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Diversity-oriented synthesis of medicinally important 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivatives and higher analogs

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1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) is a constrained analog of phenylalanine (Phe). Tic unit has been identified as a core structural element present in several peptide-based drugs and forms an integral part of various biologically active compounds. This report covers the biological significance of Tic core and provides a detailed account of various synthetic approaches available for the construction of Tic derivatives. Along with the traditional methods such as Pictet–Spengler and Bischler–Nepieralski reactions, we cover various recent approaches such as enyne metathesis, [2+2+2] cycloaddition and Diels–Alder reaction to generate Tic derivatives. In addition, syntheses of higher analogs of Tic have also been discussed.

1. Introduction and Biological Significance of Tic

To design peptide-based drugs, synthesis of various unnatural peptides as therapeutics has received much attention.[1] Metabolic instability and poor bioavailability are the major hurdles in using peptides in medicinal chemistry.[2] Further, structural flexibility of linear peptides limits their selectivity for one or other type of receptors. Selective incorporation of conformationally constrained amino acid units in a peptide chain has been identified as a useful tactic to generate metabolically stable peptides with enhanced receptor selectivity.[3] Phenylalanine (Phe) is an amino acid which constitutes an integral part of various peptides and the conformationally restricted analog of Phe such as 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) has received a great deal of attention from synthetic and medicinal chemists (Fig. 1). This section deals with the biological activity of medicinally important compounds by incorporation of Tic moiety.

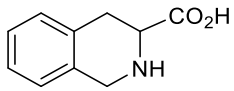

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Fig. 1 Structure of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic)

Tic serves as a surrogate for Phe in bioactive peptide ligands, thereby rendering conformational rigidity to a peptide backbone *via* pipecolinic acid bridge. Also, it serves to restrict the orientation of aromatic component to enhance the structural rigidity. Bicyclic Tic moiety features a restricted dihedral angle χ and Tic derivatives with a wide range of steric, electronic and hydrophobic characteristics have been constructed.[4]

A variety of medicinally important molecules embedded with Tic unit are displayed in Fig. 2. The utility of Tic as a structural variant of Phe in medicinal chemistry is clearly demonstrated by several reports. For example, substitution of proline residue in enalapril **2a** with Tic moiety resulted into a new and improved angiotensin converting enzyme inhibitor (ACEi), quinapril **2b** (commercialized under brand name 'accupril' by Pfizer) currently used for the treatment of hypertension and congestive heart failure.[5]

The κ–opioid receptors are associated with various physiological situations such as stress, depression, anxiety and schizophrenia.[6] Carroll and co-workers[7] have reported (JDTic) **3a** as a potent and selective κ–receptor antagonist. Preparation of various analogs of JDTic and their evaluation using a [^{35}S] GTPγS binding assay lead to the identification of most effective and selective κ–receptor antagonist **3b**.

To develop a new cholesterol acyltransferase (ACAT) inhibitor with anti-lipid peroxidative activity, Shirhase and coworkers have synthesized various tetrahydroisoquinoline derivatives.[8] Biological studies revealed that Tic derivative **4a** is a useful candidate as a phenolic anti-oxidative ACAT inhibitor. Compound **4a** is anticipated to provide a potential drug for atherosclerosis. Studies indicated that compound **4a** is suitable for oral administration as it can be absorbed efficiently at 10 mg/kg in rats and dogs and displayed strong hepatic ACAT inhibitor and displayed potential anti-foam cell formation activity.

Researchers have experimentally established the inhibition mechanism of protein tyrosine phosphatase (PTP1B). It helps toward the prolonged activation of insulin receptor via insulin signaling.[9] This aspect fueled the synthetic activity of small molecular entities suitable for inhibition of PTP1B for the treatment of type-2 diabetes.[10] Klopfenstein and coworkers[11] have demonstrated the synthesis and biological studies of PTP1B inhibitors containing sulfamic acid pTy mimetic containing the 1,2,3,4-tetrahydroisoquinoline moiety. To this end, compound **4b**

displayed a potential PTP1B inhibition and was screened for a series of 14 PTPases which revealed high selectivity in several therapeutically useful phosphatases.

Affinity labels have been served to facilitate the study of binding sites in the δ-opioid receptors.[12] Aldrich and coworkers[13] have reported a Tic based peptide **5** as an affinity label for δ-opioid receptor-selective peptide antagonist H-Tyr-Tic-Phe-Phe-OH (TIPP), potentially useful for comprehensive mapping. Incorporation of the isothiocyanate group resulted in wash-resistant inhibition of radioligand binding to δ-selective peptide antagonists. Affinity labels have a potential to serve as pharmacologically important moieties in the study of δ-opioid receptors.

The NS3 protease of hepatitis C virus (HCV) represents an excellent target for HCV therapy. The inhibition studies on HCV protease continuous assay using Tic-based macrocyclic HCV NS3 protease inhibitors **6** revealed that these macrocyclic inhibitors are 5-80 times more potent than their acyclic analogs.[14]

Peroxisome proliferator-activated receptors (PPARs) are potential targets for metabolic disease such as diabetes, dyslipidemia and atherosclerosis.[15] Biological screening revealed that Tic based PPRAγ agonist **7** is a promising candidate for anti-diabetic drug as compared to its tyrosine derivative.[16]

It is noteworthy to mention that, antithrombotic activity of Tic was found to be enhanced by introducing a dipeptide linkage at *3S*-position. Such compounds exhibit superior *in vitro* antiplatelet aggregation activity and *in vivo* antithrombotic activity.[17] Thus, the dipeptide **8** showed *in vitro* higher potencies of inhibiting arachidonic acid, platelet-activating factor (PAF), adenosine diphosphate (ADP), thrombin induced platelet aggregation and *in vivo* anti-thrombin assay.[18]

Histone deacetylase has been identified as an attractive target in connection with antitumor agents. Xu and coworkers[19] have reported ZYJ-34c **9** as a potent histone deacetylase inhibitor (HDACi) which showed higher *in vivo* antitumor activities.

Cystic fibrosis (CF) is a lethal genetic disease, due to mutation in the cystic fibrosis trans-membrane conductance regulator (CFTR) protein. Tic based diamide **10** has been identified as a new class of CFTR modulators and more active than its Phe-based analog.[20]

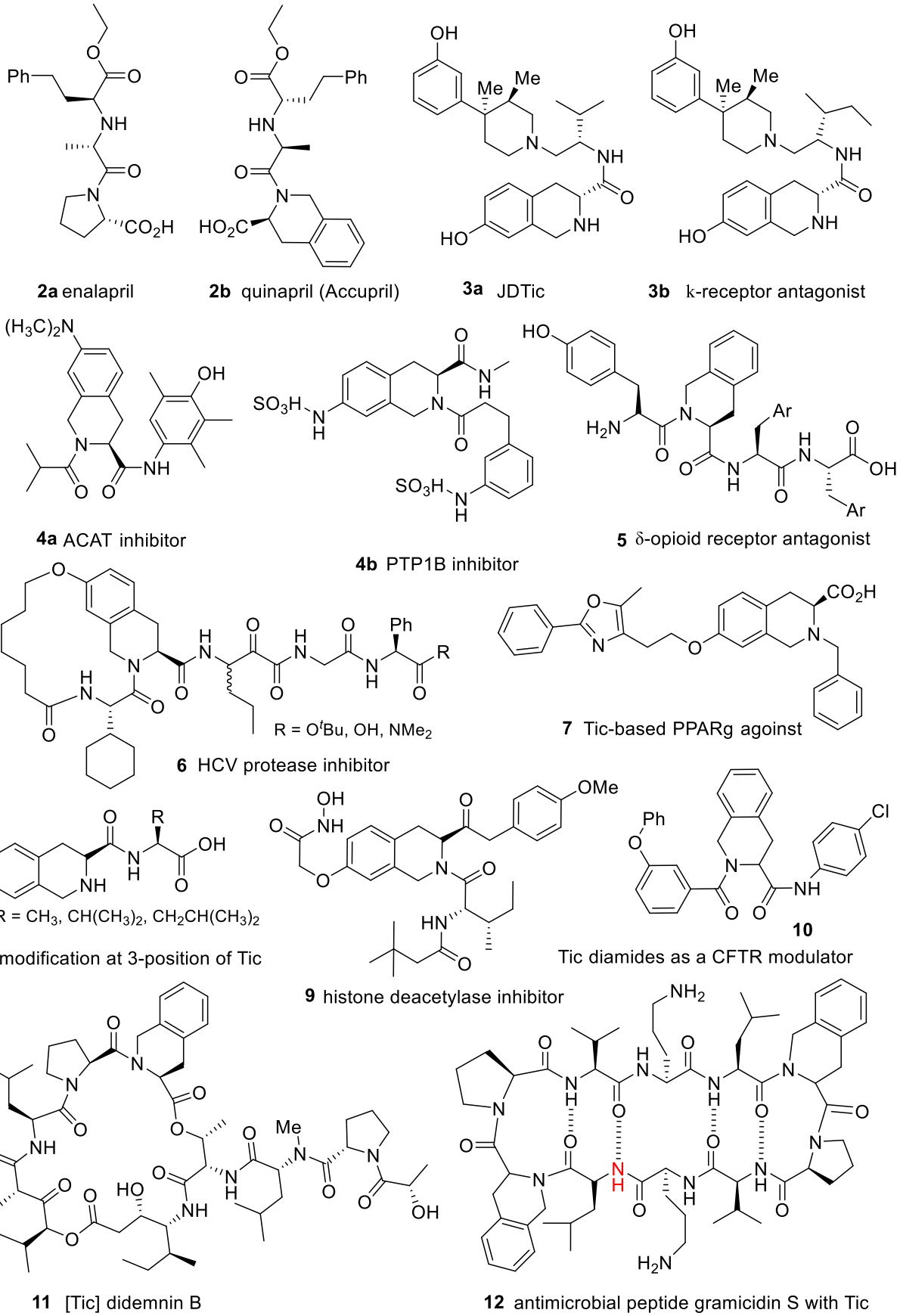


Fig. 2 List of biologically relevant molecules related to Tic

Didemnins, isolated from sea-squirt of the genus *Tridemnum* and found generally in the Caribbean sea are cyclic 23-membered depsipeptide compounds that differ only in side chains attached to nitrogen atom of threonine moiety. These species were first isolated in 1981 by Rinehart.[21] More than nine didemnins (didemnins A-E, G, X and Y)[22] isolated so far in which didemnin B family has been found to exhibit the most potent biological activitiy (e.g. antiviral, antitumor and immunosuppressant activities).[23] Pfizenmayer and co-workers[24] have prepared didemnin B analog **11** with Tic as a replacement of tyrosine to investigate the task of *N*,*O*-diMeTyr moiety. It was found to be potential protein biosynthesis inhibitor. Further, gramicidin-S (GS) is a cyclic decapeptide active against bacteria, fungi and widely studied antimicrobial peptides. Incorporation of Tic in GS (e.g. **12**) showed considerable amplification in therapeutic index.[25]

In view of extended utility of Tic derivatives, various methods have been developed by synthetic chemists for the construction of these heterocycles. This review covers several synthetic methods available for assembling Tic derivatives. Also, synthesis of higher analogs of Tic such as Sic, Hic and Nic is covered in a separate section to indicate the future perspectives in this field.

Based on the bond disconnection approach used for the synthesis of Tic derivatives, synthetic methods are divided into several sections. The following schematic representation describe various bond disconnection approaches used for assembling Tic derivatives (Fig. 3).

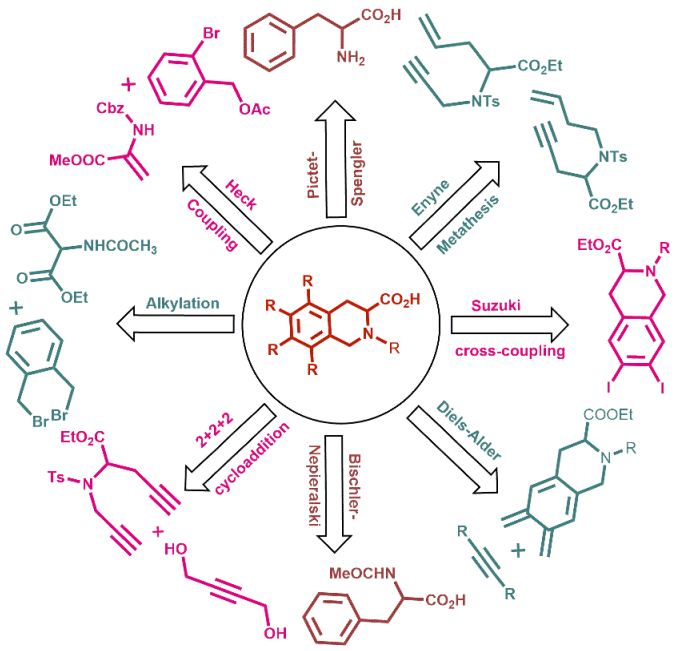
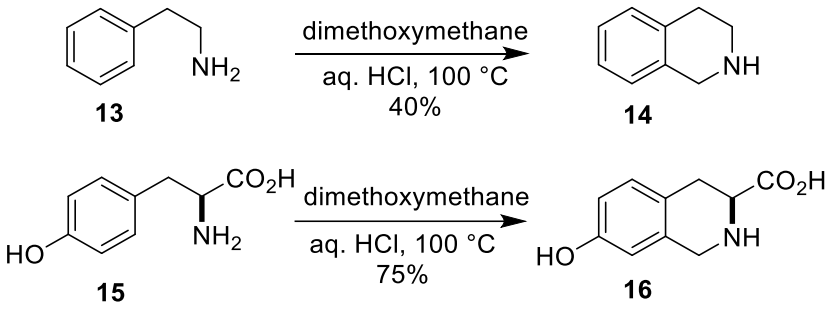


Fig 3. Bond disconnection approaches used for assembling Tic derivatives

2. Synthetic Approaches to Tic Derivatives

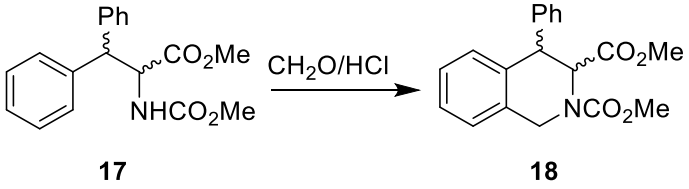
2.1. Pictet–Spengler reaction

The Pictet–Spengler reaction is a classic approach used extensively for the formation of carbon–nitrogen bond towards the synthesis of heterocycles.[26] In 1911, Pictet and Spengler reported a condensation reaction between phenylethylamine **13** with dimethoxymethane in the presence of aq. HCl at 100 °C to afford 1,2,3,4-tetrahydroisoquinoline (THIQ) **14** in 40% yield (Scheme 1).[27] Under identical conditions, tyrosine **15** gave the corresponding cyclized product **16**. The condensation reaction of substituted phenethylamines with various aldehydes was further extended by Decker and Becker.[28]



Scheme 1

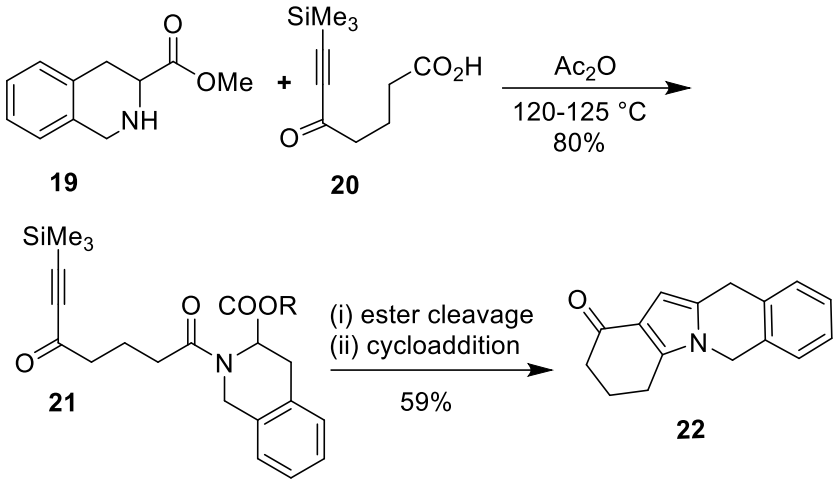
Pictet–Spengler reaction for the preparation of THIQ is a popular approach because of respectable yields and comparatively mild reaction conditions.[29] Brossi and co-workers in 1972, first time performed an asymmetric synthesis of isoquinoline alkaloids using natural amino acids.[30] Thereafter, Chen and Goel[31] reported the synthesis of *cis/trans* 4-phenyl Tic derivatives **18** using the Pictet–Spengler reaction (Scheme 2).



Scheme 2

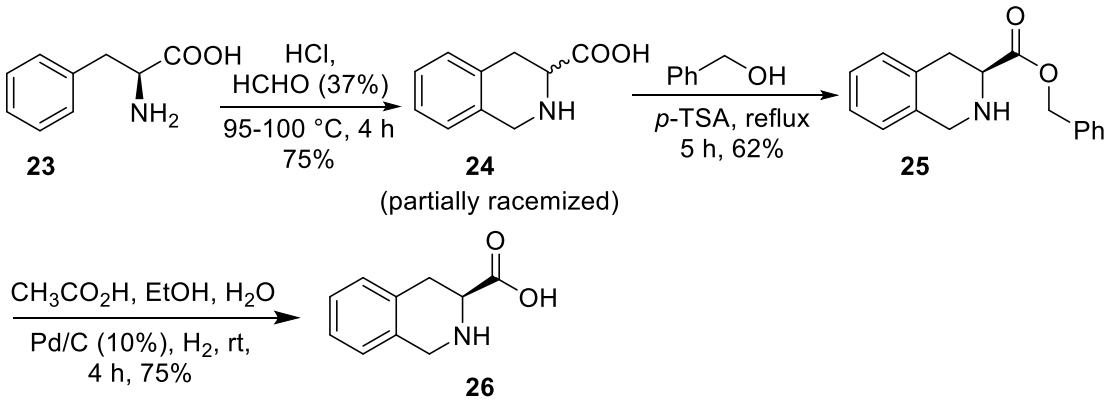
Martinelli and co-workers[32] have utilized the Pictet-Spengler reaction to construct the *N*-substituted Tic derivative **21** (Scheme 3). In this regard, the Pictet-Spengler product **19** was reacted with acetylenic keto acid **20** in the presence of acetic anhydride to deliver the Tic derivative **21** (80%). It was further converted to 4,5,6,7-tetrahydroindole derivative **22.** The structure of **22** corresponds to a part of mitoquidone nucleus exhibiting the cytotoxic (anticancer) activity.[33] A

variety of polycyclics (e.g. **22)** are proven to be important intermediates towards the synthesis of biologically active alkaloids and quinones.



Scheme 3

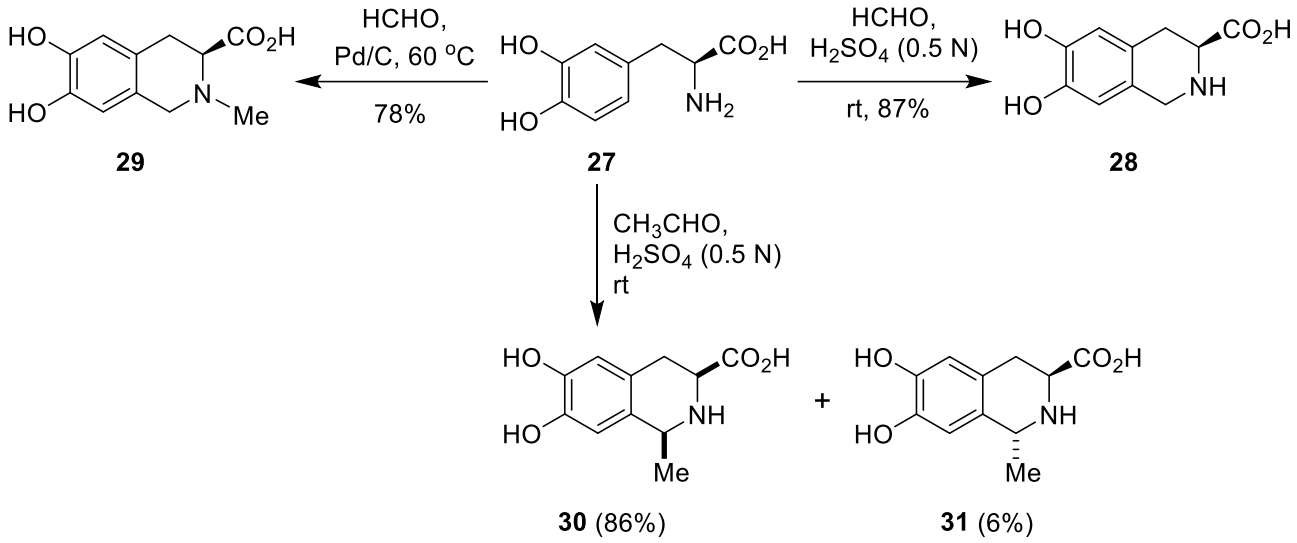
Optically active amino acids are used as critical building blocks in many active pharmaceutical ingredients. Hein and co-workers[34] showed that the treatment of Phe **23** with formaldehyde in the presence of HCl generated the Tic derivative **24** and the process is accompanied by partial racemization. The optically pure product was obtained *via* multiple crystallizations using aqueous ethanol. The process, thus becomes economically less feasible. Yoneda and co-workers[35] modified the process involving the conversion of **24** into its benzyl ester **25** which on de-protection followed by fractional crystallization gave the optically pure Tic derivative **26** in an excellent yield (Scheme 4).



Scheme 4

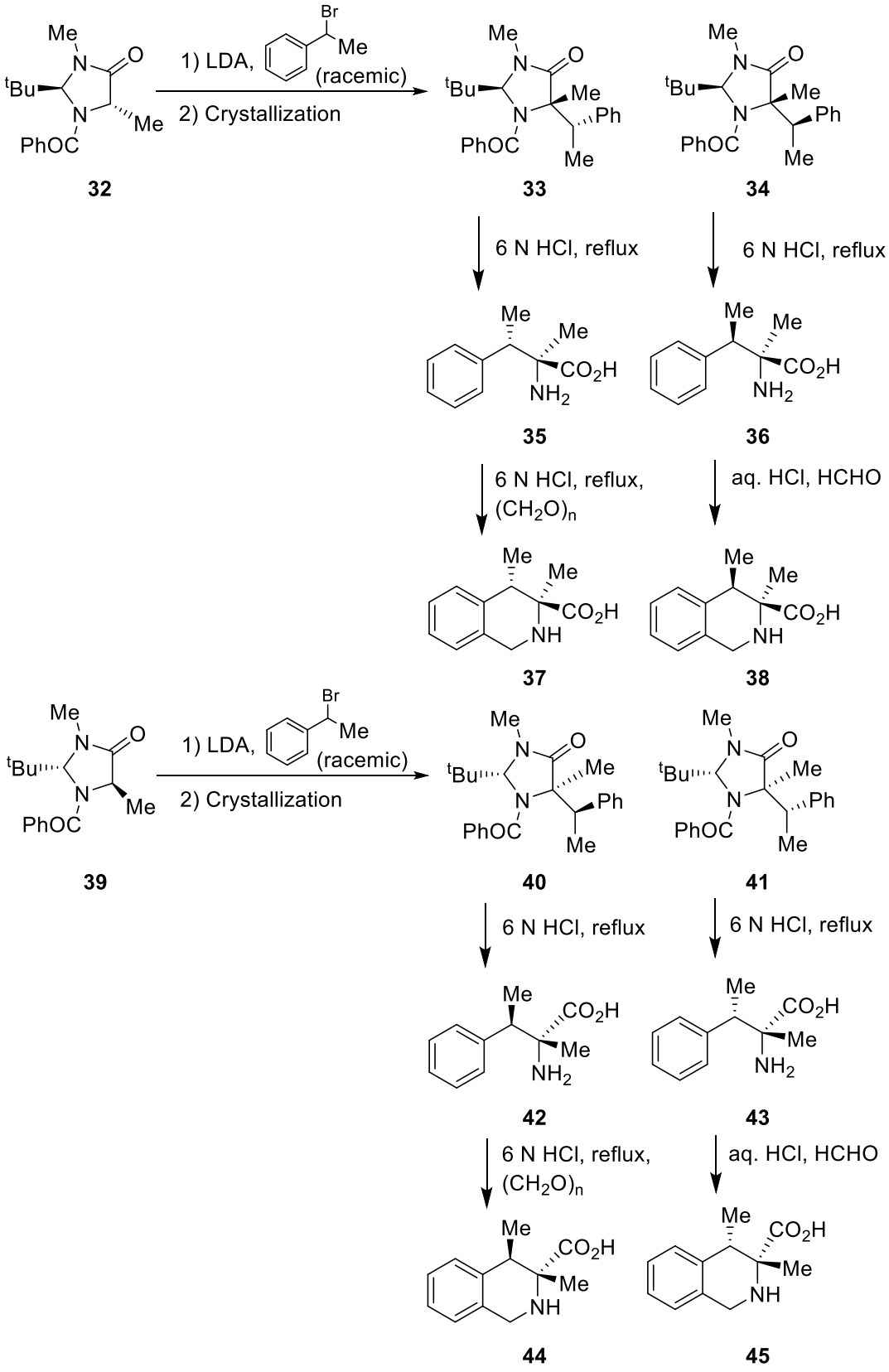
In an another event, the aqueous suspension of L-dopa **27**, formaldehyde (37% aq.) and sulfuric acid was stirred at rt for 24 h generating the Tic derivative **28** (87%). However, treatment of L-dopa with acetaldehyde in the presence of an acid delivered an isomeric mixture of two amino

acids **30** and **31** in 86% and 6% yield respectively. Tic derivative **29** has been prepared by treatment of L-dopa **27** with formaldehyde and Pd/C when the cyclization and *N*-alkylation occurred to give the Tic derivative **29** in 78% yield (Scheme 5).[30]



Scheme 5

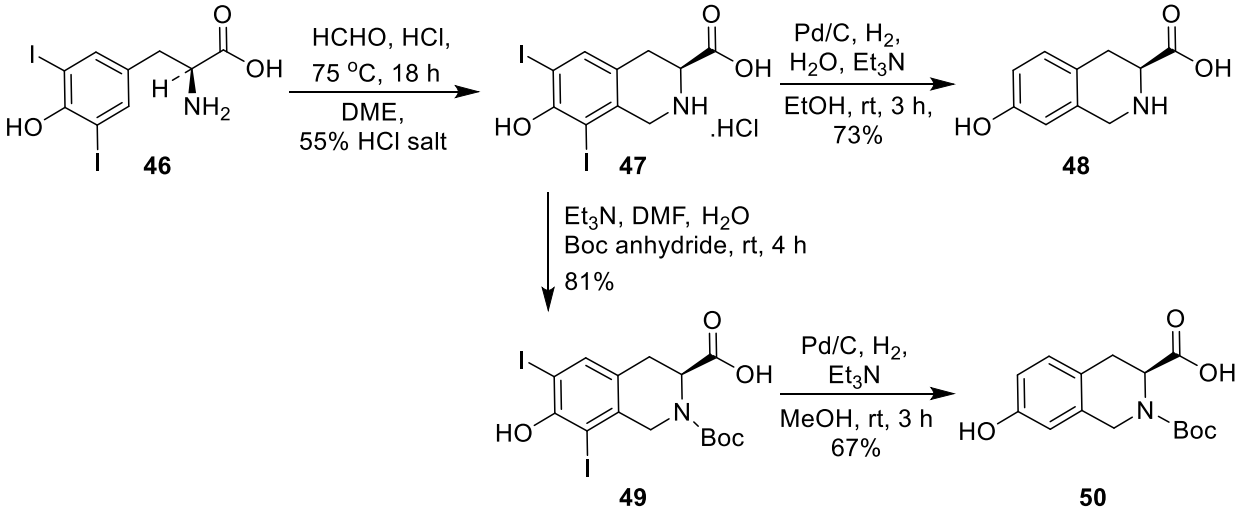
The imidazolidin-4-ones such as **32** and **39** were lithiated by Hurby and co-workers[36] by treatment with LDA. The resulting anions were treated with one equivalent of racemic (1-bromo)ethylbenzene to generate the diastereomers **33** (28%) and **34** (72%) (from **32**) as well as diastereomers **40** (25%) and **41** (75%) (from **39**) (Scheme 6). Alternatively, when three equivalents of racemic (1-bromo)ethylbenzene was used for the alkylation of **32** and **39**, only negligible amounts of diastereomers **33** (7.7%) and **40** (3%) were obtained and the reaction gave **34** (92.3%) and **41** (97%) in higher yields in a diastereoselective manner. All four diastereomers (**33, 34, 40** and **41)** were hydrolyzed with hot aqueous hydrochloric acid (6 N) to generate the hydrochloride salts of *α,β*-dimethylphenylalanine. These salts were further converted into the respective *α,β*-dimethylphenylalanine isomers (**35, 36, 42** and **43**) by the removal of HCl using ion exchange chromatography. The isomers **36** and **43** were subjected to the Pictet–Spengler reaction under classical conditions to deliver the Tic derivatives **38** and **45** respectively in a high optical purity. However, the rate of cyclization of **35** and **42** under the classical Pictet–Spengler conditions was found to be slow and the reduction of iminium cation intermediate led to the formation of *N*-methyl amino acid preceded the cyclization step.



Scheme 6

When the reactions were performed in a sealed tube in the absence of oxygen and using paraformaldehyde, cyclization of **35** and **42** proceeded in a smooth manner to deliver the Tic derivatives **37** and **44** respectively.

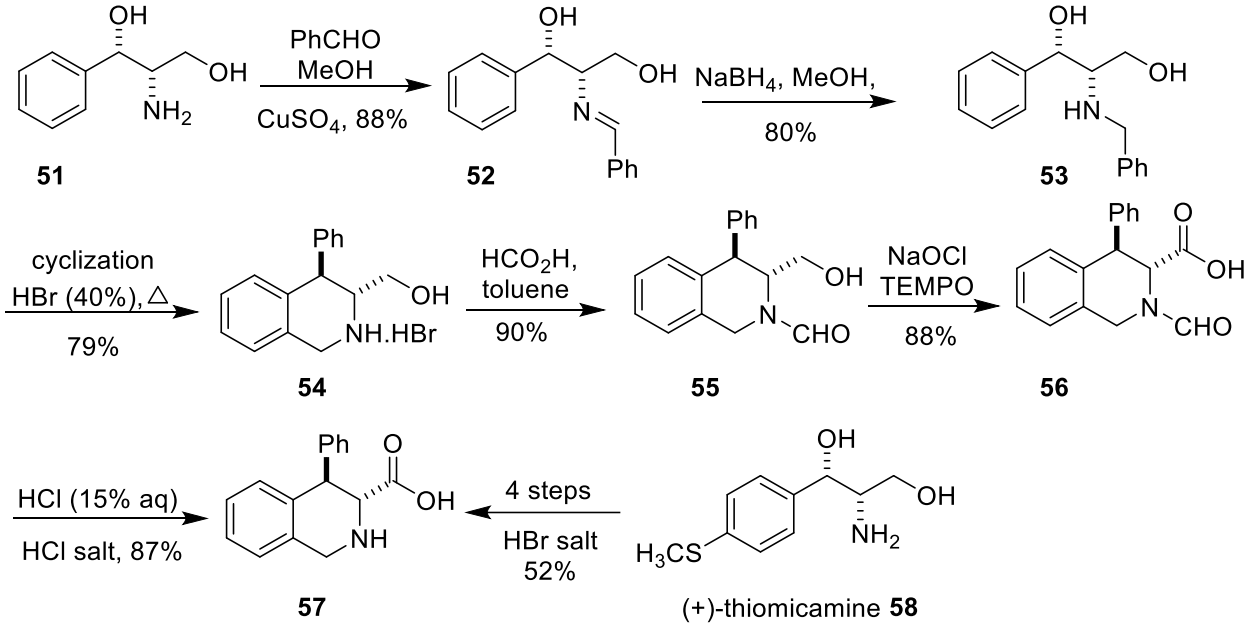
Verschueren and co-workers[37] have prepared Tic derivatives **48** and **50** by the treatment of diiodo-L-tyrosine **46** with formaldehyde and HCl. The reaction required a slightly higher temperature (85 °C) when dibromo-L-tyrosine **46** was used as a staring material. However, during the course of reaction, the use of lower reaction temperature was found to reduce the chances for the racemization which otherwise a major problem at the reflux temperature. The iodide groups were removed *via* catalytic hydrogenation using H_2-Pd/C to generate the Tic derivative **48 (**73%). Towards the preparation of Tic derivative **50**, compound **47** was protected using Boc anhydride to give **49** (81%). Later, Boc derivative **49** was subjected to hydrogenolysis to afford 7-hydroxy-Tic derivative **50** (67%) (Scheme 7).



Scheme 7

Condensation of aminodiol **51** with benzaldehyde gave the crystalline imine **52** (88%) which on reduction with sodium borohydride delivered *N*-ylamine derivative **53** (80%) (Scheme 8).[38] The cyclization of **53** in the presence of hydrobromic acid (40% aq.) furnished trans-3,4-disubstituted derivative **54** (79%) with a high diastereoselectivity. The retention of configuration has been observed during the cyclization step and configuration at 1*S* stereogenic centre in staring aminodiol **51** lead to exhibit the *R*-stereochemistry in **54**. Later, **54** was heated with formaldehyde in toluene to obtain **55** (90%) (avoiding the formation of a diformylated product). The oxidation of **55** using sodium hypochlorite and 2,2,6,6-tetramethyl-1-piperidinoxy radical (TEMPO) catalyst gave *N*-formyl acid **56** (88%) which upon acidic hydrolysis furnished the hydrochloride salt of the Tic derivative **57** (87%). Interestingly, Tic derivative **57** as a hydrobromide salt was obtained in

52% overall yield starting from an inexpensive industrial waste such as (1*S*,2*S*)-(+)-thiomicamine **58** in a four-step sequence.

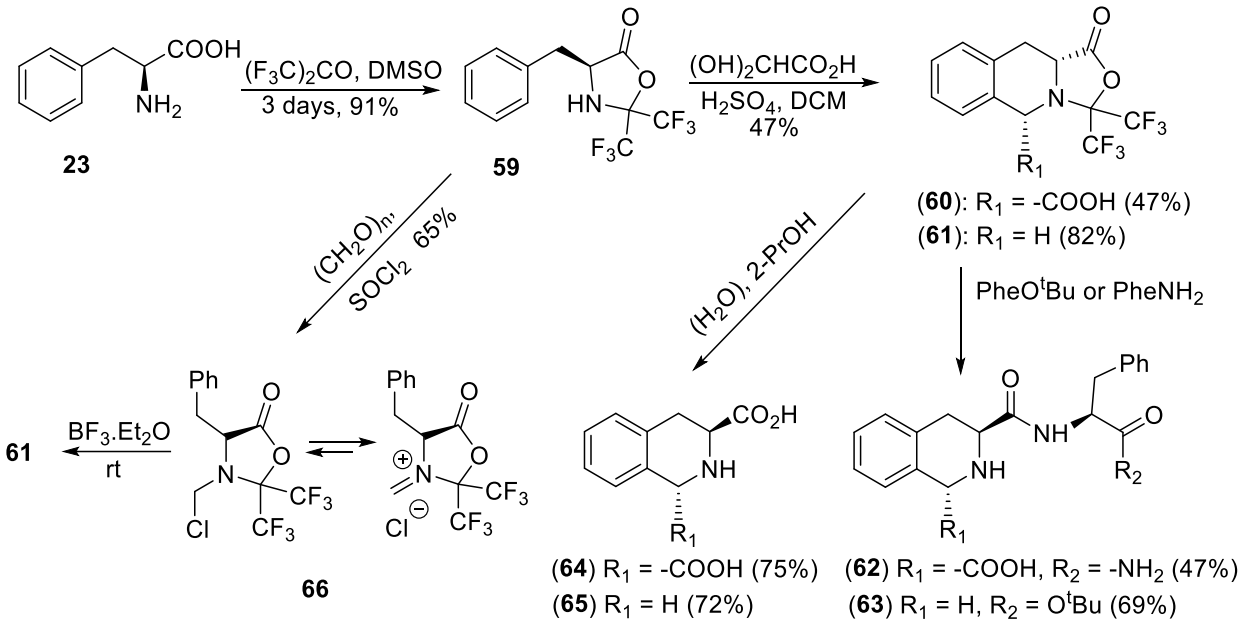


Scheme 8

Burger and co-workers[39] have described a simple route for the stereoselective synthesis of Tic derivatives using hexafluoroacetone (HFA) protected Phe and glyoxalic acid as starting materials by adopting the Pictet–Spengler reaction (Scheme 9). In this connection, Phe **23** was treated with HFA in dimethylsulfoxide (DMSO) affording the protected derivative **59** (91%).[40] It was then stirred at rt for three days with glyoxalic acid hydrate and concentrated sulfuric acid to furnish the Tic derivative **60** in 47% yield. Treatment of **60** with amino acid amides such as (*S*)-phenylalanine *tert*-butyl ester in the presence of 2-propanol delivered the dipeptide ester **62** (47%) The product **60** was hydrolyzed in the presence of aqueous 2-propanol to give the dicarboxylic acid **64** (75%). HFA-protected Phe **59** was then subjected to the condensation reaction with a variety of aldehydes and ketones. However, when it was reacted with paraformldehyde, compound **61** was obtained in 82% yield. The hydrolysis of **61** in the presence of aqueous alcohol furnished an optically pure Tic derivative **65** (72%).

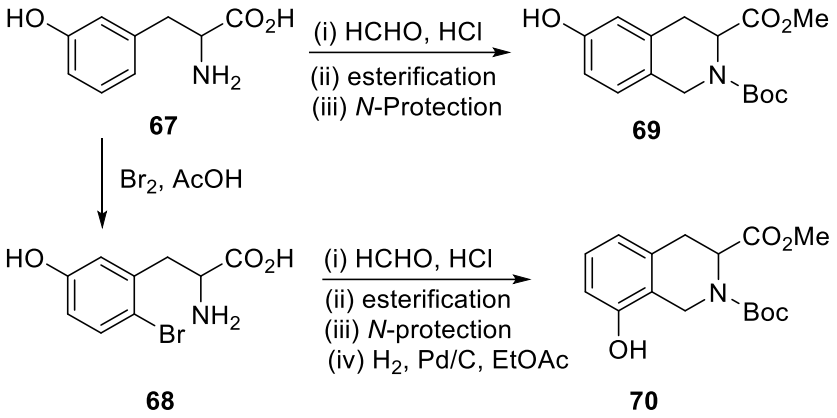
The Suzuki–Miyaura (SM) cross-coupling reaction[41] has emerged as a useful tool in the organic synthesis and has been tactically utilized toward the synthesis of conformationally constrained amino acid derivatives.[42] McKenna and co-workers[43] have regioselectively synthesized 6- and 8-aryl Tic derivatives **73** and **74** using palladium chemistry. They have utilized

the Suzuki coupling reaction as a tool by reacting triflate derivatives with a wide range of aryl boronic acids to generate highly functionalized Tic derivatives. In this context, initially the Pictet–Spengler cyclization has been carried out with Phe derivative **67** followed by an esterification and then protection to deliver 6-hydroxy substituted Tic derivative **69**.



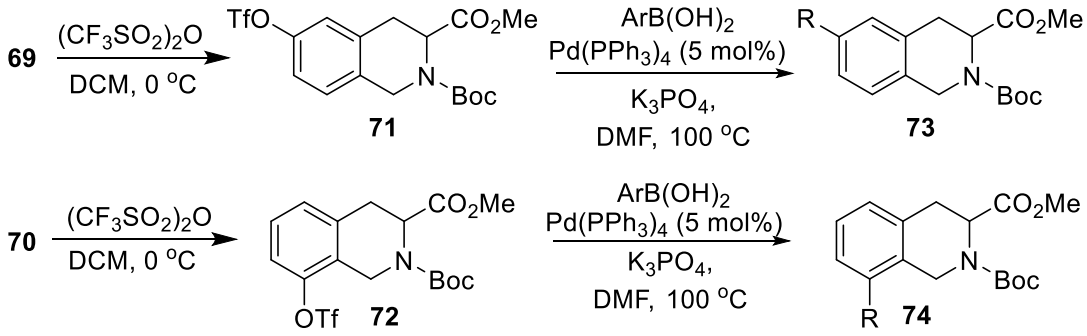
Scheme 9

Towards the synthesis of isomer **70**, the possibility of performing the Pictet–Spengler cyclization at both the *ortho* positions in *meta*-tyrosine **67** was eliminated by blocking of one of the *ortho* position *via* bromination. A reaction sequence involving cyclization, esterification and *N*-protection involving **68** followed by a treatment with H_2-Pd/C delivered the 8-hydroxy substituted Tic derivative **70** in good to moderate yield (Scheme 10).



Scheme 10

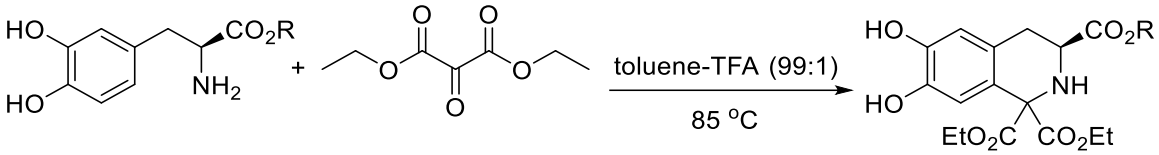
Further, 6- and 8-hydroxy substituted Tic derivatives **69** and **70** have been converted to the corresponding triflates **71** and **72** by treatment with trifluoromethanesulfonic anhydride (Scheme 11). Both the triflates were subjected to the SM cross-coupling reaction with various aryl boronic acids in the presence of K_3PO_4 using $Pd(PPh_3)_4$ catalyst to obtain 6- and 8-aryl substituted Tic derivatives **73** and **74** in good to excellent yields. This protocol opens up a possibility of introducing diverse functional groups in the isoquinoline moiety using palladium catalyzed cross-coupling reaction.



Ar	Yield (%) 73	74	Ar	Yield (%) 73	74
Ph	79	80	2-OMe-Ph	55	53
4-Cl-Ph	80	91	2,4,6-(CF_3)-Ph	66	77
3-$(CF_3)CH_2$-Ph	76	88	3-Thiophene	83	54

Scheme 11 (TL

Zhu and co-workers[44] have demonstrated the Pictet–Spengler cyclization of *β*-arylethylamines **75a-b** with diethyl oxomalonate **76** to deliver 1,1′-disubstituted tetrahydroisoquinoline derivatives **77a-b** in an excellent yield. (Scheme 12).

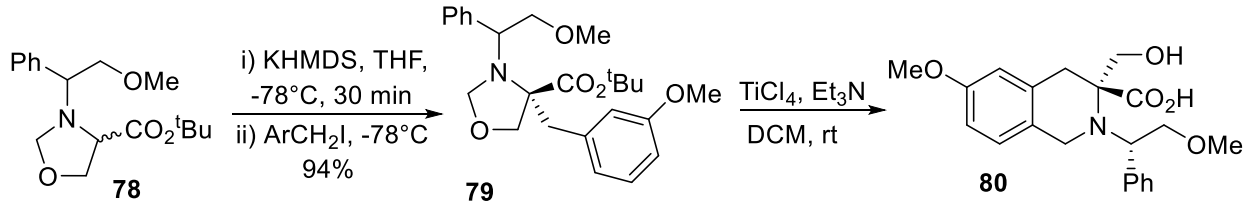


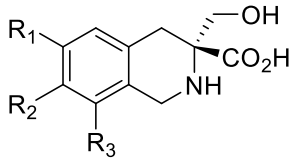
75 a (R = H) b (R = Me) **76** **77** a: R = H (98%) b: R = Me (98%)

97)

Scheme 12

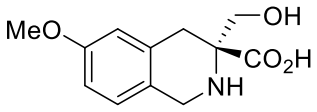
Bonin and co-workers[45] have demonstrated a versatile route for the synthesis of quaternary Tic derivatives *via* intramolecular Pictet–Spengler reaction as a key step (Scheme 13). To begin with, oxazolidine derivative **78** was reacted with potassium bis(trimethylsilyl)amide (KHMDS) followed by the reaction with aryl halide at -78 °C to generate a quaternary oxazolidine derivative **79** (94%) with good distereomeric purity. The oxazolidine ester **79** was treated with $TiCl_4$ t**o** afford the cyclized product **80.** It was observed that the protonation of oxazolidine nitrogen inhibits the Pictet–Spengler cyclization; consequently, the reaction has become irreproducible. To minimize this problem, the reaction was carried out in the presence of triethylamine and the results were consistent. Since the compound **80** and its derivatives were found to be unstable, they were directly subjected to hydrogenation using H_2-Pd/C to furnish the Tic derivatives **81a-d** in a moderate to good yield.





81b-d

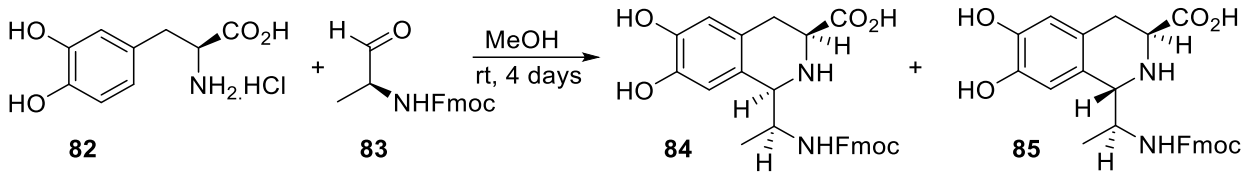
	R_1	R_2	R_3	Yield (%)
b	OMe	OMe	H	70
c	OMe	OMe	OMe	96
d	O-CH2-O		H	78



81a (30%)

Scheme 13

Grieco and co-workers[46] have reported the synthesis of new *β*-turn dipeptide derivatives containing Tic unit *via* the Pictet–Spengler reaction (Scheme 14). A mixture of L-dopa hydrochloride **82** and *N*-(9-fluorenylmethoxycarbonyl)-*L*-alaninal (Fmoc-Ala-aldehyde) (**83)** in methanol was stirred at rt for 4 days to afford Tic derivatives as an epimeric mixture of **84** and **85** (3:2).



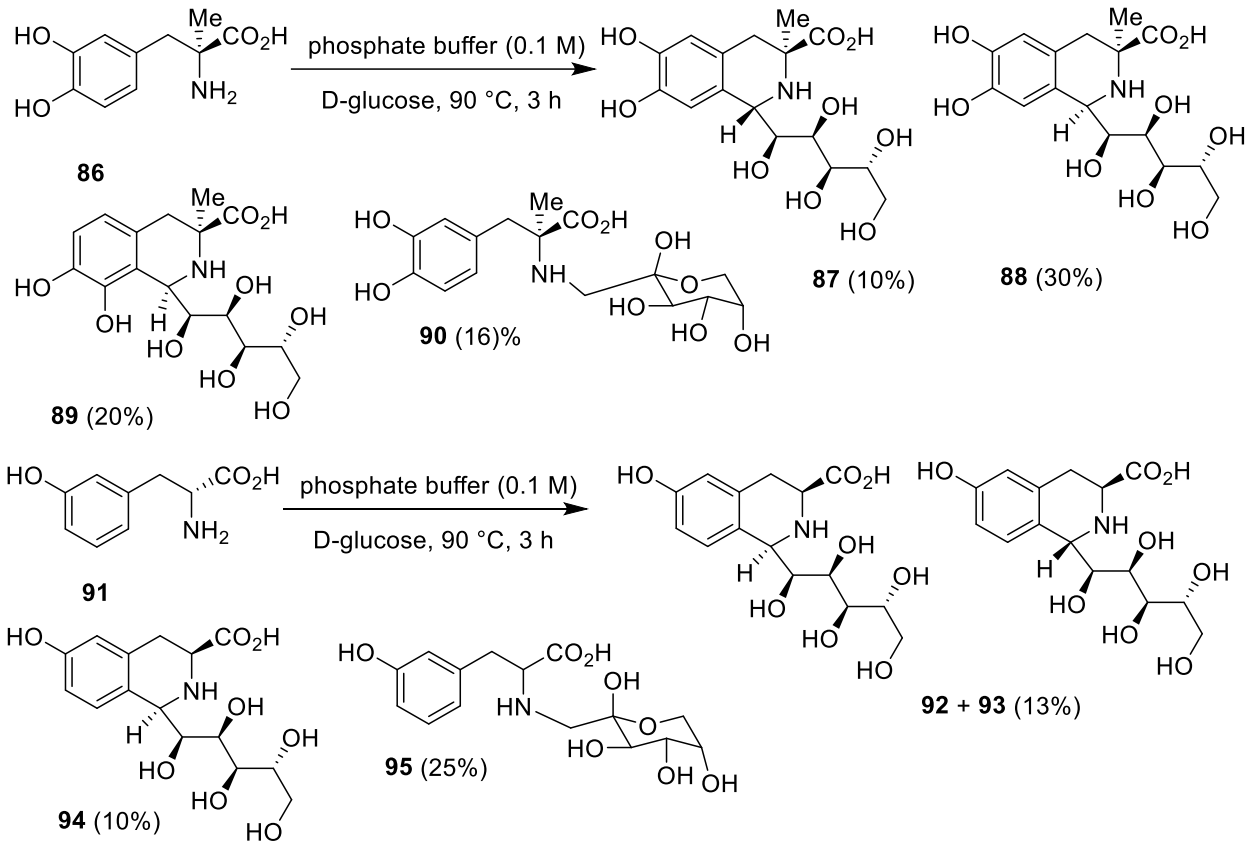
Scheme 14

d'Ischia and co-workers[47] have reported the synthesis of bioactive Tic derivatives **92-95** containing glucose moiety (Scheme 15). To start with, L-α-methyldopa **86** in phosphate buffer (0.1 M) was treated with D-glucose and the products **87**, **88** and **89** were isolated in 10, 30 and 20% yield respectively. In addition, the formation of a non-Tic derivative **90** (16%) was also observed. Under similar conditions, DL-*m*-tyrosine **91** on treatment with D-glucose, gave a mixture of **92** and **93** (13%). In the same reaction, the product **94** (10%) was also obtained along with a non-Tic product **95** (25%)**.**

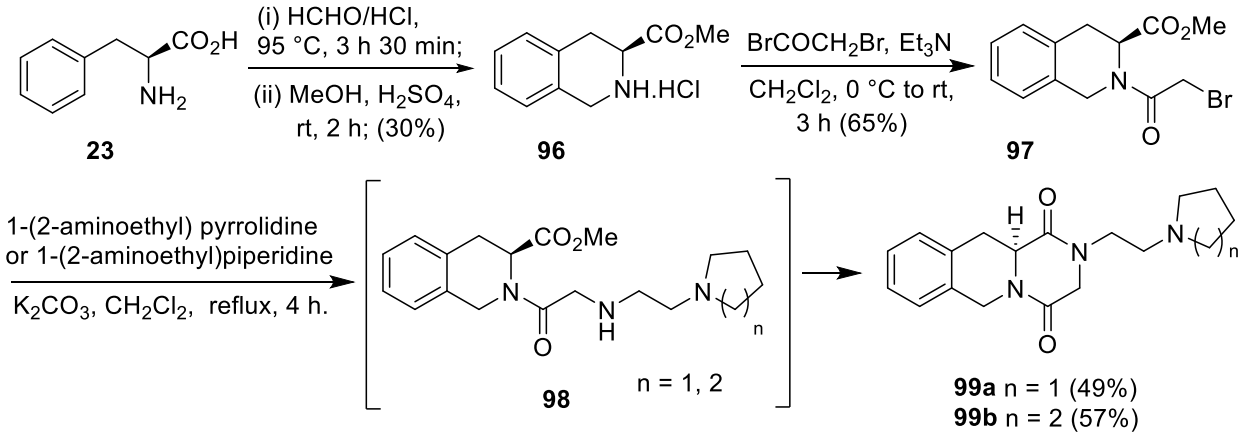
Cortes and co-workers[48] have carried out the Pictet–Spengler reaction of L-phenylalanine **23** with formaldehyde followed by the Fischer-esterification yielding a stable tetrahydroisoquinoline methyl carboxylate **96** (30%) (Scheme 16). Later, it was *N*-acylated by reacting with bromoacetyl bromide to afford the Tic derivative **97** (65%). The treatment of **97** with primary amines such as 2-pyrrolidinylethylamine and 2-piperidinylethylamine generated the corresponding Tic derivatives **98**. These compounds spontaneously underwent alkylation-cyclization to form tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-diones (**99a-b**) a in good to moderate yield. These compounds are useful for the synthesis of piperazine isoquinoline derivatives and also act as useful building blocks for natural products syntheses.[48,49]

Lemaire and co-workers[50] have reported the effect of solvent on the stereochemical outcome of the Pictet–Spengler reaction. In this regard, L-dopa **75a** was treated with benzaldehyde in the presence of K_2CO_3 using various polar solvents to give *cis*- and *trans*-Tic derivatives **100** and **101** respectively (Scheme 17). When the reaction was carried out in water at rt, a 8:2 *cis*/*trans* ratio was obtained. A selective precipitation of the crude product gave the *cis*-diastereoisomer **100** (60%). When the reaction was carried out in methanol at rt, a 7:3 *cis*/*trans* mixture was obtained. Again the selective precipitation of this mixture provided the *trans*-diastereoisomer **101** (20%). This effect has been attributed to the difference in the polarity of the solvent. When these reactions were carried out under reflux conditions, the cyclization was significantly accelerated. Kruger and co-workers[51] have used similar strategy for the preparation of oxazoline ring containing Tic derivatives **103** *via* **102**. These derivatives have been used as ligands for carrying out the stereoselective Henry reaction to give the products in high yields. Further, the derivative such as

methyl ester of **100** have been used as an intermediate for the synthesis of a series of novel dinuclear Tic containing platinum complex as cytotoxic agents against a panel of human tumor cell lines.[52]



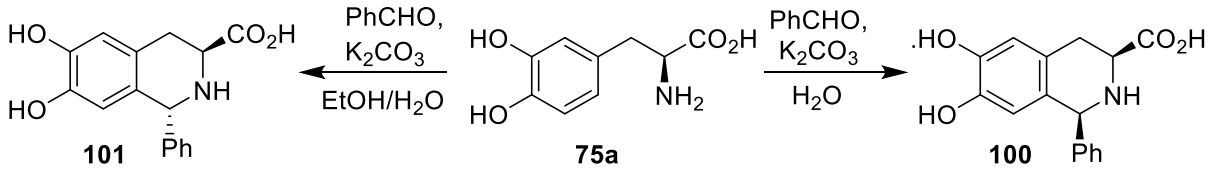
Scheme 15



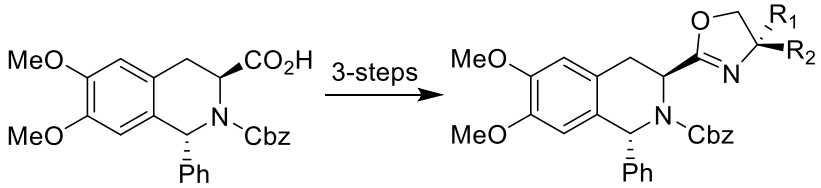
Scheme: 16

Lemaire and co-workers[50] have studied the effect of substituents on the stereochemical outcome of the Pictet–Spengler reaction. In this regard, trifluoroacetate salt of L-3,4-

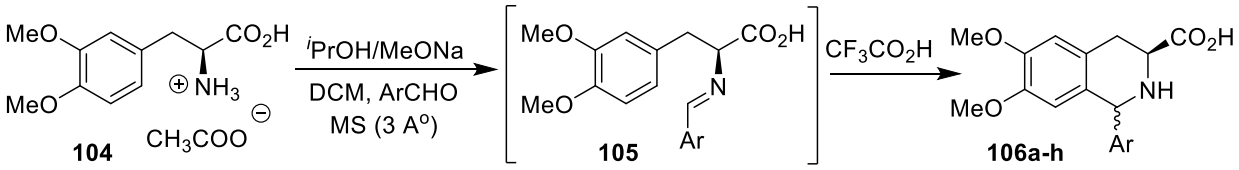
dimethoxyphenylalanine methyl ester **104** was treated with various aldehydes in the presence of sodium methoxide to form the corresponding Schiff base **105**. Refluxing the crude Schiff base with trifluoroacetic acid gave the corresponding Tic derivatives **106a-h** in good yields (Scheme 18).



Conditions	Time	cis/trans ratio (%)	Isolated Yield (%)
H_2O/20 °C	4 h	80/20	60 (cis)
H_2O/80 °C	15 min	75/25	56 (cis)
MeOH/20 °C	4 h	70/30	20 (trans)
MeOH/60 °C	15 min	65/35	22 (trans)
EtOH/60 °C	15 min	70/30	25 (cis/trans 70/30)



Scheme 17



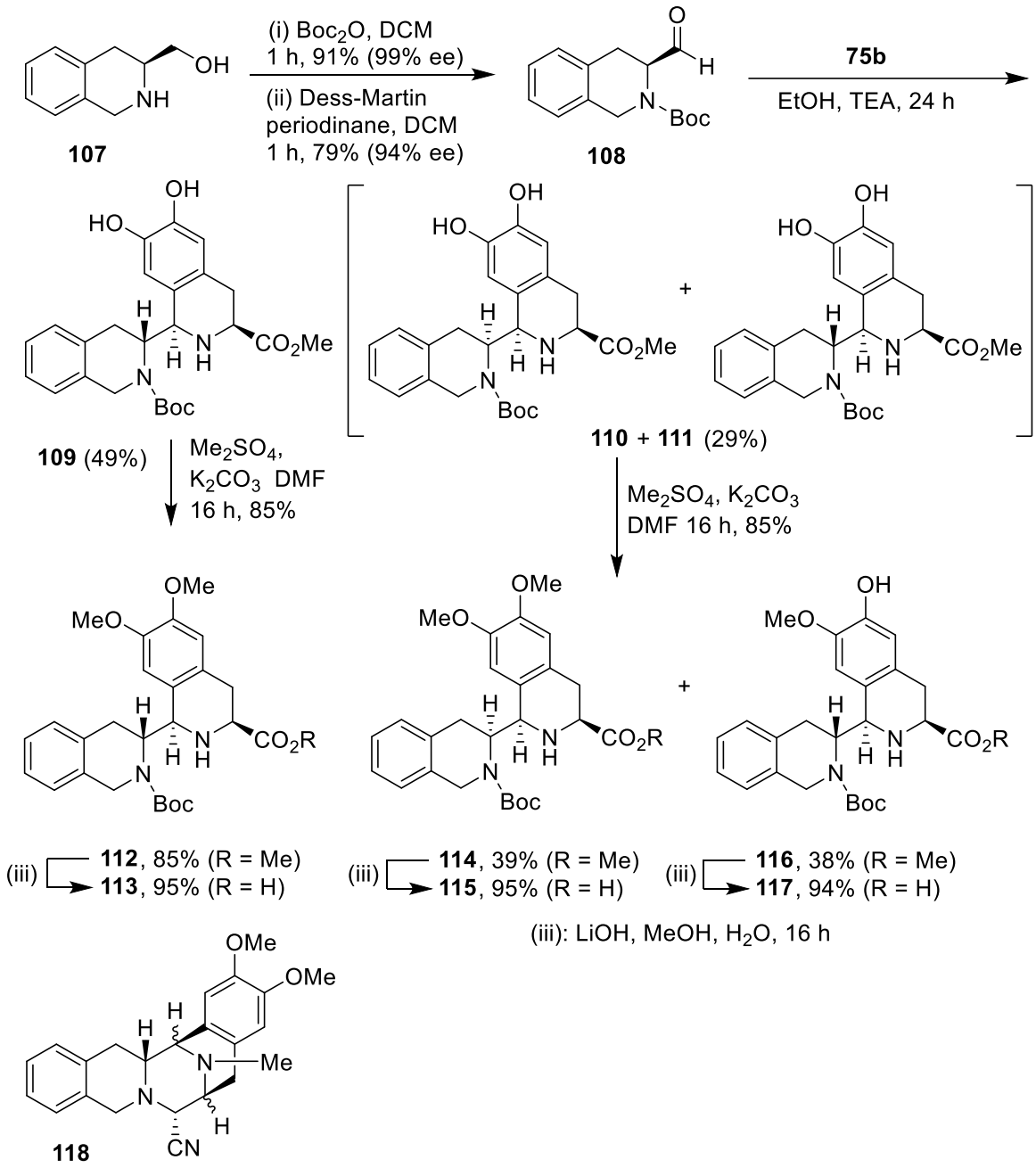
	Ar	Isolated Yield (%) Cis	Trans		Ar	Isolated Yield (%) Cis	Trans
a	C_6H_5	56	12	e	3-benzo[b]thiophene	34	31
b	4-NC-C_6H_5	70	-	f	3-(2-C_6H_5-benzo[b]thiophene)	36	08
c	4-O_2N-C_6H_5	58	10	g	2-(thiophene)	18	45
d	4-MeO-C_6H_5	31	30	h	2-(1-methylpyrrole)	traces	

Scheme 18

Lemaire and co-workers[53] have reported the synthesis of Tic derivatives **112–117,** the potential intermediates for the preparation of piperazine pentacyclic structural analogs of **118** (Scheme 19). These intermediates are considered as major building blocks towards the synthesis of piperazine core alkaloids (e.g. ecteinascidin and phthalascidin).[54] To start with, (S)-1,2,3,4-tetrahydroisoquinilinemethanol **107** was converted into its *N*-protected analog (79%, 99% ee)

followed by oxidation of the resulting alcohol with Dess-Martine periodinane gave the aldehyde derivative **108** (79%, 94% ee). The Pictet–Spengler reaction between L-dopa methyl ester **75b** and the aldehyde derivative **108** was accompanied in the presence of TEA using ethyl acetate. This is a good example of non-classical Pictet–Spengler reaction performed in the presence of a base.[55] The reaction gave three compounds related to bis-(1,3')-tetrahydroisoquinolines i.e **109** (49%) and a non-separable mixture of **110** and **111** (29%, 1:1). The compound **109** was subjected to trimethylation with an excess amount of Me_2SO_4 and K_2CO_3 in DMF at rt for 16 h to give the amino ester **112** (85%). It was hydrolyzed to the corresponding acid using LiOH to form Tic derivative **113** (95%). Similar reactions were performed with **110** and **111** to generate the amino esters **114** (39%) and **116** (38%) which on further hydrolysis with LiOH gave the Tic derivatives **115** (95%) and **117** (94%).

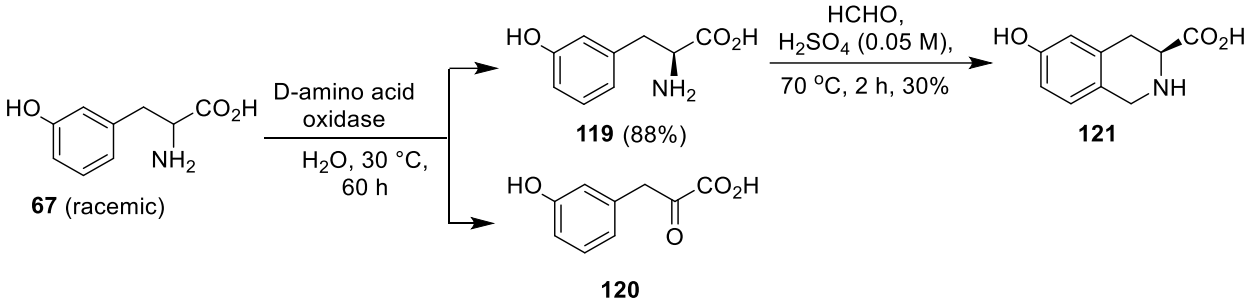
Wohlgemuth and Benz[56] have demonstrated a short co-enzymatic two-step route for the synthesis of optically pure Tic derivative **121** from commercially available DL-*m*-tyrosine **67**. In the first step, D or L-specific amino acid oxidase-catalyzed resolution of DL-*m*-tyrosine **67** was accomplished. In the second step, non-racemizing Pictet-Spengler reaction generates the target molecule **121**. In detail, DL-*m*-tyrosine **67** was incubated with D-amino acid oxidase in water followed by crystallization in ethanol gave (*S*)-*m*-tyrosine **119** (above 99% ee) in 88% overall yield. During the process, the crude *m*-hydroxyphenylpyruvic acid **120** was also isolated as a side product. In the second step, (*S*)-*m*-tyrosine **119** was subjected to the Pictet–Spengler reaction using formaldehyde (37%) and H_2SO_4 (0.05 M) at 70 °C for 2 h followed by subsequent treatment with aqueous ethanol yielded the desired Tic derivative **121** in 30% yield (Scheme 20).



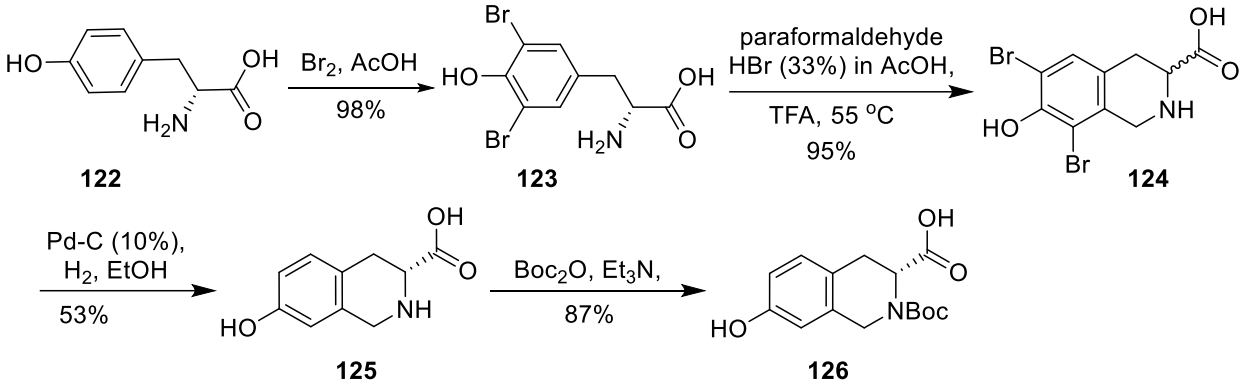
Scheme 19

Carroll and co-workers[57] have demonstrated the synthesis of an optically pure Tic derivative **126** starting from D-tyrosine **122**. In this context, D-tyrosine **122** was subjected to bromination using bromine in acetic acid to obtain 3′,5′-dibromo-D-tyrosine hydrobromide **123** in 98% yield. The Pictet–Spengler cyclization was performed on the tyrosine derivative **123** in the presence of paraformaldehyde and HBr to deliver the Tic derivative **124** (95%). The optimum *ee* of *R*-isomer was obtained when the reaction was carried out at 55 °C for 72 h. However, the compound **124** was found to be a diastereomeric mixture containing 7% of *S*-isomer which could

not be purified by recrystallization. The catalytic dehydrobromination of **124** with Pd/C gave the Tic **125** which on *N*-protection by treatment with Boc anhydride delivered the Tic derivative **126** in 87% yield (Scheme 21).

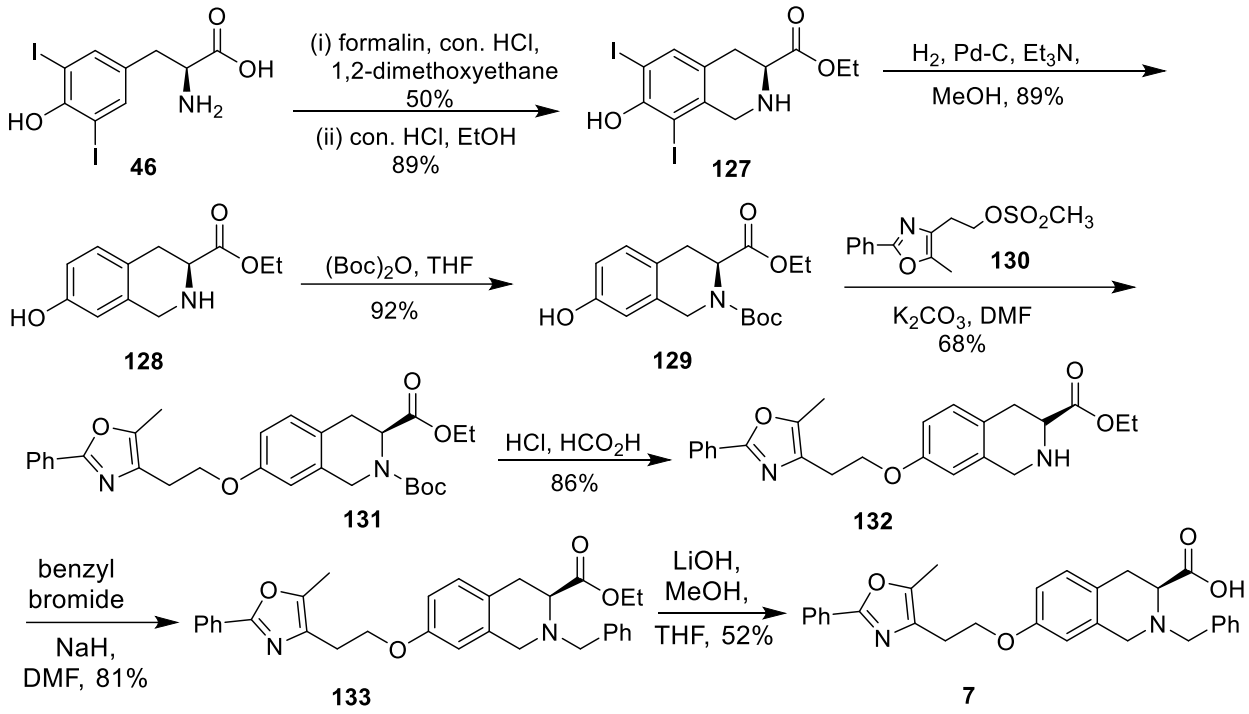


Scheme 20



Scheme 21

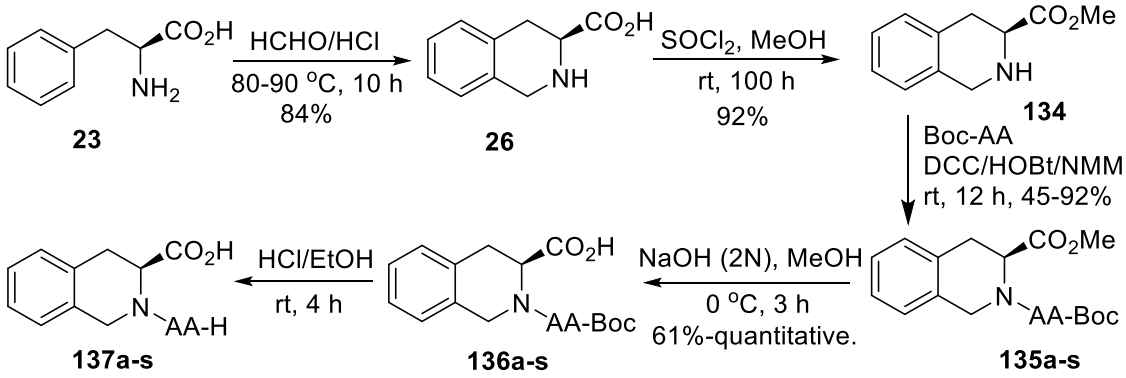
Shirahase and co-workers[16] have subjected the 3,5-diiodotyrosine derivative **46** to the Pictet–Spengler reaction to obtain the corresponding Tic derivative which upon esterification furnished the ester **127** in 89% yield (Scheme 22). The catalytic deiodination of **127** with palladium on carbon delivered the Tic derivative **128** which upon *N*-protection with Boc anhydride afforded the compound **129** (92%) which on treatment with 2-(5-methyl-2-phenyloxazol-4-yl)ethyl methanesulfonate **130** in the presence of potassium carbonate delivered an ether **131** (68%). Deprotection of **131** followed by a base-induced alkylation with benzyl bromide furnished the corresponding *N*-protected Tic derivative **133** which on hydrolysis with lithium hydroxide delivered the carboxyl containing Tic derivative **7**. The compound **7** exhibit a potent activity in human PPARγ (EC_{50} = 11.8 nM) and their studies raised the hope of finding new drug for diabetes.



Scheme 22

Zhao, Chang and Peng[17] have synthesized various dipeptide analogs containing Tic moiety. Here, the Tic based peptides **137** have been generated by subjecting **23** to the Pictet-Spengler reaction (Scheme 23). Further, the esterification of **26** gave Tic derivative **134** which was conjugated with Boc-AA using *N*,*N*-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) to deliver methyl esters **135a-s** (45–92%). These on saponification with NaOH (2N) followed by the deprotection under acidic medium delivered the Tic containing dipeptides **137a-s** in an excellent yield. These derivatives were found to be superior towards *in-vitro* antiplatelet aggregation and *in-vivo* antithrombotic activities.

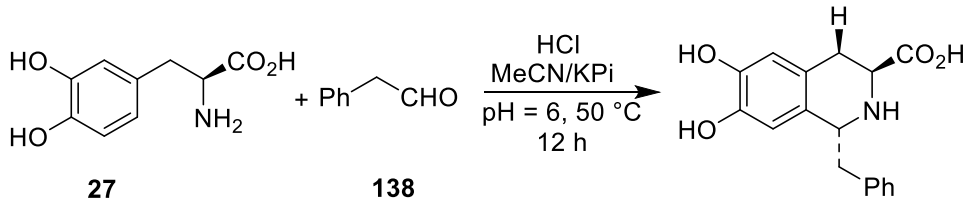
Hailes and co-workers[58] have carried out a facile one-pot synthesis of Tic derivatives **139** and **140** using phosphate mediated Pictet–Spengler reaction (Scheme 24). The amino acid **27** was treated with 2-phenylacetaldehyde **138** and inorganic phosphate salt to yield the Tic derivatives in good yield. The catalysts used such as potassium or sodium salts of phosphate, uridine monophosphate (UMP) and glucose-1-phosphate are proven to be an efficient to realize the reaction. A plausible mechanism indicates the significance of phosphate as a catalyst in biosynthesis of isoquinoline alkaloids (Fig. 4).



65%-quantitative.

	AA		AA		AA
135a-136a	Ala	135i-132i	Thr	137p	Lys
135b-137b	Gly	135j	Tyr(OBn)	135q	Asp(OBn)
135c-137c	Val	136j and 137j	Tyr	136q and 137q	Asp
135d-137d	Phe	135k-136k	Pro	135r	Glu(OBn)
135e-137e	Leu	135l-137l	Met	136r and 137r	Glu
135f-137f	Ile	135m-137m	Asn	135s and 136s	Arg(NO2)
135g-137g	Trp	135n-137n	Gln	136s and 137s	Arg
135h and 137h	Ser(Bn)	135o-137o	His		
137h	Ser	135p and 137p	Lys(Boc)		

Scheme 23



KPi = potassium salt of phosphate

139 (30%, 1*R*, 3*S*)
140 (35%, 1*S*, 3*S*)

Scheme 24

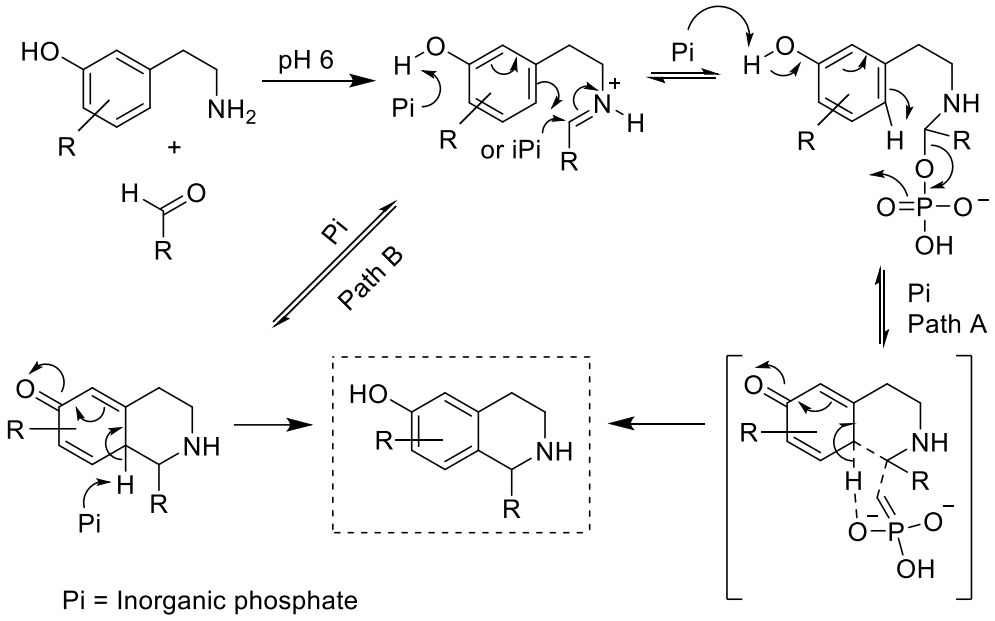
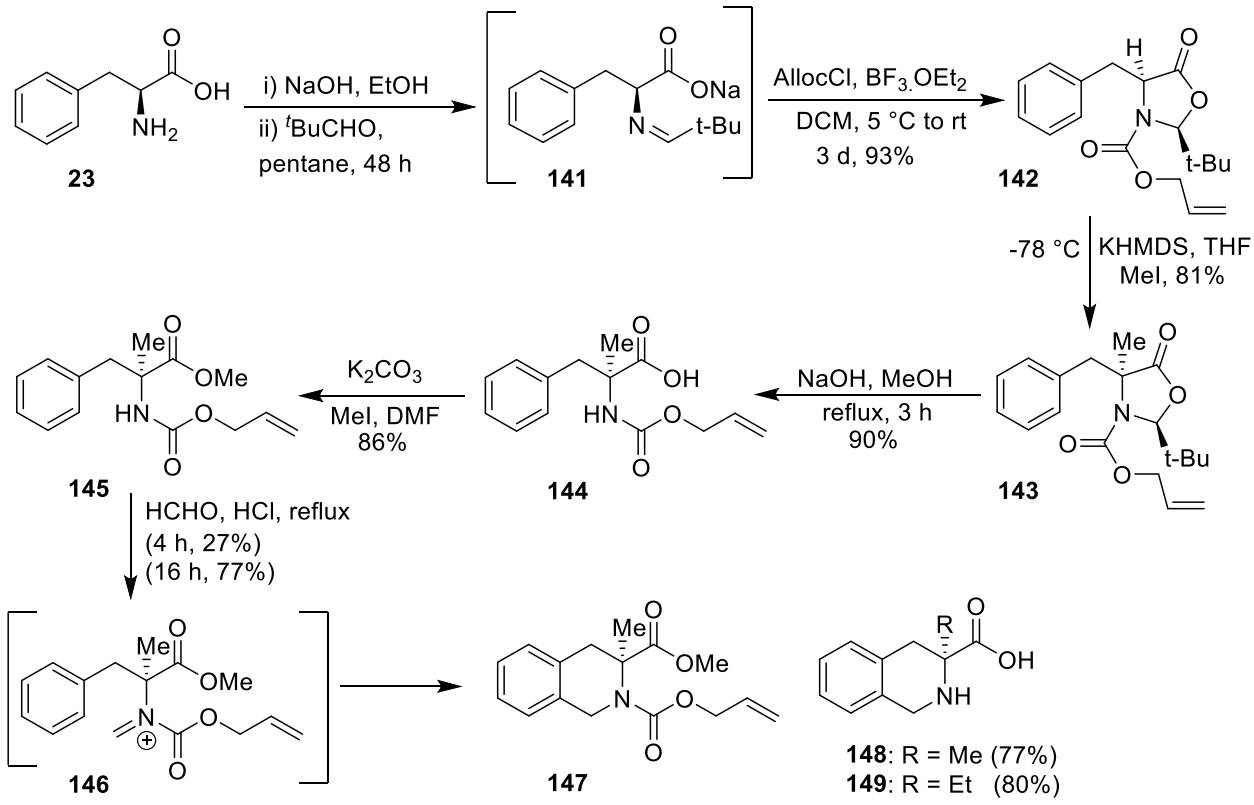


Fig. 4 Proposed mechanism for the phosphate mediated Pictet–Spengler reaction.

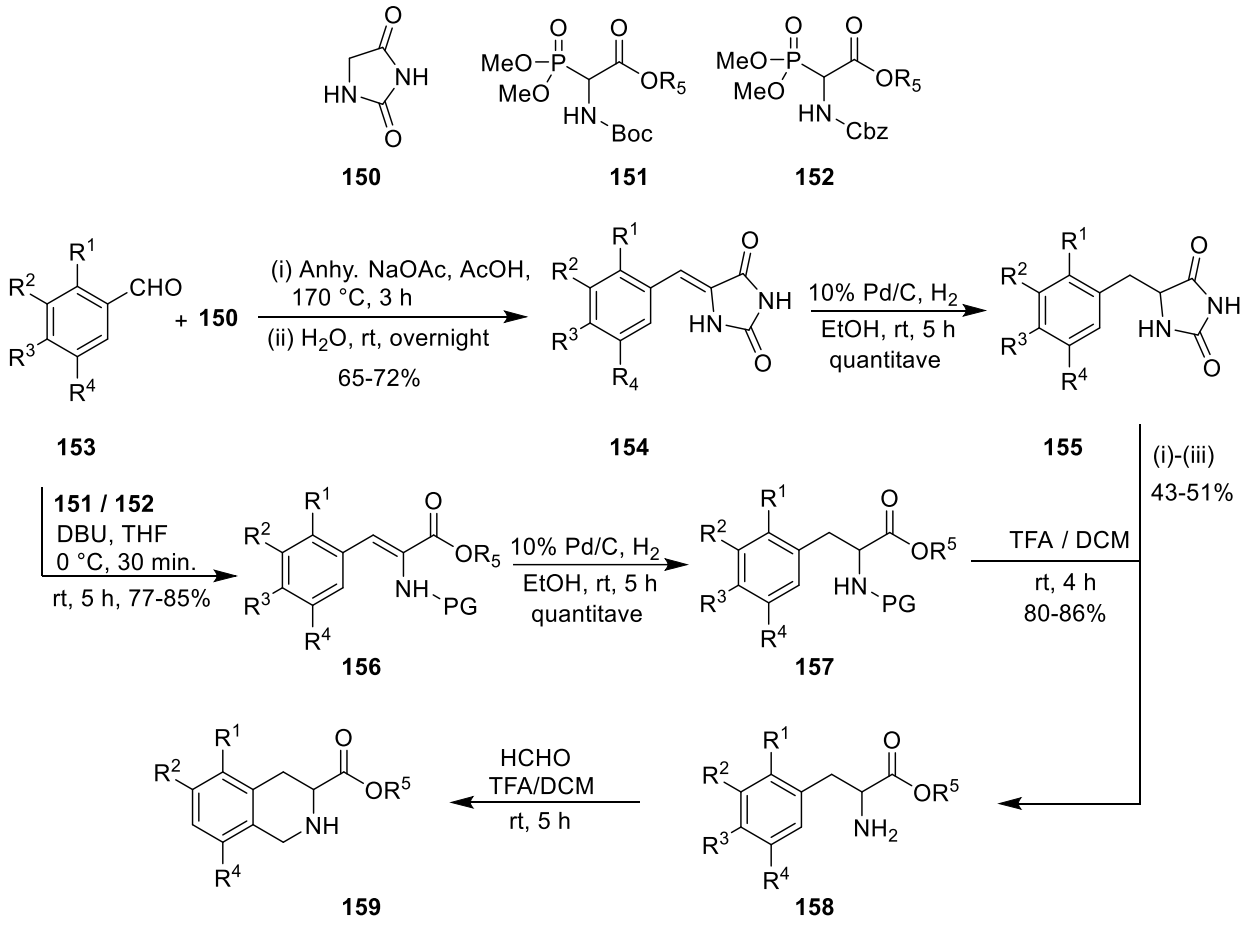
Recently, the α-alkylated non-proteinogenic amino acids have gained significant importance as biologically active agents and various methods are available for the synthesis of these derivatives.[59] To this end, Page and co-workers[60] have established a simple and highly stereoselective route to α-alkylated Tic derivatives **148** and **149** *via* the Pictet–Spengler cyclization involving the treatment of dry sodium salt of Phe **23** with pivaldehyde (Scheme 25). The resulting imine **141** was treated with allyl chloroformate to generate *N*-acylated *cis*-oxazolidinone **142**. The reaction was carried out in the presence of catalytic amount of BF_3-etherate, which resulted in reduced reaction time considerably from two weeks to three days. The compound **142** was subjected to distereoselective alkylation using methyliodide in the presence of KHMDS to furnish α-methylated oxazolidinone **143** in good yield. Hydrolysis of **143** gave the allyloxycarbonyl (alloc)-protected Phe derivative **144** (90%). Later, treatment with methyl iodide and potassium carbonate gave the ester **145** (86%). It was assumed that the Pictet–Spengler reaction of **145** would deliver an acylated nitrogen species which would result in **147** *via in-situ* formation of *N*-acyliminium ion **146**. However, **147** was obtained in low yield. The formation of **148** was also observed during the course of the reaction. When the reaction time increased from 4 h to 16 h, Tic derivative **148** was isolated in 77% yield. Similar reaction conditions were applied to isolate an ethyl substituted Tic derivative **149.**



Scheme 25

A variety of electron rich Tic derivatives have been prepared by using the Pictet Spengler reaction, Horner–Wadsworth–Emmons protocol and glycine equivalents such as hydantoin **150**, (±)-Boc-α-phosphonoglycine trimethyl ester **151** and (±)-Z-α-phosphonoglycine trimethyl ester **152**[61] were employed. The reaction of methoxy-substituted benzaldehyde **153** with hydantoin **150** in the presence of sodium acetate and acetic acid gave an intermediate **154** which was hydrogenated to imidazilidine-2,4-dione **155**. The hydantoin derivative **155** on hydrolysis using barium hydroxide octahydrate followed by treatment with sulfuric acid gave a crude amino acid which on subsequent esterification with thionyl chloride in ethanol afforded dimethoxy phenylalanine ester **158**. The Pictet–Spengler cyclization of **158** gave the corresponding Tic derivatives **159**. The same process was implemented for various substituted benzaldehydes to generate Tic derivatives in overall 21-30% yield (Scheme 26). The process was improved using two other glycine equivalents **151** and **152**. The α-proton of trialkyl phosphonate is highly acidic and formation of a strong O-P bond in the by-product dialkyl phosphate drives the addition-elimination reaction. Trimethyl phosphonate **151** was treated benzaldehyde derivative in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to yield the corresponding benzylidine **156**. It was then subjected to catalytic hydrogenation followed by acidification with TFA in DCM

to give α-amino-*β*-aryl methyl acrylate **158**. Finally, the Pictet–Spengler reaction gave the Tic derivatives **159** (43-58%). Similar reaction sequence was carried out using **152** to generate the Tic derivatives **159** (40-52%). These highly substituted and electronically rich Tic derivatives have been used as building blocks to synthesize promising anti-coagulating agents.



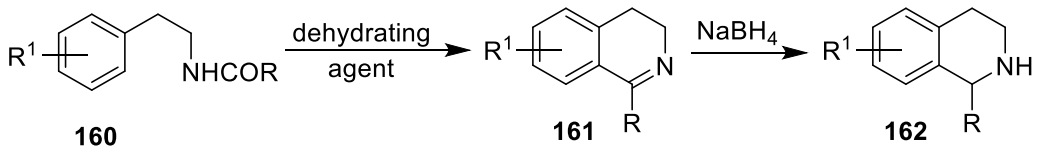
Scheme 26

2.2. Bischler─Nepieralski reaction

The Bischler–Napieralski Reaction[62] is a cyclo-dehydration process involving an acyl derivative of phenylethylamine **160** carried out in the presence of a dehydrating agent like $POCl_3$, P_2O_5, $SOCl_2$, $ZnCl_2$, $FeCl_3$, $COCl_2$, PPA, TFAA, generating 3,4-dihydroisoquinoline derivatives **161**. Subsequent reduction of **161** usually leads to the formation of Tic derivatives **162** (Scheme 27). Generally, *β*-ethylamides involved here are electron-rich arenes. Sodium borohydride in methanol or catalytic hydrogenation is commonly used for the reduction of imine derivatives such as **161**.

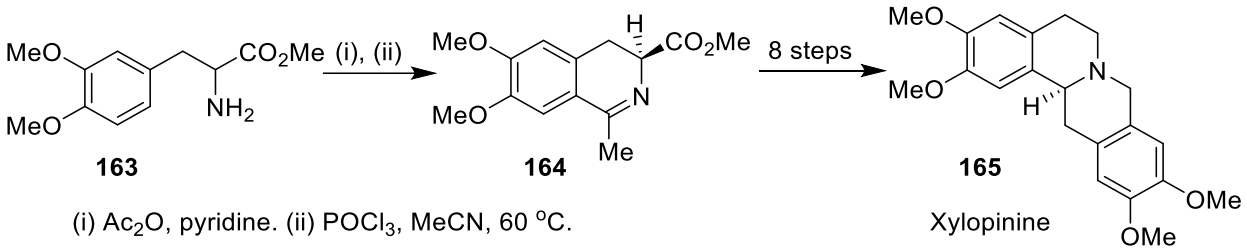
The presence of a hydroxyl group at α-position of a nitrogen in β-ethylamides leads to an additional dehydration step yielding an isoquinoline derivative.

Kametani and co-workers[63] have described a new synthetic route for (*S*)-xylopinine **165** starting from the amino ester **163** *via* the Bischler–Napieralski reaction (Scheme 28). Xylopinine, an α-receptor antagonist is an alkaloid isolated from x*ylopia discreta* and belongs to the *aporphine* category (Aporphine is one of the class of quinoline alkaloids).[64]



160 **161** **162**

Scheme 27



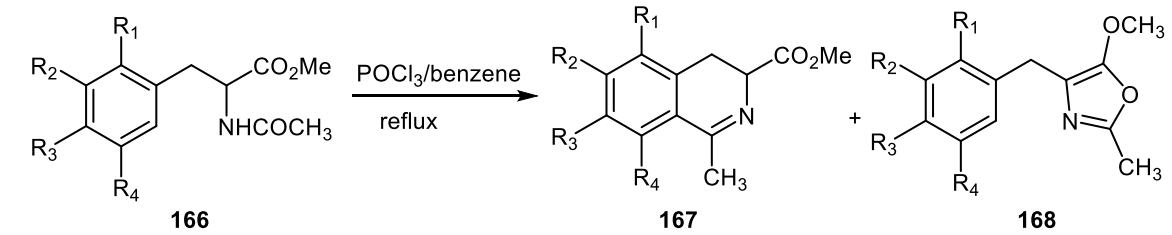
163 **164** **165**

(i) Ac_2O, pyridine. (ii) $POCl_3$, MeCN, 60 ^oC.

Scheme 28

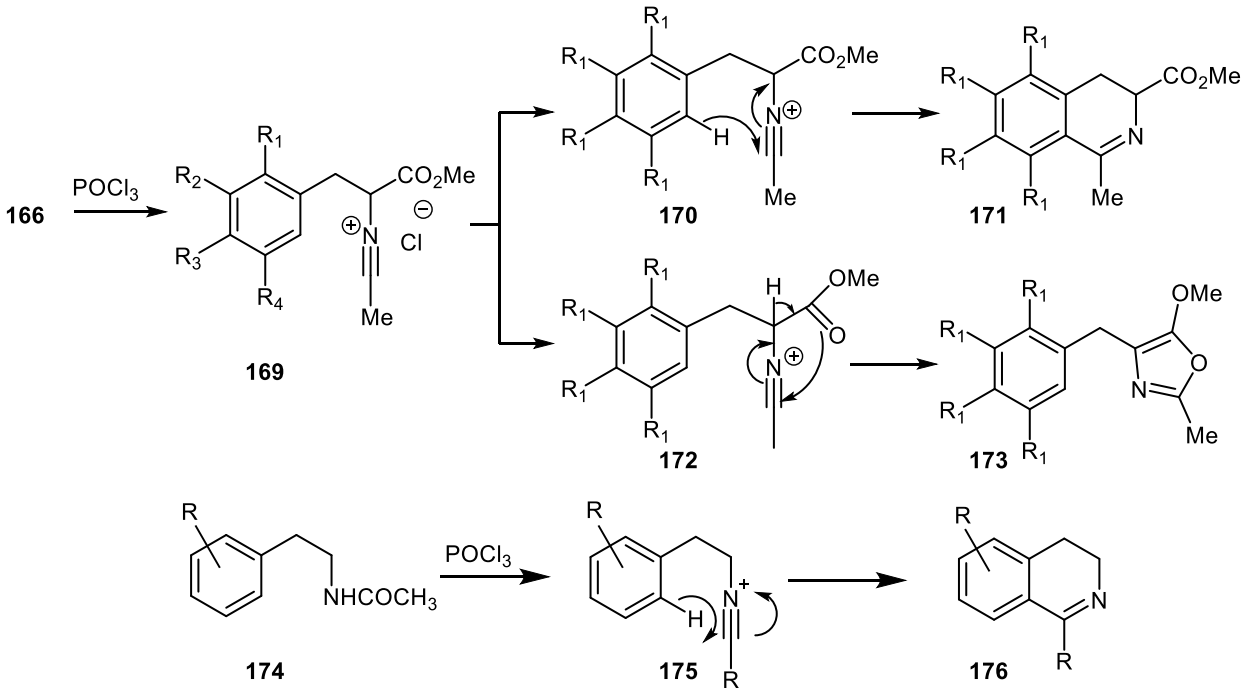
Chen and co-workers[65] have carried out the Bischler−Nepieralski reaction starting with aromatic ring-substituted *N*-acetylphenylalanine methyl esters **166.** Cyclization involving $POCl_3$ under benzene reflux conditions delivered the corresponding 3,4-dihydroisoquinoline-3-carboxylic acid methyl ester **167** along with a side product 5-benzyl-2-methyl-4-methoxy oxazole **168** (Scheme 29). It was observed that the formation of the product (e.g. **167**) mainly depend on the nature of the substituents present in the phenyl ring. The expected cyclization was found to be facilitated by the presence of a strong electron-donating group at *ortho*- and *para*-position with respect to the cyclization site to form the normal Bischler−Nepieralski product **167**. On the other hand, the cyclization was found to be impeded due to the absence or weak electron-donating groups yielding the oxazole product **168** instead of the regular Bischler−Nepieralski product. These results are explained by considering the mechanistic approach involving the Bischler−Nepieralski reaction.[66] The reaction involves *N*-imidoyl chloride **169** as a key intermediate. Due to the absence of ester functionality in the molecules such as amide derivatives of phenylethylamine **174**, the reaction possibly proceed through intra-molecular electrophilic substitution delivering the normal Bischler−Nepieralski product **176**. On the other hand, the molecules such as *N*-acetylphenylalanine methyl ester **166**, two reaction pathways are possible involving imidoyl

chloride **169** as intermediate. The first route follows the normal Bischler−Nepieralski reaction whereas in the second route; enolization of the methoxycarbonyl group followed by intramolecular *O*-alkylation gives the oxazole compound **173**. Thus, the Bischler−Nepieralski reaction involving the amido functionality can be considered as a pair of two competitive reactions that depend on the nature of substituents present in the phenyl ring.



166 167 168

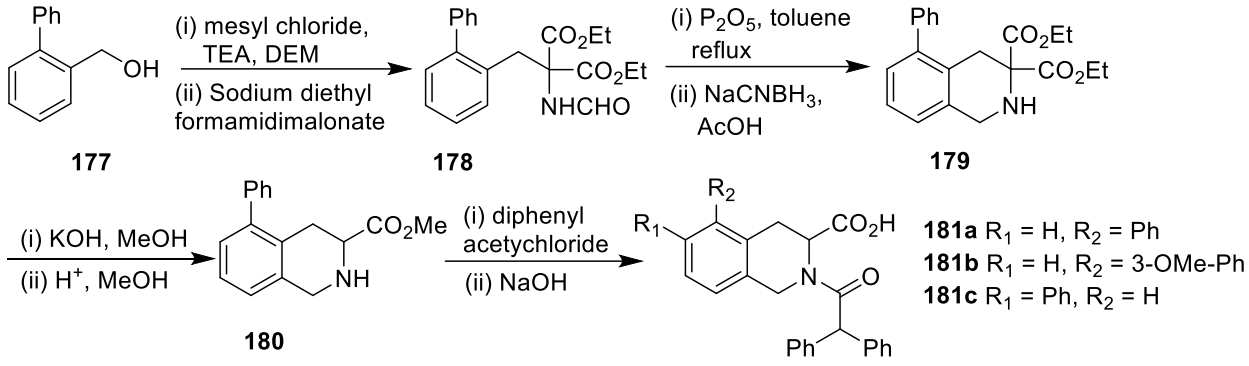
				Yield (%)	
R_1	R_2	R_3	R_4	**167**	**168**
OMe	H	-O-CH_2-O-		-	90
H	OMe	OMe	OMe	85	-
H	-O-CH_2-O-		H	60	28
H	OMe	OMe	H	82	-
H	H	H	H	-	81



Scheme 29

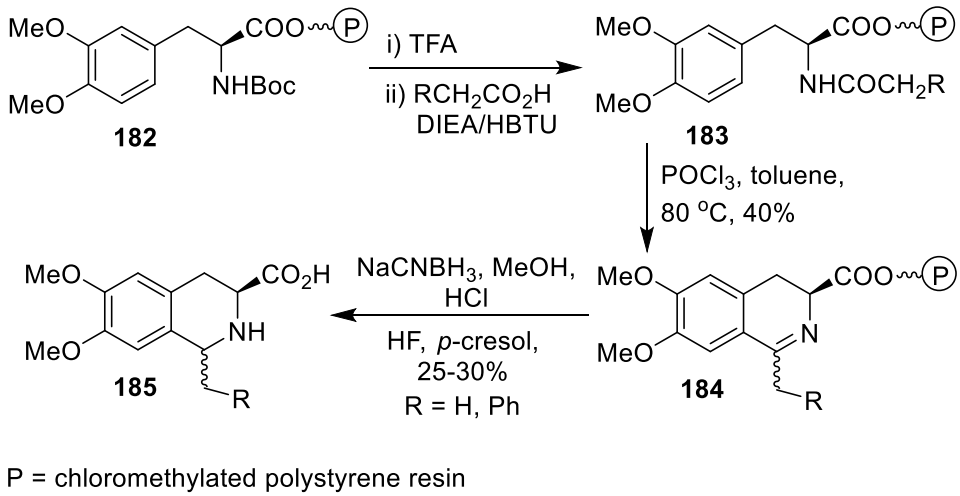
Recently, VanAtten and co-workers[67] have reported a novel series of 5- and 6-substituted Tic derivatives **181a-c**, which inhibit the binding of Ang-II to the AT_2 receptor. Here, the substituted benzyl alcohol **177** was treated with methanesulfonyl chloride in the presence of TEA to deliver the corresponding mesylate which upon reaction with sodium salt of diethyl formamidomalonate gave **178.** It was then subjected to the Bischler–Napieralski conditions using

phosphorus pentoxide in refluxing toluene, to yield the dihydroisoquinline intermediate which was reduced with sodium cyanoborohydride in the presence of glacial acetic acid to generate the Tic derivative **179**. In one-pot reaction, **179** was then hydrolyzed to the dicarboxylic acid using potassium hydroxide in methanol followed by decarboxylation giving a mono acid. The mono acid was refluxed in methanol to give the methyl ester **180.** Subsequently, **180** was subjected to acylation using diphenylacetyl chloride followed by hydrolysis to yield Tic derivative **181a** (Scheme 30)**.** Similar strategy was applied for the preparation of **181b-c**. It was found that the Bischler–Napieralski reaction is more convenient towards the synthesis of the 5-substituted Tic derivatives where as the 6-substituted Tic derivatives can be prepared with ease using the Pictet–Spengler conditions.



Scheme 30

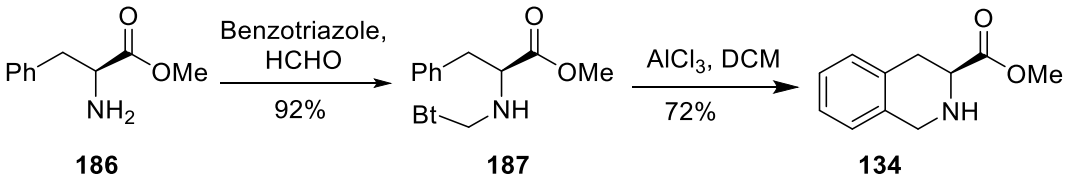
Meutermans and Alewood[68] have demonstrated a solid phase synthesis of the *cis*- and *trans*-Tic derivatives **185** using Merrifield resin as a support. In this connection, *N*-protected dimethoxyphenylalanine derivative linked to chloromethylated polystyrene resin **182** was subjected to deprotection with trifluoroacetic acid and then *N*-acylation with acetic acid or 2-phenylacetic acid in the presence of *N*,*N*-diisopropylethylamine (DIEA) and 2-(*1H*-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HBTU) to furnish the compound **183**. The Bischler–Napieralski cyclization performed on the compound **183** in the presence of $POCl_3$ lead to the formation of dihydro Tic derivative **184** (40%). The imine **184** was treated with sodium cyanoborohydride followed by treatment with HF to deliver the Tic **185 (**25-30%) showing *cis*:*trans* ratio of 6:1 by HPLC analysis (Scheme 31).



P = chloromethylated polystyrene resin

Scheme 31

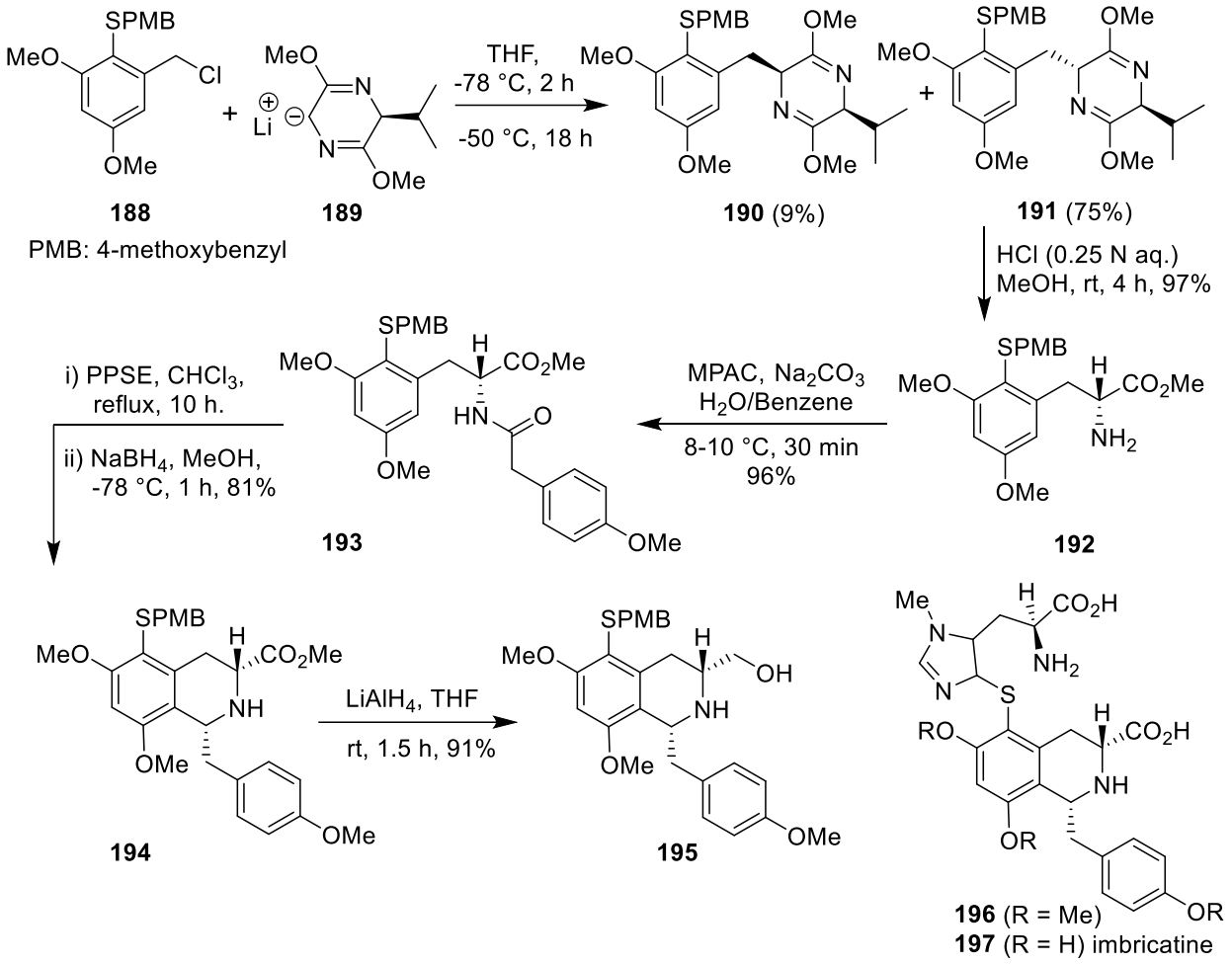
Katritzky and co-workers[69] have reported a simple route for the synthesis of chiral Tic derivative **134** involving the treatment of L-phenylalanine methyl ester **186** with benzotriazole and formaldehyde to furnish banzotriazolylmethyl derivatives **187** (92%). In the presence of aluminium trichloride, **187** undergoes an elimination of benzotriazole (Bt) anion to produce an iminium cation, which participates in the intramolecular electrophilic substitution on phenyl ring to generate optically active Tic derivative **134** in 72% yield (Scheme 32).



Scheme 32TAsy 2427

Towards the elucidation of the structure and the absolute stereochemistry of the alkaloid imbricatine **197,** Ohba and co-workers have synthesized its trimethoxy analog **196** containing Tic core (Scheme 33).[70] The benzyl chloride derivative **188**[71] was treated with an *in situ* generated organolithium reagent **189** in THF at -78 °C to give the alkylated product **191** in 75% yield along with its epimer **190**. The major isomer **191** was then hydrolyzed with aqueous HCl to provide an amino ester **192** (97%, 96% ee). The condensation of **192** under Schotten-Baumann conditions using 4-methoxyphenylacetyl chloride (MPAC) delivered the amide **193** (96%). The amide **193** was then subjected to the Bischler─Nepieralski cyclization using trimethylsilyl polyphosphate (PPSE) followed by reduction with $NaBH_4$ to deliver the cyclized product **194** (81%). The reduction of **194** using $LiAlH_4$ provided the hydroxy derivative **195** (91%). It was used further for the synthesis of tri-methoxy analog **196** of imbricatine **197**. It is worth to mention that the presence of benzyltetrahydroisoquinoline based alkaloid imbricatine in starfish *Dermasterias imbricate*

exhibits significantly special "swimming" activity in the sea anemone named as *Stomphia coccinea* at very low concentrations.

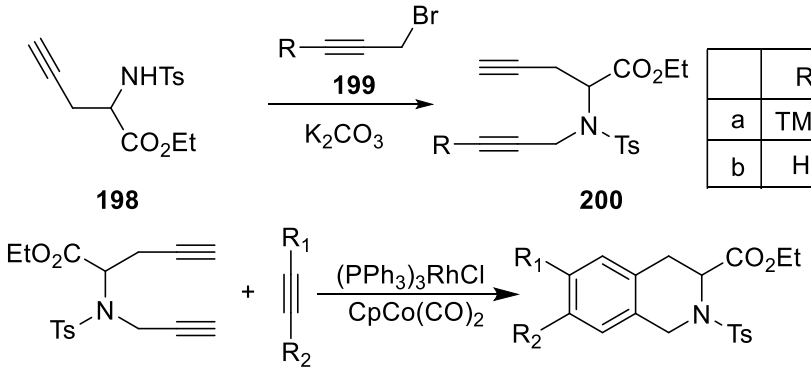


Scheme 33

2.3. Cycloaddition approaches

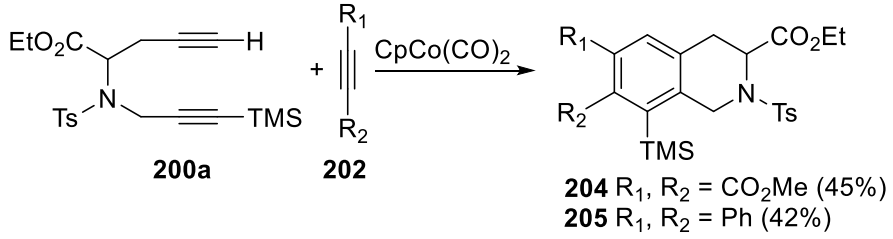
As mentioned previously, the Bischler–Napieralski and the Pictet–Spengler reactions are useful tools to generate various Tic derivatives. However, by these methods limited functional groups can be installed in the aromatic ring and the substitution pattern is decided prior to the cyclization step. In connection to generate and incorporate Tic derivatives in bioactive peptides, diverse aromatic functionalizion is necessary. Cycloaddition reaction offers a unique opportunity to achieve the goal of incorporation of diverse functional groups with varied substitution pattern by an appropriate selection of the reacting partners.[72] Kotha and co-workers have utilized [2+2+2] cycloaddition strategy to generate linearly substituted Tic derivatives.[73] The diyne precursors **200** are useful for the synthesis of Tic derivatives **203-205** and they are synthesized by alkynylation of

the building block **198** in the presence of K_2CO_3. Reaction of the diyne **201** with various monoalkynes **202** catalyzed by the Wilkinson's catalyst or $CpCo(CO)_2$ delivered various Tic derivatives **203** in 15-60% yield (Scheme 34). When bis(trimethylsilyl)acetylene (BTMSA) and dimethyl acetylenedicarboxylate (DMAD) were used as monoalkyne partner, the $CpCo(CO)_2$ catalyst is suitable for co-trimerization sequence. The presence of silyl substituents in an organic molecular frame is highly appreciated owing to their utility in electrophilic aromatic substitution reactions achieved *via ipso* attack. Moreover, the trialkylsilyl group acts as a handle to impart nonpolar hydrophobic properties. Later, the diyne **200a** was reacted with DMAD and diphenyl acetylene in the presence of $CpCo(CO)_2$ to afford the Tic derivatives **204** (45%) and **205** (42%).



	R	Yield (%)
a	TMS	98
b	H	quantitative

R_1	R_2	Catalyst	Yield (%)
CH_2OH	CH_2OH	$(PPh_3)_3RhCl$	53
Ph	Ph		15
H	Ph		30
H	CH_2OH		60
TMS	TMS	$CpCo(CO)_2$	20
CO_2Me	CO_2Me		19
Ph	Ph		30



Scheme 34

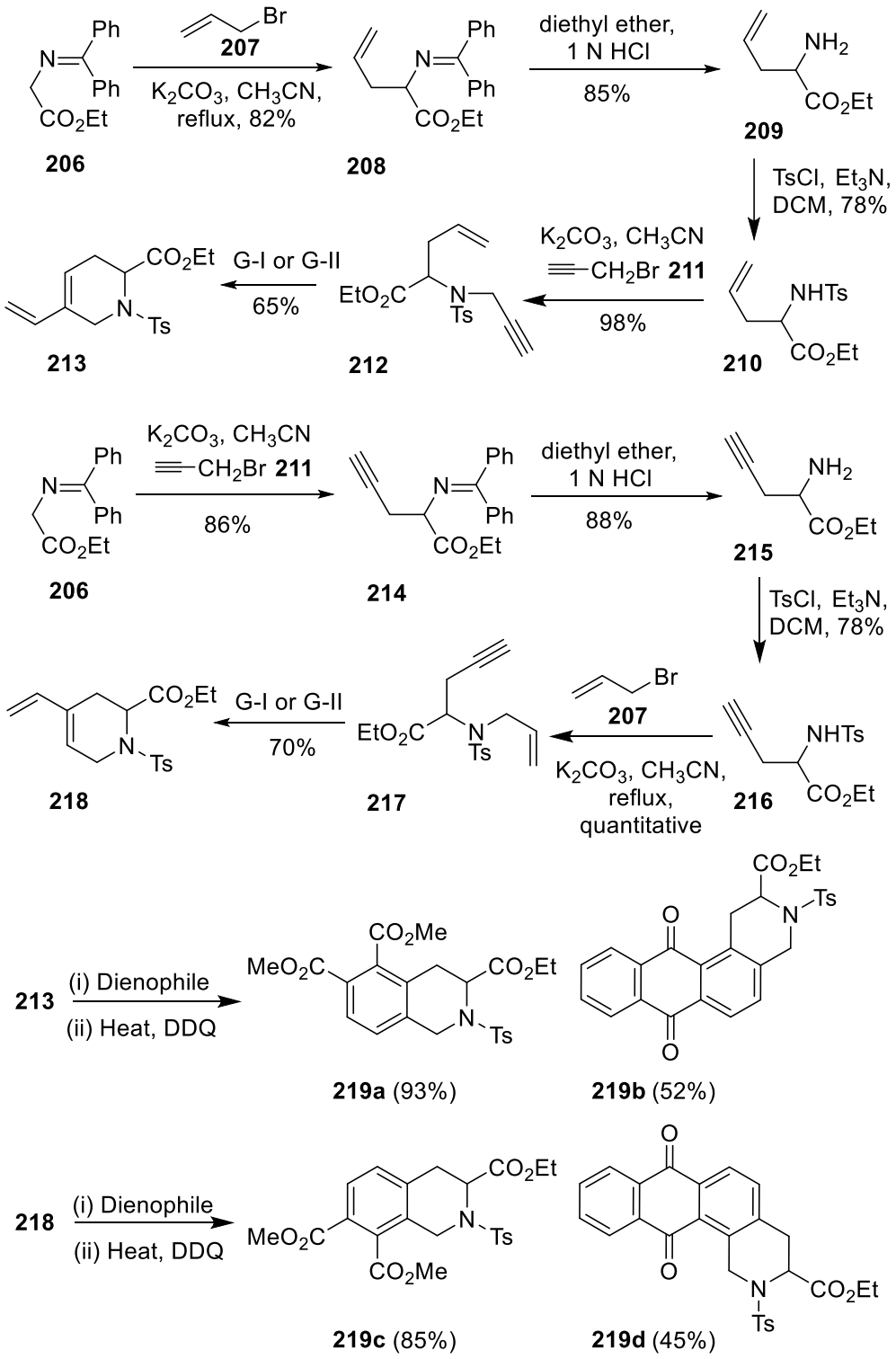
The application of cycloaddition reactions for the construction of Tic derivatives provides a unique opportunity to incorporate diverse substituents in the aromatic units. In case of the Diels–Alder reaction,[74] a variety of dienophiles can be used to incorporate the molecular diversity. Olefin

metathesis[75] has been used widely towards the design of conformationally constrained amino acids. Enyne-metathesis reaction that generate dienes suitable for the Diels–Alder reaction has proven to be useful strategy for the construction of polycyclic compounds.

Highly functionalized Tic derivatives have been synthesized using the diene building blocks **213** and **218** generated by the enyne-metathesis reaction as a key step.[76] The Schiff base **206** was treated with allyl bromide (**207)** in the presence of K_2CO_3 to obtain the allylated product **208** (82%). Further, the hydrolysis of **208** with HCl (1N) in diethyl ether gave an amino ester **209** (85%) which upon reaction with tosyl chloride furnished the *N*-tosyl derivative **210** (78%).

The compound **210** was treated with using propargyl bromide **211** in the presence of K_2CO_3 to obtain enyne building block **212** (98%). Treatment of enyne derivative **212** with the Grubbs catalyst-I (G-I) or Grubbs catalyst-II (G-II) gave the corresponding inner-outer diene building block **213**. Similar strategy using **206** involving interchange of propargylation and allylation steps delivered the diene building block **218** (70%). Further, the Diels–Alder reaction of the **213** and **218** with various dienophiles such as DMAD and naphthaquinone followed by the aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) delivered the angularly substituted Tic derivatives **219a-d** in good yields (Scheme 35).

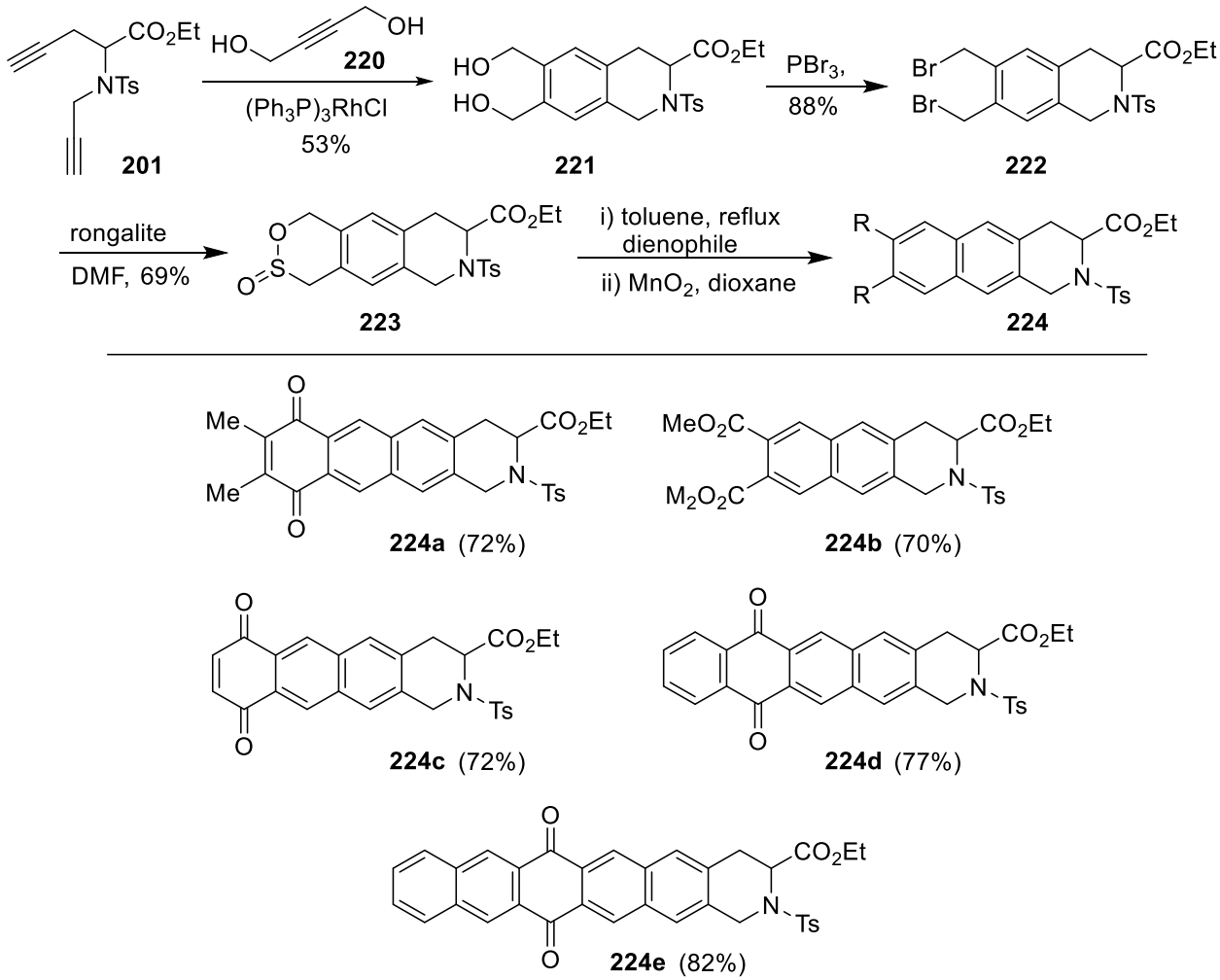
]



Scheme 35

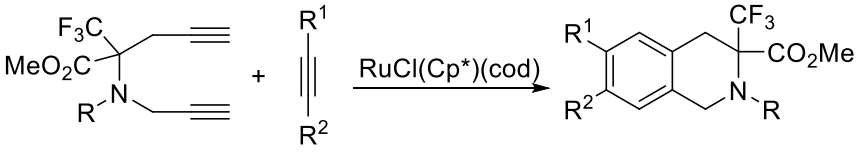
Kotha and co-workers[77] have reported a synergistic combination of a [2+2+2] and [4+2] cycloaddition reactions for the synthesis of several novel Tic derivatives. In this connection, the diol building block **221** has been prepared by the [2+2+2] cyclotrimerization[78] using alkyne derivative **201** and 2-butyn-1,4-diol **220**. The diol **221** was then treated with PBr_3 to generate the

corresponding dibromo derivative **222** (83%). The dibromo derivative was treated with rongalite[79] in the presence of tetrabutylammonium bisulphate (TBAB) in dry DMF to obtain the sultine derivative **223** as a mixture of diastereomers. It was heated at 85–90 °C in the presence of an excess amount of dienophiles to deliver the DA adducts. A slight contamination of the aromatized DA adducts was observed and therefore DA adducts were directly subjected to aromatization using activated MnO_2 to provide the Tic derivatives **224a-e** (Scheme 36).

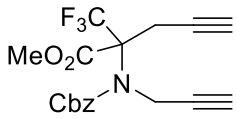
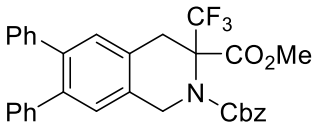
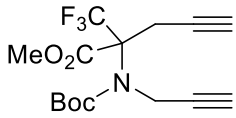
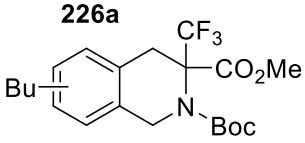
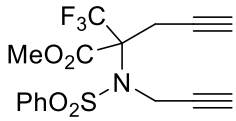
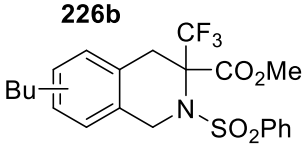
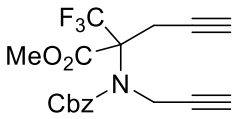
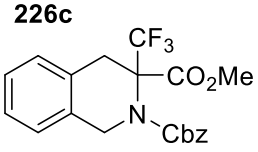


Scheme 36

In another example, ruthenium catalyzed [e.g. RuCl(Cp*)(cod)] [2+2+2] cyclotrimerization of 1,7-aza-diynes **225** containing terminal alkynes with a variety of monoynes **202** provided an easy access to trifluoromethyl substituted Tic derivatives **226** in good yields (Scheme 37).[80] Interestingly, the authors have also reported the cyclotrimerization of few diynes by using Grubbs catalyst.[80]



225 202 226

Diyne	Alkyne	Tic derivative	Yield (%)
 **225a**	 **202a**	 **226a**	25
 **225b**	 **202b**	 **226b**	89
 **225c**	 **202b**	 **226c**	82
 **225d**	 **202c**	 **226d**	86

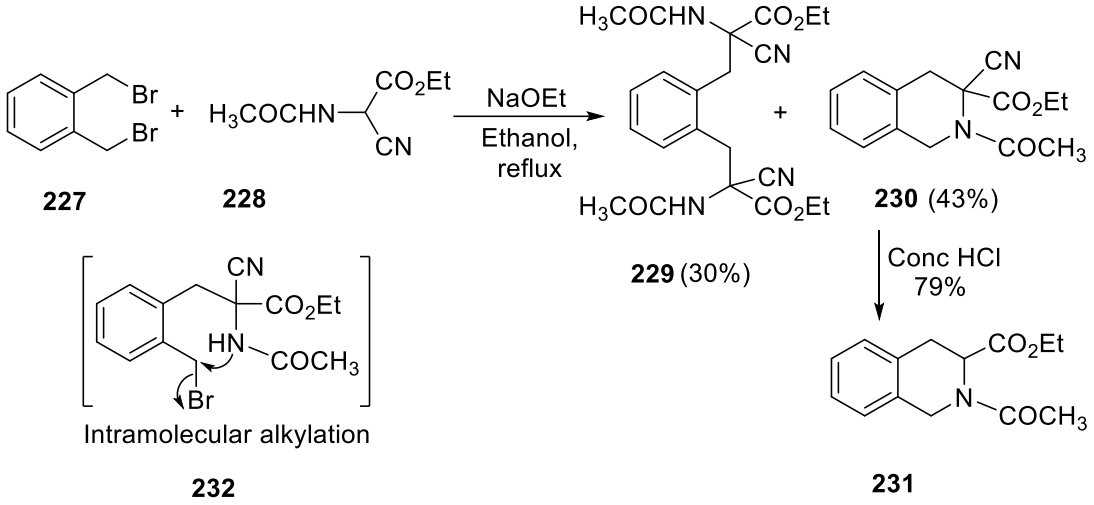
Scheme 37

2.4. Alkylation approach

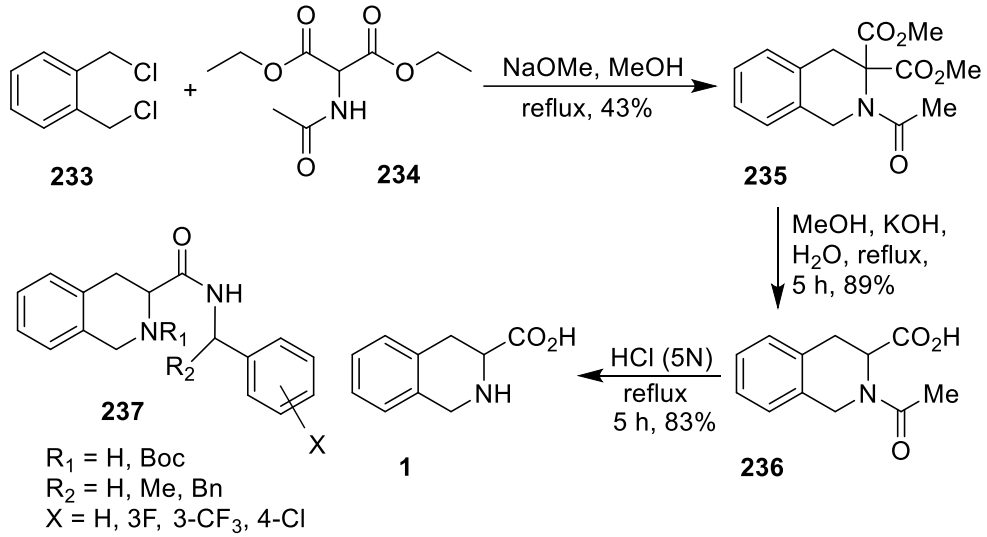
The condensation of *o*-xylene dibromide **227** with sodium salt of ethyl 2-acetamido-2-cyanoacetate **228** in anhydrous alcohol furnished ethyl 2-acetyl-3-cyano-1,2,3,4-tetrahydro-3-isoquinoline carboxylate **230** (43%) along with the bis-substituted product **229** (30%) The formation of Tic derivative **230** has been rationalized on the basis of an intramolecular alkylation of proposed intermediate **232**. The acid hydrolysis of Tic derivative **230** delivered the desired 1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid derivative **231** in 79% yield (Scheme 38).[81]

Crider and co-workers[82] have reported the synthesis of Tic **1** *via* a base catalyzed reaction. In this regard, α,α-dichloro-*o*-xylene **233** was treated with diethyl 2-acetamidomalonate (DEAM) **234** in the presence of sodium methoxide in refluxing methanol to deliver the diester **235** (435) The reaction was found to occur with complete trans-esterification. The diester **235** was then subjected to saponification followed by decarboxylation gave the *N*-substituted Tic **236** (89%).

The Tic derivative **1** was obtained in 83% yield by refluxing **236** for 5 h in hydrochloric acid (6 N aq.) and it was modified further to prepare carboxamide analogs **237** exhibiting potential anti-epilectic activity (Scheme 39).

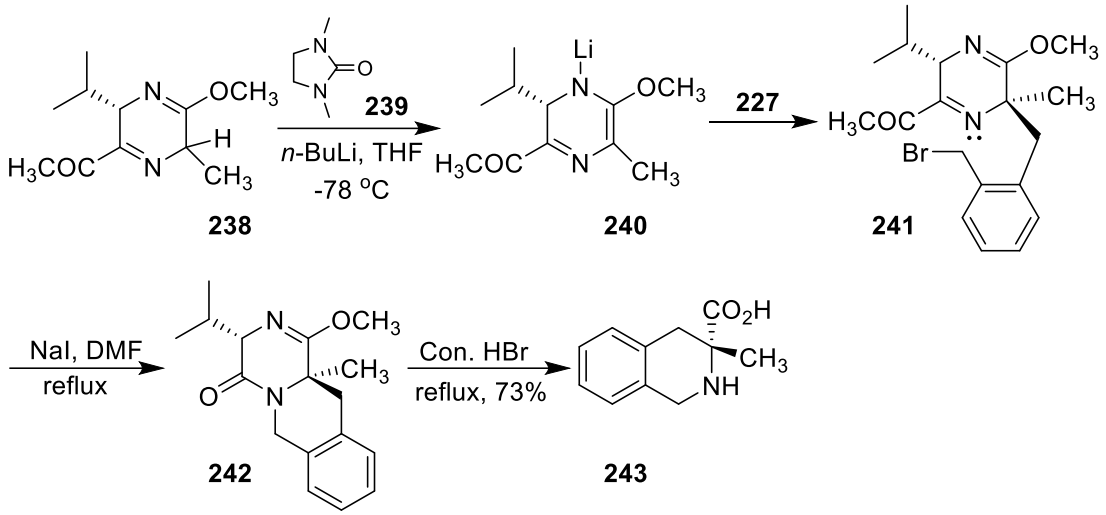


Scheme 38 JACS 56



Scheme 39

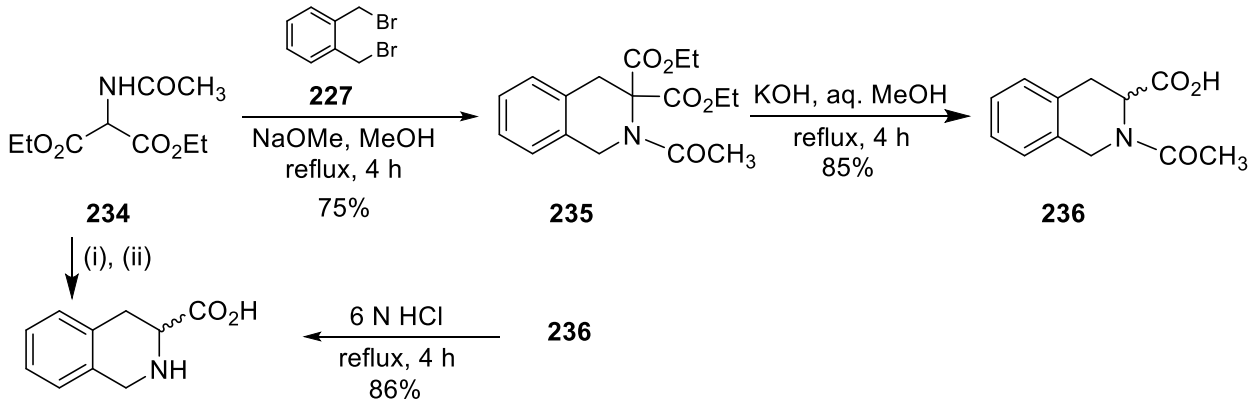
Schöllkopf and co-workers[83] have tactically utilized the commercially available chiral *bis*-lactim ether **238** to construct asymmetric Tic derivative **243**. To start with, lithilated chiral auxiliary **238** was treated with *o*-xylene dibromide **227** to furnish the bromo derivative **241.** Later, treatment with sodium iodide in DMF gave the cyclized product **242.** Hydrolysis of **242** with hydrobromic acid delivered an optically active methyl substituted Tic derivative **243** in 73% yield (Scheme 40).



Scheme 40

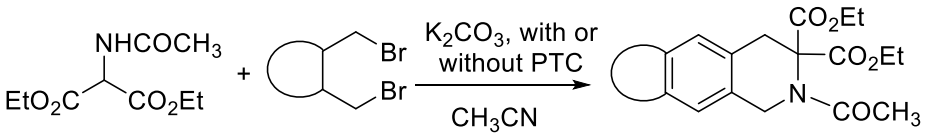
In another event, DEAM **234** has been employed as a glycine equivalent and it was treated with *o*-xylene dibromide **227** in the presence of a base to generate the Tic precursor **235** (75%).[84] It was refluxed with KOH to furnish the racemic Tic derivative **236** (85%) *via* saponification followed by decarboxylation. The amide **236** was refluxed with hydrochloric acid and then neutralized with aqueous ammonia to deliver the racemic Tic **1** (86%). Tic **1** was also obtained in one-pot reaction using **234** and *o*-xylene dibromide **227** in 65% yield (Scheme 41).

Recently, Kotha and co-workers[85a] have prepared a library of diversely functionalized Tic derivatives *via* base-catalyzed alkylation of **234**. A variety of dibromides **244a–d** were reacted with **234** in the presence of potassium carbonate and phase-transfer catalyst (PTC) such as TBAB to deliver the diversely functionalized Tic derivatives **245a-d** in 41-75% yield (Scheme 42). When the dichloro derivative **244e** was used as a precursor, the non-Tic derivative **245e** was obtained.[85b]

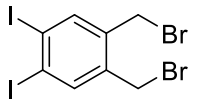
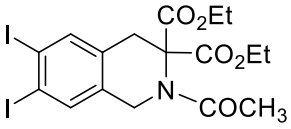
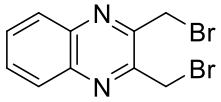
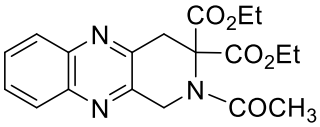
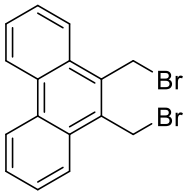
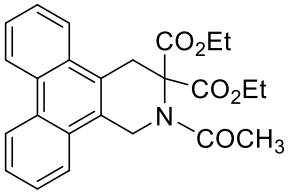
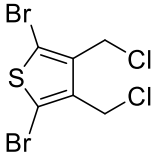
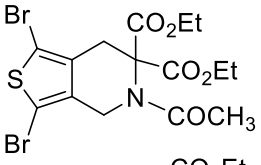
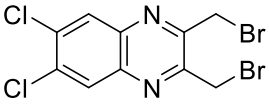
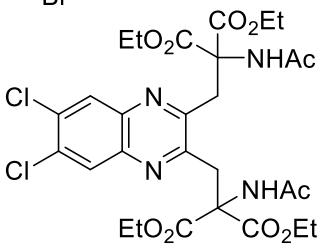


(i) **227**, NaOMe, MeOH, reflux, 4 h, (ii) 6 N HCl, reflux, 4 h, 65%.

Scheme 41



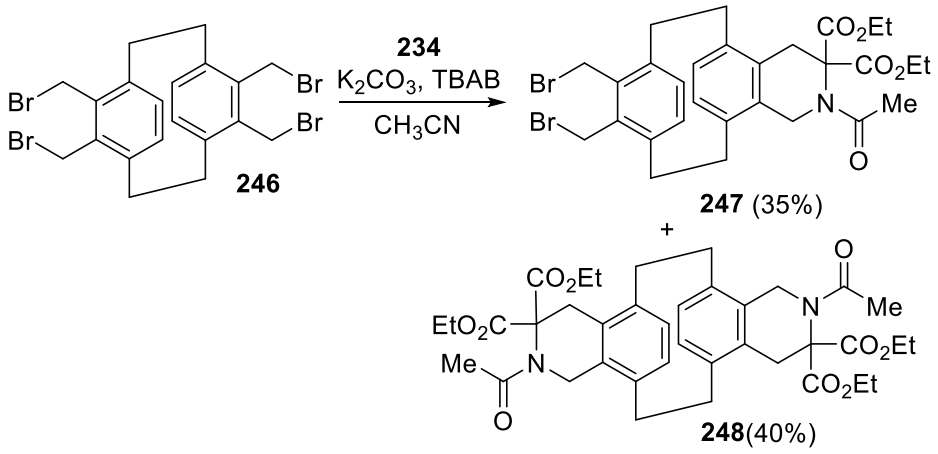
234 244 245

Dibromide substrate		Tic derivative/ Yield (%)	
	**244a**		**245a** (41)
	**244b**		**245b** (75)
	**244c**		**245c** (45)
	**244d**		**245d** (56)
	**244e**		**245e**[88b] (72)

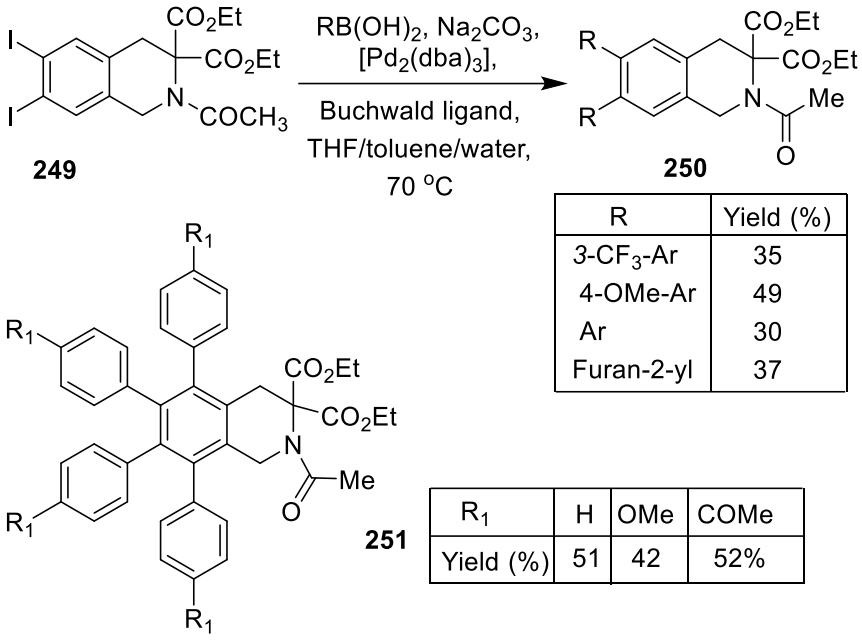
Scheme 42

The methodology has been extended towards the preparation of cyclophane-based Tic derivatives **247** and **248** which are likely to find valuable applications in bioorganic chemistry (Scheme 43)

Further, the Suzuki–Miyaura (SM) cross-coupling reaction has been tactically used to construct carbon-rich Tic derivatives (Scheme 44).[85a] When **249** was subjected to SM cross-coupling reaction with aryl boronic acids using Na_2CO_3 in the presence of the catalyst $[Pd_2(dba)_3]$ and the Buchwald ligand, highly substituted Tic derivatives **250** were generated in a moderate yield. Same strategy has been used for the preparation of tetra-substituted Tic derivatives **251**.[41a]



Scheme 43

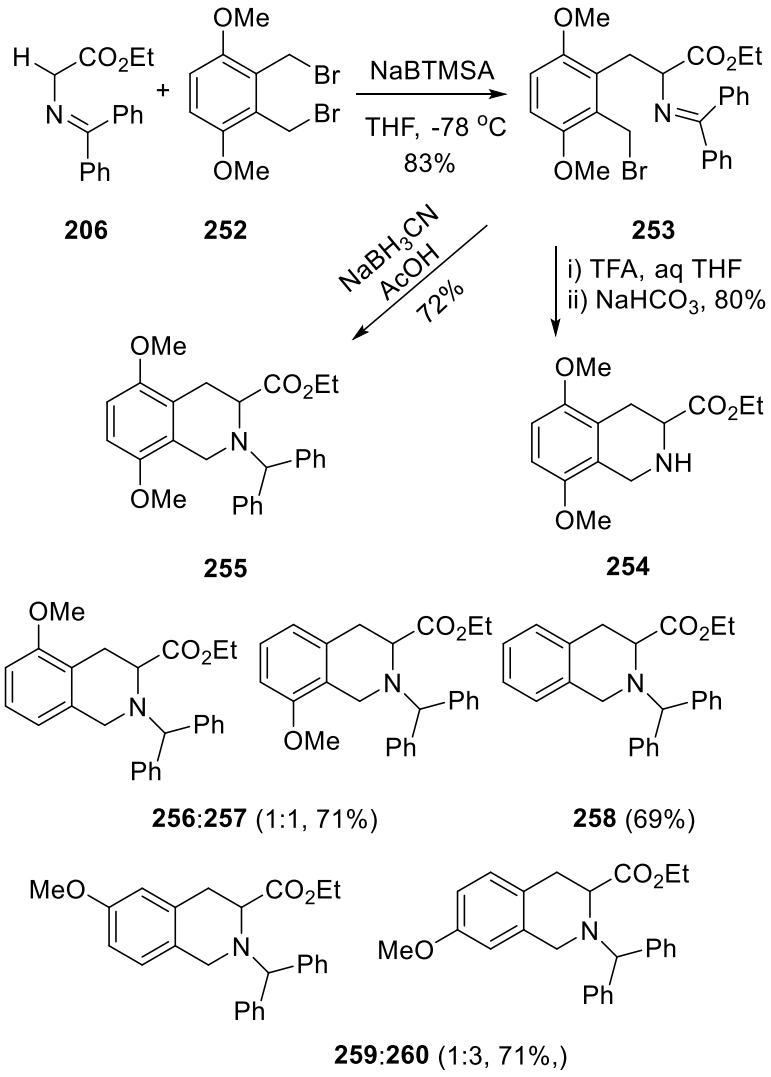


R	Yield (%)
3-CF_3-Ar	35
4-OMe-Ar	49
Ar	30
Furan-2-yl	37

R_1	H	OMe	COMe
Yield (%)	51	42	52%

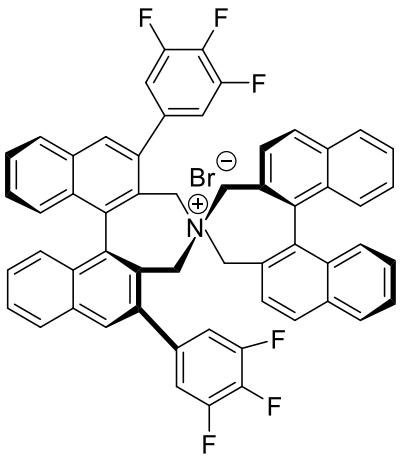
Scheme 444052

Mash and co-workers[86] have reported a variety of Tic derivatives **254-260** *via* a step-wise *C*-alkylation and *N*-alkylation approach using the Schiff base **206**. To start with, the Schiff base **206** was treated with dibromide **252** in the presence of sodium bis(trimethylsilyl)amide (NaBTMSA) in THF to deliver the partially alkylated Schiff base **253**, which on treatment with trifluoroacetic acid in aqueous THF and subsequent reaction with sodium bicarbonate furnished the Tic derivative **254** (80%). However, when the imine was reacted with sodium cyanoborohydride, *N*-(diphenyl)methyl Tic derivative **255** was isolated in 72% yield (Scheme 45). This strategy has been extended to the Tic derivatives **256-260**.



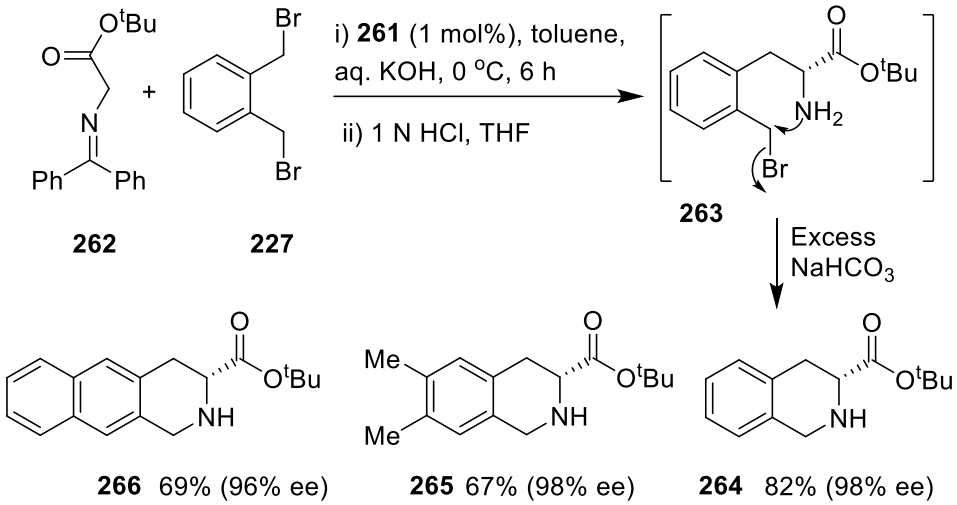
Scheme 45

Maruaka and co-workers[87] have realized the asymmetric synthesis of Tic derivatives **264-266** using C2-symmetric chiral quaternary bromide **261** (Fig. 5) as a PTC. In this regard, Schiff base **262** was subjected to alkylation with α,α′-dibromo-*o*-xylene **227** using **261** as PTC. Later, hydrolysis with 1 N HCl was anticipated to generate amine **263** *in situ* which underwent intramolecular cyclization in the presence of an excess amount of sodium bicarbonate to furnish the desired Tic derivative **264** (82%). This protocol has been extended to other Tic derivatives **265** and **266** containing different substituents in the aromatic ring in good yields (Scheme 46).



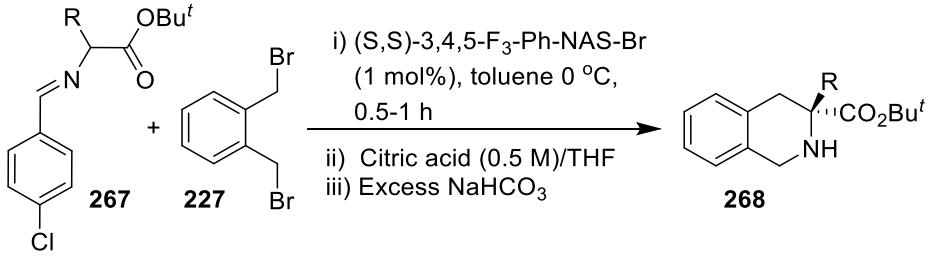
261

Fig. 5 C_2-symmetric chiral phase transfer catalyst



Scheme 46

Enantioselective alkylation of variedly substituted *p*-chloroaldehyde Schiff base **267** using the dibromide **227** in the presence of chiral PTC **261** followed by hydrolysis and sodium bicarbonate induced cyclization delivered various Tic derivatives **268** in good yields (Scheme 47).

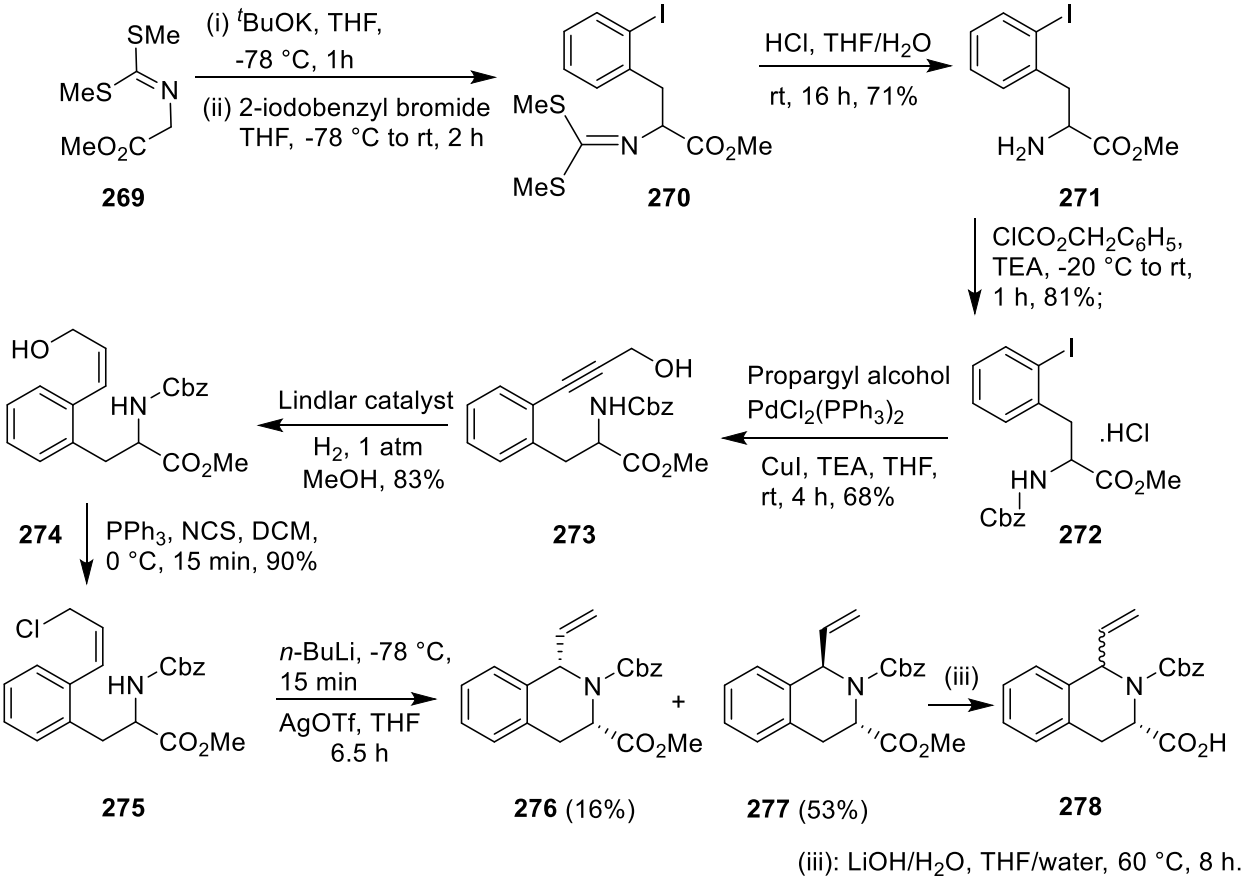


R	Yield (%)	ee (%)
Me	64	88
^{t}Bu	56	84
Bn	60	84

Scheme 47

Eustache and co-workers[88] have reported a simple method for the synthesis of Tic derivatives **276** and **277** involving Ag(I)-catalyzed intramolecular *N*-alkylation (Scheme 48). The

synthetic sequence begin with the alkylation of the enolate derived from *N*-[bis(methylthio)methylene]glycine methyl ester **269** by 2-iodobenzyl bromide to give 2-iodophenylalanine derivative **270** which on treatement with hydrochloric acid gave **271** (71%) which upon *N*-protection using benzyl chloroformate provided **272** (71%). Later, Sonogashira reaction of **272** with propargyl alcohol produced the alkyne derivative **273** which on treatment with Lindlar catalyst gave the *cis*-allylic alcohol **274** (90%). Subsequent treatment of **274** with triphenylphosphine and *N*-chlorosuccinimide delivered the chloro derivative **275 (**90%) which on deprotonation at low temperature by *n*-BuLi followed by the treatment with an excess amount of freshly recrystallized AgOTf delivered an isomeric mixture of Tic derivatives. Later, chromatographic separation gave **276** and **277** in good yields. The hydrolysis of these isomers gave the quantitative yield of the Tic derivative **278**.

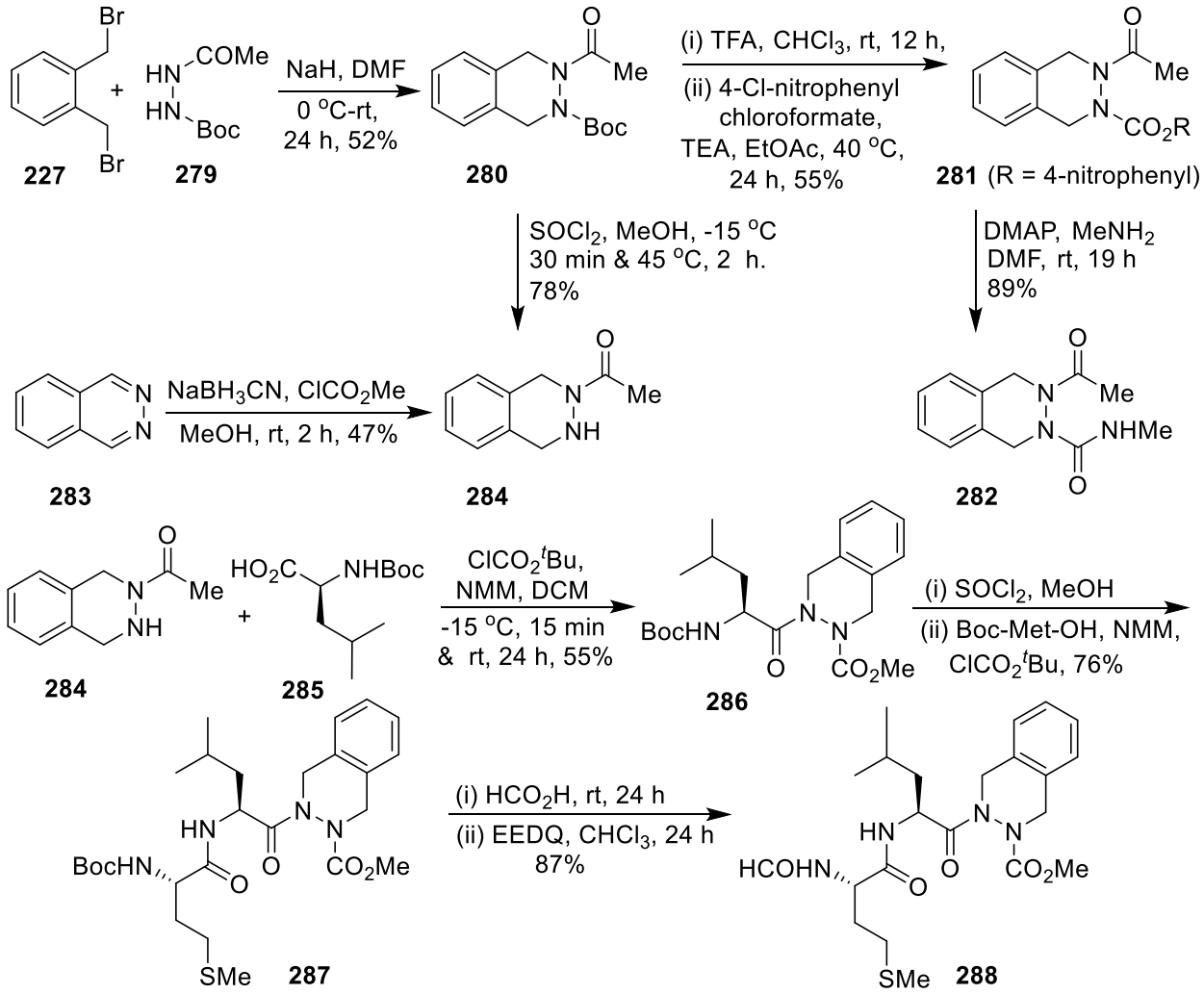


269 **270** **271** **272** **273** **274** **275** **276** (16%) **277** (53%) **278**

Scheme 48

Lucente and co-workers[89] have synthesized aza-Tic derivatives as a constrained analog of Tic (Scheme 49) in which α,α'-dibromoxylene **227** was reacted with the protected hydrazine **279** in the presence of NaH to generate the phthalazine derivative **280**, which on deprotection using

TFA followed by the acylation using 4-nitrophenylchloroformate gave the ester **281** (55%). The treatment of **281** with methylamine in the presence of 4-(dimethylamino)pyridine (DMAP) afforded the aza-Tic derivative **282** (89%). Zecchini and co-workers[90] have extended the synthetic sequence for the preparation of α-aza-Tic containing peptide. In this connection, phthalazine derivative **280** was deprotected using thionyl chloride in MeOH leading to the selective formation of **284** (78%).



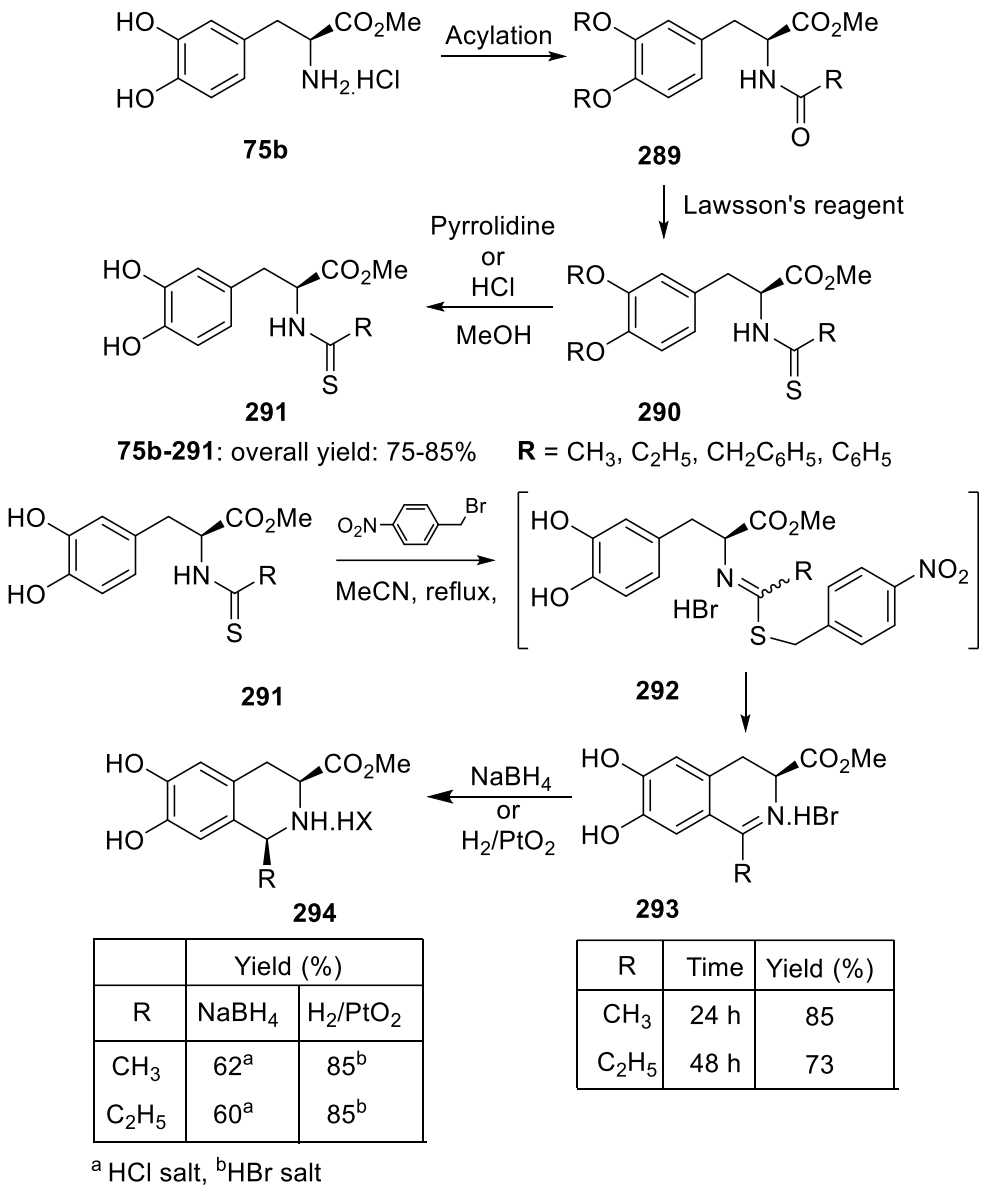
Scheme 49

Also, the same compound has been prepared in 47% yield by treatment of commercially available phthalazine with sodium cyanoborohydride and methyl chloroformate. The compound **284** was condensed with (*tert*-butoxycarbonyl)-L-leucine **285** using mixed anhydride method in the presence of isobutyl chloroformate and *N*-methylmorpholine (NMM) in DCM to deliver the azapeptide **286** (55%). The deprotection of **286** with thionyl chloride followed by the condensation with (*tert*-butoxycarbonyl)-L-methionine (Boc-Met-OH) afforded boc azatripeptide **287** (76%),

which upon treatment with formic acid followed by 2-ethoxy-l,2-dihydro-1-quinolinecarboxylate (EEDQ) delivered the formyl azapeptide **288 (**87%). It is important to mention that the aza-Tic moiety when incorporated into a chemotactic *N*-formylpeptide, the biological activity of resulting peptide was found to be profoundly influenced.

2.5. Miscellaneous methods

Ishida and co-workers[91] revealed that cyclization of *N*-alkylthiocarbonyl derivatives **291** followed by reduction can generate Tic derivatives **294** in good yields (Scheme 50). Acylation of dopa **75b** and subsequent thionation with the Lawsson's reagent furnished the thioamide **290** which upon treatment with pyrrolidine or hydrochloric acid in methanol generated *N*-alkylthiocarbonyl derivatives **291** in overall 75–85% yield. The cyclization of **291** using 4-nitroyl bromide in refluxing acetonitrile gave 1,3-disubstituted 3,4-dihydroisoquinolines **293** in excellent yields *via* the formation of thioiminium salt **292**. The stereospecific reduction of **293** with sodium borohydride furnished the desired Tic derivatives **294** as hydrochloride salt in good yields. Alternatively, reduction of dihydroisoquinolines **293** was accomplished by catalytic hydrogenation in methanol at rt to deliver Tic derivatives **294** as hydrobromide salt in a better yield as compared with sodium borohydride reduction route.



	Yield (%)	
R	$NaBH_4$	H_2/PtO_2
CH_3	62[a]	85[b]
C_2H_5	60[a]	85[b]

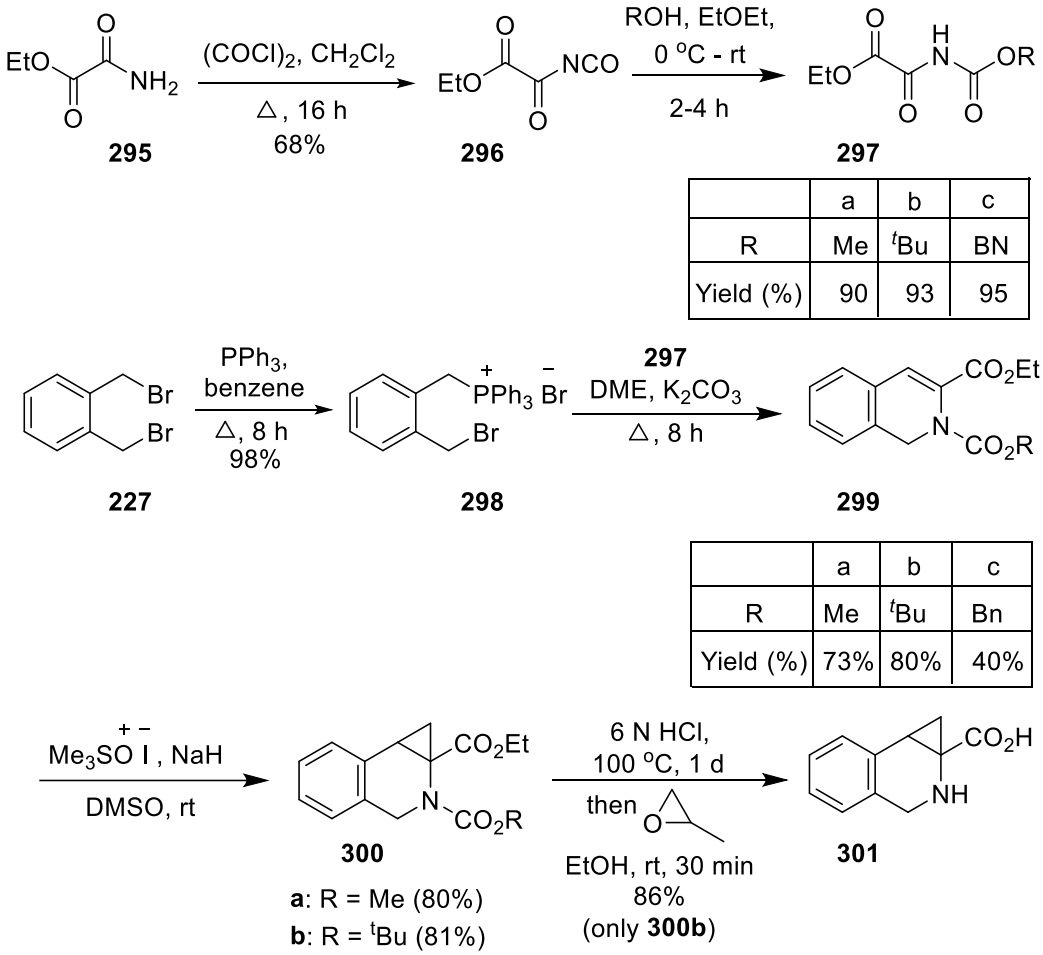
[a] HCl salt, [b]HBr salt

R	Time	Yield (%)
CH_3	24 h	85
C_2H_5	48 h	73

Scheme 50

Klimpe and co-workers[92] have demonstrated the synthesis of 3,4-methano-Tic **300** and its derivatives as desirable candidates to design conformationally constrained peptides. When ethyloxamate **295** was refluxed with an excess amount of oxalyl chloride, ethyl 2-isocyanato-2-oxoacetate **296** (68%). Treatment of **296** with various anhydrous alcohols furnished 2-alkoxycarbonyl oxamates **297a-c** in excellent yields (90-95%). Further, *o*-xylene dibromide **227** was treated with an excess amount of triphenylphosphine under reflux conditions for 8 h to isolate the phosphonium salt **298** (98%). The cyclocondensation of phosphonium salt **298** with alkoxycarbonyl-oxamates **297a-c** in 1,2-dimethoxy ethane delivered ethyl dihydroisoquinoline derivatives **299a-c**. Later, to incorporate further constraint in the Tic moiety, derivatives **299a-b** were subjected to cyclopropanation using trimethylsulfoxonium iodide with NaH in DMSO to

provide Tic derivatives **300a-b** in good yields (Scheme 51). The compound **300b** was subjected to acid hydrolysis to yield the hydrochloride salt which upon treatment with propylene oxide in ethanol gave a highly constrained 3,4-methano-Tic derivative **301**.

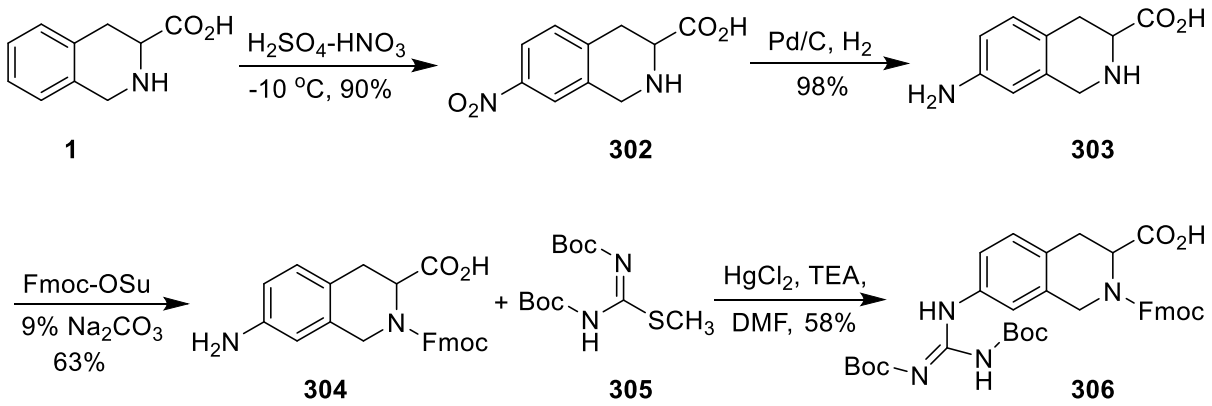


	a	b	c
R	Me	^{t}Bu	BN
Yield (%)	90	93	95

	a	b	c
R	Me	^{t}Bu	Bn
Yield (%)	73%	80%	40%

Scheme 51

Santagada and co-workers[93] have reported the synthesis of Tic derivative containing a basic guanidine group on the aromatic ring. Interestingly, *N*-Fmoc-*N*, *N*-bis-boc-7-guanyl-Tic-OH (GTIC) **306** has been considered as a combination of basic properties of arginine and aromatic features of Phe. To realize the synthesis of **306**, the Tic **1** was nitrated using fuming nitric acid and con. sulfuric acid at 10 °C to deliver 7-nitro derivative **302** (90%). Reduction of **302** using H_2-Pd/C in methanol delivered the 7-amino-Tic derivative **303** (98%) which was reacted with Fmoc-OSu in aqueous sodium carbonate to generate *N*-Fmoc derivative **304** (63%). Later, the reaction of **304** with *N*,*N*-bis-boc-*S*-methyl-isothiourea **305**, mercuric chloride and triethylamine in DMF afforded GTIC **306** in 58% yield (Scheme 52).

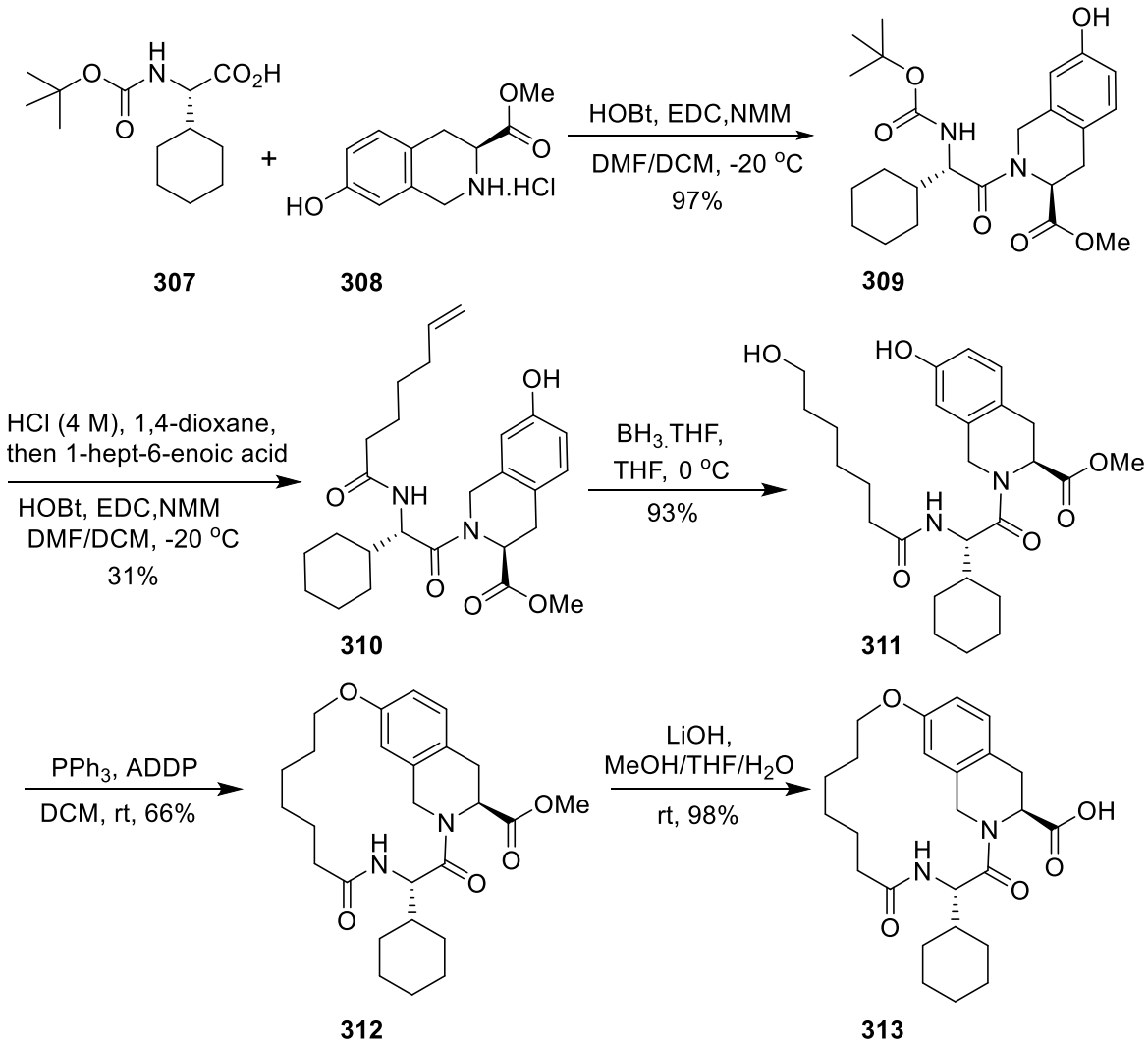


Scheme 52

The hepatitis C virus (HCV) infection has been a cause of liver cirrhosis and hepatocellular carcinoma. Studies have revealed that the NS3 protease is essential for HCV replication and rigorous research has been directed towards the synthesis of these peptide inhibitors. To this end, Chen and co-workers[14] have reported the synthesis of highly potent Tic-based macrocyclic HCV NS3 protease inhibitors. In this regard, Boc protected cyclohexylglycine **307** has been coupled with 7-hydroxy Tic derivative **308** in the presence of HOBt, NMM and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) to prepare dipeptide **309** in 97% yield. Later, it was deprotected and the resulting hydrochloride salt was treated with 1-hept-6-enoic acid to deliver the compound **310**. The primary alcohol **311** (93%) has been obtained by hydroboration/oxidation of alkene **310**. The intramolecular Mitsunobu reaction between phenol and primary alcohol moieties using triphenylphosphine and 1,1'-(azodicarbonyl) dipiperidine (ADDP) furnished 16-membered macrocyclic ester **312** (66%). Hydrolysis of **312** with lithium hydroxide delivered the macrocyclic Tic derivative **313** in 98% yield (Scheme 53).

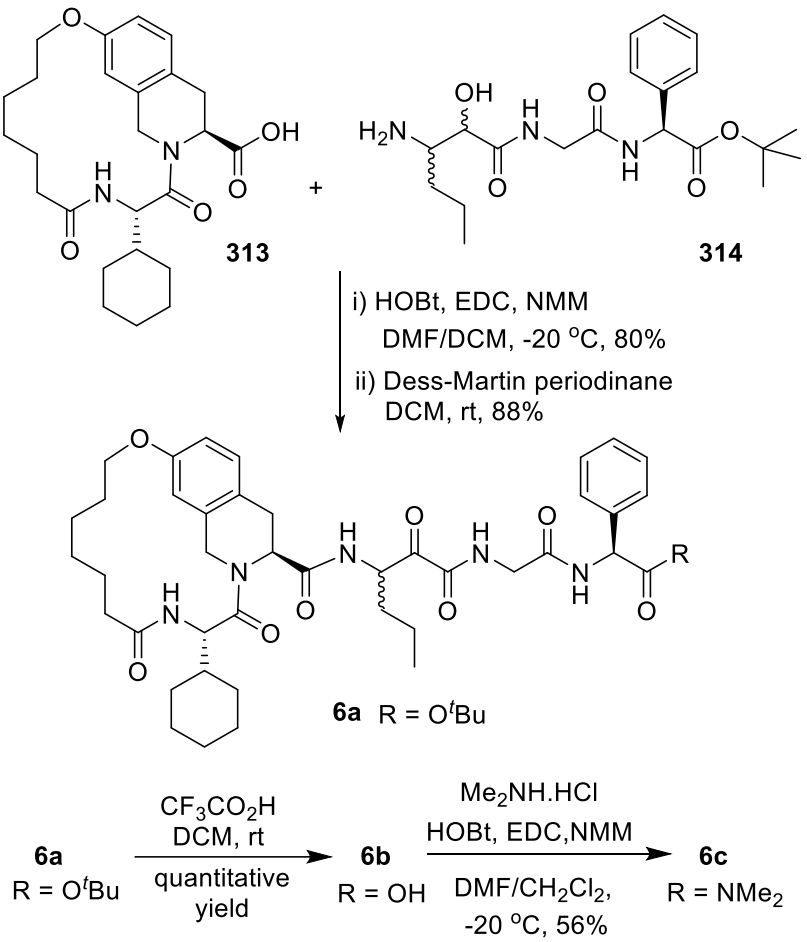
65 The coupling of macrocyclic Tic derivative **313** with tripeptide **314** followed by oxidation with Dess-Martin reagent gave the pentapeptide α-ketoamide **6a**. Deprotection of *tert*-butyl ester present in **6a** by the treatment with trifluoroacetic acid delivered carboxylic acid **6b** which upon coupling with dimethyl amine hydrochloride gave the amide **6c** (56%). The pentapeptide and its amide analog were found to be good HCV inhibitors (*Ki** = 0.021 μM) (Scheme 54).

, 5469-5475



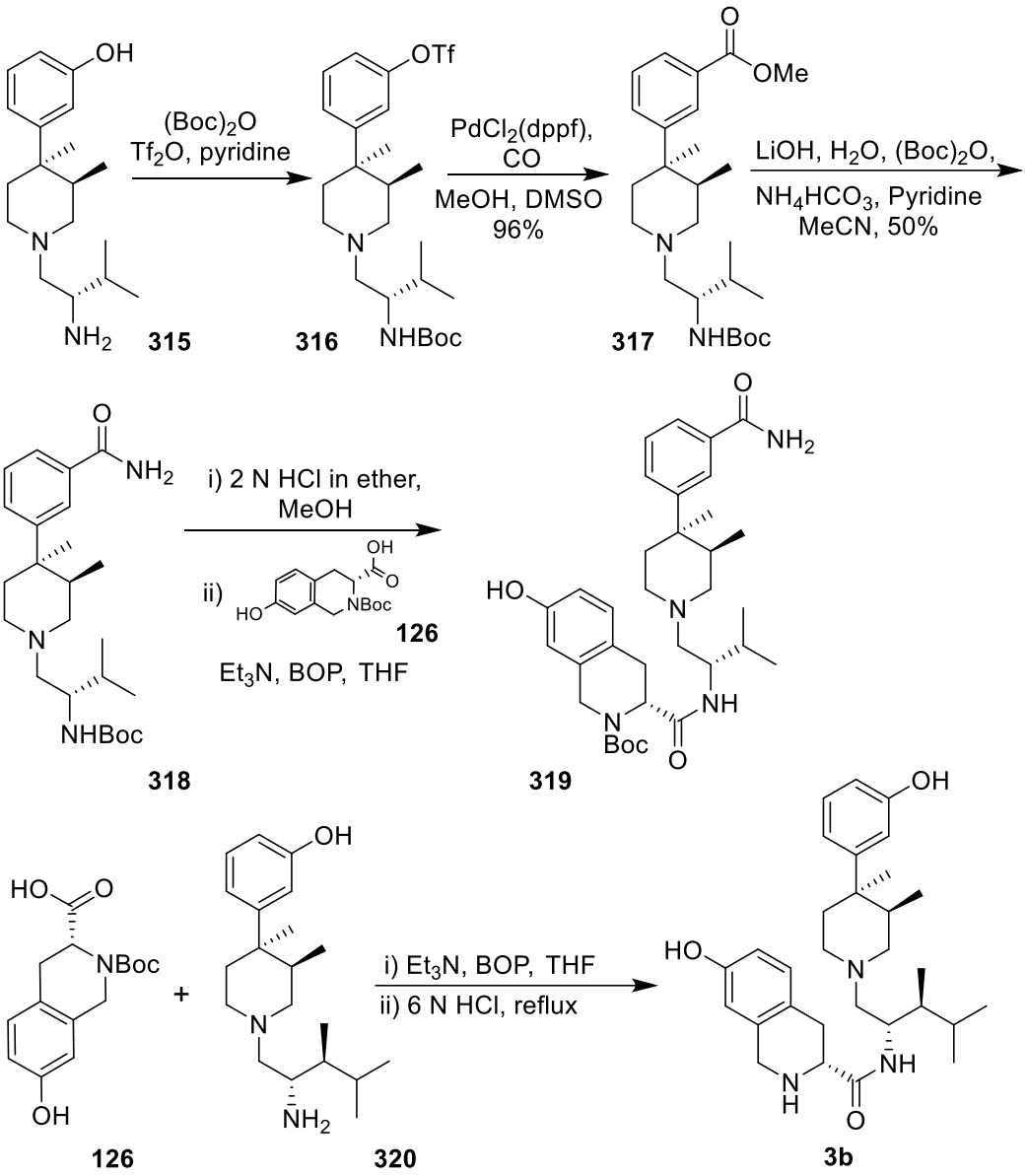
307 **308** **309** **310** **311** **312** **313**

Scheme 53



Scheme 54

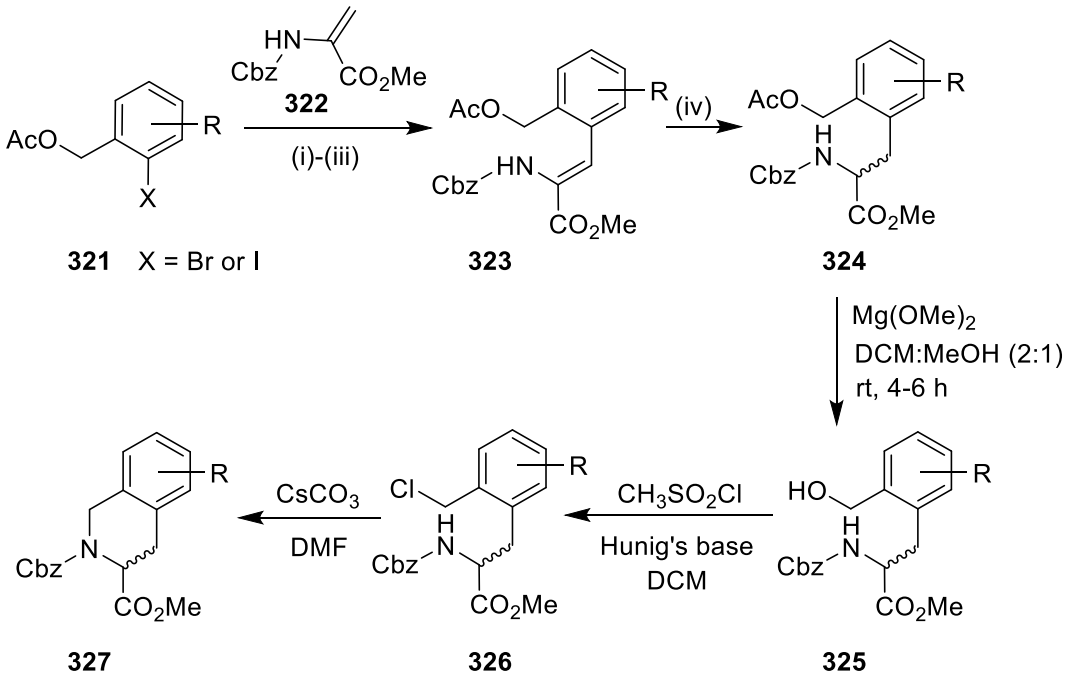
Carroll and co-workers[7] have subjected the compound **315** to *N*-protection using Boc anhydride and then the phenolic moiety was converted to the triflate **316** using triflic anhydride. Treatment of the triflate **316** with carbon monoxide in the presence of catalytic amount of $PdCl_2$(dppf) delivered the corresponding methyl ester **317** (96%). Ester hydrolysis of **317** using lithium hydroxide and subsequent amide formation by treatment with ammonium hydrogen carbonate and di-*tert*-butyl pyrocarbonate furnished **318** in 50% yield. Deprotection of **318** using HCl (2N) in ether followed by coupling with Tic derivative **126** in THF in the presence of benzotriazole-1-yloxy-tris(di-methylamino)phosphonium hexafluorophosphate (BOP) afforded functionalized Tic based carboxamido derivative **319**. Another carboxamide derivative **3b** prepared using **126** and **320** was found to be highly potent and selective *κ*-opioid receptor antagonist (Scheme 55).



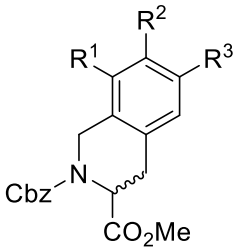
Scheme 55

Chaturvedula and co-workers[94] have demonstrated a useful approach to the synthesis of constrained Tic derivatives **327** *via* a palladium-catalyzed Heck reaction followed by rhodium (I) catalyzed asymmetric hydrogenation (Scheme 56). Various aryl halides **321** were coupled with dehydroamino acid **322** under different set of Heck reaction conditions, to generate (Z)-alkyl substituted enamines **323**. The coupled products were isolated as a single isomer with (Z)-stereochemistry in overall 38-96% yield. These enamines **323** were subjected to hydrogenation either with (+)-1,2-bis((2S,5S)diethylphospholano)benzene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate [i.e (*S*,*S*)-Et-DUPHOS-Rh][95] or its (*R*,*R*)-enantiomer using DCM or DCM-MeOH (1:1) as solvent. The reduced chiral products **324** were isolated in good chemical and optical yield (>95%, >99% ee). Further, hydrolysis using K_2CO_3 in MeOH or NaOMe gave the

corresponding alcohol **325** in good yields, but the optical yield was low (80-90% ee) and it was increased (>98% ee) when magnesium methoxide was used for hydrolysis. The treatment of these alcohols **325** with an excess amount of methanesulfonyl chloride and DIEA in DCM resulted in chlorinated compounds **326**. Later, cyclization using cesium carbonate in DMF gave Tic derivatives **327** in high optical purity.



(i): Bu_4NCl, $Pd(OAc)_2$, Et_3N, THF, 70° C, 4.5 h, (ii): *N,N*-dicyclohexylamine, bis(tri-butylphosphine)palladium (0) in doxane, 100 °C, 12 h, (iii): Bu_4NCl, $Pd(OAc)_2$, $NaHCO_3$, THF, 70° C, 6 h, (iv): (*S,S*)-Et-DUPHOS-Rh) or its (*R,R*)-enentiomer, DCM or DCM-MeOH (1:1).

Product	% Yield (ee)
 R^1, R^3 = H, R^2 = OBn, (S)-isomer	93 (97)
R^1 = H, R^2 = NHBoc, R^3 = CH_3, (R-isomer)	98 (98)
R^1 = CH_3, R^2 = NHBoc, R^3 = H (S-isomer)	98 (99)
R^1, R^3 = H, R^2 = CH_3, (S)-isomer	78[e] (not determined)
R^1 = H, R^2, R^3 = F, , (R)-isomer	65[f] (91)
R^1, R^3 = H, R^2 = NO_2 (S)-isomer	84[e] (88)
R^1, R^3 = H, R^2 = Br (S)-isomer	88[e] (not determined)

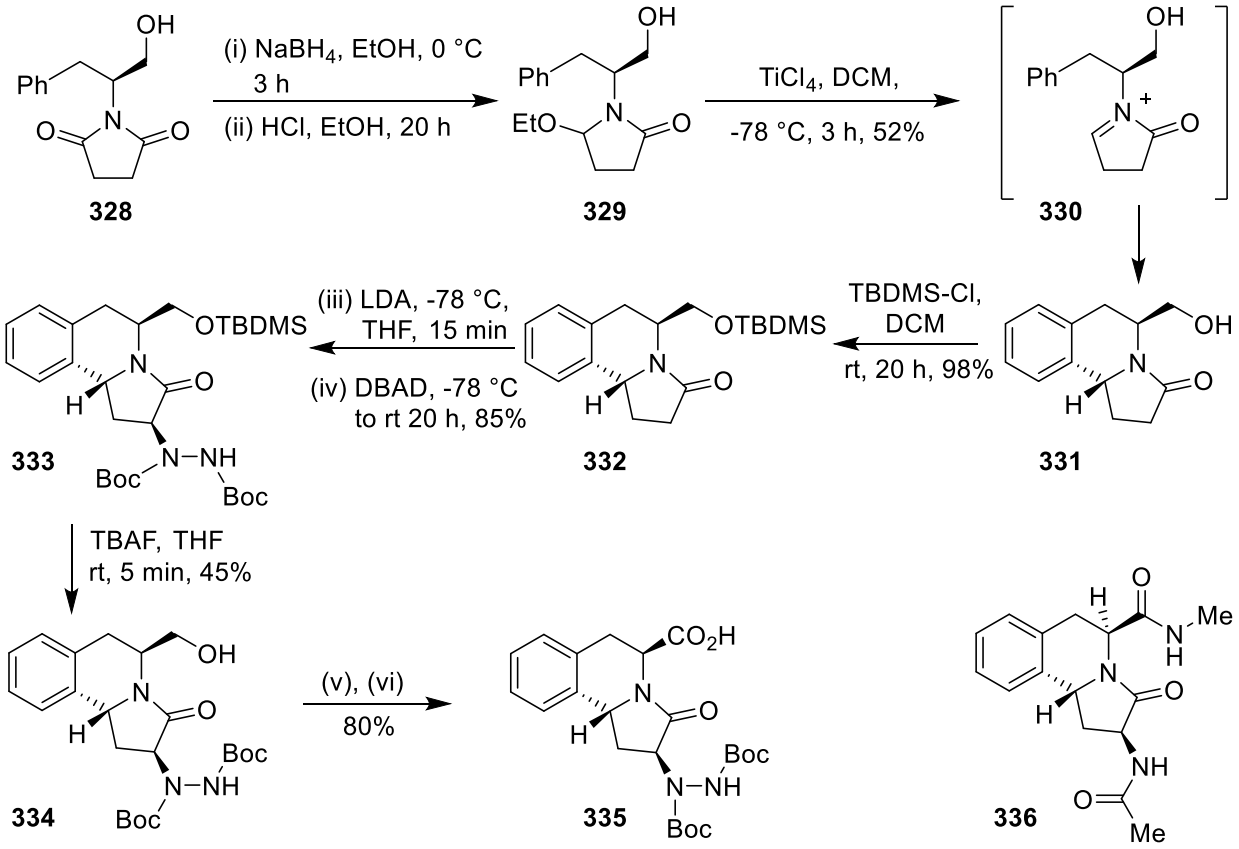
[e]Combined yield for two steps, (chloride formation and cyclization), [f]Combined yield for three steps (hydrolysis, chloride formation and cyclization)

Scheme 56

Allin and co-workers[96] have reported the synthesis of pyrroloisoquinoline derivative **336** containing Tic unit *via* a stereoselective *N*-acylation cyclization methodology coupled with an enolate amination protocol (Scheme 57). To this end, the imide **328** was subjected to reduction using sodium borohydride in ethanol followed by treatment with HCl to provide the corresponding ethoxylactum **329**. When it was treated with $TiCl_4$, the cyclized product **331** (52%) was observed. The cyclization proceeds *via* the *N*-acyliminium ion intermediate **330**. The pyrroloisoquinoline derivative **331** was converted to its silyl ether **332** by treating with *tert*-butyldimethylsilyl chloride giving **332** (98%). Enolate amination was carried out on **332** by treating it with LDA. The reaction involved the generation of lithium enolate which on subsequent treatment with the electrophilic aminating reagent such as di-*tert*-butyl azodicarboxylate (DBAD) delivered the α-hydrazino ketone **333** (85%) with high distereoselectivity. It was then desilylated using tetrabutylammonium fluoride (TBAF) in THF to give **334** (45%). Primary alcohol **334** was then subjected to oxidation to generate the Tic derivative **335** through a two-step process which was used further to assemble the pyrroloisoquinoline-based derivative **336**.

3. Synthesis of higher analogs of Tic

Higher analogs of Tic with increased number of carbons in the nitrogen-containing ring system are useful to enhance their utility in medicinal chemistry. These molecules are named as Sic (2,3,4,5-tetrahydro-*1H*-3-benzazepine-2-carboxylic acid), Hic (1,2,3,4,5,6-hexahydro-3-benzazocine-2-carboxylic acid), Nic (2,3,4,5,6,7-hexahydro-1H-3-benzazonine-2-carboxylic acid) and Xic (1,2,3,4,5,6,7,8-octahydrobenzo[d]azecine-2-carboxylic acid) and involves seven-, eight-, nine- and ten-membered ring respectively (Figure 6).[97] Recently, Kotha and co-workers have reported the substituted analog of Sic **341** and Hic **342**.[85] These molecules have been synthesized using a common methodology as outlined in scheme 42.



(v) IBX, DMSO, rt, 24 h, 61%, (vi) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, MeCN, ^tBuOH, H_2O, 0 °C, 17 h.

Scheme 57

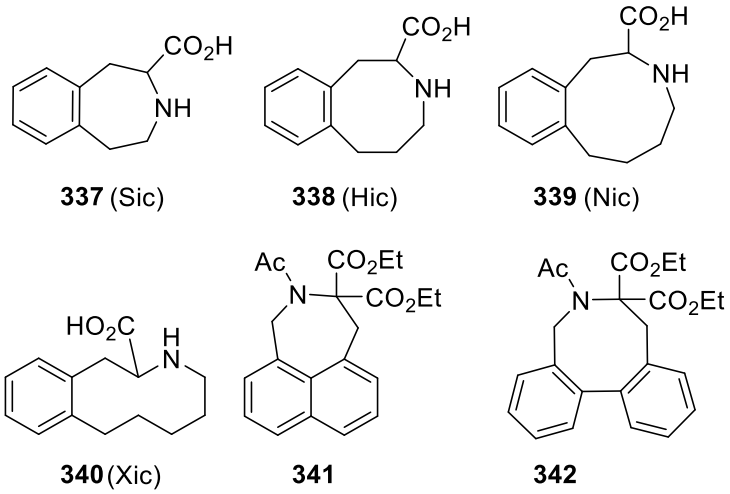
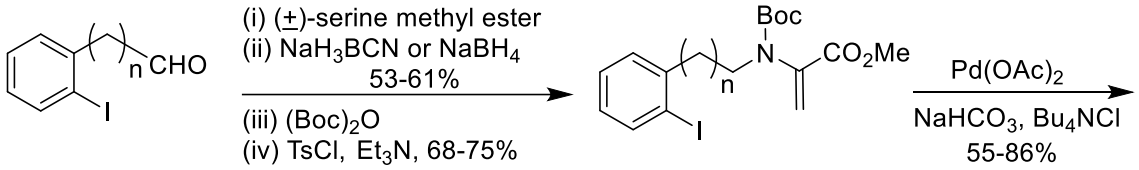


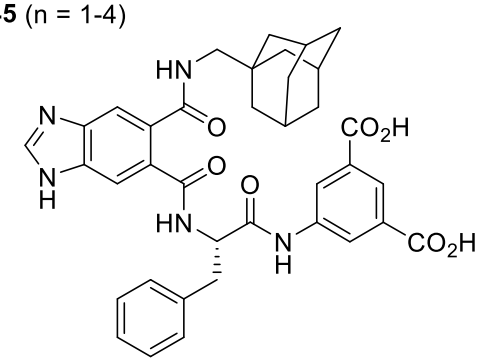
Fig. 6 Higher analogs of Tic

Gibson and co-workers[97] have reported a series of higher analogs of Tic. Their approach involves Heck reaction as a key step (Scheme 58).[98] In this context, the aldehydes **343** were subjected to reductive amination with (±)-serine methyl ester followed by *N*-protection with di-*tert*-butyl dicarbonate to form the corresponding *N*-protected derivatives in overall 53-61% yield.

These intermediates were converted to acrylate derivatives **344** suitable for Heck coupling. Cyclization of acrylates **344** using catalytic amount of palladium acetate gave the intermediates **345a-d** containing seven-, eight-, nine- and ten-membered in 55-86% yield. The cyclic intermediates **345a-d** were subjected to hydrogenation followed by hydrolysis to give the final targets **346a-d** (97-99%) as hydrochloride salts. These compounds have been used as a replacement of Phe in CCK_2 antagonists such as **348**.[97,99]

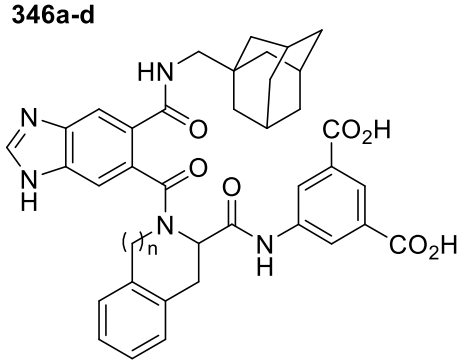


343 (n = 1-4) **344** (n = 1-4) **345** (n = 1-4) **346a-d**



347

A potent and selective CCK_2 antagonist containing Phe



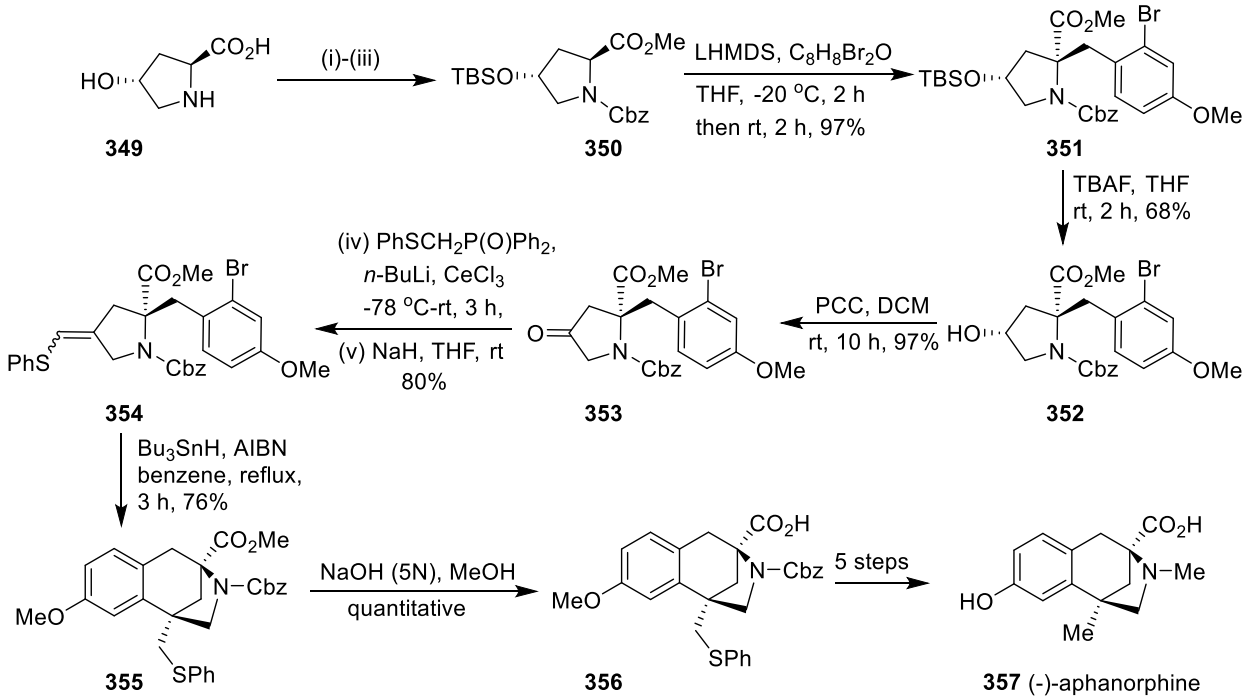
348 (n = 1-5)

CCK_2 antagonists containing Tic, Sic, Hic, Nic and Xic.

Scheme 58

Ishibashi and co-workers[100] have reported an excellent route for the synthesis of a highly constrained Sic derivative **356** using aryl radical cyclization as a key step (Scheme 59). Initially esterification of **349** has been carried out using thionyl chloride in refluxing methanol for 22 h to give the corresponding ester in 99% yield. The silylated derivative **350** (89%) has been obtained by subjecting the ester to *N*-protection using benzyl chloroformate followed by the *O*-sillylation with TBDMS (*tert*-butyldimethylsilyl) chloride in the presence of imidazole.[101] The compound **350** was then treated with lithium hexamethyldisilazide (LHMDS) in THF to generate the enolate anion which on alkylation with 2-bromo-4-methoxybenzylbromide gave alkylated derivative **351**. Further, treatment of **351** with TBAF in THF generated the alcohol **352** (68%) which on oxidation

with pyridinium chlorochromate (PCC) under mild conditions delivered the ketone **353** (97%). Next task was to generate a vinyl sulfide synthon. In this regard, the ketone **353** was subjected to Horner-Wittig reaction using *n*-BuLi and diphenyl((phenylthio)methyl)phosphine oxide[102] in the presence of $CeCl_3$ to give an adduct which on further treatment with NaH delivered the compound **354** (80%). Next, C-C bond formation involving an aryl radical cyclization was carried out to construct the constrained Sic core. In this connection, **354** was treated with tributyltin hydride in the presence of azobisisobutylonitrile to give bicyclic derivative **355** (76%) which upon alkaline hydrolysis delivered the constrained Sic derivative **356** in quantitative yield. Thus, Sic derivative prepared was further converted to an alkaloid (-)-aphanorphine **357** in five consecutive steps.

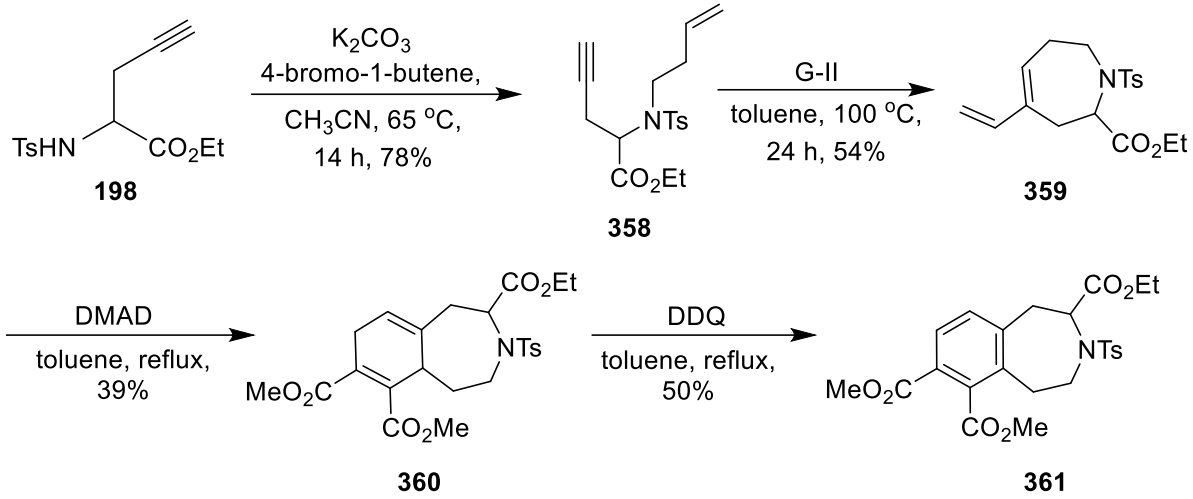


(i) $SOCl_2$, MeOH, reflux, 22 h, 99%, (ii) benzyl chloroformate, Et_3N, THF, H_2O, rt, 12 h, 99%. (iii) TBDMsCl, imidazole, DMF, rt, 7 h, 89%

Scheme 59

Recently, Kotha and co-workers have reported the synthesis of conformationally constrained Sic derivative *via* a strategic combination of ring–closing enyne metathesis (RCEM) and the Diels–Alder reaction as key steps (Scheme 60).[103] In this context, the alkyne derivative **198** was treated with 4-bromo-1-butene and K_2CO_3 to form the ester **358** in 78% yield. Initially, enyne **358** was subjected to RCEM in the presence of Grubbs first generation catalyst (G-I), under these conditions complete conversion of the starting material to the diene **359** was not observed. However, Grubbs second generation catalyst successfully delivered the desired diene **359** (54%). The diene **359** was immediately subjected to DA reaction with dimethyl acetylene dicarboxylate under toluene reflux

to furnish the compound **360** in 39% yield. Further, functionalized Sic derivative **361** (50%) was obtained by the aromatization of **360** using DDQ. The procedure is useful to incorporate various substituents in the aromatic moiety.



Scheme 60

4. Summary

This review features a variety of synthetic methods available for assembling Tic derivatives. Classical approach such as Pictet–Spengler reaction is included in this report. This methodology provides an easy access to optically pure Tic derivatives in several instances. Highly substituted Tic systems can be constructed using a combination of Pictet–Spengler reaction and Horner-Wordsworth–Emmons protocol. The variations in the reaction conditions such as use of inorganic phosphates represent the extended scope of this methodology. Bischler–Nepieralski procedure offers a limited scope towards the preparation of Tic derivatives as the process requires an additional step involving reduction of imine formed by the intramolecular electrophilic substitution reaction. Cycloaddition reactions used for the construction of Tic deliver unique examples and are attractive strategies for diversity oriented synthesis. The combination of enyne metathesis and Diels–Alder reaction offers a versatile route to assemble angularly and linearly extended aromatic components of Tic derivatives. A variety of glycine equivalents are used for the preparation of Tic derivatives via alkylation process. Diversely functionalized and also carbon-rich Tic derivatives using a combination of alkylation process involving diethylacetamidomalonate and Suzuki–Miyaura cross-coupling reaction generated a library of Tic derivatives. Construction of higher analogs of Tic is illustrated in view of their potential biological applications. Overall, the methods described here are capable of producing a library of Tic derivatives with varied steric and

electronic properties suitable for the synthesis of biologically interesting molecules. We hope that this review catalyze the use of Tic derivatives in drug design activity.

Biographies

Sambasivarao Kotha received Ph.D. from the University of Hyderabad in 1985. He joined IIT-Bombay in 1994 as an assistant professor and was promoted to professor in 2001. At present he holds Pramod Chaudhari Chair for Green Chemistry and Industrial Biotechnology. He has been a recipient of the B. M. Birla prize in Chemical Sciences, the Professor N. S. Narasimhan endowment award, the CRSI bronze medal, the Bhagyatara National Award, the Professor S. C. Bhattacharya award and Costal Chemical Research Society award for research excellence. He is a member of the editorial boards of *Indian J. Chem, Sec-B, Eur. J. Org. Chem. and J. Amino Acids.* He is an elected Fellow of the National Academy of Sciences, India, the Indian Academy of Sciences and the Royal Society of Chemistry. Recently, he has been awarded the J. C. Bose National Fellowship from DST and Professor Y. T. Thathachari Award from Bhramara Trust. His research interests include the development of new synthetic methods based on organometallics.

Deepak Deodhar was born in Mumbai in 1978. He obtained Ph.D. in July 2008 under the supervision of Prof. S. D. Samant from Institute of Chemical Technology (ICT) -Mumbai. He is having an industrial post-doctoral experience of 2.8 years at R&D center of GlaxoSmithKline Pharmaceuticals Pvt. Ltd, Thane-India, in the area of synthesis of building blocks and pharmaceutically important intermediates. In May 2010, he joined the R&D center of Watson Pharmaceuticals Pvt. Ltd. where he was responsible for the synthesis, process development, validation and technology transfer of the active pharmaceutical ingredients (APIs). In August 2013, he joined Department of Chemistry as a post-doctoral researcher at IIT-Bombay and is working with Prof. S. Kotha. His research interests are related to the synthesis of heterocycles, green chemistry and development of new methods in organic synthesis.

Priti Khedkar has obtained Ph.D. under the supervision of Prof. S. Kotha from IIT-Bombay in December 2008 and continued as a Research Associate in the same department. In August 2010, she joined the Guru Nanak Khalsa College of Arts, Science and Commerce, Matunga, Mumbai, India, as an Assistant Professor. She is a recipient of DST-Fast Track Young Scientist Award. Her research interests are related to development of new methods in organic synthesis and medicinally important compounds.

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List of Acronyms

ACAT	cholesterol acyltransferase
ACEi	angiotensin converting enzyme inhibitor
ADDP	1,1'-(azodicarbonyl)dipiperidine
ADP	adenosine diphosphate
AIBN	azobisisobutylonitrile
alloc	allyloxycarbonyl
azaTic	3,4-dihydro-2(*1H*)-phthalazinecarboxylic acid
Boc	*t*-butyloxycarbonyl
BOP	benzotriazole-1-yloxy-tris(di-methylamino)phosphonium hexafluorophosphate
BTMSA	bis(trimethylsilyl)acetylene
CCK	cholecystokinin
CF	cystic fibrosis
CFTR	cystic fibrosis trans-membrane conductance regulator
DBAD	di-tert-butyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide

DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAM	diethyl 2-acetamidomalonate
DIEA	*N*,*N*-diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EEDQ	*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
G-I	Grubbs first generation catalyst
G-II	Grubbs second generation catalyst
GS	gramicidin S
GTIC	*N*-Fmoc-*N*,*N*-bis-Boc-7-guanyl-Tic-OH
HBTU	2-(*1H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate
HCV	hepatitis C virus
HDACi	histone deacetylase inhibitor
HFA	hexafluoroacetone
Hic	1,2,3,4,5,6-hexahydro-3-benzazocine-2-carboxylic acid
HOBt	1-hydroxybenzotriazole
KHMDS	potassium bis(trimethylsilyl)amide
LHMDS	lihuim hexamethyldisilazide
NaBTMSA	sodium bis(trimethylsilyl)amide
Nic	2,3,4,5,6,7-hexahydro-*1H*-3-benzazonine-2-carboxylic acid
NMM	*N*-methylmorpholine
PAF	platelet-activating factor
PCC	pyridinium chlorochromate
Phe	phenylalanine
PPARs	peroxisome proliferators-activated receptors
PTC	phase transfer catalyst
RCEM	ring-closing enyne metathesis
Sic	2,3,4,5-tetrahydro-*1H*-3-benzazepine-2-carboxylic acid
SM	Suzuki–Miyaura
TBAB	tetrabutylammonium bisulphate
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinoxy
THF	tetrahydrofuran
THIQ	1,2,3,4-tetrahydroisoquinoline
Tic	1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
Xic	1,2,3,4,5,6,7,8-octahydrobenzo[d]azecine-2-carboxylic acid

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