Articles

Synthesis of 2β-Acyl-3β-aryl-8-azabicyclo[3.2.1]octanes and Their Binding Affinities at Dopamine and Serotonin Transport Sites in Rat Striatum and Frontal Cortex

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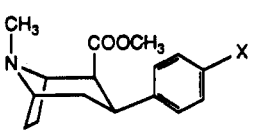
A novel entry to tropane analogs of cocaine was developed on the basis of the reaction of rhodium-stabilized vinylcarbenoids with pyrroles. These analogs were tested in binding to dopamine and serotonin (5-HT) transporters in membranes from rat striatum and frontal cortex. In all the analogs, the aryl group at the 3-position was directly bound to the tropane ring (as in WIN-35,428), and methyl or ethyl ketone moieties were present at the 2-position instead of the typical ester group. The series of analogs containing a 2-naphthyl group at the 3-position were most potent, with K_i values < 1 nM in binding to both dopamine and 5-HT transporters. Although the unsubstituted 2-naphthyl analog was nonselective at dopamine and 5-HT transport sites, other compounds were selective for either site. In general, compounds with relatively small substituents on the aromatic moiety (such as *p*-methyl or *p*-fluoro) were relatively selective for the dopamine transporters, while a *p*-isopropylphenyl derivative was selective for the 5-HT transport sites. This latter compound represents the first *N*-methyltropane derivative specific for 5-HT transporters. Resolution of two of the most significant analogs was achieved by HPLC on a chiral stationary phase; the active enantiomer of a 2-naphthyl analog exhibited K_i values of <0.1 nM at both dopamine and 5-HT transporter sites.

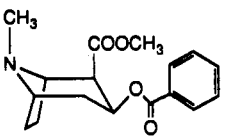
Introduction

In order to define the pharmacaphore responsible for cocaine's mode of action, a number of novel cocaine derivatives have recently been prepared and evaluated for biological activity.[1-17] A promising series of compounds are the 3β-aryltropane-2β-carboxylates, many of which are up to 500 times more potent than cocaine at binding at the dopamine transporter.[10-14] Indeed, the preferred radioligands for displacement studies at the dopamine transporter are now based on the 4-fluorophenyl derivative (CFT) **1a**[17] and 4-iodophenyl derivative (RTI-55) **1b**.[8] A particularly important goal of these research endeavours is to prepare selective ligands for the various biogenic amine transporters. Highly selective ligands for the dopamine transporter have been obtained simply by using isopropyl or phenyl esters of the 2β-carboxylates.[10] In this paper, we will describe a new synthetic route to cocaine analogs, the flexibilty of which has enabled us to prepare the most potent cocaine analogs to date and also the first tropane derivatives that are selective for the 5-HT transporter.[18]

Even though a large number of 3β-aryltropane-2β-carboxylates have been prepared, the current synthetic scheme, which begins with (−)-cocaine (**2**)[1,4,15] or tropinone[17] and proceeds through anhydroecgonine methyl ester (**3**), is not particularly general. As (−)-cocaine is the usual starting material, synthetic flexibility is naturally restricted. A second limitation is the requirement of the use of Grignard reagents in the absence of copper salts for introduction of the aryl groups onto **3** as this is a rather capricious step, successful with only certain Grignard reagents. On the basis of this analysis, an alternative synthesis of cocaine analogs was considered to be highly desirable. The new synthetic strategy that we have developed is based on the reaction between rhodium-stabilized vinylcarbenoids and pyrroles.[19] A series of methyl ketone and ethyl ketone derivatives were chosen as targets. These cocaine analogs were expected to have greater metabolic stability than cocaine as they lack ester linkages. Furthermore, their synthesis would be simplified because of the ease of cuprate-catalyzed 1,4-additions to α,β-unsaturated ketones.



1a X = F
1b X = I



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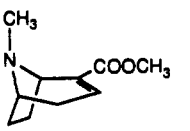

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Chemistry

Davies *et al.* previously reported that the reaction between rhodium(II)-stabilized vinylcarbenoids and *N*-(((trimethylsilyl)ethoxy)carbonyl)pyrrole is the basis of a rather direct synthesis of both anhydroecgonine methyl

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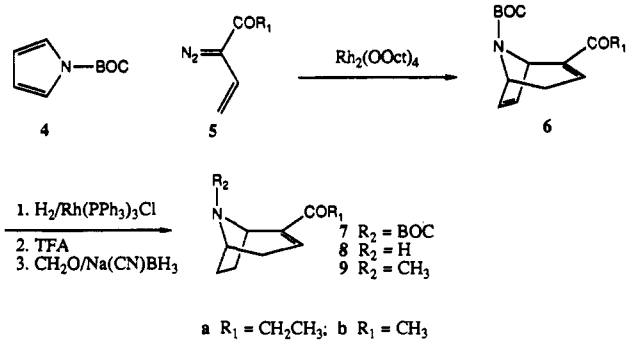
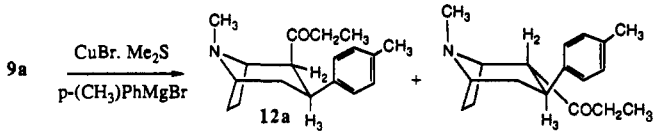
Scheme 1



Scheme 2



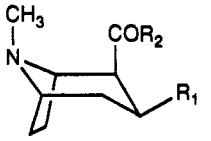
Reaction time	Quench	2β : 2α
2 h	aq HCl, 0 °C	35 : 65
12 h	aq HCl, 0 °C	63 : 37
12 h	dry HCl, -78 °C	88 : 12

ester and ferruginine (**9b**).[19] A more practical approach for large-scale synthesis begins with *N*-(*tert*-butoxycarbonyl)pyrrole (**4**) as illustrated in Scheme 1. Rhodium(II) pivalate catalyzed decomposition of either of the vinyldiazomethanes (**5a** or **5b**) resulted in the formation of the azabicyclo[3.2.1]octa-2,6-dienes in moderate yields (33% for **6a**, 56% for **6b**). The further conversion of either **6a** or **6b** to **9a** or **9b** was readily achieved in a three-step sequence; catalytic hydrogenation with Wilkinson's catalyst, TFA-induced hydrolysis of the *tert*-butoxycarbonyl protecting group, and reductive methylation with formaldehyde and sodium cyanoborohydride.

The remaining step for the synthesis of cocaine derivatives was the introduction of the aryl functionality into **9**. As expected, copper-catayzed 1,4-addition to the α,β-unsaturated ketones **9** proceeded very smoothly, and a study of the stereochemistry of this reaction was carried out for the reaction of **9a** with 4-tolylmagnesium chloride. The approach of the Grignard reagent predictably occurred from the β-face, but the stereochemistry for protonation at the 2-position was very dependent on reaction times and quenching conditions (Scheme 2). Long reaction times followed by a low-temperature quench strongly favored the formation of the desired 2β-isomer **12a**, which was readily separated from the 2α-isomer by column chromatography. Using this basic strategy, a range of 2β-acyl-3β-phenyl derivatives (**10–17**) were prepared as well as the 3β-alkyl (**18**, **19**), the 3β-(1-naphthyl) (**20**), and 3β-(2-naphthyl) derivatives (**21**) (Table 1). Stereochemical assignments in tropanes is well-precedented on the basis of coupling constants.[15] Particularly distinctive is the coupling constant between H_2 and H_3, which is ~12 Hz for the 2α,2β-isomer and ~5 Hz for the 2β,3β-isomer. Derivatives **18–21** are particularly interesting because the functionality contained in these systems had not been prepared previously, presumably because of the difficulties associated with the 1,4-addition when the unsaturated ester **3** was used as substrate.

The vinylcarbenoid chemistry resulted in the formation of derivatives **10–21** as racemic mixtures. Resolution of two of the most significant derivatives in this series, **12a** and **21a**, was achieved by chiral HPLC separation on a β-cyclodextrin column.

Table 1. IC_{50} and K_i Values of Tropane Analogs in Displacing [^{125}I]RTI-55 Binding in Rat Striatal Membranes and [^{3}H]Paroxetine Binding in Rat Frontal Cortex Membranes



analog	R_1	R_2	dopamine IC_{50} (nM)	5-HT K_i (nM)
10a	Ph	CH_2CH_3	48.3 ± 2.8[18]	1005 ± 112
10b	Ph	CH_3	114 ± 22[18]	1364 ± 616
11a	*p*-PhF	CH_2CH_3	15.3 ± 2.8	630 ± 67
11b	*p*-PhF	CH_3	70.8 ± 13[18]	857 ± 187
12a	*p*-$PhCH_3$	CH_2CH_3	8.2 ± 1.6[18]	131 ± 10
(+)-**12a**	*p*-$PhCH_3$	CH_2CH_3	4.21 ± 0.46	74 ± 12
(−)-**12a**	*p*-$PhCH_3$	CH_2CH_3	1337 ± 122	>10000
12b	*p*-$PhCH_3$	CH_3	9.8 ± 0.5[18]	122 ± 22
13b	*p*-$PhCH_2CH_3$	CH_3	152 ± 24[18]	78.2 ± 22
14a	*p*-$PhCH(CH_3)_2$	CH_2CH_3	436 ± 41	35.8 ± 4.4
15a	*p*-$PhC(CH_3)_3$	CH_2CH_3	2120 ± 630	1771 ± 474
16a	*p*-PhPh	CH_2CH_3	2.29 ± 1.08	4.31 ± 0.01
17a	*o*-$PhCH_3$	CH_2CH_3	1287 ± 322[18]	>10000
18a	CH_2CH_3	CH_2CH_3	>50000[18]	>10000
19a	c-C_6H_{11}	CH_2CH_3	4610 ± 492[18]	>10000
20a	1-naphthyl	CH_2CH_3	5.34 ± 1.27	20.9 ± 2.9
20b	1-naphthyl	CH_3	10.1 ± 2.2[18]	25.6 ± 5.1
21a	2-naphthyl	CH_2CH_3	0.115 ± 0.021	0.394 ± 0.074
(+)-**21a**	2-naphthyl	CH_2CH_3	0.043 ± 0.016	0.121 ± 0.03
(−)-**21a**	2-naphthyl	CH_2CH_3	113 ± 26	484 ± 146
21b	2-naphthyl	CH_3	0.28 ± 0.11	1.06 ± 0.36

Pharmacology

Methods. Binding. Dopamine transport sites can be measured by binding studies in brain membranes using a variety of labeled ligands. These have included [^{3}H]-mazindol,[20,21] [^{3}H]CFT (or WIN 35,428),[17] and [^{3}H]cocaine itself.[22,23] For the present studies, we have chosen [^{125}I]-RTI-55 to label dopamine transport sites in rat striatal membranes.[8,9] This ligand was chosen for several reasons. First, RTI-55 is a tropane derivative like cocaine. Studies from Madras *et al.*[17] have shown that tropane analogs demonstrate different binding characteristics than non-tropane analogs like mazindol. Since all of the analogs studied in the present experiments were tropane derivatives, RTI-55 was a logical choice. Second, RTI-55 possesses the highest affinity (K_D of 1 nM) for dopamine transport sites of the labeled tropane analogs.[8] Finally, the use of the higher specific activity ^{125}I-labeled compound required 10-fold less striatal tissue than assays using the ^{3}H-labeled compounds. For 5-HT binding studies, [^{3}H]-paroxetine is a potent (K_D = 0.15 nM) and highly selective ligand for 5-HT transporters.[23,24] No radiolabeled tropanes are yet available for specifically labeling 5-HT transport sites.

For the results listed below, potencies of all analogs in displacing [^{125}I]RTI-55 binding are expressed as IC_{50} values because the biphasic nature of radiolabeled tropane binding to striatal membranes makes determination of accurate K_i values difficult.[8,17] However, potencies of analogs in displacing [^{3}H]paroxetine binding are expressed as K_i values, as calculated by the method of Cheng and Prusoff[25] using a K_d value of 0.15 nM for [^{3}H]paroxetine binding.[23]

Biological Results and Discussion

Table 1 demonstrates IC_{50} values of 21 tropane analogs in displacing [^{125}I]RTI-55 binding at dopamine transporters and in displacing [^{3}H]paroxetine binding at 5-HT transporters. Several of these analogs were previously assayed vs [^{125}I]RTI-55 binding in rat striatal membranes.[18] The present study extends those previous findings by examining the potencies of these analogs at 5-HT transporters and by extending the list of novel tropane analogs to a total of 21. The comparison of the binding affinities between the two transporters has led to the recognition that certain structural features favor selective binding to the 5-HT transporter. In all of these studies, cocaine is the reference compound; the IC_{50} value for cocaine vs [^{125}I]RTI-55 binding was 173 nM and the K_i value for cocaine vs [^{3}H]paroxetine binding was 302 nM, compared to previously reported values of approximately 150 and 140 nM for this compound at dopamine and 5-HT transporters.[27]

All of the analogs shown in Table 1 contained either a methyl ketone or an ethyl ketone at the 2-position, instead of the native ester functionality. This functional change at the 2-position did not dramatically affect binding potency at either transporter, although the 2-propanoyl derivatives tended to have slightly higher binding affinities than the corresponding 2-acetyl derivatives. For example, the dopamine binding affinities for **10–12** shown in Table 1 are very similar in values to those for the methyl ester derivatives corresponding to **10–12** (Ph, 23 nM; PhF, 15.7 nM, *p*-PhMe, 1.71 nM).[4] The same trend was also seen in the 5-HT binding for **10–12**. The selectivities of these derivatives between the transporters were similar to but not as great as that reported for the corresponding methyl ester derivatives in which binding affinities were greater at the the dopamine transporter by a factor of 50–150.[10] These results are consistent with previous findings that a number of variations at the 2-position may be tolerated without a major effect on binding potency at the dopamine transport sites.[10,12–14]

One of the primary goals of the present study was to determine the different structural requirements for tropane binding selectivity to dopamine and 5-HT transporters. Previous QSAR studies for cocaine analogs at the dopamine transporter had shown the requirement of a hydrophobic pocket of limited size for interaction with the 3β-aryl substituent.[4] Our results showed that this requirement for binding differed considerably for the two monoamine transporters. Addition of small groups (*e.g.*, fluoro, methyl as in **11** and **12**) to the aromatic ring increased potency at both dopamine and 5-HT transporters. However, the size requirements for the aryl substituent were much more strict for the dopamine transporter compared to the 5-HT transporter. Addition of an ethyl group to the aromatic ring (**13b**) reduced potency by a factor of 2 (compared to the phenyl analog **10b**) at the dopamine transporter, but increased binding by a factor of 15 to 5-HT transport sites. A more dramatic example of this effect was seen in the isopropyl phenyl analog **14a**, which had 10-fold lower affinity at dopamine transport sites than the unsubstituted phenyl analog **10a**, but had a 30-fold increase in affinity at the 5-HT transporter compared to **11a**. This is the first reported *N*-methyltropane analog which is relatively selective for 5-HT transporters (12 times more selective for 5-HT than dopamine).[21] Further, these results suggest that the tropane binding site in the dopamine transporter has a stricter requirement for size around the 3-position than the 5-HT transporter. Increasing the size further to the *tert*-butyl derivative **15a** resulted in markedly reduced affinities to both transporters while the biphenyl derivative **16a** was very potent to both transporters

Even though moderate size at the *p*-phenyl position is tolerated, introduction of ortho functionality seriously compromises binding affinity to both transporters. This effect is clearly seen for the *o*-tolyl derivative **17a**, which is at least 100 times less potent than the *p*-tolyl derivative **11a** at both transporters.

Another shared characteristic between 5-HT and dopamine transporters was the requirement for an aromatic ring at the 3-position. Replacement of the aryl by ethyl (**18a**) or by cyclohexyl (**19a**) reduced binding affinities to >1 μM for both dopamine and 5-HT transporters.

The most potent derivatives were obtained for the naphthyl series, in which the substituted phenyl at the 3-position was replaced by either a 1-naphthyl or a 2-naphthyl group. Replacement of the substituted phenyl with a 1-naphthyl group significantly increased potency at both dopamine and 5-HT transporters, with a 10-fold increase in potency at dopamine transporters and a 50-fold increase at 5-HT transporters compared to the unsubstituted aryl analogs (*e.g.*, compare **20a** with **10a**). The finding that the potencies of these analogs were increased relatively more for the 5-HT than for the dopamine transport sites supports the concept that the tropane binding site on the 5-HT transporter can accept more bulky substituents than that of the dopamine transporter.

An even more dramatic increase in potency was observed for the 2-naphthyl series. These analogs also displayed very high affinity for 5-HT transporters. The unsubstituted 2-naphthyl analog **21a** was 400 times more potent than the unsubstituted phenyl analog **10a** at dopamine transporters and 2500 times more potent than **10a** at 5-HT transporters. Presumably, the 2-naphthyl derivatives have much higher affinities than the 1-naphthyl derivatives due to a similar steric constraint to that which was seen for the *p*- and *o*-tolyl derivatives **12a** and **17a**, although electronic effects may also contribute to the binding efficiency.

Because the vinylcarbenoid chemistry begins with achiral materials, all of the analogs were prepared as racemic mixtures. Therefore, the actual affinities of the active stereoisomers of these analogs are likely to be higher than those presented in Table 1. To confirm this possibility, stereoisomers of two analogs, the tolyl analog **12a** and the unsubstituted 2-naphthyl analog **21a**, were separated on a chiral HPLC column. The binding results showed that only one isomer of each analog was active in binding to either dopamine or 5-HT transport sites. Moreover, the selectivity of the active isomer of each analog paralleled the selectivity of the racemic mixture (Table 1). These data confirm that the selectivities reported for these analogs at dopamine and 5-HT transporters are not due to a contamination of the active isomer by another isomer with different selectivities. The actual potencies of the active isomers of **12a** and **21a** are 4.2 and 0.043 nM, respectively. The binding affinity of 0.043 nM for the naphthyl derivative (+)-**21a** is 5 times higher than that previously reported for any other cocaine analog based on the tropane structure. The IC_{50} value for the racemic 2-naphthyl analog **21a**, 0.115 nM, was previously reported

as a slightly lower affinity (0.2 nM).[18] Although the actual IC_{50} value for this compound has changed, the qualitative conclusions have remained the same: in both reports, **21a** remains the most potent analog in the series.

In addition to helping determine the structural requirements for the tropane binding site of the cocaine pharmacophore, these analogs will be useful agents in a number of biological assays. For example, approximately 90% of cocaine metabolism occurs via esterase activities;[28] therefore, the lack of ester groups on these analogs suggests that they should be much longer acting *in vivo* than cocaine. This prediction has been supported by preliminary data from both locomotor and microdialysis tests (L. Porrino, J. Smith and S. Childers, unpublished observations), which demonstrated long (>3 h) duration of action for one of these analogs (the tolyl analog **12a**). Another prediction is that changing the relative selectivity of these compounds for dopamine and 5-HT transporters should change their overall behavioral spectrum. This prediction has been supported by other preliminary data (L. Porrino, and S. Dworkin, unpublished observations) which have shown that the behavioral actions of **12a** in self-administration, drug discrimination, and stereotypy tests are significantly different from those of cocaine. These studies demonstrate how the use of analogs with specific selectivities for different monoamine transporters can help explore the roles of these different neurotransmitters in mediating the neurobiological effects of cocaine.

Conclusion

This study demonstrates that vinylcarbenoid chemistry can be utilized in synthesizing novel tropane analogs which may be useful in elucidating neurochemical mechanisms of cocaine action. These studies have synthesized tropane analogs which are specific for either 5-HT or dopamine transporters. Both transporters can accommodate fairly large planar aromatic rings at the 3-position of the tropane system, but the binding affinity at the dopamine transporter is selectively diminished by the introduction of nonplanar para substituents on the aryl ring. One of the most interesting series of these analogs contains a 2-naphthyl group on the 3-position of the tropane. These compounds are extraordinarily potent at both dopamine and 5-HT transporters. Modifications of the general 2-naphthyl structure may provide a new series of potent selective analogs which will be useful in probing the requirements of the cocaine pharmacophore.

Experimental Section

Commercial reagents were utilized without further purification unless otherwise noted. Methylene chloride was dried over calcium hydride and was freshly distilled. Diethyl ether was dried over benzophenone ketyl and was freshly distilled. NMR data were obtained on a Varian VXR 200 MHz spectrometer and are expressed as δ values. Chromatographic separations were carried out with 230–400-mesh silica (Silica 60 – EM Science). Elemental analyses were performed by Atlantic Microlab, Atlanta, GA and were within ±0.4% of the theoretical values for C, H, and N.

Binding Studies. Affinities of analogs at dopamine transport sites were determined by displacement of [^{125}I]RTI-55 binding in membranes from rat striatum.[8] Male Sprague–Dawley rats (200–250 g) were decapitated by guillotine, and striata were dissected on ice. Tissue was homogenized in 10 volumes of RTI-55 assay buffer (0.32 M sucrose, 10 mM sodium phosphate buffer, pH 7.4) with a Polytron (setting 6, 20 s) and centrifuged three times at 48000*g* for 10 min, with fresh buffer resuspension for each centrifugation. For [^{125}I]RTI-55 assays, tubes contained 0.5 mg (original wet weight) of membranes, 20 pM [^{125}I]RTI-55, and various concentrations of unlabeled drugs dissolved in RTI-55 assay buffer in a final volume of 2 mL. Tubes were incubated for 50 min at 25 °C, and the reaction was terminated by rapid filtration with 3 × 5 mL of cold Tris buffer through Whatman GF/B glass fiber filters. Nonspecific binding was determined in the presence of 30 μM cocaine.

Affinities of analogs at 5-HT transport sites were determined by displacement of [^{3}H]paroxetine binding in membranes from rat frontal cortex.[23] Tissue was obtained from rats as described above and homogenized in 10 volumes of paroxetine assay buffer (50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, pH 7.4) with a Polytron (setting 6, 20 s), and centrifuged two times at 48000*g* for 10 min, with fresh buffer resuspension for each centrifugation. For [^{3}H]paroxetine binding assays, tubes contained 50 mg (original wet weight) of membranes, 0.4 nM [^{3}H]paroxetine, and various concentrations of unlabeled drugs dissolved in paroxetine assay buffer in a final volume of 2 mL. Tubes were incubated for 60 min at 25 °C, and the reaction was terminated by rapid filtration with 3 × 4 mL of cold Tris buffer through Whatman GF/B glass fiber filters which had been presoaked in paroxetine assay buffer containing 0.05% polyethyleneimine for at least 1 h. Nonspecific binding was determined in the presence of 10 μM fluoxetine. Radioactivity was determined by liquid scintillation spectrophotometry (efficiency: 50%) after eluting filters overnight in 5 mL of Ecolite scintillation fluid (ICN).

K_i and IC_{50} values in binding assays were calculated from displacement curves using 7–10 concentrations of unlabeled analogs. All data are mean values ± SEM of at least three separate experiments, each of which was conducted in triplicate.

***N*-(*tert*-Butoxycarbonyl)pyrrole (4).** 4-(*N*,*N*-Dimethylamino)pyridine (2.38 g, 0.019 mol) and di-*tert*-butyl dicarbonate (51.07 g, 0.23 mol) were added to a stirred solution of pyrrole (16.77 g, 0.25 mol) in dry acetonitrile (25 mL) at room temperature and then stirred for 24 h. The mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel (petroleum ether) to give a colorless liquid (24.8 g, 76%): IR (neat) 2940, 1725, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.22 (t, 2 H, *J* = 2.3 Hz), 6.19 (t, 2 H, *J* = 2.3 Hz), 1.59 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 119.9, 111.8, 83.5, 27.9, 27.7.

4-Diazo-5-hexen-3-one (5a). DBU (6.21 g, 0.041 mol) was added to a stirred solution of 5-hexen-3-one (2.0 g, 0.02 mol) and *p*-acetamidobenzenesulfonyl azide (8.56 g, 0.024 mol) in acetonitrile (50 mL) at 0 °C. After stirring overnight, saturated aqueous ammonium chloride (50 mL) was added and the mixture was extracted with pentane (5×). Purification on silica gel column chromatography (5/95 ether/petroleum ether) afforded **5a** as an orange liquid (1.7 g, 68%): IR (neat) 2940, 2060, 1700, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.26 (dd, 1 H, *J* = 10.9, 17.7 Hz), 5.16 (d, 1 H, *J* = 10.9 Hz), 4.86 (d, 1 H, *J* = 17.7 Hz), 2.52 (q, 2 H, *J* = 7.4 Hz), 1.14 (t, 3 H, *J* = 7.4 Hz). Due to lack of stability, elemental analysis was not attempted.

8-(*tert*-Butoxycarbonyl)-2-(1-propanoyl)-8-azabicyclo[3.2.1]octa-2,6-diene (6a). A solution of **5a** (6.80 g, 0.055 mol) in hexane (150 mL) was added over 4 h by means of an ice-cooled dropping funnel to a stirred solution of **4** (50.0 g, 0.299 mol) and rhodium(II) octanoate (0.43 g, 0.55 mmol) in refluxing hexane (500 mL) under an argon atmosphere. The mixture was refluxed for a further 1.5 h, and the solvent was then removed under reduced pressure. Purification of the product by silica gel column chromatography (petroleum ether to ether/petroleum ether (1:4)) followed by bulb-to-bulb distillation gave **6a** as an orange liquid (4.69 g, 33%): IR (neat) 2960, 1740, 1700, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.39 (m, 2 H), 5.89 (dd, 1 H, *J* = 5.9, 2.4 Hz), 5.11 (m, 1 H), 4.62 (m, 1 H), 2.87 (m, 1 H), 2.58 (q, 2 H, *J* = 7.3 Hz), 1.91 (dd, 1 H, *J* = 19.8, 4.1 Hz), 1.39 (s, 9 H), 1.08 (t, 3 H, *J* = 7.3 Hz); MS *m*/*z* (rel intensity) 207 (14), 190 (3), 163 (17), 150 (5), 134 (8), 120 (1), 106 (57), 91 (2), 79 (7), 57 (100). Anal. ($C_{15}H_{21}NO_3$) C, H, N.

8-(*tert*-Butoxycarbonyl)-2-(1-propanoyl)-8-azabicyclo[3.2.1]oct-2-ene (7a). A solution of **6a** (1.2 g, 4.6 mmol) and $RhCl(PPh_3)_3$ (0.042 g, 0.046 mmol) in ethanol (50 mL) was pressurized with 45 psi of H_2 and shaken for 12 h. The solvent was then evaporated, and the residue was purified by bulb-to-bulb distillation (120 °C (0.8 mmHg)) to give **7a** as an orange liquid (1.15 g, 95%): IR (neat) 2960, 1760, 1710, 1640 cm^{-1}; ^{1}H

NMR ($CDCl_3$) δ 6.62 (m, 1 H), 4.89 (d, 1 H, J = 5.6 Hz), 4.37 (m, 1 H), 2.91 (d, br, 1 H), 2.61 (q, 2 H, J = 7.3 Hz), 1.41 (s, 9 H), 1.08 (t, 3 H, J = 7.3 Hz), 2.12–1.43 (m, 4 H), 2.00 (dd, 1 H, J = 19.4, 4.7 Hz); MS m/z (rel intensity) 209 (24), 192 (6), 180 (31), 150 (6), 136 (42), 122 (4), 108 (14), 91 (5), 68 (7), 57 (100). Anal. ($C_{15}H_{23}NO_3$) C, H, N.

2-(1-Propanoyl)-8-azabicyclo[3.2.1]oct-2-ene (8a). A solution of trifluoroacetic acid (0.03 mol, 0.23 mL) and **7a** (0.8 g, 0.003 mol) in CH_2Cl_2 was stirred at room temperature for 0.5 h. The solution was concentrated under reduced pressure after the addition of hexane (3×) to remove excess trifluoroacetate. A concentrated aqueous solution of Na_2CO_3 was added to the residue to form a basic solution. The solution was extracted with CH_2Cl_2, dried (Na_2SO_4), and purified by bulb-to-bulb distillation (80 °C (1 mmHg)) to afford **8a** (0.45 g, 92%): IR (neat) 3300, 2940, 1650, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.56 (t, 1 H, J = 3.6 Hz), 4.20 (d, 1 H, J = 4.5 Hz), 3.65 (t, 1 H, J = 5.7 Hz), 2.70 (m, 1 H), 2.55 (q, 2 H, J = 7.3 Hz), 1.98 (dd, 1 H, J = 19.4, 4.4 Hz), 1.87–1.77 (m, 3 H), 1.50 (m, 1 H), 1.02 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 199.6, 146.0, 135.3, 52.4, 52.1, 36.5, 36.1, 30.5, 29.7, 8.3; MS m/z (rel intensity) 165 (24), 136 (100), 108 (28), 91 (12), 80 (15), 68 (26), 57 (28); HRMS calcd for $C_{10}H_{15}NO$ 165.1153, found 165.1153.

8-Methyl-2-propanoyl-8-azabicyclo[3.2.1]oct-2-ene (9a). To a stirred mixture of **8a** (0.20 g, 1.21 mmol) and aqueous formaldehyde (0.45 mL, 6.05 mmol, 37%) in acetonitrile (15 mL) was added sodium cyanoborohydride (0.122 g, 1.937 mmol). After being stirred for 15 min the reaction mixture was made acidic by addition of glacial acetic acid (15 mL) over a 45-min period. The solution was extracted with ether and the aqueous layer was then made basic by the addition of concentrated Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3×), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **9a** as a yellow liquid (0.16 g, 73%): IR (neat) 2920, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.64 (t, 1 H, J = 3.4 Hz), 3.85 (d, 1 H, J = 5.4 Hz), 3.19 (t, 1 H, J = 5.4 Hz), 2.70 (m, 1 H), 2.57 (q, 2 H, J = 7.3 Hz), 2.26 (s, 3 H), 2.12-2.05 (m, 2 H), 1.85 (dd, 1 H, J = 19.7, 4.4 Hz), 1.65 (t, 1 H, J = 9.2 Hz), 1.43 (m, 1 H), 1.02 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 200.2, 143.0, 134.9, 57.6, 37.2, 33.7, 32.9, 29.9, 29.5, 8.5; MS m/z (rel intensity) 179 (45), 164 (9), 150 (100), 136 (12), 122 (44), 94 (17), 82 (42), 68 (8), 57 (19); HRMS calcd for $C_{11}H_{17}NO$ 179.1310, found 179.1316.

2-Acetyl-8-azabicyclo[3.2.1]oct-2-ene (9b). **9b** was prepared by an analogous procedure for the preparation of **9a**.

Typical Procedure for 1,4-Addition to 9. A solution of p-tolylmagnesium bromide (15.76 mL, 15.76 mmol, 1 M in ether) was added to dry copper bromide–dimethyl sulfide (0.4860 g, 2.364 mmol) under an argon atmosphere. The mixture was stirred for 15 min at room temperature and then cooled to 0 °C after the addition of dry ether (10 mL). A solution of **9a** (0.7063 g, 3.94 mmol) in dry ether (10 mL) was added, and the mixture was stirred for 4 h at 0 °C and then stirred overnight. The reaction was added to saturated HCl in ether (50 mL) at −78 °C and then extracted with water (3×). The aqueous layer was made basic with a few drops of concentrated NH_4OH, extracted with CH_2Cl_2 (3×), dried (Na_2SO_4), and then concentrated under reduced pressure. Purification by chromatography on silica gel (9/1 ether/triethylamine to 8.75/0.25/1 ether/methanol/ triethylamine) afforded **12a** (0.6848 g, 64% yield). For each derivative listed below the reactions times and quenching conditions are listed in parentheses.

8-Methyl-3β-phenyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (10a) (4 h at 0 °C and then stirred overnight at rt) (HCl in ether at −78 °C): 67% yield; IR (neat) 2930, 1710, 1685, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–7.11 (m, 5 H), 3.48 (d, 1 H, J = 6.7 Hz), 3.36 (m, 1 H), 3.00 (d, 1 H, J = 2.9 Hz), 2.94 (t, 1 H, J = 5.1 Hz), 2.59 (ddd, 1 H, J = 12.3, 12.3, 2.8 Hz), 2.15 (dq, 1 H, J = 17.3, 7.3 Hz), 2.11 (s, 3 H), 2.06 (dq, 1 H, J = 17.3, 7.3 Hz), 1.78–1.55 (m, 3 H), 1.67 (dt, 1 H, J = 5.4, 2.6 Hz), 0.83 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 210.1, 143.2, 127.9, 127.0, 125.6, 64.4, 62.3, 59.3, 41.9, 35.1, 34.1, 33.8, 26.3, 25.1, 7.7. Anal. ($C_{17}H_{23}NO$) C, H, N.

2β-Acetyl-8-methyl-3β-phenyl-8-azabicyclo[3.2.1]octane (10b) (4 h at 0 °C and then stirred overnight at room temperature) (HCl/ice at 0 °C): 44% yield; IR (neat) 2940, 1710, 1680, 1600, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–7.12 (m, 5 H), 3.50 (d, 1 H, J = 6.6 Hz), 3.36 (m, 1 H), 3.00 (m, 2 H), 2.54 (ddd, 1 H, J = 2.7, 12.3, 12.3 Hz), 2.25 (s, 3 H), 2.21 (2, 3 H), 2.30–2.00 (m, 3 H), 1.65–1.79 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 208.1, 143.2, 128.0, 127.1, 125.7, 64.5, 62.4, 60.1, 42.1, 34.0, 33.7, 30.1, 26.4, 25.2; MS m/z (rel intensity) 243 (33), 200 (78), 172 (13), 143 (7), 128 (7), 115 (7), 96 (71), 82 (100), 55 (7); HRMS calcd for $C_{16}H_{21}NO$ 243.1623, found 243.1624. Anal. ($C_{16}H_{21}NO \cdot 0.1H_2O$) C, H, N.

3β-(p-Fluorophenyl)-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (11a) (4 h at 0 °C and then stirred overnight at room temperature) (HCl in ether at −78 °C): 70% yield; IR (neat) 2920, 1700, 1680, 1600, 910, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19 (d, 1 H, J = 8.5 Hz), 7.16 (d, 1 H, J = 8.5 Hz), 6.92 (t, 2 H, J = 8.8 Hz), 3.48 (d, 1 H, J = 6.8 Hz), 3.35 (m, 1 H), 2.96 (d, 1 H, J = 2.9 Hz), 2.89 (t, 1 H, J = 5.1 Hz), 2.56 (ddd, 1 H, J = 12.2, 12.2, 2.7 Hz), 2.43 (dq, 1 H, J = 17.4, 7.3 Hz), 2.21 (dq, 1 H, J = 17.4, 7.3 Hz), 2.19 (s, 3 H), 2.07 (m, 1 H), 1.80–1.54 (m, 4 H), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 209.8, 163.3, 158.5, 138.9, 138.8, 128.6, 128.5, 114.8, 114.4, 64.4, 62.3, 59.3, 42.0, 34.9, 34.3, 33.5, 26.3, 25.2, 7.7; MS m/z (rel intensity) 275 (56), 218 (91), 190 (13), 146 (5), 121 (4), 97 (100), 82 (96), 57 (7); HRMS calcd for $C_{17}H_{22}NOF$ 275.1685, found 275.1683. Anal. ($C_{17}H_{22}FNO$) C, H, N.

2β-Acetyl-3β-(p-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (11b) (4 h at 0 °C and then stirred overnight at room temperature) (HCl/ice at 0 °C): 44% yield; IR (neat) 2940, 1700, 1680, 1600, 800, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00–7.14 (m, 4 H), 3.49 (m, 1 H), 3.34 (m, 1 H), 2.91 (m, 2 H), 2.50 (ddd, 1 H, J = 12.3, 12.3, 2.8 Hz), 2.19 (s, 3 H), 1.96 (s, 3 H), 2.20–2.03 (m, 1 H), 1.70–1.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 207.7, 163.4, 158.6, 138.8, 128.7, 128.5, 114.9, 114.5, 64.4, 62.4, 60.1, 42.1, 34.2, 33.4, 29.9, 26.3, 25.2; MS m/z (rel intensity) 261 (38), 218 (80), 190 (17), 161 (7), 146 (8), 133 (9), 97 (100), 82 (62), 55 (11). Anal. ($C_{16}H_{20}FNO$) C, H, N.

8-Methyl-2β-propanoyl-3β-p-tolyl-8-azabicyclo[3.2.1]octane (12a) (4 h at 0 °C and then stirred overnight at room temperature) (HCl/ice at 0 °C): 60% yield; IR (neat) 2920, 1710, 1500, 800, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (d, 2 H, J = 8.3 Hz), 7.03 (d, 2 H, J = 8.3 Hz), 3.45 (d, 1 H, J = 6.3 Hz), 3.36 (m, 1 H), 2.97 (m, 1 H), 2.90 (t, 1 H, J = 5.2 Hz), 2.55 (td, 1 H, J = 12.3, 2.8 Hz), 2.26 (s, 3 H), 2.19 (s, 3 H), 2.31–2.10 (m, 2 H), 2.05 (m, 1 H), 1.78–1.52 (m, 3 H), 0.83 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 210.3, 140.2, 134.9, 128.7, 126.9, 64.6, 62.4, 59.4, 42.1, 35.2, 34.3, 33.5, 26.4, 25.3, 20.9, 7.8; GC (R_t 9.095 min); MS m/z (rel intensity) 271 (53), 214 (86), 186 (12), 157 (5), 129 (6), 97 (96), 82 (100), 57 (9). Anal. ($C_{18}H_{25}NO$) C, H, N. The two enantiomers of **12a** were resolved on a 500 × 22.1-mm Cyclobond I (β-cyclodextrin) column using 85% (1% aqueous triethylamine adjusted to pH 4.1 with acetic acid) / 15% acetonitrile as eluant; faster running enantiomer $[\alpha]^{25}_D$ = −33.8° ($CHCl_3$, c 0.81), slower running enantiomer $[\alpha]^{25}_D$ = +33.1° ($CHCl_3$, c 0.145).

2β-Acetyl-8-methyl-3β-p-tolyl-8-azabicyclo[3.2.1]octane (12b) (4 h at 0 °C and then stirred overnight at room temperature) (HCl/ice at 0 °C): 55% yield; IR (neat) 2920, 1705, 1680, 1500, 800, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (d, 2 H, J = 8.3 Hz), 7.05 (d, 2 H, J = 8.3 Hz), 3.48 (d, 1 H, J = 6.8 Hz), 3.35 (m, 1 H), 2.96 (m, 2 H), 2.52 (ddd, 1 H, J = 12.3, 12.3, 2.8 Hz), 2.27 (s, 3 H), 2.20 (s, 3 H), 1.97 (s, 3 H), 2.20–2.01 (m, 1 H), 1.70–1.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 208.3, 140.0, 135.1, 128.7, 126.9, 64.6, 62.4, 60.2, 42.1, 34.2, 33.3, 30.2, 26.4, 25.2, 20.9; MS m/z (rel intensity) 257 (33), 214 (68), 186 (12), 157 (4), 139 (7), 115 (7), 97 (100), 96 (72), 94 (12), 83 (77), 82 (99), 55 (3). Anal. ($C_{17}H_{23}NO$) C, H, N.

2β-Acetyl-3β-(p-ethylphenyl)-8-methyl-8-azabicyclo[3.2.1]octane (13b) (4 h at 0 °C and then stirred overnight at room temperature) (HCl/ice at 0 °C): 55% yield; IR (neat) 2940, 1710, 1680, 810, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (d, 2 H, J = 8.3 Hz), 7.06 (d, 2 H, J = 8.3 Hz), 3.46 (q, 1 H, J = 7.0 Hz), 3.34 (m, 1 H), 2.94 (m, 2 H), 2.56 (q, 2 H, J = 7.6 Hz), 2.55 (m, 1 H), 2.19 (s, 3 H), 2.11 (m, 1 H), 1.96 (s, 3 H), 1.64 (m, 3 H), 1.14 (t, 3 H, J = 7.6 Hz), 1.19 (t, 1 H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 208.3, 141.5, 140.2, 127.5, 126.9, 64.5, 62.4, 60.1, 42.1, 34.1, 33.4, 30.2, 28.3, 26.4, 25.2, 15.5; MS m/z (rel intensity) 271 (43), 228 (70), 200 (9), 139 (8), 128 (6), 97 (100), 82 (90), 55 (7). Anal. ($C_{16}H_{25}NO$) C, H, N.

8-Methyl-2β-propanoyl-3β-(p-isopropylphenyl)-8-azabicyclo[3.2.1]octane (14a) (4 h at 0 °C and then stirred

overnight at room temperature) (HCl gas at −78 °C): 60% yield; IR (neat) 2940, 1710, 1680, 830, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.14 (d, 2 H, J = 8.7 Hz), 7.09 (d, 2 H, J = 8.7 Hz), 3.47 (d, 1 H, J = 6.9 Hz), 3.36 (m, 1 H), 2.98 (dd, 1 H, J = 3.8, 2.8 Hz), 2.92 (t, 1 H, J = 5.0 Hz), 2.81 (q, 1 H, J = 6.8 Hz), 2.58 (ddd, 1 H, J = 12.2, 12.2, 2.7 Hz), 2.53 (q, 2 H, J = 7.3 Hz), 2.20 (s, 3 H), 2.20–1.99 (m, 2 H), 1.78–1.52 (m, 3 H), 1.19 (d, 6 H, J = 6.8 Hz), 0.83 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 210.4, 145.9, 140.4, 126.9, 126.0, 64.5, 62.4, 59.3, 42.0, 35.2, 34.2, 33.6, 33.5, 26.4, 25.2, 23.9, 7.7; MS m/z (rel intensity) 299 (29), 242 (33), 214 (2), 201 (2), 153 (3), 97 (49), 82 (98), 57 (100). Anal. ($C_{20}H_{29}NO$) C, H, N.

3β-(*p*-*tert*-Butylphenyl)-2β-propanoyl-8-methyl-8-azabicyclo[3.2.1]octane (15a) (4 h at 0 °C and then stirred overnight at room temperature) (HCl in ether at 0 °C): 28% yield; IR (neat) 2940, 1715, 1685, 820, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26 (d, 2 H, J = 8.4 Hz), 7.14 (d, 2 H, J = 8.4 Hz), 3.47 (d, br, 1 H, J = 6.9 Hz), 3.36 (m, 1 H), 2.99 (dd, 1 H, J = 4.1, 2.9 Hz), 2.91 (dt, 1 H, J = 13.4, 5.1 Hz), 2.58 (ddd, 1 H, J = 12.3, 12.3, 2.8 Hz), 2.39 (q, 1 H, J = 7.3 Hz), 2.24 (q, 1 H, J = 7.3 Hz), 2.19 (s, 3 H), 2.18–1.98 (m, 2 H), 1.81–1.54 (m, 2 H), 1.65 (dt, 1 H, J = 12.3, 3.0 Hz), 1.26 (s, 9 H), 0.84 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 210.6, 148.3, 139.9, 126.8, 124.9, 64.6, 62.4, 59.2, 42.1, 35.2, 34.2, 33.5, 31.3, 26.4, 25.2, 7.8; MS m/z (rel intensity) 313 (45), 284 (2), 256 (74), 228 (6), 200 (3), 153 (6), 106 (13), 82 (100), 57 (40). Anal. ($C_{21}H_{31}NO$) C, H, N.

3β-(*p*-Biphenylyl)-8-methyl-2β-propanoyl-8-azabicyclo-[3.2.1]octane (16a) (4 h at 0 °C and then stirred overnight at room temperature) (HCl in ether at −78 °C): 51% yield; IR (neat) 2955, 2936, 2875, 1716, 1689, 1487, 764, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34–7.02 (m, 9 H), 3.32 (d, 1 H, J = 5.37 Hz), 3.21 (m, 1 H), 2.80 (m, 2 H), 2.43 (ddd, 1 H, J = 11.7, 11.7, 2.4 Hz), 2.03 (s, 3 H), 2.22–1.85 (m, 3 H), 1.62–1.35 (m, 4 H), 0.62 (t, 3 H, J = 7.3 Hz); ^{13}C ($CDCl_3$) δ 210.4, 142.1, 140.0, 138.5, 128.6, 127.5, 126.9, 126.7, 64.5, 62.4, 58.9, 41.9, 35.3, 34.1, 33.7, 26.3, 25.1, 7.7; MS m/z (rel intensity) 333 (72), 276 (100), 248 (5), 207 (3), 152 (4), 97 (59), 82 (95), 57 (13). Anal. ($C_{23}H_{27}NO \cdot 0.7\ H_2O$) C, H, N.

8-Methyl-2β-propanoyl-3β-*o*-tolyl-8-azabicyclo[3.2.1]-octane (17a) (4 h at 0 °C and then stirred overnight at room temperature) (HCl/ice at 0 °C): 11% yield, IR (neat) 2960, 2940, 1710, 1680, 1600, 750, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52–7.08 (m, 4 H), 3.50 (dd, 1 H, J = 6.2, 2.3 Hz), 3.42 (m, 1 H), 3.19 (dt, 1 H, J = 13.1, 4.8 Hz), 2.94 (t, 1 H, J = 3.8 Hz), 2.82 (td, 1 H, J = 12.7, 2.8 Hz), 2.45 (m, 2 H), 2.37 (s, 3 H), 2.21 (s, 3 H), 2.20–2.05 (m, 2 H), 1.91–1.73 (m, 2 H), 1.53 (dt, 1 H, J = 12.4, 3.9 Hz), 0.86 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 209.7, 140.1, 135.1, 129.9, 129.0, 125.9, 125.8, 64.5, 62.6, 42.1, 35.4, 34.8, 31.8, 26.5, 25.1, 19.5, 15.3, 7.7; MS m/z (rel intensity) 271 (66), 242 (2), 214 (74), 200 (6), 186 (7), 157 (2), 129 (3), 96 (71), 82 (100), 57 (6). Anal. ($C_{16}H_{25}NO$) C, H, N.

3β-Ethyl-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]-octane (18a) (4 h at 0 °C and then stirred overnight at room temperature) (HCl/ice at 0 °C): 55% yield; IR (neat) 2940, 1700, 1680, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.33 (dd, 1 H, J = 5.7, 2.2 Hz), 3.13 (m, 1 H), 2.51 (m, 1 H), 2.50 (dq, 1 H, J = 17.3, 7.3 Hz), 2.40 (dq, 1 H, J = 17.3, 7.3 Hz), 2.10 (s, 3 H), 2.15–1.70 (m, 4 H), 1.56–1.30 (m, 5 H), 1.00 (t, 3 H, J = 7.3 Hz), 0.73 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 211.1, 64.2, 62.5, 56.7, 42.0, 36.7, 34.9, 31.8, 25.9, 25.3, 25.1, 12.1, 8.1; MS m/z (rel intensity) 209 (43), 180 (27), 152 (21), 138 (8), 124 (19), 96 (70), 82 (100), 57 (10); HRMS calcd for $C_{13}H_{23}NO$ 209.1779, found 209.1774.

3β-Cyclohexyl-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]-octane (19a) (4 h at 0 °C and then stirred overnight at room temperature) (HCl/ice at 0 °C): 63% yield; IR (neat) 2900, 1710, 1680, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.37 (dd, 1 H, J = 4.6, 2.5 Hz), 3.16 (m, 1 H), 2.58 (dd, 1 H, J = 7.1, 2.5 Hz), 2.45 (dq, 1 H, J = 17.6, 7.2 Hz), 2.39 (dq, 1 H, J = 17.6, 7.2 Hz), 2.11 (s, 3 H), 2.00–0.60 (messy, 18 H), 1.03 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 210.9, 64.1, 62.4, 54.9, 41.8, 37.2, 35.8, 34.4, 34.3, 31.4, 30.9, 26.4, 25.7, 25.6, 25.1, 7.9; MS m/z (rel intensity) 263 (45), 234 (4), 206 (23), 192 (29), 180 (82), 154 (14), 124 (11), 96 (100), 82 (92), 57 (16). Anal. ($C_{17}H_{29}NO$) C, H, N.

8-Methyl-3β-(1-naphthyl)-2β-propanoyl-8-azabicyclo[3.2.1]-octane (20a) (4 h at 0 °C and then stirred overnight at room temperature) (HCl in ether at −78 °C): 40% yield; IR (neat) 2940, 1710, 1680, 1600, 800, 770, 730, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1 H, J = 8.3 Hz), 7.83 (dd, 1 H, J = 7.6, 1.7 Hz), 7.68 (d, 1 H, J = 2.7 Hz), 7.64 (d, 1 H, J = 1.5 Hz), 7.54–7.39 (m, 3 H), 3.79 (dt, 1 H, J = 12.6, 4.7 Hz), 3.54 (dd, 1 H, J = 6.8, 2.6 Hz), 3.47 (m, 1 H), 3.19 (t, 1 H, J = 3.4 Hz), 2.99 (ddd, 1 H, J = 12.6, 12.6, 2.6 Hz), 2.40–2.21 (m, 2 H), 2.27 (s, 3 H), 2.15–1.74 (m, 4 H), 1.62 (dt, 1 H, J = 12.2, 3.6, 3.6 Hz), 0.69 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 209.6, 137.3, 133.8, 131.3, 129.3, 127.4, 126.6, 125.7, 125.6, 124.8, 122.4, 64.6, 62.7, 57.3, 42.1, 35.2, 34.8, 30.8, 26.7, 25.2, 7.6; MS m/z (rel intensity) 307 (85), 278 (2), 250 (100), 222 (4), 193 (6), 165 (8), 152 (10), 96 (43), 82 (89), 57 (13). Anal. ($C_{21}H_{25}NO$) C, H, N.

2β-Acetyl-8-methyl-3β-(1-naphthyl)-8-azabicyclo[3.2.1]-octane (20b) (4 h at 0 °C and then stirred overnight at room temperature) (HCl/ice at 0 °C): 35% yield; IR (neat) 2940, 1705, 1680, 1590, 790, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.97–7.24 (m, 7 H), 3.76 (dt, 1 H, J = 12.9, 4.8 Hz), 3.75 (m, 1 H), 3.50 (m, 1 H), 3.17 (m, 1 H), 2.92 (ddd, 1 H, J = 12.6, 12.6, 2.9 Hz), 2.26 (s, 3 H), 1.84 (s, 3 H), 2.50–1.93 (m, 2 H), 1.61 (dt, 1 H, J = 3.8, 12.1 Hz), 1.19 (t, 1 H, J = 7.0 Hz), 1.01 (t, 1 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 207.1, 137.4, 133.8, 131.3, 129.3, 126.7, 126.1, 125.7, 125.5, 124.8, 122.4, 64.5, 62.8, 58.3, 42.2, 34.7, 30.8, 29.9, 26.7, 25.3; MS m/z (rel intensity) 293 (45), 250 (100), 193 (7), 178 (7), 165 (14), 152 (12), 141 (8), 97 (52), 82 (13), 55 (5), HRMS calcd for $C_{20}H_{23}NO$ 293.1779, found 293.1774. Anal. ($C_{20}H_{23}NO \cdot 0.4\ H_2O$) C, H, N.

8-Methyl-3β-(2-naphthyl)-2β-propanoyl-8-azabicyclo[3.2.1]-octane (21a) (4 h at 0 °C and then stirred overnight at room temperature) (HCl in ether at −78 °C): 74% yield; IR (neat) 2920, 1710, 1680, 810, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.80–7.60 (m, 4 H), 7.40–7.35 (m, 3 H), 3.52 (d, 1 H, J = 6.2 Hz), 3.42 (m, 1 H), 3.13 (m, 2 H), 2.73 (ddd, 1 H, J = 12.1, 12.1, 2.9 Hz), 2.23 (s, 3 H), 2.27 (dq, 1 H, J = 15.5, 7.3 Hz), 2.21 (dq, 1 H, J = 15.5, 7.3 Hz), 1.80 (ddd, 1 H, J = 12.1, 2.7, 2.7 Hz), 1.63 (m, 4 H), 0.80 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 210.1, 140.8, 133.4, 131.9, 127.7, 127.4, 125.8, 125.6, 125.5, 125.1, 64.6, 62.4, 59.3, 42.0, 35.1, 34.3, 34.1, 26.4, 25.3, 7.7; MS m/z (rel intensity) 307 (57), 250 (100), 222 (6), 193 (4), 165 (8), 152 (8), 82 (59), 57 (6). Anal. ($C_{21}H_{25}NO$) C, H, N. The two enantiomers of **21a** were resolved on a 500 × 22.1 mm Cyclobond I (β-cyclodextrin) column using 82% (1% aqueous triethylamine adjusted to pH 4.1 with acetic acid) / 18% acetonitrile as eluant; faster running enantiomer $[\alpha]^{25}_D$ = −55.8° ($CHCl_3$, c 0.495); lower running enantiomer $[\alpha]^{25}_D$ = +50.2° ($CHCl_3$, c 0.275).

2β-Acetyl-8-methyl-3β-(2-naphthyl)-8-azabicyclo[3.2.1]-octane (21b) (4 h at 0 °C and then stirred overnight at room temperature) (HCl in ether at −78 °C): 53% yield; IR (neat) 2940, 1700, 1680, 1590, 820, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, 2 H, J = 6.6 Hz), 7.72 (d, 1 H, J = 5.9 Hz), 7.66 (s, br, 1 H), 7.40 (m, 2 H), 7.37 (m, 1 H), 3.54 (d, 1 H, J = 6.5 Hz), 3.42 (m, 1 H), 3.12 (d, 1 H, J = 3.1 Hz), 3.19 (t, 1 H, J = 5.3 Hz), 2.68 (ddd, 1 H, J = 12.3, 12.3, 2.9 Hz), 2.24 (s, 3 H), 2.21–2.00 (m, 1 H), 1.97 (s, 3 H), 1.73 (dd, 1 H, J = 8.4, 2.2 Hz), 1.67 (t, 1 H, J = 4.0 Hz), 1.51–1.98 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 208.0, 140.7, 133.4, 131.9, 127.7, 127.4, 125.8, 125.7, 125.4, 125.1, 64.6, 62.4, 60.1, 42.1, 34.2, 33.9, 39.1, 26.4, 25.3; MS m/z (rel intensity) 293 (39), 250 (65), 193 (5), 178 (7), 165 (13), 157 (100), 141 (16), 97 (88), 82 (89), 57 (11); HRMS calcd for $C_{20}H_{23}NO$ 293.1779, found 293.1776. Anal. ($C_{20}H_{23}NO \cdot 0.7\ H_2O$) C, H, N.

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