

Selective Transformations of β -Keto Esters, Promoted by Dowex Basic Ion-Exchange Resins

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Depending on the nature of the Dowex basic ion-exchange resin, cyclic β -keto esters **1** react with α,β -unsaturated aldehydes **2** to give either the corresponding Michael adducts **3** or the highly functionalized bicyclo[3.3.1]nonanes **4** in a one-pot Michael addition–intramolecular aldolization sequence. Some selective transformations of the highly functionalized

systems **3** and **4** to provide amino azabicyclo[3.3.1]nonanones **9**, polycyclic amins **10**, and azacyclooctene **12** are also presented.

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Introduction

Control of the production of toxic waste and by-products in chemical transformations is a challenging problem from industrial, academic, and social points of view,^[1] and constitutes an active field of investigation owing to the increasing demands of environmental legislation. In recent years the development of environmentally friendly heterogeneous reagents, long known for their low cost and toxicity, has received much attention.^[2] Moreover, the products can easily be isolated in good chemical purity by simple filtration, avoiding time-consuming and tedious extractive workup. In this context, a large number of new inorganic,^[3] organic,^[4] or hybrid^[5] heterogeneous catalysts have been found to be efficient in many important organic transformations, and special attention has been given to the Michael addition.^[4b–4d,5,6] Quite surprisingly, the commercially available and environmentally benign basic ion-exchange resins have not been the center of much interest as Michael addition promoters. The pioneering studies of Schmilde,^[7] Yamada,^[8] and Bergmann^[9] in the 1950s demonstrated their efficiency in some cases, but also showed the limitations of a number of basic ion-exchange resins in Michael additions between simple donors – such as thiols, nitroalkanes, and malonic derivatives – and acrylic acceptors. Since then, conjugate additions of thiols with the aid of fluoride ion-modified Amberlyst or Dowex resins and Michael additions of nitroalkanes to methyl acrylate and

acyclic vinyl ketones promoted by Amberlyst A-21 or A-27 have also been proposed.^[10]

Results and Discussion

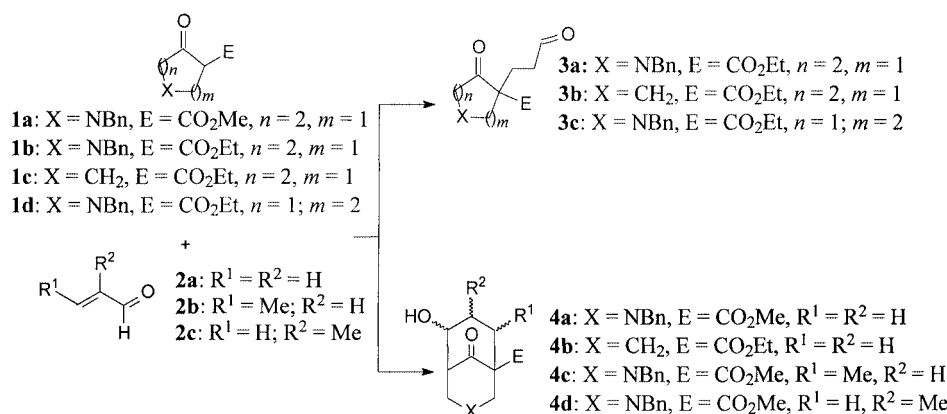
Pursuing our interest in the Michael addition^[11] we started a collaborative program aimed at the selective and efficient construction of functionalized systems of types **3** and **4** starting from simple cyclic β -keto esters **1** and α,β -unsaturated aldehydes **2** (Scheme 1).

For this purpose, we decided to study the utilization and the selectivity of two commercially available Dowex basic ion-exchange resins (Table 1), which combined the advantages of solid-phase synthesis and anionic activation and should be easily amenable to large-scale preparations.

To test the feasibility of the Michael addition under mild conditions we first selected Dowex 66, a macroporous, weakly basic hydroxide resin, in the reaction between piperidone **1a** as its commercially available hydrochloride and acrolein **2a** in MeOH, which had proven to be the best solvent.^[12] Although no reaction took place with only 20% (by weight) of resin (Table 1, run 1) a quantitative yield of the expected Michael adduct **3a** was obtained with 100% of Dowex 66 (run 2) and the same result could be achieved on scaling up the reaction to 15 grams of adduct. Interestingly, use of a large excess of resin (400%) did not affect the transformation at all and no further intramolecular aldolization to hydroxy azabicyclo[3.3.1]nonane **4a** was observed even after two days at room temperature (run 3). β -Keto ester **1b** was found to be less reactive toward acrolein **2a**, and 500% of Dowex 66 was needed to achieve total conversion in this case, after 24 h at room temperature, and to isolate a quantitative yield of the corresponding adduct **3b** (run 4). Alternatively, on treatment of **1a** with acrolein **2a**, no reaction was

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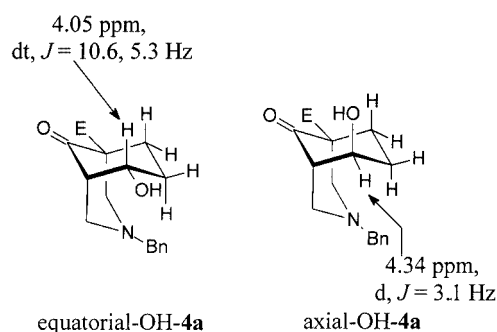
Scheme 1

Table 1. Treatment of **1** and **2** with Dowex resins

Run ^[a]	Resin (%) ^[b]	<i>t</i> (h)	Product	Yield (%) ^[c]
1	Dowex 66 (20)	2	1a ^[d]	92
2	Dowex 66 (100)	4	3a	99
3	Dowex 66 (400)	48	3a	99
4	Dowex 66 (500)	24	3b	100
5	Dowex 550A (20)	72	1a ^[d]	100
6	Dowex 550A (200) ^[e]	24	3a	100
7	Dowex 550A (300) ^[f]	5	4a ^[g]	100
8	Dowex 550A (500)	16 ^[h]	4b ^[g]	77
9	Dowex 66 (100)	24	1c ^[d] + 3c	92 ^[i]
10	Dowex 66 (300)	24	3c	80
11	Dowex 550A (300)	3 ^[h]	3c	95
12	Dowex 550A (300)	24	4c ^[j]	90
13	Dowex 550A (300)	96	4d ^[j]	92

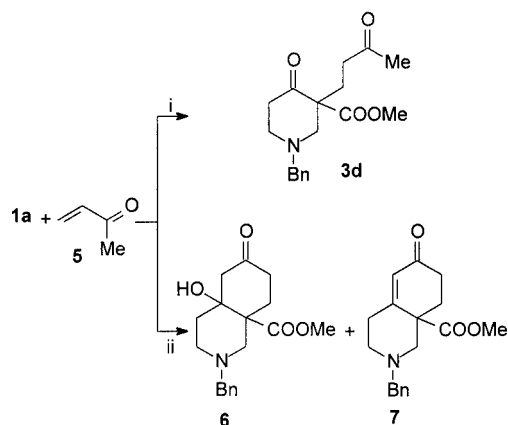
^[a] Unless otherwise noted, all reactions were performed at room temperature, in MeOH for **1a** and in EtOH for **1b** and **1c**. ^[b] Percentage by weight of **1**. ^[c] Isolated after filtration through a short pad of Celite. ^[d] Isolated at its free HCl form. ^[e] Use of 100% resulted in an incomplete transformation after 48 h. ^[f] The same result was obtained with 400% of resin after 4 h. ^[g] Two isomers in 1.3:1 ratio for **4a** and 1.2:1 ratio for **4b**. ^[h] Reflux. ^[i] Ratio **3c**/**1c** = 2.3. ^[j] Four isomers in 8:6.3:1.3:1 ratio for **4c** and 1.5:1.3:1.2:1 ratio for **4d**.

observed with 20% of the more basic Dowex 550A resin even after a prolonged reaction time (run 5), but **3a** could be obtained quantitatively with 200% of the same resin (run 6). The expected azabicyclo^[13] derivative **4a** was isolated cleanly as a 1.3 to 1 mixture of axial and equatorial epimers after 5 hours by simple filtration when 300% of Dowex 550A was used (run 7). The stereochemistry was corroborated by comparison of the NMR spectroscopic data with previous work from this laboratory (Figure 1).^[14] More specifically, the equatorial-OH-**4a** epimer shows a coupling constant ³*J*_{H2-H3} = 10.6 Hz due to *H*-C-2 at δ = 4.05 ppm (dt, *J* = 10.6, 5.3 Hz), which is in agreement with a 1,2-*trans*-diaxial arrangement for the two protons. In the major axial-OH-**4a** isomer, on the other hand, *H*-C-2 shows up at δ = 4.34 ppm as a broad doublet with *J* = 3.1 Hz, corroborating the proposed structures.

Figure 1. ¹H observations for **4a** axial-OH and equatorial-OH (E = COOMe)

Finally, the formation of the bridged bicyclic compound^[15] **4b**, the product of the reaction between **1b** and **2a**, was achieved by use of an excess of Dowex 550A in refluxing EtOH for 16 h (Table 1, run 8), once again showing lower reactivity for **1b** than for **1a**. Not unexpectedly, commercially available piperidone hydrochloride **1c** displayed lower reactivity than **1a** or **1b** toward acrolein **2a**. Regardless of the nature and the quantity of Dowex resin, the transformation always gave the Michael adduct **3c** (runs 9, 10), which could not be transformed into the corresponding bicyclic derivative even in the presence of an excess of Dowex 550A in refluxing EtOH (run 11). This result can be explained by the presence of the basic nitrogen atom in the position β to the carbonyl, which prevents the enolization needed for the intramolecular aldolization. Other aldehydes such as crotonaldehyde **2b** (run 12) and methacrolein **2c** (run 13) also gave very good results in the condensation with **1a** in the presence of Dowex 550A, allowing the one-pot syntheses of functionalized hydroxy azabicyclo[3.3.1]nonanes **4c** and **4d** in very good isolated yields and as mixtures of the four possible diastereomers in 8:6.3:1.3:1 and 1.5:1.2:1.1:1 ratios, respectively. Interestingly enough, the closely related commercially available Amberlite resins IRA 410 and the more basic IRA 400 were totally inactive for this transformation even after activation of the resins by treatment with 1 N NaOH solution.

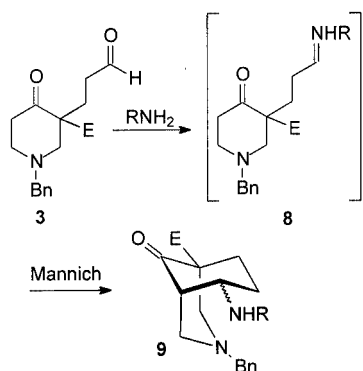
As was to be expected, when methyl vinyl ketone **5** (Scheme 2) was used in the presence of Dowex 66 (100%) the corresponding Michael adduct **3d** was formed after 120 h in 92% yield, together with unchanged starting material **1a**. On the other hand, use of Dowex 550A proved to be inefficient for the formation of bridged derivatives, the only transformation being a Robinson annulation to provide a 1:1 mixture of fused hydroxy bicyclic derivative **6** and the corresponding olefin **7** in 80% overall yield (Scheme 2).



Scheme 2. Reagents and conditions: i, Dowex 66 (100%), MeOH, room temp., 120 h, 92%. ii, Dowex 550A (300%), EtOH, room temp., 120 h, then reflux, 6 h, 80%

With an efficient and simple large-scale heterogeneous preparation of both functionalized monocyclic and bicyclic systems **3** and **4** now to hand, we turned our attention to the reactivity of these new derivatives for the selective elaboration of other valuable heterocyclic compounds.

We first decided to take advantage of the 1,5-dicarbonyl functionality of compounds **3** in the reaction with primary amines for the selective construction of 6-amino-3-azabicyclo[3.3.1]nonanones **9** by intramolecular Mannich reaction of the transient aldimines **8**^[16] (Scheme 3).



Scheme 3

Although aniline in refluxing toluene in the presence of 4-Å molecular sieves (MS) proved unreactive,^[17] we were pleased to find that benzylamine and *tert*-butylamine did indeed undergo the expected transformation, affording the

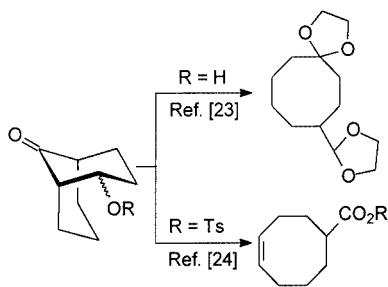
corresponding bridged compounds **9a** and **9b** in 99% and 77% yields, respectively (Table 2, runs 1–3). Alternatively, when ω -functionalized amines such as 2-aminoethanol (run 4), 1,3-diaminopropane (run 5), and 2-aminoethanethiol (run 6) were used, acetalization of both carbonyl functions resulted in the formation of tricyclic aminals **10a–c** in synthetically useful yields after a simple filtration through a short pad of Celite, generally with very high chemical purity. As recently shown in this laboratory, the mechanistic pathway probably involves an intramolecular capture of an iminium intermediate by the nucleophilic function of the amine.^[18] It is interesting to note that fused polycyclic structures including N/O- or N/N-aminals are found in biologically active natural and unnatural compounds^[19] and also constitute effective intermediates for the preparation of chiral pyrrolidines and piperidines.^[20] Unfortunately, β -alanine (run 7) was unreactive under the standard conditions and only hydroxybicyclo[3.3.1]nonane **3a**, arising from intramolecular aldolization, was isolated.

Table 2. Treatment of **3** with amines (E = CO₂Et)^[a]

Run	Amine	Product	Yield (%) ^[b]
1	PhNH ₂	No reaction	–
2	<i>t</i> BuNH ₂ ^[c]	9a	99
3	BnNH ₂	9b	77
4	3-aminopropanol	10a	80 ^[d]
5	1,3-aminopropane	10b	65 ^[e]
6	2-aminoethanethiol	10c	66 ^[d]
7	β -alanine	3a	90 ^[d]

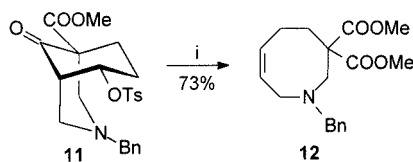
^[a] Unless otherwise noted, all reactions were performed on a 1 mmol scale in the presence of 4-Å MS in refluxing toluene for 24 h, with an adduct/amine ratio of 1:1.5. ^[b] Isolated after filtration through a short pad of Celite. ^[c] Room temperature, 24 h. ^[d] Two isomers in ratios of 1.5:1 for **9a**, 1.2:1 for **9b**, 1.2:1 for **10a**, 2:1 for **10c**, and 1.5:1 for **3a**. ^[e] Only one isomer.

A previous report on the reactivity of bicyclo[3.3.1]nonanes^[21] prompted us to surmise that the selective fragmentation of compounds **4** might provide access to substituted azacyclooctanes, as found in some bioactive natural products, such as β -carboline alkaloids.^[22] In the carbocyclic series, it is known that hydroxybicyclo[3.3.1]nonanones undergo clean fragmentation to eight-membered rings under acetalization conditions with ethylene glycol.^[23] On the other hand, it has been reported that the corresponding equatorial tosylates were easily cleaved^[24] by alkoxides through a Grob-type reaction^[25] to give the corresponding cyclooctenes (Scheme 4).



Scheme 4

In this case, although the acetalization of **3a** failed regardless of the experimental conditions, equatorial-OTs-**11** was, as expected, cleanly cleaved on treatment with diazabicycloundecene (DBU) in refluxing MeOH to give the desired azacyclooctene **12** in 73% isolated yield (Scheme 5).^[26]



Scheme 5. Reagents and conditions: i, DBU (1.5 equiv.), MeOH, reflux, 4 h

Conclusion

We have demonstrated the efficiency of two commercially available Dowex basic hydroxide resins for Michael addition of cyclic β -keto esters to α,β -unsaturated carbonyl compounds, combining the advantages of solid-phase synthesis and anionic activation. This allows the facile and environmentally friendly preparation of highly functionalized systems, precursors of polycyclic heteroatomic derivatives of potential synthetic and biological interest.

Experimental Section

General: Melting points were observed in open Pyrex capillary tubes and are uncorrected. FC (flash chromatography) was performed with Merck 60 silica gel (230–240 mesh).^[27] TLC was performed on Alugram SIL G/UV 254 silica gel analytical plates with

a 250 μ m coating. IR spectra were recorded neat or in CHCl_3 , and NMR spectra were obtained at 200 MHz in CDCl_3 with residual CHCl_3 as internal reference.

Material: Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Both Dowex and Amberlite ion-exchange resins were purchased from Aldrich.

General Procedure for Reactions in the Presence of Ion-exchange Resins. Preparation of Michael Adduct 3 and Hydroxybicyclo[3.3.1]nonanes 4: The ion-exchange resin was introduced into a solution of the β -dicarbonyl compound (1 mmol) in 25 mL of alcoholic solvent. The Michael acceptor (1.5 mmol) was then added and the reaction mixture was stirred either at room temperature or at reflux (see Table 1). After completion, simple filtration through a short pad of Celite and evaporation of the filtrate under reduced pressure gave the product in very good chemical purity as estimated by NMR (>95%), and an analytical sample was obtained by FC on SiO_2 .^[27]

Ethyl 1-Benzyl-4-oxo-3-(3-oxopropyl)piperidine-3-carboxylate (3a, from 1b and 2a): $R_f = 0.54$ (Et_2O /pentane, 9:1). IR (neat): $\tilde{\nu} = 2813, 1725, 1463 \text{ cm}^{-1}$. ^1H NMR: $\delta = 9.69$ (s, 1 H), 7.35–7.24 (m, 5 H), 4.18 (q, $J = 7.2 \text{ Hz}$, 2 H), 3.56 (s, 2 H), 3.58 (dd, $J = 11.4, 2.5 \text{ Hz}$, 1 H), 3.08–2.59 (m, 3 H), 2.49–2.01 (m, 5 H), 1.89 (m, 1 H), 1.23 (t, $J = 7.1 \text{ Hz}$, 3 H) ppm. ^{13}C NMR: $\delta = 206.2, 200.9, 171.3, 137.7, 128.8, 128.2, 127.3, 61.7, 61.4, 61.3, 60.1, 53.5, 40.4, 39.4, 24.1, 14.0$ ppm. Elemental analysis calcd. (%) for $\text{C}_{18}\text{H}_{23}\text{NO}_4$ (317.4): C 68.12, H 7.30, N 4.41; found C 68.41, H 7.28, N 3.98.

Ethyl 1-Oxo-2-(3-oxopropyl)cyclohexane-2-carboxylate (3b)^[28] (from 1c and 2a): IR (neat): $\tilde{\nu} = 3461, 2938, 1714, 1447 \text{ cm}^{-1}$. ^1H NMR: $\delta = 9.70$ (t, $J = 1.3 \text{ Hz}$, 1 H), 4.17 (dq, $J = 7.2, 2.0 \text{ Hz}$, 2 H), 2.62–2.28 (m, 6 H), 2.11 (dd, $J = 9.6, 5.5 \text{ Hz}$, 1 H), 1.97 (m, 1 H), 1.85 (dd, $J = 9.6, 5.5 \text{ Hz}$, 1 H), 1.60 (m, 2 H), 1.43 (m, 1 H), 1.24 (t, $J = 7.1 \text{ Hz}$, 3 H) ppm. ^{13}C NMR: $\delta = 207.7, 201.2, 171.8, 61.5, 59.8, 41.0, 39.3, 36.6, 27.5, 26.8, 22.5, 14.1$ ppm.

Ethyl 1-Benzyl-3-oxo-4-(3-oxopropyl)piperidine-4-carboxylate (3c, from 1d and 2a): IR (neat): $\tilde{\nu} = 3438, 2933, 2807, 1727, 1448, 1201, 1111 \text{ cm}^{-1}$. ^1H NMR: $\delta = 9.67$ (s, 1 H), 7.24 (m, 5 H), 4.14 (q, $J = 7.2 \text{ Hz}$, 2 H), 3.5 (m, 2 H), 3.15 (d, $J = 15.5 \text{ Hz}$, 1 H), 2.92 (d, $J = 15.5 \text{ Hz}$, 1 H), 2.80–1.50 (m, 8 H), 1.16 (t, $J = 7.2 \text{ Hz}$, 3 H) ppm. ^{13}C NMR: $\delta = 204.9, 201.2, 170.9, 137.1, 129.0, 128.5, 127.5, 62.5, 61.7, 61.5, 56.5, 48.7, 39.2, 31.6, 25.7, 14.1$ ppm. Elemental analysis calcd. (%) for $\text{C}_{18}\text{H}_{23}\text{O}_4\text{N}$ (317.4): C 68.12, H 7.30, N 4.41; found C 67.58, H 7.40, N 4.29.

Methyl 1-Benzyl-4-oxo-3-(3-oxobutyl)piperidine-3-carboxylate (3d, from 1a and 5): $R_f = 0.40$ (Et_2O /pentane, 7:3). IR (neat): $\tilde{\nu} = 3440, 2980, 2840, 1740, 1460, 1370, 1250 \text{ cm}^{-1}$. ^1H NMR: $\delta = 7.30$ (m, 5 H), 3.70 (s, 3 H), 3.6–2.08 (m, 12 H), 2.07 (s, 3 H) ppm. ^{13}C NMR: $\delta = 207.3, 206.0, 171.7, 137.5, 128.6, 128.2, 127.2, 61.4, 61.1, 60.7, 52.7, 57.2, 40.1, 38.5, 29.6, 25.4$ ppm. Elemental analysis calcd. (%) for $\text{C}_{18}\text{H}_{23}\text{NO}_4$ (317.4): C 68.12, H 7.30, N 4.41; found C 67.92, H 7.46, N 4.39.

Methyl 3-Benzyl-6-hydroxy-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (equatorial-OH) (4a, from 1a and 2a): $R_f = 0.47$ (Et_2O /pentane, 9:1). IR (neat): $\tilde{\nu} = 3516, 2953, 1737, 1438 \text{ cm}^{-1}$. ^1H NMR: $\delta = 7.25$ (m, 5 H), 4.05 (d, $J = 10.6, 5.3 \text{ Hz}$, 1 H), 3.63 (s, 3 H), 3.45 (m, 1 H), 3.51 (d, $J = 12.5 \text{ Hz}$, 1 H), 3.71 (d, $J = 12.5 \text{ Hz}$, 1 H), 3.08 (dd, $J = 12.5, 2.5 \text{ Hz}$, 1 H), 2.85 (m, 2 H), 1.25 (m, 1 H), 1.75 (m, 1 H) ppm. ^{13}C NMR: $\delta = 209.2, 172.2, 137.8, 128.8, 128.6, 127.5, 72.4, 61.8, 61.3, 58.2, 54.2, 54.2, 52.4, 30.4, 30.2$

ppm. Elemental analysis calcd. (%) for $C_{17}H_{21}O_4N$ (303.4): C 67.09, H 6.95, N 4.60; found C 66.87, H 7.02, N 4.48.

Methyl 3-Benzyl-6-hydroxy-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (axial-OH) (4a, from 1a and 2a): White powder; m.p. 107–109 °C; R_f = 0.31 (Et_2O /pentane, 9:1). IR (neat): $\tilde{\nu}$ = 3516, 2953, 1737, 1438 cm^{-1} . 1H NMR: δ = 7.25 (m, 5 H), 4.34 (d, J = 3.1 Hz, 1 H), 3.64 (s, 3 H), 3.40 (s, 2 H), 3.17–2.44 (m, 10 H) ppm. ^{13}C NMR: δ = 210.3, 171.1, 138.0, 128.8, 128.6, 127.4, 76.4, 61.9, 61.7, 58.2, 54.8, 56.6, 52.3, 31.7, 29.2 ppm. Elemental analysis calcd. (%) for $C_{17}H_{21}O_4N$ (303.4): C 67.09, H 6.95, N 4.60; found C 66.33, H 7.07, N 4.52.

Ethyl 4-Hydroxy-9-oxobicyclo[3.3.1]nonane-1-carboxylate (4b, from 1c and 2a, two diastereomers): IR (neat): $\tilde{\nu}$ = 3437, 3056, 2933, 1725, 1451, 1262, 1073, 736 cm^{-1} . 1H NMR: δ = 4.26 (m, 1 H), 4.15 (q, J = 7.1 Hz, 4 H), 4.03 (m, 1 H), 2.80–2.71 (m, 1 H), 2.68 (m, 1 H), 2.55 (m, 3 H), 2.31 (m, 5 H), 1.99 (m, 7 H), 1.74 (m, 5 H), 1.55 (m, 3 H), 1.23 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR: δ = 213.9, 212.9, 172.7, 76.0, 72.7, 61.33, 61.28, 58.1, 57.5, 54.4, 54.0, 36.5, 36.1, 31.2, 30.4, 28.5, 28.0, 26.5, 20.5, 19.4, 14.2 ppm. Elemental analysis calcd. (%) for $C_{12}H_{18}O_4$ (226.3): C 63.70, H 8.02; found C 63.78, H 7.82.

Methyl 3-Benzyl-6-hydroxy-8-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (4c, from 1a and 2b, four diastereomers): R_f = 0.30 (Et_2O /pentane, 7:3). IR (neat): $\tilde{\nu}$ = 3440, 2950, 2820, 1730, 1500, 1450, 1365, 1270, 1160, 1080 cm^{-1} . 1H NMR: δ = 7.30 (m, 5 H), 4.33 (s broad, 1 H), 4.08 (m, 1 H), 3.70 (s, 3 H), 3.68–3.15 (m, 3 H), 3.05 (m, 2 H), 2.85–2.35 (m, 3 H), 3.45 (s, 2 H), 0.87 (s, 3 H) ppm. ^{13}C NMR: δ = 211.2, 210.1, 209.9, 207.9, 171.0, 170.6, 170.5, 138.1, 138.0, 137.9, 137.6, 129.1, 129.0, 128.8, 128.6, 128.6, 128.5, 128.4, 127.5, 127.4, 70.5, 70.0, 63.0, 62.9, 62.3, 62.1, 62.0, 61.7, 61.2, 58.3, 56.8, 56.6, 55.9, 54.1, 54.3, 54.5, 51.7, 52.0, 52.2, 52.3, 38.8, 38.5, 38.1, 37.4, 37.1, 36.4, 35.3, 34.3, 16.3, 16.6, 18.8, 19.5 ppm. Elemental analysis calcd. (%) for $C_{18}H_{23}NO_4$ (317.4): C 68.12, H 7.30, N 4.41; found C 67.68, H 7.52, N 4.19.

Methyl 3-Benzyl-6-hydroxy-7-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (4d, from 1a and 2c, four diastereomers): R_f = 0.19 (Et_2O /pentane, 7:3). IR (neat): $\tilde{\nu}$ = 3480, 3080, 2960, 2840, 1740, 1470, 1280, 1130 cm^{-1} . 1H NMR: δ = 7.27 (m, 5 H), 4.82 (s, 1 H), 4.56 (m, 1 H), 3.71 (s, 3 H), 3.45–1.40 (m, 8 H), 1.19 (d, J = 6.3 Hz, 3 H), 1.09 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR: δ = 210.5, 209.2, 171.9, 171.0, 138.1, 138.0, 129.212, 129.0, 128.8, 128.6, 128.5, 128.4, 128.1, 127.6, 127.5, 127.4, 127.1, 80.0, 78.0, 61.8, 61.6, 61.1, 60.9, 59.6, 59.2, 58.5, 57.1, 54.6, 56.2, 56.1, 54.0, 53.5, 52.4, 41.1, 40.3, 39.3, 36.5, 36.0, 34.6, 19.5, 18.2 ppm. Elemental analysis calcd. (%) for $C_{18}H_{23}NO_4$ (317.4): C 68.12, H 7.30, N 4.41; found C 68.47, H 7.43, N 4.29.

Methyl 2-Benzyl-4a-hydroxy-6-oxooctahydroisoquinoline-8a-carboxylate (6): R_f = 0.30 (Et_2O /pentane, 9:1). 1H NMR: δ = 7.25 (m, 5 H), 4.36 (s broad, 1 H), 3.67 (s, 3 H), 3.59–3.42 (m, 1 H), 3.45 (ABq, J = 12.5 Hz, 2 H), 2.92 (m, 2 H), 2.72–1.96 (m; 9 H) ppm. ^{13}C NMR: δ = 208.2, 176.9, 138.0, 128.8, 128.5, 127.5, 78.7, 62.6, 62.1, 56.1, 53.7, 52.3, 51.2, 37.9, 34.7, 31.8 ppm. It was not possible to separate the compound from remaining starting material and elemental analysis was not performed.

Methyl 2-Benzyl-6-oxo-3,4,6,7,8,8a-hexahydro-1H-isoquinoline-8a-carboxylate (7):^[29] R_f = 0.44 (Et_2O /pentane, 9:1). IR (neat): $\tilde{\nu}$ = 2953, 2805, 1728, 1673, 1453, 1350, 1213 cm^{-1} . 1H NMR: δ = 7.33–7.27 (m, 5 H), 5.89 (s, broad, 1 H), 3.68 (s, 3 H), 3.50 (ABq, 2 H, J = 13.4 Hz), 3.38 (d, broad, J = 10.9 Hz, 1 H), 2.95 (m, 1 H), 2.82 (m, 1 H), 2.34–2.09 (m, 5 H), 1.80 (d, broad, J = 11.2 Hz,

2 H) ppm. ^{13}C NMR: δ = 198.3, 173.1, 160.3, 138.4, 128.8, 128.2, 127.3, 124.7, 62.9, 62.1, 53.7, 52.5, 49.8, 34.6, 35.5, 30.9 ppm.

Treatment of Michael Adducts with Amines. Preparation of Amino-bicycles 9 and Cyclic Aminals 10: Molecular sieves (4 Å, 6 g) were added to a solution of the Michael adduct 3 (0.70 mmol) in dry toluene (25 mL). The amine was introduced by syringe (1.05 mmol), and the reaction mixture was heated under reflux for 24 h. Simple filtration through a short pad of Celite and evaporation of the filtrate under reduced pressure usually gave the product with very good chemical purity as estimated by NMR (> 95%). Analytical samples, although very sensitive toward chromatography on silica gel, were obtained with Et_3N -neutralized SiO_2 .

Ethyl 3-Benzyl-6-tert-butylamino-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (9a, two diastereomers): IR (neat): $\tilde{\nu}$ = 2955, 2789, 1720, 1445, 1357, 1253 cm^{-1} . 1H NMR: δ = 7.23 (m, 5 H), 4.07 (q, J = 7.0 Hz, 2 H), 3.50 (m, 3 H), 3.15–1.45 (m, 5 H), 1.15 (t, J = 7.0 Hz, 3 H), 1.15–1.00 (m, 5 H), 0.92 (s, 9 H) ppm. ^{13}C NMR: δ = 210.7, 170.9, 138.4, 128.8, 128.4, 127.3, 62.1, 62.0, 61.7, 61.6, 61.2, 61.1, 57.9, 55.5, 54.5, 50.9, 51.1, 32.4, 31.7, 30.0, 14.2 ppm. MS: m/z (%) = 371 (8) [M^+], 112 (27), 91 (100), 57 (30), 29 (10).

Ethyl 3-Benzyl-6-benzylamino-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (9b, two diastereomers): IR (neat): $\tilde{\nu}$ = 2953, 2368, 1714, 1457 cm^{-1} . 1H NMR: δ = 7.85 (m, 10 H), 4.11 (q, J = 7.1 Hz, 2 H), 3.70–1.70 (m, 15 H), 1.20 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR: δ = 210.5, 210.3, 170.7, 140.1, 138.3, 128.9, 128.6, 128.5, 128.2, 128.0, 61.2, 62.1, 61.8, 61.3, 61.2, C1: 58.6, 58.2, 53.6, 52.6, 49.2, 50.6, 32.5, 31.9, 29.0, 26.8, 14.3 ppm. Elemental analysis calcd. (%) for $C_{25}H_{30}N_2O_3$ (406.5): C 73.86, H 7.44, N 6.89; found C 73.54, H 7.43, N 7.03.

Compound 10a (two diastereomers): IR (neat): $\tilde{\nu}$ = 3503, 2955, 1731, 1652, 1454, 1362 cm^{-1} . 1H NMR: δ = 7.20 (m, 5 H), 4.60 (m, 1 H), 4.40 (s broad, 1 H), 4.15–3.80 (m, 2 H), 3.76–2.20 (m, 10 H), 2.20–1.80 (m, 2 H), 1.80–1.40 (m, 3 H), 1.28–0.80 (m, 4 H) ppm. ^{13}C NMR: δ = 174.1, 142.5, 138.8, 128.8, 128.3, 127.1, 99.8, 90.6, 67.1, 61.8, 60.9, 54.1, 53.7, 49.1, 46.3, 29.6, 25.6, 25.5, 14.3 ppm. MS: m/z (%) = 283 (30), 265 (100), 191 (11), 91 (44).

Compound 10b: IR (neat): $\tilde{\nu}$ = 2938, 2799, 1729, 1647, 1457, 1359, 1256, 1212 cm^{-1} . 1H NMR: δ = 7.18 (m, 5 H), 4.62 (m, 1 H), 4.05 (m, 2 H), 3.70–1.15 (m, 18 H), 0.98 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR: δ = 174.1, 143.5, 138.6, 128.6, 128.2, 126.8, 99.0, 74.1, 60.5, 60.4, 53.8, 48.9, 47.3, 44.7, 30.5, 30.3, 27.3, 14.1 ppm. MS: m/z (%) = 282 (20), 264 (100), 209 (12), 91 (61).

Compound 10c (two diastereomers): IR (neat): $\tilde{\nu}$ = 2931, 1725, 1653, 1555, 1448, 1209 cm^{-1} . 1H NMR: δ = 7.21 (m, 5 H), 5.10–4.50 (m, 1 H), 4.09 (m, 2 H), 3.80–2.65 (m, 7 H), 2.50–1.18 (m, 5 H), 1.09 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR: δ = 174.0, 141.2, 138.7, 128.8, 128.2, 127.1, 101.1, 65.4, 61.9, 60.9, 60.0, 53.3, 50.9, 48.2, 32.1, 29.4, 28.1, 14.3 ppm. MS: m/z (%) = 285 (37), 267 (100), 91 (89).

Formation of Tosylate 11:^[30] The hydroxyazabicyclic compound equatorial-OH-4a (1.64 mmol), pyridine (3.28 mmol), and tosyl chloride (2.46 mmol) were dissolved in 5 mL of chloroform (previously filtered through a short pad of basic alumina). After the mixture had been stirred for 2 h at room temperature, Et_3N (2.46 mmol) and tosyl chloride (2.46 mmol) were added and the reaction mixture was stirred at room temperature until completion (TLC). The organic layer was washed successively with a saturated solution of $NaHCO_3$ (10 mL) and a saturated solution of NH_4Cl

(10 mL), dried with MgSO_4 , and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 .

Methyl 3-Benzyl-9-oxo-6-(toluene-4-sulfonyloxy)-3-azabicyclo[3.3.1]nonane-1-carboxylate (11, equatorial-OTs): $R_f = 0.6$ (Et_2O /pentane, 9:1). IR (neat): $\tilde{\nu} = 1735, 1747, 2361 \text{ cm}^{-1}$. ^1H NMR: $\delta = 7.27$ (m, 9 H), 4.68 (m, 1 H), 3.71 (s, 3 H), 3.62 (d, $J = 12.0$ Hz, 1 H), 3.43 (d, $J = 12.0$, 1 H), 3.15 (dd, $J = 11.5, 2.3$ Hz, 1 H), 2.90 (dd, $J = 11.6, 1.8$ Hz, 1 H), 2.44 (s, 3 H), 2.12 (m, 3 H) ppm. ^{13}C NMR: $\delta = 206.2, 170.3, 145.1, 137.5, 133.7, 130.0, 128.7, 128.5, 127.7, 127.5, 80.5, 61.6, 61.2, 58.1, 54.6, 52.5, 29.7, 27.8, 21.7$ ppm. Elemental analysis calcd. (%) for $\text{C}_{24}\text{H}_{27}\text{NO}_6\text{S}$ (457.5): C 62.86, H 5.93, N 3.05; found C 62.35, H 6.35, N 3.02.

Fragmentation of the Equatorial Tosylate 11. Preparation of Azacyclooctene (12): DBU (0.22 mmol) was added to a solution of **11** (0.22 mmol) in 15 mL of anhydrous methanol and the reaction mixture was heated under reflux for 6 h. The solvent was removed and distilled water (15 mL) was added before extraction of the mixture with diethyl ether (3×20 mL). The combined organic layers were dried with MgSO_4 and the solvents were evaporated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 .

Dimethyl 1-Benzyl-1,4,5,8-tetrahydro-2H-azocine-3,3-dicarboxylate (12): $R_f = 0.63$ (Et_2O /pentane, 9:1). IR (neat): $\tilde{\nu} = 1724, 1456 \text{ cm}^{-1}$. ^1H NMR: $\delta = 7.22$ (m, 5 H), 5.67 (m, 1 H), 3.66 (s, 6 H), 3.61 (m, 2 H), 3.33 (m, 2 H), 2.62–2.14 (m, 7 H) ppm. ^{13}C NMR: $\delta = 172.2, 140.1, 131.6, 128.4, 126.9, 126.7, 63.4, 57.3, 56.7, 54.67, 52.3, 32.9, 23.3$ ppm. Elemental analysis calcd. (%) for $\text{C}_{18}\text{H}_{23}\text{O}_4\text{N}$ (317.4): C 68.12, H 7.30, N 4.41; found C 68.50, H 7.35, N 4.40.

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