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Synthesis of benzyl substituted naphthalenes from benzylidene tetralones

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Abstract

A convenient and efficient synthesis of novel highly substituted dimethoxybenzyl naphthalenes, which are precursors to several dihydroxynaphthoic acids, is described. The approach involves the use of aldol chemistry to provide a number of benzylidene tetralones, which are converted to the target naphthalenes in three steps, with good to excellent yields. Grignard reaction of intermediate benzyl tetralones provided 1-substituted benzyl naphthalenes. The reported synthesis is flexible and scalable and provides access to naphthalenes having a variety of substitution patterns. These benzyl substituted naphthalenes are being converted to naphthoic acids and the bioactivities of these compounds are currently being investigated.

Keywords

Benzylidene tetralone; Benzylnaphthalene; Benzyltetralone

One area of our research focuses on the synthesis of highly substituted naphthoic acids as therapeutics for breast, prostate, and pancreatic cancers. 7-Benzyl-2,3-dihydroxy-6-methyl-4-propyl-1-naphthoic acid, compound **1**, has been shown to inhibit lactate dehydrogenase A (LDHA) reducing ATP levels and importantly inducing significant oxidative stress and cell death in cancer cells (Fig. 1).¹ Compound **1** also inhibits tumorigenesis in human lymphoma and pancreatic cancer xenograft models and along with another inhibitor induces lymphoma regression. The structure of compound **1** is modeled on the structure of the natural product gossypol, compound **2**, which occurs in cottonseed (Fig. 1). Gossypol itself exhibits multiple biological properties including spermicidal,² antiparasitic,^{3–6} anticancer^{7–10} and antiviral.^{11–14} Multiple bioactivities of gossypol have stimulated wide interest in the development of gossypol derivatives to explore structure–activity relationships (SARs).^{15–20} Unfortunately gossypol is toxic, due to the aldehyde groups, and derivatives which do not have an aldehyde functional group retain or show enhanced biological activity. However, these derivatives are not selective inhibitors.¹⁴ Dihydroxynaphthoic acids, which can be viewed as analogs of gossypol, are selective non-

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Supplementary data

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toxic inhibitors of LDHA. Our interest lies in synthesizing several analogs of compound **1** that could be tested for the inhibition of LDHA with the hope of developing more potent inhibitors.

The precursors needed for the synthesis of various analogs of compound **1** are benzyl substituted dimethoxynaphthalenes, similar structurally to compound **3** (Fig. 1). In order to explore SARs of various benzyl substituted naphthoic acids we developed a short, efficient, and convenient synthetic scheme to synthesize benzyl substituted dimethoxynaphthalenes from benzylidene tetralones. The synthetic schemes were designed to provide a number of 7-benzyl substituted dihydroxynaphthoic acids that could be synthesized from the benzylnaphthalenes. The benzylidene tetralones were synthesized from the known tetralones compounds **10a**²¹ and **10o**¹⁸ and the new tetralone, compound **10m**. Tetralones **10a** and **10o** were synthesized using procedures described in the literature^{18,21} except cyclization of known 4-(3,4-dimethoxyphenyl)butanoic acid to form **10a** was performed using polyphosphoric ester rather than polyphosphoric acid. Polyphosphoric ester produced better yields and purer product.

Compound **10m** was synthesized using a procedure previously described by our group¹⁸ as shown in Scheme 1. Bromination of 1-ethyl-2,3-dimethoxybenzene (**4**) at 0 °C using bromine, via an electrophilic aromatic substitution mechanism, afforded compound **5** in a 90% yield.^{22,23} In some preparations small amounts of another regioisomer 1-bromo-4-ethyl-2,3-dimethoxybenzene were formed. To avoid the formation of both isomers an alternate efficient and highly regioselective silica gel catalyzed synthesis using *N*-bromosuccinimide produced the desired regioisomer in a 97% yield²⁴ and avoided the use of corrosive bromine. Since both isomers display a pair of doublets in the aromatic area of the proton NMR spectra, HMQC and HMBC experiments confirmed that the bromine was ortho to the ethyl group in compound **5**. Additionally, confirmation of formation of the correct regioisomer came from comparison with data from the literature.^{17,18}

The synthesis of compound **7** features the incorporation of the carbon atoms for the second ring of the naphthalene system in one step by the reaction of the Grignard reagent formed from compound **5** with ethyl 3-methyl-4-oxo-2-butenate (**6**) in an 89% yield.^{17,18} Since the precursor, compound **6**, is not readily available, it was prepared by Wadsworth–Emmons reaction of pyruvic aldehyde dimethyl acetal with triethylphosphonoacetate in tetrahydrofuran or dimethylformamide followed by hydrolysis.^{25–27} The *E/Z* ratio of the product is different for the Wadsworth–Emmons reaction in the two solvents but hydrolysis in acid affords 96% of *trans* (*E*) stereospecifically. The *E/Z* ratio of compound **6** did not affect the progress of the subsequent reactions in the synthesis. The stereochemical assignment of the aldehyde, compound **6**, is based upon proton NMR analysis.^{25,26} The Grignard reagent is added slowly to a cold solution of ethyl 3-methyl-4-oxo-2-butenate (**6**) to ensure attack at the more reactive aldehyde carbonyl carbon to give an 89% yield of predominately the *E* ester. To confirm the diastereoselectivity of the reaction and the structure of the product a NOE spectrum (300 MHz) was taken. Irradiation of the methyl group in compound **7** resulted in no enhancement of the resonance of the alkene hydrogen and enhancement of the hydrogen on the alcohol carbon, which verifies that the ester has *E* stereochemistry. Pure ester was isolated by chromatography but reduction of the crude mixture or the pure compound using hydrogen in acetic acid was unsuccessful and afforded a complex mixture. Therefore the crude ester, compound **7**, was saponified using potassium hydroxide in ethanol/water and acidified to give a 90% yield of carboxylic acid, **8**, as an oil that solidified. Trituration and recrystallization from ethyl acetate/hexane afforded compound **8** as a white crystalline solid and was determined to be the *E* isomer by a NOE experiment. The infrared spectrum confirmed the presence of the allylic alcohol group, the carboxyl group and the alkene.

Hydrogenation and hydrogenolysis of the crude or pure acid, **8**, was accomplished using hydrogen in concentrated acetic acid at 60 psi (Parr hydrogenator) and 60 °C in the presence of 10% palladium on charcoal to afford the saturated acid, compound **9**, in a 75% yield. Cyclization with polyphosphoric ester in a Friedel–Crafts type of reaction gave an 88% yield of tetralone **10**. The cyclization reaction gives higher yields and purer product with polyphosphoric ester than with other reagents such as polyphosphoric acid, sulfuric acid or methanesulfonic acid.

Conversion of tetralones **10a**, **10m** and **10o** to benzylnaphthalenes, compounds **14a–14f**, **14h** and **14j–14u** is shown in Scheme 2. Benzyldiene tetralones, compounds **11a–11u**, were readily formed from tetralones **10a**, **10m** and **10o** by aldol condensation of the appropriate aldehyde in ethanolic potassium hydroxide solution in 80–95% yields.^{28–36} The proton NMR spectra of compounds **11a–11u** display a downfield shift of the vinyl proton due to the diamagnetic anisotropy effect of the carbonyl group, which indicates that the benzyldiene compounds are the *E* isomers.³⁷ The 2-bromo compound, **11i**, and the 2-trifluoromethyl compound, **11e**, gave the same type of unexpected result as observed by Yee et al. for the monomethoxy compound (2-(2-bromobenzyldiene)-6-methoxy-1-tetralone) in the proton NMR (300 MHz) spectrum.³⁸ They observed a singlet at 2.9 ppm corresponding to the four CH₂ protons of 3,4-dihydronaphthalene instead of two distinct multiplets at 2.5 and 3.0 ppm. Compound **11i** has one multiplet at 2.9 ppm and compound **11e** has a singlet at 2.9 ppm for the four CH₂ protons of the 3,4-dihydronaphthalene ring system. In all other compounds except for compound **11c**, the four CH₂ protons of the 3,4-dihydronaphthalene are two distinct multiplets at 2.5 and 3.0 ppm. Compound **11c** has two distinct multiplets but at 2.96 and 2.87 ppm. This unexpected degeneracy occurred with *ortho* substituted compounds and did not occur with *meta* or *para* substituted benzyl compounds.

Compounds **11a–11u** were hydrogenated using 10% palladium on charcoal in ethyl acetate for 1 h at 30 psi (Parr hydrogenator) to afford benzyl substituted tetralones, compounds **12a–12u**, in 80–95% yield.^{39–41} Hydrogenation in ethyl acetate using palladium on charcoal for 2 h and/or hydrogenation for 1 h using palladium on calcium carbonate resulted in loss of the double bond and bromine in compounds **11g** and **11i** to give compound **12a**. When compound **11g** was hydrogenated for 2 h in methanol using palladium on charcoal loss of the double bond, bromine, and the carbonyl oxygen resulted, affording compound **15** in a 60% yield.^{38,39} The proton NMR exhibited an upfield shift of the aromatic hydrogen due to the loss of the carbonyl group. The loss of the carbonyl group was also verified by ¹³C NMR and infrared spectroscopy.

Compounds **12a–12u** were reduced to alcohols using sodium borohydride in refluxing ethanol and then dehydrated by refluxing with aqueous hydrochloric acid to form alkenes **13a–13u** in 85–95% yield.¹⁸ The structures were verified by the loss of the carbonyl in the infrared and ¹³C NMR spectra. Furthermore the loss of a chiral center in compounds **12a–12u** by the formation of a double bond in compounds **13a–13u** resulted in well-resolved peaks in the alkyl proton area of the NMR spectrum.

Aromatization of alkenes, **13a–13u**, to compounds **14a–14u** using dichlorodicyano-benzoquinone (DDQ) in refluxing benzene did not give the desired results possibly due to the oxidation of the benzylic methylene carbon. To circumvent this difficulty an alternate aromatization using palladium on carbon in triglyme proved successful and the naphthalene compounds, **14a–14f**, **14h**, and **14j–14u** were obtained in 90–95% yields. It was observed that under these conditions compounds **13g** and **13i**, which have a bromobenzyl substituent, underwent dehalogenation, which was facilitated by the high reflux temperature and the palladium catalyst. As expected, compound **13l** did not undergo dehalogenation.

An attractive route to the formation of 1-substituted benzyl-naphthalenes is reaction of compounds **12a** and **12f** with a Grignard reagent followed by dehydration and oxidation as shown in Scheme 3. Introduction of a group ortho to the benzyl group was easily accomplished by reaction of compounds **12a** and **12f** with methylmagnesium bromide and ethylmagnesium bromide. The resulting tertiary alcohols were readily dehydrated using dilute hydrochloric acid or refluxing with magnesium sulfate in toluene to form alkenes **16a–16c** in an 80% yield.²¹ Aromatization occurred upon refluxing **16a–16c** in triglyme containing 10% palladium on charcoal to afford compounds **17a–17c** in an 80% yield.

In conclusion, a short and convenient synthetic scheme was developed to afford several benzyl substituted naphthalenes that are being converted to naphthoic acids. Bioactivities of these compounds are currently being investigated

Supplementary Material

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Acknowledgments

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Figure 1.

Scheme 1.

Synthesis of tetralone: Reagents and conditions: (a) Br_2 (1 equiv), CH_2Cl_2 , 0 °C to rt, 2 h or NBS (1.1 equiv), silica gel, CCl_4 , rt, 12 h, 90%; (b) Mg (1.5 equiv), $\text{CH}_3\text{CH}_2\text{Br}$ (0.1 equiv), I_2 , THF, reflux, 1.0 h then **6** (1.2 equiv), 0 °C to rt, 12 h, then $\text{H}_2\text{O}/\text{HCl}$, 89%; (c) KOH (4 equiv), EtOH , H_2O , reflux, 8.0 h, then HCl/ice , 90%; (d) H_2 , 10% Pd/C , HOAc , 60 psi, 60 °C, 8h, 75%; (e) PPE, CH_2Cl_2 , reflux, 5 h, then H_2O , 88%.

Scheme 2.

Synthesis of benzyl naphthalenes: Reagents and conditions: (a) R_3CHO (1.1 equiv), 5% KOH/EtOH, rt, 24–36 h, then H_2O , 80–95%; (b) H_2 , 10% Pd/C, EtOAc, 30 psi, rt, 1 h, 83–100%; (c) $NaBH_4$ (2 equiv), EtOH, reflux, 2 h then; (d) 6 M HCl, reflux, 2 h, 85–95%; (e) 10% Pd/C, triglyme, reflux, 5 h, filter then H_2O , 90–95%; (f) **11g**, H_2 , 10% Pd/C, CH_3OH , 30 psi, rt, 2 h, 60%.

Scheme 3.

Synthesis of 1-substituted benzylnaphthalenes: Reagents and conditions: (a) R₂MgBr (1.5 equiv), THF, reflux, 2.0 h, then HCl/H₂O, 75% then; (b) 6 M HCl reflux 2 h or MgSO₄, toluene, reflux, 2 h, 80%; (c) 10% Pd/C, triglyme, reflux, 4 h, filter then H₂O, 80%.