Enantiodivergent Synthesis of Steroidal Side Chains. Stereocontrol *via* S_N1 *vs.* S_N2 Type Cleavage of Acetal Templates

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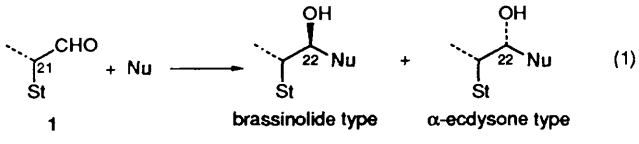
The chiral steroidal acetals **2** (*S-R,R* isomer) and **3** (*S-S,S* isomer) were prepared from the reaction of the steroidal aldehyde **1** with (2*R*,4*R*)-(−)-pentane-2,4-diol and with (2*S*,4*S*)-(+)-pentane-2,4-diol, respectively. The $TiCl_4$ mediated reaction of **2** and **3** with organometallic reagents, such as allylsilane, allyltin, allyl-9-BBN, 1-tributylstannylalk-1-ynes, and 1-trimethylsilylhex-1-yne gave a mixture of the Cram, **4** and **6**, and anti-Cram, **5** and **7**, adducts. The organometallic compounds with lower nucleophilicity (the Me_3Si and 9-BBN derivatives) gave the Cram isomer predominantly or exclusively regardless of the chirality of the acetal, whereas the reagents with higher nucleophilicity (the tributylstannyl derivatives) produced the anti-Cram isomer with good diastereoselectivity in the case of the *S-S,S* isomer **3**. This synergistic or countervailing effect of the acetal template and Cram rule is understood by considering that the chiral induction is controlled by the timing of bond breaking and bond making in the acetal template. This stereodivergent synthetic method was applied to the preparation of an α-ecdysone type steroid **17**.

The biologically active steroids, brassinolide and α-ecdysone, each have a hydroxy group at the C-22 position of the side chain, but the absolute stereochemistry is opposite; the former has a (22*R*)-hydroxy and the latter has a (22*S*)-hydroxy group. To prepare these compounds from the reaction of the steroidal aldehyde **1** with nucleophiles, an enantiodivergent

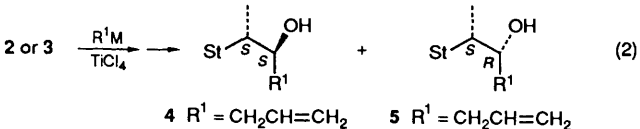


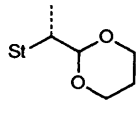
synthesis is required (eqn. 1). The brassinolide type corresponds to the Cram isomer and the α-ecdysone type to the anti-Cram isomer. The reaction of **1** with metal acetylides (Nu = RC≡CM, M=Li and MgX), which is one of the popular methods for the preparation of brassinosteroids, produces a mixture of the Cram and anti-Cram isomers with low diastereoselectivity.[1] We have found that the reaction of **1** with stannylacetylenes (M = $SnBu_3$) in the presence of $TiCl_4$ produces the Cram isomer with high diastereoselectivity.[2] Further, this high Cram selectivity also takes place in the $TiCl_4$ mediated reactions of **1** with allylstannane and allylsilane. On the other hand, the method for producing the anti-Cram isomer is limited,[3] and only alkyl groups can be utilized as the Nu.[3] For the preparation of the steroids, the introduction of appropriate functional groups is required.

We report a new method for enantiodivergent synthesis of steroidal side chains[4] and its application to the synthesis of the α-ecdysone type steroid. For the divergent synthesis, the timing of bond breaking and bond making in acetal templates becomes important.

Results and Discussion

Synergistic Effect of Acetal Template and Cram Rule.—We prepared the chiral steroidal acetals **2** (*S-R,R* isomer) and **3** (*S-S,S* isomer) from the reaction of **1** with (2*R*,4*R*)-(−)-pentane-2,4-diol and with (2*S*,4*S*)-(+)-pentane-2,4-diol, respectively. Asymmetric induction with chiral acetals has been studied widely,[5] but most of these acetal derivatives have chirality at the acetal moiety. The present systems, **2** and **3**, have an additional chiral centre at the carbon next to the acetal carbon, and therefore it is expected that a synergistic effect or countervailing effect in the asymmetric induction will be observed. Treatment of **2** and **3** with nucleophiles, such as allylic and acetylenic organometallic compounds, in the presence of $TiCl_4$ followed by the usual work-up gave the desired product **4**–**7** in good yields (eqn. 2). The results are summarized in Table 1.





Generally, the reaction was carried out in CH_2Cl_2 at −78 °C. The oxidation of the crude products with PCC followed by treatment with KOH in MeOH–THF (tetrahydrofuran) gave the steroidal alcohols **4**–**7**. The product ratio was obtained by the analysis of 400 MHz ^1H NMR spectra of the products. The

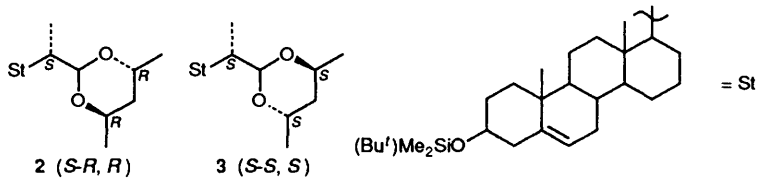


Table 1 Enantiodivergent synthesis of steroidal side chains

Entry	Steroidal acetal	R^1M	Isomer ratio	Isolated yield (%)	Chirality of a major isomer predicted by template by Cram rule	
			4:5			
1	**2**	$CH_2{=}CHCH_2SiMe_3$	99:1	93	+	+
2	**2**	$CH_2{=}CHCH_2B$⟨⟩	99:1	90	+	+
3	**2**	$CH_2{=}CHCH_2SnBu_3$	96:4	85	+	+
4	**3**	$CH_2{=}CHCH_2SiMe_3$	90:10	93	−	+
5	**3**	$CH_2{=}CHCH_2B$⟨⟩	88:12	88	−	+
6	**3**	$CH_2{=}CHCH_2SnBu_3$	30:70	84	+	−
7	**3**	$CH_2{=}CHCH_2SnPh_3$	76:24	80	−	+
			6:7			
8	**2**	$Pr^iC{\equiv}CSnBu_3$	95:5	80	+	+
9	**2**	$BuC{\equiv}CSnBu_3$	95:5	82	+	+
10	**2**	$BuC{\equiv}CSiMe_3$	98:2	72	+	+
11	**3**	$Pr^iC{\equiv}CSnBu_3$	10:90	78	+	−
12	**3**	$BuC{\equiv}CSnBu_3$	8:92	78	+	−
13	**3**	$BuC{\equiv}CSiMe_3$	92:8	82	−	+

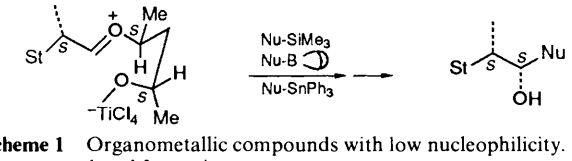
[a] +; The chirality of a major isomer is consistent with the chirality predicted either by the template or by Cram rule. −; The chirality of a maor isomer is opposite to the predicted chirality.

reaction of **2** with allyl-silane, -9-BBN (9-borabicyclo[3.3.1]-nonane) and -tributyltin produced **4** either exclusively or very predominantly (Table 1, entries 1–3). In these cases, the chirality dictated by the acetal template is in the same direction as that dictated by the Cram rule which leads to such high diastereoselectivities. The reaction of **3** with allyl-silane and -9-BBN again produced **4** predominantly (entries 4 and 5), indicating that the direction of the asymmetric induction was dictated primarily by the Cram rule with the influence of the template being negligible. However, the reaction with allyltributyltin gave **5** preferentially (entry 6), showing that violation of the Cram's rule took place and that the chiral induction was dictated essentially by the template. In contrast, allyltriphenyltin produced **4** predominantly (entry 7).

The reaction of **2** with the stannylacetylenes and silylacetylene gave **6** with very high stereoselectivity (entries 8–10). Here also, the synergistic effect of the template and Cram rule produced high stereoselectivity. The reaction of **3** with the stannyl-acetylenes gave **7** predominantly (entries 11 and 12), in which the chiral induction was dictated by the template. On the other hand, the reaction with the silylacetylene afforded **6** (entry 13), indicating that the silylacetylene gave **6** regardless of the starting acetals.

For comparison purposes, we prepared **8** from **1** and propane-1,3-diol. The reaction of **8** with allyltrimethylsilane, allyl-tributyltin and 1-tributylstannylhex-1-yne in the presence of $TiCl_4$ gave the Cram isomer predominantly; the ratio of **4**:**5** was 78:22 for allyltrimethylsilane and 68:32 for allyltributyltin, and the ratio of **6**:**7** was 56:44 for 1-tributylstannylhex-1-yne.

The above results clearly indicate the importance of the timing of bond breaking and bond making of the acetal template. The organometallic reagents with lower nucleophilicity, such as allylsilane, allyl-9-BBN, and 1-trimethylsilylhex-1-yne, presumably react after the bond breaking process and thus the chirality is dictated primarily by the Cram rule

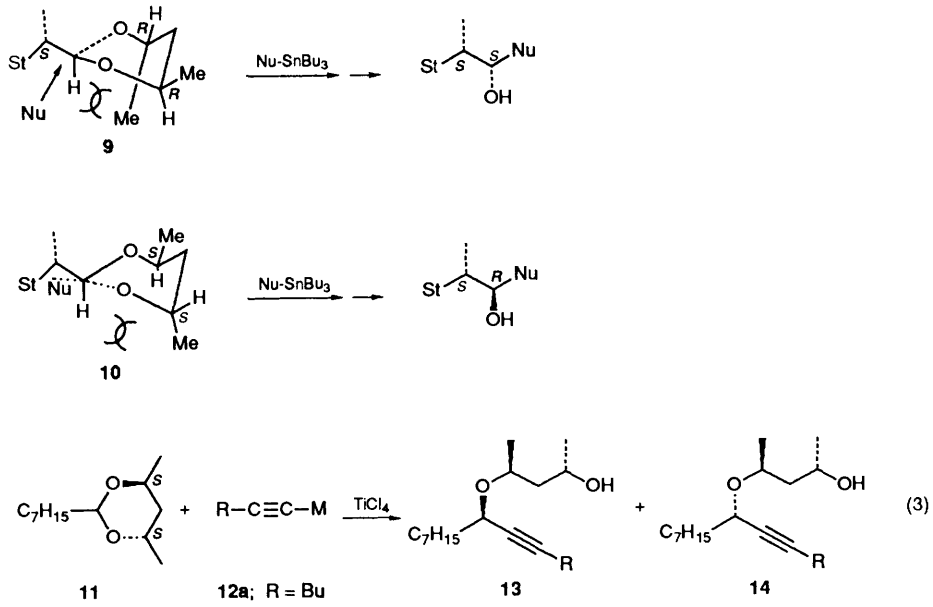


Scheme 1 Organometallic compounds with low nucleophilicity. Bond cleavage > bond formation faster

(Scheme 1). On the other hand, the tributylstannyl derivatives possess higher nucleophilicity than the silane and borane reagents, and therefore react simultaneously as the bond breaking takes place (Scheme 2). Accordingly, the chiral induction is dictated primarily by the template. As shown in **9**, the direction of chiral induction by the template is identical with that determined by the Cram rule which leads to very high diastereoselectivity in **2** (synergistic effect). However, a countervailing effect is observed in the case of **3** as shown in **10**, leading to the decreased diastereoselectivity. The nucleophilicity of the triphenylstannyl derivative is between that of the trimethylsilyl and tributyltin reagent due to the phenyl substituent. Now it is clear that the reaction of the (*S*,*S*-*S*) steroidal acetal with tributyltin acetylides must produce the anti-Cram isomer.

A Model Reaction.—To investigate the influence of organometallic species upon the diastereoselectivity of a simple acetal, we examined the reaction of **11** with various metal acetylides (eqn. 3). The results are summarized in Table 2. The highest stereoselectivity in the formation of **14**, which has the desired stereochemistry at the acetal carbon, was obtained with trimethylgermylacetylide (Table 2, entry 4), but the isolated yield was poor owing to the production of the chlorinated compound, 7-chlorotetradec-5-yne. This chlorinated compound was also obtained in the reaction of the trimethylsilylacetylide (entry 3). Among these acetylides, the tributyltin derivative gave the best result in the matter of both stereoselectivity and chemical yield. A similar trend was observed with another acetylide **12b** [R = $C(CH_3)_2OTMS$].

Synthesis of α-Ecdysone Type Side Chain.—The reaction of **3** with **12b** in the presence of $TiCl_4$ gave a mixture of **15** and **16** (eqn. 4). With M = $GeMe_3$, the reaction was very slow and most of the starting material was recovered. With M = $SnBu_3$, the anti-Cram isomer **16** was obtained predominantly as expected from the above results. With M = $PbBu_3$, both the diastereoselectivity and chemical yield decreased. The diastereo-isomers **15** and **16** were separated by silica-gel column chromatography. The anti-Cram isomer **16** was converted into **17** by reduction of the triple bond, deprotection of TBS group, and acetoxy protection of the OH group (eqn. 5). The stereochemistry of **17** was established by comparison with the spectroscopic data of the authentic sample.[7]

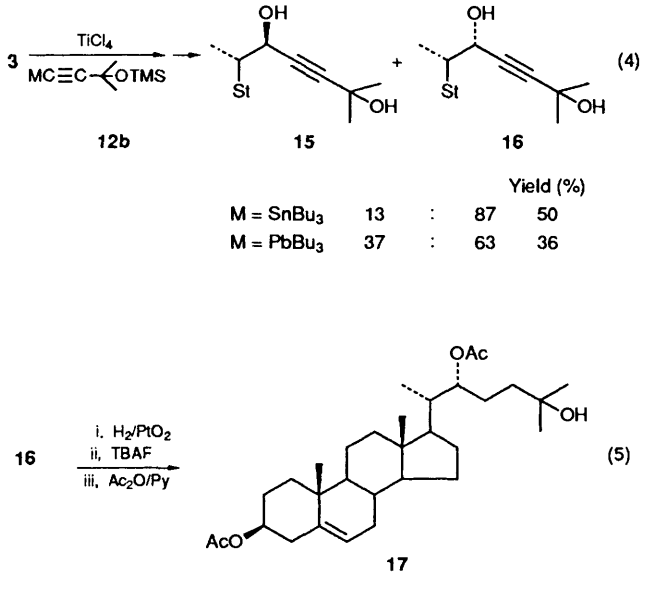


Scheme 2 Organometallic compounds with high nucleophilicity Bond cleavage ≈ bond formation; concerted process

Table 2 Reaction of **11** with **12a**

Entry	BuC≡CM M	T/°C	Product ratio[a] 13:14	Total isolated yield(%)
1	Li	−78→−40	40:60	31
2	ZnBr	−78→−40	25:75	15
3	$SiMe_3$	−78→−50	22:78	6
4	$GeMe_3$	−78→−60	1:99	30
5	$SnBu_3$	−78→−50	4:96	55
6	$PbBu_3$	−78→−70	10:90	62

[a] Determined by GLC analysis.



In conclusion, the present development provides a useful method for an enantiodivergent and diastereodivergent synthesis of chiral substances. We demonstrated the synthesis of the α-ecdysone type side chain, an anti-Cram isomer, which was not easily obtained with an ordinary method. The synthesis of the brassinolide type derivative may be carried out without difficulty since it is the Cram type isomer.

Experimental

^1H NMR spectra were recorded on a JEOL JNM-PMX 100, JEOL GSX-270, a Varian XL-200, or a JEOL GX 400 spectrometer. The chemical shifts are expressed in parts per million downfield from the tetramethylsilane internal standard. ^{13}C NMR spectra were recorded on a Varian XL-200 or a JEOL GSX-270 spectrometer. All *J* values are in Hz. IR spectra were recorded on a Hitachi Model 215. Mass spectra were recorded on a Hitachi M-52 spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-HX 110. M.p.s were determined on a Yamato MP-21 capillary melting point apparatus. M.p.s and b.p.s stated are uncorrected. The Kugelrohr distillation temperatures are oven temperatures, not b.p.s as stated.

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. All other solvents were dried and stored over 3 Å molecular sieves. Butyllithium in hexane solution was purchased and titrated prior to use. Most commercially supplied chemicals were distilled and stored over molecular sieves. The aldehyde **1** was prepared from pregnenolone by the literature procedure.[6] (2*R*,4*R*)-(−)- and (2*S*,4*S*)-(+)-pentane-2,4-diol were purchased from the Waco Chemical Ind., Japan.

Synthesis of **2** was carried out according to the literature procedure.[8] The reaction of **1** with (2*R*,4*R*)-(−)pentane-2,4-diol in the presence of catalytic amounts of PPTS (pyridinium toluene-*p*-sulphonate) gave **2** in 90% yield: m.p. 145–147 °C, ν(Nujol)/cm^{-1} 2950, 1470, 1385, 1265, 1170, 1145, 1100 and 840; δ_H(100 MHz; CCl_4) 0.05 (s, 6 H, $SiCH_3$), 0.67 (s, 3 H, CH_3), 0.89 (s, 9 H, Bu^t), 1.0 (s, 3 H, CH_3), 1.08 (d, 3, H, *J* 6, CH_3), 1.26 (d, 3 H, *J* 6, CH_3), 1.34 (d, 3 H, *J* 7, CH_3), 0.9–2.3 (m, 23 H, CH_2 and CH), 3.5 (m, 1 H, SiOCH), 3.9 (m, 1 H, OCH), 4.25 (m, 1 H, OCH), 4.8 (d, 1 H, *J* 2, CH) and 5.30 (m, 1 H, CH=C) (Found: C, 74.95; H, 11.2. Calc. for $C_{33}H_{58}O_3Si$: C, 74.66; H, 11.01%).

Synthesis of **3** was carried out similarly with (2*S*,4*S*)-(+)-pentane-2,4-diol. M.p. 137–139 °C (isolated yield, 96%); ν(Nujol)/cm^{-1} 2950, 1470, 1385, 1260, 1160, 1140, 1100, 1000 and 840; δ_H(100 MHz; CCl_4) 0.05 (s, 6 H, $SiCH_3$), 0.67 (s, 3 H, CH_3), 0.89 (s, 9 H, Bu^t), 1.0 (s, 3 H, CH_3), 0.99 (d, 3 H, *J* 6, CH_3), 1.19 (d, 3 H, *J* 6, CH_3), 1.33 (d, 3 H, *J* 7, CH_3), 0.9–2.3 (m, 23 H, CH_2 and CH), 3.4 (m, 1 H, SiOCH), 3.75 (m, 1 H, OCH), 4.2 (m, 1 H, OCH), 4.7 (bs, 1 H, CH) and 5.20 (m, 1 H, CH=C) (Found: C, 74.55; H, 11.2. Calc. for $C_{33}H_{58}O_3Si$: C, 74.66; H, 11.01%).

Synthesis of **8** was carried out with propane-1,3-diol as described above. M.p. 156–158 °C (isolated yield, 90%);

ν(Nujol)/cm^{-1} 2950, 1460, 1380, 1255, 1155, 1100, 990 and 840; δ_H(400 MHz; $CDCl_3$) 0.05191 (s, 6 H, $SiCH_3$), 0.670 23 (s, 3 H, CH_3), 0.885 49 (s, 9 H, Bu^t), 0.991 60 (s, 3 H, CH_3), 1.016 79 (d, 3 H, *J* 6.62, CH_3), 1.1–2.3 (m, 23 H, CH_2 and CH), 3.470 97 (sept., 1 H, *J* 4.57, SiOCH), 3.692 35 (dt, 1 H, *J* 2.44 and 12.21, CH), 3.770 97 (dt, 1 H, *J* 2.44 and 12.21, CH), 4.483 18 (d, 1 H, *J* 1.83, CH) and 5.306 84 (t, 1 H, *J* 1.83, CH=C) (Found: M$^+$, 502.2861. Calc. for $C_{31}H_{54}O_3Si$: *M*, 502.3842).

Reactions of **2**, **3** *and* **8** *with Organometallic Reagents.*—Allyltributylstannane, allyltriphenylstannane, and allyl-9-BBN were prepared according to the procedure reported previously.[9] Allyltrimethylsilane was purchased from Aldrich. Tributylstannylacetylenes and 1-trimethylsilylhex-1-yne were prepared from the corresponding lithium acetylides according to the reported procecure.[10] 1-Tributylstannylhex-1-yne: b.p. 120 °C/1 mmHg (Kugelrohr); δ_H(100 MHz; CCl_4) 0.9 (t, 12 H, *J* 7, CH_3), 1.0–1.8 (m, 22 H, CH_2) and 2.2 (t, 2 H, *J* 6, CH_2) (Found: M$^+$, 371.1928. Calc. for $C_{18}H_{38}Sn$: *M*, 371.1938).

1-(Tributylstannyl)-3-methylbut-1-yne: b.p. 110 °C/1 mmHg (Kugelrohr); δ_H(100 MHz; CCl_4) 0.9 (t, 9 H, *J* 7, CH_3), 1.14 (d, 6 H, *J* 7, CH_3), 1.0–1.8 (m, 18 H, CH_2) and 2.5 (quintet, 1 H, *J* 8, CH) (Found: M$^+$, 357.1660. Calc. for $C_{17}H_{34}Sn$: *M*, 357.1670). 1-(Trimethylsilyl)hex-1-yne: b.p. 80–82 °C/35 mmHg; δ_H(100 MHz; CCl_4) 0.13 (s, 9 H, $SiCH_3$), 0.90 (t, 3 H, *J* 7, CH_3), 1.30–1.50 (m, 4 H, CH_2) and 2.22 (t, 2 H, *J* 7, CH_2) (Found: M$^+$, 154.3283. Calc. for $C_9H_{18}Si$: *M*, 154.3274).

The reaction was carried out as described previously.[5b,c] To a CH_2Cl_2 solution of the acetal (1 mmol) cooled at −78 °C was added the organometallic reagent (1.1 mmol), and then a CH_2Cl_2 solution of $TiCl_4$ (1 mol dm^{-3}; 1 cm^3, 1.1 mmol) was added. After the mixture had been stirred for 10 min at this temperature, MeOH and water were added, and the resulting mixture was allowed to warm to 0 °C. The reaction mixture was neutralized with aqueous Na_2CO_3. The usual work-up gave a crude product. Without further purification and separation, this product was oxidized with pyridinium chlorochromate (PCC) (2 mmol) to give the corresponding ketone. To obtain the desired compound, the retro-Aldol reaction of the resulting ketone was performed. To a mixture of THF–MeOH–7.5 mol dm^{-3} aq. KOH (4:2:1) was added the ketone, and the mixture was stirred for 2–3 h at room temperature. The usual work-up gave the desired alcohol in good yields. The structures of **4**–**7** were confirmed by comparison with those of the authentic materials which were prepared from the reaction of **1** with allyl Grignard reagent or with the corresponding lithium acetylides.[2]

The allylated Cram isomer **4**. δ_H(400 MHz; $CDCl_3$) 0.054 20 (s, 6 H, $SiCH_3$), 0.684 73 (s, 3 H, CH_3), 0.887 78 (s, 9 H, Bu^t), 0.930 15 (d, 3 H, *J* 7.02, CH_3), 0.999 99 (s, 3 H, CH_3), 1.0–2.4 (m, 23 H, CH_2 and CH), 3.447 84 (septet 1 H, *J* 4.60, SiOCH), 3.727 46 (m, 1 H, CHO), 5.08–5.84 (m, 2 H, $=CH_2$), 5.31–5.32 (m, 1 H, CH=C) and 5.77–5.84 (m, 1 H, CH) (Found: C, 76.2; H, 11.25. Calc. for $C_{31}H_{54}O_2Si$: C, 76.48; H, 11.18%).

The allylated anti-Cram isomer **5**. δ_H(400 MHz; $CDCl_3$) 0.054 20 (s, 6 H, $SiCH_3$), 0.707 63 (s, 3 H, CH_3), 0.887 78 (s, 9 H, Bu^t), 0.947 33 (d, 3 H, *J* 6.71, CH_3), 0.999 99 (s, 3 H, CH_3), 1.0–2.4 (m, 23 H, CH_2 and CH), 3.44–3.52 (m, 1 H, SiOCH), 3.91–3.95 (m, 1 H, CHO), 5.08–5.18 (m, 2 H, $=CH_2$), 5.31–5.34 (m, 1 H, CH=C) and 5.76–5.90 (m, 1 H, CH=) (Found: C, 76.2; H, 11.25. Calc. for $C_{31}H_{54}O_2Si$: C, 76.48; H, 11.18%). The Cram and anti-Cram isomer could be distinguished by the following signals; the singlet Me (0.684 73 and 0.707 63); the doublet Me (0.930 15 and 0.947 33), the methyne bonded to OH (3.727 46 and 3.91–3.95).

The hex-1-yne derivative **6** (*Cram isomer*, R = Bu). δ_H(400 MHz; $CDCl_3$) 0.05 (s, 6 H, $SiCH_3$), 0.687 (s, 3 H, CH_3), 0.895 (s, 9 H, Bu^t), 0.911 (t, 3 H, *J* 7, CH_3), 1.00 (s, 3 H, CH_3), 1.11 (d, 3 H, *J* 7, CH_3), 1.2–2.1 (m, 25 H, CH_2 and CH), 2.2 (t, 2 H, *J* 6, CH_2), 3.48 (septet, 1 H, *J* 5, SiOCH), 4.46 (m, 1 H, CHO), 4.62 (bs, 1 H, OH) and 5.32 (m, 1 H, CH=C) (Found: C, 77.75; H, 10.85. Calc. for $C_{34}H_{58}O_2Si$: C, 77.50; H, 11.10%).

The hex-1-yne derivative **7** (*anti-Cram isomer*, R = Bu). δ_H(400 MHz; $CDCl_3$), 0.05 (s, 6 H, $SiCH_3$), 0.704 (s, 3 H, CH_3), 0.895 (s, 9 H, Bu^t), 0.919 (t, 3 H, *J* 7, CH_3), 1.00 (s, 3 H, CH_3), 1.04 (d, 3 H, *J* 7, CH_3), 1.2–2.1 (m, 25 H, CH_2 and CH), 2.2 (t, 2 H, *J* 6, CH_2), 3.48 (septet 1 H, *J* 5, SiOCH), 4.22 (m, 1 H, CHO), 4.62 (bs, 1 H, OH) and 5.32 (m, 1 H, CH=C) (Found: M$^+$, 526.4205. Calc. for $C_{34}H_{58}O_2S$: *M*, 526.4206).

The Cram isomer **6** (R = Bu) and anti-Cram isomer **7** (R = Bu) could be distinguished by the following signals; the singlet Me (0.687 and 0.704), the doublet Me (1.11 and 1.04), and the methyne bonded to OH (4.46 and 4.42).

The 3-methylbut-1-yne derivative **6** (*Cram isomer*, R = Pr^i). δ_H(400 MHz; $CDCl_3$) 0.05 (s, 6 H, $SiCH_3$), 0.696 (s, 3 H, CH_3), 0.887 (s, 9 H, Bu^t), 0.919 (s, 3 H, CH_3), 1.105 (d, 3 H, *J* 7, CH_3), 1.170 (d, 6 H, *J* 7, CH_3), 1.2–2.3 (m, 22 H, CH_2 and CH), 2.59 (quintet, 1 H, *J* 7, CH), 3.48 (septet, 1 H, *J* 5, SiOCH), 4.437 (br s, 1 H, CHO) and 5.345 (m, 1 H, CH=C) (Found: C, 77.55; H, 11.25. Calc. for $C_{33}H_{56}O_2Si$: C, 77.28, H, 11.01%).

The 3-methylbut-1-yne derivative **7** (*anti Cram isomer*, R = Pr^i). δ_H(400 MHz; $CDCl_3$) 0.05 (s, 6 H, $SiCH_3$), 0.701 (s, 3 H, CH_3), 0.887 (s, 9 H, Bu^t), 0.916 (s, 3 H, CH_3), 1.034 (d, 3 H, *J* 7, CH_3), 1.174 (d, 6 H, *J* 7, CH_3), 1.2–2.3 (m, 22 H, CH_2 and CH), 2.59 (quintet, 1 H, *J* 7, CH), 3.48 (septet, 1 H, *J* 5, SiOCH), 4.400 (br s, 1 H, CHO) and 5.309 (m, 1 H, CH=C) (Found: C, 77.6; H, 11.3. Calc. for $C_3H_{58}O_2Si$: C, 77.28; H, 11.01%).

The Cram isomer **6** (R = Pr^i) and anti-Cram isomer **7** (R = Pr^i) could be distinguished by the following signals; the singlet Me (0.696 and 0.701), the doublet Me (1.105 and 1.034) and the methyne bonded to OH (4.437 and 4.400).

The Reaction of **11** *with* **12**.—The acetal **11** was prepared from octanal and the chiral pentane-1,3-diol according to the procedure described above. Hex-1-ynylzinc bromide was prepared from the corresponding lithium acetylide and $ZnBr_2$ (1.1 equiv.) in ether. 1-(Trimethylgermyl)hex-1-yne was prepared from hex-1-ynyllithium and trimethylgermyl chloride: colourless oil, b.p. 120–130 °C/60 mmHg (Kugelrohr); δ_H(270 MHz; $CDCl_3$) 0.32 (s, 3 H), 0.91 (t, *J* 7.0, 3 H), 1.32–1.57 (m, 4 H) and 2.22 (t, *J* 7.0, 2 H); δ_C (67.5 MHz; $CDCl_3$) −0.04, 13.59, 19.53, 21.92, 31.00, 83.76 and 106.09; ν(neat)/cm^{-1} 2970, 2945, 2870, 2180, 1485, 1225, 835 and 765; 1-(Tributylplumbyl)hex-yne was prepared as follows. To MeOH (2 cm^3) in a 50 cm^3 flask cooled at 0 °C under N_2 was added Na (0.15 g, 6.5 mmol). Diethyl ether (20 cm^3) and Bu_3PBr (2.40 g, 5.2 mmol) were placed in a 100 cm^3 flask which was kept under N_2. The methanol solution of $NaOCH_3$ was added, and the resulting mixture was stirred for 90 min at room temperature. The solvents were removed under reduced pressure, and diethyl ether was added. Insoluble NaBr was separated by centrifuge. The ether solution was condensed by evaporator, and Bu_3PbOMe was obtained. To a benzene solution of Bu_3PbOMe (5 cm^3) was added hex-1-yne (1.20 cm^3, 10 mmol) under N_2. The mixture was stirred overnight at room temperature. Distillation with Kugelrohr gave the desired compound (1.69 g, 71%).

The reaction of **11** with **12** was carried out as described above. The isomer ratio of **13**:**14** was determined by GLC analysis. (7*S*)-7[(1′*S*,3′*S*)-3′-Hydroxy-1′-methylbutoxy]tetradec-5-yne **13**; δ_H(270 MHz; $CDCl_3$) 0.83–0.95 (br t, 6 H), 1.18 (d, *J* 6.8, 3 H), 1.28 (d, *J* 7.0, 3 H), 1.2–1.4 (m, 19 H), 2.22 (m, 2 H) and 3.95–4.20 (m, 3 H); ν(CCl_4)/cm^{-1} 3455, 2945, 2860, 1460, 1380, 1130 and 1070 (Found: C, 76.85; H, 12.3. Calc. for $C_{19}H_{36}O_2$: C, 76.97, H, 12.24%). (7*R*)-7-[(1′*S*,3′*S*)-3′-Hydroxy-1′-methylbutoxy]tetradec-5-yne **14**; δ_H(270 MHz; $CDCl_3$) 0.82–0.94 (br t, 6 H), 1.16 (d, *J* 6.5, 3 H), 1.24 (d, *J* 6.8, 3 H), 1.2–1.4 (m, 19 H), 2.14–2.28 (m, 2 H) and 4.0–4.20 (m, 3 H); ν(CCl_4)/cm^{-1}

3550, 2940, 2855, 1470, 1380, 1155 and 1120 (Found: C, 76.7; H, 12.05. Calc. for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24%).

The Reaction of **3** *with* 2-*Methyl*-4-(*tributylstannyl*)-2-*trimethylsilyloxybut*-3-*yne*.—This reaction was carried out as described above. Separation of **15** and **16** was carried out with flash column chromatography (Merck silica-gel 230–400 mesh) by using $CHCl_3$–EtOH (20:1) as an eluent. The Cram isomer **15** (white crystals): m.p. 196–198 °C; δ_H(400 MHz; $CDCl_3$) 0.05 (s, 6 H), 0.68 (s, 3 H), 0.88 (s, 9 H), 1.00 (s, 3 H), 1.11 (d, *J* 7.0, 3 H), 1.53 (s, 6 H), 3.48 (septet, *J* 5.0, 1 H), 4.50 (d, *J* 2.0, 1 H) and 5.32 (m, 1 H); $\nu(CCl_4)/cm^{-1}$ 2935, 2855, 1460, 1255 and 1090 (Found: M^+, 528.3996. Calc. for $C_{33}H_{56}O_3Si$: *M*, 528.3999). The anti-Cram isomer **16** (white crystals): m.p. 123–126 °C; δ_H(400 MHz; $CDCl_3$) 0.05 (s, 6 H), 0.70 (s, 3 H), 0.89 (s, 9 H), 1.00 (s, 3 H), 1.05 (d, *J* 4.0, 3 H), 1.53 (s, 6 H), 3.48 (septet, *J* 7.0, 1 H), 4.46 (d, *J* 4.0, 1 H) and 5.32 (m, 1 H); $\nu(CCl_4)/cm^{-1}$ 3400, 2945, 2860, 1460, 1380, 1255, 1090 and 835 (Found: M^+, 528.4001. Calc. for $C_{33}H_{56}O_3Si$: *M*, 528.3999). In a 30 cm^3 flask for reduction were placed **16** (0.119 g, 0.24 mmol), MeOH (4 cm^3) and PtO_2 (67 mg). The mixture was stirred for 20 min under an H_2 atmosphere. The catalyst was removed by chromatography over a short column of alumina. Removal of the solvent gave white crystals (0.117 g, 96%). In a 50 cm^3 flask kept at 0 °C under N_2 were placed this reduced compound and THF (4 cm^3). A THF solution of Bu_4NF (1 mol dm^{-3}; 0.7 cm^3, 0.7 mmol) was added to the mixture, and the resulting solution was stirred overnight. Water was added and the product was extracted with AcOEt. The organic layer was washed with saturated aq. $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of the solvent gave white crystals (0.111 g). Those white crystals were placed in a 30 cm^3 flask with pyridine (6 cm^3) and acetic anhydride (6 cm^3), and the resulting mixture was stirred overnight. The same work-up as described above gave **17**. Purification with silica-gel column chromatography by using hexane–AcOEt (25/1) as an eluent produced **17** (0.049 g): m.p. 1248–149 °C (ether–hexane) (lit.,[5] m.p. 147–148 °C).

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