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Synthetic Access to the Mandelalide Family of Macrolides: Development of an Anion Relay Chemistry Strategy

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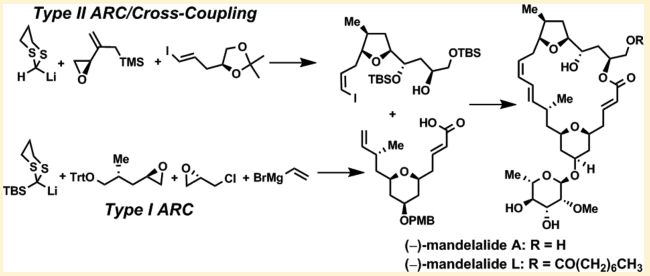
Supporting Information

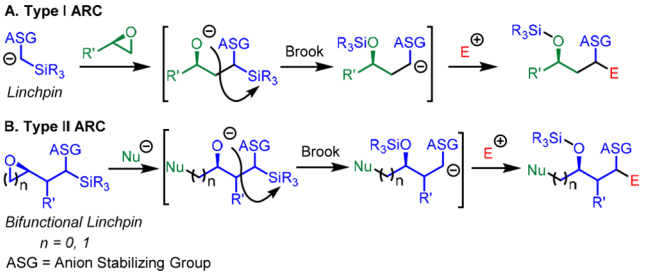
ABSTRACT: The mandelalides comprise a family of structurally complex marine macrolides that display significant cytotoxicity against several human cancer cell lines. Presented here is a full account on the development of an Anion Relay Chemistry (ARC) strategy for the total synthesis of (−)-mandelalides A and L, the two most potent members of the mandelalide family. The design and implementation of a three-component type II ARC/cross-coupling protocol and a four-component type I ARC union permits rapid access respectively to the key tetrahydrofuran and tetrahydropyran structural motifs of these natural products. Other highlights of the synthesis include an osmium-catalyzed oxidative cyclization of an allylic 1,3-diol, a mild Yamaguchi esterification to unite the northern and southern hemispheres, and a late-stage Heck macrocyclization. Synthetic mandelalides A and L displayed potent cytotoxicity against human HeLa cervical cancer cells (EC_{50}, 1.3 and 3.1 nM, respectively). This synthetic approach also provides access to several highly potent non-natural mandelalide analogs, including a biotin-tagged mandelalide probe for future biological investigation.



INTRODUCTION

The development of efficient fragment union tactics has been a hallmark of complex molecule synthesis. One such tactic, Anion Relay Chemistry (ARC), constitutes a powerful synthetic strategy that unites multiple components, in a single flask, to rapidly construct stereodefined, architecturally complex synthetic targets.[1] In a broad sense, Anion Relay Chemistry provides synthetic chemists the ability to control, in a useful fashion, the flow and reactivity of an anionic site within a growing molecule. This tactic emanated from a three-component union protocol exploiting Brook rearrangements, introduced by our laboratory for the preparation on gram scale spongistatin 1[2] and discodermolide.[3] The ARC tactic has now been extensively studied and expanded into two different types of through-space negative charge migration (Scheme 1).[4] The utility of each of these multicomponent processes has been demonstrated in the efficient construction of diverse polyketide and alkaloid natural produts[5] as well as diversity-oriented libraries comprising "natural product-like" compounds.[6] The development and application of ARC for effective construction of structurally complex molecules possessing significant biomedical properties remain a primary goal of our laboratory. Toward this end, we report here the design and implementation of an effective synthetic strategy employing *both* Type I and II ARC tactics to access members of the highly cytotoxic mandelalide class of marine natural products.[7]

Scheme 1. Through-Space Type I and Type II ARC Tactics



Marine invertebrates, such as tunicates and sponges, represent an important source of novel bioactive secondary metabolites, many of which have been developed into prescription drugs, pharmaceutical lead compounds, and molecular probes for the study of disease mechanisms.[8] Recent additions to this impressive collection of natural products are the mandelalide family of macrolides, isolated by McPhail and co-workers from the South African ascidian *Lissoclinum* species. Mandelalides A−D (**1**−**4**, Figure 1) were reported in 2012, and their structures were proposed based on extensive NMR, mass spectrometric, and GC-MS studies.[9] This series of natural products comprises an unusual polyketide scaffold that is

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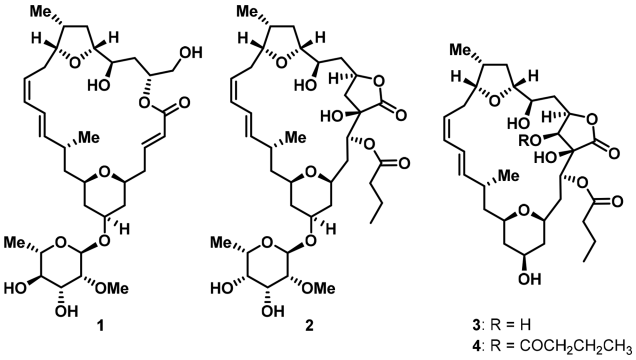

Figure 1. Proposed structures of mandelalides A–D (**1**–**4**).

characterized by a trisubstituted tetrahydrofuran moiety, a glycosylated trisubstituted tetrahydropyran ring, and a conjugated diene encased in a 24-membered macrolide framework. In addition to the intriguing architectural features, mandelalides A and B were reported by McPhail and co-workers to exhibit potent low nanomolar cytotoxicity against human NCI-H460 lung cancer cells (IC_{50}, 12 and 44 nM, respectively), thus rendering the mandelalides and analogs thereof attractive as lead structures for cancer chemotherapeutics. The minute quantities of the isolated material and the inaccessibility of the source organism however have hindered their structural and biological investigation.

Not surprisingly, the mandelalides attracted considerable interest from the synthetic community. In 2014, the Fürstner group reported the first synthetic work toward this family of cytotoxic macrolides in which they constructed the originally reported structure of (−)-mandelalide A (**1**).[10a] By comparing the spectral data of the natural product with those of the material obtained through synthesis, Fürstner revealed a structural misassignment in the originally proposed structure of **1**. The Ye group later disclosed a reassignment of the structure of (−)-mandelalide A by total synthesis (**5**, Figure 2), wherein all five stereocenters in the northern hemisphere required inversion.[11] Subsequently, Fürstner confirmed this revision by total synthesis of **5**, and in turn predicted similar revisions for mandelalides B–D (**6**–**8**, Figure 2).[10b,12] Total syntheses of the revised structure of (−)-mandelalide A (**5**) have also been reported by several research groups,[13] including our laboratory.[7]

Interestingly, inconsistent results for the cytotoxic efficacy of synthetic (−)-mandelalide A (**5**) were reported by several investigators, noting weak or disappointing biological activity against a small panel of cancer cell lines.[10b,11,13] Subsequently, recollection of the rare tunicate source by McPhail and co-workers (2013) led to additional natural congeners, mandelalides E–L (**9**–**16**, Figure 2) that facilitated further evaluation of the bioactivity of the mandelalide family.[14] The newly characterized members of the mandelalide family were classified into three different structural types (Types A–C, Figure 2), based on three different macrocyclic motifs associated with the prototype structures of mandelalides A–C. Biological evaluation of the isolated natural products together with the synthetic material supplied by our laboratory has yielded important insights into the mechanism of action and structure–activity relationship of the mandelalides and, in addition, has provided an explanation for the reported disparity with respect to biological testing of synthetic mandelalide A.[15] Results from that study demonstrated that the glycosylated

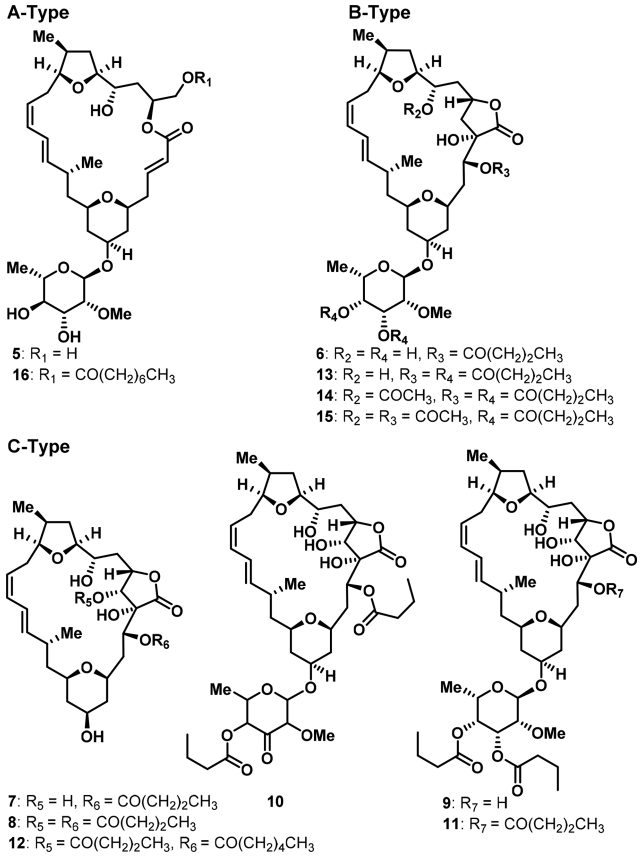

Figure 2. Revised structures of mandelalides A–D (**5**–**8**) and new mandelalides E–L (**9**–**16**).

mandelalides are effective site-specific inhibitors of mitochondrial function in living cells, and that cells with an oxidative phenotype are most sensitive to mandelalide-induced decreases in cell proliferation and viability. Notably, the synthetic work from our laboratory[7] and others[10,11,13] has illustrated the indispensable role of organic synthesis in natural products chemistry for proof of structure and to supply material for biological investigation. Herein we record a full account of our synthetic venture that exploits Anion Relay Chemistry to access the A-type members of the mandelalide family, comprising (−)-mandelalides A and L (**5** and **16**), the two most potent members of the family. Several non-natural mandelalide analogs, including a mandelalide probe with a biotinolide tag, were also constructed via this synthetic route to enable future biological studies.

RESULTS AND DISCUSSION

Retrosynthetic Analysis. Immediately after we initiated a synthetic program targeting the originally proposed structure of mandelalide A (**1**, Figure 1), Fürstner reported the synthesis of **1** and suggested the structural misassignment of mandelalide A. Noting the similarity in structure between **1** and madeirolides A and B, two marine macrolides isolated from a lithistid *Leiodermatium* sponge (**17** and **18**, Figure 3),[16,17] we decided to target structure **5**, in which the relative configurations of the five stereocenters in the northern hemisphere were inverted, as the most likely structure of mandelalide A. Indeed, our working structure for (−)-mandelalide A was later validated by Ye and co-workers.[11]

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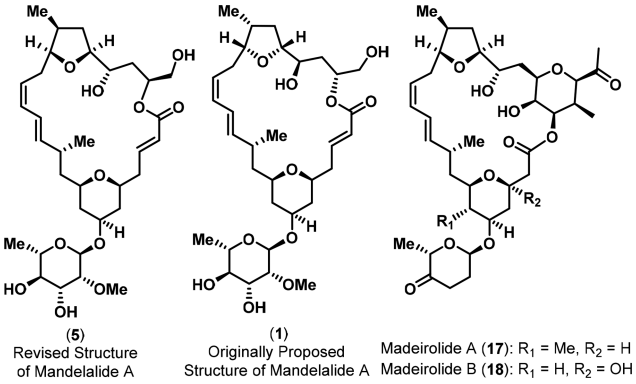
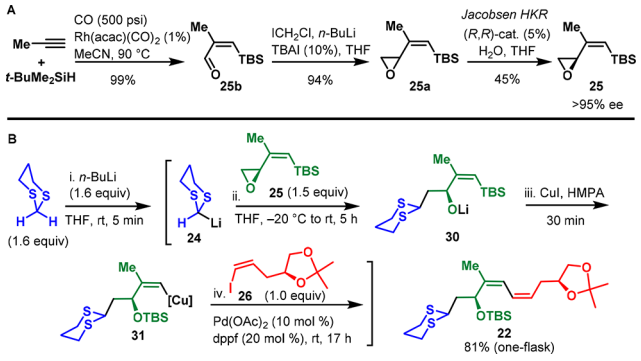


Figure 3. Similarity in structure between Mandelalide A and Madeirolides A and B.

From the retrosynthetic perspective, we envisioned construction of (−)-mandelalide A (**5**) from three subunits of comparable complexity for maximal convergency (**19**–**21**, Scheme 2). The macrocyclic aglycon of **5** would arise from advanced fragments **19** and **20**, which would be united via intermolecular esterification followed by a ring-closing Heck cross-coupling reaction tactic. Final glycosylation with the known L-rhamnose-derived thioglycosyl donor (+)-**21**[11] would then yield the natural product. The tetrahydrofuran and tetrahydropyran rings embedded in the northern and southern hemispheres in turn would be derived from advanced intermediates **22** and **23**, respectively. Importantly, Anion Relay Chemistry was envisioned to provide access to these key fragments with great stereochemical flexibility for analog development and, if needed, structural elucidation of the natural product. First, fragment **22** would emerge from a Type II ARC/cross-coupling tactic employing 2-lithio-1,3-dithiane (**24**), bifunctional linchpin **25**, and *cis*-alkenyl iodide **26**. A type I ARC reaction employing TBS dithiane **27** and epoxides **28** and **29** would give rise to fragment **23**. Given our recent integration of Anion Relay Chemistry with transition-metal-mediated transformations,[18] we reasoned that this synthetic venture could provide an excellent opportunity to showcase a first-time Type II ARC tactic in complex molecule synthesis, in which a negative charge is migrated to an sp^2-hybridized carbon center capable of undergoing a cross-coupling reaction with an electrophilic coupling partner.

Construction of the Northern Hemisphere. Synthesis of the mandelalide A northern hemisphere (**19**) began with the preparation of epoxide linchpin (−)-**25**, which was readily obtained in multigram quantity via a Rh-catalyzed silylformylation of propyne,[19] followed by epoxide formation[20] and then Jacobsen hydrolytic kinetic resolution[21] (Scheme 3A). Selective

Scheme 3. Synthesis of Linchpin 25 (A) and Application in Type II ARC/Pd Cross-Coupling (B)

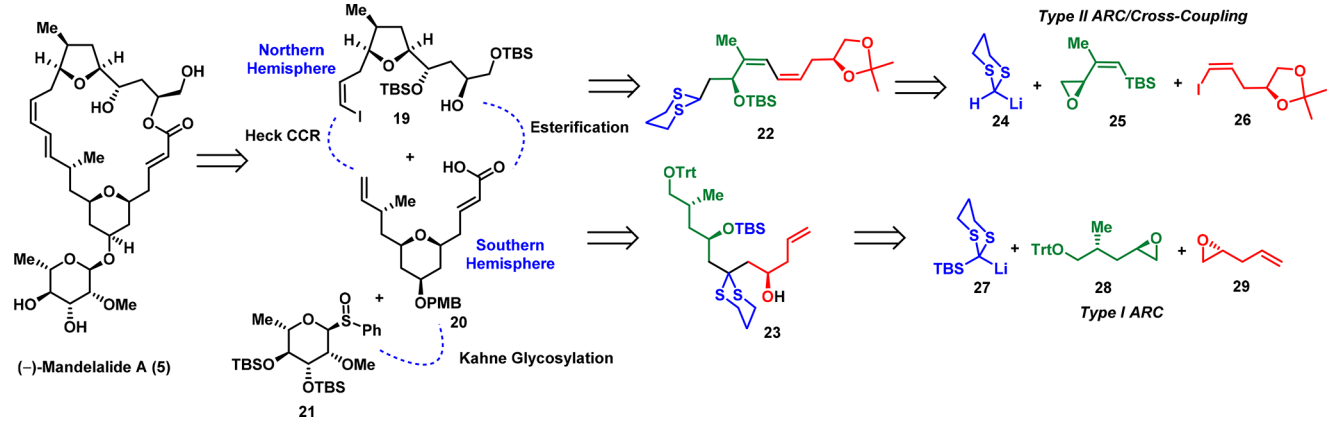


nucleophilic attack of (−)-**25** with 2-lithio-1,3-dithiane (**24**) at the least hindered site next generated alkoxide **30** (Scheme 3B). In the same flask, addition of CuI and HMPA triggered a 1,4-Brook rearrangement to form what we envisioned to be an sp^2-hybridized carbon nucleophile **31**, which readily underwent Pd-catalyzed cross-coupling reaction with the *cis*-alkenyl iodide (+)-**26**[13b] to furnish the desired tricomponent adduct (+)-**22** in 81% yield. This sequence is particularly significant, as it represents the first successful example of an ARC/Pd-catalyzed cross-coupling tactic in complex molecule synthesis.

Adduct (+)-**22** was then subjected to what we anticipated would be a chemoselective Jacobsen asymmetric epoxidation,[22] with the anticipation that the disubstituted *Z*-olefin would react selectively; subsequent alcohol deprotection and epoxide opening would then deliver **33**, possessing the furan ring system (Scheme 4). This approach, however, proved unproductive, as diene (+)-**22** quickly decomposed under the epoxidation condition. Attempts to force the five-member ring formation via selenoetherification[23] also proved unsuccessful.

After this initial setback to construct the furan ring system, we decided to revise our synthetic strategy (Scheme 5). To this end, application of the Type II ARC/Pd cross-coupling tactic to access (−)-**37** employing lithiated dithiane **24**, epoxide linchpin (−)-**25**, and now the *trans*-alkenyl iodide (+)-**36** furnished the

Scheme 2. Retrosynthetic Analysis of (−)-Mandelalide A



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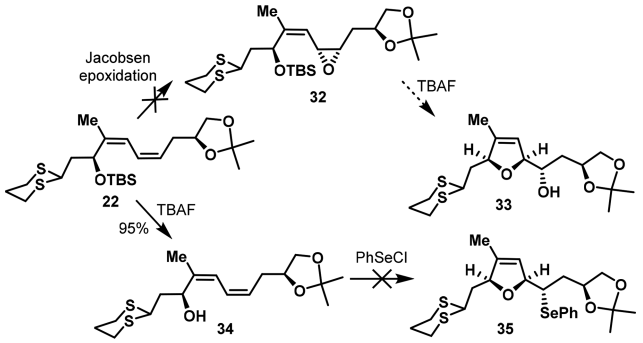
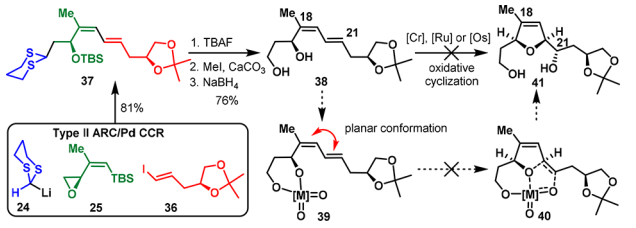
Scheme 4. Initial Strategy for Constructing the Furan Ring



Scheme 5. Revised Strategy for Constructing the Furan Ring System

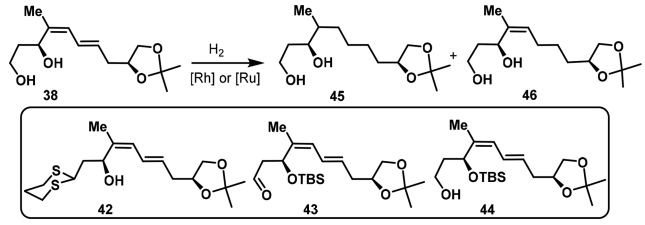


tricomponent adduct in good yield (81%). Adduct (−)-**37** in turn was subjected to alcohol deprotection, dithiane removal, and carbonyl reduction to provide diol (+)-**38** in 76% yield over the three steps.

We now envisioned exploiting the 1,3-diol to chelate to a metal catalyst, facilitating a selective, *syn*-specific oxidative cyclization on the disubstituted olefin of the diene system to generate 2,5-*cis*-dihydrofuran **41**, possessing the requisite hydroxyl group at C_{21}. A series of catalytic systems employing osmium,[24] ruthenium,[25] and chromium[26] that were previously reported to mediate oxidative cyclization of 1,2-diols onto adjacent alkenes to generate *cis*-tetrahydrofurans were screened. All attempts, however, proved unsuccessful, leading either to decomposition or to very sluggish reactions despite the use of excess metal catalysts. Several factors presumably hinder the oxidative cyclization of diol (+)-**38**, including (a) the less favorable chelate ring size of the 1,3-diol, compared to the 1,2-diol systems reported in the literature; (b) the presence of an acetonide functional group that is incompatible with the acidic conditions often required for oxidative cyclizations; and (c) the susceptibility of the allylic alcohol to undergo undesired side reactions (e.g., oxidation, racemization). The major reason however for this unproductive transformation, we reason, could be attributed to the inherent planar conformation of the conjugated diene system, which inhibits formation of the requisite transition state **40**.

One possible solution to the above problem would be to selectively hydrogenate the trisubstituted alkene of the conjugated diene, potentially by exploiting the adjacent hydroxyl group as a directing group. Alcohol **38** and several related substrates (**42**−**44**, Scheme 6) were each subjected to hydrogenation conditions employing several asymmetric ruthenium or rhodium catalysts[27] that are known to facilitate selective hydrogenation of alkenes under the influence of directing groups. All attempts toward this approach, however, also proved unproductive as the conjugated diene system remained inert to the mild conditions employed. Forcing

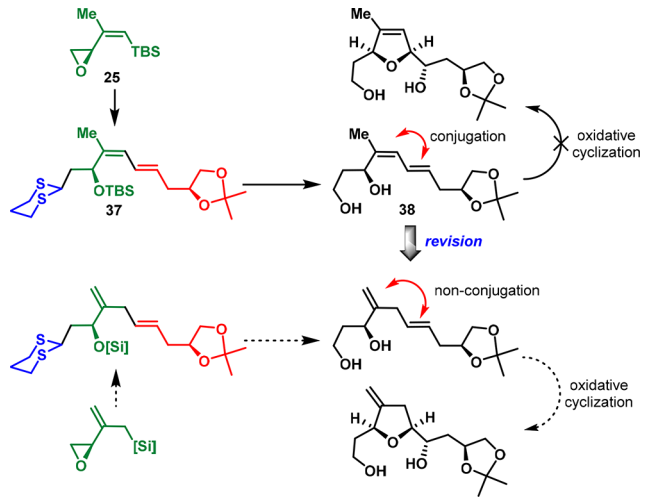
Scheme 6. Attempts at Selective Hydrogenation of Conjugated Diene



hydrogenation conditions, on the other hand, led to undesired hydrogenation of the disubstituted olefin.

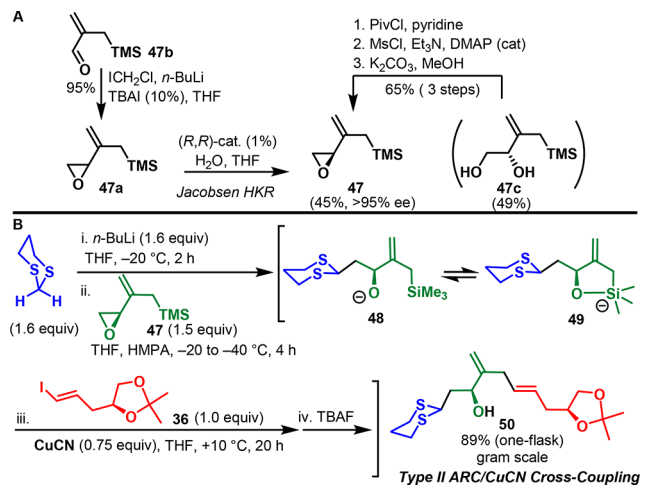
A third possible solution to the now recognized difficult cyclization would be to translocate the two double bonds in (+)-**38** to out-of-conjugation (Scheme 7). This approach

Scheme 7. Structural Modification of Linchpin



demands a structural modification of the tricomponent adduct (−)-**37**, which, given the great flexibility of the ARC protocol, pleasingly only required a simple modification of the epoxide linchpin (−)-**25**. To test this hypothesis, known epoxide **47a**[28] (Scheme 8A) possessing a terminal olefin was synthesized from

Scheme 8. Synthesis of Epoxide Linchpin 47 and Revision of the ARC Tactic



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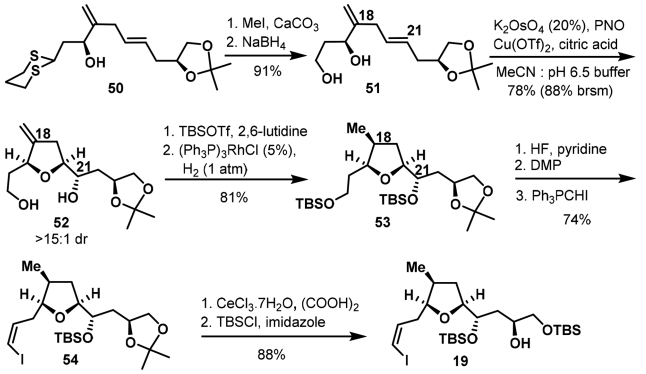
commercially available aldehyde **47b**[29] via treatment with chloromethyl lithium[20] and then subjected to Jacobsen hydrolytic kinetic resolution[21] to furnish the desired enantiomer (−)-**47**. Importantly, the diol byproduct (**47c**) from the Jacobsen resolution could also be readily converted to the desired epoxide (−)-**47** in 65% yield via a three-step reaction sequence. Pleasingly, application of the Type II ARC/cross-coupling tactic now employing 1,3-dithiane, linchpin (−)-**47**, and *trans*-alkenyl iodide (+)-**36** yielded tricomponent adduct (+)-**50** in 89% yield on gram scale, exploiting an unprecedented CuCN-mediated cross-coupling reaction (Scheme 8B).[30] Significantly, attempts to use palladium catalysis to carry out the same ARC/cross-coupling protocol failed to provide the desired adduct, demonstrating the unique utility of this CuCN-mediated cross-coupling reaction in a multicomponent union protocol (e.g., ARC). Studies to explore the generality of this reaction are ongoing in our laboratory.

Adduct (+)-**50** was then subjected to dithiane removal and carbonyl reduction to provide 1,3-diol (+)-**51** (Scheme 9), now

Scheme 9. Completion of the Northern Hemisphere

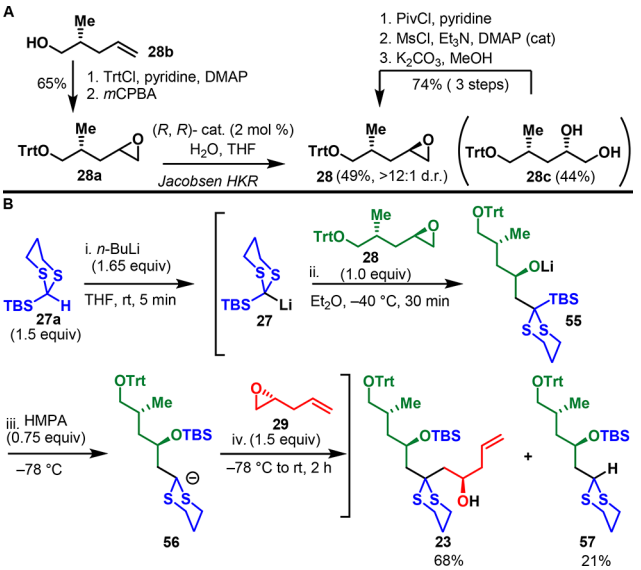


possessing a skipped diene system which, as proposed, successfully underwent an osmium-mediated oxidative cyclization[24] to provide the desired intermediate (−)-**52**. The reaction conditions for this transformation were optimized by screening solvents, acids, oxidants, temperatures, substrate concentrations, and additives.[31] Under the optimal conditions comprising pyridine *N*-oxide (PNO) as the reoxidant in combination with citric acid and $Cu(OTf)_2$ in a MeCN/pH 6.5 phosphate buffer solvent mixture, (+)-**51** was converted to (−)-**52** in good yield with excellent stereoselectivity (88% brsm, >15:1 dr). To the best of our knowledge, this is the first reported example of a transition-metal-mediated oxidative cyclization of an allylic 1,3-diol, a difficult substrate due to both the unfavorable ring size for chelation and a variety of possible side reactions. Compound (−)-**52** was then subjected to protection of the diol with TBSCl, followed by stereoselective hydrogenation with Wilkinson's catalyst to install the desired stereocenter at C_{18} in 81% yield for the two steps.

Advanced intermediate (−)-**53** was then subjected to selective desilylation of the primary alcohol, Dess-Martin periodinane oxidation, and Stork−Zhao olefination[32] to furnish (−)-**54** in 74% yield for the three steps. Final selective removal of the acetonide with $CeCl_3$-oxalic acid[33] and protection of the primary alcohol as a TBS ether then afforded the desired northern hemisphere (−)-**19**.

Construction of the Southern Hemisphere. Synthesis of the mandelalide A southern hemisphere (**20**) began with the preparation of known epoxide (+)-**28**[34] (Scheme 10A), which was readily obtained in multigram quantities from known

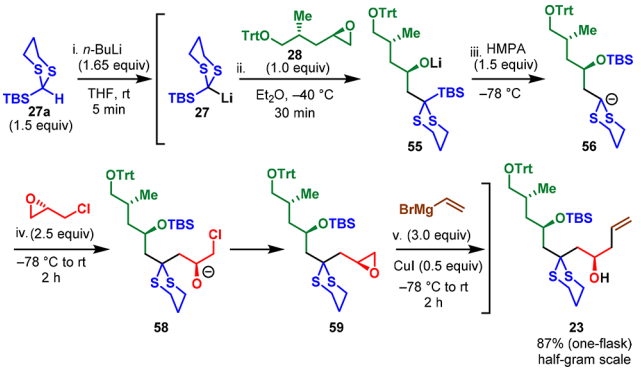
Scheme 10. Synthesis of Epoxide 28 (A) and Application of Three-Component Type I ARC (B)



alcohol (+)-**28b**[35] via *m*-CPBA epoxidation of the corresponding trityl ether, followed by Jacobsen hydrolytic kinetic resolution.[21] The diol byproduct **28c** could also be readily converted to the desired epoxide (+)-**28** in 73% yield via a three-step reaction sequence. Nucleophilic attack of (+)-**28** with 2-lithio-2-TBS-1,3-dithiane (**27**; Scheme 10B), followed by a HMPA-triggered Brook rearrangement, then generated what we envision to be a carbon nucleophile at the 2-position of the dithiane (**56**), which in turn was trapped in the same flask with epoxide (+)-**29**[36] to furnish the desired tricomponent adduct (−)-**23** in 68% yield.

A significant amount of undesired side-product **57** was generated in this process, presumably due to partial quenching of the highly basic anion **56** by the allylic proton in epoxide (+)-**29** (Scheme 10B). This problem was circumvented when we revised the Type I ARC tactic to a four-component process. As demonstrated in Scheme 11, application of a Type I ARC strategy employing TBS dithiane **27a**, epoxide (+)-**28**, and commercially available (*S*)-epichlorohydrin as the second electrophile generated chlorohydrin anion **58**, which in turn led to a new electrophilic terminal epoxide (**59**) upon warming

Scheme 11. Four-Component Type I ARC



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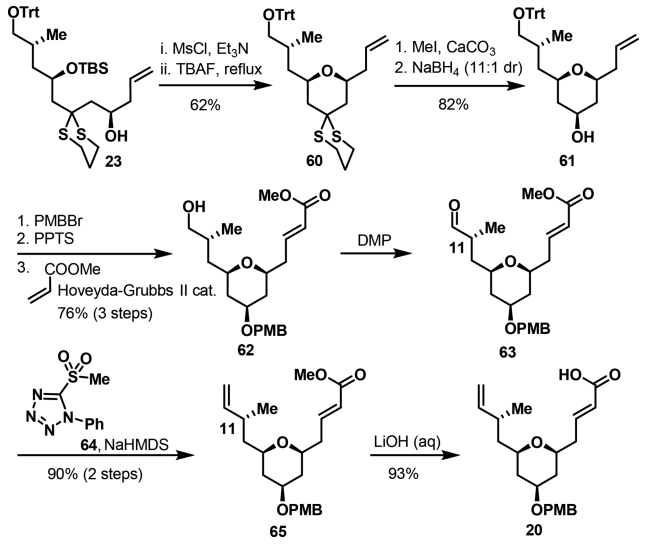
the reaction mixture to room temperature. Addition of vinylmagnesium bromide and copper iodide to the same flask completed construction of the requisite advanced homoallylic alcohol (−)-**23**, with only a trace amount of the undesired product **57** detected (i.e., NMR). Pleasingly, this four-component ARC adduct could be achieved in a single flask in 87% yield on half-gram scale, with an estimated ca. 95% average yield for each of the three carbon−carbon bond-forming steps.

Treatment of homoallylic alcohol (−)-**23** with mesyl chloride, followed by TBS removal with TBAF, resulted in tetrahydropyran (−)-**60** (Scheme 12). Dithiane removal

Scheme 12. Completion of the Southern Hemisphere

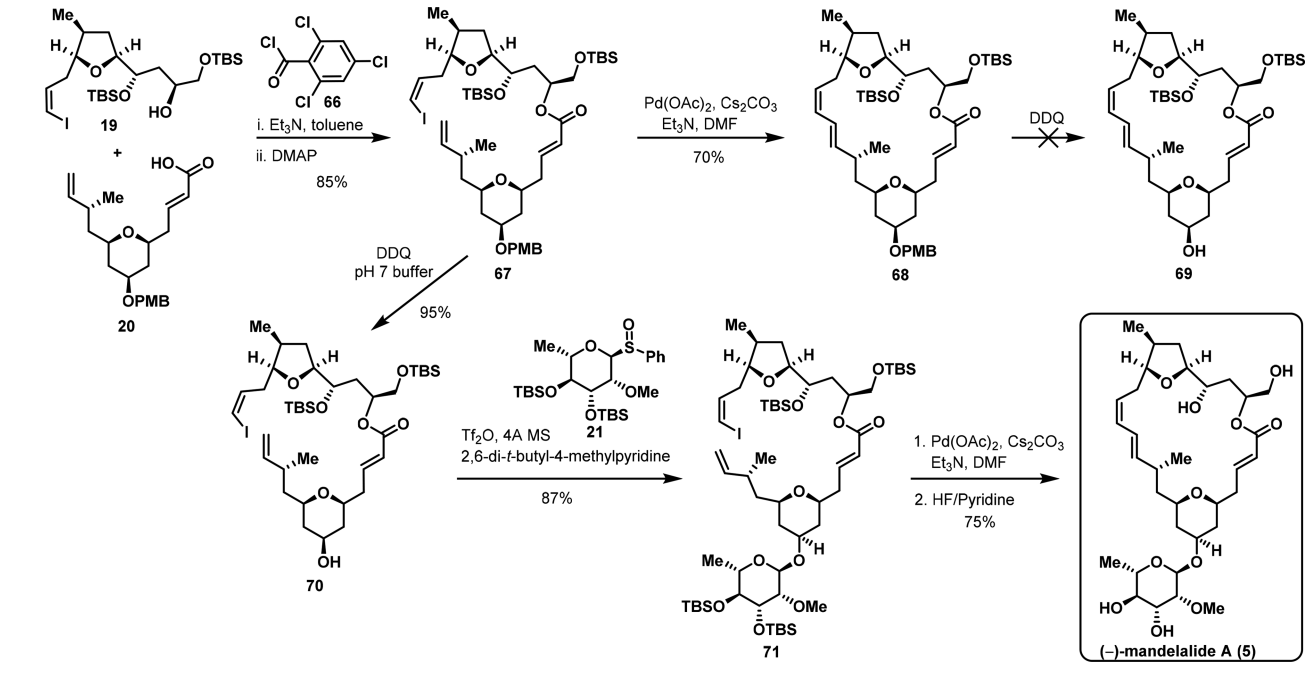


followed by diastereoselective reduction with $NaBH_4$ then led to alcohol (+)-**61** in 82% yield. Protecting group manipulations followed by alkene cross-metathesis with methyl acrylate employing the second generation Hoveyda−Grubbs catalyst then provided advanced intermediate (+)-**62** in 76% yield over the three steps. Subsequent oxidation of the primary alcohol led to the corresponding aldehyde **63**. Methylenation of this rather sensitive aldehyde at first proved problematic, as treatment with methyltriphenylphosphonium bromide and NaHMDS under standard Wittig conditions led to the desired product in only low yield with substantial epimerization at C_{11}. Attempts to improve this transformation with mild and nonbasic protocols[37] employing transition metal catalysis failed to provide the desired product. Gratifyingly, this problem could be addressed by employing the Julia−Kocienski olefination tactic with known sulfone **64**,[38] to furnish the terminal alkene (−)-**65** in good yield, importantly with no loss in stereochemical integrity. Finally, ester saponification with aqueous LiOH provided the desired southern hemisphere (−)-**20**.

Fragment Union and Completion of the Total Synthesis of (−)-Mandelalide A. Following construction of the northern and southern hemispheres, the glycosyl donor (+)-**21** was readily prepared in multigram quantity from commercially available L-rhamnose as previously reported.[11,39]

Having all fragments in hand, attention was directed toward fragment assembly (Scheme 13). To this end, the northern and southern hemispheres (−)-**19** and (−)-**20** were smoothly united via Yamaguchi esterification,[40] furnishing (−)-**67** in 85% yield. Under our reaction conditions, the desired product was readily obtained without isomerization of the enoate double bond, an issue previously observed by both Fürstner[10] and Altmann.[13a] Advanced intermediate (−)-**67** was then subjected to macrocyclization employing an intramolecular Heck reaction[41] to provide the PMB-protected aglycon **68** in good yield. Attempts to remove the PMB protecting group in **68** with DDQ, however, led to decomposition due to competing oxidation of the conjugated diene moiety. This complication was resolved by exploiting the flexibility of our synthetic strategy. Specifically, the PMB group was removed prior to macrocyclization, to furnish alcohol (−)-**70** in near quantitative yield. Kahne glycosylation[42] employing sulfoxide (+)-**21** then

Scheme 13. Fragments Union and Completion of (−)-Mandelalide A Total Synthesis



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provided glycoside (−)-**71** in excellent yield as a single diastereomer. Macrocyclization employing the Heck reaction and global desilylation with HF/pyridine then completed the total synthesis of (−)-mandelalide A (**5**). The synthetic material displayed spectral properties identical in all respects to those reported for the natural product (i.e., ^{1}H and ^{13}C NMR and HRMS).

Total Synthesis of (−)-Mandelalide L and Related Analogs. Following the original report[9] on the discovery of mandelalides A−D, recollection of the rare tunicate source by McPhail and co-workers yielded additional natural congeners of the mandelalide family, including one new member of the A-Type macrocycle.[14,15] This compound, named (−)-mandelalide L, displays nanomolar cytotoxicity against both human NCI-H460 lung cancer cells (EC_{50}, 9.8 nM) and HeLa cervical cancer cells (EC_{50}, 2.8 nM). Preliminary structure elucidation, together with comparison of NMR data between (−)-mandelalide L and (−)-mandelalide A, revealed an additional esterification at C_{24} (Figure 4). The identity of the ester side chain, however, was unclear as initial MS profiling of the minute semipure natural product sample suggested three likely possibilities: a butanoyl, a pentanoyl, or an octanoyl moiety.

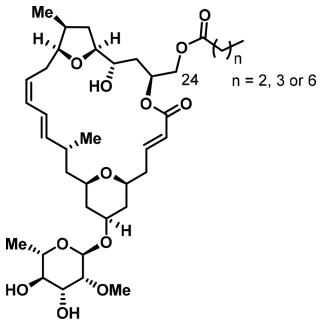

Figure 4. Proposed structures of mandelalide L.

Considering the remarkable cytotoxicity of (−)-mandelalide L, especially the intriguing role of the additional ester side chain on the biological activity, we decided to synthesize all three possible congeners to validate the structure of (−)-mandelalide L and explore their bioactivity.

To this end, the same union strategy for the construction of (−)-mandelalide A was employed with the southern hemisphere (−)-**20**, the glycosyl donor (+)-**21**, and the northern fragment (−)-**72**, the latter obtained via selective butyration of diol (−)-**19a**, to generate advanced intermediate (−)-**73** in 76% yield (Scheme 14). Macrocyclization employing a similar Heck reaction on (−)-**73** then provided compound **74**, which was subjected directly to global deprotection to furnish 24-*O*-butanoylmandelalide A [(−)-**75**]. To access the other two congeners, compound **74** was subjected to selective cleavage of the butanoyl ester side chain with K_2CO_3 in MeOH to provide (−)-**76**[43] with the free hydroxy group at C_{24}. Installation of the pentanoyl and octanoyl ester chains, followed by global desilylation, furnished (−)-**78** and (−)-**16**, respectively. Having all three congeners in hand, careful comparison of spectral data obtained from synthetic materials with those of the purified natural product unambiguously confirmed the structure of (−)-mandelalide L as 24-*O*-octanoylmandelalide A [(−)-**16**].

The cytotoxic potential of the synthetic material was evaluated against human HeLa cervical cancer cells, relative to synthetic (−)-mandelalide A, using assay conditions comparable to those employed in the original bioassay-guided drug discovery screen[14] (Table 1; Figure S1[31]). Importantly, synthetic (−)-mandelalide A and synthetic (−)-mandelalide L (EC_{50}, 1.3 and 3.1 nM, respectively) revealed biological activities that were entirely consistent with the cytotoxicity observed in earlier testing of the natural products. Synthetic (−)-**75** and (−)-**78** also proved to be fully efficacious cytotoxins with EC_{50} values of 2.1 and 0.7 nM, respectively. Seco-mandelalide A methyl ester (−)-**80**, obtained from **79** as a side product[43] during the ester saponification of **74** (Scheme

Scheme 14. Total Synthesis and Structural Validation of (−)-Mandelalide L

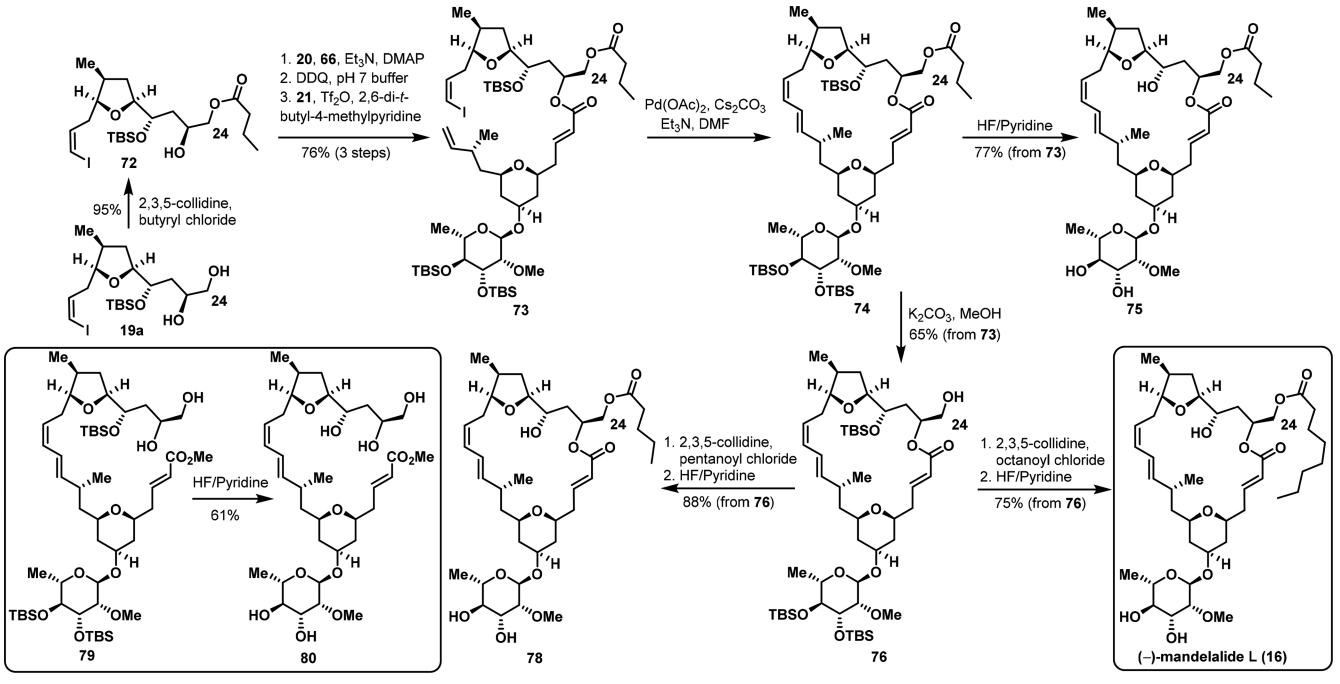

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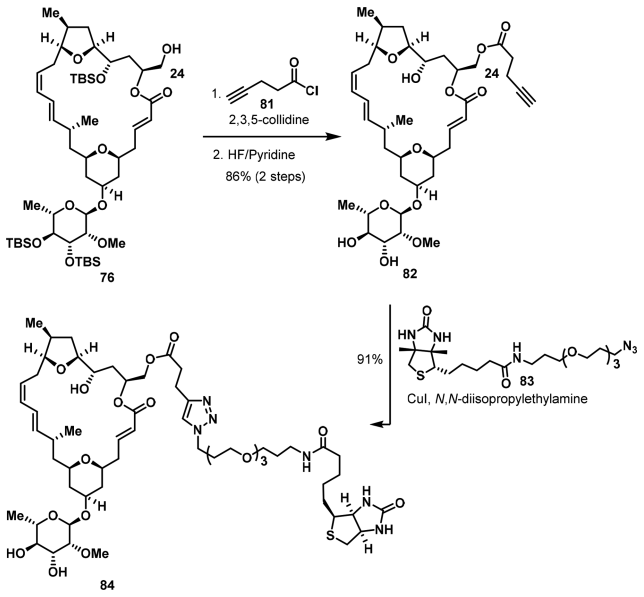
Table 1. Cytotoxicity of Synthetic Mandelalide Analogs Against Human HeLa Cells

compound	EC_{50} (nM)
5	1.3 ± 0.1
16	3.1 ± 0.4
75	2.1 ± 0.6
78	0.7 ± 0.1
80	inactive at 300 nM
82	1.5
84	18

14), displayed no biological activity against HeLa cells. These data demonstrate the essential requirement of the macrolactone moiety for the cytotoxicity of the A-Type mandelalides series. Moreover, the presence of an additional ester moiety on C_{24} has no noticeable effect on the biological activity of (−)-mandelalide A. This particularly important observation holds promise for the future determinations of the mandelalide cellular binding target by functionalization of the 24-OH with a chemical probe. To this end, two mandelalide analogs possessing alkyne and biotin probes were prepared, the latter via attachment of a biotin tether[44] via a Huisgen 1,3-dipolar cycloaddition[45] to the derived acetylenic ester (−)-**82** (Scheme 15). The polyethylene glycol (PEG) unit in turn was employed

Scheme 15. Synthesis of Biotin-Tagged Mandelalide A



as a linker molecule between biotin and mandelalide A to increase solubility of the overall molecule in water. Pleasingly, biological testing revealed that attachment of an alkyne tag [(−)-**82**] or a biotin fragment to the mandelalide A structure at C_{24} [(−)-**84**] does not significantly affect the cytotoxicity of mandelalide A (Table 1; Figure S2A[31]). Synthetic (−)-**82** and (−)-**84** displayed nanomolar potency against HeLa cell viability with an EC_{50} value of 1.5 and 18 nM, respectively. Moreover, (−)-**84** retained the ability to inhibit the complex V ATP synthase activity of isolated bovine heart mitochondria (Figure S2B[31]), providing strong evidence for an interaction between the biotin-tagged molecule and biological target of mandelalide A in cell-free assays. Together with the synthetic natural products, these non-natural analogs are currently being employed in detailed biological investigations, in conjunction with streptavidin affinity-based chromatography, to further elucidate cellular target(s) of the mandelalides.

SUMMARY

The evolution of an effective dual Anion Relay Chemistry strategy for the construction of (−)-mandelalide A has been achieved. The synthesis was completed with a longest linear reaction sequence of 16 steps from epoxide **47** in ca. 20% overall yield. Through rational design of new linchpins and the strategic selection of coupling partners, the value of both Type I and Type II ARC tactics has been demonstrated in this synthetic venture. The northern hemisphere was constructed via a novel three-component Type II ARC/CuCN-mediated cross-coupling protocol, while the southern hemisphere was secured via a highly effective four-component Type I ARC union, both conducted on preparative scale, employing readily accessible and/or commercially available building blocks. This work clearly showcases ARC as a powerful synthetic tactic for the rapid union of multiple, structurally simple starting materials in a highly efficient and iterative fashion.

Construction of the northern hemisphere also demonstrates an important advantage of ARC that permits access to a wide variety of scaffolds via ready customization of the coupling partners with programmable, preloaded functionality and stereochemistry.

In addition to the first total synthesis and structural validation of (−)-mandelalide L, this highly convergent, flexible synthetic strategy permitted rapid functionalization of mandelalide A at the 24-OH to access several Type A non-natural mandelalide analogs that exhibit potent cytotoxicity against human HeLa cervical cancer cells. Application of the strategies presented here for the synthesis of other members of mandelalide family (Types B and C) and biological investigation employing the derived synthetic material to elucidate the cellular target of this family of natural products continue in our laboratories.

EXPERIMENTAL SECTION

Material and Methods. All moisture-sensitive reactions were performed using syringe-septum cap techniques under an inert atmosphere of N_2. All glassware was flame-dried or dried in an oven (140 °C) for at least 4 h prior to use. Reactions were magnetically stirred unless otherwise stated. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), and toluene were dried by passage through alumina in a Pure Solve PS-400 solvent purification system. THF was degassed vigorously via freeze−pump−thaw before being employed in Anion Relay Chemistry protocols. Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on precoated silica gel 60 F-254 plates (particle size 40−55 μm, 230−400 mesh) and visualized by a UV lamp or by staining with PMA (2 g phosphomolybdic acid dissolved in 20 mL of absolute ethanol), $KMnO_4$ (1.5 g of $KMnO_4$, 10 g of K_2CO_3 and 2.5 mL of 5% aq. NaOH in 150 mL of H_2O), or CAM (4.8 g of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution). Column chromatography was performed using silica gel (Silacycle Silaflash, P60, 40−63 μm particle size, 230−300 mesh) and compressed air pressure with commercial grade solvents. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded at 500 MHz/125 MHz (^{1}H NMR/ ^{13}C NMR) on a Bruker Avance III 500 MHz spectrometer at 300 K. Chemical shifts are reported relative to chloroform (δ 7.26), acetone (δ 2.05), methanol (δ 3.31), or benzene (δ 7.16) for ^{1}H NMR and chloroform (δ 77.16), acetone (δ 29.84), methanol (δ 49.00), or benzene (δ 128.06) for ^{13}C NMR. ^{1}H

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NMR spectra are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, m = multiplet, b = broad), coupling constant, and integration. ^{13}C NMR spectra are tabulated by observed peak. Optical rotations were measured on a Jasco P-2000 polarimeter. Melting points were determined using a Thomas-Hoover capillar melting point apparatus and are uncorrected. Infrared spectra were measured on a Jasco FT/IR 480 plus spectrometer. High-resolution mass spectra (HRMS) were obtained at the University of Pennsylvania on a Waters GCT Premier spectrometer. GPC analysis of the polymer samples were done on a PerkinElmer Series 10 high-performance liquid chromatography (HPLC), equipped with an LC-100 column oven (30 °C), a Nelson Analytical 900 Series integration data station, a PerkinElmer 785 UV−vis detector (254 nm), a Varian star 4090 refractive index detector, and three AM gel columns (500 Å, 5 μm; 1000 Å, 5 μm; and 10^4 Å, 5 μm). THF (Fisher, HPLC grade) was used as eluent at a flow rate of 1 mL/min. SFC purifications were performed with a JASCO system equipped with a Chiralpak AD-H column (10 mm × 250 mm), a PU-280-CO2 plus CO2 Delivery System, a CO-2060 plus Intelligent Column Thermostat, an HC-2068-01 Heater Controller, a BP-2080 plus Automatic Back Pressure Regulator, an MD-2018 plus Photodiode Array Detector (200−648 nm), and PU-2080 plus Intelligent HPLC Pumps.

Preparation of Coupling Partners for Anion Relay Chemistry. *Compound* ***25b***. A tared, septum-capped, 50 mL vial containing 25 mL of MeCN and a stir bar was purged with propyne gas (1.36 g, 34.0 mmol) and weighed to determine the mass of dissolved propyne gas in solution. Liquid *tert*-butyldimethylsilane (1.9 mL, 11.3 mmol) was added via syringe, and the resulting solution was solidified by cooling down to −78 °C. The septum was removed, solid catalyst $Rh(acac)(CO)_2$ (29.2 mg, 0.113 mmol) was added, and the vial was then quickly assembled into a Parr bomb and heated to 90 °C under an atmosphere of CO (500 psi) for 15 h. The solution was then cooled to room temperature and carefully removed from the Parr bomb. The resulting mixture was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5% Et_2O/Hexanes) to afford the desired aldehyde **25b** as a yellow oil (2.06 g, 11.19 mmol, 99%): IR (film, cm^{-1}) 2939, 2854, 2738, 1687, 1594, 1470, 1362, 1323, 1252, 1029, 1008, 841, 782, 705; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1 H), 6.86 (q, *J* = 1.4 Hz, 1 H), 1.94 (d, *J* = 1.4 Hz, 3 H), 0.93 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 153.2, 150.4, 26.5, 19.2, 17.1, −2.9; HRMS (CI^+) *m*/*z* $(M - Me)^+$: calcd for $C_9H_{17}OSi$, 169.1049; found, 169.1049.

*Compound (−)-***25***.* Chloroiodomethane (2.85 mL, 39.13 mmol) was added to a stirred solution of aldehyde **25b** (2.405 g, 13.04 mmol) in 35 mL of THF at −78 °C. A solution of *n*-BuLi (2.43 M, 16.1 mL, 39.13 mmol) in hexanes was added dropwise via syringe over 15 min. The obtained solution was then stirred at −78 °C for 1 h, then tetrabutylammonium iodide (TBAI, 481.7 mg, 1.304 mmol) was added, and the solution was then stirred at room temperature for 15 h. The solution was quenched with saturated aqueous NH_4Cl (50 mL) and deionized H_2O (50 mL). The resulting mixture was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (2−5% Et_2O/Hexanes) to afford the desired epoxide **25a** as a yellow oil (2.42 g, 11.2 mmol, 94%): IR (film, cm^{-1}) 2945, 2854, 1616, 1470, 1380, 1250, 895, 841, 761, 686; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (bs, 1 H), 3.59 (t, *J* = 3.2 Hz, 1 H), 2.86 (t, *J* = 4.8 Hz, 1 H), 2.79 (dd, *J* = 5.2, 2.8 Hz, 1 H), 1.67 (d, *J* = 1.2 Hz, 3 H), 0.91 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 128.9, 53.4, 46.4, 26.5, 20.1, 17.1, −3.6, −3.7; HRMS (ES^+) *m*/*z* $(M + H)^+$: calcd for $C_{11}H_{23}OSi$, 199.1518; found, 199.1529.

To a mixture of the precatalyst (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (379 mg, 0.628 mmol) in 1 mL of toluene was added glacial acetic acid (72 μL, 1.255 mmol), and the resulting mixture was stirred at room temperature under air for 30 min. The volatile components were removed via rotary evaporation, and the remaining residue was dissolved in epoxide **25a** (2.49 g, 12.55 mmol) and 2 mL of THF. The solution was then cooled to 0 °C, and H_2O (160 μL, 8.79 mmol) was added via syringe. The resulting mixture was stirred at room temperature for 8 days, after which time Et_2O (50 mL) was added; the mixture was filtered through a short pad of silica gel and concentrated *in vacuo*. Flash chromatography on silica gel (5% Et_2O/Hexanes), followed by Kugelrohr distillation (70−90 °C, 0.025 mmHg), afforded the desired epoxide **25** as a colorless oil (1.12 g, 5.65 mmol, 45%, >95% ee based on ^{1}H NMR analysis of **37**): $[\alpha]^{20}_D$ −33.97 (*c* 1.04, CH_2Cl_2).

*Compound (−)-***47***.* Chloroiodomethane (7.03 mL, 96.45 mmol) was added to a stirred solution of aldehyde **47b** (4.575 g, 32.15 mmol) in 100 mL of THF at −78 °C. A solution of *n*-BuLi (2.5 M, 38.6 mL, 96.45 mmol) in hexanes was added dropwise via syringe over 30 min. The obtained solution was then stirred at −78 °C for 1 h, then tetrabutylamonium iodide (TBAI, 1.19 g, 3.22 mmol) was added, and the solution was then stirred at room temperature for 15 h. The solution was then quenched with saturated aqueous NH_4Cl (50 mL) and deionized H_2O (50 mL). The resulting mixture was extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (2−5% Et_2O/Hexanes) to afford the desired epoxide **47a** as a pale yellow oil (4.77 g, 30.54 mmol, 95%): IR (film, cm^{-1}) 3049, 2955, 1637, 1419, 1249, 1160, 953, 891, 852; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (bs, 1H), 4.75 (bs, 1 H), 3.26 (t, *J* = 3.0 Hz, 1 H), 2.86 (dd, *J* = 5.5, 4.2 Hz, 1 H), 2.60 (dd, *J* = 5.5, 2.6 Hz, 1 H), 1.45 (dd, *J* = 21.6, 14.1 Hz, 2 H), 0.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 109.8, 54.3, 48.2, 21.3, −1.26; HRMS (CI^+) *m*/*z* $(M - Me)^+$: calcd for $C_8H_{16}OSi$, 156.0970; found, 156.0966.

To a mixture of the precatalyst (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (147 mg, 0.244 mmol) in 1 mL of toluene was added glacial acetic acid (28 μL, 0.487 mmol), and the resulting mixture was stirred at room temperature under air for 30 min. The volatile components were removed via rotary evaporation, and the remaining residue was dissolved in epoxide **47a** (3.806 g, 24.35 mmol) and 3.4 mL of THF. The solution was then cooled to 0 °C, and H_2O (241 μL, 13.39 mmol) was added via syringe. The resulting mixture was stirred at room temperature for 5 days, after which time Et_2O (30 mL) was added; the mixture was filtered through a short pad of silica gel and concentrated *in vacuo*. Flash chromatography on silica gel (5% Et_2O/Pentanes) afforded the desired epoxide **47** as a pale yellow oil (1.71 g, 10.96 mmol, 45%, >95% ee as determined via SFC analysis of alcohol **48a**): $[\alpha]^{20}_D$ −5.12 (*c* 0.083, CH_2Cl_2). Diol **47c** (2.08 g, 49%) was also obtained following flash chromatography and could be converted to epoxide (−)-**47** in a three-step reaction sequence: to a solution of **47c** (4.28 g, 24.57 mmol) in 100 mL of CH_2Cl_2 at 0 °C was added pyridine (2.97 mL, 36.86 mmol) and pivaloyl chloride (3.33 mL, 27.03 mmol). The resulting solution was slowly warmed to room temperature over 15 h. The reaction mixture was then diluted with Et_2O (100 mL) followed by quenching with saturated aqueous NH_4Cl (50 mL). The resulting mixture was extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The obtained crude product was then taken up in 150 mL of CH_2Cl_2 at 0 °C followed by addition of Et_3N (8.56 mL, 61.43 mmol), mesyl chloride (3.81 mL, 49.14 mmol), and a catalytic amount of DMAP (150.3 mg, 1.23 mmol). The resulting solution was stirred at room temperature for 28 h. The solution was then quenched with saturated aqueous NH_4Cl (50 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The obtained crude was then directly taken in 250 mL of MeOH. Solid K_2CO_3 (7.5 g, 54.1 mmol) was added, and the resulting mixture was stirred for 37 h. The reaction mixture was then diluted with Et_2O (200 mL) followed by quenching with brine (100 mL) and deionized H_2O (100 mL). The resulting mixture was extracted with Et_2O (2 × 150 mL). The combined organic layers were

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washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (5% Et_2O/Pentanes) afforded the desired epoxide **47** as a pale yellow oil (2.50 g, 65% over the 3 steps).

*Compound (−)-**48a***. A solution of *n*-BuLi (2.48 M, 508 μL, 1.26 mmol) in hexanes was added to a stirred solution of 1,3-dithiane (151.5 mg, 1.26 mmol) in 2 mL of THF at −20 °C and stirred for 2 h. A solution of epoxide **47** (164.1 mg, 1.05 mmol) in 0.5 mL of THF was added via cannula dropwise (followed with a 0.5 mL rinse with THF). The resulting solution was stirred at −20 °C for 3 h and then cooled to −78 °C, and HMPA (183 μL, 1.05 mmol) was then added. The resulting mixture was warmed to −40 °C and stirred for another 2 h. The solution was then cooled to −78 °C, and aqueous H_2SO_4 (1 N, 2 mL) was added dropwise. The resulting mixture was warmed to room temperature and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20% Et_2O/Hexanes) to afford **48a** as a colorless oil (232.3 mg, 0.84 mmol, 80%, >95% ee via SFC analysis): $[\alpha]^{20}_D$ −7.75 (*c* 1.13, CH_2Cl_2); IR (film, cm^{-1}) 3436, 2951, 2898, 1636, 1423, 1276, 1248, 1159, 1053, 886, 853, 692, 668; ^1H NMR (500 MHz, $CDCl_3$) δ 4.98 (s, 1 H), 4.70 (s, 1 H), 4.28−4.22 (m, 2 H), 2.95−2.82 (m, 4 H), 2.17−2.10 (m, 1 H), 2.05−1.97 (m, 1 H), 1.94−1.85 (m, 2 H), 1.81−1.76 (m, 1 H), 1.63 (d, *J* = 14.1 Hz, 1 H), 1.41 (d, *J* = 13.9 Hz, 1 H), 0.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 107.6, 72.2, 44.3, 41.7, 30.4, 30.1, 26.1, 22.9, −1.08; HRMS (ES^+) *m*/*z* (M + H)$^+$: calcd for $C_{12}H_{25}OS_2Si$, 277.1116; found, 277.1110.

*Compound (+)-**36***. To a flask containing $CrCl_2$ (18.65 g, 151.7 mmol) under N_2 were added 140 mL of 1,4-dioxane and 23 mL of THF. The mixture was stirred vigorously for 45 min at room temperature to obtain a homogeneous suspension. Recrystallized CHI_3 (19.65 g, 49.91 mmol) was added, and the resulting mixture was stirred for 2 h at room temperature, at which time a solution of known aldehyde **36a** (3.13 g, 21.7 mmol) in 7 mL of 1,4-dioxane was added dropwise via cannula. The resulting mixture was stirred for 3 h at room temperature. The reaction was then quenched with 100 mL of deionized H_2O and extracted with Hexanes (3 × 100 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5% Et_2O/Hexanes) to afford the desired vinyl iodide (+)-**36** as a colorless oil (4.13 g, 15.4 mmol, 71%): $[\alpha]^{20}_D$ +6.45 (*c* 0.59, $CHCl_3$); IR (film, cm^{-1}) 2984, 2934, 2877, 1607, 1370, 1212, 1153, 1065, 948, 835; ^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (dt, *J* = 14.5, 7.3 Hz, 1 H), 6.16 (d, *J* = 14.5 Hz, 1 H), 4.15 (qn, *J* = 6.2 Hz, 1 H), 4.03 (dd, *J* = 8.0, 6.0 Hz, 1 H), 3.57 (dd, *J* = 8.0, 6.8 Hz, 1 H), 2.40−2.25 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 109.4, 77.7, 74.4, 68.8, 40.2, 27.0, 25.7; HRMS (CI^+) *m*/*z* (M − Me)$^+$: Calcd for $C_7H_{10}O_2I$, 252.9726; found, 252.9715.

*Compound (+)-**28b1***. To a 1 L round-bottomed flask containing **28b** (6.12 g, 61.1 mmol) in 190 mL of CH_2Cl_2 at 0 °C were added pyridine (12.4 mL, 153 mmol), trityl chloride (34.1 g, 122 mmol), and DMAP (1.49 g, 12.2 mmol). The resulting solution was stirred at room temperature for 39 h, after which time TLC indicated complete consumption of **28b**. The reaction mixture was diluted with CH_2Cl_2 and water at 0 °C. The resulting mixture was washed with water twice, saturated aqueous NH_4Cl twice, and brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (3% EtOAc/Hexanes) to afford **28b1** as a colorless oil (14.9 g, 43.5 mmol, 71%): $[\alpha]^{20}_D$ +0.57 (*c* 0.83, CH_2Cl_2); IR (film, cm^{-1}) 3061, 2916, 1636, 1491, 1448, 1153, 1072, 913, 744, 705; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 6 H), 7.32−7.27 (m, 6 H), 7.25−7.21 (m, 3 H), 5.75−5.65 (m, 1 H), 4.99−4.89 (m, 2 H), 2.97−2.89 (m, 2 H), 2.30−2.22 (m, 1 H), 1.96−1.79 (m, 2 H), 0.93 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 137.3, 128.9, 127.8, 126.9, 115.9, 86.3, 68.0, 38.3, 34.0, 17.1; HRMS (ES^+) *m*/*z* (M + Na)$^+$: calcd for $C_{25}H_{26}ONa$, 365.1881; found, 365.1899.

*Compound (+)-**28***. To a 1 L round-bottomed flask containing **28b1** (13.06 g, 38.1 mmol) and Na_2HPO_4 (10.8 g, 38.1 mmol) in 380 mL of CH_2Cl_2 at 0 °C was added *m*CPBA (<77% commercial supply, 12.0 g, ca. 53.5 mmol), and the resulting mixture was stirred at room temperature for 14 h, after which time TLC indicated complete consumption of **28b1**. The reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 (1:1 mixture, ca. 300 mL) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 three times, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give crude material, which was purified by silica gel column chromatography (10% Et_2O/Hexanes) to afford epoxide **28a** as a colorless oil (12.6 g, 35.1 mmol, 92%, 1:1 mixture of diastereoisomers): IR (film, cm^{-1}) 3056, 2917, 1490, 1448, 1219, 1153, 1071, 899, 764, 746, 707; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 6 H), 7.33−7.27 (m, 6 H), 7.25−7.20 (m, 3 H), 3.02−2.94 (m, 2 H), 2.91−2.82 (m, 1 H), 2.72 (t, *J* = 4.5 Hz, 0.5 H), 2.64 (t, *J* = 4.5 Hz, 0.5 H), 2.45−2.40 (m, 0.5 H), 2.37−2.33 (m, 0.5 H), 2.06−1.94 (m, 1 H), 1.78−1.67 (m, 1 H), 1.43−1.31 (m, 1 H), 1.06 (d, *J* = 6.7 Hz, 1.5 H), 1.02 (d, *J* = 6.7 Hz, 1.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 144.4, 128.9, 127.9, 127.03, 127.02, 86.4, 68.3, 67.9, 51.5, 50.9, 47.7, 47.2, 37.1, 36.9, 32.7, 32.1, 18.1, 17.4; HRMS (ES^+) *m*/*z* (M + Na)$^+$: calcd for $C_{25}H_{26}O_2Na$, 381.1831; found, 381.1829.

To a 50 mL two-necked round-bottomed flask containing precatalyst (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (404 mg, 0.669 mmol) in 8.2 mL of toluene was added glacial acetic acid (76.5 μL, 1.34 mmol), and the mixture was stirred at room temperature for 1 h. The volatile components were then removed, and the residue was dried under high vacuum (∼30 min). To the resulting residue was added a solution of epoxide **28a** (12.0 g, 33.5 mmol) in 12 mL of THF, and the resulting mixture was cooled to 0 °C. To the solution was added H_2O (332 μL, 18.4 mmol), and the mixture was stirred at room temperature for 3 days, after which ^1H NMR indicated consumption of a diastereoisomer of **28a**. The reaction mixture was purified by silica gel column chromatography (15% Et_2O/Hexanes) to afford the epoxide **28** (5.84 g, 16.3 mmol, 49%, >12:1 d.r. as determined by ^1H NMR analysis): $[\alpha]^{20}_D$ +2.52 (*c* 0.67, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 6 H), 7.33−7.27 (m, 6 H), 7.25−7.20 (m, 3 H), 3.02−2.94 (m, 2 H), 2.91−2.86 (m, 1 H), 2.72 (t, *J* = 4.5 Hz, 1 H), 2.45−2.40 (m, 1 H), 2.06−1.94 (m, 1 H), 1.78−1.72 (m, 1 H), 1.39−1.31 (m, 1 H), 1.02 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 128.9, 127.8, 127.0, 86.4, 68.3, 50.9, 47.7, 36.9, 32.1, 17.4. Diol **28c** (5.55 g, 44%) was also obtained following flash chromatography and could be converted to epoxide **28** in a three-step reaction sequence: to a solution of **28c** (8.22 g, 21.8 mmol) in 87 mL of CH_2Cl_2 at 0 °C were added pyridine (2.64 mL, 32.6 mmol) and pivaloyl chloride (3.22 mL, 26.2 mmol). The resulting solution was slowly warmed to room temperature over 8 h. The reaction mixture was then diluted with Et_2O (100 mL) followed by quenching with saturated aqueous NH_4Cl (50 mL). The resulting mixture was extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The obtained crude product was then taken up in 145 mL of CH_2Cl_2 at 0 °C followed by addition of Et_3N (7.60 mL, 54.5 mmol), mesyl chloride (3.37 mL, 43.5 mmol), and a catalytic amount of DMAP (133.2 mg, 1.09 mmol). The resulting solution was stirred at room temperature for 17 h. The solution was then quenched with saturated aqueous NH_4Cl (50 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The obtained crude product was then directly taken in 220 mL of MeOH. Solid K_2CO_3 (6.63 g, 48.0 mmol) was added, and the resulting mixture was stirred for 20 h. The reaction mixture was then diluted with Et_2O (200 mL) followed by quenching with brine (100 mL) and deionized H_2O (100 mL). The resulting mixture was extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10% Et_2O/

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Hexanes) afforded the desired epoxide **28** as a pale yellow oil (5.71 g, 73% over the 3 steps).

Procedures for Anion Relay Chemistry. *Compound (+)-**22**.* A solution of *n*-BuLi (2.4 M, 672 μL, 1.613 mmol) in hexanes was added to a stirred solution of 1,3-dithiane (193.9 mg, 1.613 mmol) in 4.5 mL of THF and stirred for 5 min at room temperature. The solution was then cooled to −20 °C, and a solution of epoxide **25** (300.0 mg, 1.512 mmol) in 1.5 mL of THF was added via cannula dropwise (followed with a 1.5 mL rinse with THF). The resulting solution was slowly warmed up to room temperature over 5 h. The solution was then cannulated (followed by a 1.5 mL rinse with THF) into another flask containing CuI (384 mg, 2.016 mmol) that was stirred in 12.0 mL of THF/HMPA mixture (1:1 in volume) at −20 °C for 20 min. The resulting suspension was stirred at room temperature for 30 min to obtain a homogeneous solution, which was then cannulated (followed with a 1.5 mL rinse with THF) into another flask containing a mixture of vinyl iodide **26** (270.2 mg, 1.008 mmol), $Pd(OAc)_2$ (22.6 mg, 0.101 mmol), and dppf (111.8 mg, 0.202 mmol) that has been stirred in 3.0 mL of THF at room temperature for 15 min. The resulting solution was then stirred at room temperature for 17 h. The solution was then quenched with saturated aqueous NH_4Cl (10 mL) and deionized H_2O (10 mL). The resulting mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5% Et_2O/Hexanes) to afford the desired three-component adduct **22** as a pale yellow oil (375 mg, 0.817 mmol, 81%): $[\alpha]^{20}_D$ +21.41 (*c* 1.45, CH_2Cl_2); IR (film, cm^{-1}) 2935, 2891, 2861, 1599, 1463, 1373, 1251, 1071, 934, 835, 775; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (t, *J* = 11.4 Hz, 1 H), 6.05 (d, *J* = 11.7 Hz, 1 H), 5.41−5.33 (m, 1 H), 4.98 (dd, *J* = 8.6, 4.7 Hz, 1 H), 4.19−4.11 (m, 1 H), 4.05−3.94 (m, 2 H), 3.60−3.53 (m, 1 H), 2.88−2.74 (m, 4 H), 2.58−2.50 (m, 1 H), 2.46−2.37 (m, 1 H), 2.14−1.99 (m, 2 H), 1.95−1.84 (m, 1 H), 1.80−1.70 (m, 1 H), 1.76 (s, 3 H), 1.43 (s, 3 H), 1.35 (s, 3 H), 0.88 (s, 9 H), 0.08 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 125.7, 125.1, 121.2, 109.1, 75.6, 69.1, 67.0, 43.9, 41.9, 31.7, 30.4, 29.9, 27.1, 26.2, 26.0, 25.8, 18.4, 18.3, −4.7, −4.9; HRMS (ES^+) *m*/*z* $(M + H)^+$: calcd for $C_{23}H_{43}O_3S_2Si$, 459.2423; found, 459.2422.

*Compound (−)-**37**.* A solution of *n*-BuLi (2.4 M, 381 μL, 0.914 mmol) in hexanes was added to a stirred solution of 1,3-dithiane (109.9 mg, 0.914 mmol) in 2.5 mL of THF and stirred for 5 min at room temperature. The solution was then cooled to −20 °C, and a solution of epoxide **25** (170 mg, 0.857 mmol) in 1 mL of THF was added via cannula dropwise (followed with a 0.7 mL rinse with THF). The resulting solution was slowly warmed up to room temperature over 5 h. The solution was then cannulated (followed with a 0.5 mL rinse with THF) into another flask containing CuI (217.5 mg, 1.142 mmol) that has been stirred in 6.8 mL of a THF/HMPA mixture (1:1 in volume) at −20 °C for 20 min. The resulting suspension was stirred at room temperature for 30 min to obtain a homogeneous solution, which was then cannulated (followed with a 1.0 mL rinse with THF) into another flask containing a mixture of vinyl iodide **36** (153 mg, 0.571 mmol), $Pd(OAc)_2$ (12.8 mg, 0.0571 mmol), and dppf (63.3 mg, 0.114 mmol) that has been stirred in 1.5 mL of THF at rt for 15 min. The resulting solution was then stirred at room temperature for 19 h. The solution was then quenched with saturated aqueous NH_4Cl (5 mL) and deionized H_2O (5 mL). The resulting mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5% Et_2O/Hexanes) to afford the desired three-component adduct **37** as a pale yellow oil (212.2 mg, 0.463 mmol, 81%): $[\alpha]^{20}_D$ −2.99 (*c* 0.82, CH_2Cl_2); IR (film, cm^{-1}) 2979, 2929, 2893, 2856, 1472, 1369, 1252, 1210, 1155, 1069, 1004, 965, 935, 837, 777, 668; ^1H NMR (500 MHz, $CDCl_3$) δ 6.43 (dd, *J* = 14.9, 11.3 Hz, 1 H), 5.8 (d, *J* = 11.1 Hz, 1 H), 5.55 (dt, *J* = 14.9, 7.2 Hz, 1 H), 4.95 (dd, *J* = 8.0, 5.1 Hz, 1 H), 4.18−4.11 (m, 1 H), 4.05−4.00 (m, 1 H), 3.97 (dd, *J* = 8.6, 5.8 Hz, 1 H), 3.60−3.54 (m, 1H), 2.88−2.77 (m, 4 H), 2.50−2.43 (m, 1H), 2.36−2.28 (m, 1 H), 2.15−2.07 (m, 1 H), 2.06−2.00 (m, 1 H), 1.94−1.84 (m, 1 H), 1.81−1.74 (m, 1 H), 1.71 (s, 3 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.2, 128.1, 126.4, 109.08, 75.5, 69.1, 67.3, 43.9, 41.9, 37.2, 30.3, 30.0, 27.0, 26.2, 26.0, 25.7, 18.3, 17.9, −4.68, −4.87; HRMS (ES^+) *m*/*z* $(M + Na)^+$: calcd for $C_{23}H_{42}O_3NaS_2Si$, 481.2242; found, 481.2245.

*Compound (+)-**50**.* A solution of *n*-BuLi (2.5 M, 4.53 mL, 11.33 mmol) in hexanes was added to a solution of 1,3-dithiane (1.36 g, 11.33 mmol) in 15 mL of THF at −20 °C and stirred for 2 h at this temperature. A solution of epoxide **47** (1.66 g, 10.62 mmol) in 13.5 mL of THF (dried over anhydrous Na_2SO_4 and degassed via freeze−pump−thaw) was added via syringe dropwise (followed with a 6 mL rinse with THF). The solution was stirred at −20 °C for 3 h and then cooled to −78 °C, and HMPA (1.85 mL, 10.62 mmol) was added dropwise. The resulting mixture was placed in a −40 °C cold bath and stirred at this temperature for 1 h. The solution was then cooled to −78 °C, and solid CuCN (476 mg, 5.31 mmol) was quickly added. The resulting bright yellow suspension was stirred at −78 °C for 45 min, and then vinyl iodide **36** (1.9 g, 7.08 mmol) in 9 mL of THF (dried over anhydrous Na_2SO_4) was added via syringe dropwise (followed with a 6 mL rinse with THF). The resulting yellow suspension was placed in a +10 °C cold bath and stirred at this temperature for 20 h to give a dark, clear solution, which was slowly warmed to room temperature over 15 h. The solution was then added to a solution of TBAF (1.0 M in THF, 42.5 mL, 42.5 mmol) and stirred at room temperature for 2 h, followed by addition of saturated aqueous NH_4Cl (50 mL) and deionized H_2O (50 mL). The resulting mixture was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (30% Et_2O/Hexanes) to afford the desired three-component adduct **50** as a pale yellow oil (2.17 g, 6.30 mmol, 89%): $[\alpha]^{20}_D$ +4.61 (*c* 0.64, CH_2Cl_2); IR (film, cm^{-1}) 3448, 2984, 2930, 1423, 1369, 1214, 1155, 1060, 974, 909, 848; ^1H NMR (500 MHz, $CDCl_3$) δ 5.58−5.44 (m, 2 H), 5.12 (s, 1 H), 4.90 (s, 1 H), 4.43−4.37 (m, 1 H), 4.23−4.18 (m, 1 H), 4.17−4.11 (m, 1 H), 4.03 (dd, *J* = 8.0, 6.0 Hz, 1 H), 3.61−3.55 (m, 1 H), 2.95−2.80 (m, 5 H), 2.77−2.70 (m, 1 H), 2.42−2.35 (m, 1 H), 2.30−2.23 (m, 1 H), 2.16−2.09 (m, 1 H), 2.00−1.85 (m, 4 H), 1.42 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 130.8, 127.6, 111.5, 109.1, 75.6, 71.5, 69.0, 44.1, 41.3, 37.0, 35.6, 30.4, 30.1, 27.0, 26.1, 25.8; HRMS (ES^+) *m*/*z* $(M + Na)^+$: calcd for $C_{17}H_{28}O_3NaS_2$, 367.1378; found, 367.1390.

*Compound (−)-**23**.* A solution of TBS-dithiane **27a** (406 mg, 1.73 mmol) in 5.4 mL of THF was treated with a solution of *n*-BuLi (2.3 M, 0.826 mL, 1.9 mmol) in hexanes at room temperature and stirred for 5 min. The reaction mixture was then cooled to −40 °C, and a solution of epoxide **28** (414 mg, 1.15 mmol) in 15 mL of Et_2O was added via syringe dropwise. The mixture was stirred at −40 °C and monitored by TLC (30% Et_2O/Hexanes). After 30 min, TLC analysis showed complete consumption of dithiane. The reaction was then cooled to −78 °C, and a solution of (*S*)-epichlorohydrin (266 mg, 2.87 mmol) in 5 mL of Et_2O (dried over anhydrous Na_2SO_4) was added dropwise via syringe, followed by HMPA (0.327 mL, 1.72 mmol). The reaction mixture was stirred at −78 °C for 5 min and then allowed to warm to 0 °C using an ice/water bath over 1 h. The cold bath was then removed, and the reaction mixture was allowed to warm to room temperature for about 1 h. Freshly prepared vinylmagnesium bromide (1.0 M, 3.5 mL, 3.5 mmol) in THF was added to a suspension of CuI (110 mg, 0.58 mmol) in 11 mL of Et_2O at −78 °C via syringe. The reaction mixture containing the ARC product was then added via syringe over 5 min. The resulting mixture was stirred at −78 °C for 30 min, and the reaction flask was then placed in an ice/water bath at 0 °C and allowed to warm to room temperature for over 1.5 h. An aqueous solution of Rochelle's salt (15% w/v) was finally added, and the resulting biphasic mixture was stirred at room temperature for 20 min and then extracted with EtOAc twice. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material obtained was purified by silica gel column chromatography (5−30% Et_2O/Hexanes) to afford **23** as a colorless oil (676 mg, 1.00 mmol, 87%): $[\alpha]^{20}_D$ −13.7 (*c* 0.65, CH_2Cl_2); IR (film, cm^{-1}) 3434, 3058, 2927, 2856, 1596, 1490, 1472, 1448, 1255,

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1069, 909, 836, 808, 774, 745, 707, 633; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.7 Hz, 6 H), 7.32−7.19 (m, 9 H), 5.89−5.77 (m, 1 H), 5.11−5.04 (m, 2 H), 4.16−4.08 (m, 1 H), 4.04−3.98 (m, 1 H), 3.93−3.89 (m, 1 H), 3.02−2.96 (m, 1 H), 2.89−2.69 (m, 4 H), 2.64−2.55 (m, 1 H), 2.30−2.03 (m, 6 H), 2.00−1.85 (m, 3 H), 1.66−1.59 (m, 1 H), 1.47−1.39 (m, 1 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.12 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 135.1, 128.9, 127.8, 126.9, 117.5, 86.4, 69.0, 68.6, 67.6, 51.5, 45.4, 45.3, 44.0, 43.0, 31.2, 26.5, 26.4, 26.3, 25.1, 18.7, 18.2, −3.0, −4.0; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{40}H_{56}O_3NaSiS_2$, 699.3338; found, 699.3328.

Synthesis of Mandelalide A Northern Hemisphere. *Compound (+)-**34**.* A solution of TBAF (1.0 M, 0.305 mL, 0.305 mmol) in THF was added to a stirred solution of compound **22** (55.9 mg, 0.122 mmol) in 2 mL of THF at room temperature. After stirring at room temperature for 7 h, the solution was quenched with deionized H_2O (10 mL). The resulting mixture was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (30% EtOAc/Hexanes) to afford the desired alcohol **34** as a pale yellow oil (39.9 mg, 0.116 mmol, 95%): $[\alpha]^{20}_D$ +27.07(c 1.04, CH_2Cl_2); IR (film, cm^{-1}) 3452, 3033, 2983, 2935, 2898, 1423, 1371, 1317, 1275, 1244, 1214, 1155, 1063, 1002, 909, 849, 790, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (t, J = 11.4 Hz, 1 H), 6.09 (d, J = 11.7 Hz, 1 H), 5.41−5.33 (m, 1 H), 5.06−4.98 (m, 1 H), 4.15−4.04 (m, 2 H), 4.03−3.95 (m, 1 H), 3.56−3.49 (m, 1 H), 2.89−2.76 (m, 4 H), 2.55−2.46 (m, 1 H), 2.44−2.34 (m, 1 H), 2.15−2.02 (m, 3 H), 1.93−1.69 (m, 2 H), 1.79 (s, 3 H), 1.40 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 125.7, 125.4, 122.1, 109.1, 75.5, 69.0, 66.5, 43.9, 40.7, 31.7, 30.1, 30.0, 27.0, 26.0, 25.7, 18.3; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{17}H_{28}O_3S_2Na$, 367.1378; found, 367.1371.

*Compound (−)-**37a**.* A solution of TBAF (1.0 M, 1.23 mL, 1.23 mmol) in THF was added to a stirred solution of compound **37** (187.8 mg, 0.409 mmol) in 6 mL of THF at room temperature. After stirring at room temperature for 3 h, the solution was quenched with deionized H_2O (15 mL). The resulting mixture was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (30% EtOAc/Hexanes) to afford the desired alcohol **37a** as a pale yellow oil (136.7 mg, 0.397 mmol, 97%): $[\alpha]^{20}_D$ −12.86 (c 0.34, CH_2Cl_2); IR (film, cm^{-1}) 3745, 2979, 2934, 2901, 1424, 1370, 1214, 1155, 1059, 961, 841, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (dd, J = 14.9, 11.3 Hz, 1 H), 5.87 (d, J = 11.1 Hz, 1 H), 5.58 (dt, J = 14.7, 7.2 Hz, 1 H), 5.03 (bs, 1 H), 4.17−4.10 (m, 2 H), 4.02 (dd, J = 7.9, 5.9 Hz, 1 H), 3.59−3.54 (m, 1 H), 2.93−2.81 (m, 4 H), 2.49−2.41 (m, 1 H), 2.36−2.28 (m, 1 H), 2.17−2.07 (m, 2 H), 1.95−1.80 (m, 2 H), 1.77 (s, 3 H), 1.41 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 129.0, 127.8, 127.6, 109.1, 75.5, 69.1, 67.1, 44.1, 40.8, 37.2, 30.2, 30.1, 27.1, 26.1, 25.8, 17.9; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{17}H_{28}O_3S_2Na$, 367.1378; found, 367.1387.

*Compound (+)-**38**.* To a solution of alcohol **37a** (39.7 mg, 0.115 mmol) in MeCN (4 mL) and deionized H_2O (0.4 mL) were added MeI (108 μL, 1.73 mmol) and $CaCO_3$ (173.2 mg, 1.73 mmol). After stirring at 65 °C for 6 h, the solution was then cooled to room temperature and filtered through a short pad of Celite. The resulting mixture was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude was then taken up in 2 mL of MeOH, and $NaBH_4$ (21.8 mg, 0.576 mmol) was added at 0 °C. After stirring for 1 h at room temperature, the solution was quenched with deionized H_2O (2 mL). The resulting mixture was extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (50% EtOAc/Hexanes) to afford diol **38** as a colorless oil (23.0 mg, 0.0897 mmol, 78%): $[\alpha]^{20}_D$ +36.47 (c 1.37, CH_2Cl_2); IR (film, cm^{-1}) 3855, 2985, 2937, 2881, 1438, 1372, 1215, 1155, 1059, 966, 848, 790; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (dd, J = 14.9, 11.3 Hz, 1 H), 5.85 (d, J = 11.1 Hz, 1 H), 5.56 (dt, J = 14.8, 7.4 Hz, 1 H), 4.93 (dd, J = 9.0, 4.3 Hz, 1 H), 4.16−4.09 (m, 1 H), 4.00 (dd, J = 7.9, 5.9 Hz, 1 H), 3.85−3.75 (m, 2 H), 3.58−3.53 (m, 1 H), 2.57−2.38 (m, 2 H), 2.35−2.27 (m, 1 H), 1.99−1.91 (m, 1 H), 1.78 (s, 3 H), 1.66−1.59 (m, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 128.6, 127.9, 126.9, 109.2, 75.6, 69.9, 69.0, 61.4, 37.2, 36.9, 27.0, 25.8, 18.2; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{14}H_{24}O_4Na$, 279.1572; found, 279.1561.

*Compound (+)-**51**.* To a solution of alcohol **50** (1.56 g, 4.53 mmol) in MeCN (150 mL) and deionized H_2O (15 mL) were added MeI (4.2 mL, 67.92 mmol) and $CaCO_3$ (6.8 g, 67.92 mmol). After stirring at 60 °C for 5 h, the solution was then cooled to room temperature and filtered through a short pad of Celite. The resulting mixture was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude was then taken up in 70 mL of MeOH, and $NaBH_4$ (0.86 g, 22.64 mmol) was added at 0 °C. After stirring for 30 min at room temperature, the solution was quenched with deionized H_2O (50 mL). The resulting mixture was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (50−100% EtOAc/Hexanes) to afford diol **51** as a colorless oil (1.06 g, 4.14 mmol, 91%): $[\alpha]^{20}_D$ +22.35 (c 0.25, CH_2Cl_2); **IR** (film, cm^{-1}) 3399, 2984, 2927, 2872, 1370, 1214, 1154, 1061, 973, 902; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59−5.44 (m, 2 H), 5.12 (s, 1 H), 4.90 (s, 1 H), 4.34 (dd, J = 7.6, 3.9 Hz, 1 H), 4.17−4.11 (m, 1 H), 4.02 (dd, J = 7.9, 6.1 Hz, 1 H), 3.88−3.78 (m, 2 H), 3.61−3.55 (m, 1 H), 2.86−2.78 (m, 1 H), 2.76−2.69 (m, 1 H), 2.53−2.32 (m, 3 H), 2.31−2.24 (m, 1 H), 1.88−1.75 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 130.9, 127.5, 110.9, 109.1, 75.6, 74.8, 68.9, 61.6, 37.0, 36.9, 35.8, 27.0, 25.7; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{14}H_{24}O_4Na$, 279.1572; found, 279.1568.

*Compound (−)-**52**.* To a solution of diol **51** (800 mg, 3.12 mmol) in 66 mL of MeCN were added 46 mL of pH 6.5 phosphate buffer, which was stirred vigorously. To the mixture was added sequentially pyridine-*N*-oxide (593 mg in 8 mL of MeCN, 6.24 mmol), citric acid monohydrate (492 mg in 8 mL of pH 6.5 phosphate buffer, 2.34 mmol), $Cu(OTf)_2$ (1.13 g in 8 mL of MeCN, 3.12 mmol) and solid $K_2OsO_4.2H_2O$ (230 mg, 0.624 mmol). The resulting mixture was stirred vigorously at room temperature for approximately 2 weeks, at which time 600 mL of EtOAc was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 300 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was quickly purified by flash chromatography on neutral alumina (1% H_2O/EtOAc) to recover starting material **51** (88 mg, 0.34 mmol) and obtain desired product **52** as a colorless oil (663 mg, 2.43 mmol, 78%, 88% b.r.s.m.): $[\alpha]^{20}_D$ −68.87 (c 0.33, CH_2Cl_2); IR (film, cm^{-1}) 3421, 2985, 2935, 2871, 1666, 1371, 1219, 1158, 1058, 881; ^{1}H NMR (500 MHz, C_6D_6) δ 4.77 (s, 1 H), 4.60 (s, 1 H), 4.37−4.28 (m, 2 H), 3.96−3.91 (m, 1 H), 3.69−3.42 (m, 5 H), 2.81 (bs, 1 H), 2.34−2.26 (m, 1 H), 2.23−2.06 (m, 2 H), 1.76−1.68 (m, 1 H), 1.62−1.50 (m, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 151.4, 108.7, 104.8, 82.1, 80.5, 74.0, 70.5, 70.2, 60.2, 38.5, 37.8, 35.1, 27.4, 26.0; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{14}H_{24}O_5Na$, 295.1521; found, 295.1520.

*Compound (−)-**52a**.* To a solution of diol **52** (400 mg, 1.47 mmol) in 24 mL of CH_2Cl_2 at −78 °C were added sequentially 2,6-lutidine (1.7 mL, 14.69 mmol) and TBSOTf (2.0 mL, 8.81 mmol) via syringe dropwise. The resulting mixture was warmed to 0 °C and stirred at this temperature for 4 h. The solution was quenched with saturated aqueous $NaHCO_3$ (20 mL). The resulting mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (2−4% EtOAc/Hexanes) to afford the desired product **52a** as a colorless oil (721 mg, 1.44 mmol, 98%): $[\alpha]^{20}_D$ −63.04 (c 0.38, CH_2Cl_2); IR (film, cm^{-1}) 2982, 2956, 2929, 2857, 1472, 1369, 1252, 1101, 836, 777; ^{1}H NMR (500 MHz, C_6D_6) δ 4.81 (bs, 1 H), 4.75 (bs, 1 H), 4.43−4.33 (m, 2 H), 4.10−4.04 (m, 1 H), 3.92−3.83 (m, 3 H), 3.71 (dt, J = 9.90,

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6.30 Hz, 1 H), 3.41−3.35 (m, 1 H), 2.23−2.10 (m, 2 H), 2.04−1.95 (m, 1 H), 1.86−1.77 (m, 1 H), 1.58−1.50 (m, 1 H), 1.44 (s, 3 H), 1.40−1.33 (m, 1 H), 1.38 (s, 3 H), 1.06 (s, 9 H), 1.01 (s, 9 H), 0.25 (s, 6 H), 0.13 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 151.9, 109.0, 104.3, 82.1, 78.2, 72.6, 72.3, 70.1, 60.5, 39.1, 37.6, 35.4, 27.5, 26.4, 26.2, 26.1, 18.60, 18.55, −3.8, −4.4, −5.05, −5.10; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{26}H_{52}O_5NaSi_2$, 523.3251; found, 523.3263.

*Compound (−)-**53**.* To a 150 mL flask was added Wilkinson's catalyst (76 mg, 0.082 mmol) under N_2. A solution of alkene **52a** (822 mg, 1.64 mmol) in toluene (70 mL, degassed by freeze−pump−thaw) was added via cannula, and the flask was purged with 10 cycles of H_2 gas/vacuum. A H_2 balloon was attached, and the resulting solution was stirred vigorously for 21 h at room temperature. The solution was then concentrated to obtain the crude as a mixture of diastereomers (d.r. = 6:1 by H NMR). Purification by flash chromatography on silica gel (2−3% EtOAc/Hexanes) afforded the desired product **53** as a colorless oil (685 mg, 1.36 mmol, 83%): $[\alpha]^{20}_D$ −50.48 (*c* 0.27, CH_2Cl_2); IR (film, cm^{-1}) 2953, 2928, 2856, 1461, 1379, 1252, 1095, 836, 776; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29−4.21 (m, 1 H), 4.04 (dd, *J* = 7.7, 5.9 Hz, 1 H), 3.91−3.82 (m, 2 H), 3.81−3.75 (m, 1 H), 3.72−3.62 (m, 2 H), 3.51−3.44 (m, 1 H), 2.32−2.20 (m, 1 H), 1.97 (dt, *J* = 12.4, 7.3 Hz, 1 H), 1.71−1.56 (m, 3 H), 1.54−1.47 (m, 1 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.24−1.18 (m, 1 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.09 (s, 6 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.7, 81.8, 78.4, 72.8, 72.0, 70.2, 61.4, 37.2, 35.7, 35.5, 34.5, 27.3, 26.18, 26.15, 26.0, 18.5, 18.4, 15.8, −3.8, −4.6, −5.1, −5.2; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{26}H_{54}O_5NaSi_2$, 525.3408; found, 525.3417.

*Compound (−)-**53a**.* To a polyethylene bottle containing a solution of compound **53** (557 mg, 1.109 mmol) in 56 mL of THF at 0 °C was added HF·pyridine (70%, 2.72 mL) via Eppendorf pipet. After stirring for 4 h at 0 °C, the solution was quenched slowly with 130 mL of saturated aqueous $NaHCO_3$. The resulting mixture was then diluted with 50 mL of EtOAc and stirred vigorously at room temperature for 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20% EtOAc/Hexanes) to afford the desired product **53a** as a colorless oil (414 mg, 1.065 mmol, 96%): $[\alpha]^{20}_D$ −46.72 (*c* 0.52, CH_2Cl_2); IR (film, cm^{-1}) 3434, 2960, 2929, 2851, 1462, 1378, 1251, 1062, 837, 777; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26−4.19 (m, 1 H), 4.04 (dd, *J* = 7.6, 6.0 Hz, 1 H), 3.98 (ddd, *J* = 10.5, 7.4, 2.6 Hz, 1 H), 3.95−3.90 (m, 1 H), 3.82−3.74 (m, 3 H), 3.51−3.46 (m, 1 H), 2.53 (bs, 1 H), 2.33 (dt, *J* = 14.5, 7.2 Hz, 1 H), 1.99−1.91 (m, 1 H), 1.75−1.63 (m, 2 H), 1.60−1.52 (m, 2 H), 1.39 (s, 3 H), 1.36−1.28 (m, 1 H), 1.33 (s, 3 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.8, 82.2, 81.4, 72.7, 70.9, 70.1, 62.1, 37.4, 35.9, 35.1, 33.2, 27.2, 26.1, 25.9, 18.3, 15.5, −4.0, −4.5; HRMS (ES$^+$) m/z (M + H)$^+$: calcd for $C_{20}H_{41}O_5Si$, 389.2723; found, 389.2739.

*Compound (−)-**54**.* To a solution of alcohol **53a** (336.7 mg, 0.866 mmol) in 30 mL of CH_2Cl_2 at 0 °C were added $NaHCO_3$ (291.1 mg, 3.466 mmol) and Dess-Martin periodinane (735 mg, 1.733 mmol). The resulting mixture was stirred at 0 °C for 5 min. The cold bath was then removed, and the solution was stirred at room temperature for another 2 h. The solution was quenched with saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous $Na_2S_2O_3$ (30 mL). The resulting mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated. The obtained crude was passed through a short pad of silica gel (wash with EtOAc) and concentrated *in vacuo* to afford the desired aldehyde, which was used directly in the next step.

A solution of NaHMDS (1.0 M, 4.07 mL, 4.07 mmol) in THF was added dropwise to a solution of $Ph_3PCH_2I_2$ (2.30 g, 4.33 mmol) in 10 mL of THF at 0 °C, and the resulting solution was stirred at this temperature for another 15 min. The solution was then cooled to −78 °C, and 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone (DMPU, 0.87 mL, 7.19 mmol) was added via syringe dropwise. A solution of the above aldehyde in 5 mL of THF was added via cannula dropwise, and the resulting mixture was stirred at −78 °C for 2.5 h. The solution was then quenched with saturated aqueous NH_4Cl (20 mL) and allowed to warm to room temperature over 45 min. The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (3% EtOAc/Hexanes) to afford the desired product **54** as a yellow oil (340.5 mg, 0.667 mmol, 77% over 2 steps): $[\alpha]^{20}_D$ −40.89 (*c* 0.29, CH_2Cl_2); IR (film, cm^{-1}) 2953, 2928, 2855, 1462, 1369, 1252, 1092, 1065, 837, 777; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35−6.29 (m, 1 H), 6.28−6.24 (m, 1 H), 4.29−4.23 (m, 1 H), 4.04 (dd, *J* = 7.7, 5.9 Hz, 1 H), 3.96−3.86 (m, 2 H), 3.72 (dt, *J* = 9.3, 6.4 Hz, 1 H), 3.53−3.47 (m, 1 H), 2.39−2.30 (m, 1 H), 2.27−2.20 (m, 2 H), 1.98 (dt, *J* = 12.5, 7.0 Hz, 1 H), 1.71−1.65 (m, 1 H), 1.55−1.49 (m, 1 H), 1.40 (s, 3 H), 1.33−1.24 (m, 1 H), 1.34 (s, 3 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 0.88 (s, 9 H), 0.09 (bs, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 108.8, 83.5, 82.1, 80.1, 72.7, 71.8, 70.2, 37.2, 37.1, 35.8, 35.4, 27.3, 26.2, 26.0, 18.4, 15.5, −3.8, −4.6; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{21}H_{39}O_4NaSiI$, 533.1560; found, 533.1570.

*Compound (−)-**19a**.* To a solution of acetonide **54** (119.6 mg, 0.234 mmol) in a mixture of THF (2.6 mL) and MeCN (10.3 mL) were added solid $CeCl_3$·$7H_2O$ (261.9 mg, 0.703 mmol) and a solution of oxalic acid dihydrate (1 mg/mL in MeCN, 1.48 mL, 0.0117 mmol). The suspension was stirred vigorously at room temperature for 30 min, then quenched with saturated aqueous $NaHCO_3$ (10 mL), and stirred for another 30 min. The resulting mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20% EtOAc/Hexanes) to afford diol **19a** as a white solid (101 mg, 0.215 mmol, 92%): $[\alpha]^{20}_D$ −29.09 (*c* 0.20, CH_2Cl_2); IR (film, cm^{-1}) 3398, 2959, 2926, 2854, 1461, 1254, 1090, 837, 777; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35−6.24 (m, 2 H), 4.01−3.87 (m, 4 H), 3.64−3.57 (m, 2 H), 3.48−3.40 (m, 1 H), 2.42−2.33 (m, 1 H), 2.27−2.22 (m, 2 H), 2.08−2.00 (m, 2 H), 1.81−1.72 (m, 1 H), 1.56−1.48 (m, 1 H), 1.29−1.23 (m, 1 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 83.8, 81.3, 80.2, 73.9, 69.3, 67.4, 37.2, 36.3, 36.1, 35.8, 26.1, 18.3, 15.5, −4.1, −4.7; HRMS (ES$^+$) m/z (M + H)$^+$: calcd for $C_{18}H_{36}O_4SiI$, 471.1428; found, 471.1434.

*Compound (−)-**19**.* To a solution of diol **19a** (104.4 mg, 0.222 mmol) in 16 mL of CH_2Cl_2 at 0 °C were added sequentially a solution of imidazole (48 mg/mL in CH_2Cl_2, 1.63 mL, 1.15 mmol) and a solution of TBSCl (80 mg/mL in CH_2Cl_2, 1.63 mL, 0.865 mmol) via syringe dropwise. The resulting mixture was stirred at room temperature for 4.5 h. The solution was quenched with saturated aqueous NH_4Cl (25 mL). The resulting mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (3% EtOAc/Hexanes) to afford the northern hemisphere **19** as a colorless oil (125 mg, 0.213 mmol, 96%): $[\alpha]^{20}_D$ −23.14 (*c* 0.58, $CHCl_3$); IR (film, cm^{-1}) 3456, 2955, 2925, 2850, 1731, 1257, 1117, 837, 777, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35−6.30 (m, 1 H), 6.28−6.23 (m, 1 H), 3.96−3.89 (m, 2 H), 3.88−3.77 (m, 2 H), 3.55−3.44 (m, 2 H), 2.96 (d, *J* = 2.8 Hz, 1 H), 2.39−2.30 (m, 1 H), 2.27−2.20 (m, 2 H), 2.05−1.97 (m, 1 H), 1.60−1.50 (m, 2 H), 1.31−1.22 (m, 1 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.06 (bs, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 83.5, 81.9, 80.2, 73.0, 68.8, 67.8, 37.2, 36.7, 35.9, 35.8, 26.2, 26.1, 18.44, 18.41, 15.5, −4.0, −4.7, −5.2; HRMS (ES$^+$) m/z (M + H)$^+$: calcd for $C_{24}H_{50}O_4Si_2I$, 585.2292; found, 585.2287.

Synthesis of Mandelalide A Southern Hemisphere. *Compound (−)-**60**.* To a solution containing alcohol **23** (1.617 g, 2.39 mmol) and Et_3N (1.032 mL, 7.41 mmol) in 12.5 mL of Et_2O was added MsCl (0.555 mL, 7.17 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h and monitored by TLC for complete consumption of **23**. To the reaction mixture was added TBAF (1.0 M in THF, 12.0 mL, 12.0 mmol), and the mixture was placed under reflux at 60 °C for 48 h. The reaction mixture was then

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cooled to room temperature and diluted with EtOAc and water. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, and filtered. The organic solvents were removed under reduced pressure to give crude material, which was purified by silica gel column chromatography (10−20% Et_2O/Hexanes) to afford **60** as a colorless foam (0.812 g, 1.49 mmol, 62%): $[\alpha]^{20}_D$ −8.67 (*c* 1.05, CH_2Cl_2); IR (film, cm^{-1}) 3057, 2916, 1684, 1653, 1636, 1557, 1490, 1448, 1424, 1374, 1339, 1266, 1220, 1152, 1070, 1002, 910, 742, 706; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.5 Hz, 6 H), 7.32−7.19 (m, 9 H), 5.85−5.74 (m, 1 H), 5.10−5.00 (m, 2 H), 3.80−3.66 (m, 2 H), 3.02 (dd, J = 8.5, 5.4 Hz, 1 H), 2.90−2.82 (m, 3 H), 2.74−2.68 (m, 1 H), 2.30−2.08 (m, 4 H), 2.07−1.97 (m, 3 H), 1.62−1.49 (m, 4 H), 1.27−1.19 (m, 1 H), 1.01 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 134.7, 128.9, 127.8, 126.9, 117.0, 86.2, 72.3, 70.6, 68.7, 48.3, 43.9, 42.9, 40.2, 39.9, 30.5, 26.1, 26.0, 17.5; HRMS (ES^+) m/z $(M + Na)^+$: calcd for $C_{34}H_{40}O_2NaS_2$, 567.2367; found, 567.2372.

*Compound (−)-**61a**.* To a solution of **60** (0.45 g, 0.826 mmol) in MeCN (10 mL) and water (3.4 mL) were added $CaCO_3$ (372 mg, 3.71 mmol) and MeI (3.0 mL, 49 mmol), followed by stirring at room temperature over 2 days for complete consumption of **60** by TLC. The suspension was then diluted with Et_2O and water. The aqueous layer was extracted with Et_2O twice, and the combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give material, which was purified by silica gel column chromatography (10−20% Et_2O/Hexanes) to afford ketone **61a** (0.364 g, 0.80 mmol, 97%) as a colorless oil: $[\alpha]^{20}_D$ −13.8 (*c* 1.0, CH_2Cl_2); IR (film, cm^{-1}) 3057, 2916, 1719, 1642, 1596, 1491, 1449, 1359, 1329, 1221, 1154, 1067, 920, 764, 746, 707, 632; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.5 Hz, 6 H), 7.32−7.20 (m, 9 H), 5.85−5.75 (m, 1 H), 5.12−5.06 (m, 2 H), 3.61−3.51 (m, 2 H), 3.03−3.00 (m, 1 H), 2.96−2.93 (m, 1 H), 2.41−2.16 (m, 6 H), 2.10−2.02 (m, 1 H), 1.79−1.70 (m, 1 H), 1.34−1.21 (m, 1 H), 0.99 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 144.5, 133.7, 128.9, 127.8, 127.0, 117.8, 86.3, 76.5, 75.0, 68.5, 48.5, 47.4, 40.6, 30.6, 17.4; HRMS (ES^+) m/z $(M + Na)^+$: calcd for $C_{31}H_{34}O_3Na$, 477.2406; found, 477.2391.

*Compound (+)-**61**.* A solution of **61a** (0.325 g, 0.715 mmol) in 9 mL of MeOH was cooled to −5 °C with an ice/brine bath. Solid $NaBH_4$ (0.135 g, 3.57 mmol) was added, and the reaction mixture was stirred at −5 °C for 40 min for complete consumption of **61a** by TLC. The reaction was then quenched with 1.0 M aqueous HCl and diluted with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate twice, and the combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the crude material, which was purified by silica gel chromatography (10−25% EtOAc/Hexanes) to afford the desired product **61** as a colorless oil (0.278 g, 0.609 mmol, 85%). The minor diastereomer was also obtained as a colorless oil (0.026 g, 0.0766 mmol, 8%): $[\alpha]^{20}_D$ +6.02 (*c* 0.51, CH_2Cl_2); IR (film, cm^{-1}) 3376, 2923, 2850, 1636, 1448, 1375, 1323, 1071, 706; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.5 Hz, 6 H), 7.30−7.21 (m, 9 H), 5.82−5.77 (m, 1 H), 5.07−5.01 (m, 2 H), 3.74−3.71 (m, 1 H), 3.30−3.22 (m, 2 H), 3.03−3.00 (m, 1 H), 2.88 (dd, J = 8.5, 2.0 Hz, 1 H), 2.32−2.28 (m, 1 H), 2.18−2.14 (m, 1 H), 2.03−1.99 (m, 1 H), 1.95−1.92 (m, 1 H), 1.88−1.84 (m, 1 H), 1.65−1.59 (m, 1 H), 1.39 (d, J = 8.5, 5 Hz, 1 H), 1.27−1.22 (m, 1 H), 1.14−1.07 (m, 2 H), 0.99 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 134.9, 128.9, 127.8, 126.9, 116.8, 86.3, 75.2, 73.4, 68.7, 68.5, 41.9, 40.9, 40.6, 40.3, 30.6, 17.6; HRMS (ES^+) m/z $(M + Na)^+$: calcd for $C_{31}H_{36}O_3Na$, 479.2562; found, 479.2561.

*Compound (+)-**62a**.* To a solution of alcohol **61** (0.63 g, 1.38 mmol) in 6.5 mL of DMF was added *tert*-BuOK (0.744 g, 6.9 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, followed by addition of *p*-methoxybenzyl bromide (0.82 mL, 5.52 mmol). The obtained mixture was then allowed to warm to room temperature and stirred overnight at which point TLC analysis showed complete consumption of **61**. The reaction was quenched with water. The aqueous layer was extracted with EtOAc. The organic extract was washed with water (twice) and brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was filtered through a pad of silica gel (20% Et_2O/Hexanes) and concentrated in *vacuo* to afford crude product, which was directly used in the next step without further purification.

To a mixture of the above crude in 14 mL of methanol was added pyridinium *p*-toluenesulfonate (1.3 g, 5.2 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with water. The aqueous layer was extracted with EtOAc twice. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude material, which was purified by silica gel chromatography (25−30% EtOAc/Hexanes) to afford primary alcohol **62a** as a colorless oil (0.38 g, 1.14 mmol, 83%): $[\alpha]^{20}_D$ +9.11 (*c* 0.51, CH_2Cl_2); IR (film, cm^{-1}) 3415, 2919, 2850, 1613, 1513, 1248, 1173, 1073, 1037, 916, 822; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2 H), 6.89 (d, J = 8.5 Hz, 2 H), 5.84−5.76 (m, 1 H), 5.11−5.06 (m, 2 H), 4.49 (s, 2 H), 3.82 (s, 3 H), 3.58−3.52 (m, 2 H), 3.41−3.35 (m, 3 H), 2.39−2.34 (m, 1 H), 2.28−2.22 (m, 1 H), 2.07−2.04 (m, 1 H), 2.00−1.97 (m, 1 H), 1.86−1.80 (m, 1 H), 1.63−1.57 (m, 1 H), 1.43−1.38 (m, 1 H), 1.30−1.18 (m, 2 H), 0.91 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 134.3, 130.7, 129.3, 117.7, 114.0, 75.6, 75.5, 74.3, 69.4, 68.5, 55.4, 41.7, 40.6, 39.1, 37.5, 34.9, 18.4; HRMS (ES^+) m/z $(M + H)^+$: calcd for $C_{20}H_{31}O_4$, 335.2222; found, 335.2221.

*Compound (+)-**62**.* Hoveyda−Grubbs' second generation catalyst (40 mg, 0.064 mmol) was added to a solution of **62a** (0.268 g, 0.801 mmol) and methyl acrylate (0.433 mL, 4.8 mmol) in 12 mL of CH_2Cl_2. The mixture was stirred for 18 h at room temperature. The resulting mixture was then concentrated to obtain the crude (E/Z > 20:1 based on ^1H NMR integration), which was purified by silica gel chromatography (20−50% EtOAc/Hexanes) to afford the desired single isomer **62** as a colorless oil (0.284 g, 0.727 mmol, 91%): $[\alpha]^{20}_D$ +5.96 (*c* 0.65, CH_2Cl_2); IR (film, cm^{-1}) 3448, 2918, 1719, 1658, 1613, 1586, 1614, 1438, 1247, 1071, 823; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 9.0 Hz, 2 H), 6.98−6.91 (m, J = 1 H), 6.89 (d, J = 9.0 Hz, 2 H), 5.90 (d, J = 15.5 Hz, 1 H), 4.49 (s, 2 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 3.57−3.37 (m, 5 H), 2.51−2.46 (m, 1 H), 2.42−2.36 (m, 1 H), 2.05−1.97 (m, 2 H), 1.86−1.80 (m, 1 H), 1.64−1.58 (m, 1 H), 1.38−1.35 (m, 1 H), 1.30−1.21 (m, 2 H), 0.92 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 159.3, 144.7, 130.6, 129.3, 123.5, 114.0, 75.2, 74.5, 74.1, 69.5, 68.4, 55.4, 51.6, 41.0, 38.9, 38.7, 37.5, 34.2, 18.0; HRMS (ES^+) m/z $(M + Na)^+$: calcd for $C_{22}H_{32}O_6Na$, 415.2097; found, 415.2097.

*Compound (−)-**65**.* To a solution of alcohol **62** (276 mg, 0.703 mmol) in 13 mL of CH_2Cl_2 at 0 °C were added $NaHCO_3$ (354.5 mg, 4.22 mmol) and Dess-Martin periodinane (894.8 mg, 2.11 mmol). The resulting mixture was stirred at 0 °C for 5 min. The cold bath was then removed, and the solution was stirred at room temperature for another 3 h. The solution was quenched with saturated aqueous $NaHCO_3$ (15 mL) and saturated aqueous $Na_2S_2O_3$ (25 mL). The resulting mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated. The obtained crude was passed through a short pad of silica gel (wash with EtOAc) and concentrated *in vacuo* to afford the desired aldehyde, which was used directly in the next step.

A solution of NaHMDS (1.0 M, 0.914 mL, 0.914 mmol) in THF was added dropwise to a solution of sulfone **64** (236.4 mg, 1.055 mmol) in 6.5 mL of THF at −78 °C, and the resulting solution was stirred at this temperature for another 30 min. A solution of the above aldehyde in 12 mL of THF was added via cannula dropwise, and the resulting mixture was slowly warmed up to room temperature over 20 h. The solution was then quenched with deionized H_2O (20 mL), and the resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5% EtOAc/Hexanes) to afford the desired product **65** as a colorless oil (245.9 mg, 0.633 mmol, 90% over 2 steps): $[\alpha]^{20}_D$ −7.86 (*c* 0.73, CH_2Cl_2); IR (film, cm^{-1}) 3073, 2999, 2919, 2851, 1722, 1658, 1612, 1586, 1513, 1437, 1355, 1248, 1173,

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1074, 1037, 912, 822, 762; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.3 Hz, 2 H), 7.01−6.93 (m, 1 H), 6.88 (d, J = 8.3 Hz, 2 H), 5.87 (d, J = 15.7 Hz, 1 H), 5.73 (ddd, J = 17.3, 10, 7.5 Hz, 1 H), 4.99−4.87 (m, 2 H), 4.48 (s, 2 H), 3.80 (s, 3 H), 3.73 (s, 3 H), 3.56−3.47 (m, 1 H), 3.40−3.26 (m, 2 H), 2.50−2.62 (m, 1 H), 2.38−2.29 (m, 2 H), 2.06−1.97 (m, 2 H), 1.66 (dt, J = 14.0, 7.3 Hz, 1 H), 1.37−1.29 (m, 1 H), 1.28−1.13 (m, 2 H), 0.99 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 159.3, 145.6, 144.6, 130.7, 129.3, 123.0, 114.0, 112.5, 74.4, 74.3, 73.8, 69.4, 55.4, 51.6, 42.7, 39.0, 38.1, 38.0, 34.2, 20.0; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{23}H_{32}O_5Na$, 411.2147; found, 411.2150.

*Compound (−)-**20**.* To a solution of methyl ester **65** (208 mg, 0.535 mmol) in 16.1 mL of THF was added aqueous LiOH solution (1.0 M, 5.35 mL) dropwise, and the resulting mixture was stirred at room temperature for 34 h. The reaction mixture was then diluted with deionized H_2O (50 mL) and EtOAc (50 mL) and cooled to 0 °C, followed by dropwise addition of aqueous HCl solution (1.0 M, 5.35 mL) to give an acidic solution (pH ≈ 2 with pH paper). The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20% EtOAc/Hexanes) to afford the desired product **20** as a colorless oil (186.5 mg, 0.498 mmol, 93%): $[\alpha]^{20}_D$ −6.36 (*c* 0.27, CH_2Cl_2); IR (film, cm^{-1}) 3069, 2920, 2853, 1696, 1654, 1612, 1513, 1420, 1357, 1248, 1173, 1073, 913, 821; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.50−10.50 (bs, 1 H), 7.25 (d, J = 8.5 Hz, 2 H), 7.13−7.03 (m, 1 H), 6.88 (d, J = 8.5 Hz, 2 H), 5.88 (d, J = 15.7 Hz, 1 H), 5.73 (ddd, J = 17.3, 10.1, 7.5 Hz, 1 H), 4.99−4.88 (m, 2 H), 4.49 (s, 2 H), 3.8 (s, 3 H), 3.57−3.49 (m, 1 H), 3.42−3.34 (m, 1 H), 3.34−3.27 (m, 1 H), 2.53−2.45 (m, 1 H), 2.41−2.29 (m, 2 H), 2.06−1.98 (m, 2 H), 1.70−1.63 (m, 1 H), 1.37−1.29 (m, 1 H), 1.28−1.12 (m, 2 H), 0.99 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 159.3, 148.3, 144.6, 130.7, 129.3, 122.5, 114.0, 112.6, 74.3, 74.1, 73.8, 69.5, 55.5, 42.7, 39.0, 38.12, 38.09, 34.2, 20.0; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{22}H_{30}O_5Na$, 397.1991; found, 397.1993.

Fragment Union and Completion of Mandelalide A Total Synthesis. *(−)-Compound **67**.* To a solution of carboxylic acid **20** (31.0 mg, 0.0827 mmol) in 0.56 mL of toluene were added a solution of Et_3N (13%v/v in toluene, 0.8 mL, 0.744 mmol) and a solution of 2,4,6-trichlorobenzoyl chloride (4.6%v/v in toluene, 0.56 mL, 0.165 mmol) via syringe dropwise. The solution was stirred at room temperature for 5 h, at which time a solution of alcohol **19** (32.2 mg, 0.0551 mmol) in 2 mL of toluene was added via cannula. A solution of DMAP (20.2 mg, 0.165 mmol) in 0.56 mL of toluene was added, and the resulting mixture was stirred for 27 h at room temperature. The solution was then quenched with saturated aqueous NH_4Cl (5 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5% EtOAc/Hexanes) to afford the desired product **67** as a colorless oil (44.1 mg, 0.0468 mmol, 85%): $[\alpha]^{20}_D$ −26.97 (*c* 0.35, CH_2Cl_2); IR (film, cm^{-1}) 2955, 2926, 2855, 1717, 1655, 1614, 1559, 1539, 1511, 1459, 1363, 1250, 1173, 1090, 837, 776; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2 H), 6.99−6.91 (m, 1 H), 6.88 (d, J = 8.5 Hz, 2 H), 6.35−6.29 (m, 1 H), 6.27−6.23 (m, 1 H), 5.88 (d, J = 15.7 Hz, 1 H), 5.71 (ddd, J = 17.3, 10.1, 7.5 Hz, 1 H), 5.05−4.99 (m, 1 H), 4.98−4.89 (m, 2 H), 4.52−4.45 (m, 2 H), 3.95−3.89 (m, 1 H), 3.80 (s, 3 H), 3.79−3.74 (m, 2 H), 3.71−3.66 (m, 2 H), 3.56−3.49 (m, 1 H), 3.41−3.27 (m, 2 H), 2.51−2.43 (m, 1 H), 2.38−2.29 (m, 3 H), 2.27−2.21 (m, 1 H), 2.06−1.97 (m, 3 H), 1.88−1.81 (m, 1 H), 1.71−1.62 (m, 2 H), 1.37−1.13 (m, 5 H), 1.01−0.97 (m, 6 H), 0.87 (bs, 18 H), 0.05−0.01 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 159.3, 145.3, 144.6, 139.1, 130.8, 129.3, 123.6, 114.0, 112.6, 83.5, 81.8, 80.2, 74.4, 74.3, 73.8, 72.0, 71.2, 69.4, 64.7, 55.4, 42.7, 39.0, 38.1, 38.0, 37.1, 35.7, 35.3, 34.4, 34.1, 26.2, 26.0, 20.0, 18.39, 18.35, 15.5, −3.8, −4.8, −5.2; HRMS (ES$^+$) m/z (M + H)$^+$: calcd for $C_{46}H_{78}O_8Si_2I$, 941.4280; found, 941.4301.

*Compound (−)-**70**.* To a solution of **67** (27.4 mg, 0.0291 mmol) in 0.7 mL of CH_2Cl_2 and 0.156 mL of pH 7 phosphate buffer (0.5 M) was added a solution of DDQ (recrystallized over $CHCl_3$, 19.8 mg, 0.0873 mmol) in 1.5 mL of CH_2Cl_2 dropwise at 0 °C. After stirring at 0 °C for 2.5 h, the mixture was then quenched with pH 7 phosphate buffer (5 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% EtOAc/Hexanes) to afford the desired product **70** as a colorless oil (22.7 mg, 0.0276 mmol, 95%): $[\alpha]^{20}_D$ −30.53 (*c* 0.40, CH_2Cl_2); IR (film, cm^{-1}) 3424, 3075, 2951, 2928, 2856, 1719, 1655, 1462, 1362, 1255, 1177, 1102, 1006, 911, 837, 777, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99−6.91 (m, 1 H), 6.36−6.30 (m, 1 H), 6.29−6.24 (m, 1 H), 5.88 (d, J = 15.7 Hz, 1 H), 5.71 (ddd, J = 17.3, 10.0, 7.5 Hz, 1 H), 5.05−4.98 (m, 1 H), 4.98−4.90 (m, 2 H), 3.95−3.89 (m, 1 H), 3.82−3.74 (m, 3 H), 3.71−3.66 (m, 2 H), 3.43−3.29 (m, 2 H), 2.50−2.43 (m, 1 H), 2.38−2.29 (m, 3 H), 2.27−2.21 (m, 1 H), 2.04−1.90 (m, 3 H), 1.88−1.80 (m, 1 H), 1.70−1.63 (m, 2 H), 1.46 (bs, 1 H), 1.38−1.26 (m, 2 H), 1.21−1.07 (m, 2 H), 1.02−0.96 (m, 6 H), 0.94−0.85 (m, 1 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.06−0.00 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 145.2, 144.5, 139.1, 123.7, 112.7, 83.6, 81.8, 80.1, 74.2, 73.7, 72.0, 71.2, 68.3, 64.6, 42.6, 41.1, 41.0, 38.8, 37.1, 35.7, 35.3, 34.4, 34.1, 26.2, 26.0, 20.1, 18.39. 18.35, 15.5, −3.8, −4.7, −5.2; HRMS (ES$^+$) m/z (M + H)$^+$: calcd for $C_{38}H_{70}O_7Si_2I$, 821.3705; found, 821.3697.

*Compound (−)-**71**.* To a flask containing activated 4A MS powder (380 mg) were added sugar donor **21** (90.1 mg, 0.175 mmol) in 1.2 mL of Et_2O and 2,6-di-*tert*-butyl-4-methylpyridine (77.0 mg, 0.375 mmol) in 0.56 mL of Et_2O, and the resulting mixture was stirred at room temperature for 1 h. The flask was the cooled to −78 °C, and a solution of Tf_2O (25.2 μL, 0.15 mmol) in 0.3 mL of Et_2O was added dropwise followed by stirring at −78 °C for 20 min. A solution of alcohol **70** (20.4 mg, 0.0248 mmol) in 2.4 mL of Et_2O was added via cannula dropwise. The resulting mixture was stirred at −78 °C for 1 h, then at −40 °C for 2 h, and at −35 °C for 1 h. The flask was then cooled to −78 °C, and the reaction was quenched with deionized H_2O (7 mL), diluted with EtOAc (10 mL), and allowed to warm to room temperature. The reaction mixture was filtered and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (3−5% EtOAc/Hexanes) to afford the desired product **71** as a colorless oil (26.1 mg, 0.0216 mmol, 87%): $[\alpha]^{20}_D$ −46.92 (*c* 0.40, CH_2Cl_2); IR (film, cm^{-1}) 2954, 2928, 2856, 1720, 1656, 1471, 1362, 1255, 1097, 1049, 1005, 837, 776, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00−6.91 (m, 1 H), 6.35−6.30 (m, 1 H), 6.29−6.23 (m, 1 H), 5.88 (d, J = 15.7 Hz, 1 H), 5.76−5.67 (m, 1 H), 5.05−4.98 (m, 1 H), 4.99−4.89 (m, 2 H), 4.88 (d, J = 2.2 Hz, 1 H), 3.95−3.90 (m, 1 H), 3.87−3.84 (m, 1 H), 3.80−3.66 (m 5 H), 3.60−3.52 (m, 2 H), 3.45 (s, 3 H), 3.42−3.30 (m, 3 H), 2.50−2.42 (m, 1 H), 2.38−2.31 (m, 3 H), 2.26−2.22 (m, 1 H), 2.05−1.91 (m, 3 H), 1.88−1.81 (m, 1 H), 1.71−1.61 (m, 2 H), 1.36−1.11 (m, 8 H), 1.02−0.96 (m, 6 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.12−0.00 (m, 24 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 145.2, 144.6, 139.1, 123.6, 112.6, 83.6, 81.8, 80.1, 74.2, 73.7, 73.5, 73.4, 72.0, 71.2, 70.5, 64.6, 58.9, 42.7, 39.3, 39.0, 37.6, 37.1, 35.7, 35.3, 34.4, 34.0, 26.5, 26.3, 26.2, 26.0, 20.0, 18.8, 18.5, 18.4, 18.3, 18.2, 15.5, −3.6, −3.8, −3.99, −4.04, −4.8, −5.2; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{57}H_{109}O_{11}NaSi_4I$, 1231.5990; found, 1231.6014.

*Compound (−)-**71a**.* To a solution of compound **71** (25.0 mg, 0.0207 mmol) in 3 mL of anhydrous DMF (degassed via freeze−pump−thaw) was added a solid mixture of $Pd(OAc)_2$ (8.4 mg, 0.0373 mmol) and Cs_2CO_3 (13.5 mg, 0.0414 mmol), followed by a solution of Et_3N (4.3 μL, 0.031 mmol) in 0.43 mL of DMF. The resulting solution was stirred at room temperature for 2 days. The reaction was quenched with deionized H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (3−4% EtOAc/Hexanes) to afford the desired product **71a** as a colorless oil (17.9 mg, 0.0165 mmol, 80%): $[\alpha]^{20}_D$ −13.44 (*c* 0.03, CH_2Cl_2); IR (film, cm^{-1}) 2952, 2928, 2892, 2856, 1720, 1653, 1471, 1389, 1359, 1254, 1126,

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1096, 1047, 863, 838, 777, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97−6.89 (m, 1 H), 6.28 (dd, J = 14.9, 11.1 Hz, 1 H), 6.05−5.94 (m, 2 H), 5.46 (dd, J = 14.9, 8.9 Hz, 1 H), 5.28 (td, J = 10.7, 4.8 Hz, 1 H), 5.07−5.01 (m, 1 H), 4.89 (d, J = 2.4 Hz, 1 H), 4.02−3.96 (m, 1 H), 3.88−3.84 (m, 1 H), 3.83−3.72 (m, 2 H), 3.66−3.29 (m, 11 H), 2.50−2.30 (m, 5 H), 2.05−1.98 (m, 1 H), 1.98−1.88 (m, 3 H), 1.73−1.56 (m, 3 H), 1.31−1.19 (m, 7 H), 1.02 (d, J = 6.7 Hz, 3 H), 0.94−0.91 (m, 12 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.85 (s, 9 H), 0.10 (s, 9 H), 0.08 (s, 3 H), 0.01 (s, 3 H), 0.01 (s, 6 H), −0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 145.8, 140.5, 130.2, 128.1, 125.1, 123.7, 83.3, 81.3, 73.9, 73.7, 73.34, 73.30, 72.8, 71.6, 70.6, 64.7, 58.9, 43.6, 39.7, 39.4, 38.1, 36.7, 36.5, 36.0, 33.5, 31.4, 29.9, 26.4, 26.2, 26.0, 18.9, 18.8, 18.5, 18.4, 18.3, 18.2, 14.7, −3.7, −4.0, −4.1, −5.0, −5.27, −5.32; HRMS (ES$^+$) m/z (M + H)$^+$: calcd for $C_{57}H_{109}O_{11}Si_4$, 1081.7047; found, 1081.7057.

*(−)-Mandelalide A (**5**).* To a solution of **71a** (7.0 mg, 0.0065 mmol) in 0.9 mL of THF in a polypropylene tube at 0 °C were added 0.9 mL of pyridine and 0.9 mL of HF·Pyridine complex (70% HF) dropwise via Eppendorf pipet. The resulting solution was stirred at 0 °C for 5 min. The cold bath was then removed, and the resulting solution was stirred at room temperature for another 29 h. The reaction was then quenched with 20 mL of sat. aq. $NaHCO_3$ solution slowly and stirred at room temperature for 30 min. The organic phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (4% MeOH/CH_2Cl_2) to afford the product **5** as colorless amorphous solid (3.8 mg, 0.00608 mmol, 94%) which displayed spectral properties identical in all respects to those reported for the natural product: $[\alpha]^{20}_D$ −53.92 (*c* 0.25, MeOH); IR (film, cm^{-1}) 3433, 2961, 2920, 2852, 1717, 1656, 1461, 1374, 1315, 1222, 1180, 1105, 1043, 731, 604; ^{1}H NMR (600 MHz, $CDCl_3$, residual solvent peak set at δ 7.24 ppm) δ 6.97 (ddd, J = 15.1, 10.4, 4.6 Hz, 1 H), 6.28 (dd, J = 14.3, 11.4 Hz, 1 H), 6.05 (t, J = 10.8 Hz, 1 H), 6.01 (d, J = 15.4 Hz, 1 H), 5.45 (dd, J = 14.7, 10.3 Hz, 1 H), 5.28 (td, J = 10.5, 5.7 Hz, 1 H), 5.25−5.20 (m, 1 H), 5.02 (s, 1 H), 4.0−3.95 (m, 1 H), 3.85−3.78 (m, 2 H), 3.71−3.65 (m, 1 H), 3.66−3.59 (m, 3 H), 3.46 (s, 3 H), 3.44−3.29 (m, 5 H), 2.63−2.57 (m, 1 H), 2.57−2.49 (m, 1 H), 2.43−2.19 (m, 7 H), 2.05−1.99 (m, 2 H), 1.91−1.85 (m, 2 H), 1.76 (t, J = 12.7 Hz, 1 H), 1.63−1.43 (m, 2 H), 1.26 (d, J = 6.2 Hz, 3 H), 1.25−1.15 (m, 4 H), 1.02 (d, J = 7.0 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, residual solvent peak set at δ 77.23 ppm) δ 167.4, 147.1, 141.5, 131.3, 126.9, 123.9, 123.1, 94.2, 83.2, 81.0, 80.8, 74.2, 73.9, 73.1, 73.0, 72.5, 72.3, 71.7, 68.2, 66.1, 59.1, 43.1, 39.7, 38.8, 37.6, 37.4, 36.8, 34.2, 34.1, 31.1, 18.3, 17.7, 14.5; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{33}H_{52}O_{11}Na$, 647.3407; found, 647.3411.

Total Synthesis of Mandelalide L and Analogs. *Compound (−)-**72**.* To a solution of diol **19a** (25.0 mg, 0.053 mmol) in 2 mL of CH_2Cl_2 at room temperature were added sequentially a solution of 2,3,5-collidine (38.8 mg/mL in CH_2Cl_2, 1.05 mL, 0.333 mmol) and a solution of butyryl chloride (22.8 mg/mL in CH_2Cl_2, 1.05 mL, 0.224 mmol) via syringe. The resulting mixture was stirred at room temperature for 7 h. The solution was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to afford the desired product **72** as a colorless oil (27.2 mg, 0.0504 mmol, 95%): $[\alpha]^{20}_D$ −25.46 (*c* 0.44, CH_2Cl_2); IR (film, cm^{-1}) 3466, 2957, 2932, 2852, 1738, 1461, 1386, 1254, 1181, 1092, 999, 837, 778; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35−6.29 (m, 1 H), 6.29−6.25 (m, 1 H), 4.12−4.04 (m, 2 H), 4.01−3.84 (m, 4 H), 3.33 (bs, 1 H), 2.41−2.34 (m, 1 H), 2.33 (t, J = 7.4 Hz, 2 H), 2.27−2.22 (m, 2 H), 2.06−1.99 (m, 1 H), 1.74−1.62 (m, 3 H), 1.59−1.52 (m, 1 H), 1.30−1.22 (m, 1 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.95 (t, J = 7.4 Hz, 3 H), 0.89 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 138.9, 83.7, 81.4, 80.2, 73.3, 68.7, 67.0, 37.1, 36.6, 36.2, 35.9, 35.8, 26.1, 18.6, 18.3, 15.5, 13.8, −4.1, −4.7; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{22}H_{41}O_5NaSiI$, 563.1666; found, 563.1667.

*Compound (−)-**73b**.* To a solution of carboxylic acid **20** (39.0 mg, 0.104 mmol) in 0.70 mL of toluene were added a solution of Et_3N (13%v/v in toluene, 1.00 mL, 0.937 mmol) and a solution of 2,4,6-trichlorobenzoyl chloride (4.6%v/v in toluene, 0.700 mL, 0.208 mmol) via syringe dropwise. The solution was stirred at room temperature for 5 h, at which time a solution of alcohol **72** (37.5 mg, 0.0694 mmol) in 2.5 mL of toluene was added via cannula. A solution of DMAP (25.4 mg, 0.208 mmol) in 0.700 mL of toluene was added, and the resulting mixture was stirred for 24 h at room temperature. The solution was then quenched with saturated aqueous NH_4Cl (5 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to afford the desired product **73b** as a colorless oil (55.4 mg, 0.0618 mmol, 89%): $[\alpha]^{20}_D$ −22.71 (*c* 0.48, CH_2Cl_2); IR (film, cm^{-1}) 2956, 2927, 2853, 1744, 1722, 1654, 1613, 1513, 1463, 1355, 1249, 1172, 1088, 836; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2 H), 7.01−6.93 (m, 1 H), 6.87 (d, J = 8.5 Hz, 2 H), 6.34−6.29 (m, 1 H), 6.28−6.24 (m, 1 H), 5.88 (d, J = 15.7 Hz, 1 H), 5.77−5.67 (m, 1 H), 5.26−5.19 (m, 1 H), 4.99−4.87 (m, 2 H), 4.49 (s, 2 H), 4.3 (dd, J = 11.8, 3.7 Hz, 1 H), 4.12 (dd, J = 11.9, 5.4 Hz, 1 H), 3.96−3.90 (m, 1 H), 3.80 (s, 3 H), 3.80−3.74 (m, 2 H), 3.57−3.49 (m, 1 H), 3.41−3.34 (m, 1 H), 3.34−3.27 (m, 1 H), 2.52−2.44 (m, 1 H), 2.38−2.20 (m, 7 H), 2.06−1.96 (m, 3 H), 1.91−1.84 (m, 1 H), 1.69−1.55 (m, 4 H), 1.37−1.12 (m, 4 H), 1.01−0.96 (m, 6 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 165.9, 159.3, 145.9, 144.6, 138.9, 130.7, 129.3, 123.1, 114.0, 112.6, 83.7, 81.6, 80.2, 74.4, 74.2, 73.7, 71.0, 69.4, 69.1, 65.5, 55.4, 42.7, 39.0, 38.11, 38.07, 37.1, 36.2, 35.7, 35.2, 34.5, 34.1, 26.1, 20.0, 18.5, 18.3, 15.5, 13.8, −3.8, −4.8; HRMS (ES$^+$) m/z (M + H)$^+$: calcd for $C_{44}H_{70}O_9SiI$, 897.3834; found, 897.3843.

*Compound (−)-**73a**.* To a solution of **73b** (46.0 mg, 0.0513 mmol) in 1.3 mL of CH_2Cl_2 and 0.275 mL of pH 7 phosphate buffer (0.5 M) was added a solution of DDQ (recrystallized over $CHCl_3$, 34.9 mg, 0.154 mmol) in 2.6 mL of CH_2Cl_2 dropwise at 0 °C. After stirring at 0 °C for 2.5 h, the mixture was then quenched with pH 7 phosphate buffer (10 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10−20% EtOAc/hexanes) to afford the desired product **73a** as a colorless oil (38.7 mg, 0.0498 mmol, 97%): $[\alpha]^{20}_D$ −29.36 (*c* 0.60, CH_2Cl_2); IR (film, cm^{-1}) 3449, 3069, 2962, 2929, 2854, 1723, 1656, 1467, 1364, 1310, 1256, 1172, 1090, 1046, 987, 906, 837, 778; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00−6.92 (m, 1 H), 6.34−6.24 (m, 2 H), 5.88 (d, J = 15.7 Hz, 1 H), 5.76−5.65 (m, 1 H), 5.25−5.19 (m, 1 H), 4.98−4.88 (m, 2 H), 4.30 (dd, J = 11.8, 3.7 Hz, 1 H), 4.11 (dd, J = 11.7, 5.4 Hz, 1 H), 3.97−3.90 (m, 1 H), 3.85−3.72 (m, 3 H), 3.44−3.30 (m, 2 H), 2.50−2.43 (m, 1 H), 2.38−2.21 (m, 7 H), 2.03−1.83 (m, 4 H), 1.70−1.52 (m, 5 H), 1.38−1.23 (m, 2 H), 1.21−1.07 (m, 2 H), 1.01−0.96 (m, 6 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 165.9, 145.8, 144.5, 138.9, 123.2, 112.7, 83.7, 81.6, 80.2, 74.1, 73.7, 70.9, 69.1, 68.2, 65.5, 42.6, 41.1, 41.0, 38.8, 37.1, 36.2, 35.6, 35.2, 34.5, 34.1, 26.1, 20.0, 18.5, 18.3, 15.4, 13.8, −3.8, −4.8; HRMS (ES$^+$) m/z (M + H)$^+$: calcd for $C_{36}H_{62}O_8SiI$, 777.3259; found, 777.3242.

*Compound (−)-**73**.* To a flask containing activated 4A MS powder (700 mg) were added sugar donor **21** (165.8 mg, 0.322 mmol) in 2.2 mL of Et_2O and 2,6-di-*tert*-butyl-4-methylpyridine (141.7 mg, 0.375 mmol) in 1.1 mL of Et_2O, and the resulting mixture was stirred at room temperature for 1 h. The flask was the cooled to −78 °C, and a solution of Tf_2O (46.4 μL, 0.276 mmol) in 0.56 mL of Et_2O was added dropwise; the mixture was stirred at −78 °C for 20 min. A solution of alcohol **73a** (35.7 mg, 0.046 mmol) in 4.5 mL of Et_2O was added via cannula dropwise. The resulting mixture was stirred at −78 °C for 1 h, then at −40 °C for 2 h, and at −35 °C for 1 h. The flask was then cooled to −78 °C, and the reaction was quenched with deionized H_2O (15 mL), diluted with EtOAc (20 mL), and allowed to warm to room temperature. The reaction mixture was filtered and extracted with

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EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5% EtOAc/Hexanes) to afford the desired product **73** as a colorless oil (47.2 mg, 0.0405 mmol, 88%): $[\alpha]^{20}_D$ −41.94 (*c* 0.60, CH_2Cl_2); IR (film, cm^{-1}) 2956, 2928, 2854, 1725, 1657, 1460, 1254, 1165, 1096, 1052, 837, 777; ^1H NMR (500 MHz, $CDCl_3$) δ 7.01−6.93 (m, 1 H), 6.34−6.24 (m, 2 H), 5.88 (d, *J* = 15.7 Hz, 1 H), 5.77−5.68 (m, 1 H), 5.25−5.19 (m, 1 H), 4.99−4.85 (m, 3 H), 4.30 (dd, *J* = 11.8, 3.5 Hz, 1 H), 4.12 (dd, *J* = 11.8, 5.3 Hz, 1 H), 3.96−3.90 (m, 1 H), 3.87−3.83 (m, 1 H), 3.82−3.69 (m, 3 H), 3.60−3.52 (m, 2 H), 3.45 (s, 3 H), 3.42−3.30 (m, 3 H), 2.49−2.41 (m, 1 H), 2.38−2.21 (m, 7 H), 2.04−1.92 (m, 3 H), 1.91−1.83 (m, 1 H), 1.68−1.53 (m, 4 H), 1.35−1.13 (m, 7 H), 1.02−0.96 (m, 6 H), 0.95−0.90 (m, 12 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.11−0.09 (m, 9 H), 0.08 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 165.9, 145.9, 144.5, 138.9, 123.1, 112.6, 83.7, 81.6, 80.2, 74.1, 73.7, 73.4, 73.3, 70.9, 70.5, 69.2, 65.5, 58.9, 42.7, 39.3, 39.0, 37.6, 37.1, 36.2, 35.7, 35.2, 34.5, 34.0, 26.4, 26.2, 26.1, 19.9, 18.8, 18.5, 18.3, 18.2, 15.5, 13.8, −2.7, −3.6, −3.8, −4.0, −4.1, −4.8; HRMS (ES^+) *m*/*z* $(M + H)^+$: calcd for $C_{55}H_{102}O_{12}Si_3I$, 1165.5724; found, 1165.5740.

Compound ***74***. To a solution of **73** (45.0 mg, 0.0386 mmol) in 5 mL of anhydrous DMF (degassed via freeze−pump−thaw) was added a solid mixture of $Pd(OAc)_2$ (15.6 mg, 0.0695 mmol) and Cs_2CO_3 (25.2 mg, 0.0772 mmol), followed by a solution of Et_3N (8.1 μL, 0.058 mmol) in 0.40 mL of DMF. The resulting solution was stirred at room temperature for 2 days. The reaction was quenched with deionized H_2O (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was filtered through a short pad of silica gel and concentrated to obtain ca. 42.0 mg of crude **74**, which was used directly in the next step without further purification.

*Compound (−)-****75***. To a solution of ca. 8.5 mg of the crude product mixture of **74** in 1.0 mL of THF in a polypropylene tube at 0 °C were added 1.0 mL of pyridine and 1.0 mL of HF·Pyridine complex (70% HF) dropwise via Eppendorf pipet. The resulting solution was stirred at 0 °C for 5 min. The cold bath was then removed, and the resulting solution was stirred at room temperature for another 28 h. The reaction was then quenched with 20 mL of sat. aq. $NaHCO_3$ solution slowly and stirred at room temperature for 30 min. The organic phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by RP18 HPLC (10−90% MeCN-H_2O, 0.05% formic acid) to afford the product **75** as colorless amorphous solid (4.2 mg, 0.0060 mmol, 77% over 2 steps): $[\alpha]^{20}_D$ −53.42 (*c* 0.13, MeOH); IR (film, cm^{-1}) 3424, 2963, 2920, 2882, 1724, 1658, 1459, 1365, 1317, 1261, 1218, 1175, 1106, 1044, 984, 814; ^1H NMR (600 MHz, $CDCl_3$, residual solvent peak set at 7.24 ppm) δ 6.95 (ddd, *J* = 15.2, 9.9, 5.0 Hz, 1 H), 6.26 (dd, *J* = 14.9, 10.9 Hz, 1 H), 6.05 (t, *J* = 10.9 Hz, 1 H), 5.95 (d, *J* = 15.8 Hz, 1 H), 5.44 (dd, *J* = 14.8, 9.8 Hz, 1 H), 5.35 (d, *J* = 11.0 Hz, 1 H), 5.27 (td, *J* = 10.8, 5.4 Hz, 1 H), 5.02 (s, 1 H), 4.35 (dd, *J* = 11.9, 3.9 Hz, 1 H), 4.07 (dd, *J* = 11.9, 4.3 Hz, 1 H), 3.98 (t, *J* = 9.9 Hz, 1 H), 3.86−3.79 (m, 1 H), 3.71−3.59 (m, 3 H), 3.46 (s, 3 H), 3.43−3.28 (m, 5 H), 2.56−2.48 (m, 1 H), 2.43−2.23 (m, 8 H), 2.06−1.97 (m, 2 H), 1.92−1.84 (m, 2 H), 1.74−1.67 (m, 1 H), 1.66−1.41 (m, 5 H), 1.27 (d, *J* = 6.2 Hz, 3 H), 1.24−1.14 (m, 4 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.92 (t, *J* = 7.4 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, residual solvent peak set at 77.0 ppm) δ 173.3, 165.8, 146.6, 141.4, 131.0, 126.7, 123.6, 122.7, 93.9, 82.9, 80.8, 80.5, 74.0, 73.7, 72.8, 72.6, 72.3, 71.4, 67.9, 67.7, 65.1, 58.9, 42.7, 39.4, 38.6, 37.3, 37.1, 36.6, 36.0, 34.0, 33.9, 30.9, 18.4, 18.1, 17.5, 14.3, 13.7; HRMS (ES^+) *m*/*z* $(M + H)^+$: calcd for $C_{37}H_{59}O_{12}$, 695.4007; found, 695.4017.

*Compound (−)-****76***. To a solution of 13.6 mg of the crude **74** in 7.0 mL of THF at 0 °C was added solid K_2CO_3 (7 mg). The resulting solution was stirred at 0 °C for 7 h. The reaction was then quenched with 10 mL of sat. aq. NH_4Cl at 0 °C. The resulting mixture was then warmed to room temperature, and the organic phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20−40% EtOAc/hexanes) to afford the desired product **76** as a colorless oil (7.9 mg, 0.0081 mmol, 65% over 2 steps): $[\alpha]^{20}_D$ −27.35 (*c* 0.20, CH_2Cl_2); IR (film, cm^{-1}) 3449, 2961, 2927, 2856, 1720, 1657, 1462, 1362, 1254, 1095, 1046, 897, 837, 777, 668; ^1H NMR (500 MHz, $CDCl_3$) δ 7.02−6.94 (m, 1 H), 6.27 (dd, *J* = 14.9, 11.3 Hz, 1 H), 6.05−5.97 (m, 2 H), 5.48 (dd, *J* = 14.9, 8.7 Hz, 1 H), 5.29 (td, *J* = 10.5, 5.2 Hz, 1 H), 5.14−5.08 (m, 1 H), 4.89 (d, *J* = 2.6 Hz, 1 H), 4.01−3.95 (m, 1 H), 3.88−3.84 (m, 1 H), 3.82−3.73 (m, 3 H), 3.65−3.52 (m, 4 H), 3.45 (s, 3 H), 3.44−3.40 (m, 1 H), 3.37−3.30 (m, 2 H), 2.47−2.32 (m, 5 H), 2.07−1.99 (m, 1 H), 1.98−1.88 (m, 3 H), 1.80−1.72 (m, 1 H), 1.64−1.49 (m, 2 H), 1.32−1.19 (8 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.95−0.91 (m, 12 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.13−0.09 (m, 9 H), 0.08 (s, 3 H), 0.04 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 146.8, 140.6, 130.3, 128.0, 124.9, 123.3, 82.8, 81.8, 81.4, 73.8, 73.5, 73.3, 73.2, 73.0, 72.8, 70.6, 66.1, 58.9, 43.5, 39.7, 39.3, 38.0, 36.5, 36.3, 35.6, 33.5, 31.3, 29.9, 26.4, 26.22, 26.16, 18.9, 18.8, 18.5, 18.3, 18.2, 14.8, −2.8, −3.7, −4.0, −4.1, −5.0; HRMS (ES^+) *m*/*z* $(M + Na)^+$: calcd for $C_{51}H_{94}O_{11}Si_3Na$, 989.6002; found, 989.6014.

The known compound **79** was obtained as a side product (in less than 10% yield) during the conversion of **74** to **76** and was subjected to global deprotection to yield seco-mandelalide A methyl ester (−)-**80**: to a solution of **79** (10.0 mg, 0.010 mmol) in 0.8 mL of THF in a polypropylene tube at 0 °C were added 0.8 mL of pyridine and 0.8 mL of HF·Pyridine complex (70% HF) dropwise via Eppendorf pipet. The resulting solution was stirred at 0 °C for 5 min. The cold bath was then removed, and the resulting solution was stirred at room temperature for another 16 h. The reaction was then quenched with 20 mL of sat. aq. $NaHCO_3$ solution slowly and stirred at room temperature for 30 min. The organic phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (8% MeOH/CH_2Cl_2) to afford the desired product **80** as colorless waxy solid (4.0 mg, 0.0061 mmol, 61%): $[\alpha]^{20}_D$ −48.07 (*c* 0.33, MeOH); IR (film, cm^{-1}) 3391, 2924, 2857, 1721, 1658, 1447, 1373, 1322, 1277, 1106, 1042, 992; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (m, 1 H), 6.26 (dd, *J* = 14.9, 11.1 Hz, 1 H), 6.04 (t, *J* = 11.1 Hz, 1 H), 5.89 (d, *J* = 15.7 Hz, 1 H), 5.59 (m, 1 H), 5.33 (m, 1 H), 5.02 (s, 1 H), 4.07−3.99 (m, 1 H), 3.98−3.91 (m, 1 H), 3.74 (s, 3 H), 3.69−3.60 (m, 4 H), 3.56−3.49 (m, 1 H), 3.48 (s, 1 H), 3.44−3.30 (m, 6 H), 2.51−2.31 (m, 7 H), 2.30−2.22 (m, 1 H), 2.11−2.05 (m, 1 H), 2.00−1.89 (m, 3 H), 1.71−1.50 (m, 4 H), 1.43−1.33 (m, 3 H), 1.30 (d, *J* = 5.9 Hz, 3 H), 1.19−1.10 (m, 2 H), 1.02 (d, *J* = 6.3 Hz, 3 H), 0.99 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.6, 147.4, 141.7, 131.0, 127.4, 125.1, 123.7, 96.6, 83.8, 83.0, 82.6, 75.4, 74.9, 74.7, 74.3, 72.2, 71.9, 70.1, 69.9, 68.0, 59.3, 52.0, 44.1, 40.3, 39.6, 38.5, 38.2, 37.04, 36.99, 34.7, 30.6, 20.8, 18.1, 15.6; HRMS (ES^+) *m*/*z* $(M + Na)^+$: calcd for $C_{34}H_{56}O_{12}Na$, 679.3669; found, 679.3696.

*Compound (−)-****77***. To a solution of compound **76** (5.0 mg, 0.0052 mmol) in 1.5 mL of CH_2Cl_2 at room temperature were added sequentially a solution of 2,3,5-collidine (19.0 mg/mL in CH_2Cl_2, 0.30 mL, 0.047 mmol) and a solution of valeroyl chloride (12.0 mg/mL in CH_2Cl_2, 0.30 mL, 0.030 mmol) via syringe. The resulting mixture was stirred at room temperature for 3 h. The solution was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (15−20% EtOAc/hexanes) to afford the desired product **77** as a colorless oil (2.5 mg, 0.0023 mmol, 45%, 95% brsm): $[\alpha]^{20}_D$ −18.30 (*c* 0.10, CH_2Cl_2); IR (film, cm^{-1}) 2956, 2927, 2867, 1725, 1467, 1380, 1263, 1147, 1090, 837, 740; ^1H NMR (600 MHz, $CDCl_3$) δ 6.95 (ddd, *J* = 15.0, 9.4, 5.1 Hz, 1 H), 6.26 (dd, *J* = 15.0, 10.9 Hz, 1 H), 6.04−5.93 (m, 2 H), 5.46 (dd, *J* = 15.0, 9.1 Hz, 1 H), 5.33−5.20 (m, 2 H), 4.89 (d, *J* = 2.8 Hz, 1 H), 4.27 (dd, *J* = 11.7, 4.2 Hz, 1 H), 4.03 (dd, *J* = 11.7, 5.0 Hz, 1 H), 3.98 (t, *J* = 9.2 Hz, 1 H), 3.88−3.71 (m, 3 H), 3.60−3.41 (m, 4 H), 3.45 (s, 3 H), 3.38−3.29 (m, 2 H), 2.49−2.27 (m, 7 H), 2.06−1.87 (m, 4 H), 1.75−1.16 (m, 14 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.87−0.82 (m, 33 H), 0.12−0.09 (m, 9 H), 0.08 (s, 3 H), 0.03 (s, 3 H), −0.04 (s,

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3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 165.8, 146.4, 140.5, 130.3, 130.0, 125.0, 123.2, 83.0, 81.3, 73.9, 73.5, 73.3, 73.2, 72.8, 70.6, 68.8, 65.5, 58.9, 43.5, 39.7, 39.4, 38.1, 36.6, 36.4, 36.2, 35.1, 34.1, 33.5, 31.3, 27.1, 26.4, 26.23, 26.16, 22.4, 22.2, 18.82, 18.78, 18.5, 18.3, 18.2, 14.7, 13.9, 13.8, −2.8, −3.7, −4.0, −4.1, −5.0; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{56}H_{102}O_{12}Si_3Na$, 1073.6577; found, 1073.6556.

*Compound (−)-**78**.* To a solution of **77** (2.0 mg, 0.0019 mmol) in 0.5 mL of THF in a polypropylene tube at 0 °C were added 0.5 mL of pyridine and 0.5 mL of HF·Pyridine complex (70% HF) dropwise via Eppendorf pipet. The resulting solution was stirred at 0 °C for 5 min. The cold bath was then removed, and the resulting solution was stirred at room temperature for another 24 h. The reaction was then quenched with 10 mL of sat. aq. $NaHCO_3$ solution slowly and stirred at room temperature for 30 min. The organic phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (2−4% MeOH/CH_2Cl_2) to afford the desired product **78** as colorless amorphous solid (1.3 mg, 0.0018 mmol, 93%): $[\alpha]^{20}_D$ −53.16 (*c* 0.071, MeOH); IR (film, cm^{-1}) 3421, 2962, 2925, 2869, 1725, 1461, 1370, 1265, 1146, 1107, 1072, 1045, 740, 668; ^{1}H NMR (600 MHz, $CDCl_3$, residual solvent peak set at 7.24 ppm) δ 6.95 (ddd, *J* = 15.1, 10.0, 4.9 Hz, 1 H), 6.26 (dd, *J* = 14.9, 10.9 Hz, 1 H), 6.05 (t, *J* = 10.9 Hz, 1 H), 5.95 (d, *J* = 15.4 Hz, 1 H), 5.44 (dd, *J* = 14.9, 9.8 Hz, 1 H), 5.35 (d, *J* = 11.6 Hz, 1 H), 5.27 (td, *J* = 10.8, 5.4 Hz, 1 H), 5.02 (s, 1 H), 4.35 (dd, *J* = 11.9, 3.9 Hz, 1 H), 4.06 (dd, *J* = 11.9, 4.3 Hz, 1 H), 3.98 (t, *J* = 9.7 Hz, 1 H), 3.86−3.79 (m, 1 H), 3.71−3.59 (m, 3 H), 3.46 (s, 3 H), 3.43−3.28 (m, 5 H), 2.59−2.49 (m, 2 H), 2.42−2.20 (m, 8 H), 2.07−1.97 (m, 2 H), 1.92−1.84 (m, 2 H), 1.74−1.67 (m, 1 H), 1.65−1.41 (m, 4 H), 1.36−1.15 (m, 9 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.89 (t, *J* = 7.3 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, residual solvent peak set at 77.0 ppm) δ 173.5, 165.7, 146.6, 141.4, 131.0, 126.6, 123.6, 122.7, 93.9, 82.9, 80.8, 80.5, 74.0, 73.8, 72.8, 72.6, 72.3, 71.4, 67.9, 67.7, 65.1, 58.9, 42.7, 39.4, 38.6, 37.3, 37.1, 36.6, 34.0, 33.92, 33.86, 30.9, 27.0, 22.2, 18.1, 17.5, 14.3, 13.7; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{38}H_{60}O_{12}Na$, 731.3982; found, 731.3986.

*(−)-Mandelalide L (**16**).* To a solution of **76** (3.0 mg, 0.0031 mmol) in 1.0 mL of CH_2Cl_2 at room temperature were added sequentially a solution of 2,3,5-collidine (11.0 mg/mL in CH_2Cl_2, 1.10 mL, 0.100 mmol) and a solution of octanoyl chloride (10.0 mg/mL in CH_2Cl_2, 1.10 mL, 0.068 mmol) via syringe. The resulting mixture was stirred at room temperature for 13 h. The solution was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to afford the desired product contaminated with octanoic acid, which was used directly in the global deprotection step.

To a solution of the above product mixture in 0.5 mL of THF in a polypropylene tube at 0 °C were added 0.5 mL of pyridine and 0.5 mL of HF·Pyridine complex (70% HF) dropwise via Eppendorf pipet. The resulting solution was stirred at 0 °C for 5 min. The cold bath was then removed, and the resulting solution was stirred at room temperature for another 38 h. The reaction was then quenched with 20 mL of sat. aq. $NaHCO_3$ solution slowly and stirred at room temperature for 30 min. The organic phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by RP18 HPLC (10−90% MeCN−H_2O, 0.05% formic acid) to afford the natural product **16** as a colorless amorphous solid (1.7 mg, 0.0023 mmol, 75% over 2 steps): $[\alpha]^{20}_D$ −52.25 (*c* 0.07, MeOH); IR (film, cm^{-1}) 3434, 2954, 2925, 2871, 1721, 1465, 1378, 1285, 1264, 1147, 1109, 1069, 737; ^{1}H NMR (600 MHz, $CDCl_3$, residual solvent peak set at 7.24 ppm) δ 6.95 (ddd, *J* = 15.1, 10.4, 4.6 Hz, 1 H), 6.26 (dd, *J* = 14.7, 11.4 Hz, 1 H), 6.05 (t, *J* = 10.6 Hz, 1 H), 5.95 (d, *J* = 15.4 Hz, 1 H), 5.44 (dd, *J* = 14.7, 9.9 Hz, 1 H), 5.35 (d, *J* = 11.0 Hz, 1 H), 5.27 (td, *J* = 10.5, 5.7 Hz, 1 H), 5.02 (s, 1 H), 4.35 (dd, *J* = 11.7, 3.7 Hz, 1 H), 4.06 (dd, *J* = 11.7, 4.0 Hz, 1 H), 3.98 (t, *J* = 9.9 Hz, 1 H), 3.86−3.79 (m, 1 H), 3.72−3.60 (m, 3 H), 3.46 (s, 3 H), 3.43−3.28 (m, 5 H), 2.61−2.48 (m, 2 H), 2.43−2.21 (m, 8 H), 2.06−1.98 (m, 2 H), 1.92−1.85 (m, 2 H), 1.74−1.68 (m, 1 H), 1.63−1.16 (m, 19 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.86 (t, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, residual solvent peak set at 77.0 ppm) δ 173.5, 165.8, 146.6, 141.4, 131.0, 126.6, 123.6, 122.7, 93.9, 82.9, 80.8, 80.5, 74.0, 73.7, 72.8, 72.6, 72.3, 71.4, 67.9, 67.7, 65.1, 58.9, 42.7, 39.4, 38.6, 37.3, 37.1, 36.6, 34.1, 34.0, 33.9, 31.7, 30.9, 29.0, 28.9, 24.9, 22.6, 18.1, 17.5, 14.3, 14.1; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{41}H_{66}O_{12}Na$, 773.4452; found, 773.4452.

*Compound (−)-**82a**.* To a solution of **76** (18.0 mg, 0.0186 mmol) in 3.5 mL of CH_2Cl_2 at room temperature were added sequentially a solution of 2,3,5-collidine (34.5 mg/mL in CH_2Cl_2, 0.89 mL, 0.25 mmol) and a solution of the acid chloride **81** (21.5 mg/mL in CH_2Cl_2, 0.60 mL, 0.11 mmol) via syringe. The resulting mixture was stirred at room temperature for 5.5 h. The solution was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to afford the desired product **82a** as a colorless oil (18.5 mg, 0.018 mmol, 95%): $[\alpha]^{20}_D$ −23.48 (*c* 0.28, CH_2Cl_2); IR (film, cm^{-1}) 2928, 2855, 1746, 1726, 1658, 1463, 1361, 1254, 1155, 1124, 1095, 1047, 898, 868, 838, 778; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (ddd, *J* = 15.1, 9.3, 5.4 Hz, 1 H), 6.26 (dd, *J* = 15.0, 10.9 Hz, 1 H), 6.06−5.92 (m, 2 H), 5.46 (dd, *J* = 14.9, 9.1 Hz, 1 H), 5.34−5.18 (m, 2 H), 4.89 (d, *J* = 2.9 Hz, 1 H), 4.31 (dd, *J* = 11.7, 4.0 Hz, 1 H), 4.05 (dd, *J* = 11.7, 5.3 Hz, 1 H), 3.98 (t, *J* = 9.2 Hz, 1 H), 3.88−3.70 (m, 3 H), 3.61−3.39 (m, 4 H), 3.45 (s, 3 H), 3.38−3.29 (m, 2 H), 2.59−2.29 (m, 9 H), 2.06−1.87 (m, 5 H), 1.75−1.14 (m, 10 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.96−0.82 (m, 30 H), 0.13−0.09 (m, 9 H), 0.08 (s, 3 H), 0.03 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 165.8, 146.6, 140.6, 130.3, 128.0, 125.0, 123.1, 82.9, 82.6, 81.3, 73.9, 73.5, 73.33, 73.28, 72.8, 70.6, 69.2, 68.7, 66.0, 58.9, 43.5, 39.7, 39.4, 38.1, 36.6, 36.4, 36.1, 33.5, 33.4, 31.3, 26.4, 26.23, 26.16, 18.83, 18.80, 18.5, 18.3, 18.2, 14.7, 14.4, −2.8, −3.7, −4.0, −4.1, −5.0; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{56}H_{98}O_{12}Si_3Na$, 1069.6264; found, 1069.6271.

*Compound (−)-**82**.* To a solution of **82a** (11.4 mg, 0.0109 mmol) in 2.0 mL of THF in a polypropylene tube at 0 °C were added 2.0 mL of pyridine and 2.0 mL of HF·Pyridine complex (70% HF) dropwise via Eppendorf pipet. The resulting solution was stirred at 0 °C for 5 min. The cold bath was then removed, and the resulting solution was stirred at room temperature for another 28 h. The reaction was then quenched with 30 mL of sat. aq. $NaHCO_3$ solution slowly and stirred at room temperature for 30 min. The organic phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (2−4% MeOH/CH_2Cl_2) to afford the desired product **82** as colorless amorphous solid (6.9 mg, 0.0098 mmol, 90%): $[\alpha]^{20}_D$ −29.97 (*c* 0.25, MeOH); IR (film, cm^{-1}) 3429, 3307, 2920, 1723, 1658, 1453, 1370, 1264, 1158, 1100, 1045, 984, 814735; ^{1}H NMR (600 MHz, $CDCl_3$, residual solvent peak set at 7.26 ppm) δ 6.97 (ddd, *J* = 15.2, 9.9, 5.1 Hz, 1 H), 6.28 (dd, *J* = 14.8, 11.0 Hz, 1 H), 6.06 (t, *J* = 10.9 Hz, 1 H), 5.97 (d, *J* = 15.9 Hz, 1 H), 5.46 (dd, *J* = 14.8, 9.9 Hz, 1 H), 5.38 (d, *J* = 12.0 Hz, 1 H), 5.29 (td, *J* = 10.8, 5.5 Hz, 1 H), 5.04 (s, 1 H), 4.40 (dd, *J* = 11.9, 3.9 Hz, 1 H), 4.10 (dd, *J* = 11.9, 4.4 Hz, 1 H), 4.00 (t, *J* = 9.2 Hz, 1 H), 3.87−3.81 (m, 1 H), 3.73−3.61 (m, 3 H), 3.47 (s, 3 H), 3.44−3.29 (m, 5 H), 2.70−2.25 (m, 12 H), 2.08−2.00 (m, 2 H), 1.98−1.86 (m, 3 H), 1.75−1.45 (m, 3 H), 1.28 (d, *J* = 6.3 Hz, 3 H), 1.26−1.16 (m, 4 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, residual solvent peak set at 77.16 ppm) δ 171.6, 165.9, 146.9, 141.6, 131.2, 126.9, 123.7, 122.8, 94.1, 83.1, 82.6, 80.9, 80.7, 74.1, 73.9, 73.0, 72.7, 72.4, 71.6, 69.2, 68.0, 67.7, 65.8, 59.1, 42.9, 39.6, 38.8, 37.5, 37.2, 36.7, 34.14, 34.06, 33.3, 31.04, 18.2, 17.6, 14.46, 14.45; HRMS (ES$^+$) m/z (M + Na)$^+$: calcd for $C_{38}H_{56}O_{12}Na$, 727.3669; found, 727.3719.

*Compound (−)-**84**.* Solid CuI (0.1 mg, 0.00043 mmol) was added to a vial containing **82** (3.0 mg, 0.0043 mmol), and the vial was purged with N_2 gas, followed by addition of 0.25 mL of MeCN (degassed by freeze−pump−thaw). To the resulting solution was added a solution of *N*,*N*-diisopropylethylamine (3% v/v in MeCN, 0.050 mL, 0.0086 mmol), followed by a solution of the biotin-azide tag **83** (15.3 mg/mL

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in MeCN, 0.20 mL, 0.0065 mmol). The obtained solution was stirred under N_2 at room temperature for 18 h. The reaction mixture was then loaded onto a silica gel column and purified by flash chromatography (10−20% MeOH/CH_2Cl_2) to afford the desired product **84** as pale yellow waxy solid (4.6 mg, 0.0039 mmol, 91%): $[\alpha]^{20}_D$ −11.19 (*c* 0.33, MeOH); IR (film, cm^{-1}) 3333, 2919, 2845, 1698, 1655, 1459, 1364, 1259, 1180, 1127, 1106, 1045; ^1H NMR (600 MHz, CD_3OD, residual solvent peak set at 4.78 ppm) δ 7.84−7.68 (m, 2 H), 6.85 (ddd, *J* = 15.1, 10.4, 4.2 Hz, 1 H), 6.14 (dd, *J* = 14.9, 10.9 Hz, 1 H), 5.91 (t, *J* = 10.9 Hz, 1 H), 5.81 (d, *J* = 16.1 Hz, 1 H), 5.35 (dd, *J* = 14.8, 9.8 Hz, 1 H), 5.24−5.11 (m, 2 H), 4.91 (s, 1 H), 4.39−4.32 (m, 2 H), 4.26 (dd, *J* = 11.8, 3.7 Hz, 1 H), 4.18 (dd, *J* = 7.9, 4.4 Hz, 1 H), 3.95−3.85 (m, 2 H), 3.80−3.71 (m, 1 H), 3.63−3.04 (m, 26 H), 2.91−2.83 (m, 2 H), 2.81 (dd, *J* = 12.7, 5.0 Hz, 1 H), 2.64−2.56 (m, 3 H), 2.44−0.99 (m, 37 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.75 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD, residual solvent peak set at 49.00 ppm) δ 176.0, 173.7, 167.7, 166.1, 148.9, 142.5, 131.8, 128.1, 125.9, 124.9, 123.6, 122.5, 96.3, 84.9, 82.7, 82.4, 75.0, 74.5, 74.3, 73.7, 73.4, 72.2, 71.6, 71.5, 71.30, 71.29, 70.1, 69.9, 69.2, 68.3, 66.7, 63.4, 61.6, 59.3, 57.0, 55.8, 44.2, 41.1, 40.9, 39.8, 38.7, 38.4, 37.8, 37.3, 36.9, 35.4, 35.0, 34.2, 32.1, 31.4, 30.4, 29.8, 29.5, 26.9, 21.8, 18.8, 18.0, 14.5; HRMS (ES^+) *m*/*z* $(M + H)^+$: calcd for $C_{58}H_{93}N_6O_{17}S$, 1177.6318; found, 1177.6328.

Chemicals and Reagents for Biological Studies. All synthetic mandelalide compounds were reconstituted in cell culture grade DMSO (100%) and stored at −20 °C until the day of treatment; final concentrations of DMSO never exceeded 0.1%. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) was from Sigma-Aldrich Corp. (St. Louis, MO), and oligomycin A, from Santa Cruz Biotechnology, Inc. (Dallas, TX). General cell culture supplies were from Thermo Fisher Scientific (Waltham, MA) or Sigma-Aldrich.

Mammalian Cell Culture and Analysis of Cell Viability. Human HeLa cervical cancer cells were from the American Type Culture Collection (ATCC) and were grown in Minimal Essential Medium Eagle (MEM) formulation (Mediatech Inc., Manassas, VA) with 10% FBS, L-glutamine (2 mM), and 1% penicillin/streptomycin. Cells were maintained in a humidified chamber at 37 °C with 5% CO_2 and seeded at 10 000 cells/well 16−18 h before treatment. The viability of cells was assessed by MTT assay after 72 h with the viability of vehicle-treated cells at the end of the experiment defined as 100%. In all studies, concentrations were studied in triplicate and the activity of **16**, **75**, **78**, **82**, and **84** was assessed relative to (−)-mandelalide A (**5**). Concentration−response relationships were analyzed using nonlinear regression analysis fit to a four-parameter logistic equation with GraphPad Prism Software (GraphPad Software Inc., San Diego, CA). EC_{50} ± SE values for inhibition of HeLa Cell viability were derived from at least three independent experiments (**5**, **16**, **75**, **78**), with the exception of **82** and **84** which were tested in parallel with **5** once (to 300 nM) in order to conserve material for advanced biological studies.

Complex V Activity Assay. Mitochondrial ATPase activity was measured with a MitoCheck Complex V activity assay kit (# 701000) from Cayman Chemical (Ann Arbor, MI). Briefly, the activity of complex V in isolated bovine heart mitochondria was determined in a colormetric assay by measuring the rate of NADH oxidation at 340 nm (captured every 30 s for 30 min) at 25 °C. The reaction rate was determined by plotting absorbance (*y*-axis), calculated from the slope for the linear portion of each curve versus time (*x*-axis). Complex V activity was calculated as % activity relative to the vehicle control:

$$\text{complex V activity (\%)} = \left[\frac{\text{rate of sample wells}}{\text{rate of vehicle control}}\right] \times 100$$

A concentration−response relationship was generated for (−)-mandelalide A (**5**), on the day of the experiment, for comparison with fixed concentrations of **84** (1 μM) or a saturating concentration of oligomycin A (12.5 μM).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00268.

^1H NMR and ^{13}C NMR spectral data of synthetic compounds, concentration−response curves for biological assays (PDF)

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Notes

The authors declare no competing financial interest.

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