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Synthetic Studies of Naphtho[2,3-*b*]furan Moiety Present in Diverse Bioactive Natural Products

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Abstract

The preparation of several functionalized furan derivatives and attempts to transform them into a derivative containing 6*H*-furo[3,4-*b*]furanone skeleton towards the construction of naphtho[2,3-*b*]furan are described. Attempted Pummerer reaction of a furan sulfoxide derivative produced four interesting furan derivatives. Base promoted annulation between methyl 2-(phenylsulfinylmethyl)-3-furoate and 2-cyclohexenone proceeded to give dihydro naphtho[2,3-*b*]furanone derivative in a regiospecific manner.

Keywords

6*H*-Furo[3,4-*b*]furanone, Naphtho[2,3-*b*]furan, Intramolecular Pummerer Reaction, Desulfanylation, Lactonization

1. Introduction

Functionally embellished naphtho[2,3-*b*]furan moiety has been widely encountered as a unique sub-structure among a diverse range of bioactive synthetic molecules and natural products. Particularly, the condensed quinone derivatives of naphtho[2,3-*b*]furans such as furonaphthoquinones have been proved to possess broad anticancer activities [1]. Recently, M. Koketsu and co-workers reported that the synthetic furonaphthoquinones showed moderate cytotoxicity against human leukemia U937 and HL-60 cells [2]. During the past decades, a wide range of furanoid natural products have been isolated from plant sources. Among these, furonapthoqui-

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nones (e.g. **1** - **9**) are prominent due to their wide biological activities and structural significance (**Figure 1**). Although some strategies have been used for the construction of furonaphthoquinone skeletons, most of the reported methods employ multistep to secure the target skeletons from readily available precursors [3]. Hence intense research in this area has been carried out in recent years leading to the development of simple and straightforward regiospecific route for the preparation of functionalized furonaphthoquinone compounds [4].

Our continued interest in the application of anionic [4 + 2] cylcoaddition [5] of isobenzofuranones prompted us to study the preparation of 6*H*-furo[3,4-*b*]furanones (**10**) towards the construction of naphtho[2,3-*b*]furan skeleton embedded in various biologically important molecules.

2. Results and Discussion

Our study began with the preparation of furanosulfoxide derivative **14**, following the literature procedure [6]. Bromination of methyl 2-methyl-furan-3-carboxylate (**11**) with *N*-bromosuccinimide (NBS) under standard condition gave bromo derivative **12** was prepared in 75% yield. Reaction of compound **12** with sodium methoxide and thiophenol gave compound **13** in 88% yield followed by oxidation with sodium periodate in methanol and water medium provided methyl 2-(phenylsulfinylmethyl)-3-furoate (**14a**) in 75% yield (**Scheme 1**). Attempted intramolecular Pummerer reaction [7] of sulfoxide **14a** with trimethylsilyl chloride (TMSCl) in dichloromethane for overnight, no reaction took place. But when this was refluxed with acetic anhydride, a polymeric product generated. When compound **14a** was refluxed with trifluro acetic anhydride or *p*-toluenesulfonic acid (PTSA), complex mixtures of products were obtained. Examination of the ^{1}H NMR spectrum of the crude products did not indicate formation of desired **10a**. The same result was obtained when the above reactions were performed on acid derivative **14b**, prepared by hydrolysis of sulfoxide ester **14a** with aqueous NaOH and ethanol.

For **Scheme 1**. *Reagents and conditions*: (i) NBS, CCl_4, $(PhCO)_2O_2$ (cat.), hν, 75%; (ii) PhSH, NaI, MeOH, reflux, 88%; (iii) $NaIO_4$, $MeOH/H_2O$, rt, 40 h, 75%; (iv) NaOH, ethanol, 85%; (v) TMSCl, CH_2Cl_2, overnight or (vi) Ac_2O, reflux, 10 h or (vii) $(CF_3CO)_2O$, reflux or PTSA, reflux.

Interestingly, treatment of sulfoxide **14a** with acetic anhydride and a catalytic amount of sodium acetate under reflux produced four different products instead of **10a**. All these products **15**, **16**, **17** and **18** were separated by column chromatography and characterized by NMR, IR studies. Under the same conditions the acid derivative **14b** produced an oily polymeric product, ^{1}H NMR spectrum of which revealed the absence of **10a**.

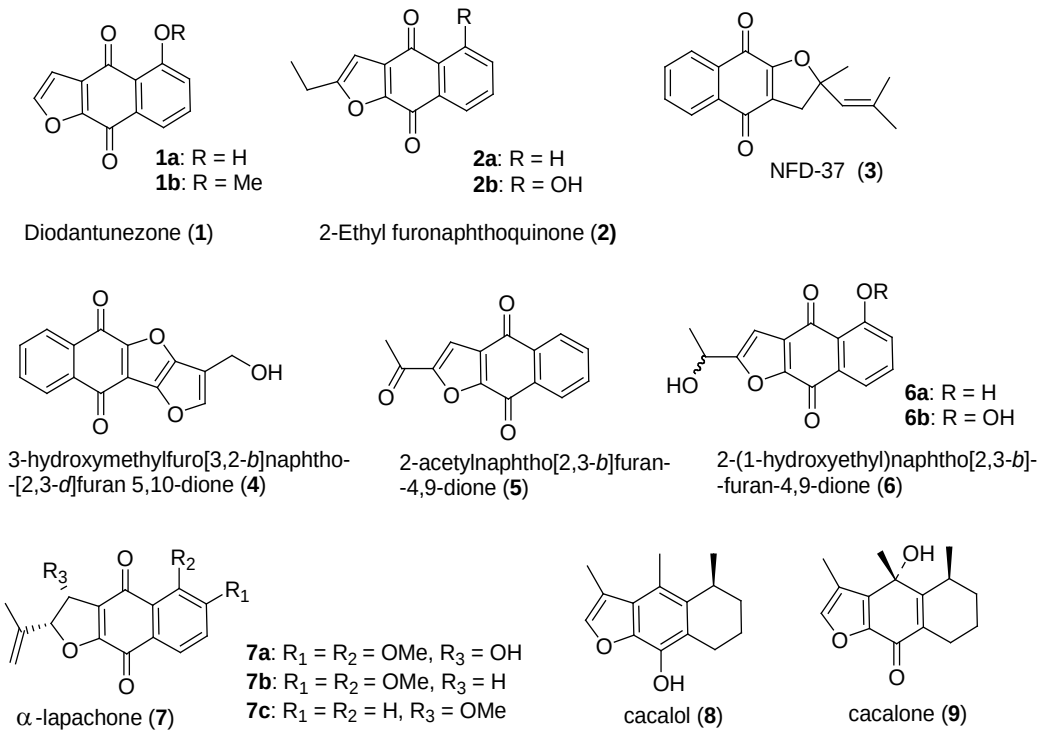


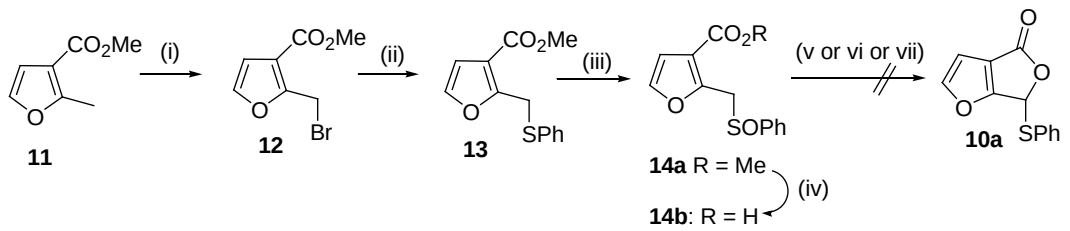
Figure 1. Structure of some biologically active naphtho[2,3-b]furan harbouring natural products.

For **Scheme 3**. *Reagents and conditions*: (viii) Ac_2O, NaOAc, reflux, 3 h, 28% (for **15**), 8% (for **16**), 6% (for **17**) and 15% (for **18**).

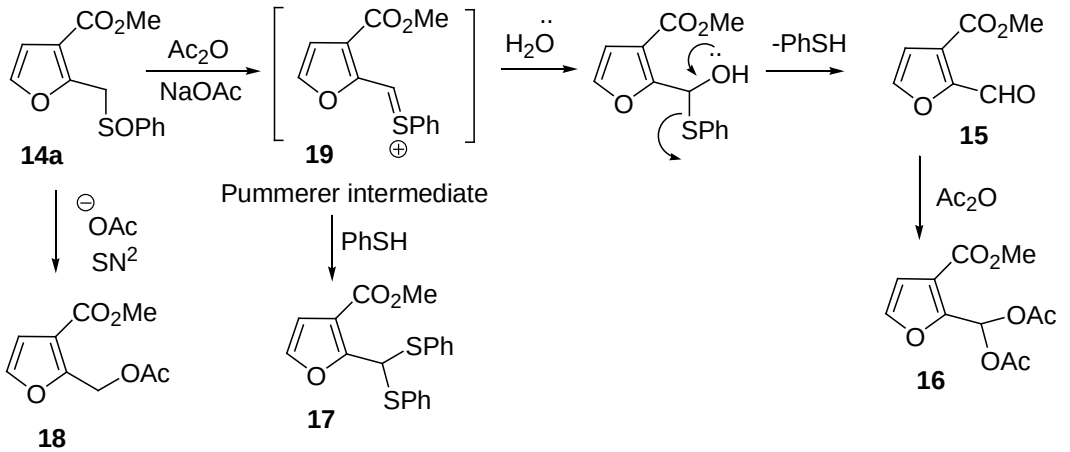
Except **18**, all these products were expectedly generated through a common Pummerer intermediate **19**. Nucleophilic addition of water to the Pummerer intermediate **19** and subsequent expulsion of thiophenol gave aldehydic ester derivative **15** as the major product (28%). Compound **15** could further be added to acetic anhydride to produce furan diacetate derivative **16** in 8% yield (**Scheme 2**).

Formation of compound **17** (6%) could be explained by addition of one equivalent of thiophenol to the common intermediate **19**. On the other hand, the acetate derivative **18** (15%) could be formed by direct nucleophilic displacement of sulfoxide group of **14a** by acetate anion.

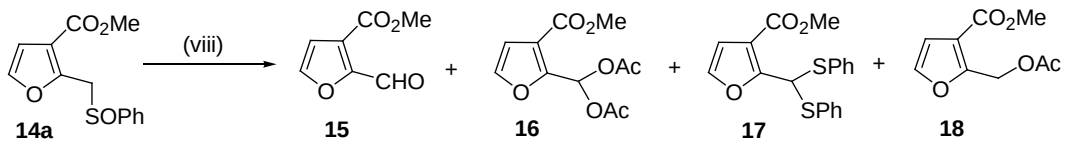
Having been successful with the above **Scheme 3**, we focused our attempts to convert ethylsulfoxide **21a** to furofuranone **10b** via an intramolecular Pummerer reaction. It was presumed that the corresponding intermediate would have favorable geometry for an intramolecular Pummerer reaction [8]. Compound **12** was converted to **20** in 87% yield by the treatment with sodium methoxide and ethanethiol in refluxing methanol. Oxidation of **20** with sodium periodate gave two products which were separated using column chromatography (1:4 mixture of ethyl acetate/petroleum ether). After column chromatography, the desired ethylsulfoxide **21a** as isolated in 56% yield and the more oxidized ethylsulfone **21b** was isolated in 33% yield as shown in **Scheme 4**. Both the com pounds **21a** and **21b** were fully characterized on the basis of spectroscopic (IR, NMR and mass spectral data) analysis. The ^{1}H NMR spectrum exhibited two doublets, one at δ 7.40 (1H) and other at δ 6.73 (1H) for furan ring. It also showed an ABq signal at δ 4.44 (2H) corresponding to two α-hydrogen atoms of ethylsulfoxide group. But, all attempts to effect intramolecular Pummerer reaction of **21a** with various reagents such as PTSA in C_6H_6, Ac_2O in toluene, $(CF_3CO)_2O$ in CH_2Cl_2, CF_3CO_2H, pyridinium PTSA in refluxing condition and phenyliodine



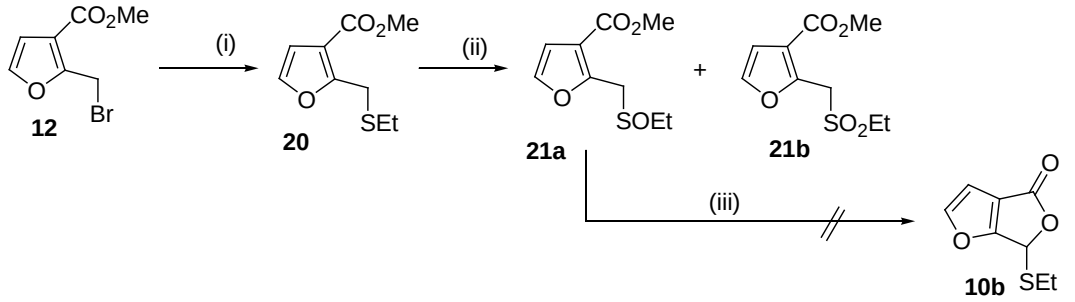
Scheme 1. Synthetic approach to furo[3,4-*b*]furanone derivative **10a**.



Scheme 2. Possible pathway for the formation of compounds **15**, **16**, **17** and **18**.



Scheme 3. Intramolecular Pummerer reaction of **14a**.



Scheme 4. Attempted intramolecular Pummerer reaction for the formation of **10b**.

diacetate (PIDA) in CH_2Cl_2 failed to give the expected furofuranone **10b**. In all the cases the ^1H NMR spectrum of the crude products consisted of broadened signals indicating polymeric materials.

For **Scheme 4**. *Reagents and conditions*: (i) EtSH, $CHCl_3$, Et_3N, rt, overnight, 87%; (ii) $NaIO_4$, MeOH, 0˚C, 2 h, 56%; (iii) PTSA in C_6H_6, reflux, 10 h or Ac_2O in toluene, reflux, 10 h or $(CF_3CO)_2O$ in CH_2Cl_2, reflux, 12 h or CF_3CO_2H, pyridinium PTSA, reflux, 12 h or PIDA in CH_2Cl_2, reflux, 12 h.

Following the above failures, we turned to preparing furan sulfoxide derivative **26** starting from 3-furoic acid and chloromethylsulfanylbenzene (**24**) and examining its intramolecular cyclisation via Pummerer reaction to obtain **10a**. Methylation of thiophenol with sodium hydroxide and dimehylsulfate in acetone under reflux condition gave **23** in 87% yield. Treatment of **23** with *N*-chlorosuccinimide in CCl_4 produced **24** in 82% yield. Then compound **24** was reacted with 3-furoic acid (**25**) in the presence of DBU to give **26** (70% yield). This was then transformed to sulfoxide **27** (76% yield) by sodium periodate ($NaIO_4$) oxidation. Both the compounds **26** and **27** gave satisfactory IR, ^1H NMR and ^{13}C NMR spectroscopic data. The ^1H NMR spectrum showed an ABq signal at δ 5.14 (2H) corresponding to two α-hydrogen atoms of phenylsulfoxide group. Several Pummerer reagents (vide reagents of **Scheme 5**) were employed for the intramolecular cyclization of **27**, but none were effective to give **10a** as shown in **Scheme 5**.

For **Scheme 5**. *Reagents and conditions*: (i) aq. NaOH, Me_2SO_4, reflux, 4 h, 87%; (ii) NCS, CCl_4, rt, 11 h, 82%; (iii) DBU, CH_3CN, 4 h, 70%; (v) $NaIO_4$, MeOH, 5 h, 76%; (vi) *p*-TsOH in C_6H_6, reflux, 10 h or Ac_2O in toluene, reflux, 10 h or $(CF_3CO)_2O$ in CH_2Cl_2, reflux, 12 h or CF_3CO_2H, pyridinium PTSA, reflux, 12 h.

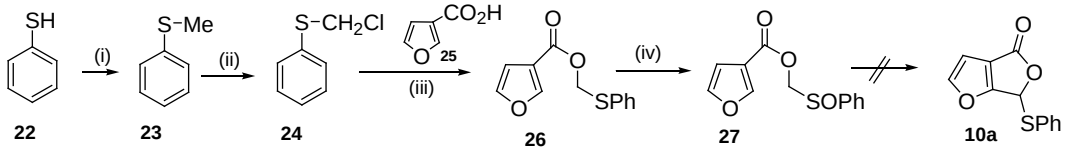
As we failed to achieve the preparation of furofuranone **10a** by Pummerer procedures, we modified our approach to synthesizing **10a** through the desulfanylation of **17**, in view of the success of this type of cyclization in benzene system reported by Hauser *et al.* [8]. Treatment of compound **15** with thiophenol and catalytic amounts of TMSCl in chloroform solvent produced **17** in 85% yield (**Scheme 6**). Attempted cyclization of **17** in trifluoroacetic acid under reflux condition failed to give expected compound **10a**. ^1H NMR spectrum of the crude product revealed that starting material decomposed during the course of reaction.

For **Scheme 6**. *Reagents and conditions*: (i) PhSH, TMSCl, $CHCl_3$, rt, 85%; (ii) CF_3CO_2H, H_2O, reflux, 12 h.

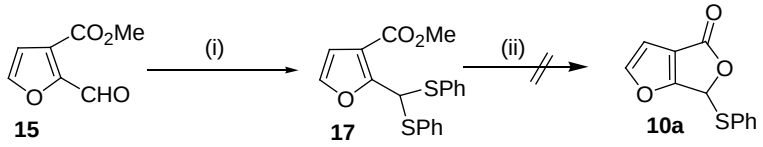
As we could not carry out the above cyclization of **17**, we thought that compound **32** might suit for this desulfanylation reaction due to lesser effect of nuclear oxygen atom. It was prepared in good yield starting from commercially available methyl 3-methyl-furan-2-carboxylate (**28**). The sequence is depicted in **Scheme 7**. NBS bromination of **28** produced dibromo derivative **29** (60%) along with monobromo derivative **30** in 25% yield. These compounds were separated using column chromatography methods (1:4 mixture of $CHCl_3$/petroleum ether). Hydrolysis of dibromo derivative **29** with silver nitrate in THF/H_2O produced furan-3-carboxaldehyde **31** in 42% yield. Finally, treatment of **31** with thiophenol and a catalytic amount of TMSCl provided compound **32**. Attempted desulfanylation of **32** with trifluoroacetic acid and water in reflux condition failed to give expected product **10c**, starting material was recovered exclusively meaning that no reaction took place.

For **Scheme 7**. *Reagents and conditions*: (i) NBS (2 equiv.), CCl_4, benzoyl peroxide, hν, 60% (for **29**) and 25% (for **30**); (ii) $AgNO_3$, THF, H_2O, 42%; (iii) PhSH, TMSCl, $CHCl_3$, rt, 80%; (iv) CF_3CO_2H, H_2O, reflux, 12 h.

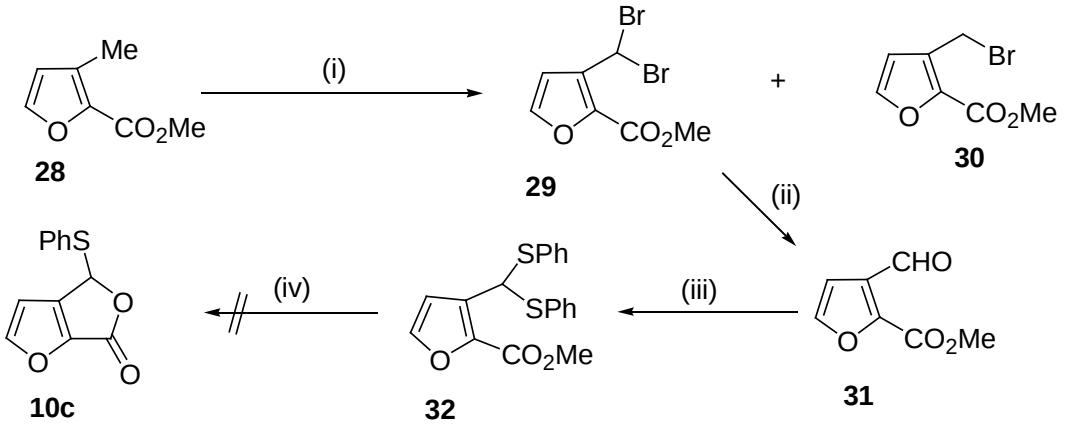
At this point, we investigated the coupling reaction between diazo derivative of tetronic acid (**36**) and vinyl acetate for synthesizing **37** from which desired furo[3,4-*b*]furanone system could be obtained. Compound **36** was prepared from tosyl azide (**34**) and tetronic acid (**35**) in the presence of triethylamine according to the literature procedure in 40% yield [9]. ^1H NMR of **36** showed only one singlet at δ 4.70 (2H, s) corresponding to -CH_2 group. Then we examined its coupling with vinyl acetate under various conditions (**Scheme 8**) [10]. But



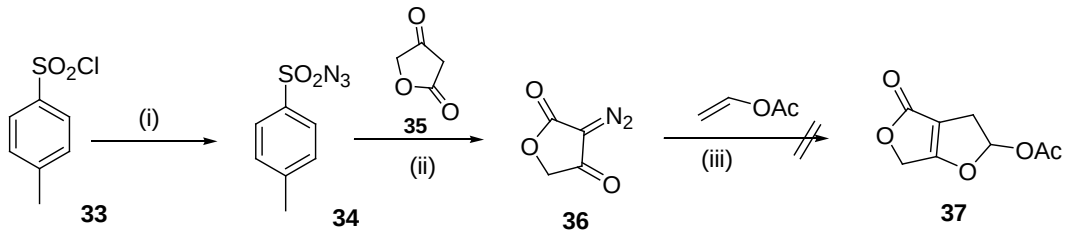
Scheme 5. Attempted intramolecular Pummerer reaction for the synthesis of **10a**.



Scheme 6. Attempted intramolecular desulfanylation of **17** to obtain **10a**.



Scheme 7. Investigation of intramolecular desulfanylation of **32**.



Scheme 8. Attempted routes to synthesis of **37**.

unfortunately, all the attempts failed to give **37**. Examination of ^{1}H NMR spectrum of the crude product indicated the exclusive presence of starting material in first two cases (with rhodium diacetate or ceric ammonium nitrate) and unidentifiable product mixture of products with PIDA treatment.

For **Scheme 8**. *Reagents and conditions*: (i) NaN_3, aq. Acetone, rt, 85%; (ii) Et_3N, CH_3CN, 40%; (iii) $Rh_2(OAc)_2$ or CAN, CH_3CN, 0˚C or $PhI(OAc)_2$.

Again we modified our route for the synthesis of furolactone **10d**, from which desired compound **10a** may be prepared. The hydroxy ester derivative **38** was prepared from **12** by heating it at 80˚C in dimetyl sulfoxide and water. The NMR data of **38** matched with literature value [11]. Then compound **38** was transformed to 2-hydroxymethyl-furan-3-carboxylic acid (**39**) in 90% yield by the treatment of 40% aqueous solution of KOH solution in methanol (**Scheme 9**).

For **Scheme 9**. *Reagents and conditions*: (i) DMSO, 80˚C, 4 h, 92%; (ii) KOH, H_2O, MeOH, 90%; (iii) attempted lactonization with $SOCl_2$ in CH_2Cl_2, DCC in DMF or in CH_2Cl_2, Ac_2O in toluene under refluxing condition and BF_3-ether in C_6H_6.

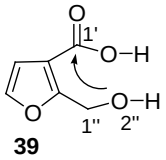
We then investigated lactonization of compound **39** with various well established literature methods. But, all

attempts for lactonization of **39** failed to give the expected furolactone **10d** as shown in **Scheme 9**. In all the cases except with $SOCl_2$, ^1H NMR spectrum of the crude products showed exclusive presence of the starting material **39**, meaning no reaction took place. Reaction with $SOCl_2$ produced intractable mixture of products which could not be identified by NMR studies. The above failure of the lactonization may be attributed due to the unfavorable distance between carbonyl "C" and hydroxyl "O" atoms in **39** compared to that in its benzene analog **40** (**Figure 2**) where lactonization is very facile. Geometries of molecules **39** and **40** were minimized by using density functional theory (DFT) calculations based on the BLYP level of theory with the DND basis set using DMol^3 package program [12].

Then we thought that sulfoxide **14a** itself may serve the purpose of furan annulating agents (*i.e.* **10a** or **10b**) for the synthesis of naphtho[2,3-*b*]furan skeleton. For that purpose, when the sulfoxide **14a** was treated with lithium *tert*-butoxide (*t*-BuOLi), a light yellow color developed, indicating the generation of carbanion α to -SOPh group, and subsequently the color of the reaction mixture changed to light brown upon addition of 2-cyclohexenone. Work up of the reaction mixture led to formation of tricyclic compound **42** as white solid in 7% yield (**Scheme 10**). Further transformation of compound **42** to desired naphtho[2,3-*b*]furan derivative was postponed due to poor yield. We were able to taken only ^1H NMR and IR spectrum of this compound. The ^1H NMR spectrum exhibited three multiplets of six protons at the region of δ 2.18 - 2.97, corresponding to the cyclohexane ring and two doublets, one at δ 7.49 (1H) and other at δ 6.94 (1H) for furan ring. It also showed a ^1H sharp singlet at δ 13.51 corresponding to hydrogen bonded 'OH' group. We repeated the above annulation three times without any improvement in the yield. We also performed this cylcoaddition reaction in presence of lithium diisopropyl amide (LDA). But, ^1H NMR spectrum of the crude indicated the formation of a polymeric material.

3. Conclusion

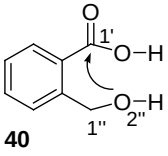
With the aim of preparing novel naphtho[2,3-*b*]furan derivatives, an investigation was carried out to synthesize, characterize and study furo[3,4-*b*]furanones by several approaches. The results showed that the intramolecular Pummerer reaction of furan sulfoxide derivative produced four interesting furan derivatives. The anionic cycloaddition between furan sulfoxide and 2-cyclohexenone produced dihydro naphtho[2,3-*b*]furanone derivative in



39

Total energy, E = - 533.1953949 a.u.

Distance between C-1' and O-2" = 4.326 Å

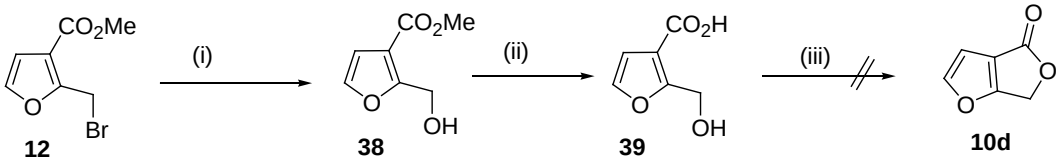


40

Total energy, E = - 535.3673350 a.u.

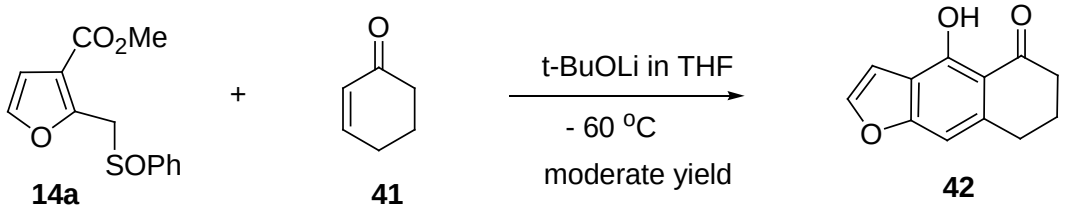
Distance between C-1' and O-2" = 3.644 Å

Figure 2. Comparison of distances between carbonyl "C" and hydroxyl "O" atoms in **39** and **40**.



12 **38** **39** **10d**

Scheme 9. Attempted lactonization of 2-hydroxymethyl-furan-3-carboxylic acid (**39**).



14a **41** **42**

Scheme 10. Synthesis of dihydro naphtho[2,3-*b*]furanone moiety **42**.

poor yield. This study reveals that synthesis of simple looking furan derivatives (like **10a-d)** was elusive and they deserve further study.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes and are uncorrected. Among the spectra, ^{1}H NMR spectra and ^{13}C-NMR spectra were recorded on 200 MHz and 300 MHz spectrometer (Brücker) as solution in ^{2}H-Chloroform with TMS as the internal standard. Chemical shifts are expressed in δ unit and ^{1}H-^{1}H coupling constant in Hz. IR spectra were recorded on a Thermo Nicolet Nexus 870 FT-IR spectrophotometers using KBr pellet. EI MS (70 eV) spectra were taken using a VG Autospec M mass spectrometer. Elemental analyses were carried out by using an elemental analyzer VARIO EL instrument. Dry solvents used for reactions were purified, before use, according to the standard protocols. All solvents for chromatography (column and preparative layer chromatography) were distilled prior to use.

4.2. Methyl 2-(Phenylsulfinylmethyl)-3-furoate (14a)

To a solution of compound **9** (5 g, 20 mmol) in MeOH (70 mL) containing water (15 mL) was added solid $NaIO_4$ (4.6 g, 21.5 mmol) in portions. The resultant mixture was stirred for 36 h at rt and the solvent was removed under reduced pressure. The resulting thick liquid was purified by column chromatography (3:7 ethyl acetate/petroleum ether, R_f 0.48) over silica gel to furnish the sulfoxide **14a** (3.99 g, 75%) as pale yellow solid. **mp**. 84˚C - 85˚C (lit. [6] mp. 85˚C - 86˚C); **FT-IR** (KBr) cm^{-1} 2935, 1714 (s), 1616, 1440 (m), 1387 (m), 1053, 756; **^{1}H NMR** (200 MHz, $CDCl_3$): *δ* 7.46 - 7.30 (m, 5H), 7.32 (d, 1H, *J* = 2 Hz), 6.65 (d, 1H, *J* = 2 Hz), 4.60 (d, 1H, *J* = 12 Hz), 4.51 (d, 1H, *J* = 12 Hz), 3.70 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): *δ* 163.1, 150.4, 142.9, 131.3, 128.9, 123.9, 117.5, 111.0, 55.6, 51.5; **MS** *m/z* (EI): 264 (M^+), 233, 186, 139 (100%), 125, 109, 97, 77.

4.3. 2-Phenylsulfinylmethyl-furan-3-carboxylic Acid (14b)

A mixture of methyl 2-(phenylsulfinylmethyl)-3-furoate **14a** (1 g, 3.78 mmol), 15 mL of 40% aqueous NaOH solution, 20 mL of MeOH and 15 mL of H_2O were stirred for 5 h at ambient temperature. On completion of the reaction, the whole mixture was diluted with water (40 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with water and 5% of HCl (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated. Purification of the crude residue by chromatography on SiO_2 (1:1 ethyl acetate/petroleum ether, R_f 0.32) gave compound **14b** (0.8 g, 85%) as white solid. **mp**. 110˚C - 112˚C; **FT-IR** (KBr) cm^{-1} 3412, 2362, 1709 (s), 1601 (m), 1444, 1260, 1060, 746; **^{1}H NMR** (200 MHz,$CDCl_3$): *δ* 7.30 (d, 1H, *J* = 2 Hz), 6.70 (d, 1H, *J* = 2 Hz), 4.62 (d, 1H, *J* = 14 Hz), 4.53 (d, 1H, *J* = 14 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): *δ* 166.8, 150.6, 143.3, 141.9, 131.7, 129.2, 124.2, 117.9, 111.5, 55.2; HRMS: calcd. for $C_{12}H_{10}O_4S$ $[M + Na]^+$ 251.0380; found 251.0388.

4.4. Methyl 2-Formyl-furan-3-carboxylate (15)

To a stirred solution of **14a** (1.0 g, 3.78 mmol) Ac_2O (10 mL) was added NaOAc (0.31 g, 3.78 mmol) and heated at 110˚C for 3 h. After completion of the reaction, the resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were washed with brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude residue by chromatography on silica gel (1:8 ethyl acetate/petroleum ether, R_f 0.52) gave **15** [13] (28%) as white crystalline solid. **mp**. 76˚C - 78˚C; **FT-IR** (KBr) cm^{-1} 3145, 2886, 1719 (s), 1678 (s), 1575, 1404, 1308, 1212 (m), 1073, 1036, 809, 761; **^{1}H NMR** (200 MHz, $CDCl_3$): *δ* 10.21 (s, 1H), 7.63 (d, 1H, *J* = 0.8 Hz), 6.88 (d, 1H, *J* = 0.8 Hz), 3.94 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): *δ* 178.7, 161.9, 152.4, 146.7, 126.2, 112.8, 52.5.

4.5. Methyl 2-Diacetoxymethyl-furan-3-carboxylate (16)

This compound was obtained as white solid in 8% yield from **14a** on treatment with Ac_2O and NaOAc, following the procedure adopted for the preparation of compound **15** from **14a**. **mp.** 96˚C; **FT-IR** (KBr) cm^{-1} 2937, 2388, 1769 (s), 1728 (s), 1623, 1378, 1236, 1200, 1044, 894, 755; **^{1}H NMR** (200 MHz, $CDCl_3$): *δ* 8.18 (s, 1H), 7.42 (d, 1H, *J* = 2 Hz), 6.74 (d, 1H, *J* = 2 Hz), 3.85 (s, 3H), 2.12 (s, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): *δ* 167.8,

162.3, 151.4, 143.0, 117.3, 112.2, 82.5, 51.9, 20.5; **Anal**. Calcd for $C_{11}H_{12}O_{17}$: C, 51.57; H, 4.72. Found: C, 51.92; H, 5.04.

4.6. Methyl 2-(Bis-phenylsulfanylmethyl)-furan-3-carboxylate (17)

Method 1: This compound was obtained as white solid in 15% yield from **14a** on treatment with Ac_2O and NaOAc, following the procedure adopted for the preparation of compound **15** from **14a**.

Method 2: To a well stirred solution of **15** (200 mg, 1.19 mmol) and thiophenol (132 mg, 1.2 mmol) in dry $CHCl_3$ (10 mL) at rt was added TMSCl (30 mg, 0.28 mmol) and stirring was continued for 5 h. After completion of the reaction, this was washed with 5% $NaHCO_3$ solution (20 mL), diluted with water (50 mL), extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude residue by chromatography on silica gel (1:2 ethyl acetate/petroleum ether, 0.68) gave **17** (360 mg, 85%) as a thick oil. **FT-IR** (KBr) cm^{-1} 3140, 1720 (s), 1591, 1475 (m), 1441, 1312 (m), 1162, 1042, 747; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.35 - 7.43 (m, 5H), 7.24 - 7.30 (m, 5H), 7.33 (d, 1H, J = 2 Hz), 6.35 (s, 1H), 3.66 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 163.0, 156.9, 142.2, 133.3, 128.9, 128.3, 114.2, 110.4, 51.4, 50.8; HRMS: calcd. for $C_{19}H_{16}O_3S_2$ $[M + H]^+$ 357.0629; found 357.0636.

4.7. Methyl 2-Acetoxymethyl-furan-3-carboxylate (18)

This compound was obtained as white solid in 15% yield from **14a** on treatment with Ac_2O and NaOAc, following the procedure adopted for the preparation of compound **15** from **14a**. **mp**. 47˚C; **FT-IR** (KBr) cm^{-1} 1723 (s), 1633 (s), 1387 (s), 1108 (m), 1041, 754; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.37 (d, 1H, J = 2 Hz), 6.70 (d, 1H, J = 2 Hz), 5.36 (s, 2H), 3.84 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 170.1, 163.1, 154.3, 142.6, 116.9, 111.0, 56.8, 51.6, 20.6; HRMS: calcd. for $C_9H_{10}O_5$ $[M + H]^+$ 199.0608; found 199.0615.

4.8. Methyl 2-Ethylsulfanylmethylfuran-3-carboxylate (20)

To a stirred solution of ethanethiol (0.16 mL, 2.15 mmol) in dry $CHCl_3$ (5 mL) and triethylamine (217 mg, 2.15 mmol) at rt was added compound **12** (470 mg, 2.15 mmol). After overnight stirring, the resulting mixture was diluted with water (130 mL) and then extracted with chloroform (3 × 40 mL), washed with 5% of HCl (20 mL), brine (30 mL) and dried (Na_2SO_4). The combined organic layer was concentrated under reduced pressure and purified by column chromatography on silica gel (1:10 chloroform/petroleum ether, R_f 0.42) to give **20** (375 mg, 87%) as an oil. **FT-IR** (KBr) cm^{-1} 3434, 2953, 1722 (s), 1599, 1441, 1308 (m), 1210, 1063, 772; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.30 (d, 1H, J = 2), 6.64 (d, 1H, J = 2.4 Hz), 4.07 (s, 2H), 3.82 (s, 3H), 2.55 (q, 2H, J = 8 Hz), 1.32 (t, 3H, J = 8 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 163.8, 158.8, 141.3, 113.9, 110.6, 51.6, 26.5, 25.9, 14.4; HRMS: calcd. for $C_9H_{12}O_3S$ $[M + H]^+$ 201.0587; found 201.0575.

4.9. Methyl 2-Ethanesulfinylmethylfuran-3-carboxylate (21a)

To a solution of compound **20** (2 g, 10 mmol) in MeOH (50 mL) containing water (5 mL) was added solid $NaIO_4$ (2.30 g, 10.7 mmol) in portions. The resultant mixture was stirred for 2 h at 0˚C and the solvent was removed under reduced pressure. The resulting crude liquid was purified by column chromatography over silica gel (1:5 chloroform/petroleum ether, R_f 0.38) to furnish the sulfoxide **21a** (1.20 g, 56%, oily liquid) as the major product along with sulfone derivative **21b** (33%). **FT-IR** (KBr) cm^{-1} 1717 (s), 1654, 1559, 1508, 769; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40 (d, 1H, J = 2 Hz), 6.73 (d, 1H, J = 2 Hz), 4.44 (ABq, 2H, J = 12 Hz), 3.85 (s, 3H), 2.72 (q, 2H, J = 8 Hz), 1.35 (t, 3H, J = 8 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 163.3, 150.6, 143.0, 117.1, 110.9, 51.5, 49.1, 45.2, 6.2; HRMS: calcd. for $C_9H_{12}O_4S$ $[M + H]^+$ 217.0536; found 217.0542.

4.10. Methyl 2-Ethanesulfonylmethylfuran-3-carboxylate (21b)

This compound was obtained in the above experiment (for the preparation of **21a**) as white solid in 33% yield. **mp**. 90˚C; **FT-IR** (KBr) cm^{-1} 2940, 1711 (s), 1600, 1508, 1445, 1307, 1042, 827; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.46 (d, 1H, J = 2 Hz), 6.75 (d, 1H, J = 2 Hz), 4.74 (s, 2H), 3.86 (s, 3H), 3.02 (q, 2H, J = 8 Hz), 1.38 (t, 3H, J = 8 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 163.2, 148.3, 143.7, 118.1, 111.1, 51.8, 50.8, 47.2, 6.10. **Anal**. Calcd

for $C_9H_{12}NO_5S$: C, 46.54; H, 5.21. Found: C, 46.57; H, 5.04.

4.11. Methylsulfanylbenzene (23)

A mixture of thiophenol **22** (5 g, 45.5 mmol) and 20% of aqueous solution NaOH (50 mL) was stirred for 30 min at rt. Then dimethyl sulfate (4.28 mL, 45.5 mmol) was added to the reaction mixture and stirring was continued for 1 h. Afterward, reaction mixture was heated at reflux for 7 h, cooled to rt, extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were washed with 10% aq. NaOH solution (30 mL), dried (Na_2SO_4) and distilled to give compound **23** [14] (4.9 g, 87%) as colorless oil. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.32 - 7.28 (m, 3H), 7.22 - 7.16 (m, 2H), 2.50 (s, 3H).

4.12. Chloromethylsulfanylbenzene (24)

To a stirred solution of compound **23** (2 g, 6.10 mmol) in CCl_4 (20 mL) was added *N*-chlorosuccinimide (2.36 g, 6.71 mmol) at room temperature and stirring was continued for 11 h. The reaction mixture then cooled (0˚C) and filtered off. The filtrate was then concentrated under reduced pressure and the residue distilled to give a brownish semisolid of **24** [15] (0.78 g, 82%). **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.58 - 7.48 (m, 2H), 7.40 - 7.14 (m, 3H), 4.97 (s, 2H).

4.13. Phenylsulfanylmethyl Furan-3-carboxylate (26)

To a stirred solution of 3-furoic acid (**25**) (1.0 g, 9.0 mmol) and DBU (1.36 g, 9.0 mmol) in dry acetonitrile (10 mL) under inert atmosphere, was added compound **24** (1.42 g, 9.0 mmol). The resulting mixture was further stirred for 4 h at rt and extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate extracts were washed with saturated solution of $NaHCO_3$ (20 mL), brine (20 mL) and dried (Na_2SO_4). Concentration of the organic layer gave a light yellow residue. This was purified by column chromatography (1:10 chloroform/petroleum ether, R_f 0.60) to give **26** (1.02 g, 70%) as an oily liquid. **FT-IR** (KBr) cm^{-1} 2930, 1730 (s), 1431, 1329, 1292, 1150 (s), 1126 (m)1078, 973, 749; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.04 (d, 1H, J = 2 Hz), 7.42 - 7.55 (m, 3H), 7.28 - 7.38 (m, 3H), 6.76 (d, 1H, J = 2 Hz), 5.58 (s, 2H); HRMS: calcd. for $C_{12}H_{10}O_3S$ $[M + H]^+$ 235.0431; found 235.0439.

4.14. Benzenesulfinylmethyl Furan-3-carboxylate (27)

To a stirred solution of compound **26** (120 mg, 0.74 mmol) in MeOH (10 mL) containing water (2 mL) was added solid $NaIO_4$ (170 mg, 0.79 mmol) in portions. The resultant mixture was stirred for 5 h at rt and the solvent was removed under reduced pressure. The resulting crude liquid was extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate extracts was washed with brine (20 mL) and dried (Na_2SO_4). Concentration of the organic layer gave a solid residue which was purified by column chromatography (1:5 chloroform/petroleum ether, R_f 0.52) to give **27** (140 mg, 76%) as a white solid. **mp.** 84˚C - 85˚C; **FT-IR** (KBr) cm^{-1} 2929, 1747 (s), 1571, 1315, 1169, 1122 (s), 1085 (m), 1049, 757; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.07 (d, 1H, J = 2 Hz), 7.66 - 7.75 (m, 2H), 7.52 - 7.58 (m, 3H), 7.41 - 7.47 (m, 1H), 5.14 (ABq, 2H, J = 12 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 161.4, 148.8, 144.1, 140.3, 131.8, 129.4, 124.5, 117.5, 109.7, 81.9; HRMS: calcd. for $C_{12}H_{10}O_4S$ $[M + H]^+$ 251.0380; found 251.0388.

4.15. Methyl 3-Dibromomethyl-furan-2-carboxylate (29)

A mixture of commercially available methyl 3-methyl-2-furoate (**28**) (2.0 g, 14.30 mmol), NBS (5.08 g, 28.60 mmol) and a pinch of benzoyl peroxide in CCl_4 (150 mL) was heated at reflux for 3.5 h under the exposure of a bulb (100 W). The reaction mixture was then cooled (0˚C) and succinimide filtered. The filtrate was concentrated under reduced pressure to give a yellowish residue which was then subjected to column chromatography over silica gel (60 - 120 mesh) using chloroform-petroleum ether mixture (3:7, v/v, R_f 0.58) as eluent to furnish dibromo compound **29** (2.54 g, 60%, white solid) as a main product along with **30** (25%). **mp.** 80˚C - 82˚C; **FT-IR** (KBr) cm^{-1} 3142, 1732 (s), 1608, 1420, 1382, 1252, 1065 (m), 875, 758; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.51 (d, 1H, J = 2 Hz), 7.36 (s, 1H), 6.92 (d, 1H, J = 2 Hz), 3.95 (s, 3H); HRMS: calcd. for $C_7H_6Br_2O_3$ $[M + H]^+$ 295.8684; found 295.8678.

4.16. Methyl 3-Bromomethyl-2-carboxylate (30)

This compound was obtained as white solid in 25% yield and co-product if **30**. **mp**. 51˚C (lit. [16] 52˚C - 53˚C); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.50 (d, 1H, J = 2 Hz), 6.60 (d, 1H, J = 2 H), 4.65 (s, 2H), 3.92 (s, 3H).

4.17. Methyl 3-Formyl-furan-2-carboxylate (31)

To a solution of compound **29** (1.28 g, 4.29 mmol) in THF (20 mL) was added aqueous solution of $AgNO_3$ (1.45 g, 8.58 mmol in 5 mL water) in portions and stirring was continued for overnight at room temperature. The resulting mixture was filtered and after usual work-up of the concentrated filtrate, the residue was purified by column chromatography (1:8 ethyl acetate/petroleum ether, R_f 0.52) to give **31** (0.28 g, 42%) as white crystalline solid. **mp**. 72˚C - 74˚C; **FT-IR** (KBr) cm^{-1} 3264, 2890, 1732 (s), 1682 (s), 1612, 1412, 1320, 1246, 1085, 756; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 10.51 (s, 1H), 7.54 (d, 1H, J = 1.8), 6.90 (d, 1H, J = 1.8), 4.0 (s, 1H).

4.18. Methyl 3-(1,1-Diphenylsulfanyl)-methylfuran-2-carboxylate (32)

This compound was prepared by reaction of **31** with thiophenol in 80% yield as yellow liquid, according to the procedure described for **17** from **15** (Method 2). **FT-IR** (KBr) cm^{-1} 3160, 1728 (s), 1592, 1470 (m), 1438, 1310 (m), 1140, 1102, 1046, 746; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.34 - 7.44 (m, 5H), 7.22 - 7.30 (m, 7H), 6.66 (d, 1H, J = 2 Hz), 6.33 (s, 1H), 3.78 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 158.9, 145.2, 138.9, 133.9, 133.5, 132.8, 128.8, 128.0, 112.5, 51.7, 49.6; **MS** *m/z* (EI): $[M + H]^+$ 357.0640.

4.19. 4-Methyl-benzenesulfonyl Azide (34)

This compound was prepared according to the procedure reported procedure [9]. A mixture of *p*-toluenesulfonyl chloride (**33**) (1.35 g, 7 mmol), NaN_3 (0.55 g, 8.5 mmol) in aqueous solution of acetone (1:2 mixture of acetone andwater) were stirred for 5 h and then acetone was removed under reduced pressure. After usual work-up, drying (Na_2SO_4), solvent was evaporated to furnish the desired product **34** [17] as light yellow liquid (1.17 g, 85%), which was sufficiently pure for the next experiment. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.82 (d, 2H, J = 8), 7.32 (d, 2H, J = 8), 2.45 (s, 3H).

4.20. 3-Diazotetrahydrofuran-2,4-dione (36)

To a stirred solution of tetrahydrofuran-2,4-dione **35** (2.0 g, 0.02 mol) and *p*-tosyl azide **34** (3.7 g, 0.02 mol) in acetonitrile (50 mL) was added triethylamine (2 g, 0.02 mol) dropswise over 15 min resulting in a darkening of the solution. After one hour stirring at room temperature the reaction mixture was concentrated and extracted with ether (3 × 50 mL). The combined organic phases were washed with 5% of HCl (20 mL), brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude residue by chromatography on silica gel (1:1 ethyl acetate/petroleum ether, R_f 0.61) gave **36** [9] (1.0 g, 40%) as a yellowish solid. **mp.** 90˚C; **FT-IR** (KBr) cm^{-1} 2166, 1760 (s), 1692 (s); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.70 (2H, s).

4.21. Methyl 2-Hydroxymethylfuran-3-carboxylate (38)

To a solution of DMSO and water (100 mL, 90:10, v/v) at 80˚C temperature was added compound **12** (1.0 g, 4.58 mmol) and stirring was continued for 4 h. The resulting reaction mixture was extracted with diethyl ether (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and the organic phase was evaporated under reduced pressure. The residue was subjected to column chromatography over silica gel (60 - 120 mesh) (1:10 ethyl acetate-petroleum ether, R_f 0.56) to furnish the alcohol **38** [11] (660 mg, 92%) as brownish liquid. **FT-IR** (KBr) cm^{-1} 3448, 2925, 1724 (s), 1438, 1260, 1024, 762; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.27 (d, 1H, J = 1.6 Hz), 6.64 (d, 1H, J = 1.6 Hz), 4.78 (s, 2H), 3.83 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 164.96, 161.25, 141.26, 114.86, 110.75, 57.23, 51.89; **MS** *m/z* (EI): $[M + 2H]^+$ 158.0267, $[M + Na\text{-}OMe]^+$ 149.0236, $[M + 2H\text{-}OH]^+$ 141.0020.

4.22. 2-Hydroxymethylfuran-3-carboxylic acid (39)

Hydroxy ester compound **38** (0.78 g, 5 mmol) was treated with a mixture of 15% solution of aqueous KOH (15 mL) and methanol (30 mL) for 2 h at rt. On completion of the reaction, 5% of HCl solution (20 mL) was added dropwise till pH 6.5. A white solid separated out from the reaction mixture, which was filtered and washed tho-

roughly with water to furnish pure acid derivative **39** (640 mg, 90%) as white solid. **mp.** 76˚C - 78˚C **FT-IR** (KBr) cm^{-1} 3455, 2924, 1686 (s), 1551 (m), 1269, 1166, 1375, 743; **^{1}H NMR** (200 MHz, d_6-DMSO): δ 7.40 (d, 1H, J = 2 Hz), 6.75 (d, 1H, J = 2 Hz), 4.81 (s, 1H), 2.59 (d, 1H, J = 2 Hz); **^{13}C NMR** (50 MHz, d_6-DMSO): δ 169.54, 165.18, 147.36, 119.82, 116.04, 59.50. HRMS: calcd. for $C_6H_6O_4$ $[M + Na]^+$ 165.0156; found 165.0166.

4.23. 4-Hydroxy-7,8-dihydro-6*H*-naphtho[2,3-*b*]furan-5-one (42)

To a stirred solution of lithium *tert*-butoxide (2.42 mmol) in THF (10 mL) at −60˚C (chloroform/liquid N_2 bath) under an inert atmosphere was added a solution of furansulfoxide (200 mg, 0.75 mmol) in THF (1.5 mL). The resulting yellowish solution was stirred at −60˚C for 25 min, after which a solution of a 2-cyclohexenone (0.90 mmol) in THF (1.5 mL) was added to it. The cooling bath was removed after about 1 h at −60˚C and the reaction mixture was brought to room temperature over a period of 1 h and further stirred for 5 h. The reaction was then quenched with 10% NH_4Cl (10 mL) and the resulting solution was concentrated under reduced pressure. The residue was diluted with ethyl acetate (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with brine (3 × 1/3 vol.), dried (Na_2SO_4) and concentrated to provide crude product. The crude solid product was purified by column chromatography on silica gel to give compound **42** (10mg, 7%) as white solid. **mp**. 118˚C - 20˚C; **FT-IR** (KBr) cm^{-1} 3405, 2940, 2502, 2375, 1982, 1630 (s), 1450, 1450 (m), 1356, 1331, 1284, 11285, 1120 (m), 1014, 814, 747; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 13.51 (s, 1H), 7.49 (d, 1H, J = 2 Hz), 6.94 (d, 1H, J = 0.8 Hz), 6.84 (s, 1H), 2.97 - 3.10 (m, 2H), 2.66 - 2.74 (m, 2H), 2.05 - 2.18 (m, 2H).

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