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A stereoselective synthesis of Malbranicin

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Abstract: In this communication we describe the first synthesis of Malbranicin, a novel antibiotic quinone, isolated from *Malbranchea cinnamomea*. Our strategy was based on a diastereoselective alkylation of a chiral oxazolidinone enolate. Our results suggest the absolute configuration of this compound. © 1997 Elsevier Science Ltd

Introduction

Malbranicin is a novel quinone isolated from the culture filtrate and mycelium of *Malbranchea cinnamomea* by Nakayama *et al.*[1] The structure was elucidated to be 6-(1-acetylethyl)-2-methoxy-2,5-cyclohexadiene-1,4-dione (**1**, Figure 1), but its absolute configuration at C-7 was not determined.

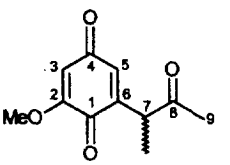

Figure 1. Malbranicin **1**.

Malbranicin exhibited antimicrobial and cytotoxic activities against Gram-positive bacteria and mammalian cell KB and P388 lines, respectively. These biological activities encouraged us to develop a stereoselective synthesis of **1**, outlined in Scheme 1.

Results and discussion

Our synthesis started from the acid **2**, which was prepared according to the precedent literature.[2] It was transformed into the corresponding acyl chloride by treatment with $SOCl_2$ (82%, yield), which gave, following the procedure of D. Evans,[3] the chiral imide **3**.[3b] The imide **3** underwent high stereoselective enolization in THF at −78°C with sodium hexamethyldisilylamide to form probably the corresponding *Z*-enolate,[3a] that was alkylated by treatment with 4 eq. of methyl iodide. The reaction mixture was quenched with acetic acid in ether,[3d] to furnish the alkylated product **4** in good yield and high diastereoselectivity (92% d.e). As expected, the major diastereoisomer was produced by the alkylation of the less shielded face of the chiral auxiliary.[3,4] Subsequent hydrolysis of the purified imide under mild basic conditions (LiOH, THF–H_2O) gave the acid **5**. The enantiomeric excess (~93%) of **5** was determined from the 250 MHz ^{1}H-NMR spectra of its corresponding methyl ester, recorded in the presence of a chiral shift reagent ($Eu(hfc)_3$), comparative to the racemic methyl ester.[5] Aldehydes and ketones[6] can be easily prepared from *N*-methoxyamides and, starting from optically active carboxylic acids, the corresponding amides can be obtained whitout racemisation.[7] So, we chose the *N*-methoxyamide **6** as precursor of the ketone **7**. In this way, acid **5** was treated with *N,O*-dimethyl hydroxylamine hydrochloride in the presence of CBr_4, PPh_3 and pyridine, following the

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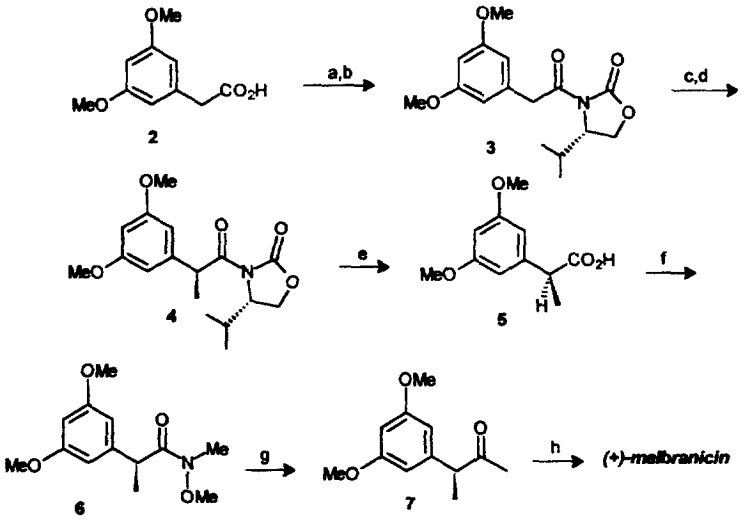

Reagents and Conditions: a: $SOCl_2$, CH_2Cl_2-DMF, 24 h, rt, 82%; b: (*S*)-4-isopropyloxazolidinone /*n*-BuLi /THF, -30°C, 4 h, 71%; c: NaHMDS, THF, -78 °C, 1 h; d: MeI, -78 °C → -30 °C, 2 h, 80%; e: LiOH, THF-H_2O, 76%; f: MeON(Me)H.HCl, DMAP, CH_2Cl_2, 88%; g: MeMgBr/ Et_2O, 85%; h: CrO_3, AcOH, 0 °C, 67%.

Scheme 1.

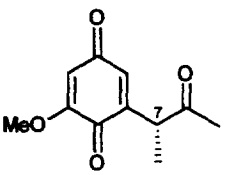

Figure 2. (*R*)-(−)-Malbranicin.

procedure described by Luche *et al.*[7] *N*-methoxyamide was obtained in 88% yield and then reacted with methylmagnesium bromide to provide the methylketone **7** (85% yield). Oxidation by CrO_3 in AcOH according to the precedent literature[2,8,9] gave Malbranicin **1**.

The optical rotation of **1**, prepared as above, was positive (+16°, c 0.01, MeOH) and opposite to that of the natural Malbranicin.[10] Our results suggest the *R*-configuration at C-7 for the (−)-Malbranicin (Figure 2).

In conclusion, the first synthesis of (*S*)-(+)-Malbranicin was developed by a seven-step sequence in 18% overall yield from (3,5-dimethoxy)-phenylacetic acid. The optical rotation of the synthetic Malbranicin was positive and opposite to that of the natural product, suggesting the *R* configuration at C-7 for the natural quinone, which could be obtained by the same synthetic strategy starting from (*R*)-4-isopropyloxazolidinone.

Experimental

General

Methylmagnesium bromide, sodium hexamethyldisilylamide and *n*BuLi were purchased from Aldrich Chemical Co. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2. Melting points (uncorrected) were determined on a Büchi 510 apparatus. NMR and IR spectra were recorded on a Bruker 250 spectrometer and on a Nicolet

FT-IR 510, respectively. UV spectra were recorded on a Beckman HP 5901A and MS spectra were determined on a Micromass Autospec Q.

Imide 3

To a solution of (*S*)-4-isopropyloxazolidinone (1,42 g, 11 mmol) in dry THF (11 mL) at −30°C under N_2, was added dropwise a solution of *n*BuLi in hexane (11 mmol) and the resulting mixture stirred for 30 min at the same temperature. Then, a solution of (3,5-dimethoxy)phenyl-acetylchloride (12 mmol) in 3 mL of dry THF was added. The reaction mixture was stirred for 4 h at −30°C, then quenched with 1 M solution of $NaHSO_4$ (75 mL). The mixture was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers washed with water and dried over $MgSO_4$. After filtration and solvent removal *in vacuo*, the residue was purified by flash chromatography on silica gel (eluent: hexane–EtOAc, 70:30) to give **3** in 71% yield as a colorless viscous oil. IR (neat): ν_{max} 3005, 2969, 1782, 1708, 1599 cm^{-1}; ^{1}H-NMR: δ 6.70–6.58 (m, 3H); 4.53–4.42 (m, 1H); 4.38–4.15 (m, 2H); 4.26 (d, *J*=15.2 Hz, 2H); 3.82 (s, 6H); 2.35 (m, 1H); 0.90 (d, *J*=7Hz, 3H); 0.87 (d, *J*=7.1Hz, 3H) ppm. ^{13}C-NMR: δ 172.1 (s); 154.1 (s); 140.2 (s); 132.1 (s); 130.9 (d); 129.5 (d); 62.8 (t); 59.9 (d); 57.8 (q); 57.4 (q); 41.2 (t); 28.7 (d); 17.9 (q); 14.3 (q) ppm. MS (%): m/z 307 (12) [M^+]; 178 (100); M^+. Calcd. for $C_{16}H_{21}NO_5$: 307.1419; Found: 307.1415.

Imide 4

To a solution of imide **3** (1.59 g, 5 mmol) in dry THF (30 mL) at −78°C, under N_2, was added dropwise 1 M solution of NaHMDS in THF (5.5 mL) over a period of 5 min., resulting in a red solution. After stirring for 1 h at −78°C, MeI (3.5 g, 25 mmol) was added all at once. The mixture was stirred for 1 h at −78°C, then allowed to warm up −30°C which resulted in a yellow solution. After stirring for an additional 1 h, the reaction mixture was quenched with AcOH (15 mL) in Et_2O (20 mL) and filtered over a pad of Celite. The filtrate was concentrated *in vacuo* and the residue (ds ratio 9:1, from ^{1}H-NMR of the crude product), was purified by flash chromatography on silica gel (hexane/EtOAC, 4:1) to provide the alkylated imide **4** as a viscous oil (80% yield). IR (neat): ν_{max} 3003, 2967, 1784, 1706, 1598 cm^{-1}; ^{1}H-NMR: δ 6.71–6.68 (m, 3H); 5,08 (q, *J*=7 Hz, 1H); 4.30 (m, 1H); 4.20–4.05 (m, 2H); 3.82 (s, 6H); 2.35 (m, 1H); 1.52 (d, *J*=7.2 Hz, 3H); 0.90 (d, *J*=7Hz, 3H); 0.87 (d, *J*=7.1 Hz, 3H) ppm. ^{13}C-NMR: δ 172.0 (s); 153.9 (s); 140.8 (s); 132.2 (s); 130.8 (d); 129.3 (d); 62.6 (t); 60.1 (d); 57.8 (q); 57.6 (q); 49.9 (d); 28.6 (d); 19.8 (q); 17.7 (q); 14.5 (q) ppm. MS (%): m/z 321 (9) [M^+]; 192 (100); M^+. Calcd. for $C_{17}H_{23}NO_5$: 321.1576; Found: 321.1585.

Acid 5

A mixture of the alkylated oxazolidinone **4** (642 mg, 2 mmol), LiOH (132 mg, 6 mmol) in THF (10 mL): H_2O (5 mL) was stirred at 0°C for 2 h. After warm up to room temperature the solvent was removed *in vacuo* and the residue washed with EtOAc (3×5 mL). The aqueous layer was then acidified (concentrated HCl), until pH 1 and extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration furnished an oil that was purified by flash chromatography (EtOAc–hexane 1:1). Acid **5** was obtained in 76% yield. IR (neat): ν_{max} 3540–2540, 1711, 1601, 1153, 832 cm^{-1}. ^{1}H-NMR: δ 9.0 (br, 1H); 6.45 (m, 3H); 4.02 (q, *J*=7.3 Hz, 1H); 3.82 (s, 6H); 1.47 (d, *J*=7.2 Hz, 3H) ppm. ^{13}C-NMR: δ (s); 140.6 (s); 132.0 (s); 129.9 (d); 129.3 (d); 57.7 (q); 57.5 (q); 40.5 (d); 19.8 (q) ppm. MS (%): m/z 210 (10) [M^+]; 195 (23); 182 (52); 165 (100); M^+. Calcd. for $C_{11}H_{14}O_4$: 210.0892; Found: 210.0899.

Amide 6

To a stirred mixture of the acid **5** (514 mg, 2 mmol), *O,N*-dimethyl-hydroxylamine hydrochloride (111 mg, 2.4 mmol), dry pyridine (189.4 mg, 2.4 mmol) and carbon tetrabromide (2.4 mmol) in 8 mL of dry CH_2Cl_2, at room temperature, and triphenylphosphine (629.5 mg, 2.4 mmol) were added portionwise over 5 min. The resulting mixture was stirred for 1 h and then the solvent was evaporated and a 1:1 mixture of hexane–ethyl acetate added. The solid triphenylphosphine oxide was filtered off,

the solvents removed at reduced pressure and the crude material purified by flash chromatography (hexane–EtOAc, 1:1). The amide **6** was obtained in 88% yield. IR (neat): ν_{max} 1711, 1601, 1153, 832 cm^{-1}. ^{1}H-NMR: δ 6.52 (m, 3H); 3.99 (q, *J*=7 Hz, 1H); 3.82 (s, 6H); 3.50 (s, 3H); 3.22 (s, 3H); 1.45 (d, *J*=7.3 Hz, 3H) ppm. ^{13}C-NMR: δ 176.1 (s); 140.6 (s); 132.0 (s); 129.9 (d); 129.3 (d); 57.7 (q); 57.5 (q); 40.5 (d); 19.8 (q) ppm. MS (%): m/z 253 (10) [M^+]; 195 (23); 182 (52); 165 (100); M^+. Calcd. for $C_{13}H_{19}NO_4$: 253.1314; Found: 253.1317.

Ketone 7

To a stirred solution of the amide **6** (974 mg, 3.85 mmol) in dry diethylether (30 mL), at 0°C was added dropwise a 3 M solution of methylmagnesium bromide (3.85 mmol). The reaction was complete within 2 h and was quenched by cannulation into a vigorously stirring solution of ammonium chloride (15 mL). The layers were separated, and the aqueous phase was extracted with diethylether (4×20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (EtOAc–hexane 1:3), provided the desired ketone in 85% yield. IR (neat): ν_{max} 1711, 1601, 1153, 832 cm^{-1}. ^{1}H-NMR: δ 6.52 (m, 3H); 3.99 (q, *J*=7 Hz, 1H); 3.82 (s, 6H); 3.50 (s, 3H); 3.22 (s, 3H); 1.45 (d, *J*=7.3 Hz, 3H) ppm. ^{13}C-NMR: δ 176.1 (s); 140.6 (s); 132.0 (s); 129.9 (d); 129.3 (d); 57.7 (q); 57.5 (q); 40.5 (d); 19.8 (q) ppm. MS (%): m/z 208 (10) [M^+]; 195 (23); 182 (52); 165 (100); M^+. Calcd. for $C_{12}H_{16}O_3$: 208.1099; Found: 208.1103

(+)-Malbranicin

To a stirred solution of chromium trioxide (458 mg, ~4.58 mmol) in water (1.5 mL) and acetic acid (6.0 mL) was added dropwise a solution of the ketone **7** (239 mg, ~1.15 mmol) in acetic acid (7.5 mL).The resulting mixture was stirred at 0°C for 1 h and then at room temperature for 3 h and poured into water and ice. The crude product was extracted with EtOAc (4×30 mL) and after concentration, washed with brine and water. Drying over Na_2SO_4, filtration and concentration gave an orange solid that was purified by preparative TLC (EtOAc–hexane 10%). Yield: 67% (160mg). $[\alpha]_D$ +16° (*c* 0.01, MeOH); MP: 113–115°C (Lit.:[1] 112–114°C); UV (MeOH): λ_{max} 362, 259 nm; IR (neat): ν_{max} 2993, 2988, 2950, 1703, 1682, 1645, 1238 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.58 (m, 1H); 5.87 (d, *J*=2.3 Hz, 1H); 3.97 (m, 1H); 3.82 (s, 3H); 2.27 (s, 3H); 1.33 (d, *J*=7.6 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 204.1 (s); 186.2 (s); 179.3 (s); 158.9 (s); 144.9 (s); 134.2 (d); 107.3 (d); 56.4 (q); 45.0 (d); 28.2 (q); 14.7 (q) ppm. MS (%): m/z 208 M^+ (22); 166 (100); 165 (12); 151 (6); 138 (31); M^+. Calcd. for $C_{11}H_{12}O_4$: 208.0735; Found: 208.0753.

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