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Developments of Corey-Fuchs Reaction in Organic and Total Synthesis of Natural Products

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Abstract: Corey-Fuchs olefination is a two-step reaction, involving the reaction of an aldehyde and tetrabromomethane (CBr_4) in the presence of the triphenylphosphine (Ph_3P) to synthesize 1,1-dibromoolefins. In the second step, the conversion of the dibromoolefins to alkynes occurred in the presence of *n*-BuLi as the base. This transformation was first discovered by E. J. Corey and P. L. Fuchs in 1972. Due to the importance of terminal alkynes in the synthetic organic chemistry, the Corey-Fuchs reaction has found many applications in organic transformations; particularly in the total synthesis of several biologically active natural products, often as starting materials.

Keywords: Corey-Fuchs, Olefination, 1,1-Dibromoolefins, Total synthesis, Organic synthesis, Terminal alkynes, Triphenylphosphine.

1. INTRODUCTION

The Corey-Fuchs reaction, also known as the Ramirez-Corey-Fuchs reaction is a two-step methodology, allowing the synthesis of terminal alkynes from aldehyde [1]. The first step, which was discovered by Desai, McKelvie, and Ramirez, leads to 1,1-dibromoolefins, which involves the reaction of an aldehyde with phosphine-dibromomethylenes, obtained from the reaction of triphenylphosphine (Ph_3P) and tetrabromomethane (CBr_4) [2]. The second step is the Fritsch-Buttenberg-Wiechell rearrangement, which involves the conversion of dibromoolefins to alkynes in the presence of *n*-BuLi or LDA as a base [3]. Corey and Fuchs combined these two reactions to develop a useful strategy for the transformation of aldehydes to alkynes [1].

The terminal alkynes have several uses in the synthetic organic chemistry, including many name reactions such as Sonogashira [4], Glaser [5], and Eglinton coupling reactions [6]. As an example, Sonogashira coupling is an effective C-C bond formation strategy, involving the Pd-catalyzed reaction of aryl halides with terminal acetylenes. This carbon-carbon bond formation has been widely applied in organic reactions and natural product synthesis [4]. Above all, terminal alkynes are one of the essential components of an important and versatile reaction, for the synthesis of 1,2,3-trizoles, namely Huisgen reaction [7], which was developed by K.B Sharpless and his co-workers [8] as click reaction, which attracted attentions of the synthetic organic research groups, for the regioselective synthesis of 1,2,3-triazole derivatives [9-11].

In the continuation of our interest in the recent advancement of the named reactions in the organic and total synthesis [12-19] using asymmetric synthesis [14, 20-22] and application of terminal alkynes [23-27]. In this review, we tried to underscore the applications of another important name reaction, called Corey-Fuchs reaction.

2. COREY-FUCHS REACTION IN ORGANIC SYNTHESIS

The Corey−Fuchs reaction occurs *via* initial reaction of triphenylphosphine (Ph_3P) (**1**) and tetrabromomethane (CBr_4). The provided active reagent is triphenyl(trihalomethyl)phosphonium halide **3**. The one-carbon homologation of an aldehyde (**4**) to dibromoolefin (**5**) occurred by the brominating agent (**3**). Finally, dibromoolefin was treated with *n*-BuLi to produce a terminal alkyne (**8**) (Scheme **1**) [28].

The Corey-Fuchs reaction was employed in the preparation of (±)-4-ethynyl[2.2]paracyclophane (PCP-C≡CH) (**12**) and 4,16-diethynyl[2.2]paracyclophane (**14**). The racemic terminal alkynes (**13** and **14**) were prepared *via* a two-step synthesis [1]. In the first step, interaction of zinc, CBr_4 and PPh_3 followed by addition of the formyl derivatives **9-10** gave the dibromoolefins **11** and **12** with 90-95% yields. The desired Corey-Fuchs products (**13** and **14**) were obtained by the treatment of **11** and **12** with *n*-BuLi in THF, followed by hydrolysis, in 80-90% yields. Furthermore, the ethynyl derivative **13** was coordinated to various mono- and dinuclear complexes and played a key role in a carbon-carbon coupling reaction (Scheme **2**) [29].

Corey-Fuchs reaction is a prominent transformation using strong bases such as BuLi for the conversion of an aldehyde **4** by the chain extension into a 1,1-dibromovinyl derivative **15**, which leads to an alkyne. 1,1-dibromoalkenes **15** which was subjected to Suzuki-Miyaura conditions using different kinds of boronic acids [30]. Graham *et al.* represented cyclobutene-1,2-*bis*(imidazolium) salt **17** is an effective catalyst for the one-pot tandem Suzuki-Miyaura/dehydrobromination reactions (Scheme **3**). This procedure involved the treatment of 1,1-dibromoalkenes **15** and palladium(II) acetate, aryl boronic acids, and potassium *tert*-butoxide in toluene under Corey-Fuchs conditions to give the corresponding alkynes **16** in the temperature range of 65-90 °C in good to excellent yields (71-83%) [31]. The Suzuki-Miyaura treatment of a variety of boronic acids and boronic esters with tri- and tetra-substituted alkenes, (*Z*)-1-aryl- or (*Z*)-alkenyl-1-bromoalk-1-enes and internal alkynes were shown in Fig. (**1**) [32-35].

Charette *et al.* [36] reported the synthesis of 1-iodoalkynes **19** as an important building block applicable in the several synthetic methodologies, total syntheses, pharmaceutical, and material/polymer applications [37-41]. There are several methods for the synthesis of 1-iodoalkynes **19** such as iodination of metal acetylides [42-43], direct iodination of the corresponding terminal alkyne [44-45],

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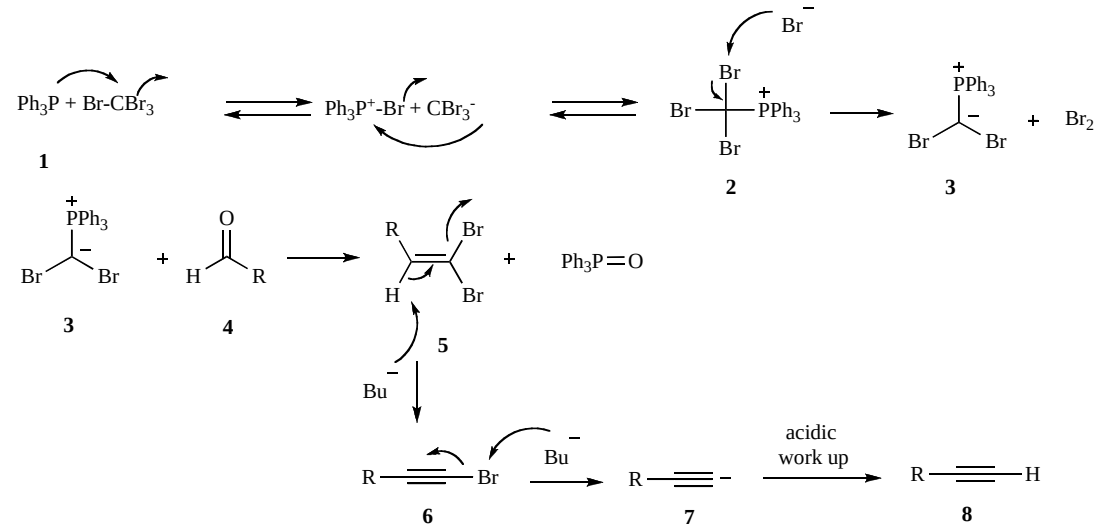
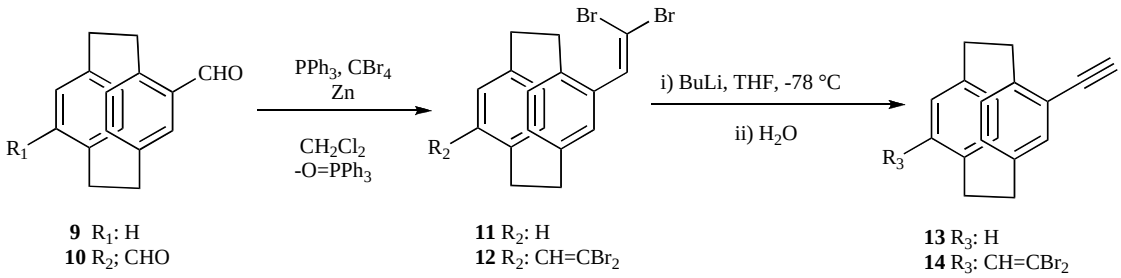


Scheme 1. Mechanism of Corey−Fuchs reaction *via* preparation of dibromoolefin (**5**) and terminal alkyne (**8**).



Scheme 2.

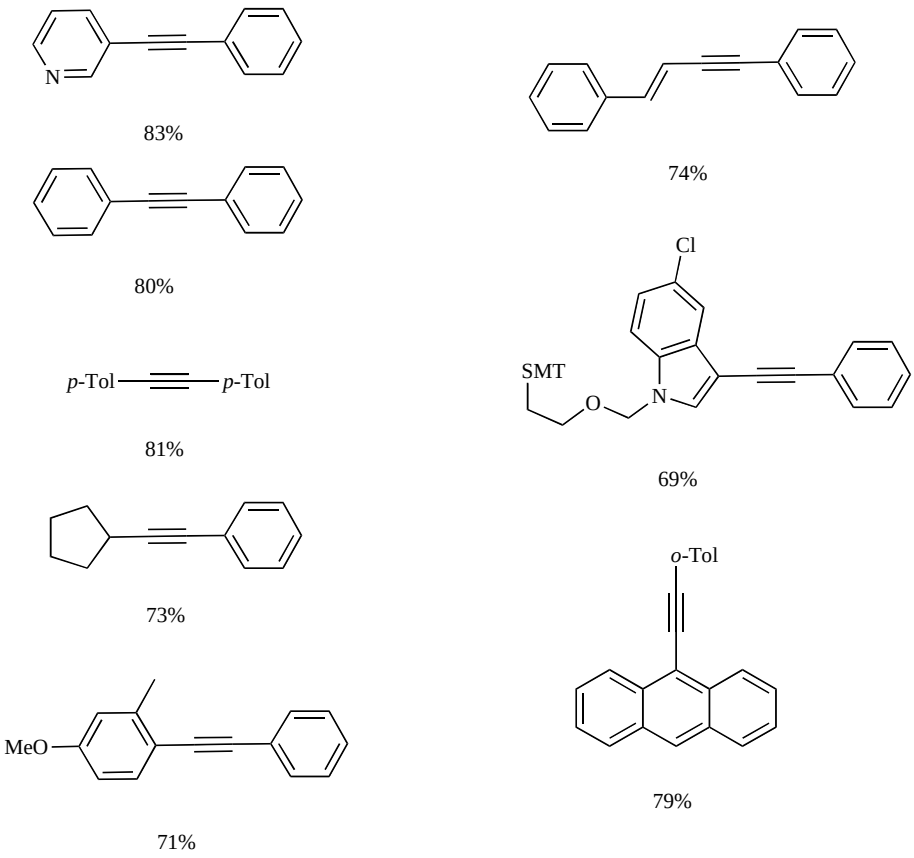
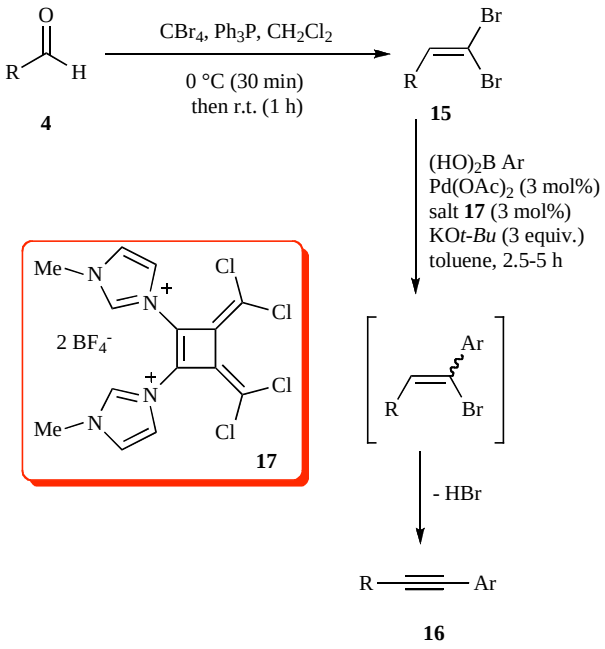
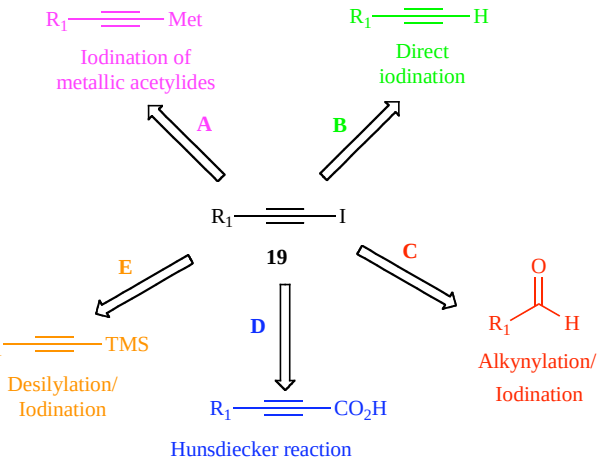


Fig. (1).



Scheme 3.

Et_3N-catalyzed Hüunsdiecker reaction with NIS [46-47], and two step homologation/iodination sequence, starting from an aldehyde (Corey-Fuchs reaction) (Scheme **4**, A-C) [1, 48-49] or $AgNO_3$-mediated direct iodination of trimethylsilylacetylenes (D and E) [50].



Scheme 4. Various methodologies employed for the synthesis of 1-iodoalkynes **19**.

Charette and his group employed Corey-Fuchs iodoalkynylation conditions through one-pot homologation/double elimination from commercially available benzylic and allylic bromides **18** (Scheme **5**). This reaction was extended to various benzylic bromides derivatives **18** and the results showed that the electron-donating groups provided higher yields than those performed with electron-withdrawing substituents as shown in Fig. (**2**).

Scott *et al.* described the synthesis of the polycyclic aromatic hydrocarbons (PAHs) containing a newly formed naphthalene ring,

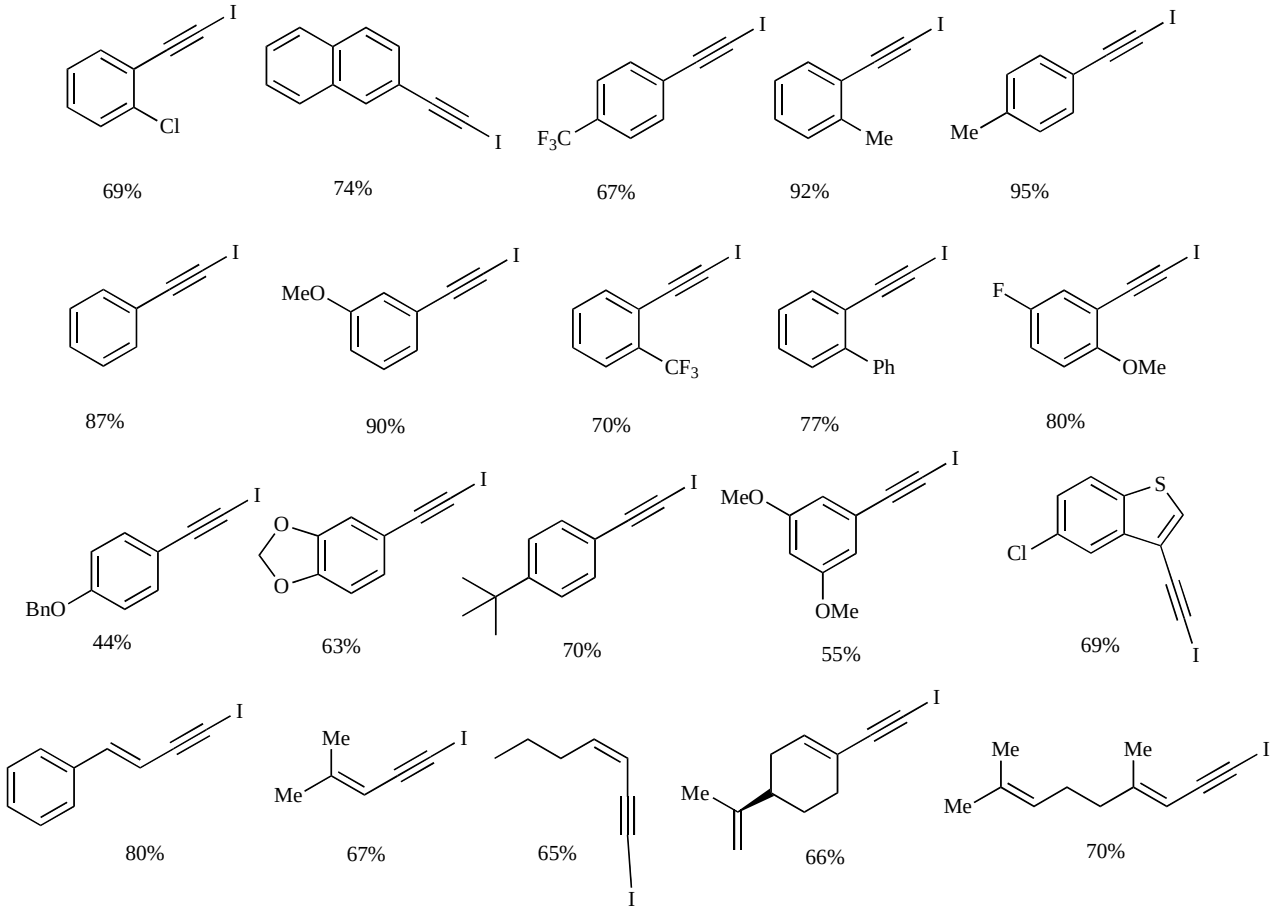
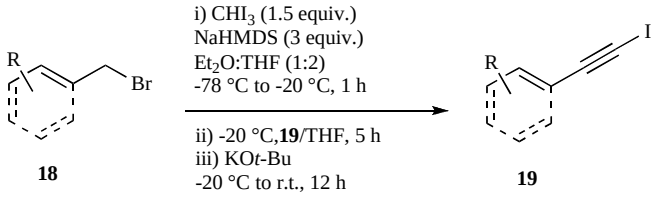
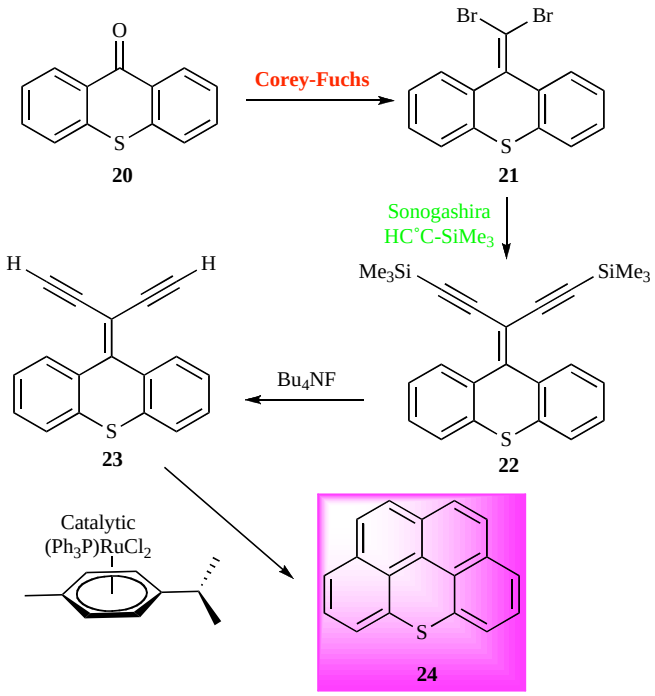


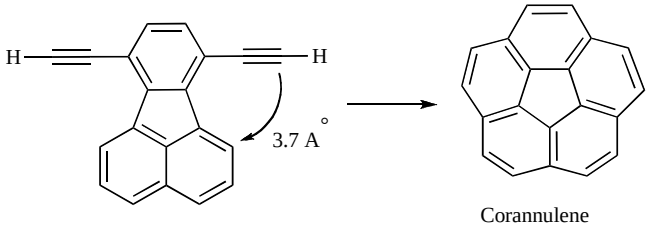
Fig. (2).



Scheme 5. Synthesis of 1-iodoalkynes **19** from their corresponding benzylic or allylic bromides **18**.



Scheme 6.



Scheme 7.

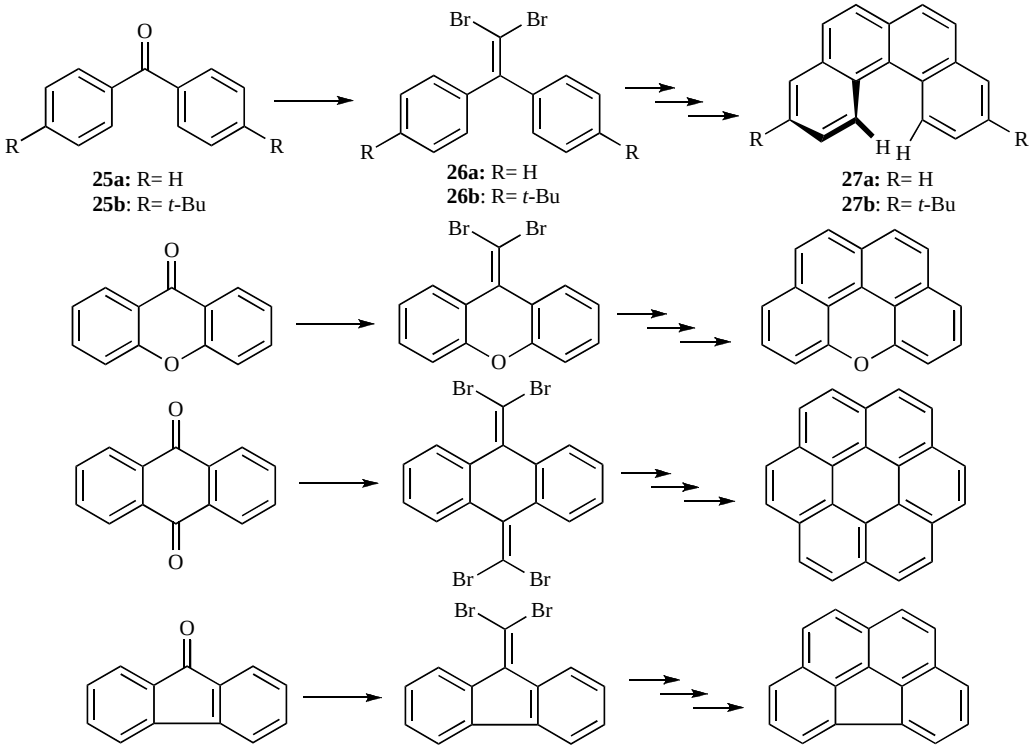
starting from diaryl ketones. The procedure involve four steps, which begins with a Corey-Fuchs olefination of the starting ketone **20**. Then a double Sonogashira coupling [51-53] with trimethylsilylacetylene would occurr and is followed by desilylation with tetra-*n*-butylammonium fluoride, which provide the parent diyne **23**. In the last step, a ruthenium-catalyzed or Pt-catalyzed cycloisomerization is performed in refluxing 1,2-dichloroethane to give 1,8,9-perinaphthothioxanthene **24** in 95% yield (Scheme **6**) [54].

As shown in Scheme **7**, this step works well when the distance between the atoms being joined are less than about 3.35-3.40 Å.

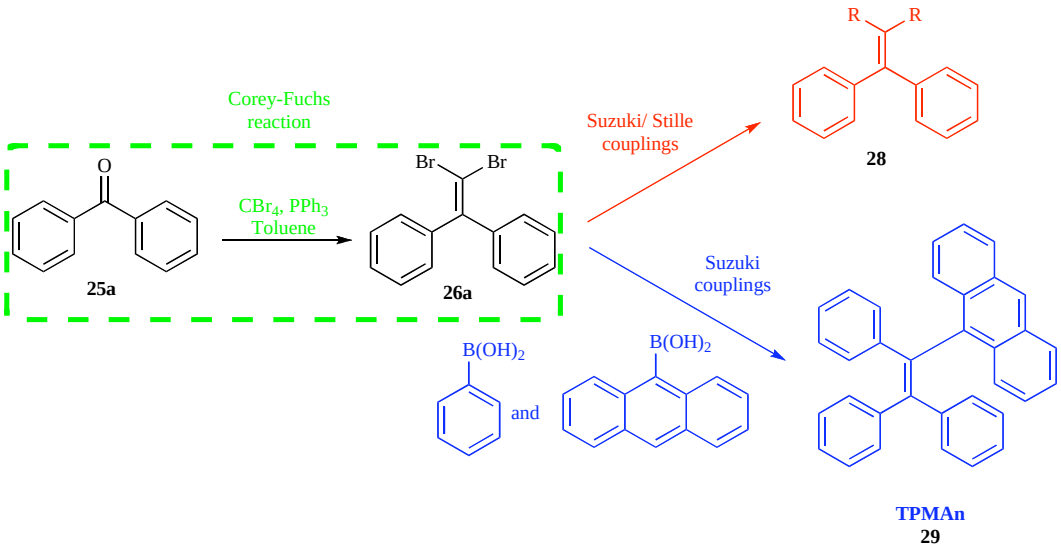
The Corey-Fuchs olefination was used for several xanthenone **25,** leading to dibromoalkene **26** with subsequent Sonogashira coupling and transition metal-catalyzed double ring closures which gave cyclized product **27** (Scheme **8**) [54].

The Corey−Fuchs reaction of diaryl ketones **25a** led to dibromo olefination **26a**, followed by Suzuki or Suzuki/Stille coupling leading to novel TAE fluorophores with tunable fluorescence (**28** and **29**). The products of this reaction, showed the aggregation-induced emission characteristic (Scheme **9**) [55].

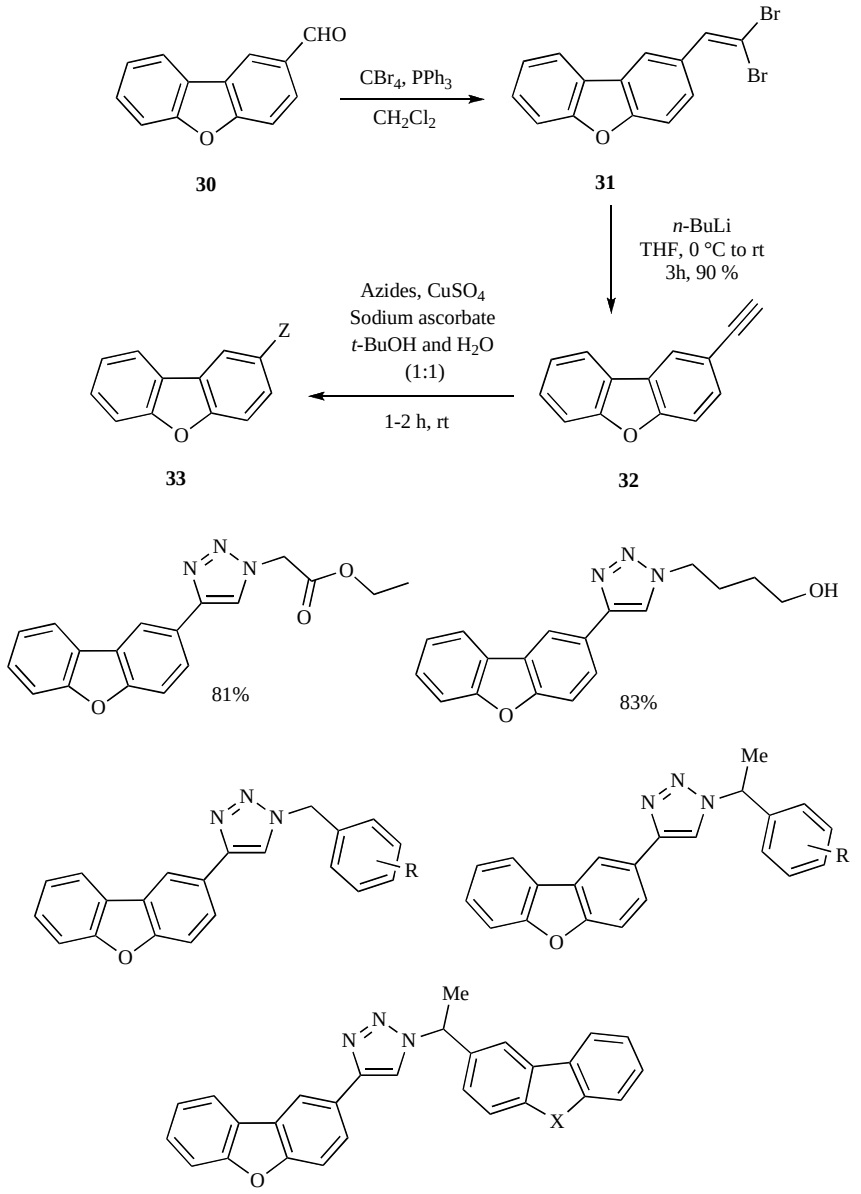
In 2014, Kantevari *et al.* reported a novel method for the generation of dibenzo[*b*,*d*] furan-1,2,3-triazole conjugates **33** using click chemistry and Corey-Fuchs reaction (Scheme **10**) [56]. Dibenzo[*b*,*d*]furan-2-caraboxaldehyde **30** as starting material was prepared by the formylation of dibenzofuran. In the next step, 2-



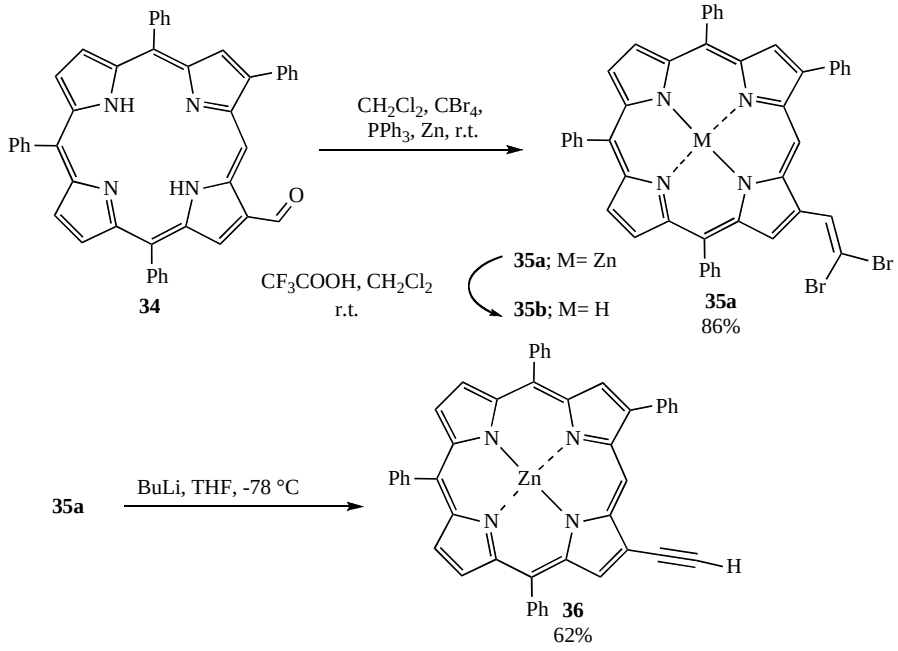
Scheme 8.



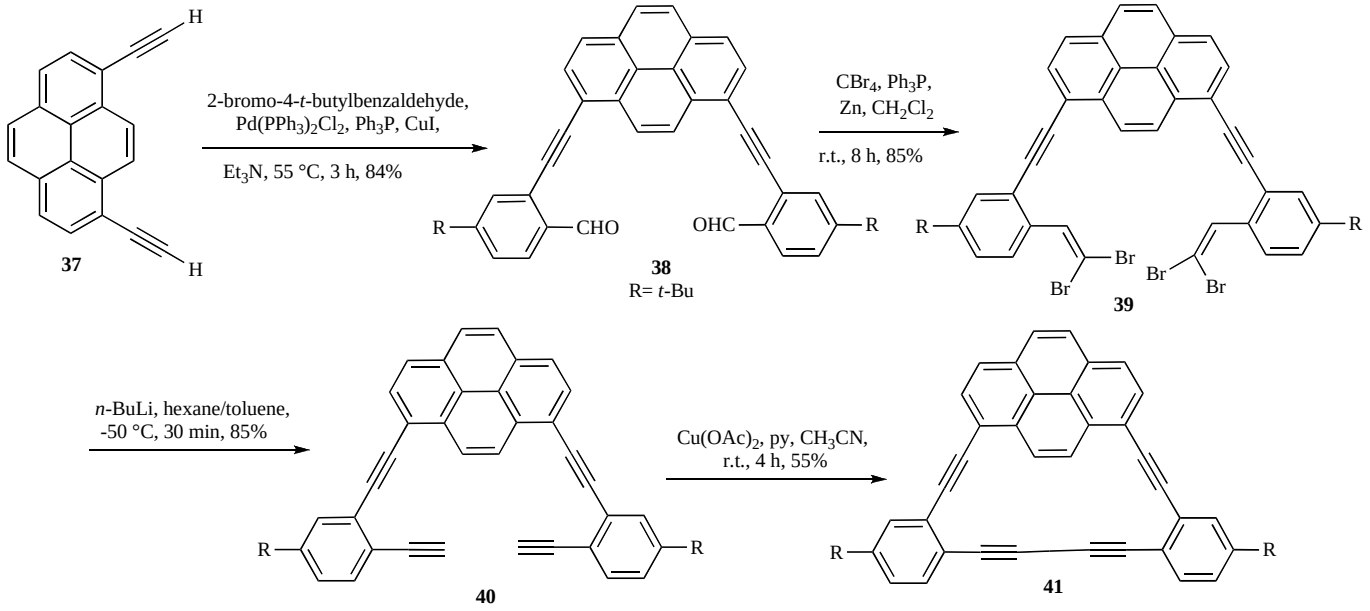
Scheme 9. Synthetic Route of the TAE Compounds.



Scheme 10. Synthesis of dibenzo[*b*,*d*]furan-1,2,3-triazole **33**.



Scheme 11.



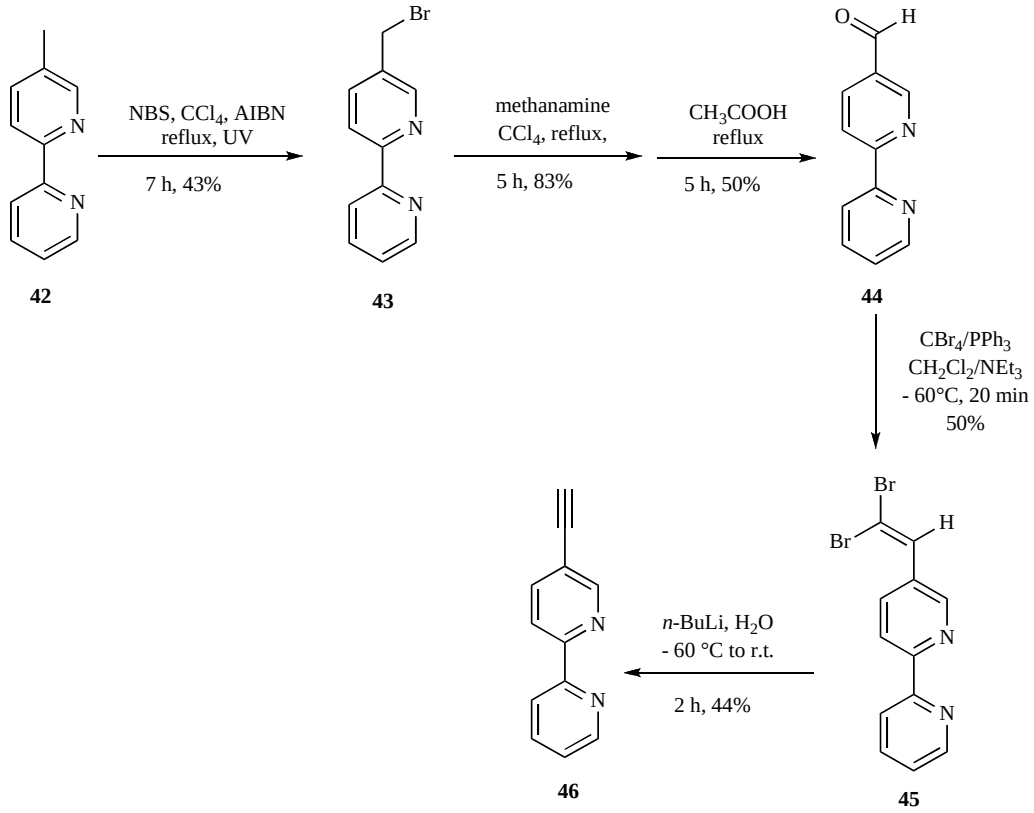
Scheme 12.

(2,2-dibromovinyl)dibenzo[*b*,*d*]furan **31** was synthesized in the presence of CBr_4 and PPh_3 in high yield. Noticeably, the conversion of **31** to 2-ethynyldibenzo[*b*,*d*]furan **32** under standard conditions of Corey-Fuchs reaction [57-59] failed. The further experiments revealed the optimized conditions for this reaction is using *n*-butyl lithium (1.6 M) in THF at 0 °C followed by 3h stirring of the reaction mixture at ambient temperature. Finally the desired products were obtained *via* Huisgen's (3+2) cycloaddition using $CuSO_4$ catalyst, sodium ascorbate in *t*-butanol and water to give dibenzo[*b*,*d*] furan-1,2,3-triazole **33**.

Another application of Corey-Fuchs reaction was reported by König *et al*. in the synthesis of alkyne-substituted porphyrins **36** as a building block for the synthesis of extended photoactive porphyrin arrays. In this procedure, 2-formyl-5,10,15,20-tetraphenylporphyrin **34** was used as a starting material and the desired product **36** was obtained in two steps. First, a Corey-Fuchs reaction converts **34** to the *gem*-dibromoalkene **35** under standard conditions using a large excess of CBr_4, triphenylphosphine and zinc [60]. Using trifluoroacetic acid leads to demetallation of the zinc porphyrin **35a** to **35b** [61] then the introduction of BuLi caused the rearrangement of **2a** to the corresponding product **36** with overall yield 53% over two steps (Scheme **11**) [62].

The product **36** can be applied in palladium-catalyzed coupling reactions with aryl iodides to give the extended photoactive porphyrin arrays under standard conditions [63-64].

Sankararaman and his group disclosed a new multistep system for the preparation of dehydrobenzoannulenes **41** (DBAs), which known as benzocyclynes. DBAs are in great interest because of their applications as starting materials for new forms of carbon allotropes [65], building blocks for 2D carbon networks [66-67], optoelectronic materials [68-69], and as sensitive probes for the investigation of tropicity of the annulene ring [70-71].



Scheme 13.

In this multistep system, the Corey-Fuchs methodology was used in the conversion of polyaldehyde precursors **38** to poly terminal alkynes **40**. In addition, for the synthesis of final pyrene-based dehydrobenzoannulenes **41**, Sonogashira and oxidative coupling (Eglinton coupling) were applied (Scheme **12**) [72].

Polin and co-workers disclosed a new multicatalytic system involving, both Corey-Fuchs olefination and hydrolysis for the synthesis of 5-ethynyl-2,2′-bipyridine **46** from 2,2′-bipyridine-5-carbaldehyde **44** as outlined in Scheme **15**. 5-Methyl-2,2′-bipyridine **42** was used as a common starting material, which was converted to **44** conversion of the methyl derivative (Scheme **13**) [73].

Neidlein *et al*. [74] employed a Corey-Fuchs procedure in the reaction of cyclic diketones **47** and **51** to have access to dibromoalkenes **48** and **52** respectively. These products in addition to **55** underwent an alkynylation reaction to give geminal enediynes **49a-e**, **53a-e**, and **56a-c**. The results showed that when the backbone of the precursor was cyclohexane, which could be oxidized with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) leading to the *p*-quinoid systems **50a,b** (Scheme **14**).

In the past decade, triptycene derivatives have received considerable attention for their applications in the supramolecular chemistry [75-76], materials science [77-79], and synthetic molecular machines [80-83] with unique three dimensional rigid structures.

As illustrated in Scheme **15**, 2-formyltriptycene **57** could be conveniently converted into 2-ethynyltriptycene **59** by Corey−Fuchs reaction in two steps with 59% total yield [84].

3-Deoxy-2-ulosonic acids is an important class of acidic monosaccharides and have specific roles in biological systems [85-86]. After oxidation to the corresponding aldehyd while having alcohol **60b** on hand, it underwent Corey-Fuchs reaction to create the desired alkyne **61b**. The latter can be used for the synthesis of 3-deoxy-D-*manno*-octulosonic acid (KDO) as a key core structure of lipopolysaccharides (LPSs) in several steps (Scheme **16**) [87].

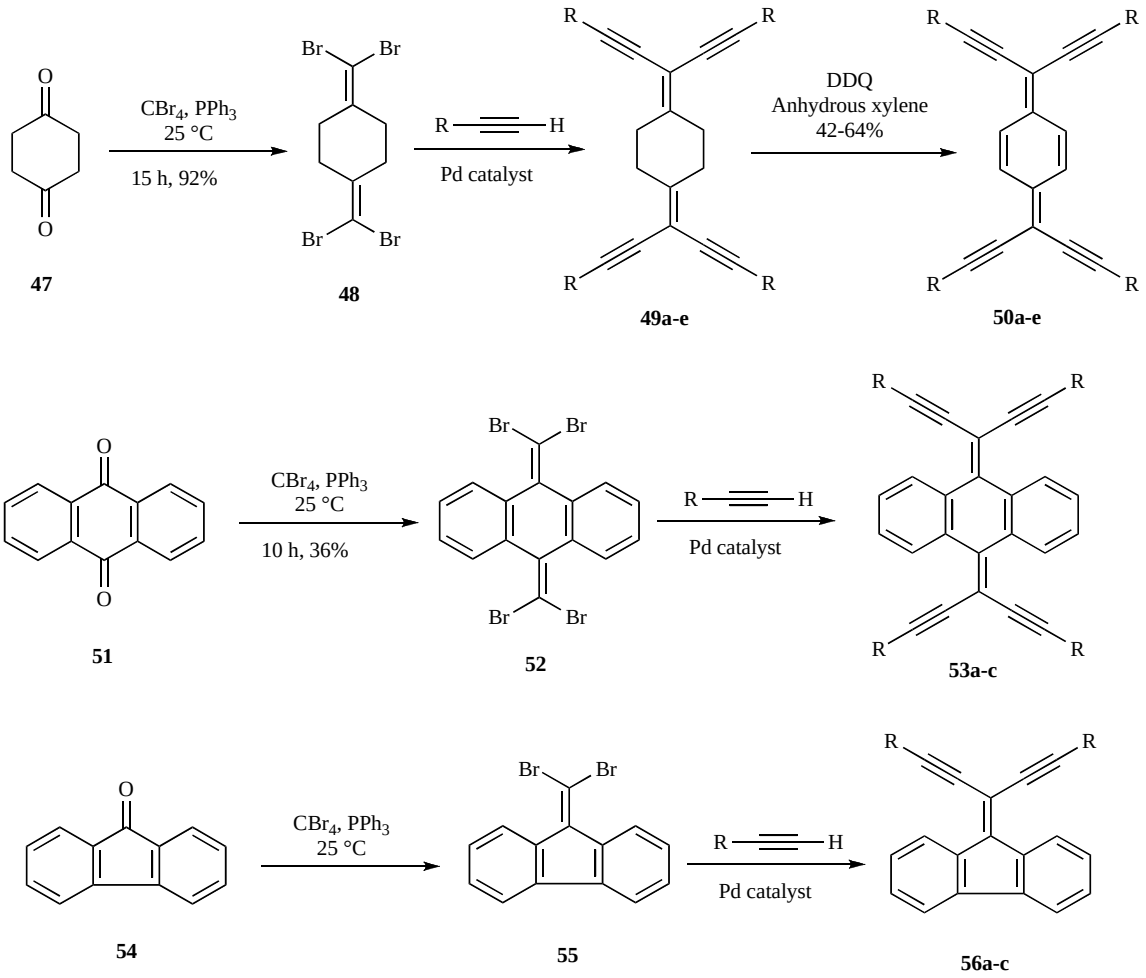
The same sequence, which is used for KDO, the total synthesis of 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH) **65** is an intermediate in the biosynthesis of amino acids. In a key step, the Corey-Fuchs alkynylation of alditol **63** turns into alkyne **64** and was employed (Scheme **17**) [88].

Ferrocene alkynes are the building blocks of some natural products [89] and valuable ligands for material science and organometallic synthesis [90].

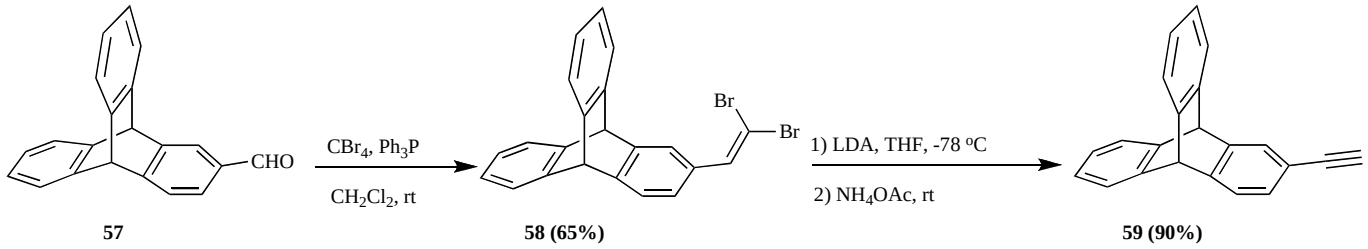
A Corey-Fuchs methodology was employed for the synthesis of novel functionalized ferrocene alkyne $Ph_2P(S)fcC{\equiv}CH$ (**68**; fc = ferrocene-1,1'-diyl) from $Ph_2P(S)fcCHO$ **66**. The latter can be converted to the mercury(II) acetylide $Hg(C{\equiv}CfcP(S)Ph_2)_2$ **69** and trimetallic Co_2Fe complex $[(\mu\text{-}\eta^2{:}\eta^2\text{-}1)(Co(CO)_3)_2](Co\text{-}Co)$ **70** (Scheme **18**) [91].

Hafner *et al.* developed a synthetic route of mono- and polyethynylated azulenes **73a-h,** which employs a versatile procedure for the new carbon-carbon bond formation. The classical Corey-Fuchs reaction was used as a key step. Azulenes ethynylated in the five-member ring can be obtained on a multigram scale *via* Pd-catalyzed cross-coupling of iodo- or bromoazulenes by trimethylsilyl-acetylene followed by desilylation.

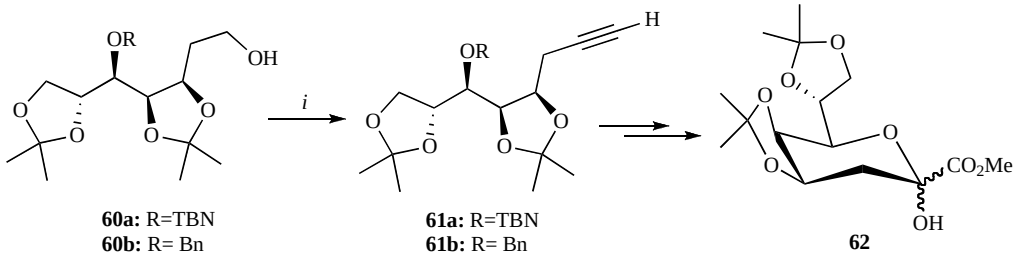
The reaction of the corresponding 5,7-diformylazulene **71** with triphenylphosphine and tetrabromomethane in dichloromethane furnished, after chromatography on alumina (BII-III) using *n*-hexane as an eluent, greenish blue crystals of the tetrabromodiolefin **72** was obtained in 70% yield. The latter could be converted into the 5,7-diethynylazulene **73h** (86%) upon treatment with 6 equiv. of LDA followed by hydrolysis (Scheme **19**) [92].



Scheme 14.

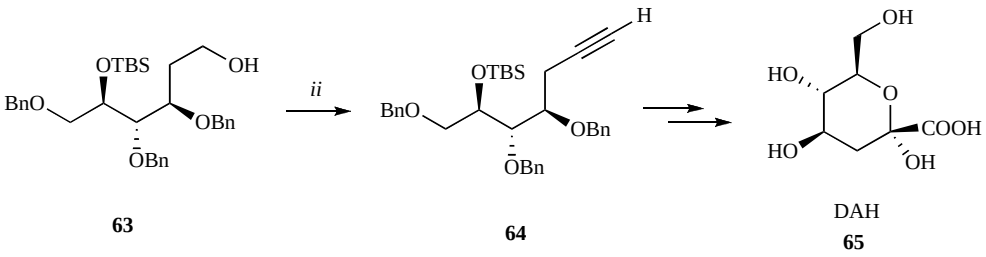


Scheme 15.



i) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 2 h;
2) CBr_4, TPP, Et_3N, CH_2Cl_2, 0 °C, 2 h;
3) EtMgBr, THF, -78 to 0 °C, 1 h;
for **61a** 65% over three steps and **61b** 70% over three steps

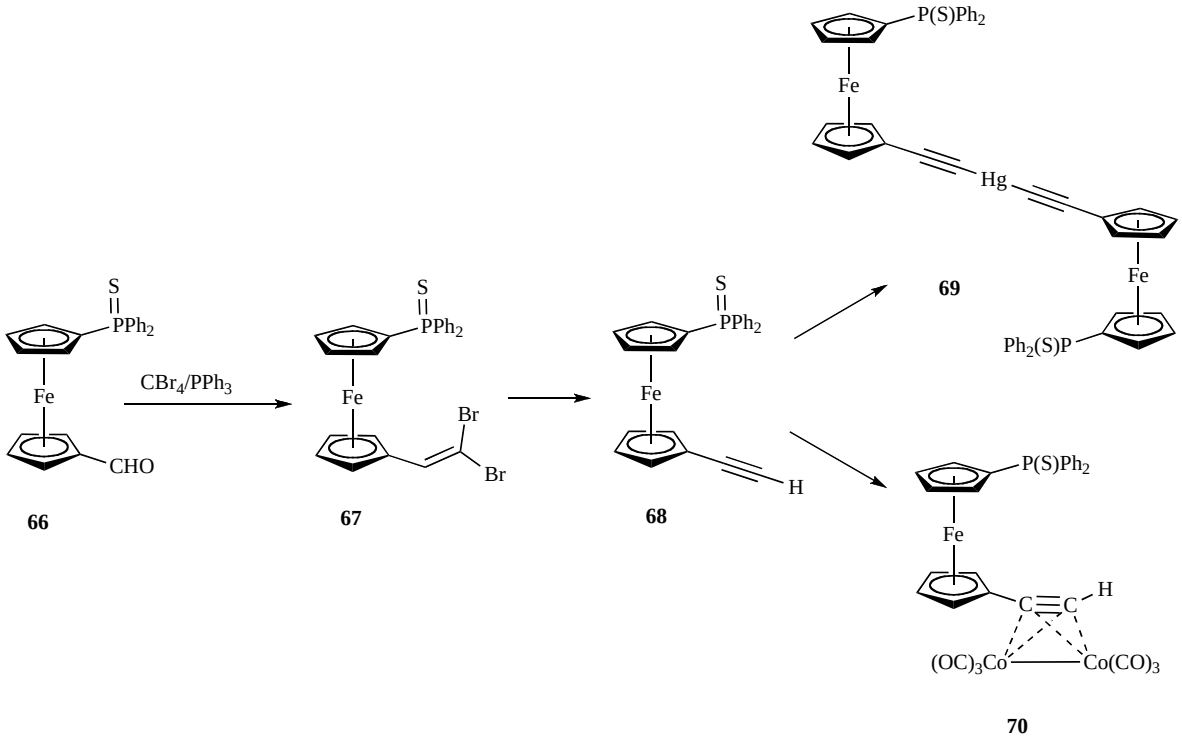
Scheme 16.



63 **64** **65**

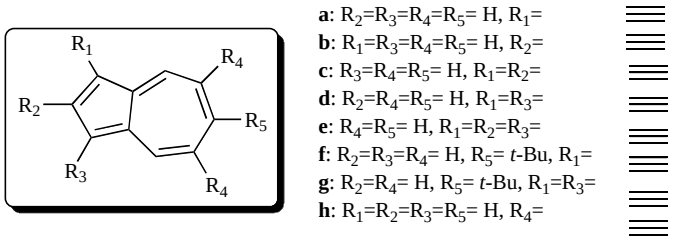
(*ii*) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 2 h; 2) CBr_4, TPP, Et_3N, CH_2Cl_2, 0 °C, 1 h; 3) EtMgBr, THF, -78 to 0 °C, 1 h, 60% over three steps

Scheme 17.

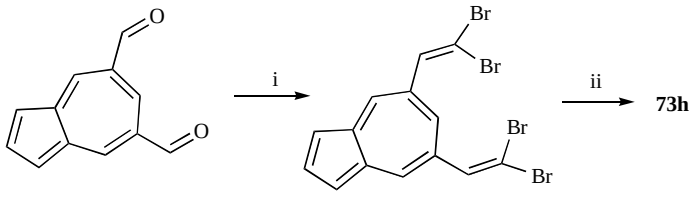


66 **67** **68** **69** **70**

Scheme 18.



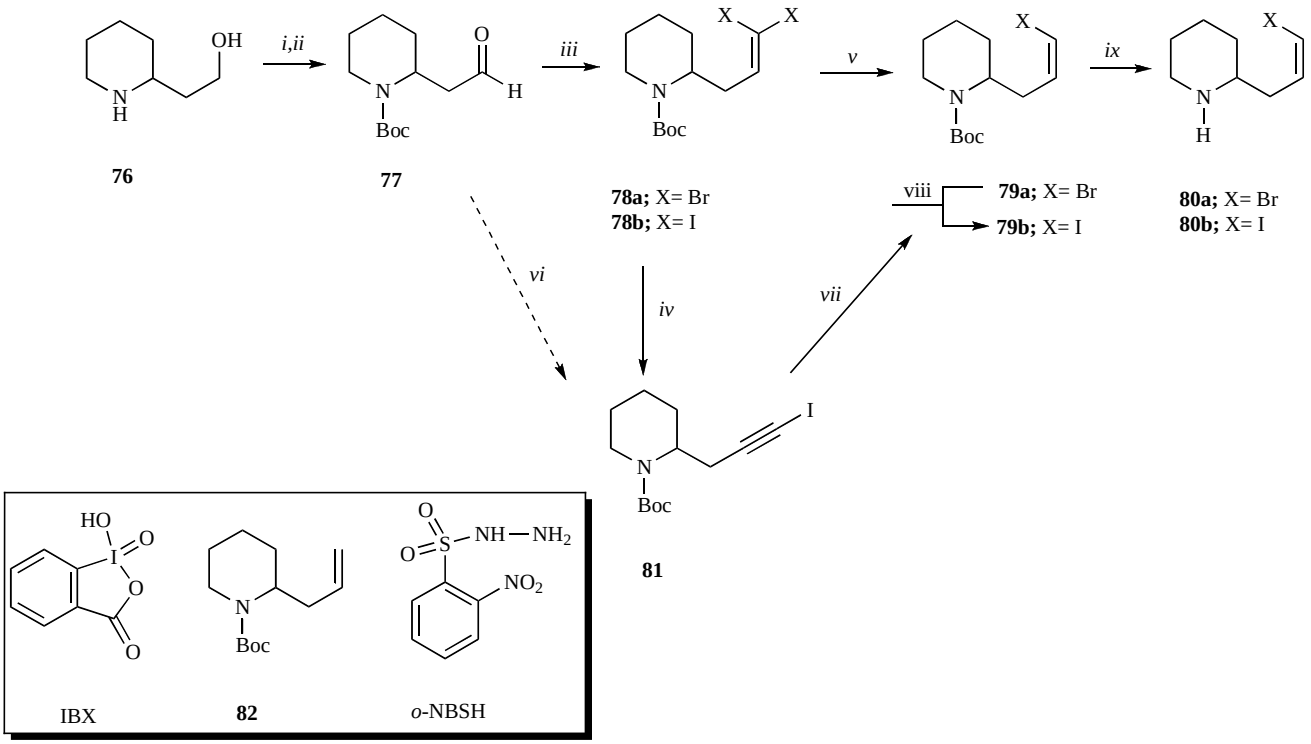
a: R_2=R_3=R_4=R_5= H, R_1=
b: R_1=R_3=R_4=R_5= H, R_2=
c: R_3=R_4=R_5= H, R_1=R_2=
d: R_2=R_4=R_5= H, R_1=R_3=
e: R_4=R_5= H, R_1=R_2=R_3=
f: R_2=R_3=R_4= H, R_5= *t*-Bu, R_1=
g: R_2=R_4= H, R_5= *t*-Bu, R_1=R_3=
h: R_1=R_2=R_3=R_5= H, R_4=



71 **72** **73h**

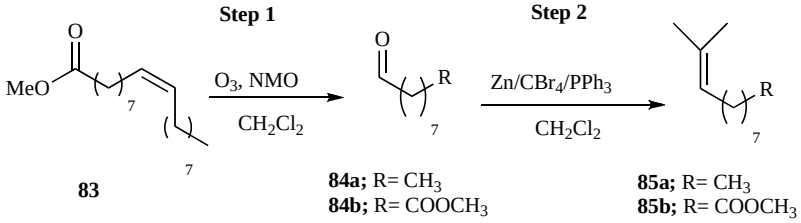
(i) PPh_3, CBr_4, CH_2Cl_2, rt; (ii) 6 equiv. LDA, THF, - 90°C, rt

Scheme 19.



(i) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 99%; (ii) IBX, EtOAc, 75 °C, 95%; (iii) **78a**: CBr_4, PPh_3,Et_3N, THF, -78 °C to rt, 87%. **78b**: CHI_3, PPh_3, *t*-BuOK, THF, rt, 68%; (iv) *n*-BuLi, THF, -78 to 0 °C then I_2,95-99%; (v) *n*-Bu_3SnH, $Pd(PPh_3)_4$, toluene, rt, **79a**: 82%, **79b**: 39%; (vi) CHI_3, PPh_3, *t*-BuOK, THF, rt, 40%; (vii) *o*-NBSH, Et_3N, *i*-PrOH-THF, rt, 73%; (viii) NaI, CuI, $(CH_3NHCH_2\text{-})_2$, *n*-BuOH, 120 °C, 47%; (ix) TFA, CH_2Cl_2, rt, **80a**: 92%, **80b**: 94%.

Scheme 20.



Scheme 21.

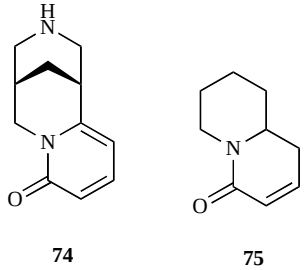
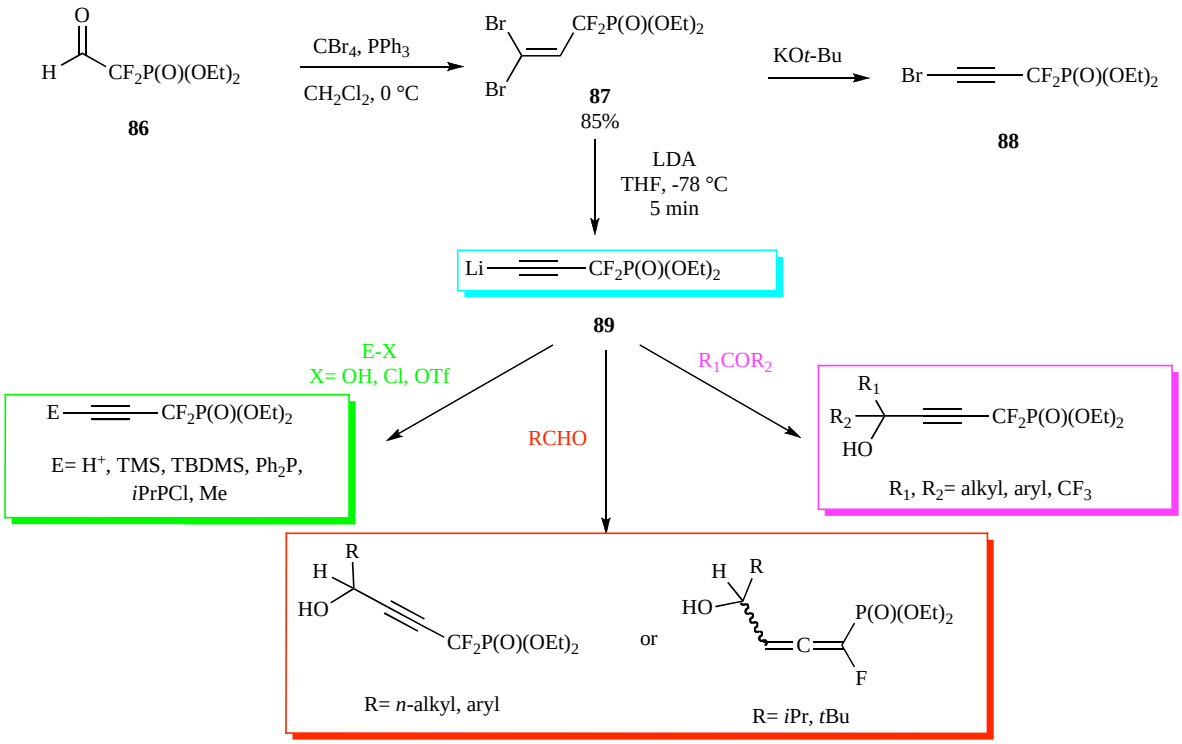


Fig. (3). (-)-cytisine **74** and model lactam **75**.

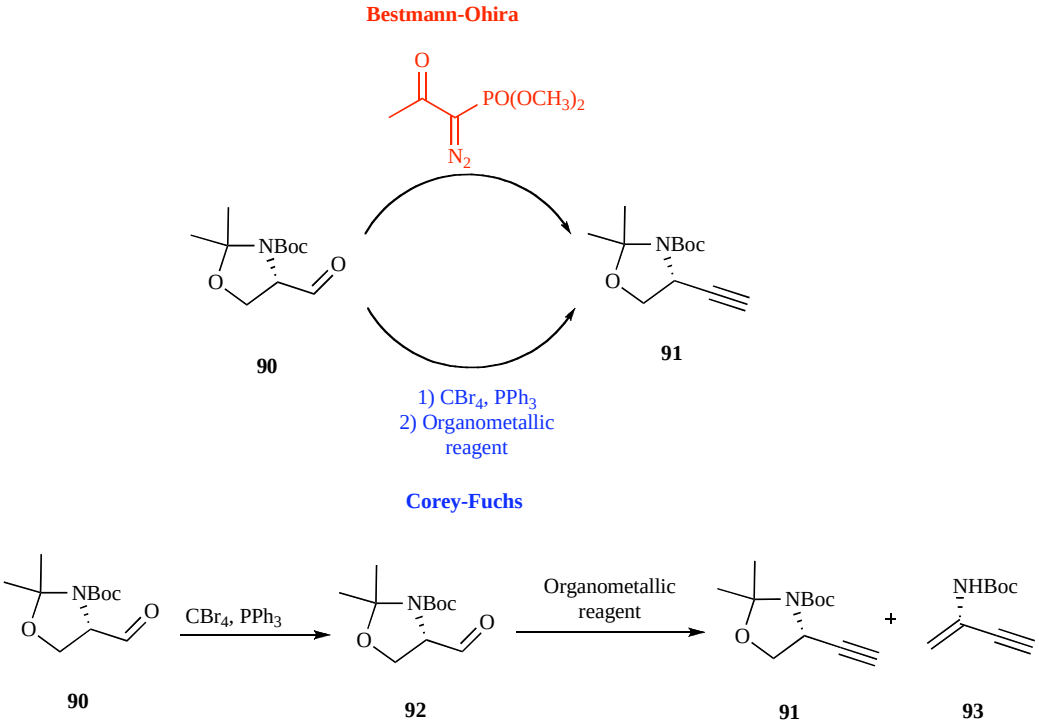
In 2004, a novel lactam annulation on a model compound (lactam **75**) has been developed by Rouden *et al*. (Fig. **3**). This compound was established from (2-hydroxyethyl)-piperidine **76** in a linear synthesis involving a Corey-Fuchs olefination **81** of the aldehyde by a selective reduction. *o*-Nitrobenzenesulfonylhydrazide (*o*-NBSH) was applied as diimide equivalent for an iodoalkyne into a (*Z*)-iodopropene piperidine (Scheme **20**) [93].

Brown *et al.* reported the preparation of a versatility of dibromoolefins (DBOs). These reactions proceeded in two steps; the first one was oxidative cleavage of alkene **83** by ozonolysis of esters which can be combined with a Corey-Fuchs type dibromoolefination. The second step involves using phosphorous yilide to produce alkene **85** (Scheme **21**) [94].

Another application of Corey−Fuchs-type sequence was described by Pajkert and his co-worker. This methodology led to novel alkynes with a difluoromethylenephosphonate function using (diethoxyphosphoryl)difluoroacetic aldehyde **86** as the precursor. The first step the Corey−Fuchs-type reaction of corresponding aldehyde **86** led to (3,3-dibromodifluoroallyl)phosphonate **87**. Then the dehydrobromination of intermediate **87** occurred in the presence of potassium *tert*-butoxide to create bromoalkyne **88**. For the first time, the reaction **87** with lithium base led to the preparation of ((diethoxyphosphoryl)difluoropropynyl)lithium **89**. The compound **89** can be used as a valuable reagent for the synthesis of different propargyl phosphonates by the treatment with various electrophiles



Scheme 22.

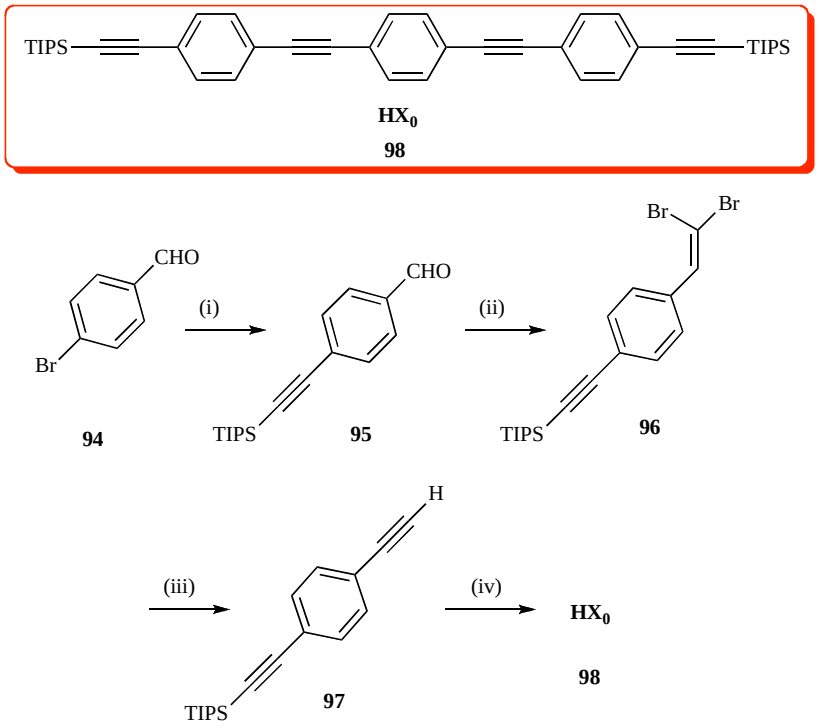


Scheme 23. Degradation product **93** observed in the preparation of **91** (variable amounts).

such as aldehydes, ketones, triflates, chlorophosphines, and chlorosilanes (Scheme **22**) [95].

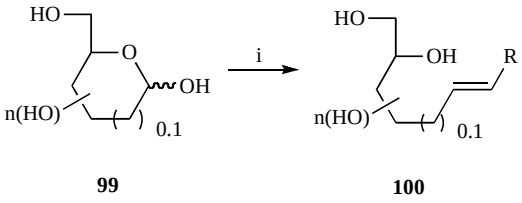
The synthesis of ethynylglycine synthon **91** as a valuable material is in great demand. There are two common pathways for the generation **91,** as illustrated in Scheme **25**. The first one is known as the Seyferth-Gilbert strategy and the second method is the Corey-Fuchs reaction. The synthesis of ethynylglycine synthon **91** *via* Corey-Fuchs reaction occurred by the addition of BuLi **90** followed by preparation of dibromovinyl **92** as an intermediate to give the corresponding alkyne **91**. The ratio of main product **91** is higher than by-product **93** and the amount of the by-product increased by introducing a large excess of base for longer time (Scheme **23**) [96-100].

Nierengarten and his co-workers synthesized branched conjugated systems with a terminal alkyne function *via* Corey-Fuchs dibromoolefination. This reaction was carried out by treatment of



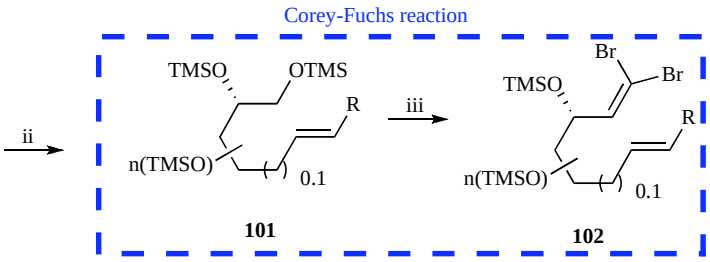
(i) triisopropylsilylacetylene, $PdCl_2$-$(PPh_3)_2$, CuI, PPh_3,Et_3N, THF (98%);
(ii) CBr_4, PPh_3, Zn dust, CH_2Cl_2 (99%);
(iii) LDA, THF then NH_4Cl, H_2O (90%);
(iv) 1,4-diiodobenzene, $PdCl_2(PPh_3)_2$, CuI, PPh_3,Et_3N, THF (84%).

Scheme 24.



R= CO_2Et, CO_2t-Bu, CO_2Me, CN

(i) $BrCH_2R$ (2 equiv), *n*-Bu_3P (2 equiv), Zn (2 equiv), 1,4-dioxane, reflux



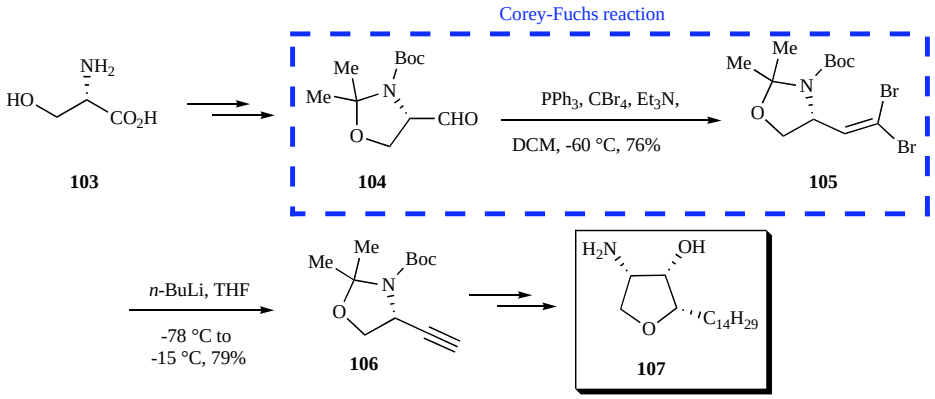
(ii) BSC (1.2 equiv per OH), TBAF (0.01 equiv), NMP, rt.
(iii) (a) $(COCl)_2$ (3 equiv),DMSO (6 equiv), CH_2Cl_2, -70°C then Et_3N,
(b) Ph_3PCHBr_3 (2.2 equiv), *t*-BuOK (2.1 equiv), THF, rt.

Scheme 25.

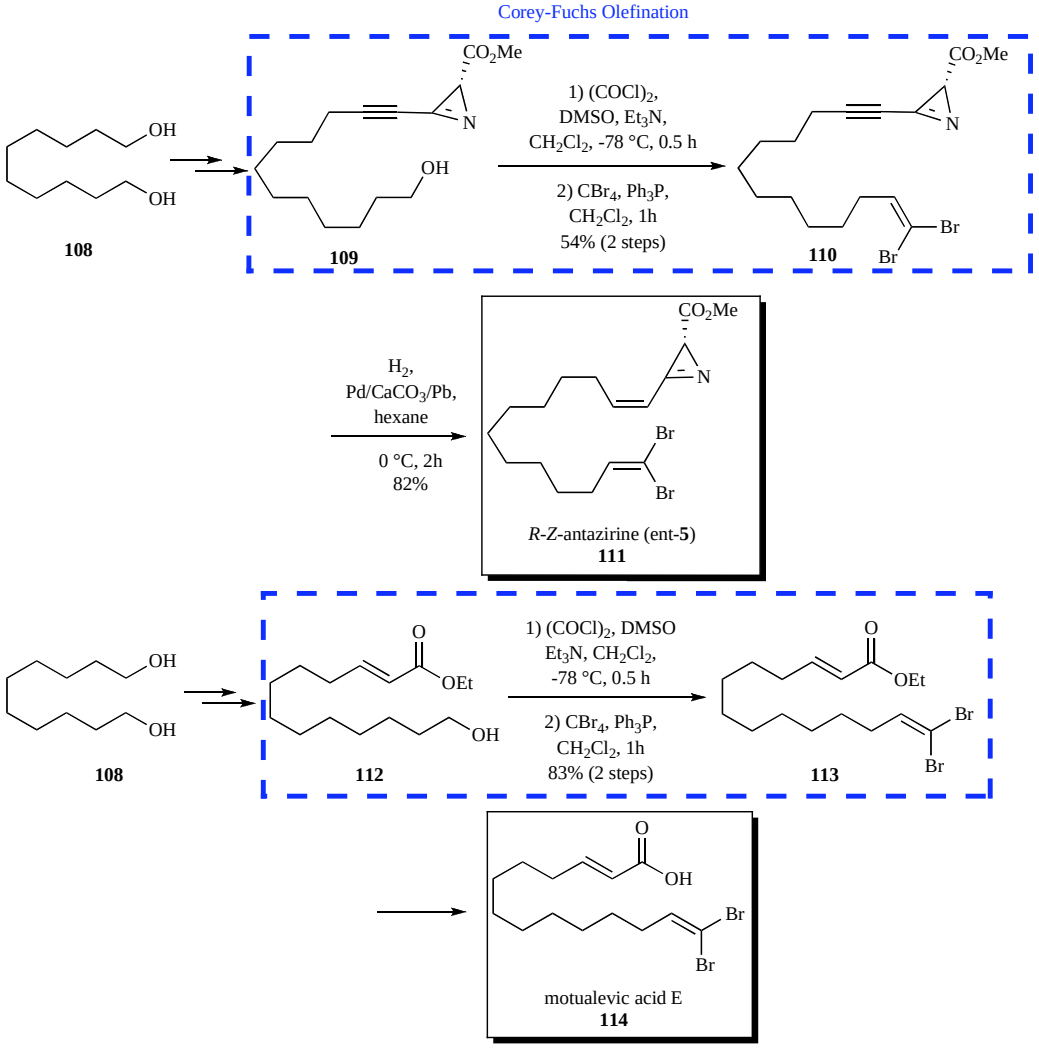
94 with an excess of LDA. Compound HX0 **98** was prepared using $CBr_4/PPh_3/Zn$ under the conditions introduced by Corey-Fuchs. Under this reaction conditions, dibromoolefine **96** in 99% yield was produced (Scheme **24**) [101].

3. COREY-FUCHS REACTION IN TOTAL SYNTHESIS

Corey-Fuchs olefination as a powerful tool, has been used as a key step in total synthesis of several, naturally occurring com-



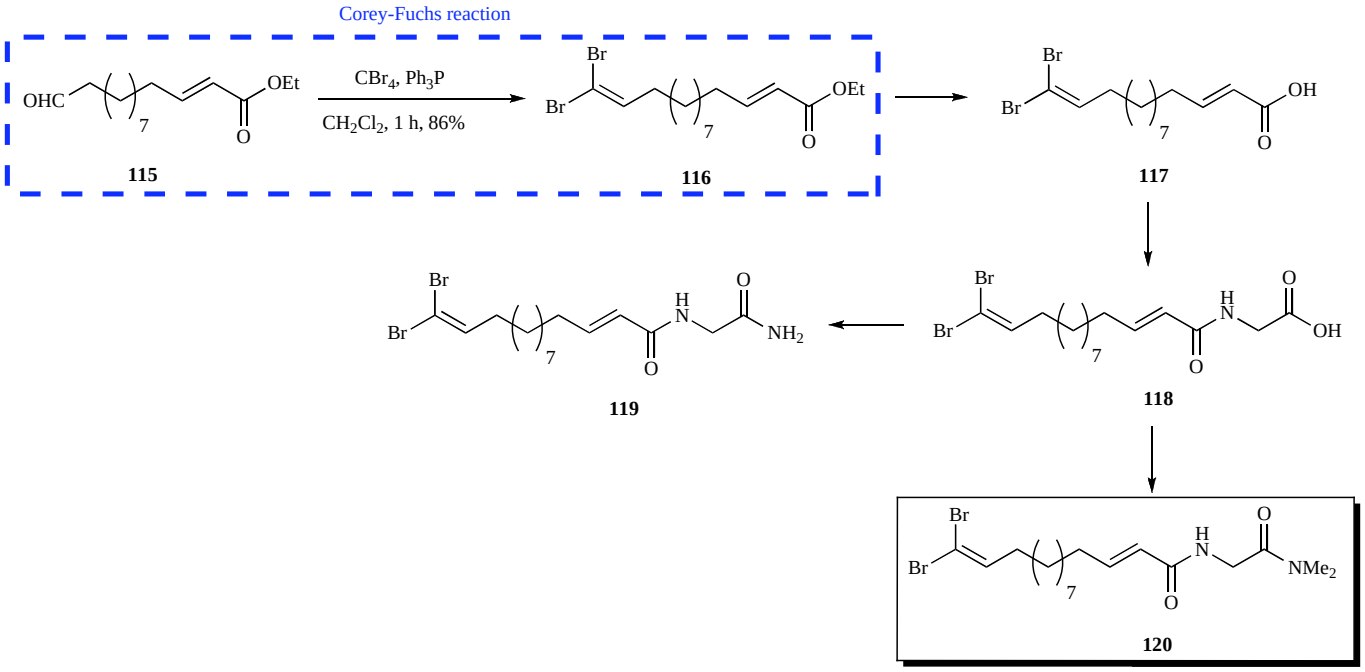
Scheme 26.



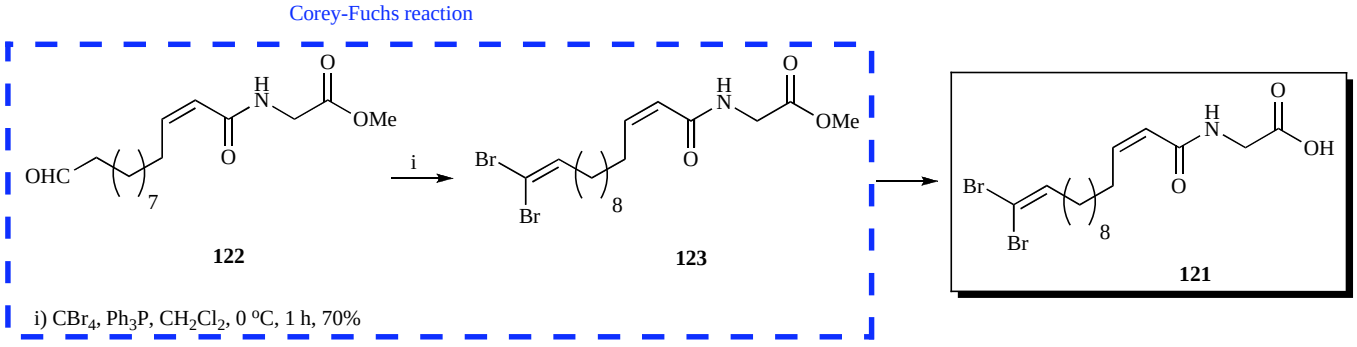
Scheme 27.

pounds. Lievre and his co-workers reported the efficient and quick synthesis of carbohydrate-derived 2,7- and 2,8-dienes [102]. This reaction started by the quick conversion of *D*-glucose **99** to the corresponding **100**, bearing carbon-carbon double bond, *via* Wittig reaction. The latter was transformed **101** in several steps. The compound **101** can be converted to the desired natural product, **102** under Corey-Fuchs reaction conditions. It's worthy to mention that in **101** the hydroxyl groups were protected as -OTMS. (Scheme **25**) [103].

The synthesis of naturally occurring compound, jaspine B (pachastrissamine) **107**, has been accomplished *via* the Corey-Fuchs reaction as an important step. Jaspine B **107** was first isolated from the Okinawa marine sponge *Pachastrissa sp*. by Higa and his co-workers in 2002 [104]. In this route, compound **104** as a suitable precursor for Corey-Fuchs reaction was provided *via* a multi-step reaction, starting from *L*-serine **103**. The obtained, aldehyde **104**, then underwent Corey-Fuchs reaction to afford the respect **105**. Treatment of **105** with 2 equiv. of *n*-BuLi at -78 °C generated al-



Scheme 28.



Scheme 29.

kyne **106** which was converted to the desired natural product **107** in several steps (Scheme **26**) [105].

Terminal halogenated antazirine analogs were initially isolated from *D. fragilis* sponge and *D. fragilis*. It has been found that they show modest cytotoxicity toward HCT-116 cells [106-107]. Correspondingly, motualevic acids such as **114** as ω-dibrominated unsaturated fatty acids were isolated and extracted from *Siliquariaspongia* sp [108].

In 2015, Sudhakar *et al.* described the total synthesis of geometrical isomer of (*E*) and (*Z*)-antazirine **111** and motualevic acids **114** as key intermediates for the total synthesis of several naturally occurring compounds. These compounds could be prepared *via* using several reactions involving Wittig olefination, Corey-Fuchs reaction, Neber reaction, amide coupling.

1,10-Decanediol **108** was employed as a readily available starting material. Initially, Corey-Fuchs reaction resulted in the transformation of **109** to **110** and ultimately the desired target **111** was synthesized. In another Corey-Fuchs strategy, **113** was created from **112** and motualevic acids **114** was provided (Scheme **27**) [109].

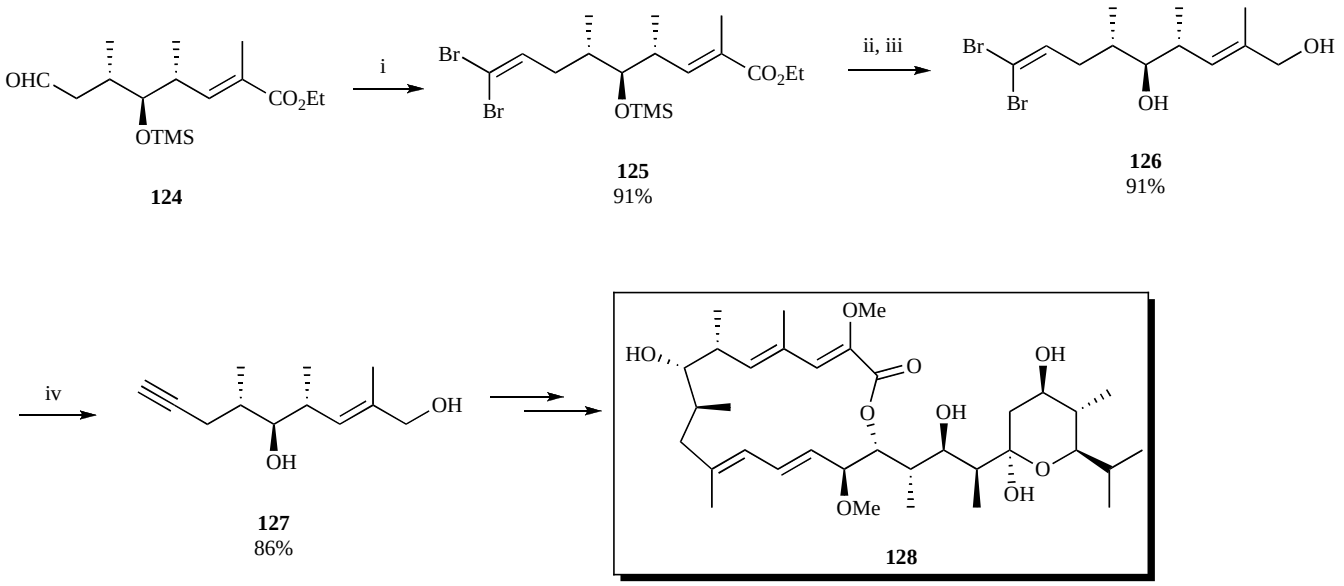
The main step in the first total synthesis of motualevic acids A-E **117-121**, is a new class of brominated long chain acids relied on Corey-Fuchs reaction.

Under the Corey-Fuchs reaction conditions, aldehyde **115** gave *gem*-dibromoalkene **116** in 86% yield which can be directly converted to motualevic acid E **117**. The latter is a key intermediate in the synthetic pathway of motualevic acids A **118**, C **119** and D **120** (Scheme **28**). In another synthetic strategy, aldehyde **122** yielded terminal dibromide **123** by Corey-Fuchs reaction [110] in 70% yield to be converted into the motualevic acid B **121**, which is the *Z* isomer of motualevic acid A **118** (Scheme **29**) [111].

The enantiopure C_1-C_{11} fragment of bafilomycin A_1 **128** which related to macrolides (16-membered lactones) was synthesized with a 4% overall yield and high stereoselectivity by Lett and coworkers [112].

For the first time, Corey and Ponde assigned the absolute configuration and stereochemistry of bafilomycin and some related macrolides based on the ^{1}HNMR coupled with the computer modeling [113] and also X-ray crystallography [114].

Formation of alkyne **127** from **124** was achieved through the methodology of Corey and Fuchs [115]. The optimal reaction conditions for obtaining the intermediate dibromoolefine **125** from **124** without deprotection of the silylether and further change the corresponding alcohol into the bromide were determined in the mixture of Ph_3P, CBr_4 and NEt_3 [116-118]. After reduction of **125** with



124

125
91%

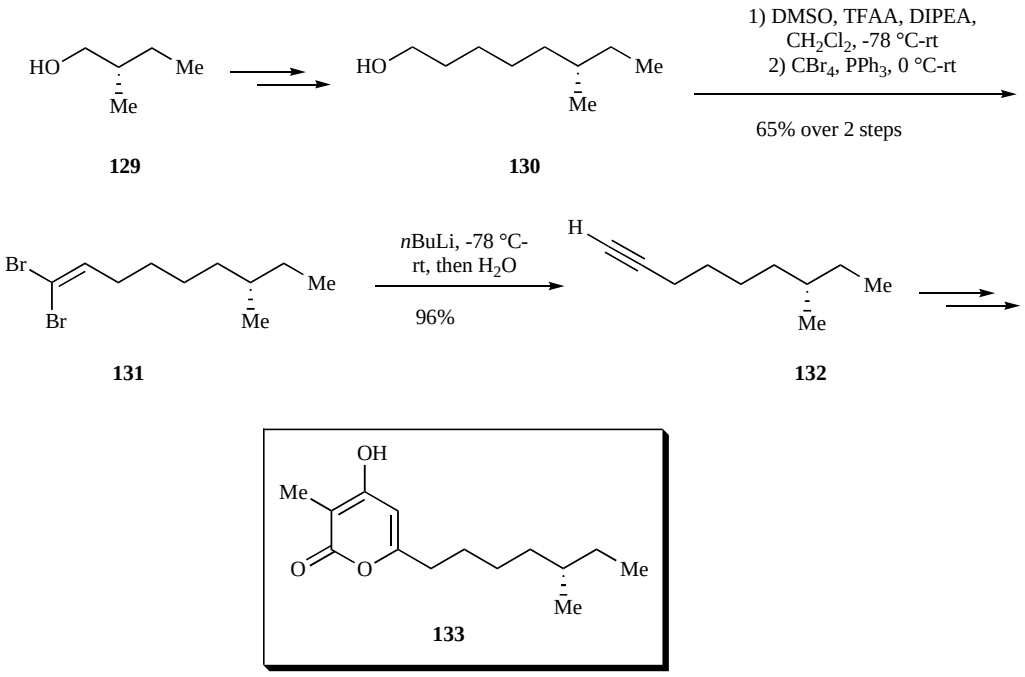
126
91%

127
86%

128

(i) PPh_3 (4 equiv), CBr_4 (2 equiv), CH_2Cl_2, then NEt_3 (8 equiv), rt, 15 min, then -78 °C, 10 and -78 °C to rt, 7 h;
(ii) DIBAH (3 equiv), toluene, -78 °C, 3 h;
(iii) TBAF 1 M (1.1 equiv), THF, rt, 2 h;
(iv) 12, THF, -78 °C, then *n*-BuLi 1.6 M in hexanes (5 equiv), 1 h and -78 °C to rt, 2 h.

Scheme 30.



129

130

131

132

133

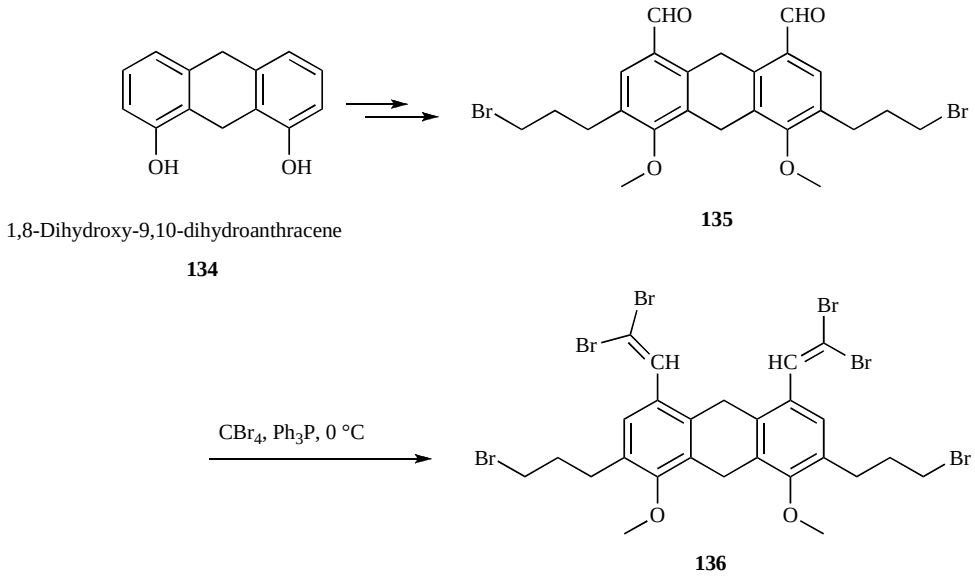
Scheme 31.

DIBAH, the hydroxyl group of product was deprotected as TMS ether group in order to avoid partial deprotection and intermolecular *trans*-silylation in the next step. Then, dibromoolefin **126** generated compound **127**, derived from **125** in 71% overall yield (four steps) (Scheme **30**) [112].

The first total synthesis of (+)-violapyrone C **133**, isolated from *Streptomyces sp.*, has been reported by Lee and his research group in 2014. The total synthesis, started from (*S*)-(-)-2-methylbutanol **129** which was converted to the aldehyde **130** in several steps. The latter was then sujected to the Corey-Fuchs reagents in CH_2Cl_2 to give **131** followed by lithium-bromine exchange with *n*-butyllithium and then elimination to give corresponding terminal alkyne **132** which is a key intermediate in this total synthesis (Scheme **31**) [119].

Traditional organic chromophores are present in a series of organic molecules that include electron-accepting and electron-donating groups joined by a conjugated π system called D-π-A structure.

In a series of H-shaped chromophores, which have two parallel and non-conjugated D-π-A units, 9,10-dihydroanthracene **134** was



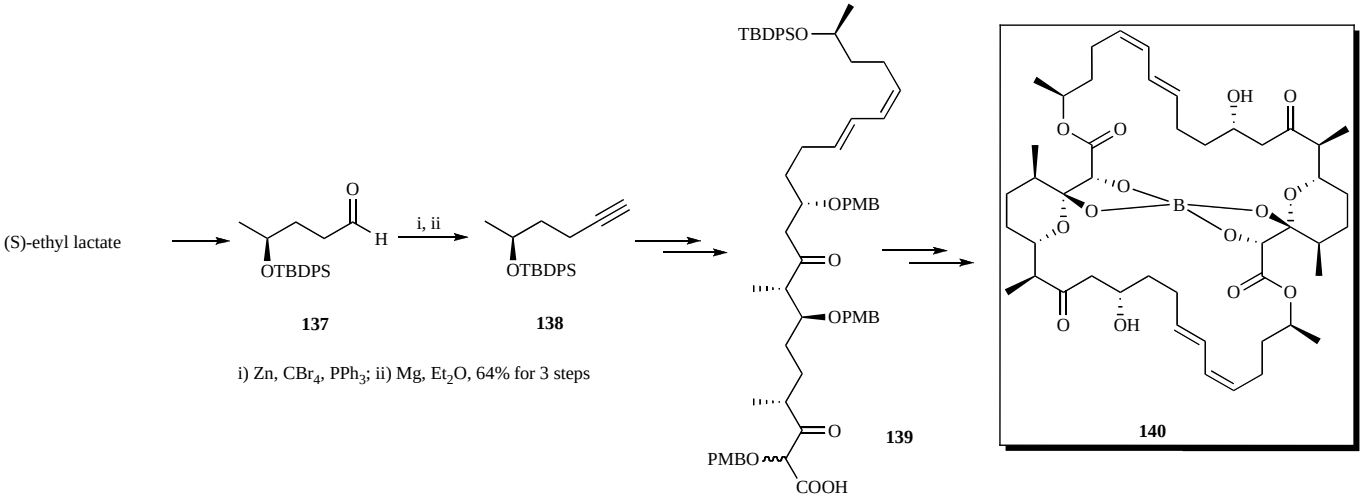
1,8-Dihydroxy-9,10-dihydroanthracene

134

135

136

Scheme 32.



137 **138**

i) Zn, CBr_4, PPh_3; ii) Mg, Et_2O, 64% for 3 steps

139 **140**

Scheme 33.

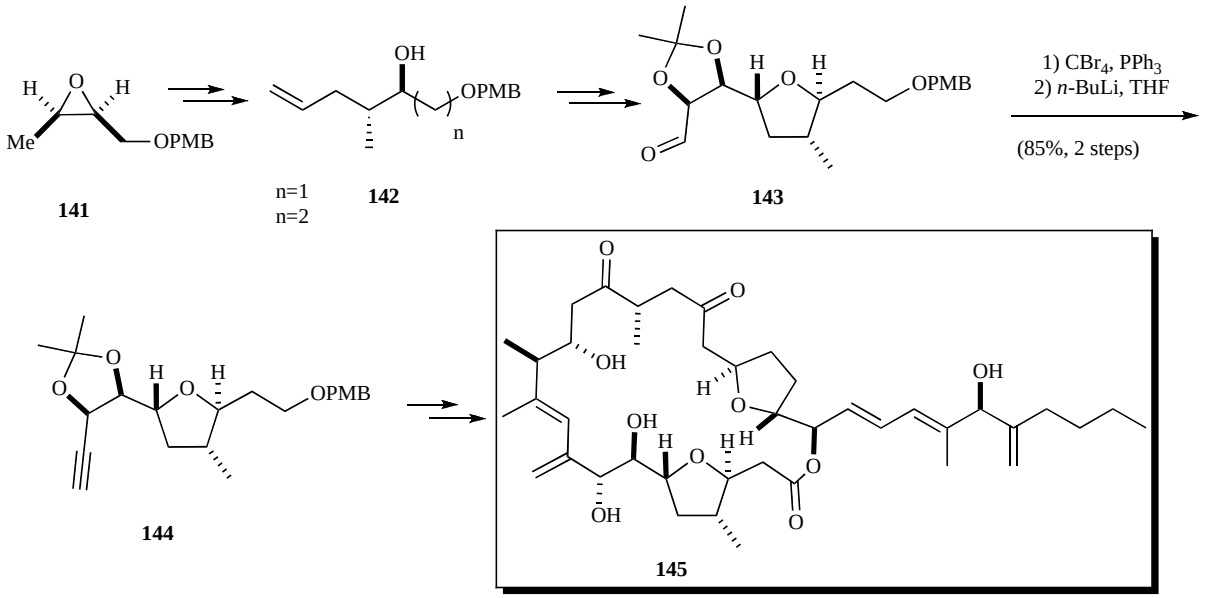
applied as molecular backbone. Lu and his co-workers synthesized compound **136** of these H-shaped chromophores *via* Corey-Fuchs reaction in a total yield of about 12.5 % [120]. The Corey-Fuchs reaction of dialdehyde **135** with triphenylphosphine and carbon tetrabromide carried out under nitrogen atmosphere at 0 °C to yield geminated dibromo alkene chromophore **136** (Scheme **32**) [121-123].

Mulzer and his co-workers suggested an efficient synthesis of the protected seco acid **139** of the antibiotic macrodiolide tartrolon **140** as an inhibitor of Gram-positive bacteria with a broad antibiotic spectrum [124], based on the Corey-Bakshi-Shibata (CBS) reduction. In this synthesis pathway, (*S*)-ethyl lactate was utilized as an appropriate precursor and alkyne **138** can be produced from aldehyde **137** *via* a Corey-Fuchs sequence in 64% yield (Scheme **33**) [125].

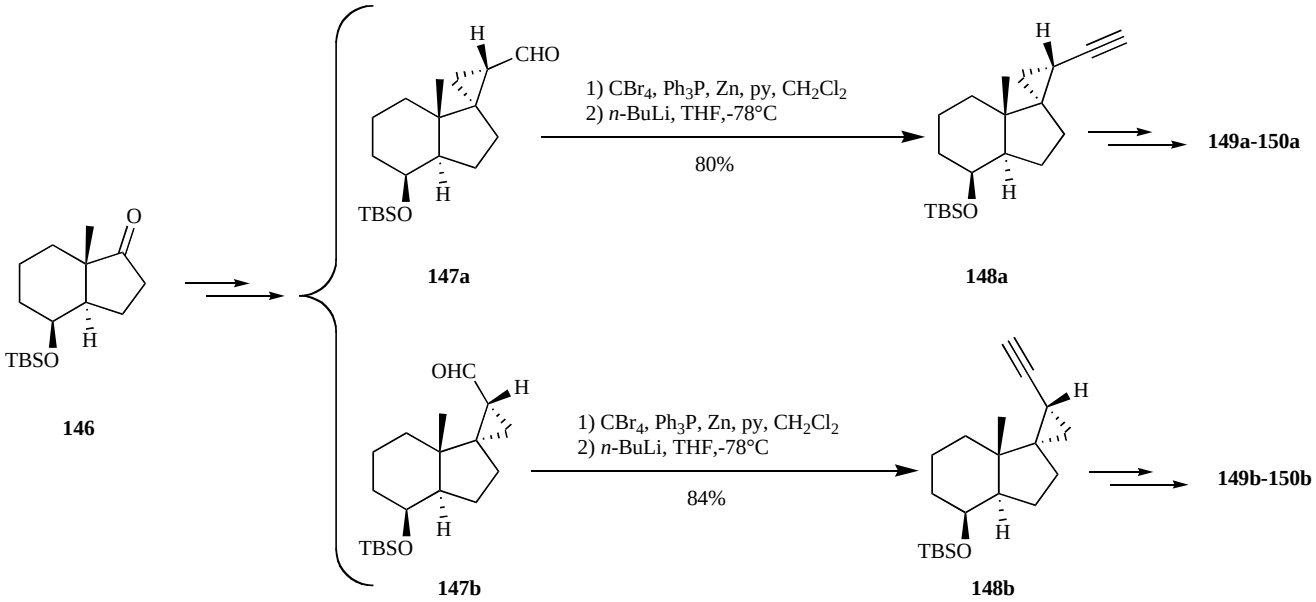
Amphidinolide C **145** with potent bioactivities is one of the most complex members of amphidinolides, which is present in various families of biologically active macrolides and linear polyketides. Notably, they are initially isolated by extraction and fractional separation from the symbiotic marine dinoflagellate *Amphidinium* sp. [126-127]. Initially, the ring opening of epoxide **141**, provided by Sharpless asymmetric epoxidation [128], protected by PMB ether afforded **142** after several steps. The key step in the synthesis of the latter is the Corey-Fuchs reaction of **143** to produce alkyne **144** in 85% yield (Scheme **34**) [129].

The alkynyl side chain in vitamin D analogues was prepared *via* Corey-Fuchs homologation, followed by alkylation. Enzymatic C_1-hydroxylation of 25-hydroxyvitamin D_3 [25-OH-D_3], which is the main circulating form of vitamin D produced hormonally active form of vitamin D_3, calcitriol [1α,25-dihydroxyvitamin D_3, 1α,25-$(OH)_2$-D_3] [130]. Calcitriol also has a wide spectrum of biological functions which regulate the calcium and phosphorus metabolism in the inhibition of the proliferation of various types of malignant cells, and in the immune response [131].

Vitamin D analogues **149a**, **150a** (C_{20} stereochemistry similar to 20*R*-natural configuration) and their 20-epimers **149b**, **150b** (C_{20} stereochemistry similar to 20*S*-epiconfiguration) were synthesized in 20-32% and 25% overall yield from **146**, respectively (Fig. **4**). In this synthesis pathway, the installation of both the alkynyl and the (*Z*)-alkenyl side chains was achieved *via* Corey-Fuchs homologation



Scheme 34. Completion of the C(1)-C(9) fragment of amphidinolide C **145**.



Scheme 35.

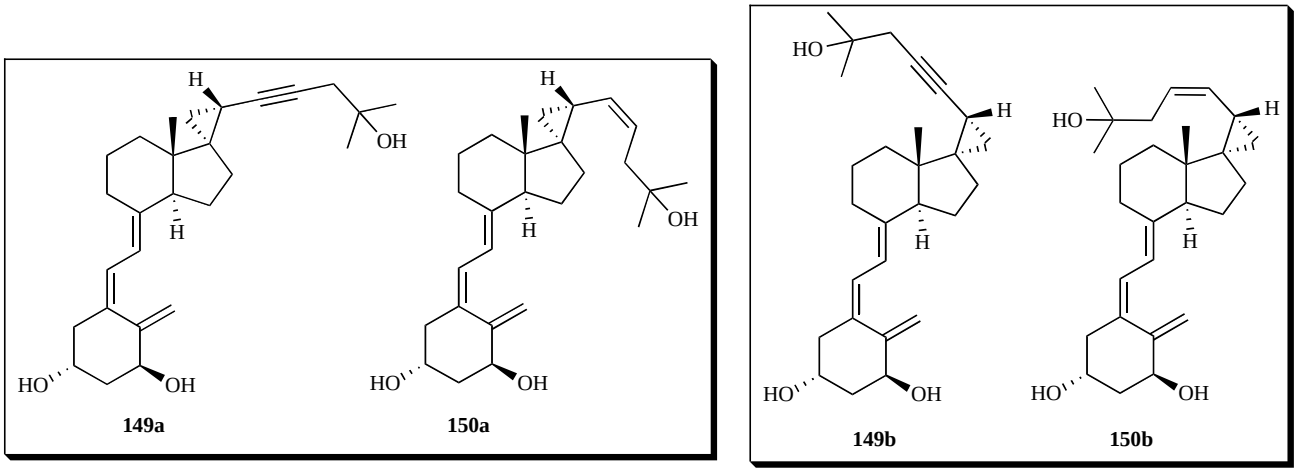
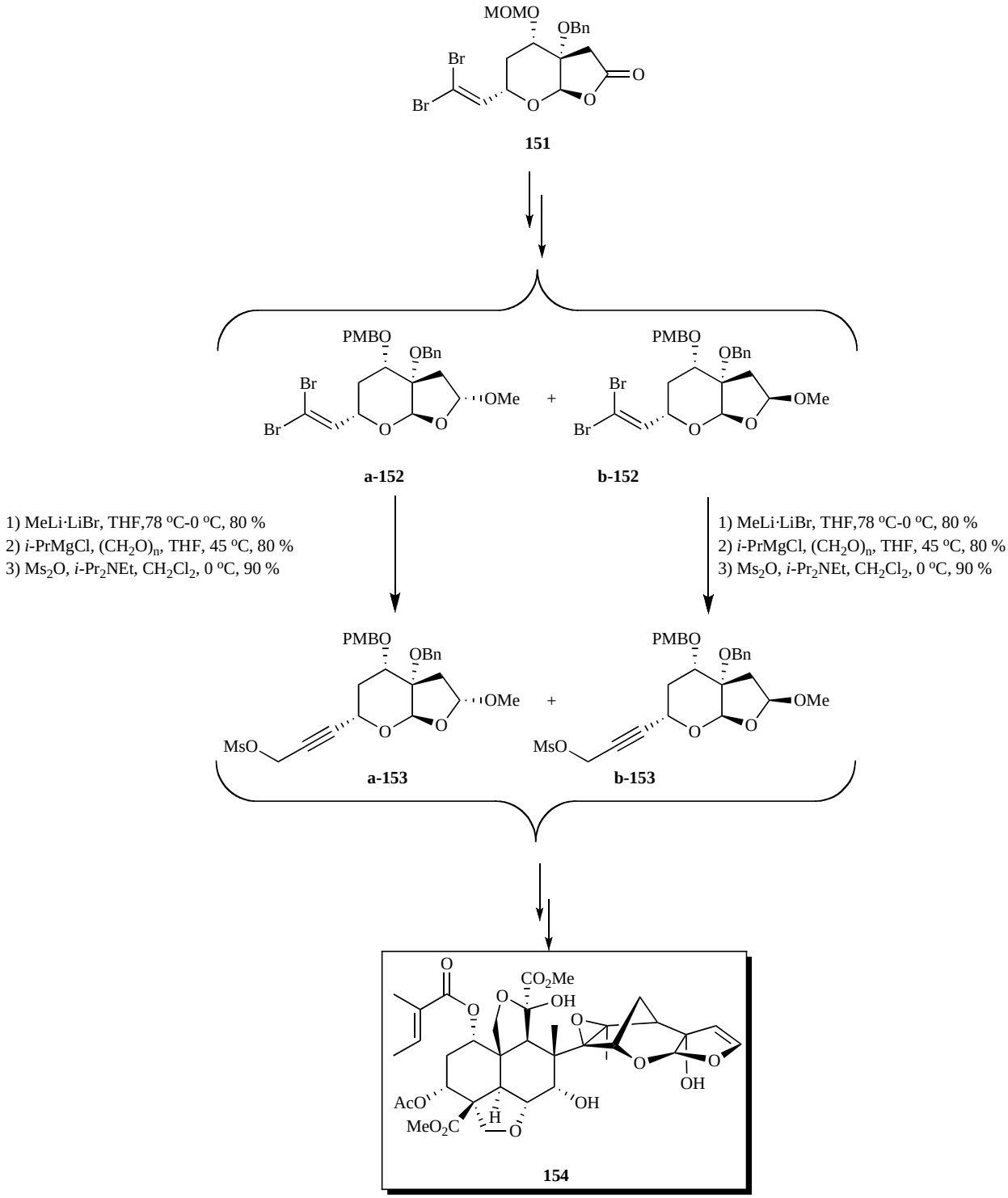


Fig. (4).



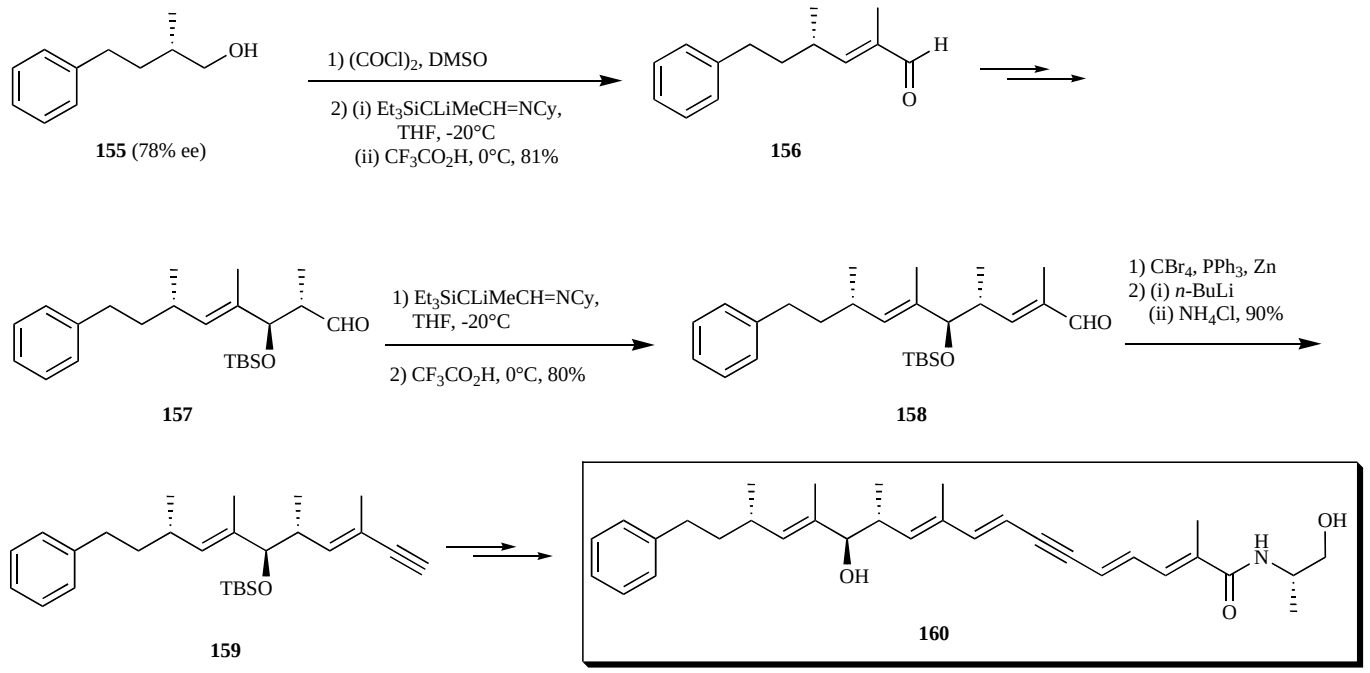
Scheme 36.

of **147a** and **147b** to afford the alkyne **148a** and **148b** respectively (Scheme **35**) [132].

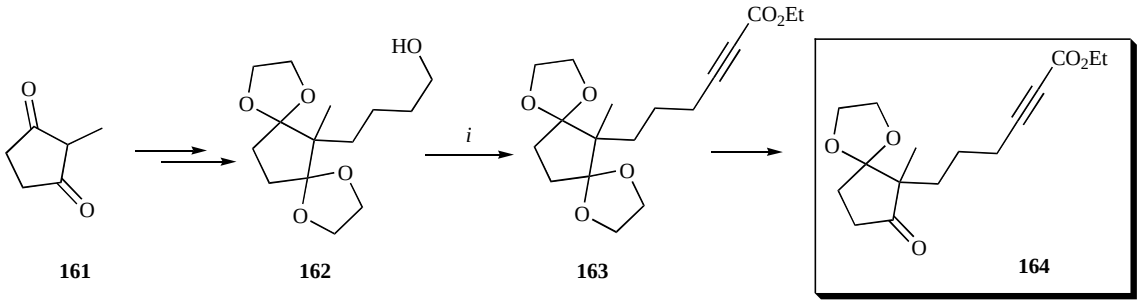
A long, but successful route for the synthesis of complex is the natural product azadirachtin **154** [133-137], isolated from the Indian neem tree *Azadirachta indica* in 1968, was reported by Ley *et al* [138].

Under the presented conditions in Scheme **36**, the two epimers of **152,** which originated from compound **151**, provided the desired propargylic mesylates α**-153** and β**-153** *via* Corey-Fuchs alkynylation following by homologation with *para*-formaldehyde and treatment of resulting propargylic alcohols with methanesulfonic anhydride [139].

The efficient and selective synthesis of 6,7-dehydrostipiamide **160** as a non-natural multi drug resistance reversal agent of high potency and low toxicity was achievable *via* Corey-Peterson olefination and Corey-Fuchs reaction over 15 steps in 23% overall yield [140-141].



Scheme 37.



i: (a) SO_3, Py, Et_3N, DMSO, CH_2Cl_2, 0 °C to 20 °C, 1 h (81%);
(b) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0 °C to 20 °C, 2 h (70%);
(c) *n*-BuLi, $ClCO_2Et$, THF, -78 °C to 20 °C, 4 h (78%)

Scheme 38.

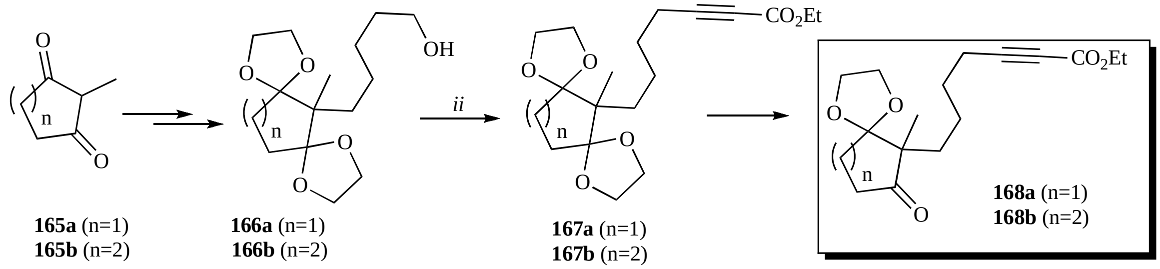
Aldehyde **156** of >99% *E* in 81% yield was produced after Swern oxidation of **155** and the Corey-Peterson olefination of the crudely formed aldehyde in the presence of *N*-cyclohexyl(2-triethylsilylpropylidene)imine and *s*-BuLi at -78 °C, followed by treatment with CF_3COOH. Negishi *et al*. initially transformed **155** into **156** in a three steps sequential reaction, involving the Swern oxidation of **155**, Corey-Fuchs reaction/ conversion of the obtained 1,1-dibromo-1-alkene into the corresponding methylalkyne and hydrozirconation and carbonylation with *n*-BuNC. However, the conditions shown in Scheme **37** found to be more efficient for this conversion. After several steps the **156** was transformed into the intermediate **157** which under another effective Corey-Peterson olefination gave compound **158** in 80% yield (>99% *E*). The Corey-Fuchs reaction of **158** followed by acidification afforded intermediate **159** in 92% yield [142]. After several steps, the latter was converted to the desired target **160**.

The Corey-Fuchs reaction is a key step in the introduction of the alkynyl moiety in the synthesis of racemic and enantiomerically pure acetylenic ω-keto esters **164**. In the first stage, Corey-Fuchs reaction of the hydroxy derivative **162**, which derived from 2-methyl-1,3-cyclopentanedione **161**. The oxidation of the hydroxy group in **162,** afforded *bis*-dioxolane **163** as an intermediated for the total synthesis of desired acetylenic ω-keto ester **164** in 13% overall yield from **161** (Scheme **38**).

To increase the length of the tether, the same reaction condition as mentioned before was used to produce the di-protected diones **167a,b**. Monodeprotection of the latter gave the acetylenic ω-keto esters **168a,b** in 43% overall yield from **165a,b** and 39% overall yield from **166a,b** (Scheme **39**) [143].

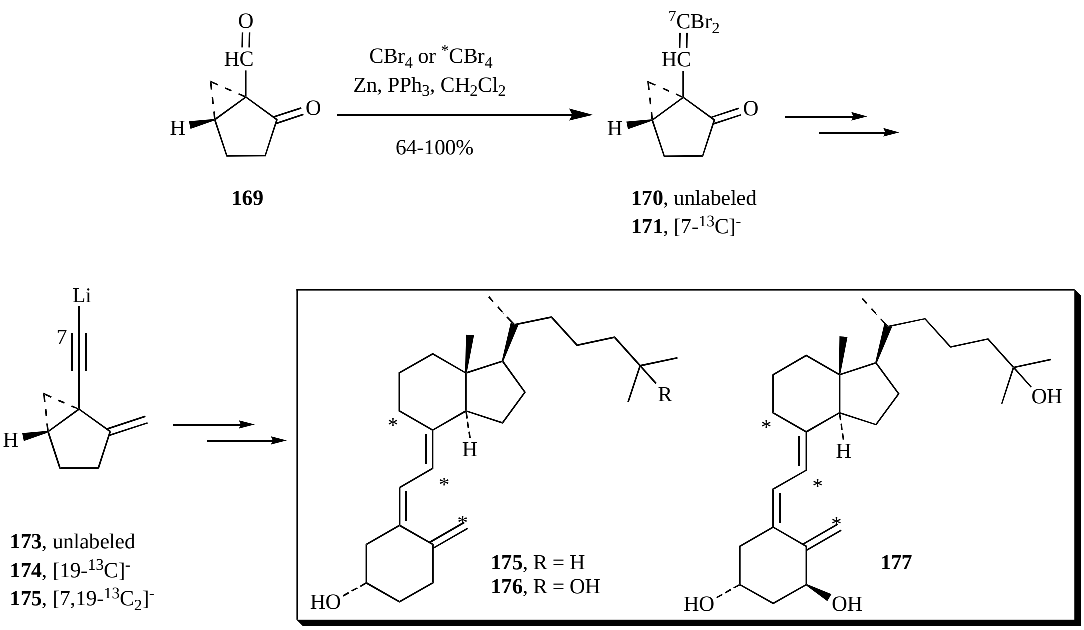
In recent years, the vitamin D metabolic system shows a broad range of biological activities in the treatment of the human diseases as skin diseases, cancer, and diseases related to calcium metabolism and aberrant immunological responses [144-145]. Isotope-labeled drug molecules are useful for searching by NMR spectroscopy the formation of ligand with biological hosts as proteins and membranes.

Triple-labeled [7,9,19-$^{13}C_3$]-vitamin D_3 **175** and its 25-hydroxylated **176** and 1α,25-dihydroxylated **177** synthesized employing Corey-Fuchs reaction following a normal Wittig process on keto aldehyde **169** to achieve the C-7,19 double labeling of the A-



ii: (a) SO_3, Py, Et_3N, DMSO, CH_2Cl_2, 0 °C to 20 °C, 1 h (n = 1: 91%; n = 2: 70%);
(b) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0° C to 20 °C, 12 h (n = 1: 77%; n = 2: 95%);
(c) *n*-BuLi, $ClCO_2Et$, THF, -78 °C to 20 °C, 20 h (n = 1: 86%; n = 2: 89%)

Scheme 39.



Scheme 40.

ring enyne **174** which is an intermediate in this route. The latter was transformed into desired target **175** in several other steps including functional group transformations (Scheme **40**) [145].

Piper species are wide spread plant groups. They were being used as traditional medicine which have been used in China and India [146]. These materials initially were isolated from different sources *i.e.*, the roots of *Piper chaba* and exhibited hepatoprotective activity [147]. Piperamides (alkenamides) frameworks contain conjugated linear chain attached in the sides with as well as different amides and aromatic moiety.

Suresh Babu and his co-workers described the synthesis of guineensine **185**. The latter was found being secondary metabolite of the Piperaceae family. The strategy started with **178**, which upon deprotection and oxidation is converted to **180** *via* **179**. Subsequent Corey-Fuchs homologation of aldehyde **180** followed by dibromomethylenation with CBr_4 and PPh_3 furnished the dibromo olefin **181** in essentially quantitative yield. In continuation of the strategy, followed by esterification the latter was transformed to **182**. The latter was converted *via* a two-step synthesis, to the desired target **185**. (Scheme **41**) [148].

PMB ether of 5,6-epoxyisoprostane E2 **191** was prepared in 11.6% overall yield by bromohydrination, aldol and Corey−Fuchs reactions *via* several steps. The Corey−Fuchs reaction of **188** followed by debromination with *n*-BuLi gave the Li anion **190**, which was quenched to produce **189** (Scheme **42**) [149].

CONCLUSION

In the progress of the modern organic synthesis, especially in the field of total synthesis of natural product, the Corey-Fuchs reaction plays a key role in one or more steps, to provide the appropriate alkyne useful for many divers conversion, usually as the precursor. The aim of this review is to exhibit the advantages and merits of the Corey-Fuchs reaction presenting it as an invaluable strategy to the organic synthetic chemists to be considered in their design toward the total synthesis of natural products.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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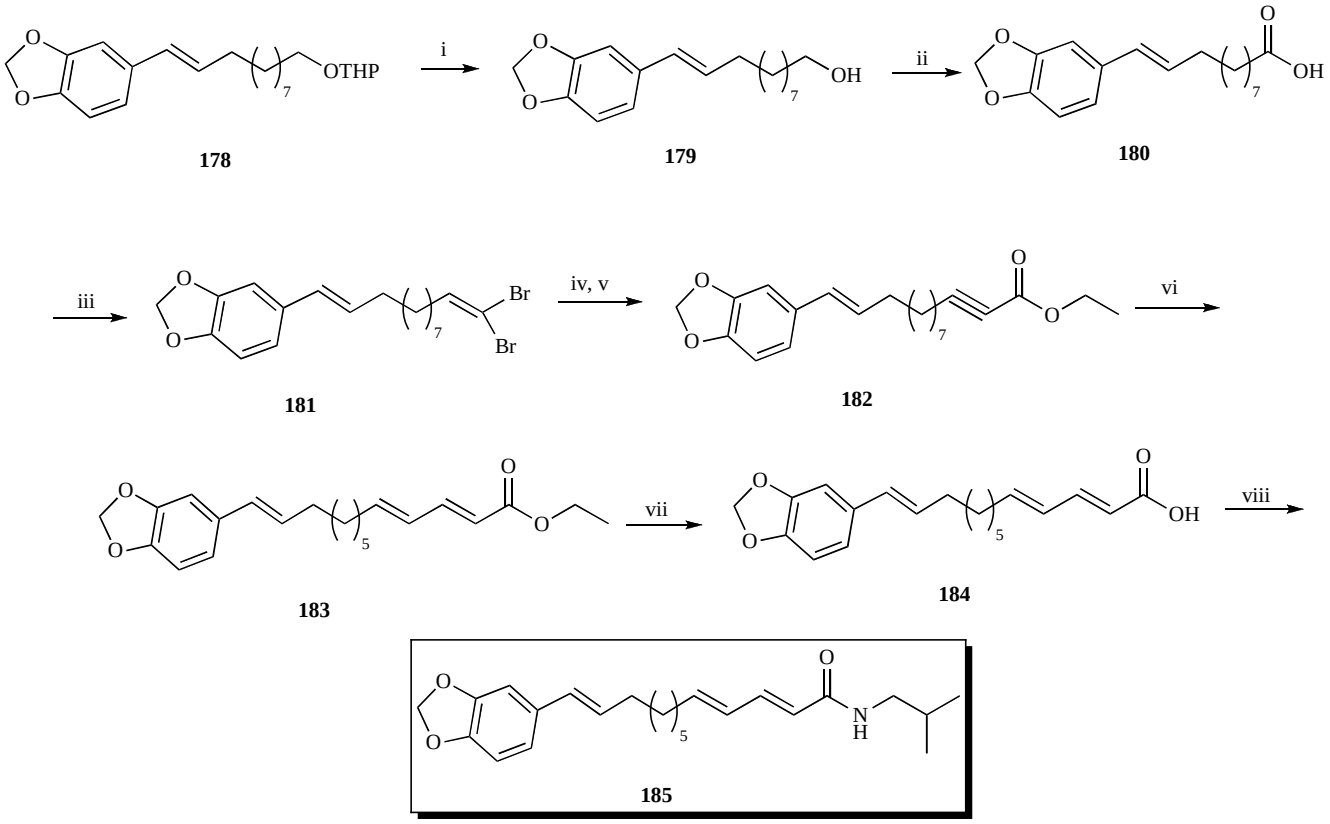
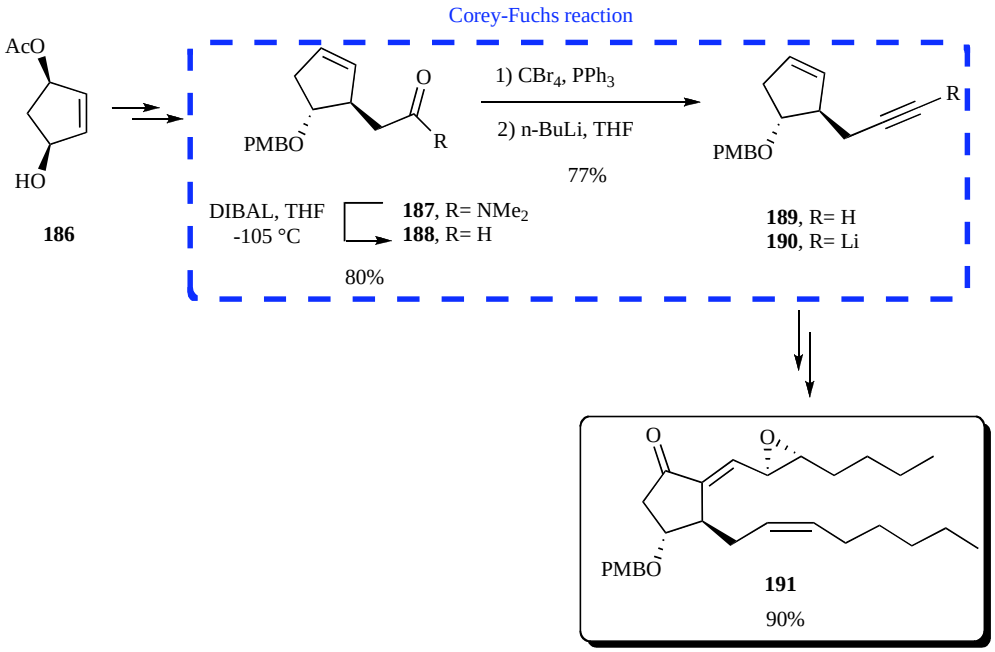


(i) PTSA, MeOH, 0°C, 45 min, 95%;
(ii) IBX, DMSO, THF, rt, 98%;
(iii) CBr_4, TPP, dry DCM, 0°C, 2 h, 95%;
(iv) *n*-BuLi, dry THF, -78°C;
(v) chloroethyl formate, dry THF, -78°C, 2 h, 90%;
(vi) TPP, phenol, benzene, reflux, 95%;
(vii) LiOH, THF/H_2O, rt, 12 h, 96%;
(viii) EDC, HOBt, isobutyl amine, DCM, 0°C to rt, 8 h, 90%.

Scheme 41.



Scheme 42.

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