Stereoselective Synthesis of either (±)-*exo*- or (±)-*endo*-Brevicomin *via* Hydride Reduction of a 2-Acylpyranyl Intermediate

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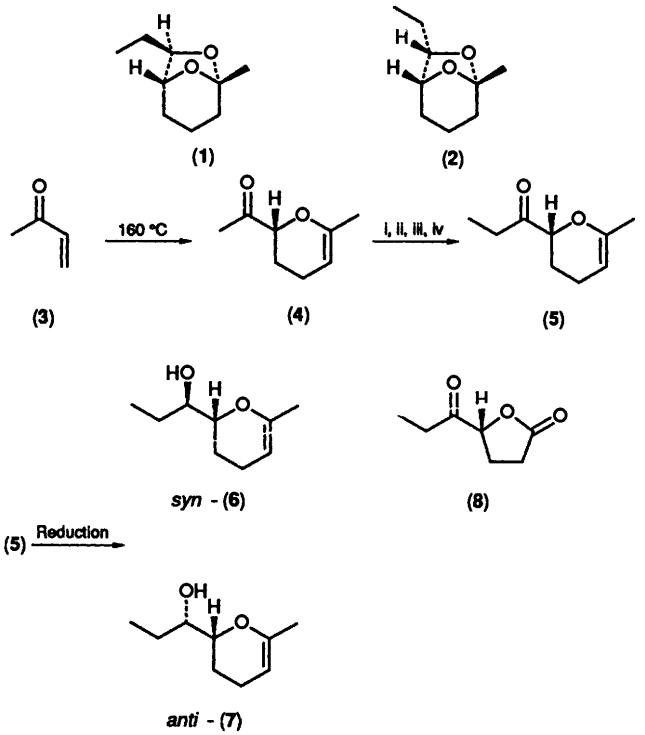
Reduction of the ethyl ketone (**5**) with L-Selectride or zinc borohydride proceeds stereoselectively to give the alcohols *syn*-(**6**) or *anti*-(**7**), respectively, which are converted, in turn, into (±)-*exo*-brevicomin and (±)-*endo*-brevicomin.

The *exo* (**1**) and *endo* (**2**) isomers of brevicomin are of central importance to the chemical ecology of *Dendroctonus* pine beetles, several species being serious timber pests in North America. The aggregation pheromones of several *Dendroctonus* species contain *exo*-brevicomin as a key attractive component, including that from the female Western Pine beetle (*D. brevicomis*) which contains (**1**) and (**2**).[1,2] Aggregation of the destructive Southern Pine beetle (*D. frontalis*) is inhibited by (**2**).[3] Several syntheses of racemic and the naturally occurring (1*R*,7*R*)-(+)-form of (**1**) have been reported.[4] Stereoselective synthesis of (**2**) has received limited attention.[5] The recent stereoselective synthesis of (**1**) by Larcheveque and Lalande involving controlled reduction of 4-acylbutanolides[6] prompts us to disclose our work in this area. We report an efficient synthetic approach in which complementary and stereoselective metal hydride reductions of the intermediate 2-acylpyranyl system (**5**) allow synthesis of *either exo*- or *endo*-brevicomin. Stereoselective production of either (**1**) or (**2**) from a common intermediate has been reported only once before.[7]

Preparation of (**5**) begins with a Diels–Alder dimerization of (**3**) to give the ketone (**4**) using Lundy's methods.[8] Methylation of (**4**) is performed *via* the anion of its cyclohexylimine derivative as approaches using LDA,[9] or more hindered bases,[10] directly with (**4**) are not regioselective. In this manner (**5**) is produced in 53% overall yield with ⩽3% of the regioisomeric methylation product (GC-MS).

We studied reduction of (**5**) with several types of reagents to determine complementary conditions leading selectively to either of the alcohols *syn*-(**6**) or *anti*-(**7**) *en route* to (**1**) and (**2**).[11] With each reagent type, the effect of temperature and metal counterion on the reduction stereoselectivity were evaluated. Results are expressed as a *syn*-(**6**): *anti*-(**7**) ratio in the Table.

In accordance with Lundy's observations,[8] reduction of (**5**) with sodium borohydride in methanol at 0 °C is weakly selective for the *syn*-isomer (59:41; 76% yield). The stereoselectivity of this reduction with simple borohydride reagents (methanol) is invariant with respect to temperature and counterion as sodium, lithium, and potassium borohydride all gave the same ratio (55:45 ± 2) from 25 to −60 °C. These results stand in contrast to work by Larcheveque and Lalande in which reduction of ketone ester (**8**) was a key step in a synthesis of (**1**).[6] Sodium borohydride reduction of (**8**) was selective for the *anti*-alcohol (35:65; 0 °C) and *anti* selectivity



Scheme. i, Cyclohexylamine, 3 Å sieves; ii, EtMgBr, THF, reflux; iii, MeI; iv, HOAc, H_2O.

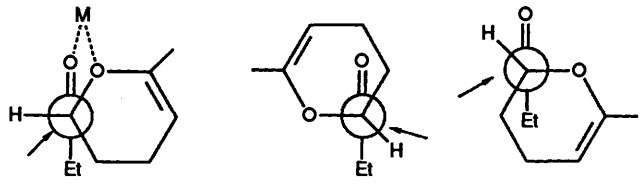
increased to 22:78 at −80 °C, results which are consistent with chelation-controlled reduction after Cram's rules. Selective reduction to *anti*-(**7**) from (**5**) would be expected to proceed *via* the chelated intermediate (**9**). However, Bartlett[12] has pointed out that counterion chelation by substrates is unlikely for borohydride reduction in hydroxylic solvents which is supported by our data.

Paralleling Larcheveque and Lalande's results, reduction of (**5**) with zinc borohydride was selective for the *anti*-alcohol (**7**) (27:73; 0 °C; ether). Surprisingly, reduction of (**8**) with this better chelating reagent actually lead to a decrease in the

Table. Stereoselectivity of reduction of ketone (5)[a]

Reagent	Temp. (°C)	*syn*-(6):*anti*-(7)	Reagent	Temp. (°C)	*syn*-(6):*anti*-(7)
$Zn(BH_4)_2$	RT	47:53	N-Selectride	RT	49:51
	0	27:73		0	51:49
	−30	20:80		−30	55:45
	−60	18:82		−60	57:43
				−80	70:30
L-Selectride	RT	75:25	K-Selectride	RT	65:35
	0	81:19		0	68:32
	−30	81:19		−30	75:25
	−60	87:13		−60	75:25
	−80	93:7		−80	80:20

[a] Ratios determined by gas chromatography on Carbowax 20M.



(9) (10) (11)

syn:*anti* ratio (30:70 at 0 °C) relative to $NaBH_4$.[6] Our results with $Zn(BH_4)_2$ show a dependence on reaction temperature: the *syn*:*anti* ratio decreases from 47:53 at 25 °C to 18:82 at −60 °C. Selective formation of *anti*-(7) is consistent with reduction *via* (9). Thus, the ketone (5), which contains a dihydropyran system, appears to more strongly chelate $Zn(BH_4)_2$ than the ketone (8) which involves a γ-lactone. Stereoselective reductions with $Zn(BH_4)_2$ have been reported for a range of ketones, including β-keto esters,[13] α- and β-keto amides,[14] β-hydroxy ketones,[15] β-alkoxy ketones,[15,16] and α,β-epoxy ketones.[17] Our work with $Zn(BH_4)_2$ is the first in which the oxygen substituent α to the ketone is a medium-sized cyclic ether.

The stereoselectivity in reduction of (5) can be reversed to favour the *syn*-isomer (6) with tri-s-butylborohydride (Selectride) reducing agents. We examined reduction of (5) using the three commercially available reagents (L-, N-, and K-Selectride). Reduction with these reagents, which are very bulky and have low co-ordinating ability, should follow the open-chain model of Felkin and Ahn,[18] and occur *via* conformers (10) or (11). The latter, leading to *anti*-(7), should be less stable due to steric interactions between the ethyl group and the dihydropyran system. The Selectride reagents produce (6) selectively under all conditions studied, and the stereoselectivity with all three reagents increases with decreasing temperature. This trend expresses the increasing importance of the stability difference between (10) and (11) as temperature is lowered.

The highest stereoselectivity was observed with L-Selectride at −80 °C giving a *syn*-(6):*anti*-(7) ratio of 93:7. Reduction with K-Selectride at −80 °C was significantly less stereoselective (80:20) in contrast to reductions of (8) which were essentially identical with K-(100% *syn*, −80 °C) and L-Selectride (99:1, −80 °C). Our results also diverge from several other comparison studies,[14,16,18] which have found K-Selectride to be the more selective reagent. At any given temperature our Selectride results also show that the nature of the counterion does not produce a straightforward effect on the degree of stereoselectivity. Ibarra has recently examined the effects of ion pairing and solvent complexation of metal counterions in reductions of chiral ketones with these reagents and has found K-Selectride to be the more selective reagent due to its greater 'effective volume.'[19] Our results show that the stereoselectivity of Selectride reductions does not derive simply from the steric bulk of these reagents, as is widely held, but must also depend on the degree of ion pairing present, as influenced by the metal counterion and reaction solvent.

Treatment of the *syn*-alcohol (6) (from L-Selectride reduction at −80 °C) and the *anti*-alcohol (7) (from $Zn(BH_4)_2$ reduction at −60 °C) with dilute toluene-*p*-sulphonic acid in benzene gave the target pheromones (1), (71%) and (2) (66%) respectively. The ^1H NMR spectra and electron impact mass spectra (GC-MS) of these materials were identical with those previously published,[1] which confirmed the structures of our synthetic products.

Experimental

Preparation of Compounds (6) *and* (7) via *Stereoselective Reduction of the Ketone* (5). *Compound* (6).—To a solution of (5) (50 mg, 32 mmol) in THF (2.5 ml) at −80 °C was added L-Selectride (0.49 ml, 0.49 mmol; Aldrich) as a 1.0M THF solution. After 1 h, 2M NaOH (2 ml) and 30% H_2O_2 (1.5 ml) were added successively *via* syringe, and the reaction was warmed to room temperature. The resulting mixture was diluted with ether (10 ml), the layers were separated, and the organic layer was washed twice with saturated aqueous NH_4Cl (5 ml), dried (Na_2SO_4), and evaporated under reduced pressure to afford a colourless oil (36–47 mg, 71–93%) which GLC analysis showed to be a 93:7 mixture of (6) and (7). This mixture was carried on to compound (1) without purification. Compound (6); $\delta_H(CDCl_3$; 200 MHz) 4.48 (1 H, m), 3.65 (1 H, m), 3.50 (1 H, m), 2.1–1.9 (4 H, m), 1.75 (3 H, br s), and 1.02 (3 H, t, *J* 7 Hz).

Compound (7).—A solution of compound (5) (100 mg, 0.65 mmol) in anhydrous diethyl ether (1 ml) was added, *via* a cannula, to a $Zn(BH_4)_2$–diethyl ether solution[20] (0.15M; 6.5 ml, 0.97 mmol) at −60 °C. A second portion (1 ml) of ether was used to rinse the flask originally containing (5) and this was added to the reaction *via* a cannula. After 3 h, water (1 ml) was added carefully *via* a syringe to quench excess of hydride and the reaction was warmed to room temperature. The resulting mixture was diluted with ether (10 ml) and washed twice with saturated aqueous NH_4Cl (5 ml) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a colourless oil (70–75 mg; 69–74%) which GLC analysis showed to be a 18:82 mixture of (6) and (7). This mixture was carried on to compound (2) without purification. Compound (7); $\delta_H(CDCl_3$; 200 MHz) 4.48 (1 H, m), 3.7 (2 H, m), 2.1–1.9 (4 H, m), 1.75 (3 H, br s), and 1.02 (3 H, t, *J* 7 Hz).

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