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A facile synthesis of fused spiroketal skeleton: 2,2′-spirobi(4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrochroman)

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Abstract—A one-pot synthesis of fused spiroketal skeleton, 2,2′-spirobi(4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrochroman) **4a–c**, has been achieved for the first time by an application of Michael reaction between dimedone (5,5-dimethylcyclohexan-1,3-dione) **1** and *trans*,*trans*-diarylideneacetone (1,5-diaryl-1,4-pentadien-3-one) **2** using anhydrous $ZnCl_2$ as catalyst. The spiroketalization was achieved efficiently via intramolecular cyclization of the Michael 1:2 adduct.

The chemistry of spiroketals has received much attention over the years due to their presence as substructures in the increasing number of medicinally and ecologically important compounds occurring in natural products from various sources including insects, microbes, plants, fungi, and marine organisms.[1] The increasing pharmacological importance of compounds having spiroketal moieties has aroused intense interest in both their synthesis and chemical reactivity. It is evident from the literature that among many strategies, which have evolved for the synthesis of spiroketals, the acid-catalyzed cyclization of dihydroxyketones, or an equivalent thereof, is the predominant ring-forming process. Later many methods were developed for the synthesis of dihydroxyketone precursors. Livant et al. reported[2] the synthesis of fused aromatic spiroketal by carrying out the acid-catalyzed reaction of resorcinol with phorone (2,6-dimethyl-2,5-heptadien-4-one) and *trans*,*trans*-dibenzylideneacetone (1,5-diphenyl-1,4-pentadien-3-one) whereby the dihydroxyketone precursor was obtained as Michael 1:2-adduct (2 being resorcinol). This adduct underwent subsequent cyclization yielding the C_2-symmetric spirochroman where the oxygen atoms were derived from two aromatic hydroxy groups. Recently, newer methods have been reported[3,4] for the synthesis of partly and fully fused aromatic spiroketals, which exhibited antifungal and antibiotic activity. Examples of partially reduced aromatic rings or partly unsaturated rings fused with spiroketal ring systems do not appear to be reported in the literature. Our present work has been focused on the synthesis of spiroketals containing such ring systems. Due to the similarities in the selected structure to other reported medicinally important spiroketals, our target compounds are also expected to be bioactive. The idea of the present investigation originated from our previous work on the synthesis of 2,4′-diaryl-5-oxo-5,6,7,8-tetrahydro-2-chromen.[5] In the present letter, we wish to report the synthesis of (C_2-symmetric) 2,2′-spirobi(4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrochroman) **4a–c**, in which the spiroketal rings are fused with substituted cyclohexane ring moiety (Scheme 1).

For our investigation, Michael reaction was carried out between dimedone **1** in 2 molar excess and diarylideneacetones **2a–c** in molar proportion in a mixture of boiling toluene and *n*-heptane for 16 h in the presence of anhydrous zinc chloride acting as catalyst. *trans*,*trans*-Diarylideneacetones **2a–c** were prepared by literature procedure with modifications, wherever necessary.[6] The water formed in the reaction was removed by a

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Keywords: Fused spiroketals; Acid catalyzed; Michael addition.

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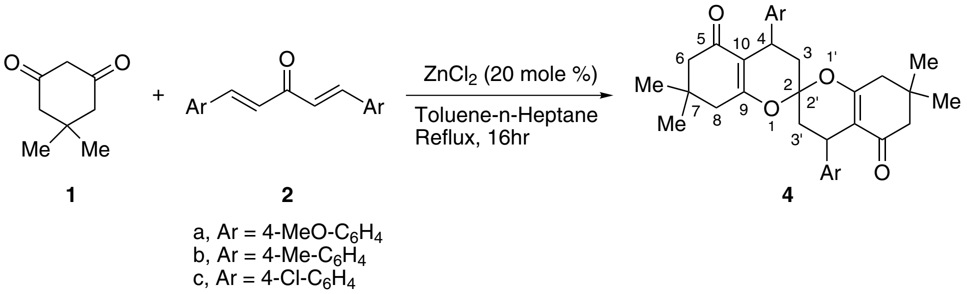
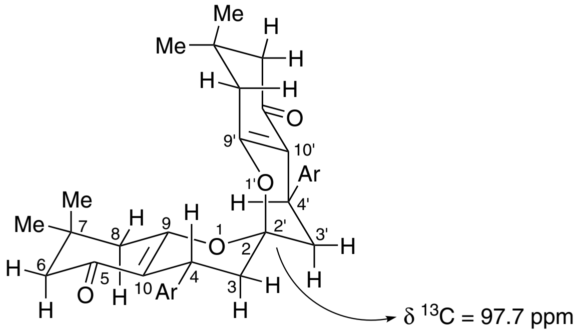


Scheme 1. Synthesis of fused spiroketal **4**.

Dean–Stark attachment. The reaction mixture was cooled, reduced in volume, neutralized with 5% aqueous $NaHCO_3$, and extracted with ether. The residual mass from the ether extract was purified by recrystallizations and **4a–c** were obtained. Compounds **4a–c** were fully characterized by IR, ^1H and ^{13}C NMR (1D and 2D), ^{13}C DEPT NMR, LRMS, HRMS (FAB), and elemental analyses.[7] From two-dimensional NMR spectra (^1H–^1H COSY, ^1H–^1H NOESY, and ^1H–^{13}C COSY) it was possible to assign all the protons and carbons. The coupling constants were determined from one-dimensional ^1H NMR spectra. In the case of each of the compounds **4a–c**, only one diastereomer was isolated almost certainly the one in which both pendent aryl groups are in pseudoequatorial positions (Fig. 1). It is possible that other diastereomers were also formed in this reaction, which we could not isolate.

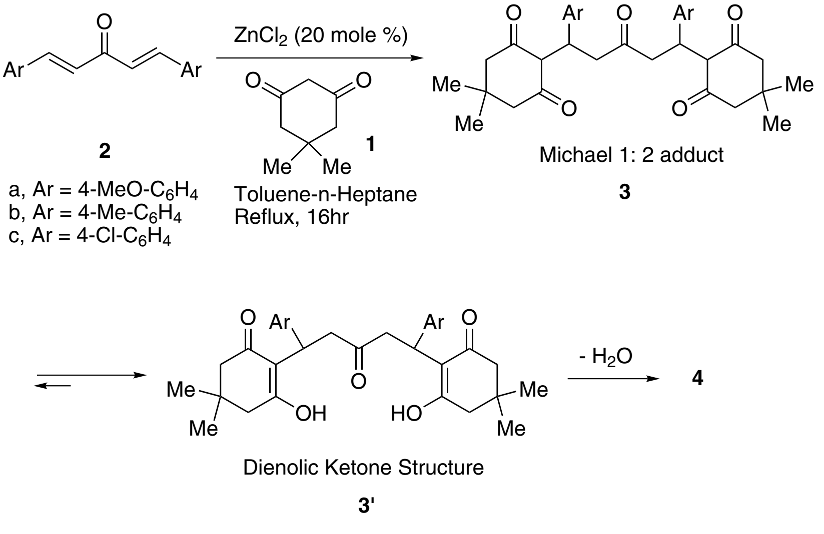


4

H_{ax}-3 (1.80, dd, J_{gem} = 14.1 Hz, J_{aa} = 12.0 Hz)
H_{eq}-3 (2.32, dd, J_{gem} = 14.1 Hz, J_{ae} = 7.0 Hz)
H_{ax}-4 (3.93, dd, J_{aa} = 12.0 Hz, J_{ae} = 7.0 Hz)
H_{ax}-8 (2.16, dd, J_{gem} = 17.4 Hz, J_{aa} = 2.5 Hz)
H_{eq}-8 (2.43, brd, J_{gem} = 17.4 Hz)
H_{ax}-6 (2.15, dd, J_{gem} = 16.5 Hz, J_{aa} = 2.5 Hz)
H_{eq}-6 (2.22, d, J_{gem} = 16.5 Hz)

Figure 1. Fused spiroketal skeleton **4** (Ar = 4-MeO–C_6H_4).

MM2 calculations predict this to be the lowest energy diastereomer (1.5 kcal/mol lower than di-axial; 2.1 kcal/mol lower than axial–equatorial).[2] This was evident from the ^1H NMR coupling constants of H-4 (chroman numbering), 7.0 and 12.0 Hz, are consistent with the di-equatorial diastereomer. A report on NMR data of a similar compound 2,2′-spirobi(7-hydroxy-4-phenylchroman) is available in the literature.[2] The ^{13}C chemical shifts (δ ^{13}C 97.5–97.7) of the spirocarbons C-2 in compounds **4a–c** compare very well with those in the spiroketal fragment of spirofungins (δ ^{13}C 95.7),[8] in 2,2′-spirobi(7-hydroxy-4-phenylchroman) (δ ^{13}C 97.7),[2] and in 2,2′-spirobi(7-hydroxy-4,4-dimethylchroman) (δ ^{13}C 99.9).[9] The ^{13}C NMR chemical shift of the spirocarbon reported in the cases of the aforementioned spiro-



Scheme 2. A plausible route for the formation of fused spiroketal **4**.

ketals has been focused to be diagonistic for the bis-diaxial C–O arrangement in the conformation of the parent 1,7-dioxaspiro[5,5]undecane ring systems.[10] It is evident from the aforementioned literature report that the ^{13}C chemical shifts of the spirocarbons of compounds **4a–c** are typical for a bis-diaxial orientation (Fig. 1).

The formation of the spiroketal structures **4a–c** may be explained by the initial formation of Michael 1:2 adducts (2 being dimedone) **3a–c**, which presumably underwent cyclization (Scheme 2). In this mechanistic pathway the dihydroxyketone precursor for the acid-catalyzed dehydrative spiroketalization was probably the dienolic structure **3′a–c**. We however could not isolate this intermediate probably due to a large thermodynamic difference between the structures **3** and **4**. For the production of C_2-symmetric spirochromans **4a–c**, the oxygen atoms were derived from two enolic hydroxy groups, which originated from dimedone moiety.

Our methodology provides a route for an efficient one-pot synthesis of spirochromans in which the spiroketal ring systems are fused with partially reduced aromatic rings. It also provides an option for functionalization of the reduced ring by starting from substituted 1,3-cyclohexanediones as well as the substituted aryl groups at the 4-position. This synthetic work is in progress in our laboratory. In addition, the bioactivity of all synthesized compounds will be evaluated.

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7. Typical procedure for **4**: A mixture of dimedone **1** (3.08 g, 22 mmol), *trans*,*trans*-diarylideneacetones **2a–c** (10 mmol) and 20 mol % anhydrous $ZnCl_2$ (0.273 g, 2 mmol) in boiling *n*-heptane (30 mL) and toluene (30 mL) was refluxed for 16 h under Dean–Stark attachment. The progress of the reaction was monitored and the purity of product was checked by TLC. The reaction mixture was allowed to cool at rt, reduced in volume and neutralized with 5% aqueous $NaHCO_3$ solution and then extracted with ether (3 × 20 mL). The ether extract was dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product was purified by recrystallizations from a suitable solvent.

Compound **4a**: 2,2′-spirobi(4-methoxyphenyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrochroman). Recrystallized from rectified spirit. Yield 76%; mp 245–247 °C; R_f 0.57 ($CHCl_3$–EtOAc, 15:1); IR (KBr pellet) ν 1660, 1620, 1505 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.05 (s, 3H, Me-7), 1.15 (s, 3H, Me-7), 1.80 (dd, 1H, H_{ax}-3, $J_{gem} = 14.1$ Hz, $J_{aa} = 12.0$ Hz), 2.15 (dd, 1H, H_{ax}-6, $J_{gem} = 16.5$ Hz, $J_{aa} = 2.5$ Hz between H_{ax}-6 and H_{ax}-8), 2.16 (dd, 1H, H_{ax}-8, $J_{gem} = 17.4$ Hz, $J_{aa} = 2.5$ Hz between H_{ax}-6 and H_{ax}-8), 2.22 (d, 1H, H_{eq}-6, $J_{gem} = 16.5$ Hz), 2.32 (dd, 1H, H_{eq}-3, $J_{gem} = 14.1$ Hz, $J_{ae} = 7.0$ Hz), 2.43 (br d, 1H, H_{eq}-8, $J_{gem} = 17.4$ Hz), 3.75 (s, 3H, MeO), 3.93 (dd, 1H, H_{ax}-4, $J_{aa} = 12.0$ Hz, $J_{ae} = 7.0$ Hz), 6.81 (d, 2H, Ar, $J = 8.5$ Hz), 7.07 (d, 2H, Ar, $J = 8.5$ Hz); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ (ppm) 27.8 (Me), 28.8 (Me), 31.9 (C-7), 32.7 (C-4), 41.6 (C-3), 42.4 (C-8), 51.1 (C-6), 55.1 (MeO), 97.7 (C-2), 113.9 (Ar, C-3′,5′), 114.8 (C-10), 127.7 (Ar, C-2′,6′), 136.2 (Ar, C-4′), 157.8 (Ar, C-1′), 166.1 (C-9), 196.4 (C-5); HRMS (FAB): Calcd for $C_{35}H_{40}O_6$: 556.7025; Found 556.2332; LRMS (FAB): *m*/*z* 557 (M^++1, 100%), 556 (M^+, 48%), 297 (60%), 259 (70%), 191 (40%), 154 (25%), 83 (13%). Anal. Calcd for $C_{35}H_{40}O_6$: C, 75.51; H, 7.24. Found: C, 75.27; H, 7.22.

Compound **4b**: 2,2′-spirobi(4-methylphenyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrochroman). Recrystallized from chloroform–pet. ether. Yield 73%; mp 255–256 °C; R_f 0.20 ($CHCl_3$); IR (KBr pellet) ν 1650, 1620, 1505 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.05 (s, 3H, Me-7), 1.15 (s, 3H, Me-7), 1.81 (dd, 1H, H_{ax}-3, $J_{gem} = 14.2$ Hz, $J_{aa} = 12.0$ Hz), 2.15 (dd, 1H, H_{ax}-6, $J_{gem} = 16.1$ Hz, $J_{aa} = 2.5$ Hz between H_{ax}-6 and H_{ax}-8), 2.16 (dd, 1H, H_{ax}-8, $J_{gem} = 17.4$ Hz, $J_{aa} = 2.5$ Hz between H_{ax}-6 and H_{ax}-8), 2.22 (d, 1H, H_{eq}-6, $J_{gem} = 16.1$ Hz), 2.32 (dd, 1H, H_{eq}-3, $J_{gem} = 14.2$ Hz, $J_{ae} = 7.0$ Hz), 2.29 (s, 3H, Me), 2.43 (br d, 1H, H_{eq}-8, $J_{gem} = 17.4$ Hz), 3.94 (dd, 1H, H_{ax}-4, $J_{aa} = 12.0$ Hz, $J_{ae} = 7.0$ Hz), 7.04 (d, 2H, Ar, $J = 8.0$ Hz), 7.08 (d, 2H, Ar, $J = 8.5$ Hz); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ (ppm) 21.0 (Me), 27.9 (Me), 28.9 (Me), 31.9 (C-7), 33.2 (C-4), 41.6 (C-3), 42.4 (C-8), 51.1 (C-6), 97.7 (C-2), 114.7 (C-10), 126.7 (Ar, C-3′,5′), 129.3 (Ar, C-2′,6′), 135.6 (Ar, C-4′), 141.3 (Ar, C-1′), 166.2 (C-9), 196.4 (C-5); HRMS (FAB): Calcd for $C_{35}H_{40}O_4$: 524.7037; Found 524.3019; LRMS (FAB): *m*/*z* 524 (M^+, 100%), 525 (M^++1, 40%), 523 (20%), 283 (50%), 281 (50%), 243 (50%), 227 (10%), 191 (30%), 83 (13%). Anal. Calcd for $C_{35}H_{40}O_4$: C, 80.12; H, 7.68. Found: C, 79.85; H 7.73.

Compound **4c**: 2,2′-spirobi(4-chlorophenyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrochroman). Recrystallized from chloroform–pet. ether. Yield 70%; mp 285–286 °C dec; R_f 0.85 ($CHCl_3$–EtOAc, 1:4); IR (KBr pellet) ν 1660, 1620, 1505 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.06 (s, 3H, Me-7), 1.15 (s, 3H, Me-7), 1.78 (dd, 1H, H_{ax}-3, $J_{gem} = 14.0$ Hz, $J_{aa} = 12.0$ Hz), 2.15 (dd, 1H, H_{ax}-6, $J_{gem} = 16.5$ Hz, $J_{aa} = 2.5$ Hz between H_{ax}-6 and H_{ax}-8), 2.17 (dd, 1H, H_{ax}-8, $J_{gem} = 17.4$ Hz, $J_{aa} = 2.5$ Hz between H_{ax}-6 and H_{ax}-8), 2.22 (d, 1H, H_{eq}-6, $J_{gem} = 16.5$ Hz), 2.32 (dd, 1H, H_{eq}-3, $J_{gem} = 14.0$ Hz, $J_{ae} = 7.0$ Hz), 2.43 (br d, 1H, H_{eq}-8, $J_{gem} = 17.4$ Hz), 3.94 (dd, 1H, H_{ax}-4, $J_{aa} = 12.0$ Hz, $J_{ae} = 7.0$ Hz), 7.08 (d, 2H, Ar, $J = 8.2$ Hz), 7.23 (d, 2H, Ar, $J = 8.2$ Hz); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ (ppm) 27.9 (Me), 28.7 (Me), 32.0 (C-7), 33.1 (C-4), 41.3 (C-3), 42.4 (C-8), 51.0 (C-6), 97.5 (C-2), 114.2 (C-10), 128.2 (Ar, C-3′,5′), 128.7 (Ar, C-2′,6′), 131.8 (Ar, C-4′), 142.7 (Ar, C-1′), 166.5 (C-9), 196.4 (C-5); HRMS (FAB): Calcd for $C_{33}H_{34}Cl_2O_4$: 564.5379; Found 564.1259; LRMS (FAB): *m*/*z* 565 (M^++1($^{35}Cl_2$), 100%), 567 (M^++1(^{35}Cl–^{37}Cl), 70%), 564 (M^+($^{35}Cl_2$), 15%), 569 (13%), 303 (40%), 302 (25%), 270 (25%), 191

(30%), 154 (40%), 136 (28%). Anal. Calcd for $C_{33}H_{34}Cl_2O_4$: C, 70.09; H, 6.06. Found: C, 69.87; H, 6.02.

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