A Short, High-yield, Stereoselective Synthesis of Racemic *exo*- and *endo*-Brevicomin

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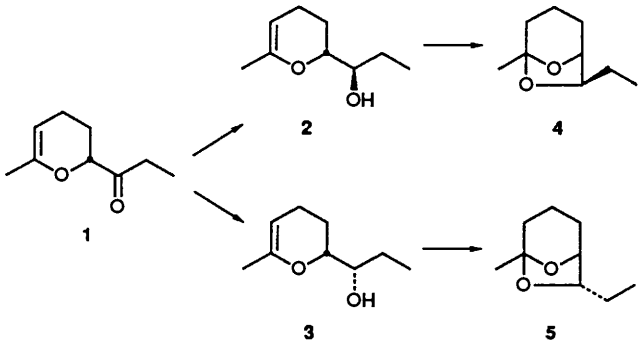
Stereoselective reduction and cyclization of 6-methyl-2-propionyl-2,3-dihydro-4*H*-pyran provides brevicomin in quantitative yield as a 86:14 or a 17:83 mixture of *exo* and *endo* isomers through DIBAH reduction in ether at reflux or $Zn(BH_4)_2$ in the presence of $ZnCl_2$ in ether at 0 °C, respectively.

The *exo* and *endo* isomers of brevicomin are exuded by the frass of the western pine beetle, *Dendroctonus brevicomis*, and the *exo* isomer **4** is known to be a key component of the aggregation pheromone of this destructive pest.[1] The *endo* isomer **5** is a potent inhibitor of the aggregation behaviour of the likewise destructive southern pine beetle.[2] Several syntheses of brevicomin have been published in the literature.[3] In this investigation, we report a stereoselective reduction of 6-methyl-2-propionyl-2,3-dihydro-4*H*-pyran **1** followed by a cyclization in one flask to produce either *exo*- or *endo*-brevicomins (Scheme 1).



Scheme 1

For the stereoselective reduction of the ketone **1** which is prepared from methyl vinyl ketone (MVK) dimer,[4] it is postulated that hydride attack on the ketone occurs from the less encumbered side of the ring methylene or the ring oxygen. Models A, B and C are proposed. A is the Cram chelate rule model,[5] while B and C correspond to the Cornforth dipolar model[6] and the Felkin model.[7] The bridged structure A is expected to control the stereoselectivity when the reagent is capable of chelation with the ring oxygen and the carbonyl oxygen. The *erythro* alcohol **3** could be derived from this chelating structure. Structures B and C are assumed to be important in the absence of chelation to the ring oxygen. The nonchelating structures B and C should favour the *threo* isomer **2** (Fig. 1).

Diisobutylaluminium hydride (DIBAH), $Zn(BH_4)_2$, K- or L-Selectride, $LiAlH_4$ and $NaBH_4$ have been applied under several conditions to the reduction of MVK dimer (Table 1) which is

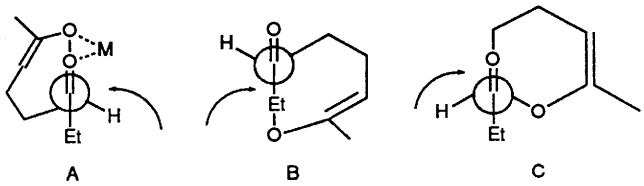


Fig. 1

Table 1 Stereoselective reduction of methyl vinyl ketone dimer

Entry	Reducing agent	Solvent	Temp. (°C)	*threo*–*erythro*
1	DIBAH	Et_2O	reflux	84:16
2	DIBAH	Et_2O	room temp.	82:18
3	DIBAH	Et_2O	0	75:25
4	DIBAH	Et_2O	−20	68:32
5	DIBAH	Et_2O	−78	68:32
6	DIBAH	CH_2Cl_2	reflux	80:20
7	DIBAH	CH_2Cl_2	room temp.	78:22
8	DIBAH	CH_2Cl_2	−20	65:35
9	DIBAH	CH_2Cl_2	−78	69:31
10	DIBAH	THF	reflux	68:28
11	DIBAH	THF	room temp.	70:30
12	DIBAH	THF	−20	70:30
13	DIBAH	THF	−78	83:17
14	$Zn(BH_4)_2$–$ZnCl_2$	Et_2O	room temp.	40:60
15	$Zn(BH_4)_2$–$ZnCl_2$	Et_2O	0	20:80
16	$Zn(BH_4)_2$–$ZnCl_2$	Et_2O	−78	80:20
17	$Zn(BH_4)_2$–$ZnCl_2$	CH_2Cl_2	room temp.	32:68
18	$Zn(BH_4)_2$–$ZnCl_2$	CH_2Cl_2	0	19:81
19	$Zn(BH_4)_2$–$ZnCl_2$	CH_2Cl_2	−78	86:14
20	$Zn(BH_4)_2$–$ZnCl_2$	THF	room temp.	39:61
21	$Zn(BH_4)_2$–$ZnCl_2$	THF	0	35:65
22	$Zn(BH_4)_2$–$ZnCl_2$	THF	−78	81:19

similar to **1**. DIBAH is known as a non-chelating reagent[8] and gives the expected non-chelating product (*threo* alcohol) in our system as a major isomer (entries 1–13). Solvent and temperature effects were noticed; higher temperature was more effective in diethyl ether (entry 1) or CH_2Cl_2 (entry 6), but lower temperature was favoured in THF (entry 13) for *threo* selectivity. Also, *erythro* selectivity is known in the reduction of α,β-epoxy ketones by using $Zn(BH_4)_2$ which can form a chelated transition state.[9] In our system, only a slight excess of *erythro* isomer was formed by the $Zn(BH_4)_2$ reduction, but this was much enhanced by the addition of $ZnCl_2$. *erythro*-Selectivity was not much improved in DIBAH–$ZnCl_2$ reduction. At lower temperature (−78 °C), the chelating ability of $Zn(BH_4)_2$ was assumed to be depressed even with $ZnCl_2$ (entries 16, 19, 22). The best *erythro* selectivity was achieved at 0 °C in diethyl ether (entry 15) or CH_2Cl_2 (entry 18).

The *threo* **2** and *erythro* **3** alcohols are converted into *exo* **4** and *endo* **5** isomers of brevicomin, respectively, by acid ring closure reaction using toluene-*p*-sulphonic acid at reflux.[10] We found that acidic work-up (2 min shaking) of the reduced alcohol with 15% aqueous HCl was enough for the cyclization into brevicomin in quantitative yield.

For the *exo*-brevicomin **4**, DIBAH (2 equiv.) was added dropwise to 1 mol. equiv. of the ketone **1** which was dissolved and refluxed in dry ether under anhydrous conditions. After 1 h reflux of this reaction mixture, acidic work-up (15% HCl solution) allowed the isolation of a 86:14 mixture of *exo* **4** and *endo* **5** isomers. The isomeric brevicomins were identified by

comparison of their GC, IR and ^1H NMR characteristics with reported values.[11]

For the *endo*-brevicomin **5**, 1 mol. equiv. of the ketone **1** was added to $ZnCl_2$ (2 equiv.) in dry ether at 0 °C. After being stirred for 1 h at 0 °C, $Zn(BH_4)_2$ (3 equiv.) was slowly added to this reaction mixture and stirred for 2 h at the same temperature. Acidic work-up (15% HCl solution) and extraction with ether of this reduced mixture allowed brevicomin in quantitative yield as a 17:83 mixture of *exo* **4** and *endo* **5** isomers.

The present synthesis is by far the simplest to perform and provides the highest yields obtained to date.[3]

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