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Synthesis and applications of sulfur-substituted *cis*-hexahydro-2-quinolinones

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ABSTRACT

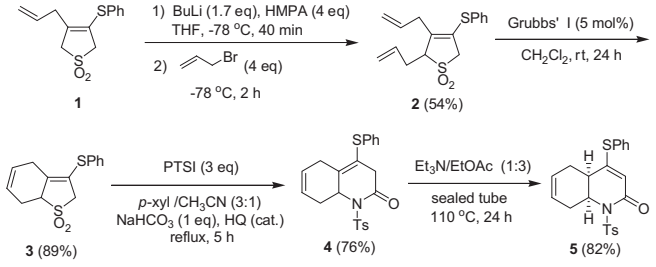
An efficient synthesis of sulfur-substituted *cis*-hexahydro-2-quinolinones has been achieved by an aza-Diels–Alder reaction of *p*-toluenesulfonyl isocyanate with a diene precursor derived from a bicyclic 3-sulfolene via ring-closing metathesis. Some synthetic tranformations have also been carried out.

1. Introduction

Quinolinone alkaloids have been isolated from various sources, and some of them show interesting biological activities.[1] The quinoline or quinolinone moieties are also important part of other more complex natural products.[2] There are many different strategies for constructing these alkaloids,[3] but we are more interested in developing a method for constructing the heretofore unknown hexahydro-2-quinolinone structures. We have previously developed a new aza-Diels–Alder reaction of thio-substituted 3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) to synthesize piperidine derivatives.[4] We have also used this method to prepare some indolizidines and quinolizidines,[5] and other heterocyclic compounds.[6] We now report our successful synthesis of sulfur-substituted hexahydro-2-quinolinones and some of their reactions.

2. Results and discussion

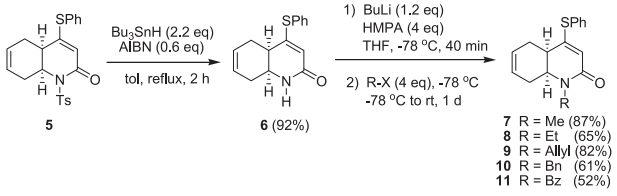
Deprotonation of 3-allyl-4-(phenylthio)-3-sulfolene (**1**)[7] in THF with BuLi at −78 °C in presence of hexamethylphosphoric amide (HMPA), followed by reaction with allyl bromide gave the bis-allyl product **2** (Scheme 1). Ring-closing metathesis of **2** with Grubbs' catalyst-I yielded the bicyclic 3-sulfolene **3**. Heating compound **3** with *p*-toluenesulfonyl isocyanate (PTSI)[2] gave the aza-Diels–Alder product **4**. Isomerization of the double bond under basic condition yielded mostly the conjugated product *cis*-**5**. The stereochemistry of compound **5** is proven by its X-ray crystal structure (Fig. 1),[8] which also shows that H_{8a} is at the axial position and H_{4a} at the



Scheme 1.

equatorial position. Using the Hyperchem AM1 method, we calculated the heat of formation for both the cis and trans isomers of compound **5**, and found that the trans isomer is more stable by 1.2 kcal/mol. Thus we propose that deprotonation of compound **4** at C-3 followed by reprotonation at C-4a occurred under kinetic control; the proton is added from the less hindered side (the same side as the H_{8a}) to give *cis*-product **5**.

Removal of the tosyl group of compound **5** with Bu_3SnH/AIBN[9] yielded the hexahydro-2-quinolinone **6**. Deprotonation by BuLi at low temperature followed by reaction with an alkyl or an acyl halide produced the *N*-substituted derivatives **7**–**11** in fair to good yields.



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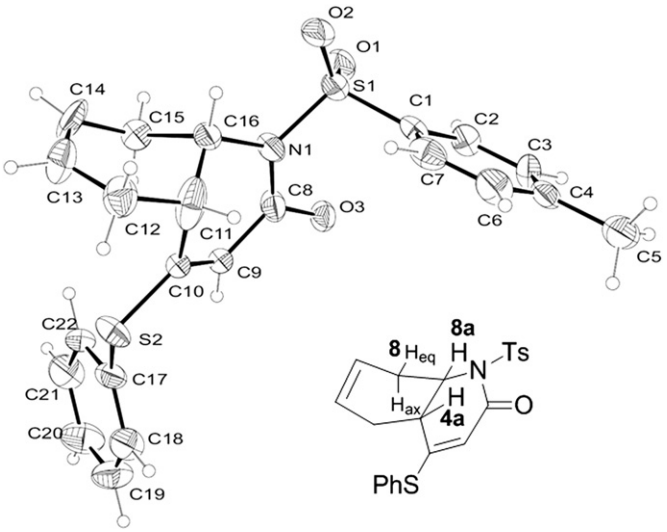


Fig. 1. X-ray crystal structure of compound **5**.

Reaction of compound **4** with NBS (1.2 equiv) in refluxing CH_3CN gave the allylic bromide **12**. Its *cis*-stereochemistry is shown by the X-ray crystal structure (Fig. 2).[8] We propose that NBS approaches from the less hindered side of compound **4** (the same side as the H_{8a}) to give the *cis*-product **12**.

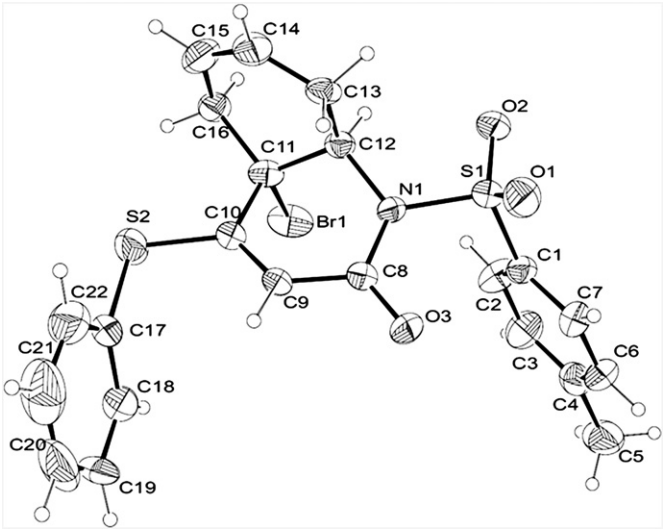
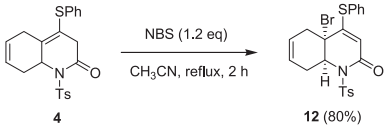
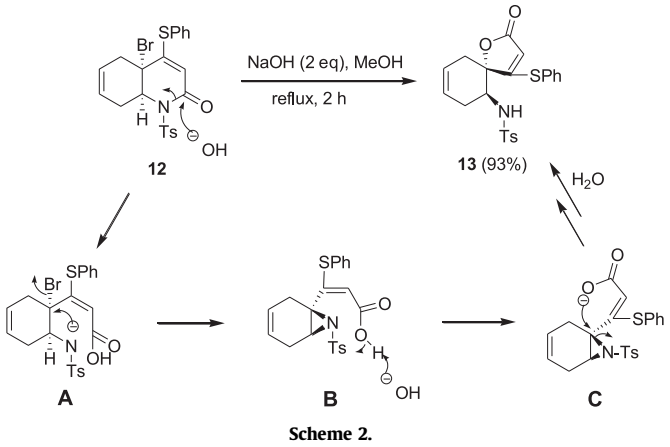


Fig. 2. X-ray crystal structure of compound **12**.



Treatment of compound **12** with NaOH/MeOH under reflux did not lead to the expected elimination product, but gave a novel spiro bicyclic lactone **13** in excellent yield (Scheme 2). The stereochemistry of compound **13** is proven by its X-ray crystal structure (Fig. 3),[8] which shows clearly that the carbon bearing the bromine atom in compound **12** was converted to the C–O bond in product **13** with retention of configuration. We propose that sodium hydroxide first attacks the amide group of compound **12** to give an amide anion **A**, which then undergoes an intramolecular cyclization to give an aziridine intermediate **B**. Deprotonation of intermediate **B** yields a carboxylate anion **C**, which attacks the aziridine from the back side. After protonation, the retention product **13** would be obtained after two inversions.



Scheme 2.

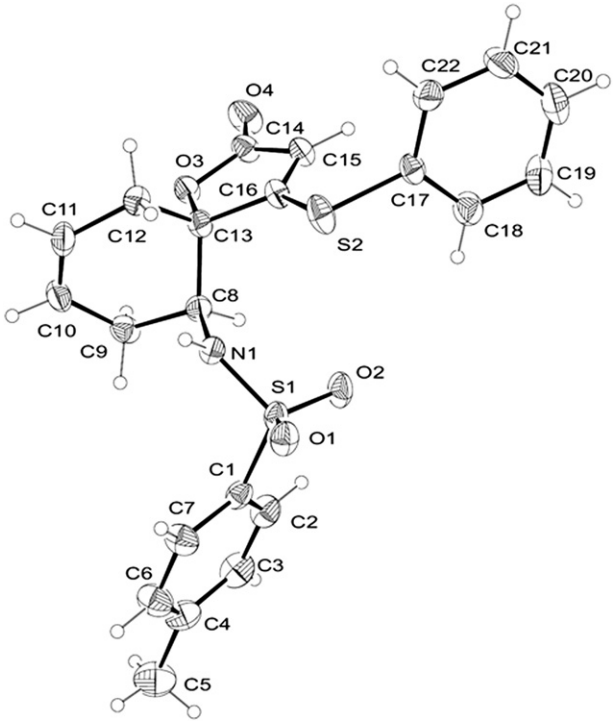


Fig. 3. X-ray crystal structure of compound **13**.

3. Conclusions

The aza-Diels–Alder reaction of *p*-toluenesulfonyl isocyanate with bicyclic 3-sulfolene **3** gave the cycloaddition product **4**, which upon isomerization of the double bond yielded the sulfur-substituted *cis*-hexahydro-2-quinolinone **5**. The tosyl group of compound **5** was efficiently cleaved by Bu_3SnH/AIBN to give the secondary amide **6**, which was readily converted to the N-substitution products **7**–**11**. Compound **4** also reacted efficiently with NBS to give the *cis*-allylic bromide **12**. The reaction of compound **12** with NaOH/MeOH provided a novel spiro bicyclic lactone **13** with complete stereospecificity in excellent yield.

4. Experimental section

4.1. General

Melting points were determined with a SMP3 melting apparatus. Infrared spectra were recorded with a Perkin–Elmer 100 series FTIR spectrometer. ^{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). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN–O–S-Rapid Analyzer or Elementar Vario EL III. Flash column chromatographic purifications were performed using Merck 60H silica gel.

*4.1.1. 2,3-Diallyl-4-(phenylthio)-3-sulfolene (**2**).* To a solution of compound **1** (1.6 g, 6.01 mmol) and HMPA (4.19 mL, 24.1 mmol) in THF (40 mL) at −78 °C under nitrogen was added dropwise a solution of BuLi (2.5 M in hexane, 4.09 mL, 10.2 mmol). After stirring at −78 °C for 40 min, allyl bromide (2.08 mL, 24.1 mmol) was added in one portion, and the reaction mixture was stirred at −78 °C for another 2 h before it was poured into saturated ammonium chloride solution. The solvent was removed by rotary evaporation, and the residue was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexanes (1:7) as eluent to give compound **2** (1.0 g, 54%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.37–7.26 (5H, m), 5.95–5.71 (2H, m), 5.29–5.17 (4H, m), 3.89 (1H, t, J=6.0 Hz), 3.63–3.56 (3H, m), 2.97 (1H, dd, J=15.0, 6.9 Hz), 2.69 (2H, t, J=6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 140.2, 132.6, 132.3, 131.5, 131.3, 129.7, 128.2, 124.7, 119.6, 118.4, 67.8, 58.0, 33.7, 32.5; FAB-MS (rel intensity) m/z 307 (M^++H, 1), 73 (52), 71 (58), 69 (83), 57 (89), 55 (100), 43 (93), 41 (83); FAB–HRMS m/z calcd for $C_{16}H_{18}O_2S_2$ $[M]^+$ 306.0748, found 306.0748.

*4.1.2. 3-(Phenylthio)-2,4,7,7a-tetrahydrobenzothiophene 1,1-dioxide (**3**).* A mixture of compound **2** (177.0 mg, 0.58 mmol) and Grubbs' I catalyst (24.0 mg, 0.029 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 24 h. The solvent was then evaporated under vacuum, and the residue was purified by flash chromatography using ethyl acetate/hexanes (1:7) as eluent to give compound **3** (144.0 mg, 89%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.37–7.28 (5H, m), 5.87–5.74 (2H, m), 3.99 (1H, t, J=6.0 Hz), 3.76 (1H, dd, J=15.9, 4.2 Hz), 3.64 (1H, d, J=15.9 Hz), 3.45 (1H, d, J=21.6 Hz), 2.95 (1H, d, J=21.6 Hz), 2.66–2.63 (2H, m); ^{13}C NMR ($CDCl_3$) δ 137.3, 131.4, 131.3, 129.7, 128.2, 124.3, 123.4, 120.5, 63.5, 58.0, 28.4, 24.6; FAB-MS (rel intensity) m/z 278 (M^++H, 21), 218 (53), 215 (56), 214 (74), 154 (66), 137 (61), 136 (100), 105 (96), 103 (99), 91 (60), 77 (62); FAB–HRMS m/z calcd for $C_{14}H_{14}S$ $[M^+-SO_2]$ 214.0816, found 214.0816.

*4.1.3. 4-(Phenylthio)-1-tosyl-3,5,8,8a-tetrahydroquinolin-2-one (**4**).* A mixture of compound **3** (445.0 mg, 1.60 mmol), $NaHCO_3$ (134.5 mg, 1.60 mmol), hydroquinone (8.8 mg, 0.08 mmol), and PTSI (0.75 mL, 4.80 mmol) in p-xylene/CH_3CN (6 mL:2 mL) was heated at reflux under nitrogen for 5 h. After cooling in an ice bath, 5% aq NaOH was slowly added to decompose the excess PTSI. The solvent CH_3CN was removed under vacuum, and the residue was purified by flash chromatography using ethyl acetate/hexanes (1:6) as eluent to give compound **4** (500.0 mg, 76%) as a white solid: mp 104–105 °C (recryst from CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.93 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 7.27–7.20 (5H, m), 5.78–5.68 (2H, m), 5.18–5.13 (1H, m), 3.80 (1H, d, J=18.9 Hz), 3.17 (1H, dt, J=16.2, 5.1 Hz), 3.07–2.96 (3H, m), 2.42–2.30 (4H, m); ^{13}C NMR ($CDCl_3$) δ 166.8, 145.1, 136.8, 136.2, 132.3, 130.9, 129.4, 129.3, 129.2, 127.6, 126.5, 124.5, 117.7, 59.1, 38.3, 37.5, 32.9, 21.7; FAB-MS (rel intensity) m/z 412 (M^++H, 35), 154 (57), 136 (80), 91 (100), 89 (53), 77 (68), 69 (64), 57 (71), 55 (89), 43 (75), 41 (74); FAB–HRMS m/z calcd for $C_{22}H_{21}NO_3S_2$ $[M]^+$ 411.0963, found 411.0961.

*4.1.4. cis-4-(Phenylthio)-1-tosyl-4a,5,8,8a-tetrahydroquinolin-2-one (**5**).* A mixture of compound **4** (500.0 mg, 1.21 mmol) in Et_3N (2 mL) and ethyl acetate (6 mL) was heated in a sealed tube at 110 °C for 24 h. The solvent was then removed under vacuum, and the residue was purified by flash chromatography using ethyl acetate/hexanes (1:5) as eluent to give, besides recovered starting material **4** (73.0 mg, 15%), product **5** (412.0 mg, 82%) as a white solid: mp 160–161 °C (recryst from CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.94 (2H, d, J=8.4 Hz), 7.43–7.36 (5H, m), 7.27 (2H, d, J=8.4 Hz), 5.78–5.64 (2H, m), 5.02 (1H, d, J=2.4 Hz), 4.95 (1H, ddd, J=10.7, 6.3, 4.8 Hz), 3.43–3.40 (1H, m), 2.83 (1H, dd, J=18.6, 4.8 Hz), 2.63 (1H, br d, J=18.6 Hz), 2.51–2.33 (5H, m); ^{13}C NMR ($CDCl_3$) δ 163.7, 160.8, 144.6, 136.8, 135.7, 130.4, 130.1, 129.2, 129.0, 127.6, 125.5, 124.5, 114.4, 54.0, 38.3, 28.1, 26.5, 21.7; FAB-MS (rel intensity) m/z 412 (M^++H, 100), 149 (45), 69 (54), 57 (58), 55 (71), 43 (49), 41 (56); FAB–HRMS m/z calcd for $C_{22}H_{21}NO_3S_2$ $[M]^+$ 411.0963, found 411.0956.

*4.1.5. cis-4-(Phenylthio)-4a,5,8,8a-tetrahydro-1H-quinolin-2-one (**6**).* To a refluxing solution of compound **5** (394.0 mg, 0.96 mmol) in degassed toluene (10 mL) was added in one portion a solution of Bu_3SnH (0.57 mmol, 2.11 mmol) and AIBN (94.3 mg, 0.57 mmol) in toluene (2 mL). The reaction mixture was refluxed for another 2 h. The solvent was then evaporated under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexanes (1:3–1:1) as eluent to give compound **6** (227.0 mg, 92%) as a white solid: mp 228–229 °C (recryst from CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.52–7.42 (5H, m), 5.83–5.80 (1H, m), 5.64–5.61 (1H, m), 5.43 (1H, br s), 5.19 (1H, d, J=0.6 Hz), 3.96 (1H, br s), 2.53–2.43 (3H, m), 2.23–2.04 (2H, m); ^{13}C NMR ($CDCl_3$) δ 166.5, 162.4, 135.4, 130.1, 130.0, 128.4, 126.7, 122.3, 113.3, 48.5, 37.7, 29.8, 27.1; EI-MS (rel intensity) m/z 257 (M^+, 10), 203 (66), 202 (100), 91 (37); EI-HRMS m/z calcd for $C_{15}H_{15}NOS$ $[M]^+$ m/z 257.0874, found 257.0872.

4.2. General procedure for the N-substitution of amide 6

To a solution of compound **6** (50.0 mg, 0.19 mmol) and HMPA (0.14 mL, 0.78 mmol) in THF (5 mL) at −78 °C under nitrogen was added dropwise a solution of BuLi (2.5 M in hexane, 0.09 mL, 0.23 mmol). After stirring at −78 °C for 40 min, the electrophile (0.78 mmol) was added in one portion, and the reaction mixture was slowly warmed to room temperature and stirred for another 24 h before it was poured into saturated ammonium chloride solution. The solvent was removed by rotary evaporation, and the residue was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexanes (1:3) as eluent to give purified products **7**–**11**.

*4.2.1. cis-1-Methyl-4-(phenylthio)-4a,5,8,8a-tetrahydroquinolin-2-one (**7**).* Yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.50–7.40 (5H, m), 5.79–5.68 (2H, m), 5.22 (1H, s), 3.71–3.65 (1H, m), 3.08–3.03 (1H, m), 2.96 (3H, s), 2.60–2.37 (4H, m); ^{13}C NMR ($CDCl_3$) δ 164.3, 157.7, 135.7, 129.95, 129.91, 128.7, 125.8 124.3, 115.5, 55.6, 37.8, 31.1, 26.7, 26.2; EI-MS (rel intensity) m/z 271 (M^+, 3), 218 (18), 217 (86), 216 (100), 184 (9), 42(8); EI-HRMS m/z calcd for $C_{16}H_{17}NOS$ $[M]^+$ 271.1031, found 271.1035.

*4.2.2. cis-1-Ethyl-4-(phenylthio)-4a,5,8,8a-tetrahydroquinolin-2-one (**8**).* Yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.51–7.38 (5H, m), 5.79–5.67 (2H, m), 5.21 (1H, d, J=1.5 Hz), 3.83 (1H, dq, J=21, 7.2 Hz), 3.74–3.68 (1H, m), 3.08–2.97 (2H, m), 2.63–2.56 (1H, m), 2.51–2.33 (3H, m), 1.14

(3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 163.5, 157.1, 135.6, 129.93, 129.88, 128.7, 125.6, 124.7, 115.9, 53.6, 38.8, 38.2, 26.9, 26.7, 14.2; EI-MS (rel intensity) m/z 285 (M^+, 4), 232 (20), 231 (100), 230 (47), 203 (52), 202 (37), 86 (27), 84 (41), 51 (14), 49 (42); EI-HRMS m/z calcd for $C_{17}H_{19}NOS$ $[M]^+$ 285.1187, found 285.1184.

*4.2.3. cis-1-Allyl-4-(phenylthio)-4a,5,8,8a-tetrahydroquinolin-2-one (**9**).* Yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.50–7.41 (5H, m), 5.85–5.67 (3H, m), 5.23–5.14 (3H, m), 4.53 (1H, dd, J=15.9, 4.8 Hz), 3.74–3.68 (1H, m), 3.53 (1H, dd, J=15.9, 6.6 Hz), 3.09–3.07 (1H, m), 2.61 (1H, br d, J=18.9 Hz), 2.50–2.42 (1H, m), 2.32 (2H, br s); ^{13}C NMR ($CDCl_3$) δ 163.5, 157.8, 135.6, 134.4, 129.9 (×2), 128.6, 125.5, 124.8, 116.8, 115.5, 53.2, 46.1, 38.0, 26.6, 26.4; EI-MS (rel intensity) m/z 297 (M^+, 19), 244 (22), 243 (100), 242 (77), 229 (15), 228 (99), 226 (12), 77 (12), 41 (13); EI-HRMS m/z calcd for $C_{18}H_{19}NOS$ $[M]^+$ 297.1187, found 297.1184.

*4.2.4. cis-1-Benzyl-4-(phenylthio)-4a,5,8,8a-tetrahydroquinolin-2-one (**10**).* Yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.57–7.25 (10H, m), 5.73–5.62 (2H, m), 5.29 (1H, d, J=1.2 Hz), 5.22 (1H, d, J=15.6 Hz), 4.03 (1H, d, J=15.6 Hz), 3.69–3.63 (1H, m), 3.05–3.03 (1H, m), 2.58 (1H, br d, J=19.5 Hz), 2.43–2.28 (2H, m), 2.20–2.14 (1H, m); ^{13}C NMR ($CDCl_3$) δ 163.8, 158.0, 138.4, 136.1, 135.7, 130.0, 128.7, 128.6, 127.7, 127.3, 125.4, 124.7, 115.3, 53.2, 47.0, 38.0, 26.6, 26.3; EI-MS (rel intensity) m/z 347 (M^+, 32), 294 (30), 293 (98), 292 (70), 187 (22), 109 (14), 105 (15), 91 (100), 77 (20), 65 (17); EI-HRMS m/z calcd for $C_{22}H_{21}NOS$ $[M]^+$ 347.1344, found 347.1339.

*4.2.5. cis-1-Benzoyl-4-(phenylthio)-4a,5,8,8a-tetrahydroquinolin-2-one (**11**).* Yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.54–7.33 (10H, m), 5.81–5.72 (2H, m), 5.18 (1H, d, J=2.1 Hz), 4.80–4.73 (1H, m), 3.47 (1H, br s), 2.87 (1H, br d, J=18.3 Hz), 2.66–2.61 (2H, m), 2.40–2.30 (1H, m); ^{13}C NMR ($CDCl_3$) δ 173.4, 165.1, 163.2, 136.4, 135.8, 131.4, 130.4, 130.2, 128.2, 128.0, 127.7, 126.2, 124.2, 115.0, 53.3, 37.9, 27.1, 26.5; EI-MS (rel intensity) m/z 361 (M^+, 18), 279 (24), 278 (12), 177 (25), 150 (12), 149 (100), 105 (88), 77 (40), 73 (37), 65 (11), 44 (27); EI-HRMS m/z calcd for $C_{22}H_{19}NO_2S$ $[M]^+$ 361.1136, found 361.1133.

*4.2.6. cis-4a-Bromo-4-(phenylthio)-1-tosyl-4a,5,8,8a-tetrahydroquinolin-2-one (**12**).* A mixture of compound **4** (220 mg, 0.53 mmol) and NBS (114.0 mg, 0.64 mmol) in CH_3CN (15 mL) was heated at reflux under nitrogen for 2 h. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexanes (1:6) as eluent to give product **12** (209.0 mg, 80%) as a yellow solid: mp 139–140 °C (recryst from CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.03 (2H, d, J=8.4 Hz), 7.46–7.36 (5H, m), 7.29 (2H, d, J=8.4 Hz), 5.78–5.72 (1H, m), 5.63–5.57 (1H, m), 5.17 (1H, dd, J=9.0, 7.2 Hz), 5.07 (1H, s), 3.48 (1H, dd, J=18.0, 5.4 Hz), 3.20 (1H, d, J=18.0 Hz), 2.89–2.80 (1H, m), 2.51–2.40 (4H, m); ^{13}C NMR ($CDCl_3$) δ 162.4, 159.2, 145.0, 135.8, 135.6, 130.6, 130.3, 129.5, 129.1, 127.0, 126.4, 124.1, 116.7, 61.5, 60.5, 38.9, 33.3, 21.7; FAB-MS (rel intensity) m/z 490 (M^++H, 7), 147 (32), 73 (100); FAB–HRMS m/z calcd for $C_{22}H_{20}{}^{79}BrNO_3S_2$ $[M]^+$ 489.0068, found 489.0073.

*4.2.7. 2-Oxo-4-(phenylthio)-10β-tosylamido-1α-oxaspiro[4.5]deca-3,7-diene (**13**).* A mixture of compound **12** (200.0 mg, 0.41 mmol) and NaOH (32.6 mg, 0.82 mmol) in methanol (10 mL) was heated at reflux under nitrogen for 2 h. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexanes (1:4) as eluent to give product **13** (232 mg, 93%) as a white solid: mp 182–183 °C (recryst from CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.76 (2H, d, J=8.4 Hz), 7.54–7.41 (5H, m), 7.33 (2H, d, J=8.4 Hz), 5.76–5.61 (2H, m), 5.12 (1H, s), 4.63 (1H, d, J=10.2 Hz), 3.71 (1H, dt, J=10.2, 5.1 Hz), 2.75–2.61 (2H, m), 2.48–2.40 (4H, m), 2.04–1.96 (1H, m); ^{13}C NMR ($CDCl_3$) δ 175.1, 169.1, 144.1, 137.5, 134.8, 130.6, 130.2, 130.0, 128.9, 127.3, 124.1, 123.7, 112.0, 86.1, 53.3, 33.5, 30.6, 21.7; FAB-MS (rel intensity) m/z 428 (M^++H, 6), 91 (61), 89 (52), 57 (60), 55 (78), 43 (82), 41 (100), 39 (77), 27 (55); FAB–HRMS m/z calcd for $C_{22}H_{21}NO_4S_2$ $[M]^+$ 427.0912, found 427.0919.

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References and notes

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