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Anti-AIDS agents 68. The first total synthesis of a unique potent anti-HIV chalcone from genus *Desmos*

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Abstract—The first total synthesis of a unique highly functionalized and potent anti-HIV chalcone **1**, isolated from genus *Desmos*, was achieved from commercially available 2,4,6-trihydroxytoluene (**3**) or 2,4,6-trihydroxybenzaldehyde (**2**) in five (from **3**) or six steps (from **2**).

Desmos (Annonacease) spp., distributed in southern Asia, are widely used as folk medicines in China as antimalarial, insecticidal, antirheumatic, antispasmodic, and analgesic agents.[1] In our recent study of the anti-HIV-1 effects of selected flavonoids from these species,[2] chalcone **1**, 2-methoxy-3-methyl-4,6-dihydroxy-5-(3′-hydroxy) cinnamoylbenzaldehyde, isolated from the roots of *Desmos dumosus* in 1999,[3] demonstrated potent activity with $EC_{50} = 0.022$ μg/mL and therapeutic index = 489. This was the first report that β-hydroxychalcones possess promising anti-HIV activity, although other biological activities of related β-hydroxychalcones have been reported.[4]

Chalcone **1** was first isolated from *Unona lawii* in 1976 by Joshi et al.[5] Due to chelation of all three hydroxy groups, enolic form **1a** is more favorable than either the conceivable diketo form **1b** or cyclic hemiketal forms **1c** and **1d**. ^{1}H NMR analysis[6] confirmed this postulate based on the three OH protons observed at very low fields (15.23, 14.75, and 14.33 ppm) (Fig. 1). The stabilization of **1** by three H-bonds is unique. Not many β-hydroxychalcones have been isolated from natural products,[7] as they are usually easily transformed into related flavone skeletons.

Chalcone **1** strongly attracted our interest as both a challenging synthetic target, because it contains a unique highly functionalized A-ring bearing an aldehyde, and an anti-HIV candidate, due to its notable anti-HIV activity. We report herein the first short total synthesis of chalcone **1** without the use of any protecting groups (Scheme 1).

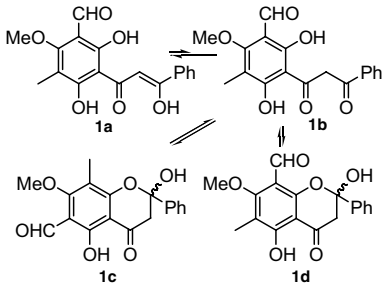
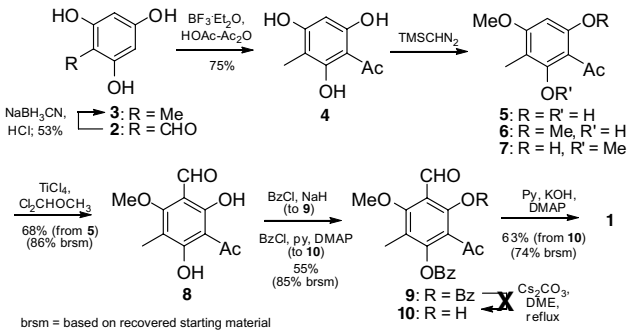


Figure 1.



Scheme 1.

Keywords: Chalcone; Anti-HIV; *Desmos*.
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2,4,6-Trihydroxybenzaldehyde **2** was reduced under acidic conditions[8] to 2,4,6-trihydroxytoluene **3**, which is also commercially available. Compound **3** was treated with HOAc in the presence of Ac_2O[9] and $BF_3{\cdot}OEt_2$ to obtain monoacetyl **4**[10] in a 75% yield. The subsequent methylation of **4** was dependent on the reaction temperature. After monomethylation to give **5**, a second methylation could occur, preferably on the less hindered phenolic position to provide **6**, rather than on the OH between the methyl and acetyl groups to give **7**.[11] For example, with 3 M equiv of $TMSCHN_2$ at rt, compounds **5**, **6**, and **7** were obtained in 16%, 44%, and 12% yields, respectively. The structures of dimethoxy compounds **6** and **7** were determined from NOESY spectral data (Fig. 2). The major and more polar dimethoxy product **6** showed NOE cross-peaks between the aromatic proton and both dimethoxy groups. In contrast, in the minor dimethoxy product **7**, the aromatic proton was correlated with only one methoxy group, while the second methoxy group was correlated with both methyl and acetyl protons. Attempts at demethylation of **6** or **7** into monomethoxy **5** using $AlCl_3$ or $LiPPh_2$[12] were unsuccessful. However, selective monomethylation of the most acidic hydroxy group on **4** was accomplished by a careful treatment with excess $TMSCHN_2$ at −40 °C. Compound **5** was obtained in a 47% yield together with a 30% yield of recovered starting material, which was recyclable.

Monomethoxy **5** was formylated with Cl_2CHOCH_3 in the presence of $TiCl_4$[13] to obtain **8** in a 68% yield as a separable mixture of rotational isomers **8a** and **8b** (Fig. 3).[14] The major isomer (**8a**) was less polar and more stable than the minor isomer (**8b**). In the ^1H NMR spectrum of **8a**, the hydroxy protons were present at 15.02 and 14.10 ppm, compared with 14.01 and 12.56 ppm in **8b**. The significant downfield shift was indicative of strong hydrogen bonding for both hydroxy protons. Accordingly, we determined the structures of **8a** and **8b** as shown in Figure 3. Moreover, purification of **8b** was difficult because of its ready transformation into the more stable **8a**.

Treating **8** with excess BzCl in the presence of NaH gave the dibenzoate ester **9** in an 81% yield (Scheme 1). However, the conversion of **9** directly to the desired β-hydroxychalcone or selectively to the monobenzoate **10** by removing one benzoyl group[15] was difficult. Therefore, in an alternate esterification, the treatment of **8** with BzCl (1.6 equiv) in the presence of DMAP (1.0 equiv) in pyridine at 60 °C proceeded regioselectively to give monobenzoate **10** in a 55% yield, along with a 35% yield of recyclable recovered starting material. The structure of **10** was verified from NOESY spectroscopic data, which revealed NOE between the aldehyde and the hydroxy protons as well as between the 2′,6′-protons and the methyl and acetyl protons (Fig. 4). The Baker–Venkataraman rearrangement[16] of **10** was performed using KOH powder in pyridine at 50 °C for 4.5 h in order to transfer the benzoyl group to the methyl of the acetyl group and obtain the desired chalcone **1** in a 74% yield (based on recovered starting material).

In a second attempted synthetic route to the desired β-hydroxychalcones, the chalcone skeleton was constructed before formylation (Scheme 2). Chalcone **11**, which readily converts to cyclic hemiketal forms,[17] and chalcone **12**[18] were obtained in good yields in a one-pot reaction using Kraus conditions[19] from monomethoxy **5** and dimethoxy **6**, respectively. For chalcone **13**, dimethoxy compound **7** was first treated with BzCl in the presence of NaH to provide the corresponding benzoate ester, which then underwent an acyl shift under basic conditions (Py, KOH). The attempted formylation of **11** and **12** via the Reimer–Tiemann reaction using basic conditions ($CHCl_3$, n-Bu_4N, NaOH)[20] gave only decomposition products. The aforementioned Cl_2CHOCH_3 method or Vilsmeier[21] and Gattermann[22] reactions did not give the desired products but rather gave flavone mixtures **14**,[23] **15**,[23,24] and **16**,[25] **17**, respectively, due to the acidic conditions. Compound **17** was produced by formylation at the active methylene between the 1,3-diketone, followed by cyclization. Flavones **14**–**16** could not be cleaved to the corresponding β-hydroxychalcones despite repeated attempts under basic conditions. However, **11**–**17** are well suited for a planned structure–activity relationship (SAR) study.

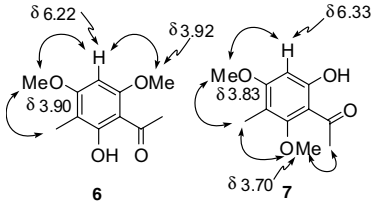


Figure 2. NOESY correlations of dimethoxy **6** and **7**.

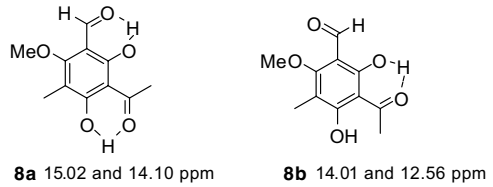


Figure 3. Rotational isomers of **8** and ^1H NMR chemical shifts of the hydroxy groups.

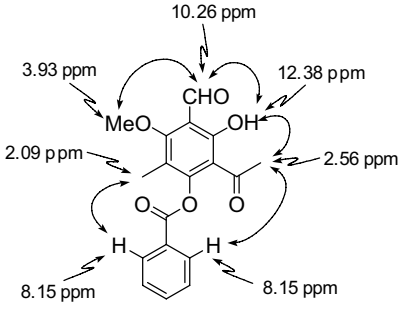
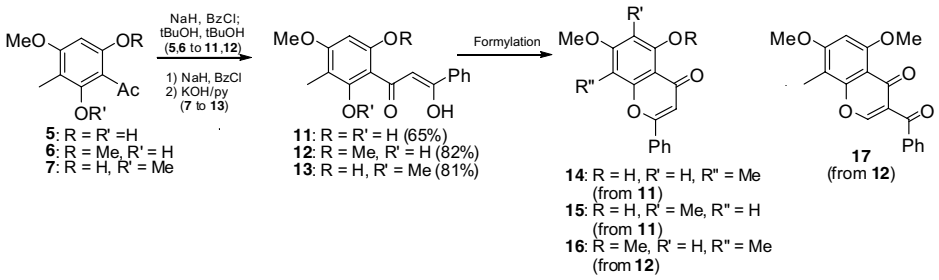
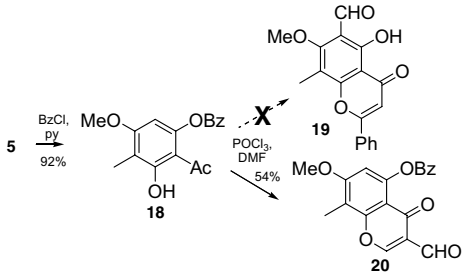


Figure 4. NOESY correlations of monobenzoate ester **10**.



Scheme 2.



Scheme 3.

As shown in Scheme 3, monobenzoate ester **18** was obtained in a 92% yield by treating **5** with BzCl in pyridine. We expected that the subsequent formylation of **18** would occur on the aromatic position, to hopefully provide formylated flavone **19**. However, the Vilsmeier reaction of **18** instead gave chromenone **20**. The acetyl group, rather than the aromatic ring, apparently reacted first followed by cyclization and formylation.[26] The structure of **20** is similar to that of **17** and was confirmed by NOESY and HMBC experiments (Fig. 5).

In summary, we succeeded in the first total synthesis of potent anti-HIV-1 chalcone **1** in five or six simple steps without any protecting groups. This straightforward synthetic strategy can be efficiently modified to produce derivatives for SAR studies or with improved pharmacological properties (Fig. 6). For example, starting with various trihydroxyacylphenones (**21**) rather than **2** or using various substituted aromatic acyl chlorides in the fifth step should give many different β-hydroxychalcones (**22**). The synthesis of additional modified **1**-analogs to establish SAR and generate an optimized anti-HIV lead is in progress.

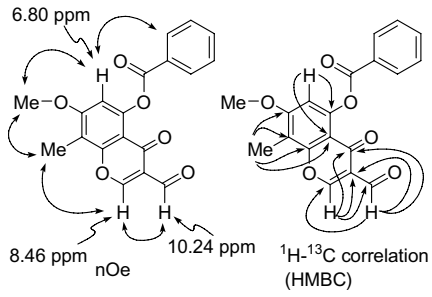


Figure 5. NOESY and HMBC correlations of **20**.

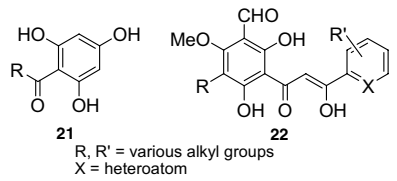


Figure 6.

Acknowledgement

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Supplementary data

Experimental procedures and full characterization details. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.110.

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