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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Total Synthesis of (−)-Mandelalide A Exploiting Anion Relay Chemistry (ARC): Identification of a Type II ARC/CuCN Cross-Coupling Protocol

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Supporting Information

ABSTRACT: Anion relay chemistry (ARC), an effective, multicomponent union tactic, was successfully employed for the total synthesis of the highly cytotoxic marine macrolide (−)-mandelalide A (**1**). The northern hemisphere was constructed via a new type II ARC/CuCN cross-coupling tactic, while the southern hemisphere was secured via a highly efficient four-component type I ARC union. Importantly, the synthesis of **1** showcases ARC as a rapid, scalable coupling strategy for the union of simple readily available building blocks to access diverse complex molecular fragments with excellent stereochemical control.

The mandelalides constitute a family of unusual, variously glycosylated polyketide macrolides isolated by McPhail et al.[1] via bioassay guided fractionation of the cytotoxic extracts of a rare species of *Lissoclinum* ascidian collected from Algoa Bay, South Africa. Among this family, (−)-mandelalide A (**1**, Figure 1) was reported to exhibit the most potent biological activity,

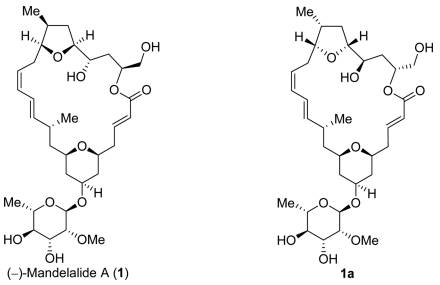


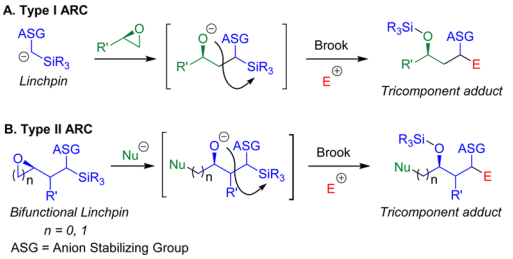
Figure 1. Structure of (−)-mandelalide A (**1**) and originally assigned structure (**1a**).

with nanomolar cytotoxicities against both human NCI-H460 lung cancer cells (IC_{50}, 12 nM) and mouse Neuro-2A neuroblastoma cells (IC_{50}, 29 nM), thus rendering (−)-mandelalide A (**1**) and analogs attractive as lead structures for cancer chemotherapeutics. The inaccessibility of the source organism[2] however precludes ready biological investigation.

Notsurprisingly, this architecturally interesting family of natural products has become of considerable interest to the synthetic community, leading recently to the revision via synthesis[3,4b] of the stereochemical configuration of (−)-mandelalide A (Figure 1).[3−7] Interestingly, initial evaluations of the synthetic material against a small panel of cancer cell lines by several investigators yielded contradictory cell toxicity data,[8] pressing the demand for a modular preparative synthesis of (−)-**1** for detailed evaluation and future analog development.

Anion relay chemistry (ARC), an effective, multicomponent union protocol, introduced and developed in our laboratory for the rapid elaboration of structurally complex scaffolds in a "single-flask" entails the ability to control the migration of negative charge.[9] Over the past decade, we have reported extensive studies in the area of through-space ARC employing Brook rearrangements, which led to the evolution of types I and II ARC union tactics (Scheme 1).[10] The potential of each of the

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



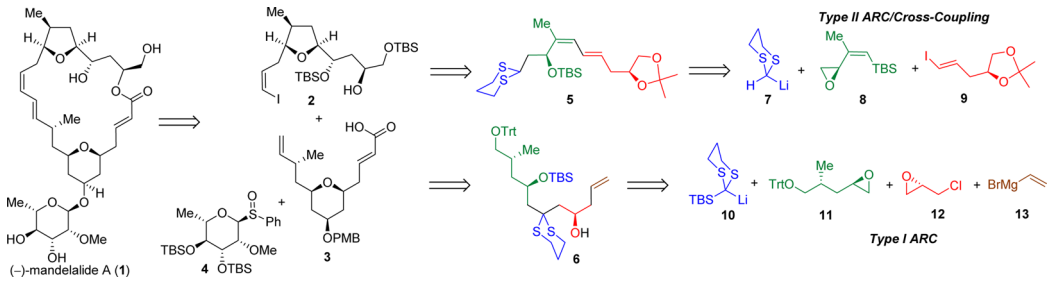
ARC tactics has been demonstrated separately in a number of completed or ongoing synthetic ventures, including those on (+)-spongistatin 1 and 2,[11] (+)-spirastrellolide A and B,[12] (−)-secu'amamine A,[13] and most recently (−)-enigmazole A.[14] Herein, we illustrate the strategic value of *both* types I and II ARC union tactics with a total synthesis of (−)-mandelalide A (**1**). In addition we demonstrate for the first time the combination of through-space negative charge migration, followed by a new CuCN-mediated cross-coupling of significant value for complex molecule synthesis.

From the retrosynthetic perspective (Scheme 2), we envisioned the macrocyclic aglycon of (−)-mandelalide A (**1**) to arise from advanced fragments **2** and **3**, which in turn would be united via a Yamaguchi esterification, followed by a ring-closing Heck reaction. Glycosylation with the known 2-*O*-methyl-α-L-rhamnose-based fragment (+)-**4**[3] would then yield the natural product **1**. The tetrahydrofuran and tetrahydropyran structural motifs embedded in the northern and southern hemispheres in

Received: February 16, 2016

DOI: 10.1021/jacs.6b01731
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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

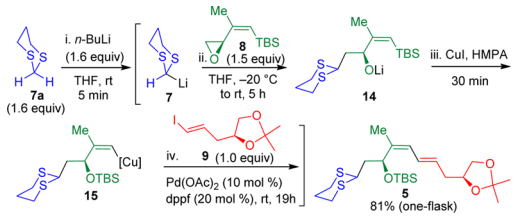


turn would be constructed from advanced intermediates **5** and **6**, respectively.

Anion Relay Chemistry (ARC) was envisioned to provide access to both **5** and **6** with great stereochemical flexibility for future analog development, employing commercially available and/or readily prepared intermediates or building blocks **7**−**13** (Scheme 2).[15] Importantly, the proposed construction of advanced intermediate **5** would showcase a novel type II ARC tactic featuring the migration of negative charge to a sp^2-hybridized carbon center capable of undergoing cross-coupling with an electrophilic partner.[16]

The synthesis of (−)-mandelalide A (**1**) began with the construction of the northern hemisphere (**2**; Scheme 3). Toward

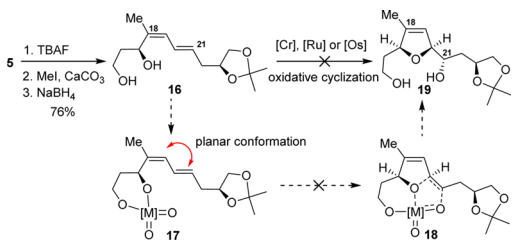
Scheme 3. Type II ARC/Pd Cross-Coupling



this end, nucleophilic attack of the vinyl epoxide linchpin (−)-**8**[15] with 2-lithio-1,3-dithiane (**7**), followed by a CuI-triggered Brook rearrangement to what we envisioned to be a sp^2-hybridized carbon nucleophile **15**, then readily underwent Pd-catalyzed cross-coupling reaction with vinyl iodide (+)-**9** to furnish advanced intermediate **5** in a "single flask" in excellent yield (81%).

Adduct **5** in turn was subjected to the reaction sequence of alcohol deprotection, dithiane removal, and carbonyl reduction to furnish diol (+)-**16** (Scheme 4), setting the stage to explore the key strategic construction of the required tetrahydrofuran ring. Here we envisioned the 1,3-diol to chelate to a metal catalyst to facilitate a selective, *syn*-specific oxidative cyclization on the disubstituted alkene of the conjugated diene system to generate

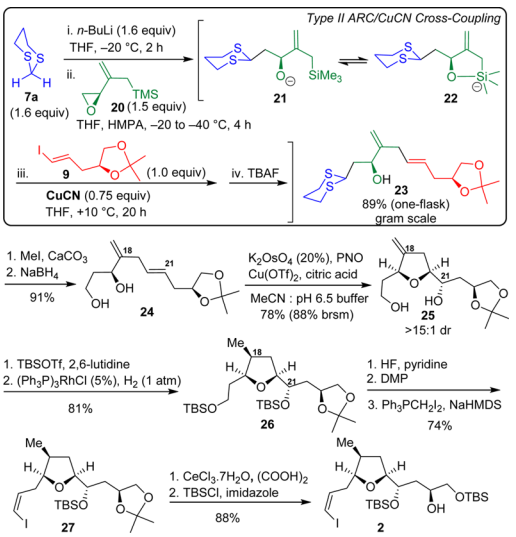
Scheme 4. Planar Conformation Inhibits Oxidative Cyclization



2,5-*cis*-dihydrofuran **19** in a stereocontrolled fashion, possessing the requisite hydroxyl group at C_{21}. A series of catalytic systems employing various metals (e.g., osmium,[17] ruthenium[18] and chromium[19]) known to facilitate oxidative cyclization of vicinal diols adjacent to alkenes to generate *cis*-tetrahydrofurans was screened. All attempts toward this end however proved unsuccessful, leading either to very sluggish reactions or to decomposition. We reason that the major reason for this difficulty could be attributed to the inherent planar conformation of the conjugated diene system which inhibits formation of the requisite transition state **18**.

Gratifyingly, a solution to this problem could be achieved exploiting the flexibility of the ARC tactic (Scheme 5).

Scheme 5. Revision of the ARC Tactic and Construction of the Northern Hemisphere

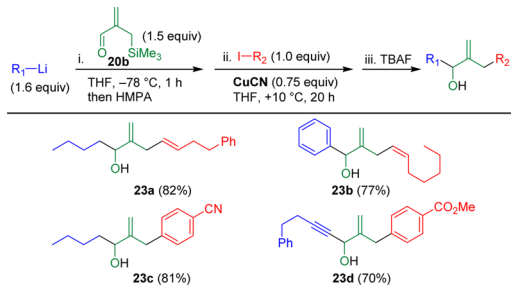


Application of the type II ARC/cross-coupling strategy employing 1,3-dithiane, vinyl iodide (+)-**9** with the redesigned vinyl epoxide linchpin (−)-**20**,[15,20] now possessing a terminal olefin, furnished tricomponent adduct (+)-**23** in excellent yield (89%) on a gram scale. Dithiane removal revealed 1,3-diol (+)-**24**, now possessing a skipped diene system which underwent an efficient, albeit slow,[21] stereocontrolled osmium-catalyzed oxidative cyclization[17] to provide the desired advanced intermediate [(−)-**25**] in good yield with excellent stereoselectivity (88% brsm, >15:1 dr). The great advantage of ARC to readily customize coupling partners [e.g., (−)-**8** and (−)-**20**] with programmable, preloaded functionality and stereochemistry to access a wide variety of scaffolds was thus demonstrated. Particularly important, we identified during this study a copper cyanide-mediated cross-coupling reaction between vinyl iodide

DOI: 10.1021/jacs.6b01731
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(+)-**9** and allyl silane **21**, activated via what we presume to be a pentavalent silicon-ate (**22**) derive from an adjacent alkoxide group.[22] *Interestingly, attempts to use palladium catalysis to carry out the same ARC/cross-coupling protocol failed to provide the desired adduct in more than 5% yield, demonstrating the unique utility of this CuCN-mediated reaction in a multicomponent union protocol (i.e., ARC).* A preliminary study on the substrate scope of this ARC/CuCN cross-coupling strategy is outlined in Scheme 6.

Scheme 6. Multicomponent Union Featuring a Type II ARC/CuCN Cross-Coupling Protocol

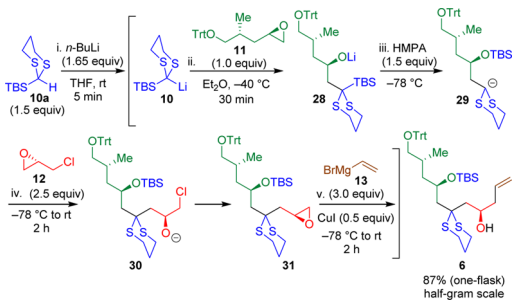


Also of significance in the construction of (−)-**25** is the transition-metal-mediated oxidative cyclization of an allylic 1,3-diol, known to be a difficult substrate, due both to the unfavorable chelate ring size and to a variety of possible side reactions (e.g., allylic alcohol oxidation, racemization of allylic alcohol, and product instability).

Advanced intermediate (−)-**25** (Scheme 5) was next subjected to bis-hydroxy protection (TBSCl), followed by hydrogenation with Wilkinson catalyst to install the desired stereocenter at C_{18}. Selective desilylation of primary alcohol, Dess-Martin periodinane oxidation, and Stork-Zhao olefination[23] then provided advanced intermediate (−)-**27** in 74% yield. Further protecting group manipulations (two steps) completed the construction of the mandelalide A northern hemisphere (−)-**2**.

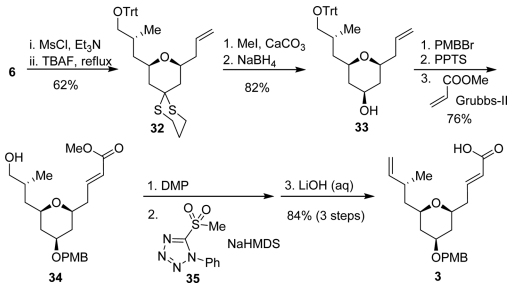
We next turned attention to the construction of the mandelalide A southern hemisphere aglycon (**3**), which as outlined earlier would rely on a type I ARC tactic[24] (Scheme 7).

Scheme 7. Four-Component Type I ARC



Nucleophilic attack of known epoxide (+)-**11**[15,25] with 2-lithio-2-TBS-1,3-dithiane (**10**), followed by a solvent-triggered Brook rearrangement generated what we envision to be a carbon nucleophile at the 2-position of the dithiane (**29**). In the same flask, (*S*)-epichlorohydrin was added as the second electrophile, to generate chlorohydrin anion **30**, which in turn formed a new electrophilic terminal epoxide upon warming the reaction mixture to room temperature. Addition of vinylmagnesium bromide and copper iodide completed the construction of the requisite advanced homoallylic alcohol (−)-**6**. *Pleasingly, this four-component adduct could be generated in a single flask in 87% yield on half-gram scale, with an average yield for each of the three carbon−carbon bond-forming steps over 95%.* Mesylation of the free hydroxyl group (Scheme 8) then set the stage for ring

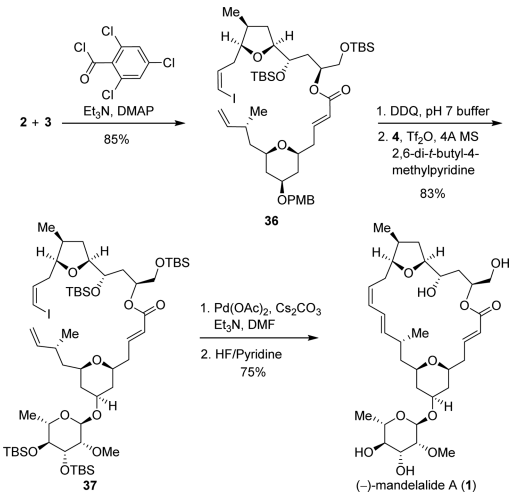
Scheme 8. Construction of the Southern Hemisphere



formation upon TBS group removal, to yield tetrahydropyran (−)-**32**. Removal of dithiane, followed by reduction with $NaBH_4$ next led with high stereocontrol to alcohol (+)-**33** in 82% yield. Further protecting group manipulations and cross-metathesis with methyl acrylate furnished advanced intermediate (+)-**34** in 76% yield for the three steps. Alcohol (+)-**34** was then subjected to Dess-Martin periodinane oxidation, Julia-Kocienski olefination with known sulfone **35**,[26] and ester saponification to complete the construction of the southern hemisphere (−)-**3** in 84% yield for the three steps.

Having the northern and southern fragments (−)-**2** and (−)-**3** in hand, final elaboration to (−)-mandelalide A (**1**) is outlined in Scheme 9. To this end, (−)-**2** and (−)-**3** were smoothly united

Scheme 9. Fragments Union



via Yamaguchi esterification, to furnish (−)-**36** in 85% yield, without isomerization of the enoate double bond, an issue previously observed both by Furstner[4] and Altmann.[6] Removal of PMB protecting group, followed by Kahne glycosylation[27] with sulfoxide (+)-**4**[3] then furnished (−)-**37** in 83% yield. Macrocyclization employing Heck reaction[28] on (−)-**37** then proceeded with remarkable ease. Global desilylation with HF/pyridine completed the synthesis of (−)-mandelalide A (**1**), which displayed spectral properties identical in all respects to those reported for the natural product.[15]

In summary, a highly convergent, modular synthesis of (−)-mandelalide A (**1**) has been achieved exploiting ARC. The

DOI: 10.1021/jacs.6b01731
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central features of this synthetic venture entailed the development of a novel three-component type II ARC/CuCN cross-coupling protocol and a four-component type I ARC union, both performed on preparative scale employing commercially available and/or readily accessible building blocks. The advantages of the ARC tactic are evident in the short synthetic sequences[29] and the excellent stereochemical control, holding the promise for all possible stereogenicities in the macrocyclic aglycon of mandelalide A (**1**). Also of significance, we have identified an effective new CuCN-mediated cross-coupling reaction of allyl silanes with vinyl and aryl iodides that is compatible with the ARC multicomponent union protocol. Application of the strategies presented here for the synthesis of other members of mandelalide family and analogs thereof continues in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01731.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the NIH through Grant CA-19033 and in part by GM-29028. T.K. thanks JSPS for a Fellowship for Young Japanese Scientist. We also thank Drs. George Furst and Jun Gu and Dr. Rakesh K. Kohli for assistance obtaining NMR and high-resolution mass spectra, respectively.

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(29) The total synthesis has been achieved with a longest linear reaction sequence of 17 steps from known (*rac*)-**20**, comparing quite favorable to all previous total syntheses (21 steps from known materials).

DOI: 10.1021/jacs.6b01731
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX