SYNOPSIS

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The thesis entitled **"Development of alkyne-assisted approaches to the synthesis of benzofurans, furan and furan-fragment of furanocembranoid-1,** has been divided in to four chapters**.**

CHAPTER-I: Introduction of benzofurans and furans.

CHAPTER-II: Synthesis of 2, 3-disubstituted benzofurans from TBS-protected alkynols.

Benzofurans are an important class of bicyclic heterocyclic compounds containing benzene ring fused with furan. Substituted benzofurans display diverse pharmacological activities. Among these, 2, 3-disubstituted benzofurans have great considerable attention as a synthetic targets due to the presence of their skeleton as an integral part of various biologically active natural products as well as pharmaceutical compounds. For example (Figure **1**), the tetracyclic meroterpenoid natural product (+)-liphagal (**1**), a selective inhibitor of phosphatidylinositol 3-kinase (PI3K), isolated from the Caribbean sponge Aka coralliphaga; ii) amiodarone (**2**), a clinically used drug for controlling intractable cardiac arrhythmias; iii) a phenolic compound (**3**), inhibitor against testosterone 5α-reductase, isolated from the stems of Dalbergia cochinchinensis. In addition, numerous 2, 3-disubstituted benzofurans have been reported to possess antifungal, antiviral, antidiabetic and antiparasitic activity.

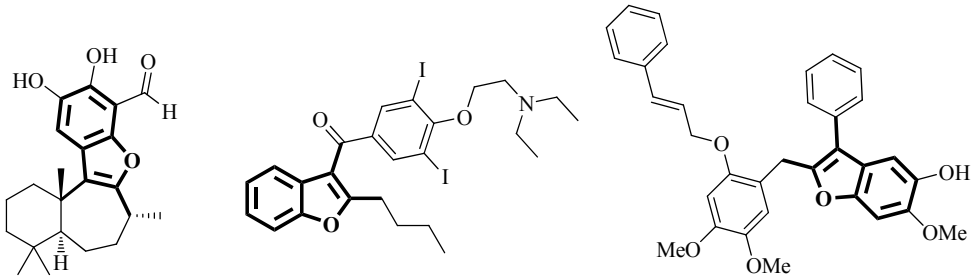
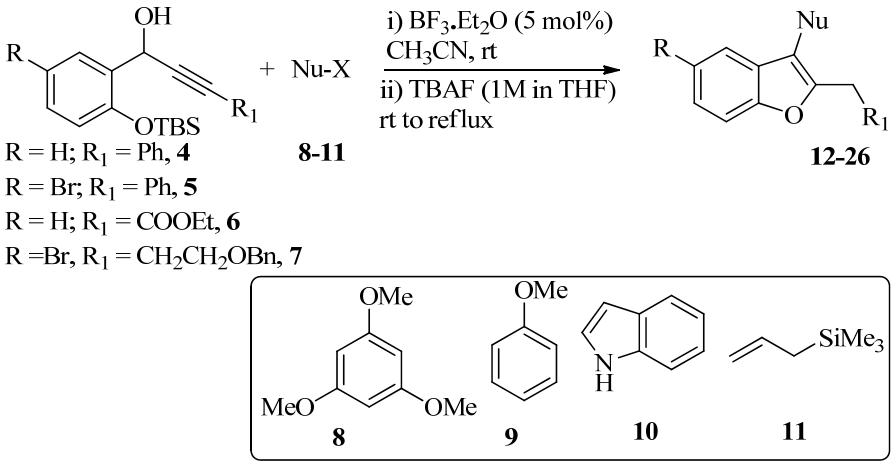


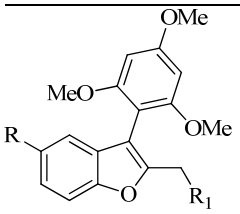
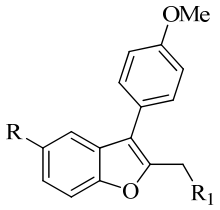
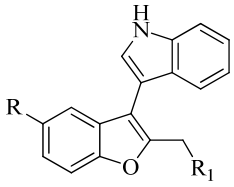
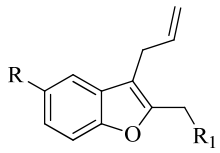
Figure 1: Structure of selected benzofuran-based molecules.

Herein we describe the synthesis of substituted benzofurans from TBS-protected alkynols in one-pot reaction and this method involves sequential Lewis acid catalysed nucleophilic substitution and TBAF mediated desilylation followed by *exo-dig*-cycloisomerization to give diversely substituted benzofurans in good yields shown in (Scheme 1 and Table 1).

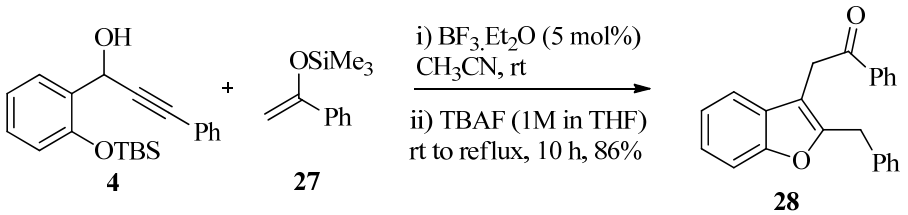


Scheme 1

Table 1: One pot synthesis of 2,3-disubstituted benzofurans.

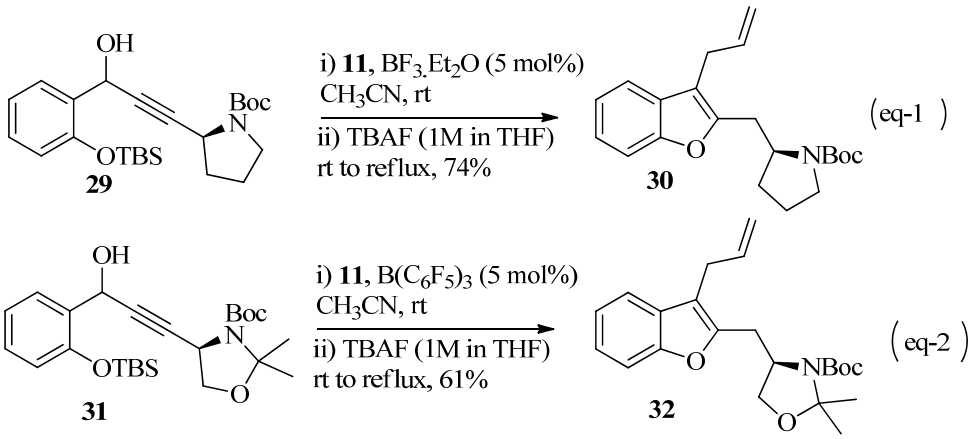
Product / reaction time / yield				
	R = H R_1 = Ph **12**, 8 h, 94%	R = Br R_1 = Ph **16**, 14 h, 86%	R = H R_1 = COOEt **20**, 12 h, 78%	R = Br R_1 = CH_2CH_2OBn **23**, 15 h, 83%
	R = H R_1 = Ph **13**, 12 h, 92%	R = Br R_1 = Ph **17**, 16 h, 91%	R = H R_1 = COOEt **21**, 12 h, 92%	R = Br R_1 = CH_2CH_2OBn **24**, 12 h, 89%
	R = H R_1 = Ph **14**, 12 h, 88%	R = Br R_1 = Ph **18**, 14 h, 84%	inseparable mixture of products	R = Br R_1 = CH_2CH_2OBn **25**, 16 h, 81%
	R = H R_1 = Ph **15**, 10 h, 81%	R = Br R_1 = Ph **19**, 10 h, 93%	R = H R_1 = COOEt **22**, 10 h, 82%	R = Br R_1 = CH_2CH_2OBn **26**, 10 h, 86%

Later, the reactivity of silylenol ether **27** with **4** also tested under the present one-pot reaction conditions and to our delight, the reaction provided the corresponding benzofurans **28** in 86% yield (Scheme **2**).



Scheme 2

In subsequent studies, we also investigated the reactivity of propargylic alcohols **29** and **31**, obtained from the reaction of TBS-protected salicylaldehyde with alkynes derived from Boc-protected prolinol and Garner's aldehyde, with allyltrimethylsilane (**11**). From these reactions, the corresponding 3-allylbenzofuran **30** and **32** were obtained in 74% and 61% yields, respectively (Scheme **3,** eq-**1**). The reaction of **29** with **11** proceeded under the described reaction conditions, whereas in the case of **31**, we found that 5 mol% $B(C_6F_5)$ was a suitable acid catalyst for the nucleophilic substitution reaction; see (Scheme **3,** eq-**2**) because the acid labile acetonide group was not stable in the presence of $BF_3{\cdot}EtO$.



Scheme 3

CHAPTER-III: Synthesis of 5-substituted 3-furanoates from Morita-Baylis-Hillman acetates of acetylenic aldehyde.

Furans are among the most important five member heterocycles in organic and pharmaceutical chemistry. They are not only significant as key motifs in many natural products, but also as versatile building block for the construction of various complex

molecules. And appear as a subunit in many natural products, agrochemicals, functional materials and cosmetics, etc. Precisely, 5-substituted furan-3-carboxylate has been recognized as one of the important frameworks due to its occurrence in many bio-active natural products. For example, flufuran (**33**), tournefolin C (**34**), angelone (**35**) and pukalide class of molecules (**36**) are some of the representative natural products possessing furan-3-carboxylate skeleton embedded in their structures (Figure 2). Further, 5-substituted 3-furanoates were also present in valuable intermediates for the synthesis of bioactive molecules including pesticides such as pyrethroid resmethrin, a synthetic insecticide (**37**, Figure 2).

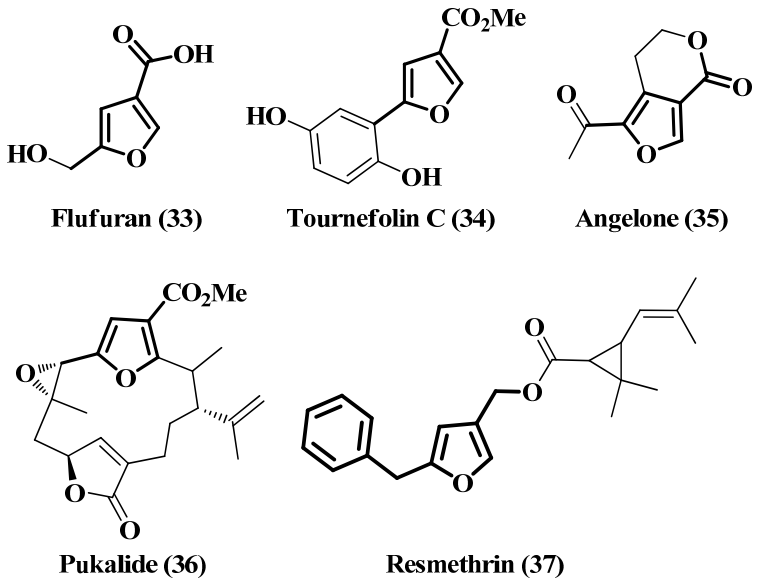
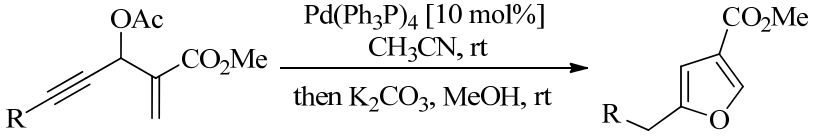


Figure 2: Structures of 5-substituted 3-furanoate molecules.

Herein we describe the synthesis of 5-substituted furan-3-carboxylates from Morita-Baylis-Hillman acetates of acetylenic aldehydes is reported. The process involves palladium-catalyzed isomerization followed by base-promoted deacetylation and

cycloisomerization reactions. The utility of this chemistry is further demonstrated by the synthesis of Elliott's alcohol, a key intermediate of the pyrethroid resmethrins.

Table 2: Synthesis of 5-substituted 3-furanoates.



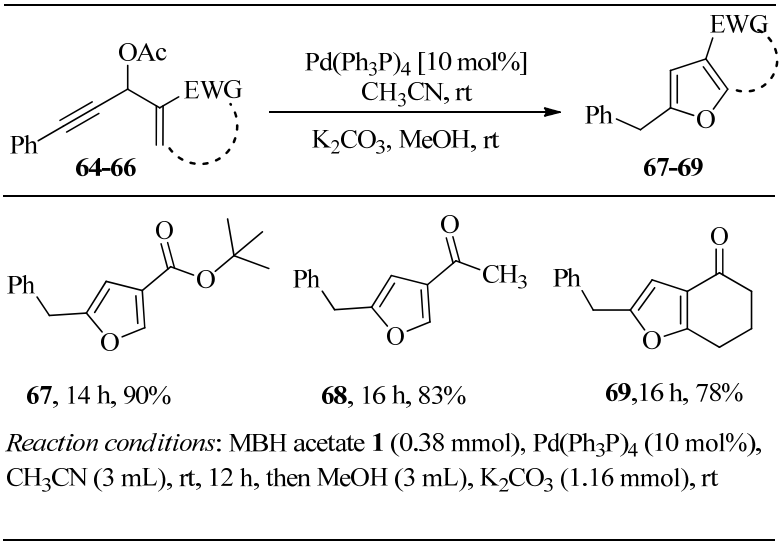
38-50 **51-63**

Entry	MBH acetate (**1**)	Time (h)	Furan (**2**)[b]	Yield (%)[c]
1	R = Ph, **38**	16	**51**	85
1	R = 4-Me-Ph, **39**	14	**52**	85
2	R = 1-Napthyl, **40**	14	**53**	80
3	R = 4-MeO-Ph, **41**	14	**54**	88
4	R = 2-MeO-Ph, **42**	15	**55**	81
5	R = 4-Cl-Ph, **43**	16	**56**	86
6	R = 4-CN-Ph, **44**	14	**57**	84
7	R = 4-$COCH_3$-Ph, **45**	14	**58**	88
8	R = 2-Thiophenyl, **46**	14	**59**	89
9	R = PhCH=CH, **47**	15	**60**	72
10	R = nC_3H_7, **48**	15	**61**	64
11	R = nC_5H_{11}, **49**	14	**62**	68
12	R = nC_6H_{13}, **50**	15	**63**	66

Additionally, MBH acetate **64**, obtained from the reaction of 3-phenylpropiolaldehyde with *t*-butyl acrylate, was found to be good substrate in providing 5-benzyl t-butyl furan-3-carboxylate in 90% yield. Interestingly, MBH acetate **65**, derived from methyl

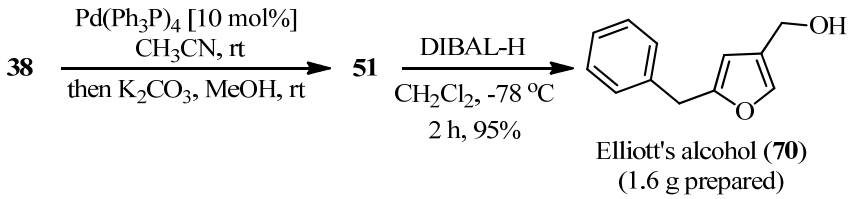
vinyl ketone, underwent tandem isomerization/deacetylation/cycloisomerization reactions to give the corresponding aceto-furanone **68** in 83% yield. Similarly, the present protocol was also extended to MBH acetate **66**, prepared from cyclohexenone, which successfully furnished the tri-substituted furanone **69** in 78% yield (Table 3).

Table 3: Synthesis of substituted furanones



Reaction conditions: MBH acetate **1** (0.38 mmol), $Pd(Ph_3P)_4$ (10 mol%), CH_3CN (3 mL), rt, 12 h, then MeOH (3 mL), K_2CO_3 (1.16 mmol), rt

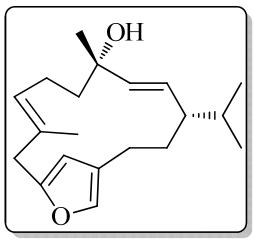
Encouraged by the above success, we turned our attention to show the applicability of the obtained 3-furanoates having ester as a handle for further elaboration towards the useful derivatives. In this direction, methyl 5-benzylfuran-3-carboxylate **51**, achieved from MBH acetate **38**, was converted to (5-benzylfuran-3-yl)methanol (**70**), Elliott's alcohol, by reduction of the ester using DIBAL-H in dichloromethane (Scheme 5). The resulting Elliott's alcohol (**70**) is a key intermediate for the manufacture of resmethrins, pyrethroid insecticides (Figure 2).



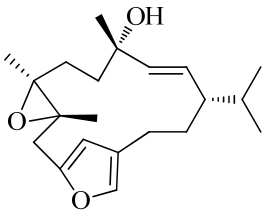
Scheme 4

CHAPTER-IV: Synthesis of furan-fragment of furanocembranoid-1.

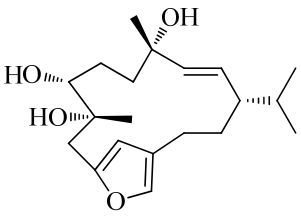
In 2007, Khanitha Pudhom et *al.* isolated a class of furanocembranoids 47-50 (Figure 3) from the hexane extract of croton oblengifolius roxb sp. Furanocembranoids-1 was obtained as colorless oil. It showed cytotoxicities againest BT474 (human breast ductol carcinoma), CHAGO (human undifferentiate lung carcinoma), Hep-G2 (human liver hepatoblastoma), KATO-3 (human gastric carcinoma) and SW-6 (human colon adreno carcinoma).



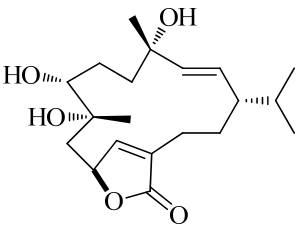
furanocembranoid-1 (71)



furanocembranoid-2 (72)



furanocembranoid-3 (73)

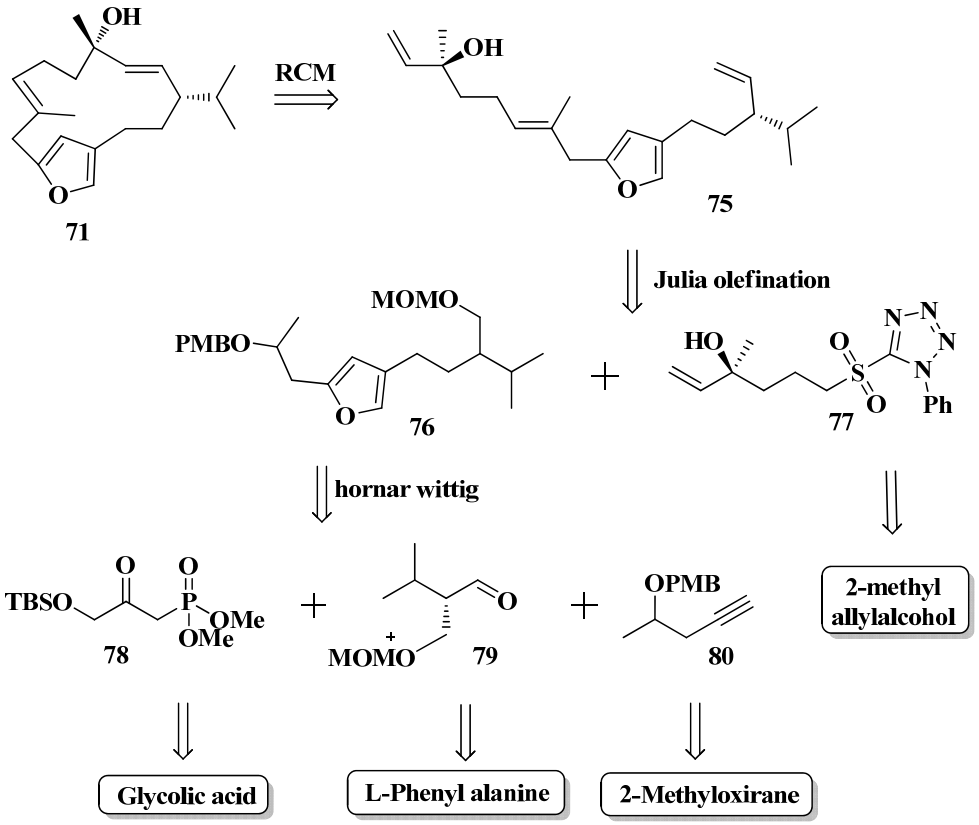


furanocembranoid-4 (74)

Figure 3: Structures of furanocembranoids **71-74**.

The presence of two stereogenic centers and a network of diverse and distributed functionalities on its novel framework, together with its potential bioactivity, make furanocembranoid-1 (**71**) a challenging and attractive target molecule for synthetic chemists. Strategically, the most challenging problem is the construction of the furan ring system as well as the structural moiety possessing the asymmetric centers bearing a isopropyl group and trans double bonds. In continuation of our focus on the synthesis of bioactive natural products, we herein, developed the synthetic approach toward construction of furan-fragment of furanocembranoid-1.

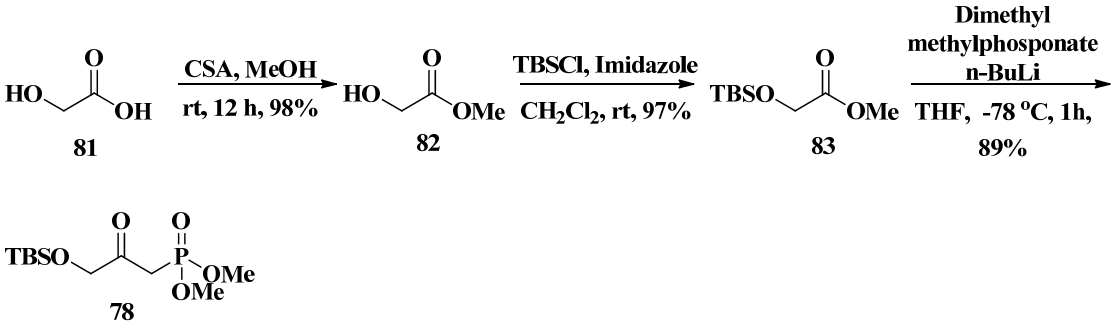
The retrosynthetic analysis of **71** was outlined in scheme **6**. As indicated, our initial disconnections of the target molecule involved C_2-C_3 and C_7-C_8 double bonds to give fragments **76** and **77.** In requisite fragment **76**, could be accessed from coupling of fragments **78**, **79** and **80**. These three fragments are synthesized from glycolic acid, L-phenylalanine and 2-methyloxirane respectively. In this, Horner-Wittig, asymmetric Aldol and Gilman epoxide opening type reactions are involved as on key steps. On the other hand, fragment **77** was synthesized from 2-methylallylalcohol.



Scheme 5: Retrosynthetic analysis of furanocembranoid-1.

Synthesis of fragment of 78

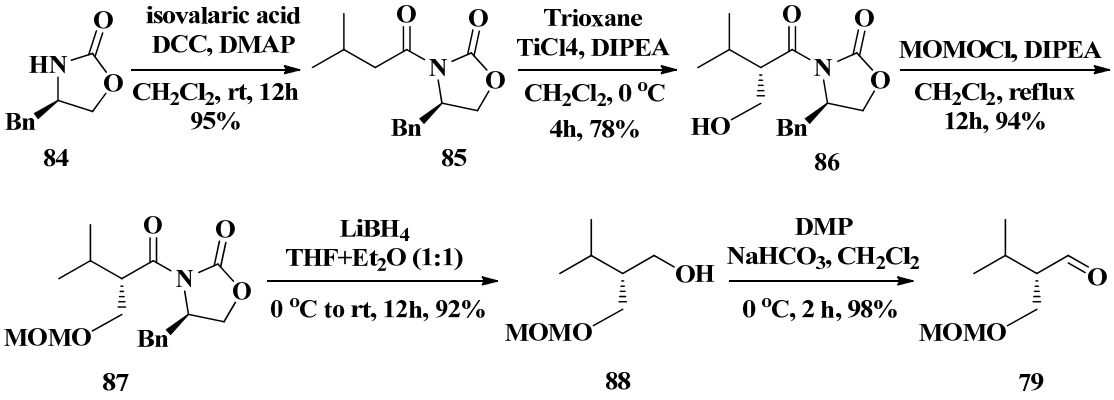
The preparation of fragment **78** was accomplished by readily available glycolic acid **81** with known procedure. As shown in (Scheme 6), the acid group of glycolic acid subjected to esterification in presence of CSA and methanol to give ester **82** which was further subjected to protection of primary alcohol with *tert*-butyl dimethyl silylchloride in presence of imidazole and dichloromethane result furnish **83** in good yield. Than ester was treated with dimethyl methylphosponate in presence of n-butyl lithium to give fragment **78**.



Scheme 6

Synthesis of fragment 79

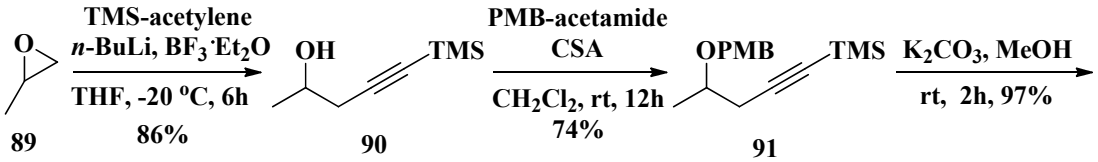
Synthesis fragment **79** was accomplished by from readily available L-phenylalanine with known procedure (Scheme 7). Initially, L-phenylalanine was reduced under iodine and $NaBH_4$ in tetrahydrofuran at reflux 12 h to give alcohol and which upon cyclization furnished chiral auxiliary **84**. The auxiliary was reacted with isovalaric acid in the presence of DCC, DMAP in dichloromethane to give compound **85**. The compound **85** was subjected to chiral aldol reaction in presence of *s*-trioxane, $TiCl_4$ and DIPEA in dichloromethane to give compound **86** in 95% yield. The primary alcohol of compound **86** was protected with MOMCl in presence of DIPEA and dichloromethane at reflux for 12 h to furnish compound **87** in 94% yield, Next the auxiliary was removed by reduction of compound **87** with lithium borohydride in presence of tetrahydrofuran at room temperature for 12 h to offer compound **88** in 92% yield. Finally, the alcohol undergoes oxidation with Dess-Martin periodinane in dichloromethane at room temperature to provide aldehyde **79** in 98% yield.

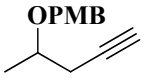


Scheme 7

Synthesis of fragment 80

Synthesis of fragment **80** was achieved starting from methyloxirane as shown in scheme 9, in which the epoxide opening with trimethylsilyl acetylene in presence of *n*-BuLi and tetrahydrofuran at -78 ^{o}C to give compound **89** in 86% yield. The secondary alcohol of compound **89** was protected with *p*-Methoxybenzyl trichloroacetamide (synthesized from *p*-Methoxy benzylalcohol treated with trichloroacetonitrile in presence of sodium hydride and dichloromethane) in presence of CSA and dichloromethane to give compound **90** in 74 % yield. Trimethylsilyl removed by potassium carbonate in methanol at room temperature to offered fragment **80** in 97% yield.



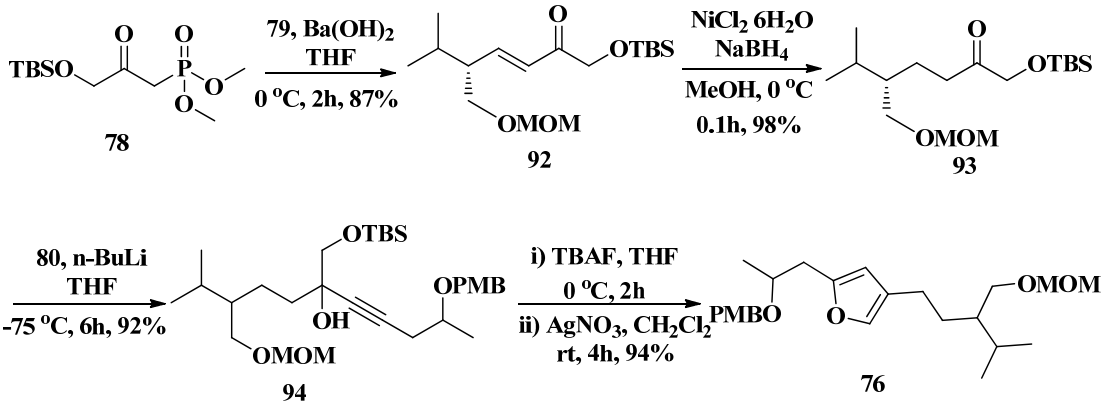


80

Scheme 8

Synthesis of furan-fragment 76

Synthesis of main fragment **76** demonstrate in scheme 10. Initially the phosponate **78** react with aldehyde **79** in presence of barium hydroxide and tetrahydrofuran to offered α, β- unsaturated ketone **92** in 87% yield. Next the double bond of compound **92** reduction with Hexahydrate nickel chloride and sodium borohydride in presence of methanol to provide saturated ketone **93** in 98% yield. The ketone of compound **93** was treated with terminal alkyne **79** in presence of *n*-butyl lithium and Tetrahydofuran at -78 ^{o}C to provide compound **94** in 92% yield. Finally deprotection of *tert*-butyldimethylsilyl ether with *tert*-butyl ammonium fluoride in presence tetrahydrofuran followed by furan formation under silver nitrate reaction condition to offered furan-fragment **76** of furanocembranoid-1(**71**) in 94% yield.



Scheme 9

Conclusion

By utilizing the high yielding chemical transformations, we have delineated a stereoselective and convergent approach towards the synthesis of furan-fragment **76** of furanocembranoid-1 (**71**). Initial retrosynthetic analysis on scheme 6 identified three

key segments **78**, **79** and **80**. The preparation of furan-fragment **76** a perpouse of providing an advanced intermediate towards the synthesis of furanocembranoid-1(**71**) by usin alkyne chemistry.