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Synthetic Strategy toward the C44−C65 Fragment of Mirabalin

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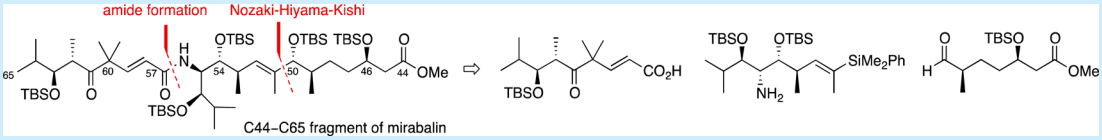
Supporting Information



ABSTRACT: A convergent and flexible stereoselective synthesis of one isomer of the C44−C65 fragment of mirabalin is described. The key steps include organocatalytic aldolization, ruthenium-catalyzed asymmetric hydrogenation, amide formation, Marshall stereoselective allenylation, and the Nozaki−Hiyama−Kishi reaction.

Isolated in 2008 from the marine sponge *Siliquariaspongia mirabilis*, mirabalin[1] was found to inhibit the growth of the tumor cell line HCT-116 with an IC_{50} value of 0.27 μM. This compound is a new member of the chondropsin family of macrolide lactams that currently comprises chondropsins A−D, 73-deoxychondropsin A, and poecillastrins A−C.[2] Chondropsins and poecillastrins are potent cancer cell growth inhibitors that possess a 33-, 35-, or 37-membered macrolide lactam ring. The chondropsin class of macrolide lactams has attracted the attention of organic and medicinal chemists because of their potent cytotoxicity due to the inhibition of vacuolar-type (H^+)-ATPase (V-ATPase), which is an emerging target for the development of therapeutic agents.[3] From a structural point of view, mirabalin (**1**) exhibits a fully conjugated pentaene system and a tetrasubstituted tetrahydropyran ring embedded in a 35-membered lactam core. In addition, a linear polyketide side-chain connected through an amide linkage incorporates a unique C51−C72 moiety possessing a trisubstituted (*E*)-alkene adjacent to a methylhydroxyaminohydroxy stereotetrad (Figure 1).

The polyketide-type structure of mirabalin (**1**) could not be stereochemically assigned completely due to the large number of stereogenic centers present in the molecule and because of the small amount of material available from the natural source (1.5 mg from 6 g of the frozen sponge). Nevertheless, prompted by the potent biological properties of the chondropsin family, coupled with their unique structure, and as part of our work on total synthesis of relevant biomolecules,[4,5] we decided to undertake the synthesis of a member of this family and we focused our efforts toward the total synthesis of one isomer of mirabalin. We report here a convergent access to the mirabalin side chain C44−C65 wherein the unknown C46, C49, C50, C53, and C71 stereogenic centers were arbitrarily assigned to be all (*R*). Accordingly, a modular route was devised in order to be able to produce all 32 isomers of the targeted fragment C44−C65 with respect to the five unassigned stereogenic carbon atoms (Scheme 1).

We envisioned a convergent approach to this fragment involving the assembly of subunits **A** and **B** through a peptidic

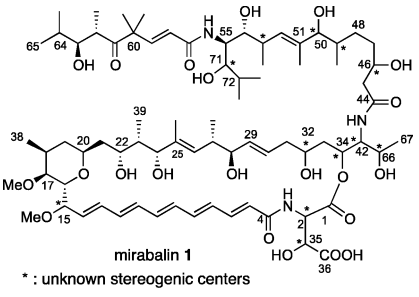
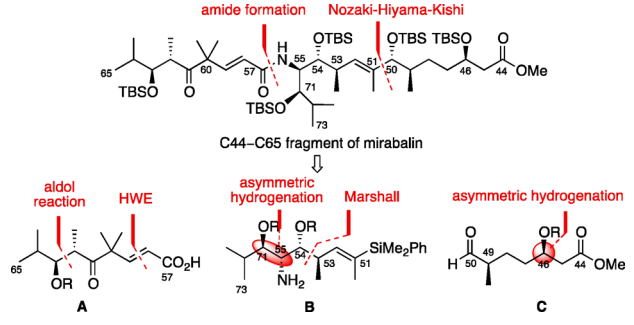


Figure 1. Structure of mirabalin (**1**).

Scheme 1. Retrosynthetic Strategy To Access Mirabalin Side Chain C44−C65



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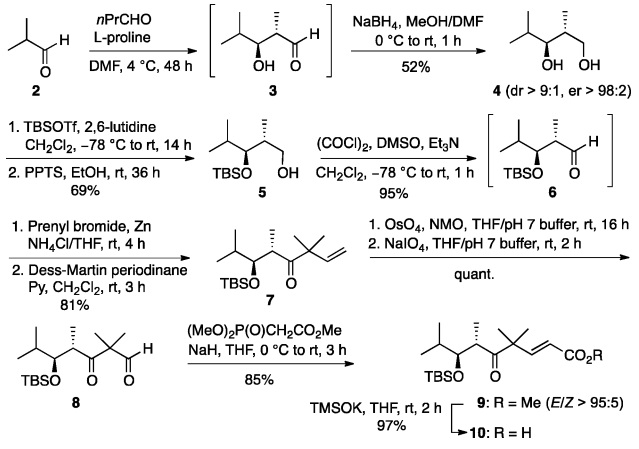
type coupling reaction for the formation of the amide linkage followed by a Nozaki–Hiyama–Kishi reaction with aldehyde **C** to install the C50–C51 bond. Carboxylic acid **A** would be obtained from isobutyraldehyde via an *anti*-selective organocatalytic aldol reaction followed by a Horner–Wadsworth–Emmons olefination for the formation of the (*E*)-alkene moiety. The preparation of subunit **B** would rely on a stereoselective Marshall allenylation to install the C53–C54 bond, whereas the (*E*)-trisubstituted vinylsilane moiety would be formed from the newly introduced internal alkyne through silylcupration. The amino- and hydroxyl-bearing stereocenters in subunits **B** and **C**, namely C55, C71, and C46, would be controlled by ruthenium-catalyzed asymmetric hydrogenation. Finally, the methyl-bearing stereocenter (*R*)-C49 would arise from commercially available (*S*)-Roche ester. It is worth noting that this versatile strategy would open access to all 32 isomers of the mirabalin side chain since upon varying the reaction conditions for the ruthenium-catalyzed hydrogenation and Marshall allenylation the (*R*) or (*S*) configurations at C46, C71, and C53 stereocenters can be easily controlled at will, whereas starting from the (*R*)-Roche ester, the opposite (*S*)-configuration at C49 could be obtained (Scheme 1).

The synthesis of subunit **A**, compound **10**, commenced with an organocatalytic aldolization involving isobutyraldehyde and propanal in the presence of L-proline according to the procedure reported by MacMillan et al.[6] (Scheme 2). Direct

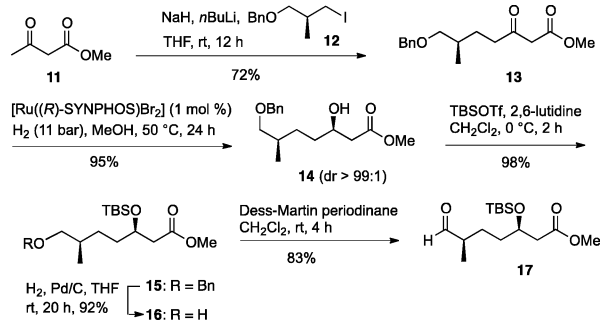
Scheme 2. Synthesis of the C57–C65 Subunit 10



protection of the corresponding aldol **3** as its silyl ether **6** resulted in low yields due to the formation of side products. Thus, we decided to reduce **3** in situ with sodium borohydride (MeOH/DMF, 0 °C to rt) in order to obtain diol **4** which could be readily oxidized to aldehyde **6** (Swern oxidation) after a selective protection/deprotection sequence (TBSOTf, 2,6-lutidine; PPTS, EtOH).[7] A Barbier type addition of prenyl bromide onto **6**, in the presence of zinc dust, followed by Dess–Martin oxidation furnished ketone **7** in 81% yield. A Lemieux–Johnson oxidative cleavage of the olefin quantitatively yielded aldehyde **8**, which was converted into the corresponding α,β-unsaturated ester **9** via a Horner–Wadsworth–Emmons olefination (E/Z > 95:5, 85% yield). Finally, treatment of the unsaturated ester with potassium trimethylsilanolate enabled the cleavage of the methyl ester, delivering the requisite carboxylic acid **10** in 97% yield, thereby affording the C57–C65 subunit with an overall yield of 22.8% from isobutyraldehyde (Scheme 2).

We next turned our attention to the preparation of the C44–C50 fragment **C**, compound **17**. The synthesis started with the alkylation of methylacetoacetate **11** with the known iodide **12**[8] (readily obtained from (*S*)-Roche ester) providing the corresponding β-keto ester **13** required for the ruthenium-catalyzed asymmetric hydrogenation step[9] (Scheme 3).

Scheme 3. Synthesis of the C44–C50 Subunit 17



The stereoselective reduction of the ketone function was carried out using the chiral complex [Ru((*R*)-SYNPHOS)-Br_2][10] prepared in situ from [Ru(COD)(2-methylallyl)$_2$] according to the procedure disclosed in one of our laboratories[11] and delivered **14** as a single diastereomer in excellent yield (dr > 99:1). After conversion of the newly formed hydroxyl function into a TBS ether, deprotection of the primary alcohol (H_2, Pd/C, THF, rt) and subsequent oxidation with Dess–Martin periodinane furnished aldehyde **17** corresponding to the C44–C50 subunit (Scheme 3).

With subunits **A** and **C** in hand, we next focused on the preparation of subunit **B**. The synthesis began with ruthenium-catalyzed asymmetric hydrogenation through dynamic kinetic resolution of the racemic α-amino-β-keto ester hydrochloride[12] **18**[12b,c] (Scheme 4). The reaction was conducted in CH_2Cl_2/MeOH at 50 °C under 13 bar of H_2 in the presence of 1 mol % of $[[RuCl((R)\text{-SYNPHOS})]_2(\mu\text{-}Cl)_3]^-[Me_2NH_2]^+$ complex,[13] and after protection as a *N*-*tert*-butyl carbamate, the *N*-protected *anti*-amino alcohol (2*R*,3*R*)-**19** was isolated in high diastereo- and enantioselectivities (de = 97%, ee = 98%). Conversion of the hydroxyl into a TBS ether followed by reduction of the ester group to the corresponding aldehyde furnished **21**, which was subjected to a Marshall reaction.[14] Accordingly, addition onto **21** of a chiral allenylzinc reagent prepared in situ by palladozincation of the (*S*)-propargylic mesylate (*S*)-**22**[15] delivered alcohol **23** with a good diastereoselectivity in favor of the *anti,syn,anti*-isomer (dr = 87:13). The two diastereomers were separated by flash chromatography on silica gel. At this point of the synthesis, we needed to convert the alkynyl moiety into the corresponding (*E*)-trisubstituted alkenylsilane which would be iododesilylated at a later stage, after formation of the amide with subunit C57–C65 **A**. Consequently, compound **23** was subjected to a silylcupration[16] at −78 °C in the presence of the in situ generated bis(dimethylphenylsilyl)copper–lithium which produced the corresponding vinylsilane **24** in 85% yield with complete regio- and stereoselectivities (E/Z > 99:1). Interestingly, when the reaction was carried out at 0 °C, the related oxazolidinone **25** was obtained as the sole product in 73% yield. Iododesilylation of **25** furnished crystalline vinyl iodide **26**, the structure of which was unambiguously confirmed by X-ray crystallographic analysis. Having in hand a properly

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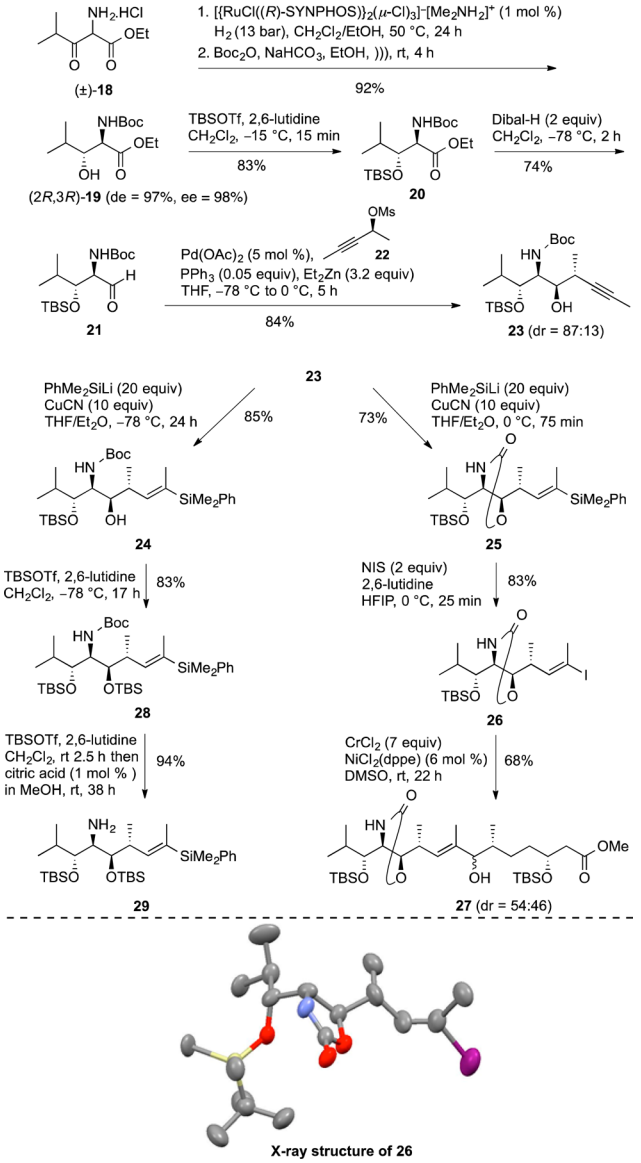
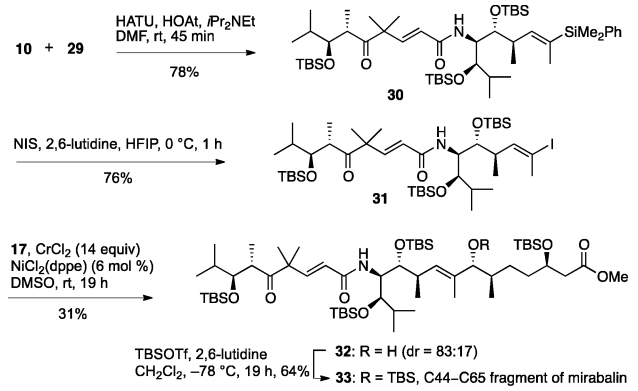
Scheme 4. Synthesis of the C51−C73 Subunit 29



Scheme 5. Completion of the C44−C65 Fragment 33



protected vinyl iodide, we decided to subject **26** to a Nozaki−Hiyama−Kishi reaction with aldehyde **17**. The reaction pleasingly afforded the corresponding alcohol **27** as a mixture of diastereomers (dr = 54:46) in 68% yield. Unfortunately, attempts at cleaving the oxazolidinone failed to deliver the requisite free amine required for the amidation with carboxylic acid **10**. Nevertheless, starting from compound **24**, TBS protection of the hydroxy group and cleavage of the *N*-Boc group readily afforded the targeted C51−C73 subunit **29**.

With subunits C51−C73 and C57−C65 in hand, we then examined the coupling reaction between **10** and **29** to form the amide bond (Scheme 5). Although a variety of conditions are available for this transformation,[17] HATU, HOAt, and iPr$_2$NEt were used and allowed the formation of the expected amide **30** in 80% yield. Subsequent iododesilylation with *N*-iodosuccinimide (NIS) in hexafluoroisopropyl alcohol (HFIP)[18] successfully furnished the requisite (*E*)-iodoalkene **31** with complete retention of the double bond geometry. The key Nozaki−Hiyama−Kishi reaction[19] between **31** and aldehyde **17** was then investigated. The reaction was performed in DMSO using $CrCl_2$ (14 equiv) in the presence of a catalytic amount of $NiCl_2$(dppe) (6 mol %). Under these conditions, alcohol **32** was obtained in 31% yield (quantitative yield based on the recovered starting material) as a mixture of diastereomers (dr = 83:17) which were separated by flash chromatography on silica gel.[20] Finally, the fully protected C44−C65 fragment of mirabalin, compound **33**,[21] was obtained after silylation of alcohol **32** with TBSOTf under standard conditions.

In summary, we have developed a flexible strategy toward the C44−C65 fragment of mirabalin. Our convergent and versatile approach relies on organocatalytic aldolization, ruthenium-catalyzed asymmetric hydrogenation, amidation, Marshall stereoselective allenylation, and the Nozaki−Hiyama−Kishi reaction. Most importantly, this strategy is suitable for the preparation of all the other isomers of the C44−C65 fragment of mirabalin. Further studies directed toward the preparation of the macrocyclic core of mirabalin are currently investigated in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This manuscript is dedicated to Prof. Max Malacria on the occasion of his 65th birthday.

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(20) The configuration at C50 of compound **32** (major diastereomer) was assigned by NOESY experiments; see the Supporting Information.

(21) Comparison of the NMR spectra of fragment **33** with the natural product **1** did not allow us to deduce the correct configuration on the natural product.

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