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Short and efficient synthesis of alkylresorcinols: a route for the preparation of cannabinoids†

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Alkylresorcinols (ARs) are phenolic lipids present in several plants and, from a synthetic point of view, are also versatile key intermediates for the production of many biologically active molecules. In this work, we describe a general and efficient method for the preparation of ARs, also in deuterated form. Finally, this methodology was conveniently exploited for a very rapid approach to synthesize cannabidiol (CBD) and cannabidivarin (CBDV), two non-psychotropic cannabinoids with a bicyclic scaffold present in *Cannabis sativa*.

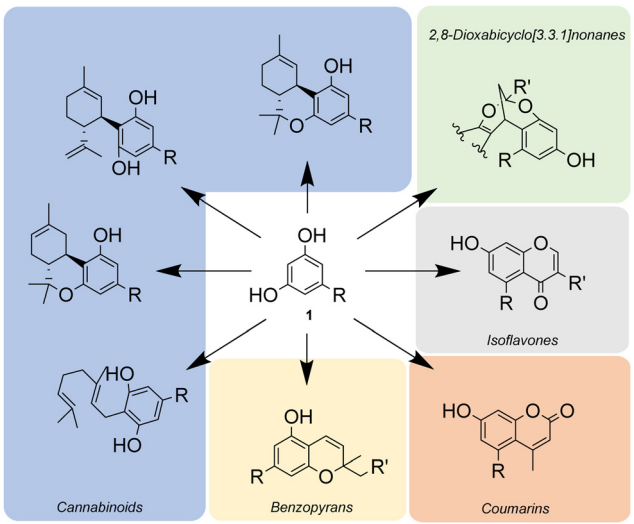
Introduction

Alkylresorcinols (ARs) or 1,3-dihydroxy-5-*n*-alkylbenzenes are phenolic lipids present in several plants, bacteria and marine sponges.[1] Some of these molecules, with alkyl chains in the range of C_{15} to C_{25}, are found in whole grain and bran products and consequently they are used as objective dietary biomarkers that reflect the intake of certain foods.[2] Others, with alkyl chains of different length, have been tested for various *in vitro* bioactivities (colon cancer cell growth inhibition, antioxidant activity, lipase activity inhibition, antibacterial activity, *etc.*)[2,3] with interesting results and in fact, ARs can be used as adjuvants for antimicrobial and anticancer treatment.[3b]

ARs, in addition to being target products, are also very common structural subunits in natural and pharmaceutically active products. As such, they are extensively used in organic chemistry as versatile starting materials for the synthesis of a broad range of complex molecular scaffolds: coumarins,[4] 2,8-dioxabicyclo[3.3.1]nonanes,[5] isoflavones,[6] benzopyrans[7] and cannabinoids[8] (Scheme 1).

In the light of these considerations, the development of effective and versatile protocols for their synthesis is highly desirable. In this context, the design of practical synthetic strategies for the production of several structurally different ARs using a minimum number of steps and readily available inexpensive starting materials, as well as the elaboration of methodologies that can also be exploited for the synthesis of deuterated analogues, is a fascinating challenge.

Generally, traditional approaches for the synthesis of ARs involve Grignard and related reactions, palladium-catalysed Suzuki coupling, reductive alkylation followed by oxidative decarboxylation or Wittig reaction (Scheme 2).[1,9–13] Some of these strategies are characterized by a rather high number of steps that inevitably lead to a reduction in the total yield of the process, expensive reagents, highly reactive organometallic species which require an accurate control of experimental parameters and very dry conditions. A further disadvantage is



Scheme 1 Synthesis of complex molecular scaffolds starting from ARs **1**.

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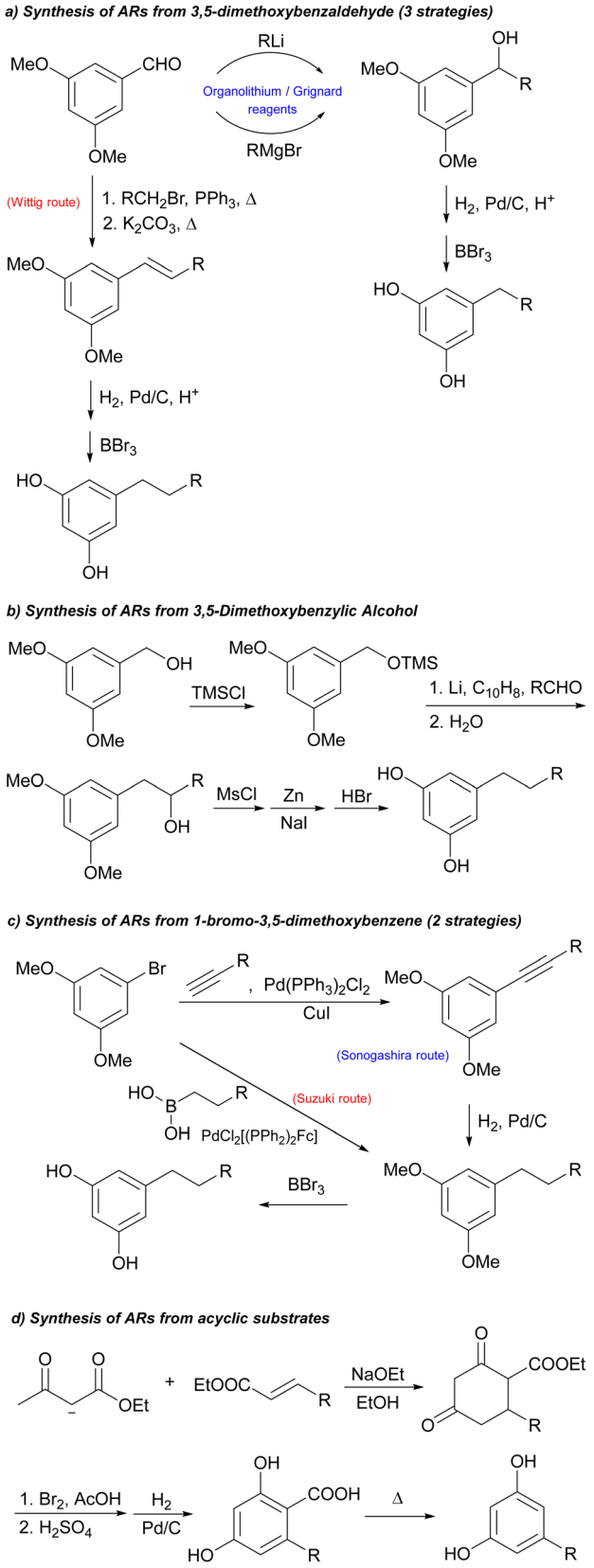


Scheme 2 Some synthetic strategies for the production of ARs reported in the literature.

that only some of such strategies have also been exploited for the synthesis of the corresponding deuterated analogues (above all with short saturated alkyl chain).[14–16]

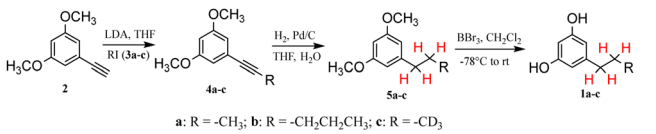
We report here a simple methodology for the preparation of ARs, as such or chemoselectively deuterated, in high yields.

Finally, in order to explore further the synthetic utility of this strategy, ARs produced through this optimized procedure were used as starting materials to synthesize two non-psychotropic bicyclic cannabinoids[17,18] (CBD and CBDV) and their deuterium labelled analogues *via* conventional terpenylation. The elaboration of new efficient synthetic procedures for the production of cannabinoids, in order to produce adequate quantities of products for clinical uses, is strongly desirable for their promising therapeutic potential (migraine and headaches, glaucoma, convulsions, *etc.*).[19–22] In particular, the development of protocols potentially applicable to automated processes (flow synthesis) represents a future challenge. In this regard, the first automation of the terpenylation step[23] of the synthesis of CBD and CBDV for possible large-scale industrial applications opens up new perspectives and renders the development of simple and efficient methodologies for the production of ARs even more important. In addition, having versatile methodologies that can also be used for the synthesis of deuterated ARs and, consequently, deuterated cannabinoids suitable as internal standards for mass spectrometric analyses, or as starting materials for the production of deuterated metabolites for the study of cannabinoid metabolism and pharmacokinetics in animals and humans, is also important.

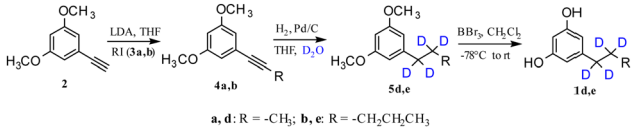
Results and discussion

As delineated in Scheme 3, our strategy for the synthesis of ARs **1** started from the reaction between the commercially available 1-ethynyl-3,5-dimethoxybenzene **2** and an appropriate alkyl iodide **3** in the presence of LDA. This methodology proved to be effective with three different alkyl iodides (also the deuterated **3c**), giving only products **4** in quantitative yields and without the formation of side-products, so the crude product was used without any further purification. For short chain alkyl halides, LDA was indispensable to obtain the desired product. Alternative bases such as nBuLi[24] or KOH in DMSO[25] also gave rise to competitive alkylation of the aromatic ring with production of complex reaction mixtures that were difficult to separate.

The following Pd/C-catalysed reduction of the triple bond in **4** with H_2 in H_2O/THF or alternatively in EtOH provided the product **5** with the suitable saturated side chain (C_3 in **5a** and



Scheme 3 Synthetic sequence for the production of ARs.



a, d: R = -CH_3; **b, e**: R = -$CH_2CH_2CH_3$

Scheme 4 Synthetic sequence for the production of deuterated ARs *via* deuteration of the triple bond.

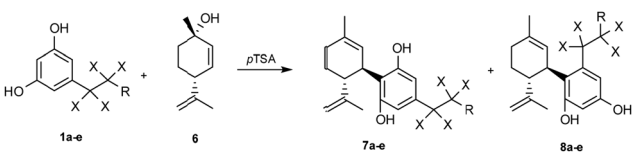
5c or C_5 in **5b**) and its subsequent demethylation[16] by BBr_3 in CH_2Cl_2 gave the ARs **1a–c**.

Therefore, deuterated ARs could be prepared with the same synthetic strategy in Scheme 3 by using deuterated alkyl iodides **3**, but also in a very convenient and economic way. The triple bond of the product **4** was not only able to be easily and selectively hydrogenated but also deuterated thus allowing the introduction of four deuterium atoms in the alkyl chain. This approach is particularly useful and convenient when the appropriate deuterated alkyl iodide is not commercially available or is too expensive.

In fact, when the Pd/C-catalysed reduction of the triple bond with H_2 was realized in D_2O/THF instead of H_2O/THF,[26,27] the complete deuteration of the triple bond afforded the deuterated products **5d** and **5e** in quantitative yields (Scheme 4). Therefore, the Pd/C-catalysed H_2–D_2 exchange reaction using H_2–D_2O provided an efficient, cheap and environmentally friendly way for the *in situ* preparation of D_2. Gratifyingly, these reactions were efficient, with >95% deuterium incorporation,[28] no competitive deuteration of the aromatic ring observed, and a site-selective incorporation of deuterium on the alkyl chain achieved.

All reactions of this multistep synthetic sequence (Schemes 3 and 4) were cleaned and characterized by very simple work-ups; ARs **1a–e** (deuterated or not) were isolated in high yields (≥ 87% overall yield from **2**, higher than those reported in the literature using different synthetic strategies[23]) over only 3 steps without isolation of the intermediate products **4** and **5**, thus allowing a beneficial reduction in the amount of used organic solvents.

Importantly, the methodology is very versatile and it could be potentially used to prepare new ARs with different length or completely deuterated side chains, simply by appropriately selecting the alkyl halide **3** for the alkylation reaction (first step) and the solvent for the triple bond reduction (second step). Finally, this protocol was readily scalable (up to 10 mmol) without substantial change in efficiency.



a: X = H, R = -CH_3; **b**: X = H, R = -$CH_2CH_2CH_3$; **c**: X = H_n R = -CD_3; **d**: X = D, R = -CH_3; **e**: X = D, R = -$CH_2CH_2CH_3$

Scheme 5 Synthesis of bicyclic cannabinoids (normal and abnormal scaffolds) *via* terpenylation.

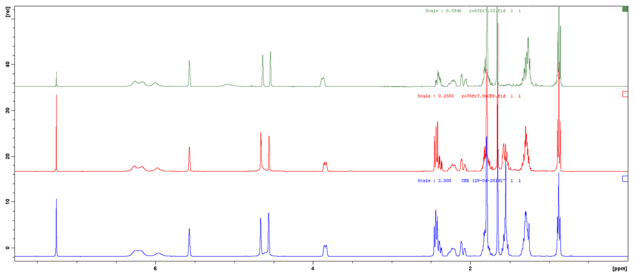


Fig. 1 ^{1}H NMR spectra of pure botanical CBD supplied by GW Research Ltd, now a part of Jazz Pharmaceuticals, Inc. (blue), synthetic CBD **7b** (red) and its deuterated analogue **7e** (green).

To further explore the synthetic value of this strategy, we applied the methodology described here to prepare two bicyclic cannabinoids (CBD and CBDV) and their deuterated analogues.

As depicted in Scheme 5, all ARs **1a–e** were condensed with commercially available (1*S*,4*R*)-4-isopropenyl-1-methyl-2-cyclohexen-1-ol **6** in the presence of 33 mol% wet *p*TSA to afford the *trans* bicyclic cannabinoids as a mixture of normal and abnormal scaffolds.[8] The products **7** (up to 26% yield) and **8** (up to 38% yield) were isolated after a chromatographic column and, importantly, under these experimental conditions, no tricyclic structure was produced. The yields of this last reaction of terpenylation were comparable with those reported in the literature.[8]

The coupling of ARs **1b** and **1e** with **6** afforded CBD **7b** and its deuterated analogue **7e**, respectively, as confirmed by the ^{1}H-NMR spectra. The ^{1}H NMR spectra of botanical purified CBD supplied by GW Research Ltd, now a part of Jazz Pharmaceuticals, Inc., and synthetic CBD **7b** matched perfectly (Fig. 1, blue *vs.* red) confirming that the structure and the relative configuration of the stereogenic centers were the same (*trans*). The absolute configuration of natural CBD was elucidated by Mechoulam as *R* at both C-3 and C-4.[29] Also, in the synthetic CBD **7b** the absolute configuration at C-4 was *R* because it was derived from the chiral building block **6** (chiral pool approach). Consequently, the configuration at C-3 was also assigned as *R*, as in botanical CBD. In parallel, the spectrum of **7e**, while confirming all the previous considerations, shows loss of signals at 2.4–2.5 ppm and 1.6 ppm due to the deuterium contributions (Fig. 1, green).

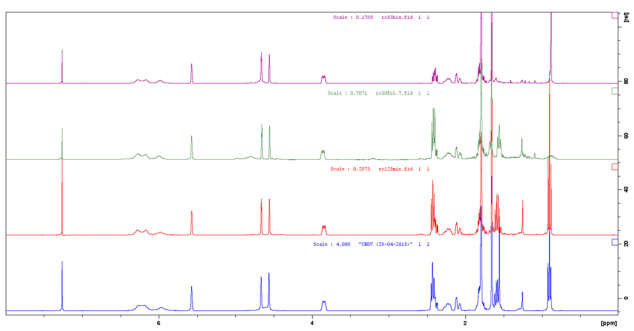


Fig. 2 ^{1}H NMR spectra of pure botanical CBDV supplied by GW Research Ltd, now a part of Jazz Pharmaceuticals, Inc. (blue), synthetic CBDV **7a** (red) and its deuterated analogues **7c** (green) and **7d** (purple).

A similar NMR comparison was also realized for pure botanical CBDV supplied by GW Research Ltd, now a part of Jazz Pharmaceuticals, Inc., (Fig. 2, blue), synthetic CBDV **7a** (Fig. 2, red) and its deuterated analogues **7c** and **7d** (Fig. 2, green and purple respectively) with similar results to those highlighted for CBD.

Conclusions

In summary, the methodology described in this paper offers an easy and efficient approach to the synthesis of an interesting class of molecules known as alkylresorcinols (ARs). This methodology is general and versatile, and suitable for the construction of a library of ARs and their deuterated analogues in only 3 steps. The deuterium labelled analogues can easily be synthesized using a deuterated building block (alkyl iodide) but also by the complete deuteration of the triple bond *via* Pd/C-catalysed exchange reaction between H_2 and D_2O.

Key advantages of this synthetic sequence are that all reactions led to the corresponding products with high yields, without the formation of side-products and requiring only column chromatographic purification of the final AR, with a reduction in the amount of solvent and energy needed for separation and purification.

All these features make this strategy particularly useful for the production of ARs on a medium scale, allowing them to be used as starting materials in the synthesis of complex molecular scaffolds (as exemplified here by the application of the method to two bicyclic cannabinoids and their deuterium labelled analogues), under batch but also, in perspective, in flow chemistry conditions for possible large-scale industrial applications.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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