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TOTAL SYNTHESIS OF MAGNOLAMIDE[≠]

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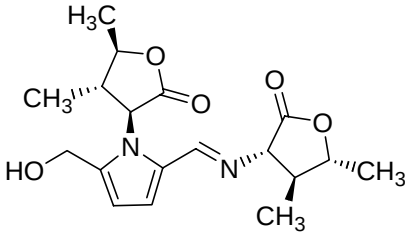
Abstract-The first total synthesis of magnolamide, a new alkaloid from *Magnolia coco,* has been achieved using the titanium (IV) isopropoxide-mediated Paal-Knorr synthesis of the core pyrrole system.

In 1984, we reported the discovery of compounds (**1**-**4**) as main secondary metabolites of the Central American tree *Quararibea funebris* (Llave) Vischer (Bombacaceae).[1] Subsequently several related compounds (**5**) and (**6**) from *Q. funebris*,[2, 3] and (**7**) from *Pisum sativum*,[4] were isolated. The *N*-



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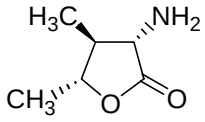

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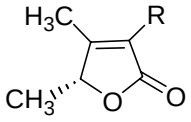
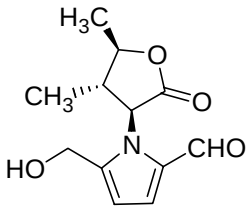


3; R=NH_2
4; R=OH



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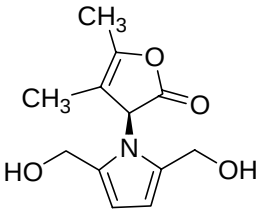

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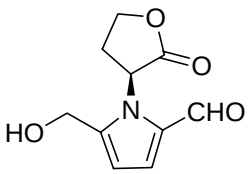

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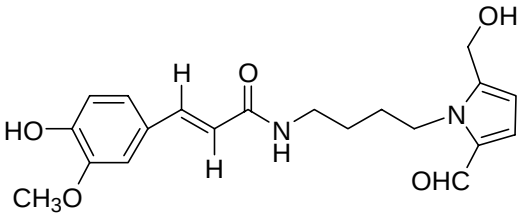
substituted 2-formyl-5-hydroxymethyl group, or the corresponding diol, is a common functional array among compounds (**1**), (**5**), (**6**), and (**7**), which, taken together with considerations of biological activity, suggests that this atomic grouping may be a new pharmacophore. Recently magnolamide (**8**) has been obtained from *Magnolia coco* (Lour.) DC. (Magnoliaceae).[5] The easy formal dissection of this structure

[≠] Dedicated to Professor James P. Kutney on the occasion of his seventieth birthday.



magnolamide (**8**)

into hexose, 1, 4-diaminobutane, and ferulic acid moieties supports our original proposal[1] for the likely biosynthesis of the *N*, 2, 5-trisubstituted pyrrole portion of funebrine (**1**). We now report our application of methodologies developed for the synthesis of **1** and **5**[6] to a synthesis of magnolamide (**8**).

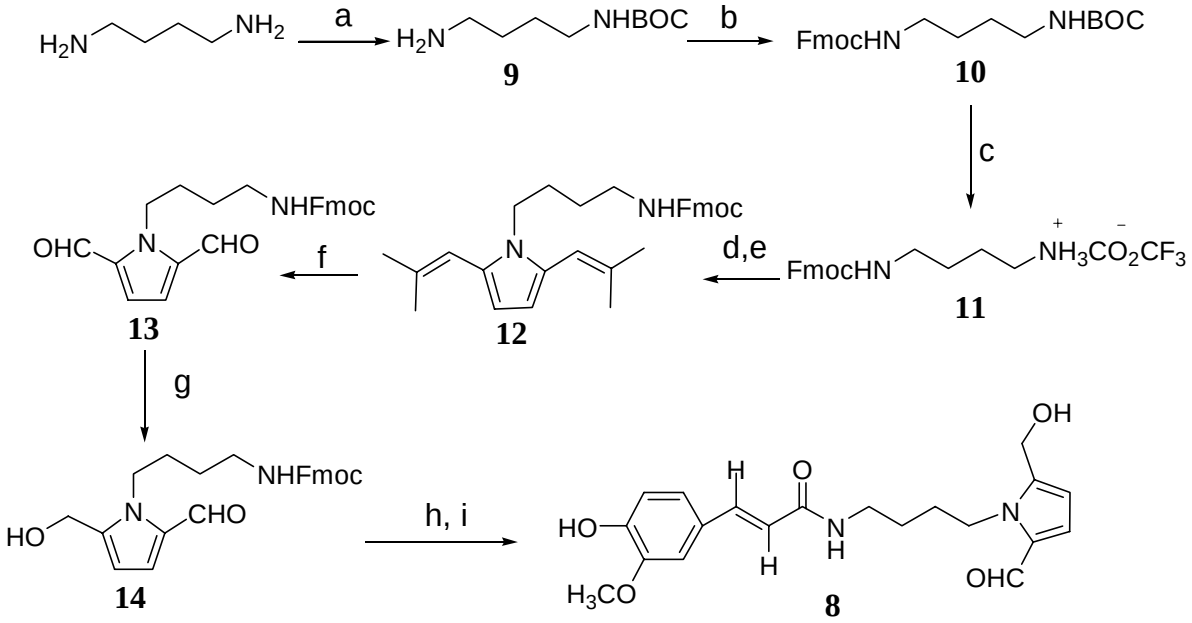
The total synthesis is shown in Scheme 1. Subjection of the mono-BOC derivative of 1,4-diaminobutane[7] to the Ti(O-*i*Pr)$_4$ - catalyzed Paal-Knorr condensation[6] gave a very low yield (8 %) of the *N*, 2, 5-trisubstituted pyrrole, probably because of Lewis acid-mediated de-BOC protection by Ti(O-*i*Pr)$_4$. In contrast, Fmoc-butanediamine trifluoroacetate[8] condensed with 2,9-dimethyldeca-2,8-diene-4,7-dione[9] under the influence of Ti(O-*i*Pr)$_4$ to give **12** in 74 % yield. Oxidation, followed by selective reduction by $NaBH_3CN$ of **12**, generated the desired pyrrole (**14**) bearing *N*-alkyl, 2-formyl, and 5-hydroxymethyl substituents. Since the free amino aldehyde derived from **14** is subject to rapid self-condensation, we deprotected it with triethylamine (20 % in THF) and in the same pot, condensed the resulting amino-aldehyde with ferulic acid (1 equiv.) using CMC/HOBt. Magnolamide (**8**) was slowly produced, and isolated by chromatography (silica gel, CH_2Cl_2/CH_3OH, 10:1) in 40% yield together with some unreacted ferulic acid. The spectral characteristics of synthetic and natural magnolamide (**8**) were identical. This route is adaptable to the synthesis of numerous magnolamide analogues.

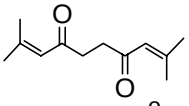
EXPERIMENTAL

Materials and Methods: Chromatography refers to flash chromatography on silica gel according to the method of Still.[10] *N*-*tert*-Butoxycarbonyl-1,4-dibutanediamine (**9**)[7], *N*-fluorenylmethoxycarbonyl-*N'*-*tert*-butoxycarbonylbutanediamine (**10**)[8] and *N*-fluorenylmethoxycarbonylbutanediamine trifluoroacetate (**11**)[8] were prepared by procedures previously reported. All other reagents were used as purchased.

Synthesis of 1-(N-fluorenylmethoxycarbonylamino)butyl-2,5-bis(isobutenyl)pyrrole (12). To a suspension of *N*-fluorenylmethoxycarbonylbutanediamine trifluoroacetate (**11**)[8] (3.47 g, 8.18 mmol) in 120 mL of dry toluene was added $Ba(OH)_2$ powder (1.40 g, 8.18 mmol). The mixture was stirred at 20 °C for 2 h under nitrogen. In a separate flask, a solution of 2,9-dimethyldeca-2,8-diene-4,7-dione[9] (1.59 g, 8.18 mmol) and titanium tetraisopropoxide (2.45 mL, 8.18 mmol) in 120 mL of dry toluene was stirred at 20 °C. The two solutions were then mixed and heated under reflux for 24 h. Water was removed by a Dean-Stark trap. The reaction mixture was cooled to 20 °C and solvent evaporated under reduced

Scheme1: Synthetic route to magnolamide (**8**)



(a) $(BOC)_2O$, dioxane, 20 ^oC, 22 h, 98%; (b) FmocCl, THF, 10% aq. Na_2CO_3, 20 ^oC, 20 h, 79%; (c) CF_3CO_2H, 20 ^oC, 30 min, 98%; (d) $Ba(OH)_2$, toluene; (e)  , $Ti(O\text{-}iPr)_4$, toluene, reflux, 20 h, 74%; (f) $NaIO_4/OsO_4$, THF-H_2O, 20 ^oC, 22 h, 38%; (g) $NaBH_3CN$, HCO_2H, dioxane-H_2O, 20 ^oC, 2 h, 90%; (h) Et_3N, THF, 20 ^oC, 4 h; (i) ferulic acid, CMC, HOBt, THF, 20 ^oC, 48 h, 40%

pressure. The brown solid residue was subjected to chromatography (100% hexane to 20% ethyl acetate/hexane, v/v), to give the crude product which crystallized from hexane as a pale yellow solid (mp 58.5-60.5 °C) which was unstable to aerial oxidation (1.76 g, 74%); ^1H NMR (300 MHz, acetone-d_6) δ 1.43-1.57 (m, 2H), 1.57-1.66 (m, 2H), 1.86 (d, J = 6.0 Hz, 6H), 2.08, (s, 6H), 3.14 (q, J = 6.2 Hz, 2H), 3.88 (t, J = 6.9 Hz, 2H), 4.20 (t, J = 6.8 Hz, 1H), 4.32 (d, J = 7.3 Hz, 2H), 6.03 (br, 2H), 6.12 (br, 2H), 6.43 (br, 1H), 7.30 (t, J = 7.4 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.66 (d, J = 7.4 Hz, 2H), 7.84 (d, J = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 26.9, 28.0, 40.6, 42.9, 47.2, 66.5, 108.3, 114.5, 120.0, 124.9, 127.0, 127.6, 129.6, 134.6, 141.2, 143.9, 156.3. This was immediately subjected to the next step.

Synthesis of 1-(N-fluorenylmethoxycarbonylamino)butyl-2,5- diformylpyrrole (13). Osmium (VIII) oxide (60 mg, 0.24 mmol) and then, in several portions over an 1 hour period, sodium metaperiodate (4.82 g, 22.5 mmol) were added at 20 °C to a stirred solution of 1-(*N*-fluorenylmethoxycarbonylamino)-butyl-2,5-bis(isobutenyl)pyrrole (**12**) (1.64 g, 0.425 mmol) in a mixture of THF (125 mL) and water (25

mL). The reaction was allowed to proceed for 22 h under nitrogen, after which TLC analysis indicated complete consumption of the starting material. The reaction mixture was diluted with water (125 mL) and extracted with CH_2Cl_2 (500 mL, then 2 x 125 mL). The combined organic layers were washed with water (2 x 100 mL), brine (2 x 125 mL), then dried (Na_2SO_4), and concentrated under vacuum. Chromatography (3:2; hexanes : ethyl acetate, v/v) of the crude product gave pure 1-(*N*-fluorenylmethoxycarbonylamino)-butyl-2,5-diformylpyrrole (**13**) as unstable colorless needles (0.54 g, 36%); mp 116.3-119.4 °C (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44-1.55 (m, 2H), 1.61-1.75 (m, 2H), 3.17 (q, J = 6.2 Hz, 2H), 4.29 (d, J = 7.0 Hz, 2H), 4.66 (t, J = 7.4 Hz, 2H), 5.15 (t, J = 5.3 Hz, 1H), 6.87 (s, 2H), 7.21 (t, J = 7.3 Hz, 2H), 7.30 (t, J = 7.4 Hz, 2H), 7.51 (d, J = 7.4 Hz, 2H), 7.65 (d, J = 7.7 Hz, 2H), 9.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 28.1, 40.0, 46.0, 47.2, 66.4, 119.8, 122.3, 125.0, 126.9, 127.5, 135.8, 141.2, 144.0, 156.4, 182.1. The compound deteriorated too rapidly for accurate microanalysis.

Synthesis of 1-(N-fluorenylmethoxycarbonylamino)butyl-2-formyl-5-hydroxymethylpyrrole (14). 1-(*N*-Fluorenylmethoxycarbonylamino)butyl-2,5-diformylpyrrole (**13**) (362.4 mg, 0.871 mmol) was dissolved in dioxane (10 mL), and mixed with water (1.0 mL) and HCOOH (1.0 mL). Then $NaBH_3CN$ (57.6 mg, 0.871 mmol) was added at once, and the mixture stirred at 20 °C for 2 h. After neutralization to pH 7.0 by the addition of $NaHCO_3$ (2.19 g), the mixture was extracted thoroughly with ether (3 x 50 mL). The combined organic layers were washed with H_2O (2 x 40 mL) and brine (2 x 30 mL), and dried (Na_2SO_4). The dried ether solution was evaporated under reduced pressure to give a yellow solid as crude product which was further purified by chromatography (50% to 70%; ethyl acetate in hexanes) to give pure 1-(*N*-fluorenylmethoxycarbonylamino)butyl-2-formyl-5-hydroxymethylpyrrole (**14**) (330 mg, 91%) as unstable colorless crystals; mp 121.2-123.5 °C (from ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57-1.63 (m, 2H), 1.74-1.81 (m, 2H), 2.08 (br, 1H), 3.22 (q, J = 6.4 Hz, 2H), 4.20 (t, J = 6.9, 2H), 4.38 (m, 2H), 4.62 (s, 2H), 5.27 (t, J = 5.3 Hz, 1H), 6.21 (d, 1H, J = 4.0 Hz), 6.88 (d, 1H, J = 4.0 Hz), 7.29 (t, J = 7.4 Hz, 2H), 7.39 (t, J = 7.4, Hz, 2H), 7.59 (d, J = 7.4 Hz, 2H), 7.74 (d, J = 7.7 Hz, 2H), 9.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 27.9, 39.7, 45.1, 47.2, 56.3, 66.5, 110.4, 119.9, 125.0, 127.0, 127.6, 132.4, 141.3, 143.9, 156.7, 179.5; GC-MS (m/z) 196, 178, 165, 152, 139, 126, 115, 98, 82, 72. The compound deteriorated too rapidly for accurate microanalysis.

Synthesis of magnolamide (8). In a round-bottom flask (25 mL), 1-(*N*-fluorenylmethoxycarbonylamino)-butyl-2-formyl-5-hydroxymethylpyrrole (**14**) (330 mg, 0.789 mmol) was dissolved in THF (3 mL). Triethylamine (1 mL) was added to the solution through a syringe, and the reaction mixture was stirred at 21 °C for 4 h. In a separate flask, CMC (379 mg, 0.868 mmol) was suspended in THF (3 mL), followed by the addition of HOBt (106.6 mg, 0.789 mmol) and ferulic acid (155 mg, 0.789 mmol). The mixture was stirred at 21 °C for 10 min, then added to the first solution by Pasteur pipette. Stirring was continued at the same temperature for 60 h. The reaction mixture was then diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). After washing with water (2 x 20 mL) and brine (20 mL), the organic layer was

dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was washed with hexane (3 x 30 mL) and purified by column chromatography (5% CH_3OH in CH_2Cl_2), to give magnolamide (**8**) as a colorless oil (65 mg, 22%; the yield is 40% based on recovered ferulic acid); ^{1}H NMR (300 MHz, acetone-d_6) δ 1.54-1.65 (m, 2H), 1.74-1.85 (m, 2H), 3.35 (q, J = 6.6 Hz, 2H), 3.87 (s, 3H), 4.41 (t, J = 6.4 Hz, 2H), 4.58 (br, 1H), 4.67 (s, 2H), 6.20 (d, J = 3.6 Hz, 1H), 6.50 (d, J = 15.6 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 4.5 Hz, 1H), 7.05 (dd, J = 8.1, 1.8 Hz, 1H), 7.15 (d, J = 1.8 Hz, 1H), 7.44 (d, J = 15.6 Hz, 1H), 8.10 (br, 1H), 9.49 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 27.6, 30.6, 39.1, 45.7, 56.1, 56.2, 110.4, 111.2, 116.0, 119.8, 122.4, 124.7, 128.1, 133.0, 140.4, 143.7, 148.4, 149.0, 166.5, 179.5. These spectral data are identical with those reported in the literature.[5]

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