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EUDISTOMIN U, ISOEUDISTOMIN U, AND RELATED INDOLE COMPOUNDS: SYNTHESIS AND BIOLOGICAL ACTIVITY

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Abstract – Eudistomin U and isoeudistomin U are important derivatives of β-carboline, tryptophan-derived metabolites. These natural products and related 2-substituted 1,2,3,4-tetrahydroeudistomins U demonstrate antibacterial, antimalarial, and anticancer activities, as well as a DNA-binding ability and strong KSP inhibition, that makes them very attractive targets for synthetic chemists. This manuscript highlights advances in the synthesis of eudistomin U, isoeudistomin U, their derivatives, and related compounds bearing an indole unit. A detailed discussion of biological activities, including structure-activity relationships, and future prospects, are also presented.

CONTENTS

1. INTRODUCTION

The great variety of marine alkaloids[1] and a broad spectrum of their biological activities make them promising starting points for the search for new medicinally relevant molecules, and drug design.[2] However, the most of marine compounds are usually isolated in a very small quantity that hinders further studies to establish their biological activity and structure-activity relationship (SAR). Therefore, the development of new synthetic approaches to these targets is a prominent challenge for organic chemists.

Eudistomins[3] constitute a class of β-carboline alkaloids which are known as tryptophan-derived metabolites possessing wide-ranging biological properties.[4] One of the most interesting members of this family is eudistomin U **1**[5] isolated, along with isoeudistomin U **2**,[6] from the Caribbean *Lissoclinum fragile* in 1994 (Figure 1). The unique structures of these natural products include a privilege indole scaffold[7] linked to β-carboline or 3,4-dihydro-β-carboline fragments. To date, a high DNA-binding ability,[8] as well as antibacterial,[9] antimalarial, and anticancer activities[10] of compounds **1**, **2**, and 2-substituted 1,2,3,4-tetrahydroeudistomins U, have been reported. Moreover, several patents[11] involving these structures have been described, that illustrates their value and importance from a commercial standpoint.

This manuscript attempts to provide an overview of advances in the synthesis of eudistomin U **1**, isoeudistomin U **2**, their derivatives, and related compounds bearing an indole unit. A detailed discussion of biological activities of these compounds is also presented.

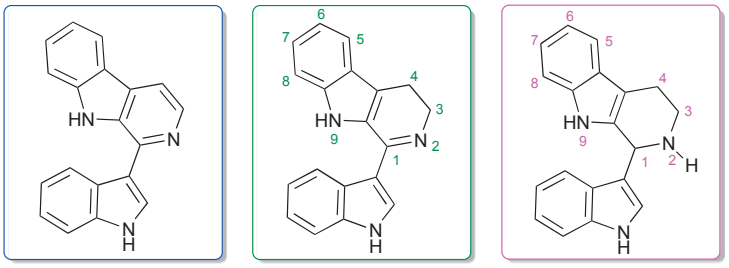
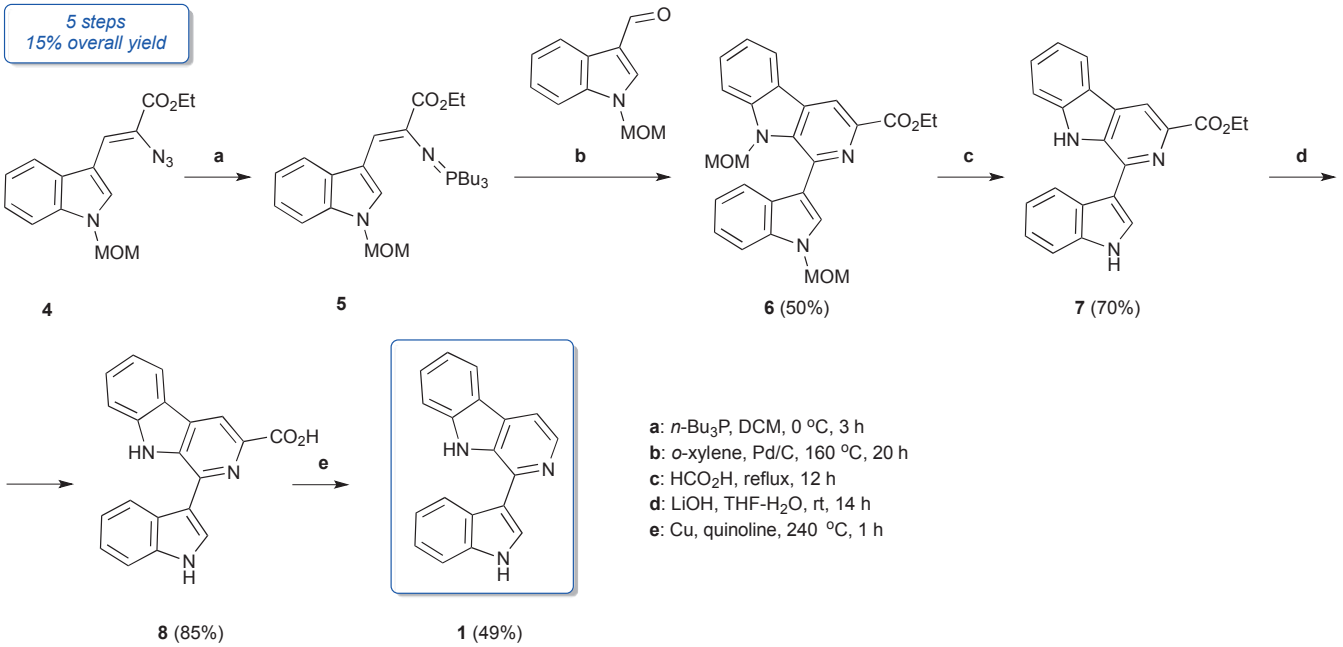


Figure 1. Structures of eudistomin U **1**, isoeudistomin U **2**, and 1,2,3,4-tetrahydroeudistomin U **3**

2. SYNTHESIS OF EUDISTOMIN U

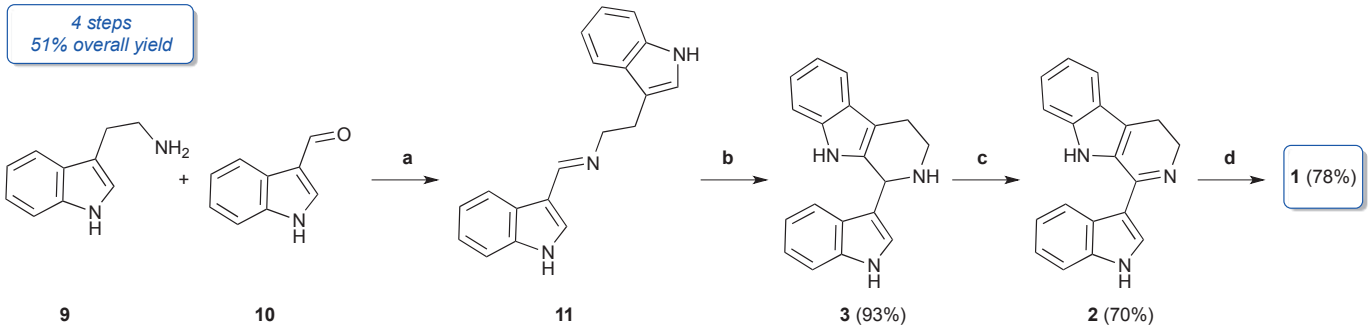
The pioneering work in the total synthesis of eudistomin U was reported by Molina *et al.* in 1995. The authors used an aza-Wittig reaction-electrocyclic ring closure strategy which led to the target alkaloid in five steps and 15% overall yield (Scheme 1). Firstly, the Staundinger reaction of the α-azido-[β-(3-indolyl)propenoate **4**, readily available from *N*-methoxymethyl-3-formylindole and ethyl azidoacetate, with tributylphosphine in dichloromethane, provided the iminophosphorane **5**. The latter reacted with *N*-methoxymethyl-3-formylindole in the presence of palladium on carbon, affording

indol-3-ylcarboline **6** that completed the assemblage of the carbon framework of the target alkaloid. The compound **6** was converted into the eudistomin U **1** *via* deprotection of the *N*-methoxymethyl substituent (MOM), hydrolysis of the ester group, and final decarboxylation using copper/quinoline system.[12]



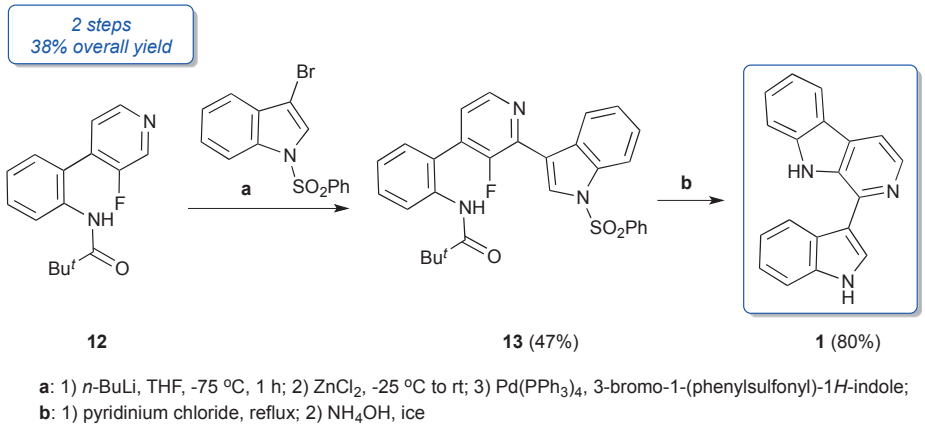
Scheme 1. Molina's synthesis of eudistomin U (1995)

The same year, Massiot *et al.* described a more efficient four-step approach to eudistomin U **1** *via* Pictet–Spengler cyclization (Scheme 2). The intermediate imine **11**, obtained from tryptamine **9** and 3-formylindole **10**, was directly cyclized into 1,2,3,4-tetrahydroeudistomin U **3**. The further oxidation of **3** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature provided isoeudistomin U **2**, which afforded the target compound **1** in 78% yield (51% overall yield).[6a]



Scheme 2. Massiot's synthesis of eudistomin U (1995)

Also, in 1995, Quéguiner and co-workers suggested a straightforward synthesis of eudistomin U, performed from one benzene and one pyridine building block *via* metalation and cross-coupling reactions. The synthetic sequence included 2 steps and gave the desired product in 38% overall yield (Scheme 3). Firstly, regioselective metalation of **12** with *n*-butyllithium was followed by a transmetalation of the resulting lithium species with zinc chloride. The subsequent reaction with 3-bromo-*N*-(phenylsulfonyl)indole in the presence of a catalyst afforded the corresponding trisubstituted pyridine **13**. Finally, the resulting pyridine **13** was cyclized to alkaloid **1** *via* the reflux with pyridinium chloride, followed by the treatment with a base.[13]



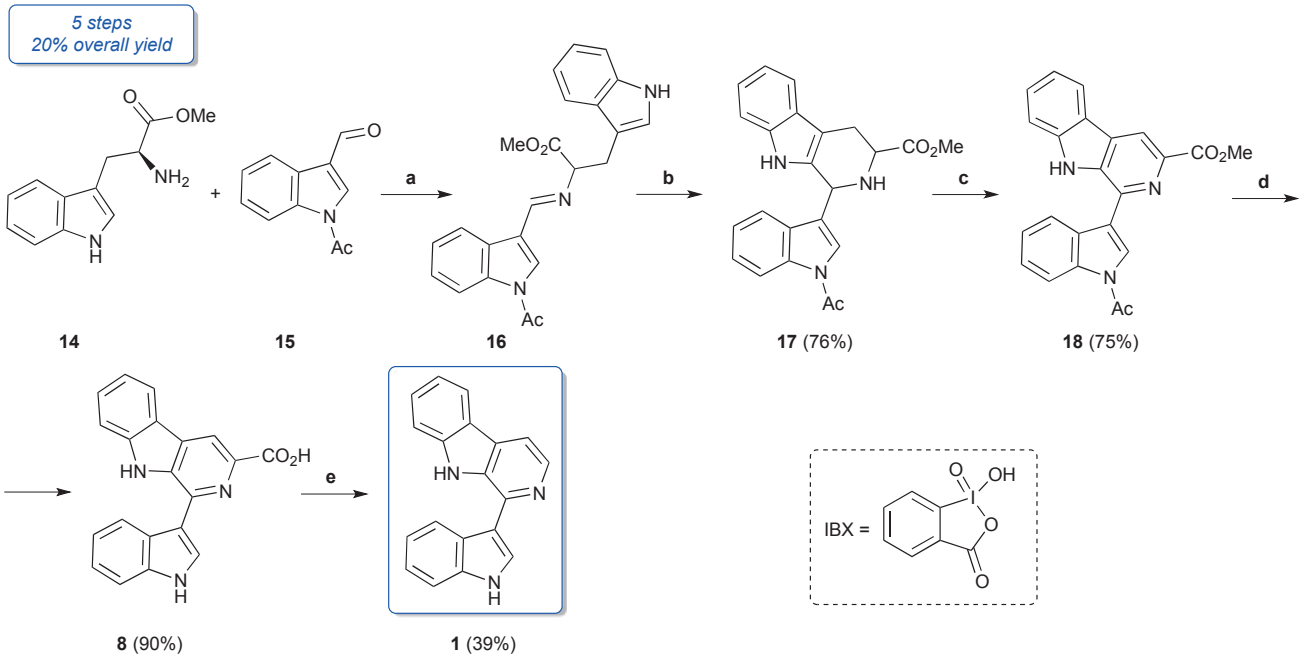
a: 1) *n*-BuLi, THF, -75 °C, 1 h; 2) $ZnCl_2$, -25 °C to rt; 3) $Pd(PPh_3)_4$, 3-bromo-1-(phenylsulfonyl)-1*H*-indole;
b: 1) pyridinium chloride, reflux; 2) NH_4OH, ice

Scheme 3. Quéguiner's synthesis of eudistomin U (1995)

Waters *et al.* described a small modification of Massiot's protocol in 2010 (Scheme 4). However, the modified approach including 5 steps and leading to eudistomin U in 20% overall yield, was not the optimal. The authors performed Pictet–Spengler cyclization of tryptophan methyl ester **14** with *N*-acetyl-indole-3-carboxaldehyde **15** on the first steps and obtained tetrahydro-β-carboline **17**. Dehydrogenation of **17** with 2-iodoxybenzoic acid (IBX) afforded β-carboline **18**. Further, saponification of the ester moiety was accompanied by the removal of the *N*-acetyl group to provide carboxylic acid **8**. And finally, copper-mediated decarboxylation of **8** furnished eudistomin U **1**.[14]

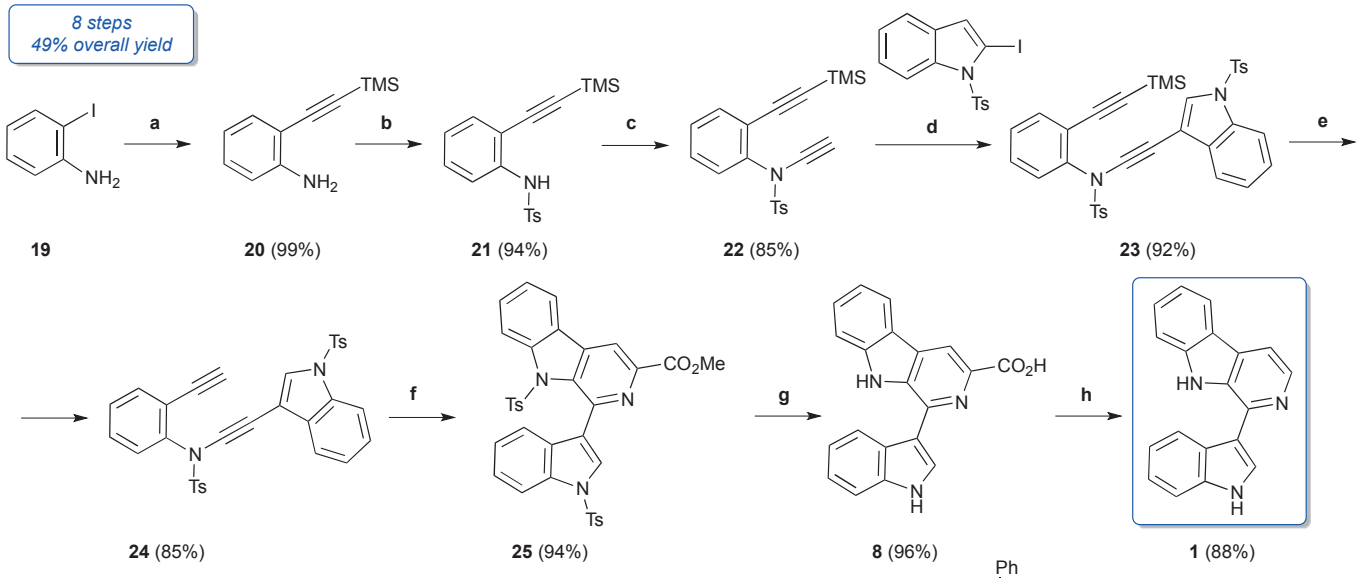
In 2011, Witulskii and co-workers applied transition metal-catalyzed [2+2+2] cycloaddition between yne-ynamides and methyl cyanoformate, for the synthesis of the target eudistomin. The total synthesis was achieved in 8 steps and 49% overall yield, starting from commercially available 2-iodoaniline **19** (Scheme 5). Firstly, 2-iodoaniline was transformed into the yne-ynamide **22** *via* three steps including a Sonogashira coupling with trimethylsilylacetylene, and the *N*-ethynylation of the tosylamide moiety with ethynyliodonium triflate. The Negishi reaction of **22** with 3-iodo-*N*-tosylindole was followed by a desilylation to provide the yne-ynamide **24**. The ruthenium-catalyzed [2+2+2] cycloaddition of **24** with methyl cyanoformate gave β-carboline ester **25** which was further saponificated with simultaneous

removal of the *N*-tosyl groups to provide the β-carboline carboxylic acid **8**. Finally, decarboxylation of **8** with copper powder under microwave irradiation afforded the target natural product **1**.[15]



a: benzene, reflux, 2 h; **b**: TFA, $CHCl_3$, 0 °C to rt, 23 h; **c:** 2 equiv. IBX, TBAB, MeCN, rt, 2 h; **d**: LiOH, THF, H_2O, reflux, 22 h
e: Cu, quinoline, 210 °C, 70 min

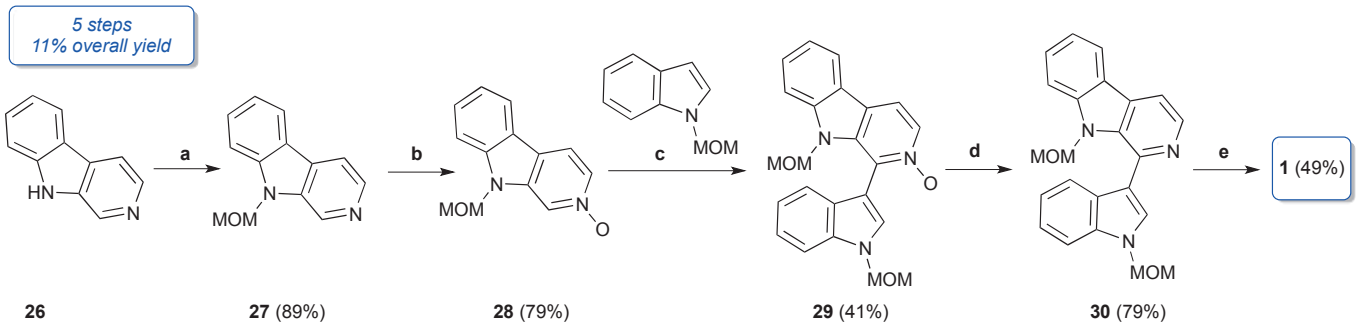
Scheme 4. Waters' synthesis of eudistomin U (2010)



a: TMS—≡, $PdCl_2(PPh_3)_2$, CuI, TEA, DMF; **b**: TsCl, pyridine, THF, rt; **c**: 1) KHMDS, toluene, DCM, 0 °C; 2) ≡—I(Ph)—OTs;
d: 1) LiHMDS, $ZnBr_2$, THF, -40 °C; 2) 2-iodo-N-tosylindole, $Pd(dba)_2$, PPh_3, THF, rt; **e**: TBAF, THF, 0 °C, **f**: $NCCO_2Me$, Cp*RuCl(cod), DCM, 40 °C, 2 h;
g: KOH, MeOH, THF, 80 °C, 3 h; **h**: Cu, quinoline, MW, 240 °C, 10 min

Scheme 5. Witulski's synthesis of eudistomin U (2011)

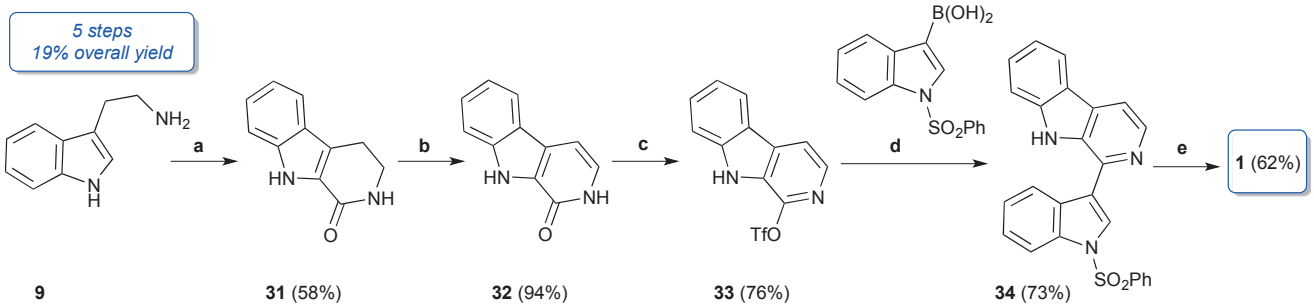
Later, a novel approach to eudistomin U, based on the palladium-catalyzed CH-CH coupling reaction of MOM-protected indole with *N*-oxide of β-carboline, was reported by Yamaguchi, Itami, and co-workers (Scheme 6). The total synthesis included 5 steps and gave the target compound in 11% overall yield. Firstly, MOM protection of commercially available β-carboline **26**, followed by (methyltrioxorhenium)-catalyzed pyridine oxidation afforded the corresponding *N*-oxide **28**. The subsequent CH-CH coupling reaction of indole and **28** in the presence of a palladium catalyst provided the desired eudistomin U derivative **29**. After the reduction of the *N*-oxide with phosphorus trichloride, the follow-up deprotection of MOM groups with formic acid in water completed the total synthesis of eudistomin U **1**.[16]



Scheme 6. Yamaguchi-Itami's synthesis of eudistomin U (2011)

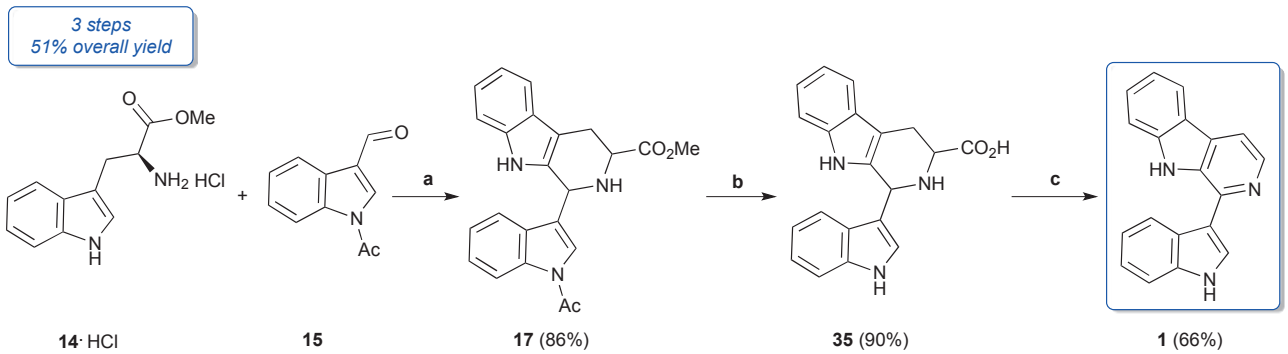
In 2014, Mulcahy *et al.* described a new five-step synthesis of the target alkaloid **1** (19% overall yield) *via* the Bischler–Napieralski reaction and Suzuki cross-coupling (Scheme 7). The synthesis started with commercially available tryptamine, which underwent a cyclization to provide the lactam **31**. Further, oxidation of **31** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone provided pyridone **32**. The compound **32** was transformed into triflate **33** using trifluoromethanesulfonic anhydride under basic conditions. Next, the Suzuki cross-coupling provided the eudistomin U derivative **34**. And finally, the removal of the benzenesulfonyl group under basic conditions gave the natural product **1**.[9]

In 2015, Kamal and co-workers reported a three-step synthesis of eudistomin U *via* iodobenzene diacetate-mediated oxidative decarboxylation (Scheme 8). This approach led to the desired product in 51% overall yield. Similarly to Waters' protocol, the strategy started with a Pictet–Spengler condensation of tryptophan methyl ester **14** with *N*-acetylindole-3-carboxaldehyde **15** to provide the corresponding tetrahydro-β-carboline ester **17**. The subsequent saponification of ester **17** was accompanied by the removal of the *N*-acetyl group, providing carboxylic acid **35**. The latter underwent oxidative decarboxylation with iodobenzene diacetate, affording eudistomin U.[17]



a: 1) bis(trichloromethyl) carbonate, TEA, toluene; 2) HBr; **b**: DDQ, dioxane; **c**: Tf_2O, pyridine;
d: $Pd_2(dba)_3$, aq. Na_2CO_3, PPh_3, EtOH, toluene; **e**: KOH; MeOH, THF

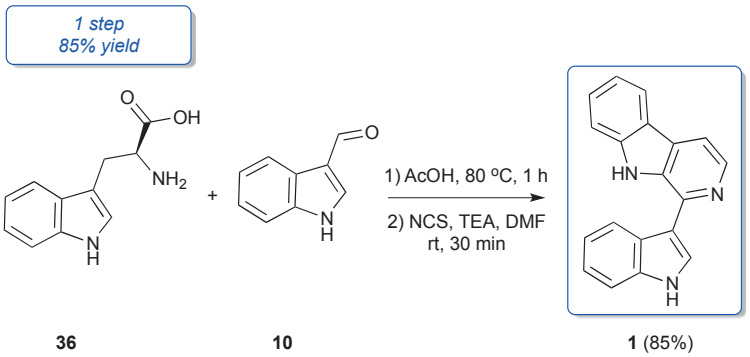
Scheme 7. Mulcahy's synthesis of eudistomin U (2014)



a: EtOH, reflux, 12 h; **b**: LiOH, THF, H_2O, reflux, 12 h; **c**: $PhI(OAc)_2$, DMF, rt, 1 h

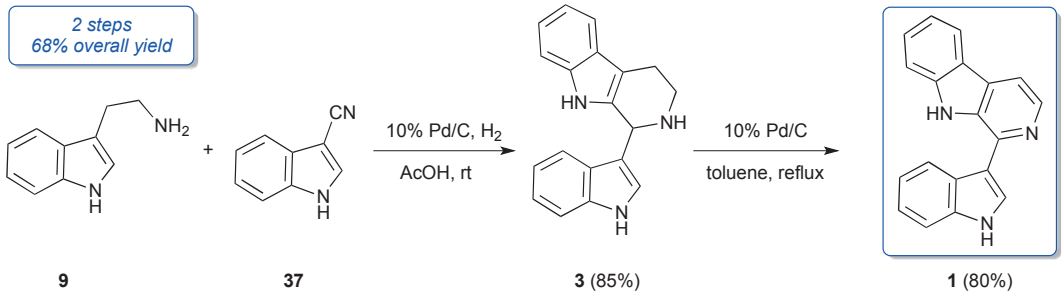
Scheme 8. Kamal's synthesis of eudistomin U (2015)

The same authors described a more straightforward version of this method which represents the most efficient synthesis of eudistomin U currently. It includes the Pictet–Spengler condensation of commercially available L-tryptophan **36** and indole-2-carbaldehyde **10**, followed by the reaction with *N*-chlorosuccinimide (NCS) in one-pot manner (Scheme 9). Employing this strategy, the target alkaloid **1** was obtained in 85% yield.[18]



Scheme 9. Kamal's one-pot synthesis of eudistomin U (2015)

Also, a new synthesis of eudistomin U *via* the reductive Pictet–Spengler condensation of tryptamine **9** with 1*H*-indole-3-carbonitrile **37**, followed by dehydrogenation with palladium on carbon, was described by Kusurkar *et al.* in 2015. The desired product **1** was obtained in 2 steps and 68% overall yield (Scheme 10).[19]

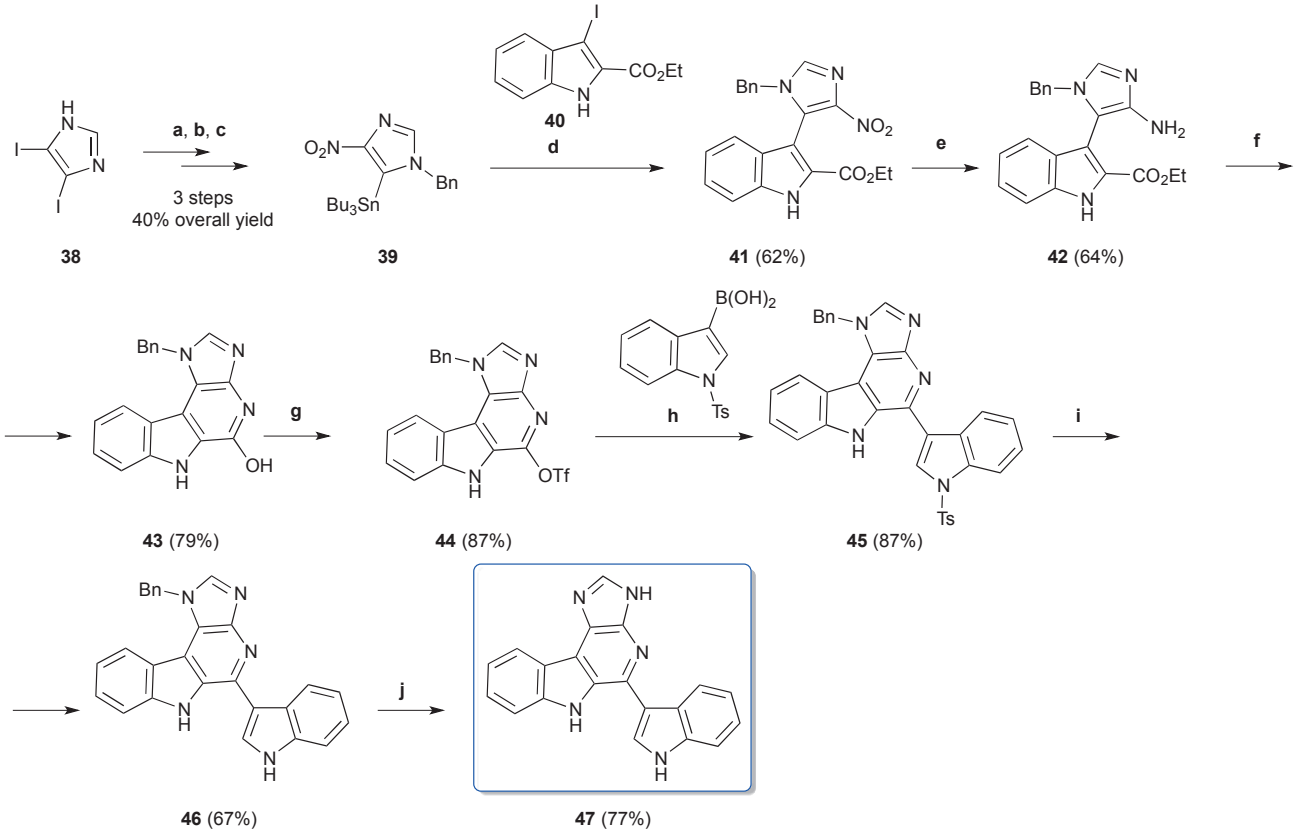


Scheme 10. Kusurkar's synthesis of eudistomin U (2015)

3. SYNTHESIS OF DERIVATIVES AND ANALOGUES OF EUDISTOMIN U

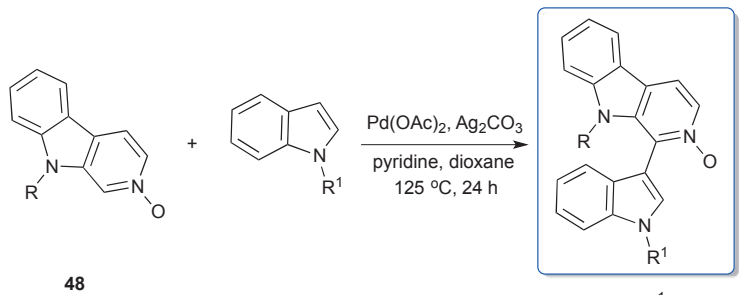
In 2001, Achab *et al.* described a novel eudistomin U analogue **47** bearing an imidazopyrido[3,4-*b*]indole fragment. For its synthesis, the authors used intramolecular electrocyclization of indolo-1,3,5-hexatriene system (Scheme 11). Firstly, cross-coupling of stannane **39**, readily available from 4,5-diiodo-1*H*-imidazole **38**, with iodoindole **40** furnished the 2-ethoxycarbonyl-3-(4-nitro-5-imidazolyl)indole **41**. The subsequent reduction of **41** gave 4-amino derivative **42**. Further, intramolecular ring-closure of **42** in *ortho*-dichlorobenzene under reflux, provided pyridone **43**, which was transformed into triflate **44** upon the treatment with triflic anhydride in pyridine. Finally, the coupling reaction of triflate **44** with (1-tosyl-1*H*-indol-3-yl)boronic acid afforded the derivative **45**, which furnished the eudistomin analogue **47** after the deprotection.[20]

The palladium-catalyzed CH-CH coupling reaction of *N*-substituted indoles with *N*-oxide of β-carboline **48** was used by You and co-workers for the synthesis of derivatives of eudistomin U **49** (Scheme 12). Thus, employing silver carbonate as an oxidant and pyridine as an additive, in the presence of palladium(II) acetate, the compounds **49** were obtained in 22-70% yields. After screening different directing groups, it was found that the *N,N*-dimethylcarbamoyl group gave the highest yield of the CH-CH cross-coupling products. In this case, the reaction with *N*-benzylindole afforded the derivative **49d** in 70% yield.[21]



a: HNO_3, AcOH, KI; **b**: K_2CO_3, MeCN, BnBr, reflux, 3 h; **c**: $(n\text{-}Bu_3Sn)_2$, $PdCl_2(PPh_3)_2$, DMF, 120 °C, 2 h; **d**: $Pd(PPh_3)_4$, CuI, DMF, 2.5 h; **e**: Raney-Ni, H_2, MeOH, rt, 2.5 h; **f**: *o*-$Cl_2C_6H_4$, reflux, 48 h; **g**: Tf_2O, pyridine, 0 °C, 30 min, then rt, overnight; **h**: $Pd(PPh_3)_4$, K_2CO_3, H_2O, LiCl, dioxane, reflux, 2-3 h; **i**: KOH, EtOH-THF, reflux, 2.5 h; **j**: NH_4HCO_2, Pd/C, EtOH, reflux, 8 h

Scheme 11. Synthesis of analogue **47** (Achab, 2001)

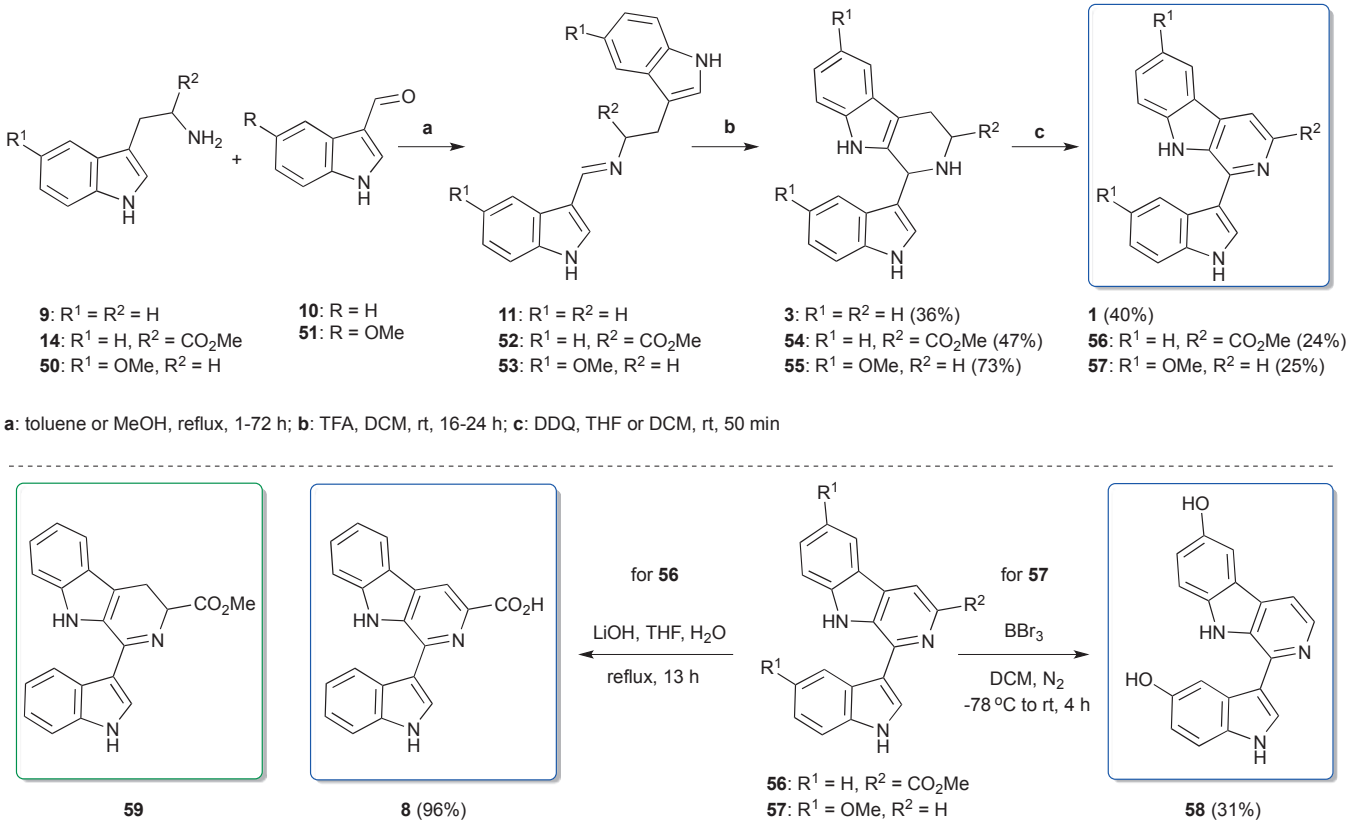


49a: R = Me, R^1 = Me (40%)
49b: R = Ph(O)C, R^1 = Me (22%)
49c: R = $PySO_2$, R^1 = Me (26%)
49d: R = $Me_2N(O)C$, R^1 = Me (68%)
49d: R = $Me_2N(O)C$, R^1 = Bn (70%)

Scheme 12. Synthesis of derivatives of eudistomin U **49** (You, 2014)

Massiot's protocol was employed by Liew and co-workers for the synthesis of new derivatives of eudistomin U **56-58** (Scheme 13). Thus, the reaction of *L*-tryptophan methyl ester **14** or 5-methoxytryptamine **50** with indoles **10** or **51** afforded 1,2,3,4-tetrahydro-β-carbolines **54** and **55** in two steps. The latter gave ester **56** and methyl ether **57** upon oxidation. Further, deprotection steps afforded

acid **8** and dihydroxy derivative **58**. Notably, in the case of the transformation of 1,2,3,4-tetrahydro-β-carboline **54**, a derivative of isoeudistomin U **59** could be also isolated from the reaction mixture.[10]



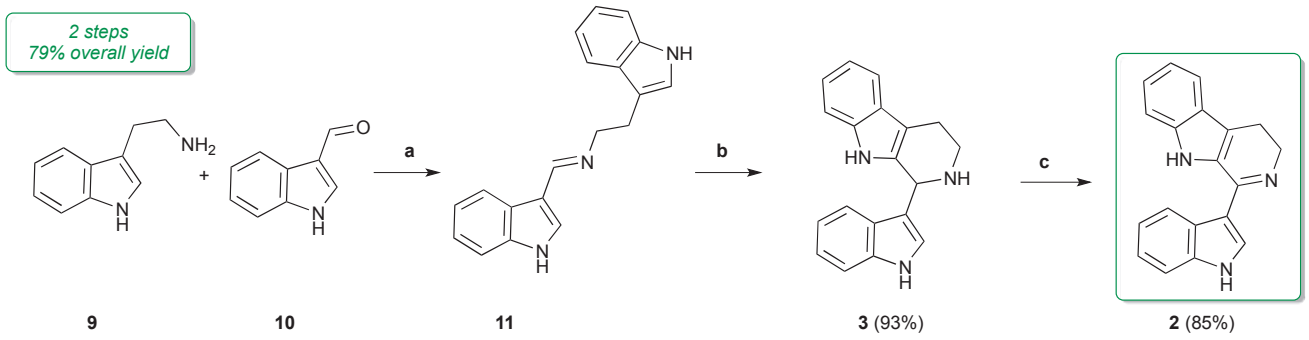
Scheme 13. Synthesis of derivatives **56-58** and **59** (Liew, 2014)

4. SYNTHESIS OF ISOEUDISTOMIN U

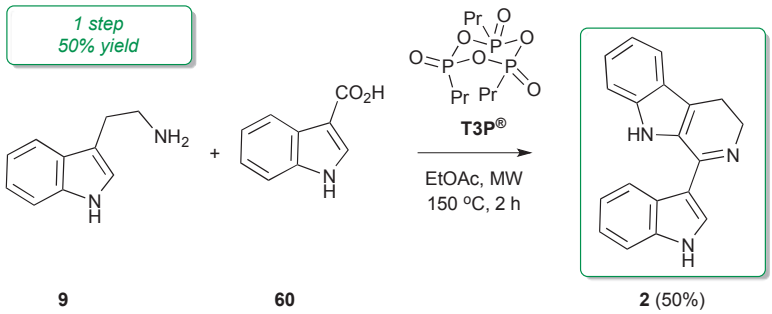
Dihydroeudistomin U or isoeudistomin U **2**, which can be considered a precursor of the fully aromatic eudistomin U, was obtained in 65% overall yield *via* Massiot's protocol, namely Pictet–Spengler cyclization and mild oxidation of 1,2,3,4-tetrahydroeudistomin U **3** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (see also Scheme 2).[6a]

In 2014, an aerobic oxidation of 1,2,3,4-tetrahydroeudistomin U **3** in the presence of 1,10-phenanthroline-5,6-dione (phd)/zinc iodide, was described by Stahl. Using this procedure, the product **2** was obtained in 3 steps and 79% overall yield. The starting 1,2,3,4-tetrahydroeudistomin U **3** was also synthesized, according to Massiot's protocol (Scheme 14).[22]

Later, a one-pot method for the synthesis of 1-substituted-3,4-dihydro-β-carbolines from tryptamine and carboxylic acids in the presence of 1-propanephosphonic acid cyclic anhydride (T3P®), has been developed by Ábrányi-Balogh and co-workers. The reaction was successfully applied for the synthesis of isoeudistomin U **2** (Scheme 15). The target alkaloid **2** was obtained in 50% yield.[23]



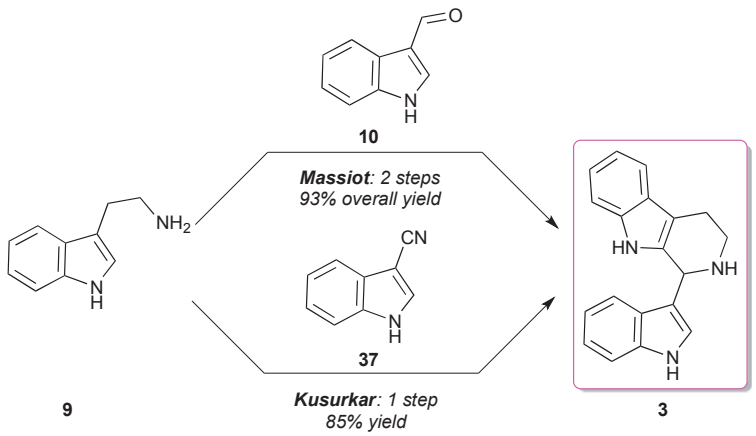
Scheme 14. Stahl's synthesis of isoeudistomin U (2014)



Scheme 15. Ábrányi-Balogh's synthesis of isoeudistomin U (2016)

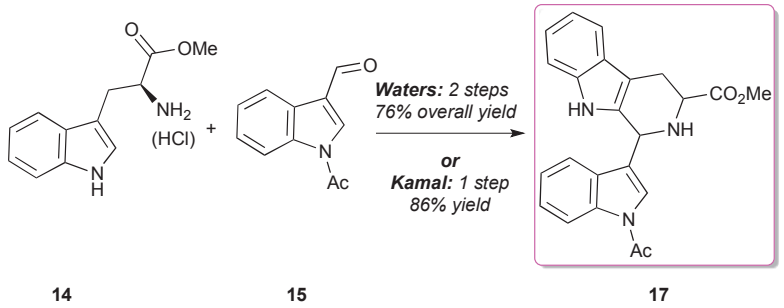
5. SYNTHESIS OF 1,2,3,4-TETRAHYDROEUDISTOMIN U AND ITS DERIVATIVES

The Pictet–Spengler cyclization represents the most well-known route to 1,2,3,4-tetrahydroeudistomin U **3**. For example, Massiot's[6a] and Kusurkar's[19] protocols efficiently provide the target compound **3** in high yields (Scheme 16; also, see Schemes 2 and 10).



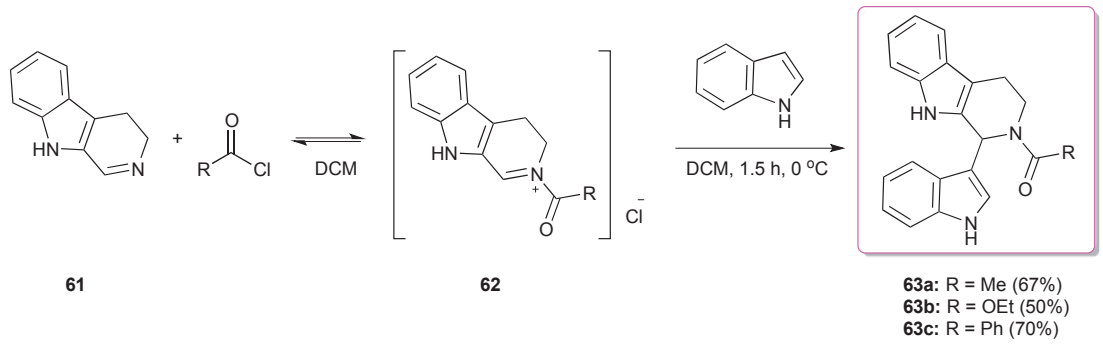
Scheme 16. Approaches to 1,2,3,4-tetrahydroeudistomin U

Additionally, Waters'[14] and Kamal's[17] approaches allow for the preparation of ester derivatives of *N*-protected 1,2,3,4-tetrahydroeudistomin U **17** (Scheme 17; also, see Schemes 4 and 8).



Scheme 17. Approaches to ester derivative of 1,2,3,4-tetrahydroeudistomin U **17**

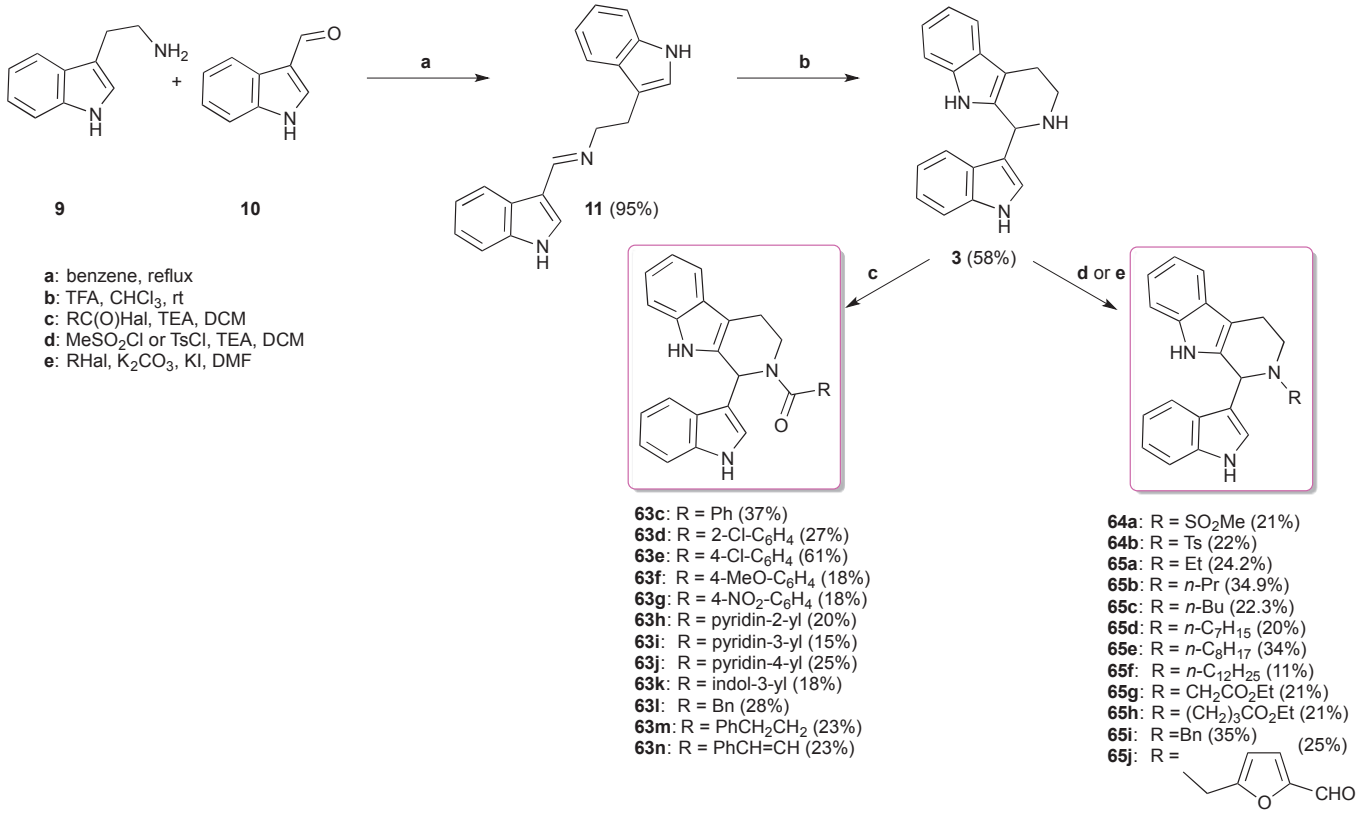
In 2004, Donova *et al.* reported the synthesis of derivatives of 1,2,3,4-tetrahydroeudistomin U **63** *via* amidoalkylation of indole. In particular, *N*-acyliminium reagents **62**, formed from 3,4-dihydro-β-carboline **61** and acyl chlorides, afforded compounds **63a-c** in 50-70% yields (Scheme 18).[24]



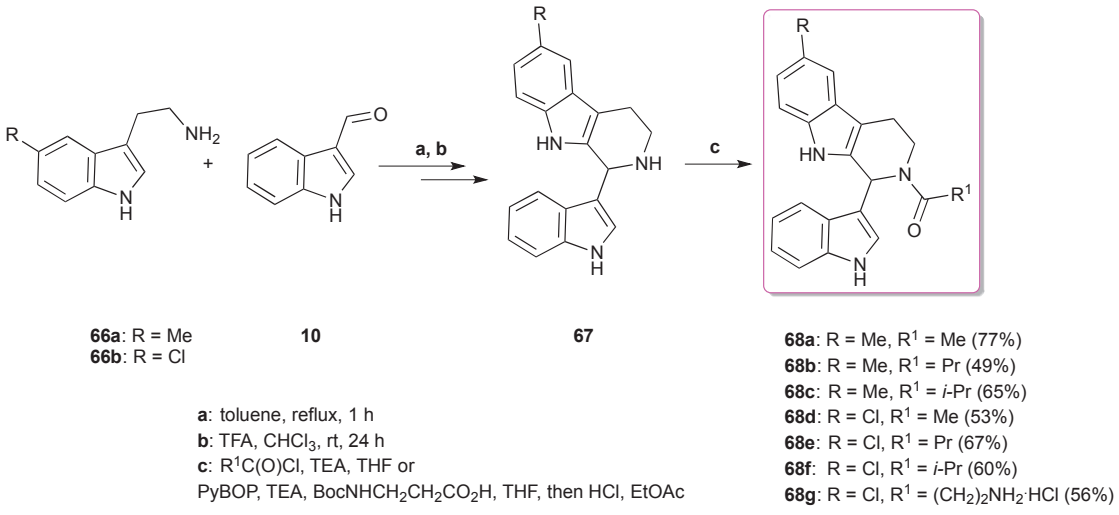
Scheme 18. Synthesis of derivatives **63** (Donova, 2004)

A series of 2-substituted 1,2,3,4-tetrahydroeudistomins U **63-65** was synthesized by Wen and co-workers *via* the Pictet–Spengler cyclization approach. The intermediate imine **11** was isolated in 95% yield on the first step. The resulted 1,2,3,4-tetrahydroeudistomin U **3** was *N*-acylated with acyl halides or *N*-alkylated with alkyl halides under basic conditions to provide compounds **63** and **65** in low to moderate yields. The reaction with sulfonic acids chlorides afforded the correspondent products **64** in low yields (Scheme 19).[25]

The related derivatives **68** were synthesized by You *et al.* in 2010. The condensation reaction between tryptamines and 1*H*-indole-3-carbaldehyde gave the corresponding imines, and then, an intramolecular cyclization catalyzed by trifluoroacetic acid furnished substituted 1,2,3,4-tetrahydroeudistomins **67** (Scheme 20). The subsequent treatment of **67** with diverse acyl chlorides provided compounds **68a-g** in moderate yields.[26]

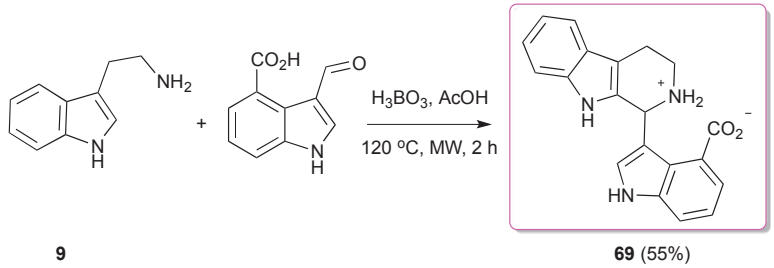


Scheme 19. Synthesis of derivatives **63-65** (Wen, 2008)



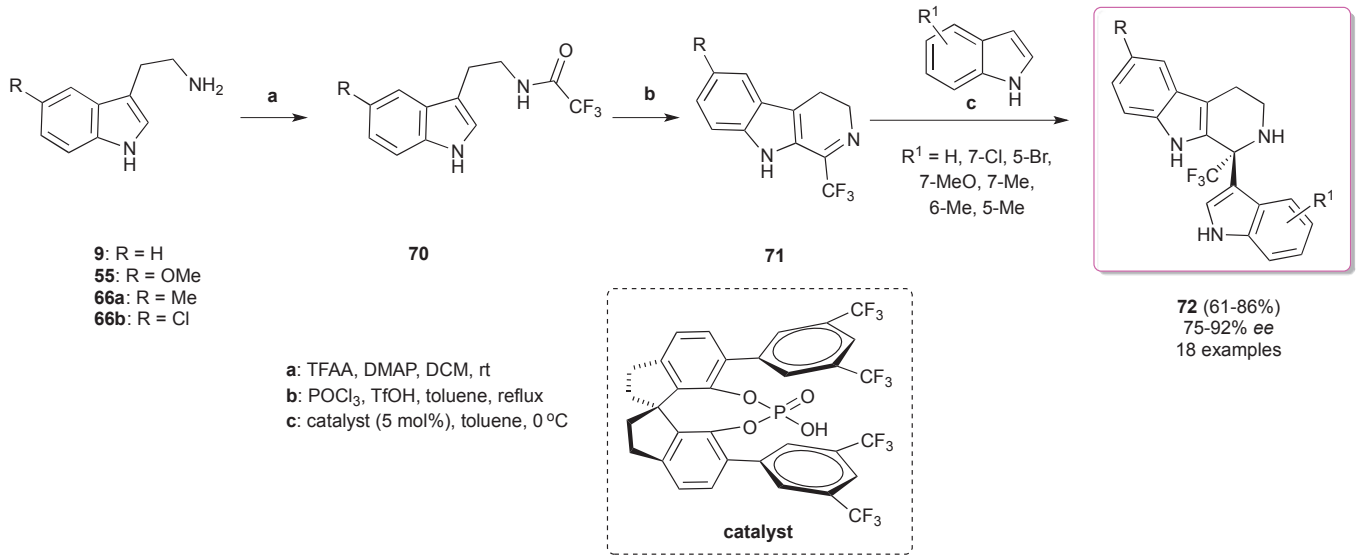
Scheme 20. Synthesis of derivatives **67** and **68** (You, 2010)

A new microwave-assisted Pictet–Spengler protocol employing boric acid/acetic acid as a catalytic system was described in 2013. The reaction of tryptamine **9** with 3-formyl-1*H*-indole-4-carboxylic acid provided carboxy derivative of 1,2,3,4-tetrahydroeudistomin U with a zwitterionic structure **69** in 55% yield (Scheme 21).[27]



Scheme 21. Synthesis of derivative **69** (Cśampai, 2013)

Recently, an enantioselective *aza*-Friedel–Crafts alkylation reaction of indoles with 3,4-dihydro-β-carbolines, affording derivatives of 1,2,3,4-tetrahydroeudistomin U, was reported.[28a,b] Initially, the amidation reaction of tryptamines **9**, **55** and **66** with trifluoroacetic anhydride catalyzed by 4-dimethylaminopyridine (DMAP) gave the corresponding trifluoroacetamides **70** (Scheme 22). The subsequent cyclization of the trifluoroacetamides **70** in the presence of trifluoromethanesulfonic acid (TfOH) and phosphoryl chloride produced 1-trifluoromethyl-3,4-dihydro-β-carbolines **71** in moderate yields. Finally, the *aza*-Friedel–Crafts reacton of **71** with indoles led to the products **72** in 68-86% yields with high enantioselectivities up to 92%.[28a]



Scheme 22. Synthesis of derivatives **72** (Lin, 2017)

Natural alkaloid bengacarboline **80a**, bearing a tetrahydro-β-carboline core linked at C1 with tryptamine and an indol unit, can be also considered as 1,2,3,4-tetrahydroeudistomin U derivative (Figure 2).[29]

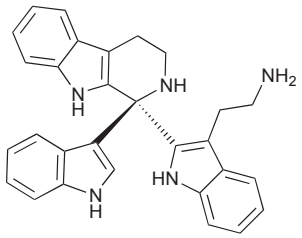
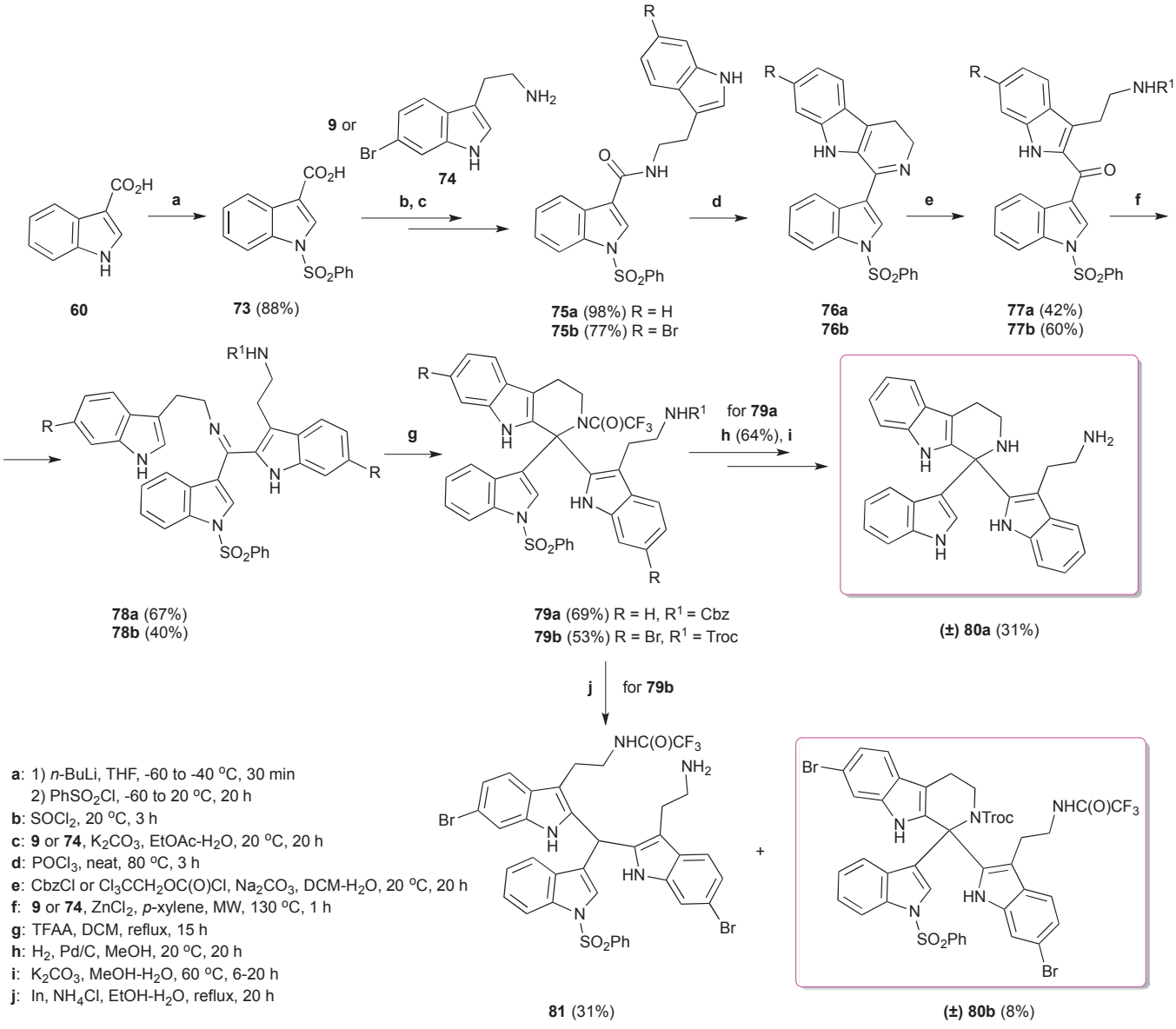


Figure 2. Absolute configuration of bengacarboline **80a**

The first synthesis of (±)-bengacarboline **80a** was performed by Langlois and co-workers in 2003.[30] The same strategy, reported in 2005, provided the best yield of (±)-bengacarboline **80a** over two last steps (20% versus 19%). It started with protection of nitrogen in indole-3-carboxylic acid **60** affording the *N*-sulfonyl derivative **73** (Scheme 23). Then, amide **75a** was obtained from the compound **73** and



Scheme 23. Synthesis of (±)-bengacarboline **80a** and its derivative **80b** (Langlois, 2005 and 2008)

tryptamine **9** in a good yield. The subsequent Bischler–Napieralski cyclization in the presence of phosphoryl chloride afforded dihydro-β-carboline **76a** which was acylated with carbobenzyloxy chloride under Schotten–Baumann conditions. The spontaneous ring opening reaction yielded the keto derivative **77a**. The subsequent condensation of tryptamine **9** with the compound **77a** under microwave irradiation in *para*-xylene in the presence of zinc dichloride provided the imine derivative **78a**. The further reflux of **78a** with trifluoroacetic anhydride in dichloromethane resulted in formation of tetrahydro-β-carboline **79a** as trifluoroacetamide derivative. Finally, the deprotection of compound **79a** was performed in two steps and afforded (±)-bengacarbolin **80a**.[31]

The similar synthesis of (±)-bengacarboline derivative **80b** was described by the Langlois group in 2008 (Scheme 23). However, the target (±)-**80b** was obtained as a minor product, along with the compound (±)-**81**, in a very low yield.[32]

6. BIOLOGICAL ACTIVITIES

Generally, β-carboline alkaloids are known to display a wide spectrum of biological activities.[4] Remarkably, tetrahydro-β-carbolines are usually more active than their fully aromatic analogues, that can be also observed among eudistomin U and its tetrahydro-derivatives. To date, a DNA-binding ability, antibacterial, anticancer, antimalarial, and antioxidant activities of compounds **1**, **2**, and their derivatives, including 2-substituted 1,2,3,4-tetrahydroeudistomins U, were disclosed.

6.1. ANTIBACTERIAL ACTIVITY

Strong antibacterial activity of eudistomin U **1** and isoeudistomin U **2** against *Agrobacterium tumefaciens* was reported in 1994. However, no quantitative data were given.[5]

In 2014, a more detailed biological profile of the alkaloid **1** was described. Thus, it was shown that the Gram-positive bacteria (*S. pyogenes*, *S. aureus*, and *M. smegmatis*) were most susceptible to the treatment

Table 1. Cytotoxicity of eudistomin U **1** in bacteria organisms

Entry	Organism	IC_{50} (μg/mL)[a]
1	*Streptococcus pyogenes*	3.4
2	*Mycobacterium smegmatis*	3.6
3	*Staphylococcus aureus*	6.4
4	*Escherichia coli*	12.3
5	*Pseudomonas aeruginosa*	27.7

[a]Cytotoxicity (IC_{50}) is the concentration of **1** that causes 50% growth inhibition relative to an untreated control.

with the compound **1**. The corresponding IC_{50} values (3.4-6.4 μg/mL) were nearly two-fold more potent than Gram-negative bacteria (Table 1).[9]

6.2. ANTICANCER ACTIVITY

In 2004, preliminary data indicating anticancer activity of eudistomin U **1** were reported.[33]

Later, low cancer cell cytotoxicity of eudistomin U **1** against three different cell lines was described (Table 2). The best IC_{50} was observed for C19 leukemia cells (15.6 μg/mL).[9]

Table 2. Cytotoxicity of eudistomin U **1** in human cancer organisms

Entry	Organism	IC_{50} (μg/mL)[a]
1	C19 leukemia	15.6
2	CaOV3 ovarian	24.9
3	WM266-4 melanoma	27.5

[a]Cytotoxicity (IC_{50}) is the concentration of **1** that causes 50% growth inhibition relative to an untreated control.

Also in 2014, compounds **1**, **3**, **8**, **54-59** were studied to evaluate their cytotoxicity *in vitro* disease-oriented primary antitumor screen (Table 3, Figure 3). The preliminary tests illustrated that most of the eudistomin U derivatives were inactive against tumor cell line COLO 205 (mean cell growth 65.6-98.6%). However, the dimethoxy compound **57** showed modest antyleukemic activity towards the HL-60(TB) cell line (LC_{50} = 4.2 μM).[10]

Table 3. Cytotoxicity of compounds **1**, **3**, **8**, **54-59** against human tumor cell line (COLO 205) organisms, sorted from active (green) to less active (red red)

Entry	Compound	COLO 205 Mean cell growth (%)
1	**57**	26.2
2	**59**	65.6
3	**1**	67.9
4	**56**	73.1
5	**55**	85.3
6	**3**	87.8
7	**58**	96.4
8	**8**	97.1
9	**54**	98.6

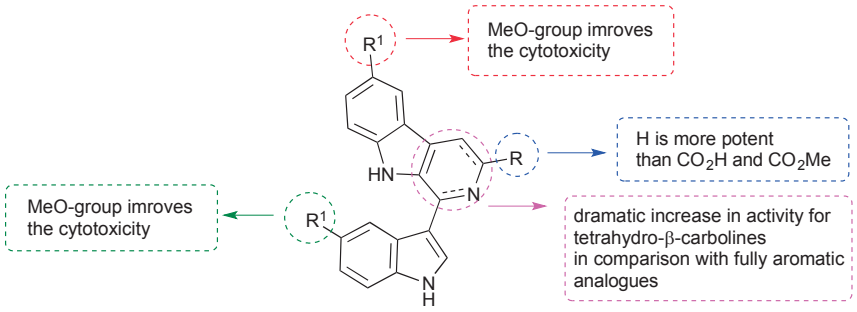


Figure 3. SAR for compounds **1**, **3**, **8**, **54-59** as anticancer agents

In vitro antitumor activity of 2-substituted derivatives of 1,2,3,4-tetrahydroeudistomin U **63-65** was evaluated using *Pyricularia oryzae* Cavara and Caco-2 cancer cells in 2008 (Tables 4 and 5, Figures 4 and 5). Most of the 2-alkylated derivatives **65** showed potent inhibitory activities in both of the biological tests. Thus, the compounds **65c**,**d**,**h** showed the best activities with the MIC value of 1.6 μg/mL on *P. oryzae*. Additionally, the MTT assay *in vitro* showed that **65a-d** suppressed Caco-2 cancer cell proliferation with a low IC_{50} value of 1.2-3.6 μM. Among the *N*-acylated derivatives **63**, only **63j** exhibited potent inhibitory activity against the Caco-2 cancer cell (1.61 μM), whereas it was inactive against *P. oryzae*.[25]

Table 4. Cytotoxicity of compounds **63-65** against *Pyricularia oryzae* Cavara cancer cells, sorted from active (green) to less active (red)

Entry	Compound	*P. oryzae* MIC (μg/mL)	Entry	Compound	*P. oryzae* MIC (μg/mL)
1	**65c**	1.6	13	**65j**	50
2	**65d**	1.6	14	**63d**	100
3	**65h**	1.6	15	**63h**	100
4	**65b**	12.5	16	**63i**	100
5	**65i**	12.5	17	**63l**	100
6	**65f**	25	18	**65g**	100
7	**63c**	50	19	**63f**	200
8	**63e**	50	20	**63g**	200
9	**63m**	50	21	**63j**	200
10	**63n**	50	22	**63k**	200
11	**64b**	50	23	**64a**	200
12	**65a**	50	24	**65e**	200

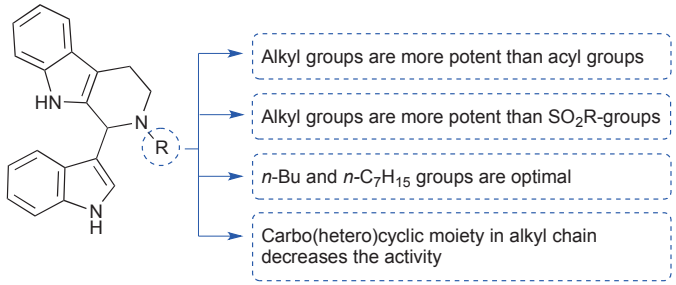


Figure 4. SAR for compounds **63-65** as anticancer agents

Table 5. Cytotoxicity of compounds **63-65** against Caco-2 cancer cells, sorted from active (green) to less active (red)

Entry	Compound	Caco-2 IC_{50} (μM)	Entry	Compound	Caco-2 IC_{50} (μM)
1	**65c**	1.2	13	**65i**	19.1
2	**65b**	1.3	14	**63e**	19.4
3	**63j**	1.61	15	**65f**	23.3
4	**65a**	2.1	16	**63l**	24.4
5	**65d**	3.6	17	**63h**	27.8
6	**65j**	4.5	18	**64a**	29.4
7	**63i**	7.01	19	**63k**	34.5
8	**65e**	7.5	20	**63m**	41.1
9	**63c**	13.1	21	**64b**	50.1
10	**65h**	13.5	22	**63g**	79.1
11	**63d**	14.8	23	**63n**	89.8
12	**65g**	18.3	24	**63f**	132.2

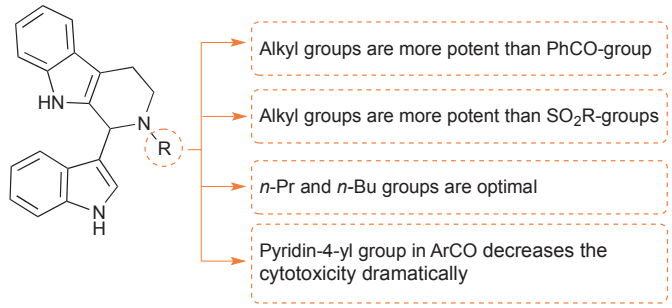


Figure 5. SAR for compounds **63-65** as anticancer agents

1-(3-Indolyl)-2-acyl-6-methyltetrahydro-β-carbolines **68a-g** were found to exhibit kinesin spindle protein (KSP) enzymatic inhibition (Tables 6 and 7, Figure 6). These inhibitors represent a promising class of anticancer agents which contribute to the formation of mitotic spindle during cell division.[34] The best

KSP activity (IC_{50} < 1 μM) was observed for the 2-isobutyryl **68c**, in comparison with the corresponding 2-acetyl and 2-butyryl compounds **68a** and **68b**. Interestingly, the 6-chloro analogues **68d-g** were found to be 7- to 160-fold less potent than the corresponding 6-methyl derivatives **68a-c**. However, their loss in KSP potency leads to the increase in cellular activity. 1-(3-Indolyl)-6-chloro-tetrahydro-β-carboline **68g** bearing an amino group at the terminal of 2-propionyl chain, displayed nearly 40-fold and 4-fold of improvements in KSP and cellular inhibitory activities, respectively, in comparison with 2-isobutyryl derivative **68e**.[26]

Table 6. Inhibitory activity of compounds **68a-g** against KSP, sorted from highly active (blue) to active (green)[a]

Entry	Compound	KSP IC_{50} (μM)
1	**68c**	<0.001
2	**68g**	0.043
3	**CK0106023** (control)	0.049
4	**68a**	0.051
5	**68f**	0.163
6	**68b**	0.216
7	**68d**	0.337
8	**68e**	1.703

[a]The inhibitory activities against KSP were determined by measuring the MT-activated ATPase activity.

Table 7. Cellular activity of compounds **68a-g** against human lung carcinoma cells A549, sorted from active (green) to less active (red)

Entry	Compound	A549 IC_{50} (μM)
1	**68g**	1.79
2	**CK0106023** (control)	7.02
3	**68e**	6.83
4	**68f**	9.11
5	**68d**	9.80
6	**68a**	>10
7	**68b**	>10
8	**68c**	>10

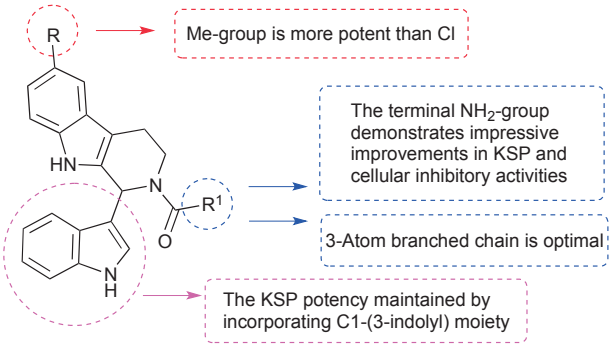


Figure 6. SAR for compounds **68a-g** as KSP inhibitors

The most promising compounds **68f** and **68g** were selected for further evaluation for their anti-proliferative cytotoxic activity against other human tumor cell lines, such as AGS (stomach), HepG2 (liver), HT-29 (colon) and PC-3 (prostate). It was found, that they displayed good anti-proliferative profiles (Tables 8, 9). The best results were observed for the compound **68g** against A549 and PC-3 cells (IC_{50} < 2 μM).[26]

Table 8. Cellular activity of compound **68f** against 5 cancer cell lines

Entry	Cell line	IC_{50} (μM)
1	HT-29	5.86
2	A549	6.83
3	AGS	7.06
4	PC-3	7.29
5	HepG2	7.64

Table 9. Cellular activity of compound **68g** against 5 cancer cell lines

Entry	Cell line	IC_{50} (μM)
1	PC-3	1.55
2	A549	1.79
3	AGS	6.16
4	HT-29	6.28
5	HepG2	>10

Bengacarboline **80a** was reported to be cytotoxic toward a 26 cell line human tumor panel *in vitro* with a mean IC_{50} of 0.9 μg/mL, as well as to inhibit the catalytic activity of topoisomerase II at 32 μM.[29]

The data concerning six tumor cell lines used to evaluate the anti-proliferative potential of (±)-**80a** are presented in Table 10. The compound (±)-**80a** showed low cytotoxicities toward human lung carcinoma

A549 epithelial cells, MCF7 breast cancer cells, Namalwa cells derived from a human Burkitt lymphoma, the SKOV3 human ovary carcinoma cells, and LoVo cell line.[32]

Table 10. Cytotoxicity of (±)-bengacarboline **80a** in human cancer organisms

Entry	Cell line	IC_{50} (μg/mL)
1	A549	7.1
2	MCF7	8.6
3	LoVo	9.9
4	BxPC3	10
5	Namalwa	>10
6	SKOV3	>10

6.3. ANTIMALARIAL ACTIVITY

Compounds **1**, **3**, **8**, **54-59** were studied to evaluate their activity against a chloroquine-resistant strain (FcB1) of *P. falciparum* (Table 11, Figure 7). Among all derivatives, eudistomin U analogue **57** was found to be the most active (IC_{50} = 4.7 μg/mL). The data demonstrated that more enhanced activity was observed for hydroxylated or methoxylated derivatives (**58** and **57**) in comparison with compounds bearing an ester group **56** (IC_{50} >29 μg/mL) or a carboxyl group **8** (IC_{50} >31 μg/mL). Remarkably, the 1,2,3,4-tetrahydro-β-carbolines exhibited either comparable (**55** versus **57**) or enhanced antimalarial activity (**3** versus **1**, **54** versus **56**) versus the corresponding fully aromatic β-carboline structures.[10]

Table 11. Antimalarial activity of compounds **1**, **3**, **8**, **54-59** against a chloroquine-resistant strain (FcB1) of *P. falciparum*, sorted from active (green) to less active (red)

Entry	Compound	IC_{50} (μg/mL)[a]
1	**57**	4.7±1.3
2	**3**	5.1±0.4
3	**55**	8.0±1.8
4	**58**	11.0±1.4
5	**54**	13.6±8.4
2	**1**	14.4±4.9
6	**56**	>29*
7	**59**	>29*
8	**8**	>31*

[a]IC_{50} values are presented as the mean ± SEM (n = 4), except for values marked with an asterisk for which n = 2.

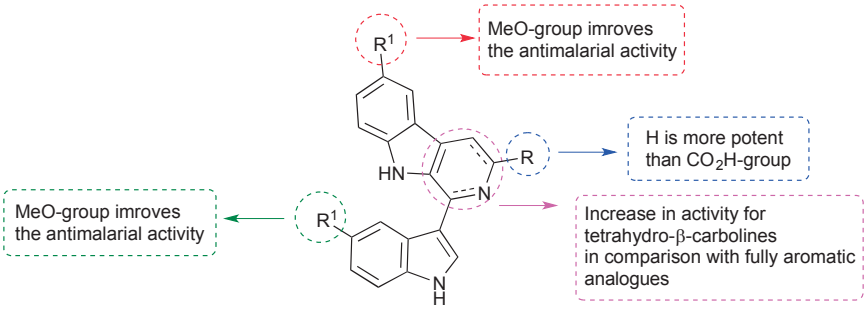


Figure 7. SAR for compounds **1**, **3**, **8**, **54-59** as antimalarial agents

6.4. ANTIOXIDANT ACTIVITY

Interestingly, compound **58** bearing two phenolic hydroxyl groups was reported to demonstrate antioxidant activity. The activity was measured in a quantitative ORAC assay against ascorbic acid. The relative ORAC value was expressed as Trolox equivalents and amounted 5.66. Also, the compound **58** displayed significant activity over vitamin C (positive control, ORAC value of 0.48). Obviously, it could be explained by the presence of two hydroxyl groups in its structure.[10]

6.5. DNA-BINDING

In 1994, eudistomin U **1** and isoeudistomin U **2** were found to be capable of binding to DNA, but their detailed biological profiles have not been determined.[5]

In 2016, a weak binding between eudistomin U **1** and DNA was confirmed; however no specific interaction with small DNA oligomers were found. That fact proved a complex binding mechanism which requires further studies.[8]

7. CONCLUSIONS

Over the last decade, synthetic strategies leading to marine alkaloid eudistomin U have been developed from a five-step protocol, providing the target compound in a low overall yield, to an efficient one-pot approach. Several facile strategies for the synthesis of isoeudistomin U and 1,2,3,4-tetrahydroeudistomin U were also reported. To date, some derivatives of eudistomin U, isoeudistomin U, and 1,2,3,4-tetrahydroeudistomin U, have been prepared, although their number is not numerous. We believe that the recent progress in the synthesis of the titled compounds will fill this gap.

The biological profiles of eudistomin U and its derivatives illustrate their potential as antibacterial, anticancer, antimalarial, and DNA-binding agents. However, the improvement in their activity is still required. Thus, among all studied derivatives of eudistomin U, dimethoxy compound **57** showed the best antimalarial activity, but it cannot be considered as promising one. Additionally, the same compound showed modest antileukemic activity, whereas eudistomin U itself generally demonstrated low cancer cell

cytotoxicity. Antibacterial activity was reported for eudistomin U and isoeudistomin U, but there are no data concerning their derivatives, and no SAR studies were performed. The promising KSP activity was disclosed for 1-(3-indolyl)-2-acyl-6-methyltetrahydro-β-carbolines **68f** and **68g**, which demonstrated modest to good activities against 5 cancer cell lines. Undoubtedly, further modification of these structures could provide compounds possessing strong anticancer activity. Finally, the DNA-binding mechanism of eudistomin U also requires additional studies. We hope that further investigations will make it clear, inspiring chemists to synthesize new derivatives which could be considered as suitable drug candidates.

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