Chapter 6

Diastereoselective Synthesis of 2-(*N*-Tosylamido)-2-(chroman-2-yl)ethanols and Related Compounds via ArO–C Bond-Forming Intramolecular Aziridine Ring-Opening Cyclization

Work of this Chapter has been *accepted* for publication:

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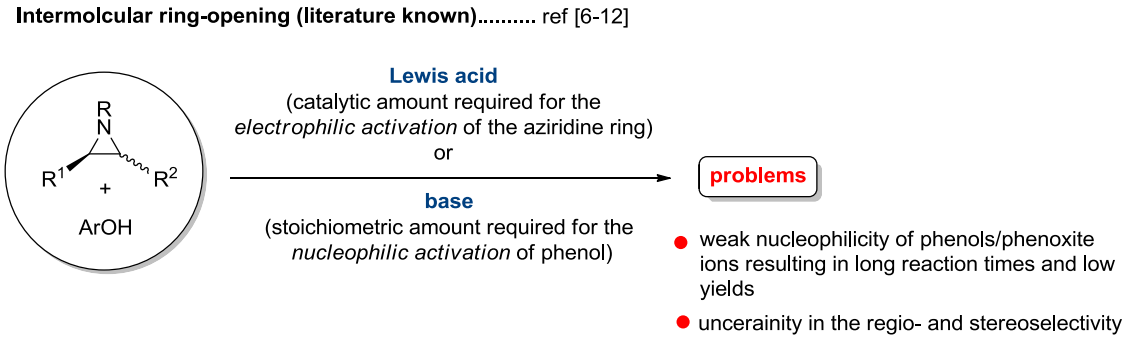
6.1. Introduction

N-Activated aziridines serve as versatile building blocks to generate (*N*-derivatized)aminoethyl fragment-bearing compounds via inter- and intramolecular nucleophilic ring-opening reactions [1-6]. Today, the portfolio of nucleophiles that are widely used in the manipulations of aziridine ring-opening chemistry includes diverse carbon- and hetero-nucleophiles. Along this line, phenols are notable exceptions as they are scarcely found in the gamut of main line nucleophiles used in the aziridine ring-opening chemistry [7-13]. This dearth is apparently due to the poor nucleophilicity of phenols/phenolates. Intermolecular ring-opening reactions of aziridines by phenols/phenolates often suffer from disadvantages such as long reaction times, low yields, poor regio- and stereoselectivity, use of expensive reagents and tedious operations (Scheme 6.1). These shortcomings have been critical obstructions for further advances in the aziridine ring-opening chemistry.

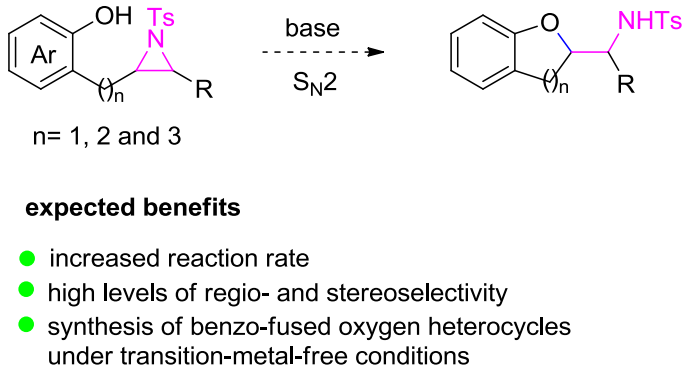


Scheme 6.1. Common problems associated with intermolecular ring-opening of aziridines by phenols

Moreover, regioselectivity can be a problematic issue for such reactions, making the scenario further complicated. Excellent regioselectivities are usually obtained with terminal and aryl/vinyl-substituted aziridines, while regiocontrol is generally difficult to grasp for the ring-opening of unsymmetrically-disubstituted ones. Thus, use of phenols as hetero-nucleophiles in the stereo- and regioselective ring-opening of unsymmetrical di- and tri-substituted aziridines has received considerably less attention. In fact, only a few reports have carefully studied this aspect [14-17]. Fine tuning of the steric and electronic effects on the two aziridine-carbon atoms have been the key for the success.

6.2. Background and Objectives

As already mentioned in the **Chapter 1** of this thesis, benzoxacycles such as 2,3-dihydrobenzofuran, chroman, 1,4-benzodioxane, and 1-benzoxepane ring systems are integral parts of a large number of biologically important natural and synthetic compounds. Despite the availability of a plethora of synthetic methods for benzoxacycles, the development of new approaches for their synthesis involving various advantageous features, such as complete atom-economy, transition-metal-free conditions, shorter reaction time, ambient temperature, operational simplicity, and high yields are still in high demand. We recognized a base-mediated intramolecular ring-opening cyclization of an *N*-activated aziridine such as *N*-tosyl aziridine with a tethered phenol would satisfy such synthetic features (Scheme 6.2).



Scheme 6.2. Our envisioned approach for the synthesis of benzoxacycles

Driven by the entropy factor and guided by the Baldwin's rules, phenolate-induced intramolecular aziridine ring-opening should be more synthetically useful (than the intermolecular one), and would not only broaden the impact of aziridines as synthetic building blocks but also unveil a new entry to the synthesis benzoxacycles, including chroman-based amino alcohols which could not be synthesized by us via dienone-phenol rearrangement of a spiro-fused cyclohexadienone ─ tetrahydrofuran system (Chapter 5).

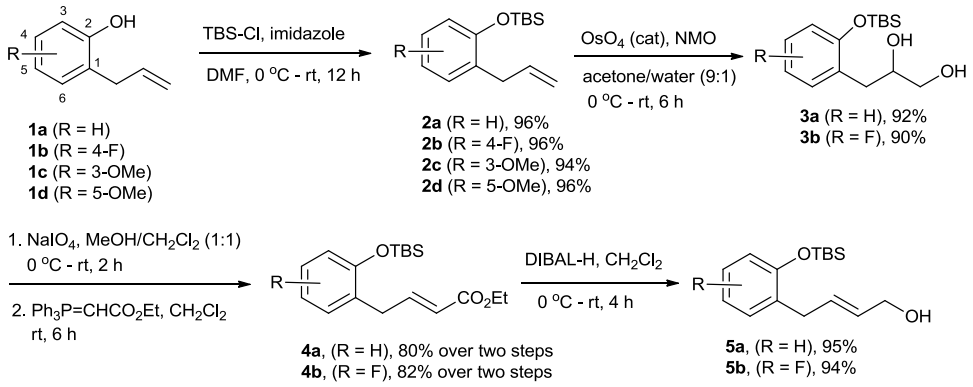
The aim of the research work described in this chapter was to synthesize 2,3-dihydrobenzofuran, chroman, and 1-benzoxepane-containing amino alcohol and other derivatives based on the above-mentioned envisioned approach. Surprisingly, however, to the best of our knowledge, such a process has heretofore not been reported, although De Kimpe et al. elegantly showcased, only on one occasion, its potential in a reaction mechanism step while demonstrating the synthesis of 1,4-benzodioxane derivatives [15].

6.3. Results and Discussion

6.3.1. Preparation of Olefin Substrates

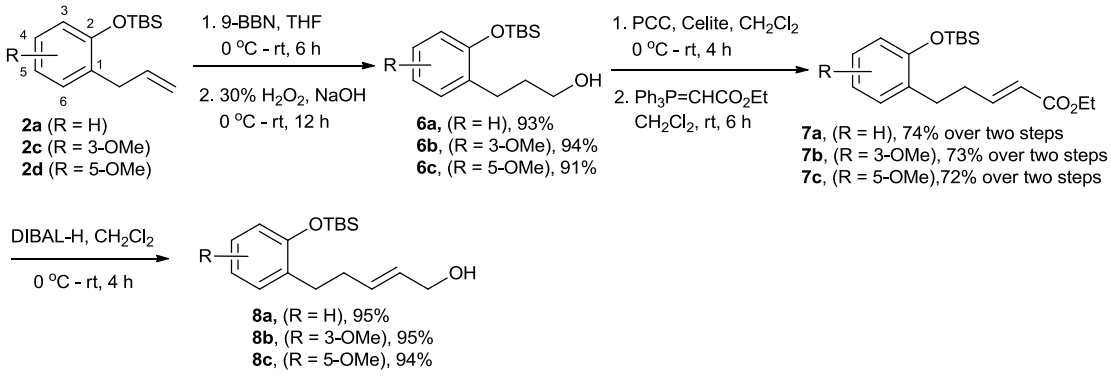
In order to utilize *N*-tosylaziridines for the synthesis of benzoxacycles, first synthesis of a set of substituted olefins *ortho*-tethered to a protected phenol component by different lengths was necessary. As shown in Schemes 6.3, 6.4 and 6.5, using well-established protocols, we synthesized *E*-allylic alcohols **2a-b**, **5a-b**, **8a-c**, and **11** as olefin substrates in multistep but high overall yielding reaction sequences.

We started our investigation by *t*-butyldimethylsilylation of 2-allylphenols **1a-d** with *t*-butyldimethylsilyl chloride and imidazole in DMF (Scheme 6.3). The corresponding TBS ethers (**2a-d**) were obtained in excellent yields. Compounds **2a**,**b** were dihydroxylated dihydroxylation reaction under Upjohn conditions (OsO_4 and NMO) to afford diols **3a**,**b**. Next, oxidative cleavage of **3a**,**b** with $NaIO_4$ and subsequent Wittig olefination of the resulting crude aldehydes with (carbethoxymethylene)triphenyl phosphorene ($Ph_3P{=}CHCO_2Et$) afforded (*E*)-α,β-unsaturated esters **4a**,**b**. DIBAL-H reduction of compounds **4a**,**b** gave the corresponding *E*-allylic alcohols **5a**,**b** in high yields.



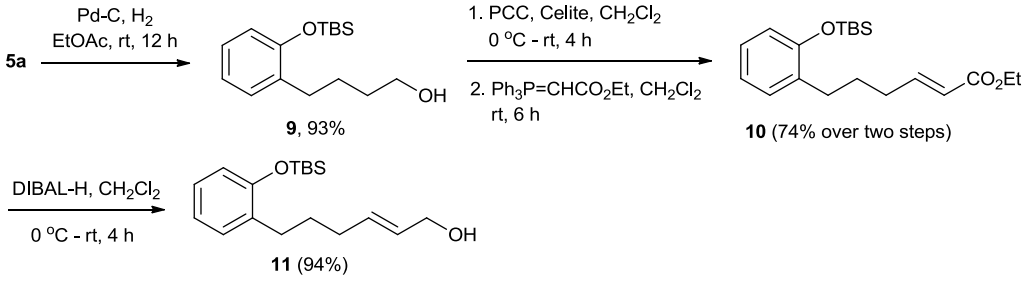
Scheme 6.3. Synthesis of *E*-allylic alcohols 5a,b

For the synthesis of homologues *E*-allylic alcohols **8a-c**, first hydroboration (9-BBN) ─ oxidation (H_2O_2, NaOH) of **2a**, **2c** and **2d** was performed to obtain primary alcohols **6a**, **6b** and **6c**, respectively (Scheme 6.4). PCC oxidation of **6a-c** followed by Wittig olefination of the resulting crude aldehydes with $Ph_3P{=}CHCO_2Et$ afforded (*E*)-α,β-unsaturated esters **7a-c** which were then reduced by DIBAL-H to obtain *E*-allylic alcohols **8a-c**.



Scheme 6.4. Synthesis of *E*-allylic alcohols 8a-c

On the other hand, hydrogenation (Pd-C, H_2) of **5a** furnished saturated alcohol **9** which was then converted to *E*-allylic alcohol **11** in a similar fashion to the synthesized homologues **8a-c** (Scheme 6.5). Noteworthy is that in all of these cases, frequently used benzyl group was not chosen as the phenolic-OH protecting group since aziridine ring of the corresponding *N*-tosylaziridine substrates would be prone to hydrogenolysis during the debenzylation process [18].



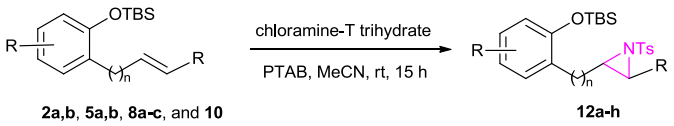
Scheme 6.5. Synthesis of *E*-allylic alcohols 8a-c

6.3.2. Aziridination of Olefins to Access *N*-Tosylaziridines

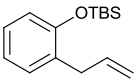
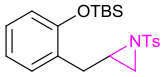
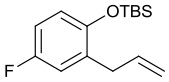
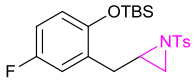
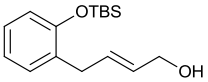
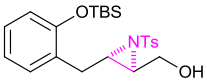
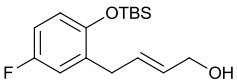
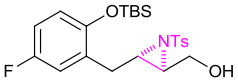
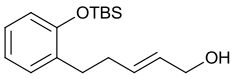
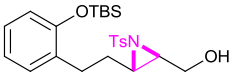
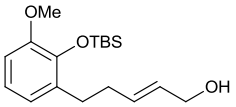
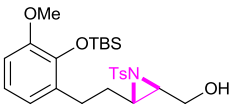
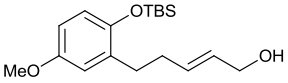
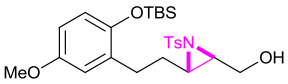
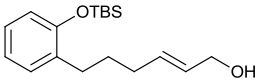
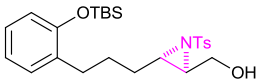
We then opted for the aziridination of terminal alkenes **2a,b** and *E*-allylic alcohols **5a-b**, **8a-c**, and **11** to synthesize the corresponding *N*-tosylaziridines using the standard Sharpless aziridination conditions [19]. Thus, aziridination of these olefin substrates with 1.1 equiv of chloramine-T trihydrate ($TsNClNa\cdot 3H_2O$) in the presence of 10 mol % of phenyltrimethylammonium tribromide (PTAB) in acetonitrile gave the corresponding *N*-tosylaziridines **12a-h** (Table 6.1). Noticeably, the yields of **12c-h** were much higher than **12a,b** ─ possibly due to the important roles played by the proximate hydroxyl group in the allylic alcohol substrates [19]. Also, as expected, *N*-tosyl-2,3-aziridino alcohols **12c-h** were formed in completely diastereoselective fashion.

Efforts were also given to develop a five-step enantioselective synthesis of aziridine **12e** from **8a** using Sharpless asymmetric epoxidation as the source of chirality (not shown here), but these attempts were unfortunately abortive [20].

Table 6.1. Synthesis of *N*-tosylaziridines[a]



2a,b, **5a,b**, **8a-c**, and **10** — **12a-h**

entry	olefin	*N*-tosylaziridine
1	 **2a**	 **12a** (62%)
2	 **2b**	 **12b** (65%)
3	 **5a**	 **12c** (92%)
4	 **5b**	 **12d** (90%)
5	 **8a**	 **12e** (90%)
6	 **8b**	 **12f** (87%)
7	 **8c**	 **12g** (89%)
8	 **11**	 **12h** (90%)

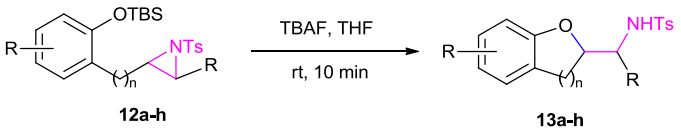
[a]Reaction conditions: olefin (1.0 equiv), $TsNClNa \cdot 3H_2O$ (1.1 equiv), PTAB (0.1 equiv)

6.3.3. Intramolecular Ring-Opening Cyclization of *N*-Tosylaziridines

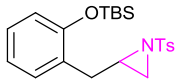
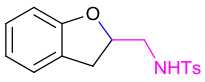
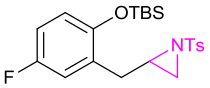
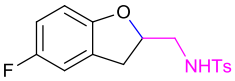
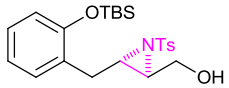
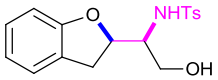
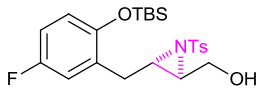
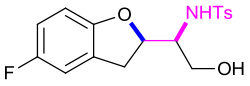
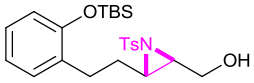
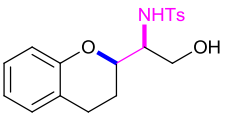
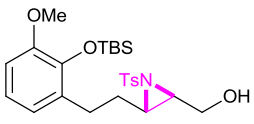
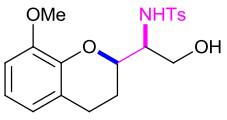
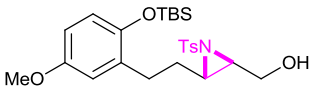
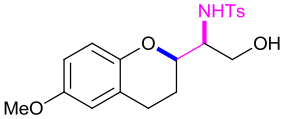
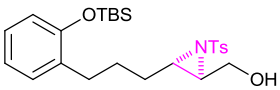
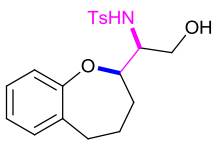
With *N*-tosylaziridines **12a-h** in hand, we were now ready to study their intramolecular ring-opening cyclization reactions. Along this line, first we treated

compounds **12a,b** with tetrabutylammonium fluoride (TBAF) in THF under a typical TBS deprotection reaction conditions (Table 6.2, entries 1 and 2). We were delighted to see that the reactions furnished 2-tosylamidomethyl-2,3-dihydrobenzofurans **13a,b** as the corresponding cyclized products in very high yields within very short reaction time.

Table 6.2. Synthesis of benzoxacycles from *N*-tosylaziridines[a]



12a-h **13a-h**

entry	*N*-tosylaziridine	benzoxacycle
1	 **12a**	 **13a** (96%)
2	 **12b**	 **13b** (95%)
3	 **12c**	 **13c** (95%)
4	 **12d**	 **13d** (93%)
5	 **12e**	 **13e** (94%)
6	 **12f**	 **13f** (96%)
7	 **12g**	 **13g** (95%)
8	 **12h**	 **13h** (89%)

[a]Reaction conditions: *N*-tosylaziridine (1.0 equiv), TBAF (1.1 equiv)

Preferential formation of the 2,3-dihydrobenzofuran ring over the chroman ring was confirmed on the basis of the chemical shifts of the protons and carbons at C-1', C-2 and C-3 of **13a**,**b**. For example, in the ^{1}H NMR spectrum compound **13a**, these protons appeared at δ 4.88-4.79 (m, 2H, C2-H and N-H), 3.35-3.22 (m, 2H, C1'-H_2), 3.17-3.11 (m, 1H, C1-H_a) and 2.96 (dd, *J* = 15.6, 7.3 Hz, 1H, C1-H_b) (Figure 6.1). Its ^{13}C NMR spectrum showed four signals at δ 80.66, 46.95, 32.50, and 21.52 ppm for C-2, C-1', C-3 and C (CH_3 of Ts), respectively (Figure 6.1).

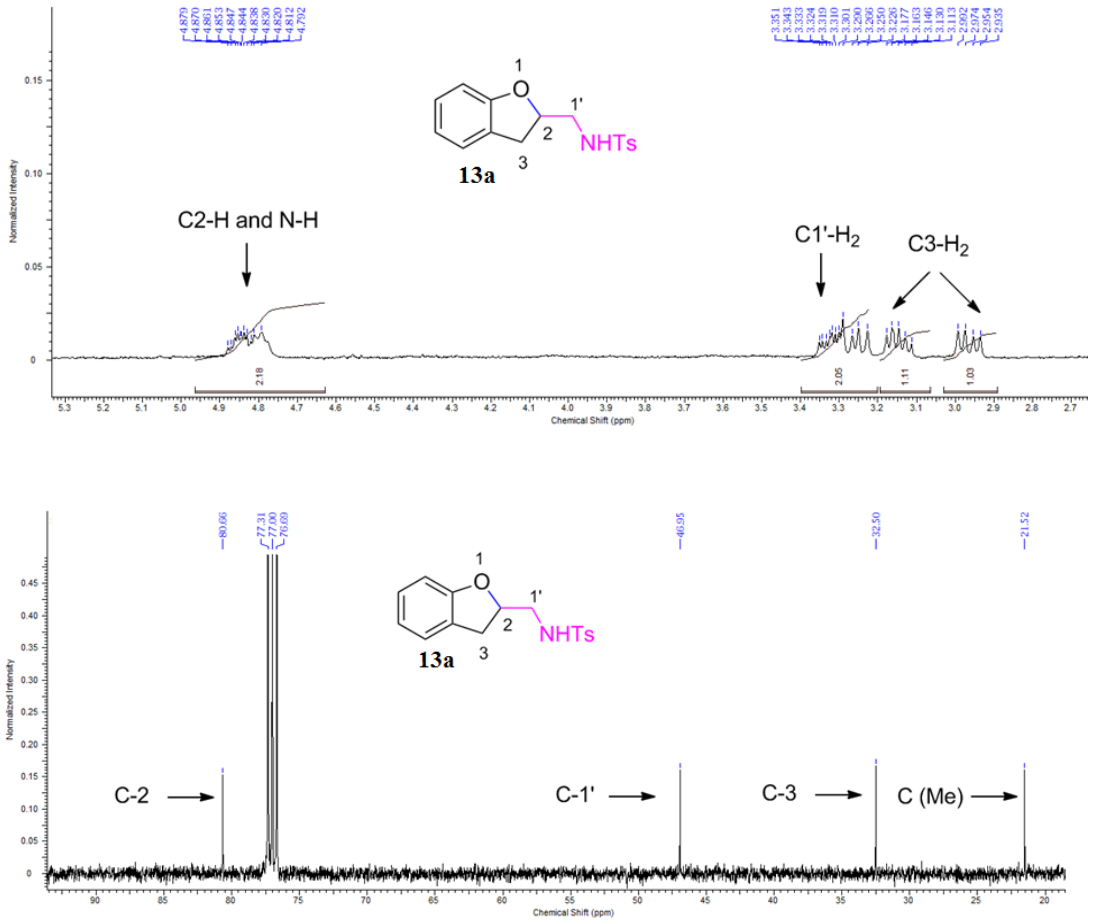


Figure 6.1. ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra (partial) of 13a

Meanwhile, treatment of **12c-h** with TBAF furnished the corresponding benzoxacycles **13c-h** also in excellent yields via *exo-tet* cyclization (no *endo-tet* cyclization was observed). Synthesis of the 1-benzoxepane derivative **13h** might be given special attention as its formation involved a relatively uncommon 7-*exo-tet* cyclization.

The aziridine ring-opening cyclizations were so fast that in none of these cases we could detect the corresponding intermediate phenolic derivative. The reactions clearly involved a tandem TBS-deprotection ─ *exo*-tet aziridine ring-opening cyclization by the in situ generated phenolate anion. This mode of cyclization, obeying the Baldwin rules, is consistent with previous findings on the cyclization reactions of similar epoxide-bearing substrates [21-23]. However, the very short reaction time in the present scenario further supports the fact that *N*-tosylaziridines are more reactive than epoxides towards ring-opening process [1-6].

The structures of benzoxacycles **13c-h** were assigned by NMR spectroscopy, mass spectrometry and elemental analysis, and further unambiguously verified by single crystal X-ray diffraction analysis of **13e** (Figure 6.2). The X-ray structure showed that the intramolecular nucleophilic attack of phenolate ion onto the aziridine ring had occurred *anti* to the C3─NTs bond in a typical S_N2 fashion to provide the expected relative stereochemistry between the two adjacent stereocenters in **13e**. The stereostructure and ring size of the benzoxacycles of **13c**,**d** and **13f-h** were thus confirmed by analogy.

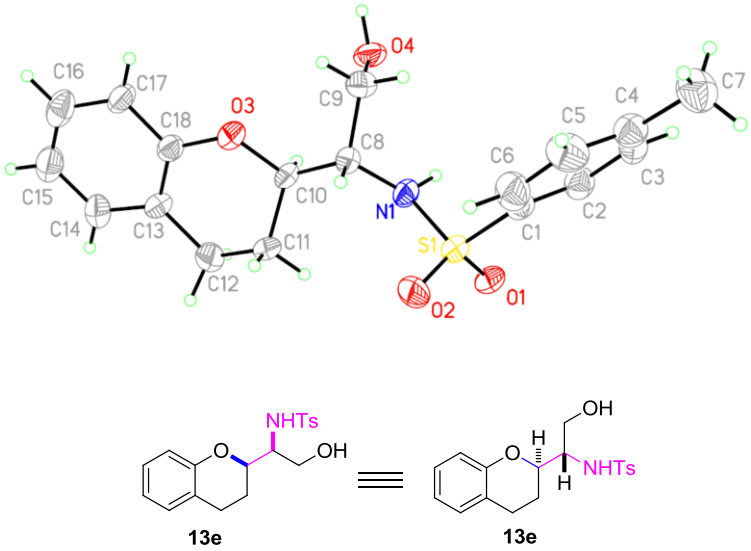


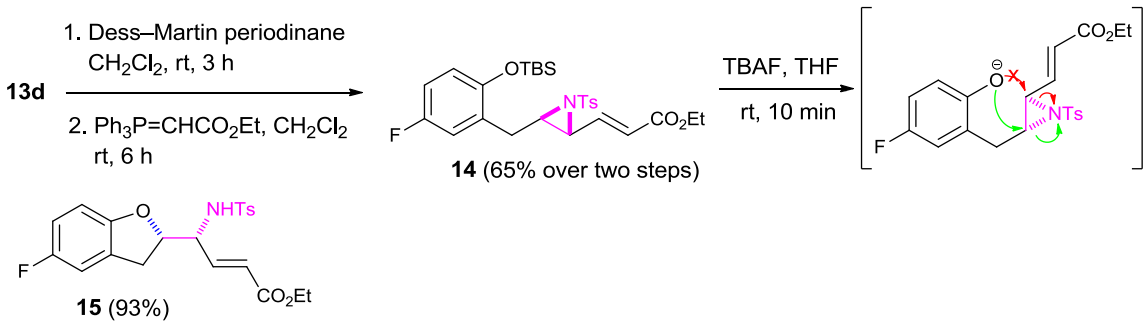
Figure 6.2. ORTEP of compound 13e with 35% probability ellipsoid (only one asymmetric molecule is displayed for clarity)

We have already demonstrated (**Chapter** 4, Scheme **5.1)** that introduction of azido functionality (via S_N2 azidation) on the secondary carbon adjacent to a pre-formed chroman ring is a quite difficult task. In contrast, the presented phenolate induced diastereo- and regioselective intramolecular ring-opening of *N*-tosylaziridines (Table 6.2)

should be an efficient pathway for installation of the nitrogen functionality in the synthesis of β-amino alcohols or their derivatives of type **13c-h**. Cyclic nature of the aziridine moiety, which renders competing elimination processes stereoelectronically unfavourable, is the key for this success. It is important to mention that 2-(*N*-tosylamido)-2-(benzoxacycle-2-yl)ethanols **13c-h** represent a new class of amino alcohol derivatives as β-amino alcohols or their derivatives of type **13c-h** are yet to be reported.

With enantiomerically pure/enriched *N*-tosylaziridine substrates, it has been proved that their inter- or intramolecular ring-opening reactions induced by hetero-nucleophiles are stereospecific in nature [1-6]. Thus, although we could not develop an asymmetric version of this methodology (because of our inability to synthesize enantiomerically pure *N*-tosylaziridines; *vide supra*), this phenoxide-ion induced stereoselective aziridine ring-opening chemistry should by no means be considered to be applicable to only racemic *N*-tosylaziridines.

Meanwhile, nucleophilic ring opening of vinyl aziridines have been known to take place at both the two aziridine-carbon atoms (S_N2 attack), in addition to the double bonded remote carbon atom (S_N2' attack) [6]. Hard nucleophiles normally provide the S_N2 process whereas soft nucleophiles often prefer S_N2' route. We were very much curious about the possible outcome of the intramolecular nucleophilic attack of phenolate anion on a vinyl aziridine system. As shown in Scheme 6.6, vinyl aziridine derivative **14**, prepared by a two-step reaction sequence involving Dess-Martin oxidation of **13d** followed by Wittig olefination of the resulting crude aldehyde, smoothly underwent phenolate-ion induced intramolecular aziridine 5-*exo*-*tet* ring-opening cyclization, providing **15** as a sole product in high yield (93%).



Scheme 6.6. Synthesis of 2,3-dihydrobenzofuran derivative by intramolecular aziridine ring-opening cyclization of vinyl aziridine

In the ^{1}H NMR spectrum of **15**, while the C2-H appeared as a doublet of doublets of doublets (ddd) at δ 4.82 (*J* = 9.6, 7.3, 5.0 Hz), the two protons attached to C-3 appeared as doublet of doublets (dd) at δ 3.23 (dd, *J* = 16.5, 9.6 Hz, 1H) and 2.99 (*J* = 16.5, 7.0 Hz, 1H) (Figure 6.3). Had the cyclic product been a chroman derivative **15a**, the protons attached to C-2, C-3 and C-4 in **15a** would have appeared with different chemical shifts and/or different splitting patterns in its ^{1}H NMR spectrum. Thus, the preferential formation of 2,3-dihydrobenzofuran derivative **15** over chroman derivative **15a** was confirmed.

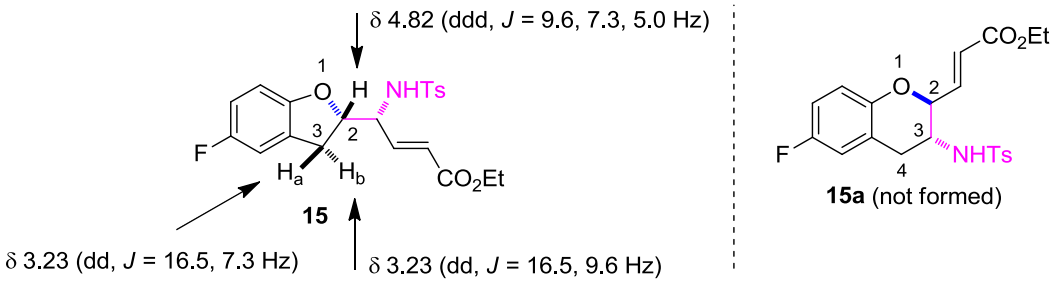
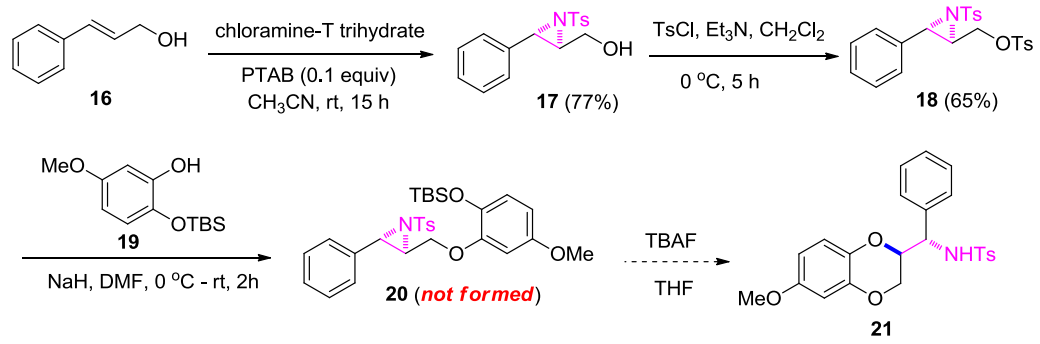


Figure 6.3. Structure confirmation of 15 by ^{1}H NMR

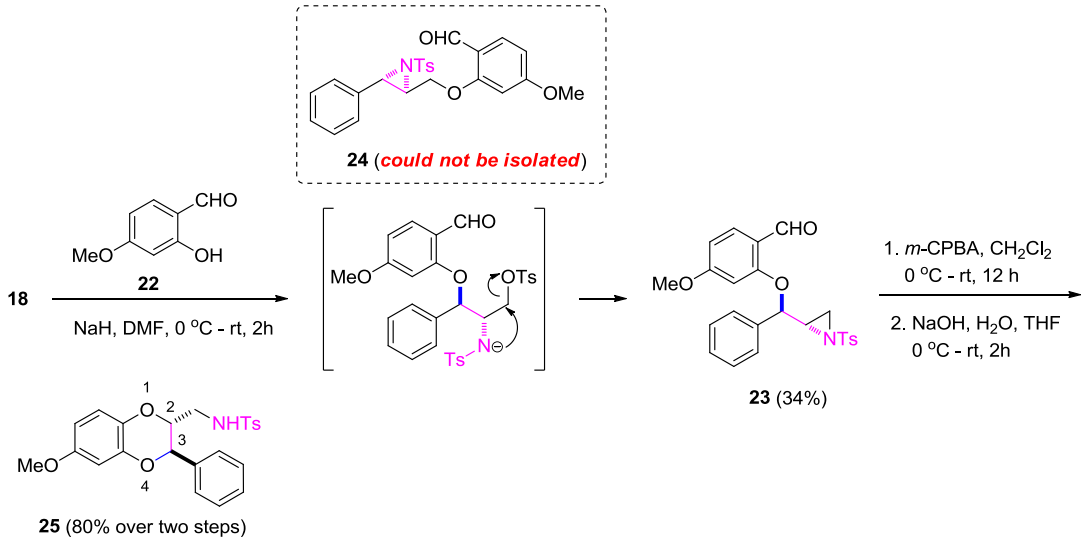
Our final effort was to apply the intramolecular aziridine ring-opening cyclization for the construction of 1,4-benzodioxane ring. Schemes 6.7 and 6.8 summarize our effort along this direction. First, *E*-cinnamyl alcohol **16** was subjected to the Sharpless aziridination reaction to obtain *N*-tosyl-2,3-aziridino alcohol **17** which on tosylation produced aziridino tosylate **18** (Scheme 6.7). Next, we attempted NaH-mediated alkylation of TBS-monoprotected catechol derivative **19** with **18**. Unfortunately, the reaction resulted in complete decomposition of electron rich **19**, resulting in inaccessibility of compound **20** that was supposed to provide 1,4-benzodioxane derivative **21** in the next (planned) step of tandem TBS-deprotection and 6-*exo*-*tet* ring opening of epoxide ring by the in situ generated phenolate anion. Attempts of alkylating phenol **19** with **17** or **18** under other reaction conditions were also met with failures (not shown here).

Given this experimental outcome, an alternative synthetic approach was necessitated for obtaining **21.** Ultimately, we decided to alkylate relatively less electron-rich 2-hydroxy-4-methoxybenzaldehyde **22** with **18** (Scheme 6.8). This choice was based on a well-established approach of exploiting aromatic aldehyde/ketone group as a masked phenolic hydroxyl group [24].



Scheme 6.7. Attempted synthesis of 1,4-benzodioxane derivatives by intramolecular aziridine ring-opening cyclization

However, alkylation reaction between **22** (1 equiv.) and **18** (1 equiv.) mediated by NaH was complex in nature, and we could isolate only aziridine derivative **23** in 34% yield. Clearly, tosylate **18** underwent an S_N2 ring-opening at the benzylic position of the aziridine ring by the in situ generated phenolate to yield an intermediate which, in turn, suffered aziridination via intramolecular S_N2 to produce **23** [25]. Aziridine derivative **24** might have been produced, but we could not isolate it in the pure form from the complex reaction mixture. Nonetheless, compound **23** on Bayer-Villiger oxidation with *m*-CPBA followed by tandem saponification and 6-*exo*-tet aziridine ring-opening cyclization furnished *trans*-3,4-disubstituted-1,4-benzodioxane derivative **25** in high yield. The *trans* relationship between the 2-tosylamidomethyl and 3-phenyl groups was established by the large coupling constant between the two protons attached to C-2 and C-3 (the proton attached to C-3 appeared as a doublet with J = 9.1 Hz at δ 4.80), consistent with that in other *trans*-2,3-disubstituted-1,4-benzodioxane derivatives [26].



Scheme 6.8. Successful synthesis of 1,4-benzodioxane derivatives

Noteworthy is that De Kimpe *et al*. utilized *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl) aziridine and unprotected catechols in the synthesis of 2-monosubstituted-1,4-benzodioxane derivatives [15]. With unsymmetrically substituted catechols, their methodology might suffer from regioselectivity. However, use of a salicyaldehyde derivative as a surrogate for an unsymmetrically substituted catechol moiety, as described in the Scheme 6.8, should allow the stereo- and regioselective synthesis of diverse 3,4-disubstituted-1,4-benzodioxanes.

6.4. Conclusion

In summary, we have developed a new method for the assembly of 2,3-dihydrobenzofuran, chroman, 1,4-benzodioxane, and 1-benzoxepine skeletons via phenolate-induced intramolecular ring-opening cyclization of *N*-tosylaziridines involving ArO─C bond-forming cyclization under metal-free conditions. The *exo-tet* nucleophilic cyclizations were shown to proceed very rapidly in a completely regio- and diastereoselective fashion. The ability to synthesize 2-(*N*-tosylamido)-2-(benzoxacycle-2-yl)ethanols that are troublesome, if not impossible, to access by traditional synthetic routes, is one of the best opportunities now available to diversify the chemistry of β-amino alcohols. Given the vast chemistry associated with synthetic applications of functionalized benzoxacycles, we anticipate that this methodology should be useful in organic synthesis and medicinal chemistry.

6.5. Experimental Section

6.5.1. General Remarks

Same as described in the **Chapter 2**, **Section 2.6.1** of this thesis.

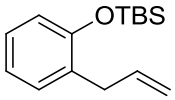
6.5.2. Preparation of Compounds

General Procedure A: *tert*-butyldimethylsilylation of 2-allylphenols

To a stirred solution of 2-allylphenol **1** (15 mmol) in anhydrous DMF (50 mL) were added *tert*-butyldimethylsilyl chloride (2.83 g, 18.75 mmol) and imidazole (1.53 g, 22.5 mmol) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 12 h at room temperature. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (75 mL × 3). The combined organic layers were washed with brine (100

mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (0-4% ethyl acetate/hexanes) furnished the desired product **2**.

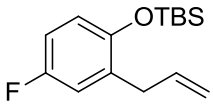
(2-Allylphenoxy)(*tert*-butyl)dimethylsilane (2a):



2a

According to the **General Procedure A**, 2-allylphenol **1a** (2.01 g, 15 mmol) was subjected to *tert*-butyldimethylsilylation reaction to obtain the title compound **2a** as a colorless oil (3.58 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.06 (m, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.00 (ddt, *J* = 18.9, 9.4, 6.6 Hz, 1H), 5.12–4.98 (m, 2H), 3.39 (d, *J* = 6.5 Hz, 2H), 1.03 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 137.0, 130.7, 130.1, 127.0, 121.1, 118.4, 115.4, 34.4, 25.7, 18.3, −4.1. Spectroscopic data were consistent with those previously reported [27].

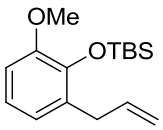
(2-Allyl-4-fluorophenoxy)(*tert*-butyl)dimethylsilane (2b):



2b

According to the **General Procedure A**, 2-allyl-4-fluorophenol **1b** (2.28 g, 15 mmol) was subjected to *tert*-butyldimethylsilylation reaction to obtain the title compound **2b** as a colorless oil (3.83 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85–6.65 (m, 3H), 6.05–5.85 (m, 1H), 5.15 (d, *J* = 1.5 Hz, 1H), 5.05 (dd, *J* = 9.5, 1.5 Hz, 1H), 3.35 (d, *J* = 8.5 Hz, 2H), 1.05 (s, 9H), 0.2 (s, 6H). Spectroscopic data were consistent with those previously reported [28].

(2-Allyl-6-methoxyphenoxy)(*tert*-butyl)dimethylsilane (2c):

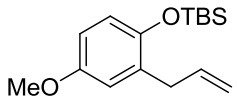


2c

According to the **General Procedure A**, 2-allyl-6-methoxyphenol **1c** (2.46 g, 15 mmol) was subjected to *tert*-butyldimethylsilylation reaction to obtain the title

compound **2c** as a colorless oil (3.92 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (t, 1H, *J* = 7.8 Hz), 6.76-6.70 (m, 2H), 6.02-5.92 (m, 1H), 5.08-5.05 (m, 1H), 5.04-5.02 (m, 1H), 3.78 (s, 3H), 3.42 (d, 2H, *J* = 6.5 Hz), 1.00 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 142.6, 137.1, 131.4, 121.9, 120.7, 115.5, 109.4, 54.8, 34.3, 26.1, 18.9, -3.9. Spectroscopic data were consistent with those previously reported [29]

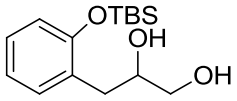
(2-Allyl-4-methoxyphenoxy)(*tert*-butyl)dimethylsilane (2d):



2d

According to the **General Procedure A**, 2-allyl-4-methoxyphenol **1d** (2.46 g, 15 mmol) was subjected to *tert*-butyldimethylsilylation reaction to obtain the title compound **2d** as a colorless oil (4.00 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78–6.69 (m, 2 H), 6.64 (dd, *J* = 8.6, 3.3 Hz, 1 H), 5.98 (ddt, *J* =17.7, 9.6, 6.6 Hz, 1 H), 5.12–5.05 (m, 2 H), 3.90 (s, 3 H), 3.35 (dt, *J* = 1.5 Hz, 2 H), 1.03 (s, 9 H), 0.21 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 147.6, 137.2, 131.9, 119.3, 116.1, 116.1, 112.2, 56.0, 35.0, 26.2, 18.6, −3.8. Spectroscopic data were consistent with those previously reported [30].

3-**(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)propane-1,2-diol (3a):**

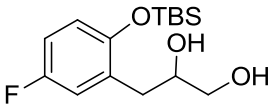


3a

To a stirred mixture of olefin **2a** (4.0 g, 16.10 mmol) and NMO (3.77 g, 32.20 mmol) in acetone (70 mL) and water (10 mL) was added OsO_4 (4% w/w in H_2O, 5.6 mL, 0.84 mmol) at 0°C. The reaction mixture was allowed to come to room temperature and stirred for 6 h. An aqueous saturated $NaHSO_3$ solution (30 mL) was added to it, and the stirring was continued for an additional 15 min. Acetone was removed under reduced pressure and the resulting suspension was then extracted with EtOAc (50 x 2 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by a silica gel column chromatography (10-40% EtOAc in hexanes) to obtain diol **3a** as a colorless gum. Yield: 92% (4.18 g); R_f: 0.33 (silica gel, 40% EtOAc in hexanes); ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.18-7.11 (m, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 3.98-3.92 (m, 1H), 3.64 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.48 (dd, *J* = 11.4, 6.4 Hz, 1H), 2.85-2.74 (m, 2H), 2.51 (brs, 2H), 1.03 (s, 9H),), 0.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 131.5, 128.3, 127.7, 121.4, 118.7, 72.3, 66.1, 34.6, 25.8, 18.2, –4.1; This is a known compound [31].

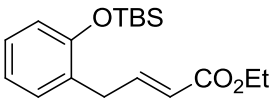
3-(2-((*tert*-Butyldimethylsilyl)oxy)-5-fluorophenyl)propane-1,2-diol (3b):



3b

Olefin **2b** (2.0 g, 7.50 mmol) was dihydroxylated essentially in the same manner as described for the dihydroxylation of **3a**. The crude product was purified by a silica gel column chromatography (10-40% EtOAc in hexanes) to obtain diol **3b** as a colorless gum. Yield: 90% (2.03 g); R_f: 0.29 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (dd, *J* = 8.7, 3.2 Hz, 1H), 6.81 (td, *J* = 8.3, 3.2 Hz, 1H), 6.74 (dd, *J* = 8.7, 4.6 Hz, 1H), 3.96–3.90 (m, 1H), 3.63 (dd, *J* = 11.4, 3.2, 1H), 3.47 (dd, *J* = 11.4, 6.9, 1H), 2.80-2.71 (m, 3H), 2.49 (br. s, 1H), 1.01 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2 (d, *J* = 239.6 Hz), 149.6, 130.1 (d, *J* = 7.7 Hz), 119.3 (d, *J* = 8.6 Hz), 117.7 (d, *J* = 22.0 Hz), 113.8 (d, *J* = 23.0 Hz), 72.1, 66.0, 34.5, 25.7, 18.2, −4.2; Anal. Calcd for $C_{15}H_{25}FO_3Si$: C, 59.97; H, 8.39, found: C, 59.89; H, 8.36.

(*E*)-Ethyl 4-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)but-2-enoate (4a):

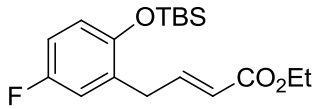


4a

To an ice-cooled solution of diol **3a** (4.0 g, 14.16 mmol) in methanol (50 mL) was added a solution of $NaIO_4$ (4.54 g, 21.24 mmol) in water (25 mL). After stirring the reaction mixture at 0 °C for 2 h, methanol was evaporated under reduced pressure. The resulting suspension was extracted with CH_2Cl_2 (50 x 2 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the corresponding crude aldehyde (3.35 g) as a colorless gum which was used for the next step without further purification.

To a stirred solution of the above crude aldehyde in dichloromethane (50 mL), was added (carbethoxymethylene) triphenylphosphorane (6.17 g, 17.70 mmol) and the reaction was further stirred for an additional 2 h. Removal of the solvent under reduced pressure gave the crude product which was purified by silica gel column chromatography (0-5% ethyl acetate in hexanes) to afford an inseparable mixture of *trans*-α,β-unsaturated ester **4a** and its *cis* isomer as a colorless oil (*trans* : *cis* = 4.2 : 1). Yield (over two steps): 80% (3.62 g); R_f: 0.52 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (only peaks for the *trans* isomer are reported, 400 MHz, $CDCl_3$): δ 7.15- 7.10 (m, 3H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.77 (d, *J* = 15.6 1H), 4.17 (q, *J* = 7.3 Hz, 2H), 3.51 (d, *J* = 5.9 Hz, 2H), 1.27 (t, *J* = 7.3 Hz, 3H), 1.01 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (only peaks for the *trans* isomer are reported, 100 MHz, $CDCl_3$): δ 166.6, 153.5, 147.3, 130.5, 128.4, 127.7, 121.9, 121.2, 118.4, 60.1, 33.0, 25.7, 18.2, 14.2, - 4.2.

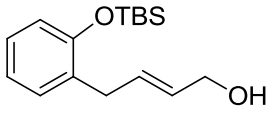
(*E*)-Ethyl 4-(2-((*tert*-butyldimethylsilyl)oxy)-5-fluorophenyl) but-2-enoate (4b):



4b

Diol **3b** (4.0 g, 13.31 mmol) was subjected to $NaIO_4$ oxidation─Wittig olefination reaction sequence essentially in the same manner as described for the synthesis of **4a**. The crude product was purified by silica gel column chromatography (0-5% ethyl acetate in hexanes) to afford an inseparable mixture of *trans*-α,β-unsaturated ester **4b** and its *cis* isomer as a colorless oil (*trans* : *cis* = 4.1 : 1). Yield (over the two steps): 82% (3.69 g); R_f: 0.47 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (only peaks for the *trans* isomer are reported, 400 MHz, $CDCl_3$): δ 7.10- 7.03 (m, 1H), 6.82-6.72 (m, 3H), 5.77 (d, *J* = 15.6 Hz, 1H), 4.18 (q, *J* = 7.3 Hz, 2H), 3.47 (d, *J* = 5.5 Hz, 2H), 1.27 (t, *J* = 7.3 Hz, 3H), 0.99 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (only peaks for the *trans* isomer are reported, 100 MHz, $CDCl_3$): δ 166.4, 157.1 (d, *J* = 239.6 Hz), 149.4, 146.2, 129.8 (d, *J* = 6.7 Hz), 122.5, 119.0 (d, *J* = 8.6 Hz), 116.8 (d, *J* = 23.0 Hz), 113.8 (d, *J* = 23.0 Hz), 60.2, 32.9, 25.7, 18.2, 14.2, - 4.2.

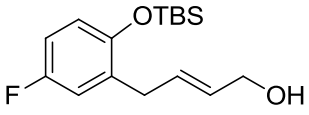
(*E*)-4-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)but-2-en-1-ol (5a):



5a

To a stirred solution of compounds **4a** and its *cis* isomer (as obtained from the Wittig olefination reaction; 1.0 g, 3.12 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C under nitrogen was added DIBAL-H (7.8 mL, 1.0 M in CH_2Cl_2, 7.8 mmol). The solution was stirred at this temperature for 2 h. The reaction was quenched by careful addition of methanol (2 mL) and then allowed to warm to room temperature. Saturated aq. potassium sodium tartrate (15 mL) and EtOAc (80 mL) were added and the mixture was stirred vigorously for 1 hour. The phases were then separated and the aqueous phase was extracted with EtOAc (25 x 2 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by a silica gel column chromatography (5-15% EtOAc in hexanes) to afford an inseparable mixture of *trans*-α,β-unsaturated alcohol **5a** and its *cis* isomer as a colorless gum (*trans* : *cis* = 4.2 : 1). Yield: 95% (825 mg); R_f: 0.37 (silica gel, 20 % EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, only peaks for the *trans* isomer are reported): δ 7.16-7.09 (m, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.91-5.84 (m, 1H), 5.72-5.65 (m, 1H), 4.11 (d, *J* = 5.5 Hz, 2H), 3.39 (d, *J* = 6.9 Hz, 2H), 1.76 (br. s, 1H), 1.05 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, only peaks for the *trans* isomer are reported): δ 153.2, 131.2, 130.6, 130.1, 129.9, 127.1, 121.1, 118.4, 63.5, 32.9, 25.7, - 4.2.

(*E*)-4-(2-((*tert*-Butyldimethylsilyl)oxy)-5-fluorophenyl)but-2-en-1-ol (5b):

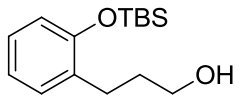


5b

A mixture of esters **4b** and its *cis* isomer (as obtained from the Wittig olefination reaction; 1.0 g, 2.95 mmol) were subjected to DIBAL-H reduction essentially in the same manner as described for the synthesis of **5a**. The crude product was purified by silica gel column chromatography (5-15% ethyl acetate in hexanes) to afford an inseparable mixture of *trans*-α,β-unsaturated alcohol **5b** and its *cis* isomer as a colorless gum (*trans* : *cis* = 4.1 : 1). Yield: 94% (828 mg); R_f: 0.32 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (only peaks for the *trans* isomer are reported, 400 MHz, $CDCl_3$): δ

6.85- 6.70 (m, 3H), 5.86-5.77 (m, 1H), 5.72-5.66 (m, 1H), 4.12 (dd, *J* = 5.0 Hz, 2H), 3.34 (d, *J* = 6.4 Hz, 2H), 1.65 (br. s, 1H), 1.01 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (only peaks for the *trans* isomer are reported, 100 MHz, $CDCl_3$): δ 157.3 (d, *J* = 238.7 Hz), 149.2, 132.2 (d, *J* = 7.7 Hz), 130.7, 130.2, 119.0 (d, *J* = 7.7 Hz), 116.3 (d, *J* = 23.0 Hz), 113.1 (d, *J* = 23.0 Hz), 63.5, 32.8, 25.7, -4.2.

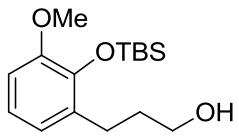
3-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)propan-1-ol (6a):



6a

To stirred solution of **2a** (1.5 g, 6.04 mmol) in anhydrous THF (30 mL) was added 9-BBN (0.5 M solution in THF, 25.0 mL, 12.5 mmol) dropwise under a nitrogen atmosphere at 0 °C. The mixture was then stirred at room temperature for 6 h. The reaction was carefully terminated by the addition of H_2O (2 mL) at 0 °C. Next, 1 M NaOH solution (15 mL) and 30% H_2O_2 (10 mL) were added to it sequentially and the reaction mixture was stirred for an additional 12 h at rt. The reaction mixture was then partitioned between brine (40 mL) and EtOAc (40 mL). The layers were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5-15% ethyl acetate in hexanes) to afford the title compound **6a** as a colorless oil. Yield: 93% (1.49 g); R_f: 0.39 (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.08 (td, *J* = 7.8, 1.8 Hz, 1H), 6.89 (td, *J* = 7.4, 1.1 Hz, 1H), 6.80 (dd, *J* = 8.1, 1.0 Hz, 1H), 3.62 (t, *J* = 6.1 Hz, 2H), 2.74–2.64 (m, 2H), 1.92–1.80 (m, 2H), 1.58 (t, *J* = 5.3 Hz, 1H), 1.02 (s, 9H), 0.24 (s, 6H); Spectroscopic data were consistent with those previously reported [32].

3-(2-((*tert*-Butyldimethylsilyl)oxy)-3-methoxyphenyl)propan-1-ol (6b):

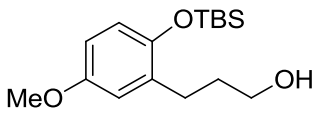


6b

Compound **2c** (1.5 g, 5.38 mmol) was subjected to hydroboration (9-BBN)─oxidation (H_2O_2, NaOH) essentially in the same manner as described for the synthesis of **6a**. The

crude product was purified by silica gel column chromatography (5-15% ethyl acetate in hexanes) to afford the title compound **6b** as a colorless oil. Yield: 94% (1.49 g); R_f: 0.37 (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (t, *J* = 7.8 Hz, 1H), 6.77 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.73 (dd, *J* = 7.8, 1.4 Hz, 1H), 3.79 (s, 3H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 1.90–1.83 (m, 3H), 1.02 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 142.7, 132.9, 121.9, 120.9, 109.1, 62.1, 54.6, 32.9, 26.3, 26.1, 18.9, −3.9; Anal. Calcd. for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52, found: C, 64.96; H, 9.61.

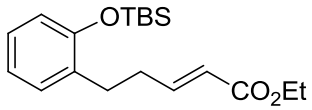
3-(2-((*tert*-Butyldimethylsilyl)oxy)-5-methoxyphenyl)propan-1-ol (6c):



6c

Compound **2d** (1.5 g, 5.38 mmol) was subjected to hydroboration (9-BBN)─oxidation (H_2O_2, NaOH) essentially in the same manner as described for the synthesis of **6a**. The crude product was purified by silica gel column chromatography (5-15% ethyl acetate in hexanes) to afford the title compound **6c** as a colorless oil. Yield: 91% (1.45 g); R_f: 0.35 (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72-6.58 (m, 3H), 3.72 (s, 3H), 3.60 (t, *J* = 6.3 Hz, 2H), 2.66 (t, *J* = 7.4 Hz, 2H), 1.90–1.85 (m, 2H), 1.71 (s, 1 H), 1.02 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 147.7, 133.5, 119.5, 116.2, 111.9, 62.5, 56.0, 33.4, 27.1, 26.2, 18.6, −3.8; Spectroscopic data were consistent with those previously reported [30,33].

(*E*)-Ethyl 5-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)pent-2-enoate (7a):

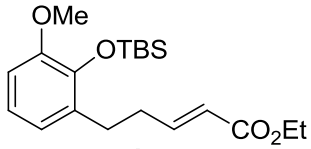


7a

To an ice-cooled mixture of **6a** (1.0 g, 3.75 mmol) and Celite® (500 mg) in anhydrous CH_2Cl_2 (20 mL) was added PCC (1.21 g, 5.63 mmol) under an atmosphere of nitrogen. The reaction was stirred vigorously for 4h at rt. (Carbethoxymethylene)triphenylphosphorane (1.74 g, 5.0 mmol) was then added and the reaction was further stirred for 6h at rt. The reaction mixture was concentrated under reduced pressure. The resulting residue was suspended in EtOAc/hexanes (1:1, 50 mL),

stirred vigorously for 10 min and filtered. Filtrate was concentrated under reduced pressure and the resultant crude product was subjected to further purification involving a silica gel column chromatography (0-5% ethyl acetate in hexanes) to afford *trans*-α,β-unsaturated ester **7a** as a colorless oil. Yield (over the two steps): 74% (929 mg); R_f: 0.49 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (dt, *J* = 15.9, 7.2 Hz, 1H), 6.71-6.60 (m, 3 H), 5.83 (d, *J* = 15.9 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.48 (td, *J* = 7.9, 7.0 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.01 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 154.0, 149.8, 132.2, 130.5, 127.7, 121.5, 118.7, 60.2, 33.0, 29.5, 26.2, 18.5, 14.5, −4.1; Spectroscopic data were consistent with those previously reported [34].

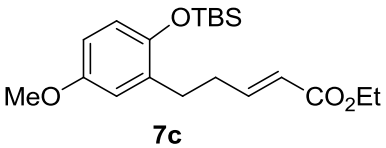
(*E*)-Ethyl 5-(2-((*tert*-Butyldimethylsilyl)oxy)-5-methoxyphenyl)pent-2-enoate (7b):



7b

Compound **6b** (1.0 g, 3.37 mmol) was subjected to sequential PCC oxidation─Wittig olefination essentially in the same manner as described for the synthesis of **7a**. The crude product was purified by silica gel column chromatography (0-8% ethyl acetate in hexanes) to afford *trans*-α,β-unsaturated ester **7b** as a colorless oil. Yield (over the two steps): 73% (897 mg); R_f: 0.41 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (dt, *J* = 16.0, 6.4 Hz, 1H), 6.84 (dd, *J* = 8.7, 7.3 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.86 (d, *J* = 16.0 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 2.79 (t, *J* = 7.3 Hz, 2H), 2.52-2.47 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.01 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 149.8, 148.6, 142.7, 132.1, 121.7, 121.4, 120.7, 109.5, 60.1, 54.7, 32.6, 29.1, 26.1, 18.8, 14.2, -3.8; Anal. Calcd. for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85, found: C, 65.76; H, 8.89.

(*E*)-Ethyl 5-(2-((*tert*-Butyldimethylsilyl)oxy)-5-methoxyphenyl)pent-2-enoate (7c):

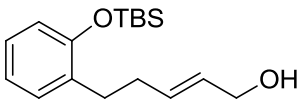


7c

Compound **6c** (1.0 g, 3.37 mmol) was subjected to sequential PCC oxidation─Wittig olefination essentially in the same manner as described for the synthesis of **7a**. The crude

product was purified by silica gel column chromatography (0-8% ethyl acetate in hexanes) to afford *trans*-α,β-unsaturated ester **7c** as a colorless oil. Yield (over the two steps): 72% (885 mg); R_f: 0.41 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (dt, *J* = 15.9, 7.2 Hz, 1H), 6.71-6.60 (m, 3 H), 5.83 (d, *J* = 15.9 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.48 (td, *J* = 7.9, 7.0 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.01 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 154.2, 148.8, 147.8, 132.6, 122.0, 119.3, 116.1, 112.2, 60.5, 56.0, 33.0, 29.9, 26.2, 18.6, 14.7, −3.8; Spectroscopic data were consistent with those previously reported [33].

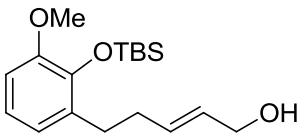
(*E*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)pent-2-en-1-ol (8a):



8a

Compound **7a** (500 mg, 1.49 mmol) was subjected to DIBAL-H reduction essentially in the same manner as described for the synthesis of **5a**. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **8a** as a colorless oil. Yield: (415 mg, 95%); R_f: 0.44 (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 7.4 and 1.6 Hz, 1H), 7.09 (td, *J* = 7.8, 1.8 Hz, 1H), 6.89 (td, *J* = 7.4 and 1.1 Hz, 1H), 6.80 (dd, *J* = 8.1, 1.0 Hz, 1H), 5.81-5.56 (m, 2H), 4.06 (d, *J* = 5.6 Hz, 2H), 2.67 (t, *J* = 7.9 Hz, 2H), 2.36-2.30 (m, 2H), 1.43 (br s, 1H), 1.04 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 132.7, 132.1, 130.1, 129.2, 126.8, 119.9, 118.2, 63.6, 32.5, 30.2, 25.7, 18.1, -3.9; Spectroscopic data were consistent with those previously reported [34].

(*E*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)-3-methoxyphenyl)pent-2-en-1-ol (8b):

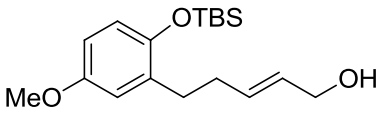


8b

Compound **7b** (500 mg, 1.37 mmol) was subjected to DIBAL-H reduction essentially in the same manner as described for the synthesis of **5a**. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **8b** as a colorless oil. Yield: (419 mg, 95%); R_f: 0.35 (silica gel, 25%

EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (t, *J* = 7.8 Hz, 1H), 6.75-6.72 (m, 2H), 5.79-5.62 (m, 2H), 4.08 (d, *J* = 5.5 Hz, 2H), 3.77 (s, 3H), 2.72 (t, *J* = 8.0 Hz, 2H), 2.37-2.31 (m, 2H), 1.35 (br s, 1H), 1.01 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9, 142.7, 133.0, 129.9, 129.2, 121.9, 120.6, 109.2, 63.8, 54.7, 32.7, 30.2, 26.1, 18.9, -3.8; Anal. Calcd. for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38, found: C, 67.21; H, 9.34.

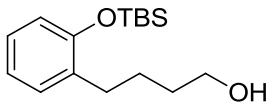
(*E*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)-5-methoxyphenyl)pent-2-en-1-ol (8c):



8c

Compound **7c** (500 mg, 1.37 mmol) was subjected to DIBAL-H reduction essentially in the same manner as described for the synthesis of **5a**. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **8c** as a colorless oil. Yield: (416 mg, 94%); R_f: 0.32 (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72-6.59 (m, 3H), 5.75-5.62 (m, 2H), 4.08 (d, *J* = 5.6 Hz, 2H), 3.77 (s, 3H), 2.73 (t, *J* = 7.8 Hz, 2H), 2.36-2.29 (m, 2H), 1.38 (br s, 1H), 1.03 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 147.1, 133.0, 132.3, 129.1, 118.0, 115.6, 111.1, 63.4, 55.4, 32.3, 30.3, 25.6, 18.0, -4.2; Spectroscopic data were consistent with those previously reported [33].

4-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)butan-1-ol (9):

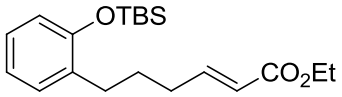


9

A mixture of **5a** (600 mg, 2.15 mmol) and 10% Pd-C (75 mg) in EtOAc (15 mL) was stirred for 12 h at room temperature under pressure of a hydrogen balloon. The reaction mixture was filtered through a pad of Celite® and the filter pad was well-washed with EtOAc. The filtrates were combined and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (5-15% ethyl acetate in hexanes) to afford the title compound **9** as a colorless oil. Yield (over two steps): 93% (562 mg); R_f: 0.42 (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.07 (td, *J* = 8.2, 1.8 Hz, 1H), 6.88 (t, *J* = 7.3

Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.63 (t, *J* = 6.9 Hz, 2H), 1.68-1.62 (m, 4H), 1.35 (br s, 1H), 1.03 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 132.8, 130.1, 126.7, 120.9, 118.4, 63.0, 32.7, 30.3, 26.2, 25.8, 18.2, -4.2. Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 68.52; H, 10.06, found C, 68.59; H, 10.09.

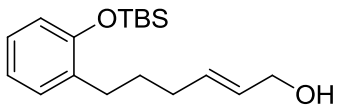
(*E*)-Ethyl 6-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)hex-2-enoate (10):



10

Compound **9** (500 mg, 1.78 mmol) was subjected to sequential PCC oxidation─Wittig olefination essentially in the same manner as described for the synthesis of **7a**. The crude product was purified by silica gel column chromatography (0-5% ethyl acetate in hexanes) to afford *trans*-α,β-unsaturated ester **10** as a colorless semi-solid. Yield (over the two steps): 74% (460 mg); R_f: 0.52 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.06 (m, 2H), 7.03-6.95 (m, 1H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.83 (d, *J* = 15.6 Hz, 1H), 4.19 (q, *J* = 7.3 Hz, 2H), 2.62 (t, *J* = 7.3 Hz, 2H), 2.23 (q, *J* = 7.3 Hz, 2H), 1.79-1.72 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.02 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 153.5, 149.1, 132.3, 130.1, 126.9, 121.5, 120.9, 118.4, 60.1, 32.0, 30.1, 28.3, 25.8, 18.2, 14.3, −4.2; Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25, found C, 68.81; H, 9.31.

(*E*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)hex-2-en-1-ol (11):



11

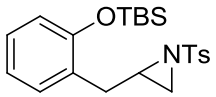
Compound **10** (401 mg, 1.15 mmol) was subjected to DIBAL-H reduction essentially in the same manner as described for the synthesis of **5a**. The resulting crude product was purified by silica gel column chromatography (5-10% EtOAc in hexanes) to obtain the title compound **11** as a colorless semi-solid. Yield: (331 mg, 94%); R_f: 0.52 (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.06 (m, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.76-5.60 (m, 2H), 4.09 (d, *J* = 5.5 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.10 (q, *J* = 7.3 Hz, 2H), 1.72-1.64 (m, 2H), 1.26 (t, *J* = 7.6 Hz, 1 H); 1.03 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 133.2, 132.9, 130.1,

129.1, 126.7, 120.9, 118.3, 63.8, 32.2, 30.1, 29.4, 25.8, 18.2, -4.2; Anal. Calcd for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87, found C, 70.68; H, 9.93.

General Procedure B: Aziridination of alkenes by Sharpless aziridination method:

To a stirred mixture of chloramine-T trihydrate (1.1 equiv) and an appropriate alkene (1.0 equiv) in CH_3CN (5 mL/mmol) was added phenyltrimethylammonium tribromide (PTAB) (0.1 equiv) at room temperature. The reaction was stirred vigorously for 15 h and then concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 and filtered through a short column of silica gel (eluted with 30% EtOAc in hexanes). After removal of the solvent, the resultant crude product was subjected to further purification involving a silica gel column chromatography (EtOAc/hexanes) to give the corresponding aziridine product.

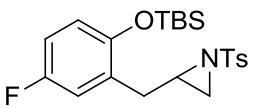
2-(2-((*tert*-Butyldimethylsilyl)oxy)benzyl)-1-tosylaziridine (12a):



12a

Following the **General Procedure B**, compound **2a** (745 mg, 3.0 mmol) was subjected to the Sharpless aziridination reaction. The resulting crude product was purified by silica gel column chromatography (2-12% EtOAc in hexanes) to obtain the title compound **12a** as a light yellow gum**.** Yield: (777 mg, 62%); R_f: 0.49 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.04 (td, *J* = 7.8, 1.8 Hz, 1H), 6.93 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.72-6.68 (m, 2H), 3.04-2.98 (m, 1H), 2.81 (dd, *J* = 14.2, 5.5 Hz, 1H), 2.70 (d, *J* = 6.9 Hz, 1H), 2.63 (dd, *J* = 14.2, 6.9 Hz, 1H), 2.41 (s, 3H), 2.16 (d, *J* = 4.6 Hz, 1H), 1.01 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 144.1, 130.7, 129.5, 127.7, 127.62, 127.57, 121.0, 118.1, 40.3, 32.9, 32.4, 25.8, 21.6, -4.1; Anal. Calcd. for $C_{22}H_{31}NO_3SSi$: C, 63.27; H, 7.48; N, 3.35, found: C, 63.38; H, 7.52; N, 3.31.

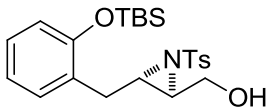
2-(2-((*tert*-Butyldimethylsilyl)oxy)-5-fluorobenzyl)-1-tosylaziridine (12b):



12b

Following the **General Procedure B**, compound **2b** (799 mg, 3.0 mmol) was subjected to the Sharpless aziridination reaction. The resulting crude product was purified by silica gel column chromatography (2-12% EtOAc in hexanes) to obtain the title compound **12b** as a light yellow gum**.** Yield: (850 mg, 65%); R_f: 0.45 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.69 (td, *J* = 8.7, 3.2 Hz, 1H), 6.61 (dd, *J* = 9.1, 5.0 Hz, 1H), 6.52 (dd, *J* = 8.7, 3.2 Hz, 1H), 2.95-2.89 (m, 2H), 2.77 (d, *J* = 6.4 Hz, 1H), 2.41 (s, 3H), 2.36 (dd, *J* = 15.1, 9.2 Hz, 1H), 2.17 (d, *J* = 4.1 Hz, 1H), 1.00 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6 (d, J_{C-F} = 239.6 Hz), 149.2 (d, J_{C-F} = 1.9 Hz), 144.3, 134.5, 129.5, 129.3 (d, J_{C-F} = 6.7 Hz), 127.6, 118.5 (d, J_{C-F} = 8.6 Hz), 117.1 (d, J_{C-F} = 23.0 Hz), 113.6 (d, J_{C-F} = 23.0 Hz), 40.2, 32.4 (d, J_{C-F} = 7.7 Hz), 25.8, 21.5, 18.2, -4.2; Anal. Calcd. for $C_{22}H_{30}FNO_3SSi$: C, 60.66; H, 6.94; N, 3.22, found: C, 60.78; H, 6.99; N, 3.15.

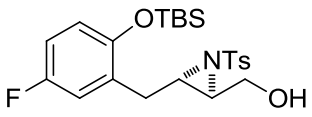
((2*R,3*S**)-3-(2-((*tert*-Butyldimethylsilyl)oxy)benzyl)-1-tosylaziridin-2-yl)methanol (12c):**



12c

Following the **General Procedure B**, a mixture of compound **5a** and its *cis* isomer (as obtained from the DIBAL-H reduction; 557 mg, 2.0 mmol) was subjected to the Sharpless aziridination reaction. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **12c** as a colorless gum**.** Yield: (665 mg, 92%; calculated with respect to the starting *E*-isomer); R_f: 0.41 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.09 (td, *J* = 8.2, 1.8 Hz, 1H), 6.85 (d, *J* = 6.4 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.70 (t, *J* = 7.3 Hz, 1H), 4.13-4.08 (m, 1H), 3.98-3.89 (m, 1H), 3.31-3.27 (m, 1H), 3.06-3.02 (m, 1H), 2.94 (dd, *J* = 14.2, 5.5 Hz, 1H), 2.83-2.82 (m, 1H), 2.70 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.43 (s, 3H), 1.01 (s, 9H), 0.25 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 143.9, 136.9, 130.6, 129.5, 127.8, 127.7, 127.2, 121.1, 118.2, 60.9, 51.6, 46.0, 31.7, 25.8, 21.6, 18.2, -4.2; HRMS (ESI/$[M+H]^+$) Calcd. for $C_{23}H_{34}NO_4SSi$: 448.1978, found 448.1982.

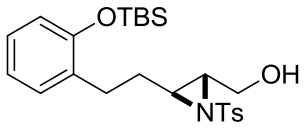
((2*R,3*S**)-3-(2-((*tert*-Butyldimethylsilyl)oxy)-5-fluorobenzyl)-1-tosylaziridin-2-yl)methanol (12d):**



12d

Following the **General Procedure B**, a mixture of compound **5b** and its *cis* isomer (as obtained from the DIBAL-H reduction; 593 mg, 2.0 mmol) was subjected to the Sharpless aziridination reaction. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **12d** as a colorless semi-solid**.** Yield: (674 mg, 90%; calculated with respect to the starting *E*-isomer); R_f: 0.38 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.74 (td, *J* = 8.7, 3.2 Hz, 1H), 6.67 (dd, *J* = 8.7, 5.5 Hz, 1H), 6.42 (dd, *J* = 8.7, 5.5 Hz, 1H), 4.18-4.11 (m, 1H), 4.01-3.94 (m, 1H), 3.27-3.23 (m, 1H), 3.05-3.00 (m, 2H), 2.88 (dd, *J* = 9.6, 4.6 Hz, 1H), 2.45-2.42 (m, 4H), 1.00 (s, 9H), 0.25 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8 (d, *J* = 239.6 Hz), 149.4 (d, *J* = 1.9 Hz), 144.2, 136.5, 129.5, 129.4 (d, *J* = 7.7 Hz), 127.2, 118.7 (d, *J* = 8.6 Hz), 117.0 (d, *J* = 23.0 Hz), 113.9 (d, *J* = 23.0 Hz), 60.7, 51.7, 45.5, 32.0, 25.7, 21.5, 18.2, -4.2, -4.3; Anal. Calcd. for $C_{23}H_{32}FNO_4SSi$: C, 59.32; H, 6.93; N, 3.01, found: C, 59.19; H, 6.86; N, 3.07.

((2*R,3*S**)-3-(2-((*tert*-Butyldimethylsilyl)oxy)phenethyl)-1-tosylaziridin-2-yl)methanol (12e):**

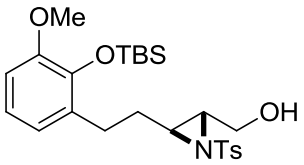


12e

Following the **General Procedure B**, compound **8a** (293 mg, 1.0 mmol) was subjected to the Sharpless aziridination reaction. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **12e** as a colorless gum. Yield: (416 mg, 90%); R_f: 0.43 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.10-7.04 (m, 2H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 3.92-3.73 (m, 2H), 2.96-2.92 (m, 1H), 2.81-2.71 (m, 1H), 2.68-2.53 (m, 3H), 2.44 (s, 3H), 2.01-1.85 (m, 2H), 0.99 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 153.5, 144.2, 137.3, 130.9, 130.3, 129.6, 127.4, 127.3, 121.2, 118.6, 61.0, 51.6, 46.2, 30.3, 28.3, 25.8, 21.6, 18.2, -4.2; Anal. Calcd. for $C_{24}H_{35}NO_4SSi$: C, 62.44; H, 7.64; N, 3.03, found: C, 62.56; H, 7.69; N, 3.07.

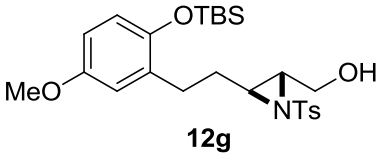
((2*R,3*S**)-3-(2-((*tert*-Butyldimethylsilyl)oxy)-3-methoxyphenethyl)-1-tosylaziridin-2-yl)methanol (12f):**



12f

Following the **General Procedure B**, compound **8b** (323 mg, 1.0 mmol) was subjected to the Sharpless aziridination reaction. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **12f** as a colorless gum. Yield: (428 mg, 87%); R_f: 0.35 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 6.8 Hz, 1H), 6.66 (d, *J* = 7.3 Hz, 1H), 3.91-3.77 (m, 5H), 2.96-2.91 (m, 1H), 2.79-2.75 (m, 1H), 2.69-2.62 (m, 3H), 2.43 (s, 3H), 2.05-1.83 (m, 2H), 0.98 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 144.1, 142.6, 137.2, 131.6, 129.6, 127.2, 121.9, 120.9, 109.6, 61.0, 54.6, 51.4, 46.3, 30.4, 28.0, 26.1, 21.5, 18.8, -3.9; Anal. Calcd. for $C_{25}H_{37}NO_5SSi$: C, 61.07; H, 7.58; N, 2.85, found: C, 61.22; H, 7.52; N, 2.81.

((2*R,3*S**)-3-(2-((*tert*-Butyldimethylsilyl)oxy)-5-methoxyphenethyl)-1-tosylaziridin-2-yl)methanol (12g):**

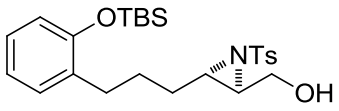


12g

Following the **General Procedure B**, compound **8c** (323 mg, 1.0 mmol) was subjected to the Sharpless aziridination reaction. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **12g** as a colorless gum. Yield: (437 mg, 89%); R_f: 0.32 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 6.69-6.60 (m, 3H), 3.93-3.88 (m, 1H), 3.79-3.73 (m, 4H), 2.96-2.92 (m,

1H), 2.81-2.78 (m, 1H), 2.63-2.51 (m, 3H), 2.43 (s, 3H), 1.99-1.81 (m, 2H), 0.97 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 147.2, 144.2, 137.3, 131.8, 129.6, 127.3, 119.1, 115.8, 112.0, 61.0, 55.6, 51.6, 46.1, 30.4, 28.5, 25.8, 21.6, 18.1, -4.2; Anal. Calcd. for $C_{25}H_{37}NO_5SSi$: C, 61.07; H, 7.58; N, 2.85, found: C, 61.17; H, 7.63; N, 2.89.

((2*R,3*S**)-3-(3-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)propyl)-1-tosylaziridin-2-yl)methanol (12h):**



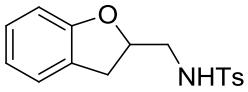
12h

Following the **General Procedure B**, compound **11** (306 mg, 1.0 mmol) was subjected to the Sharpless aziridination reaction. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **12h** as a colorless gum. Yield: (428 mg, 90%); R_f: 0.48 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.09-7.05 (m, 1H), 6.98-6.97 (m, 1H), 6.85 (t, *J* = 6.9 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 4.14-4.08 (m, 1H), 3.93-3.98 (m, 1H), 2.95-2.93 (m, 2H), 2.73 (br s, 1H), 2.53 (t, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 1.67-1.46 (m, 4H), 0.99 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 144.2, 137.1, 132.0, 129.9, 129.6, 127.3, 126.9, 120.9, 118.4, 60.9, 51.9, 46.2, 30.1, 29.8, 27.3, 25.7, 21.6, 18.2, -4.2; Anal. Calcd. for $C_{25}H_{37}NO_4SSi$: C, 63.12; H, 7.84; N, 2.94, found: C, 63.29; H, 7.89; N, 2.96.

General Procedure C: intramolecular aziridine ring-opening cyclization

To a stirred solution of appropriate *N*-tosylaziridine derivative (1 equiv) in anhydrous THF (5 mL/mml) was added TBAF (1.1 equiv) dropwise under a nitrogen atmosphere at 0 °C. The reaction mixture was stirred at room temperature for 10 min. The reaction mixture was then diluted with ethyl acetate and water. The phases were separated, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the corresponding benzo-fused oxygen heterocycles**.**

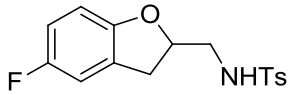
***N*-((2,3-Dihydrobenzofuran-2-yl)methyl)-4-methylbenzenesulfonamide (13a):**



13a

Following the **General Procedure C**, compound **12a** (418 mg, 1.0 mmol) was subjected to the intramolecular aziridine ring-opening reaction. The resulting crude product was purified by silica gel column chromatography (10-25% EtOAc in hexanes) to obtain the title compound **13a** as a white crystalline solid**.** Yield: (291 mg, 96%); mp: 160–162 °C; R_f: 0.34 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.11 (dd, *J* = 17.4, 7.8 Hz, 2H), 6.85 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 4.88-4.79 (m, 2H), 3.35-3.22 (m, 2H), 3.17-3.11 (m, 1H), 2.96 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 143.6, 136.8, 129.8, 128.2, 127.0, 126.0, 125.1, 120.9, 109.5, 80.7, 46.9, 32.5, 21.5; MS (ESI) *m*/*z*: 304 $(M + H)^+$; Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62, found: C, 63.27; H, 5.63; N, 4.67.

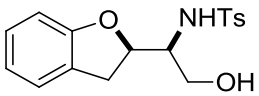
***N*-((5-Fluoro-2,3-dihydrobenzofuran-2-yl)methyl)-4-methylbenzenesulfonamide (13b):**



13b

Following the **General Procedure C**, compound **12b** (436 mg, 1.0 mmol) was subjected to the intramolecular aziridine ring-opening reaction. The resulting crude product was purified by silica gel column chromatography (10-25% EtOAc in hexanes) to obtain the title compound **13b** as a white crystalline solid. Yield: (305 mg, 95%); mp: 145–147 °C; R_f: 0.32 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 8.7 Hz, 1H), 6.60 (dd, *J* = 8.2, 3.7 Hz, 1H), 4.89-4.82 (m, 2H), 3.32-3.10 (m, 3H), 2.98 (dd, *J* = 16.0, 6.9 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6 (d, $J_{C\text{-}F}$ = 237.7 Hz), 154.6 (d, $J_{C\text{-}F}$ = 1.9 Hz), 143.7, 136.7, 129.8, 127.4 (d, $J_{C\text{-}F}$ = 9.6 Hz), 127.0, 114.3 (d, $J_{C\text{-}F}$ = 23.9 Hz), 112.2 (d, $J_{C\text{-}F}$ = 24.9 Hz), 109.5 (d, $J_{C\text{-}F}$ = 8.6 Hz), 81.3, 46.7, 32.7 (d, $J_{C\text{-}F}$ = 1.9 Hz), 21.5; MS (ESI) *m*/*z*: 322 $(M + H)^+$; Anal. Calcd. for $C_{16}H_{16}FNO_3S$: C, 59.80; H, 5.02; N, 4.36, found: C, 59.95; H, 5.09; N, 4.33.

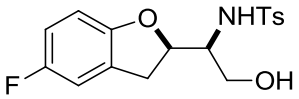
***N*-((*S**)-1-((*R**)-2,3-Dihydrobenzofuran-2-yl)-2-hydroxyethyl)-4-methylbenzenesulfonamide (13c):**



13c

Following the **General Procedure C**, compound **12c** (448 mg, 1.0 mmol) was subjected to the intramolecular aziridine ring-opening reaction. The resulting crude product was purified by silica gel column chromatography (10-30% EtOAc in hexanes) to obtain the title compound **13c** as a white crystalline solid**.** Yield: (317 mg, 95%); mp: 110–112 °C; R_f: 0.36 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.13-7.07 (m, 2H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.56 (d, *J* = 8.7 Hz, 1H), 4.79-4.73 (m, 1H), 3.83 (dd, *J* = 11.0, 2.7 Hz, 1H), 3.45-3.37 (m, 2H), 3.23 (dd, *J* = 16.5, 9.6 Hz, 1H), 3.13 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.43 (s, 3H), 2.18 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 143.7, 137.5, 129.8, 128.0, 127.0, 125.9, 125.2, 121.0, 109.3, 80.9, 60.7, 57.7, 32.4, 21.5; MS (ESI) *m*/*z*: 334 $(M + H)^+$; Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20, found: C, 61.39; H, 5.79; N, 4.11.

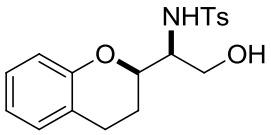
***N*-((*S**)-1-((*R**)-5-Fluoro-2,3-dihydrobenzofuran-2-yl)-2-hydroxyethyl)-4-methylbenzenesulfonamide (13d):**



13d

Following the **General Procedure C**, compound **12d** (65 mg, 0.14 mmol) was subjected to the intramolecular aziridine ring-opening reaction. The resulting crude product was purified by silica gel column chromatography (10-30% EtOAc in hexanes) to obtain the title compound **13d** as a white crystalline solid**.** Yield: (46 mg, 93%); mp: 125–127 °C; R_f: 0.32 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 7.3 Hz, 1H), 6.78 (t, *J* = 8.7 Hz, 1H), 6.59 (dd, *J* = 8.7, 4.1 Hz, 1H), 5.24 (d, *J* = 8.7 Hz, 1H), 4.81-4.75 (m, 1H), 3.83 (d, *J* = 11.0 Hz, 1H), 3.44-3.16 (m, 4H), 3.23 (s, 3H), 2.44 (s, 3H), 1.87 (br s, 1H); MS (ESI) *m*/*z*: 352 $(M + H)^+$; Anal. Calcd for $C_{17}H_{18}FNO_4S$: C, 58.11; H, 5.16; N, 3.99, found: C, 58.26; H, 5.07; N, 4.08.

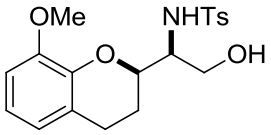
***N*-((*S**)-1-((*R**)-Chroman-2-yl)-2-hydroxyethyl)-4-methylbenzenesulfonamide (13e):**



13e

Following the **General Procedure C**, compound **12e** (231 mg, 0.5 mmol) was subjected to the intramolecular aziridine ring-opening reaction. The resulting crude product was purified by silica gel column chromatography (10-30% EtOAc in hexanes) to obtain the title compound **13e** as a white crystalline solid**.** Yield: (163 mg, 94%); mp: 135–138 °C; R_f: 0.34 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.09-7.03 (m, 2H), 6.86 (t, *J* = 6.87, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 5.35 (d, *J* = 8.2 Hz, 1H), 4.05 (ddd, *J* = 10.5, 5.9, 1.8 Hz, 1H), 3.93 (dd, *J* = 10.5, 2.7 Hz, 1H), 3.47-3.41 (m, 2H), 2.81-2.77 (m, 2H), 2.44 (s, 3H), 2.15-2.08 (m, 1H), 2.02 (br s, 1H), 1.85-1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 143.7, 137.7, 129.8, 129.6, 127.3, 127.0, 121.9, 120.9, 116.6, 75.9, 60.8, 57.2, 24.3, 24.0, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{22}NO_4S$ $[M + H]^+$: 348.1270, found: 348.1284.

***N*-((*S**)-2-Hydroxy-1-((*R**)-8-methoxychroman-2-yl)ethyl)-4 methylbenzenesulfonamide (13f):**

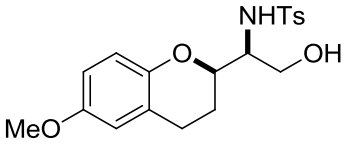


13f

Following the **General Procedure C**, compound **12f** (246 mg, 0.5 mmol) was subjected to the intramolecular aziridine ring-opening reaction. The resulting crude product was purified by silica gel column chromatography (10-30% EtOAc in hexanes) to obtain the title compound **13f** as a white crystalline solid**.** Yield: (181 mg, 96%); mp: 90–92 °C; R_f: 0.30 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.80 (t, *J* = 7.8 Hz, 1H), 6.70-6.65 (m, 2H), 5.63 (br s, 1H), 4.14 (t, *J* = 7.3 Hz, 1H), 3.88 (dd, *J* = 11.4, 2.3 Hz, 1H), 3.80 (s, 3H), 3.44-3.34 (m, 2H), 2.78-2.77 (m, 2H), 2.43 (s, 3H), 2.14-2.11 (m, 1H), 1.86-1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 143.6, 142.9, 137.8, 129.8, 127.0, 122.7,

121.4, 120.2, 109.2, 61.1, 56.7, 55.7, 24.0, 23.9, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{24}NO_5S$ $[M + H]^+$: 378.1375, found: 378.1370.

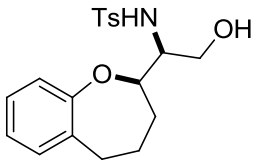
_N_-((_S_*)-2-Hydroxy-1-((_R_*)-6-methoxychroman-2-yl)ethyl)-4-methylbenzenesulfonamide (13g):



13g

Following the **General Procedure C**, compound **12g** (246 mg, 0.5 mmol) was subjected to the intramolecular aziridine ring-opening reaction. The resulting crude product was purified by silica gel column chromatography (10-30% EtOAc in hexanes) to obtain the title compound **13g** as a white crystalline solid**.** Yield: (179 mg, 95%); mp: 111–113 °C; *R*f: 0.28 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 6.65-6.64 (m, 2H), 6.58-6.57 (m, 1H), 5.36 (d, *J* = 8.7 Hz, 1H), 3.99 (ddd, *J* = 10.5, 5.9, 1.8 Hz, 1H), 3.91 (dd, *J* = 10.5, 2.7 Hz, 1H), 3.74 (s, 3H), 3.44-3.37 (m, 2H), 2.79-2.75 (m, 2H), 2.43 (s, 3H), 2.11-2.06 (m, 2H), 1.83-1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 147.9, 143.8, 137.8, 129.9, 127.2, 122.6, 117.3, 114.1, 113.5, 76.1, 61.0, 57.2, 55.8, 24.7, 24.1, 21.6; MS (ESI) *m*/*z*: 378 $(M + H)^+$; Anal. Calcd for $C_{19}H_{23}NO_5S$: C, 60.46; H, 6.14; N, 3.71, found: C, 60.34; H, 6.18; N, 3.67.

_N_-((_S_*)-2-Hydroxy-1-((_R_*)-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)ethyl)-4-methylbenzenesulfonamide (13h):

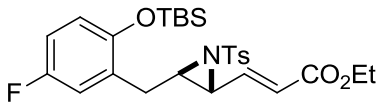


13h

Following the **General Procedure C**, compound **12h** (238 mg, 0.5 mmol) was subjected to the intramolecular aziridine ring-opening reaction. The resulting crude product was purified by silica gel column chromatography (10-30% EtOAc in hexanes) to obtain the title compound **13h** as a white crystalline solid**.** Yield: (161 mg, 89%); mp: 105–107 °C; R_f: 0.35 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.12-7.08 (m, 2H), 6.98 (t, *J* = 7.4 Hz,

1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.69 (d, *J* = 8.7 Hz, 1H), 4.01 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.64 (dd, *J* =10.9, 4.1 Hz, 1H), 3.45 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.34-3.30 (m, 1H), 2.80 (t, *J* = 13.0 Hz, 1H), 2.66 (dd, *J* = 14.6, 5.5 Hz, 1H), 2.39 (s, 4H), 2.01-1.95 (m, 2H), 1.81-1.70 (m, 1H), 1.43-1.32 (m, 1H), 1.31-1.26 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 143.6, 137.7, 135.2, 130.3, 129.7, 127.5, 127.0, 124.1, 120.8, 85.0, 61.1, 58.0, 33.9, 33.6, 25.6, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{24}NO_4S$ $[M + H]^+$: 362.1426, found: 362.1392. MS (ESI) *m*/*z*: 362 $(M + H)^+$; Anal. Calcd. for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88, found: C, 63.31; H, 6.48; N, 3.95.

(*E*)-Ethyl 3-((2*R,3*R**)-3-(2-((*tert*-butyldimethylsilyl)oxy)-5-fluorobenzyl)-1-tosylaziridin-2-yl)acrylate (14):**



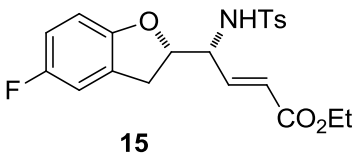
14

To a stirred solution of **12d** (104 mg, 0.223 mmol) in CH_2Cl_2 (5 mL) was added sodium bicarbonate (25 mg, 0.3 mmol) and Dess-Martin periodinane (119 mg, 0.28 mmol) at 0 °C. The reaction mixture was stirred for 3 h at rt and then quenched with saturated solutions of Na_2SO_3 (5 mL) and $NaHCO_3$ (5 mL). The reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered through a pad of Celite and phases were separated. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the corresponding crude aldehyde as a colorless gum.

To a stirred solution of the above crude aldehyde in dichloromethane (5 mL) was added (carbethoxymethylene)triphenylphosphoraneafforded (116 mg, 0.335 mmol) and the reaction mixture was further stirred for an additional 6 h. Removal of the solvent under reduced pressure gave the crude product which was purified by silica gel column (2-10% ethyl acetate in hexanes) to afford compound **14** as a white solid compound; Yield: (78 mg, 65% over two steps); mp: 100–102 °C; R_f: 0.46 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.03 (dd, *J* = 15.6, 9.1 Hz, 1H), 6.74 (td, *J* = 8.7, 3.2 Hz, 1H), 6.67 (dd, *J* = 9.1, 5.0 Hz, 1H), 6.47 (dd, *J* = 8.70, 3.2 Hz, 1H), 6.16 (d, *J* = 15.1 Hz, 1H), 4.28-4.15 (m, 2H), 3.31-3.24 (m, 2H), 3.03 (dd, *J* = 14.2, 5.0 Hz, 1H), 2.63 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.42 (s, 3H), 1.30 (t, *J* =7.3 Hz, 3H), 1.00 (s, 9H), 0.25 (s, 6H), 0.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 156.8 (d, *J* = 239.6 Hz), 149.4 (d, *J* = 1.9 Hz), 144.4, 140.3,

136.0, 129.5, 129.4 (d, *J* = 7.7 Hz), 127.4, 126.9, 118.7 (d, *J* = 7.7 Hz), 117.0 (d, *J* = 23.0 Hz), 114.0 (d, *J* = 23.0 Hz), 60.7, 48.7, 48.4, 31.8, 25.8, 21.6, 18.2, 14.2, -4.1, -4.3; Anal. Calcd for $C_{27}H_{36}FNO_5SSi$: C, 60.76; H, 6.80; N, 2.62, found C, 60.90; H, 6.91; N, 2.69.

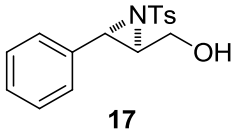
(*R,*E*)-Ethyl 4-((*S**)-2,3-dihydrobenzofuran-2-yl)-4-(4-methylphenylsulfonamido) but-2-enoate (15):**



15

Following the **General Procedure C**, compound **14** (50 mg, 0.094 mmol) was subjected to the intramolecular aziridine ring-opening reaction. The resulting crude product was purified by silica gel column chromatography (10-25% EtOAc in hexanes) to obtain the title compound **15** as a white crystalline solid. Yield: (37 mg, 93%); mp: 110–112 °C; R_f: 0.38 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.81-6.74 (m, 2H), 6.59-6.53 (m, 2H), 5.78 (d, *J* = 16.0 Hz, 1H), 5.14 (d, *J* = 8.7 Hz, 1H), 4.84-4.79 (m, 1H), 4.16-4.07 (m, 3H), 3.23 (dd, *J* = 16.5, 9.6 Hz, 1H), 2.99 (dd, *J* = 16.5, 7.0 Hz, 1H), 2.42 (s, 3H), 1.22 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 157.6 (d, *J* = 238.6 Hz), 154.7 (d, *J* = 1.9 Hz), 143.8, 140.4, 137.3, 129.7, 127.2, 126.8 (d, *J* = 9.6 Hz), 125.0, 114.5 (d, *J* = 23.9 Hz), 112.1 (d, *J* = 24.9 Hz), 109.5 (d, *J* = 8.6 Hz), 83.6, 60.6, 57.8, 32.1 (d, *J* = 1.9 Hz),, 21.5, 14.0; MS (ESI) *m*/*z*: 420 $(M + H)^+$; Anal. Calcd for $C_{21}H_{22}FNO_5S$: C, 60.13; H, 5.29; N, 3.34, found C, 60.28; H, 5.21; N, 3.37.

((2*S,3*R**)-3-Phenyl-1-tosylaziridin-2-yl)methanol (17):**

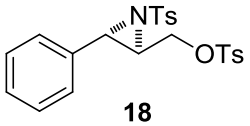


17

Following the **General Procedure B**, cinnamyl alcohol **16** (1.21 g, 9.0 mmol) was subjected to the Sharpless aziridination reaction. The resulting crude product was purified by silica gel column chromatography (5-10% EtOAc in hexanes) to obtain the title compound **17** as a colorless semi-solid**.** Yield: (2.1 g, 77%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.29-7.25 (m, 5H), 7.14-7.11 (m, 2H), 4.31 (ddd, *J* = 13.4, 10.1, 3.2 Hz, 1H), 4.18 (ddd, *J* = 13.5, 8.5, 4.8 Hz, 1H), 4.01 (d, *J* = 4.4 Hz, 1H),

3.18 (ddd, *J* = 7.9, 3.7, 1.4 Hz, 1H), 3.12 (dd, *J* = 10.0, 4.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 137.0, 134.5, 129.7, 128.6, 128.4, 127.1, 126.4, 60.7, 54.8, 46.3, 21.6. Spectral data were in complete agreement with the literature data [25].

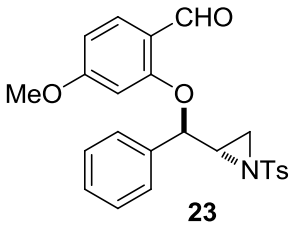
((2*S,3*R**)-3-phenyl-1-tosylaziridin-2-yl)methyl 4-methylbenzenesulfonate (18):**



18

To a stirred solution of aziridino alcohol **17** (2.1 g, 7.0 mmol) in CH_2Cl_2 (50 mL) at 0 ^{o}C was added triethylamine (1.5 mL, 10.47 mmol) followed by tosyl chloride (2.0 g, 10.47 mmol) and kept in the refrigerator for 12 h. The reaction mixture was diluted with H_2O (100 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The resulting crude product was purified by silica gel column chromatography (5-10% EtOAc in hexanes) to obtain the title compound **18** as a colorless solid**.** Yield: (2.08 g, 65%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.29–7.11 (m, 9H), 4.69 (dd, *J* = 11.4, 5.7 Hz, 1H), 4.58 (dd, *J* = 11.3, 7.3 Hz, 1H), 3.87 (d, *J* = 4.1 Hz), 3.12 (ddd, *J* = 7.3, 5.8, 4.0 Hz, 1H), 2.43 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.2, 144.6, 136.4, 133.6, 130.0, 129.7, 128.6, 128.0, 127.6, 126.8, 66.7, 47.9, 47.3, 21.64, 21.59. Spectral data were in complete agreement with the literature data [25].

4-Methoxy-2-((*R)-phenyl((*S**)-1-tosylaziridin-2-yl)methoxy)benzaldehyde (23):**

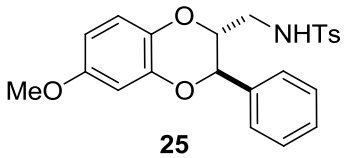


23

To a stirred suspension of sodium hydride (96 mg, 4.0 mmol) in DMF (10 mL), was added a solution of 2-hydroxy-4-methoxybenzaldehyde **22** (0.5 g, 3.28 mmol) in dry DMF (10 mL) dropwise at 0 °C under N_2 atmosphere. The resulting mixture was stirred for 5 min, and then a solution of **18** (1.5 g, 3.28 mmol) in DMF (15 mL) was added dropwise. The solution was stirred for an additional 2 h at 0 °C. Saturated aqueous NH_4Cl (15 mL) and Et_2O (80 mL) were added and the mixture was stirred vigorously for

10 min. The phases were then separated and the aqueous phase was extracted with Et_2O (25 x 2 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **23** as a colorless semi-solid. Yield: (488 mg, 34%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.27-7.23 (m, 7H), 6.49 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.20 (d, *J* = 2.3 Hz, 1H), 5.17 (d, *J* = 4.6 Hz, 1H), 3.69 (s, 3H), 3.26-3.22 (m, 1H), 2.78 (d, *J* = 7.3 Hz, 1H), 2.45 (s, 3H), 2.37 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.8, 165.6, 161.2, 144.9, 136.1, 134.1, 130.4, 129.7, 128.8, 128.7, 127.9, 126.4, 119.4, 106.9, 100.5, 78.7, 55.5, 42.6, 30.3, 21.7; Anal. Calcd. for $C_{24}H_{23}NO_5S$: C, 65.89; H, 5.30; N, 3.20, found: C, 65.77; H, 5.36; N, 3.28.

_N_-(((2_R_*,3_R_*)-6-Methoxy-3-phenyl-2,3-dihydrobenzo[_b_][1,4]dioxin-2-yl)methyl)-4-methylbenzenesulfonamide (25):



25

To a solution of compound **23** (400 mg, 0.914 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (77% purity, 338 mg, 1.37 mmol) at 0 °C and the mixture was stirred overnight at rt. The mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with aq solutions of Na_2SO_3 (10 mL) and $NaHCO_3$ (10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

To a stirred solution of the above crude product in THF (5 mL) was added saturated 10% NaOH solution (4 mL) at 0 ^{o}C and the resulting solution was stirred vigorously for 2 h. Water (10 mL) was added to the resulting residue. The mixture was extracted with EtOAc (20 mL) washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (5-15% EtOAc in hexanes) to obtain the title compound **25** as a colorless crystalline solid. Yield: (311 mg, 80% over two steps); mp: 160–162 °C; R_f: 0.29 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.2 Hz, 2H), 7.30-7.25 (m, 1H; overlapped with the peak for residual $CHCl_3$, resulting in higher integrated area of 3 instead of 1), 7.21 (d, *J* = 4.6 Hz, 4H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.50 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.44 (d, *J* = 3.2 Hz, 1H),

4.92 (d, *J* = 8.7 Hz, 1H), 4.81 (d, *J* = 9.2 Hz, 1H), 4.59 (dd, *J* = 12.8, 2.7 Hz, 1H),), 4.29 (d, *J* = 12.4 Hz, 1H), 3.95-3.91 (m, 1H), 3.68 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 149.0, 143.8, 143.2, 137.3, 136.5, 129.5, 128.54, 128.47, 127.1, 126.8, 120.5, 109.5, 106.1, 84.6, 74.0, 59.5, 55.6, 21.5. MS (ESI) *m*/*z*: 426 $(M + H)^+$; Anal. Calcd. for $C_{23}H_{23}NO_5S$: C, 64.92; H, 5.45; N, 3.29, found: C, 65.11; H, 5.52; N, 3.32.

6.5.3. X-ray Crystallography Data

X-ray reflections were collected on a Bruker APEX-II, CCD diffractometer using Mo Kα (λ = 0.71073 Å) radiation. Data reduction was performed using Bruker SAINT Software [35]. Intensities for absorption were corrected using SADABS. Structures are solved and refined using SHELXL-2014 with anisotropic displacement parameters for non-H atoms. Hydrogen atoms on O and N are experimentally located in all crystal structures. All C–H atoms are fixed geometrically using the HFIX command in SHELX-TL [36]. A check of the final CIF file using PLATON have not shown any missed symmetry [37,38]. Compound **13e** was crystallized (from its solution in ethyl acetate/hexane) in non-enantiogenic orthogonal space group $Pna2_1$. Crystal structure was solved and refined with two symmetry independent molecules. The ORTEP is already shown in Figure 6.2. The crystallographic data and hydrogen bond matrices are shown in Table 6.3 and Table 6.4, respectively.

Table 6.3. Crystallographic data of chroman derivative 13e

Formula unit	$C_{18}H_{21}NO_4S$
Formula wt.	347.42
Crystal system	Orthorhombic
T [K]	100
a [Å]	19.409 (11)
b [Å]	22.804 (14)
c [Å]	7.899 (5)
α [°]	90
β [°]	90
γ [°]	90
Volume [$Å^3$]	3496 (4)
Space group	$Pna2_1$

Z	8
D_{calc} [g cm^{-3}]	1.320
μ/mm^{-1}	0.206
Reflns. Collected	36469
Unique reflns.	7968
Observed reflns.	3221
R_1 [I>2σ(I)], wR_2	0.0692; 0.1375
GOOF	0.933
Instrument	Bruker APEX-II CCD
X-ray	MoK\α; λ=0.71073
CCDC Reference	1840365

Table 6.4. Hydrogen bond matrices of 13e

Interaction	H···A (Å)	D···A (Å)	D–H···A (º)	Symmetry Code
N_1–H_{1A}···O_8	1.98(9)	2.957(7)	176(10)	1/2-x,-1/2+y,-1/2+z
N_2–H_{2A}···O_4	2.16(7)	2.923(7)	157(7)	1/2-x,1/2+y,1/2+z
O_4–H_{4A}···O_1	2.12(11)	2.854(6)	138(8)	x,y,-1+z
O_4–H_{4A}···O_6	2.50(10)	3.202(6)	135(8)	1/2-x,-1/2+y,-1/2+z
O_8–H_{8A}···O_6	2.14(6)	2.889(6)	161(7)	x,y,1+z
C_{35}–H_{35}···O_5	2.45(5)	3.369(8)	168(6)	x,y,1+z
C_{21}–H_{21}···O_2	2.54(5)	3.435(8)	161(6)	-
Intra C_2–H_2···O_1	2.60(4)	2.932(7)	102(6)	-
Intra C_8–H_8···O_2	2.52(6)	2.977(8)	108(4)	-
Intra C_{20}–H_{20}···O_5	2.58(6)	2.928(7)	103(6)	-
Intra C_{26}–H_{26}···O_5	2.52(6)	2.997(8)	109(4)	-

Two 2-fold screw axis related molecules form a dimer via strong N–H···O hydrogen bonding between the amine NH of first molecule to the second molecules OH group (Figure 6.4). The dangling OH groups form O–H···O hydrogen bonds with the sulfonamide oxygen of nearby dimer extending the structure into a one dimensional molecular tapes along [001] crystallographic axis. These tapes are connected primarily via C–H···π interactions that completes the 3D packing of the molecules.

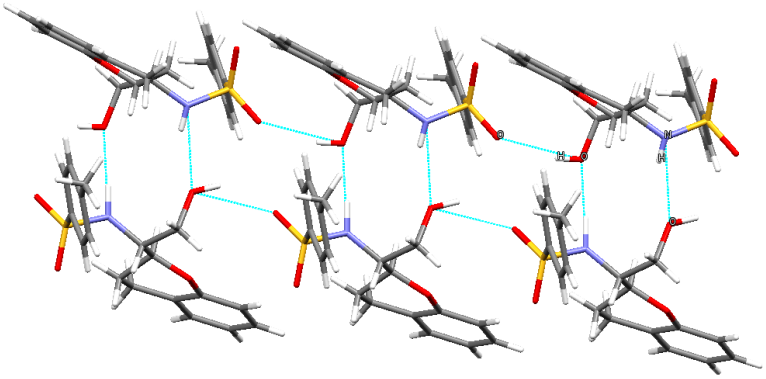


Figure 6.4. Hydrogen bonding in the solid-state structure of 13e

6.6. References

[1] Hu, X. E. Nucleophilic ring opening of aziridines. *Tetrahedron*, 60(12):2701-2743, 2004.

[2] Lu, P. Recent developments in regioselective ring opening of aziridines. *Tetrahedron*, 66(14):2549-2560, 2010.

[3] Wang, P. A. Organocatalyzed enantioselective desymmetrization of aziridines and epoxides. *Beilstein Journal of Organic Chemistry*, 9:1677-1695, 2013

[4] Huang, C. Y. and Doyle, A. G. The Chemistry of Transition Metals with Three-Membered Ring Heterocycles. *Chemical Reviews*, 114(16):8153-8198, 2014.

[5] Callebaut, G., Meiresonne, T., De Kimpe, N., and Mangelinckx, S. Synthesis and Reactivity of 2-(Carboxymethyl)aziridine Derivatives. *Chemical Reviews*, 114(16):7954-8015, 2014.

[6] Ohno, H. Synthesis and Applications of Vinylaziridines and Ethynylaziridines. *Chemical Reviews*, 114(16):7784-7814, 2014.

[7] Shahi, C. K., Bhattacharyya, A., Nanaji, Y., and Ghorai, M. K. A Stereoselective Route to Tetrahydrobenzoxazepines and Tetrahydrobenzodiazepines via Ring-Opening and Aza-Michael Addition of Activated Aziridines with 2-Hydroxyphenyl and 2-Aminophenyl Acrylates. *The Journal of Organic Chemistry*, 82(1):37-47, 2016.

[8] Bailey, S. J., Wales, S. M., Willis, A. C., and Keller, P. A. Ring-Opening and -Expansion of 2,2′-Biaziridine: Access to Diverse Enantiopure Linear and Bicyclic Vicinal Diamines. *Organic Letters*, 16(16):4344-4347, 2014.

[9] Ji, F., Lv, M. F., Yi, W. B., and Cai, C. Synthesis of 1, 4-Benzoxazepine Derivatives via a Novel Domino Aziridine Ring-Opening and Isocyanide-Insertion Reaction. *Advanced Synthesis & Catalysis*, 355(17):3401-3406, 2013.

[10] Takehiroa, Y., Hirotakia, K., Takeshitaa, C., Furunob, H., and Hanamotoa, T. Regioselective ring-opening reaction of 2-trifluoromethyl-*N*-tosylaziridine with some nucleophiles under basic conditions. *Tetrahedron*, 69(35):7448-7454, 2013.

[11] Chouhan, G. and Alper, H. Domino Ring-Opening/Carboxamidation Reactions of N-Tosyl Aziridines and 2-Halophenols/Pyridinol: Efficient Synthesis of 1,4-Benzo- and Pyrido-oxazepinones. *Organic Letters*, 12(1):192-195, 2009.

[12] Ottesen, L. K., Jaroszewski, J. W., and Franzyk, H. Ring Opening of a Resin-Bound Chiral Aziridine with Phenol Nucleophiles. *The Journal of Organic Chemistry*, 75(15):4983-4991, 2010.

[13] Rao, R. K., Naidu, A. B., and Sekar, G. Highly Efficient Copper-Catalyzed Domino Ring Opening and Goldberg Coupling Cyclization for the Synthesis of 3, 4-Dihydro-2*H*-1, 4-benzoxazines. *Organic Letters*, 11(9):1923-1926, 2009.

[14] Kelley, B. T., Carroll, P., and Joullie, M. M. Possible Reason for the Unusual Regioselectivity in Nucleophilic Ring Opening of Trisubstituted Aziridines under Mildly Basic Conditions. *The Journal of Organic Chemistry*, 79(11):5121-5133, 2014.

[15] Kenis, S., D'hooghe, M., Verniest, G., Reybroeck, M., Thi, T. A. D., The, C. P., Pham, T. T., Törnroos, K. W., Tuyen, N. V., Kimpe, N. D. Nucleophile-Directed Selective Transformation of *cis*-1-Tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine into Aziridines, Azetidines, and Benzo-Fused Dithianes, Oxathianes, Dioxanes, and (Thio)morpholines. *Chemistry: A European Journal*, 19(19): 5966-5971, 2013.

[16] Forbeck, E. M., Evans, C. D., Gilleran, J. A., Li, P., and Joullié, M. M. A Regio- and Stereoselective Approach to Quaternary Centers from Chiral Trisubstituted Aziridines. *Journal of the American Chemical Society*, 129(46):14463-14469, 2007.

[17] Li, P., Forbeck, E. M., Evans, C. D., and Joullié, M. M. Trisubstituted Aziridine Ring-Opening by Phenol Derivatives: Stereo-and Regioselective Formation of Chiral Tertiary Alkyl-Aryl Ethers. *Organic Letters*, 8(22):5105-5107, 2006.

[18] Lim, Y. and Lee, W. K. Regiospecific reductive ring cleavage of *N*-substituted

aziridine-2-carboxylates and an aziridine-2-methanol via catalytic hydrogenation using Pd as a catalyst. *Tetrahedron Letters*, 36(46):8431-8434, 1995.

[19] Jeong, J. U., Tao, B., Sagasser, I., Henniges, H., and Sharpless, K. B. Bromine-Catalyzed Aziridination of Olefins. A Rare Example of Atom-Transfer Redox Catalysis by a Main Group Element. *Journal of the American Chemical Society*, 120(27):6844-6845, 1998.

[20] Yadav, J. S., Bandyopadhyay, A., and Reddy, B. V. S. Indium-Mediated Efficient Conversion of 2-Iodomethyl Aziridines to Chiral Allylic Amines. *Synlett*, 2001(10):1608-1610, 2010.

[21] Bhoga, U. A new synthetic approach to enantiomerically enriched dihydrobenzofurans: use of a hydrolytic kinetic resolution and an intramolecular epoxide ring opening protocol using 1-benzyloxy-2-oxiranylmethylbenzenes. *Tetrahedron Letters*, 46(31):5239-5242, 2005.

[22] Dinda, S. K., Das, S. K., and Panda, G. Application of Phenolate Ion Mediated Intramolecular Epoxide Ring Opening in the Enantioselective Synthesis of Functionalized 2, 3-Dihydrobenzofurans and 1-Benzopyrans. *Synthesis*, 2009(11):1886-1896, 2009.

[23] Das, S. K. and Panda, G. β-Hydroxy-α-tosyloxy esters as chiral building blocks for the enantioselective synthesis of benzo-annulated oxa-heterocycles: scope and limitations. *Tetrahedron*, 64(19):4162-4173, 2008.

[24] Birch, A. M., Bradley, P. A., Gill, J. C., Kerrigan, F., and Needham, P. L. *N*-Substituted (2,3-Dihydro-1,4-benzodioxin-2-yl)methylamine Derivatives as D2 Antagonists/5-HT1A Partial Agonists with Potential as Atypical Antipsychotic Agents. *Journal of Medicinal Chemistry*, 42(17):3342-3355, 1999.

[25] Ma, L., Jiao, P., Zhang, Q., and Xu, J. Rigid backbone 1,8-anthracene-linked bis-oxazolines (AnBOXes): Design, synthesis, application and characteristics in catalytic asymmetric aziridination. *Tetrahedron Asymmetry*, 16(22):3718-3734, 2005.

[26] Novotná, M., Gažák, R., Biedermann, D., Di Meo, F., Marhol, P., Kuzma, M., Bednárová, L., Fuksová, K., Trouillas, P., and Křen, V. *cis–trans* Isomerization of Silybins A and B. *Beilstein Journal of Organic Chemistry*, 10:1047-1063, 2014.

[27] Pelly, S. C., Govender, S., Fernandes, M. A., Schmalz, H. G., and de Koning, C. B. Stereoselective Syntheses of the 2-Isopropenyl-2,3-dihydrobenzofuran

Nucleus: Potential Chiral Building Blocks for the Syntheses of Tremetone, Hydroxytremetone, and Rotenone. *The Journal of Organic Chemistry*, 72(8):2857-2864, 2007.

[28] Chandrasekhar, S. and Reddy, M. V. Enantioselective Total Synthesis of the Antihypertensive Agent (*S,R,R,R*)-Nebivolol. *Tetrahedron*, 56(34):6339-6344, 2000.

[29] Shigehisa, H., Hayashi, M., Ohkawa, H., Suzuki, T., Okayasu, H., Mukai, M., and Fukuyama, A. Catalytic Synthesis of Saturated Oxygen Heterocycles by Hydrofunctionalization of Unactivated Olefins: Unprotected and Protected Strategies. *Journal of the American Chemical Society*, 138(33):10597-10604, 2016.

[30] Manetsch, R., Zheng, L., Reymond, M. T., Woggon, W. D., and Reymond, J. L. A Catalytic Antibody against a Tocopherol Cyclase Inhibitor. *Chemistry-A European Journal*, 10(10):2487-2506, 2004.

[31] Suga, T., Hamashima, Y., Asakawa, M., and Kawamura, D. *Chemical synthesis method of functional polyphenol derivatives*. Japanese Kokai Tokkyo Koho, JP 2013151488 A 20130808, 2013.

[32] Song, X. G., Zhu, S. F., Xie, X. L., and Zhou, Q. L. Enantioselective Copper-Catalyzed Intramolecular Phenolic O-H Bond Insertion: Synthesis of Chiral 2-Carboxy Dihydrobenzofurans, Dihydrobenzopyrans, and Tetrahydrobenzooxepines. *Angewandte Chemie, International Edition*, 52(9):2555-2558, 2013.

[33] Trost, B. M., Shen, H. C., Dong, L., Surivet, J. P., and Sylvain, C. Synthesis of Chiral Chromans by the Pd-Catalyzed Asymmetric Allylic Alkylation (AAA): Scope, Mechanism, and Applications. *Journal of the American Chemical Society*, 126(38):11966-11983, 2004.

[34] Labrosse, J.-R., Poncet, C., Lhoste, P., and Sinou, D. Asymmetric palladium(0)-mediated synthesis of 2-vinylchroman. *Tetrahedron*: *Asymmetry*, 10(6):1069-1078, 1999.

[35] SAINT Plus, Bruker AXS Inc.: Madison, WI, 2008; BRUKER AXS (v 6.14).

[36] Bruker AXS Inc.: Madison, WI, 2008.

[37] PLATON, A Multipurpose Crystallographic Tool; A. L. Spek, Utrecht University: Utrecht, Netherland, 2002.

[38] A. L. Spek. Single-crystal structure validation with the program PLATON. *Journal of Applied Crystallography*. 36(1):7-13, 2003.

6.7. NMR Spectra of Selected Compounds

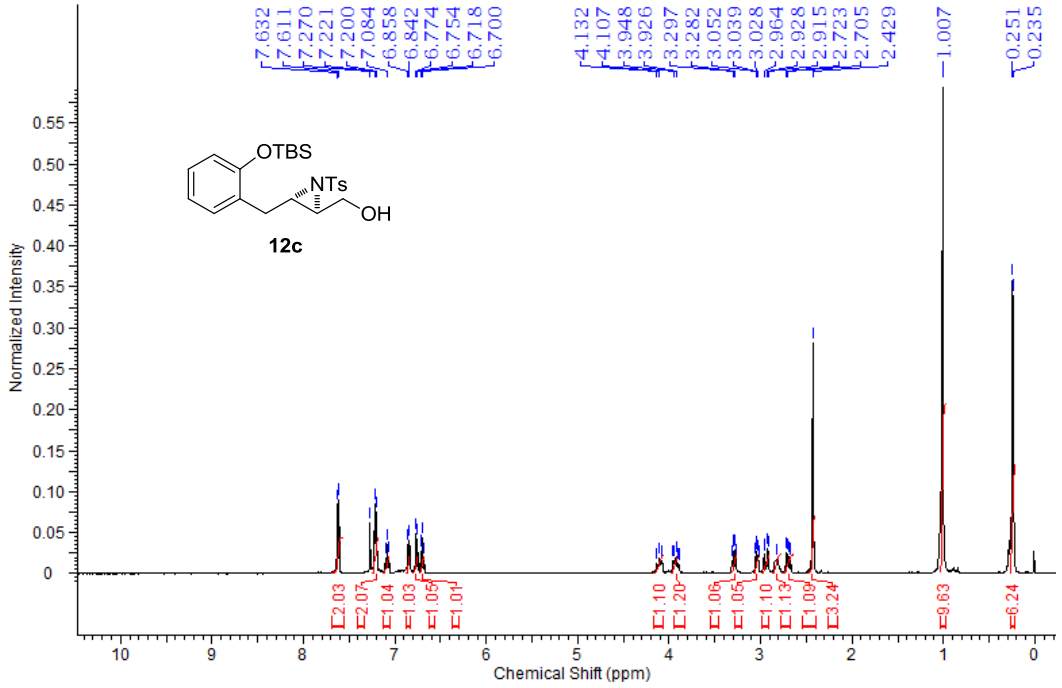


Figure 6.5. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 12c

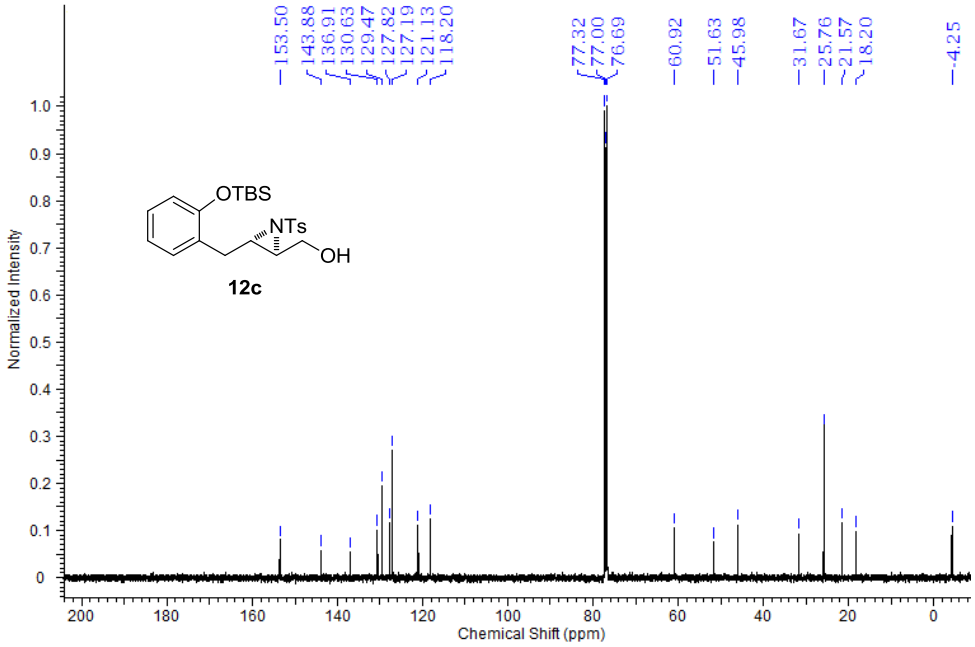


Figure 6.6. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 12c

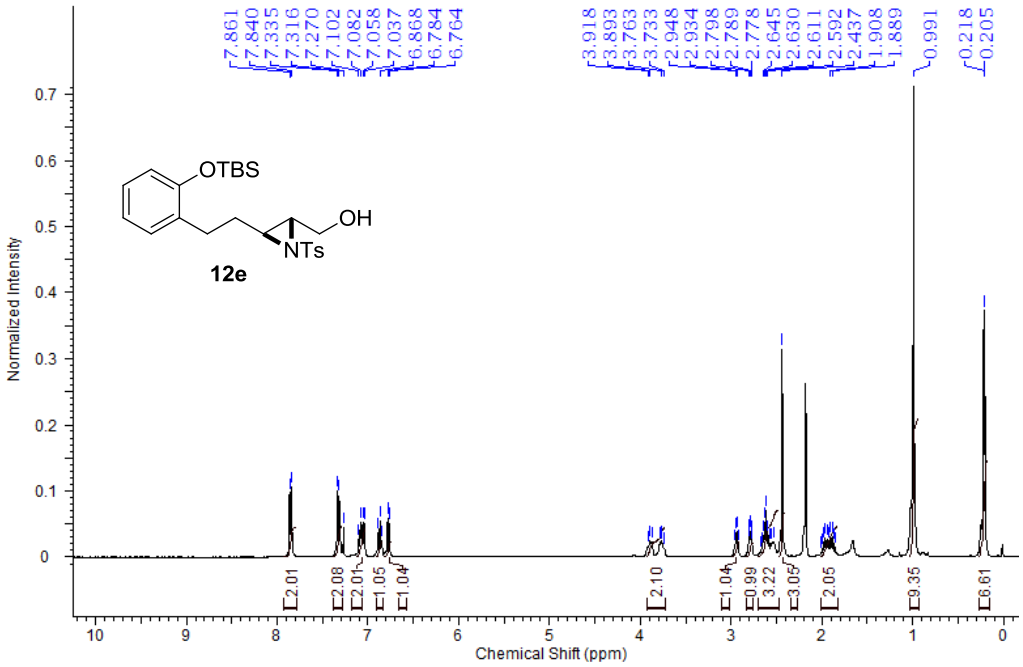


Figure 6.7. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 12e

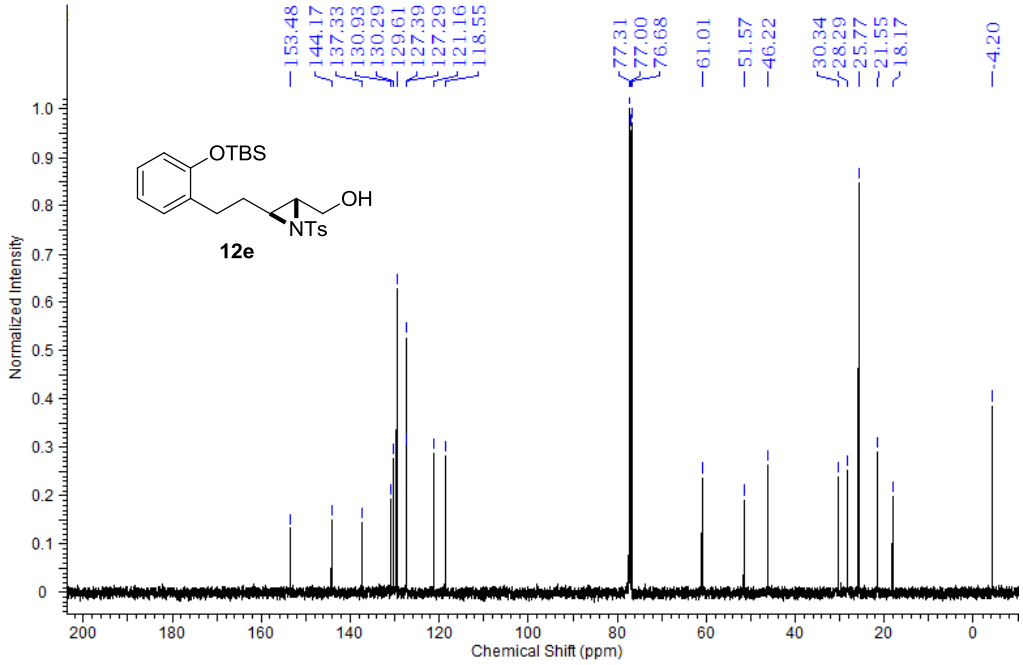


Figure 6.8. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 12e

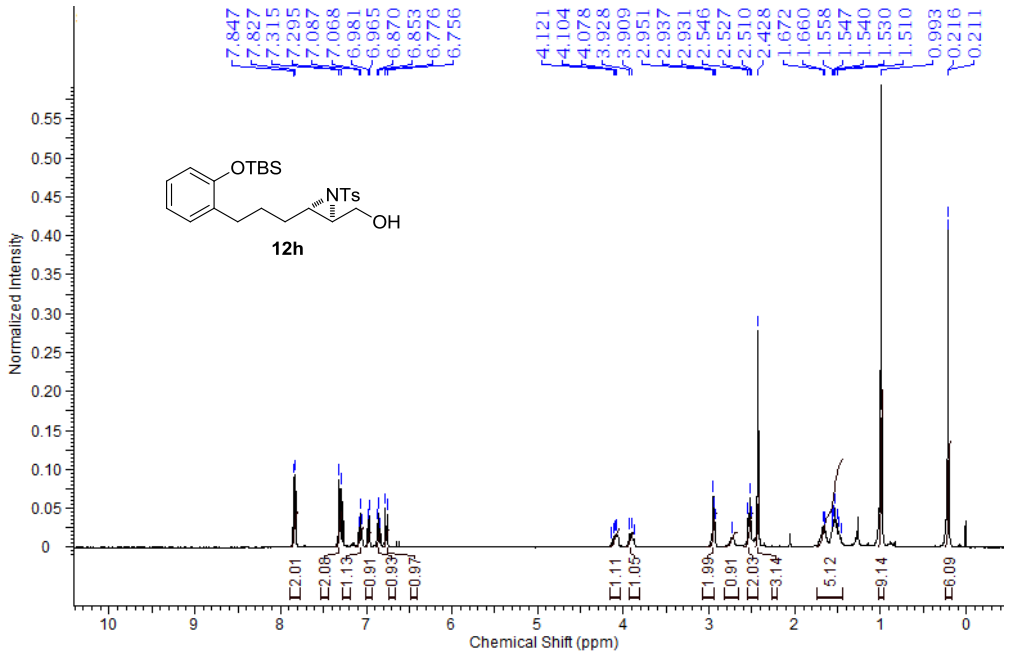


Figure 6.9. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 12h

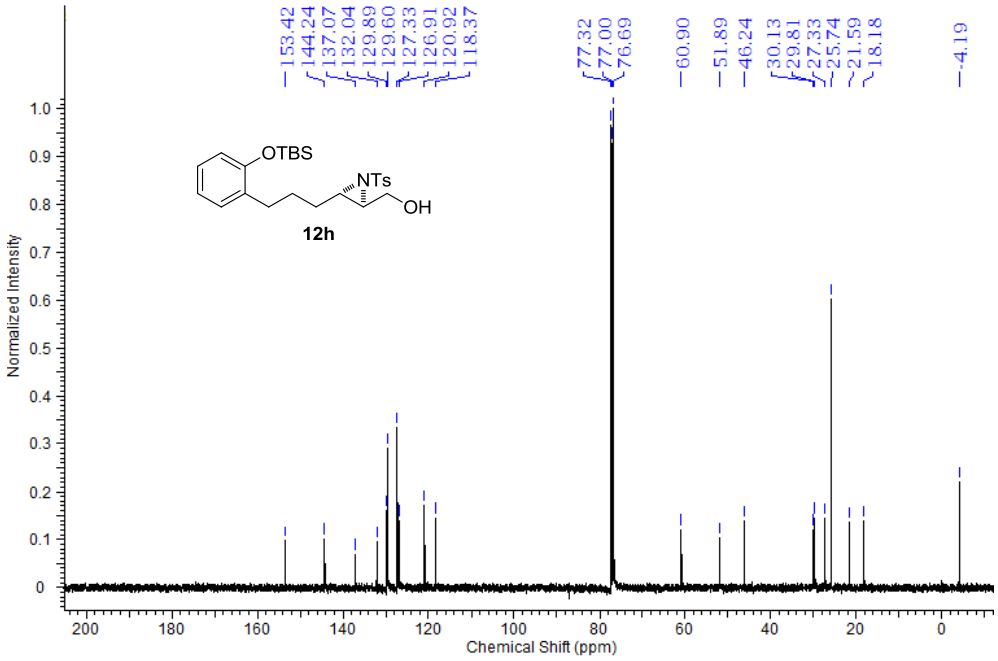


Figure 6.10. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 12h

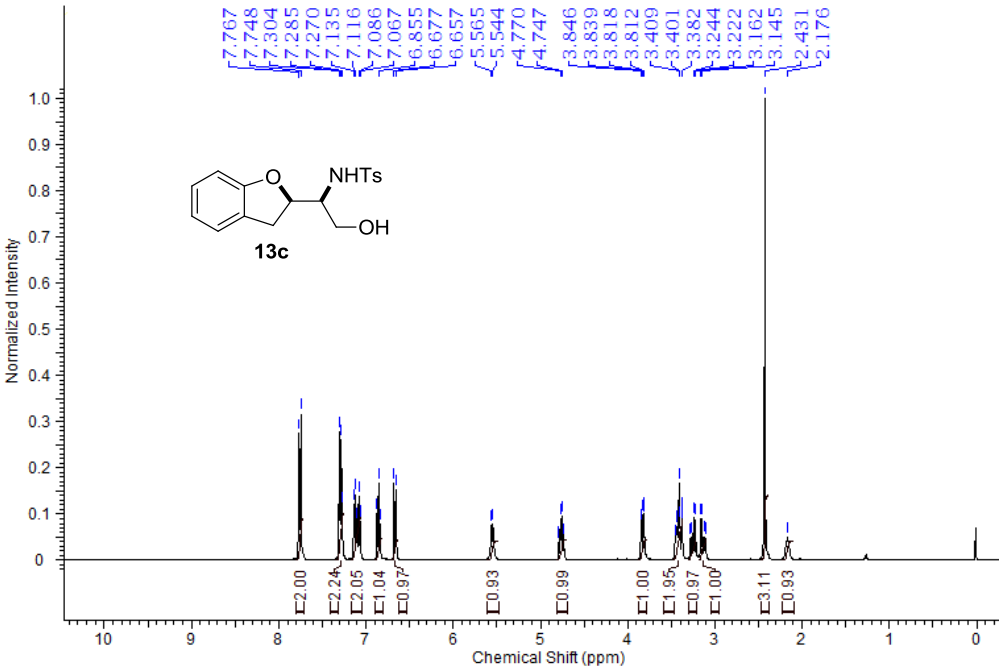


Figure 6.11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 13c

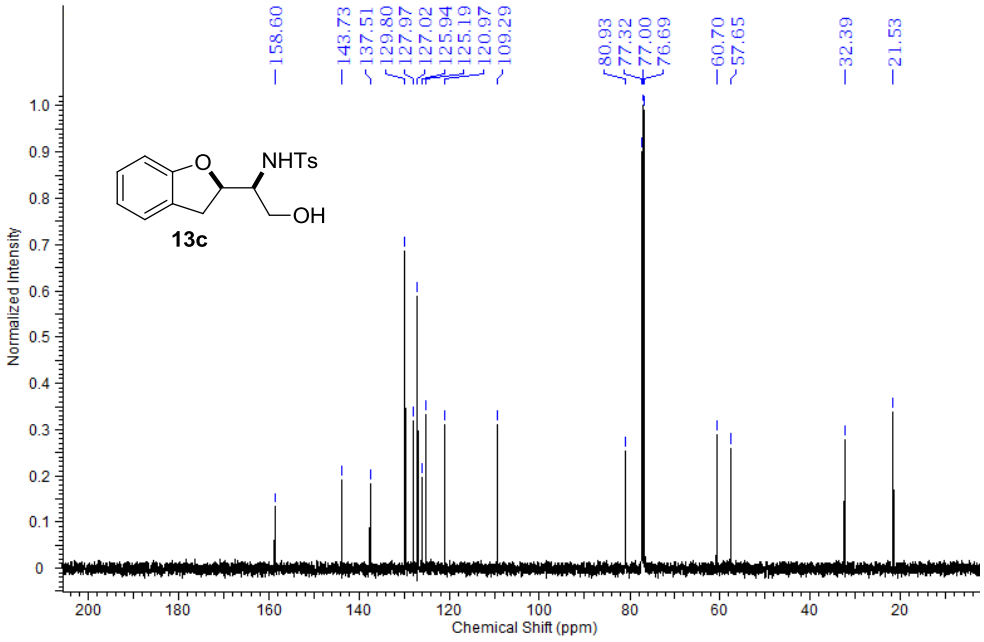


Figure 6.12. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 13c

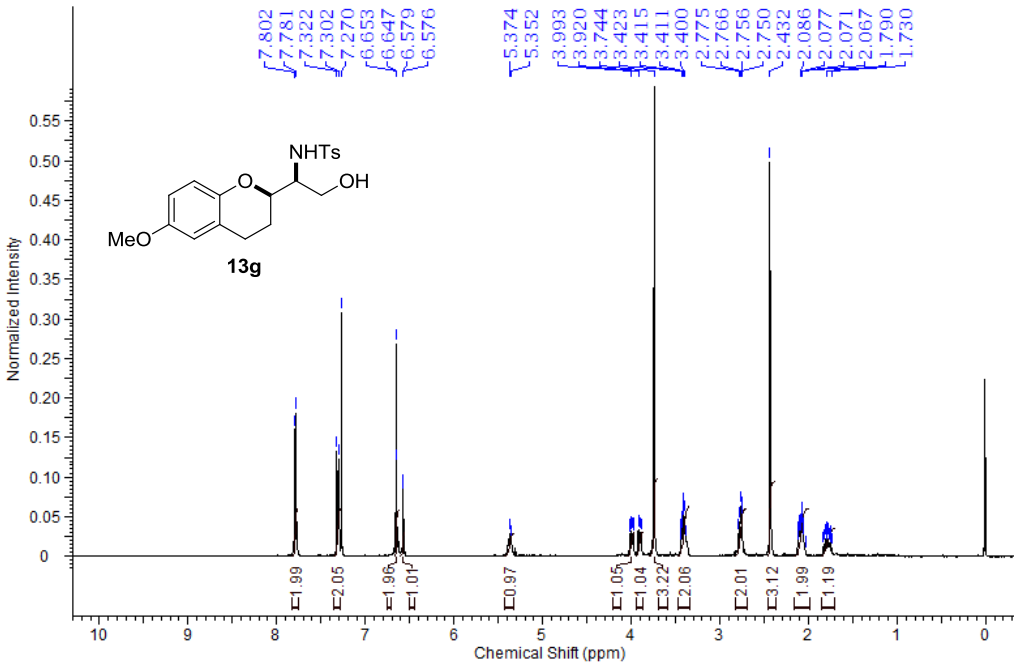


Figure 6.13. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 13g

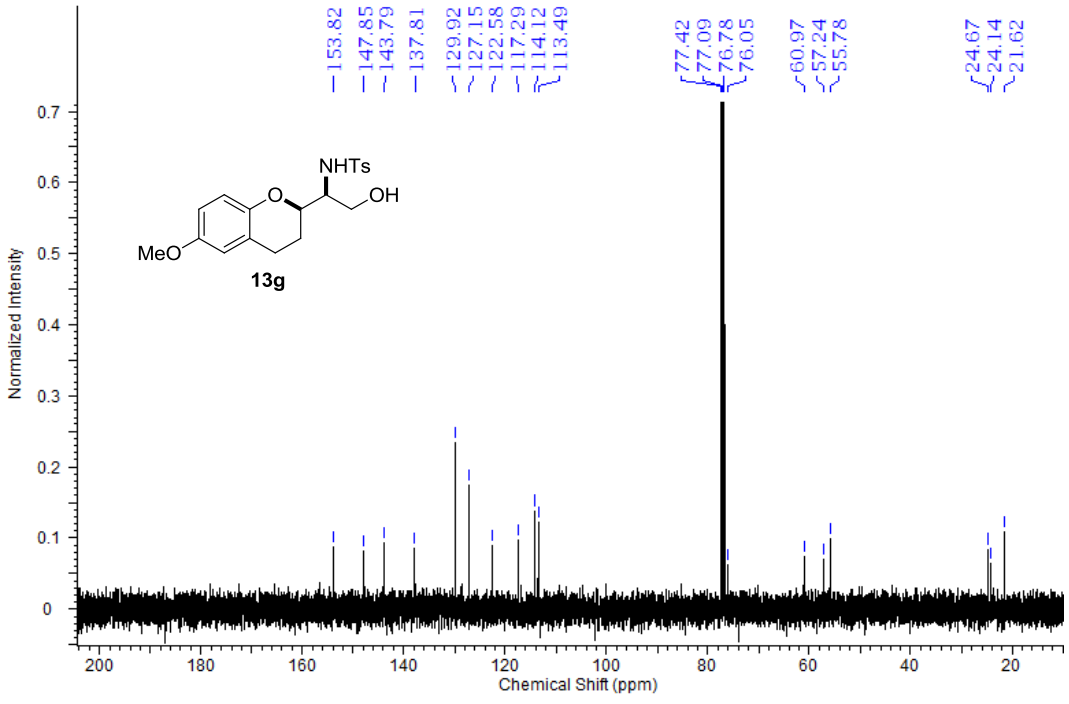


Figure 6.14. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 13g

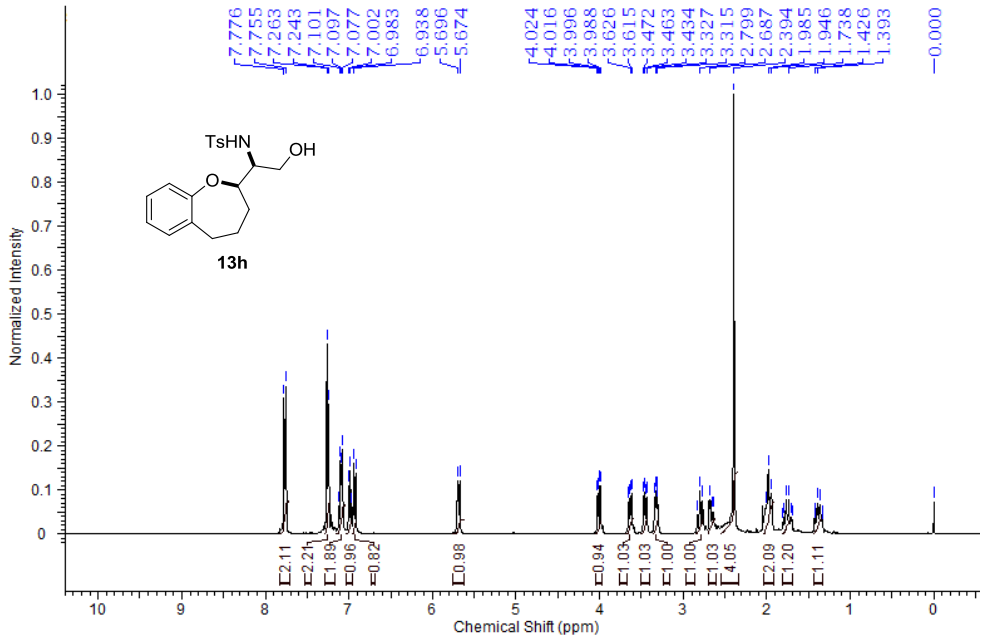


Figure 6.15. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 13h

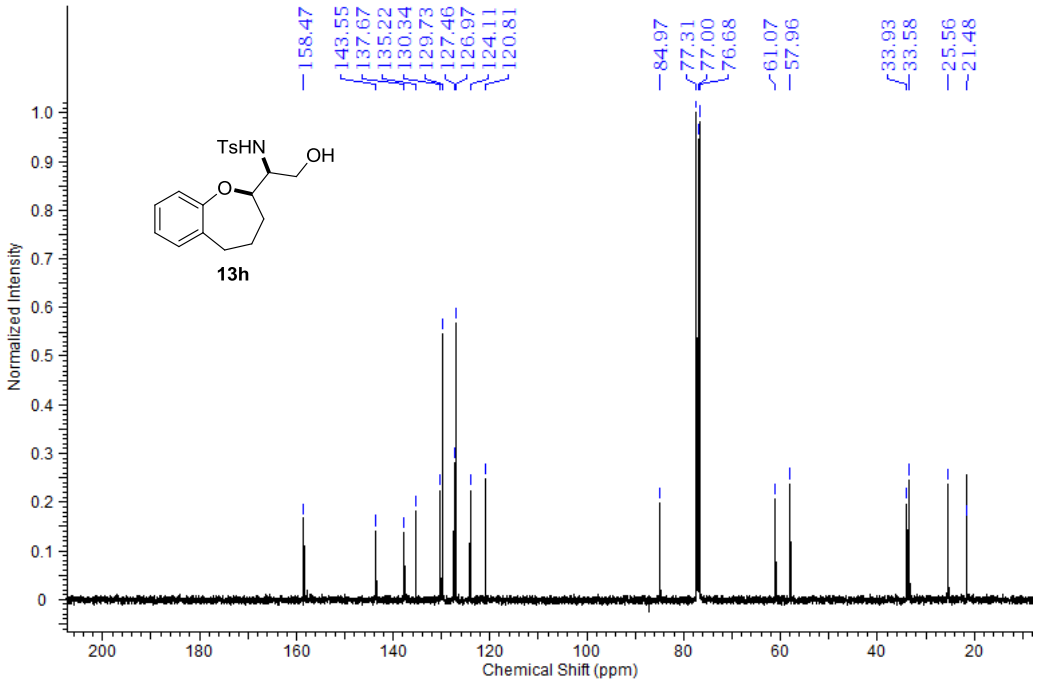


Figure 6.16. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 13h

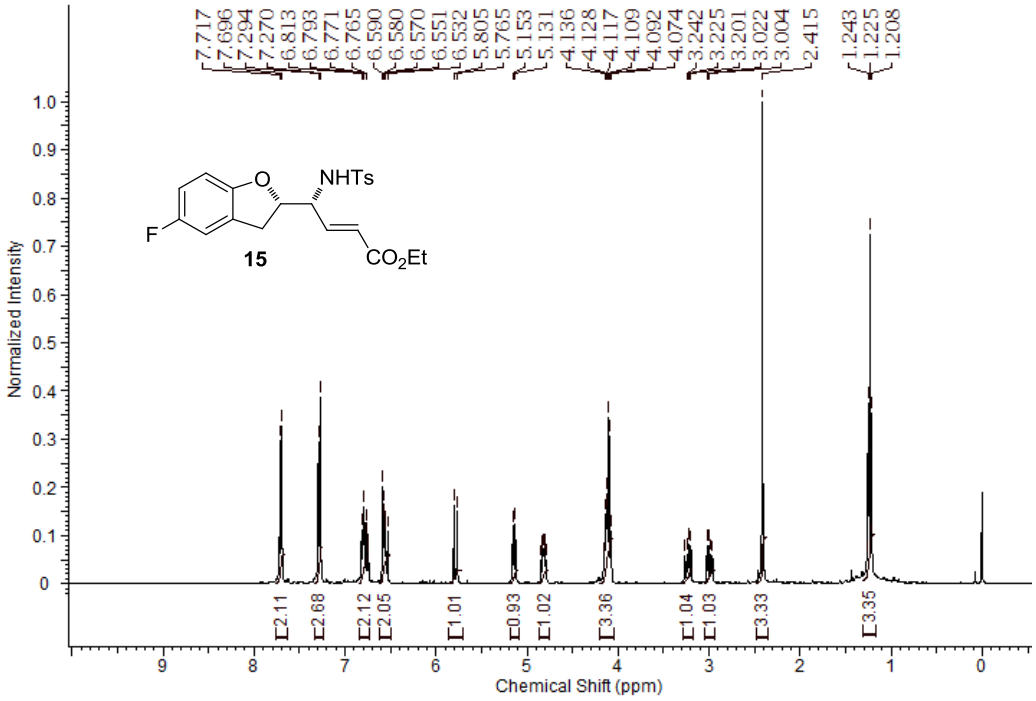


Figure 6.17. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 15

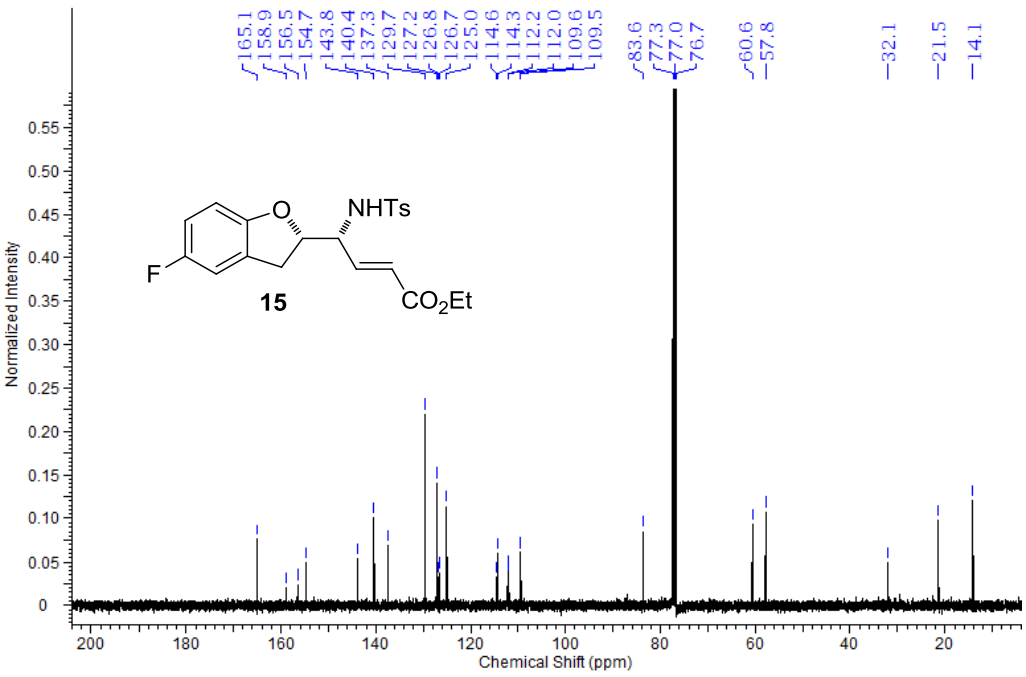


Figure 6.18. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 15

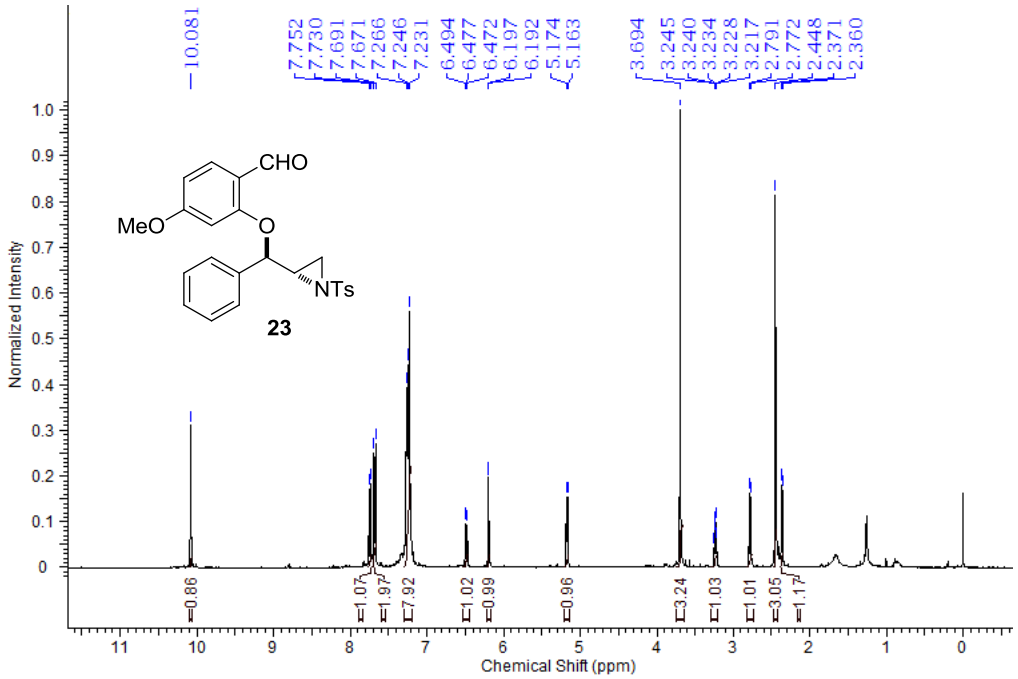


Figure 6.19. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 23

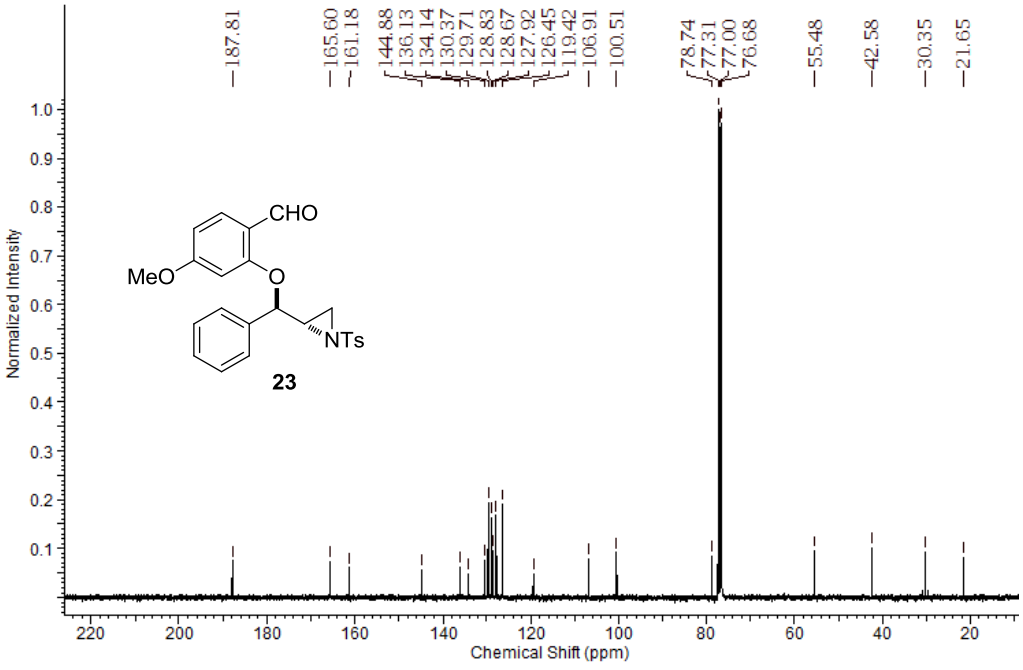


Figure 6.20. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 23

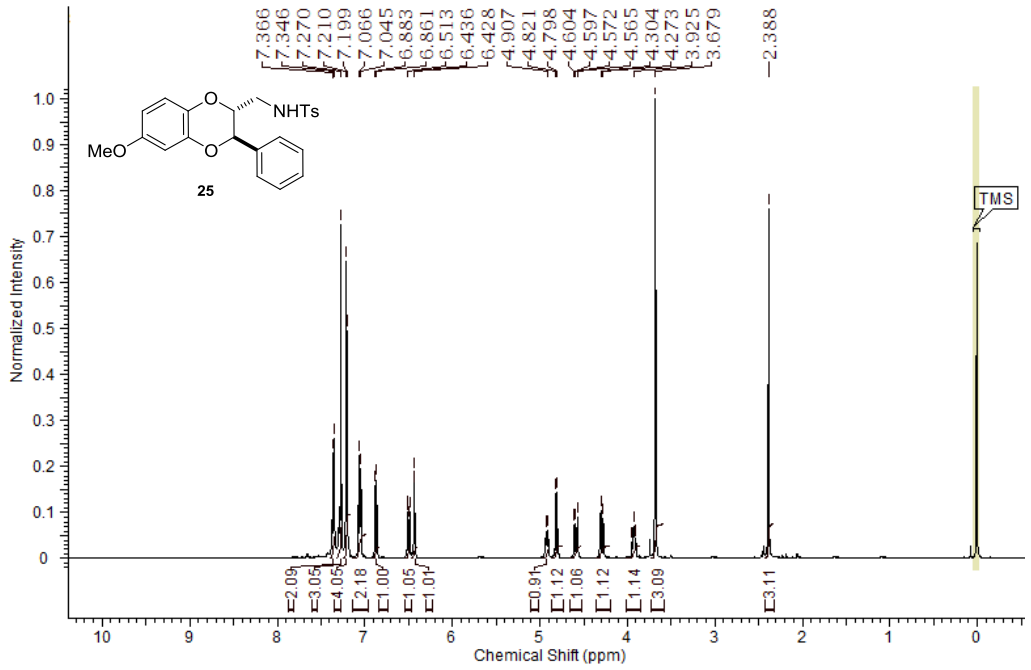


Figure 6.21. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 25

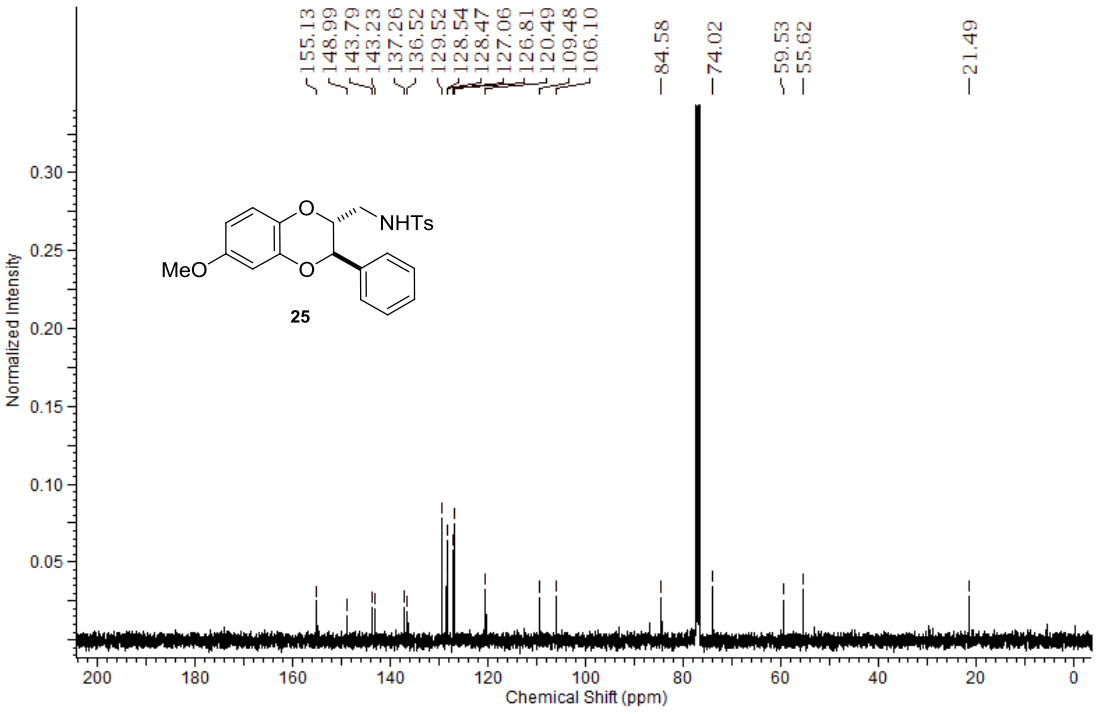


Figure 6.22. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 25