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Preparation of seven- and eight-membered rings by carbon–carbon bond formation induced by samarium diiodide: 7-*endo*- and 8-*endo-trig* type cyclization to bicyclo[5.3.0]decanolone, bicyclo[5.4.0]undecanolone, and bicyclo[6.4.0]dodecanolone

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ABSTRACT

Compounds with an enone-aldehyde/ketone were treated with SmI_2 to form the bicyclic ketols, bicyclo[5.3.0]decanolones, and bicyclo[5.4.0]undecanolones, in different ratios depending on the reaction conditions (with or without different amounts of additives, low temperature or rt). The tendency to form seven-membered rings was different from that of six-membered rings and the mechanisms for these reactions are proposed. Cyclization to an eight-membered ring was attempted realizing in the yield of 26%.

1. Introduction

One-electron transfer from SmI_2 is used for the reduction of a broad range of compounds because it is selective, fast, gives a high yield, and is easy to handle.[1–4] We have been studying a series of reductive cyclization reactions yielding such compounds as perhydronaphthalenones[5,6] and hydrindanones[7,8] through a 6-*endo-trig* type of cyclization. In these studies, the reaction pathways change depending on conditions such as the presence or absence of an additive, namely a proton source, for example, MeOH or H_2O, to give different stereoisomers.[5–8] We have already speculated on the reaction mechanism involved in such reactions, although the radical species has not yet been fully verified spectroscopically.[9] We now plan reactions to form seven-membered carbocycles to determine the scope and limitation of this type of reaction for compounds **1**–**5** (Fig. 1) through a 7-*endo-trig* type of cyclization.[10] Terpenoids, which have seven-membered rings are frequently found in nature, for example, ambrosin (**7**)[11] and allocyathin B_2 (**8**),[12,13] and can also have both seven- and five- or six-membered rings. We have previously reported the application of the RCM reaction of **9** for the construction of the seven-membered ring of a cyathane skeleton, such as **10** (Scheme 1).[13c] In this synthesis only the cis-fused seven-membered ring of a cyathane skeleton was realized. Compound **12** has a partial cyathane structure and compound **11** can be synthesized by cyclization of compound **3**. Ambrosin (**7**) can also be synthesized from compound **14**, because it has a trans-fused octahydroguaiane skeleton, which could in turn be prepared from compound **1** (Scheme 2). These bicyclic intermediates can be prepared by cyclization of enone-aldehyde induced by SmI_2. We briefly determined the ability of compound **6** to cyclize to an eight-membered ring through an 8-*endo-trig* type of cyclization.[14] We now report the details of our results on the formation of bicyclo[5.3.0]decanolones and bicyclo[5.4.0]undecanolones, as well as bicyclo[6.4.0]dodecanolone.

2. Results and discussion

2.1. Cyclization of 5-(2-methyl-5-oxo-1-cyclopenten-1-yl)pentanal (1)

5-(2-Methyl-5-oxo-1-cyclopenten-1-yl)pentanal (**1**) was treated with SmI_2 in THF at rt or 0 °C to give four products **13**–**16**, depending on the conditions shown in Table 1. Compound **16** was the major product in entries 1 and 2. When MeOH was added as a proton source, the product ratio did not change very much (entries 3 and 4). However, addition of HMPA reduced the ratio of compound **16**, and

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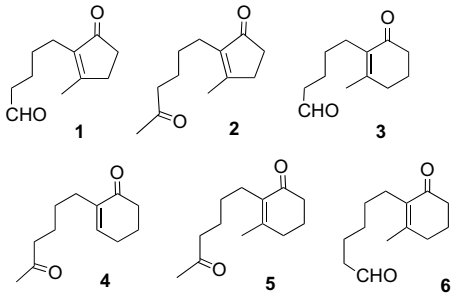


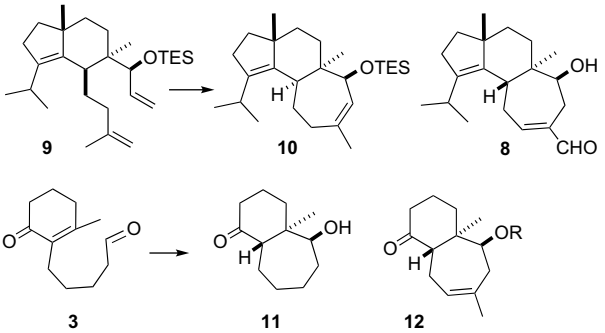
Figure 1. Substrates **1**–**6**.

the other products remained almost equal (entry 5). Because addition of HMPA increases the reduction power,[15] the yield was raised than in entry 2. Addition of NiI_2 did not change the product ratio very much (entries 6, 7), although there are some reports on the acceleration effects for NiI_2.[16]

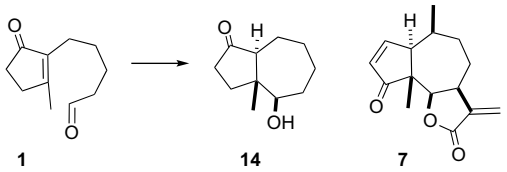
The products were separated by HPLC and their structures were determined based on spectroscopic data. All four products had the molecular formula $C_{11}H_{18}O_2$ (HRMS) and the IR spectra showed the presence of a hydroxy (3450–3500 cm^{-1}) and a carbonyl (1730–1740 cm^{-1}) group. Therefore, they were bicyclic enols with five- and seven-membered carbocycles. The stereochemistry was deduced by NOESY spectra.[17] The methyl group at C-1 of compound **13** showed NOE correlations with H-7 and H-10β. The H-2 correlated with H-10α. Therefore, H-7, Me-1, and OH-2 were all cis in compound **13**. In compound **14**, because H-2 and H-7 had NOE correlation and Me-1 showed an NOE correlation with H-9β, this was a trans-fused isomer of compound **13**. Compound **15** was an epimer at C-2 of compound **13**, because Me-1 showed NOE correlations with H-7 and H-2. While in compound **16**, Me-1 showed NOE correlations with H-6β and H-2, indicating a trans isomer of compound **15**. In order to secure the structure, each product was subjected to isomerization conditions (K_2CO_3, MeOH) to determine the isomeric pairs (Scheme 3). It was shown that compounds **13** and **14**, and compounds **15** and **16** were the pairs of isomers relating to the configuration of the α-position to the carbonyl group. The product ratio indicated that trans isomers were more stable than the cis congeners. The corresponding steric energies and the most stable conformations were calculated by MM2 CONFLEX (Fig. 2).[18] However, the steric energies for the pair of compounds **13** and **14**, and **15** and **16** were almost the same.

2.2. Cyclization of 3-methyl-2-(5-oxohexyl)cyclopent-2-enone (2)[19]

3-Methyl-2-(5-oxohexyl)cyclopent-2-enone (**2**)[19] was treated with 3 equiv of SmI_2 in THF at rt, and most of the starting material was recovered with or without MeOH as a proton source (Table 2, entries 1 and 2). The addition of more reagent did not change the situation, but provided messy products. Addition of HMPA afforded reduced compound **17** at a yield of 64% (entry 3). Addition of NiI_2 resulted in messy products. No cyclization occurred for this compound presumably because there were two methyl groups attached to both ends of the bond formation.



Scheme 1. Compound **11** derived from **3** as a precursor of **12** or **8**, being different from **10** prepared from **9** by RCM.



Scheme 2. Compound **14** derived from **1** as a precursor of **7**.

2.3. Cyclization of 5-(2-methyl-6-oxocyclohex-1-enyl)pentanal (3)

Aldehyde **3** was treated with 3 equiv of SmI_2 and the products were analyzed. These structures were determined based on spectroscopic analysis (Table 3). In this case a spiro compound **21** was also produced along with all four possible decahydrobenzocycloheptenone isomers **11** and **18**–**20**.

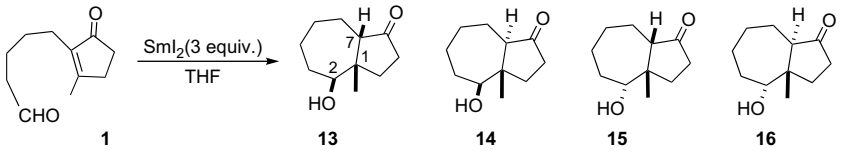
Compound **18** was the most abundant product in entries 1–4. When HMPA was added, compounds **20** and **21** were the major products (entry 5). This was presumably due to the fact that the rate of reduction was increased and the radical formed by one-electron reduction was further reduced very quickly to afford an anion at the β-position of the carbonyl group. This anion was quenched and the aldol reaction then occurred with the aldehyde group. It is also possible that the aldol cyclization forming a spiro compound occurred easily followed by further reduction and quenching. Addition of NiI_2[16] did not change the product ratio very much (entry 6).

The structures were determined as follows: all the products had the molecular formula $C_{12}H_{20}O_2$ (HRMS) and the IR spectra indicated the presence of both hydroxy (3350–3450 cm^{-1}) and carbonyl (1700–1710 cm^{-1}) group. The stereochemistry was revealed by the NOESY spectra.[17] The NOE correlations between Me-1/H-7, Me-1/H-3β, H-7/H3β, and H-2/H-3α were detected for compound **18** and the orientation of H-7, Me-1, and OH were all determined to be in β. In compound **19**, the NOE correlation was detected between H-7 and H-2, establishing the trans-fused stereochemistry of compound **18**. In the case of compound **20**, NOE correlations between Me-1/H-7 and Me-1/H-2 were detected. This was therefore, the C-2 epimer of compound **18**. The stereochemistry of compound **11** was established as a result of the NOE correlations between Me-1/H-2, Me-1/H-6β, and H-7/H-11α to be the trans isomer of compound **20**. Finally compound **21** had a doublet methyl group (δ 0.99) and a quaternary carbon (δ 58.2) in its ^1H and ^{13}C NMR spectra, respectively. Therefore, this compound was not a fused bicyclic one, but a spiro compound. Because the NOE correlations between Me/H-5β, Me/H-1, and H-1/H-5β were detected, the stereochemistry was suggested as depicted in the formula. In order to determine the pair of compounds **11** and **18**–**20**, each product was subjected to isomerization conditions (K_2CO_3, MeOH) to validate each isomer at the α-position of the carbonyl group (Scheme 4). Both isomers exist in almost equal amount. The CONFLEX calculation also supported these data (Fig. 3).[18]

2.4. Cyclization of 2-(5-oxohexyl)cyclohex-2-enone (4)

When compound **4** was subjected to the reaction induced by SmI_2, the most abundant product of reductive cyclization at rt was

Table 1
The reaction of compound **1** with SmI_2

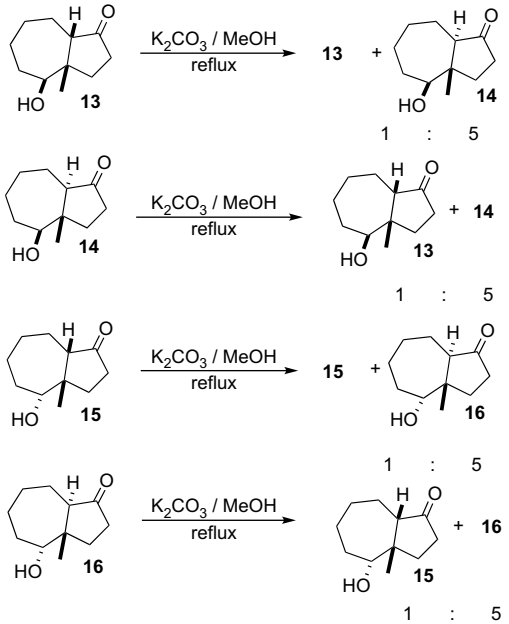


Entry	Additive (equiv)	Temp (°C)	Yield (%)	Ratio by GC–MS			
				13	**14**	**15**	**16**
1	None	0	79	19	16	12	53
2	None	rt	46	15	10	14	61
3	MeOH (2)	rt	69	10	23	8	59
4	MeOH (10)	rt	82	10	12	28	50
5	HMPA (12)	rt	78	24	31	20	25
6	NiI_2 (0.1)	0	69	13	18	24	45
7	NiI_2 (0.1)	rt	31	20	15	20	44

24, in which the conjugated double bond was reduced (Table 4, entry 1). When 6 equiv of the reagent was used, **22** and **23** (isomers at the C-2 position) were obtained in a total yield of 74% (entry 2). Compounds **22** and **23** were separated and their structures were determined by spectroscopic analysis. The stereochemistry of each cyclized product was established by NOESY spectra.[17] Addition of a proton source did not give cyclized products in a higher yield (entries 3 and 4). The rest of the compounds in the Table was unidentified messy mixture presumably due to the presence of various alcohols with or without a double bond. A ketone group reacts very slowly, but the enone group was reduced very quickly, resulting in the predominant formation of compound **24**. To our surprise, the addition of HMPA retarded the reaction rate (entry 5) and 45% of the starting material was recovered. The addition of NiI_2 slightly raised the ratio of **22** and **23** compared to entry 1 (entry 6).

2.5. Cyclization of 3-methyl-2-(5-oxohexyl)cyclohex-2-enone (5)

In the case of compound **5**, there were two methyl groups at both positions of the bond formation (Table 5). The major products in entries 1 and 2 were reduction products **26** and **27**. With the addition of MeOH as a proton source, a small amount of cyclized product, **25** was obtained (entries 3 and 4). The structure of **25** was established by X-ray crystallographic analysis. The addition of HMPA greatly interfered with the rate of the reaction and gave a reduction product **26** as well as the starting material (entry 5). It was not clear why no reaction occurred on addition of NiI_2. The introduction of two methyl groups at both ends of the bond formation created significant steric hindrance.



Scheme 3. Isomerization of compounds **13**–**16**.

2.6. Cyclization of 6-(2-methyl-6-oxocyclohex-1-enyl)-hexanal (6)

Because the formation of seven-membered carbocycles was realized using this methodology, we next evaluated the cyclization reaction into eight-membered compounds using aldehyde **6**.

When compound **6** was treated with 3 equival of SmI_2, compounds **29**–**34** were formed depending on the reaction conditions (Table 6). Compound **29** was produced in a yield of 7%, as well as 11% of **30** in entry 1. The structure of compound **29** was established based on 2D NMR spectra as well as X-ray crystallographic analysis. Unfortunately, the structure determination of **30** was not feasible due to the broadness of the NMR spectra. However, from MS and IR

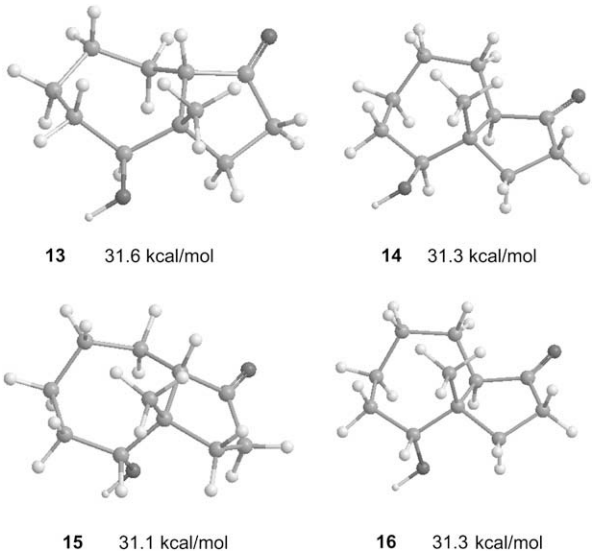
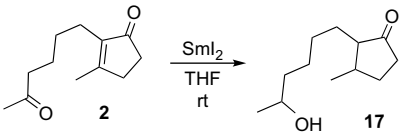


Figure 2. Most stable conformations of compounds **13**–**16** calculated by CONFLEX and their steric energies.

Table 2
The reaction of compound **2** with SmI_2

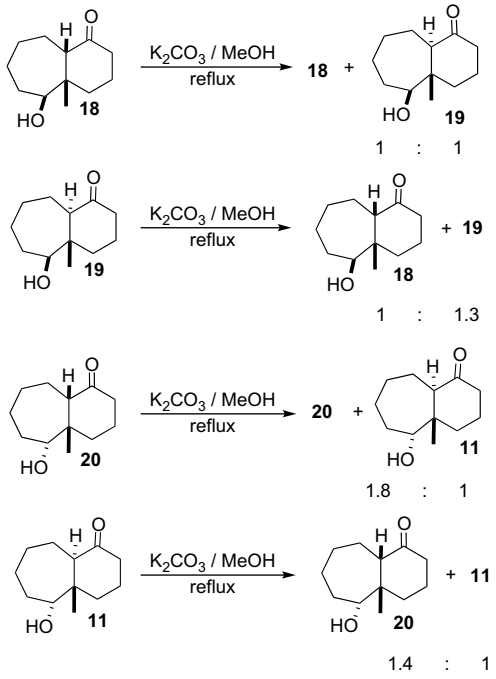


Entry	Additive (equiv)	SmI_2 (equiv)	Recovery (%)	Yield (%) **17**
1	None	3	86	0
2	MeOH (10)	8	19	0
3	HMPA (19)	8	0	64

data, **30** seemed to be one of the stereoisomers of bicyclic ketols. Compounds **32** and **34** were analyzed and found to be diastereoisomeric mixtures, respectively. At rt without additive, 54% of compound **31** was observed (entry 2), however, the use of more SmI_2 produced more **29** and less **31**, as well as **34**. Addition of MeOH retarded the reactivity and afforded **31** and **33** with 60% recovery of the starting material. Addition of HMPA dramatically changed the reactivity and afforded an eight-membered compound **29** as well as reduction products **31** and **34** (entry 5). Molander reported that eight-membered compounds were obtained by ketyl–olefin coupling reactions induced by SmI_2 and the application of this 8-*endo-trig* type of cyclization to the synthesis of schizandrins natural products.[14] Another applications were also reported by Reissig's group.[20] In the case of NiI_2, more **31** and less **29** were formed (entry 6).

2.7. Mechanism

The reaction of compound **3**, in the absence of additive, started with a one-electron transfer from SmI_2 to an aldehyde carbonyl group. When SmI_2 reduced the aldehyde group, the conformation of the samarium-coordinated group should adopt the outside position in its predominant form (A_1), followed by further reduction to make a carbon–carbon bond (A_2) through a 7-*endo-trig* type cyclization. Although **18** and **19** were not very different energetically, protonation from the upside must be faster for kinetic reasons (Fig. 4). Thus, compound **18** was predominant in entries 1 and 2 (Table 3). However, when a proton source is present, we propose that protonation occurs prior to the carbon–carbon bond formation producing α-protonated ketone as illustrated in Figure 5. The side chain must adopt the equatorial position for energetic reasons. From here there are four possibilities (C to F route) and the E and F routes must be predominant because the C and D routes are hindered by the axial hydrogen α to the carbonyl group. Thus, compounds **18** and **20** were obtained as major products.



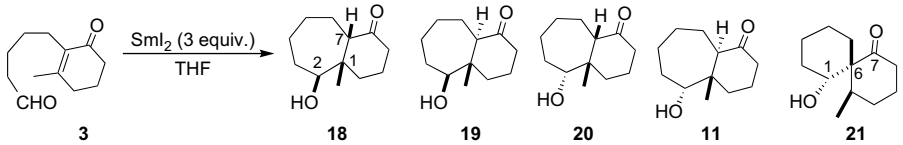
Scheme 4. Isomerization of compounds **11** and **18**–**20**.

The cyclization mechanism for compound **1** is similar to that explained above. However, the tendency is more apparent in the case of compound **3**.

3. Conclusion

Cyclization reactions of both compounds **1** and **3** afforded all possible isomers. This is different from those of perhydronaphthalenones and other cases reported previously,[5,8] and is probably because the present mechanism depends on the late-transition states, namely the conformation of the intermediates close to the products, which are responsible for the formation of the products having the requisite stereochemistry. The steric energies of the isomeric pairs of compounds were very close to each other and this is the main reason that the reaction afforded all the possible isomers. However, we do not suppose cis–trans isomerization in the reaction mixture. This phenomenon was similar in the case of compounds **1** and **3**. In these cases, in the presence of the proton source, the protonation of samarium enolate was faster than the carbon–carbon bond formation of the radicals. The reaction yields were moderate-to-high, although some were poor. We believe that

Table 3
The reaction of compound **3** with SmI_2



Entry	Additive (equiv)	Temp (°C)	Yield (%)	Ratio by GC–MS				
				18	**19**	**20**	**11**	**21**
1	None	0	82	64	10	9	17	0
2	None	rt	75	78	0	7	15	0
3	MeOH (2)	rt	83	63	0	20	17	0
4	MeOH (10)	rt	84	59	0	34	7	0
5	HMPA (12)	rt	45	28	0	34	5	33
6	NiI_2 (0.1)	0	95	57	23	10	10	0

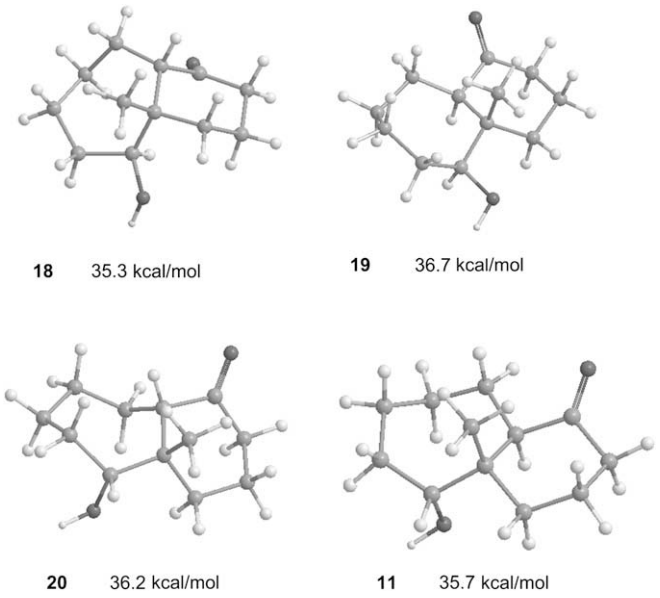


Figure 3. Most stable conformations of compounds **11** and **18**–**20** calculated by CONFLEX and their steric energies.

this type of reaction can be used in the preparation of octahydroazulenones and decahydrobenzocycloheptenones.

4. Experimental

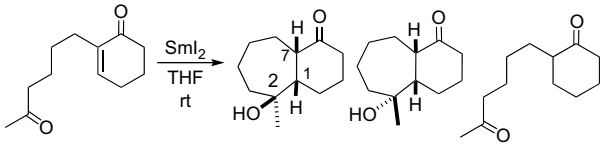
4.1. General procedure of SmI_2-induced cyclization

To a stirred solution of SmI_2 in THF (0.1 M, 0.3–0.9 mmol) substrates (0.1–0.3 mmol) were added at the temperatures listed in the Table for 2–5 h. The reaction was quenched with a saturated aqueous solution of Rochelle's salt. Organic materials were extracted with diethyl ether, washed with brine, and dried ($MgSO_4$). The products were purified by silica gel flash chromatography and HPLC. Gas chromatographic analyses were carried out on a capillary column.

4.1.1. (1S,2S*,7S*)-2-Hydroxy-1-methylbicyclo[5.3.0]decan-8-one (**13**)*

Oil; MS (CI) *m*/*z* 183 $[M+H]^+$, 182, 165 (base), 147, 97; HRMS (CI) found *m*/*z* 183.1390 (calcd for $C_{11}H_{19}O_2$ 183.1385); IR 3450, 1740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.11 (3H, s, CH_3), 1.25–1.32 (1H, m), 1.42–1.49 (2H, m), 1.64–1.68 (1H, m), 1.73–1.92 (6H, m), 2.01 (1H, m), 2.29 (1H, dddd, *J*=19.2, 9.6, 2.4, 0.5 Hz), 2.39 (1H, dddd, *J*=19.2, 12, 9.6, 1.2 Hz), 3.70 (1H, dd, *J*=10.8, 3.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.7 (CH_3), 27.1 (CH_2), 27.3 (CH_2), 29.0 (CH_2), 34.2 (CH_2), 34.4 (CH_2), 36.1 (CH_2), 46.7 (C-1), 59.9 (C-7), 79.5 (C-2), 222.3 (C-8).

Table 4
The reaction of compound **4** with SmI_2



Entry	Additive (equiv)	SmI_2 (equiv)	Recovery (%) **4**	Yield (%)		
				22	**23**	**24**
1	None	3	0	3	10	38
2	None	6	6	19	55	16
3	MeOH (2)	3	0	3	12	36
4	MeOH (10)	3	0	0	6	38
5	HMPA (12)	3	45	0	0	3
6	NiI_2 (0.2)	3	6	13	31	14

4.1.2. (1S,2S*,7R*)-2-Hydroxy-1-methylbicyclo[5.3.0]decan-8-one (**14**)*

Oil; MS (EI) *m*/*z* 182 (M^+), 167, 154, 149, 97 (base); HRMS (EI) found *m*/*z* 182.1305 (calcd for $C_{11}H_{18}O_2$ 182.1307); IR 3450, 1740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.91 (3H, s, CH_3), 1.29 (1H, m), 1.40–1.47 (2H, m), 1.53 (1H, m), 1.68 (2H, m), 1.84 (1H, m), 1.96 (1H, m), 1.99–2.05 (3H, m), 2.21 (1H, ddd, *J*=19.5, 11.5, 8.8 Hz), 2.32 (1H, ddt, *J*=19.5, 9.5, 1.1 Hz), 3.51 (1H, dd, *J*=11.3, 4.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.7 (CH_3), 21.5 (CH_2), 22.3 (CH_2), 23.9 (CH_2), 34.4 (C-10), 34.6 (C-9), 36.1 (C-3), 47.2 (C-1), 53.7 (C-7), 82.7 (C-2), 220.3 (C-8).

4.1.3. (1S,2R*,7S*)-2-Hydroxy-1-methylbicyclo[5.3.0]decan-8-one (**15**)*

Oil; MS (EI) *m*/*z* 182 (M^+), 167, 154, 149, 122, 109, 97 (base); HRMS (EI) found *m*/*z* 182.1311 (calcd for $C_{11}H_{18}O_2$ 182.1306); IR 3500, 1735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.22 (3H, s, CH_3), 1.46 (1H, m), 1.53 (1H, m), 1.62–1.74 (3H, m), 1.75–1.88 (4H, m), 2.04 (1H, m), 2.28–2.36 (2H, m), 2.43 (1H, ddd, *J*=18.4, 11.2, 7.1 Hz), 3.79 (1H, d, *J*=7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.5 (CH_2), 25.9 (CH_2), 26.8 (CH_2), 29.2 (CH_3), 31.9 (CH_2), 32.0 (C-10), 37.0 (C-9), 47.1 (C-1), 58.5 (C-7), 79.1 (C-2), 215.6 (C-8).

4.1.4. (1S,2R*,7R*)-2-Hydroxy-1-methylbicyclo[5.3.0]decan-8-one (**16**)*

Oil; MS (CI) *m*/*z* 183 $[M+H]^+$, 165 (base), 164, 97, 89; HRMS (CI) found *m*/*z* 183.1380 (calcd for $C_{11}H_{19}O_2$ 183.1385); IR 3500, 1730 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.92 (3H, s, CH_3), 1.39 (1H, ddt, *J*=11.9, 2.9, 2.9 Hz), 1.41 (1H, m), 1.45 (1H, m), 1.50 (1H, m), 1.64 (1H, tdt, *J*=14.7, 11.8, 2.0 Hz), 1.78 (1H, ddt, *J*=14.7, 11.5, 2.5 Hz), 1.86 (1H, m), 1.89 (1H, m), 2.03 (1H, m), 2.24 (1H, m), 2.32 (1H, m), 2.34 (1H, m), 2.61 (1H, ddd, *J*=11.9, 5.6, 1.2 Hz), 3.76 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.2 (CH_3), 19.8 (C-4), 21.8 (C-6), 24.9 (C-5), 29.5 (C-10), 34.6 (C-3), 35.2 (C-9), 47.7 (C-1), 50.0 (C-7), 73.5 (C-2), 221.4 (C-8).

*4.1.5. 2-(5-Hydroxyhexyl)-3-methylcyclopentanone (**17**)*

Oil; MS (EI) *m*/*z* 198 $(M)^+$, 180, 165, 147, 139, 111, 98, 83 (base); HRMS (EI) found *m*/*z* 198.1623 (calcd for $C_{12}H_{22}O_2$ 198.1620); IR 3460, 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.16 (3H, d, *J*=6.6 Hz), 1.19 (3H, d, *J*=6.6 Hz), 1.20–1.75 (8H, m), 1.80–2.55 (7H, m), 3.80 (1H, m).

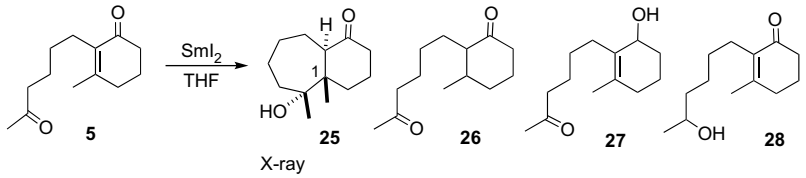
4.1.6. (1S,2S*,7S*)-2-Hydroxy-1-methylbicyclo[5.4.0]undecan-8-one (**18**)*

Oil; MS (EI) *m*/*z* 196 (M^+), 178, 163, 153, 135, 125, 111 (base); HRMS (EI) found *m*/*z* 196.1471 (calcd for $C_{12}H_{20}O_2$ 196.1464); IR 3450, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, s, H-10), 1.34 (1H, m, H-9), 1.40–1.48 (2H, m, H-7,8), 1.55 (1H, m, H-6), 1.65 (1H, m, H-8), 1.72–1.82 (3H, m, H-3,4,6), 1.84–1.89 (3H, m, H-4,7,9), 1.93 (1H, m, H-3), 2.12 (1H, dd, *J*=9.0, 1.0 Hz, H-9a), 2.26 (1H, m, H-2), 2.31 (1H, m, H-2), 3.61 (1H, d, *J*=9.9 Hz, H-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.9 (CH_3), 21.8 (C-10), 26.7 (C-5), 27.5 (C-4), 29.9 (C-9), 34.0 (CH2), 32.3 (C-3), 33.2 (C-11), 39.0 (C-9), 43.4 (C-1), 60.6 (C-7), 80.9 (C-2), 215.3 (C-8).

4.1.7. (1S,2S*,7R*)-2-Hydroxy-1-methylbicyclo[5.4.0]undecan-8-one (**19**)*

Oil; MS (EI) *m*/*z* 196 (M^+), 181, 163, 153, 135, 125, 111 (base); HRMS (EI) found *m*/*z* 196.1472 (calcd for $C_{12}H_{20}O_2$ 196.1464); IR

Table 5
The reaction of compound **5** with SmI_2



Entry	Additive (equiv)	SmI_2 (equiv)	Temp (°C)	Recovery (%) **5**	Yield (%)			
					25	**26**	**27**	**28**
1	None	3	0	31	0	30	13	0
2	None	3	rt	8	9	42	35	0
3	MeOH (2)	4	rt	55	14	18	0	0
4	MeOH (10)	3	rt	12	4	18	0	50
5	HMPA (12)	3	0	43	0	53	0	0

3450, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.80 (3H, s, H-10), 1.33–1.41 (3H, m), 1.53 (1H, m), 1.61 (1H, td, J=13.4, 4.1 Hz), 1.66–1.85 (4H, m), 2.00 (1H, m), 2.09–2.13 (2H, m,), 2.19 (1H, d, J=9.6 Hz, H-9a), 2.31 (1H, tdd, J=13.0, 6.6, 0.8 Hz), 2.38 (1H, m), 3.49 (1H, d, J=10.2 Hz, H-5).

4.1.8. (1S,2R*,7S*)-2-Hydroxy-1-methylbicyclo[5.4.0]undecan-8-one (**20**)*

Oil; MS (EI) m/z 196 (M^+), 181, 167, 153, 136, 123, 111 (base); HRMS (EI) found m/z 196.1468 (calcd for $C_{12}H_{20}O_2$ 196.1463); IR 3350, 1710 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.10 (3H, s, H-10), 1.36 (1H, td, J=12.9, 5.8 Hz), 1.49 (1H, dd, J=12.9, 6.0 Hz), 1.56–1.67 (6H, m), 1.73–1.75 (2H, m), 1.79–1.94 (3H, m), 2.01–2.05 (2H, m), 3.93 (1H, t, J=3.0 Hz, H-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.7 (CH_3), 20.2 (CH_2), 24.2 (CH_2), 24.3 (CH_2), 25.4 (CH_2), 31.1 (CH_2), 38.9 (CH_2), 41.2 (C-11), 46.4 (C-1), 52.5 (C-7), 84.3 (C-2), 214.6 (C-8).

4.1.9. (1S,2R*,7R*)-2-Hydroxy-1-methylbicyclo[5.4.0]undecan-8-one (**11**)*

Oil; MS (EI) m/z 196 (M^+), 181, 163, 153, 135, 125, 111 (base); HRMS (EI) found m/z 196.1458 (calcd for $C_{12}H_{20}O_2$ 196.1463); IR 3450, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.84 (3H, s, H-10), 1.27 (1H, m, H-9), 1.35 (1H, m, H-8), 1.50 (1H, m, H-7), 1.55 (1H, m, H-4), 1.75–1.80 (2H, m, H-6,8), 1.81–1.91 (3H, m, H-3,6,7), 2.00–2.10 (3H, m, H-3,4,9), 2.26–2.33 (2H, m, H-2), 2.59 (1H, d, J=9.6 Hz, H-9a), 3.56 (1H, d, J=6.6 Hz, H-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.0 (CH_3), 21.8 (C-6), 22.1 (C-10), 23.9 (C-4), 26.7 (C-5), 30.5 (C-3), 33.7 (C-11), 41.0 (C-9), 46.3 (C-1), 56.4 (C-7), 79.7 (C-2), 213.8 (C-8).

4.1.10. (1R,6R*,11R*)-1-Hydroxy-11-methylspiro[5.5]undecan-7-one (**21**)*

Oil; MS (EI) m/z 196 (M^+), 194, 178, 163, 111 (base); HRMS (EI) found m/z 196.1461 (calcd for $C_{12}H_{20}O_2$ 196.1463); IR 3450, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.99 (3H, d, J=6.9 Hz, H-10), 1.26 (1H, m, H-3), 1.33 (1H, td, J=13.5, 3.0 Hz, H-5), 1.56 (1H, m, H-4), 1.60–1.74 (4H, m, H-3,9,10,10), 1.92 (2H, m, H-2,2), 2.03 (1H, m, H-9), 2.14 (1H, m, H-5), 2.18 (1H, m, H-8), 2.42 (1H, m, H-11), 2.64 (1H, m, H-8), 3.52 (1H, br s, H-1); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.2 (C-12), 22.0 (C-4), 24.9 (C-3), 27.2 (C-5), 27.3 (C-9), 28.8 (C-10), 31.7 (C-2), 38.5 (C-11), 39.4 (C-8), 58.2 (C-6), 71.8 (C-1), 220.1 (C-7).

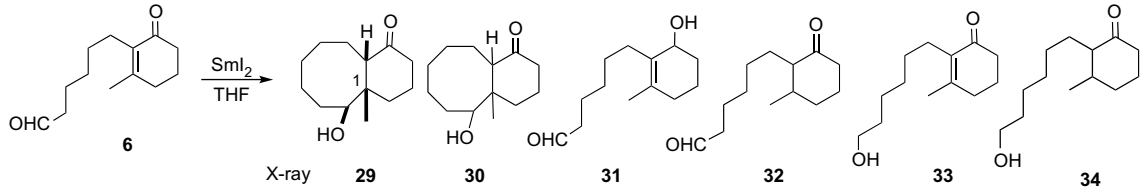
4.1.11. (1S,2S*,7S*)-2-Hydroxy-2-methylbicyclo[5.4.0]undecan-8-one (**22**)*

Oil; MS (EI) m/z 196 (M^+), 178, 163, 153, 135, 120, 111, 97 (base), 84, 71; HRMS (EI) found m/z 196.1458 (calcd for $C_{12}H_{20}O_2$ 196.1464); IR 3450, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.27 (3H, s), 1.50–1.65 (5H, m), 1.67–1.81 (7H, m), 1.89 (1H, m), 2.06 (1H, m), 2.23 (1H, br d, J=14.1 Hz), 2.42 (1H, ddd, J=14.1, 13.2, 6.6 Hz), 2.81 (1H, dtd, J=10.7, 4.1, 1.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7 (CH_2), 22.7 (C-11), 25.2 (C-10), 26.1 (CH_2), 26.9 (CH_2), 31.8 (CH_3), 36.1 (C-3), 37.9 (C-9), 52.2 (C-7), 52.5 (C-1), 75.0 (C-2), 214.8 (C-8).

4.1.12. (1S,2R*,7S*)-2-Hydroxy-2-methylbicyclo[5.4.0]undecan-8-one (**23**)*

Oil; MS (EI) m/z 196 $(M)^+$, 178, 163, 153, 135, 120, 111, 97 (base), 84, 71; HRMS (EI) found m/z 196.1464 (calcd for $C_{12}H_{20}O_2$ 196.1463); IR 3500, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.30

Table 6
The reaction of compound **6** with SmI_2



Entry	SmI_2 (equiv)	Additive (equiv)	Temp (°C)	Recovery (%) **6**	Yield (%)					
					29	**30**	**31**	**32**	**33**	**34**
1	3	None	0	0	7	11	0	0	3	0
2	3	None	rt	0	7	0	54	0	0	0
3	6	None	rt	0	10	7	5	0	0	26
4	3	MeOH (2)	rt	60	2	0	26	0	6	0
5	3	HMPA (12)	rt	0	26	0	30	0	4	39
6	3	NiI_2 (0.17)	rt	0	5	0	50	0	0	2

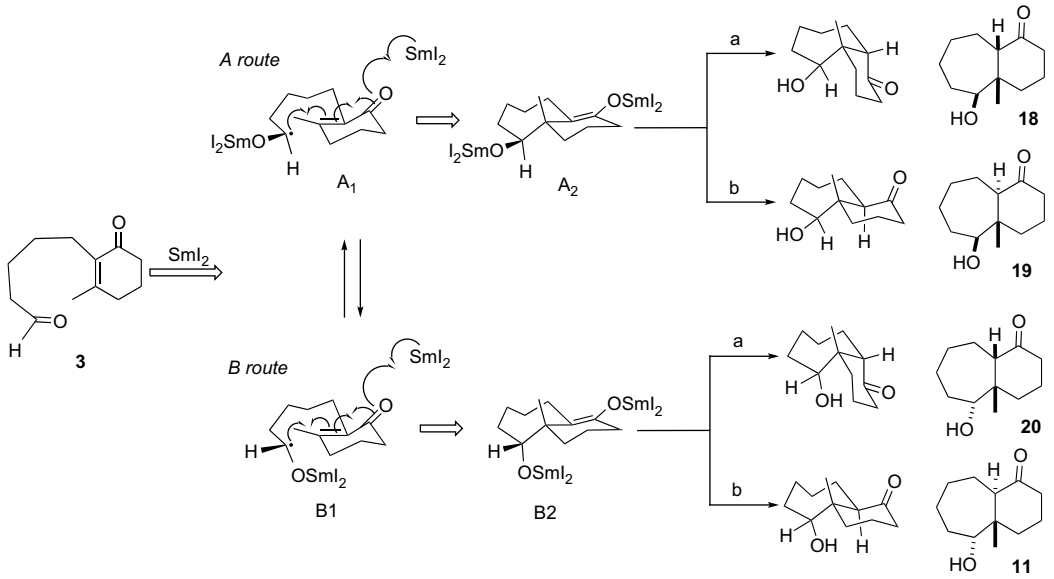


Figure 4. The mechanism without the additive.

(3H, s), 1.44–1.51 (3H, m), 1.58 (1H, m), 1.63–1.78 (6H, m), 1.96 (1H, m), 2.10 (1H, m), 2.22 (1H, m), 2.28 (1H, m), 2.41 (1H, m), 2.43 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4 (C-4), 24.2 (C-10), 25.8 (C-5), 26.2 (C-11), 27.7 (C-6), 30.8 (CH_3), 40.5 (C-9), 41.6 (C-3), 51.4 (C-7), 53.3 (C-1), 74.4 (C-2), 214.5 (C-8).

*4.1.13. 2-(5-Oxohexyl)cyclohexanone (**24**)*

Oil; MS (EI) *m*/*z* 196 $(M)^+$, 178, 163, 149, 139, 111, 98 (base), 93, 83, 70; HRMS (EI) found *m*/*z* 196.1458 (calcd for $C_{12}H_{20}O_2$ 196.1463); IR 1700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20 (1H, m), 1.25–1.31 (2H, m), 1.38–1.78 (1H, m), 1.54–1.60 (2H, m), 1.63–1.71 (2H, m), 1.78 (1H, m), 1.85 (1H, m), 2.03 (1H, m), 2.09 (1H, m), 2.13 (3H, s), 2.23–2.34 (2H, m), 2.38 (1H, m), 2.43 (2H, t, *J*=7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.8, 24.9, 26.7, 28.0, 29.1, 29.9, 33.9, 42.0, 43.5, 50.5, 209.2 (CO), 213.4 (CO).

4.1.14. (1S,2R*,7R*)-1,2-Dimethyl-2-hydroxybicyclo-[5.4.0]undecan-8-one (**25**)*

Crystal; mp 128–130 °C (EtOAc); MS (EI) *m*/*z* 210 (M^+), 192, 177, 167, 149, 135, 125, 111 (base), 97; HRMS (EI) found *m*/*z* 210.1625

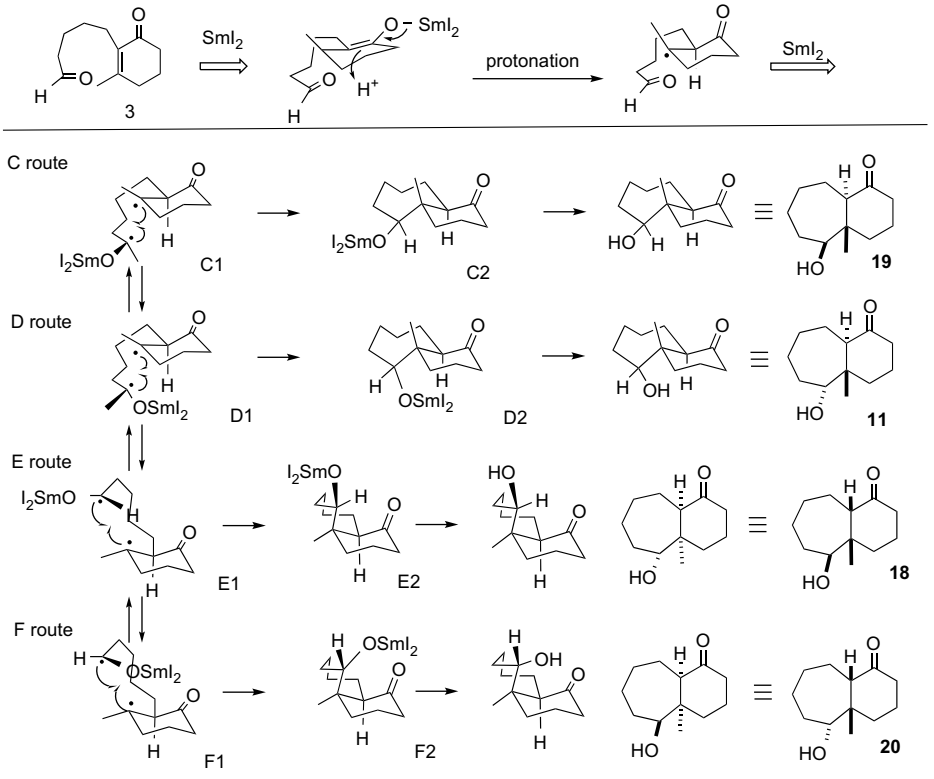


Figure 5. The mechanism with the proton source.

(calcd for $C_{13}H_{22}O_2$ 210.1620); IR 3380, 1690 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.80 (3H, s), 1.21 (3H, s), 1.36 (1H, m), 1.43–1.52 (3H, m), 1.66 (1H, m), 1.68 (1H, m), 1.74 (1H, m), 1.80 (1H, m), 1.93 (1H, m), 2.01 (1H, m), 2.14 (1H, m), 2.16 (1H, m), 2.29 (1H, m), 2.34 (1H, m), 2.69 (1H, d, J=10.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.2 (CH_3), 20.3 (CH_2), 21.5 (CH_2), 22.4 (CH_2), 24.5 (CH_2), 28.2 (CH_3), 32.8 (CH_2), 36.8 (CH_2), 41.9 (CH_2), 49.2 (C), 55.4 (CH), 77.3 (CH), 214.6 (C).

*4.1.15. 3-Methyl-2-(5-oxohexyl)cyclohexanone (**26**)*

MS (EI) m/z 210 (M^+), 192, 177, 153, 112, 97 (base), 81, 69; HRMS (EI) found m/z 210.1600 (calcd for $C_{13}H_{22}O_2$ 210.1620); IR 1710 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.04 (3H, d, J=6.6 Hz), 1.19 (1H, m), 1.31 (1H, m), 1.40–1.72 (7H, m), 1.86 (1H, m), 1.96–2.03 (2H, m), 2.14 (3H,s), 2.26 (1H, dddd, J=13.2, 11.4, 5.4, 1.3 Hz), 2.36 (1H, dtd, J=13.2, 4.8, 1.4 Hz), 2.43 (2H, t, J=7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5 (CH_3), 24.1 (CH_2), 25.6 (CH_2), 26.5 (CH_2), 26.8 (CH_2), 29.9 (CH_3), 33.2 (CH_2), 38.4 (CH), 41.6 (CH_2), 43.6 (CH_2), 57.2 (CH), 209.4 (CO), 213.2 (CO).

*4.1.16. 3-Methyl-2-(5-oxohexyl)cyclohex-2-en-1-ol (**27**)*

MS (CI) m/z 209 $(M-H)^+$, 193 (base), 175, 135, 111, 93, 81, 55; HRMS (CI) found m/z 209.1516 $(M-H)^+$ (calcd for $C_{13}H_{21}O_2$ 209.1542); IR 3440, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26–1.69 (9H, m), 1.63 (3H, s), 1.93 (2H, br s), 2.14 (3H, s), 2.20–2.48 (2H, m), 2.45 (2H, t, J=15.0 Hz), 4.03 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (CH_2), 19.2 (CH_3), 24.0 (CH_2), 28.5 (CH_2), 29.9 (CH_3), 30.1 (CH_2), 32.0 (CH_2), 32.2 (CH_2), 43.7 (CH_2), 67.4 (CH), 131.9 (C), 132.0 (C), 209.3 (C).

*4.1.17. 2-(5-Hydroxyhexyl)-3-methyl-2-cyclohex-1-enone (**28**)*

MS (EI) m/z 210 (M^+), 195, 177, 163, 151, 135 (base), 124, 96, 79, 67; HRMS (EI) found m/z 210.1613 (calcd for $C_{13}H_{22}O_2$ 210.1619); IR 3450, 1660, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, d, J=6.3 Hz), 1.25–1.70 (8H, m), 1.93 (3H, s), 1.88–1.97 (2H, m), 2.25–2.40 (5H, m), 3.79 (1H, sextet, J=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (CH_3), 22.3 (CH_2), 23.5 (CH_3), 25.1 (CH_2), 25.9 (CH_2), 29.1 (CH_2), 32.8 (CH_2), 37.9 (CH_2), 39.1 (CH_2), 68.1 (CH), 135.7 (C), 155.3 (C), 198.9 (C).

4.1.18. (1S,2S*,8S*)-2-Hydroxy-1-methylbicyclo[6.4.0]dodecan-9-one (**29**)*

Crystal; mp 105–107 °C (hexane–EtOAc); MS (EI) m/z 210 (M^+), 195, 177, 167, 149, 125, 119, 111 (base), 97; HRMS (EI) found m/z 210.1613 (calcd for $C_{13}H_{22}O_2$ 210.1619); IR 3440, 1690 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (3H, s), 1.40–1.46 (3H, m), 1.54–1.92 (11H, m), 2.18 (1H, ddd, J=13.7, 4.6, 1.9 Hz), 2.34 (1H, dd, J=5.4, 1.5 Hz), 2.44 (1H, td, J=13.7, 6.9 Hz), 3.84 (1H, dd, J=7.2, 2.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.3 (CH_3), 21.4 (CH_2), 24.9 (CH_2), 26.1 (CH_2), 26.7 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 33.9 (CH_2), 37.2 (CH_2), 43.6 (C), 58.0 (CH), 75.2 (CH), 215.0 (C).

*4.1.19. 6-(6-Hydroxy-2-methylcyclohex-1-enyl)hexanal (**31**)*

Oil; MS (CI) m/z 211 $(M+H)^+$, 210, 209, 194, 193 (base), 175, 111; HRMS (CI) found m/z 209.1529 $(M-H)^+$ (calcd for $C_{13}H_{21}O_2$ 209.1542); IR 3400, 1720 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.26 (1H, m), 1.35 (1H, m), 1.42 (2H, m), 1.55–1.68 (5H, m), 1.63 (3H, s), 1.77 (1H, m), 1.79 (1H, m), 1.94 (2H, m), 2.13 (1H, m), 2.16 (1H, m), 2.43 (2H, td, J=7.4, 1.6 Hz), 4.03 (1H, br s), 9.77 (1H, t, J=1.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.8 (CH_2), 19.2 (CH_3), 22.0 (CH_2), 28.7 (CH_2), 29.4 (CH_2), 30.1 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 43.9 (CH_2), 67.3 (CH), 131.8 (C=), 132.1 (CH=), 202.9 (CO).

*4.1.20. 6-(6-Methyl-2-oxocyclohexyl)hexanal (**32**)*

Oil; MS (EI) m/z 210 (M^+), 167, 125, 112, 97 (base); HRMS (EI) found m/z 210.1628 (calcd for $C_{13}H_{22}O_2$ 210.1620); IR 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.04 (3H, d, J=6.6 Hz), 1.17–1.76 (11H, m), 1.86 (1H, m), 1.95–2.03 (2H, m), 2.26 (1H, m), 2.38 (1H, m), 2.43 (2H, td, J=7.2, 1.9 Hz), 9.76 (1H, t, J=1.9 Hz).

*4.1.21. 3-Methyl-2-(6-hydroxyhexyl)cyclohex-2-enone (**33**)*

Oil; MS (EI) m/z 210 (M^+), 195 (base), 177, 151, 137, 124, 96, 79, 67; HRMS (EI) found m/z 210.1626 (calcd for $C_{13}H_{22}O_2$ 210.1620); IR 3450, 1680, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25–1.75 (10H, m), 1.95 (3H, s), 2.21–2.40 (6H, m), 3.39 (1H, td, J=6.6, 1.0 Hz), 3.61 (2H, t, J=6.6 Hz).

*4.1.22. 3-Methyl-2-(6-hydroxyhexyl)cyclohexanone (**34**)*

Oil; MS (EI) m/z 212 (M^+), 169, 151, 125, 112, 97 (base), 84; HRMS (EI) found m/z 212.1756 (calcd for $C_{13}H_{24}O_2$ 212.1777); IR 3400, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.04 (3H, d, J=6.6 Hz), 1.21 (1H, m), 1.24–1.38 (5H, m), 1.44 (1H, m), 1.49 (1H, m), 1.54–1.59 (2H, m), 1.61–1.74 (3H, m), 1.87 (1H, m), 1.97 (1H, m), 1.99 (1H, m), 2.26 (1H, dddd, J=13.5, 9.0, 6.0, 1.2 Hz), 2.37 (1H, dtd, J=13.5, 4.8, 1.2 Hz), 3.64 (2H, t, J=6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.5 (CH_3), 25.4 (CH_2), 25.5 (CH_2), 26.9 (CH_2), 27.3 (CH_2), 29.7 (CH_2), 32.7 (CH_2), 33.0 (CH_2), 38.3 (CH), 41.4 (CH_2), 57.4 (CH), 63.0 (CH_2), 213.4 (C).

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Supplementary data

Experimental procedures for preparation of the substrates **1**–**6**, X-ray ORTEP figures as well as several parameters of compounds **25** and **29**, NOE correlations of compounds **11**,**13**–**16**, **18**–**20**, **22**, and **23**, and ^1H NMR and ^{13}C NMR spectra of all new compounds have been included. Supplementary data 1 and 2 associated with this article can be found in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.073.

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