Efficient Conversion of Aucubin into 6-*epi*-Aucubin

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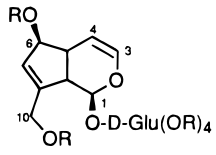
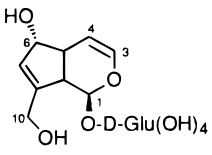
Received October 16, 1998

Selective deprotection of *per*acetylaucubin (**3**) by use of KCN led to 6-*O*-acetylaucubin (**4**), which was readily converted into 2′,3′,4′,6′,10-penta-*O*-benzoylaucubin (**7**). Configuration inversion performed on **7**, using a modified Mitsunobu reaction, followed by deprotection, afforded 6-*epi*-aucubin (**2**).

Iridoids represent a large group of natural monoterpenoids, which can be advantageously used as starting material for the chiral pool synthesis of various bioactive compounds.[1−5] For instance, the synthesis of chiral prostanoids from iridoid glycosides is well documented.[5−15] Aucubin (**1**) is often used as starting material in these syntheses, because it can be readily extracted in large amounts from the fruits or leaves of *Aucuba japonica* Thunb.[16] (Cornaceae). Very often an inversion of the configuration of the carbon derived from C-6 of aucubin has to take place during the synthesis, to obtain the desired final compound. This reaction, performed in the course of a complex synthesis, generally involves oxidation of the secondary alcohol into a ketone, followed by nonstereospecific hydride reduction, with the double disadvantage of a moderate yield and a tedious separation of isomers.[7−8] There is, therefore, a need for a readily available source of 6-*epi*-aucubin (**2**), as the natural occurrence of **2** appears very limited.[17,18] Consequently, an efficient conversion of aucubin (**1**) into 6-*epi*-aucubin (**2**) appeared highly desirable, inasmuch as the only route previously described[17] involves a multistep process and results only in a 3% overall yield, starting from *per*acetylaucubin (**3**).



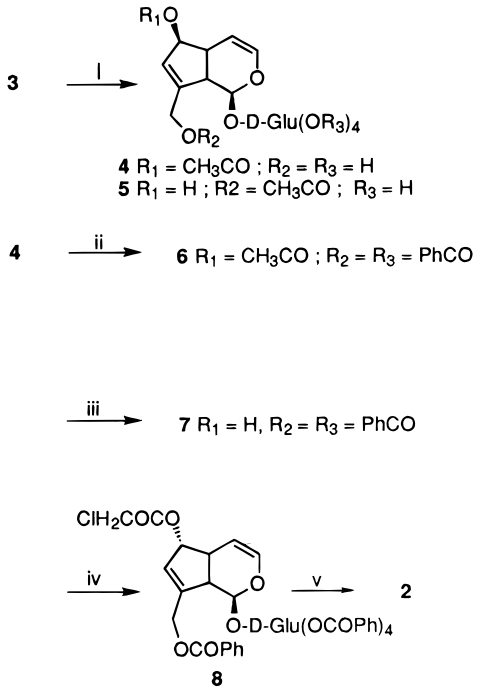
1 R = H
3 R = CH_3CO



2

Aucubin was first converted to its *per*acetyl derivative **3** in almost quantitative yield. Selective deacetylation of **3** could be ensured by use of a catalytic amount of potassium cyanide (Scheme 1), previously shown to permit selective deacetylation reactions in the field of sugar chemistry.[19] This reaction led, within 7 h at 20 °C, to 6-*O*-acetylaucubin (**4**) in 45% yield, accompanied by fully deprotected aucubin, which could be readily separated and recycled. Longer reaction time resulted in the formation of significant amounts of 10-*O*-acetylaucubin (**5**),[20,21] most probably arising from **4** by a transesterification process. Benzoylation of **4** to **6** was successfully achieved in almost quantitative yield by use of benzoic anhydride in the presence of 4-(dimethylamino)pyridine (4-DMAP). Selective deprotection of the *O*-acetyl group of **6** was not observed when DBU

Scheme 1[a]



[a] (i) KCN, CH_2Cl_2-MeOH, room temperature; (ii) $(PhCO)_2O$, 4-DMAP, Pyr, 0 °C−room temperature; (iii) $Mg(OCH_3)_2$, CH_2Cl_2−MeOH, room temperature; (iv) PPh_3, DEAD, $ClCH_2COOH$, THF, 0 °C−room temperature; (v) MeONa, CH_2Cl_2−MeOH, room temperature.

was employed as a base. In contrast, the use of magnesium methoxide,[22] which had been previously shown to hydrolyze *O*-acetyl groups more rapidly than *O*-benzoyl groups, smoothly afforded the required deprotected compound **7** in 60% yield. Finally, the configuration inversion at C-6 was achieved in 80% yield by a modified Mitsunobu reaction.[23] Monochloroacetic acid, a low pK_a carboxylic acid partner, was chosen to take into account the steric hindrance of the alcoholic function at C-6. Classical Zemplen[24] transesterification of **8** finally afforded 6-*epi*-aucubin (**2**).

In conclusion, we report here an efficient conversion of aucubin into its 6-epimer with a 20% overall yield, which can be increased to 35% by recycling. This route can easily be performed on a gram scale.

Experimental Section

General Experimental Procedures. Spectra were recorded on the following apparatus: MS, Nermag R10−10C (DCIMS using NH_3 as reagent gas), Analytica source (electrospray); IR, Perkin−Elmer FT-IR 1600; NMR, Bruker AC 300, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz). Chemical

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10.1021/np9804583 CCC: $18.00
Published on Web 01/21/1999

shifts are given in parts per million ppm, using the solvent peaks as internal standards (MeOH-d_4: δ 3.40, $CDCl_3$: δ 7.27); J values are given in Hertz. The signals of ^1H and ^{13}C spectra were unambiguously assigned by use of 1D homonuclear decoupling experiments and carbon−proton shift correlation spectra. Elemental analyses were performed at the I. C. S. N. (CNRS, Gif-sur-Yvette, France). Optical rotations were measured on a Perkin−Elmer 241 polarimeter (c in g/100 mL). Melting points are not corrected. TLC were performed on Merck Si gel $60F_{254}$ aluminum sheets using sulfuric vanillin as spray reagent. Column chromatographies were conducted using flash Si gel 60 Merck (35−70 μm). Compound **1** was isolated from *Aucuba japonica* using a previously reported procedure.[12] Compound **3** was obtained according to the classic acetylation method.[1] The analytical and spectral data of compounds **2**[17,21,25−29] and **3**[1,30] were identical to those previously published.

6-*O*-Acetylaucubin (4). To a solution of **3** (2.0 g, 3.34 mmol) in a 2:1 mixture of anhydrous MeOH and anhydrous CH_2Cl_2 (15 mL), anhydrous KCN (22 mg, 0.33 mmol) was added under argon. The reaction mixture, monitored by TLC, was stirred 7 h at room temperature and then stopped by filtration on Si gel. The solvent was removed in a rotary evaporator, and the residue (1.5 g) was chromatographed on Si gel by eluting with CH_2Cl_2−MeOH 9:1 to afford **4**[32] as an amorphous powder (585 mg, 1.50 mmol, yield 45%) and also aucubin **1** (519 mg, 1.50 mmol).

6-*O*-Acetyl-2′, 3′, 4′, 6′, 10-penta-*O*-benzoylaucubin (6). Compound **4** (1.22 g, 3.14 mmol) was dissolved with stirring in anhydrous pyridine (60 mL) and cooled at 0 °C with an ice bath. After addition of benzoic anhydride (10 equiv, 7.11 g, 31 mmol) and 4-DMAP (0.1 equiv, 38 mg, 0.31 mmol), the reaction mixture was allowed to stand at room temperature and stirred over 24 h. Excess benzoic anhydride was quenched with ice. The mixture was extracted with CH_2Cl_2 (3 × 150 mL). The organic layers were washed with aqueous 10% HCl until neutral, water, and brine. The combined extracts were dried over Na_2SO_4. Filtration and evaporation of the solvent gave a residue (8.5 g) that was chromatographed on a Si gel column (cyclohexane−Me_2CO 85:15) to afford **6** (2.80 g, 98%) as a crystalline compound. Recrystallization (*n*-hexane−Me_2CO 8:2) gave colorless needles, mp 116−117 °C; $[\alpha]^{20}_D$ −79.7 (c 1.2, $CHCl_3$); IR (NaCl film) ν_{max} 3064.4, 2928.4, 1731.2, 1712.5, 1661.7, 1602.0, 1584.5, 1492.2, 1452.8, 1372.2, 1269.9, 1177.6, 1111.9, 1026.1, 969.0, 854.1, 803.1, 708.1 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10−7.70 (10H, m, *Ph*-CO), 7.60−7.20 (15H, m, *Ph*-CO), 5.95 (1H, t, $J_{3'-2'} = J_{3'-4'} = 9.5$ Hz, H-3′), 5.90 (1H, dd, $J_{3-4} = 6$ Hz, $J_{3-5} = 2$ Hz, H-3), 5.88 (1H, dd, $J_{7-6} = J_{7-9} = 1.5$ Hz, H-7), 5.72 (1H, t, $J_{4'-3'} = J_{4'-5'} = 9.5$ Hz, H-4′), 5.58 (1H, dd, $J_{2'-3'} = 9.5$ Hz, $J_{2'-1'} = 8$ Hz, H-2′), 5.32 (1H, d, $J_{1-9} = 4.5$ Hz, H-1), 5.25 (1H, d, $J_{1'-2'} = 8$ Hz, H-1′), 5.22 (1H, m, H-6), 5.05 (1H, d, $J_{10a-10b} = 15$ Hz, H-10a), 4.95 (1H, d, $J_{10b-10a} = 15$ Hz, H-10b), 4.68 (1H, dd, $J_{6'a-6'b} = 12$ Hz, $J_{6'a-5'} = 3.5$ Hz, H-6′a), 4.55 (1H, dd, $J_{4-3} = 6$ Hz, $J_{4-5} = 2.5$ Hz, H-4), 4.48 (1H, dd, $J_{6'b-6'a} = 12$ Hz, $J_{6'b-5'} = 5$ Hz, H-6′b), 4.18 (1H, ddd, $J_{5'-4'} = 9.5$ Hz, $J_{5'-6'b} = 5$ Hz, $J_{5'-6'a} = 3.5$ Hz, H-5′), 3.28 (1H, m, $J_{9-1} = 4.5$ Hz, H-9), 2.78 (1H, m, H-5), 2.05 (3H, s, CH_3-CO); ^{13}C NMR ($CDCl_3$) δ 170.7 (CH_3CO), 165.9, 165.7, 165.0, 164.9 (Ph-*C*O), 144.4 (C-8), 139.5 (C-3), 139.5, 133.3, 133.1, 133.0, 130.0, 129.7, 129.6, 129.3, 128.6, 128.2 (*Ph*-CO), 127.1 (C-7), 104.0 (C-4), 96.4 (C-1′), 93.9 (C-1), 82.3 (C-6), 72.6 (C-3′), 72.4 (C-5′), 71.2 (C-2′), 69.4 (C-4′), 62.8 (C-6′), 61.7 (C-10), 47.0 (C-9), 39.2 (C-5), 21.0 (CH_3CO); Electrospray m/z 931 $[M + Na]^+$; *anal.* C 68.14%, H 4.93%, calcd for $C_{52}H_{44}O_{15}$, 0.4 H_2O, C 68.16%, H 4.93%.

2′, 3′, 4′, 6′, 10-Penta-*O*-benzoylaucubin (7). Compound **6** (129 mg, 0.14 mmol) was dissolved in a 1:1 mixture of anhydrous MeOH and anhydrous THF. A 10% magnesium methoxide solution (73 mL; 0.6 equiv, 0.08 mmol) was added dropwise under nitrogen. The reaction mixture was stirred for 6.5 h at room temperature and then quenched by addition of HCl 0.4 N (1.5 mL). The suspension was filtered on Si gel and the solvent evaporated in vacuo to give a residue that was chromatographed on Si gel using cyclohexane−EtOAc 7:3 as eluting solvent. Compound **7** (81 mg, 66%) was obtained as a crystalline powder. Recrystallization (cyclohexane−Me_2CO 2:1) gave colorless needles, mp 178−179 °C; $[\alpha]^{20}_D$ −34.7° (c 1.05, $CHCl_3$); IR (NaCl film) ν_{max} 3495.1, 3060.4, 2918.2, 1726.4, 1654.3, 1601.9, 1451.4, 1266.5, 1109.1, 1069.7, 1026.4, 708.6 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10−7.70 (10H, m, *Ph*-CO), 7.60−7.20 (15H, m, *Ph*-CO), 5.98 (1H, dd, $J_{3-4} = 6.5$ Hz, $J_{3-5} = 1.5$ Hz, H-3), 5.95 (1H, t, $J_{3'-2'} = J_{3'-4'} = 9.5$ Hz, H-3′), 5.88 (1H, dd, $J_{7-6} = J_{7-9} = 1.5$ Hz, H-7), 5.70 (1H, t, $J_{4'-3'} = J_{4'-5'} = 9.5$ Hz, H-4′), 5.60 (1H, dd, $J_{2'-3'} = 9.5$ Hz, $J_{2'-1'} = 8$ Hz, H-2′), 5.27 (1H, d, $J_{1'-2'} = 8$ Hz, H-1′), 5.22 (1H, d, $J_{1-9} = 5.5$ Hz, H-1), 5.07 (1H, d, $J_{10a-10b} = 14.5$ Hz, H-10a), 4.95 (1H, d, $J_{10b-10a} = 14.5$ Hz, H-10b), 4.62 (1H, dd, $J_{4-3} = 6.5$ Hz, $J_{4-5} = 3.5$ Hz, H-4), 4.58 (1H, dd, $J_{6'a-6'b} = 12.5$ Hz, $J_{6'a-5'} = 3.5$ Hz, H-6′a), 4.50 (1H, dd, $J_{6'b-6'a} = 12.5$ Hz, $J_{6'b-5'} = 5$ Hz, H-6′b), 4.38 (1H, m, H-6), 4.18 (1H, ddd, $J_{5'-4'} = 9.5$ Hz, $J_{5'-6'b} = 5$ Hz, $J_{5'-6'a} = 3.5$ Hz, H-5′), 3.20 (1H, m, $J_{9-1} = 5.5$ Hz, H-9), 2.65 (1H, m, H-5); ^{13}C NMR ($CDCl_3$) δ 166.0, 165.7, 165.1, 164.9 (Ph-*C*O), 142.0 (C-8), 139.4 (C-3), 133.4, 133.0, 131.2, 129.7, 129.6, 129.3, 128.6, 128.3 (*Ph*-CO, C-7), 104.7 (C-4), 96.4 (C-1′), 94.7 (C-1), 81.3 (C-6), 72.6 (C-3′), 72.4 (C-5′), 71.3 (C-2′), 69.6 (C-4′), 62.8 (C-6′), 62.0 (C-10), 46.7 (C-9), 43.1 (C-5); MS-DIC (NH_3) m/z 884 $[M + NH_4]^+$; *anal.* C 68.81%, H 4.98%, calcd for $C_{50}H_{42}O_{14}$, 0.6 H_2O, C 68,41%, H 4,97%.

6-*O*-Chloroacetyl-2′, 3′, 4′, 6′, 10-penta-*O*-benzoyl-*epi*-aucubin (8). To an anhydrous mixture of triphenylphosphine (4 equiv, 0.71 mmol, 187 mg), **7** (154 mg, 0.17 mmol) and monochloroacetic acid (3 equiv, 0.53 mmol, 50 mg), anhydrous THF (5 mL) was added under argon. The solution was cooled at 0 °C and diethylazodicarboxylate (4 equiv, 0.71 mmol, 0.1 mL) was added dropwise. The reaction mixture was allowed to stand at room temperature and stirred over 2.5 h. The solvent was removed *in vacuo*, and the residue was chromatographed on Si gel by eluting with cyclohexane−EtOAC 9:1 to afford **8** (167 mg, 82%) as an amorphous powder: $[\alpha]^{19.5}_D$ −31.4° (c 2.4, $CHCl_3$); IR (NaCl film) ν_{max} 3064.2, 2957.7, 1731.4, 1652.0, 1601.6, 1584.0, 1491.9, 1451.5, 1370.2, 1273.9, 1177.3, 1110.2, 1069.9, 1026.3, 970.8, 853.6, 801.8, 708.7 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10−7.80 (10H, m, *Ph*-CO), 7.60−7.20 (15H, m, *Ph*-CO), 6.25 (1H, dd, $J_{3-4} = 6.5$ Hz, $J_{3-5} = 2$ Hz, H-3), 5.98 (1H, t, $J_{3'-2'} = J_{3'-4'} = 9.5$ Hz, H-3′), 5.95 (1H, m, H-7), 5.75 (1H, t, $J_{4'-3'} = J_{4'-5'} = 9.5$ Hz, H-4′), 5.70 (1H, m, H-6), 5.62 (1H, dd, $J_{2'-3'} = 9.5$ Hz, $J_{2'-1'} = 8$ Hz, H-2′), 5.30 (1H, d, $J_{1'-2'} = 8$ Hz, H-1′), 5.20 (1H, d, $J_{10a-10b} = 15$ Hz, H-10a), 5.05 (1H, d, $J_{10b-10a} = 15$ Hz, H-10b), 4.98 (1H, d, $J_{1-9} = 7.5$ Hz, H-1),4.65 (1H, m, H-4), 4.65 (1H, m, $J_{6'a-6'b} = 12$ Hz, H-6′a), 4.50 (dd, $J_{6'b-6'a} = 12$ Hz, $J_{6'b-5'} = 5$ Hz, H-6′b), 4.20 (1H, m, H-5′), 3.90 (2H, s, CH_2), 2.98 (1H, m, H-5), 3.20 (1H, m, $J_{9-1} = 5.5$ Hz, H-9); ^{13}C NMR ($CDCl_3$) δ 166.1−164.5 (Ph-*C*O), 147.9 (C-8), 142.5 (C-3), 133.5−128.0 (*Ph*-CO), 126.3 (C-7), 99.95 (C-4), 97.6 (C-1′), 97.6 (C-1), 79.5 (C-6), 72.7 (C-3′), 72.5 (C-5′), 71.5 (C-2′), 69.6 (C-4′), 62.9 (C-6′), 62.4 (C-10), 46.7 (C-9), 40.4 (CH_2), 39.1 (C-5); electrospray m/z 983 $[M + K]^+$; HRFABMS m/z 943.2388 (calcd for $C_{52}H_{44}O_{15}Cl$, 942.2368).

Deprotection of 8. Compound **8** (35 mg, 0.037 mmol) was dissolved in a 1:1 mixture of anhydrous CH_2Cl_2 and anhydrous MeOH (2 mL). The solution was cooled at 0 °C and sodium methoxide (6.6 equiv, 0.24 mmol, 13 mg) was added. The ice-bath was removed, and the reaction mixture was stirred under argon for 3 h. Silica was added to neutralize the NaOMe excess. The suspension was stirred for 15 min. Evaporation of the solvent, followed by flash chromatography of the residue on Si gel (eluted with 8:2 CH_2Cl_2−MeOH), gave **2** (11 mg, 85%) as a colorless oil, whose spectral data were identical with those previously published, $[\alpha]^{19.5}_D$ −59.3° (c 1.0, MeOH) [lit.[17] $[\alpha]^{25}_D$ −58.9° (c 0.7, MeOH)].

Acknowledgment. We thank Dr. Y. Rolland (Laboratoires Servier, Neuilly, France) for helpful discussions on the chemistry of aucubin.

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NP9804583