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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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, 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,−]-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.6b 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

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followed by oxidation of the free alcohol led to the corresponding aldehyde, which upon treatment with 1,3-propanedithiol and BF$_3$·Et$_2$O furnished dithiane 16 with concomitant removal of the triyl group. Subsequent C-silylation with TMSCl/n-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-BuLi and allyl bromide as the initiating nucleophile and terminating electrophile, respectively. After preliminary screenings, we discovered that addition of n-BuLi to the linchpin in Et$_2$O at −78 °C, followed by introduction of allyl bromide and HMPA in Et$_2$O 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$_2$O 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 allyl lithium, 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 furnished 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 analysis 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). 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 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
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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
C2-symmetric, 38-membered macrodiolide isolated from the
myxobacterium Myxococcus stipitatus5 that displays impressive
biological properties, including selective potent cytotoxicity
against a range of human cancer cell lines,12 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
was constructed from diol 31 as follows: monoprotection with
TBSCl followed by Parikh−Doering oxidation8a afforded
aldehyde 32; Takai olefination8b then delivered 29 in 77% yield
(Figure 5A). In turn, elaboration of 30 entailed the asymmetric
crotylation of aldehyde 338c 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-iodosuccinimide17b,c
resulted in diastereomeric mixtures when applied to the Boc
carbonate of (−)-34, while iodine17a 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).

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 monorhizopodin12d (Figure
6).

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

Figure 5. ARC: synthesis of pronucleophile and electrophile.

Figure 6. Fragment assembly via Type II ARC.
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