Tetrahedron Letters, Vol. 34, No. 32, pp. 5031-5034, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

# (+)-EXO-BREVICOMIN *VIA* AN ORGANOMETALLIC BOULEVARD

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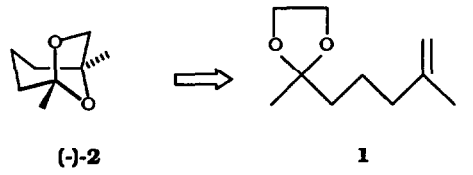
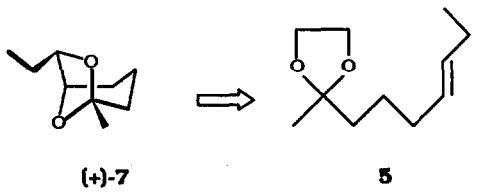
**Abstract.** *The brevicomin carbon skeleton was efficiently constructed through a novel 2 + 3 + 4 sequence via organocuprate and Suzuki couplings. The Sharpless catalytic asymmetric dihydroxylation provided either naturally occurring (+)-exo-brevicomin* **(+)-7** *or its enantiomer,* **(-)-7**, *both in 95% ee, in 61% overall yield from allyl bromide.*

Popular targets for synthetic chemists,[2a,b] the bicyclic ketals, (-)-frontalin, **(-)-2**, and (+)-*exo*-brevicomin, **(+)-7**, aggregation pheromones of the southern and western pine beetles, *Dendroctonus frontalis* and *Dendroctonus brevicomis*, respectively, have been prepared through a variety of synthetic strategies. We recently described a new scalemic synthesis of **(-)-2** where, after assembling the carbon framework through first, copper- and then, palladium-based couplings, the Sharpless catalytic asymmetric dihydroxylation (AD) of **2** provided the pheromone in 35% ee.[3] The modest optical yield notwithstanding, we felt that the skeletal construction was particularly meritorious and envisaged that with a *simple modification of one step*, the versatility of this approach could be demonstrated with the asymmetric synthesis of **7** rather than of **2** (*cf.* Schemes 1 and 2). The ketone equivalent of **5** (*i.e.* **9**) is well-known to lead to **(±)-7** through the Os-based *cis*-dihydroxylation[2a,b] and its stoichiometric reaction with a chiral amine-$OsO_4$ complex gives **(+)-7** in 91% ee.[2c] We felt that **5**, with its *trans* configuration, provided the ideal substrate to demonstrate the efficacy of the Sharpless catalytic protocol,[4] leading to **7** with the pure *exo* stereochemistry in far higher optical purity than was achieved in **2**. Moreover, because the accelerating phthalazine ligands (*i.e.* dihydroquinine- ( $(DHQ)_2$-PHAL ) or dihydroquinidine- ( $(DHQD)_2$-PHAL ) based) exhibit essentially the reverse enantioselectivities, either enantiomer of **7** would be available from **5** depending upon the choice of the ligand[4] employed in the AD (Scheme 3).

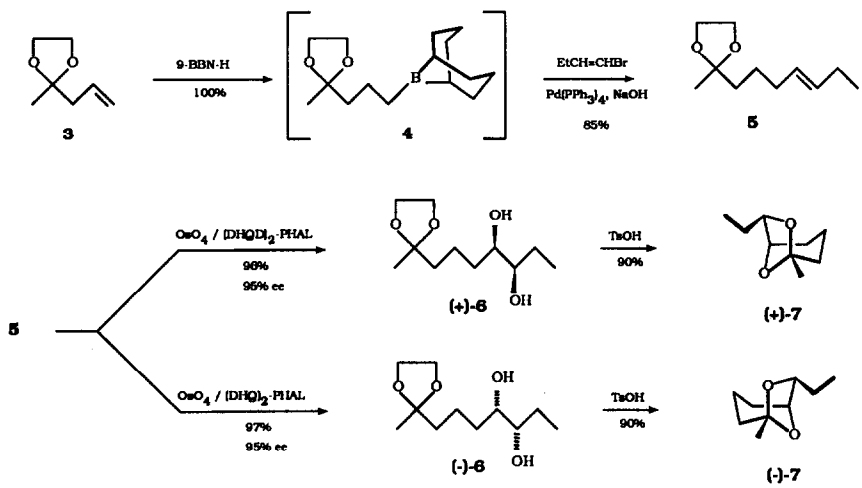



**Scheme 1**




**Scheme 2**

**Scheme 3**




As earlier described,[3] **3** was prepared in 83% yield from the coupling of allyl bromide with a higher-order α-methoxyvinylcuprate followed by ketalization. We chose not to isolate **4**,[3] but rather to carry out its *in situ* cross coupling with *trans*-1-bromobutene[5] which gave **5** in 85% yield as the pure *trans* isomer.[6,7]

The racemic dihydroxylation of **5** was accomplished using the $OsO_4/K_3Fe(CN)_6$/DABCO method[8] to afford **(±)-6**, quantitatively. The Sharpless $(DHQD)_2$-PHAL AD produced **(+)-6** ($[\alpha]_D^{25}$ + 16.2° (c, 0.129, $CHCl_3$) in 96% yield.[9] Repeating this process with the $(DHQ)_2$-PHAL ligand gave **(-)-6** in 97% yield ($[\alpha]_D^{25}$ - 15.3° (c, 0.127, $CHCl_3$). Each of these diols was converted to the corresponding Mosher's diesters (**8**) ((2*S*)-MTPA-Cl, DMAP, THF, 25 °C, 2 h) and these were quantitatively analyzed by $^{13}C$ NMR. C-4' (encircled) provided particularly well-resolved signals at δ 75.3 and 74.7 ppm for the **(4'*R*,5'*R*)-8** (from **(+)-6**) and **(4'*S*,5'*S*)-8** (from **(-)-6**) isomers, respectively (Figure 1). The peak shapes while differing somewhat integrate to equal areas (±2%) for this carbon in each of the diastereomeric diesters, **8**, derived from **(±)-6**, as we have previously observed in related systems.[3,4d] Integration of these signals in **8** derived from either **(+)-6** or **(-)-6** consistently results in a 98-97:2-3 (or *vice versa*) area ratio or *ca.* 95% de in **8** in each case.

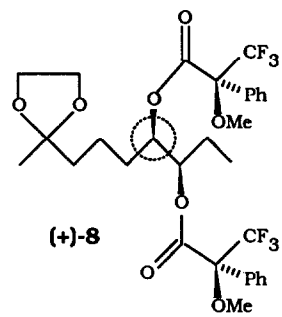
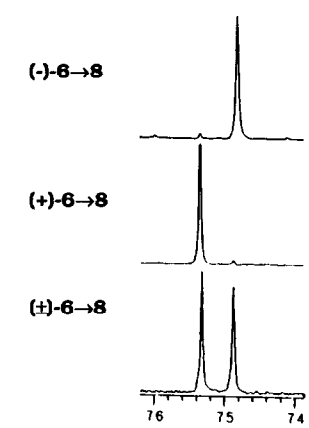
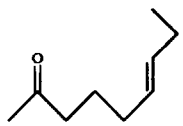



**Figure 1.** $^{13}C$ NMR for C-4' in **8**.




The clean conversions of **(+)-6** → **(+)-7** and **(-)-6** → **(-)-7** were effected under standard conditions (*p*-TsOH (0.75 equiv), $CH_2Cl_2$,

25 °C, 2 h) which provided the desired enantiomers of *exo*-brevicomin in *ca.* 90% yields ((+)-**7**: $[\alpha]_D^{25}$ + 59.6° (c 0.069, $CHCl_3$); (-)-**7**: $[\alpha]_D^{25}$ - 59.4° (c 0.068, $CHCl_3$). As noted by Mori,[2a] the reported [α] values for **7** vary over a wide range (*ca.* 34°), are solvent dependent and we also observed an increase in the $[\alpha]_D^{25}$ (*e.g.* - 65.4° (c 0.026, $CHCl_3$) with dilution.




**9**

It was recently suggested by Weigel[4c] that a remote ketone functionality may lower the observed ee from the AD compared to substrates lacking this functionality. In accord with this postulate, the AD (DHQ ligand) of **9** produced **(-)-7** directly, in an estimated 74% ee ($[\alpha]_D^{25}$ - 50.7° (c 0.026, $CHCl_3$)), lower than from **5**.

Sharpless has recently published the X-ray structure of his $(DHQD)_2$-PHAL catalyst.[4b] To appreciate the essentially "enantiomeric" environment brought to a metal atom by these ligands, the MMX-minimized structures for this ligand and its $(DHQ)_2$-PHAL counterpart, are illustrated with "mirror image" orientations in Figure 2. These minima differ from the X-ray structure for $(DHQD)_2$-PHAL in that the quinuclidine N-C-C-O(PHAL) array is calculated to be more stable in a nearly *antiperiplanar* arrangement rather than the *gauche-type* conformation of these atoms observed in the solid state (*cf.* ref. 4b).

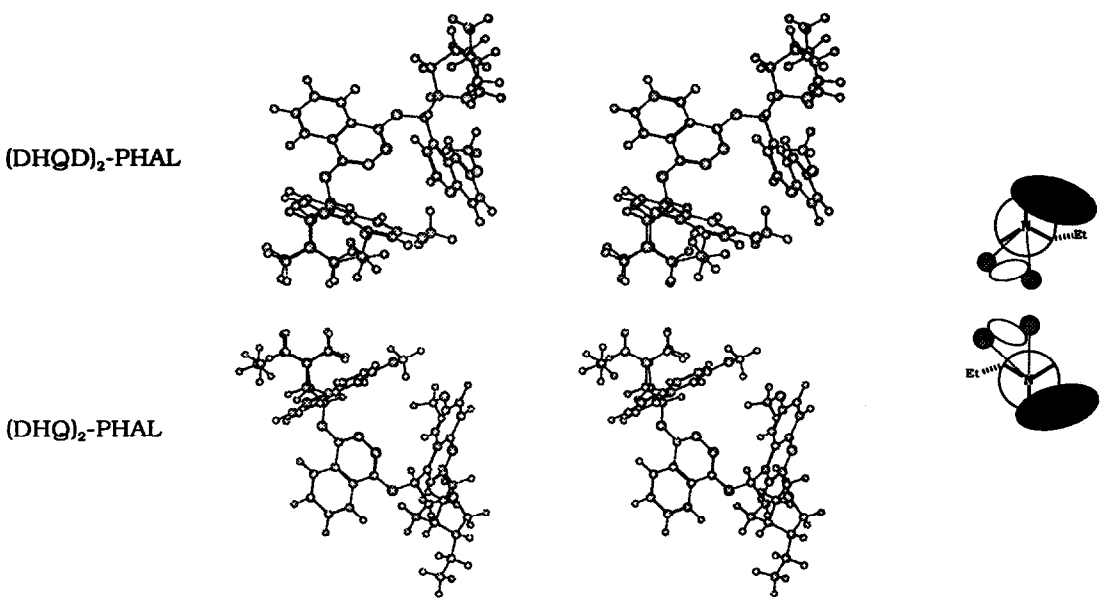



**Figure 2.** MMX-Minimized Structures (Stereoview) for $(DHQD)_2$-PHAL (top left) and $(DHQ)_2$-PHAL (bottom left) and a Model for the Preferred Enantiofacial Selectivity of *trans*-Alkenes (right).

These diastereomeric ligands differ from true enantiomers only in their having a common (5*R*)-ethyl group in each of the DHQD (or DHQ) components. Each quinuclidine in both functions independently,[4b] with the DHQD *vs* DHQ catalysts exhibiting essentially

opposite enantioselectivities (*e.g.* **6**)[4b] which are ultimately determined with the formation of the osmate ester.[10] Regardless of the precise nature of the L--$OsO_4$--alkene interactions (*i.e.* L•$OsO_4$ + alkene[10a,b] or osmaoxetane[10a,c] + L), the enantioselectivities observed with *trans*-1,2-dialkyl substrates such as **5** are probably largely sterically based, with electronic factors undoubtedly playing a larger role in the AD of unsymmetrical alkenes.[4] Our MMX structures suggest that the "enantiomeric" orientation of the protruding quinoline rings may be responsible for the chirality transfer to the alkene (Cartoon, Figure 2), regardless of the precise manner by which osmium brings these species into proximity.

Through three isolated intermediates, both enantiomeric forms of *exo*-brevicomin have been prepared from allyl bromide (61% overall yield) *via* organometallics and the remarkable Sharpless catalytic asymmetric dihydroxylation.

**ACKNOWLEDGMENTS.** The support of NSF EPSCoR of PR (Dr. Manuel Gómez, Program Director) and helpful discussions with Professor K. B. Sharpless are gratefully acknowledged.

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6. **5**: To a solution of 9-BBN-H (3.66 g, 30.0 mmol) in pentane (20 mL) at 25 °C was added **1** (3.371 g, 26.3 mmol). After 4 h, NaOH (2.4 g, 60 mmol) in water (10 mL) was added, and this heterogeneous mixture was added to a flask containing $Pd(PPh_3)_4$ (0.4 g, 0.35 mmol), *trans*-1-bromo-1-butene (7.1 g (53% GC purity), 28.0 mmol)[5] in THF (20 mL). After heating for 2 h at 50-60 °C, pentane (50 mL) was added and the organic phase was washed with water (5 X 20 mL) and filtered through neutral $Al_2O_3$ (50 g) with $C_5H_{12}$ (100 mL). Concentration followed by distillation gave 4.114 g (85%) of **5**[7] (bp 69 °C, 0.7 Torr, > 98% GC purity). $^1H$ NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.5 Hz, 3H), 1.26 (s, 3H), 1.41 (m, 2H), 1.58 (m, 2H), 1.95 (m, 4H), 3.88 (m, 4H), 5.33 (dt, *J* = 15.3, 5.4 Hz, 1H), 5.41 (dt, *J* = 15.4, 5.4 Hz); $^{13}C$ NMR ($CDCl_3$) δ 13.8, 23.6, 24.0, 25.5, 32.6, 38.6, 64.5, 110.0, 128.8, 132.3; IR (TF) 2878, 1710, 1460, 1060, 965 $cm^{-1}$; MS *m/z* (rel abundance) 184 ($M^{\ddagger}$, 0.5), 87 (100).

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9. **(-)-6**: To a well-stirred mixture of $(DHQ)_2$-PHAL (0.078 g, 0.1 mmol), $K_3Fe(CN)_6$ (6.6 g, 20 mmol), $K_2CO_3$ (2.8 g, 20 mmol), $H_2O$ (20 mL), *t*-BuOH (20 mL), $OsO_4$ (0.100 mL, of 0.4 M in PhMe) at 0 °C, was added $MeSO_2NH_2$ (0.475 g, 5 mmol) followed by **5** (0.921 g, 5 mmol) and after 32 h, solid $NaHSO_3$ (5 g) was added, the mixture was stirred for 1 h, extracted with EtOAc (3 X 25 mL) and the organics were washed with 2 M KOH (3 x 5 mL), dried over $MgSO_4$ and concentrated to give 1.055 g (97%) of **(-)-6** ($[\alpha]_D^{25}$ - 15.3° (c 0.127, $CHCl_3$). Similarly, $(DHQD)_2$-PHAL gave **(+)-6** ($[\alpha]_D^{25}$ + 16.2° (c 0.129, $CHCl_3$)) and DABCO[8] gave **(±)-6**. $^1H$ NMR ($CDCl_3$) δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.35 (s, 3H), 1.50 (m, 8H), 2.34 (bs, 2H), 3.36 (dt, *J* = 8.4, 4.5 Hz, 1H), 3.44 (quint, *J* = 7.5, 4.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 9.8, 20.1, 23.6, 26.3, 33.6, 38.9, 64.4, 73.7, 75.6, 110.0; IR (TF) 3440, 2980, 1740, 1375 $cm^{-1}$; Anal. calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.49; H, 10.19.

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(Received in USA 20 April 1993; accepted 11 May 1993)