

A NEW APPROACH TOWARDS THE SYNTHESIS OF BENZO[*b*]FLUORENE CORE

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New approach towards a benzo[*b*]fluorene core is described. The model compound, 10-methoxy-11*H*-benzo[*b*]fluoren-11-one was prepared in five steps starting from dibenzylmalonic acid. The key step was the metal-catalyzed rearrangement of 3,3'-dihalo-2,2'-spirobiindan-1,1'-dione. The choice and proper activation of the metal was critical for assembly of the benzo[*b*]fluorenone system. The zinc-mediated rearrangement of the corresponding dibromo derivative led to the 10-hydroxy-11*H*-benzo[*b*]fluoren-11-one derivative in 52% yield. The structure of the product was established by spectroscopic methods and was additionally confirmed by standard methylation reaction to the 10-methoxy derivative, which is known in the literature.

Keywords: synthesis; benzo[*b*]fluorene; rearrangement

НОВ ПРИСТАП КОН СИНТЕЗАТА НА БЕНЗО[*b*]ФЛУОРЕНСКОТО ЈАДРО

Опишан е нов пристап кон синтезата на бензо[*b*]флуоренското јадро. Моделното соединење, 10-метокси-11*H*-бензо[*b*]флуорен-11-он, беше синтетизирано во пет чекори почнувајќи од дибензилмалонска киселина. Клучниот чекор беше металокатализираното преместување на 3,3'-дихало-2,2'-спиробииндан-1,1'-дион. Изборот и соодветното активирање на металот беа клучни за подготвување на бензо[*b*]флуоренскиот систем. При преместувањето на соодветниот дибром-дериват во присуство на цинк се добива 10-хидрокси-11*H*-бензо[*b*]флуорен-11-он во 52% принос. Структурата на продуктот беше одредена со спектроскопски методи и беше додатно потврдена со стандардна реакција на метилирање до 10-метокси-дериватот, кој е познат во литературата.

Клучни зборови: синтеза; бензо[*b*]флуорен; преместување

1. INTRODUCTION

In the 21st century, one of the tasks for the chemist that has carried over from the previous century is the search for and preparation of new antibiotics [1, 2]. In the last several decades, one structural motif that has attracted significant attention is the benzo[*b*]fluorene skeleton (Fig. 1). Several biologically potent secondary metabolites containing the benzo[*b*]fluorene subunit, such as stealthin C [3] and prekinamycin [3, 4], have been isolated and characterized (Fig. 2). The kinamycin family of antibiotics has been found in extracts from *Streptomyces murayamaensis* [5, 6]. Taking into consid-

eration the practical importance of the above-mentioned antibiotics, their precursors, such as **4**, are important synthetic targets [7, 8] (Fig. 2). The regioselectivity during the construction of the benzo[*b*]fluorene tetracyclic carbon skeleton is not a trivial undertaking at all, and assembling certain substitution patterns remains a challenge [9].

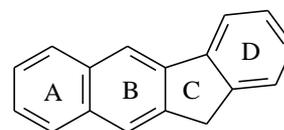


Fig. 1. Ring system of tetracyclic benzo[*b*]fluorene

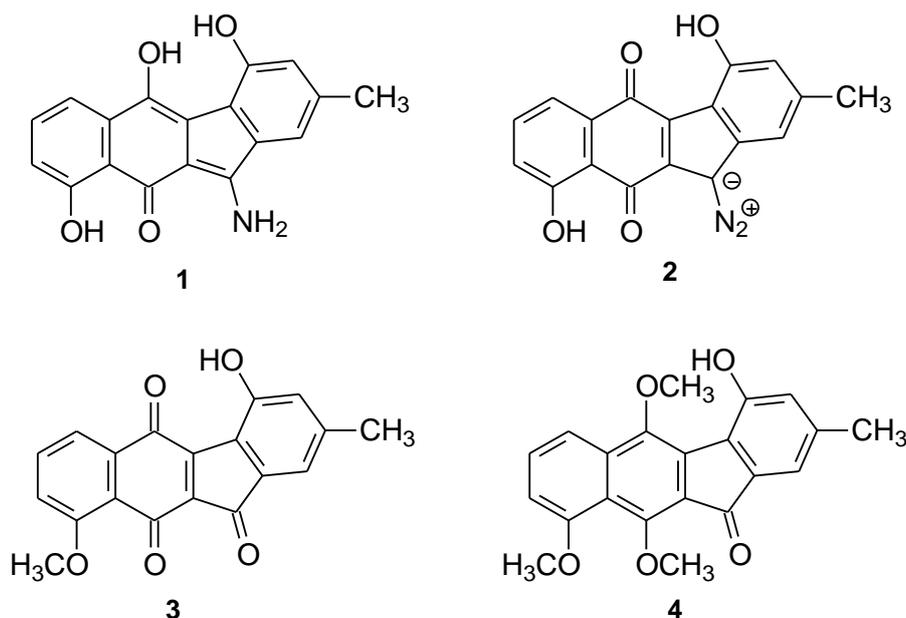
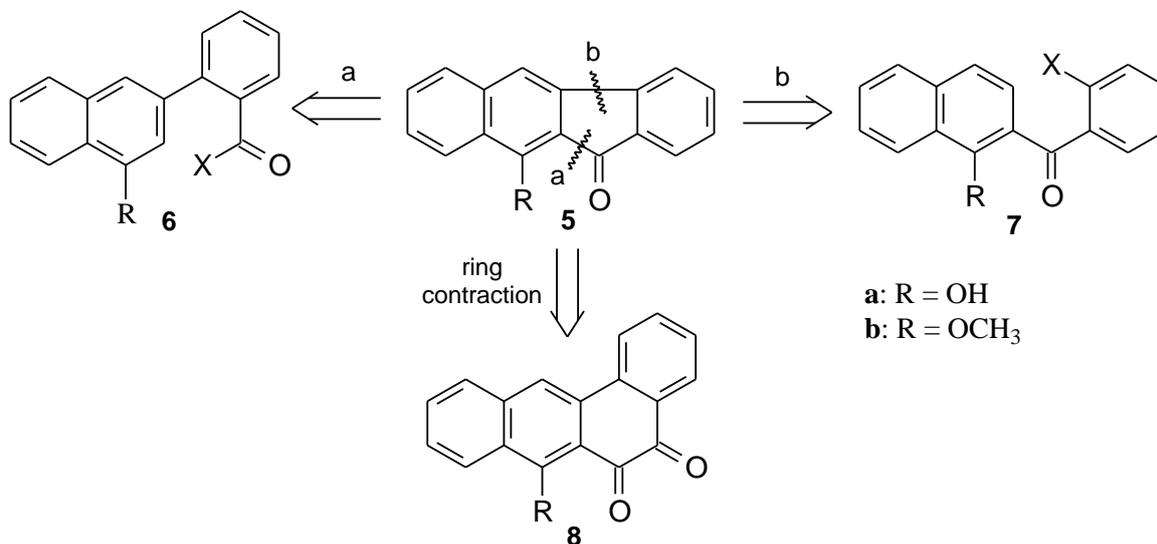


Fig. 2. Structures of benzo[*b*]fluorene antibiotics: stealthin C (1), prekinamycin (2), kinafluorenone (3), common benzo[*b*]fluorenone synthetic precursor (4)

The most common approaches towards benzo[*b*]fluorenone can be divided roughly into Friedel-Crafts-type closures of acyl derivatives [10] (Scheme 1, path a) or transition metal-catalyzed

arylations (Scheme 1, path b) [11–15]. Another approach by Mal *et al.* was based on ring contraction via the benzil-benzilic acid rearrangement of benzo[*a*]anthracene-5,6-diones [16].



Scheme 1. Synthetic approaches toward the basic benzo[*b*]fluorenone skeleton (5)

Other noteworthy approaches are those utilizing [4+2] cycloadditions [17, 18], other cycloadditions [17, 19, 20], and oxidative free radical cyclizations [21]. Birman and co-workers achieved the rapid ring construction of benzo[*b*]fluorenes via reaction of 1-indanone dianions with phthalate diesters. They accomplished quite a feat, because

the synthesis of prekinamycin, **2**, was completed in 3 steps with a 68% overall yield [22].

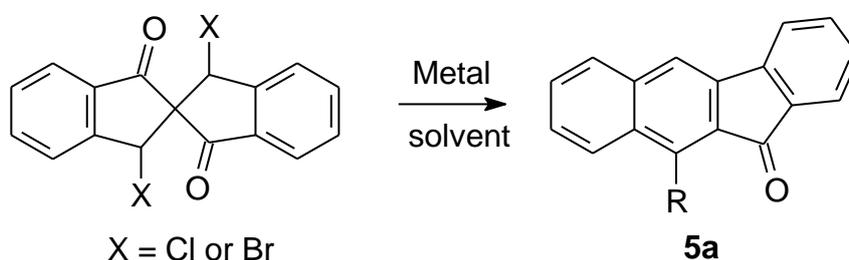
Several total synthesis of these biologically-active benzo[*b*]fluorenes natural products and derivatives have been reported: antibiotic WS-5995A by Watanabe *et al.* [23], Tamayo *et al.* [11] and Qabaja *et al.* [13, 24]; kinamycins C, F, and J

by Nicolau and co-workers [25], (–)-kinamycin C by Lei *et al.* [26], total syntheses of *O*-4,9-dimethyl stealthins A and C by Koyama [27], and the total synthesis of the structure proposed for prekinamycin by Hauser and co-workers [28]. One of the targets (*i.e.* model benzo[*b*]fluorenone system) for checking the synthetic methodology is **5b** (R = OCH₃) (Scheme 1). The methoxy derivative is known in the literature [13, 16] and serves as a convenient model target for synthetic methodology development.

From the previous experience on benzylic bromination (exhaustive or partial) of the 2,2'-spirobiindan-1,1'-dione systems, it was concluded that the functionalization can be reproducibly

achieved with the control of *N*-bromosuccinimide (NBS). Partial benzylic bromination with ca. 2 equivalents of NBS would lead to the dibromo intermediate, which could serve as a valuable synthetic precursor [29]. By treating the 3,3'-dihalo-2,2'-spirobiindan-1,1'-dione with the Zn/Cu couple **5a** (R = OH), the orange product was obtained in low yield (18%), as confirmed by NMR experiments (Scheme 2). As a follow-up of these studies, the next goal was to improve the yields of this approach in order to make it synthetically useful.

Herein, we would like to present the improved preparation of the model benzo[*b*]fluorenone derivative (**5b**, R = OCH₃) by a novel metal-mediated rearrangement approach.



Scheme 2. Metal-catalyzed rearrangement of 3,3'-dihalo-2,2'-spirobiindan-1,1'-diones (R = OH)

2. EXPERIMENTAL

2.1 General

Dichloromethane, hexane, benzene, and ethyl acetate were obtained from Sigma-Aldrich and used without further purification. Tetrahydrofuran was dried over sodium benzophenone ketyl before use. Powdered zinc was activated by washing with diluted hydrochloric acid, distilled water, absolute ethanol and anhydrous ether, followed by drying *in vacuo*. *N*-bromosuccinimide (NBS) was recrystallized from water and dried *in vacuo*. Dibenzylmalonic acid was prepared according to the previously published procedures [30]. Melting points were determined using Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were recorded on a Bruker 400 MHz instrument using deuterated chloroform as a solvent and tetramethylsilane as an internal standard. Preparative flash chromatography [31] was performed using Merck silica gel 60 (230–400 mesh), and TLC was carried out using Merck pre-coated plates (60 F₂₅₄, 250 μm). The zinc/copper reagent was prepared by modification of the original procedure by Smith and Simmons [32]. Zinc powder was washed rapidly by 1% HCl (3 × 5 ml),

distilled water (5 × 10 ml), 2% copper sulfate solution (5 × 7.5 ml), distilled water (5 × 10 ml), absolute ethanol (4 × 10 ml) and finally with absolute ether (5 × 10 ml). The Zn/Cu couple was transferred to a Büchner funnel and washed with additional diethyl ether (2 × 10 ml). It was placed in a round bottomed-flask and dried *in vacuo* overnight. The reagent was stored in a desiccator containing phosphorous pentoxide, and was suitable for use for several weeks if properly handled and protected from moisture.

2.2 Synthesis

2,2'-Spirobiindan-1,1'-dione was prepared from dibenzylmalonic acid (**9**) either directly [30] using the phosphorous pentoxide double ring closure protocol or via the dibenzylmalonic acid dichloride and FeCl₃-promoted Friedel-Crafts protocol [29] with an mp of 172–174 °C (lit. [33] 174 °C, lit. [34] 173–176 °C).

Bromination of 2,2'-spirobiindan-1,1'-dione with NBS. A mixture of 2,2'-spirobiindan-1,1'-dione (3.891 g, 15.40 mmol), *N*-bromosuccinimide (1.7 eq. 4.660 g, 26.18 mmol), benzoyl peroxide (0.150 g, 0.619 mmol) and carbon tetrachloride (140 ml) was refluxed for 36 hours. The mixture

was cooled to room temperature and diluted with dichloromethane (250 ml) and extracted with water (3 × 300 ml). The organic layer was dried over sodium sulfate and removal of the solvent gave a crude yellow product, which mostly contained the desired symmetrical 3,3'-dibromo-2,2'-spirobiindan-1,1'-dione (**10a**), non-symmetrical-3,3'-dibromo-2,2'-spirobiindan-1,1'-dione (**10b**), the monobromide (3-bromo-2,2'-spirobiindan-1,1'-dione) and the undesired, geminal dibromide (3,3-dibromo-2,2'-spirobiindan-1,1'-dione), and tribromide (3,3,3'-tribromo-2,2'-spirobiindan-1,1'-dione). Column chromatography, eluting with 20% hexane in benzene, gave 2.812 g (44% yield) of light yellow solid which contained 88% **10a**, ~9% of **10b** and ~3% of 3,3,3'-tribromo-2,2'-spirobiindan-1,1'-dione. This mixture of 3,3'-dibromo-2,2'-spirobiindan-1,1'-diones was of sufficient purity for the rearrangement studies. Analytically pure **10a** and **10b** were obtained by careful column chromatography separation, followed by recrystallization from benzene or carbon tetrachloride.

Symmetrical-3,3'-Dibromo-2,2'-spirobiindan-1,1'-dione (10a). Light yellow solid mp 169–172°C; ¹H NMR (400 MHz, CDCl₃): 7.84 – 7.72 (m, 4 H), 7.64 (d, *J* = 7.6 Hz, 2 H), 7.52 – 7.44 (m, 4 H), 5.78 (s, 2 H); ¹³C NMR (100 MHz, CDCl₃): 193.37, 154.83, 136.44, 132.48, 130.17, 125.93, 125.73, 81.96, 49.53, 37.91; EI-MS (*m/z*, relative intensity): 327 (M⁺ + 2 – Br, 36%), 325 (M⁺ – Br, 36%), 247 (20%), 246 (M⁺ – 2Br, 100%), 218 (17%), 190 (9%), 189 (45%), 187 (10%), 163 (7%), 123 (10%).

Non-symmetrical-3,3'-Dibromo-2,2'-spirobiindan-1,1'-dione (10b). mp 189–191°C dec.; ¹H NMR (400 MHz, CDCl₃): 7.90 – 7.50 (m, 8 H), 6.20 (s, 1 H), 6.10 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃): 195.56, 194.34, 153.59, 152.19, 136.97, 136.87, 134.98, 134.16, 130.78, 130.46, 127.81, 127.39, 125.20, 124.57, 74.38, 50.74, 47.95; EI-MS (*m/z*, relative intensity): 327 (M⁺ + 2 – Br, 36%), 325 (M⁺ – Br, 36%), 247 (20%), 246 (M⁺ – 2Br, 100%), 218 (17%), 190 (9%), 189 (45%), 187 (10%), 163 (7%), 123 (10%).

10-Hydroxy-11H-benzo[*b*]fluoren-11-one (5a) via zinc mediated rearrangement. A mixture of 3,3'-dibromo-2,2'-spirobiindan-1,1'-diones (**10a** and **10b**, 0.280 g, 0.68 mmol), activated zinc (1.600 g, 24.48 mmol) in absolute ethanol (25 ml) was stirred at room temperature for 24 hours. As the reaction proceeded, the mixture started to become darker, from yellow to orange to brown. Dichloromethane (50 ml) was added and the mixture was filtered through funnel with a small pad of glass wool,

and magnesium sulfate. The orange residue (0.432 g) was subjected to flash column chromatography (silica gel) and eluted first with benzene followed by dichloromethane and ethyl acetate to give 0.088 g (52%) of orange solid which was pure 10-hydroxy-11-*H*-benzo[*b*]fluoren-11-one, **11**. mp 242–244 °C; ¹H NMR (400 MHz, d₈-THF): 9.05 (s, 1 H, OH), 8.19 (d, *J* = 8.36 Hz, 1 H), 8.13 (d, *J* = 7.58 Hz, 1 H), 7.94 (d, *J* = 8.02 Hz, 1 H), 7.81 (s, 1 H), 7.66 (d, *J* = 7.40, 1 H), 7.64 – 7.22 (m, 4 H); ¹³C NMR (100 MHz, d₈-THF): 192.90 (C=O), 149.19 (C), 145.83 (C), 136.51 (C), 136.25 (C), 135.54 (CH), 134.99 (C), 131.90 (CH), 131.34 (C), 128.77 (CH), 128.42 (CH), 127.77 (CH), 125.57 (CH), 124.45 (CH), 122.73 (CH), 122.15 (C), 118.74 (CH); ESI-MS- (*m/z*, relative intensity): 246 (M+1 – H 19%), 245 (M–H, 100%); Anal. Calc for C₁₇H₁₀O₂: C, 82.91; H 4.09. Found: C, 82.79; H 4.22.

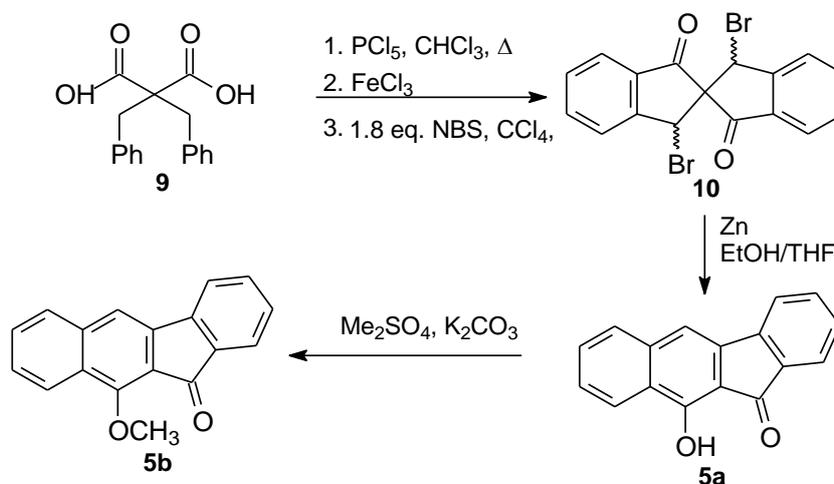
10-Hydroxy-11H-benzo[*b*]fluoren-11-one (5a) via zinc/copper couple mediated rearrangement. A mixture of 3,3'-dibromo-2,2'-spirobiindan-1,1'-diones (**10a** and **10b**, 0.140 g, 0.344 mmol), was first dissolved in THF (6 ml), then absolute ethanol (8 ml) was added, followed by the Zn/Cu couple (0.80 g). The reaction mixture was stirred at room temperature for 25 hours and subjected to work-up as described above. The orange-yellow residue was subjected to flash column chromatography (silica gel) and eluted first with benzene followed by dichloromethane and ethyl acetate to give 0.021 g (25%) of orange solid, which was pure **11**.

10-Methoxy-11H-benzo[*b*]fluoren-11-one (5b) [13, 16]. 10-Hydroxy-11-*H*-benzo[*b*]fluoren-11-one, **5a**, (0.050 g, 0.204 mmol), potassium carbonate (0.118 g, 0.850 mmol) and dimethyl sulfate (0.156 g, 1.239 mmol) were dissolved in acetone (3 ml) and refluxed for 36 hours. The reaction mixture was cooled to ambient temperature and filtered through a pad of Celite; the filtrate was then concentrated *in vacuo* and dissolved in ether. Triethylamine was added, stirred for 15 min, and then the ether layer was washed with water and 10% hydrochloric acid. The ether layer was dried over sodium sulfate, and the solvent was removed to give a solid residue which was subjected to flash column chromatography (85:15 hexane/ethyl acetate). The title compound was obtained in 82% yield (0.0435 g) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): d = 8.27 (d, *J* = 8.1 Hz, 1 H), 7.79 – 7.68 (m, 2 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 7.56 (s, 1 H), 7.59 – 7.38 (m, 3 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 4.35 (s, 3 H); Anal. Calc for C₁₈H₁₂O₂: C, 83.06; H 4.64. Found: C, 83.28; H 4.79.

3. RESULTS AND DISCUSSION

The necessary 2,2'-spirobiindan-1,1'-dione was prepared from dibenzylmalonic acid using an adaptation of literature procedures [30]. From previous studies of benzylic bromination of spirodione [29], it was established that 3,3'-dibromospirodione, **10**, is the dominant product. From the three possible diastereomeric 3,3'-dibromospirodione racemates, only two were detected and isolated. Also, it was established that using two or more equivalents of NBS led to a higher proportion of the undesirable 3,3,3'-tribromo-2,2'-spirobiindandione,

which posed a separation problem. After optimization of the reaction conditions, it was concluded that 1.7 equivalents of NBS were optimal and a combined yield of 44% of 3,3'-dibromo 2,2'-spirobiindan-1,1'-diones (**10a** + **10b**) was obtained after purification by flash column chromatography. The monobromodione could be conveniently separated from the other products by column chromatography and subjected to NBS bromination to obtain additional **10a** and **10b**. The mixture of the two dibromo diastereoisomers (**10a** + **10b**) was used for assembly of the benzo[*b*]fluorene system (Scheme 3).



Scheme 3. Synthesis of 10-methoxy-11*H*-benzo[*b*]fluorene-11-one (**5b**)

First, it was attempted to assemble the skeleton using the alkaline metals (Li, Na K). The reactivity of these metals limits the choice of solvents that can be used for this transformation. Also, the organosodium and organolithium reagents tend to undergo Wurtz-type coupling [35] and, in our specific case, an intramolecular Wurtz-type coupling is able to provide cyclopropanes. Tetrahydrofuran was used because **10a** and **10b** have low solubility in diethyl ether. Treatment of **10** with these alkaline metals in THF resulted in complex mixtures. This was not surprising because such metals are strong reducing agents [36] and, even if the desired product, **5a**, is formed, the corresponding radical anion can undergo further transformations (*i.e.* over-reduction). The magnesium metal was not suitable because the corresponding Grignard reagent (RMgBr) may undergo intra- or intermolecular reactions with the ketone moiety of **10**. The copper itself was not reactive enough to promote rearrangements.

Organozinc reagents, despite their considerable basicity, are compatible with a large number

of sensitive functional groups [37]. Oxidative additions of zinc to alkyl halides can be accomplished by activated zinc. Usually, freshly activated Zn is obtained by dilute acid wash or by another classical activation by the Zn/Cu couple [32]. Initially **10** was treated with Zn/Cu couple in ethanol and **5a** was isolated for the first time, albeit in low yield (18%). By adjusting the reaction conditions and using an ethanol/THF mixture, the yield was increased to 25%. Several different conditions utilizing this reagent and several solvent systems were employed, but the yield could not be further improved. It was decided to use pure freshly activated zinc and try the reaction using ethanol, THF or a combination of the two. Early in the search for the proper reaction conditions, the need to carry out the reactions in high dilution in order to minimize the intermolecular reactions and favor intramolecular processes was established. Also, it was determined that the starting material, **10**, being benzylic secondary dibromide, is susceptible to solvolysis, and should not be heated for prolonged periods in hydroxylic solvents. By employing freshly

activated zinc in absolute ethanol, with vigorous stirring at ambient temperature for 25 hours, the mixture of 3,3'-dibromospirodiones underwent rearrangement to give the desired 10-hydroxy-11*H*-benzo[*b*]fluoren-11-one derivative in 52% yield. The results of all of the metal-mediated rearrangements of **10** are given in Table 1.

Table 1

Metal mediated rearrangement of 10

| Metal | Solvent | Product | Yield (%) |
|-------|----------|-------------------|-----------|
| Na | THF | c.m. ^a | / |
| K | THF | c.m. ^a | / |
| Cu | EtOH | n.r. ^b | / |
| Zn/Cu | EtOH | 5a | 18 |
| Zn/Cu | EtOH/THF | 5a | 25 |
| Zn | EtOH | 5a | 52 |

^a Complex mixture of products. ^b No reaction.

The by-products of the above mentioned reaction are zinc halides, which are moderate Lewis acids, and their presence in solution may influence the outcome of certain chemical reactions. It is tempting to propose the following possible mechanism: the zinc promotes the intramolecular Wurtz-type reaction, which results in spirocyclopropyl derivative. This derivative is unstable and undergoes facile (cyclopropylmethyl cation) rearrangement in the presence of the liberated Lewis acid, ZnBr₂. Mechanistic studies for this transformation are currently underway, as well as synthetic strategies to isolate potential intermediates.

The structure of **5a** was established based on the spectroscopic data. First, it was observed that the spiro connectivity was lost, as indicated by the absence of the peak from **10a** at ca. 80 ppm in the ¹³C NMR spectrum. Second, the absence of both bromines was established based on the mass spectral data. The compound had a molecular ion peak at 246 amu and was not soluble in nonpolar organic solvents. The proton NMR spectrum revealed only protons in the aromatic region and one phenolic O-H at 9.05 ppm. This compares well with structurally-related intramolecularly hydrogen bonded phenols such as 1-hydroxy-9-fluorenone (8.42 ppm) and 7-hydroxyindan-1-one (9.04 ppm) [38]. The number of hydrogens per carbon was determined by a combination of broadband decoupled ¹³C NMR and ¹³⁵DEPT NMR experiments, and were in agreement with the proposed structure. The final structure proof was done by converting the phenolic ketone **5a** to the corresponding methyl

ether **5b**, using standard chemistry (dimethyl sulfate/potassium carbonate). The spectroscopic data of the methoxy ketone, **5b**, was in accordance with the previously published data [13, 16].

4. CONCLUSION

A new approach towards benzo[*b*]fluorene was described. The model compound, 10-methoxy-11*H*-benzo[*b*]fluoren-11-one, was prepared in five steps starting from dibenzylmalonic acid. The key step was the metal-catalyzed rearrangement of the spirodibromodione derivative. The zinc-mediated rearrangement of the mixture of two 3,3'-dibromospirodione diastereomers gave the 10-hydroxy-11*H*-benzo[*b*]fluoren-11-one derivative in 52% yield. The structure of the product was established by spectroscopic methods and by its conversion to the methoxy derivative, 10-methoxy-11*H*-benzo[*b*]fluoren-11-one, which is known in the literature. This methodology for the preparation of benzo[*b*]fluorene is complementary to existing ones and has the potential to be extended to other diarylmethylmalonic acid derivatives.

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