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Synthesis of methoxy and hydroxy containing tetralones: versatile intermediates for the preparation of biologically relevant molecules

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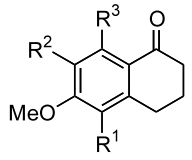
Abstract—The synthesis of 5-hydroxy-6-methoxy-1-tetralone and the 7-hydroxy regioisomer along with the corresponding 5,7-dihyroxy analog has been achieved using an efficient directed metallation procedure followed by a regioselective methylene oxidation. This methodology represents a general synthetic route for the preparation of highly oxygenated tetralone analogs which are versatile building blocks for the construction of molecules of biological interest.

Tetralones bearing different oxygen functional groups on the aromatic ring are important intermediates for the synthesis of a wide variety of compounds, many of which are useful as chemotherapeutic agents. In the course of our studies on the synthesis and biological activity of vascular targeting agents,[1] we found that 3,4-dihydronaphthalene systems, bearing an aryl substituent at the 1-position, show varying degrees of biological efficacy in terms of inhibition of tubulin assembly. We further noticed that the presence of a methoxy group at the 6-position of the dihydronaphthalene ring greatly enhances the tubulin binding properties in comparison to the compounds having methoxy groups at other positions.[2] In terms of structural activity relationship studies, we were curious in regard to what effect a second or third oxygen function on the aromatic ring would have in terms of biological activity with the tubulin-microtubule system. Accordingly, we decided to introduce hydroxy groups on the aromatic ring of the dihydronaphthalene, which could then be converted to water-soluble functional groups (such as disodium phosphate salts) in order to carry out in vivo studies of these compounds to determine their efficacy as vascular targeting agents for cancer chemotherapy. Herein, we report our approaches for the construction of tetralones of general structure **1** (Fig. 1), which are the basic building blocks for conversion to 3,4-dihydronaphthalene systems substituted at the 1-position.

LaLonde and co-workers have reported the synthesis of 6-methoxy-7-hydroxy-1-tetralone by DDQ oxidation of 6-methoxy-7-acetoxy-1,2,3,4-tetrahydronaphthalene.[3] Although the synthesis of 5-hydroxy-6-methoxy-1-tetralone was not reported, we found this pathway to be an attractive one. We selected inexpensive commercially available 6-methoxy-1,2,3,4-tetrahydronaphthalene (**2**) as the starting material. After exploring a variety of different methods,[4] with limited success, we found that a slightly modified procedure by Beak and co-workers[5] led to the conversion of tetrahydronaphthalene **2** to 5-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (**3**) and 7-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (**4**) in approximately 1:2 ratio in 69% overall yield (Scheme 1). Thus, a mixture of tetrahydronaphthalene **2** and TMEDA was treated with *sec*-butyllithium at



1

a, R^1 = OH, R^2 = H, R^3 = H
b, R^1 = OH, R^2 = OMe, R^3 = H
c, R^1 = H, R^2 = OMe, R^3 = OH
d, R^1 = R^2 = OH, R^3 = H

Figure 1.

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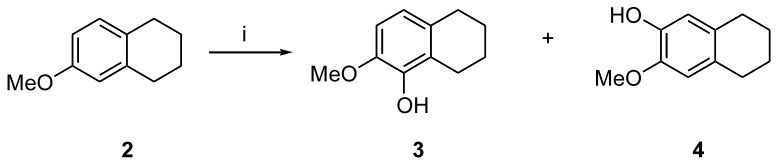
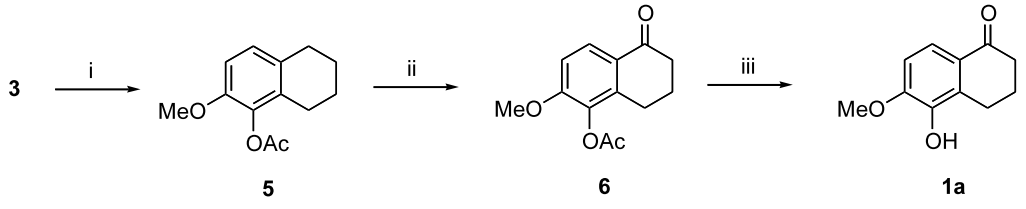


Scheme 1. *Reagents and conditions*: (i) (a) TMEDA, 1.3 (M) *sec*-BuLi, 0°C, 45 min at rt, (b) $B(OMe)_3$, 0°C, 1 h at rt, (c) HOAc, 35% H_2O_2, 0°C, overnight at rt, 69%, ratio **3**/**4**:1/2.

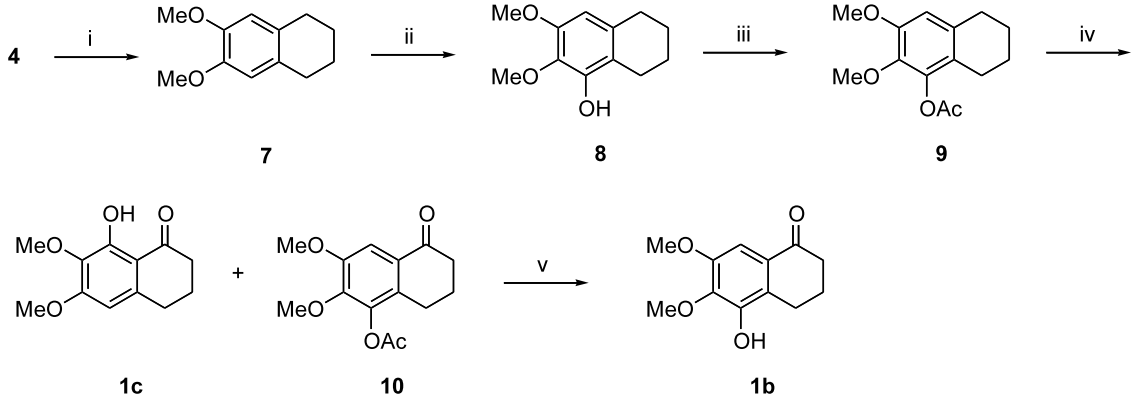
room temperature to generate the anion. Trimethyl borate was then added and the resultant mixture was subsequently treated with acetic acid and 35% hydrogen peroxide to form the hydroxytetrahydronaphthalenes **3** and **4** (Scheme 1), which were easily separated by column chromatography. The 5-hydroxy isomer **3** was converted to 5-acetoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (**5**) in 95% yield (Scheme 2). Reaction of the acetoxytetrahydronaphthalene **5** with DDQ in dioxane–water (LaLonde's conditions[3]) led to the formation of tetralone **6** as a single isomer in 96% yield. The correct position of the keto group was confirmed by X-ray crystallography.[6] The *para*-directing effect of the methoxy group led to exclusive formation of tetralone **6**. The acetate was removed by treating tetralone **6** with sodium bicarbonate in methanol to form 5-hydroxy-6-methoxy-1-tetralone (**1a**).[7,8]

In order to further extend the SAR, it proved desirable to introduce a second methoxy group onto the aromatic ring of the tetralone, keeping the position of the hydroxy group intact. The 7-hydroxy isomer (**4**) is the ideal precursor for obtaining 5-hydroxy-6,7-dimethoxy-1-tetralone (**1b**). 6-Methoxy-7-hydroxy-1,2,3,4-tetrahydronaphthalene (**4**) was converted to 6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (**7**) by refluxing with dimethyl sulfate and potassium carbonate in acetone in nearly quantitative yield (Scheme 3). The hydroxy group was introduced smoothly, using the earlier procedure, to form 5-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (**8**), which was converted to the acetate **9** and treated with DDQ. The two tetralones **10** and **1c** were obtained in a 1:1.5 ratio in 78% yield. Due to the steric congestion that may occur between the acetoxy at the 8-position and the keto group in tetralone **1c**, the acetate group proved to be labile during the course of the reaction. Tetralone **1c** was formed in higher amount possibly due to the greater stability of the product provided by hydrogen bonding between the phenolic hydrogen and the keto group (evident from the extremely downfield shift of the phenolic proton to δ 12.39). Tetralone **10** was converted to tetralone (**1b**) by treatment with potassium carbonate.

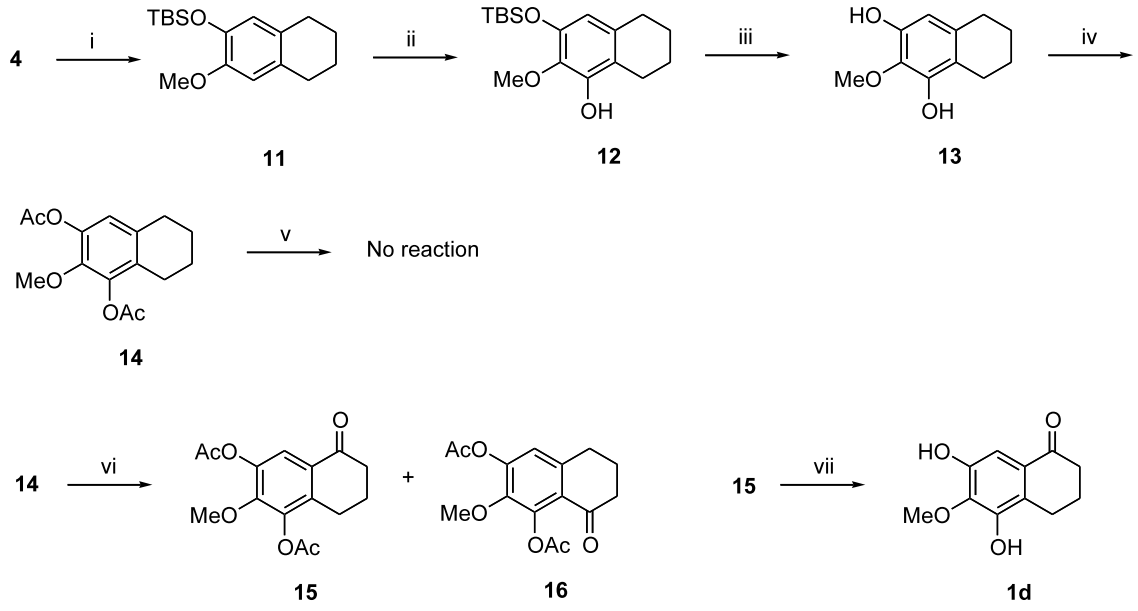
In order to study the effect of two hydroxy groups on the aromatic ring of the 3,4-dihydronaphthalene system in terms of tubulin binding properties, it proved neces-



Scheme 2. *Reagents and conditions*: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95%; (ii) DDQ, dioxane, 96%; (iii) $NaHCO_3$, MeOH, 90%.



Scheme 3. *Reagents and conditions*: (i) Me_2SO_4, K_2CO_3, acetone, reflux, 30 min, 94%; (ii) (a) TMEDA, 1.3 (M) *sec*-BuLi, 0°C, 45 min at rt, (b) $B(OMe)_3$, 0°C, 1 h at rt, (c) HOAc, 35% H_2O_2, 0°C, overnight at rt, 69%; (iii) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (iv) DDQ, dioxane, 69%, ratio **1c**/**10**:1.5/1; (v) K_2CO_3, MeOH.



Scheme 4. *Reagents and conditions*: (i) TBSCl, imidazole, DMAP, CH_2Cl_2, 73%; (ii) (a) TMEDA, 1.3 (M) *sec*-BuLi, 0°C, 45 min at rt, (b) $B(OMe)_3$, 0°C, 1 h at rt, (c) HOAc, 35% H_2O_2, 0°C, overnight at rt, 31%; (iii) 1 M TBAF, CH_2Cl_2, 0°C; (iv) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 73% (two steps from **12**); (v) DDQ, dioxane; (vi) CrO_3, HOAc, H_2O, 54% of **15**, 5% of **16**; (vii) K_2CO_3, MeOH, 81%.

sary to synthesize 5,7-dihydroxy-6-methoxy-1-tetralone (**1d**). Protection of the 7-hydroxy group in the tetrahydronaphthalene **4** as its corresponding TBS ether (**11**) proceeded in high yield (Scheme 4). In regard to regioselective introduction of the hydroxy group, we anticipated that due to different *ortho*-directing effects of methoxy and -OTBS groups, it should prove possible to obtain one of the isomers in a much higher amount over the other. Accordingly, when tetrahydronaphthalene **11** was treated sequentially with *sec*-butyllithium-TMEDA, trimethylborate, acetic acid, and 35% hydrogen peroxide, to our pleasant surprise, 5-hydroxy-6-methoxy-7-(*tert*-butyldimethylsiloxy)-1,2,3,4-tetrahydronaphthalene (**12**) was obtained as a single product. Quite possibly the superior *ortho*-directing effect of the methoxy over the -OTBS group directs the hydroxy group to the 5-position. The TBS protecting group was removed by treating tetrahydronaphthalene **12** with 1 M TBAF in THF and the two hydroxy groups of tetrahydronaphthalene **13** were converted to the corresponding acetates to give 5,7-diacetoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (**14**). Unfortunately, all of our efforts to convert the tetrahydronaphthalene **14** to the corresponding tetralone failed using DDQ under various conditions. In order to overcome the problem of oxidation, we considered different oxidizing agents. After various trials, chromium(VI) oxide in acetic acid–water was found to be the reagent of choice. Thus, tetrahydronaphthalene **14** was converted to 5,7-diacetoxy-6-methoxy-1-tetralone (**15**)[9] in 54% yield. Approximately 5% of isomeric tetralone **16** was also formed. Again in this case, the *para*-directing effect of the methoxy group led to the formation of the tetralone **15** predominantly. The acetates in tetralone **15** were removed by treatment with potassium carbonate in methanol to produce 5,7-dihydroxy-6-methoxy-1-tetralone (**1d**). Structural assignment of regioisomers **15** and **16** was accomplished by spectral characterization in analogy to tetralone **6**. In the ^1H NMR of tetralone **6**, the hydrogen atom at C-8 appears approximately 1 ppm downfield compared to the corresponding hydrogen atom in tetrahydronaphthalene **5** due to the deshielding effect of the carbonyl group. Since the structure of **6** is established by X-ray analysis, we can unequivocally assign the NMR values for the hydrogen atoms at C-7 and C-8 in tetralone **6**. By analogy, in tetralone **15**, the hydrogen at C-8 shifts downfield nearly 1 ppm compared to tetrahydronaphthalene **14**. However, in tetralone **16**, the NMR shift of the hydrogen at C-8 remains almost unchanged from **14**.

In conclusion, we have synthesized a number of 1-tetralone analogs, incorporating hydroxy and methoxy functionality on the aromatic ring. Although there certainly are a wide variety of other synthetic approaches to the tetralone core structure,[8,10] including ring closing reactions, that could potentially be employed to form the analogs detailed herein, the methodology, as described, represents a facile and versatile entry into these oxygenated tetralone derivatives. Work is underway to convert these analogs to 1-aryl-substituted 3,4-dihydronaphthalene derivatives and to evaluate their tubulin binding properties and their efficacy as vascular targeting agents for cancer chemotherapy.

Acknowledgements

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6. Structure of tetralone (**6**) was confirmed by single-crystal X-ray analysis, Kautz, J.; Pinney, K. G. Baylor University, unpublished results, 2002.
7. 5-Hydroxy-6-methoxy-1-tetralone (**1a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (m, 2H), 2.60 (t, 2H, $J=6.2$ Hz), 2.93 (t, 2H, $J=6.1$ Hz), 3.95 (s, 3H), 5.75 (bs, 1H), 6.83 (d, 1H, $J=8.6$ Hz), 7.68 (d, 1H, $J=8.6$ Hz).
8. A thorough search of the peer-reviewed literature reveals no reference to tetralone **1a** to date. However, after our study was complete, we discovered a report of the synthesis of this compound contained in two patent applications. This route relies on the initial synthesis of 5,6-dimethoxy-1-tetralone by a somewhat lengthy but noteworthy synthesis (Lahiri, S.; Ramarao, C.; Rao, B. V.; Rao, A. V. R.; Chorghade, M. S. *Organic Process Research & Development*, **1999**, *3*, 71) followed by the regioselective deprotection of the 5-methoxy group ((a) Denny, W. A.; Hutchings, R. H.; Johnson, D. S.; Kaltenbronn, J. S.; Lee, H. H.; Leonard, D. M.; Milbank, J. B. J.; Repine, J. T.; Rewcastle, G. W.; White, A. D. *PCT Int*. *Appl*., 2001, WO 01/79180; (b) Day, W. W.; Johnson, K. A.; Prakash, C. A.; Eggler, J. F. *PCT Int*. *Appl*., 2001, WO 01/77093). It is our contention that the route we describe in this manuscript is both highly versatile and extremely efficient in terms of preparing hydroxy and alkoxy containing tetralone analogs, and as such, is advantageous over the previously reported route.
9. 5,7-Diacetoxy-6-methoxy-1-tetralone (**15**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08–2.14 (m, 2H), 2.32 (s, 3H), 2.36 (s, 3H), 2.61 (t, 2H, $J=6.6$ Hz), 2.74 (t, 2H, $J=6.0$ Hz), 7.69 (s, 1H).
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