Catalytic Aldol Reaction with Sm(HMDS)$_3$ and Its Application for the Introduction of a Carbon–Carbon Triple Bond at C-13 in Prostaglandin Synthesis

Hiroaki Sasai, Shigeru Arai, and Masakatsu Shibasaki*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

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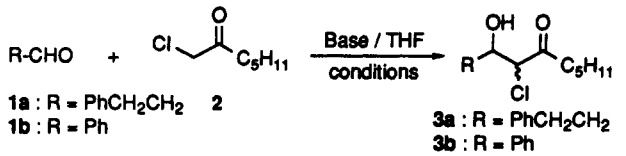
Recently, considerable work concerning new reactions mediated by rare earth metal reagents has been reported.[1] We too have investigated the reactivity of rare earth metal alkoxides as basic reagents. We have found that rare earth metal alkoxides such as La$_3$(O-*t*-Bu)$_9$, Y$_3$(O-*t*-Bu)$_8$Cl, and Y$_5$(O-*i*-Pr)$_{13}$O can be used as bases in catalytic aldol, cyanosilylation, and nitroaldol reactions.[2a] Furthermore, we have succeeded in developing several asymmetric BINOL–rare earth metal complexes, which have been found to be quite effective in catalytic asymmetric nitroaldol reactions.[2] In reactions that employ metal alkoxides as catalysts, the alkoxide anions generated from these reagents abstract acidic protons from substrates. Therefore, the use of rare earth alkoxides as basic reagents is limited to acidic substrates whose pK_a values are lower than those of alcohols. The fact that hexamethyldisilazane is a weaker acid than alcohols suggests that rare earth hexamethyldisilazides would be more useful basic reagents than rare earth alkoxides. Indeed, hexamethyldisilazides of several alkaline metals have been utilized as basic reagents in various reactions. Thus, we have examined the reactivity of rare earth hexamethyldisilazides as basic reagents. Among rare earth hexamethyldisilazides, known Sm(HMDS)$_3$[3] (HMDS: hexamethyldisilazide), readily obtainable from inexpensive SmCl$_3$ and NaHMDS, seemed most promising.[4] Although almost all rare earth metal alkoxides exist as oligomers because of their high coordination ability,[5] Sm(HMDS)$_3$ is thought to exist as a monomer owing to the steric hindrance of the bulky HMDS group.[6] This monomeric character was also expected to be quite beneficial in the preparation of a single asymmetric Sm complex[7] from Sm(HMDS)$_3$ and to give more possibilities for developing an effective asymmetric base. Herein, we report a catalytic aldol reaction with Sm(HMDS)$_3$ and its application to the synthesis of prostacyclin analogs **11a** and **11b**, which have a carbon–carbon triple bond at C-13 (PG numbering). This is the first example of the use of Sm(HMDS)$_3$ as a basic catalyst.

Table 1. Catalytic Aldol Reaction of α-Chloro Ketone 2 with Aldehyde 1[a]



1a : R = PhCH$_2$CH$_2$ **2**
1b : R = Ph

3a : R = PhCH$_2$CH$_2$
3b : R = Ph

entry	aldehyde	base (mol %)	temp (°C)	time (h)	yield of **3** (%)
1	**1a**	Sm(HMDS)$_3$ (10)	−30	13	84
2	**1b**	Sm(HMDS)$_3$ (10)	−30	18	90
3	**1b**	La(O-*i*-Pr)$_3$ (10)	−30	24	56
4	**1b**	Sm(O-*i*-Pr)$_3$ (10)	−30	24	47
5	**1a**	LDA (100)	−78	1	18

[a] Two equivalents of **2** was utilized in all the reactions except entry 5 (1.0 equiv).

Initial work focused on the aldol reactions of α-chloro ketone **2** with aldehydes **1a** and **1b**. We were pleased to find that the reaction of **2** with hydrocinnamaldehyde **1a** in THF containing 10 mol % of Sm(HMDS)$_3$ at −30 °C proceeded smoothly, giving cross-coupling product **3a** in 84% yield as a mixture of diastereomers. No homocoupling products were obtained. Benzaldehyde (**1b**) was found to afford **3b** in 90% yield. These results clearly indicated that Sm(HMDS)$_3$ was a strong enough base for catalytic aldol reactions with α-chloro ketones. In addition, it is noteworthy that under the reaction conditions described above none of the corresponding epoxides or dehydration products were detected. In order to compare the reactivity of Sm(HMDS)$_3$ with that of rare earth metal alkoxides, the aldol reaction of α-chloro ketone **2** with benzaldehyde (**1b**) mediated by Sm(O-*i*-Pr)$_3$[8] or La(O-*i*-Pr)$_3$[9] was also carried out. Under conditions similar to those described above, these reactions were relatively slow, giving **3b** in only 47 and 56% yields, respectively.[10] The results are summarized in Table 1. It should be relatively simple to convert aldol products **3** to *trans*-epoxides,[11] *Z*-α-chloro enones,[12] and acetylenic compounds.[12]

(1) For carbon–carbon bond-forming reactions, see: (a) Molander, G. A.; Hoberg, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 3123. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Weghe, P. V.; Collin, J. *Tetrahedron Lett.* **1993**, *34*, 3881. (d) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392, and references cited therein. For carbon–nitrogen bond-forming reactions, see: (e) Gagne, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108. (f) Gagne, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275. For Lewis acids, see: (g) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815. (h) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1985**, *26*, 2507. (i) Gu, J.-H.; Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 1465. (j) Matsubara, S.; Takai, T.; Utimoto, K. *Chem. Lett.* **1991**, 1447. For reductions, see: (k) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945. (l) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (m) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447. (n) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906.

(2) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851. (c) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 855. (d) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657. (e) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372.

(3) Bradley, D. C.; Ghotra, J. S.; Hart, F. A. *J. Chem. Soc., Dalton Trans.* **1973**, 1021.

(4) Sm(HMDS)$_3$ was prepared according to the procedure of Bradley *et al.* (see ref 3) as follows: To a stirred solution of anhyd SmCl$_3$ (2.57 g, 10 mmol) in THF (30 mL) was added a solution of NaHMDS (5.50 g, 30 mmol) in THF (85 mL) under an argon atmosphere. After being stirred for 23 h at rt, the suspension was concentrated. The residue was extracted three times with pentane (total 100 mL) under an argon atmosphere, and the combined pentane extracts were concentrated to give a pale yellow solid. The crude hexamethyldisilazide was sublimed at 100–130 °C under 10^{-4} mmHg to give 2.23 g (35% yield) of Sm(HMDS)$_3$ as a pale yellow solid. Other inexpensive rare earth chlorides (LaCl$_3$, PrCl$_3$, NdCl$_3$) gave none of the corresponding hexamethyldisilazides because of the low reactivity of the starting chlorides.

(5) For oligomeric rare earth metal complexes, see: (a) Bradley, D. C.; Chudzynska, H.; Hursthouse, M. B.; Motevalli, M. *Polyhedron* **1991**, *10*, 10. (b) Mehrotra, R. C.; Singh, A.; Tripathi, U. M. *Chem. Rev.* **1991**, *91*, 1287, and references cited therein.

(6) For other monomeric rare earth metal complexes, see: Hitchcock, P. B.; Lappert, M. F.; Smith, R. G.; Bartlett, R. A.; Power, P. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1007.

(7) It appears that conversion of an oligomeric rare earth metal complex to a single asymmetric catalyst is difficult.

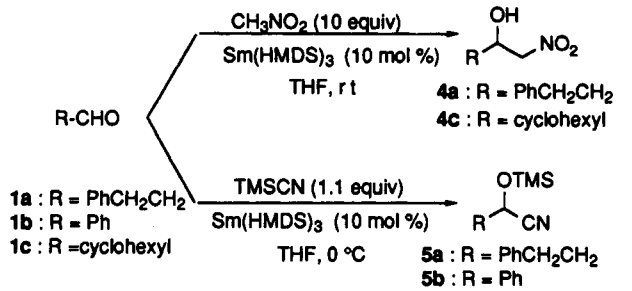
(8) Prepared from Sm metal and *i*-PrOH in the presence of HgCl$_2$ (0.01 mol %/g-atom of Sm). See, Vaughn, J. W.; Seiler, G. J.; Johnson, M. W.; Traister, G. L. *Inorg. Chem.* **1970**, *9*, 2786.

(9) Purchased from Soekawa Chemical Co., Ltd., Tokyo, Japan.

(10) The lower yields could also be ascribed to the structural difference of the intermediary oligomeric rare earth enolates.

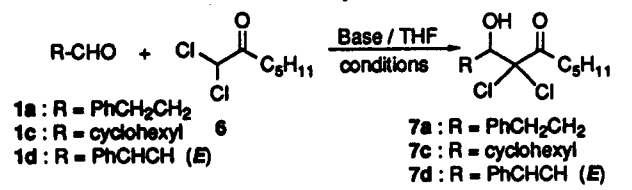
0022-3263/94/1959-2661$04.50/0

Table 2. Catalytic Nitroaldol and Cyanosilylation Reactions



entry	aldehyde	nucleophile	time (h)	yield of 4 or 5 (%)
1	1a	CH_3NO_2	3	98
2	1c	CH_3NO_2	25	100
3	1a	TMSCN	1.5	95
4	1b	TMSCN	4	100

Table 3. Catalytic Aldol Reaction of α,α-Dichloro Ketone 6 with Aldehyde 1



entry	aldehyde	base (mol %)	temp (°C)	time (h)	yield of 7 (%)
1	1a	$Sm(HMDS)_3$ (10)	−50	64	100
2	1c	$Sm(HMDS)_3$ (10)	−30	42	58
3	1d	$Sm(HMDS)_3$ (10)	−30	69	50
4	1a	$Zr(O\text{-}t\text{-}Bu)_4$ (280)	−50	2	54
5	1a	$HN(TMS)_2$ (100)	rt	57	0[a]
6	1a	NaO-t-Bu (10)	−50	23	79
7	1a	LDA (100)	−78	0.5	67

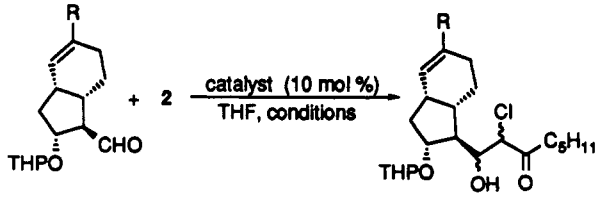
[a] No reaction occurred.

Nitroaldol reactions and cyanosilylation reactions also proceeded smoothly when a catalytic amount of $Sm(HMDS)_3$ (10 mol %) was used. The results are summarized in Table 2.

The aldol reaction with dichloro ketone **6**, which is more acidic than **2**, was further investigated. We expected this reaction to proceed at an even lower temperature than the reaction of α-chloro ketone **2**. In fact, the aldol reaction with dihydrocinnamaldehyde (**1a**), dichloro ketone **6**, and a catalytic amount of $Sm(HMDS)_3$ (10 mol %) in THF was found to proceed cleanly even at −50 °C to afford coupling product **7a** in quantitative yield. The results are summarized in Table 3. It is noteworthy that the use of stoichiometric quantities of $Zr(O\text{-}t\text{-}Bu)_4$[13] and $HN(TMS)_2$ gave **7a** in only 54 and 0% yields, respectively. Furthermore, the use of LDA as a base afforded **7a** in only 67% yield, and the use of NaO-t-Bu furnished **7a** in 79% yield.

Having established that $Sm(HMDS)_3$ is a useful basic catalyst for aldol reactions with either α-chloro ketones or α,α-dichloro ketones, for nitroaldol reactions and for cyanosilylation reactions, we made an effort to apply this methodology, in particular the aldol reaction, to the synthesis of bioactive molecules. It is well known that Z-α-chloro enones are excellent precursors for the preparation of acetylenic ketones,[12] thereby offering effective synthetic routes to prostaglandin analogs with enhanced metabolic stability.[14] We have already reported that prostaglandin analogs of this type can be synthesized by means of aldol reactions between aldehydes and α-bromo ketones in the presence of stoichiometric quantities of $Zr(O\text{-}t\text{-}Bu)_4$.[13] After several attempts, we were pleased to find that treatment of aldehyde **8a**[15] with α-chloro ketone **2** in THF containing 10 mol % of $Sm(HMDS)_3$ at −30 °C for 25 h gave cross coupling product **9a** in 98% yield as a mixture of diastereomers (Table 4). In this case, LiHMDS was also examined as a base catalyst (37 mol %). However, the strong basicity of LiHMDS was found to cause the decomposition of both **2** and **8a**. As shown in Scheme 1, the cross-coupling products **9a** and **9b** were then readily converted into Z-α-chloro enones **10a** and **10b**, respectively, via the corresponding mesylates. Compounds **10a** and **10b** are the key intermediates for the synthesis of prostacyclin analogs **11a** and **11b**, which have a triple bond at C-13.

Table 4. Catalytic Aldol Reaction of 2 with Intermediate 8 for Prostacyclin Analog

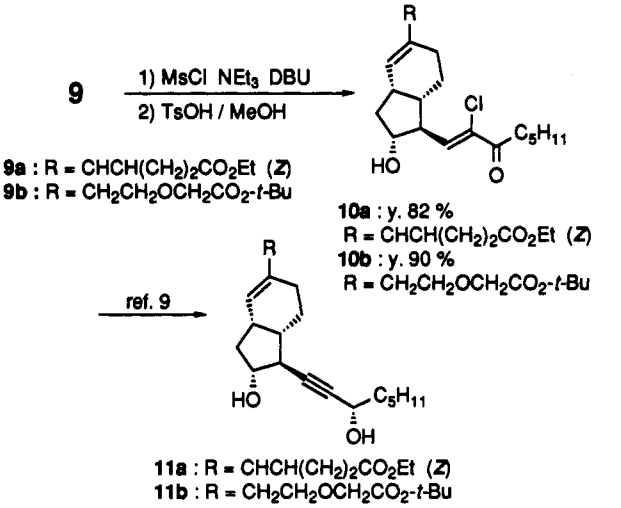


8a : R = $CHCH(CH_2)_2CO_2Et$ (Z)
8b : R = $CH_2CH_2OCH_2CO_2$-t-Bu
9a : R = $CHCH(CH_2)_2CO_2Et$ (Z)
9b : R = $CH_2CH_2OCH_2CO_2$-t-Bu

entry	aldehyde	catalyst	temp (°C)	time (h)	yield of 9 (%)
1	8a	$Sm(HMDS)_3$	−30	25	9a:98[a]
2	8b	$Sm(HMDS)_3$	−30	6	9b:98[a]
3	8b	$Sm(HMDS)_3$	−30	42	9b:75[b]
4	8a	$Sm(HMDS)_3$	−40	50	9a:67[b]
5	8b	$La(O\text{-}i\text{-}Pr)_3$	−30	30	9b:60[b]

[a] Five equivalents of **2** was utilized. [b] A THF solution of **2** (2.0 equiv) was gradually added over 7–10 h by syringe pump.

Scheme 1. Conversion of 9 to Prostacyclin Analog 11



(11) Mukaiyama, T.; Haga, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1601.
(12) Narita, S.; Takahashi, A.; Sato, H.; Aoki, T.; Yamada, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 4041, and references cited therein.
(13) Sasai, H.; Kirio, Y.; Shibasaki, M. *J. Org. Chem.* **1990**, *55*, 5306.
(14) Takahashi, A.; Shibasaki, M. *J. Org. Chem.* **1988**, *53*, 1227, and references cited therein.
(15) (a) Takahashi, A.; Shibasaki, M. *Tetrahedron Lett.* **1987**, *28*, 1893. (b) Shibasaki, M.; Takahashi, A.; Aoki, T.; Sato, H.; Yamada, S.; Kudo, M.; Kogi, K.; Narita, S. *Chem. Pharm. Bull.* **1992**, *40*, 279.

In conclusion, we have found that readily available Sm(HMDS)$_3$ is quite useful as a basic reagent for catalytic aldol reactions with either α-chloro ketones or α,α-dichloro ketones, for catalytic nitroaldol and for catalytic cyanosilylation reactions. Furthermore, using this reagent, we have developed an efficient synthetic route to a prostaglandin analog with a triple bond at C-13. Application of Sm(HMDS)$_3$ to development of new asymmetric catalysts is under investigation.[16]

Experimental Section

^{1}H and ^{13}C NMR spectra were measured at 270 or 400 MHz with Me_4Si as an internal reference and $CDCl_3$ as the solvent. All solvents were dried prior to use.

General procedure for the aldol reaction: **2-Chloro-1-hydroxy-1-phenyl-3-octanone (3b).** To a stirred solution of benzaldehyde (**1b**) (24 μL, 0.24 mmol) and 1-chloro-2-heptanone (**2**) (69.5 mg, 0.48 mmol) in THF (1.2 mL) was added slowly a solution of Sm(HMDS)$_3$ (0.024 mmol) in THF (1.2 mL) at −30 °C under an argon atmosphere. After stirring for 18 h, the mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (12 mL × 3). The combined organic layers were dried over anhyd Na_2SO_4. Removal of the solvent and flash column chromatography (silica gel, 30:1 hexane–EtOAc) gave desired aldol adduct **3b** (55.1 mg, 90%) as a colorless oil: ^{1}H NMR δ 0.86 (t, J = 7.0 Hz, 0.58 × 3H), 0.89 (t, J = 7.0 Hz, 0.42 × 3H), 1.10–1.42 (m, 4H), 1.44–1.68 (m, 2H), 2.32–2.78 (m, 2H), 2.89 (d, J = 4.0 Hz, 0.42 × 1H), 3.02 (d, J = 4.4 Hz, 0.58 × 1H), 4.34 (d, J = 8.1 Hz, 0.58 × 1H), 4.44 (d, J = 5.1 Hz, 0.42 × 1H), 5.05 (dd, J = 8.1, 4.4 Hz, 0.58 × 1H), 5.20 (dd, J = 5.1, 4.0 Hz, 0.42 × 1H), 7.22–7.48 (m, 5H); IR (neat) 3472, 1718 cm^{-1}; MS m/z 256, 254 (M$^+$), 219, 201, 148, 107 (base peak); HRMS calcd for $C_{14}H_{19}ClO_2$ 254.1073, found 254.1048.

4-Chloro-3-hydroxy-1-phenyl-5-decanone (3a). By means of the general procedure for the aldol reaction, aldehyde **1a** (13 μL 0.1 mmol) gave desired product **3a** (23.8 mg, 84%): ^{1}H NMR δ 0.90 (t, J = 6.6 Hz, 3H), 1.23–1.42 (m, 4H),1.48–1.74 (m, 2H), 1.77–1.88 (m, 1H), 1.90–2.18 (m, 1H), 2.32–3.00 (m, 5H), 3.98–4.18 (m, 1H), 4.18 (d, J = 8.1 Hz, 0.56 × 1H), 4.22 (d, J = 5.1 Hz, 0.44 × 1H), 7.15–7.38 (m, 5H); IR (neat) 3460, 1716 cm^{-1}; MS m/z 284, 282 (M$^+$), 266, 264, 247, 229, 134 (base peak); HRMS calcd for $C_{16}H_{23}ClO_2$ 282.1386, found 282.1393. Anal. Calcd for $C_{16}H_{23}ClO_2$: C, 66.01; H, 7.52. Found: C, 65.92; H, 7.58.

General procedure for the nitroaldol reaction: **1-Nitro-4-phenyl-2-butanol (4a).** To a stirred solution of dihydrocinnamaldehyde (**1a**) (13 μL, 0.1 mmol) and nitromethane (54 μL, 1.0 mmol) in THF (0.1 mL) at rt was added a solution of Sm(HMDS)$_3$ (0.01 mmol) in THF (0.5 mL) under an argon atmosphere. After stirring for 3 h, the mixture was quenched with a NH_4Cl solution and extracted with ethyl acetate (12 mL × 3). The combined extracts were dried over anhyd Na_2SO_4. Removal of the solvent and preparative TLC (silica gel, 5:1 hexane–EtOAc) gave desired nitroaldol adduct **4a** (19.1 mg, 98%): ^{1}H NMR δ 1.65–1.96 (m, 2H), 2.58 (d, J = 4.0 Hz, 1H), 2.68–2.72 (m, 2H), 4.18–4.45 (m, 3H), 7.08–7.40 (m, 5H); IR (KBr) 3431, 1545, 1385 cm^{-1}; MS m/z 195 (M$^+$), 130, 105, 91 (base peak); HRMS calcd for $C_{10}H_{13}NO_3$ 195.0896, found 195.0900; mp 87.5–88 °C.

1-Cyclohexyl-2-nitroethanol (4c). By means of the general procedure for the nitroaldol reaction, aldehyde **1c** (12 μL, 0.1 mmol) gave desired product **4c** (17.3 mg, 100%): ^{1}H NMR δ 1.00–1.40 (m, 5H), 1.41–1.58 (m, 1H), 1.60–1.93 (m, 5H), 2.40 (d, J = 5.0 Hz, 1H), 4.08–4.22 (m, 1H), 4.38–4.58 (m, 2H); IR (neat) 3447, 1554, 1383 cm^{-1}; MS m/z 174 (M + H$^+$), 156, 126, 109, 99, 83, 55 (base peak); HRMS calcd for $C_8H_{16}NO_3$ 174.1130, found 174.1134.

General procedure for the cyanosilylation reaction: **4-Phenyl-2-[(trimethylsilyl)oxy]butyronitrile (5a).** To a stirred solution of dihydrocinnamaldehyde (**1a**) (13 μL, 0.1 mmol) and trimethylsilyl cyanide (15 μL, 0.11 mmol) in THF (0.1 mL) at 0 °C was added a solution of Sm(HMDS)$_3$ (0.01 mmol) in THF (0.5 mL) under an argon atmosphere. After stirring for 90 min, the mixture was diluted with Et_2O and filtered through Celite. Removal of the solvent gave desired product **5a** (22.4 mg, 95%): ^{1}H NMR δ 0.20 (s, 9H), 2.12 (dt, J = 6.6, 8.4 Hz, 2H), 2.80 (t, J = 8.4 Hz, 2H), 4.79 (t, J = 6.6 Hz, 1H), 7.10–7.38 (m, 5H); ^{13}C NMR δ 140.2, 128.9, 128.7, 126.7, 120.2, 61.0, 38.0, 30.9, 0.0; IR (neat) 2958, 2236 cm^{-1}; MS m/z 233 (M$^+$), 218, 143 (base peak). Anal. Calcd for $C_{13}H_{19}NOSi$: C, 66.91; H, 8.20; N, 6.00. Found: C, 67.02; H, 7.93; N, 5.84.

2-Phenyl-2-[(trimethylsilyl)oxy]acetonitrile (5b). By means of the general procedure for the cyanosilylation reaction, aldehyde **1b** (10 μL, 0.1 mmol) gave desired product **5b** (19.5 mg, 100%). Spectral data were compatible with those reported[17] previously for this compound.

4,4-Dichloro-3-hydroxy-1-phenyl-5-decanone (7a). By means of the general procedure for the aldol reaction, aldehyde **1a** (16 μL, 0.12 mmol) gave desired product **7a** (42.1 mg, 100%): ^{1}H NMR δ 0.90 (t, J = 7.0 Hz, 3H), 1.25–1.42 (m, 4H), 1.60–1.75 (m, 2H), 1.95–2.05 (m, 1H), 2.18–2.27 (m, 1H), 2.70–2.80 (m, 1H), 2.90 (dt, J = 7.3, 1.5 Hz, 2H), 2.94–3.04 (m, 1H), 4.22 (dd, J = 10.1, 2.0 Hz, 1H), 7.18–7.48 (m, 5H); IR (neat) 3470, 1725 cm^{-1}; MS m/z 320, 318, 316 (M$^+$), 302, 300, 298, 283, 281, 134 (base peak); HRMS calcd for $C_{16}H_{22}Cl_2O_2$ 316.0969, found 316.0997.

2,2-Dichloro-1-cyclohexyl-1-hydroxy-3-octanone (7c). By means of the general procedure for the aldol reaction, aldehyde **1c** (19 μL, 0.16 mmol) gave desired product **7c** (27.2 mg, 58%): ^{1}H NMR δ 0.91 (t, J = 5.9 Hz, 3H), 1.08–1.30 (m, 10H), 1.62–2.16 (m, 8H), 2.65 (d, J = 6.8 Hz, 1H), 2.91 (t, J = 7.1 Hz, 2H), 4.07 (dd, J = 7.1, 6.8 Hz, 1H); IR (neat) 3468, 1726 cm^{-1}; MS m/z 299, 297, 295 (M$^+$), 281, 279, 277, 261, 259, 82 (base peak); HRMS, calcd for $C_{14}H_{25}Cl_2O_2$ 295.1224, found 295.1209.

(*E*)-4,4-Dichloro-3-hydroxy-1-phenyl-1-decen-5-one (7d). By means of the general procedure for the aldol reaction, aldehyde **1d** (19 μL, 0.15 mmol) gave desired product **7d** (28.7 mg, 50%): ^{1}H NMR δ 0.91 (t, J = 6.9 Hz, 3H), 1.25–1.48 (m, 4H), 1.62–1.78 (m, 2H), 2.95 (t, J = 7.3 Hz, 2H), 3.02 (d, J = 5.9 Hz, 1H), 4.98 (ddd, J = 6.1, 5.9, 1.3 Hz, 1H), 6.38 (dd, J = 15.8, 6.1 Hz, 1H), 6.88 (dd, J = 15.8, 1.3 Hz, 1H), 7.22–7.48 (m, 5H); IR (KBr) 3649, 1715 cm^{-1}; MS m/z 318, 316, 314 (M$^+$), 237, 227, 133 (base peak); HRMS calcd for $C_{16}H_{20}Cl_2O_2$ 314.0842, found 314.0839. Anal. Calcd for $C_{16}H_{20}Cl_2O_2$: C, 60.97; H, 6.39. Found: C, 61.03; H, 6.37; mp 41–43 °C.

General procedure for the aldol reaction for PG synthesis: **(1*R*,6*S*,7*S*,8*R*)-7-(2-Chloro-1-hydroxy-3-oxooctyl)-3-[(*Z*)-4-(ethoxycarbonyl)-1-butenyl]-8-(tetrahydropyranyloxy)-bicyclo[4.3.0]non-2-ene (9a).** To a solution of **8a** (13.2 mg, 0.035 mmol) and Sm(HMDS)$_3$ (0.0035 mmol) in THF (0.1 mL) at −40 °C was gradually added a solution of **2** (10.3 mg, 0.07 mmol) in THF (0.2 mL) by syringe pump over 10 h under an argon atmosphere. After stirring for 50 h, the mixture was quenched with a saturated NH_4Cl solution and extracted with CH_2Cl_2 (3 mL × 5). The combined extracts were dried over anhydrous Na_2SO_4. Removal of the solvent and flash column chromatography (silica gel, 20:1 hexane–acetone, 1% NEt_3) gave a mixture of desired aldol adduct **9a** (12.2 mg, 67%): ^{1}H NMR δ 0.90 (t, J = 6.6 Hz, 3H), 1.30 (t, J = 6.9 Hz, 3H), 1.08–1.41 (m, 6H), 1.42–1.94 (m, 8H), 1.95–2.62 (m, 7H), 2.35 (t, J = 7.3 Hz, 2H), 2.62–2.80 (m, 2H), 2.94–3.01 (br s, 0.33 × 1H), 3.13 (d, J = 6.9 Hz, 0.67 × 1H), 3.45–3.58 (m, 1H), 3.78–3.98 (m, 1H), 4.00–4.13 (m, 2H), 4.13 (q, J = 6.9 Hz, 2H), 4.28–4.42 (m, 0.60 × 1H), 4.54 (br s, 0.65 × 1H), 4.61–4.68 (m, 0.40 × 1H), 4.79 (br s, 0.35 × 1H), 5.10–5.23 (m, 1H), 5.58 (br s 1H), 5.80, (br d, J = 11.6 Hz, 1H); IR (neat) 3583, 1734 cm^{-1}; MS m/z 428, 426 (M + H$^+$ − $C_6H_{11}O$), 410, 408, 99, 85 (base peak). Anal. Calcd for $C_{29}H_{45}ClO_6$: C, 66.33; H, 8.64. Found: C, 66.09; H, 8.34.

(1*R*,6*S*,7*S*,8*R*)-3-[4-(*tert*-Butoxycarbonyl)-3-oxabutyl]-7-(2-chloro-1-hydroxy-3-oxooctyl)-8-(tetrahydropyranyloxy)-bicyclo[4.3.0]non-2-ene (9b). By means of the general procedure for the aldol reaction, aldehyde **8b** (15.5 mg, 0.039 mmol) gave desired product **9b** (15.8 mg, 75%): ^{1}H NMR δ 0.90 (t, J = 6.9 Hz, 3H), 1.20–1.38 (m, 4H), 1.48 (s, 9H), 1.40–2.10 (m, 16 H), 2.06–2.46 (m, 3H), 2.50–2.90 (m, 2H), 2.99 (d, J = 5.3 Hz, 0.5

(16) The asymmetric catalyst prepared from Sm(HMDS)$_3$ and 1 equiv of BINOL didn't give satisfactory results in the synthesis of **7**.

(17) Costa, D. J.; Boutin, N. E.; Riess, J. G. *Tetrahedron* **1974**, *30*, 3793.

× 1H), 3.11 (d, J = 7.3 Hz 0.5 × 1H), 3.40–3.55 (m, 1H), 3.57 (t, J = 7.3 Hz, 2H), 3.85–3.96 (m, 1H), 3.95 (s, 2H), 3.96–4.19 (m, 2H), 4.22–4.30 (m, 1H), 4.50–4.80 (m, 1H), 5.42 (br s, 1H); IR (neat) 3852, 1735, 1715 cm^{-1}; MS m/z 474, 472 (M + H^+ – THP), 456, 454, 99, 85 (base peak), 57. Anal. Calcd for $C_{30}H_{49}ClO_7$: C, 64.68; H, 8.86. Found: C, 64.76; H, 9.01.

General procedure for conversion of **9** to hydroxy enone **10**: **(1*R*,6*S*,7*S*,8*R*)-7[(*Z*)-2-Chloro-3-oxo-1-octenyl)]-3-[(*Z*)-4-(ethoxycarbonyl)-1-butenyl)]-8-hydroxybicyclo[4.3.0]non-2-ene (10a).** To a stirred solution of aldol adduct **9a** (15.3 mg, 0.029 mmol) in CH_2Cl_2 (0.97 mL) at –50 °C were added NEt_3 (81 μL, 0.58 mmol) and methanesulfonyl chloride (45 μL, 0.58 mmol) under an argon atmosphere. The reaction mixture was allowed to warm to –10 °C over a period of 2 h. DBU (87 μL, 0.58 mmol) was then added, and the reaction mixture was warmed up to 10 °C. After stirring for 2 h, the reaction mixture was quenched with phosphate buffer (pH = 7.0) and extracted with CH_2Cl_2 (5 mL × 3). The combined extracts were dried over anhyd Na_2SO_4, and the solvent was removed. The residue thus obtained was dissolved in MeOH (1.5 mL), and $TsOH·H_2O$ (11.0 mg, 0.58 mmol) was added at rt. After stirring for 30 min, the mixture was quenched with phosphate buffer (pH = 7.0) and extracted with CH_2Cl_2 (5 mL × 3). The combined extracts were dried over anhyd Na_2SO_4. Removal of the solvent and column chromatography (silica gel 1:2 hexane–Et_2O) gave desired product **10a** (10.0 mg, 82%): ^1H NMR δ 0.91 (t, J = 6.9 Hz, 3H), 1.25 (t, J = 6.9 Hz, 3H), 1.30–1.45 (m, 5H), 1.50–1.78 (m, 4H), 2.32–2.48 (m, 2H), 2.38 (t, J = 6.6 Hz, 2H), 2.50–2.69 (m, 3H), 2.70–2.85 (m, 1H), 2.88 (t, J = 7.3 Hz, 2H), 2.94 (dd, J = 18.5, 9.9 Hz, 1H), 3.15–3.28 (m, 1H), 3.67 (s, 1H), 3.96–4.18 (m, 1H), 4.13 (q, J = 6.9 Hz, 2H), 5.30–5.45 (m, 1H), 5.66 (br s, 1H), 6.01 (br d, J = 11.5 Hz, 1H), 6.84 (d, J = 9.9 Hz, 1H); ^{13}C NMR δ 194.8, 173.0, 140.9, 138.5, 135.1, 134.8, 129.7, 126.0, 78.2, 60.39, 60.37, 55.2, 46.1, 45.9, 40.6, 40.2, 38.8, 34.6, 31.3, 24.4, 23.7, 22.4, 14.2, 13.9; IR (neat) 3583, 1723, 1692 cm^{-1}; MS m/z 425, 423 (M + H^+), 393, 391, 347, 345, 99 (base peak); HRMS calcd for $C_{24}H_{35}{}^{35}ClO_4$ 422.2223, found 422.2216, calcd for $C_{24}H_{35}{}^{37}ClO_4$ 424.2196, found 422.2202.

(1*R*,6*S*,7*S*,8*R*)-3-[4-(*tert*-Butoxycarbonyl)-3-oxabutyl]-7-[(*Z*)-2-chloro-3-oxo-1-octenyl)]-8-hydroxybicyclo[4.3.0]non-2-ene (10b). By means of the general procedure for conversion to hydroxy enone **10**, aldol adduct **9b** (22.3 mg, 0.041 mmol) gave desired product **10b** (16.3 mg, 90%): ^1H NMR δ 0.90 (t, J = 6.9 Hz, 3H), 1.22–1.41 (m, 4H), 1.47 (s, 9H), 1.58–1.78 (m, 5H), 1.80–1.95 (m, 2H), 2.00–2.40 (m, 4H), 2.66 (br s, 1H), 2.76 (t, J = 7.3 Hz, 2H), 3.02–3.22 (m, 1H), 3.61 (t, J = 6.3 Hz, 2H), 3.75 (br t, J = 6.3 Hz, 1H), 3.95 (s, 2H), 4.06 (br t, J = 6.9 Hz, 1H), 5.44 (br s, 1H), 6.81 (d, J = 9.9 Hz, 1H); IR (neat) 3483, 1748, 1694 cm^{-1}; MS m/z 457, 455 (M + H^+), 401, 399, 383, 381, 307, 305, 99, 57 (base peak). Anal. Calcd for $C_{25}H_{39}ClO_5$: C, 65.99; H, 8.64. Found: C, 65.78; H, 8.88.

Supplementary Material Available: ^1H NMR spectra for all aldol adducts and for **10a** and **10b** and the ^{13}C NMR spectrum for **10a** (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.