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Synthesis of fused bicyclic glutarimides

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Abstract—We describe an efficient route towards the synthesis of fused bicyclic glutarimides using facile [3+3] reaction of α-sulfonylacetamides with different α,β-unsaturated esters as the key step. Intramolecular cyclization of 4-substituted 3-sulfonylglutarimide to form 5,6-, 6,6- or 6,7-fused bicyclic glutarimides was accomplished via alkylation, oxidative cyclization or ring-closing metathesis in modest yield.

1. Introduction

Glutarimides (piperidine-2,6-diones) possess various biological activities,[1] therefore, the synthesis of these glutarimide derivatives[2,3] (cyclic imides) such as cycloheximide,[2a] thalidomide[3a–e] and aminoglutethimide[3b–d,g] has attracted considerable attention. In most cases, glutarimides are obtained via cyclization of δ-dinitriles in an acidic solution or monoamides with acid in the presence of thionyl chloride or BOP. Owing to the harsh reaction conditions, some milder methods have been reported,[3b,c] such as the condensation of a diacidic compound with amine.

Recently, we reported a facile stepwise [3+3] annulation reaction between different α-sulfonylacetamides derivatives and a series of the α- or β-, aryl or alkyl substituted acyclic α,β-unsaturated alkyl esters leading to the corresponding glutarimides in good yields.[4] This method has been used to the syntheses of natural products and potential biological drugs.[4]

Continuing our investigation on the application of this methodology to the synthesis of alkaloids, we describe herein the efficient construction potentially useful fused bicyclic glutarimides as shown in Figure 1.

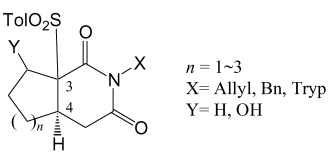

Figure 1. Skeleton of fused bicyclic glutarimides.

Keywords: bicyclic glutarimides; stepwise [3+3] annulation; intramolecular alkylation; oxidative cyclization or ring-closing metathesis.
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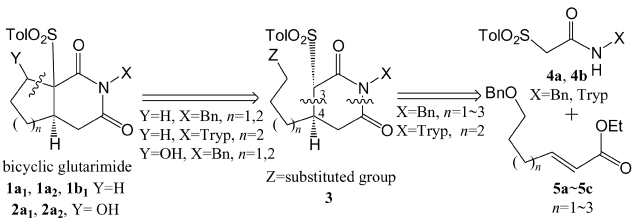
2. Results and discussion

2.1. Retrosynthetic approach to 5,6- and 6,6-fused bicyclic glutarimides 1 and 2

The retrosynthetic approach to 5,6- and 6,6-fused bicyclic glutarimides **1** and **2** is shown in Scheme 1.[5,6] Compounds **1** and **2** were prepared from 4-substituted 3-sulfonylglutarimides **3** by intramolecular cyclization. The reaction of α-sulfonylacetamides **4** (**4a** X=Bn, **4b** X=Tryp)[4d] with α,β-unsaturated ethyl esters **5a–c** was the key step in the formation of **3**. Functional group transformation of **3** was performed in a straightforward way involving hydrogenolysis of **3**, mesylation and alkylation or oxidation.

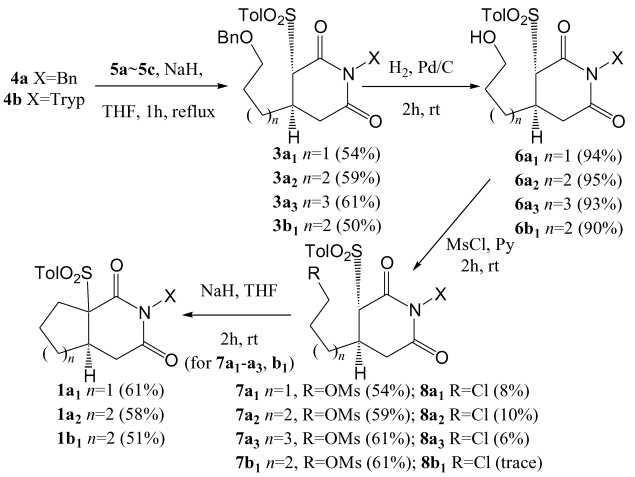


Scheme 1. Retrosynthetic analysis of 5,6-and 6,6-fused bicyclic glutarimides **1** and **2**.

2.2. Synthetic approach to 5,6- and 6,6-fused bicyclic glutarimides 1 and 2

2.2.1. Synthesis of 5,6- and 6,6-fused bicyclic glutarimides 1 via intramolecular alkylation. α-Sulfonylacetamides **4a** and **4b** were produced by acetylation of benzylamine and tryptamine with chloroacetyl chloride followed by nucleophilic substitution of *p*-toluenesulfinic acid sodium salt. Esters **5a–5c** were produced from diol compounds via a three-step reaction of monobenzylation of

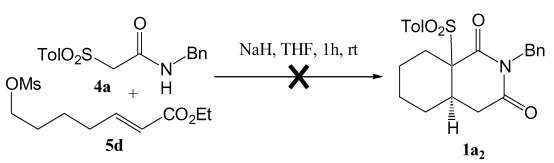
a diol (NaH/BnBr), oxidation (PCC) and olefination (Ph_3-P=$CHCO_2Et$) in modest yields. As shown in Scheme 2, **3a$_1$**–**3a$_3$** or **3b$_1$** were produced in moderate yields by the concise reaction of **4a** or **4b** with a variety of **5a**–**5c**. The stereochemical relationship between 4-substituents and 3-sulfonyl group was proven as the *trans* form by ^{1}H NMR spectral analysis (ca. δ 4.0, br s, H-3) and the previous studies.[4e]



Scheme 2. Synthesis of 5,6-and 6,6-fused bicyclic glutarimides **1** via intramolecular alkylation.

O-Debenzylation of **3a$_1$**–**3a$_3$** or **3b$_1$** with hydrogen and palladium on carbon as the catalyst in ethyl acetate gave alcohols **6a$_1$**–**6a$_3$** or **6b$_1$**. Mesylation of **6a$_1$**–**6a$_3$** or **6b$_1$** with methanesulfonyl chloride in pyridine gave two kinds of products. The ratio of mesylates **7a$_1$**–**7a$_3$** to chlorides **8a$_1$**–**8a$_3$** was 6:1–10:1. The structure of **8a$_3$** was determined by single-crystal X-ray analysis. But the chloride **8b$_1$** was only produced in trace amounts (<4%). When the mesylates **7a$_1$**–**7a$_2$** or **7b$_1$** were reacted with sodium hydride, the sole fused bicyclic 5,6- or 6,6-fused glutarimides **1a$_1$**–**1a$_2$** or **1b$_1$** were obtained in moderate yields.

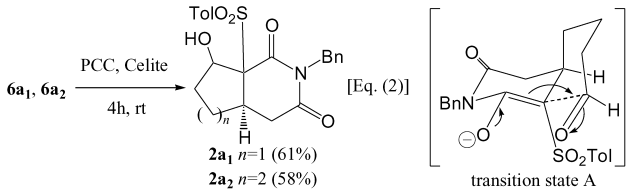
Chlorides **8a$_1$** or **8a$_2$** was also converted to **1a$_1$** or **1a$_2$** by the same method. Compound **1b$_1$** is a reasonable precursor for the synthesis of yohimbane skeleton.[7] We also examined a one-pot reaction of **4a** with *O*-mesylate ester **5d** for the formation of the **1a$_2$**, however, the resulting product could not be characterized [Eq. (1)].



(1)

The stereochemistry assignments of key ^{1}H peaks cannot be assigned with confidence using the proton NMR spectra of **1a$_1$**–**1a$_2$** or **1b$_1$**. Therefore, we could not determined the specific *cis* or *trans* stereochemistry of sole compounds **1a$_1$**–**1a$_2$** or **1b$_1$**. It is an ambiguous result. In order to produce the natural glutaimides, we examined the desulfonylation of the fused glutarimides with sodium amalgam. We initially used glutarimide **1a$_1$** as a model substrate to synthesize the 5,6-fused bicyclic glutarimide without the sulfonyl group, but desulfonylation of **1a$_1$** produced complex results. The six-membered ring of **1a$_1$** can open in the basic desulfonylation, producing other compounds as monitored by TLC.[4c]

2.2.2. Synthesis of 5,6- and 6,6-fused bicyclic glutarimides 2 via oxidative cyclization. An alternative route to 5,6- and 6,6-fused bicyclic glutarimides **2** was examined. When alcohols **6a$_1$** or **6a$_2$** was oxidized with pyridinium chlorochromate (PCC, 1.1 equiv.) and Celite, cyclized products **2a$_1$** or **2a$_2$** was produced immediately. To the best of our knowledge, the formation of bicyclic glutarimide by PCC-mediated oxidative cyclization has not been reported. We isolated **2a$_1$** as two isomers in 1:1 ratio in 61% yield and **2a$_2$** as a unique isomer in 58% yield [Eq. (2)]. The stereoselective outcome of **2a$_2$** can be rationalized as an intramolecular aldol cyclization by the formation of chair form transition state A. Compound **2a$_1$** is generated as a mixture due to the lack of the formation of chair form transition state.



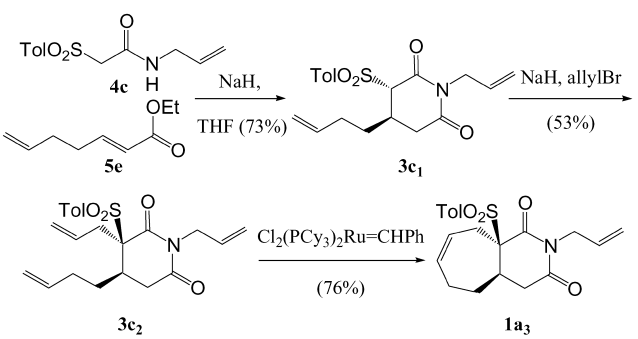
(2)

Treatment of **6a$_2$** with Swern oxidation also yielded the same bicyclic products **2a$_2$** under the basic work-up condition. The aldehyde product was not isolated. We believe the generation of aldehyde group initiated the intramolecular cyclization. Therefore, PCC or Swern oxidation-mediated cyclization is an interesting reaction to form the bicyclic glutarimides under the one-pot condition.

2.3. Synthesis of 6,7-fused bicyclic glutarimide 1a$_3$ via ring-closing metathesis

Following the same approach, attempts to form 6,7-fused bicyclic glutarimide, using mesylate **7a$_3$** or chloride **8a$_3$** as starting materials under a variety of basic conditions were unsuccessful. Finally, the 6,7-fused bicyclic glutarimide skeleton were obtained via the ring-closing metathesis (RCM) method.[8–9]

We first synthesized tris-olefin **3c$_2$**, starting material for ring-closing metathesis, by allylation of **3c$_1$** as shown in Scheme 3. The bis-olefin **3c$_1$** was synthesized from the



Scheme 3. Synthesis of 6,7-fused bicyclic glutarimides **1a$_3$** via ring-closing metathesis.

concise [3+3] reaction of **4c** with ester **5e**. α-Allylation of $\mathbf{3c_1}$ was reacted with sodium hydride and allyl bromide to yield the sole product $\mathbf{3c_2}$. Treatment of $\mathbf{3c_2}$ with Grubbs catalyst [$Cl_2(PCy_3)_2Ru{=}CHPh$] produced the 6,7-fused bicyclic glutarimide $\mathbf{1a_3}$ in 76% yield. The structure of $\mathbf{1a_3}$ was determined by single-crystal X-ray analysis as shown in Diagram 1. During the ring closure process, the product with bridge bicyclic [5.2.2] and [4.3.1] frameworks were not observed.

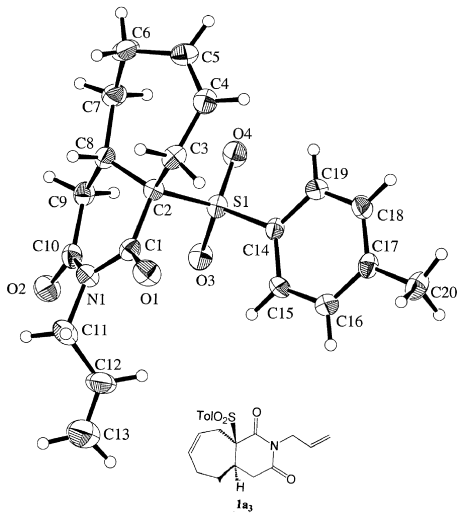


Diagram 1. X-Ray crystallography of $\mathbf{1a_3}$

3. Conclusion

In conclusion, we have explored a formal [3+3] cycloaddition strategy that is synthetically useful for constructing 3-sulfonylglutarimides and further utilized it to build up the bicyclic glutarimides skeleton via alkylation, oxidative cyclization and ring-closing metathesis.

4. Experimental

4.1. General

Dichloromethane (DCM) and tetrahydrofuran (THF) were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. All reported melting temperatures are uncorrected.

4.2. Procedure of *N*-substituted α-sulfonylacetamide 4 (X=benzyl, tryptaminyl and allyl)[4d]

A solution of amine (10.0 mmol) and triethylamine (1.11 g, 11.0 mmol) in THF (100 mL) was added to chloroacetyl chloride (1.2 g, 10.6 mmol) in THF (40 mL) at ice bath for 1 h. After the reaction mixture was stirred at rt for 4 h, the mixture was concentrated under reduced pressure. Water (30 mL) was added to the crude product, and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Without further purification, the crude product was refluxed with *p*-toluenesulfinic acid sodium salt ($TolSO_2Na\text{-}2H_2O$, 15.0 mmol) in the co-solvent of dioxane (150 mL) and water (150 mL) for 10 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Recrystallization on hexane and ethyl acetate (ca. 1:1) yielded the products **4a**–**4c**. The spectral data of **4a** and **4b** (IR, HRMS, NMR and Anal. calcd) were in accordance with those reported in Ref. 4d.

4.2.1. 1-Allyl-2-(4-methylphenylsulfonyl)acetamide (4c). Yield 85%; mp 136–137°C (hexane/ethyl acetate); EI-MS: $C_{12}H_{15}NO_3S$ *m/z* (%)=98 (100), 253 (M^+, 1); HRMS (EI, M^+) calcd for $C_{12}H_{15}NO_3S$ 253.0773, found 253.0770; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 6.90 (br s, 1H), 5.82–5.73 (m, 1H), 5.24–5.12 (m, 2H), 4.00 (s, 2H), 3.86–3.83 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.60, 145.64, 135.29, 133.10, 130.05 (2×), 128.18 (2×), 117.00, 62.06, 42.34, 21.66.

4.3. Preparation of various α,β-unsaturated esters 5

A solution of diols (50.0 mmol) in THF (100 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 1.6 g, 40.0 mmol) in THF (500 mL). After the reaction mixture was stirred at rt for 1 h, a solution of benzyl bromide (6.84 g, 40.0 mmol) in THF (200 mL) was added for 2 h. The resulting mixture was stirred at rt for 20 h, quenched with $NH_4Cl_{(aq)}$ and concentrated under reduced pressure. The resulting residue was extracted with ethyl acetate (3×200 mL), and the combined organic layers were washed with brine, dried, filtered and evaporated. The crude products in DCM (100 mL) were added to a mixture of pyridinium chlorochromate (8.62 g, 40.0 mmol) and Celite (30 g) in DCM (150 mL). After being stirred at rt for 4 h, the reaction mixture was filtered through a short silica gel column. The filtrate was dried, filtered and added to a rapidly stirred solution of $Ph_3P{=}CHCO_2Et$ (10.8 g, 31.0 mmol) in DCM (200 mL). After the reaction mixture was stirred at rt for 2 h, the resulting mixture was concentrated under reduced pressure. Water (100 mL) was added to the residue, and extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Evaporation of the solvent followed purification the crude product by column chromatography on silica gel with hexane/ethyl acetate (20/1–15/1) yielded various α,β-unsaturated ethyl esters **5a**–**5c**. Diols were converted to **5a**–**5c** in three steps of monobenzylation, oxidation and olefination. The total yield is 50% from 1,4-butanediol, 41% from 1,5-pentanediol and 44% from 1,6-hexanediol.

4.4. Procedure of formal [3+3] cycloaddition reaction using N-substituted α-sulfonylacetamides 4 and α,β-unsaturated ethyl esters 5

A solution of **4** (1.0 mmol) in THF (10 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 88 mg, 2.2 mmol for **4a**, **4c**; 132 mg, 3.3 mmol for **4b**) in THF

(10 mL). After the reaction mixture was stirred at rt for 5 min, a solution of **5** (1.0 mmol) in THF (10 mL) was added. The resulting mixture was heated at reflux temperature for 1 h, quenched with $NH_4Cl_{(aq)}$ and concentrated under reduced pressure. The resulting residue was extracted with ethyl acetate (3×20 mL), and the combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) yielded **3a$_1$**–**3a$_3$**, **3b$_1$**, or **3c$_1$**.

4.4.1. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(3-benzyloxy-propyl)piperidine-2,6-dione (3a$_1$). Yield 54%; mp 79–82°C (hexane/ethyl acetate); IR ($CHCl_3$) 2938, 2860, 1727, 1680, 1382, 1148, 737 cm^{-1}; ESI-MS: $C_{29}H_{32}NO_5S$ *m/z* (%)=91 (100), 181 (19), 398 (4), 506 (M^++1, 18); HRMS (ESI, M^++1) calcd for $C_{29}H_{32}NO_5S$ 506.2002, found 506.2001; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J*=8.3 Hz, 2H), 7.35–7.23 (m, 12H), 5.06 (d, *J*=14.0 Hz, 1H), 4.85 (d, *J*=14.0 Hz, 1H), 4.43 (s, 2H), 3.94 (br s, 1H, H-3), 3.48 (dd, *J*=6.0, 18.1 Hz, 1H), 3.46–3.37 (m, 2H), 3.02–2.98 (m, 1H, H-4), 2.70 (d, *J*=18.1 Hz, 1H), 2.42 (s, 3H), 1.55–1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.39, 164.32, 145.68, 138.13, 136.42, 134.59, 129.81 (3×), 128.94 (4×), 128.63 (2×), 128.44 (2×), 128.35, 127.71, 127.48, 73.09, 70.75, 69.12, 43.36, 34.33, 30.99, 28.75, 26.94, 21.76. Anal. calcd for $C_{29}H_{31}NO_5S$ C, 68.89; H, 6.18. Found C, 69.16; H, 6.03.

4.4.2. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(4-benzyloxy-butyl)piperidine-2,6-dione (3a$_2$). Yield 59%; mp 67–70°C (hexane/ethyl acetate); IR ($CHCl_3$) 2938, 2860, 1728, 1682, 1383, 750 cm^{-1}; ESI-MS: $C_{30}H_{34}NO_5S$ *m/z* (%)=91 (100), 181 (11), 520 (M^++1, 5); HRMS (ESI, M^++1) calcd for $C_{30}H_{34}NO_5S$ 520.2159, found 520.2158; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J*=8.3 Hz, 2H), 7.34–7.23 (m, 12H), 5.06 (d, *J*=14.0 Hz, 1H), 4.85 (d, *J*=14.0 Hz, 1H), 4.44 (s, 2H), 3.90 (br s, 1H, H-3), 3.47 (dd, *J*=6.1, 18.1 Hz, 1H), 3.39 (t, *J*=5.9 Hz, 2H), 2.97–2.95 (m, 1H, H-4), 2.69 (d, *J*=18.1 Hz, 1H), 2.42 (s, 3H), 1.55–1.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.41, 164.32, 145.68, 138.39, 136.44, 134.58, 129.81 (3×), 128.94, 128.66 (3×), 128.40 (2×), 128.35, 127.67 (2×), 127.61, 127.50, 72.95, 70.73, 69.54, 43.32, 34.31, 33.80, 29.16, 28.80, 23.47, 21.74. Anal. calcd for $C_{30}H_{33}NO_5S$ C, 69.34; H, 6.40. Found C, 69.39; H, 6.38.

4.4.3. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(5-benzyloxy-pentyl)piperidine-2,6-dione (3a$_3$). Yield 61%; mp 51–53°C (hexane/ethyl acetate); IR ($CHCl_3$) 2936, 2858, 1727, 1681, 1382, 736 cm^{-1}; HRMS (EI, M^+) calcd for $C_{31}H_{35}NO_5S$ 533.2238, found 533.2239; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J*=8.3 Hz, 2H), 7.33–7.23 (m, 12H), 5.06 (d, *J*=14.0 Hz, 1H), 4.85 (d, *J*=14.0 Hz, 1H), 4.46 (s, 2H), 3.88 (br s, 1H, H-3), 3.47 (dd, *J*=6.1, 18.1 Hz, 1H), 3.40 (t, *J*=6.4 Hz, 2H), 2.98–2.95 (m, 1H, H-4), 2.68 (d, *J*=18.1 Hz, 1H), 2.42 (s, 3H), 1.54–1.27 (m, 8H).

4.4.4. 1-[2-(3-Indolyl)ethyl]-3-(4-methylphenylsulfonyl)-4-(4-benzyloxybutyl)piperidine-2,6-dione (3b$_1$). Yield 50%; gum; ESI-MS: $C_{33}H_{37}N_2O_5S$ *m/z* (%)=91 (54), 143 (100), 234 (18), 573 (M^++1, 42); HRMS (ESI, M^++1) calcd for $C_{33}H_{37}N_2O_5S$ 573.2425, found 573.2429; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (br s, 1H), 7.73–7.76 (m, 3H), 7.39–7.24 (m, 8H), 7.18–7.09 (m, 2H), 7.00 (d, *J*=2.2 Hz, 1H), 4.47 (s, 2H), 4.18–4.03 (m, 2H), 3.94 (s, 1H, H-3), 3.50–3.35 (m, 3H), 3.03–2.88 (m, 3H), 2.64 (d, *J*=17.9 Hz, 1H), 2.45 (s, 3H), 1.56–1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.34, 164.42, 145.83, 138.39, 136.24, 135.06, 138.08 (2×), 128.94 (3×), 128.45 (3×), 127.71, 127.39, 122.40, 122.00, 119.40, 119.11, 112.21, 111.13, 73.00, 70.76, 69.66, 40.59, 34.28, 33.55, 29.16, 28.86, 23.59, 23.38, 21.80.

4.4.5. 1-Allyl-3-(4-methylphenylsulfonyl)-4-(1-butenyl)-piperidine-2,6-dione (3c$_1$). Yield 56%; mp 106–108°C (hexane/ethyl acetate); HRMS (EI, M^+) calcd for $C_{19}H_{23}NO_4S$ 361.1348, found 361.1358; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J*=8.3 Hz, 2H), 7.35 (d, *J*=8.6 Hz, 2H), 5.81–5.65 (m, 2H), 5.27–5.00 (m, 4H), 4.38–4.37 (m, 2H), 3.95 (t, *J*=1.6 Hz, 1H, H-3), 3.43 (dd, *J*=6.0, 17.9 Hz, 1H), 3.02–2.97 (m, 1H, H-4), 2.67 (dt, *J*=1.8, 17.9 Hz, 1H), 2.45 (s, 3H), 2.14–2.08 (m, 2H), 1.55–1.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.90, 164.07, 145.84, 136.10, 134.96, 131.31, 129.92 (2×), 128.96 (2×), 117.75, 116.51, 70.61, 42.08, 34.17, 32.90, 30.70, 28.32, 21.75.

4.5. Procedure of debenzylation using hydrogen and 10% palladium on activated carbon as catalyst

10% Palladium on activated carbon (20 mg) as catalyst was added to a solution of **3a$_1$**–**3a$_3$** or **3b$_1$** (0.5 mmol) in ethyl acetate (20 mL). Then hydrogen was bubbled into the reaction mixture for 10 min, and stirring occurred at rt for 2 h. Filtration through a short plug of Celite and washing with ethyl acetate (3×10 mL) resulted in the desired product. Purification on silica gel (hexane/ethyl acetate=1/1–1/2) yielded **6a$_1$**–**6a$_3$** or **6b$_1$**.

4.5.1. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(3-hydroxy-propyl)piperidine-2,6-dione (6a$_1$). Yield 94%; mp 97–100°C (hexane/ethyl acetate); IR ($CHCl_3$) 3390, 2941, 2868, 1727, 1679, 1383, 1148, 744 cm^{-1}; ESI-MS: $C_{22}H_{26}NO_5S$ *m/z* (%)=91 (100), 137 (19), 154 (18), 260 (10), 416 (M^++1, 50); HRMS (ESI, M^++1) calcd for $C_{22}H_{26}NO_5S$ 416.1533, found 416.1536; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J*=8.3 Hz, 2H), 7.37–7.15 (m, 7H), 5.06 (d, *J*=14.0 Hz, 1H), 4.85 (d, *J*=14.0 Hz, 1H), 3.94 (br s, 1H, H-3), 3.67 (t, *J*=5.7 Hz, 2H), 3.49 (dd, *J*=6.1, 18.1 Hz, 1H), 3.03–2.95 (m, 1H, H-4), 2.70 (d, *J*=18.1 Hz, 1H), 2.42 (s, 3H), 1.75–1.23 (m, 5H). Anal. calcd for $C_{22}H_{25}NO_5S$ C, 63.59; H, 6.06. Found C, 63.16; H, 6.21.

4.5.2. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(4-hydroxy-butyl)piperidine-2,6-dione (6a$_2$). Yield 95%; mp 80–83°C (hexane/ethyl acetate); IR ($CHCl_3$) 3390, 2938, 2863, 1727, 1681, 1386, 753 cm^{-1}; ESI-MS: $C_{23}H_{28}NO_5S$ *m/z* (%)=91 (100), 430 (M^++1, 22); HRMS (ESI, M^++1) calcd for $C_{23}H_{28}NO_5S$ 430.1689, found 430.1690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J*=8.1 Hz, 2H), 7.35–7.23 (m, 7H), 5.05 (d, *J*=14.0 Hz, 1H), 4.85 (d, *J*=14.0 Hz, 1H), 3.92 (br s, 1H, H-3), 3.54 (t, *J*=5.3 Hz, 2H), 3.47 (dd, *J*=6.0, 18.1 Hz, 1H), 3.00–2.95 (m, 1H, H-4), 2.69 (d, *J*=18.1 Hz, 1H), 2.41 (s, 3H), 1.75–1.23 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.47,

164.33, 145.74, 136.40, 134.50, 129.83 (2×), 128.94 (2×), 128.69 (2×), 128.34 (2×), 127.53, 70.70, 62.13, 43.34, 34.31, 33.80, 31.92, 28.80, 22.95, 21.74. Anal. calcd for $C_{23}H_{27}NO_5S$ C, 64.31; H, 6.34. Found C, 64.21; H, 6.40.

4.5.3. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(5-hydroxy-pentyl)piperidine-2,6-dione ($6a_3$). Yield 93%; mp 60–62°C (hexane/ethyl acetate); IR ($CHCl_3$) 3391, 2935, 2860, 1727, 1679, 1383, 751 cm^{-1}; HRMS (EI, M^+) calcd for $C_{24}H_{29}NO_5S$ 443.1768, found 443.1761; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J=8.2 Hz, 2H), 7.32–7.23 (m, 7H), 5.05 (d, J=14.0 Hz, 1H), 4.85 (d, J=14.0 Hz, 1H), 3.90 (br s, 1H, H-3), 3.55 (t, J=6.4 Hz, 2H), 3.46 (dd, J=6.1, 18.1 Hz, 1H), 2.99–2.95 (m, 1H, H-4), 2.68 (d, J=18.1 Hz, 1H), 2.41 (s, 3H), 1.62–1.29 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.49, 164.37, 145.74, 136.42, 134.50, 129.83 (2×), 129.18 (2×), 128.94 (2×), 128.69 (2×), 127.53, 70.81, 62.47, 43.34, 34.30, 33.95, 32.18, 28.73, 26.33, 25.29, 21.75.

4.5.4. 1-[2-(3-Indolyl)ethyl]-3-(4-methylphenylsulfonyl)-4-(4-hydroxybutyl)piperidine-2,6-dione ($6b_1$). Yield 90%; gum; ESI-MS: $C_{26}H_{31}N_2O_5S$ *m/z* (%)=143 (70), 173 (30), 255 (16), 483 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{26}H_{31}N_2O_5S$ 483.1955, found 483.1947; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.71–7.67 (m, 3H), 7.36–7.31 (m, 3H), 7.19–7.09 (m, 2H), 7.03 (s, 1H), 4.16–4.05 (m, 2H), 3.93 (s, 1H, H-3), 3.56 (t, J=6.0 Hz, 2H), 3.40 (dd, J=6.0, 17.9 Hz, 1H), 2.99 (t, J=7.9 Hz, 2H), 2.97–2.90 (m, 1H, H-4), 2.64 (d, J=17.9 Hz, 1H), 2.45 (s, 3H), 1.54–1.24 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.31, 164.42, 145.85, 136.33, 135.03, 129.98 (2×), 128.95 (2×), 127.56, 122.35, 122.04, 119.46, 119.12, 112.31, 111.05, 70.72, 62.25, 40.52, 34.31, 33.52, 31.90, 28.87, 23.31, 23.08, 21.79.

4.6. Procedure of mesylation using methanesulfonyl chloride and pyridine

A solution of methanesulfonyl chloride (115 mg, 1.0 mmol) in DCM (1 mL) was added to a solution of **$6a_1$–$6a_3$** or **$6b_1$** (0.4 mmol) in pyridine (10 mL), and the reaction mixture was stirred for 2 h at rt. The resulting mixture was poured into 2N HCl (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried, filtered and concentrated. Purification on silica gel (hexane/ethyl acetate=1/1–1/2) yielded **$7a_1$–$7a_3$** or **$7b_1$** and **$8a_1$–$8a_3$**.

4.6.1. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(3-methane-sulfonylpropyl)piperidine-2,6-dione ($7a_1$). Yield 54%; mp 104–106°C (hexane/ethyl acetate); IR ($CHCl_3$) 2933, 1732, 1673 cm^{-1}; HRMS (EI, M^+) calcd for $C_{23}H_{27}NO_7S_2$ 493.1230, found 493.1233; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=8.3 Hz, 2H), 7.33–7.24 (m, 7H), 5.07 (d, J=14.0 Hz, 1H), 4.85 (d, J=14.0 Hz, 1H), 4.16 (t, J=6.0 Hz, 2H), 3.92 (br s, 1H, H-3), 3.51 (dd, J=6.1, 18.1 Hz, 1H), 3.00–2.95 (m, 1H, H-4), 2.96 (s, 3H), 2.69 (d, J=18.1 Hz, 1H), 2.43 (s, 3H), 1.82–1.40 (m, 4H).

4.6.2. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(4-methane-sulfonylbutyl)piperidine-2,6-dione ($7a_2$). Yield 59%; gum; IR ($CHCl_3$) 2940, 1733, 1676 cm^{-1}; HRMS (EI, M^+) calcd for $C_{24}H_{29}NO_7S_2$ 507.1387, found 507.1388; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=8.3 Hz, 2H), 7.33–7.24 (m, 7H), 5.06 (d, J=14.0 Hz, 1H), 4.85 (d, J=14.0 Hz, 1H), 4.15 (t, J=6.2 Hz, 2H), 3.89 (br s, 1H, H-3), 3.45 (dd, J=6.1, 18.1 Hz, 1H), 3.00–2.95 (m, 1H, H-4), 2.96 (s, 3H), 2.68 (d, J=18.1 Hz, 1H), 2.42 (s, 3H), 1.70–1.39 (m, 6H).

4.6.3. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(5-methane-sulfonylpentyl)piperidine-2,6-dione ($7a_3$). Yield 61%; mp 110–112°C (hexane/ethyl acetate); IR ($CHCl_3$) 2938, 1736, 1674 cm^{-1}; HRMS (EI, M^+) calcd for $C_{25}H_{31}NO_7S_2$ 521.1543, found 521.1536; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J=8.1 Hz, 2H), 7.32–7.24 (m, 7H), 5.05 (d, J=14.0 Hz, 1H), 4.85 (d, J=14.0 Hz, 1H), 4.14 (t, J=6.3 Hz, 2H), 3.89 (br s, 1H, H-3), 3.47 (dd, J=6.1, 18.1 Hz, 1H), 3.00–2.95 (m, 1H, H-4), 2.97 (s, 3H), 2.67 (d, J=18.1 Hz, 1H), 2.42 (s, 3H), 1.70–1.33 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.33, 164.28, 145.79, 136.41, 134.48, 129.86 (2×), 128.96 (2×), 128.71 (2×), 128.37 (2×), 127.56, 70.75, 69.45, 43.35, 37.41, 34.27, 33.80, 28.80, 28.70, 26.00, 25.04, 21.76.

4.6.4. 1-[2-(3-Indolyl)ethyl]-3-(4-methylphenylsulfonyl)-4-(4-methanesulfonylbutyl)piperidine-2,6-dione ($7b_1$). Yield 61%; gum; ESI-MS: $C_{27}H_{33}N_2O_7S_2$ *m/z* (%)=154 (100), 391 (13), 460 (3), 562 (M^++1, 100); HRMS (EI, M^+) calcd for $C_{27}H_{32}N_2O_7S_2$ 561.1731, found 561.1733; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.69–7.67 (m, 3H), 7.37–7.32 (m, 3H), 7.18–7.08 (m, 2H), 7.03 (s, 1H), 4.18–4.06 (m, 4H), 3.89 (s, 1H, H-3), 3.40 (dd, J=6.0, 17.9 Hz, 1H), 3.03–2.89 (m, 2H, H-4), 2.98 (s, 3H), 2.92–2.88 (m, 1H), 2.60 (d, J=17.9 Hz, 1H), 2.46 (s, 3H), 1.61–1.56 (m, 3H), 1.38–1.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.08, 164.29, 145.92, 136.31, 135.07, 130.01 (2×), 128.97 (2×), 127.36, 122.40, 122.04, 119.45, 119.07, 112.18, 111.09, 70.67, 69.00, 40.50, 37.50, 34.18, 33.00, 28.77, 28.58, 23.20, 22.80, 21.80.

4.6.5. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(3-chloro-propyl)piperidine-2,6-dione ($8a_1$). Yield 8%; mp 114–116°C (hexane/ethyl acetate); IR ($CHCl_3$) 2938, 1729, 1683, 1333 cm^{-1}; HRMS (EI, M^+) calcd for $C_{22}H_{24}NO_4SCl$ 433.1116, found 433.1121; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=8.3 Hz, 2H), 7.33–7.24 (m, 7H), 5.07 (d, J=14.0 Hz, 1H), 4.86 (d, J=14.0 Hz, 1H), 3.89 (br s, 1H, H-3), 3.51 (dd, J=6.1, 18.1 Hz, 1H), 3.46 (t, J=6.3 Hz, 2H), 3.01–2.95 (m, 1H, H-4), 2.69 (d, J=18.1 Hz, 1H), 2.43 (s, 3H), 1.83–1.49 (m, 4H).

4.6.6. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(4-chloro-butyl)-piperidine-2,6-dione ($8a_2$). Yield 10%; mp 56–59°C (hexane/ethyl acetate); IR ($CHCl_3$) 2937, 1726, 1683, 1330 cm^{-1}; HRMS (EI, M^+) calcd for $C_{23}H_{26}NO_4SCl$ 447.1273, found 447.1280; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=8.3 Hz, 2H), 7.33–7.24 (m, 7H), 5.06 (d, J=14.0 Hz, 1H), 4.86 (d, J=14.0 Hz, 1H), 3.91 (br s, 1H, H-3), 3.50 (dd, J=6.1, 18.1 Hz, 1H), 3.44 (t, J=6.3 Hz, 2H), 3.00–2.95 (m, 1H, H-4), 2.69 (d, J=18.1 Hz, 1H), 2.42 (s, 3H), 1.70–1.40 (m, 6H).

4.6.7. 1-Benzyl-3-(4-methylphenylsulfonyl)-4-(5-chloro-pentyl)-piperidine-2,6-dione ($8a_3$). Yield 6%; mp 116–118°C (hexane/ethyl acetate); IR ($CHCl_3$) 2938, 1728, 1682,

1323 cm^{-1}; HRMS (EI, M^+) calcd for $C_{24}H_{28}NO_4SCl$ 461.1429, found 461.1433; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=8.3 Hz, 2H), 7.34–7.24 (m, 7H), 5.05 (d, J=14.0 Hz, 1H), 4.85 (d, J=14.0 Hz, 1H), 3.89 (t, J=1.5 Hz, 1H, H-3), 3.49 (dd, J=6.1, 18.1 Hz, 1H), 3.45 (t, J=6.3 Hz, 2H), 2.97–2.94 (m, 1H, H-4), 2.68 (dd, J=1.5, 18.1 Hz, 1H), 2.42 (s, 3H), 1.70–1.20 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.36, 164.31, 145.76, 136.41, 134.55, 129.85 (2×), 128.96 (2×), 128.71 (2×), 128.37 (2×), 127.56, 70.79, 44.64, 43.35, 34.28, 33.87, 32.07, 28.72, 26.32, 25.87, 21.77; The structure of chloride **8a$_3$** was also determined by single-crystal X-ray analysis: monoclinic $P2_1/c$, a=14.652(4) Å, b=14.510(5) Å, c=11.545(4) Å, β=102.78(3)°, V=2393.7(13) Å^3, Z=4, d_{calcd}=1.282 g/cm^3, $F(000)$=975.89, 2θ range 14.84–33.03.

4.7. Procedure of anionic cyclization using sodium hydride

Sodium hydride (20 mg, 0.5 mmol for **7** or 4 mg, 0.1 mmol for **8**) was added to a solution of **7a$_1$**–**7a$_2$** or **7b$_1$** (0.1 mmol) or **8a$_1$** or **8a$_2$** (0.01 mmol) in THF (10 mL). The reaction mixture was stirred at rt for 2 h. The resulting mixture was poured into water (1 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) yielded **1a$_1$**–**1a$_2$** or **1b$_1$**.

4.7.1. 2-Benzyl-7a-(4-methylphenylsulfonyl)hexahydro [2]-pyridine-1,3-dione (1a$_1$). Yield 61%; viscous oil; IR ($CHCl_3$) 2960, 1725, 1681, 1315, 758 cm^{-1}; HRMS (EI, M^+) calcd for $C_{22}H_{23}NO_4S$ 397.1349, found 397.1348; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.24 (m, 7H), 7.18 (d, J=8.3 Hz, 2H), 5.16 (d, J=14.0 Hz, 1H), 4.85 (d, J=14.0 Hz, 1H), 3.41 (dd, J=6.4, 18.1 Hz, 1H), 3.24–3.21 (m, 1H, H-4), 2.81 (dd, J=1.6, 18.1 Hz, 1H), 2.39 (s, 3H), 2.24–2.14 (m, 3H), 1.71–1.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.61, 168.02, 145.51, 136.67, 133.18, 130.09, 129.33 (2×), 128.63 (2×), 128.36 (2×), 127.45 (2×), 75.67, 43.93, 34.96, 34.76, 33.79, 31.77, 21.73, 21.03. Anal. calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83. Found: C, 66.52; H, 5.88.

4.7.2. 2-Benzyl-8a-(4-methylphenylsulfonyl)hexahydro-isoquinoline-1,3-dione (1a$_2$). Yield 58%; mp 46–48°C (hexane/ethyl acetate); IR ($CHCl_3$) 2938, 1725, 1674, 1380, 1180, 756 cm^{-1}; HRMS (EI, M^+) calcd for $C_{23}H_{25}NO_4S$ 411.1506, found 411.1514; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.15 (m, 9H), 5.25 (d, J=13.9 Hz, 1H), 4.86 (d, J=13.9 Hz, 1H), 3.76 (dd, J=6.0, 18.3 Hz, 1H), 2.80–2.77 (m, 1H, H-4), 2.56 (d, J=18.3 Hz, 1H), 2.38 (s, 3H), 1.90–1.80 (m, 2H), 1.62–1.48 (m, 3H), 1.27–1.13 (m, 2H), 0.96–0.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.10, 166.99, 145.58, 136.70, 131.48, 130.56 (3×), 129.24 (2×), 129.06 (2×), 128.29, 127.44, 72.03, 43.89, 37.64, 31.99, 31.02, 30.49, 24.06, 22.28, 21.68.

4.7.3. 2-[2-(3-Indolyl)ethyl]-8a-(4-methylphenylsulfonyl) hexa-hydroisoquinoline-1,3-dione (1b$_1$). Yield 51%; gum; ESI-MS: $C_{26}H_{29}N_2O_4S$ m/z (%)=143 (100), 464 (36), 465 (M^++1, 50); HRMS (ESI, M^++1) calcd for $C_{26}H_{29}N_2O_4S$ 465.1850, found 465.1851; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.78 (d, J=7.6 Hz, 1H), 7.61–7.57 (m, 2H), 7.37–7.30 (m, 3H), 7.19–7.10 (m, 2H), 7.06 (d, J=2.2 Hz, 1H), 4.24–4.17 (m, 2H), 3.69 (dd, J=5.9, 18.2 Hz, 1H), 3.07 (t, J=7.9 Hz, 2H), 2.76–2.73 (m, 1H, H-4), 2.52 (d, J=0.7, 18.2 Hz, 1H), 2.44 (s, 3H), 1.93–1.90 (m, 1H), 1.76–1.72 (m, 1H), 1.57–1.43 (m, 3H), 1.25–0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.00, 167.26, 145.73, 136.24, 131.99, 130.55 (2×), 129.42 (2×), 127.61, 122.44, 122.02, 119.47, 119.21, 112.59, 111.03, 76.12, 41.02, 37.55, 31.55, 31.02, 30.87, 24.02, 23.38, 22.29, 21.73.

4.8. Procedure of oxidative cyclization using pyridinium chlorochromate

A solution of **6a$_1$** or **6a$_2$** (0.1 mmol) in DCM (5 mL) was added to a mixture solution of pyridinium chlorochromate (24 mg, 0.11 mmol) and Celite (100 mg) in DCM (5 mL). After being stirred at rt for 4 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=2/1–1/1) yielded **2a$_1$** or **2a$_2$**.

4.8.1. 2-Benzyl-7-hydroxy-7a-(4-methylphenylsulfonyl)-hexa-hydro[2]pyridine-1,3-dione (2a$_1$). Yield 61%; viscous oil; HRMS (EI, M^+) calcd for $C_{22}H_{23}NO_5S$ 413.1298, found 413.1289; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51–7.43 (m, 2H), 7.37–7.19 (m, 7H), 5.12–5.00 (m, 1H), 4.88–4.82 (m, 1H), 4.61–4.43 (m, 1H), 3.38–3.23 (m, 2H), 2.74–2.69 (m, 1H), 2.41–2.38 (m, 1H), 2.38 (s, 3H), 2.16–2.00 (m, 2H), 1.52–1.46 (m, 2H).

4.8.2. 2-Benzyl-8-hydroxy-8a-(4-methylphenylsulfonyl)-hexa-hydroisoquinoline-1,3-dione (2a$_2$). Yield 58%; mp 160–163°C (hexane/ethyl acetate); HRMS (EI, M^+) calcd for $C_{23}H_{25}NO_5S$ 427.1455, found 427.1457; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J=8.1 Hz, 2H), 7.37–7.24 (m, 5H), 7.09 (d, J=8.1 Hz, 2H), 5.22 (d, J=13.9 Hz, 1H), 4.86 (d, J=13.9 Hz, 1H), 3.96 (dd, J=4.1, 11.4 Hz, 1H), 3.89 (dd, J=6.3, 18.6 Hz, 1H), 3.80 (brs, 1H), 2.74–2.69 (m, 1H, H-4), 2.55 (d, J=18.6 Hz, 1H), 2.36 (s, 3H), 1.95–1.90 (m, 1H), 1.83–1.79 (m, 1H), 1.70–1.64 (m, 1H), 1.51–1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.63, 169.80, 145.16, 136.29, 136.21, 130.14 (2×), 129.12 (2×), 128.96 (2×), 128.47 (2×), 127.72, 75.54, 72.93, 43.81, 37.03, 33.40, 32.71, 32.49, 22.42, 21.65.

4.9. Procedure of ring-closing metathesis using Grubb's catalyst

Grubbs catalyst $Cl_2(Pcy_3)_2Ru$=CHPh (7 mg, 0.009 mmol) was added to a solution of **3c$_2$** (40 mg, 0.1 mmol) in 1,2-dichloroathane (3 mL) and the reaction mixture was refluxed under nitrogen atmosphere for 3 h. The mixture was concentrated and purified by flash column chromatography (hexane/ethyl acetate=2/1–1/1) to yield **1a$_3$** as a solid (24 mg, 65%).

4.9.1. 2-Allyl-9a-(4-methylphenylsulfonyl)-4,4a,5,8,9,9a-hexa-hydrocyclohepta[*c*]pyridine-1,3-dione (1a$_3$). Mp 150–152°C (hexane/ethyl acetate); HRMS (EI, M^+) calcd for $C_{20}H_{23}NO_4S$ 373.1348, found 373.1342; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J=8.1 Hz, 2H), 7.30 (d, J=8.1 Hz, 2H), 6.06–6.00 (m, 1H), 5.90–6.80 (m, 1H), 5.51–5.45 (m, 1H), 5.34–5.19 (m, 2H), 4.41–4.39 (m, 2H),

3.52 (dd, J=13.4, 18.5 Hz, 1H), 2.78–2.70 (m, 2H), 2.59–2.54 (m, 2H), 2.43 (s, 3H), 2.51–2.43 (m, 1H), 2.34 (dd, J=5.6, 15.3 Hz, 1H), 2.20–2.14 (m, 1H), 1.57–1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.09, 168.60, 145.68, 134.61, 131.78, 130.81 (2×), 129.24 (2×), 123.82 (2×), 118.02, 71.67, 43.45, 41.28, 38.14, 31.30, 26.64, 26.04, 21.73. Single-crystal X-ray diagram: crystal of **1a$_3$** was grown by slow diffusion of ethyl acetate into a solution of **1a$_3$** in dichloromethane to yield colorless prism. The compound crystallizes in the primitive orthorhombic crystal system, space group $P2_12_12_1$ (#19), a=8.277(4) Å, b=9.891(3) Å, c=22.523(4) Å, V=1843.9(9) Å^3, Z=4, d_{calcd}=1.345 g/cm^3, F(000)=792.00, 2θ range 20 (9.0–14.2°).

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