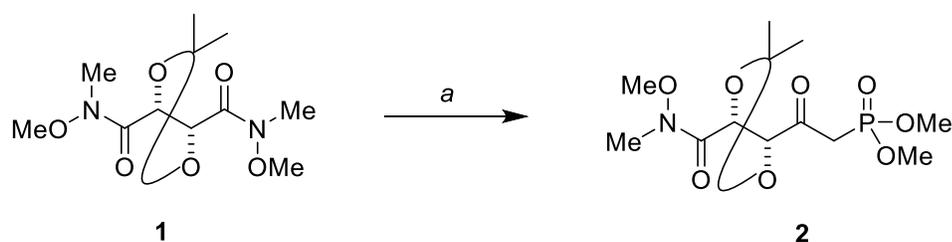


SYNOPSIS

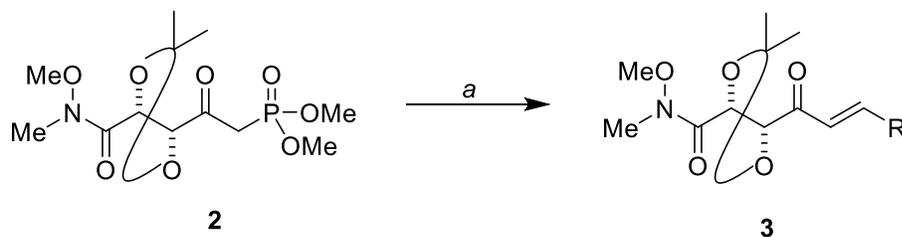
The thesis entitled “ *β -Keto phosphonates from tartaric acid in the total synthesis of (+)-4-epi-gabosine A, (+)-dihydrokawain-5-ol, (-)-bengamide E and Identification of MPK-09: A small molecule that restores the wild type function of mutant p53.*” demonstrates the utility of β -keto phosphonate derived from tartaric acid as a building block in the synthesis of bioactive natural products small molecules of therapeutic importance. The thesis is divided into three sections.

Section I of the thesis deals with the utility of new β -keto phosphonate **1**, derived by desymmetrization of *bis*-Weinreb amide of L-(+)-tartaric acid (Scheme 1).



Scheme 1: (a) MeP(O)(OMe)_2 , $n\text{-BuLi}$, THF, -78°C , 1.5 h, 91%.

A series of functionalized aldehydes were used in the Horner-Wadsworth-Emmons type reaction of phosphonate **2**. Under the optimized condition, a series of aldehydes including aryl, aliphatic aldehydes with chiral centers next to the aldehyde functionality underwent facile olefination to yield the α,β unsaturated ketones in good yields (Scheme 2).

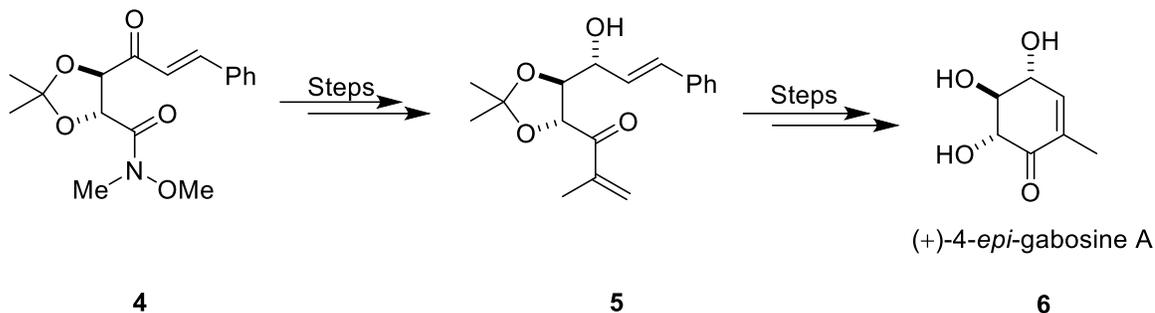


Scheme 2. (a) Cs_2CO_3 , aldehyde, $^i\text{PrOH}$, rt, 1 h.

Application of the synthesized unsaturated ketones in the synthesis of various molecular architectures of therapeutic importance was undertaken. Application of this strategy in the total synthesis of (+)-4-epi-gabosine A and (+)-dihydrokawain-5-ol is delineated.

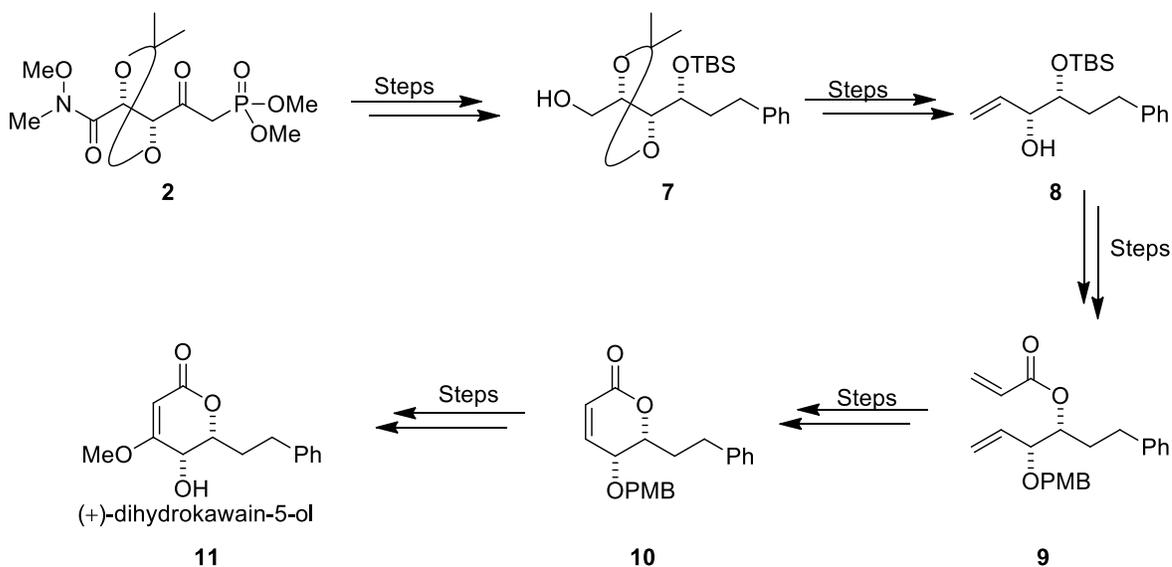
The γ -keto amides were reduced with good diastereoselectivity with NaBH_4 to afford the γ -hydroxy amide which was transformed to the diene. Ring closing metathesis of the diene led to the cyclohexenone which on deprotection gave (+)-4-epi-gabosine A (Scheme 3). The key

reactions during the synthesis are Horner-Wadsworth-Emmons reaction, stereoselective reduction and ring closing metathesis as shown in Scheme 3.



Scheme 3: Stereoselective total synthesis of (+)-4-*epi*-gabosine A.

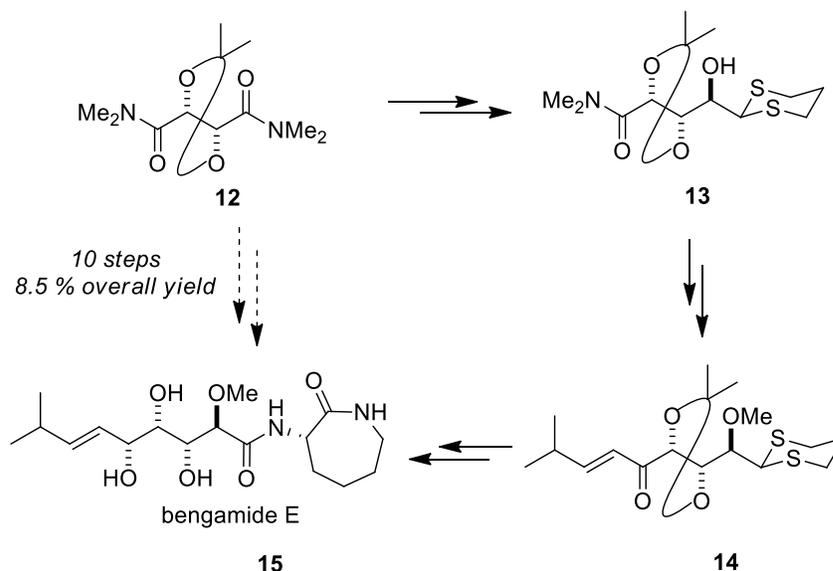
Dihydrokawain-5-ol **11** is a unique 6-alkyl-5-hydroxy-5,6-dihydropyran-2-one isolated from the methanol extracts of the kava plant (*Piper mythicum*), a Polynesian shrub of the pepper family and exhibits promising biological activities. Stereoselective total synthesis of this natural product from tartaric acid is described in this section. Key features of the synthesis include the elaboration of the unsaturated ketone obtained from the phosphonate to the allylic alcohol **8** and further elaboration to the natural product **11** as depicted in Scheme 4.



Scheme 4: Total synthesis of (+)-dihydrokawain-5-ol.
(Part of this work has been communicated).

Section II of the thesis deals with the enantiospecific total synthesis of (–)-bengamide E. Bengamide E was isolated from the jaspidase sponges by the Crew research group. Enantiospecific total synthesis of bengamide E was accomplished in 8.5% overall yield in a linear sequence of 10 steps starting from the *bis*-(dimethylamide) unit of tartaric acid as chiral

pool precursor (Scheme 5). Key features of the synthesis includes combination of the addition of 1, 3-dithian-2-yl lithium, stereoselective reduction and Horner-Wadsworth-Emmons reaction.



Scheme 5: *Enantiospecific total synthesis of bengamide E.*

(This work has been published: Metri, P. K.; Schiess, R.; Prasad, K. R. *Chem. Asian. J.* **2013**, 8, 488).

Section III of the thesis deals with **MPK-09** and a series of novel lactones, structurally similar to bioactive styryllactones synthesized from tartaric acid and studied their *in vitro* ability to inhibit the growth and induce apoptosis in human tumor cell lines. It was found that **MPK-09** a small molecule in the series is more cytotoxic towards cancer cell lines harboring p53 mutation E285K and R273C. Ectopic expression of p53 plasmids harboring various hotspot mutations, demonstrated that **MPK-09** was more effective on the tested p53 mutants compared to the wt p53 harboring cells. The restoration of p53 function was further corroborated by the transactivation of its pro-apoptotic signaling pathways as shown by the induction of p21 and Bax protein expression by western analysis. It was demonstrated that the activity was due to the restoration of the wild type conformation of mutant p53.

(Part of this work is published: Metri, P. K.; Naz, S.; Kondaiah, P.; Prasad, K. R. *ACS Chem. Biol.* **2013**, 8, 1429).