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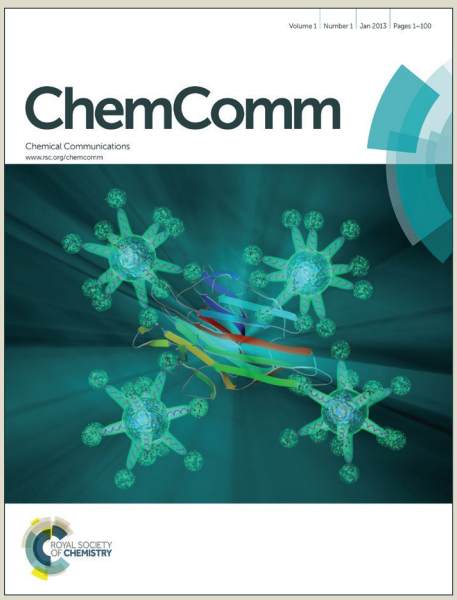

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COMMUNICATION

Protecting Group Free Enantiospecific Total Syntheses of Structurally Diverse Natural Products of Tetrahydrocannabinoid Family

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

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A simple, highly diastereoselective, *Lewis* acid catalyzed Friedel Crafts coupling of cyclic allylic alcohol with resorcinol derivatives has been developed. The method was applied for the enantiospecific total syntheses of structurally diverse natural products such as machaeriol-D, Δ^8-THC, Δ^9-THC, *epi*-perrottetinene and their analogues. Synthesis of both natural products and their enantiomers has been achieved with high atom economy, protecting group free manner and in less than 6 steps longest linear sequence in very good overall yield starting from *R*-(+) and *S*-(-)-limonene.

The ever growing field of total synthesis of natural products continues to be the source of inspiration for many synthetic chemists worldwide.[1-3] Natural product synthesis also plays an important role in developing many areas of modern day biology. Over the century, total synthesis has now reached a stage where within given sufficient time and effort, synthetic chemists are able to construct almost any known natural product in small quantity. However, gram scale synthesis of complex natural products for further biological studies, using minimum number of synthetic transformations, labour and material expenses present significant challenges to organic chemists. Total synthesis in 21st century should be an ideal synthesis[4] starting with readily available, inexpensive starting materials in simple, protecting group free, safe, environmental friendly and cost effective manner, which proceeds quickly and in quantitative yield. In this context, we have developed a simple, short, protecting group free, atom economical and a universal strategy for the synthesis of structurally diverse

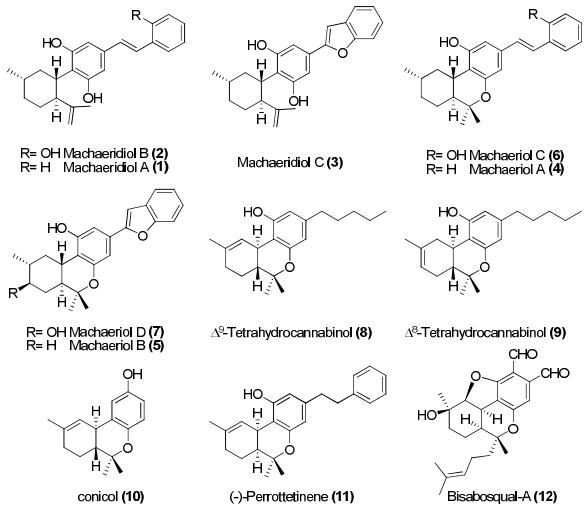

Figure 1. Selected naturally occurring hexahydro-6H-benzo[*c*]-chromenes

natural products and natural product analogues of different classes. We are able to solve several different and difficult problems in complex molecule synthesis by using the simple and well studied reaction, the Friedel-Crafts reaction. Machaeriols are a structurally diverse and biologically potent group of tetrahydrocannabinoids containing linearly fused 6,6,6-tricyclic ring system. Machaeridiol A-C, **1-3**, and Machaeriol A-D, **4-7**, were isolated by Muhammad et al. in 2003, from the stem bark of *Machaerium multiflorum spruce*.[5] The first member of this family, Δ^9-trans-tetrahydrocannabinol **8** (Δ^9-THC) was isolated from *Cannabis sativa var. indica* in

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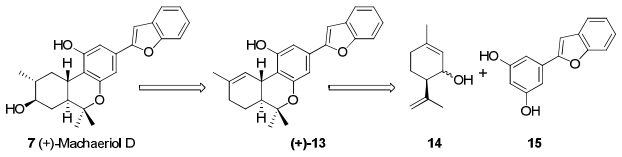
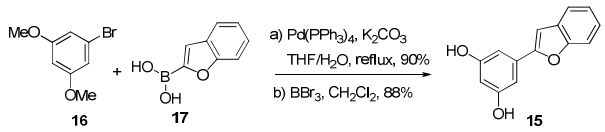
1964.[6] Subsequently, several additional cannabinoids, such as Δ^8-trans-THC **9**,[7] conical **10**,[8] perrottetinene **11**,[9] bisabosqual-A **12**[10] have been isolated and structurally characterized. Since its isolation Δ^9-THC, Δ^8-THC and related tetrahydrocannabinols are among the most highly sought synthetic targets.[11] Recently research groups of She and Pan have reported elegant approach for the first enantioselective total synthesis of (+)-machaeriol-D **7** using S_N2' reaction as a key step with longest linear sequence of 18 steps.[12] Herein we report atom economic, protecting group free six step total synthesis of both the enantiomers of machaeriol-D **7** facilitated by newly developed methodology for one pot C-C and C-O bond formation and a strategic effort to avoid the use of protecting group and expensive reagents.

It was envisioned that machaeriol-D **7** could be synthesized from compound **13** by allylic oxidation and further diastereoselective double bond reduction. Compound **13** in turn could be prepared from coupling of allylic alcohol **14** and electron rich aromatic moiety **15** by concomitant formation of C-C and C-O bonds. So our strategy was based on well studied Friedel-Crafts reaction but in modified way which is unprecedented in literature.

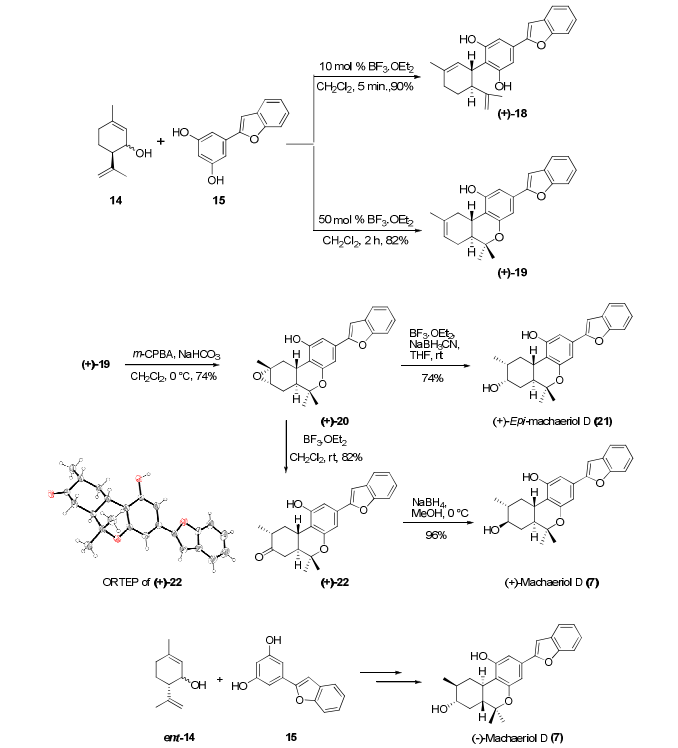


Scheme 1. Retrosynthetic analysis for machaeriol-D



Scheme 2. Synthesis of precursor 15

To begin with, compound **15** was prepared using known two step protocol by Suzuki coupling of compound **16** and **17** followed by demethylation (*Scheme* 2). Allylic alcohol **14** was obtained from limonene by allylic oxidation followed by reduction of the ketone thus formed (See supporting). After having key coupling partners in the hand, various acids were screened such as p-TSA, TFA, $BF_3{\cdot}OEt_2$, $AlCl_3$, $InCl_3$ for coupling reaction. Among these $BF_3{\cdot}OEt_2$ was found to be best catalyst for the cyclization reaction. Compound **15** and allylic alcohol **14** were merged without protecting groups using 10 mol% $BF_3{\cdot}OEt_2$ to furnish compound **18** as a single diastereomer in 90% isolated yield in just 5 min. at room temperature. Excellent diastereoselectivity was observed possibly due to the adjacent bulkier isopropenyl group[13]. Interestingly when 50 mol% of $BF_3{\cdot}OEt_2$ was used and reaction allowed to stir for 2 hrs, we also observed formation of pyran ring along with isomerization of double bond to generate the core of machaeriol-D **19**. It is presumed that double bond isomerisation might be due to the thermodynamic stability of compound **19** over **13**. *m*-CPBA mediated epoxidation of double bond in compound **19** generated the epoxide **20** in 74% yield as a single diastereoisomer. At this stage we could not assign the stereochemistry of epoxide. Regioselective opening of epoxide using combination of $NaBH_3CN$ and $BF_3{\cdot}OEt_2$ generated the compound **21**, whose ^1H and ^{13}C data were not matching with machaeriol-D **7**. This made us to realize that epoxidation has occurred from the α-face. Interestingly $BF_3{\cdot}OEt_2$ catalyzed semipinacol rearrangement[14] of epoxide generated the ketone **22** in 82% yield as a single diastereoisomer. The structure and stereochemistry of ketone **22** was established by single crystal X-ray analysis.[15] Reduction of ketone **22** using $NaBH_4$ at 0 °C furnished the natural product (+)-machaeriol-D **7** in 96% yield.



Scheme 3. Total Synthesis of (+) and (-)-Machaeriol-D and *epi*-machaeriol-D

When $NaBH_4$ reduction was carried out at room temperature, minor amount (6%) of other diastereomer was observed, whose spectral data was identical with compound **21** obtained from epoxide **20** by reductive epoxide opening. This further confirms the stereochemistry of epoxide **20** and *epi*-machaeriol **21**. So in six simple steps from *S*-(-)-limonene, (+)-machaeriol-D is now accessible in large quantities via direct coupling of alcohol **14** and resorcinol derivative **15**. Similarly (-)-machaeriol-D **7** was synthesized starting from *R*-(+)-limonene. On the way, we have also accomplished the one pot total synthesis of (+) and (-)-Δ^9-THC **8**, (+) and (-)-Δ^8-THC **9**, *epi*-perrottetinene **23** and their analogues as shown in *Scheme 4*.

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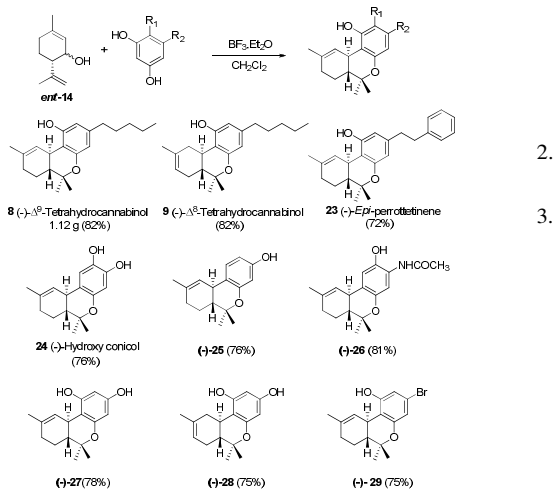

Scheme 4. Synthesis of analogues of tetrahydrocannabinols

Independent coupling of alcohol **14** and *ent*-**14** with olivetol furnished both the enantiomers of Δ^8- and Δ^9-THC. Furthermore, this reaction was robust and was conducted on a gram-scale synthesis of Δ^9-THC yielding 1.12 g of it. Coupling of alcohol **14** with various resorcinol derivatives generated half a dozen congeners of tetrahydrocannabinols **23-29**. Although till date many syntheses of Δ^9- THC are reported in literature, to best of our knowledge, only one synthesis each of Δ^8-THC **9**,[16] conicol **10**,[17] perrottetinene **11**[18] and *epi*-perrottetinene **23**[18] are reported in literature.

Conclusions

Using a simple strategy we have achieved enantiospecific total syntheses of structurally diverse natural products isolated from different sources and having wide range of biological activities. Synthesis of both natural products and their enantiomers has been achieved in highly atom economical, protecting group free and in less than 6 steps longest linear sequence starting from *R*-(+) and *S*-(-)-limonene. Finally it is worth mentioning that with a good strategy, even the Friedel-Crafts reaction can help solve total synthesis problems that have either not yet been solved or have required many steps through other routes.

We thank Prof. Viresh H. Rawal, University of Chicago, for his suggestions and comments to improve the manuscript substantially. We thank Mr. Dipankar Sahoo and Prosenjit Daw for crystal structures. R. D. E., S. D. and V. K. thank CSIR, New Delhi, and S. M. thanks UGC, New Delhi, for the award of research fellowship. Financial support from IIT Kanpur and DST, New Delhi (SB/S_1/OC-01/2014) is gratefully acknowledged.

Notes and references

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† Electronic supplementary information (ESI) available. CCDC 1017678 (**+22**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000000x/

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