# A New Access to the 6,8-Dioxabicyclo[3.2.1]octane Ring System Using a Three-Component Reaction: Enantioselective Synthesis of (+)-iso-*exo*-Brevicomin

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**Abstract:** The combination of a catalytic hetero-Diels–Alder–allylboration sequence and a ruthenium-catalyzed isomerization of an allylic alcohol moiety as key steps open a new route for the asymmetric synthesis of 6,8-dioxabicyclo[3.2.1]octane subunits. The application of this strategy to the synthesis of (+)-iso-*exo*-brevicomin is also reported.

**Key words:** natural product, asymmetric catalysis, cycloaddition, boron, redox isomerization

Development of new approaches for the construction of 6,8-dioxabicyclo[3.2.1]octane ring system is an attractive goal due to the number of natural products that contain this unit, as insect pheromones[1] or more complex natural products.[2] Most of them exhibited promising bioactive profiles, such as cyclodidemniserinol trisulfate, isolated from the Palauan Ascidian *Didemnum guttatum*, which is an inhibitor of HIV-1 integrase (Figure 1).[3] These properties have drawn widespread attention and Ley and coworkers recently used this 6,8-dioxabicyclo[3.2.1]octane ring system as scaffold for the discovery of new biologically active compounds.[4]

Among recent strategies reported in the literature for the construction of this fused bicyclic acetal may be mentioned the elegant ketalization–ring-closing metathesis sequence[5] and the cycloisomerization of alkynediols with various metals.[6] However, the synthesis of dihydroxyketones followed by an intramolecular acetalization remains the most widely used process for the preparation of 6,8-dioxabicyclo[3.2.1]octane skeleton.[7]

Recently, we and Hall's group have simultaneously described an efficient three-component cycloaddition–allylboration sequence using Jacobsen's chiral Cr(III) catalyst **2**,[8] to give α-hydroxyalkyl dihydropyrans **3**.[9] This sequence begins by an inverse electron-demand hetero-[4+2] cycloaddition that affords a cyclic allylboronate, which is then able to react with an aldehyde to give the six-membered adducts with two contiguous asymmetric centers. The efficiency of this methodology in terms of stereoselectivity and yields has been validated by the synthesis of various natural products.[10]

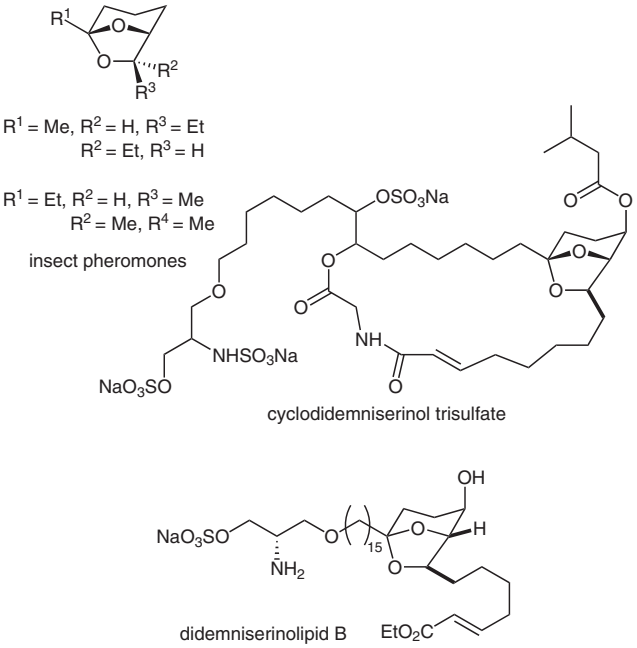


**Figure 1** Natural products containing the 6,8-dioxabicyclo[3.2.1]octane ring system

On the basis of these precedents, we envisioned that α-hydroxyalkyl dihydropyran derivatives **3** could be good precursors in an alternative strategy for the asymmetric construction of 6,8-dioxabicyclo[3.2.1]octane ring system. This approach can generate molecular diversity due to the multicomponent methodology, but also because of the presence of a double bond that can be easily further functionalized. To illustrate the versatility of this approach, an efficient synthesis of (+)-iso-*exo*-brevicomin is also presented (Scheme 1).

The α-hydroxyalkyl dihydropyran derivatives **3a–d** were prepared using our previously described tandem reaction with a high enantio- and diastereoselectivity.[9c] Formation of the 6,8-dioxabicyclo[3.2.1]octane ring system from **3a** under aqueous acidic conditions led to the desired product in the presence of substantial quantity of starting material (6 M HCl–THF, **4a**: 50%). Transformation of acetals **3** into **4** were found to be cleaner and more efficient using boron trifluoride etherate as Lewis acid (Scheme 2). For example, reaction of **3d** with 1.1 equivalents of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ for 10 minutes at 0 °C provided **4d** in 95% yield after purification.[11]

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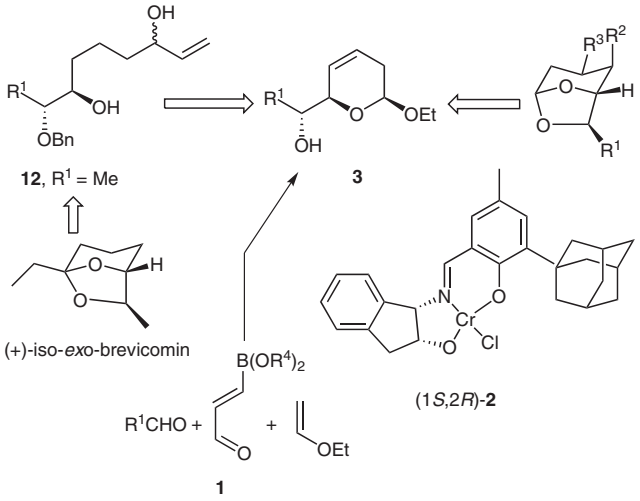
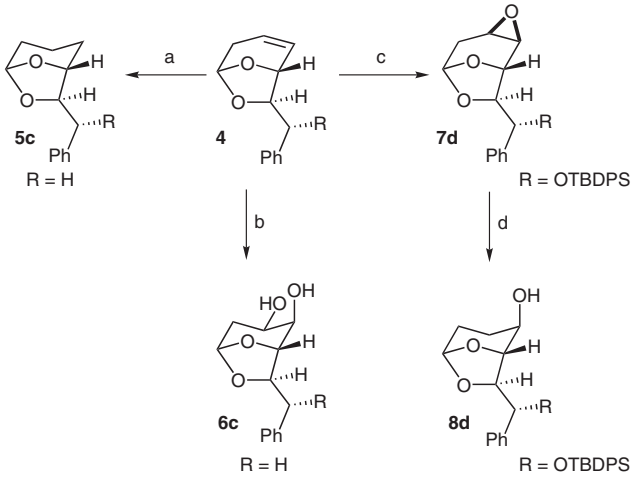



**Scheme 1** Retrosynthetic analysis



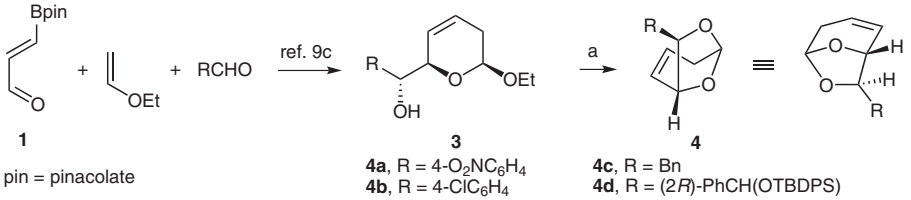

**Scheme 3** *Reagents and conditions*: a) $H_2$ (1 atm), 10% Pd(C), $Et_2O$, r.t., 2 h, 98%; b) cat. $OsO_4$ (0.3 mol%), NMO (1.5 equiv), acetone–$H_2O$, r.t., 12 h, 70%; c) MCPBA (3 equiv), $CH_2Cl_2$, 0 °C to r.t., 93%; d) $LiAlH_4$ (3 equiv), THF, 0 °C to r.t., 87%.

With these structurally diverse bicyclic acetals in hand, our next aim was to show that the double bond present in these units is a point of chemical diversification. Hydrogenation of **4c** using palladium on charcoal in $Et_2O$ led to the formation of the expected product **5c** (Scheme 3). On the other hand, the double bond of **4c** was subjected to the usual dihydroxylation conditions using a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide as a co-oxidant, to afford the desired diol **6c** as a single diastereomer. In light of this result, we envisaged the installation of the C2 axial alcohol, present on 6,8-dioxabicyclo[3.2.1]octane nucleus of numerous natural products, using an epoxidation–LAH reduction protocol. The olefin of bicyclic acetal **4d** underwent a stereoselective epoxidation with MCPBA at room temperature in $CH_2Cl_2$ to afford **7d** in 93% yield as a unique diastereomer. It is interesting to note that the epoxide **7d** can be also obtained from **3d** with a 60% yield, using a 2:1 mixture of MCPBA and $BF_3{\cdot}OEt_2$ reagents in a 'one-pot' process. Reductive *trans*-diaxial opening of epoxide **7d** was accomplished by treatment of $LiAlH_4$ at 0 °C. This procedure was successfully reported in the literature on similar structures.[5b] Under these nonoptimized conditions, the desired axial alcohol **8d** was obtained in 87% yield.[12]

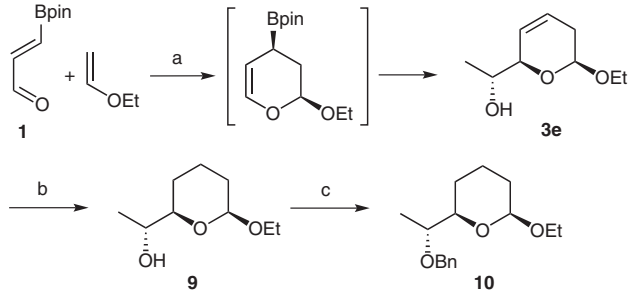
In order to show also the interest of this approach for accessing molecules possessing a central 6,8-dioxabicyclo[3.2.1]octane core with two appended alkyl chains, we decided to synthesize (+)-iso-*exo*-brevicomin. This natural product is an aggregation pheromone produced by the Western pine beetle *Dendroctonus ponderosae*, a principle pest in the timber regions of west coast of North America.[13] To the best of our knowledge, several syntheses of iso-*exo*-brevicomin were reported,[13,14] but only one for the dextrogyre enantiomer[14d] in which stereochemical centers are generated by carbon–carbon bond formation.

Our work began by the preparation of the new dihydropyran **3e** possessing the requisite configuration, using the asymmetric catalyzed hetero-Diels–Alder–allylboration sequence (Scheme 4). After completion of the cycloaddition step which led to the formation of cyclic allylboronate, freshly distilled acetaldehyde was added. The mixture was then warmed at 40 °C for 5 hours to furnish intermediate **3e** in 70% yield as a single diastereomer in a >95% enantiomeric excess.[15] Hydrogenation of the double bond in presence of Pd/C, followed by benzylation of the hydroxy group using standard conditions, afforded the benzyl ether **10** with a 69% overall yield for the two steps.

As mentioned in the retrosynthetic analysis, our plan was to install the ketone function via a redox isomerization of allylic alcohol **12**. It was important to note that few examples of this reaction have been employed in total synthesis.[16] For this purpose, hydrolysis of ethyl lactol **10** was carried out with camphorsulfonic acid in an aqueous mixture at room temperature to give the compound **11**, which was converted into a mixture of diastereomers of allylic alcohol **12** by addition of vinylmagnesium chloride (Scheme 5). Considerable effort was devoted to the transposition of allylic alcohols into saturated carbonyls medi-




**Scheme 2** *Reagents and conditions*: a) $BF_3{\cdot}OEt_2$ (1.1 equiv), $CH_2Cl_2$, r.t.; **4a**: 92%, **4b**, 93%, **4c**: 87%, **4d**: 95%.

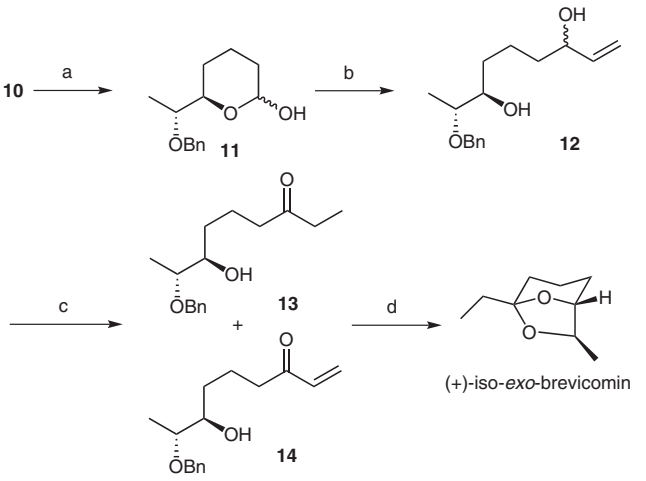



**Scheme 4** *Reagents and conditions*: a) **2** (0.01 equiv), 4 Å MS, r.t., 2 h then MeCHO (10 equiv), 40 °C, 5 h, 70%; b) $H_2$ (1 atm), 10% Pd/C, $Et_2O$, r.t., 2 h, 96%; c) NaH (1.3 equiv), BnBr (1.5 equiv), $Bu_4N^+I^-$ (0.1 equiv), THF, r.t., 24 h, 72%.

ated by transition-metal catalysts.[17] Recently, we reported that ruthenium (II) complex $[RuCp^*(MeCN)_3][PF_6]$ is able to catalyze this transformation of functionalized substrates under smooth conditions.[18] In a first experiment for the transformation of **12** into carbonyl compound **13**, we used reaction conditions similar to those previously described (acetonitrile as solvent, potassium carbonate as base, and 2 mol% of catalyst). After one hour at reflux, the desired product was not detected by $^1H$ NMR analysis of the crude reaction mixture. The best conditions were found in changing the solvent and increasing the quantity of catalyst to 20 mol%. In toluene at room temperature, the carbonyl compound **13** was obtained in the presence of α,β-unsaturated carbonyl **14** in a ratio 7:3, respectively, with 75% overall yield.[19] This result clearly confirms our postulated mechanism in which the catalyst $[RuCp^*(MeCN)_3][PF_6]$ reacts firstly by a β-hydride elimination, followed in a second time by the 1,4-addition of the ruthenium monohydride species on the α,β-unsaturated ketone. We did not seek to improve the ratio in favor of saturated carbonyl compound taking into account that the hydrogenation reaction of the mixture, in presence of palladium on charcoal and a trace of acid, could lead to the formation of the same product.

Indeed, the (+)-iso-*exo*-brevicomin was obtained in 60% yield after purification on silica gel[20] {$[\alpha]_D^{25}$ +53 (*c* 0.3, $CHCl_3$); lit.[14d] $[\alpha]_D$ +54 (*c* 0.5, $CHCl_3$)} and with an overall yield of 12.3% starting from the (2*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enal (**1**,[21] 7 steps).

In conclusion, we reported in this paper a new approach for the asymmetric synthesis of the 6,8-dioxabicyclo-[3.2.1]octane ring system based on a three component hetero-Diels–Alder–allylboration sequence. This strategy was validated by the total synthesis of (+)-iso-*exo*-brevicomin including a redox isomerization of an allylic alcohol among the key steps. Use of this new route for the synthesis of more complex molecules comprising a 6,8-dioxabicyclo[3.2.1]octane skeleton is currently under way in our laboratory.




**Scheme 5** *Reagents and conditions*: a) CSA (1.5 equiv), MeCN–$H_2O$ (1:1), r.t., 18 h, 90%; b) vinylmagnesium chloride (2.2 equiv), THF, 0 °C, 63%; c) $[RuCp^*(MeCN)_3][PF_6]$ (20 mol%), $K_2CO_3$ (1.2 equiv), toluene, r.t., 24 h, 75%; d) $H_2$ (1 atm), 10% Pd/C, MeOH, 3 M HCl, r.t., 18 h, 60%.

## Acknowledgment

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(11) **General Procedure and Selected Characterization Data**
To a stirred solution of **3** (0.3 mmol) in $CH_2Cl_2$ (3 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (0.33 mmol). After 10 min, the resulting solution was warmed to r.t. and stirred for 90 min (excepted in the case of **3d**). The reaction mixture was quenched with sat. aq $NaHCO_3$ (1 mL), and the aqueous phase was extracted with $Et_2O$ (2 × 2 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Compounds **4** were purified by flash chromatography on silica gel (210–400 mesh).
Compound **4d** was obtained as a colorless oil (95%). $[\alpha]_D^{25}$ +33.5 (*c* 1.75, $CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 9 H), 1.91–1.97 (m, 1 H), 2.33–2.42 (m, 1 H), 4.26 (d, 1 H, *J* = 8.4 Hz), 4.44 (d, 1 H, *J* = 8.8 Hz), 4.47 (d, 1 H, *J* = 4.9 Hz), 5.50–5.52 (m, 1 H), 5.60–5.63 (m, 1 H), 5.98–6.04 (m, 1 H), 7.20–7.28 (m, 7 H), 7.35–7.49 (m, 6 H), 7.66–7.71 (m, 2 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 19.4, 26.9, 33.8, 72.0, 75.0, 88.7, 100.9, 124.3, 127.4, 127.5, 127.6, 127.7, 128.0, 128.9, 129.7, 129.8, 133.0, 134.0, 135.9, 136.0, 141.4. Anal. Calcd for $C_{29}H_{32}O_3Si$: C, 76.28; H, 7.06. Found: C, 76.35; H, 7.01.
(12) Compound **8** was obtained as colorless oil (87%). $[\alpha]_D^{25}$ +20.3 (*c* 1.30, $CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 9 H), 1.45–1.88 (m, 4 H), 2.29 (br s, 1 H), 3.60–3.63 (m, 1 H), 4.04 (d, 1 H, *J* = 7.3 Hz), 4.20–4.25 (m, 1 H), 4.49 (d, 1 H, *J* = 7.3 Hz), 5.32 (br s, 1 H), 7.21–7.33 (m, 7 H), 7.35–7.48 (m, 6 H), 7.61–7.69 (m, 2 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 19.4, 23.8, 26.8, 26.9, 66.7, 76.1, 77.2, 78.9, 81.5, 102.5, 127.4, 127.6, 127.8, 128.1, 129.6, 129.8, 133.1, 133.8, 135.9, 136.0, 140.9. Anal. Calcd for $C_{29}H_{34}O_4Si$: C, 73.38; H, 7.22. Found: C, 73.37; H, 7.11.
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(19) 1-Phenylpropan-1-one can be obtained from the corresponding allylic alcohol in 97% yield with only 2 mol% of $[RuCp^*(MeCN)_3][PF_6]$ in toluene at r.t. These new conditions represent an improvement of the previously described process with this catalyst.
(20) **Characterization Data for Key Synthetic Intermediates**
Compound **3e** was obtained from **1** in 70% yield as a colorless oil. $[\alpha]_D^{25}$ +72 (*c* 0.59, $CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.25 (m, 6 H), 2.19–2.22 (m, 2 H), 2.72 (br s, 1 H), 3.53 (dq, 1 H, *J* = 7.1, 9.3 Hz), 3.69–3.72 (m, 1 H), 3.96 (dq, 1 H, *J* = 7.1, 9.3 Hz), 3.98–4.03 (m, 1 H), 4.72 (dd, 1 H, *J* = 4.8, 6.1 Hz), 5.60–5.63 (m, 1 H), 5.78–5.80 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 15.2, 18.6, 31.1, 64.4, 69.6, 78.8, 98.5, 124.9, 126.1. HRMS (EI): *m/z* [M – $\cdot OCH_2CH_3$]$^+$ calcd for $C_7H_{11}O_2$: 127.0759; found: 127.0755.
Compound **12** was obtained as colorless oil (mixture of diastereomers, 63%). $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, 3 H, *J* = 5.9 Hz), 1.35–1.70 (m, 6 H), 1.81 (br s, 1 H), 2.68 (br s, 1 H), 3.40–3.43 (m, 2 H), 4.09–4.12 (m, 1 H), 4.43 (d, 1 H, *J* = 11.5 Hz), 4.68 (d, 1 H, *J* = 11.5 Hz), 5.11 (dd, 1 H, *J* = 1.2, 10.4 Hz), 5.23 (d, 1 H, *J* = 17.2 Hz), 5.88 (ddd, 1 H, *J* = 6.2, 10.4, 17.2 Hz), 7.26–7.43 (m, 5 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 15.5, 21.3, 21.4, 32.5, 32.6, 36.9, 71.0, 73.0, 73.1, 74.8, 74.9, 78.3, 78.4, 114.5, 114.6, 127.7, 127.8, 128.5, 138.3, 141.1, 141.2. ESI-HRMS: *m/z* [M + Na]$^+$ calcd for $C_{16}H_{24}O_3Na$: 287.1623; found: 287.1623.
(+)-Iso-*exo*-brevicomin was obtained as a colorless oil (highly volatile, 60%): $[\alpha]_D^{25}$ +53 (*c* 0.3, $CHCl_3$); lit.[14d] $[\alpha]_D$ +54 (*c* 0.5, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, 3 H, *J* = 7.9 Hz), 1.18 (d, 3 H, *J* = 6.5 Hz), 1.43–1.95 (m, 8 H), 4.06 (br s, 1 H), 4.22 (q, 1 H, *J* = 6.5 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 7.3, 17.1, 21.6, 28.0, 30.6, 33.5, 75.5, 79.9, 109.5. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.27; H, 10.41.
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