

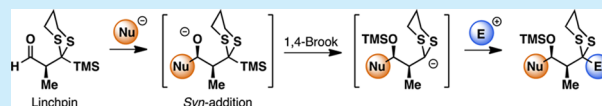
An Effective Bifunctional Aldehyde Linchpin for Type II Anion Relay Chemistry: Development and Application to the Synthesis of a C16–C29 Fragment of Rhizopodin

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S Supporting Information

ABSTRACT: The design, synthesis, and validation of a new bifunctional aldehyde linchpin for Type II anion relay chemistry have been achieved. For this linchpin, the initial nucleophilic addition proceeds under Felkin–Anh control to generate the *syn*-alkoxide, which undergoes a 1,4-Brook rearrangement to relay the negative charge, thus leading to the formation of a dithiane-stabilized carbanion. Subsequent trapping with an electrophile furnishes a tricomponent adduct with an embedded propionate subunit, a ubiquitous structural motif found in polyketides. The utility of this new linchpin is demonstrated with the construction of a potential C16–C29 fragment for the synthesis of rhizopodin, an actin-binding macrolide.



Propionate and polypropionate subunits are ubiquitous structural motifs found in many polyketide natural products possessing diverse biological properties.¹ Stereocontrolled synthesis of such structural motifs has attracted considerable interest in the synthetic community due to the challenges that arise from the inherent architectural complexity of many bioactive natural products.² Multicomponent anion relay chemistry (ARC), a highly effective, stereocontrolled fragment union process pioneered in our laboratory,³ holds significant promise for the rapid construction of diverse polyketide natural products.

Over the past decade, we have reported extensive studies in the area of fragment union.⁴ In the area of through-space anion relay chemistry (ARC) (i.e., negative charge migration), we exploited [1,*n*]-Brook rearrangements that have led to the discovery of Type I and Type II ARC union tactics (Figure 1).⁵ In Type I ARC, an anion is first generated on linchpin 1 facilitated by an

anion-stabilizing group (ASG, e.g., dithiane), which adds to an epoxide to form an alkoxide (2). Upon Brook rearrangement, the negative charge is relayed back to the originating carbon, which is then terminated with either the same electrophile (i.e., homocoupling) or a different electrophile (i.e., heterocoupling) to deliver the three-component adduct 3. In Type II ARC, an external nucleophile is first added to a bifunctional linchpin (4) to generate alkoxide 5, which upon triggering the Brook rearrangement, either by change in solvent polarity, temperature, and/or counterion, the negative charge is then transferred to a new carbon site.^{5b} Subsequent trapping with an electrophile furnishes the three-component adduct 6. Linchpins can also be added in iterative fashion to form multicomponent adducts such as 8 via a process not dissimilar to living polymerization.⁶

Given the considerable potential of the multicomponent ARC tactic in assembling diverse molecular scaffolds with precise stereocontrol, we initiated a program to focus on the design, synthesis, and validation of a new aldehyde linchpin 9 that would enable the construction of propionate-containing natural products exploiting the Type II ARC tactic. The proposed Type II ARC tactic with linchpin 9 is depicted in Figure 2A. Here, addition of an external nucleophile to the aldehyde (9) would proceed under Felkin–Anh control⁷ to generate *syn*-alkoxide 10, which would then undergo 1,4-Brook rearrangement, triggered by the addition of a polar additive (i.e., HMPA), to form anionic dithiane 11. Termination with an electrophile would deliver the three-component adduct 12, which upon reductive dithiane removal would reveal a methylene group (13) or upon dithiane hydrolysis a carbonyl group (14) for further functionalization.

To explore this scenario, we first constructed the prospective racemic aldehyde linchpin 9 from 2-methyl-1,3-propanediol 15 (Figure 2B). Monoprotection of the diol with trityl chloride

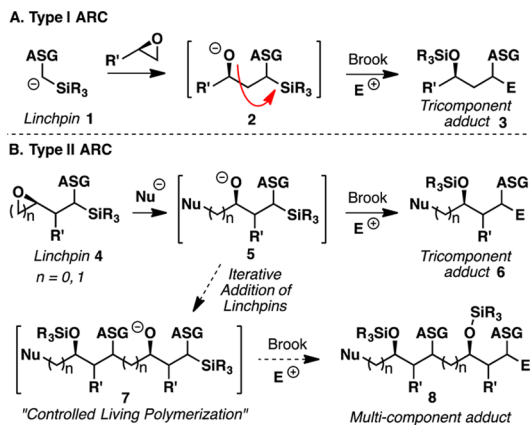


Figure 1. Through-space Type I and Type II ARC tactics. ASG: Anion-Stabilizing Group.

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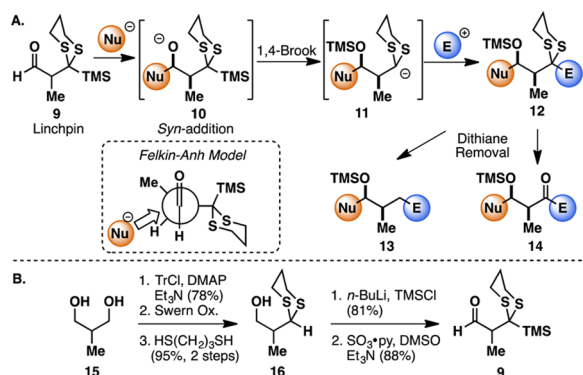


Figure 2. (A) Type II ARC employing aldehyde linchpin 9. (B) Linchpin synthesis in racemic series.

followed by oxidation of the free alcohol led to the corresponding aldehyde, which upon treatment with 1,3-propanedithiol and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ furnished dithiane 16 with concomitant removal of the trityl group. Subsequent C-silylation with $\text{TMSCl}/n\text{-BuLi}$ followed by Parikh–Doering oxidation of the free alcohol delivered the desired linchpin 9. This linchpin was also prepared in highly enantiomerically enriched fashion starting from either commercially available Roche ester (vide infra).

With the prospective linchpin in hand, we turned to the proposed Type II ARC reaction. We first investigated $n\text{-BuLi}$ and allyl bromide as the initiating nucleophile and terminating electrophile, respectively. After preliminary screenings, we discovered that addition of $n\text{-BuLi}$ to the linchpin in Et_2O at -78°C , followed by introduction of allyl bromide and HMPA in Et_2O and warming of the reaction mixture to ambient temperature over 4 h, furnished the desired three-component adduct 17 as a single *syn*-diastereomer (vide infra) in 74% yield after acid-mediated removal of the TMS group (Table 1, entry 1). The use of Et_2O as the reaction solvent for the initial nucleophilic addition proved critical, since performing the reaction in THF leads to premature Brook rearrangement, even at low temperature (not shown).

Having established the optimal reaction conditions, a brief substrate scope study was performed. As illustrated in Table 1, phenyl-, alkynyl-, and allyllithium, as well as lithiated 2-methyl-1,3-dithiane all proved viable initiating nucleophiles, with the reactions proceeding to deliver the three-component adducts as single *syn*-diastereomers in moderate to good yields (entries 2–5). A range of electrophiles including benzaldehyde, (*R*)-1,2-epoxybutane, (*S*)-epichlorohydrin, and (*R*)-glycidol benzyl ether (entries 6–9) readily participated as electrophiles in the ARC reactions to furnish the corresponding three-component adducts also in good yield with excellent *syn*-selectivity as expected. The relative stereochemistry of the three-component adduct 21 (entry 5) was confirmed by single-crystal X-ray diffraction and that of the other congeners was assigned by analogy. Further confirmation was obtained by Mosher ester analysis⁸ of a derivatized pre-Brook alcohol (see the Supporting Information).

Further validation of the new protocol as a viable synthetic tactic logically required the synthesis of both enantiomers of 9. To this end, (+)-9 was prepared first from known compound (–)-16, the latter constructed from commercially available (*R*)-Roche ester (–)-26 in four steps (Figure 3).⁹ Silylation at the dithiane 2-position followed by Parikh–Doering oxidation furnished aldehyde linchpin (+)-9 in 66% yield over two steps. Importantly, following the oxidation step, removal of excess

Table 1. Tricomponent Type II ARC with Linchpin 9^a

Entry	NuLi	Electrophile	Yield	<i>syn:anti</i> ^b	Product
1)	BuLi	CH ₂ =CHBr	74%	≥ 20:1	17
2)	PhLi	CH ₂ =CHBr	73%	≥ 20:1	18
3)	Bn-C≡C-Li	CH ₂ =CHBr	66%	≥ 20:1	19
4)	CH ₂ =CH-Li	CH ₂ =CHBr	58%	≥ 20:1	20
5)	Me-C(S)-Li	CH ₂ =CHBr	52%	≥ 20:1	21
6)	BuLi	PhCHO	72%	≥ 20:1	22 ^c
7)	BuLi	(R)-epoxybutane	74%	≥ 20:1	23 ^c
8)	BuLi	(S)-epichlorohydrin	74%	≥ 20:1	24 ^c
9)	BuLi	(R)-glycidol benzyl ether	65%	≥ 20:1	25 ^c OBn

^aReaction conditions: (i) NuLi, Et_2O , -78°C , 30 min; (ii) electrophile, HMPA/ Et_2O (1/10, v/v), -78°C to rt, 1 h, then rt, 3 h; and/or (iii) 1.0 N aq HCl, overnight. ^b*Syn/anti* ratio was determined by ¹H NMR analysis of the crude reaction mixture. ^cThe adduct was obtained as a 1:1 mixture of diastereomers.

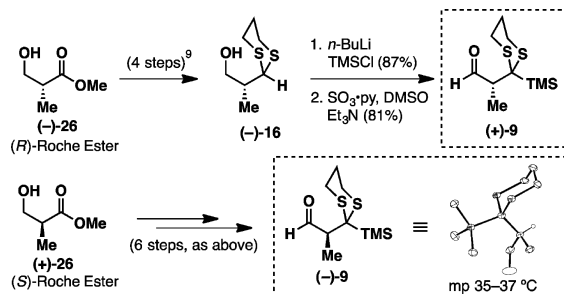


Figure 3. Synthesis of (+)- and (–)-9.

triethylamine from the crude reaction mixture employing satd aq CuSO_4 proved critical in preserving the optical purity of the linchpin. The enantiomer (–)-9 was then prepared in a similar fashion. Pleasingly, X-ray quality crystals were obtained in this case. Both series were carried out on multigram scale; chiral phase

chromatography indicated high levels of enantiomeric excess (>98%, see the Supporting Information).

With an effective bifunctional linchpin for Type II ARC in hand, we turned to demonstrate the synthetic utility in polyketide synthesis by employing linchpin (+)-9 in a convergent synthesis of a potential C16–C29 fragment for rhizopodin (27, Figure 4), a

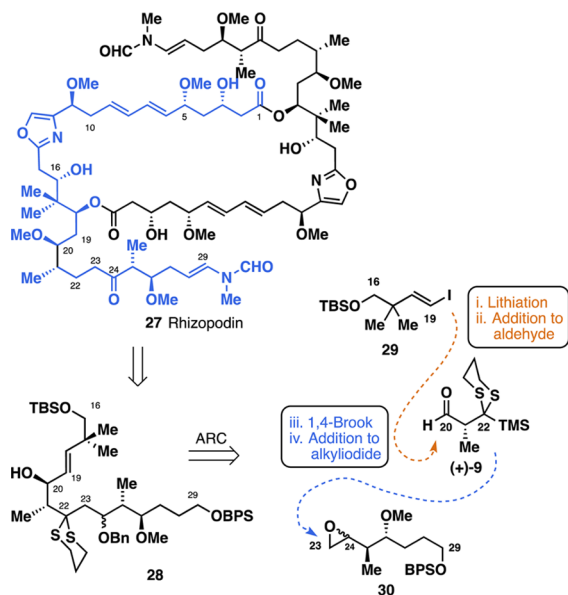
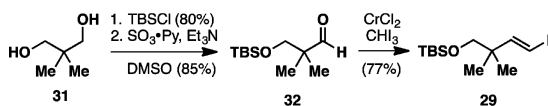


Figure 4. Retrosynthetic analysis of the C16–C29 side chain of rhizopodin.

C₂-symmetric, 38-membered macrodiolide isolated from the myxobacterium *Myxococcus stipitatus*¹⁰ that displays impressive biological properties, including selective potent cytotoxicity against a range of human cancer cell lines,¹¹ with the enamide side chain, a highly conserved moiety, responsible for protein recognition.¹² As such, 27 has been the object of numerous synthetic efforts.¹³ Our retrosynthetic analysis of the C16–C29 fragment is depicted in Figure 4. Here, we envisioned a highly convergent assembly of the full C16–C29 carbon segment 28 via a single-flask Type II ARC tactic, involving lithiation of vinyl iodide 29, Felkin-controlled addition to aldehyde (+)-9, [1,4]-Brook rearrangement, and termination with epoxide 30.

The synthesis of 28 thus began with the preparation of the requisite ARC fragments, 29 and 30 (Figure 5). Vinyl iodide 29

A. Synthesis of vinyl iodide 29.



B. Synthesis of epoxide 30.

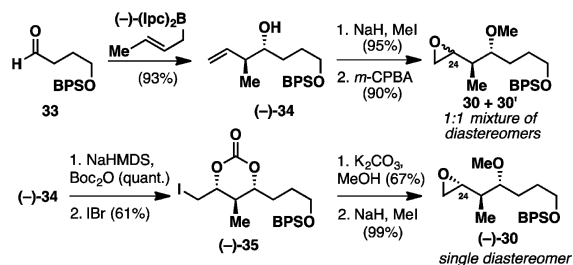


Figure 5. ARC: synthesis of pronucleophile and electrophile.

was constructed from diol 31 as follows: monoprotection with TBSCl followed by Parikh–Doering oxidation¹⁴ afforded aldehyde 32; Takai olefination¹⁵ then delivered 29 in 77% yield (Figure 5A). In turn, elaboration of 30 entailed the asymmetric crotylation of aldehyde 33¹⁶ to furnish homoallylic alcohol (–)-34 in 93% yield. *O*-Methylation followed by epoxidation led to 30, obtained as a 1:1 mixture of diastereomers at C24, and then employed as such in preliminary studies of the ARC key step; in fact, the stereoconfiguration at C24 ultimately becomes irrelevant as it comprises a carbonyl in the targeted natural product (see Figure 4). Having demonstrated the viability of 30 as a terminating electrophile for the key fragment union (not shown), we decided to move forward in our rhizopodin synthetic studies with a single diastereomer of 30 in order to facilitate both reaction monitoring and chromatographic separation. We thus turned to the iodo carbonate cyclization of (–)-34 to install the requisite epoxide functionality, which generally favors formation of 1,3-*syn* stereoarrays with good selectivities.¹⁷ To our surprise, the well-established protocols employing *N*-iodosuccinimide^{17b,c} resulted in diastereomeric mixtures when applied to the Boc carbonate of (–)-34, while iodine^{17a} led to loss of the terminal BPS protection. Pleasingly, use of iodine monobromide, a protocol developed in our laboratory,^{17d} cleanly furnished the desired stereoisomer (dr 11:1; the minor diastereomer was removed by column chromatography). The synthesis of (–)-30 was thus completed by removal of the Boc-carbonate under basic conditions with concomitant closure of the oxirane ring, followed by *O*-methylation (Figure 5B).

With the three molecular fragments in hand [29, (+)-9 and (–)-30], we turned to the central Type II ARC tricomponent fragment union employing the new aldehyde linchpin (Figure 6).

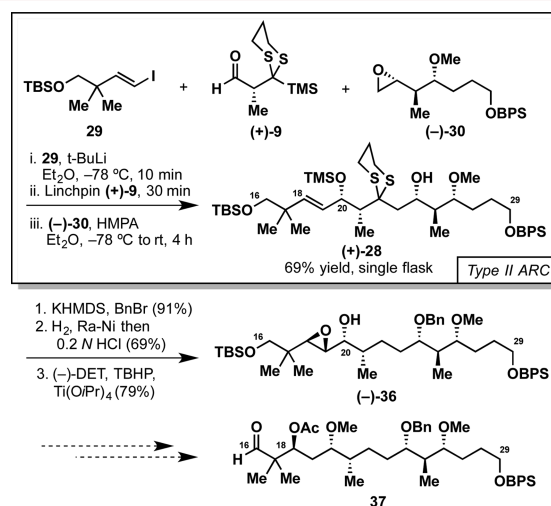


Figure 6. Fragment assembly via Type II ARC.

To our delight, addition of the vinyl lithium species derived from 29 to linchpin (+)-9, followed by triggering of the [1,4]-Brook rearrangement with HMPA and trapping of epoxide (–)-30 delivered the desired adduct (+)-28 in 69% yield, thus permitting a highly convergent construction of the C16–C29 carbon framework of rhizopodin.

Having validated the key step, we focused on the further elaboration of the ARC adduct [(+)-28] with the goal of accessing aldehyde 37, a potentially suitable partner for the union with the C1–C15 fragment developed by Nicolaou et al. in their synthesis of related natural product monorhizopodin^{12d} (Figure

6). The synthesis of such aldehyde would require, notably (i) reductive removal of the C22-dithiane and (ii) stereoselective installation of the C18-acetate, the latter planned via Sharpless asymmetric epoxidation¹⁸ followed by reductive epoxide opening.¹⁹ Prior protection of the C24-hydroxyl was achieved employing KHMDS and excess BnBr in up to 91% yield. Of note, these conditions proved critical to suppress the byproduct arising from undesired migration of the neighboring TMS with concomitant benzylation of the C20-hydroxyl (see the [Supporting Information](#)). Subsequent dithiane removal mediated by Raney nickel under a hydrogen atmosphere, followed by a mild acidic workup (0.2 N aq HCl), provided the free allylic alcohol without loss of the terminal BPS ether (69% yield). Next, Sharpless asymmetric epoxidation was accomplished utilizing (–)-diethyl-D-tartrate [(–)-DET] as ligand to furnish the single diastereomer (–)-36 in 73% yield. Disappointingly, all attempts to date to effect the desired epoxide opening directed by the C20 hydroxyl, utilizing hydrides at various temperatures (e.g., Red-Al, LiAlH₄)^{19a,b} or protocols relying on single-electron transfer,^{19c,d} have proved unfruitful, presumably due to the significant steric hindrance at the projected reactive site. Alternative pathways are currently being investigated in our laboratory.

In summary, we have achieved the design, synthesis and validation of a new effective aldehyde bifunctional linchpin (9) for Type II ARC fragment unions. Importantly, this linchpin enables the rapid construction of propionate-containing polyketide fragments for natural product total synthesis, exploiting highly efficient multicomponent ARC tactics. The utility of this new protocol is demonstrated in ongoing synthetic studies toward the C16–C29 fragment of rhizopodin.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.5b03235](https://doi.org/10.1021/acs.orglett.5b03235).

Experimental procedures and NMR spectra for obtained compounds ([PDF](#))

X-ray data for compound **9** ([CIF](#))

X-ray data for compound **21** ([CIF](#))

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Notes

The authors declare no competing financial interest.

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