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Ring opening of dihydro-2-pyridones and intramolecular Diels–Alder reactions

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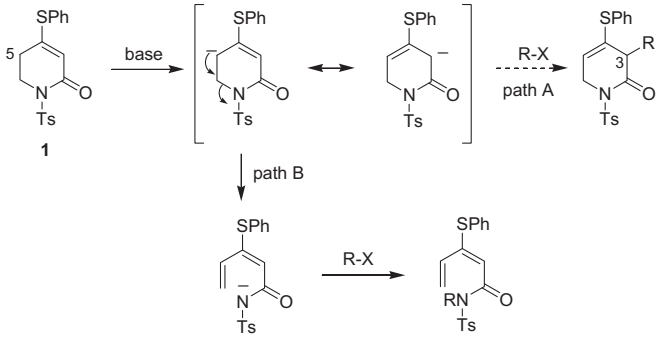
ABSTRACT

A new ring-opening reaction of 5,6-dihydro-2-pyridones was discovered. Compounds **1** and **7** were converted to the dienoic amides **2** and **8** by reaction with sodium hydride at room temperature. N-Allylation of compounds **2** and **8** followed by IMDA reaction provided the *cis*-fused hexahydro-1-indolones **5** and **10**, respectively. Treatment of compounds **5** and **10** with DBU in refluxing ethyl acetate gave the conjugated products **6** and **11**, which were further transformed to the amides **12**–**15**. The phenylthio group of compound **11** was substituted by a methyl group to give product **16**.

1. Introduction

Piperidine derivatives are widely present in many natural and synthetic compounds with various biological activities.[1] Many synthetic methods have been developed,[2] among them the aza-Diels–Alder reaction is one of the most versatile routes.[3] We have previously developed a new aza-Diels–Alder reaction of thio-substituted 3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) to synthesize sulfur-substituted piperidine derivatives,[4] and have reported some of their synthetic applications.[5]

In continuation with our previous studies, we intended to deprotonate compound **1** at C-5 to generate a carbanion, which could then react with an electrophile at C-3 (Scheme 1, path A). However, the carbanion underwent an unexpected ring-opening reaction (path B) and then reacted with the electrophile at the nitrogen atom. To the best of knowledge, this ring-opening process has never been reported for the 5,6-dihydro-2-pyridones. We now describe the use of this method in combination with the intramolecular Diels–Alder reaction (IMDA)[6] to construct the hexahydro-1-isoindolones.[7] Muironolide A, isolated from the *Phorbas* sp. of marine sponge, has an uncommon isoindolone polyketide macrolide,[8] and the isoindolone core has very recently been constructed by IMDA.[9] Isoindolones have also been reported as important intermediates for the synthesis of natural products jamtine[10] and kainic acids.[11]



Scheme 1.

2. Results and discussion

Treatment of compound **1**[4] with NaH (3 equiv) in CH_2Cl_2 at room temperature followed by workup with saturated ammonium chloride provided the ring-opening product **2** in good yield (Table 1, entry 1). However, the reaction was quite slow, requiring 3 days to complete, probably due to the low solubility of NaH in CH_2Cl_2. So we carried out the reaction in refluxing CH_2Cl_2 (entry 2), and the reaction was complete in one day giving a similar yield of product **2**. The reaction of compound **1** with NaH in THF at reflux (entry 3) or at room temperature (entry 4) only gave unidentified mixture of products. The reaction in CH_2Cl_2 proceeded much faster if 20 equiv of NaH was used (entry 5). Furthermore, the reaction was even faster when carried out with NaH (3 equiv) in *N*,*N*-dimethylformamide (DMF) at room temperature to give very good yield

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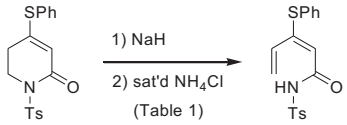
Table 1
Ring-opening of compound **1** to give product **2**



1 **2**

Entry	NaH (equiv)	Reaction conditions	Yield (%)
1	3	CH_2Cl_2, rt, 3 days	70
2	3	CH_2Cl_2, reflux, 1 days	67
3	3	THF, reflux, 3 days	ND[a]
4	3	THF, rt, 3 days	ND[a]
5	20	CH_2Cl_2, rt, 3 h	70
6	3	DMF, rt, 2 h	85
7	3	CH_2Cl_2/DMF (4:1), rt, 2 h	87

[a] An unidentified mixture of products was obtained.

of product **2** (entry 6). Since DMF was rather difficult to remove, we found that a mixture of CH_2Cl_2 and DMF (4:1) was the best solvent system for the reaction, and an excellent yield of product **2** was obtained (entry 7). The structure of compound **2** was proven by X-ray crystallography (Fig. 1).[12] Some 2,4-hexadienoic amides were found to exhibit potent antimicrobial activities.[13]

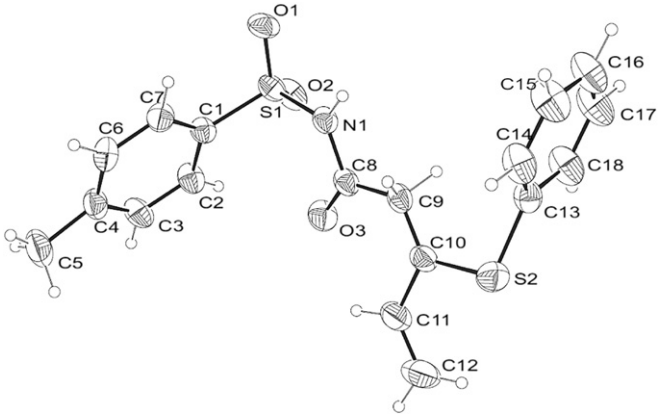
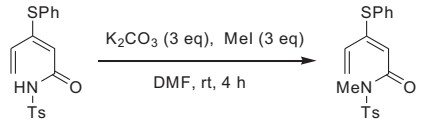


Fig. 1. X-ray crystal structure of compound **2**.

We then investigated the reaction conditions for N-methylation of compound **2**. Treatment of a mixture of compound **2** and methyl iodide (3 equiv) in CH_2Cl_2 with NaH (3 equiv) at room temperature for 18 h only gave the recovered starting material **2**. We thought this might be due to the low solubility of NaH in CH_2Cl_2, so we used a mixture of CH_2Cl_2 and DMF (4:1) as the solvent, but an unidentified mixture of products was obtained. Since the N–H of compound **2** is rather acidic, we then used K_2CO_3 as the base, and the reaction proceed well in DMF at room temperature to give a fair yield of product **3**.



2 **3** (63%)

Compound **2** was similarly *N*-allylated to give product **4**, which underwent the intramolecular Diels–Alder reaction by refluxing in toluene in the presence of 1.2 equiv of $NaHCO_3$ to afford the bicyclic product **5** in excellent yield. It should be noted that without the $NaHCO_3$ the yield was lowered, probably because the diene moiety in compound **4** was quite sensitive to acid. The structure of compound **5** was proven by X-ray crystallography (Fig. 2),[12] which

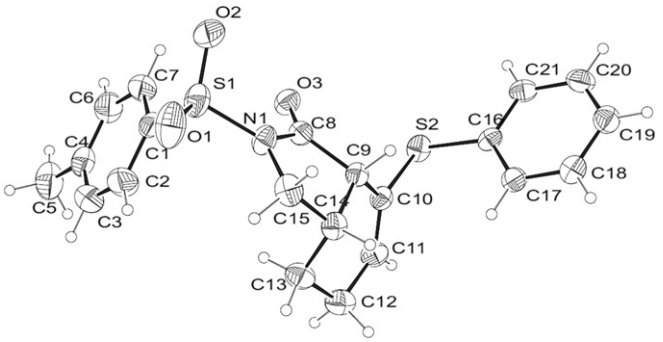
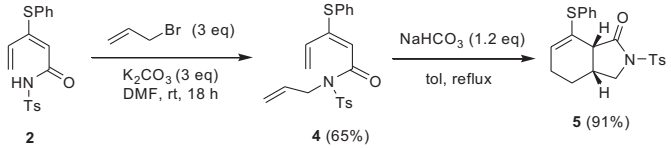


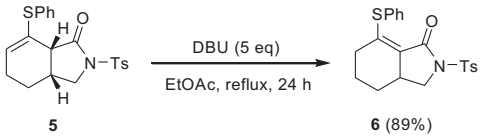
Fig. 2. X-ray crystal structure of compound **5**.

shows the cis ring fusion. It was reported in the literature that the IMDA of *N*-allyl 2(*E*),4-hexadienoic amides in toluene usually gave a mixture of *cis*- and *trans*-fused products.[14] However, the specific formation of the *E*-configuration around the α,β-double bond of compound **4** (cis configuration based on the carbon skeleton) strongly favors the *exo* transition state,[6] which led only to the *cis* product **5**. This is a very important improvement over the literature methods.[9,14]



2 **4** (65%) **5** (91%)

We then investigated the reaction conditions for converting compound **5** to the conjugated product **6**. Using Et_3N as the base and ethyl acetate as the solvent, the reaction did not proceed either at room temperature or at reflux. A very good yield of the conjugated product **6** was obtained when compound **5** was refluxed with 5 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethyl acetate for 24 h. The structure of compound **6** was proven by X-ray crystallography (Fig. 3).[12]



5 **6** (89%)

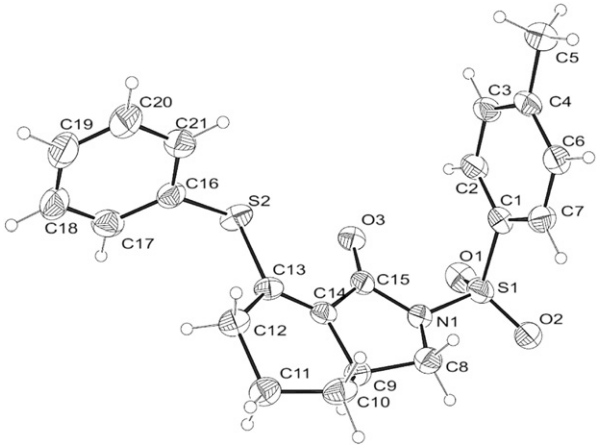
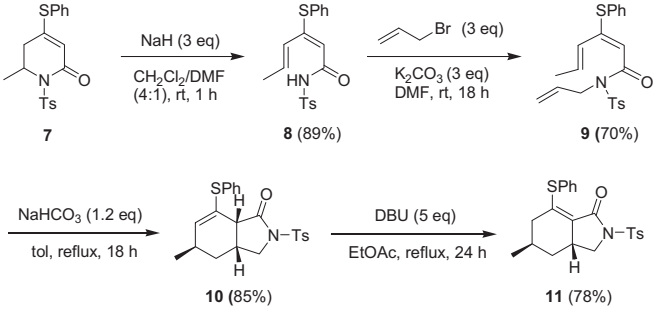


Fig. 3. X-ray crystal structure of compound **6**.

We have also carried out similar transformations of the C-6 methylated dihydropyridone **7** to the bicyclic compound **11** (Scheme 2). Treatment of compound **7** with NaH (3 equiv) in CH_2Cl_2/DMF (4:1) at room temperature for 1 h gave the ring-opening product **8**, the ^{1}H NMR of which showed that the C=C bond at the γ,δ-position has the trans configuration. Reaction of compound **8** with allyl bromide and K_2CO_3 afforded the N-allylation product **9**. Intramolecular Diels–Alder reaction of compound **9** proceeded well in refluxing toluene in the presence of K_2CO_3 to give the bicyclic product **10** in good yield. The structure of compound **10** was proven by X-ray crystallography (Fig. 4).[12] Apparently, the IMDA reaction proceeded through the *exo* transition state and with retention of configuration of the C=C bond of the diene moiety of compound **9**. Compound **10** was further converted to its conjugated isomer **11** by treatment with DBU in refluxing ethyl acetate. The structure of compound **11** was also confirmed by X-ray crystallography (Fig. 5).[12]



Scheme 2.

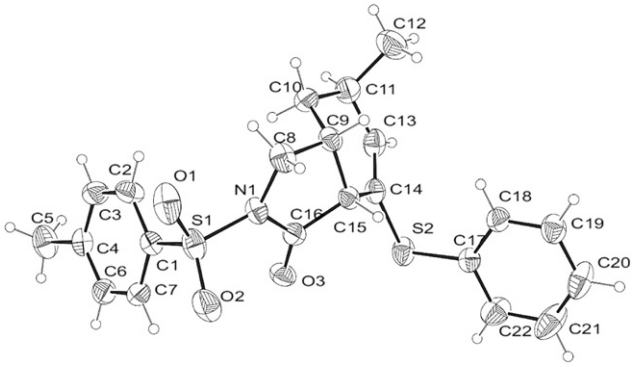


Fig. 4. X-ray crystal structure of compound **10**.

The tosyl group of compounds **6** and **11** were cleaved by Bu_3SnH/AIBN[15] to give the secondary amides **12** and **13**, respectively. Deprotonation of amides **12** and **13** with NaH in THF followed by the reaction with an electrophile gave the tertiary amides **14** and **15**, respectively (Table 2).

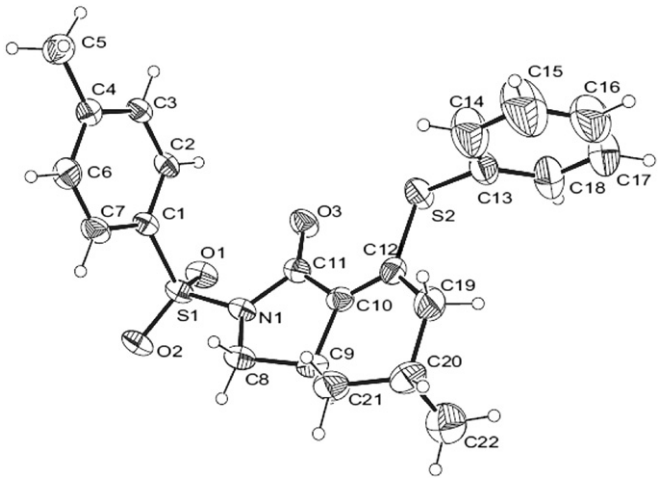
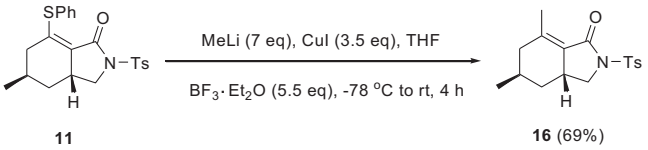


Fig. 5. X-ray crystal structure of compound **11**.

Table 2
Synthesis of compounds **14** and **15** from compounds **12** and **13**

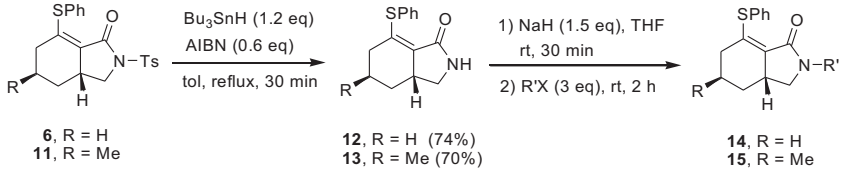
Entry	R′–X	R′	Product (% yield)	
1	MeI	CH_3	**14a** (82)	**15a** (92)
2	EtI	CH_3CH_2	**14b** (60)	**15b** (81)
3	Allyl–Br	CH_2=$CHCH_2$	**14c** (66)	**15c** (68)
4	BnBr	$PhCH_2$	**14d** (54)	**15d** (64)
5	BzCl	PhCO	**14e** (75)	**15e** (79)

Compound **11** was effectively converted to the methyl-substituted product **16** by treatment with Me_2CuLi in the presence of $BF_3 \cdot Et_2O$ in THF.[5f]



3. Conclusions

We have discovered a new ring-opening reaction of 5,6-dihydro-2-pyridones **1** and **7** to the corresponding dienoic amides **2** and **8** by reaction with sodium hydride in a mixture of CH_2Cl_2 and DMF at room temperature. N-Allylation of compounds **2** and **8** followed by IMDA reaction provided the *cis*-fused hexahydro-1-indolones **5** and **10**, respectively. Compounds **5** and **10** upon treatment with DBU in refluxing ethyl acetate were further converted to the conjugated



products **6** and **11**, which could be transformed to the amides **12**–**15**. The phenylthio group of compound **11** was also successfully substituted by a methyl group to give product **16**.

4. Experimental section

4.1. General

Melting points were determined with a SMP3 melting apparatus. Infrared spectra were recorded with a Perkin–Elmer 1600 or 100 series FTIR spectrometer using the ATR (attenuated total reflectance) mode. ^{1}H and ^{13}C NMR spectra were 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. X-ray crystal structures were obtained with an Enraf–Nonius FR-590 diffractometer (CAD4, Kappa CCD). Column chromatographic purifications were performed using Merck silica gel 60 (40–60 μm).

*4.1.1. (E)-3-(Phenylthio)-N-tosylpenta-2,4-dienamide (**2**).* To a solution of compound **1** (500 mg, 1.39 mmol) in CH_2Cl_2 (8 mL) and DMF (2 mL) at room temperature under nitrogen was added NaH (50% in oil dispersion, 100 mg, 4.17 mmol). The mixture was stirred for 2 h, and was then poured into saturated ammonium chloride (50 mL) and CH_2Cl_2 (20 mL). The aqueous solution was extracted with CH_2Cl_2 (3×20 mL), and the organic layers were combined and dried ($MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography using ethyl acetate/hexane (1:3) as eluent to give crude product **2**, which was further recrystallized from CH_2Cl_2/hexane to give purified product **2** (0.435 g, 87%) as a white solid: mp 134.3–135.6 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (1H, br s), 7.81 (2H, d, J=8.4 Hz), 7.64 (1H, dd, J=17.4, 10.8 Hz), 7.46 (2H, d, J=8.4 Hz), 7.33–7.28 (5H, m), 6.02 (1H, d, J=17.4 Hz), 5.52 (1H, d, J=10.8 Hz), 5.00 (1H, s), 2.45 (3H, s); ^{13}C NMR ($CDCl_3$) δ 161.0, 159.9, 144.8, 135.6, 132.0, 130.1, 130.0, 129.5, 128.4, 128.2, 122.2, 110.8, 21.6; IR (ATR, film) v: 3229, 3060, 2923, 2868, 1685, 1555, 1440, 1345, 1147, 1084 cm^{-1}; FABMS (rel intensity) m/z 360 (M+H, 100), 341 (13), 209 (17), 189 (26), 184 (35); Exact mass calcd for $C_{18}H_{18}O_3NS_2$ m/z 360.0728; FAB–HRMS m/z 360.0725.

*4.1.2. (E)-N-Methyl-3-(phenylthio)-N-tosylpenta-2,4-dienamide (**3**).* To a mixture of compound **2** (100 mg, 0.28 mmol) and anhydrous K_2CO_3 (90 mg, 0.84 mmol) in DMF (2 mL) at room temperature under nitrogen was added methyl iodide (0.053 mL, 0.84 mmol). After stirring for 4 h, the reaction mixture was poured into ethyl acetate (50 mL) and water (30 mL). The organic solution was washed with water (3×30 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography using ethyl acetate/hexane (1:6) as eluent to give compound **3** (65.3 mg, 63%) as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 7.59–7.56 (2H, m), 7.51–7.49 (3H, m), 7.42 (2H, d, J=8.4 Hz), 7.25–7.21 (3H, m), 6.00 (1H, d, J=17.4 Hz), 5.99 (1H, s), 5.48 (1H, d, J=11.1 Hz), 3.15 (3H, s), 2.42 (3H, s); ^{13}C NMR ($CDCl_3$) δ 164.3, 156.2, 144.4, 136.2, 135.8, 132.5, 129.8 (×2), 129.7, 129.2, 127.0, 121.4, 114.1, 32.7, 21.5; IR (ATR, film) v: 3061, 2989, 2952, 2918, 1667, 1551, 1359, 1210, 1163, 1088 cm^{-1}; EI-MS (rel intensity) m/z 373 (M^+, 8), 252 (14), 218 (22), 202 (14), 189 (100), 128 (18), 109 (15), 91 (31); Exact mass calcd for $C_{19}H_{19}NO_3S_2$ m/z 373.0806; HRMS m/z 373.0807.

*4.1.3. (E)-N-Allyl-3-(phenylthio)-N-tosylpenta-2,4-dienamide (**4**).* To a mixture of compound **2** (500 mg, 1.39 mmol) and anhydrous K_2CO_3 (450 mg, 4.17 mmol) in DMF (10 mL) at room temperature under nitrogen was added allyl bromide (0.40 mL, 4.17 mmol). After stirring for 18 h, the reaction mixture was poured into ethyl acetate (50 mL) and water (30 mL). The organic solution was washed with water (3×30 mL) and dried ($MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography using ethyl acetate/hexane (1:4) as eluent to give crude product **4**, which was further recrystallized from CH_2Cl_2/hexane to give purified product **4** (360 mg, 65%) as a white solid: mp 93.8–94.4 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (2H, d, J=8.4 Hz), 7.54–7.44 (5H, m), 7.31 (1H, dd, J=17.4, 10.8 Hz), 7.23 (2H, d, J=8.4 Hz), 5.98 (1H, d, J=17.4 Hz), 5.74 (1H, s), 5.72–5.61 (1H, m), 5.47 (1H, d, J=10.8 Hz), 5.06–4.99 (2H, m), 4.27 (2H, d, J=5.4 Hz), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$) δ 163.9, 157.2, 144.3, 136.7, 135.7, 132.7, 132.5, 129.9, 129.4 (×2), 129.1, 127.8, 121.5, 117.8, 113.2, 48.5, 21.5; IR (ATR, film) v: 3058, 3022, 2925, 2851, 1738, 1669, 1356, 1169, 1089 cm^{-1}; FABMS (rel intensity) m/z 400 (M+H, 13), 244 (13), 190 (14), 189 (100), 155 (17), 128 (11), 91 (52), 81 (37), 69 (59); Exact mass calcd for $C_{21}H_{22}NO_3S_2$ m/z 400.1041; FAB–HRMS m/z 400.1039.

*4.1.4. cis-7-(Phenylthio)-2-tosyl-2,3,3a,4,5,7a-hexahydro-1H-isoindol-1-one (**5**).* A mixture of compound **4** (100 mg, 0.25 mmol) and $NaHCO_3$ (25 mg, 0.3 mmol) in toluene (10 mL) was heated under nitrogen at reflux for 18 h. The solvent was then evaporated under vacuum, and the residue was purified by column chromatography using ethyl acetate/hexane (1:4) as eluent to give crude product **5**, which was further recrystallized from CH_2Cl_2/hexane to give purified product **5** (91 mg, 91%) as a white solid: mp 130.4–131.6 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (2H, d, J=8.1 Hz), 7.38–7.20 (7H, m), 6.09 (1H, t, J=3.6 Hz), 3.87 (1H, dd, J=10.2, 6.0 Hz), 3.65 (1H, d, J=10.2 Hz), 3.09 (1H, d, J=6.6 Hz), 2.55–2.40 (4H, m), 2.21–2.11 (2H, m), 1.81–1.60 (1H, m), 1.40–1.21 (1H, m); ^{13}C NMR ($CDCl_3$) δ 170.5, 145.0, 135.0, 134.1, 133.9, 131.2, 129.6, 129.0, 128.1, 127.1, 126.9, 50.4, 46.2, 32.1, 24.8, 23.2, 21.6; IR (ATR, film) v: 3061, 2956, 2923, 2871, 2855, 1733, 1597, 1334, 1164, 1091 cm^{-1}; FABMS (rel intensity) m/z 400 (M+H, 12), 252 (12), 167 (20), 154 (32), 136 (58), 89 (76), 77 (100); Exact mass calcd for $C_{21}H_{22}NO_3S_2$ m/z 400.1041; FAB–HRMS m/z 400.1046.

*4.1.5. 7-(Phenylthio)-2-tosyl-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**6**).* A solution of compound **5** (0.5 g, 1.25 mmol) and DBU (0.93 mL, 6.25 mmol) in ethyl acetate (30 mL) was stirred at room temperature for 24 h, and was then poured into 10% H_2SO_4 (20 mL). The aqueous solution was extracted with ethyl acetate (3×25 mL), and the combined organic layer was dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by column chromatography using ethyl acetate/hexane (1:1) as eluent to give crude product **6**, which was further recrystallized from CH_2Cl_2/hexane to give purified product **6** (445 mg, 89%) as a white solid: mp 176.1–177.2 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (2H, d, J=8.1 Hz), 7.47 (2H, d, J=6.9 Hz), 7.40–7.26 (5H, m), 4.18 (1H, t, J=8.7 Hz), 3.27 (1H, t, J=9.5 Hz), 2.91–2.77 (1H, m), 2.43 (3H, s), 2.02–1.70 (4H, m), 1.59–1.35 (1H, m), 1.19–1.05 (1H, m); ^{13}C NMR ($CDCl_3$) δ 165.0, 149.2, 144.7, 136.2, 135.5, 129.5, 129.4, 129.1, 128.9, 128.2, 122.0, 51.4, 36.2, 30.0, 25.8, 22.4, 21.6; IR (ATR, film) v: 3055, 2956, 2925, 2868, 1709, 1610, 1356, 1169, 1084 cm^{-1}; FABMS (rel intensity) m/z 400 (M+H, 6), 252 (12), 167 (20), 154 (32), 136(58), 89 (76), 77 (100); Exact mass calcd for $C_{21}H_{22}NO_3S_2$ m/z 400.1041; FAB–HRMS m/z 400.1049.

*4.1.6. (2E,4E)-3-(Phenylthio)-N-tosylhexa-2,4-dienamide (**8**).* To a solution of compound **7** (500 mg, 1.34 mmol) in CH_2Cl_2 (8 mL) and DMF (2 mL) at room temperature under nitrogen was added NaH (50% in oil dispersion, 100 mg, 4.17 mmol). The mixture was stirred for 1 h, and was then poured into saturated ammonium chloride (50 mL) and CH_2Cl_2 (20 mL). The aqueous solution was extracted with CH_2Cl_2 (3×20 mL), and the organic layers were combined and dried ($MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography using ethyl acetate/hexane (1:3) as eluent to give crude product **8**,

which was further recrystallized from CH_2Cl_2/hexane to give purified product **8** (44.5 mg, 89%) as a white solid: mp 160.1–161.4 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, br s), 7.79 (2H, d, J=8.4 Hz), 7.46–7.34 (6H, m), 7.28 (2H, d, J=8.4 Hz), 6.62 (1H, dq, J=15.6, 6.9 Hz), 4.82 (1H, s), 2.41 (3H, s), 1.87 (3H, dd, J=6.9, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 161.1, 160.1, 144.7, 136.1, 135.9, 135.6, 130.0, 129.9, 129.4, 128.8, 128.2, 126.8, 108.7, 21.6, 18.8; IR (ATR, film) ν: 3261, 3061, 2924, 2855, 1717, 1688, 1553, 1441, 1339, 1161, 1085 cm^{-1}; FABMS (rel intensity) m/z 374 (M+H, 67), 341 (9), 203 (51), 172 (23), 155 (36), 147 (35), 137 (68); Exact mass calcd for $C_{19}H_{20}O_3NS_2$ m/z 374.0885; FAB–HRMS m/z 374.0890.

*4.1.7. (2E,4E)-N-Allyl-3-(phenylthio)-N-tosylhexa-2,4-dienamide (**9**).* To a mixture of compound **8** (500 mg, 1.34 mmol) and anhydrous K_2CO_3 (435 mg, 4.02 mmol) in DMF (10 mL) at room temperature under nitrogen was added allyl bromide (0.34 mL, 4.02 mmol). After stirring for 18 h, the reaction mixture was poured into ethyl acetate (50 mL) and water (30 mL). The organic solution was washed with water (3×30 mL), dried ($MgSO_4$) and concentrated to give compound **9** (387 mg, 70%) as a light yellow solid: mp 93.7–94.2 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (2H, d, J=8.4 Hz), 7.52–7.44 (5H, m), 7.23 (2H, d, J=8.4 Hz), 7.16 (1H, d, J=15.8 Hz), 6.59 (1H, dq, J=15.8, 6.8 Hz), 5.73–5.60 (1H, m), 5.64 (1H, s), 5.06–5.00 (2H, m), 4.27 (2H, d, J=5.4 Hz), 2.41 (3H, s), 1.88 (3H, dd, J=1.2, 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 164.1, 157.8, 144.3, 136.9, 135.8, 135.5, 132.9, 129.9 (×2), 129.6, 129.5, 127.9, 127.3, 117.8, 111.1, 48.5, 21.6, 18.9; IR (ATR, film) ν: 3057, 2959, 2918, 2874, 1741, 1668, 1548, 1354, 1167, 1088 cm^{-1}; FABMS (rel intensity) m/z 414 (M+H, 16), 258 (21), 203 (100), 191 (12), 155 (15), 147 (57), 91 (46); Exact mass calcd for $C_{22}H_{24}NO_3S_2$ m/z 414.1197; FAB–HRMS m/z 414.1209.

4.1.8. (3aR,5R*,7aS*)-5-Methyl-7-(phenylthio)-2-tosyl-2,3,3a,4,5,7a-hexahydro-1H-isoindol-1-one (**10**).* A mixture of compound **9** (100 mg, 0.24 mmol) and $NaHCO_3$ (25 mg, 0.29 mmol) in toluene (10 mL) was heated under nitrogen at reflux for 18 h. The solvent was then evaporated under vacuum, and the residue was purified by column chromatography using ethyl acetate/hexane (1:4) as eluent to give crude product **10**, which was further recrystallized from CH_2Cl_2/hexane to give purified product **10** (85 mg, 85%) as a white solid: mp 133.4–135.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (2H, d, J=8.4 Hz), 7.34–7.20 (7H, m), 6.05 (1H, dd, J=4.5, 1.5 Hz), 3.90 (1H, dd, J=10.0, 6.6 Hz), 3.61 (1H, dd, J=10.0, 2.4 Hz), 3.06 (1H, d, J=7.2 Hz), 2.66–2.56 (1H, m), 2.44 (3H, s), 2.40–2.32 (1H, m), 1.50–1.48 (2H, m), 1.07 (3H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 170.4, 145.0, 139.9, 135.0, 134.0, 131.0, 129.6, 129.0, 128.1, 127.0, 126.0, 50.0, 46.2, 30.1, 29.2, 28.9, 21.6, 20.4; IR (ATR, film) ν: 3060, 2959, 2925, 2868, 1740, 1357, 1171, 1091 cm^{-1}; FABMS (rel intensity) m/z 414 (M+H, 22), 258 (51), 203 (47), 155 (38), 115 (36), 91 (100), 77 (79), 39 (51), 28 (32); Exact mass calcd for $C_{22}H_{24}NO_3S_2$ m/z 414.1197; FAB–HRMS m/z 414.1204.

4.1.9. (3aR,5R*)-5-Methyl-7-(phenylthio)-2-tosyl-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**11**).* A solution of compound **10** (500 mg, 1.21 mmol) and DBU (0.90 mL, 6.05 mmol) in ethyl acetate (30 mL) was stirred at room temperature for 24 h, and was then poured into 10% H_2SO_4 (20 mL). The aqueous solution was extracted with ethyl acetate (3×25 mL), and the combined organic layer was dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by column chromatography using ethyl acetate/hexane (1:1) as eluent to give crude product **11**, which was further recrystallized from CH_2Cl_2/hexane to give purified product **11** (390 mg, 78%) as a white solid: mp 158.4–160.1 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (2H, d, J=8.1 Hz), 7.47 (2H, d, J=7.2 Hz), 7.42–7.33 (5H, m), 4.20 (1H, t, J=8.7 Hz), 3.20 (1H, t, J=9.0 Hz), 3.03–2.89 (1H, m), 2.44 (3H, s), 2.14–2.02 (2H, m), 1.79–1.63 (2H, m), 1.30 (1H, dt, J=3.6, 9.0 Hz), 0.89 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 165.1, 148.5, 144.8, 136.2, 135.7, 129.7, 129.5, 129.4, 129.1, 128.4, 121.5, 51.7, 36.9, 31.7, 26.9, 26.8, 21.7, 19.6; IR (ATR, film) ν: 3055, 2957, 2918, 2874, 1710, 1609, 1359, 1169, 1084 cm^{-1}; EI-MS (rel intensity) m/z 413 (M$^+$, 55), 349 (13), 348 (8), 258 (32), 240 (67), 216 (25), 201 (41), 160 (53), 109 (14), 91 (100), 84 (90), 65 (28); Exact mass calcd for $C_{22}H_{23}NO_3S_2$ m/z 413.1119; EI-HRMS m/z 413.1128.

*4.1.10. 7-(Phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**12**).* To a refluxing solution of compound **6** (500 mg, 1.25 mmol) and Bu_3SnH (0.40 mL, 1.50 mmol) in degassed toluene (50 mL) was added in three portions of AIBN (123 mg, 0.75 mmol) every 30 min. The reaction mixture was refluxed for another 30 min. The solvent was then evaporated under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:1) containing 5% Et_3N as eluent to give compound **12** (227 mg, 74%) as a white solid: 176.5–178.2 °C (decomp.); ^{1}H NMR ($CDCl_3$) δ 7.60–7.51 (2H, m), 7.38–7.30 (3H, m), 6.75–6.60 (1H, m), 3.55 (1H, t, J=8.3 Hz), 3.02 (1H, t, J=8.3 Hz), 2.98–2.85 (1H, m), 2.07–1.89 (3H, m), 1.88–1.73 (1H, m), 1.59–1.44 (1H, m), 1.27–1.14 (1H, m); ^{13}C NMR ($CDCl_3$) δ 171.3, 140.5, 136.1, 130.3, 128.8, 128.7, 124.9, 46.9, 39.2, 29.7, 26.3, 22.8; IR (ATR, film) ν: 3210, 3066, 2930, 2863, 1683, 1626, 1439, 1248 cm^{-1}; EI-MS (rel intensity) m/z 245 (M$^+$, 23), 203 (13), 149 (30), 136 (21), 129 (46), 125 (42), 91 (66), 77 (68), 71 (48), 57 (100); Exact mass calcd for $C_{14}H_{15}NOS$ m/z 245.0874; EI-HRMS m/z 245.0868.

4.1.11. (3aR,5R*)-5-Methyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**13**).* Using a procedure similar to that for the preparation of compound **12**, compound **11** (500 mg, 1.21 mmol) gave product **13** (220 mg, 70%) as a white solid: 178.1–179.5 °C (decomp.); ^{1}H NMR ($CDCl_3$) δ 7.56–7.52 (2H, m), 7.38–7.32 (3H, m), 6.22 (1H, s), 3.60–3.51 (1H, m), 3.13–2.98 (2H, m), 2.21–2.02 (2H, m), 1.80–1.71 (2H, m), 1.43–1.32 (1H, m), 0.94 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 171.3, 139.7, 135.9, 130.8, 128.9, 128.8, 124.5, 47.3, 36.7, 34.5, 32.2, 27.2, 19.6; IR (ATR, film) ν: 3276, 3066, 2955, 2922, 2870, 1683, 1626, 1340, 1239, 1069 cm^{-1}; EI-MS (rel intensity) m/z 259 (M$^+$, 100), 244 (4), 230 (23), 216 (29), 201 (40), 160 (49), 147 (10), 109 (11); Exact mass calcd for $C_{15}H_{17}NOS$ m/z 259.1031; EI-HRMS m/z 259.1024.

4.2. General procedure for the N-substitution of amides 12 and 13

To a solution of compound **12** (50 mg, 0.20 mmol) in THF (5 mL) at room temperature under nitrogen was added NaH (50% in oil dispersion, 30 mg, 0.61 mmol). After stirring for 30 min, the electrophile (0.61 mmol) was added in one portion. The reaction mixture was stirred for 2 h, and was then poured into saturated ammonium chloride (20 mL) and CH_2Cl_2 (20 mL). The aqueous solution was extracted with CH_2Cl_2 (3×20 mL), and the organic layers were combined and dried ($MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography using ethyl acetate/hexane as eluent to give products **14** and **15**.

*4.2.1. 2-Methyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**14a**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.57–7.53 (2H, m), 7.38–7.30 (3H, m), 3.47 (1H, t, J=8.6 Hz), 2.99 (1H, t, J=8.6 Hz), 2.92 (3H, s), 2.90–2.75 (1H, m), 2.07–1.76 (4H, m), 1.61–1.43 (1H, m), 1.24–1.10 (1H, m); ^{13}C NMR ($CDCl_3$) δ 168.3, 138.8, 136.1, 130.7, 128.6 (×2), 125.7, 53.8, 36.6, 29.8, 29.6, 26.3, 22.9; IR (ATR, film) ν: 3056, 2933, 2862, 1675, 1632, 1439, 1398, 1274 cm^{-1}; EI-MS (rel intensity) m/z 259 (M, 61), 218 (100), 187 (27), 160 (26), 147 (63), 146 (45), 118 (37), 109 (84), 91 (31), 86 (45), 84 (55); Exact mass calcd for $C_{15}H_{17}NOS$ m/z 259.1031; EI-HRMS m/z 259.1040.

*4.2.2. 2-Ethyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**14b**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.52–7.48 (2H, m),

7.36–7.25 (3H, m), 3.50–3.25 (3H, m), 2.96 (1H, t, J=8.6 Hz), 2.83–2.72 (1H, m), 2.02–1.75 (4H, m), 1.58–1.41 (1H, m), 1.22–1.10 (1H, m), 1.12 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.9, 138.8, 136.2, 130.9, 128.8 (×2), 126.3, 50.9, 37.2, 36.9, 29.7, 26.5, 23.1, 12.7; IR (ATR, film) ν: 3060, 2973, 2932, 2863, 1674, 1631, 1424, 1271, 1067 cm^{-1}; FABMS (rel intensity) m/z 274 (M+H, 100), 273 (30), 272 (16), 69 (13); Exact mass calcd for $C_{16}H_{20}NOS$ m/z 274.1265; FAB–HRMS m/z 274.1256.

*4.2.3. 2-Allyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**14c**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.56–7.53 (2H, m), 7.36–7.29 (3H, m), 5.78 (1H, tdd, J=6.3, 9.9, 16.2 Hz), 5.25–5.16 (2H, m), 4.11 (1H, tdd, J=1.2, 6.0, 15.0 Hz), 3.79 (1H, tdd, J=1.2, 5.7, 15.0 Hz), 3.46 (1H, t, J=8.6 Hz), 2.93 (1H, t, J=8.6 Hz), 2.87–2.73 (1H, m), 2.05–1.74 (4H, m), 1.58–1.41 (1H, m), 1.25–1.09 (1H, m); ^{13}C NMR ($CDCl_3$) δ 167.9, 139.5, 136.2, 133.0, 130.8, 128.8 (×2), 125.9, 117.9, 51.1, 45.4, 36.8, 29.7, 26.4, 23.0; IR (ATR, film) ν: 3066, 2925, 2855, 1677, 1631, 1435, 1411, 1269 cm^{-1}; FABMS (rel intensity) m/z 286 (M+H, 15), 123 (12), 119 (11), 111 (11), 109 (25), 97 (25), 95 (45), 81 (53), 55 (100); Exact mass calcd for $C_{17}H_{20}NOS$ m/z 286.1265; FAB–HRMS m/z 286.1252.

*4.2.4. 2-Benzyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**14d**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.59–7.45 (2H, m), 7.41–7.27 (8H, m), 4.76 (1H, d, J=14.7 Hz), 4.28 (1H, d, J=14.7 Hz), 3.37 (1H, t, J=8.3 Hz), 2.89 (1H, t, J=8.3 Hz), 2.88–2.71 (1H, m), 2.01–1.79 (4H, m), 1.59–1.40 (1H, m), 1.22–1.13 (1H, m); ^{13}C NMR ($CDCl_3$) δ 167.9, 139.7, 136.9, 136.1, 130.7, 128.7 (×2), 128.5, 128.3, 127.4, 125.6, 50.9, 46.6, 36.7, 29.6, 26.2, 22.9; IR (ATR, film) ν: 3055, 3022, 2925, 2857, 1674, 1415, 1267, 1248 cm^{-1}; FABMS (rel intensity) m/z 336 (M+H, 100), 335 (26), 334 (17), 102 (11), 91 (92), 77 (10); Exact mass calcd for $C_{21}H_{22}NOS$ m/z 336.1422; FAB–HRMS m/z 336.1407.

*4.2.5. 2-Benzoyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**14e**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.70–7.66 (2H, m), 7.55–7.47 (3H, m), 7.44–7.33 (5H, m), 4.13 (1H, dd, J=10.6, 8.2 Hz), 3.44 (1H, t, J=10.4 Hz), 3.00–2.86 (1H, m), 2.15–1.87 (4H, m), 1.64–1.50 (1H, m), 1.29–1.15 (1H, m); ^{13}C NMR ($CDCl_3$) δ 171.2, 166.5, 150.5, 136.5, 134.8, 131.8, 129.6, 129.3, 129.1 (×2) 127.9, 123.6, 51.1, 35.5, 30.4, 26.3, 22.7; IR (ATR, film) ν: 3059, 2937, 2860, 1714, 1667, 1605, 1308, 1192, 1150 cm^{-1}; FABMS (rel intensity) m/z 350 (M+H, 51), 349 (11), 348 (10), 109 (14), 105 (100), 81 (33); Exact mass calcd for $C_{21}H_{20}NO_2S$ m/z 350.1214; FAB–HRMS m/z 350.1211.

4.2.6. (3aR,5R*)-2,5-Dimethyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**15a**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.52–7.45 (2H, m), 7.33–7.26 (3H, m), 3.44 (1H, t, J=7.8 Hz), 2.96 (1H, t, J=8.2 Hz), 2.96–2.87 (1H, m), 2.89 (3H, s), 2.15–1.99 (2H, m), 1.76–1.59 (2H, m), 1.35–1.26 (1H, m), 0.89 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.3, 138.0, 135.9, 131.1, 128.8, 128.6, 125.4, 54.1, 36.5, 32.1, 31.9, 30.0, 27.1, 19.6; IR (ATR, film) ν: 3055, 2955, 2920, 2871, 1679, 1631, 1424, 1397, 1286, 1253, 1072 cm^{-1}; FABMS (rel intensity) m/z 274 (M+H, 100), 273 (22), 272 (15); Exact mass calcd for $C_{16}H_{20}NOS$ m/z 274.1265; FAB–HRMS m/z 274.1273.

4.2.7. (3aR,5R*)-2-Ethyl-5-methyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**15b**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.52–7.49 (2H, m), 7.33–7.26 (3H, m), 3.52–3.40 (2H, m), 3.38–3.24 (1H, m), 2.96 (1H, t, J=8.1 Hz), 2.96–2.83 (1H, m), 2.15–1.99 (2H, m), 1.76–1.59 (2H, m), 1.36–1.27 (1H, m), 1.13 (3H, t, J=7.4 Hz), 0.89 (3H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.8, 137.8, 135.9, 131.2, 128.8, 128.6, 125.8, 51.1, 37.3, 36.5, 32.2, 32.1, 27.2, 19.7, 12.8; IR (ATR, film) ν: 3055, 2957, 2925, 2870, 1676, 1632, 1422, 1240, 1252, 1068 cm^{-1}; FABMS (rel intensity) m/z 288 (M+H, 100), 287 (22), 286 (17); Exact mass calcd for $C_{17}H_{22}NOS$ m/z 288.1422; FAB–HRMS m/z 288.1412.

4.2.8. (3aR,5R*)-2-Allyl-5-methyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**15c**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.52–7.48 (2H, m), 7.33–7.26 (3H, m), 5.75 (1H, tdd, J=6.3, 10.2, 16.2 Hz), 5.22–5.12 (2H, m), 4.11 (1H, tdd, J=1.5, 6.0, 15.0 Hz), 3.76 (1H, dd, J=6.0, 15.0 Hz), 3.50–3.39 (1H, m), 2.97–2.82 (2H, m), 2.17–2.00 (2H, m), 1.87–1.65 (2H, m), 1.38–1.23 (1H, m), 0.89 (3H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.7, 138.5, 135.8, 132.9, 130.9, 128.7, 128.5, 125.2, 117.7, 51.2, 45.3, 36.4, 32.0, 31.8, 27.0, 19.5; IR (ATR, film) ν: 3073, 3055, 2956, 2920, 2870, 1678, 1630, 1438, 1412, 1251, 1239 cm^{-1}; FABMS (rel intensity) m/z 300 (M+H, 100), 299 (28), 298 (13), 281 (14), 221 (26), 207 (29), 147 (17), 136 (13), 97 (10), 95 (14), 91 (18), 81 (17); Exact mass calcd for $C_{18}H_{22}NOS$ m/z 300.1422; FAB–HRMS m/z 300.1435.

4.2.9. (3aR,5R*)-2-Benzyl-5-methyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**15d**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.57–7.53 (2H, m), 7.38–7.25 (8H, m), 4.80 (1H, d, J=14.4 Hz), 4.27 (1H, d, J=14.4 Hz), 3.42–3.32 (1H, m), 2.98–2.83 (2H, m), 2.20–2.00 (2H, m), 1.73–1.61 (2H, m), 1.38–1.25 (1H, m), 0.92 (3H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 168.0, 138.9, 137.0, 135.9, 131.0, 128.8, 128.7 (×2), 128.4, 127.5, 125.2, 51.2, 46.8, 36.6, 32.1, 32.0, 27.1, 19.7; IR (ATR, film) ν: 3060, 3029, 2951, 2923, 2855, 1677, 1418, 1239, 1251, 1077 cm^{-1}; FABMS (rel intensity) m/z 350 (M+H, 37), 131 (10), 123 (11), 119 (13), 117 (11), 109 (21), 105 (25), 91 (60), 81 (46), 55 (100); Exact mass calcd for $C_{22}H_{24}NOS$ m/z 350.1578; FAB–HRMS m/z 350.1581.

4.2.10. (3aR,5R*)-2-Benzoyl-5-methyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**15e**).* Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.70–7.66 (2H, m), 7.55–7.49 (3H, m), 7.45–7.33 (5H, m), 4.14 (1H, dd, J=8.1, 10.5 Hz), 3.45 (1H, t, J=10.7 Hz), 3.10–2.98 (1H, m), 2.26–2.18 (2H, m), 1.89 (1H, td, J=3.6, 12.3 Hz), 1.75 (1H, dd, J=2.4, 17.5 Hz), 1.40 (1H, dt, J=2.4, 12.3 Hz), 0.99 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 171.0, 166.3, 149.5, 136.2, 134.7, 131.7, 129.4, 129.3, 129.03, 128.97, 127.7, 122.6, 51.1, 37.0, 31.8, 30.5, 26.9, 19.5; IR (ATR, film) ν: 3058, 2957, 2923, 2896, 1716, 1667, 1608, 1319, 1306, 1223, 1149 cm^{-1}; FABMS (rel intensity) m/z 364 (M+H, 26), 105 (100), 91 (24), 81 (27); Exact mass calcd for $C_{22}H_{22}NO_2S$ m/z 364.1371; FAB–HRMS m/z 364.1373.

4.2.11. (3aR,5R*)-5,7-Dimethyl-2-tosyl-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (**16**).* To a mixture of CuI (33 mg, 0.172 mmol) in THF (1 mL) at 0 °C was added dropwise a solution of MeLi (2.2 M in THF, 0.156 mL, 0.343 mmol). After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C, and $BF_3\cdot OEt_2$ (d=1.12, 0.034 mL, 0.264 mmol) was added and stirred for 5 min. Then a solution of compound **11** (20 mg, 0.048 mmol) in THF (1 mL) precooled at −78 °C was added dropwise. The reaction mixture was slowly warmed to room temperature, stirred for another 4 h, and quenched with saturated ammonium chloride. The aqueous solution was extracted with ethyl acetate (3×20 mL), combined with the organic layer, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by chromatography using ethyl acetate/hexane (1:5) and then recrystallized with CH_2Cl_2/hexane to give product **16** (10.6 mg, 69%) as a white solid, mp 129.7–130.8 °C: ^{1}H NMR ($CDCl_3$) δ 7.96 (2H, d, J=8.2 Hz), 7.34 (2H, d, J=8.2 Hz), 4.15 (1H, t, J=8.7 Hz), 3.23 (1H, t, J=9.3 Hz), 2.92–2.77 (1H, m), 2.44 (3H, s), 2.37–2.25 (1H, m), 2.21–2.09 (1H, m), 2.05 (3H, d, J=2.4 Hz), 1.92–1.75 (2H, m), 1.29 (1H, dt, J=3.6, 12.0 Hz), 0.95 (3H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.5, 148.2, 144.8, 135.9, 129.6, 128.2, 124.2, 51.3, 39.7, 32.1, 30.3, 25.74, 25.65, 21.7, 19.8; IR (ATR, film) ν: 2956, 2920, 2868, 1720, 1669, 1358, 1170, 1048 cm^{-1}; EI-MS (rel intensity) m/z 319 (M^+, 10), 256 (21), 255 (22), 199 (12), 198 (100), 155 (48), 137 (13), 136 (19),

94 (12), 93 (14), 91 (55); Exact mass calcd for $C_{17}H_{21}NO_3S$ *m*/*z* 319.1242; EI-HRMS *m*/*z* 319.1241.

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12. Crystallographic data (excluding structure factors) for compounds **2**, **5**, **6**, **10**, and **11** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 839219 (compound **2**), 839220 (compound **5**), 839221 (compound **6**), 839222 (compound **10**), and 839223 (compound **11**). 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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