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Synthetic Studies toward the C14−C29 Fragment of Mirabalin

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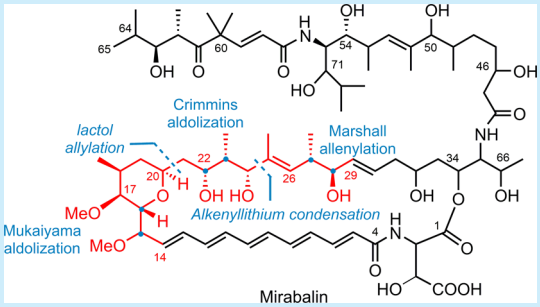
Supporting Information

ABSTRACT: A convergent synthesis of one isomer of the C14−C29 fragment of mirabalin is disclosed. The key steps include a Marshall allenylation, a Mukaiyama aldol reaction and a Crimmins aldolization, which allow the control of 10 out of 25 stereogenic centers present in the molecule.



Marine sponges belonging to the *Theonellidae* family are an important source of macrolides exhibiting remarkable biological activities.[1] Among them, the macrocyclic mirabalin has been extracted from *Siliquariaspongia mirabilis*, a lithistid demosponge collected from the archipelago of Chuuk, Micronesia.[2] Mirabalin was found to inhibit the cell proliferation in the tumor cell line HCT-116 (human colon carcinoma) with an IC_{50} of 270 nM (±90 nM). In contrast, the growth of monkey kidney carcinoma or human cervical carcinoma was not affected by mirabalin even at a concentration as high as 70 μM. In addition, the presence of the macrocycle appeared crucial to the biological activity as no inhibition of the proliferation of HCT-116 was observed when treated with the pendant polyketide side chain. The structure of mirabalin was partially elucidated using 2D NMR experiments, ESIMS, and tandem MS techniques. From all these data, mirabalin was identified as a 35-membered lactam ring embedding a tetrasubstituted tetrahydropyran as well as a fully conjugated pentaene moiety. A linear polyketide side chain is connected to the macrocycle ring via an amide bond. However, due to the scarce natural availability of mirabalin and the structural complexity of the molecule, the absolute configuration of 12 out of the 25 stereocenters could not be assigned. In contrast, the geometry of the double bonds was established unambiguously.

In the course of our ongoing studies toward the synthesis of antiproliferative agents,[3] we embarked on the synthesis of mirabalin. These synthetic studies could help in establishing the precise structure of mirabalin and allow the access to isomers and/or analogues, which might eventually be shown to be more bioactive and selective than the natural product itself. To begin, the unknown stereocenters were arbitrarily assigned, and compound **1** was targeted (Figure 1). Some efforts were made to design a modular route that could open the way to the

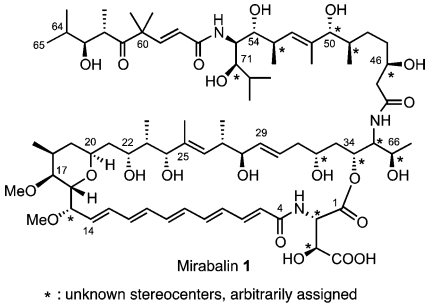


Figure 1. Structure of mirabalin, isomer **1**.

synthesis of a library of isomers. Recently, we reported a convergent and versatile synthetic strategy toward the C44−C65 polyketide side chain of mirabalin.[4] Herein, we disclose the synthesis of the C14−C29 fragment of mirabalin including the tetrasubstituted tetrahydropyran and a (*E*)-trisubstituted double bond. It is worth noting that the absolute configuration of nine of the ten stereogenic centers present in this fragment has been established previously.

Initially, a convergent synthesis of the C14−C29 fragment **A** was envisioned from the stereoselective addition of a vinyl metal prepared from the corresponding iodide **C** onto the Weinreb amide **B**. The preparation of the vinyl iodide **C** would rely on a stereoselective Marshall allenylation to control the C27 and C28 stereocenters and the stereocenters at C22−C23 in Weinreb amide **B** would be introduced by a Crimmins aldolization (Scheme 1).

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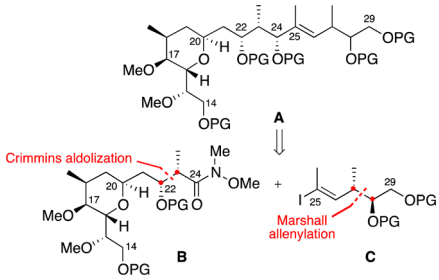
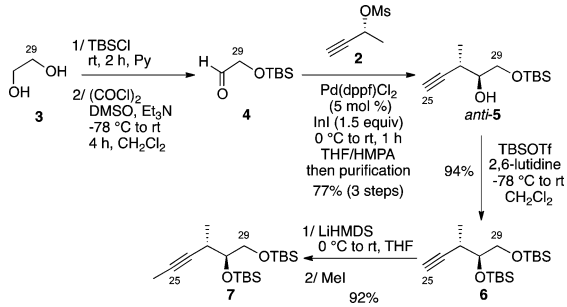
Scheme 1. Retrosynthetic Approach toward A



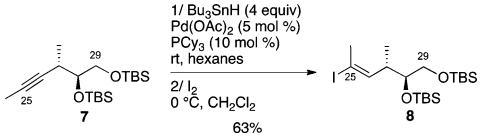
The synthesis of the C25−C29 fragment started with the monoprotection of ethylene glycol and a subsequent Swern oxidation of the primary alcohol to give aldehyde **4**. The latter was subjected to a Marshall allenylation in the presence of the optically active mesylate **2**.[5] Using an excess of indium iodide and a catalytic amount of $Pd(dppf)Cl_2$, the homopropargylic alcohols were obtained in good yield (88%) with a diastereomeric ratio of 90:10 in favor of the *anti*-diastereomer. Pleasingly, the two diastereomers were separable by purification on silica gel, and the desired *anti*-**5** secondary alcohol was isolated with an overall yield of 77% from **3**. After protection of the latter as a *tert*-butyldimethylsilyl (TBS) ether, the terminal alkyne was methylated (LiHMDS, 0 °C to rt followed by addition of MeI) to afford the internal alkyne **7** (Scheme 2).

Scheme 2. Synthesis of Alkyne 7



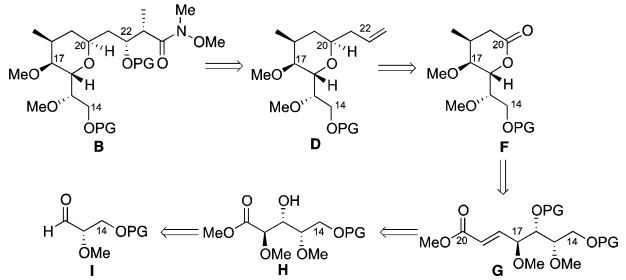
A range of conditions for the metalation/iododemetalation sequence was then examined to access the vinyl iodide **8** from the internal alkyne **7** (see the Supporting Information for details). Finally, when a catalytic system composed of $Pd(OAc)_2$ and PCy_3 was employed in the presence of Bu_3SnH, an excellent yield of 77% was obtained in favor of the vinylstannane, which was then converted into the corresponding iodide **8** upon treatment with iodine (Scheme 3).[6]

Scheme 3. Stannylation/Iododestannylation Process



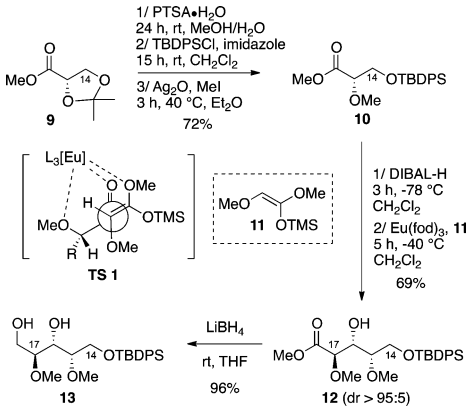
We next turned our attention to the preparation of fragment **B** containing the tetrasubstituted tetrahydropyran that could be synthesized from tetrahydropyran (THP) **D** resulting from the addition of an allylsilane on lactone **F**. The latter would be formed from the unsaturated ester **G** after a stereocontrolled 1,4-addition of a methyl cuprate to introduce the stereocenter at C18 followed by lactonization. The precursor of compound **G** would be ester **H** in which the configuration of the stereogenic centers at C16 and C17 would be controlled by a stereoselective Mukaiyama aldol reaction applied to the (*R*)-*α*-methoxy aldehyde **I** (Scheme 4).

Scheme 4. Retrosynthesis of Fragment B



The synthesis of Weinreb amide **B** started from the commercially available methyl isopropylidene-L-glycerate, which was converted into ester **10** in three steps. An acidic treatment ($PTSA{\cdot}H_2O$, $MeOH/H_2O$) allowing the cleavage of the acetal followed by a subsequent monoprotection of the resulting diol and an etherification of the secondary alcohol (Ag_2O, MeI) afforded ester **10** with a global yield of 72%. To permit the Mukaiyama aldol condensation, **10** was treated with DIBAL-H, and the resulting aldehyde was directly treated with the silyl enol ether **11** in the presence of a catalytic amount of $Eu(fod)_3$.[7] The resulting alcohol was produced with a good yield of 69% (two steps) and an excellent diastereocontrol (dr >95:5).[8] This high diastereoselectivity could be explained by a tridentate coordination of the Lewis acid, which takes place in the transition state **TS 1**. The ester was then reduced to the primary alcohol **13** using $LiBH_4$ (Scheme 5).

Scheme 5. Synthesis of Diol 13



To access the ester **17**, the primary alcohol present in **13** had to be oxidized to an aldehyde, which would be then engaged in a Wittig reaction. However, due to difficulties encountered in selectively oxidizing the primary alcohol, diol **13** was fully protected using an excess of TBSOTf (2,6-lutidine, −78 °C to rt, CH_2Cl_2) and then selectively deprotected with PPTS (rt, EtOH). An oxidation of the resulting primary alcohol (TEMPO, BAIB) was achieved, and the resulting aldehyde was treated in the same pot with the ylide $Ph_3P{=}CHCO_2Me$ **15** to provide the unsaturated ester **16** with an excellent (*E*)/(*Z*) ratio superior to 95:5.[9] When Me_2CuLi was added to the unsaturated

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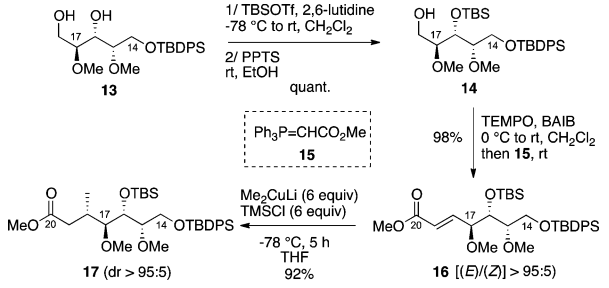
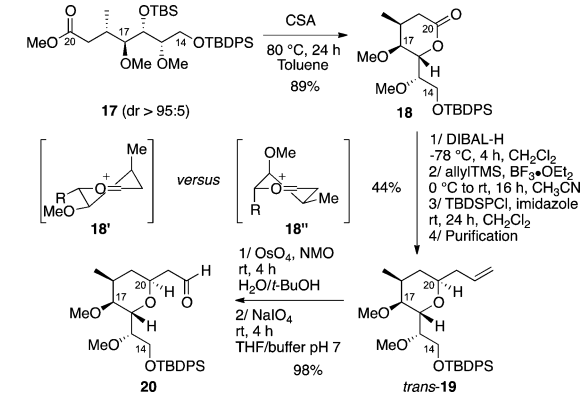
ester **16** in the presence of TMSCl, compound **17** featuring four contiguous stereogenic centers was isolated in 92% yield as a single diastereomer (Scheme 6).[10−12]

Scheme 6. Access to Ester 17



Upon treatment with CSA, ester **17** was transformed into lactone **18** in 89% yield. To control the stereocenter at C20, we planned to perform a diastereoselective allylation of the lactol derived from lactone **18** that should deliver the *trans*-tetrahydropyran as the major product.[13] Thus, lactone **18** was reduced by DIBAL-H and the obtained lactol was treated with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$. Under these conditions, an efficient allylation of the lactol was obtained, albeit with concomitant deprotection of the primary alcohol. In addition, no diastereoselectivity was observed as *cis*- and *trans*-THP were formed in a 55:45 ratio through a nucleophilic addition on the oxocarbenium ions **18′** and **18″**.[14,15] Fortunately, after reprotection of the primary alcohol using *tert*-butyldiphenylsilyl chloride (TBDPSCl), the two diastereomers *trans*-**19** and *cis*-**19** could be separated by flash chromatography on silica gel allowing the isolation of the desired tetrahydropyran *trans*-**19**.[16] An oxidative cleavage of the double bond then afforded aldehyde **20** (Scheme 7).

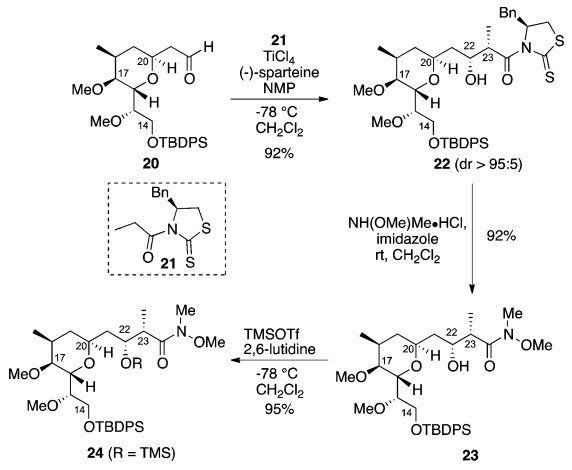
Scheme 7. Synthesis of Aldehyde 20



To control the stereocenters at C22 and C23, a Crimmins aldolization of aldehyde **20** was envisioned.[17] Thus, an aldol reaction involving the chiral thiooxazolidinone **21** and aldehyde **20** was performed in the presence of $TiCl_4$, (−)-sparteine, and *N*-methylpyrrolidinone (NMP). Gratifyingly, the reaction afforded the expected aldol product as a single diastereomer with an excellent yield (92%). The chiral auxiliary was cleaved by a transamination with the Weinreb amide, and the secondary alcohol was protected as a trimethylsilyl ether (Scheme 8).

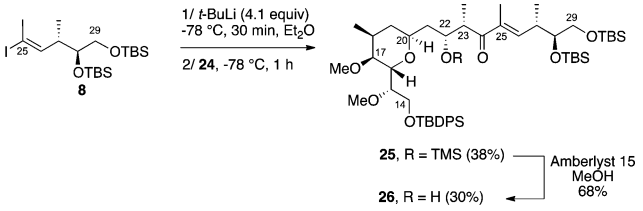
Having fragments **8** and **24** in hand, the coupling reaction was realized. After transformation of the vinyl iodide **8** to the

Scheme 8. Crimmins Aldolization



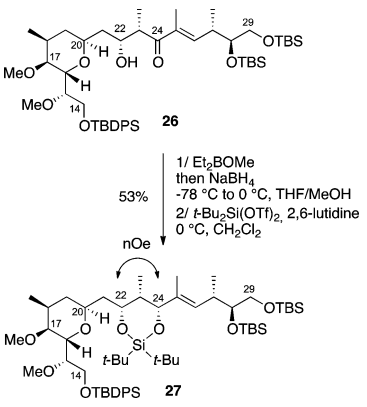
corresponding vinyllithium reagent (*t*-BuLi, Et_2O, −78 °C), the latter was condensed on the Weinreb amide **24** to produce the expected ketone **25** as well as ketone **26** in which the TMS ether was cleaved. Treatment of **25** with Amberlyst 15 afforded the secondary alcohol **26** in 68% yield (Scheme 9).

Scheme 9. Synthesis of Ketone 26



The stereocenter at C24 was then introduced using a Prasad reduction (Et_2BOMe, $NaBH_4$),[18] and the resulting 1,3-diol was transformed to the cyclic silyl ether **27**. The relative stereochemistry of the hydroxyl groups at C22 and C24 was confirmed by nOe experiments (Scheme 10).

Scheme 10. Access to Fragment C14−C29 of Mirabalin (1)



In summary, a synthesis of the C14−C29 fragment of mirabalin was developed to allow the control of 10 stereocenters. The strategy involved a Marshall allenylation, a Mukaiyama aldol reaction, and a Crimmins aldolization as the key steps. This work is the first synthetic approach of this mirabalin fragment and

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constitutes a significant breakthrough toward the synthesis of the molecule.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02162.

Experimental procedures and full spectroscopic data for all new compounds (PDF)
X-ray data for compound *cis*-**19′** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) At this stage, the absolute configuration of stereocenter C18 could not be undoubtedly assigned using ^{1}H NMR spectroscopy. It was confirmed by X-ray analysis of *cis*-**19′**, vide infra; see ref 16.

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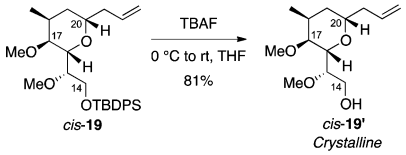
(15) Similar results were obtained with the acetate derived from the lactol.

(16) Interestingly, the alcohol *cis*-**19′** obtained after treatment of *cis*-**19** with TBAF was crystalline, and an X-ray diffraction analysis confirmed the relative stereochemistry of all the stereogenic centers (see the Supporting Information for details).



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