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PII: S0040-4039(19)31029-9
DOI: https://doi.org/10.1016/j.tetlet.2019.151249
Reference: TETL 151249

To appear in: *Tetrahedron Letters*

Received Date: 29 June 2019
Revised Date: 26 September 2019
Accepted Date: 2 October 2019

Please cite this article as: Chavan, S.P., Kawale, S.A., Chavan, P.N., Formal Synthesis of Brivaracetam: A Key to Construct the Pyrrolidone Scaffold Using Pd-Catalyzed Oxidative Cyclization and Ring-Closing Metathesis Reaction, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151249

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Graphical Abstract

Formal Synthesis of Brivaracetam: A Key to Construct the Pyrrolidone Scaffold Using Pd-Catalyzed Oxidative Cyclization and Ring-Closing Metathesis Reaction

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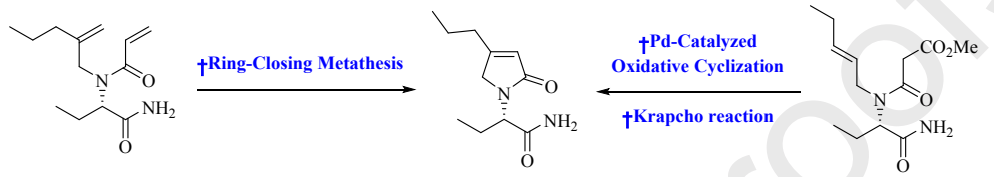
Subhash P. Chavan*[a,b], Sanket A. Kawale[a,b], Prakash N. Chavan[a]



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Formal Synthesis of Brivaracetam: A Key to Construct the Pyrrolidone Scaffold Using Pd-Catalyzed Oxidative Cyclization and Ring-Closing Metathesis Reaction

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Pd-catalyzed oxidative cyclization
Ring-closing metathesis reaction
Pyrrolinone
Antiepileptic drugs

ABSTRACT

A short and efficient synthetic approach for brivaracetam has been accomplished *via* two different routes which utilize Pd-catalyzed oxidative cyclization and ring-closing metathesis (RCM) as the key reaction. These two routes are novel, simple, scalable and rely on (*E*)-pent-2-en-1-ol and vareladehyde as a commercially available starting material to yield brivaracetam with good overall yield.

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1. Introduction

About 1% of worldwide populations have been affected by epilepsy, which is the most common neurological disorders.[1] An epileptic seizure is a time of side effects due to anomalous unnecessary or synchronous neuronal movement in the mind. The risk of premature death in people with epilepsy is up to three times higher than in the general population. While epilepsy can occur at any age, it is most commonly observed among young and older (> 65 years) people. For most of the cases reason of epilepsy is totally unknown but, in some cases, it arises due to the brain malformations, head injuries, tumors, encephalitis, metabolic disorders, strokes and neurodegenerative diseases.[2] Epilepsy can be controlled about 70% with medicines, neurostimulation, surgery and dietary changes.

Pharmacological therapy is the first choice for the treatment of epilepsy. The drug design and development studies led to different types of antiepileptic drugs (AED). Levetiracetam **1**, brivaracetam **2** and seletracetam **3** are important AEDs developed by varying different substituents and groups on pyrrolidone skeleton (Figure **1**).[3] The synaptic vesicle protein 2A (SV2A) is responsible for a neurological disorder and its mechanism get retarded after bonding with AEDs.[4] Brivaracetam **2** developed as a chemical analog of levetiracetam **1**. Levetiracetam **1**, an antiepileptic drug marketed under the trade name Keppra® has some adverse effects like depression, anger and even psychosis which limit its uses. While, brivaracetam **2** is more advantages over the previous one because of its bioavailability and the ability to get absorbed quickly into the brain and used to treat all different type of seizures.[5] Recently,

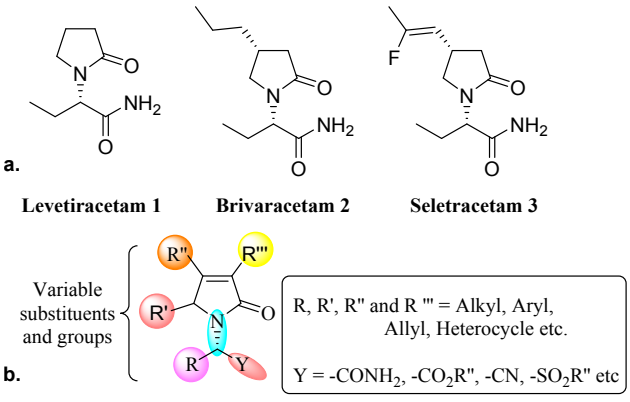

Fig **1**: a. Antiepiletic drug; b. Variables for synthesis of pyrrolinone analogues.

brivaracetam **2** is strongly recommended 3rd-generation antiepileptic drugs in the USA and Europe for the treatment of partial-onset seizures related to epilepsy.[6a] Seletracetam **3** was developed by UCB Pharmaceuticals along with brivaracetam **2** as a more potent and effective anticonvulsant drug to replace levetiracetam **1.** Production of seletracetam **3** was halted due to the investigation of a newer antiepileptic drug brivaracetam **2**.[6b]

Pharmacological and physiological significant properties of brivaracetam **2** have been attracted the organic community to pursue the synthesis of antiepileptic drugs. As a result, various synthetic approaches of brivaracetam **2** have been reported in the literature as shown in figure **2**.[7] Most of these synthesis involved chiral resolution and asymmetric synthesis and some of these methods have been accompanied with several drawbacks such as

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condition which adversely affect the enantiomeric purity, used hazardous alkylating agents, poor product yield by diastereomeric mixture separation, tedious and time consuming

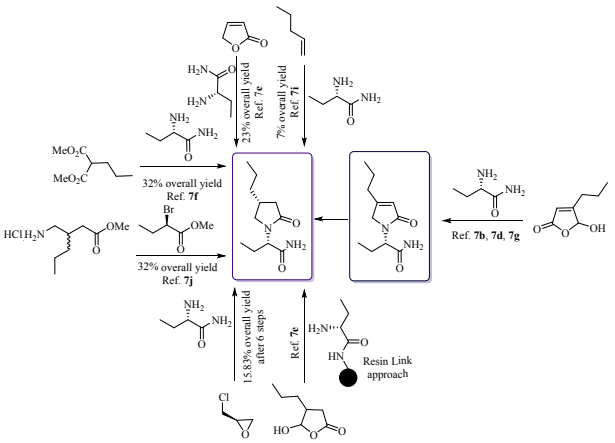


Fig **2**: Key synthetic routes of brivaracetam **2**

experimental procedure. Considering the key problems of the reported methods there is a huge scope to design and develop a short, simple and highly economical, scalable synthesis of brivaracetam **2**. The key task for the chemist is to fix the desired stereochemistry of the propyl chain at 4th position on pyrrolidone ring.

In the recent post, we have exploited a novel palladium-catalyzed oxidative cyclization as key step to assemble five membered lactam of 3-ethyl-4-methyl pyrroline-2-one[8] and six membered lactam D-ring of comptothecin.[9] As a continuation of our efforts to explore the new synthetic methods for biologically active compounds[10] and knowing the pharmaceutical significance of brivaracetam **2** which contains pyrrolinone motif, herein we present two different routes for enantioselective formal synthesis of brivaracetam **2** utilizing Pd-catalyzed oxidative cyclization and ring-closing metathesis (RCM) as key transformations respectively. In addition, our synthetic design offers the flexibility to vary various substituents and groups on pyrrolinone ring by proper choice of starting material thus giving rise to various pyrrolinone analogues as shown in figure **1b**.

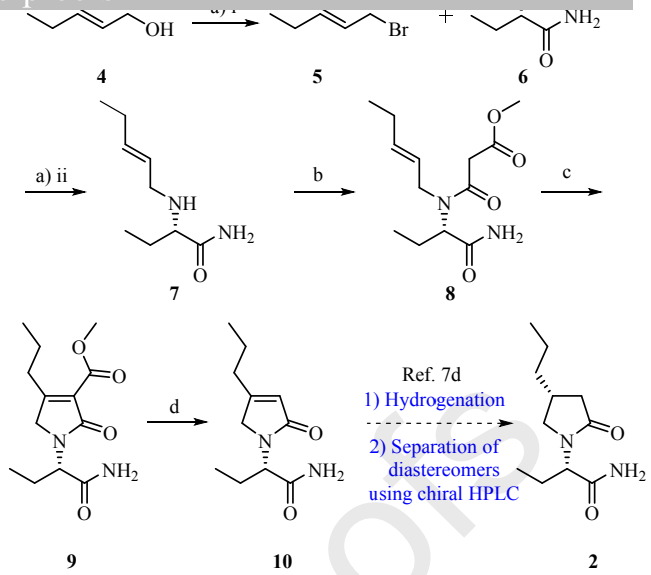
2. Result and discussion

2.1. Pd-catalyzed oxidative cyclization approach

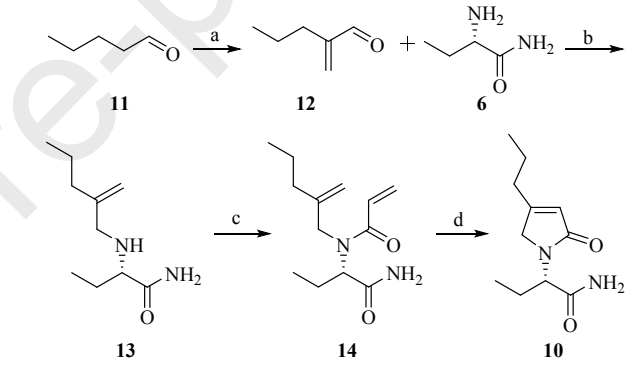
According to our plan, synthesis commenced with (*E*)-pent-2-en-1-ol **4**, which was converted into its bromide **5** by using PBr_3. The crude bromide **5** was subjected to *N*-alkylation with (*S*)-2-aminobutanamide **6** using K_2CO_3 in DMF as a solvent to afford compound **7** in 83% yield over 2 steps. Next plan was to prepare intermediate **8** for Pd-catalyzed oxidative cyclization. Accordingly, the amine **7** was heated at 110 °C in dimethyl malonate to furnish key intermediate 8 in 85% yield. According to strategy, compound **8** was subjected to oxidative cyclization reaction using $PdCl_2/CuCl_2.H_2O$ in DMF:H_2O to obtained five membered cyclized lactam 9 in 50% yield[8a] which further on Krapcho decarboxylation[8a,11] led to known intermediate **10** in 87% yield. Compound **10** could be easily converted into brivaracetam **2** using literature known procedure (Scheme **1**).[7d]

2.2. Ring-closing metathesis approach

Alternative strategy was planned to improve the yield for the key intermediated **10** by employing ring-closing metathesis



Scheme 1. Reagents and conditions: a) i) PBr_3, Et_2O, 0 °C, 12 h; ii) K_2CO_3, DMF, 0 °C - rt, 12 h, 83 % over 2 steps; b) Dimethyl malonate, 110 °C, 24 h, 85%; c) $PdCl_2$, $CuCl_2.H_2O$, DMF:H_2O:3:1, 80 °C, 2 h, 50%; d) NaCl, DMSO, 140 °C, 12 h, 87%.



Scheme 2. Reagents & reaction: a) *p*-N,N'-Dimethyl amine benzoic acid, pyrrolidine, HCHO, DCM, 45 °C, 0.75 h, 85%; b) (i) 3A° molecular seives, DCM, rt, 12 h; (ii) $NaBH_4$, EtOH, 12 h, 80% over 2 steps; c) Acrolyl chloride, Et_3N, DCM, 0 °C, 1 h, 90%; d) Grubbs 2nd gen. cat, toluene, 80 °C, 24 h, 84%.

reaction.[8a,12] Accordingly, 2-methylenepentanal **12** obtained by organocatalysed α-methylenation of valeraladehyde **11** in 85% yield.[13] The, aldehyde **12** upon treatment with (*S*)-2-aminobutanamide **6** in presence of 3 Å molecular sieves followed by reduction with $NaBH_4$ of resulted imine gave *N*-alkylated product **13** in 80% yield.[14] Next task was to obtained RCM precursor diene **14**, which was prepared by using **13** and acrolyl chloride to afford diene **14** in 90% yield. Finally, the diene **14** smoothly underwent ring closing metathesis reaction using Grubbs' II gen. catalyst in toluene solvent at 80 °C to give intermediate **10** in 84% yield. (Scheme **2**)

3. Conclusion

In conclusion, we have successfully investigated two different tactics for formal synthesis of the brivaracetam starting from alcohol and aldehyde as commercially available materials with 30.6% and 51.4% overall yield in 4 steps each respectively. The novel palladium-catalyzed intramolecular cyclization and Ring-Closing Metathesis (RCM), which have been successfully

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expl h) synthesis involved inexpensive starting materials, simple reaction condition, use of nonhazardous reagents and product formation in excellent yield. The present protocols can be scalable for the brivaracetam synthesis and could be helpful to prepare a library of pyrrolinone derivatives as well.

4. Acknowledgments

S. A. K and P. N. C thank CSIR, New Delhi for research fellowship. We thank Dr. U. R. Kalkote for useful discussion. The authors thank CSIR, New Delhi for financial support as of XII Five Year Plan program under title ORIGIN (CSC-0108) and ACT (CSC-0301).

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- Two efficient approaches for synthesis of brivaracetam are reported.
- The syntheses were accomplished from the known and Cost-effective starting materials.
- Intramolecular Pd-catalyzed oxidative cyclization and Ring-Closing metathesis reaction were used to construct pyrolinone skeleton.