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Parallel modification of tropane alkaloids

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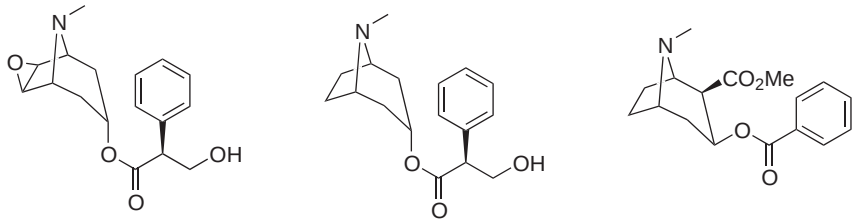
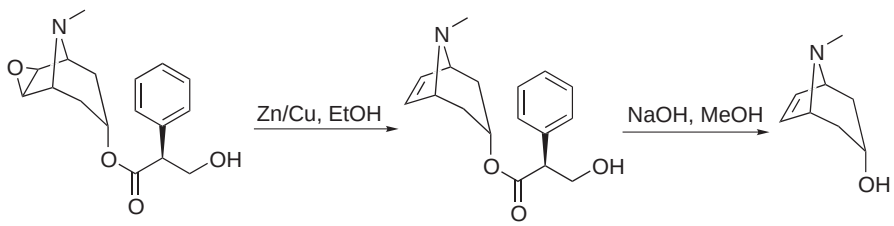
Abstract—Various tropane alkaloids have been prepared by structural modification of the readily available natural product, scopolamine **1**. Reaction of isocyanates with 6,7-dehydrotropine **5** provided a number of urethanes **6a**–**e**. Reductive amination of tropinone **7** and subsequent reaction with isocyanates provided ureas **9a**–**f**. Mitsunobu inversion of the C-3 alcohol of tropine **10** afforded the epimeric ester **11**.

Tropane alkaloids are a class of naturally occurring compounds that display a diverse range of biological activities and are used in a variety of medicinal indications. Various tropane derivatives are also finding application as novel imaging agents.[1,2] Representative examples of this class of compound include scopolamine **1**, atropine **2** and cocaine **3**.



1 **2** **3**

Given the diverse range of activities displayed by molecules based upon the tropane framework, there is a reasonable expectation that analogues based on this framework would display new and interesting properties. In light of this, we became interested in the concept of a systematic application of combinatorial techniques aimed at producing a range of tropane-based structural analogues. Prior to our own work, approaches to tropane libraries have employed organometallic methodology[3] and [4+3] cycloaddition chemistry.[4] Our approach was to identify new tropanes by addressing the latent diversity elements presented by readily available tropane natural products. Here, we report our



1 **4** **5**

Scheme 1.

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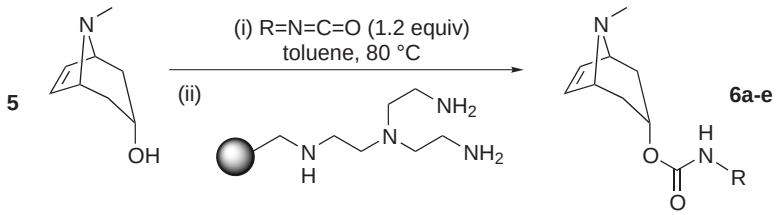


Scheme 2.

Table 1. Tropane derivatives **6a–e** and **9a–f** produced via Schemes 2 and 3

Entry	Nucleophile	Isocyanate (R-C=N=O)	Product	$[M+H]^+$ Calculated	$[M+H]^+$ Observed	δ C-3 Proton[a]
1	**5**	Phenyl	**6a**	259.3	259.2	5.02
2	**5**	Pentafluorophenyl	**6b**	349.3	349.0	4.95
3	**5**	2-Chloro-4-(trifluoromethyl)phenyl	**6c**	361.8	361.0	5.18
4	**5**	3-Chloro-4-methoxyphenyl	**6d**	323.8	323.0	5.00
5	**5**	Cyclopentyl	**6e**	251.3	251.0	4.26
6	**8**	Phenyl	**9a**	349.5	350.2	4.52
7	**8**	Pentafluorophenyl	**9b**	439.4	440.2	4.42
8	**8**	2-Chloro-4-(trifluoromethyl)phenyl	**9c**	451.9	–[b]	4.64
9	**8**	3-Chloro-4-methoxyphenyl	**9d**	413.9	414.2	4.54
10	**8**	Cyclopentyl	**9e**	341.5	342.0	4.38
11	**8**	Diphenylmethyl	**9f**	439.6	440.4	4.46

[a] C-3 *exo* protons for **5** and **8** appeared at δ 3.78 and 3.14, respectively.
[b] Urea **9c** failed to ionize under our ESI conditions, however, all other spectroscopic data were consistent with the assigned structure.

initial studies where we explored structural modification at the C-3 and 6,7-positions of the tropane framework.

The synthesis of the first group of analogues commenced with the readily available natural product scopolamine **1** (Scheme 1). Reductive elimination of the epoxide of **1** was accomplished using a Zn/Cu couple[5] to produce 6,7-dehydroatropine **4** from which the ester was removed by alkaline hydrolysis to provide 6,7-dehydrotropine **5** in overall yield of 86%.

The C-3 alcohol of **5** was then used as a site of diversification to produce an array of urethanes. Thus, exposure of **5** (1.0 mmol) to a range of isocyanates (1.2 mmol) in toluene at 80°C for 24 h followed by removal of excess isocyanate by use of polymer-bound trisamine (1.5 mmol)[6,7] afforded a range of urethanes **6a–e** (Scheme 2).

The purity and identity of these compounds was confirmed by LCMS, ^{1}H and ^{13}C NMR and it was pleasing to note that there was no evidence of any isocyanate persisting in any of these samples (Table 1). A representative HPLC trace of these compounds is provided by pentafluorophenyl urethane **6b** and is shown in Fig. 1.

We next investigated the introduction of various urea side chains at C-3. To install the required amine functionality at this position, we employed reductive amination of tropinone **7**. Reaction of **7** with benzylamine in the presence of sodium triacetoxyborohydride, produced exclusively the C-3-*endo*-secondary amine **8** in 64% yield (Scheme 3).[8] The stereochemical outcome of this reaction was consistent with *exo*-face attack by the hydride reagent on the intermediate iminium species and was confirmed by examination of the coupling of C-3 to the C-2 and C-4 protons in the ^{1}H NMR spectrum. The C-3 proton of amine **8** appeared as a

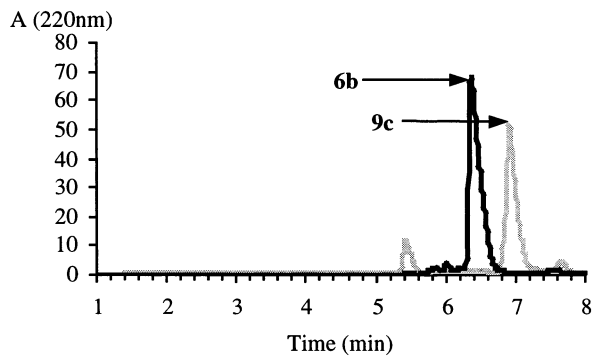
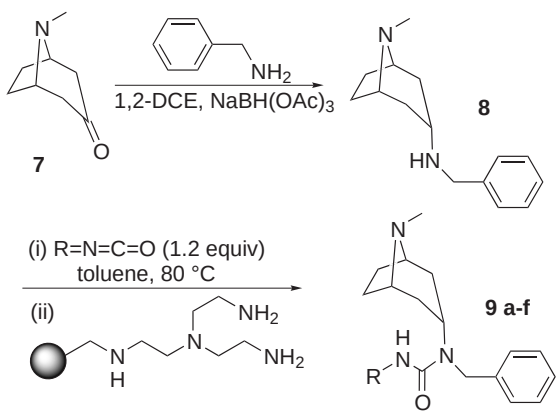
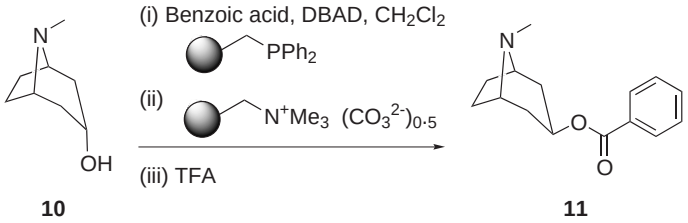


Figure 1. HPLC analysis of crude **6b** and **9c**.



Scheme 3.



10 **11**

Scheme 4.

triplet (J 5.5 Hz) in the ^{1}H NMR spectrum at δ 3.14. By way of comparison, the corresponding proton of **5** also appeared as a triplet (J 5.5 Hz) at δ 3.78. Furthermore, in compounds epimeric with **5** and **8** where the C-3 proton occupies an *endo* position, this proton appears as a multiplet by virtue of its coupling to all four protons at the C-2 and C-4 positions.

Secondary amine **8** was sufficiently pure for it to be used directly in subsequent reactions and so it was reacted with a range of isocyanates under similar conditions to those used for the formation of urethanes **6a**–**e**. Again, excess isocyanate was removed by reaction with polymer-bound trisamine and the urea derivatives **9a**–**f** were isolated by evaporation of the solvent. The identity of ureas **9a**–**f** was again confirmed by LCMS, ^{1}H and ^{13}C NMR (Table 1).

There is currently great interest in the discovery of new variants of tropanes whose stereochemistry at C-3 resembles that of cocaine **3**.[9] To explore the possibility that our methodology might be used for the preparation of arrays of simple cocaine analogues, we have examined the use of Mitsunobu chemistry for the inversion of stereochemistry in alcohols such as **5**.[10] To this end, tropine **5** (1.0 mmol) was exposed to polymer-immobilized triphenylphosphine (1.2 mmol) in the presence of benzoic acid (1.2 mmol) and di-*tert*-butyl azodicarboxylate (DBAD) (1.2 mmol) in dichloromethane for 24 h at room temperature (Scheme 4).[11] After filtration to remove resin-bound phosphine oxides, excess benzoic acid was removed by addition of carbonate resin (1.1 mmol) and stirring for 24 h then filtration.[7] Finally, excess DBAD and associated biproducts were decomposed by addition of trifluoroacetic acid. Following neutralization and extraction, tropacocaine **11** and unchanged **10** were isolated as a mixture in 1:2 ratio. This ratio could be improved to 1:1 by conducting the Mitsunobu reaction in the same solvent at reflux. Further elevation of the temperature led to decomposition of the starting material, presumably by radical pathways involving thermolytic decomposition of the DBAD.

In summary we have shown that the C-3 position of tropane alkaloids is a readily accessible position and lends itself well to parallel modification. Future reports in this area will concern modifications of other positions of the tropane framework and disclosure of biological activities.

Acknowledgements

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