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Atom Transfer Radical Cyclization of Trichloroacetamides to Electron-Rich Acceptors Using Grubbs' Catalysts: Synthesis of the Tricyclic Framework of FR901483

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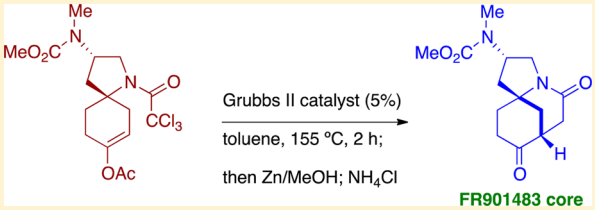
Supporting Information

ABSTRACT: Intramolecular Kharasch-type additions of trichloroacetamides on anisole and enol acetates catalyzed by Grubbs' ruthenium carbenes are described. This protocol provides access to highly functionalized 2-azaspiro[4.5]decanes, morphan compounds, and the azatricyclic core of FR901483.



Since 1999, when Snapper reported the use of Grubbs' first generation catalyst (**G-1**) as a promoter in the Kharasch intermolecular reaction of chloroform and alkenes,[1] the number of reported atom transfer radical reactions catalyzed by Grubbs' ruthenium carbene complexes has been growing. An extended version of the process has been applied intramolecularly in the synthesis of γ-lactones and γ-lactams,[2] as well as in both intra- and intermolecular tandem processes involving olefin ring-closing metathesis (RCM) and atom transfer radical processes (ATRC).[3] These two C−C bond-forming steps were also mediated by Grubbs' second generation catalyst (**G-2**) in preparative yields.[4]

The intramolecular processes reported to date are limited to substrates embodying simple alkenes as radical acceptors. This encouraged us to investigate ATRC[5] promoted by Grubbs' catalysts using substrates in which electron-rich double bonds (e.g., anisole or enol acetate substrates) act as radical acceptors. We report herein the use of a Grubbs' catalyst (**G-2**) to promote reactions of trichloroacetamides upon anisoles to afford, through a dearomative cyclization, 2-azaspiro[4.5]decane derivatives (Figure 1), whose skeleton occurs in several natural compounds,[6] as well as upon cyclic enol acetates to give morphan compounds.[7] The latter procedure was also applied to synthesize the azatricyclic framework of the immunosuppressant FR901483[8,9] by the elaboration of the bridged nucleus.

We began by examining the feasibility of applying the **G-2**-mediated ATRC to anisole derivatives bearing a trichloroacetamide handle (i.e., **1**) to achieve 1-azaspiro[4.5]decane compounds.[10,11] On the basis of our previous results in dearomatizing radical spirocyclization upon inactivated benzene promoted by Cu(I),[11d] we used the *tert*-butyl derivative **1a** as the substrate. The required trichloroacetamide **1a** was prepared through imine formation from 4-methoxybenzaldehyde and *tert*-butylamine, followed by reduction and trichloroacetylation.

Treatment of **1a** with 5% of **G-2** at 155 °C for 30 min in 0.2 mL of toluene provided **2a** in very good yield (Table 1, entry 1). The importance of having a *tert*-butyl group on the nitrogen to lock the substrate in a conformation prone to cyclization was once again evident, since the reaction with **1b** in the same conditions provided the corresponding azaspirocycle **2b** in poor yield (entry 2). Microwave activation gave the azaspirodecane derivative with a lower yield (entry 3), and switching to **G-1** or Hoveyda−Grubbs' second generation catalyst (**G-3**) did not improve the results (entries 4 and 5). When **1a** was treated overnight with 30% of CuCl at 80 °C, **2a** was also isolated in an acceptable yield (61%), although accompanied by the secondary amide **1g** ($R^1 = R^2 = H$) arising from the cleavage of the *tert*-butyl group in **1a** (entry 6).

The results of optimization studies carried out with **1a** prompted us to apply the cyclization procedure to more substituted methoxybenzenes (Table 1, entries 7 and 8). It was

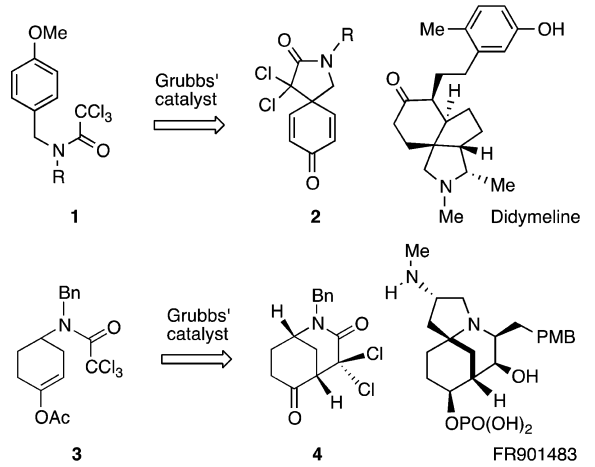


Figure 1. An approach to 2-azaspiro[4.5]decanes and 2-azabicyclo[3.3.1]nonanes by a radical cyclization using Grubbs' catalyst.

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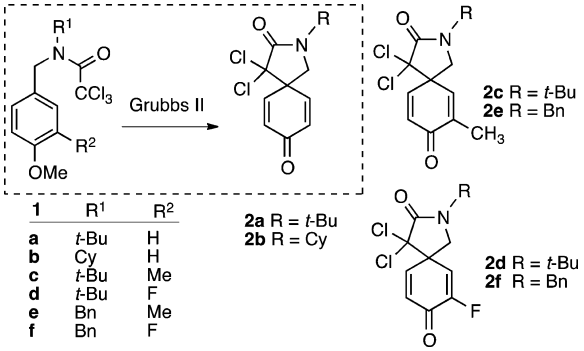
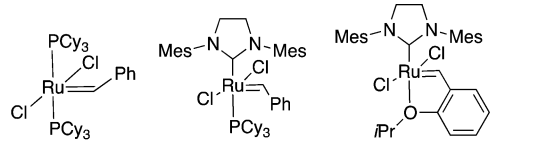
Table 1. Ruthenium(II)-Catalyzed ATRC in the Synthesis of 2-Azaspirodecanes



1	R^1	R^2
a	*t*-Bu	H
b	Cy	H
c	*t*-Bu	Me
d	*t*-Bu	F
e	Bn	Me
f	Bn	F

entry	compd	catalyst[a] (mol %)	method[b]	compd (yield %)[c]
1	**1a**	**G-2** (5)	A	**2a** (81)
2	**1b**	**G-2** (5)	A	**2b** (17)
3	**1a**	**G-2** (5)	B	**2a** (32)[d]
4	**1a**	**G-1**(5)	A	**2a** (58)[e]
5	**1a**	**G-3** (5)	A	**2a** (35)[e]
6	**1a**	CuCl (30)	C	**2a** (61)[e]
7	**1c**	**G-2** (5)	A	**2c** (72)
8	**1d**	**G-2** (5)	A	**2d** (54)
9	**1e**	**G-2** (5)	A	**2e** (52)
10	**1f**	**G-2** (5)	A	**2f** (37)

[a]



Grubbs I catalyst **G-1** | Grubbs II catalyst **G-2** | Hoveyda-Grubbs II catalyst **G-3**

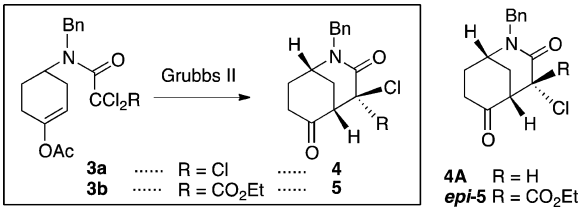
[b]A: 100 mg scale in 0.2 mL of toluene at 155 °C for 30 min. B: 200 mg scale in 1.5 mL of toluene at 120 °C for 1 h, μW. C: 200 mg scale in 2 mL of CH_3CN at 80 °C, overnight. [c]Yields refer to pure products isolated by flash chromatography. [d]**1a** was also recovered (20%). [e]The de-*tert*-butyl derivative **1g** ($R^1 = R^2 = H$) was also isolated (36%, entry 4, 21%, entry 5, 35%, entry 6).

found that the substrate **1d**, with an electron-withdrawing group (F) at the arene ring, underwent spirocyclization in lower yield than from the anisole **1c** bearing an electron-neutral group (Me). We also explored the spirocyclization using substrates embodying two aromatic rings with different electronic properties (Table 1, entries 9 and 10). In both cases the cyclization took place on the anisole ring, and once again the substrate with the higher electron density in the aromatic ring (i.e., **1e**) underwent the spirocyclization in better yield than compound **1f** bearing a fluorine atom in the aromatic ring. The lower yield in the series with a *N*-benzyl substituent (**1e**, **1f**) compared with the series with a *N*-*tert*-butyl substituent (**1a**, **1c**, **1d**) may be attributed to the mixture of rotamers (1:1 ratio) in the former.

To our knowledge, this 2-azaspiro[4.5]decadienone synthetic entry is the first reported Grubbs' catalyst-promoted dearomatizing cyclization of benzene compounds.

These promising results encouraged us to explore the Ru-catalyzed coupling of the amino-tethered trichloroacetamide and enol acetate **3a** to achieve morphan compounds.[12] Thus, **3a** was treated with **G-2** (5%) in 0.4 mL of toluene, and after 2 h of reaction at 155 °C, **4** was isolated in 61% yield, together with some starting material (Table 2, entry 1). A longer reaction time

Table 2. Ruthenium(II)-Catalyzed ATRC in Morphan Synthesis



entry	catalyst (%)	conditions[a]	yield (%)
1	**G-2** (5)	2 h, 155 °C, 0.64 M	61[b]
2	**G-2** (5)	4 h, 155 °C, 0.64 M	67
3	**G-2** (5)	30 min, 155 °C, 1.3 M	68
4	**G-2** (5)	15 min, 155 °C μW, 0.26 M	65[c]
5	**G-1** (5)	15 min, 155 °C μW, 0.26 M	52[d]
6[e]	**G-2** (5)	6 h, 155 °C, 0.23 M	50[e]

[a]Reactions on 100 mg scale in toluene. [b]12% of **3** was recovered. [c]Overall yield of a 4:1 mixture of **4** and **4A**, respectively. [d]10% of starting material was recovered. [e]Reaction from **3b** leading to a 1:1 mixture of **5** and *epi*-**5**.

was required to achieve a full conversion, providing **4** in 67% yield (entry 2), but the reaction time was shortened to 30 min by increasing the concentration in the reaction mixture to 1.5 M (entry 3). Microwave activation (entry 4) also reduced the reaction time, giving a similar result, although **4** was partially monodechlorinated to morphan **4A**,[13] and no improvement was obtained when using **G-1** (entry 5). The procedure was also applied to dichloroester **3b**, which furnished morphan **5** in 52% yield as a mixture of diastereomers at C-4 (entry 6).

In summary, to our knowledge, using this protocol to obtain morphan compounds (**3** → **4**/**5**), we have described the first intramolecular C−C bond between a trichloroacetamide and an enol acetate promoted by Grubbs' ruthenium carbenes,[14] thus expanding the scope of these catalysts beyond the metathesis reaction.[15]

With these results in hand, we investigated the potential synthetic utility of the procedure to achieve the core structure of the immunosuppressant FR901483.[8,9] The major stumbling blocks in the synthesis of this alkaloid[16] are the generation of the spirocenter at C(10a) and the assembly of the bridged framework.[17] The synthetic strategies adopted to construct the bridged framework of FR901483 from a functionalized 1-azaspiro[4.5]decanone, involving the formation of C(6)−C(7), are outlined in Scheme 1, which for the sake of clarity omits the substituents in the tricyclic framework. Almost all of the strategies developed for the synthesis of the FR901483 skeleton based on a ring closure of a 1-azaspiro[4.5]decane derivative utilize aldol processes,[16a−e,h,17g] while the other procedures are based on a palladium-promoted coupling of a vinyl halide and ketone enolate[17d,e,i,j] or a Bu_3SnH-promoted radical closure from an alkyne tethered with a trimethylsilyl enol ether.[17b]

We observed some time ago that using reductive processes to form the FR901483 skeleton,[18] such as the radical cyclization of trichloroacetamides upon silyl enol ether analogues of **A** (TMS instead of Ac, Scheme 1), gave poor results,[19] probably because the starting trichloroacetamide was reluctant to undergo the required conformational change. The energy barrier required to axially locate the trichloroacetamide unit has been evaluated to

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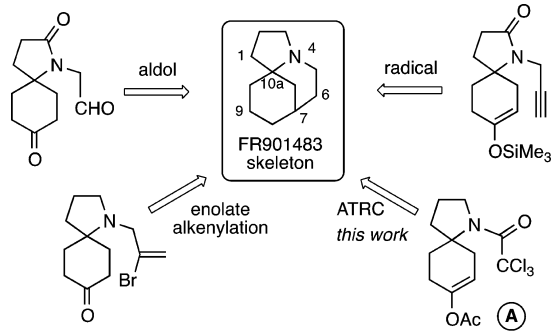
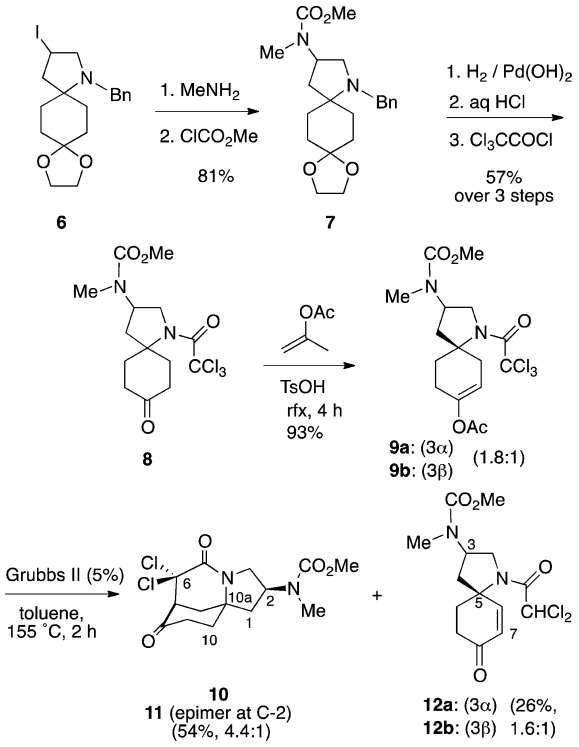
Scheme 1. Synthesis of the FR901483 Core by Piperidine Ring Closure



be approximately 3 kcal/mol in similar systems.[20] Since the process is slow, the reduction of the dichlorocarbamoylmethyl radical strongly competed with the cyclization process.

In the light of these previous results, a nonreductive process such as the ATRC studied here seemed a promising alternative to achieve the radical cyclization toward the diazatricyclic core of the natural product. The proradical trichloroacetamide required was prepared from azaspirodecane **6**,[21] via carbamate **7**,[17d] following the transformations depicted in Scheme 2, with a final

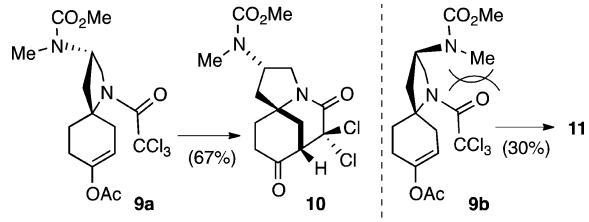
Scheme 2. Grubbs II Catalyst-Mediated ATRC Leading to the FR901483 Framework



treatment of ketone **8** with isopropenyl acetate to yield a regioisomeric mixture of enol acetates **9** in a 1.8:1 ratio. When the nonseparated mixture of **9** was treated with **G-2** at 155 °C for 2 h, the diazatricyclic derivative **10** and its epimer **11** were obtained in a 4.4:1 ratio and 54% overall yield,[22] in addition to the unexpected epimeric mixture of enones **12** (Scheme 2).

The yield for the cyclization step was 67% in the case of **9a**, but only 30% for **9b**. It is plausible that this different behavior could be due to the steric crowding of the *N*-methyl carbamate substituent with the trichloroacetyl group in the conformer required for the cyclization of **9b** to **11**. This steric effect was not present in the transition state of the cyclization leading to **10** from **9a** (Scheme 3).

Scheme 3. Steric Grounds for the ATRC of 9



The formation of enones **12** from **9** arises from a 1,5-H hydrogen transfer from the same dichlorocarbamoyl radical intermediate that gave **10** and **12a** from **9a**. The formation of **12a** again made evident that, for conformational reasons, the activation required for the radical cyclization allows competitive reaction pathways. As illustrated in Figure 2, we have

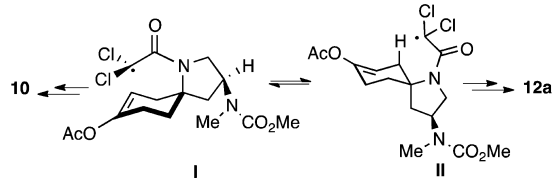


Figure 2. Competing radical pathways: cyclization versus 1,5-hydrogen atom transfer.

rationalized these observations in terms of conformers **I** and **II**. While **I** can adopt the geometry necessary for 6-*exo* cyclization to take place, **II** is unable to cyclize.[17b] However, **II** does meet the stereoelectronic requirements for a 1,5-transfer of the adjacent allylic hydrogen atom. The allylic radical thus generated undergoes an atom transfer with the pendant trichloroacetamide to form **12a**. The same pathway led to **12b** from **9b**.

The structure of **12a**, with relative configuration (3*S*,5*R*), was ascertained by chemical correlation with azaspiro **12c**,[23] which has a *N*-Boc substituent and known configuration.[24]

Treatment of **10** and **11** with zinc afforded the corresponding dechlorinated derivatives **13** and **14**, the partially reduced compound **15** also being isolated from **11**. The stereochemistry of the synthesized azatricyclic compounds was elucidated by 2D NMR spectra (COSY, HSQC, NOESY). The relative configuration (relationship between C-2 and C-10a) in both series of FR901483 skeletons was fixed by NOESY experiments. The NOESY correlation of the *N*-methyl group with the H-10eq in compound **13** indicated that this group is on the same side of the pyrrolidine ring as C-10, which occurs only when the relative configuration is (2*S*,10a*S*). This assignment for **13** established the relative configuration of its dichlorinated precursor **10**. The relative configuration (2*R*,10a*S*) for the epimeric series was confirmed in compound **15** (Figure 3), based on the correlation between H-2 and H-10eq observed in the NOESY NMR spectrum.[25] In turn, this assignment ensured the relative stereochemistry of the synthetically interrelated **11** and **14**. The ^{1}H and ^{13}C NMR spectra of azatricyclic compounds show two patterns, according to the relative configuration at C-2 versus C-10a. Hence, the isomers **10** and **13** with the chemical

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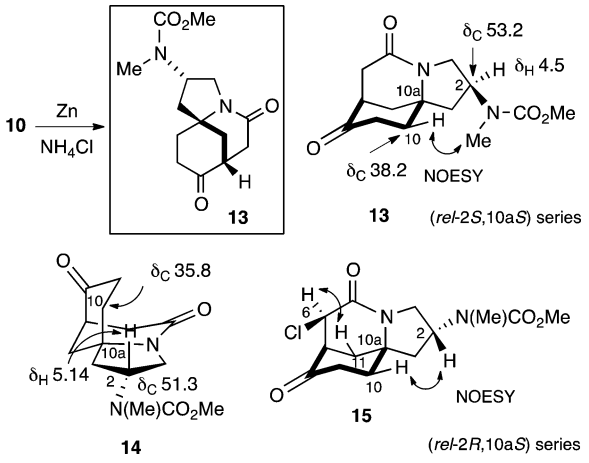

Figure 3. Representative NMR data of azatricyclic compounds **13**−**15**.

shift δ 4.55 for H-2 and δ ~53.5 for C-2 correspond to the FR901483 relative configuration, while the epimeric isomers **11**, **14**, and **15** showed a chemical shift δ ~5.15 for H-2 and δ ~51.5 for C-2. These downfield and upfield effects, compared with the data in the FR901483 stereochemistry series, are a consequence of the compression[26] of the C10−C10a bond with the H-2 in compounds with the relative configuration (2*R*,10a*S*) for the key stereogenic atoms in the azatricyclic ring.

In summary, we have reported here the first intramolecular ATRC between a trichloroacetamide and an enol acetate using Grubbs' second generation catalyst, which was applied to synthesize the morphan ring. The reaction then enabled us to build the tricyclic skeleton of the immunosuppressant FR901483. Moreover, the process was also used with electron-rich arenes for the preparation of 2-azaspirodecadienes. We have therefore described the first ATRC using Grubbs II catalyst on substituted electron-rich double bonds as radical acceptors.

EXPERIMENTAL SECTION

General. All product mixtures were analyzed by thin layer chromatography using TLC silica gel plates with a fluorescent indicator (λ = 254 nm). The spots were located by UV light or a 1% $KMnO_4$ aqueous solution. Unless otherwise noted, chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, 200−500 mesh). Drying of the organic extracts during the reaction workup was performed over anhydrous Na_2SO_4. A CEM Discover microwave reactor with an external sensor was used. Infrared spectra were recorded on a FT-IR spectrometer. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. All NMR data assignments are supported by gCOSY and gHSQC experiments.

***N*-(*tert*-Butyl)-2,2,2-trichloro-*N*-(4-methoxybenzyl)acetamide (1a).** From 4-methoxybenzaldehyde (2 g, 14.7 mmol) and *tert*-butylamine (1.75 g, 23.9 mmol), following the three-step procedure previously described,[11d] **1a** was obtained as a white solid (4.43 g, 85%): mp 68−70 °C; IR (film) 2998, 2968, 2934, 2835, 1714, 1683, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H, CH_3), 3.81 (s, 3H, OCH_3), 4.98 (br s, 2H, CH_2Ar), 6.88 (d, J = 8.4 Hz, 2H, ArH), 7.19 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1 (CH_3), 50.5 (CH_2Ar), 55.3 (OCH_3), 61.8 (C), 95.5 (CCl_3), 113.8 (*m*-C), 127.7 (*ipso*-C), 130.4 (*o*-C), 158.7 (*p*-C), 160.8 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{19}Cl_3NO_2$ 338.0476; found 338.0484.

2,2,2-Trichloro-*N*-cyclohexyl-*N*-(4-methoxybenzyl)acetamide (1b). Operating as above, **1b** was obtained from 4-methoxybenzaldehyde (4 g, 29.4 mmol) and cyclohexylamine (3.5 g, 35.29 mmol) as a white solid (9.73 g, 91% over three steps): mp 109−110 °C; IR (film) 3004, 2935, 2855, 1673, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (m, 1H), 1.32 (m, 2H), 1.51 (m, 2H), 1.66 (d, J = 13.2 Hz, 1H), 1.81 (d, 2H), 1.90 (d, J = 11.2 Hz, 2H), 3.78 (s, 3H), 4.44 (t, J = 11.4 Hz, 1H), 4.53 (s, 2H), 6.84 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (CH_2), 25.6 (CH_2), 31.0 (CH_2), 47.3 (CH_2), 55.2 (CH_3), 59.3 (CH), 93.9 (C), 113.8 (CH), 127.8 (C), 129.7 (CH), 158.5 (CH), 160.6 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{21}Cl_3NO_2$ 364.0632; found 364.0642.

***N*-*tert*-Butyl-2,2,2-trichloro-*N*-(4-methoxy-3-methylbenzyl)-acetamide (1c).** Operating as above, from 4-methoxy-3-methylbenzaldehyde (2 g, 13.3 mmol) and *tert*-butylamine (1.85 mL, 17.3 mmol), **1c** was obtained (1.90 g, 40% over three steps) after chromatography (hexane/CH_2Cl_2 3:1 to CH_2Cl_2) as an amorphous solid: mp 113−114 °C; IR (KBr) 3014, 2955, 2926, 2837, 1678, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 2.21 (s, 3H), 3.82 (s, 3H), 4.95 (br s, 2H), 6.78 (d, J = 8.4 Hz, 1H), 7.01 (br s, 1H), 7.06 (dd, J = 8.4, 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (CH_3), 28.0 (CH_3), 50.5 (CH_2), 55.3 (CH_3), 61.7 (C), 95.4 (C), 109.6 (CH), 124.9 (CH), 126.6 (C), 128.7 (CH), 129.8 (C), 156.8 (C), 160.7 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{20}Cl_3NNaO_2$ 374.0452; found 374.0457.

***N*-*tert*-Butyl-2,2,2-trichloro-*N*-(3-fluoro-4-methoxybenzyl)-acetamide (1d).** Operating as above, from 3-fluoro-4-methoxybenzaldehyde (0.5 g, 3.24 mmol) and *tert*-butylamine (0.45 mL, 4.21 mmol), **1c** was obtained (0.72 g, 63%) after chromatography (hexane/CH_2Cl_2 3:1 to CH_2Cl_2) as an amorphous solid: mp 131−132 °C; IR (KBr) 3007, 2975, 2938, 2845, 1663, 1628 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.89 (s, 3H), 4.96 (br s, 2H), 6.91−7.04 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1 (CH_3), 50.1 (CH_2), 56.3 (CH_3), 61.9 (C), 95.2 (C), 113.3 (d, J = 2.3 Hz, CH), 114.4 (d, J = 19.3 Hz, CH), 122.11 (d, J = 3.9 Hz, CH), 131.5 (d, J = 5.4 Hz, C), 146.7 (d, J = 10.1 Hz, C), 152.3 (d, J = 245.4 Hz, CF), 160.7 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{17}Cl_3FNNaO_2$ 378.0201; found 378.0205.

***N*-Benzyl-2,2,2-trichloro-*N*-(4-methoxy-3-methylbenzyl)-acetamide (1e).** Operating as above, from 4-methoxy-3-methylbenzaldehyde (2 g, 13.3 mmol) and benzylamine (1.9 mL, 17.3 mmol), **1e** was obtained (4.6 g, 89% over three steps) after chromatography (hexane/CH_2Cl_2 1:1 to CH_2Cl_2) as a yellow oil: IR (film) 3063, 3029, 3003, 2948, 2835, 1680, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 2 rotamers δ 2.18 and 2.21 (2s, 3H), 3.80 and 3.82 (2s, 3H), 4.49 and 4.55 (2s, 2H), 4.81 and 4.88 (2s, 2H), 6.70−7.42 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (CH_3), 49.6 and 49.8 (CH_2), 51.6 (CH_2), 55.2 (CH_3), 93.3 (C), 109.9 (CH), 125.8 (CH), 126.2 (C), 126.8 (CH), 126.9 (C),127.1 (CH), 127.6 (CH), 127.8 (CH), 127.9 (CH), 128.7 (CH), 128.8 (CH), 129.5 (CH), 130.6 (CH), 135.1 and 135.7 (C), 157.4 (C), 161.1 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{19}Cl_3NO_2$ 386.0476; found 386.0475.

***N*-Benzyl-2,2,2-trichloro-*N*-(3-fluoro-4-methoxybenzyl)acetamide (1f).** Operating as above, from 3-fluoro-4-methoxybenzaldehyde (0.5 g, 3.24 mmol) and benzylamine (0.46 mL, 4.21 mmol), **1f** (1.18 g, 93%) was obtained after chromatography (hexane/CH_2Cl_2 1:1 to CH_2Cl_2) as a yellow oil: IR (film) 3065, 3031, 2935, 2839, 1678, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 2 rotamers δ 3.87 (s, 3H), 4.47 and 4.55 (2s, 2H), 4.81 and 4.90 (2s, 2H), 6.92 (m, 3H), 7.12−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 49.3 and 49.9 (CH_2), 51.0 and 52.0 (CH_2), 56.1 (CH_3), 93.0 (C), 113.4 (CH), 115.0 (d, J = 18.6 Hz, CH), 116.0 (d, J = 18.6 Hz, CH), 123.2 (CH), 124.2 (CH), 127.3 (CH), 128.1 (CH), 128.9 (CH), 134.7 (C), 135.3 (C), 147.2 (d, J = 10.1 Hz, C), 152.2 (d, J = 245.4 Hz, CF), 161.1 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{16}Cl_3FNO_2$ 390.0225; found 390.0226.

2-*tert*-Butyl-4,4-Dichloro-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2a). *Method A*: A mixture of Grubbs II catalyst (12.5 mg, 0.015 mmol, 5%) and **1a** (100 mg, 0.3 mmol) in toluene (0.2 mL) was heated at 155 °C for 30 min in a sealed tube. The dark solution was allowed to reach rt and purified by chromatography (hexane/CH_2Cl_2 1:1 to CH_2Cl_2) to yield **2a**[11d] (70 mg, 81%). *Method B*: In a 10 mL vessel were placed Grubbs II catalyst (25 mg, 0.03 mmol, 5%) and **1a** (200 mg, 0.59 mmol) in toluene (1.5 mL), and the mixture was heated to 120 °C while stirring using microwave irradiation for 1 h. After concentration,

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the reaction mixture was purified by chromatography (hexane/CH_2Cl_2 4:6 to CH_2Cl_2) to yield **1a** (40 mg, 20%) and then **2a** (54 mg, 32%). *Method C*: To a suspension of CuCl (17.5 mg, 0.18 mmol, 30%) in acetonitrile (2 mL) was added **1a** (200 mg, 0.59 mmol), and the mixture was heated at 80 °C overnight in a sealed tube. The solution was then allowed to reach rt, concentrated, and purified by chromatography (hexane/CH_2Cl_2 1:1 to CH_2Cl_2) to yield **2a**[11d] (104 mg, 61%) and secondary amide **1g**[27] as a solid (58 mg, 35%). For **1g** (see Table 1): IR (film) 3316, 3044, 3002, 2955, 2838, 1693, 1659, 1615, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 3H), 4.48 (s, 2H), 6.90 (dm, J = 8.6 Hz, 2H), 7.24 (dm, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.9 (CH_2), 55.3 (CH_3), 92.6 (CCl_3), 114.3, 129.2, 128.3, 159.5, 161.7 (NCO). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}Cl_3NO_2$ 281.9850; found 281.9835.

4,4-Dichloro-2-cyclohexyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2b). See Table 1. Yellow oil; IR (film) 2923, 2854, 1727, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (m, 1H), 1.38 (m, 4H), 1.72 (br d, J = 13.6 Hz, 1H), 1.84 (m, 4H), 3.44 (s, 2H,), 4.03 (tt, J = 12, 3.6 Hz, 1H), 6.50 (dm, J = 10.4 Hz, 2H), 6.96 (dm, J = 10.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (two signals, CH_2), 29.7 (CH_2), 48.1 (C-1), 52.0 (C-5), 52.5 (CH), 87.4 (C-4), 132.3 (C-7 and C-9), 143.5 (C-6 and C-10), 164.3 (C-3), 184.0 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{18}Cl_2NO_2$ 314.0709; found 314.0708.

2-*tert*-Butyl-4,4-dichloro-7-methyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2c). A mixture of Grubbs II catalyst (12 mg, 0.014 mmol, 5%) and **1c** (100 mg, 0.28 mmol) in toluene (0.2 mL) was heated at 155 °C for 4 h in a sealed tube. Chromatography (hexane to hexane/CH_2Cl_2 1:9) afforded **2c** (62 mg, 72%) as a yellow oil: IR (film) 2953, 2923, 2854, 1724, 1668, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H, CH_3), 1.99 (d, J = 1.6 Hz, 3H, CH_3), 3.48 (d, J = 10.4 Hz, 1H, H-1), 3.51 (d, J = 10.4 Hz, 1H, H-1), 6.48 (d, J = 10 Hz, 1H, H-9), 6.75 (m, 1H, H-6), 6.92 (dd, J = 10, 3.2 Hz, 1H, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (CH_3), 27.1 (CH_3), 50.1 (C-1), 51.3 (C-5), 55.9 (C), 88.4 (C-4), 131.9 (CH), 138.6 (CH), 139.5 (C-7), 143.5 (CH), 164.7 (C-3), 184.8 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{18}Cl_2NO_2$ 302.0709; found 302.0721. $[M + Na]^+$ calcd for $C_{14}H_{17}Cl_2NNaO_2$ 324.0529; found 324.0531.

2-*tert*-Butyl-4,4-dichloro-7-fluoro-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2d). A mixture of Grubbs II catalyst (12 mg, 0.014 mmol, 5%) and **1d** (100 mg, 0.28 mmol) in toluene (0.2 mL) was heated at 155 °C for 4 h in a sealed tube. After chromatography (hexane/CH_2Cl_2 3:1 to CH_2Cl_2), **2d** (46 mg, 54%) was obtained as a yellow oil: IR (film) 2954, 2924, 2854, 1724, 1691, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H, CH_3), 3.54 (dd, J = 10.4, 1.2 Hz, 1H, H-1), 3.61 (d, J = 10.4 Hz, 1H, H-1), 6.52 (dd, J = 10.4, 6.8 Hz, 1H, H-9), 6.59 (dd, J = 12.4, 3.2 Hz, 1H, H-6), 6.96 (dd, J = 10, 3.2 Hz, 1H, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1 (CH_3), 50.0 (d, J = 3.1 Hz, C-1), 53.3 (d, J = 7 Hz, C-5), 56.1 (C), 87.6 (C-4), 119.9 (d, J = 17.8 Hz, CH), 131.3 (d, J = 4.6 Hz, CH), 144.5 (d, J = 2.3 Hz, CH), 155.9 (d, J = 267.8 Hz, CF), 164.2 (C-3), 176.8 (d, J = 21.7 Hz, C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{15}Cl_2FNO_2$ 306.0458; found 306.0469. $[M + Na]^+$ calcd for $C_{13}H_{14}Cl_2FNNaO_2$ 328.0278; found 328.0278.

2-Benzyl-4,4-dichloro-7-methyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2e). A mixture of Grubbs II catalyst (22 mg, 0.026 mmol, 5%) and **1e** (200 mg, 0.51 mmol) in toluene (0.4 mL) was heated at 155 °C for 4 h in a sealed tube. After chromatography (3:1 hexane/CH_2Cl_2 to CH_2Cl_2), **2e** (90 mg, 52%) was isolated as a yellow oil: IR (film) 3031, 2918, 2849, 1730, 1671, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92 (d, J = 1.6 Hz, 3H, CH_3), 3.28 (d, J = 10.4 Hz, 1H, H-1), 3.32 (d, J = 10.4 Hz, 1H, H-1), 4.57 (d, J = 14.8 Hz, 1H), 4.61 (d, J = 14.8 Hz, 1H), 6.41 (d, J = 9.6 Hz, 1H, H-9), 6.66 (m, 1H, H-6), 6.83 (dd, J = 9.6, 3.2 Hz, 1H, H-10), 7.27 (m, 2H), 7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1 (CH_3), 48.0 (CH_2), 51.1 (C-1), 51.9 (C-5), 87.3 (C-4), 128.3 (CH), 128.5 (CH), 129.1 (CH), 131.8 (CH), 134.0 (C), 138.3 (CH), 139.3 (C-7), 143.0 (CH), 165.1 (C-3), 184.6 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}Cl_2NO_2$ 336.0553; found 336.0553.

2-Benzyl-4,4-dichloro-7-fluoro-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2f). A mixture of Grubbs II catalyst (11 mg, 0.013 mmol, 5%) and **1f** (100 mg, 0.26 mmol) in toluene (0.2 mL) was heated at 155 °C for 1.5 h in a sealed tube. Chromatography (3:1 hexane/CH_2Cl_2 to CH_2Cl_2) afforded **2f** (32 mg, 37%) as a yellow oil: IR (film) 2954, 2923, 2853, 1731, 1689, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.32 (d, J = 10 Hz, 1H, H-1), 3.43 (d, J = 10 Hz, 1H, H-1), 4.60 (s, 2H, CH_2), 6.44 (dd, J = 10, 6.8 Hz, 1H, H-9), 6.51 (dd, J = 12.4, 3.2 Hz, 1H, H-6), 6.84 (dd, J = 10, 3.2 Hz, 1H, H-10), 7.27 (m, 2H), 7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.1 (CH_2), 50.9 (d, J = 2.3 Hz, C-1), 53.9 (d, J = 7.2 Hz, C-5), 86.6 (C-4), 119.6 (d, J = 17.8 Hz, CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 131.2 (d, J = 4.6 Hz, CH), 133.8 (C), 144.0 (d, J = 2.4 Hz, CH), 155.8 (d, J = 268.7 Hz, CF), 164.6 (C-3), 176.7 (d, J = 22.4 Hz, C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}Cl_2FNO_2$ 340.0302; found 340.0311. $[M + Na]^+$ calcd for $C_{16}H_{12}Cl_2FNNaO_2$ 362.0121; found 362.00128.

2-Benzyl-4,4-dichloro-2-azabicyclo[3.3.1]nonane-3,6-dione (4). *Method A*: A mixture of Grubbs II catalyst (11 mg, 0.013 mmol, 5%) and enol acetate **3a**[13] (100 mg, 0.26 mmol) in toluene (0.4 mL) was heated at 155 °C for 4 h in a sealed tube. The dark solution was allowed to reach rt and purified by chromatography (hexane/EtOAc 8:2 to 7:3) to yield morphan **4** (54 mg, 67%). NMR spectra matched those previously reported.[13] *Method B*: In a 10 mL vessel were placed Grubbs II catalyst (11 mg, 0.013 mmol, 5%) and **3a** (100 mg, 0.26 mmol) in toluene (1 mL), and the mixture was heated to 155 °C while stirring using microwave irradiation for 15 min. After concentration the reaction mixture was purified by chromatography (hexane/EtOAc 8:1 to 1:1) to yield successively **4**[13] (38 mg, 47%) and **4A**[13] (13 mg, 18%).

Ethyl (1*RS*,4*SR*,5*RS*)- and (1*RS*,4*RS*,5*RS*)-2-Benzyl-4-chloro-3,6-dioxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (5a and *epi*-5). According to the above Method A, the reaction of **4b** (100 mg, 0.23 mmol), toluene (0.2 mL), and Grubbs II catalyst (10 mg, 5% catalyst loading) for 6 h at 155 °C afforded a 1:1 epimeric mixture of **5** and *epi*-**5** (41 mg, 50%). Spectroscopic properties matched those previously described.[28]

1-Benzyl-3-(*N*-methyl-*N*-methoxycarbonyl)amino-1-azaspiro[4.5]decan-8-one Ethylene Acetal (7). A solution of iodo derivative **6**[21] (4.51 g, 10.9 mmol) in an aqueous solution of methylamine at 40% (50 mL) was heated in a sealed tube at 100 °C overnight. The mixture was extracted with CH_2Cl_2, and the organic extracts were dried and concentrated to yield the corresponding amine, which was used in the next step without further purification (3.4 g): ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 1H), 1.54 (dd, J = 12.9, 5.7 Hz, 1H), 1.55 (m, 1H), 1.61−1.82 (m, 5H), 1.91 (td, J = 13.2, 4.2 Hz, 1H), 2.17−2.25 (dd, J = 12.9, 8.4 Hz, 1H), 2.31 (s, 3H), 2.55 (dd, J = 9.5, 4.5 Hz, 1H), 2.80 (dd, J = 9.5, 6.6 Hz, 1H), 3.11 (m, 1H), 3.54 and 3.69 (2d, J = 13.2 Hz, 1H each), 3.94 (s, 4H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8 (CH_2), 30.9 (CH_2), 32.4 (CH_2), 32.5 (CH_2), 34.6 (CH_3), 41.7 (CH_2), 51.8 (CH_2), 56.4 (CH_2), 56.7 (CH), 61.9 (C), 64.1 (CH_2), 108.4 (C), 126.3 (CH), 127.9 (CH), 128.0 (CH), 140.6 (C). To a solution of the above amine (3.4 g, 10.7 mmol) in CH_3CN (180 mL) were added K_2CO_3 (3.02 g, 21.8 mmol) and methyl chloroformate (1.7 mL, 21.8 mmol), and the mixture was stirred at rt for 4 h. After concentration the residue was treated with a saturated aqueous sodium bicarbonate solution (100 mL) and extracted with CH_2Cl_2. The combined organic phases were dried, concentrated, and purified by chromatography (CH_2Cl_2 to 98:2 CH_2Cl_2/MeOH) to yield carbamate **7** (3.3 g, 81% over two steps) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$, COSY) δ 1.51−1.56 (m, 3H, H-4, H-7 and H-10), 1.65−1.73 (m, 3H, H-6, H-7 and H-10), 1.78−1.82 (m, 2H, H-6 and H-9eq), 2.06 (td, J = 12.2, 3.8 Hz, 1H, H-9ax), 2.35−2.48 (m, 1H, H-4), 2.68 (m, 2H, H-2), 2.77 (s, 3H, NCH_3), 3.24 (d, J = 13.2, 4.5 Hz, 1H, CH_2Ar), 3.64 (s, 3H, OCH_3), 3.92 (d, J = 13.2 Hz, 1H, CH_2Ar), 3.95 (s, 4H, CH_2O), 4.79 (m, 1H, H-3), 7.27 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, HSQC) δ 25.0 (br, C-10), 28.4 (br, NCH_3), 30.9 (C-6), 32.3 (C-7), 32.9 (C-9), 38.2 (C-4), 51.9 (C-3), 52.0 (CH_2Ar), 52.4 (OCH_3), 53.6 (C-2), 62.5 (C-5), 64.1 and 64.2 (OCH_2), 108.4 (C-8), 126.5 (*p*-Ar), 128.0 (*o*-, *m*-Ar), 140.4 (*ipso*-Ar), 156.8 (CO_2Me). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{31}N_2O_4$ 375.2278; found 375.2275.

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1-Tricloroacetyl-3-(*N*-methyl-*N*-methoxycarbonyl)amino-1-azaspiro[4.5]decan-8-one (8). To a solution of carbamate **7** (1.04 g, 2.78 mmol) in MeOH (70 mL) was added 10% $Pd(OH)_2/C$ (0.23 g), and the mixture was stirred at 60 °C under 400 psi hydrogen atmosphere overnight. The mixture was filtered on a Celite pad, concentrated, and purified by chromatography (Al_2O_3, CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to yield the corresponding secondary amine (0.64 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (m, 2H), 1.81−2.38 (m, 8H), 2.95 (s, 3H), 3.38 (dd, J = 12.3, 7.8 Hz, 1H), 3.62 (dd, J = 12.3, 9.5 Hz, 1H), 3.72 (s, 3H), 3.94 (s, 4H), 4.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6 (CH_3), 30.9 (CH_2), 31.6 (CH_2), 32.7 (2 CH_2), 36.6 (CH_2), 43.9 (CH_2), 52.9 (CH_3), 53.4 (CH), 64.2 (CH_2), 64.3 (CH_2), 65.8 (C), 106.7 (C), 156.5 (CO_2Me). To a solution of the above amine (1.58 g, 5.56 mmol) in THF (80 mL) was added a 10% HCl aqueous solution (160 mL), and the mixture was stirred at rt overnight. The solution was basified with K_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was purified by chromatography (Al_2O_3, hexane/CH_2Cl_2 3:2 to CH_2Cl_2/MeOH 99:1) to yield the corresponding deprotected ketone (0.92 g, 73%), which was used directly in the next step: ^{1}H RMN (300 MHz, $CDCl_3$) δ 1.66−1.74 (m, 2H), 1.82−1.94 (m, 3H), 1.98 (dd, J = 7.5, 6.3 Hz, 1H), 2.07 (dd, J = 12.9, 9.0 Hz, 1H), 2.25−2.35 (m, 2H), 2.50−2.68 (m, 2H), 2.87 (s, 3H), 2.98 (dd, J = 12.0, 6.9 Hz, 1H), 3.20 (dd, J = 12.0, 7.9 Hz, 1H), 3.70 (s, 3H), 4.69 (dt, J = 15.6, 8.4 Hz, 1H); ^{13}C RMN (75 MHz, $CDCl_3$) δ 28.9 (CH_2), 29.7 (CH_2) 30.0 (CH_3), 37.4 (CH_2), 38.0 (CH_2), 39.1 (CH_2), 47.4 (CH_2), 52.3 (CH_3 and CH), 59.8 (C), 156.4 (NCO), 210.6 (CO). To a solution of the above ketone (0.55 g, 2.3 mmol) in CH_2Cl_2 (5 mL) were added successively Et_3N (0.63 mL, 0.45 mmol) and trichloroacetyl chloride (0.39 mL, 3.4 mmol) at 0 °C, and the mixture was stirred at rt overnight. The mixture was quenched with water, extracted with CH_2Cl_2, dried, and concentrated. After chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1) **8** was isolated (0.85 g, 96%) as a colorless viscous oil: IR (film) 2954, 2880, 1708, 1681 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.80 (m, 2H, H-6eq and H-10eq), 2.04 (t, J = 12.4 Hz, 1H, H-4), 2.30−2.42 (m, 2H, H-7ax and H-9ax), 2.48 (dd, J = 12.4, 6.4 Hz, 1H, H-4), 2.54 (dm, J = 16.2 Hz, 1H, H-9eq), 2.68 (dtd, J = 16.2, 5.2, 1.6 Hz, 1H, H-7eq), 2.91 (s, 3H, NCH_3), 3.00 (td, J = 13.2, 6 Hz, 1H, H-10ax), 3.19 (td, J = 12.4, 5.2 Hz, 1H, H-6ax), 3.69 (t, J = 10.8 Hz, 1H, H-2), 3.75 (s, 3H, CH_3O), 4.39 (dd, J = 10.8, 7.2 Hz, 1H, H-2), 4.79 (br s, 1H, H-3); ^{13}C NMR (100 MHz) δ 29.0 (C-10), 29.4 (NCH_3), 32.9 (C-6), 37.7 (C-9), 38.1 (C-4 and C-7), 50.5 (C-2), 52.2 (C-3), 53.1 (OCH_3), 67.1 (C-5), 94.2 (CCl_3), 156.8 (CO_2Me), 158.6 (NCO), 209.5 (C-8). Anal. Calcd For $C_{14}H_{19}Cl_3N_2O_4$: C, 43.60; H, 4.97; N, 7.26. Found: C, 43.53; H, 5.00; N, 7.09. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}Cl_3N_2O_4$ 385.0483; found 385.0477.

8-Acetyloxy-1-tricloroacetyl-3-(*N*-methyl-*N*-methoxycarbonyl)amino-1-azaspiro[4.5]dec-7-ene (9). A mixture of **8** (0.64 g, 1.66 mmol) and *p*-toluenesulfonic acid monohydrate (0.32 g, 1.66 mmol) in isopropenyl acetate (5 mL) was heated to reflux for 4 h. The mixture was allowed to reach rt, treated with sodium hydrogen carbonate, filtered, concentrated, and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1) to yield **9**, a colorless viscous oil, as a 1.8:1mixture of epimers (0.76 g, 93%): IR (film) 2953, 2850, 1749, 1680 cm^{-1}; ^{1}H NMR (400 MHz) major epimer δ 1.55 (dm, J = 12.8 Hz, 1H, H-10eq), 1.87 (m, 1H, H-4), 1.98 (dm, J = 16.8 Hz, 1H, H-6), 2.12 (s, 3H, CH_3CO), 2.19 (m, 1H, H-9ax), 2.34 (dd, J = 12, 6,4 Hz, 1H, H-4), 2.44 (m, 1H, H-9eq), 2.87 (s, 3H, NCH_3), 3.17 (td, J = 12.8, 6.4 Hz, 1H, H-10ax), 3.30 (br d, J = 16.8 Hz, 1H, H-6), 3.64 (q, J = 10.8 Hz, 1H, H-2), 3.73 (s, 3H, OCH_3), 3.37 (dt, J = 10.8, 6.4 Hz, 1H, H-2), 4.74 (br s, 1H, H-3), 5.29 (dm, J = 5.2 Hz, 1H, H-7); minor epimer δ 1.60 (dm, J = 12.4 Hz, 1H, H-10eq), 1.93 (m, 1H, H-6), 2.11 (s, 3H, $COCH_3$), 2.87 (s, 3H, NCH_3), 3.02 (td, 1H, J = 12.4, 6.8 Hz, H-10ax), 3.74 (s, 3H, OCH_3), 5.36 (dm, 1H, J = 6 Hz, H-7). Only the different signals are mentioned: ^{13}C NMR (100 MHz) major epimer δ 20.9 (CH_3CO), 25.2 (C-9), 29.1 (NCH_3), 29.5 (C-6), 30.4 (C-10), 37.2 (C-4), 50.6 (C-2), 52.1 (C-3), 52.9 (OCH_3), 66.7 (C-5), 94.3 (CCl_3), 112.3 (C-7), 147.2 (C-8), 156.8 (NCO_2), 158.3 (NCO), 169.4 (CO); minor epimer δ 25.3 (C-9), 26.1 (C-10), 29.1 (NCH_3), 32.5 (C-6), 50.8 (C-2), 52.0 (C-3), 66.8 (C-5), 112.1 (C-7), 146.8 (C-8). Only the different signals are mentioned. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}Cl_3N_2O_5$ 427.0589; found 427.0581.

(2*RS*,7*RS*,10a*RS*)- and (2*RS*,7*SR*,10a*SR*)-6,6-Dichloro-2-[*N*-(methoxycarbonyl)-*N*-methylamino]hexahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-5,8-dione (10 and 11). A mixture of **9** (100 mg, 0.23 mmol) and Grubbs II catalyst (10 mg, 0.012 mmol) in toluene (0.15 mL) was heated in a sealed tube at 155 °C for 2 h. The mixture was concentrated and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1) to afford the following three products: **10** (32 mg, 39%) as a brown oil, a 2:1 ratio of **10** and **11** (12 mg, 15%), and a 1.6:1 epimeric mixture of azaspiro derivatives **12** (21 mg, 26%). A more enriched sample of **11** was obtained with an additional chromatography using the same conditions.

10: IR (film) 2954, 1723, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (m, 1H, H-10ax), 2.12 (m, 1H, H-1), 2.30 (d, J = 14.4 Hz, 1H, H-11 *pro*-S), 2.33 (dd, J = 14, 10.4 Hz, 1H, H-1), 2.51 (m, 3H, H-9 and H-10eq), 2.63 (dt, J = 14, 3.2 Hz, 1H, H-11*pro*-R), 2.93 (s, 3H, NCH_3), 3.50 (brt, J = 11.6 Hz, 1H, H-3), 3.55 (m, 1H, H-7), 3.72 (s, 3H, OCH_3), 4.33 (dd, J = 12, 8 Hz, 1H, H-3), 4.53 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.3 (NCH_3), 35.9 (C-9), 36.9 (C-11), 37.9 (C-10), 39.7 (C-1), 45.2 (C-3), 52.9 (OCH_3), 53.9 (C-2), 60.8 (C-10a), 63.0 (C-7), 80.5 (C-6), 156.3 (CO_2), 161.4 (C-5), 203.4 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}Cl_2N_2O_4$ 349.0716; found 349.0722.

11: IR (film) 2954, 2926, 1718, 1697, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83 (ddd, J = 14, 12, 6 Hz, 1H, H-10ax), 2.06 (dd, J = 12.4, 10.4 Hz, 1H, H-1), 2.17 (dd, J = 12.4, 7.6 Hz, 1H, H-1), 2.22 (m, 1H, H-10eq), 2.38 (dd, J = 14.4, 3.6 Hz, 1H, H-11 *pro*-S), 2.49 (m, 2H, H-9), 2.61 (dt, J = 14.4, 3.6 Hz, 1H, H-11 *pro*-R), 2.84 (s, 3H, NCH_3), 3.59 (m, 1H, H-7), 3.73 (s, 3H, OCH_3), 3.75 (m, 2H, H-3), 5.17 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.0 (NCH_3), 35.4 (C-9), 35.7 (C-10), 36.6 (C-11), 40.7 (C-1), 46.7 (C-3), 51.7 (C-2), 53.1 (OCH_3), 61.5 (C-10a), 63.1 (C-7), 80.5 (C-6), 156.7 (CO_2), 161.7 (C-5), 203.1 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}Cl_2N_2O_4$ 349.0716; found 349.0723.

1-Dicloroacetyl-3-[(*N*-methoxycarbonyl)-*N*-methyl]amino-1-azaspiro[4.5]dec-6-en-8-one (12a and 12b). Two isomers were observed in the NMR spectra in a 1.6:1 ratio. IR (film) 2955, 1680 cm^{-1}. For NMR data of the major epimer **12a**, see below (**12c** → **12a**). Minor epimer **12b**: ^{1}H NMR (400 MHz) δ 1.82 (ddd, J = 14.4, 12.4, 6.4 Hz, 1H, H-10ax), 2.00 (m, 1H, H-4), 2.21 (m, 1H, H-10eq), 2.32 (m, 1H, H-4), 2.49 (m, 2H, H-9), 2.90 (s, 3H, NCH_3), 3.65 (m, 1H, H-2), 3.74 (s, 3H, OCH_3), 4.03 (dd, J = 10, 8.4 Hz, 1H, H-2), 4.95 (m, 1H, H-3), 5.97 (d, J = 10 Hz, 1H, H-7), 6.06 (s, 1H, $CHCl_2$), 6.77 (dd, J = 10, 2 Hz, 1H, H-6); ^{13}C NMR (100 MHz) δ 30.0 (NCH_3), 34.6 (C-4), 34.9 (C-9), 35.7 (C-10), 47.3 (C-2), 53.1 (C-3), 53.1 (OCH_3), 64.0 (C-5), 66.0 ($CHCl_2$), 127.6 (C-7), 153.5 (C-6), 156.7 (CO_2), 161.7 (NCO), 196.8 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}Cl_2N_2O_4$ 349.0716; found 349.0717.

Chemical Correlation of 12a from 12c. To a solution of enone **12c**[23] (30 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.068 mL, 0.9 mmol), and the mixture was stirred at rt for 2 h. The reaction was concentrated, to the resulting residue dissolved in CH_2Cl_2 (1 mL) were added Et_3N (0.06 mL, 0.45 mmol) and dichloroacetyl chloride (0.026 mL, 0.27 mmol), and the mixture was stirred at rt for 2 h. Water was added, and the mixture was extracted with CH_2Cl_2. The organics were dried, concentrated, and purified by chromatography (from CH_2Cl_2 to 3:1 CH_2Cl_2/EtOAc) to yield **12a** (22 mg, 71%): ^{1}H NMR (400 MHz) δ 1.92 (dm, J = 12.8 Hz, 1H, H-10eq), 2.35 (dd, J = 12.4, 7.2 Hz, 1H, H-4), 2.43 (t, J = 12.4 Hz, 1H, H-4), 2.50 (ddd, J = 17.6, 14, 4.8 Hz, 1H, H-9ax), 2.66 (dm, J = 17.6, 1H, H-9eq), 2.91 (s, 3H, NCH_3), 3.23 (ddd, J = 14, 12.8, 4.8 Hz, 1H, H-10ax), 3.66 (t, J = 10.4 Hz, 1H, H-2), 3.75 (s, 3H, OCH_3), 4.18 (dd, J = 10.4, 7.2 Hz, 1H, H-2), 4.73 (tt, J = 10.8, 7.2 Hz, 1H, H-3), 5.96 (d, J = 10 Hz, 1H, H-7), 6.09 (s, 1H, $CHCl_2$), 6.90 (dd, J = 10, 2 Hz, 1H, H-6); ^{13}C NMR (100 MHz) δ 30.0 (NCH_3), 32.9 (C-10), 35.0 (C-9), 39.8 (C-4), 48.0 (C-2), 53.1 (C-3 and OCH_3), 64.1 (C-5), 66.4 ($CHCl_2$), 127.8 (C-7), 154.1 (C-6), 156.7 (CO_2), 161.8 (NCO), 196.8 (C-8)

1-Acetyl-3-[*N*-(methoxycarbonyl)-*N*-methyl]amino-1-azaspiro[4.5]decan-8-one (12d). Yellow oil; IR (film) 2955, 2924, 1853,

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1698, 1644 cm^{-1}; ^1H NMR (400 MHz) δ 1.73 (m, 2H, H-6eq and H-10eq), 1.99 (t, J = 12.4 Hz, 1H, H-4), 2.04 (s, 3H, CH_3CO), 2.32 (m, 2H, H-7ax and H-9ax), 2.45 (dd, J = 12.4, 7.2 Hz, 1H, H-4), 2.45 (masked, 1H, H-9eq), 2.63 (dtd, J = 15.6, 4.8, 1.6 Hz, 1H, H-7eq), 2.89 (s, 3H, NCH_3), 2.97 (tdd, J = 13.6, 5.6, 1.2 Hz, 1H, H-10ax), 3.29 (td, J = 13.2, 5.2 Hz, 1H, H-6ax), 3.42 (t, J = 10.4 Hz, 1H, H-2), 3.70 (t, J = 8.8 Hz, 1H, H-2), 3.75 (s, 3H, OCH_3), 4.81 (br s, 1H, H-3); ^{13}C NMR (100 MHz) δ 24.9 (CH_3CO), 29.1 (NCH_3), 30.0 (C-10), 33.6 (C-6), 37.9 (C-7 and C-9), 38.5 (C-4), 49.4 (C-2), 51.5 (C-3), 53.0 (OCH_3), 63.2 (C-5), 157.0 (CO_2Me), 169.5 ($NCOCH_3$), 210.2 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{23}N_2O_4$ 283.1652; found 283.1656.

(2*RS*,7*SR*,10a*RS*)-2-[*N*-(Methoxycarbonyl)-*N*-methylamino]-hexahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-5,8-dione (13). To a solution of **10** (36 mg, 0.10 mmol) in MeOH (2 mL) at 0 °C were added NH_4Cl (33 mg, 0.62 mmol) and then Zn (67.4 mg, 1.03 mmol) portionwise over 1 h. The mixture was allowed to reach rt, stirred overnight, filtered on a Celite pad, concentrated, and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to yield **13** (16 mg, 58%) as a white solid: mp 152−154 °C; IR (film) 2953, 1697, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.95 (td, J = 14, 5.2 Hz, 1H, H-10ax), 2.01 (m, 1H, H-1), 2.05 (m, 1H, H-11 *pro*-R), 2.27 (m, 2H, H-1 and H-11 *pro*-S), 2.36 (m, 1H, H-10eq), 2.37 (dd, J = 16, 6 Hz, 1H, H-9eq), 2.44 (d, J = 19.2 Hz, 1H, H-6eq), 2.57 (ddd, J = 16, 13.2, 7.2 Hz, 1H, H-9ax), 2.67 (dd, J = 19.2, 7.2 Hz, 1H, H-6ax), 2.83 (br s, 1H, H-7), 2.90 (s, 3H, NCH_3), 3.29 (t, J = 10.8 Hz, 1H, H-3), 3.72 (s, 3H, OCH_3), 4.42 (dd, J = 11.6, 7.6 Hz, 1H, H-3), 4.55 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.8 (NCH_3), 33.9 (C-6), 34.9 (C-9), 38.0 (C-1), 38.2 (C-10), 40.2 (C-11), 44.1 (C-7 and C-3), 52.8 (OCH_3), 53.2 (C-2), 59.2 (C-10a), 156.6 (NCO), 166.6 (C-5), 210.5 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{21}N_2O_4$ 281.1496; found 281.1501.

(2*RS*,7*RS*,10a*SR*)-2-[*N*-(Methoxycarbonyl)-*N*-methylamino]-hexahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-5,8-dione (14). Operating as above, from an enriched sample of **11** (18 mg, 0.05 mmol), MeOH (1 mL), NH_4Cl (16.5 mg, 0.31 mmol), and Zn (33.7 mg, 0.52 mmol), **14** was isolated, slightly contaminated with **13**, after chromatography (9.4 mg, 65%): IR (film) 2952, 1698, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.81 (td, J = 13.2, 5.6 Hz, 1H, H-10ax), 1.93 (dt, J = 13.2, 3.6 Hz, 1H, H-11 *pro*-R), 1.99 (m, 1H, H-1), 2.11 (dd, J = 12.4, 7.6 Hz, 1H, H-1), 2.22 (m, 1H, H-10eq), 2.36 (m, 1H, H-11 *pro*-S), 2.39 (m, 2H, H-9), 2.45 (d, J = 19.6 Hz, 1H, H-6eq), 2.67 (dd, J = 18.8, 7.6 Hz, 1H, H-6ax), 2.82 (s, 3H, NCH_3), 2.87 (m, 1H, H-7), 3.71 (m, 2H, 4-CH_2), 3.73 (s, 3H, OCH_3), 5.14 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6 (NCH_3), 34.2 (C-6), 34.4 (C-9), 35.8 (C-10), 37.9 (C-11), 40.8 (C-1), 44.4 (C-7), 45.5 (C-3), 51.3 (C-2), 53.0 (CH_3O), 59.9 (C-10a), 157.0 (CO_2), 167.2 (C-5), 210.3 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{21}N_2O_4$ 281.14966; found 281.1497. In another run, the partially reduced azatricyclic lactam **15** was isolated as a waxy solid: IR (film) 2924, 2854, 1717, 1697, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.82 (td, J = 13.6, 5.6 Hz, 1H, H-10ax), 2.02 (t, J = 12 Hz, 1H, H-1), 2.12 (dd, J = 12.4, 7.6 Hz, 1H, H-1), 2.14 (m, 1H, H-11*pro*-R), 2.21 (m, 1H, H-10eq), 2.43 (dd, J = 14, 4 Hz, 1H, H-11 *pro*-S), 2.52 (m, 2H, H-9), 2.83 (s, 3H, NCH_3), 3.21 (br s, 1H, H-7), 3.72 (s, 3H, OCH_3), 3.75 (m, 2H, H-3), 4.61 (d, J = 7.2 Hz, 1H, H-6ax), 5.13 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.0 (CH_3N), 35.2 (C-9), 35.4 (C-10), 38.8 (C-11), 40.6 (C-1), 46.2 (C-3), 51.8 (C-2), 52.0 (C-7), 53.0 (CH_3O), 54.4 (C-6), 60.7 (C-10a), 156.7 (CO_2), 164.0 (C-5), 206.0 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}ClN_2O_4$ 315.1106; found 315.1103.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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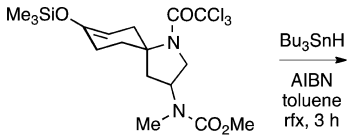

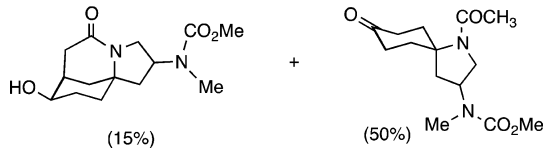

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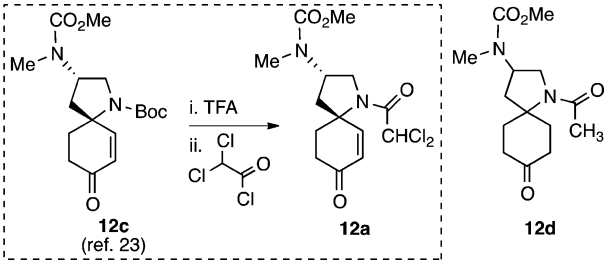

(25) The configuration at C-6 in **15** was ascertained by the NOESY correlation of H-6_{ax} with the H-$11_{pro\text{-}R}$ as the coupling constant (J = 7.2 Hz) of H-6_{ax}/H-7. For this type of bridged compounds, the coupling constant of H6_{eq}/H7 is near zero; see, for example, NMR data for compounds **13** and **14**.

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