Palladium-Catalyzed intramolecular Cyclization of '2-bromo-1,5-di-ene-7-yne'System: A Versatile Route to the Poly-ene Substituted Cyclohexenols

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Abstract: A general and efficient methodology has been developed for the synthesis of substituted cyclohexenol system with conjugated bis-exocyclic diene via Pd-catalyzed intramolecular 6-*exo-dig* cyclization of 'ene-yne' moiety. This method is straight forward and high yielding.

Poly-ene-substituted cyclohexenol moiety has been found as a useful scaffold for the construction of numerous naturally occurring and biologically active molecules (Figure 1).

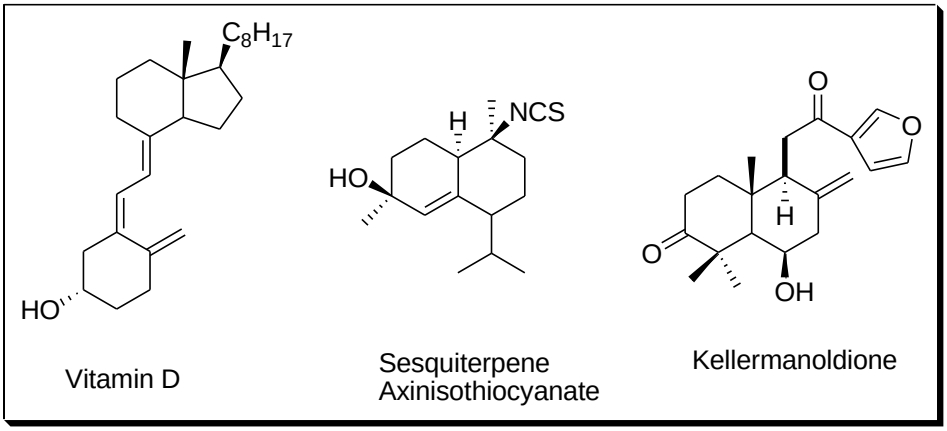
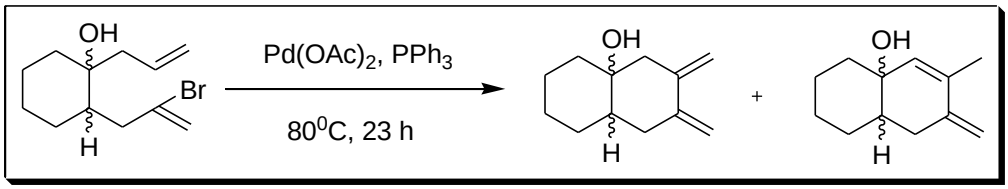


Figure 1: Natural products containing polyene substituted cyclohexenols

Vitamin D attracts much attention due to the unique specificity and selectivity of their formation *in vivo*, as well as their bioactivity and the therapeutic properties[1]. Bicyclic sesquiterpenes containing isocyano, isothiocyanate are secondary metabolites isolated from sponges of the genus *Axinyssa*. Biological activities such as antihelmintic, antimicrobial, and cytotoxic properties have been ascribed to these nitrogen containing sesquiterpenes[2]. Kellermanoldione,

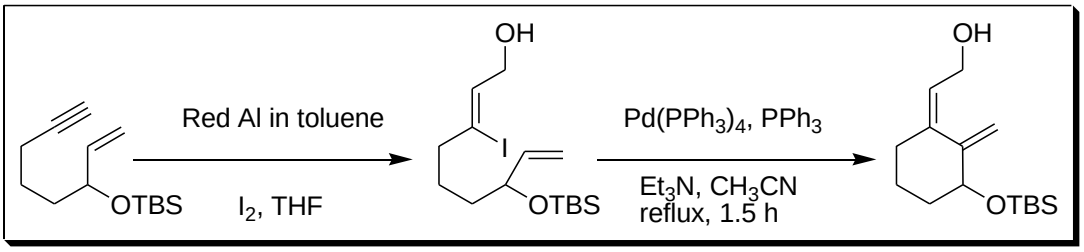
containing cyclohexanol moiety with exocyclic double bond, is a labdane diterpene isolated from *Brickellia kellermanii* Grenm, a shrub which is reported to have potent antidiarrhetic properties and is used in Mexican folk medicine[3].

Rhodium- and Palladium-catalysed formation of six-membered ring with conjugated mono- and bis-exocyclic diene was reported by Grigg and coworkers (Scheme 1)[4].



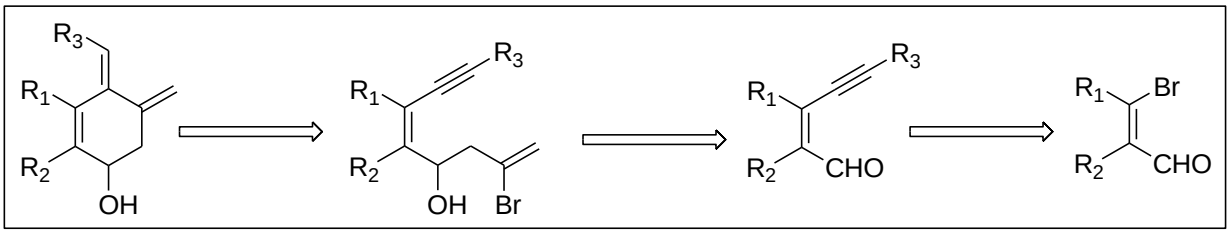
Scheme 1: Synthesis of conjugated 6-membered bis-exocyclic dienes

Mascareñas and coworkers synthesized *bis*-exocyclic conjugated diene system of vitamin D r synthons by palladium-catalyzed intramolecular cyclization of the (Z)-iodoalkene resulting from the stereoselective hydrometallation-iodinolysis of propargylic alcohol (Scheme 2)[5].



Scheme 2: Synthesis of *bis*-exocyclic conjugated diene system of vitamin D ring A synthons

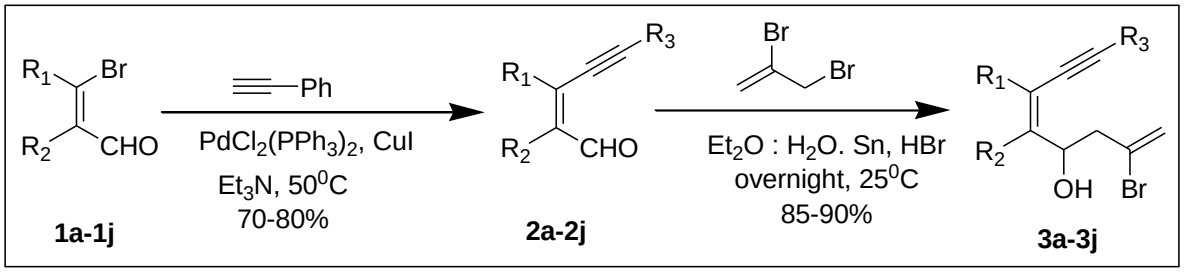
On the basis of our previous studies on the Pd catalyzed cyclization of substrates derived from *β*-bromovinyl aldehydes[6-31], here we planned to develop a new route to cyclohexenol skeleton with conjugated diene by exploiting intramolecular Heck cyclization starting from a novel substrate (Scheme 3).



Scheme 3: Disconnection approach from cyclohexenol to bromo-vinyl aldehyde

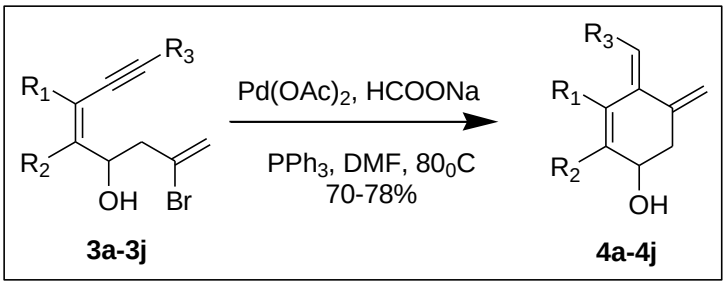
Results and Discussion:

The convergent method involved the preparation of the precursors (**3a-3j**) which were synthesized from *β*-bromovinyl aldehydes as per Scheme 4.



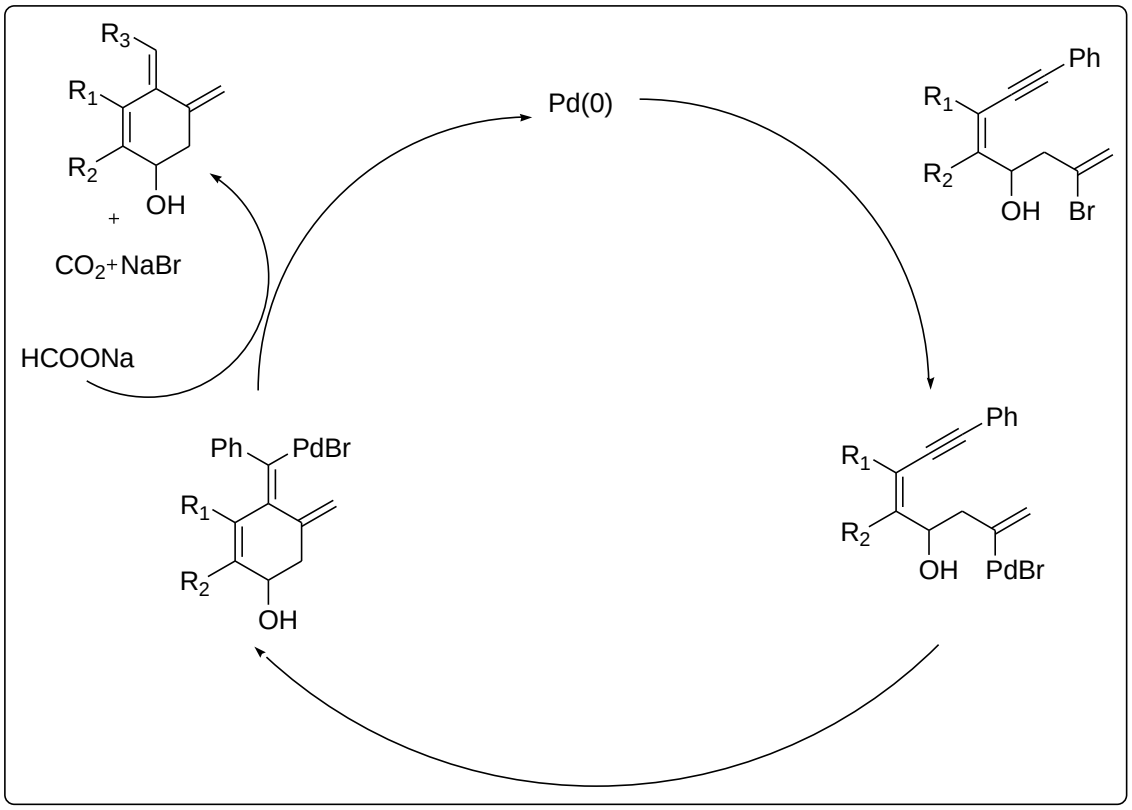
Scheme 4: Preparation of 2-bromo-8-phenyl-octa-1,5-diene-7-yn-4-ol

The precursors were synthesized in good to excellent yield by Sonogashira coupling5 of *β*-bromovinylaldehydes with ethynyl benzene using PdCl2(PPh3)2 (2 mol%) and CuI (1 mol%) as catalyst in Et3N as solvent at 50 ºC for 6-7 hr. followed by Sn (1.5 mmol) mediated allylation6 with 2,3-dibromo propene (3 mmol) in Et_2O:H_2O (3:1) medium to afford the precursor 2-Bromo-8-phenyl-octa-1,5-diene-7-yn-4-ol (**3a-3j**) in good (85-90%) yield (Scheme 1.42). The Heck precursors on treatment with Pd(OAc)2 (5 mol %), PPh3 (0.5 mmol) and HCOONa (1.0 mmol) in DMF at 80 °C yielded 4-benzylidene- 5-methylene-cyclohex-2-enol (**4a-4j**) as the only isolable product.



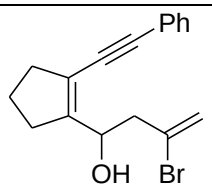
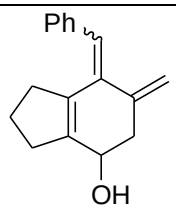
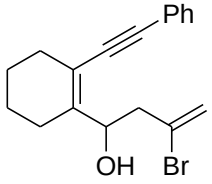
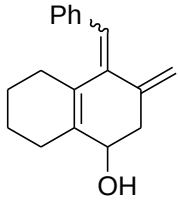
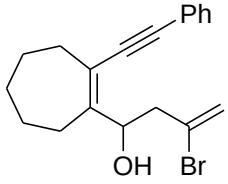
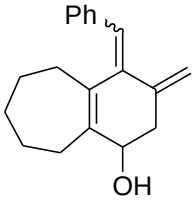
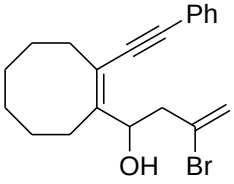
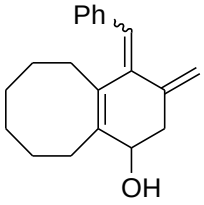
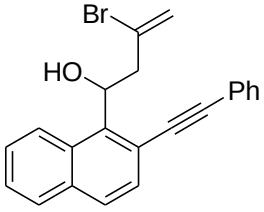
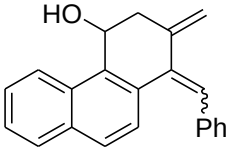
Scheme 5: Heck cyclization of 2-bromo-8-phenyl-octa-1,5-diene-7-yn-4-ol

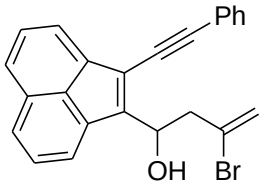
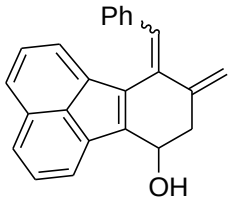
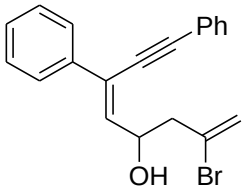
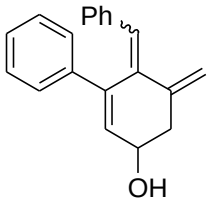
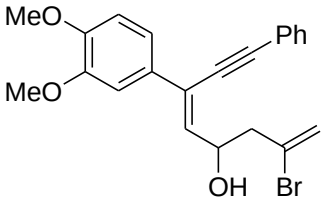
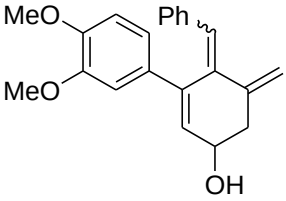
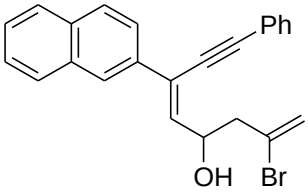
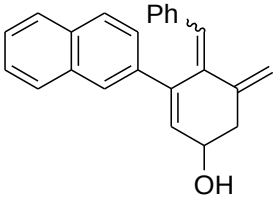
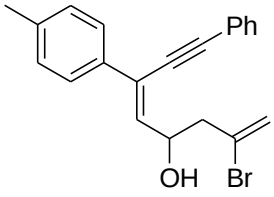
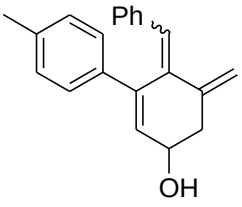
Stereoselectively only one isomer was isolated. However stereochemistry of the product was rigorously established and also based on the mechanism of palladium-catalyzed-*exo-dig* cyclization[32] followed by trapping of cyclopalladium intermediate with the hydride, the stereochemistry of product is expected to be the more stable *E*-isomer as shown in Scheme 6[33, 34]. Several applications and usefulness have been cited in recent publications ranging from natural product derivation to biomedical applications[15, 17, 35-53].



Scheme 6: Mechanism of Pd-catalyzed *exo*-dig cyclization

With this strategy a number of 6-membered bis-exocyclic dienes were synthesized (Table 1)

Entry	Substrate	Product	Yield (%)
1	 **3a**	 **4a**	85
2	 **3b**	 **4b**	84
3	 **3c**	 **4c**	84
4	 **3d**	 **4d**	87
5	 **3e**	 **4e**	85

Entry	Substrate	Product	Yield (%)
6	 **3f**	 **4f**	80
7	 **3g**	 **4g**	67
8	 **3h**	 **4h**	66
9	 **3i**	 **4i**	67
10	 **3j**	 **4j**	68

Conclusion:

In short, we have outlined an important synthetic protocol for the construction of 6- membered ring via Pd-catalyzed intramolecular 6-*exo-dig* cyclization of 'ene-yne' moiety. The developed method is simple, straight forward and high yielding. The formed cyclohexenol system with conjugated bis-exocyclic diene can be taken as an effective Diels-Alder precursor.

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References:

1. Dmitrenko, O.; Frederick, J.; Reischl, W., Ab initio study of conformational stability in previtamin D, vitamin D and related model compounds. *Journal of Molecular Structure: THEOCHEM* **2000,** *530* (1-2), 85-96.
2. Zubia, E.; Ortega, M. J.; Hernández-Guerrero, C. J.; Carballo, J. L., Isothiocyanate sesquiterpenes from a sponge of the genus Axinyssa. *Journal of natural products* **2008,** *71* (4), 608-614.
3. Jung, M. E.; Cordova, J.; Murakami, M., Total Synthesis of (±)-Kellermanoldione: Stepwise Cycloaddition of a Functionalized Diene and Allenoate. *Organic letters* **2009,** *11* (17), 3882-3885.
4. Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T., Palladium (II) catalysed construction of tetrasubstituted carbon centres, and spiro and bridged-ring compounds from enamides of 2-lodobenzoic acids. *Journal of the Chemical Society, Chemical Communications* **1986,** (23), 1697-1699.
5. Mascareñas, J. L.; García, A. M.; Castedo, L.; Mouriño, A., A short, efficient route to 1-hydroxylated vitamin D ring A fragments. *Tetrahedron letters* **1992,** *33* (30), 4365-4368.
6. Ghosh, M.; Ray, J. K., Ten years advancement in the synthetic applications of 2-bromo-cyclohexenecarbaldehydes and 2-bromobenzaldehydes and derived substrates under palladium-catalyzed cross-coupling conditions. *Tetrahedron* **2017,** *73* (27-28), 3731-3799.
7. Roy, B. C.; Gupta, M. D.; Bhoumik, L.; Ray, J. K., Spectroscopic investigation of water-soluble polyaniline copolymers. *Synthetic Metals* **2002,** *130* (1), 27-33.
8. Brahma, S.; Ray, J. K., Halovinyl aldehydes: useful tools in organic synthesis. *Tetrahedron* **2008,** *64* (13), 2883-2896.
9. Ray, J.; Bhowmik, L., Sol Gel Technique to Prepare Composite Material of Glass-Dye-Polymers. **2021**.
10. Ray, J.; Bhowmik, L., Preparation and Evaluation of Novel Bamboo-Polymer Composites. **2021**.
11. Sarkar, P.; Ahmed, A.; Ray, J. K., Suzuki cross coupling followed by cross dehydrogenative coupling: An efficient one pot synthesis of Phenanthrenequinones and analogues. *Tetrahedron Letters* **2020,** *61* (13), 151701.

12. Ray, J. K.; Singha, R.; Ray, D.; Ray, P.; Rao, D. Y.; Anoop, A., Palladium-catalyzed expedient Heck annulations in 1-bromo-1,5-dien-3-ols: Exceptional formation of fused bicycles. *Tetrahedron Letters* **2019,** *60* (13), 931-935.
13. Ray, J. K.; Paul, S.; Ray, P.; Singha, R.; Rao, D. Y.; Nandi, S.; Anoop, A., Pd-catalyzed intramolecular sequential Heck cyclization and oxidation reactions: a facile pathway for the synthesis of substituted cycloheptenone evaluated using computational studies. *New Journal of Chemistry* **2017,** *41* (1), 278-284.
14. Chaudhuri, S.; Maity, S.; Roy, M.; Ray, P.; Ray, J. K., A Vinyl Radical Cyclization Route to Hydroxycyclohexene Fused Carbocycles. *Asian Journal of Chemistry* **2016,** *28* (1).
15. Brahma, S.; Ray, P.; Singha, R.; Ray, J. K., Visible Colourimetric and Ratiometric Fluorescent Chemosensors for Cu (II) and Ni (II) Ions. *Asian Journal of Chemistry* **2016,** *28* (5), 1035.
16. Nandi, S.; Singha, R.; Ray, J. K., Palladium catalyzed intramolecular cascade type cyclizations: Interesting Approach towards naphthoquinone derivatives having an O-containing heterocyclic skeleton. *Tetrahedron* **2015,** *71* (4), 669-675.
17. Ray, D.; Nasima, Y.; Sajal, M. K.; Ray, P.; Urinda, S.; Anoop, A.; Ray, J. K., Palladium-Catalyzed Intramolecular Oxidative Heck Cyclization and Its Application toward a Synthesis of (±)-β-Cuparenone Derivatives Supported by Computational Studies. *Synthesis* **2013,** *45* (09), 1261-1269.
18. Nandi, S.; Singha, R.; Samanta, S.; Ray, J. K., Synthesis of pentalongin and C (1)-and C (3)-substituted pentalongin using intramolecular Heck reaction. *Tetrahedron Letters* **2012,** *53* (21), 2659-2661.
19. Paul, S.; Samanta, S.; Ray, J. K., Palladium-catalyzed one-pot Suzuki coupling followed by arylpalladium addition to aldehyde: A convenient route to fluoren-9-one derivatives. *Tetrahedron Letters* **2010,** *51* (42), 5604-5608.
20. Samanta, S.; Mohapatra, H.; Jana, R.; Ray, J. K., Pd (0) catalyzed intramolecular Heck reaction: a versatile route for the synthesis of 2-aryl substituted 5-, 6-, and 7-membered O-containing heterocycles. *Tetrahedron Letters* **2008,** *49* (50), 7153-7156.
21. Jana, R.; Samanta, S.; Ray, J. K., Substrate dependent intramolecular palladium-catalysed cyclisation and subsequent β-H elimination or C–H activation: a general method for the synthesis of fused pyran rings. *Tetrahedron Letters* **2008,** *49* (5), 851-854.
22. Jana, R.; Chatterjee, I.; Samanta, S.; Ray, J. K., Novel and rapid palladium-assisted 6pi electrocyclic reaction affording 9,10-dihydrophenanthrene and its analogues. *Org Lett* **2008,** *10* (21), 4795-7.
23. Ray, D.; Ray, J. K., Novel Synthetic Approach Toward (±)-β-Cuparenone via Palladium-Catalyzed Tandem Heck Cyclization of 1-Bromo-5-methyl-1-aryl-hexa-1, 5-dien-3-ol Derivatives. *Organic letters* **2007,** *9* (2), 191-194.
24. Mal, S. K.; Ray, D.; Ray, J. K., Palladium-catalyzed tandem oxidative cyclization of 1-bromohexa-1,5-dien-3-ols: easy access to cyclopentenones. *Tetrahedron Letters* **2004,** *45* (2), 277-279.
25. Ray, J. K., Stereoselective Synthesis of Bioactive Compounds (Track) Use of "halo vinyl aldehydes" in organic synthesis and chemo selective functional group transformations in gamma lactam derivatives.
26. Ray, P.; Gidley, D.; Badding, J. V.; Lueking, A. D., UV and chemical modifications of polymer of Intrinsic Microporosity 1 to develop vibrational spectroscopic probes of surface chemistry and porosity. *Microporous and Mesoporous Materials* **2019,** *277*, 29-35.

27. Ray, P.; Xu, E.; Crespi, V. H.; Badding, J. V.; Lueking, A. D., In situ vibrational spectroscopy of adsorbed nitrogen in porous carbon materials. *Physical Chemistry Chemical Physics* **2018,** *20* (22), 15411-15418.
28. Ray, P.; Gray, J. L.; Badding, J. V.; Lueking, A. D., High-Pressure Reactivity of Triptycene Probed by Raman Spectroscopy. *The Journal of Physical Chemistry B* **2016,** *120* (42), 11035-11042.
29. Ray, P., Interactions of nitrogen and hydrogen with various 1D and 3D carbon materials probed via in-situ vibrational spectroscopy. *Ph. D. Thesis* **2016**.
30. Wang, C.-Y.; Ray, P.; Gong, Q.; Zhao, Y.; Li, J.; Lueking, A. D., Influence of gas packing and orientation on FTIR activity for CO chemisorption to the Cu paddlewheel. *Physical Chemistry Chemical Physics* **2015,** *17* (40), 26766-26776.
31. Brahma, S.; Ray, P.; Ray, J. K., Synthesis of azirines containing aldehyde functionality and their utilization as synthetic tools for five membered oxazoles and isoxazoles (vol 45, pg 311, 2008). *JOURNAL OF HETEROCYCLIC CHEMISTRY* **2021,** *58* (6), 1388-1388.
32. Roesch, K. R.; Larock, R. C., Synthesis of isoquinolines and pyridines by the palladium/copper-catalyzed coupling and cyclization of terminal acetylenes and unsaturated imines: the total synthesis of decumbenine B. *The Journal of organic chemistry* **2002,** *67* (1), 86-94.
33. Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J., Facile one-pot synthesis of bromo homoallyl alcohols and 1, 3-keto acetates via allyltin intermediates. *The Journal of Organic Chemistry* **1984,** *49* (1), 172-174.
34. Oh, C. H.; Park, S. J., Palladium-catalyzed cycloreductions of haloene-ynes in the presence of triethylsilane. *Tetrahedron letters* **2003,** *44* (19), 3785-3787.
35. Das, A.; Haque, I.; Ray, P.; Ghosh, A.; Dutta, D.; Quadir, M.; De, A.; Gunewardena, S.; Chatterjee, I.; Banerjee, S.; Weir, S.; Banerjee, S. K., CCN5 activation by free or encapsulated EGCG is required to render triple-negative breast cancer cell viability and tumor progression. *Pharmacol Res Perspect* **2021,** *9* (2), e00753.
36. Ray, P.; Haideri, N.; Haque, I.; Mohammed, O.; Chakraborty, S.; Banerjee, S.; Quadir, M.; Brinker, A. E.; Banerjee, S. K., The Impact of Nanoparticles on the Immune System: A Gray Zone of Nanomedicine. *Journal of Immunological Sciences* **2021,** *5* (1).
37. Ray, P.; Dutta, D.; Haque, I.; Nair, G.; Mohammed, J.; Parmer, M.; Kale, N.; Orr, M.; Jain, P.; Banerjee, S.; Reindl, K. M.; Mallik, S.; Kambhampati, S.; Banerjee, S. K.; Quadir, M., pH-Sensitive Nanodrug Carriers for Codelivery of ERK Inhibitor and Gemcitabine Enhance the Inhibition of Tumor Growth in Pancreatic Cancer. *Molecular Pharmaceutics* **2021,** *18* (1), 87-100.
38. Ray, P.; Kale, N.; Quadir, M., New side chain design for pH-responsive block copolymers for drug delivery. *Colloids and Surfaces B: Biointerfaces* **2021,** *200*, 111563.
39. Babak, K.; Torabi, M.; Foad, K.; Priyanka, R., *Novel β-Cyclodextrin Functionalized Core-Shell Fe3O4 Magnetic Nanoparticles for the Removal of Toxic Metals from Water*. 2021.
40. Abdullah, C. S.; Ray, P.; Alam, S.; Kale, N.; Aishwarya, R.; Morshed, M.; Dutta, D.; Hudziak, C.; Banerjee, S. K.; Mallik, S.; Banerjee, S.; Bhuiyan, M. S.; Quadir, M., Chemical Architecture of Block Copolymers Differentially Abrogate Cardiotoxicity and Maintain the Anticancer Efficacy of Doxorubicin. *Molecular Pharmaceutics* **2020,** *17* (12), 4676-4690.
41. Clément, M.; Abdellah, I.; Ray, P.; Martini, C.; Coppel, Y.; Remita, H.; Lampre, I.; Huc, V., Synthesis and NMR study of trimethylphosphine gold(i)-appended calix[8]arenes as precursors of gold nanoparticles. *Inorganic Chemistry Frontiers* **2020**.

42. Confeld, M. I.; Mamnoon, B.; Feng, L.; Jensen-Smith, H.; Ray, P.; Froberg, J.; Kim, J.; Hollingsworth, M. A.; Quadir, M.; Choi, Y.; Mallik, S., Targeting the tumor core: hypoxia-responsive nanoparticles for delivery of chemotherapy to pancreatic tumors. *Molecular Pharmaceutics* **2020**.
43. Sarker, N. C.; Ray, P.; Pfau, C.; Kalavacharla, V.; Hossain, K.; Quadir, M., Development of Functional Nanomaterials from Wheat Bran Derived Arabinoxylan for Nucleic Acid Delivery. *Journal of Agricultural and Food Chemistry* **2020,** *68* (15), 4367-4373.
44. Ray, P.; Confeld, M.; Borowicz, P.; Wang, T.; Mallik, S.; Quadir, M., PEG-b-poly (carbonate)-derived nanocarrier platform with pH-responsive properties for pancreatic cancer combination therapy. *Colloids and Surfaces B: Biointerfaces* **2019,** *174*, 126-135.
45. Ray, P.; Ferraro, M.; Haag, R.; Quadir, M., Dendritic Polyglycerol-Derived Nano-Architectures as Delivery Platforms of Gemcitabine for Pancreatic Cancer. *Macromol Biosci* **2019,** *19* (7), e1900073.
46. Ray, P.; Nair, G.; Ghosh, A.; Banerjee, S.; Golovko, M. Y.; Banerjee, S. K.; Reindl, K. M.; Mallik, S.; Quadir, M., Microenvironment-sensing, nanocarrier-mediated delivery of combination chemotherapy for pancreatic cancer. *Journal of Cell Communication and Signaling* **2019**.
47. Ray, P.; Alhalhooly, L.; Ghosh, A.; Choi, Y.; Banerjee, S.; Mallik, S.; Banerjee, S.; Quadir, M., Size-Transformable, Multifunctional Nanoparticles from Hyperbranched Polymers for Environment-Specific Therapeutic Delivery. *ACS Biomaterials Science & Engineering* **2019,** *5* (3), 1354-1365.
48. Ghosh, A.; Sarkar, S.; Ghosh, S.; Ray, P.; Quadir, M.; Banerjee, S. K.; Banerjee, S., Abstract 1234: Zoledronic acid-induced suppression of invasive phenotypes of pancreatic cancer cells is mediated through downregulation of CYR61/CCN1. *Cancer Research* **2019,** *79* (13 Supplement), 1234.
49. Ray, P.; Clément, M.; Martini, C.; Abdellah, I.; Beaunier, P.; Rodriguez-Lopez, J.-L.; Huc, V.; Remita, H.; Lampre, I., Stabilisation of small mono- and bimetallic gold–silver nanoparticles using calix[8]arene derivatives. *New Journal of Chemistry* **2018,** *42* (17), 14128-14137.
50. André, E.; Boutonnet, B.; Charles, P.; Martini, C.; Aguiar-Hualde, J. M.; Latil, S.; Guérineau, V.; Hammad, K.; Ray, P.; Guillot, R.; Huc, V., A New, Simple and Versatile Strategy for the Synthesis of Short Segments of Zigzag-Type Carbon Nanotubes. *Chemistry* **2016,** *22* (9), 3105-14.
51. Singha, R.; Roy, S.; Nandi, S.; Ray, P.; Ray, J. K., Palladium-catalyzed one-pot Suzuki–Miyaura cross coupling followed by oxidative lactonization: a novel and efficient route for the one-pot synthesis of benzo[c]chromene-6-ones. *Tetrahedron Letters* **2013,** *54* (7), 657-660.
52. Ray, P., Curing Cancer with Nanotherapy Continues to be an Elusive Goal. *Journal of Immunological Sciences* **2021,** *5* (2).
53. Ray, P. Calixarenes and Nanoparticles: Synthesis, Properties and Applications. Paris 11, 2013.