

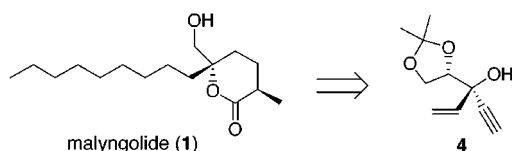
# Pseudo- $C_3$ -Symmetric Tertiary Alcohol Building Block via Group-Selective Hydroalumination: A Synthesis of (–)-Malyngolide

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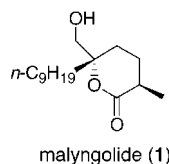
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## ABSTRACT

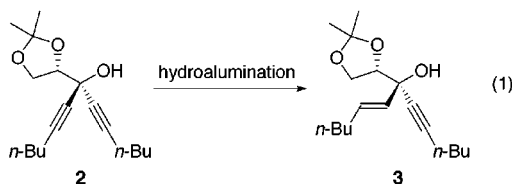


The stereocontrolled preparation of tertiary alcohol **4** and its TMS surrogate **5**, which share a *pseudo-C<sub>3</sub>*-symmetry, is described. Compound **4** was used for the synthesis of (–)-malyngolide.

Stereogenic tertiary alcohols are embedded in many biologically active natural products, such as malyngolide (**1**).<sup>1</sup>



Recently, we developed a new approach to such structural motifs by the *group-selective* hydroalumination of bis-alkynyl alcohols armed with an adjacent chiral center. The reaction scheme is exemplified by eq 1, which gives **3** as



the sole product under suitable conditions.<sup>2</sup> Among the potential utilities of this finding, we became particularly intrigued by the structure of **3**, which might allow us the

“three-directional elaboration” schematically depicted in Figure 1.

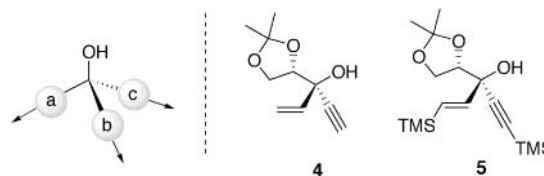


Figure 1.

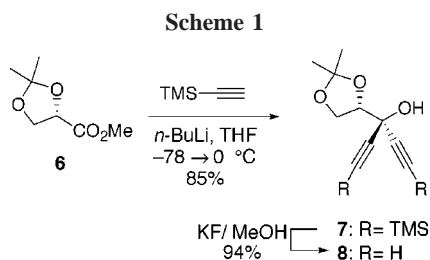
This aspect would be highlighted if the *n*-butyl groups in **3** were replaced by hydrogens (see **4**) or trimethylsilyls (see **5**), since all three substituents (a, b, c) are two-carbon units

(1) For isolation of **1**, see: Cardllina, J. H.; Moore, R. E.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1979**, *44*, 4039. For previous total syntheses, see: (a) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470. (b) Trost, B. M.; Tang, W.; Schulte, J. L. *Org. Lett.* **2000**, *2*, 4013. Reference 1a reports the most recent synthesis and ref 1b the next most recent, compiling the 27 previous syntheses.

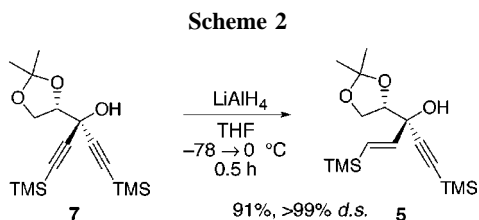
(2) Ohmori, K.; Suzuki, T.; Taya, K.; Tanabe, D.; Ohta, T.; Suzuki, K. *Org. Lett.* **2001**, *3*, 1057.

that are nicely differentiated. This Letter reports the synthesis of the aesthetically pleasing structures of **4** and the TMS surrogate **5** with *pseudo*-C<sub>3</sub>-symmetry and its application to the synthesis of malyngolide (**1**).<sup>3</sup>

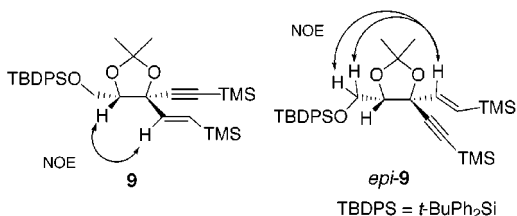
The known glycerate derivative **6**,<sup>4</sup> readily available from L-serine, was treated with Me<sub>3</sub>SiC≡CLi to give the bis-TMS-ethynyl alcohol **7** in 85% yield. Desilylation of **7** gave the bis-ethynyl alcohol **8** in 94% yield, ready for the hydroalumination reaction (Scheme 1).



Thus, treatment of **7** with LiAlH<sub>4</sub> in THF (−78 → 0 °C, 30 min) gave the monoreduction product **5** as the *sole* stereoisomer in 91% yield (Scheme 2),<sup>5</sup> whose stereochem-

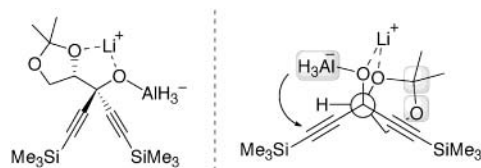


istry was assigned on the basis of NOE studies on the cyclic acetal derivative **9** [(1) 80% AcOH, (2) TBDPSCI, imidazole, (3) Me<sub>2</sub>C(OMe)<sub>2</sub>, *p*-TsOH, 77% overall yield] shown in Figure 2. The acetal **9** showed a diagnostic NOE between the hydrogens as shown.<sup>6</sup>



**Figure 2.**

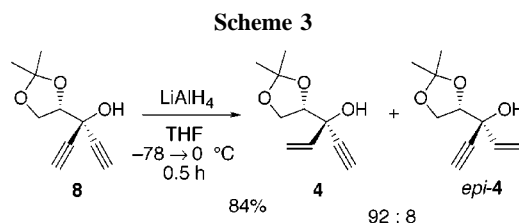
The perfect group selectivity observed for **7** can be explained by the chelation model shown in Figure 3 as previously reported.<sup>2</sup> In the five-membered lithium chelate, the steric repulsion of the cyclic acetal moiety puts the



**Figure 3.**

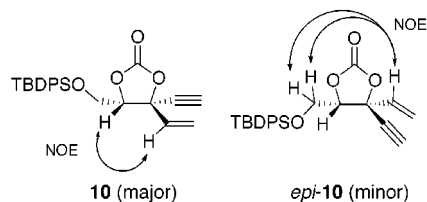
aluminate at the opposite side, and the alkyne group in the vicinity is selectively reduced.

Under the same reaction conditions, we next attempted the hydroalumination of alcohol **8** possessing terminal ethynyl groups, obtaining a 92/8 mixture of the corresponding monoreduction products **4** and *epi-4* in 84% combined yield (Scheme 3). Although the diastereomers were inseparable,



the <sup>1</sup>H NMR spectrum of **4/epi-4** gave signals resolved enough to assess the selectivity as a mixture.

Stereochemical assignment of **4** was based on NOE studies of the cyclic carbonate derivatives (Figure 4). Again, the



**Figure 4.**

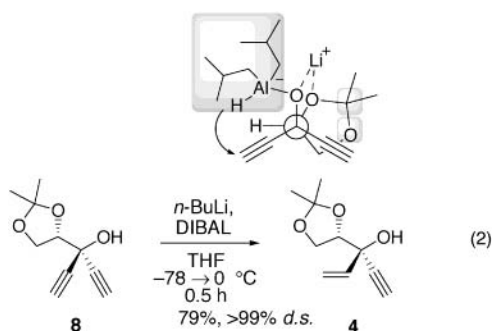
cyclic carbonates **10** and *epi-10* gave a well-resolved spectrum, allowing NOE study of the mixture [(1) 80% AcOH, (2) TBDPSCI, imidazole, (3) triphosgene, pyridine, 0 °C, 40% overall yield].

(3) This marine natural product, which is a kind of symbolic compound for synthetic practice, and as many as 29 chiral synthetic routes have been documented with the present synthesis being the 30th one!

(4) Lok, C. M.; Ward, J. P.; van Dorp, D. A. *Chem. Phys. Lipids* **1976**, *16*, 115.

(5) **Experimental procedure for the hydroalumination of 7 with LiAlH<sub>4</sub>**: To a solution of LiAlH<sub>4</sub> (77.5 mg, 2.04 mmol) in THF (4 mL) was slowly added a solution of **7** (331 mg, 1.02 mmol) in THF (6 mL) at −78 °C. The reaction was gradually warmed to 0 °C, and stirring was continued for 30 min. After careful addition of Na<sub>2</sub>SO<sub>4</sub>·10H<sub>2</sub>O, the mixture was filtered through a Celite pad and evaporated. Flash column chromatography (SiO<sub>2</sub>, hexane/EtOAc = 95/5) gave **5** (302 mg, 91%, >99% ds) as a colorless oil.

At this stage, we hoped to improve this high, but imperfect selectivity of the reaction of **8** (cf. Scheme 2). The clue was our previous finding that one could expect to enhance the selectivity by increasing the steric bulkiness of the Al ligands by a modified procedure using *n*-BuLi and DIBAL (see eq 2).<sup>2</sup>



Indeed, we were delighted to observe a virtually perfect group selectivity, upon treatment of **8** with *n*-BuLi (1.0 equiv,  $-78\text{ }^{\circ}\text{C}$ , 30 min) in THF followed by DIBAL (1.0 equiv) to give alcohol **4** as the sole detectable product in 79% yield (eq 2).<sup>7, 8</sup>

With the desired building blocks, **4** and **5**, now in hand, we turned our attention to the synthesis of (–)-malynolidine (**1**). Figure 5 shows our plan of three-directional elaboration

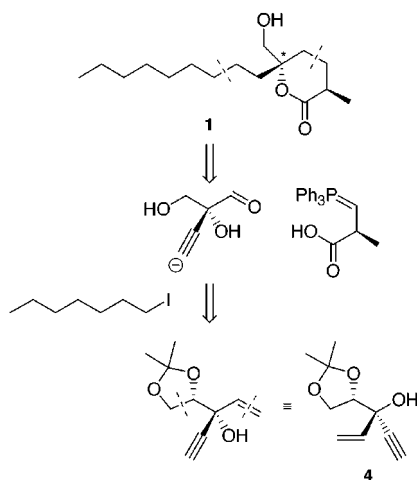


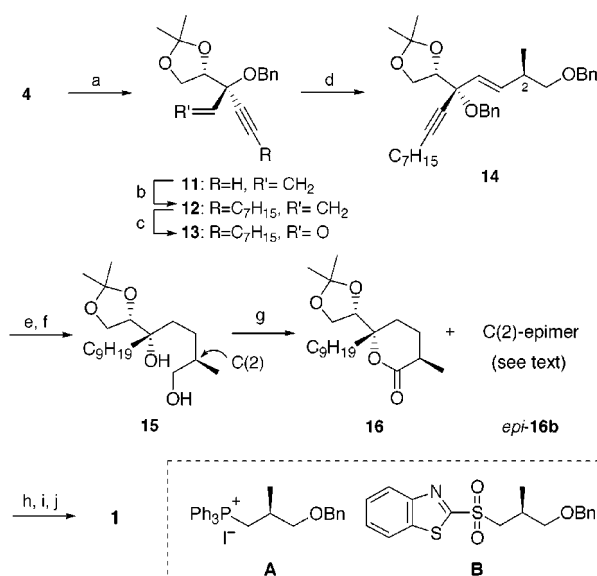
Figure 5.

of the two-carbon units in **4**, and Scheme 4 shows the synthesis executed along these lines.

The *tert*-hydroxyl group in **4** was first protected by a benzyl group to give the benzyl ether **11** in 94% yield. The alkyne **11** was lithiated (*n*-BuLi,  $0\text{ }^{\circ}\text{C}$ , 30 min) and then

(6) Though no rationale is available, use of Et<sub>2</sub>O for the hydroalumination of **7** only gave a 6/4 group selectivity of **5** and *epi*-**5**, which were separated and used for the structure assignment. Thus, *epi*-**5** was similarly converted to the cyclic derivative *epi*-**9**, which showed again diagnostic NOE as shown in Figure 2.

Scheme 4<sup>a</sup>



<sup>a</sup> (a) BnBr, NaH, Bu<sub>4</sub>NI, THF, 22 h, 94%, (b) *n*-BuLi; C<sub>7</sub>H<sub>15</sub>I, THF, HMPA,  $-78 \rightarrow 0\text{ }^{\circ}\text{C}$ , 91%, (c) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>,  $-78\text{ }^{\circ}\text{C}$ ; Me<sub>2</sub>S, 95%, (d) **B**, LiN(TMS)<sub>2</sub>, THF, 90% (*E/Z* = 97/3), (e) Ca, NH<sub>3</sub>, THF, 2 h, (f) H<sub>2</sub>, PtO<sub>2</sub>, MeOH, 1 h, 87% (two steps), (g) PDC, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 3 days **16**: 85%, *epi*-**16**: 3%, (h) CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>,  $0 \rightarrow 25\text{ }^{\circ}\text{C}$ , 3 h, (i) Pb(OAc)<sub>4</sub>, benzene, 15 min, (j) NaBH<sub>4</sub>, MeOH, 77% (three steps).

treated with *n*-heptyl iodide (THF, HMPA,  $-78 \rightarrow 0\text{ }^{\circ}\text{C}$ ) to give the alkylated product **12** in 91% yield. Ozonolysis of **12** in CH<sub>2</sub>Cl<sub>2</sub> at  $-78\text{ }^{\circ}\text{C}$  followed by workup with Me<sub>2</sub>S ( $-78 \rightarrow 25\text{ }^{\circ}\text{C}$ ) cleanly afforded aldehyde **13** in 95% yield.

Introduction of the chiral, nonracemic four-carbon unit to **13** was first examined with the Wittig reagent derived from

(7) **Procedure for the hydroalumination of 8 with *n*-BuLi and DIBAL:** To a solution of **8** (200 mg, 1.11 mmol) in THF (11 mL) was added *n*-BuLi (1.50 M hexane solution, 0.74 mL, 1.1 mmol) at  $-78\text{ }^{\circ}\text{C}$ . After stirring for 30 min, DIBAL (1.01 M hexane solution, 1.10 mL) was added. The temperature was gradually raised to  $0\text{ }^{\circ}\text{C}$ , and stirring was continued for 30 min. After quenching with saturated aqueous potassium sodium tartrate, extractive workup followed by flash column chromatography (SiO<sub>2</sub>, hexane/EtOAc = 85/15) gave **4** (160 mg, 79%, >99% ds) as a colorless oil.

(8) Data for **4** (>99% ds): <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  1.44 (s, 3H), 1.57 (s, 3H), 2.10 (s, 1H), 2.91 (brs, 1H), 3.78–3.85 (m, 2H), 3.96–4.04 (m, 1H), 5.04 (dd, 1H, *J* = 9.8, 1.9 Hz), 5.61 (dd, 1H, *J* = 16.6, 1.9 Hz), 5.83 (dd, 1H, *J* = 16.6, 9.8 Hz); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  25.4, 26.4, 65.9, 72.3, 74.9, 81.5, 82.8, 110.6, 116.5, 137.7; IR (neat) 3420, 3265, 3090, 2990, 2940, 2895, 2110, 1875, 1640, 1480, 1455, 1410, 1375, 1260, 1215, 1155, 1075 cm<sup>-1</sup>; [ $\alpha$ ]<sub>D</sub><sup>22</sup> +18 (*c* 1.1, CHCl<sub>3</sub>). Anal. Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>3</sub>: C, 65.92; H, 7.74. Found: C, 65.70; H, 8.04. **5**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.09 (s, 9H), 0.19 (s, 9H), 1.37 (s, 3H), 1.48 (s, 3H), 2.74 (s, 1H), 3.95 (dd, 1H, *J* = 8.3, 6.6 Hz), 3.99 (dd, 1H, *J* = 8.3, 6.6 Hz), 4.08 (dd, 1H, *J* = 6.6, 6.6 Hz), 5.93 (d, 1H, *J* = 18.5 Hz), 6.27 (d, 1H, *J* = 18.5 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  -1.4, -0.2, 25.6, 26.4, 66.1, 74.0, 81.0, 92.3, 103.3, 110.5, 132.6, 143.3; IR (neat) 3440, 2990, 2960, 2920, 2170, 1945, 1615, 1480, 1455, 1370, 1305, 1250, 1215, 1160, 1075, 1015 cm<sup>-1</sup>; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +6.9 (*c* 1.1, CHCl<sub>3</sub>). Anal. Calcd for C<sub>16</sub>H<sub>30</sub>O<sub>3</sub>Si: C, 58.84; H, 9.26. Found: C, 58.54; H, 9.44. *epi*-**5**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.16 (s, 9H), 0.17 (s, 9H), 1.38 (s, 3H), 1.47 (s, 3H), 2.55 (s, 1H), 4.081 (d, 1H, *J* = 7.6 Hz), 4.084 (d, 1H, *J* = 5.4 Hz), 4.15 (dd, 1H, *J* = 7.6, 5.4 Hz), 5.77 (d, 1H, *J* = 14.6 Hz), 6.23 (d, 1H, *J* = 14.6 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, TMS)  $\delta$  -0.3, 1.4, 25.3, 26.3, 65.9, 72.6, 81.3, 91.0, 103.7, 110.4, 133.1, 145.6; IR (neat) 3420, 2985, 2955, 2900, 2360, 2170, 1730, 1610, 1480, 1455, 1380, 1370, 1340, 1250, 1215, 1160, 1075, 1010 cm<sup>-1</sup>; [ $\alpha$ ]<sub>D</sub><sup>21</sup> +129 (*c* 1.07, CHCl<sub>3</sub>).

the known phosphonium salt **A**.<sup>9</sup> However, under a variety of reaction conditions, the yield of the desired olefin **14** was poor (30–40%), which can be attributed to steric hindrance around the formyl group in **13**. At this juncture, use of the Julia protocol by exploiting the benzothiazolyl sulfone derivative **B**<sup>10</sup> offered a nice solution to the problem. Thus, the sulfone **B** was lithiated with LiN(TMS)<sub>2</sub> in THF (0 °C, 30 min), which was allowed to react with aldehyde **13** (–78 → 25 °C, then 9 h), with smooth olefination occurring to afford the corresponding olefin in excellent yield with high (*E*)-selectivity.

The remaining tasks were (1) saturation of the C=C and the C≡C bonds, (2) removal of two benzyl groups, and (3) one-carbon degradation. Thus, hydrogenation of **14** was attempted by using 10% palladium on charcoal in MeOH. However, steric hindrance made the reaction extremely slow, and moreover, product **15** was found to suffer from substantial epimerization at C2. Judging from the <sup>1</sup>H NMR, the epimer ratio was 80/20. To suppress this stereomutation,

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(9) Gargiulo, D.; Blizzard, T. A.; Nakanishi, K. *Tetrahedron* **1988**, *45*, 5423.

(10) (a) Baudine, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175. (b) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285. (c) Drew, M. G. B.; Harwood; L. M.; Jahans, A.; Robertson, J.; Swallow, S. *Synlett* **1999**, 2, 185.

various attempts to optimize the reaction were conducted with limited success.

The final solution was achieved in the following manner. The benzyl protecting groups were detached under Birch conditions (Ca, NH<sub>3</sub>, THF, –45 °C, 2 h),<sup>11</sup> in which part of the diol product underwent partial saturation of the triple bond. Subjection of this mixture to hydrogenation (PtO<sub>2</sub>, MeOH, 25 °C, 1 h) gave the corresponding fully saturated diol **15** in 87% yield with minimal epimerization (95:5). Upon treatment of diol **15** with PDC (pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 3 days), the oxidation proceeded cleanly to give lactone **16** in 85% yield and the epimer *epi*-**16** in 3% yield, which were easily separated by SiO<sub>2</sub> column chromatography.

Acid hydrolysis of the acetal **16** followed by glycol cleavage and borohydride reduction gave (–)-malyngolide (**1**) in 77% yield. The spectroscopic data coincided with those of the natural product.<sup>1</sup>

In summary, we have described an easy route to the *pseudo*-C<sub>3</sub>-symmetric tertiary alcohol **4** and its TMS surrogate **5**, which will find versatile use in organic synthesis.

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(11) (a) Birch, A. J. *J. Chem. Soc.* **1944**, 403. (b) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.