BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 1794—1797 (1972)

Chemical Constituents of *Alnus sieboldiana* (BETULACEAE). III. The Synthesis and Stereochemistry of Yashabushiketols

Yoshinori ASAKAWA

Department of Chemistry, Faculty of Science, Hiroshima University, Higashisenda-machi, Hiroshima

(Received August 30, 1971)

Dihydroyashabushiketol (**2**), isolated previously from the male flower of *Alnus sieboldiana*, has been synthesized by the condensation of benzaldehyde with acetylacetone, followed by hydrogenation. The absolute configuration at C_5 of yashabushiketol (**1**) and **2** has been identified as S. The geometry between the *trans* double bond and the carbonyl group in **1** was established to be *s-cis*. Eleven more minor components of a known aromatic compound were identified at the same time.

Preceding studies[1,2] of the male flower constituents of *Alnus sieboldiana* belonging to the Betulaceae family have shown the presence of two new ketols, yashabushiketol (**1**) and dihydroyashabushiketol (**2**), with the biosynthetically interesting C_6-C_7-C_6 skeleton and four new flavonoids, together with various phenylpropanoids. The present paper will describe the synthesis of **2**, the stereochemistry of **1** and **2**, and the isolation of other phenylpropanoids from the male flower of *A. sieboldiana*.

Results and Discussion

Synthesis of Dihydroyashabushiketol (2). In connection with the study of the biosynthesis of two new ketols, **1** and **2**, we have examined the synthesis of **2**. The reaction of benzaldehyde with a complex of acetylacetone and boron trioxide in the presence of triisopropyl borate and *n*-butylamine gave dicinnamoylmethane (**3**) in a good yield. The catalytic hydrogenation of **3** over platinum oxide afforded dihydroyashabushiketol (**2**) (the *dl* form of **2**), along with saturated diketone (**4**). The sodium borohydride reduction of the diketone (**4**) easily afforded diol (**5**), which has also been prepared from **2** by the same procedure. The oxidation of **2** with active manganese dioxide gave the diketone (**4**).

Stereochemistry of Yashabushiketol (1) and Dihydroyashabushiketol (2). The absolute configuration at C_5 of **1** and **2** was determined by applying the benzoate rule[3] and Horeau's asymmetric synthesis.[4] The benzoylation of **1** with benzoyl chloride and with 3,5-dinitrobenzoylchloride yielded the corresponding benzoates. The benzoate rule predicts that its benzoates would be more dextrorotatory if the configuration at C_5 had S. Actually, the difference in the molecular rotation ($[M]_{Benzoate}$—$[M]_{Alc.}$) between the benzoates and the ketol (**1**) was positive. It follows that the configuration at C_5 is S. This was corroborated by the asymmetric esterification employing α-phenylbutyric anhydride. The reaction of **1** with an excess of (±)-α-phenylbutyric anhydride resulted in recovery of (−)-α-phenylbutyric acid.

1) a) Y. Asakawa, F. Genjida, S. Hayashi, and T. Matsuura, *Tetrahedron Lett.*, **1969**, 3235. b) Y. Asakawa, This Bulletin, **43**, 575 (1970). c) Y. Asakawa, *ibid.*, **43**, 2223 (1970).

2) a) Y. Asakawa, F. Genjida, and T. Suga, *ibid.*, **44**, 297 (1971). b) Y. Asakawa, *ibid.*, **44**, (1971), in press.

3) J. H. Brewster, *Tetrahedron*, **13**, 106 (1961).

4) A. Horeau and H. B. Kagan, *ibid.*, **20**, 2431 (1964).

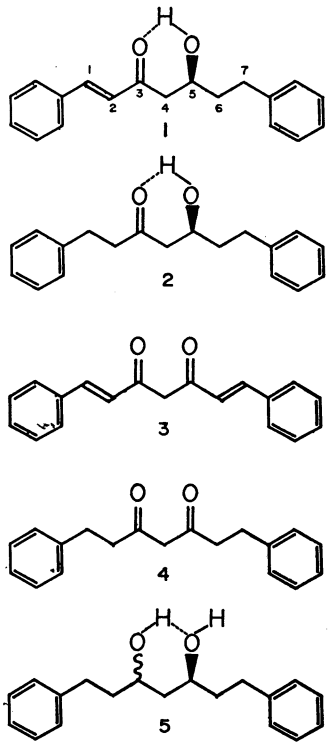

Fig. 1.

Hence, the configuration at C_5 may be deduced to be S. The configuration at C_5 of **2** was also established to be S by the method described above.

Yashabushiketol (**1**) may exist in two geometries, s-*cis* and s-*trans*, with respect to the C_2-C_3 single bond. An inspection of the molecular model predicted that the former form, with a planar zig-zag arrangement of the carbon chain, will be energetically favored over the latter. The infrared spectrum of **1** in nujol mull showed two intense carbonyl bands ($\nu_{C=O}$ 1703 cm^{-1} and $\nu_{C=O}$ 1678 cm^{-1}) and a more intense band of the *trans* ethylenic bond[5] ($\nu_{C=C}$ 1607 cm^{-1}). The arithmetical differences[6] in frequency between $\nu_{C=O}$ and $\nu_{C=C}$ are 96 cm^{-1} and 71 cm^{-1}. These data indicate that **1** is in the *s-cis* form. The infrared spectrum in the hydroxyl strechng region of **1** in carbon tetrachloride showed a concentration-independent band at 3520 cm^{-1} (ε, 32). This surely indicates the existence of an intramolecular hydrogen bonding between the hydroxyl group and the lone-pair electron on the carbonyl oxygen, thus supporting the special arrangement shown in Formula 1.

Previously-known Aromatic Compounds. The isolation of eleven minor components, benzaldehyde, γ-phenylpropyl acetate, cinnamyl acetate, coumarin, cinnamyl cinnamate, β-phenylethyl-β-phenylpropionate, methyl cinnamate, benzoic acid,[7] phenylacetic acid, β-phenylpropionic acid, and eugenol, was performed by a combination of column and preparative thin-layer chromatographies. All the compounds isolated were identified by direct comparisons (mixed mp, UV, IR, NMR and mass spectra) with authentic specimens. It is characteristic that almost all the compounds isolated from the male flower of *A. sieboldiana* carry one or two of the monosubstituted benzene-rings which would arise from shikimic acid. From the viewpoint of biosynthesis it is also interesting that the male flower of *A. sieboldiana* contains only benzaldehyde, whereas that of *A. pendula* contains only cinnamaldehyde.[8]

Experimental

All the melting points are uncorrected. The UV, IR, NMR, and mass spectra and the gas chromatograms were measured in the same manner as reported in the preceding paper.[1c] The optical rotations were measured on a Japan Spectroscopic Co., Ltd., automatically-recording spectropolarimeter, Model ORD/UV-5.

*Dicinnamoylmethane (**3**).* The preparation of dicinnamoylmethane was performed on one-tenth the scale of the Pabon's procedure[9]; 42% yield; mp 141—142°C (lit,[9] 140.5°C); λ_{max}^{EtOH} 235 nm (log ε, 3.41), 310 (3.48), 395 (4.04), 418 (3.87); ν_{max}^{Nujol} 1626 (CO–CH=COH), 1148, 1143, 980 (*trans* CH=CH), 878, 795, 723, 690 cm^{-1}; δ_{ppm} ($CDCl_3$) 5.82 (s, 1H), 6.11 (d, J=16 Hz, 2H), 7.42 (m, 10H), 7.67 (d, J=16 Hz, 2H); *m/e* 276 (M^+), 258 ($M-H_2O$), 248 (M–CO), 199, 171, 157, 145, 144, 131 (base), 117, 115, 103, 91, 77, 69, 51.

Found: C, 82.37; H, 5.81%. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84%.

*Hydrogenation of Dicinnamoylmethane (**3**).* Dicinnamoylmethane (**3**) (307 mg) was hydrogenated over a prereduced PtO_2 (68 mg) in methanol for 9 hr under ambient conditions. After the catalyst had been filtered off, the filtrate was evaporated *in vacuo*. The product showed two spots on tlc; it was subjected to preparative thin-layer chromatography, using a 4 : 1 mixture of *n*-hexane and ethyl acetate to give diketone (**4**) (197 mg) as yellow oil and dihydroyashabushiketol (**2**) (90 mg) mp 69—70.5°C (from *n*-hexane); $[\alpha]_D^{25}$ ±0° (*c* 1.6, in $CHCl_3$). The diketone (**4**) showed the following properties: λ_{max}^{EtOH} 272 (4.35), $\lambda_{max}^{n\text{-Hexane}}$ 279 (3.96), $\lambda_{max}^{n\text{-Hexane+NaOH}}$ 297 (4.25); $\nu_{max}^{Liq.}$ 3450, 3026, 1726, 1706, 1626, 1606, 1498, 1455, 751, 704; δ_{ppm} ($CDCl_3$) 2.32—3.08 (m), 3.45 (s, CO–C<u>H</u>$_2$–CO), 5.41 (s, CO–C<u>H</u>=C–), 7.22 (s, 10H); *m/e* 280 (M^+), 262 ($M-H_2O$), 175, 133, 105, 104, 91 (base), 77, 65, 51, 43, 39.

Found: C, 81.58; H, 7.10%. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19%.

*Reduction of Diketone **4** to Diol **5**.* Into a solution of **4** (140 mg) in dioxane–water (50 m*l*, 4 : 1 by volume) we stirred sodium borohydride (500 mg) dissolved in dioxane (25 m*l*), and then the mixture was allowed to stand overnight. The mixture was acidified with 1 N hydrochloric acid, and then the solvent was removed *in vacuo*. The residue, after water (10 m*l*) had been added, was extracted with chloroform. The removal of the solvent from the dried extract gave **5** as a colorless oil (130 mg): $[\alpha]_D^{25}$ ±0° (*c* 2.0, in $CHCl_3$); λ_{max}^{EtOH} 247 (2.47), 253 (2.59), 255 (2.59), 259 (2.66), 262 (2.68), 265 (2.56), 269 (2.60); $\nu_{max}^{Liq.}$ 3356, 1601, 1496, 1416, 1336, 1130, 746, 699; δ_{ppm} ($CDCl_3$) 1.30 (m,

5) R. Hirschman, S. C. Snaddy, Jr., C. F. Hiskey, and N. L. Wendler, *J. Amer. Chem. Soc.*, **76**, 4013 (1954); O. Wintersteiner and M. Moore, *ibid.*, **78**, 6193 (1956).

6) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, **1955**, 3766.

7) Extreme care was taken to avoid airing. However, there is a small possibility that benzoic acid was produced from benzaldehyde during the extraction procedures.

8) T. Suga, Y. Asakawa, and N. Iwata, unpublished data.

9) H. J. J. Pabon, *Rec. Trav. Chim.*, **83**, 379 (1964).

6H), 2.70 (m, 4H), 3.90 (s, 2 OH), 3.85 (quin. 2H, J=6 Hz), 7.23 (s, 10H); *m/e* 284 (M^+), 266 ($M-H_2O$), 248, 149, 91 (base), 77.

Found: C, 80.56; H, 8.59%. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51%.

*Reduction of Dihydroyashabushiketol (**2**) to Diol (**5**).* The reduction of **2** (62 mg) with sodium borohydride (250 mg) in the manner described in the preceding paragraph gave a yellow oil (48 mg): $[\alpha]_D^{25}$ +0.66 (*c* 2.6, in $CHCl_3$); $\nu_{max}^{CCl_4(0.0060\ mol)}$ 3665 (ε, 78), 3538 (ε, 20). This oil was identical in all respects to the **5** derived from the diketone (**4**).

*Oxidation of Dihydroyashabushiketol (**2**) to Diketone (**4**).* A solution of **2** (50 mg) in dry chloroform (20 m*l*) was stirred with activated manganese dioxide (0.920 g) at room temperature over a 5-day period. The mixture was filtered, and the precipitate was washed thoroughly with chloroform. The combined filtrate was evaporated *in vacuo* to give a yellow oil (15 mg) which was identical in all respects to **4**.

*The Benzoate of Yashabushiketol (**1**).* Into a solution of **1** (42 mg) in a mixture of dry benzene (1.5 m*l*) and dry pyridine (0.15 m*l*), we stirred benzoyl chloride (0.3 m*l*) at 0°C. The mixture, after having been allowed to stand overnight, was worked up as usual to give the benzoate (30 mg): mp 94—95°C (from *n*-hexane); $[M]_{Benzoate}$ +61.69; $[M]_{Benzoate}-[M]_{Alc.}$=+6.42; λ_{max}^{EtOH} 280 (3.49); ν_{max}^{Nujol} 1715, 1280, 740, 695; M^+ 384 ($C_{26}H_{24}O_3$).

*The 3,5-Dinitrobenzoate of Yashabushiketol (**1**).* The benzoylation was performed using 50 mg of **1**, 92 mg of 3,5-dinitrobenzoyl chloride, 25 m*l* of benzene, and 1.0 m*l* of pyridine in the same manner as above. The crude product was purified on TLC to give the benzoate as a pale yellow oil (77 mg): $[M]_{Benzoate}$+92.20; $[M]_{Benzoate}-[M]_{Alc.}$= +36.93; λ_{max}^{EtOH} 300 (3.98); $\nu_{max}^{Liq.}$ 1725, 1280, 755, 720, 708, M^+ 474 ($C_{26}H_{22}O_7N_2$).

*The Benzoate of Dihydroyashabushiketol (Natural Product) (**2**).* The method described above was employed using 80 mg of **2** and 50 mg of benzoylchloride; it gave the benzoate (105 mg): $[M]_{Benzoate}$+45.93; $[M]_{Benzoate}-[M]_{Alc.}$= +38.16; λ_{max}^{EtOH} 282 (2.08); $\nu_{max}^{Liq.}$ 1725, 1280, 1114, 755, 720, 708; M^+ 386 ($C_{26}H_{26}O_3$).

*The 3,5-Dinitrobenzoate of Dihydroyashabushiketol (**2**).* The benzoylation of **2** (50 mg) with 3,5-dinitrobenzoyl-chloride (92 mg) in dry pyridine gave the benzoate as a yellow oil (72 mg): $[M]_{Benzoate}$+73.56; $[M]_{Benzoate}-[M]_{Alc.}$=+65.78; λ_{max}^{EtOH} 295 (3.38); $\nu_{max}^{Liq.}$ 1730, 1450, 1354, 1285, 1170; M^+ 476 ($C_{26}H_{24}O_7N_2$).

The benzoates and 3,5-dinitrobenzoates of **1** and **2** described above are very unstable compounds. After having been allowed to stand at room temperature for 2 or 3 days, all the benzoates decomposed and showed two spots on tlc. All attempted elemental analyses of these benzoates failed to obtain satisfactory values.

*Reaction of Yashabushiketol (**1**) with α-Phenylbutyric anhydride.* A solution of **1** (2.14×10^{-4} mol) and α-phenylbutyric anhydride (5.83×10^{-4} mol), prepared by refluxing α-phenylbutyric acid with acetic anhydride, in pyridine (2.5 m*l*) was allowed to stand overnight. The excess anhydride was decomposed by adding water, and then the solution was allowed to stand 7 hr at room temperature. The solution was extracted with ether. The ether extract was washed successively with water, 5% sodium bicarbonate (10 m*l*× 3), and water (three times). The combined aqueous extract was washed with chloroform and acidified with 1 N sulfuric acid. The acidified solution was extracted with chloroform, after which the chloroform extract was dried and evaporated. α-Phenylbutyric acid (96 mg) was recovered: $[\alpha]_D^{25}$ −3.12° (*c* 1.92, in benzene), theoretical[4] $[\alpha]_D$=96.5°/2(2.71)−1=−21.5°. The optical yield was, therefore, 3.12/21.5=14.5% (−).

The neutral fraction in the ether solution was washed thoroughly with water, 1 N sulfuric acid, and water successively. The removal of the solvent from the ether solution gave the ester (54 mg), which was then purified by tlc to give the pure ester (44 mg): λ_{max}^{EtOH} 300 (3.95); $\nu_{max}^{Liq.}$ 1725, 1168, 750, 701; M^+ 426.

Found: C, 81.20; H, 6.90%. Calcd for $C_{29}H_{30}O_3$: C, 81.66; H, 7.09%.

*Reaction of Dihydroyashabushiketol (**2**) with α-Phenylbutyric anhydride.* The method described above was employed, using **2** (3.3×10^{-4} mol) and α-phenylbutyric anhydride (1.01×10^{-3} mol). The recovered α-phenylbutyric acid weighed 209 mg: $[\alpha]_D^{25}$ −0.34° (*c* 2.90, in benzene); the optical yield was 1.5% (−). On the other hand, the ether extract was worked up as above to obtain the ester (64 mg): λ_{max}^{EtOH} 293 (2.47); $\nu_{max}^{Liq.}$ 1727, 1496, 1170, 746, 709; M^+ 428.

Found: C, 82.78; H, 7.46%. Calcd for $C_{29}H_{32}O_3$: C, 82.27; H, 7.53%.

Extraction and Isolation. The benzene extract (750 g) of the male flower of *A. sieboldiana* was extracted first with a saturated sodium bisulfite solution to isolate the aldehyde fraction (1.24 g), and then it was separated into a neutral fraction (50 g), an acidic fraction (8.0 g), and a phenolic fraction (8.4 g), as has been shown previously.[2b]

Benzaldehyde: The decomposition of the sodium bisulfite solution with 20% sodium hydroxide, followed by extraction with ether, yielded a pale yellow oil (1.24 g); this oil showed one peak on the gas chromatogram and one spot on tlc. The spectral data were completely identical with those of authentic benzaldehyde. The 2,4-dinitrophenylhydrazone derivative melted at 240—241°C.

γ-Phenylpropyl Acetate, β-Phenylethyl β-Phenylpropionate, Coumarin, Cinnamyl Acetate, Cinnamyl Cinnamate, and Methyl Cinnamate: After the isolation of the major components, β-phenylethyl cinnamate, pinostrobin, pinosylvin dimethyl ether and ketols, **1** and **2**, from the neutral fraction, the brown oil (845 mg) remaining unidentified was further chromatographed carefully on silica gel using a mixture of *n*-hexane and ethyl acetate. From the 19 : 1 (by volume) *n*-hexane - ethyl acetate fraction, a colorless oil (80 mg) was obtained. This oil was then subjected to preparative thin-layer chromatography to give γ-phenylpropyl acetate (18 mg) and β-phenylethyl β-phenylpropionate (24 mg). γ-Phenylpropyl acetate: λ_{max}^{EtOH} 260 (3.34); $\nu_{max}^{Liq.}$ 1735, 1240; δ_{ppm} ($CDCl_3$) 2.03 (s, 3H), 1.92 (q, J=8 Hz, 2H), 2.70 (t, J=8 Hz, 2H), 4.08 (t, J=8 Hz, 2H), 7.24 (s, 5H). β-Phenylethyl β-phenylpropionate: $\nu_{max}^{Liq.}$ 1735; δ_{ppm} ($CDCl_3$) 2.49 and 2.85 (t, J=7.5 and 1.5 Hz, A_2B_2, 4H, C_6H_5-C<u>H</u>$_2$-C<u>H</u>$_2$-CO), 2.81 (t, J=7.5 Hz, 2H, C_6H_5-C<u>H</u>$_2$-CH_2-O-), 4.18 (t, J=7.5 Hz, 2H, -CH_2-C<u>H</u>$_2$-O-), 7.11 (s, 10H); *m/e* 254 (M^+), 133, 105, 91 (base).

A pale yellow oil (500 mg) obtained from the 4 : 1 *n*-hexane - ethyl acetate fraction was further subjected to column chromatography on silica gel using a mixture of *n*-hexane, benzene, and ethyl acetate to give coumarin (10 mg), cinnamyl acetate (22 mg), cinnamyl cinnamate (100 mg), and methyl cinnamate (47 mg). Coumarin: mp 70—71°C; δ_{ppm} ($CDCl_3$) 6.42 (d, J=9 Hz, 1H), 7.00 (d, J=9 Hz, 1H), 7.41 (m, 4H). Cinnamyl acetate: λ_{max}^{EtOH} 250 (3.68); $\nu_{max}^{Liq.}$ 1735, 1240; δ_{ppm} ($CDCl_3$) 2.06 (s, 3H), 4.70 (d, J=6 Hz, 2H), 6.17 (d, J_{AB}=16 Hz, t, J_{BX}=6 Hz, 1H), 6.69 (d, J_{AB}=16 Hz, 1H), 7.33 (s, 5H). Cinnamyl cinnamate: mp 40—41°C; λ_{max}^{EtOH} 255 (4.09), 275 (4.13);

$\nu_{max}^{Liq.}$ 1710, 1635, 1450, 1165, 965; δ_{ppm} ($CDCl_3$) 4.84 (d, $J_{BX}=6$ Hz, 2H), 6.30 (d, $J_{AB}=16$ Hz, t, $J_{BX}=6$ Hz, 1H), 6.45 (d, $J=16$ Hz, 1H), 6.63 (d, $J=16$ Hz, 1H), 7.43 (m, 10H), 7.74 (d, $J=16$ Hz, 1H). The hydrolysis of the ester with an alcoholic potassium hydroxide solution gave cinnamic acid and cinnamyl alcohol. Methyl cinnamate: $\nu_{max}^{Liq.}$ 1712, 976; δ_{ppm} ($CDCl_3$) 3.82 (s, 3H), 6.45 (d, $J=16$ Hz, 1H), 7.49 (m, 5H), 7.78 (d, $J=16$ Hz, 1H).

Benzoic Acid, Phenylacetic Acid, and β-Phenylpropionic Acid. These acids were identified as their methyl esters. After the isolation of alnustinol (3,5,7-trihydroxy-6-methoxyflavanone) from the acidic fraction by crystallization, the combined filtrate was methylated with diazomethane. The main component of methyl cinnamate was removed by crystallization, and the residual oil (320 mg) was chromatographed on silica gel using a mixture of *n*-hexane, benzene, and ethyl acetate to give methyl benzoate (25 mg), methyl phenylacetate (8 mg), and methyl β-phenylpropionate (80 mg). Methyl benzoate: $\nu_{max}^{Liq.}$ 1740, 1257, 1161; δ_{ppm} ($CDCl_3$) 3.90 (s, 3H), 7.50 (m, 3H), 8.15 (m, 2H). Methyl phenylacetate: $\nu_{max}^{Liq.}$ 1725, 1274, 1109; δ_{ppm} ($CDCl_3$) 3.63 (s, 2H), 3.70 (s, 3H), 7.37 (s, 5H); *m/e* 150 (M^+), 91 (base). Methyl β-phenylpropionate: $\nu_{max}^{Liq.}$ 1740, 1169, 748; δ_{ppm} ($CDCl_3$) 3.77 (s, 3H), 2.82 (m, 4H), 7.28 (s, 5H); *m/e* 164 (M^+), 133, 105, 104 (base), 91.

Eugenol: After the isolation of flavonoids from the phenolic fraction by crystallization, the filtrate (60 mg) was converted into the trimethylsilyl derivative, which was then subjected to gas chromatography and tlc to identify eugenol.

The author wishes to express his hearty gratitude to Professor Kenji Fukui and Dr. Takayuki Suga of Hiroshima University for their guidance and encouragement.