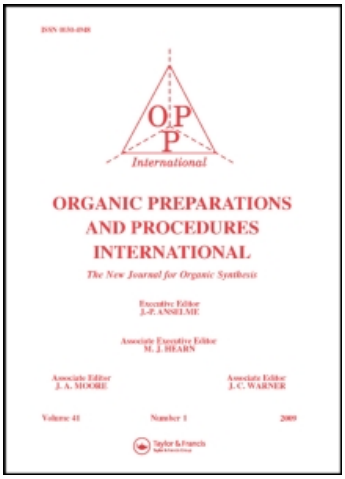

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SYNTHESIS OF 2,4-DIMETHYL-5-IODOBENZALDEHYDE

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SYNTHESIS OF 2,4-DIMETHYL-5-IODOBENZALDEHYDE

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(07/06/01)

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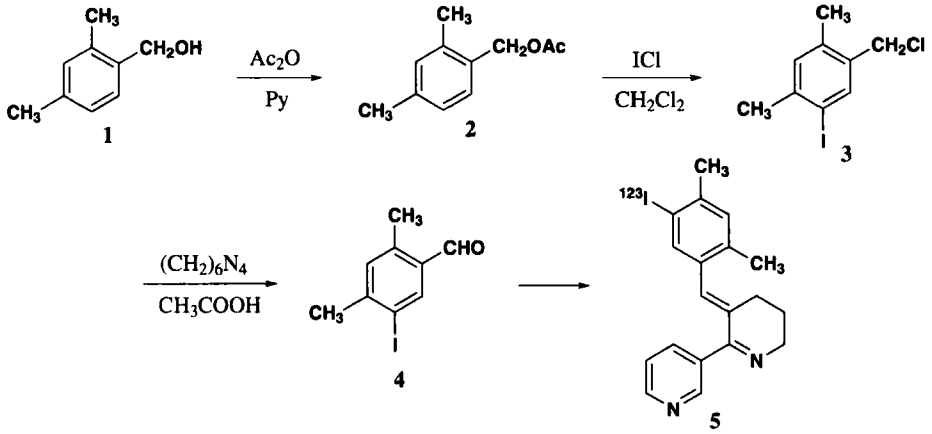
Our recent efforts to synthesize radioiodinated benzylideneanabaseine **5** as a potential marker to detect small cell lung carcinoma[1] required large quantities of 2,4-dimethyl-5-iodobenzaldehyde (**4**) as starting material. Interestingly, the synthesis of **4** has never been reported. A number of attempts to prepare **4** from commercially available materials failed. These attempts included iodination of 2,4-dimethylbenzaldehyde using either iodine monochloride[2] or NaI in the presence of chloramine-T,[3] Vilsmeier formylation[4] of 4-iodo-*m*-xylene, as well as a Gatterman aldehyde[5] synthesis. We now report the synthesis of title compound **4** in three steps from 2,4-dimethylbenzyl alcohol (**1**) in 51% overall yield.

Alcohol **1** was converted to acetate **2** by treatment with acetic anhydride and pyridine at room temperature for 24 h. Acetate **2** was then allowed to react with iodine monochloride in methylene chloride and acetic acid at room temperature for 15 h to obtain 2,4-dimethyl-5-iodobenzyl chloride, **3**. Sommelet oxidation of benzyl chloride **3** to the requisite aldehyde **4** was accomplished using hexamethylenetetramine in acetic acid.



EXPERIMENTAL SECTION

Reactions were conducted under a nitrogen atmosphere. All glassware and syringes were oven-dried. Methylene chloride was dried over calcium hydride. Starting materials and reagents were purchased from Aldrich Chemical Co. ^{1}H NMR and ^{13}C NMR data were recorded on a 250 MHz spectrometer. Melting points were determined on a Thomas Hoover Electro thermometer. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

2,4-Dimethylbenzyl Acetate (2).- A mixture of 2,4-dimethylbenzyl alcohol (**1**) (6.80 g, 50.0 mmol), acetic anhydride (30 mL) and pyridine (4 mL) was stirred at room temperature overnight. The reaction mixture was poured into crushed ice and extracted with ether (3 x 100 mL). The combined ethereal extracts were washed sequentially with aqueous HCl (2 x 50 mL, 1 *N*), water, brine, and then dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure to obtain 7.82 g (88%) of a colorless oil. Product **2** was used without further purification. ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H), 2.30 (s, 6H), 5.50 (s, 2H), 6.90-7.05 (m, 2H) and 7.15-7.30 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 18.60, 20.74, 20.89, 64.47, 126,49, 129.43, 130.78, 131.06, 136.79, 138.20 and 170.77.

2,4-Dimethyl-5-iodobenzyl Chloride (3).- To a solution of **2** (8.80 g, 50.0 mmol) in CH_2Cl_2 (75 mL) was added acetic acid (4.4 mL) followed by iodine monochloride (8.12 g, 50.0 mmol). The mixture was stirred overnight at room temperature. Excess iodine was decomposed using 10% aqueous sodium thiosulfate. The organic solvent was washed thoroughly with water, dried (anhydrous Na_2SO_4), filtered, and the solvent removed *in vacuo* to give an oil. The product was purified by column chromatography (SiO_2), eluting with petroleum ether to obtain 9.84 g (71%) of a colorless oil. ^1H NMR ($CDCl_3$): δ 2.25 (s, 3H), 2.35 (s, 3H), 4.45 (s, 2H), 7.05 (s, 1H) and 7.70 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 18.26, 27.54, 43.46, 97.25, 129.46, 132.0l, 134.02, 137.19, 139.65. HR MS for $C_9H_{10}ICl$. 279.9506, Calcd. 279.9516.

2,4-Dimethyl-5-iodobenzaldehyde (4).- Hexamethylenetetramine (5.60 g, 40.0 mmol) was suspended in a solution of 2,4-dimethyl-5-iodobenzyl chloride (5.60 g, 20.0 mmol) in 50% aqueous acetic acid (20 mL). The mixture was heated to reflux. After 15 minutes, an oil separated out. Reflux was continued for 2h and then the reaction mixture was allowed to cool to RT. Conc. HCl (10 mL) was added and the mixture refluxed for an additional 15 minutes. The reaction mixture was then extracted into ether (3 x 50 mL) and the ethereal extracts were washed sequentially with 10% Na_2CO_3, and brine. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure to obtain a solid that was purified by flash chromatography (SiO_2), using petroleum ether: ethyl acetate (30:1) as eluent to give 4.26 g (82%) of a colorless solid; mp 60-71°. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H), 2.50 (s, 3H), 7.10 (s, 1H), 8.20 (s, 1H) and 10.15 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 19.36, 28.59, 43.46, 97.77, 133.49, 133.91, 140.70, 142.59, 148.02 and 191.06. 2,4-DNP derivative, m.p. 244-246°.

Anal. Calcd for $C_{15}H_{13}N_4IO_4$: C, 40.93, H, 2.96, N, 12.72, I, 28.83. Found: C, 41.16, H, 2.98, H, 12.46, I, 28.46

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A MULTI-GRAM SYNTHESIS OF 1,2:5,6-DI-*O*-ISOPROPYLIDENE-3-*C*-TRIMETHYLSILYLMETHYL-α-D-ALLOFURANOSE. AN IMPROVED PREPARATION OF 3-*C*-HYDROXYMETHYL-α-D-GLUCO- AND 3-*C*-METHYL-α-D-ALLOFURANOSE DERIVATIVES

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The use of carbohydrates as chiral building blocks in natural product synthesis is still a challenging area of contemporary synthetic organic chemistry. As part of our work on branched-chain sugars and cyclitols related to natural products such as amipurimycin,[1] paniculide C,[2] and tetrodotoxin,[3] we required a large amount of 3-*C*-hydroxymethyl-α-D-glucofuranose derivative (**4**),[4] for which a key-intermediate is 1,2:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose (**3**).[5] Compound **3** has been prepared from a 3-ulose derivative **1**[6] by the conventional Wittig reaction using methyltriphenylphosphonium bromide and *n*-butyllithium (or sodium hydride). However, the large-scale preparation of **3** *via* a Wittig reaction is not amenable in terms of yield (65-73%) and the handling of a large amount of *n*-butyllithium; in addition, the time-consuming purification of **3** by column chromatography requires a large amount of silica gel.

Therefore, we now describe, an improved, large-scale preparation of **3** *via* a facile Peterson olefination of 1,2:5,6-di-*O*-isopropylidene-3-*C*-trimethylsilylmethyl-α-D-allofuranose (**2**),[7] which was obtained in large quantity in high yield (>90%) by reacting **1** (50g scale) with (trimethylsilylmethyl)magnesium chloride. In contrast to unstable and syrupy **1**, compound **2** is shelf-stable and crystalline and may be converted into 3-*C*-methylene derivative **3** in better than 95% yield by simple heating with sodium hydride in THF for 3 hrs. The work-up is very simple and the product may be used directly for the next reaction without purification.