Total Synthesis Hot Paper

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Total Synthesis and Stereochemical Reassignment of Mandelalide A**

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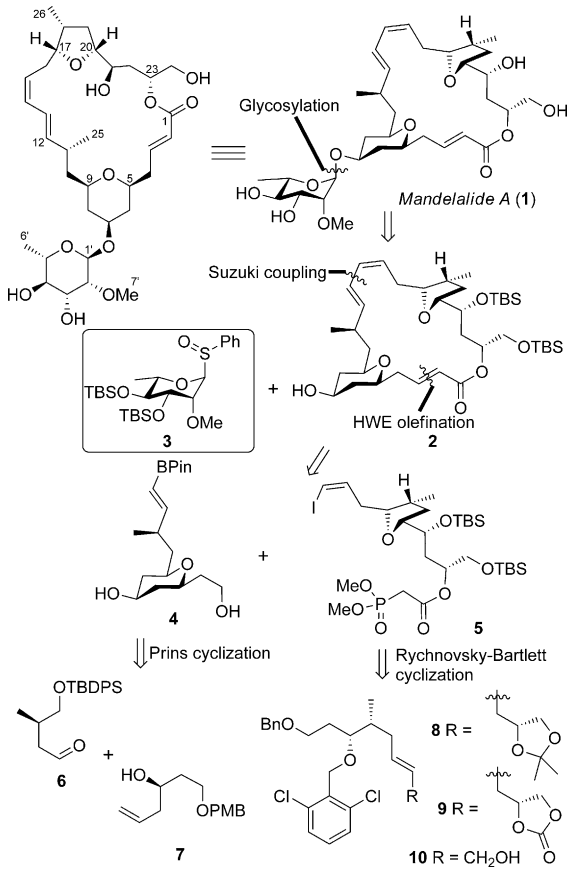
Abstract: *The total synthesis of the tunicate metabolite mandelalide A and the correction of its originally assigned stereochemistry are reported. Key features of the convergent, fully stereocontrolled route include the use of a Prins cyclization for the diastereoselective construction of the tetrahydropyran subunit, Rychnovsky–Bartlett cyclization for the preparation of the tetrahydrofuran moiety, Suzuki coupling, Horner–Wadsworth–Emmons macrocyclization, and glycosylation to append the* L*-rhamnose-derived pyranoside.*

Mandelalide A (**1**) is an extraordinary glycosylated macrolide that was recently isolated from a new species of *Lissoclinum* ascidian, collected from Algoa Bay, South Africa.[1] The assignment of the relative configuration was accomplished by considering the homonuclear and heteronuclear coupling constants in tandem with ROESY data. The absolute configuration of mandelalide A was assigned through chiral GC-MS analysis of the hydrolyzed monosaccharide and correlation with ROESY data.[1] Intriguing structural features of mandelalide A include a 24-membered α,β-unsaturated macrolactone, which entails a conjugated diene, a trisubstituted tetrahydrofuran (THF) moiety, and a trisubstituted tetrahydropyran (THP) fragment appended with an unusual carbohydrate unit, 2-*O*-methyl-α-L-rhamnose. Furthermore, a total of nine stereogenic centers are present in the carbon backbone of mandelalide A. Mandelalide A exhibited potent cytotoxicity to human NCI-H460 lung cancer cells (IC_{50}: 12 nM) and mouse Neuro-2A neuroblastoma cells (IC_{50}: 29 nM).[1] We have been engaged in a program devoted to the total synthesis of biologically active marine natural products.[2] Herein, we disclose the total synthesis of mandelalide A and the resulting reassignment of the stereochemical configuration of the natural product.

Our retrosynthetic analysis of mandelalide A **1** is shown in Scheme 1. It is envisaged that a late-stage glycosylation[3] of



Scheme 1. Retrosynthetic analysis of mandelalide A (**1**).

the aglycone fragment **2** with the L-rhamnose-derived thioglycosyl donor **3** would produce the natural product in its protected form. Careful inspection of the complete aglycone framework reveals that the 24-membered macrocycle could be assembled from two subunits, that is **4** and **5**, of comparable complexity through Suzuki coupling and Horner–Wadsworth–Emmons (HWE) macrocyclization.[4] Fragment **5**, which entails the tetrahydrofuran motif, could be accessed through a Rychnovsky–Bartlett cyclization[5] of a suitable alkene (**8**, **9**, or **10**). Subunit **4**, which contains the tetrahydropyran ring, would arise from Prins cyclization[6] of aldehyde **6** and alcohol **7**.

The synthesis of fragment **5** commenced from the known homoallylic alcohol **11**.[7] As shown in Scheme 2, homoallylic alcohol **11** was protected as its 2,6-dichlorobenzyl ether, and

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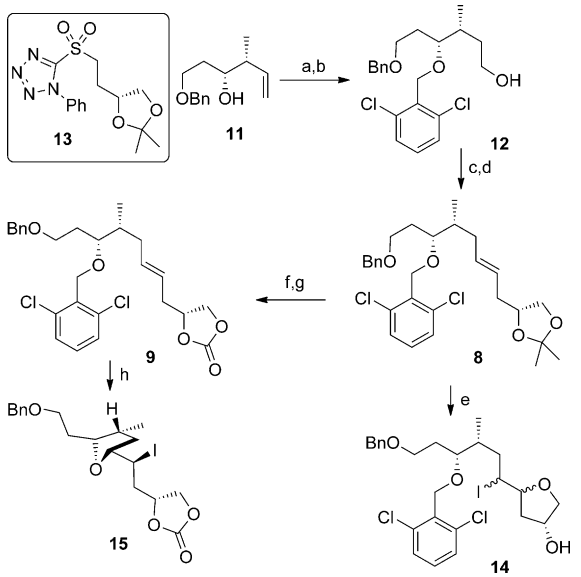
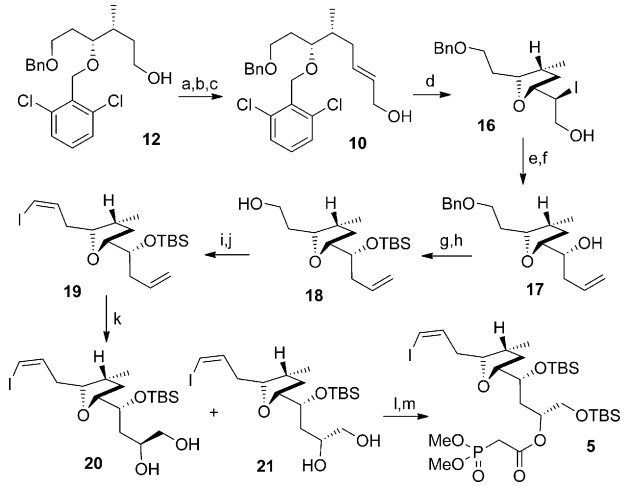


Scheme 2. Rychnovsky–Bartlett cyclization of **8** and **9**. a) NaH, 2,6-dichlorobenzyl bromide, Bu_4NI, THF, 0 °C→RT, 94 %; b) 9-BBN, 0 °C→RT; then NaOH, H_2O_2, reflux, 96 %; c) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C→RT, 98 %; d) **13**, KHMDS, DME, −78 °C, 90 %; e) I_2, CH_3CN, 0 °C→RT, 61 %; f) CSA, MeOH, RT, 91 %; g) diethyl carbonate, K_2CO_3, 80 °C, 95 %; h) I_2, CH_3CN, 0 °C→RT, 95 %. 9-BBN = 9-borabicyclo-[3.3.1]nonane, CSA = camphorsulfonic acid, DME = dimethoxyethane, DMP = Dess–Martin periodinane; KHMDS = potassium bis(trimethylsilyl)amide.

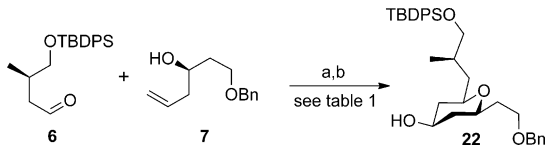


Scheme 3. Synthesis of subunit **5**. a) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C→RT; b) LiCl, trimethyl phosphonoacetate, DIPEA, CH_3CN, RT, 95 %; c) DIBAL-H, THF, −78 °C→−40 °C, 98 %; d) I_2, CH_3CN, 0 °C→RT, 94 %; e) K_2CO_3, MeOH, RT, 84 %; f) CuI, vinylmagnesium bromide, THF, −78 °C→−20 °C, 95 %; g) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C→−30 °C, 98 %; h) DDQ, CH_2Cl_2, RT, 89 %; i) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C→RT, 96 %; j) $[ICH_2PPh_3]I$, NaHMDS, HMPA, THF, −78 °C, 82 %; k) AD-mix-α, *t*BuOH/H_2O, 0 °C, **20**/**21** = 1:2, 82 %; l) TBSCl, imidazole, DMAP, CH_2Cl_2, RT, 96 %; m) dimethylphosphonoacetic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N; then DMAP, toluene, 0 °C→RT, 92 %. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride, DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, HMPA = hexamethylphosphoramide, NaHMDS = sodium bis(trimethylsilyl)amine, TBSCl = *tert*-butyldimethylsilyl chloride, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, THF = tetrahydrofuran.

the terminal alkene was subjected to hydroboration with 9-BBN to afford the corresponding primary alcohol **12** in 90 % yield. Dess–Martin oxidation of alcohol **12** afforded the corresponding aldehyde, which was then coupled with chiral sulfone **13**[8] through a Kocieński–Julia olefination[9] to give **8** in 88 % yield. Unfortunately, Rychnovsky–Bartlett cyclization[5] of alkene **8** led to the undesired 2,4-disubstituted tetrahydrofuran **14** as the major product (61 % yield), which is formed through iodoetherification of the acetonide moiety.[10] Removal of the acetonide moiety in **8**, followed by re-protection of the resulting diol gave rise to cyclic carbonate **9** in 86 % yield. When **9** was submitted to the conditions for a Rychnovsky–Bartlett cyclization, the expected tetrahydrofuran **15** was obtained in 95 % yield. However, attempts to convert this iodide into the corresponding alcohol ($AgCO_2CF_3$, DME, then H_2O) met with failure.[11]

Bearing in mind the problems encountered with precursors **8** and **9**, we embarked on the ultimately successful route towards the construction of tetrahydrofuran **5** (Scheme 3). Alcohol **12** was homologated into allylic alcohol **10** in 91 % yield by a three-step sequence that included Dess–Martin oxidation, Horner–Wadsworth–Emmons olefination, and reduction of the resulting α,β-unsaturated ester with DIBAL-H. 2,5-Dichlorobenzyl ether **10** was treated with iodine in acetonitrile at low temperature to afford the desired 2,5-*cis*-disubstituted tetrahydrofuran **16** as the sole stereoisomer in 94 % yield. Tetrahydrofuran **16** was then converted into allylic alcohol **17** in 80 % yield by a two-step sequence, namely base-promoted epoxide formation followed by nucleophilic opening of the resulting epoxide with vinylmagnesium bromide in the presence of catalytic amounts of CuI. The secondary alcohol of **17** was protected as its TBS ether, and the benzyl ether was cleaved according to the procedure of Mori and co-workers[12] to afford alcohol **18** in 89 % yield. Dess–Martin oxidation of alcohol **18** afforded the corresponding aldehyde, which was converted into the requisite (*Z*)-vinyl iodide **19** in 82 % yield according to the Wittig–Stork–Zhao olefination protocol.[13] A selective dihydroxylation of the terminal olefin of **19** using the Sharpless AD-mix-α reagent[14] provided diol **21** (55 % yield) together with its minor diastereoisomer **20** (27 % yield).[15] The primary alcohol of **21** was protected as its TBS ether, and the secondary alcohol was condensed with dimethylphosphonoacetic acid under the Yamaguchi conditions[16] to produce phosphonate **5** in 88 % yield.

We next explored an intermolecular Prins cyclization for the construction of the tetrahydropyran subunit **4** (Scheme 4).



Scheme 4. Prins cyclization of aldehyde **6** and homoallylic alcohol **7**. a) TFA, pentane, −5 °C; b) K_2CO_3, MeOH, RT, 54 % over 2 steps. TFA = trifluoroacetic acid.

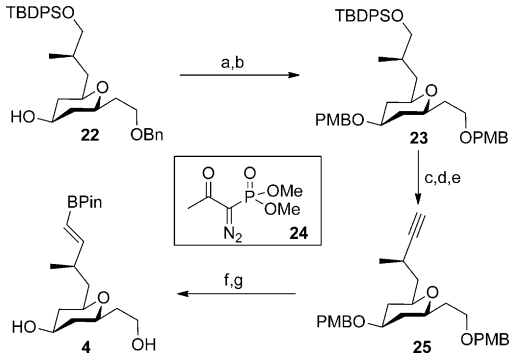
Condensation of aldehyde **6**[17] with homoallylic alcohol **7**[18] in the presence of trifluoroacetic acid induced the Prins cyclization[6] and afforded the corresponding tetrahydropyranyl trifluoroacetate, which was not isolated, but immediately treated with potassium carbonate in methanol to give rise to tetrahydropyran **22** in good yield. As shown in Table 1, lowering the reaction temperature to −20 °C led to a decrease in reactivity, and prolonged reaction times resulted in disappointingly low diastereoselectivity (entry 2).[19] Under the optimized conditions (entry 4; TFA, pentane, −5 °C, 1 h), **22** was obtained in 54 % yield with a diastereomeric ratio of 7:1.

Table 1: Prins cyclization of aldehyde **6** and homoallylic alcohol **7**.

Entry	*t* [h]	Solvent	*T* [°C]	d.r.[a]	Yield [%]
1	3	CH_2Cl_2	0	5:1	44
2	24	CH_2Cl_2	−20	1:1	41
3	1	CH_2Cl_2	−5	6:1	42
4	1	pentane	−5	7:1	54

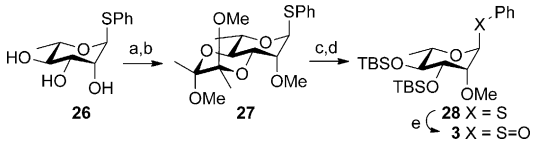
[a] d.r. determined by NMR analysis.

The synthesis of vinyl boronate **4** commenced with hydrogenolysis of the benzyl ether in **22** to afford the corresponding diol, which was re-protected as the bis-PMB-protected ether **23** (Scheme 5). The fully protected tetrahydropyran **23** was converted into terminal alkyne **25** in 89 % yield through a three-step sequence that involved TBAF-mediated desilylation, Dess–Martin oxidation, and subsequent homologation of the resulting aldehyde with the Ohira–Bestmann reagent (**24**).[20] Dicyclohexylborane-mediated hydroboration of terminal alkyne **25** with pinacolborane[21] gave rise to the corresponding (*E*)-1-alkenylboronic acid pinacol ester, which was treated with DDQ in dichloromethane/ buffer solution (pH 7.1) to provide fragment **4** in 68 % yield over two steps.



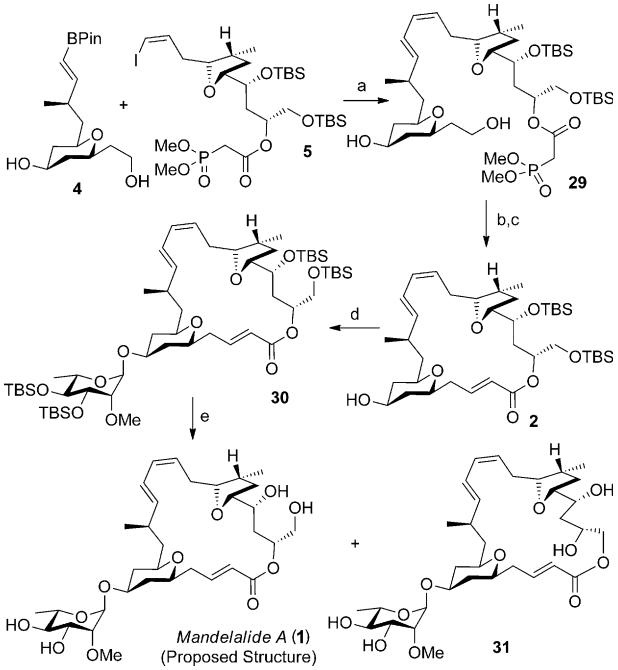
Scheme 5. Synthesis of vinyl boronate **4**. a) Pd/C, H_2, MeOH, RT, 97 %; b) NaH, PMBBr, Bu_4NI, THF, 0 °C→RT, 97 %; c) TBAF, THF, RT, 97 %; d) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C→RT, 98 %; e) **24**, K_2CO_3, MeOH/THF, 0 °C, 94 %; f) pinacolborane, dicyclohexylborane, THF, 0 °C→RT; g) DDQ, CH_2Cl_2/buffer (pH 7), RT, 68 % over 2 steps. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, PMBBr = *p*-methoxybenzyl bromide.

The synthesis of glycosyl donor **3** began with the selective protection of known phenyl-1-thio-α-L-rhamnopyranoside (**26**)[22] as its bis-acetal **27** (Scheme 6).[23] The remaining hydroxy group was immediately methylated (NaH, MeI) to afford the corresponding methyl ether in 88 % yield.[24] Removal of the bis-acetal (TFA, CH_2Cl_2/H_2O) followed by re-protection of the resulting diol afforded the bis-TBS ether **28**, which was then submitted to a *m*-CPBA oxidation to afford sulfoxide **3** in 90 % yield.[25]



Scheme 6. Synthesis of glycosyl donor **3**. a) trimethyl orthoformate, 2,2,3,3-tetramethoxybutane, CSA, MeOH, reflux, 98 %; b) NaH, MeI, DMF, 0 °C→RT, 88 %; c) TFA, CH_2Cl_2/H_2O, 0 °C→RT, 97 %; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95 %; e) *m*-CPBA, CH_2Cl_2, −78 °C, 90 %. *m*-CPBA = *meta*-chloroperoxybenzoic acid.

Our fragment assembly started with Suzuki reaction of vinyl boronate **4** with vinyl iodide **5**, which proceeded smoothly to give the desired diene **29** in 88 % yield (Scheme 7). The primary hydroxy group was selectively oxidized using the Piancatelli protocol[26] to provide the macrocyclization precursor, which was then subjected to an intramolecular HWE reaction under Roush–Masamune conditions[27] to afford aglycone fragment **2** in 44 % yield over two steps. Coupling of **2** and **3** by a Kahne glycosylation[25] through sulfoxide activation[28] furnished **30** in 66 % yield as a single diastereomer. Global desilylation of **30** using tris(dimethyla-



Scheme 7. Synthesis of proposed mandelalide A (**1**). a) $[Pd(PPh_3)_4]$, Ag_2O, THF/H_2O, RT, 88 %; b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, RT; c) LiCl, DIPEA, CH_3CN, RT, 44 % over 2 steps; d) **3**, M.S. (4 Å), DTBMP, Tf_2O, −78 °C→−35 °C, 66 %; e) TASF, DMF/THF, 0 °C. (**1**: 43 % yield; **31**: 9 % yield). DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, TASF = tris(dimethylamino)sulfur (trimethylsilyl)difluoride, M.S. = molecular sieves, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.

mino)sulfur (trimethylsilyl)difluoride (TASF) provided the targeted product **1** (43% yield)[29] along with the isomer obtained through macrolide ring expansion **31** (9% yield). Unfortunately, neither the ^{1}H nor the ^{13}C NMR spectra of **1** were identical with those reported for natural mandelalide A,[1] which suggested that the reported structure (i.e., **1**) must be incorrect.[30] As shown in Figure 1, the ^{13}C NMR chemical shifts of the carbohydrate unit of **1** matched closely

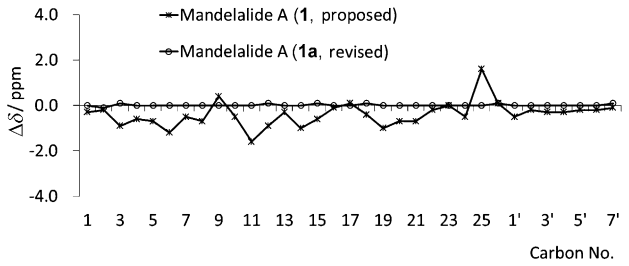


Figure 1. Differences in the ^{13}C NMR chemical shifts between natural mandelalide A and synthetic samples.

with the values reported for the natural product. However, there were obvious discrepancies between the chemical shifts in the regions of the tetrahydrofuran and tetrahydropyran subunits; in particular, the observed ^{13}C NMR chemical shifts for the C11 stereogenic center and its appended methyl substituent (C25) significantly deviated from those for the natural product.

Having established that the published structure was incorrect, we wished to elucidate the correct structure of mandelalide A. The actual structure of mandelalide A appeared to be epimeric to the proposed structure (**1**) at one or more stereogenic centers in the ring system. As the relative stereochemistry of **1** was assigned by considering homonuclear and heteronuclear coupling constants in tandem with ROESY data measured on a macrolide possessing considerable flexibility, an error in the relative stereochemistry between the tetrahydrofuran subunit and the tetrahydropyran fragment seemed most likely. As shown in Figure 2, mandelalide A shares several structural features with the scarce marine sponge metabolite madeirolide A.[31] A comparison of the structure proposed for mandelalide A (**1**) with that of madeirolide A (**32**) reveals a critical difference in the proposed relative stereochemistry between the tetrahydrofuran moiety and the tetrahydropyran fragment of the molecule. The methyl-substituted stereogenic centers and the tetrahydropyran rings of mandelalide A and madeirolide A have the same absolute configuration, whereas the tetrahydrofuran moieties are enantiomeric. On the basis of the original data in conjunction with our synthetic efforts and biosynthetic considerations, we postulated that the correct structure of mandelalide A was a diastereomer of **1** for which the whole tetrahydrofuran moiety had been inverted. As the configuration of the C23 stereogenic center could be ambiguous, we chose to synthesize both the C23-(*S*) and C23-(*R*) epimers of mandelalide A with an inverted tetrahydrofuran moiety (**1a** and **1b**; Figure 2). Given our convergent approach, testing this hypothesis was straightforward.

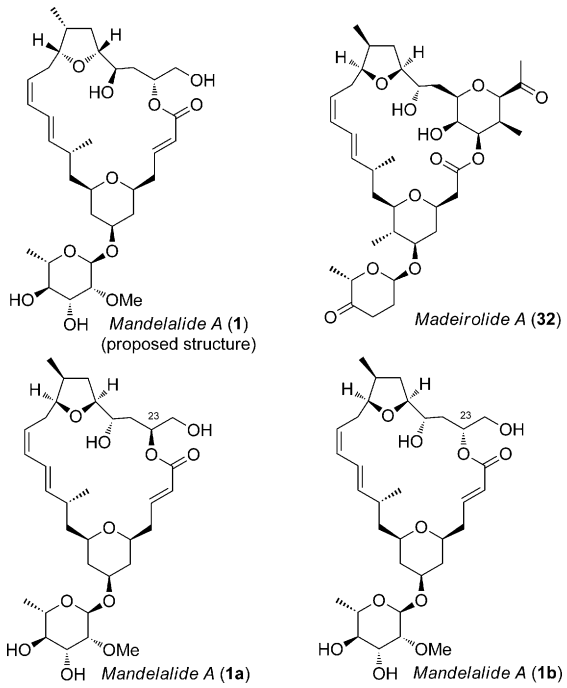
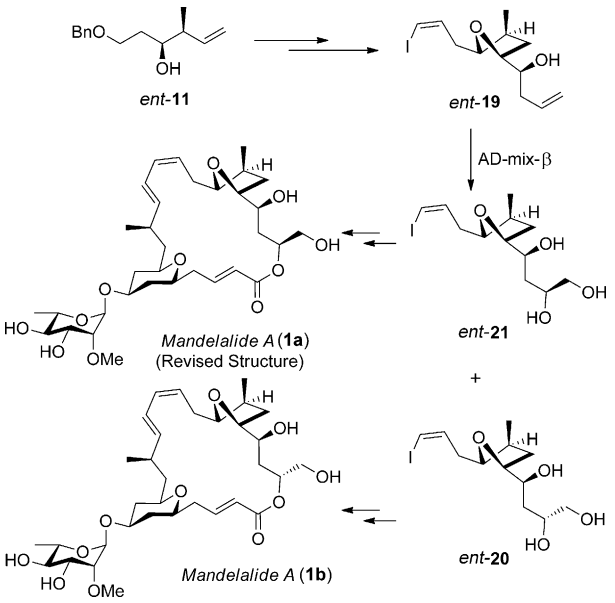


Figure 2. Structures of proposed mandelalide A (**1**), madeirolide A (**32**), and the two diastereomers **1a** and **1b**.

With many building blocks already in hand, the next step was to prepare a batch of *ent*-**11**, and this was readily achieved by following the same synthetic procedure as for **11**, but using the enantiomer of the previously employed crotylation agent. As shown in Scheme 8, *ent*-**11** was transformed into *ent*-**19** by following the same synthetic procedure as for **19**. A selective dihydroxylation of the terminal olefin of *ent*-**19** using the Sharpless AD-mix-β reagent[14] provided the desired diol *ent*-**21** together with its minor diastereoisomer *ent*-**20**.[15] Further elaboration of *ent*-**21** and *ent*-**20** into **1a** and **1b** included the



Scheme 8. Synthesis of revised mandelalide **1a** and its C23 epimer **1b**.

incorporating of vinyl boronate **4** under the previously described conditions, through Suzuki coupling, HWE macrocyclization, and glycosylation. These were readily achieved, and **1a** and **1b** were obtained in 5.2% and 1.9% overall yield starting from *ent*-**11**, respectively. Unlike the proposed structure of mandelalide A (**1**), which readily underwent ring expansion to afford **31**, both **1a** and **1b** were found to be stable under the desilylation conditions. Gratifyingly, ^{1}H, ^{13}C, and mass spectra of **1a** were found to be completely identical to those of natural mandelalide A, which led us to the conclusion that **1a** indeed corresponds to the actual stereochemistry of mandelalide A. Interestingly, the optical rotation value of our synthetic sample [**1a**; $[\alpha]_D^{20}=-34.6$ ($c=0.25$, MeOH)] is higher than that reported for the natural material [$[\alpha]_D^{23}=-9$ ($c=0.25$, MeOH)].[1] The reason for the low optical rotation value for the natural mandelalide A is unclear at present, although it might be attributed to contamination by a small amount of a highly optically active impurity in the natural sample.

An initial cytotoxicity evaluation of the synthetic mandelalide A and its diastereomers (including one aglycone) was performed across a panel of ten cancer cell lines of different histological origins.[32] These studies revealed no significant cytotoxicities for the tested synthetic mandelalide A or its analogues. It should be noted that the related structural analogue madeirolide A, which was isolated by Winder and Wright, also exhibited very minimal inhibition of proliferation against the AsPC-1 and PANC-1 pancreatic cancer cell lines at 10 $\mu g\,mL^{-1}$.[31a]

In summary, we have achieved the total synthesis of the proposed and revised structures of mandelalide A (**1** and **1a**) along with two analogues (**31** and **1b**), which enabled us to revise the structure that was originally proposed for natural mandelalide A. The convergent approach features a highly diastereoselective Prins cyclization for the construction of the tetrahydropyran subunit and Rychnovsky–Bartlett cyclization for the preparation of the tetrahydrofuran moiety. Suzuki coupling, Horner–Wadsworth–Emmons macrocyclization, and glycosylation also served as key reactions for the total synthesis. The application of this strategy to the synthesis of mandelalide B is in progress, and the results will be reported in due course.

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Keywords: configuration determination · diastereoselectivity · marine macrolides · structure elucidation · total synthesis

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Communications

Total Synthesis

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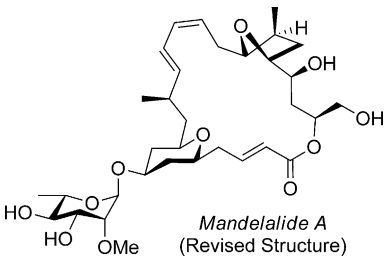
Total Synthesis and Stereochemical Reassignment of Mandelalide A



Mandelalide A
(Revised Structure)

Structural revision: A revised configurational assignment for the marine macrolide mandelalide A is proposed and validated by total synthesis. This study is one of several recent examples in a growing list of investigations that correct misassigned structures of natural products by stereocontrolled total synthesis.