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Tetrahedron Letters 46 (2005) 5177–5180
Tetrahedron Letters

Hydrogenation of substituted aromatic aldehydes: nucleophilic trapping of the reaction intermediate, application to the efficient synthesis of methylene linked flavanol dimers

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Received 11 April 2005; revised 24 May 2005; accepted 27 May 2005
Available online 15 June 2005

Abstract—The synthesis of dimeric flavanols is the consequence of the possible trapping of the reaction intermediates generated in the course of the reductive hydrogenation of substituted benzaldehydes. The scope of this reaction is investigated.

Dimeric flavanols linked through a methylene bridge and related unsymmetrical diaromatic methylene have been recently described as natural substances from *Glycosmis montana*[1] (**1**, **2**), *Agrimonia pilosa*[2] (**3**) or produced by fermentation of cacao liquor[3] (**4**) (Fig. 1). Moreover, this type of linkage has also been found to be a significant transformation pathway for flavanols during red wine ageing.[4,5] Polymerizations of (+)-catechin with formaldehyde,[6] acetaldehyde,[7–10] furfural[11] phloroglucinol-aldehyde[12–15] or with tartaric and glyoxylic acid[16–19] leading to such compounds have therefore been extensively studied but the procedures described, designed to have a biomimetic significance, gave in all cases only moderate yields of dimeric compounds beside complex mixtures of higher oligomers. The proposed mechanism[9,18,19] of the formation of these flavanol derivatives however suggests the formation of an aldehydic intermediate, which reacts with another aromatic compound (namely another flavanol molecule), leading to a bis-benzylic alcohol, which is presumably reduced in situ to furnish the corresponding pseudo-dimeric flavanol linked through a methylene or methine bridge.

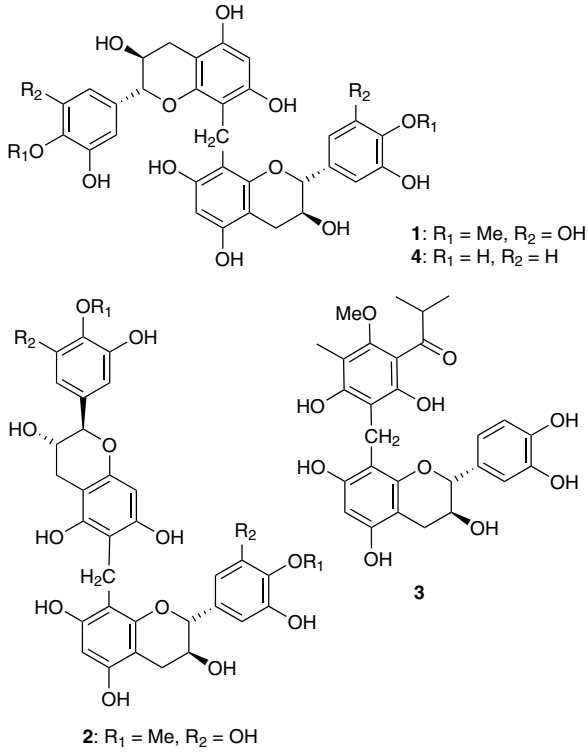

Figure 1.

Based on the mechanistic features arising from these condensation reactions already reported in the literature and on our own observation that the reduction of aromatic aldehydes upon hydrogenation (H_2, Pd/C) could lead, depending on the substitution pattern of the aromatic ring, a complex mixture of compounds resulting

Keywords: Flavanol; Catechin; Hydrogenation.
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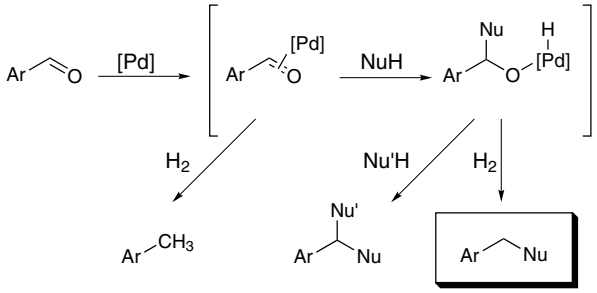
doi:10.1016/j.tetlet.2005.05.132



Scheme 1.

from polycondensation side reactions, we present here new reaction conditions allowing the palladium intermediate generated in the hydrogenation process to be trapped by an aromatic nucleophilic species (Scheme 1). Reaction conditions have been optimized (mainly concentration of starting material and nucleophile) in order to minimize direct reduction of the carbonyl group and formation of double condensation products.

The starting point of our work has indeed been the observation that the hydrogenation of very simple compounds such as **5a** or **5b** (Table 1, entries 1 and 2) could either be a quite quantitative process (**5b**) or lead to the formation of a complex mixture of products, MS analysis of which reveals the presence of oligomeric compounds. In the case of **5a**, the formation of such compounds can be explained by the known high nucleophilic potency of phloroglucinol derivatives. These observations prompted us to assume the reaction pathway described on Scheme 1 to be feasible, assuming that the less the aldehyde will be easily reduced, the more the nucleophilic trapping pathway would be effective. The major problem relied however on the possibility of managing the ability of the aldehyde to be reduced versus the nucleophilic potency of the aromatic nucleophile used.

We therefore tried this reaction on various aromatic aldehydes (Fig. 2) with Pd on charcoal (10%) as catalyst either in the presence of hydrogen or not and using either phloroglucinol **8** or catechin **9** as aromatic nucleophilic

Table 1. Hydrogenation/nucleophilic addition sequence on aldehydes **5a**–**h**–**7**

	Ar=O	Cond.	Concn	NuH	Products (yields of isolated products)		
					Ar–CH3	Ar–Nu	Nu'/Ar/Nu
1	**5a**	A	0.12 M	—		Complex mixture	
2	**5b**	A	0.12 M	—	100	—	—
3	**5a**	B	0.12 M	**8**	—	38	—
4	**5b**	B	0.12 M	**8**	—	54	—
5	**5c**	B	0.12 M	**8**	32	—	12[a]
6	**5d**	B	0.12 M	**8**	33	—	—
7	**5e**	B	0.12 M	**8**	—	12	—
8	**7**	B	0.12 M	**8**	—	46	—
9	**5a**	B	0.12 M	**9**	—	43 (3:2)[b]	—
10	**5b**	B	0.12 M	**9**	—	22 (4:1)[b]	—
11	**5g**	B	0.12 M	**9**	—	8 (9:1)[b]	—
12	**5c**	B	0.12 M	**9**	—	—	36 (60:37:3)[c]
13	**5h**	B	0.12 M	**9**	—	19[d]	31[c]
14	**6**	A	1.4×10^{-2} M	—	50[e]	50[e]	—
15	**6**	A	4×10^{-2} M	—	25[e]	75[e]	—
16	**6**	B	4×10^{-2} M	**9**	—	47 (3:2)[b]	—
17	**6**	B	4×10^{-2} M	**8**	—	33	—
18	**5a**	C	0.12 M	**8**	—	—	—
19	**5c**	C	0.12 M	**8**	—	—	70[a]
20	**5b**	C	0.12 M	**8**	—	—	11[f]

Conditions: A: H_2 (1 atm), Pd/C 10% (10% w), MeOH 18 h; B: NuH (3–5 equiv), H_2 (1 atm), Pd/C 10% (10% w), MeOH 18 h; C: NuH (3–5 equiv), Pd/C 10% (10% w), MeOH 18 h.

[a] Nu′H = NuH.

[b] Mixture of regioisomers (see text) determined by ^{1}H NMR.

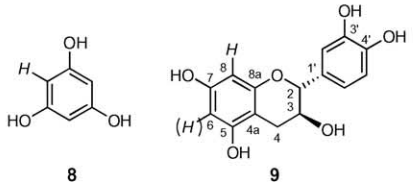
[c] Nu′H = NuH, mixture of regio- or stereoisomers determined by HPLC DAD-MS.

[d] Mixture of regioisomers determined by HPLC DAD-MS.

[e] NuH = $ArCH_3$, conversion of aldehyde is complete and the yields reported correspond to the relative proportions of the two products of the reaction determined by ^{1}H NMR.

[f] Nu′H = MeOH.

NuH =



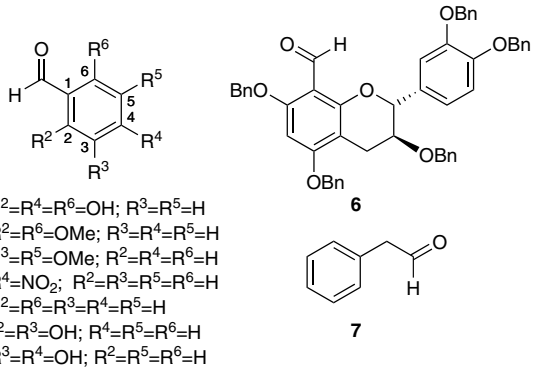


Figure 2.

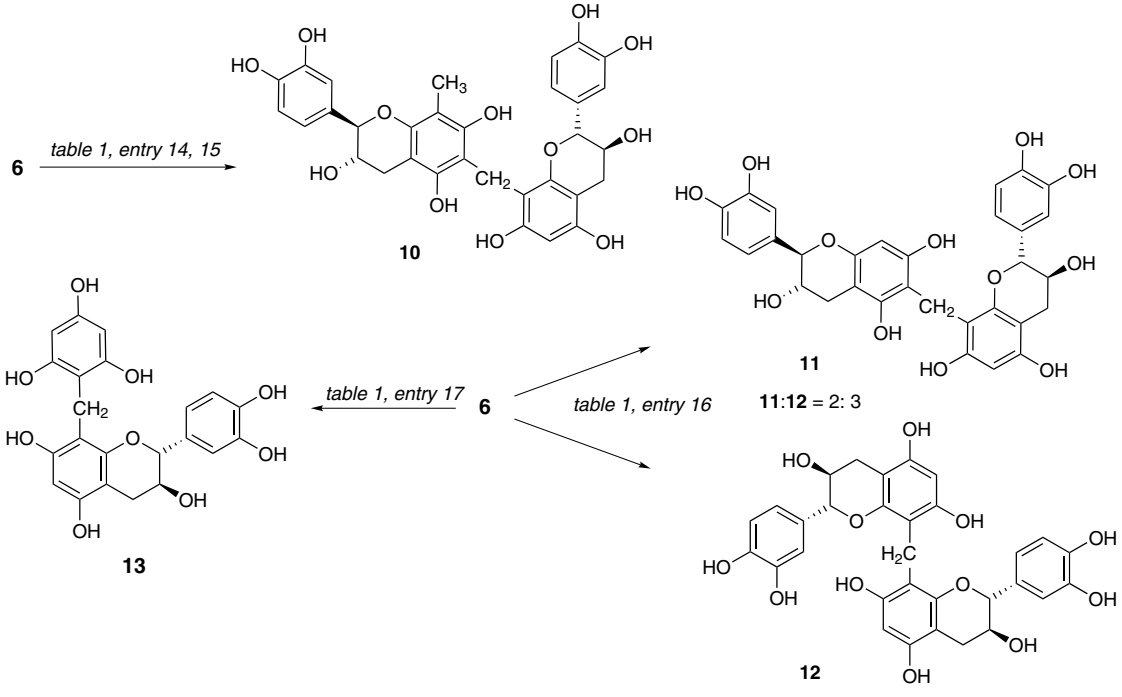
species in order to be able to have access to compounds related to natural products **3** and **1** (or **2**), respectively. Results are gathered in Table 1 and in Scheme 2.

The best way of preventing the direct reduction of the carbonyl group was in fact to perform the reaction in the absence of hydrogen (conditions C, entries 18–20). However, for the three aldehydes tested in these conditions, results were somehow disappointing, since indeed, for **5a**, no reaction occurred at all and for **5b** and **5c**, beside a large amount of degradation products, the only compound obtained corresponded to a double addition of a nucleophile. Noteworthy, when the aldehyde is sterically highly hindered (**5b**) and although the yield was low, the bulky phloroglucinol was replaced in the second addition reaction by methanol (used as solvent) as the nucleophilic species.

In the presence of hydrogen, the direct reduction of the carbonyl group occurred in some cases as an important reaction pathway, but the nucleophilic addition was however in most cases predominant. It is important to note that the substitution pattern of the aromatic ring obviously influences the course of the reaction and that, in the case of the very reactive aldehyde **5c** (entry 12), the double addition compound may become the major product of the reaction, even with very bulky nucleophiles such as catechin **9** (as already known for catechin, exhibiting two nucleophilic sites at C-6 and C-8, the most reactive site is C-8 and the proportions of regioisomers formed in the course of the reactions reported in Table 1 are always in favour of the product where the methylene is linked to the C-8 of **9**).

In the case of aldehyde **6**[20] as starting material, the main problem raised from the high reactivity of this compound, thus forcing us to decrease the concentration of substrate to alleviate side reactions. However, even at the lowest concentration tested and in the absence of other nucleophile (entry 14), the product of the hydrogenation of the carbonyl group ($ArCH_3$) acted as a nucleophile and the dimeric compound **10**[21] was obtained in 50% yield. At an intermediate concentration ($4\ 10^{-2}$ M, entry 15), the production of dimeric compound **10** raised up to 75%. In the presence of an excess of another nucleophile, the best results were also obtained at $4\ 10^{-2}$ M. In these optimized conditions and in the presence of **9** or **8** as nucleophile (5 equiv; entries 16 and 17), aldehyde **6** nicely reacted to afford the desired pseudo-dimers (**11**, **12**) and **13**, respectively,[21] (Scheme 2); in these conditions, the formation of **10** was not observed.

Noteworthy also, homobenzylic aldehyde **7**, which is not supposed to be reduced in these hydrogenation conditions, nevertheless reacted in our conditions with phloro- glucinol as nucleophilic species. But, on the



Scheme 2.

other hand, the same conditions tested on various acetophenones unfortunately gave no satisfactory results.

In conclusion, the most important feature of the reaction described in this paper is not only to give a general access to the methylene linked flavanol pseudo-dimers, which play an important role in the quality of various food products and for which already reported preparation procedures are available, but also to allow the preparation of unsymmetrical diaromatic methylenes such as **13** using very easily carried out reaction conditions. Such compounds are currently tested for their antioxidant activities, which will be reported in due course.

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21. Compound **10**: ^{13}C NMR (75 MHz, CD_3OD) δ = 155.73 (C), 154.07 (C), 153.07 (C), 152.65 (2C), 151.70 (C), 146.77 (C), 146.40 (C), 146.10 (C), 145.99 (C), 132.79 (C), 130.66 (C), 120.56 (CH), 119.78 (CH), 116.42 (CH), 116.10 (CH), 115.68 (CH), 115.09 (CH), 108.22 (C), 106.80 (C), 105.09 (C), 101.92 (C), 101.80 (C), 96.97 (CH), 84.29 (CH), 92.46 (CH), 69.00 (CH), 68.04 (CH), 28.81 (CH_2), 28.64 (CH_2), 18.15 (CH_2), 8.59 (CH_3). ^{1}H NMR (300 MHz, CD_3OD) δ = 6.90–6.89 (br s, 1H), 6.82–6.66 (m, 5H), 6.12 (s, 1H), 4.75 (d, J = 8.1 Hz, 1H), 4.57 (d, J = 6.9 Hz, 1H), 4.11 (q, J = 7.8 Hz, 1H), 3.91 (q, J = 7.5 Hz, 1H), 3.65 (s, 2H), 2.91 (dd, J = 16.2, 5.4 Hz, 1H), 2.78 (dd, J = 15.6, 4.8 Hz, 1H), 2.59–2.46 (m, 2H), 1.90 (s, 3H). ESI MS *m/z* (%) 607 (MH^+) (100). Product ions [607]: 455, 317, 303. Ratio **11**/**12** (3:2) was determined by ^{1}H NMR and HPLC DAD-MS analysis. Compound **11**: data in agreement with the literature.[6] Compound **12**: ^{13}C NMR (75 MHz, CD_3COCD_3) δ = 155.45 (C), 154.94 (C), 155.87 (C), 154.58 (C), 154.15 (C), 152.77 (C), 146.35 (C), 145.93 (C), 145.70 (C), 145.65 (C), 132.36 (C), 130.55 (C), 120.60 (CH), 119.99 (CH), 116.11 (CH), 115.79 (CH), 115.69 (CH), 115.15 (CH), 107.12 (C), 106.20 (C), 102.13 (C), 101.88 (C), 97.35 (CH), 96.00 (CH), 84.31 (CH), 82.58 (CH), 68.42 (CH), 67.65 (CH), 28.93 ($2CH_2$), 17.37 (CH_2). ^{1}H NMR (300 MHz, CD_3COCD_3) δ = 7.00 (d, J = 1.2 Hz, 1H), 6.86–6.78 (m, 3H), 6.76 (d, J = 7.8 Hz, 1H), 6.69 (dd, J = 7.8, 1.2 Hz, 1H), 6.16 (s, 1H), 5.92 (s, 1H), 4.78 (d, J = 7.8 Hz, 1H), 4.52 (d, J = 7.8 Hz, 1H), 4.20–4.14 (m, 1H), 3.97–3.90 (m, 1H), 3.69 (s, 2H), 2.99 (dd, J = 16.5, 5.7 Hz, 1H), 2.81 (dd, J = 16.5, 5.4 Hz, 1H), 2.60 (dd, J = 17.0, 8.7 Hz, 1H), 2.45 (dd, J = 16.8, 7.8 Hz, 1H). ESI MS *m/z* (%) 593 (MH^+) (100), 441 (10), 303 (10). Product ions [593]: 441, 423, 303, 291. Compound **13**: ^{13}C NMR (75 MHz, CD_3COCD_3) δ = 158.11 (C), 156.93 (2C), 155.42 (C), 154.93 (C), 152.73 (C), 146.33 (C), 145.92 (C), 130.69 (C), 120.55 (CH), 116.12 (CH), 115.68 (CH), 106.28 (C), 106.22 (C), 101.71 (CH), 97.49 (CH), 96.52 (2CH), 84.25 (CH), 67.78 (CH), 29.14 (CH_2), 17.01 (CH_2). ^{1}H NMR (300 MHz, CD_3COCD_3) δ = 7.06 (d, J = 1.2 Hz, 1H), 6.95–6.90 (m, 2H), 6.19 (s, 1H), 5.97 (s, 2H), 4.82 (d, J = 7.8 Hz, 1H), 4.21–4.18 (m, 1H), 3.72 (s, 2H), 3.09–3.02 (m, 1H + 1OH), 2.65 (dd, J = 15.6, 8.1 Hz, 1H). ESI MS *m/z* (%) 429 (MH^+) (100), 411 (10), 277 (80). Product ions [429]: 411, 303, 289, 277, 151.