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Stereogenic *tert*-alcohols via group-selective hydroalumination: further scope

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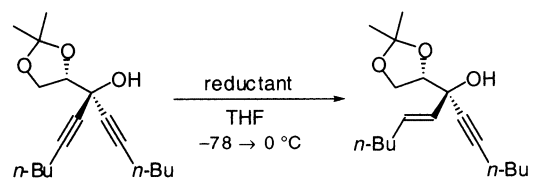
Abstract—Two classes of bis-alkynyl alcohols were subjected to hydroalumination reaction, which, under suitable conditions, proceeded in a highly group-selective manner. © 2002 Elsevier Science Ltd. All rights reserved.

Previous reports from this laboratory have described the group-selective hydroalumination of bis-alkynyl alcohols possessing an adjacent chiral center.[1] Eq. (1) is illustrative, where one of the diastereotopic alkynyl groups in **1** undergoes reduction upon treatment with $LiAlH_4$ (protocol A). The selectivity was further improved by increasing the steric bulk of the aluminum ligands (see protocol B by using *n*-BuLi–DIBAL), thereby giving **2** as the sole product.[1]



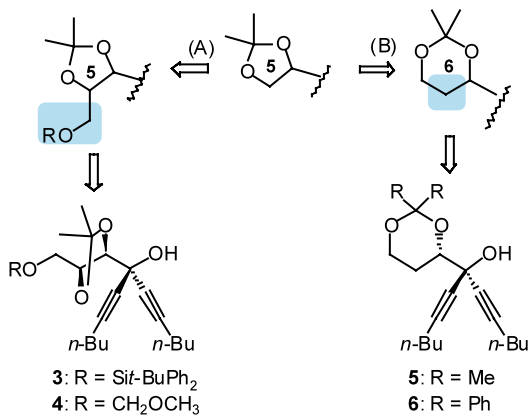
1 **2** (1)

protocol A: $LiAlH_4$ (90%, 96% *d.s.*)

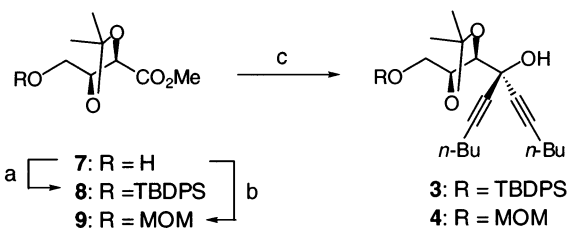
protocol B: *n*-BuLi, DIBAL (94%, >99% *d.s.*)

In an effort to explore the scope and limitations of this process, we examined the group-selective hydroalumination of various related bis-alkynyl alcohols. Two classes of substrates have been tested (Scheme 1), which differ from **1** in (A) the substituent at the dioxolane moiety (**3** and **4**) and (B) the ring size, that is, the dioxanes **5** and **6**. Under suitable conditions, high group selectivities were attained for the reaction of these bis-alkynyl alcohols, which will be described in this communication.

Starting materials **3** and **4** were prepared from the known compound **7**[2] derived from (*R*,*R*)-tartaric acid (Scheme 2), and substrates **5** and **6** were obtained from the (*S*)-malic acid derivative **10**[3] (Scheme 3).



Scheme 1.



Scheme 2. (a) TBDPSCl, imidazole, DMF, 90%; (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 89%; (c) *n*-BuC≡CH, *n*-BuLi, THF, 91% for **3** and 93% for **4**. TBDPS = *t*-butyldiphenylsilyl, MOM = methoxymethyl.

Keywords: hydroalumination; group selectivity; chelation.

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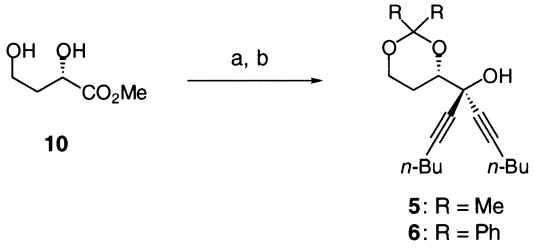


Scheme 3. (a) 2-Methoxypropene, PPTS, acetone, 84% or $Ph_2C(OMe)_2$, *p*-TsOH, benzene, 74%; (b) *n*-BuC≡CH, EtMgBr, THF, 92% for **5** and 79% for **6**. PPTS = pyridinium *p*-toluenesulfonate.

Table 1 summarizes the reactions of the tartaric acid-derived substrates **3** and **4**. Treatment of **3**, possessing a *t*-butyldiphenylsilyl (TBDPS) group, with $LiAlH_4$ (added at −78°C, and warmed immediately to 0°C followed by stirring for 1 h) afforded the corresponding mono-hydroalumination product **11** with high group selectivity (run 1).[4,5] In terms of the mode of group selection, *the alkynyl group anti to the adjacent oxygen* reacted, as had been the case with the substrate **1** without the siloxymethyl substituent (vide supra, Eq. (1)). The selectivity was further improved by using the *n*-BuLi–DIBAL procedure (run 2).

Although the reactivity was inferior with the latter protocol in that some starting material remained unchanged, the product **11** was obtained as a single isomer.

The group selectivity is explained by the 'space-filling model' (Fig. 1), which we previously proposed for the simpler cases without the additional substituent (Eq. (1); vide supra).[1] Since the siloxymethyl substituent (yellow) fills the space that is remote from the reaction site, it poses little, if any, influence on the reaction course.[6]

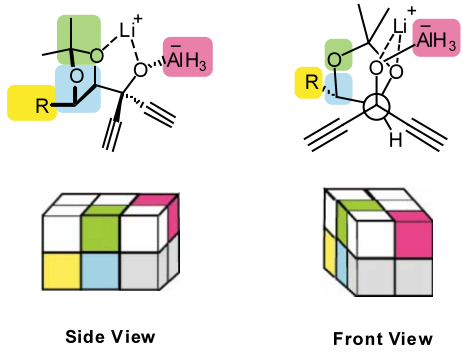


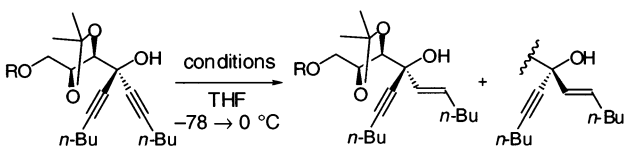
Figure 1.

In line with this view, the silyl protecting group in **3** could be replaced by a chelating group, such as a MOM group without loss of the group selectivity. Thus, upon treatment of **4** with $LiAlH_4$ under essentially the same conditions as those for run 1, the hydroalumination proceeded with high group selectivity (92%) to give the enynyl alcohol **12** (run 3).[7] Again, the selectivity was reinforced to a near perfect level by employing the *n*-BuLi–DIBAL procedure (run 4). The improved selectivity with the *n*-BuLi–DIBAL protocol (runs 2 and 4) may stem from the increased steric bulk of the aluminum ligands.[1]

The hydroalumination of malic acid-derived substrates **5**, having a 1,3-dioxane ring, are summarized in Table 2.

In contrast to the dioxolane cases, the dioxane substrate **5** reacted with $LiAlH_4$ in a non-selective manner, thereby giving a 55/45 mixture of **13** and *epi*-**13** (run 1). The *n*-BuLi–DIBAL procedure proceeded with somewhat better group selectivity to give a 73/27 mixture of **13** and *epi*-**13** (run 2). Importantly, however, the sense of group selection was opposite to that of previous

Table 1.



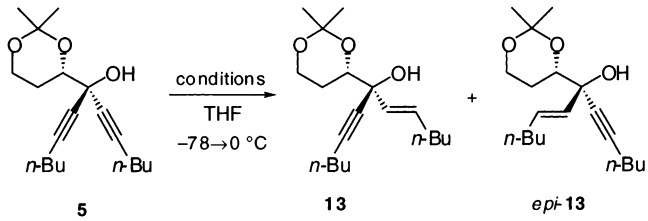
3: R = TBDPS
4: R = MOM

11: R = TBDPS *epi*-**11**: R = TBDPS
12: R = MOM *epi*-**12**: R = MOM

Run	R	Conditions	Time (h)[c]	Yield (%)	Group selectivity
1	TBDPS	$LiAlH_4$[a]	1	94	95/5
2	TBDPS	*n*-BuLi, DIBAL[b]	5	84[d]	>99/<1
3	MOM	$LiAlH_4$[a]	1.5	92	92/8
4	MOM	*n*-BuLi, DIBAL[b]	4.5	83[e]	>99/<1

[a] $LiAlH_4$ (2.0 mol equiv.).
[b] *n*-BuLi (1.2 equiv.), DIBAL (1.3 equiv.).
[c] Reaction time at 0°C.
[d] Recovery of **3** (12%).
[e] Recovery of **4** (14%).
TBDPS = *t*-butyldiphenylsilyl, MOM = methoxymethyl.

Table 2.



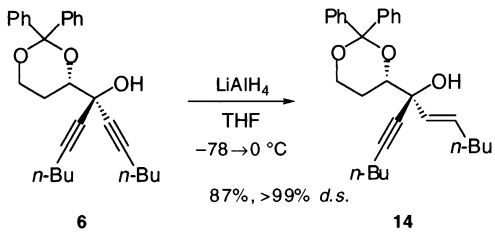
Run	Reagents	Time (h)[c]	Yield (%)	**13**/*epi*-**13**
1	$LiAlH_4$[a]	2	87[d]	55/45
2	*n*-BuLi, DIBAL[b]	18	83[d]	73/27

[a] $LiAlH_4$ (2.0 mol equiv.).
[b] *n*-BuLi (1.2 equiv.), DIBAL (1.3 equiv.).
[c] Reaction time at 0°C.
[d] Recovery of **5** [5% (run 1), 11% (run 2)].

dioxolane cases (cf. Eq. (1)). Indeed, *the alkynyl group syn to the adjacent oxygen took part in the reaction* in this case, whereas the one *anti* to the adjacent oxygen underwent the hydroalumination in the dioxolane cases.

This apparent reversal of the reaction mode could be explained again by the space-filling model as shown in Fig. 2A. The important difference from the dioxolane case (cf. Fig. 2B) is that the location of the isopropylidene that directs the placement of the aluminate, and thus, the preferred alkynyl group becomes different, if not exclusive, that undergoes the hydroalumination.

This model suggested that the selectivity would be improved, if the steric demand of the acetal moiety was increased. Indeed, the attempted reaction of the diphenylmethylidene acetal **6** afforded the enynyl alcohol **14** as the exclusive product (Eq. (2)).[7]



(2)

Further study showed that the selectivity is highly dependent on the countercation of the reducing agent (Table 3). Na^+ and K^+ gave poor selectivities (runs 1 and 2), which strongly suggested the importance of the chelation effect in the group selectivity. *A surprising finding along these lines was that the magnesium alkoxide led to the opposite group selection*, thereby giving *epi*-**13** in high selectivity (run 3). This suggests that a dual approach to stereoisomeric *tert*-alcohols such as **13** and *epi*-**13** in high selectivity is possible. We are currently studying the improvement of the yield as well as the rationale for the reversal of the group selectivity.

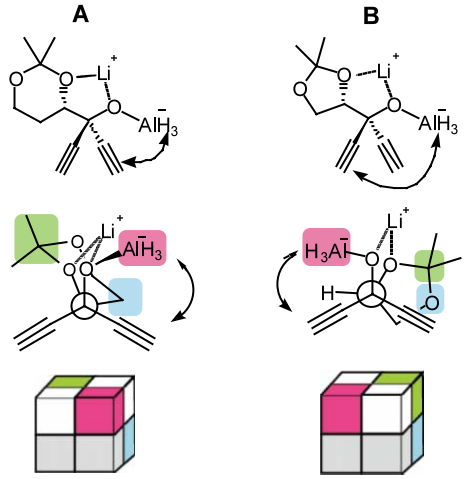
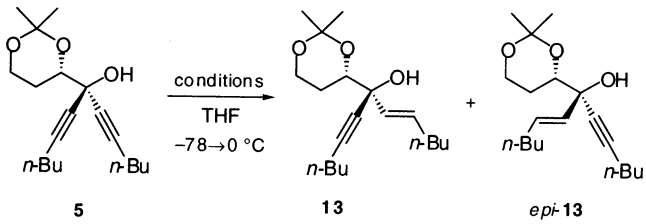


Figure 2.

Table 3.



Run	Reagents	Time (h)[d]	Yield (%)	**13**/*epi*-**13**
1	NaH, DIBAL[a]	4	64[e]	44/56
2	KH, DIBAL[b]	3.5	75[e]	43/57
3	EtMgBr, DIBAL[c]	6	56[e]	5/95

[a] NaH (1.2 equiv.), DIBAL (1.3 equiv.).
[b] KH (1.2 equiv.), DIBAL (1.3 equiv.).
[c] EtMgBr (1.2 equiv.), DIBAL (1.3 equiv.).
[d] Reaction time at 0°C.
[e] Recovery of **5** [18% (run 1), 20% (run 2), 36% (run 3)].

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4. All new compounds were fully characterized by spectroscopic means. The diastereomer ratios of the products were determined by NMR (500 MHz) analysis. Stereochemical assignments were based on extensive correlation studies.

5. **Experimental procedure for the hydroalumination of 3 with $LiAlH_4$**: To a solution of $LiAlH_4$ (28.2 mg, 0.743 mmol) in THF (0.5 mL) was added **3** (208 mg, 0.371 mmol) in THF (1.9 mL) at −78°C. The temperature was raised to 0°C, and stirring was continued for 1 h. The reaction was stopped by adding $Na_2SO_4 \cdot 10H_2O$. After stirring for 3 h at room temperature, white solid was filtered off and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane/acetone/EtOAc = 91/3/6) to afford the mixture of **11** and *epi*-**11** (196 mg, 94%, **11**/*epi*-**11** = 95/5) as colorless oil.

   Experimental procedure for the hydroalumination of 3 with *n*-BuLi and DIBAL: To a solution of **3** (263 mg, 0.469 mmol) in THF (1.9 mL) was added *n*-BuLi (0.22 mL, 2.6 M hexane solution, 0.57 mmol) at −78°C, and the mixture was stirred for 30 min. To the resulting solution was added DIBAL (0.22 mL 2.9 M hexane solution, 0.65 mmol), and stirring was continued for 30 min. The temperature was raised to 0°C, and stirring was continued for 6.5 h. The reaction was stopped by adding aqueous potassium sodium tartrate. After stirring for 10 h at room temperature, the products were extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane/acetone/EtOAc = 95/3/2) to afford **11** (223 mg, 84%, >99% d.s.) with a recovery of **3** (31 mg, 12%). **11** (colorless oil): $[\alpha]_D^{28} = -39$ (*c* 1.0, $CHCl_3$); IR (neat) 3455, 2930, 2860, 2240, 1590, 1430, 1380, 1245, 1215, 1115, 975, 825, 740, 705, 615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 6H, $J = 6.9$ Hz), 1.06 (s, 9H), 1.28–1.44 (m, 8H), 1.49 (s, 3H), 1.50 (s, 3H), 1.93–2.06 (m, 2H), 2.17 (t, 2H, $J = 6.9$ Hz), 2.75 (s, 1H), 3.65 (dd, 1H, $J = 11.1$, 3.6 Hz), 3.91 (dd, 1H, $J = 11.1$, 2.1 Hz), 4.12–4.19 (m, 2H), 5.46 (d, 1H, $J = 15.3$ Hz), 6.04 (dt, 1H, $J = 15.3$, 6.9 Hz), 7.33–7.46 (m, 6H), 7.68–7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 13.9, 18.4, 19.3, 22.0, 22.3, 26.8, 27.3, 27.6, 30.5, 31.1, 31.6, 64.0, 71.9, 78.4, 79.1, 81.5, 88.2, 109.7, 127.6, 129.5, 129.6, 129.7, 133.2, 133.3, 133.9, 135.7; Anal. calcd for $C_{35}H_{50}O_4Si$: C, 74.68; H, 8.95. Found: C, 74.59; H, 9.24.
6. In our previous experiences (Ref. 1a), the silyloxy group, if proximal to reaction site, was labile under these reaction conditions. Desilylation was the major event observed.
7. **Experimental procedure for the hydroalumination of 5 with EtMgBr and DIBAL**; To a solution of **5** (165 mg, 0.538 mmol) in THF (2.0 mL) was added EtMgBr (1.7 M hexane, 0.38 mL, 0.65 mmol) at 0°C, and the mixture was stirred for 1 h at 25°C. After cooling to −78°C, to the resulting solution was added DIBAL (2.9 M hexane, 0.24 mL, 0.70 mmol), and stirring was continued for 15 min. The temperature was raised to 0°C, and stirring was continued for 6 h. The reaction was stopped by adding aqueous potassium sodium tartrate, after stirring for 10 h at room temperature, the products were extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/acetone = 95/5) to afford the mixture of **13** and *epi*-**13** (93.2 mg, 56%) as colorless oil.