THE JOURNAL OF Organic Chemistry

VOLUME 45, NUMBER 21

OCTOBER 10, 1980

Total Synthesis of the Chartreusin Aglycon

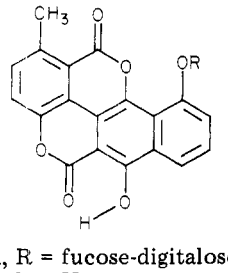
Frank M. Hauser*[1] and Donald W. Combs

Department of Chemistry and Biochemical Sciences, Oregon Graduate Center, Beaverton, Oregon 97006

Received May 13, 1980

A regiospecific synthesis of the aglycon (**1b**) of chartreusin (**1a**) is described. The anion of 4-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**3b**), generated with lithium *tert*-butoxide at −78 °C, was condensed with 6-methyl-1(2*H*)-benzopyran-2-one (**2b**) to afford 7,12-dihydroxy-11-methoxy-2-methyl-6*H*-benzo[*b*]-naphtho[2,3-*d*]pyran-6-one (**4c**). Monobenzylation of the 12-phenolic group of **4c** followed by methylation of the 7-phenolic moiety furnished **4g**. Basic hydrolysis of **4g** with subsequent methylation afforded methyl 4-(benzyloxy)-1,5-dimethoxy-3-(2-methoxy-5-methylphenyl)-2-naphthoate (**5a**). Hydrogenolysis of the benzyl ether of **5a** followed by reaction with phosgene gave chloroformyl derivative **5c**. Treatment of **5c** with aluminum chloride in carbon disulfide effected intramolecular cyclization and demethylation of the cyclization product gave the chartreusin aglycon **1b**.

The recent finding that the antibiotic chartreusin (**1a**) possesses significant anticancer activity[2] has stimulated interest in the synthesis of its aglycon (**1b**). To date, a synthetic study[3] and one total synthesis[4] of the aglycon **1b** have been reported.



1a, R = fucose-digitalose
b, R = H

We report here a regiospecific total synthesis of the aglycon of chartreusin (**1b**). The plan for the synthesis of **1b** is shown in Scheme I and is an adaptation of the annelation methods for the regiospecific synthesis of hydroxylated polycyclic aromatic systems previously reported by us.[5]

To establish the feasibility of the projected route we initially needed to explore the scope of the condensation reaction between benzopyran-2-ones and 3-(phenylsulfonyl)-1(3*H*)-isobenzofuranones because the former had not been used by us as Michael acceptors. The facility of the reaction between benzopyran-2-one (**2a**) and the anion of isobenzofuranone **3a** was demonstrated when, on condensation, benzonaphthopyran-6-one **4a** was isolated in 65% yield. However, in the same reaction using 6-methylbenzopyran-2-one (**2b**), the yield of 2-methylbenzonaphthopyran **4b** was only 5%.

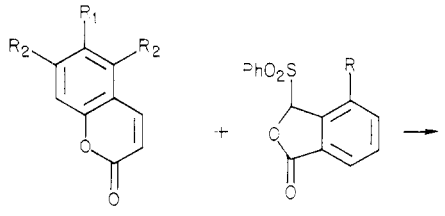
Examination of the approximate pK_a values of the reactants[6] provided a plausible explanation. Under the very basic reaction conditions (lithium diisopropylamide, THF, −78 °C) used to generate the anion of isobenzofuranone **3a**, the methyl group on the Michael acceptor might be attacked. Accordingly, a weaker base was chosen, resulting in marked improvement in yield. Substitution of either potassium or lithium *tert*-butoxide for lithium diisopropylamide in the reaction between **2b** and **3a** gave a 50% yield of 2-methylbenzonaphthopyran **4b**. In order to construct the intermediate with the hydroxylated terminal ring, methoxyisobenzofuranone **3b** was condensed with **2b**, under the same conditions, to furnish **4c** in 35% yield.

Introduction of the remaining lactone carbonyl group was undertaken next. Treatment of **4c** with phosgene in benzene containing pyridine gave dichloroformyl derivative **4d**, which on attempted intramolecular Friedel–Crafts cyclization[7] with a number of catalysts failed to give the chartreusin ring system. Examination of models provided an explanation. Because of the planarity and rigidity of the 6*H*-benzo[*b*]naphtho[2,3-*d*]pyran-6-one skeleton, the π and σ complexes required for Friedel–Crafts acylation[8]

(1) Recipient of a Research Career Development Award, 1978–1983, from the National Cancer Institute (CA 00486).
(2) McGovren, J. P.; Neil, G. L.; Crampton, S. L.; Robinson, M. I.; Douros, J. D. *Cancer Res.* **1977**, *37*, 1666.
(3) Müller, P.; Venakis, T.; Eugster, C. H. *Helv. Chim. Acta* **1979**, *62*, 2833.
(4) Kelly, T. R.; Magee, J. A.; Weibel, F. R. *J. Am. Chem. Soc.* **1980**, *102*, 798.
(5) Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1977**, *99*, 4533; *J. Org. Chem.* **1978**, *43*, 178.
(6) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; p 494.
(7) A related reaction, the intramolecular Friedel–Crafts cyclization of the chloroformyl derivative of 2-phenylphenol to afford dibenzo[*b*,-*d*]pyran-6-one, has been described: *Chem. Abstr.* **1975**, 82, 87699.

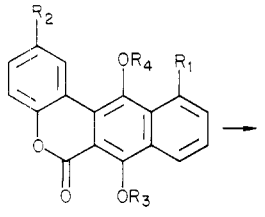
0022-3263/80/1945-4071$01.00/0

Scheme I

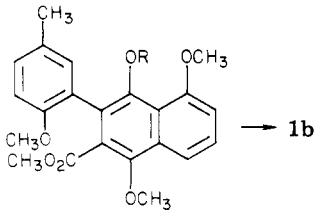


2a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$

3a, R = H
b, R = OCH_3



4a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$
c, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = R_4 = H$
d, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = R_4 = COCl$
e, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_2Ph$
f, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = R_4 = CH_2Ph$
g, $R_1 = OCH_3$; $R_2 = R_3 = CH_3$; $R_4 = CH_2Ph$



5a, R = CH_2Ph
b, R = H
c, R = COCl

cannot form. In order to convert the benzonaphthopyran ring system to a less rigid intermediate capable of forming the obligatory complexes, the lactone would have to be opened.

Selective manipulation of the phenolic groups was performed, prior to opening the lactone ring, to achieve regiospecific introduction of the chloroformyl group on the 12-phenolic moiety and thus ensure a cleaner intramolecular Friedel–Crafts acylation. Alkylation of **4c** with 1 equiv of benzyl bromide afforded monobenzyl ether **4e** in 56% yield and the corresponding dibenzyl derivative **4f**[9] in 25% yield. Methylation of **4e** with dimethyl sulfate in potassium carbonate and acetone gave **4g** in 75% yield. Next, the lactone ring was cleaved in aqueous sodium hydroxide and the resulting sodium salt was suspended in acetone containing potassium carbonate and dimethyl sulfate to afford upon workup a 90% yield of permethyl product **5a**. Hydrogenolysis of the benzyl ether functionality of **5a** was achieved with 10% palladium on carbon, yielding the selectively functionalized phenylnaphthoate **5b**.

Treatment of **5b** with phosgene in benzene in the presence of pyridine gave chloroformyl derivative **5c**, which was not purified because of its anticipated instability but directly subjected to Friedel–Crafts conditions ($AlCl_3$, CS_2). The ^1H NMR spectrum of the resulting crude product indicated that the mixture contained cyclized material. The methyl group which appeared at δ 2.25 in **5b** was now present at δ 2.7 due to its proximity and coplanarity with the deshielding cone of the newly formed lactone carbonyl group. Some demethylation also occurred since the mass spectrum showed a molecular ion corresponding to chartreusin aglycon **1b**. The product was treated with hydrogen bromide to complete the demethylation and effect cyclization. Crystallization and sublimation afforded the chartreusin aglycon **1b**.

The route developed here for the total synthesis of **1b** can be employed to prepare analogues, and further work on this aspect is in progress.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Ultraviolet spectra were run on a Cary 15 (Varian) ultraviolet–visible spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian Model HA-100 spectrometer, using tetramethylsilane as an internal standard. Mass spectra were obtained with a CEC Dupont Model 21-110B spectrometer at an ionizing voltage of 70 eV. Carbon–hydrogen analyses were performed by Galbraith Laboratories of Knoxville, TN.

Reactions of Benzopyran-2-ones with Isobenzofuranones. General Procedure. Method A. To a stirred solution of lithium diisopropylamide at −78 °C, prepared from diisopropylamine (16 mmol), THF (100 mL), and *n*-BuLi (16 mmol) under N_2 at 0 °C, was added a slurry of the appropriate 3-(phenylsulfonyl)-1-(3*H*)-isobenzofuranone (7.27 mmol) in tetrahydrofuran (100 mL). To the resulting yellow anion, still at −78 °C, was added 1.5 equiv of the benzopyran-2-one.[10] The mixture was allowed to come to room temperature before being heated at reflux for 1 h. After cooling, the mixture was acidified with 3 N hydrochloric acid and the solvent removed on a rotary evaporator. The residue was dissolved in acetone with heating and allowed to stand overnight, yielding crystals of benzonaphthopyran.

4a (65%): mp 253–254 °C; mass spectrum, *m/z* 278 ($M^{+\cdot}$).

4b (5%): mp 249–252 °C; ^1H NMR (Me_2SO-d_6) δ 2.42 (s, 3 H, $ArCH_3$), 7.2–8.5 (m, 7 H, Ar H, OH), 9.18 (s, 1 H, Ar H), 12.65 (s, 1 H, OH).

Method B. The reaction was run in the same manner as above with the exception of the use of *tert*-butyl alcohol instead of diisopropylamine to yield **4b** (50%) and **4c** (35%): mp 239–240 °C; mass spectrum, *m/z* 322 ($M^{+\cdot}$); ^1H NMR ($CDCl_3$) δ 2.6 (s, 3 H, Ar CH_3), 4.3 (s, 3 H, OCH_3), 7.2 (d, J = 9 Hz, 1 H, Ar H), 7.4 (d, J = 10 Hz, 2 H, Ar H), 7.6 (t, J = 8 Hz, 1 H, Ar H), 8.25 (d, J = 9 Hz, 1 H, Ar H); UV (EtOH) λ_{max} 435 nm, 415, 395 (sh), 365, 350, 260, 220, 200 (ϵ 4400, 5030, 3470, 5890, 4600, 38 700, 27 400, 27 500).

Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.81; H, 4.35. Found: C, 70.44; H, 4.41.

2-Methyl-7-hydroxy-11-methoxy-12-(benzyloxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]pyran-6-one (4e). A magnetically stirred (350 mL) solution of **4c** (1.95 g, 6.05 mmol), K_2CO_3 (10 g), and benzyl bromide (0.74 mL, 6.05 mmol) in acetone (350 mL) was heated at reflux under nitrogen overnight at which time TLC analysis showed three products (monobenzyl, hydroquinone, dibenzyl). The reaction mixture was filtered and the filtrate evaporated at reduced pressure. Since considerable yellow material was present on the filter, the solids were suspended in water and hydrochloric acid was added to dissolve the carbonate salts. The solution was extracted with ether, dried ($MgSO_4$), filtered, combined with the original filtrate, and evaporated. The residue was chromatographed on silica gel eluted with methylene chloride to give 1.66 g of monobenzyl compound (contaminated with hydroquinone), mp 190–193 °C, and 0.62 g of dibenzyl compound: mp 188–189 °C; ^1H NMR ($CDCl_3$) δ 2.1 (s, 3 H, Ar CH_3), 3.85 (s, 3 H, OCH_3), 4.8 (m, 2 H, OCH_2Ar), 6.9–7.5 (m, 9 H, Ar H), 8.1

(8) Carey, F. A.; Sundberg, R. J. "Advanced Organic Chemistry"; Plenum: New York, 1977; Part A, p 385.

(9) The dibenzyl ether **4f** can be recycled in the sequence to **4c** by hydrogenolysis of the benzyl groups.

(10) Coumarin and 6-methylcoumarin were obtained from the Aldrich Chemical Co. and used without purification. 5,7-Dimethylcoumarin was synthesized from 3,5-dimethylphenol and malic acid by the method of Hershfield and Schmir (*J. Am. Chem. Soc.* **1973**, *95*, 7359).

(d, J = 8 Hz, 1 H, Ar H), 8.9 (s, 1 H, Ar H), 12.9 (s, 1 H, OH).

Anal. Calcd for $C_{26}H_{20}O_5$: C, 75.72; H, 4.85. Found: C, 75.81; H, 4.96.

2-Methyl-7,11-dimethoxy-12-(benzyloxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]pyran-6-one (4g). A magnetically stirred solution of monobenzyl ether **4e** (1.66 g, 4.05 mmol), K_2CO_3 (10 g), and excess dimethyl sulfate (2 mL, 21 mmol) in acetone (350 mL) was heated at reflux under nitrogen overnight. The solution was cooled, filtered, and evaporated at reduced pressure. The residue was taken up in ether and triethylamine (10 mL) was added. After standing for 1 h, the mixture was washed repeatedly with water, 10% HCl, and brine, then dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (silica gel, CH_2Cl_2) to afford 1.21 g of pure **4g** which was recrystallized from acetone: mp 158–60 °C; ^{1}H NMR ($CDCl_3$) 4.8 (s, 2 H, OCH_2Ar), 7.0 (d, J = 8 Hz, 1 H, Ar H), 7.1 (s, 2 H, Ar), 7.3–7.5 (m, 6 H, Ar H), 7.97 (d, J = 8 Hz, 1 H, Ar H), 8.86 (s, 1 H, Ar H).

Anal. Calcd for $C_{27}H_{22}O_5$: C, 76.06; H, 5.16. Found: C, 75.81; H, 5.12.

Methyl 3-(2-Methoxy-5-methylphenyl)-1,5-dimethoxy-4-(benzyloxy)-2-naphthoate (5a). Dimethoxybenzyloxy compound (**4g**) (0.605 g, 1.42 mmol) was suspended in 2 equiv of sodium hydroxide (0.114 g, 2.45 mmol) in water (100 mL) and heated on a steam bath overnight. The sides of the flask were washed down with acetone at irregular intervals. The homogeneous solution was evaporated to dryness and the residue suspended in acetone. Potassium carbonate (5 g) and dimethyl sulfate (2 mL) were added and the mixture was heated at reflux overnight. The reaction mixture was filtered and evaporated and the residue taken up in diethyl ether. Triethylamine (5 mL) was added and the mixture allowed to stand for 1 h before being washed repeatedly with water, dilute HCl, and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give 0.825 g of crude **5a**. Chromatography on silica gel afforded 0.58 g of an oil: ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3 H, Ar CH_3), 3.47 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.56 (d'd, J = 9 Hz, 2 H, OCH_2Ph), 6.6–7.2 (m, 9 H, Ar H), 7.32 (t, J = 8 Hz, 1 H, Ar H), 7.72 (d, J = 8 Hz, 1 H, Ar H).

Methyl 3-(2-Methoxy-5-methylphenyl)-1,5-dimethoxy-4-hydroxy-2-naphthoate (5b). Trimethoxy(benzyloxy)-3-aryl-2-naphthoate ester **5a** (0.580 g, 1.23 mmol) dissolved in absolute ethanol (100 mL) containing palladium on carbon (10%, 300 mg) was shaken under 20 psi of H_2 gas for 2.5 h in a Parr hydrogenator. The solution was filtered through Celite and the filtrate evaporated. The residue was chromatographed (silica gel, CH_2Cl_2) to afford 0.350 g of **5b**: mp 141–143 °C; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3 H, Ar CH_3), 3.5 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 3.9 (s, 6 H, OCH_3), 6.65–7.2 (m, 4 H, Ar H), 7.3 (t, J = 8 Hz, 1 H, Ar H), 7.7 (d, J = 8 Hz, 1 H, Ar H), 9.4 (s, 1 H, OH); UV (EtOH) λ_{max} 345 nm, 330, 317, 291, 230 (ϵ 2175, 1720, 1565, 1490, 25 000).

Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.11; H, 5.76. Found: C, 69.07; H, 5.83.

Chartreusin Aglycon (1b). To naphthoate **5b** (0.323 g, 0.846 mmol) dissolved in benzene (100 mL) and cooled in an ice bath was added cold condensed phosgene (20 mL) and pyridine (2 mL) while the mixture was stirred vigorously. The mixture was allowed to come to room temperature and stir for 1 h before the phosgene was removed by boiling on a steam bath under a hood. The benzene was removed under reduced pressure and the residue suspended in carbon disulfide (200 mL). An excess of aluminum chloride (5 g) was added and the mixture heated at reflux overnight. The solvent was evaporated and the dark green residue suspended in water and methylene chloride. The aqueous layer was removed and the organic layer dried ($MgSO_4$) and filtered. The filtercake was washed repeatedly with hot methylene chloride until the green color vanished. The filtrate was concentrated to 100 mL and cooled, yielding a green amorphous powder. Further concentration gave a second crop of material. The two crops were sublimed (250 °C, 0.03 mm) separately and found to have ultraviolet–visible spectra identical with the natural chartreusin aglycon (**1b**); mass spectrum, m/z 334 ($M^{+\cdot}$), with fragmentation pattern the same as the authentic material.

The mother liquor from the above precipitation was evaporated to dryness and the dark residue dissolved in 100 mL of acetic acid saturated with hydrobromic acid. The mixture was heated at reflux for 24 h and the green solution evaporated to dryness under reduced pressure. The residue was suspended in dilute HCl solution and heated at reflux overnight. The solvent was removed at reduced pressure and the residue was dissolved in hot methylene chloride. The green powder which precipitated upon cooling was sublimed (250 °C, 0.05 mm). The amorphous sublimate, while too insoluble for NMR spectroscopy, had ultraviolet, visible (EtOH), infrared ($CHCl_3$), and mass spectra (m/z 334 ($M^{+\cdot}$)) identical with natural chartreusin aglycon (**1b**). The melting point of the synthetic material (mp 302 °C) was undepressed when a mixture melting point[11] with an authentic sample (mp 313–314 °C) was taken, giving a value of 308–309 °C. The overall yield of aglycon from **5b** was 48%.

Acknowledgment. We are grateful to Dr. T. Ross Kelly of Boston College for providing a generous sample of natural chartreusin aglycon and for his extremely helpful comments concerning the purification of the final product. This work was generously supported by the National Cancer Institutes of the Department of Health, Education, and Welfare, Grant CA 18141.

Registry No. 1b, 34170-23-5; **2a**, 91-64-5; **2b**, 92-48-8; **3a**, 65131-08-0; **3b**, 74724-81-5; **4a**, 74724-82-6; **4b**, 74724-83-7; **4c**, 74724-84-8; **4e**, 74724-85-9; **4f**, 74744-16-4; **4g**, 74724-86-0; **5a**, 74724-87-1; **5b**, 74724-88-2; **5c**, 74724-89-3; phosgene, 75-44-5.

(11) The mixture melting point was taken in a sealed capillary on a Thomas-Hoover melting-point apparatus.

Structural Biochemistry. 20. Methylation of Purine Nucleosides[1]

George R. Pettit,* Richard M. Blazer, James J. Einck, and Kiyoshi Yamauchi

Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received April 15, 1980

Experimental methods have been devised for the permethylation of both adenosine (**1a** → **1b**) and guanosine (**2a** → **2b** + **3a**) employing trimethylanilinium methoxide (TMAM). Reaction of the TMAM reagent with inosine (**5a**) and xanthosine (**11**) was found to promote imidazole ring and/or riboside cleavage (e.g., **5a** → **7a** and **10**). While methylation of inosine resulted in a variety of such reaction pathways, xanthosine followed essentially a single direction, leading to caffeine (**12**) as the major product. Reaction conditions developed for permethylation of these purine nucleosides with the TMAM reagent should prove useful with other such heterocyclic glycoside systems.

The selective methylation of tRNA and DNA by species specific methyl transferases may provide some of the structural integrity (by conformational changes) that inhibits ready incorporation of similar nucleic acids from

0022-3263/80/1945-4073$01.00/0