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Synthesis of Proposed Aglycone of Mandelalide A

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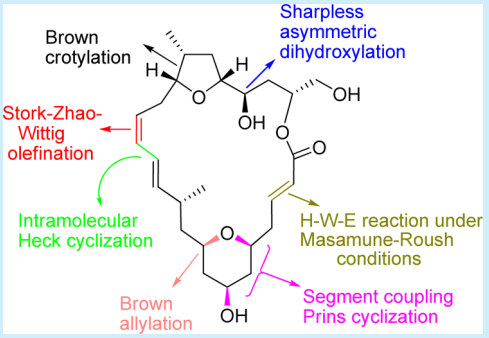
Supporting Information

ABSTRACT: A highly convergent synthesis of the proposed mandelalide A aglycone is reported. The cornerstones of the synthetic strategy include the following: *E*-selective intramolecular Heck cyclization, Masamune–Roush olefination, Stork–Zhao–Wittig olefination, modified Prins cyclization; Sharpless asymmetric dihydroxylation followed by Williamson-type etherification, Julia–Kocienski olefination, Brown crotylation, and Brown allylation reactions.



Ascidians, commonly known as sea squirts, are a vital source of marine natural products with wide ranging biological activities. Natural products isolated from sea squirts have a huge potential to become drugs, and they have already provided two important drugs in clinical use for cancer therapy.[1] In 2012, McPhail and co-workers isolated a new class of unusual glycosylated polyketide macrolides, called mandelalides A–D[2] (Figure 1), via bioassay guided fractionation of the cytotoxic

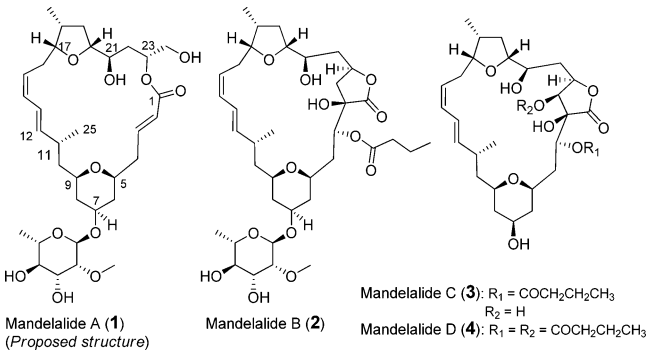


Figure 1. Mandelalides A–D.

extracts of a new Lissoclinum species from Algoa Bay, South Africa. The absolute structures were confirmed by extensive NMR, mass spectral, and GC studies.

Biological evaluation of mandelalides A and B revealed remarkably potent cytotoxic activity against cancer cell lines in human lung cancer cells (NCI-H460, IC_{50} = 12 nM, 29 nM respectively) and mouse neuroblastoma (Neuro-2A, IC_{50} = 44 nM, 84 nM respectively). This promising preliminary cytotoxicity result against two different cancer cell lines demands detailed biological evaluations of the Mandelalide family. However, such biological studies are hampered by their low natural abundance. Thus, a complex architecture and promising biological activities, along with limited availability from natural sources, impelled us to undertake a total synthesis of highly potent mandelalide A. While we were attempting to communicate our results in the form of the present manuscript, Fürstner and Willwacher[3] reported an elegant synthesis of mandelalide A, where they claimed that the structure of mandelalide A, proposed by McPhail et al., does not correspond to the originally published structure. As they observed significant ^{13}C NMR chemical shift variation particularly with respect to the C25 and C11 carbons, this prompted them to attempt a synthesis of its C11-epimer, but this also showed spectral deviation from the reported natural product, which led them to conclude more than one misassignment in the originally proposed structure of mandelalide A. This account describes the synthesis of a fully functionalized aglycone of the originally reported structure of mandelalide A.

The retrosynthetic analysis outlined in Scheme 1 shows that the disconnection of **5** would lead to the phosphonate **6** and aldehyde **7**. Assembly of the 24-membered macrocyclic core **5** would proceed through Masamune–Roush olefination between **6** and **7** at C2–C3 which would be followed by *E*-selective intramolecular Heck cyclization at C12–C13. The phosphonate **6** would be derived from aldehyde **8** via Stork–Zhao–Wittig olefination followed by acylation with diethyl phosphonoacetic acid, and **8** could be obtained from alcohol **9** by Sharpless asymmetric dihydroxylation followed by Williamson-type etherification. The aldehyde **7**, with a pyran unit, could be obtained from ester **10** by utilizing segment coupling Prins cyclization, developed by Rychnovsky and co-

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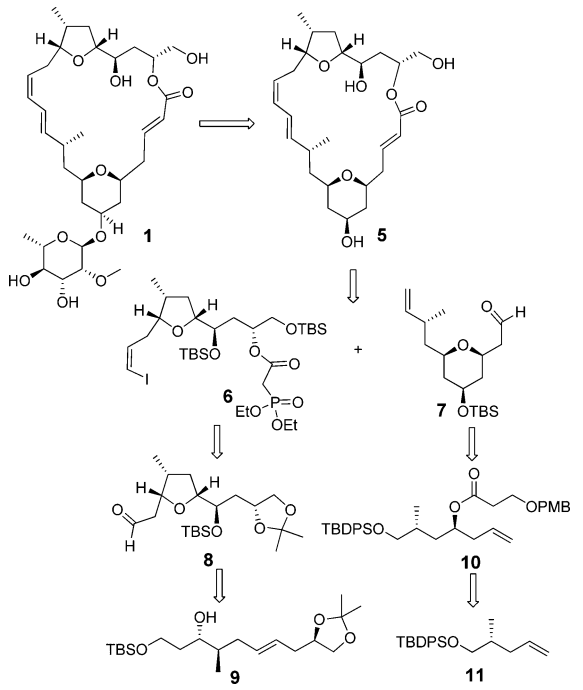
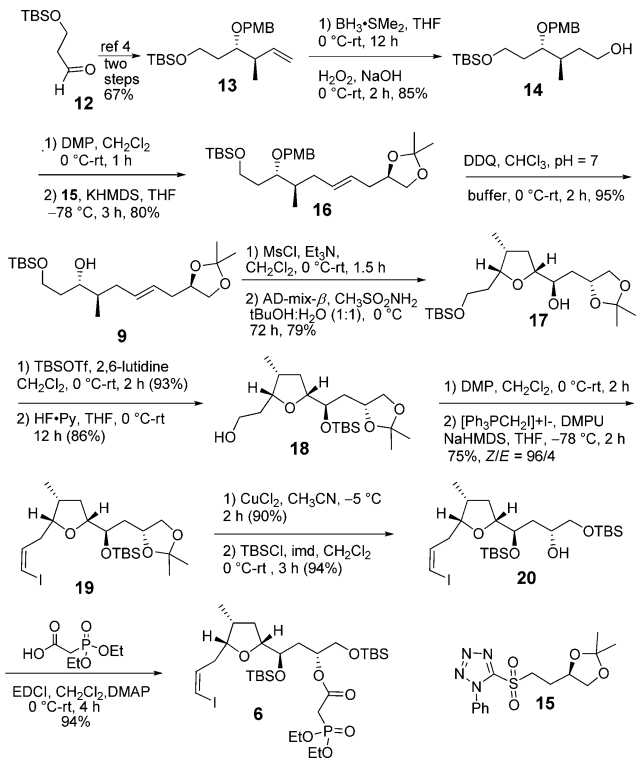
Scheme 1. Retrosynthesis of Mandelalide A Aglycone



workers. The ester **10** was expected to be prepared from alkene **11** by Brown allylation followed by acylation.

The synthesis of phosphonate **6** commenced from known compound **13**[4] (Scheme 2), which was readily obtained from **12** by Brown crotylation followed by protection of the hydroxyl group as a PMB ether. Hydroboration[5] of **13** with $BH_3{\cdot}Me_2S$ followed by oxidation gave primary alcohol **14** in 85% yield which, on Dess-Martin periodinane[6] oxidation, followed by

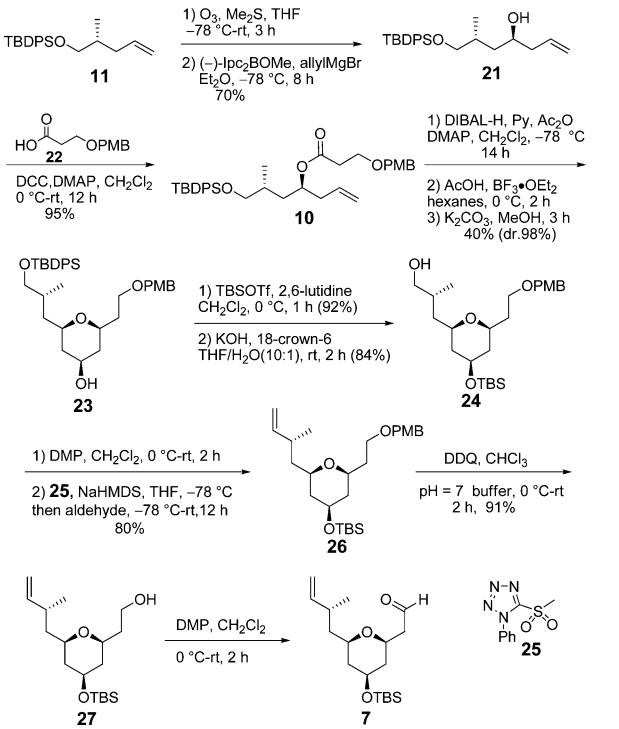
Scheme 2. Synthesis of Phosphonate Fragment 6



modified Julia-olefination[7] with the known sulfone **15**[8] afforded the chromatographically pure *E*-olefin **16** in 80% yield (two steps). Cleavage of the PMB ether with buffered DDQ[9] afforded the alcohol **9** in 95% yield. The secondary alcohol **9** was converted to its mesylate by MsCl and Et_3N, which upon Sharpless asymmetric dihydroxylation[10] with AD-mix-β afforded diol, which underwent *in situ* Williamson-type etherification[11] to provide exclusively THF alcohol **17** with excellent diastereoselectivity (79% yield, two steps). The rigorous five-membered-ring selectivity in Williamson-type etherification can be explained in terms of extended Baldwin rules[12] where the 5-*exo-tet* cyclization is favored over the 6-*exo-tet* cyclization. Alcohol **17** upon silylation with TBSOTf, followed by selective desilylation of the primary TBS with HF-Py, furnished primary alcohol **18** in 80% yield over two steps. Dess-Martin periodinane oxidation of primary alcohol **18** afforded aldehyde, which was eventually converted to terminal *Z*-vinyl iodide **19** by Stork–Zhao–Wittig olefination protocol[13] with (iodomethyl)triphenylphosphonium iodide in 75% yield (Z/E = 96:4). Selective hydrolysis of the acetonide of **19**[14] followed by chemoselective TBS protection of the primary alcohol provided **20** (84% yield, over two steps) which, upon esterification with diethyl phosphonoacetic acid under EDCI, DMAP conditions, afforded phosphonate **6** in 94% yield.

The synthesis of pyran segment **7** commenced from known compound **11**[15](Scheme 3). Ozonolysis of **11** furnished an

Scheme 3. Synthesis of Pyran Aldehyde 7



aldehyde, which was subjected to Brown asymmetric allylation[16] with (−)-Ipc_2BOMe and allyl magnesium bromide at −78 °C to give alcohol **21** in 70% yield as a single diastereomer (dr > 20:1). Acylation of **21** with acid **22** under DCC–DMAP conditions provided compound **10** in 95% yield. Careful reduction of compound **10** followed by acetyl protection of the resulting lactol gave α-acetoxy ether[17] which, on segment coupling Prins cyclization[18] with $BF_3{\cdot}OEt_2$

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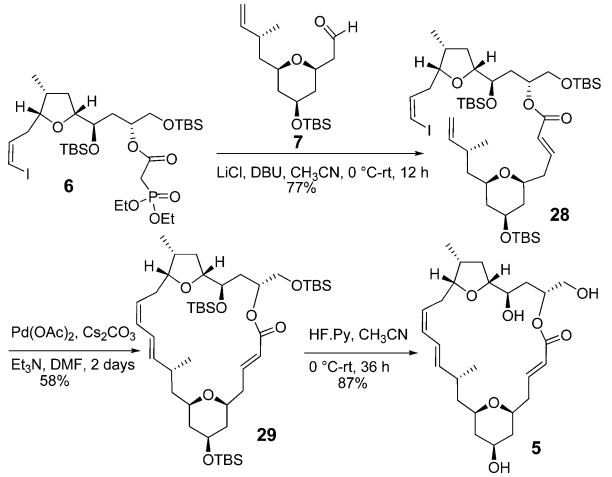
and acetic acid in hexanes at 0 °C, followed by C4-OAc deprotection of the resulting pyran ring, afforded the desired pyran alcohol **23** in 40% yield (three steps). This, upon TBS protection with TBSOTf, followed by selective deprotection of TBDPS under basic conditions,[19] furnished primary alcohol **24** in 77% yield over two steps. Alcohol **24** was oxidized with Dess-Martin periodinane to give an aldehyde which was subjected to Julia–Kocienski olefination with known sulfone **25**,[20] to give olefin **26** in 80% yield. Finally DDQ mediated PMB deprotection followed by oxidation of the resulting primary alcohol completed the synthesis of the aldehyde fragment **7**.

The end game for the construction of the aglycone is depicted in Scheme 4. The Horner–Wadsworth–Emmons

Scheme 4. Synthesis of Mandelalide A Aglycone 5



reaction under Masamune–Roush conditions[21] between **6** and **7** in the presence of LiCl and DBU in MeCN at 0 °C furnished coupled product **28** in 77% yield (two steps). This set the stage for the crucial intramolecular Heck reaction.[22] Accordingly compound **28** on treatment with $Pd(OAc)_2$ and Cs_2CO_3 in DMF furnished the cyclized compound **29** in 58% yield with the required geometry of the diene unit, which on global desilylation afforded **5** in 87% yield and thus the synthesis of aglycone with all required functionalities was completed. The spectral data of **5** (^1H and ^{13}C)[23] closely matched the data of the macrocyclic core of the structure synthesized by Fürstner.

In conclusion we have developed a convergent synthetic strategy for the synthesis of the aglycone of the proposed structure of mandelalide A in 32 total steps (18 longest linear sequence from compound **12**) with 6.3% overall yield. The strategy developed here is flexible and can be used for the synthesis of various stereochemical analogues of the proposed structure of mandelalide A for structural reassignment. Efforts toward this are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all 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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(23) A detailed comparison of ^1H and ^{13}C chemical shifts between mandelalide A (isolation), mandelalide A (synthetic), and compound **5** is available in the Supporting Information.

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