

Preparation of Seven-Membered Carbocycles Using Ring-Closing Metathesis Reaction and Application to Syntheses of Tormesol and Cyathane Skeleton

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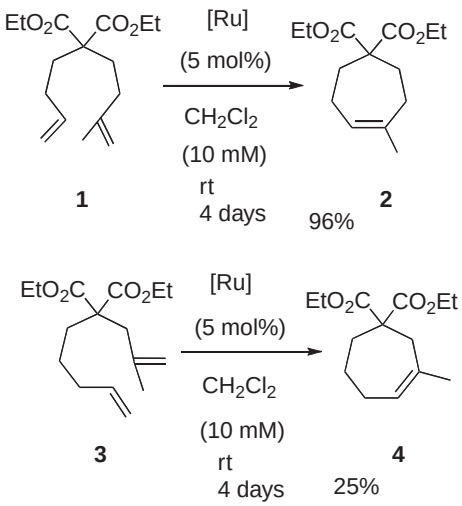
Various precursors were synthesized and were reacted with the Grubbs reagent as well as the second generation Grubbs reagent to cyclize them into seven-membered carbocycles with di- or tri-substituted double bonds. These reactions were used to synthesize (−)-tormesol, which is an enantiomer of sphenolobane-type diterpene that was isolated from *Halimium viscosum*, and a basic skeleton of cyathane-type diterpene.

Seven-membered carbocycles are frequently found in natural products.[1] Syntheses of seven-membered rings are usually carried out by aldol condensations,[2] ene-reactions,[3] and so on. We recently communicated[4] the total synthesis of sphenolobane-type diterpene isolated from the liverwort *Anastrophyllum aurium*[5b] and reported an effective way to prepare cycloheptenones with a tri-substituted double bond using ring-closing metathesis (RCM) reaction catalyzed by the first generation Grubbs reagent.[6] As Grubbs himself reported,[7] the syntheses of seven-membered carbocycles are highly dependent on the substrate structure. For example, diene **1** cyclized to afford a seven-membered ring compound **2** in 96% yield. In contrast, diene **3** gave compound **4** only in 25% yield (Scheme 1).[7] This is probably due to the conformation of the diene substrate, because the RCM reaction mechanism is not dependent on the ionic species. Although, two olefinic moieties do not have any affinity for reaction, under the reaction conditions, the second generation Grubbs catalyst[8] works very effectively for most of the substrates. In the previous report,[4] the second generation Grubbs catalyst[8] could not be used. Therefore, it is worth studying how the second generation Grubbs catalyst[8] works for the construction of seven-membered carbocycles, and we have applied this methodology to the synthesis of tormesol (**5**) (Chart 1).[9]



Scheme 1. Reported examples.

(+)-Tormesol (**5**)[9] is a diterpene, which was isolated from *Halimium viscosum* by Urones et al., and it belongs to a sphenolobane family.[5,9,10] We have, recently, reported the synthesis of two sphenolobane-type diterpenoids[4] isolated from the liverwort *Anastrophyllum aurium*[5b] using the RCM reaction applied to the formation of seven-membered carbocycles. There have been several reports towards the synthesis of tormesol (**5**),[9] but, to the best of our knowledge, no successful example has appeared. Since we had a synthetic intermediate for the above-mentioned diterpenes,[4] it was used for the synthesis of (−)-tormesol (**5**), which is the enantiomer of the natural product, in this study.

Cyathanes were first isolated from the bird's nest fungi *Cyathus earlei* by Ayer,[11] then, from the fungi *Hericium erinaceum*[12] and *Sarcodon scabrosus*,[13] and the liverwort *Jamesoniella tasmanica*.[14] We have synthesized allocyathine B_2 (**6**),[15] which is a seven-membered carbocycle, via aldol cyclization.

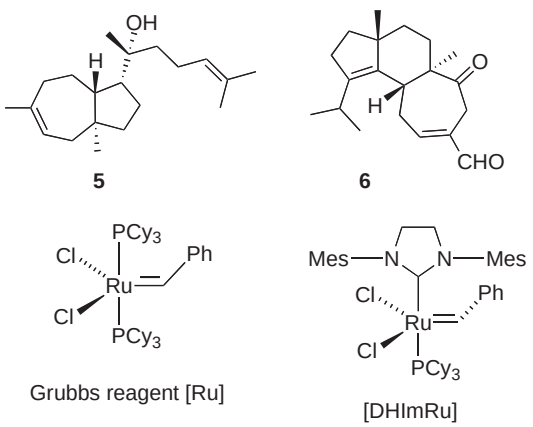


Chart 1.

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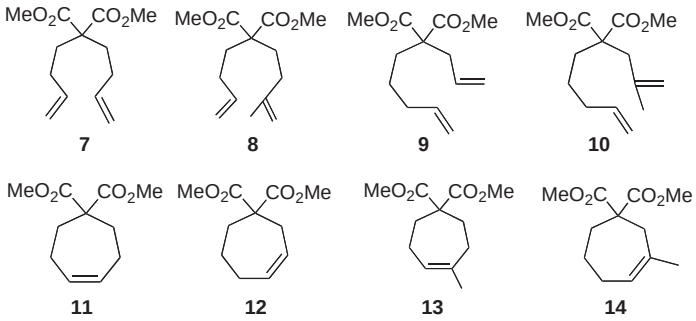
Table 1. RCM Reactions Producing Seven-Membered Carbocycles



Entry	Substrate	Reagent/mol %	Solvent[a)]	Temp (time/h)	Products (yield/%)
1	**7**	[Ru] (3)	CH_2Cl_2	reflux (2)	**11** (96)
2	**7**	[DHImRu] (3)	CH_2Cl_2	reflux (18)	**11** (68), **12** (23)
3	**7**	[DHImRu] (3)	PhH	reflux (18)	**11** (60), **12** (33)
4	**8**	[Ru] (5)	CH_2Cl_2	rt (39)	**13** (96)
5	**8**	[DHImRu] (5)	CH_2Cl_2	rt (39)	**13** (98)
6	**8**	[DHImRu] (3)	CH_2Cl_2	reflux (2)	**13** (86)
7	**9**	[Ru] (3)	CH_2Cl_2	reflux (2)	**12** (95)
8	**9**	[DHImRu] (3)	CH_2Cl_2	reflux (2)	**11** (13), **12** (79)
9	**10**	[Ru] (3)	CH_2Cl_2	reflux (2)	**14** (23)
10	**10**	[DHImRu] (3)	CH_2Cl_2	reflux (2)	**14** (100)

a) The concentration was 10 mM.

RCM reactions have not been applied to the synthesis of cyathanes. Therefore, the construction of the seven-membered ring in the cyathane-type diterpene using RCM reactions was also investigated. Here, we report the details of these results.

Results and Discussion

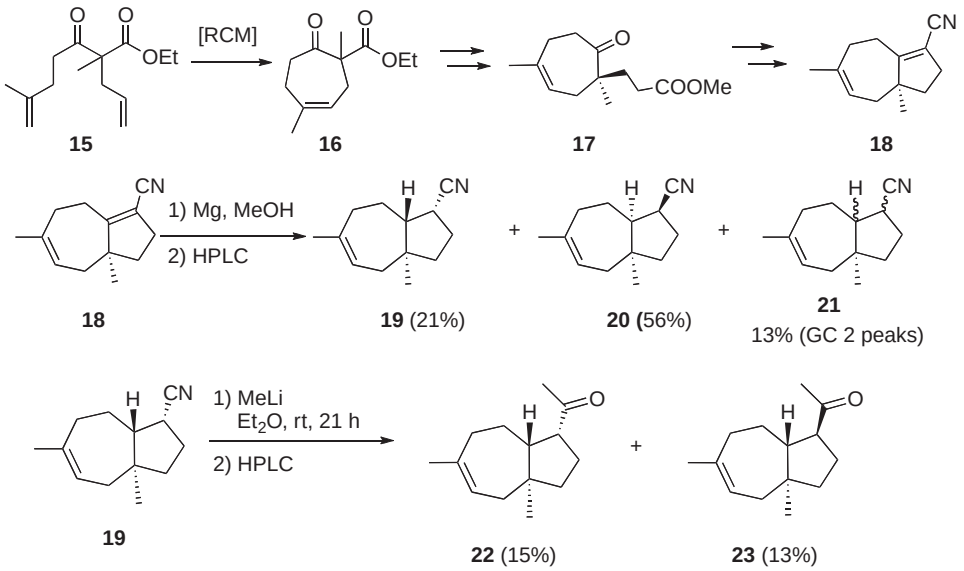
At first, we checked the formation of seven-membered carbocycles with di-substituted double bond using both [Ru] and [DHImRu] as shown in Table 1. When diene **7**[16] was treated with [Ru] in CH_2Cl_2 under reflux for 2 h, cycloheptene **11**[16,17] was formed in 96% yield (Entry 1). However, when [DHImRu] was used, isomer **12**[17] was formed in 23% yield along with **11**[16,17] (68%) (Entry 2). This was presumably formed by isomerization of **11**.[16,17] The total yield of **11**[16,17] and **12**[17] in PhH was slightly better than that in CH_2Cl_2 (Entry 3). Diene **9** was treated with [Ru] in CH_2Cl_2 to produce **12**[17] in 95% yield (Entry 7). However, when [DHImRu] was used, **12**[17] was formed in 79% yield along with a small amount of **11**[16,17] (13%) (Entry 8). Thus, isomerization tends to occur when the second generation reagent was used. Compounds **8** and **10** were treated with [Ru] and [DHImRu], although the cyclization of the corresponding ethyl ester with [Ru] was already reported by Grubbs.[7] The reported yield of compound **13** was very high, although normally the formation of a ring with the tri-substituted double bond using [Ru] is not easy. The yields for compounds **13** and **14** with [Ru] were 96 and 23%, respectively (Entries 4 and 9). When [DHImRu] was used, yields for **13** and **14** were 86 and 100%, respectively (Entries 6 and 10). When the reaction was carried out at rt for 39 h, the yield of **13** improved to 98% (Entry 5). These results were better than the results with Grubbs reagent, which was quite reasonable in view of higher reactivity of a second generation Grubbs reagent. Thus, seven-membered carbocycles can be prepared effectively by using the second generation Grubbs reagent (Table 1).

Chiral cycloheptenone derivative **17**[18] was prepared from a keto ester derivative **15** which was described in our previous report (Scheme 2).[4] Since the second generation Grubbs reagent[8] worked very well as demonstrated, we have reinvestigated the conversion of **15** into **16** using this catalyst. The results are listed in the Table 2.

Compound **15** did not afford carbocycle **16** in good yield using Grubbs reagent [Ru] (Entry 1) as described in our previous report.[4] One mol % of the new reagent [DHImRu] at rt successfully gave **16** in 82% yield (Entry 2). Moreover, at reflux temperature the yield of **16** improved to 95% (Entry 5). The yield only slightly changed depending on work-up[19] (Entries 4 and 5). Thus, the effectiveness of the reagent [DHImRu] in this cyclization is obvious.

The synthesis of bicyclic compound **22** was carried out according to the procedure in the previous paper[4] as summarized in Scheme 2. After methylation of **19**, without isomerization as before, direct separation of the crude mixture yielded **22** and **23**, in 15 and 13% yields, respectively, which were lower than expected. Finally, methyl ketone **22** was alkylated using 5-bromo-2-methyl-2-pentene under lithium exchange conditions in ether at $-78\,^{\circ}C$ to furnish in 24% yield a single isomer, which was *ent*-tormesol (**5**). The spectral data for **5** were completely identical with those provided by Prof. Urones, except that the sign of the specific rotation was opposite (see the Experimental). Preferential formation of 13*R* stereocenter is presumably explained by a Felkin–Anh model as shown in Fig. 1. In the most stable conformation calculated by CONFLEX,[20] the carbonyl group was located on the same side as that of the methyl group at the C-6 position. Thus, the reagent must approach from the less hindered right-hand side in Fig. 1 to afford the desired configuration needed for tormesol (**5**) synthesis.[21]

Therefore, we have succeeded in the total synthesis of (−)-



Scheme 2. Preparation of ketone **22**.

Table 2. RCM of **15** into **16** in CH_2Cl_2

Entry	Reagent/mol %	Conc./mM	Temp/°C	Results/%	Work up[16]
1[a)]	[Ru] (30)	10	40	**15**:**16** = 1:1 (GC-MS)	
2	[DHImRu] (1.0)	100	rt	82	
3	[DHImRu] (1.0)	100	reflux	88	
4	[DHImRu] (1.0)	100	reflux	90	Ph_3PO
5	[DHImRu] (1.0)	100	reflux	95	DMSO

a) $Ti(OiPr)_4$ (1.0 equiv) was added.

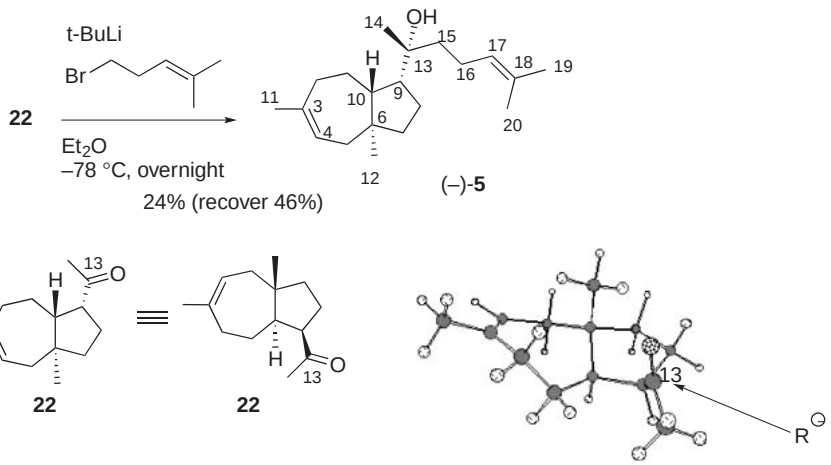


Fig. 1. The Felkin–Anh model of **22**.

tormesol (**5**) starting from keto ester **15** using the RCM reaction as the key steps for the construction of the seven-membered carbocycle. These syntheses support the absolute stereochemistry of tormesol (**5**) as well as configuration at C-13 position (*S* in the natural product), which was deduced by NOE experiment by Urones et al.[9] Compounds **24** and **25**, isolated from the liverwort,[5b] have the absolute configuration shown in Fig. 2 as demonstrated by our synthesis.[4] Compounds **26** and **27** were isolated from the liverwort[5a] and should have the same absolute configuration as **24** and **25**. However, (+)-tormesol (**5**), isolated

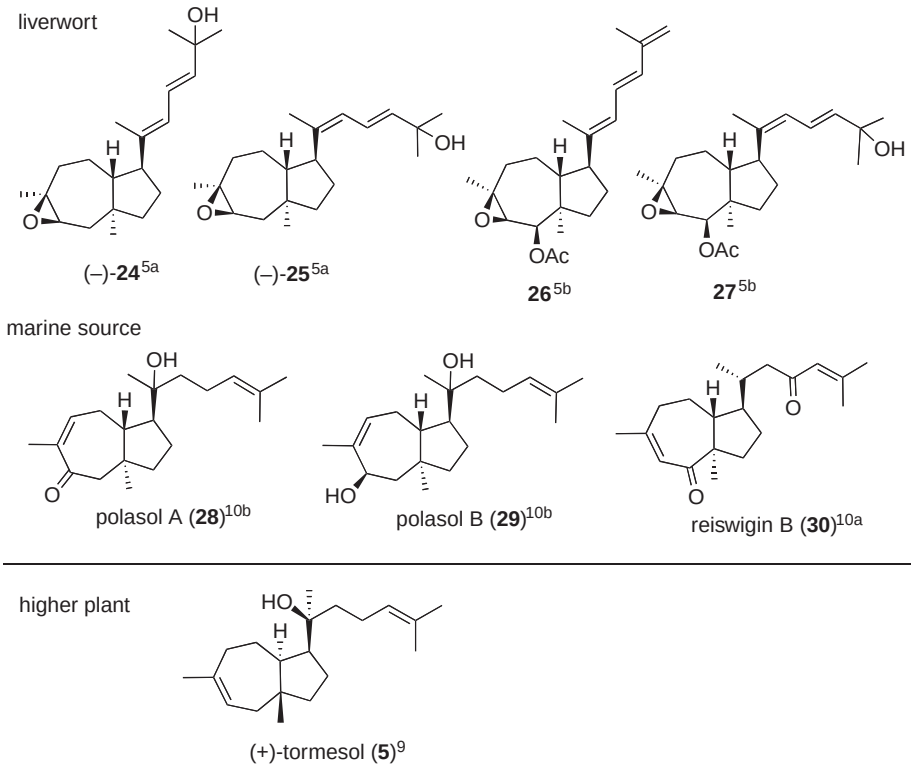
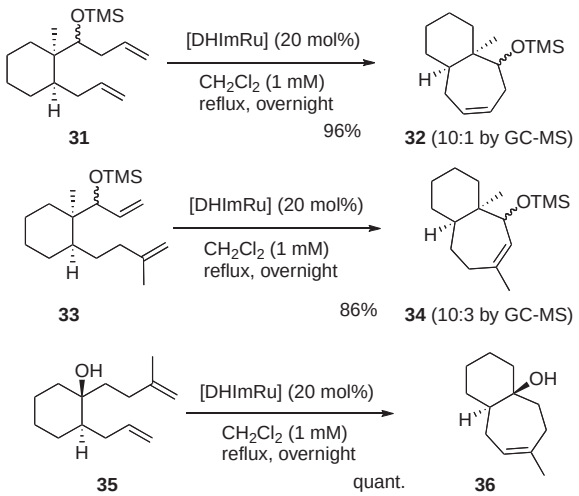


Fig. 2. Absolute configuration of sphenolobane-type diterpenes.



Scheme 3. Preparation of seven-membered rings.

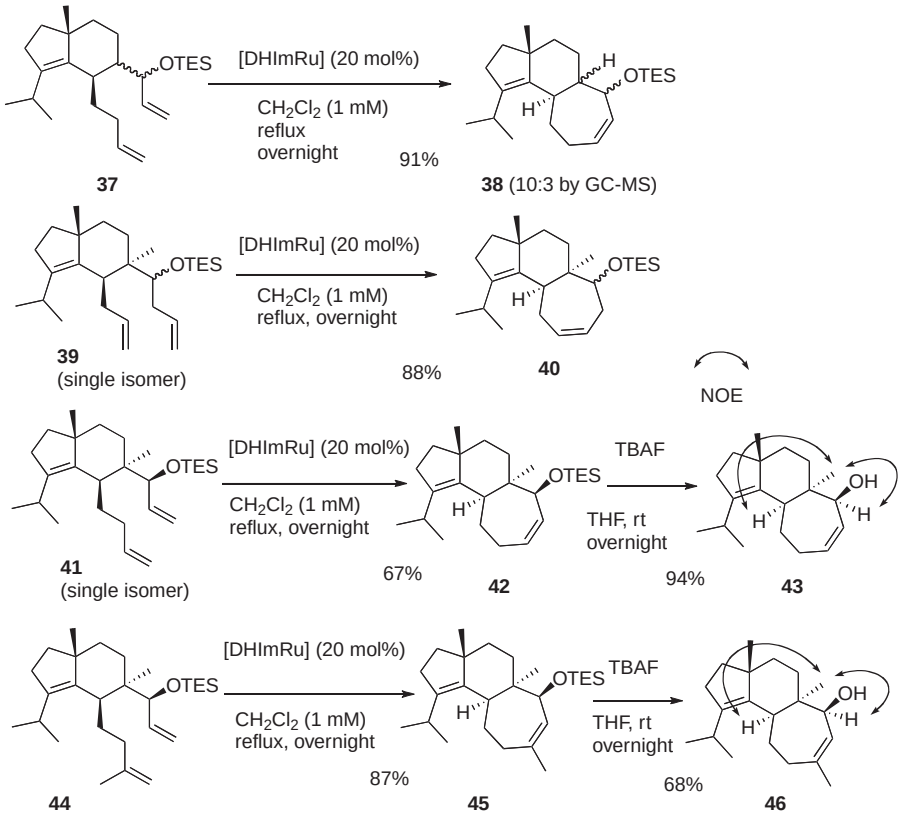
from the terrestrial higher plant, has the opposite absolute configuration[9] to those of the sphenolobane diterpenes isolated from the liverwort[5] or marine sources[10] as shown in Fig. 2.

Fused bicyclic systems of six- and seven-membered carbocycles included in cyathane-type diterpenes[11–14] were next attempted to prepare by RCM reactions. Compound **31**[22] derived from cyclohexanone was treated with 20 mol % of [DHImRu] in CH_2Cl_2 to give **32** in 96% yield as a 10:1 diastereomeric mixture detected by GC-MS based on the configuration of the oxymethine (Scheme 3). Compound **33**[22] was converted to a tri-substituted cycloheptene **34** in 86% yield (10:3 mixture by GC-MS). For **33**, it was necessary to protect the hydroxy group with TMS, otherwise isomerization or loss of one carbon takes place as reported.[23] The position of cyclization of compound **35**[22] is the same as that of **31**, and the yield of product **36** was 100% in this case.

Compound **37**[22] was prepared by modifying the method used to prepare allocyathine B_2 (**6**)[15] (Scheme 4). Similarly 20 mol % of [DHImRu] worked well to cyclize **37**, and tricyclic cycloheptene **38** was obtained in 91% yield. The position of the bond to be formed in the reaction of **39**[22] is shifted to the next one compared with that of **37**. Compound **39**[22] afforded **40** in 88% yield. This change had little effect on the yield. Substrate **41**[22] was taken from the total synthesis of allocyathine B_2 (**6**).[15] Compound **41**[22] cyclized into **42** in 67% yield. Since the stereochemistry of **42** was single, it was established by NOESY experiment at the stage of **43**. Finally, compound **44**[22] was treated with 20 mol % of [DHImRu] to provide compound **45** in 87% yield, the stereochemistry of which was also established by NOESY experiment of deprotected compound **46**. Compound **46** has all the carbon atoms required for the cyathane skeleton, although the configuration of the C-5 position is opposite. Thus, a cyathane skeleton has been synthesized using the RCM reaction.

Conclusion

We have developed the synthesis of cycloheptenes by RCM reactions and described its application to the synthesis of tormesol and a cyathane skeleton. This study shows that the use of the first and second generation Grubbs catalyst depends on the substrate structure. The synthesis of (−)-tormesol supported the assignment of the absolute configuration of the natural product reported by Urones, and its absolute configuration was clearly different from those originated from marine sources, liverworts, and higher plants.



Scheme 4. Preparation of seven-membered carbocycles in a cyathane-skeleton.

Experimental

General. All reactions were carried out under an argon atmosphere. Yields refer to chromatographically and spectroscopically homogeneous materials. Anhydrous solvents were purchased from Kanto Chemical Co., Inc. Reagents were purchased at the highest commercial quality and used without further purification. The IR spectra were measured on a JASCO FT/IR 500 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 600, a JEOL ECP-400, a Varian Mercury 300, a Varian Unity 200, or a Varian Gemini 200 spectrometer. The solvent used for NMR spectra was $CDCl_3$ unless otherwise stated. MS spectra were measured on a JEOL JMS-700 MStation spectrometer. Silica-gel BW-300 (200–400 mesh, Fuji Silycia) was used for column chromatography, and silica gel $60F_{254}$ plate (0.25 mm, Merck) was used for TLC.

General Procedure for RCM Reactions. RCM reactions were carried out by slow addition of a solution of [Ru] or [DHImRu] (3 to 20 mol %) in CH_2Cl_2 or PhH into a stirred solution of a substrate in the same solvent (10 mM) under Ar atmosphere. The mixture was stirred at rt or refluxed for certain period of time, and then, the seal was removed to expose the open air for 30 min. The solvent was evaporated, and the residue was purified by silica-gel column chromatography to afford the product, which sometimes needs further purification.

Synthesis of 22 and 23. To a stirred solution of **19**[4] (52.3 mg, 0.28 mmol) in ether (4 mL) was added MeLi (1.14 M ether soln., 1.15 mL, 1.3 mmol) at 0 °C, and the mixture was stirred for 19 h at rt. More MeLi (1.14 M ether soln., 0.23 mL, 0.26 mmol) was added, and the mixture was further stirred for 2 h. Hydrochloric acid (1 M) was added, and the mixture was extracted with ether. The ether-layer was washed with sat. NaCl aq, and dried ($MgSO_4$), and the solvent was evaporated to afford a residue (38.8 mg). The residue was separated by silica-gel column chromatography (hexane:EtOAc = 100:0–85:15) followed by HPLC (Nucleosil 50–5, 4.6ϕ × 250 mm, hexane:EtOAc = 95:5, flow rate: 1.5 mL min^{-1}) to give **22** (8.1 mg, 15%) and **23** (7.0 mg, 13%). **22**: $[\alpha]_D^{20}$ −108.2 (c 0.8, $CHCl_3$); FTIR 2920, 1710, 1450, 1350, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (3H, s), 1.30–1.57 (2H, m), 1.60–1.69 (1H, m), 1.71–1.91 (2H, m), 1.74 (3H, t, J = 1.5 Hz), 1.96–2.11 (4H, m), 2.12 (3H, s), 3.24 (1H, td, J = 9.9, 6.9 Hz), 5.34–5.42 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8 (CH_3), 23.8 (CH_2), 25.1 (CH_3), 27.0 (CH_3), 32.3 (CH_3), 34.7 (CH_3), 41.1 (CH_3), 41.8 (CH_3), 42.5 (C), 55.0 (CH), 57.1 (CH), 122.8 (CH), 138.9 (C), 211.6 (C); MS (EI) m/z 206 (M^+), 188, 163, 121, 107, 95 (base); HRMS (EI) Found m/z 206.1693 (M^+), $C_{14}H_{22}O$ requires 206.1670. **23**: $[\alpha]_D^{19}$ +35.5 (c 0.7, $CHCl_3$); FTIR 1710, 1450, 1360 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (3H, s), 1.10–1.27 (1H, m), 1.43 (1H, q, J = 3.0 Hz), 1.41–1.51 (1H, m), 1.47 (1H, dd, J = 8.7, 5.7 Hz), 1.57–1.71 (2H, m), 1.74 (3H, s), 1.78 (1H, td, J = 11.4, 3.0 Hz), 1.89–2.15 (4H, m), 2.15 (3H, s), 2.67 (1H, td, J = 11.1, 6.3 Hz), 5.38 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (CH_3), 24.7 (CH_2), 25.2 (CH_2), 27.1 (CH_3), 29.7 (CH_3), 33.8 (CH_2), 40.2 (CH_2), 40.5 (CH_2), 42.2 (C), 56.3 (CH), 56.7 (CH), 122.3 (CH), 139.4 (C), 212.2 (C); MS (EI) m/z 206 (M^+), 188, 163, 121, 107, 95 (base); HRMS (EI) Found m/z 206.1684 (M^+), $C_{14}H_{22}O$ requires 206.1670.

Synthesis of (−)-5. A solution of 5-bromo-2-methylpentene (128 mg, 0.78 mmol) in ether (1.7 mL) was treated with t-BuLi (1.51 M ether soln., 0.48 mL, 0.72 mmol) at −78 °C under Ar. The mixture was stirred for 8.6 h. This solution (1.1 mL) was added into a solution of **22** (8.1 mg, 0.039 mmol) in ether (1 mL) at

−78 °C, and the mixture was stirred for 3.3 h. More lithiated solution (1.1 mL) was added, and the mixture was stirred for 4 h more. A sat. NH_4Cl aq was added and the mixture was extracted with ether. The organic layer was washed with sat. NaCl aq, and dried ($MgSO_4$), and the solvent was evaporated to give a residue (39.4 mg). The residue was washed with silica-gel column chromatography (hexane:EtOAc = 100:0–1:1) followed by HPLC (Nucleosil 50–5, 4.6ϕ × 250 mm, hexane:EtOAc = 95:5, flow rate: 1.5 mL min^{-1}) to yield (−)-**5** (2.7 mg, 24%); $[\alpha]_D^{17}$ −30.0 (*c* 1.34, $CHCl_3$); FTIR 3470, 1450, 1380, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, s), 1.19 (3H, s), 1.63 (3H, s), 1.69 (3H, d, J = 0.8 Hz), 1.74 (3H, s), 1.79–1.89 (1H, m), 1.93–2.14 (6H, m), 2.41 (1H, dt, J = 10.6, 9.9 Hz), 5.09–5.16 (1H, m), 5.39 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8 (CH_3), 19.2 (CH_3), 22.8 (CH_2), 24.0 (CH_2), 25.8 (CH_3), 26.3 (CH_2), 27.0 (CH_3), 27.8 (CH_3), 36.0 (CH_2), 40.1 (CH_2), 41.4 (CH_2), 42.4 (C), 42.4 (CH_2), 52.6 (CH), 56.7 (CH), 75.8 (C), 122.8 (CH), 124.7 (CH), 131.7 (C), 139.1 (C).

Synthesis of 32. A solution of [DHImRu] (3.4 mg, 0.004 mmol) in degassed CH_2Cl_2 (5 mL) was added into refluxing CH_2Cl_2 (15 mL) solution of compound **31** (6.6 mg, 0.02 mmol). The solution was heated overnight under reflux. The mixture was cooled to rt and stirred in the air before evaporation of the solvent. The residue was subjected to silica-gel column chromatography (hexane:AcOEt = 95:5–4:1) to afford compound **32** (6.0 mg, 96%); FTIR 1650 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$); δ 0.09 (9H, s), 0.99 (3H, s), 0.99–1.51 (12H, m), 1.57 (3H, m), 1.67–2.64 (9H, m), 3.68 (1H, br d, J = 10.8 Hz), 3.70 (1H, s), 5.61–5.68 (2H, m); MS (CI) m/z 252 (M^+), 237, 205, 163 (base), 162, 117, 89; HRMS (CI) Found m/z 252.1911 (M^+). Calcd for $C_{15}H_{28}OSi$ 252.1909.

Synthesis of 34. A solution of [DHImRu] (25.6 mg, 0.03 mmol) in degassed CH_2Cl_2 (30 mL) was added into refluxing CH_2Cl_2 (150 mL) solution of compound **33** (50.9 mg, 0.151 mmol). The solution was heated overnight under reflux. The mixture was cooled to rt and stirred in the air before evaporation of the solvent. The residue was subjected to silica-gel column chromatography (hexane:$CHCl_3$ = 9:1–0:100) to afford compound **34** (38.5 mg, 86%); FTIR 1680 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.30 (9H, s), 0.98 (1H, s), 1.10 (3H, s), 1.25 (3H, s), 1.95 (4H, s), 1.49–1.94 (15H, m), 1.99–2.50 (6H, m), 4.27–4.28 (1H, m), 5.36–5.39 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.20 (CH_3), 21.5 (CH_2), 21.6 (CH_2), 23.8 (CH_3), 24.6 (CH_3), 26.0 (CH_2), 28.3 (CH_2), 30.7 (CH_2), 32.5 (CH_2), 44.7 (CH), 39.7 (C), 78.8 (CH), 131.0 (CH_2), 137.4 (C); MS (CI) m/z 266 (M^+), 265, 177, 156, 89 (base), 61; HRMS (CI) Found m/z 266.2044 (M^+). Calcd for $C_{16}H_{30}OSi$ 266.2066.

Synthesis of 36. A solution of [DHImRu] (40.82 mg, 0.048 mmol) in degassed CH_2Cl_2 (25 mL) was added into refluxing CH_2Cl_2 (240 mL) solution of compound **35** (50 mg, 0.24 mmol). The solution was heated overnight under reflux. The mixture was cooled to rt and stirred in the air before evaporation of the solvent. The residue was subjected to silica-gel column chromatography (CH_2Cl_2) to afford compound **36** (56.3 mg, 100%); FTIR 3485, 1672 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.17–1.76 (15H, m), 2.28–2.34 (1H, m), 2.55 (1H, dd, J = 9.4, 8.6 Hz), 5.50–5.55 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (CH_2), 25.6 (CH_3), 26.2 (CH_2), 27.6 (CH_2), 30.0 (CH_2), 30.3 (CH_2), 40.7 (CH_2), 41.0 (CH_2), 44.7 (CH), 73.1 (C), 125.1 (CH), 140.8 (C); MS (CI) m/z 180 (M^+), 162 (base), 134, 133, 105, 93, 43; HRMS (CI) Found m/z 180.1499 (M^+). Calcd for $C_{12}H_{20}O$ 180.1514.

Synthesis of 38. To a stirred solution of **37**[22] (10.8 mg, 0.027 mmol) in degassed CH_2Cl_2 (20 mL) was added a solution of [DHImRu] (5.2 mg, 0.006 mmol) in degassed CH_2Cl_2 (7 mL), and the mixture was refluxed overnight. The solvent was evaporated, and the residue was purified by silica-gel column chromatography (hexane:EtOAc = 100:0–93:7) to afford **38** (9.2 mg, 91%); FTIR 1680, 1630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) isomer 1; δ 0.59 (6H, q, J = 7.8 Hz), 0.93 (6H, d, J = 7.5 Hz), 0.96 (9H, t, J = 7.8 Hz), 1.01 (3H, s), 1.36–1.44 (4H, m), 1.55–1.69 (4H, m), 1.98–2.16 (4H, m), 2.58 (1H, sep, J = 6.6 Hz), 2.99 (1H, dd, J = 10.2, 5.4 Hz), 3.84 (1H, d, J = 9.6 Hz), 4.26 (1H, d, J = 7.5 Hz), 5.54 (1H, dd, J = 3.3, 1.5 Hz), 5.62 (1H, d, J = 2.4 Hz); isomer 2; δ 0.62 (6H, q, J = 7.8 Hz), 0.95 (6H, d, J = 7.5 Hz), 0.96 (9H, t, J = 7.8 Hz), 0.99 (3H, s), 1.45–1.54 (4H, m), 1.62–1.89 (4H, m), 2.13–2.36 (4H, m), 2.67 (1H, sep, J = 6.6 Hz), 2.99 (1H, dd, J = 10.2, 5.4 Hz), 3.83 (1H, d, J = 9.6 Hz), 4.25 (1H, d, J = 7.5 Hz), 5.54 (1H, dd, J = 3.3, 1.5 Hz), 5.62 (1H, d, J = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.9 (CH_2 × 6), 7.0 (CH_3 × 6), 21.3 (CH_3), 21.4 (CH_3 × 2), 21.5 (CH_3), 23.9 (CH_2), 24.6 (CH_3), 26.1 (CH_2), 26.1 (CH_2), 26.3 (CH), 26.8 (CH), 27.4 (CH_2), 27.5 (CH_2), 27.6 (CH_2), 27.7 (CH_2), 28.8 (CH_2), 29.5 (CH_3), 34.9 (CH), 35.1 (CH_2), 39.7 (CH_2, CH), 41.0 (CH_2), 41.2 (CH_2), 42.7 (CH_2), 46.1 (C), 46.4 (C), 46.6 (CH), 46.7 (CH), 74.0 (CH), 77.3 (CH), 127.6 (CH), 128.4 (CH), 133.6 (CH), 136.8 (C), 138.1 (CH), 140.0 (C), 141.9 (C), 143.0 (C); MS (EI) m/z 374 (M^+), 359, 331, 227, 184, 117, 103 (base), 75; HRMS (EI) Found m/z 374.2999 (M^+), $C_{24}H_{42}OSi$ requires 374.3005.

Synthesis of 40. To a stirred solution of **39**[22] (4.2 mg, 0.01 mmol) in degassed CH_2Cl_2 (5 mL) was added a solution of [DHImRu] (1.9 mg, 0.0022 mmol) in degassed CH_2Cl_2 (5 mL) and the mixture was refluxed overnight. The solvent was evaporated and the residue was purified by silica-gel column chromatography (hexane:EtOAc = 100:0–95:5) to afford **40** (3.4 mg, 88%); FTIR 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (6H, q, J = 7.9 Hz), 0.78 (3H, s), 0.91 (3H, d, J = 6.8 Hz), 0.95 (3H, d, J = 6.8 Hz), 0.96 (9H, t, J = 7.9 Hz), 0.98 (3H, s), 1.38–1.71 (7H, m), 1.91 (1H, dd, J = 13.4, 7.5 Hz), 2.13 (1H, dd, J = 15.0, 8.4 Hz), 2.25 (1H, ddd, J = 15.8, 9.0, 7.1 Hz), 2.41 (1H, d, J = 11.5 Hz), 2.46–2.54 (1H, m), 2.59 (1H, t, J = 6.9 Hz), 2.64–2.72 (1H, m), 3.75 (1H, dd, J = 10.5, 1.3 Hz), 5.62 (1H, quint, J = 11.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.2 (CH_2 × 3), 7.1 (CH_3 × 3), 17.6 (CH_3), 21.1 (CH_3), 21.5 (CH_3), 24.9 (CH_3), 26.2 (CH), 27.8 (CH_2), 29.4 (CH_2), 33.1 (CH_2), 33.9 (CH_2), 36.7 (CH_2), 40.8 (C), 41.7 (CH_2), 42.0 (CH), 46.2 (C), 79.1 (CH), 126.5 (CH), 127.4 (CH), 128.7 (CH), 131.4 (CH), 140.1 (C), 141.4 (C); MS (EI) m/z 388 (M^+), 359, 256, 241, 214, 169 (base), 133, 103; HRMS (EI) Found m/z 388.3148 (M^+), $C_{25}H_{44}OSi$ requires 388.3161.

Synthesis of 42. To a stirred solution of **41**[22] (7.4 mg, 0.018 mmol) in degassed CH_2Cl_2 (10 mL) was added a solution of [DHImRu] (3.4 mg, 0.0036 mmol) in degassed CH_2Cl_2 (8 mL), and the mixture was refluxed overnight. The solvent was evaporated, and the residue was purified by silica-gel column chromatography (hexane:EtOAc = 100:0–97:3) to afford **42** (4.7 mg, 67%); FTIR 1460 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.58 (6H, q, J = 7.9 Hz), 0.83 (3H, s), 0.92 (3H, d, J = 7.0 Hz), 0.96 (9H, t, J = 7.9 Hz), 0.96 (3H, d, J = 7.0 Hz), 1.01 (3H, s), 1.17–1.38 (3H, m), 1.43–1.58 (2H, m), 1.60–1.75 (2H, m), 1.81 (1H, dd, J = 12.2, 4.0 Hz), 2.02–2.10 (3H, m), 2.17–2.32 (2H, m), 2.63 (1H, quint, J = 6.8 Hz), 4.18 (1H, dd, J = 4.6, 1.6 Hz), 5.60 (1H, ddd, J = 10.5, 4.7, 1.5 Hz), 5.79 (1H, tdd, J = 10.0, 6.0, 1.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 5.0 (CH_2 × 3), 6.9 (CH_3 × 3), 21.2 (CH_3), 23.6 (CH_3), 25.2 (CH_3), 26.0 (CH_3),

26.1 (CH), 27.4 (CH_2), 27.7 (CH_2), 29.7 (CH_2), 36.2 (CH_2), 40.4 (C), 42.6 (CH_2), 46.1 (C), 46.4 (CH), 78.2 (CH), 130.0 (CH), 136.9 (CH), 139.0 (C), 142.4 (C); MS (CI) m/z 389 $[M + H]^+$, 388 (base), 359, 257, 255, 197, 184; HRMS Found m/z 388.3153 (M^+), $C_{25}H_{44}OSi$ requires 388.3162.

Synthesis of 43. A solution of **42** (4.7 mg, 0.012 mmol) in THF (2 mL) was added TBAF (1.0 M in THF, 0.02 mL, 0.02 mmol), and the mixture was stirred overnight. Water was added, and the solvent was evaporated. The residue was extracted with ether, and the organic layer was washed with sat. NaCl aq, and dried ($MgSO_4$). The solvent was evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 100:0–9:1) to afford **43** (3.1 mg, 94%); FTIR 3400, 1460 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.91 (3H, s), 0.93 (3H, d, $J = 6.9$ Hz), 0.97 (3H, d, $J = 6.9$ Hz), 1.03 (3H, s), 1.25–1.32 (2H, m), 1.40 (1H, td, $J = 13.8$, 4.2 Hz), 1.48 (1H, td, $J = 15.9$, 9.1 Hz), 1.57 (1H, dt, $J = 13.2$, 3.4 Hz), 1.67 (1H, dd, $J = 12.0$, 6.9 Hz), 1.76 (1H, dddd, $J = 14.5$, 12.0, 11.9, 2.8 Hz), 1.86 (1H, td, $J = 13.9$, 4.0 Hz), 2.04–2.14 (2H, m), 2.11 (1H, dd, $J = 15.3$, 8.5 Hz), 2.23 (1H, ddd, $J = 16.4$, 9.5, 7.1 Hz), 2.32 (1H, dd, $J = 12.0$, 2.9 Hz), 2.63 (1H, sep, $J = 6.9$ Hz), 4.25 (1H, d, $J = 3.8$ Hz), 5.65 (1H, ddd, $J = 10.8$, 4.8, 2.2 Hz), 5.88 (1H, dddd, $J = 11.3$, 5.9, 5.9, 2.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.1 (CH_3), 21.3 (CH_3), 23.1 (CH_2), 24.6 (CH_3), 26.1 (CH), 27.5 (CH_2), 27.7 (CH_2), 29.6 (CH_2), 36.1 (CH_2), 39.9 (C), 42.7 (CH_2), 46.1 (C), 46.4 (CH), 78.1 (CH), 131.2 (CH), 134.8 (CH), 139.6 (C), 141.7 (C); MS (EI) m/z 274 (M^+), 259 (base), 241, 204, 191, 189, 175, 135, 105, 91; HRMS (EI) Found m/z 274.2293 (M^+), $C_{19}H_{30}O$ requires 274.2296.

Synthesis of 45. To a stirred solution of **44**[22] (14.3 mg, 0.033 mmol) in degassed CH_2Cl_2 (25 mL) was added a solution of [DHImRu] (6.2 mg, 0.0073 mmol) in degassed CH_2Cl_2 (8 mL), and the mixture was refluxed overnight. The solvent was evaporated, and the residue was purified by silica-gel column chromatography (hexane:EtOAc = 100:0–95:5) to afford **45** (11.6 mg, 87%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.58 (6H, q, $J = 7.9$ Hz), 0.83 (3H, s), 0.92 (3H, d, $J = 6.9$ Hz), 0.95 (3H, d, $J = 6.9$ Hz), 0.96 (9H, t, $J = 7.9$ Hz), 1.01 (3H, s), 1.16–1.57 (9H, m), 1.71 (3H, s), 1.76–1.88 (1H, m), 2.05–2.27 (3H, m), 2.59 (1H, sep, $J = 6.8$ Hz), 4.12 (1H, d, $J = 3.9$ Hz), 5.28 (1H, br s); MS (EI) m/z 402 (M^+), 211 (base), 190, 175, 115, 103.

Synthesis of 46. A solution of **45** (11.6 mg, 0.029 mmol) in THF (2 mL) was added TBAF (1.0 M in THF, 0.043 mL, 0.043 mmol), and the mixture was stirred overnight. Water was added, and the solvent was evaporated. The residue was extracted with ether, and the organic layer was washed with sat. NaCl aq, and dried ($MgSO_4$). The solvent was evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 100:0–94:6) to afford **46** (5.6 mg, 68%); FTIR 3440, 1450 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, s), 0.93 (3H, d, $J = 6.9$ Hz), 0.96 (3H, d, $J = 6.9$ Hz), 1.02 (3H, s), 1.25–1.30 (2H, m), 1.38 (1H, td, $J = 13.7$, 4.1 Hz), 1.47 (1H, td, $J = 15.6$, 9.1 Hz), 1.53–1.56 (2H, m), 1.67 (1H, dd, $J = 11.7$, 6.9 Hz), 1.67 (1H, ddd, $J = 12.4$, 2.4, 1.8 Hz), 1.76 (3H, t, $J = 1.5$ Hz), 1.81 (1H, td, $J = 13.8$, 4.1 Hz), 1.88 (1H, ddt, $J = 14.4$, 6.0, 1.6 Hz), 2.11 (1H, dd, $J = 15.6$, 9.1 Hz), 2.17 (1H, dd, $J = 14.1$, 12.2 Hz), 2.22 (1H, ddd, $J = 15.3$, 10.8, 6.9 Hz), 2.29 (1H, dd, $J = 12.9$, 3.3 Hz), 2.63 (1H, sep, $J = 6.8$ Hz), 4.19 (1H, d, $J = 3.8$ Hz), 5.31 (1H, sep, $J = 1.6$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2 (CH_3), 21.3 (CH_3), 23.0 (CH_2), 24.5 (CH_3), 24.7 (CH_3), 26.1 (CH), 26.3 (CH_3), 27.5 (CH_2), 29.2 (CH_2), 33.2 (CH_2), 36.0 (CH_2), 40.0 (C), 42.7 (CH_2), 46.1 (C), 78.2 (C), 156.5 (C); MS (CI) m/z 289 $[M + H]^+$, 288, 287 (base), 271, 243, 189; HRMS Found m/z 288.2460 (M^+), $C_{20}H_{32}O$ requires 288.2453.

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Supporting Information

Experimental procedures for the preparation of compounds **8**–**14**, **31**, **33**, **35**, **37**, **39**, **41**, and **44**, ^1H NMR spectra of new compounds and some important compounds on the way to the substrates described in the manuscript. This material is available free of charge on the Web at http://www.csj.jp/journals/bscj/.

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