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Chlorine Atom Transfer Radical 6-*exo* Cyclizations of Carbamoyldichloroacetate-Tethered Alkenes, Enol Acetates and α,β-Unsaturated Nitriles Leading to Morphans

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The Cu^I-mediated atom transfer radical cyclization of amino-tethered dichloromalonamides and electron-rich, electron-poor, and nonactivated double bonds is a useful methodology for the synthesis of 2-azabicyclo[3.3.1]nonanes. A study of the reaction conditions and the scope of the process is reported. Cyclopropane ring formation was observed from the resulting 1,3-dichlorides in some morphan substrates using either Cu^I, Pd, or Zn.

Introduction

The morphan nucleus (2-azabicyclo[3.3.1]nonane ring) is found in many alkaloids[1] belonging to highly diverse biogenetic families (Figure 1). In earlier work, we developed a synthetic entry to morphan derivatives based on the reductive cyclization of trichloroacetamides, using tributyltin hydride as well as tris(trimethylsilyl)silane.[2] Recently, based on the well-known ability of copper(I) complexes to catalyze atom transfer radical cyclization (ATRC) reactions of olefins with polyhalogenated compounds,[3] we reported a new synthetic route to polyfunctionalized morphan compounds.[4] The procedure was based on the use of a Cu^I complex with TPMA [tris(2-pyridylmethyl)amine] in conjunction with the additive AIBN,[5] which regenerates the catalytically active copper(I) species by reduction of the Cu^{II} complex.

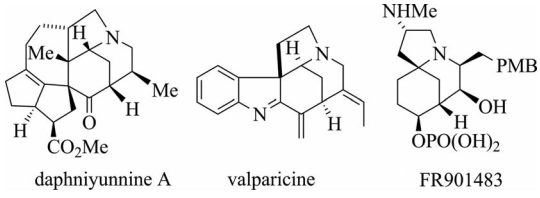
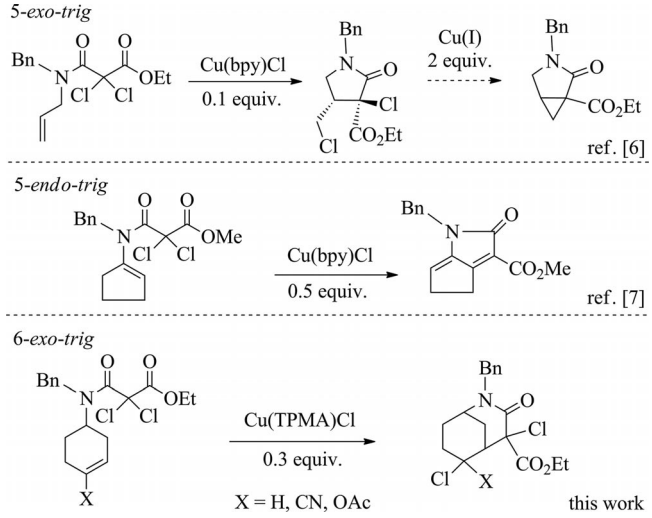


Figure 1. Alkaloids embodying the azabicyclic morphan framework.

In the synthesis of nitrogen-containing heterocycles,[6,7] the use of α,α-dichloro β-dicarbonylated substrates as pro-radicals[8] has been far less studied (Scheme 1) than the use of trichloro- or dichloroacetamides.[9] We report herein the first 6-*exo*-*trig* radical cyclization of α,α-dichloroamido esters (Scheme 1). The purpose of this work is to examine the scope and limitations of this radical methodology in the search for nitrogen-containing building blocks that might be useful in alkaloid synthesis. The process was studied with three types of radical acceptors: α,β-unsaturated nitriles, alkenes, and enol acetate moieties, each with different electron density. The stereochemical course of the reactions as well as the chemical behavior of the resulting azabicyclic compounds is also reported.



Scheme 1. Atom transfer radical cyclization (ATRC) of dichloromalonamides.

Results and Discussion

The dichlorocarbamoylacetates (α,α-dichloro-β-amido esters) required for this study were prepared from the

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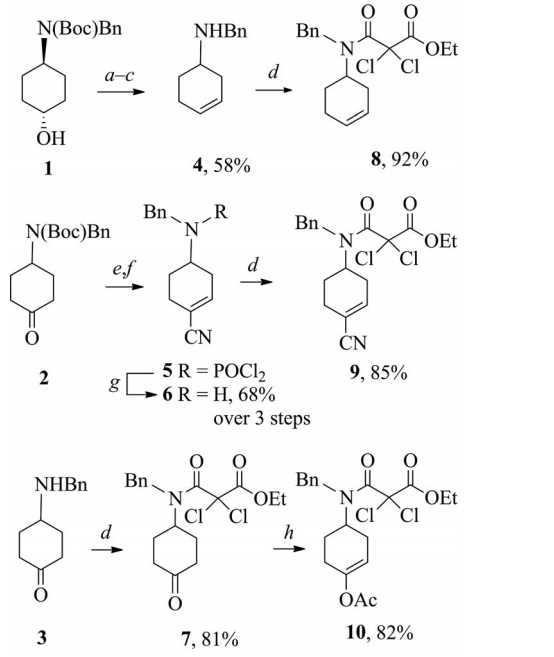
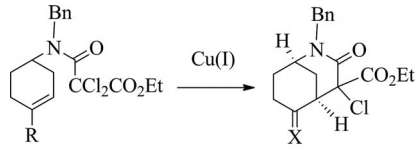
known aminocyclohexane derivatives **1**[10] and **2**–**3**,[2a] by following the synthetic sequences depicted in Scheme 2.



Scheme 2. Preparation of the starting dichloromalonamides **8**–**10**. Reagents and conditions: (a) MsCl, iPr_2EtN, CH_2Cl_2, room temp., 3 h; (b) *t*BuOK, *t*BuOH, 90 °C, 24 h; (c) 10% HCl, THF, reflux, 2 h; (d) EtO_2CCl_2COCl, Et_3N, CH_2Cl_2, room temp., overnight; (e) TMSCN, CsF, CH_3CN, room temp., overnight; (f) $POCl_3$, pyridine, benzene, reflux, 5 h; (g) 10% HCl, THF, reflux, 5 h; (h) isopropenyl acetate, TsOH, reflux, 5 h.

took place without standard ligands when *N*,*N*-dimethylformamide (DMF) was used as the solvent[11] with 30% catalyst loading (42% combined yield, diastereomeric mixture: entry 2).

Table 1. ATRC from α-carbamoyl-α,α-dichloro esters **8**–**10** using CuCl.[a]



8 X = H
9 X = CN
10 X = O

11a/12a X = Cl, H
11b/12b X = Cl, CN
16/17 X = O

Entry	Compd.	Ligand (%)	Additive (%)	Solvent	Yield (%)[c] 11	12	13
1	**8**	TPMA (30)	AIBN (50)	DCE	29	–[b]	42
2	**8**	none	none	DMF	18	24	–
3[c]	**9**	TPMA (30)	AIBN (50)	DCE	28	–[d]	49
4	**9**	none	none	DMF	35	–	36
5	**10**	TPMA (30)	AIBN (50)	DCE		55[e]	
6	**10**	none	none	DMF		56[e]	

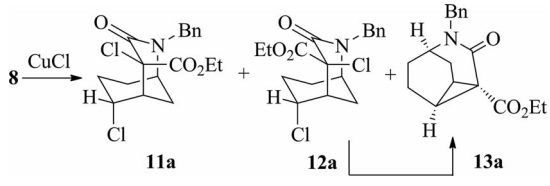
[a] Reaction conditions (unless noted otherwise): CuCl (30%) and either 60 °C, 48 h, DCE or 80 °C overnight DMF. [b] When AIBN was omitted, **12a** was isolated (ca. 25%) and the yield of **13a** decreased. [c] In this series, **14** (9%) and **15** (15%) were isolated under these reaction conditions (Figure 3). [d] When AIBN was omitted, **12b** was isolated (ca. 22%) and the yield of **13b** decreased. [e] Mixture of compounds **16** and **17** (1:1).

Cyclization of Alkene 8

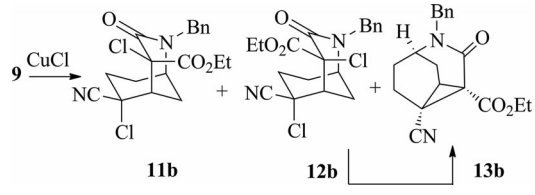
Representative results of the studies carried out with amido ester **8**, which bears an alkene as the radical acceptor (Scheme 3), are summarized in Table 1.Thus, in the presence of 0.3 equiv. of CuCl and TPMA and 0.5 equiv. of AIBN at 60 °C in 1,2-dichloroethane (DCE) (entry 1), dichloride **8** underwent the desired cyclization reaction to give the expected atom transfer product **11a** (29%) and the azatricyclic compound **13a** (42%). The latter presumably arose from the epimer **12a** by a sequence of homolytic cleavage of the axial C–Cl bond at C-4 promoted by CuCl, reduction of the intermediate radical into the Cu^{II} enolate, and intramolecular cyclopropane ring formation by displacement of the axial chlorine atom at C-6. This intramolecular S_N2 reaction has been previously observed in dichlorides with a 1,3-relationship.[6] Interestingly, the cyclization process also

Cyclization of α,β-Unsaturated Nitrile 9

The cyclization process using dichloroamido ester **9**, in which the radical acceptor shows a lower electron density than in **8**, proceeded in a similar manner (Table 1, entry 3; Scheme 4). Of the two isomeric morphans, **11b** was stable in the reaction medium whereas the epimer **12b**, with the axial chlorine at C-4, quickly evolved to the cyclopropane **13b**. In this series, using the reaction conditions of CuCl/DMF, the cyclopropanation process from **12b** was also observed[12] (Table 1, entry 4). The relative configuration of **11b** was determined by X-ray crystal structure analysis (Figure 2). For a detailed NMR analysis of morphans **11**–**12**, see below. The structure of **11b** unambiguously showed that the radical cyclization leading to the compound with the chlorine atom equatorially located at C-4 gave a stable



Scheme 3. ATRC from dichloroamido ester **8**.



Scheme 4. ATRC from dichloroamido ester **9**.

epimer in the reaction medium and did not undergo the cyclopropanation process observed from the epimer **12b**, in which the chlorine atom at C-4 was axially located.

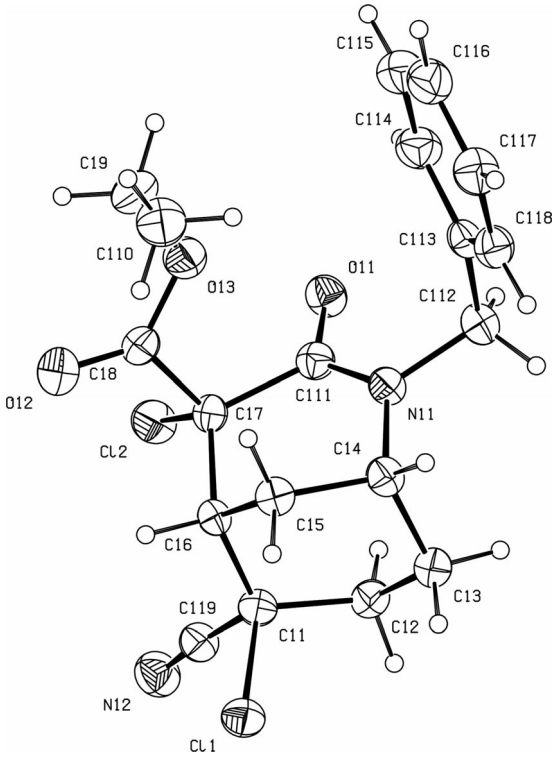


Figure 2. ORTEP drawing of morphan **11b**. Elipsoid plots drawn with 50% probability.

The minor compounds morphan **14**, arising from a dehydrohalogenation process from **11a**, and normorphan **15**, generated directly from the carbocyclic starting material **9**, were also isolated (Figure 3). The unexpected normorphan **15** came from the initial α-dicarbonylic radical after a 1,4-hydrogen transfer, which generated a benzylic radical that reacted with the unsaturated nitrile leading to the normorphan derivative. It is notable that, to the best of our knowledge, this reaction pathway has never been observed in radical reactions using *N*-benzylacetamides other than in our previous studies on related *N*-(1-phenylethyl)trichloroacetamides.[13] The stereochemistry of **15** was initially only tentative due to the formation of a mixture of epimers, each with two rotamers, at the stereogenic carbon atom in the side chain, which gave a complex NMR spectrum. After the reduction of both C–Cl bonds, the NMR spectroscopic data allowed the unequivocal assignment of the relative configuration of both normorphans (see below).

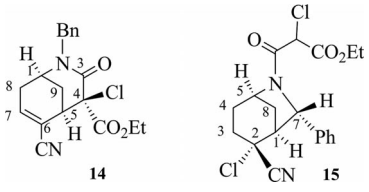
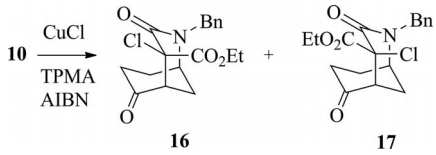


Figure 3. Compounds **14** and **15** and numbering of morphan and normorphan derivatives.

Cyclization of Enol Acetate 10

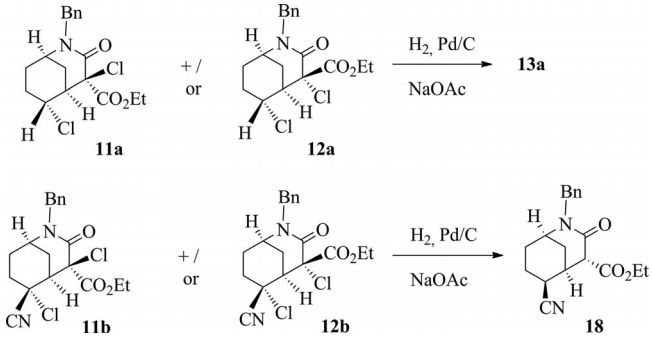
Finally, we examined the Cu^{I}-catalyzed annulation of enol acetate **10** (Scheme 5), with an electron-donating group upon the alkene radical acceptor. Interestingly, treatment of **10** either under the standard cyclization conditions using TPMA and AIBN or without additives (Table 1, entries 5 and 6) afforded ketone derivatives **16** and **17** as a 1:1 mixture of epimers in 55% yield. They were formed when the initial annulation products (i.e., α-chloro acetoxy intermediates, see Scheme 1) evolved into the more stable ketone either under the reaction conditions or during workup.



Scheme 5. ATRC from dichloroamido ester **10**.

Reduction Processes from Dihalides 11 and 12

We examined the behavior of the synthesized dichloromorphans in reduction processes by using either a hydrogenation reaction or treatment by zinc metal. Catalytic hydrogenation of either **11a** or **12a**, as well as the epimeric mixture of both, quantitatively gave rise to the cyclopropane derivative **13a** (Scheme 6). The formation of cyclopropane compounds from 1,3-dichlorides by using metals has been reported,[14] but to the best of our knowledge there are no examples of the use of Pd as a promoter in a hydrogenation process.

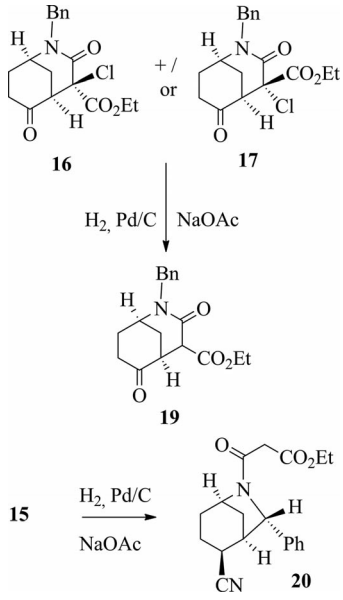


Scheme 6. Hydrogenation processes from morphans **11** and **12** (series **a**–**b**).

In contrast, epimeric dichloro derivatives with an equatorial cyano group at C-6 (**11b** and **12b**) instead of a hydrogen atom, as in **11a** and **12a**, behaved differently in the hydrogenation process.[15] In this case, both dichlorides gave the same morphan compound **18** without any detectable cyclopropanation. The epimer **12b** evolved easily to morphan **18**, whereas catalytic hydrogenation of **11b** was slow. It is noteworthy that the stereochemical result at C-4 was the same regardless of the configuration of this carbon atom in the starting material. In the stereochemical arrangement of **18**, in which the ethoxycarbonyl group was in an axial disposi-

tion, the 1,3-diaxial interaction with the equatorial substituent at C-6 was avoided.

Interestingly, when the hydrogenation was carried out from the chloro compounds **16** and **17**, irrespective of which epimer was used, a mixture of amido esters **19**, epimers at C-4, was isolated. (Scheme 7). This probably reflects the fact that when C-6 has an sp^2 hybridization both epimers of **19** show similar stability, since the 1,3-diaxial interaction between the equatorial substituents at C-4 and C-6 in morphan compounds does not take place.



Scheme 7. Hydrogenation processes from morphans **16**–**17** and normorphan **15**.

The minor normorphan product **15** was also submitted to the hydrogenation process to ascertain the configuration at the benzylic methine at C-7 (see below for NMR studies); in this case, normorphan **20** was isolated (Scheme 7).

The reduction of chlorinated morphans by using Zn afforded similar results. Whereas the reduction of the epimeric mixture of morphans **11a** and **12a** again gave the cyclopropane derivative **13a** (now as a methyl ester, due to a transesterification process in the reaction medium),[16] the reduction of nitrile **12b** gave **18** together with small quantities of its epimer at C-6 and cyclopropane **13b** (as a methyl ester). The reduction of chloro ketones **16** and **17** afforded the same epimeric mixture as in the hydrogenation process (i.e., **19**).

NMR Studies

The stereochemistry of all synthesized morphans was established on the basis of their ^1H and ^{13}C NMR spectroscopic data by considering the electronic, anisotropic, and steric effects of the chlorine[17] and ester substituents. The relative configuration at C-6 for the 6-monosubstituted morphans **11a** and **12a** (for numbering of these compounds, see Figure 3) was easily established by the coupling constant pattern arising from H-6, which appears as a broad singlet, indicating its equatorial location. The stereochemistry at C-6 in **11b** and **12b**, in which C-6 is quaternary, was established by X-ray analysis of the former (Figure 2). This stereochemical assignment is consistent with mechanistic considerations, since the configuration at C-6 arose from the transfer of the chlorine atom from the less hindered face of the cyclohexane ring generated after the radical cyclization, which locates the chlorine in an axial disposition.

On the other hand, the configuration at the quaternary C-4 position (disubstituted with chloro and ethoxycarbonyl groups) in **11**, **12** (both series a/b), **16** and **17** was deduced from the chemical shift of the axial H-9 in the piperidone ring, which always appears upfield (δ = 1.95–2.05 ppm) when it has a 1,3-diaxial relationship with the ester at C-4, compared with the chemical shift observed (δ = 2.55–2.8 ppm) in the epimeric counterparts. A greater deshielding effect of the chlorine atom with respect to the ethoxycarbonyl group on hydrogen atoms with a 1,3-diaxial relationship was also observed in the chemical shift of H-6_{eq} when comparing the values in **11a** (δ = 5.0 ppm) and **11b** (δ = 4.3 ppm). It is also noteworthy that, in compounds with the chlorine atom equatorial with respect to the piperidone ring, the chemical shift of H-5 was always more deshielded than in the corresponding epimer in which the chlorine atom was axial. In the ^{13}C NMR spectra of compounds with the ester group located axially (**11a**, **11b**, and **16**) the ester carbonyl group resonated at lower field (ca. 1.5 ppm) than in the corresponding epimers in which the ester groups were located equatorially.

The stereostructure of normorphan **20**, and hence of its precursor normorphan **15**, was ascertained on the basis of the NMR spectroscopic data by comparison with a normorphan analogue lacking the phenyl group at C-7.[10] The ^{13}C NMR chemical shift of C-8 (δ = 31.9 ppm) in **20** was shifted upfield with respect to that found in the compound unsubstituted at C-7 (δ = 35.5 ppm). This result indicates a compression upon H-8_{eq}, which is only possible with the stereochemistry assigned to **20**, considering that the cyano group at C-2 is located equatorially.

Conclusions

The synthetic studies have revealed the ability of radical species with electron-withdrawing groups to undergo cyclization processes leading to morphan compounds, irrespective of the nature of the radical acceptor. Because the intramolecular addition products are 1,3-dichlorides, under some conditions we observed an additional dehalogenation step leading to cyclopropanes embedded in the morphan nucleus.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. ^1H chemical shifts are reported as δ values (ppm) relative to internal Me_4Si, and ^{13}C NMR spectra are referenced to the deuterated solvent signal ($CDCl_3$: δ = 77.00 ppm). All NMR

spectroscopic data assignments are supported by COSY and HSQC experiments. Infrared spectra were recorded with a Nicolet 320 FTIR spectrophotometer. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located under UV light or by staining with a 1% $KMnO_4$ aqueous solution. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh). CuCl (99.99%) was purchased from Sigma–Aldrich and was used as received. All reactions were carried out under an argon atmosphere with anhydrous, freshly distilled solvents, under anhydrous conditions. Drying of the organic extracts during reaction workup was performed over anhydrous Na_2SO_4.

***N*-Benzyl-*N*-(3-cyclohexenyl)amine (4):** A solution of alcohol **1**[10] (3.85 g, 12.6 mmol) and *i*Pr_2EtN (6.5 mL, 37.9 mmol) in CH_2Cl_2 (50 mL) was cooled in an ice bath, then $MeSO_2Cl$ (1.5 mL, 18.95 mmol) was added dropwise. After stirring at 0 °C for 1 h and at room temp. for 3 h, the reaction mixture was washed with brine and the aqueous phase was extracted with CH_2Cl_2. The organics were dried, concentrated, dissolved in *t*BuOH, and treated with *t*BuOK (1 M in *t*BuOH, 63 mL, 63 mmol) in *t*BuOH (200 mL) at 90 °C for 24 h. The reaction mixture was concentrated and the residue was diluted with CH_2Cl_2 and washed with brine. The organics were dried, concentrated, and purified by chromatography (hexane/EtOAc, 80:20) to give the corresponding alkene (2.43 g, 67%). A mixture of the above alkene (4.06 g, 14.13 mmol), hydrochloric acid (10%, 70 mL), and THF (50 mL) was heated to reflux for 2 h. The reaction was allowed to reach room temp., then NaOH aqueous solution (2.5 M) was added until pH 11, and the mixture was extracted with CH_2Cl_2. The organics were dried and concentrated to yield the corresponding secondary amine **4** (2.30 g, 87%). For NMR spectroscopic data see Quirante et al.[10]

4-(Benzylamino)cyclohex-1-encarbonitrile (6): To a solution of ketone **2** (4.1 g, 12.53 mmol) in CH_3CN (15 mL) at room temp., were added successively CsF[18] (0.19 g, 1.25 mmol) and TMSCN (1.78 mL, 13.79 mmol) and the mixture was stirred overnight. The mixture was then filtered through a Celite pad and concentrated to yield the corresponding cyanohydrin (not shown), which was used in the next step without further purification. To a solution of the above cyanohydrin in benzene (4 mL), were added pyridine (21 mL, 26.1 mmol) and $POCl_3$ (3.73 mL, 40.75 mmol). The mixture was heated to reflux for 5 h, concentrated, diluted in CH_2Cl_2, and washed with HCl (1 N) and then brine. The organics were dried and concentrated to give **5**, which was redissolved in THF (50 mL) and HCl (10%, 70 mL), and heated at reflux for 5 h. The mixture was then basified with NaOH (2 N) and extracted with CH_2Cl_2. The organics were dried and concentrated, giving **6** (1.8 g, 68%, yield over three steps). For NMR spectroscopic data see ref.[2a]

Ethyl 3-[Benzyl(cyclohex-3-en-1-yl)amino]-2,2-dichloro-3-oxopropanoate (8): To a solution of secondary amine **4** (0.42 g, 2.35 mmol) and Et_3N (0.65 mL, 4.7 mmol) in CH_2Cl_2 (5 mL) cooled in an ice bath, ethyl 2,2,3-trichloro-3-oxopropanoate[19] (0.62 g, 2.82 mmol) was added dropwise. The reaction mixture was warmed to room temp. while stirring overnight. The mixture was diluted with CH_2Cl_2, washed with brine, dried, concentrated, and purified by chromatography (hexane/EtOAc, 80:20) to give **8** (765 mg, 92%) as a waxy solid. IR (NaCl): $\tilde{\nu}$ = 3088, 3063, 3029, 2983, 2935, 2840, 1761, 1740, 1680, 1655 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.37 (t, J = 7.2 Hz, 3 H, CH_3), 1.74 and 1.86 (2m, 2 H), 2.19 (m, 4 H), 4.33 (m, 1 H), 4.38 (q, J = 7.2 Hz, 2 H, CH_2O), 4.52 (d, J = 15.6 Hz, 1 H, CH_2Ph), 4.67 (d, J = 15.6 Hz, 1 H, CH_2Ph), 5.56 (br. d, J = 10.0 Hz, 1 H, =CH), 5.63 (br. d, J = 10.0 Hz, 1 H, =CH), 7.18–7.35 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_3), 25.5 (CH_2), 27.4 (CH_2), 29.3 (CH_2), 46.6 (CH_2Ar), 55.3 (CH), 64.7 (OCH_2), 80.3 (CCl_2), 124.5 (=CH), 126.6 (=CH), 126.2, 126.9, 128.5 (Ph), 137.6 (*ipso*-C), 162.4 (CO), 163.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}Cl_2NO_3$ [M^+ + 1] 370.0971; found 370.0968.

Ethyl 3-[Benzyl(4-cyanocyclohex-3-en-1-yl)amino]-2,2-dichloro-3-oxopropanoate (9): Operating as above, starting from **6** (0.77 g), after chromatography, **9** (1.21 g, 85%) was obtained (*Z*/*E* rotamers, 4:1 ratio, estimated by ^1H NMR) as an amorphous white solid; m.p. 133–134 °C. IR (NaCl): $\tilde{\nu}$ = 3062, 3031, 2981, 2937, 2873, 2215, 1759, 1739, 1679, 1655 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (Z rotamer) = 1.36 (t, J = 7.2 Hz, 3 H, CH_3), 1.81 and 1.96 (2m, 2 H), 2.34 (m, 4 H), 4.37 (m, 2 H, OCH_2), 4.46 (m, 1 H), 4.49 (d, J = 16.4 Hz, 1 H, CH_2Ph), 4.46 (m, 1 H), 4.66 (d, J = 16.4 Hz, 1 H, CH_2Ph), 6.48 (br. s, 1 H, =CH), 7.25 (m, 5 H, PhH) ppm. δ (*E* rotamer; main different signals) = 2.87 (br. s, 1 H), 3.44 (m, 1 H), 4.70 and 4.80 (2d, J = 16.4 Hz, 1 H each, CH_2Ph), 6.43 (br. s, 1 H, =CH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (*Z* rotamer) = 13.7 (CH_3), 26.2 (CH_2), 27.1 (CH_2), 29.6 (CH_2), 46.3 (CH_2Ar), 53.3 (CH), 64.8 (OCH_2), 79.9 (CCl_2), 112.1 (C=), 118.3 (CN), 136.9 (*ipso*-C), 142.1 (CH=), 162.4 (CO), 163.2 (CO) ppm. δ (*E* rotamer; main different signals) = 24.0 (CH_2), 27.6 (CH_2), 52.5 (CH_2Ph), 55.9 (CH), 118.7 (CN), 126.0, 127.1, 128.6 (Ar-CH), 111.6 (=C), 127.3, 128.1, 128.6 (Ph), 135.2 (*ipso*-C), 143.0 (=CH) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}Cl_2N_2O_3$ [M^+ + 1] 395.0924; found 395.0926.

Ethyl 3-{[4-(Acetyloxy)cyclohex-3-en-1-yl]benzylamino}-2,2-dichloro-3-oxopropanoate (10): Operating as above, starting from **3** (0.8 g), after chromatography, **7** (1.22 g, 81%) was obtained as a yellowish viscous oil. IR (NaCl): $\tilde{\nu}$ = 3061, 3029, 1758, 1718, 1677, 1654 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (t, J = 7.2 Hz, 3 H, CH_3), 1.86–2.28 (m, 4 H), 2.42 (m, 4 H), 4.41 (q, J = 7.2 Hz, 2 H, CH_2O), 4.60 (s, 2 H, CH_2Ph), 4.74 (m, 1 H), 7.15–7.40 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_3), 29.8 (CH_2), 39.7 (CH_2), 46.5 (CH_2Ph), 56.5 (CH), 64.9 (CH_2O), 80.2 (CCl_2), 126.3, 127.2, 128.6 (Ph), 137.2 (*ipso*-C), 162.4 (CO), 163.4 (CO), 207.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}Cl_2NO_4$ [M^+ + 1] 386.0920; found 386.0917.

A solution of ketone **7** (0.5 g, 1.29 mmol) and *p*TsOH (0.295 g, 1.55 mmol) in isopropenyl acetate (17 mL) was heated to reflux for 5 h. The mixture was then concentrated and purified by chromatography to give enol acetate **10** (0.453 mg, 82%). IR (NaCl, neat): $\tilde{\nu}$ = 3062, 3029, 2984, 2935, 2852, 1758, 1679, 1655 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (t, J = 7.2 Hz, 3 H, CH_3), 1.94 (m, 2 H), 2.10 (s, 3 H, CH_3CO), 2.14–2.46 (m, 4 H), 4.39 (q, J = 7.2 Hz, 2 H, CH_2O), 4.42 (m, 1 H), 4.52 (d, J = 16.0 Hz, 1 H, CH_2Ph), 4.67 (d, J = 16 Hz, 1 H, CH_2Ph), 5.26 (br. s, CH=), 7.16–7.34 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_3), 20.9 (CH_3CO), 26.7 (CH_2), 26.9 (CH_2), 27.1 (CH_2), 46.6 (CH_2Ph), 54.5 (CH), 64.8 (OCH_2), 80.1 (CCl_2), 111.8 (CH=), 126.1, 127.0, 128.5 (Ph), 137.3 (*ipso*-C), 147.3 (C=), 162.6 (CO), 163.5 (CO), 169.2 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{24}Cl_2NO_5$ [M^+ + 1] 428.1026; found 428.1021.

General Procedures for Atom Transfer Radical Cyclization of Dichloroacetamides 8–10

Procedure A (Cu^I, TPMA, AIBN): To a suspension of CuCl (15.2 mg, 0.15 mmol, 30%) in 1,2-dichloroethane (4 mL) were successively added TPMA (44 mg, 0.15 mmol), AIBN (41.6 mg, 0.25 mmol, 50%), and nitrile **9** (200 mg, 0.51 mmol) and the mixture was heated at 60 °C for 48 h in a sealed tube. The solution was then allowed to reach room temp., concentrated, and purified by chromatography (hexane/EtOAc, 8:2 to hexane/EtOAc, 3:7).

Procedure B (Cu^I, DMF): A mixture of CuCl (7.6 mg, 0.07 mmol, 30%) and nitrile **9** (100 mg, 0.26 mmol) in DMF (1 mL) was heated at 80 °C overnight in a sealed tube. The solution was then concentrated and purified by chromatography by using the same conditions as in procedure A.

For the overall results, see Table 1.

Ethyl (1*RS*,4*SR*,5*RS*,6*RS*)-2-Benzyl-4,6-dichloro-3-oxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (11a): Colorless oil. IR (NaCl): $\tilde{\nu}$ = 3063, 3029, 2943, 2860, 1739, 1667 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 1.77 (br. d, J = 14.8 Hz, 1 H, 8-H_{eq}), 1.85–2.07 (m, 4 H, 7-CH_2, 8-H_{ax} and 9-H), 2.39 (dt, J = 14.0, 3.2 Hz, 1 H, 9-H), 2.87 (br. d, J = 3.2 Hz, 1 H, 5-H), 3.52 (br. s, 1 H, 1-H), 3.82 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.31 (m, 2 H, OCH_2), 4.99 (br. s, 1 H, 6-H), 5.49 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.26–7.37 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (CH_3), 22.2 (C-8), 24.6 (C-7), 25.0 (C-9), 44.1 (C-5), 48.8 (CH_2Ph), 50.9 (C-1), 57.7 (C-6), 63.7 (OCH_2), 71.6 (C-4), 127.7, 127.9, 128.7 (Ph), 136.5 (*ipso*-C), 164.6 (C-3), 168.2 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}Cl_2NO_3$ [M^+ + 1] 370.0971; found 370.0968.

Ethyl (1*RS*,4*SR*,5*RS*,6*RS*)-2-Benzyl-4,6-dichloro-6-cyano-3-oxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (11b): White solid; m.p. 124–125 °C (Et_2O/CH_2Cl_2, 9:1). IR (NaCl): $\tilde{\nu}$ = 3062, 3030, 2981, 2960, 2940, 2214, 1741, 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 1.95 (m, 2 H, 8-CH_2), 2.04 (br. d, J = 15.2 Hz, 1 H, 9-H), 2.33 (m, 2 H, 7-CH_2), 2.54 (dt, J = 15.2, 3.2 Hz, 1 H, 9-H), 3.29 (br. s, 1 H, 5-H), 3.50 (br. s, 1 H, 1-H), 3.88 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.34 (m, 2 H, OCH_2), 5.45 (d, J = 14.8 Hz, 1 H, CH_2Ph), 7.27–7.38 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_3), 23.3 (C-8), 26.6 (C-9), 30.1 (C-7), 46.0 (C-5), 49.0 (CH_2Ph), 49.2 (C-1), 59.6 (C-6), 64.2 (OCH_2), 69.8 (C-4), 118.9 (CN), 128.0, 128.1, 128.8 (Ph), 136.1 (*ipso*-C), 163.6 (C-3), 167.2 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}Cl_2N_2O_3$ [M^+ + 1] 395.0924; found 395.0916.

Ethyl (1*RS*,4*RS*,5*RS*,6*RS*)-2-Benzyl-4,6-dichloro-3-oxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (12a): Colorless oil. IR (NaCl): $\tilde{\nu}$ = 3089, 3061, 3029, 2953, 2938, 2867, 1736, 1658 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (t, J = 7.2 Hz, 3 H, CH_3), 1.71 (br. d, J = 14.8 Hz, 1 H, 8-H_{eq}), 1.84 (m, 1 H, 7-H_{eq}), 1.87 (tdd, J = 14, 4.4, 2.4 Hz, 1 H, 8-H_{ax}), 2.33 (ddt, J = 16, 12.4, 3.2 Hz, 1 H, 7-H_{ax}), 2.38 (t, J = 3.2 Hz, 2 H, 9-CH_2), 2.77 (m, 1 H, 5-H), 3.58 (br. s, 1 H, 1-H), 3.87 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.31 (m, 1 H, 6-H), 4.39 (m, 2 H, OCH_2), 5.28 (d, J = 14.8 Hz, 1 H, CH_2Ph), 7.26–7.37 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_3), 22.5 (C-8), 23.5 (C-7), 25.0 (C-9), 47.2 (C-5), 48.7 (CH_2Ar), 51.3 (C-1), 57.8 (C-6), 63.4 (OCH_2), 69.1 (C-4), 127.8, 128.8 (Ph), 136.5 (*ipso*-C), 164.6 (C-3), 166.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}Cl_2NO_3$ [M^+ + 1] 370.0971; found 370.0971.

Ethyl (1*RS*,4*RS*,5*RS*,6*RS*)-2-Benzyl-4,6-dichloro-6-cyano-3-oxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (12b): IR (NaCl): $\tilde{\nu}$ = 3087, 3062, 3029, 2982, 2962, 2939, 2870, 2243, 1762, 1736, 1664 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (t, J = 7.2 Hz, 3 H, CH_3), 1.82 (br. d, J = 14.4 Hz, 1 H, 8-H_{eq}), 1.93 (tdd, J = 14.4, 4.4, 2.4 Hz, 1 H, 8-H_{ax}), 2.13 (dm, J = 15.2 Hz, 1 H, 7-H_{eq}), 2.53 (t, J = 3.2 Hz, 2 H, 9-CH_2), 2.78 (ddd, J = 15.2, 12.4, 5.2 Hz, 1 H, 7-H_{ax}), 3.08 (br. s, 1 H, 5-H), 3.59 (br. s, 1 H, 1-H), 4.19 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.45 (q, J = 7.2 Hz, 2 H, OCH_2), 5.10 (d, J = 14.8 Hz, 1 H, CH_2Ph), 7.25–7.38 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.5 (CH_3), 23.4 (C-8), 25.1 (C-9), 29.1 (C-7), 49.3 (CH_2Ar), 49.8 (C-1), 49.9 (C-5), 59.1 (C-6), 64.0 (CH_2O), 68.9 (C-4), 117.7 (CN), 127.8, 128.0, 128.9 (Ph), 136.2 (*ipso*-C), 164.1 (C-3), 165.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}Cl_2N_2O_3$ [M^+ + 1] 395.0924; found 395.0924.

Ethyl (1*RS*,2*RS*,5*RS*,8*SR*)-4-Benzyl-3-oxo-4-azatricyclo[3.3.1.$0^{2,8}$]-nonane-2-carboxylate (13a): Yellowish oil. IR (NaCl): $\tilde{\nu}$ = 3061, 3028, 2935, 2868, 1729, 1642 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (dm, J = 12 Hz, 1 H, 6-H_{eq}), 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 1.50 (ddd, J = 12, 8, 4 Hz, 1 H, 6-H_{ax}), 1.86 (m, 1 H, 7-H_{eq}), 1.88 (dt, J = 13.2, 2.4 Hz, 1 H, 9-H), 1.96 (dm, J = 13.2 Hz, 1 H, 9-H), 2.08 (m, 1 H, 1-H), 2.10 (m, 1 H, 7-H_{ax}), 2.13 (m, 1 H, 8-H), 3.40 (br. s, 1 H, 5-H), 4.25 (q, J = 7.2 Hz, 2 H, OCH_2), 4.37 and 4.89 (2d, J = 14.8 Hz, 1 H each, CH_2Ph), 7.23–7.32 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2 (CH_3), 16.9 (C-7), 22.7 (C-8), 24.6 (C-6), 25.5 (C-9), 26.2 (C-1), 35.4 (C-2), 49.3 (CH_2Ph), 50.7 (C-5), 61.3 (OCH_2), 127.4, 128.2, 128.5 (Ph), 137.8 (*ipso*-C), 166.5 (C-3), 170.0 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}NO_3$ [M^+ + 1] 300.1600; found 300.1597.

Ethyl (1*RS*,2*SR*,5*RS*,8*RS*)-4-Benzyl-8-cyano-3-oxo-4-azatricyclo-[3.3.1.$0^{2,8}$]nonane-2-carboxylate (13b): White solid; m.p. 79–80 °C. IR (NaCl): $\tilde{\nu}$ = 3061, 3030, 2938, 2871, 2235, 1735, 1652 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.37 (m, 1 H, 6-H_{eq}), 1.39 (t, J = 7.2 Hz, 3 H, CH_3), 1.58 (ddd, J = 13.6, 8.8, 4.8 Hz, 1 H, 6-H_{ax}), 1.95 (br. s, 2 H, 9-CH_2), 2.64 (br. s, 1 H, 1-H), 3.48 (br. s, 1 H, 5-H), 4.34 (d, J = 14.0 Hz, 1 H, CH_2Ph), 4.36 (m, 2 H, OCH_2), 4.85 (d, J = 14.0 Hz, 1 H, CH_2Ph), 7.24–7.35 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_3), 17.5 (C-8), 21.2 (C-7), 24.2 (C-6), 24.2 (C-9), 28.5 (C-1), 41.3 (C-2), 49.5 (C-5), 49.9 (CH_2Ph), 62.7 (OCH_2), 119.6 (CN), 128.0, 128.2, 128.8 (Ph), 136.7 (*ipso*-C), 162.7 (C-3), 165.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}N_2O_3$ [M^+ + 1] 325.1547; found 325.1555.

Ethyl (1*RS*,4*SR*,5*RS*)-2-Benzyl-4-chloro-6-cyano-3-oxo-2-azabicyclo[3.3.1]non-6-ene-4-carboxylate (14): Yellow solid; m.p. 148–149 °C. IR (NaCl): $\tilde{\nu}$ = 3060, 3028, 2935, 2218, 1739, 1664 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 1.95 (ddd, J = 14.4, 4.4, 1.6 Hz, 1 H, 9-H), 2.22 (dm, J = 14.4 Hz, 1 H, 9-H), 2.38 (dm, J = 20.6 Hz, 1 H, 8-H), 2.61 (dd, J = 20.6, 4.4 Hz, 1 H, 8-H), 3.45 (br. s, 1 H, 5-H), 3.72 (br. s, 1 H, 1-H), 3.82 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.34 (m, 2 H, OCH_2), 5.54 (d, J = 15.2 Hz, 1 H, CH_2Ph), 6.77 (t, J = 3.6 Hz, 1 H, 7-H), 7.28–7.38 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (CH_3), 26.7 (C-9), 31.2 (C-8), 38.9 (C-5), 48.1 (C-1), 49.2 (CH_2Ph), 63.8 (OCH_2), 70.5 (C-4), 113.5 (C-6), 118.8 (CN), 127.9, 128.0, 128.8 (Ph), 136.2 (*ipso*-C), 144.3 (C-7), 163.2 (C-3), 167.4 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{20}ClN_2O_3$ [M^+ + 1] 359.1157; found 359.1157.

Ethyl 2-Chloro-3-(2-chloro-2-cyano-7-phenyl-6-azabicyclo[3.2.1]oct-6-yl)-3-oxopropanoate (15): IR (NaCl): $\tilde{\nu}$ = 1768, 1668 cm^{-1}. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 and 14.1 (CH_3), 23.8 and 24.0 (C-3), 27.2 and 27.4 (C-4), 31.3, 33.1, 35.0 (C-2 and C-8), 54.3 and 55.4 (CHClCO), 54.2 and 54.3 (C-5), 56.1, 56.3 (C-1), 63.0 and 63.6 (OCH_2), 62.1 and 64.6 (C-7), 118.5, 119.0 (CN), 125.6, 125.7, 128.7, 128.8, 129.4, 129.5 (Ph), 138.1, 138.5 (*ipso*-C), 163.0, 163.8, 163.9, 164.9 (CO) ppm. Minor signals for rotamer of each epimer were also observed. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}Cl_2N_2O_3$ [M^+ + 1] 395.0924; found 395.0923.

Ethyl (1*RS*,4*SR*,5*RS*)-2-Benzyl-4-chloro-3,6-dioxo-2-azabicyclo-[3.3.1]nonane-4-carboxylate (16): White solid. IR (NaCl): $\tilde{\nu}$ = 3063, 3029, 2931, 2853, 1754, 1720, 1662 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 1.82 (tdd, J = 14, 5.2, 2.4 Hz, 1 H, 8-H_{ax}), 2.01 (dt, J = 14.4, 3.2 Hz, 1 H, 9-H), 2.30 (dm, J = 14.0 Hz, 1 H, 8-H_{eq}), 2.50 (dd, J = 15.6, 5.2 Hz, 1 H, 7-H_{eq}), 2.58 (dq, J = 14.4, 3.2 Hz, 1 H, 9-H), 2.72 (ddd, J = 15.6, 14.0, 7.2 Hz, 1 H, 7-H_{ax}), 3.31 (br. s, 1 H, 5-H), 3.70 (br. s, 1 H, 1-

H), 4.03 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.36 (m, 2 H, OCH_2), 5.54 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.28–7.39 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (CH_3), 29.9 (C-8), 31.0 (C-9), 35.0 (C-7), 49.2 (CH_2Ph), 50.6 (C-1), 55.1 (C-5), 63.9 (OCH_2), 67.1 (C-4), 127.9, 128.0, 128.9 (Ph), 136.2 (*ipso*-C), 164.3 (C-3), 167.2 (CO), 204.3 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{21}ClNO_4$ [M^+ + 1] 350.1154; found 350.1152.

Ethyl (1*RS*,4*RS*,5*RS*)-2-Benzyl-4-chloro-3,6-dioxo-2-azabicyclo-[3.3.1]nonane-4-carboxylate (17): White solid. IR (NaCl): $\tilde{\nu}$ = 3062, 3028, 2938, 1760, 1715, 1659 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (t, J = 7.2 Hz, 3 H, CH_3), 1.79 (tdd, J = 13.6, 5.2, 2.4 Hz, 1 H, 8-H_{ax}), 2.03 (dt, J = 14.4, 2.8 Hz, 1 H, 9-H), 2.25 (m, 1 H, 8-H_{eq}), 2.50 (dd, J = 15.6, 5.2 Hz, 1 H, 7-H_{eq}), 2.87 (m, 1 H, 9-H), 2.91 (ddd, J = 15.6, 13.6, 7.2 Hz, 1 H, 7-H_{ax}), 3.12 (br. s, 1 H, 5-H), 3.73 (br. s, 1 H, 1-H), 4.09 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.29 (q, J = 7.2 Hz, 2 H, OCH_2), 5.36 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.28–7.37 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.7 (CH_3), 29.5 (C-9), 29.6 (C-8), 35.3 (C-7), 48.9 (CH_2Ph), 50.9 (C-1), 56.9 (C-5), 63.9 (OCH_2), 68.2 (C-4), 127.8, 128.0, 129.0 (Ph), 136.2 (*ipso*-C), 164.5 (C-3), 166.1 (CO), 205.6 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{21}ClNO_4$ [M^+ + 1] 350.1154; found 350.1152.

Ethyl (1*RS*,4*RS*,5*RS*,6*SR*)-2-Benzyl-6-cyano-3-oxo-2-azabicyclo-[3.3.1]nonane-4-carboxylate (18): A mixture of morphans **11b** and **12b** (25 mg, 0.06 mmol) was hydrogenated using Pd-C (3 mg) and NaOAc (15 mg, 0.18 mmol) in ethanol (2.5 mL). After purification, morphan **18** (14 mg, 70%) was isolated as a white solid; m.p. 114–115 °C. IR (NaCl): $\tilde{\nu}$ = 3063, 3028, 2872, 2237, 1734, 1645, 1734, 1651 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, J = 7.2 Hz, 3 H, CH_3), 1.42 (tdd, J = 14.4, 4.4, 2.4 Hz, 1 H, 8-H_{ax}), 1.60 (dm, J = 13.6 Hz, 1 H, 9-H), 1.72 (qd, J = 14, 4.4 Hz, 1 H, 7-H_{ax}), 1.89 (dm, J = 14.0 Hz, 1 H, 8-H_{eq}), 2.00 (dm, J = 14.0 Hz, 1 H, 7-H_{eq}), 2.39 (ddt, J = 13.6, 3.6, 2.4 Hz, 1 H, 9-H), 2.65 (br. s, 1 H, 5-H), 2.82 (dt, J = 13.2, 4.0 Hz, 1 H, 6-H), 3.52 (br. s, 1 H, 1-H), 3.74 (br. s, 1 H, 4-H), 3.90 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.26 (m, 2 H, OCH_2), 5.39 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.24–7.37 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1 (CH_3), 20.8 (C-7), 27.1 (C-8), 28.6 (C-9), 32.7 (C-6), 34.0 (C-5), 48.3 (CH_2Ph), 49.6 (C-1), 49.9 (C-4), 62.0 (CH_2O), 120.0 (CN), 127.6, 128.7 (Ph), 136.6 (*ipso*-C), 165.8 (CO), 170.4 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{23}N_2O_3$ [M^+ + 1] 327.1703; found 327.1700.

Ethyl 2-Benzyl-3,6-dioxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (19): A 1:1 mixture of morphans **16** and **17** (40 mg, 0.11 mmol), NaOAc (26.7 mg, 0.33 mmol), and a catalytic amount of Pd-C (4 mg, 10%) in ethanol (3 mL) was stirred under a hydrogen atmosphere overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated and purified by chromatography (hexane/EtOAc, 9:1 to 6:4) to give **19** (27 mg, 73%) as a 1:1 epimeric mixture. IR (NaCl): $\tilde{\nu}$ = 2928, 2871, 1737, 1715, 1644 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (t, J = 7.2 Hz, 3 H, CH_3), 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 1.70–1.86 (m, 2 H, 8-H_{ax} of both), 1.96 (dm, J = 14.0 Hz, 1 H, 9-H), 2.10 (dt, J = 13.6, 3.2 Hz, 1 H, 9-H), 2.18 (dt, J = 13.6, 3.2 Hz, 1 H, 9-H), 2.22 (m, 2 H, 8-H_{eq} of both), 2.45 (m, 3 H, 7-H_{eq}, 7-CH_2), 2.59 (dq, J = 14.0, 3.2 Hz, 1 H, 9-H), 2.88 (ddd, J = 15.2, 14, 7.2 Hz, 1 H, 7-H_{ax}), 2.98 (br. s, 1 H, 5-H), 3.04 (br. s, 1 H, 5-H), 3.49 (s, 1 H, 4-H), 3.69 (br. s, 2 H, 1-H of both), 3.76 (d, J = 6 Hz, 1 H, 4-H), 4.03 and 4.13 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.13 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.15–4.30 (m, 4 H, OCH_2 of both), 5.32 (d, J = 15.2 Hz, 1 H, CH_2Ph), 5.49 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.29–7.38 (m, 10 H, PhH of both) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (CH_3), 14.0 (CH_3), 29.2 (C-9), 29.5 (C-8), 29.6 (C-8), 32.7 (C-9), 34.3 (C-7), 35.0 (C-7), 47.6 (C-5), 48.4 (CH_2Ph), 48.6 (CH_2Ph), 50.0 (C-1), 50.2 (C-4), 50.5 (C-1), 52.6 (C-4), 61.9 (OCH_2), 62.1 (OCH_2), 127.7, 127.9, 128.1, 128.8, 128.9 (Ph), 136.5 (*ipso*-C), 136.8 (*ipso*-C), 165.0 (C-3), 165.4 (C-3), 168.6 (CO), 169.4 (CO), 208.2 (CO), 208.9 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}NO_4$ [M^+ + 1] 316.1543; found 316.1551.

The same stereochemical result was observed when the hydrogenation reaction was performed from **16** or **17** (20 mg in each case).

Ethyl (1*RS*,2*SR*,5*RS*,7*SR*)-3-(2-Cyano-7-phenyl-6-azabicyclo[3.2.1]-oct-6-yl)-3-oxopropanoate (20): IR (NaCl): $\tilde{\nu}$ = 3026, 2955, 2925, 2855, 2235, 1734, 1651 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (*E*-rotamer) = 1.28 (t, J = 7.6 Hz, 3 H, CH_3), 1.39 (d, J = 12.0 Hz, 1 H, 8-H_{ax}), 1.46 (m, 1 H, 4-H), 2.12 (m, 2 H, 3-CH_2), 2.17 (m, 1 H, 8-H_{eq}), 2.41 (m, 1 H, 4-H), 2.54 (br. s, 1 H, 1-H), 2.86 (ddd, J = 9.0, 7.2, 2.4 Hz, 1 H, 2-H), 3.07 and 3.18 (2d, J = 15.6 Hz, 1 H each, $NCOCH_2$), 4.19 (q, J = 7.6 Hz, 2 H, OCH_2), 4.66 (t, J = 5.2 Hz, 1 H, 5-H), 5.07 (s, 1 H, 7-H_{eq}), 7.20–7.42 (m, 5 H, PhH) ppm; minor signals for *Z* rotamer were also observed at δ = 3.43 and 3.53 (2d, J = 15.0 Hz, $NCOCH_2$), 4.39 (t, J = 5.2 Hz, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1 (CH_3), 22.6 (C-3), 27.3 (C-4), 31.9 (two peaks, C-2 and C-8), 42.4 (CH_2CO), 47.8 (C-1), 54.3 (C-5), 61.6 (OCH_2), 63.9 (C-7), 121.3 (CN), 125.7, 128.1, 129.1 (Ph), 140.2 (*ipso*-C), 165.3 (CO), 167.4 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{23}N_2O_3$ [M^+ + 1] 317.1703; found 327.1702.

Single-Crystal X-ray Analysis of 11b: The structures were solved by direct methods by using the SHELXS computer program and refined by full-matrix least-squares method with SHELX97.[20] CCDC-967928 (for **11b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data, X-ray Data Collection and Refinement Results of Morphan 11b: $C_{19}H_{20}Cl_2N_2O_3$; M = 395.27; monoclinic; space group $P2_1/c$; a = 10.688(6) Å, b = 32.756(15) Å, c = 12.276(8) Å, α = 90°, β = 117.00(4)°, γ = 90°; V = 3829(4) $Å^3$; Z = 8; D = 1.371 $Mg\,m^{-3}$; λ(Mo-K_α) = 0.71073 Å; F(000) = 1648; T = 293(2) K. The sample (0.12 × 0.09 × 0.08 mm) was studied with a diffractometer with an image plate detector. The data collection (θ_{max} = 32.33°, range of *hkl*: *h* –12→11, *k* –44→47, *l* –15→18) gave 16555 reflections with 6288 unique reflections from which 4408 with $I > 2.0\sigma(I)$.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of all compounds, three dimensional drawings of morphans **11**, **12**, **16**–**18** with the NMR spectroscopic data embedded, and additional X-ray crystallographic data and ORTEP plots of **11b**.

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