

Efforts Towards The Total Synthesis Of Dichocetide C

In partial fulfilment for the requirement for the degree of

Master of Science

By

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(Roll No. CY17MSCST11021)

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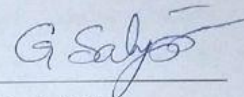


(Shovan Debsarma)

(cy17msect11021)

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.



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SHOVAN DEBSARMA

(CY17MSCST11021)

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Abbreviations Used:

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

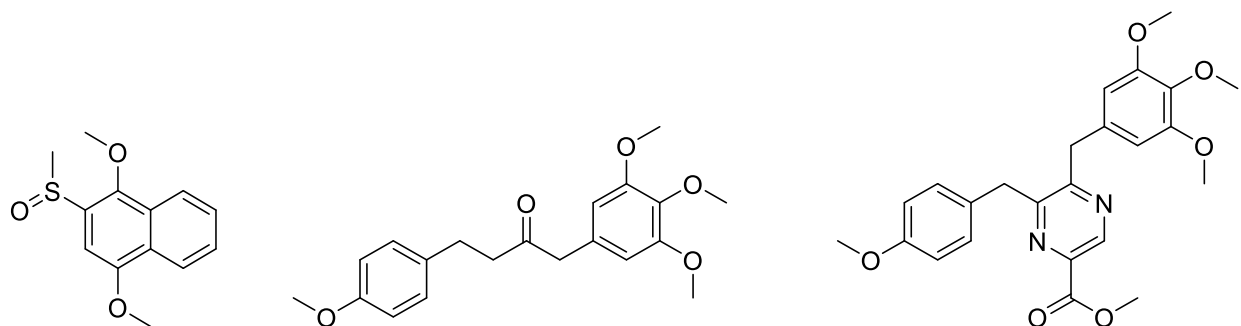
1. Abstract:

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 diversified biological activities. Dichocetide C was discovered from the cultural broth of the fungal strain *Dichotomomyces cejpui* F31-1 by *Lan et al*, who isolated *Dichotomomyces cejpui* 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⁾

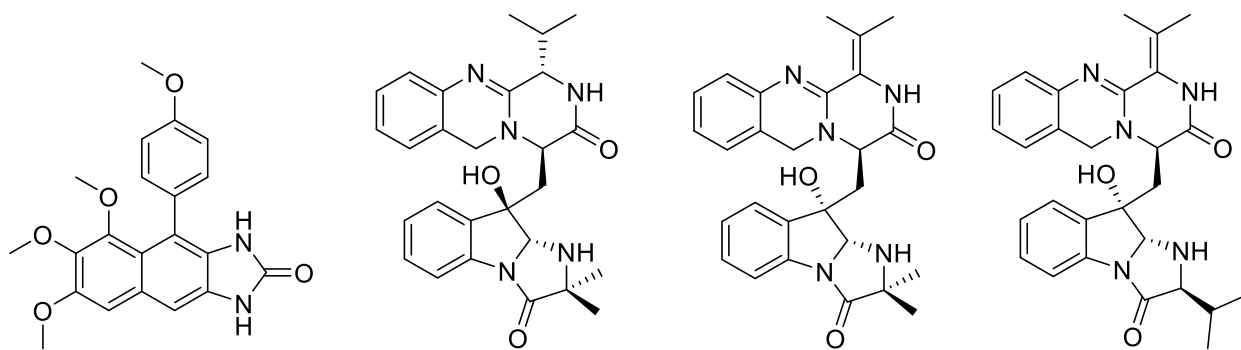
Figure 1. Natural products which are discovered from the cultural broth of *Dichotomomyces cejpü F31-1* by the group *Lan et al* ⁽¹⁾:



1 Dichocetide B

2 Dichocetide C

3 Dichotomocej E



4 Dichotomocej F

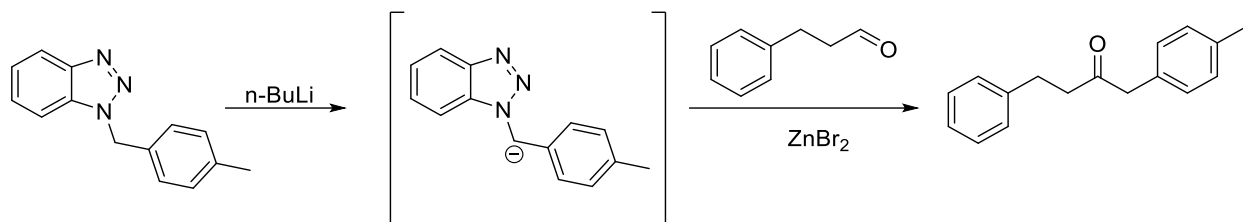
5 Scequinadoline A

6 Quinadoline A

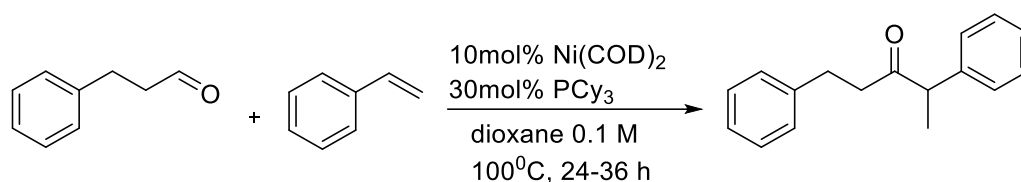
7 Scequinadoline E

Dichocetide C (**2**) is an alpha aryl ketone where two benzene rings are connected with an aliphatic chain consisting four carbon atoms. A CH₂CH₂COCH₂ 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 substituents has been reported by various ways:

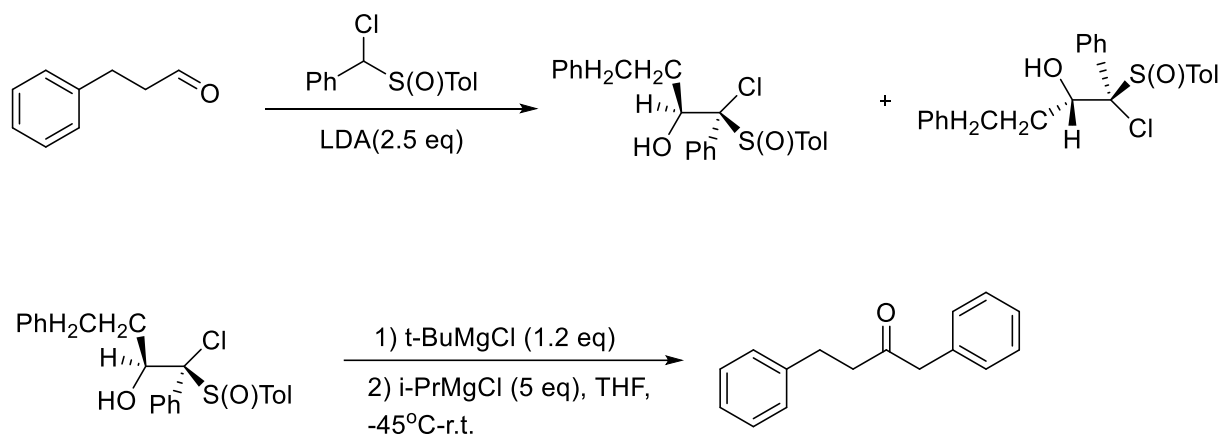
(1) By benzotriazole stabilized carbanion insertion to 3-phenylpropanal by *Katritzky et al*⁽³⁾:



(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⁾:



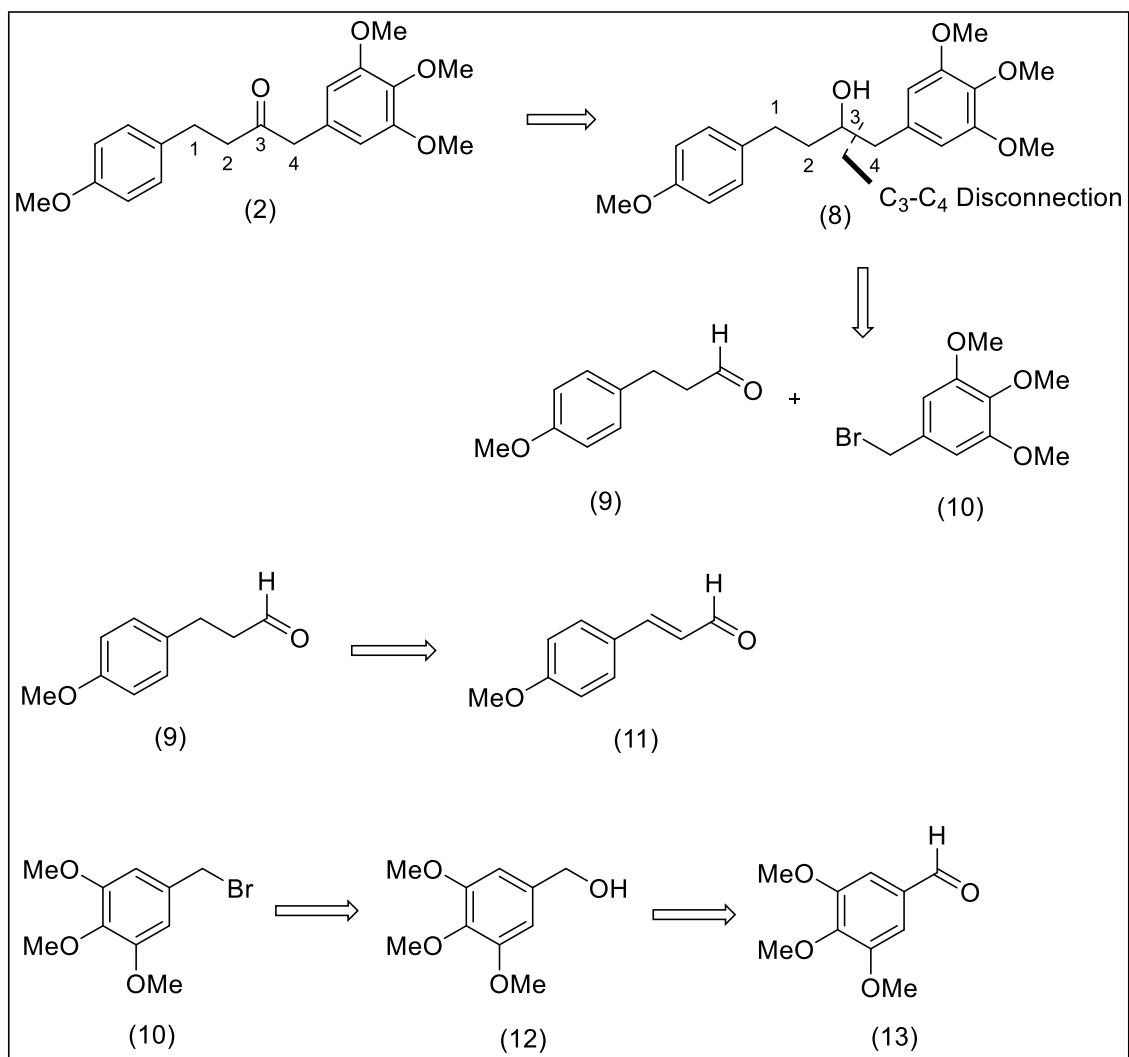
In this work, some new strategies are taken to synthesize the target molecule Dichocetide C, which is a derivative of the core structure 1,4-diphenylbutan-2-one.

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 C₃-C₄ bond disconnection (**Scheme 1A**) and another is C₂-C₃ bond disconnection approach

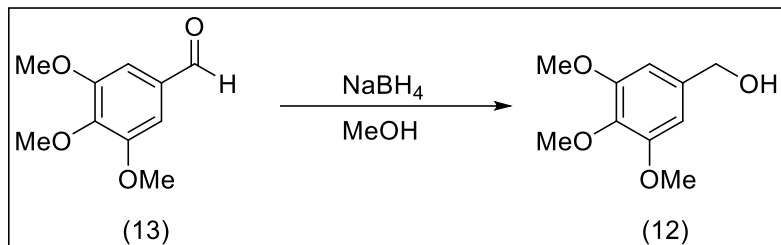
(Scheme 2A). According to Scheme 1A and Scheme 2A, forwarded reactions are also planned (Scheme 1B and Scheme 2B respectively)

Scheme 1A. Retrosynthetic approach of Dichocetide C by C₃-C₄ bond disconnection:

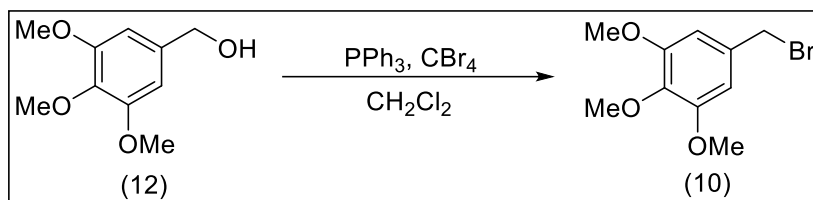


Scheme 1B. Planned step by step forward reactions according to the previous retrosynthesis approach:

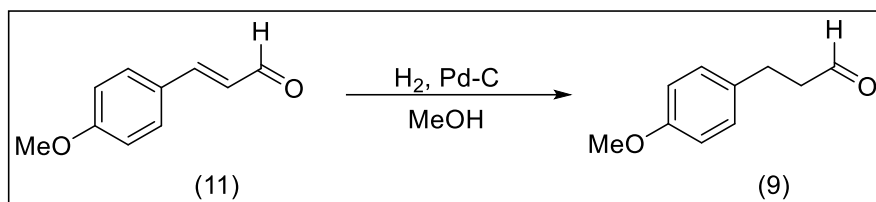
Step-1: Reduction of **13** by NaBH₄ in methanol to give **12**.⁽⁶⁾



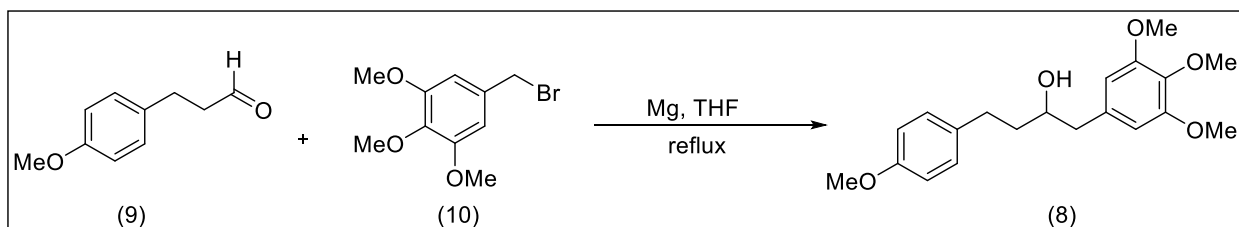
Step-2: Appel reaction of **12** to give **10**.⁽⁷⁾



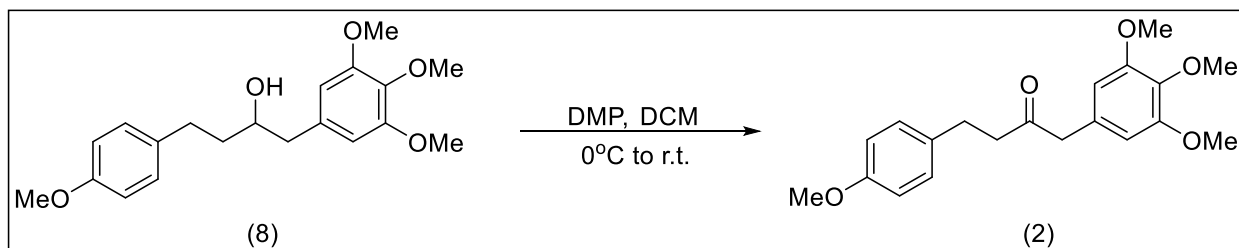
Step-3: C=C reduction of **11** to give **9**.⁽⁸⁾



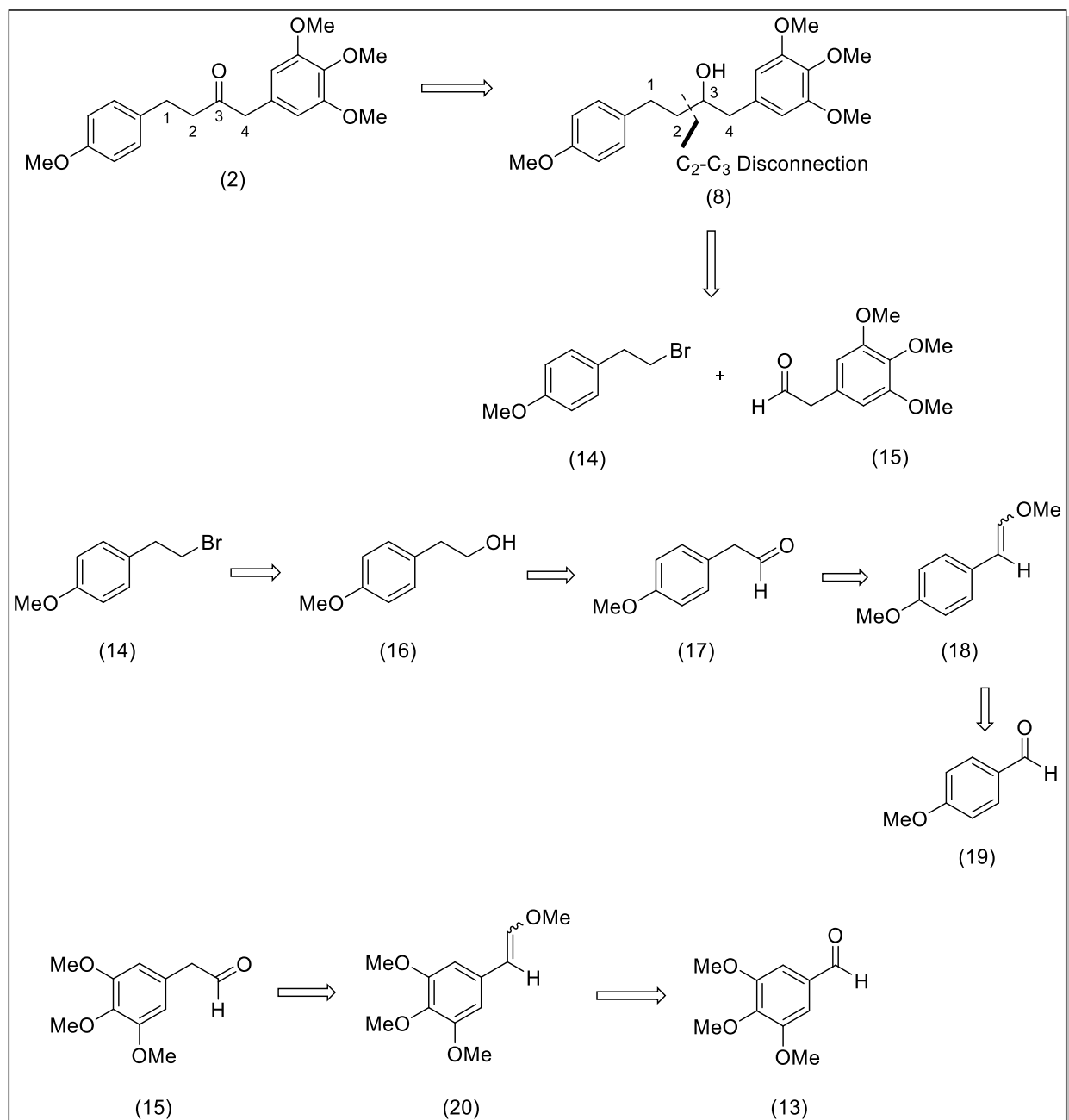
Step-4: Grignard Reaction between **10** and **9** to give **8**.⁽⁹⁾



Step-5: Oxidation of **8** to give **2**.⁽¹⁰⁾

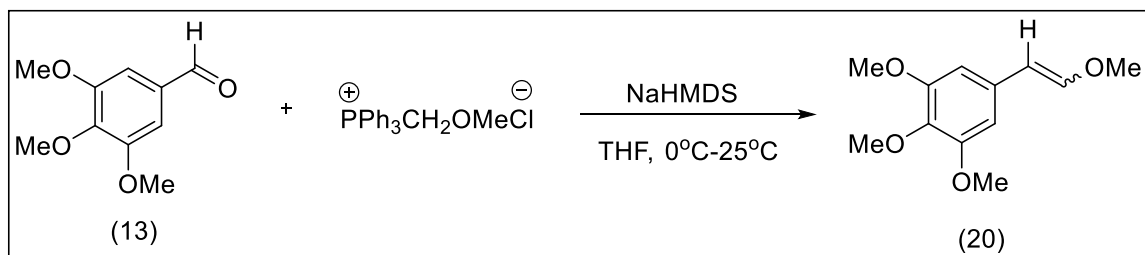


Scheme 2A. Retrosynthetic approach of Dichocetide C by C₂-C₃ bond disconnection:

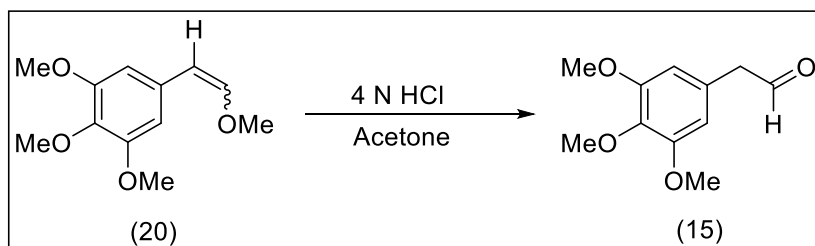


Scheme 2B. Planned step by step forward reactions according to the previous retrosynthesis approach:

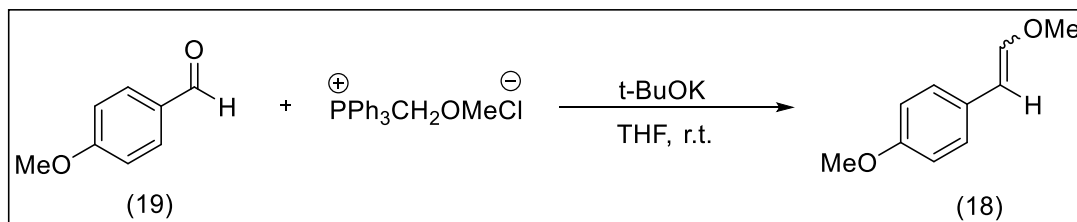
Step-1: Synthesis of enol-ether **20** by *Wittig reaction* from the aldehyde **13**:⁽¹¹⁾



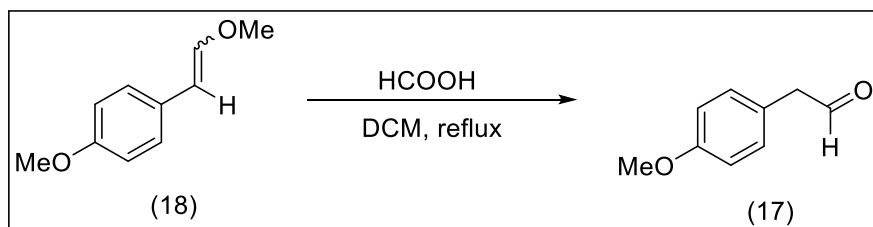
Step-2: Hydrolysis of **20** to synthesize **15**:⁽¹¹⁾



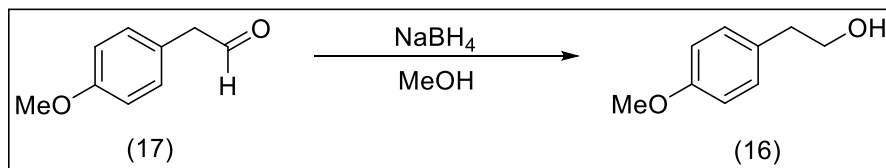
Step-3: Synthesis of enol-ether **18** by *Wittig reaction* from the aldehyde **19**:⁽¹²⁾



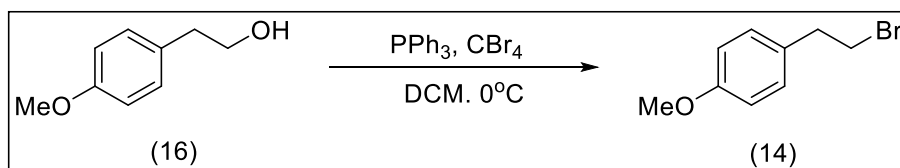
Step-4: Hydrolysis of **18** to synthesize **17**:⁽¹²⁾



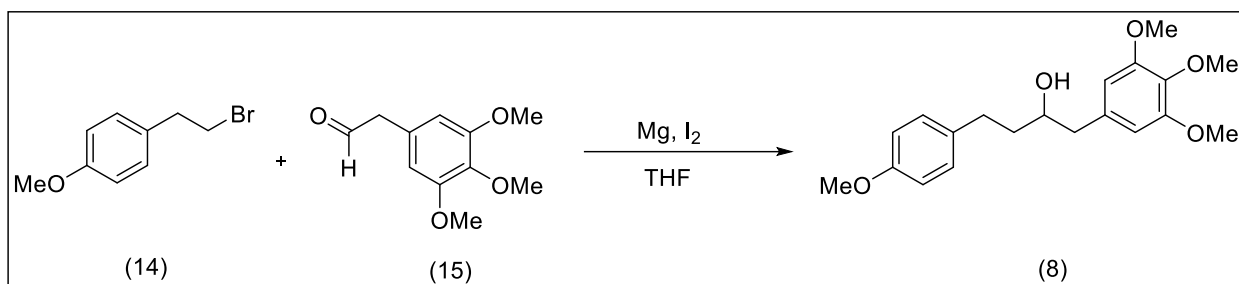
Step-5: Reduction of **17** by NaBH₄ to give **16**:⁽¹³⁾



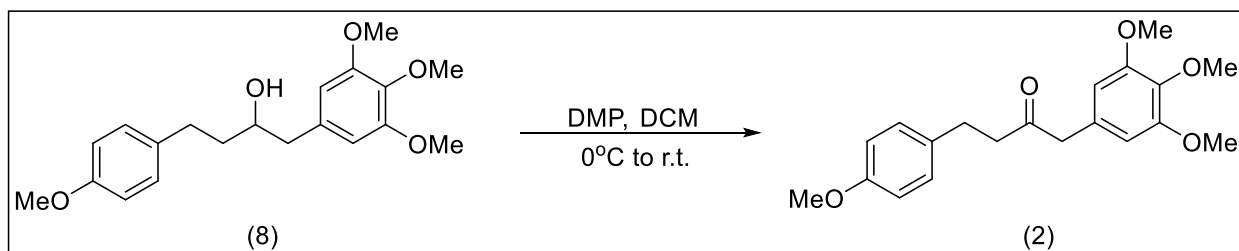
Step-6: Appel reaction of **16** to synthesize **14**:⁽¹⁴⁾



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



Step-8: Oxidation of **8** to synthesize **2**:⁽¹⁰⁾



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 H₂ reduction in presence of Pd-C as catalyst.

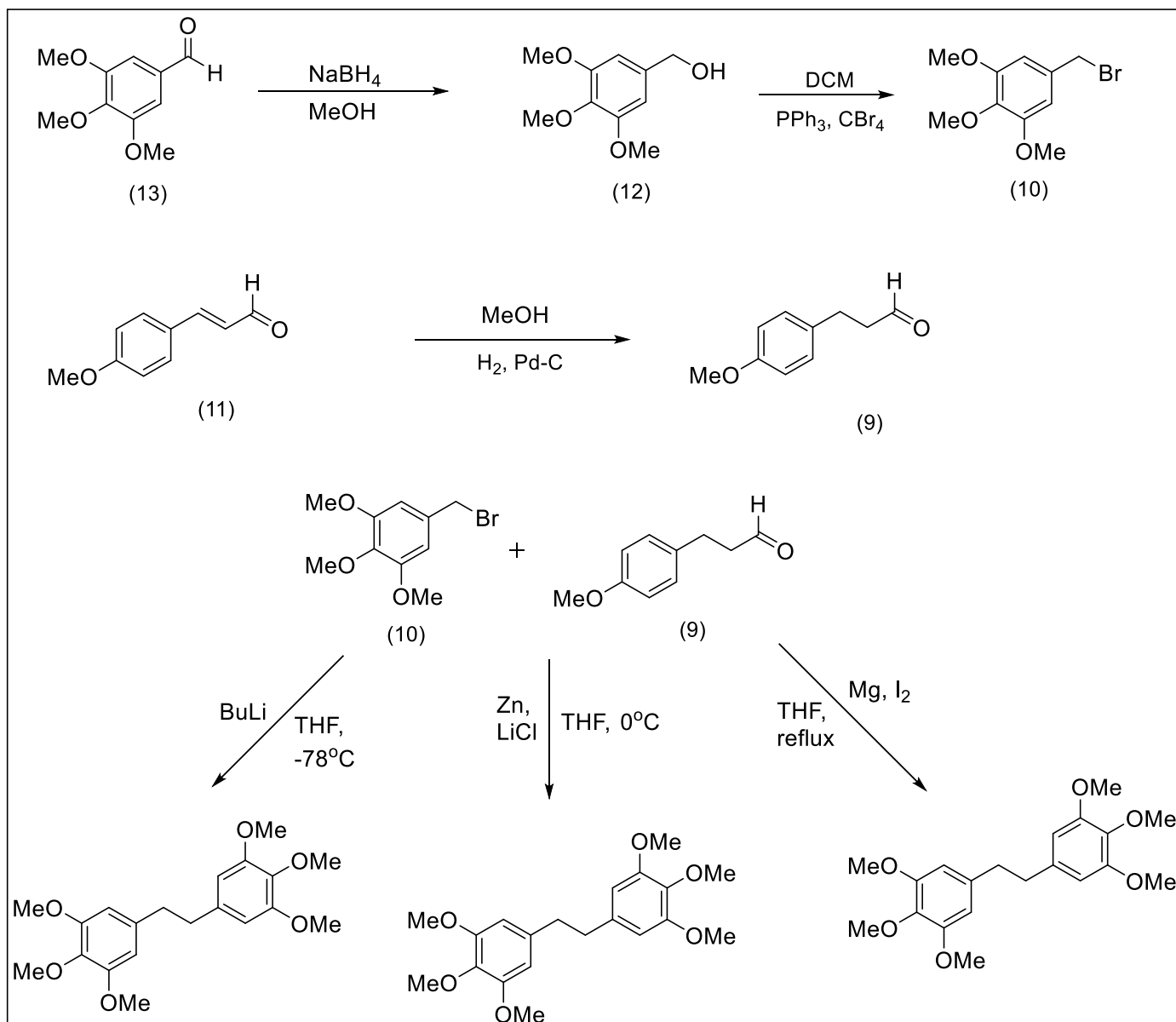
Synthesis of **12** and **9** was previously reported. The same reactions were performed to synthesize the starting materials.

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°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°C.⁽¹⁵⁾

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

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

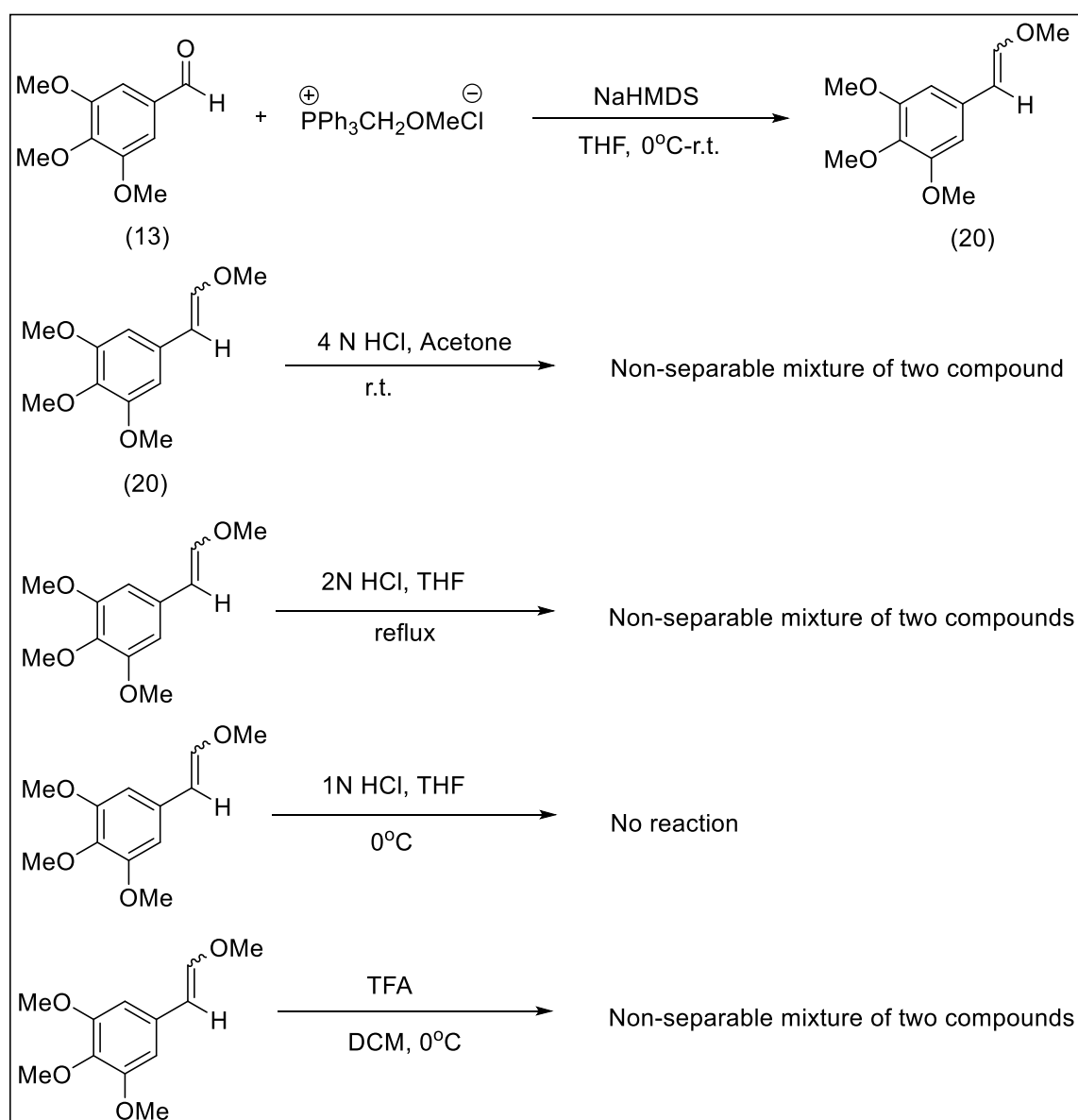


According to **Scheme 2A** and **Scheme 2B**,

1,2,3-trimethoxy-5-(2-methoxyvinyl)benzene **20** was synthesized from commercially available 3,4,5-trimethoxybenzaldehyde **13**, using mom-Wittig salt $^+\text{PPh}_3\text{CH}_2\text{OMeCl}^-$ 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.

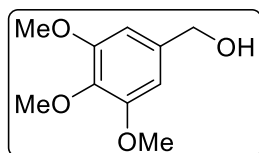


4. Experimental Section:

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. ^1H 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.

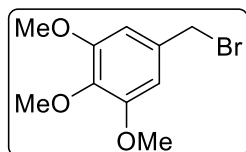
3,4,5-trimethoxybenzyl alcohol (**12**).



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°C .

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**).

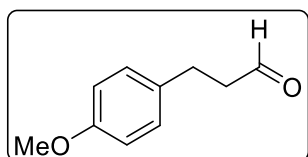


To a stirred solution of **12** (2.0 g, 10.08 mmol) and CBr_4 (5.019 g, 20.18 mmol) in 20 ml DCM, PPh_3 (5.293 g, 15.135 mmol) was added at 0°C . After the completion of reaction after 1h (monitored by TLC), the reaction mixture

was thoroughly washed with 1:1 Hexane- Et_2O solution and solvent was evaporated under *vacuo*.

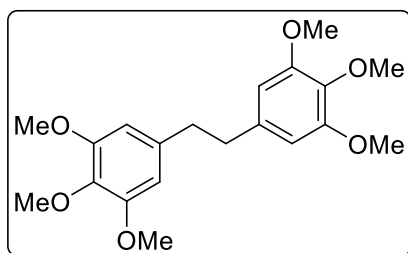
The residue was purified over 60-120 silica gel column chromatography by 8% EtOAc in Hexane. Upon purification, it gave **10** (1.391 g, 53.02%) as a white crystalline solid, m.p. 59-62°C. ¹H NMR (400 MHz, CDCl₃) δ 6.60 (s, 2H), δ 4.45 (s, 2H), δ 3.85 (s, 6H), δ 3.83 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 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 H₂ atmosphere (using H₂ 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%).

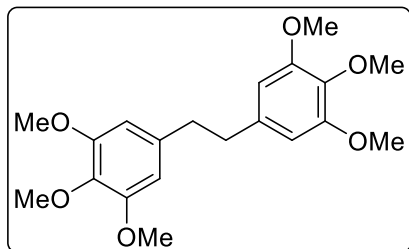
Grignard Reaction between **9** and **10**: Formation of Dimerized product of **10**.



To the oven dried two necked round bottomed flask, Mg turnings (29.232 mg, 1.218 mmol) was added and was activated by I₂. In that r.b., **10** (477.05mg, 3 eq), dissolved in 2mL freshly dried THF, is added and kept for reflux at 80°C. After 40-50 mins, all Mg turnings had been dissolved. Keeping it at 0°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 Na₂SO₄. 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. ¹H NMR (400 MHz,

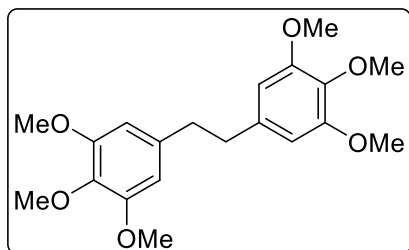
CDCl_3) δ 6.36 (s, 4H), δ 3.83 (s, 18H), δ 2.85 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.06, 137.34, 136.25, 105.51, 60.87, 56.07, 38.43.

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).

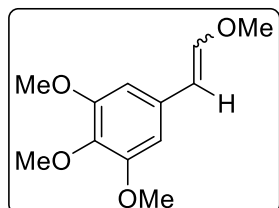
Preparation of organolithium reagent and formation of 10 and formation of dimerized product of 10.



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 -78°C 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°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. 1H 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.; Szeszak, 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 ^1H and ^{13}C spectral datas are given below. ^1H NMRs are taken in 400 MHz instrument and ^{13}C NMRs are taken in 100 MHz instruments.

