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COMMUNICATION

An RCM-Based Total Synthesis of the Antibiotic Disciformycin B

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This paper is dedicated to our late friend Maurizio Botta, who left us much too early.

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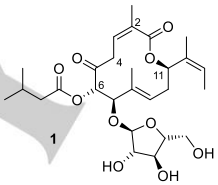
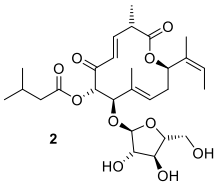
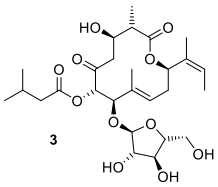
Abstract: The total synthesis of the potent new antibiotic disciformycin B (**2**) is described, which shows significant activity against methicillin- and vancomycin-resistant *Staphylococcus aureus* (MRSA/VRSA) strains. The synthetic route is based on macrocyclization of a tetraene substrate to the 12-membered macrolactone core by ring-closing olefin metathesis (RCM). Although macrocyclization was accompanied by concomitant cyclopentene formation by an alternative RCM pathway, conditions could eventually be established that gave the macrocycle as the major product. Key steps in the construction of the RCM-substrate included a highly efficient Evans *syn*-aldol reaction, the asymmetric Brown allylation of angelic aldehyde and the stereoselective $Zn(BH_4)_2$-mediated 1,2-reduction of an enone. The synthesis was completed by late-stage dehydrative glycosylation to introduce the D-arabinofuranosyl moiety and final chemoselective allylic alcohol oxidation.

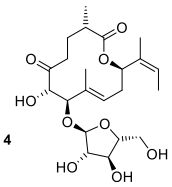
Disciformycins A (**1**) and B (**2**) are polyketide-derived macrolide glycosides that were isolated in 2014 by Müller and co-workers from the myxobacterium *Pyxidicoccus fallax* strain AndGT8.[1] The biological assessment of these compounds revealed significant antibacterial activity against Gram-positive bacteria, including methicillin- and vancomycin-resistant *Staphylococcus aureus* (MRSA/VRSA) strains, with **2** being more active than **1**. Furthermore, the lack of cross-resistance with other antibiotics classes pointed to a novel mechanism of action for the disciformycins.[1][2] Concurrently with the disclosure of disciformycins A (**1**) and B (**2**) by Müller and co-workers, Nett and co-workers reported the isolation of a structurally related pair of macrolides, gulmirecins A (**3**) and B (**4**), from the predatory bacterium *Pyxidicoccus fallax* HKI 727. Like disciformycins A (**1**) and B (**2**), the gulmirecins displayed pronounced antibiotic activity against several strains of Gram-positive bacteria; **3**, but not **4**, also showed promising activity against MRSA.[3]

In the broader context of the ever growing threat posed by antibiotic-resistant bacteria and the pressing need for the development of new antibiotics,[4] we considered disciformycins and gulmirecins important targets for total synthesis. The chemistry developed in the course of a successful total synthesis campaign provides the foundation for systematic structure-activity relationship (SAR) studies and the eventual discovery of analogs with improved overall profiles for drug development. Similar considerations have underlain the work of Fürstner and co-workers, who have reported the only total synthesis of a disciformycin/gulmirecin so far (disciformycin B (**2**)),[5] based on macrocycle formation by ring-closing alkyne metathesis (RCAM) between C8 and C9. While this reaction could be accomplished with remarkable efficiency, the elaboration of the resulting macrocyclic alkyne into the disciformycin B aglycone proved to be difficult and less efficient, owing largely to the limited stability of several intermediates. Fürstner's work also showed that **2** cleanly isomerizes to the less active **1** under mildly basic conditions.









Subsequent to Fürstner's work, Wolling and Kirschning described an alternative approach towards the disciformycin B aglycone, employing a macrolactonization strategy.[6] More recently, Rengarasu and Maier have described the synthesis of a C1-C12 fragment of gulmirecin B (**4**),[7] and Ichikawa and co-workers have reported the synthesis of a fully protected version of C5-O dihydro gulmirecin A. Ichikawa's approach entailed macrocyclization at C7-C8 by Ni(0)-mediated reductive cyclization of an ynal intermediate;[8] unfortunately, deprotection of the advanced gulmirecin A precursor could not be achieved.

Based on the superior antibiotic activity of disciformycin B (**2**) over **1**, **3**, and **4**, our own work, as for Fürstner and co-workers, has focused on disciformycin B (**2**) as the primary target for total synthesis. As depicted in Scheme 1, our synthesis was to be based on macrocyclization at C8-C9 by means of ring-closing olefin metathesis (RCM) of tetraene **7** as the crucial step. Obviously, this strategy entailed some risk, due to the possibility of 5-membered ring formation by RCM between the disubstituted terminal double bond and the internal double bond in **7** (corresponding to the C3-C4 double bond in **2**), which might in

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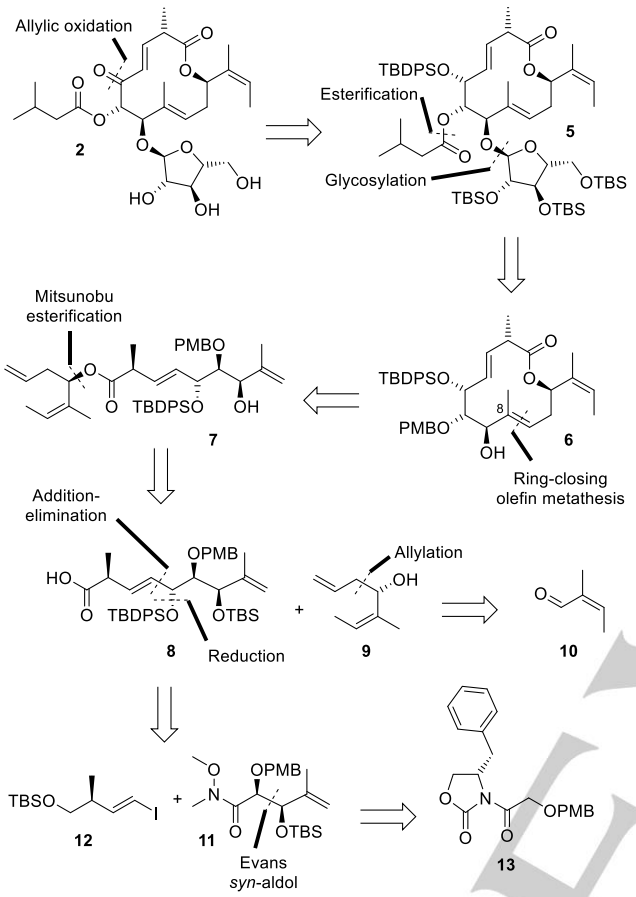
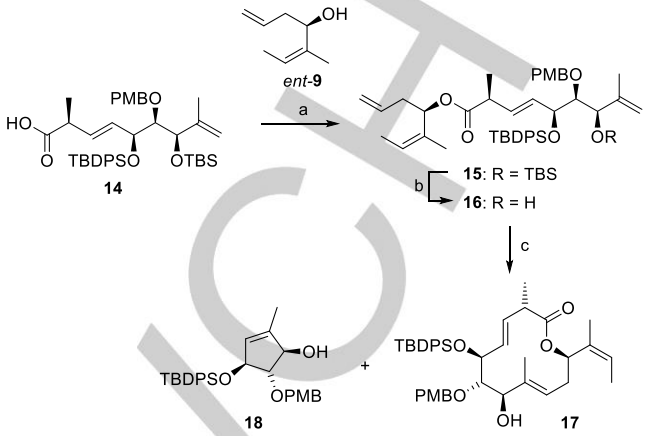
fact have been expected to be the preferred reaction path. However, we were hopeful that the desired macrocycle (with a *trans*-configured C8-C9 double bond) might still be accessed using appropriate protecting groups and careful tuning of the reaction conditions.[9]



Scheme 1. Retrosynthesis of disciformycin B (**2**). PMB = *p*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

The RCM-product **6** was to be elaborated into disciformycin B (**2**) by α-selective glycosylation, cleavage of the PMB-ether at C6, esterification, global deprotection, and, in the final step, establishment of the C3-C5 enone moiety by chemoselective oxidation of the allylic hydroxy group.[10] Formation of the enone moiety in the final step would eliminate any potential difficulties arising from the reactivity of this group and/or double bond migration.[5] Tetraene **7** was to be prepared by Mitsunobu esterification of acid **8** and alcohol **9** (*vide infra*); the latter was envisioned to be accessible from angelic aldehyde (**10**)[11] by means of asymmetric allylation. Carboxylic acid **8** would be obtained from known vinyl iodide **12**[12] and Weinreb amide **11** by addition-elimination followed by diastereoselective carbonyl reduction. Weinreb amide **11** was to be prepared from N-acyl oxazolidinone **13**[13] by Evans *syn*-aldol reaction with methacrolein.

The retrosynthesis depicted in Scheme 1 includes some specific learnings from a prior approach towards **2** that had included tetraene **16** as the substrate for RCM-based macrocyclization (Scheme 2). The latter had been obtained by DCC/DMAP-mediated esterification[14] of acid **14** with alcohol *ent*-**9** followed by selective TBS-ether cleavage with CSA in CH_2Cl_2/MeOH. (For the synthesis of **14** and *ent*-**9** see the SI).



Scheme 2. a) *ent*-**9**, DCC, DMAP, CH_2Cl_2, –30 °C, 25 h, 77%; dr 92:8; b) CSA, CH_2Cl_2/MeOH (1:1), rt, 8.5 h, 68% (80% based on recovered **15**), dr 92:8; c) 1 mM **16**, Grubbs II (60 mol%), benzene, 80 °C, 45 h, **17**: ca. 21% (*E*/*Z* > 95:5, the material contained minor inseparable impurities), **18**: 48%. CSA = (±)-camphor-10-sulfonic acid, DCC = *N*,*N*'-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, PMB = *p*-methoxybenzyl, TBDPS = *tert*-butyl-diphenylsilyl, TBS = *tert*-butyldimethylsilyl.

While tetraene **16** did undergo RCM to the desired macrocycle **17**, the latter was obtained in a disappointingly low yield of only 21% at best (Scheme 2); the major product of the reaction was in fact cyclopentene **18** that could be isolated in 48% yield. However, differences in RCM efficiency between diastereoisomers of the same diene have been described in the literature,[15] which encouraged us to investigate the effect of inverting the configuration of the C5 stereocenter in **16** from *S* to *R* on RCM efficiency, hence leading to **7** as an alternative RCM substrate (Scheme 1). As a second issue in our first generation approach towards **2**, the esterification of **14** with *ent*-**9** was accompanied by significant epimerization and even under optimized conditions (1.3 equiv. DCC, 0.05 equiv. DMAP, CH_2Cl_2, –30 °C, 25 h), the ester product was obtained in an inseparable mixture with ca. 8% of its C2-epimer (disciformycin numbering). As a consequence, the assembly of diene **7** was planned to entail Mitsunobu esterification of acid **8** and alcohol **9** (Scheme 1).

Following the provisions of the retrosynthesis summarized in Scheme 1, the synthesis of carboxylic acid building block **8** departed from N-acyl oxazolidinone **13**.[13] As depicted in Scheme 3, the reaction of methacrolein with the dibutylboron enolate derived from **13** afforded *syn*-aldol product **19** in excellent yield (97%) and with high diastereoselectivity (dr > 95:5). Imide **19** was transformed into the desired Weinreb amide **11** by reaction with $AlMe_3$ and MeNH(OMe)·HCl and subsequent TBS-protection of the secondary hydroxy group in 78% overall yield. Reaction of **11** with the vinyllithium species derived from vinyl iodide **12**[12] by iodine-lithium exchange with *t*BuLi at –78 °C then furnished ketone **20** in high yield (85%). The latter could be reduced with freshly prepared $Zn(BH_4)_2$[16] at –78 °C to –10 °C, to deliver allylic alcohol **21** in 75% yield and with excellent diastereoselectivity (dr > 95:5). The reaction appeared to be scale-dependent, with yields of **21** of 54%, 75%, and 65% on a 50 mg, 700 mg, and 2 g scale of **20**, respectively. Protection of the newly formed secondary

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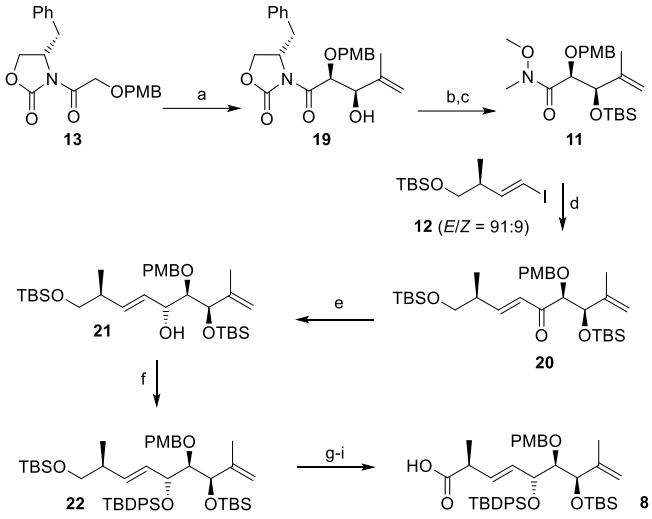
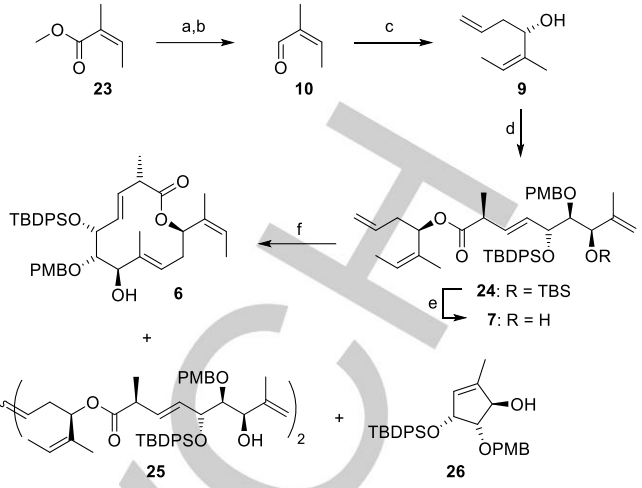
hydroxy group as a TBDPS-ether, to deliver **22** in 97% yield, enabled selective liberation of the primary hydroxy group by TBS-ether cleavage with HF•pyridine (81% yield). The ensuing primary alcohol was then converted into the desired carboxylic acid **8** by treatment with Dess-Martin periodinane[17] followed by oxidation of the ensuing (crude) aldehyde under Pinnick-Kraus conditions[18] in excellent overall yield (89%).



Scheme 3. a) i. **13**, Bu_2BOTf, NEt_3, toluene, −50 °C, 1.5 h; ii. methacrolein, −78 °C to 0 °C, 2 h, 97%, dr > 95:5; b) i. MeNH(OMe)·HCl, $AlMe_3$, THF, 0 °C to rt, 30 min; ii. **19**, −20 °C to 0 °C, 3 h; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 78% (two steps); d) i. **12**, *t*BuLi, Et_2O, −78 °C, 1 h; ii. **11**, −78 °C to −50 °C, 2 h, 85%, *E*/*Z* > 95:5; e) $Zn(BH_4)_2$, Et_2O, −78 °C to −10 °C, 40 min, 75% (710 mg **20**), dr > 95:5; f) TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt to 50 °C, 18 h, 97%; g) HF·pyridine, THF, 0 °C to 4 °C, 43 h, 81%; h) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 1 h; i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene/*t*BuOH (1:1), H_2O, 0 °C, 1.5 h, 89% (two steps). Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, DMAP = 4-dimethylaminopyridine, Ph = phenyl, PMB = *p*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

As depicted in Scheme 4, treatment of angelic aldehyde (**10**) (obtained from commercially available methyl angelate (**23**) by $LiAlH_4$ reduction followed by oxidation of the ensuing alcohol with activated MnO_2 in CH_2Cl_2)[11] with (-)-Ipc_2Ballyl at –100 °C[19] gave alcohol **9** in good yield (52% overall from **23**)[20] with high enantioselectivity (> 90% ee) and without noticeable isomerization of the double bond (*Z*/*E* > 95:5). Esterification of alcohol **9** with carboxylic acid **8** under Mitsunobu conditions[21] proceeded smoothly to afford tetraene **24** in 83% yield with complete inversion of configuration (dr > 95:5). In order to prevent impairment of the subsequent metathesis reaction by the presence of a bulky substituent adjacent to one of the double bonds,[22] **24** was then converted into the free secondary alcohol **7** by selective cleavage of the TBS-ether with CSA in CH_2Cl_2/MeOH (1:1) in 57% yield (82% based on recovered **24**).
With tetraene **7** in hand, the stage was set to investigate the crucial RCM step. These experiments were focused on optimizing the ring-closure with Grubbs II catalyst,[23] which had produced reasonably promising results in initial experiments (see the SI).



Scheme 4. a) $LiAlH_4$, Et_2O, 0 °C to rt, 24 h; b) MnO_2, CH_2Cl_2, rt, 16 h, *Z*/*E* > 95:5; c) (-)-Ipc_2Ballyl, Et_2O, -100 °C, 1 h, 52% (three steps), *Z*/*E* > 95:5, > 90% ee; d) **8**, DEAD, PPh_3, THF, 0 °C to rt, 4 h, 83%, dr > 95:5; e) CSA, CH_2Cl_2/MeOH (1:1), rt, 2 h, 57% (82% based on recovered **24**); f) 1 mM **7**, Grubbs II (75 mol%), benzene, 80 °C, 6 h, **6**: ca. 37% (*E*/*Z* > 95:5, contains < 10% linear dimer **25**), **26**: 31%. CSA = (±)-camphor-10-sulfonic acid, DEAD = diethyl azodicarboxylate, Ipc = isopinocampheyl, PMB = *p*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

Under optimized conditions (i. e. 1 mM **7**, 75 mol% catalyst added portionwise, benzene, 80 °C, 6 h), the desired macrocycle **6** was obtained in ca. 37% yield; the isolated material contained < 10% of linear dimer **25** that could not be removed at this point.[24] In addition, cyclopentene **26** was isolated in 31% yield.
The protected aglycone **6** was then submitted to dehydrative glycosylation[25] with TBS-protected D-arabinofuranose **27** (prepared from D-arabinose in 2 steps)[26] (Scheme 5). Thus, treatment of **6** with Ph_2SO, Tf_2O, and TTBP in CH_2Cl_2/toluene (1:10) furnished the desired α-anomer **28** in 60% isolated yield (with an α/β selectivity of the reaction of 3:1).[27] DDQ-mediated cleavage of the PMB-ether, followed by esterification of the ensuing secondary alcohol with isovaleroyl chloride gave the fully protected intermediate **5** in 51% overall yield from **28**.
Not unexpectedly, the subsequent removal of the four silyl protecting groups proved to be a significant challenge, due to facile migration of the isovaleroyl residue to the allylic hydroxy group. Best results were obtained by treatment of **5** with HF•pyridine in THF/pyridine (1:1) at room temperature for 24 h; importantly, the reaction needed to be terminated before complete conversion was reached (i.e. before complete removal of the more stable TBDPS-group from **30**) and a slightly acidic quench (SiO_2) was crucial, as the addition of base caused further undesired migration. Within these confines, the desired tetrol **31** could be isolated in 51% yield after flash column chromatography on silica, together with its regioisomer **32** (26%) and TBDPS-protected intermediate **30** (16%). The undesired ester **32** could be equilibrated to a mixture of **31** and **32** in a 1:2 ratio (based on ^{1}H-NMR analysis of the crude product mixture) by stirring in THF/aqueous saturated $KHCO_3$ (1:1), which allows for partial recycling.

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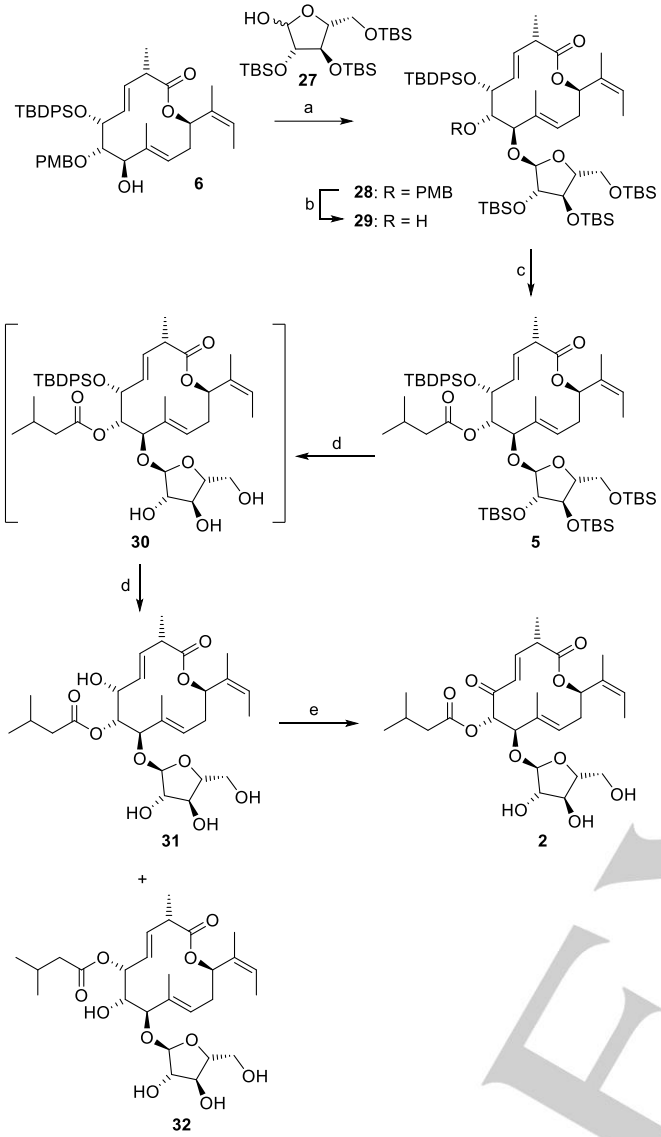

Scheme 5. a) **27** (α/β = 2.5:1), Ph_2SO, Tf_2O, TTBP, 3Å MS, CH_2Cl_2/toluene (1:10), –78 °C to rt, overnight, 60% (**28**, α-anomer), α/β = 3:1; b) DDQ, CH_2Cl_2/pH 7 buffer (6:1), rt, 22 h, 79%; c) isovaleroyl chloride, pyridine, DMAP, CH_2Cl_2, 50 °C, 14 h, 65% after recrystallization; d) HF·pyridine, THF/pyridine (1:1), 0 °C to rt, 24 h, 51% (**31**, 61% based on recovered **30**), 26% (**30**), 16% (**32**); e) 4-acetylamino-2,2,6,6-tetramethyl-piperidine-1-oxo-ammonium tetrafluoro-borate, SiO_2, CH_2Cl_2, rt, 1 h, 71%. DDQ = 2,3-dichloro-5,6-cyano-*p*-benzoquinone**,** DMAP = 4-dimethylaminopyridine, MS = molecular sieves, Tf_2O **=** trifluoromethanesulfonic anhydride**,** THF = tetrahydrofuran, TTBP = 2,4,6-tri-*tert*-butyl-pyridine**.** TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, PMB = *p*-methoxybenzyl

Finally, the allylic hydroxy group in tetrol **31** was chemoselectively oxidized with 4-acetylamino-2,2,6,6-tetramethyl-piperidine-1-oxoammonium tetrafluoroborate (Bobbitt's salt)[28] to afford disciformycin B (**2**) in 71% yield (Scheme 5).[29] Notably, the enone functionality was quickly generated (1 h at room temperature) in the presence of three unprotected sugar hydroxy groups and purification of the reaction mixture included simple SiO_2 column chromatography. No isomerization to the less potent disciformycin A (**1**) was observed under these conditions.

In conclusion, we have completed a convergent total synthesis of the potent antibiotic disciformycin B (**2**) that was built around macrocyclic ring-closure by RCM of the multireactive tetraene **7**. The reaction delivered the desired macrocycle **6** as the major product in 37% yield, closure of the macrocycle thus being favored over competing cyclopentene formation. Importantly, macrocyclization was significantly more efficient with **7** than its diastereomer **16**.[30] Other key steps in the synthesis of **2** included (a) the stereoselective Brown allylation of isomerization-prone angelic aldehyde (**10**); (b) the stereoselective reduction of ketone **20**, to establish the more favorable configuration at C5 (disciformycin numbering) for RCM-mediated macrocyclization; (c) the dehydrative glycosylation of the C7-hydroxy group with tris-TBS-protected D-arabinofuranose; and, finally, (d) the mild chemoselective oxidation of allylic alcohol **31** to install the sensitive enone functionality. Our route allows for late-stage derivatization of the macrocycle, which has provided access to a number of analogs of disciformycin B (**2**) for SAR studies. The results of these studies will be reported in due course.

Acknowledgements

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Keywords: disciformycin • macrocycle • natural products • ring-closing metathesis • total synthesis

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[20] Neither the intermediate alcohol nor aldehyde **10** could be extensively purified, due to their high volatility. In particular, **10** could only be isolated as a mixture with CH_2Cl_2. Thus, an accurate yield for the allylation reaction could not be calculated. However, the allylation was clean and gave **9** in estimated yields of around 80% from **10** (calculated based on the CH_2Cl_2 content of **10**).

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[29] NMR-spectroscopic data for **2** were in full agreement with those reported in the literature.[1][5] The specific rotation of synthetic **2** was lower than reported for the natural material[1] (i. e. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +35 (c = 0.2, MeOH) for synthetic **2** *vs*. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}$ = +64 (c = 0.4, MeOH) for natural **2**). Fürstner and co-workers have reported $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +188 (c = 0.04, MeOH)[5]. Synthetic **2** co-eluted with natural **2** from a chiral, normal phase Daicel Chiralpak AD-H column.

[30] As pointed out by one of the reviewers, the difference in the efficiency of the RCM between dienes **7** and **16** may well be ascribed to differences in the degree of conformational pre-organization for ring-closure. This proposal is in line with observations by Ichikawa et al. in their studies towards the synthesis of gulmirecin A,[8] where they observed a pronounced dependence of the efficiency (or even feasibility) of the Ni(0)-mediated reductive cyclization to the 12-membered ring on the structure of the ynal precursor.

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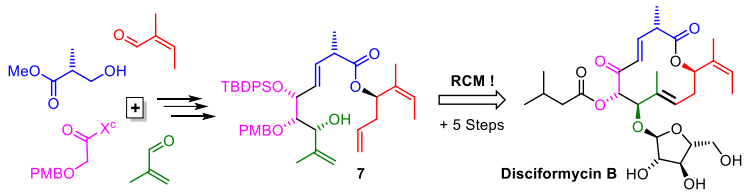

Large or small (ring), that was the question. The antibiotic disciformycin B has been synthesized in 18 linear steps from simple starting materials. Key step was the macrocyclization of tetraene **7** by RCM. Under optimized conditions, the desired 12-membered macrolactone was obtained in preference over the cyclopentene arising from competing RCM with the internal double bond. The synthesis was completed by an exceptionally mild chemoselective oxidation of an allylic hydroxy group.

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