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SYNTHESIS AND APPLICATIONS OF A NEW EPOXY-ISOINDOLINONE

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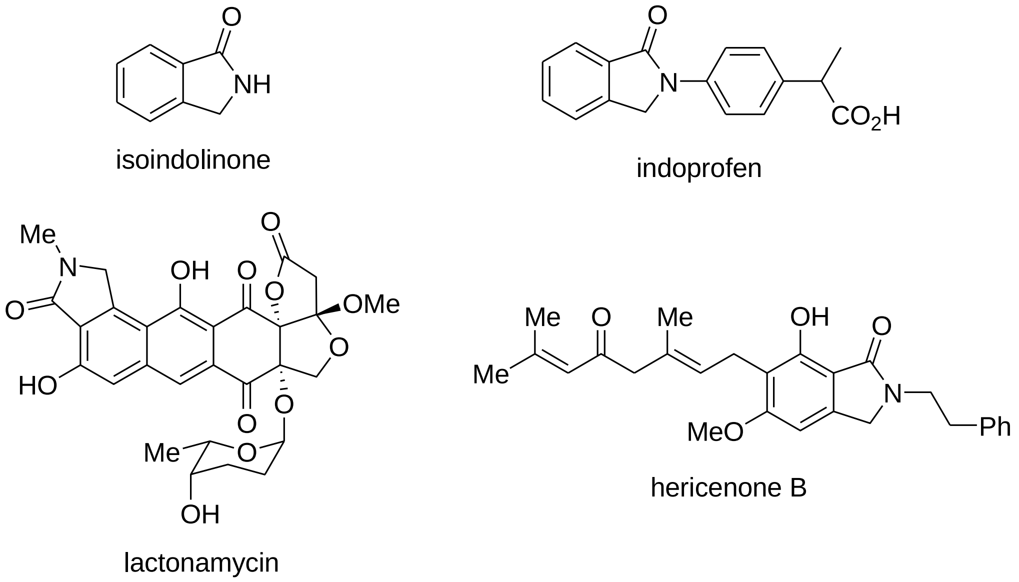
Abstract – A new epoxy-isoindolinone was stereoselectively synthesized, and its reactions gave several interesting products including a new 6-azabicyclo[3.2.1]octane derivative.

INTRODUCTION

The isoindole structure has attracted scientists for decades.[1] Within this category, isoindolinone skeletons are frequently found in bioactive natural products and pharmaceuticals, e.g., indoprofen (antiinflammatory),[2] lactonamycin (antibacterial),[3] and hericenone B (platelet aggregation inhibitory)[4] (Figure 1). A variety of synthetic methods for simple and stable isoindolinones has been reported.[5]


isoindolinone

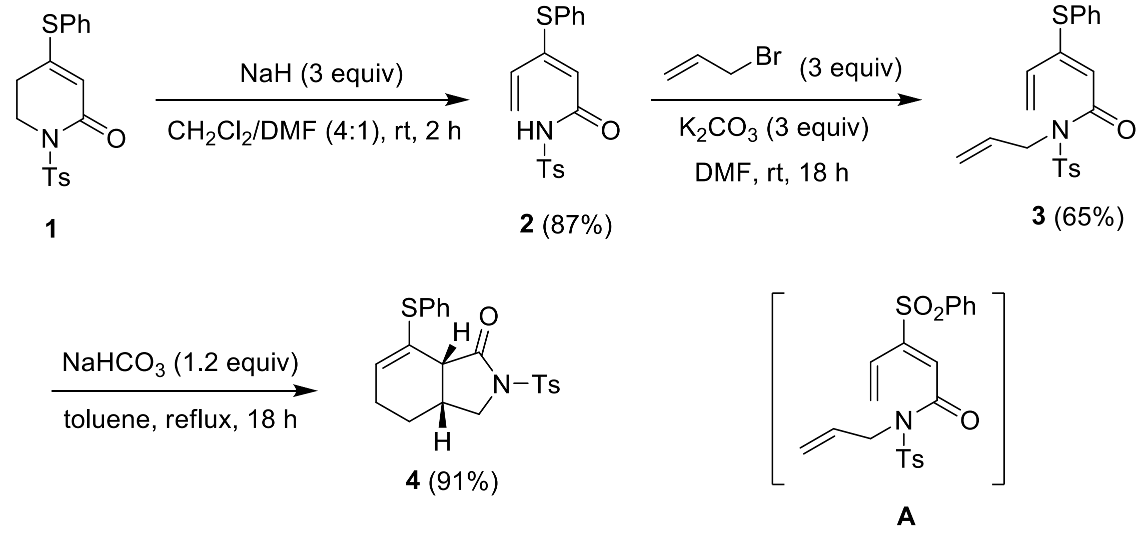
indoprofen

lactonamycin

hericenone B

Figure 1. Isoindolinones structures

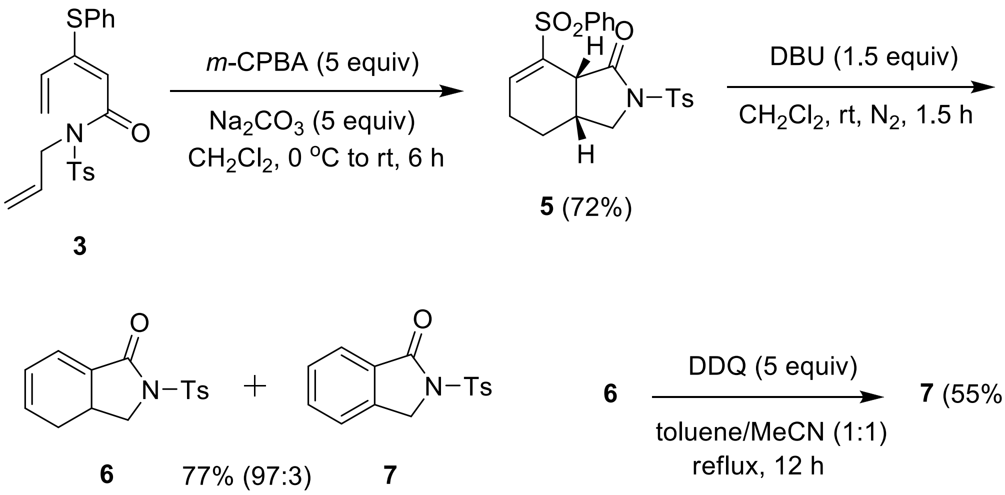
We have recently reported a new method for the synthesis of sulfur-substituted dihydro-isoindolinones (Scheme 1).[6] 5,6-Dihydro-2-pyridone **1**, prepared by an aza-Diels–Alder reaction developed by us,[7] could be converted to the dienyl amide **2** upon treatment with a strong base. Allylation of compound **2** gave the *N*-allyled compound **3**, which could undergo the intramolecular Diels−Alder (IMDA) reaction in the presence of base to give the dihydro-isoindolinone product **4** in excellent yield. However, the IMDA of compound **3** required refluxing in toluene for a long period of time. We thought that the corresponding sulfone-substituted diene **A** would probably react faster, because the sulfonyl group should lower the LUMO of the diene significantly so that an inverse-electron demand Diels−Alder reaction would take place more effectively.



Scheme 1. Synthesis of isoindolinone derivative **4**

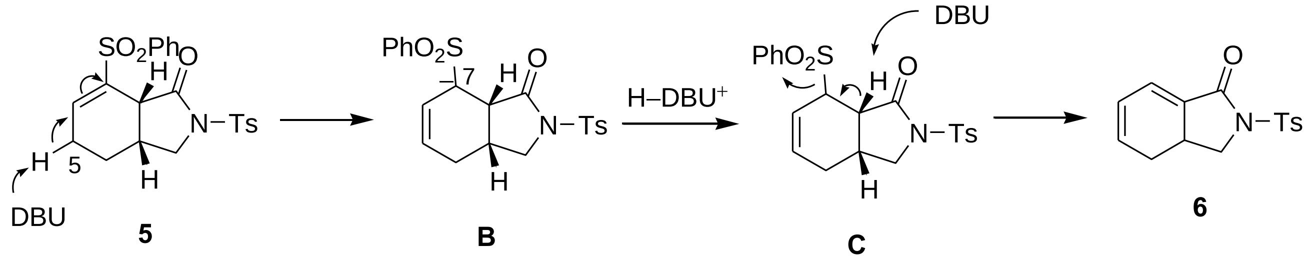
RESULTS AND DISCUSSION

Treatment of compound **3** with *m*-CPBA at room temperature under basic condition yielded directly the bicyclic sulfone **5** in good yield (Scheme 2). This reaction presumably proceeds through the sulfone intermediate **A**, which then undergoes the tandem IMDA reaction to give product **5** directly. Judged by the reaction conditions, the IMDA reaction of the sulfone intermediate **A** is indeed much faster than that of the corresponding diene **3** (Scheme 1). The reaction of compound **5** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature gave the dihydro-isoindolinone **6**, together with a small amount of the aromatic compound **7**.[8] Compound **6** could also be converted to compound **7** by heating with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).



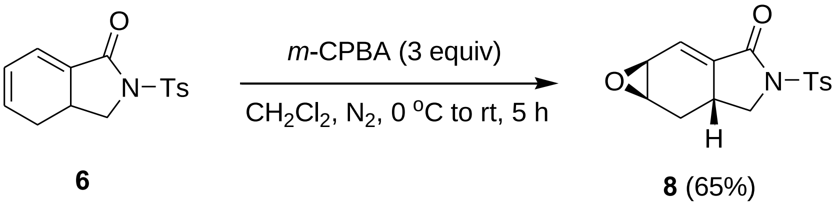
Scheme 2. Synthesis of compounds **6** and **7**

A plausible mechanism for the formation of compound **6** from compound **5** is shown in Scheme 3. Deprotonation of compound **5** by DBU at C-5 would give an intermediate **B**, which is protonated at C-7 to give another intermediate **C**. Further elimination of benzenesulfinic acid would yield the product **6**. Air oxidation of compound **6** would give the aromatic compound **7**.



Scheme 3. Plausible mechanism for the formation of compound **6** from compound **5**

Reaction of compound **6** with *m*-CPBA (3 equiv) at room temperature provided the epoxide **8** (Scheme 4). The stereochemistry of compound **8** was established by X-ray crystallography (Figure 2),[9] which indicates that the epoxidation proceeds from the same side as the ring junction hydrogen, probably due to steric effect.



Scheme 4. Oxidation of compound **6** to epoxide **8**

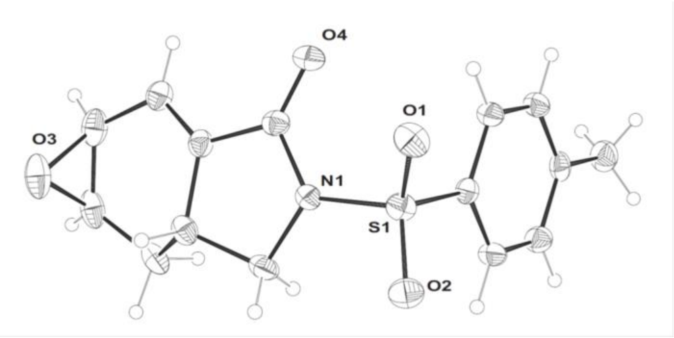
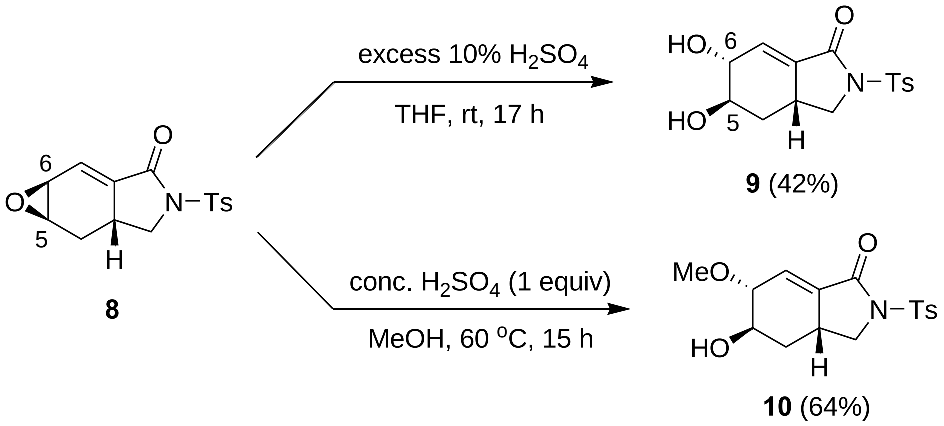


Figure 2. X-Ray crystal structure of compound **8**

Reaction of compound **8** with 10% aqueous sulfuric acid in THF at room temperature gave the *trans*-diol **9** (Scheme 5). The stereochemistry of compound **9** was established by X-ray crystallography (Figure 3),[9] which shows that the hydroxyl group at C-5 is *cis* to the ring junction hydrogen. We propose that compound **8** was first protonated at the epoxide group, and then water attacks from the back side of the C-6 because of greater positive charge at this carbon. The reaction of compound **8** with methanol at 60 °C in the presence of one equivalent of concentrated sulfuric acid gave the methoxy alcohol **10**. The structure of compound **10** was elucidated from comparison of its spectral data with those of compound **9**.



Scheme 5. Nucleophilic substitution reactions of compound **8**

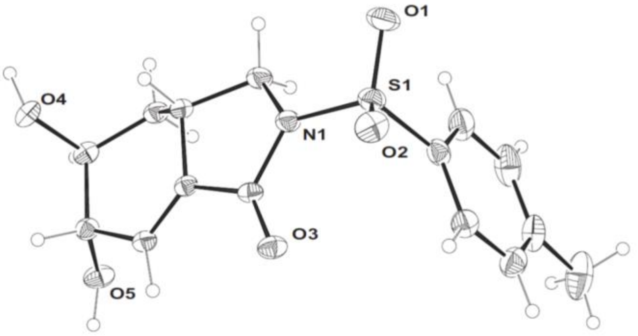
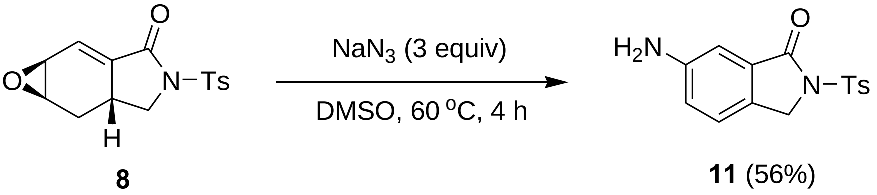


Figure 3. X-Ray crystal structure of compound **9**

Reaction of compound **8** with sodium azide in DMSO at 60 ºC gave the unexpected 6-aminoisoindolinone **11** in 56% yield (Scheme 6), the structure of which was established by X-ray crystallography (Figure 4).[9] A tentative mechanism for its formation is proposed in Scheme 7. Ring opening of the epoxide of compound **8** at C-6 followed by protonation would give an intermediate **D**. The azido group is then converted by heating in a polar solvent to give a nitrene intermediate **E**,[10] which is transformed to an amino intermediate **F**. Further dehydration and air oxidation would then give the amino product **11**. This reaction could also be carried out in DMF under a similar condition to give product **11** in 34% yield.



Scheme 6. Substitution reaction of compound **8** to form product **11**

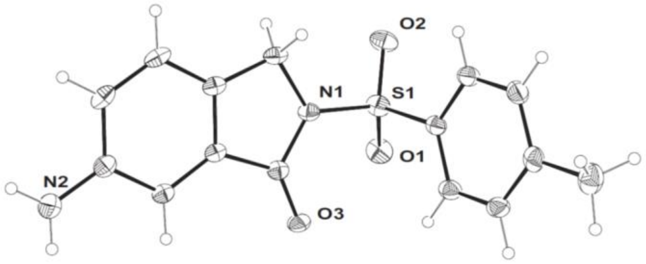
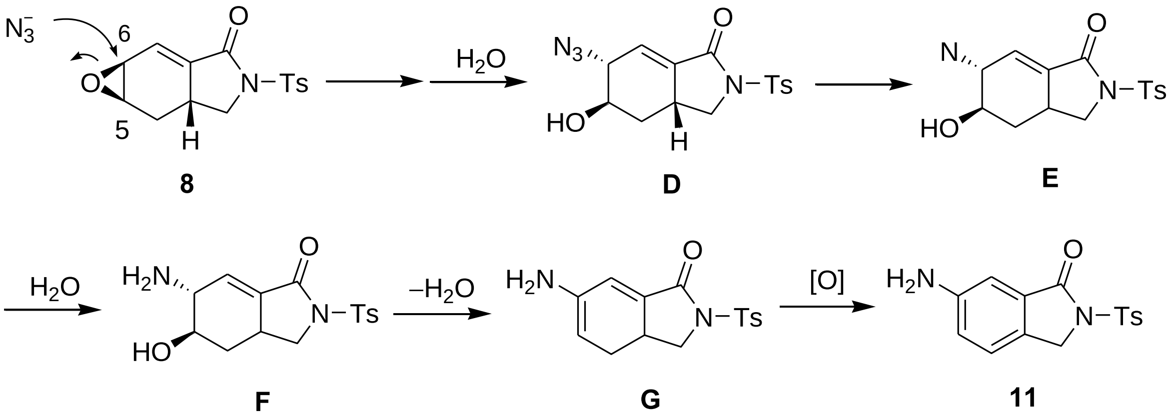
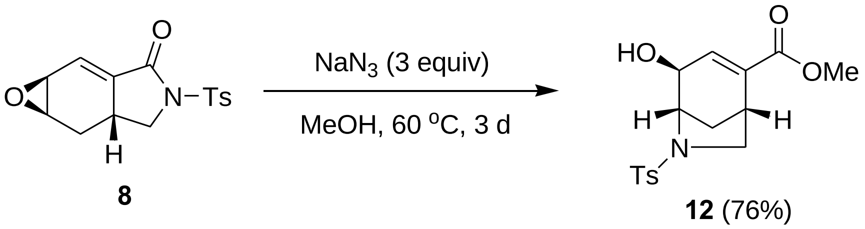


Figure 4. X-Ray crystal structure of compound **11**



Scheme 7. Mechanism for the formation of compound **11** from compound **8**

If the reaction of compound **8** with sodium azide was carried out in methanol at 60 °C, a totally different product **12** was obtained (Scheme 8), which has the interesting 6-azabicyclo[3.2.1]octane skeleton. The structure of compound **12** was established by X-ray crystallography (Figure 5).[9]



Scheme 8. Reaction of compound **8** with NaN$_3$ to form product **12**

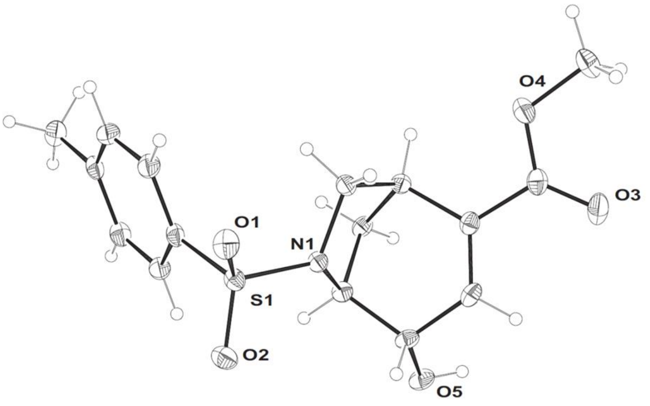
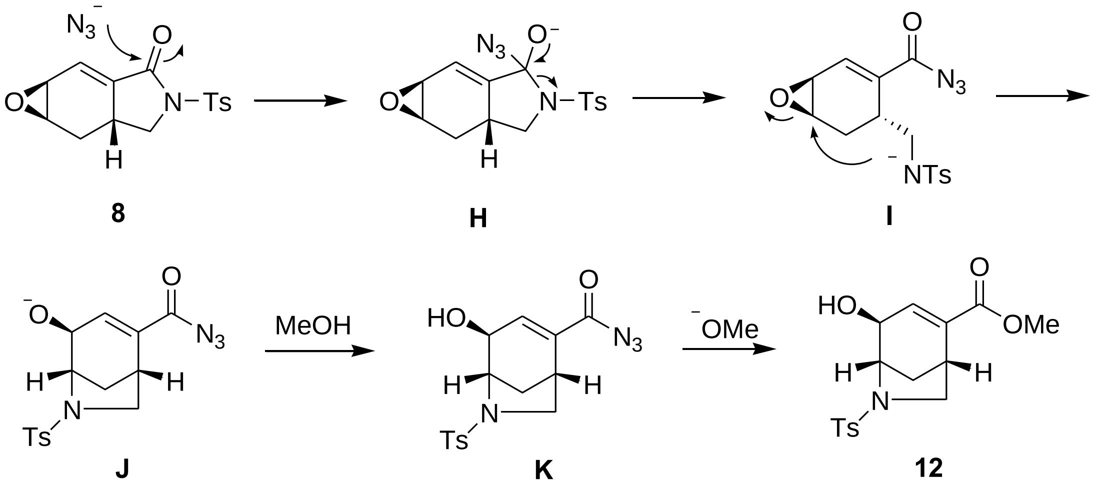


Figure 5. X-Ray crystal structure of compound **12**

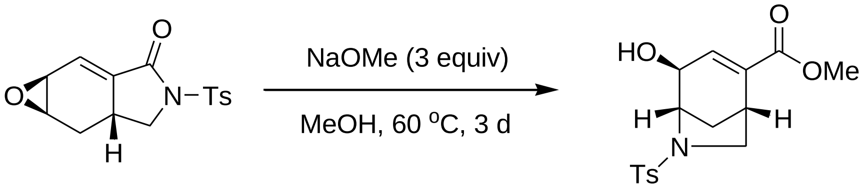
A plausible mechanism for the formation of compound **12** from compound **8** is shown in Scheme 9. Attack of the azide anion at the carbonyl group of compound **8** would give an acyl azide **I**, which could undergo an intramolecular substitution reaction with the epoxide group to afford an intermediate **J**.



Scheme 9. Mechanism for the formation of compound **12** from compound **8** and NaN$_3$

Protonation would then give an alcohol intermediate **K**. Further substitution of the azido group by the methoxide ion would then give the product **12**. It is interesting to note that the azide anion exhibits two different reaction pathways with compound **8** in DMSO and MeOH (Scheme 7 and Scheme 9, respectively).

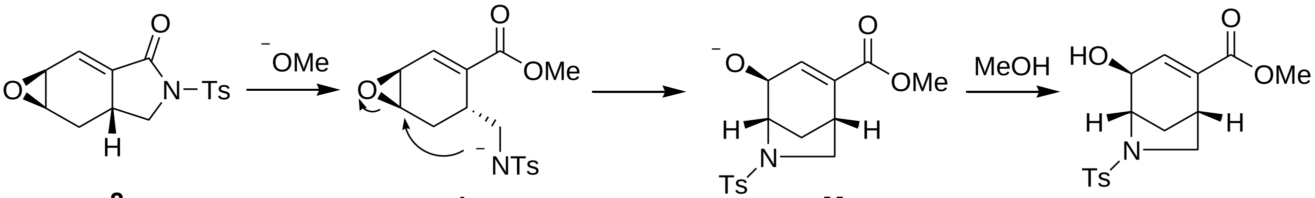
We found that the reaction of compound **8** with NaOMe in methanol also afforded product **12**, albeit in much lower yield (Scheme 10).



8 **12** (38%)

Scheme 10. Reaction of compound **8** with NaOMe to form product **12**

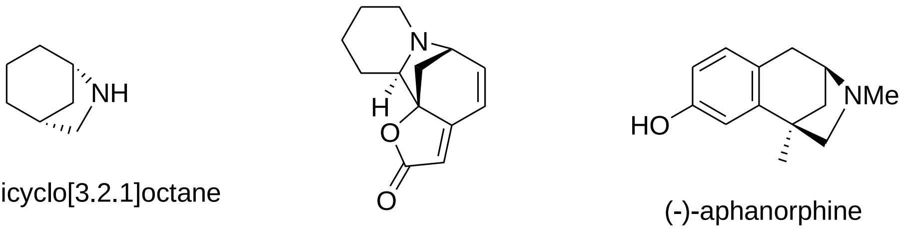
A different mechanism is proposed (Scheme 11). The reaction of compound **8** with NaOMe would give the ring opening intermediate **L**, which could undergo an intramolecular substitution reaction with the epoxide group to afford the intermediate **M**. Protonation would then give the product **12**.



8 **L** **M** **12**

Scheme 11. Mechanism for the formation of compound **12** from compound **8** and NaOMe

The 6-azabicyclo[3.2.1]octane skeleton is found in a wide variety of naturally occurring and pharmacologically active molecules. Some examples include natural products such as the GABA$_A$ receptor antagonist securinine[11] and analgesic aphanorphine.[12]



6-azabicyclo[3.2.1]octane

securinine

(-)-aphanorphine

Figure 6. 6-Azabicyclo[3.2.1]octane structures

CONCLUSION

Bicyclic sulfone **5** was prepared directly from dienyl amide **3** by tandem oxidation and intramolecular Diels−Alder reaction. Treatment of compound **5** with DBU gave the dihydro-isoindolinone **6**, which was oxidized by *m*-CPBA to give the epoxy-isoindolinone **8**. Nucleophilic substitution reactions of compound **8** gave products **9-12**. Compound **12** has a very interesting 6-azabicyclo[3.2.1]octane skeleton.

EXPERIMENTAL

Melting points were determined with a SMP3 melting apparatus. Infrared spectra (ATR) were recorded with a Perkin Elmer 100 series FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were mostly recorded on a Bruker Avance 300 spectrometer operating at 300 and at 75 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. Flash column chromatographic purifications were performed using Merck 60 H silica gel.

cis-7-(Phenylsulfonyl)-2-tosyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-1-one (5)

To a solution of compound **3** (115.8 mg, 0.29 mmol) and sodium carbonate (153.7 mg, 1.45 mmol) in CH_2Cl_2 (11 cm^3) at 0 ^{o}C was added in portions of *m*-CPBA (70% in H_2O, 357.5 mg, 1.45 mmol). The mixture was stirred at room temperature for 6 h, and then sequentially washed with saturated aq. sodium thiosulfate solution (5 cm^3 x 2) and saturated aq. sodium bicarbonate solution (5 cm^3 x 2). The organic layer was dried ($MgSO_4$), evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 1) as eluent to give **5** (90.4 mg, 72%) as a white solid; mp 185.6−186.1 ^{o}C; ν_{max} (film/cm^{-1}) 3060, 2951, 2911, 2857, 1742, 1359, 1306, 1169, 1142, 1088 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.94 (2H, d, *J* = 7.2 Hz), 7.82 (2H, d, *J* = 8.4 Hz), 7.64−7.58 (1H, m), 7.54−7.48 (2H, m), 7.31 (2H, d, *J* = 8.1 Hz), 7.18−7.12 (1H, m), 3.93 (1H, dd, *J* = 5.1, 9.9 Hz), 3.82 (1H, d, *J* = 6.6 Hz), 3.66 (1H, d, *J* = 9.9 Hz), 2.45 (3H, s), 2.39−2.35 (3H, m), 1.80−1.75 (1H, m), 1.33−1.25 (1H, m); δ_C (75 MHz; $CDCl_3$) 168.8, 145.2, 143.3, 14.2, 137.2, 134.7, 133.2, 129.7, 128.7, 128.6, 127.9, 50.7, 43.1, 31.0, 24.7, 22.3, 21,6; HRMS (EI) Found: M$^+$, 431.0865. $C_{21}H_{21}NO_5S_2$ requires 431.0861 ; EI-HRMS *m/z* 431.0865.

2-Tosyl-2,3,3a,4-tetrahydro-1*H*-isoindol-1-one (6)

To a solution of compound **5** (151.0 mg, 0.35 mmol) in CH_2Cl_2 (15 cm^3) under nitrogen at room temperature was added slowly DBU (160 mg, 1.05 mmol). After stirring at room temperature for 1.5 h, the reaction mixture was washed with saturated aq. ammonium chloride solution (10 cm^3 x 2). The aqueous solution was extracted with CH_2Cl_2 (10 cm^3 x 3). The combined organic solution was dried (MgSO4) and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 2) as eluent to give **6** (77.9 mg, 77%) as a white solid; mp 156.3－158.7 °C; ν_{max} (film/cm^{-1}) 2928, 1720, 1660, 1596, 1566, 1358, 1233, 1169, 1088, 1056, 704, 661; δ_H (300 MHz; $CDCl_3$) 7.99 (2H, d, *J* = 8.2 Hz), 7.34 (2H, d, *J* = 8.2 Hz), 6.79 (1H, d, *J* = 3.6 Hz), 6.23－6.13 (2H, m), 4.36 (1H, t, *J* = 9.3 Hz), 3.28 (1H, dd, *J* = 9.0, 8.4 Hz), 2.96－2.85 (1H, m), 2.62-2.51 (1H, m), 2.42 (3H, s), 2.03－1.90 (1H, m); δ_C (75 MHz; $CDCl_3$) 164.8, 145.1, 135, 132, 129.9, 129.5, 128.1, 127.9, 124.6, 51.9, 29.2, 27.4, 21.5. HRMS (FAB) Found: M^+, 289.0769. $C_{15}H_{15}NO_3S$ requires 289.0773. The ^1H NMR of compound **6** showed the presence of about 3% of compound **7** which cannot be separated by recrystallization or chromatography.

2-Tosylisoindolin-1-one (7)

A mixture of compound **6** (12.7 mg, 0.044 mmol) and DDQ (49.94 mg, 0.22 mmol) in toluene (5 cm^3) and MeCN (5 cm^3) was refluxed under nitrogen for 12 h. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 2) as eluent to give **7** (6.9 mg, 55%) as a white solid.[8]

(3a*R**,5*R**,6*R**)-2-Tosyl-2,3,3a,4,5,6-hexahydro-1*H*-5,6-epoxy-isoindol-1-one (8)

To a solution of compound **6** (26.2 mg, 0.091 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C was added in portions of *m*-CPBA (70% in H_2O, 67 mg, 0.273 mmol). The mixture was stirred at room temperature for 5 h, diluted with CH_2Cl_2 (30 cm^3), and then sequentially washed with saturated aq. sodium thiosulfate solution (5 cm^3 x 2) and saturated aq. sodium bicarbonate solution (5 cm^3 x 2). The organic layer was dried ($MgSO_4$), evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 1) as eluent to give **8** (17.9 mg, 65%) as a white solid; mp 173.5－175.0 °C; ν_{max} (film/cm^{-1}) 3046, 2992, 2953, 2869, 1717, 1667, 1569, 1481, 1358, 1335, 1227, 1212, 1172, 1088, 1040, 949, 922, 822, 809, 772, 736, 663; δ_H (300 MHz; $CDCl_3$) 7.93 (2H, d, *J* = 8.2 Hz), 7.34 (2H, d, *J* = 8.2 Hz), 6.89 (1H, t, *J* = 3.6 Hz), 4.24 (1H, t, *J* = 9.4 Hz), 3.61－3.49 (1H, m), 3.48 (1H, t, *J* = 3.9 Hz), 3.37 (1H, dd, *J* = 9.4, 8.2 Hz), 2.95－2.88 (1H, m), 2.65 (1H, ddd, *J* = 2.4, 8.2, 14.1 Hz), 2.43 (3 H, s), 1.35 (1H, dd, *J* = 11.7, 14.1 Hz); δ_C (75 MHz; $CDCl_3$) 164.5, 145.3, 136.2, 134.9, 129.7, 129.5, 128.1, 53.9, 50.6, 46.2, 29.6, 25.7, 21.6. HRMS (FAB) Found: M^+, 305.0727. $C_{15}H_{15}NO_4S$ requires 305.0722.

(3a*R**,5*R**,6*R**)-5,6-Dihydroxy-2-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one (9)

A solution of compound **8** (26 mg, 0.085 mmol) and 10% H_2SO_4 (10 cm^3) in THF (5 cm^3) was stirred at room temperature under nitrogen for 17 h. The solvent was evaporated under vacuum, and 5% NaOH (5 cm^3) and saturated aq. sodium bicarbonate solution (5 cm^3) were added. The mixture was extracted with EtOAc (10 cm^3 x 3), dried ($MgSO_4$) and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc as eluent to give **9** (11.5 mg, 42%) as a white solid; mp 174.6—176.8 ^oC; ν_{max} (film/cm^{-1}) 3353, 2922, 2852, 1725, 1678, 1457, 1361, 1166, 1089, 1022, 813, 730, 662; δ_H (300 MHz; $CDCl_3$) 7.8 (2H, d, *J* = 8.2 Hz), 7.31 (2H, d, *J* = 8.2 Hz), 6.38 (1H, t, *J* = 2.6 Hz), 4.12 (1H, t, *J* = 8.9 Hz), 3.89—3.85 (2H, m), 3.22—3.18 (1H, m), 3.16 (1H, d, *J* = 9.1 Hz), 2.99—2.95 (1H, m), 2.33 (3H, s), 1.98—1.91 (1H, m), 1.32 (1H, ddd, *J* = 1.9, 11.2, 13.0 Hz); δ_C (75 MHz; $CDCl_3$) 167.6, 147.0, 137.2, 136.4, 132.7, 130.9, 129.2, 70.6, 68.6, 52.6, 30.4, 29.1, 21.7. HRMS (FAB) Found: M$^+$, 323.0827. $C_{15}H_{17}NO_5S$ requires 323.0827.

(3a*R,5*R**,6*R**)-5-Hydroxy-6-methoxy-2-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one (10)**

A solution of compound **8** (11.1 mg, 0.036 mmol) and concentrated H_2SO_4 (2 uL, 0.036 mmol) in MeOH (5 cm^3) was stirred at room temperature under nitrogen for 15 h. To the reaction mixture was added 5% NaOH aqueous solution (5 cm^3), and was then extracted with $CHCl_3$ (5 cm^3 x 3). The organic solution was extracted with EtOAc (10 cm^3 x 3), dried ($MgSO_4$) and evaporated under vacuum to give **10** (6.8 mg, 55%) as a white solid; mp 149.6—152.4 ^oC; ν_{max} (film/cm^{-1}) 3475, 2922, 2849, 1727, 1596, 1358, 1186, 1089, 814, 736, 663; δ_H (300 MHz; $CDCl_3$) 7.91 (2H, d, *J* = 8.4 Hz), 7.31 (2H, d, *J* = 8.4 Hz), 6.61 (1H, t, *J* = 3.2 Hz), 4.24 (1H, t, *J* = 8.9 Hz), 4.13 (1H, d, *J* = 2.2 Hz), 3.60 (1H, dd, *J* = 7.9, 3.4 Hz), 3.42 (3H, s), 3.23 (1H, t, *J* = 9.1 Hz), 3.13—3.07 (1H, m), 2.42 (3H, s), 2.08—2.02 (1H, m), 1.77 (2H, s), 1.41 (1H, ddd, *J* = 15.8, 10.7, 2.5 Hz); δ_C (75 MHz; *d*-MeOH) 167.4, 147.1, 138.1, 136.5, 131.1, 130.6, 129.3, 78.2, 67.4, 67.4, 58.4, 30.5, 29.9, 21.7. HRMS (FAB) Found: M$^+$, 337.0988. $C_{16}H_{19}NO_5S$ requires 337.0984

6-Amino-2-tosylisoindolin-1-one (11)

A mixture of compound **8** (20.1 mg, 0.067 mmol) and NaN_3 (12.9 mg, 0.198 mmol) in DMSO or DMF (2 cm^3) was heated under nitrogen at 60 ^oC for 4 h. The solvent was removed under vacuum, saturated aq. ammonium chloride solution (5 cm^3) was added, and the mixture was extracted with CH_2Cl_2 (10 cm^3 x 3). The combined organic solution was dried ($MgSO_4$), evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 1) as eluent to give **11** (12 mg, 56%) as a white solid; mp 248.6 ^oC (decomp.); ν_{max} (film/cm^{-1}) 3373, 2922, 1719, 1633, 1503, 1354, 1166, 1086, 814, 665; δ_H (300 MHz; $CDCl_3$) 8.01 (2H, d, *J* = 8.3 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 7.22 (1H, d, *J* = 8.2 Hz), 7.01 (1H, d, *J* = 2.1 Hz), 6.92 (1H, dd, *J* = 8.2, 2.2 Hz), 4.79 (2H, s), 3.88 (2H, br s), 2.41 (3H, s); δ_C (75 MHz; $CDCl_3$) 166.5, 147.3, 145.1, 135.6, 131.4, 130.9, 129.8, 128.2, 124.0, 121.5, 109.3, 49.6, 21.7.

HRMS (FAB) Found: M$^+$, 302.0730. $C_{15}H_{14}N_2O_3S$ requires 302.0725.

(1*R**,4*S**,5*S**)-Methyl 4-hydroxy-6-tosyl-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylate (12)

A mixture of compound **8** (20 mg, 0.066 mmol) and NaN_3 (12.9 mg, 0.198 mmol) in MeOH (10 cm^3) was heated in a sealed tube at 60 °C for 3 d. The solvent was removed under vacuum, 5% NaOH aqueous solution (5 cm^3) was added, and the mixture was extracted with $CHCl_3$ (10 cm^3 x 3). The combined organic solution was dried ($MgSO_4$), evaporated under vacuum to give **12** (16.7 mg, 76%) as a white solid; mp 155.6—157.3 °C; ν_{max} (film/cm^{-1}) 3481, 2953, 1714, 1438, 1337, 1252, 1085, 1042, 816, 685, 662; δ_H (300 MHz; $CDCl_3$) 7.70 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 6.72 (1H, dd, *J* = 4.0, 1.5 Hz), 4.38 (1H, t, *J* = 3.5 Hz), 4.07 (1H, t, *J* = 1.6 Hz), 3.74 (3H, s), 3.27 (1H, t, *J* = 4.0 Hz), 3.23 (1H, dd, *J* = 1.2, 8.8 Hz), 3.04 (1H, dd, *J* = 4.5, 8.8 Hz), 2.39 (3H, s), 1.72 (1H, d, *J* = 11.6 Hz), 1.21-1.19 (1H, m); δ_C (75 MHz; $CDCl_3$) 166.0, 143.7, 136.6, 136.3, 135.1, 129.8, 127.1, 68.5, 59.9, 53.1, 52.1, 34.6, 29.0, 21.5. HRMS (FAB) Found: M$^+$, 337.0984. $C_{16}H_{19}NO_5S$ requires 337.0984.

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9. Crystallographic data (excluding structure factors) for compounds **8**, **9**, **11**, and **12** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1042917−1042919 and 1043256, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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