



# Intramolecular carbonyl-ene reactions in the synthesis of *peri*-oxygenated hydroaromatics



Shyam Basak, Dipakranjan Mal\*

Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721302, India

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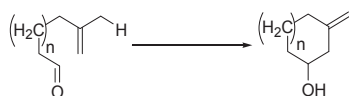
## ABSTRACT

2-Methallyl aromatic aldehydes, synthesized by Suzuki coupling of 2-formylphenylboronic acids, are shown to provide cycloalkylidene ene products under acidic conditions. Susceptibility of the products to aromatization is manoeuvred by varying the reaction conditions and catalysts including binol-derived Brønsted acid catalysts. A *peri*-effect is identified as a controlling factor for the aromatizations. Several oxidative transformations of an ene product are carried out as model studies of hydroaromatic polyketide natural products.

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## 1. Introduction

The ene reaction is a fundamentally important carbon–carbon single bond forming reaction.<sup>1</sup> It has been a key step in many classic syntheses including asymmetric syntheses.<sup>2</sup> Studied in depth by many researchers, it continues to attract attention of the organic chemists due to its enormous applicability in organic synthesis. Among the various subclasses of the ene reactions, type-II intramolecular carbonyl-ene reaction (ICE) (Scheme 1) is more elaborately studied.<sup>1</sup>



**Scheme 1.** Typical type-II carbonyl-ene reaction of an alicyclic compound.

Like the general ene reaction, type-II ICE reaction has facilitated many total syntheses in atom-economic manner and made their ways to the industries. Examples of the total syntheses are those of natural products (+)-cassiol, laulimalide, (+)-azaspiracid-1 etc.<sup>3</sup> The mechanistic aspects of the reaction have thoroughly been examined.<sup>4</sup> However, its scope is largely confined to the alicyclic compounds.<sup>1</sup>

\* Corresponding author. Fax: +91 3222282252; e-mail address: [dmal@chem.iitkgp.ernet.in](mailto:dmal@chem.iitkgp.ernet.in) (D. Mal).

The present report stems from the seminal work of Hauser and Mal on carbonyl-ene reaction in the construction of hydroaromatic ring A of anthracylines. Treatment of a methallylanthraquinone carboxaldehyde with  $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$  in DCM resulted in the formation of a tetracycle.<sup>5</sup> It is presumably the first report of a type-II ICE reaction in the formation of a hydroaromatic system. The applications of such reactions, however, are limited to few methoxyanthraquinone-embedded precursors.<sup>6</sup> In view of the wide occurrence<sup>7</sup> of hydroaromatics, especially the *m*-cresol unit in natural products **1–9** (Fig. 1), we intended to validate the potential of the reaction for a general synthesis of oxygenated hydroaromatics.

Herein, we report regiocontrolled construction of oxygenated hydroaromatics with naphthalene, anthracene and naphthacene nuclei, as well as their ene precursors. Susceptibility of the ene products to aromatization has been correlated with their structures.<sup>8</sup> Oxidation chemistry of an ene product has been briefly explored as models, for the terminal ring in the natural products.

## 2. Results and discussion

**Synthesis of the aldehyde-ene precursors:** The majority of the ene-precursors of this study are not reported in the literature. In general, the synthesis of methallylarenes is scarcely reported.<sup>9a</sup> The Suzuki coupling<sup>9b,9c</sup> was adopted as the key step for the synthesis of ene-precursors **10–16** (**10**<sup>9b</sup>, **11**<sup>9d</sup>, **12**<sup>9e</sup>, **14**<sup>9f–h</sup>) and boronic acids **17–26** (**18**<sup>10a,10b</sup>, **22**<sup>10c</sup>) were employed for this coupling reactions (Scheme 2). Initial attempt of the coupling of **17** with methallyl bromide in presence of  $\text{PdCl}_2(\text{PPh}_3)_2$  gave the desired product **10** in

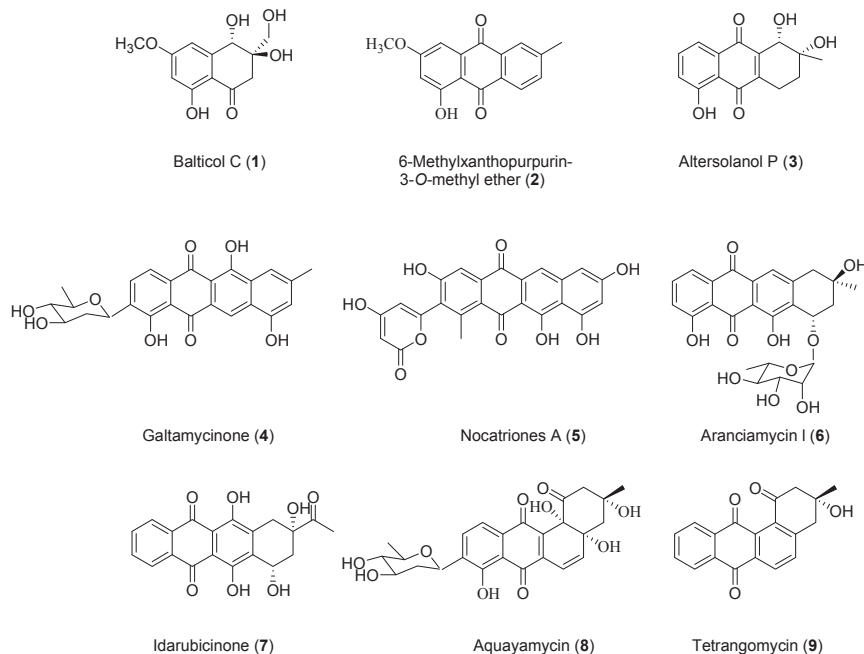
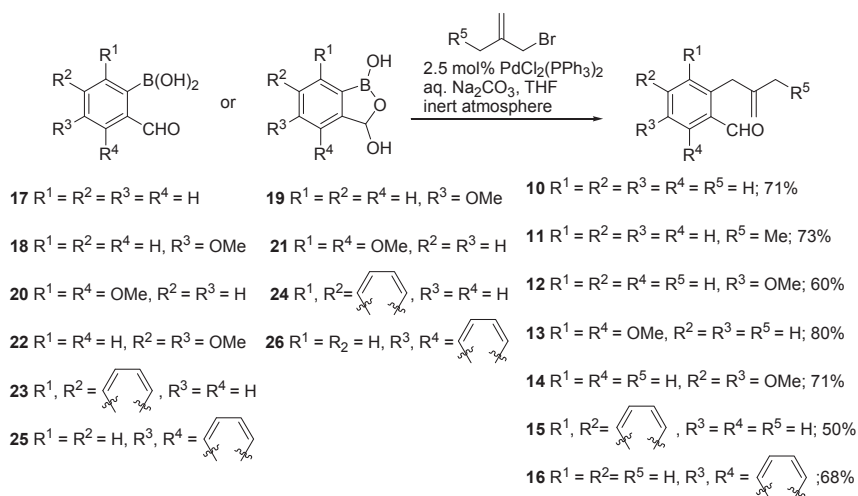


Fig. 1. Structures of selected natural products with oxygenated tetralin skeletons.



Scheme 2. Synthesis of ene-precursors by Suzuki reaction.

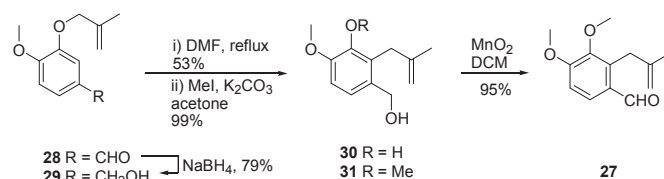
40% yield. However, the yield could be significantly improved i.e. up to 71% by adding the boronic acid **17** portion wise as well as increasing the amount of the methyl allyl bromide. This modification was applied for the synthesis of all other compounds (**11**–**16**). This modification allowed minimum formation of the biphenyl dicarboxaldehyde.

Ene precursor **27** was synthesized in four steps from isovanillin derivative **28**<sup>11</sup>. It was reduced to **29** with NaBH<sub>4</sub>, which was thermally rearranged to give **30**. *O*-methylation of compound **30** followed by MnO<sub>2</sub> oxidation of **31** furnished aldehyde **27** (Scheme 3).

Keeping in the mind the structural features of altersolanol P<sup>7b</sup> (**3**) as well as truncated anthracyclines<sup>12a</sup>, naphthaldehyde **32** was chosen as the model substrate. It was prepared in seven steps as shown in Scheme 4. Hauser annulation<sup>12c-d</sup> of cyanophthalide **33**<sup>12e</sup> with methyl acrylate was performed to give 1,4-naphthoquinol **34**, which was selectively monomethylallylated to give **35**.

After *O*-methylation of **35**, the resulting ether **36** was subjected to Claisen rearrangement in refluxing DMF followed by methylation to give naphthalene derivative **37**. LAH reduction of **37** to alcohol **38** followed by PCC oxidation of **38** provided ene precursor **32** (Scheme 4).

Alkylidene malonate **39** was prepared by Knoevenagel reaction of **10** with dimethyl malonate in the presence of piperidine and



Scheme 3. Synthesis of methylallylbenzaldehyde **27**.

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