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A novel route for the construction of Taxol ABC-ring framework: skeletal rearrangement approach to AB-ring and intramolecular aldol approach to C-ring

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Abstract

We report here on the construction of the ABC-ring framework of (±)-Taxol using an intramolecular aldol reaction as a key step. AB-ring compound **8** was converted to ketoaldehyde **25** as a precursor of an aldol reaction via introduction of oxygen-functionalities and a methoxycarbonyl group, which can be converted to a methyl group, in the proper positions of the B-ring. An aldol reaction of ketoaldehyde with LDA led to the formation of the desired product **27**, which corresponds to the ABC-ring framework of (±)-Taxol.

1. Introduction

Taxol (**1**), a naturally occurring diterpenoid, which was isolated from the pacific yew *Taxus brevifolia* by Wani and Wall in 1971, is one of the most exciting antitumor agents available today.[1] It is currently used for the treatment of refractory ovarian, metastatic breast, and non-small-cell lung cancer. Due to its therapeutic potential and its limited availability, numerous efforts have been directed toward the chemical synthesis of Taxol in the past decades, and this remains one of the most challenging targets for the synthetic chemists because of its structural features (Fig. 1).[2]

We have already established a unique method for the construction of the AB-ring core of Taxol utilizing a novel skeletal rearrangement reaction as a key step.[3] In our work, the acid-catalyzed rearrangement[4] of cyclopentenone-allene photoadduct **3** gave a bridged seven-membered ketone **4**. Ketone **4** was easily transformed, using an intramolecular Suzuki–Miyaura coupling to **6** and oxidative cleavage of the vicinal diol **7**, to the bicyclic diketone **8** corresponding to the AB-ring core of Taxol (Scheme 1). We report herein on the synthesis of an ABC-ring framework from the Taxol AB-ring system using an intramolecular aldol reaction as a key strategy.

Seven total syntheses of Taxol have been independently reported to date: Holton,[5] Nicolaou,[6] Danishefsky,[7] Wender,[8] Mukaiyama,[9] Kuwajima,[10] and Takahashi.[11] Moreover, there are numerous reports on the synthetic study of related compounds. Among them, some have utilized an intramolecular aldol reaction for the construction of a C-ring.[8b,12] These all involve the C–C bond connection between C-7 (Taxoid numbering is being used throughout the text.) and C-8 by the aldol reaction for C-9 carbonyl with the four-carbon aldehyde tethered at C-3 (Scheme 2, route a). Our strategy represents the

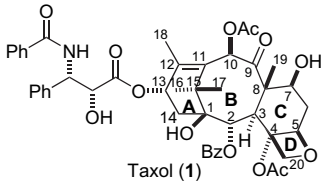

Figure 1. Taxol.

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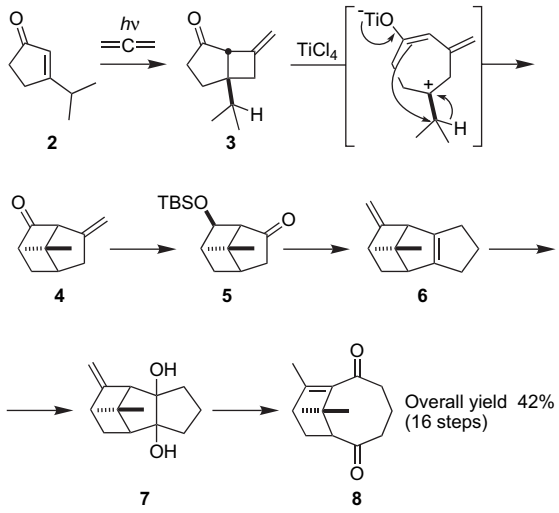
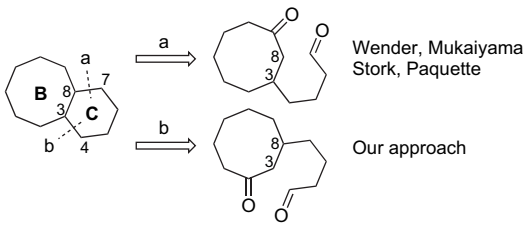


Scheme 1. Synthesis of AB-ring core of (±)-Taxol utilizing acid-catalyzed skeletal rearrangement reaction.



Scheme 2. Aldol-approaches to C-ring construction.

first approach to C-ring construction using an intramolecular aldol reaction accompanied with the bond connection between C-3 and C-4 (Scheme 2, route b).

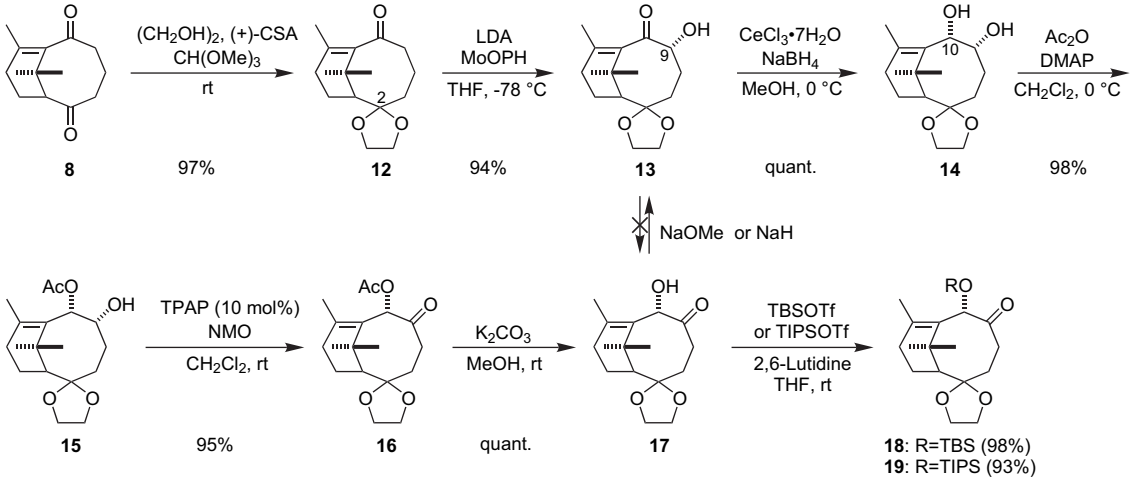
2. Results and discussion

2.1. First approach to the synthesis of cyclization precursor

A major aim of this research is to build up the ABC-ring fragment of Taxol via functionalization on the B-ring and introduction of the four-carbon side chain, which would constitute the C-ring. The retrosynthetic analysis for compound **9** is shown in Scheme 3. Our strategy for the construction of the C-ring core centered on the utilization of intramolecular aldol reaction technology of 2-oxofunctionality on B-ring with a butanal side chain to C-8. The butanal side chain would be introduced to C-8 of ketone **11**, which could be prepared from diketone **8**, and the subsequent deprotection of acetal provides ketoaldehyde **10**.

Scheme 3. Retrosynthetic analysis.

The carbonyl group at the C-2 position of diketone **8** was protected selectively with ethylene glycol, and the remaining ketone at C-10 was allowed to react with LDA and MoOPH[13] to give hydroxyketone **13** in 94% (Scheme 4). Unfortunately, direct transposition of the hydroxyketone **13** to **17** under basic conditions (NaOMe or guanidium salt[8b]) did not proceed. Conversely, treatment of **17** with alkali bases, such as NaOMe and NaH, led to the transposition to give **13** easily. Therefore, we chose a detour route to **17**. The subsequent Luche reduction of the C-10 carbonyl group gave *cis*-diol **14** in quantitative yield. X-ray crystallography analysis revealed that both hydroxyl groups are in α-configuration on the B-ring skeleton



Scheme 4. Introduction of oxofunctionalities into the proper positions on the B-ring.

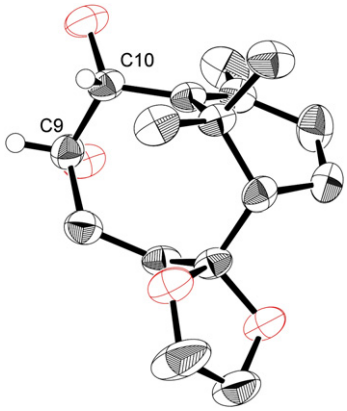


Figure 2. X-ray structure analysis of diol **14**. The molecular structure is drawn with 50% thermal probability ellipsoids.

(Fig. 2). The stereoselectivity of the reduction can be rationalized as follows: the chelation of cerium chloride through the C-9 hydroxyl and the C-10 carbonyl groups would prevent the reductant from approaching the concave face of hydroxyketone **13**. Selective protection of the allylic hydroxyl group in **14** provided monoacetate **15** in 98%. After oxidation of **15** with catalytic TPAP, hydrolytic deprotection of acetate furnished hydroxyketone **17** quantitatively. Hydroxyketone **17** was allowed to react with TBS or TIPS triflate to afford ketone **18** or **19** in excellent yield.

Introduction of a methyl group at C-8 of ketone **18** was carried out using LDA/HMPA, resulting in the formation of **11** in 84% as a single isomer (Scheme 5). The stereochemistry of a hydrogen atom at β-face was assigned by NOESY spectrum through the hydrogen atoms of the bridged methyl group. We attempted the intramolecular aldol reaction of **11** with a 4-hydroxybutanal derivative, but the desired product was not obtained. Alkylation of C-8 carbon with allyl iodide also failed. Moreover, treatment of **11** with TMSCl in the presence of LDA afforded no silylated product. DFT calculation (B3LYP/6-31G*)[14] on **11** shows that the hydrogen atom at C-8 and the C-9 carbonyl group are located on the same plane, approximately (Fig. 3). This indicates that deprotonation is difficult, because there is, on the

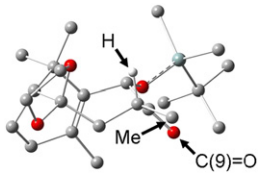


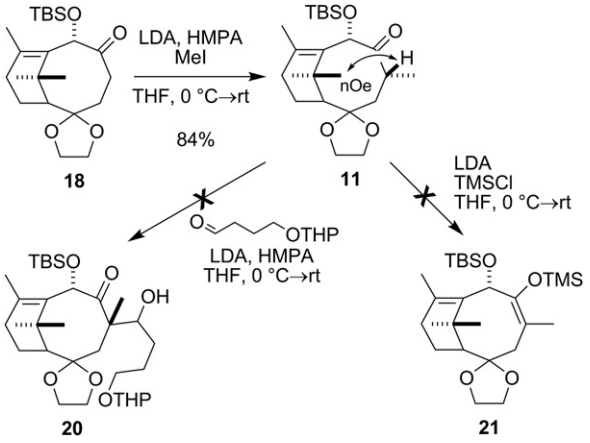
Figure 3. DFT calculation on **11**.

rigid conformation of **11**, little stereoelectronic interaction between the π* orbital of the carbonyl system and the σ orbital of C–H bond at C-8. Previously, similar phenomena have been observed by Mukaiyama[12b] and Stork[12c] independently in the construction of the C-ring. Therefore, we next planned to introduce the additional carbonyl group outside of the strained B-ring system, which can rotate relatively easily without restraint. Since it was elucidated that the TBS group at C-10 was not stable to a certain extent under the basic conditions, the TIPS derivative **19** was employed for the following transformations.

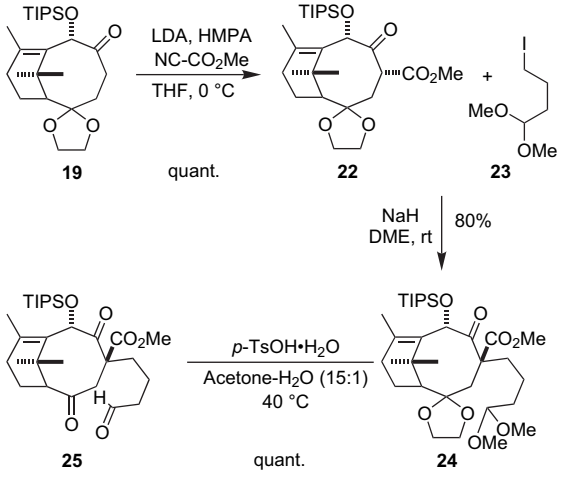
2.2. Modified approach to the synthesis of cyclization precursor

A methoxycarbonyl group, which could be transformed to a methyl group afterward, was introduced via deprotonation with LDA/HMPA, followed by trapping it with some carbonate electrophiles. For the trapping with methyl chloroformate, only an *O*-acylated product was obtained, while use of methyl cyanoformate led to C-acylation to give the desired ester **22** quantitatively (Scheme 6). This esterification did not proceed in the absence of HMPA. It was established by X-ray structure analysis that the introduced ester group in **22** is arranged at the α-face (Fig. 4).

We next examined the ester group-assisted deprotonation of the C-8 proton, followed by the alkylation with 4-iodobutanal dimethylacetal **23**[15] to give acetal **24**. Among the various ethereal solvents tested, dimethoxyethane (80% yield of **24**) was the solvent of choice: THF, 30%; Et_2O, 10%; CPME 0%; TBME 0% yield. X-ray crystallographic analysis showed



Scheme 5. Intermolecular aldol reaction for the C-ring.



Scheme 6. Synthesis of ketoaldehyde **25**.

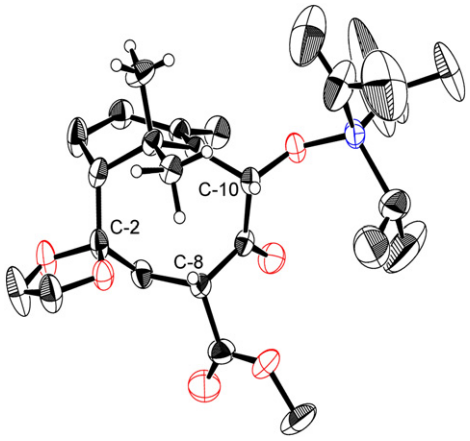
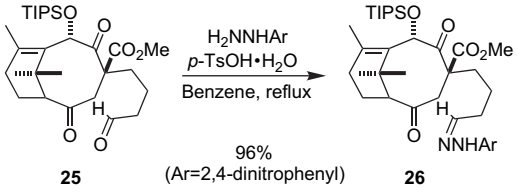


Figure 4. X-ray structure analysis of ester **22**. The molecular structure is drawn with 30% thermal probability ellipsoids.

that a butanal chain is introduced at the α-face. Thus, the butanal side chain approaches from the opposite side of the bulky isopropylidene bridge. The subsequent deprotection with *p*-TsOH gave ketoaldehyde **25** quantitatively (Scheme 6).

In order to establish the stereochemistry of the introduced alkyl chain in **24**, ketoaldehyde **25** was converted, with 2,4-dinitrophenylhydrazine under an acidic condition, to the corresponding hydrazone **26** in 96% yield (Scheme 7, Fig. 5). X-ray crystallographic analysis of **26** clarified the stereochemistry of the C-8 position, which matches Suzuki's report that 3-methoxycarbonyl-*d*-camphor was alkylated with high selectivity from the concave face to avoid the bulky isopropylidene bridge.[16]



Scheme 7. Hydrazone derivative.

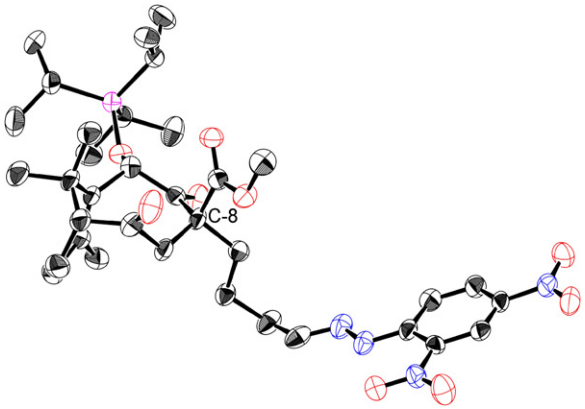
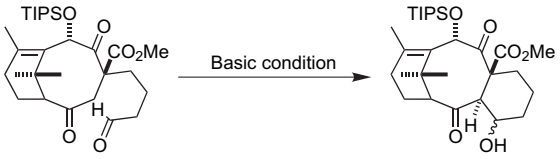


Figure 5. X-ray structure analysis of hydrazone **26**. The molecular structure is drawn with 30% thermal probability ellipsoids.

2.3. Intramolecular aldol reaction

Next, the intramolecular aldol reaction of ketoaldehyde **25** was investigated under various basic conditions (Table 1). When **25** was treated with amines, such as DBU and DMAP,[8b] as a base, no aldol product **27** was obtained (entries 1–3). Use of NaOMe[18] led to the complete consumption of **25**, however, resulting in a complex mixture (entry 4). Among more basic alkali amides tested (entries 5–10), only LDA worked well to give the desired aldol **27** in 56% yield (entry 6), along with 24% of unreacted ketoaldehyde **25**. ^{1}H NMR spectra showed that **27** was obtained as 1:1 mixture of two inseperable diastereomers. Compound **27** was also identified as the desired aldol product by FAB-HRMS (calcd for $[M+Na]^+$: 543.3118, found: 543.3116). The NOESY experiment with the diastereomeric mixture clarified that H-3 of each diastereomer located near the methyl group at C-18 (Fig. 6). Thus H-3 was assigned to be in α-face. We postulate the origin of the resulting stereochemistry at C-3 position for the intramolecular aldol reaction as follows: β-H at C-3 might be deprotonated predominantly to generate the *Z*-enolate (Scheme 8). Therefore, the aldehyde moiety would approach from the outside of B-ring and provided trans-annulated C-ring.[19]

Table 1
Intramolecular aldol reaction of ketoaldehyde **25**[a]



Entry	Base (equiv)	Additive (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	DBU (0.5)	—	THF–*t*-BuOH	rt–40	50	0 (24)[d]
2	DBU (1)	K_2CO_3 (1)	THF–*t*-BuOH	rt	24	n.r.
3	DMAP (5)	—	CH_2Cl_2	rt	7	n.r.
4	NaOMe (5)	—	MeOH	rt	20	Complex mix.
5	LDEA (10)[b]	—	THF	−78	2	0 (45)[d]
6	LDA (10)[b]	—	THF	−78	2	56 (24)[d]
7	LTMP (10)[b]	—	THF	−78	2	0
8	LHMDS (10)	—	THF	−78	2	0 (61)[d]
9	KHMDS (10)	—	THF	−78	2	0 (16)[d]
10	MgBrN*i*Pr$_2$ (20)[c]	—	Et_2O	rt	24	0
11	LDA (10)[b]	HMPA (4)	THF	−78	2	31 (23)[d]
12	LDA (10)[b]	CuI (4)	THF	−78	2	26 (44)[d]
13	LDA (10)[b]	$MgBr_2$: OEt_2 (4)	Et_2O	−78	2	Complex mix.
14	LDA (10)[b]	$ZnCl_2$ (5)	THF	−78	2	n.r.
15	LDA (10)[b]	$Sc(OTf)_3$ (5)	THF	−78	2	11 (74)[d]
16	LDA (10)[b]	$ZrCl_4$ (5)	THF	−78	2	n.r.

[a] Ketoaldehyde (5 mg, 10 μmol) was used in each entry.
[b] LDEA, LDA, and LTMP were generated freshly with *n*-BuLi and distilled Et_2NH, *i*Pr_2NH, and 2,2,6,6-tetramethylpiperidine, respectively.
[c] See Ref. 17.
[d] Recovery yield of ketone **25** was shown in parenthesis.

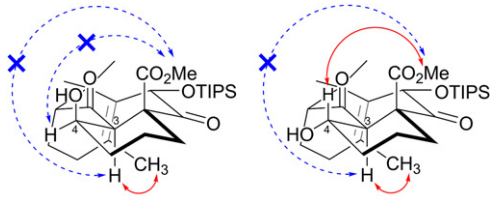
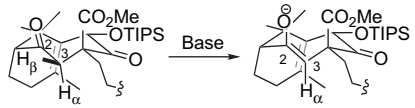


Figure 6. NOE correlations in the NOESY spectrum of diastereomeric mixture of **27**. Observed NOE correlations were expressed by red arrows, and unobserved ones were expressed by blue dashed arrows.



25

Scheme 8. Deprotonation of **25**.

In order to improve the efficiency of the aldol reaction, a variety of additives were examined (entries 11–16). Addition of HMPA as a highly polar cosolvent led to the formation of **27**, although in lower yield (31%, entry 11). We attempted to promote the reaction by addition of metal salt, which would make the reaction sites close through the chelation of two carbonyls to one metal center. Metal salts, such as CuI and $Sc(OTf)_3$ lowered the yield of **27** (entries 12 and 15),[20] while, for $MgBr_2$, $ZnCl_2$, and $ZrCl_4$, no formation of the aldol product was observed (entries 13–14 and 16).

3. Conclusions

We have described the synthesis of the ABC-ring compound of (±)-Taxol using an intramolecular aldol reaction as a key reaction. A methoxycarbonyl group, which could be transformed to C-19 methyl group, was introduced to the AB-ring of previously synthesized compound **8**. The methoxycarbonyl group enabled deprotonation of the hydrogen atom at C-8, therefore, followed by alkylation with a four-carbon aldehyde moiety, to give the precursor **25** of the intramolecular aldol reaction. Finally, we succeeded in the intramolecular aldol reaction with LDA and afforded ABC-ring compound **27**. Studies on the further transformation toward Taxol are now underway.

4. Experimental section

4.1. General procedures and measurements

All dry solvents were purified before use by standard procedures. All reactions were carried out under inert gas (N_2) unless otherwise stated. Flash column chromatography on silica gel was carried out with Merck silicagel 60. NMR spectra were measured with JEOL JMN-ECP500 and JEOL JMN-ECP600 spectrometers. Chemical shifts in ^1H NMR were reported in parts per million (δ) units relative to the singlet at 0.00 ppm for TMS as an internal standard. ^{13}C NMR spectra were reported in parts per million (δ) units relative to the center line of a triplet at 77.0 ppm for chloroform-*d* as an internal standard. Infrared spectra were measured with JASCO FT/IR-420. High resolution mass spectra were measured with JEOL JMS-700. Single crystal X-ray structure analyses were carried out in RIGAKU R-AXIS RAPID/S (3 kW).

*4.1.1. Ketone **12***

To a solution of diketone **8** (0.16 g, 0.072 mmol) in anhydrous methylene chloride (20 mL), ethylene glycol (8.1 mL, 0.15 mol), and D-(+)-10-camphorsulfonic acid (84 mg, 0.36 mmol) were added. The reaction mixture was stirred at room temperature for 48 h. The reaction was quenched with cooled satd $NaHCO_3$ aq. The resulting mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=4/1) afforded ketone **12** (0.19 g, 97%) as a colorless solid (needle). Compound **12**: mp 102.9–103.5 °C; ^1H NMR (500.16 MHz, $CDCl_3$) δ 3.91–3.88 (m, 2H), 3.85 (dd, J=12.8, 6.3 Hz, 1H), 3.76 (dd, J=12.8, 6.3 Hz, 1H), 2.46 (td, J=14.4, 4.3 Hz, 1H), 2.34 (d, J=15.2 Hz, 1H), 2.28–2.19 (m, 1H), 2.14–1.93 (m, 4H), 1.81 (d, J=9.2 Hz, 1H), 1.84–1.72 (m, 3H), 1.59 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 221.8, 141.1, 131.3, 113.7, 64.9, 62.8, 52.6, 45.0, 35.1, 33.5, 31.0, 26.9, 26.0, 21.7, 19.9 (2C); IR (cm^{-1}, KBr) ν_{max} 3351, 1686, 1459, 1414, 1390, 1360, 1294, 1207, 1173, 1103, 1051, 992, 936; HRMS (FAB, *m*-NBA) calcd for $C_{16}H_{24}O_3$ $[M]^+$: 264.1725, found: 264.1731; Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15; found: C, 72.91; H, 9.28.

*4.1.2. Hydroxyketone **13***

To a solution of diisopropylamine (0.39 mL, 2.81 mmol) at −40 °C, 1.6 M solution of *n*-BuLi in hexane (1.76 mL, 2.81 mmol) was added, and stirred at −40 °C for 1 h. To the LDA solution prepared above, a solution of ketone **12** (185.9 mg, 0.70 mmol) in THF (21 mL) was added. The reaction mixture was allowed to warm to 0 °C, stirred for 1 h. Then, the mixture was cooled to −20 °C, MoOPH (2.43 g, 5.62 mmol) was added, and stirred at −20 °C for 17 h. The reaction was quenched with satd $NaHCO_3$ aq. The resulting mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=4/1) afforded hydroxyketone **13** (184.7 mg, 94%) as a colorless solid (needle). Compound **13**: mp 131.1–131.9 °C; ^1H NMR (500.16 MHz, $CDCl_3$) δ 4.82 (dd, J=10.7, 6.4 Hz, 1H), 3.95 (dd, J=7.1, 6.9 Hz, 2H), 3.88–3.83 (m, 2H), 3.80–3.70 (m, 1H), 2.36 (dd, J=18.9, 12.8 Hz, 1H), 2.18–2.10 (m, 1H), 2.10–2.00 (m, 1H), 1.95–1.86 (m, 1H), 1.90 (d, J=7.9 Hz, 1H), 1.64 (s, 3H), 1.64–1.57 (m, 2H), 1.48–1.40 (m, 1H), 1.37 (s, 3H), 1.37–1.08 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 200.8, 140.6, 137.7, 114.0, 74.6, 65.2, 62.8, 51.3, 35.4, 31.5, 30.5, 28.95, 28.73, 26.7, 21.1, 20.2; IR (cm^{-1}, KBr) ν_{max} 2477, 2897, 1685, 1637, 1543,

1458, 1105, 1046, 1004, 945; HRMS (FAB, *m*-NBA) calcd for $C_{16}H_{24}O_4$ $[M]^+$: 280.1675, found: 280.1666; Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63; found: C, 68.65; H, 8.86.

4.1.3. Diol **14**

To a solution of hydroxyketone **13** (421.2 mg, 1.50 mmol) in anhydrous methanol (21 mL), cerium chloride hepta-hydrate (700 mg, 1.80 mmol) was added, and stirred until all of the reagents were dissolved completely. Then, the solution was allowed to cool to 0 °C, and sodium borohydride (70.1 mg, 1.80 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C, and then satd $NaHCO_3$ aq was added. The resulting mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=2/1) afforded diol **14** (426.5 mg, quant.) as a colorless solid (prism). Compound **14**: mp 134.1–136.8 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 4.53 (d, J=4.3 Hz, 1H), 4.04 (t, J=4.3 Hz, 1H), 3.87 (td, J=6.1, 1.85 Hz, 2H), 3.81 (dd, J=13.45, 7.35 Hz, 1H), 3.75 (dd, J=14.05, 7.35 Hz, 1H), 2.31 (m, 1H), 2.10–1.92 (m, 6H), 1.98 (s, 3H), 1.74 (dd, J=7.3, 3.1 Hz, 1H), 1.32–1.23 (m, 1H), 1.25 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ (ppm) 136.23, 132.34, 114.29, 73.16, 72.08, 64.69, 62.59, 53.24, 37.14, 31.92, 30.36, 29.65, 25.84, 25.35, 23.00, 19.83; IR (cm^{-1}, KBr) ν_{max} 3439, 2935, 2877, 1655, 1467, 1449, 1389, 1364, 1271, 1121, 1070, 953, 795; HRMS (FAB, *m*-NBA) calcd for $C_{16}H_{26}O_4$ $[M]^+$: 282.1831; found: 282.1827; Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28; found: C, 67.98; H, 9.53.

4.1.4. Acetate **15**

To a solution of diol **14** (426.5 mg, 1.51 mmol) in anhydrous methylene chloride (175 mL) were added 4-(dimethylamino)pyridine (283.1 mg, 2.32 mmol) and acetic anhydrite (210 μL, 2.27 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature and then was added satd $NaHCO_3$ aq. The resulting mixture was extracted with methylene chloride (×5), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=2/1) afforded monoacetate **15** (480.8 mg, 98%) as a colorless solid (needle). Compound **15**: mp 139.9–140.2 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ (ppm) 5.34 (d, J=3.05 Hz, 1H), 4.11–4.08 (m, 1H), 3.88 (td, J=6.10, 1.55 Hz, 2H), 3.83 (dd, J=12.66, 6.27 Hz, 1H), 3.75 (dd, J=14.35, 7.05 Hz, 1H), 2.32–2.21 (m, 1H), 2.08 (s, 3H), 2.13–2.02 (m, 2H), 1.98–1.90 (m, 4H), 1.87 (s, 3H), 1.76 (dd, J=6.10, 4.3 Hz, 1H), 1.38 (s, 3H), 1.34–1.22 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 169.54, 136.46, 130.07, 114.21, 75.07, 71.64, 64.76, 62.63, 53.07, 37.33, 30.82, 29.92, 28.98, 26.07, 25.59, 22.97, 21.09, 19.78; IR (cm^{-1}, KBr) 3453, 3036, 3006, 2967, 2933, 2891, 1737, 1372, 1255, 1238, 1191, 1133, 1112, 1072, 1021, 984, 956, 926, 887, 837, 741; HRMS (FAB, *m*-NBA) calcd for $C_{18}H_{28}O_5$ $[M]^+$: 324.1937, found: 324.1927; Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 9.28; found: C, 66.41; H, 8.82.

4.1.5. Ketone **16**

In the dried vessel under N_2 atmosphere, tetrapropylammonium perruthenate (24.8 mg, 5.0 mol %) and 4-methylmorphorine *N*-oxide were placed and dissolved in anhydrous methylene chloride (13 mL). A solution of monoacetate **15** (458.6 mg, 1.414 mmol) in anhydrous methylene chloride (57 mL) was added into the flask. The reaction mixture was stirred for 5 h at room temperature, and then the precipitate catalyst was filtered off on Celite pad. The solution was concentrated, the purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=2/1) afforded ketone **16** (433.5 mg, 95%) as a colorless solid (needle). Compound **16**: mp 158–161 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 5.90 (s, 1H), 3.96–3.93 (m, 2H), 3.87 (ddd, J=7.6, 6.9, 4.8 Hz, 1H), 3.77 (dd, J=14.2, 6.9 Hz, 1H), 2.85 (dd, J=14.4, 9.3 Hz, 1H), 2.36 (dd, J=13.8, 11.8 Hz, 1H), 2.37–2.30 (m, 1H), 2.16 (s, 3H), 2.05–1.90 (m, 2H), 2.05–2.00 (m, 1H), 1.85 (d, J=7.7 Hz, 1H), 1.74 (dd, J=15.3, 11.8 Hz, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.56 (dd, J=15.3, 11.8 Hz, 1H), 1.17 (s, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 200.2, 169.9, 141.4, 128.0, 113.1, 75.9, 65.2, 63.0, 53.2, 36.9, 36.1, 34.6, 29.9, 29.1, 28.9, 20.9, 20.7, 19.6; IR (cm^{-1}, KBr) ν_{max} 2955, 2892, 1742, 1717, 1440; HRMS (FAB, *m*-NBA) calcd for $C_{18}H_{26}O_5$ $[M]^+$: 322.1780, found: 322.1780; Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13; found: C, 66.86; H, 8.30.

4.1.6. Hydroxyketone **17**

To a suspension of potassium carbonate (251.8 mg, 1.82 mmol) in anhydrous methanol (60 mL) was added ketone **16** (393.0 mg, 1.22 mmol) via cannula. The reaction mixture was stirred for 2 h at room temperature and then was added satd NH_4Cl aq. The resulting mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=3/1) gave hydroxyketone **17** (337.0 mg, 99%) as a colorless solid (needle). Compound **17**: mp 103–105 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 4.98 (s, 1H), 3.96–3.93 (m, 2H), 3.90–3.87 (m, 1H), 3.78 (dd, J=13.9, 7.2 Hz, 1H), 3.61 (s, 1H), 2.86 (dd, J=14.5, 9.5 Hz, 1H), 2.47 (dd, J=14.5, 9.4 Hz, 1H), 2.40–2.34 (m, 1H, C8), 2.07–1.97 (m, 2H), 1.89 (ddd, J=18.6, 9.1, 5.4 Hz, 1H), 1.83 (d, J=7.5 Hz, 1H), 1.74 (dd, J=15.2, 11.5 Hz, 1H), 1.66–1.58 (m, 1H), 1.59 (s, 3H), 1.50 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 206.7, 138.9, 130.1, 113.1, 74.6, 65.1, 63.0, 53.3, 36.8, 35.4, 34.3, 30.3, 29.6, 29.5, 20.1, 19.6; IR (cm^{-1}, KBr) ν_{max} 3489, 2890, 2854, 1696, 1474, 1434, 1377; HRMS (FAB, *m*-NBA) calcd for $C_{16}H_{24}O_4$ $[M]^+$: 280.1675, found: 280.1675; Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63; found: C, 68.06; H, 8.71.

4.1.7. TIPS-ketone **19**

To a solution of hydroxyketone **17** (304.7 mg, 1.09 mmol) in anhydrous methylene chloride (22 mL) were added 2,6-lutidine (1.14 mL, 9.78 mmol) and triisopropylsilyl triflate (0.87 mL, 3.26 mmol). The reaction mixture was stirred for 2 h at room temperature and then was added satd $NaHCO_3$ aq. The resulting mixture was extracted with methylene

chloride, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=5/1) and removing triisopropylsilanol by glass tube oven (10 mmHg, 100 °C) afforded TIPS-ketone **19** (441.9 mg, 93%) as a colorless solid (needle). Compound **19**: mp 87–88 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 5.07 (s, 1H), 3.94–3.84 (m, 3H), 3.77 (q, J=7.1 Hz, 1H), 2.70 (dd, J=14.2, 9.1 Hz, 1H), 2.33–2.26 (m, 1H), 2.26 (t, J=14.2 Hz, 1H), 2.04–1.95 (m, 2H), 1.90 (dq, J=18.2, 4.7 Hz, 1H), 1.80 (d, J=8.0 Hz, 1H), 1.73 (dd, J=15.1, 12.1 Hz, 1H), 1.69 (s, 3H), 1.55 (dd, J=15.1, 12.1 Hz, 1H), 1.50 (s, 3H), 1.19 (s, 3H), 1.14–1.04 (m, 3H), 1.05 (d, J=4.7 Hz, 18H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 204.3, 139.8, 130.9, 113.5, 76.7, 65.1, 62.9, 53.6, 36.7, 35.8, 34.3, 30.6, 29.7, 29.0, 20.5, 19.7, 18.0 (6C), 12.3 (3C); IR (cm^{-1}, KBr) ν_{max} 2939, 1714, 1464; Anal. Calcd for $C_{25}H_{44}O_4Si$: C, 68.76; H, 10.16; found: C, 68.61; H, 10.07.

4.1.8. TBS-ketone *18*

To a solution of hydroxyketone **17** (31.5 mg, 0.11 mmol) in anhydrous methylene chloride (5 mL) was added 2,6-lutidine (25.6 μL, 0.22 mmol) and *tert*-butyldimethylsilyl triflate (27.8 μL, 0.12 mmol). The reaction mixture was stirred for 2 h at room temperature and then was added satd $NaHCO_3$ aq. The resulting mixture was extracted with methylene chloride, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=4/1) and removing *tert*-butyldimethylsilanol by glass tube oven (10 mmHg, 60 °C) afforded TBS-ketone **18** (42.6 mg, 98%) as a colorless oil. Compound **18**: ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 4.94 (s, 1H), 3.95–3.84 (m, 3H), 3.76 (dd, J=9.3, 6.8 Hz, 1H), 2.71 (dd, J=14.0, 9.0 Hz, 1H), 2.26 (dd, J=15.0, 11.5 MHz, 2H), 2.05–1.85 (m, 3H), 1.79 (br d, J=7.0 Hz, 1H), 1.71 (dd, J=15.0, 11.5 MHz, 1H), 1.64 (s, 3H), 1.55 (dd, J=15.0, 8.5 Hz, 1H), 1.49 (s, 3H), 1.17 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 204.5, 139.0, 130.9, 113.5, 75.4, 65.1, 62.9, 53.4, 36.7, 35.9, 34.4, 30.8, 29.6, 28.9, 25.8 (3C), 20.4, 19.7, 18.3, −4.7, −4.9; IR (cm^{-1}, neat) ν_{max} 2954, 2883, 2852, 1717, 1470, 1389, 1364, 1252, 1104, 1080, 1033, 979, 838, 775, 670; HRMS (FAB, *m*-NBA) calcd for $C_{22}H_{38}O_4Si$ $[M]^+$: 394.2539, found: 394.2524.

4.1.9. 8-Methyl-TBS-ketone *11*

To a solution of LDA (0.11 mL, 1.5 M solution in cyclohexane, 1.63 mmol) in anhydrous THF (8 mL) at −78 °C, HMPA (0.28 mL, 1.63 mmol) and a solution of TBS-ketone **18** (128.6 mg, 0.32 mmol) in anhydrous THF (5.5 mL) were added and stirred at 0 °C for 1 h. To the reaction mixture, iodomethane (0.20 mL, 3.25 mmol) was added and stirred at room temperature for 3.5 h. The reaction was quenched with satd NH_4Cl aq. The resulting mixture was extracted with ether, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=6/1) provided 8-methyl-TBS-ketone **11** (109.8 mg, 84%) as a colorless solid (needle) and unreacted ketone (11.4 mg, 9%). Compound **11**: mp 63–64 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 4.89 (s, 1H), 3.95–3.92 (m, 2H), 3.86 (q, J=6.7 Hz, 1H), 3.77 (q, J=6.7 Hz, 1H), 2.84 (t, J=6.7 Hz, 1H), 2.31–2.24 (m, 1H), 2.03–1.92 (m, 2H), 1.88–1.81 (m, 1H), 1.77 (d, J=7.3 Hz, 1H), 1.70 (dd, J=15.3, 7.3 Hz, 1H), 1.63 (s, 3H), 1.51 (s, 3H), 1.26 (d, J=15.3 Hz, 1H), 1.17 (s, 3H), 1.02 (d, J=6.7 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 206.5, 139.8, 131.0, 113.6, 76.1, 65.3, 62.9, 53.4, 44.1, 37.2, 36.8, 30.9, 29.6, 29.1, 25.8 (3C), 20.5, 20.2, 19.8, 18.2, −4.8, −5.0; IR (cm^{-1}, film) ν_{max} 2928, 1721, 1470, 1251, 1105, 1035, 1004, 960, 836, 776; HRMS (FAB, *m*-NBA) calcd for $C_{23}H_{40}O_4Si$ $[M]^+$: 408.2696, found: 408.2692.

4.1.10. Ester *22*

Preparation of LDA solution in THF: to a solution of diisopropylamine (120 μL, 0.85 mmol) in THF (1.0 mL) was added 1.6 M solution of *n*-BuLi in *n*-hexane (0.53 mL, 0.85 mmol) at −40 °C, and the mixture was stirred for 30 min at −40 °C. To a solution of TIPS-ketone **19** (37.1 mg, 0.085 mmol) in THF (1.5 mL) were added HMPA (0.3 mL, 1.72 mmol) and LDA solution prepared above at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then methyl cyanoformate (0.13 mL, 1.64 mmol) was added. After further stirring for 2 h at 0 °C, the reaction was quenched with water. The resulting mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=50/1) gave ester **22** (43.1 mg, quant.) as a colorless solid (block). Compound **22**: mp 133 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 5.13 (s, 1H), 3.89–3.77 (m, 5H), 3.66 (s, 3H), 2.30 (d, J=15.3 Hz, 1H), 2.33–2.26 (m, 1H), 2.05–1.96 (m, 1H), 1.99–1.96 (m, 1H), 1.91–1.84 (m, 1H), 1.77 (d, J=7.5 Hz, 1H), 1.66 (s, 3H), 1.59 (dd, J=15.3, 7.5 Hz, 1H), 1.49 (s, 3H), 1.17 (s, 3H), 1.13–1.05 (m, 3H), 1.04 (d, J=4.9 Hz, 18H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 200.2, 171.7, 141.8, 130.0, 112.8, 76.3, 65.2, 62.9, 53.7, 52.3, 50.4, 36.8, 36.4, 30.8, 29.6, 29.3, 20.5, 19.7, 17.9 (6C), 12.1 (3C); IR (cm^{-1}, KBr) ν_{max} 2944, 1752, 1716, 1465; HRMS (FAB, *m*-NBA) calcd for $C_{27}H_{46}O_6Si$ $[M]^+$: 494.3064, found: 494.3064; Anal. Calcd for $C_{27}H_{46}O_6Si$: C, 65.55; H, 9.37; found: C, 65.83; H, 9.64.

4.1.11. Ketoacetal *24*

NaH (60%) dispersion in mineral oil (388.1 mg) was stored in a dried vessel under N_2 gas and was washed with dried hexane in two times. To a suspension of NaH in dimethoxyethane (10 mL) at 0 °C, a solution of ester **22** (394.7 mg, 0.808 mmol) in dimethoxyethane (20 mL) was added via cannula. After stirring at 0 °C for 20 min, 4-iodobutanal dimethylacetal **23**[15] (1.97 g, 10 equiv) in dimethoxyethane (10 mL) was added. The reaction mixture was stirred at room temperature for 15 h. The reaction was quenched with 1 N HCl aq. The

resulting mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=4/1) provided ketoacetal **24** (390.2 mg, 0.65 mmol, 80%) as colorless oil. Compound **24**: ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 5.48 (s, 1H), 4.33 (t, J=5.80 Hz, 1H), 3.84 (m, 2H), 3.81 (td, J=12.7, 4.70 Hz, 2H), 3.63 (s, 3H), 3.31 (s, 3H), 3.28 (s, 3H), 2.33 (m, 1H), 2.14 (d, J=15.3 Hz, 1H), 2.13 (td, J=12.7, 4.50 Hz, 1H), 2.03–1.96 (m, 1H), 1.92–1.83 (m, 2H), 1.89 (d, J=15.3 Hz, 1H), 1.75 (d, J=8.0 Hz, 1H), 1.69 (td, J=12.7, 4.5 Hz, 1H), 1.61 (s, 3H), 1.62–1.50 (m, 3H), 1.38 (s, 3H), 1.33–1.22 (m, 1H), 1.18–1.06 (m, 3H), 1.13 (s, 3H), 1.08 (d, J=7.9 Hz, 9H), 1.06 (d, J=7.9 Hz, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 203.01, 173.50, 138.54, 132.86, 113.84, 104.25, 75.82, 66.05, 62.36, 60.17, 54.58, 52.94, 52.30, 51.69, 46.12, 42.05, 36.84, 32.94, 30.02, 28.92, 28.76, 20.79, 20.25 (3C), 19.76 (3C), 18.12, 18.03, 12.65 (3C); IR (cm^{-1}, neat) ν_{max} 2943, 1727, 1463, 1384, 1225, 1129, 1086; HRMS (FAB, *m*-NBA) calcd for $C_{33}H_{58}O_8SiNa$ $[M+Na]^+$: 633.3799, found: 633.3797.

4.1.12. Ketoaldehyde 25

To a solution of ketoacetal **24** (15.5 mg, 0.025 mmol) in acetone (2.53 mL) and water (0.17 mL), *p*-TsOH·H_2O (6.3 mg, 0.033 mmol) was added. The reaction mixture was allowed to warm at 40 °C, and stirred for 18 h. The reaction was quenched with satd $NaHCO_3$ aq. The resulting mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=2/1) provided ketoaldehyde **25** (13.2 mg, quant.) as a colorless solid (block). Compound **25**: mp 87.0–89.0 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 9.75 (t, J=1.2 Hz, 1H), 5.36 (s, 1H), 3.70 (s, 3H), 2.68 (s, 2H), 2.51 (d, J=8.0 Hz, 1H), 2.51–2.38 (m, 3H), 2.11–2.02 (m, 2H), 1.97–1.84 (m, 3H), 1.69 (s, 3H), 1.60 (quint., J=7.7 Hz, 2H), 1.28 (s, 3H), 1.19 (s, 3H), 1.15–1.05 (m, 3H), 1.07 (d, J=6.1 Hz, 9H), 1.06 (d, J=6.1 Hz, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 210.62, 202.09, 201.34, 171.48, 141.41, 133.14, 75.35, 62.38, 61.17, 52.42, 44.04, 38.03, 36.63, 28.83, 28.27, 27.75, 20.89, 19.76, 18.08 (3C), 17.98 (3C), 17.64, 14.15, 12.52 (3C); IR (cm^{-1}, KBr) ν_{max} 2940, 2864, 1721, 1688, 1462, 1390, 1242, 1148, 1088; HRMS (FAB, *m*-NBA) calcd for $C_{29}H_{48}O_6SiNa$ $[M+Na]^+$: 543.3118, found: 543.3113.

4.1.13. Hydrazone 26

To a solution of ketoaldehyde **25** (10.0 mg, 19.2 μmol) in anhydrous benzene (5 mL), 2,4-dinitrophenylhydrazine (containing 50% of water, 9.1 mg, 23.0 μmol) and *p*-TsOH·H_2O (4.4 mg, 23.0 μmol) were added. The reaction mixture was allowed to warm at reflux temperature, and stirred for 6 h. The reaction was quenched with satd $NaHCO_3$ aq. The resulting mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=5/1) provided hydrazone **26** (12.9 mg, 96%) as a yellow crystal (platelet). Compound **26**: mp 141–143 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 11.04 (s, 1H), 9.12 (d, J=2.6 Hz, 1H), 8.29 (dd, J=9.6, 2.6 Hz, 1H), 7.95 (d, J=9.6, 2.6 Hz, 1H), 7.55 (m, 1H), 5.39 (s, 1H), 3.73 (s, 3H), 2.77 (d, J=12.5 Hz, 1H), 2.68 (d, J=12.5 Hz, 1H), 2.53 (d, J=7.1 Hz, 1H), 2.45 (dd, J=12.5, 7.1 Hz, 2H), 2.12–1.91 (m, 5H), 1.70 (s, 3H), 1.68–1.60 (m, 3H), 1.32 (s, 3H), 1.21 (s, 3H), 1.15–1.01 (m, 3H), 1.08 (d, J=5.8 Hz, 9H), 1.07 (d, J=5.8 Hz, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 210.4, 201.4, 171.4, 151.8, 145.1, 141.4, 137.8, 133.3, 129.9, 128.8, 123.5, 116.6, 75.3, 64.8, 62.3, 61.2, 52.5, 45.2, 36.6, 32.7, 28.9, 28.4, 27.8, 21.6, 20.9, 20.0, 18.0 (3C), 17.9 (3C), 12.5 (3C); IR (cm^{-1}, neat) ν_{max} 3450 (br), 3287, 2943, 1722, 1617, 1515, 1434, 1329, 1138, 1078; HRMS (FAB, *m*-NBA) calcd for $C_{35}H_{52}O_9N_4SiNa$ $[M+Na]^+$: 723.3401, found: 723.3387; Anal. Calcd for $C_{35}H_{52}N_4O_9Si$: C, 59.98; H, 7.48; N, 7.99; found: C, 59.39; H, 7.58; N, 7.80.

4.1.14. Aldol 27

Preparation of 0.2 M LDA solution in THF: to a solution of diisopropylamine (135 μL, 0.97 mmol) in THF (4 mL) was added 1.6 M solution of *n*-BuLi in *n*-hexane (0.6 mL, 0.96 mmol) at −40 °C and the mixture was stirred for 30 min at −40 °C. To a solution of ketoaldehyde **25** (5.3 mg, 10 μmol) in THF (0.5 mL), 0.2 M LDA solution prepared above was added at −78 °C. The reaction mixture was stirred for 2 h at −78 °C. The reaction was quenched with satd NH_4Cl aq. The resulting mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (SiO_2, hexane/AcOEt=2/1) provided aldol **27** (3.6 mg, 0.79 mmol, 56%) as colorless oil. Compound **27**: colorless oil; ^{1}H NMR (600.17 MHz, $CDCl_3$) δ 5.37 (s, 0.5H)+5.35 (s, 0.5H), 4.06 (m, 1H), 3.71 (s, 1.5H)+3.70 (s, 1.5H), 3.12 (s, 0.5H)+3.05 (s, 0.5H), 2.67 (d, J=15.5 Hz, 2H), 2.63 (dd, J=12.7, 2.6 Hz, 0.5H)+2.60 (dd, J=12.7, 2.6 Hz, 0.5H), 2.56–2.52 (m, 2H), 2.47 (t, J=15.5 Hz, 1H), 2.13–1.96 (m, 2H), 1.91–1.81 (m, 2H), 1.71 (s, 1.5H)+1.70 (s, 1.5H), 1.66–1.58 (m, 2H),1.25 (s, 3H), 1.20 (s, 3H), 1.09–1.06 (m, 21H).; ^{13}C NMR (125.78 MHz, $CDCl_3$) δ 210.9, 209.8, 171.7, 141.3, 133.1+133.09, 75.42+75.36, 67.1+66.7, 62.49+62.48, 61.30+61.17, 52.39+52.36, 50.00+49.79, 45.66+45.27, 36.6, 36.47+36.12, 30.80, 28.83+28.80, 28.2+27.8, 20.93+20.90, 20.8+20.5, 19.9, 18.0 (6C), 12.5 (3C); IR (cm^{-1}, neat) ν_{max} 3480 (br), 2928, 2865, 2252, 1714, 1463, 1366, 1237, 1148, 1067, 914, 883, 845, 796, 734, 682; HRMS (FAB, *m*-NBA) calcd for $C_{29}H_{48}O_6SiNa$ $[M+Na]^+$: 543.3118, found: 543.3116.

4.2. Crystal structure analysis

Measurements were made on a Rigaku R-AXIS RAPID Imaging Plate diffractometer with Mo Kα radiation at 296 K. Compound **14**: $(C_{16}H_{26}O_4)\times2$, a colorless prism (0.50×0.30×0.25 mm), triclinic, space group *P*-1 (#2), Z=2, a=11.2586(15) Å, b=15.0787(19) Å, c=10.2056(16) Å, V=1541.8(4) Å^3, ρ_{calcd}=1.216 g cm^{-3}. Of 6569 reflections up to 2θ=55.0°,

6569 were independent (R_{int}=0.065) and 5038 with $I>2\sigma(I)$. The structure was solved with direct methods and refined with full matrix against all F^2 data. Hydrogen atoms were calculated in 'riding' positions. wR=0.1783 and R=0.1413. CCDC file number is 671220. Compound **22**: $C_{27}H_{46}O_6Si$, colorless block (0.70×0.66×0.44 mm), orthorhombic, space group $Pca2_1$ (#29), Z=4, a=25.993(7) Å, b=8.6398(16) Å, c=12.694(3) Å, V=2850.7(11) Å^3, ρ_{calcd}=1.153 g cm^{-3}. Of 25,559 reflections up to 2θ=55.0°, 6472 were independent (R_{int}=0.019) and 4860 with $I>2\sigma(I)$. The structure was solved and refined in an analogous manner to **14**. wR=0.1819 and R=0.0663. CCDC file number is 671221. Compound **26**: measured at 193 K, $C_{35}H_{52}N_4O_9Si$, a yellow platelet (0.04×0.04×0.02 mm), monoclinic, space group $P2_1/a$ (#14), Z=4, a=14.4321(16) Å, b=9.1847(10) Å, c=28.177(3) Å, V=3685.6(7) Å^3, ρ_{calcd}=1.263 g cm^{-3}. Of 26,227 reflections up to 2θ=55.0°, 6463 were independent (R_{int}=0.133) and 1968 with $I>2\sigma(I)$. The structure was solved and refined in an analogous manner to **14**. wR=0.1130 and R=0.0542. CCDC file number is 671222.

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