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Synthesis of an epoxyquinol analog: efficient methodology for the insertion of side chains into cyclohexenone cores

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ABSTRACT

A novel epoxyquinol analog was prepared by molecular simplification of monomeric and dimeric scaffolds. A feasible methodology for the insertion of side chains into cyclohexenone skeleton was developed. Insertion of the hydroxymethyl side chain was achieved through α-sulfonylcarbanion chemistry. The alkenyl chain was inserted through palladium cross-coupling strategy.

Cyclic epoxyquinols are relatively abundant in nature and display a wide range of biological activities.[1] Several compounds of this type, such as torreyanic acid, ambuic acid, and epoxyquinols A, B, and C (Scheme 1) have been studied due to their attractive and complex structures, and promising biological properties. In relation to these structures it is common to find dimers along with their corresponding monomers in the same natural source. Torreyanic acid, a dimeric epoxyquinone which exhibits antitumor properties, was isolated from *Pestalotiopsis microspora*, an endophytic fungus associated to *Torreya taxifolia*.[2] The related monomer, ambuic acid, was isolated from the same fungus; it is a highly functionalized epoxyquinol with antifungal activity.[3] Highly oxygenated heptacyclic structures, such as epoxyquinols A, B, and C, and epoxytwinol A, exhibiting interesting antiangiogenic activities, were isolated from an unidentified fungus along with their monomer ECH, a receptor-mediated apoptosis inhibitor.[4,5] Biosynthesis of torreyanic acid and epoxyquinols is likely to occur through an oxidative dimerization cascade pathway that involves a Diels–Alder dimerization between two epimeric 2*H*-pyrans, which are constructed from the natural monomers.[2,6–12] Stereochemistry of torreyanic acid and epoxyquinol A arises as a consequence of the opposite orientation of the side chains in the *endo* [4+2] adduct. Inspired by this dimerization cascade several research groups have embraced biomimetic approaches for the synthesis of these structurally attractive compounds.[7,8,13–19]

As part of our ongoing program concerning asymmetric synthesis of natural epoxyquinols,[20–22] our research group developed a new strategy for the introduction of the side chains of these complex natural products. In this approach, molecular simplifications of the mentioned structures were designed, aiming to develop an efficient methodology and to prepare simplified analogs. Scheme 1 shows the simplifications proposed for ambuic acid and ECH for the synthesis of deoxygenated monomers, as well as torreyanic acid and epoxyquinol simplifications for the synthesis of deoxygenated dimers.

The proposed methodology for the insertion of a methoxymethyl chain is shown in Scheme 2. It is based on the acidity of α-sulfonyl hydrogen atoms. This strategy has been previously used in our research group for the synthesis of prelunularin.[23] For this purpose, Michael addition of sodium *p*-toluensufinate followed by basic conditions generates the α-sulfonylcarbanion that attacks the appropriate electrophile.[24–27] Further α-halogenation followed by palladium cross-coupling reaction allows the insertion of the alkenyl side chain.[28]

Introduction of a hydroxymethyl chain precursor was possible through derivatization of the β position of the α,βunsaturated ketone. Michael addition of sodium *p*-toluensulfinate on cyclohexenone in acidic conditions afforded **1** in 73% yield. Carbonyl protection with ethyleneglycol afforded compound **2** in 99% yield. In the presence of *n*-BuLi this compound acts as an excellent nucleophile against choromethylmethylether and compound **3** was obtained in 60% yield. Acidic treatment of this compound leads to ketal hydrolysis and elimination of *p*-toluensulfinic acid.[23] Therefore, restoring the α,β-insaturated ketone with HF afforded **4**[29] in

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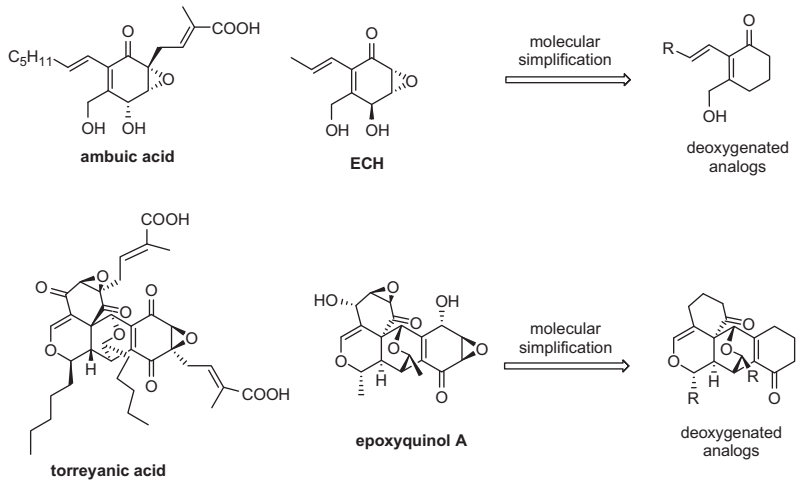
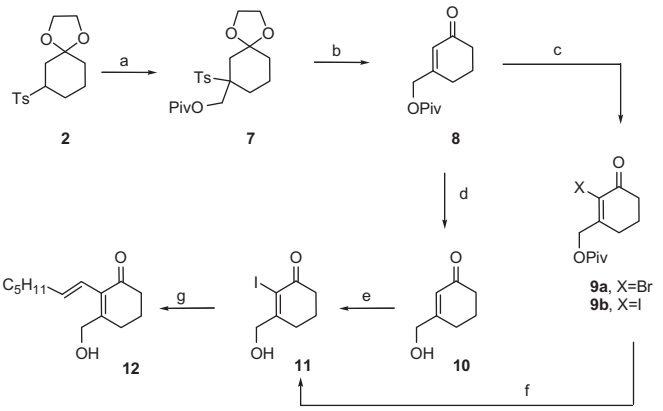


Scheme 1. Molecular simplification of ambuic acid, ECH and dimeric compounds.

87% yield. An addition-elimination reaction of iodine in the presence of DMAP[30] permits to obtain **5** in 40% yield. Finally, Suzuki cross-coupling reaction[28] between β-iodoenone **5** and *trans*-1-heptenyl boronic acid[31] leads to deoxygenated monomer analog **6**.

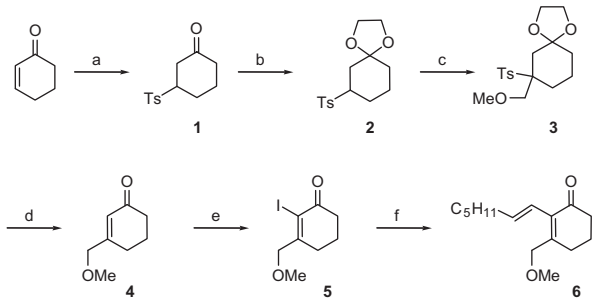
To be able to study oxidative dimerization of this type of deoxygenated analogs, the electrophile used to functionalize β-position must be changed, in order to insert a substituent that can be easily converted into a free alcohol.

Similarly, compound **2** affords **7** in 78% yield in the presence of chloromethylpivalate[32] and *n*-BuLi (Scheme 3). Ketal hydrolysis occurs with simultaneous elimination in acidic medium producing compound **8** in 56% yield as described above. α-Halogenation was performed under several conditions. Only trace amounts of the expected halogenated products were obtained (compounds **9a–b**). The reaction course appeared to be sensitive to steric hindrance of the substituted olefin. So, we decided to remove the pivalic ester by reacting **8** with K_2CO_3 and MeOH. α-Halogenation of hydroxymethylenone **10**[33] occurs in 40% yield to afford enone **11**. Attempts to optimize the halogenation yield of **10** and **4** did not result in significant improvements. The alkenyl side chain was inserted by the cross-coupling protocol previously mentioned to afford deoxygenated analog **12** in 51% yield. Oxidation of **12** with *o*-iodoxybenzoic acid (IBX) triggers the reaction to **13**[34] through a electrocyclization-Diels–Alder cascade (Scheme 4). Relative stereochemistry of this product was deduced by comparison of spectral data with torreyanic acid[7] and epoxyquinol A,[15] displaying the two pentenyl side chains opposite one another as already seen in these natural products.

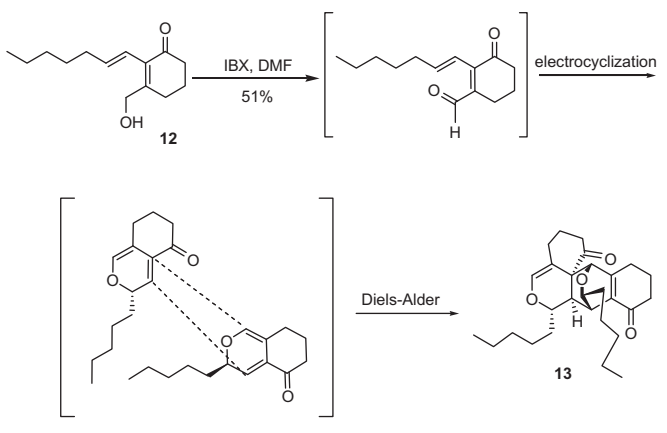


Scheme 3. Insertion of hydroxymethyl and alkenyl chains for the synthesis of deoxygenated analogs **10** and **12**. Reagents and conditions: (a) $PivOCH_2Cl$, *n*-BuLi, THF, 0 °C to rt, 3 h, 78%; (b) HF aq, CH_3CN, rt, 4 h, 56%; (c) **9a**: Br_2, NEt_3, CH_2Cl_2, reflux, 12 h, 5%, **9b**: I_2, DMAP, CH_2Cl_2, reflux, 12 h, 5%; (d) K_2CO_3, MeOH, rt, 5 h, 93%; (e) I_2, DMAP, CH_2Cl_2, reflux, 8 h, 40%; (f) K_2CO_3, MeOH, rt, 5 h, 55%; (g) $H_{11}C_5CH{=}CHB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, THF, H_2O, reflux, 12 h, 51%

To summarize, the methodology developed for the insertion of side chains present in epoxyquinol-type natural products, proved to be useful for the preparation of novel deoxygenated analogs.



Scheme 2. Insertion of methoxymethyl and alkenyl chains over cyclohexenone for the synthesis of deoxygenated analogs **4** and **6**. Reagents and conditions: (a) *p*-TsNa, AcOH, MeOH, rt, 24 h, 73%; (b) ethyleneglycol, *p*-TsOH, toluene, reflux, 2 h, 99%; (c) CH_3OCH_2Cl, *n*-BuLi, THF, rt, 2 h, 60%; (d) HF aq, CH_3CN, rt, 4 h, 87%; (e) I_2, DMAP, CH_2Cl_2, reflux, 8 h, 40%; (f) $H_{11}C_5CH{=}CHB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, THF, H_2O, reflux, 12 h, 27%.



Scheme 4. Oxidative dimerization of **12**.

In a model study, we have previously achieved the total asymmetric synthesis of a simplified analog of ambuic acid[20] and naturally occurring epoxyquinols,[21] through a chemoenzymatic strategy. The coupling methodology described in this work will be useful for the synthesis of natural epoxyquinols. Synthetic results, as well as results concerning biological evaluation of analogs will be reported in due course.

Acknowledgments

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34. *Spectral data for* **13**: ^{1}H NMR ($CDCl_3$) δ (ppm) 6.36 (d, J = 1.2 Hz, 1H), 4.57 (s, 1H), 4.23 (dt, J_1 = 0.9 Hz, J_2 = 7.2 Hz, 1H), 4.06 (dd, J_1 = 4.5 Hz, J_2 = 9.8 Hz, 1H), 3.23 (t, J = 1.6 Hz, 1H), 2.54 (m, 9H), 2.26 (m, 2H), 2.17 (m, 2H), 2.00 (m, 4H), 1.24 (m, 12H), 0.85 (m, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) 203.7, 190.4, 138.7, 128.0, 113.3, 100.0, 79.1, 73.2, 72.4, 53.4, 38.7, 37.5, 37.2, 36.3, 35.1, 32.7, 31.8, 31.4, 31.3, 29.7, 27.7, 26.2, 25.0, 22.7, 22.6, 22.5, 14.0; IR (KBr) 2926, 2855, 1726, 1670, 1273, 1348, 722 cm^{-1}; HRMS: m/z calcd $(C_{28}H_{40}O_4Na)^+$: 463.2827; exp: 463.2810.