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Natural Product Synthesis

An Expedient Synthesis of a Functionalized Core Structure of Bielschowskysin**

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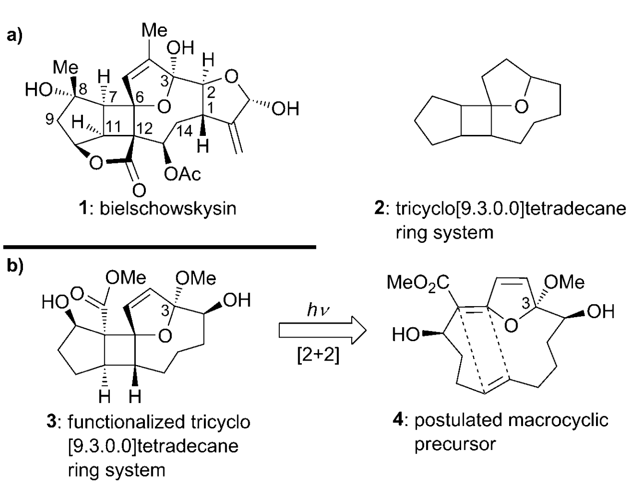
Bielschowskysin (**1**, Scheme 1 a) is a recently discovered marine natural product that possesses a novel molecular architecture and impressive biological properties.[1] Isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos* and characterized by spectroscopic and X-ray crystallographic analysis, bielschowskysin boasts an unprecedented tricyclo[9.3.0.0]tetradecane ring system (see **2**, Scheme 1 a) decorated with a large number of oxygen-containing functional groups and with 11 stereogenic centers.[1] Its biological properties include antimalarial activity against *Plasmodium falciparum* ($IC_{50} = 10\ \mu g\,mL^{-1}$) and potent and selective cytotoxicity against EKVX nonsmall lung cancer cells ($GI_{50} < 10$ nM) and CAKI-1 renal cancer cells ($GI_{50} =$ 510 nM).[1]



Scheme 1. a) Molecular structures of bielschowskysin (**1**) and its tricyclo[9.3.0.0]tetradecane ring system (**2**) and b) functionalized tricyclo[9.3.0.0]tetradecane ring system (**3**), and its postulated macrocyclic precursor (**4**).

As a consequence of its natural scarcity, the full biological profile of bielschowskysin remains unexplored, and its absolute configuration is unknown. These factors leave little doubt, if any, of the worthiness of bielschowskysin as a synthetic target, since an endeavor toward its total synthesis may provide an opportunity to develop new synthetic strategies and techniques, render the compound readily available for biological investigations, allow studies of the structure–activity relationship, and reveal its absolute stereochemistry. Herein, we report our preliminary forays toward the total synthesis of bielschowskysin that culminated in the construction of a functionalized tricyclo[9.3.0.0]tetradecane ring system **3** (Scheme 1 b) of the molecule and its 2-*epi* enantiomer (2-*epi*-*ent*-**3**). The reported route is notable for its cascade sequences, brevity, and efficiency.[2]

In contemplating a plan for the total synthesis of bielschowskysin (**1**), an intramolecular [2+2] photocycloaddition[3] similar to a postulated biosynthetic scheme[4] came to mind. To test this hypothesis, we designed a functionalized tricyclo[9.3.0.0]tetradecane ring system **3** (Scheme 1 b) and its proposed macrocyclic precursor **4** (Scheme 1 b), the latter generated through a retro [2+2] photocycloaddition reaction, as shown.

Scheme 2 summarizes the short and enantioselective route to macrocyclic [2+2] photocycloaddition precursor **4** and its 2-*epi* enantiomer 2-*epi*-*ent*-**4**. Thus, acyl furan **5** was reduced enantioselectively with the Noyori catalyst **A**[5] to alcohol **6** (84 % yield, 92 % *ee*) and then combined with β-ketoester **7** in the presence of CAN in MeOH to afford a conjugated ketoester as a mixture of α- and β-methoxy epimers **8** and 3-*epi*-**8** (58 % yield, ca. 1:1 ratio), which were separated by chromatography.[6] The geometry of the enol ether bond in these products was tentatively assigned at this stage on the basis of NMR spectroscopy, and subsequently proven by X-ray crystallographic analysis of a subsequent derivative (see below). This highly productive and efficient process, which rapidly generates structures **8** and 3-*epi*-**8**, is presumed to proceed through the mechanism depicted in Scheme 3. The importance of *exo*-enol ether/cyclic ketals (as in **8** and 3-*epi*-**8**) in natural products chemistry and the challenge of their construction have been recently noted by Pattenden in a series of elegant studies.[7] This CAN-mediated

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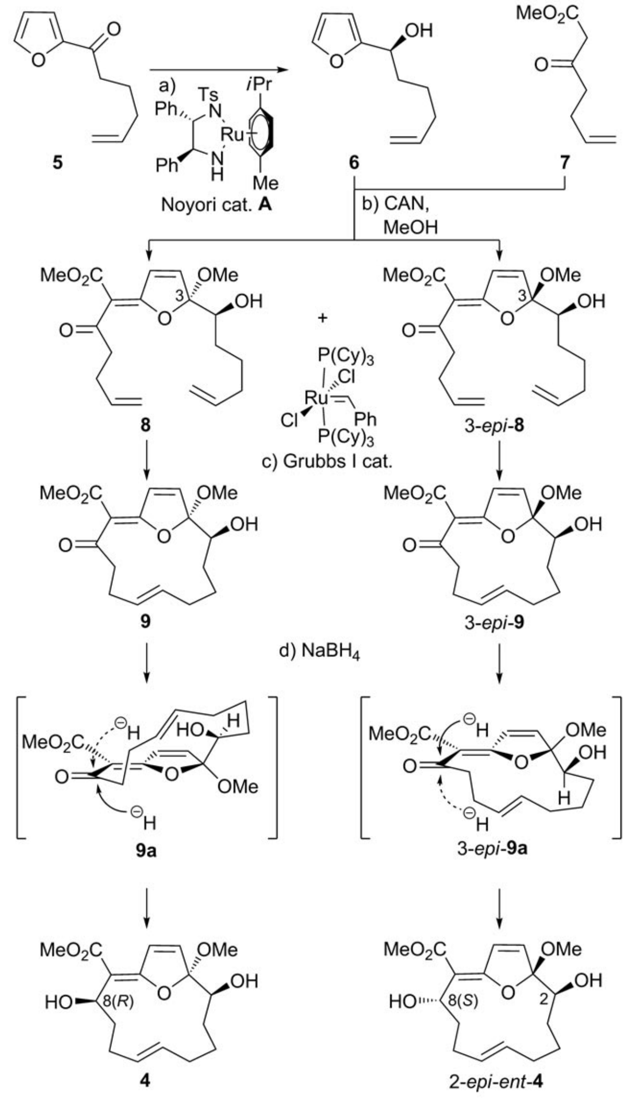
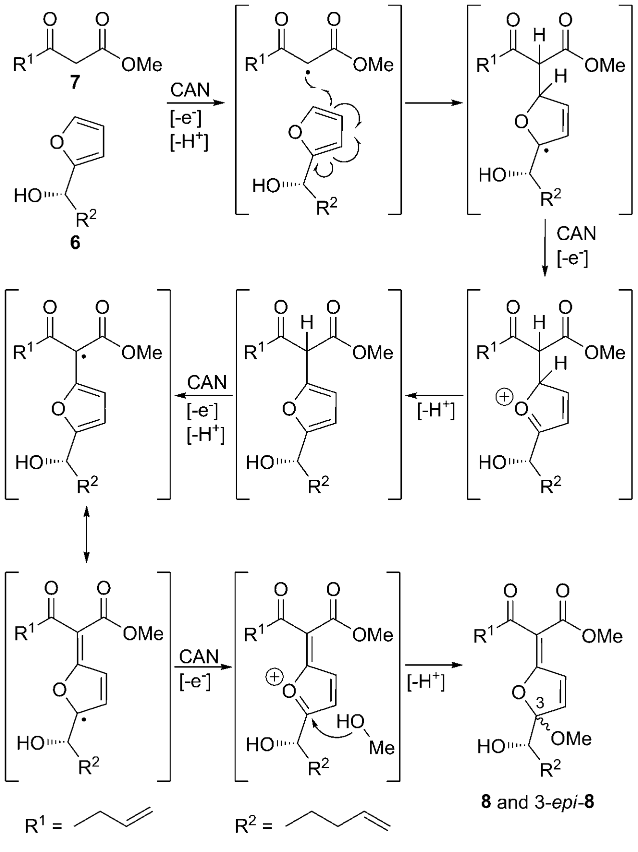


Scheme 2. Construction of macrocyclic precursor **4**. Reagents and conditions: a) Noyori cat. **A** (0.025 equiv), HCOONa (10 equiv), nBu$_4$Cl (0.3 equiv), CH_2Cl_2/H_2O (1:1), 25 °C, 15 h; then Noyori cat. **A** (0.01 equiv), 12 h, 84 %, 92 % *ee*; b) **6** (1.0 equiv), **7** (1.2 equiv), CAN (4.0 equiv), MeOH, 0 °C, 58 % (d.r. ca. 1:1); c) Grubbs I cat. (0.3 equiv for **8**, 0.25 equiv for 3-*epi*-**8**), CH_2Cl_2, reflux, 4 h, 90 % for **9** (*trans*/*cis* ca. 15:1), 71 % for 3-*epi*-**9** (*trans*/*cis* ca. 3:1); d) NaBH$_4$ (6.0 equiv), THF/H_2O (2:1), 0 °C, 30 min, 83 % for **4**, 63 % for 2-*epi*-*ent*-**4**. CAN = ammonium cerium nitrate, Cy = cyclohexyl, Ts = toluene-4-sulfonyl.

coupling process provides rapid access to the *exo*-enol ether structural motif, as exemplified in Scheme 2.

Treatment of **8** and 3-*epi*-**8** separately with Grubbs I catalyst[8] resulted in ring closure to furnish the corresponding macrocyclic hydroxy ketones with the newly generated double bond predominantly *trans* (**9**, 90 % yield, *trans*/*cis* ca. 15:1; 3-*epi*-**9**, 71 % yield, *trans*/*cis* ca. 3:1, separated by chromatography; Scheme 2). X-ray crystallographic analysis of the 3,5-dinitrobenzoate derivatives of **9** [(+)-**9**-**DNB**, m.p. 196–197 °C (Et$_2$O/MeOH/CH$_2$Cl$_2$, 1:1:1); Figure 1][9] and 3-*epi*-**9** [(+)-3-*epi*-**9**-**DNB**, m.p. 215–217 °C (Et$_2$O/MeOH/CH$_2$Cl$_2$, 1:1:2); Figure 2][9] confirmed their structures, including the geometry of the enol ether double bond, and that of their precursors (i.e. **8** and 3-*epi*-**8**).



Scheme 3. Proposed mechanism for the coupling reaction of **6** and **7** under the influence of CAN.

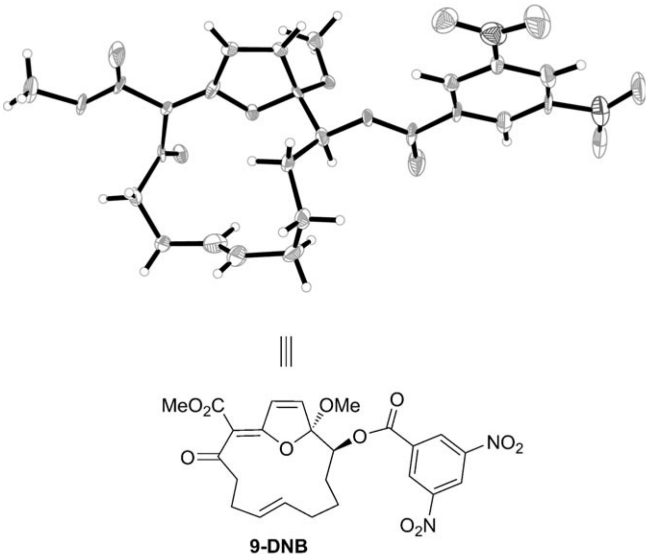
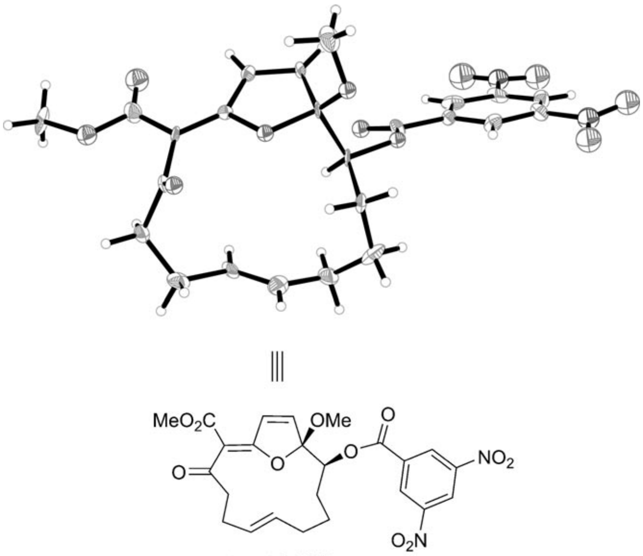


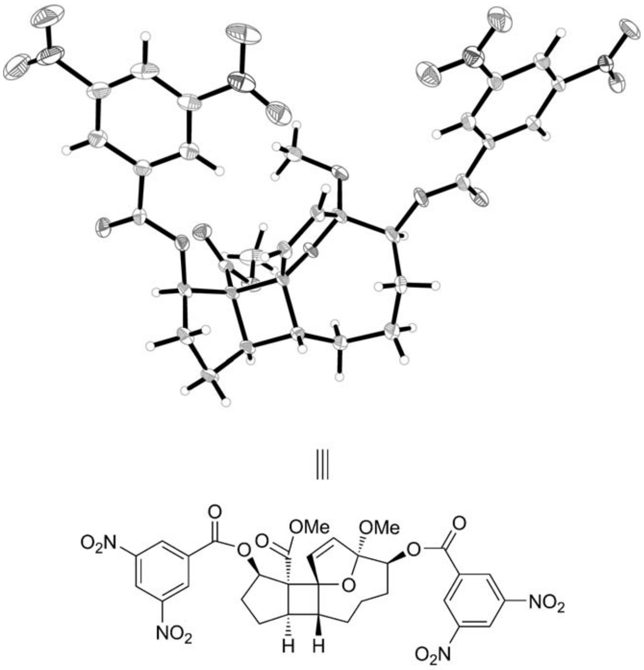
Figure 1. ORTEP representation of 3,5-dinitrobenzoate (+)-**9-DNB** (thermal ellipsoids at 30 % probability).

Attempts to induce photolytically the desired intramolecular [2+2] cycloaddition with **9** or 3-*epi*-**9** proved unproductive, with starting material persisting and partial enol



3-*epi*-**9**-**DNB**

Figure 2. ORTEP representation of 3,5-dinitrobenzoate (+)-(3-*epi*-**9**-**DNB**) (thermal ellipsoids at 30% probability).



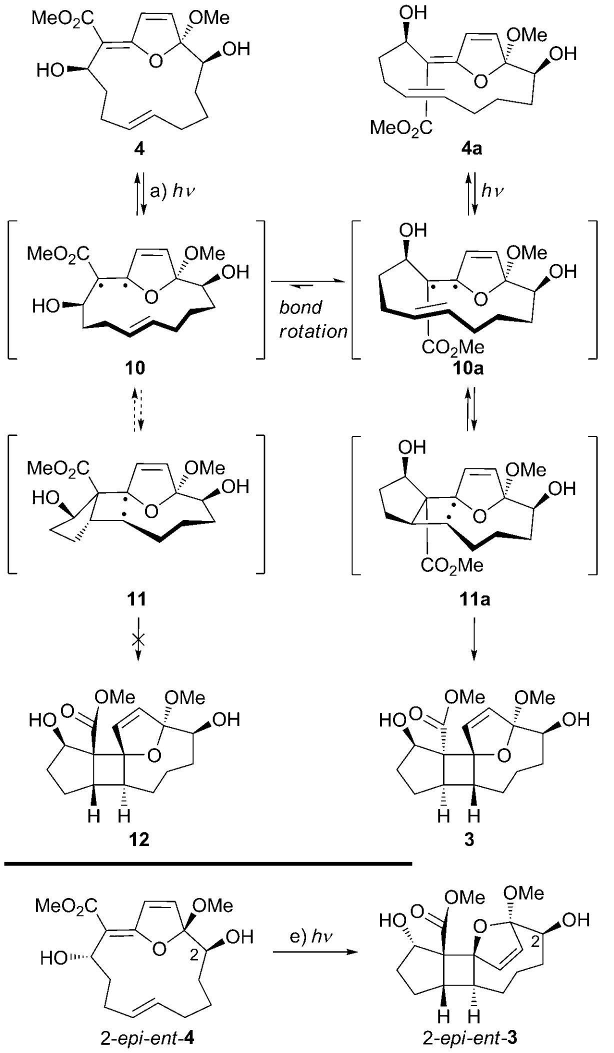
3-bDNB

Figure 3. ORTEP representation of (±)-**3**-**bDNB** (thermal ellipsoids at 30% probability).

ether isomerization occurring. This failure was presumably due to the conjugation of the enol ether olefinic bond with the two carbonyl groups and/or the presence of the sp^2 carbon atom of the macrocycle carbonyl group, thereby resulting in a prohibitive strain in the expected polycyclic product. This carbonyl group was, therefore, reduced within each of the two methoxy epimers (hydroxy ketones **9** and 3-*epi*-**9**) with $NaBH_4$ to produce, in each case, a single diastereoisomeric diol (**4**, 83% yield, and 2-*epi*-*ent*-**4**, 63% yield; Scheme 2). The configuration of the newly formed hydroxy group in **4** and 2-*epi*-*ent*-**4** was tentatively assigned at this stage on the basis of manual molecular models, which indicated a favored external hydride delivery by the reducing agent (see **9a** and 3-*epi*-**9a**; Scheme 2), and was later confirmed through X-ray crystallographic analysis of downstream intermediates (see below). Note that an internal hydroxy-directed hydride delivery in this reduction (i.e. **9** and 3-*epi*-**9** to **4** and 2-*epi*-*ent*-**4**, respectively) may also explain this stereochemical outcome, as seen by manual molecular modeling studies.

Pleasingly, irradiation of a benzene or chloroform solution of macrocycle **4** with UV light (450 Watt Hanovia, >254 nm or Rayonet, >254 nm) for 48 h resulted in the formation of tetracycle **3** (90% yield) as a single diastereoisomer. The structure of compound **3** was unambiguously proven by X-ray crystallographic analysis of its racemic bis-3,5-dinitrobenzoate ester [(±)-**3**-**bDNB**, m.p. 203–205 °C (Et_2O/CH_2Cl_2, slow diffusion); Figure 3].[9] The [2+2] photocycloaddition of **4** is presumed to proceed through a radical mechanism and the intermediacy of its transient enol ether geometrical isomer **4a**, as shown in Scheme 4. Thus, photoexcitation of the chromophore of substrate **4** under the influence of light may furnish diradical **10**, which apparently undergoes C–C bond rotation to afford the less-strained diradical **10a**. The latter species suffers, according to the rule of fives,[10] facile and regioselective ring closure to afford cyclopentane intermediate diradical **11a**, which then undergoes a second ring closure, facilitated by the newly acquired rigidity and proximity, to afford the observed tetracyclic product **3**. Indeed, NMR spectroscopic monitoring of the reaction reveals initial formation of the enol ether isomer of **4**, namely compound **4a**, which dissipates with time to the final product, presumably through radical species **10a** and **11a**. Interestingly, isolated geometrical isomer **4a** only partially reverts back to the original geometrical isomer **4** under the irradiation conditions, which suggests the equilibrium between **10** and **10a** lies far to the right, in favor of **10a**. The alternative pathway of diradical **10** to **12** through **11** is apparently shut, most likely because of unfavorable geometrical constraints imposed by strain in the macrocycle.

Macrocycle 2-*epi*-*ent*-**4** was also converted into a [9.3.0.0] tetracyclic core structure (2-*epi*-*ent*-**3**, 88% yield; Scheme 4) by employing the same photoirradiation conditions (see the Supporting Information). Although no olefin isomerization of 2-*epi*-*ent*-**4** (as with **4**) was observed by NMR spectroscopic or TLC analysis, the transient existence of the corresponding geometrical isomer may be inferred by examination of the structure of the product 2-*epi*-*ent*-**3**. The structure of 2-*epi*-*ent*-**3** was confirmed by X-ray crystallographic analysis of its racemic bis-4-methoxybenzoate derivative [(±)-(2-*epi*-*ent*-**3**-**bMB**), m.p. 207–209 °C ($MeOH/CH_2Cl_2$, 5:1); Figure 4].[9] Racemic bis-dinitrobenzoate (±)-**3**-**bDNB** and racemic bis-methoxybenzoate (±)-(2-*epi*-*ent*-**3**-**bMB**) were prepared from racemic alcohol (±)-**6** (obtained by Grignard addition to furfural). Interestingly, their enantiomeric counterparts obtained from enantiopure **3** and 2-*epi*-*ent*-**3**, respectively, did not yield suitable crystals for X-ray crystallographic analysis. It should be noted that the asymmetric creation of the first stereocenter of the molecule in step one (i.e. in **6**) allows the



Scheme 4. Photocycloaddition of macrocyclic precursor **4** and 2-*epi*-*ent*-**4**. Conditions: a) C_6H_6 or $CHCl_3$, ambient temperature, *hν* (Hanovia 450 Watt, >254 nm or Rayonet, >254 nm), 48 h for **3**, 90%; 16 h for 2-*epi*-*ent*-**3**, 88%.

construction of a complex structure (i.e. **3**) containing the [9.3.0.0] ring framework, seven stereogenic centers, and five functional groups from two simple starting materials (i.e. acylfuran olefin **5** and β-ketoester olefin **7**).

The described route provides a five-step enantioselective entry into the novel carbocyclic [9.3.0.0] core structure of bielschowskysin (from simple building blocks **6** and **7**), which bears substantial functionality that may endow it with the potential to serve as a scaffold for building further molecular complexity and possibly imparting biological activity. Such studies may prove useful in the total synthesis of the natural product and its mimics for biological investigations.

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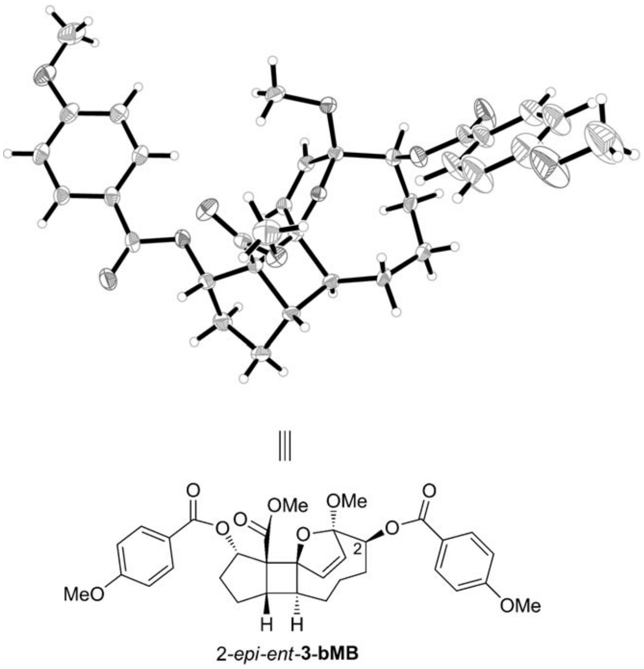

Figure 4. ORTEP representation of (±)-(2-*epi*-*ent*-**3**-**bMB**) (thermal ellipsoids at 30% probability).

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