Synthetic Approaches to 3*H*-Naphtho[2,1-*b*]pyrans and 2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyrans

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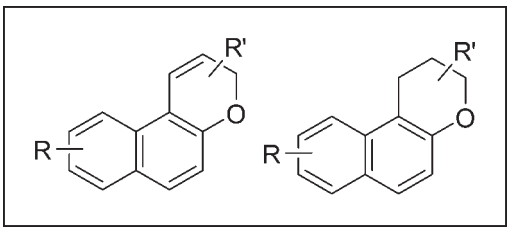

Naphtho[2,1-*b*]pyran nuclei are prevalent in natural products with significant biological and medicinal properties. 3,3-Disubstituted 3*H*-naphtho[2,1-*b*]pyrans are photochromic and find use in electronic display systems, ophthalmic lenses, optical switches, and temporary or permanent memories. Of the various possible structural isomers of naphthopyran framework, this review is an account of reported synthetic procedures to produce 3*H*-naphtho[*2*,1-*b*]pyrans and their dihydro analogs, 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans. The advantages and disadvantages of each procedure in terms of yields, complexity, formation of side-products, use of uncommon/expensive reagents, *etc*., are also described.

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INTRODUCTION

The pyran ring in the dihydronaphthopyran skeletons can be linearly or angularly fused to a naphthalene nucleus sharing one bond in several orientations. This leads to six different dihydronaphthopyran skeletons as shown in Figure 1. These compounds can also be viewed as dihydrobenzochromenes or dihydrobenzoisochromenes. This review deals with 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (a.k.a. 2,3-dihydro-1*H*-benzo[*f*]chromenes or 1*H*-benzo[*f*]chromans) and their dehydro analogs 3*H*-naphtho[*2*,1-*b*]pyrans (a.k.a. 3*H*-benzo[*f*]chromenes).

KNOWN PROPERTIES OF NAPHTHOPYRAN DERIVATIVES

3*H*-Naphtho[2,1-*b*]pyrans, also known as 3*H*-benzo[*f*]-chromenes (**1**), are well documented for their photochromic properties [1,2]. Photochromism can be seen as a reversible transformation of a chemical species induced in one or both directions by absorption of electromagnetic radiation. The mechanism involves facile electrocyclic reaction of pyran ring opening to yield a mixture of yellow or purple colored isomers (**2**). These colored species gradually cyclize, returning to the colorless pyran (**1**) ring upon thermal reaction (Scheme 1) [1,2].

This characteristic led to their application in transition lenses, which tinted upon exposure to the sunlight [3]. Photochromic properties of 3*H*-naphtho[2,1-*b*]pyrans also make them valuable to be used for a variety of other applications such as electronic display systems, optical switches, and temporary or permanent memories [4–6]. Furthermore, 3*H*-naphtho[2,1-*b*]pyrans and their oxygenated and/or partially reduced congeners have also been isolated from natural sources [7–9]; several analogs are reported to posses interesting biological activities [8–12]. Molecular structures of several representative examples are shown in Figure 2. A homoprenylated 3*H*-naphtho[2,1-*b*]pyran **3** was isolated from the roots of *Pentas bussei* [7]. In another case, several naphthopyrans including Adenaflorins C (**4**) were isolated from young leaves of *Adenaria floribunda* and bioassays show these compounds have cytotoxic effect against human cancer cells [8]. Bioassay-guided fractionation of extract of *Musa paradisiaca* cultivar using the quinone reductase induction assay led to the isolation of tetrahydro naphtho[2,1-*b*]pyran **5** (stereochemistry relative) [9]. Braccio *et al*. reported potent antiproliferative and cytotoxic properties of 1-*N*,*N*-dialkylamino-3*H*-naphtho[2,1-*b*]pyran-3-ones **6** [10]. Unsubstituted 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-3-one (**7**), a.k.a. splitomicin, its oxygenated analogs (**8**) and the dehydro-analog **9** were identified as a small molecule inhibitors of Sir2p, an NAD^+-dependent histone deacetylase required for chromatin-dependent silencing in yeast [11,12].

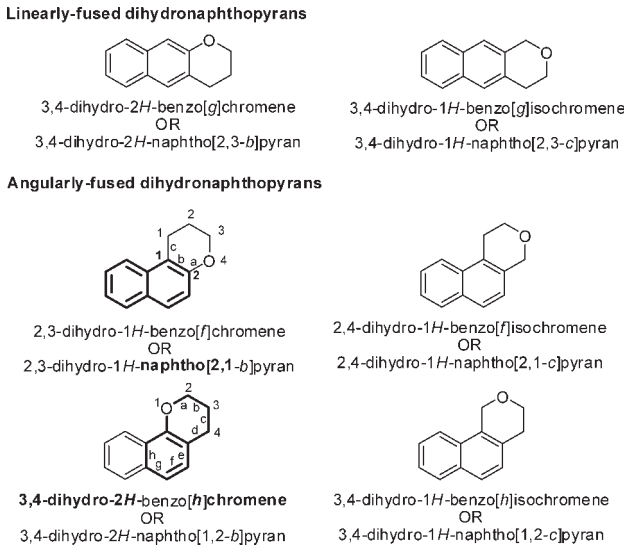


Figure 1. Dihydronaphthopyran skeletons sharing one bond between naphthalene and pyran.

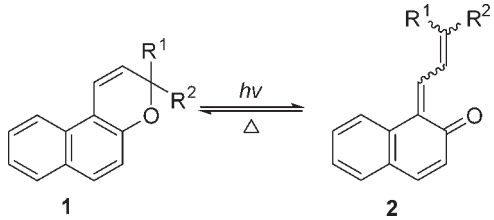
METHODS OF SYNTHESIS OF 3*H*-NAPHTHO[2,1-*b*]PYRANS

Synthesis and properties of 3*H*-naphtho[2,1-*b*]pyrans have been studied and reported extensively, providing a wide knowledge-base for these molecules. A review on the synthesis and photochromic properties of 3*H*-naphtho[2,1-*b*]pyrans was published in 2005 [13]. Although this review focuses mainly on the synthetic routes to 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans, a brief review of synthetic approaches to its dehydro analogs 3*H*-naphtho[2,1-*b*]pyrans will be presented here providing the update since last review [13] and highlighting the variety in chemical synthesis.

Some methodologies for preparing 3*H*-naphtho[2,1-*b*]pyrans involve multi-step strategies. Hepworth and his colleagues reported a synthesis of 1-bromo-3*H*-naphtho[2,1-*b*]pyrans (**11**) from the corresponding ketones (**10**) and PBr_3. 1-Substituted-3*H*-naphtho[2,1-*b*]pyrans (**12**) can then be further synthesized by reacting **11** with a wide range of electrophiles (Scheme 2) [14].

Jacobson and Vander Valde reported the synthesis of enantioenriched 3-methyl-3-(4-methylpent-3-enyl)-3*H*-naphtho[2,1-*b*]pyran-9-yl acetate (**16**) by kinetic resolution of the racemic mixture while attempting to synthesize (+)-teretifolione B (**14**), the monomer component of the potent anti-HIV agent concurvone (**15**, Scheme 3) [15]. Reaction of *E*-citral with 2,7-dihydroxynaphthalene produced racemic compound **16** in good yield [16]. Subsequent acylation followed by kinetic resolution using a manganese complex ((*R,R*)-**17**)-catalyzed asymmetric epoxidation at −78°C resulted in isolation of optically active (+)−**13** in 15% yield and 91% ee (Scheme 3).

Scheme 1. Pericyclic ring opening/closure in 3*H*-naphtho[2,1-*b*]pyrans.



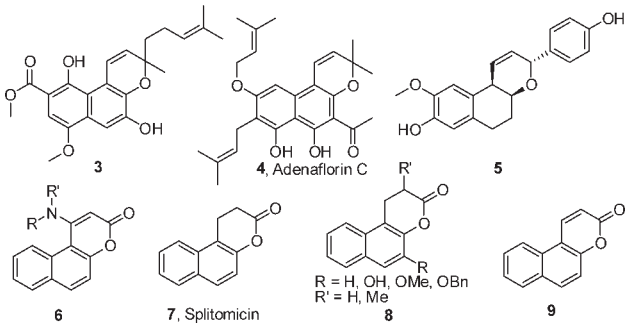


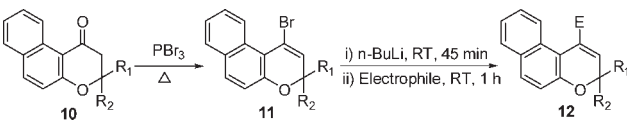
Figure 2. Examples of naturally occurring and biologically active 3*H*-naphtho[2,1-*b*]pyran derivatives.

While attempting removal of prenyl groups from protein by nucleophilic cleavage, Epstein and coworkers discovered that the 2-naphthoxide nucleophile produces prenylated 3*H*-naptho[2,1-*b*]pyrans [17]. They synthesized the prenylated 3*H*-naptho[2,1-*b*]pyrans **18** and **19** by carrying out an independent synthesis as depicted in Scheme 4. Reaction of sodium 2-naphthoxide with farnesyl bromide and geranylgeranyl chloride yielded 1-alkylated products **20** and **21**, respectively. DDQ-promoted oxidation of **20** and **21** resulted in formation of prenylated 3*H*-naptho[2,1-*b*]pyrans **18** and **19,** respectively [17].

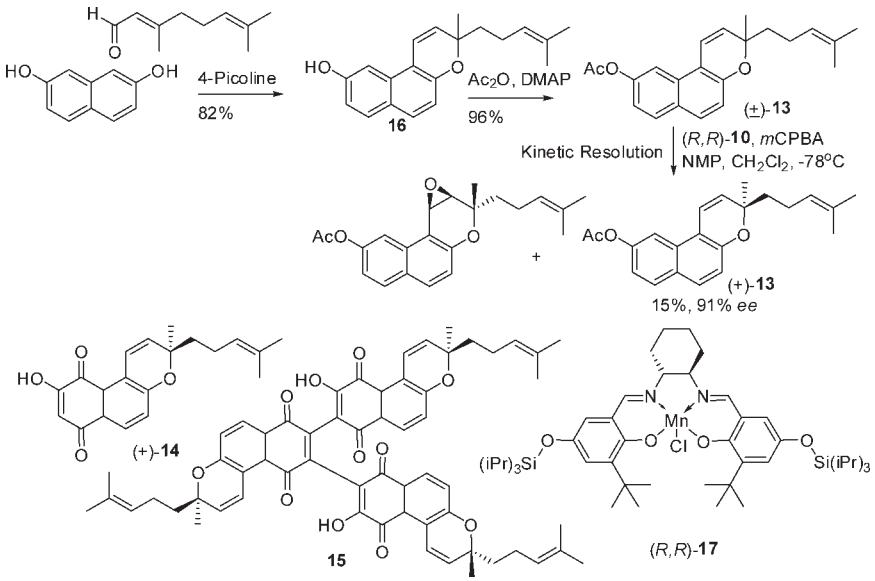
Epstein group then went on to provide more convincing evidence to the observation made during the reaction of prenylated proteins with 2-naphthoxide. They treated 2-naphthoxide with *S*-prenylated cysteine methyl ester with 2-naphthoxide in refluxing dioxane and obtained ~18% of prenylated 3*H*-naphtho[2,1-*b*]pyran **19** (Scheme 5) [17]. The reaction presumably involved C-1 alkylation, aerial oxidation, and [4+2] cycloaddition to yield the product.

Sosnovskikh and coworkers reported an interesting synthesis of a fused oxygen polycycle bearing 3*H*-

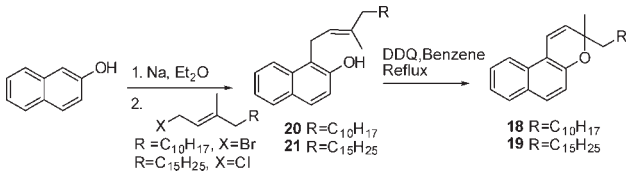
Scheme 2. Synthesis of 1-substituted-3*H*-naphtho[2,1-*b*]pyrans (**12**) from pyranones **10**.



Scheme 3. Synthesis of racemic and enantioenriched 3-methyl-3-(4-methylpent-3-enyl)-3*H*-naphtho[2,1-*b*]pyran-9-yl acetate (**13**).



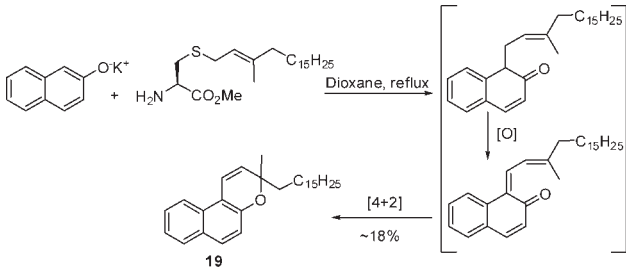
Scheme 4. Synthesis of prenylated 3*H*-naphtho[2,1-*b*]pyrans (**18** and **19**).



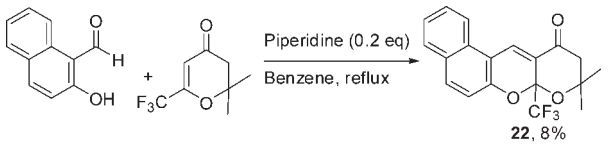
naphtho[2,1-*b*]pyran nucleus (**22**) in 8% yield by reacting polyhaloalkyl-substituted pyrones with 2-hydroxy-1-naphthaldehyde in presence of catalytic piperidine in refluxing benzene (Scheme 6) [18]. Similar reactions with other substituted salicyaldehydes gave higher product yields (12–94%). The authors proposed that a three-component adduct is initially formed either by Michael addition/Schiff's base formation or through Baylis-Hillman protocol, which cyclizes with concomitant elimination of the secondary amine [18].

Yadav and coworkers [19] have reported an elegant procedure to produce 1,3-disubstituted 3*H*-naphtho[2,1-*b*]pyrans (**23**) from 2-naphthol, a terminal acetylene and an aldehyde in presence of 10 mol % $GaCl_3$ in refluxing toluene (Scheme 7). The terminal acetylene and the aldehyde can have an aryl or an alkyl substituent. The authors proposed that the reaction proceeds *via* arylation of alkyne to afford vinyl naphthalen-2-ol. This intermediate subsequently undergoes cyclization with an aldehyde to give the desired naphthopyran.

Scheme 5. Synthesis of prenylated 3*H*-naphtho[2,1-*b*]pyran **19** from *S*-prenylated cysteine methyl ester as the prenyl donor.

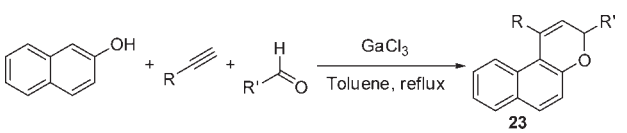


Scheme 6. Synthesis of an oxygen polycycle bearing 3*H*-naphtho[2,1-*b*]pyran nucleus (**22**).

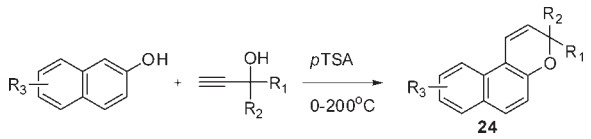


One of the most studied procedures for the preparation of 3*H*-naptho[2.1-*b*]pyrans uses the Claisen rearrangement of propargyl ethers obtained *in situ* from reaction of α,α-disubstituted propargyl alcohols with 2-naphthol under acidic conditions. For instance, 2-naphthol derivatives reacted with disubstituted propargyl alcohol in 1:1 molar ratio with *p*-toluenesulfonic acid (*p*TSA) as a catalyst (Scheme 8) to give naphthopyrans **24** [20]. The starting materials were dissolved in an aprotic organic solvent and reacted at temperatures

Scheme 7. Synthesis of 1,3-disubstituted 3*H*-naphtho[2,1-*b*]pyrans (**23**).



Scheme 8. 3,3-Disubstituted 3*H*-naphtho[2,1-*b*]pyrans (**24**) from 2-naphthols and α,α-disubstituted propargyl alcohols.



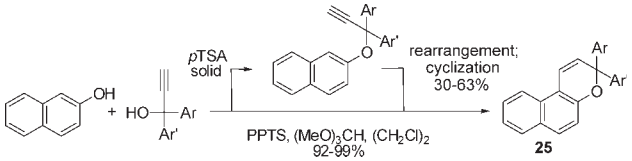
within the range of 0–200°C. However, this procedure did not provide satisfactory yield of the products (4–39%) [20].

In an improvement of this procedure, Tanaka reported a one-pot synthesis of naphthopyrans in the solid state. This reaction involved *p*TSA-catalyzed condensation of disubstituted propargyl alcohol with 2-naphthol in the first step. In the second step, naphthopyran derivatives (**25**) were obtained in moderate yield (30–63%) *via* cyclization of propargyl ether (Scheme 9) [21]. Hence, this solid-state reaction provided a green solvent-free efficient method for the synthesis of naphthopyran derivatives. Catalysts such as pyridinium *p*-toluenesulfonate (PPTS) have been used to improve yields in reactions of this nature. Zhao and Carreira used $(MeO)_3CH$ as a dehydrating agent to improve the synthesis of benzo/naphthapyrans derivatives (92–99%) [22]. In their report, disubstituted propargyl alcohols reacted with naphthol derivatives in the presence of 5 mol % PPTS and 2 equivalents of $(MeO)_3CH$ to yield various types of photochromic pyran systems (**25**, Scheme 9).

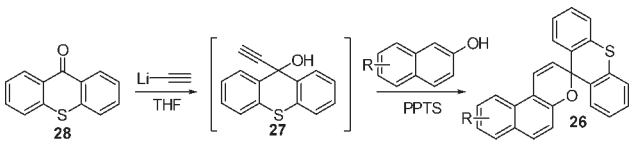
As shown in Scheme 10, Coelho *et al*. prepared spiro[thioxantene-naphthopyrans] **26** through a sequence of reactions. The alcohol intermediate (**27**) was obtained through the reaction of thioxanthone **28** with lithium acetylide in dry THF at 25°C, and reacted with 2-naphthol analogs without isolation to avoid degradation. After work-up, the desired 3*H*-naphtho[2,1-*b*]pyran products were obtained in low to moderate yield (9–61%) [23].

In another variation of this protocol, zeolite was used to condense 2-naphthols with α-alkynols to prepare 3*H*-naphtho[2,1-*b*]pyrans in reasonable yields (65–75%) [24]. Uemura's group used a thiolate-bridged diruthenium complex $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*Cl]$ to effect the same transformation with decent yields (64–97%) [25]. While the use of catalysts facilitate the formation of transition state intermediates, *in situ* ether formation, followed by Claisen rearrangement and cycloaddition is

Scheme 9. Condensation of 2-naphthols and diaryl propargyl alcohols.



Scheme 10. PPTS-catalyzed synthesis of spiro[thioxantene-naphthopyrans] (**26**).

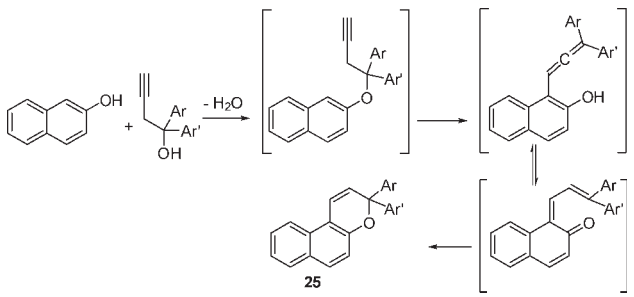


generally accepted mechanism for this transformation (Scheme 11) [24].

A large number of decorated 3*H*-naphtho[2,1-*b*]pyrans have been prepared using this protocol or a slightly modified version in the pursuit of photochromic naphthopyrans with interesting/desired properties. A sample of molecular diversity bearing photochromic 3*H*-naphtho[2,1-*b*]pyran core reported in recent literatures in presented in Figure 3. Chamontin *et al*. reported the synthesis of formyl-substituted naphthopyrans (*e.g*., **29**) either by starting the reaction from formylated 2-naphthol or by conducting formylation on the naphthopyran products [26]. These formylated naphthopyrans can be used to produce an array of derivatives. Navarro and coworkers derivatized compound **29** with 1,4-dithiafulvenes to produce (1,4-dithiafulven-6-yl)substituted 3*H*-naphtho[2,1-*b*]pyrans (*e.g*., **30**), which dimerized after electrochemical treatment; compound **31** was isolated to confirm this observation [27]. Zhao and Carreira reported the synthesis and photochromic properties of symmetrical phyenylene-linked bisnaphthopyrans (**32, 33**) initiating the synthesis from isoterephthaloyl and terephthaloyl chlorides to make the bisketones, which were converted to bispropargyl alcohols required for the synthesis of the desired naphtho[2,1-*b*]pyrans [28].

Coelho *et al*. also produced a number of symmetrical photochromic di/trinaphtho[2,1-*b*]pyrans (*e.g*., **34, 35**) by preparing appropriate bis/tris-ketones, followed by propargylation and annulation (with 2-naphthol) sequence [29]. The same research group prepared unsymmetrical photochromic *bis*-naphthopyrans (*e.g*., **36**) using the same general chemistry where the annulation with naphthol analogs were conducted sequentially

Scheme 11. Generally accepted mechanism of formation of 3*H*-naphtho[2,1-*b*]pyrans (**25**) from 2-naphthols and α-alkynols.



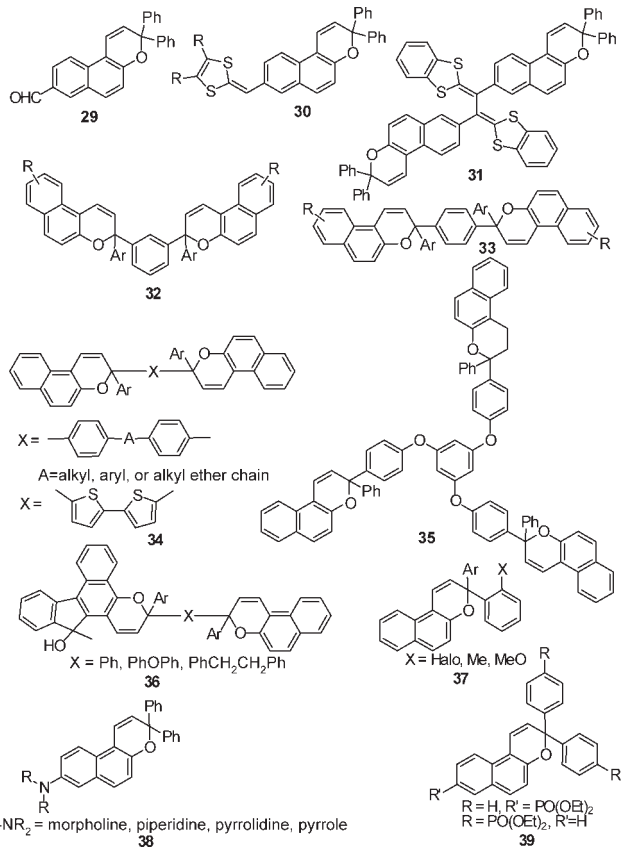
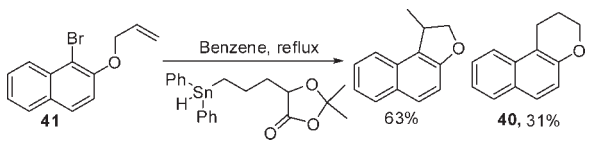


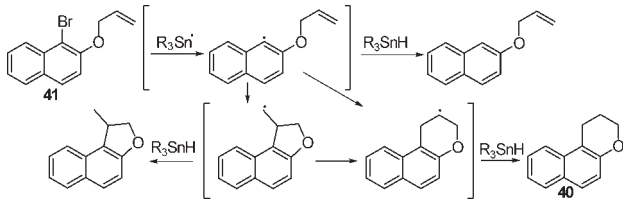
Figure 3. A sample of molecular diversity bearing photochromic 3*H*-naphtho[2,1-*b*]pyran core.

on the bispropargyl alcohol [30]. Effect of *ortho*-substituents on the 3-aryl group of 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyran on photochromism was studied by Gabutt, Heron, and Instone where they synthesized a number of 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyrans bearing substituents on the *ortho*-position of one of the 3-aryl groups (*e.g.*, **37**) [31]. Shilova *et al*. prepared a series of cyclic amine-substituted 3,3-diphenyl-3*H*-naphtho[2,1-*b*]pyrans (**38**) by using the Buchwald C—N coupling protocol on the corresponding bromo-substituted naphthopyrans in an effort to study their effect on photochromism [32]. In a similar endeavor, Campredon and coworkers prepared diethyl phosphonate-substituted 3*H*-naphtho[2,1-*b*]pyrans (**39**) for corresponding bromo-substituted naphthopyrans using Pd-catalyzed diethyl phosphate [33].

Scheme 12. C—C bond formation in 2-allyloxy-1-bromonaphthalene using a modified stannane.



Scheme 13. Proposed mechanism of Sn-mediated C—C bond formation in 2-allyloxy-1-bromonaphthalene (**41**).



METHODS OF SYNTHESIS OF 2,3-DIHYDRO-1*H*-NAPHTHO[2,1-*b*]PYRANS

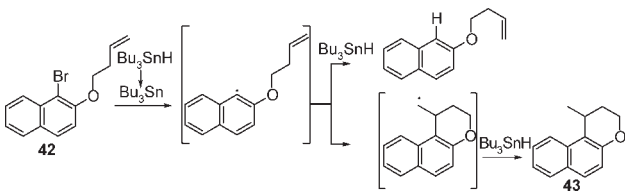
There are numerous procedures related to one another that are known for the synthesis of the 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran analogs with a saturated pyran ring, *i.e*., 1*H*-benzo[*f*]chromans, which are devoid of photochromic characteristics. In a publication by Clive and Wang, 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**40**) was prepared in 31% yield by heating 2-allyloxy-1-bromonaphthalene (**41**) and azobisisobutyronitrile (AIBN) in benzene using a modified stannane reagent (Scheme 12) [34]; the conventional reagent, Bu_3SnH, gave very poor (~17%) yield [35]. Stannanes such as Bu_3SnH and Ph_3SnH are used in standard free radical reactions [35]. In case of modified stannane reagent, the tin-containing byproducts can be easily removed by mild hydrolysis.

The mechanism of stannane-mediated cyclization involves formation of a free radical at the carbon atom bearing the bromine. This intermediate then cyclizes with the alkenyl substituent leading to a 5- or 6-membered ring structure (Scheme 13) [35].

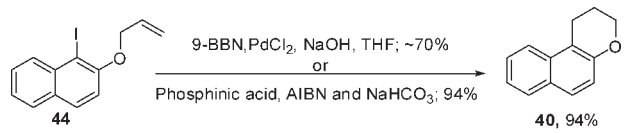
When 1-bromo-2-but-3-enyloxy-naphthalene (**42**) was used as starting material, dihydronaphthopyran **43** was obtained as one of the products (Scheme 14) [36]. The cyclization resulted in formation of a more stable 6-membered ring rather than a 7-membered ring.

According to numerous reports, the cross-coupling reaction of organic electrophiles with organometallic reagents in the presence of transition metals is generally a mild and straightforward method to form a C—C bond. Suzuki and coworkers published a related experiment where they initiated from 2-allyloxy-1-iodonaphthalene (**44**) using 9-borabicyclo[*3.3.1*]nonane (9-BBN) and palladium-catalyzed intramolecular cross-coupling

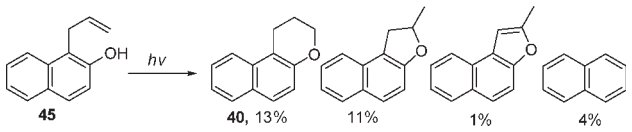
Scheme 14. Synthesis of dihydronaphthopyran **43** from 1-bromo-2-but-3-enyloxynaphthalene (**42**).



Scheme 15. Formation of dihydronaphthopyran **40** *via* intramolecular cross-coupling.



Scheme 16. Dihydronaphthopyran **40** *via* singlet excited-state H-transfer from **45**.



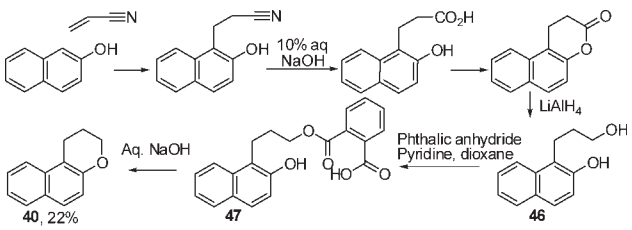
reaction. The desired dihydronaphthopyran **40** was obtained in ~70% yield *via* this reaction (Scheme 15) [37]. Another reaction on 2-allyloxy-1-iodonaphthalene leading to same product in nearly quantitative yield, using phosphinic acid, AIBN, and $NaHCO_3$, is also known (Scheme 15) [38,39].

Chow *et al*. discovered that singlet excited-state proton transfer of 1-allyl-2-naphthol (**45**) causes cyclization and results in formation of **40** in 13% yield. It was noted that secondary photodehydrogenation of the dihydronaphthofuran and formation of naphthalene are competing side reactions (Scheme 16) [40].

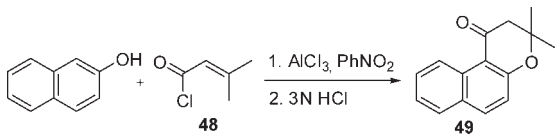
Dihydronaphthopyran **40** was also obtained from 2-naphthol and acrylonitrile by a 6-step reaction sequence in low yield (~22%; Scheme 17) [41]. 1-(3-Hydroxypropyl)naphthalen-2-ol (**46**) was obtained through 2-naphthol and acrylonitrile mixture by Michael addition, hydrolysis, and reduction sequence. It reacted with phthalic anhydride and pyridine to give acid phthalate (**47**), which yielded dihydronaphthopyran **40** upon addition of weak aqueous NaOH solution.

Livingstone has published a one-pot annulation reaction to prepare naphthopyrans [42]. As depicted in Scheme 18, 2-naphthol was mixed with 3-methylbut-2-enoyl chloride (**48**) in nitrobenzene and small amount of anhydrous aluminum chloride was added. The reaction was set aside for 12 days when the desired naphthopyran (**49**) was formed (yield not reported).

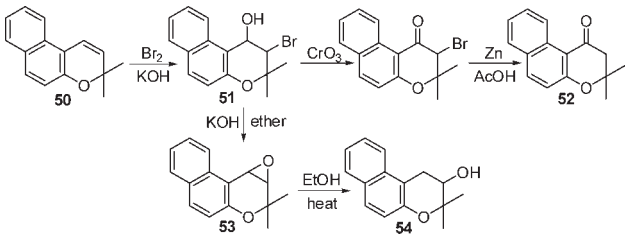
Scheme 17. Dihydronaphthopyran **40** *via* multistep intramolecular cyclization.



Scheme 18. Preparation dihydronaphthopyranone **49** from 2-naphthol *via* Friedel Craft acylation.



Scheme 19. Multiple step synthesis of dihydronaphthopyran derivatives.



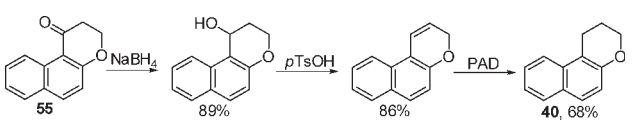
Livingstone subsequently reported a multi-step synthesis of dihydronaphtho[2,1-*b*]pyran derivatives (Scheme 19). 3,3-Dimethyl-3*H*-naphtho[2,1-*b*]pyran (**50**) was first converted to its bromohydrin **51** followed by CrO_3 oxidation and subsequent reduction *via* Zn/AcOH to afford 3,3-dimethyl-2,3-dihydronaphtho[2,1-*b*]pyran-1-one (**52**). Application of potassium hydroxide on the bromohydrin **51** resulted in an epoxide intermediate (**53**), which was later converted to 3,3-dimethyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-2-ol (**54**) [43]. Product yields were not reported.

Another multi-step synthesis of dihydronaphthopyran **40** from 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-1-one (**55**) involves sodium borohydride reduction followed by a dehydration and hydrogenation sequence. Selective reduction of the double bond was achieved by potassium azodicarboxylate (PAD) reduction (Scheme 20) [44].

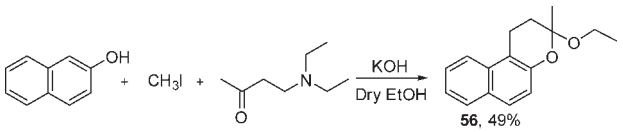
The same research article also reported the synthesis of 3-ethoxy-2,3-dihydro-3-methyl-1*H*-naphtho[2,1-*b*]pyran (**56**) [44]. In this reaction, methyl iodide was added to 1-(*N*,*N*-diethylamino)butan-3-one in dry ethanol. The mixture was then added to a solution of 2-naphthol and potassium hydroxide. The final product **56** was obtained in 49% yield after refluxing for 30 min (Scheme 21).

Scheme 22 depicts an electron transfer reaction where methylene blue-catalyzed photodecarboxylation of 1-allyl-2-naphthoxy acetic acid (**57**) led to formation of 2-

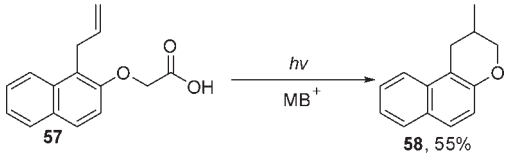
Scheme 20. Dihydronaphthopyran **40** from corresponding 4-pyranone **55**.



Scheme 21. Formation of 3-ethoxy-2,3-dihydro-3-methyl-1*H*-naphtho[2,1-*b*]pyran (**56**).



Scheme 22. Methylene blue-catalyzed photodecarboxylation and cyclization.



Scheme 23. Au-catalyzed intramolecular cycloalkylation of 2-naphthyloxy-propyl sulfonate **59**.

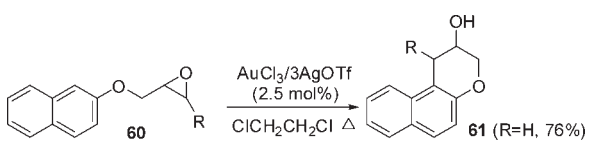
methyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**58**) in 55% yield [45,46].

Gold-catalyzed organic transformations have been studied quite extensively in recent years. Remarkable results were published by Sih and He who used relatively expensive Au(III) to catalyze carbon—carbon bond formation of 2-naphthyloxy-propyl triflate or methane sulfonate ester (**59**) and obtained 90% yield of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**40**, Scheme 23) [47].

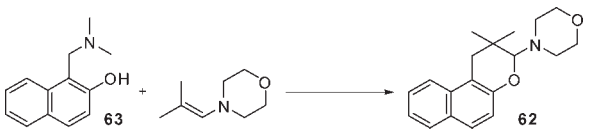
In a related endeavor, the same group reported Au(III)-catalyzed intramolecular cycloalkylation of substituted 2-(2-naphthyloxymethyl)oxiranes (**60**) to substituted 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-1-ols (**61**) in good yields (Scheme 24) [48].

Strandtmann and his research group reported a new strategy to produce 3-morpholino-2,2-dimethyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**62**) from 2-naphthol Mannich bases (**63**) and an enamine (Scheme 25; yield not reported) [49,50]. The proposed mechanism involved elimination of the dimethylamine from the Mannich base followed by a Michael-type addition to the enamine. The resulting intermediate then cyclized to give an amine substituted naphthopyran derivative.

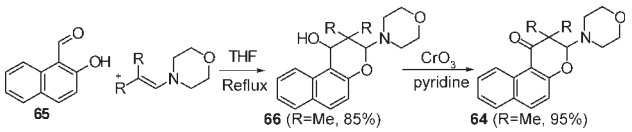
Scheme 24. Au(III)-catalyzed cycloalkylation of 2-(2-naphthyloxymethyl)oxiranes (**60**).



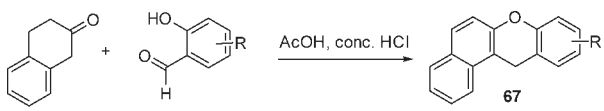
Scheme 25. Morpholino-dihydronaphthopyran **62** from 2-naphthol Mannich base **63**.



Scheme 26. Synthesis of morpholino-dihydronaphthopyranone **64** from 2-hydroxy-1-naphthaldehyde and appropriate enamine.



Scheme 27. 12*H*-benzo[*a*]xanthenes (**67**) from 2-tetralone and substituted salicylaldehydes.

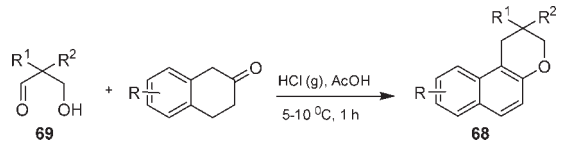


In a similar perspective, Dean *et al*. published a simple method of preparing 3-dialkylamino-2,2-dialkylnaphtho[2,1-*b*]pyran-1-ones (**64**) [51]. The reaction between 2-hydroxy-1-naphthaldehyde (**65**) and enamines gave 3-dialkylamino-2,2-dialkylnaphtho[2,1-*b*]pyran-1-ols (**59**) in high yield. Subsequently, the resulting compounds were oxidized by Sarett's reagent to produce 3-dialkylamino-naphthopyranones **64** in nearly quantitative yeilds (Scheme 26).

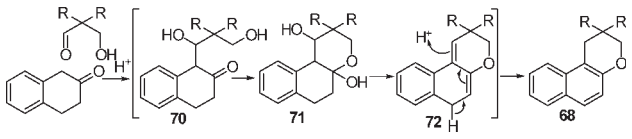
Our research group is also actively engaged in exploitation of 2-naphthol and 2-tetralone analogs to produce novel molecular frameworks [52–58]. Our efforts have also led to synthesis of three kinds of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans [56–58]. Reaction between 2-tetralone and substituted *ortho*-hydroxy aromatic aldehydes under acidic conditions resulted in formation of benzene-fused 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans or 12*H*-benzo[*a*]xanthenes (**67**, Scheme 27) in moderate to excellent yields (55–94%) [56].

This study was later expanded to expeditiously and conviniently prepare 2,2,-dialkyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**68**, Scheme 28) in 51–96% yeild range from 2-tetralone analogs and 2,2-dialkyl-3-

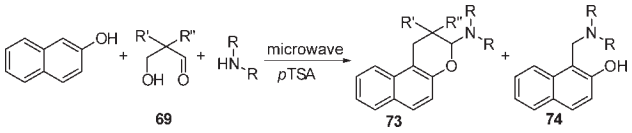
Scheme 28. Synthetic scheme for preparing 2,2,-dialkyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**68**) for 2-tetralone analogs.



Scheme 29. Most plausible mechanism of formation of 2,2-dialkyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**68**) from 2-tetralone.



Scheme 30. Formation of dialklamino-dihydronaphthopyrans (**66**) from 2-naphthol.

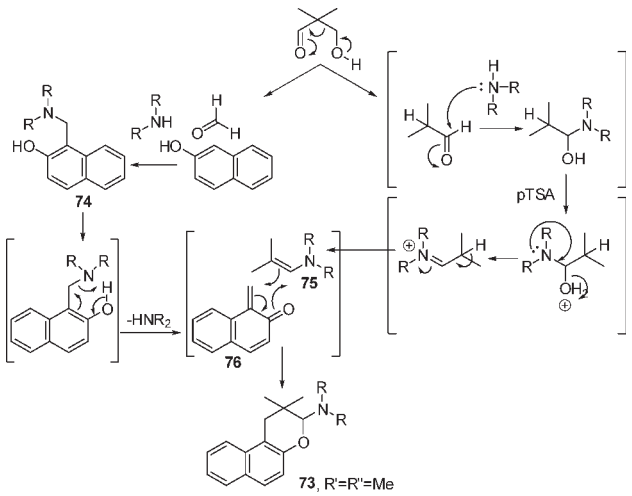


hydroxy propanaldehydes (**69**) under anhydrous acidic conditions [57].

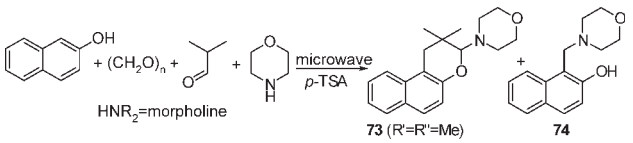
The overall reaction is tendam aldol condensation and hemiacetal formation followed by double dehydration. The most plausible mechanism involves the formation of aldol product (**70**) between the active methylene of 2-tetralone and the corresponding aldehyde. Subsequently, cyclization *via* nucleophilic attack leading to formation of the hemiacetal intermediate (**71**) followed by double dehydration (**72**) and aromatization by proton rearrangement produces stable products (**68**, Scheme 29) [57].

In another endeavor, we developed a microwave-assisted synthesis of 3-(dialklamino)-2,2-dialkyl-1,2-dihydro-naphtho[2,1-*b*]pyrans (**73**) [58]. These series of compounds were formed in moderate to good yields (45–72%) from 2-naphthol, a secondary amine, and 3-hydroxy-2,2-dialkylpropanaldehydes (**69**) in presence of

Scheme 31. Most plausible mechanism of formation of dialkylamino-dihydronaphthopyrans **73** from 2-naphthol, hydroxyl aldehydes **69**, and 2° amines.



Scheme 32. *p*-TSA-catalyzed four-component reaction for the synthesis of 2,2-dimethyl-3-morpholino-1,2-dihydro-naphtho[2,1-*b*]pyran.



catalytic amount of *p*-toluenesulfonic acid using focused microwave radiation as energy source (Scheme 30).

The formation of 1-dialkylaminomethyl-2-naphthol byproducts (**74**) gave us a vital clue in discerning the mechanism of this reaction. We elucidated that under applied reaction conditions, 2,2-dialkyl-3-hydroxy-propanaldehydes undergoes retro-aldol condensation to produce formaldehyde and 2,2-dialkylacetaldehydes. These aldehydes meet different fates resulting in facile formation of 1-dialkylaminomethyl-2-naphthols (**74**) and 2,2-dialkylacetaldehyde/secondary amine enamines (**75**). Again, under the used reaction conditions, 1-dialkylaminomethyl-2-naphthols deaminate to naphthoquinone methide (**76**). Pericyclic cycloaddtion between electron deficient **76** and electron rich enamine **75** results in dialkylamino-dihydronaphthopyrans **73** with aromatization being the driving force (Scheme 31) [40].

Subsequently, we substantiated this mechanistic pathway by developing a *p*TSA catalyzed four-component reaction involving 2-naphthol, paraformaldehyde, isobutyraldehyde, and morpholine (1 molar equivalent each) under microwave conditions identical to the original three component reaction [58]. This indeed led to formation of **73** (R′=R"=Me, —NR_2=morpholine) and **74** (—NR_2=morpholine) in 52% and 43% yields, respectively (Scheme 32).

It is abundantly clear from the preceding discussions that 3*H*-naphtho[2,1-*b*]pyran and dihydro-1*H*-naphtho[2,1-*b*]pyran nuclei can be derived from a variety of synthetic routes. Evidently, the majority of these procedures lack simplicity and satisfactory yields; many are accompanied by one or more side-products. Since naphthopyran nuclei are biologically relevant and commercially important, it is paramount to develop expeditious, facile, and convenient synthetic routes to these types of molecular frameworks.

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