PROBLEM 52

[SUPPL Problem 52 # 1]

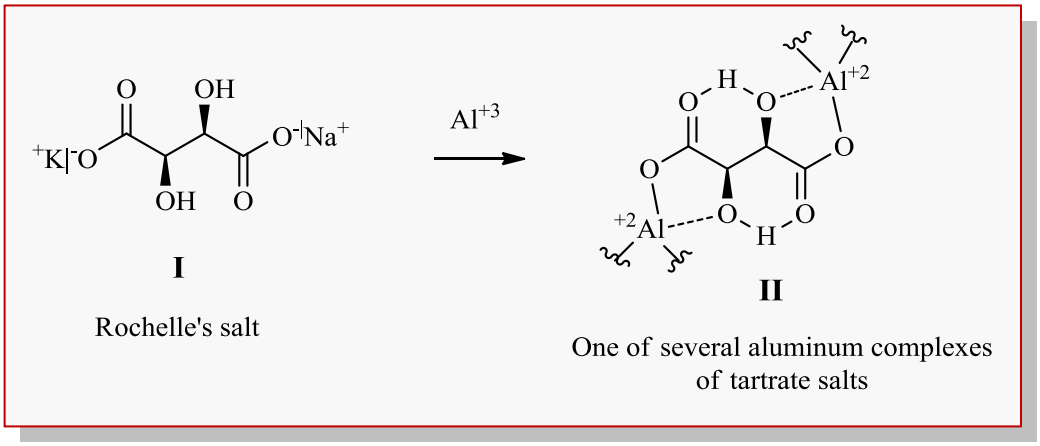
Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

In Perspective

Two subjects at the opening:

1) **Rochelle's salt and**
2) **The research interest behind compound 1**

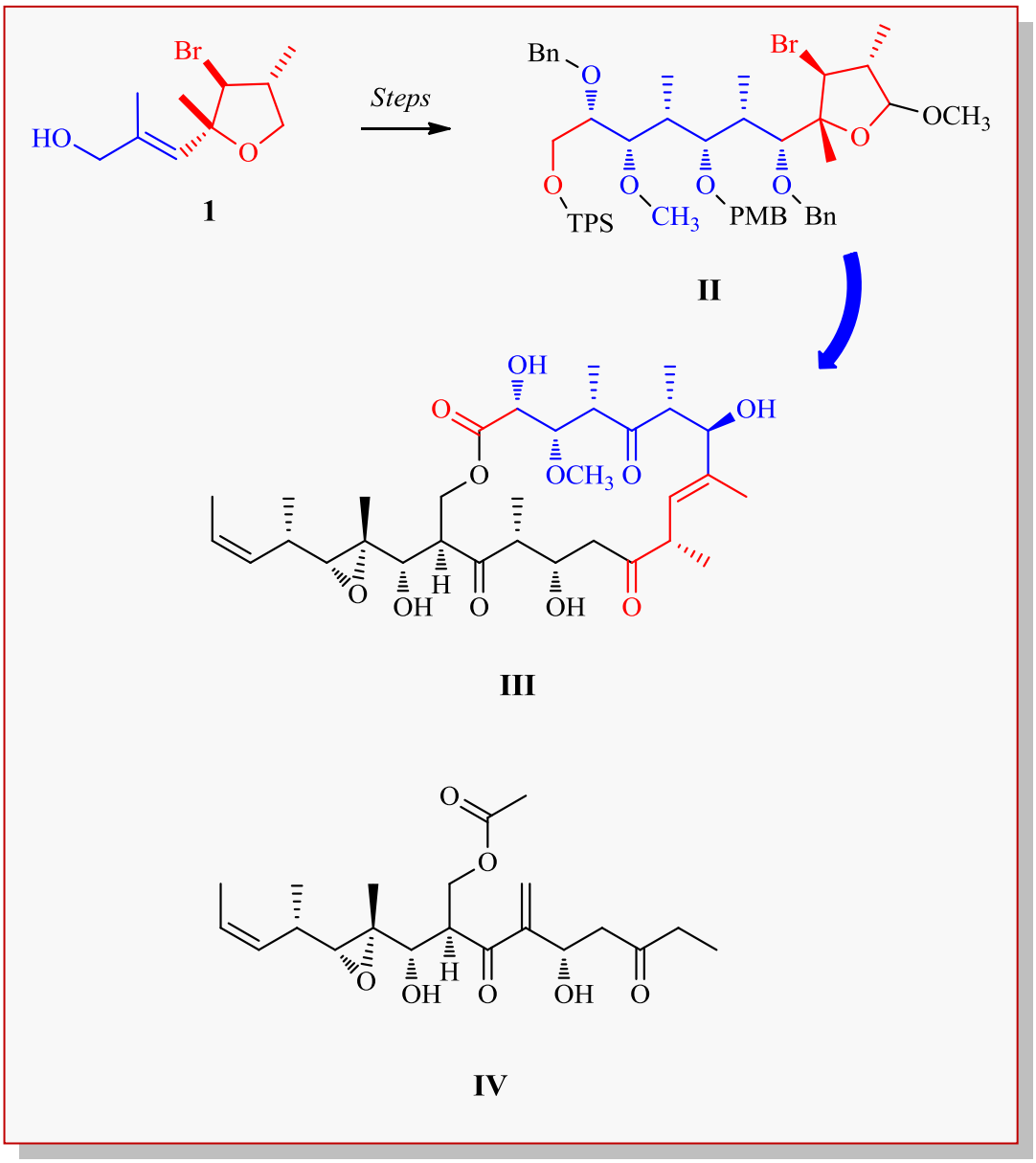
Rochelle's salt: this is probably the first thing you may wish to know about TAPSOC Scheme 52.1 experimental details, if you don't already. Although reference to this compound is made along the discussion, I thought it might interest you to know at the onset that this is the mixed Na/K salt of tartaric acid (**I**). This water soluble salt binds exceedingly well to $Al^{(III)}$ residues after reactions with $AlCl_3$, LAH, DIBAL, mixed hydrides and so forth. A saturated aqueous solution of Rochelle's salt (1.39 g/L) is added dropwise at workup. Aluminum compounds are supposed to be removed quantitatively as tartrate complexes like **II, s**o it is a great substitute for NaOH, ammonium chloride or other methods. Rochelle's salt story is a curious one [1,2].



SCHEME SP52.1.1

What drives this research

Compound **I** (TAPSOC Scheme 52.1) is the kind of product one takes the burden to synthesize for a good reason. No natural product or direct derivative has the particular structure of **I** with a bromine at a chiral carbon, one of three in the molecule. Authors Michael Jung and Dongwong Yoo at the University of California Los Angeles, had a brave target in mind: Tedanolide (**III**), one of several potent antitumor, citotoxic and antiviral agents that attracts Jung's research group attention.



SCHEME SP52.1.2

Tedanolide was first isolated in 1984 from a Caribbean fire sponge (*Tedania ignis*). The name *ignis* (burn) comes from the burning sensation in the skin after touching it, in company with the deep orange coloration of this thing. The actual pharmacophore region is the entire southern section of the molecule, which happens to be structurally very similar to myriaporone 1 (**IV**) [3], isolated from another marine organism, *Myriapora truncata*, a briophoran.

Jung's synthesis blueprint included the transformation of **1** into the northern section of **III** in a few steps, with total control over the nine chiral carbons of the immediate target compound **II**, a task involving careful orchestration of stereochemical contributors and many obstacles.

As it happens with many other synthetically challenging and biologically potent compounds, tedanolide and its deoxy analog were synthesized soon after (2008) by, alas, another research team, prof. William Roush's at Scripps Florida and coworkers from the University of Michigan [4,5]. But it may be said that lessons learned along the way in the organic reaction and mechanism areas are as valuable as achieving the final target.

REFERENCES AND SIDE NOTES

[1] *The commercial source of Rochelle's salt is the wine industry. During fermentation of grapes, tartaric acid precipitates out as the alcohol concentration increases, forming a solid crust with other materials that includes tannins from the grapes. This solid is removed by hand and sent for processing. Tartrate is extensively used in the food industry (have you heard of the "cream of tartar"?) whereas Rochelle's salt is used for a number of applications as laxative, in Fehling's reagent, electroplating and so forth. It forms great, large crystals as well as piezoelectric materials (crystals that generate electricity when bent or squeezed; Pierre and Paul Jacques Curie discovered this property in 1880 using Rochelle's salt and later, quartz). The tartrate double salt is in fact one of the most powerful piezoelectric substances known.*

[2] *If you are not interested in the history of science and chemistry do not bother to read on. But I am and wish to share bits of Rochelle's salt story with you. The discovery of Rochelle's salt is a fun story. The inventor of Rochelle's salt was not monsieur Rochelle as the name suggests, but some apothecary by the name of Pierre Seignette around 1665-75 (Isaac Newton was in his early thirties then) who happened to live in La Rochelle, a city-port of France not far from Bordeaux. With so many wineries around and all that tartaric waste… His salt was also known as Seigne's. Pierre Seignette belonged to a family of pharmacists (apothecaries at the time) and was himself a medical doctor. Until the XVII century laxatives were mostly herb preparations and plant extracts but undesirable side effects seemed unavoidable. As the story goes, somehow the family came to the conclusion that tartrate salts could do the job, perhaps out of its umpleasant taste and after trial and error on themselves. Besides, they were mesmerized by the fact that diluting the salt in water cooled significantly the solution, so wondrous properties were expected. No one knows exactly why Pierre and family tried sodium and potassium as cations or their source of the latter (Na came from carbonate) but it was the mixed salt which gave the best results (one half to one ounce in a glass of water). The double salt was a success and the Seignettes commercialized it as Polychreste Salt (Salt of many virtues) making a lot of money out of their finding. So the manufacturing process was kept a family secret for over half a century. The salt continued to be sold in pharmacies in many conutries for over 200 years.*

[3] A full PhD. Dissertation on the synthesis of myriaporone 1 and similar compounds can be downloaded freely from: http://etd.nd.edu/ETD-db/theses/available/etd-04132004-132533/unrestricted/FlemingKN042004.pdf

[4] Dunetz JR, Julian LD, Newcomb JS, Rousch WJ. J. Am. Chem. Soc. 2008;130:16407-16416.

[5] For a review on the complex issue of tedanolide synthesis, although previous to W. Roush publication, see: Kalesse RM. Nat. Prod. Rep. 2008;(5):862-870.