Synthesis of Isagarin, a New Type of Tetracyclic Naphthoquinone from *Pentas longiflora*

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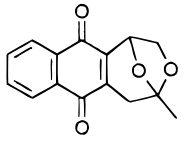
Isagarin (**1**) was synthesized in four steps from 1,4-dimethoxynaphthaldehyde (**4**). The key intermediate 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone (**3**) was found to react with acylated pyridinium ylides to afford, after spontaneous intramolecular condensation, the desired natural product isagarin (**1**). Depending on the type of acylated pyridinium ylides, different types of new pyranonaphthoquinone derivatives were obtained.

Introduction

Pentas longiflora Oliv. (Rubiaceae), a woody herb from oriental intertropical Africa, also locally known as Isagara, is used in the African traditional medicine (Rwanda) to treat scabies and the skin mycosis *pityriasis versicolor*.[1] Two major constituents, mollugin and pentalongin, were isolated before from the bark of the roots of *P. longiflora*,[1,2] and in a bioassay guided phytochemical study, pentalongin was identified as the antifungal principle.[3] Recently, isagarin (**1**), a new type of tetracyclic naphthoquinone, was isolated from *P. longiflora* and identified as 1,4-epoxy-4-methyl-1,2,4,5-tetrahydronaphtho[2,3-d]oxepin-6,11-dione.[4] In this paper, the first synthesis of isagarin (**1**) is reported.



1 (isagarin)

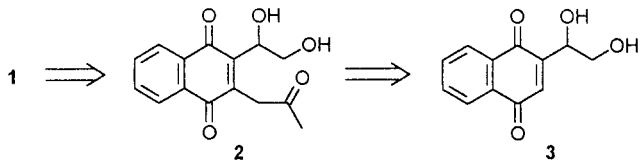
Results and Discussion

A retrosynthetic analysis illustrates that isagarin (**1**) can be synthesized from naphthoquinone **2**, as a result of intramolecular condensation (Scheme 1). Since quinones are known to undergo acetonylation with the corresponding pyridinium ylide,[5] 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone (**3**) was considered as the key intermediate in the synthesis.

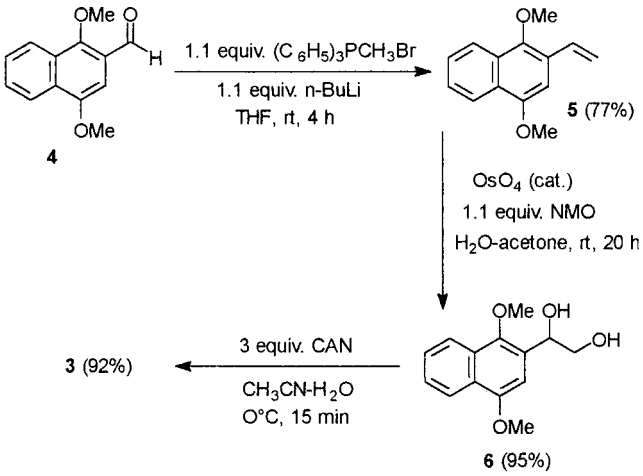
The synthesis of **3** is depicted in Scheme 2, starting from 1,4-dimethoxynaphthaldehyde (**4**)[6] which was converted to 1,4-dimethoxy-2-vinylnaphthalene (**5**) by means of a Wittig reaction, using methyltriphenylphosphonium bromide in the presence of *n*-butyllithium. Vicinal dihydroxylation of the double bond of the vinylnaphthalene **5** with a catalytic amount of osmium(VIII) tetraoxide and *N*-methylmorpholine *N*-oxide resulted in the formation of 2-(1,2-dihydroxyethyl)-1,4-dimethoxynaphthalene (**6**) in a yield of 95%. Then, cerium(IV) ammonium nitrate was used as a selective oxidant to convert **6** into the desired 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone (**3**) in 92% yield.

The introduction of an acetonyl group was performed by Michael addition of acetylmethyl pyridinium ylide, generated in situ by treatment of acetylmethyl pyridinium chloride with 1 equiv of triethylamine in acetonitrile (Scheme 3). The intermediate naphthoquinone **2**

Scheme 1



Scheme 2



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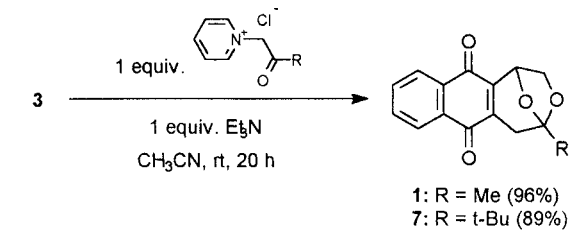
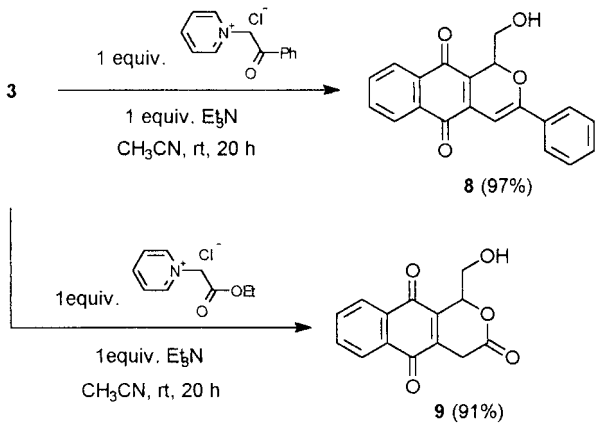
Scheme 3



Scheme 4



was never isolated and underwent spontaneous intramolecular condensation to give isagarin (**1**) in 96% yield.

As an extension to the synthesis of isagarin we investigated also the addition of some other acylated pyridinium ylides to the key intermediate naphthoquinone **3**. As expected, the introduction of a pivaloyl group, using (pivaloylmethyl)pyridinium chloride in the presence of 1 equiv of triethylamine gave the 4-*tert*-butyl analogue of isagarin i.e., 1,4-epoxy-4-*tert*-butyl-1,2,4,5-tetrahydronaphtho[2,3-d]oxepin-6,11-dione (**7**), in 89% yield (Scheme 3). Surprisingly, when a phenacyl group was introduced under the same conditions, compound **8** was obtained as a result of dehydration of the intermediate hemiacetal (Scheme 4). The extension of the conjugation is probably the driving force for this reaction. Finally, when [(ethoxycarbonyl)methyl]pyridinium ylide was reacted with the dihydroxylated naphthoquinone **3**, intramolecular transesterification with the secondary alcohol function gave rise to the lactone **9**, in 91% yield.

Experimental Section

General Procedures. All solvents and reagents were obtained from commercial suppliers and were used without purification. Dry tetrahydrofuran (THF) was obtained by distillation from sodium benzophenone ketyl. ^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were recorded in $CDCl_3$. All pyridinium salts were prepared according to literature methods.[5]

1,4-Dimethoxy-2-vinylnaphthalene (5). To an ice-cold stirred suspension of methyltriphenylphosphonium bromide (7.7 mmol, 2.75 g) in dry THF (20 mL) was added dropwise a solution of *n*-butyllithium, 2.5 M in hexane (7.7 mmol, 3.08 mL). After 30 min at this temperature, a homogeneous solution was obtained, and a solution of 1,4-dimethoxynaphthaldehyde (**4**)[6] (7 mmol, 1.51 g) in dry THF (10 mL) was added and the reaction mixture allowed to reach room temperature over a period of 4 h. The reaction was quenched by the addition of methanol (1 mL), and the solvent was evaporated under reduced pressure. Then, hexane (30 mL) was added, and the reaction mixture was heated under reflux for 5 min. The hexane extract was separated from the precipitate by decantation, filtered over Celite, and evaporated under reduced pressure. Flash chromatography on silica gel using 5% ethyl acetate in hexane as eluent gave 1,4-dimethoxy-2-vinylnaphthalene (**5**) (1.15 g, 77%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.86 (3H, s), 3.93 (3H, s), 5.38 (1H, dd, J = 10.9 Hz, 1.0 Hz), 5.80 (1H, dd, J = 17.8 Hz, 1.0 Hz), 7.25 (1H, dd, J = 17.8 Hz, 10.9 Hz), 6.89 (1H, s), 7.40−7.53 (2H, m), 8.04−8.21 (2H, m). ^{13}C NMR ($CDCl_3$): δ 55.51, 62.46, 100.01, 114.32, 122.17, 122.35, 125.32, 125.64, 126.72, 126.79, 128.86, 131.41, 147.38, 151.97. IR (NaCl): ν_{max} 1625, 1595, 1460, 1370, 1220, 1095, 1000, 775 cm^{-1}. MS *m*/*z* (%): 214(M$^+$, 88), 199(100), 184(29), 171(22), 168(12), 141(20), 128(29). Anal. Calcd for $C_{14}H_{14}O_2$: C 78.48%, H 6.59%. Found: C 78.12%, H 6.59%.

2-(1,2-Dihydroxyethyl)-1,4-dimethoxynaphthalene (6). To an ice-cold stirred solution of 1,4-dimethoxy-2-vinylnaphthalene (**5**) (2 mmol, 0.43 g) and 4-methylmorpholine *N*-oxide monohydrate (2.2 mmol, 0.30 g) in acetone (15 mL) and water (10 mL) was added a catalytic amount of osmium(VIII) tetraoxide, and the solution was allowed slowly to reach room temperature over a period of 20 h. Then, sodium hydrogen sulfite (1 g) was added to the stirred solution, and most of the acetone was removed by evaporation under reduced pressure. The resulting reaction mixture was poured into 2 N HCl and extracted three times with ether. The combined extracts were washed with sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on silica gel with 20% hexane in ethyl acetate as eluent gave 2-(1,2-dihydroxyethyl)-1,4-dimethoxynaphthalene (**6**) (0.47 g, 95%), mp 79−81 °C. ^{1}H NMR ($CDCl_3$): δ 3.10 (1H, broad s), 3.71−3.81 (2H, m), 3.85 (3H, s), 3.92 (3H, s), 5.33 (1H, dd, J = 8.1 Hz, 3.8 Hz), 6.85 (1H, s), 7.44−7.50 (2H, m), 7.94−8.21 (2H, m). ^{13}C NMR ($CDCl_3$): δ 55.56, 62.59, 67.37, 69.61, 101.62, 121.78, 122.41, 125.50, 126.23, 126.63, 128.14, 128.41, 146.07, 152.25. IR (NaCl): ν_{max} 3325 (OH), 1595, 1460, 1370, 1120, 910, 730 cm^{-1}. MS *m*/*z* (%): 248(M$^+$, 30), 217(100), 202(39), 189(32), 187(45), 174(21). Anal. Calcd for $C_{14}H_{16}O_4$: C 67.73%, H 6.50%. Found: C 67.58%, H 6.38%.

2-(1,2-Dihydroxyethyl)-1,4-naphthoquinone (3). To an ice-cold stirred solution of 2-(1,2-dihydroxyethyl)-1,4-dimethoxynaphthalene (**6**) (1 mmol, 250 mg) in acetonitrile (5 mL) was added dropwise a solution of cerium(IV) ammonium nitrate (3 mmol, 1.63 g) in water (10 mL). The reaction mixture was stirred for 15 min at 0 °C and then poured in water and extracted with ethyl acetate. The combined extracts were washed with sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure. After recrystallization from dichloromethane, 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone (**3**) was obtained as a white powder (200 mg, 92%), mp 143 °C. ^{1}H NMR ($CDCl_3$): δ 2.90 (1H, broad s), 3.68 (1H, d×d, J = 11.2 Hz, 6.3 Hz), 4.03 (1H, dd, J = 11.2 Hz, J = 3.6 Hz), 4.99−5.03 (1H, m), 7.13 (1H, d, J = 1.3 Hz), 7.74−7.78 (2H, m), 8.06−8.12 (2H, m). ^{13}C NMR ($CDCl_3$): δ 65.86, 68.98, 126.30, 126.59, 132.15, 132.43, 134.07, 134.18, 135.00, 150.33, 185.17, 185.59. IR (KBr): ν_{max} 3430 (OH), 3330 (OH), 1655 (C═O), 1590 (C═C) cm^{-1}. MS *m*/*z* (%): no M$^+$, 210-(M$^+$ − 18, 17), 188(100), 187(29), 159(36). Anal. Calcd for $C_{12}H_{10}O_4$: C 66.05%, H 4.62%. Found: C 65.84%, H 4.43%.

Addition of Acylated Pyridinium Ylides to 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone (3). General Procedure. To a stirred solution of 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone (**3**) (2 mmol, 0.44 g) and pyridinium salt (2 mmol) in acetonitrile (50 mL) at 50−60 °C was added dropwise and under a nitrogen atmosphere a solution of triethylamine (2 mmol, 202 mg) in acetonitrile (3 mL). Stirring was continued at room temperature for 20 h, and then most of the acetonitrile was removed by evaporation under reduced pressure. The resulting reaction mixture was poured into 2 N HCl, extracted with ethyl acetate, washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to afford crude product isagarin (**1**). Recrystallization from absolute ethanol gave **1** (0.49 g, 96%) as a yellow powder, mp 165.1−165.4 °C (lit.,[4] mp 160.9−161.4 °C). ^{1}H NMR ($CDCl_3$): δ 1.68 (3H, s), 2.73 (1H, d, J = 19.5 Hz), 2.88 (1H, dd, J = 19.5 Hz, 1.3 Hz), 3.96−4.05 (2H, m), 5.57 (1H, d, J = 4.3 Hz), 7.72−7.76 (2H, m), 8.06−

8.10 (2H, m). ^{13}C NMR ($CDCl_3$): δ 23.99, 36.30, 70.15, 72.99, 106.36, 126.31, 126.41, 131.61, 132.06, 133.85, 133.91, 141.70, 143.99, 182.57, 184.15. IR (KBr): ν_{max} 1661 (C═O), 1632 (C═O), 1595 (C═C) cm^{-1}. MS *m*/*z* (%): 256(M$^+$, 23), 226(26), 214(14), 197(60), 187(17), 43(100). Anal. Calcd for $C_{15}H_{12}O_4$: C 70.31%, H 4.72%. Found: C 70.12%, H 4.46%. All spectrometric data (^{1}H NMR, ^{13}C NMR, IR, and MS) were identical with the reported data of the natural product.[4]

1,4-Epoxy-4-*tert*-butyl-1,2,4,5-tetrahydronaphtho[2,3-d]oxepin-6,11-dione (7). Recrystallization from absolute ethanol gave **7** (0.53 g, 89%) as a brown powder, mp 160.6−161.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.10 (9H, s), 2.66 (1H, d, J = 19.8 Hz), 3.03 (1H, dd, J = 19.8 Hz, 1.7 Hz), 3.86−3.90 (1H, m), 4.01 (1H, d, J = 7.3 Hz), 5.55 (1H, d, J = 4.3 Hz), 7.69−7.76 (2H, m), 8.05−8.11 (2H, m). ^{13}C NMR ($CDCl_3$): δ 24.60, 30.51, 37.11, 70.26, 73.22, 111.52, 126.23, 126.41, 131.61, 132.15, 133.78, 133.83, 142.64, 144.02, 182.66, 184.42. IR (KBr): ν_{max} 1658 (C═O), 1629 (C═O), 1594 (C═C) cm^{-1}. MS *m*/*z* (%): 298(M$^+$, 33), 267(16), 253(17), 213(15), 197(100). Anal. Calcd for $C_{18}H_{18}O_4$: C 72.47%, H 6.08%. Found: C 72.11%, H 5.87%.

1-(Hydroxymethyl)-3-phenyl-1H-naphtho[2,3-c]pyran-5,10-dione (8). Recrystallization from ethanol gave **8** (0.62 g, 97%) as dark red needles, mp 152 °C. ^{1}H NMR ($CDCl_3$): δ 2.16 (1H, broad s), 3.79 (1H, dd, J = 12.2 Hz, 3.6 Hz), 4.07 (1H, dd, J = 12.2 Hz, 7.6 Hz), 5.87 (1H, dd, J = 7.6 Hz, 3.6 Hz), 6.68 (1H, s), 7.41−7.47 (3H, m), 7.68−7.77 (2H, m), 7.82−7.87 (2H, m), 8.06−8.13 (2H, m). ^{13}C NMR ($CDCl_3$): δ 61.92, 75.02, 92.69, 123.66, 126.07, 126.59, 126.27, 128.73, 131.07, 131.71, 132.65, 132.83, 133.33, 134.12, 138.38, 159.94, 182.08, 182.33. IR (KBr): ν_{max} 3461 (OH), 1662 (C═O), 1635 (C═O), 1583 (C═C), 1531 (C═C) cm^{-1}. MS *m*/*z* (%): 318(M$^+$, 7), 287(100), 202(15), 105(25). Anal. Calcd for $C_{20}H_{14}O_4$: C 75.46%, H 4.43%. Found: C 75.57%, H 4.31%.

3,4-Dihydro-1-(hydroxymethyl)-1*H*-naphtho[2,3-*c*]pyran-3,5,10-trione (9). Recrystallization from acetonitrile gave **9** (0.47 g, 91%) as a yellow powder, mp 184 °C. ^{1}H NMR (acetone-d_6): δ 2.80 (1H, broad s), 3.49 (1H, dd, J = 22.1 Hz, 2.1 Hz), 3.65 (1H, dd, J = 22.1 Hz, 1.3 Hz), 3.92−4.09 (2H, m), 5.61−5.64 (1H, m), 7.89−7.93 (2H, m), 8.09−8.13 (2H, m). ^{13}C NMR (acetone-d_6): δ 28.81, 65.25, 78.96, 127.01, 132.77, 132.95, 135.11, 138.42, 141.29, 167.92, 182.67, 183.03. IR (KBr): ν_{max} 3407 (OH), 1723 (C═O), 1661 (C═O), 1590 (C═C) cm^{-1}. MS *m*/*z* (%): 228(M$^+$ − 30, 100), 227(12), 200(26), 172(31), 115(29). Anal. Calcd for $C_{14}H_{10}O_4$: C 65.12%, H 3.90%. Found: C 65.05%, H 3.71%.

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