Enantio- and Diastereo-selective Reaction of But-2-enylstannane with Glyoxylate Esters and its Application to a Short Synthesis of Verrucarinolactone

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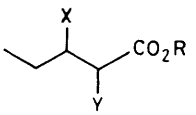
The *erythro*-3-alkyl-2-hydroxypropionate unit in (**4**) is predominantly obtained *via* the reaction of but-2-enylstannane (**2a**) with glyoxylate esters (**3**) while the *threo*-isomer (**5**) is preferentially produced *via* 9-but-2-enyl-9-borabicyclo[3.3.1]nonane (**2b**); the former reaction has been applied to the enantioselective synthesis of verrucarinolactone (**6**).

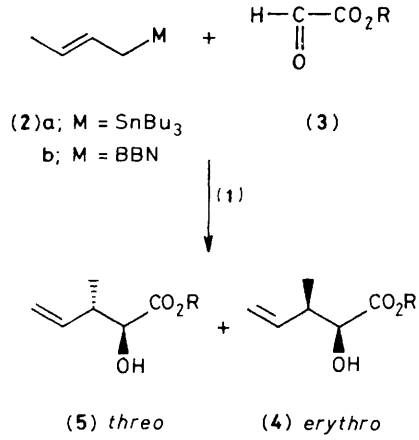
The diastereo- and enantio-selective synthesis of the 2-alkyl-3-hydroxypropionate unit in (**1a**) has received wide attention and a number of excellent methods have been reported.[1] On the other hand, diastereo- and enantio-selective methods for synthesising the 3-alkyl-2-hydroxypropionate unit in (**1b**) seem to be inadequate despite its frequent occurrence in many important natural products.[2] We report an allylic organometallic solution to this problem (equation 1) and its application to the enantioselective synthesis of verrucarinolactone (**6**). The reaction of the but-2-enyl organometallic compounds (**2**) with the glyoxylate esters (**3**) was examined and the results are summarised in Table 1.



(**1**) **a**; X = OH, Y = Me
b; X = Me, Y = OH

The *erythro*-isomer (**4**) was obtained predominantly *via* (**2a**) and the selectivity was enhanced with increasing steric bulk of the ester groups. In contrast, the *threo*-isomer (**5**) was produced preferentially *via* (**2b**) and again the selectivity was enhanced with increasing steric bulk. Although the *threo*-selectivity was not high (3 : 1 at most), the *erythro*-selectivity exhibited with the Pr^i group appeared to be suitable for further synthetic applications. We chose verrucarinolactone (**6**),[4] the left half of the macrocyclic portion of verrucarin A, as the target molecule.

It was thought that (**2a**) would attack the carbonyl group of the glyoxylate ester of 8-phenylmenthol (**7**)[5] from the *si*-

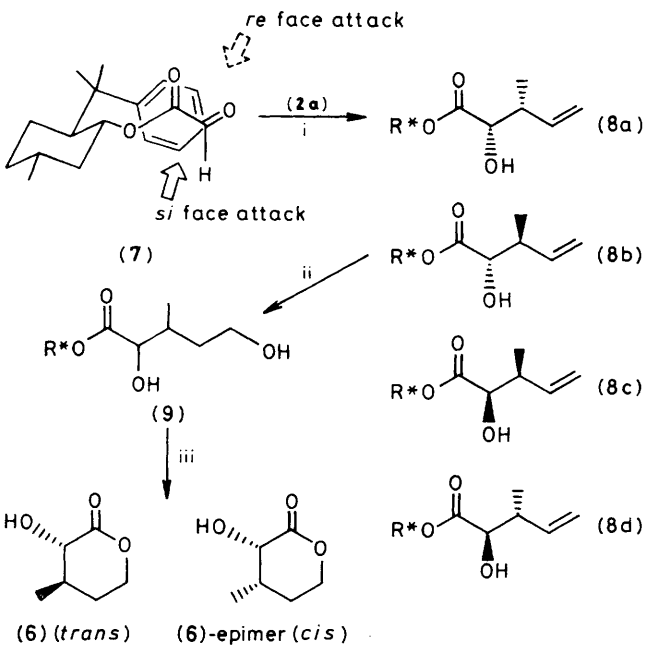


BBN = 9-borabicyclo[3.3.1]nonan-9-yl.

Table 1. Reaction of but-2-enyl organometallic compounds (**2**) with (**3**).[a]

(2)	(3) (R)	Solvent	Product ratio/%[b] (4) *erythro*	(5) *threo*
(**2a**)	Me	CH_2Cl_2	75	25
	Bu^n	CH_2Cl_2	80	20
	Pr^i	CH_2Cl_2	90	10
(**2b**)	Me	Et_2O	40	60
	Bu^n	Et_2O	30	70
	Pr^i	Et_2O	25	75

[a] All reactions were carried out on a 1 mmol scale as previously described.[3] Total yields (isolated) were in the range 75—85% for (**2a**) and 80—90% for (**2b**). [b] By g.l.c. (CW 6000, 5%, 2 m).



i, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 80%; ii, $BH_3{\cdot}SMe_2$, hexane; NaOH–H_2O_2, 70%; iii, *p*-$MeC_6H_4SO_3H$, CH_2Cl_2, 30—35 °C, 24 h, 60%. R* = 8-phenylmenthyl.

face, since the phenyl group would block the attack from the *re*-face. Thus, it is clear that (**8a**) and (**8b**) result from attack at the *si*-face of (**7**), and (**8c**) and (**8d**) from attack at the *re*-face of (**7**). The aldehyde proton of (**7**) appeared at δ 8.37 (CCl_4, Me_4Si) owing to the shielding of the aromatic ring. The reaction of (**7**) with (**2a**) in the presence of one equivalent of $BF_3{\cdot}OEt_2$ afforded (**8a**) as a major product; (**8a**):(**8b**):(**8c**) + (**8d**) = 84:9:7. The ratio of these four diastereoisomers was determined by g.l.c. (DC 550, 10%, 3 m) and ^1H n.m.r. analysis† (CCl_4, Me_4Si); (**8a**), δ 0.72 (3H, d, *J* 6.9 Hz), 0.8—2.2 (18H, m), 2.47 (1H, d, *J* 5.4), 3.02 (H, dd, *J* 5.4 and 3.0), 4.80 (3H, m), 5.60 (1H, m), and 7.20 (5H, m); (**8b**), 0.8—2.2 (21H, m), 2.43 (1H, d, *J* 5.3), 2.98 (1H, dd, *J* 5.3 and 2.4), 4.78 (3H, m), 5.57 (1H, m), and 7.20 (5H, m); (**8c**) + (**8d**), not separable. Hydroboration–oxidation of the mixture of these isomers (**8**) gave the diol (**9**) in 70% yield, which in turn was treated with toluene-*p*-sulphonic acid. The usual work-up afforded white crystals, m.p. 93—94 °C. ^1H N.m.r. spectroscopy showed a ratio of (**6**) to its epimer of 90:10; the methyl proton of (**6**) resonated at δ 1.21, while that of its epimer resonated at δ 1.02. Recrystallization from ether gave pure (**6**), m.p. 101—102 °C, $[\alpha]_D^{21.5}$ −8.82° (10 cm cell, *c* 0.57, $CHCl_3$), 91% enantiomeric excess. The similar reaction with (**2b**) gave (**8b**) as the major product, though the selectivity was low in comparison with the selectivity *via* (**2a**); (**8a**):(**8b**):(**8c**) + (**8d**) = 30:52:18.‡ The simple procedure and high levels of enantio- and diastereo-selectivity attainable with (**2a**) may provide a practical method for the asymmetric synthesis of (**6**).

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2 T. Sato, K. Tajima, and T. Fujisawa, *Tetrahedron Lett.*, 1983, 729 and references cited therein.

3 Y. Yamamoto, H. Yatagai, Y. Naruta, and K. Maruyama, *J. Am. Chem. Soc.*, 1980, **102**, 7107; Y. Yamamoto, H. Yatagai, and K. Maruyama, *ibid.*, 1981, **103**, 1969. The relative configurations of (**4**) and (**5**) were assigned through transformations into racemic verrucarinolactone and its epimer.

4 For the recent synthesis of (**6**), see B. M. Trost and P. McDougal, *Tetrahedron Lett.*, 1982, 5497; W. R. Roush, T. A. Blizzard, and F. Z. Basha, *ibid.*, 1982, 2331; W. C. Still and H. Ohmizu, *J. Org. Chem.*, 1981, **46**, 5242; K. Tomioka, F. Sato, and K. Koga, *Heterocycles*, 1982, **17**, 311; P. Mohr, M. Tori, P. Grossen, P. Herold, and C. Tamm, *Helv. Chim. Acta*, 1982, **65**, 1412.

5 For asymmetric synthesis *via* this chiral auxiliary, see J. K. Whitesell, A. Bhattacharya, and K. Henke, *J. Chem. Soc., Chem. Commun.*, 1982, 988; 989; W. Oppolzer and H. J. Loher, *Helv. Chim. Acta*, 1981, **64**, 2808; E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, 1975, **97**, 6908.

† The absolute configurations of (**8a**) was determined from the known absolute configuration of (−)-verrucarinolactone. (**8a**) + (**8b**) could be separated from (**8c**) + (**8d**) by silica gel column chromatography using hexane–ether (20:1) as eluant. The ratio of (**8a**) to (**8b**) was 9:1. This mixture was converted into verrucarinolactone and the ratio of (**6**) to its epimer was 9:1. Since the separation at the initial stage is not easy, recrystallization at the final stage is recommended for preparative purposes.

‡ Here again, (**8a**) + (**8b**) were separated from (**8c**) + (**8d**), and converted into a mixture of verrucarinolactone (**6**) and its epimer.