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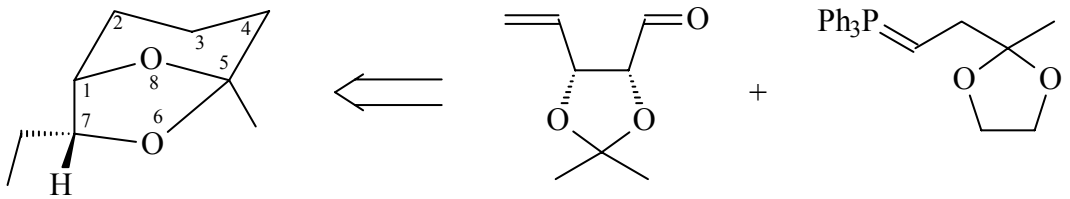
A CONCISE SYNTHESIS OF (-)-*ENDO*-BREVICOMIN

John K. Gallos,* Loukia C. Kyradjoglou, and Theocharis V. Koftis

Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 540 06, Greece, e-mail: igallos@chem.auth.gr

Abstract*- A new method for the synthesis of* (-)*-endo-brevicomin from* D*-ribose in four steps is reported.*

endo-Brevicomin[1] is the aggregation pheromone of different bark beetle species of the *Dendroctonus* and *Dryocoetes* family, with its (+)-enantiomer {(1*R*,5*S*,7*S*)-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane} being bioactive.[2] In connection with our ongoing program for the synthesis of enantiomerically pure pheromones[3] and in addition to several asymmetric syntheses of both enantiomers of *endo*-brevicomin which appeared recently in the literature,[4] we report herein a new concise synthesis of (-)-*endo*-brevicomin (**1**) (Figure 1), starting from *D*-ribose.



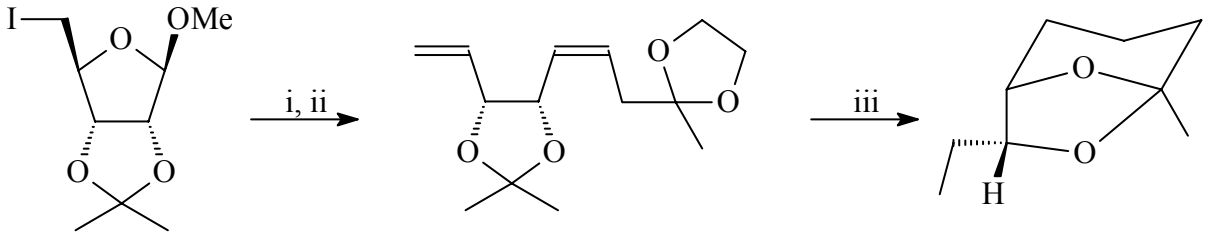
(-)-*endo*-Brevicomin (1) **2** **3**

Figure 1

It is evident from Figure 1, that the configuration of the two chiral centers of (4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolane-4-carbaldehyde (**2**), easily accessible from *D*-ribose,[5] is identical to those of C-1 and C-7 carbons of (-)-*endo*-brevicomin (**1**). Furthermore, aldehyde (**2**) has the proper skeleton size and functionalities to give the desired (-)-*endo*-brevicomin (**1**), upon Wittig olefination with the ylide (**3**),[6] and subsequent conventional hydrogenation and reacetalisation. Evidently, its enantiomeric (+)-*endo*-brevicomin could be prepared by using the enantiomer of aldehyde (**2**), whereas the respective (+)- and (-)-*exo*-brevicomins could result from the olefination of ylide (**3**) with the two epimeric *threo*-isomers of aldehyde (**2**).

Iodide (**4**) (Scheme 1), obtained from *D*-ribose in two steps, was converted to aldehyde (**2**) by treatment with powdered Zn in refluxing ethanol, according to the literature.[5] In our hands, aldehyde (**2**), thus prepared, was isolated by filtering off the solids and careful complete evaporation of the solvent in a

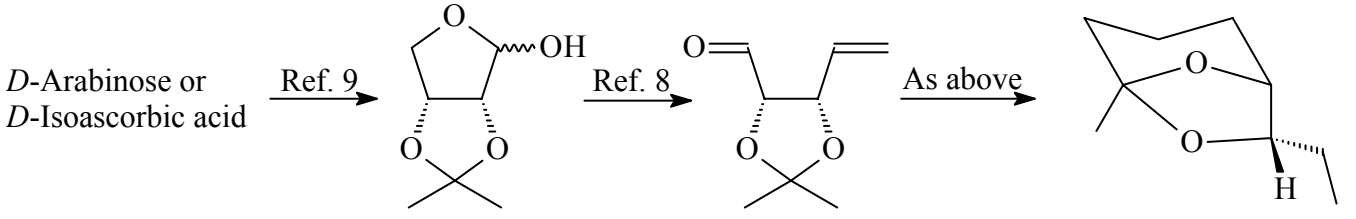
rotary evaporator at temperatures not exceeding 35 ˚C, to avoid coevaporation of the volatile aldehyde (**2**).[7] Subsequent Wittig olefination with the ylide (**3**) gave compound (**5**) in 65% yield. Attempted H_2-Pd/C (10%) catalytic hydrogenation caused extended decomposition of **5**, whereas the hydrogenation of **5** over Raney Ni in ether, followed by treatment with *p*-toluenesulfonic acid and water gave good yield of (-)-*endo*-brevicomin (**1**), with physical and NMR spectral data identical to those reported in the literature.[2,4]



4 **5** **1**

Scheme 1 *Reagents and Conditions: i, Zn powder, 95% EtOH, reflux, 1 h; ii, [2-(2-methyl-1,3-dioxolan-2-yl)ethyl](triphenyl)phosphonium bromide, 1.6 M n-BuLi in hexane, 12-crown-4, –78 ºC, THF, 65% from* **4***; iii, H_2, Raney Ni, ether, 20 ºC, 5 h, then p-TsOH, H_2O, 20 ºC, 3 h, 76% overall.*

(4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolane-4-carbaldehyde (**ent-2**) (Scheme 2) is also readily prepared from protected *D*-erythrose (**6**) in two steps, namely Wittig olefination with $Ph_3P{=}CH_2$ and Swern oxidation of the resulting alcohol.[8] *D*-Erythrose (**6**) in turn is easily available from the naturally abundant *D*-arabinose[9a] or *D*-isoascorbic acid.[9b] The synthesis thus of the biologically active (+)-*endo*-brevicomin (**ent-1**) can be accomplished when applying the reaction sequence of Scheme 1. It is evident that aldehyde (**2**) used in the synthesis of (-)-*endo*-brevicomin (**1**) can alternatively be obtained from *L*-arabinose.[8,9]



6 **ent-2** **(+)-*endo*-Brevicomin (ent-1)**

Scheme 2

In conclusion, we have developed a short method for the synthesis of (-)-*endo*-brevicomin (**1**) from aldehyde (**2**), easily accessible from *D*-ribose. Since the enantiomer of this aldehyde (**ent-2**) is also readily available from *D*-arabinose or *D*-isoascorbic acid, our method is suitable for the synthesis of both (+)- and (-)-*endo*-brevicomin.

EXPERIMENTAL

(4S,5R)-2,2-dimethyl-4-[(Z)-3-(2-methyl-1,3-dioxolan-2-yl)-1-propenyl]-5-vinyl-1,3-dioxolane (**5**). To a well stirred solution of **4**[5] (0.314 g, 1 mmol) in EtOH 95% (5 mL) was added powdered Zn (0.65 g, 10

mmol) and the mixture was refluxed for 1 h, while the reaction progress was monitored by TLC. The solids were then filtered off and the solvent was carefully evaporated in a rotary evaporator under reduced pressure with the bath temperature not exceeding 35 ˚C. The resulting aldehyde (**2**) was of satisfactory purity and was used without any further purification.

In a separate flask, ylide (**3**) was prepared from [2-(2-methyl-1,3-dioxolan-2-yl)ethyl](triphenyl)phosphonium bromide[6] (2.75 g, 6 mmol) in dry THF (150 mL) by adding dropwise 1.6 M of *n*-BuLi in hexane (4.1 mL, 6.6 mmol) at –78 ˚C in the presence of 12-crown-4 (0.211 g, 1.2 mmol). The mixture was then allowed to warm to 0 ˚C and cooled again to –78 ˚C. The above prepared aldehyde (**2**) was added at this temperature and the resulting solution was allowed overnight stirring to warm to rt, quenched by adding H_2O (100 mL) and extracted with EtOAc (100 mL). The aqueous layer was extracted again with CH_2Cl_2 (3x50 mL). The combined organic layer was dried over Na_2SO_4, the solvent was evaporated and the residue was chromatographed on silica gel using hexane/EtOAc 5:1 as the eluent to give compound (**5**) as an oil (0.165 g, 65%); $[\alpha]_D^{27}$ +28.6 º (c 0.12, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz) 1.31 (s, 3 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 2.44 (d, *J* 7.7, 2 H), 3.94 (br s, 4 H), 4.57 (t, *J* 6.5, 1 H), 4.95 (dd, *J* 9.0, 6.5, 1 H), 5.20 (d, *J* 11.2, 1 H), 5.29 (d, *J* 16.9, 1 H), 5.54 (dd, *J* 10.8, 9.0, 1 H), and 5.75 (m, 2 H); δ_C ($CDCl_3$, 75 MHz) 20.08, 25.53, 28.04, 37.45, 64.71, 74.22, 79.75, 108.65, 109.35, 117.76, 128.38, 128.46, and 134.42; Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.98; H, 8.84.

(-)-endo-Brevicomin (**1**). To a solution of compound (**5**) obtained as above (0.127 g, 0.5 mmol) in ether (20 mL) was added Raney Ni (5 mg) and the mixture was stirred at rt under 1 atm H_2 at 20 ˚C for 5 h. The solids were filtered off, *p*-TsOH·H_2O (10 mg, 0.05 mmol) and H_2O (1 mL) were added and the mixture was stirred at 20 ˚C for 3 h and then washed with 10% aqueous Na_2CO_3 (20 mL) and H_2O (20 mL) and dried over Na_2SO_4. The solvent was evaporated under atmospheric pressure and the residue was chromatographed on silica gel using CH_2Cl_2 as the eluent to give (-)-*endo*-brevicomin (**1**) as an oil (0.059 g, 76%); $[\alpha]_D^{27}$ -77.4 º (c 0.2, ether) [lit.,[2] $[\alpha]_D^{21}$ –75.9 º (c 0.717, $CHCl_3$)]; δ_H ($CDCl_3$, 300 MHz) 0.99 (t, *J* 7.2, 3 H), 1.44 (s, 3 H), 1.52-2.00 (m, 8 H), 4.00 (dt, *J* 7.0, 4.0, 2 H), and 4.22 (m, 1 H); δ_C ($CDCl_3$, 75 MHz) 10.93, 17.52, 21.88, 23.63, 24.99, 34.44, 76.53, 81.68, and 106.99.

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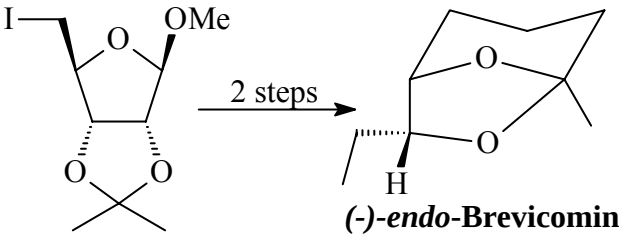
Graphical Abstract



***(-)-endo*-Brevicomin**