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Multi-component coupling reactions of aldehydes and amides with maleic anhydride: synthesis of 7-oxo-6-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acids

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Abstract—A new protocol for the synthesis of a series of 7-oxo-6-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acids from simple aldehydes, amides and maleic anhydride was developed. Key step is an efficient three-component coupling reaction of two molecules of aldehyde with an amide to give a 1-acylamino-1,3-butadiene derivative which easily undergoes Diels–Alder addition to maleic anhydride. Thermic rearrangement of the cycloadducts affords the bicyclic target compounds. The new one-pot protocol gives higher yields than standard multi-step sequences due to the selective in situ trapping of one acylamino diene isomer. The target compounds can be further elaborated into arenes, cage molecules and natural product precursors. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The chemistry of 6-azabicyclo[3.2.1]octane derivatives has attracted the interest of several research groups in many respects. Considerable efforts have been undertaken by physical organic chemists to study the structural and spectroscopic characteristics of bridged bicyclic carbonyl structures, which 6-azabicyclo[3.2.1]octanes have been fruitful model compounds for. Moreover, an extensive amount of research has been accorded to skeletal rearrangements of various related ring systems.[1] Recently, the major interest in these structures especially arose from the fact that several highly active natural products such as the securinega,[2] aristotelia,[3] and other[4] families contain a 6-azabicyclo[3.2.1]octane motif embedded in polycyclic alkaloid skeletons.

Prominent among the early synthetic methods for the preparation of 6-azabicyclo[3.2.1]octane derivatives are the Hofmann–Löffler–Freytag reaction of monocyclic *N*-chloro amines[5] and the reductive cyclization of aminobenzoic acids or benzamides.[6] More recently, several highly efficient strategies based on rearrangement reactions have been reported on.[7] A rapid entry into structurally simple systems that relies upon a chromium-mediated higher-order cycloaddition has been introduced by Rigby and co-workers.[8] Oppolzer and others made use of elegant Diels–Alder reactions with aminodienes to synthesize several substituted 6-azabicyclo[3.2.1]octane derivatives.[9] These multi-step reaction sequences comprise the preparation of aminodiene building blocks, subsequent Diels–Alder addition to maleic anhydride and intramolecular rearrangement followed by sufficient reduction to give the bicyclic target compounds. Despite synthetic advantages such as high diversity and excellent stereocontrol, this route is still hampered by the laborious multi-step preparation of substituted aminodienes.[10]

During our studies on the palladium-catalyzed coupling reaction of aldehydes, carbon monoxide and amides,[11] nitriles[12] or ureas[13] to give *N*-acyl α-amino acid derivatives,[14] we observed the formation of 1-*N*-acetylamino-2-methyl-1,3-pentadiene (**1a**, $R^1=R^2=Me$)[15] as a by-product (<5%). Obviously, **1a** is formed by simple condensation of two molecules of propionaldehyde with acetamide (Scheme 1). Upon optimization and extension to other aldehydes and amides, we were able to elaborate this side reaction to a new multi-component coupling protocol for the synthesis of substituted 1-amido-2-cyclohexenes and 1-amido-3,5-cyclohexadienes.[16] With this domino reaction[17] in hand, we set out to test the suitability of a one-pot approach for the selective synthesis of a series of 6-azabicyclo[3.2.1]octane derivatives. In this paper, we present a full account on these efforts. Paralleling Oppolzer's strategy,[9a] we especially envisaged the synthesis of 7-oxo-6-aza-bicyclo[3.2.1]oct-2-ene-8-carbox-ylic acids

Keywords: multi-component reaction; Diels–Alder reaction; aminodience; maleic anhydride; 6-azabicyclo[3.2.1]octane; bicyclic ketones; bicylic lactams.

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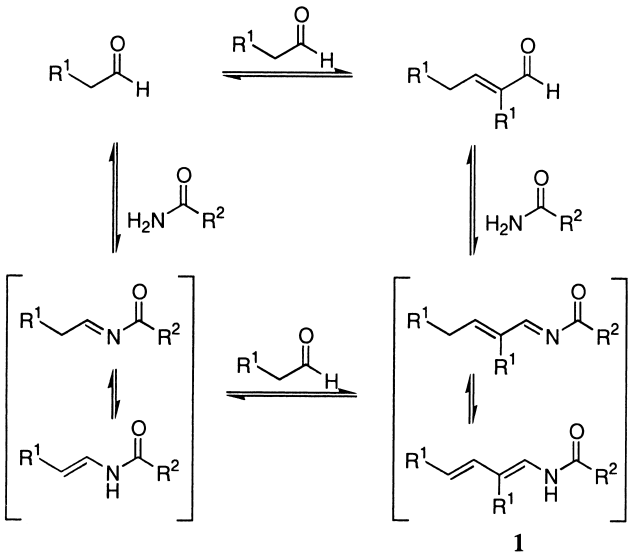


Scheme 1. Equilibria involved in the formation of amidodiene **1**.[18]

via subsequent condensation of aldehydes and amides, Diels–Alder addition to maleic anhydride and intramolecular amidation at elevated temperature.

2. Results and discussion

Our recently developed one-pot synthesis of substituted 1-acylamino-1,3-butadienes[16] involves sequential addition and condensation reactions of simple aldehydes and amides (Scheme 1).[18] In order to increase the yield in **1a** (R^1=R^2=Me), different reaction parameters including solvent, temperature, concentration, and additives were varied. Using toluene, chloroform or ethanol as solvent, the reaction merely afforded the corresponding aminal. The use of *N*-methylpyrrolidinone (NMP) or DMF proved pivotal for the desired procedure.

Addition of catalytic amounts of *p*-toluenesulfonic acid as well as stoichiometric amounts of acetic anhydride considerably accelerated the reaction. The optimized set of conditions, with the molar ratio aldehyde/amide being 1/1, gave all-*trans* **1a** (R^1=R^2=Me) in 30% isolated yield at 80°C.[15,16]

Under the reaction conditions, amidodienes **1** exist as a mixture of several equilibrating isomers (rotamers, double bond isomers). For 1-acetamido-2-methyl-1,3-pentadiene (**1a**), we were able to isolate the 1*E*,3*E* (all-*trans*) and 1*Z*,3*E* isomers in a 90:10 ratio.[15] Computational calculations support this observation and predict the prevailing existence of the all-*trans* isomer on the basis of thermodynamic equilibration.[19]

The presence of several equilibrating adducts and isomers accounts for the moderate yields in **1**. Obviously, a selective trapping of the 1-amido-1,3-diene species would shift the equilibria well to the right, and therefore significantly improve the yield of follow-up products of **1**.

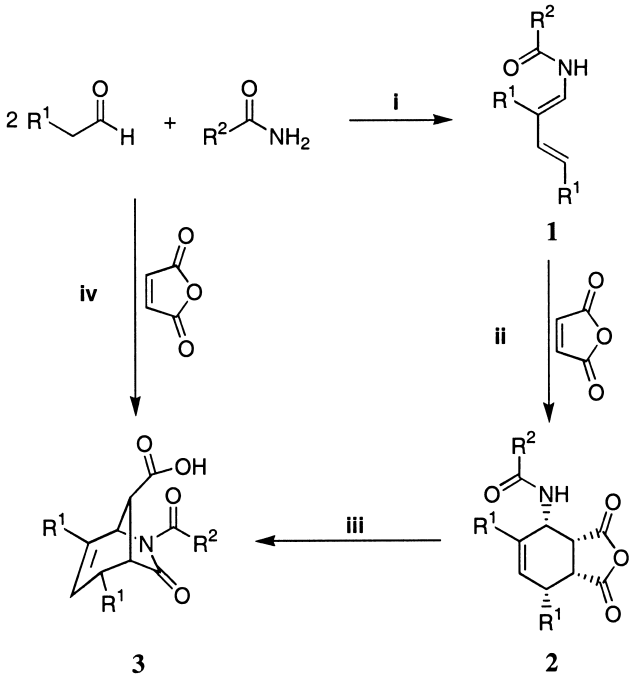
2.1. Synthesis

With maleic anhydride as a truly powerful electron-deficient dienophile, we were able to synthesize a small library of substituted 7-oxo-6-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid derivatives (**3**). Basically, two different strategies can be adopted en route to the target molecules (Scheme 2). A multi-step protocol, which involves isolation of the amidodiene derivatives prior to subjection to Diels–Alder conditions (Scheme 2, (i) and (ii)), preliminarily affords the 3-*N*-acylamino-1,2,3,6-tetrahydrophthalic anhydrides (**2**) which easily rearrange upon heating (iii).[20]

All-*trans* 1*E*,3*E*-1-acetamido-2-methyl-1,3-pentadiene (**1a**) was prepared in a one-pot procedure (30%). Subsequent reaction with maleic anhydride in toluene gave 3-*N*-acetylamino-1,2,3,6-tetrahydro-4,6-dimethylphthalic anhydride (**2a**) in 96% yield. As evidenced by ^{1}H NMR data, **2a** features *cis*-fused rings in an *endo* configuration bearing all substituents on the same side of the cyclohexene ring (all-*syn*).[16] On account of the all-*syn* geometry along the cyclohexene backbone, **2a** easily rearranged upon further stirring at 100°C and afforded the desired lactam **3a** in 89% yield.

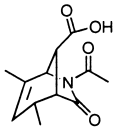
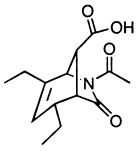
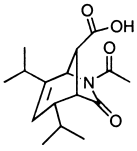
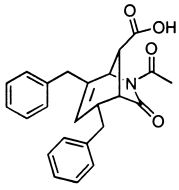
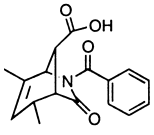
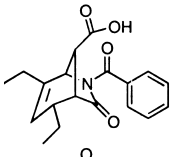
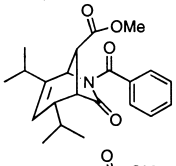
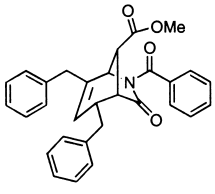
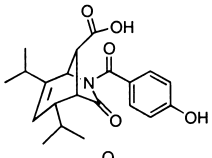
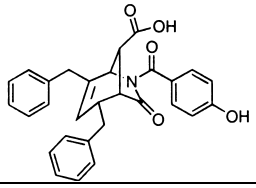
This reaction implies an intramolecular ring-closing carboxamidation of one of the carboxylic moieties to give a five-membered lactam.[16a] Besides the laborious work-up and isolation procedures, this route clearly suffers from the low yield in amidodiene **1a**. The overall yield of this multi-step route totals 26%, referenced to propionaldehyde.

On the other hand, target compounds **3** can also be accessed by applying a more elegant domino protocol which would obviate the need for intermediate work-up and purification



Scheme 2. One-pot (left) and multi-step access routes to bicyclic lactams **3**. (i) TSA, Ac_2O, NMP, 80°C, 16 h; (ii) toluene, 50°C, 20 min; (iii) NMP, 100°C, 12 h; (iv) TSA, Ac_2O, NMP, 120°C, 24 h.[20]

Table 1. One-pot synthesized 7-oxo-6-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid derivatives **3a**–**3j**[20]

	R^1	R^2	Product	Yield (%)
3a	Me	Me		69
3b	Et	Me		63
3c	*i*-Pr	Me		69
3d	Bn	Me		81
3e	Me	Ph		74
3f	Et	Ph		66
3g	*i*-Pr	Ph		60
3h	Bn	Ph		67
3i	*i*-Pr	*p*-HO–C_6H_4		81
3j	Bn	*p*-HO–C_6H_4		60

procedures. Indeed, the one-pot multi-component coupling reaction of propionaldehyde, acetamide and maleic anhydride at 120°C afforded 7-oxo-6-azabicyclo[3.2.1]-2,4-dimethyloct-2-ene-8-carboxylic acid (**3a**) in 69% yield (Scheme 2, (iv).[16] With almost tripled yield in **3a**, this one-pot approach significantly outperforms the multi-step route in efficiency as well as simplicity.

Diversity was introduced into the cyclic backbone of **3** by employing several linear and branched aldehydes bearing a β-CH_2 moiety. Ubiquitously available acetamide and benzamides were employed as acylamino equivalents. Upon combination of the starting materials aldehyde and amide, numerous substituted 7-oxo-6-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid derivatives (**3**) can be synthesized. A sample selection of which is shown in Table 1.[20]

The isolated yields of one-pot derived products **3a**–**j** cluster around 70%. Reactions were usually accomplished after 24 h in NMP at 120°C in the presence of catalytic amounts of *p*-toluenesulfonic acid and stoichiometric amounts of acetic anhydride. Since chromatographic purification of the crude carboxylic acids proved intricate in some cases, derivatization with MeOH/$TMSCHN_2$ gave the corresponding methyl ester derivatives which could be readily isolated by silica gel chromatography (ethyl acetate/*n*-heptane). Starting materials, additives and solvent were used without prior purification (off-shelf). Even the exclusion of air and moisture is not necessary over the course of the reaction, making the overall procedure extremely simple and straightforward.

2.2. Characterization

Spectroscopic characterization of the adducts was achieved by NMR and MS. The latter exhibited the parent ions and the expected fragmentation patterns involving cleavage of the acyl, amide, and alkyl moieties. NMR spectra of the target molecules showed only one set of signals accounting for a racemic mixture of one isomer. Two-dimensional ^1H–^1H and ^1H–^{13}C NMR experiments established the

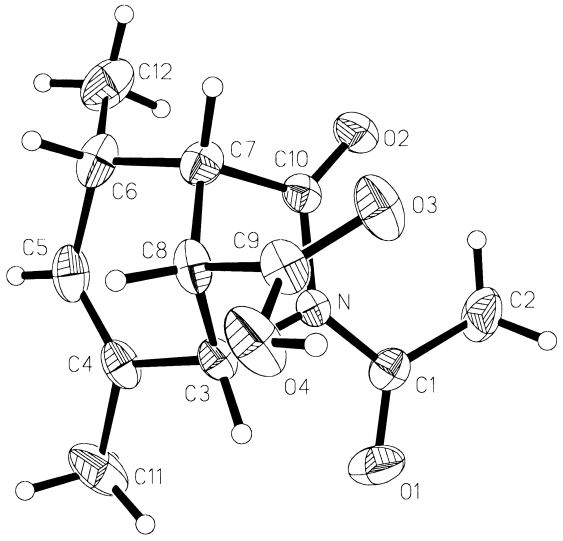


Figure 1. Crystal structure of **3a** (ellipsoids at the 30% level). Selected bond lengths (Å) and angles (°): C3–C4 1.527(4), C4–C5 1.324(5), C6–C7 1.545(4), C7–C8 1.516(4), C3–C8 1.540(4), C7–C10 1.515(4), C10–N 1.397(3), C3–N 1.490(4), C3–C8–C7 99.0(2), C8–C3–C4 109.2(3), C3–C4–C5 117.4(3), C4–C5–C6 125.0(3), C5–C6–C7 110.4(3), C5–C6–C7 110.4(3), C6–C7–C8 108.6(3), C6–C7–C10 111.4(2), C7–C10–N 107.1(2), C10–N–C3 108.7(2), N–C3–C4 109.8(2).[21]

constitution and configuration of the synthesized products. In no case, hetero Diels–Alder adducts were observed. All Diels–Alder adducts feature *cis*-fused rings in an *endo* configuration bearing all substituents on the same side of the cyclohexene ring (all-*syn*). The lack of observable coupling between C*H*N and C*H*COOR hydrogens is also in accord with an all-*cis* model (dihedral angle ~90°). The exclusive formation of the all-*syn* products verifies that only the *s-cis*-1*E*,3*E*-dienamide isomers (**1**) cyclized in Diels–Alder fashion. The all-*syn* geometry along the cyclohexene backbone facilitates the arrangement of the intermediate phthalic anhydrides (**2**) at elevated temperature to give bicylic lactams **3**.

In addition, we were able to confirm the structure of **3a** by X-ray analysis (Fig. 1).[21] Suitable crystals were obtained by recrystallization from toluene. Bond lengths and angles are unexceptional. All substituents on the cyclohexene ring are *syn*.

3. Summary and outlook

In order to extend the scope of our new multi-component aldehyde–amide–olefin methodology,[16] we aimed at the synthesis of new 7-oxo-6-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid derivatives with a diverse substitution pattern along the bicyclic backbone. The synthesis of a series of 10 target compounds was accomplished in good yields (60–81%). The corresponding standard multi-step procedure was also investigated but proved less efficient with much lower yields (e.g. 26% for **3a**).

The most attractive features of the presented reactions are the simplicity and the ease of the method. The synthesized compounds are readily accessible in a one-pot procedure from commercially available starting materials. In a combinatorial sense, this one-pot reaction exhibits significant increase in both complexity and diversity, and therefore typifies a reaction with high exploratory power.[22] The bicyclic target molecules contain several chemical functionalities (NCOR, C=O, COOR, CH=CR_2, Ph, C_6H_4OH). Given the various proffering post-synthesis modifications including reduction of the keto moiety or decarboxylation, the target compounds constitute versatile precursor compounds paving the way for further elaboration to a variety of cyclic compounds ranging from simple phthalic acid derivatives and highly substituted arenes to more complex cage molecules.[9a,23] Sufficient $LiAlH_4$-reduction, as performed by Oppolzer,[9a] would afford 6-azabicyclo-[3.2.1]octane derivatives which constitute important building blocks in several natural products.[2–4] Further approaches to apply the methodology for the preparation of natural product analogs are currently being investigated.

4. Experimental

4.1. General procedures

Reagents and solvents were used as received from commercial suppliers. Threaded Aldrich ACE pressure tubes were used as reaction vessels. Exclusion of moisture and air was not necessary. Column chromatography was performed with 230–400 mesh ASTM silica gel from Merck. Uncorrected melting points were recorded on a Galen III Cambridge Instr. IR spectra were recorded as KBr pellets on a Nicolet Magna 550. ^{1}H and ^{13}C NMR data were recorded on a Bruker ARX 400 with QNP probe head and are reported relative to DMSO-d_6 or $CDCl_3$. MS data were obtained on AMD 402 (EI 70 eV, CI *i*-butane). Combustion analyses were performed by the Microanalytical Laboratory, Department of Chemistry at the University of Rostock.

4.1.1. All-*trans* 1-*N*-acetylamino-2-methyl-1,3-pentadiene (1a, R^1=R^2=Me). Propionaldehyde (15 mmol), acetamide (15 mmol), acetic anhydride (15 mmol), and *p*-toluene sulfonic acid monohydrate (1.5 mol%) were combined in a threaded tube, and NMP (10 mL) was added. Then, the reaction was stirred at 80°C. Over the course of the reaction, the solution turned slightly orange. After 16 h, the solvent and other volatile compounds were removed by oil pump vacuum to give an orange residue. Silica gel column chromatography (heptane/ethyl acetate 1/2) afforded **1a** as a white solid.

R_f=0.35; yield: 30%; mp 108°C (decomp.). IR (KBr): 3301s, 1664s, 1737s, 1508s, 1368s, 1266s, 1167s, 960s. MS (EI): 139 ([**1a**]$^+$, 71%); 97 ([**1a**−Ac]$^+$, 100%); 82 ([**1a**−AcNH]$^+$, 98%); 57 ([AcNH]$^+$, 23%); 43 ([Ac]$^+$, 87%); no other peaks of >15%. HRMS: Calcd for $C_8H_{13}NO$: 139.0997; Found: 139.0966. NMR (DMSO-d_6): ^{1}H 9.30 (d, *J*=10.3 Hz, 1H, N*H*); 6.60 (d, *J*=10.3 Hz, 1H, C*H*NH); 6.03 (d, *J*=15.3 Hz, 1H, C*H*=CHMe); 5.44 (m, 1H, CH=C*H*Me); 1.96 (s, 3H, *Me*CO); 1.71 (d, *J*=5.9 Hz, 3H, CH=CH*Me*); 1.70 (s, 3H, *Me*C=CHNH). ^{13}C{^{1}H} 167.4 (*C*O); 133.5 (*C*H=CHMe); 122.1 (=*C*HNH); 120.4 (=*C*HMe); 115.8 (Me*C*=); 22.6 (*Me*CO); 18.1 (*Me*CH=); 11.3 (*Me*C=).

4.1.2. 3-*N*-Acetylamino-*cis*-1,2,3,6-tetrahydro-4,6-dimethyl phthalic anhydride (2a, R^1=R^2=Me). A 100 mL flask was charged with **1a** (0.5 g, 3.6 mmol) and maleic anhydride (0.49 g, 5 mmol), and toluene (20 mL) was added. The mixture was stirred at 50°C. After 20 min, the solvent was removed under reduced pressure. Silica gel chromatography (ethyl acetate/heptane 3/1) of the off-white residue afforded **2a**.

R_f=0.2; yield: 96% (white solid), mp 143°C. IR (KBr): 3411s, 2974m, 2942m, 2918w, 2882w, 1771s, 1681s, 1530s, 1179s, 979s, 920s. MS (CI): 238 ([**2a**]$^+$, 99%); 196 ([**2a**−Ac]$^+$, 100%); no other peaks of >8%. HRMS: Calcd for $C_{12}H_{15}NO_4$: 237.10050; Found: 237.10011. NMR ($CDCl_3$): ^{1}H 7.91 (d, *J*=9.1 Hz, 1H, N*H*); 5.44 (m, 1H, =C*H*); 4.60 (m, 1H, C*H*NH); 3.58–3.54 (dd, *J*=8.9/6.1 Hz, 1H, NHCHC*H*CO); 3.45–3.41 (dd, *J*=8.9/7.4 Hz, 1H, MeCHC*H*CO); 2.52–2.48 (m, 1H, C*H*Me); 1.97 (s, 3H, *Me*CO); 1.67 (s, 3H, *Me*C=); 1.23 (d, *J*=7.3 Hz, 3H, *Me*CH). ^{13}C{^{1}H} 173.9 (Me*C*O); 170.2 and 170.0 (*C*O_2*C*O); 138.4 (=*C*); 127.7 (=*C*H); 47.1 (*C*HNH); 45.9 and 45.0 (2*C*HCO); 30.0 (*C*HMe); 23.2 (*Me*CO); 18.5 and 16.4 (2*Me*).

4.1.3. 6-Acetyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-dimethyl-8-carboxylic acid (3a). *Procedure A*. A 100 mL

flask was charged with **2a** (0.5 g, 2.1 mmol) and NMP (10 mL). The mixture was stirred at 100°C. After 12 h, the solvent was removed by oil pump vacuum. Silica gel chromatography (ethyl acetate/heptane 2/1) gave white **3a** (89%). For analytical data and procedure B see below.

4.2. General procedure for multi-component coupling reactions

Procedure B. Aldehyde (15 mmol), amide (15 mmol), maleic anhydride (10 mmol), acetic anhydride (15 mmol), and *p*-toluene sulfonic acid monohydrate (1.5 mol%) were combined in a threaded tube, and NMP (10 mL) was added. Then, the reaction was stirred at 120°C. Over the course of the reaction, the solution turned slightly yellow or orange. After 24 h, the solvent and other volatile compounds were removed by oil pump vacuum to give an orange or red residue. Silica gel chromatography (ethyl acetate/heptane 2/1) afforded the corresponding carboxylic acid derivatives. For purification reasons, carboxylic acids of **3g** and **3h** were subsequently treated with excess trimethylsilyl diazomethane in methanol (rt, 10 min). Repeated silica gel chromatography (2/1) gave pure methyl esters **3g** and **3h**.

4.2.1. 6-Acetyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-dimethyl-8-carboxylic acid (3a). R_f=0.22; yield: 69% (white solid), mp 167°C. Calcd for $C_{12}H_{15}O_4N$: C, 60.75; H, 5.91; N, 6.33. Found: C, 60.90; H, 6.32; N, 5.93. IR (KBr): 3095–2880m, 3028w, 2977m, 2939m, 1754s, 1708s, 1694s. MS (EI): 237 ([**3a**]$^+$, 15%); 195 ([**3a**−Ac]$^+$, 26%); 149 ([**3a**−Ac-COOH]$^+$, 17%); 107 (80%); 43 ([Ac]$^+$, 100%). NMR (DMSO-d_6): ^{1}H 12.91 (broad s, 1H, COO*H*); 5.22 (s, 1H, *H*C═); 4.60 (s, 1H, C*H*COOH); 2.98 (s, 1H, C*H*N); 2.88 (d, *J*=5.2 Hz, 1H, C*H*CO); 2.73 (m, 1H, MeC*H*); 2.28 (s, 3H, *Me*CO); 1.82 (s, 3H, *Me*C═); 0.96 (d, *J*=7.3 Hz, 3H, *Me*CH). ^{13}C{^{1}H} 173.1, 172.6, and 168.8 (3*C*O); 137.9 (*C*═); 126.7 (═*C*H); 57.4 (*C*HCOOH); 49.3 (*C*HCO); 48.4 (*C*HN); 33.5 (Me*C*H); 24.2 (CO*Me*); 21.5 (*Me*C═); 18.4 (*Me*CH).

4.2.2. 6-Acetyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-diethyl-8-carboxylic acid (3b). R_f=0.45; yield: 63% (white solid), mp 115°C. Calcd for $C_{14}H_{19}O_4N$: C, 63.39; H, 7.17; N, 5.28. Found: C, 63.43; H, 7.05; N, 5.20. IR (KBr): 3500–2500m, 2966s, 2933s, 2878s, 1741s, 1694s. MS (EI): 265 ([**3b**]$^+$, 44%); 223 ([**3b**−Ac]$^+$, 88%); 194 ([**3b**−Ac-Et]$^+$, 48%); 178 ([**3b**−Ac-COOH]$^+$, 39%); 135 (47%); 107 (39%); 79 (68%); 43 ([Ac]$^+$, 100%). NMR ($CDCl_3$): ^{1}H 10.11 (broad s, 1H, COO*H*); 5.22 (s, 1H, *H*C═); 4.82 (s, 1H, C*H*COOH); 3.16 (d, *J*=3.6 Hz, 1H, COC*H*); 2.92 (s, 1H, NC*H*); 2.47 (m, 1H, CH_2CH); 2.39 (s, 3H, *Me*CO); 2.23 (m, 2H, MeCH_2C═); 1.41 (m, 2H, MeCH_2CH); 1.00 and 0.99 (2*Me*). ^{13}C{^{1}H} 176.5, 172.8, and 170.0 (3*C*O); 144.2 (*C*═); 123.3 (═*C*H); 56.8 (*C*HCOOH); 49.0 (*C*HN); 47.6 (*C*HCO); 41.4 (CH_2CH); 28.1 (CH_2C═); 26.2 (*C*H_2CH); 24.7 (CO*Me*); 11.5 (*Me*CH_2C═); 11.3 (*Me*CH_2CH).

4.2.3. 6-Acetyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-diisopropyl-8-carboxylic acid (3c). R_f=0.45; yield: 69% (colorless oil). IR (KBr): 3217m, 2963s, 1744s, 1040m, 877m. MS (EI): 293 ([**3c**]$^+$, 30%); 250 ([**3c**−*i*Pr]$^+$, 22%); 208 ([**3c**−*i*Pr−Ac)$^+$, 56%); 43 ([*i*Pr or Ac]$^+$, 100%). HRMS: Calcd for $C_{16}H_{23}O_4N$: 293.16272. Found: 293.16610. NMR (DMSO-d_6): ^{1}H 12.84 (broad s, 1H, COO*H*); 5.44 (s, 1H, *H*C═); 4.77 (s, 1H, C*H*COOH); 3.14 (d, *J*=4.9 Hz, 1H, C*H*CO); 2.87 (s, 1H, C*H*N); 2.45 (sept, *J*=6.9 Hz, 1H, Me_2CHC═); 2.26 (s+m, 4H, *Me*CO and Me_2CHCH); 1.40 (m, 1H, Me_2CHCH); 0.99 (m, 12H, 2Me_2CH). ^{13}C{^{1}H} 173.8, 172.7, and 168.3 (3*C*O); 148.3 (*C*═); 120.7 (*C*H═); 55.2 (*C*HCOOH); 49.4 (*C*HN); 46.6 (*C*HCO); 45.5 (Me_2CH*C*H); 32.4 (Me_2*C*HC═); 30.2 (Me_2*C*HCH); 24.3 (*Me*CO); 21.7, 20.4, 20.4, and 20.2 (4*Me*).

4.2.4. 6-Acetyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-dibenzyl-8-carboxylic acid (3d). R_f=0.45; yield: 81% (white solid), mp 176°C. IR (KBr): 3448b, 3026w, 1742s, 1701s, 1283s, 702s. MS (EI): 389 ([**3d**]$^+$, 100; 347 ([**3d**−Ac]$^+$, 28%); 298 ([**3d**−Bn]$^+$, 40%); 256 ([**3d**−Ac-Bn]$^+$, 61%); 211 (17%); 167 (54%); 135 (24%); 91 ([Bn]$^+$, 100%); 43 ([Ac]$^+$, 69%). HRMS: Calcd for $C_{24}H_{23}O_4N$: 389.16272. Found: 389.16400. NMR (DMSO-d_6): ^{1}H 12.91 (broad s, 1H, COO*H*); 7.31–7.20 (m, 10H, 2*Ph*); 5.28 (s, 1H, *H*C═); 4.67 (s, 1H, C*H*COOH); 3.49 (s, 2H, PhCH_2C═); 2.98 and 2.93 (2m, 3H, C*H*CO, BnC*H* and C*H*N); 2.62 (m, 2H, PhCH_2CH); 2.36 (s, *Me*CO). ^{13}C{^{1}H} 173.1, 172.3, and 168.9 (3*C*O); 141.9, 139.1, and 138.3 (2*i*-Ph and *C*═); 129.3, 128.9, 128.5, 128.3 (2*o*-Ph and 2*m*-Ph); 126.4 and 126.2 (2*p*-Ph); 126.4 (*C*H═); 55.8 (*C*HCOOH); 48.5 (*C*HN); 47.2 (*C*HCO); 41.3 (Bn*C*H); 41.1 (Ph*C*H_2C═); 38.4 (Ph*C*H_2CH); 24.4 (CO*Me*).

4.2.5. 6-Benzoyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-dimethyl-8-carboxylic acid (3e). R_f=0.25; yield: 74% (colorless, viscid oil). IR (KBr): 3428w, 2968m, 2922m, 1735s, 1713s, 1675s, 1296s, 1212m, 1157m, 697s. MS (EI): 299 ([**3e**]$^+$, 28%); 194 ([**3e**−Bz]$^+$, 7%); 105 ([Bz]$^+$, 100%); 77 ([Ph]$^+$, 27%); no other peaks of >3%. HRMS: Calcd for $C_{17}H_{17}NO_4$: 299.11922; Found: 299.11990. NMR (DMSO-d_6): ^{1}H 13.4–12.6 (broad s, 1H, COO*H*); 7.57–7.35 (m, 5H, *Ph*); 5.29 (s, 1H, ═C*H*); 4.54 (s, 1H, C*H*COOH); 3.12 (s, 1H, C*H*N); 2.90 (d, *J*=4.4 Hz, 1H C*H*CO); 2.76 (m, 1H, MeC*H*); 1.95 (s, 3H, *Me*C═); 0.91 (d, *J*=7.2 Hz, 3H, *Me*CH). ^{13}C{^{1}H} 173.2 (*C*OOH); 172.1 and 168.4 (2*C*O); 137.7 and 134.1 (═*C* and *i*-Ph); 131.9 and 128.5 (*m*- and *p*-Ph); 127.9 and 127.1 (*o*-Ph and ═*C*H); 59.4 (*C*HN); 49.1 and 48.8 (*C*HCO and *C*HCOOH); 33.5 (*C*HMe); 21.5 and 18.3 (2*Me*).

4.2.6. 6-Benzoyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-diethyl-8-carboxylic acid (3f). R_f=0.25; yield: 66% (colorless, viscid oil). IR (KBr): 3423w, 2964m, 2933m, 2877w, 1747s, 1708s, 1682s, 1449m, 1292s, 1226m, 1169m, 879m, 794m, 697s. MS (EI): 327 ([**3f**]$^+$, 13%); 105 ([Bz]$^+$, 100%); 77 ([Ph]$^+$, 23%), no other peaks of >5%. HRMS: Calcd for $C_{19}H_{21}NO_4$: 327.14770; Found: 327.14706. NMR (DMSO-d_6): ^{1}H 13.10 (broad s, 1H, COO*H*); 7.54–7.39 (m, 5H, *Ph*); 5.31 (s, 1H, ═C*H*); 4.62 (s, 1H, C*H*COOH); 3.05 (2m, 2H, C*H*CO and C*H*N); 2.55 (m, 1H, C*H*Et); 2.33–2.28 (m, 2H, $CHCH_2$); 1.36–1.30 (m, 1H of ═CCH_2); 1.22–1.15 (m, 1H of ═CCH_2); 1.01 (t, *J*=7.4 Hz, 3H, $CHCH_2Me$); 0.93 (t, *J*=7.3 Hz, 3H, ═CCH_2Me). ^{13}C{^{1}H} 173.3, 172.2, and 168.2 (3*C*O); 143.4 (═*C*); 134.2 (*i*-Ph); 131.8 (*p*-Ph); 128.4 and 127.8 (*o*- and *m*-Ph); 123.9 (═*C*H); 58.6 (*C*HCOOH); 49.2 and 46.7 (*C*HN and *C*HCO); 40.4

(*C*HEt); 27.4 (CH*C*H$_2$); 25.7 (=C*C*H$_2$); 11.7 (CHCH$_2$*Me*); 11.0 (=CCH$_2$*Me*).

4.2.7. Methyl 6-benzoyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-diisopropyl-8-carboxylate (3g). R_f=0.65; yield: 60%; mp 75°C. IR (KBr): 3449w, 2960s, 2872m, 2826w, 1754s, 1734s, 1672s, 1308s, 1290s, 1231m, 1201m, 1165s, 940m, 732m, 698m. MS (EI): 369 ([**3g**]$^+$, 36%); 326 ([**3g**−*i*Pr]$^+$, 21%); 220 ([**3g**−*i*Pr-Bz]$^+$, 9%); 105 ([Bz]$^+$, 100%); 77 ([Ph]$^+$, 37%); 43 ([*i*Pr]$^+$, 25%); no other peaks of >5%. HRMS: Calcd for $C_{22}H_{27}O_4N$: 369.19590. Found: 369.19400. NMR (DMSO-d_6): ^{1}H 7.52 (m, 1H, *p*-Ph); 7.44–7.40 (m, 4H, *o*- and *m*-Ph); 5.53 (s, 1H, =C*H*); 4.81 (s, 1H, C*H*COOMe); 3.72 (s, 3H, COO*Me*); 3.19 (dm, *J*=4.7 Hz, 1H, C*H*CO); 3.10 (s, 1H, C*H*N); 2.68 (sept, *J*=7.0 Hz, 1H, Me$_2$C*H*C=); 2.32–2.27 (m, 1H, Me$_2$CHC*H*); 1.38–1.32 (m, 1H, Me$_2$C*H*CH); 1.03 (d, *J*=7.0 Hz, 6H, *Me*$_2$CHC=); 0.97 (d, *J*=6.6 Hz, 6H, *Me*$_2$CHCH). ^{13}C{^{1}H} 172.2, 172.0, and 167.8 (3*C*O); 148.1 (=*C*); 134.2 (*i*-Ph); 131.7 (*p*-Ph); 128.3 and 127.8 (*o*- and *m*-Ph); 120.8 (=*C*H); 56.6 (*C*HCOOMe); 52.3 (COO*Me*); 49.4 (*C*HN); 46.2 (*C*HCO); 45.6 (Me$_2$CH*C*H); 32.1 (Me$_2$*C*HC=); 30.1 (Me$_2$*C*HCH); 21.7, 20.4, 20.3, and 20.2 (4*Me*).

4.2.8. Methyl 6-benzoyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-dibenzyl-8-carboxylate (3h). R_f=0.65; yield: 67%, mp 143°C. IR (KBr): 3449w, 3059m, 3026m, 3000w, 2951m, 2908m, 2853m, 1753s, 1737s, 1670s, 1310s, 1229s, 1201s, 1167s, 843m, 702s. MS (EI): 465 ([**3h**]$^+$, 16%); 374 ([**3h**−Bn]$^+$, 8%); 105 ([Bz]$^+$, 100%); 91 ([Bn]$^+$, 20%); 77 ([Ph]$^+$, 28%); no other peaks of >10%. HRMS: Calcd for $C_{30}H_{27}O_4N$: 465.19330. Found: 465.19400. NMR (DMSO-d_6): ^{1}H 7.58 (t, *J*=7.0 Hz, 1H, *p*-PhCO); 7.53–7.44 (m, 4H, *o*- and *m*-PhCO); 7.33 (m, 2H, *p*-Ph); 7.28–7.19 (m, 8H, *o*- and *m*-Ph); 5.36 (s, 1H, =C*H*); 4.56 (s, 1H, C*H*COOMe); 3.74 (d, *J*=15.4 Hz, 1H of C*H*$_2$C=); 3.64 (d, *J*=15.4 Hz, 1H of C*H*$_2$C=); 3.63 (s, 3H, COO*Me*); 3.17 (s, 1H, CHN); 3.04 (m, 1H, CH$_2$C*H*); 2.92 (m, 1H, C*H*CO); 2.62–2.50 (m, 2H, C*H*$_2$CH). ^{13}C{^{1}H} 171.8, 171.7, and 168.4 (3*C*O); 141.5, 138.9, 138.4, and 133.8 (*C*= and 3*i*-Ph); 132.1 (*p*-PhCO); 129.3 and 128.9 (*o*- or *m*-Ph); 128.7 (*o*- or *m*-PhCO); 128.5 and 128.2 (*o*- or *m*-Ph); 127.9 (*o*- or *m*-PhCO); 126.8 (=*C*H); 126.3 and 126.1 (2*p*-Ph); 57.48 (*C*HCOOMe); 52.4 (COO*Me*); 48.8 (*C*HN); 46.4 (*C*HCO); 41.3 (*C*HCH$_2$); 40.8 (*C*H$_2$C=); 38.1 (*C*H$_2$CH).

4.2.9. 6-*p*-Hydroxyphenyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-diisopropyl-8-carboxylic acid (3i). R_f=0.45; yield: 81% (white solid), mp 77°C. IR (KBr): 3377m, 2963s, 2903w, 1736s, 1608s, 1515s. MS (EI): 371 ([**3i**]$^+$, 14%); 328 ([**3i**−*i*Pr]$^+$, 5%); 250 ([**3i**−*p*HOBz]$^+$, 24%); 121 ([*p*HOBz]$^+$, 100%); 43 ([*i*Pr]$^+$, 23%). HRMS: Calcd for $C_{21}H_{25}O_5N$: 371.17328. Found: 371.17480. NMR (DMSO-d_6): ^{1}H 12.92 (broad s, 1H, COO*H*); 10.22 (broad s, 1H, O*H*); 7.35 (d, *J*=8.7 Hz, 2H, *o*-PhCO); 6.75 (d, *J*=8.7 Hz, 2H, *m*-PhCO), 5.50 (broad s, 1H, *H*C=); 4.69 (broad s, 1H, C*H*COOH); 3.15 (d, *J*=4.8 Hz, 1H, C*H*CO); 3.00 (s, 1H, C*H*N); 2.68 (sept, *J*=6.7 Hz, 1H, Me$_2$C*H*C=); 2.23 (broad m, 1H, Me$_2$CHC*H*); 1.36 (m, 1H, Me$_2$C*H*CH); 1.00 (d, *J*=6.7 Hz, 6H, *Me*$_2$CHC=); 0.97 (m, 6H, *Me*$_2$CHCH). ^{13}C{^{1}H} 173.2, 172.5, and 167.5 (3*C*O); 161.4 (*i*-PhOH); 148.5 (*C*=); 131.5 (*o*-PhCO); 124.4 (*i*-PhCO); 120.6 (*C*H=); 114.5 (*m*-PhCO); 57.3 (*C*HCOOH); 49.9 (*C*HN); 46.1 (*C*HCO); 45.5 (Me$_2$CH*C*H); 31.9 (Me$_2$*C*HC=); 30.2 (Me$_2$*C*HCH); 21.7, 20.6, 20.4, and 20.3 (4*Me*).

4.2.10. 6-*p*-Hydroxyphenyl-7-oxo-6-azabicyclo[3.2.1]oct-3-ene-2,4-dibenzyl-8-carboxylic acid (3j). R_f=0.45; yield: 60% (white solid), mp 125°C. IR (KBr): 3432m, 3026w, 2903w, 1735s, 1710s, 1607s, 702s. MS (EI): 467 ([**3j**]$^+$, 5; 346 ([**3j**−HOBn]$^+$, 10%); 121 ([HOBn]$^+$, 92%); 91 ([Bn]$^+$, 100%). HRMS: Calcd for $C_{29}H_{25}O_5N$: 467.17328. Found: 467.17040. NMR (DMSO-d_6): ^{1}H 12.93 (broad s, 1H, COO*H*); 10.31 (broad s, 1H, O*H*); 7.44 (d, *J*=8.6 Hz, 2H, *o*-PhCO); 7.33–7.16 (m, 10H, 2*Ph*CH$_2$); 6.80 (d, *J*=8.6 Hz, 2H; *m*-PhCO); 5.33 (broad s, 1H, *H*C=); 4.45 (broad s, 1H, C*H*COOH); 3.77 (d, *J*=15.2 Hz, 1H of PhC*H*$_2$C=); 3.62 (d, *J*=15.2 Hz, 1H of PhC*H*$_2$C=); 3.00 (s, 1H, C*H*N); 2.98 (broad m, 1H, BnC*H*); 2.89 (d, *J*=4.5 Hz, 1H, C*H*CO); 2.56 (m, 2H, PhC*H*$_2$CH). ^{13}C{^{1}H} 173.0, 172.1, and 168.0 (3 CO); 161.6 (*i*-PhOH); 141.9, 139.2, 138.7 (2*i*-Bn, and *C*=); 131.7 (2*o*-PhCO); 129.4, 129.0, 128.5, 128.3 (2*o*-Bn and 2*m*-Bn); 126.7 (*C*H=); 126.3 and 126.1 (2*p*-Bn); 124.0 (*i*-PhCO); 114.6 (2*m*-PhCO); 58.2 (*C*HCOOH); 49.2 (*C*HN), 46.3 (*C*HCO); 41.3 (Bn*C*H); 40.8 (Ph*C*H$_2$C=); 38.2 (Ph*C*H$_2$CH).

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18. Not all possible rotamers and double bond isomers are depicted.
19. For details on computations see supporting information of Ref. 16a.
20. Products are *racemic* mixtures of one diastereomer. Only one enantiomer is depicted.
21. X-Ray data of **3a** were collected on a STOE-IPDS diffractometer using graphite monochromated Mo Kα radiation. The structure was solved by direct methods (Sheldrick, G. M. SHELXS-86 *Acta Crystallogr., Sect. A* **1990**, *46*, 467) and refined by full matrix least square techniques against F^2 (Sheldrick, G. M. *SHELXL-93*; University of Göttingen: Germany, 1993). XP (Siemens Analytical X-ray Instruments, Inc.) was used for structure representations. Crystallographic data (excluding structure factors) for **3a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 176070. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Crystal data for **3a**: crystal dimensions: 0.5·0.4·0.3, colorless prisms, space group $P2_1/c$, monoclinic, a=10.175(2), b=7.979(2), c=15.612(3) Å, β=104.37(3)°, V=1227.8(5) Å^3, Z=4, ρ_{calcd}=1.283 g cm^{-1}, 6231 reflections measured, 1951 were independent of symmetry and 1144 were observed ($I>2\sigma(I)$), $R1$=0.049, wR^2(all data)=0.137, 175 parameters.
22. Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329.
23. Bischler–Napiralski reaction with 7-oxo-6-azabicyclo[3.2.1]-octanes: Bonjoch, J.; Mestre, E.; Cortes, R.; Granados, R.; Bosch, J. *Tetrahedron* **1983**, *39*, 1723–1728.