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SYNTHESIS OF OXEPANES *VIA* INDIUM CHLORIDE MEDIATED AND TIN CHLORIDE CATALYZED PRINS-TYPE CYCLIZATION

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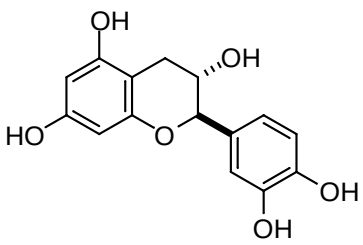
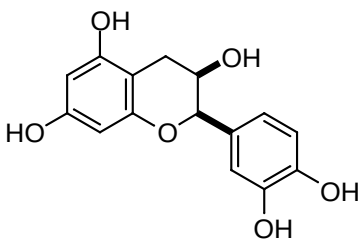
Abstract-Various potential cancer-preventive agents, oxepanes, were synthesized by indium(III) chloride mediated, tin chloride(IV) catalyzed cyclization of allylphenol with aldehydes and ketones.

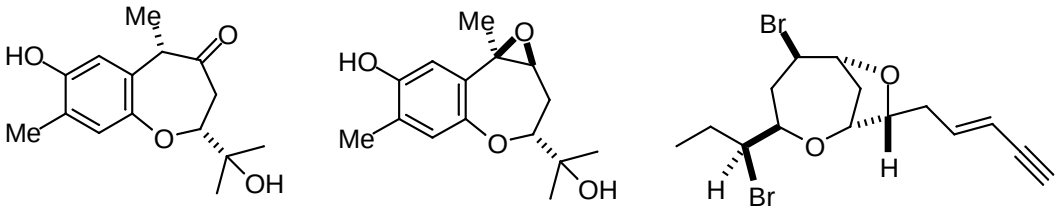
Recently, the phytochemicals found in green tea have attracted considerable attention for their anti-cancer activities and their potentials as cancer chemo-preventive agents.[1] The major components that have been identified in green tea include (+)-catechin (**1**), (-)-epicatechin (**2**), as well as other related benzopyran derivatives.[2] In addition, many natural products, such as (+)-heliannuol F(**3**), (-)-heliannuol F (**4**), and isoprelaurefucin (**5**), bearing oxepane framework and exhibiting interesting biological activities have also been reported.[3] These heterocycles often have interesting biological activities.[4] To develop new cancer-preventive and therapeutical agents that are structurally similar to (+)-catechin and derivatives, we herein wish to report a convenient synthesis of oxepanes *via* indium chloride mediated and tin chloride catalyzed Prins-type cross-cyclization of aldehydes with 2-allylphenol (Scheme 1).



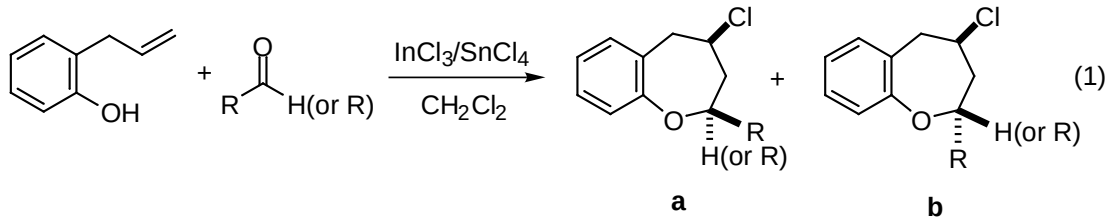
(+)-Catechin (**1**)



(-)-Epicatechin (**2**)



(+)-Heliannoul F (**3**) (-)-Heliannoul F (**4**) Isoprelaurefucin (**5**)



The starting 2-allylphenol can be obtained readily from Claisen rearrangements of allyl ethers of phenols.[5] Previously, we have shown that indium chloride[6] mediated Prins-type cyclization provided tetrahydropyran derivatives effectively.[7] When a mixture of the allylphenol, benzaldehyde, and indium chloride was stirred in dichloromethane at room temperature for 4-5 hours, only about 5% of the desired products were isolated. When a catalytic amount of tin chloride was added, the yield of the product was significantly improved. This could be due to the higher Lewis acidity of tin chloride. Prolonged stirring of the reaction mixture was not beneficial to the product formation and resulted in the formation of several unidentified by-products. It was found that lower temperature could impede the formation of the by-products; however, the yield of the product also decreased correspondingly. Subsequently, various aldehydes were reacted at room temperature with the combination of indium and tin chlorides for about 5h to give the corresponding oxepane derivatives (Table 1).[8] In each case, two diastereomers (**a** and **b**) of the cyclization products were isolated with the *cis* product as the major one as shown by the ROESY experiments in which cross-peaks between the hydrogens on the two stereogenic centers were observed for the major isomer. The diastereoselectivity of the cyclization ranges from 4:1 to 10:1 depending on the aldehyde being used. Aldehydes with strong electron withdrawing groups, such as nitro group or cyano group, could react with 2-allylphenol readily.

Besides aldehydes, a series of ketones have also been tested for the cyclization. The results were shown in Table 2. It was found that, for the cyclization of cyclic ketones, the yield of the desired product was related to the steric environment of the ketones. Such an effect was observed for both cyclic ketones and acyclic ketones. The mechanism of the reaction appeared similar to the ones that we proposed before involving a Prins-type cation-olefin cyclization.[7] Currently, we are exploring the application of this methodology in synthesizing natural products and pharmaceutical agents.

ACKNOWLEDGMENT

We are grateful to the NSF (CAREER), a NSF-EPA joint program, and LEQSF for partial support of our research. We thank Dr. K. Maskos for ROESY experiments.

Table 1. Synthesis of Oxepanes *via* Cross-Cyclization of Allylphenol and Aldehydes

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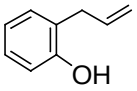
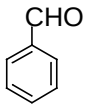
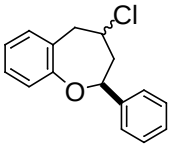
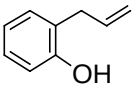
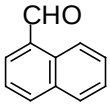
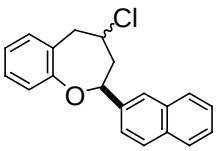
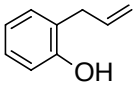
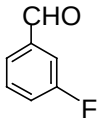
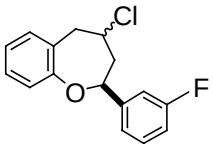
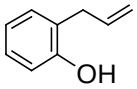
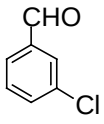
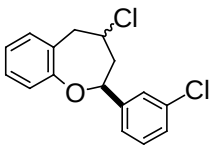
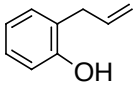
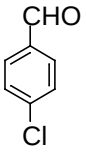
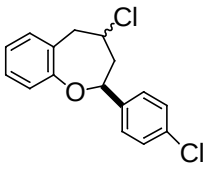
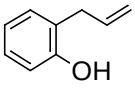
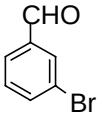
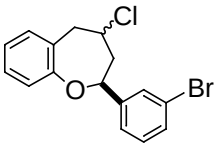
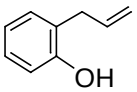
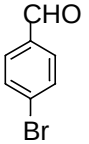
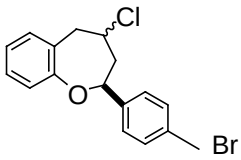
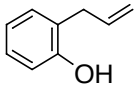
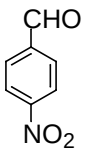
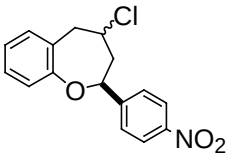
1				a: 8% b: 34%	42
2				a:1% b:32%	33
3				a:9% b:37%	46
4				a:3% b:35%	38
5				a:10% b:43%	53
6				a:1% b:41	42
7				a:2% b:41%	43
8				a:1% b:34%	35

Table 2. Cyclization of Allylphenols with Ketones

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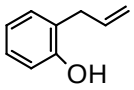
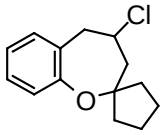
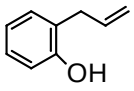
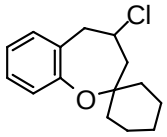
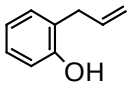
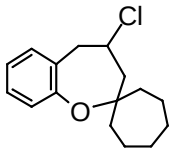
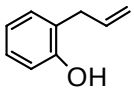
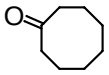
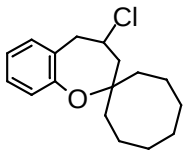
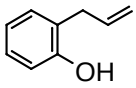
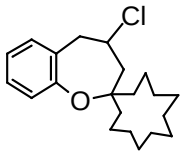
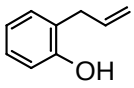
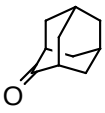
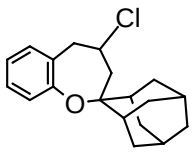
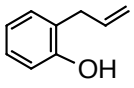
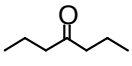
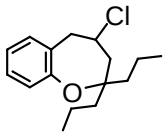
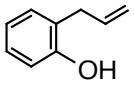
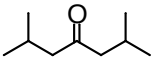
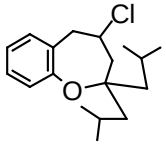
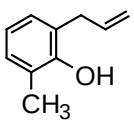
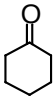
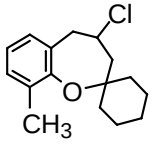
1				37
2				43
3				45
4				42
5				37
6				31
7				30
8				5
9				28

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8. A general experimental procedure is as following: To a mixture of 2-allylphenol (238 mg, 2 mmol), benzaldehyde (318 mg, 3 mmol) in 20 mL dry methylene chloride was added indium chloride (666 mg, 3 mmol). To the reaction mixture, a catalytic amount of tin chloride (53 mg, 0.2 mmol) was added. The mixture was stirred at rt for 4 h and was quenched with 20 mL of de-ionized water. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified through column chromatograph on silica gel (eluent: hexane/ ethyl acetate= 40:1).