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Enantioselective Total Synthesis of (−)-Blennolide A

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Abstract: Blennolide A can be synthesized through an enantioselective domino-Wacker/carbonylation/methoxylation reaction of **7a** with 96% *ee* and an enantioselective Wacker oxidation of **7b** with 89% *ee*. Further transformations led to the α,β-unsaturated ester (*E*)-**17**, which was subjected to a highly selective Michael addition, introducing a methyl group to give **18a**. After a threefold oxidation and an intramolecular acylation, the tetrahydroxanthenone **4** was obtained, which could be transformed into (−)-blennolide A (*ent*-**1**) in a few steps.

Keywords: domino-reactions · Michael reaction · natural product · palladium · Wacker oxidation · xanthenone

Introduction

Blennolide A (**1**) is a fungal metabolite that was isolated in 2008 from the endophytic fungus *Blennoria* sp. of the succulent *Carpobrotus edulis*, which grows on the island La Gomera of the Canaries (see Figure 1).[1] It contains a highly functionalized tetrahydroxanthenone skeleton and possesses some interesting biological activities that include antibacterial, antifungal, and antialgal properties. Blennolide A's absolute configuration was determined by Krohn et al.[1] using CD spectroscopy combined with time-dependent density functional theory (TDDFT) calculations. It is the seco-unit of secalonic acid B (**2**), which is a 2,2′-connection of two blennolide A molecules. The secalonic acids were isolated from different fungi, such as *Claviceps purpurea*,[2] and their structure was determined by Franck et al.[3] Other dimeric compounds, such as the dicerandrols,[4] that contain a hydroxymethyl or acetoxymethyl group at C-4a (numbering as in **1**) as well as the phomoxanthones[5] are connected through a 2,2′- and a 4,4′-biaryl bond, respectively. We have recently published syntheses of enantiopure 4-dehydroxydiversonol[6] and (−)-diversonol[7] (**3**) using an enantioselective domino-Wacker/carbonylation/methoxylation reaction. The domino process[8] has also been used for the synthesis of chromans, dioxins, and oxazins.[9]

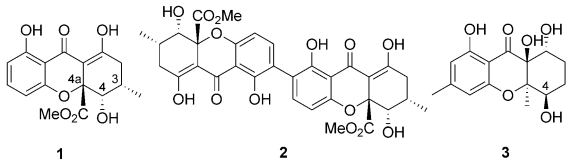
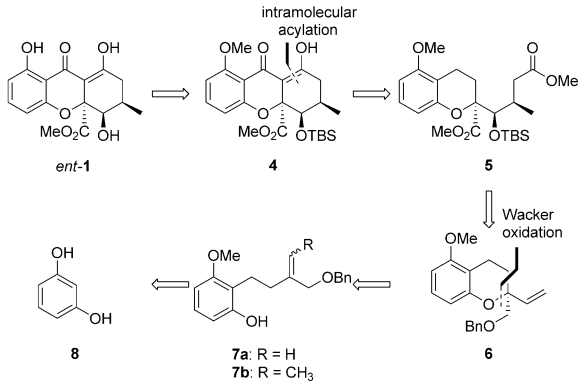


Figure 1. Blennolide A (**1**), secalonic acid B (**2**), and (−)-diversonol (**3**).

Here, we describe the first total synthesis of enantiopure (−)-blennolide A (*ent*-**1**). As key transformation in the synthesis, an enantioselective domino-Wacker/carbonylation/methoxylation reaction in the presence of a chiral BOXAX ligand can be employed. Moreover, we have also used an enantioselective Wacker oxidation for the preparation of an intermediate in the synthesis of *ent*-**1**.

Results and Discussion

The retrosynthetic analysis of *ent*-**1** leads to the chroman **5**, which can be transformed into *ent*-**1** via **4** through a benzylic oxidation and an intramolecular acylation (Scheme 1). Chroman **5** should be accessible from **6** by dihydroxylation, selective oxidation of the primary hydroxyl group to give an aldehyde moiety, and a Wittig–Horner reaction followed by a Michael addition. The chroman **6**, with one stereogenic



Scheme 1. Retrosynthetic analysis of (−)-blennolide A (*ent*-**1**).

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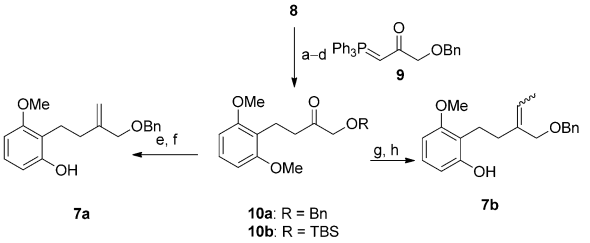
center, could be formed by an enantioselective domino-Wacker/carbonylation/methoxylation reaction of **7a**, which can be synthesized from resorcin (**8**). On the other hand, chroman **6** would also be accessible from the alkene **7b** by using an enantioselective Wacker oxidation.

According to the retrosynthetic analysis, resorcin (**8**) was transformed into 2,6-dimethoxybenzaldehyde in 88% yield over two steps (Scheme 2).[10,11] A Wittig reaction with the



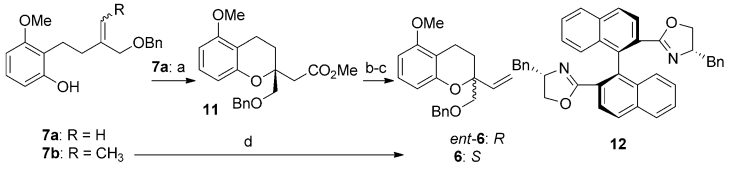
Scheme 2. Synthesis of **7a** and **7b**: a) Me_2SO_4, K_2CO_3, acetone, reflux, 25 h, 96%; b) *n*BuLi, TMEDA, Et_2O, 0°C→45°C, 3 h, DMF, RT, 3 h, 92%; c) **9**, toluene, 120°C, 26.5 h, 96%; d) 1. 5 mol% PtO_2, H_2 (1 atm), EtOH, RT, 2.25 h; 2. IBX, MeCN, 80°C, 2 h, 95% (2 steps); e) Ph_3PCH_3Br, *n*BuLi, THF, 0°C→RT, 4 h, 91%; f) NaSEt, DMF, 120°C, 24 h, 96%; g) $Ph_3PCH_2CH_3Br$, *n*BuLi, THF, 0°C→RT, 2.5 h, 91% (*E*/*Z*=1:1.7); h) NaSEt, DMF, 120°C, 24 h, 95%.

phosphorane **9**[12] and a hydrogenation of the formed olefinic double bond were used to give ketone **10a** using platinum(IV) dioxide in ethanol and hydrogen. The corresponding alcohol was obtained as a side product by over-reduction and can easily be reoxidized using 2-iodoxybenzoic acid (IBX) to yield the ketone **10a** in an overall yield of 95%. For the synthesis of **7a**, a precursor of the domino-Wacker/Carbonylation/methoxylation process, a Wittig reaction of **10a** with methyltriphenylphosphonium bromide in the presence of *n*BuLi was performed to give the corresponding methylene compound, which was followed by a selective cleavage of one of the methyl ether moieties using sodium ethanethiolate in 87% yield over two steps. The high selectivity of the monodeprotection with a thiolate can be explained by the formation of a negatively charged phenolate as an intermediate, which is not suitable for a second nucleophilic substitution due to an electrostatic interaction. On the other hand, cleavage of the methyl ether moiety in the corresponding OTBS-protected compound **10b**, again using ethanethiolate, was not suitable, since the OTBS group is not stable under these reaction conditions, giving rise to a complex product mixture. In a similar sequence as described for **7a**, compound **7b** was also prepared by using a Wittig reaction of **10a** with ethyltriphenylphosphonium bromide in the presence of *n*BuLi to afford a 1:1.7 *E*/*Z* mixture of the corresponding alkylidene compound in 91% yield; by using sodium ethanethiolate the desired (*E*/*Z*)-**7b** was obtained in 95% yield by a selective cleavage of one of the methyl ether moieties.

Reaction of **7a** in the presence of the (*R*,*R*)-Bn-BOXAX ligand[13] *ent*-**12** and catalytic amounts of palladium(II) trifluoracetate [$Pd(OTFA)_2$] under a carbon monoxide atmosphere in methanol gave **11** in 74% yield and 96% *ee* (Scheme 3). Reduction of ester **11** with $LiAlH_4$ yielded the corresponding alcohol, which was then transformed into *ent*-**6** through a selenoether formation using *o*-NO_2-C_6H_4SeCN followed by oxidation and elimination.[14] The vinyl chroman **6** can also be prepared by an enantioselective Wacker oxidation of **7b** in the presence of the (*S*,*S*)-Bn-BOXAX ligand[13] **12** and catalytic amounts of palladium(II) trifluoracetate [$Pd(OTFA)_2$] in methanol, however, with lower enantioselectivity.

Using the *E*/*Z* mixture of **7b** with a 1:1.7 ratio, as formed in the Wittig reaction of **10a**, the vinyl chroman **6** was obtained in 82% yield and 85% *ee*. To investigate the influence of the configuration of the double bond in **7b** on the enantioselectivity of the Wacker oxidation, we separated the two diastereomers by HPLC. The pure *Z* compound gave **6** with an *ee* value of 89%, whereas the *E* compound furnished **6** with 72% *ee*. It should be stressed that the separation of the *E*/*Z* mixture of **7b** by HPLC is difficult and not suitable for larger amounts. In the two Wacker processes, *p*-benzoquinone was employed to oxidize the intermediately formed Pd^0 to give Pd^{II}, which is needed for the Wacker oxidation. The use of oxygen and a copper salt was not suitable, since the starting material is not stable under these conditions.

For the introduction of the necessary hydroxyl group at C-4 (numbering as in **1**), we used a Sharpless dihydroxylation[15] of the vinyl chroman **6** using AD-mix-α and methanesulfonamide as additives (Scheme 4). Under these conditions, the diols *syn*/*anti*-**13** were obtained as a 1:2.4 mixture of inseparable diastereomers in 95% yield. Neither a selective oxidation of the primary alcohol in the presence of the secondary alcohol moiety nor a selective protection of the secondary alcohol function were successful; we therefore performed a bis-silylation of the diol **13** with TBSOTf and 2,6-lutidine to give **14** in quantitative yield. This was followed by a selective removal of the primary TBS group with HF/pyridine, which afforded the alcohol **15** in 90% and the diol **13** in 5% yield. The primary alcohol moiety in **15** was



Scheme 3. Synthesis of **6** and *ent*-**6**: a) 5 mol% [$Pd(OTFA)_2$], 20 mol% (*R*,*R*)-Bn-BOXAX (*ent*-**12**), *p*-benzoquinone, CO (1 atm), MeOH, RT, 22 h, 74%, 96% *ee*; b) $LiAlH_4$, Et_2O, 0°C→RT, 1.25 h, 98%; c) 1. nBu_3P, *o*-NO_2-C_6H_4SeCN, THF, 0°C, 1.5 h; 2. *m*CPBA, $Na_2HPO_4{\cdot}2H_2O$, CH_2Cl_2, −40°C, 1 h, iPr_2NH, −40°C→RT, 15.5 h, 95% (2 steps); d) 10 mol% [$Pd(OTFA)_2$], 10 mol% (*S*,*S*)-Bn-BOXAX (**12**), *p*-benzoquinone, MeOH, 60°C, 24 h, for (*E*/*Z*)-**7b** (*E*/*Z*=1:1.7): 82%, 85% *ee*; for (*E*)-**7b**: 81%, 72% *ee*; for (*Z*)-**7b**: 79%, 89% *ee*.

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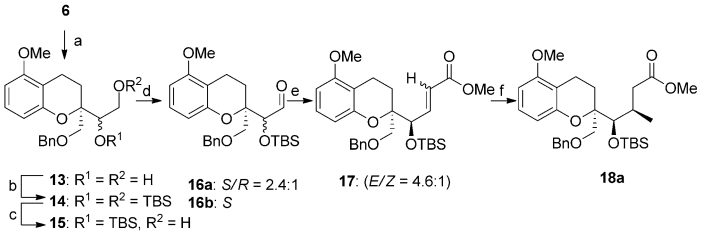
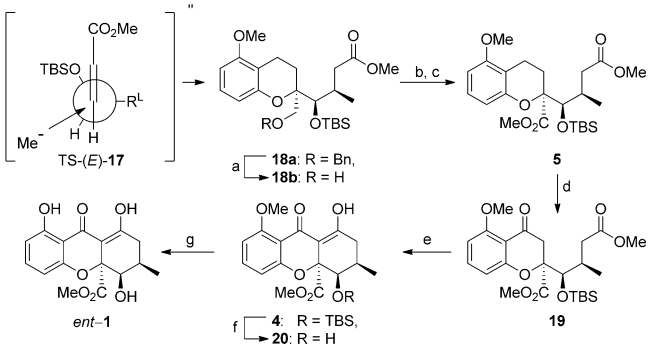


Scheme 4. Synthesis of **18a**: a) AD-mix-α, $CH_3SO_2NH_2$, *t*BuOH/H_2O (1:1), RT, 4 d, 95%, (*syn*/*anti* = 1:2.4); b) 2,6-lutidine, TBSOTf, CH_2Cl_2, 0°C, 2.5 h, quant; c) HF•pyridine, THF/pyridine, 0°C, 1 h, then RT, 26 h, 90%, (9% **13**); d) DMP, CH_2Cl_2, RT, 2 h, 94%; e) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0°C→RT, 1.5 h, *E* compound 82%, *Z* compound 18%; f) CuBr•Me_2S, MeLi, TMSCl, THF, −35°C, 1 h, 91%.



Scheme 5. Synthesis of *ent*-**1**: a) 15 mol% Pd/C, H_2 (1 atm), HOAc, MeOH, RT, 26 h, 99%; b) DMP, CH_2Cl_2, RT, 2 h, 95%; c) KOH, I_2, MeOH, RT, 4 h, quant; d) $KMnO_4$, 15% aqueous $MgSO_4$, acetone, 60°C, ultrasonic, 11.5 h, 71%, (88% brsm); e) $TiCl_4$, NEt_3, CH_2Cl_2, 0°C, 1 h, 78%; f) NEt_3•3HF, 1,4-dioxane, 50°C, 6 d, 77% (96% brsm); g) BBr_3, CH_2Cl_2, RT, 4 h, 86%; R^L = Chromanyl.

oxidized with Dess–Martin periodinane (DMP) to yield the corresponding diastereomeric aldehydes **16a** in 94% yield. At this stage, the diastereomers formed in the Sharpless dihydroxylation could be easily separated by standard column chromatography. For further transformations, we used **16b** with the *S* configuration at C-4 (numbering as in **1**), which showed an *anti*-orientation of the substituents at C-4a and C-4, as found in blennolide A (**1**). The next step followed a Wittig–Horner reaction by treating the *anti*-aldehyde **16b** with $(MeO)_2P(O)CH_2CO_2Me$ and sodium hydride to provide a *E*/*Z* mixture of the α,β-unsaturated ester **17** (*E*/*Z* = 4.6:1) in quantitative yield, which could easily be separated by column chromatography. For the introduction of a methyl group in (*E*)-**17** at C-3 (numbering as in **1**), we employed a Michael addition using CuBr•Me_2S, TMSCl, and methyl lithium. In this highly diastereoselective reaction, the only obtained product was **18a**, with the *R* configuration at C-3 in 91% yield. The very active copper(I) bromide-dimethylsulfide complex[16] allowed a complete transformation at −35°C within one hour. Using CuI, MeLi•LiBr, and TMSCl, either in THF or CH_2Cl_2,[17] only an incomplete reaction was observed. Moreover, the obtained mixture of starting material and product was not separable due to similar polarities. Interestingly, (*Z*)-**17** did not react under the described conditions. The high stereoselectivity in the introduction of the methyl group in (*E*)-**17** can be explained by assuming a Felkin–Anh-type transition state[17a,18] TS-(*E*)-**17**, without any chelating effects (Scheme 5).

For the transformation of the benzyloxymethyl group at C-4a in **18a** (numbering as in **1**) into the required CO_2Me functionality, the benzyl ether was cleaved under hydrogenolytic conditions with Pd/C in an acetic acid/methanol mixture to give **18b** in 99% yield (Scheme 5). At this stage, it was possible to improve the enantiopurity of the products obtained in the enantioselective domino-Wacker/carbonylation/methoxylation reaction and the enantioselective Wacker oxidation from 96% *ee* and 89% *ee*, respectively, to >99% *ee*, as found for **18b** after using HPLC on a chiral support (Daicel IA column). The following oxidation of the formed primary alcohol moiety in **18b** with DMP yielded the corresponding aldehyde in 95% yield, which was treated with potassium hydroxide and iodine in methanol to form the ester **5** in quantitative yield. Oxidation of **5** at the benzylic position upon treatment with potassium permanganate in an ultrasonic bath gave the chromanone **19** in 71% yield (86% brsm). For the intramolecular acylation, **19** was treated with $TiCl_4$ and NEt_3 in dichloromethane at 0°C to yield the tetrahydroxanthenone **4** in 78%, along with some material (about 5%) in which the methyl ether moiety had been cleaved. Desilylation of **4** with NEt_3•3 HF provided **20** in 77% yield, which was treated with BBr_3 to give the desired, almost enantiopure (−)-blennolide A (*ent*-**1**) by cleavage of the methyl ether moiety in 86% yield.

All spectroscopic data including ^1H and ^{13}C NMR spectroscopy and mass spectrometry are in complete agreement with the published information of the isolated (+)-blennolide A. We have prepared *ent*-**1**, which has a negative optical rotation. For *ent*-**1** an $[\alpha]_D^{23}$ value of −198.7 ($CHCl_3$) was measured, whereas the natural compound **1** shows an optical rotation of $[\alpha]_D^{20} = +181.8$ ($CHCl_3$).[19]

Conclusion

We have developed the first enantioselective total synthesis of (−)-blennolide A (*ent*-**1**). Key steps are an enantioselective Pd-catalyzed domino-Wacker/carbonylation/methoxylation reaction, an enantioselective Wacker oxidation, and a highly selective Michael reaction.

Experimental Section

Synthesis of 4, 6, 11, 13, (*E*)-17, 18a, 19, and *ent*-1: The syntheses of all other new compounds including spectroscopic data can be found in the Supporting Information.

Methyl (*R*)-2-[2-(benzyloxymethyl)-5-methoxychroman-2-yl]acetate (11): A solution of $Pd(OTFA)_2$ (57.7 mg, 174 μmol, 5 mol%) and (*R*,*R*)-Bn-BOXAX (*ent*-**12**) (397 mg, 694 μmol, 20 mol%) in MeOH (3 mL) was stirred at RT for 15 min. After addition of a solution of phenol **7a** (1.04 g, 3.47 mmol, 1.00 equiv) in MeOH (7 mL) and *p*-benzoquinone

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(1.50 g, 13.9 mmol, 4.00 equiv), carbon monoxide was passed through the resulting mixture for 2 min before being stirred under a CO atmosphere (1 atm) at RT for a further 22 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 12:1) to give a crude product, which was dissolved in Et_2O (150 mL). After washing with an aq solution of NaOH (1 M, 3×30 mL) and brine (30 mL), the organic layer was dried over Na_2SO_4 and concentrated in vacuo. Chroman **11** was obtained as a yellow oil (912 mg, 2.56 mmol, 74 %, 96 % *ee*). Analytical HPLC (*Daicel* Chiralpak® IA, *n*-hexane/*i*PrOH = 99.5:0.5, flow rate: 0.8 mL min^{-1}, wavelength: 205 nm): t_R = 17.8 (−)-(*S*)-**11**, 2.2 %; 20.1 min, (+)-(*R*)-**11**, 97.8 %; *ee*: 96 %; a = 1.18; R_f = 0.47 (petroleum ether/EtOAc = 5:1); $[\alpha]_D^{25}$ = +6.1 (c = 0.49 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (t, J = 6.9 Hz, 2H, 3′-H_2), 2.64 (br t, J = 6.9 Hz, 2H, 4′-H_2), 2.72 (d, J = 14.4 Hz, 1H, 2-H_a), 2.84 (d, J = 14.4 Hz, 1H, 2-H_b), 3.62 (s, 3H, $COOCH_3$), 3.67 (br s, 2H, CH_2OBn), 3.80 (s, 3H, 5′-OCH_3), 4.54 (d, J = 12.0 Hz, 1H, OCH_aPh), 4.62 (d, J = 12.0 Hz, 1H, OCH_bPh), 6.41 (d, J = 8.4 Hz, 1H, 6′-H), 6.46 (d, J = 8.4 Hz, 1H, 8′-H), 7.05 (t, J = 8.4 Hz, 1H, 7′-H), 7.22–7.35 ppm (m, 5H, 5×Ph-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1 (C-4′), 26.2 (C-3′), 39.3 (C-2), 51.5 ($COOCH_3$), 55.4 (5′-OCH_3), 72.7 (CH_2OBn), 73.4 (OCH_2Ph), 76.3 (C-2′), 101.8 (C-6′), 110.8, 110.8 (C-8′, C-4a′), 127.0 (C-7′), 127.5, 127.5 (Ph-C_o, Ph-C_p), 128.2 (Ph-C_m), 138.1 (Ph-Ci), 153.5 (C-8a′), 157.6 (C-5′), 170.6 ppm ($COOCH_3$); IR (film): $\tilde{\nu}$ = 2949, 1737, 1592, 1469, 1439, 1347, 1267, 1249, 1200, 1096, 1018, 902, 772, 738, 699 cm^{-1}; UV (CH_3OH): λ_{max} (lg ε) = 204.0 (4.716), 271.5 (3.117), 279.0 nm (3.126); MS (ESI): m/z (%): 735.3 (40) $[2M+Na]^+$, 379.2 (100) $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{21}H_{24}O_5$ (356.41): 379.1521 $[M+Na]^+$; found: 379.1518.

(*S*)-2-(Benzyloxymethyl)-5-methoxy-2-vinylchroman (6): A solution of $Pd(OTFA)_2$ (121 mg, 365 μmol, 10 mol %) and (*S*,*S*)-Bn-BOXAX (**12**) (209 mg, 365 μmol, 10 mol %) in MeOH (3.6 mL) was stirred at RT for 30 min. After addition of a solution of phenol **7b** (*E*/*Z* = 1:1.7, 1.14 g, 3.65 mmol, 1.00 equiv) in MeOH (5.4 mL) and *p*-benzoquinone (1.58 g, 14.6 mmol, 4.00 equiv), the mixture was heated at 60 °C for 24 h and then cooled to RT. Filtration over a pad of silica gel (15×6 cm, washing with petroleum ether/EtOAc = 10:1, TLC monitoring), evaporation of the solvent in vacuo, and column chromatography on silica gel (petroleum ether/EtOAc = 30:1) provided vinylchroman **6** as a colorless oil (933 mg, 3.01 mmol, 82 %, 85 % *ee*). (*Z*)-**7b** and (*E*)-**7b** were also transformed into **6** using the same procedure: for (*Z*)-**7b** (79 %, 89 % *ee*); for (*E*)-**7b** (81 %, 72 % *ee*). Analytical HPLC (*Daicel* Chiralcel® OD, *n*-hexane/*i*PrOH = 99:1, flow rate: 0.8 mL min^{-1}, wavelength: 205 nm): t_R = 12.0 (−)-(*S*)-**6**, 92.4 %; 17.0 min (+)-(*R*)-**6**, 7.6 %; *ee*: 85 %; a = 1.83; R_f = 0.35 (petroleum ether/EtOAc = 20:1); $[\alpha]_D^{20}$ = −52.9 (c = 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87–2.08 (m, 2H, 3-H_2), 2.44 (ddd, J = 17.1, 10.8, 6.6 Hz, 1H, 4-H_a), 2.73 (ddd, J = 17.1, 4.8, 3.9 Hz, 1H, 4-H_b), 3.53 (d, J = 16.5 Hz, 1H, CH_aOBn), 3.57 (d, J = 16.5 Hz, 1H, CH_bOBn), 3.79 (s, 3H, 5-OCH_3), 4.59 (d, J = 12.3 Hz, 1H, OCH_aPh), 4.63 (d, J = 12.3 Hz, 1H, OCH_bPh), 5.17 (dd, J = 10.8, 1.5 Hz, 1H, 2′-H_a), 5.25 (dd, J = 17.4, 1.5 Hz, 1H, 2′-H_b), 5.85 (dd, J = 17.4, 10.8 Hz, 1H, 1′-H), 6.40 (d, J = 8.1 Hz, 1H, 6-H), 6.58 (d, J = 8.1 Hz, 1H, 8-H), 7.06 (t, J = 8.1 Hz, 1H, 7-H), 7.23–7.38 ppm (m, 5H, 5×Ph-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4 (C-4), 26.6 (C-3), 55.5 (5-OCH_3), 73.7 (OCH_2Ph), 75.6 (CH_2OBn), 78.8 (C-2), 101.6 (C-6), 109.8 (C-8), 110.8 (C-4a), 116.2 (C-2′), 126.9 (C-7), 127.5 (Ph-C_p), 127.6 (Ph-C_o), 128.3 (Ph-C_m), 137.8 (C-1′), 138.3 (Ph-Ci), 154.4 (C-8a), 157.5 ppm (C-5); IR (film): $\tilde{\nu}$ = 2934, 2856, 1592, 1468, 1409, 1345, 1315, 1267, 1250, 1193, 1167, 1096, 1028, 929, 773, 738, 698 cm^{-1}; UV (CH_3OH): λ_{max} (lg ε) = 204.0 (4.701), 271.5 (3.113), 279.0 nm (3.121); MS (ESI): m/z (%): 643.3 (53) $[2M+Na]^+$, 333.2 (100) $[M+Na]^+$, 311.2 (25) $[M+H]^+$; HRMS (ESI): m/z calcd for $C_{20}H_{22}O_3$ (310.39): 311.1642 $[M+H]^+$, 333.1461 $[M+Na]^+$; found: 311.1641, 333.1460.

2-(*R*/*S*)-[1-(*R*)-2-(Benzyloxymethyl)-5-methoxychroman-2-yl]ethane-1,2-diol (13): A suspension of AD-mix-α (57.6 g) in *t*BuOH/H_2O (1:1, 180 mL) was stirred at RT for 30 min before addition of a solution of vinylchroman **6** (6.40 g, 20.6 mmol, 1.00 equiv) in *n*-hexane (25 mL) and $CH_3SO_2NH_2$ (1.96 g, 20.6 mmol, 1.00 equiv) at RT. Stirring was continued at RT for 4 d, then the reaction was quenched by addition of saturated aq Na_2SO_3 solution (70 mL) at 0 °C with stirring for another 60 min. After addition of water (300 mL), the aqueous layer was extracted with EtOAc (3×230 mL), combined organic layers were dried over Na_2SO_4, and the solution was concentrated in vacuo. Column chromatography of the residue on silica gel (petroleum ether/EtOAc = 3:2→1:1) furnished a mixture of the diols *syn*/*anti*-**13** as a colorless oil (*syn*/*anti* = 1:2.4, 6.70 g, 19.5 mmol, 95 %). R_f = 0.37 (petroleum ether/EtOAc = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, *syn*/*anti* = 1:2.4): δ = 1.78–2.20 (m, 4H, 3′-$H_{2syn+anti}$), 2.38–2.80 (m, 6H, 4′-$H_{2syn+anti}$, 1-$OH_{syn+anti}$), 2.93–3.04 (m, 2H, 2-$OH_{syn+anti}$), 3.50–3.70 (m, 4H, $CH_2OBn_{syn+anti}$), 3.71–3.96 (m, 12H, 1-$H_{syn+anti}$, 2-$H_{2syn+anti}$, 5′-$OCH_{3syn+anti}$), 4.43–4.59 (m, 4H, $OCH_2Ph_{syn+anti}$), 6.41 (d, J = 8.1 Hz, 2H, 6′-$H_{syn+anti}$), 6.46 (d, J = 8.1 Hz, 1H, 8′-H_{anti}), 6.47 (d, J = 8.1 Hz, 1H, 8′-H_{syn}), 7.04 (t, J = 8.1 Hz, 2H, 7′-$H_{syn+anti}$), 7.22–7.37 ppm (m, 10H, 5×Ph-$H_{syn+anti}$); ^{13}C NMR (125 MHz, $CDCl_3$, *syn*/*anti* = 1:2.4): δ = 15.7, 15.7 (C-4′$_{syn}$, C-4′$_{anti}$), 23.1 (C-3′$_{syn}$), 23.5 (C-3′$_{anti}$), 55.5 (5′-$OCH_{3syn+anti}$), 62.0 (C-2$_{anti}$), 62.3 (C-2$_{syn}$), 69.0 (C-1$_{syn}$), 70.2 (C-1$_{anti}$), 73.9 (OCH_2Ph_{syn}), 74.0 (OCH_2Ph_{anti}), 74.2 (CH_2OBn_{syn}), 75.4 (CH_2OBn_{anti}), 77.6 (C-2′$_{anti}$), 78.2 (C-2′$_{syn}$), 102.0 (C-6′$_{syn+anti}$), 109.7, 109.7 (C-8′$_{syn}$, C-8′$_{anti}$), 110.3 (C-4a′$_{syn}$), 110.4 (C-4a′$_{anti}$), 127.0, 127.0 (C-7′$_{syn}$, C-7′$_{anti}$), 127.6, 127.7, 127.9, 127.9, 128.4 (Ph-$C_{o\ syn+anti}$, Ph-$C_{m\ syn+anti}$, Ph-$C_{p\ syn+anti}$), 137.1 (Ph-$C_{i\ syn}$), 137.2 (Ph-$C_{i\ anti}$), 153.2 (C-8a′$_{syn}$), 153.3 (C-8a′$_{anti}$), 157.5 (C-5′$_{syn}$), 157.6 ppm (C-5′$_{anti}$); IR (film): $\tilde{\nu}$ = 3406, 2938, 1592, 1469, 1347, 1251, 1191, 1095, 1028, 909, 771, 737, 699 cm^{-1}; UV (CH_3OH): λ_{max} (lg ε) = 204.5 (4.716), 271.0 (3.168), 279.0 nm (3.156); MS (ESI): m/z (%): 711.3 (55) $[2M+Na]^+$, 367.1 (100) $[M+Na]^+$; HRMS (ESI): m/z calcd (%) for $C_{20}H_{24}O_5$ (344.40): 367.1521 $[M+Na]^+$; found: 367.1517.

Methyl (3*R*,4*R*)-4-[(*R*)-2-(benzyloxymethyl)-5-methoxychroman-2-yl)-4-(*tert*-butyldimethylsilyloxy)-3-methylbutanoate (18a): MeLi (72.4 mL of a 1.6 M solution in Et_2O, 116 mmol, 12.0 equiv) was added to a suspension of CuBr·Me_2S (11.9 g, 57.9 mmol, 6.00 equiv) in THF (80 mL) at −35 °C, and the resulting mixture was stirred for 40 min at −35 °C. Then, TMSCl (7.40 mL, 6.29 g, 57.9 mmol, 6.00 equiv) and a solution of ester (*E*)-**17** (4.95 g, 9.65 mmol, 1.00 equiv) in THF (110 mL) were added and stirring was continued at −35 °C for 60 min. Afterwards, the reaction was quenched by careful addition of NEt_3 (165 mL) and water (400 mL). The aqueous layer was extracted with *t*BuOMe (2×200 mL), and the combined organic layers were washed with water (250 mL), dried over Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (petroleum ether/EtOAc = 20:1→15:1) provided ester **18a** as a colorless oil (4.62 g, 8.74 mmol, 91 %). R_f = 0.51 (petroleum ether/*t*BuOMe = 7:1); $[\alpha]_D^{23}$ = −15.1 (c = 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.02 (s, 3H, $Si(CH_3)_a$), 0.13 (s, 3H, $Si(CH_3)_b$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.06 (d, J = 6.9 Hz, 3H, 3-CH_3), 1.87–2.06 (m, 2H, 3′-H_2), 2.15 (dd, J = 15.9, 10.2 Hz, 1H, 2-H_a), 2.30–2.54 (m, 2H, 3-H, 4′-H_a), 2.67 (dd, J = 15.9, 2.7 Hz, 1H, 2-H_b), 2.72 (ddd, J = 17.1, 5.1, 3.6 Hz, 1H, 4′-H_b), 3.52 (s, 2H, CH_2OBn), 3.59 (s, 3H, $COOCH_3$), 3.79 (s, 3H, 5′-OCH_3), 3.94 (d, J = 0.9 Hz, 1H, 4-H), 4.40 (d, J = 12.0 Hz, 1H, OCH_aPh), 4.50 (d, J = 12.0 Hz, 1H, OCH_bPh), 6.37 (d, J = 8.1 Hz, 1H, 6′-H), 6.43 (d, J = 8.1 Hz, 1H, 8′-H), 7.02 (t, J = 8.1 Hz, 1H, 7′-H), 7.19–7.33 ppm (m, 5H, 5×Ph-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.8 ($Si(CH_3)_a$), −3.7 ($Si(CH_3)_b$), 15.9 (C-4′), 18.7 ($SiC(CH_3)_3$), 20.9 (C-3′), 21.0 (3-CH_3), 26.2 ($SiC(CH_3)_3$), 30.9 (C-3), 36.5 (C-2), 51.3 ($COOCH_3$), 55.3 (5′-OCH_3), 70.1 (CH_2OBn), 73.6 (OCH_2Ph), 80.0 (C-4), 81.2 (C-2′), 101.3 (C-6′), 110.2 (C-4a′), 110.3 (C-8′), 126.8 (C-7′), 127.4 (Ph-C_p), 127.5 (Ph-C_o), 128.2 (Ph-C_m), 138.1 (Ph-Ci), 153.9 (C-8a′), 157.6 (C-5′), 174.4 ppm ($COOCH_3$); IR (neat): $\tilde{\nu}$ = 2952, 2852, 1738, 1591, 1468, 1251, 1136, 1092, 1037, 1004, 832, 770, 738 cm^{-1}; UV (CH_3OH): λ_{max} (lg ε) = 204.0 (4.732), 273.0 (3.115), 280.0 nm (3.103); MS (ESI): m/z (%): 551.3 (100) $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{30}H_{44}O_6Si$ (528.75): 551.2805 $[M+Na]^+$; found: 551.2799.

Methyl (3*R*,4*R*,4a*S*)-4-(*tert*-butyldimethylsilyloxy)-1-hydroxy-8-methoxy-3-methyl-9-oxo-2,3,4,4a-tetrahydroxanthene-4a-carboxylate (4): A solution of $TiCl_4$ (2.47 mL of a 1.0 M solution in CH_2Cl_2, 2.47 mmol, 2.60 equiv) was added slowly to a stirred solution of chromanone **19** (456 mg, 949 μmol, 1.00 equiv) and NEt_3 (390 μL, 288 mg, 2.85 mmol, 3.00 equiv) in CH_2Cl_2 (7 mL) at 0 °C, and stirring was continued at 0 °C for 60 min. Then, the reaction was quenched by addition of a saturated aq solution of NH_4Cl (4 mL). Water (60 mL) was added and the aqueous layer was extracted with EtOAc (3×60 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Column chro-

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matography of the residue on silica gel (petroleum ether/EtOAc = 5:1) yielded the tetrahydroxanthenone **4** as a colorless foam (331 mg, 738 μmol, 78%) and the corresponding tetrahydroxanthenone with a phenolic hydroxyl group as a pale-yellow solid (22.0 mg, 51.0 μmol, 5%). R_f = 0.18 (petroleum ether/EtOAc = 5:1); $[\alpha]_D^{24} = -141.4$ (c = 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 3H, $Si(CH_3)_a$), 0.14 (s, 3H, $Si(CH_3)_b$), 0.81 (s, 9H, $SiC(CH_3)_3$), 1.03 (d, J = 6.9 Hz, 3H, 3-CH_3), 1.90–2.05 (m_c c = complex, 1H, 3-H), 2.29 (dd, J = 18.6, 6.0 Hz, 1H, 2-H_a), 2.41 (dd, J = 18.6, 11.1 Hz, 1H, 2-H_b), 3.60 (s, 3H, $COOCH_3$), 3.90 (s, 3H, 8-OCH_3), 4.12 (d, J = 1.2 Hz, 1H, 4-H), 6.53 (dd, J = 8.4, 0.9 Hz, 1H, 5-H), 6.57 (dd, J = 8.4, 0.9 Hz, 1H, 7-H), 7.32 (t, J = 8.4 Hz, 1H, 6-H), 16.19 ppm (brs, 1H, 1-O*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.4, −3.5 ($Si(CH_3)_2$), 18.3 (3-CH_3), 18.6 ($SiC(CH_3)_3$), 26.1 ($SiC(CH_3)_3$), 29.8 (C-3), 34.8 (C-2), 53.1 ($COOCH_3$), 56.2 (8-OCH_3), 73.0 (C-4), 84.6 (C-4a), 101.4 (C-9a), 105.2 (C-5), 109.8 (C-8a), 110.2 (C-7), 135.4 (C-6), 159.0 (C-10a), 160.5 (C-8), 172.0 ($COOCH_3$), 180.2 (C-9), 185.4 ppm (C-1); IR (neat): $\tilde{\nu}$ = 2953, 2929, 1737, 1599, 1472, 1249, 1101, 1078, 1068, 1038, 834, 774, 737, 539 cm^{-1}; UV (CH_3OH): λ_{max} (lg ε) = 204.0 (4.235), 279.0 (3.545), 333.0 nm (4.095); MS (ESI): m/z (%): 1367.5 (15) $[3M+Na]^+$, 919.4 (100) $[2M+Na]^+$, 471.2 (17) $[M+Na]^+$, 449.2 (7) $[M+H]^+$; HRMS (ESI): m/z calcd for $C_{23}H_{32}O_7Si$ (448.58): 449.1996 $[M+H]^+$, 471.1815 $[M+Na]^+$; found: 449.1990, 471.1810.

Methyl (3*R*,4*R*,4a*S*)-1,4,8-trihydroxy-3-methyl-9-oxo-2,3,4,4a-tetrahydroxanthene-4a-carboxylate ((−)-blennolide A) (*ent*-1): A solution of BBr_3 (0.76 mL of a 1.0 M solution in CH_2Cl_2, 0.76 mmol, 15 equiv) was added slowly to a stirred solution of methyl ether **20** (17 mg, 51 μmol, 1.0 equiv) in CH_2Cl_2 (2.8 mL) at 0 °C, and stirring was continued for 4 h at RT. Then, the reaction was quenched by addition of a saturated aq solution of $NaHCO_3$ (5 mL) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 150:1) to give (−)-blennolide A (*ent*-**1**) as a pale-yellow solid (14 mg, 44 μmol, 86%). R_f = 0.43 (CH_2Cl_2/MeOH = 200:1); $[\alpha]_D^{23} = -198.7$ (c = 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (d, J = 6.6 Hz, 3H, 3-CH_3), 1.99–2.15 (m_c, 1H, 3-H), 2.35 (dd, J = 18.9, 6.0 Hz, 1H, 2-H_a), 2.49 (dd, J = 18.9, 11.1 Hz, 1H, 2-H_b), 2.54 (brs, 1H, 4-OH), 3.65 (s, 3H, $COOCH_3$), 4.08 (s, 1H, 4-H), 6.47 (dd, J = 8.4, 0.9 Hz, 1H, 5-H), 6.53 (dd, J = 8.4, 0.9 Hz, 1H, 7-H), 7.31 (t, J = 8.4 Hz, 1H, 6-H), 11.33 (brs, 1H, 8-OH), 13.97 ppm (brs, 1H, 1-OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4 (3-CH_3), 28.5 (C-3), 32.5 (C-2), 53.3 ($COOCH_3$), 71.2 (C-4), 84.7 (C-4a), 100.0 (C-9a), 107.1 (C-8a), 107.8 (C-5), 111.1 (C-7), 137.5 (C-6), 157.6 (C-10a), 162.0 (C-8), 171.1 ($COOCH_3$), 179.7 (C-1), 187.4 ppm (C-9); IR (neat): $\tilde{\nu}$ = 3537, 1740, 1609, 1583, 1561, 1459, 1228, 1029, 829, 766, 714, 531 cm^{-1}; UV (CH_3OH): λ_{max} (lg ε) = 205.0 (4.184), 277.0 (3.587), 331.0 nm (4.174); MS (ESI): m/z (%): 663.2 (100) $[2M+Na]^+$, 343.1 (40) $[M+Na]^+$. HRMS (ESI): m/z calcd for $C_{16}H_{16}O_7$ (320.29): 321.0974 $[M+H]^+$, 343.0794 $[M+Na]^+$; found: 321.0969, 343.0792.

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[1] W. Zhang, K. Krohn, Z. Ullah, U. Flörke, G. Pescitelli, L. Di Bari, S. Antus, T. Kurtán, J. Rheinheimer, S. Draeger, B. Schulz, *Chem. Eur. J.* **2008**, *14*, 4913–4923.
[2] F. Kraft, *Archiv der Pharmazie* **1906**, *244*, 336–359.
[3] B. Franck, E. M. Gottschalk, U. Ohnsorge, F. Hueper, *Chem. Ber.* **1966**, *99*, 3842–3862.
[4] M. M. Wagenaar, J. Clardy, *J. Nat. Prod.* **2001**, *64*, 1006–1009.
[5] M. Isaka, A. Jaturapat, K. Rukseree, K. Danwisetkanjana, M. Tanticharoen, Y. Thebtaranonth, *J. Nat. Prod.* **2001**, *64*, 1015–1018.
[6] L. F. Tietze, D. A. Spiegl, F. Stecker, J. Major, C. Raith, C. Grosse, *Chem. Eur. J.* **2008**, *14*, 8956–8963.
[7] L. F. Tietze, S. Jackenkroll, C. Raith, D. A. Spiegl, J. R. Reiner, M. C. Ochoa Campos, *Chem. Eur. J.* **2013**, *19*, 4876–4882.
[8] For recent reviews on domino reactions, see: a) L. F. Tietze, M. A. Düfert, S. C. Schild in *General Principles of Diastereoselective Reactions: Diastereoselective Domino Reactions in Comprehensive Chirality, Vol. 2* (Eds. E. M. Carreira, H. Yamamoto), Elsevier, Amsterdam, **2012**, pp. 97–121; b) L. F. Tietze, S. Stewart, M. A. Düfert in *Domino Reactions in the Enantioselective Synthesis of Bioactive Natural Products in Modern Tools for the Synthesis of Complex Bioactive Molecules* (Eds.: J. Cossy, S. Arseniyades), Wiley, Hoboken, **2012**; c) Hélène Pellissier, *Adv. Synth. Catal.* **2012**, *354*, 237–294; d) S. Giboulot, F. Liron, G. Prestat, B. Wahl, M. Sauthier, Y. Castanet, A. Montreux, G. Poli, *Chem. Commun.* **2012**, *48*, 5889–5891; e) M. Platon, R. Amardeil, L. Djakovitch, J.-C. Hierso, *Chem. Soc. Rev.* **2012**, *41*, 3929–3968; f) L. F. Tietze, A. Düfert, *Pure Appl. Chem.* **2010**, *82*, 1375–1392; g) L. F. Tietze, A. Düfert in *Domino Reactions Involving Catalytic Enantioselective Conjugate Additions in Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Cordova), Wiley-VCH, Weinheim, **2010**, pp. 321–350; h) C. Grondall, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178; i) L. F. Tietze, L. Levy in *The Mizoroki–Heck Reaction in Domino Processes* (Ed.: M. Oestreich), Wiley, Chichester, **2008**, pp. 281–344; j) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*; Wiley-VCH, Weinheim, **2006**; k) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; l) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; m) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163.
[9] a) L. F. Tietze, A. Heins, M. Soleiman-Beigi, C. Raith, *Heterocycles* **2009**, *77*, 1123–1146; b) L. F. Tietze, J. Zinngrebe, D. A. Spiegl, F. Stecker, *Heterocycles* **2007**, *74*, 473–489.
[10] R. N. Mirrington, G. I. Feutrill, *Org. Synth.* **1973**, *53*, 90–93.
[11] B. M. Trost, H. C. Shen, L. Dong, J.-P. Surivet, C. Sylvain, *J. Am. Chem. Soc.* **2004**, *126*, 11966–11983.
[12] D. M. Bradley, R. Mapitse, N. M. Thomson, C. J. Hayes, *J. Org. Chem.* **2002**, *67*, 7613–7617.
[13] a) H. Hocke, Y. Uozumi, *Tetrahedron* **2003**, *59*, 619–630; b) T. D. Nelson, A. I. Meyers, *J. Org. Chem.* **1994**, *59*, 2655–2658.
[14] P. Wipf, C. R. J. Stephenson, *Org. Lett.* **2005**, *7*, 1137–1140.
[15] a) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, X.-L. Zhang, *J. Org. Chem.* **1992**, *57*, 2768–2771; b) H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
[16] K. Yamamoto, H. Ogura, J. Jukuta, H. Inoue, K. Hamada, Y. Sugiyama, S. Yamada, *J. Org. Chem.* **1998**, *63*, 4449–4458.
[17] a) S. Hanessian, K. Sumi, *Synthesis* **1991**, 1083–1089; b) S. Hanessian, N. Chahal, S. Giroux, *J. Org. Chem.* **2006**, *71*, 7403–7411; c) N. Asao, S. Lee, Y. Yamamoto, *Tetrahedron Lett.* **2003**, *44*, 4265–4266; d) J. Yang, G. B. Dudley, *Tetrahedron Lett.* **2007**, *48*, 7887–7889.
[18] a) Y. Chounan, Y. Ono, S. Nishii, H. Kitahara, S. Itob, Y. Yamamoto, *Tetrahedron* **2000**, *56*, 2821–2831; b) A. E. Dorigo, K. Morokuma, *J. Am. Chem. Soc.* **1989**, *111*, 6524–6536; c) Y. Yamamoto, S. Nishii, T. Ibukab, *J. Chem. Soc. Chem. Commun.* **1987**, 464–466.
[19] Blennolide B and C have already been synthesized by: a) E. M. C. Gérard, S. Bräse, *Chem. Eur. J.* **2008**, *14*, 8086–8089; b) K. C. Nicolaou, A. Li, *Angew. Chem.* **2008**, *120*, 6681–6684; *Angew. Chem. Int. Ed.* **2008**, *47*, 6579–6582; c) T. Qin, R. P. Johnson, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2011**, *133*, 1714–1717.

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