Tetrahedron Vol. 45, No. 17, pp. 5511 to 5516, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
Pergamon Press plc

SYNTHESES OF 4-HYDROXY-5-IODO-2,3-DIMETHOXY-6-METHYLBENZOIC ACID AND 5-BROMO-4-HYDROXY-2,3-DIMETHOXY-6-METHYLBENZOIC ACID - AROMATIC CONSTITUENTS OF THE CALICHEMICINS[1]

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(*Received in Germany* 17 *March* 1989)

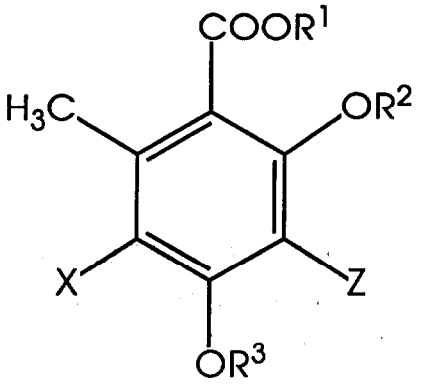
Abstract *- 4-Hydroxy-5-iodo-2,3-dimethoxy-6-methylbenzoic acid (1) and 5-bromo-4-hydroxy-2,3-dimethoxy-6-methylbenzoic acid (2) are the polysubstituted aromatic carboxylic acids found in calichemicin antibiotics.[1] The title compounds are synthesized on preparative scale from readily available methyl 4-O-benzylorsellinate* (3) *in six steps without any chromatographic separation needed [(1) : 41 %, (2) : 44 %, overall yield].*

The calichemicins produced by *Micromospora echinospora* ssp. calichensis represent a new class of antitumor antibiotics with an enediyne moiety. The biological activity of the calichemicins is extraordinary, they are approximately 4000-fold more active against murine tumors than adriamycin[1a,b]. Consequently they are very interesting target molecules for syntheses.

Calichemicin γ_1^I whose structure was elucidated by Lee et al.[1a,b] contains 4-hydroxy-5-iodo-2,3-dimethoxy-6-methylbenzoic acid (1) as aromatic constituent; other members of the calichemicin antibiotics contain the bromo analogue (2).[1c] Highly substituted aromatic carboxylic acids with similar substitution patterns are also parts of other natural products with remarkable antibiotic activity. Thus dichloroisoeverninic acid[2a,b] (4) e.g. is a constituent of the orthosomycins[3], the 3,5-dichloro-6-ethyl-4-hydroxy-2-methoxy-benzoic acid is a part of the macrocyclic antibiotic lipiarmycin.[4]

The first synthesis of the methylester (5) was published by Nicolaou et al.[5] recently. The authors started from 3,4,5-trimethoxytoluene and synthesized (5) in 5 steps in 22% overall yield. In this reaction sequence two regioselective conversions were involved: the de-O-methylation of one of the "outer" methoxy groups and the introduction of the carboxymethyl group. Both reactions gave mixtures of three isomers each which makes laborious separations necessary. Furthermore the corresponding bromo analogue (6) is not accessible in this way.

From our experience in the synthesis of dichloroisoeverninic acid[2] (4) it seemed obvious to synthesize the target molecules (1) and (2) starting from the readily available methyl 4-O-benzylorsellinate (3).[6]



Nr.	R^1	R^2	R^3	X	Z
1	H	CH_3	H	I	OCH_3
2	H	CH_3	H	Br	OCH_3
3	CH_3	H	Bn	H	H
4	H	CH_3	H	Cl	Cl
5	CH_3	CH_3	H	I	OCH_3
6	CH_3	CH_3	H	Br	OCH_3
7	CH_3	H	H	H	H
8	CH_3	H	Bn	H	CHO
9	CH_3	H	H	H	CHO
10	CH_3	H	Bn	H	OH
11	CH_3	CH_3	Bn	H	OCH_3
12	CH_3	CH_3	H	H	OCH_3
13	CH_3	H	Bn	H	I

Results

Methyl orsellinate (**7**) was benzylated[6] with benzyl bromide in acetone using potassium carbonate as base (80 %). Introduction of the 3-hydroxy function is achieved by selective ortho-formylation and successive Dakin oxidation to the corresponding phenol[7a,b]: (**3**) is selectively formylated to (**8**) by treatment with dichloromethyl methyl ether and titanium tetrachloride in 74 % yield. Methyl haematommate (**9**), which is a byproduct formed by acidic cleavage of the benzyl ether, can be separated as the corresponding sodium salt with aqueous 1N sodium hydroxide. The formyl derivative (**8**) is rearranged to the phenol (**10**) by oxidation with hydrogen peroxide in alkaline solution (90 %). Methylation of (**10**) with dimethyl sulfate in acetone in the presence of potassium carbonate gives (**11**) in 81 % yield. The benzyl ether protecting group can easily be removed by hydrogenolysis on a palladium catalyst (97 %). Mild iodination is achieved with iodine chloride in dichloromethane to yield (**5**) in 90 %. The bromo compound (**6**) can be obtained with bromine in an analogous manner (95 %). Alkaline hydrolysis of the methyl esters (**5**) and (**6**) gives the title compounds (**1**) and (**2**), respectively.

The presented synthesis offers high flexibility to achieve other substitution patterns which are important to explore structure-activity relationships. Thus treatment of (**10**) with iodine in the presence of mercury (II) acetate gave selective ortho-iodination to yield (**13**) in 70 %.

In summary the outlined reaction sequence leads to the target molecules (**1**) and (**2**), respectively, in six steps on preparative scale with good overall yields [(**1**) : 41 %, (**2**) : 44 %], starting from the readily available (**3**). No chromatographic separations are necessary.

Experimental

General. - Melting points were determined with a Büchi 510 K melting point apparatus and are uncorrected. ^{1}HNMR spectra were recorded on a Varian VXR 300 (300 MHz) spectrometer, ^{13}C NMR spectra using a Varian VXR 300 (75 MHz). IR spectra were recorded with a Perkin-Elmer 377 spectrophotometer.

Methyl 4-benzyloxy-2-hydroxy-6-methylbenzoate **(3).**[6] - A mixture of methyl orsellinate (7) (30 g, 0.165 mol), benzyl bromide (30 g, 0.175 mol) and potassium carbonate (85 g) in acetone (600 ml) was heated under reflux for 6 h. After cooling to room temperature the mixture was poured into ice-cold dilute hydrochloric acid. It was extracted with ether and dried ($MgSO_4$). Removal of the solvent and recrystallization from ethanol afforded 36 g (80 %) (3); m.p. 69°C (lit.[8] 68 - 69°C).

Methyl 4-benzyloxy-3-formyl-2-hydroxy-6-methylbenzoate **(8).** - A solution of $TiCl_4$ (21 g, 111 mmol) in dry dichloromethane (20 ml) was added dropwise to a vigorously stirred cooled (-10°C) solution of (3) (12 g, 44.1 mmol) and dichloromethyl methyl ether (CAUTION) (11 g, 96 mmol) in dry dichloromethane (150 ml) under nitrogen atmosphere. Stirring was continued for a further one hour at -10°C, the mixture was then poured into ice-cold dilute hydrochloric acid. The resulting suspension was extracted with chloroform. The organic layer was washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was extracted with boiling hexane. After cooling to room temperature the crystals were collected to yield 6.7 g (50 %) of (8).

The mother liquor was concentrated and the residue vigorously stirred with aqueous 1 N sodium hydroxide for 12 h at 25°C. The unsoluble sodium salt of (8) was separated and dissolved in dilute hydrochloric acid. The resulting aqueous layer was extracted with chloroform, the organic layer washed with water, dried ($MgSO_4$) and concentrated to yield a further 3,1 g (24 %) of (8). The alkaline filtrate contained methyl haematommate (9) as its sodium salt; m.p. 147°C (lit.[9] 147°C).

An analytically pure sample of (8) was obtained by recrystallization from ethanol as light yellow crystals; m.p. 92°C (lit.[10] 91°C). - ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H, $ArCH_3$), 3.88 (s, 3H, $COOCH_3$), 5.11 (s, 2H, CH_2, Bn), 6.31 (s, 1H, ArH), 7.3-7.5 (m, 5H, ArH, Bn), 10.26 (s, 1H, CHO), 12.54 (s, 1H, OH). - ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.63 ($ArCH_3$), 52.14 (OCH_3), 70.65 (CH_2, Bn), 104.54 (C-5), 108.86 (C-3), 115.19 (C-1), 127.39, 128.46, 128.74 ($C_{ortho,meta,para}$, Bn), 135.38 (C-1, Bn), 148.93 (C-6), 161.80, 161.94 (C-2, -4), 167.02 (COOR), 193.19 (CHO). - IR: 1728 (CHO), 1630 ($COOCH_3$). - Anal. calcd. for $C_{17}H_{16}O_5$ (300.31): C, 67.99; H, 5.37. Found: C, 67.92; H, 5.40 %.

Methyl 4-benzyloxy-2,3-dihydroxy-6-methylbenzoate **(10).** - A solution of (8) (9.6 g, 32.0 mmol) in a mixture of dioxane (150 ml) and 40% aqueous sodium hydroxide (6.8 ml) was stirred and cooled below 10°C under nitrogen atmosphere. Hydrogen peroxide (30 %, 60 ml) in dioxane (120 ml) was added slowly at a rate such that the temperature did not rise above 10°C. After stirring for a further one hour the solution was poured into ice-cold dilute hydrochloric acid and extracted with ether. The organic layer was washed with water and dried ($MgSO_4$). The ether was removed and the solid residue recrystallized from ethanol to yield 8.3 g (90 %) (10) as colorless crystals; m.p. 98°C. - ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H, $ArCH_3$), 3.87 (s, 3H, $COOCH_3$), 5.12 (s, 2H, CH_2, Bn), 5.53 (broad s, 1H, 3-OH), 6.32 (s, 1H, ArH), 7.24-7.44 (m, 5H, ArH, Bn), 11.67 (s, 1H, 2-OH). - ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.83 ($ArCH_3$), 51.96 ($COOCH_3$), 70.76 (CH_2, Bn), 106.13 (C-1), 108.27 (C-5), 127.46, 128.13, 128.60 ($C_{ortho,meta,para}$, Bn), 131.93, 132.66 (C-3, -6), 136.32 (C-1, Bn), 149.11, 150.91 (C-2, -4), 172.11 (COOR). - Anal. calcd. for $C_{16}H_{16}O_5$ (288.30): C, 66.66; H, 5.59. Found: C, 66.63; H, 5.60 %.

Methyl 4-benzyloxy-2,3-dimethoxy-6-methylbenzoate **(11).** - Potassium carbonate (16 g) was suspended with vigorous stirring in a solution of (10) (8.1 g; 28.1 mmol) in acetone (250 ml). Dimethyl sulfate (CAUTION) (7.8 g, 61.8 mmol) was added at room temperature, the reaction mixture was then stirred for 18 h. The K_2CO_3 was filtered off and washed with acetone. The solvent was evaporated and the residue was stirred for a further 2 h with aqueous potassium carbonate. The suspended product was filtered off and washed with water, dried in vacuo and recrystallized from ethanol to yield 7.2 g (81 %) (11) as colorless crystals; m.p. 86°C.- ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H, $ArCH_3$), 3.85, 3.88, 3.91 (3s, 3 x 3H, 2 x OCH_3, $COOCH_3$), 5.10 (s, 2H, CH_2, Bn), 6.54 (s, 1H, ArH), 7.27-7.45 (m, 5H, ArH, Bn). - ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.56 ($ArCH_3$), 52.06 ($COOCH_3$), 60.92, 61.77 (2 x OCH_3), 70.86 (CH_2, Bn), 111.13 (C-5), 121.68 (C-1), 127.23, 128.00, 128.58 ($C_{ortho,meta,para}$, Bn), 131.41 (C -6), 136.64 (C-1, Bn), 140.49 (C-3), 151.37 (C-4),153.52 (C-2), 168.17 (*C*OOR). - Anal. calcd. for $C_{18}H_{20}O_5$ (316.35): C, 68.34; H, 6.37. Found: C, 68.19; H, 6.31 %.

Methyl 4-hydroxy-2,3-dimethoxy-6-methylbenzoate **(12).** - A solution of (11) (7.0 g, 22.1 mmol) in EtOAc (150 ml) was shaken with 10% Pd on charcoal (1 g) under hydrogen for 3 h. The catalyst was removed by filtration and washed thoroughly with EtOAc. The combined filtrates were concentrated yielding 4.9 g (97 %) (12); m.p. 76°C. - ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, $ArCH_3$), 3.87 (2s, 6H, 2 x OCH_3), 3.89 (s, 3H, OCH_3), 6.12 (broad s, 1H, OH), 6.55 (s, 1H, ArH). - ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.42 ($ArCH_3$), 52.10 ($COOCH_3$), 60.87 (OCH_3), 61.30 (OCH_3), 112.55 (C-5), 120.56 (C-1), 132.42 (C-6), 137.54 (C-3), 150.48, 150.63 (C-2, -4), 168.21 (*C*OOR). - Anal. calcd. for $C_{11}H_{14}O_5$ (226.23): C, 58.40; H, 6.24. Found: C, 58.28; H, 6.12 %.

Methyl 4-hydroxy-5-iodo-2,3-dimethoxy-6-methylbenzoate **(5).** - Iodine chloride (3.6 g, 22.2 mmol) in dichloromethane (50 mmol) was added to a stirred solution of (12) (4.6 g, 20.3 mmol) in dichloromethane (100 ml) within one hour at 25°C. The mixture was stirred for an hour, washed with water, aqueous $Na_2S_2O_3$ - solution and again with water. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was dissolved in 1 : 2 EtOAc-cyclohexane (100 ml) and was filtered over a short column of silica gel (5 cm). The solvent was evaporated and the solid residue recrystallized from ethanol/hexane to afford 6.5 g (90 %) (5); m.p. 134-135°C (lit.[5] : 134-135°C). The NMR data are in agreement with the reported data.[5] - ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, $ArCH_3$), 3.88, 3.91, 3.91 (3s, 3 x 3H, 2 x OCH_3, $COOCH_3$), 6.38 (s, 1H, OH). - ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.27 ($ArCH_3$), 52.45 ($COOCH_3$), 61.05, 61.37 (2 x OCH_3), 83.99 (C-5), 121.87 (C-1), 134.12, 136.58 (C-3, -6), 149.64, 150.49 (C-2, -4), 167.81 (*C*OOR). - Anal. calcd. for $C_{11}H_{13}O_5I$ (352.13): C, 37.52; H, 3.72. Found: C, 37.67; H, 3.81 %.

Methyl 5-bromo-4-hydroxy-2,3-dimethoxy-6-methylbenzoate **(6).** - To a stirred solution of (12) (1.0 g, 4.4 mmol) in dichloromethane (25 ml) bromine (0.8 g, 5.0 mmol) in dichloromethane (15 ml) was added within one hour at 25°C. The mixture was stirred for an hour, then washed with water. The organic layer was dried ($MgSO_4$) and the solvent removed. The residue was dissolved in 1 : 2 EtOAc-cyclohexane (25 ml) and was filtered over a short column of silica gel (5 cm). The solvent was evaporated to afford 1.3 g (95 %) (6) after recrystallization from ethanol/hexane; m.p. 91°C. - ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, $ArCH_3$), 3.88, 3.90, 3.91 (3s, 3 x 3H, 2 x OCH_3, $COOCH_3$), 6.31 (s,

1H, OH). - ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.90 ($ArCH_3$), 52.45 ($COOCH_3$), 61.05, 61.47 (2 x OCH_3), 107.18 (C-5), 121.95 (C-1), 130.97 (C-6), 137.99 (C-3), 148.21, 149.01 (C-2, -4), 167.68 (COOR). - Anal. calcd. for $C_{11}H_{13}O_5Br$ (305.12): C, 43.30; H, 4.29. Found: C, 43.38; H, 4.49 %.

4-Hydroxy-5-iodo-2,3-dimethoxy-6-methylbenzoic acid **(1)**. - A solution of **(5)** (1 g, 2.8 mmol) in 2.5 N aqueous sodium hydroxide (20 ml) was heated under reflux for 2 h. The reaction mixture was poured into ice-cold dilute hydrochloric acid and then extracted with ether. The organic layer was washed with water and dried ($MgSO_4$). Recrystallization from ethanol/water afforded 0.83 g (87 %) **(1)**; m.p. 62°C. - ^{1}H NMR (300 MHz, D_6-DMSO): δ 2.29 (s, 3H, $ArCH_3$), 3.74, 3.79 (2s, 2 x 3H, 2 x OCH_3), 10.1 (broad s, 1H, ArOH), 13.0 (broad s, 1H, COOH). - ^{13}C NMR (75 MHz, D_6-DMSO): δ 25.08 ($ArCH_3$), 60.56, 60.86 (2 x OCH_3), 86.51 (C-5), 122.37 (C-1), 131.85, 137.40 (C-3, -6), 149.24, 150.88 (C-2, -4), 168.07 (COOH).

5-Bromo-4-hydroxy-2,3-dimethoxy-6-methylbenzoic acid **(2)**. - Starting from **(6)** (1 g, 3.3 mmol) **(2)** was synthesized analogous to **(1)**. Recrystallization from ethanol/water afforded 0.84 g (88 %) **(2)**; m.p. 132°C. - ^{1}H NMR (300 MHz, D_6-DMSO): δ 2.25 (s, 3H, $ArCH_3$), 3.76, 3.81 (2s, 2 x 3H, 2 x OCH_3), 9.95 (broad s, 1H, ArOH), 13.1 (broad s, 1H, COOH). - ^{13}C NMR (75 MHz, D_6-DMSO): δ 19.73 ($ArCH_3$), 60.62, 60.99 (2 x OCH_3), 107.99 (C–5), 122.54 (C–1), 128.87 (C-6), 138.93 (C-3), 148.58, 148.75 (C-2, -4), 167.89 (COOH).

Methyl 4-benzyloxy-2-hydroxy-3-iodo-6-methylbenzoate **(13)**. - A solution of iodine (4.7 g, 18.5 mmol) in dichloromethane (200 ml) was added within 3 h to a stirred mixture of **(10)** (5.0 g, 18.4 mmol) and mercury (II) acetate (5.9 g, 18.5 mmol) in dichloromethane (50 ml) at room temperature. It was stirred for a further 14 h, the mercury (II) iodide was filtered off then and washed with dichloromethane. The combined organic layers were washed with water and dried ($MgSO_4$). Evaporation of the solvent and recrystallization from ethanol afforded 5.1 g (70%) **(13)**; m.p. 149°C. The position of iodine was confirmed by CH-couplings and NOE experiments. - ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, $ArCH_3$), 3.89 (s, 3H, $COOCH_3$), 5.12 (s, 2H, CH_2, Bn), 6.25 (s, 1H, ArH), 7.2-7.5 (m, 5H, ArH, Bn), 12.61 (s, 1H, OH). - ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.67 ($ArCH_3$), 52.31 ($COOCH_3$), 70.60 (CH_2, Bn), 73.97 (C-3), 106.37 (C-1), 107.76 (C-5), 126.75, 127.89, 128.51 ($C_{ortho,meta,para}$, Bn), 135.90 (C-1, Bn), 143.82 (C-6), 161.39 (C-4), 163.28 (C-2), 171.65 (COOR), ^{3}J[$ArCH_3$, H-5] : 5.5 Hz.

Acknowledgements. - We thank Degussa (Hanau) for the palladium catalyst and Dr. Jan Runsink for recording the NMR spectra.

References

≠ Dedicated to Günther Ohloff on the occasion of his 65th birthday.

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