PROBLEM 59

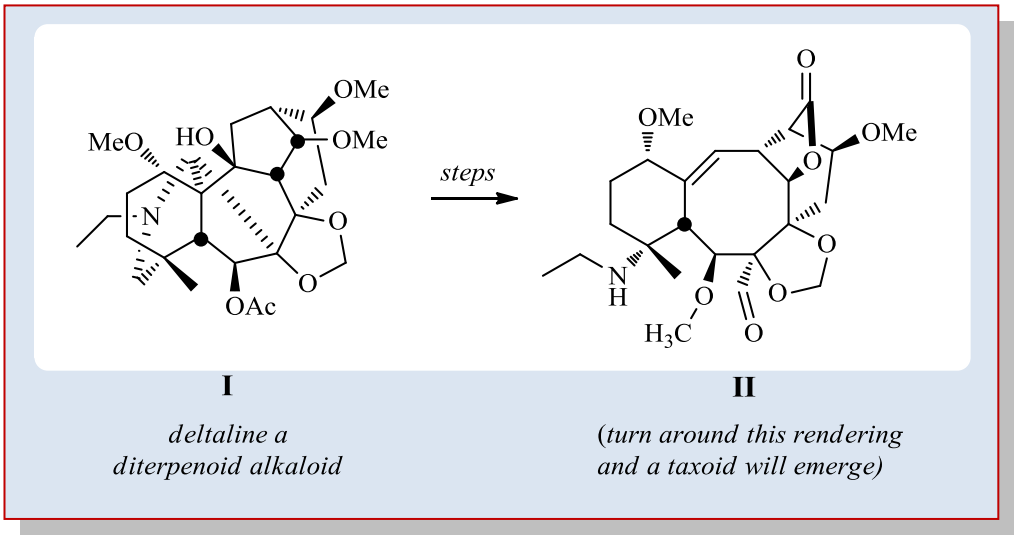
[SUPPL Problem 59 # 1]

Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

In Perspective

The sole view of the labyrinthine structures of Scheme 59.1 may drive more than a few readers to think that this is just too much for a workbook like this, even hardened problem solvers. Never mind as there is *always* a solution. I selected this particular reaction to show that taking a few preliminary, well planned actions will alleviate and improve a great deal the design of a reasonable mechanism. Even in taxing situations like this one, the problem analysis and solving techniques described in TAPSOC can drive you to a reasonable solution. As the old Greek philosophers thought, understanding the parts guides the comprehension of the whole. This takes time in the current problem so be prepared for a hefty series of reaction schemes in two separate sets, one for each reaction.

This elegant work, led by professor Feng-Peng Wang of Sichuan University in China, was conceived within an even more astounding frame: the conversion of diterpenoid alkaloid deltaline (**I**) to a fundamental part of the core of the always attractive taxoid skeleton **II** in 12 steps, using quite unsophisticated reagents and a great deal of ingenuity [1].



SCHEME SP59.1.1

Deltaline is a member of the aconitine family of alkaloids. Their complex framework, intricate chemistry and potent biological activity have provided enormous stimulus for scientists to look into the innards of the *Aconitum* and *Delphinium* plant genera (more than 250 species worldwide) (Ranunculaceae) where they are generated.

On account of these substances there is considerable risk of exposure to *Aconitum napellus*, a common garden species and among the most toxic in the Northern Hemisphere. Leaf and flower are shown here as prophylactic advice.

FIGURE SP58.1.1. Leaf and flower heads of common aconitum – Monkshood- (*Aconitum napellus*). Picture at left by Frank Vincentz (under GNU Free Documentation License.

Aconitine (**III**), the parent alkaloid, also known as the Queen of Poisons [LD_{50} (oral) = 1 mg/kg], is absorbed quickly not only through the intestinal mucosa but also passes across the skin [2]. It binds strongly to the cells voltage gated sodium channels keeping them open. This property is shared by other natural poisons like the brevetoxins [3]. An uncontrolled flush of Na^+ passes through causing severe electrical potential disruption. In active cells of excitable tissues like neurons, this means persistent voltage activation which leads cells to become resistant to controlled activation. The Na^+/K^+ ATP pump is inhibited with serious effects on neurotransmitter levels [4].

Recent toxicological studies of aconitine show additional physical damages to neurons morphology: synapses are fractured, cell membranes become fragmented, cell mitochondria swell, the energy metabolism is disrupted, you name it! [4].

This biochemical turmoil translates into acute macroscopic paralysis of skeletal muscles, cardiotoxic and neurotoxic effects, and othres [5]. All it takes is to swallow a small portion of the tuberous roots which may contain up to 3% w/w of alkaloid load (aerial parts are also alkaloidal). Animals and people are severely affected. A bit surprisingly, common aconitum species, known as “chuanwu” and “caowu”, are used in herbal Chinese and Japanese folk medicines as cardiotonic (antiarrhythmic), analgesic and anti-inflammatory, hopefully in minute amounts; more predictably, there are cases of severe poisoning during medicinal treatments with these aconitum herbs [6].

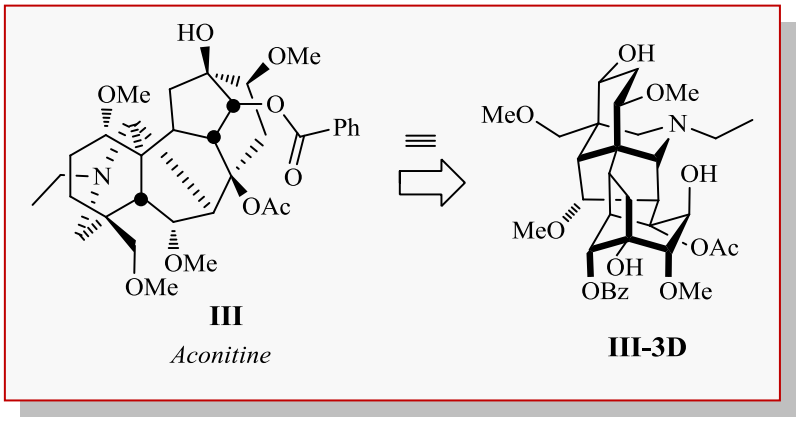


FIGURE SP58.1.2. Two renderings of Aconitine.

The total synthesis of the boxy aconitine skeleton is a most demanding task. For a recent and illuminating synthesis of a nor-aconitine (one carbon missing but same structural scaffold), see the multi-institutional work of profs. Derek Tan, Yuan Shi and David Y Gin (who passed away, still a young promising scientist, in 2010) and collaborators [7]. A couple of curious mechanisms appear embedded there (much more accessible than TAPSOC problem 59, by the way), still worth challenging your mates with over a cup of coffee.

REFERENCES AND NOTES

[1] Alkaloids of the general aconitine carbon framework are conceivable starting materials for taxanes by more than one synthetic strategy. See: Zou CL, Ji H, Xie GB, Wang FP, Jian XX, Song L, Liu XY, Chen DL, Chen QH. Tetrahedron 2008;64:7594-7604.

[2] Anything with a LD_{50} < 5 mg/kg of body weight is considered extremely hazardous (class Ia) according to the World Health Organization. (LD_{50} is dose (mg or μg/kg) that kills 50% of the population of tested organisms in 24 h).

[3] Trainer VL, Edwards RA, Szmant AM, Stuart AM, Mende TJ, Baden DG. Marine Toxins. In ACS Symposium Series, Vol 418, Chapter 11, 1990, pp. 165-175.

[4] Peng C, Zheng T, Yang F, Li YX, Zhang DK. Arch. Pharm. Res. 2009;32:1533-1543.

[5] Chan TY. Clin. Toxicol. (Philadelphia) 2009;279-285.

[6] Chan TY, Tomlinson B, Tse LK, Chan JC, Chan WW, Critchley HA. Vet. Hum. Toxicol. 1994;36:452-455.

[7] Shi Y, Wilmot JT, Nordstrøm LU, Tan DS, Yin DY. J. Am. Chem. Soc. 2013;135:14313-14320.