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SHORT COMMUNICATION

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A Defunctionalization Concept for the Convenient Synthesis of Bis(5-arylfuran-2-yl)methane Scaffolds

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The bis(5-arylfuran-2-yl)methane framework has been obtained through defunctionalization of aryl ketones, derived from abundantly available L-(+)-tartaric acid, under the influence of acid. The stereocomponents present in these starting aryl ketones have been found to be insignificant for this transformation.

Introduction

The use of biomass as renewable feedstock for the production of valuable chemicals is one of the most ambitious projects around the world.[1] Defunctionalization of carbohydrates, in particular, has been most attractive.[2] Difurylmethanes **1a** or aryl(furyl)methanes **1b**[3] have attracted the attention of synthetic organic chemists due to their industrial importance.[4] Such compounds have been identified in licorice flavors,[4a] coffee volatiles,[4b] convenient precursors in the synthesis of various condensed heterocyclic systems[4c] and as monomers and cross-linking reagents in polymer manufacturing.[4d] In this context, an ambitious defunctionalization scheme entailing the use of tartaric acid and/or erythritol from nature's biomass was envisaged for the synthesis of bis(furyl)methanes **2** in particular. The objective necessitated assembling architecture **3**, before embarking upon exhaustive defunctionalization. The four-carbon fragment, C_2–C_5 in the general structure **3** was visualized to originate from erythritol or tartaric acid as renewable materials (Figure 1). The work presented in this paper provides proof of concept for this objective.

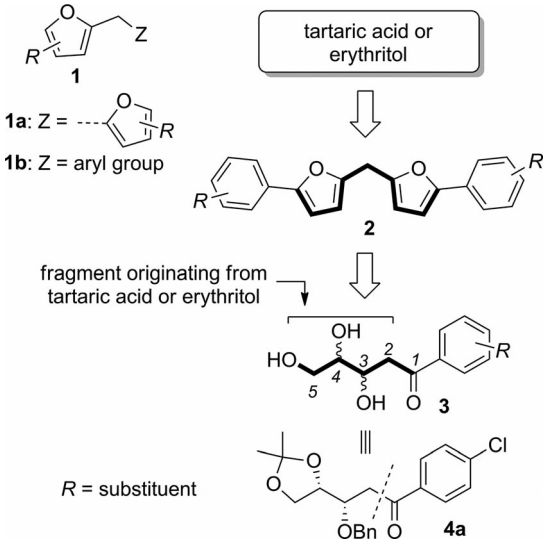
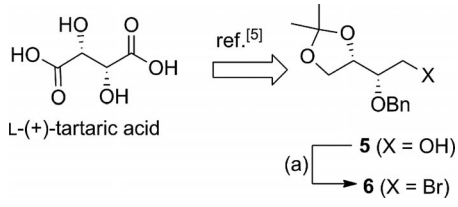


Figure 1. Hydroxylated architecture **3** from tartaric acid or erythritol for defunctionalization.

Results and Discussion

Presuming the intrinsic stereocomponent originating from the starting material is inconsequential during defunctionalization and generation of the target bis(5-arylfuran-2-yl)methane derivatives **2**, the synthesis of **4a** as an equivalent and representative of general structure **3** was planned. Because the two hydroxy groups in L- or D-tartaric acid are equivalent due to C_2-symmetry, we chose to use the known threitol derivative **5**, which can be easily obtained from abundant L-(+)-tartaric acid[5] in a few steps, as a convenient building block for the synthesis of **4a** (Scheme 1).



Scheme 1. Synthesis of bromide **6** via **5** from L-(+)-tartaric acid. (a) Triphenylphosphine (PPh_3), *N*-bromosuccinimide (NBS), *N*,*N*-dimethylformamide (DMF), 60 °C, 2.5 h, 83%.

The incorporation of the arylacyl residue was envisaged through the use of α-amino nitrile as an acyl anion equivalent.[6] The α-amino nitrile **7**, which is an example of an

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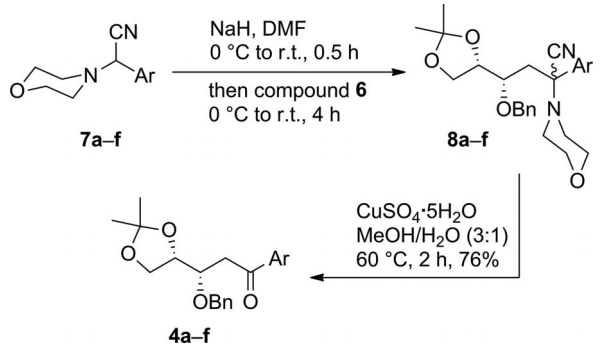
arylacyl anion precursor, underwent clean alkylation with bromide **6** to afford the alkylated products **8** as diastereoisomeric mixtures in 80–85% yield (Scheme 2). The progress of the reaction could be easily monitored by the gradual decrease of the deep-yellow color of the carbanion after addition of the electrophile. The alkylated diastereoisomeric mixture of **8a** was directly subjected to hydrolysis using $CuSO_4 \cdot 5H_2O$ in aqueous methanol at 60 °C.[7] Clean unmasking of the oxo functionality occurred, furnishing the desired aryl ketone **4a** in 76% yield. The reaction sequence afforded the other *threo*-configured aryl ketones **4b–f** with equal ease and in good yields (Table 1). The ^1H and ^{13}C NMR spectra for aryl ketone **4** were recorded in [D_6]-DMSO.



Scheme 2. Synthesis of *threo*-configured aryl ketones **4** through alkylation of α-amino nitriles **7** with bromide **6** and subsequent direct hydrolysis of the alkylated products **8**.

Table 1. Synthesis of *threo*-configured aryl ketones **4** through alkylation of α-amino nitriles **7**.

Entry	Ar	Aryl ketone **4**	Yield [%][a]
1	4-chlorophenyl	**4a**	76
2	4-methylphenyl	**4b**	71
3	phenyl	**4c**	80
4	3,4-dichlorophenyl	**4d**	81
5	4-fluorophenyl	**4e**	63
6	4-methoxyphenyl	**4f**	66

[a] Isolated yield.

The anticipated potential of architecture **3** towards defunctionalization and transformation into substituted furan derivatives was clearly revealed during our attempts to record the ^1H NMR spectrum of aryl ketone **4a** in $CDCl_3$. Apparently, the trace acidity and the moisture content of $CDCl_3$ were sufficient to induce hydrolysis of the isopropylidene ketal protection in **4a** and subsequent annulation. Isolation and purification of the newly formed compound in $CDCl_3$ solution of **4a** was indeed found to be a furan derivative, as evident from two prominent doublet signals [δ = 6.21 (J = 3. 2 Hz), 6.57 (J = 3.2 Hz) ppm] in the ^1H NMR spectrum corresponding to the unsubstituted positions in the furan ring. A sharp singlet (δ_H = 4.12 ppm) correlating with an upfield carbon signal (δ_C = 27.9 ppm) in the HSQC spectrum (see the Supporting Information) and a careful analysis of the integration values indeed suggested the isolated product was bis[5-(4-chlorophenyl)-furan-2-yl]methane (**2a**). X-ray diffraction studies on the crystal finally confirmed the structure of **2a** (Figure 2).

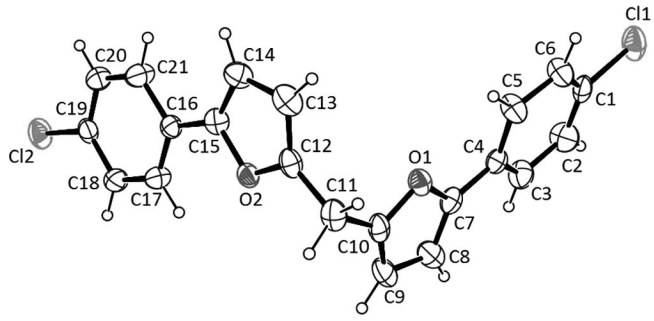
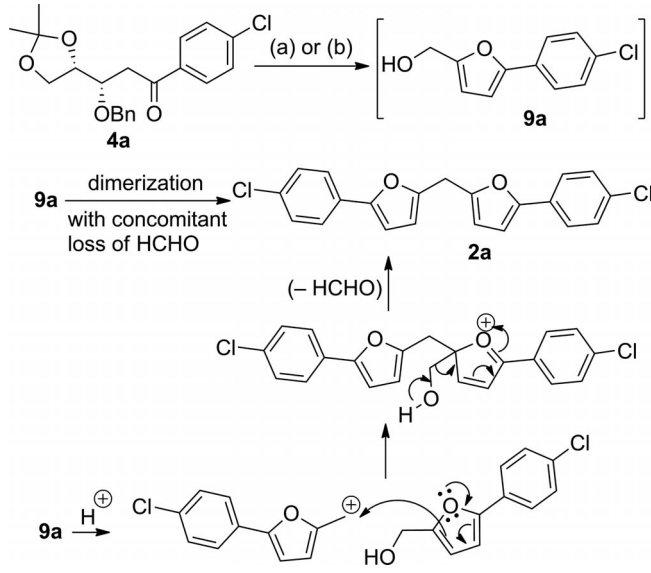


Figure 2. ORTEP diagram of **2a**.

The formation of **2a** is a result of dimerization of the initially formed furan derivative **9a** via a highly stable benzylic carbocation intermediate and concomitant loss of a formaldehyde molecule (Scheme 3). The transformation was independently effected with the use of 15 equiv. of trifluoroacetic acid (TFA) in aqueous tetrahydrofuran (THF) (THF/H_2O, 3:1) at 40–45 °C in 3–4 h.



Scheme 3. Aryl ketone **4a** cascade reaction to bis(5-arylfuran-2-yl) methane on exposure to acid. (a) Traces of aqueous protic acid, slow conversion to **2a** through **9a**; (b) CF_3COOH, THF/H_2O (3:1), 40–45 °C, 3–4 h.

The generality of the acid-promoted defunctionalization was demonstrated when other aryl ketones **4b–f** underwent equally facile transformation into the corresponding bis(5-arylfuran-2-yl)methanes **2b–f** under the same reaction conditions (Table 2).

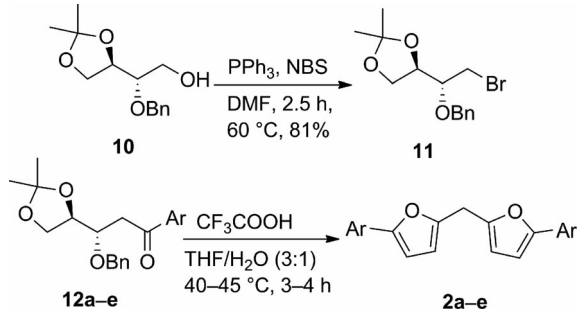
The successful cascade of *threo*-configured aryl ketones **4** to bis(5-arylfuran-2-yl)methane derivatives **2** under the acidic conditions validated the original proposal of synthesizing **2** through exhaustive defunctionalization of biomass material. To address the presumed insignificance of the stereocomponent of the starting ketones **4**, *erythro*-configured

Table 2. Bis(5-arylfuran-2-yl)methanes **2** from *threo*-configured aryl ketones **4**, respectively.

Entry	Bis(5-arylfuran-2-yl)methane **2**	Yield [%][a]
1	**2a**	63
2	**2b**	74
3	**2c**	71
4	**2d**	55
5	**2e**	65
6	**2f**	75

[a] Isolated yield.

aryl ketones **12** were synthesized by using the same strategy described for the *threo*-configured aryl ketones **4**. Although enantiopure erythritol derivative **10**[8–11] was used for the synthesis of **12** via bromide **11**, this is certainly not required. To our delight, *erythro*-configured aryl ketones **12** underwent equally facile conversion into bis(5-arylfuran-2-yl)-methanes **2** (Scheme 4), thereby demonstrating the insignificance of the stereocomponent in the starting aryl ketones and confirming the importance of functional architecture for defunctionalization and convergence to bis(5-arylfuran-2-yl)methane scaffold **2** (Table 3).



Scheme 4. Synthetic route for bis(5-arylfuran-2-yl)methanes **2** from erythritol **10**.

Table 3. Bis(5-arylfuran-2-yl)methanes **2** from D-*erythro*-configured aryl ketones **12**.

Entry	**12**	Yield [%][a]	**2**	Yield [%][a]
1	**12a**	68	**2a**	65
2	**12b**	63	**2b**	67
3	**12c**	67	**2c**	66
4	**12d**	61	**2d**	60
5	**12e**	66	**2e**	64

[a] Isolated yield.

The proposed intermediacy of **9a** during the formation of bis(5-arylfuran-2-yl)methane derivatives **2** from both the *erythro*- and *threo*-configured aryl ketones **4** and **12**, respectively, under acidic conditions, was unequivocally established by its isolation when the reaction was quenched before reaching completion. Thus, the deacetalization reaction of **4a**, using trifluoroacetic acid in THF/H_2O (3:1) at 40–45 °C, was quenched after 1.5 h (before its convergence to the final product **2a**) to furnish the proposed intermediate **9a** in 47% yield together with product **2a** in 10% yield. Intermediate **9a** was isolated from reaction mixture and fully characterized by ^1H and ^{13}C NMR and X-ray diffraction studies.[12] As expected, compound **9a**, prepared by an alternative route,[13] converged to product **2a** under the same reaction conditions.

Conclusions

Bis(5-arylfuran-2-yl)methane compounds have been successfully obtained through defunctionalization of readily accessed derivatives from abundantly available L-(+)-tartaric acid as renewable biomass. With the advent of solid acid catalysis,[14] the acid-promoted defunctionalization disclosed herein should be of great value for the industrial production of bis(5-arylfuran-2-yl)methane frameworks.

Experimental Section

General Procedure for the Preparation of (*S*)-4-[(*R*)-1-(Benzyloxy)-2-bromoethyl]-2,2-dimethyl-1,3-dioxolane (6):[10] To a solution of **5**[5] (0.87 g, 3.43 mmol) in anhydrous DMF (8 mL), solid PPh_3 (2.25 g, 8.58 mmol) and NBS (1.53 g, 8.58 mmol) were added (addition of NBS was exothermic) under nitrogen. The reaction mixture was heated at 60 °C with constant stirring under an inert gas for 2.5 h (the progress of the reaction was monitored by TLC). Upon total consumption of reactant, the mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate (3× 10 mL). The combined organic layers were washed with water (10 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give a solid crude residue, which was further purified by silica gel column chromatography to give **6** (0.89 g, 83%) as a colorless liquid.

General Procedure for the Preparation of *threo*-Configured Aryl Ketones: To a suspension of NaH (94 mg, 2.35 mmol) in DMF (2 mL), a solution of previously azeotropically (toluene, 3× 3 mL) dried α-amino nitrile **7a** (464 mg, 1.96 mmol) in DMF (4 mL) was added dropwise at 0 °C under nitrogen. The mixture was stirred for 30 min, then a solution of **6** (614 mg, 1.96 mmol) in DMF (2 mL) was added slowly at 0 °C. The reaction mixture was stirred at room temperature for 4 h (TLC analysis revealed the formation of a diastereomeric mixture of alkylated product **8a**). Finally, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The organic layer was washed with water (4× 5 mL), dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure followed by flash chromatography with silica gel. The diastereomeric mixture of alkylated product **8a** (560 mg, 1.19 mmol) was subjected to hydrolysis with $CuSO_4·5H_2O$ (1.2 g, 4.80 mmol) dissolved in MeOH/H_2O (6 mL, 3:1) at 60 °C for 2 h. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure, and the organic compound was extracted with ethyl acetate (3× 5 mL). The organic layer was dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexanes) to give **4a** (339 mg, 76%) as a colorless liquid.

General Procedure for the Preparation of Bis(5-arylfuran-2-yl)methane 2 from *threo*-Configured Aryl Ketone 4 and *erythro*-Configured Aryl Ketone 12: Aryl ketone **4a** (298 mg, 0.79 mmol) was dissolved in THF/H_2O (3:1; 4 mL) followed by TFA (11.9 mmol), and the reaction mixture was stirred at 40–45 °C. Upon complete consumption of starting material (reaction monitored by TLC), the mixture was concentrated under vacuum to dryness. Saturated aqueous

$NaHCO_3$ solution was added, and the mixture was extracted with ethyl acetate (3 × 5 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated to give a crude mass, which was purified by silica gel column chromatography (ethyl acetate/hexanes) to obtain **2a** (94 mg, 63%) as a colorless crystalline compound.

X-ray Crystallography: CCDC-915971 (**2a**), -915970 (**2b**), -915972 (**2c**), and -915969 (**9a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental details, copies of the ^1H and ^{13}C NMR spectra, HRMS of all key intermediates and final products, X-ray crystal data for compounds **2a**–**c** and **9a**.

Acknowledgments

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[12] Compound **9a**: Yield: 20 mg (47%); colorless crystalline solid; m.p. 80–82 °C; R_f = 0.2 (hexane/EtOAc, 9:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 8.4 Hz, 2 H), 7.34 (d, J = 8.8 Hz, 2 H), 6.58 (d, J = 3.2 Hz, 1 H), 6.38 (d, J = 3.2 Hz, 1 H), 4.66 (s, 2 H), 1.65 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0 (Ar*C*), 153.1 (Ar*C*), 133.2 (Ar*C*), 129.2 (Ar*C*), 129.0 (Ar*C*H), 125.1 (Ar*C*H), 110.2 (Ar*C*H, furan), 106.3 (Ar*C*H, furan), 57.7 (CH_2OH) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3409, 2830, 1594, 1480, 1408, 1383, 1352 cm^{-1}. Crystallographic data deposition number: CCDC-915969.

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