PROBLEM 42

[SUPPL Problem 42 # 1]

Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

In Perspective

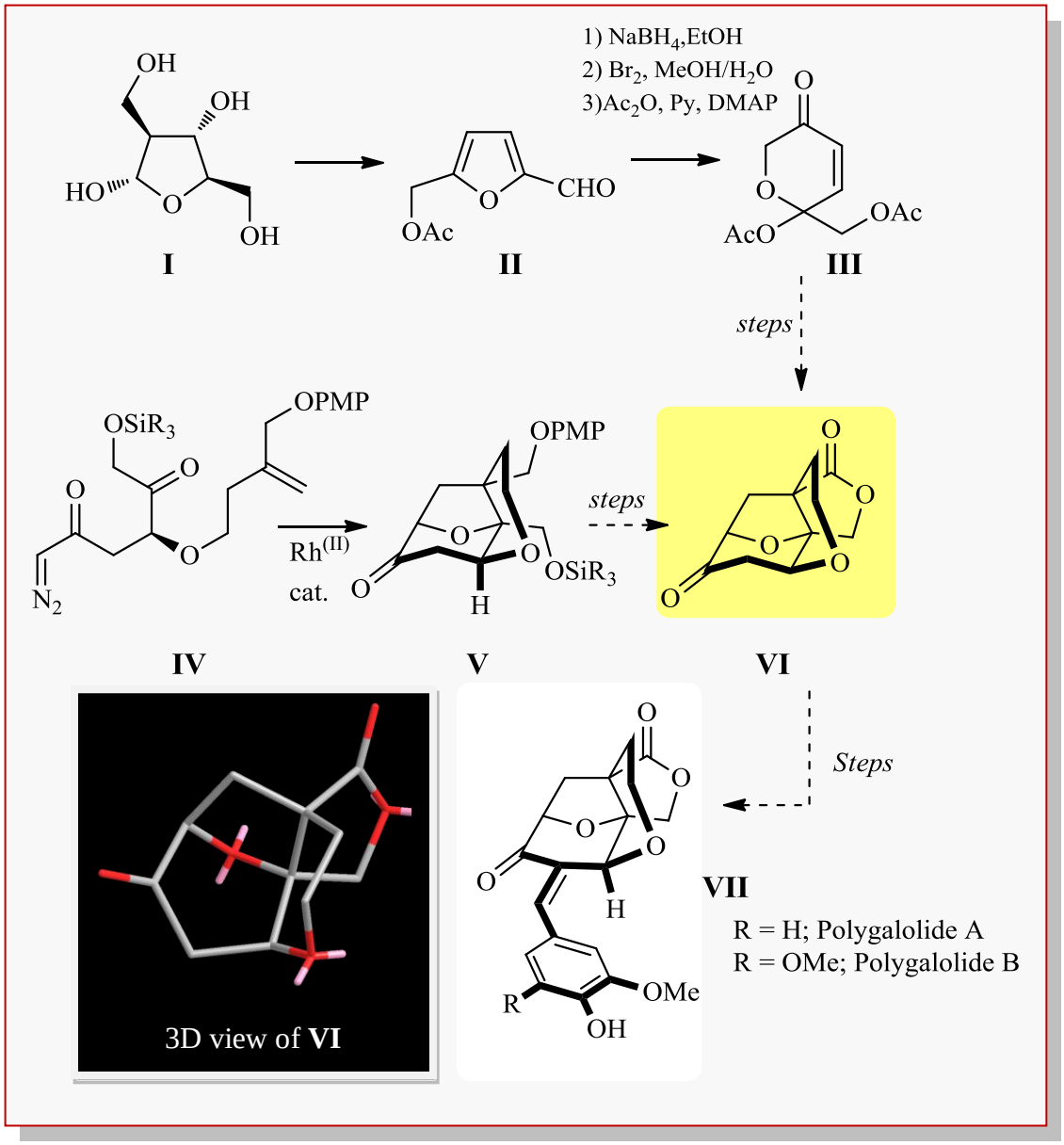
The elaborate target of this reaction is the architectural core of two phenolic compounds, polygalolides A and B (**8**), found in *Polygala fallax*. In Chinese medicine this plant is reputed for its anti-hepatitis properties.

In 2006, Profs. Seiichi Nakamura and Shunichi Hashimoto at Hokkaido and Nagoya Universities, respectively, synthesized optically pure **3** by an amazing convergent scheme from diazoketone **6** and concluded that the natural polygalolides were almost racemic (Scheme SP42.1.1)[1]. This is a most remarkable feature of a natural product.

These secondary metabolites are synthesized by trains of enzymes in the cell microtubular body where ribosomes reside. These corpuscles work like an assembly line to manufacture the very many natural products through tandem enzymatic reactions in the great majority of steps. Enzymes generally discriminate one enantiomer from another [2]. Therefore, chiral organic substrates in the train are selectively accepted and transformed within the enzyme machinery depending strictly on the configuration of their chiral centers.

In collaboration with Prof. Barry Snider from Brandeis University, the Japanese group developed the elegant, short biomimetic scheme to racemic **3** from **1** and **2** (TAPSOC numbering)**,** which carries a conceptually important surprise. Compound **1** is derived from furfural **II** (Scheme SP42.1.1 next page) which in turn stems naturally from fructose (**I**) and acetylation, a sequence you may enjoy solving as a side problem

[3]. In addition, α-methylenebutyrolactone (**2**) could emerge from isopentenyl pyrophosphate so Nature could use a similar route to prepare the polygalolides.



SCHEME SP41.1.1: For clarity, hydrogens have been removed in the 3D rendering of VI, thus only the core scaffold is shown. This structure can be downloaded (Comp 42-VI.mol) from TAPSOC website.

REFERENCES

[1] Sugano Y, Kikuchi F, Toita A, Nakamura S, Hashimoto S. Chem. Eur. J. 2012;18:9682-9690.

[2] Enzymes bound to a solid matrix are frequently used for the separation of enantiomeric mixtures, and the stereoselective conversion of substrates even in reaction mixtures. See, for example: Kaki SS, Aflerkreutz P. Biotechnol. Bioeng. 2012;110:78-86.

[3] Nakamura S, Sugano Y, Kikuchi F, Hashimoto S. Angew. Chem. Int. Ed. 2006;45:6532-6535.