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A HIGH YIELDING SYNTHESIS OF [5-^{14}C]-5H-DIBENZO[a,d]CYCLOHEPTEN-5-ONE (DIBENZOSUBERENONE) USING [^{14}C]-DIMETHYLFORMAMIDE

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SUMMARY

A seven step synthesis of dibenzosuberenone **1** is presented in which [^{14}C]-DMF is used in *lieu* of $^{14}CO_2$ to prepare the carboxylic acid intermediate **8**. The advantages of this procedure over other commonly used methods is discussed. The title compound was obtained at a specific activity of 53 mCi/mmol (61% overall radiochemical yield).

Key Words: metallation, [^{14}C]-dimethylformamide, formylation, carbon-14, stilbenes

A quantity of not less than 100 mCi of the symmetrical ketone dibenzosuberenone **1** was required as a starting material for a multi-step radiosynthesis. It was initially thought that the labelled material could be obtained directly from **2** *via* Friedel-Crafts cyclization[1]. The acid, in turn, could be prepared by carboxylation[2] of the known 2'-bromostilbene **3**[2] with $^{14}CO_2$. Although this approach represented the shortest of the possible routes, the projected yield of **1** was 18% based on ^{12}C precedents.

The problematic transformation in this short sequence is the low yielding Friedel-Crafts cyclization. A review of the literature revealed that when the ethylene linker is replaced with a *saturated* two carbon tether (i.e. **4**), the cyclization[3,4] proceeds in good yield. The ethane derivative **4** is simply the double bond reduction product of **2**. Thus, the requisite carbon skeleton could be accessed in as few as three steps: carboxylation of **3**, hydrogenation of **2**, and cyclization of **4** to **5**. There was ample literature precedent demonstrating that **5** could easily be converted to **1**[3,5,6].

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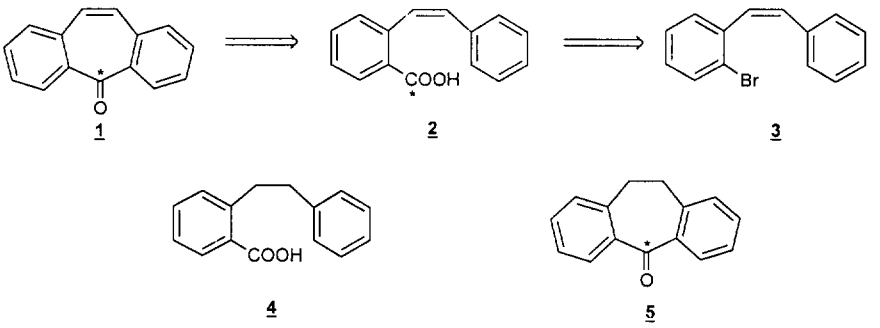
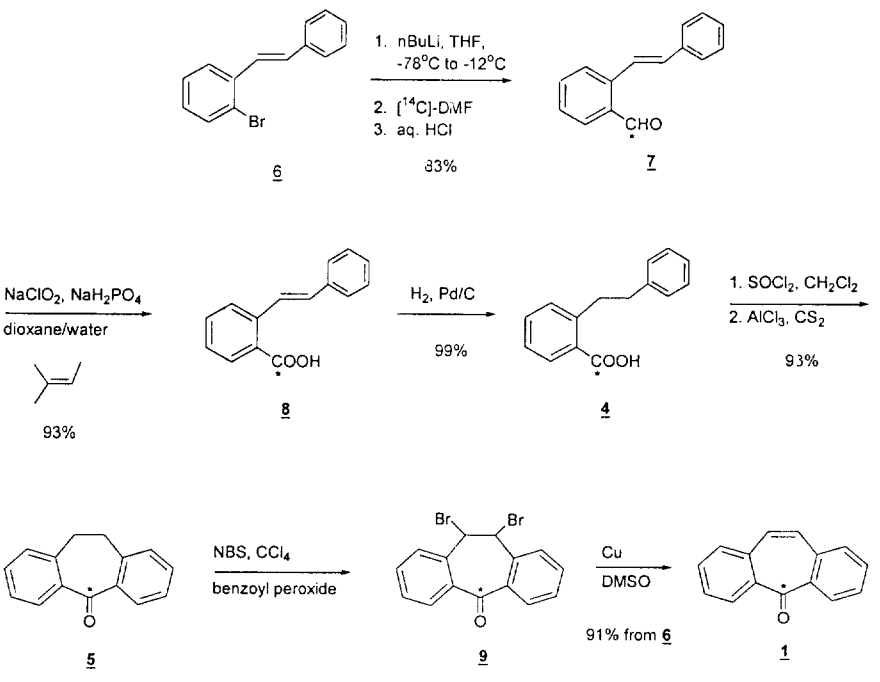


The revised synthesis that was used to furnish the title compound is shown in Scheme 1. Since the starting material need not possess *cis* olefin geometry, the more readily available **6**[7] was employed as the starting material. Lithium-halogen exchange with 1.1 equivalents of *n*-BuLi was complete at -12°C; quenching the anion with [^{14}C]-DMF afforded aldehyde **7** in 82% yield after hydrolysis and purification by flash chromatography. Subsequent oxidation with sodium chlorite[8] gave the acid **8** in high

SCHEME 1



yield. The overall yield (77%) is superior to those reported for the direct carboxylation of metallated 2'-halostilbenes with carbon dioxide[2].

This efficient, albeit unconventional, approach to preparing [^{14}C]-carboxylic acids has several advantages over the more commonly used methods. One of the drawbacks to $Ba^{14}CO_3$ and $K^{14}CN$ is the high volatility of the associated compounds $^{14}CO_2$ and $H^{14}CN$. Dimethylformamide, however, is an easy to handle liquid of relatively low volatility; therefore no special equipment or glassware was required for the manipulation of the radiolabelled reagent. Additionally, DMF is water soluble, and unused reagent and reaction by-products were easily removed and contained upon aqueous workup. Finally, the initial formylation step provides easy access to a very versatile, labelled functional group.

Hydrogenation[9] and Friedel-Crafts cyclization[3] of the acid chloride derived from **4** provided [5-^{14}C]-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (dibenzosuberone) **5**. The synthesis of **5** (71% overall yield from **6**) compares favorably with others reported in the literature. Singly labelled [^{14}C]- and [^{13}C]-dibenzosuberone have been prepared by Maul[4] (6 steps from *o*-bromotoluene, 47% overall yield) and Hawkins[10] (5 steps from *o*-bromotoluene, 9% overall yield) respectively. Vicinal dibromination[5] under free radical conditions afforded **9** as a mixture of isomers; didebromination with copper bronze as the reducing agent provided the desired compound **1** in 91% yield.

[5-^{14}C]-Dibenzosuberenone was prepared in seven steps (61% overall radiochemical yield, specific activity 53 mCi/mmol). The synthesis features an efficient and operationally simple carboxylic acid synthesis utilizing the commercially available and easy to handle [^{14}C]-dimethylformamide as the carbon-14 source.

EXPERIMENTAL

[^{14}C]-Dimethylformamide (190 mCi @ 57 mCi/mmol) was obtained from Amersham Life Science. E-2'-bromostilbene was prepared according to a literature method[7]. All

other reagents were obtained from J. T. Baker or Aldrich and used without further purification. Flash chromatography was performed according to the method of Still using Merck silica gel (grade 9385, 230-400 mesh, 60 angstrom). All chromatography solvents were obtained from BrandNu Laboratories and were used without further purification. Radiochemical purity of the final material was determined as follows. A sample of the purified material was adsorbed onto a 5 x 20 cm silica gel coated TLC plate and developed. A Bioscan TLC Scanner (P10 counting gas) was used to measure total counts for each of the components; peak integrals and radiochemical purity were then determined from the above data using Winscan (LabLogic) software. Liquid scintillation counting was performed on a Packard 2500 TR Liquid Scintillation Counter using 3a70B counting cocktail from Research Products International Corporation. NMR spectra were recorded by Mr. George Morton, Discovery Analytical Chemistry, Wyeth-Ayerst Research, Pearl River, NY.

[^{14}C]-*E*-stilbene-2′-carboxaldehyde (7). An oven-dried, 50 mL round bottomed flask containing a Teflon coated stir bar was charged with 6 (0.858 g, 3.32 mmol) and 22 mL of anhydrous ether. The resulting solution was cooled to -78°C then 0.315 mL (3.90 mmol) of a 1.24M solution of *n*-BuLi in hexane was added dropwise by syringe. The bright yellow reaction mixture was stirred at -78°C for 10 minutes, then the dry ice/acetone bath was replaced with an ice/acetone bath (-12°C), and the reaction mixture was stirred for an additional 80 minutes. A solution of [^{14}C]-DMF (190 mCi, 3.33 mmol) in 3 mL of anhydrous ether was added dropwise and rapidly via syringe (1 mL rinse), and the resulting light yellow solution was stirred overnight at room temperature. The reaction mixture was treated with 9 mL of 1N aqueous HCl and stirred vigorously for one hour. The organic layer was washed with water (1 x 3 mL) and brine (1 x 3 mL). The aqueous washes and original aqueous layer were combined and extracted with ether (1 x 10 mL). The combined ether layers were dried over $MgSO_4$, filtered, and concentrated

under reduced pressure (aspirator) to give crude 7 as a yellow oil (0.69 g). The aldehyde was purified by flash chromatography (40 x 150 mm column of silica gel; 97:3 hexane:ethyl acetate; 105 x 8 mL fractions). Fractions 15-25 contained *E*-stilbene (0.067 g, 11%); fractions 45-103 contained 7 (colorless oil, 0.583 g, 83 %). ^{1}H NMR[11] ($CDCl_3$, ppm): δ 10.34 (s, 1H), 8.03 (1H, d, J = 16.2 Hz), 7.84-7.29 (9H, m), 7.04 (1H, d, J = 16.2 Hz); analytical TLC on silica gel, 1:4 hexane:ethyl acetate, R_f = 0.52, the R_f exhibited by 7 was identical to that of authentic C-12 material in both side by side comparisons and co-spotted samples.

[^{14}C]-*E*-stilbene-2'-carboxylic acid (8). A 50 mL round bottomed flask containing a Teflon coated stir bar was charged with a solution of 7 (0.583 g, 2.79 mmol) in 6.4 mL of dioxane and 2-methyl-2-butene (3.8 mL, 36 mmol). A solution containing NaH_2PO_4 (0.478 g, 3.46 mmol) and $NaClO_2$ (0.383 g of 80% technical grade, 0.31 g, 3.4 mmol) in 6.4 mL of water was added, and the biphasic, yellow mixture was stirred vigorously at room temperature for 48 hours. The aqueous layer was extracted with ethyl acetate (3 x 7 mL). The combined extracts and the orignal dioxane layer were dried over $MgSO_4$, filtered, and concentrated under reduced pressure (aspirator) to give 8 as a light yellow solid (0.585 g, 93%). ^{1}H NMR[12] ($CDCl_3$, ppm): δ 12.0 (1H, br s), 8.08 (1H, dd, J = 7.5, 1.2 Hz), 8.06 (1H, d, J = 16.2 Hz), 7.76-7.29 (8H, m), 7.03 (1H, d, J = 16.2 Hz); analytical TLC on silica gel, 1:4 hexane:ethyl acetate, R_f = 0.25, the R_f exhibited by 8 was identical to that of authentic C-12 material in both side by side comparisons and co-spotted samples. The acid was used directly in the next step without further purification.

[^{14}C]-10, 11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (5). A 500 mL Parr shaker bottle was charged with a solution of 8 (0.585 g, 2.60 mmol) in 85 mL of absolute ethanol and a suspension of 5% Pd on carbon (58 mg) in 10 mL of ethanol. The mixture

was shaken under 40 psi of hydrogen for 2 hours at room temperature. The reaction mixture was filtered through a 5 mm pad of Celite, and the filter cake was washed with ethanol (4 x 80 mL). The combined filtrates were concentrated under reduced pressure (aspirator) to afford **4** as a grey solid (0.582 g, 99%). This product was used directly in the next step without further purification.

A 100 mL round bottomed flask containing a Teflon coated stir bar was charged with a solution of **4** (0.582 g, 2,56 mmol) in 18 mL of dichloromethane and 0.65 mL (8.7 mmol) of thionyl chloride. The flask was fitted with an efficient condenser stoppered with a drying tube containing Drierite. The resulting dark brown solution was refluxed for 26 hours, cooled, and concentrated under reduced pressure (aspirator) to afford a brown oil which was dried *in vacuo* for 3 hours. An oven-dried, 100 mL round bottomed flask was charged with a solution of the crude acid chloride in 23 mL of carbon disulfide. Aluminum trichloride (0.54 g, 4.0 mol) was then added all at once, and the reaction mixture was stirred for 20 hours at room temperature. The carbon disulfide supernatant was decanted away from a brown viscous oil. The oil was treated with water (50 mL) and the resulting white suspension added to a separatory funnel. Ether (40 mL) and the carbon disulfide layer were subsequently added, and the layers mixed well. The aqueous layer was treated with 1N aqueous HCl and extracted with ether (1 x 30 mL). The combined organic layers were washed with water (1 x 12 mL) and brine (1 x 12 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure (aspirator) to afford an amber oil. The crude ketone was adsorbed onto a 30 x 40 mm plug of silica gel and eluted with 4:1 hexane:ethyl acetate (250 mL). The filtrate was concentrated under reduced pressure (aspirator) to give **5** as a yellow oil (0.502 g, 93%). ^{1}H NMR ($CDCl_3$, ppm): δ 8.00 (2H, d, J = 5.8 Hz), 7.45-7.22 (6H, m), 3.22 (4H, s); analytical TLC on silica gel, 1:4 hexane:ethyl acetate, $R_f = 0.53$, the R_f exhibited by **5** was identical to that of authentic C-12 material in both side by side comparisons and co-spotted samples. The

product was of sufficient purity to be used directly in the next step without further purification.

[^{14}C]-5H-dibenzo[a,d]cyclohepten-5-one (1). A 25 mL round bottomed flask containing a Teflon coated stir bar was charged with a solution of **5** (0.502 g, 2.39 mmol) in 8.6 mL of carbon tetrachloride, benzoyl peroxide (.038 g, 0.016 mmol), and NBS (0.911 g, 5.11 mmol). The mixture was refluxed and irradiated with a 60 Watt sun lamp for 1.25 hours. The reaction mixture was cooled and filtered to remove a yellow solid which contained both succinimide and the dibromide **9**. The solid was slurried in water (20 mL), filtered and dried *in vacuo*. The carbon tetrachloride filtrate from above was washed with water (1 x 5 mL) and concentrated under reduced pressure (aspirator) to afford additional **9**. A 25 mL round bottomed flask containing a Teflon coated stir bar was charged with crude dibromide (0.88 g), 13 mL of DMSO, and copper bronze (0.190 g, 2.99 mmol). The dark brown suspension was stirred at room temperature for 24 hours then poured into 55 mL of water. The diluted reaction mixture was placed in a separatory funnel and swirled with ether (35 mL). The layers were separated, and the aqueous layer treated with 1N aqueous HCl until a homogeneous solution resulted. The ether layer was returned to the separatory funnel, and the two phases were mixed well. The aqueous layer was then extracted with fresh ether (1 x 25 mL). The combined organic extracts were washed with 1N aqueous HCl (1 x 10 mL), water (1 x 10 mL), and brine (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure (aspirator) to give a yellow solid. The crude product was adsorbed onto a 40 x 40 mm plug of silica gel and eluted with 4:1 hexane:ethyl acetate (9 x 40 mL). Fractions 1-4 contained **1** [white solid, 0.451 g, (116 mCi), 91%]. ^{1}H NMR ($CDCl_3$, ppm): δ 8.21 (2H, dd, J = 5.9, 1.2 Hz), 7.6-7.4 (6H, m), 7.06 (2H, s); analytical TLC on silica gel, 1:4 hexane:ethyl acetate, R_f = 0.49, the R_f exhibited by **1** was identical to that of authentic C-12 material

in both side by side comparisons and co-spotted samples, radiochemical purity: 98.8% (see General section of the Experimental), specific activity: 53 mCi/mmol.

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