PROBLEM 57

[SUPPL Problem 57 # 1]

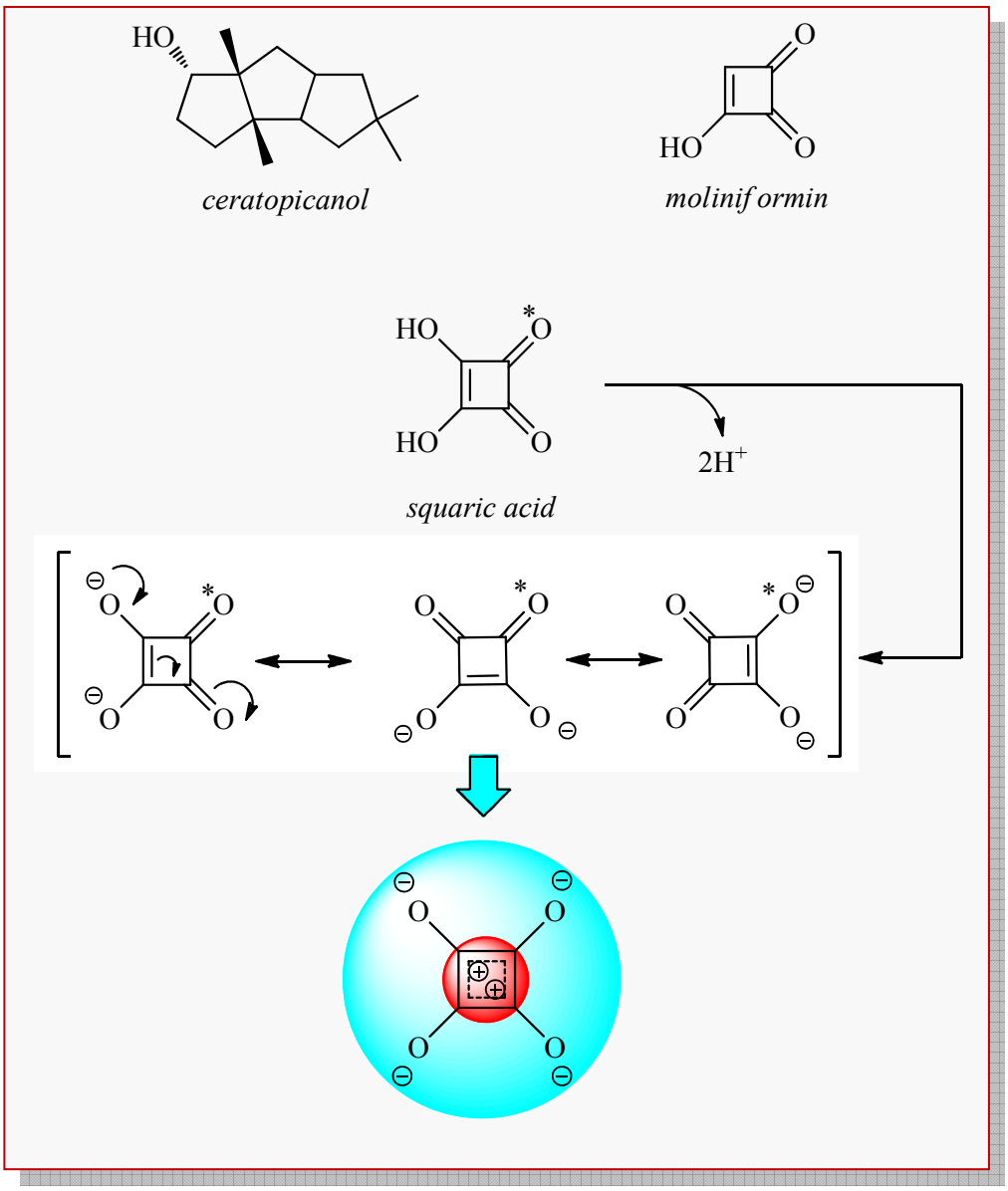
Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

In Perspective

The reaction of TAPSOC Scheme 57.1, designed by Professor Leo Paquette and collaborators at Ohio State University, is the first application of cyclobutenedione **1** to a natural product synthesis, this time to ceratopicanol (Scheme SP57.1). This is one of those secondary metabolites endowed with fused cyclopentanes mentioned earlier (Supplementary material for problem 56). There are a few other compounds from Nature sharing this *hirsutane* nucleus, also a subject covered in this book (see problem 11).

The synthesis of ceratopicanol emerges after several years of studying the outstanding properties of 'squarate' ester **1.** A strained and functionally dense molecule [1], compound **1** was just a theoretical entity a few decades ago with an unpromising future in the synthesis field. However, Nature produces closely related compounds (e.g. moniliformin, a problematic toxin from fungi of the *Fusarium* genus, a true agricultural and food scourge). In fact, despite the considerable ring strain, squaric acid is stable at high temperature(mp. > 300 ºC) boasting strongly acidic protons (pKa_1= 1.5; pKa_2 = 3.4). Would you have an answer before having a peek at Scheme SP57.1.1, on next page?

Yes, you had it right if your reasoning appealed to resonance structures of the anions. The combined resonance hybrid lays out a uniform distribution of the anionic character in all four O atoms, leading to a fascinating oddity: **a doubly positive cyclic nucleus with a negatively charged crown** (in blue circle at bottom).

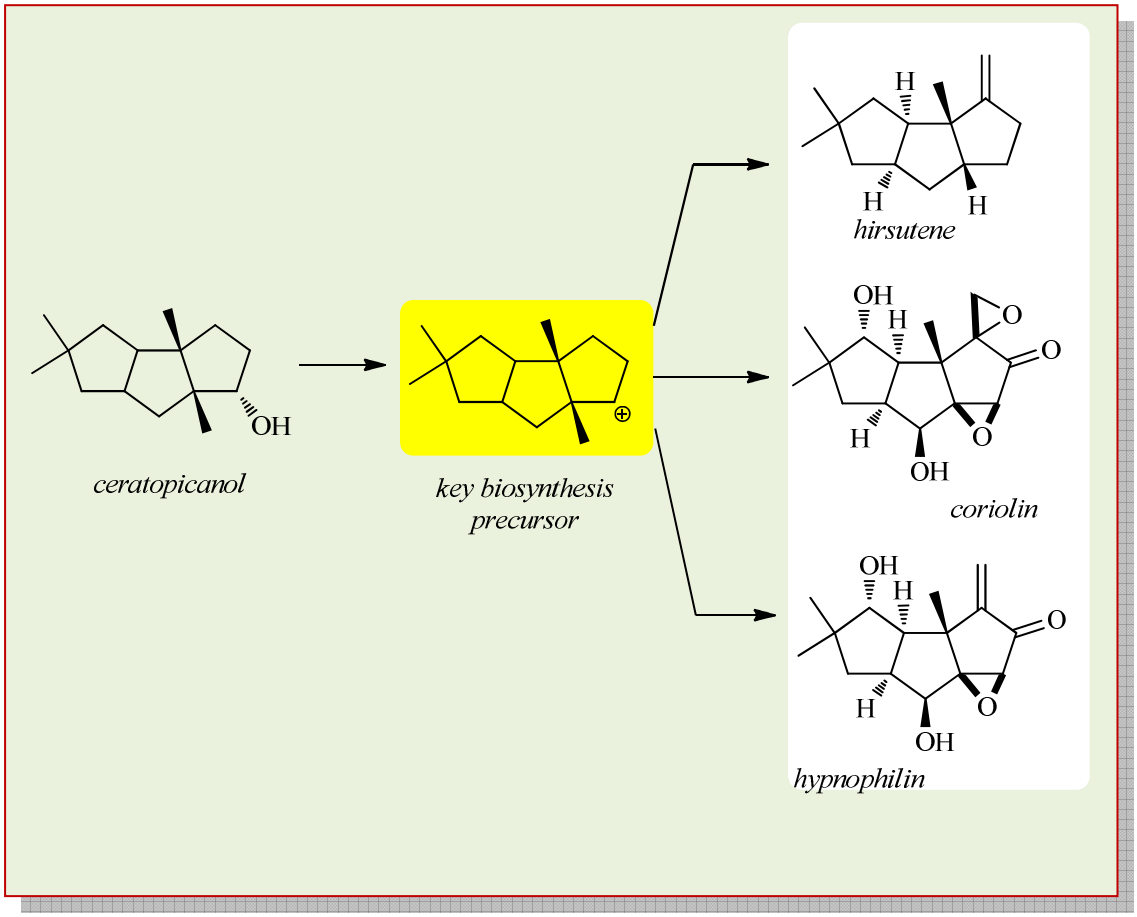


SCHEME 57.1.1

The comparatively appeased esters like **1** in TAPSOC Scheme 57.1 are now synthetically accessible [2]. Endowed with a powerful LEDZ character, squarates display intense reactivity towards 1,2 and 1,4 additions with nucleophiles in addition to

products emerging from mono- and dianionic intermediates. The mechanism underlying TAPSOC Scheme 57.1 focuses on the way these intriguing aspects can be harnessed to build impressive molecular complexity from quite simple starting materials.

As for ceratopicanol, all this fuss around this material without known biological potencies as far as I was able to find in the literature, arises from another source of interest. It is a key precursor in the biosynthesis of other far more active and remarkable plant and marine organism secondary metabolites. The simple act of substracting OH from it *in vivo* is taken as evidence of a carbenium ion created in an organism in its way to bioactive hirsutene, coriolin and hypnophilin [3].



SCHEME SP57.1.2

Interest in the synthesis of ceratopicanol does not die off with prof. Paquette's contribution as it continues to attract the attention of the synthetic community [4].

Indeed, the hirsutane manifold has turned into a true playground for the development of novel reactions.

REFERENCES:

[1] For an early and most gratifying report, see: Negri JT, Morwick T, Doyon J, Wilson PD, Paquette LA. J. Am. Chem. Soc. 1993;115:12189-12190.

[2] Liu H, Tomooka CS, Moore HW. Synth. Commun. 1997;27:2177-2180; Mukanti A, Periasami M. Arkivoc 2005;(XI):48-77.

[3] Clive DLJ, Magnuson SR. Tetrahedron Lett 1995;36:15-18.

[4] For ingenious ways to build this hirsutane scaffold applied to ceratopicanol, see, for example: Mukai C, Kobayashi M, Kim IJ, Hanaoka M. Tetrtahedron 2002; 58:5255-5230. Lee SS, Kim WY, Lee HY. Chem. Asian J. 2012;7:2450-2456.