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Cyclization into perhydronaphthalenones using samarium diiodide

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Abstract—Samarium(II) diiodide has been employed to promote the intramolecular cyclization reactions of aldehydes or ketones onto α,β-unsaturated ketones. The cyclization reactions described herein provide a general approach to the syntheses of perhydronaphthalenones with a *cis*-relationship between the OH at C-5 and the proton or methyl group at C-4a with good diastereoselectivity under mild reaction conditions.

1. Introduction

Samarium (lII) diiodide (SmI_2) is a powerful, one-electron reducing reagent, capable of reducing a wide range of functional groups with a high stereo and/or regio selectivity.[1] One of the widely applied processes using SmI_2 involves the intramolecular ketyl olefin radical coupling reaction to achieve carbon–carbon bond formations between aldehydes or ketones and olefins. Most of the reactions are classified as 4-*exo*,[2] 5-*exo*-,[3] 6-*exo*,[4] or 7-*exo-trig*[5] type cyclizations. Baldwin reported on the rules for ring closure in the literature precedents.[6] In Trigonal system, 3 to 7-*exo-trig* are all favored processes. While 3 to 5-*endo-trig* are disfavored and 6 to 7-*endo-trig* are favored, respectively. Our interest has focused on the 6-*endo-trig*-type cyclization.

Noteworthy, the reducing potential of SmI_2 can be tuned with solvents, co-solvents, and additives, or by changes in the reaction conditions. For example, the addition of HMPA to the THF solution of SmI_2 can change the reducing potential of SmI_2, referred to as $Ag/AgNO_3$ electrode, from −1.33 to −2.05 V depending on the concentration of HMPA.[7] On the other hand, comparison of the half-wave potential of α,β-unsaturated carbonyls with those of corresponding saturated carbonyl compounds has been extensively studied in electrochemistry.[8] The first waves of carbonyl groups, referred to as SCE, are −2.45 V (cyclohexanone), −2.25 V (methyl ethyl ketone), −1.8 V (propionaldehyde), −1.55 V (2-cyclohexen-1-one), −1.50 V (acrolein), and −1.42 V (methyl vinyl ketone), respectively. Therefore, there is a possibility that the regio- or stereo-selectivity will be changed according to reducing potential of SmI_2.

Moreover, some reactions of SmI_2 are greatly accelerated by addition of catalytic amount (1%) of NiI_2.[9] As a consequence, the chemoselectivity of this reducing reagent is also highly adjustable.[10] Therefore, we are interested in the trend in the diastereoselectivity of the reductive cyclization reaction using SmI_2 with various additives.

Recently, we reported the ability of SmI_2 to promote the cyclization of aldehyde–enone compounds having the general structure **1** resulting in the formation of several hydrindanones having the general structure **2** in moderate to good yield.[11] The addition of a proton source such as MeOH and/or HMPA dramatically changes the product configuration in some cases.

The studies described herein further detail the SmI_2-promoted 6-*endo* intramolecular reductive cyclization reaction of enone- or ketone–enones **3** into perhydronaphthalenones **4**, although a simple construction of the perhydronaphtalene using SmI_2 has been reported.[12] For our study, three continuous stereocenters were newly constructed during the reductive cyclization. The *cis* arrangement for the hydroxyl group at C-5 and juncture proton or methyl group at C-4a is predominant under the conditions we used. The product configurations of the juncture positions were changed by the addition of MeOH or HMPA in some cases. The thermodynamic stability between the *cis* and *trans* perhydronaphthalenones has also been studied (Scheme 1).

Keywords: samarium diiodide; cyclization; perhydronaphthalenones.

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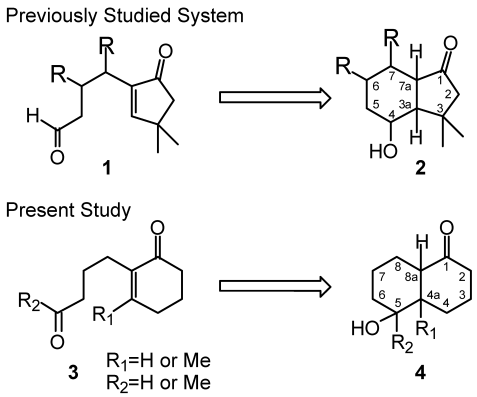


Scheme 1.

2. Results and discussion

2.1. Synthesis of carbonyl compounds 10a, 10b, 10c,[16] and 10d

The simple aldehyde **10a** and aldehyde **10b** having a β-methyl group were prepared from cyclohexenone or methylcyclohexenone with silyl protected bromobutanol via the enone–alcohol **7a** or **7b** as summarized in Scheme 2. The simple ketone **10c** and ketone **10d** having a β-methyl group were prepared from cyclohexenone or methylcyclohexenone with acetal **9** via the enone–ketone **7c** or **7d**, respectively.

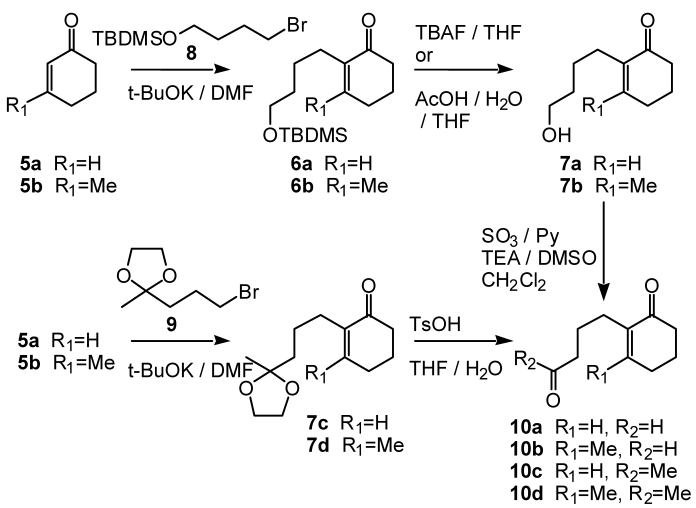
2.2. Cyclization with SmI_2

The cyclization reactions were performed on a 0.1–0.3 mmol scale of the starting material. The amount of SmI_2 employed was 3.0 equiv. for the simple enone–aldehyde **10a**. After the cyclization reaction, the cyclization products were separated as a mixture of diastereoisomers by silica gel column chromatography. Each diastereoisomer was purified by HPLC, and the structure was determined by mainly using 2D NMR experiments. The yields were calculated from the mixture of the cyclization products and the ratios of the diastereoisomers were determined by GC–MS analysis (identified by the retention time and the mass fragment pattern).

The results of the reductive cyclization of the aldehyde **10a** are shown in Table 1. The *cis* arrangement for the hydroxyl group at C-5 and the juncture proton at C-4a is also seen in **11a**[14,19] and **12a**,[14,17–19] which were the major products (entries 1, 2). When the reaction was performed at rt, compound **14a**[13,17,19] was produced (entry 1). When MeOH was added as a proton source, the ratio of **12a** slightly increased (entries 3–6). In the presence of HMPA, the yield of the cyclized products decreased (entries 7, 8). An effect due to the addition of NiI_2 was not particularly observed (entries 9, 10). Compounds **11a** and **12a** were subjected to the isomerization conditions (K_2CO_3 in MeOH, reflux) and the equilibration ratio was found to be **11a/12a**=0:100 by GC. Under the equilibration conditions, compound **14a** did not afford the isomer **13a**,[19] which was not isolated from this cyclization reaction.

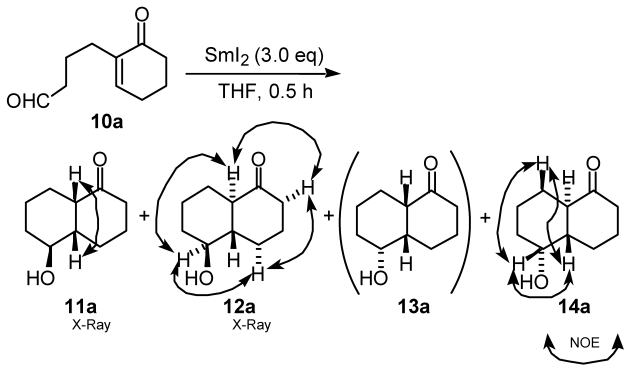
The reaction of aldehyde **10b** was next investigated and these results are summarized in Table 2. Without any additive, alcohol **11b**[13] was the main product (entries 1, 2). The hydroxyl group at C-5 and the juncture proton at C-4a were *cis* to each other as revealed by the NOESY spectrum. When MeOH was added, the ratio of alcohol **12b**[13] was raised regardless of the reaction temperature (entries 3–6). The addition of HMPA or NiI_2 produced a low yield (entries 7–10). Under the equilibration conditions (K_2CO_3 in MeOH, reflux) compound **11b** afforded a mixture of **11b** and **12b** (ca. 21:79). Compound **12b** isomerized into the mixture of **11b** and **12b** (ca. 16:84). Ketone **14b**[13] became equilibrated as a mixture of **13b**[15] and **14b** (18:82) under the same conditions.

The ketone–enone **10c** was next studied (Table 3). Without any additive at 0°C, the diastereoisomers **11c**,[13] **12c**,[14] **13c**,[15] and **14c**[13] were all produced (entries 1, 2). In the presence of MeOH, compound **12c** was the main product (entries 3–6). When HMPA was added, both compounds **11c** and **12c**, which had a *cis* relation about the hydroxyl group at C-5 and methyl group at C-4a, were obtained in low



Scheme 2.

Table 1. Reductive cyclization of **10a**

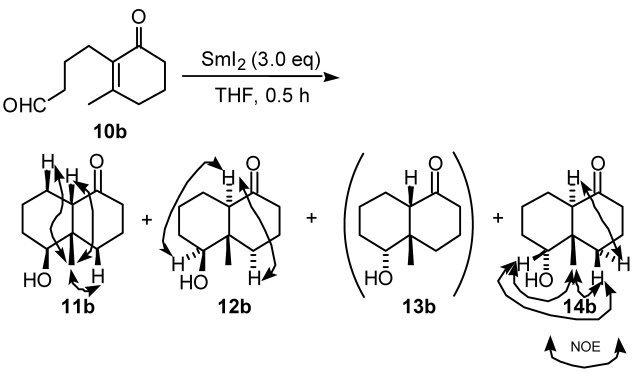


Entry	Additives (equiv.)	Temperature (°C)	Yield (%) [ratio[a]] (**11a/12a/13a/14a**)
1	–	rt	100 [28:61:0:11]
2	–	0	100 [40:60:0:0]
3	MeOH (2)	rt	97 [20:70:0:10]
4	MeOH (2)	0	96 [21:68:0:11]
5	MeOH (10)	rt	91 [20:66:0:14]
6	MeOH (10)	0	99 [13:77:0:10]
7	HMPA (12)	rt	50 [30:57:0:13]
8	HMPA (12)	0	43 [34:58:0:8]
9	NiI_2 (2.0)	rt	95 [35:50:0:15]
10	NiI_2 (2.0)	0	97 [30:61:0:9]

[a] Ratios were determined by GC analyses.

yield (entries 7, 8). With NiI_2 at rt, compounds **11c** and **12c** were produced in moderate yields (entry 9). When NiI_2 was used at 0°C, the yield was worse than the reaction at rt (entry 10). Compounds **11c** and **12c** were subjected to the isomerization conditions (K_2CO_3 in MeOH, reflux) and the equilibration ratio was found to be **11c/12c**=11:89. Compound **14c** afforded a mixture of isomers **13c**[15] and **14c** (5:95) under the same equilibrium conditions.

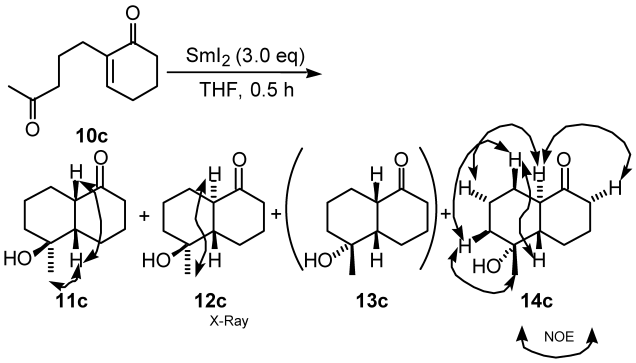
Table 2. Reductive cyclization of **10b**



Entry	Additives (equiv.)	Temperature (°C)	Yield (%) [ratio[a]] (**11b.12b/13b**[15]**/14b**)
1	–	rt	54 [92:0:0:8]
2	–	0	67 [100:0:0:0]
3	MeOH (2)	rt	97 [54:46:0:0]
4	MeOH (2)	0	81 [58:42:0:0]
5	MeOH (10)	rt	92 [53:45:2:0]
6	MeOH (10)	0	88 [55:43:2:0]
7	HMPA (12)	rt	64 [57:31:0:12]
8	HMPA (12)	0	75 [69:31:0:0]
9	NiI_2 (2.0)	rt	51 [100:0:0:0]
10	NiI_2 (2.0)	0	30 [71:20:0:9]

[a] Ratios were determined by GC analyses.

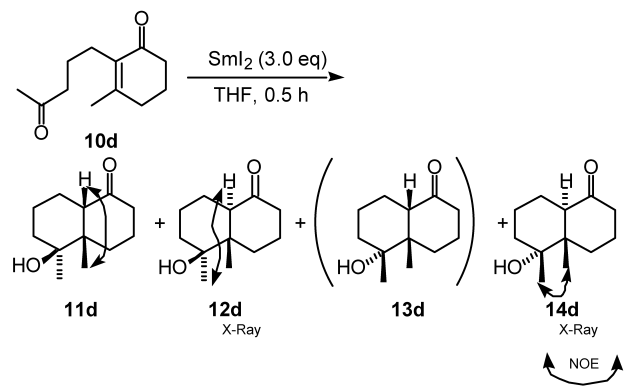
Table 3. Reductive cyclization of **10c**



Entry	Additives (equiv.)	Temperature (°C)	Yield (%) [ratio[a]] (**11c/12c/13c**[15]**/14c**)
1	–	rt	87 [42:30:0:28]
2	–	0	100 [46:0:19:35]
3	MeOH (2)	rt	82 [0:91:0:9]
4	MeOH (2)	0	85 [0:93:0:7]
5	MeOH (10)	rt	81 [4:86:0:10]
6	MeOH (10)	0	96 [2:92:0:6]
7	HMPA (12)	rt	10 [0:100:0:0]
8	HMPA (12)	0	33 [44:56:0:0]
9	NiI_2 (2.0)	rt	85 [38:44:0:18]
10	NiI_2 (2.0)	0	54 [0:100:0:0]

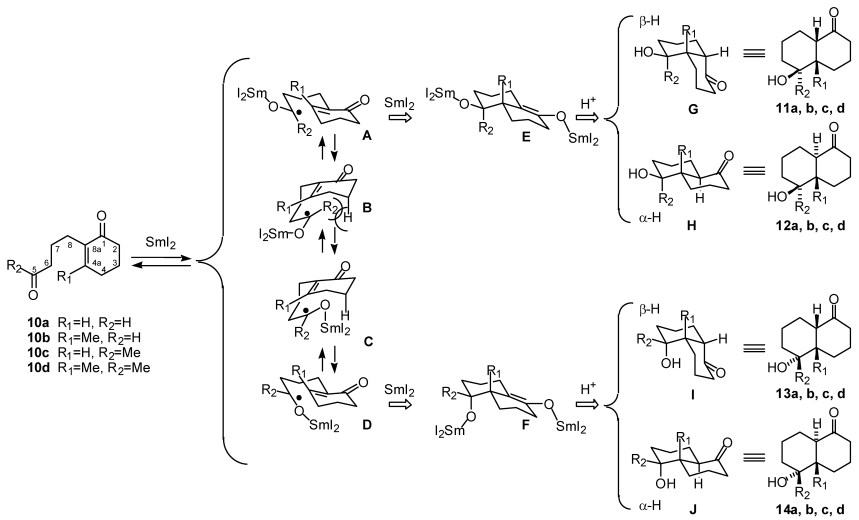
[a] Ratios were determined by GC analyses.

Table 4. Reductive cyclization of **10d**



Entry	Additives (equiv.)	Temperature (°C)	Yield (%) [ratio[a]] (**11d/12d/13d**[15]**/14d**)
1	–	rt	100 [69:19:3:9]
2	–	0	56 [52:25:0:23]
3	MeOH (2)	rt	91 [30:51:11:8]
4	MeOH (2)	0	100 [26:63:5:6]
5	MeOH (10)	rt	76 [26:56:15:3]
6	MeOH (10)	0	58 [24:61:9:6]
7	HMPA (12)	rt	00[b]
8	HMPA (12)	0	00[b]
9	NiI_2 (2.0)	rt	71 [64:20:10:6]
10	NiI_2 (2.0)	0	86 [67:20:0:13]

[a] Ratios were determined by GC analyses.
[b] Starting material was recovered.



Scheme 3.

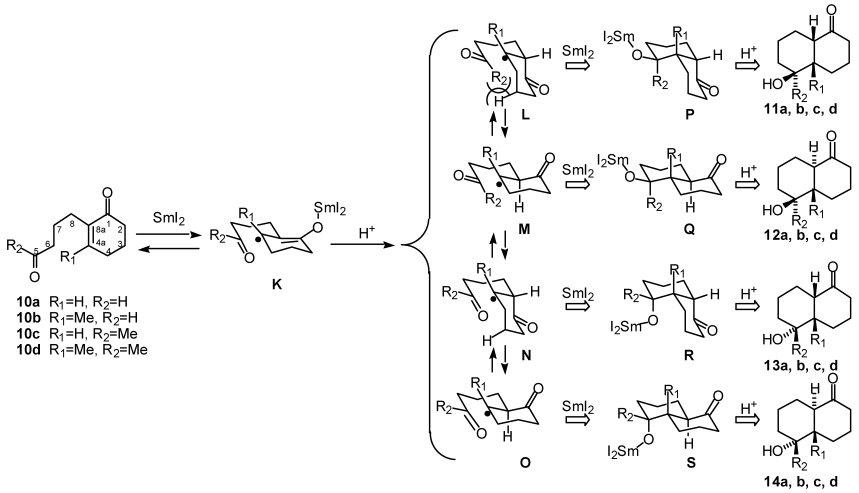
Finally, the enone **10d**, which has a methyl group at the β position, was subjected to a reaction with SmI_2. As shown in Table 4, compounds **11d**[13] and **12d**[14] were mainly observed regardless of the reaction temperature and the addition of MeOH (entries 1–6). Without any additive, the ratio of **11d** was greater than that of **12d** (entries 1, 2). On the other hand, the ratios of **12d** were grater than that of **11d** when MeOH was added (entries 3–6). When HMPA was added, the starting material **10d** was recovered and no cyclized products were obtained (entries 7, 8). This is presumably because the ketone of the side chain and the substituted β-position of the enone system are less reactive. With the addition of NiI_2, the ratios of products were almost the same as that of the reaction with no additive (entries 9, 10). Under the equilibration conditions (K_2CO_3 in MeOH, reflux), compounds **11d** and **12d** were isomers of each other and the ratio was 52:48. Compound **14d**[14] afforded the isomer **13d**[15] (**13d/14d**=6:94).

Without any additive, **12a**, **11b**, **11c** and **11d** were the major products, respectively. The plausible mechanism is shown below (Scheme 3).

Samarium(II) reduces the aldehyde or ketone to afford radicals **A**, **B**, **C**, and **D**. When assessing the contribution of various transition structures to the observed diastereoselectivities, we have postulated that conformations **C** and **D** are unfavorable relative to conformations **A** and **B** (an oxygen atom of the side chain locates outside of the molecule), because the samarium-coordinated species are sterically bulky. As conformation **B** has a steric hindrance of proton at C-3 with R_2, the conformation **A** must be favorable. Thus the cyclization leads to the *cis* arrangement for the hydroxyl group at C-5 and the juncture hydrogen at C-4a as observed in compounds **G** and **H**.

When aldehyde **10a** or **10b** is reduced by SmI_2, intermediate **A** (R_2=H) is dominant. Therefore, the yields of **13a**, **14a** or **13b**, **14b** are very low. On the other hand, when ketone **10c** or **10d** is reduced, the bulkiness of R_2 leads the stabilization of intermediate **D** (R_2=Me) more than in the time of **10a** or **10b**. As a result, the yields of cyclized products **13c**, **14c** or **13d**, **14d** are increased.

Aldehyde **10a** which does not have methyl group on the cyclohexene ring, is reduced to afford intermediate **E** (R_2=H) in Scheme 3. The intermediate **E** can be protonated from both α and β side. On the other hand, the decaline



Scheme 4.

frame is bent due to the presence of the methyl group of intermediate **E** derived from **10b**. The protonation of **E** occurs kinetically at the β face (convex face) to afford ketone **11b**.

When MeOH was added as a proton source, the ratios of **12a**, **12b**, **12c**, and **12d** were increased, respectively. We considered the mechanism as below. The reduction of carbonyl groups by SmI_2 proceeds under equilibrium conditions, and the radical coupling and the protonation of samarium enolates are competitive as illustrated in Scheme 4. If a proton source is present, after the enolate **K** is protonated, the carbonyl groups of the side chain are reduced to afford intermediates **L**, **M**, **N**, and **O**, which have equatorial side chains. The side chain locates outside of the molecule due to the same reason as mentioned above. Conformer **L** has a steric hindrance between the R_2 group and the hydrogen at C-3. Therefore, conformer **M** is favored to form the cyclized product **Q** giving **12a**, **12b**, **12c**, and **12d**.

Addition of HMPA causes deterioration of yield. A rate of reduction of a radical to the anion increased rapidly with increasing HMPA concentration.[1] This may cause decline of the yield of cyclized products.

NiI_2 did not change the stereoselectivity of the intramolecular coupling reaction described herein.

3. Conclusion

Enone–aldehydes and -ketones were efficiently cyclized with SmI_2 in an intramolecular 6-*endo-trig* manner, providing the corresponding perhydronaphthalenones.

In general, the syntheses of perhydronaphthalenones with a *cis*-relationship between the OH at C-5 and the substituent at C-4a with good diastereoselectivity under mild reaction conditions were achieved using SmI_2.

4. Experimental

4.1. General

Tetrahydrofuran (THF) was distilled from $LiAlH_4$ under Ar and then redistilled from sodium–benzophenone ketyl prior to use. Samarium metal was purchased from Strem, Inc., and stored under Ar. Iodine was purchased from Aldrich. HMPA was purchased from Aldrich and was distilled from CaH_2 and stored over 4 Å molecular sieves under Ar. *t*-BuOH was purchased from Aldrich and was distilled from magnesium and stored over 4 Å molecular sieves under Ar. All the other commercially available reagents were used without further purification. Standard benchtop techniques were employed for handling air-sensitive reagents, and all reactions were performed under Ar.

4.2. Experimental procedure for precursors 10a–d

4.2.1. Synthesis of 6a. To a DMF (5 mL) solution of *t*-BuOK (539.0 mg, 4.8 mmol) was added cyclohexenone (196.0 mg, 2.04 mol) in DMF (15 mL). The reaction mixture was stirred for 30 min at rt and a DMF (25 mL) solution of **8** (0.80 g, 3.01 mmol) and Et_4NI (0.76 g, 2.96 mmol) were added. After 2.5 h the reaction was quenched with sat. NH_4Cl aq and Et_2O was added. The organic layer was separated and the aqueous layer was extracted with several portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10–20% Et_2O in hexane) to yield **6a** (144.8 mg, 26%).

Compound **6a**. Oil; FTIR: 2931, 2858, 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.87 (9H, s), 1.42 (4H, m), 1.95 (2H, quint, J=6.3 Hz), 2.17 (2H, m), 2.33 (2H, m), 2.40 (2H, dd, J=7.2, 6.3 Hz), 3.58 (2H, t, J=6.3 Hz), 6.69 (1H, br t, J=4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 ($2CH_3$), 18.4 (C), 23.2 (CH_2), 24.7 (CH_2), 26.0 ($3CH_3$), 26.1 (CH_2), 29.2 (CH_2), 32.6 (CH_2), 38.6 (CH_2), 63.1 (CH_2), 139.7 (C), 145.0 (CH), 199.5 (C); MS (CI, CH_4) m/z 283 $(M+H)^+$, 267, 225, 189, 151 (base), 133, 89, 75, 56; HRMS (CI) found m/z 283.2097 $(M+H)^+$. $C_{16}H_{31}O_2Si$ requires 283.2093.

4.2.2. Synthesis of 7a. Enone **6a** (160.0 mg, 0.57 mmol) was treated with AcOH/H_2O/THF (3:1:1, 5 mL) for 5 h at rt. The reaction was quenched with 1 M NaOH aq and Et_2O was added. The organic layer was separated and the aqueous layer was extracted with several portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10–20% Et_2O in hexane) to yield **7a** (70.8 mg, 74%).

Compound **7a**. Oil; FTIR: 3371, 2936, 2866, 1706, 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38–1.59 (4H, m), 1.87 (1H, br s), 1.95 (2H, quint, J=6.3 Hz), 2.18 (2H, br t, J=7.3 Hz), 2.33 (2H, br dd, J=10.4, 5.9 Hz), 2.40 (2H, dd, J=7.3, 6.3 Hz), 3.62 (2H, t, J=6.3 Hz), 6.71 (1H, t, J=4.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9 (CH_2), 24.6 (CH_2), 25.9 (CH_2), 29.0 (CH_2), 32.1 (CH_2), 38.4 (CH_2), 62.1 (CH_2), 139.4 (C), 145.5 (CH), 199.8 (C); MS (EI) m/z 168 (M^+), 150, 135, 122, 111, 107, 94, 79 (base), 67; HRMS (EI) found m/z 168.1155 (M^+). $C_{10}H_{16}O_2$ requires 168.1151.

4.2.3. 6-Oxo-1-cyclohexene-1-butanal (10a). A solution of **7a** (200.0 mg, 1.20 mmol) in CH_2Cl_2 (8 mL) was oxidized with SO_3–Py (477.0 mg, 3.0 mmol), DMSO (1.3 mL, 18.0 mmol), and Et_3N (2.5 mL, 18.0 mmol) at for 2 h. The organic materials were extracted with Et_2O, washed with brine and dried over $MgSO_4$. The products were purified by silica gel flash chromatography (SiO_2 15 g, 20–40% AcOEt in hexane) to afford **10a** (105.9 mg, 57%).

Compound **10a**. Oil; FTIR: 2937, 2870, 2721, 1725, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.71 (2H, br quint, J=7.5 Hz), 1.94 (2H, quint, J=6.4 Hz), 2.18 (2H, br tq, J=7.8, 1.2 Hz), 2.29–2.42 (6H, m), 6.71 (1H, t, J=4.2 Hz), 9.72 (1H, t, J=1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 (CH_2), 23.0 (CH_2), 26.0 (CH_2), 29.0 (CH_2), 38.4 (CH_2), 43.4 (CH_2), 138.8 (C), 146.0 (CH), 199.3 (C), 202.5 (CH); MS (EI) m/z 166 (M^+), 149, 138, 123 (base),

110, 95, 79, 67, 55; HRMS (EI) found *m/z* 166.0965 (M^+). $C_{10}H_{14}O_2$ requires 166.0994.

4.2.4. Synthesis of 6b. To a THF (200 mL) solution of *t*-BuOK (21.60 g, 0.19 mol) was added 3-methylcyclohexenone (8.76 g, 79.6 mol) in THF (300 mL) at rt. The reaction mixture was stirred for 30 min at rt and a THF (200 mL) solution of **8** (5.81 g, 21.8 mmol) was added. After 7 h the reaction was quenched with sat NH_4Cl aq and Et_2O was added. The organic layer was separated and the aqueous layer was extracted with several portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield **6b** (17.70 g).

Compound **6b**. FTIR: 2929, 2858, 1667, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.87 (9H, s), 1.32 (2H,m), 1.50 (2H, m), 1.90 (2H, m), 1.91 (3H, s), 2.24–2.37 (6H, m), 3.58 (2H, t, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.26 (CH_3), −3.57 (CH_3), 18.3 (C), 21.2 (CH_3), 22.3 (CH_2), 24.9 (CH_2), 25.3 (CH_2), 25.7 (CH_3), 26.0 ($2CH_3$), 32.8 (CH_2), 32.9 (CH_2), 37.8 (CH_2), 63.1 (CH_2), 135.7 (C), 155.3 (C), 198.8 (C); MS (CI, CH_4) *m/z* 297 ($M+H^+$, base), 281, 239, 213, 165, 135, 89, 75, 61; HRMS (CI) found *m/z* 297.2267 $(M+H)^+$. $C_{17}H_{33}O_2Si$ requires 297.2250.

4.2.5. Synthesis of 7b. Enone **6b** (17.70 g) in THF (50 mL) was treated with TBAF (1.0 M in THF, 96 mL, 96 mmol) for 12 h at rt. The reaction was quenched with water and Et_2O was added. The organic layer was separated and the aqueous layer was extracted with several portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (50–100% AcOEt in hexane) to yield **7b** (2.32 g, 58%, 2 steps).

Compound **7b**. FTIR: 3421, 2934, 2865, 1714, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (2H, m), 1.56 (2H, m), 1.85–2.05 (3H, m), 1.93 (3H, s), 2.26–2.38 (6H, m), 3.64 (2H, t, J=6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (CH_3), 22.2 (CH_2), 24.6 (CH_2), 25.1 (CH_2), 32.3 (CH_2), 32.8 (CH_2), 37.8 (CH_2), 62.5 (CH_2), 135.5 (C), 155.7 (C), 199.2 (C); MS (EI) *m/z* 182 (M^+), 164, 149 (base), 137, 125, 111, 93, 79, 67, 55; HRMS (EI) found *m/z* 182.1293 (M^+). $C_{11}H_{18}O_2$ requires 182.1306.

4.2.6. 2-Methyl-6-Oxo-1-cyclohexene-1-butanal (10b). A solution of **7b** (50.0 mg, 0.27 mmol) in CH_2Cl_2 (2 mL) was oxidized with SO_3–Py (115.0 mg, 0.72 mmol), DMSO (349.0 mg, 4.47 mmol), and Et_3N (450.0 mg, 3.23 mmol) at for 2 h. The organic materials were extracted with Et_2O, washed with brine and dried over $MgSO_4$. The products were purified by silica gel flash chromatography (SiO_2 15 g, 50–70% AcOEt in hexane) to afford **10b** (27.7 mg, 57%).

Compound **10b**. FTIR: 2937, 2869, 2721, 1722, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (2H, m), 1.90 (2H, m), 1.95 (3H, s), 2.28–2.38 (6H, m), 2.42 (2H, td, J=7.4, 1.7 Hz), 9.75 (1H, t, J=1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3 (CH_3), 21.4 (CH_2), 22.2 (CH_2), 24.5 (CH_2), 32.8 (CH_2), 37.8 (CH_2), 43.8 (CH_2), 134.8 (C), 156.3 (C), 198.7 (C), 202.7 (C); MS (EI) *m/z* 180 (M^+), 151, 137 (base), 124, 109, 96, 79, 69, 55; HRMS (EI) found *m/z* 180.1127 (M^+). $C_{11}H_{16}O_2$ requires 180.1150.

4.2.7. Synthesis of 7c. To a DMF (80 mL) solution of *t*-BuOK (7.88 g, 70.4 mmol) was added cyclohexenone (2.84 g, 29.6 mmol) in DMF (240 mL) at rt. The reaction mixture was stirred for 50 min at rt and a DMF (240 mL) solution of **9** (9.15 g, 44.0 mmol) was added. After 3 h the reaction was quenched with sat NH_4Cl aq and Et_2O was added. The organic layer was separated and the aqueous layer was extracted with several portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (30–60% Et_2O in hexane) to yield **7c** (1.09 g, 17%).

Compound **7c**. Oil; FTIR: 2930, 2855, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (3H, s), 1.50 (2H, m), 1.63 (2H, m), 1.97 (2H, q, J=6.4 Hz), 2.19 (2H, tq, J=7.5, 1.3 Hz), 2.34 (2H, ddt, J=10.2, 6.0, 1.4 Hz), 2.42 (2H, dd, J=6.9, 6.6 Hz), 3.92 (4H, m), 6.72 (1H, br t, J=4.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.0 (CH_2), 23.1 (CH_2), 23.7 (CH_3), 26.0 (CH_2), 29.4 (CH_2), 38.5 (CH_2), 38.8 (CH_2), 64.5 ($2CH_2$), 110.0 (C), 139.5 (C), 145.2 (CH), 199.5 (C); MS (EI) *m/z* 224 (M^+), 209, 192, 121, 115, 87 (base), 79, 71, 55; HRMS (EI) found *m/z* 224.1414 (M^+). $C_{13}H_{20}O_3$ requires 224.1412.

4.2.8. 2-(4-Oxopentyl)-2-cyclohexen-1-one (10c). Enone **7c** (338.3 mg, 1.51 mmol) in THF (15 mL) was treated with TsOH (67.7 mg, 0.36 mmol) and H_2O (3 mL) for 48 h at rt. The reaction was quenched with sat. $NaHCO_3$ and Et_2O was added. The organic layer was separated and the aqueous layer was extracted with several portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (5–45% Et_2O in hexane) to yield **10c** (156.7 mg, 58%).

Compound **10c**. Oil; FTIR: 2937, 2869, 1713, 1672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (2H, br quint, J=7.8 Hz), 1.98 (2H, quint, J=6.4 Hz), 2.14 (3H, s), 2.17 (2H, br td, J=7.8, 1.4 Hz), 2.32–2.37 (2H, m), 2.39–2.56 (4H, m), 6.74 (1H, br t, J=4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6 (CH_2), 22.9 (CH_2), 25.8 (CH_2), 28.7 (CH_2), 29.7 (CH_3), 38.3 (CH_2), 43.0 (CH_2), 138.8 (C), 145.5 (CH), 199.2 (C), 208.7 (C); MS (EI) *m/z* 180 (M^+), 165, 137, 123 (base), 110, 95, 81, 67, 55; HRMS (EI) found *m/z* 180.1150 (M^+). $C_{11}H_{16}O_2$ requires 180.1150.

4.2.9. Synthesis of 7d. To a THF (80 mL) solution of *t*-BuOK (852.8 mg, 7.6 mmol) was added 3-methylcyclohexenone (495.0 mg, 4.5 mmol) in THF (3.0 mL) at rt. The reaction mixture was stirred for 50 min at rt and a DMF (240 mL) solution of **9** (1.00 g, 4.84 mmol) was added. After 3 h the reaction was quenched with sat NH_4Cl aq and Et_2O was added. The organic layer was separated and the aqueous layer was extracted with several portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield **7d** (1.01 g, 94%).

Compound **7d**. Oil; FTIR: 2980, 2940, 2880, 1660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (3H, s), 1.40 (2H, m), 1.61–1.68 (2H, m), 1.94 (3H, s), 1.85–1.98 (2H, m), 2.26–2.40 (6H, m), 3.92 (4H, s); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.2 (CH_3), 22.3 (CH_2), 23.6 (CH_2), 23.7 (CH_3), 25.2 (CH_2), 32.8 (CH_2), 37.9 (CH_2), 39.0 (CH_2), 64.6 ($2CH_2$), 110.1 (C), 135.7 (C), 155.3 (C), 198.7 (C); MS (EI) *m/z* 238 (M^+), 223, 193, 151, 135, 115, 87 (base), 79, 55; HRMS (EI) found *m/z* 238.1547 (M^+). $C_{14}H_{22}O_3$ requires 238.1569.

4.2.10. 3-Methyl-2-(4-oxopentyl)-2-cyclohexen-1-one (10d). Enone **7d** (1.01 g, 4.2 mmol) in THF (8 mL) was treated with TsOH (40.0 mg, 0.21 mmol) and H_2O (2 mL) for 12 h at rt. The reaction was quenched with sat. $NaHCO_3$ and Et_2O was added. The organic layer was separated and the aqueous layer was extracted with several portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10–45% AcOEt in hexane) to yield **10d** (513.6 mg, 63%).

Compound **10d**. Oil; FTIR: 2930, 2870, 1710, 1660, 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.51–1.66 (2H, m), 1.96 (3H, s), 1.88–1.99 (2H, s), 2.14 (3H, s), 2.24–2.47 (8H, m); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.2 (CH_2), 22.2 (CH_3), 23.1 (CH_2), 24.4 (CH_2), 29.8 (CH_3), 32.8 (CH_2), 37.8 (CH_2), 43.4 (CH_2), 135.1 (C), 156.1 (C), 198.7 (C), 209.1 (C); MS (EI) *m/z* 194 (M^+), 151, 137 (base), 124, 108, 96, 79, 67, 55; HRMS (EI) found *m/z* 194.1308 (M^+). $C_{12}H_{18}O_2$ requires 194.1307.

4.3. Preparation of the SmI_2 solution

Samarium metal (496.3 mg, 3.3 mmol) was added under flowing of Ar to an oven-dried, round-bottomed two-necked flask containing a magnetic stirring bar and septum inlet. Diiodomethane (803.5 mg, 3.0 mmol) was added to a vigorously stirred suspension of samarium metal in THF (30 mL). The mixture was vigorously stirred for 3 h at rt. The resultant deep blue–green solution was directly used to effect the following reactions.

4.4. General procedure for the synthesis of perhydronaphthalenes

A solution of SmI_2 in THF was cooled to a fixed temperature. A substrate and an additive in THF were slowly added dropwise. The mixture was stirred at the specific temperature for 30 min. The reaction was quenched with a saturated aq. solution of Rochelle's salt. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. The products were purified by silica gel flash chromatography and HPLC. Gas chromatographic analyses were carried out on a capillary column [HP-20M 25 m×0.2 mm×0.2 μm, 50–100°C (20°C/min) followed by 100–200°C (5°C/min)].

4.5. SmI_2 reduction of 10a (Table 1)

Entries 1 and 2. A solution of **10a** (49.8 mg, 0.3 mmol) in THF (1 mL) was treated with SmI_2 (0.1 M, 9 mL, 0.9 mmol) according to the general procedure to afford a mixture of cyclized products (50.2 and 50.3 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 3 and 4. A solution of **10a** (49.8 mg, 0.3 mmol) and MeOH (19.0 mg, 0.6 mmol) in THF (1 mL) was treated with SmI_2 (0.1 M, 9 mL, 0.9 mmol) according to the general procedure to afford a mixture of cyclized products (48.8 mg and 48.4 mg respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 5 and 6. A solution of **10a** (49.8 mg, 0.3 mmol) and MeOH (96.0 mg, 3 mmol) in THF (1 mL) was treated with SmI_2 (0.1 M, 9 mL, 0.9 mmol) according to the general procedure to afford a mixture of cyclized products (45.9 and 49.8 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 7 and 8. A solution of **10a** (49.8 mg, 0.3 mmol) in THF (1 mL) was treated with SmI_2 (0.1 M, 9 mL, 0.9 mmol) and HMPA (645.0 mg, 3.6 mmol) according to the general procedure to afford a mixture of cyclized products (25.2 and 21.6 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 9 and 10. A solution of **10a** (49.8 mg, 0.3 mmol) in THF (1 mL) was treated with SmI_2 (0.1 M, 9 mL, 0.9 mmol) and NiI_2 (10.0 mg, 0.03 mmol) according to the general procedure to afford a mixture of cyclized products (47.8 and 48.9 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Ketol **14a** was purified on flash chromatography (SiO_2, 20–60% AcOEt in $CHCl_3$). Ketols **11a** and **12a** were purified on HPLC (Nucleosil 380-05, 10ϕ×250 mm, 40% AcOEt in hexane) and recrystallization ($CHCl_3$–AcOEt).

4.5.1. (4a*S*,5*S*,8a*S*)-Rel-octahydro-5-hydroxy-1(2*H*)-naphthalenone (11a). Retention time on GC: 8.60 min; crystal: mp 100.8–102.5°C; FTIR: 3394, 2938, 2871, 1704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.19 (1H, ddr, *J*=13.3, 11.1, 4.9 Hz), 1.31 (1H, dddd, *J*=12.6, 11.5, 9.8, 4.7 Hz), 1.34 (1H, br s), 1.54–1.65 (2H, m), 1.70 (1H, ddt, *J*=13.9, 11.5, 4.3 Hz), 1.86–1.97 (3H, m), 2.07–2.13 (2H, m), 2.23 (1H, br dq, *J*=13.9, 4.2 Hz), 2.29 (1H, ddd, *J*=14.5, 11.5, 6.7, 1.3 Hz), 2.40 (1H, dtd, *J*=14.5, 4.5, 1.5 Hz), 2.70 (1H, q, *J*=4.9 Hz), 3.50 (1H, td, *J*=9.8, 4.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.0 (CH_2), 22.3 (CH_2), 24.7 (CH_2), 25.2 (CH_2), 34.8 (CH_2), 41.3 (CH_2), 46.6 (CH), 49.5 (CH), 68.7 (CH), 212.3 (C); MS (EI) *m/z* 168 (M^+), 150, 111, 97 (base), 79, 67, 55; HRMS (EI) found *m/z* 168.1150 (M^+). $C_{10}H_{16}O_2$ requires 168.1151.

4.5.2. (4a*S*,5*S*,8a*R*)-Rel-octahydro-5-hydroxy-1(2*H*)-naphthalenone (12a). Retention time on GC: 8.51 min; crystal: mp 115.4–119.0°C; FTIR: 3394, 2931, 2862, 1705 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 0.83 (1H, ddd, *J*=13.2, 11.5, 3.8 Hz), 0.86–0.97 (4H, m), 1.17–1.22 (1H, m), 1.26 (1H, qt, *J*=13.6, 4.1 Hz), 1.38 (1H, tdd, *J*=11.8, 3.3, 1.1 Hz), 1.51 (1H, m), 1.59–1.64 (2H, m), 1.80 (1H, br tdd, *J*=13.6, 6.2, 1.1 Hz), 1.86 (1H, m), 2.08 (1H, m), 2.22 (1H, d quint, *J*=13.6, 2.1 Hz), 2.87 (1H, br td, *J*=10.0, 4.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.0 (CH_2), 25.1 (CH_2), 26.1 (CH_2), 28.3 (CH_2), 35.5 (CH_2), 41.5 (CH_2), 51.7

(CH), 53.0 (CH), 74.7 (CH), 209.3 (C); MS (EI) *m/z* 168 (M^+), 150, 121, 111, 97 (base), 84, 79, 67, 55; HRMS (EI) found *m/z* 168.1150 (M^+). $C_{10}H_{16}O_2$ requires 168.1151.

4.5.3. (4a*S*,5*R*,8a*R*)-Rel-octahydro-5-hydroxy-1(2*H*)-naphthalenone (14a). Retention time on GC: 8.78 min; oil; FTIR: 3453, 2932, 2864, 1704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.20–1.28 (2H, m), 1.45 (1H, tdd, *J*=13.6, 5.0, 2.4 Hz), 1.53 (1H, tdd, *J*=12.2, 3.0, 2.3 Hz), 1.57–1.71 (4H, m), 1.80 (1H, m), 1.85 (1H, qd, *J*=12.2, 3.6 Hz), 1.94 (1H, m), 2.11 (1H, m), 2.32 (1H, tdd, *J*=13.6, 6.2, 1.2 Hz), 2.37 (1H, m), 2.48 (1H, br td, *J*=12.2, 3.3 Hz), 3.95 (1H, br q, *J*=2.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.8 (CH_2), 24.9 (CH_2), 26.2 (CH_2), 28.6 (CH_2), 33.1 (CH_2), 41.7 (CH_2), 48.0 (CH), 48.2 (CH), 69.6 (CH), 213.5 (C); MS (EI) *m/z* 168 (M^+), 150, 135, 122, 111, 97 (base), 84, 79, 67, 55; HRMS (EI) found *m/z* 168.1150 (M^+). $C_{10}H_{16}O_2$ requires 168.1151.

4.6. Isomerization of 11a

K_2CO_3 (2.0 mg) was added to a MeOH (2 mL) solution of **11a** (1.1 mg, 0.01 mmol) and the mixture was stirred vigorously and refluxed for 12 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, **12a** (1.0 mg) was prepared.

4.7. Isomerization of 12a

K_2CO_3 (2.0 mg) was added to a MeOH (2 mL) solution of **12a** (4.0 mg, 0.02 mmol) and the mixture was stirred vigorously and refluxed for 12 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, **12a** (3.9 mg) was recovered.

4.8. Isomerization of 14a

K_2CO_3 (6.0 mg) was added to a MeOH (4 mL) solution of **14a** (3.0 mg, 0.02 mmol) and the mixture was stirred vigorously and refluxed for 13 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, **14a** (3.0 mg) was recovered.

4.9. SmI_2 reduction of 10b (Table 2)

Entries 1 and 2. A solution of **10b** (20.0 mg, 0.11 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 3.3 mL, 0.33 mmol) according to the general procedure to afford a mixture of cyclized products (10.9 and 13.6 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 3 and 4. A solution of **10b** (20.0 mg, 0.11 mmol) and MeOH (7.0 mg, 0.22 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 3.3 mL, 0.33 mmol) according to the general procedure to afford a mixture of cyclized products (19.6 and 16.3 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 5 and 6. A solution of **10b** (20.0 mg, 0.11 mmol) and MeOH (35.0 mg, 1.1 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 3.3 mL, 0.33 mmol) according to the general procedure to afford a mixture of cyclized products (18.6 and 17.7 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 7 and 8. A solution of **10b** (20.0 mg, 0.11 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 3.3 mL, 0.33 mmol) and HMPA (237.0 mg, 1.32 mmol) according to the general procedure to afford a mixture of cyclized products (13.0 and 15.1 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 9 and 10. A solution of **10b** (20.0 mg, 0.11 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 3.3 mL, 0.33 mmol) and NiI_2 (3.0 mg, 0.01 mmol) according to the general procedure to afford a mixture of cyclized products (10.3 and 6.0 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Ketol **11b** was purified on flash chromatography (SiO_2, 20–60% Et_2O in hexane). Keto-ols **12b** and **14b** were purified on HPLC (Nucleosil 50-5, 10ϕ×250 mm, 30% AcOEt in hexane).

4.9.1. (4a*S*,5*S*,8a*S*)-Rel-octahydro-5-hydroxy-4a-methyl-1(2*H*)-naphthalenone (11b). Retention time on GC: 8.88 min; oil; FTIR: 3448, 2940, 2871, 1699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.11 (3H, S), 1.40–1.48 (2H, m), 1.53–1.62 (4H, m), 1.74 (1H, m), 1.86–1.95 (2H, m), 1.98 (1H, dq, *J*=12.3, 4.12 Hz), 2.18 (1H, dtd, *J*=13.8, 4.5, 1.6 Hz), 2.25 (1H, dddd, *J*=14.4, 11.1, 7.1, 1.3 Hz), 2.30 (1H, br t, *J*=4.1 Hz), 2.42 (1H, dtd, *J*=14.7, 4.7, 1.6 Hz), 3.56 (1H, dd, *J*=9.0, 4.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.8 ($2CH_2$), 20.9 ($2CH_2$), 30.3 (CH_2), 33.3 (CH_2), 40.7 (CH_2), 42.9 (C), 55.5 (C), 70.4 (CH), 212.4 (C); MS (EI) *m/z* 182 (M^+), 164, 149,125, 111 (base), 97, 79, 67, 55; HRMS (EI) found *m/z* 182.1292 (M^+). $C_{11}H_{18}O_2$ requires 182.1307.

4.9.2. (4a*S*,5*S*,8a*R*)-Rel-octahydro-5-hydroxy-4a-methyl-1(2*H*)-naphthalenone (12b). Retention time on GC: 9.06 min; oil; FTIR: 3439, 2937, 2867, 2360, 1707 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.78 (3H, s), 1.25–1.30 (1H, m), 1.35 (1H, tdd, *J*=13.8, 12.0, 3.6 Hz), 1.46 (1H, tdd, *J*=13.1, 12.0, 4.2 Hz), 1.54 (1H, td, *J*=13.2, 4.4 Hz), 1.59 (2H, m), 1.73 (1H, m), 1.80 (1H, m), 1.88 (1H, m), 2.03 (1H, m), 2,09 (1H, m), 2.16 (1H, dd, *J*=11.4, 3.2 Hz), 2.32 (1H, td, *J*=7.2, 1.2 Hz), 2.35 (1H, m), 3.49 (1H, dd, *J*=11.1, 4.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.1 (CH_3), 19.8 (CH_2), 22.5 (CH_2), 22.7 (CH_2), 30.0 (CH_2), 36.3 (CH_2), 41.1 (CH_2), 44.7 (C), 56.7 (CH), 78.5 (CH), 212.0 (C); MS (EI) *m/z* 182 (M+), 167, 149,135, 111 (base), 98, 82, 67, 55; HRMS (EI) found *m/z* 182.1297 (M+). $C_{11}H_{18}O_2$ requires 182.1307.

4.9.3. (4a*S*,5*R*,8a*R*)-Rel-octahydro-5-hydroxy-4a-methyl-1(2*H*)-naphthalenone (14b). Retention time on GC: 9.13 min; oil; FTIR: 3450, 2927, 2867, 1701 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.81 (3H, s), 1.25 (1H, br s), 1.31 (1H, dt, *J*=13.8, 3.0 Hz), 1.43 (1H, m), 1.55 (1H, m), 1.59 (2H, m), 1.63 (1H, m), 1.82 (1H, m), 1.89 (1H, m), 2.01 (1H, m), 2.22 (1H, td, *J*=13.2, 4.6 Hz), 2.31 (2H, m), 2.69

(1H, dd, J=12.3, 2.9 Hz), 3.52 (1H, br q, J=3.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.2 (CH_3), 18.8 (CH_2), 20.0 (CH_2), 22.2 (CH_2), 28.6 (CH_2), 33.9 (CH_2), 41.2 (CH_2), 43.5 (C), 50.8 (CH), 74.0 (CH), 213.9 (C); MS (EI) m/z 182 (M^+), 164, 149,135, 125, 111 (base), 98, 82, 67, 55; HRMS (EI) found m/z 182.1293 (M^+). $C_{11}H_{18}O_2$ requires 182.1307.

4.9.4. (4a*S*,5*R*,8a*S*)-Rel-octahydro-5-hydroxy-4a-methyl-1(2*H*)-naphthalenone (13b). The peak of **13b** on GC–MS was identified by isomerization of **14b**. Retention time on GC: 9.00 min; GC–MS (EI) m/z 182 (M^+), 164, 149,138, 131, 125, 111 (base), 98, 95.

4.10. Isomerization of 11b

K_2CO_3 (6.0 mg) was added to a MeOH (3 mL) solution of **11b** (10.0 mg, 0.05 mmol) and the mixture was stirred vigorously and refluxed for 16 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, the mixture (8.4 mg) of **11b** and **12b** (21:79) was produced.

4.11. Isomerization of 12b

K_2CO_3 (4.0 mg) was added to a MeOH (3 mL) solution of **12b** (1.6 mg, 0.01 mmol) and the mixture was stirred vigorously and refluxed for 37 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, the mixture (1.6 mg) of **11b** and **12b** (16:84) was produced.

4.12. Isomerization of 14b

K_2CO_3 (3.0 mg) was added to a MeOH (3 mL) solution of **14b** (1.4 mg, 0.01 mmol) and the mixture was stirred vigorously and refluxed for 37 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, the mixture (0.9 mg) of **13b** and **14b** (18:82) was produced.

4.13. SmI_2 reduction of 10c (Table 3)

Entries 1 and 2. A solution of **10c** (25.0 mg, 0.14 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 4.2 mL, 0.42 mmol) according to the general procedure to afford a mixture of cyclized products (22.1 and 25.2 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 3 and 4. A solution of **10c** (25.0 mg, 0.14 mmol) and MeOH (9.0 mg, 0.28 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 4.2 mL, 0.42 mmol) according to the general procedure to afford a mixture of cyclized products (20.7 and 21.5 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 5 and 6. A solution of **10c** (25.0 mg, 0.14 mmol) and MeOH (45.0 mg, 1.4 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 4.2 mL, 0.42 mmol) according to the general procedure to afford a mixture of cyclized products (20.7 and 24.2 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 7 and 8. A solution of **10c** (25.0 mg, 0.14 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 4.2 mL, 0.42 mmol) and HMPA (300.0 mg, 1.68 mmol) according to the general procedure to afford a mixture of cyclized products (2.5 and 8.4 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 9 and 10. A solution of **10c** (25.0 mg, 0.14 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 4.2 mL, 0.42 mmol) and NiI_2 (5.0 mg, 0.02 mmol) according to the general procedure to afford a mixture of cyclized products (21.4 and 13.7 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Compounds **11c**, **12c**, and **14c** were purified on flash chromatography (SiO_2, 50–60% Et_2O in hexane) and HPLC (Nucleosil 50-5, 10∅250 mm, 20% AcOEt in $CHCl_3$).

4.13.1. (4a*S*,5*S*,8a*S*)-Rel-octahydro-5-hydroxy-5-methyl-1(2*H*)-naphthalenone (11c). Retention time 8.99 GC: 00 min; oil; FTIR: 3441, 2943, 2865, 1703 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.50–1.64 (7H, m), 1.65–1.73 (3H, m), 1.81 (1H, br dt, J=10.8, 5.1 Hz), 2.08 (1H, m), 2.23 (1H, m), 2.46 (1H, ddd, J=14.7, 13.5, 6.5 Hz), 2.87 (1H, br dt, J=13.2, 4.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.8 (CH_2), 22.2 (CH_2), 24.4 (CH_2), 25.3 (CH_2), 29.7 (CH_3), 33.8 (CH_2), 37.6 (CH_2), 48.4 (C), 49.1 (C), 71.0 (C), 214.7 (C); MS (EI) m/z 182 (M^+), 164, 149, 139, 124 (base), 111, 97, 84, 79, 67, 55; HRMS (EI) found m/z 182.1296 (M^+). $C_{11}H_{18}O_2$ requires 182.1307.

4.13.2. (4a*S*,5*S*,8a*R*)-Rel-octahydro-5-hydroxy-5-methyl-1(2*H*)-naphthalenone (12c). Retention time on GC: 8.82 min; crystal: mp 93.0–100.5°C; FTIR: 3440, 2935, 2864, 1705 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.25–1.35 (3H, m), 1.43–1.47 (2H, m), 1.57–1.66 (2H, m), 1.72–1.77 (2H, m), 1.87–1.94 (1H, m), 2.06–2.19 (3H, m), 2.28 (1H, tdd, J=13.8, 6.6, 1.2 Hz), 2.40 (1H, dquin, J=13.8, 2.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.6 (CH_3), 22.1 (CH_2), 24.8 (CH_2), 25.1 (CH_2), 26.0 (CH_2), 41.8 (CH_2), 42.1 (CH_2), 52.0 (C), 53.9 (CH), 72.7 (C), 212.1 (C); MS (EI) m/z 182 (M^+), 164, 149, 139, 131, 124 (base), 111, 97, 84, 79, 67, 55. Anal. found C, 72.65: H, 10.23: N, 0.02. requires $C_{11}H_{18}O_2$ C, 72.49: H, 9.95.

4.13.3. (4a*S*,5*R*,8a*R*)-Rel-octahydro-5-hydroxy-5-methyl-1(2*H*)-naphthalenone (14c). Retention time on GC: 8.75 min; oil; FTIR: 3385, 2932, 2858, 1685 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 0.83 (3H, s), 0.87 (1H, td, J=11.8, 3.5 Hz), 0.95 (1H, td, J=13.5, 4.6 Hz), 1.19 (1H, tdd, J=13.2, 4.2, 3.3 Hz), 1.21–1.33 (4H, m), 1.35–1.39 (1H, m), 1.42 (1H, tt, J=13.3, 3.7 Hz), 1.46–1.49 (1H, m), 1.60 (1H, qt, J=6.2, 3.1 Hz), 1.86 (1H, br td, J=13.6, 6.2 Hz), 2.05 (1H, m), 2.11 (1H, tdd, J=11.8, 3.4, 1.1 Hz), 2.24 (1H, m); ^{13}C NMR (150 MHz, C_6D_6) δ 20.4 (CH_2), 24.5 (CH_2), 25.7 (CH_2), 26.0 (CH_2), 28.7 (CH_3), 40.2 (CH_2), 41.5 (CH_2), 49.7 (CH_2), 52.0 (CH), 70.2 (C), 210.8 (C); MS (EI) m/z 182 (M^+), 164, 149, 139, 124 (base), 111, 97, 84, 79, 67, 55;

HRMS (EI) found *m/z* 182.1292 (M^+). $C_{11}H_{18}O_2$ requires 182.1306.

4.13.4. (4a*S*,5*R*,8a*S*)-Rel-octahydro-5-hydroxy-5-methyl-1(2*H*)-naphthalenone (13c). The peak of **13c** on GC–MS was identified by isomerization of **14c**. Retention time on GC: 8.66 min; MS (EI) *m/z* 182 (M^+), 164, 149, 139, 124, 111, 97 (base), 84, 79, 67, 55.

4.14. Isomerization of 11c

K_2CO_3 (2.0 mg) was added to a MeOH (3 mL) solution of **11c** (2.9 mg, 0.02 mmol) and the mixture was stirred vigorously and refluxed for 14 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, the mixture (2.8 mg) of **11c** and **12c** (11:89) was produced.

4.15. Isomerization of 12c

K_2CO_3 (11.0 mg) was added to a MeOH (11 mL) solution of **12c** (15.0 mg, 0.08 mmol) and the mixture was stirred vigorously and refluxed for 14 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, the mixture (14.8 mg) of **11c** and **12c** (11:89) was produced.

4.16. Isomerization of 14c

K_2CO_3 (4.0 mg) was added to a MeOH (5 mL) solution of **14c** (3.2 mg, 0.02 mmol) and the mixture was stirred vigorously and refluxed for 10 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, the mixture (3.2 mg) of **13c** and **14c** (5:95) was produced.

4.17. SmI_2 reduction of 10d (Table 4)

Entries 1 and 2. A solution of **10d** (39.0 mg, 0.2 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 6 mL, 0.6 mmol) according to the general procedure to afford a mixture of cyclized products (39.3 and 22.0 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 3 and 4. A solution of **10d** (39.0 mg, 0.2 mmol) and MeOH (13.0 mg, 0.4 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 6 mL, 0.6 mmol) according to the general procedure to afford a mixture of cyclized products (35.9 and 39.4 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 5 and 6. A solution of **10d** (39.0 mg, 0.2 mmol) and MeOH (64.0 mg, 2 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 6 mL, 0.6 mmol) according to the general procedure to afford a mixture of cyclized products (29.9 and 22.9 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Entries 7 and 8. A solution of **10d** (39.0 mg, 0.2 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 6 mL, 0.6 mmol) and HMPA (430.0 mg, 2.4 mmol) according to the general procedure. Only the starting material was recovered.

Entries 9 and 10. A solution of **10d** (39.0 mg, 0.2 mmol) in THF (0.5 mL) was treated with SmI_2 (0.1 M, 6 mL, 0.6 mmol) and NiI_2 (6.0 mg, 0.02 mmol) according to the general procedure to afford a mixture of cyclized products (28.0 and 33.8 mg, respectively) after flash chromatography (SiO_2, 0–60% AcOEt in $CHCl_3$).

Compounds **11d**, **12d**, and **14d** were purified on flash chromatography (SiO_2, 0–100% AcOEt in hexane) and HPLC (Nucleosil 50-5, 10∅250 mm, 20% AcOEt in hexane).

4.17.1. (4a*S*,5*S*,8a*S*)-Rel-octahydro-5-hydroxy-4a,5-dimethyl-1(2*H*)-naphthalenone (11d). Retention time on GC: 9.56 min; oil; FTIR: 3480, 2940, 2870, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.15 (3H, s), 1.35–1.39 (2H, m), 1.51 (1H, ddd, *J*=11.4, 5.4, 1.3 Hz), 1.56–1.62 (2H, m), 1.68–1.76 (2H, m), 1.77–1.87 (2H, m), 1.93–1.97 (1H, m), 2.01 (1H, td, *J*=18.6, 4.8 Hz), 2.12–2.18 (1H, m), 2.45 (1H, dd, *J*=11.4, 4.2 Hz), 2.48–2.55 (1H, m); ^{13}C NMR (600 MHz, $CDCl_3$) δ 18.6 (CH_3), 20.4 (CH_2), 21.7 (CH_2), 25.1 (CH_3), 26.6 (CH_2), 26.8 (CH_2), 35.3 (CH_2), 36.3 (CH_2), 43.2 (C), 54.9 (CH), 72.9 (C), 215.6 (C); MS (EI) *m/z* 196 (M^+), 181, 163, 137, 125, 111 (base), 97, 84; HRMS (EI) found *m/z* 196.1463 (M^+). $C_{12}H_{20}O_2$ requires 196.1463.

4.17.2. (4a*S*,5*S*,8a*R*)-Rel-octahydro-5-hydroxy-4a,5-dimethyl-1(2*H*)-naphthalenone (12d). Retention time on GC: 9.48 min; crystal; mp 122.0–124.2°C; FTIR: 3470, 2940, 2870, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (3H, s), 1.26–1.32 (2H, m), 1.36 (3H, s), 1.39–1.42 (1H, m), 1.45–1.49 (1H, m), 1.51 (1H, br s), 1.60–1.64 (1H, m), 1.70–1.76 (2H, m), 1.77–1.88 (3H, m), 1.97–2.02 (1H, m), 2.23–2.29 (1H, m) 2.30–2.37 (2H, m); ^{13}C NMR (600 MHz, $CDCl_3$) δ 14.3 (CH_3), 20.3 (CH_2), 21.8 (CH_2), 22.1 (CH_2), 22.7 (CH_3), 31.1 (CH_2), 37.0 (CH_2), 41.2 (CH_2), 46.0 (C), 54.8 (CH), 74.4 (C), 212.7 (C); MS (EI) *m/z* 196 (M^+), 181, 138, 125, 111 (base), 97, 84; HRMS (EI) found *m/z* 196.1458 (M^+) $C_{12}H_{20}O_2$ requires 196.1463.

4.17.3. (4a*S*,5*R*,8a*R*)-Rel-octahydro-5-hydroxy-4a,5-dimethyl-1(2*H*)-naphthalenone (14d). Retention time on GC: 9.42 min; crystal; mp 100.8–102.5°C; FTIR: 3400, 2930, 2830, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.82 (3H, s), 1.16 (3H, s), 1.30 (1H, br s), 1.36–1.42 (2H, m), 1.56–1.60 (2H, m), 1.62–1.67 (2H, m), 1.73–1.84 (2H, m), 1.99–2.04 (1H, m), 2.08 (1H, td, *J*=13.2, 4.2 Hz), 2.29–2.32 (2H, m), 2.77 (1H, dd, *J*=12, 3 Hz); ^{13}C NMR (600 MHz, $CDCl_3$) δ 16.8 (CH_3), 20.0 (CH_2), 20.3 (CH_2), 22.2 (CH_2), 24.8 (CH_3), 30.4 (CH_2), 35.5 (CH_2), 41.2 (CH_2), 46.2 (C), 52.5 (CH), 74.0 (C), 214.3 (C); MS (EI) *m/z* 196 (M^+), 181, 163, 138, 125, 111 (base), 97, 84; HRMS (EI) found *m/z* 196.1473 (M^+). $C_{12}H_{20}O_2$ requires 196.1463.

4.17.4. (4a*S*,5*R*,8a*S*)-Rel-octahydro-5-hydroxy-4a,5-dimethyl-1(2*H*)-naphthalenone (13d). The peak of **13d** on GC–MS was identified by isomerization of **14d**.

Retention time on GC: 9.00 min; MS (EI) *m/z* 196 (M^+), 181, 163, 138, 125, 111 (base), 97, 84, 71.

4.18. Isomerization of 11d

K_2CO_3 (4.0 mg) was added to a MeOH (3 mL) solution of **11d** (3.4 mg, 0.02 mmol) and the mixture was stirred vigorously and refluxed for 41 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, the mixture (3.3 mg) of **11d** and **12d** (51:49) was produced.

4.19. Isomerization of 12d

K_2CO_3 (6.0 mg) was added to a MeOH (6 mL) solution of **12d** (5.2 mg, 0.03 mmol) and the mixture was stirred vigorously and refluxed for 41 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, the mixture (5.1 mg) of **11d** and **12d** (52:48) was produced.

4.20. Isomerization of 14d

K_2CO_3 (7.0 mg) was added to a MeOH (7 mL) solution of **14d** (6.5 mg, 0.03 mmol) and the mixture was stirred vigorously and refluxed for 27 h. The organic materials were extracted with diethyl ether, washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuo, the mixture (6.4 mg) of **13d** and **14d** (6:94) was produced.

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