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Intramolecular isomünchnone cycloaddition approach to the antitumor agent camptothecin

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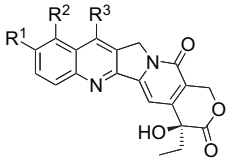
ABSTRACT

A novel, convergent approach to the antitumor agent camptothecin has been developed with a rhodium (II)-catalyzed intramolecular [3+2] cycloaddition as the key step.

1. Introduction

Camptothecin (**1**, Fig. 1) is a naturally occurring DNA topoisomerase I poison, which was first isolated from *Camptotheca acuminata* by Monroe Wall and co-workers in 1966.[1] Owing to its remarkable antiproliferative activity, this pentacyclic alkaloid has attracted enormous attention from different members of the synthetic community, particularly since the discovery by Liu and coworkers that the cytotoxicity of camptothecin is due to a novel mechanism of action that involves the ubiquitous nuclear enzyme topoisomerase I.[2] To date, two water-soluble camptothecin derivatives have gained FDA approval: Irinotecan (**2**, Camptosar)[3] to treat colorectal cancers and topotecan (**3**, Hycamtin)[4] for ovarian and small-cell lung cancers (Fig. 1).



1, $R^1 = R^2 = R^3 = H$ (Camptothecin)

2, $R^1 = OH$, $R^2 = CH_2NMe_2$, $R^3 = H$ (Topotecan)

3, $R^1 = OOCPipPip$, $R^2 = H$, $R^3 = Et$ (Irinotecan)

Fig. 1. Camptothecin and analogs.

It can be expected that additional camptothecinoids will emerge as anticancer drugs as many other analogs of **1**, such as lurtotecan (**4**), exatecan (**5**), karenitecin (**6**), and diflomotecan (**7**), are currently in clinical evaluation (Fig. 2).[5]

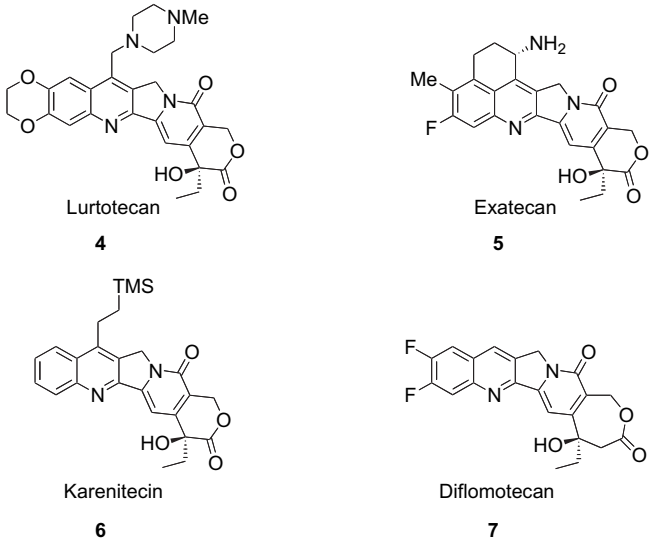


Fig. 2. Structures of lurtotecan, exatecan, karenitecin, and diflomotecan.

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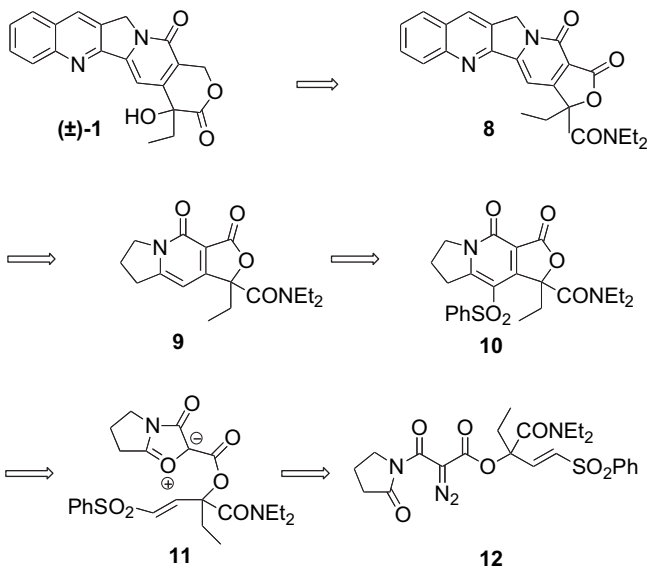
A number of elegant total syntheses of camptothecin have been reported[6] since the first success achieved by Stork and Schultz in 1971.[7] Because of the pharmacological importance of camptothecinoids and their challenging structural features, we too have been interested in developing new synthetic strategies for this important class of compounds.[8,9] Herein, a convergent approach to camptothecin, employing a novel intramolecular [3+2] isomünchnone cycloaddition, is described.

As outlined retrosynthetically in Scheme 1, the γ-lactone derivative **8** was envisaged as the direct precursor of camptothecin; a one-pot conversion of this derivative into camptothecin had earlier been described by Bristol-Myers Squibb researchers.[10] The pentacycle **8** would be formed by a Friedländer reaction,[11] employing the ketone derived by benzylic-type oxidation of pyridone **9**. This pyridone would in turn be produced from sulfone **10** by reduction. The required sulfone **10** was viewed as arising through an intramolecular [3+2] cycloaddition of the isomünchnone intermediate **11**,[12] which would be generated from the densely functionalized diazoimide **12**. It should be pointed out that the need of an EWG for this cyclization to proceed was recognized during preliminary experimentation.[13] The phenylsulfonyl group was chosen in the belief that it could be readily introduced and subsequently removed selectively.

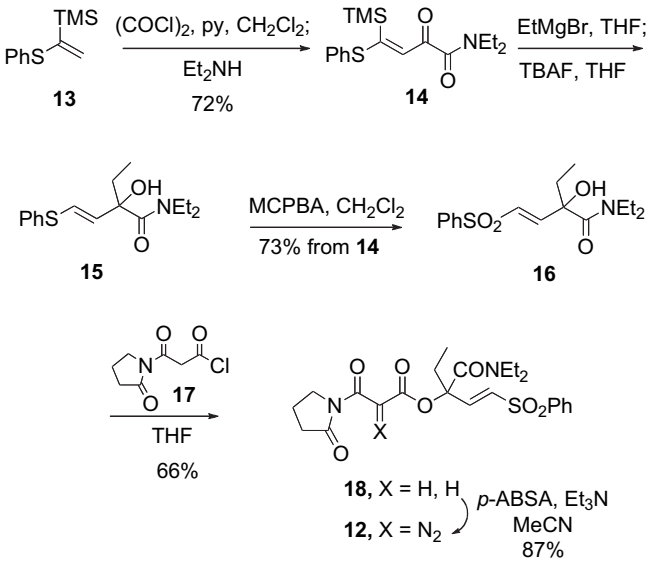


Scheme 1. Retrosynthesis of camptothecin.

2. Results and discussion

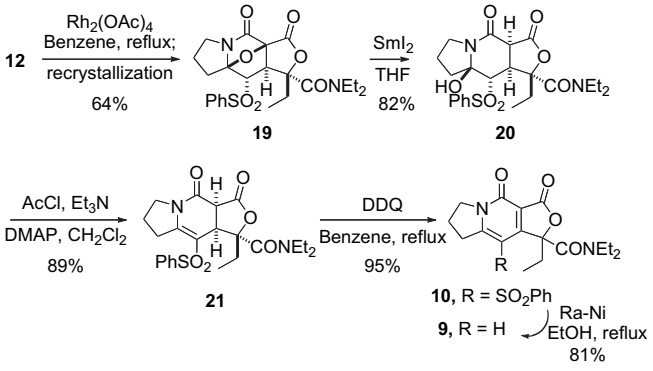
The preparation of the key substrate **12** began with the synthesis of hydroxy sulfone **16**, which was easily accessible starting from vinylsilane **13**[14] (Scheme 2). The olefin was first acylated with oxalyl chloride in the presence of pyridine, following the protocol developed by Hojo and co-workers.[15] The resulting acid chloride, without isolation, was then treated with diethylamine to provide the desired α-ketoamide **14** as a 10:1 *E*/*Z* mixture in 72% yield. The addition of ethylmagnesium bromide to **14**, followed by desilylation, produced alcohol **15**, which was oxidized with *m*-chloroperbenzoic acid to afford the desired *E*-hydroxy sulfone **16** in 73% overall yield after purification (three steps).

Hydroxy sulfone **16** was next transformed into ester **18** through acylation with acid chloride **17**, derived from the corresponding carboxylic acid (prepared from commercially available trimethylsilylpyrrolidinone and Meldrum's acid[16]). Diazo transfer using 4-acetamidobenzenesulfonyl azide (*p*-ABSA) then smoothly converted **18** into the cyclization substrate **12**. The overall yield for the six-step sequence was 30% (82%/step).



Scheme 2. Synthesis of diazoimide **12**.

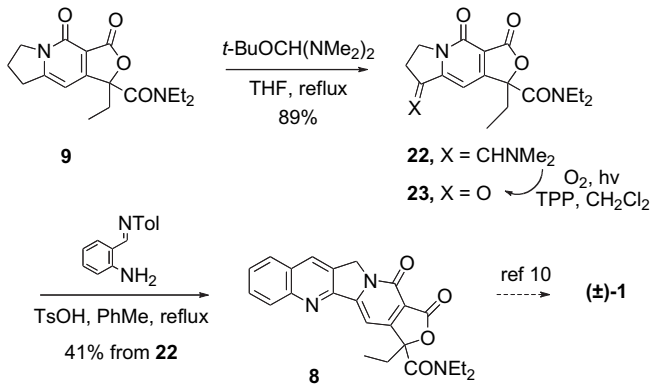
Gratifyingly, the crucial intramolecular cycloaddition of **12** proceeded smoothly in the presence of rhodium acetate in refluxing benzene to produce a 5:1 mixture of cycloadducts (Scheme 3). The major isomer **19** was easily isolated in 64% yield by recrystallization from ethyl acetate.[17] Although both diastereoisomers should meld in a subsequent intermediate, only the major isomer was advanced.



Scheme 3. Synthesis of pyridone **9**.

Conversion of piperidone **19** into pyridone **9** began with samarium (II) iodide-promoted bridge cleavage to afford **20** in high yield.[18] Dehydration of this intermediate could then be accomplished under acetylation conditions to provide in 89% yield the unsaturated sulfone **21**. Dehydrogenation of this compound in the presence of DDQ, followed by sulfone reduction with Raney-nickel in refluxing ethanol, gave pyridone **9** in 81% yield (56% from **19**).[19]

Benzylic-type oxidation of **9** to the corresponding ketone was first attempted through hydroxylation [SeO_2 or NaHMDS–O_2–$P(OEt)_3$], followed by Dess–Martin periodinane oxidation, as used with related compounds in our previous work.[8] Unfortunately, this approach proved unsuccessful. The desired Friedländer substrate **23** could be effectively secured, however, by using *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent)[20] (⟶**22**, 89%), followed by photooxygenation in the presence of tetraphenylporphine (TPP) at low temperature (Scheme 4).[20b,21,22] This SiO_2-sensitive ketone was used directly in the Friedländer condensation to afford the target quinoline **8** in 41% non-optimized yield (two steps). The spectral data for this compound were in excellent accord with those recorded in the literature.[10]



Scheme 4. Synthesis of γ-lactone **8**.

3. Conclusion

In summary, we have developed an original approach to racemic camptothecin, based on an intramolecular 1,3-dipolar cycloaddition involving a highly functionalized isomünchnone intermediate, that is relatively concise and flexible. Asymmetric ethylation of α-ketoamide **14** should be feasible,[23] which would provide access to natural camptothecin and several new derivatives. This possibility and other aspects of the approach are currently under study in our laboratory.

4. Experimental section

4.1. General

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. Reactions were monitored by TLC using silica gel $60F_{254}$ 0.2 mm-thickness plates with visualization by UV (254 nm) and through staining with a phosphomolybdic acid or $KMnO_4$ solution in EtOH. For preparative scale chromatography, silica gel 60 (0.04–0.063 mm) was used. Melting point determinations were carried out on a Büchi B-545 apparatus. IR spectra were recorded with a Nicolet iS10FT-IR spectrometer using a diamond ATR Golden Gate sampler. NMR spectra were recorded at 300 MHz or 400 MHz on Bruker spectrometers. The chemical shifts are given in parts per million (δ) and referenced to the residual solvent peak. Unless otherwise stated, $CDCl_3$ was used as the solvent. High resolution mass spectra (HRMS) were recorded on a Thermoquest Orbitrap spectrometer at the LCOSB, Université Pierre et Marie Curie, Paris.

*4.1.1. N,N-Diethyl-2-oxo-4-(phenylthio)-4-(trimethylsilyl)but-3-enamide (**14**).* Pyridine (1.68 mL, 20.8 mmol) was added to a solution of oxalyl chloride (2.72 mL, 30.7 mmol) in dichloromethane (80 mL) at 0 °C. The resulting yellow solution was stirred for 1 h, after which 1-(trimethylsilyl-1-phenylthio)ethylene[14] (4.34 g, 20.8 mmol) was added dropwise. The mixture was stirred at 20 °C for 3 days, whereupon diethylamine (10.8 mL, 103.5 mmol) was added dropwise at −60 °C. The mixture was stirred overnight and then quenched with water and extracted with ether. The combined organic phases were washed with 1 N HCl, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (pentane/ether, from 10/90 to 40/60) to give ketoamide **14** (5.06 g, 72%, 10:1 *E*/*Z* mixture) as an orange solid: IR (cm^{-1}) υ: 2971, 1635, 1502, 1477, 1439, 1249, 1084, 843; ^1H NMR (400 MHz) major isomer: δ 0.36 [s, 9H, $Si(CH_3)_3$], 1.07–1.11 [m, 6H, $CON(CH_2CH_3)_2$], 3.20 [q, 2H, J=7.2 Hz, $CON(CH_2CH_3)CH_2CH_3$], 3.30 [q, 2H, J=7.2 Hz, $CON(CH_2CH_3)CH_2CH_3$], 6.23 (s, 1H,C=CHCO), 7.40–7.50 (m, 5H, $C_{Ar}H$); ^{13}C NMR (75 MHz): δ −0.9 [$Si(CH_3)_3$], 12.6 [$CON(CH_2CH_3)CH_2CH_3$], 14.4 [$CON(CH_2CH_3)CH_2CH_3$], 39.1 [$CON(CH_2CH_3)CH_2CH_3$], 41.9 [$CON(CH_2CH_3)CH_2CH_3$], 123.7 (C=CH), 129.9 (C_{Ar}), 130.0 ($C_{Ar}H$), 134.9 ($C_{Ar}H$), 167.6 ($CONEt_2$), 173.2 (C=CH), 185.1 ($COCONEt_2$); HRMS (ESI) calcd for $C_{17}H_{25}NO_2SSiNa$: 358.1267; found: 358.1260.

*4.1.2. (±)-(E)-2-Ethyl-2-hydroxy-N,N-diethyl-4-(phenylthio)but-3-enamide (**15**).* A 1.0 M solution of ethylmagnesium bromide in THF (24.2 mL, 24.2 mmol) was added to a solution of ketoamide **14** (5.06 g, 15.1 mmol) in THF (175 mL) at −65 °C. The mixture was stirred below −30 °C for 2.5 h, after which it was quenched with a saturated aqueous solution of ammonium chloride. The crude product was isolated with ether and then treated with a solution of $TBAF\cdot 3H_2O$ (3.67 g, 14.0 mmol) in THF (25 mL). The reaction mixture was stirred under argon for 1.5 h, whereupon the solvent was removed by rotary evaporation under reduced pressure. The resulting residue was partially purified by silica gel column chromatography (ether) to provide alcohol **15** (3.75 g) as a yellow oil. An analytical sample was obtained from comparable material by a second silica gel column chromatography (pentane/ether, 90/10). IR (cm^{-1}) υ: 3360, 2974, 2933, 2876, 1622, 1461, 1439, 1378, 1344, 1264; ^1H NMR (400 MHz): δ 0.84 (t, 3H, J=7.6 Hz, CH_3CH_2), 1.09 [t, 6H, J=6.8 Hz, $CON(CH_2CH_3)_2$], 1.80 (q, 2H, J=7.6 Hz, CH_3CH_2), 3.16–3.53 [m, 4H, $CON(CH_2CH_3)_2$], 5.26 (br, 1H, OH), 5.87 (d, 1H, J=15.2 Hz, PhSCH=CH), 6.54 (d, 1H, J=15.2 Hz, PhSCH=CH), 7.15–7.35 (m, 5H, $C_{Ar}H$); ^{13}C NMR (100 MHz): δ 7.7 (CH_3CH_2), 12.4 [$CON(CH_2CH_3)CH_2CH_3$], 13.7 [$CON(CH_2CH_3)CH_2CH_3$], 31.1 (CH_3CH_2), 41.6 [$CON(CH_2CH_3)CH_2CH_3$], 42.2 [$CON(CH_2CH_3)CH_2CH_3$], 76.0 (COH), 126.5 (PhCH=CH), 127.1 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 130.2 ($C_{Ar}H$), 132.3 (PhSCH]CH), 134.2 (C_{Ar}), 172.4 ($CONEt_2$); HRMS (ESI) calcd for $C_{16}H_{23}NO_2SNa$: 316.1342; found: 316.1331.

*4.1.3. (±)-(E)-2-Ethyl-2-hydroxy-N,N-diethyl-4-(phenylsulfonyl)but-3-enamide (**16**).* *m*-CPBA (7.24 g, 70%, 29.4 mmol) was added to a solution of the above alcohol **15** in dichloromethane (120 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and then aqueous NaOH was added. The crude product was isolated with dichloromethane (150 mL) in the usual manner and purified by silica gel column chromatography (pentane/ethyl acetate, 50/50) to provide hydroxy sulfone **16** (3.58 g, 73% from **14**) as a colorless oil. IR (cm^{-1}) υ: 3440, 2977, 2920, 2851, 1625, 1442, 1312, 1141; ^1H NMR (400 MHz): δ 0.87 (t, 3H, J=7.6 Hz, CH_3CH_2), 1.06–1.26 [br, 6H, $CON(CH_2CH_3)_2$], 1.78–2.00 (m, 2H, CH_3CH_2), 3.19–3.65 [br, 4H, $CON(CH_2CH_3)_2$], 5.31 (s, 1H, OH), 6.73 (d, 1H, J=4.4 Hz, $PhSO_2CH$=CH), 7.12 (d, 1H, J=14.4 Hz, $PhSO_2CH$=CH), 7.51–7.55 (m, 2H, $C_{Ar}H$), 7.60–7.64 (m, 1H, $C_{Ar}H$), 7.84–7.87 (m, 2H, $C_{Ar}H$); ^{13}C NMR (100 MHz): δ 7.6 (CH_3CH_2), 12.5 [$CON(CH_2CH_3)CH_2CH_3$], 13.8 [$CON(CH_2CH_3)CH_2CH_3$], 29.6 (CH_3CH_2), 41.7 [$CON(CH_2CH_3)_2$], 75.8 (COH), 127.7 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 132.4 ($PhSO_2CH$=CH), 133.6 ($C_{Ar}H$), 139.9 ($C_{Ar}H$), 145.3 ($PhSO_2CH$=CH), 170.3 ($CONEt_2$); HRMS (ESI) calcd for $C_{16}H_{23}NO_4SNa$: 348.1240; found: 348.1227.

*4.1.4. (±)-(E)-3-(Diethylcarbamoyl)-1-(phenylsulfonyl)pent-1-en-3-yl 3-oxo-3-(2-oxopyrrolidin-1-yl)propanoate (**18**).* A 2.5 M solution of *n*-butyllithium in hexanes (10.5 mL, 26.3 mmol) was added to a solution of 3-oxo-3-(2-oxopyrrolidin-1-yl)propanoic acid[16] (4.58 g, 26.8 mmol) in dry THF (160 mL) at −78 °C and the resulting solution was stirred for 15 min. Oxalyl chloride (2.3 mL, 26.8 mmol) was added and the resulting yellow solution was stirred at −78 °C for 15 min and then at 0 °C for 24 h. After being stirred for 1 h at 20 °C, the reaction mixture was treated with a solution of hydroxy sulfone **16** (1.29 g, 4.0 mmol) in dry THF (10 mL) and stirred for 24 h. Water (30 mL) and then a saturated aqueous solution of sodium bicarbonate (90 mL) were added and the product was extracted with dichloromethane. The combined organic phases were washed with water, dried over

anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by sílica gel column chromatography (dichloromethane/ethyl acetate, 85/15) to give ester **18** (1.26 g, 66%) as a white solid: mp 37–38 °C; IR (cm^{-1}) υ: 2977, 2936, 1748, 1695, 1645, 1401, 1148; ^1H NMR (300 MHz): δ 0.78 (t, 3H, J=7.2 Hz, CH_3CH_2), 1.02 [t, 6H, J=6.9 Hz, $CON(CH_2CH_3)_2$], 1.93–2.15 (m, 3H, CH_3CH_2, $N_{py}CH_2CHH$), 2.33–2.64 (m, 3H, $N_{py}CH_2CHH$, $N_{py}COCH_2$), 3.10–3.51 [br, 4H, $CON(CH_2CH_3)_2$], 3.80 (t, 2H, J=7.2 Hz, $N_{py}CH_2$), 3.97 (s, 2H, $COCH_2CO$), 6.58 (d, 1H, J=15.3 Hz, $PhSO_2CH$=CH), 7.10 (d, 1H, J=15.3 Hz, $PhSO_2CH$=CH), 7.48–7.72 (m, 3H, $C_{Ar}H$), 7.80–7.97 (m, 2H, $C_{Ar}H$); ^{13}C NMR (75 MHz): δ 6.8 (CH_3CH_2), 11.7 [$CON(CH_2CH_3)CH_2CH_3$], 13.3 [$CON(CH_2CH_3)CH_2CH_3$] 16.6 (CH_3CH_2), 28.6 ($N_{py}CH_2CH_2$), 32.7 ($N_{py}CH_2CH_2CH_2$), 40.4 [$CON(CH_2CH_3)_2$], 43.3 ($COCH_2CO$), 44.9 ($N_{py}CH_2$), 84.8 (CO_2C), 127.3 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 130.6 ($PhSO_2CH$=CH), 133.4 ($C_{Ar}H$), 139.6 ($C_{Ar}H$), 142.9 ($PhSO_2CH$=CH), 164.1 (CO), 164.9 (CO), 165.4 (CO), 175.3 (CO); HRMS (ESI) calcd for $C_{23}H_{30}N_2O_7SNa$: 501.1666; found: 501.1661.

*4.1.5. (±)-(E)-3-(Diethylcarbamoyl)-1-(phenylsulfonyl)pent-1-en-3-yl 2-diazo-3-oxo-3-(2-oxopyrrolidin-1-yl)propanoate (**12**).* To a solution of ester **18** (0.970 g, 2 mmol) in acetonitrile (1.3 mL) were added triethylamine (550 μL, 3.9 mmol) and 4-acetamidobenzenesulfonyl azide (450 mg, 1.9 mmol). The reaction mixture was stirred overnight at 20 °C and then concentrated under reduced pressure. Dichloromethane (4 mL) was added and the solids were filtered and rinsed with the same solvent. The filtrate was concentrated to afford the crude product, which was purified by silica gel column chromatography (pentane/ethyl acetate, from 60/40 to 40/60) to give diazo compound **12** (820 mg, 87%) as a white solid: mp 46–47 °C; IR (cm^{-1}) υ: 3047, 2974, 2936, 2145, 1733, 1700, 1650, 1327, 1144; ^1H NMR (300 MHz): δ 0.71 (t, 3H, J=7.5 Hz, CH_3CH_2), 0.85–1.09 [br, 6H, $CON(CH_2CH_3)_2$], 1.92–2.10 (m, 3H, CH_3CH_2, $N_{py}CH_2CHH$), 2.38–2.57 (m, 3H, $N_{py}CH_2CHH$, $N_{py}COCH_2$), 3.08–3.42 [br, 4H, $CON(CH_2CH_3)_2$], 3.75 (t, 2H, J=6.9 Hz, NCH_2), 6.65 (d, 1H, J=15.3 Hz, $PhSO_2CH$=CH), 7.01 (d, 1H, J=15.3 Hz, $PhSO_2CH$=CH), 7.44–7.65 (m, 3H, $C_{Ar}H$), 7.78–7.90 (m, 2H, $C_{Ar}H$); ^{13}C NMR (75 MHz): δ 6.9 (CH_3CH_2), 11.9 [$CON(CH_2CH_3)CH_2CH_3$], 13.3 [$CON(CH_2CH_3)CH_2CH_3$], 17.5 (CH_3CH_2), 28.6 ($N_{py}CH_2CH_2$), 32.5 ($N_{py}CH_2CH_2CH_2$), 40.6 [$CON(CH_2CH_3)_2$], 46.2 ($N_{py}CH_2$), 70.1 (C]N_2), 85.3 (CO_2C), 127.5 ($C_{Ar}H$), 129.2 ($C_{Ar}H$), 131.3 $PhSO_2CH$=CH, 133.6 ($C_{Ar}H$), 139.7 (C_{Ar}), 142.6 ($PhSO_2CH$=CH), 158.7 (CO), 159.3 (CO), 165.5 (CO), 173.9 (CO); HRMS (ESI) calcd for $C_{23}H_{28}N_4O_7SNa$: 527.1571; found: 527.1565.

*4.1.6. (1SR,3aSR,8aRS,9SR,9aRS)-1-Ethyl-3a,8a-epoxy-N,N-diethyl-3,4-dioxo-9-(phenylsulfonyl) decahydrofuro[3,4-f]indolizine-1-carboxamide (**19**).* A mixture of diazo compound **12** (400 mg, 0.8 mmol) and $Rh_2(OAc)_4$ (7 mg, 0.016 mmol) was dried under high vacuum for 1 h. Dry benzene (13 mL) was then added and the mixture was refluxed for 1.5 h. After being cooled, the reaction mixture was filtered through Celite and the solids were rinsed with dichloromethane. The filtrate was concentrated under reduced pressure and the resulting solid was recrystallized from ethyl acetate to provide pure piperidone **19** (240 mg, 64%) as a white solid: mp 212–214 °C; IR (cm^{-1}) υ: 2901, 1803, 1739, 1632, 1445, 1378, 1309, 1150; ^1H NMR (400 MHz): δ 0.81 (t, 3H, J=7.6 Hz, CH_3CH_2), 1.15 [t, 3H, J=7.2 Hz, $CON(CH_2CH_3)CH_2CH_3$], 1.19 [t, 3H, J=7.2 Hz, $CON(CH_2CH_3)CH_2CH_3$], 1.81–2.03 (m, 2H, CH_3CH_2), 2.14–2.33 (m, 3H, $N_{py}CH_2CH_2$, $N_{py}CH_2CH_2CHH$), 2.97–3.05 (m, 1H, $N_{py}CH_2CH_2CHH$), 3.17–3.27 [m, 2H, $CON(CHHCH_3)CHHCH_3$], 3.39–3.53 [m, 2H, $N_{py}CHH$, $CON(CHHCH_3)CH_2CH_3$], 3.70–3.84 [m, 2H, $CON(CH_2CH_3)CHHCH_3$], 3.91 (d, 1H, J=4.4 Hz, $PhSO_2CHCH$), 4.14 (d, 1H, J=4.4 Hz, $PhSO_2CH$), 7.56 (t, 2H, J=8.0 Hz, $C_{Ar}H$), 7.67 (t, 1H, J=8.0 Hz, $C_{Ar}H$), 8.09 (d, 2H, J=8.0 Hz, $C_{Ar}H$); ^{13}C NMR (100 MHz): δ 7.9 (CH_3CH_2), 12.3 [$CON(CH_2CH_3)CH_2CH_3$], 14.4 [$CON(CH_2CH_3)CH_2CH_3$], 25.8 ($N_{py}CH_2CH_2$), 28.1 ($NCH_2CH_2CH_2$), 29.3 (CH_3CH_2), 42.2 [$CON(CH_2CH_3)CH_2CH_3$], 42.4 [$CON(CH_2CH_3)CH_2CH_3$], 44.2 ($N_{py}CH_2$), 53.8 ($PhSO_2CHCH$), 68.8 ($PhSO_2CH$), 85.3 (COCCO), 89.7 (CO_2C), 107.4 ($N_{py}CCHSO_2Ph$), 128.7 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 134.2 ($C_{Ar}H$), 138.2 (C_{Ar}), 162.5 (CO), 167.0 (CO), 168.1 (CO); HRMS (ESI) calcd for $C_{23}H_{28}N_2O_7SNa$: 499.1509; found: 499.1508.

*4.1.7. (1SR,3aSR,8aRS,9SR,9aSR)-1-Ethyl-8a-hydroxy-N,N-diethyl-3,4-dioxo-9-(phenylsulfonyl) decahydrofuro[3,4-f]indolizine-1-carboxamide (**20**).* Piperidone **19** (210 mg, 0.44 mmol) was treated with a 0.1 M solution of SmI_2 in THF (30 mL, 3 mmol) at −78 °C. The reaction mixture was stirred below −40 °C for 1.5 h, after which saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$ were added. The mixture was extracted with dichloromethane, which was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude solid was recrystallized from ethyl acetate to provide alcohol **20** (174 mg, 82%) as a white solid: mp 159–161 °C; IR (cm^{-1}) υ: 3169, 2989, 2966, 2889, 1784, 1634, 1460, 1307, 1251, 1151, 1006, 965; ^1H NMR (400 MHz, DMSO-d_6): δ 0.59 (t, 3H, J=7.2 Hz, CH_3CH_2), 0.99–1.11 [m, 6H, $CON(CH_2CH_3)_2$], 1.87–2.14 (m, 5H), 3.02–3.22 (m, 4H), 3.34–3.48 (m, 3H), 3.62–3.64 (br, 1H), 4.18 (s, 1H), 4.57–4.72 (br, 1H), 6.81 (s, 1H, OH), 7.67 (t, 2H, J=7.6 Hz, $C_{Ar}H$), 7.77 (t, 1H, J=7.6 Hz, $C_{Ar}H$), 7.91 (d, 2H, J=7.6 Hz, $C_{Ar}H$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 7.5 (CH_3CH_2), 12.2 [$CON(CH_2CH_3)CH_2CH_3$], 13.8 [$CON(CH_2CH_3)CH_2CH_3$], 20.2 ($N_{py}CH_2CH_2$), 25.6 (CH_3CH_2), 37.4 (CH_2), 40.9 (CH), 41.8 [$CON(CH_2CH_3)_2$], 44.5 ($N_{py}CH_2$), 46.8 (CH), 64.6 ($PhSO_2CH$), 88.1 ($N_{py}CCHSO_2Ph$), 89.6 (CO_2C), 128.7 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 134.3 ($C_{Ar}H$), 137.8 ($C_{Ar}H$), 161.2 (CO), 167.5 (CO), 171.3 (CO); HRMS (ESI) calcd for $C_{23}H_{30}N_2O_7SNa$: 501.1666; found: 501.1661.

*4.1.8. (1SR, 3aSR, 9aRS)-1-Ethyl-N,N-diethyl-3,4-dioxo-9-(phenylsulfonyl)-1,3,3a,4,6,7,8,9a-octahydrofuro[3,4-f]indolizine-1-carboxamide (**21**).* DMAP (59 mg, 0.48 mmol) and triethylamine (0.52 mL, 3.7 mmol) were added to a solution of alcohol **20** (49 mg, 0.102 mmol) in dichloromethane (5 mL) under argon. The resulting solution was cooled to −78 °C and acetyl chloride (0.032 mL, 0.45 mmol) was added in dichloromethane (1 mL). The reaction mixture was allowed to warm to 20 °C and stirred for 30 h, whereupon it was treated with aqueous NH_4Cl. The mixture was extracted with chloroform, which was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/ethyl acetate, 40/60) to give sulfone **21** (42 mg, 89%) as a yellow solid: dec 229–230 °C; IR (cm^{-1}) υ: 3060, 2919, 2845, 1790, 1687, 1628, 1381, 1310, 1210, 1127, 1077; ^1H NMR (400 MHz): δ 0.92 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.10–1.35 [m, 7H, CH_3CHH, $CON(CH_2CH_3)_2$], 1.93–2.05 (m, 2H, $N_{py}CH_2CH_2$), 2.35–2.47 (m, 1H, CH_3CHH), 2.70–2.82 (m, 1H, $N_{py}CH_2CH_2CHH$), 2.99–3.11 (m, 1H, $N_{py}CH_2CH_2CHH$), 3.15–3.47 [m, 4H, $CON(CH_2CH_3)_2$], 3.55–3.70 (m, 1H, $N_{py}CHH$), 3.77 (d, 1H, J=11.0 Hz, $PhSO_2CCH$), 3.80–3.90 (m, 1H, $N_{py}CHH$), 4.44 (d, 1H, J=11.0 Hz, COCHCO), 7.54–7.66 (m, 3H, $C_{Ar}H$), 8.15–8.21 (m, 2H, $C_{Ar}H$); ^{13}C NMR (100 MHz): δ 8.0 (CH_3CH_2), 12.3 [$CON(CH_2CH_3)CH_2CH_3$], 14.3 [$CON(CH_2CH_3)CH_2CH_3$], 21.0 ($N_{py}CH_2CH_2$), 27.8 (CH_3CH_2), 31.2 ($N_{py}CH_2CH_2CH_2$), 42.8 ($PhSO_2CCH$), 42.9 [$CON(CH_2CH_3)CH_2CH_3$], 43.0 [$CON(CH_2CH_3)CH_2CH_3$], 45.5 (COCHCO), 47.3 ($N_{py}CH_2$), 91.3 (CO_2C), 108.6 ($PhSO_2C$), 128.4 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 133.3 ($C_{Ar}H$), 141.5 (C_{Ar}), 153.7 ($PhSO_2CCN$), 159.7 (CO), 165.7 (CO), 167.8 (CO); HRMS (ESI) calcd for $C_{23}H_{28}N_2O_6SNa$: 483.1560; found: 483.1556.

*4.1.9. (±)-1-Ethyl-N,N-diethyl-3,4-dioxo-9-(phenylsulfonyl)-1,3,4,6,7,8-hexahydrofuro[3,4-f]indolizine-1-carboxamide (**10**).* A mixture of sulfone **21** (39 mg, 0.085 mmol) and DDQ (34 mg, 0.15 mmol) in dry benzene (4.5 mL) was heated at reflux for 7 h and then concentrated under reduced pressure. The residue was diluted with dichloromethane, which was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was

purified by silica gel column chromatography (EtOAc) to give sulfone **10** (37 mg, 95%) as a white solid: mp 110–112 °C; IR (cm^{-1}) υ: 3060, 2966, 2930, 1770, 1684, 1637, 1566, 1501, 1442, 1307, 1207, 1151, 1083; ^1H NMR (400 MHz): δ 0.79 (t, 3H, J=7.5 Hz, CH_3CH$_2$), 1.02–1.37 [m, 6H, CON(CH$_2$CH_3)$_2$], 2.09–2.29 (m, 2H, NCH$_2$CH_2), 2.43–2.55 (m, 1H, CH$_3$CHH), 2.67–2.79 (m, 1H, NCH$_2$CH$_2$CHH), 3.13–3.26 (m, 1H, CH$_3$CHH), 3.28–3.40 [m, 4H, CON(CH_2CH$_3$)$_2$], 3.40–3.53 (m, 1H, NCH$_2$CH$_2$CHH), 3.99–4.08 (m, 1H, NCHH), 4.22–4.31 (m, 1H, NCHH), 7.52–7.66 (m, 3H, C$_{Ar}H$), 8.19–8.25 (m, 2H, C$_{Ar}H$); ^{13}C NMR (100 MHz): δ 8.3 (CH_3CH$_2$), 12.3 [CON(CH$_2$CH_3)CH$_2$CH$_3$], 14.1 [CON(CH$_2$CH$_3$)CH$_2$CH_3], 20.7 (N$_{py}$CH$_2$CH_2), 28.6 (CH$_3$CH_2), 33.9 (N$_{py}$CH$_2$CH$_2$CH_2), 42.1 [CON(CH_2CH$_3$)$_2$], 49.5 (N$_{py}$CH_2), 92.5 (CO$_2$C), 112.1 (C$_{py}$), 114.5 (C$_{py}$), 128.0 (C$_{Ar}$H), 129.1 (C$_{Ar}$H), 133.7 (C$_{Ar}$H), 141.4 (C$_{Ar}$), 155.1 (C$_{py}$NCO), 161.9 (PhSO$_2$C$_{py}$C$_{py}$), 165.6 (CO), 166.1 (CO); HRMS (ESI) calcd for $C_{23}H_{26}N_2O_6SNa$: 481.1404; found: 481.1399.

*4.1.10. (±)-1-Ethyl-N,N-diethyl-3,4-dioxo-1,3,4,6,7,8-hexahydrofuro [3,4-f]indolizine-1-carboxamide (**9**).* To a solution of sulfone **10** (30 mg, 0.065 mmol) in ethanol (0.5 mL) was added Raney Nickel (~1 g). The mixture was then heated at reflux for 6 h, after which it was cooled to 20 °C and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (CH_2Cl_2/methanol, 95/5) to give pyridone **9** (17 mg, 81%). IR (cm^{-1}) υ: 3056, 2980, 2939, 2882, 1771, 1666, 1632, 1590, 1562, 1435, 1264, 1084, 1052; ^1H NMR (400 MHz): δ 0.86 (t, 3H, J=7.2 Hz, CH_3CH$_2$), 1.12 [t, 3H, J=6.9 Hz, CON(CH$_2$CH$_3$)CH$_2$CH_3], 1.22 [t, 3H, J=6.8 Hz, CON(CH$_2$CH_3)CH$_2$CH$_3$], 1.93–2.11 (m, 1H, CH$_3$CHH), 2.19–2.40 (m, 3H, CH$_3$CHH and N$_{py}$CH$_2$CH_2), 3.07–3.33 [m, 4H, CON(CH$_2$CH$_3$)CHHCH$_3$, CON(CHHCH$_3$)CH$_2$CH$_3$ and N$_{py}$CH$_2$CH$_2$CH_2], 3.41–3.55 [m, 1H, CON(CH$_2$CH$_3$)CHHCH$_3$], 3.82–3.98 [m, 1H, CON(CHHCH$_3$)CH$_2$CH$_3$], 4.10–4.30 (m, 2H, N$_{py}$CH_2), 6.69 (s, 1H, C$_{py}H$); ^{13}C NMR (100 MHz): δ 7.5 (CH_3CH$_2$), 12.4 [CON(CH_2CH$_3$)CH$_2$CH$_3$], 14.7 [CON(CH$_2$CH$_3$)CH_2CH$_3$], 21.3 (N$_{py}$CH$_2$CH_2), 31.9 (CH$_3$CH_2), 32.8 (NCH$_2$CH$_2$CH_2), 42.7 [CON(CH_2CH$_3$)$_2$] 48.8 (N$_{py}$CH_2), 88.1 (CO$_2$C), 98.5 (C$_{py}$H), 110.1 (COC$_{py}$CO), 156.4 (C$_{py}$NCO), 158.6 (C$_{py}$HC$_{py}$C$_{py}$), 166.3 (CO), 166.9 (CO), 168.3 (CO); HRMS (ESI) calcd for $C_{17}H_{22}N_2O_4Na$: 341.1472; found: 341.1461.

*4.1.11. (±)-(E)-8-[(Dimethylamino)methylene]-1-ethyl-N,N-diethyl-3,4-dioxo-1,3,4,6,7,8-hexahydrofuro[3,4-f]indolizine-1-carboxamide (**22**).* Bredereck's reagent (0.025 mL, 0.121 mmol) was added to a solution of pyridone **9** (16 mg, 0.050 mmol) in THF (0.8 mL). The reaction mixture was refluxed for 45 min and then concentrated under reduced pressure. The crude solid was triturated with ether to give enamine **22** (17 mg, 89%) as an ochre solid: mp 157–159 °C; IR (cm^{-1}) υ: 3107, 2975, 2936, 1746, 1619, 1534, 1378, 1280, 1113, 1048; ^1H NMR (400 MHz): δ 0.87 (t, 3H, J=7.3 Hz, CH_3CH$_2$), 1.12 [t, 3H, J=7.0 Hz, CON(CH$_2$CH$_3$)CH$_2$CH_3], 1.20 [t, 3H, J=6.9 Hz, CON(CH$_2$CH_3)CH$_2$CH$_3$], 1.89–2.00 (m, 1H, CH$_3$CHH), 2.24–2.38 (m, 1H, CH$_3$CHH), 3.10 [s, 6H, (CH_3)$_2$NCH=C], 3.12–3.28 [m, 4H, CON(CH$_2$CH$_3$)CHHCH$_3$, CON(CHHCH$_3$)CH$_2$CH$_3$, N$_{py}$CH$_2$CH$_2$CH_2], 3.32–3.51 [m, 1H, CON(CH$_2$CH$_3$)CHHCH$_3$], 3.74–3.89 [m, 1H, CON(CHHCH$_3$)CH$_2$CH$_3$], 4.04–4.22 (m, 2H, N$_{py}$CH_2), 6.38 (s, 1H, C$_{py}H$), 6.98 [s, 1H, (CH$_3$)$_2$NCH=C]; ^{13}C NMR (100 MHz) δ 7.7 (CH_3CH$_2$), 12.4 [CON(CH$_2$CH_3)CH$_2$CH$_3$], 14.8 [CON(CH$_2$CH$_3$)CH$_2$CH_3], 25.2 (N$_{py}$CH$_2$CH_2), 32.8 (CH$_3$CH_2), 42.4 [(CH_3)$_2$NCH=C], 42.8 [CON(CH_2CH$_3$)CH$_2$CH$_3$], 43.0 [CON(CH$_2$CH$_3$)CH$_2$CH$_3$], 46.6 (N$_{py}$CH_2), 87.6 (CO$_2$C), 89.0 (C$_{py}$H), 99.4 [(CH$_3$)$_2$NCH=C], 102.6 (COC$_{py}$CO), 143.0 [(CH$_3$)$_2$NCH=C], 157.3 (C$_{py}$NCO), 160.5 (C$_{py}$HC$_{py}$C$_{py}$), 166.4 (CO), 167.2 (CO), 167.8 (CO); HRMS (ESI) calcd for $C_{20}H_{27}N_3O_4Na$: 396.1894; found: 396.1895.

*4.1.12. (±)-3-Ethyl-N,N-diethyl-11,13-dihydro-1,13-dioxo-1H,3H-furo [3′,4′:6,7]indolizino[1,2-b]-quinoline-3-carboxamide (**8**).* A solution of enamine **22** (15 mg, 0.040 mmol) and 5,10,15,20-tetraphenylporphine (1.5 mg, 0.002 mmol) in dry dichloromethane (3 mL) at −78 °C under oxygen was irradiated with a 500-W lamp for 35 min. Evaporation of the solvent under reduced pressure gave crude ketone **23**, which was used in the next step without purification: ^1H NMR (300 MHz): δ 0.87 (t, 3H, J=7.5 Hz, CH_3CH$_2$), 1.13 [t, 3H, J=6.9 Hz, CON(CH$_2$CH_3)CH$_2$CH$_3$], 1.24 [t, 3H J=6.8 Hz, CON(CH$_2$CH$_3$)CH$_2$CH_3], 2.04–2.22 (m, 1H), 2.30–2.45 (m, 1H), 3.01 (t, 2H, J=6.9 Hz), 3.11–3.54 (m, 3H), 4.37 (t, 2H, J=6.9 Hz), 7.40 (s, 1H, C$_{py}H$).

A solution of the crude ketone **23**, (*E*)-*N*-(2-aminobenzylidene)-4-methylaniline (65 mg, 0.31 mmol), and *p*-toluenesulfonic acid monohydrate (2.1 mg, 0.01 mmol) in toluene (6 mL) was refluxed for 1 h (Dean–Stark equipped condenser). The mixture was diluted with chloroform and washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (ethyl acetate) to provide quinoline **8** (7 mg, 41%, two steps) as a yellow solid: mp 206–208 °C; IR (cm^{-1}) υ: 3066, 2971, 2936, 2877, 1761, 1675, 1628, 1592, 1540, 1431, 1372, 1216, 1160, 1051; ^1H NMR (400 MHz): δ 0.93 (t, 3H, J=7.4 Hz, CH_3CH$_2$), 1.16 [t, 3H, J=7.0 Hz, CON(CH$_2$CH$_3$)CH$_2$CH_3], 1.27 [t, 3H, J=7.0 Hz, CON(CH$_2$CH_3)CH$_2$CH$_3$], 2.18–2.31 (m, 1H, CH$_3$CHH), 2.42–2.53 (m, 1H, CH$_3$CHH), 3.15–3.38 (m, 2H), 3.46–3.55 (m, 1H), 3.91–4.00 (m, 1H), 5.33 (d, 1H, J=23 Hz, N$_{py}$CHH), 5.38 (d, 1H, J=23 Hz, N$_{py}$CHH), 7.70 (t, 1H, J=7.2 Hz, C$_{Ar}H$), 7.85 (t, 1H, J=7.2 Hz, C$_{Ar}H$), 7.88 (s, 1H, C$_{Ar}H$), 7.96 (d, 1H, J=8.0 Hz, C$_{Ar}H$), 8.24 (d, 1H, J=8.4 Hz, C$_{Ar}H$), 8.43 (s, 1H, C$_{Ar}H$); ^{13}C NMR (100 MHz): δ 8.7 (CH_3CH$_2$), 12.5 [N(CH$_2$CH_3)CH$_2$CH$_3$], 14.8 [N(CH$_2$CH$_3$)CH$_2$CH$_3$], 31.7 (CH$_3$CH_2), 42.7 [N(CH_2CH$_3$)CH$_2$CH$_3$], 42.8 [N(CH$_2$CH$_3$)CH$_2$CH$_3$], 50.3 (NCH$_2$C$_{Ar}$), 88.8 (CO$_2$C), 97.9 (C$_{py}$H), 112.3 (C$_{Ar}$), 128.1 (C$_{Ar}$H), 128.5 (C$_{Ar}$), 128.6 (C$_{Ar}$H), 129.6 (C$_{Ar}$), 130.1 (C$_{Ar}$H), 130.8 (C$_{Ar}$H), 131.2 (C$_{Ar}$H), 149.1 (C$_{Ar}$), 151.6 (C$_{Ar}$), 152.2 (C$_{Ar}$), 156.0 (C$_{Ar}$), 166.3 (CO), 166.6 (CO), 168.8 (CO); HRMS (ESI) calcd for $C_{24}H_{23}N_3O_4Na$: 440.1581; found: 440.1578.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra of all new compounds. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.017. These data include MOL files and InChIKeys of the most important compounds described in this article.

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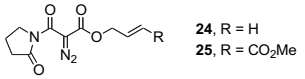

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25, R = CO_2Me

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