WINSTEIN-BAIRD-MASAMUNE ALKYLATIVE DEAROMATIZATION

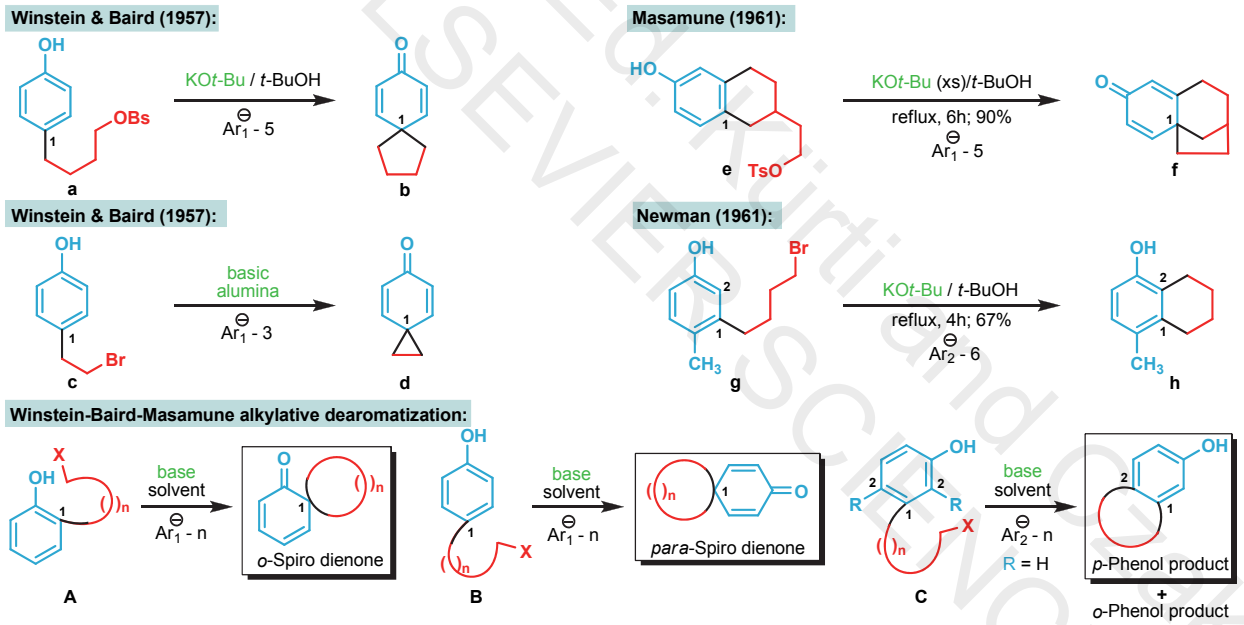
(References are on page XXX)

Importance:

[*Seminal Publications*[1]*; Reviews*[2]*; Modifications & Improvements*[3]; *Theoretical Studies*]

In 1957, S. Winstein and R. Baird reported that under basic conditions, appropriately substituted phenols undergo a facile intramolecular geminal cyclization to form dienones via participation of the neighboring phenoxide ion ($Ar_1^{\ominus}$-participation).[1a,1c] For example, 4-*p*-hydroxyphenyl-1-butyl *p*-bromobenzenesulfonate was efficiently converted to spiro[4.5]deca-6,9-dien-8-one (**a**→**b**) upon treatment with a slight excess of potassium *tert*-butoxide in anhydrous *t*-butanol. The highly reactive spiro[2.5]octa-1,4-diene-3-one (**c**→**d**) could be readily prepared by passing 2-*p*-hydroxyphenyl-1-ethyl bromide through basic alumina. A few years later S. Masamune demonstrated that the bicyclo[3.2.1]octane system (**f**), a common structural unit of diterpenes and diterpene alkaloids, could be accessed also via $Ar_1^{\ominus}$-participation from highly substituted phenols (**e**) under basic conditions.[3b] The first example of an $Ar_2^{\ominus}$-participation (**g**→**h**) in which fused phenols were obtained instead of spirodienones was published by M.S. Newman et al.[3a] The base-mediated conversion of substituted phenols to cyclohexadienones or fused phenols with the concomitant formation of a new carbon-carbon bond is known as the *Winstein-Baird-Masamune (WBM) alkylative dearomatization*.

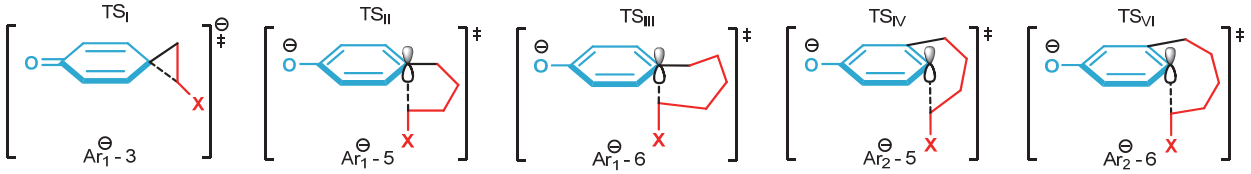
The general features of this transformation are: **(1)** the reaction can be both intra- and intermolecular, however, most known examples are intramolecular; **(2)** the intramolecular alkylation of phenoxide ions is classified by the following general notation: $Ar_{\alpha}^{\ominus}$-*n*, where Ar represents the aryl group, α refers to the position of the participating aryl group involved in the creation of the ring, while *n* indicates the size of the ring being made (usually n=3-6); **(3)** only a single product can be obtained in $Ar_1^{\ominus}$-*n* cyclizations (**A** and **B**), whereas two regioisomers are possible as a result of $Ar_2^{\ominus}$-*n* cyclizations (**C**); **(4)** the initially formed dienone intermediates in $Ar_2^{\ominus}$-*n* cyclizations undergo spontaneous tautomerization to afford the more stable phenol products (when R=H); **(5)** the necessary phenoxide intermediate alternatively can be accessed from trialkylsilyl-protected phenols by treatment with a fluoride source (F^-) in aprotic solvents[4] or by basic hydrolysis of phenolic esters and **(6)** the leaving group X is usually a halogen or a sulfonate ester, but phenolic epoxides, aldehydes, ketones, enones and esters have also been successfully cyclized;[2b] **(7)** the dienone products can readily undergo the *dienone-phenol rearrangement* under acidic conditions.



X = Cl, Br, I, OMs, OTs, OBs, epoxide, aldehyde, ketone, ester; base: KO*t*-Bu, basic alumina, *i*-Pr_2NEt, K_2CO_3, KOH; solvent: *t*-BuOH, CH_2Cl_2, THF, i-PrOH

Mechanism:[5]

Stereoelectronic factors are significant in the cyclization of phenoxides (*see* transition states below). Neighboring group participation is the greatest in $Ar_1^{\ominus}$-3 cyclizations due to the overlap of the aryl π-system and the high *p*-character ring-bonds of the three-membered ring which results in a lower free energy of the transition state. The relative rates of ring-closure in $Ar_1^{\ominus}$-*n* type of cyclizations are: 3 > 5 > 6 >> 4. The relative rates for ring-clousre in $Ar_2^{\ominus}$-*n* cyclizations are: 6 > 5. To date there have been no reports of $Ar_2^{\ominus}$-3, $Ar_2^{\ominus}$-4 and $Ar_2^{\ominus}$-7 cyclizations.



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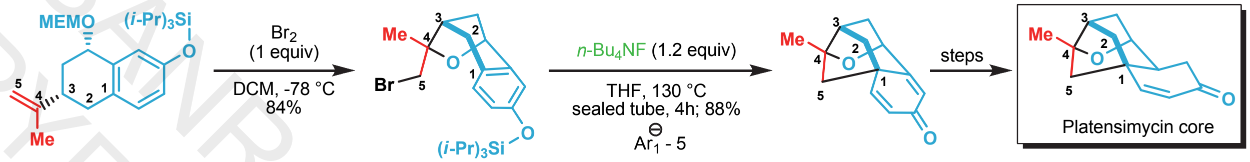
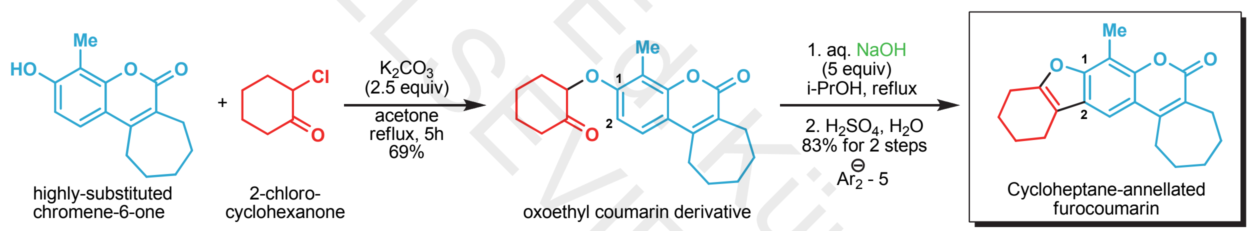
(Sample experimental procedure is on page XXX)

Synthetic Applications:

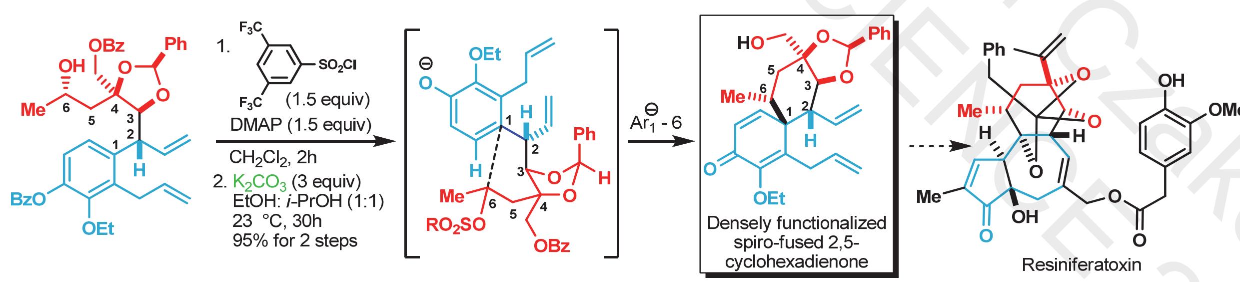
(1) A highly enantioselective route to the core of the novel antibiotic platencimycin has been developed in the laboratory of E.J. Corey.[4] Key steps included a highly enantioselective, triethylamine-accelerated, conjugate addition of an alkenyl trifluoroborate (*Hayashi reaction*) and an $Ar_1^{\ominus}$-5 *Winstein-Baird-Masamune alkylative dearomatization* of a TIPS-protected tricyclic phenol intermediate. The primary alkyl bromide intermediate was obtained as a single diastereomer by the addition of one equivalent of Br_2 to a 2-propenyl substituted bicyclic MEM ether. The phenoxide ion was generated by exposing the TIPS ether to a slight excess of TBAF in THF under forcing conditions. The formation of a new carbon-carbon bond between C1 and C5 created a five-membered ring and delivered the complex tetracyclic framework of the natural product in high yield.



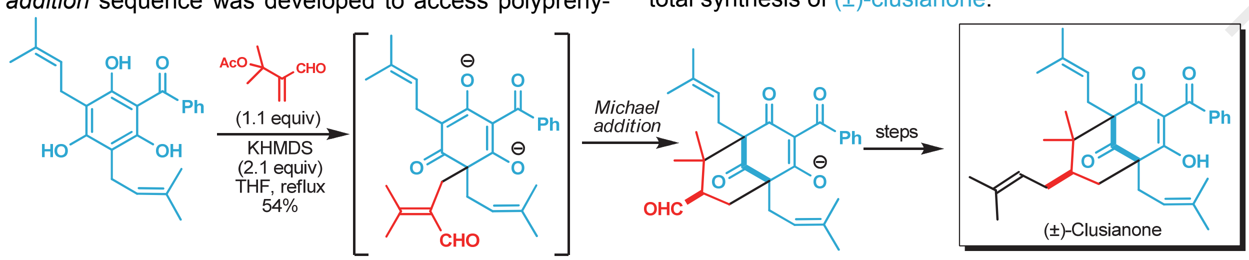
(2) Naturally-occurring furocoumarins and their synthetic derivatives often display exciting physiological properties. For example, furocoumarins with annellated carbocycles at their 5,6-positions exhibit photoantiproliferative and cardiotropic activities and act as CNS stimulants. Y.L. Garazd and co-workers prepared dozens of cycloheptane-annelated furocoumarins by the $Ar_2^{\ominus}$-5 *WBM alkylative dearomatization* of highly substituted chromen-6-one derivatives.[6] The phenol substrate (prepared by the *von Pechman reaction*) was *O*-alkylated with 2-cholorcyclohexanone under Williamson ether synthesis conditions. The resulting oxoethyl coumarin derivative was heated with excess 1N NaOH solution in isopropanol that brought about the cyclization. The initially formed dienone intermediate immediately tautomerized to form the more stable phenol product. Finally, treatment with aqueous sulfuric acid afforded the desired cycloheptane-annellated furocoumarin derivative.



(3) A completely diastereoselective route was developed by E.M. Carreira et al. for the synthesis of a densely functionalized spiro-fused 2,5-cyclohexadienone which would serve as a key intermediate en route to the synthesis of diterpene natural product resiniferatoxin.[7] The key step was an $Ar_1^{\ominus}$-6 *WBM alkylative dearomatization*. Sulfonate ester formation at C6 was followed by treatment with K_2CO_3 in 2-propanol/ethanol at room temperature to afford the desired cyclohexadienone as a single disatereomer. A complete inversion of configuration occurred at C6 while a quaternary center was created at C1. The careful choice of base and solvent mixture was critical for the success of this transformation.



(4) In the laboratory of J.A. Porco, an *intermolecular WBM alkylative dearomatization – intramolecular Michael addition* sequence was developed to access polyprenylated phloroglucins which feature bicyclo[3.3.1]nonane carbocyclic frameworks. This method was applied for the total synthesis of (±)-clusianone.[8]



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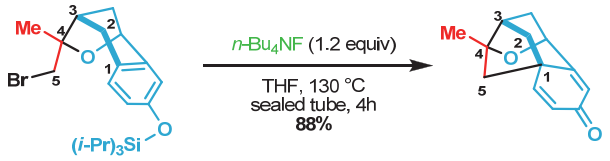

A B

Ref: Lalic, G., Corey, E. J. An Effective Enantioselective Route to the Platensimycin Core. *Org. Lett.* **2007**, 9, 4921-4923.

Procedure: To a solution of **A** (3.77 g, 1.00 equiv, 8.58 mmol) in THF (60 mL) in a Schlenk flask was added 1M solution of TBAF in THF (10.3 mL, 1.20 equiv, 10.3 mmol) at room temperature. The flask was sealed and placed in a 130 °C oil bath. After 4 h, the reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with sat. aq. NH_4Cl and brine. The aqueous phase was extracted with EtOAc, and the combined organic extracts were dried over MgSO4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (10% to 80% EtOAc in hexane) to yield **B** as a white amorphous powder (1.53 g, 88% yield).

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