Efficient synthesis of *exo*- and *endo*-brevicomin from a single precursor

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Diastereoselective reduction of 2-propionyl-6-methyl-3,4-dihydropyran and its ring opened derivatives, followed by acidic work-up, gives mixtures rich (>9:1) of either *exo*- or *endo*-brevicomin.

Key words: *exo*- and *endo*-brevicomin, diastereoselective ketone reduction.

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La réduction diastéréosélective du propionyl-2 méthyl-6 dihydro-3,4 pyranne et de ses dérivés en chaîne ouverte, suivie d'une extraction en milieu acide, conduit à des mélanges riches (>9:1) soit en *exo*- ou en *endo*-brévicomine.

Mots clés : *exo*- et *endo*-brévicomine, réduction diastéréosélective des cétones.

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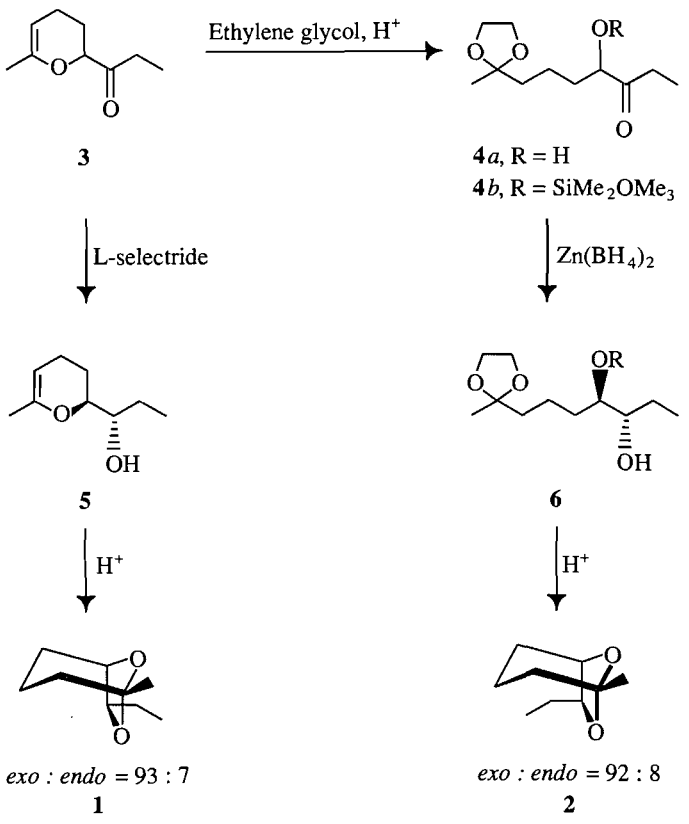
Introduction

We recently reported (1) an investigation of chelation and non-chelation controlled organometallic addition to acrolein dimer as a route to the economically important bicyclic ketals *exo*-brevicomin **1** and *endo*-brevicomin, **2**.[2] Although diastereoselectivity of organometallic addition was quite high, the approach was beset by the difficult vinyl metalation. The present investigation was undertaken to develop an efficient route to racemic **1** and **2** from a single inexpensive intermediate. We have achieved highly diastereoselective chemical reduction of **3** (2) and its acyclic analogs **4***a* and **4***b*. The dihydroxyketones (**5** and **6**) generated in each case readily cyclize in acid to mixtures of alkylated 2,6-dioxabicyclo[3.2.1]octanes (**1** and **2**).

Results and discussion

threo-Selective chemical chemical reduction of **3**, **4***a*, or **4***b* is required to produce **1**. *threo*-Selective reduction of α- and β-oxy-carbonyl compounds is usually achieved by delivery of a hydride from the least hindered side of the carbonyl in the presence of a reagent capable of enhancing the dipolar repulsion between the carbonyl and the α-oxy function but devoid of bidentate chelating ability (non-chelation control). The *erythro*-selective chemical reduction required to produce **2** is usually achieved through use of a Lewis acid capable of coordination of both the carbonyl and α-oxy function followed by hydride delivery from the less hindered side (chelation control) (for an excellent discussion, see ref. 3). Selectride^R reagents effect *threo*-selective reductions while, owing to its superior chelating ability, zinc borohydride is the efficient reagent for *erythro*-selective reductions (4–8).

We found the reductions of **3** and its acyclic derivatives, **4***a* and **4***b*, with several hydride reducing agents are highly diastereoselective (Table 1). The stereochemical course of these reductions was followed by conversion of intermediates **5** and **6** to **1** and **2**, respectively. As previously reported (9), reduction of **3** with $NaBH_4$ in methanol did not show useful selectivity (Table 1, entry 1). Use of either lithium tetrahydridoaluminate or diisobutylaluminum hydride in the reduction of **3** gave similar low diastereoselectivity (entries 2 and 3). Addition of $CeCl_3$ as a chelating agent unexpectedly gave an increased proportion of *threo* product **1** in the reduction of **3** by $NaBH_4$ (entry 4). Neither **4***a* nor **4***b* underwent diastereoselective reduction with $NaBH_4$ (entries 5 and 6). Reduction of **3** with potassium tri(*sec*-butyl)borohydride (10*a*) (K-Selectride^R, entry 7) gave an increased proportion of *threo* product **1**, which was not significantly increased upon addition of BF_3 (entry 8). Reduction of **4***a* or **4***b* with K-Selectride^R offered no advantage in production of **1** (entries 9 and 10). The highest proportion of *threo* product (93:7) from reduction of **3** was achieved using lithium tri(*sec*-butyl)borohydride (10*b*) (Li-Selectride^R, entries 11 and 12). This reducing agent was also the most *threo* selective in reductions of **4***a* (entry 13) and **4***b* (entry 14). The lower yields obtained with BF_3 (entries 8 and 12) may be attributed to competing Lewis acid catalyzed polymerization of the substrates.



SCHEME 1

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[2]For other syntheses of these pheromones see references cited in ref. 1.

TABLE 1. Hydride reduction of **3**, **4***a*, and **4***b*

Entry	Substrate	Hydride donor	Lewis acid	1/2[a]	Yield(%)[b]
1	**3**	$NaBH_4$	None	55/45	78[c]
2	**3**	$LiAlH_4$	None	55/45	88[c]
3	**3**	Dibal-H	None	67/33	92[c]
4	**3**	$NaBH_4$	$CeCl_3$	70/30	58
5	**4***a*	$NaBH_4$	None	53/47	71
6	**4***b*	$NaBH_4$	None	48/52	71
7	**3**	K-selec	None	79/21	94
8	**3**	K-selec	BF_3	82/18	41
9	**4***a*	K-selec	None	71/29	92
10	**4***b*	K-selec	None	80/20	100
11	**3**	L-selec	None	93/7	88[c]
12	**3**	L-selec	BF_3	93/7	44
13	**4***a*	L-selec	None	89/11	82
14	**4***b*	L-selec	None	86/14	85
15	**3**	$Zn(BH_4)_2$	None	27/73	91[c]
16	**3**	K-selec	$ZnCl_2$	74/26	93
17	**3**	L-selec	$ZnCl_2$	80/20	80
18	**4***a*	$Zn(BH_4)_2$	None	8/92	93[c]
19	**4***b*	$Zn(BH_4)_2$	None	22/78	92
20	**3**	K-selec	$MgBr_2$	21/79	85
21	**3**	L-selec	$MgBr_2$	89/11	82
22	**4***a*	K-selec	$MgBr_2$	48/52	93
23	**4***b*	K-selec	$MgBr_2$	22/78	82

[a]Estimated by gas chromatographic analysis (please see Experimental).
[b]Unless otherwise specified, yields determined by gas chromatographic analysis (please see Experimental).
[c]Isolated yields.

Chelation controlled reduction of **3** with zinc borohydride (10*c*) afforded a *threo*:*erythro* ratio of 27:73 (entry 15). Use of K- or Li-Selectride^R with $ZnCl_2$ (entries 16 and 17, respectively) did not dramatically improve *erythro* selectivity. We reasoned that *erythro* selectivity would be increased if the α-oxygen were more available for complexation. Indeed, when **4***a* was reduced with zinc borohydride *erythro* selectivity improved significantly (entry 18).

Addition of $MgBr_2$–Et_2O effected a dramatic alteration of the stereochemical outcome of reduction of **3** by Li-Selectride^R (compare entries 7 and 20) but had little effect in the case of Li-Selectride^R (compare entries 11 and 21). In the former reaction KBr precipitates from the reaction, giving a reducing agent most probably coordinated with magnesium. Lewis acid mediated reversal of selectivity was not observed when $ZnCl_2$ was added to Li-Selectride^R reduction of **3** (compare entries 11 and 17). No improvements of selectivity were observed when **4***a* and **4***b* were reduced with Li-Selectride^R in the presence of $MgBr_2$–Et_2O (compare entries 9, 10, 22, and 23).

Experimental

The nmr spectra were recorded using Bruker WM400 and SY100 spectrometers. Infrared spectra were recorded of neat films between NaCl plates on a Perkin Elmer 599B spectrophotometer. Low resolution mass spectra were recorded on an in-house Hewlett–Packard 5985B GC/MS/DS system operating at 70 eV. Gas chromatographic analysis utilized a Hewlett–Packard 5880A operated with a J + W fused silica DB-1 capillary column (15 m × 0.25 mm), a flame ionization detector, and linear oven temperature programs initiated at 60°C (Program 1) or 100°C (Program 2) and increased at 5°C/min to 200°C. Elemental analyses were performed at the microanalytical laboratory of the Department of Biological Sciences, Simon Fraser University, on a Perkin Elmer Model 240 elemental analyzer.

Chromatography sovents were distilled before use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. All reactions involving air or moisture sensitive reagents were performed under an argon atmosphere.

*Preparation of 2-propionyl-6-methyl-2,3-dihydro-4*H*-pyran, **3***

Fractional distillation of 200 g of an aged (6 months) sample of methyl vinyl ketone afforded 88 g (44%) of methyl vinyl ketone dimer: bp 65–70°C (20 Torr; 1 Torr = 133.3 Pa), lit. (11) bp 68°C (13 Torr); ir (film): 1720 and 1684 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.83 (d, J = 1.0 Hz, 3H), 1.95 (m, 4H), 2.22 (s, 3H), 4.25 (m, 1H), 4.50 (bs, 1H).

The *N*-cyclohexyl imine of methyl vinyl ketone dimer was prepared according to the procedure of Chaquin *et al.* (2); ir (film): 1685 and 1668 cm^{-1}. This compound was treated sequentially with ethylmagnesium bromide in ether and iodomethane to give **3** in 75% overall yield from methyl vinyl ketone dimer; bp, Kugelrohr, 40°C (0.25 Torr), lit. (2) bp 83°C (14 Torr).

*Preparation of **4**a*

A mixture of 0.79 g (5.13 mmol) of **3**, 0.31 g (5 mmol) of ethylene glycol, and ca. 5 mg of oxalic acid monohydrate was kept stirred at 25°C for 48 h. The reaction mixture was chromatographed on 25 g of neutral activity grade 3 alumina using 10–30% ether in hexanes (v/v, gradient) to afford 0.931 g (84%) of **4***a* as a colorless, thermally unstable oil that cyclized to **3** slowly upon standing and rapidly upon attempted distillation. The oil was therefore used immediately following chromatography; ir (film): 3450, 1715 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.027 (t, J = 7.3 Hz, 3H), 1.20 (t, J = 7.2 Hz, 2H), 1.38 (s, 3H), 1.4–2.05 (m, 4H), 2.60 (m, 2H), 3.50 (m, 4H), 3.72 (br t, 1H), 4.08 (dd, J = 11.7, 3 Hz, 1H). Low resolution CIMS (isobutane) m/e: 217 ($M + H^+$). *Anal.* calcd. for $C_{11}H_{20}O_4$: C 61.09, H 9.32; found: C 61.02, H 9.25.

*Preparation of **4**b*

To a solution of 0.532 g (2.0 mmol) of **4***a* and 0.33 g (2.2 mmol) of *tert*-butyldimethylchlorosilane in 2.0 mL of dichloromethane were added 0.164 g (2.08 mmol) of pyridine and ca. 5 mg of DMAP and the reaction mixture was kept stirred at 25°C for 3 h. The reaction mixture was then diluted with 50 mL of ether and washed successively with 2 × 10 mL of 0.05 M KH_2PO_4 and 10 mL of H_2O, dried ($MgSO_4$), and solvents removed *in vacuo*. The residue, upon chromatography on 25 g of neutral activity grade 3 alumina using 10–30% ether in hexane (v/v, gradient) to afford 0.535 g (81%) of **4***b* as a colorless oil, was also thermally unstable and therefore must be stored in the fridge and used within a few days of purification; ir (film): 1720, 1052 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.054 (s, 6H), 0.88 (s, 9H), 1.03 (t, J = 7 Hz, 3H), 1.36 (s, 3H), 1.2–2.0 (m, 6H), 2.61 (q, J = 7 Hz, 2H), 3.52 (m, 2H), 3.75 (m, 2H), 4.23 (dd, J = 11.7, 2.5 Hz, 1H). *Anal.* calcd. for $C_{17}H_{34}O_4Si$: C 61.77, H 10.37; found: C 61.71, H 10.16.

*General procedure for hydride reduction of **3**, **4**a, and **4**b*

In the case of reduction by $NaBH_4$ the reaction was conducted at 0°C in methanol. All other reductions were conducted in dry THF. Thus, typically, the substrate (~0.5 mmol) was dissolved in 2 mL of dry THF and maintained under an atmosphere of argon. The solution was cooled to −78°C and the accompanying salt, if any (2 equivalents), was added. Next, a twofold excess of hydride reagent was added and the reaction was allowed to stir for 1 h at −78°C, then warmed slowly to room temperature. Excess hydride was quenched by addition of a proton source. In the case of $LiAlH_4$ reductions, reaction mixtures were treated with aqueous 5 M NaOH until aluminum salts precipitated. In the case of Dibal-H reductions, reaction mixtures were treated with methanol to achieve precipitation of aluminum salts. The salts were filtered and washed with ether. The aqueous portion of each reaction was extracted with 3 × 10 mL of ether. The combined ether extracts and washings were treated with 2 mL of 2 M H_2SO_4 if this was not already part of the work-up. The ether phase was separated and dried over anhydrous $MgSO_4$ and, where isolation was pursued, these ether extracts were concentrated *in vacuo* to give mixtures of *exo*- and *endo*-brevicomin in the yields and ratios reported in Table 1. Where isolation was not pursued, yields were estimated by capillary gas

chromatographic analyses of the ether extracts to which a known amount of *n*-dodecane internal standard had been added prior to treatment with aqueous 2 M H_2SO_4 and extraction with ether.

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