On the syntheses of dibenzosuberenone and 2,8-dimethyl-dibenzosuberenone

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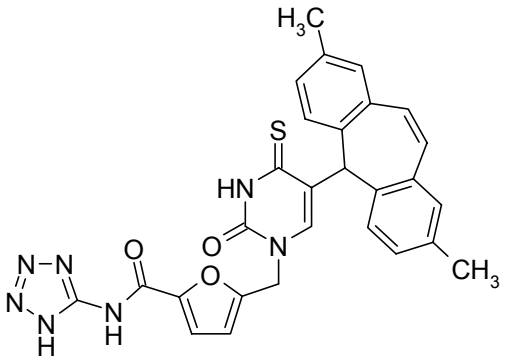
Abstract
Catalytic dehydrogenation of dibenzosuberone to dibenzosuberenone was performed upon microwave irradiation. Although high yields could be obtained after a short reaction time of 30 minutes for unsubstituted dibenzosuberone, the procedure unexpectedly failed if 2,8-dimethyl-dibenzosuberone was used as a reactant. An alternative method for the preparation of 2,8-dimethyldibenzosuberenone involving radical bromination with 2,2'-azo-*bis*-isobutyronitrile (AIBN) and dehydrohalogenation under basic conditions was thus applied to obtain the target compound.

Keywords: Microwave-assisted synthesis, dehydrogenation, dibenzosuberone, dibenzosuberenone

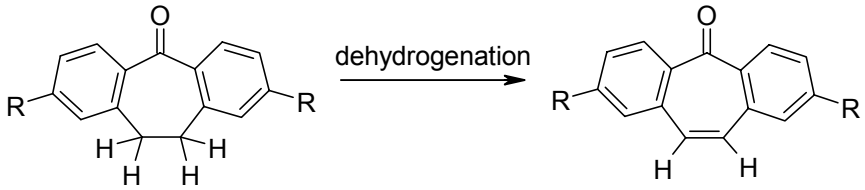
Introduction

We were interested in synthesizing AR-C118925 (5-[[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]methyl]-*N*-[1*H*-tetrazol-5-yl]-2-furancarboxamide, **1**), the only currently known selective $P2Y_2$ receptor antagonist,[1,2] as a pharmacological reference compound.

In the course of the synthesis of **1**, the need to obtain 2,8-dimethyldibenzosuberenone (2,8-dimethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, **2**) arose. While dibenzosuberone (5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, **3**) and dibenzosuberenone (10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-one, **4**) are common and readily available substances, only a few examples for the synthesis of substituted derivatives can be found in the literature.



Scheme 1. AR-C118925 (**1**).

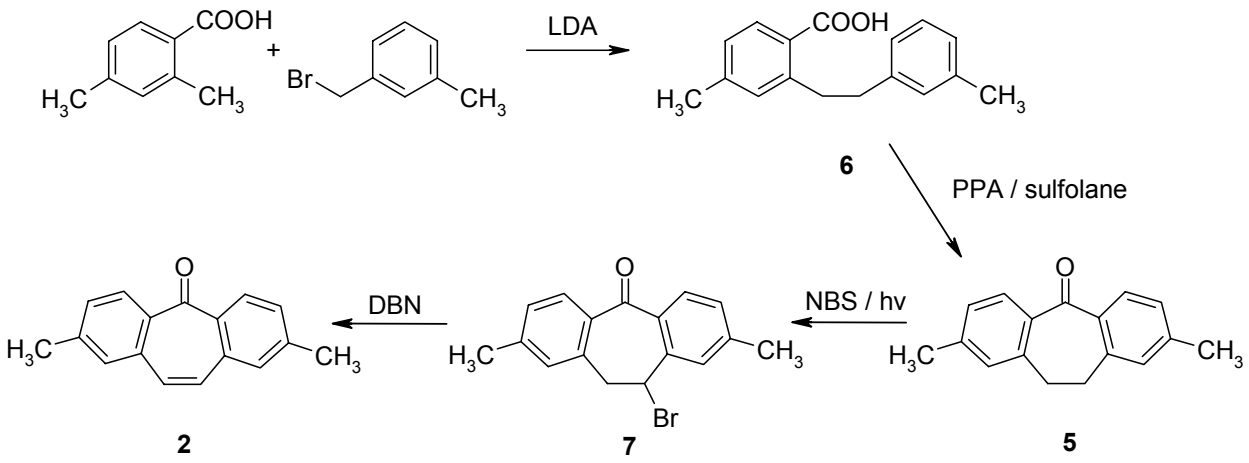


R = H: dibenzosuberone (**3**)
R = Me: 2,8-dimethyldibenzosuberone (**5**)

R = H: dibenzosuberenone (**4**)
R = Me: 2,8-dimethyldibenzosuberenone (**2**)

Scheme 2. Dehydrogenation reaction.

According to a method described by Wild *et al.* in a European patent, 2,8-dimethyl-dibenzosuberenone (**2**) can be prepared from 2,4-dimethylbenzoic acid and 3-methylbenzyl bromide. The procedure begins with a dilithiation of the acid, followed by coupling with 3-methylbenzyl bromide. Ring closure to 2,8-dimethyldibenzosuberone (10,11-dihydro-2,8-dimethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, **5**) is performed by heating the 4-methyl-2-[2-(3-methylphenyl)ethyl]benzoic acid (**6**) thus obtained to 110°C in a solution of 80% polyphosphoric acid in sulfolane for 4 hours. The dehydrogenation of **5** is carried out as a photo-induced mono-bromination followed by a dehydrohalogenation using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as a base (scheme 3).[3]



Scheme 3. Literature synthesis of 2,8-dimethyldibenzosuberenone (**2**).

While trying to reproduce this method, several problems have been encountered. A detailed description of these problems and attempts to overcome them are presented.

Results and Discussion

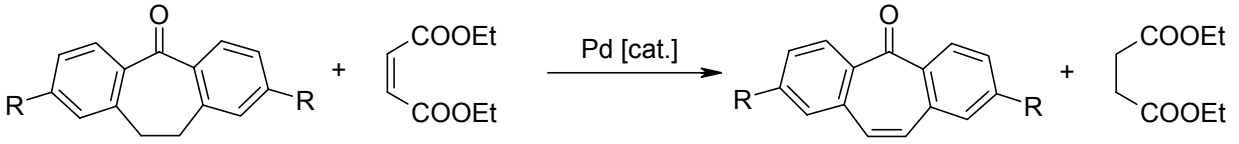
The first step towards 4-methyl-2-[2-(3-methylphenyl)ethyl]benzoic acid (**6**) was performed as described by Wild *et al.*[3] However, it proved to be very difficult to separate the excess 2,4-dimethylbenzoic acid from product **6**, even by column chromatography, so a 4:6 mixture (mass) of these two substances (as quantified by NMR) was used for the next step.

The ring closure reaction to obtain 2,8-dimethyldibenzosuberone (**5**) was also performed as described in the patent. It was observed that it is essential to use a large excess of reagent (40 g of polyphosphoric acid/sulfolane per 1 g of the mixture obtained in the first step) to avoid undesired reactions of 2,4-dimethylbenzoic acid with 4-methyl-2-[2-(3-methylphenyl)ethyl]benzoic acid (**6**). It was further found that heating to 80°C for one hour was sufficient to complete the reaction. The workup was simplified in comparison to the described method: addition of a large quantity of water, followed by extraction with petrol ether and washing of the organic phase with 2 N sodium hydroxide to remove all acidic components led to sufficiently pure product **5**.

As indicated above, the dehydrohalogenation of 2,8-dimethyldibenzosuberone (**5**) to 2,8-dimethyldibenzosuberenone (**2**) was described as a two-step procedure: light-induced radical halogenation with *N*-bromosuccinimide was followed by dehydrohalogenation using DBN as a base. This reaction is complicated by the fact that there are several "benzylic" positions amenable to radical bromination and only one of the possible products (10-bromo-2,8-dimethyldibenzosuberenone, **7**) is a substrate for the desired dehydrohalogenation. Although several experiments were performed in a photoreactor (Hg medium-pressure lamp), we were not

able to raise the yield above 11% of the theoretical value, which is considerably lower than the claimed yield of 65%.[3]

Due to these problems, we searched for alternatives. One promising approach was disclosed by Lambrecht *et al.* in a German patent. The authors used catalytic dehydrogenation with maleic acid esters as hydride acceptors and a palladium catalyst.[4]



Scheme 4. Catalytic dehydrogenation of dibenzosuberone derivatives.[4]

The only example given in the patent is the reaction of dibenzosuberone (**3**) with dibutyl-maleate at 220°C for 6 hours (72% yield). We decided to use this commercially available substance as a model compound to adapt the method to microwave conditions. First experiments with dibenzosuberone (**3**), diethyl maleate, and palladium on charcoal led to violent reactions, including wreckage of reaction vessels, which are designed to hold up to 25 bar internal pressure. Performance of this reaction under argon led to the same effect, indicating that the charcoal did not just "burn" with oxygen present in the reaction vessel, but in fact reacted with other reaction components. This problem was finally overcome by the use of palladium on barium sulfate, and the reaction proceeded smoothly at 200°C within 30 minutes to yield 96% of dibenzosuberenone (**4**). Encouraged by these results, we applied this method to 2,8-dimethyldibenzosuberone (**5**). Unexpectedly, no conversion was observed, even after raising the reaction temperature to 300°C under microwave conditions. The use of platinum on aluminum oxide as an alternative catalyst was to no avail. After 6 days at 200°C (pressure tube / thermal conditions), and 10mol% of palladium on charcoal, 25% conversion was observed (as determined by NMR).

As these results were not satisfactory, we turned back to the bromination-dehydro-halogenation method. To avoid side-reactions, milder bromination conditions were applied: Although no change on TLC (toluene) could be observed if 2,8-dimethyldibenzosuberone (**5**), N-bromosuccinimide, and AIBN were heated in tetrachloromethane at 70°C for 22 hours, the product of this reaction (presumably the bromo compound **7**) was converted readily to 2,8-dimethyldibenzosuberenone (**2**) by treatment with DBN at 80°C. Further experiments showed that stirring of the intermediate with triethylamine at room temperature was indeed sufficient to achieve dehydrohalogenation. By this procedure we were able to raise the yield of the desired 2,8-dimethyldibenzosuberenone (**2**) from 11% to 25% of the theoretical value. Apart from that, up to 30% of undesired 10,11-dibromo-2,8-dimethyldibenzosuberone (**8**) could be isolated by column chromatography.

Experimental Section

General Procedures. Microwave-assisted reactions were carried out in 10 ml sealed glass tubes in a focused mono-mode microwave oven ("Discover", CEM Corporation, Matthews, NC, USA). Maximum power levels, target temperatures and reaction times are given. All commercially available reagents and solvents were used without further purification. Petrol ether with a boiling point of 40-60°C was used, if not otherwise noted. TLC plates coated with silica gel 60 F_{254} were used without prior activation. Mass spectra were recorded on a MS-50 spectrometer at the Chemical Institute, University of Bonn. ^{1}H and ^{13}C NMR spectra were performed on a Bruker Avance 500 MHz spectrometer. The chemical shifts of the remaining protons of the deuterated solvent served as internal standard.

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-one (4). 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (3, 0.42 g, 2.0 mmol) was added to a mixture of 1 g of diethyl maleate and 30 mg of 5% palladium on barium sulfate. After microwave heating (60 W, 200°C, 30 min), the mixture was transferred to a round bottom flask by the addition of ethanol. Approx. 5 ml of 20% aqueous KOH were added, followed by heating to reflux for 10 min. This solution was then extracted with three 10 ml portions of diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield 0.40 g (96%) of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one as a yellow wax (purity >95% (NMR), identity confirmed by comparison with a commercial substance (TLC & NMR)).

4-Methyl-2-[2-(3-methylphenyl)ethyl]benzoic acid (6)[3] . To a mixture of 25 ml (45 mmol) of 1.8 M lithium diisopropylamide in THF/toluene/ethylbenzene (Aldrich) and 20 ml of anhydrous THF, 3.00 g (20 mmol) 2,4-dimethylbenzoic acid (dissolved in 20 ml anhydrous THF) was added at 10 to 20°C over 15 min. This mixture was left stirring for 60 min at r.t. To this dark red solution 4.44 g (24 mmol) of 3-methylbenzyl bromide (dissolved in 20 ml anhydrous THF) were added at -10 to -20°C over 30 min. After stirring at r.t. for another 30 min, the solvent was removed by distillation under reduced pressure. 20 ml of 2 N HCl were added to the residue and extraction with three portions of 20 ml of ethyl acetate was performed. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude orange oil was purified by column chromatography (60 g silica gel, first pure petrol ether, followed by 20% of ethyl acetate in petrol ether as eluents). A mixture of the desired product **6** and 2,4-dimethylbenzoic acid (3,67 g) was thus obtained. The ratio of the components was determined by comparing the integrations of the singlet methyl peak at 2.62 ppm belonging to 2,4-dimethylbenzoic acid (3H) and the double doublet methylene peak at 3.25 ppm belonging to the product (2H). It was found to be 45 : 55 for product : 2,4-dimethylbenzoic acid. Taking into account the molecular masses of the compounds, this can be converted to a content of 58% (mass) and thus a yield of 2.13 g (8.4 mmol, 42%) of 4-methyl-2-[2-(3-methylphenyl)ethyl]benzoic acid (**6**). Although 2,4-dimethylbenzoic acid could be removed by extraction with boiling water, it proved to be more efficient to use this mixture directly for the ring closure reaction.

10,11-Dihydro-2,8-dimethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (5)[3] . The yellow oil obtained (0.87 g containing 2.0 mmol of 4-methyl-2-[2-(3-methylphenyl)ethyl]benzoic acid (**6**)) was mixed with 30 g of a solution of 80% polyphosphoric acid in sulfolane and stirred at 80°C for 60 min. After the addition of 200 ml water, the mixture was extracted with two portions of 50 ml petrol ether. The combined organic phases were washed with 2 N NaOH to remove 2,4-dimethylbenzoic acid, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 0.36 g (1.52 mmol, 76%) of 10,11-dihydro-2,8-dimethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**5**) as a light brown solid (purity >90% (NMR)).

2,8-Dimethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (2) and 10,11-dibromo-2,8-dimethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (8). 10,11-Dihydro-2,8-dimethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**5**, 0.82 g, 3.45 mmol), *N*-bromosuccinimide (0.93 g, 1.5 eq.), and AIBN (30 mg, 5 mol%) were stirred in 20 ml of tetrachloromethane at 70°C for 22 h. After cooling to room temperature, the suspension was filtered and the solid was washed with 2 ml of tetrachloromethane. Triethylamine was slowly added to the combined filtrates until a basic reaction could be measured with wet pH indicator paper. If necessary, further triethylamine was added at room temperature for 60 min to maintain a basic pH. Silica gel 60 (5 g) was added to the mixture and all volatile components were distilled off under reduced pressure. Column chromatography was performed with the powder obtained (40 g silica gel, toluene as eluent).

2,8-Dimethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (2).[3] Yield: 204 mg yellowish crystals (25%), mp 83-89°C, R_f = 0.3 (toluene). ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 2.44 (s, 6H, CH_3), 6.97 (s, 2 H), 7.31 (s, 2H), 7.3 (m, 2H), 8.16 (d, *J* = 7.9 Hz, 2H). Purity: >95% (NMR). MS (EI): 234 (100), 206 (60).

10,11-Dibromo-2,8-dimethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (8). Yield: 235 mg yellow crystals (17%), mp 138-140°C, R_f = 0.55 (toluene). ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 2.41 (s, 6H, CH_3), 5.71 (s, 2 H), 7.17 (s, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 8.03 (d, *J* = 7.9 Hz, 2H).

References and Footnotes

1. Kindon, N.; Meghani, P.; Thom, S. World Pat. 98/54180, 1998.
2. Brunschweiger, A.; Müller, C. *Curr. Med. Chem*. **2006**, *13*, 289.
3. Wild, H.; Hansen, J.; Lautz, J.; Paessens, A. Eur. Pat. 589,322, 1993.
4. Lambrecht, S.; Surburg, H. Ger. Pat. 199,41,211, 2001