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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 819–821

Chiron approach for the synthesis of (1*S*,2*R*,5*R*,7*S*)-2-hydroxy-*exo*-brevicomin☆

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Received 20 January 2006; accepted 15 February 2006

Abstract—(1*S*,2*R*,5*R*,7*S*)-2-Hydroxy-*exo*-brevicomin *ent*-**1** was synthesized from 1,2;5,6-di-*O*-isopropylidene-D-glucose in seven steps. The key reaction in our synthesis is the formation of bicyclic ketal **7** under acid mediated acetal exchange of a 1,2-acetonide of D-glucose derivative **6**.

1. Introduction

The 6,8-dioxabicyclo[3.2.1]octane skeleton is a common structural subunit in the pheromones of a variety of bark beetle species. Brevicomin (7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane) **A** was the first of these bicyclic acetals identified from the frass of female western pine beetles.[1] In 1996, Francke et al.[2] reported the isolation and identification of several new 6,8-dioxabicyclo[3.2.1]octane derivatives, such as **B**–**G**, and **1** (Fig. 1) as the components of the head-space volatiles obtained from the male mountain pine beetle, *Dendroctonus ponderosae*. They synthesized the enantiomers and/or racemates of the following compounds: (1*S*,5*R*,7*S*)-**B**, (1*R*,1′*R*,5′*R*,7′*R*)-**D**, (±)-**D**, (±)-**E**, (1*R*,2*R*,5*S*,7*R*)-**F**, (1*R*,2*R*,5*S*,7*S*)-**G**, and (±)-**1**. Amongst these, compound **1** is less abundant and the absolute configuration of **1** was not determined at that time. However, comparative NMR studies showed that **1** could be an *exo*-isomer with an equatorial OH group in the second position.[2] In 1997, Mori et al.[3] synthesized (1*R*,2*S*,5*S*,7*R*)-**1** employing a Sharpless asymmetric dihydroxylation protocol, and with this reference, the absolute configuration of **1** is determined as (1*R*,2*S*,5*S*,7*R*).

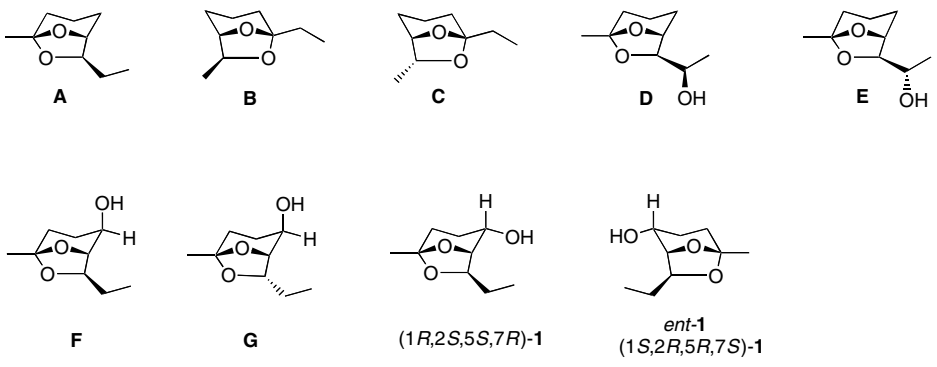

Figure 1.

☆ IICT Communication No. 051108.

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0957-4166/$ - see front matter
doi:10.1016/j.tetasy.2006.02.020

2. Results and discussion

As part of our ongoing research, we undertook the synthesis of these hydroxy brevicomins and consequently reported the asymmetric synthesis of (1*R*,1′*R*,5′*R*,7′*R*)-**D**, (1*S*,1′*R*,5′*R*,7′*R*)-**E** using a Sharpless asymmetric dihydroxylation protocol, starting from α-picoline[4] and a chiron approach for the synthesis of (1*R*,2*R*,5*S*,7*R*)-**F**[5] and (1*R*,2*R*,5*S*,7*S*)-**G**[6] starting from D-mannose and D-ribose, respectively. Herein, we report a short chiron approach for the synthesis of *ent*-**1**.

Earlier approaches for both (±)-**1**[2] and (1*R*,2*S*,5*S*,7*R*)-**1**[3] involved organometallic reagents to construct the required carbon skeleton for the epoxidation or asymmetric dihydroxylation respectively, whereas in our approach the adjacent chiral hydroxy centers of *ent*-**1** were obtained from D-glucose (Scheme 1).

As shown in Scheme 1, our synthesis commenced with removal of the 5,6-*O*-isopropylidene group in compound **2**, which was prepared from D-glucose according to the reported procedure,[7] to give compound **3**. The cleavage of the glycol moiety in compound **3** by periodate in aqueous methanol, followed by Wittig olefination of the resulting 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose **4** with (2-oxopropylidene)triphenylphosphorane in DCM, resulted in the formation of three carbon extended α,β-unsaturated ketone **5**. Hydrogenation of enone **5** in the presence of catalytic Pd/C gave an equilibrium mixture of **6a** and **6b** (in 3:7 ratio by ^{1}H NMR). This mixture was converted to bicyclic ketal derivative **7** with TFA–water solution (3:2) and the resultant aldehyde **7** was directly subjected to a Wittig reaction, without any further purification with methylidenetriphenylphosphorane to give the corresponding olefin **8** in 30% yield from **6** (the average yield for each step is 67%). Finally, palladium catalyzed hydrogenation of **8** gave (1*S*,2*R*,5*R*,7*S*)-**1** in 94% yield as a colorless oil. The spectroscopic data of *ent*-**1** is in accordance with the reported values of **1**.[2,3]

3. Conclusions

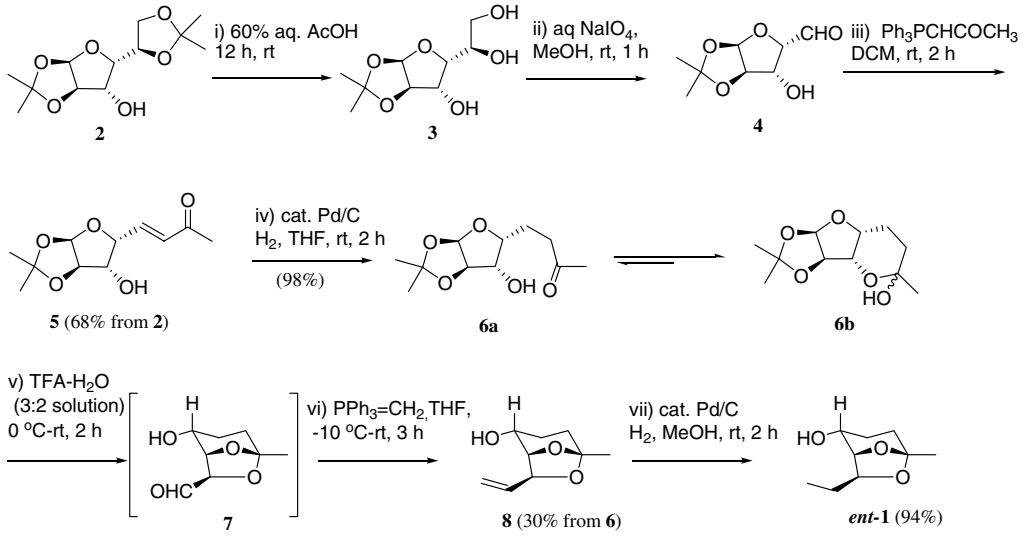
In conclusion, we have demonstrated a short chiron approach for the synthesis of (1*S*,2*R*,5*R*,7*S*)-**1** starting from D-glucose with minimum usage of protecting groups. It should be noted that within our scheme is the formation of anticipated bicyclic skeleton **7** in acid hydrolysis of 1,2-acetonide of compound **6**.

4. Experimental

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR (200 MHz) spectra were recorded on a Varian Gemini-200 MHz spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker Avance-300 MHz spectrometer. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.1. (*E*)-5,6,8-Trideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-oct-5-eno-1,4-furanos-7-ulose 5

A solution of compound **2** (5 g, 19.23 mmol) in 60% aqueous acetic acid (75 mL) was stirred for 12 h and then concentrated to give 1,2-*O*-isopropylidene-α-D-glucofuranose **3**. To a stirred solution of this crude material **3** in methanol (60 mL) at 0 °C was added an aqueous solution of sodium periodate (4.52 g, 21.22 mmol, 15 mL). After 1 h, the mixture was concentrated. To the residue was added DCM (20 mL), and the resultant solids removed by filtration and then washed with DCM (20 mL × 2). The combined filtrate and washings were concentrated to give 1,2-*O*-isopro-



Scheme 1.

pylidene-α-*xylo*-pentodialdo-l,4-furanose **4** (4 g). A solution of the crude aldehyde **4** and (2-oxopropylidene)triphenylphosphorane (8.14 g, 25.60 mmol) in DCM (50 mL) was stirred at room temperature for 2 h and then water was added (50 mL). The aqueous layer was extracted with DCM (50 mL × 2) and the combined organic layers dried over Na_2SO_4 and concentrated. The residue was then chromatographed on silica gel (ethyl acetate/hexane = 1:3) to give compound **5** (3 g, 68%) as a white solid. $[\alpha]_D^{28} = -59.8$ (*c* 0.57, $CHCl_3$); mp 90–92 °C; IR ν_{max} (neat, cm^{-1}): 3450, 2928, 1637, 1377, 1218, 1165, 1076; ^1H NMR (300 MHz, $CDCl_3$): δ 6.71 (dd, 1H, $J = 4.5$, 15.9 Hz), 6.47 (br d, 1H, $J = 15.9$ Hz), 5.92 (d, 1H, $J = 3.7$ Hz), 4.81 (m, 1H), 4.52 (d, 1H, $J = 3.7$ Hz), 4.19 (br s, 1H), 2.27 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1, 139.6, 132.2, 112.1, 104.8, 85.1, 79.8, 76.2, 27.8, 26.7, 26.2; ESI-MS: 229 $[M+H]^+$; ESI-HRMS for $[M+Na]^+$: calcd for $C_{11}H_{16}O_5Na = 251.0895$, found: 251.0905.

4.2. 5,6,8-Trideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-octano-1,4-furanos-7-ulose 6a and 2,3-*O*-isopropylidene-5-methylperhydrofuro[3,2-*b*]pyran-5-ol 6b

Hydrogenation of compound **5** (0.85 g, 3.73 mmol) was carried out with a catalytic amount of Pd/C (5% on carbon) in THF (10 mL). After being stirred for 2 h at room temperature, the catalyst was removed by filtration. The filtrate was concentrated in vacuo and purified by chromatography (ethyl acetate/hexane = 1:3) to give an inseparable mixture of **6a** and **6b** (0.84 g, 98%) in 3:7 ratio. White solid, mp 68 °C. ^1H NMR for minor isomer **6a** (300 MHz, $CDCl_3$): δ 5.80 (d, 1H, $J = 3.7$ Hz), 4.48 (d, 1H, $J = 3.7$ Hz), 3.92 (m, 1H), 3.83 (br s, 1H), 3.05 (br s, 1H), 2.74 (ddd, 1H, $J = 5.2$, 6.8, 18.9 Hz), 2.55 (ddd, 1H, $J = 4.5$, 8.3, 18.9 Hz), 2.18 (s, 3H), 1.56–1.47 (m, 2H), 1.45 (s, 3H), 1.28 (s, 3H); ^1H NMR for major isomer **6b** (300 MHz, $CDCl_3$): δ 5.82 (d, 1H, $J = 3.7$ Hz), 4.41 (d, 1H, $J = 3.7$ Hz), 4.16–4.12 (m, 2H), 2.16–1.64 (m, 4H), 1.47 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H); ESI-HRMS for $[M+Na]^+$: calcd for $C_{11}H_{18}O_5Na = 253.1051$, found: 253.1042.

4.3. (1*S*,2*R*,5*R*,7*S*)-*exo*-2-Hydroxy-5-methyl-7-vinyl-6,8-dioxabicyclo[3.2.1]octane 8

A solution of **6** (0.40 g, 1.74 mmol) in TFA–water (7.5 mL, 3:2) was stirred from 0 °C to room temperature for 2 h under a N_2 atmosphere. The solvent was removed in vacuo and the resultant crude aldehyde was taken up in dry THF (10 mL) and cooled to −10 °C. To the above aldehyde **7** was added methylidene triphenylphosphorane generated from methyl triphenylphosphonium iodide (3.50 g, 8.66 mmol) and KO^{t}Bu (0.78 g, 6.95 mmol) in THF (50 mL). After being stirred for 3 h at room temperature, water (15 mL) was added to the reaction mixture and volatiles removed in vacuo. The residue was partitioned between water (15 mL) and ethyl acetate (15 mL) and the aqueous layer extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over Na_2SO_4, concentrated and purified by chromatography (ethyl acetate/hexane = 1:4) to give olefin **8** (90 mg, 30%, from compound **6**) as a colorless oil. $[\alpha]_D^{26.4} = -42.7$ (*c* 0.53, $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 3448, 2926, 2854, 1453, 1385, 1232, 1196, 1175, 1042; ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (ddd, 1H, $J = 6.8$, 10.5, 17.3 Hz), 5.28 (td, 1H, $J = 1.5$, 17.3 Hz), 5.12 (td, 1H, $J = 1.5$, 9.8 Hz), 4.61 (d, 1H, $J = 6.8$ Hz), 3.98 (br d, 1H, $J = 3.8$ Hz), 3.89 (m, 1H), 1.89 (m, 1H), 1.80–1.60 (m, 3H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 115.8, 107.7, 82.0, 76.7, 66.2, 34.9, 26.5, 23.7; ESI-HRMS for $[M-H]^-$: calcd for $C_9H_{13}O_3 = 169.0864$, found: 169.0861.

4.4. (1*S*,2*R*,5*R*,7*S*)-2-Hydroxy-*exo*-brevicomin *ent*-1

The hydrogenation of **8** (40 mg, 0.23 mmol) was carried out with catalytic amount of Pd/C (5% on carbon) in MeOH. After being stirred for 2 h at room temperature, the catalyst was removed by filtration. The filtrate was concentrated in vacuo and purified by chromatography (ethyl acetate/hexane = 1:4) to give *ent*-**1** (38 mg, 94%) as a colorless oil. The GLC analysis of this compound showed 99.7% purity. $[\alpha]_D^{25} = -32.0$ (*c* 0.6, $CHCl_3$) {lit.[3] for **1**, $[\alpha]_D^{25} = +33.3$, (*c* 1.94, $CHCl_3$)}; IR ν_{max} (neat, cm^{-1}): 3448, 2926, 1458, 1030; ^1H NMR (200 MHz, C_6D_6): δ 4.16 (t, 1H, $J = 6.3$ Hz), 3.76 (d, 1H, $J = 3.8$ Hz), 3.58 (m, 1H), 1.70–1.38 (m, 6H), 1.44 (s, 3H), 0.90 (t, 3H, $J = 7.6$ Hz), 0.76 (br s, 1H); ^{13}C NMR (75 MHz, C_6D_6): δ 106.8, 80.8, 77.1, 66.1, 35.1, 28.6, 26.7, 24.1, 9.8, $[M+H]^+$; ESI-HRMS for $[M+H]^+$: calcd for $C_9H_{17}O_3 = 173.1177$, found: 173.1173.

Acknowledgements

D.N.K. thanks the UGC and D.G. thanks the CSIR, for financial support. The authors thank Dr. J. S. Yadav, A. C. Kunwar and T. K. Chakraborthy, for their help and suggestions.

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