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The synthesis of model compounds for the rearrangement of prephenic acid

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**THE SYNTHESIS OF MODEL COMPOUNDS
FOR THE REARRANGEMENT OF PREPHENIC ACID**

A Thesis

Presented to

The Faculty of the Department of Chemistry

San Jose State University

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

By

Jinghua Yu

December, 1998

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ABSTRACT

The Synthesis of Model Compounds for the Rearrangement of Prephenic Acid

by Jinghua Yu

Because of the importance of prephenic acid in the biosynthesis of many primary and secondary plant metabolites, the chemistry of this compound has drawn scientists' attention for more than 40 years. Stereoelectronic considerations have led us to propose a 1,7/1,2 hydride shift sequence as an alternative to the 1,6 hydride shift currently accepted as the explanation for the base-catalyzed conversion of prephenic acid to *para*-hydroxyphenyllactic acid. To distinguish between these two mechanisms, a series of synthetic analogs of prephenic acid were prepared. In this thesis, synthetic approaches to two model compounds for this rearrangement will be described. Initial experiments on the hydride rearrangements of these compounds will be reported. In addition, other interesting reactions of anthrone derivatives will be discussed and the future directions of this project will be explored.

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Introduction

Prephenic acid (1) is an integral part of the shikimic acid pathway and acts as the biosynthetic precursor for the aromatic amino acids phenylalanine and tyrosine which are human “essential amino acids” (**Scheme 1**).¹ It is a vital connecting link between the “aliphatic” and “aromatic” domains.² Because prephenic acid is very important in cellular metabolism, it has been the subject of substantial research attention. The structure of prephenic acid was first determined by Weiss, et al.³ in 1954, and its essential chemistry was reported by Gilvarg⁴ in 1955. In 1979, Danishefsky’s group² published the total synthesis of prephenic acid and investigated the mechanism of its conversion to *para*-hydroxyphenyllactic acid in aqueous base.

The essential chemistry of prephenic acid (1) is summarized in **Scheme 2**. In acidic medium (2N HCl) at 25 °C, both prephenic acid and its epimer (2) readily convert to phenylpyruvic acid (3). However, in base (2N NaOH) at 100 °C, prephenic acid transforms to *para*-hydroxyphenyllactic acid; its epimer (2) is unreactive. It is this particular transformation which we have investigated.

Scheme 1. The Partial Shikimic Acid Pathway

Scheme 2. Transformation of Prephenic Acid²

Four mechanisms for the base-promoted rearrangement reaction of prephenic acid had been proposed prior to Danishefsky's work (Scheme 3). In 1955, Gilvarg⁴ suggested **mechanism a**, an initial enolization of the sidechain ketone, decarboxylation of the resulting glutaconate system, and again tautomerization from the product. In 1962, Plieninger⁵ suggested **mechanism b** which involves a 1,2-hydride shift driven by decarboxylation and followed by tautomerization from the aromatic product, and **mechanism c** which involves a 1,6-hydride shift followed by loss of carbon dioxide and subsequent aromatization. In 1977, Danishefsky² and his coworkers suggested then disproved **mechanism d** which starts with Gilvarg's enolization but is then followed by a 1,5-hydride shift and loss of carbon dioxide.

All theories about the mechanism of this rearrangement were entirely speculative until Danishefsky completed his synthesis of prephenic acid.² A byproduct of the synthesis was epiprephenic acid (2). The fact that epiprephenic acid was unable to undergo the same sort of rearrangement effectively ruled out mechanistic proposals **a** and **b**. Since the base-promoted thermal rearrangement works for only one epimer, the hydride transfer must be intramolecular. Only **mechanisms c** and **d** require intramolecular hydride transfer. Additionally, **mechanisms a**, **b**, and **d** were ruled out by a labelling experiment.² Danishefsky, et al. deuterated both sites at carbon-5 of prephenic acid then performed the same rearrangement reaction with this deuterioprephenic acid.

Mechanism a, b and d

Mechanism c

Scheme 3. Four Mechanistic Explanations for the Rearrangement

The product was formed with both deuterium atoms still bonded to carbon-5. This experiment ruled out **mechanism c**. By process of elimination, the accepted 1,6-hydride

shift (**mechanism d**) of Plieninger was the only proposal not contradicted by the experimental evidence.

Our group has suggested a fifth mechanism¹² which is a 1,7-hydride shift followed by a 1,2-hydride shift and final decarboxylation and aromatization to the product (**Scheme 4**). Research on stereoelectronic effects^{6,7,8,9} indicates that there is a well-defined minimum energy pathway for nucleophilic approach to a carbonyl carbon. The approach angle was found to closely approximate 109° (**Figure 1**).

Figure 1. Stereoelectronic Preference of a Carbonyl Reduction

Comparing the trajectories of hydride transfer to the ketone and carboxylate carbonyl of prephenic acid shows that the 1,7 shift to the carboxylate is much closer to a tetrahedral angle than the 1,6 shift to the ketone. Examination of Drieding models and computer models shows that if the optimal tetrahedral approach angle is maintained, then the ground-state distance from the transferring hydride to the ketone carbonyl is quite long compared with the distance from to the carboxylate carbonyl. There is a good precedent for the second step of our proposed mechanism. The Cannizaro rearrangement involves a

Scheme 4. Comparison of a 1,6-shift (Mechanism c) with a 1,7/1,2 shift (Mechanism e)

1,2-hydride shift from the same type of intermediate we are postulating (**Scheme 5**).

There is a problem with our proposed mechanism. A hydride normally reacts much more rapidly with a ketone than with a carboxylate carbonyl. However, we believe that this

electronic factor is outweighed by the three-dimensional stereoelectronic requirement of the reaction. As proven in numerous examples in the aforementioned papers, the further the alignment of the reactants is from the optimal trajectory, the less likely is reaction.

Scheme 5. The Cannizzaro Rearrangement

Since the two mechanistic pathways (Scheme 4) are both intramolecular, they are indistinguishable by kinetic studies or isotopic labeling. We plan to distinguish the two mechanisms by using a series of synthetic analogs (Figure 2) which share all of the essential steric and electronic features of prephenic acid. The 9,10-dihydroanthracene system was chosen for our model compounds because it accurately represents the conformational mobility of dihydrobenzenoid structure of prephenic acid, yet is

synthetically more accessible than the monocyclic system. The two fused rings of the 9,10-dihydroanthracene system permit more straightforward functionalization of the three carbon sidechain than would the cyclohexadiene system.

Prephenic Acid

1

Model I

R=H, CH₃, Ph
X=CO₂, Ph

Model II

R=H, CH₃, Ph
X=CO₂, Ph

Model III

R=H, CH₃, Ph
X=CO₂, Ph

Figure 2. The Series of Synthetic Analogs for Prephenic Acid Study

On the basis of work by Rabideau, Lipkowitz, et al.,¹⁰ we know that planar conformations are the energy minima for both 1,4-dihydrobenzenes and 9,10-dihydroanthracenes, although dihydroanthracene has a shallower energy well and ring puckering can occur more easily.

The electronic factors are comparable in the original prephenate and in our models (**Figure 2**). “X” can be a carboxyl group as in the original compound but this greatly increases the synthetic challenge. Since neither the 1,6- nor 1,7-hydride shift mechanism relies on a decarboxylation for initiation of the reaction, any convenient “X” group may be chosen. There are several reasons to select the phenyl group to substitute for the carboxyl group. Geometrically the phenyl group is similar to the carboxyl carbon in having an sp^2 hybridized carbon bound to the anthronyl 10-position. The phenyl group causes less distortion from a planar conformation of the anthrone ring system than does an sp^3 hybridized substituent because the phenyl ring can adopt a position perpendicular to the tricyclic ring system. Thus peri interactions are minimized.¹¹ Ease of synthesis is also of great importance. A phenyl substituent removes the possibility of aromatization. Additionally, the large phenyl group might increase the diastereoselectivity in the reduction of the anthrone carbonyl. In addition to the “X” substituent, the side chain in the models offers numerous functionalization possibilities which preserve the general stereoelectronic constraints of the original prephenate which we are seeking to model. **Model I** (X=Ph, R=H) seemed to be a promising test for the possibility of 1,6-hydride shifts in this system. If the 1,6-hydride shift proposal is true, then the lack of a deactivating carboxylate group and the greater reactivity of an aldehyde as opposed to a ketone should result in a rapid rearrangement. If, however, our proposal is correct, there should be no reaction. **Model II** and **Model III** can provide further evidence

distinguishing between the two mechanisms. **Model II** (X=Ph, R=H), which has the carbonyl located at the third carbon of the side chain, was designed to test the possibility of a 1,7-hydride shift mechanism. If the 1,7-hydride shift is true, then the rearrangement should be expected in this model. If the 1,6-hydride shift is correct for the natural product, there may or may not be a reaction with this model. **Model III** (X=Ph, R=H) clearly establishes a competition between the 1,6- and 1,7-hydride shifts with no 1,2-shift possible. The **Model III** (X=Ph, R=O⁻) is the positive control side chain containing the functionality of the natural product. One problem with aldehyde model compounds **I** and **II** which we did not fully anticipate was the possibility that base-catalyzed condensation reactions might compete with intramolecular hydride transfer. If the side reactions of aldehydes are faster than the expected hydride transfers, then this type of model compound should be replaced by terminal ketone model compounds, e.g., **Model I** (X=Ph, R=CH₃, Ph), or **Model II** (X=Ph, R=CH₃, Ph). **Scheme 6** shows our retrosynthetic strategy for the synthesis of these model compounds from compound **7**.

The long range goal of this research project is the synthesis of a series of analogs of prephenic acid to investigate the mechanism of the base-catalyzed hydride transfer. Four Masters students, Jessica Carr, Rekha P. Bansal, Kate Jin and Yanzhou Liu have previously worked on this project and made tremendous progress.^{12,13,14,15} Based on their work, NBS radical bromination was selected as the best way to make

10-bromoanthrone.¹⁴ 10-Phenylanthrone was prepared by Friedel-Crafts alkylation of benzene with the bromoanthrone.¹² The synthesis¹² of 10-allyl-10-phenylanthrone (7) by thermolysis of 9-allyoxy-10-phenylanthracene and the subsequent mechanistic investigation¹³ have established this quantitative transformation as a very general and useful synthetic method.

Reduction of the anthrone carbonyl is a key step necessary for the synthesis of the model compounds. Jessica Carr and Kate Jin^{12,14} made many efforts to solve the problem. 9-Borabicyclo[3,3]nonane and lithium aluminum hydride were completely ineffective for this purpose.¹⁴ Superhydride (lithium triethylborohydride) gave a low yield of the expected reduction products, but the reaction was not good enough to apply toward the model compounds.¹⁴ My research has focused primarily on solving the problem of cleanly reducing the anthrone carbonyl and making new progress toward the long range goal of preparing model compounds for our mechanistic investigation. Since we experienced difficulties in the two-electron hydride reduction of the carbonyl, we changed the strategy by using a one electron dissolving metal reduction. Sodium amalgam,¹⁶ rarely used nowadays but once a very common reducing agent, solved the reduction problem in over 95% yield. The mechanistic explanation will be given in the following section.

After solving the reduction problem, our research focus was turned to finding a good synthetic strategy to obtain the 2- or 3-carbon side chains required for our model compounds. Originally, we planned to protect the newly formed alcohol at the 9-position and then to oxidize the allyl group at the 10-position. However, the alcohol, either protected or not, was so easily reoxidized that this synthetic strategy was terminated.

We eventually settled on a strategy which began with oxidation of the allylic side chain of compound **7**. Next the side chain carbonyl was protected, then the anthrone carbonyl was reduced. Deprotection of the side chain completed this strategy. By following this protocol, **Model I** and **Model II** were prepared. The base-catalyzed reactions of these model compounds will be discussed in the following section. From the key intermediate **7** to make **Model I** and **Model II**, many new reactions were utilized. Seventeen new compounds were prepared during the course of these investigations and three unusual reactions were discovered. For each of these reactions, detailed discussions of both mechanistic and experimental considerations are provided in the discussion section. We believe that our successful synthetic strategy may apply to the further model compounds in this project. A greater understanding of 9,10-dihydroanthracene stereochemistry and

Scheme 6. Retrosynthetic Plan for the Preparation of Model Compounds
(R=H, CH₃ or Phenyl)

transannular reactions has resulted from the unusual reactions we have discovered. This thesis builds on many years of synthetic effort and represents the first time we have prepared the models necessary to test the 1,6- and 1,7- hydride shift mechanisms. Although the results are more complicated than we expected, future work should still benefit from our current efforts.

Results and Discussion

In pursuing our long range synthetic goals, 10-bromoanthrone (5), 10-phenylanthrone (6), and 10-allyl-10-phenylanthrone (7) were made by using the synthetic methods previously reported by the Branz group.^{12,13,14,15} Since the 9-position carbonyl of compound 7 cannot be reduced by the more common complex metal hydride,¹⁴ a dissolving metal one electron reduction was utilized.¹⁶ This sodium mercury amalgam reduction was successfully performed in over 95% yield.

Figure 3. Mechanistic Comparison Between Two Kinds of Reduction

The key difference between the two types of reducing agents is the stereoelectronic requirement in the case of the hydride reagents. The hydride reducing agent only can attack a ketone at a trajectory of approximately 109° relative to the carbonyl. However, the two bulky substituents at the 10-position of compound **7** block the pathway required for hydride reduction. On the other hand, sodium can easily provide one electron to reduce the carbonyl at carbon-9 because there is no stereoelectronic restriction on the approach of an electron (**Figure 3**). The nearly 1:1 ratio of the two isomers from the sodium reduction is good mechanistic evidence in support of this explanation. Our initial synthetic strategy¹² was to reduce intermediate **7**, then protect the new benzhydrylic alcohol before modifying the allyl side chain, and finally deprotecting the alcohol (**Scheme 7**). However, the benzyl protected 10-allyl-9-hydroxy-10-phenyl-9,10-dihydroanthracene (**15**) (10-allyl-9-benzyloxy-10-phenyl-9,10-dihydroanthracene (**16**)) was easily reoxidized when compound **16** was treated with MCPBA to make the epoxide side chain. Finally, an alternative synthetic strategy (**Scheme 8**) was used in which the allyl side chain of intermediate **7** was oxidized first then protected prior to reducing the 9-position carbonyl, then finally deprotecting the side chain carbonyl to obtain the model compounds.

10-(2-Oxoethyl)-10-phenylanthrone (**9**) and 10-(3-oxopropyl)-10-phenylanthrone (**12**) are two important intermediates to **Model I** and **Model II**. Based on our retrosynthetic analysis 10-oxiranylmethyl-10-phenylanthrone (**8**) was the next synthetic target. There is

literature precedent¹⁸ for Lewis acid promoted epoxide ring opening with a simultaneous hydride shift to give terminal aldehydes as the major products. Epoxidation of 10-allyl-10-phenylanthrone (**7**) by *meta*-chloroperbenzoic acid¹⁷ was a very successful reaction giving the product **8** in over 95% yield. However, treatment of the epoxide (**8**) with BF₃ etherate in different solvents and at different temperatures did not offer any sign of our expected aldehyde (**12**), so, we abandoned this route (**Scheme 9**).

Hydroboration of the side chain terminal olefin followed by oxidation is another possible way to make compound **12**, but one additional synthetic step would have been needed. Brown, et al¹⁹ reported a highly selective conversion of terminal olefins into aldehydes in a one pot procedure by using a new highly selective borane reagent, bis(3-methyl-2-butyl)borane. By following their procedure and even trying 9-borabicyclo[3.3.1]nonane as an alternative, the initial hydroboration failed. Comparing our olefin with those compounds cited in the literature, it appears that our compound is too sterically crowded around the allylic double bond. Finally, we used the simplest possible reagent, the diborane/THF complex. The desired aldehyde (**12**) and the methyl ketone (**17**) (2.6:1) were obtained after *in situ* pyridinium chlorochromate (PCC) oxidation (**Scheme 10**). We believe that selecting a medium size borane reagent may increase the specificity in this reaction because of steric consideration. To obtain compound **9**, a sequence of reactions equivalent to the ozonolysis of key intermediate **7**

Scheme 7. Original Synthetic Strategy (R=H, alkyl, or aryl)

was chosen. Periodic acid cleavage of the epoxide (8) in aqueous solution²⁰ was used to prepare compound 9 in 84% yield (Scheme 11).

Scheme 8. Alternative Successful Synthetic Strategy for Models I and II
 (R=H, alkyl, or aryl; X= dione protective group)

Scheme 9. Attempted Syntheses of Compound 12

Our next synthetic challenge was the selective monoprotection of the side chain aldehydes of compounds 9 and 12 in the presence of the anthrone carbonyl. Furthermore, the protecting group chosen had to be inert to sodium mercury amalgam reduction and be

easily deprotected to regenerate the aldehyde without reoxidizing the benzhydrylic alcohol. The dimethyl acetal was chosen as the protective group to meet our needs. In these reactions, the dimethyl acetals were prepared by the *para*-toluenesulfonic acid catalyzed exchange with a slight excess of trimethylorthoformate. Under these conditions, compound 9 was converted to compound 10 in 96% yield, and compound 11 was converted to compound 13 in 76% yield (Scheme 12).

Scheme 10. Synthesis of Compound 12

Scheme 11. Synthesis of Compound 9

Compounds **10** and **13** were purified and fully characterized. Because the sodium mercury amalgam reduction had been so successful, we anticipated that it would succeed with compounds **10** and **13** to make the diastereomeric alcohols **11a** and **11b** and the diastereomeric alcohols **14a** and **14b** respectively. Both products were obtained in over 95% yield. The compounds were identified by NMR, IR, and MS (**Scheme 13**). Because the cis/trans diastereomers were difficult to separate from one another, we decided to continue the synthesis with both isomers. Luckily, we do have two methods to identify

which isomer is which. By using NMR NOE (Nuclear Overhauser Effect), the stereoisomer could, in principle, be assigned by the correlations between H-9 and side chain at the 10-position.

Scheme 12. Protection of Side-Chain Aldehyde

In practice we did not use NOE but instead utilized an unambiguous synthetic method to prepare a reference compound of defined stereochemistry. By comparison, this was used to assign stereochemistry in all other related compounds. The epoxide **8** was treated with lithium aluminum hydride to cleanly obtain compound **18** in only one of its two

Scheme 13. Sodium Mercury Amalgam Reduction

diastereomeric forms. The mechanism of this reaction is shown in **Scheme 14**. Hydride is delivered internally to the anthrone carbonyl from the alkoxyaluminum hydride formed by reduction of the epoxide. The intramolecular nature of this reaction determined that only the syn-isomer would be formed. Recall that 10-allyl-10-phenylanthrone (**7**) was inert to lithium aluminum hydride reaction, a lack of reactivity attributed to steric blocking of intermolecular hydride delivery. Reduction of the compound **8** to compound **18** is only possible in an intramolecular sense because tetrahedral approach to the carbonyl is not blocked.

Although this reaction generates the synisomer with a different side chain from model compounds, the proton NMR chemical shifts of the protons at C-9 should be similar. This is very important information in monitoring the base-catalyzed rearrangements of our model compounds. By comparison, we can determine if hydride reductions in other compounds are intramolecular or not. Since we believe that compound **18** shares the same configuration (-OH and -Ph syn) as our expected **Model I** and **Model II**, the chemical shift of protons H_a and H_b should be similar. The assignment syn and anti structures by comparison with compound **18** is shown in **Table 1**. The chemical shift of the aldehydic proton was assigned by integration. From trial experiments to hydrolyze the acetals of compound **11** and compound **14**, we found that 10,10-disubstituted anthracene compounds easily undergo transannular reactions in acidic condition. This is a serious problem that lowers the yields of our model compounds. We decided to lower the acidity

of the catalyst to solve the problem. In the literature, dimethylacetals have been selectively hydrolyzed by stirring in a mixture of chloroform and 50% ethanol/water trifluoroacetic acid (2:1) at room temperature²² or by using acidic silica gel as a catalyst.²³

Scheme 14. Synthesis of Stereochemical Reference Compound

We chose the ethanol/water trifluoroacetic acid method. Compound 11 was hydrolyzed to yield compound 23 in 79% yield (NMR); compound 14 was hydrolyzed to compound 24 in 56% yield (NMR) (Scheme 15). Because the aldehydes 23 and 24 (**Model I** and **Model II**) are sensitive to silica gel, we decided to continue without further purification.

Prior to completing this study we prepared compound 22 (by sodium borohydride reduction of compound 9 (Scheme 16)) as an NMR reference standard.

Scheme 15. Acetal Hydrolyses of Compounds 11 and 14

If compound 23 undergoes an intramolecular 1,6-hydride transfer, then compound 22 should be seen in the product spectrum, and the appearance of this compound should correlate with the disappearance of only one of the two diastereomeric starting materials (Scheme 17). Because prephenate is water soluble, Danishefsky's original study of the intramolecular hydride rearrangement reaction took place in 2N sodium hydroxide

solution at 100 °C.² However, **Model I** and **Model II** are not water soluble; they can dissolve only in organic solvents. Furthermore, the aldehyde functionality of our model compounds is susceptible to basic²⁴ aldol condensation,²⁵ and the reaction condition of the base catalyzed thermal hydride rearrangement should be controlled very carefully. Consequently, we chose to investigate five different base/solvent systems for the rearrangement reactions. By NMR, we monitored for the disappearance of starting material peaks and the appearance of the peaks of the expected products (**18** and **22** which were both synthesized independently).

Scheme 16. Hydride Reduction of Compound 9

Three systems were proved to be inappropriate, because the aldehyde peaks from both epimers disappeared. As mentioned above, these systems, (1) sodium ethoxide/ethanol/ether, (2) potassium t-butoxide/t-butanol/ether and (3) sodium hydroxide/

pyridine/water, may be too basic. Aldol reactions or other aldehyde related side reactions appear to be competitive with or much faster than the hydride transfer reaction. Two other systems, (4) sodium hydroxide/THF/water and (5) sodium hydroxide/dioxane/water, showed the aldehyde peaks decreasing as well. However, by NMR we found that the aldehyde peak and other characteristic peaks from the syn epimer **Model I** (the model for 1,6 hydride shift mechanism) were decreasing more rapidly than those from the anti epimer. The difference between the reactivity of the two isomers indicates that syn isomer is consumed more rapidly than the anti isomer, presumably by a hydride transfer reaction (not possible for the anti isomer). Similarly for **Model II** (the model for 1,7/1,2 hydride shift mechanism) under the same conditions, NMR peaks assignable to the syn isomer were decreasing more rapidly than those of the anti isomer. Again, we suspect that a 1,7 hydride shift mechanism is preferentially consuming the syn isomer. Unfortunately, no evidence for the expected products has been found by NMR. Nevertheless, further transformations of the expected products are quite reasonable and lack of direct experimental evidence for their formation does not rule out their transient existence.

Future work on this project should include synthesis of the less reactive terminal methyl ketone and phenyl ketone models (**Figure 2**). These may avoid unwanted side reactions possible only for aldehydes. Compound **17** is an example which was prepared by palladium chloride catalyzed oxidation of terminal olefin **7**.²⁶ The key features of this

reaction are the rapid oxidation of the π -coordinated terminal olefin by Pd(II), followed by rapid reoxidation of Pd(0) by Cu(I).

Scheme 17. Anticipated Results from an Intramolecular 1,6-Hydride Transfer

Cu(0) produced by reduction of Cu(I) is then reoxidized by O_2 . The mechanism was proposed by Backvall²⁷ (Scheme 18).

Scheme 18. Mechanism of Pd (II) Catalyzed Wacker Oxidation

	Ha	Hb	Hc
<p>18</p>	5.74 ppm	7.77 ppm
<p>23a</p>	5.70 ppm	7.70 ppm	9.17 ppm
<p>23b</p>	5.24 ppm	7.58 ppm	9.51 ppm
<p>24a</p>	5.85 ppm	7.73 ppm	9.39 ppm
<p>24b</p>	5.47 ppm	7.57 ppm	9.44 ppm

Table 1. Proton NMR Data Comparison to Assign the Correlated syn Isomers

During the course of this work, a number of unexpected transannular reactions were discovered. Intramolecular hydride reduction of anthrone (**Scheme 14**) was discussed earlier in this thesis. **Scheme 19**, **Scheme 20**, and **Scheme 21** present three other transannular reactions.

9-Allyl-10-phenylanthracene (**20**) was obtained as the unexpected major product from two different reactions. The first reaction was an attempt to use dimethoxymethane and phosphorus pentoxide to protect the alcohol of compound **15**.²⁸ The second simply tested the stability of compound **15** under trifluoroacetic acid reaction condition. However, the identical compound 9-allyl-10-phenylanthracene (**20**) was obtained from each of these reactions. Because the common feature of both reactions is dehydration, we have proposed an intramolecular nucleophilic attack of the allyl group at the C-9 position (either a cation or a protonated alcohol; **Scheme 19**).

Compound **19** was the major product of lithium aluminum hydride reduction of epoxide **8**. By comparing the minor product, compound **18**, and major compound **19**, we believe that compound **18** is the mechanistic precursor to compound **19** (**Scheme 20**). Nucleophilic attack of the side chain alcohol at C-9 is the key step in the formation of the bridged product.

Scheme 19. Reaction to Obtain Compound 20

The sodium mercury amalgam reduction of compound 17 was expected to reduce only the anthrone carbonyl. To our surprise the product showed no evidence of a carbonyl. Based on the characteristic proton NMR spectrum, we proposed the diol 21 as the

Scheme 20. Transannular Reaction to Form Compound 19

structure of this unanticipated product. **Scheme 21** details a plausible mechanism for its formation.

Conclusion

In contrast to complex metal hydride reductions, dissolving metal reduction successfully converts the carbonyl groups of hindered 10,10-disubstituted anthrones to the corresponding alcohols. This breakthrough, plus successful protection/deprotection of two carbon and three carbon side chain aldehydes enabled us to synthesize **Model I** and **Model II** compounds needed to test the ability of hydride to undergo 1,6 vs 1,7 intramolecular migration.

Because aldehyde models are kinetically unstable, future work should be focused on synthesizing ketone side chain models. **Scheme 22** shows possible synthetic approaches to these types of compounds. Ketones will be less prone to aldol reactions and possibly less likely to undergo transannular reactions.

In both sodium hydroxide/THF/water or sodium hydroxide/dioxane/water, the base-catalyzed hydride rearrangements of **Model I** and **Model II** were tested. From the NMR analysis, we suspect that both 1,6-shifts and 1,7-shifts may have comparable rates when aldehydes serve as the hydride accepters. Since model studies have shown that the

aldehydes are not stable to the basic conditions needed to accomplish hydride transfer, further work should be directed toward the synthesis of more stable model compounds, perhaps having ketones rather than aldehydes at carbon-2 or carbon-3 of the side chain.

Scheme 22. Future Work

Seventeen new compounds were prepared in the course of this thesis work. Most of them were intermediates leading to the synthesis of model compounds. However, three unexpected products let us to explore some unusual transannular reactions of 10,10-disubstituted anthrones and 10,10-disubstituted-9,10-dihydroanthranols. These reactions are novel and interesting in their own right. Furthermore, the understanding we have gained about anthrones and reduced anthrones may be significant to future model compound syntheses.

In summary, we have synthesized the aldehyde side-chain model compounds, then tested them under basic conditions. However, due to the chemical reactivity of the aldehydes, there is no significant evidence to support either 1,6 hydride shift or 1,7 hydride shift mechanism. To pursue this research in the future, a series of monoketone, diketone and α -dicarbonyl side chain compounds must be synthesized. Since ketones are kinetically more stable than aldehydes in basic reaction condition, we anticipate that the ketone models will prove or disprove our hypothesis.

Experimental

General Procedures: Reactions were routinely run under a nitrogen atmosphere with magnetic stirring. Melting points were determined with an Electrothermal Inc. IA9200 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a

Perkin-Elmer 1600 series FT infrared spectrophotometer. Band positions are recorded in reciprocal centimeters (cm^{-1}). ^1H -NMR spectra were recorded at 300 MHz and ^{13}C NMR were recorded at 75 MHz on a GE QE Plus NMR spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. Mass spectra were run on Finnigan Mat 8230. Elemental analyses were performed by Chemical Analytical Services, UC Berkeley, California. Flash column chromatographic separations utilized EM Reagent silica gel 60 (0.040-0.063 mm) and hexane-ethyl acetate gradient elution.

5

6

7

Bromoanthrone (5). Prepared by the procedure of Branz, Jin, Liu and Dao^{14, 15} on a 154.0 mmol scale. A saturated sodium thiosulfate solution was substituted for saturated sodium bicarbonate solution (91% yield). ^1H -NMR (300 MHz, CDCl_3) δ 6.64 (s, 1 H_{He}), 7.52 (DT, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2 H_{c} or 2 H_{b}), 7.64 (DT, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2 H_{b} or 2 H_{c}), 7.72 (dd, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2 H_{d}), 8.27 (dd, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2 H_{a}).

10-Phenylanthrone (6). Prepared by the procedure of Branz and Carr¹² on a 30 g scale using CH_2Cl_2 (800 mL) as solvent. ^1H -NMR (300 MHz, CDCl_3) δ 5.42 (s, 1 H_{e}), 7.11

(dd, $J_{\text{ortho}}=8.0$ Hz, $J_{\text{meta}}=1$ Hz, $2H_d$), 7.25 (m, 5H phenyl), 7.42 (dt, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, $2H_b$ or $2H_c$), 7.49 (dt, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, $2H_c$ or $2H_b$), 8.39 (dd, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, $2H_a$).

10-Allyl-10-phenylanthrone (7). Alkylation of 10-phenylanthrone with allyl bromide followed by rearrangement of O/C alkylation mixture was carried out by the procedure of Branz and Carr¹² on a 154.0 mmol scale. ¹H-NMR (300 MHz, CDCl₃) δ 3.26 (d, $J=7.1$ Hz, $2H_c$), 4.49 (dd, $J_{\text{trans}}=16.9$ Hz, $J_{\text{gem}}=2$ Hz, $1H_h$), 4.62 (dd, $J_{\text{cis}}=10.2$ Hz, $J_{\text{gem}}=2$ Hz, $1H_g$), 4.96 (ddt, $1H_f$), 7.05 (dd, $J_{\text{ortho}}=7.9$ Hz, $J_{\text{meta}}=1$ Hz, $2H_d$), 7.28 (m, 5H phenyl), 7.37 (dt, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, H_b or H_c), 7.46 (dt, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, H_b or H_c), 8.34 (dd, $J_{\text{ortho}}=7.8$ Hz, $J_{\text{meta}}=1$ Hz, $2H_a$).

10-Allyl-9-hydroxy-10-phenyl-9,10-dihydroanthracene (15). Mercury (60.0 g, 0.299 mol) was added to a 250-mL two neck round-bottom flask with magnetic stirring. One neck of the flask was connected to nitrogen flow; the other neck was opened as a vent.

After flushing with nitrogen for 10 min, sodium metal pieces (2.00 g, 86.9 mmol; cleaned by washing with hexane, then methanol, then cut into small pieces) were added to the stirred mercury. The reaction mixture was stirred until the sodium slowly formed a solid amalgam with the mercury. 10-Allyl-10-phenylanthrone (**7**) [1.00 g, 3.22 mmol in THF (50mL)] was transferred into the reaction flask, then 100% ethanol (30 mL) was added. The reaction was stirred under nitrogen at 50 °C. After 10 h, the reaction was shown to be complete by TLC (silica gel; hexane: ethyl acetate, 8:2). The reaction solution was poured into DI water (200 mL). The mixture was extracted with ethyl ether (3 x 80 mL), then the combined ether solution was washed with 10% citric acid (2 x 80 mL), followed by sat'd. NaCl solution (2 x 100 mL). The organic layer was dried (MgSO₄) then concentrated under vacuum. Compound **15** (1.0 g of a 50:50 mixture of cis and trans isomers, 99% crude yield) was obtained as yellow oil: ¹H-NMR (300 MHz, CDCl₃) δ 3.1 (d, J=7.2 Hz, 2H_c cis isomer), 3.22 (d, J=7.2, 2H_c trans isomer), 4.61-4.87 (m, 1H_g and H_h cis and trans isomers), 5.19 (ddt, 1H_f cis isomer), 5.34 (ddt, 1H_f trans isomer), 5.63 (s, 1H_i trans isomer), 5.67 (s, 1H_i cis isomer), 6.88 (d, J=7.2 Hz, 2H_d cis isomer), 6.97 (d, J=7.2 Hz, 2H_d trans isomer), 7.11-7.31 (m, 9H cis and trans isomers), 7.62 (d, J=7.2 Hz, 2H_a trans isomer), 7.76 (d, J=7.2 Hz, 2H_a cis isomer).

10-Allyl-9-benzyloxy-10-phenyl-9,10-dihydroanthracene (16). 10-Allyl-9-hydroxy-10-phenyl-9,10-dihydroanthracene (**15**) (0.20 g, 0.64 mmol) was dissolved in dry THF (10 mL), and sodium hydride (0.03 g, of a 60% dispersion in mineral oil, 0.018 g NaH,

0.75 mmol) was gradually added with stirring at room temperature. After 5 min, tetrabutyl ammonium iodide (0.0042 g, 0.0114 mmol) was introduced, and then benzyl bromide (0.11 g, 0.64 mmol) was added. The reaction was stirred under N₂ at RT. After 29 h, the reaction was stopped and quenched with DI water (40 mL). The mixture was extracted by methylene chloride (3 x 10 mL). The combined methylene chloride solution was washed with 10% citric acid solution (2 x 15 mL), satd. sodium chloride solution (2 x 25 mL), then dried (MgSO₄). The dried organic solution was concentrated by vacuum. Compound 16 was obtained (0.2 g of a 50:50 mixture of cis and trans isomers, 80% yield): ¹H NMR (300 MHz, CDCl₃) δ 3.12 (d, J=7.2 Hz, 2H_e cis isomer), 3.35 (d, J=7.2, 2H_e trans isomer), 4.2 (s, 2H_j cis isomer), 4.43 (s, 2H_j trans isomer), 4.54-4.87 (m, 1H_g, 1H_h cis and trans isomers), 5.1 (ddt, 1H_f cis isomer), 5.61 (ddt, 1H_f trans isomer), 5.64 (s, 1H_i trans isomer), 5.96 (s, 1H_i cis isomer), 6.93 (d, J=7.2 Hz, 2H_d cis isomer), 7.0 (d, J=7.2 Hz, 2H_d trans isomer), 7.14-7.39 (m, 14H trans and cis isomers), 7.62 (d, J=7.2 Hz, 2H_a trans isomer), 7.78 (d, J=7.2 Hz, 2H_a cis isomer).

10-(2-Oxopropyl)-10-phenylanthrone (17). A 100-mL, three-necked, round-bottomed flask was fitted with a magnetic stirrer and a pressure-equalizing dropping funnel containing 10-allyl-10-phenylanthrone (7) in methylene chloride solution (1.00 g, 3.22 mmol in 10 mL CH₂Cl₂). The flask was charged with a mixture of palladium chloride (PdCl₂, 0.057 g, 0.322 mmol), cuprous chloride (CuCl, 0.32 g, 3.22 mmol), and aqueous dimethylformamide (DMF/H₂O, 7:1; 3 mL). With the other outlet securely stoppered and

wired down, an oxygen-filled balloon was placed over one neck, and the solution was stirred at room temperature to allow oxygen uptake. After 1 h, the 10-allyl-10-phenylanthrone solution (10 mL) was added over a 10 min period using a dropping funnel. Vigorous stirring was continued for 70 h, then the mixture was poured into 1N hydrochloric acid (45 mL) and extracted with ethyl ether (4 x 10 mL). The ether extracts were combined and washed successively with sat'd. sodium bicarbonate and sat'd. sodium chloride aqueous solution. The washed organic solution was dried (MgSO₄) and concentrated by vacuum. The light yellow product was recrystallized from hexane and ethyl ether to give a crystalline white solid **17** (0.73 g, 70% yield): mp 220-222 °C; IR (film) 1724 (methyl ketone), 1662 (9-ketone), 1601 (conjugated C=C) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.61 (s, 3H, H_f), 3.8 (s, 2H, H_e), 7.08 (dd, J_{ortho}=7.5, J_{meta}=1 Hz, 2H_d), 7.16-7.29 (m, 5H_{phenyl}), 7.4 (dt, J_{ortho}=7.5 Hz, J_{meta}=1 Hz, H_b or H_c), 7.47 (dt, J_{ortho}=7.5 Hz, J_{meta}=1 Hz, H_c or H_b), 8.4 (dd, J_{ortho}=7.5 Hz, J_{meta}=1 Hz, 2H_a); ¹³C NMR (75 MHz, CDCl₃) δ 31.14, 47.10, 55.14, 126.77, 127.02, 127.18, 127.51, 128.70, 128.78, 131.48, 133.40, 146.90, 147.58, 183.45, 204.30; MS (EI, relative intensity), m/z 326 (M⁺, 14), 269 (100), 270 (22), 239 (24). Anal. Calcd for C₂₃H₁₈O₂: C, 84.64; H, 5.56. Found: C, 83.70; H, 5.45.

10-Oxiranylmethyl-10-phenylanthrone (8). In a 100-mL round-bottom flask, compound **7** (3.00 g, 9.68 mmol) was dissolved in methylene chloride (20 mL) with magnetic stirring. m-Chloroperbenzoic acid solution (85% MCPBA, 3.92 g, 0.019

mmol) in methylene chloride (20 mL) was dropwise added. The reaction was stirred at room temperature. After 12 h, the reaction was shown to be complete by TLC (silica gel, hexane:ethyl acetate, 9:1, new spot at lower R_f). The product solution was washed with 10% sodium sulfite (until starch-iodide paper gave a negative response), then with sat'd. sodium bicarbonate (2 x 20 mL), and finally sat'd. sodium chloride (2 x 20 mL). The methylene chloride solution was dried (MgSO_4) and concentrated by vacuum. The crude product was obtained as a white solid (2.99 g, 95% yield). An analytical sample of compound **8** was purified by column chromatography (silica gel, hexane:ethyl acetate, 9:1): mp 140.5-141.3 °C; IR (film) 1659 (9-ketone), 1601 (conjugated C=C), 1155 (epoxide C-O) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.69 (dd, $J_{\text{gg}}=6$ Hz, $J_{\text{g}'}=2$ Hz, 1 H_{g}), 2.0 (dd, $J_{\text{gg}}=6$ Hz, $J_{\text{g}'}=1$ Hz, 1 H_{g}), 2.22 (m, 1 H_{f}), 2.42 (dd, $J_{\text{cc}}=14$ Hz, $J_{\text{c}'}=8$ Hz, 1 H_{c}), 3.13 (dd, $J_{\text{cc}}=14$ Hz, $J_{\text{c}'}=4$ Hz, 1 H_{c}), 7.03 (dd, $J_{\text{ortho}}=8$ Hz, $J_{\text{meta}}=1$ Hz, 1 H_{d} or 1 H_{d}), 7.11 (dd, $J_{\text{ortho}}=8$ Hz, $J_{\text{meta}}=1$ Hz, 1 H_{d} or 1 H_{d}), 7.2-7.53 (m, 5 H_{phenyl}), 8.4 (dm, $J_{\text{ortho}}=8$ Hz, $J_{\text{meta}}=1$ Hz, 1 H_{a} and 1 H_{a}); ^{13}C NMR (75 MHz, CDCl_3) δ 46.79, 46.86, 48.57, 49.18, 126.87, 127.05, 127.07, 127.11, 127.16, 127.90, 128.63, 129.30, 129.43, 131.07, 131.29, 133.55, 133.78, 146.78, 148.07, 148.42, 183.58; MS (EI, relative intensity), m/z 326 (M^+ , 4), 269 (100), 270 (24), 252 (14), 239 (41). Anal. Calcd for $\text{C}_{23}\text{H}_{18}\text{O}_2$: C, 84.64; H, 5.56. Found: C, 83.86; H, 5.66.

9-Hydroxy-10-(2-hydroxypropyl)-10-phenyl-9,10-dihydroanthracene (18) and 10-Phenyl-9,10-dihydro-9,10-(2-methyl-1-oxapropane)anthracene (19).

Epoxide compound 8 (0.13 g, 0.399 mmol,) was dissolved in dry THF (3 mL) under nitrogen gas at RT. Lithium aluminum hydride (0.03 g, 0.798 mmol) was suspended in dry THF (1 mL) and added to the epoxide solution slowly by syringe. The reaction solution was stirred at RT under N₂ over night. When the reaction was shown to be complete by TLC (two new spots at lower R_f), the reaction mixture was quenched with water (20 mL) and extracted by ethyl ether (3 x 5 mL). The combined ether extracts were washed with 10% citric acid (2 x 5 mL) and sat'd. NaCl (2 x 5 mL). The ether solution was dried (MgSO₄) then concentrated by vacuum. After the purification by silica gel column chromatography (8:1, hexane:ethyl acetate), compounds 18 (0.02 g, 15% yield) and 19 (0.08 g, 64% yield) were obtained.

Compound 18: ¹H NMR (300 MHz, CDCl₃) δ 0.88 (d, J=6 Hz, 3H_g), 2.52 (d, J=3 Hz, 2H_e), 3.44 (m, 1H_f), 5.74 (s, 1H_h), 6.84 (t, J=7.5 Hz, 2H_d), 7.1-7.3 (m, 2H_b, 2H_c and 5H_{phenyl}), 7.77 (d, J=7.5 Hz, 2H_a).

Compound **19**: mp 177-179 °C; IR (film) 1600 (conjugated C=C) cm^{-1} ; 1068 (C-O) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.11 (d, $J=6$ Hz, 3H_g), 2.04 (dd, $J_{\text{e'f}}=15$ Hz, $J_{\text{ce'}}=11$ Hz, $1\text{H}_{\text{e'}}$), 2.37 (dd, $J_{\text{ce'}}=11$ Hz, $J_{\text{ef}}=4$ Hz, 1H_{e}), 3.37 (m, 1H_{f}), 5.63 (s, 1H_{h}), 6.40 (d, $J=7$ Hz, 1H_{d} or $1\text{H}_{\text{d'}}$), 6.94 (d, $J=7$ Hz, 1H_{d} or $1\text{H}_{\text{d'}}$), 7.02 (dd, $J_{\text{ortho}}=7$ Hz, $J_{\text{meta}}=1$ Hz, 2H_{j}), 7.15 (tt, $J_{\text{ortho}}=7$ Hz, $J_{\text{meta}}=1$ Hz, 1H_{k}), 7.22 (dt, $J_{\text{ortho}}=7$ Hz, $J_{\text{meta}}=1$ Hz, 1H_{b} and 1H_{b} or 1H_{c} and 1H_{c}), 7.30 (dt, $J_{\text{ortho}}=7$ Hz, $J_{\text{meta}}=1$ Hz, 1H_{c} and 1H_{c} or 1H_{b} and 1H_{b}), 7.41 (dd, $J_{\text{ortho}}=7$ Hz, $J_{\text{meta}}=1$ Hz, 1H_{a} and 1H_{a} or 2H_{i}), 7.50 (dd, $J_{\text{ortho}}=7$ Hz, $J_{\text{meta}}=1$ Hz, 1H_{a} and 1H_{a} or 2H_{i}); ^{13}C NMR (75 MHz, CDCl_3) δ 22.11, 44.34, 52.20, 69.00, 77.57, 125.82, 126.00, 126.09, 126.35, 126.84, 127.06, 127.24, 127.81, 127.92, 128.01, 128.15, 135.90, 140.53, 142.95, 145.73, 149.12; MS (EI, relative intensity), m/z 312 (M^+ , 100), 268 (M^+-44 , 50), 254 (M^+-58 , 40). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{O}$: C, 88.43; H, 6.45. Found: C, 87.47; H, 6.46.

10-(2-Oxoethyl)-10-phenylanthrone (9). In a 100-mL round-bottom flask equipped with a condenser, compound **8** (2.1 g, 6.44 mmol) was dissolved in THF (30 mL).

Periodic acid (2.8 g, 6.44 mmol, dissolved in 20 mL water) was slowly introduced. The reaction was stirred and heated to 60 °C. After 16 h, the reaction was shown to be complete by TLC (new spot at lower R_f , hexane : ethyl acetate, 9:1). The reaction solution was poured into 1 N sodium hydroxide aqueous solution (50 mL) and extracted with methylene chloride (3 x 15 mL). The combined organic layers were washed successively with 10% citric acid (2 x 15 mL), followed by sat'd. sodium chloride solution (2 x 15 mL), then dried (MgSO_4). The product was concentrated by vacuum. The crude yellow product (2.03 g, 84% crude yield) was obtained. An analytical sample of compound **9** (white solid) was purified by recrystallization (hexane/ether): mp 97-99 °C, IR (film) 1658 (RCHO), 1605 (9-carbonyl), 1552.50 (conjugated C=C) cm^{-1} ; ^1H NMR δ 3.60 (d, $J = 2.5$ Hz, 2H_c), 7.14-7.33 (m, 2H_d and $5\text{H}_{\text{phenyl}}$), 7.44 (dt, $J_{\text{ortho}} = 7.5$ Hz, $J_{\text{meta}} = 1$ Hz, 2H_c or 2H_b), 7.53 (dt, $J_{\text{ortho}} = 7.5$ Hz, $J_{\text{meta}} = 1$ Hz, 2H_b or 2H_c), 8.42 (dd, $J_{\text{ortho}} = 7.5$ Hz, $J_{\text{meta}} = 1$ Hz, 2H_d), 9.12 (t, $J = 2.5$ Hz, 1H_f); ^{13}C NMR (75 MHz, CDCl_3) δ 47.53, 55.08, 127.08, 127.42, 127.48, 127.56, 128.88, 129.32, 130.86, 134.12, 146.04, 146.97, 183.00, 199.87; MS (EI, relative intensity), m/z 312 (M^+ , 8), 269 (100), 239 (38).

10-(2,2-Dimethoxyethyl)-10-phenylanthrone (10). Compound **9** (1.9 g, 6.13 mmol) was dissolved in methylene chloride (20 mL). *p*-Toluenesulfonic acid (0.02 g) and trimethylorthoformate (0.67 g, 6.31 mmol) were introduced. The reaction was stirred at RT overnight until the reaction was shown to be complete by TLC (new spot at higher R_f , hexane : ethyl acetate, 9:1). The reaction solution was washed with sat'd. sodium bicarbonate (3 x 20 mL), sat'd. sodium chloride solution (2 x 20 mL), then dried (MgSO_4). The product was concentrated by vacuum. A crude yellow product (2.02 g, 96% crude yield) was obtained. An analytical sample of compound **10** was obtained as a white solid following purification by column chromatography (silica gel, hexane:ethyl acetate, 9:1): IR (film) 1663 (9-ketone), 1601 (conjugated C=C), 1155 (C-O) cm^{-1} ; ^1H NMR δ 2.00 (s, 6H_g), 2.91 (d, $J=5$ Hz, 2H_e), 3.60 (t, 1H, $J=5$ Hz, H_f), 7.06 (dd, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2H_d), 7.18-7.28 (m, 5H_{phenyl}), 7.39 (dt, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2H_c or 2H_b), 7.47 (dt, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2H_c or 2H_b), 8.37 (dd, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2H_j). MS (EI, relative intensity), m/z 358 (M^+ , 4), 269 (100), 239 (43), 89 (13), 75 (72). Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{O}_3$: C, 80.42; H, 6.19. Found: C, 80.78; H, 5.64.

10-(2,2-Dimethoxyethyl)-9-hydroxy-10-phenyl-9,10-dihydroanthracene (11).

Mercury (6.00 g, 29.9 mmol) was added to a 25-mL two neck round-bottom flask with magnetic stirring. One neck of the flask was connected to nitrogen flow; the other neck was opened as a vent. After flushing with nitrogen for 10 min, sodium metal (0.22 g, 8.69 mmol; cleaned, washing with hexane, then methanol, then cut into small pieces) was

added to the stirred mercury. The reaction mixture was stirred until sodium slowly formed a solid amalgam with the mercury. Compound **10** (0.12 g, 0.35 mmol) in THF (5mL) was transferred into the reaction flask, then 100% ethanol (3 mL) was added. The reaction was stirred under nitrogen at 50 °C. After 10 h, the reaction was shown to be complete by TLC (silica gel; hexane: ethyl acetate, 8:2). The reaction solution was poured into DI water (200mL). The mixture was extracted with ethyl ether (3 x 10 mL), then the combined ether layers were washed with 10% citric acid (2 x 10 mL), followed by sat'd. NaCl solution (2 x 10 mL). The organic layer was dried (MgSO₄) and then concentrated under vacuum. The residue was yellow oil **11** (0.13 g of a 60:40 mixture of cis and trans isomers, crude yield 95%). An analytical sample (light yellow solid oil) was purified by column chromatography (silica gel, hexane/ethyl acetate, 9/1): ¹H-NMR (300 MHz, CDCl₃) δ 2.68 (s, 6H_g trans isomer), 2.69 (d, J=5 Hz, 2H_c cis isomer), 2.82 (s, 6H_g cis isomer), 2.83 (d, J=5 Hz, 2H_c trans isomer), 3.83 (t, J=5 Hz, 1H_f cis isomer), 3.99 (t, J=5 Hz, 1H_f trans isomer), 5.70 (s, 1H_h trans isomer), 5.76 (s, 1H_h, cis isomer), 6.82 (d, J=7.2 Hz, 2H_d trans isomer), 6.85 (d, J=7.2 Hz, 2H_d cis isomer), 7.12-7.3 (m, 9H, trans and cis isomers), 7.65 (d, J=7.2 Hz, 2H_a trans isomer), 7.8 (d, J=7.2 Hz, 2H_a cis isomer). MS (CI, relative intensity), m/z 360 [(M-H₂O+NH₄)⁺, 10], 343 [(M-H₂O+H)⁺, 100], 269 (20). Anal. Calcd for C₂₄H₂₄O₃: C, 79.97; H, 6.71. Found: C, 79.53; H, 7.22.

23

12

9-Hydroxy-10-(2-oxoethyl)-10-phenyl-9,10-dihydroanthracene (23). In a 10-mL round-bottom flask, compound 11 (0.1 g, 0.28 mmol) was dissolved in methylene chloride (6 mL), trifluoroacetic acid (1 mL), 100% ethanol solution (1 mL) was slowly introduced. The reaction was stirred under N₂ at RT. After 20 h, the reaction was shown to be complete by silica gel TLC (hexane/ethyl acetate, 8/2, new spot at higher R_f). The completed reaction solution was diluted with methylene chloride (10 mL), washed with sat'd. sodium bicarbonate solution (3 x 10 mL), followed by sat'd. sodium chloride solution, then dried (MgSO₄). The dried solution was concentrated by vacuum. After purification by column chromatography (silica gel, hexane: ethyl acetate, 9:1), compound 23 (0.07 g of a 60:40 mixture of cis and trans isomers, clear oil, 79.5% yield) was obtained: ¹H-NMR (300 MHz, CDCl₃) δ 3.39 (d, J=2.5 Hz, 2H_e cis isomer), 3.5 (d, J=2.5 Hz, 2H_e trans isomer), 5.24 (s, 1H_g trans isomer), 5.71 (s, 1H_g cis isomer), 7.0-7.33 (m, 5H_{phenyl} and 2H_b, and 2H_c, and 2H_d cis and trans isomers), 7.58 (d, J=7.2 Hz, 2H_a trans isomer), 7.71 (d, J=7.2 Hz, 2H_a cis isomer), 9.18 (t, J=2.5 Hz, 1H_f cis isomer), 9.52 (t, J=2.5 Hz, 1H_f trans isomer).

10-(3-Oxopropyl)-10-phenylanthrone (12). Compound 7 (2.06 g, 6.64 mmol) was dissolved in dry THF (20 mL). The solution was stirred at 0 °C. 1M BH₃-THF (12 mL, 0.012 mmol) was added by syringe. After 30 min, the reaction was concentrated to dryness by vacuum and diluted with methylene chloride (10 mL), then solution of PCC (7.16 g, 33.3 mmol) in methylene chloride (20 mL) was added. The reaction was stirred at reflux for 3 h, then cooled to RT. The solution was passed through an alumina column (50 g) which was then washed with additional methylene chloride. The combined organic solution was concentrated by vacuum. Column chromatography (silica gel, hexane/ ethyl acetate, 9/1) effectively separated compound 12 (0.57 g, 27% yield) from isomeric compound 17 (0.22g, 10% yield). Compound 12: mp 151-152 °C, IR (film) 2820(CH from aldehyde), 2684 (CH from aldehyde), 1722 (RCHO), 1660 (9-carbonyl), 1601 (conjugated C=C) cm⁻¹; ¹H NMR δ 1.82 (t, J= 7.5 Hz, 2H_f), 2.90 (t, J= 7.5 Hz, H_e), 7.06 (dd, J_{ortho}= 7.5 Hz, J_{meta}= 1Hz, H_d), 7.25 (m, 5H_{phenyl}), 7.42 (dt, J_{ortho}= 7.5 Hz, J_{meta}= 1 Hz, 2H_c or 2H_b), 7.48 (dt, J_{ortho}= 7.5 Hz, J_{meta}= 1Hz, 2H_b or 2H_c), 8.39 (dd, J_{ortho}= 7.5 Hz, J_{meta}= 1Hz, 2H_a), 9.44 (s, 1H_g); MS (EI, relative intensity), m/z 326 (M⁺, 8), 269 (100), 239 (33). Anal. Calcd for C₂₃H₁₈O₂: C, 84.64; H, 5.56. Found: C, 84.26; H, 5.64.

Attempted preparation of 10-(3-Oxopropyl)-10-phenylanthrone (12) by other methods.

Lewis acid method with different conditions:

1). Compound **8** (0.28 g, 0.86 mmol) was dissolved in benzene (5 mL), and boron trifluoride etherate (0.25 g, 1.76 mmol, $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$) was introduced. The reaction was stirred under N_2 at RT. After 30 min, the starting epoxide had been consumed; however, NMR showed no evidence of the expected aldehyde.

2). Compound **8** (0.145 g, 0.468 mmol) was dissolved in ethyl ether (3 mL), and boron trifluoride etherate (0.25 g, 1.76 mmol, $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$) was introduced. The reaction was stirred under N_2 at 0 °C. After 5 h, the starting epoxide had been consumed; however, NMR showed no evidence of the expected aldehyde.

3). Compound **8** (0.12 g, 0.368 mmol) was dissolved in methylene chloride (3 mL), and boron trifluoride etherate (0.42 g, 2.96 mmol, $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$) was introduced. The reaction was stirred under N_2 at -78 °C. After 10 h, the starting epoxide had been consumed; however, NMR showed no evidence of the expected aldehyde.

Wittig Reaction Method:

Sodium hydride (0.14 g, 5.8 mmol) was washed with anhydrous ether, then the last trace of ether was removed by vacuum. Dry DMSO (10 mL) was introduced to the sodium hydride, and the mixture was stirred with N_2 and placed in an oil bath (60 °C). After 20 min, the oil bath was removed. Until the mixture was cooled to 23 °C, methoxymethyltriposponium ($\text{Ph}_3\text{PCH}_2\text{OCH}_3\text{Cl}$, 3 g, 8.79 mmol) was added to produce a deep red solution. The solution was stirred for an additional 15 min, then compound **9** (0.18 g, 0.58 mmol) in DMSO (5 mL) was introduced by syringe. This mixture was then allowed to stir at 45 °C overnight. The resultant mixture was cooled to RT, poured into

ice-water, then extracted with CH_2Cl_2 thoroughly. The combined organic layers were washed with water, followed by brine, then dried (MgSO_4). After filtration, the product was concentrated to dryness. There was no evidence of compound 12 in the crude reaction product.

10-(3,3-Dimethoxypropyl)-10-phenylanthrone (13). Compound 12 (0.2 g, 0.61 mmol) was dissolved in methylene chloride (5 mL). *p*-Toluenesulfonic acid (0.05 g), and trimethylorthoformate (0.066 g, 0.62 mmol) were added. The mixture was stirred overnight at RT. The reaction solution was washed with sat'd. sodium bicarbonate (2 x 15 mL) and sat'd. sodium chloride aqueous solution (2 x 15 mL). The washed solution was dried (MgSO_4) and concentrated by vacuum. After the purification by column chromatography (silica gel, hexane : ethyl acetate, 9:1), a white solid was obtained. Compound 13 (0.18 g, yield: 76%): mp 106-108 °C. IR (film) 1659 (9-carbonyl), 1601 (conjugated C=C), 1127 (C-O) cm^{-1} ; ^1H NMR δ 0.92 (ddt, $J_{\text{ef}}=7$ Hz, $J_{\text{hf}}=5$ Hz, $J_{\text{ff}}=2$ Hz, 2H_f), 2.62 (dt, $J_{\text{ef}}=7$ Hz, $J_{\text{ee}}=2$ Hz, 2H_e), 3.05 (s, 6H_g), 4.12 (t, $J_{\text{hf}}=5$ Hz, 1H_h), 7.08 (d, $J=7.5$ Hz, 2H_d), 7.20-7.25 (m, $5\text{H}_{\text{phenyl}}$), 7.39 (t, $J=7.5$ Hz, 2H_c or 2H_b), 7.47 (t, $J=7.5$ Hz, 2H_c or 2H_b), 8.37 (d, $J=7.5$ Hz, 2H_a). MS (EI, relative intensity), m/z 372

(M⁺, 16), 269 (100), 239 (40.5), 75 (79), 71 (48). Anal. Calcd for C₂₅H₂₄O₃: C, 80.62; H, 6.49. Found: C, 80.43; H, 6.51.

10-(3,3-Dimethoxypropyl)-9-hydroxy-10-phenyl-9,10-dihydroanthracene (14).

Mercury (13 g, 64.8 mmol) was added to a 25-mL two neck round-bottom flask with magnetic stirring. One neck of the flask was connected to nitrogen flow; the other neck was opened as a vent. After flushing with nitrogen for 10 min, sodium metal (0.30 g, 3 mmol, cleaned washing with hexane, then methanol, then cut into small pieces) was added to the stirred mercury. The reaction mixture was stirred until sodium had slowly formed solid amalgam with the mercury. Compound 13 (0.36 g, 0.93 mmol) in THF (10 mL) was transferred into the reaction flask, then 100% ethanol (6 mL) was added. The reaction was stirred under nitrogen at 50 °C. After 10 h., the reaction was shown to be complete by TLC (silica gel; hexane: ethyl acetate, 9:1). The reaction was poured into DI water (50 mL). The aqueous solution was extracted by ethyl ether (3 x 15 mL). The combined ether layers were washed with 10% citric acid (2 x 15 mL) and followed by saturated NaCl solution (2 x 20 mL). The organic layer was dried (MgSO₄) then concentrated by vacuum. The residue was shown as yellow oil 14 (0.34 g of a 55:45 mixture of cis and trans isomers, crude yield 95%). The analytical sample (light yellow oil) was obtained by column chromatography (silica gel, hexane/ethyl acetate, 9/1). Compound 14: IR (film) 3576 (O-H), 1600 (conjugated C=C), 1126 (C-O) cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 1.04 (ddt, J_{er}=7 Hz, J_{hr}=5 Hz, J_{rr}=2 Hz, 2H, cis isomer), 1.32

(ddt, $J_{ef}=7$ Hz, $J_{hf}=5$ Hz, $J_{ff}=2$ Hz, $2H_f$ trans isomer), 2.41 (dt, $J_{ef}=7$ Hz, $J_{ee}=2$ Hz, $2H_e$ cis isomer), 2.52 (dt, $J_{ef}=7$ Hz, $J_{ee}=2$ Hz, $2H_e$ trans isomer), 3.05 (s, $6H_g$ trans isomer), 3.08 (s, $6H_g$ cis isomer), 4.14 (t, $J_{hf}=5$, $1H_h$ cis isomer), 4.16 (t, $J_{hf}=5$, H_h trans isomer), 5.71 (s, $1H_i$ trans isomer), 5.74 (s, $1H_i$ cis isomer), 6.89 (d, $J_{ortho}=7.5$ Hz, $J_{meta}=1$ Hz, H_d cis isomer), 7.0 (d, $J_{ortho}=7.5$ Hz, $J_{meta}=1$ Hz, $2H_d$ trans isomer), 7.1-7.28 (m, $5H_{phenyl}$, and $2H_b$, and $2H_c$ cis and trans isomers), 7.66 (d, $J_{ortho}=7.5$ Hz, $J_{meta}=1$ Hz, H_a trans isomer), 7.73 (d, $J_{ortho}=7.5$ Hz, $J_{meta}=1$ Hz, H_a cis isomer); MS (EI, relative intensity), m/z 374 (M^+ , 8), 342 (24), 310 (66), 271 (100). Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 75.91; H, 7.41.

9-Hydroxy-10-(3-oxopropyl)-10-phenyl-9,10-dihydroanthracene (24). Compound 14 (0.1 g, 0.26 mmol) was dissolved in methylene chloride (6 mL) and stirred under N_2 . Trifluoroacetic acid (1 mL) 100% ethanol (1 mL) and water (1 drop) was slowly introduced. After 20 h at RT, the reaction was shown to be complete by TLC (hexane/ethyl acetate, 8/2, new spot at higher R_f). Methylene chloride (10 mL) was

added to the solution which was washed with sat'd. sodium bicarbonate (2 x 10 mL), sat'd. sodium chloride (2 x 10 mL), then dried (MgSO₄). The dried solution was concentrated by vacuum. After the purification by column chromatography (silica gel, hexane: ethyl acetate, 9:1), compound 24 (clear oil, 0.05 g of a 55:45 mixture of cis and trans isomers, 56%) was obtained: ¹H-NMR (300 MHz, CDCl₃) δ 1.85 (t, J_{ef}=7.5 Hz, 2H_f, cis isomer), 2.3 (t, J_{ef}=7.5 Hz, 2H_f, trans isomer), 2.71 (t, J_{ef}=7.5 Hz, 2H_e, cis isomer), 2.85 (t, J_{ef}=7.5 Hz, 2H_e, trans isomer), 5.47 (s, 1H_h, trans isomer), 5.85 (s, H_h, cis isomer), 6.88 (d, J=7.5 Hz, 2H_d, cis isomer), 6.94 (d, J=7.5 Hz, 2H_d, trans isomer), 7.1-7.29 (m, 5H_{phenyl}, and 2H_b, and 2H_c, cis and trans isomers), 7.57 (d, J=7.5 Hz, 2H_a, trans isomer), 7.73 (d, J=7.5 Hz, 2H_a, cis isomer), 9.28 (s, 1H_g, trans isomer), 9.44 (s, 1H_g, cis isomer).

9-Allyl-10-phenylanthracene (20). Compound 15 (0.2 g, 0.64 mmol) was dissolved in chloroform (10mL), then aqueous trifluoroacetic acid solution (5 mL; acid:water, 1:1) was introduced. The reaction was stirred at RT overnight. After the reaction was completed, the reaction mixture was extracted with chloroform (3 x 15 mL) and the combined chloroform layers were washed with sat'd. NaHCO₃ (3 x 10 mL) and sat'd. NaCl (2 x 10 mL), dried (MgSO₄) and concentrated by vacuum. The product was purified by silica gel column chromatography. Compound 20 (0.16 g, 85% yield): mp 180-182 °C; IR (film) 1549 (conjugated C=C) cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 4.45 (d, J=7.5 Hz, 2H_e), 5.05 (dd, J_{gf}=17.4 Hz, J_{gg}=1.6 Hz, 1H_g), 5.12 (dd, J_{gf}=10.2 Hz, J_{gg}=1.6 Hz, 1H_g),

6.26 (m, 1H_f), 7.34 (dt, J_{ortho}=7.5 Hz, J_{meta}=1 Hz, 2H_i), 7.41 (dd, J_{ortho}=7.5 Hz, J_{meta}=1 Hz, 2H_h), 7.5-7.6 (m, 1H_j, 2H_b and 2H_c), 7.67 (dd, J_{ortho}=7.5 Hz, J_{meta}=0.5 Hz, 2H_d), 8.30 (dd, J_{ortho}=7.8 Hz, J_{meta}=0.5 Hz, 2H_e). ¹³C NMR (75 MHz, CDCl₃) δ 32.22, 116.14, 124.52, 124.76, 125.36, 126.04, 127.35, 127.42, 127.76, 127.84, 128.32, 129.56, 130.11, 131.35, 136.47; MS (EI, relative intensity), m/z 294 (M⁺, 100), 279 (18), 252 (24), 217 (24). Anal. Calcd for C₂₃H₁₈: C, 93.84; H, 6.16. Found: C, 91.63; H, 6.34.

9-Allyl-10-phenylanthracene (20) in attempted preparation of methoxymethyl protected alcohol. Compound 15 (0.17g, 0.54 mmol) was dissolved in chloroform (10mL). Dimethyloxymethane (3 mL, large excess) and phosphorus pentoxide (1.5 g, 10.56 mmol) were added. The reaction was stirred at RT under N₂. After 24 hours, the reaction was completed and poured into an ice-cooled sat'd. sodium carbonate solution. The remaining substance in the reaction flask was washed out with additional sat'd. sodium carbonate solution and the combined mixture was extracted with ethyl ether (3 x 10 mL). The combined ether layers were washed with sat'd. NaCl solution, dried (MgSO₄), then concentrated by vacuum. The product was compound 20, not the anticipated alcohol.

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9-Hydroxy-10-phenyl-9,10-dihydro-9,10-(1-hydroxy-1-methyl)ethanoanthracene

(21). Mercury (13 g, 64.8 mmol) was added to a 25-mL two neck round-bottom flask with magnetic stirring. One neck of the flask was connected to nitrogen flow; the other neck was opened as a vent. After flushing with nitrogen for 10 min, sodium metal (0.3 g, 13 mmol; cleaned washing with hexane, then methanol, then cut into small pieces) was introduced to the stirred mercury. The reaction was stirred until the sodium had slowly formed a solid amalgam with the mercury. Compound 17 (0.136 g, 0.42 mmol) was dissolved into THF (10 mL) and transferred into the flask which contained the sodium mercury amalgam. 100% Ethanol (5 mL) was added, then reaction was stirred under N₂ at 50 °C. After 10 h, the reaction was shown to be complete by TLC (silica gel plate, hexane: ethyl acetate, 9:1). The reaction mixture was cooled and poured into DI water (50 mL). The aqueous solution was extracted by ethyl ether (3 x 15 mL), then the combined ether layers were washed with 10% citric acid (2 x 15 mL), sat'd. NaCl solution (2 x 20 ml), then dried (MgSO₄). The dried ether solution was concentrated by vacuum. Compound 21 (0.06 g, 43.5% yield) was isolated as a white solid by column

chromatography (silica gel, hexane:ethyl acetate, 8:2). Compound **21**: mp 246.2-246.7 °C; ¹H NMR (300 MHz, CDCl₃) δ 0.98 (s, 3H_f), 2.16 (d, J=12.9 Hz, 1H_c or 1H_e), 2.26 (d, J=12.9 Hz, 1H_c or 1H_e), 5.26 (s, 1H_h), 5.45 (s, 1H_g), 6.71 (dd, J_{ortho}=7.5 Hz, J_{meta}=1.1 Hz, 1H_d or 1H_{d'}), 6.76 (dd, J_{ortho}=7.5 Hz, J_{meta}=1.1 Hz, 1H_d or 1H_{d'}), 6.94 (dt, J_{ortho}=7.5 Hz, J_{meta}=1.4 Hz, 1H_c or 1H_c or 1H_b or 1H_{b'}), 6.97 (dt, J_{ortho}=7.5 Hz, J_{meta}=1.4 Hz, 1H_c or 1H_c or 1H_b or 1H_{b'}), 7.10 (dt, J_{ortho}=7.5 Hz, J_{meta}=1.1 Hz, 1H_c or 1H_c or 1H_b or 1H_{b'}), 7.14 (dt, J_{ortho}=7.5 Hz, J_{meta}=1.1 Hz, 1H_c or 1H_c or 1H_b or 1H_{b'}), 7.41 (m, 5H_{phenyl}), 7.54 (dd, J_{ortho}=7.5 Hz, J_{meta}=1.4 Hz, 1H_a or 1H_{a'}), 7.56 (dt, J_{ortho}=7.5 Hz, J_{meta}=1.4 Hz, 1H_a or 1H_{a'}); MS (CI, relative intensity), m/z 674 [(2M+NH₄)⁺, 6], 346 [(M+NH₄)⁺, 100], 328 [(M-H₂O), 10], 270 (20). Anal. Calcd for C₂₃H₂₀O₂: C, 84.12; H, 6.14. Found: C, 83.46; H, 6.20.

10-(2-Hydroxyethyl)-10-phenylanthrone (22). Compound **9** (0.08 g, 0.258 mmol) was dissolved in THF (6 mL) and ethanol (3 mL) was added. Sodium borohydride (0.03 g, 0.794 mmol), water (1 mL) was introduced dropwise by syringe. The reaction was stirred under N₂ at RT. After 20 min, the reaction was judged to be completed by TLC. Concentrated 15 N NH₄OH (1 mL) was added. The mixture was stirred for another hour and poured into cold water (40 mL). The aqueous solution was extracted with ether (2 x 10 mL) and the combined ether layers washed with 1N HCl solution (2 x 10mL), followed by sat'd. NaHCO₃ (2 x 10 mL) and satd. NaCl (2 x 10 mL). The neutralized

ether solution was dried (MgSO_4) and concentrated by vacuum. Compound **22** was obtained as a white solid (0.026 g, 33% yield): $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 2.18 (s, 1H_g), 2.90 (t, $J=7.5$ Hz, 2H_c), 3.04 (t, $J=7.5$ Hz, 2H_f), 7.11 (d, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=0.5$ Hz, 2H_d), 7.20-7.28 (m, 5H_{phenyl}), 7.40 (dt, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=0.5$ Hz, 2H_c), 7.48 (dt, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2H_b), 8.36 (dd, $J_{\text{ortho}}=7.5$ Hz, $J_{\text{meta}}=1$ Hz, 2H_a). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 45.70, 48.56, 58.96, 126.68, 126.99, 127.89, 128.56, 128.60, 129.20, 130.98, 133.85, 147.31, 148.38, 183.72; MS (CI, relative intensity), m/z 332 [(M+NH₄)⁺, 98], 315 [(M+H)⁺, 100], 269 (25). Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{O}_2$: C, 84.05; H, 5.77. Found: C, 81.50; H, 6.40.

Attempted hydride rearrangement investigations of compound 23 (Model I) and 24 (Model II).

Three sets of basic reaction conditions were used in the attempt to effect an intramolecular hydride transfer to the side chain carbonyl:

1) The aldehyde model compound (0.03 g, either compound **23** or compound **24**) was dissolved in pyridine (3mL) with stirring under N_2 . 4 N Sodium hydroxide (3 mL) was introduced. The reaction was refluxed for 24 h, cooled to RT, then poured into cold 1N hydrochloric acid (10 mL). The acidic solution was extracted with ether (3 x 5 mL), and the combined ether layers were washed with sat'd. NaHCO_3 (2 x 10 mL), water (2 x 10 mL), then dried (MgSO_4). The dried solution was concentrated by vacuum and its proton NMR was recorded.

2) Sodium metal (0.37 g, 16 mmol) was dissolved in 100% ethanol (8 mL) with stirring and under N₂ to form sodium ethoxide. Next, the aldehyde model compound (0.05 g) in ether (2.5 mL) was introduced. The reaction was stirred at reflux for 18 h then cooled to RT. The cooled solution was poured into cold 1N hydrochloric acid (20 mL). The acidic solution then was extracted with ether (3 x 5 mL). The combined ether layers were washed with sat'd. NaHCO₃ (2 x 10 mL), water (2 x 10 mL), then dried (MgSO₄). The dried solution was concentrated by vacuum and its proton NMR was recorded.

3) Potassium metal (0.68 g, 7.4 mmol) was dissolved in 100% tert-butyl alcohol (8 mL) with stirring and under N₂ to form sodium tert-butoxide. Next, the aldehyde model compound (0.05 g) in ether (2.5 mL) was introduced. The reaction was stirred at reflux for 18 h then cooled to RT. The cooled solution was poured into cold 1 N hydrochloric acid (20 ml). The acidic solution then was extracted with ether (3 x 5 mL), and the combined ether layers were washed with sat'd. NaHCO₃ (2 x 10 mL), water (2 x 10 mL), then dried (MgSO₄). The dried solution was concentrated by vacuum and its proton NMR was recorded.

These last two solvent/base systems were apparently more effective, but still did not give clean products:

1) The aldehyde model compound (0.03 g) was dissolved in THF (3mL) with stirring and under N₂ and 4N sodium hydroxide aqueous solution (3 mL) was introduced. The

reaction was refluxed for 24 h then cooled to RT. After the reaction mixture was poured into cold 1 N hydrochloric acid (10 mL), the acidic solution was extracted with ether (3 x 5 mL), and the combined ether layers were washed with sat'd. NaHCO_3 (2 x 10 mL), water (2 x 10 mL), then dried (MgSO_4). The dried solution was concentrated by vacuum and its proton NMR was recorded.

2) The aldehyde model compound (0.03 g) was dissolved in dioxane (3mL) with stirring and under N_2 . 4 N Sodium hydroxide (3 mL) was introduced. The reaction was refluxed for 14 h then cooled to RT and poured into cold 1N hydrochloric acid (10 mL). The acidic solution was extracted with ether (3 x 5 mL). The combined ether layers were washed with sat'd. NaHCO_3 (2 x 10 mL), water (2 x 10 mL) and finally dried (MgSO_4). The dried solution was concentrated by vacuum and its proton NMR was recorded.

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