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A Unified Strategy for the Asymmetric Total Syntheses of Diversonol and Lachnone C

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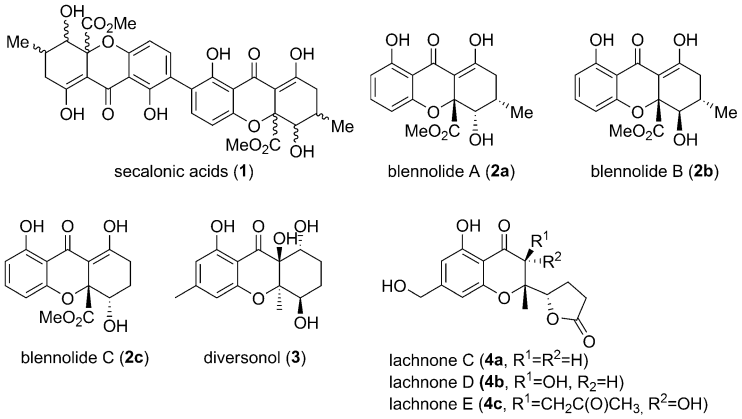
Abstract: A unified synthetic strategy for the asymmetric syntheses of the natural products diversonol and lachnone C was developed by using the domino vinylogous aldol–oxa-Michael reaction as the enantioselective key step. Further transformations include dihydroxylation, lactol-opening by a Wittig-reaction, and lactonization. The obtained chromone lactones, a class of mycotoxins, can further be converted to tetrahydroxanthones by a Dieckmann condensation. This general method allows for the first time the enantioselective access to these classes of natural products and should be applicable to other members of the tetrahydroxanthone and chromone lactone families.

Keywords: asymmetric synthesis · diversonol · domino reactions · lachnone · natural products · tetrahydroxanthones

Introduction

Tetryhydroxanthones are a fast growing class of mycotoxins with interesting biological activities. The secalonic acids (compounds of type **1**) are symmetric or unsymmetric dimers of blennolides A–C (**2a**–**2c**) and show cytostatic, antibacterial, and anti-HIV properties.[1] Diversonol (**3**) is a secondary metabolite first isolated by Turner in 1978 from *P. diversum*.[2] Lachnones C–E (**4a**–**4c**) belong to a class of chromone lactones isolated from the filamentous fungus *Lachnum* sp. BCC 2424.[3]



Different strategies for the racemic synthesis of blennolides and diversonol have been published to date. Our group used the domino oxa-Michael–aldol reaction[4] between a substituted salicylaldehyde and 4-hydroxycyclohexenone as key step for the first syntheses of diversonol (**3**)[5] and blennolide C (**2c**).[6] The same compounds were synthesized by Nicolaou et al. by connection of the outer rings followed by a domino deallylation–oxa-Michael reaction sequence.[7] Recently, the Porco group published a very elegant and short approach to blennolides B and C (**2b** and **2c**) employing a vinylogous addition of siloxyfurans to benzylpyryliums followed by a Dieckmann cyclization.[8]

The only enantioselective approaches to this class of compounds were undertaken by Tietze[9] and by our group[10] and led to the synthesis of dehydroxydiversonol. However, the introduction of the 4-hydroxy group was up to now not possible.

Recently, Pescitelli and Krohn proposed the absolute configuration of **3** on the means of TDDFT ECD calculations.[11]

Our goal is to establish a general method for the asymmetric synthesis of this class of compounds. We assumed that the vinylogous aldol–oxa-Michael domino reaction, which was developed in our group[12] some years ago and has been used later for the syntheses of dehydroxydiversonol,[10] α-tocopherol,[13] confluentin, and daurichromenic

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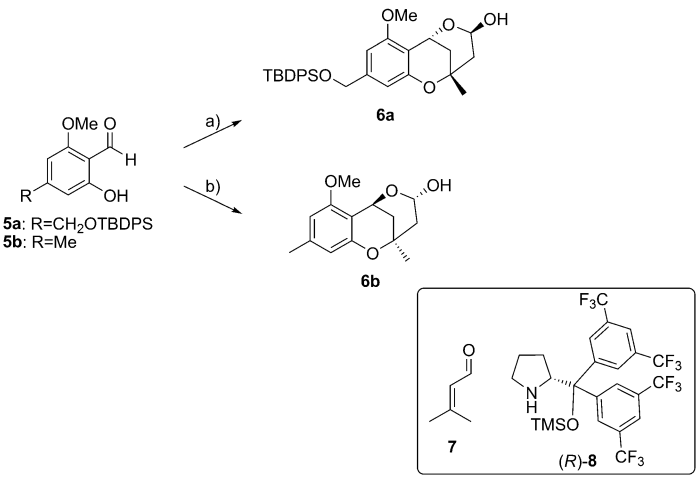
acid,[14] is particularly suitable for the construction of both the lachnone and the tetrahydroxanthone structures.

Herein, we report the first enantioselective syntheses of *epi*-lachnone C (*epi*-**4a**), lachnone C (**4a**) and diversonol (**3**) as well as the determination of their absolute configurations.

Results and Discussion

The asymmetric domino reactions between salicylaldehydes **5** and prenal (**7**) were performed with Jørgensen's catalysts[15] (*R*)-**8** and (*S*)-**8** and gave, depending of the catalyst used, tricyclic lactols **6a** and **6b** in 99% enantiomeric excess (*ee*) and 83% *ee*, respectively (Scheme 1). The absolute configuration of **6a** was determined by analysis of the crystal structure (Figure 1).



Scheme 1. Reagents and conditions: a) (*R*)-**8** (0.3 equiv), benzoic acid (0.3 equiv), toluene, then **7** (syringe pump), RT, 72 h, 63% (99% *ee*); b) (*S*)-**8** (0.3 equiv), benzoic acid (0.3 equiv), toluene, then **7** (syringe pump), RT, 72 h, 67% (83% *ee*).

To introduce the required hydroxy group, we first used a model compound and envisaged the direct α-hydroxylation of lactone **9**, which could be easily obtained by oxidation of **6c**[10] using Davis' oxaziridine.[16] However, no product could be isolated, probably due to the instability of the mentioned lactone with strong bases. We could successfully circumvent this problem by an elimination–dihydroxylation sequence, which gave a separable mixture of diols **12c** and **13c** in 58% overall yield (Scheme 2).

This strategy was then also applied for lactols **6a** and **6b**. Elimination with methanesulfonyl chloride (MsCl) gave the enolethers **11a**/**11b** in excellent yields (90/92%). Dihydroxylation with *N*-methylmorpholine-*N*-oxide (NMO)/OsO_4 gave ≈4.5:1 mixtures of diols **12a**/**13a** and **12b**/**13b**, which could easily be separated by column chromatography (Scheme 3). The absolute configuration of diol **13b** could be proven by X-ray structure analysis and is very likely *S*,*S*,*S*,*S* (Hooft's *y*-parameter = 0.08(85))[17] (Figure 1)).

For the synthesis of *epi*-lachnone C (*epi*-**6**), diol **12a** was opened using a Wittig reaction. Interestingly, the outcome of the reaction was strongly dependent on temperature and the phosphonate used (Table 1). When performed in hot toluene, the reaction of diol **12a** with the stabilized ylide **A**

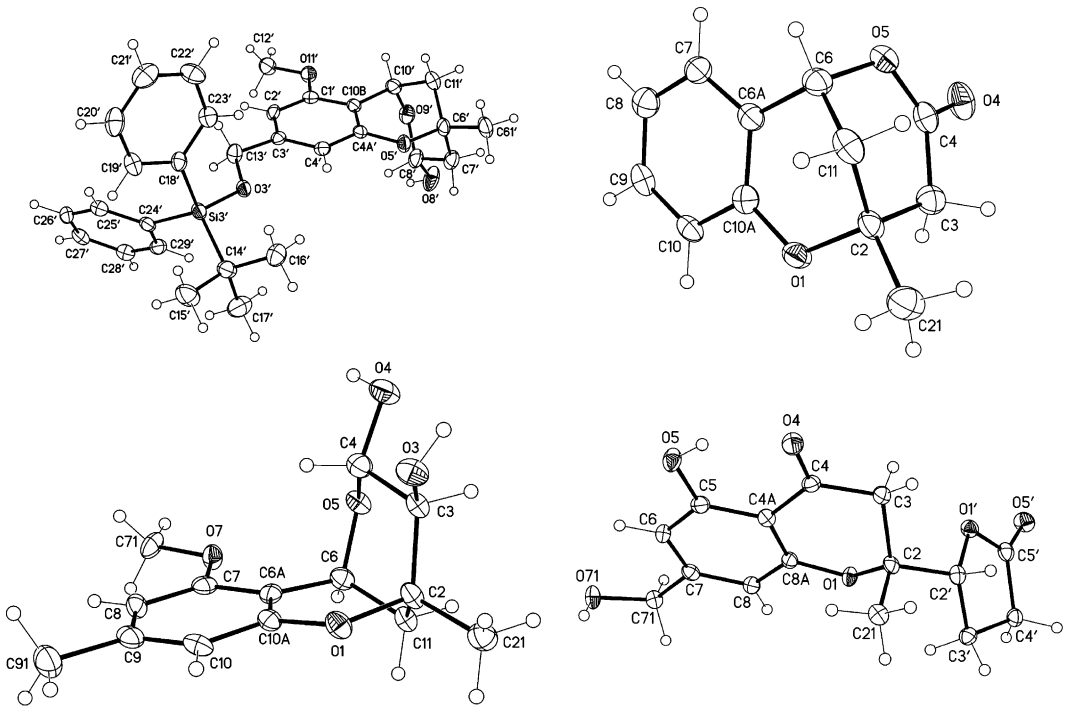
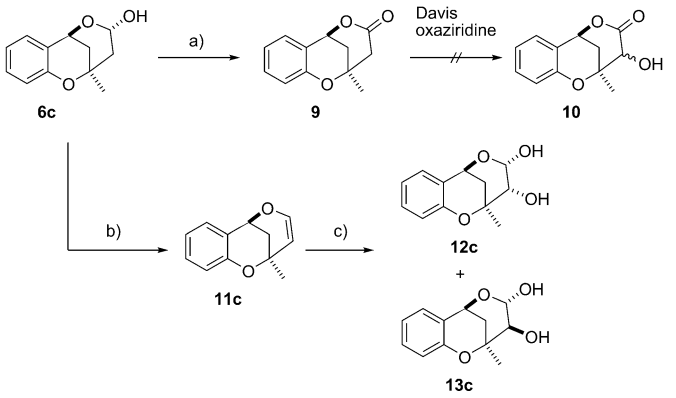
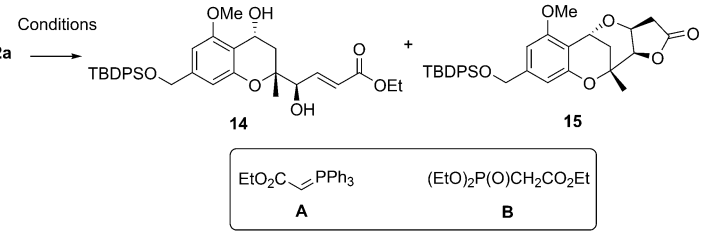


Figure 1. Visualizations of the X-ray structures of lactol **6a** (top left, one of the two crystallographic independent molecules), lactone **9** (top right), diol **13b** (bottom left, one of the two crystallographic independent molecules), and *epi*-lachnone *epi*-**4a** (bottom, right); displacement parameters are drawn at 50% probability level.[18]



Scheme 2. Reagents and conditions: a) PCC, CH_2Cl_2, 6 h, RT, 80%; b) MsCl (2.5 equiv), NEt_3 (8.0 equiv), THF, 0°C to RT, 3 h, 86%; c) NMO (4.0 equiv), OsO_4 (0.1 equiv), acetone/H_2O 9:1, RT, 4 d, 67% (4:1 ratio of **12c** and **13c**).

Table 1. Conditions and product yields for the reaction of **12a**.



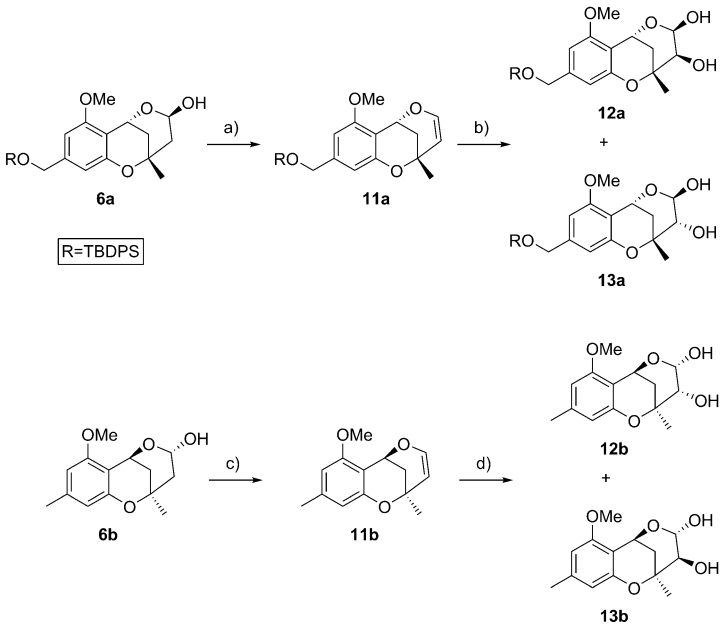
Entry	Reagent/Solvent	T [°C]	Yield **14** [%][a]	Yield **15** [%][a]
a	**A**/toluene	100	32	43
b	**B**/THF	−78 to 0	–	68
c	**A**/THF	60	85	–

gave a mixture of the desired alkene **14** and tetracyclic compound (**15**, see Table 1). The latter was the only product formed when phosphonate **B** was used. Eventually, alkene **14** could selectively be obtained as a single *E* isomer by lowering the temperature to 60°C (Table 1).

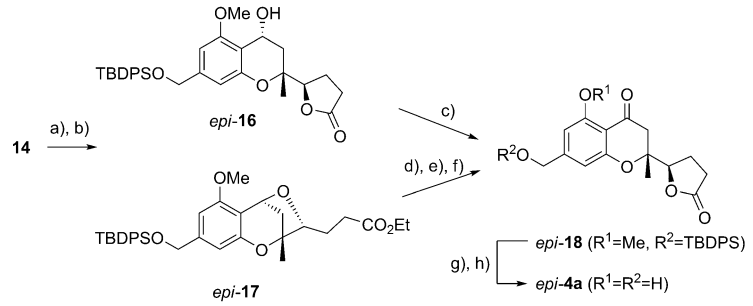
Hydrogenation of **14** (in 90% yield) followed by lactonization with TsOH gave the desired lactone *epi*-**16** in poor yield (39%) due to formation of ether *epi*-**17** (in 42% yield). However, both products could be converted to ketone *epi*-**18**. Lactone *epi*-**16** was oxidized to *epi*-**18** (98%) with pyridinium chlorochromate (PCC), whereas ether *epi*-**17** could be converted to *epi*-**18** (90%) in a three step procedure using *p*-toluenesulfonic acid (TsOH) in refluxing benzene, followed by hydrogenation with $Pd/BaSO_4$ (95%) and benzylic oxidation with $Mn(OAc)_3$/*t*BuOOH (83%). Final deprotection of the phenolic hydroxyl group with MgI_2-$(Et_2O)_2$ (98%) and the benzylic *tert*-butyldiphenylsilyl (TBDPS)-ether with tetrabutylammonium fluoride (TBAF) gave (−)-*epi*-lachnone C (*epi*-**4a**) in 57% yield (Scheme 4). A representation of the X-ray structure of *epi*-**4a** is shown in Figure 1.

The same reaction sequence was performed for the synthesis of lachnone C (**4a**), starting from diol **13a**. Wittig reaction (78%), hydrogenation (97%) and treatment with TsOH gave a mixture of lactone **16** (18%) and ether **17** (64%). Both were converted to **18** by either PCC oxidation of **16** (90%) or by the previously described three step procedure starting from **17** (41% over three steps). Deprotection of the methyl ether (99%) and the TBDPS group (39%) gave **4a** (Scheme 5). Although the α_D value of the synthesized compound is higher than in the literature, a positive value indicates that it has the same absolute configuration as the natural product.

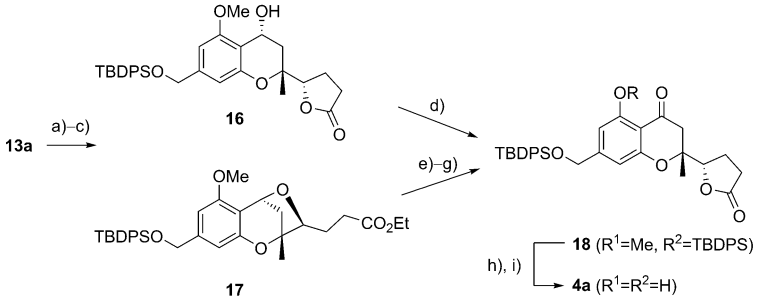
We then turned our focus on the synthesis of diversonol (**3**). We presumed that chromone lactone **19** should be a precursor for Dieckmann condensation to tetrahydroxanthone **20** (Scheme 6). This was recently described by Porco et al. as the "retrobiomimetic" synthesis,[8] although chromone lactones are probably formed by a hydrolysis/lactonization sequence of tetrahydroxanthones.[19,20]



Scheme 3. Reagents and conditions: a) MsCl (2.5 equiv), NEt_3 (8.0 equiv), THF, 0°C to RT, 3 h, 90%; b) NMO (4.0 equiv), OsO_4 (0.1 equiv), acetone/H_2O 9:1, RT, 4 d, 86% (4.4:1 ratio of **12a** and **13a**); c) MsCl (2.5 equiv), NEt_3 (8.0 equiv), THF, 0°C to RT, 3 h, 92%; d) NMO (4.0 equiv), OsO_4 (0.1 equiv), acetone/H_2O 9:1, RT, 4 d, 80% (4.7:1 ratio of **12b** and **13b**).



Scheme 4. Reagents and conditions: a) Pd (5% wt)/$BaSO_4$ (0.05 equiv), H_2 (1 bar), EtOAc, RT, 1 h, 90%; b) *p*-TsOH (0.1 equiv), THF, RT, 24 h, 81% (1:1.1 ratio of *epi*-**16** and *epi*-**17**); c) PCC (1.3 equiv), CH_2Cl_2, 3.5 h, 98%; d) *p*-TsOH (0.05 equiv), benzene, reflux, 16 h, 90%; e) Pd (5% wt)/$BaSO_4$ (0.05 equiv), H_2 (1 bar), EtOAc, RT, 1 h, 95%; f) $Mn(OAc)_3$ (0.2 equiv), *t*BuOOH (10 equiv), 3 Å MS, EtOAc, RT, 4 d, 83%; g) Mg (2.6 equiv), I_2 (2.4 equiv), benzene/Et_2O 2:1, 2.5 h; then *epi*-**18**, reflux, 16 h, 98%; h) TBAF (1.3 equiv), THF, RT, 1 h, 57%.



Scheme 5. Reagents and conditions: a) $Ph_3P{=}CHCO_2Et$, THF, reflux, 4 h, 78%; b) Pd (5% wt)/$BaSO_4$ (0.05 equiv), H_2 (1 bar), EtOAc, RT, 2.5 h, 97%; c) *p*-TsOH (0.1 equiv), THF, RT, 3 d, 18% **16** and 64% **17**; d) PCC (1.3 equiv), CH_2Cl_2, 5 h, 90%; e) *p*-TsOH (0.05 equiv), benzene, reflux, 16 h, 91%; f) Pd (5% wt)/$BaSO_4$ (0.05 equiv), H_2 (1 bar), EtOAc, RT, 12 h, 87%; g) $Mn(OAc)_3$ (0.2 equiv), *t*BuOOH (10 equiv), 3 Å MS, EtOAc, RT, 4 d, 52%; h) Mg (2.6 equiv), I_2 (2.4 equiv), benzene/Et_2O 2:1, 2.5 h; then *epi*-**18**, reflux, 16 h, 99%; i) TBAF (1.3 equiv), THF, RT, 1 h, 39%.

As the precursor for **19** is the minor diol **13b**, we first turned our attention to the synthesis of **19** from major diol **12b**, which implies an inversion of the hydroxyl group. Opening of lactol **12b** by Wittig reaction gave unsaturated ester **21** in 83% yield. Selective *tert*-butyldimethylsilyl (TBS) protection of the benzylic hydroxyl group (85%) and hydrogenation (54%) gave ester **23** through compound **22**. Mesylation of the free alcohol led to concomitant elimination of the TBS ether (61%). Hydrolysis of the ester **24** gave a mixture of acid **25** (72%) and lactone **26** (4%), whereas the acid could be converted to **26** by Cs_2CO_3 promoted lactonization (79%). Hydrogenation of the double bond (79%) and benzylic oxidation with $Mn(OAc)_3$/*t*BuOOH (66%) gave chromone lactone *ent*-**19** as the precursor for the Dieckmann cyclization (Scheme 7). *ent*-**19** was also obtained from the minor diol **13b** by using a similar reaction sequence as previously described for the syntheses of lachnone C (**4a**) and *epi*-lachnone C (*epi*-**4a**; Scheme 8).

The Dieckmann condensation of chromone lactone *ent*-**19** using NaOMe as a base[8] gave tetrahydroxanthone *ent*-**20** in 41% yield (Scheme 9). Deprotection of the methyl ether with BBr_3 gave triol **32** (81%), which was converted to diversonol in two further steps according to Nicolaou et al.[7] Comparison of the α_D with published data[11] showed that the enantiomer of natural (+)-diversonol was synthesized. No traces of the other enantiomer were detected by HPLC, which indicated enantiomer enrichment during the synthesis. The result was confirmed by comparison of the circular dichroism (CD) spectra of synthesized diversonol (Figure 2) and an authentic sample kindly provided by Dr. G. Pescitelli and Prof. K. Krohn. Herewith, we proved the absolute configuration of natural diversonol to be 5*S*,5a*S*,8*S*,8a*R*.

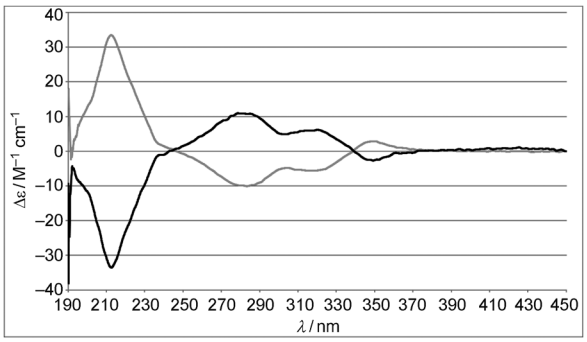
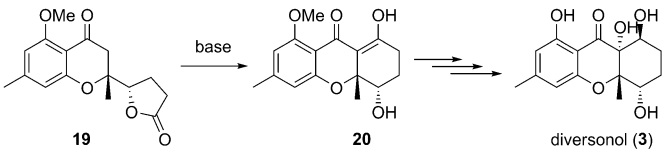
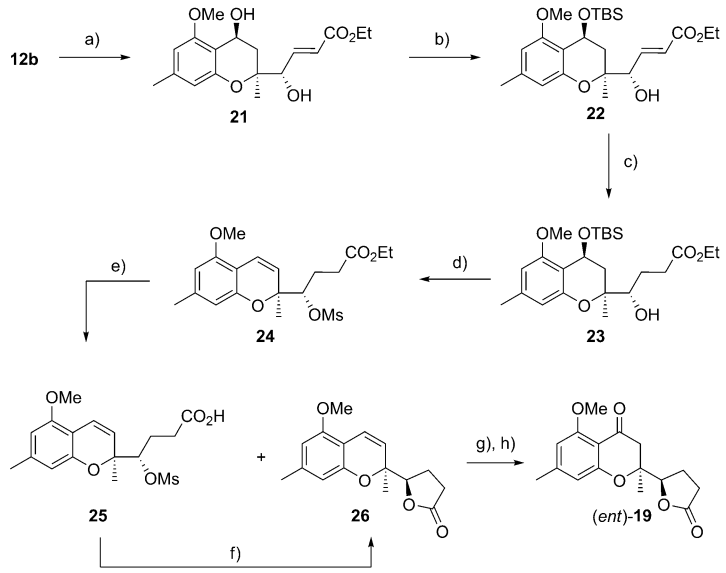


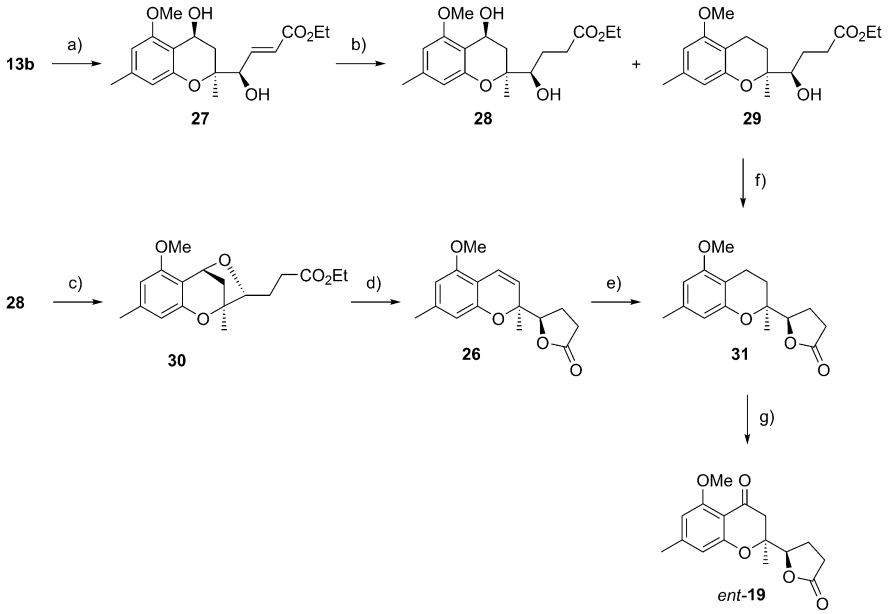
Figure 2. Circular dichroism (CD) spectrum of natural (+)-diversonol (grey line) and unnatural (−)-diversonol (black line) in methanol.



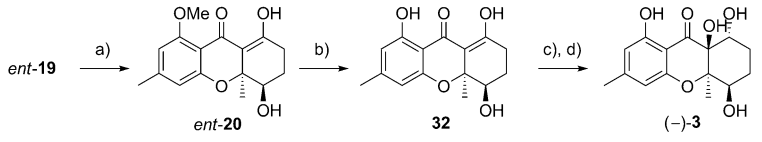
Scheme 6. Planned retrobiomimetic conversion of lactone **19** to tetrahydroxanthenone **20** as a precursor of diversonol (**3**).



Scheme 7. Reagents and conditions: a) $Ph_3P{=}CHCO_2Et$ (1.5 equiv), THF, 60 °C (sealed tube), 12 h, 83 %; b) TBSOTf (1.02 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0 °C, 1.5 h, 85 %; c) Pd (5 % wt)/$BaSO_4$ (0.05 equiv), H_2 (1 bar), EtOAc, RT, 12 h, 54 %; d) MsCl (1.5 equiv), NEt_3 (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 °C to RT, 3 h, 61 %; e) LiOH (1.5 equiv), dioxane/H_2O 4:1, RT, 18 h, 72 % **25**, 4 % **26**; f) Cs_2CO_3 (6.0 equiv), 18-crown-6 (2.5 equiv), toluene, 90 °C, 79 %; g) Pd (5 % wt)/$BaSO_4$ (0.05 equiv), H_2 (1 bar), EtOAc, RT, 1 h, 79 %; h) $Mn(OAc)_3$ (0.2 equiv), *t*BuOOH (10 equiv), 3 Å MS, EtOAc, RT, 4 d, 66 %.



Scheme 8. Reagents and conditions: a) $Ph_3P{=}CCO_2Et$ (1.5 equiv), THF, 60 °C (sealed tube), 15 h, 98 %; b) Pd (5 % wt)/$BaSO_4$ (0.05 equiv), H_2 (1 bar), EtOAc, RT, 1 h, 74 % **28**, 14 % **29**; c) *p*-TsOH (0.1 equiv), THF, RT, 12 h, 94 %; d) *p*-TsOH (0.05 equiv), benzene, reflux, 20 h, 88 %; e) Pd (5 % wt)/$BaSO_4$ (0.05 equiv), H_2 (1 bar), EtOAc, RT, 1 h, 79 %; f) CSA (0.1 equiv), THF, reflux, 12 h, 93 %; g) $Mn(OAc)_3$ (0.2 equiv), *t*BuOOH (10 equiv), 3 Å MS, EtOAc, RT, 4 d, 66 %.



Scheme 9. Reagents and conditions: a) NaOMe (2.0 equiv), THF, 0 °C, 1 h, 41 %; b) BBr_3 (10 equiv), CH_2Cl_2, RT, 16 h, 81 %; c) MMPP (0.75 equiv), EtOH, RT, 30 min; d) $NaBH_4$ (1.0 equiv), MeOH/CH_2Cl_2 1:1, −78 °C, 5 min, 52 % over two steps. MMPP = magnesium monoperoxyphthalate hexahydrate.

Conclusion

We have established the first asymmetric syntheses of diversonol (**3**), lachnone C (**4a**) and *epi*-lachnone C (*epi*-**4a**). The strategy should be applicable for the syntheses of many members of the tetrahydroxanthone and chromone lactone families. As both (*R*)- and (*S*)-Jørgensen catalysts are commercially available, both enantiomers of each target molecule are accessible.

Experimental Section

For full experimental details see the Supporting Information.

Acknowledgements

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[18] CCDC-825881 (**6a**), 825882 (**9**), 825883 (**13b**), and 825884 (*epi*-**4a**) contain the supplementary crystallographic data for this paper (excluding structure factors). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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