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A Sonogashira Cross-Coupling/5-*exo*-dig Cyclization/Ionic Hydrogenation Sequence: Synthesis of 4-Substituted 3-Azabicyclo[3.1.0]hexan-2-ones from 2-Iodocyclopropanecarboxamides

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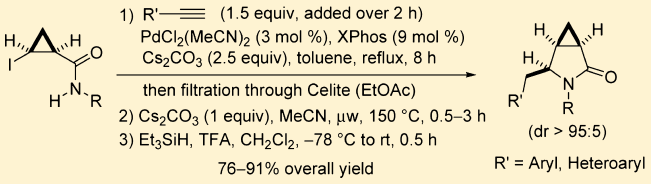
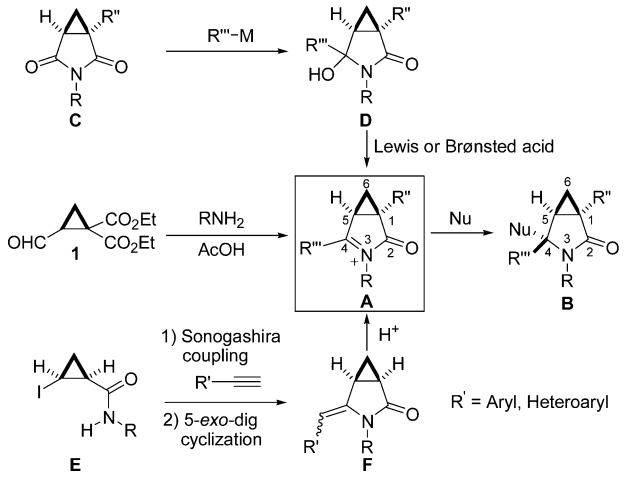
Supporting Information

ABSTRACT: A variety of 4-substituted 3-azabicyclo[3.1.0]-hexan-2-ones have been prepared from 2-iodocyclopropane-carboxamides by a three-step sequence involving a copper-free Sonogashira coupling with terminal aryl- or heteroarylalkynes, followed by a 5-*exo*-dig cyclization and an ionic hydrogenation.



The development of synthetic methods toward substituted 3-azabicyclo[3.1.0]hexanes, which are encountered in a wide variety of bioactive compounds and behave as conformationally constrained analogues of piperidines, has attracted considerable interest.[1,2] The three- or five-membered rings in 3-azabicyclo[3.1.0]hexanes are often constructed from unsaturated five-membered nitrogen heterocycles[3] or appropriately substituted cyclopropanes[4] respectively, followed by further functionalization to reach the desired substitution pattern. The bicyclic *N*-acyliminium ions **A** have proven to be useful synthetic intermediates since they can be captured by a nucleophile with high diastereoselectivity, in an inter- or intramolecular fashion, providing 4-substituted 3-azabicyclo[3.1.0]hexan-2-ones **B** (Scheme 1).[5−8] One of the earliest applications, developed during the course of the total synthesis of *vinca* alkaloids, involved condensation of cyclopropanecarboxaldehyde **1** with tryptamine under acidic conditions and further reaction of the indole with the *in situ* generated *N*-acyliminium ion in a Pictet−Spengler cyclization.[6] Bicyclic imides **C** can also be precursors of *N*-acyliminium ions **A** by addition of a nucleophile to the less-hindered carbonyl group (organometallic reagent or metal hydride) followed by treatment of the resulting hemiaminals **D** (or their derivatives) with a Lewis or Brønsted acid.[7,8] Recently, we demonstrated that the copper-free Sonogashira coupling between 2-iodocyclopropanecarboxamides **E** and terminal aryl- or heteroarylalkynes, followed by 5-*exo*-dig cyclization of the nitrogen amide onto the alkyne, provided a remarkably efficient access to 4-(arylmethylene)-3-azabicyclo[3.1.0]hexan-2-ones **F**.[9] The bicyclic *N*-acyliminium ions **A** generated by protonation of enamides **F** can be involved in Pictet−Spengler cyclizations leading to 3-azabicyclo[3.1.0]hexanes **B** possessing a quaternary center at C4.[9] This latter strategy provides a unique access to *N*-acyliminium ions **A** substituted by an aryl- or heteroarylmethyl group at C4. The synthesis of similar species from imides **C** would imply the initial addition of a benzylic organometallic reagent whose preparation is not always trivial compared to the availability of the terminal alkynes used as partners in the Sonogashira coupling (Scheme 1).

Scheme 1. Synthesis of *N*-Acyliminium Ions A



To further illustrate the interest of this alternative strategy toward *N*-acyliminium ions **A**, we report herein another application to the synthesis of 3-azabicyclo[3.1.0]hexan-2-ones **B** substituted at C4 by an aryl- or heteroarylmethyl group (R′ = aryl or heteroaryl) from 2-iodocyclopropanecarboxamides **E**.

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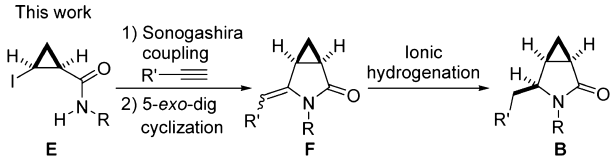
The three-step sequence involves a copper-free Sonogashira coupling and a 5-*exo*-dig cyclization followed by a diastereoselective ionic hydrogenation of the resulting bicyclic enamides **F** (Scheme 2).

Scheme 2. Synthesis of 4-Substituted 3-Azabicyclo[3.1.0]hexan-2-ones from 2-Iodocyclopropanecarboxamides



The 2-iodocyclopropanecarboxamides **2**–**6** were involved in a copper-free Sonogashira coupling with different terminal aryl- or heteroarylalkynes (1.5 equiv, slow initial addition over 2 h) under our previously optimized conditions [$PdCl_2(MeCN)_2$ (3 mol %), XPhos (9 mol %), Cs_2CO_3 (2.5 equiv), toluene, reflux, 8 h].[10] After filtration of the reaction mixture through Celite to remove the palladium catalyst, the resulting crude 2-alkynylcyclopropanecarboxamides were not purified and directly subjected to a 5-*exo*-dig cyclization[11] by heating in the presence of Cs_2CO_3 (1 equiv) in acetonitrile at 150 °C (sealed tube) under microwave (μw) irradiation.[9] The corresponding substituted 4-methylene-3-azabicyclo[3.1.0]-hexan-2-ones **7**–**15** were generally isolated in high yields (84–99%) irrespective of the substituent on the nitrogen atom and the alkyne partner (Table 1, entries 1–4 and 6–8). In the case where the alkyne was substituted by an electron-rich *p*-methoxyphenyl group (Table 1, entry 5), a higher temperature was required to achieve an efficient 5-*exo*-dig cyclization of the nitrogen amide (200 °C, 0.75 h). Conventional heating with an oil bath could also be applied (MeCN, 100 °C) as shown for enamides **10** (Table 1, entry 4), **13** (Table 1, entry 7), and **15** (Table 1, entry 9), but longer reaction times were generally required. Except for **11**, **12**, and **14**, the bicyclic enamides resulting from the 5-*exo*-dig cyclization were obtained as mixtures of geometric isomers. Although this has no consequence for the subsequent generation of a *N*-acyliminium ion **A** by protonation of the enamide, it is worth mentioning that the (*Z*) isomer can be stereoselectively obtained if required by achieving the cyclization with EtONa in EtOH (150 °C, μw) and that subsequent isomerization under acidic conditions (cat. TsOH, toluene, reflux) produces the (*E*) isomer.[9]

Reduction of the carbon–carbon double bond of enamide **7** (Table 1, entry 1) was initially attempted by hydrogenation in the presence of a heterogeneous catalyst [H_2 (1 bar), cat. Pd/C, EtOH, rt, 16 h], but ring opening of the cyclopropane (hydrogenolysis of the C5–C6 bond) also took place concomitantly as a side reaction under these conditions.[12,13] The chemoselective reduction of enamides **7**–**14** was more conveniently achieved by ionic hydrogenation with triethylsilane in the presence of trifluoroacetic acid (TFA) under mild conditions (CH_2Cl_2, −78 °C to rt).[14] The corresponding 4-substituted 3-azabicyclo[3.1.0]-hexan-2-ones **16**–**23** were obtained with high diastereoselectivity (dr > 95:5), due to hydride transfer on the less congested face of the *N*-acyliminium ion,[15] and were isolated in excellent yields (90–97%) (Table 1, entries 1–8). It is noteworthy that no competing Pictet–Spengler cyclization was observed for the *N*-acyliminium ions generated from enamides **7**–**12** since this would require the formation of a five-membered ring which is disfavored (5-*endo*-trig process).[16–19] Formation of a seven-membered ring by competitive Pictet–Spengler cyclization was also not observed as a side reaction in the case of enamides **13** and **14**.[18,19] By contrast for enamide **15**,[9] derived from homoveratrylamine, the intermolecular reduction can compete with the Pictet–Spengler cyclization which leads to the formation of a six-membered ring. Thus, under the previously developed conditions, a mixture of pyrrolidone **24** and tetracyclic compound **25** was obtained in a 20:80 ratio. When the reaction was carried out without solvent, the proportion of compound **24** increased slightly (**24**/**25** = 40:60) but the intramolecular Pictet–Spengler reaction leading to **25** was still favored.

In conclusion, we have shown that 2-iodocyclopropanecarboxamides **E** can be used as useful precursors for a variety of 4-substituted 3-azabicyclo[3.1.0]hexan-2-ones, a scaffold of interest in medicinal chemistry, by a three-step sequence involving a copper-free Sonogashira coupling with terminal aryl- or heteroarylalkynes, followed by a 5-*exo*-dig cyclization and an ionic hydrogenation of the resulting bicyclic enamides. The products are obtained with high diastereoselectivities (dr > 95:5) and satisfying overall yields (76–91%).

EXPERIMENTAL SECTION

A Biotage Initiator was used as a microwave reactor, and the temperature was monitored by an external surface sensor. High resolution mass spectra were obtained by electrospray ionization with an orbitrap mass analyzer.

(1*S,2*S**)-*N*-(3-Methoxybenzyl)-2-iodocyclopropanecarboxamide (3) (Representative Procedure).** To a solution of *cis*-2-iodocyclopropanecarboxylic acid[10] (500 mg, 2.36 mmol) in CH_2Cl_2 (20 mL) were added *i*-Pr_2NEt (482 μL, 2.83 mmol, 1.2 equiv), 3-methoxybenylamine (372 μL, 2.83 mmol, 1.2 equiv), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (678 mg, 3.54 mmol, 1.5 equiv), and 1-hydroxybenzotriazole hydrate (11.5 mg, 84.9 μmol, 3.6 mol %). After 17 h at rt, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether (PE)/EtOAc 50:50) afforded **3** (717 mg, 92%) as a white solid: mp 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (apparent t, J = 7.9 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.89 (m, 1H), 6.82 (dd, J = 8.2, 2.5 Hz, 1H), 6.06 (br s, 1H, NH), 4.55 (dd, J = 14.7, 6.0 Hz, 1H), 4.43 (dd, J = 14.7, 5.5 Hz, 1H), 3.80 (s, 3H), 2.75 (apparent td, J = 8.0, 6.3 Hz, 1H), 1.66 (apparent td, J = 8.3, 6.3 Hz, 1H), 1.49 (apparent q, J = 6.2 Hz, 1H), 1.45 (apparent td, J = 8.3, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 159.9, 139.7, 129.7, 120.2, 113.3, 113.2, 55.3, 44.0, 20.7, 14.8, −14.1; HRMS (ESI) calcd for $C_{12}H_{14}INO_2Na$ (M+Na^+) 353.9961, found 353.9963; IR ν 3275, 1647, 1561, 1229, 690 cm^{-1}.

(1*S,2*S**)-*N*-(3,4-Dimethoxybenzyl)-2-iodocyclopropanecarboxamide (4).** Yield 94% (804 mg) using 3,4-dimethoxybenzylamine; waxy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 8.1, 2.0 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.05 (br s, 1H, NH), 4.56 (dd, J = 14.5, 6.2 Hz, 1H), 4.35 (dd, J = 14.5, 5.3 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.75 (apparent td, J = 8.0, 6.3 Hz, 1H), 1.68 (apparent td, J = 8.4, 6.3 Hz, 1H), 1.49 (apparent q, J = 6.2 Hz, 1H), 1.45 (apparent td, J = 8.4, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 149.1, 148.4, 130.8, 120.2, 111.3, 111.0, 56.0, 55.9, 43.9, 20.7, 14.8, −14.0; HRMS (ESI) calcd for $C_{13}H_{16}INO_3Na$ (M+Na^+) 384.0067, found 384.0066; IR ν 3308, 1645, 1518, 1225, 1139, 1020, 748 cm^{-1}.

(1*S,2*S**)-*N*-[3-(3,4-Dimethoxyphenyl)propyl]-2-iodocyclopropanecarboxamide (5).** Yield 86% (788 mg) using 3-(3,4-dimethoxyphenyl)propan-1-amine;[20,21] white solid: mp 95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 8.6 Hz, 1H), 6.73–6.71 (m,

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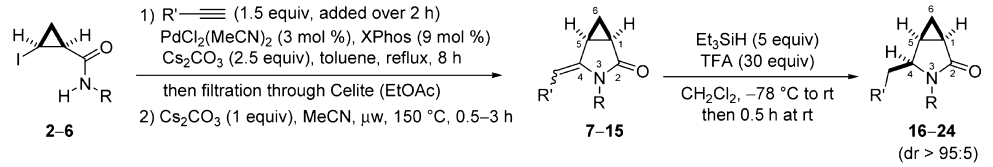
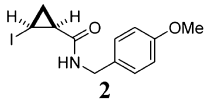
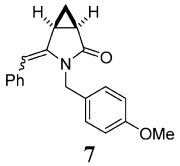
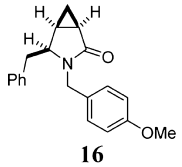
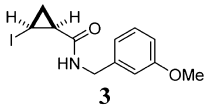
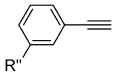
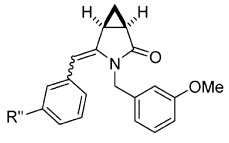
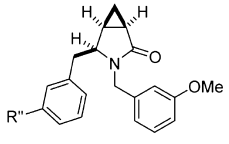
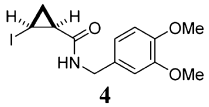
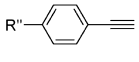
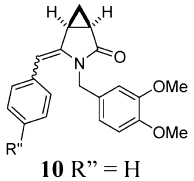
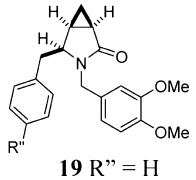
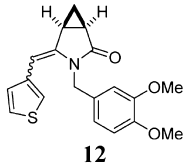
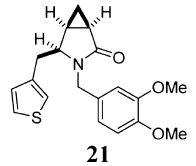
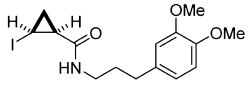
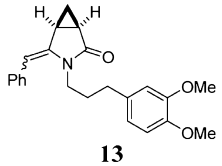
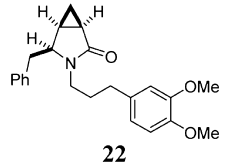
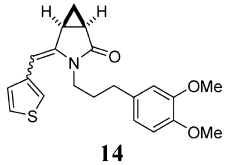
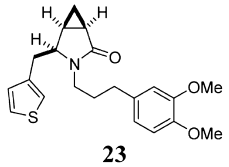
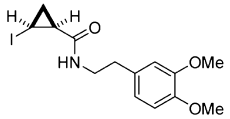
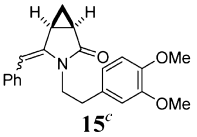
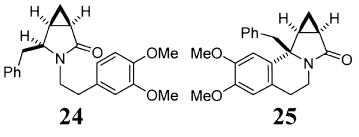
Table 1. Synthesis of 4-Substituted 3-Azabicyclo[3.1.0]hexan-2-ones B from 2-Iodocyclopropanecarboxamides



2–6 → **7–15** → **16–24** (dr > 95:5)

entry	substrates	alkynes	enamides	yield	*Z*/*E*	products	yield
1	 **2**		 **7**	92%	70:30	 **16**	95%
	 **3**						
2			**8** R" = H	84%	75:25	**17** R" = H	90%
3			**9** R" = CF_3	96%	40:60	**18** R" = CF_3	91%
	 **4**						
4			**10** R" = H	89% 76%	75:25 85:15[b]	**19** R" = H	92%
5			**11** R" = OMe[a]	94%	> 95:5	**20** R" = OMe	91%
6			 **12**	94%	> 95:5	 **21**	97%
7	 **5**		 **13**	93% 92%	75:25 90:10[b]	 **22**	94%
8			 **14**	89%	> 95:5	 **23**	92%
9	 **6**		 **15**[c]	99%	90:10[b]	 **24** **25**	
						24/**25** = 20:80 **24**/**25** = 40:60[d]	-- 73%[e]

[a]The 5-*exo*-dig cyclization was carried out at 200 °C (μw, 0.75 h). [b]With oil bath heating (MeCN, 100 °C, 45 h for **10**, 19 h for **13** and 5 h for **15**). [c]See ref 9. [d]The reaction was carried out in the absence of CH_2Cl_2 at rt. [e]Combined yield of **24** and **25**.

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2H), 5.92 (br t, J = 4.9 Hz, 1H, NH), 3.85 (s, 3H), 3.83 (s, 3H), 3.44−3.36 (m, 1H), 3.33−3.25 (m, 1H), 2.70 (apparent td, J = 8.0, 6.3 Hz, 1H), 2.62 (t, J = 7.4 Hz, 2H), 1.84 (quint, J = 7.2 Hz, 2H), 1.61 (apparent td, J = 8.3, 6.4 Hz, 1H), 1.44−1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 148.8, 147.2, 134.1, 120.1, 111.7, 111.2, 55.9, 55.8, 39.7, 32.8, 31.6, 20.6, 14.5, −14.0; HRMS (ESI) calcd for $C_{15}H_{20}INO_3Na$ ($M+Na^+$) 412.0380, found 412.0383; IR ν 3288, 1641, 1516, 1226, 1027, 810 cm^{-1}.

Representative Procedure for the Sonogashira Coupling/5-*exo*-dig Cyclization. *(1R*,5S*)-4-Benzylidene-3-(4-methoxybenzyl)-3-azabicyclo[3.1.0]hexan-2-one (**7**).* An oven-dried resealable vial was charged with $PdCl_2(MeCN)_2$ (3.1 mg, 12 μmol, 3 mol %), XPhos (17 mg, 36 μmol, 9 mol %), Cs_2CO_3 (327 mg, 1.00 mmol, 2.5 equiv), and amide **2**[10] (133 mg, 0.402 mmol, 1 equiv) followed by toluene (3.5 mL). The resulting mixture was degassed by argon bubbling for 10 min. The vial was sealed (Teflon cap) and immersed in a preheated oil bath at 100 °C, and a solution of phenylacetylene (66 μL, 0.60 mmol, 1.5 equiv) in toluene (0.6 mL) was added in 10 portions at 10−12 min intervals within 2 h. After 6 h at 100 °C, the reaction mixture was filtered through Celite (EtOAc) and the filtrate was evaporated under reduced pressure. To a solution of the crude material in MeCN (3 mL) in a resealable vial was added Cs_2CO_3 (131 mg, 0.402 mmol, 1.0 equiv). The vial was sealed and heated at 150 °C under microwave irradiation for 0.5 h. The reaction mixture was filtered through Celite (EtOAc), and the filtrate was concentrated under reduced pressure. Analysis by ^{1}H NMR spectroscopy (400 MHz, acetone-d_6) indicated the formation of **7** (Z/E = 70:30). Purification by flash chromatography on silica gel (PE/EtOAc 70:30) afforded **7**[9] (113 mg, 92%, Z/E = 70:30) as a waxy solid.

(1R,5S*)-4-Benzylidene-3-(3-methoxybenzyl)-3-azabicyclo-[3.1.0]hexan-2-one (**8**).* Yield 84% (68.3 mg, Z/E = 75:25; PE/EtOAc 70:30, 60:40); orange oil: ^{1}H NMR (400 MHz, acetone-d_6) (Z)-isomer δ 7.36−7.23 (m, 3H), 7.12−7.07 (m, 2H), 7.07 (t, J = 8.0 Hz, 1H), 6.73 (dd, J = 7.8, 2.0 Hz, 1H), 6.23 (d, J = 7.6 Hz, 1H), 6.10 (apparent t, J = 2.0 Hz, 1H), 5.88 (br s, 1H), 4.74 (d, J = 15.3 Hz, 1H), 4.21 (d, J = 15.3 Hz, 1H), 3.68 (s, 3H), 2.58 (dddd, J = 7.4, 5.7, 3.6, 0.6 Hz, 1H), 2.31 (ddd, J = 8.7, 5.6, 3.4 Hz, 1H), 1.27 (ddd, J = 8.4, 7.4, 4.2 Hz, 1H), 0.74 (apparent q, J = 3.5 Hz, 1H); (E)-isomer δ 7.44−7.42 (m, 2H), 7.36−7.23 (m, 3H), 7.18 (m, 1H), 6.91−6.89 (m, 2H), 6.85 (dd, J = 8.2, 2.5 Hz, 1H), 5.92 (br s, 1H), 4.74 (d, J = 16.1 Hz, 1H), 4.68 (d, J = 16.1 Hz, 1H), 3.80 (s, 3H), 2.87−2.83 (m, 1H), 2.35 (ddd, J = 8.5, 5.7, 3.6 Hz, 1H), 1.58 (ddd, J = 8.4, 7.8, 4.2 Hz, 1H), 1.03 (apparent q, J = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) (Z)-isomer δ 176.4, 160.5, 140.0, 139.7, 137.1, 130.6 (2C), 130.0, 128.6 (2C), 127.2, 119.9, 113.6, 113.2, 104.0, 55.4, 44.6, 19.6, 19.5, 14.8; (E)-isomer δ 174.3, 161.0, 142.6, 139.7, 137.7, 130.5, 129.2 (2C), 128.9 (2C), 126.4, 120.1, 113.8, 113.3, 104.1, 55.5, 43.5, 20.9, 17.8, 16.8; HRMS (ESI) calcd for $C_{20}H_{19}NO_2Na$ ($M+Na^+$) 328.1308, found 328.1309; IR ν 1716, 1662, 1346, 1261, 700 cm^{-1}.

(1R,5S*)-3-(3-Methoxybenzyl)-4-(3-trifluoromethylbenzylidene)-3-azabicyclo[3.1.0]-hexan-2-one (**9**).* Yield 96% (95.0 mg, Z/E = 40:60; PE/EtOAc 70:30); orange oil: ^{1}H NMR (400 MHz, acetone-d_6) (Z)-isomer δ 7.56 (m, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.29−7.26 (m, 1H), 7.05 (t, J = 7.9 Hz, 1H), 6.71 (dd, J = 7.9, 2.1 Hz, 1H), 6.13 (d, J = 7.6 Hz, 1H), 6.03−6.02 (m, 1H), 5.89 (br s, 1H), 4.72 (d, J = 16.0 Hz, 1H), 4.20 (d, J = 16.0 Hz, 1H), 3.68 (s, 3H), 2.67 (dddd, J = 7.4, 5.6, 3.6, 0.6 Hz, 1H), 2.37 (ddd, J = 8.8, 5.6, 3.4 Hz, 1H), 1.36 (ddd, J = 8.4, 7.4, 4.2 Hz, 1H), 0.92 (m, 1H); (E)-isomer δ 7.74 (d, J = 7.8 Hz, 1H), 7.70 (br s, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.28 (t, J = 8.2 Hz, 1H), 6.93−6.89 (m, 2H), 6.86 (ddd, J = 8.2, 2.5, 0.7 Hz, 1H), 6.03 (br s, 1H), 4.78 (d, J = 15.8 Hz, 1H), 4.69 (d, J = 15.8 Hz, 1H), 3.80 (s, 3H), 2.88 (dddd, J = 7.6, 5.6, 3.8, 1.0 Hz, 1H), 2.41 (ddd, J = 8.6, 5.7, 3.6 Hz, 1H), 1.65 (ddd, J = 8.4, 7.7, 4.2 Hz, 1H), 1.11 (apparent q, J = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) (Z)-isomer δ 176.3, 160.6, 141.4, 139.0, 138.2, 134.3, 130.6 ($^2J_{C-F}$ = 30.7 Hz), 130.0, 129.3, 126.9 ($^3J_{C-F}$ = 3.6 Hz), 125.3 ($^1J_{C-F}$ = 271 Hz), 123.7 ($^3J_{C-F}$ = 3.9 Hz), 119.2, 113.3, 112.7, 102.2, 55.3, 44.8, 19.9, 19.7, 15.6; (E)-isomer δ 174.4, 161.0, 144.6, 139.4, 139.0, 132.2, 131.1 ($^2J_{C-F}$ = 31.8 Hz), 130.6, 130.2, 125.4 ($^1J_{C-F}$ = 270 Hz), 125.2 ($^3J_{C-F}$ = 3.9 Hz), 122.7 ($^3J_{C-F}$ = 3.7 Hz), 120.1, 113.8, 113.4, 102.7, 55.5, 43.5, 21.0, 17.7, 17.1; HRMS (ESI) calcd for $C_{21}H_{18}F_3NO_2Na$ ($M+Na^+$) 396.1182, found 396.1187; IR ν 1717, 1650, 1324, 1161, 1119, 1072, 700 cm^{-1}.

(1R,5S*)-4-Benzylidene-3-(3,4-dimethoxybenzyl)-3-azabicyclo-[3.1.0]hexan-2-one (**10**).* Yield 89% (79.8 mg, Z/E = 75:25; PE/EtOAc 50:50); orange oil: ^{1}H NMR (400 MHz, acetone-d_6) (Z)-isomer δ 7.37−7.32 (m, 2H), 7.30−7.25 (m, 1H), 7.17−7.14 (m, 2H), 6.73 (d, J = 8.2 Hz, 1H), 6.18 (dd, J = 8.2, 2.0 Hz, 1H), 6.08 (d, J = 2.0 Hz, 1H), 5.87 (br s, 1H), 4.74 (d, J = 15.1 Hz, 1H), 4.13 (d, J = 15.1 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.55 (dddd, J = 7.3, 5.5, 3.6, 0.5 Hz, 1H), 2.29 (ddd, J = 8.7, 5.6, 3.3 Hz, 1H), 1.24 (ddd, J = 8.4, 7.3, 4.1 Hz, 1H), 0.66 (apparent q, J = 3.5 Hz, 1H); (E)-isomer δ 7.44−7.42 (m, 2H), 7.37−7.32 (m, 2H), 7.20−7.14 (m, 1H), 6.94 (d, J = 1.9 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.87 (dd, J = 8.2, 2.0 Hz, 1H), 5.96 (br s, 1H), 4.70 (d, J = 15.5 Hz, 1H), 4.62 (d, J = 15.5 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.82 (dddd, J = 7.6, 5.6, 3.8, 1.0 Hz, 1H), 2.34 (ddd, J = 8.5, 5.7, 3.6 Hz, 1H), 1.57 (ddd, J = 8.4, 7.7, 4.2 Hz, 1H), 1.00 (apparent q, J = 3.7 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) (Z)-isomer δ 176.5, 149.9, 149.5, 140.1, 137.3, 130.7, 130.6 (2C), 128.7 (2C), 127.2, 120.2, 112.5, 112.0, 104.0, 56.1, 55.9, 44.2, 19.5, 19.3, 14.5; (E)-isomer δ 174.4, 150.5, 149.7, 142.6, 137.8, 130.5, 129.2 (2C), 128.9 (2C), 126.3, 120.4, 112.8, 112.1, 104.2, 56.14, 56.11, 43.3, 20.9, 17.7, 16.7; HRMS (ESI) calcd for $C_{21}H_{21}NO_3Na$ ($M+Na^+$) 358.1414, found 358.14103; IR ν 1716, 1662, 1514, 1261, 1237, 1140, 1027, 750, 701 cm^{-1}.

(1R,5S*)-3-(3,4-Dimethoxybenzyl)-4-(Z)-(4-methoxybenzylidene)-3-azabicyclo[3.1.0]-hexan-2-one (**11**).* Yield 94% (85.9 mg, Z/E > 95/5; PE/EtOAc 50:50); orange oil: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.02 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.2 Hz, 1H), 6.19 (dd, J = 8.2, 2.0 Hz, 1H), 6.07 (d, J = 2.0 Hz, 1H), 5.76 (br s, 1H), 4.69 (d, J = 15.1, 1H), 4.12 (d, J = 15.1 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.62 (s, 3H), 2.48 (dddd, J = 7.3, 5.6, 3.6, 0.4 Hz, 1H), 2.23 (ddd, J = 8.6, 5.6, 3.3 Hz, 1H), 1.18 (ddd, J = 8.4, 7.4, 4.1 Hz, 1H), 0.60 (apparent q, J = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 176.4, 159.3, 149.9, 149.4, 139.4, 131.7 (2C), 130.8, 129.3, 120.1, 114.1 (2C), 112.5, 111.9, 103.7, 56.1, 55.9, 55.6, 44.2, 19.6, 19.3, 14.4; HRMS (ESI) calcd for $C_{22}H_{23}NO_4Na$ ($M+Na^+$) 388.1519, found 388.1524; IR ν 1715, 1663, 1606, 1509, 1238, 1027, 755 cm^{-1}.

(1R,5S*)-3-(3,4-Dimethoxybenzyl)-4-(Z)-(thiophen-3-ylmethylidene)-3-azabicyclo-[3.1.0]hexan-2-one (**12**).* Yield 94% (85.1 mg, Z/E > 95/5; PE/EtOAc 50:50, 40:60); orange oil: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.43 (dd, J = 5.1, 2.8 Hz, 1H), 7.12 (m, 1H), 6.91 (d, J = 5.5 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.27 (dd, J = 8.2, 1.8 Hz, 1H), 6.20 (d, J = 2.0 Hz, 1H), 5.71 (br s, 1H), 4.77 (d, J = 15.2 Hz, 1H), 4.25 (d, J = 15.2 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.57−2.53 (m, 1H), 2.28 (ddd, J = 8.7, 5.6, 3.3 Hz, 1H), 1.24 (m, 1H), 0.68 (apparent q, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 176.3, 149.9, 149.4, 140.6, 137.2, 130.8, 130.6, 125.5, 123.8, 120.0, 112.4, 111.9, 98.3, 56.0, 55.9, 44.0, 19.5, 19.3, 14.6; HRMS (ESI) calcd for $C_{19}H_{19}NO_3SNa$ ($M+Na^+$) 364.0978, found 364.0978; IR ν 1715, 1666, 1514, 1262, 1140, 1026 cm^{-1}.

(1R,5S*)-4-Benzylidene-3-[3-(3,4-dimethoxyphenyl)propyl]-3-azabicyclo[3.1.0]hexan-2-one (**13**).* Yield 93% (89.9 mg, Z/E = 75:25; PE/EtOAc 70:30, 60:40); orange oil: ^{1}H NMR (400 MHz, acetone-d_6) (Z)-isomer δ 7.37−7.32 (m, 2H), 7.28−7.22 (m, 3H), 6.74 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 6.45 (dd, J = 8.1, 2.0 Hz, 1H), 5.87 (br s, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.49 (ddd, J = 13.8, 10.0, 6.3 Hz, 1H), 2.98 (ddd, J = 13.8, 9.6, 5.2 Hz, 1H), 2.51 (m, 1H), 2.17 (ddd, J = 8.6, 5.6, 3.3 Hz, 1H), 1.97 (ddd, J = 12.1, 9.9, 6.2 Hz, 1H), 1.84 (ddd, J = 13.5, 9.7, 6.2 Hz, 1H), 1.32−1.16 (m, 3H), 0.73 (apparent q, J = 3.5 Hz, 1H); (E)-isomer δ 7.47−7.44 (m, 2H), 7.37−7.32 (m, 2H), 7.17 (m, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.75−6.73 (m, 1H), 5.81 (br s, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.59−3.40 (m, 2H), 2.74 (m, 1H), 2.20−2.15 (m, 1H), 2.00−1.92 (m, 1H), 1.88−1.80 (m, 1H), 1.32−1.16 (m, 2H), 1.40 (ddd, J = 8.3, 8.0, 4.4 Hz, 1H), 0.88 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6) (Z)-isomer δ 176.0, 150.2, 148.5, 140.5, 137.3, 134.9, 130.5 (2C), 128.7 (2C), 127.3, 120.8, 113.0, 112.9, 103.0, 56.2, 56.0, 41.1, 33.0, 30.3, 19.8, 19.5, 16.0; (E)-isomer δ 174.0, 150.3, 148.7,

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140.9, 137.9, 135.0, 129.2 (2C), 128.9 (2C), 126.2, 121.1, 113.4, 113.0, 102.9, 56.2, 56.1, 39.4, 33.2, 29.6, 20.9, 17.6, 17.0; HRMS (ESI) calcd for $C_{23}H_{25}NO_3Na$ (M+Na$^+$) 386.1727, found 386.1730; IR ν 1716, 1661, 1515, 1260, 1234, 1155, 1140, 1028, 1006, 733, 702 cm^{-1}.

(1R,5S*)-3-[3-(3,4-Dimethoxyphenyl)propyl]-4-(Z)-(thiophen-3-ylmethylidene)-3-aza-bicyclo[3.1.0]hexan-2-one* (**14**). Yield 89% (87.9 mg, Z/*E* > 95/5; PE/EtOAc 50:50); orange oil: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.50 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.25 (m, 1H), 7.07 (d, *J* = 4.9 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 6.56 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.73 (br s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.55 (ddd, *J* = 13.8, 10.1, 6.2 Hz, 1H), 3.11 (ddd, *J* = 13.8, 9.8, 5.0 Hz, 1H), 2.55 (ddd, *J* = 7.3, 5.8, 3.6 Hz, 1H), 2.20 (ddd, *J* = 8.6, 5.6, 3.3 Hz, 1H), 2.11 (ddd, *J* = 13.6, 10.0, 6.1 Hz, 1H), 2.01 (ddd, *J* = 13.6, 9.0, 6.1 Hz, 1H), 1.43−1.25 (m, 3H), 0.76 (apparent q, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 175.9, 150.3, 148.7, 141.5, 137.3, 135.1, 130.6, 125.8, 123.8, 120.9, 113.2, 113.1, 97.3, 56.3, 56.1, 41.0, 33.3, 30.6, 19.8, 19.6, 16.1; HRMS (ESI) calcd for $C_{21}H_{23}NO_3SNa$ (M+Na$^+$) 392.1291, found 392.1297; IR ν 1715, 1664, 1514, 1260, 1234, 1139, 1027, 808 cm^{-1}.

Representative Procedure for the Reduction of Enamides 7−14. *(1R*,4S*,5S*)-4-Benzyl-3-(4-methoxybenzyl)-3-azabicyclo-[3.1.0]hexan-2-one* (**16**). TFA (594 μL, 8.00 mmol, 30 equiv) and Et_3SiH (213 μL, 1.33 mmol, 5 equiv) were added to a solution of **7** (81.4 mg, 0.267 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C. After 10 min, the reaction mixture was warmed to rt, stirred for 0.5 h, then poured into a saturated aqueous solution of $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Analysis by ^{1}H NMR spectroscopy indicated a single diastereomer (dr > 95:5). Purification by flash chromatography on silica gel (PE/EtOAc 50:50, 40:60) afforded **16** (77.9 mg, 95%) as a white solid: mp 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.20 (m, 3H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.12−7.10 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.86 (d, *J* = 15.0 Hz, 1H), 3.88 (d, *J* = 15.0 Hz, 1H), 3.81 (s, 3H), 3.70 (ddd, *J* = 10.8, 5.4, 4.1 Hz, 1H), 3.06 (dd, *J* = 12.8, 4.1 Hz, 1H), 2.36 (dd, *J* = 12.7, 10.8 Hz, 1H), 1.96 (ddd, *J* = 8.5, 6.2, 3.0 Hz, 1H), 1.59 (m, 1H), 1.00 (m, 1H), 0.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 158.9, 137.2, 129.3 (2C), 129.0 (2C), 128.7, 128.5 (2C), 126.6, 114.0 (2C), 58.2, 55.2, 43.2, 37.4, 20.3, 17.0, 9.8; HRMS (ESI) calcd for $C_{20}H_{21}NO_2Na$ (M+Na$^+$) 330.1464, found 330.1458; IR ν 1673, 1513, 1243, 743 cm^{-1}.

(1R,4S*,5S*)-4-Benzyl-3-(3-methoxybenzyl)-3-azabicyclo[3.1.0]-hexan-2-one* (**17**). Yield 90% (45.8 mg) (PE/EtOAc 40:60); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.20 (m, 4H), 7.12−7.10 (m, 2H), 6.84−6.82 (m, 2H), 6.79 (m, 1H), 4.85 (d, *J* = 15.2 Hz, 1H), 3.96 (d, *J* = 15.2 Hz, 1H), 3.80 (s, 3H), 3.74 (m, 1H), 3.05 (dd, *J* = 12.7, 4.1 Hz, 1H), 2.37 (dd, *J* = 12.7, 10.9 Hz, 1H), 1.98 (ddd, *J* = 8.4, 6.2, 3.1 Hz, 1H), 1.61 (m, 1H), 1.01 (apparent td, *J* = 8.0, 4.7 Hz, 1H), 0.84 (apparent q, *J* = 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 159.9, 138.3, 137.1, 129.6, 129.0 (2C), 128.4 (2C), 126.6, 120.3, 113.4, 112.9, 58.4, 55.2, 43.9, 37.4, 20.3, 17.0, 9.8; HRMS (ESI) calcd for $C_{20}H_{21}NO_2Na$ (M+Na$^+$) 330.1464, found 330.1462; IR ν 1682, 1411, 1258, 1047, 737, 699 cm^{-1}.

(1R,4S*,5S*)-3-(3-Methoxybenzyl)-4-(3-trifluoromethylbenzyl)-3-azabicyclo[3.1.0]-hexan-2-one* (**18**). Yield 91% (83.2 mg) (PE/EtOAc 45:55); yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.39 (apparent t, *J* = 7.7 Hz, 1H), 7.35 (br s, 1H), 7.31−7.25 (m, 2H), 6.85−6.82 (m, 2H), 6.78 (m, 1H), 4.84 (d, *J* = 15.2 Hz, 1H), 3.99 (d, *J* = 15.2 Hz, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.10 (dd, *J* = 12.9, 4.1 Hz, 1H), 2.44 (dd, *J* = 12.9, 10.8 Hz, 1H), 2.01 (ddd, *J* = 8.4, 6.2, 3.1 Hz, 1H), 1.59 (m, 1H), 1.05 (apparent td, *J* = 8.3, 4.8 Hz, 1H), 0.85 (apparent q, *J* = 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 159.9, 138.10, 138.06, 132.4, 130.8 ($^2J_{C-F}$ = 31.9 Hz), 129.7, 128.9, 125.6 ($^3J_{C-F}$ = 3.5 Hz), 123.9 ($^1J_{C-F}$ = 271 Hz), 123.6 ($^3J_{C-F}$ = 3.3 Hz), 120.1, 113.5, 112.9, 58.2, 55.2, 44.0, 37.3, 20.3, 16.8, 9.8; HRMS (ESI) calcd for $C_{21}H_{20}NO_2F_3Na$ (M+Na$^+$) 398.1338, found 398.1345; IR ν 1685, 1331, 1161, 1120, 1073, 756, 702 cm^{-1}.

(1R,4S*,5S*)-4-Benzyl-3-(3,4-dimethoxybenzyl)-3-azabicyclo-[3.1.0]hexan-2-one* (**19**). Yield 92% (74.4 mg) (PE/EtOAc 20:80); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.20 (m, 3H), 7.13−7.11 (m, 2H), 6.84−6.79 (m, 3H), 4.86 (d, *J* = 15.0 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (d, *J* = 15.0 Hz, 1H), 3.72 (ddd, *J* = 10.8, 5.2, 4.1 Hz, 1H), 3.09 (dd, *J* = 12.8, 4.1 Hz, 1H), 2.38 (dd, *J* = 12.8, 10.8 Hz, 1H), 1.97 (ddd, *J* = 8.4, 6.2, 3.1 Hz, 1H), 1.61 (m, 1H), 1.01 (apparent td, *J* = 7.9, 4.6 Hz, 1H), 0.83 (apparent td, *J* = 4.4, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 149.1, 148.4, 137.1, 129.2, 129.0 (2C), 128.4 (2C), 126.6, 120.3, 111.1, 110.9, 58.2, 55.85, 55.80, 43.6, 37.4, 20.3, 17.0, 9.8; HRMS (ESI) calcd for $C_{21}H_{23}NO_3Na$ (M+Na$^+$) 360.1570, found 360.1571; IR ν 1681, 1514, 1259, 1235, 1139, 1026, 731, 701 cm^{-1}.

(1R,4S*,5S*)-3-(3,4-Dimethoxybenzyl)-4-(4-methoxybenzyl)-3-azabicyclo[3.1.0]hexan-2-one* (**20**). Yield 91% (77.6 mg) (PE/EtOAc 10:90); yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.6 Hz, 2H), 6.84−6.77 (m, 5H), 4.85 (d, *J* = 15.0 Hz, 1H), 3.89 (s, 3H), 3.87 (d, *J* = 15.0 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.67 (m, 1H), 3.02 (dd, *J* = 12.8, 4.1 Hz, 1H), 2.33 (dd, *J* = 12.8, 10.8 Hz, 1H), 1.97 (ddd, *J* = 8.4, 6.2, 3.0 Hz, 1H), 1.61 (m, 1H), 1.00 (apparent td, *J* = 8.0, 4.7 Hz, 1H), 0.81 (apparent q, *J* = 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 158.3, 149.2, 148.4, 129.9 (2C), 129.3, 129.1, 120.3, 113.9 (2C), 111.2, 110.9, 58.4, 55.9, 55.8, 55.2, 43.6, 36.5, 20.3, 17.0, 9.8; HRMS (ESI) calcd for $C_{22}H_{25}NO_4Na$ (M+Na$^+$) 390.1676, found 390.1676; IR ν 1681, 1511, 1027, 732 cm^{-1}.

(1R,4S*,5S*)-3-(3,4-Dimethoxybenzyl)-4-(thiophen-3-ylmethyl)-3-azabicyclo[3.1.0]-hexan-2-one* (**21**). Yield 97% (55.9 mg) (PE/EtOAc 20:80, 10:90); yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 4.9, 2.9 Hz, 1H), 6.97 (m, 1H), 6.88 (dd, *J* = 4.9, 1.2 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.78−6.75 (m, 2H), 4.80 (d, *J* = 15.0 Hz, 1H), 3.88 (d, *J* = 15.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.74 (ddd, *J* = 10.6, 5.3, 4.4 Hz, 1H), 3.08 (dd, *J* = 13.4, 4.1 Hz, 1H), 2.47 (dd, *J* = 13.4, 10.6 Hz, 1H), 1.98 (ddd, *J* = 8.4, 6.2, 3.0 Hz, 1H), 1.71 (m, 1H), 1.00 (apparent td, *J* = 7.8, 4.7 Hz), 0.79 (apparent q, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 149.2, 148.4, 137.2, 129.3, 128.2, 125.7, 121.9, 120.3, 111.1, 110.9, 57.6, 55.9, 55.85, 43.7, 32.0, 20.3, 17.3, 9.7; HRMS (ESI) calcd for $C_{19}H_{21}NO_3SNa$ (M+Na$^+$) 366.1134, found 366.1137; IR ν 1677, 1513, 1259, 1235, 1139, 1025, 759 cm^{-1}.

(1R,4S*,5S*)-4-Benzyl-3-[3-(3,4-dimethoxyphenyl)propyl]-3-azabicyclo[3.1.0]hexan-2-one* (**22**). Yield 94% (81.2 mg) (PE/EtOAc 20:80, 10:90); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 2H), 7.28−7.23 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.75 (s, 1H), 6.75−6.72 (m, 1H), 3.92−3.86 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.54 (ddd, *J* = 14.2, 9.1, 7.0 Hz, 1H), 3.01−2.94 (m, 2H), 2.63−2.50 (m, 2H), 2.43 (dd, *J* = 12.7, 10.6 Hz, 1H), 1.90 (ddd, *J* = 8.5, 6.2, 3.0 Hz, 1H), 1.90−1.72 (m, 2H), 1.62 (m, 1H), 0.96 (ddd, *J* = 8.4, 7.8, 4.7 Hz, 1H), 0.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 148.8, 147.2, 137.1, 134.0, 129.0 (2C), 128.5 (2C), 126.7, 119.9, 111.6, 111.2, 58.7, 55.8, 55.7, 39.6, 37.6, 32.7, 29.1, 20.3, 16.7, 9.4; HRMS calcd for $C_{23}H_{27}NO_3Na$ (M+Na$^+$) 388.1883, found 388.1883; IR ν 1681, 1514, 1257, 1235, 1027, 700 cm^{-1}.

(1R,4S*,5S*)-3-[3-(3,4-Dimethoxyphenyl)propyl]-4-(thiophen-3-ylmethyl)-3-azabicyclo-[3.1.0]hexan-2-one* (**23**). Yield 92% (79.2 mg) (PE/EtOAc 20:80); yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.06 (dd, *J* = 3.0, 1.0 Hz, 1H), 7.00 (dd, *J* = 4.9, 1.3 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 6.74−6.71 (m, 1H), 3.90 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.50 (ddd, *J* = 14.0, 9.2, 6.9 Hz, 1H), 2.99 (dd, *J* = 13.4, 4.3 Hz, 1H), 2.95 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1H), 2.61−2.48 (m, 3H), 1.92 (ddd, *J* = 8.4, 6.2, 3.1 Hz, 1H), 1.88−1.69 (m, 3H), 0.95 (apparent td, *J* = 8.2, 4.7 Hz, 1H), 0.70 (apparent td, *J* = 4.4, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 148.7, 147.1, 137.2, 134.0, 128.1, 125.8, 121.8, 119.9, 111.6, 111.2, 58.0, 55.8, 55.7, 39.6, 32.7, 32.1, 29.1, 20.2, 17.0, 9.3; HRMS calcd for $C_{21}H_{25}NO_3SNa$ (M+Na$^+$) 394.1447, found 394.1448; IR ν 1677, 1514, 1258, 1235, 1027, 762 cm^{-1}.

Reaction of **15** *with* Et_3SiH/TFA. TFA (497 μL, 6.69 mmol, 30 equiv) was added to a mixture of **15**[9] (77.9 mg, 0.223 mmol) and Et_3SiH (1.07 mL, 6.69 mmol, 30 equiv) at rt. After 0.5 h, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Analysis by ^{1}H NMR spectroscopy indicated the formation of **24** and **25** (40:60

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ratio). Separation by preparative TLC on silica gel (PE/EtOAc 30:70, two elutions) afforded **25** (35 mg, 45%) as a white solid[9] and **24** (22 mg, 28%) as a viscous oil.

(1R,4S*,5S*)-4-Benzyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-3-azabicyclo[3.1.0]hexan-2-one (**24**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 3H), 7.19−7.17 (m, 2H), 6.81 (d, J = 8.6 Hz, 1H), 6.76−6.73 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.78 (m, 1H), 3.70 (ddd, J = 14.0, 8.9, 6.4 Hz, 1H), 3.14 (ddd, J = 14.0, 8.7, 6.1 Hz, 1H), 2.98 (dd, J = 12.8, 4.4 Hz, 1H), 2.82 (ddd, J = 13.6, 8.8, 6.2 Hz, 1H), 2.73 (ddd, J = 13.6, 8.8, 6.2 Hz, 1H), 2.37 (dd, J = 12.8, 10.4 Hz, 1H), 1.90 (ddd, J = 8.5, 6.2, 3.0 Hz, 1H), 1.58 (m, 1H), 0.95 (apparent td, J = 8.1, 4.7 Hz, 1H), 0.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 148.9, 147.6, 137.2, 131.5, 129.0 (2C), 128.6 (2C), 126.7, 120.7, 112.0, 111.3, 59.1, 55.95, 55.90, 41.7, 37.7, 33.6, 20.3, 16.9, 9.4; HRMS calcd for $C_{22}H_{25}NO_3Na$ ($M+Na^+$) 374.1727, found 374.1726; IR ν 1679, 1514, 1260, 1235, 1027, 730, 700 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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