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Article

Enantioselective Total Synthesis of Taiwaniadducts I, J, and L

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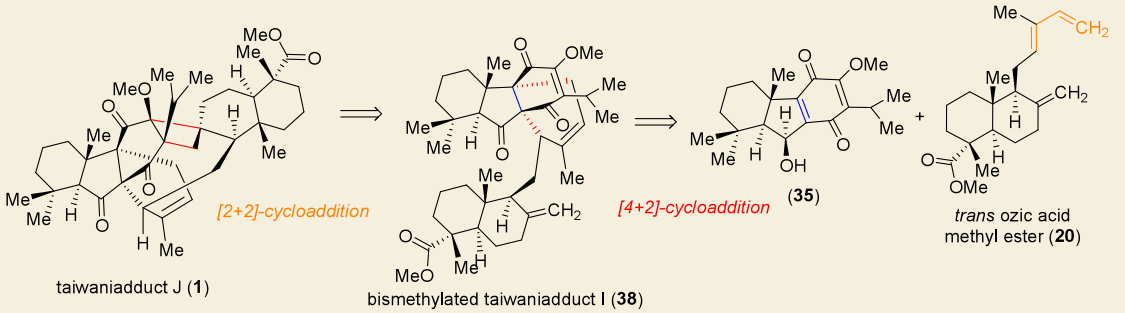

ABSTRACT: The first enantioselective total synthesis of the structurally unique tetraterpenoid, (+)-taiwaniadduct J (**1**), has been accomplished via late-stage pericyclic reactions involving an intermolecular Diels−Alder reaction followed by an intramolecular [2 + 2]-cycloaddition reaction. In this reaction, *trans*-ozic acid methyl ester (**20**) serves as the diene (HOMO counterpart) and a *p*-benzoquinone of *abeo*-abietane **5** serves as the corresponding LUMO counterpart to affect the [4 + 2]-cycloaddition to set vicinal all-carbon quaternary stereogenic centers. In the process, the first total syntheses of (−)-taiwaniadducts I (**2**) and L (**3**) were also accomplished. The absolute configuration of (+)-taiwaniadduct J (**1**) was confirmed through an enantioselective total synthesis and X-ray analysis. This synthesis demonstrates the elegant application of pericyclic reactions, such as the Diels−Alder cycloaddition and [2 + 2] cycloaddition, to construct multiple quaternary centers in the synthesis of taiwaniadduct J (**1**).

KEYWORDS: *Aromatic tetraterpenoids, abeo-Abietane, Diels−Alder reaction, Biomimetic approach, Taiwaniadduct J*

Taiwaniaquinoids are a class of tetraterpenoids isolated from the endemic evergreen species *Taiwania cryptomerioides*[1] and possess impressive biological activities. The most complex congener, taiwaniadduct J (**1**),[2] along with taiwaniadduct I (**2**) were isolated in 1997 by Fang et al. Very recently, in 2023, taiwaniadduct L (**3**) was isolated by Kong et al. from the same *Taiwania* species.[3] Although a comprehensive biological profiling of these architecturally intriguing tetraterpenoids is yet to be undertaken, the preliminary studies revealed that taiwaniadduct L (**3**) demonstrated a 9.18-fold enhancement in bortezomib (BTZ) susceptibility at a tested concentration of 20 μM, outperforming the positive control verapamil.[3] However, the limited availability of taiwaniadduct J (**1**) in Nature has impeded its further biological evaluation. Therefore, it is necessary to develop an efficient method for synthesizing these complex taiwaniadducts and their derivatives.

From a biosynthetic perspective, taiwaniadduct J (**1**) (Figure 1),[2] the most complex molecule among them, could be derived from taiwaniadduct I (**2**) through a photoinduced [2 + 2]-cycloaddition reaction, and **2** may arise from an intermolecular Diels−Alder reaction between naturally occurring *trans*-ozic acid (**4**)[2] and a hypothetical *abeo*-abietane monomer (**5**). Taiwaniadduct L (**3**)[3] is presumably the regioisomer of **2** from the Diels−Alder reaction.[4] The structures of **1**−**3** were

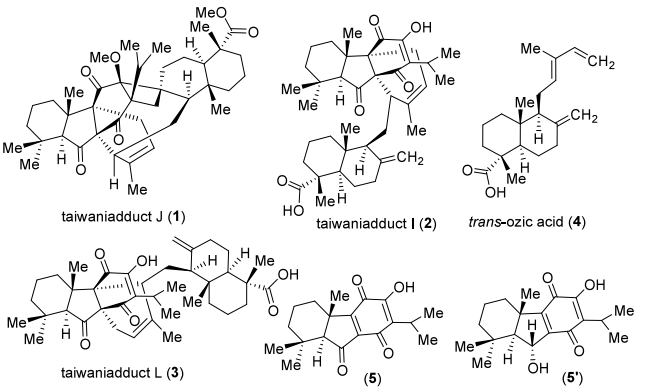

Figure 1. Naturally occurring taiwaniadducts J (**1**), I (**2**), and L (**3**).

identified by a combination of detailed NMR spectroscopic analysis and ECD calculations.[4] The emerging biological

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activities of tetraterpenoids have drawn considerable attention from the synthetic community. The cyclohexene motif of (+)-taiwaniadduct J (**1**) could be biogenetically constructed from two modified abietane diterpenoids through an intermolecular Diels–Alder reaction between a hypothetical diene **4** (HOMO counterpart) and dienone **5** (corresponding LUMO counterpart). Nature uses pericyclic reactions, the most sustainable process that uses heat and light, for the construction of complex molecular architectures.[5,6] These reactions generally require few external resources, primarily depending on heat and light as energy sources, which are both abundant and ecofriendly. This aspect of Nature's chemistry is gaining increasing attention in synthetic chemistry, as researchers strive to replicate these environmentally benign processes to synthesize complex molecules in a more sustainable way. Impressively, the [4 + 2]-cycloaddition is one of the most fundamental reactions that creates structural complexity in the secondary metabolites.[7,8] In this regard, Li et al. reported an elegant approach to the taiwaniadducts B, C, and D through a bioinspired Diels–Alder cycloaddition as the key strategy.[4]

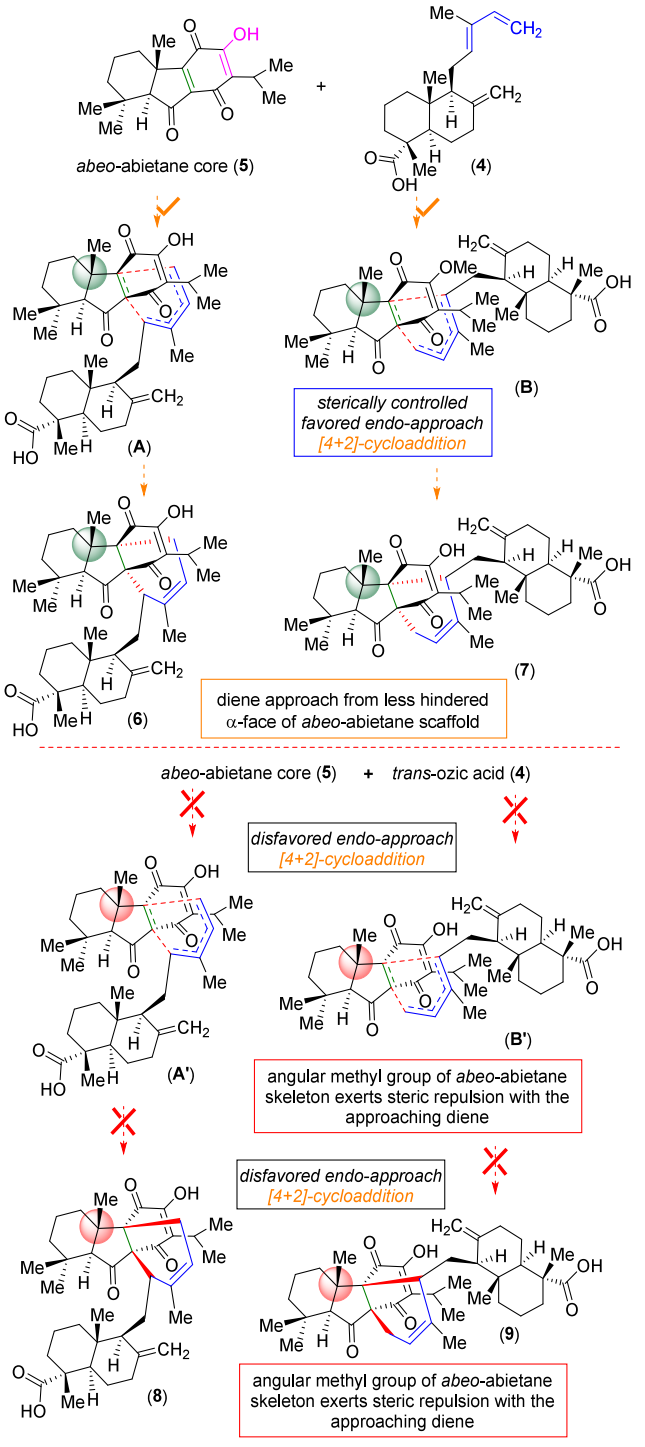
Herein, we describe the first total synthesis of the most complex member of this class of taiwaniadducts, (+)-taiwaniadduct J (**1**), through a bioinspired Diels–Alder reaction between a hypothetical diene **4** and a dienophile, dienone **5** (Figure 1). Considering the secondary orbital interactions that would directly influence the *endo*-selectivity through the constructive nonbonding interactions of Ψ2 of the electron-rich diene **4** with Ψ3 of the electron-deficient α,β-unsaturated portion of dienophile **5** in the [4 + 2]-cycloaddition,[9,10] it is hypothesized that electron-rich diene **4** would selectively differentiate one of the olefins from dienone **5** (shown in green; Scheme 1).

Further, because of the steric repulsions exerted by the angular methyl group of modified abietane scaffolds in diene **4** and dienophile **5**, one would expect selective formation of Diels–Alder adducts **6** and **7** rather than **8** and **9** (Scheme 1). Therefore, establishing this selectivity under the Diels–Alder reaction[11−13] in order to prove the biosynthesis of (+)-taiwaniadduct J (**1**) is worth investigating. This led to the first enantioselective total synthesis of (+)-taiwaniadduct J (**1**).

Our efforts began with identifying a practical synthesis of *trans*-ozic acid (**4**) sharing a *trans*-decalin system and an *abeo*-abietane diterpenoid scaffold, either **5** or **5′** (Figure 1). Toward the catalytic asymmetric synthesis of *trans*-ozic acid (**4**), Cp_2TiCl_2-catalyzed extended epoxy-ene-type cyclization was explored (Scheme 2). A site-selective allylic oxidation of commercially available 2*E*,6*E*-farnesyl acetate (**10**) (*trans*-*trans*-) delivered required allylic alcohol **11** in 52% yield based on recovered starting materials (brsm).[14] A catalytic asymmetric Sharpless allylic epoxidation afforded epoxy alcohol **12** in 95% yield with 94% ee (Scheme 2).[15]

Dess-Martin periodinane (DMP) oxidation of alcohol **12** (see, aldehyde **13**) followed by a Pinnick oxidation[16] and methylation of the resultant carboxylic acid gave **14** in 77% yield over 3 steps. At this stage, a Cp_2TiCl_2-catalyzed[29] epoxy-ene-type cyclization furnished *trans*-decalin product in 58% yield. Impressively, in this process, two C–C bond-forming (76% yield for each C–C bond formation) events led to the construction of five consecutive stereogenic centers, where two of them are all-carbon quaternary stereogenic centers.[17] Later, secondary alcohol was removed in a two-step protocol to form

Scheme 1. Rationale of Diels–Alder Reaction



compound **16** in 73% yield over 2 steps, namely xanthate formation of secondary alcohol followed by reductive removal of xanthate using *n*-tributyltin hydride in the presence of catalytic AIBN. Deprotection of acetate gave homoallylic alcohol **17** in 96% yield. Next, one-carbon homologation of the *trans*-decalin system was carried out via a two-step protocol in an overall yield of 71%, viz. DMP oxidation followed by Wittig olefination concomitant with hydrolysis of the resultant methyl vinyl ether using dilute hydrochloric acid.[18] Finally, two consecutive Wittig reactions [the first one with stabilized Wittig to obtain **19** in 92% yield and a second methyl Wittig to

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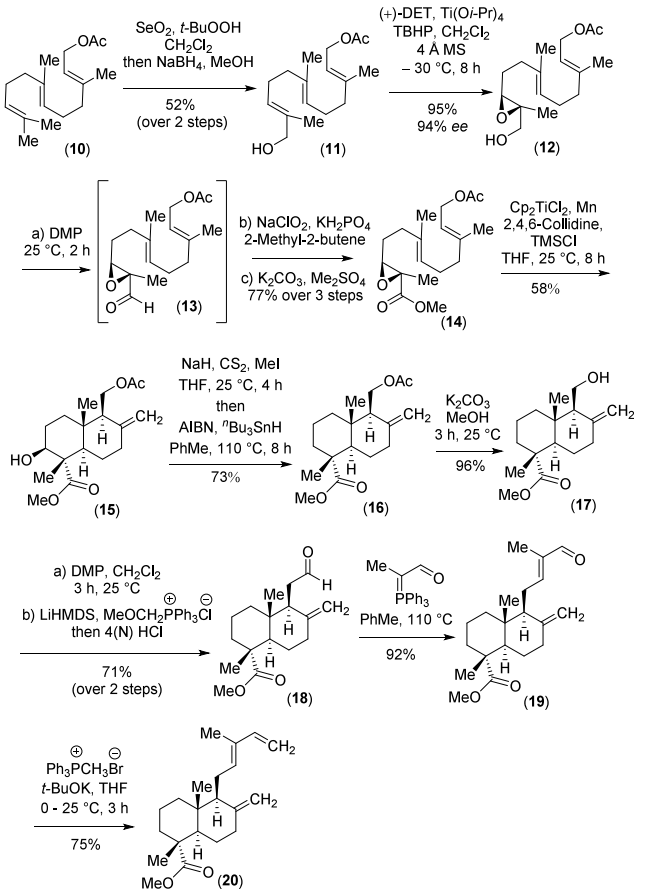
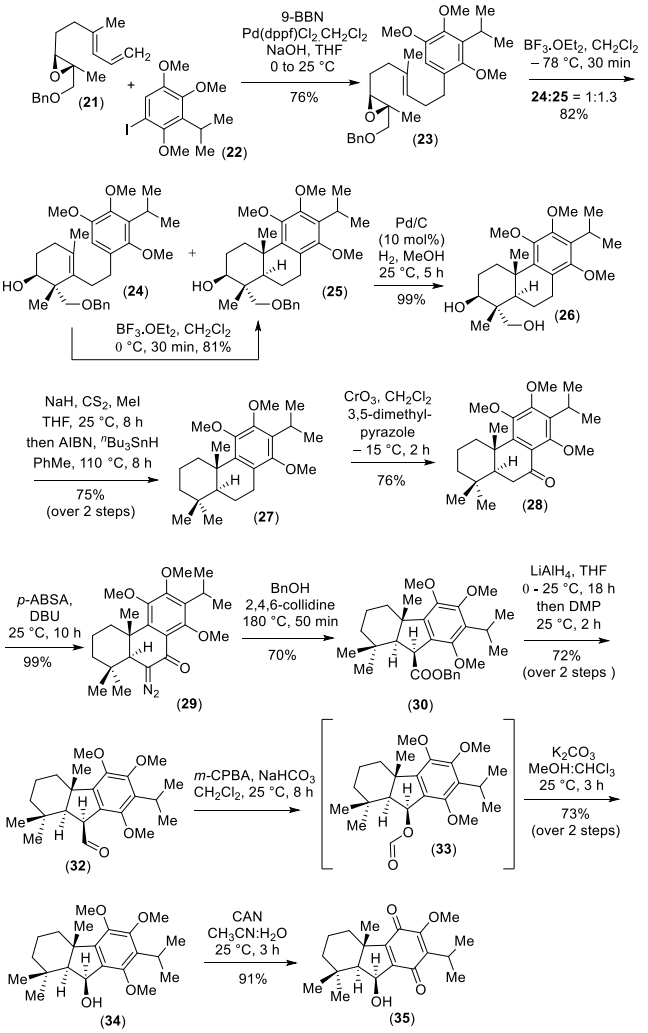
Scheme 2. Asymmetric Synthesis of *trans*-Ozic Acid Methyl Ester



Scheme 3. Asymmetric Synthesis of *abeo*-Abietane Diterpenoid



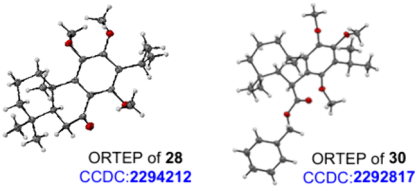


Figure 2. X-ray structures of **28** and **30**.

obtain **20** in 75% yield] completed the synthesis of *trans*-ozic acid methyl ester **20** (Scheme 2).

Further, in the literature, abietane ring contraction following a decomposition of α-diazoketone is one of the popular ways to access the *abeo*-abietane skeleton. In this regard, it was envisioned to synthesize an abietane skeleton followed by the synthetic manipulation. Prior elegant approaches to catalytic asymmetric synthesis of monomeric abietanes have been independently developed by Loh ($SnCl_4$-mediated polyene cyclization in the presence of chiral acetal),[19] Corey (catalytic alkyne activation by In(III) followed by cyclization[20] and $SbCl_5$-mediated polyene cyclization),[21] Carreira [Ir(I)-catalyzed enantioselective cyclization],[22,23] Baran[24] (epoxide-initiated polyene cyclization), Krische ($TiCl_4$-promoted Friedel–Crafts type alkylation/cyclization),[25] Carter (utilizing Pummerer rearrangement),[26] and others.[27]

We imagined accessing a highly functionalized abietane scaffold starting from enantiopure epoxy-ether **21** (Scheme 3). As per the protocol reported by Tanis et al.[28] and Baran et al.,[24] enantioenriched diene **23** was prepared in 76% yield from a literature-known diene **21** by a reaction with 9-BBN followed by a Suzuki coupling reaction with iodoarene **22** on greater than 10 g scale (Scheme 3).

Next, a $BF_3{\cdot}OEt_2$-promoted polyene cyclization afforded functionalized abietane core **25** having four consecutive stereogenic centers in 46% yield along with tetrasubstituted cyclohexene **24** in 36% yield (Scheme 4). Gratifyingly, $BF_3{\cdot}OEt_2$-promoted cyclization of **24** could be carried out to afford the required abietane core **25** in 81% yield (see SI for details).

Later, debenzylation of benzyl ether of **25** followed by the removal of both hydroxyl groups (via xanthate formation followed by reductive removal of xanthate under Barton-McCombie condition) furnished carbotricyclic core **27** in 74% yield over 3 steps (Scheme 4). Next, following a protocol reported by Li et al.,[8] benzylic oxidation of compound **27** followed by a reaction with *p*-ABSA gave diazoketone **29**. A base-promoted ring contraction via the decomposition of diazoketone afforded *abeo*-abietane core **30** in 70% yield (Scheme 4). Further, $LiAlH_4$ reduction, followed by DMP oxidation (see aldehyde **32**) and Bayer-Villiger oxidation, furnished formate **33**. Later, saponification of formate **33** (see secondary alcohol **34**) followed by an oxidative dearomatization with ceric(IV) ammonium nitrate (CAN) afforded *p*-

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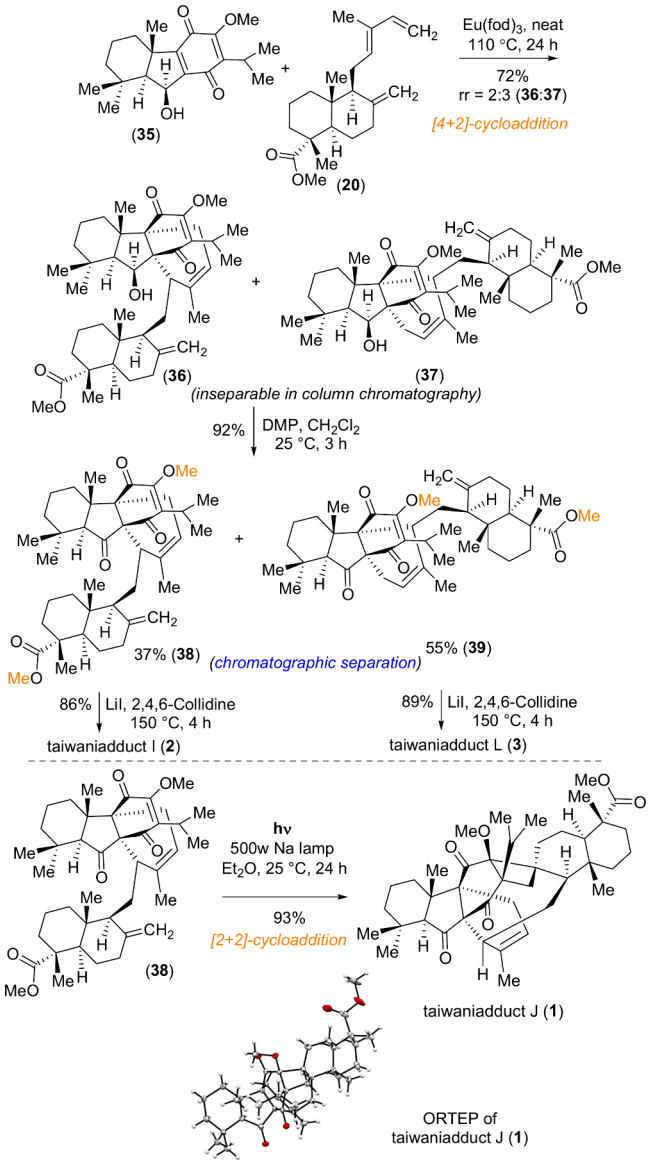
Scheme 4. Total Synthesis of Taiwaniadduct J (1)



benzoquinone derivative **35** in a synthetically useful yield (Scheme 3).

Next, we shifted our attention to the first chemical synthesis of the most complex (+)-taiwaniadduct J (**1**) via two consecutive pericyclic reactions, i.e. [4 + 2]- and [2 + 2]-cycloaddition triggered by light. Therefore, fragment coupling reactions of *abeo*-abietane **35** and *trans*-ozic acid methyl ester **20** were influenced by Lewis acids. Following an exhaustive optimization, we were pleased to find that 20 mol % of $Eu(fod)_3$ could efficiently connect fragments **35** and **20** through an *endo*-selective Diels–Alder reaction to afford only one pair of regioisomers, i.e., **36** and **37** (Scheme 4). Delightfully, the angular methyl group completely controls the regioselectivity in this beautiful transformation to set the vicinal all-carbon quaternary stereogenic centers in the newly generated cyclohexene scaffold (see Scheme 1). Since the regioisomers, i.e., **36** and **37**, were inseparable in column chromatography, these mixtures were oxidized with DMP to furnish **38** and **39**, where both these ketones were separated in column chromatography. The demethylation of cycloadducts (**38** and **39**) in the presence of LiI completed the first total synthesis of taiwaniadducts I (**2**) and L (**3**). All the characterization data are suitably matched with isolation data (see Supporting Information).

Finally, irradiation with light, through [2 + 2]-cycloaddition compound **38**, was smoothly converted to the architecturally complex naturally occurring tetraterpenoid, (+)-taiwaniadduct J (**1**), having congested cyclobutane with three contiguous quaternary stereogenic centers. The synthetic (+)-**1** has all characterization data that are in good agreement with the isolation sample. Moreover, the single crystal X-ray analysis of (+)-taiwaniadduct J (**1**) unequivocally proved all the bond connections as well as established all stereogenic centers. So, through a unified strategy utilizing a pericyclic reaction, we have synthesized three complex natural products, taiwaniadduct I, J, and L.

In conclusion, we have accomplished the first catalytic enantioselective total synthesis of taiwaniadducts I (**2**), J (**1**), and L (**3**) and also confirmed their absolute configuration. Our synthesis demonstrates the ability of Diels–Alder reaction followed by a [2 + 2]-cycloaddition in creating the most intricate and complex molecular scaffolds under ambient conditions. The effectiveness of this approach has been shown by the 23-step longest linear synthesis of taiwaniadducts I (**2**), J (**1**), and L (**3**) from commercially available geranyl acetate (see, SI for details).[28]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c01276.

All the experimental procedures including data characterization (PDF)

Spectral data (PDF)

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Author Contributions

Alakesh Bisai wrote the manuscript with the help of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Debgopal Jana** conceptualization, data curation, formal analysis, investigation, validation, methodology; **Arindam Khatua** formal analysis, investigation, methodology; **Sourav Kundu** data curation, investigation, validation; **Suman Noskar** data curation, formal analysis, investigation; **Monosij Nandy** data curation, investigation, validation; **Alakesh Bisai** conceptualization, formal analysis, funding acquisition, investigation, project administration, resources, supervision, validation, writing -original draft, writing-review and editing.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

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