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Anion Relay Chemistry Extended. Synthesis of a Gorgonian Sesquiterpene

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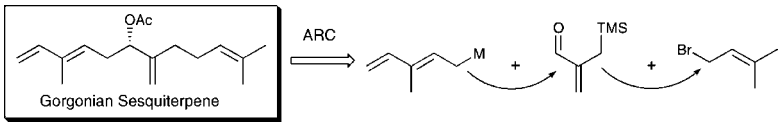
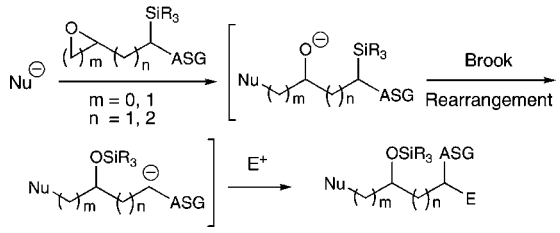
ABSTRACT



Extension of anion relay chemistry (ARC) beyond the area of dithianes has been achieved by the design of two effective ARC linchpins capable of three- and four-component couplings. To showcase the ARC tactic in natural product synthesis, a cytotoxic gorgonian linear sesquiterpene was constructed, and the absolute configuration assigned via the Kakisawa/Mosher method. The synthesis proceeded in five steps with an overall yield of 22%.

Efficient fragment union with high stereocontrol comprises a critical issue in the rapid construction of architecturally complex natural and/or natural product-like molecules possessing important bioregulatory properties.[1] Toward this end, we developed a multicomponent, "one-flask" linchpin coupling protocol of 2-silyl 1,3-dithianes,[2] which has proved valuable in a number of our and other synthetic ventures, including spongistatin 1 and 2,[3a,b] (+)-rimocidin,[3c] and the indolizidine alkaloids, (−)-223AB and (−)-205B,[3d−f] and the Hale bryostatin work.[3g,h] More recently, we introduced a new tactic for multicomponent coupling, termed anion relay chemistry (ARC) (Scheme 1).[4] Early ARC studies focused on the use of the dithiane moiety both as the initial nucleophile and as the anion stabilizing group (ASG). In this letter, we disclose efforts to extend the one-flask ARC protocol beyond the dithiane arena to three- and four-component unions. To showcase the utility of the ARC concept, an effective, five-step synthesis of a cytotoxic gorgonian sesquiterpene was achieved.

Scheme 1. Anion Relay Chemistry (ARC)



The viability of cyano and allyl groups as the anion stabilizing groups (ASGs) in anion relay chemistry was initially demonstrated by Matsuda and co-workers[5] and more recently our group,[6] respectively. On the basis of this precedent, two linchpins **2** and **4** were designed (Scheme 2).

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(1) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365.

(2) (a) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925. (b) Smith, A. B., III; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 14435.

(3) (a) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191. (b) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196. (c) Smith, A. B., III; Pitram, S. M.; Fuertes, M. J. *Org. Lett.* **2003**, *5*, 2751. (d) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2004**, *6*, 1493. (e) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2005**, *7*, 3247. (f) Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547. (g) Hale, K. J.; Hummersone, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189. (h) Manaviazar, S.; Frigerio, M.; Bhatia, G. S.; Hummersone, M. G.; Aliev, A. E.; Hale, K. J. *Org. Lett.* **2006**, *8*, 4477.

(4) (a) Smith, A. B., III; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66. (b) Smith, A. B., III; Xian, M.; Kim, W.-S.; Kim, D.-S. *J. Am. Chem. Soc.* **2006**, *128*, 12368.

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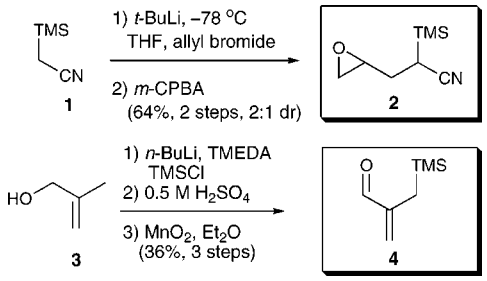
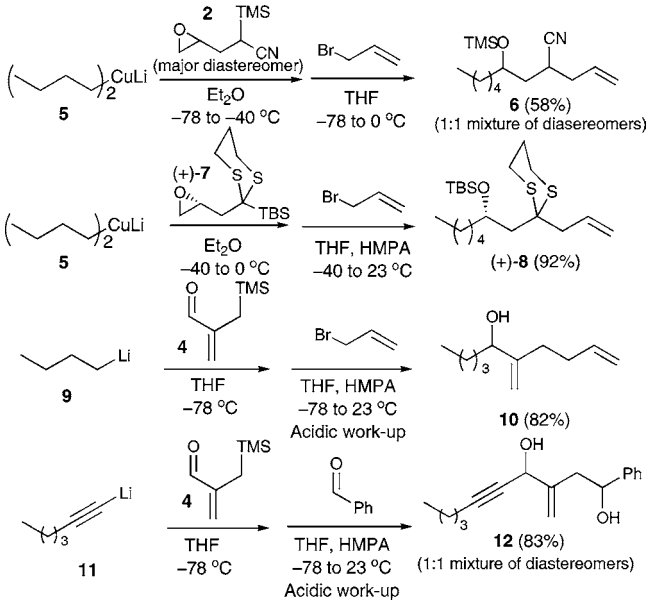
Scheme 2. Preparation of Linchpins **2** and **4**



Epoxide **2** is readily available in two steps as a separable mixture (2:1) of diastereomers from commercially available TMS-acetonitrile **1**: allylation, followed by epoxidation with *m*-CPBA. Enal **4** was prepared from commercially available alcohol **3** in three steps by the Trost procedure.[7]

With the two linchpins in hand, we first explored the viability of the one-flask three-component union tactic. Pleasingly, nitrile **2** proved to be a competent linchpin for the ARC process. Employing lithium dibutylcuprate (**5**) as the initial nucleophile and allyl bromide as the terminal electrophile, the three-component adduct **6** was obtained in 58% yield as a mixture (1:1) of diastereomers (Scheme 3).

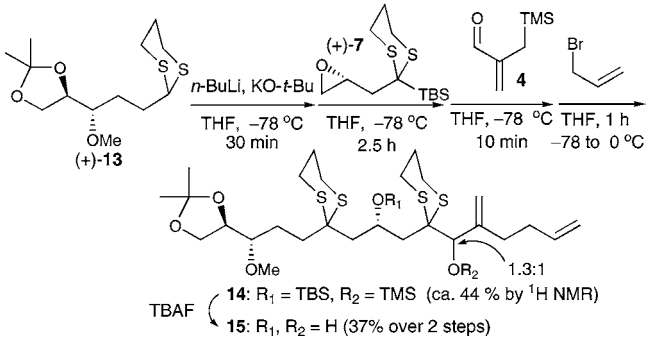
Scheme 3. ARC Employing Linchpins **2** and **4**



Cuprate **5** also served as a competent nucleophile for our previously introduced dithiane linchpin (+)-**7**,[4a] again with allyl bromide to furnish adduct (+)-**8** in excellent yield (92%). Linchpin **4** proved equally viable. Employing *n*-butyl lithium (**9**) as the initial nucleophile and allyl bromide as the terminal electrophile, the one-flask anion relay tactic with **4** furnished allylic alcohol **10** in 82% yield after acidic workup. As the fourth example, lithium acetylide **11** was employed as the initial nucleophile, with linchpin **4** and benzaldehyde as the terminal electrophile; diol **12** was obtained in 83% yield as a mixture (1:1) of diastereomers.

Encouraged by these results, as well as new reaction conditions (*n*-BuLi/KO-*t*-Bu, THF, −78 °C) for the ARC tactic protocol, developed in conjunction with our ongoing spirastrellolide A synthesis,[8] we next explored a one-flask, four-component union employing the consecutive addition of two different linchpins (Scheme 4). Such a process, if

Scheme 4. A Four-Component Union via the ARC Tactic



general, would hold great promise for the rapid construction of structurally diverse natural and unnatural products. To this end, dithiane (+)-**13**, an advanced intermediate in the spirastrellolide venture,[8] was treated with the Schlosser base (*n*-BuLi/KO-*t*-Bu).[9] The resulting anion was then treated in sequence with linchpin (+)-**7** at −78 °C, a second linchpin **4** at −78 °C, and a final electrophile, allyl bromide; pleasingly, adduct **14** comprised of four components was obtained in ca. 44% yield (by NMR). Treatment of the mixture with TBAF furnished diol **15** as a separable mixture (1.3:1) of diastereomers in 37% isolated yield over the two steps.

To illustrate the utility of the ARC tactic in natural product synthesis, we reasoned that the gorgonian sesquiterpene (+)-**16** might comprise a viable target. Sesquiterpene (+)-**16** was isolated from the Caribbean gorgonian *Plexaurella grisea* in 2001 by Salva and co-workers (Figure 1).[10] The structure was based on NMR, IR, and MS data, albeit the absolute configuration was not assigned. The sesquiterpene exhibits mild cytotoxicity for a variety of mouse and human cell lines [IC_{50} values (μg/mL): 2.5 for P-388 (mouse lymphoma), 5.0 for A-549 (human lung carcinoma), 5.0 for

(5) In conjunction with the development of a preparatively useful synthesis of trimethylsilyl acetonitrile ($TMSCH_2CN$), Matsuda et al. reported an early example of a multicomponent union employing the lithium anion of $TMSCH_2CN$ and a series of epoxides; see: Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 26.

(6) Smith, A. B., III; Duffey, M. O. *Synlett* **2004**, 1363.

(7) Trost, B. M.; Nanninga, T. N.; Satoh, T. *J. Am. Chem. Soc.* **1985**, *107*, 721.

(8) See accompanying paper: Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2007**, *9*, 3311.

(9) Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741.

(10) Rueda, A.; Zubia, E.; Ortega, M. J.; Salva, J. *J. Nat. Prod.* **2001**, *64*, 401.

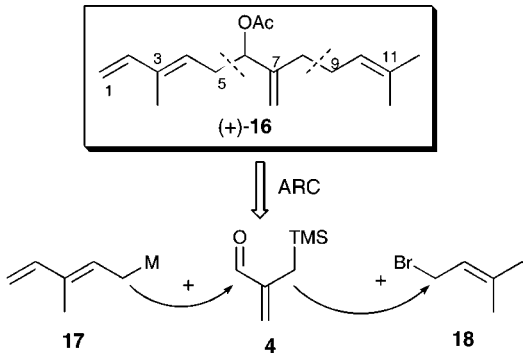


Figure 1. Sesquiterpene (+)-**16**: metabolite derived from the Caribbean gorgonian coral *Plexaurella grisea*.

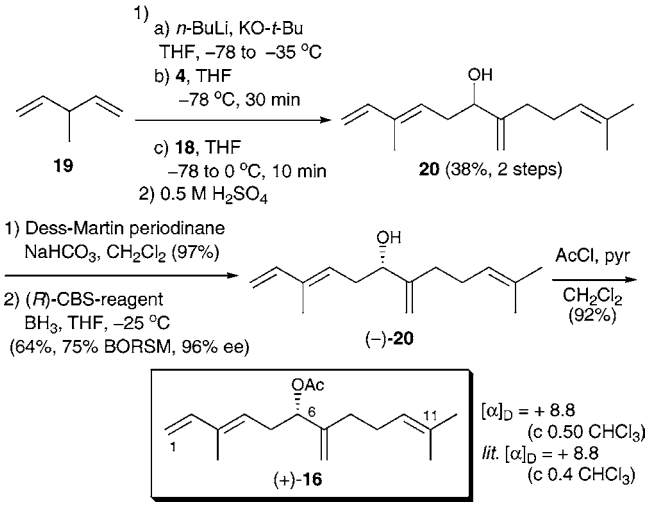
HT-29 (human colon carcinoma), and 5.0 for MEL-28 (human melanoma)].

To access (+)-**16** via the ARC tactic, a six-carbon nucleophile (**17**), a four-carbon linchpin (**4**), and a five-carbon electrophile (**18**) would be required to secure the linear 15-carbon backbone of sesquiterpene (+)-**16** (Figure 1). Oxidation, followed by asymmetric reduction, would then set the C(6) configuration in a stereocontrolled manner. Acetylation would then complete the synthesis.

With this scenario in mind, the initial nucleophile, pentadienyl anion **17**, was generated from the commercially available skipped diene **19** with Schlosser base (*n*-BuLi/KO-*t*-Bu)[11] and treated with linchpin **4**. The resulting oxyanion was then treated with allyl bromide. Under the Schlosser base conditions, the Brook rearrangement proceeds without the need for HMPA, as required for earlier ARC protocols involving lithium alkyl anions. The desired three-component adduct (**20**) was obtained in 38% yield over the two steps after removal of TMS group under acidic conditions (Scheme 5). Although the yield of **20** is at best moderate, the rapid assembly of the carbon skeleton is relatively efficient.

To obtain enantiomerically pure alcohol **20**, a two-step sequence involving Dess-Martin oxidation,[12] followed by asymmetric CBS reduction,[13] was employed; alcohol (−)-**20** was obtained in 62% overall yield with 96% ee (chiral HPLC). The absolute configuration of (−)-**20** was assigned via the Kakisawa modified Mosher method.[14] Acetylation with AcCl delivered sesquiterpene (+)-**16**, identical in all respects (e.g., 500 MHz ^{1}H, 125 Hz ^{13}C NMR, IR, HRMS, and chiroptical properties) with the data reported for the

Scheme 5. Synthesis of the Gorgonian Coral Sesquiterpene (+)-**16** via the ARC Tactic



natural sesquiterpene.[10] Thus the absolute configuration of (+)-**16** is 6*S* as illustrated in Scheme 5.

In summary, we have developed two non-dithiane linchpins, nitrile **2** and aldehyde **4**, for the ARC tactic and demonstrated that both cuprates and acetylides are competent initial nucleophiles. In addition, we have demonstrated the feasibility of a four-component union employing the sequential addition of linchpins. Finally exploiting the ARC tactic, the synthesis of the gorgonian sesquiterpene (+)-**16** was accomplished in five total steps and 22% overall yield. Studies directed at the design and synthesis of related linchpins and on the scope and limitations of a wide variety of nucleophiles, linchpins, and electrophiles employing anion relay chemistry continue in our laboratory.

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Supporting Information Available: Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Schlosser, M.; Zellner, A.; Leroux, F. *Synthesis* **2001**, 1830.
(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(13) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
(14) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. See Supporting Information for the analysis of (−)-**20**.