Natural Product Synthesis

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Total Syntheses and Structural Revision of α- and β-Diversonolic Esters and Total Syntheses of Diversonol and Blennolide C**

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The structures of α- and β-diversonolic esters (**1** and **2**; Figure 1)[1] define the key structural motifs of a growing xanthone family of natural products, some members of which exhibit striking antibiotic activities. Among them are diversonol (**3**; Scheme 1),[2] the first member of the monomeric series within the class, as well as the rugulotrosins,[3] secalonic acids[4] and hirtusneanoside,[5] all of which are dimeric in nature.

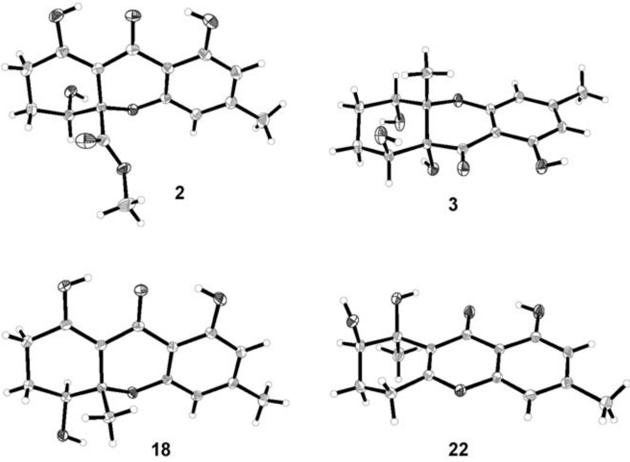
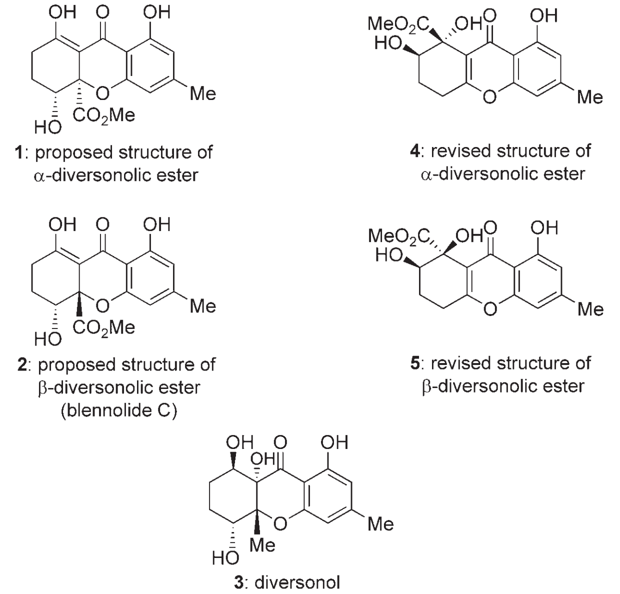


Figure 1. ORTEP plots of compounds **2**, **3**, **18**, and **22** derived from X-ray crystallographic analysis (non-hydrogen atoms are shown with ellipsoids at 30% probability).



1: proposed structure of α-diversonolic ester

4: revised structure of α-diversonolic ester

2: proposed structure of β-diversonolic ester (blennolide C)

5: revised structure of β-diversonolic ester

3: diversonol

Scheme 1. Structures of α- and β-diversonolic esters (**1**, **2**, **4**, and **5**) and diversonol (**3**).

In a program directed towards the total synthesis of these molecules, we focused initially on the development of new synthetic technologies for the synthesis of the basic molecular framework of these xanthones; therefore, we turned our attention to α- and β-diversonolic esters (**1** and **2**) and diversonol (**3**), the simplest members of the family. Herein, we report the development of an expedient synthetic strategy for the construction of the diversonolic architecture, its application to the concise total syntheses of all three structures **1**–**3**, and the revision of the originally proposed structures for α- and β-diversonolic esters **1** and **2** to **4** and **5**, respectively.

Scheme 2 summarizes the devised synthesis of the originally assigned structures of α- and β-diversonolic esters **1** and **2**. Thus, treatment of racemic enone **6** with Et_2AlCN followed by trapping with TMSCl in the presence of pyridine furnished the corresponding enol ether, which was transformed (without isolation) into nitrile enone **7** through the action of IBX·MPO,[6] in 62 % overall yield. Conversion of **7** into its ester enone counterpart **8** required reduction with DIBAL-H (hydroxy aldehyde), oxidation with DMP (keto aldehyde; 83 % yield over two steps), Pinnick oxidation, and treatment with $TMSCHN_2$ (90 % yield over two steps). Ester enone **8** was then converted into bromo hydroxy ester **9** (ca. 1.3:1 d.r.) through sequential treatment with bromine and Et_3N (bromo enone; 94 % yield), followed by reduction with $NaBH_4/CeCl_3$ (91 % yield). Deprotonation of **9** with MeLi (1.1 equiv)

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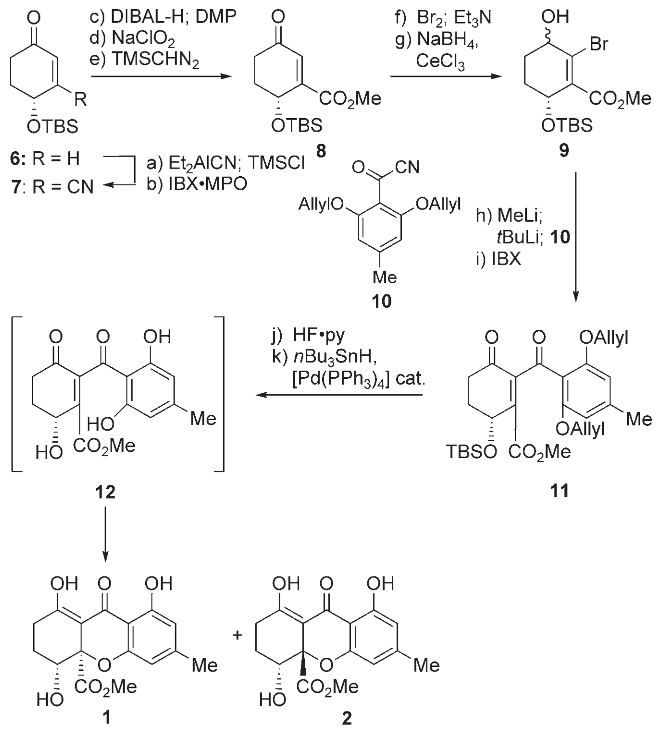
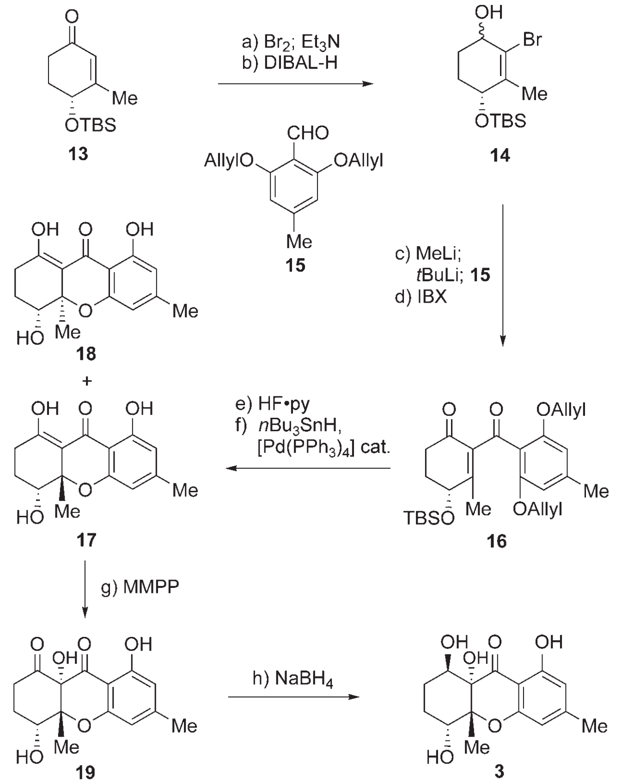


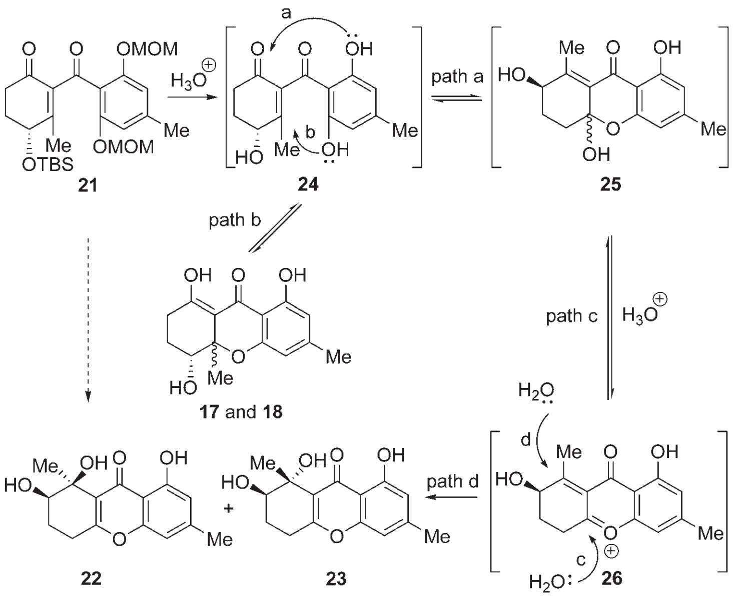
Scheme 2. Synthesis of the proposed structures of α- and β-diversonolic esters (**1** and **2**). Reagents and conditions: a) Et_2AlCN (1.0 M in toluene, 1.2 equiv), toluene, 23 °C, 30 min; then pyridine (3.0 equiv), TMSCl (1.8 equiv), $0\rightarrow23$ °C, 1 h; b) IBX (1.2 equiv), MPO (1.2 equiv), DMSO, 23 °C, 1 h, 62 % (over 2 steps); c) DIBAL-H (1.0 M in CH_2Cl_2, 2.5 equiv), toluene, $-78\rightarrow-40$ °C, 30 min; then DMP (1.2 equiv), CH_2Cl_2, 23 °C, 45 min, 83 %; d) $NaClO_2$ (3.0 equiv), 2-methyl-2-butene (10 equiv), NaH_2PO_4 (5.0 equiv), tBuOH/H_2O (1:1), 23 °C, 1 h; e) $TMSCHN_2$ (2.0 M in diethyl ether, 2.0 equiv), MeOH, 0 °C, 20 min, 90 % (over 2 steps); f) Br_2 (1.05 equiv), CH_2Cl_2, 0 °C, 5 min; then Et_3N (1.5 equiv), 0 °C, 5 min, 94 %; g) $CeCl_3\cdot7H_2O$ (1.2 equiv), $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 30 min, 91 % (ca. 1.3:1 d.r.); h) MeLi (1.6 M in diethyl ether, 1.1 equiv), diethyl ether, −78 °C, 15 min; then tBuLi (1.7 M in pentane, 2.2 equiv), −78 °C, 15 min; then **10** (1.5 equiv), $-78\rightarrow-40$ °C, 40 min; i) IBX (2.0 equiv), DMSO, 23 °C, 1 h, 41 % (over 2 steps); j) HF·py/THF (1:5), 23 °C, 12 h, 89 %; k) $n$$Bu_3SnH$ (2.2 equiv), AcOH (2.2 equiv), $[Pd(PPh_3)_4]$(0.05 equiv), benzene, 23 °C, 1 h, 60 % (**1**/**2** ca. 2:1 d.r.). DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin periodinane, DMSO = dimethyl sulfoxide, IBX = *o*-iodoxybenzoic acid, MPO = 4-methoxypyridine-*N*-oxide, py = pyridine, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl.

followed by sequential treatment with tBuLi and acyl cyanide **10** afforded the expected alcohol (ca. 1.3:1 d.r.), which was oxidized with IBX to give diketone **11** in 41 % overall yield. Finally, desilylation of **11** (HF·py) followed by deallylation ($n$$Bu_3SnH$, $[Pd(PPh_3)_4]$ cat.) furnished compounds **1** and **2** (**1**/**2** ca. 2:1, separated by chromatography), presumably through intermediate **12**. However, the spectroscopic data (^1H and ^{13}C NMR analysis) of these compounds did not match those reported[1] for the natural products α- and β-diversonolic esters. The skeletal connectivity of compounds **1** and **2** was established by HMBC studies and their relative stereochemistry was assigned by comparison of NMR data with similar compounds.[7] The structure of **2** (m.p. 183–184 °C, EtOAc/hexanes 1:1) was verified by X-ray crystallographic analysis (see the ORTEP plot; Figure 1).[8]

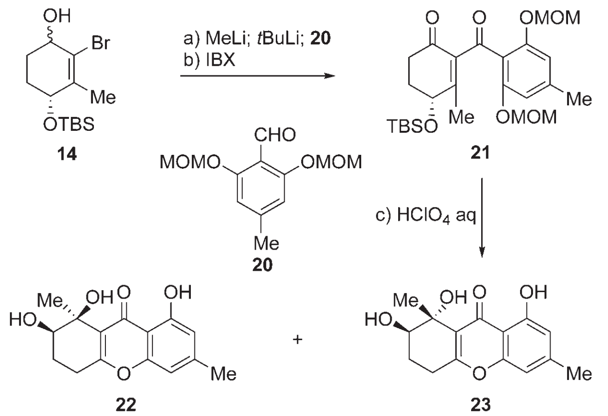


Scheme 3. Total synthesis of diversonol (**3**). Reagents and conditions: a) Br_2 (1.05 equiv), CH_2Cl_2, 0 °C, 5 min; then Et_3N (1.5 equiv), 0 °C, 5 min, 90 %; b) DIBAL-H (1.0 M in hexanes, 1.5 equiv), THF, $-78\rightarrow-40$ °C, 30 min, 95 % (ca. 1:1 d.r.); c) MeLi (1.6 M in diethyl ether, 1.1 equiv), diethyl ether, −78 °C, 15 min; then tBuLi (1.7 M in pentane, 2.2 equiv), −78 °C, 15 min; then **15** (1.5 equiv), $-78\rightarrow-40$ °C, 40 min; d) IBX (3.0 equiv), DMSO, 23 °C, 1 h, 72 % (over 2 steps); e) HF·py/THF (1:5), 23 °C, 12 h, 96 %; f) $n$$Bu_3SnH$ (2.2 equiv), AcOH (2.2 equiv), $[Pd(PPh_3)_4]$ (0.05 equiv), benzene, 23 °C, 1 h, 90 % (**17**/**18** ca. 2:1 d.r.); g) MMPP (0.75 equiv), EtOH, 23 °C, 30 min; h) $NaBH_4$ (1.0 equiv), MeOH/CH_2Cl_2 (1:1), −78 °C, 15 min, 73 % (over 2 steps). MMPP = magnesium monoperoxophthalate.

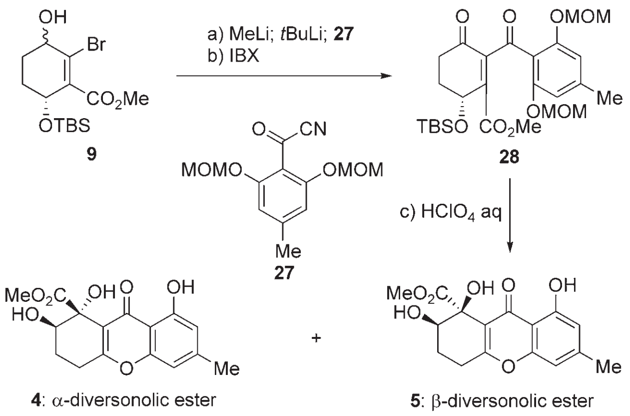
At this stage, and not yet knowing the true structures of α- and β-diversonolic esters, we turned our attention to the synthesis of diversonol (**3**) through application of the synthetic strategy we had developed. Thus, by substituting the nitrile moiety with a methyl group in the starting enone (now **13**; Scheme 3) and following a similar route as before, but proceeding through intermediates **14**–**19** (**17**/**18** ca. 2:1), we arrived at diversonol (**3**) in eight steps as summarized in Scheme 3. The spectroscopic data (^1H and ^{13}C NMR analysis) of synthetic diversonol matched those reported for the natural substance[2] and those of another sample of synthetic diversonol, which was kindly provided by Professor S. Bräse (whose group was the first to synthesize this natural product).[9] The structures of synthetic compounds **18** (m.p. 154–155 °C, EtOAc/hexanes 1:1) and **3** were also confirmed by X-ray crystallographic analysis (see the ORTEP plot; Figure 1).[8] In what turned out to be a fortunate twist of fate, and while aiming to improve and streamline our synthesis of diversonol (**3**), we decided to employ MOM protecting groups on the aromatic segment of the molecule (aldehyde **20**; Scheme 4). Therefore, we proceeded with preparing intermediate **21** (Scheme 3) by the same route as above, and where global removal of the protecting groups of **21**, under acidic conditions, was expected to give compound **17** (Scheme 3) in one step rather than two steps, thus avoiding the organometallic reagent and catalyst employed in the first route. Upon exposure of **21** to aqueous $HClO_4$, however, we did not observe any of the expected products (i.e. **17** and **18**; Scheme 3), but instead we obtained two new compounds (ca. 2:1, chromatographically separated, silica gel, EtOAc/hexanes 1:1) which were isomeric in nature relative to the previously obtained products (**17** and **18**). Fortunately, one of these compounds (the less polar) crystallized from EtOAc/hexanes (1:1) to form beautiful colorless needles (m.p. 175–176 °C, EtOAc/hexanes 1:1). Single crystal X-ray analysis (see the ORTEP plot; Figure 1)[8] revealed its structure as **22**, and hence, the structure of the other isomer was **23** (Scheme 3).



Scheme 5. Postulated mechanism of the formation of **22** and **23**.



Scheme 4. Construction of compounds **22** and **23**. Reagents and conditions: a) MeLi (1.6 M in diethyl ether, 1.1 equiv), diethyl ether, −78 °C, 15 min; then *t*BuLi (1.7 M in pentane, 2.2 equiv), −78 °C, 15 min; then **20** (1.5 equiv), −78→−40 °C, 40 min; b) IBX (3.0 equiv), DMSO, 22 °C, 1 h, 78 % (over 2 steps); c) 1.0 M aqueous $HClO_4$/THF (1:1), 40 °C, 2 h, 90 % (**22**/**23** ca. 2:1 d.r.). MOM = methoxymethyl.



Scheme 6. Total synthesis of the revised structures of α- and β-diversonolic esters (**4** and **5**). Reagents and conditions: a) MeLi (1.6 M in diethyl ether, 1.1 equiv), diethyl ether, −78 °C, 15 min; then *t*BuLi (1.7 M in pentane, 2.2 equiv), −78 °C, 15 min; then **20** (1.5 equiv), −78→−40 °C, 40 min; b) IBX (2.0 equiv), DMSO, 23 °C, 1 h, 45 % (over 2 steps); c) 1.0 M aqueous $HClO_4$/THF (1:1), 50 °C, 2 h, 80 % (**4**/**5** ca. 1:3 d.r.).

The proposed mechanism for the formation of compounds **22** and **23** from **21**, through postulated intermediates **24**–**26** (Scheme 5), served as the basis for the total synthesis and structural revision of the α- and β-diversonolic esters. Apparently, the initially formed structures undergo skeletal rearrangements to give structures such as **22** and **23** under the acidic conditions employed for the deprotection. The similarity of the NMR data of **22** and **23** to those of the natural diversonolic esters led us to propose structures **4** and **5** as the revised structures of **1** and **2**, respectively. Scheme 6 summarizes our syntheses of **4** and **5** starting with the hydroxy bromo ester **9** and bisMOM-protected acyl cyanide **27**, and which proceeds through intermediate **28** (**4**/**5** ca. 1:3 d.r.). The spectroscopic properties of synthetic diversonolic esters **4** and **5** were consistent with their structures and matched those reported[1] for the naturally occurring substances. The structural connectivity of **4** and **5** were established by HMBC studies, and their relative stereochemistries were assigned by nOe analysis. The revised structures of α- and β-diversonolic esters (**4** and **5**) also explain the ambiguities in the spectroscopic and chemical properties of these compounds which were described in the original isolation report.[1]

In a final twist, a naturally occurring compound named blennolide C, bearing the structure of **2**, was reported[10] while this manuscript was in preparation. Although a natural product with the structure **1** has not yet been reported, it can be predicted to exist, especially as it is present as a monomeric unit in some dimeric natural products such as the rugulotrosins.[3]

Besides uncovering the true structures of α- and β-diversonolic esters and thus rendering them, diversonol, and blennolide C readily available, the described chemistry opens an expedient entry into these and the more complex members of this class of natural products, which include their enantiomerically pure forms and their analogues. As both enantiomers of the starting materials (**6**[11] and **13**[12]) are known, the as yet undetermined absolute stereochemistry of all three natural products (**3**–**5**) should now be easily discernable. Finally, biological investigations using the synthesized compounds may reveal interesting properties.

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