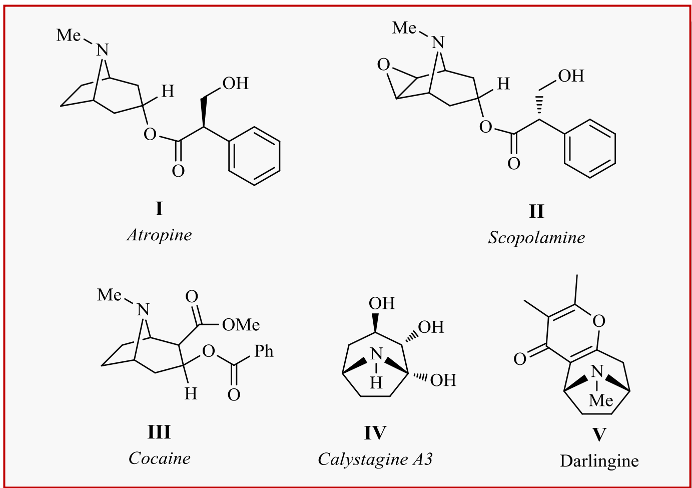
PROBLEM 55

[SUPPL Problem 55 # 1]

Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

In Perspective

For those of you a bit familiar with natural products in general and alkaloids in particular, the structure of products **3** and **4** of TAPSOC's Scheme 55.1 may sound familiar. Yes, they display the distinctive [3.2.1] azabicyclo scaffold of tropane alkaloids; like atropine (**I**), one of the components of the pretty garden plant, deadly nightshade (*Atropa belladonna*), and scopolamine (**II**) from *Datura strammonium* – both from the Solanaceae plant family, the same of the tomatoes and eggplants. Brugmansias (ex-*Datura*) also accumulate these alkaloids, as well as several other plant genera [1].



SCHEME SP55.1.1

Brugmansia arborea from Venezuela. Photo: M. Alonso

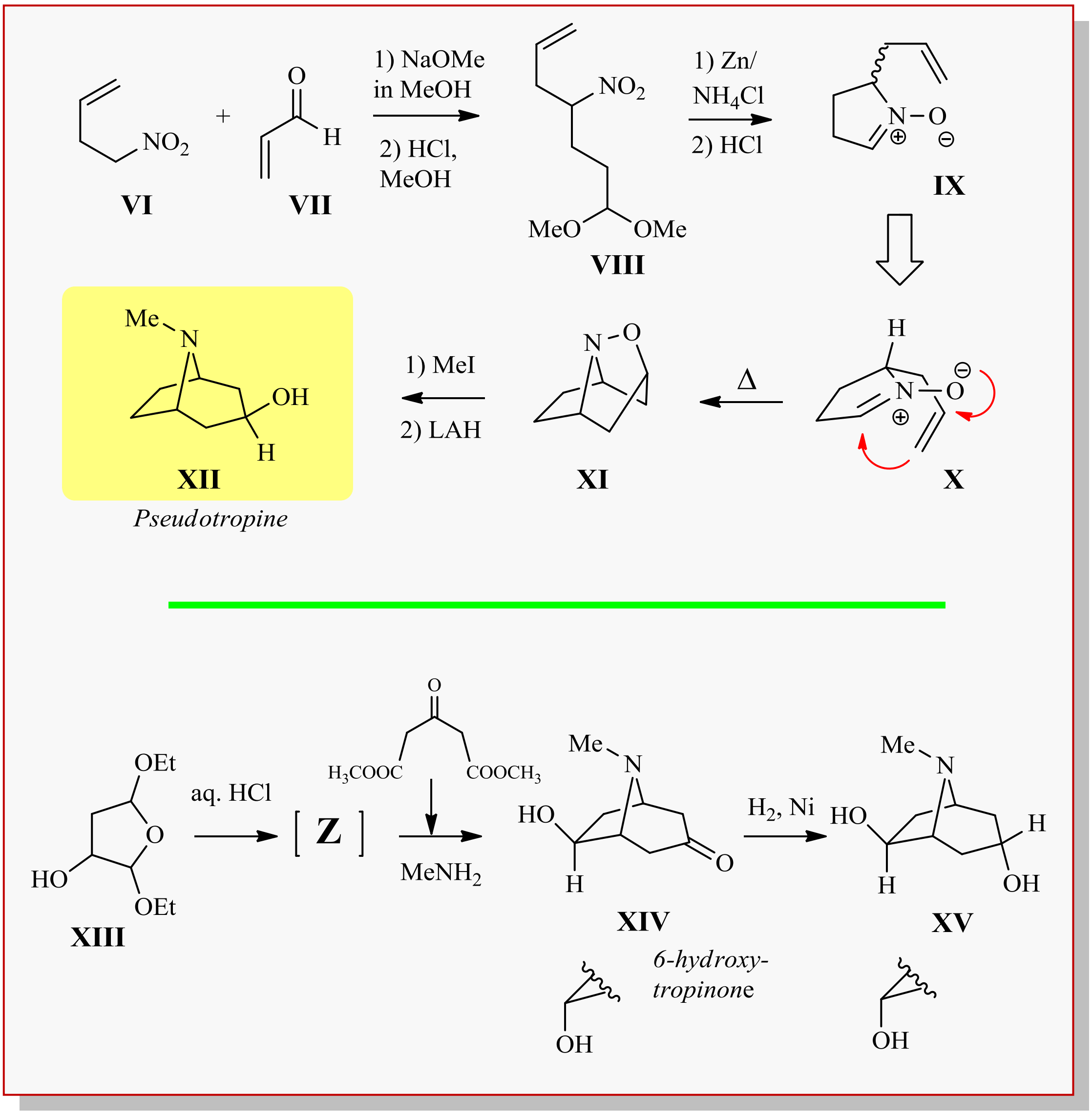
Apart from illegal uses as hallucinogens, these compounds have found useful application in the medical science, from Parkinson's disease to irritable bowel syndrome. The size of pharmaceutical industries business amounts to about 4 billion

$/Y. It is very likely that anyone visiting his/her ophthalmologist will have had a few drops of atropine in the eye to relax and dilate the pupils, so the doctor can peek into the retina. Injected in the vein or muscle, atropine increases the heart rate during episodes of heart failure with the immediate effect of bringing back to life the ill-fated subject. Tropanes show up in other less extreme situations, in Coca Cola to name one (first introduced into the formula in 1886). Paradoxically, tropane alkaloids can also be used against alkaloid addiction.

Once inside the body, these compounds are transformed into several products. For example, the liver quickly metabolizes cocaine by hydrolyzing the ester to the carboxylate and other minor products and sends it to excretion through urine. This compound, benzoylecgonine, is itself a topical analgesic.

There are other interesting life-saving applications of tropane alkaloids, themselves among the oldest of plant medicines known to man, a remarkable feat for such uncomplicated compounds [2]. Tropanes were the first alkaloids to be isolated (as early as 1830) and chemically characterized.

Not surprisingly, these compounds have attracted a considerable body of research in the synthesis field from the dawn of this science. Two Nobel Prize winners are associated with cocaine's synthesis: Richard M. Wilstetter (1915) and Sir Robert Robinson (1947). Among many others, two conceptually interesting and smartly simple syntheses of the tropane nucleus are shown in Scheme SP55.1.2 (next page) although unrelated to TAPSOC Problem 55. Both respond to the sort of organic chemistry preceding today's enantioselective catalysis or chiral attendant groups. Only ingenuity was there to help. In fact, notice that both stereoisomers of **IX** afford **XI**, thus there is no yield loss. Stereocontrol is perfect [3]. Brief as it is, however, the synthesis of 6-hydroxytropinone from **XIII** cannot be praised in the same terms if a specific enantiomer of **XIII** was not previously defined (it was not) [4]. By the way, compound **Z** is for you to solve and envision the **XIII** → **XIV** mechanism. It calls for nothing but fundamental chemistry.



SCHEME SP55.1.2

As for TAPSOC Problem 55, the formation of a dearth of products is generally a nightmarish prospect for anyone in the synthesis field. This predicament, endured by Professor Huw Davies and his coworkers, now at Emory University in Atlanta, turned into one of a mechanistically attractive series of results cropping up while attempting (later successfully) to apply the diazocarbonyl/pyrrole chemistry to the enantioselective synthesis of bioactive tropane alkaloids using the transfer of steric information from ligands on the Rh complex as well as on the reactants, a widespread strategy to get to chiral products.

REFERENCES

[1] Griffin WJ, Lin GD. Phytochemistry 2000;53:623-637. Lounasmaa M, Tamminen T. The Tropane Alkaloids: Chemistry and Biology. In: Cordell GA (ed.) The Alkaloids, Vol 44, Academic Press, New York 1993, pp 1-114.
[2] For a short review, see: Grynkiewicz G, Gadzikowska M. Pharm. Rep. 2008;60:439-463.
[3] Tufariello JJ, Trybulski EJ. J. Chem. Soc. Chem. Commun. 1973;720-720 (yes, one page).
[4] Stoll A, Lindermann A, Jucker E. Helv. Chim. Acta 1953;36:1500-1505.