Asymmetric Synthesis of (−)-*exo*-Brevicomin. Chirality Transfer from a Chiral (Tetrahydropyranyloxyallyl)boronate in the Condensation with Aldehydes

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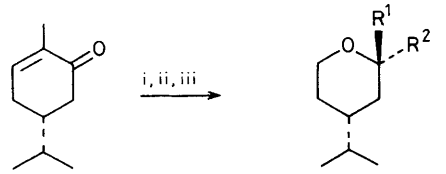
Chirality transfer from a chiral (γ-tetrahydropyranyloxyallyl)boronate is employed to secure the asymmetry in the synthesis of (−)-*exo*-brevicomin.

During the course of our studies on the chemistry of (γ-alkoxyallyl)boronates[1] we observed that (γ-tetrahydropyranyloxyallyl)boronates upon reaction with aldehydes gave the expected *erythro* diol derivatives but unexpectedly we found that upon examination of the ^{13}C n.m.r. spectra of these compounds only a single diastereoisomer was produced. This observation implied that the chirality of the tetrahydropyranyl (THP) anomeric centre was transferred to the two new chiral centres in the product diol. As a result, we reasoned that the use of a chiral THP group should result in asymmetric induction and allow preparation of chiral 1,2-diol derivatives.

We now describe the synthesis of a chiral (γ-tetrahydropyranyloxyallyl)boronate and its application to the synthesis of (−)-*exo*-brevicomin (**8**).



(**1**)

(**2**) $R^1, R^2 = H, OH$

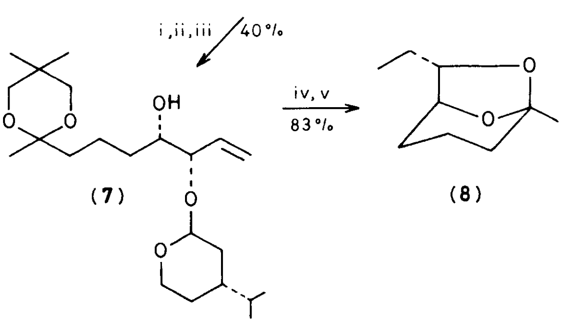
(**3**) $R^1 = H, R^2 = OCH_2CH{=}CH_2$

(**4**) $R^1 = OCH_2CH{=}CH_2, R^2 = H$

Reagents: i, O_3, hexane; $LiAlH_4$; ii, $NaIO_4$; iii, $CH_2{=}CHCH_2OH$, $p\text{-}MeC_6H_4SO_2OH$.

Preparation of the required chiral acetal (**4**) utilized (−)-(*R*)-dihydrocarvone (94% enantiomeric excess) as a source of chirality. Ozonolysis of dihydrocarvone (**1**) followed by reductive work-up ($LiAlH_4$) gave a triol which was treated with $NaIO_4$ to afford hemiacetal (**2**). Conversion of the hemiacetal into allyl acetals (**3**) and (**4**)† proceeded smoothly

(**4**)



(**7**) (**8**)

Reagents: i, Bu^sLi; ii, (**5**); iii, (**6**); iv, H_2/Pd; v, H_3O^+.

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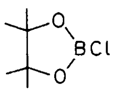
† α-Anomer: $[\alpha]_D^{20}$ −127.7° (*c* 6.350, $CHCl_3$); b.p. 101 °C (12 Torr); ^1H n.m.r. ($CDCl_3$) δ 5.95 (m, 1H), 5.30 (m, 1H), 5.17 (m, 1H), 4.89 (d, *J* 4.32 Hz, 1H), 4.18 (m, 1H), 3.96 (m, 1H), 3.78 (m, 1H), 3.63 (m, 1H), 1.82—1.27 (m, 6H), 0.88 (d, *J* 7.68 Hz, 3H), 0.87 (d, *J* 7.68 Hz, 3H); i.r. (film) 2960, 2880, 1750, 1470, 1400, 1135, 1090, 1055 cm^{-1}. β-Anomer: $[\alpha]_D^{20}$ +46.45° (*c* 7.670, $CHCl_3$); b.p. 110 °C (12 Torr); ^1H n.m.r. ($CDCl_3$) δ 5.95 (m, 1H), 5.30 (m, 1H), 5.18 (m, 1H), 4.35 (m, 2H), 4.05 (m, 2H), 3.41 (dt, J_1 2.40, J_2 10.56 Hz, 1H), 1.85 (m, 1H), 1.55—1.15 (m, 5H), 0.89 (d, *J* 6.72 Hz, 6H).



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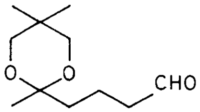

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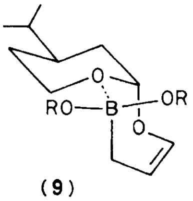

(9)

giving a 3 : 1 anomeric mixture which was easily separated by spinning band distillation.

In procedures similar to those previously described,[2] the allyl ether (**4**) was treated with Bu^sLi at −78 °C to generate an allyl anion which was quenched with 2-chloro-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5**)[3] to afford the chiral (γ-alkoxyallyl)boronate (**9**). Treatment of boronate (**9**) with aldehyde (**6**) provided a 25 : 2 : 1 diastereoisomeric mixture of diol derivatives. The major isomer, diol derivative (**7**), was chromatographically isolated and converted into (−)-*exo*-brevicomin (**8**) by hydrogenation and acid treatment. Comparison of the optical rotation of the synthetic material $\{[\alpha]_D^{29}$ $-60.0°$ (c 2.57, Et_2O)$\}$ with enantiomers of known absolute configuration $\{[\alpha]_D^{24}$ $-80.6°$ (c 1.60, Et_2O)$\}$[4] established its identity as unnatural (−)-(1*S*,7*S*)-*exo*-brevicomin (**8**).[‡]

Explanation of the observed diastereoselectivity relies on intramolecular co-ordination of the tetrahydropyranyl ring oxygen with boron. Of the possible conformers, (**9**) is expected to be favoured over other possible conformers, owing to the less serious interactions of ring carbons with the double bond. Aldehyde addition presumably proceeds by initial complex formation with inversion at pseudotetrahedral boron, followed by adoption of a Zimmerman type six-centre transition state after rotation of the boron nucleus away from the chiral auxiliary. The overall transformation results in the creation of two *S* chiral centres from the original *S* centre of the acetal.

In conclusion, we have shown that chirality may readily be transferred from a chiral (γ-tetrahydropyranyloxyallyl)boronate to afford optically active diol derivatives.

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Added in proof: R. W. Hoffmann has informed us that he has made a similar observation concerning chirality transfer of this type.

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References

1 P. G. M. Wuts and S. S. Bigelow, *J. Org. Chem.*, 1982, **47**, 2498.
2 P. G. M. Wuts and S. S. Bigelow, *Synth. Commun.*, 1982, **12**, 779.
3 A. Mendoza and D. S. Matteson, *J. Organomet. Chem.*, 1978, **156**, 149.
4 R. Bernardi, C. Fuganti, and P. Grasselli, *Tetrahedron Lett.*, 1981, **24**, 4021.

[‡] The 360 MHz ^{1}H n.m.r. spectrum of the optically active material was identical with the racemic mixture: see ref. 2.