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An Efficient Access to Enantiopure 1,3-disubstituted Isoindolines from Selective Catalytic Fragmentation of Original Desymmetrized Rigid Overbred Template

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An efficient and scalable synthesis of various enantiopure 1,3- disubstituted isoindolines are reported. The base catalyzed nucleophilic fragmentation of a rigid overbred template is established with various substrates to afford corresponding 1,3-disubstituted isoindoline ester, amide, thioate, 1,3-amino alcohol and isoindolylcarboxylic acid. The crucial rigid overbred template is synthesized in optically pure form in multigram scale by asymmetric desymmetrization of corresponding *meso* compound.

Introduction

Chiral 1-substituted isoindolinone (**1a,2**), 1-isoindolyl-carboxylic acid (**1b**) and 1,3-disubstituted isoindolines (**1c**) are constituents of many pharmaceuticals[1] and different natural products.[2] Studies done *in vitro* as well as *in vivo* have revealed that 1,3-disubstituted isoindoline derivatives if administered with the cancer drug restores intracellular level of drugs and some are found to exhibit antitumor activity in human melanoma cells.[3] Apart from this property, these molecules are reported to inhibit enzymes such as prolyl dipeptidase DPP8 and DPP9.[4] They are also found to act as N-methyl-D-aspartate antagonist,[5] modulators for endothelin(**3**),[6] 5-H2C and 5TH1A receptors and HIV-1 reverse transcriptase inhibitors.[7]

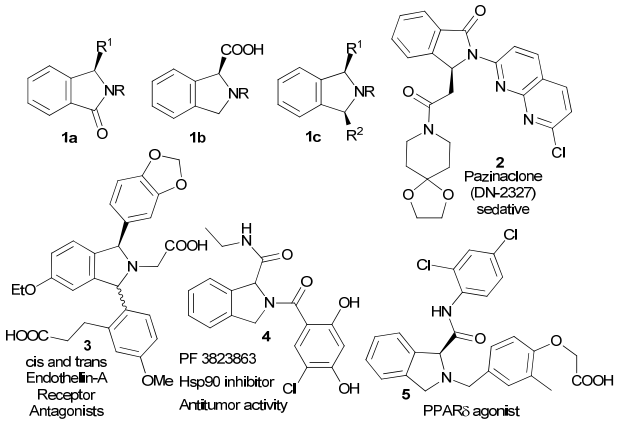
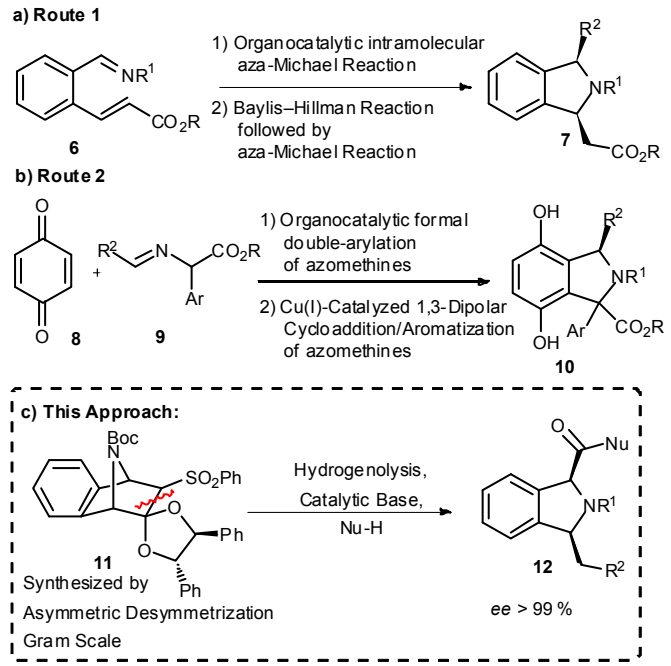


Fig. 1 Substituted Isoindolines.

Furthermore, disubstituted isoindolines are shown to inhibit amyloid protein aggregation;[8] show antibacterial, diuretic activity and antitumor activity (**4**).[9] They are also identified as a potent selective human peroxisome proliferator-activated receptor (PPARδ) agonists (**5**) and lead candidates for the treatment of diabetes.[10a] The substituted isoindoline carboxylic acid is also constituents of angiotensin converting enzyme inhibitors and are employed in SAR studies.[10b,c] Moreover, substituted isoindolines are also being explored as candidates in organic light emitting diodes.[11] Therefore, it is imperative to explore a practical and scalable route for the asymmetric synthesis of these isoindolines.

However, till date there are only few strategies known for the synthesis of 1, 3-disubstituted isoindolines in both racemic[12] as well as in optically active forms.[13] These are mainly chiral auxiliary based approaches since fixing stereocenter adjacent to a benzyl moiety is the most challenging task in their synthesis. More recently, optically active 1,3-disubstituted isoindolines (**7**) are obtained either by 1,2-addition of a nucleophile onto a bifunctional ε-benzoiminoenoates (**6**) followed by intramolecular aza-Michael reaction (route 1, Scheme 1)[14] or (**10**) by the cycloaddition of the azomethine ylide from imino ester (**9**) with quinone (**8**) in the presence of suitable chiral catalysts (route 2, Scheme 1).[15] Although promising, these methods suffer from several drawbacks such as requirement of expensive catalysts, non-scalability and inconsistent enantioselectivity. In the context of designing an entirely new strategy for the synthesis of enantiomerically pure **12**, we envisaged fixing stereochemistry of the benzylic stereocentre in the beginning itself by involving an optically pure rigid overbred template **11** as a precursor (Scheme 1).



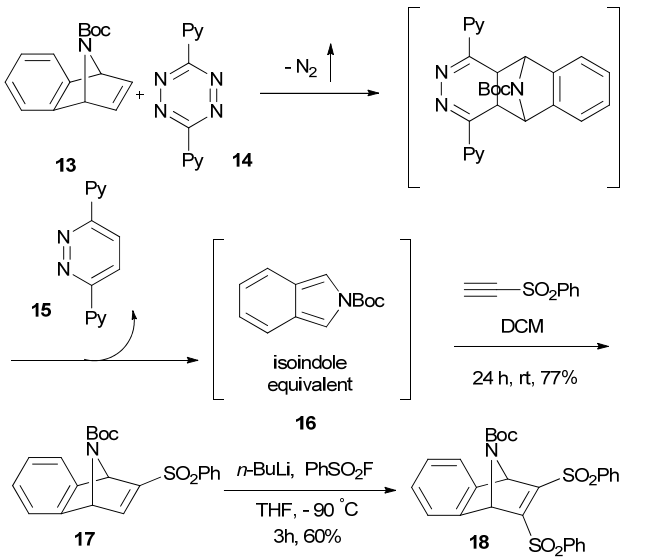
Scheme 1 Approaches towards asymmetric synthesis of 1,3-disubstituted isoindolines

The overbred precursor is the compound which possesses one or more excess C-C bond which on cleavage affords the desired skeleton.[16] This precursor was envisaged owing to presence of considerable distortion in it allowing selective carbon-carbon/heteroatom bond cleavages.[17]

We would like to report herein our success in this endeavour by preparing optically pure overbred template **11** (*ee* >99%) in multigram scale[18] by asymmetric desymmetrization of corresponding *meso* compound and its successful transformation to enantiomerically pure (*ee* = 99%) **12** by selective catalytic C2-C3 bond cleavage. To the best of our knowledge, this is the first strategy of synthesizing **12** with consistent enantioselectivity over entire range of reported substrates.

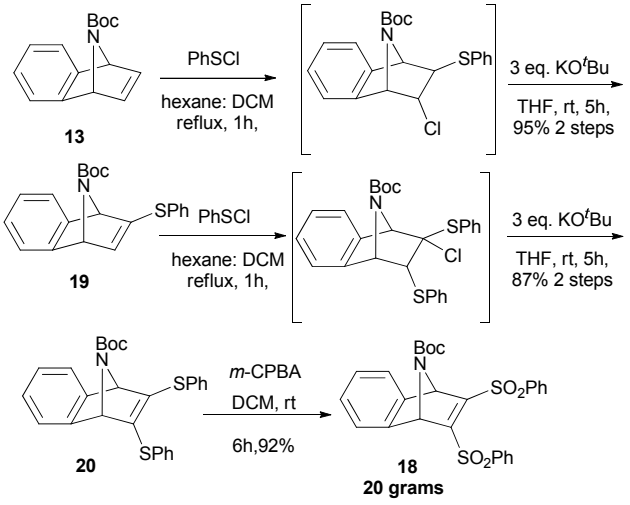
Results and Discussion

We began our research in this area first by developing a protocol for the synthesis of *meso*-**18** by following the sequence as shown in Scheme 2. Reaction of *N*-Boc-1,4-dihydro-1,4-epiminonaphthalene (**13**)[19] with *N*-Boc-pyrrole in the presence of an equimolar amount of tetrazine (**14**) and ethynyl phenyl sulfone in dry DCM afforded **17** in 77 % yield. The reaction presumably involved cycloaddition of *in situ* generated isoindole (**16**)[20] with ethynyl phenyl sulfone as shown in Scheme 2. β-Metalation (*n*-BuLi, anhydrous THF, -90 °C) of **17** followed by addition of benzene sulfonyl fluoride afforded desired *meso*-**18** in 60% yield (Scheme 2). Use of expensive tetrazine for *in situ* generation of isoindole and formation of large amount of side product **15** led us to abandon this route and began to explore another alternative protocol for its synthesis.



Scheme 2 Synthesis of *meso*-**18**

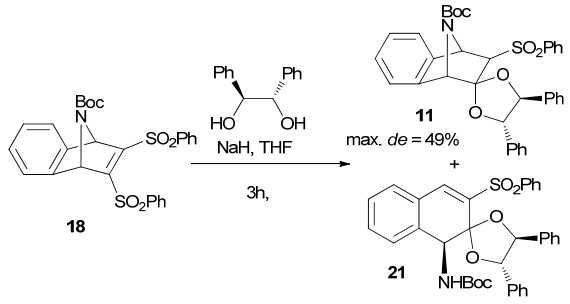
Subsequently, we evaluated an alternative strategy as shown in Scheme 3. *N*-Boc-1,4-epiminonaphthalene (**13**) was refluxed with benzenesulfenyl chloride[21] in a mixture of hexane : DCM (1:1) for 1 h and the corresponding addition product on treatment with 3 eq. of KO^{t}Bu afforded **19** in 95% yield. Repetition of the same reaction sequence with **19** afforded **20** in 87% yield which on oxidation using 4.5 eq. of *m*-chloroperbenzoic acid yielded *meso*-**18** in 92% yield. This approach of obtaining *meso*-**18** (three steps one pot reaction, 76% in overall yield) was scaled up to 20 g level and thus can be considered as the first step towards the scalable synthesis of 1,3-disubstituted isoindolines (Scheme 3).



Scheme 3 Alternative route for synthesis of *meso*-**18**

Having *meso*-**18** in hand, we proceeded with its desymmetrization using (*S,S*)-hydrobenzoin.[22] However, to our disappointment, diastereoselectivity as well as the yield of the desired **11** was found to be low due to the formation of **21** as

the major product. Our several attempts to optimize the yield and diastereoselectivity remained unsatisfactory (Table 1).



Entry	Solvent	T (°C)	yield of **11** (%)	*de* of **11** (%)[a]	yield of **21** (%)
1	THF	25	45	30	55
2	THF	0	35	32	65
3	THF	- 20	25	35	75
4	THF	- 78	20	49	80

[a] Determined by HPLC analysis, (Atlantis T-3, MeOH:H2O = 80:20, 0.5mL/min)

Table 1 Optimization of reaction condition for asymmetric desymmetrization of *meso*-**18**

A plausible mechanism for the formation of **11** and **21** is shown in Figure 2.

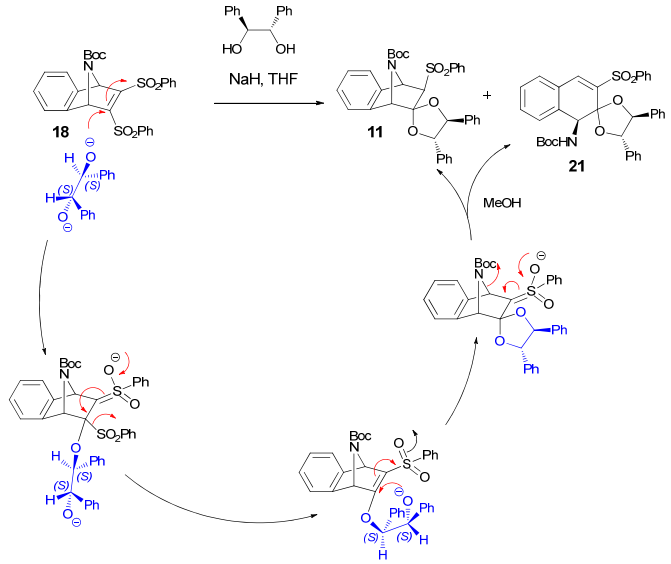


Fig. 2 Plausible Reaction mechanism

Poor diastereoselectivity was attributed to non-selective approach of (*S*,*S*)-hydrobenzoin anion from both the faces of *meso*-**18** as depicted with structure **A** and **B** whereas the formation of **21** can be explained due to the stabilization of the anion on to the nitrogen atom of the *N*-Boc group during desymmetrization and extended conjugation of the resulting double bond with the aromatic ring (Fig. 3).

Therefore, we realized that in order to achieve higher diastereoselectivity, the attack of the anion of the (*S*,*S*)-hydrobenzoin on vinylic carbon of *meso*-**18** should be specifically from only one of the β-face through least encumbered trajectory in which phenyl group should be upward opposite to bulky -SO_2Ph moiety.

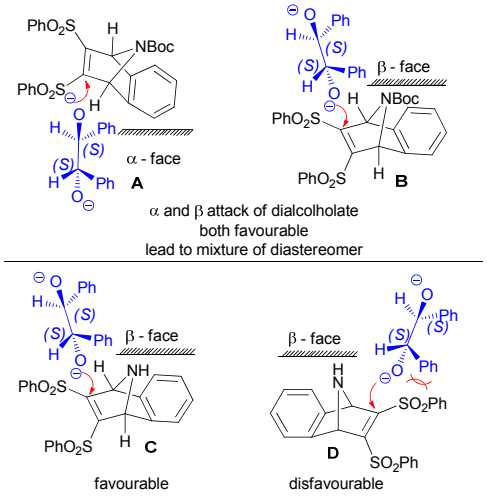
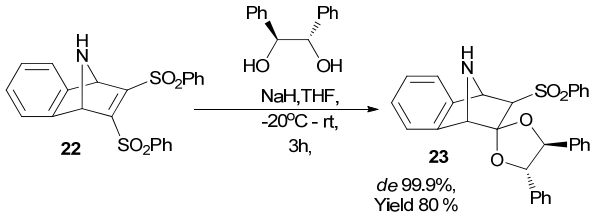


Fig. 3 Plausible explanation for preferred β-face attack anion of the (*S*,*S*)-hydrobenzoin

Thus, it was envisaged that reducing steric bulk on β-face of **22**, obtained by deprotection of *N*-Boc group, may possibly favour the β-facial attack of (*S*,*S*)-hydrobenzoin anion owing to the situation as depicted with structure **C** in comparison to unfavourable situation shown with structure **D.** Furthermore, it was also envisaged that in the case of **22**, non-stabilization of the resultant anion during nucleophilic addition will also possibly reduce the formation of undesired **21**.

Armed with this proposition, desymmetrization of *meso*-**22** was carried out with (*S*,*S*)-hydrobenzoin anion which afforded **23** as a single pure diastereomer in 80% yield under optimized experimental condition (Table-2).



Entry	Solvent	T (°C)	time (h)	yield (%)	*de* (%)[a]
1	THF	25	1.5	87	44
2	THF	0	2.5	85	82
3	THF	- 20	3	80	> 99

Table 2 Optimization of Reaction Condition for Asymmetric Desymmetrization of *meso*-**22**

In order to establish the absolute stereochemistry of **23**, its free -NH moiety was re-protected as *N*-Boc (Boc anhydride/DMAP, 82% yield,) and recrystallized for single crystal X-ray diffraction analysis (Fig. 4).[23]

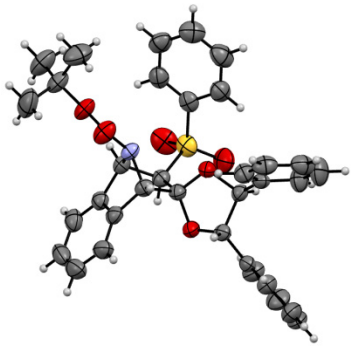
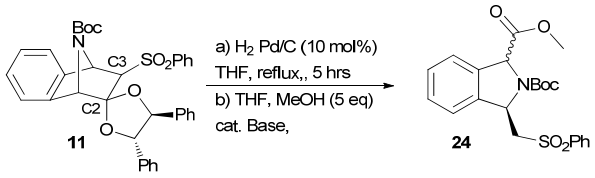


Fig. 4 ORTEP Diagram for compound **11**

With enantiomerically pure **11** in hand, we proceeded with the planned C2-C3 bond cleavage in order to obtain **24**. Towards this end, **11** was subjected to catalytic hydrogenolysis (Pd/C, 10 mol %, 1 atm. H_2, NaOMe, 10 mol%, reflux, 5 h) in THF-MeOH (1:1) which afforded, to our delight, **24** quantitatively**.** However, detailed spectroscopic analyses suggested **24** to be the mixture of diastereomers. Appropriate controlled experiments (Table 3) suggested that refluxing under this experimental condition is the root cause for the formation of diastereomers. Thus, in order to achieve selectivity, first hydrogenogenolysis was carried out in THF at reflux temperature followed by the addition of methanol and base at 0 °C which afforded corresponding optically pure (*ee* >99%) *cis*-1,3 disubstituted isoindoline ester **24** in 95 % yield.



Entry	Base	Temperature (°C)	time (min.)	Yield (%)	*cis/trans*[b]
1	NaOMe (1 eq.) [a]	65	10	90	1 : 1
2	KO^{t}Bu (1 eq.) [a]	65	10	95	1 : 3
3	NaOMe (0.1 eq) [a]	25	20	96	8 : 2
4	NaOMe (0.1 eq.) [a]	0	45	90	only cis
5	KO^{t}Bu (0.1 eq) [a]	0	45	95	only cis

[a] Sequencial addition of MeOH and base after hydrogenolysis
[b] isolated yield

Table 3 Optimization of Reaction condition for C2-C3 bond cleavage

The generality of the protocol was established by studying C2-C3 bond cleavage reaction with various substrates and results are shown in Table 4. It was pleasing to note that the enantioselectivity of all the isolated isoindolines remained consistent (*ee* >99%).

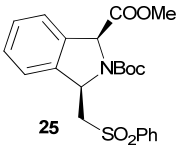
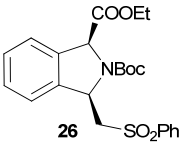
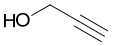
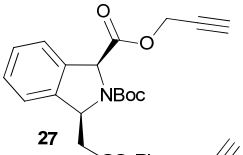
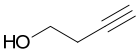
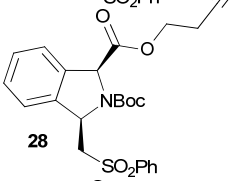
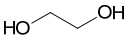
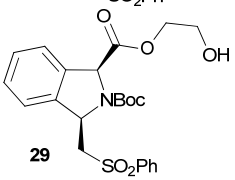
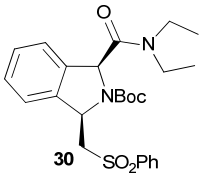
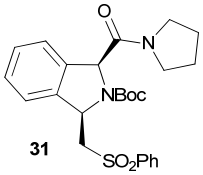
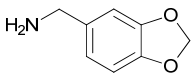
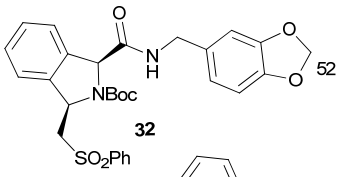
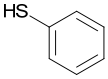
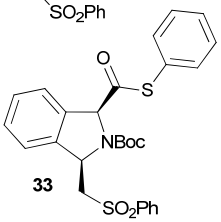
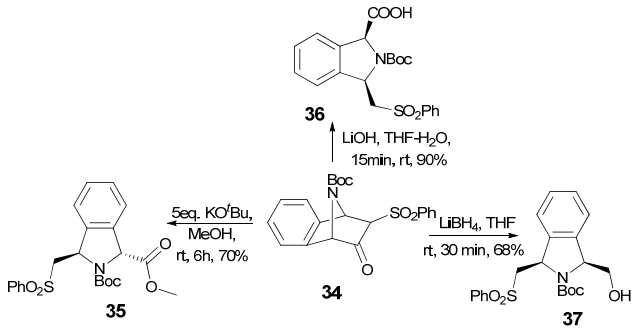
Entry	Substrate	1,3-disubstituted isoindoline	Yield (%)
1	MeOH	 **25**	95
2	EtOH	 **26**	92
3		 **27**	90
4		 **28**	83
5		 **29**	**83**
6		 **30**	72
7		 **31**	65
8		 **32**	52
9		 **33**	90

Table 4 Synthesis of various 1,3-disubstituted isoindoline

This spectacular success led us to consider the synthesis of *trans*-1,3-disubstituted isoindoline **35** as well (Scheme 4). In this context, the cleavage of C2-C3 bond of **34**, obtained by the hydrogenolysis of **11**, was carried out by stirring in MeOH for 6 h in the presence of the excess of KO^{t}Bu (5 eq.) which afforded **35** as a major product post epimerization. The *trans*-stereochemistry in **35** was established by detailed NOSEY and COSEY NMR analyses. Similarly, stirring of **34** with LiOH in THF:H_2O (1:1) at rt afforded conformationally constrained amino acid[24] **36** in 90% yield. Furthermore, treatment of **34** with $LiBH_4$ in THF produced corresponding isoindoline 1,2-amino alcohol **37** directly in 68% yield.



Scheme 4 C2-C3 bond cleavage of **34**

Conclusion

In conclusion, we have developed a conceptually new strategy for the synthesis of both *cis*- as well as *trans*-1,3-disubstituted isoindolines in optically pure form from a catalytic selective bond cleavage of a rigid bridged overbred template. Asymmetric desymmetrization protocol has been developed for the enantioselective synthesis rigid bridged overbred template. Furthermore, it has been demonstrated that this strategy can be scaled up to multigram level.

Experimental Section

Synthesis of *tert*-butyl 1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (13):

To a 1000 mL three neck round bottom flask fitted with condenser, magnetic stir bar and dropping funnel, activated magnesium turning (10.36 g, 0.426 gram atom) was added and the flask was flame dried under vacuum. The system was flushed with argon and allowed to cool. *N*-Boc-pyrrole (64 mL, 370 mmol) in 240 mL of dry THF was introduced in to the flask and heated to gentle reflux. *o*-fluorobromobenzene (44.8 mL, 408 mmol) dissolved in 200 mL of dry THF was added drop wise under argon atmosphere over a period of 30 min and refluxed for 2 h. The initiation of reaction was indicated by solution turning turbid followed by yellow in colour. The solution was cooled and poured into a flask containing 500 mL aqueous solution of ammonium chloride (300 g) and concentrated ammonium hydroxide (10 mL, 28.0% w/w NH_3). The aqueous layer was extracted with petroleum ether (3 X 400 mL), combined organic layer dried over anhydrous sodium sulphate and concentrated. The resulting dark oil on column chromatography (SiO_2, Hexane/EtOAc : 95:5) followed by crystallization in hexane afforded **11** as a white crystalline solid (56 g, 60 % yield, m.p. 72-73 ºC) R_f = 0.7 (Hexane/ EtOAc : 90:10); IR (KBr) ύ 3015, 1693, 1598, 1337, 1081, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H) 6.99-6.96 (m, 4H) 5.50(bs, 2H) 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.07, 148.23, 143.43, 142.29, 124.87, 121.02, 120.57, 80.49, 66.73, 66.14, 28.08; HRMS (ESI) *m/z* 266.1151 [(M + Na)$^+$; calcd for ($C_{15}H_{17}NO_2Na)^+$: 266.1157]

Synthesis of (±) *tert*-butyl 2-(phenylsulfonyl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (17):

To a solution of **13** (5 g, 20.55 mmol) in 210 mL of dry DCM was added (ethynylsulfonyl)benzene (3.42 g, 20.55 mmol) and tetrazine **14** (4.85 g, 20.55 mmol). The reaction mixture was stirred at rt for 18 h, diluted with 100 mL of diethyl ether and washed with water (3 X 50 mL). The organic phase was dried over sodium sulphate and solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, Hexane/ EtOAc : 8:2) to give **17** as a white solid (6.1 g, 77 % yield, m.p. 168-169 °C) R_f = 0.4 (Hexane/EtOAc : 80:20); IR (KBr) ύ = 3057, 1699, 1575, 1365, 1154, 1089, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 1.3 Hz, 2H), 7.65 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.28 (m, 2H), 6.99 (t, *J* = 7.34, 1H), 5.7 (bs , 1H), 5.53 (s,1H), 1.28 (s, 9H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.35, 146.06, 138.85, 133.82, 131.98, 130.45, 129.49, 129.40, 128.10, 125.84, 125.76, 121.78, 121.72, 81.67, 67.6, 66.98, 27.6; HRMS (ESI) *m/z* 384.1279, 406.1077 [(M + H)$^+$ (calcd for ($C_{21}H_{22}NO_4S)^+$: 384.1270 ; (M + Na)$^+$ calcd for ($C_{21}H_{21}NO_4SNa)^+$: 406.1089]

Phenylsulfonylation of alkene (17) for the synthesis of *tert*-butyl 2,3-bis(phenylsulfonyl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (18):

To a vacuum dried 250 mL two neck round-bottom flask, **17** (5.0 g, 13.04 mmol) dissolved in anhydrous THF (60 mL) was added while stirring. The flask was cooled to -90 °C and *n*-BuLi (1.6 M solution in hexane, 8.56 mL, 13.69 mmol) followed by benzene sulfonyl fluoride (1.65 mL, 13.69 mmol) solution in anhydrous THF (5 mL) was introduced drop wise into the flask. The reaction mixture was allowed to warm to rt and was quenched slowly with aqueous NH_4Cl solution (10 mL). The reaction mixture was extracted with EtOAc (3 X 100 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc: 7:3) to afford **18** (4.1 g, 60% yield, m.p. 185 – 186 °C) R_f = 0.3 (hexane/EtOAc: 7:3); IR (KBr) ύ = 3043, 2983, 1712, 1324, 1161, 1085, 758, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 4H), 7.67 (m, 2H), 7.53 (m, 4H), 7.25 – 6.96 (m, 4H), 5.88 (bs, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.07, 138.7, 134.59, 129.31, 128.93, 126.38, 126.36, 122.32,

122.07, 82.63, 71.77, 27.74; HRMS (ESI) *m/z* 546.1016 [(M + Na)$^+$ calcd for ($C_{27}H_{25}NO_6S_2Na$)$^+$: 546.1021]

Synthesis of (±) *tert*-butyl 2-(phenylthio)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (19):

A vacuum dried two neck round bottom flask (2L), equipped with reflux condenser and dropping funnel, was charged with **13** (12 g, 49 mmol) followed by dry hexane (1000 mL). A solution of benzenesulfenyl chloride (6.27 mL, 54.25 mmol) in dry DCM (300 mL) was introduced to the flask drop wise under argon atmosphere while refluxing. The reaction mixture was allowed to reflux for additional 5 min and solvent was removed under reduced pressure.

Crude reaction mixture was dissolved in dry THF (150 mL) and a solution of *t*-BuOK (1.0 M in 150 mL THF) was added in portions over a period of 15 min. The reaction mixture was stirred for additional 5 h. The solvent was removed under reduced pressure and was diluted with water (200 mL), extracted with hexane (3 X 500 mL), washed with brine and dried over Na_2SO_4. Removal of hexane followed by purification of the residue by column chromatography (SiO_2, hexane/EtOAc: 95:5) afforded **19** as a yellowish oil (16.5 g, 95% yield) R_f = 0.5 (hexane/EtOAc: 95:5); IR (KBr) ύ = 3057, 1699, 1575, 1365, 1154, 1089, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.39 (m, 2H) 7.37-7.27 (m, 3H), 7.25-7.19 (m, 2H) 7.0.-6.94 (m, 2H), 6.69 (s, 1H), 5.59 (bs, 1H), 5.23(bs, 1H) 1.42 (s, 9H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.78, 147.08, 132.51, 131.85, 129.28, 129.22, 128.96, 127.83, 126.52, 126.20, 125.58, 125.50, 124.90, 80.86, 69.02, 67.38, 28.11; HRMS (ESI) *m/z* 352.1361, 374.1177 [(M + H) (calcd for ($C_{21}H_{22}NO_2S$)$^+$: 352.1371 ; (M + Na)$^+$ calcd for ($C_{21}H_{21}NO_2SNa$)$^+$: 374.1191]

Synthesis of *tert*-butyl 2,3-bis(phenylthio)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (20):

The same reaction sequence as described above was repeated with **19** (10 g, 28.4 mmol) to afford **20** (semi solid, 11.4 g, 87% yield). R_f = 0.6 (Hexane/EtOAc: 90:10); IR (KBr) ύ = 3057, 1699, 1575, 1365, 1154, 1089, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 4H), 7.44 (t, *J* = 7.3 Hz, 4 H), 7.38 (d, *J* = 3 Hz, 2H), 7.19 (m, 2H), 7.02 (dd, *J* = 4.9 , 2.9 Hz, 2 H), 5.4 (m, 2 H), 1.49 (s, 9H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.02, 132. 67, 131.27, 130.51, 129.21, 127.63, 125.48, 120.54, 120.17, 81.09, 70.46, 69.82, 28.11; HRMS (ESI) *m/z* 482.1229 [(M + Na)$^+$ calcd for ($C_{27}H_{25}NO_2S_2Na$)$^+$: 482.1224]

Oxidation of bisulfide (20) for the synthesis of *tert*-butyl 2,3-bis(phenylsulfonyl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (18):

To a stirring solution of **20** (20 g, 43.51 mmol) in dichloromethane (500 mL) was added a solution of *m*-CPBA (48.76 g, 217.5 mmol, 77%) in dichloromethane (400 mL) drop wise at 0 °C. The reaction mixture was allowed to warm to rt and stirred for an additional 5 h. Aqueous $Na_2S_2O_3$ (1 M, 300 mL) was added and mixture washed with H_2O (300 mL) followed by aqueous Na_2CO_3 (10%, 1000 mL). The organic layer was dried over Na_2SO_4, concentrated and residue on purification by column chromatography (SiO_2, hexane/EtOAc: 4:1) gave **18** as a white solid (21 g, 92 % yield).

Synthesis of (−)-(1*S*,3*R*,4*R*,4'*S*,5'*S*)-*tert*-butyl 4',5'-diphenyl-3-(phenylsulfonyl)-3,4-dihydro-1H-spiro[1,4-epiminonaphthalene-2,2'-[1,3]dioxolane]-9-carboxylate (11):

To an ice-cold anhydrous THF (10 mL) solution containing suspension of NaH (0.33, 8.4 mmol, 60% suspension in mineral oil) was added a solution of (*S,S*)-hydrobenzoin (0.9 g, 4.2) in THF (10 mL) drop wise. After completion of addition, the mixture was allowed to warm to rt and allowed to stir for additional one hour and then kept at the desired temperature (Table 1). A solution of *meso*-**18** (2 g, 3.82 mmol) in 20 mL THF was added drop wise and stirred at the same temperature for another 2 h. After allowing it to warm to rt, MeOH (5 mL) was added. Usual workup afforded a mixture of **11** and **21** that was separated by column chromatography (SiO_2, hexane/EtOAc : 60:40).

Data for (−)-(1*S*,4*R*,4'*S*,5'*S*)-*tert*-butyl 4',5'-diphenyl-3-(phenylsulfonyl)-3,4-dihydro-1H-spiro[1,4-epiminonaphthalene-2,2'-[1,3]dioxolane]-9-carboxylate (11):

R_f = 0.45 (hexane/EtOAc: 70:30); (m.p. 180 – 181 °C); IR (KBr) ύ = 3433, 3064, 3033, 2978, 1706, 1354, 1274, 1146, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.6 Hz, 2H), 7.60 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.35 (m, 4H), 7.34 – 7.29 (m, 4H), 7.27 – 7.12 (m, 6H), 5.62 (bd, 1H), 5.27 (bs, 1H), 4.97 (bs, 1H), 4.71 (d, *J* = 8.8 Hz, 1H), 3.67 (bs, 1H), 1.31 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.79, 143.19, 141.94, 138.44, 134.75 133.53, 130.20, 128.55, 128.51, 128.30, 127.94, 127.62, 126.15, 126.05, 123.94, 123.29, 120.43, 119.77, 111.81, 86.40, 80.89, 75.74, 69.140. 63.62, 28.05; HRMS (ESI) *m/z* 618.1920 [(M + Na)$^+$ calcd for ($C_{35}H_{33}NO_6SNa$)$^+$: 618.1926]

Diastereomeric excess was determined by HPLC with Atlantis T3 5 µm column at 254 nm (MeOH:H_2O = 80:20 flow rate 0.5 mL/min) t_{major} = 17.1 min, t_{minor} = 17.9, 19.9, 21.8 min.

$[\alpha]_D^{19} = -156.11$ (*c* = 0.5, EtOH)

Data for *tert*-butyl ((1'S,4S,5S)-4,5-diphenyl-3'-(phenylsulfonyl)-1'H-spiro[[1,3]dioxolane-2,2'-naphthalen]-1'-yl)carbamate (21):

R_f = 0.4 (hexane/EtOAc: 70:30); IR (KBr) ύ = 3468, 2927, 2975, 1719, 1620, 1587, 1479, 1451, 1368, 1244, 1148, 1087, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.7-7.96 (m, 3H), 7.72-7.59 (m, 5H), 7.52 – 7.5 (m , 1H) 7.25 – 7.14 (m , 5H), 7.04 – 7.00 (m , 3H) 6.73 – 6.56 (m , 2H), 5.6 – 5.57 (m, 2H), 5.60 – 5.57 (m , 2H), 1.46 (bs, 9H) ^{13}C NMR (100 MHz, $CDCl_3$) δ153.77, 148.27, 141.48, 138.67, 137.49, 137.26, 135.98, 133.25, 132.25, 132.04, 130.50, 130.10, 129.83, 129.16, 127.99, 127.81, 127.53, 127.32, 126.74, 125.87, 125.07, 119.46, 90.01 80.92, 79.07, 28.118 ; HRMS (ESI) *m/z* 618.1918 [(M + Na)$^+$ calcd for ($C_{35}H_{33}NO_6SNa$)$^+$: 618.1926]

$[\alpha]_D^{22} = -62.22$ (*c* = 0.1, CH_2Cl_2)

Synthesis of 2,3-bis(phenylsulfonyl)-1,4-dihydro-1,4-epiminonaphthalene (22):

To a solution of **18** (70 g, 133 mmol) in dry DCM (700 mL) was added trifluoroacetic acid (51 mL, 668 mmol) drop wise at 0 °C and allowed to warm to rt. The reaction mixture was further stirred at room temperature for 5 h and the progress of the reaction was monitored by TLC. After complete disappearance of starting material, solvent and trifluoroacetic acid were evaporated off, diluted with EtOAc (500 mL), washed with aqueous $NaHCO_3$ (10%, 300 mL) and water (500 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford yellowish semi-solid **22** (51 g, 90% yield, m.p 146 – 148 °C) which was processed without further purification. R_f = 0.3 (100 % EtOAc); IR (KBr) ύ = 3434, 3286, 3063, 2923, 2853, 1622, 1581, 1448, 1334, 1317, 1154, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.3, 1 Hz, 4H), 7.65 (m, 2H), 7.49 (t, J = 8 Hz, 4H), 7.08 (dd, J = 5.3, 2 Hz, 2H), 6.90 (dd, J = 5.3, 2 Hz, 2H), 5.46 (s, 2H), 2.95 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.52, 138.578, 134.55, 129.37, 128.70, 128.11, 127.83, 122.27, 71.62; HRMS (ESI) *m/z* 424.0668, 446.0491 [$(M + H)^+$ (calcd for ($C_{22}H_{18}NO_4S_2)^+$: 424.0677 ; $(M + Na)^+$ calcd for $(C_{22}H_{17}NO_4S_2Na)^+$: 446.0497]

Synthesis of (−)-(1S,3R,4R,4'S,5'S)-4',5'-diphenyl-3-(phenylsulfonyl)-3,4-dihydro-1H-spiro[1,4-epiminonaphthalene-2,2'-[1,3]dioxolane] (23):

To an ice-cold anhydrous THF (250 mL) solution containing suspension of NaH (14.2 g, 354 mmol, 60% suspension in mineral oil) was added a solution of (*S,S*)-hydrobenzoin (25.3 g, 118 mmol) in THF (250 mL) drop wise. After completion of addition, the mixture was allowed to warm to rt and allowed to stir for additional one hour and then cooled to -20 °C. A solution of *meso*-**22** (50 g, 118mmol) in 500 mL THF was added drop wise and stirred at the same temperature for another 2 h. After allowing it to warm to rt, MeOH (100 mL) was added. Usual workup followed by column chromatography (SiO_2, hexane/EtOAc: 60:40) afforded **23** as a yellowish white solid (46.8 g, 80% , m.p. 182-184 °C). R_f = 0.5 (hexane/EtOAc: 50:50); IR (KBr) ύ = 3430, 3264, 3035, 1366, 1294, 1240, 1145, 1081, 755, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.3 Hz, 2H),7.70 (m, 1H), 7.62 (m, 2H), 7.40 – 7.34 (m, 4H), 7.30 – 7.25 (m, 3H), 7.22 – 7.14 (m 5H), 7.03 – 7.01 (m, 2H), 5.02 (s, 1H), 4.73 (d, J = 9.1 Hz, 1H), 4.51 (s, 1H), 4.49 (d, J = 9.1 Hz, 1H), 3.73 (s, 1H), 1.66 (bs, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.72, 141.88, 139.94, 136.06, 134.73, 133.63, 129.19, 128.88, 128.56, 128.48, 128.43, 127.68, 127.32, 127.24, 126.26, 123.23, 119.78, 115.86, 86.62, 86.33, 73.06, 69.19, 63.36; HRMS (ESI) *m/z* 496.1579, 518.1400 [$(M+H)^+$ (calcd for ($C_{30}H_{26}NO_4S)^+$: 496.1583 ; $(M+Na)^+$ calcd for $(C_{30}H_{25}NO_4SNa)^+$: 518.1402]

Distereomeric excess was determined by HPLC with Atlantis T3 5 µm column at 254 nm (MeOH:H_2O = 80:20 flow rate 0.5 mL/min) t_{major} = 17.1 min, t_{minor} = 17.9, 19.9, 21.8 min.

de > 99

$[\alpha]_D^{22} = -226.10$ (c = 1, EtOH)

Synthesis of (−)-(1*S*,3*R*,4R,4'S,5'S)-*tert*-butyl 4',5'-diphenyl-3-(phenylsulfonyl)-3,4-dihydro-1H-spiro[1,4-epiminonaphthalene-2,2'-[1,3]dioxolane]-9-carboxylate (11):

To a solution of anhydrous acetonitrile (800 mL) containing **23** (40 g, 80.7 mmol) was added catalytic dimethylaminopyridine (0.986 g, 8.07 mmol) and allowed to stir at 0 °C. Di-*tert*-butyl dicarbonate (37 mL, 161.4 mmol) was added drop wise and reaction mixture was allowed to warm to room temperature while stirring. The progress of reaction was monitored by TLC. After 24 h, solvent was evaporated off and residue separated by column chromatography (SiO_2, hexane/EtOAc: 80:20) to afford product **11** (42.5 g, 88%, m.p. 180 – 181 °C).

General Procedure for nucleophilic assisted anionic fragmentation (25 – 33):

A round bottom flask containing, 11 (1 mmol) added THF (1M) was added Pd/C (10 mol%,) and hydrogenated at balloon pressure at reflux for 5 h. After all the starting material gets consumed, to the same pot added catalytic KO^{t}Bu (0.05mmol) and corresponding alcohol or amine (5 mmol) at room temperature while stirring. The progress of reaction was monitored by TLC. The reaction mixture was quenched by addition of amberlite weakly acidic cation exchanger resin until pH 7. The solution was filtered, evaporated and purified by column chromatography.

(−)-(1*S*,3*R*)-2-*tert*-butyl 1-methyl 3-((phenylsulfonyl)methyl) isoindoline-1,2-dicarboxylate (25):

Yield: 95% (0.41 g), R_f = 0.5 (hexane/ethylacetate: 70:30); IR (KBr) ύ = 3438, 3067, 2977, 2930, 1752,1703, 1390, 1309, 1158, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) mixture of rotamers[25] δ 7.96 (m, 3H), 7.65 (m, 3H), 7.4 (m, 3H), 5.76 (d, J = 9.6 Hz, 0.5 H), 5.67 (d, J = 9.6 Hz, 0.5 H), 5.55 (s , 0.5H), 5.43 (s, 0.5H), 4.27 (dd, J = 13.85, 2.27 Hz 0.5 H), 3.93 (dd, J = 13.85, 1.76 Hz, 0.5 H), 3.75 (s, 3H), 3.44 (m, 1H) 1.54, 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers δ 171.02, 170.95, 152.89, 152.41, 140.62, 140.38, 139.30, 138.70, 134.55, 134.48, 133.84, 133.65, 129.42, 129.24, 129.10, 128.65, 128.61, 127.92, 127.62, 125.45, 125.16, 122.85, 122.61, 81.86, 81.16, 64.59, 64.15, 61.80, 59.79, 57.52, 57.24, 52.71, 52.60, 28.47, 28.18; HRMS (ESI) *m/z* 454.1298 [$(M + Na)^+$; calcd for $(C_{22}H_{25}NO_6SNa)^+$: 454.1300] HPLC: CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 90:10 flow rate 1.5 mL/min) t_{major} = 7.9 min, t_{minor} = 6.9 min.

$[\alpha]_D^{23} = -30.105$ (c = 1, EtOH)

(−)- (1*S*,3*R*)-2-*tert*-butyl 1-ethyl 3-((phenylsulfonyl)methyl) isoindoline-1,2-dicarboxylate (26):

Yield: 92% (0.42 g), R_f = 0.4 (hexane/EtOAc: 80:20); IR (KBr) ύ = 3472, 3067, 1747, 1703, 1568, 1478, 1390, 1370, 1191, 915, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 8.30 – 7.88 (m, 3H), 7.68 – 7.56 (m, 3H), 7.45 – 7.34 (m, 3H), 5.75 (dd, J = 9.4, 1.5 Hz, 0.5 H), 5.66, (dd J = 9.5, 1.9 Hz, 0.5H), 5.52, (s, 0.5 H), 5.4 (s, 0.5 H), 4.26 (dd, J = 13.9, 2.3 Hz, 0.5H), 4.20 (q, J = 7.04 Hz, 2H), 3.93(dd, 13.9 , 2 Hz, 0.5H), 3.44(m, 1H), 1.54 – 1.43 (s, 9H) 1.28 (td, J = 7.04, 3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers

δ170.53, 170.42, 152.88, 152.44, 140.69, 140.45, 139.36, 138.74, 134.77, 134.67, 133.81, 133.62, 129.42, 129.23, 129.03, 128.62, 128.59, 127.90, 127.62, 125.45, 125.16, 122.78, 122.56, 81.78, 81.10, 64.70, 64.28, 61.87, 61.72, 61.63, 59.87, 57.52, 57.22, 28.48, 28.21, 14.25, 14.09; HRMS (ESI) *m/z* 468.1452 [(M + Na)$^+$; calcd for $(C_{23}H_{27}NO_6SNa)^+$: 468.1457] HPLC: CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 95:5 flow rate 1.5 mL/min) t_{major} = 10.8 min, t_{minor} = 9.7 min.
$[\alpha]_D^{22} = -30.6$ (*c* = 0.5, EtOH)

(−)-(1*S*,3*R*)-2-*tert*-butyl 1-prop-2-yn-1-yl 3-(phenylsulfonyl) methyl)isoindoline-1,2-dicarboxylate (27):
Yield: 90% (0.4 g), R_f = 0.49 (hexane/EtOAc: 70:30); IR (KBr) ύ = 3271, 3067, 2977, 2930, 1757, 1702, 1448, 1389, 1308, 1158, 1176, 1118, 996, 755, 688, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 8.02 (d, *J* = 7.3 Hz, 1 H), 7.98 – 7.89(m, 2H), 7.61-7356 (m, 3H), 7.49-7.37 (m, 3H), 5.77,5.67 (d, *J* = 8.5 Hz, 1H), 5.57, 5.47 (s, 1H), 4.81-4.65 (m, 2H), 4.25 (dd, *J* = 13.8 , 2 Hz, 0.5 H), 3.92 (dd, *J* = 13.8, 1.8 Hz, 0.5H), 3.44 (ddd, *J* = 19.9, 13.8, 9.6 Hz , 1H), 2.47, 2.43 (t, *J* = 2.27 Hz 1H), 1.54, 1.44 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers δ 169.83, 169.69, 152.84, 152.28, 140.62, 140.39, 139.38, 138.76, 134.13, 133.97, 133.83, 133.64, 129.42, 129.22, 128.70, 128.68, 127.89, 127.61, 125.50, 125.17, 122.93, 122.66, 81.97, 81.36, 76.85, 75.51, 64.43, 64.05, 61.81, 59.80, 57.50, 57.20, 53.07, 52.92, 28.45, 28.16 HRMS (ESI) *m/z* 478.1294 [(M + Na)$^+$; calcd for $(C_{24}H_{25}NO_6SNa)^+$: 478.1300]
$[\propto]_D^{21}$= - 29.389 (c = 2 in CH_2Cl_2)

(−)- (1*S*,3*R*)-1-but-3-yn-1-yl 2-*tert*-butyl 3-((phenylsulfonyl) methyl)isoindoline-1,2-dicarboxylate (28)*:*
Yield: 83% (0.39 g), R_f = 0.45 (hexane/EtOAc: 70:30); IR (KBr) ύ = 3471, 3293, 3067, 2977, 2931, 2254, 1750, 1702, 1390, 1308, 1185, 1158, 1002, 755, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 8.02 (d, *J* = 7.3 Hz, 1H) 7.93 (m, 2H), 7.62 (m, 3H), , 7.51 – 7.34 (m , 3H), 5.76 - 5.68 (d, *J* = 9.06 Hz 1H), 5.55 - 5.44 (s, 1H), 4.31-4.19 (m, 2H), 3.46 (td , *J* = 14.7, 9.7 Hz, 2H), 2.52 (m , 3H), 1.54, 1.43 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers 170.29, 170.10, 152.85, 152.33, 140.65, 140.43, 139.33, 138.76, 134.46, 134.29, 133.84, 133.64, 129.43, 129.23, 129.13, 128.64, 127.90, 127.65, 125.44, 125.12, 123.06, 122.74, 81.86, 81.21, 79.83, 79.60, 70.25, 70.03, 64.58, 64.20, 63.17, 61.82, 59.87, 57.50, 57.21, 28.47, 28.23, 18.95, 18.87; HRMS (ESI) *m/z* 492.1445 [(M + Na)$^+$; calcd for $(C_{25}H_{27}NO_6SNa)^+$: 492.1456]
HPLC: CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 80:20 flow rate 1.5 mL/min) t_{major} = 10.8 min, t_{minor} = 12.3 min., *ee* > 99
$[\alpha]_D^{23} = -22.4$ (*c* = 0.5, CH_2Cl_2)

(−)-(1S,*3R)* *2-tert*-butyl 1-(2-hydroxyethyl) 3-((phenylsulfonyl) methyl)isoindoline-1,2-dicarboxylate (29) :
Data: Yield: 92% (0.43 g), R_f = 0.2 (hexane/EtOAc: 60:40); IR (KBr) ύ = 3470, 2932, 2976, 1747, 1701, 1392, 1307, 1189, 1158, 1085, 969, 756, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 8.01 – 7.86 (m, 3H), 7.60-7.57 (m, 3H), 7.43-7.36 (m, 3H), 5.77 – 5.67 (m, 1H), 5.55, 5.47 (s, 1H) 4.29 – 4.26 (m, 2H), 4.2 – 4.17 (dd, *J* =14, 2.4 Hz, 0.5H) 3.91- 3.87 (dd *J* = 13.7, 2.1 Hz, 0.5 H), 3.82 (m, 2H), 3.49 (td, *J* = 13.2, 9.1 2H), 1.53, 1.43 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers δ 170.85, 170.50, 153.36, 152.57, 140.57, 140.42, 139.22, 138.61, 134.51, 134.16, 134.13, 133.89, 133.71, 133.67, 129.47, 129.25, 129.14, 128.76, 127.86, 127.61, 125.17, 125.01, 122.85, 122.65, 82.32, 81.37, 67.16, 64.74, 64.45, 61.67, 60.87, 60.73, 59.62, 57.70, 57.31, 28.45, 28.21 HRMS (ESI) *m/z* 484.1400 [(M + Na)$^+$; calcd for $(C_{23}H_{27}NO_7SNa)^+$: 484.1406]
$[\alpha]_D^{23} = -41.2$ (*c* = 1, CH_2Cl_2)

(−)- (1*S*,3*R*)-*tert*-butyl 1-(diethylcarbamoyl)-3-((phenylsulfonyl)methyl)isoindoline-2-carboxylate (30):
Yield: 72% (0.35 g) , R_f = 0.4 (hexane/EtOAc: 50:50); IR (KBr) ύ = 3451, 3068, 2978, 2934, 1698, 1650, 1393, 1306, 1157, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 8.00- 7.91 (m, 3H), 7.64-7.50 (m, 3H), 7.41 – 7.17(m , 3H), 5.88 – 5.76 (m , 2H), 4.26 – 3.9 (m, 1H), 3.789 – 3.62 (m , 3H), 3.52 (dq, *J* = 13.7,7 Hz, 1H), 3.19 (m , 1H), 1.54 – 1.44 (s, 9H), 1.48 - 1.39 (m, 3H), 1.13-1.06 (m , 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers δ 170.01, 169.58, 152.89, 152.31, 140.73, 140.66, 140.19, 139.60, 136.80, 136.57, 133.58, 133.37, 129.22, 129.05, 128.60, 128.33, 127.876, 127.62, 125.52, 125.22, 121.27, 121.16, 81.27, 81.10, 62.26,61.68, 61.56, 60.25, 57.50, 57.26, 42.60, 42.37, 41.08, 40.90, 28.53, 28.45, 14.99, 14.94; HRMS (ESI) *m/z* 495.1635 [(M + Na)$^+$; calcd for $(C_{25}H_{32}N_2O_5SNa)^+$: 495.1930]
$[\alpha]_D^{23} = -68.7$ (*c* = 0.52, CH_2Cl_2)

(−)-(1*R*,3*S*)-*tert*-butyl 1-((phenylsulfonyl)methyl)-3-(pyrrolidine-1-carbonyl)isoindoline-2-carboxylate (31):
Yield: 65% (0.31 g), R_f = 0.35 (hexane/EtOAc: 50:50); IR (KBr) ύ = 3451, 2931, 2969, 1699, 1651, 1448, 1387, 1159, 1113, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.95 – 7.80 (m, 3H), 7.61 – 7.46 (m, 3H), 7.36 – 7.121 (3H), 5.77 – 5.63 (m, 2H), 4.23 – 3.87 (m , 1H), 3.84 - 3.78 (m, 2H), 3.75 – 3.64 (m ,1H), 3.51 – 3.44 (m , 1H), 3.42 – 3.30 (m, 1H), 2.06 – 2.00 (m , 2H), 1.91 – 1.84 (m , 2H), 1.51 – 1.39 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers δ 168.83, 168.78, 152.68, 151.98, 140.53, 140.44, 139.92, 139.31, 136.48, 136.31, 133.46, 133.25, 129.10, 128.91, 128.43, 128.40, 128.21, 128.19, 127.59, 127.37, 125.30, 124.98, 121.26, 121.23, 81.20, 80.52, 63.40, 63.12, 62.14, 60.03, 57.20, 57.08, 46.93, 46.89, 28.37, 28.13, 26.16, 26.02, 23.97, 23.90 ; HRMS (ESI) *m/z* 471.1949, 493.1769 [(M + H)$^+$ = calcd for $(C_{25}H_{31}N_2O_5SNa)^+$: 471.1953 , (M + Na)$^+$; calcd for $(C_{25}H_{30}N_2O_5SNa)^+$: 493.1773]
HPLC: CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 60:40 flow rate 1.5 mL/min) t_{major} = 3.4 min, t_{minor} = 4.3 min., *ee* >99

$[\alpha]_D^{21} = -118.4$ ($c = 0.54$, CH_2Cl_2)

(−)-(1*S*,3*R*)-*tert*-butyl 1-((benzo[d][1,3]dioxol-5-ylmethyl)carbamoyl)-3-((phenylsulfonyl)methyl)isoindoline-2-carboxylate (32) :

Yield: 52 % (0.29 g), R_f = 0.3 (hexane/EtOAc: 50:50); IR (KBr) ύ = 3432, 2923, 1698, 1670, 1547, 1490, 1446, 1392, 1253, 1158, 1122, 1038, 927, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 8.13 (bs 1H), 7.61 – 7.57 (m, 3H), 7.45 – 7.15 (m, 4H), 7.15 – 6.7 (m, 4H) 5.88 (s, 2H), 5.54 – 5.37 (bs,1H) 4.47 – 4.29 (m, 3H), 3.62 – 3.47 (m, 1H) 1.56 – 1.41 (bs , 9H); ^{13}C NMR(100 MHz, $CDCl_3$) δ mixture of rotamers 169.98, 154.70, 147.69, 146.69, 140.20, 137.91, 135.93, 133.59, 132.39, 130.10, 129.43, 129.13, 128.56, 128.47,128.29, 128.26, 127.70, 127.51, 126.79, 123.46, 108.80, 108.11, 107.43, 102.55, 102.50, 100.82, 81.91, 68.31, 67.46, 60.32, 57.27, 43.00, 28.10 ; HRMS (ESI) *m/z* 551.1843, 573.1667 [(M + H)$^+$ = calcd for $(C_{29}H_{31}N_2O_7S)^+$: 551.1852 , (M + Na)$^+$; calcd for $(C_{29}H_{31}N_2O_7S)^+$: 553.1671]HPLC: CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 60:40 flow rate 1.5 mL/min) t_{minor} = 8.3 min, t_{major} = 10.5 min., *ee* >99

$[\alpha]_D^{21} = -23.5$ ($c = 0.3$, CH_2Cl_2)

(−)-(1*R*,3*S*)-*tert*-butyl 1-((phenylsulfonyl)methyl)-3-((phenylthio)carbonyl)isoindoline-2-carboxylate (33)

Yield: 90% (0.46 g), R_f = 0.49 (hexane/EtOAc: 70:30); IR (KBr) ύ = 3424, 3064, 2977, 2929, 1706, 1476, 1446, 1372, 1308, 1159, 1118, 750, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 8.06 - 7.95 (m, 3H), 7.69 – 7.57 (m, 3H), 7.48 – 7.32 (m, 8H), 5.85 – 5.58 (m, 1H), 4.33 (d , J = 13.6 Hz 1H), 3.64 (dd J = 13.5, 9.4 Hz, 2H) 1.58, 1.51 (s, 9H)) ; ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers δ 197.34, 196.88, 153.24, 152.70, 140.59, 140.56, 140.25, 139.22, 138.63, 134.56, 134.48, 134.9, 133.89, 133.73, 129.64, 129.57, 129.46, 129.40, 129.33, 129.28, 129.21, 128.84, 128.78, 128.02, 127.66, 126.55, 125.38, 125.12, 123.10, 122.83, 82.37, 81.94, 71.54, 71.17, 61.93, 60.28, 58.15, 57.79, 28.31 HRMS (ESI) *m/z* 532.1221 [(M + Na)$^+$; calcd for $(C_{27}H_{27}NO_5S_2Na)^+$: 532.1228]

$[\propto]_D^{20} = -18.887$ (c = 2 in CH_2Cl_2)

Synthesis of (−)-(1*S*,3*R*,4*R*)-*tert*-butyl 2-oxo-3-(phenylsulfonyl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (34) :

A round bottom flask containing, 11 (40 g, 67.15 mmol) in THF (40 mL) was added Pd/C (8 g,) and hydrogenated at balloon pressure at reflux for 5 h. The reaction mixture was filtered over a bed of celite and solvent was removed under reduced pressure. The crude mixture on column chromatography purification afforded 34 (26.5 g, 98%) yield based on recovered starting material, m.p. 148 – 150 °C). The remaining starting material (2.4 g) was further recycled.

R_f = 0.5 (hexane/EtOAc : 70:30); IR (KBr) ύ = 3425, 3079, 2929, 1767, 1711, 1695, 1322, 1154, 1097, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96, 7.76 (d, J = 7.6 Hz, 2H), 7.65 (m, 1H), 7.56 (m, 2H), 7.47 – 7.22 (m, 4H), 5.39- 5.77 (s, d 1H), 5.12-5.04 (s 1H), 3.64 (s, 1H), 1.41-1.37 (s, 9H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.00, 192.31, 153.50, 153.6, 144.11, 144.09, 140.96, 138.85, 138.29, 136.05, 134.25, 134.03, 129.24, 129.21, 129.05, 128.94, 128.88, 128.64, 128.56, 124.16, 123.40, 122.68, 121.29, 82.59, 81.39, 69.63, 68.82, 68.20, 68.14, 62.39, 62.12, 29.58, 28.00; HRMS (ESI) *m/z* 422.1032 [(M + Na)$^+$; calcd for $(C_{21}H_{21}NO_5SNa)^+$: 422.1038]

$[\alpha]_D^{22} = -78.5$ ($c = 1$, EtOH)

Compound **34** was unstable on HPLC Column and hence its enantiomeric ratio was determined by converting into its corresponding either methyl (**25)** or ethyl ester (**26**). (*ee* > 99 %)

(+)-(1*R*,3*R*)-2-*tert*-butyl 1-methyl 3-((phenylsulfonyl)methyl) isoindoline-1,2-dicarboxylate (35):

Yield: 70 % (0.3 g), R_f = 0.45 (Hexane/EtOAc: 70:30); IR (KBr) ύ = 3435, 2995, 2983, 1750, 1703, 1448, 1391, 1309, 1161, 1086, 1022, 746, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.71-7.56 (m, 2H), 7.58 (m , 1H), 7.5 – 7.26 (m , 6H), 5.66 – 5.6 (m , 1H), 5.36 – 5.32 (m, 1H), 4.26 (dd J = 14.6, 5.8 Hz, 1H) 3.89 – 3.85 (m, 1H), 3.73-3.71 (s, 3H), 1.51 – 1.41 (s, 9H) ;^{13}C NMR(100 MHz, $CDCl_3$) δ mixture of rotamers 170.90, 153.07, 140.63, 137.19, 134.74, 133.31, 129.27, 129.06, 129.00, 128.75, 123.92, 122.42, 81.21, 65.79, 59.27, 56.81, 52.41, 28.17 HRMS (ESI) *m/z* 454.1296 [(M + Na)$^+$; calcd for $(C_{22}H_{25}NO_6SNa)^+$: 454.1300]

$[\alpha]_D^{22} = +32.6$ ($c = 1$, CH_2Cl_2)

(−)-(1*S*,3*R*)-2-(*tert*-butoxycarbonyl)-3-((phenylsulfonyl) methyl)isoindoline-1-carboxylic acid (36) :

Yield: 90 % (0.37 g), R_f = 0.3 (100% EtOAc); IR (KBr) ύ = 3432, 2977, 2926, 1681, 1620, 1416, 1306, 1157, 1131, 1086, 1020, 754, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.92 (d, J = 7.6 Hz, 2H), 7.82 – 7.74 (m, 2H), 7.65 (dt, J = 13.8 , 7.2 Hz, 1H), 7.55 (dt, J = 15.5,7.6 Hz, 2H), 7.47 – 7.34 (m, 3H), 5.72 – 5.60 (m, 1H), 4.13 (m ,0.6 H), 3.86 (d, J = 13.3 Hz 0.6 H), 3.59 (dd, J = 13.6, 9.1 Hz, 0.6 H), 3.46 (dd, J = 13.6 , 9.3 Hz 0.6 H), 1.51 – 1.42 (s, 9H) ^{13}C NMR(100 MHz, $CDCl_3$) δ mixture of rotamers 174.53, 174.30, 153.37, 152.76, 140.49, 140.14, 138.95, 138.00, 134.01, 133.86, 133.70, 129.44, 129.25, 129.18, 128.75, 127.81, 127.63, 127.89, 123.19, 122.88, 82.37, 81.74, 64.85, 64.18, 61.51, 58.92, 58.01, 57.46, 28.43, 28.13; HRMS (ESI) *m/z* 440.1138 [(M + Na)$^+$; calcd for $(C_{21}H_{23}NO_6SNa)^+$: 440.1143]

$[\alpha]_D^{23} = -44.242$ ($c = 0.1$, CH_2Cl_2)

(−)-(1*S*,3*R*)-*tert*-butyl 1-(hydroxymethyl)-3-((phenylsulfonyl)methyl)isoindoline-2-carboxylate (37) :

Yield: 68 % (0.27 g), R_f = 0.22 (Hexane/EtOAc: 60:40); IR (KBr) ύ = 3450, 2976, 2828, 1693, 1448, 1394, 1305, 1158, 1117, 1019, 756, 565cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.93 (d, J = 7.6 Hz, 2H), 7.76-7.56 (m, 4H), 7.35-7.23 (m, 3H), 5.72 (d, J = 7.8 Hz, 1H), 5.20 (s, 1H), 4.5 (d, J = 7.6 Hz, 1H), 3.91, (bs, 1H), 3.74 (d, J = 12.6 Hz, 1 H), 3.45, (m, 2H), 1.54 (s, 9H);^{13}C NMR(100 MHz, $CDCl_3$) mixture of

rotamers δ156.56, 140.70, 139.84, 138.52, 137.53, 136.77, 133.83, 129.44, 129.30, 128.53, 127.92, 127.81, 127.61, 124.49, 122.53, 82.10, 67.25, 65.71, 62.31, 57.74, 28.46 HRMS (ESI) *m/z* 426.1346 [(M + Na)$^+$; calcd for $(C_{21}H_{25}NO_5SNa)^+$: 426.1351]

$[\alpha]_D^{22} = -19.6$ (c = 1, CH_2Cl_2)

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Notes and references

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