



World News of Natural Sciences

An International Scientific Journal

WNOFNS 36 (2021) 88-98

EISSN 2543-5426

Generating Organic Compounds by Retrosynthetic Pathway via Typical Corey's Synthesis

**Chinonso Godwin Ononiwu¹, Onyekachi Oluchi Enwereuzo²,
Obinna Chigoziem Akakuru³, Chukwudima Benaiah Ejiogu¹,
Chinonso Uchenna Onumah⁴, Chinedu Kingsley Achukee⁵,
Tobechukwu Nnamdi Umaefulam⁶, Nkechi Nancy Abaekwume⁷
and Ozioma Udochukwu Akakuru^{8,*}**

¹Department of Science Education, University of Nigeria, Nsukka, Enugu State, Nigeria.

²Department of Geography and Environmental Management, Imo State University, Owerri, Nigeria

³Department of Geology, Federal University of Technology, Owerri, Nigeria.

⁴Department of Economics, Imo State University, Owerri, Nigeria

⁵Department of Biochemistry, University of Calabar, Calabar, Nigeria

⁶Department of Crop Science and Technology, Federal University of Technology, Owerri, Nigeria

⁷Department of Social Science Education, University of Nigeria, Nsukka, Enugu State, Nigeria

⁸Department of Pure and Applied Chemistry, University of Calabar, Calabar, Nigeria

*E-mail address: ozioa.akakuru@yahoo.com , ozioa@nimte.ac.cn

ABSTRACT

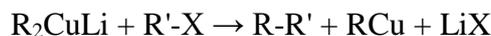
Several methods exist for the synthesis of alkanes including Corey's synthesis, Wurtz reaction, reduction of alcohols and aldehydes, Kolbe's electrolysis, hydrogenation of alkenes, and Grignard reaction. Among the available methods, the age-long Corey's synthesis presents robust advantages of yielding symmetrical, unsymmetrical, straight chain and branched chain alkanes. Moreover, it allows of generating high yields of alkanes by utilizing primary alkyl halide and an array of lithium dialkyl copper ranging from primary, secondary to tertiary. Corey's synthesis has also been implicated in the synthesis of various organic compounds such as (+)-taylorone, terminal alkynes, caribanol A, ketones, and aldehydes. In this work, an explanation of the general concept in the Corey's synthesis is provided. Furthermore, specific examples of Corey's reactions and modifications are discussed. Finally, an outlook into the benefits of the Corey's synthesis in present-day organic synthesis is provided, which is

expected to enhance the understanding of organic reaction mechanisms for the development of various organic compounds as drugs for treating diseases.

Keywords: Corey's synthesis, alkanes, organic compounds, organic reaction mechanism, alkynes, aldehydes, ketones

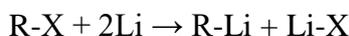
1. INTRODUCTION

Elias James Corey, an American organic chemist born in 1928 won the Nobel Prize in Chemistry in 1990 for his development of "the theory and methodology of organic synthesis", specifically retrosynthetic analysis ^[1]. He also developed various synthetic reagents, methodologies and total syntheses and has advanced the science of organic synthesis considerably. A very significant synthesis by Corey is the Corey–House synthesis (also called the Corey–Posner, Whitesides–House reaction and other permutations), which is an organic reaction that involves the reaction of a lithium dialkyl cuprate with an alkyl halide to form a new alkane, an organocopper compound and a lithium halide:

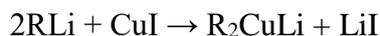


This reaction occurs in two steps. The alkyl halide is treated with lithium metal, and solvated in dry ether, which converts the alkyl halide into an alkyl lithium compound, R-Li.

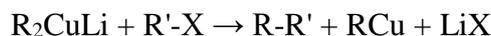
The starting R-X can be primary, secondary or tertiary alkyl halide:



The second step requires the alkyl lithium compound to be treated with cuprous iodide (CuI). This creates a lithium dialkyl cuprate compound. These compounds were first synthesized by Henry Gilman of Iowa State University, and are usually called Gilman reagents in honor of his contributions:



The lithium dialkyl cuprate is then treated with the second alkyl halide, which couples to the compound:



If second alkyl halide is not the same as the first, then cross-products are formed. It is important to note that for this reaction to work successfully, the second alkyl halide must be a methyl halide, benzyl halide, primary alkyl halide or a secondary cyclo alkyl halide. The relative simplicity of this reaction makes it a useful technique for synthesizing organic compounds.

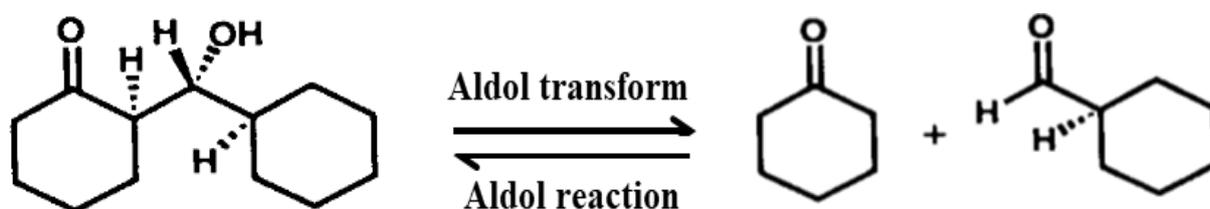
A multistep synthesis of carbogenic complexes has also been put forward by Corey. Carbogens, members of the family of carbon-containing compounds, can exist in an infinite variety of compositions, forms and sizes. The naturally occurring carbogens, or organic

substances as they are known more traditionally, constitute the matter of all life on earth, and their science at the molecular level defines a fundamental language of that life. The chemical synthesis of these naturally occurring carbogens and many millions of unnatural carbogenic substances has been one of the major enterprises of science in this century. That fact is affirmed by the award of the Nobel Prize in Chemistry for 1990 for the “development of the theory and methodology of organic synthesis”. Chemical synthesis is uniquely positioned at the heart of chemistry, the central science, and its impact on our lives and society is all pervasive ^[2, 3]. For instance, many of today’s medicines are synthetic and many of tomorrow’s will be conceived and produced by synthetic chemists ^[4-6]. In the field of synthetic chemistry lies an array of responsibilities which are crucial for the future of mankind, not only with regard to the health, material and economic needs of our society, but also for the attainment of an understanding of matter, chemical change and life at the highest level of which the human mind is capable ^[1].

Retrosynthetic pathway was utilized by Corey in the synthesis of various complexes. *Retrosynthetic* (or *antithetic*) analysis is a problem-solving technique for transforming the structure of a *synthetic target* (TGT) molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis. The transformation of a molecule to a synthetic precursor is accomplished by the application of a *transform*, the exact reverse of a *synthetic reaction*, to a target structure.

Each structure derived antithetically from a TGT then itself becomes a TGT for further analysis. Repetition of this process eventually produces a tree of intermediates having chemical structures as nodes and pathways from bottom to top corresponding to possible synthetic routes to the TGT. Such trees, called EXTGT trees since they grow out from the TGT, can be quite complex since a high degree of branching is possible at each node and since the vertical pathways can include many steps. This central fact implies the need for strategies which control or guide the generation of EXTGT trees so as to avoid explosive branching and the proliferation of useless pathways.

Each retrosynthetic step requires the presence of a target structure of a keying structural subunit or *retron* which allows the application of a particular transform. For example, the retron for the aldol transform consists of the subunit HO-C-C-C=O, and it is the presence of this subunit which permits transform function, e.g. as shown in **Scheme 1**.



Scheme 1. Illustrating retrosynthetic pathway in organic synthesis.

Transforms vary in terms of their power to simplify a target structure. The most powerful of simplifying transforms, which reduce molecular complexity in the retrosynthetic direction, occupy a special position in the hierarchy of all transforms. Their application, even when the appropriate retron is absent, may justify the use of a number of non-simplifying transforms to

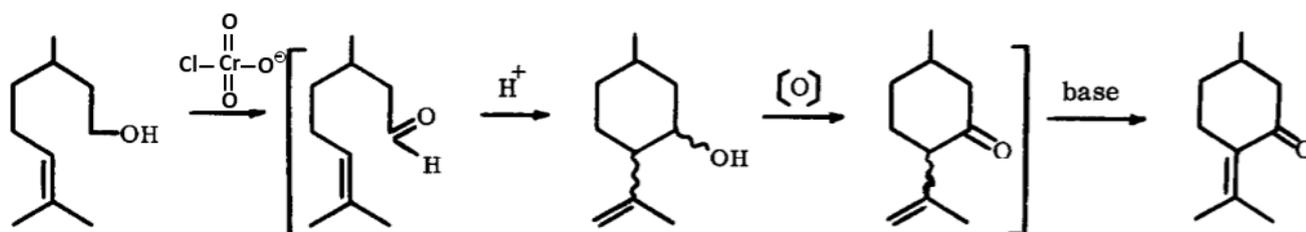
generate that retron [7, 8]. In general, simplifying transforms function to modify structural elements which contribute to molecular complexity: molecular size, cyclic connectivity (topology), stereocenter content, element and functional group content, chemical reactivity, structural instability, and density of complicating elements. Other examples of the Corey synthesis are discussed below.

2. SPECIFIC USES OF COREY'S SYNTHESIS

2. 1. Synthesis of Carbonyls

E.J. Corey has developed several new synthetic reagents. For instance, pyridinium chlorochromate (PCC), also referred to as the Corey-Suggs reagent, is widely used for the oxidation of alcohols to corresponding ketones and aldehydes [9]. PCC has several advantages over other commercial oxidants. One of these advantages is that the compound is available as an air-stable yellow solid that is not very hygroscopic. Unlike other oxidizing agents, PCC can accomplish single oxidations with only about 1.5 equivalents. The alcohol performs nucleophilic attack to the electropositive chromium (VI) metal displacing chlorine. The chloride anion then acts as a base to afford the aldehyde product and chromium (IV).

The slightly acidic character of PCC makes it useful for cyclization reactions with alcohols and alkenes (**Scheme 2**) [10].



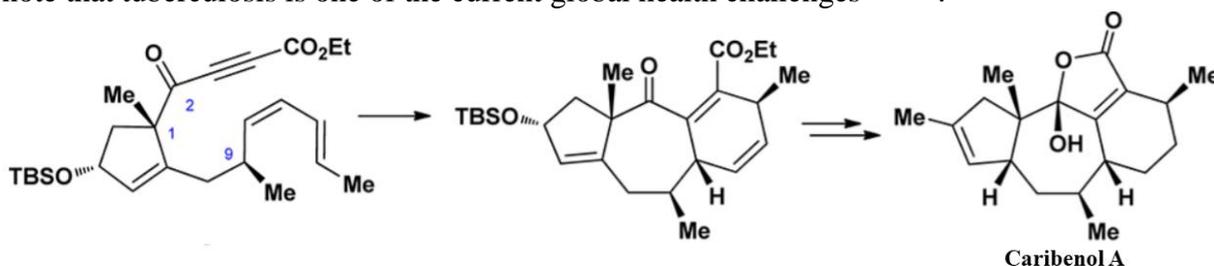
Scheme 2. Oxidation of a primary alcohol by PCC to obtain a ketone [10].

2. 2. Synthesis of Caribenol A

The total synthesis of the caribenol A, a novel natural product with a fascinating tetracyclic framework, was achieved by a strategy that was originally developed by Corey. Natural products represent an important class of organic compounds which have led to the development of numerous drugs for treating human and animal diseases [11-13]. The synthesis of caribenol A featured an intramolecular Diels–Alder (IMDA) reaction for the facile construction of the tricyclic [5–7–6] skeleton of caribenol A and a biomimetic oxidation reaction for the formation of the 2-hydroxyfuran-2(5H)-one motif of caribenol A as key steps (**Scheme 3**) [14].

In a related report, Corey's synthesis was also modified to obtain caribenol A via IMDA reaction [15]. Generally, the asymmetric total synthesis of caribenol A was completed in about 17 steps using an IMDA reaction to construct the 5–7–6 tricyclic core of caribenol A and a biomimetic oxidation to incorporate the hydroxyl group into its unique butenoid moiety as the key steps. Interestingly, the developed chemistry could be applicable for the syntheses of the caribenol-type of natural product-like compounds, which could be utilized for exploring their

structure–activity relationship against *Mycobacterium tuberculosis* (H37Rv). It is important to note that tuberculosis is one of the current global health challenges ^[16, 17].

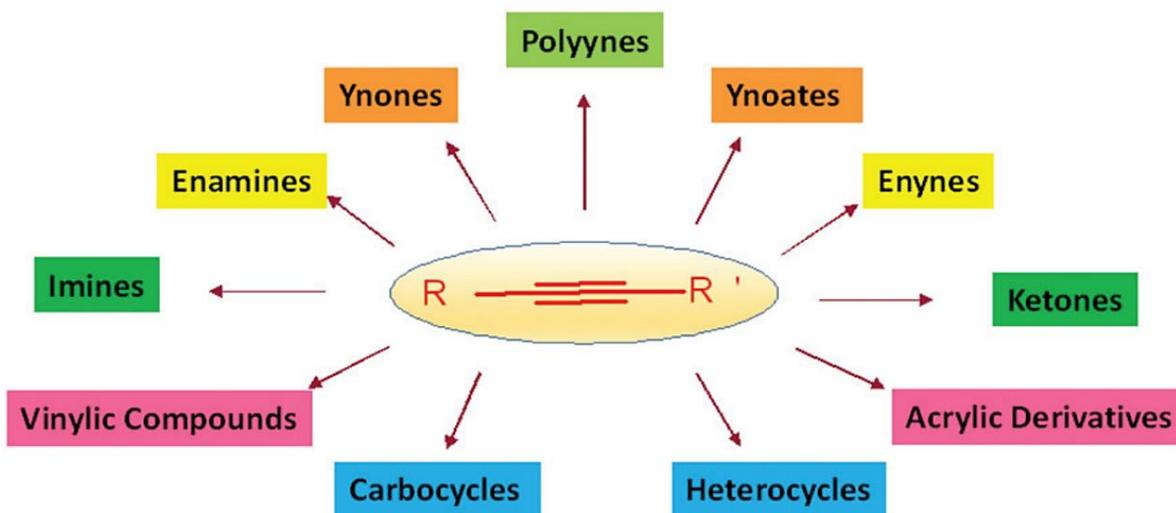


Scheme 3. General illustration of the synthesis of caribenol A ^[14].

Several reactions developed in Corey's lab have become commonplace in modern synthetic organic chemistry. At least 302 methods have been developed in the Corey group since 1950. Several reactions have been named after him:

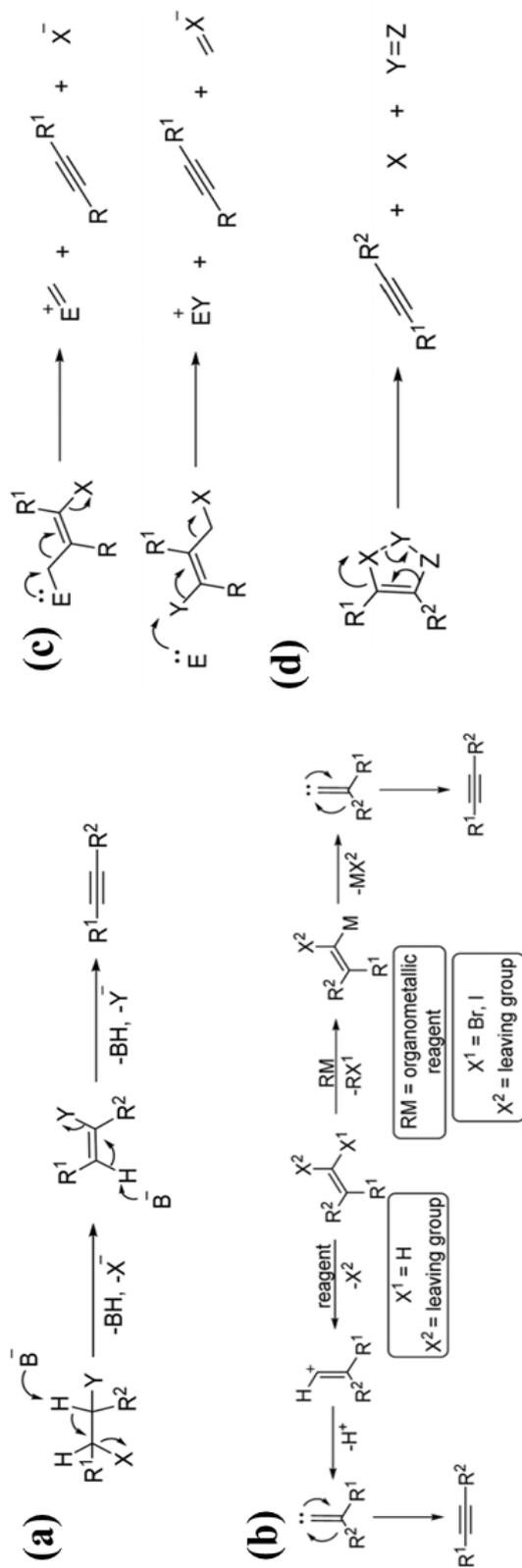
2. 3. Synthesis of alkynes and (+)-taylorione

Alkynes have many beneficial synthetic applications. A recent study outlined the various applications of alkynes such as in the synthesis of polyynes, ynoates, ynones, enamines, enynes, imines, ketones, vinyl compounds, acrylic derivatives, carbocycles and heterocycles (**Scheme 4**) ^[18].



Scheme 4. Synthetic applications of alkynes ^[18].

Various methods have been reported for the synthesis of alkynes. For instance, alkynes have been synthesized by α,β -elimination reactions ^[19, 20]. This involves a process where geminal or vicinal leaving groups undergo elimination reaction by involving an adjacent atom or group to afford the desired alkynes (**Scheme 5a**).

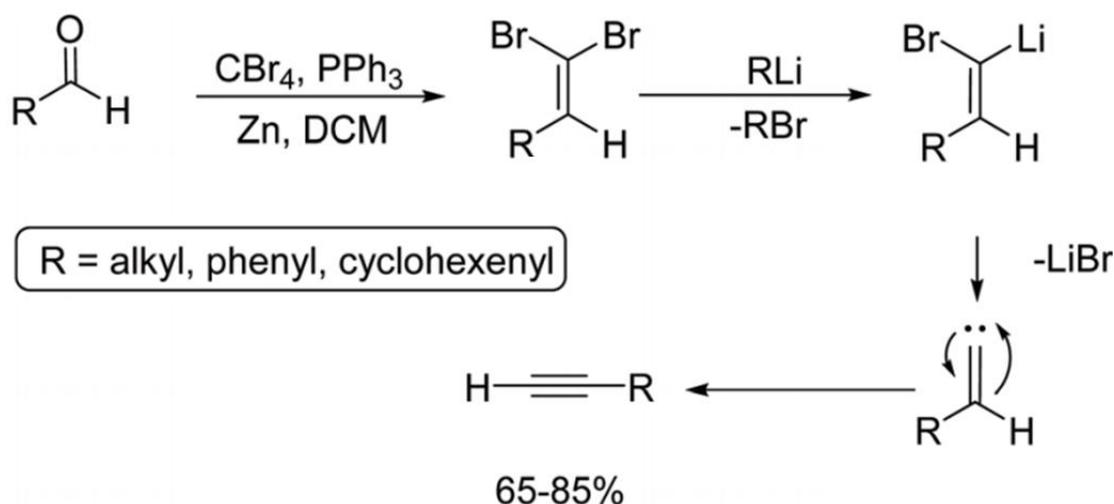


Scheme 5. Synthesis of alkynes by **(a)** α,β -elimination reactions, **(b)** carbene rearrangement, **(c)** fragmentation, and **(d)** cyclic elimination ^[19-24].

Alkynes have also been synthesized by carbene rearrangement [21-24]. Specifically, the alkynes are synthesized through a carbene intermediate, followed by intramolecular rearrangement (**Scheme 5b**). Additionally, alkynes can be successfully synthesized by various miscellaneous reactions such as fragmentation (**Scheme 5c**) and cyclic elimination (**Scheme 5d**). However, fragmentation or cyclic elimination reactions may take place during pyrolysis in some cases.

Corey-Fuchs alkyne synthesis was successfully used to generate terminal alkynes through a one-carbon homologation of aldehydes using triphenylphosphine and carbon tetrabromide [25].

The mechanism is similar to that of the Wittig reaction by the formation of a phosphorus ylide with triphenylphosphine and carbon tetrabromide. Reacting the phosphorus ylide with the aldehyde substrate yields a dibromoolefin. Upon treatment with two molar equivalents of *n*-BuLi, lithium halogen exchange and deprotonation yields a lithium acetylide species that undergoes hydrolysis to yield the terminal alkyne product (**Scheme 6**).

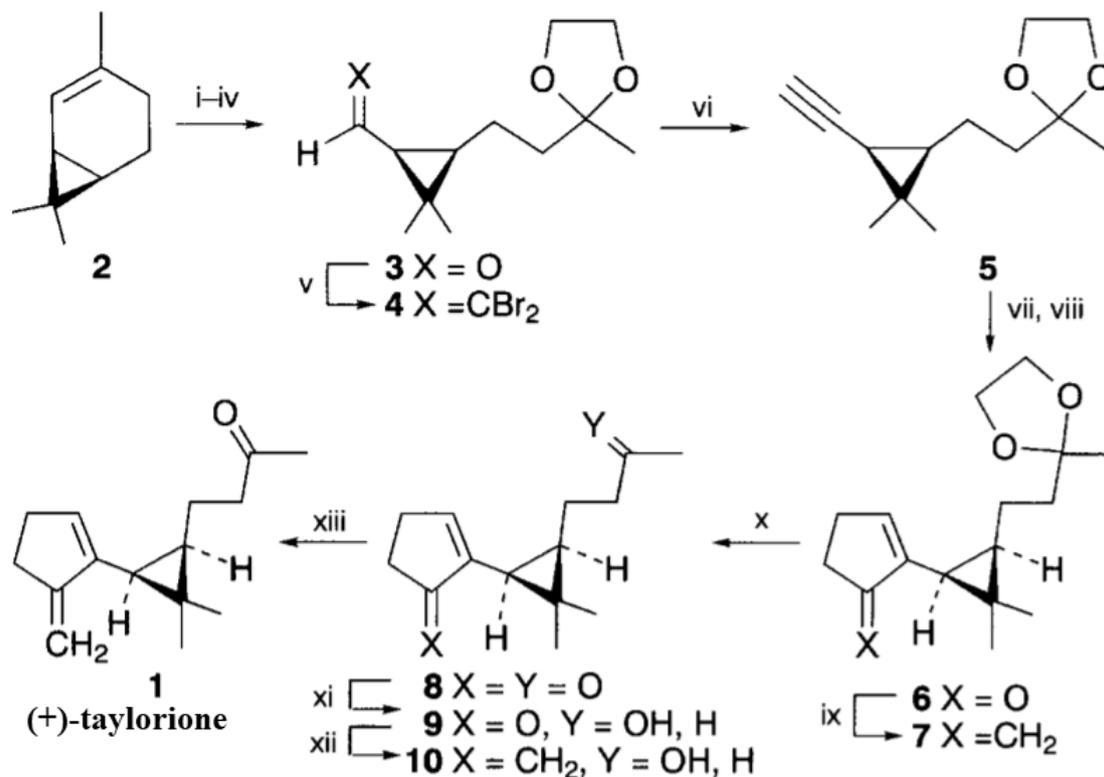


Scheme 6. Corey-Fuchs synthesis of a terminal alkyne [18].

More recently, a one-pot synthesis using a modified procedure has been developed. This synthetic transformation has been proven successful in the total synthesis of (+)-taylorione by Johnstone et al. [26] as shown in **Scheme 7**.

The Corey–Kim oxidation is a well-designed transformation for the conversion of alcohols into corresponding aldehydes and ketones, preceded by base treatment [27]. This process offers a less toxic alternative to chromium based oxidations with the use of *N*-chlorosuccinimidosulfonium chloride (NCS), dimethylsulfide (DMS), and triethylamine (TEA). The Corey-Kim reagent is formed in situ when NCS and DMS are reacted to form dimethylsuccinimidosulfonium chloride species.

The alkoxy sulfonium salt is deprotonated at the alpha position with triethylamine to afford the oxidized product. The reaction accommodates a wide array of functional groups, but allylic and benzylic alcohols are typically transformed into allylic and benzylic chlorides. Its application in synthesis is based on the mild protocol conditions and functional and protecting group compatibility.



Scheme 7. Synthesis of (+)-taylorione from (+)-2-carene ^[26].

Corey-Nicolaou macrolactonization provides the first method for preparing medium to large sized lactones such as macrolactone ^[28]. Previously, intermolecular outcompeted intramolecular lactonization even at low concentrations. One big advantage of this reaction is that it is performed under neutral conditions allowing the presence of acid and base-labile functional groups. To date, rings of 7 to 48 members have been successfully synthesized using this method. The reaction occurs in the presence of 2,2'-dipyridyl disulfide and triphenylphosphine. The reaction is generally refluxed in a nonpolar solvent such as benzene.

The mechanism begins with formation of the 2-pyridinethiol ester. Proton-transfer provides a dipolar intermediate in which the alkoxide nucleophile attacks the electrophilic carbonyl center, providing a tetrahedral intermediate that yields the macrolactone product.

3. CONCLUSIONS

There are numerous strategies that are available for the synthesis of alkanes. These include Corey's synthesis, Wurtz reaction, reduction of alcohols and aldehydes, Kolbe's electrolysis, hydrogenation of alkenes, and Grignard reaction. Corey's synthesis has several benefits in the synthesis of alkanes, such as yielding symmetrical, unsymmetrical, straight chain and branched chain alkanes. Additionally, high yields of alkanes can be obtained via Corey's synthesis, especially when primary alkyl halide and primary, secondary or tertiary lithium dialkyl copper are used. Not just alkanes, Corey's synthesis has also been found useful for the

synthesis of various organic compounds such as (+)-taylorione, terminal alkynes, caribenol A, ketones, and aldehydes. The general concept in the Corey's synthesis was explained in details in this works. Specific examples of Corey's reactions were provided to through more light on the beneficial modifications of the Corey's synthesis. There are so much to leverage from the concept and mechanism of the Corey's synthesis. More research is suggested in further developing this synthetic route to pave the way for generating various organic compounds which could serve as drugs for treating many diseases.

Acknowledgement

The authors are grateful to the University of Nigeria, Nsukka, Nigeria, Imo State University, Owerri, Nigeria, Federal University of Technology, Owerri, Nigeria, and University of Calabar, Calabar, Nigeria for providing enabling environments for this research. The authors also thank Prof. Arthur Jideonwo of the University of Benin, Nigeria for his advice in the course of this study.

References

- [1] Corey, E.J. The Logic of Chemical Synthesis: Multistep Synthesis of Complex Carbogenic Molecules (Nobel Lecture). *Angew. Chem. Int. Ed. Engl.* 30 (1991) 455-465
- [2] Akakuru, O.U. Louis, H. Amos, P.I. Akakuru, O.C. Nosike, E.I. and Ogulewe, E.F. The chemistry of chitin and chitosan justifying their nanomedical utilities. *Biochemistry and Pharmacology*, 7 (2018) 1000241
- [3] Josh, A.K., Purohit, D.M. Synthesis and antimicrobial activity of 5-(2'-n-butyl4'-chloro-1'-H-imidazol-5'-yl)-3-aryl-4,5-dihydro-{1-H/1-acetyl/1-phenyl}-pyrazoles. *World News of Natural Sciences* 35 (2021) 38-47
- [4] Arockia doss, M., Rajkumar R., Prabhakaran, A., Dhineshkumar, E., Uma D. Antimicrobial evaluation of 1-(2-(2,3,5-triphenylcyclopenta-2,4-dien-1-yl)ethyl)piperazine and their derivatives. *World News of Natural Sciences* 30(2) (2020) 213-219
- [5] Blessing, E.N. Chukwuemeka, I.S. David, U.C. and Onuawuchi, U.G. Antibacterial properties of probiotics bacterial isolated from human breast milk. *World News of Natural Sciences* 29(3) (2020) 290-297
- [6] Akakuru, O.U. Liu, C. Iqbal, M.Z. Dar, G.I. Yang, G. Qian, K. Nosike, E.I. Xing, J. Zhang, J. Li, Y. Li, J. and Wu, A. A hybrid organo-nanotheranostic platform of superlative biocompatibility for near-infrared-triggered fluorescence imaging and synergistically enhanced ablation of tumors. *Small* 16(41) (2020) 2002445
- [7] Sakhivel, A., Gopalakrishnan, A. Prevalence and pathology manifestation of *Acanthocephalus ranae* infestation in finfishes of Tamil Nadu, southeast coast of India. *World News of Natural Sciences* 33 (2020) 1-19
- [8] Akakuru, O.U. Louis, H. Oyebanji, O.O. Ita, B.I Amos, P.I. and Philip, M. Utility of nanomedicine for cancer treatment. *Journal of Nanomedicine and Nanotechnology*, 9(1) (2018) 1-6

- [9] Corey, E. J. and Boger, D. Oxidative cationic cyclization reactions effected by pyridinium chlorochromate. *Tetrahedron Lett.* 19 (1978) 2461-2464
- [10] Corey, E.J. and Suggs, W. Pyridinium chlorochromate. An efficient reagent for oxidation of primary and secondary alcohols to carbonyl compounds. *Tetrahedron Lett.* 31 (1975) 2647-2650
- [11] Olamilekan, A.R. Therapeutic effects of Cucumis metuliferus fruits on avian viruses. *World News of Natural Sciences* 35 (2021) 68-82
- [12] Akakuru, O.U. and Isiuku, B.O. Chitosan hydrogels and their glutaraldehyde-crosslinked counterparts as potential drug release and tissue engineering systems - synthesis, characterization, swelling kinetics and mechanism. *Journal of Physical Chemistry and Biophysics*, 7(3) (2017) 1000256
- [13] Enwereuzo, O.O. Akakuru, O.C. Uwaoma, R.C. Elemike, E.E. and Akakuru, O.U. Self-Assembled Membrane-Polymer Nanoparticles of Top-Notch Tissue Tolerance for the Treatment of Gastroesophageal Reflux Disease. *Journal of Nanostructure in Chemistry* (2021), <https://doi.org/10.1007/s40097-021-00394-w>
- [14] Han, J. Liu, L. Chang, Y. Yue, G. Guo, J. Zhou, L. Li, C. and Yang, Z. Asymmetric Total Synthesis of Caribenol A via an Intramolecular Diels–Alder Reaction. *J. Org. Chem.* 78 (2013) 5492-5504
- [15] Liu, L. Han, J. Yue, G. Li, C. And Yang, Z. Asymmetric total synthesis of caribenol A. *J. Am. Chem. Soc.* 132 (2010) 13608-13609
- [16] Khusro, A. and Aarti, C. Extrapulmonary tuberculosis: An overview on infection beyond lungs. *World News of Natural Sciences* 28 (2020) 131-141
- [17] Akakuru, O.U., Iqbal, M.Z., Liu, C., Li, Z., Yang, G., Xu, C., Nosike, E.I., Dar, G.I., Yang, F. and Wu, A. (2020). Revisiting and old friend TiO₂; a crucial assessment of its current biosafety. *Nano Biomedicine and Engineering*, 12, 1, 21-45
- [18] Shaw, R. Elagamy, A. Althagafi, I. and Pratap, R. Synthesis of alkynes form non-alkyne sources. *Org. Biomol. Chem.* 18 (2020) 3797
- [19] Blanksby, S.J. and Elison, G.B. Bond dissociation energies of organic molecules. *Acc. Chem. Res.* 36 (2003) 255-263
- [20] Orita, A. and Otera, J. Elimination strategy of aromatic acetylenes. *Chem. Rev.* 106 (2006) 5387-5412
- [21] Eymery, F. Iorga, B. and Savignac, P. The Usefulness of Phosphorus Compounds in Alkyne Synthesis. *Synthesis* 2 (2000) 185-213
- [22] Eisler, S. Slepko, A.D. Elliot, E. Luu, T. McDonald, R. Hegmann, F.A and Tykwinski, R.R. Polyynes as a Model for Carbyne: Synthesis, Physical Properties, and Nonlinear Optical Response. *J. Am. Chem. Soc.* 127 (2005) 2666-2676
- [23] Eisler, S. Chahal, N. McDonald, R. and Tykwinski, R.R. Alkyne Migration in Alkylidene Carbenoid Species: A New Method of Polyynes Synthesis. *Chem. – Eur. J.* 9 (2003) 2547-2550

- [24] Meng, T. Zhang, H. and Xi, Z. Synthesis of *gem*-dihaloenynes and butatrienes from *gem*-dihalovinyl derivatives. *Tetrahedron Lett.* 53 (2012), 4555-4557
- [25] Corey, E.J. and Fuchs, P.L. A synthetic method for formyl→ethynyl conversion (RCHO→RC≡CH or RC≡CR'). *Tetrahedron Lett.* 1972, 13, 3769-3772
- [26] Johnstone, C. Kerr, W.J. and Lange, U. Total synthesis of (+)-taylorione utilising modified Pauson–Khand reaction methodology. *J. Chem. Soc. Chem. Commun.* 4 (1995) 457-458
- [27] Corey, E.J. and Kim, C.U. New and highly effective method for the oxidation of primary and secondary alcohols to carbonyl compounds. *J. Am. Chem. Soc.* 94 (1972) 7586-7587
- [28] Parenty, A. Moreau, X. Campagne, J.-M. Macrolactonizations in the Total Synthesis of Natural Products. *Chem. Rev.* 106 (2006) 911-939