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Dimericbiscognienyne A: A Meroterpenoid Dimer from *Biscogniauxia* sp. with New Skeleton and Its Activity

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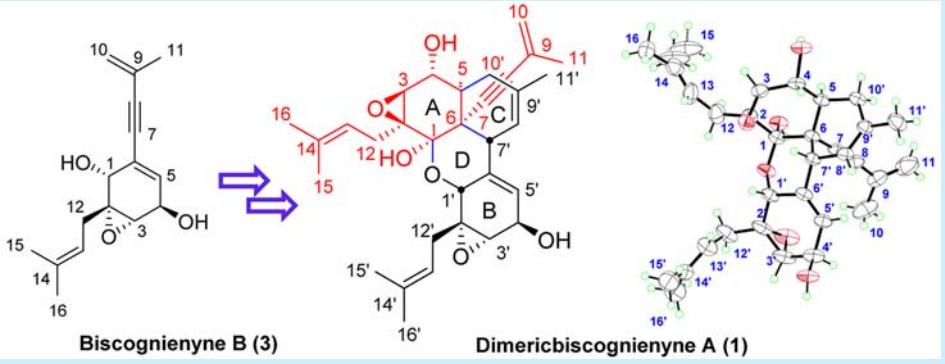
Supporting Information



ABSTRACT: Dimericbiscognienyne A (**1**), an unusual diisoprenyl-cyclohexene-type meroterpenoid dimer, was isolated from *Biscogniauxia* sp. together with three new monomeric diisoprenyl-cyclohexene-type meroterpenoids (**2**−**4**) and one new isoprenyl-benzoic acid-type meroterpenoid (**5**). All structures were determined by extensive NMR spectroscopic methods, quantum chemical calculations, chemical derivatization, and X-ray crystallography. The formation of **1** is related to a unique intermolecular redox coupling Diels−Alder adduct reaction. Their cytotoxicities and short-term memory enhancement activities against Alzheimer's disease were assessed.

Meroterpenoids are complex natural products that partially originate from the terpenoid biosynthetic pathway, such as from the hybrid polyketide-terpenoid and hybrid shikimate-terpenoid pathways.[1] Meroterpenoids have attracted much attention for their quite diverse structures, special hybrid biosynthetic mechanisms, and wide range of bioactivities.[1] Diisoprenyl-cyclohexene/ane analogues, composed of a cyclohexene/ane moiety (C_6 unit) and two isoprenyl chains (C_5 unit), are one kind of meroterpenoid originating from the hybrid shikimate-terpenoid biosynthesis. To date, more than 55 diisoprenyl-cyclohexene/anes have been reported from fungi (such as *Pestalotiopsis* sp.,[2] *Isariopsis* sp.,[3] and *Truncatella* sp.[4]) and plants (such as *Ophryosporus lorentzii*[5] and *Cephalozia otaruensis*[6]). Their structural diversity mainly depends on the diverse cyclization of the two isoprenyl units. These include monocyclic,[2a,4] bicyclic (such as furan-cyclohexene/ane fused[4] and pyran-cyclohexene/ane fused[3c]), and tricyclic [such as furan-cyclohexene/ane-pyran fused,[2c,4] pyran-cyclohexene/ane-pyran fused,[3c] cyclopropane moiety joined spirally to cyclohexene/ane-pyran fused,[2b] and cyclohexene/ane moiety joined spirally to 1,1′-bi(cyclohexane)[2f]] systems. Most reported diisoprenyl-cyclohexene/anes are monomeric. Only pestalofones B and C from *Pestalotiopsis* sp.[2f] (which possess a 2-cyclohexylspiro[5.5]undecane ring system) are dimeric.

During our ongoing search for bioactive secondary metabolites from fungi,[7] a chemical investigation on secondary metabolites of *Biscogniauxia* sp. (No. 71-10-1-1) isolated from the lichen *Usnea mutabilis* stirt. was carried out. This led to the isolation of one new skeleton diisoprenyl-cyclohexene-type meroterpenoid dimer (dimericbiscognienyne A, **1**) along with three related new monomeric diisoprenyl-cyclohexene-type meroterpenoids (biscognienynes A−C, **2**−**4**) and one isoprenyl-benzoic acid-type meroterpenoid (biscogniacid A, **5**) (Figure 1). On the basis of the structural characteristics of **1**−**5**, dimericbiscognienyne A (**1**) should derive from a unique intermolecular redox coupling Diels−Alder adduct reaction. Herein, we describe the isolation and structural elucidation of **1**−**5**, including their bioactivities. In addition, a plausible biogenetic pathway of **1**−**5** is proposed.

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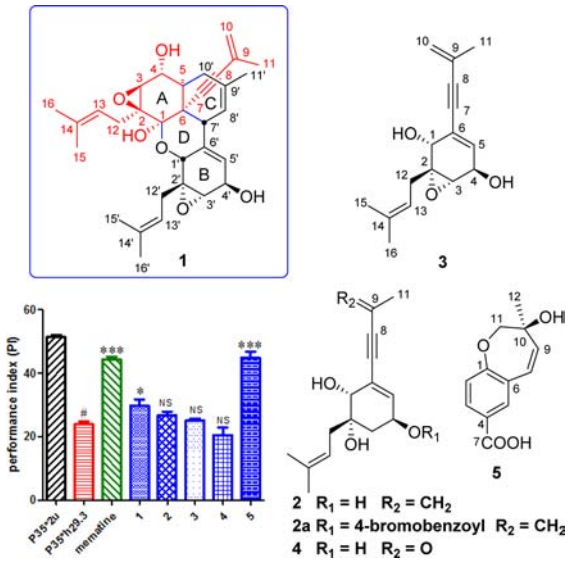

Figure 1. Structures and short-term memory enhancement activities of **1**−**5** in transgenic human-Aβ_{42} AD fly model.

Dimericbiscognienyne A (**1**) was obtained as colorless block-shaped crystals. The molecular formula of **1** was established as $C_{32}H_{40}O_6$ (13 degrees of unsaturation) from its HR-ESI-MS (*m*/*z* 543.2720 $[M + Na]^+$, calcd for $C_{32}H_{40}O_6Na$: 543.2723). The ^{13}C NMR spectrum showed 32 carbon signals. Combined with data from the DEPT 135 experiment, these carbons can be categorized as ten aromatic or olefinic carbons, two sp quaternary carbons, four sp^3 quaternary carbons, seven sp^3 methine carbons, three sp^3 methylene carbons, and six methyl carbons. All of the unexchangeable proton resonances were assigned to the relevant carbon atoms by the HSQC data (Table S1). The $^1H-^1H$ COSY data of **1** revealed the presence of five spin-coupling systems shown in bold blue lines in Figure 2. The key HMBC correlations

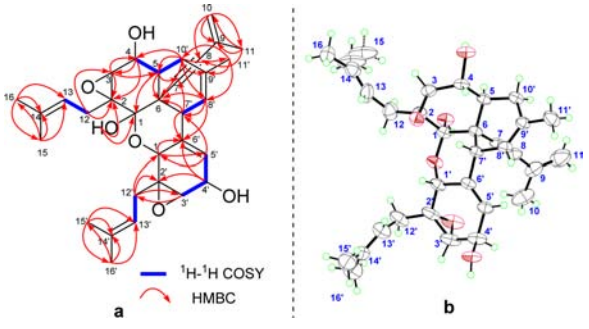

Figure 2. (a) Key $^1H-^1H$ COSY and HMBC correlations and (b) X-ray crystallographic analysis of **1** .

(Figure 2) revealed the partial structure of **1**. On the basis of the molecular formula information, the degree of unsaturation, the chemical shift characteristics, and the above analyses of $^1H-^1H$ COSY and HMBC data, the planar structure was established as shown in Figure 2. The X-ray crystallographic analysis of **1** (Figure 2; CCDC 1508935) confirmed the above deduction, and the value of the Flack parameter [0.01 (16)] allowed the absolute configuration of **1** to be assigned as 1*R*, 2*S*, 3*S*, 4*R*, 5*S*, 6*R*, 1′*R*, 2′*R*, 3′*S*, 4′*R*, 7′*R*. The ROESY correlations of between H-3 and H-13, between H-5 and 1-OH, between H-1′ and H-3′/H-7′/Ha-12′/Hb-12′, and between H-3′ and Hb-12′/H-13′ were consistent with the deduced configuration from X-ray crystallographic analysis (Table S1).

Biscognienyne A (**2**) was obtained as yellowish needle-like crystals. From the HR-ESI-MS and NMR data of **2** (Table S2-1), we deduced the planar structure as shown in Figure 1. The X-ray crystallographic analysis of **2** (Figure S7; CCDC 1508936) suggested the absolute configuration of **2** as 1*R*, 2*S*, 4*S*. However, the Flack parameter [−0.2 (4)] is not good enough to unambiguously establish the absolute configuration. For this deduction to be confirmed, the ECD experiment of **2** was carried out. In light of the lack of strong enough Cotton effects, **2** was treated with 4-bromobenzoyl chloride to yield the 4-bromobenzoic acylated product (**2a**),[8] which had enhanced Cotton effects (Figure 3). The absolute configurations of C-1, C-

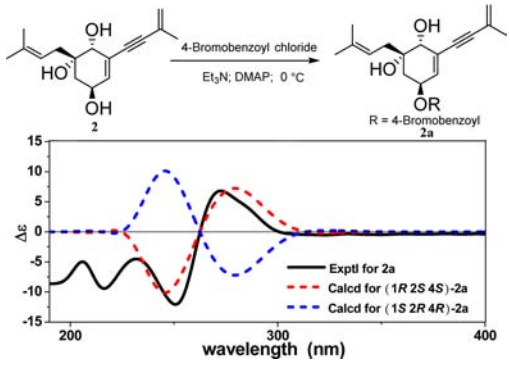

Figure 3. Experimental ECD spectra of **2a** and calculated ECD spectra of (1*R*, 2*S*, 4*S*)-**2a** and (1*S*, 2*R*, 4*R*)-**2a** (UV correction = −10 nm, bandwidth σ = 0.3 eV).

2, and C-4 in **2a** were determined by quantum chemical ECD calculations at the APFD/6-311++g (2d, p) level. Because the predicted ECD curve of (1*R*, 2*S*, 4*S*)-**2a** was similar to the experimental one (Figure 3 and see Supporting Information), the absolute configuration of **2a** was established as 1*R*, 2*S*, 4*S*, which is consistent with the deduction from X-ray crystallography. Therefore, the absolute configuration of **2** was established as 1*R*, 2*S*, 4*S*.

Biscognienyne B (**3**) was obtained as a yellowish oil. From detailed analyses of the HR-ESI-MS and NMR data of **3** (Table S3), we deduced the planar structure as shown in Figure 1. For the existence of the 7-oxabicyclo[4.1.0]hept-3-ene system determining the relative configurations of C-2 and C-3 (2*R**, 3*S**), there were four possible relative configurations for **3**, including (1*R**, 2*R**, 3*S**, 4*R**)-**3**, (1*R**, 2*R**, 3*S**, 4*S**)-**3**, (1*S**, 2*R**, 3*S**, 4*R**)-**3**, and (1*S**, 2*R**, 3*S**, 4*S**)-**3**. To determine the relative configuration of **3**, the key $^1H-^1H$ coupling constants of the above four relative configurations were calculated by quantum chemical methods at three levels of B3LYP/6-311+g (2d, p),[9] APFD/6-311++g (2d, p),[10] and B3PW91/6-311++g (2d, p) (Supporting Information).[11] All of the calculated results showed that the calculated $^1H-^1H$ coupling constants of (1*R*, 2*R*, 3*S*, 4*R*)-**3** were similar to the experimental one (Figure 4). Therefore, the relative configuration of **3** was assigned as 1*R**, 2*R**, 3*S**, 4*R**. The ROESY correlations of between H-1 and Ha-12/Hb-12 and between H-3 and Hb-12 were consistent with the deduced relative configuration. Because **3** and **2** coexist in the same strain, the absolute configurations of C-1 and C-4 in **3** should be the same as those in **2**.

Biscognienyne C (**4**) was obtained as a yellowish oil. From the HR-ESI-MS and NMR data of **4** (Table S4), we deduced the

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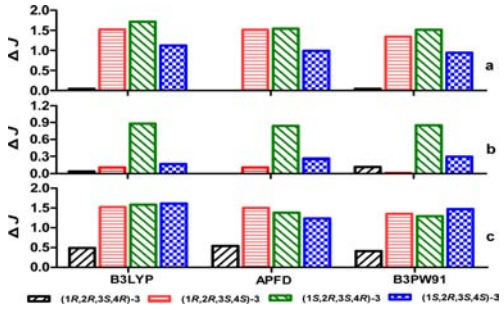


Figure 4. Differences between experimental data and calculated $^{1}H-^{1}H$ coupling constants of four isomers of **3** at the level of B3LYP/6-311+g (2d, p), APFD/6-311++g (2d, p), and B3PW91/6-311++g (2d, p); (a) $|\Delta J_{H3/H4}|$ = lexptl ($J_{H3/H4}$) − calcd ($J_{H3/H4}$)l; (b) $|\Delta J_{H3/H5}|$ = lexptl ($J_{H3/H5}$) − calcd ($J_{H3/H5}$)l; (c) $|\Delta J_{H4/H5}|$ = lexptl ($J_{H4/H5}$) − calcd ($J_{H4/H5}$)l.

planar structure as shown in Figure 1. The relative configuration of **4** was assigned as 1*R**, 2*S**, 4*S** (Figure 1) based on the large $^{3}J_{Hb\text{-}3,\ H\text{-}4}$ (J = 9.8 Hz) and the observed ROESY correlations (between H-1 and Hb-3/Ha-12/Hb-12) consistent with those in **2**. Because **4** and **2** coexist in the same strain, the absolute configurations of C-1, C-2, and C-4 in **4** should be the same as those in **2**.

Biscogniacid A (**5**) was obtained as colorless needle-like crystals. From the HR-ESI-MS, NMR data, and X-ray crystallographic data of **5** (Figure S8; CCDC 1508937), we deduced the structure as shown in Figure 1, and the assignment of the absolute configuration as 10*S* (Figure 1).

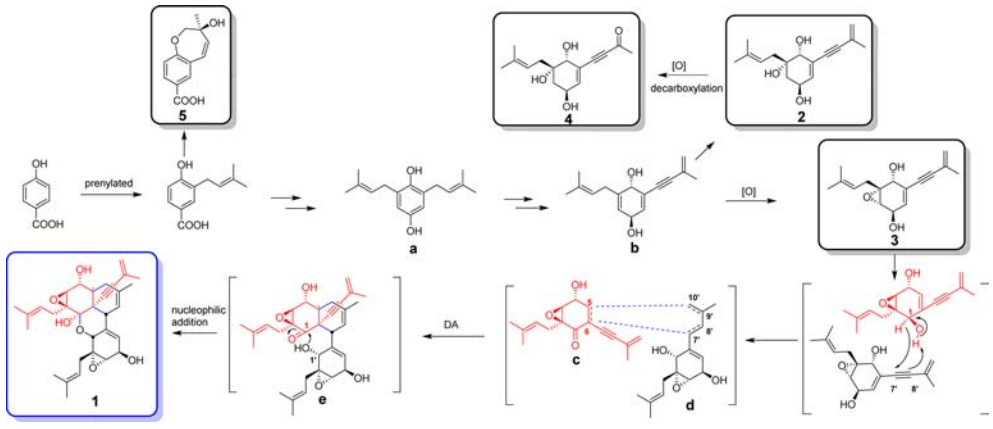
For their fascinating structures and important biological activities, meroterpenoids such as pyripyropene A (acylCoA:cholesterol acyltransferase inhibitor),[12] merochlorin A (antibiotic),[13] and territrem B (acetylcholinesterase inhibitor)[14] have attracted broad interest from chemists and pharmacologists.[1] The development of gene technologies have allowed the elucidation of the biosynthetic gene clusters of some meroterpenoids, such as viridicatumtoxin,[15] austinol,[16] fumagillin,[17] and terretonin.[18] Because these results are very exciting, an increasing number of scientists have begun showing interest in this field. In our chemical investigation on *Biscogniauxia* sp. (No. 71-10-1-1), two types of meroterpenoids were obtained, including diisoprenyl-cyclohexene-type meroterpenoids (**1**−**4**) and an isoprenyl-benzoic acid-type meroterpenoid (**5**). Eneyne analogues are rare in natural products. Diisoprenyl-cyclohexene-type meroterpenoids (**1**−**4**) are new members of natural eneynes. In addition, dimericbiscognienyne A (**1**) possesses an unprecedented hexadecahydrobenzo[kl]xanthene core with three isoprenyl chains, which could derive from two monomeric diisoprenyl-cyclohexene-type meroterpenoids (**3**) via a unique intermolecular redox coupling Diels−Alder adduct and a nucleophilic addition reaction (Scheme 1). As long as two molecules of **3** are close enough in space, the intermolecular redox reaction would be triggered and form the DA reactants (intermediates **c** and **d**). Then, the C ring of **1** would be formed by the DA reaction between intermediates **c** (C-5 and C-6) and **d** (C-7′ and C-10′). At the same time, the D ring would be formed by nucleophilic addition reaction for the attack of 1′−OH to C-1. In light of the structural characteristics of **2**−**5**, *p*-hydroxybenzoic acid is proposed as their biosynthetic precursor. Intermediate **a** would be generated from *p*-hydroxybenzoic acid by isopentenyl transferase and FAD-binding monooxygenase catalyst (Scheme 1).[19] Then, **2**−**4** would originate from intermediate **a** under complex enzymatic systems (including hydroxylase, dehydrogenase, reductase, cyclase, oxidase, and hydrolytic enzymes).

Cytotoxicities of **1**−**5** against HeLa, SW480, and PANC-1 human cancer cell lines were evaluated by cell count kit 8 (CCK-8) assay using cisplatin as the positive control. The results showed that only **4** had cytotoxic activities against HeLa and SW480 cancer cell lines with IC_{50} values of 38.6 and 16.3 μM, respectively (Table S14).

Furthermore, the anti-Alzheimer's disease (AD) activities of **1**−**5** were also evaluated by AD fly model with memantine as the positive control (Figure 1). The transgenic AD fly carries human $A\beta_{42}$ gene, which causes the expression of $A\beta_{42}$ peptide in fly brain and induces AD pathological phenotypes. For its cheapness, easy and fast breeding, and AD pathological similarity, the AD fly model has been used as a powerful tool for screening anti-AD drugs.[20] Using the AD fly assay, we have successfully discovered several natural products with potential anti-AD effects.[7b,21] After the AD fly assay, **1** and **5** showed short-term memory enhancement activities in AD flies.

Among the obtained diisoprenyl-cyclohexene-type meroterpenoids (**1**−**4**), **1** showed short-term memory enhancement activity in AD flies, and **4** showed cytotoxic activity against HeLa and SW480 cancer cell lines. These discoveries of biological functions are noteworthy. However, the fascination of molecular structures does not rest only on their practical values.[22] The structural shapes of **1**−**4** are intriguingly similar to flying birds

Scheme 1. Plausible Biosynthetic Pathway of Compounds 1−5



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with different poses. Interestingly, dimericbiscognienyne A (**1**) looks like two loving birds together (Figure S10).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03264.

General experimental procedures, fungus materials and fermentation, extraction and isolation, preparation of the 4-mono-*O*-(4-bromobenzoyl) derivative of **2** (**2a**), quantum chemical ECD calculations of **2a**, $^{1}H-^{1}H$ coupling constant calculations of **3**, cytotoxicity assays of **1**−**5**, short-term memory assays of **1**−**5** on the transgenic AD fly model, aesthetic figure of diisoprenyl-cyclohexene type meroterpenoids, and NMR data, assignments, and spectra (PDF)

X-ray crystallographic analyses of **1** (CIF)

X-ray crystallographic analyses of **2** (CIF)

X-ray crystallographic analyses of **5** (CIF)

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Notes

The authors declare no competing financial interest.

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