Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of Spiro Oxindoles, Azaoxindoles, and Dihydroisoquinolone

Sharada S. Labadie [a] & Christa Parmer [a]

[a] Department of Medicinal Chemistry, Roche Palo Alto LLC, Palo Alto, California, USA

Published online: 29 Apr 2011.

To cite this article: Sharada S. Labadie & Christa Parmer (2011): Facile Synthesis of Spiro Oxindoles, Azaoxindoles, and Dihydroisoquinolone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:12, 1742-1751

To link to this article: http://dx.doi.org/10.1080/00397911.2010.492079

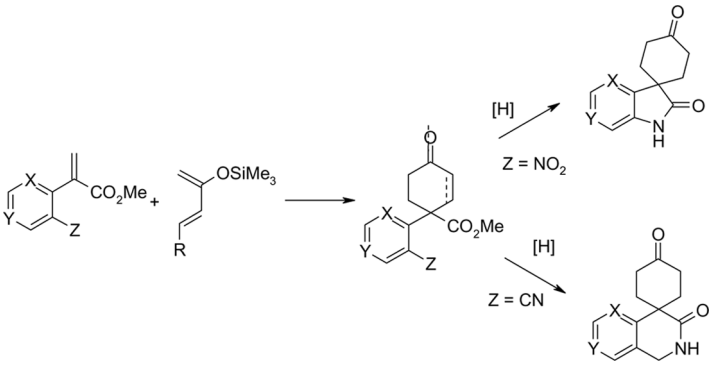
Synthetic Communications®, 41: 1742–1751, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.492079

FACILE SYNTHESIS OF SPIRO OXINDOLES, AZAOXINDOLES, AND DIHYDROISOQUINOLONE

Sharada S. Labadie and Christa Parmer
Department of Medicinal Chemistry, Roche Palo Alto LLC, Palo Alto, California, USA

GRAPHICAL ABSTRACT



Abstract *Formation of 1-aryl-4-oxo-cyclohexa(e)nonecarboxylates from the Diels–Alder cycloaddition of 2-trimethylsilyloxy-1,3-butadiene and Danishefsky diene with aryl- and pyridylacrylates and further conversion thereof to spirocycles is described. This provides an efficient method for spiro oxindoles, azaoxindoles, and dihydroisoquinolones.*

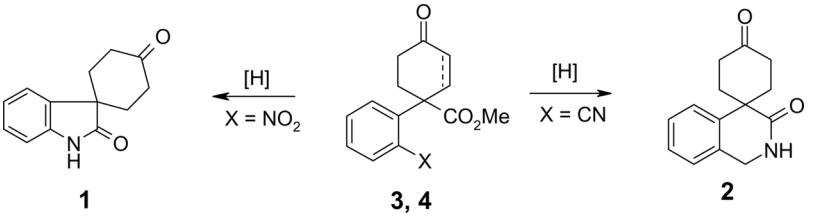
Keywords Azaoxindoles; Diels–Alder reaction; dihydroisoquinolone; spirocycles

A concise synthesis of the spirocyclic compounds **1** and **2** was required in one of our medicinal chemistry projects. A literature search revealed only a limited number of methods for the synthesis of spirocyclohexanones **1** starting from oxindoles[1] or indolones[2] or by radical cyclization of appropriately substituted benzamides.[3] These synthesis were multistep in nature, and the yields of the desired products were poor. In addition, no syntheses of the spiro-1,4-dihydro-2H-isoquinolin-3-one **2** were found.[4] It was envisioned that appropriately substituted derivatives of the cyclohexyl compounds **3** and **4** might be useful precursors of the spirocyclohexanones **1**

Received January 29, 2010.

Current name and affiliation for Christa Parmer: Christa Tatyosian, Bio-Rad Laboratories, Hercules, California, USA.

Address correspondence to Sharada S. Labadie, Genentech, MS: 18B, 1 DNA Way, So. San Francisco, CA 94080-4990, USA. E-mail: labadie.sharada@gene.com

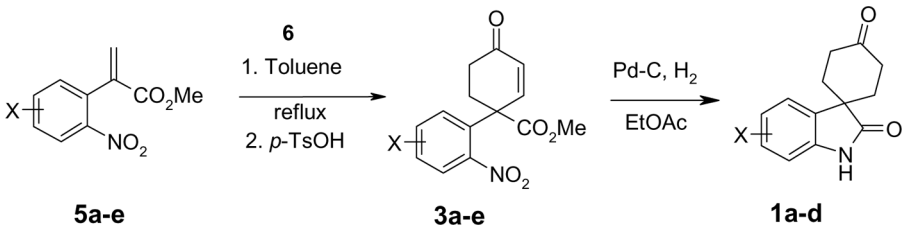


Scheme 1. Synthetic strategy for spirocycles.

and **2** and congeners thereof (Scheme 1).[5] Compounds of type **3** and **4** have been prepared by the arylation of ethyl 4-oxocyclohex-2-encarboxylates with aryllead(IV) tricarboxylates[6] and by a tandem Michael–Dieckmann condensation, followed by decarboxylation.[7] Also, the Diels–Alder reaction[8] of 2-trimethylsilyoxy-1,3-butadienes with various dienophiles is reported to generate various cyclohexyl derivatives,[9] but surprisingly this process has not been used to synthesize[10] 1-aryl-4-oxo-cyclohex-2-enone and cyclohexanonecarboxylates **3** and **4**. Herein, we describe the application of this cycloaddition reaction to the generation of various 1-aryl-4-oxo-cyclohexen-2-one and cyclohexanonecarboxylates **3** and **4** and the subsequent conversion thereof into derivatives of the spirocyclic systems **1** and **2**.

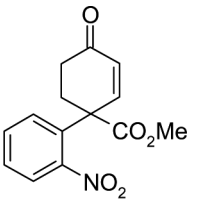
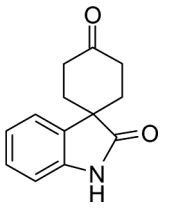
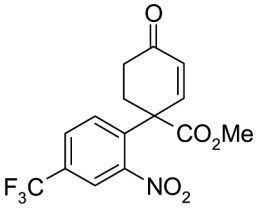
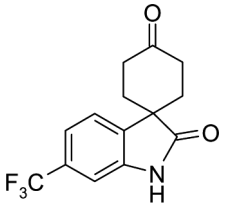
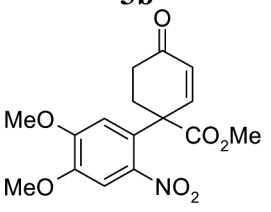
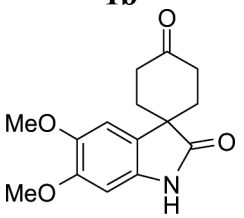
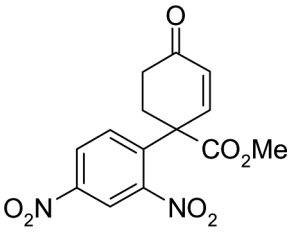
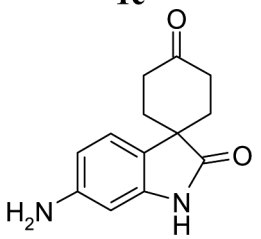
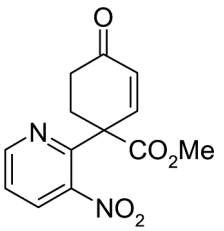
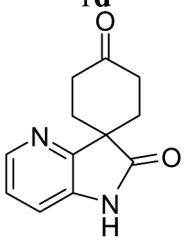
The cycloaddition of methyl 2-(2-nitrophenyl)acrylate[11] **5a** and *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene **6** (toluene/reflux/20 h), followed by the deprotection of the silyloxy intermediate (*p*-toluenesulfonic acid; Scheme 2) provided the cyclohexenone **3a** in 50% yield (entry 1, Table 1). This process also proceeded well with various substituted methyl 2-(2-nitrophenyl)acrylates and with a methyl nitropyridylacrylate to afford the corresponding cyclohexenones in good to excellent yields (entries 2–5, Table 1).

With various cyclohexenones in hand, the conversion thereof into the spirocycles was investigated. Catalytic hydrogenation of **3a** (10% Pd-C, ethyl acetate), at atmospheric pressure, proceeded uneventfully to give **1a** in 80% yield (Table 1, entry 1). The 4-trifluromethyl compound **1b** was obtained equally efficiently (entry 2). In contrast, the conversion of the 4,5-dimethoxy and 4-nitro compounds **3c** and **3d** into the desired spirocyclic oxindoles was not straightforward under these conditions. Furthermore, catalytic reduction of the pyridyl compound **3e** followed a different and unexpected reaction course. Thus, hydrogenation of the dimethoxy



Scheme 2. Synthesis of cyclohexenones and their conversion to spiro oxindoles.

Table 1. Formation of spiro oxindole via cyclohexenones as in Scheme 2

Entry	Cyclohexenone	Yield[a] (%)	Spiro oxindole	Yield[a] (%)
1	 **3a**	50	 **1a**	80
2	 **3b**	82	 **1b**	80
3	 **3c**	80	 **1c**	50[b]
4	 **3d**	92	 **1d**	—[c]
5	 **3e**	71	 **1e**	—[d]

[a]All are isolated yields and are not optimized.

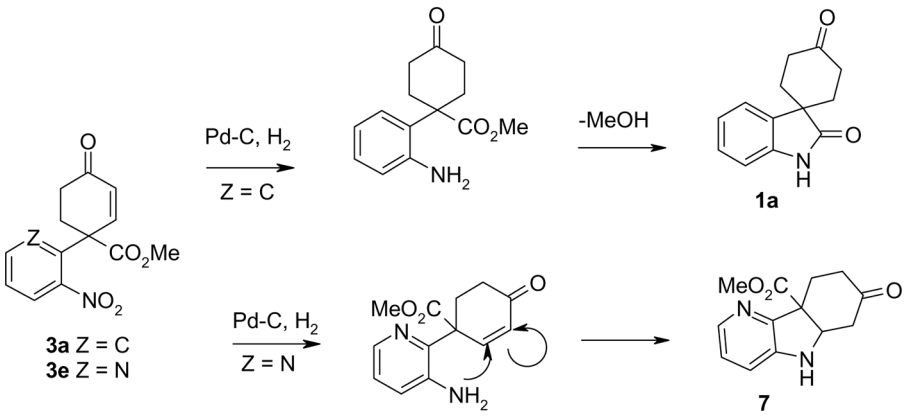
[b]Hydrogenation in the presence of Pd-C and subsequent treatment with Zn/AcOH was required for the formation of **1c**.

[c]An inseparable mixture of the desired product and a side product with 16 mass units higher was obtained.

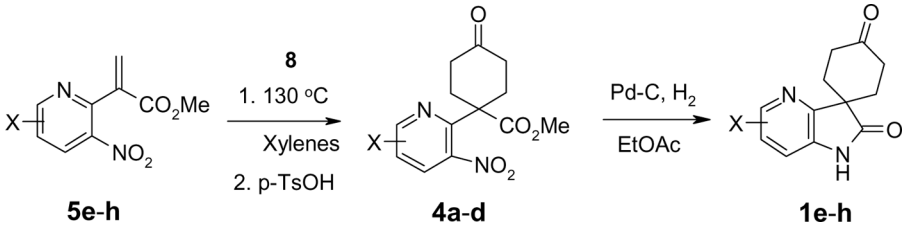
[d]None of the desired spirocycle was formed.

compound, **3c** did not go to completion, and a compound believed to be the nitroso cyclohexanone was formed. This supposition was supported by its mass spectral molecular weight and by conversion into the desired spirocycle **1c** upon further reduction with zinc in acetic acid solution. Catalytic reduction of **3d** did appear to give the desired spirocyclic compound **1d**, but it was admixed with an inseparable impurity having very similar thin-layer chromatography (TLC) polarity and a mass spectral molecular weight 16 mass units higher than that expected for **1d**. In the case of pyridyl compound **3e**, none of the expected spirocyclic compound was formed. Instead, the tricyclic compound **7**, an azahexahydrocarbazole, was formed exclusively.[12] This compound obviously was formed by Michael addition of the anilino moiety to the enone system, indicating that reduction of the enone double bond must be considerably slower than that of the nitro group. This result contrasted sharply with those obtained for compounds **3a–c** where reduction of the enone double bond must have occurred prior to that of the nitro group, resulting in the formation of the spirocyclic oxindoles **1a–c** (Scheme 3). These results suggested that reduction of nitropyridylcyclohexanones corresponding to **4a** would indeed produce the desired spirocyclic systems, and this prompted us to devise a synthesis of such compounds. The Diels–Alder reaction of the methyl nitropyridylacrylate **5e** with 2-trimethylsilyloxy-1,3-butadiene **8** (Scheme 4) produced the required cyclohexanone **4a**, palladium-catalyzed hydrogenation of which did indeed give the expected spirocycle **1e** (entry 1, Table 2). Several other pyridyl-containing cyclohexanones were also prepared and converted into the desired spirocyclic azaoxindoles (Table 2).

Finally, the Diels–Alder cycloaddition of ethyl 2-(2-cyanophenyl)acrylate **9** and *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene **6** provided ethyl 1-(2-cyanophenyl)-4-oxo-cyclohex-2-enecarboxylate **10** in 67% yield. Ethyl 2(2-cyanopheyl)acrylate was prepared by the Suzuki coupling between the 2-cyanobenzeneboronic acid and ethyl 2-bromoacrylate in 30% yield. The required conversion of the cyano moiety into the intermediate aminomethyl compound turned out to be nontrivial. Nevertheless, this transformation did occur since catalytic hydrogenation of **10** over Pd/C followed by hydrogenation over neutral Raney nickel (commercial

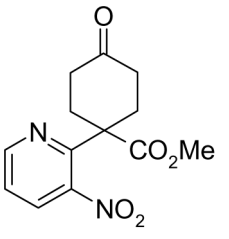
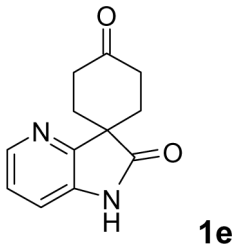
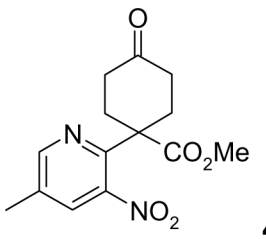
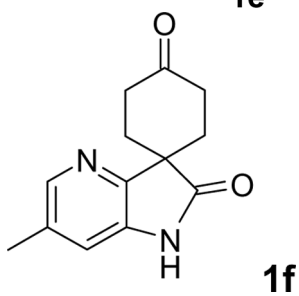
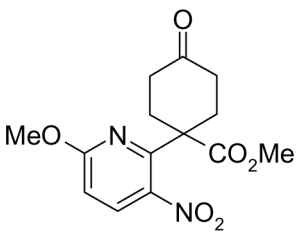
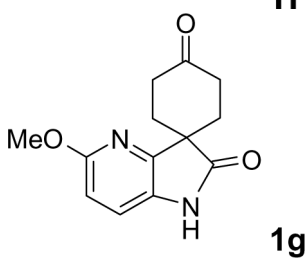
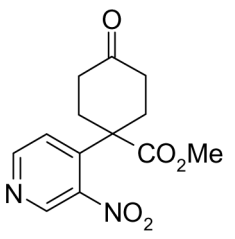
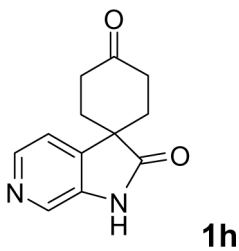


Scheme 3. Mechanism of spirocycle and hexahydrocarbazole formation.

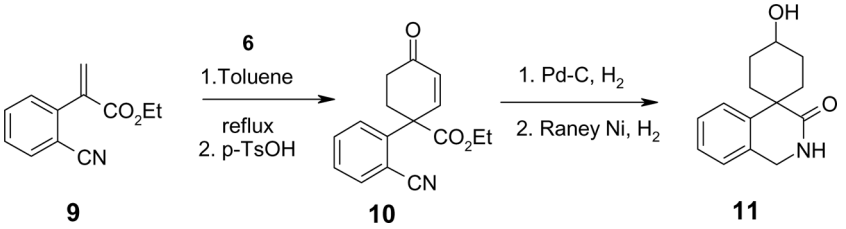


Scheme 4. Synthesis of cyclohexanones and their conversion to spiro azaoxindoles.

Table 2. Formation of spiro azaoxindoles via cyclohexanones as in Scheme 4

Entry	Cyclohexanone	Yield[a] (%)	Spiro azaoxindole	Yield[a] (%)
1	 **4a**	50	 **1e**	72
2	 **4b**	71	 **1f**	60
3	 **4c**	53	 **1g**	83
4	 **4d**	47	 **1h**	63

[a]All are isolated yields and are not optimized.



Scheme 5. Synthesis of spiro dihydroisoquinolone.

alkaline catalyst washed to neutrality with water) produced the hydroxyl compound **11** (40%, Scheme 5), resulting from overreduction. Presumably the ketone **2** could be generated by oxidation of **11**.

In summary, we have described a simple syntheses of various spirocyclic oxindole, azaoxindole, and 1,4-dihydro-2H-isoquinolin-2-one containing systems. We have also demonstrated the utility of the Diels–Alder reaction for the synthesis of various 1-aryl-4-oxo-cyclohexylcarboxylates, which are useful precursors of the aforementioned spirocyclic systems.

EXPERIMENTAL

General Procedure for the Cycloaddition of Methyl 2-(2-Nitroaryl)acrylate with *trans*-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene

Methyl 1-(2-nitrophenyl)-4-oxo-cyclohex-2-enecarboxylate 3a. A mixture of methyl 2-(2-nitrophenyl)acrylate (0.56 g, 2.7 mmol) and *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (0.89 g, 5.1 mmol) in toluene (5 mL) was heated at reflux in a sealed tube for 20 h. Solid *p*-toluenesulfonic acid monohydrate (0.07 g, 0.36 mmol) was added in one portion to the resulting pale yellow solution, and the heating was discontinued. The resulting red mixture was stirred for one 1 h and then diluted with ethyl acetate (50 mL). The resulting solution was washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 10–30% EtOAc/hexane) to obtain **3a** (0.36 g) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.07$–7.93 (m, 1 H), 7.70–7.58 (m, 1 H), 7.58–7.42 (m, 2 H), 6.87–6.74 (m, 1 H), 6.33 (d, $J = 10.2$ Hz, 1 H), 3.71 (s, 3 H), 3.36–3.17 (m, 1 H), 3.06–2.83 (m, 1 H), 2.38 (m, 2 H). Anal. calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.91; H, 4.80; N, 5.12.

The following were prepared in a similar fashion.

Methyl 1-(2-nitro-4-trifluoromethylphenyl)-4-oxocyclohex-2-enecarboxylate 3b. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.31$–8.22 (m, 1 h), 7.94–7.82 (m, 1 H), 7.70–7.57 (m, 1 H), 6.80–6.72 (m, 1 H), 6.38 (d, $J = 10.1$ Hz, 1 H), 3.72 (s, 3 H), 3.35–3.23 (m, 1 H), 3.08–2.92 (m, 1 H), 2.45–2.29 (m, 2 H). Anal. calcd. for $C_{15}H_{12}F_3NO_5$: C, 52.49; H, 3.52; N, 4.08. Found: C, 52.28; H, 3.49; N, 3.97.

Methyl 1-(4,5-dimethoxy-2-nitrophenyl)-4-oxocyclohexen-2-enecarboxylate 3c. Mp 149–150 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, DMSO-d_6)

δ = 7.74–7.64 (m, 1 H), 6.99–6.88 (m, 2 H), 6.32–6.18 (m, 1 H), 3.89 (d, J = 4.1 Hz, 6 H), 3.57 (s, 3 H), 3.01–2.88 (m, 1 H), 2.81–2.60 (m, 1 H), 2.50 (dt, J = 1.7, 3.7 Hz, 2 H). Anal. calcd. for $C_{16}H_{17}NO_7$: C, 57.31; H, 5.11; N, 4.18. Found: C, 57.29; H, 4.93; N, 4.17.

Methyl 1-(2,4-dinitrophenyl)-4-oxo-cyclohex-2-enecarboxylate 3d. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.83 (d, J = 2.6 Hz, 1 H), 8.46 (dd, J = 2.6, 8.7 Hz, 1 H), 7.72 (d, J = 8.7 Hz, 1 H), 7.26 (s, 1 H), 6.76 (d, J = 10.2 Hz, 1 H), 6.39 (d, J = 10.2 Hz, 1 H), 3.72 (s, 3 H), 3.40–3.21 (m, 1 H), 3.10–2.91 (m, 1 H), 2.48–2.32 (m, 2 H), MS (ESI): m/e = 321 (M + 1).

Methyl 1-(3-nitropyridin-2-yl)-4-oxo-cyclohexen-2-enecarboxylate 3e. ^{1}H NMR (300 MHz, Chloroform-d) δ = 8.83 (dd, J = 1.7, 4.7 Hz, 1 H), 8.34 (dd, J = 1.5, 8.3 Hz, 1 H), 7.52 (dd, J = 4.7, 8.1 Hz, 1 H), 7.05 (d, J = 10.2 Hz, 1 H), 6.22 (d, J = 10.2 Hz, 1 H), 3.73 (s, 3 H), 2.96 (d, J = 9.1 Hz, 2 H), 2.81–2.58 (m, 2 H), MS (ESI): m/z = 277 (M + 1).

Ethyl 1-(2-cyanophenyl)-4-oxo-cyclohexen-2-enecarboxylate 10. ^{1}H NMR (300 Hz, $CDCl_3$) δ = 7.75 (dd, J = 1.5, 8.3 Hz, 1 H), 7.65–7.56 (m, 1 H), 7.49–7.36 (m, 2 H), 7.07 (d, J = 10.2 Hz, 1 H), 6.33 (d, J = 10.2 Hz, 1 H), 4.32 (q, J = 7.2 Hz, 2 H), 3.11–2.97 (m, 1 H), 3.04 (s, 1 H), 2.83–2.69 (m, 1 H), 2.53–2.39 (m, 1 H), 2.34–2.20 (m, 1 H); MS (EI): m/z: 269 (M+).

General Method for the Cycloaddition with 2-Trimethylsilyloxy-1,3-butadiene 8

Methyl (3-nitro-pyridin-2-yl)-4-oxo-cyclohexanecarboxylate 4a. A mixture of methyl 2-(3-nitropyridin-2-yl)acrylate **5e** (0.8 g, 3.8 mmol) and 2-trimethylsilyloxy-1,3-butadiene **8** (1.5 g, 7.0 mmol) in xylenes (5 mL) was maintained at 130 °C in a sealed tube for 20 h. *p*-Toluenesulfonic acid monohydrate (0.1 g, 0.5 mmol) was added to the resulting pale yellow, and the heating was discontinued. The mixture was stirred for 2 h, and the red mixture was diluted with ethyl acetate (50 mL), washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 10–40% EtOAc/hexane) to obtain **4a** (0.52 g): ^{1}H NMR (300 MHz, chloroform-d) δ = 8.82 (dd, J = 1.7, 4.7 Hz, 1 H), 8.27 (dd, J = 1.7, 8.1 Hz, 1 H), 7.54–7.40 (m, 1 H), 3.70 (s, 3 H), 2.78–2.44 (m, 8 H); MS (ESI): m/z = 279 (M + 1).

The following were prepared in a similar fashion:

Methyl 1-(5-methyl-3-nitro-pyridin-2-yl)-4-oxo-cyclohexanecaboxylate 4b. Mp 86–87 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.63 (s, 1 H), 8.06 (d, J = 1.5 Hz, 1 H), 3.69 (s, 3 H), 2.72–2.47 (m, 8 H), 2.47 (s, 3 H). Anal. calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.42; H, 5.21; N, 9.56.

Methyl 1-(6-methoxy-3-nitro-pyridin-2-yl)-4-oxo-cyclohexanecaboxylate 4c. Mp 108–109 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.30 (d, J = 8.7 Hz, 1 H), 6.80 (d, J = 9.0 Hz, 1 H), 4.03 (s, 3 H), 3.70 (s, 3 H), 2.80–2.43 (m, 8 H). Anal. calcd. for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.44; H, 5.01; N, 9.04.

Methyl 1-(3-nitro-pyridin-4-yl)-4-oxo-cyclohexanecarboxylate 4d. Mp 123–125 °C (EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.06$ (s, 1 H), 8.84 (d, $J = 5.6$ Hz, 1 H), 7.56 (d, $J = 5.6$ Hz, 1 H), 3.73 (s, 3 H), 2.88–2.63 (m, 4 H), 2.47–2.21 (m, 4 H). Anal. calcd. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 55.85; H, 4.95; N, 9.96.

General Procedure for the Synthesis of Spirocyclohexanones

Spiro oxindole 1a. A mixture of **3a** (0.20 g, 0.7 mmol) and Pd-C (0.05 g) in ethyl acetate (20 mL) was hydrogenated using a balloon for 20 h. The reaction mixture was filtered through Celite, while washing with ethyl acetate, and the filtrate was concentrated in vacuo to obtain **1a** (0.13 g) as an off-white solid: mp 198–199 °C (EtOAc/hexane) [lit.[2] mp 200–201]; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.23$ (br. s., 1 H), 7.30–7.20 (m, 2 H), 7.12–7.03 (m, 1 H), 6.95 (d, $J = 7.7$ Hz, 1 H), 3.23–3.09 (m, 2 H), 2.58–2.44 (m, 2 H), 2.29–2.11 (m, 4H).

Compound 1b. Mp 232–234 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.67$ (br. s., 1 H), 7.39–7.29 (m, 2 H), 7.18–7.15 (m, 1 H), 3.25–3.11 (m, 2 H), 2.54–2.43 (m, 2 H), 2.23 (s, 4 H). Anal. calcd. for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.95. Found: C, 59.10; H, 4.13; N, 4.99.

Compound 1e. Mp 225–226 °C (EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.53$ (br. s., 1 H), 8.24 (d, $J = 3.5$ Hz, 1 H), 7.27–7.15 (m, 2 H), 3.06 (ddd, $J = 5.6$, 9.6, 15.2 Hz, 2 H), 2.76 (dt, $J = 5.9$, 15.0 Hz, 2 H), 2.34–2.24 (m, 2 H), 2.23–2.14 (m, 2 H); Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.31; H, 5.54; N, 12.81.

Compound 1f. Mp 205–207 °C (EtOAc/hexane); ^{1}H NMR (300 Hz, $CDCl_3$) $\delta = 8.38$ (br. s., 1 H), 8.06 (s, 1 H), 7.07 (s, 1 H), 3.02 (dd, $J = 5.8$, 9.6 Hz, 2 H), 2.85–2.64 (m, 2 H), 2.39 (s, 3H), 2.32–2.08 (m, 4 H). MS (ESI): $m/e = 231$ (M + 1).

Compound 1g. Mp 210–212 °C (EtOAc/hexane); ^{1}H NMR (300 Hz, $CDCl_3$) $\delta = 8.30$ (br. s., 1 H), 7.23 (d, $J = 8.7$ Hz, 1 H), 6.67 (d, $J = 8.7$ Hz, 1 H), 3.89 (s, 3 H), 3.18–3.04 (m, 2 H), 2.78–2.64 (m, 2 H), 2.36–2.24 (m, 2 H), 2.13 (m, 2 H). Anal. calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.42; H, 5.70; N, 11.43.

Compound 1h. Mp 203–205 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.88$ (br. s., 1 H), 8.42 (d, $J = 4.9$ Hz, 1 H), 8.37 (s, 1 H), 7.23 (d, $J = 4.5$ Hz, 1 H), 3.15 (ddd, $J = 6.4$, 10.0, 15.7 Hz, 2 H), 2.53 (dt, $J = 5.4$, 15.6 Hz, 2 H), 2.34–2.11 (m, 4 H). Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.53; H, 5.52; N, 12.86.

Compound 1c. A mixture of **3c** (0.20 g, 0.6 mmol) and Pd-C (0.05 g) in ethyl acetate (20 mL) was hydrogenated using a balloon for 20 h. The reaction mixture was filtered through Celite, while washing with ethyl acetate, and the filtrate was concentrated in vacuo. The residue was dissolved in dichloromethane (10 mL), and zinc (0.5 g) and acetic acid (0.5 mL) were added. The mixture was stirred for 20 h at room temperature. Zinc was removed by filtration through Celite while washing with dichloromethane. The filtrate was washed with saturated sodium bicarbonate

(20 mL) and brine, dried over sodium sulfate, and concentrated. The residue was triturated with hexane/ethyl acetate to obtain **1c** (0.08 g); mp 190–192 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.14$ (br. s., 1 H), 6.79 (s, 1 H), 6.58 (s, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.27–3.14 (m, 2 H), 2.53–2.41 (m, 2 H), 2.25–2.10 (m, 4 H). Anal. calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.44; H, 6.24; N, 5.14.

1,4-Dihydro-2H-isoquinolin-3-one 11

A mixture of **10** (0.10 g, 0.37 mmol) and Pd-C (0.02 g) in ethyl acetate (10 mL) was hydrogenated using a balloon for 20 h. The reaction mixture was filtered through Celite, while washing with ethyl acetate, and the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate (10 mL) and added to a flask containing Raney Ni (which was washed three times with 5 mL water), and the mixture was stirred for 20 h at room temperature. The catalyst was removed by filtration through Celite while washing with dichloromethane. The filtrate was concentrated in vacuo. The residue was purified by flash (silica gel, 5–10% MeOH/DCM) to obtain **11** (0.034 g): mp 192–194 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.45$–7.39 (m, 1 H), 7.34–7.20 (m, 2 H), 7.18–7.12 (m, 1 H), 6.04 (br. s., 1 H), 4.50 (d, $J = 3.4$ Hz, 1 H), 3.77–3.62 (m, 1 H), 2.29–2.16 (m, 2 H), 2.14–1.92 (m, 4 H), 1.76 (m, 2 H). MS (APCI): $m/z = 232$ (M + 1).

ACKNOWLEDGMENTS

The authors acknowledge Dr. Francisco Talamas and Dr. Josh Taygerly for their valuable input and the analytical department for providing the spectroscopic and physical data.

REFERENCES

1. (a) Venkatesan, H.; Davis, M. C.; Atlas, Y.; Snyder, J. P.; Liotta, D. C. Total synthesis of SR 121463 A, a highly potent and selective vasopressin V receptor antagonist. *J. Org. Chem.* **2001**, *66*, 3653–3661; (b) Marco, L.; Carreiras, M. C. Galanthamine, a natural product for the treatment of Alzheimer's disease. *Recent Patents CNS Drug Discov.* **2006**, *1*, 105–111.
2. Beccalli, E. M.; Clerici, F.; Gelmi, M. L. A new synthetic procedure to spiro(cyclohexane-1,3′-indolone)-2′,4-diones. *Tetrahedron* **2003**, *59*, 4615–4622.
3. (a) González-López de Turiso, F.; Curran, D. P. Radical cyclization approach to spirocyclohexadienones. *Org. Lett.* **2005**, *7*, 151–154; (b) Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. Diethylphosphine oxide (DEPO): High-yielding and facile preparation of indolones in water. *Org. Lett.* **2003**, *5*, 2971–2974.
4. (a) Barbry, D.; Sokolowski, G.; Champagne, P. A convenient synthesis of 1,4-dihydroisoquinolin-3-one. *Synth. Commun.* **2002**, *32*, 1787–1790.
5. Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. Azomethine ylide cycloaddition/reductive heterocyclization approach to oxindole alkaloids: Asymmetric synthesis of (−)-horsfiline. *J. Org. Chem.* **2001**, *66*, 8447–8453.
6. Ackland, D. J.; Pinhey, J. T. The chemistry of aryl-lead(iv) tricarboxylates: Reaction with vinylogous p-keto esters. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2689–2694.

7. Elliott, J. M.; Castro, J. L.; Chicchi, G. G.; Cooper, L. C.; Dinnell, K.; Hollingworth, G. J.; Ridgill, M. P.; Rycroft, W.; Kurtz, M. M.; Shaw, D. E.; Swain, C. J.; Tsao, K.-L.; Yang, L. 4,4-Disubstituted cyclohexylamine NK1 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1755–1758.
8. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels–Alder reaction in total synthesis. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698.
9. (a) Scott, J. P.; Hammond, D. C.; Beck, E. M.; Brands, K. l. M. J.; Davies, A. J.; Dolling, U.-H.; Kennedy, D. J. Expedient Diels–Alder assembly of 4-aryl-4-phenylsulfonylcyclohexanones. *Tetrahedron. Lett.* **2004**, *45*, 3345–3348; (b) Begue, J. P.; Bonnet-Delpon, D.; Lequeux, T.; D'Angelo, J.; Guingant, A. First direct access to angularly trifluoromethyl-substituted tricyclic compounds via a Diels–Alder reaction performed with a trialkyl olefin. *Synlett* **1992**, 146–148; (c) Bonnet-Delpon, D.; Begue, J.-P.; Lequeux, T.; Ourevitch, M. Trifluoromethylalkenes in cycloaddition reactions. *Tetrahedron* **1996**, *52*, 59–70; (d) Hamilton, C. J.; Fairlamb, A. H.; Egleston, I. M. Regiocontrolled synthesis of the macrocyclic polyamine alkaloid (±)-lunarine, a time-dependent inhibitor of trypanothione reductase. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1115–1123.
10. Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M. Jr.; Fritsch, N.; Clardy, J. Derivatives of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene for Diels–Alder reactions. *J. Am. Chem. Soc.* **1979**, *101*, 7001–7008.
11. (a) Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. A direct synthesis of 2-arylpropenoic acid esters having nitro groups in the aromatic ring: A short synthesis of (±)-coerrulescine and (±)-Horsfliline. *Tetrahedron Lett.* **2002**, *43*, 9175–9179; (b) Lange, J. H. M.; Coolen, H. K. A. C.; Van Stuivenberg, H. H.; Dijksman, J. A. R.; Herremans, A. H. J.; Ronken, E.; Keizer, H. G.; Tipker, K.; McCreary, A. C.; Veerman, W.; Wals, H. C.; Stork, B.; Verveer, P. C.; Den, H.; Arnold, P.; De Jong, N. M. J.; Adolfs, T. J. P.; Hoogendoorn, J.; Kruse, C. G. Synthesis, biological properties, and molecular modeling investigations of novel 3,4-diarylpyrazolines as potent and selective CB1 cannabinoid receptor antagonists. *J. Med. Chem.* **2004**, *47*, 627–643.
12. Labadie, S. S.; Parmer, C. Efficient synthesis of hexahydrocarbazoles. *Synth. Commun.* **2011**, *41*, 1752–1758.