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Research Article

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Synthetic Protocols of a Top-Selling Anti-Hypertensive Drug 'Captopril': A Synthon Disconnection Approach

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ABSTRACT

Synthesis plays a central role in any pharmaceutical development endeavor. Design synthetic routes to pharmaceuticals/drugs in convergent and efficient manner are very fundamental to synthetic organic/medicinal chemistry. Synthon disconnection approach / retrosynthetic analysis advocated by Prof.E.J.Corey has emerged as powerful means in designing synthetic routes to small molecule pharmaceuticals. Taking the privilege of this approach, a number of synthesis schemes has been proposed for a potent anti-hypertensive drug 'Captopril' on the basis of its retrosynthetic analysis. The proposed synthesis schemes being a theoretical exploration, the actual laboratory implementation requires the cross examination of a considerable number of factors such as reactions, reagents and order of events. Generally, the route which is cost-effective, safe, employ readily available starting materials and produce maximum yield in a short reaction time under robust condition is most viable.

Keywords: ACE inhibitor, antihypertensive, captopril, retrosynthetic analysis, synthesis, synthon disconnection approach.

INTRODUCTION

Medicinal chemistry involves the design and synthesis of biologically active molecules, with therapeutic properties suitable for clinical application. The design and development of flexible and economic synthetic routes to pharmaceutical/drugs of interest is of paramount importance for an efficient drug discovery program. A more formal approach to synthesis design to any synthetic target of interest is promulgated as a result of Prof.E.J.Corey's development of synthon disconnection approach / retrosynthetic analysis, for which he won the Noble Prize for Chemistry in 1990. "Retrosynthetic analysis is a problem solving technique for transforming the structure of synthetic target molecule (TM) to a sequence of progressively simpler structures by disconnection of bonds and functional group interchange along the pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis" [1, 2, 3, 4]. Every disconnection part is an idealized fragment, called 'synthon'. The synthons when joined by known or conceivable synthetic operations result in the formation of target molecule. Although a number of synthetic routes are possible from the retrosynthetic analysis of the target structure, the route which is cost-effective, safe, employ readily available starting materials and produce maximum yield in a short reaction time under robust condition is most viable.

Hypertension (HTN) is a chronic medical condition in which there is persistent, nonphysiologic elevation of systemic blood pressure in the arteries for which the heart has to work harder than normal to circulate blood through the blood vessels. It is the most important modifiable risk factor for coronary heart disease, stroke, congestive heart failure, end-stage renal disease, and peripheral vascular disease and is a cause of chronic kidney disease. Even moderate elevation of arterial blood pressure is associated with a shortened expectancy. Hypertension is now one of the most common worldwide diseases afflicting humans and is estimated to cause 7.1 million premature deaths and 4.5% of the global disease burden [5].It is becoming an increasingly common health problem world wide because of increasing longevity and prevalence of contributing factors such as obesity, physical activity and an unhealthy

diet[6,7]. The pathogenesis of hypertension is multifactorial and highly complex. Several classes of medications, collectively referred to as anti-hypertensive drugs are currently available for treating hypertension. Angiotention Converting Enzyme (ACE) inhibitors are pharmaceutical drugs used primarily for the treatment of hypertension (high blood pressure) and cognitive heart failure. ACE inhibitors inhibit angiotension-converting enzyme (a component of the blood pressure-regulating rennin-angiotension system), thereby decreasing the tension of blood vessels and blood volume, thus lowering blood pressure. ACE inhibitors also increase blood flow, which helps to decrease the amount of work the heart has to do and can help protect the kidneys from the effects of hypertension and diabetes. "Captopril" (2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid (fig:1) is a potent, competitive, orally active Angiotension Converting Enzyme (ACE) inhibitor used for the treatment of hypertension and some type of congestive heart failure. It works by decreasing certain chemicals that tighten the blood vessels, so blood flows more smoothly and the heart can pump blood more efficiently. It is also used for preventing kidney failure due to high blood pressure and diabetes. Owing to its large prescription, it finds adequate position in Top-Selling Drug List.

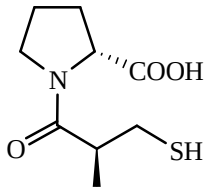


Fig: 1

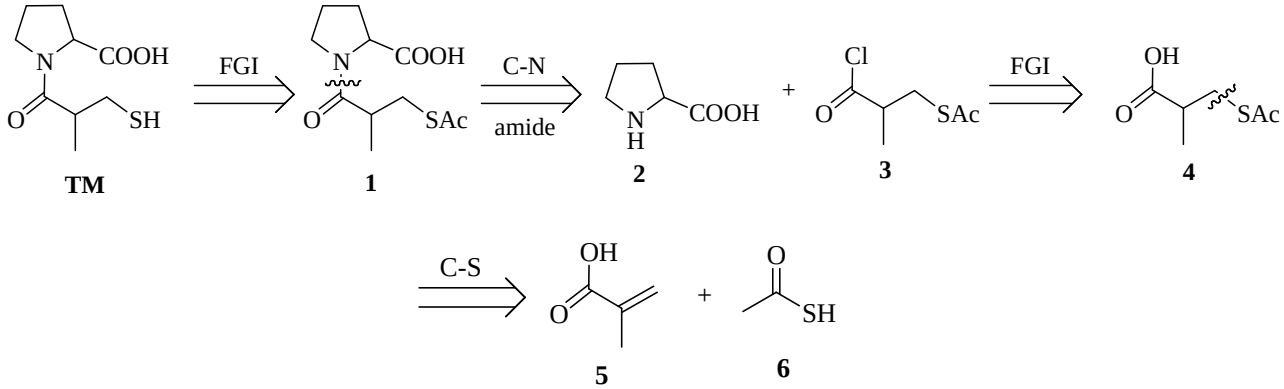
Despite the appearance of few synthetic approaches to 'Captopril' in literature, some alternative synthetic routs are still required for its commercial success. Keeping an overview on the published works both in journals[8-14] and patent literatures[15,16], we focus our research diligence to propose a good number of synthesis schemes for a top selling anti-hypertensive drug-Captopril based on synthon disconnection approach/ retrosynthetic analysis. To our current knowledge, this type of work is literature unprecedented. The choice of this molecule for synthesis planning is obvious as Captopril is one among the widely prescribed medication which has revolutioalised the treatment of anti-hypertension and cognitive heart failure.

EXPERIMENTAL SECTION

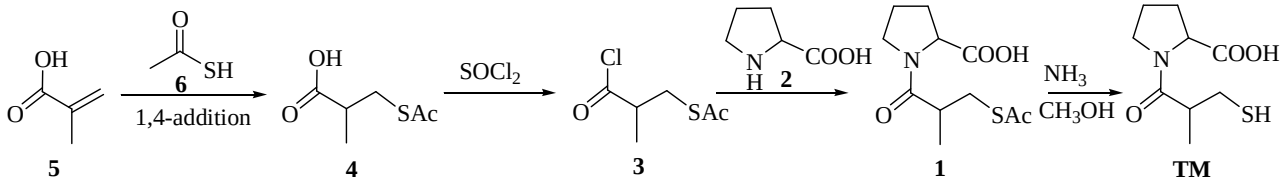
The structure and information about Captopril as drug candid has been collected from different books [17-20]. The proposed synthesis plannings are then exploited in a novel way from the result of the retrosynthetic analysis of the drug structure using the basic principle outlined in the pioneering works of Prof. E.J. Corey. The symbols and abbreviations are synonymous to that represented in books [21-27]. The analysis–synthesis schemes being theoretical propositions; obviously the syntheses have not been executed in the laboratory. The actual laboratory execution requires the cross examination of a considerable number of factors such as reactions, reagents, order of events, readily available starting materials, environmental benign and economically viable short scalable synthesis.

RESULTS AND DISCUSSION

Retrosynthetic Analysis-1

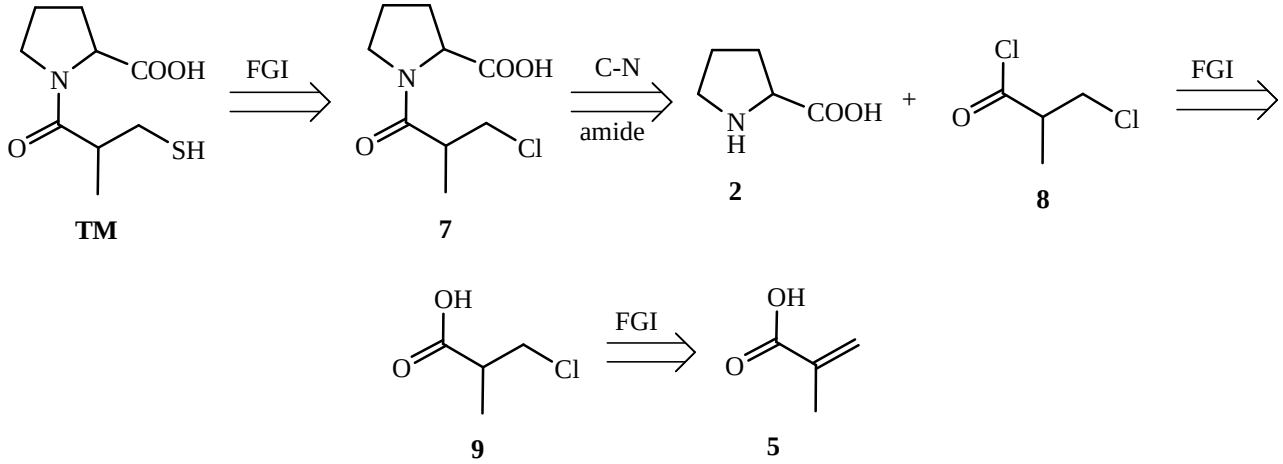


Synthesis-1

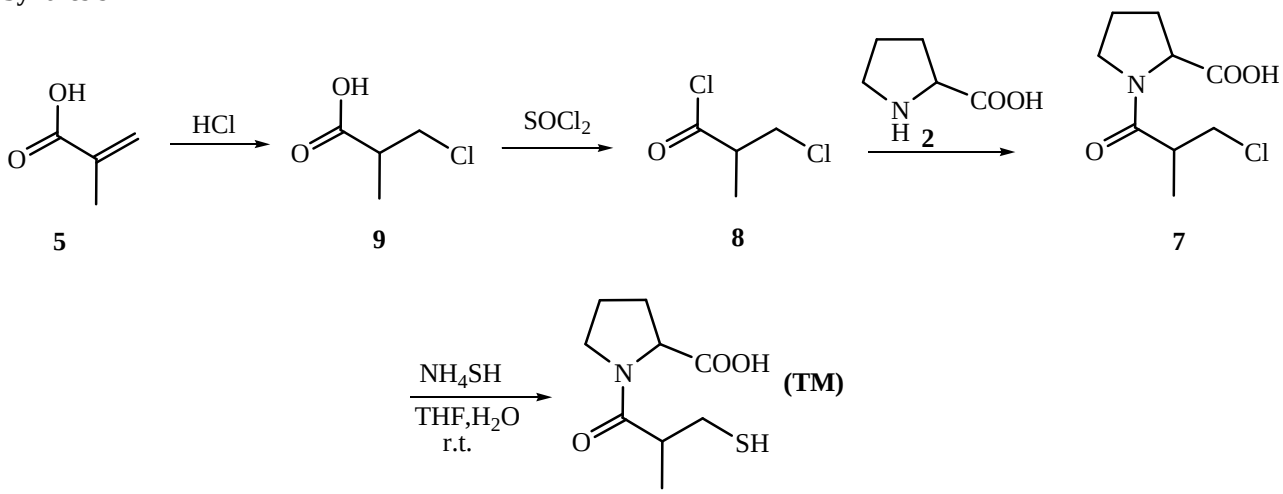


1, 4-Addition of methacrylic acid **5** and thiolactic acid **6** forms 3-acetylthio-2-methyl propanoic acid **4**.The acid forms its corresponding acid chloride **3** by reaction with $SOCl_2$.Direct acylation of L-Proline **2** with acid chloride **3** affords **1**.Amonolysis of **1** with alcoholic ammonia forms the target molecule (**TM**).

Retrosynthetic Analysis-2

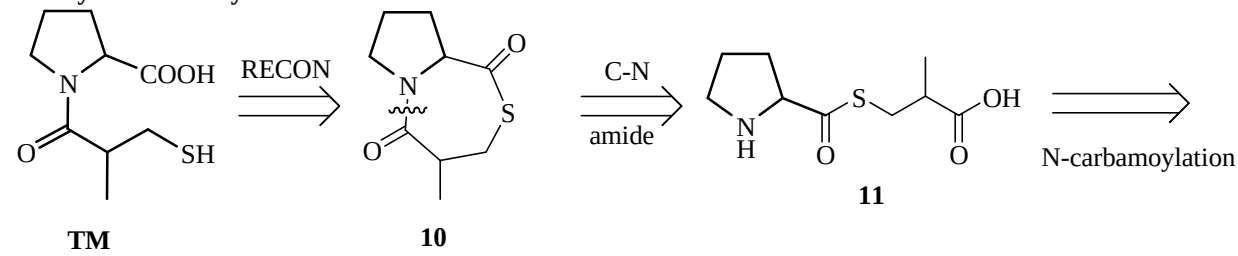


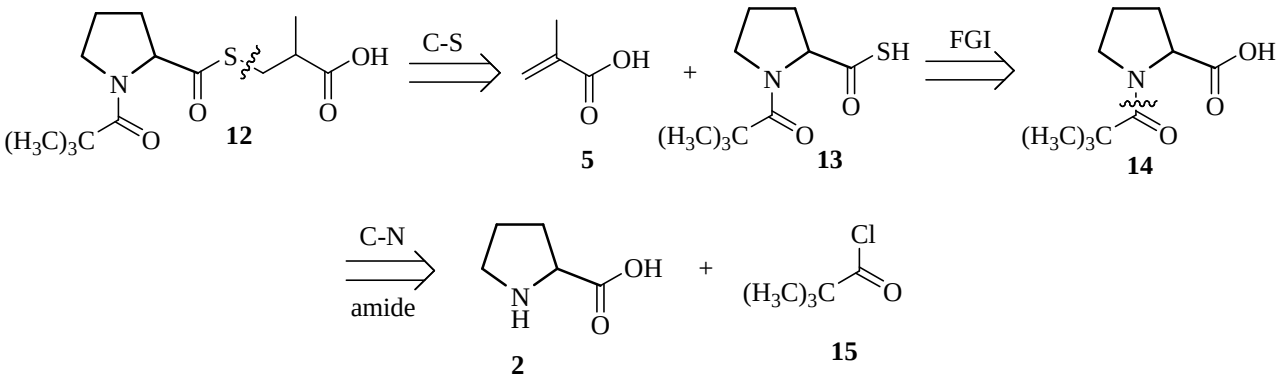
Synthesis-2



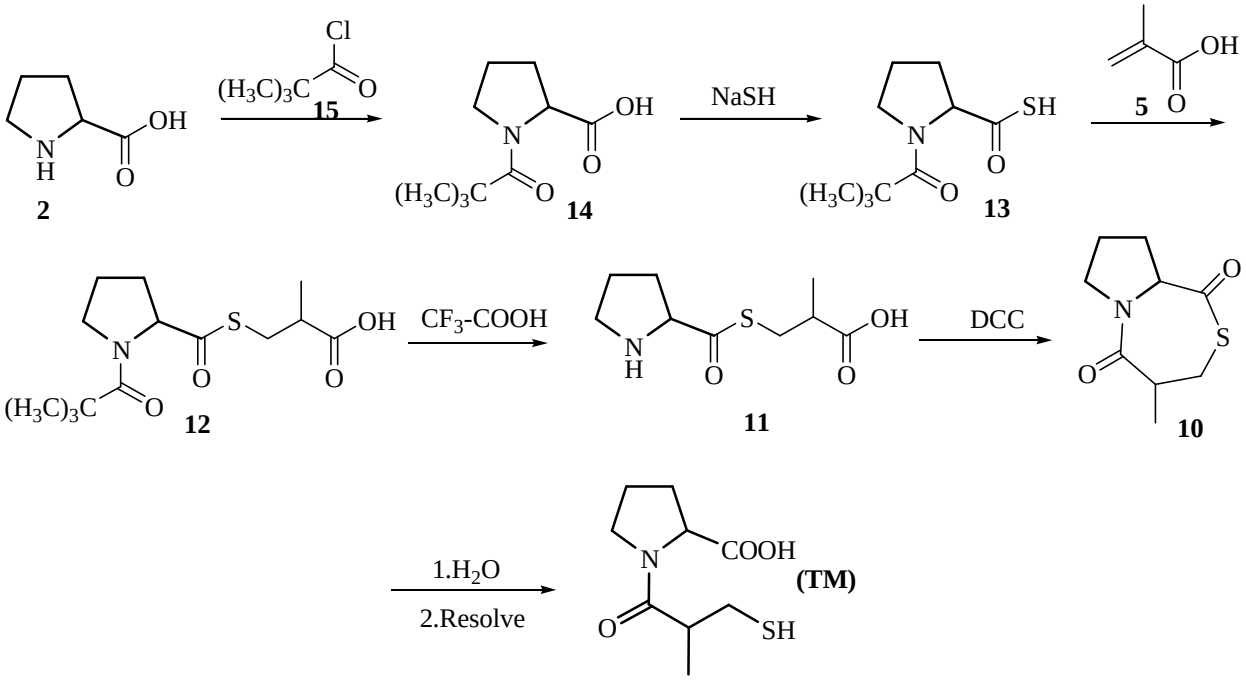
Treatment of methacrylic acid **5** with HCl forms 3-chloro-2-methylpropanoic acid **9**. $SOCl_2$ converts the acid **9** to corresponding acid chloride **8** .Reaction of **8** with L-Proline **2** gives *N*-(RS)-3-chloro-2-methyl propanoyl)-L-Prolin **7**.Separation of isomers followed by treatment with NH_4SH affords the target molecule (**TM**).

Retrosynthetic Analysis-3



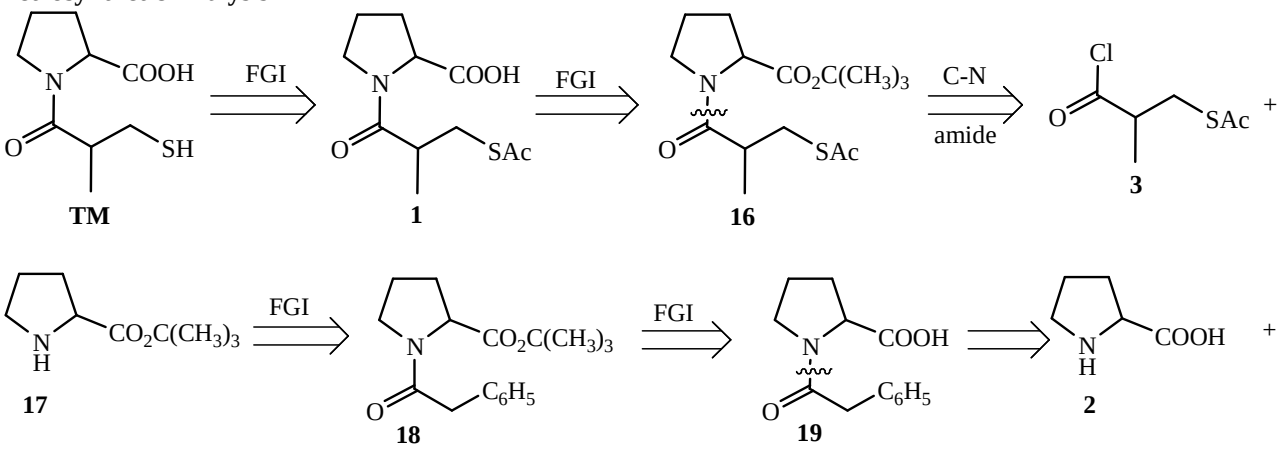


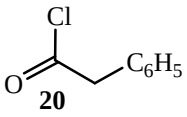
Synthesis-3



L-Proline **2** is first acetylated with pivaloyl chloride **15** to **14**, which on treatment with NaSH forms *N*-t-butyloxy carbonyl L-thioproline **13**. Reaction of **13** with methacrylic acid **5** forms **12**.Hydrolysis of **12** with trifluoroacetic acid produces 1-(3-acetylthio-2-methyl-propanoyl)-L-proline **11**.Treatment of **11** with DCC followed by subsequent hydrolysis and resolution affords the target molecule (**TM**).

Retrosynthetic Analysis-4





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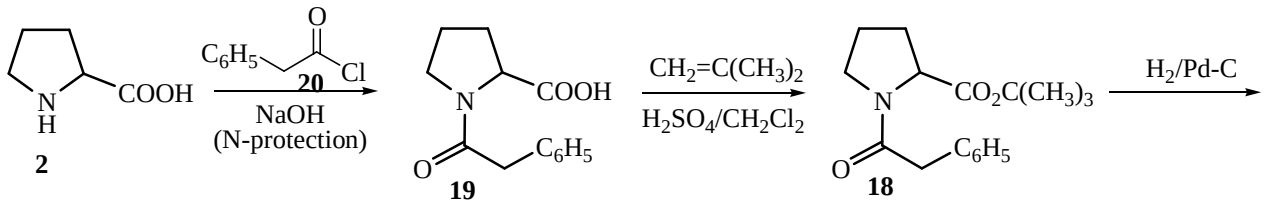
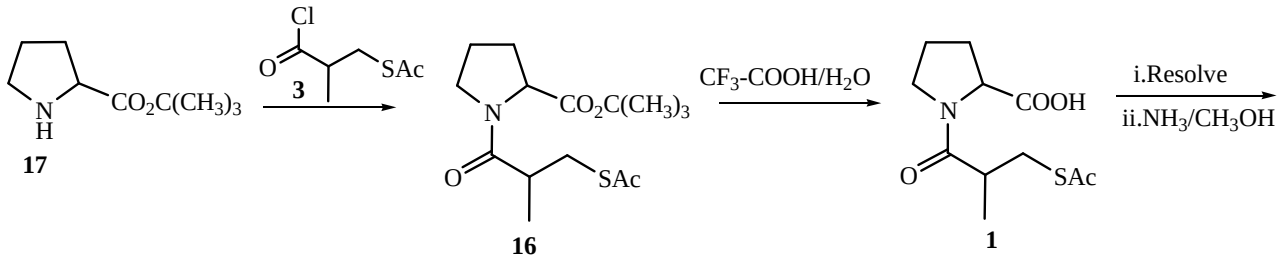
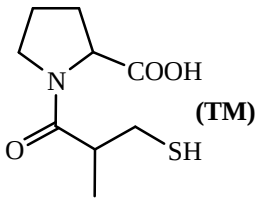
Synthesis-4

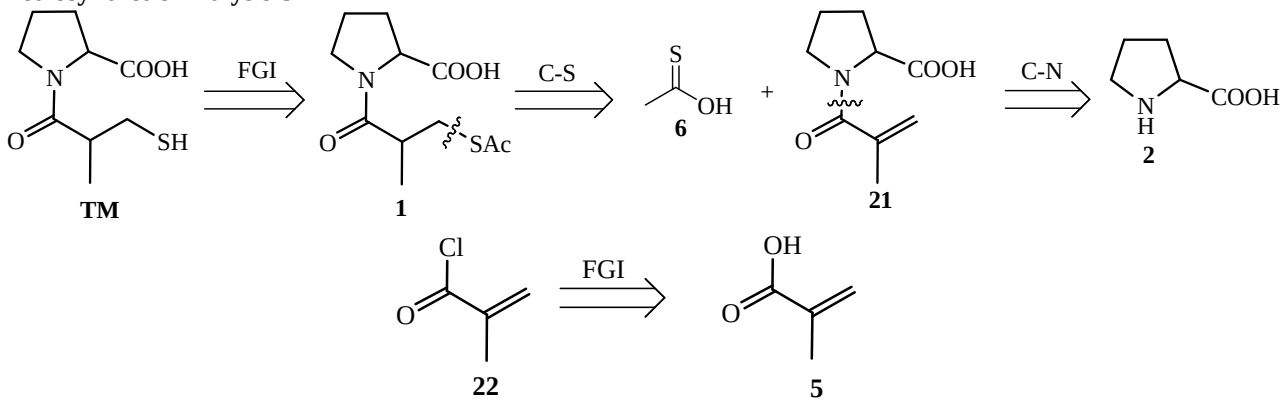




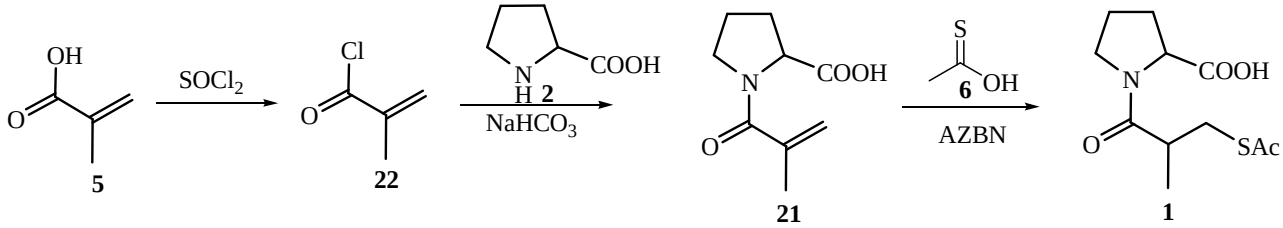


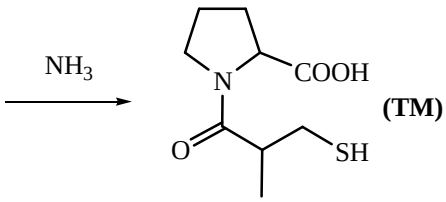
L-Proline **2** is acetylated by phenyl acetyl chloride **20** to form *N*-benzoyloxycarbonyl L- praline **19**. Acid catalysed esterification of **19** with isobutylene gives its t-butyl ester**18**.The ester is then reduced with H_2 to give L-proline t-butyl ester **17**.Acetylation of *N*-function of **17** with 3-acetylthio-2-methylpropanoyl chloride **3** forms **16**.Hydrolysis of **16** with trifluoroacetic acid forms 1-(3-acetylthio-2-methyl-propanoyl)-L-proline**1**. Resolution of 1 followed by subsequent ammonolysis produces the target compound (**TM**).

Retrosynthetic Analysis-5



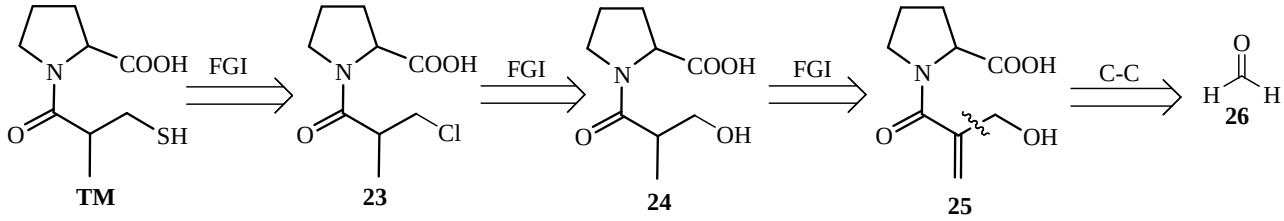
Synthesis-5

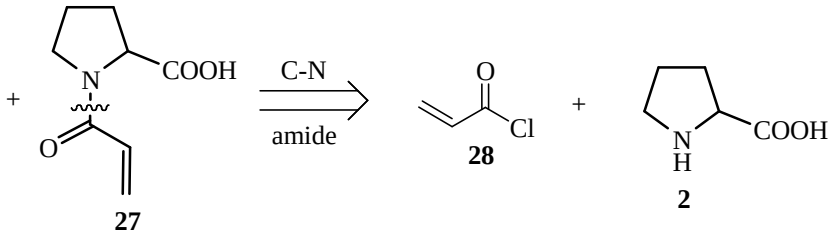




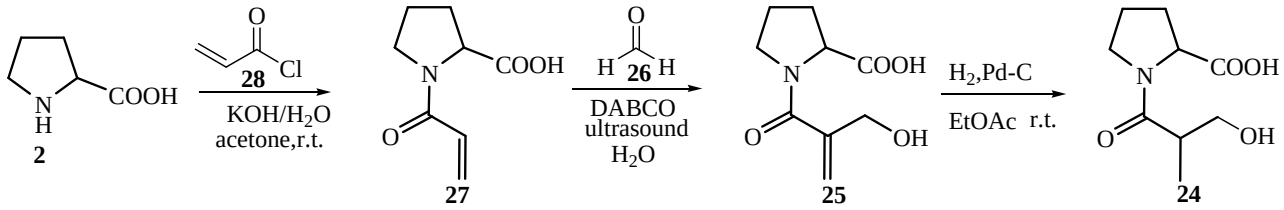
Methacrylic acid **5** is converted to methacryloyl chloride **22** by $SOCl_2$ which condenses with L-Proline **2** by $NaHCO_3$ to form *N*-methacryloyl-L-Proline **21**.Treatment of **21** with thiolactic acid **6** in presence of azobisisobutyronitrile (AZBN) forms **1**.Treatment **1** with NH_3 forms the target molecule (**TM**).

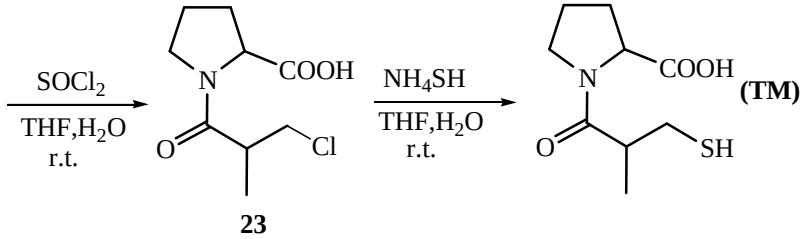
Retrosynthetic Analysis-6





Synthesis-6





Reaction of (S)-proline **2** with acryloyl chloride **28** in the presence of potassium hydroxide produces *N*-acryloylproline **27**. DABCO catalysed Baylis-Hillman reaction between *N*-acryloylproline **27** and formaldehyde **26** forms the hydroxyacrylamide **25**.Catalytic reduction of hydroxyacrylamide **25** produces the hydroxyamide **24**. Reaction of **24** with thionyl chloride forms the chloroamide **23** which on treatment with NH_4SH in H_2O/THF furnishes the target molecule (**TM**).

CONCLUSION

The power of synthon disconnection approach /retrosynthetic analysis becomes evident in the design of a synthesis. It is a paper exercise; a full analysis of this type will provide new and innovative synthetic strategies in a logical manner for design, execution and development of new synthesis or effect improvements in existing processes. As a consequence of this approach, we have proposed a good number of synthesis schemes for a top selling anti-hypertensive drug -Captopril. Scalable synthetic routes for newly discovered natural products, pharmaceuticals/drugs, useful compounds not available in adequate quantities from natural resources and even the

target molecules that have never been synthesized earlier can be best provide by this approach. With the manifestation of novel methods and transformations using new reagents and chemical reactions, it is now time to rethink the synthesis of best selling pharmaceuticals through this approach in the later stages of drug research and development.

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REFERENCES

[1] E J. Corey**.** *Pure. Appl. Chem*. **1967,** *14* (1) 19-38.
[2] E J. Corey; Wipke, W.T**.,** *Science*. **1969,***166*, 178-192.
[3] E J. Corey**.** *Q. Rev .Chem. Soc*. **1971,** *25*, 455-482.
[4] E J. Corey. *Angew.Chem.Int.Ed.Eng*. **1991**, *30* (5), 455–465.
[5] World Health Organization. *The World Health Report* **2002**: *Risks to Health* **2002.** Geneva.
[6] RB Singh.; IL Suh.;S Chaithiraphan.; P, Laothavorn.;RG. Sy. *Hum Hypertensions*, **2000**,*14*, 749-763.
[7] S Yusuf.;.S Reddy.;S Ounpuu. ; S Anand. *Circulation*. **2001,** *104***,** 2746- 2753.
[8] MA Ondetti.; B Rubin.; DW Cushman. *Science*.**1977**,*196*, 441-444.
[9] M Shimazaki, J Hasegawa, K Kan, K Namura, Y Nose, H Kondo,T Ohashi, K Watanabe, *Chem.Pharm.Bull*. **1982,** *30* (9), 3139-3146.
[10] DH Nam, CS Lee, DD Ryu. *J.Pharm.Sci*. **1984**, *73* (12), 1843-1344.
[11] SG Davies *Pure & Appl.Chem*.**198**8, *60*, 13.
[12] H B Lee.; Y G Kim.; *J. Ind. Eng. Chem*. **1998**, *4*(2), 127-134.
[13] RR.Chirumamilla., R Marchant., P Nigam. *J Chem Technol Biotechnol*. **2001**, *76* (2)123-127.
[14] M P Feltrin., W P Almeida. *Synth. Commun*. **2003**, *33*(I7) 1141-1146.
[15] MA Ondetti; DW Cushman. US Patent.**1977**, 4,046,889.
[16] Robert, P.J.; Casta, Lv r. J.; Drug Fut, **1978**,3,11,795.
[17] W O Foys.; T L Lemke.; D A Williams. Foye's Principles of Medicinal Chemistry. Lippinicott Williams & Wilkins, Philadelphia, **2007**;pp-742.
[18] R B Silverman. The Organic Chemistry of Drug Design and Drug Action. Academic Press**, 2004;** pp-247-248.
[19] D Ledincer.; LA Mitscher. The Organic Chemistry of Drug synthesis, Vol- 3. John Wiley & Sons, New York, **1990**; pp-128.
[20] A Korolkovas. Essentials of Medicinal Chemistry, 2nd Ed. John Wiley & Sons**,** New York**, 2005;** pp-504-505**.**
[21] EJ Corey.; XM Chang., The Logic of Chemical Synthesis. John Wiley, New **York**. 1989.
[22] F.Serratosa.; J.Xicart. Organoc Chemistry in Action:The Design of Organic Synthesis.Elsevier, **1996.**
[23] S Warren. Designing Organic Synthesis: A Programme Introduction to Synthon Approach. John Wiley and Sons, New York**. 1978.**
[24] S Warren. Organic Synthesis-The Disconnection Approach. John Wiley and Sons, New York, **1982**.
[25] J Clayden.; N Greeves.; S Warren.; P. Wothers. Retrosynthetic Analysis In Organic Chemistry. Oxford University Press Inc., New York; **2001;** pp. 773-778.
[26] J-H Fuhrhop. ; G Li. Organic Synthesis: Concepts and Methods.Wiley-VC GmbH & Co.KGaA, **2003.**
[27] M. Harmata. Strategies and Tactics in Organic Synthesis, Volume -7. Academic Press, **2008.**