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Domino ring opening–ring closing metathesis (ROM–RCM) strategy toward bicyclo[*n*.3.0]cycloalkenes

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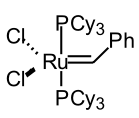
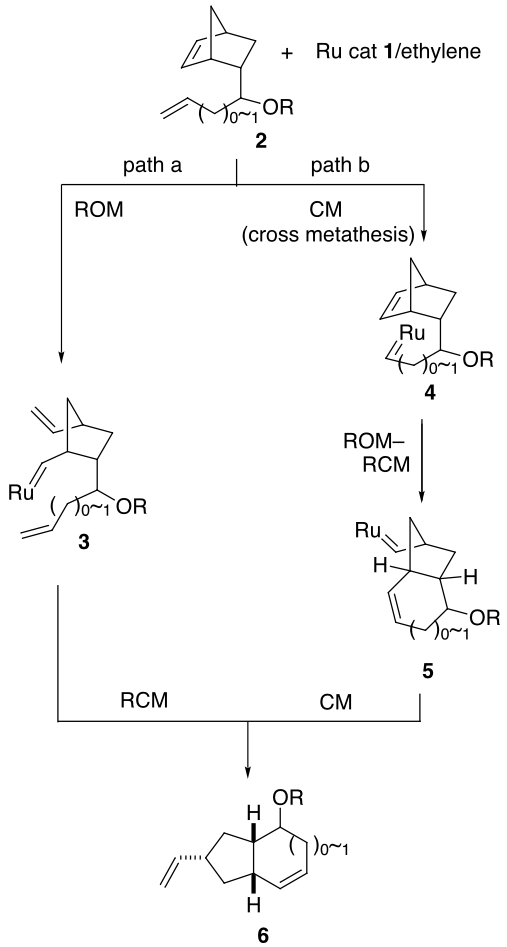
Abstract—Treatment of bicyclo[2.2.1]heptene having an *exo*- or *endo*-olefinic side chain with a catalytic amount of Grubbs' Ru carbene complex under ethylene atmosphere provided bicyclo[3.3.0]octene or bicyclo[4.3.0]nonene compounds by domino ROM–RCM reaction.

Olefin metathesis reaction, recombination of olefinic moieties, is now a very versatile synthetic method since the invention of stable and soluble Ru carbene complex **1** (Fig. 1) by Grubbs et al.[1] Especially, ring-closing olefin metathesis reaction (RCM) has became a general synthetic tool in the construction of larger cyclic molecules hitherto difficult to prepare by other means, and numerous successful applications have appeared.[2] The milder reaction condition is a further advantage, in which various functional groups can survive. In comparison with RCM, utility of ring-opening olefin metathesis reaction (ROM) in organic synthesis is not well recognized because of the rather limited requirement of bis-olefinic compounds. However, domino combination of ROM with RCM would be an attractive subject in view of efficiency in carbocyclic ring construction by the domino strategy.[3] Following the pioneering work by Grubbs et al.,[4a] there has already been exemplified the usefulness of domino ROM–RCM reaction[4] employing distorted olefins such as cyclobutene. As one easily available strained olefinic substrate, bicyclo-[2.2.1]heptene derivatives are a plausible candidate for such purpose. Actually, Blechert,[5a,b] Hoveyda[5c,e,g] or Arjona[5d,f] reported domino ROM–RCM reactions starting from related substrates. We report herein our independent results showing the additional scope and limitation of the ROM–RCM reaction starting from bicyclo[2.2.1]heptene derivatives (Scheme 1). The products, bicyclo[3.3.0]octene or bicyclo[4.3.0]nonene derivatives **6**, are a common



1

Figure 1.



Scheme 1.

Keywords: bicyclic aliphatic compounds; metathesis; ring transformations; ruthenium and compounds.

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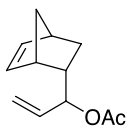
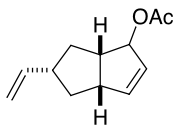
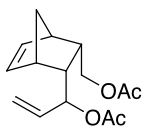
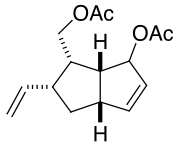
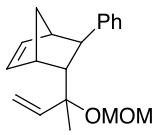
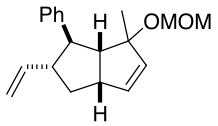
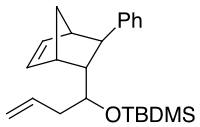
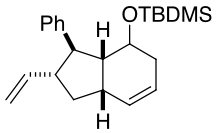
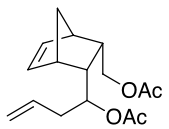
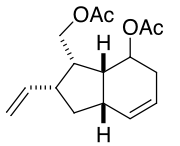
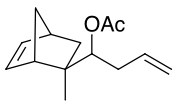
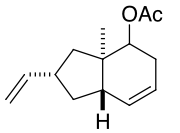
Table 1. Synthesis of bicyclo[*n*.3.0]compounds via domino ROM–RCM reaction

Entry	Bicyclo[2.2.1]heptene	Product
1	 **7**	 **8** 56%
2	 **9**	 **10** 81%
3	 **11**	 **12** 58%
4	 **13**	 **14** 75%
5	 **15**	 **16** 81%
6	 **17**	 **18** 48%

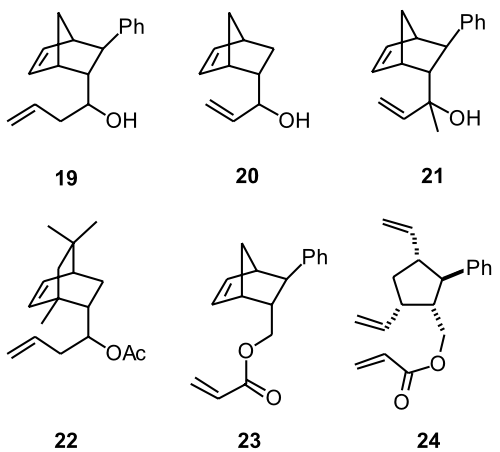


Figure 2.

structural unit in several natural products such as sesquiterpenoid triquinanes.[6]

The starting bicyclo[2.2.1]heptene derivatives **7**, **11**, **13** and **17** were prepared by Diels–Alder reaction of cyclopentadiene with acrolein, benzalacetone, cinnamaldehyde or metacrolein, respectively, followed by addition of a vinyl or an allyl group. Compounds **9** and **15** were prepared from commercially available norbornene dicarboxylic anhydride. In the case where diastereomers were separable, one diastereomer was subjected to the present reaction. All reactions were carried out in CH_2Cl_2 at room temperature at lower concentration (~0.02 M). In order to terminate the ROM–RCM reaction without polymerization of intermediates, ethylene was employed as the most powerful trapping agent of the intermediary Ru carbene complex. Results are summarized in Table 1.

The desired bicyclic compounds were obtained in moderate to good yields. At elevated temperature, a complex mixture of products was obtained in entry 1. The bicyclo[4.3.0]-nonene architecture having a *trans* ring juncture in the product **18** in entry 6 is not available by conventional means and would be a useful precursor for steroid synthesis. In spite of the report on activation of the RCM process by allylic alcohol,[7] the allylic or homoallylic hydoxy group must be protected, since compound **19**, **20** or **21** (Fig. 2) having a free hydroxy group was recovered intact under the reaction condition. The ROM process might be disturbed by coordination of the Ru complex to the hydroxy group. In the reaction of bicyclo[2.2.2]octene compound **22**, the reaction resulted in complete recovery probably because of the less strained nature of the carbocyclic framework. In the case of acrylate **23**, only ROM reaction proceeded to give olefin **24** in 55% yield. Addition of titanium tetraisopropoxide was not effective. These results, along with the successful transformation of the *exo*-olefinic compound **17** in entry 6 suggest that in the present protocol ROM proceeded at first and subsequently RCM followed via path a. Higher yields in entries 2 and 5 may be understood by the more efficient ROM process than other substrates, owing to steric repulsion between two *endo*-substituents in compound **9** or **15**. Such repulsion would be helpful to drive the ROM process efficiently. Since metathesis reaction is essentially thermodynamically controlled, subtle difference in stability in substrates or intermediates might affect the reaction. In path b, a highly strained Ru metallocycle embedded in the tetracyclo[5.3.0.0^{2,5}0^{3,9}]decane framework is involved during cycloreversion of Ru carbene complex **4** into **5** (Scheme 1).

Since bicyclo[2.2.1]heptene compounds are now available by asymmetric Diels–Alder reaction in highly enantiomeric form, the present protocol offers efficient methodology for the synthesis of optically active bicyclo[3.3.1]octene or bicyclo[4.3.1]nonene derivatives, which are good starting materials for natural product synthesis.

1. Experimental

1.1. General

IR spectra were recorded on a Shimadzu FT/IR-4200

spectrophotometer for solutions in carbon tetrachloride. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) instrument with tetramethylsilane as internal standard. ^{13}C NMR spectra were measured with Varian Gemini 200H (50 MHz) instrument. Mass spectral data were run on a Hitachi M-80B or a JEOL GC-Mate instrument. Medium-pressure liquid chromatographies (MPLC) were carried out on a GL Science PU 612 instrument with a silica gel packed column. Microanalyses were carried out in the microanalytical laboratory of the Instrumental Analysis Center for Chemistry, Tohoku University.

1.1.1. 5-Vinyl-1,4,5,6,3a,6a-hexahydropentalenyl acetate (8). To a solution of the Ru catalyst **1** (12 mg, 0.014 mmol) in degassed CH_2Cl_2 (10 ml) was added the allyl acetate **7** (49 mg, 0.25 mmol) in CH_2Cl_2 (10 ml). After being stirred at room temperature for 22.5 h under ethylene atmosphere, reaction was quenched by addition of DMSO (100 μl). The solution was passed through silica-gel short column and concentrated in vacuo. The residue was purified by MPLC (AcOEt/hexane 1:5) to afford **8** (27 mg, 56%); ν_{max} (cm^{-1}) 3088, 2950, 1782, 161, 1444, 1362, 1236, 1113, 1019, 914 and 762; ^{1}H NMR (200 MHz) δ (ppm) 1.07 (m, 2H), 2.04 (s, 3H), 2.04–2.23 (m, 2H), 2.41–2.64 (m, 2H), 3.31 (m, 1H), 4.86–5.05 (m, 2H), 5.39 (br s, 1H), 5.63 (m, 1H), 5.76 (ddd, 1H, J=17.3, 10.3, 7.0 Hz) and 6.06 (dd, 1H, J=5.7, 2.1 Hz); ^{13}C NMR (50 MHz) δ (ppm) 21.36 (q), 37.44 (t), 37.44 (t), 46.21(d), 49.10(d), 49.30 (d), 85.70 (d), 113.30 (t), 126.16 (d), 141.35 (d), 142.97 (d) and 171.08 (s); m/z 132 ($M^+-CH_3CO_2H$, 44%), 117 (81), 91 (83) and 78 (100); (Found: 192.1229; $C_{12}H_{16}O_2$ requires 192.1150).

1.1.2. 6-(Acetyloxymethyl)-5-vinyl-1,4,5,6,3a,6a-hexahydropentalenyl acetate (10). To a solution of the Ru catalyst **1** (34 mg, 0.041 mmol) in degassed CH_2Cl_2 (30 ml) was added the allyl acetate **9** (213 mg, 0.806 mmol) in CH_2Cl_2 (10 ml). After being stirred at room temperature for 21.5 h under ethylene atmosphere, the solution was concentrated in vacuo and the residue was purified by MPLC (AcOEt/hexane 1:4) to afford **10** (172 mg, 81%); ν_{max} (cm^{-1}) 3088, 3051, 2903, 1743, 1644, 1425, 1366, 1233, 1111, 1032, 952, 918 and 797; ^{1}H NMR (200 MHz) δ (ppm) 1.51 (m, 1H), 1.96 (m, 1H), 2.03 (s, 6H), 2.51 (m, 1H), 2.69–2.84 (m, 2H), 3.44 (m, 1H), 4.14 (dd, 1H, J=11.5, 7.3 Hz), 4.22 (dd, 1H, J=11.4, 7.0 Hz), 4.90–5.22 (m, 2H), 5.58–5.78 (m, 3H) and 6.08 (dd, 1H, J=5.1, 2.3 Hz); ^{13}C NMR (50 MHz) δ (ppm) 20.88 (q), 21.22 (q), 34.96 (t), 44.03 (d), 47.34 (d), 49.42 (d), 50.50 (d), 63.28 (t), 81.15 (d), 116.0 (t), 128.1 (d), 138.3 (d), 142.5 (d), 170.6 (s) and 170.8 (s); (Found: C, 68.09, H, 7.86; $C_{15}H_{20}O_4$ requires C, 68.16, H, 7.63%).

1.1.3. 4-(Methoxymethoxy)-4-methyl-3-phenyl-2-vinyl-1,2,3,4,3a,6a-hexahydropentalene (12). To a solution of the Ru catalyst **1** (10 mg, 0.012 mmol) in degassed CH_2Cl_2 (7 ml) was added the allyl acetate**11** (47 mg, 0.165 mmol) in CH_2Cl_2 (10 ml). After being stirred at room temperature for 24 h under ethylene atmosphere, reaction was quenched by addition of DMSO (100 μl). The solution was passed through silica-gel short column and concentrated in vacuo. The residue was purified by MPLC (AcOEt/hexane 1:3) to afford **16** (27 mg, 58%); ν_{max} (cm^{-1}) 3082, 2842, 1641, 1601, 1450, 1367 and 1226; ^{1}H NMR (200 MHz) δ (ppm) 1.26 (s, 3H), 1.38 (ddd like, 1H), 2.20 (ddd, 1H, J=12.4, 8.4, 6.7 Hz), 2.52–2.98 (m, 3H), 3.23 (s, 3H), 3.24 (m, 1H), 4.45 (s, 2H), 4.72 (m, 1H), 4.80 (m, 1H), 5.70–5.57 (m, 2H), 5.78 (dd, J=5.7, 2.0 Hz) and 7.20 (m, 5H); m/z 284 (M^+, 1%), 252 (13), 222 (10), 168 (33), 142 (38), 91 (33) and 45 (81); (Found: 284.1779; $C_{19}H_{24}O_2$ requires 284.1776).

1.1.4. 1-(3-Phenyl-2-vinyl(2,3,4,5,3a,7a-hexahydroinden-4-yloxy))-1,1,2,2-tetramethyl-1-silapropane (14). To a solution of the Ru catalyst **1** (9 mg, 0.01 mmol) in degassed CH_2Cl_2 (10 ml) was added the homoallyl acetate **13** (75 mg, 0.21 mmol) in CH_2Cl_2 (10 ml). After being stirred at room temperature for 2 h under ethylene atmosphere, reaction was quenched by addition of DMSO (100 μl). The solution was passed through silica-gel short column and concentrated in vacuo. The residue was purified by MPLC (AcOEt/hexane 1:19) to afford **14** (56 mg, 75%); ν_{max} (cm^{-1}) 3082, 2955, 1642, 1603, 1253, 1093, 1068, 912 and 839; ^{1}H NMR (200 MHz) δ (ppm) 0.09 (S, 3H), 0.05 (S, 3H), 0.70 (s, 9H), 0.82 (m, 1H), 1.45 (m, 1H), 1.98–2.12 (m, 3H), 2.34 (td like, 1H), 2.42–2.81 (m, 2H), 2.89 (dd, 1H, J=10.1, 8.2 Hz), 3.97 (ddd like, 1H), 4.71 (m, 2H), 5.40–5.74 (m, 2H), and 7.20 (m, 5H); ^{13}C NMR (50 MHz) δ (ppm) 145.6, 141,1, 130.8, 128.1, 125.6, 121.6, 113.6, 67.8, 53.2, 52.1, 51.3, 40.2, 39.0, 32.0, 25.9, 18.0, −4.68 and −4.73; (Found: C, 77.77, H, 9.80; $C_{23}H_{34}OSi$ requires C, 77.90, H, 9.66%).

1.1.5. 3-(Acetyloxymethyl)-2-vinyl-2,3,4,5,3a,7a-hexahydroinden-4-yl acetate (16). To a solution of the Ru catalyst **1** (10 mg, 0.012 mmol) in degassed CH_2Cl_2 (10 ml) was added the homoallyl acetate **15** (70 mg, 0.25 mmol) in CH_2Cl_2 (7.5 ml). After being stirred at room temperature for 9 h, Ru catalyst **1** (2.8 mg, 0.0034 mmol) was added, stirring was continued for an additional 12.5 h under ethylene atmosphere. Then the solution was concentrated in vacuo and the residue was purified by MPLC (AcOEt/hexane 1:5) to afford **16** (56 mg, 81%); ν_{max} (cm^{-1}) 3031, 2932, 2876, 2855, 1741, 1370, 1238, 1034, 918 and 747; ^{1}H NMR (200 MHz) δ (ppm) 1.36 (ddd, 1H, J=13.3, 10.9, 7.5 Hz), 1.90 (m, 1H), 2.02 (s, 3H), 2.05 (s, 3H), 2.13–2.59 (m, 4H), 2.60–2.91 (m, 2H), 3.99 (dd, 1H, J=11.3, 8.1 Hz), 4.18 (dd, 1H, J=11.3, 6.1 Hz), 4.92–5.04 (m, 3H), 5.53 (m, 1H) and 5.68–5.86 (m, 2H); ^{13}C NMR (50 MHz) δ (ppm) 20.92 (q), 21.39 (q), 30.94 (t), 38.24 (t), 40.82 (d), 43.76 (d), 43.85 (d), 45.15 (d), 63.44 (t), 70.36 (d), 115.54 (t), 122.27 (d), 130.03 (d), 140.01 (d), 170.59 (s) and 170.98 (s); m/z 235 (M^+–Ac, 4%), 217 (5), 176 (18), 158 (77), 143 (80), 129 (90), 91 (92), 69 (29) and 43 (100); (Found: 278.1530; $C_{16}H_{22}O_4$ requires 278.1518).

1.1.6. 3a-Methyl-2-vinyl-2,3,4,5,3a,7a-hexahydroinden-4-yl acetate (18). To a solution of the Ru catalyst **1** (8.6 mg, 0.011 mmol) in degassed CH_2Cl_2 (16 ml) was added the homoallyl acetate **17** (39 mg, 0.18 mmol) in CH_2Cl_2 (6 ml). The solution was stirred for 3 h at room temperature under ethylene atmosphere and concentrated in vacuo. The residue was purified by MPLC (AcOEt/hexane 1:5) to afford **18** (18 mg, 48%); ν_{max} (cm^{-1}) 3088, 3027, 2899, 1735, 1640, 1423, 1373, 1242, 1211, 1040 and 912; ^{1}H NMR (200 MHz) δ (ppm) 0.79 (s, 3H), 1.18 (dd, 1H, J=12.6, 3.2 Hz), 1.24–1.48 (m, 2H), 1.98 (m, 1H), 2.07 (s,

3H), 2.38–2.60 (m, 2H), 2.75 (m, 1H), 4.85–5.01 (m, 3H), 5.50 (m, 1H), 5.81 (m, 1H) and 5.93 (ddd, J=17.2, 10.0, 7.2 Hz); ^{13}C NMR (50 MHz) δ (ppm) 18.45 (q), 21.37 (q), 30.53 (t), 32.62 (t), 37.88 (t), 39.72 (d), 40.02 (d), 43.48 (s), 73.01 (d), 111.95 (t), 123.85 (d), 128.16 (d), 144.66 (d) and 170.85 (s); *m/z* 160 ($M^+-CH_3CO_2H$, 56%), 145 (80), 131 (54), 117 (42), 106 (88), and 91 (100); (Found: 220.1432; $C_{14}H_{20}O_2$ requires 220.1463).

2. Note added in proof

Successful domino ROM-RCM reaction of bicyclo[2.2.2]-octene has been reported. See Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357.

Acknowledgments

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