DIVERGENT AND CONCISE TOTAL SYNTHESES OF DIHYDROCHALCONES: TACCABULIN A, TACCABULIN D AND TACCABULIN E

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Abstract: Dihydrochalcones are the compounds possessing various interesting biologically activities. Herein, we report the concise and divergent total syntheses of three naturally occurring dihydrochalcones from readily available starting materials. The divergent strategy is based around manipulation of a common chalcone scaffold and features application of Grignard Reaction followed by oxidation for synthesising ketones. This is the first reported total synthesis of Taccabulin D.Concise and flexible route should be readily amenable to future analogue generation. Furthermore, this work provides an illustration of the utility of divergent synthesis for the convenient and step-economical preparation of natural product libraries of various dehydrochalcones.

***IndexTerms* - Component, formatting, style,styling,insert.**

I. INTRODUCTION

Flavonoids are a family ofcompounds contains polyphenols. They are omnipresent in plants,[1] and epitomize dietary ingredients of potential significance to health.[2]Flavanoids are one of the potentially important emerging new class of pharmaceutical compounds.[1]Amongst the numerous classes of flavonoids, have been reported to exhibit a range of biologically interesting properties, including antioxidant,[3,4]antiinflammatory,[5]antileishmanial,[6]antidiabetic,[7]anticancer[8]andmolluscidal[9] activities etc.Consequently, dihydrochalcones attracted interest from both the synthetic and medicinal chemistry communities.[10]Recently, Peng et al. isolated and characterized five new dihydrochalconesfrom *Tacca chantrieri* and *Tacca integrifolia*plantextracts, named taccabulins and evelynin B (5) (Fig. 1).[11]Interestinglysome of these compounds were found to have antiproliferativeactivities against HeLa, A549 and PC-3cell lines.[12]

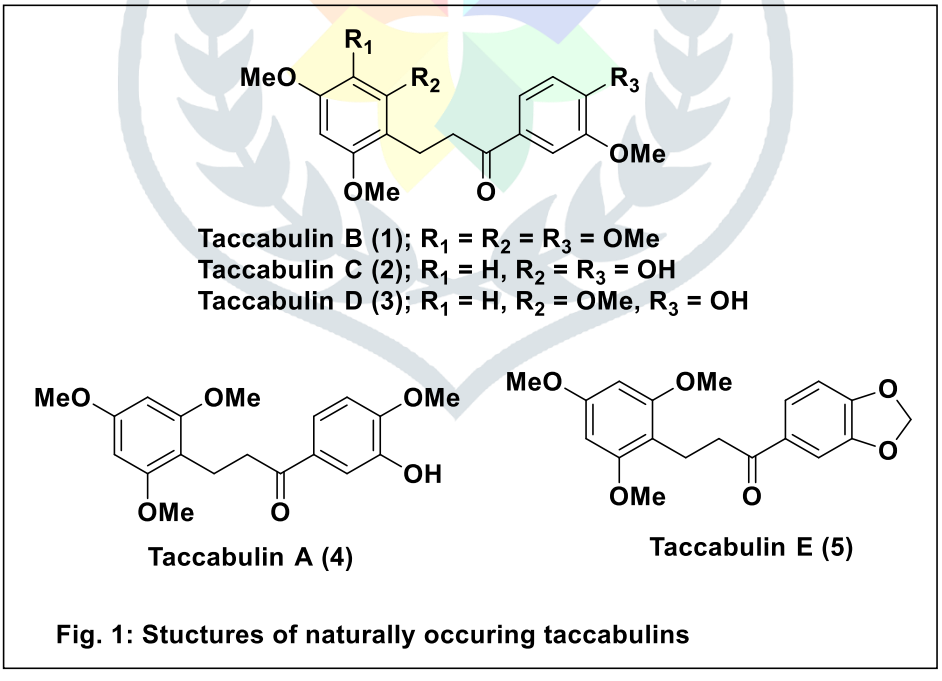
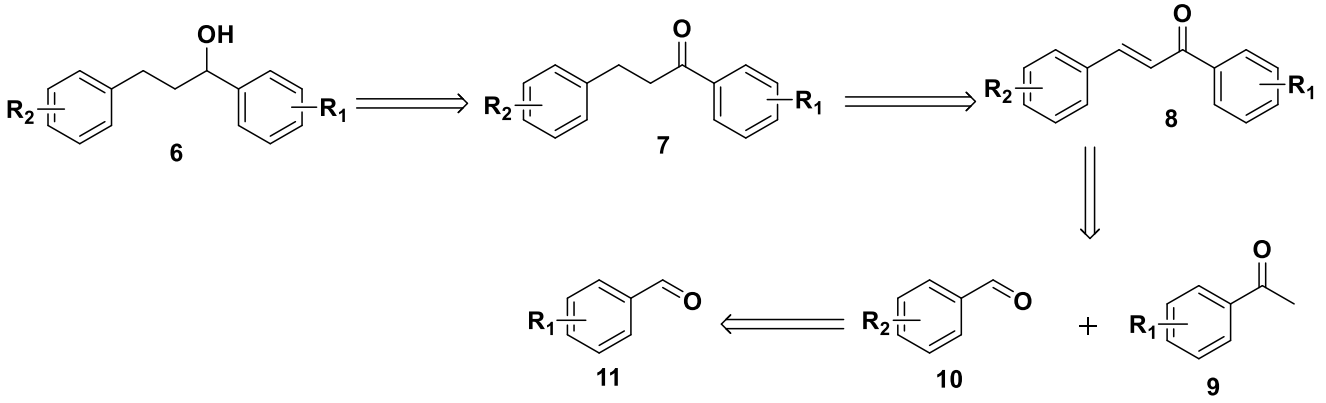


Fig. 1: Stuctures of naturally occuring taccabulins

Due to variety of biological activities of dihydrochalcones, we were interested in synthesise of taccabulin A, taccabulin D and taccabulin E. Furthermore, we have an on-going interest in exploring novel congeners, syntheses and studyingtheir antiproliferative activities.Thus, we pursued to develop a concise synthetic route that would provide efficient access to all of these natural compounds and their congeners for later library production. Herein, we report the novel and divergent route for the convenient synthesis of taccabulin A, taccabulin D and taccabulin E.

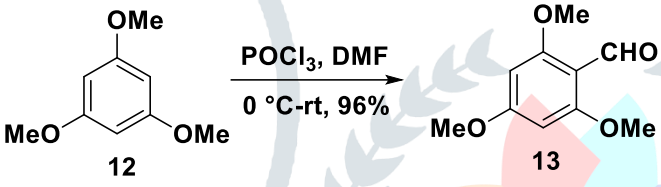


Scheme 1: Retrosynthetic analysis for synthesis of dihydrochalcone

II. RESULT AND DISCUSSION

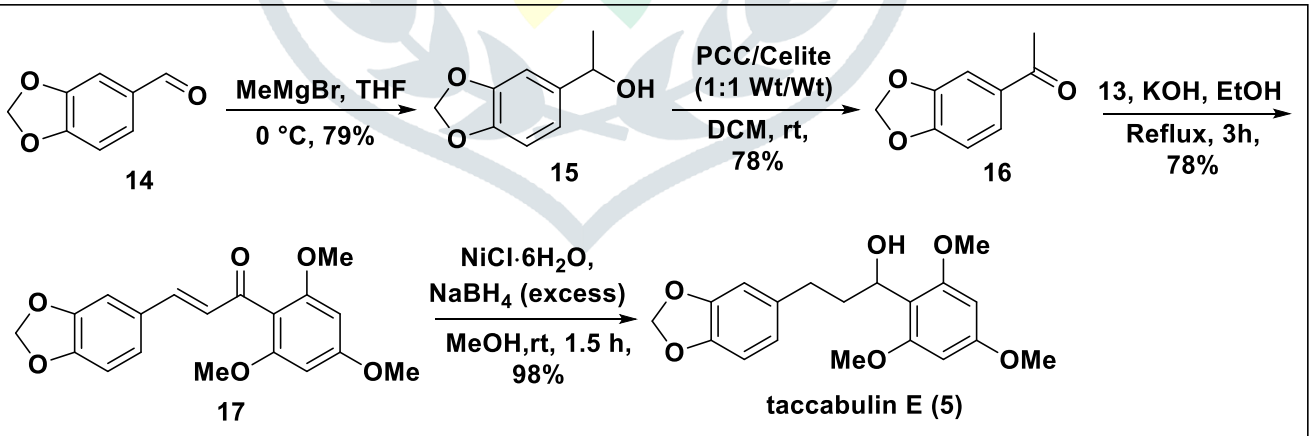
Inspired from workof Zhang et al.,a divergent synthetic strategy towards taccabulins based on the use of a general chalcone scaffold (9) as the crucial branching point was anticipated (Scheme 1).[9]It was envisioned that hydrogenation of compounds 9 would yield desired dihydrochalcones 10. It was presumed that chalcones 9 could be easily accessed via a Claisen-Schmidt aldol condensation between benzaldehydes 12 and acetophenones 13[9]Which can be accessed from corresponding aldehydes by Grignard Reaction followed by oxidation.

In actual synthesis, we began with commonly needed aldehyde from commercially available starting material 1,3,5-trimethyl benzene (12) by Vilsmeier-Haack reaction in 96% yield (Scheme 2).



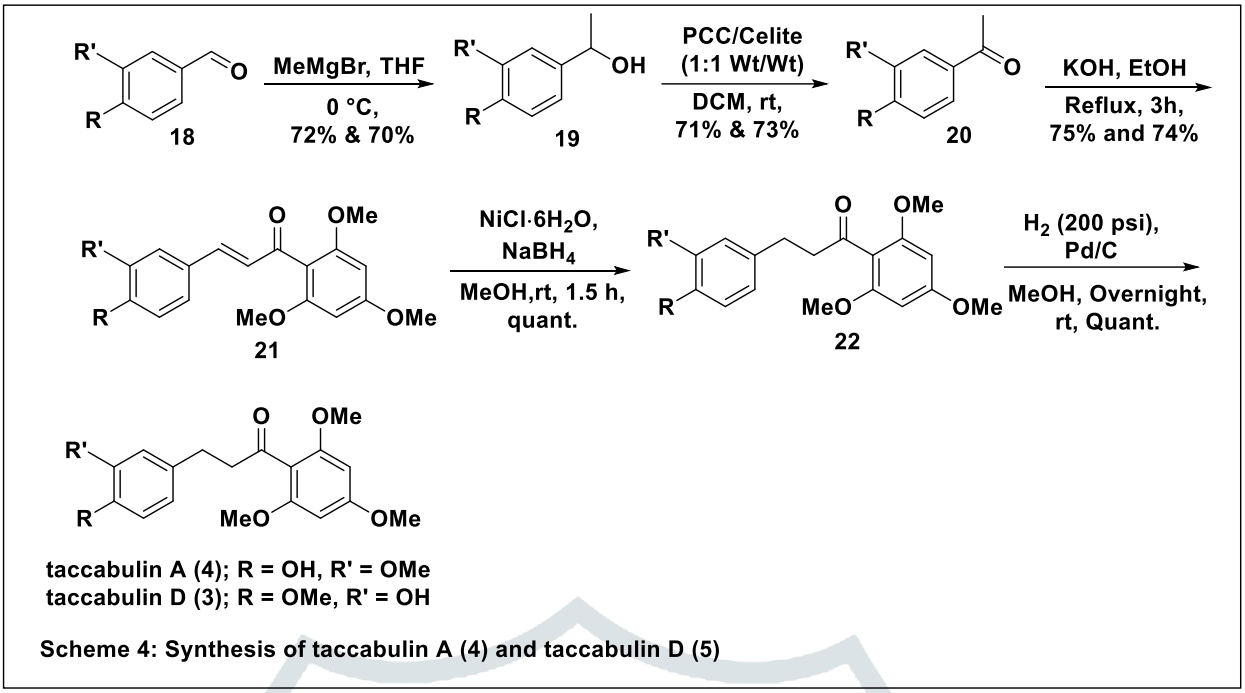
Scheme 2: Synthesis of 2,4,6-trimethoxybenzaldehyde (13)

In the synthesis of taccabulin E, we subjected commercially available aldehyde (14) under Grignard condition to obtain secondary alcohol(15) in 79% yield in 3 h. Thus formed alcohol on oxidation with PCC accessed the acetophenone (16) in 78% yield. The acetophenone (16) and Aldehyde (13) under Claisen-Schmidt conditions gave the chalcone (17). This chalcone on iterative olefinic and carbonyl group reduction in presence of catalytic nickel chloride hexahydrate and excess of sodium borohydride afforded the target molecule taccabulin E (5) in 47% overall yield[13] (Scheme 3).



Scheme 3: Synthesis of taccabulin E (5)

The syntheses of taccabulin A(4) and D(3) were achieved in more or less similar manner. In this synthesis benzyl protected vanillin(18a) and isovanillin(18b) were treated with methyl magnesium bromide to give corresponding secondary alcohol (19a &19b) in 77% and 79% yields respectively. Obtained secondary alcohols on oxidation with PCC yielded corresponding acetophenone (20a &20b). Thus obtained compounds 20a& 20b are subjected to Claisen-Schmidt conditions and accessed the chalcone 21a&21b in 78% and 81% yield. These chalcones on olefin reduction[13] followed by benzyl deprotection resulted into the formation of targeted molecule taccabulin A(4) and taccabulin D(5) in 36.4% and 37.8 % overall yields respectively (Scheme 4).



Scheme 4: Synthesis of taccabulin A (4) and taccabulin D (5)

III. CONCLUSION

In summary, the total synthesis of taccabulins A, D and E was accomplished from commercially available starting materials. A concise divergent strategy was employed wherein a common chalcone skeleton was prepared by a Claisen-Schmidt condensation and transformed into the dihydrochalcone. All the final natural products were generated on multimilligram scale, to afford sufficient material for characterisation. The results from this work should yield additional valuable information on the biological capabilities of these compounds. The work reported herein provides an illustrationof the utility of divergent synthesis for the expedient andstep-economical preparation of natural product and their congeners. Theconciseness and flexibility of this divergent route should make itreadily amenable. The synthesis of structurallyrelated unnatural chalcones is currentlyunderway. The results from these investigations, along withthe outcomes of SAR studies, will be reported in duecourse.

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