Efforts Towards The Total Synthesis Of Dichocetide C

In partial fulfilment for the requirement for the degree of

Master of Science

By

Shovan Debsarma

(Roll No. CY17MSCST11021)

Under The Supervision Of:

Prof. Faiz Ahmed Khan

Department Of Chemistry

Indian Institute Of Technology Hyderabad

Declaration

I declare that this written submission represents my ideas in my own words, and where others' ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be a cause for disciplinary action by the Institute and can also evoke penal action from the sources that have thus not been properly cited, or from whom proper permission has not been taken when needed.

(Signature of supervisor)

Shovan Debsarma.

(Shovan Debsarma)

(cy17mscst11021)

Approval Sheet

This thesis entitled **Efforts towards the total synthesis of Dichocetide C** by **Shovan Debsarma** is approved for the degree of Master of Science from IIT Hyderabad.

Prof. G. Satyanarayana
Professor
Department of Chemistry
Examiner

Dr Ashutosh Kumar Mishra
Assistant professor
Department of Chemistry
Examiner

Prof. F.A. Khan
Professor
Department of Chemistry
Supervisor

ACKNOWLEDGEMENT:

I wholeheartedly express my immense respect and deep sense of gratitude to my project supervisor **Prof. Faiz Ahmed Khan**, whose excellent guidance resulted in this piece of work. I am greatly fortunate to have a teacher like him for the work freedom he has given, helped me to learn a number of new things, which otherwise would have been very difficult for me. I am greatly indebted to him for teaching me and also want to take the opportunity to thank him heartedly for bestowing me of chemistry and moral values of the life. I am also thankful to Prof. G Satyanarayana, Dr. Ashutosh Kumar Mishra, Dr. Vekata Rao Kotagiri and Dr. D S Sharada for their evaluation of my project work and sincere discussions.

I also want to thank the all lab members in the research group, who always support and give suggestions for research. I am also grateful to Department of Chemistry, IIT Hyderabad for giving this opportunity.

SHOVAN DEBSARMA

(CY17MSCST11021)

Contents:

1. Abstract
2. Introduction
3. Results and Discussions
4. Experimental Section
5. Conclusion
6. References
7. Spectral DATAs

Abbreviations Used:

- **THF=** Tetrahydro Furan
- **EtOAc=** Ethyl Acetate
- **NaHMDS=** Sodium bis(trimethylsilyl)amide
- **TLC=** Thin Layer Chromatography
- **DCM=** Dichloro methane

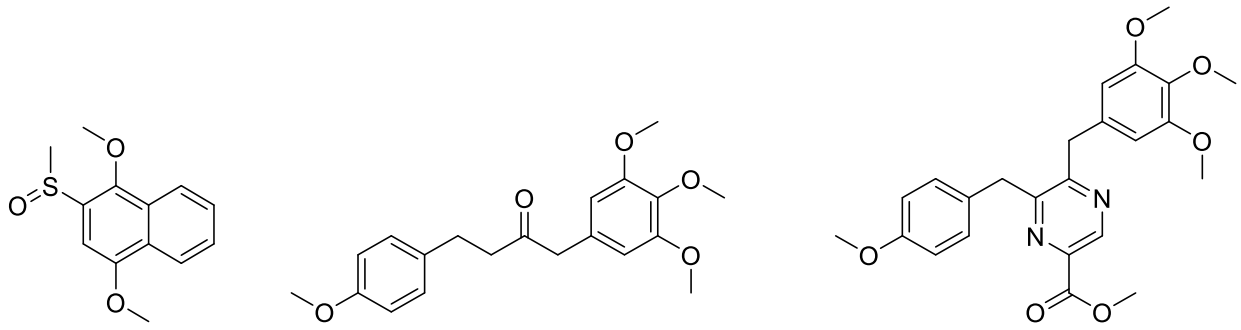
1. Abstract:

The attempts towards the synthesis of the fragments for total synthesis of Dichocetide C has been reported by two retrosynthetic approaches. First retrosynthetic approach involves reduction of aldehyde to alcohol, bromination of alcohol by appel reaction, hydrogenation of alkene bond and organomagnesium, organozinc and organolithium reactions. Second retrosynthesis approach involves one carbon homologation reaction of aldehydes by Wittig reaction followed by hydrolysis, reduction of aldehyde to alcohol, bromination of alcohol and Grignard reaction. Unfortunately the schemes were failed, the synthesis of the retrons is reported.

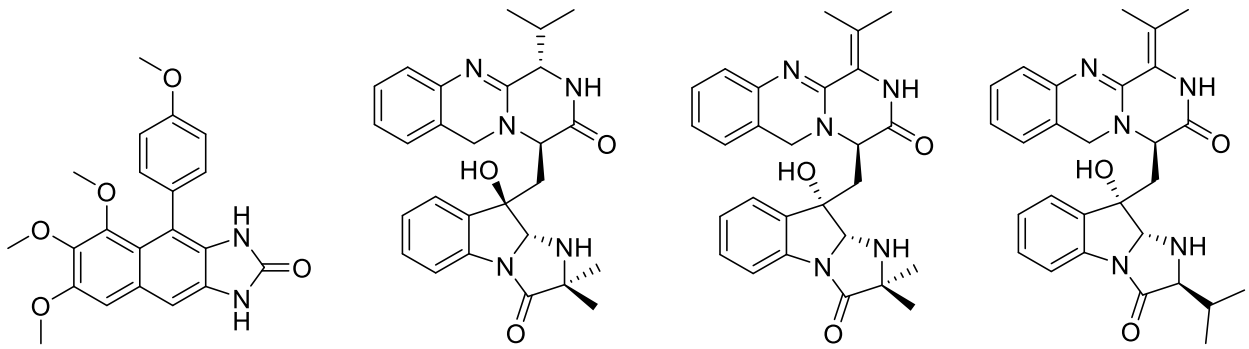
2. Introduction:

Marine derived organisms are very interesting to the organic chemists because they are very important to get new functionalized natural products with various diversed biological activities. Dichocetide C was discovered from the cultural broth of the fungal strain *Dichotomomyces cejpii* F31-1 by ***Lan et al***, who isolated *Dichotomomyces cejpii* F31-1 from the soft coral *Lobophytum crassum.* Lobophytum is a genus of soft coral which is generally found in a wide area of the tropical Indo-Pacific. From the cultural broth, twenty eight diverse compounds were obtained[(2)]. Three known fumiquinazoline: scequinadoline A(**5**), quinadoline A(**6**), and scequinadoline E(**7**) have been isolated by isolation and purification. Two new polyketides dichocetide B and C (**1 and 2**) and two new alkaloids dichotomocejs E and F (**3 and 4**), were discovered from the cultural broth along with these fumiquinazolines.[(1)]

Figure 1. Natural products which are discovered from the cultural broth of *Dichotomomyces cejpii* F31-1 by the group *Lan et al* [(1)]:



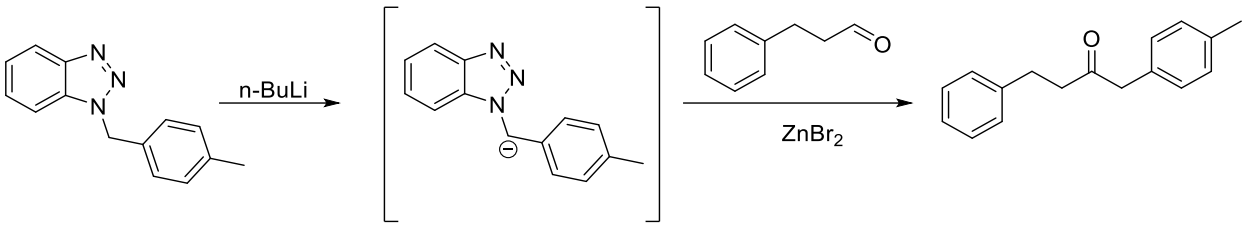
1 Dichocetide B **2** Dichocetide C **3** Dichotomocej E



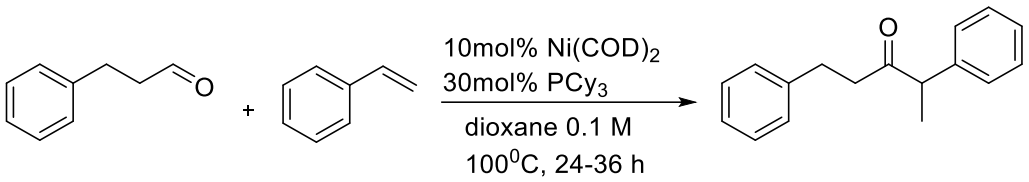
4 Dichotomocej F **5** Scequinadoline A **6** Quinadoline A **7** Scequinadoline E

Dichocetide C **(2)** is an alpha aryl ketone where two benzene rings are connected with an aliphatic chain consisting four carbon atoms. A $CH_2CH_2COCH_2$ chain interlinks between para substituted and 1,3,4,5- tetrasubstituted benzene rings. The synthesis of the core structure of Dichocetide C (i.e. 1,4-diphenylbutan-2-one) with different substitutents has been reported by various ways:

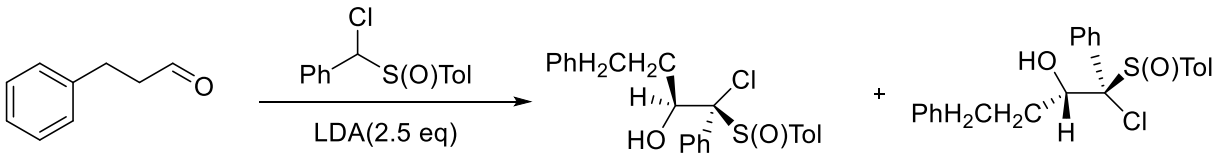
(1) By benzotriazole stabilized carbanion insertion to 3-phenylpropanal by ***Katritzky et al***[3]:

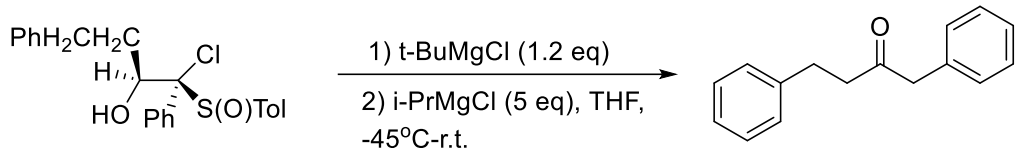


(2) By nickel-catalyzed hydroacylation of styrenes with 3-phenylpropanal by ***Zhou et al***[4]:



(3) By β-oxido carbenoid rearrangement by ***S Fukuda et al***[5]:





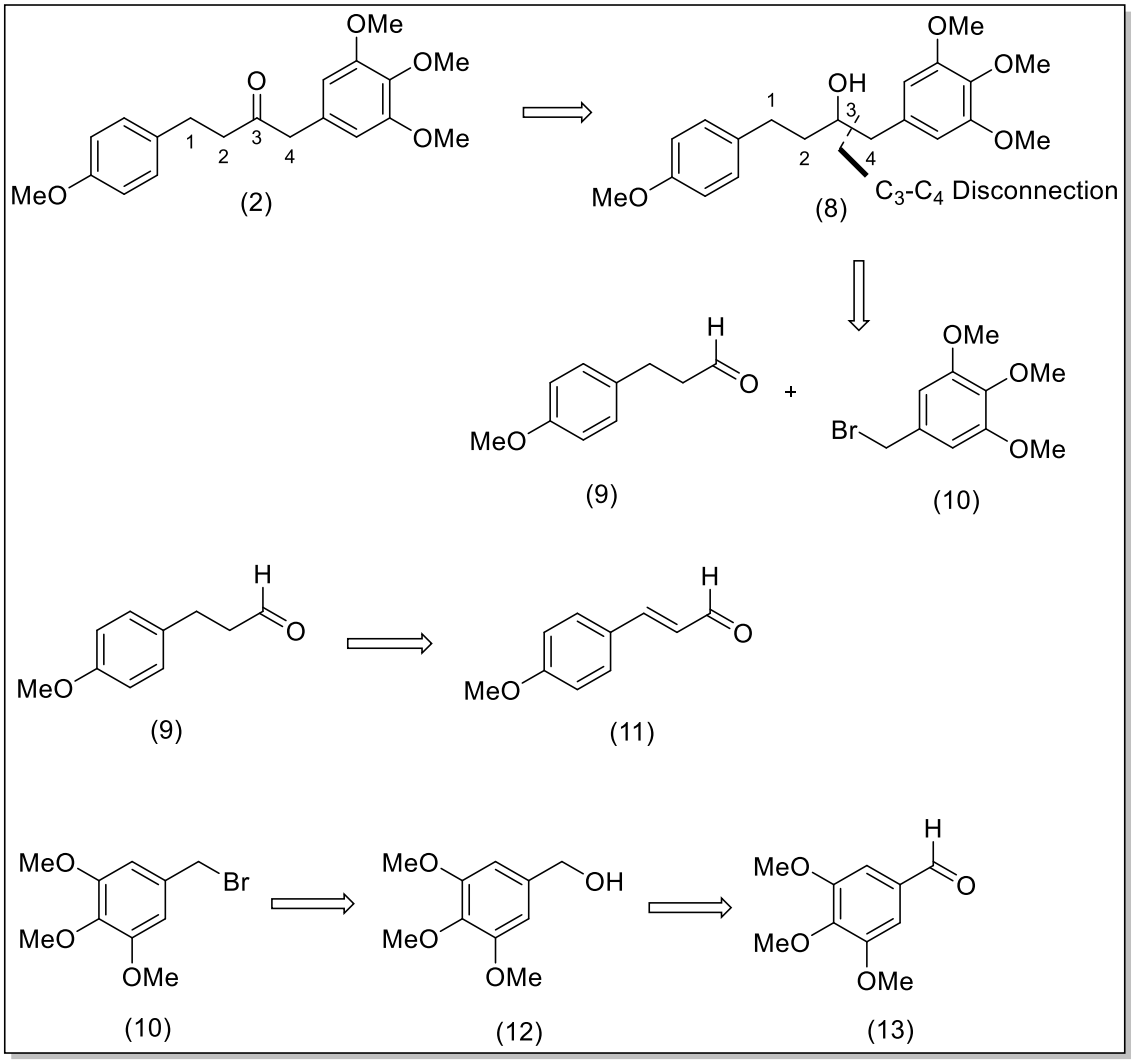
In this work, some new strategies are taken to synthesize the target molecule Dichocetide C, which is a derivative of the core structure 1,4-diphenylbutan-2-one.

The synthetic strategies of the target molecule is as follows:

The retrosynthetic approach of the target molecule has been classified into two schemes: one is C_3-C_4 bond disconnection **(Scheme 1A)** and another is C_2-C_3 bond disconnection approach

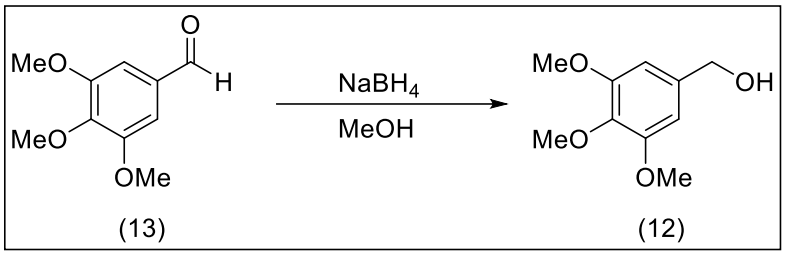
(Scheme 2A). According to Scheme 1A and Scheme 2A, forwarded reactions are also planned **(Scheme 1B** and **Scheme 2B** respectively**)**

Scheme 1A. Retrosynthetic approach of Dichocetide C by C_3-C_4 bond disconnection:

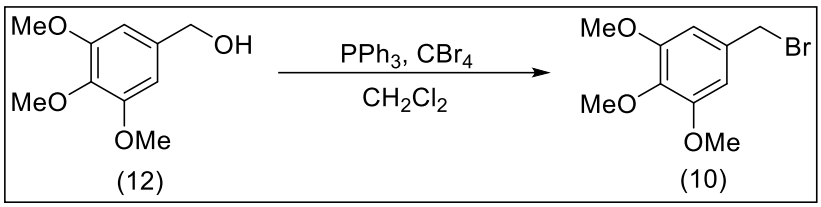


Scheme 1B. Planned step by step forward reactions according to the previous retrosynthesis approach:

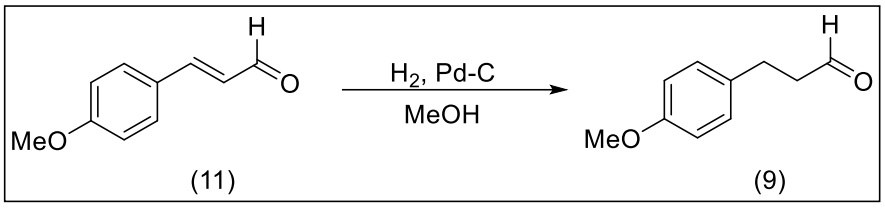
Step-1: Reduction of **13** by $NaBH_4$ in methanol to give **12**:[6]



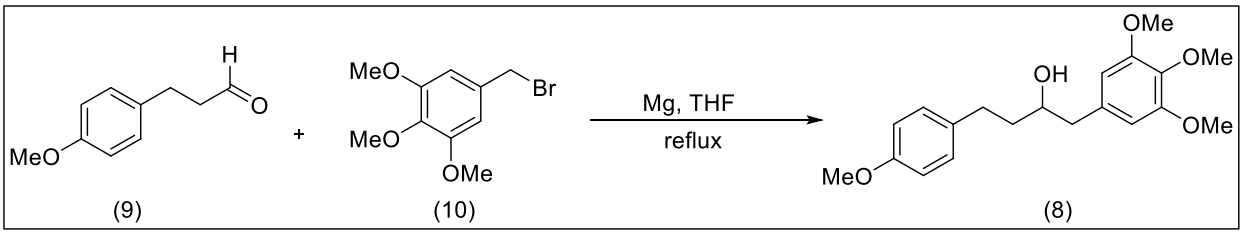
Step-2: *Appel reaction* of **12** to give **10**:[7]



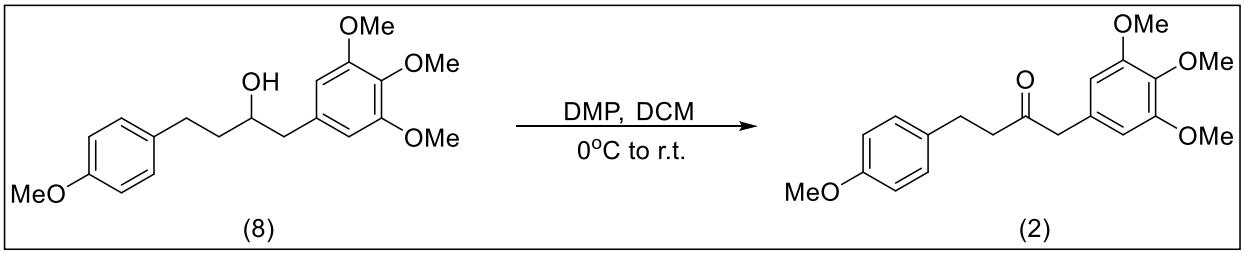
Step-3: C=C reduction of **11** to give **9**:[8]



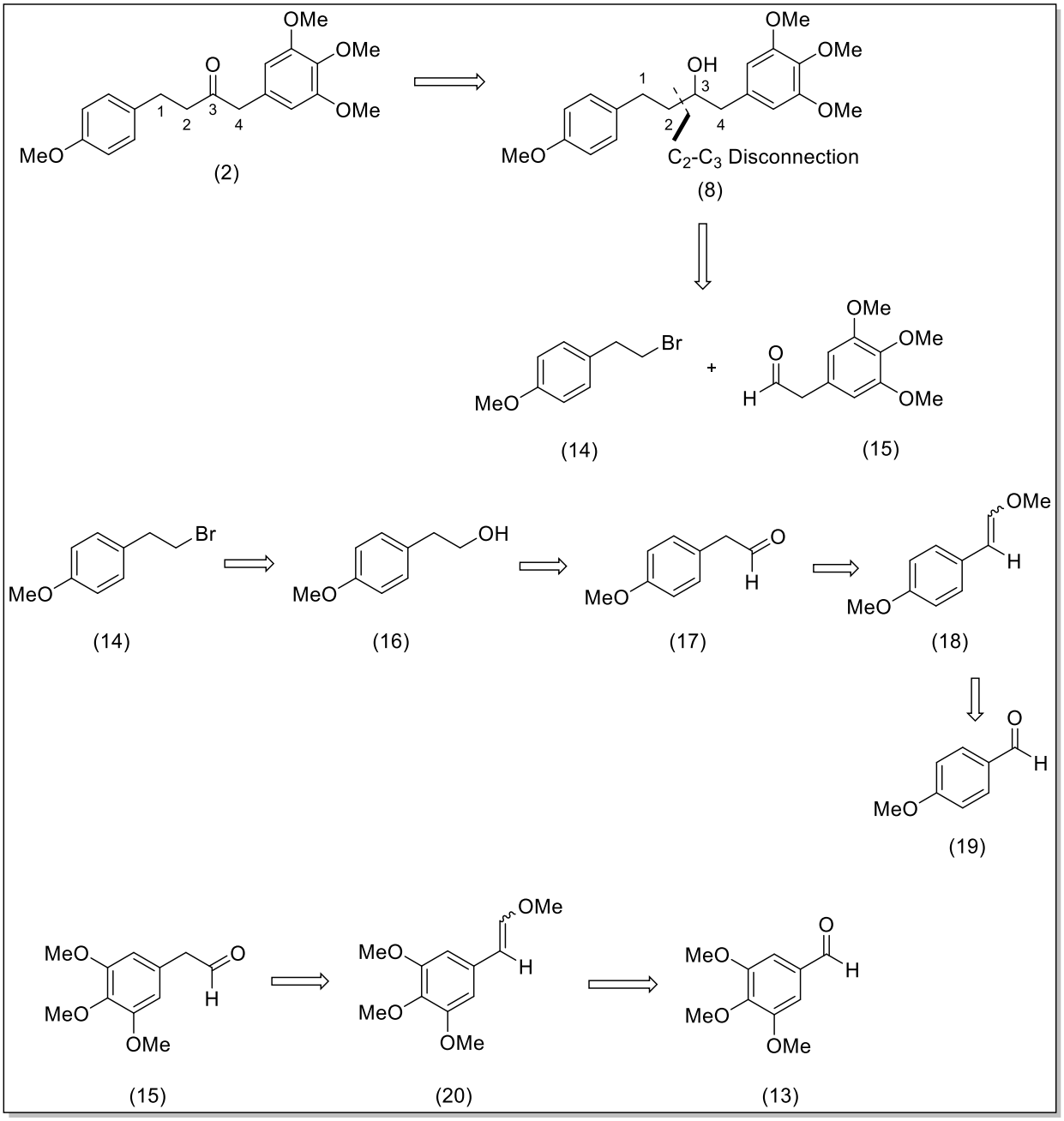
Step-4: Grignard Reaction between **10** and **9** to give **8**:[9]



Step-5: Oxidation of **8** to give **2**:[10]

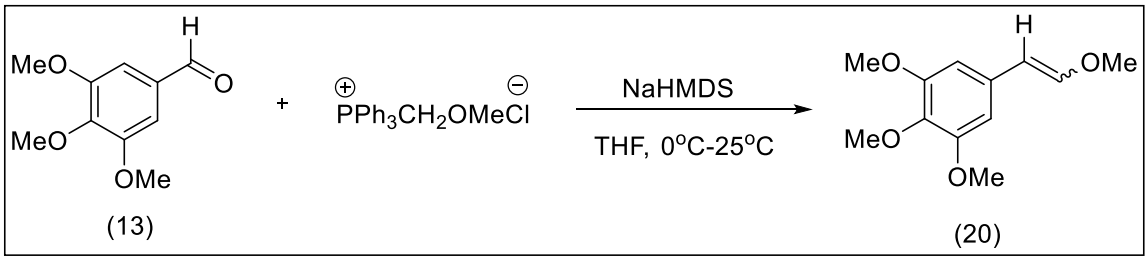


Scheme 2A. Retrosynthetic approach of Dichocetide C by C_2-C_3 bond disconnection:

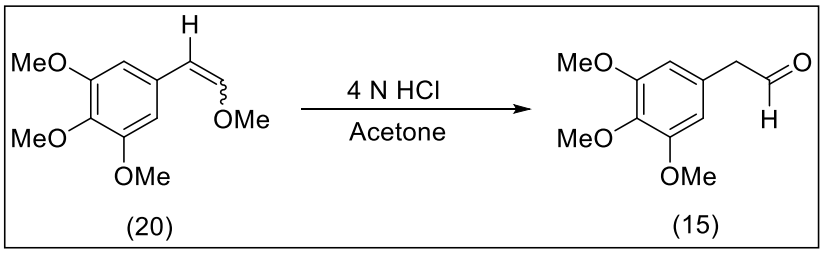


Scheme 2B. Planned step by step forward reactions according to the previous retrosynthesis approach:

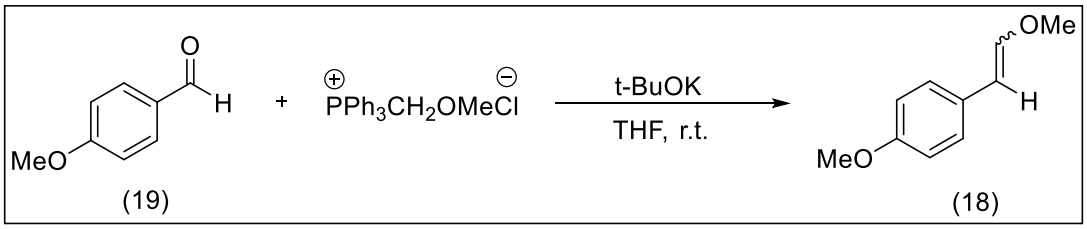
Step-1: Synthesis of enol-ether **20** by *Wittig reaction* from the aldehyde **13**: [11]



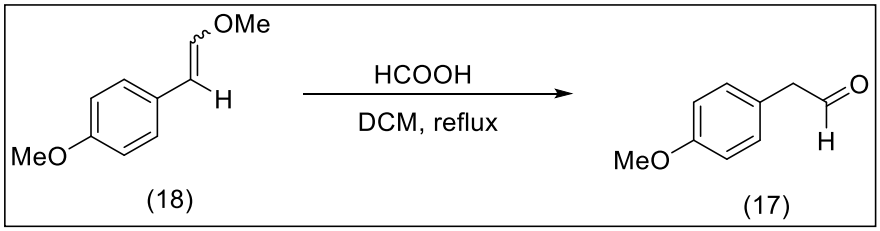
Step-2: Hydrolysis of **20** to synthesize **15**: [11]



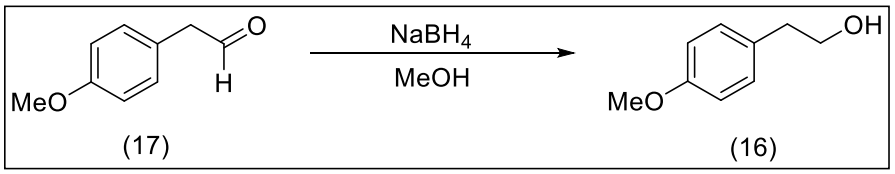
Step-3: Synthesis of enol-ether **18** by *Wittig reaction* from the aldehyde **19**: [12]



Step-4: Hydrolysis of **18** to synthesize **17**: [12]

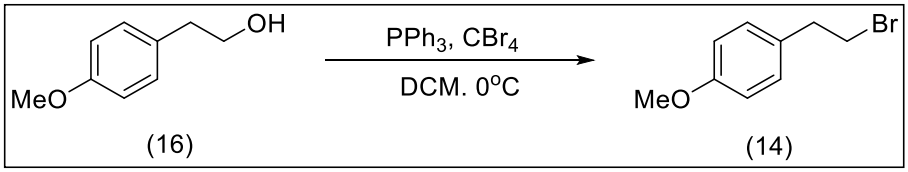


Step-5: Reduction of **17** by $NaBH_4$ to give **16**: [13]



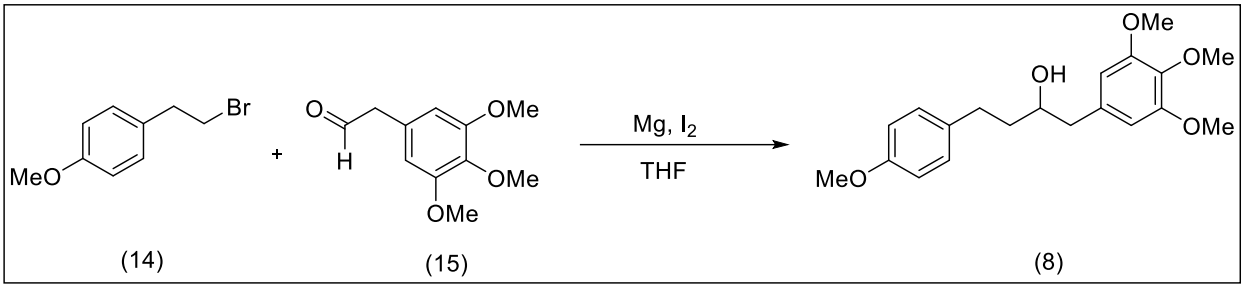
(17) (16)

Step-6: *Appel reaction* of **16** to synthesize **14**: [14]



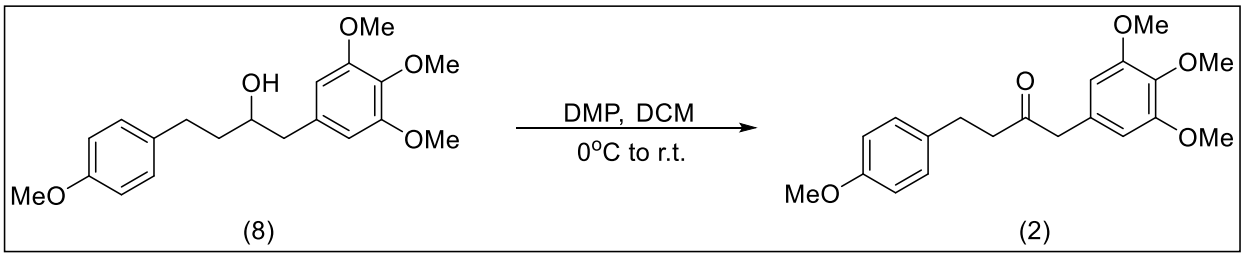
(16) (14)

Step-7: *Grignard* reaction between **14** and **15** to synthesize **8**:



(14) (15) (8)

Step-8: Oxidation of **8** to synthesize **2**: [10]



(8) (2)

3. **Results and Discussions:**

According to **Scheme 1A** and **Scheme 1B,**

3,4,5-Trimethoxybenzyl alcohol **12** was synthesized from the commercially available *3,4,5-trimethoxybenzaldehyde* **13**, by reduction with Sodium Borohydride in methanol. **12** was further used for so called Appel reaction to form *3,4,5-trimethoxybenzyl bromide* **10**. **10** was kept as one fragment to initiate the Grignard reaction with *3-(4-methoxyphenyl)propanal* **9. 9** was synthesized from commercially available *4-methoxycinnamaldehyde* **11,** by H_2 reduction in presence of Pd-C as catalyst.

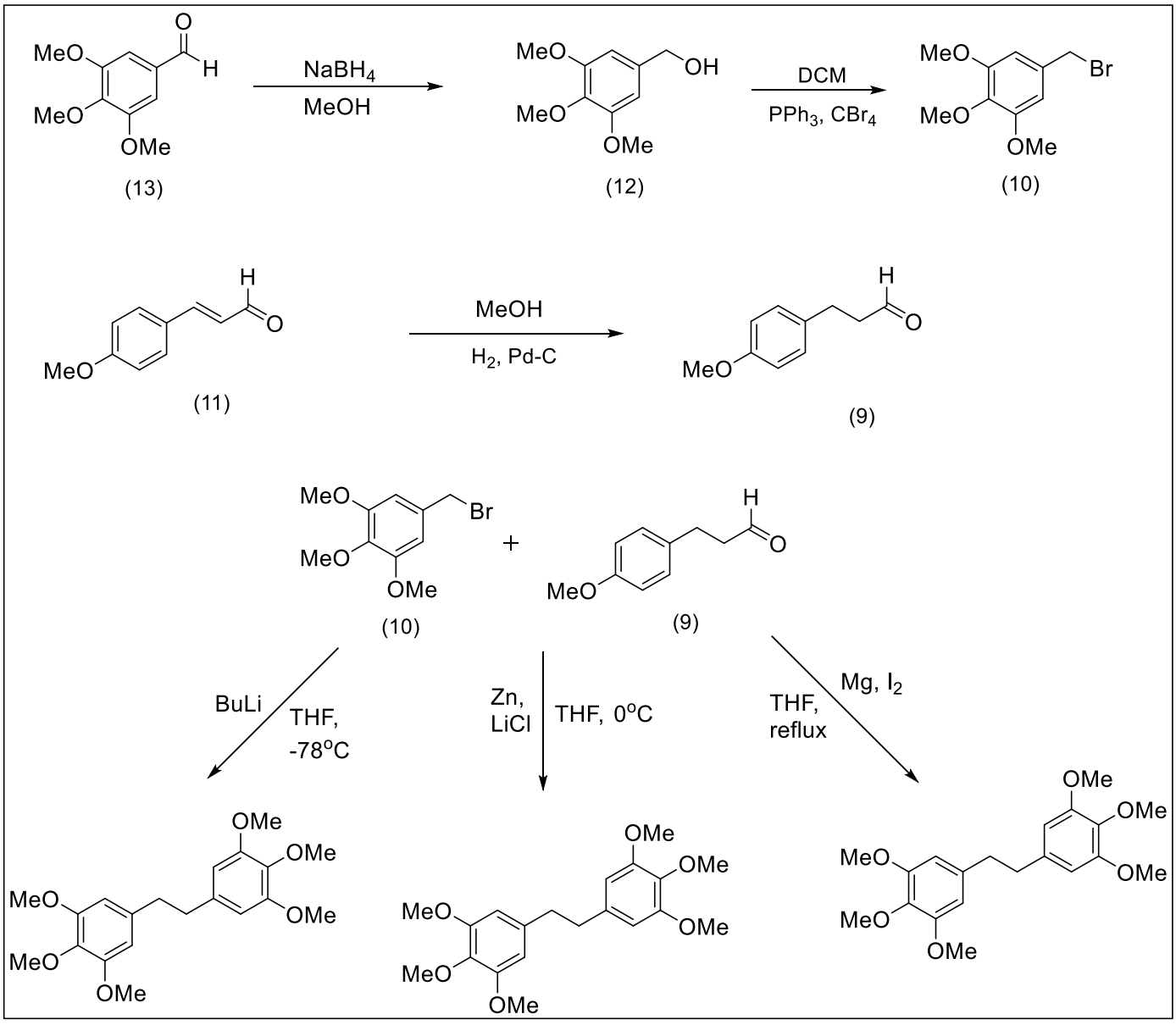
Synthesis of **12** and **9** was previously reported. The same reactions were performed to synthesize the strating materials.

During the Grignard reaction between **9** and **10**, at room temperature, the Grignard reagent was not generating neither in diethyl ether nor in THF medium. At elevated temperature, during refluxing the system at 80^{o}C in THF medium, the Grignard reagent was generating but again and again it was giving the dimerized product of **10.**

By formation of benzylic zinc bromide reagent of **10** in presence of LiCl, and followed by nucleophilic attack to the electrophile **9**, was also failed as here also, **10** was forming dimerized product at 0^{o}C.[15]

After the failure of these two paths, the reaction with organo lithium reagent has been tried in presence of BuLi at -78^{o}C in THF. In this case also, dimerized product of **10** has been obtained[16] **(Scheme 3).**

Scheme 3. Strating Materials Preaparation according to scheme 1A and scheme 1B and formation of dimerised product as end-product:

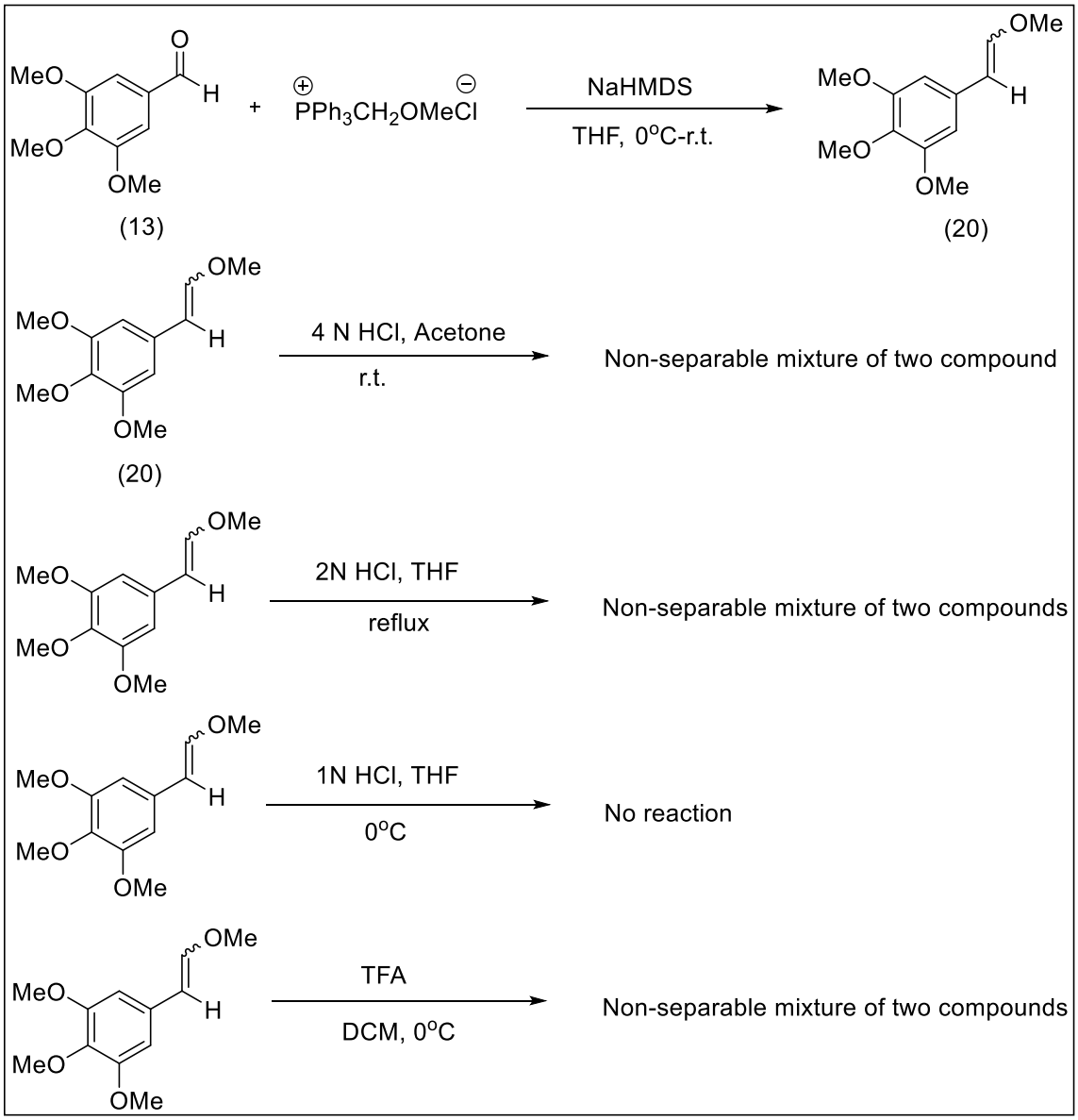


According to **Scheme 2A** and **Scheme 2B,**

1,2,3-trimethoxy-5-(2-methoxyvinyl)benzene **20** was synthesized from commercially available *3,4,5-trimethoxybenzaldehyde* **13,** using mom-Wittig salt $^{+}PPh_3CH_2OMeCl^{-}$ in presence of a base NaHMDS. **20** was isolated as E and Z mixture.

During the hydrolysis of **20** in different conditions, e.g. 4N HCl in Acetone, 2N HCl in THF, TFA in DCM etc, a non-separable mixture has been found **(Scheme 4).**

Scheme 4.

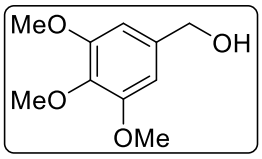


4. Experimental Section:

General Methods:

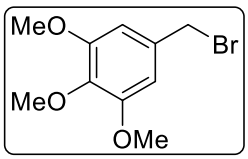
All reactions were performed in oven dried apparatus. Commercial grade solvents were distilled before use. For Grignard reaction, THF and diethyl ether were highly dried for Grignard reaction. THF was dried in Stille Apparatus. Melting point is recorded in open capillary. ^{1}H NMR is recorded in 400MHz machine. Proton decoupled ^{13}C NMR spectra is recorded in 100 MHz. Chemicals are bought from standard vendors like Avra Chemicals, Alfa Aesar, Sigma Aldrich, SRL Chemicals etc.

3,4,5-trimethoxybenzyl alcohol (12).



To a stirred solution of **13** (500 mg, 2.548 mmol) in 5 ml Methanol, Sodium borohydride ($NaBH_4$) was added portionwise (145 mg, 37.83 mmol) at 0^oC. After the completion of reaction after 1h (monitored by TLC), MeOH was evaporated under *vacuo*, then the reaction mixture was extracted by EtOAc-H_2O (1:1) mixture (10 ml: 10ml). Then the reaction was washed with Brine, dried over Na_2SO_4 and concentrated over reduced pressure. The residue was purified over 60-120 silica gel column chromatography using 60% EtOAc in Hexane. Upon purification, it gave **12** (464 mg, 92%) as a viscous liquid.

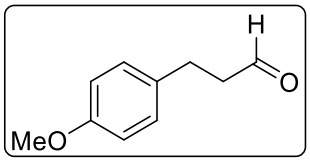
3,4,5-trimethoxybenzyl bromide (10).



To a stirred solution of **12** (2.0 g, 10.08 mmol) and CBr_4 (5.019 g, 20.18 mmol) in 20 ml DCM, PPh_3 (5.293 g, 15.135 mmol) was added at 0^oC. After the completion of reaction after 1h (monitored by TLC), the reaction mixture was thoroughly washed with 1:1 Hexane-Et_2O solution and solvent was evaporated under *vacuo*.

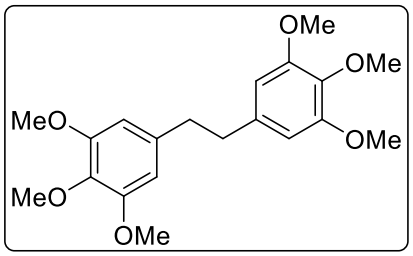
The residue was purified over 60-120 silica gel column chromatography by 8% EtOAc in Hexane. Upon purification, it gave **10** (1.391 g, 53.02%) as a white crystalline solid, m.p. 59-62^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 2H), δ 4.45 (s, 2H), δ 3.85 (s, 6H), δ 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.29, 133.19, 106.14, 60.86, 56.14, 34.29.

3-(4-methoxyphenyl)propanal (9).



The suspension of **10** (2.0 g, 12.33 mmol) and Pd-C (162 mg, 1.52 mmol) in 20 ml Methanol was stirred under H_2 atmosphere (using H_2 balloon). After the completion of reaction after 4h (monitored by TLC), the MeOH was evaporated under *vacuo*. The crude was filtered on Celite by EtOAc. Then EtOAc was evaporated and the residue was purified over 60-120 silica gel column chromatography by 8% EtOAc in Hexane. **9** was isolated as colourless liquid (1.838 g, 93.20%).

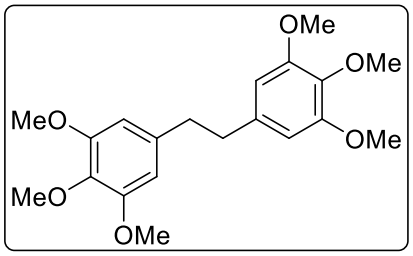
Grignard Reaction between 9 and 10: Formation of Dimerized product of 10.



To the oven dried two necked round bottomed flask, Mg turnings (29.232 mg, 1.218 mmol) was added and was activated by I_2. In that r.b., **10** (477.05mg, 3 eq)**,** dissolved in 2mL freshly dried THF, is added and kept for reflux at 80^{o}C. After 40-50 mins, all Mg turnings had been dissolved. Keeping it at 0^{o}C, **9** (100 mg, 0.609 mmol) was added. The reaction was kept for 3 hrs. After the completion of reaction, the reaction was quenched with EtOAc, washed with water. Then the reaction mixture was extracted with EtOAc (10ml), washed with brine, dried over Na_2SO_4. EtOAc was evaporated under *vacuo*. The residue was purified over 60-120 silica gel column chromatography with 15% EtOAc in Hexane mixture. After purification the dimerized product of **10** was found (162 mg, 77.14%) as white solid. ^{1}H NMR (400 MHz,

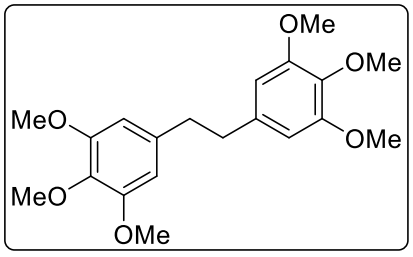
$CDCl_3$) δ 6.36 (s, 4H), δ 3.83 (s, 18H), δ 2.85 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.06, 137.34, 136.25, 105.51, 60.87, 56.07, 38.43.

Benzylic Zinc Bromide Reagent of 10 formation reaction: Formation of dimerized product of 10.



In an oven-dried two necked r.b., activated Zn (49.689 mg, 0.760 mmol) & LiCl (32.219 mg, 0.760 mmol) were added. After then, 3mL highly dried THF was added and stirred for a few minutes. Then **10** (119.32 mg, 0.456 mmol) was added and stirred for 3 hrs. Then **9** (50 mg, 0.304 mmol), dissolved in dry THF was added and stirred for 6 hrs. After completion of reaction, the reaction was quenched with EtOAc and was extracted with EtOAc and water. Washed with Brine and dried over Na_2SO_4. EtOAc was evaporated under *vacuo.* The residue was purified over 60-120 silica gel column chromatography with 15% EtOAc in hexane mixture. After purification, dimerized product of 10 was got, which was checked by the authentic in TLC (R_f = 0.2 in 10% EtOAc-Hexane).

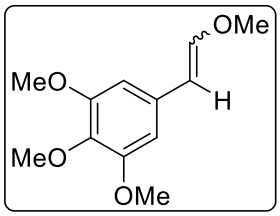
Preparation of organolithium reagent and formation of 10 and formation of dimerized product of 10.



In an oven dried two necked r.b., cooled under nitrogen, 10 (500 mg, 1.91 mmol) was taken and dissolved in purely dried THF. The system was taken at -78oC in Julabo and BuLi (1.5 ml, 2.2 mmol) was added dropwise. After stirring for 30 mins, 9 (328.40 mg, 2.00 mmol) dissolved in dry THF was added dropwise. The reaction was kept for stirring for 2 hrs. The progress of reaction was monitored by TLC. During checking TLC, the

product was checked with the authentic of the dimerized product of 10, but they came in the same R_f value in TLC (0.2 in 10% EtOAc-Hexane).

1,2,3-trimethoxy-5-(2-methoxyvinyl)benzene (20).



In an oven dried two neck r.b., Mom Wittig salt $^{+}PPh_3CH_2OMeCl^{-}$ (2620.71 mg, 7.645 mmol) was taken and dissolved in THF at 0^{o}C. After 5 mins of stirring, NaHMDS (7.6 ml, 7.645 mmol) was added dropwise and kept in stirring for 45 mins. After the formation of a deep red colour, **13** (1000 mg, 5.097 mmol)**,** dissolved in THF. was added dropwise and the reaction was kept for 3 hrs. The completion of the reaction was monitored by TLC. The reaction was quenched by satd. NH_4Cl solution and extracted with EtOAc-H_2O mixture, washed with Brine, and dried over Na_2SO_4. EtOAc was evaporated under *vacuo.* The residue was purified 60-120 silica gel column chromatography with 10% EtOAc-hexane mixture. After purification, **20** was got (998 mg, 95%) as a white low melting solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 6.98 (d, J= 12.84 Hz, 1H), 6.84 (s, 2H), 6.45 (s, 2H), 6.10 (d, J= 7.08 Hz, 1H), 5.75 (d, J= 12.92 Hz, 1H), 5.15 (d, J= 7.12 Hz, 1H), 3.86 (s, 6H), 3.86 (s,6H), 3.83 (s,3H), 3.78 (s, 3H), 3.68 (s,6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.8, 148.6, 147.5, 136.3, 132.1, 131.5, 105.6, 105.5, 105.1, 102.2, 60.9, 60.8, 60.7, 56.5, 56.0, 56.05, 56.01.

5. Conclusion:

During synthesis of Dichocetide C by two retrosynthetic approaches, first retrosynthetic path was five steps process, but after step 4, dimerized product had been formed and the corresponding scheme had been failed. Second retrosynthetic path consists of eight steps, but during second step, i.e. hydrolysis of enol ether gives the nonseparable mixture of two products. In this case also, the scheme is failed.

6. References:

1. Chen, Y.; Xu, M.; Li, H.; Zeng, K.; Ma, W.; Tian, G.; Xu, J.; Yang, D.; Lan, W. *Mar. Drugs* **2017**, *15*, 339-352
2. Wu, D.; Li, H.; Smith, D.; Jaratsittisin, J.; Ma, W.; Guo, Y.; Dong, J.; Shen, J.; Yang, D.; Lan, W. *Mar. Drugs*, **2018**, *16*, 229-239
3. Katritzky, A.; Xie, L.; Toader, D.; Serdyuk, L. *J. Am. Chem. Soc.* **1995**, *117*, 12015-12016
4. Xiao, L.; Fu, X-N.; Zhou, M-J.; Xie, J-H.; Wang, L-X.; Xu, X-F.; Zhou, Q-L. *J. Am. Chem. Soc.* **2016**, *138*, 2957−2960
5. Fukuda, S.; Tsuji, K.; Musashi, J.; Nonaka, R.; Kimura, T.; Satoh, T. *Synthesis*, **2011**, 22, 3615-3626
6. Mace, Y.; Bony, E.; Delvaux, D.; Pinto, A.; Mathieu, V.; Kiss, R.; Feron, O.; Quetin-Leclercq, J.; Riant, O. *Med Chem Res*, **2015**, *24*, 3143-3156
7. Garofalo, A.; Parat, A.; Bordeianu, C.; Ghobril, C.; Kueny-Stotz, M.; Walter, A.; Jouhannaud, J., Begin-Colin, S.; Felder-Flesch, D. *New J. Chem.*, **2014**, *38*, 5226-5239
8. Lee, J-H.; Shin, S.; Seo, S.; Seo, Y.; Jeong, N.; Kim, C-W.; Kim, E.; Keum, G. *Bioorganic & Medicinal Chemistry Letters*, **2017**, *27*, 237–241
9. Sudhakar, G.; Raghavaiah, J.; Mahesha, G.; Singarapu, K. *Org. Biomol. Chem.*, **2016,** *10*, 2866-2872
10. Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* **2004**, *6*, 18, 3047-3050
11. Gemma, S.; Brogi, S.; Patil, P.; Giovani, S.; Lamponi, S.; Cappelli, A.; Novellino, E.; Brown, A.; Higgins, M.; Mustafa, K.; Szestak, T.; Craig, A.; Campiani, G.; Butini, S.; Brindisi, M. *RSC Adv.*, **2014**, *4*, 4769-4781

12. Al-Smadi, D.; Enugala, T.; Norberg, T.; Kihlberg, J.; Widersten, M. *Synlett*, **2018**, *29*, 1187–1190

13. Tassano, E.; Faber, K.; Hall, M. *Advanced Synthesis & Catalysis*, **2018**, *14*, 2742-2751

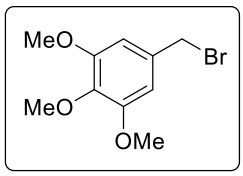
14. Han, Y.; Zheng, B.; Peng, Y. *Advanced Synthesis & Catalysis*, **2015**, *6*, 1136-1142

15. Metzger, A.; Schade, M.; Manolikakes, G.; Knochel, P. *Chem. Asian J.* **2008**, *3*,1678 – 1691

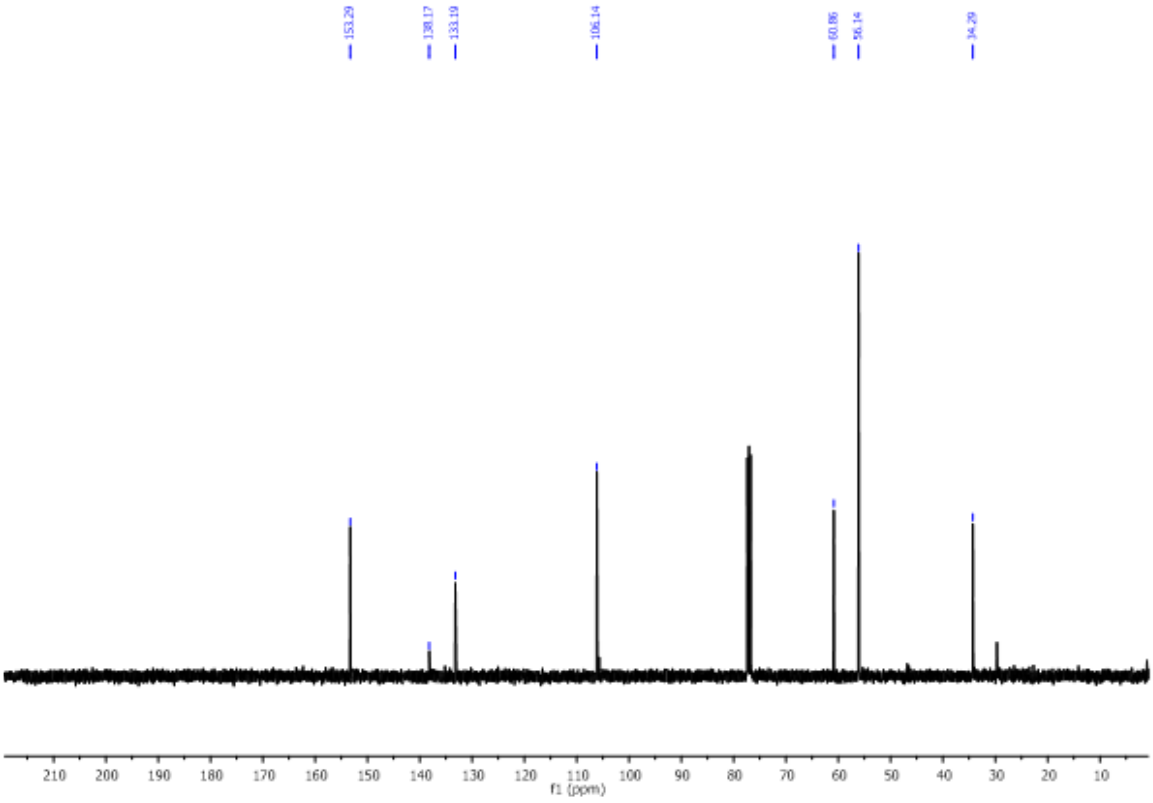
16. Mühlthau, F.; Bach, T. *Synthesis*, **2005**, *19*, 3428-3436

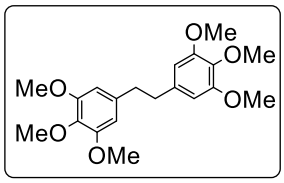
7. Spectral DATAs:

Some ^{1}H and ^{13}C spectral datas are given below. ^{1}H NMRs are taken in 400 MHz instrument and ^{13}C NMRs are taken in 100 MHz instruments.

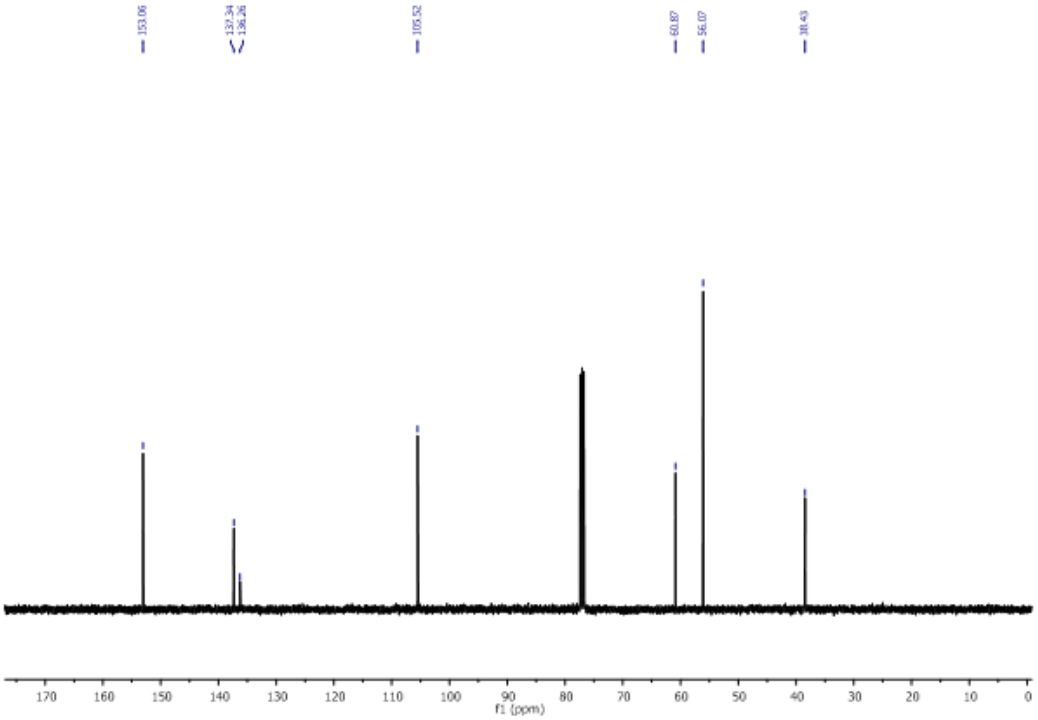

MeO
Br
MeO
OMe

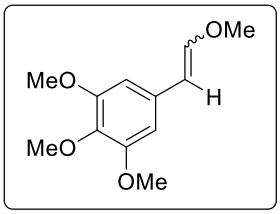
6.61
4.45
3.85
3.83
2.11
2.09
6.20
3.22
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


153.29
138.17
133.19
106.14
60.86
56.14
34.29
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

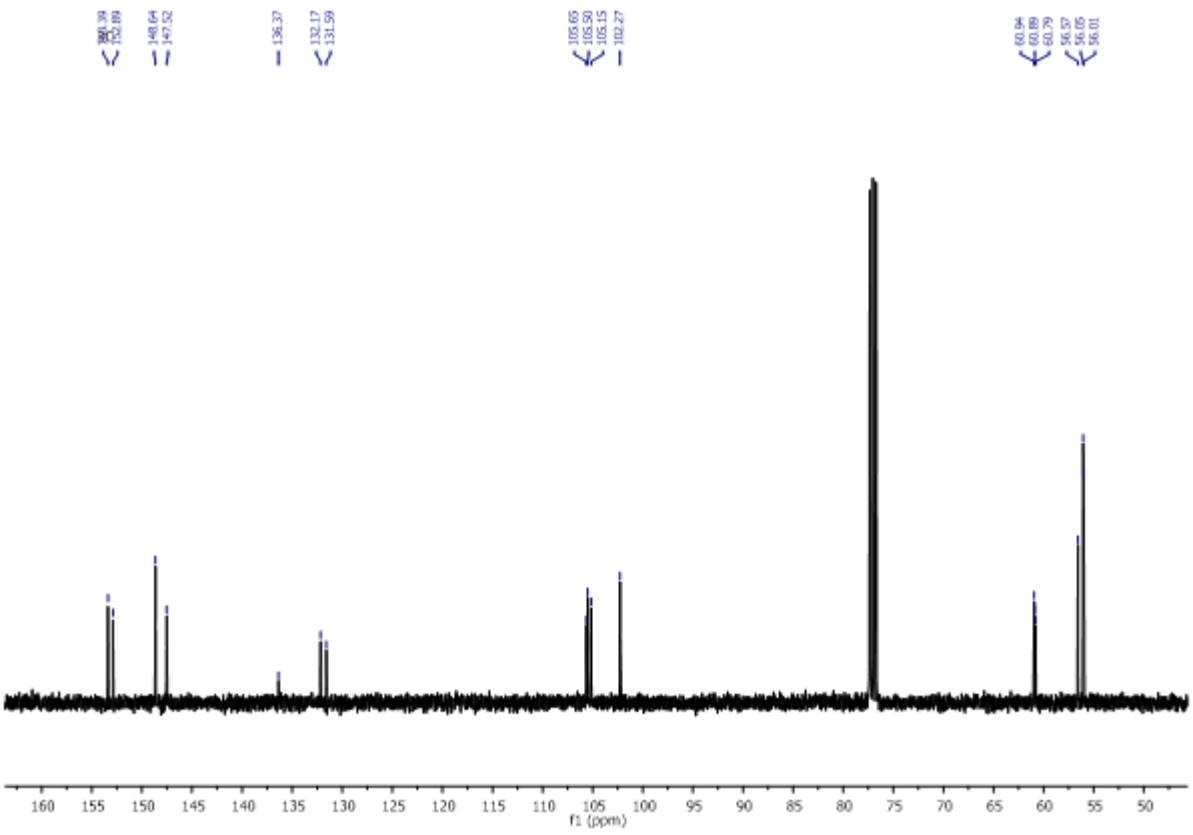

OMe
OMe
MeO
OMe
MeO
OMe

6.37
3.83
2.85
4.00
15.06
4.12
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


153.06
137.34
136.26
105.52
60.87
56.07
38.43
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMe
MeO
H
MeO
OMe

f1 (ppm)


f1 (ppm)