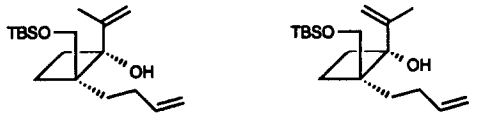
19 ΔE strain 22.75 Kcal/mol

19

Global minimum energy conformation of **9**, **17** and **19** as determined by molecular mechanics calculations (Chem-3D output).

Figure 2

The stereochemical outcome of this tandem reaction could be rationalized *via* the sterically preferred conformation **6a** rather than **6b** (Figure 3).



6a **6b**

Figure 3

Finally, the desilylation of **17** with Bu^n_4NF furnished the hydrindan alcohol **18** (72%).[11] Thus, we could disclose a new route to hydrindan ring system. The methodology described here might be applied to the alkenic cyclobutanol like **16** to give the trans fused hydrindans such as **1** - **4** and studies are in progress along with this concept.

Experimental Section

General: All reactions were carried out under a positive atmosphere of dry N_2 unless indicated otherwise. Solvents were freshly distilled prior to use: THF and Et_2O were distilled from sodium benzophenone, and DMSO, DMF, CH_2Cl_2, and Et_3N were distilled from CaH_2 and kept over 4 Å molecular sieves. The phrase "residue upon workup" refers to the residue obtained when the organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Silica gel column chromatography was carried out with Wako gel C-200, while Merck Kieselgel 60 Art. 9385 was used for flash chromatography.

1-(*tert*-Butyldiphenylsiloxy)hex-5-en-2-one (11). To a stirred solution of the hydroxamate **10**[6] (10.9 g, 30.6 mmol) in THF (40 mL) was added a solution of 3-butenylmagnesium bromide [prepared from magnesium (4.46 g, 183 mmol) and 1-bromo-3-butene (9.31 ml, 91.7 mmol)] in THF (45 mL) at -78 °C, and stirring was continued for 1.5 h at 0 °C. The reaction mixture was treated with 10% HCl solution and extracted

with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (49 : 1 v/v) as eluant to give the ketone **11** (10.2 g, 95%) as a colorless oil. IR (neat): 1733 and 1715 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (9H, s), 2.26 - 2.37 (2H, m), 2.63 (2H, t, J = 6.9 Hz), 4.18 (2H, s), 4.96 (1H, dd, J = 1.5 and 9.0 Hz), 5.01 (1H, dd, J = 1.5 and 17.3 Hz), 5.70 - 5.87 (1H, m) and 7.33 - 7.68 (15H, m). HRMS: calcd for $C_{18}H_{19}O_2Si$ 295.1154 (M^+ -57), found 295.1141. *Anal.* Calcd for $C_{22}H_{28}O_2Si$: C, 74.95; H, 8.01. Found C, 75.02; H, 8.05.

2-Cyclopropylidene-5-hexenol (13). To a stirred suspension of NaH (1.30 g, of 60% oil suspension, 32.4 mmol) in THF (50 mL) was added cyclopropyltriphenylphosphonium bromide (12.4 g, 32.4 mmol) at room temperature. After the mixture had been stirred for 10 h at 62 °C, a solution of the ketone **11** (4.22 g, 12.0 mmol) in THF (20 mL) was added in 10 min and stirring was continued for 4 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (99 : 1 v/v) as eluant to give the cyclopropylideneethyl silyl ether **12** which was subjected to the next reaction. Thus, to a stirred solution of the silyl ether **12** obtained above in THF (10 mL) was added 1 M solution of $^nBu_4NF$ in THF (20 ml, 20 mmol) at room temperature, and stirring was continued for 3.5 h at the same temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (19 : 1 v/v) as eluant to give the alcohol **13** (1.57 g, 95% form **11**) as a colorless oil. IR (neat): 3320 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 - 1.19 (4H, m), 1.55 (1H, t, J = 6.0 Hz), 2.24 - 2.41 (4H, m), 4.24 (2H, d, J = 6.0 Hz), 4.95 (1H, dd, J = 1.5 and 9.9 Hz), 5.03 (1H, dd, J = 1.5 and 17.3 Hz) and 5.76 - 5.94 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 1.3, 1.4, 31.8, 32.0, 65.8, 114.5, 117.8, 127.3 and 138.7. HRMS: calcd for $C_9H_{13}O$ 137.0966 (M^+ -1), found 137.0962.

2-(3-Butenyl)-2-hydroxymethylcyclobutanone (14). To a stirred solution of the alcohol **13** (95.1 mg, 0.689 mmol) in CH_2Cl_2 (2 mL) was added a solution of MCPBA (149 mg, of 80% purity, 0.689 mmol) in CH_2Cl_2 (1 mL) at 0 °C and stirring was continued for 1 h at room temperature. The mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous Na_2CO_3 and NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (9 : 1 v/v) as eluant to give the cyclobutanone **14** (56.0 mg, 53%) as a colorless oil. IR (neat): 3430 and 1765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.58 - 2.30 (7H, m), 2.92 - 3.04 (2H, m), 3.65 and 3.79 (each 1H, each dd, J = 5.1 and 10.8 Hz), 4.97 (1H, dd, J = 1.5 and 8.8 Hz), 5.04 (1H, dd, J = 1.5 and 16.9 Hz), and 5.71 - 5.93 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.9, 28.4, 30.5, 43.3, 64.0, 69.9, 114.9, 137.8 and 215.7. HRMS: calcd for $C_9H_{14}O_2$ 154.0994 (M^+), found 154.1012.

2-(3-Butenyl)-2-*tert*-butyldimethylsiloxymethylcyclobutanone (15). To a stirred solution of the alcohol **14** (1.7 g, 11.1 mmol), imidazole (1.28 g, 18.9 mmol) and a catalytic amount of DMAP in DMF (12 mL) was added TBSCl (2.5 g, 16.6 mmol) at room temperature and stirring was continued for 1.5 h at the same temperature. The reaction mixture was diluted with Et_2O and 10% HCl and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (49 : 1 v/v) as eluant to give the silyl ether **15** (2.78 g, 94%) as a colorless oil. IR (neat): 1770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.05 (3H, s), 0.88 (9H,

s), 1.45 - 2.27 (6H, m), 2.77 - 2.98 (2H, m), 3.52 and 3.75 (each 1H, each d, J = 9.5 Hz), 4.96 (1H, dd, J = 1.5 and 10.3 Hz), 5.02 (1H, dd, J = 1.5 and 17.2 Hz) and 5.68 - 5.88 (1H, m). ^{13}C NMR (75 Hz, $CDCl_3$): δ -5.5, 18.3, 19.3, 25.9, 28.8, 30.9, 43.9, 65.0, 70.1, 114.9, 138.1 and 214.8. HRMS: calcd for $C_{15}H_{28}O_2Si$ 268.1859 (M^+), found 268.1812. *Anal.* Calcd for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.51. Found C, 66.88; H, 10.57.

[(1R, 2R) and (1S, 2R)]-2-(3-Butenyl)-2-*tert*-butyldimethylsiloxymethyl-1-isopropenylcyclobutanol (5 and 16). To a stirred suspension of cerium chloride (2.1 g, 8.52 mmol) in THF (20 mL) was added a solution of isopropenylmagnesium bromide [prepared from magnesium (463 mg, 19.1 mmol) and 2-bromopropene (0.757 ml, 8.52 mmol)] in THF (20 mL) at -78 °C. After stirring had been continued for 1 h, a solution of the cyclobutanone **15** (681 mg, 2.54 mmol) in Et_2O (10 mL) was added dropwise to this reaction mixture at the same temperature and the temperature was then raised to room temperature in 3 h. The reaction mixture was treated with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (99 : 1 v/v) to give the cyclobutanol **16** (153 mg, 19%) as a colorless oil from the first fraction. IR (neat): 3460 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.09 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 1.34 - 1.46 (2H, m), 1.50 - 1.57 (1H, m), 1.57 - 1.67 (1H, m), 1.76 (3H, s), 1.78 - 1.90 (2H, m), 1.92 - 2.02 (1H, m), 2.35 - 2.44 (1H, m), 3.68 and 3.93 (each 1H, each d, J = 10.4 Hz), 4.07 (1H, s), 4.85 - 5.01 (4H, m) and 5.69 - 5.80 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.6, -5.5, 18.1, 19.9, 21.2, 25.8, 28.4, 30.0, 31.2, 50.5, 65.5, 82.0, 111.3, 114.2, 139.1 and 146.9. HRMS: calcd for $C_{14}H_{25}O_2Si$ 253.1624 (M^+ -57), found 253.1640. *Anal.* Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found C, 69.79; H, 11.02. The second fraction afforded the cyclobutanol **5** (603 mg, 76%) as a colorless oil. IR (neat): 3440 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ -0.01 (3H, s), 0.00 (3H, s), 0.85 (9H, s), 1.25 - 1.33 (1H, m), 1.56 (1H, s), 1.65 - 1.84 (4H, m), 1.77 (3H, s), 1.86 - 1.96 (1H, m), 1.97 - 2.06 (1H, m), 2.32 - 2.45 (1H, m), 3.36 and 3.52 (each 1H, each d, J = 10.4 Hz), 4.84 and 4.87 (each 1H, each d, J = 1.2 Hz), 4.91 (1H, dd, J = 1.2 and 9.8 Hz), 5.00 (1H, dd, J = 1.2 and 17.1 Hz) and 5.77 - 5.91 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.8, -5.7, 18.3, 19.8, 23.1, 25.9, 28.5, 28.9, 29.4, 50.8, 64.6, 81.7, 111.0, 114.0, 139.6 and 147.3. HRMS: calcd for $C_{14}H_{25}O_2Si$ 253.1624 (M^+ -57), found 253.1630.

Tandem Ring Expansion and Insertion Reaction of the Alkenic Cyclobutanol 5. To a stirred solution of the cyclobutanol **5** (25.2 mg, 0.0812 mmol) in 1,2-dimethoxyethane (2 mL) was added bis-(acetonitrile)palladium chloride (21 mg, 0.0812 mmol) at room temperature and stirring was continued for 1 h at the same temperature. After stirring had been continued for 18 h at 85 °C, the solvent was evaporated and the residue was chromatographed on silica gel with hexane-AcOEt (99 : 1 v/v) to give the silyl ether **17** (7.24 mg, 29%) which was then subjected to the next reaction. Thus, to a stirred solution of the silyl ether **17** obtained above was added 1 M solution of ^{n}Bu$_4$NF in THF (1.0 ml, 1.0 mmol) at room temperature, and stirring was continued for 3.5 h at the same temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (17 : 3 v/v) as eluant to give the hydrindan alcohol **18** (3.29 mg, 72%) as colorless needles, mp 114 - 115 °C (from hexane-Et_2O). IR ($CHCl_3$): 3430 and 1720 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (3H, s), 1.59 (1H br s), 1.70 (3H, s), 1.72 - 1.82 (2H, m), 1.94 - 2.07 (2H, m), 2.09 - 2.23 (2H, m), 2.25 - 2.36 (1H, m), 2.38 - 2.48 (1H, m), 3.26 and 3.48 (each 1H, each d, J = 10.4

Hz) and 5.31 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 23.8, 26.4, 30.2, 34.1, 34.3, 44.1, 50.0, 65.0, 119.5, 132.7, and 220.3. HRMS: calcd for $C_{12}H_{18}O_2$ 194.1307 (M^+), found 194.1311.

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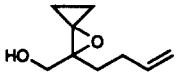
8. The presumed initial product, bicyclooxapentane **i** rearranged to give **14** directly under the reaction conditions. The direct conversion of **12** into **15** was also examined to give the only messy products.



i

9. The stereochemistry of **5** was determined by observation of NOE between the CH_3 of isopropenyl group and the CH_2 of silyloxymethyl group.
10. GMMX (Version 1.0), Serena Software, P. O. Box 3076, Bloomington, IN.
11. The structure of **18** (and also **17**) was determined mainly by ^1H NMR (500 MHz) studies of **18** as follows. Namely, the definite NOE enhancement between methyl and hydroxymethyl groups confirmed the ring juncture to be cis and the olefinic hydrogen was observed at 5.31 ppm as a broad singlet showing the position of olefin to be that of **17** and **18**.

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