Synthesis of Model Compounds for Coal Liquefaction Research

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FOREWORD

This is the final progress report on IITRI Project No. C06722, Contract No. DE-AC-22-90-PC-900-37-000. This incorporates the results of the work carried out during the period April 15, 1990 through April 14, 1991. The objective of this study was to develop and optimize an appropriate method for the synthesis of a model compound, viz., containing tetrahydronaphthalene, naphthalene, and phenyl moieties linked by "Methylene, Ethylene and Ether Bonds," that is required by the U.S. Department of Energy in connection with their studies on the mechanism of coal liquefaction. The technical approach adopted by us in this research has been shown to be feasible. However, toward the conclusion of this project, we have recommended the pursuit of an alternate synthetic approach based on the use of commercially available (off-the-shelf) compounds in the intermediate stages.

We are happy to have been involved in this research and will greatly appreciate any future opportunities for contributing toward your efforts in the subject area.

Yours truly,

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ABSTRACT

Coal liquefaction investigations required the availability of model compounds for mechanistic investigations. Towards this end, IITRI was funded to develop an approach for the synthesis of one of the target compound. This study was carried out in several phases as outlined here. Initial synthetic investigations on obtaining 2-tetrolol was carried out using high pressure and temperature reduction with Raney nickel catalyst. The next step consisted in incorporation of a hydroxymethylene group at the C-3 position. This was successfully carried out utilizing 2-tetralol, formaldehyde, and calcium oxide. An alternate improved method was developed using 3-carboxyl-2-naphthol. This required less time, gave a cleaner product in higher yield. Efforts at the introduction of a chloromethylene group only yielded polymeric material or starting material in spite of protecting the phenolic group by various groups.

The synthesis of 3, 5-dimethyl-6-bromobenzyl chloride was successfully carried out by performing the Blank reaction on 2, 4-dimethyl bromobenzene. The product was characterized by GC/MS. Purification was not possible, as it was a complex mixture. Efforts at converting it to the acetate followed by separation too was not feasible. Unlike in the case of 2-hydroxytetralol, hydroxymethylation by established procedure yielded only the starting materials.

Commercially available 4-methoxy-1-naphthaldehyde was protected as the ethylene acetal. The Wittig reagent 3-chlorobenzyl phosphonium bromide was prepared and condensed with 4-methoxy-1-naphthaldehyde successfully and proved that the overall synthetic approach was proceeding in the desired direction.

All the necessary intermediates have been synthesized, and we have demonstrated using model compounds, that the synthetic objective can be attained.

1. INTRODUCTION

The processing of coal to yield diverse, economically useful products, clean energy and free from sulfur dioxide effluents necessitates a continuing investigation on the changes undergone by coal when it is subjected to a beneficiation process. One such process is the liquefaction of coal itself. During the beneficiation process, chemicals present in coal undergo a multitude of reactions, such as reduction and coupling to phenolic compounds present in coal. As a result, a whole new range of products are formed which could have economic significance. It is also known that inorganic salts present in the coal play an important function in chemical processing.

An ongoing interest in coal research is to obtain fundamental scientific information on the processes that occur to coal chemicals during the beneficiation and coal liquefaction process. This type of study has provided information on techniques for reducing sulfur dioxide and oxides of nitrogen emissions. Equally helpful has been the insight gained on the products obtained during these steps. The mechanistic aspects of chemical changes occurring in coal-based organic compounds has been investigated utilizing synthetic model compounds. A wide range of such model compounds have been synthesized and studied.

This current project concerns the synthesis of a compound which has as its structural features a tetrahydro naphthalene ring, a naphthol component and finally, a dimethyl substituted benzene ring. These three components are linked together in a highly organized manner. The linkage of the components are by methylene, ethylene, and ether bonds in an organized manner. It has been investigated under IITRI Project No. C06722, entitled "Synthesis of Model Compounds for Coal Liquefaction Research." In addition to this, due to practical problems of purification, the model compound has been modified. The dimethyl substituted benzene component has been replaced by a non substituted benzene ring in the modified final product. Approaches to this modified target compound is discussed in this report. The synthesis of the modified target compound was at the recommendation and suggestion of the sponsor.

The specific objective of this project was to synthesize one of the target compounds of interest to the Department of Energy, i.e, a Model Compound Containing Tetrahydronaphthalene, Naphthalene, and Phenyl Moieties Linked by "Methylene, Ethylene and Ether Bonds" under IITRI Project No. C06722, entitled "Synthesis of Model Compounds for Coal Liquefaction Research." A modified target compound synthesis as suggested by the sponsor is also described.

2. RETROSYNTHETIC ANALYSIS OF THE TARGET COMPOUND

2.1 Overall Approach

In order to carry out the synthesis of the above target compound, suitable intermediates had to be identified and synthesized. Toward this objective, a retrosynthetic analysis of the target compound was carried out. The objective of this was to use where possible commercially available starting compounds which could be converted to the reactive intermediate via known organic chemical manipulations. The target compound can be fragmented into three different reactive intermediates which, when linked in a particular order, is expected to yield the desired target compound.

The three reactive intermediates we thought would lead to the target compound were (1) substituted tetrahydronaphthalene [compound A], the 1-methoxynaphthaldehyde [B] 3,5-dimethyl-6-chlorobenzyl bromide [C]. Of these, the intermediate [B], 4-methoxy-1-naphthaldehyde, is commercially available and was purchased for this investigation. The intermediates [A], 5,6,7,8-tetrahydro-3-carboxyl-2-tetralol and 3,5-dimethyl-6-chlorobenzyl bromide had to be synthesized using commercially available compounds which could be by a series of chemical transformations be converted to [A] and [C].

3. EXPERIMENTAL METHODS

3.1 Synthesis of 5,6,7,8-Tetrahydro-3-Carboxyl-2-Tetralol

Commercially available Raney Nickel Catalyst was employed in the initial studies. No reduction of the starting material 2-naphthol (2) was observed as followed by UV scans of the reaction product. We had used literature stated conditions of 125° to 130°C temperatures and 1200 atmospheres of pressure.

Freshly prepared Raney Nickel Catalyst (W-6) was used in all studies at this point. Reduction proceeded in a facile manner to yield a product which was a mixture of the desired product (4) and the undesired cyclohexanol derivative (3). Compound (4) was separated from (3) by extraction with aqueous sodium hydroxide. The phenolic compound (4) was obtained by acidification of the basic extracts with hydrochloric acid and extracting the aqueous solution with an organic solvent such as ether.

3.2 Derivatization of 5,6,7,8-Tetrahydro-2-Tetralol

Literature reports indicate that Blank reactions are performed on protected compounds. We proposed to protect the phenolic hydroxyl group as the cathylate derivative (5) or the methyl ether derivative (6A). The derivative (6A/6B) is readily prepared by first converting 2-naphthol to the methyl ether by refluxing 2-naphthol with methanol in the presence of concentrated sulfuric acid. High pressure hydrogenation of the methyl ether under conditions established for 2-naphthol yielded the desired tetralin derivative (6). The reduction product is a mixture of the desired phenolic ether (6A) and the cyclohexyl methyl ether isomer (6B). The separation of (6A) from the cyclohexanol product (6B) is very impractical. So this procedure was slightly modified. The modification consisted of first reducing 2-naphthol to the mixture of (4). The undesired cyclohexanol derived product (3), followed by separation of (4) from (3) and finally derivatization either as the methyl ether (6A) or the cathylate (5). Yield = 45% for compound (4).

3.3 Cathylation of 5,6,7,8-Tetrahydro-2-Tetralol (4)

Prior to carrying out a Blank reaction, the cathylation of the starting material (4) was carried out. The starting tetralin [7.0 gm (4)] was dissolved in dry benzene (50 mL) followed by the addition of triethylamine (5 mL, 5.6 gm). To the above stirred reaction mixture, cathyl chloride (7.7 mL, 6.6 gm) was added drop-wise. The reactants were allowed to stir at 50°C for 1 hour and worked upon. NMR of the crude reaction mixture showed that the desired cathylate (5) had been obtained. This reaction was performed several times to standardize conditions.

3.4 Introduction of Hydroxymethylene and Chloromethylene Groups into Desired Starting Compounds

In order to synthesize the target compound, it is necessary to introduce functionalized C-1, units in intermediates [A] and [C]. For this purpose we investigated two reactions, i.e, (i) the Blank reaction whereby a chloromethylene group is incorporated into the target compound and (ii) a hydroxymethylene group. The latter can be further modified by a variety of ways to enable further condensation reactions.

3.4.1 Utilization of Blank Reaction for the Synthesis of 3,5-Dimethyl-6-bromobenzylchloride

Several reactions were carried out to standardize the process with the objective of obtaining the pure product (8) in high yield. Initial investigations were performed using small quantities of 2,4-dimethylbromobenzene (7). The starting material (7, 1.85 g), and formalin (1.3 mL) were mixed, and anhydrous hydrogen chloride gas was bubbled through the reaction mixture, maintained at 70° to 75°C for 8 hours. The product was isolated and subjected to GC/MS analysis. It was a complex mixture, the desired product (8) along with compounds (9) and (10) were identified to be present in the reaction mixture. Due to the structural similarity separation was not attempted.

A greater yield of (8) was obtained when the reaction was allowed to proceed for 16 hours at the above conditions but separation problems persisted.

3.4.2 Use of Paraformaldehyde

The next modification consisted in changing the source of formaldehyde. Thus paraformaldehyde was used in place of formalin. The other parameters remained unchanged. This was done to maintain a large excess of formaldehyde in the reaction mixture. Replacement with paraformaldehyde did not improve the yield of (8).

To date the best results have been obtained by using formalin and bubbling dry HCl gas for 16 hours at 70° to 75°C.

The problem of purification of the product has yet to be solved as the boiling points of the starting material and the reaction products particularly the isomeric products are expected to be very close. Lack of a spinning band distillation apparatus has made purification difficult.

3.4.3 Alternate Approach

We proposed to overcome the problem of separation of starting materials and products by the approach shown below. The reaction mixture obtained, i.e., (8, 9, and 10), will now be represented by the number (11).

We expected to separate the Blank reaction products (8, 9) and (10) collectively labelled as (11) by converting to the respective acetates. A crude mixture containing the desired compound (8) (1.0 g) was dissolved in dry DMF, followed by the addition of anhydrous potassium acetate (0.19 g). The reaction mixture was worked up the next day. IR spectral analysis did show a weak peak at 1750 cm^{-1} indicating the presence of a carbonyl compound, but the yields were low and this approach was not pursued.

3.4.4 Introduction of a Hydroxymethylene Group Into 2,4-Dimethyl Bromobenzene

Due to the problems presented in separating the products of the Blank reaction, it was decided to attempt a hydroxymethylation of the starting material (7). This was done as the reaction product being polar would have substantially different boiling points than the starting materials, which would have enabled us to carry out an effective separation.

Thus 2,4-dimethylbromobenzene (1.85 g), water (8.0 mL), formalin (0.9 mL), and calcium oxide (0.28 g) were mixed and stirred for a long period. IR and NMR spectra of the product showed only unchanged starting material, and none of the desired compounds (12). This approach was not further pursued.

3.4.5 Chloromethylation of 5,6,7,8-Tetrahydro-2-Hydroxycathylate

We attempted the chloromethylation of 5,6,7,8-tetrahydro-2-hydroxycathylate (5) according to a modified procedure of the Blank reaction. The reaction was performed at 0°C instead of the standard conditions of 70° to 75°C . This was done to avoid polymerization and also deprotection of the phenolic group. Thus the cathylate (5, 500 mg) was transferred to a clean three-necked flask fitted with stirring arrangement, a condenser and a hydrogen chloride inlet. Formalin (0.5 mL) and concentrated HCl was added. The reaction mixture was stirred at 0° in a stream of HCl gas. A tacky product (13) was isolated. A GC/MS analysis showed that only starting material had been recovered. This indicated that incorporation of the $\text{CH}_2\text{-Cl}$ group would be difficult by this approach, and it was not pursued any further.

3.4.6 Hydroxymethylation of 5,6,7,8-Tetrahydro-2-Hydroxy Cathylate

The problems posed by the Blank reaction suggested to us that an alternate route be investigated and developed for the incorporation of a functionalized C unit. The incorporation of a hydroxy methylene group results in generating great flexibility in terms of chemical transformations, leading to a reactive intermediate.

We proposed to investigate the possibility of incorporating the hydroxymethylene group into the cathylate (5) by a known literature procedure. Several reactions were carried out in order to standardize the process. Overall, the cathylate (5, 1.4 g) water (8.0 mL), formalin (0.9 mL), and calcium oxide (0.28 g) were mixed together and shaken in a wrist shaker for 16 hours at room temperature. The product was isolated. Both NMR and IR confirmed that a hydroxymethylene group had been incorporated into the reaction product. IR spectral analysis showed a broad absorbance at 3350 to 3550 cm^{-1} (OH group). NMR spectra showed a singlet for CH_2OH . We expect that the product has the desired structure (14) based on the fact that hydroxylation at C-1 is not sterically unfavorable. This step was standardized and yield scaled up to a 10-12 gram quantity level.

3.4.7 Hydroxymethylation of 5,6,7,8-Tetrahydro-2-Hydroxy Tetralol

Having established the possibility of introducing a hydroxymethylene group into (5) we were interested in carrying out the same reaction on 5,6,7,8-Tetrahydro-2-Tetralol (4). The objective of attempting this reaction was to study the possibility of using unprotected tetrolol (4) as it would save time and increase the yield of the desired intermediate.

The target compound was successfully synthesized, thereby eliminating at this stage the need for cathylation. Thus the starting material (4, 1.48 g), formalin (0.9 mL), and water (8.0 mL), and calcium oxide (0.28 g) were mixed and shaken at room temperature for very long periods of time. The reaction product was isolated and the structure was established by an NMR analysis which showed a singlet for the CH_2OH . In addition the product on oxidation with pyridinium chlorochromate yielded a compound whose IR had a carbonyl absorption, confirming the introduction of a CH_2OH group into (4).

This step has been scaled up to the 10.0 gram quantities successfully. Efforts at hydroxymethylation of 1-naphthol only yielded a gummy tacky material which was not characterized by spectral methods.

3.5 Synthesis of the Ethylene Ketal of 4-Methoxy-1-Naphthaldehyde

At this stage of the investigations we had developed and standardized methods for the synthesis of 5,6,7,8-tetrahydro-2-hydroxytetralol and 3,5-dimethyl-6-chlorobenzyl bromide, the latter in a crude form. We had identified a source for 1-hydroxy-4-naphthaldehyde which would form the [B] component of the target compound.

Attempts at the incorporation of a C-1 unit into 1-naphthol showed that practical difficulties will arise and also identification of a commercial source for 4-methoxy-1-naphthaldehyde resulted in the saving of considerable time. [B] was functionally and correctly set up. However, the aldehyde group had to be protected as an ethylene ketal in order to eliminate side reactions. For this purpose the following procedure was adopted. Commercially available 4-methoxy-1-naphthaldehydes (25.0 gm), ethylene glycol (13.0 mL), tosic acid, and benzene (250 mL) were reacted utilizing a Stark water separator: the product was isolated by standard procedure. Unreacted starting material was removed by washing the reaction mixture with sodium bisulfite, and the product was characterized by IR spectral analysis which showed the absence of a carbonyl peak (1695 to 1725 cm^{-1}), 2700 and 2900 cm^{-1} peaks (aldehydic hydrogen) supporting the structure of the product (16).

3.6 Preparation of Wittig Reagent from 3-Chlorobenzyl Bromide

As a requirement of the synthesis, a Wittig reagent for 3-chloro-benzylbromide is necessary. For this purpose under anhydrous conditions 3-chlorobenzyl bromide (17) (4.3 mL, 5.0 g), triphenyl phosphine (8.8 g), and anhydrous benzene (30 mL) were allowed to react at room temperature. A solid white compound precipitated out of the reaction solution to yield the triphenyl phosphonium bromide solid (18). Yield = 6.95 g.

3.7 Wittig Condensation Product between Ylide (24) and 4-Methoxy-1-Naphthaldehyde (16)

As part of the standardization of the Wittig condensation reaction, the aldehyde [B] was condensed with the phosphonium salt (18). In a clean dry three necked flask under anhydrous conditions (3-chlorobenzyl) triphenyl phosphonium bromide (18) (4.664 g) was added. To this anhydrous ether (50 mL) was added and the slurry stirred for 15 min at room temperature, followed by the addition of phenyl lithium (5.5 mL, 1.8 Molar solution). The reaction mixture turned orange-red indicating the formation of the ylide (19).

To the ylide (19), an ethanol solution of the aldehyde ([B], 2.2 g) was added dropwise. The progress of the reaction was monitored by the disappearance of the orange-red solution. The product (20) was isolated by standard procedure. The GC/MS of the product showed it to be a single component with the expected parent peak at 294.5 and fragmentation pattern was consistent with the assigned structure (20). IR spectrum verified the structure assigned to the product. IR showed the total absence of a carbonyl absorption and also that of the aldehydic hydrogen.

4. PRESENTATION OF RESEARCH RESULTS AT DOE, PITTSBURGH

4.1 Modified Target Compound Synthesis

As a result of a technical presentation made at the DOE facilities at Pittsburgh to Dr. Udhaya Rao and Dr. Malvina Farcasiu, it was decided to incorporate certain modifications into the structure of the final target compound. In the original target compound the substituted benzene component consisted of 3,5-dimethyl-6-chlorobenzyl moiety. Although the synthesis of 3,5-dimethyl-6-chlorobenzyl chloride had been carried out successfully, the separation of the target compound from the reaction mixture was presenting problems. We were advised at the above meeting to use 3-chlorobenzyl bromide (17) as it is commercially available. We have followed up on this advice and carried out studies on model Wittig reaction. In addition, commercially available intermediate [B] was used for appropriate investigations.

In our earlier experimental study, the synthesis of 3-hydroxymethylene-5,6,7,8-tetrahydro-2-tetralol (15) was carried out successfully using a multi-step process and the product was obtained in low yield. This step has also been scaled up to the 10.0 g scale. We have now developed a new alternate route to the carboxylic acid using 3-carboxyl-2-naphthol (21) and is outlined below. This compound will also allow the synthesis of the target compound.

The advantage of this new approach to secure desirably substituted functionalized tetralin derivative were the following. The reduction took place only in the unsubstituted ring of naphthalene ring. This was chemically proved by the fact that pyridinium chlorochromate oxidation of the reduction product did not yield a ketone. This would have been the case if the cyclohexanol product (23) were also formed. The non-formation of the cyclohexanol product (23) resulted in the elimination of a purification step resulting in a modest increase in the yield of the reduced product. The phenolic acid (22) has great flexibility in terms of manipulation of functional groups for condensation purposes with (16).

Thus 3-carboxyl-2-naphthol was dissolved in ethanol and hydrogenated at 1400 atm/210°C for 80 hours to give a product whose structure has been confirmed by NMR and IR and UV.

The NMR spectra of this product showed the presence of the cyclohexyl methylene protons (1.8 to 2.8 ppm) and the aromatic protons (6.5 to 6.8 ppm). The IR of the product showed a broadband (3200 to 3600 cm^{-1} -OH group) (1650 to 1675 cm^{-1}) and UV showed the total absence of the starting material. This approach by us resulted in a cleaner product since hydrogenation is known to proceed only in the unsubstituted ring. This approach yielded an intermediate tetralin which is substituted in the desired manner, and can be manipulated functionally to yield the desired intermediate. In addition, unlike the reduction of the methyl ether of β -naphthol wherein separation of the phenolic

component from the cyclohexanol component is essential, the new approach eliminates separation and the yields are excellent.

4.2 Synthesis of the Acid Chloride of 5,6,7,8-Tetrahydro-3-Carboxy-2-Tetralol

- CHEMICALS:
1. 3-carboxyl-2-tetralol = 5.0 gm
 2. C_6H_6 = 10.0 mL
 3. $SOCl_2$ = 3.0 mL

The acid chloride was prepared by dissolving the tetralin derivative (22, 5.0 g) in benzene (10.0 mL) at room temperature under anhydrous conditions. To this, thionyl chloride (3.0 mL) was added dropwise and the reaction mixture was stirred overnight. The following day all unreacted benzene and thionyl chloride were removed under vacuum to yield a product (25) that was characterized by IR alone as acid chlorides tend to hydrolyze readily. IR showed a strong carbonyl absorption at approximately 1765 cm^{-1} . This was used immediately after preparation in order to avoid problems of hydrolysis.

4.3 Friedel-Crafts Reaction between Acid Chloride (25) and 4-Methoxycarbonylbenzaldehyde Ethylene Ketal (16)

- CHEMICALS:
1. Acid chloride (25) = 2.0 gm
 2. $AlCl_3$ = 1.27 gm
 3. Protected aldehyde (2) = 1.77 gm
 4. $PhNO_2$ = 5.0 mL

In a clean dry three-necked flask nitrobenzene (5.0 mL) was transferred, followed by aluminum chloride (1.27 g). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen. To this solution of aluminum chloride in nitrobenzene, the acid chloride (25) (2.0 g) was added and stirred for a further period of 15 min. At the end of this time, the protected aldehyde (2) (9.77 gm) whose synthesis had already been reported earlier by us was added and the reaction was stirred at room temperature. The course of the reaction was followed by IR and monitoring for the disappearance of the

acid chloride. The sample was worked up by pouring it into crushed ice containing HCl, extracting with dimethyl ether, washing with a sodium bicarbonate solution, water, and drying over sodium sulfate. A small amount of the product was isolated and the IR showed a peak in the keto region (1695 to 1705 cm^{-1}). We have repeated this experiment with 1,1,2,2-tetrachloroethane following the above procedure utilizing the quantities of starting materials, reagent and solvent.

1. Acid chloride = 5.48 gm
2. Arethoxy-1-naphthaldehyde ethylene actual = 6.57 g
3. Aluminum chloride = 3.47 g
4. 1,1,2,2-tetrachloroethane = 50 mL

A product has been isolated and its structure is being currently investigated by IR, NMR, and GC/MS. It is expected to have the structure (26). The change from nitrobenzene to tetrachloroethane was made as literature information show that a higher yield of the Friedel-Crafts reaction product is obtained when the latter solvent is used.

5. CONCLUSION

Several steps toward the synthesis of the final target compound has been successfully carried out. In particular, it is observed that a simple, and what appears to be a new approach for the synthesis of 3-carboxy-5,6,7,8-tetrahydro-2-tetralol (21), has been developed and scaled up to the 50 g scale. The product is more pure than that obtained by the standard method. Important steps such as model reaction of the Wittig condensation between the ylide 3-chlorobenzyl bromide (17) and 4-methoxy-1-naphthaldehyde (B), has been carried out successfully, indicating that the proposed synthetic pathways represent workable solutions towards the synthesis of the target compound. The modified target compound has eliminated the problems of poor yield and purity of the substituted benzene constituents. This would add to the prospects of an overall success of the project.

In addition, scale up to 10.0 g quantities of materials indicates that further scale-up of the intermediates may not pose difficult problems. We feel that if a continuation of the project were supported financially, the target compound could be prepared.

6. PROPOSED APPROACH FOR COMPLETION OF THE SYNTHESIS OF MODIFIED TARGET COMPOUND

6.1 Synthesis of Modified Target Compound

A major problem in the synthesis of the target compound rests on the synthesis and purification of the reactive intermediate, 3,5-dimethyl-6-bromobenzyl chloride (8) starting from 2,4-dimethyl bromobenzene (7). Blank reaction performed on the starting material yields several isomeric products as shown earlier.

As stated earlier, this was not anticipated in the initial phase of the work. In addition purification and separation of the isomers is a task all by itself. Our reports clearly have indicated the associated problems.

During our discussions with Dr. Rao and Dr. Farcasiu at the time of our technical presentation this point was raised and it was decided to replace (7) with 3-chlorobenzyl bromide which is properly substituted in terms of obtaining the modified target compound.

We are of the opinion as has also been communicated to Dr. Rao, that the modified target compound will have to be synthesized in two or three phases, these phases pertain to (1) standardization of the preparative procedure for gram quantities of the target compound, (2) scale-up to the 50.0 gm amounts, and (3) either synthesize several batches of 50.0 gm amount or standardize scale-up to the 200 gm level and prepare two batches at the 200.0 gm lots.

We have performed several steps towards proving the feasibility of our synthetic approach. The problem has been made easier due to the intermediate [7] being commercially available. As discussed earlier in this report the intermediate (22) is correctly substituted and can be used to carry out Friedel-Crafts condensation reaction with [16]. This condensation initially has been attempted with the acid chloride (25). We are currently investigating the products of this condensation, which we predict to be (26).

We are also proposing that compound (22) be transformed to the alcohol (24) as shown in the flow scheme below.

Prior to the reduction of (22) to (24), we are currently investigating protecting the phenolic group as its TBDMS derivative (27). This is being pursued as Friedel-Crafts condensation of (28) with (16), two protected phenolic groups will be obtained in the product (29). Normally, phenolic groups are protected as their phenolic ether. In this case, if both phenolic groups are protected as the methyl ethers, selectivity with respect to deprotection will be lost in all probability. The TBDMS deprotection, however, is carried out by tetra-n-butyl ammonium chloride or 0.1 N HF and NaF reagent. Methyl ethers are deprotected by TMSI and hence, by this method we will be obtaining great selectivity.

The phenol will be protected as the TBDMS derivative using TBDMSiCl. We have carried out a preliminary investigation of this reaction.

Friedel-Crafts reaction between (28) and (16) will directly introduce the methylene bridge as required in the target amount to yield the intermediate (29) as shown below

6.2 Wittig Condensation on Compound (30)

Model studies of the Wittig reaction between naphthaldehyde [16] and the Wittig reagent (17) has been successfully carried out in good yield. We believe that a good yield will also result with compound (30) after acid catalyzed deprotection to yield aldehyde as shown above in the scheme.

The intermediate (31) will be deprotected using either tetra-n-butyl ammonium bromide or 0.1 N hydrofluoric acid in the presence of sodium fluoride to yield the phenol (32). In the presence of a base, (32) is expected to undergo cyclization to yield the methyl ether of the target compound (33). Deprotection of the methyl ether will have to be standardized to deprotect preferentially the methyl ether and not the iphenyl ether bond to yield the unsaturated target compound (34). Hydrogenation will yield the target compound. Intermediate (32) may be first hydrogenated to (35) and then subjected to the above cyclization steps to yield (34).

Since there are sufficient quantities of the intermediates [B] and [17] and the tetralin carboxylic acid (22), we feel confident that with additional funding support we will be able to deliver the target compound initially at the gram scale.

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