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A Novel Entry into the 6-Azabicyclo[3.2.1]octane System via Radical Rearrangement of a Tropane Derivative

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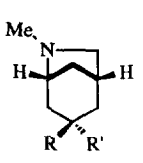
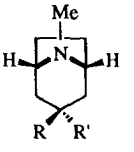
Summary: The conversion of an enantiomerically pure tropane derivative, obtained from chromium(0)-promoted [6π + 2π] cycloaddition, into a functionalized 6-azabicyclo[3.2.1]octane has been achieved *via* a novel radical rearrangement process.

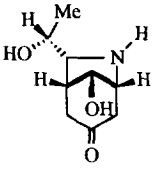
Derivatives of the 6-azabicyclo[3.2.1]octane system have been observed to exhibit potentially valuable biological activities. Carroll and coworkers have found azaprophen (**1**) to be a potent muscarinic



1, R = H,
R' = Ph_2CMeCO_2
2, R = $PhCO_2$, R' = H



3, R = $PhCO_2$,
R' = H



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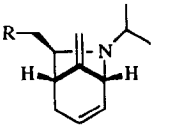
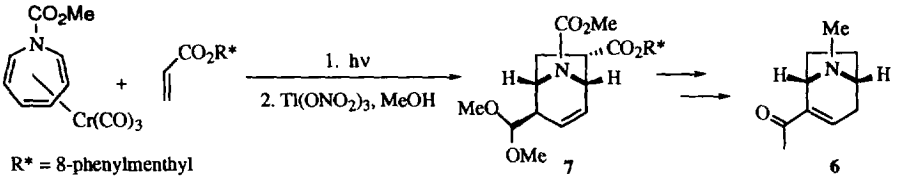


5, R = 3-indolyl

antagonist.[1] Further, **1** appears to interact with the muscarinic receptor in a unique way, and as such could function as a lead compound in the development of other novel muscarinic antagonists and agonists.[2] Compound **2** has been found to bind to the cocaine receptor site with an affinity similar to that of β-tropacocaine (**3**), suggesting that derivatives of **2** may serve as novel cocaine analogs.[3] Additionally, several naturally occurring compounds, such as actinobolamine (**4**)[4] and peduncularine (**5**)[5] also exhibit the 6-azabicyclo[3.2.1]octane skeleton.

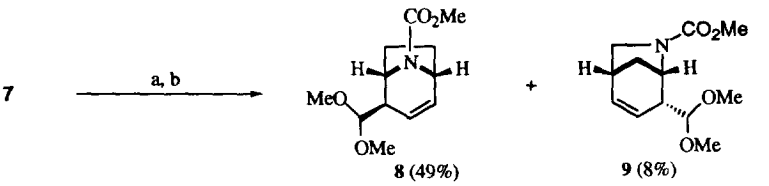
The synthesis of **1** and **2**, while straightforward, has not, however, been extended to derivatives possessing more elaborate functionality, and the production of enantiomerically pure **1** was achieved only through classical resolution.[6] At the present time, there are relatively few routes into this potentially interesting ring system.[7] Thus, a new means of obtaining functionalized 6-azabicyclo[3.2.1]octane derivatives in optically pure form would represent a worthwhile synthetic objective.

We recently reported a novel asymmetric synthesis of the tropane alkaloid (+)-ferruginine (**6**) utilizing a two-step protocol involving a diastereoselective Cr(0)-promoted [6 + 2] cycloaddition of N-carbomethoxyazepine followed by a regioselective thallium(III)-mediated oxidative ring contraction (Scheme 1).[8] A key transformation in this synthesis entailed the reductive decarboxylation of optically



Scheme 1

pure **7** *via* the derived pyridine-2-thione-N-oxycarbonyl (PTOC) ester (Scheme 2).[9] The reaction delivered the desired decarboxylated tropane **8** in 49% yield ($[\alpha]_D$ = –74.3) along with a minor byproduct

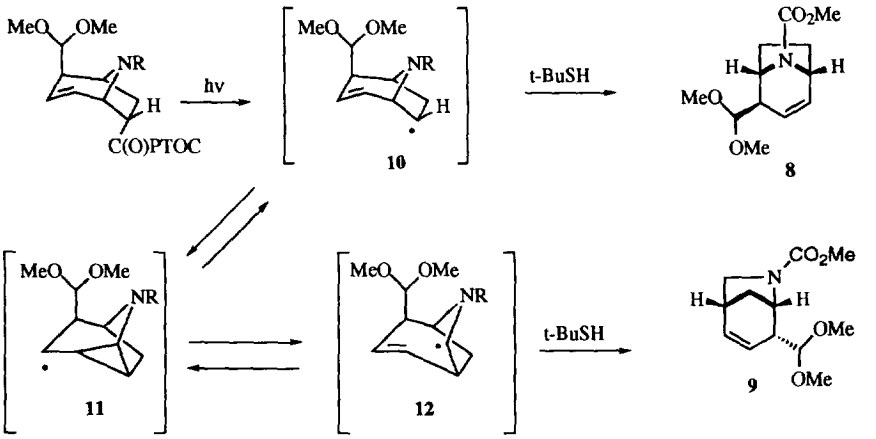


a) LiOH, 84% b) *i*. N-methylmorpholine, isobutylchloroformate, THF; *ii*. N-hydroxypyridine-2-thione, Na salt, TEA; *iii*. hv, t-BuSH

Scheme 2

(8%) that was eventually identified as the 6-azabicyclo[3.2.1]octane, **9** ($[\alpha]_D$ = –89.8).[10,11]

A possible mechanistic rationale for the formation of **9** is presented in Scheme 3. Photochemically

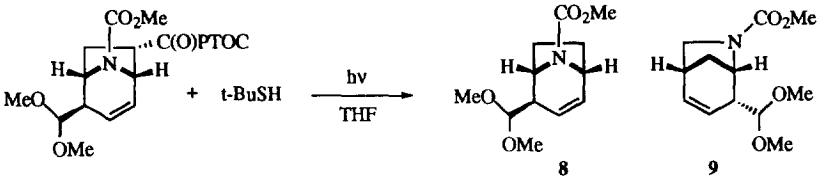


Scheme 3

induced decarboxylation of the PTOC ester initially affords radical **10**. Hydrogen atom abstraction by this species would deliver the tropane **8**. Alternatively, the geometrically constrained secondary radical in **10** could add transannularly to the proximal double bond to afford the corresponding cyclopropylcarbinyl radical **11**.[12] Fragmentation of this intermediate results in the formation of **12**, which upon hydrogen abstraction, leads to **9** without loss of stereochemical integrity.

Due to the potential utility of functionalized, enantiomerically pure 6-azabicyclo[3.2.1]octane derivatives, our attention was directed toward finding reaction conditions that would provide compound **9** as the major product. Kinetic data obtained from other radical processes indicate that the rate of H-atom abstraction from *tert*-butylmercaptan is on the order of ~10^7 M^{-1} s^{-1}, whereas the rate of rearrangement of the 2,2-dimethyl-3-butenyl radical (proceeding through a cyclopropylcarbinyl intermediate) is ~10^6 s^{-1}.[13] Thus, it was reasoned that at high concentrations of the PTOC ester and t-BuSH the rearrangement leading to **9** would be suppressed in favor of simple reductive decarboxylation. Conversely, lower reactant concentrations should favor rearrangement to the isomeric 6-azabicyclo[3.2.1]octane. The results of these studies are summarized in Table 1. The data in entry 1 reveal that high concentrations of the PTOC ester

Table 1



entry	[M]	[M]	Yield (%)	Ratio		
1	0.13	1.30	57	5.7	:	1.0
2	0.05	0.50	56	1.5	:	1.0
3	0.03	0.15	61	1.0	:	2.2
4	0.03	0.06	46	1.0	:	4.1

and thiol do indeed result in preferential formation of tropane **8**. Furthermore, as reactant concentrations were reduced, rearranged **9** was produced in increasing quantities. The optimum yield of rearranged product was obtained using the conditions in entry 3, in which **9** was isolated in 42% yield along with 19% of **8**. A further decrease in the concentration of thiol (entry 4) afforded a more favorable ratio of **9**:**8**, but at the expense of a decrease in overall yield. Additionally, reactions run at concentrations lower than 0.03 M in PTOC ester resulted in lower conversion efficiences and a reduced ratio of **9**:**8**.

In conclusion, a novel radical-based rearrangement of a tropane derivative to afford useful quantities of a functionalized, enantiomerically pure 6-azabicyclo[3.2.1]octane has been developed. The absolute stereochemistry of this material has been confirmed by correlation with (+)-ferruginine.[8] The functionality present in **9** is ideally suited for elaboration into structurally complex analogs that may exhibit interesting biological properties. Work along these lines is currently underway and will be reported in due course.

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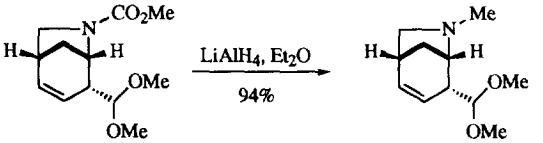
10. All new compounds exhibited spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (combustion analysis and/or HRMS) data consistent with the assigned structures. Optical rotations were measured in $CHCl_3$.
11. Compound **9** was further characterized as the corresponding N-methyl amine:[10]



9 $[\alpha]_D = -28.4$

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