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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 family of natural products, some members of which exhibit striking antibiotic activities. Among them are diversonol (**3**, Figure 1),[2] the first member of the monomeric series within the class, and the rugulotrosins,[3] secalonic acids[4] and hirtusneanoside,[5] all of which are dimeric in nature.

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 the class, and, therefore, turned our attention to α - and β -diversonolic esters (**1** and **2**) and diversonol (**3**), the simplest members of the family. In this communication we report the development of an expedient synthetic strategy for the construction of the diversonolic architecture, its application to 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, through total synthesis.

Scheme 1 summarizes the devised synthesis of the originally assigned structures of α - and β -diversonolic esters **1** and **2**. Thus, reaction of racemic enone **6** with Et_2AlCl followed by trapping with TMSCl in the presence of pyridine furnished the corresponding nitrile TMS enol ether, which was transformed without isolation to nitrile enone **7** through the action of $\text{IBX}\cdot\text{MPO}$,[6] in 62 % overall yield. Conversion of the latter to its ester enone counterpart (**8**) required DIBAL-H reduction (hydroxy aldehyde), DMP oxidation (ketoaldehyde, 83 % yield, two steps), Pinnick oxidation, and treatment with TMSCHN_2 (90 % yield, two steps). Ester enone **8** was then converted to bromo hydroxy ester **9** (ca. 1.3:1 dr) through sequential reaction with bromine and Et_3N (bromo enone, 94 % yield), followed by reduction with

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NaBH₄-CeCl₃ (91 % yield). Deprotonation of bromo hydroxy ester **9** with MeLi (1.1 equiv) followed by sequential treatment with *t*BuLi and acyl cyanide **10** afforded the expected alcohol (ca. 1.3:1 dr), which was oxidized with IBX to give diketone **11** in 41 % overall yield. Finally, desilylation of **11** (HF•py), followed by deallylation (*n*Bu₃SnH, Pd(PPh₃)₄ cat.), furnished structures **1** and **2** (**1**:**2** ca. 2:1, chromatographically separated), presumably through the intermediacy of **12**. The spectroscopic data (¹H and ¹³C NMR) of these compounds, however, 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 ORTEP drawing, Figure 2).[8]

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 developed synthetic strategy. Thus, substituting the nitrile with a methyl group in the starting enone (now **13**, Scheme 2) 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 2. The spectral data (¹H and ¹³C NMR) of synthetic diversonol matched those reported for the natural substance[2] and those of synthetic diversonol 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 crystallographic analysis (ORTEP drawing, Figure 2).[8]

In what turned out to be a fortunate twist of fate, and aiming improving and streamlining our synthesis of diversonol (**3**), we decided to employ MOM protecting groups on the aromatic segment of the molecule (aldehyde **20**, Scheme 3). We, therefore, proceeded to prepare, by the same route, intermediate **21** (Scheme 3), whose global deprotection under acidic conditions was expected to give compound **17** (Scheme 2) in one step, rather than two, and avoiding the organometallic reagent and catalyst employed in the first route. Upon exposure of **21** to aqueous HClO₄, however, we did not observe any of the expected products (*i.e.* **17** and **18**, Scheme 2), but instead obtained two new compounds (ca. 2:1 ratio) isomeric in nature to the previously obtained products (**17** and **18**) and to each other. Fortunately, one of these compounds (major, less polar, silica gel, hexanes: EtOAc 1:1) crystallized from hexanes: EtOAc (1:1) in beautiful colorless needles (m.p. 175–176 °C, EtOAc:hexanes 1:1). One of these crystals was subjected to X-ray crystallographic analysis (see ORTEP drawing, Figure 2),[8] which revealed its structure as **22**, and hence, that of the other isomer as **23** (Scheme 3).

The proposed mechanism for the formation of compounds **22** and **23** from **21** through postulated intermediates **24**–**26** (Scheme 4) served as the basis for the total synthesis and structural revision of α- and β-diversonolic esters. Apparently, the initially formed structures undergo skeletal rearrangements to 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 5 summarizes our syntheses of **4** and **5** starting with hydroxy bromo ester **9** and bis-MOM protected acyl cyanide **27** and proceeding through intermediate **28** (**4**:**5** ca. 1:3 dr). The spectral 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** was established by HMBC studies and their relative stereochemistry was assigned by nOe studies. The revised structures of α- and β-diversonolic esters (**4** and **5**) also explain the ambiguities in the spectral and chemical properties of these compounds 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 rendering them and diversonol as well as blennolide C readily available, the described chemistry opens an expedient entry into these and the more complex members of this class of natural products, including their enantiomerically pure forms and their analogs. Since both enantiomers of starting materials (**6**[11] and **13**[12]) are known, the as yet undetermined absolute stereochemistry of all three natural products (**3–5**) should be easily discernable. Finally, biological investigations with the synthesized compounds may reveal interesting properties.

Supplementary Material

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References

1. Holker JSE, O'Brien E, Simpson TJ. *J. Chem. Soc Perkin Trans. 1* 1983;1365–1368.
2. Turner WB. *J. Chem. Soc., Perkin Trans. 1* 1978;1621.
3. Stewart M, Capon RJ, White JM, Lacey E, Tennant S, Gill JH, Shaddock MP. *J. Nat. Prod* 2004;67:728–730. [PubMed: 15104517]
4. Franck B, Gottschalk EM, Ohnsorge U, Baumann G. *Angew. Chem* 1964;76:438–439. *Angew. Chem. Int. Ed.* **1964**, 3, 441–442
5. Rezanka T, Sigler K. *J. Nat. Prod* 2007;70:1487–1491. [PubMed: 17822296]
6. Nicolaou KC, Gray DLF, Montagnon T, Harrison ST. *Angew. Chem* 2002;114:1038–1042. *Angew. Chem. Int. Ed.* **2002**, 41, 996–1000
7. Ducrot PH, Lallemand JY, Milat ML, Blen JP. *Tetrahedron Lett* 1994;47:8797–8800. The spectra of **1** and **2** also showed great similarity to those of **18** and **17**, respectively.
8. CDCC-689919, -689920, -689921, and -689922 contain the supplementary crystallographic data of compounds **2**, **3**, **18** and **22**, respectively. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
9. Nising CF, Ohnemüller UK, Bräse S. *Angew. Chem* 2006;118:313–315. *Angew. Chem. Int. Ed.* **2006**, 45, 307–309
10. Zhang W, Krohn K, Ullah Z, Flörke U, Pescitelli G, Di Bari L, Antus S, Kurtán T, Rheinheimer J, Draeger S, Schulz B. *Chem. Eur. J* 2008;14:4913–4923. These authors apparently recognized that the structure of the diversonoic ester needed to be revised. The spectroscopic data of synthesis **2** were identical to those reported for natural blennolide C.
11. a) Hua Z, Yu W, Su M, Jin Z. *Org. Lett* 2005;7:1939–1942. [PubMed: 15876024] b) Audia JE, Boisvert L, Patten AD, Villalobos A, Danishefsky SJ. *J. Org. Chem* 1989;54:3738–3740.
12. a) Nicolaou KC, Li H, Nold AL, Pappo D, Lenzen A. *J. Am. Chem. Soc* 2007;129:10356–10357. [PubMed: 17676854] b) Xia J, Brown LE, Konopelski JP. *J. Org. Chem* 2007;72:6885–6890. [PubMed: 17685656]

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

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

Figure 2.
ORTEP drawings of compound **2**, **3**, **18** and **22** derived from X-ray crystallographic analysis (non-hydrogen atoms are shown as 30 % ellipsoids).

Scheme 1.

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→23 °C, 1 h; b) IBX (1.2 equiv), MPO (1.2 equiv), DMSO, 23 °C, 1 h, 62 % over two steps; c) DIBAL-H (1.0 M in CH_2Cl_2 , 2.5 equiv), toluene, -78→-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), $t\text{BuOH}/\text{H}_2\text{O}$ (1:1), 23 °C, 1 h; e) TMSCHN_2 (2.0 M in ether, 2.0 equiv), MeOH, 0 °C, 20 min, 90 % over two 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) $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$ (1.2 equiv), NaBH_4 (2.0 equiv), MeOH, 0 °C, 30 min, 91 %, ca. 1.3:1 dr; h) MeLi (1.6 M in ether, 1.1 equiv), ether, -78 °C, 15 min; then $t\text{BuLi}$ (1.7 M in pentane, 2.2 equiv), -78 °C, 15 min; then **10** (1.5 equiv), -78→-40 °C, 40 min; i) IBX (2.0 equiv), DMSO, 23 °C, 1 h, 41 % over two steps; j) $\text{HF}\cdot\text{py}/\text{THF}$ (1:5), 23 °C, 12 h, 89 %; k) $n\text{Bu}_3\text{SnH}$ (2.2 equiv), AcOH (2.2 equiv), $\text{Pd}(\text{PPh}_3)_4$ (0.05 equiv), benzene, 23 °C, 1 h, 60 %, **1:2** ca. 2:1 dr. DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin periodinane, IBX = *o*-iodoxybenzoic acid, MPO = 4-methoxypyridine-*N*-oxide, py = pyridine, TMS = trimethylsilyl.

Scheme 2.

Total synthesis of diversenol (**3**). Reagents and conditions: a) Br₂ (1.05 equiv), CH₂Cl₂, 0 °C, 5 min; then Et₃N (1.5 equiv), 0 °C, 5 min, 90 %; b) DIBAL-H (1.0 M in hexanes, 1.5 equiv), THF, -78 → -40 °C, 30 min, 95 %, ca. 1:1 dr; c) MeLi (1.6 M in ether, 1.1 equiv), ether, -78 °C, 15 min; then *t*BuLi (1.7 M in pentane, 2.2 equiv), -78 °C, 15 min; then **15** (1.5 equiv), -78 → -40 °C, 40 min; d) IBX (3.0 equiv), DMSO, 23 °C, 1 h, 72 % over two steps; e) HF·py/THF (1:5), 23 °C, 12 h, 96 %; f) *n*Bu₃SnH (2.2 equiv), AcOH (2.2 equiv), Pd(PPh₃)₄ (0.05 equiv), benzene, 23 °C, 1 h, 90 %, **17:18** ca. 2:1 dr; g) MMPP (0.75 equiv), EtOH, 23 °C, 30 min; h) NaBH₄ (1.0 equiv), MeOH/CH₂Cl₂ (1:1), -78 °C, 15 min, 73 % over two steps. MMPP=magnesium monoperoxophthalate.

Scheme 3.

Construction of compounds **22** and **23**. Reagents and conditions: a) MeLi (1.6 M in ether, 1.1 equiv), 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 two steps; c) 1.0 M HClO₄ aq. /THF (1:1), 40 °C, 2 h, 90 %, **22:23** ca. 2:1 dr.

Scheme 4.
Postulated mechanism of the formation of **22** and **23**.

Scheme 5.

Total synthesis of the revised structures of α - and β -diversonolic esters (**4** and **5**). Reagents and conditions: a) MeLi (1.6 M in ether, 1.1 equiv), 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), $-78 \rightarrow -40^{\circ}\text{C}$, 40 min; b) IBX (2.0 equiv), DMSO, 23°C , 1 h, 45 % over two steps; c) 1.0 M HClO₄ aq./THF (1:1), 50°C , 2 h, 80 %, **4**:**5** ca. 1:3 dr.