Rearrangement of a Mesylate Tropane Intermediate in Nucleophilic Substitution Reactions. Synthesis of Aza-Bicyclo[3.2.1]octane and Aza-Bicyclo[3.2.2]nonane Ethers,† Imides, and Amines

Lionel Ogier,‡ Frédéric Turpin,§ Ronald M. Baldwin,‡ Françoise Riché,|| Ho Law,⊥ Robert B. Innis,‡ and Gilles Tamagnan*,‡

Department of Psychiatry, Yale University and VA CT HCS, West Haven, Connecticut, CIS Bio International, filiale de SCHERING S.A. 91192 Gif-sur-Yvette, France, Laboratoire d'Etudes Dynamiques et Structurales et de la Sélectivité, Grenoble I, France, and ERAS Labo, 38330 St Nazaire les Eymes, France

gilles.tamagnan@yale.edu

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Nucleophilic substitution of 2β-mesyloxymethyl-*N*-methyl-3β-*p*-tolyl-tropane intermediate with alkoxides, metal imides, or amines was found to lead not only to the expected bicyclo[3.2.1]octane (tropane) ether, imide, and amine derivatives but also to unexpected bicyclo[3.2.2]nonane derivatives. When alkoxides were used as nucleophile, only the rearranged bicyclo[3.2.2]nonane structure was obtained, whereas the use of amines or imides as nucleophile afforded a mixture of the two structures. The bicyclo[3.2.2]nonane structure was assigned by NMR analysis.

Introduction

The tropane moiety, 8-azabicyclo[3.2.1]octane, is found in the natural substance cocaine **1**. Cocaine is known to have multiple effects on the central nervous system, mainly by binding to transporter proteins for the monoamine neurotransmitters dopamine (DA), serotonin (5-HT), and norepinephrine (NE). Alterations of the density and function of these transporters have been implicated in neurological disorders such as Parkinson's disease,[1,2] depression,[3,4] and schizophrenia.[5] Two major uses of imaging the density of such transporters with radiolabeled tracers would be to diagnose patients at early stages of the disorder and to monitor the progression of the disease. Therefore, many efforts have been expended to synthesize specific probes labeled either with β^+ emitters (^{18}F, ^{11}C)[6−8] used for PET (positron emission tomography) or with γ emitters (^{123}I, ^{99m}Tc)[9−11] used for SPECT (single photon emission computed tomography). A number of potent cocaine analogues have been synthesized to better understand the pharmacological properties of this drug[12] and to find new dopamine transporter (DAT) ligands.[6−10,11]

In tropane derivatives such as cocaine, the presence of 2β-substituents is important for the binding affinity.[13−15] However, since the axial 2β-ester group in cocaine tends to epimerize under basic conditions,[16,17] other functional groups (e.g., ketone,[18] alkyl,[19,20] ether[21,22]) have been substituted and found to retain high potency for DAT.

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‡ Yale University and VA CT HCS.

§ CIS Bio International.

|| Laboratoire d'Etudes Dynamiques et Structurales et de la Sélectivité.

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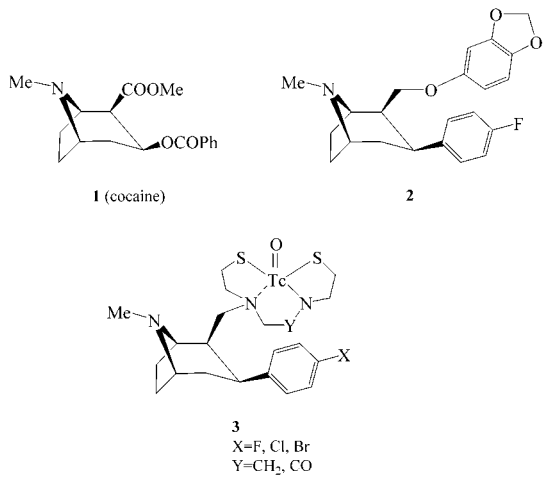

Figure 1.

One of our goals was to synthesize tropane intermediates that could be used either in basic or acidic conditions without fear of epimerization, starting with ethers and amines, i.e., 2β-alkoxymethyl ether or 2β-aminomethyl groups. Our interest in the ethers was piqued by results from Carroll's group showing apparently anomalously low binding affinity of the ether derivative **2**, a rigid analogue of paroxetine,[21] compared to that of a tropane iodopropyl ether described by Neumeyer et al.[22] (Figure 1). The reported synthesis of **2** proceeded through alkylation of a tropane mesylate intermediate with the sodium salt of 3,4-methylenedioxyphenol (sesamol). Another method to get tropane ethers consists of using the alkoxide of the tropane alcohol **4** as nucleophile; however, this method has been reported[22] to give unreliable yields. Concerning the 2β-aminomethyl derivatives, only a few compounds have been reported[9] such as TRODAT (**3**). Those were synthesized from acyl chloride derivatives and reduction of the amide intermediate.

We therefore investigated the synthesis of 2β-alkylated tropane derivatives (ethers and amines) in greater detail, using the mesylate **5** (Scheme 1) from 2β-hydroxymethyl-3β-(4-methylphenyltropane) **4**,[21,23] readily available from cocaine. Here we report that rearrangement occurred when 2β-methanesulfonyloxymethyl-*N*-methyltropane intermediate **5** was used in nucleophilic substitution reactions with alcohols, imides, or amines, to lead to aza-bicyclo[3.2.2]nonane derivatives **6**−**12**. Depending on the nature of the nucleophile, a mixture of rearranged and nonrearranged derivatives could be obtained from **5**. The nonrearranged aza-bicyclo[3.2.1]octane compounds **13**−**21** could be synthesized exclusively by alternate routes using either the tropane alcohol **4** as nucleophile, the acyl chloride derivative **22**, or the *N*-tosyl triflate intermediate **28** as electrophile (Scheme 1).

Results and Discussion

Unstable mesylate intermediate **5** was synthesized by esterification of alcohol **4**[21,23] with methanesulfonic anhydride[21] or methanesulfonyl chloride. In our study, we observed (TLC, NMR) that mesylate **5** rapidly generated its azetidinium salt form **5a**, resulting from the attack of the lone pair of electrons of the tertiary amine of **5** on its electrophilic carbon C_9, displacing the mesyloxy group (Scheme 2). Such a cyclization reaction has been described with aziridine,[24] aminoiodohydrin,[25] and 2β-chloromethyl tropane derivatives.[26]

Table 1. ^{1}H and ^{13}C NMR Chemical Shifts of Rearranged (6−12) and Nonrearranged (13, 14, 16−19) Ethers and Amines

	δ (ppm)								
	C_1	C_3	C_5	C_9	H_1	H_3	H_5	H_{9a}	H_{9b}
4	68	36	62	63	3.4	3.0	3.2	4.6	3.3
2[a]	**84**	34	**55**	**51**	4.3	3.4	3.0	3.0	2.4
Ethers Structure II									
6	**86**	34	**56**	**51**	3.4	3.2	2.9	3.1	**2.1**
7	**85**	35	**56**	**51**	3.3	3.4	2.8	3.1	**2.1**
8	**84**	35	**56**	**51**	4.4	3.4	3.0	3.0	**2.4**
Amines, Imides Structure II									
10	56	35	**57**	**53**	4.8	4.2	3.0	2.9	2.9
11	56	33	**55**	**52**	3.1	3.2	2.9	2.9	2.4
12	63	34	**56**	**52**	2.8	3.8	2.9	3.0	2.3
Ethers Structure I									
13	63	34	**62**	70	3.4	3.0	3.3	3.6	2.8
14	63	35	**62**	69	3.5	3.0	3.1	4.0	3.1
16	64	35	**62**	68	3.4	3.0	3.1	4.1	3.3
Amines, Imides Structure I									
17	64	35	**63**	38	3.0	3.2	3.4	4.0	3.4
18	63	34	**61**	40	3.3	3.0	3.2	2.7	2.3
19	66	35	**62**	49	3.2	3.0	3.2	2.7	2.4

[a] The chemical shifts for **2** were taken from the literature[21] and assigned according to the present study.

In the reaction with alkoxides, amide and imide salts, or amines, we observed a competition between C_1 and C_9 as reactive site for the substitution reaction (no trace of C_5 substitution). Therefore, the structure of the resulting products could be a 1-C-substituted-aza-bicyclo[3.2.2]-nonane (structure **II**) or a 2-C-substituted-aza-bicyclo-[3.2.1]octane (structure **I,** Scheme 3).

Synthesis of Aza-Bicyclo Alkyl Ethers. By reacting **5a** with freshly prepared sodium salts of methanol, allyl alcohol, or sesamol, we obtained exclusively the rearranged derivatives **6**, **7**, and **8**, respectively (Scheme 2, Table 1). N-Demethylation of derivative **8** with 1-chloroethyl chloroformate followed by methanol gave the corresponding sesamol ether derivative **9** (45%) with secondary amine (Scheme 2, R_2 = H).

The unrearranged derivative **13** was synthesized (41%) using sodium bis(trimethylsilyl)amide as a base to form the alkoxide of alcohol **4** and reacting this alkoxide with methyl trifluoromethanesulfonate (Scheme 4). Likewise, the allyl ether derivative **14** was obtained (84%) by reacting the alkoxide with ethyl allyl carbonate in the presence of 1,4-bis(diphenylphosphino)butane and tris-(dibenzylideneacetone) dipalladium(0).[27] The synthesis of aryl ether **16** could not use this route. In fact, reaction of the alkoxide with mesylate reagent **23** led to transesterification[28] to generate the tropane mesylate **5** and the alkoxide of sesamol, which reacted with rearrangement to give derivative **8**, formerly obtained by another route

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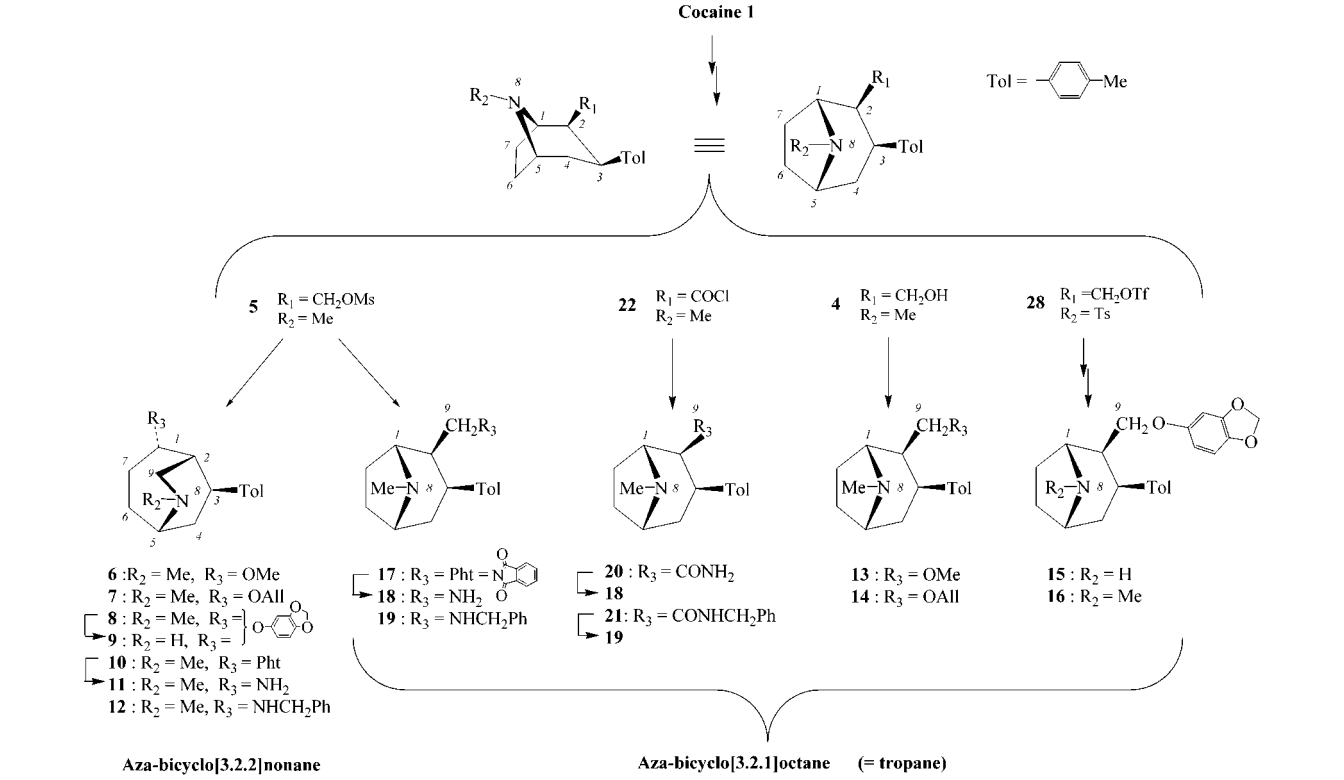
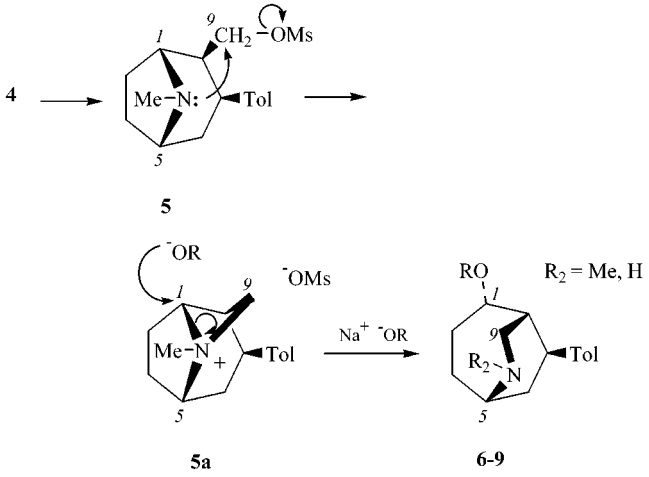
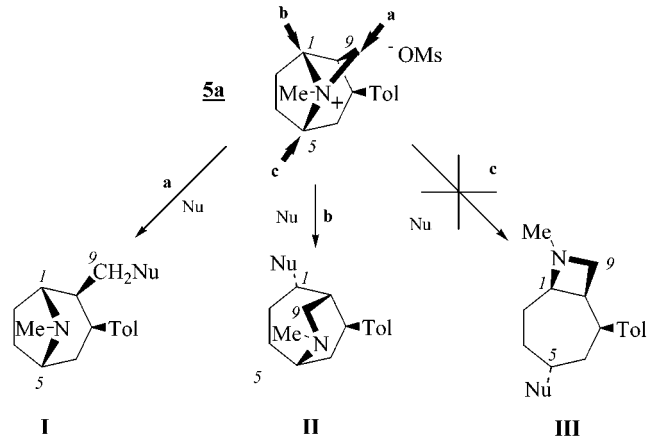
Scheme 1



Scheme 2



Scheme 3



(Scheme 1). Spectrometric data (NMR and IR) of the two products matched each other and corresponded to the structure of **8**.

Neither Mitsunobu reaction between alcohol **4** and sesamol nor catalyzed (Pd, Ni) coupling reactions of **4** with 4-bromo-1,2-(methylenedioxy)benzene yielded **16**.[29−32] However, N-demethylation of the 2β-carbomethoxy derivative **24**[33] with 1-chloroethyl chloroformate and methanol (Scheme 5) gave the nortropane intermediate **25** (75%). Tosylation of **25** with *p*-toluenesulfonyl chloride in the presence of triethylamine gave **26** (84%), which was reduced with lithium aluminum hydride in THF to give alcohol intermediate **27** (85%). The resulting sulfonamide bond, conjugated with the lone pair of electrons of the nitrogen, was intended to prevent the intramolecular rearrangement observed with **5**. The alcohol group was activated as the triflate intermediate **28** (96%) using trifluoromethanesulfonic anhydride and was used without purification for the next step. Nucleophilic substitution of **28** with the freshly prepared sodium salt of sesamol gave a 3:1 mixture (69%) of the expected alkylated derivative **29** mixed with alkene **30**, product of elimination. Deprotection of the nitrogen by refluxing **29** with sodium−mercury amalgam and sodium hydrogen phosphate in methanol gave the nortropane intermediate **15** (86%). Methylation with formaldehyde in refluxing methanol followed by reduction with $NaBH_4$ gave **16** (82%).

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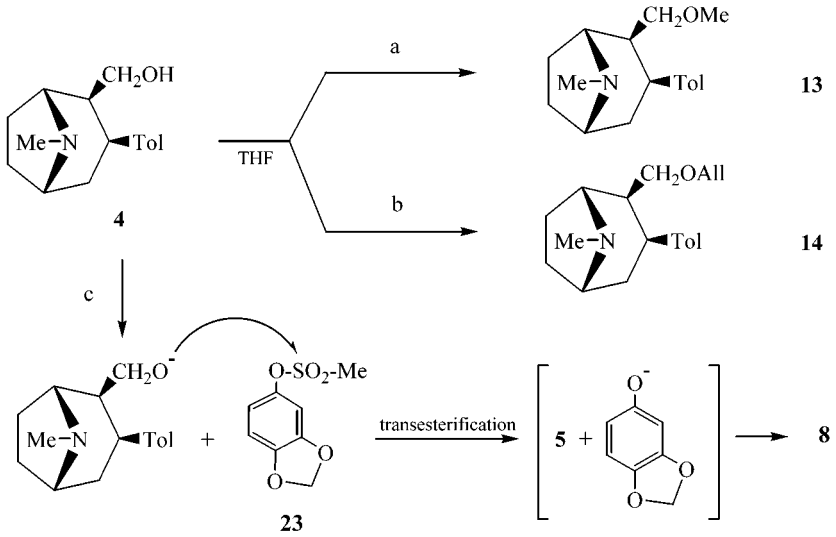
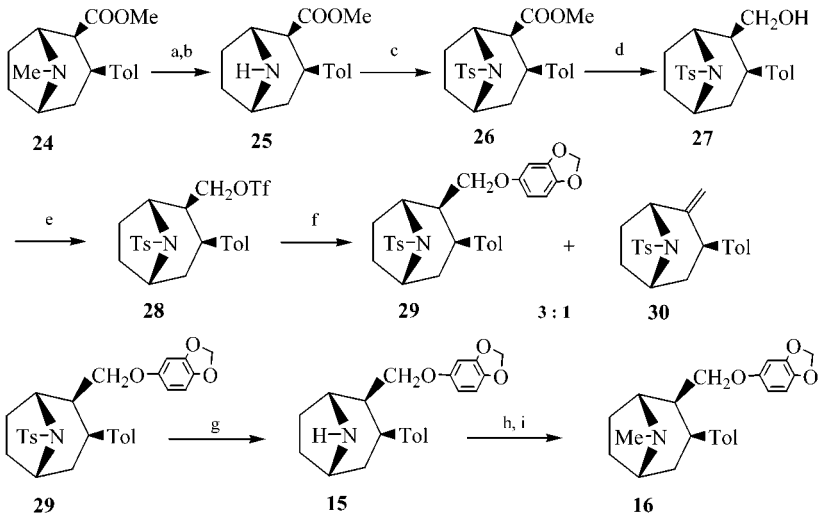
Scheme 4[a]



[a] Reagents: (a) $NaN(Me_3)_2$, MeOTf; (b) $Pd_2(dba)_3$, dppb, allyl ethyl carbonate, reflux; (c) NaOH, DMSO or $NaN(Me_3)_2$, THF.

Scheme 5[a]



[a] Reagents: (a) ACE-Cl, dichloroethane, reflux; (b) MeOH, reflux; (c) TsCl, Et_3N; (d) $LiAlH_4$, THF, rt; (e) Tf_2O, collidine, CH_2Cl_2; (f) sesamol, Na, THF; (g) Na/Hg, Na_2HPO_4, MeOH, reflux; (h) formaldehyde (37% in water), MeOH, reflux; (i) $NaBH_4$/MeOH.

Synthesis of Aza-Bicyclo Alkylamines and Imides. Mesylate **5a** was reacted with potassium phthalimide (KPht) in toluene with phase transfer catalyst to lead to an 85:15 mixture (96%) of the rearranged phthalimido derivative **10** and the tropane derivative **17**, respectively (Scheme 6). Hydrazinolysis of **17** and **10** yielded the aminomethyl tropane derivative **18** and the rearranged amino derivative **11**, respectively, in quantitative yield. Similarly, when benzylamine was used as nucleophile, a 35:65 mixture (59%) of the rearranged benzylamino derivative **12** and the tropane derivative **19** was obtained (Scheme 6).

Derivatives **17**−**19** were characterized by comparing their NMR spectra with those of derivatives obtained exclusively from the acyl chloride tropane intermediate **22** (Scheme 7). The aminomethyl tropane **18** was synthesized by two other synthetic routes. In the first one, acyl chloride **22**[34,35] was treated with ammonia at 0 °C to give amide **20** (70%), followed by borane reduction of the amide group (42%). In the second route, **22** was treated with benzylamine to give *N*-benzylamide intermediate **21** (90%) and then reduced with borane to **19** (60%), which was quantitatively reduced to amine **18** by catalytic hydrogenation. Reaction with phthalic anhydride gave the *N*-phthalimidotropane **17** (72%).

NMR Study of Bicyclo[3.2.1]octanes and Bicyclo[3.2.2]nonane. In the tricyclic structure of mesylate **5a**, three electrophilic carbons could be the site of a nucleophilic substitution reaction, and depending on the attack of the nucleophile on these carbons we could obtain the three different azabicyclo structures **I**, **II**, or **III** (Scheme 3). For all derivatives, C_3 was determined considering the fact that it was the only tertiary carbon in the range 33−36 ppm and because the chemical shift value of C_3 should not vary from the nonrearranged to the rearranged structure. In this range of values, C_3 was also the only

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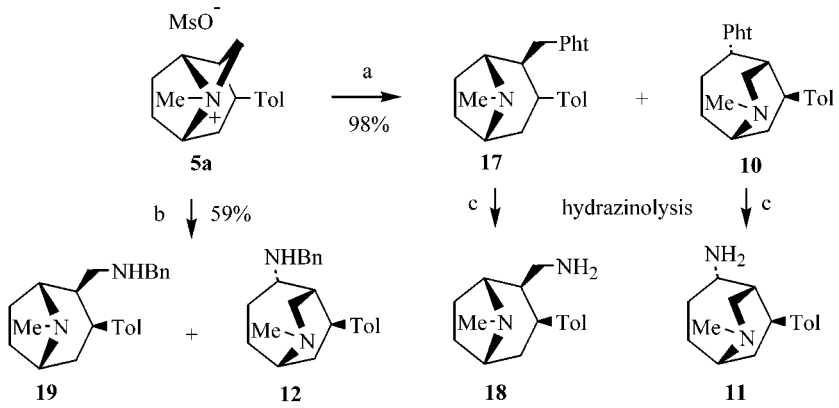
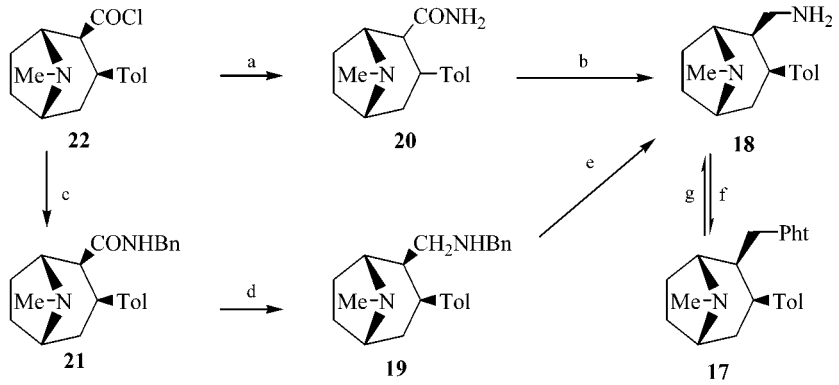
Scheme 6[a]



[a] Reagents: (a) KPht, PhMe, reflux; (b) $BnCH_2$, PhMe, reflux; (c) NH_2NH_2, EtOH, reflux.

Scheme 7[a]



[a] Reagents: (a) NH_4OH, 0 °C; (b) BH_3, THF; (c) $PhCH_2NH_2$, CH_3Cl_2, Et_3N; (d) BH_3, THF; (e) H_2, Pd/C, MeOH; (f) phthalic anhydride, $CHCl_3$; (g) NH_2NH_2, EtOH, reflux.

tertiary carbon whose proton was coupled with three protons (H_2, H_{4a}, and H_{4b}). In the rearranged structure, proton H_2 showed $^1H-^1H$ correlations with four protons, the correlation with H_3 being part of them. Two other correlations were observed with methylenic protons (H_2/H_{9a} and H_2/H_{9b}), which were coupled with a characteristic carbon of vicinal nitrogen (chemical shift in the range 51−53 ppm). The last correlation was observed with a highly deshielded proton (H_2/H_1), which was coupled with an extremely deshielded tertiary carbon, in the case of ether derivatives. The only rearranged structure that could corroborate these results was structure **II**. Structure **II** was established unambiguously by NMR analysis (^1H, ^{13}C, COSY H−H, and GHMQC $^1J_{C-H}$) of rearranged derivatives **6**−**12** compared to the tropane structure of derivatives **13**−**19** (structure **I**). Each proton and carbon in tropane alcohol **4** was formally assigned and taken as reference for structure **I**.

Derivatives **13**, **14**, and **16**−**19** were obtained by unambiguous route from natural (−)-cocaine, and their NMR data were in agreement with the configuration (1*R*,2*S*,3*S*,5*S*) of the tropane structure **I**.[23−36] Comparison between the established tropane structure of alcohol **4** and derivatives **13**, **14**, and **16**−**19** showed close chemical shift values in both carbon and proton NMR. In every case the chemical shifts of C_1 and C_5 were in the range 61−68 ppm, which is characteristic of bridgehead carbons in structure **I**. Compared to its chemical shift in alcohol **4**, C_9 was slightly deshielded (5−9 ppm) in ether derivatives **13**, **14**, and **16**, whereas shielded (14−25 ppm) in amine and imide derivatives **17**−**19**, as expected. In ^1H NMR, the chemical shifts of H_1 and H_5 were identical to those in alcohol **4** and the two protons H_{9a} and H_{9b} showed a shielding effect, which varied according to the nature (ether, amine, imide) of the resulting functional group and to the substitution (alkyl, aryl) of the nucleophile itself.

In the ^{13}C NMR spectra of ether derivatives **6**−**8** and according to the data above, we expected a deshielding effect for C_9 and chemical shifts of C_1 and C_5 in the range 61−68 ppm if structure **I**, but in each case we obtained C_1 close to 85 ppm (15 ppm of deshielding caused by the vicinal oxygen in structure **II**), C_5 close to 55 ppm (less strained in structure **II** because of ring expansion), and C_9 close to 51 ppm (shielding by the vicinal nitrogen). In the case of nitrogen compounds **10**−**12** the three positions 1, 5, and 9 showed a shielding effect (5−12 ppm) in ^{13}C NMR, which could be explained with both the vicinity of nitrogen atoms and by the ring expansion. In ^1H NMR, only four protons (H_1, H_3, H_5, and H_{9a}) were present beyond 2.7 ppm instead of the five expected for structure **I** (H_1, H_3, H_5, H_{9a}, and H_{9b}); however, this could be explained by the interaction of the shielding cone of the aromatic ring on C_3 with one of the protons on C_9. In the case of derivatives **2**, **8**, and **10**, we observed significant deshielding for H_1; this can be explained by the influence of aromatic rings (sesamol, phthalimide) close to this position in structure **II**. For imide derivative **10**, this deshielding extended to H_2 and H_3. The same deshielding effect was observed for H_{9a} in structure **I**, with derivatives

Table 2. ^{1}H and ^{13}C NMR Chemicals Shifts for N−Me and N−H Bicyclic Compounds 16 and 15 (Structure I) Compared to Rearranged Bicyclic Compounds 8 and 9 (Structure II)

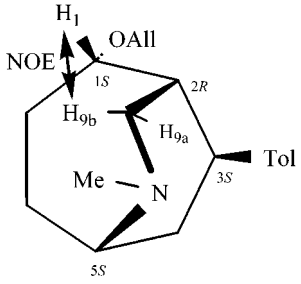
	δ (ppm)						
	C_1	C_5	C_9	H_1	H_5	H_{9a}	H_{9b}
16 (NMe)	**64**	**62**	68	**3.4**	**3.1**	4.1	3.3
15 (NH)	**57**	**55**	68	**3.6**	**3.6**	3.9	3.3
8 (NMe)	84	**56**	**51**	4.4	**3.0**	**3.0**	**2.4**
9 (NH)	84	**48**	**41**	4.3	**3.3**	**3.2**	**2.8**

16 and **17**. ^{13}C and ^{1}H NMR data of ether derivative **2**, formerly described as a tropane derivative, matched those found in the rearranged structure **II** of ether derivative **8** ($\delta C_1 = 84$, $\delta C_9 = 51$, and $\delta H_{9b} = 2.4$ ppm). Therefore, we conclude that **2** is an aza-bicyclo[3.2.2]nonane derivative and not the reported[21] tropane derivative.

It is known[37] that when the nitrogen of tropane derivatives (structure **I**) is demethylated, both H_1 and H_5 shift to lower field. Such a difference (+0.3 to +0.5 ppm) in the chemical shifts of H_1 and H_5 was observed between derivative **16** and its nor-tropane analogue **15** (Table 2). On the other hand, when **8** was N-demethylated to give the free base **9**, protons H_5, H_{9a}, and H_{9b} shifted to lower field and the chemical shift of H_1 remained unchanged. Therefore, we conclude that C_1 is not a carbon vicinal to nitrogen and is no longer a bridgehead carbon in the aza-bicyclo mainframe of structure **II**. Conversely, we conclude that the bonds between the nitrogen and the carbons C_9 and C_5 occur as in structure **II**.

The rearranged derivatives were prepared from alcohol intermediate **4**, whose configuration (1*R*,2*S*,3*S*,5*S*) is also known.[23] The proposed mechanism of the rearrangement (Scheme 2) predicts the absolute configuration of structure **II** to be (1*S*,2*R*,3*S*,5*S*), after inversion of configuration for C_1 and a change in naming group priorities for C_2. The *S* configuration of C_1 (resulting from SN2-type reaction) was unambiguously established in derivative **7** by the detection of nuclear Overhauser effect between H_1 and H_{9b}, an effect that would not be possible with an *R* configuration.

C_1/C_9 Selectivity According to the Nature of the Nucleophile. Mesylate intermediate **5a** can lead to structures **I**, **II**, and **III** (Scheme 3). However, structure **III** implies a four-membered ring, which is not favored compared to the five- or six-membered rings found in structures **I** and **II**; in fact, structure **III** has never been observed in our study. According to the nature (hard or soft) of the nucleophile used in the substitution reaction, we observed a different C_1/C_9 selectivity. Nucleophiles such as alkoxides or phthalimide (hard) led exclusively or preferentially to bicyclo[3.2.2]nonane (**II**), whereas



7 (Structure **II**)

Figure 2.

Table 3. Selectivity of the Nucleophilic Substitution with Intermediate 5a

nucleophile	total yield (%)	% structure **I**	% structure **II**
MeO^-	66	0	100
$AllO^-$	70	0	100
$SesO^-$	73	0	100
$PhtN^-$	65	15	85
$PhCH_2NH_2$	59	64	36

benzylamine (soft) showed a preferential affinity for C_9 and led to bicyclo[3.2.1]octane (**I**) (Table 3).

Conclusion

To summarize the present work, it was shown that the use of mesylate intermediate **5** in nucleophilic substitution reactions led to unexpected bicyclo[3.2.2]nonane derivatives. This rearranged structure **II** was obtained exclusively with ether derivatives or mixed with the expected bicyclo[3.2.1]octane structure **I** (tropane) in the case of amine and imide derivatives. The new structure was established by NMR analysis, and the structure **I**/structure **II** selectivity was found to be dependent on the affinity of the nucleophile used with the softer character of C_9 compared to C_1. The present results have an important implication in the understanding of the biological activity of earlier reported ether derivatives,[21] and the compounds synthesized in this work will be tested for their affinity with the DAT.

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Supporting Information Available: Experimental procedures and analytical data of ether, amine, and imide tropane and rearranged derivatives, geometry, and population analysis of mesylate intermediate **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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