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Concise synthesis and confirmation of the absolute configurations of naturally occurring bioactive 2,7′-cyclolignans

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ABSTRACT

A concise asymmetric synthesis of naturally occurring bioactive 2,7′-cyclolignans, namely 4,4′-dihydroxy-3′,5,5′-trimethoxy-2,7′-cyclolignan and 4,4′-dihydroxy-3,3′,5-trimethoxy-2,7′-cyclolignan, possessing the uncommon 8,8′-*syn* dimethyl stereochemistry and unsymmetrical C-6 units with 7′,8′-*anti*-orientation is described using a substrate-controlled stereoselective Friedel-Crafts cyclization as the key step. The products were obtained in good yields with high stereoselectivity. The absolute configurations of natural 4,4′-dihydroxy-3′,5,5′-trimethoxy-2,7′-cyclolignan and those of natural 4,4′-dihydroxy-3,3′,5-trimethoxy-2,7′-cyclolignan were assigned as (7′*S*,8*S*,8′*S*) and (7′*R*,8*R*,8′*R*), respectively, based on the experimental circular dichroism (CD) spectra of the corresponding synthesized compounds.

Introduction

Podophyllotoxin and related aryltetralin cyclolignans are important natural products which have received widespread attention in the pharmaceutical industry due to their remarkable biological activities including antiviral, antitumor, anti-oxidant, antimicrobial and anti-malarial properties [1–3]. Aiming at improving the bioactivities, water solubility, and decreasing the toxicity of these natural compounds, current research on the isolation [4–8], synthesis [9–15], and structure–activity relationship (SAR) studies of podophyllotoxin derivatives and related aryltetralin cyclolignans attracts much attention and is an active area in chemistry and biology.

4,4′-Dihydroxy-3′,5,5′-trimethoxy-2,7′-cyclolignan (**1**) and 4,4′-dihydroxy-3,3′,5-trimethoxy-2,7′-cyclolignan (**2**) are naturally occurring 2,7′-cyclolignans isolated from an ethanol extract of the barks of *Machilus robusta* [5] and *Macchilus wangchianan* [6], respectively (Fig. 1). It was reported that **1** reduced DL-galactosamine (GalN)-induced hepatocyte (WBF344 cells) damage and **2** inhibited the release of β-glucuronidase in rat polymorphonuclear leukocytes (PMNs) induced by platelet-activating factor (PAF). SG-1 (**3**), a fully methylated derivative of **1** obtained *via* a semi-synthesis, was identified as a potent HIV-1 non-nucleoside reverse transcriptase inhibitor [16]. In light of the interesting biological profiles of **1**–**3**, we were inspired to develop a concise asymmetric approach to access **1** and **2** and their derivatives. The goals of the present work were not only to facilitate the biological activity screening of **1** and **2** and their derivatives, but also to confirm the reported absolute configurations which are crucial for SAR studies. Structurally, **1** and **2** share a rare 8,8′-*syn* dimethyl stereochemistry and unsymmetrical C-6 units (the two aromatic rings) with 7′,8′-*anti* orientation. The atropdiastereomers were not reported for both **1** and **2** suggesting free rotation around the 1′,7′ bond. Although there are numerous reports regarding the synthesis of 2,7′-cyclolignans [17–22], the asymmetric synthesis of **1** and **2** has not been reported.

As outlined in Scheme 1, the synthesis of **1** and the enantiomer of **2** (*ent*-**2**) was planned through key substrates 1,4-diarylbutane derivatives **4a** and **4b**, respectively. Upon treatment of **4a** and **4b** with a mild acid, an oxocarbenium ion **I** should be readily formed which subsequently undergoes a substrate-controlled stereoselective Friedel-Crafts cyclization to provide **1** and *ent*-**2**, respectively. The stereoselectivity of the cyclization is proposed to be governed by the inherent stereochemistry of the methyl groups. 1,4-Diarylbutanes **4a** and **4b** could be readily prepared from alkene (2*S*,3*R*)-**5** after oxidative cleavage of the double bond to yield the respective aldehyde, followed by reaction with an aryllithium. Alkene (2*S*,3*R*)-**5** could be obtained from aryl ketone (2*R*,3*R*)-**6** after reduction of the carbonyl group followed by deoxygenation. Finally, the synthesis of aryl ketone (2*R*,3*R*)-**6** was planned to start from Weinreb amide (2*R*,3*R*)-**7** containing the 2,3-*anti*-dimethyl moieties required for **1** and *ent*-**2**.

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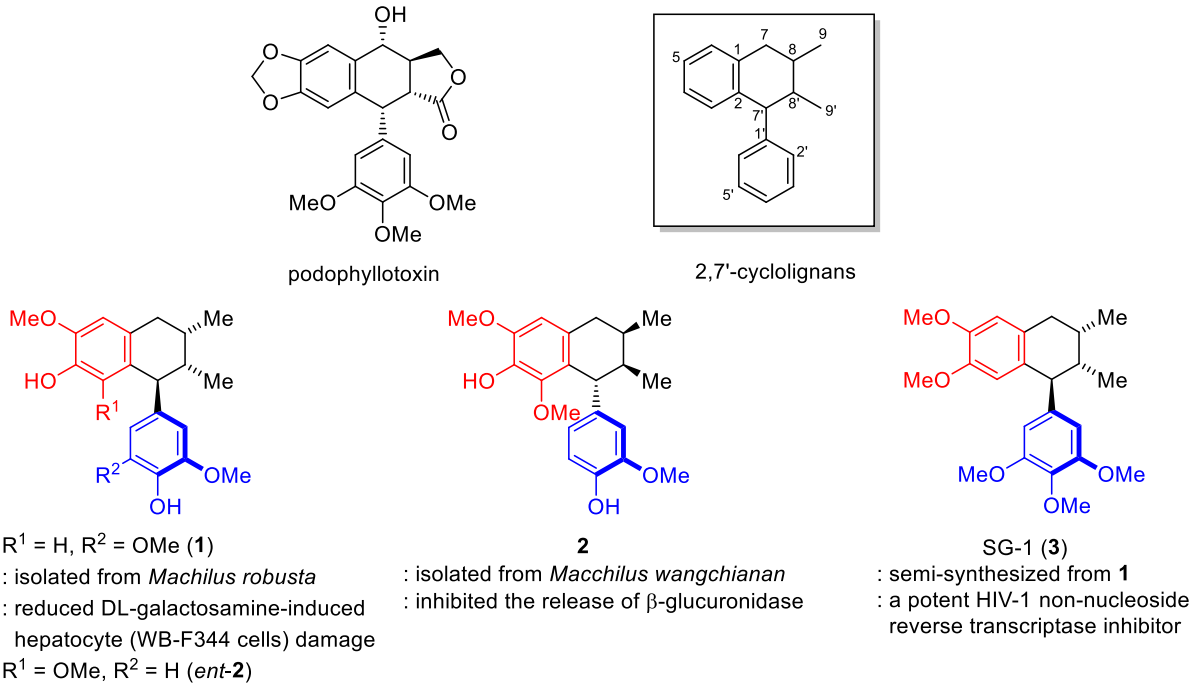
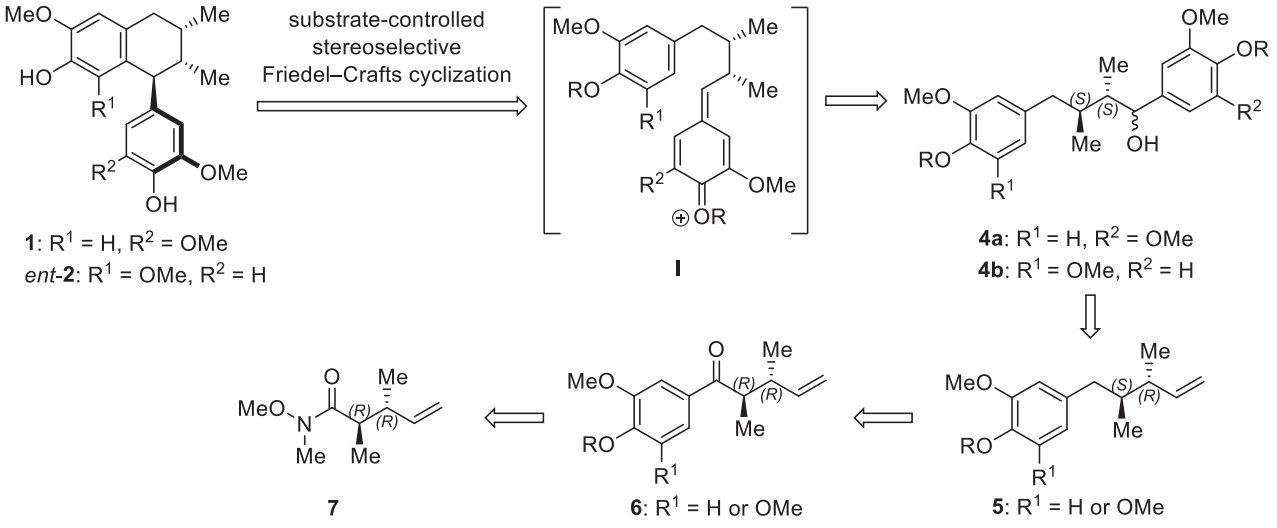


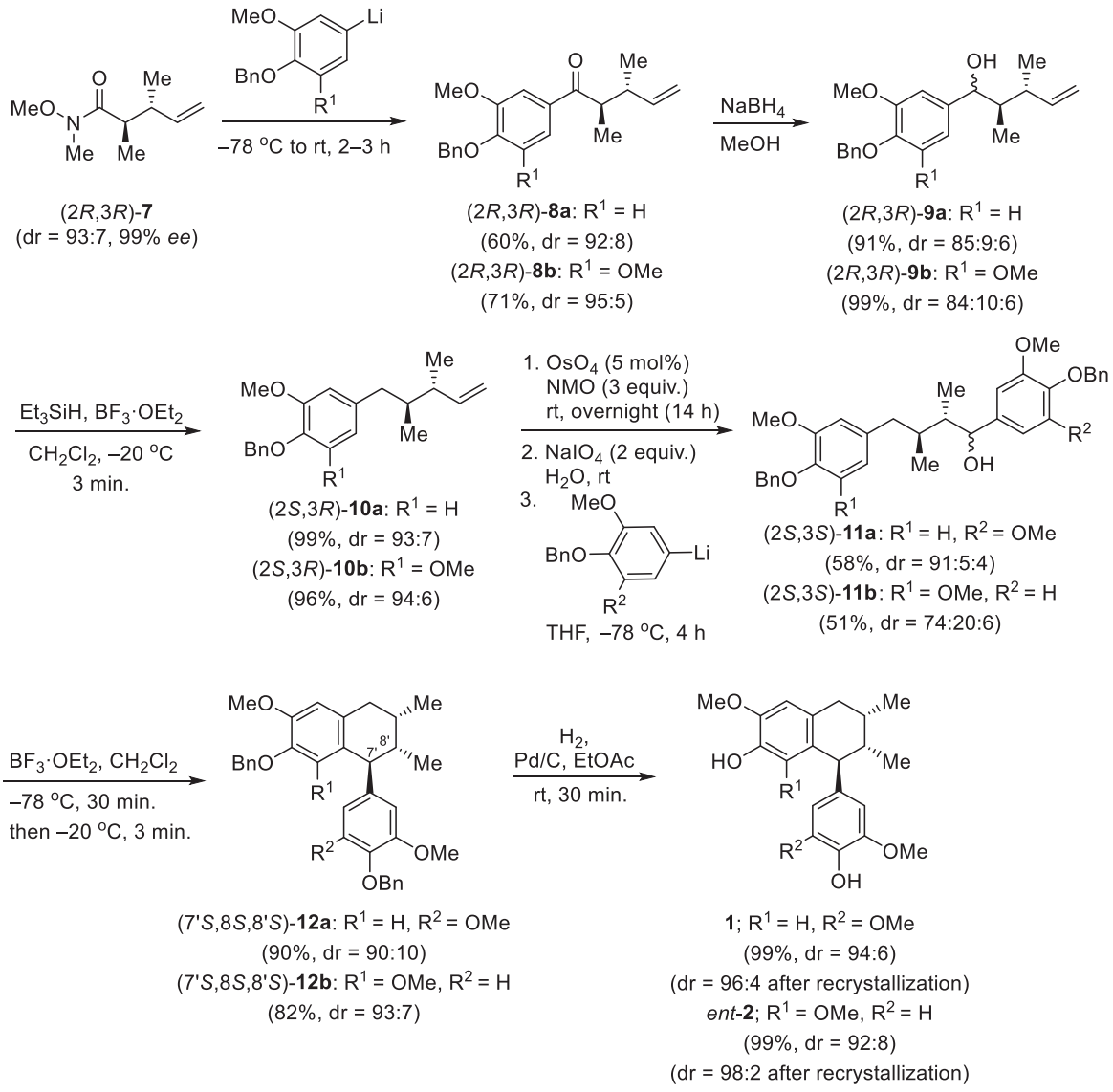
Fig. 1. The structures of podophyllotoxin, **1**, **2**, *ent*-**2**, and SG-1 (**3**).



Scheme 1. Retrosynthetic analysis of **1** and *ent*-**2**.

Results and discussion

The synthesis of **1** started from Weinreb amide (2*R*,3*R*)-**7** (dr = 93:7, 99% *ee*) [23,24] which upon treatment with [4-(benzyloxy)-3-methoxyphenyl]lithium [freshly generated *via* lithium/bromine exchange of 1-(benzyloxy)-4-bromo-2-methoxybenzene (1.2 equiv.) using *n*-BuLi (1.6 M in hexanes) (1.2 equiv.) at −78 °C for 10 min] gave aryl ketone (2*R*,3*R*)-**8a** (60% yield, dr = 92:8, ^{1}H NMR analysis) (Scheme 2). Subsequent reduction of the carbonyl group of (2*R*,3*R*)-**8a** using $NaBH_4$ (4 equiv.) in MeOH at −78 °C gave the corresponding alcohol **9a** in 91% yield as a mixture of diastereomers (dr = 85:9:6). Deoxygenation of **9a** using triethylsilane (Et_3SiH) (5 equiv.) and boron trifluoride diethyl etherate (BF_3OEt_2) (3 equiv.) in dry CH_2Cl_2 at −20 °C rapidly took place within approximately 3 min to provide the desired alkene (2*S*,3*R*)-**10a** in a nearly quantitative yield (99% yield, dr = 93:7). Oxidative cleavage of the double bond of (2*S*,3*R*)-**10a** using OsO_4 (5 mol%) and NMO (3 equiv.) in a mixture of water and CH_2Cl_2 at room temperature for 14 h (overnight) followed by treatment with $NaIO_4$ (2 equiv.) afforded the corresponding aldehyde. Without chromatographic purification, the obtained aldehyde was treated with [4-(benzyloxy)-3,5-dimethoxyphenyl]lithium to give alcohol **11a** in 58% yield as a mixture of diastereomers (dr = 91:5:4). Friedel-Crafts cyclization of **11a** mediated by BF_3OEt_2 (3 equiv.) in dry CH_2Cl_2 provided the desired product **12a** in 90% yield with high diastereoselectivity (dr = 90:10). The relative stereochemistry at the 7′,8′-position was determined by the coupling constant between H-7′ and H-8′ ($^3J_{7',8'}$ = 6.8 Hz) suggesting an *anti* relationship between H-7′ and H-8′. Additionally, the stereochemistry of **12a** was confirmed on the basis of NOESY experiments (see the ESI). Finally, debenzylation of **12a** was conducted [H_2, Pd/C (2 equiv.), dry EtOAc, rt, 30 min] to afford **1** in nearly quantitative

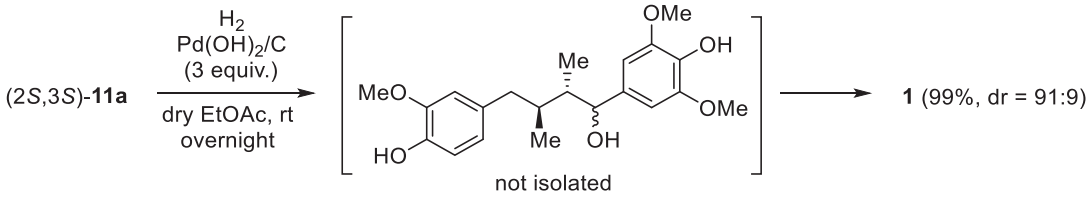


Scheme 2. Synthesis of **1** and *ent*-**2**.

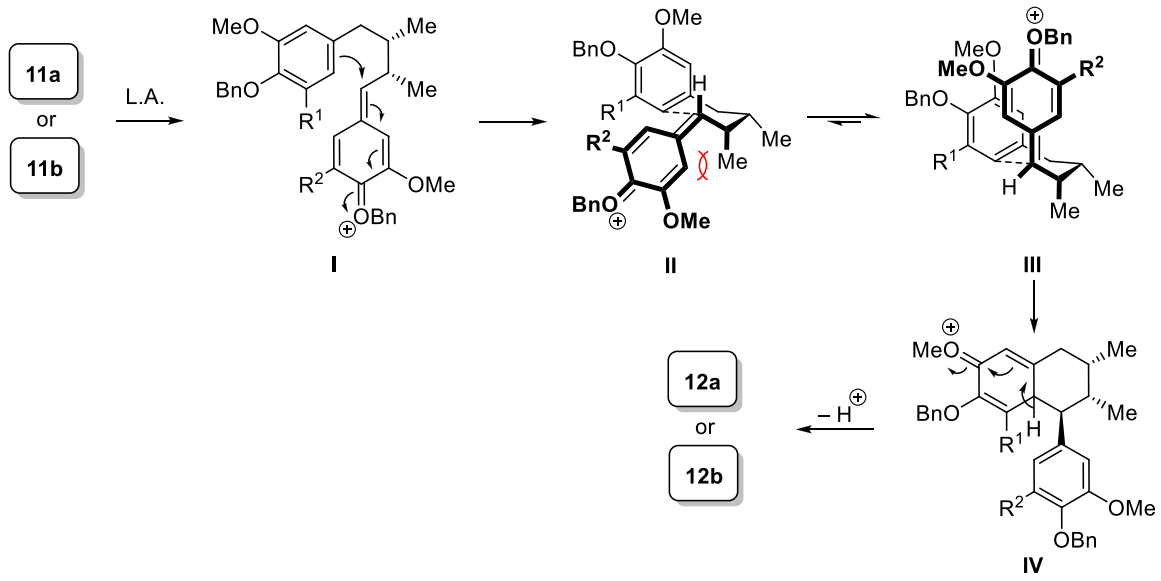
yield (99% yield, dr = 94:6) which, after a single recrystallization (CH_2Cl_2:hexanes), gave **1** with an improved diastereomeric ratio (dr = 96:4). It should be noted that under standard hydrogenolysis conditions [H_2, $Pd(OH)_2$/C, dry EtOAc, rt, overnight], **11a** can be converted to **1** with comparable efficiency (99% yield, dr = 91:9) (Scheme 3). Using a similar synthetic pathway for **1**, *ent*-**2** (dr = 92:8) could be synthesized in a highly stereoselective manner starting from the respective precursor (Scheme 2). To our delight, *ent*-**2** with dr = 98:2 was obtained after recrystallization (CH_2Cl_2:hexanes).

At this stage, the substrate-controlled stereoselective Friedel-Crafts cyclization of **11a** and **11b** leading to **12a** and **12b** with high stereoselectivity should be discussed. As depicted in Scheme 4, upon treatment of **11** with BF_3OEt_2, an oxonium ion intermediate **I** was generated and rapidly underwent cyclization through a more favorable transition state **III** (**II** *vs.* **III**) leading to cyclized intermediate **IV**. Deprotonation and re-aromatization of **IV** then provided **12**.

The synthesized compounds **1** (dr = 96:4) and *ent*-**2** (dr = 98:2) displayed similar spectroscopic data with those of the natural



Scheme 3. Hydrogenolysis of (2*S*,3*S*)-**11a** leading to **1**.



Scheme 4. Proposed mechanism for the substrate-controlled stereoselective Friedel-Crafts cyclization.

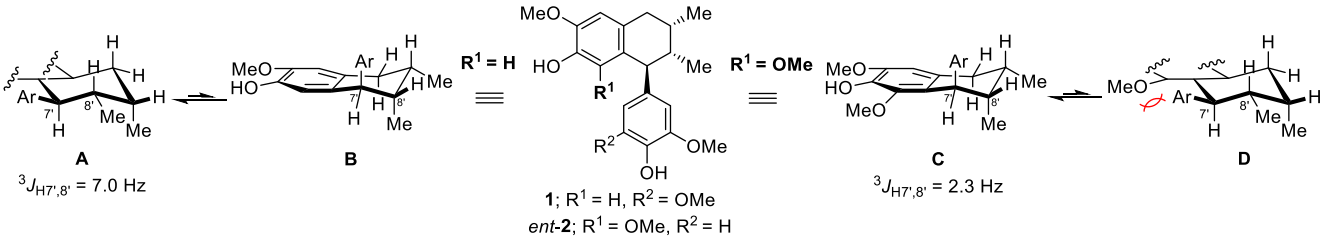


Fig. 2. The conformers of **1** and *ent*-**2**.

compounds previously reported in the literature (see the ESI). Compound **1** favorably existed in conformer **A** (*trans* diaxial relationship between H-7′ and H-8′) according to the observed large vicinal coupling constant between H-7′ and H-8′ ($^3J_{7',8'}$ = 7.0 Hz; 180° dihedral angle). In contrast, *ent*-**2** which more preferably adopted conformer **C** (*trans* diequatorial relationship between H-7′ and H-8′; 60° dihedral angle) showed a small vicinal coupling constant between H-7′ and H-8′ ($^3J_{7',8'}$ = 2.3 Hz). NOESY experiments were employed to further confirm the relative stereochemistry and preferred conformation assigned (Fig. 2). The experimental circular dichroism (CD) spectrum of synthesized **1** was in close agreement with that of natural **1**; a first negative Cotton effect (CE) at 287 nm and a second positive CE near 272 nm (see the ESI). By comparison of the specific rotation values [synthesized **1**, $[\alpha]_D^{25}$ +82.2 (*c* 0.1, $CHCl_3$), and natural **1**, $[\alpha]_D^{20}$ +97 (*c* 0.1, $CHCl_3$)], the experimental CD spectra, and a review by Loike and Ayres [25] stating that 7′*S*-aryltetralins displayed a first negative CE near 290 nm and a second positive CE near 270 nm while the 7′*R*-configuration showed an opposite pattern, the absolute configurations of synthesized **1** could be confirmed as (7′*S*,8*S*,8′*S*) and were the same as those assigned for natural **1**. In contrast, the experimental CD spectrum of *ent*-**2** showed a first negative CE near 289 nm and a second positive CE at 275 nm which is opposite to that reported for natural **2**. By comparison of the specific rotation values [*ent*-**2**, $[\alpha]_D^{25}$ +96.0 (*c* 0.03, $CHCl_3$), and natural **2**, $[\alpha]_D^{20}$ −13 (*c* 0.03, $CHCl_3$)] and the patterns of the CD spectra, the absolute configurations of synthesized *ent*-**2** were thus concluded as (7′*S*,8*S*,8′*S*) which is the enantiomer of natural **2** for which the enantiomeric purity was implied to be 13.5% *ee*.

Conclusion

A concise asymmetric synthesis of 2,7′-cyclolignans, namely (7′*S*,8*S*,8′*S*)-4,4′-dihydroxy-3′,5,5′-trimethoxy-2,7′-cyclolignan (**1**) and (7′*S*,8*S*,8′*S*)-4,4′-dihydroxy-3,3′,5-trimethoxy-2,7′-cyclolignan (*ent*-**2**) was described. Starting from a readily available chiral Weinreb amide precursor, the synthesis of compounds **1** and *ent*-**2** bearing three contiguous stereocenters can be achieved with high stereoselectivity in 28% overall yield after eight synthetic transformations. The present work provides important information on the stereochemistry of bioactive 2,7′-cyclolignans which should be useful for further SAR study. Additionally, the developed synthetic approach should also be useful for the asymmetric synthesis of various bioactive 2,7′-cyclolignans especially those containing the 8,8′-*syn* dimethyl stereochemistry and unsymmetrical C-6 units.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152827.

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