Evolution of multi-component anion relay chemistry (ARC): construction of architecturally complex natural and unnatural products†

Amos B. Smith, III* and William M. Wuest

Received (in Cambridge, UK) 18th June 2008, Accepted 1st August 2008
First published as an Advance Article on the web 30th September 2008
DOI: 10.1039/b810394a

Efficient construction of architecturally complex natural and unnatural products is the hallmark of organic chemistry. Anion relay chemistry (ARC)—a multi-component coupling protocol—has the potential to provide the chemist with a powerful synthetic tactic, enabling efficient, rapid elaboration of structurally complex scaffolds in a single operation with precise stereochemical control. The ARC tactic can be subdivided into two main classes, comprising the relay of negative charge either through bonds or through space, the latter with aid of a transfer agent. This review will present the current state of through-space anion relay, in conjunction with examples of natural and unnatural product syntheses that illustrate the utility of this synthetic method.

Introduction

Nature elegantly constructs diverse structural motifs, often in an iterative fashion with exquisite efficiency and stereochemical control.[1] For more than a century, chemists have attempted to replicate the ingenuity of Nature in the laboratory, albeit with modest success. Although numerous innovative strategies have been devised for the construction of highly functionalized compounds, most individual reactions yield only modest structural augmentation.[2] In addition the multistep sequences mandate numerous purifications, thus adding time, cost, and material loss at each stage. Anion relay chemistry (ARC),[3] a multi-component union protocol,[4] stands as a promising method to alleviate these shortcomings.

In the broadest sense, anion relay chemistry (ARC) can be divided into two classes involving negative charge migration: either "through-bonds" or "through-space" (Fig. 1). Through-bond ARC encompasses transfer of a negative charge from one locus to another through the bonding system of a molecule. A common example of through-bond ARC is the widely implemented conjugate addition reaction, where a nucleophile adds in 1,4-fashion, thus propagating the negative charge *via* the unsaturated π-system to generate a new anion (*cf.* enolate). Conversely, through-space ARC exploits a "carrier" species that can relay a negative charge employing σ-bonded intermediates. A specific example of this variant is the [1,2]-Brook

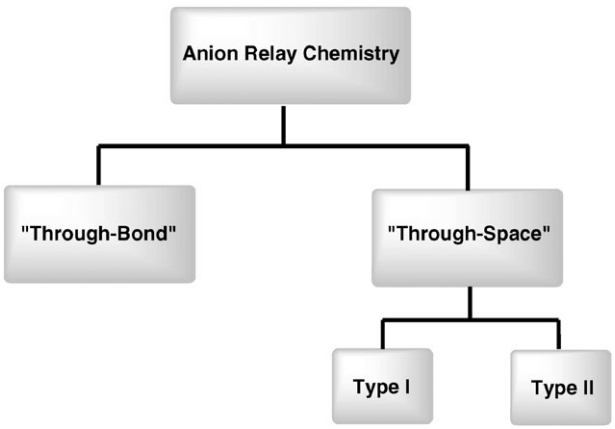


Fig. 1 Schematic of the hierarchy of anion relay chemistry.

Department of Chemistry, Penn Center for Molecular Discovery, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.
E-mail: smithab@sas.upenn.edu; Fax: +1-(215) 898-5129; Tel: +1-(215) 898-4860

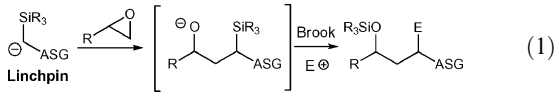
† Dedicated to Professor Andrew B. Holmes, friend, editorial colleague, and chemist/scholar extraordinaire on the occasion of his 65th birthday.

Amos B. Smith, III received a BS–MS degree in chemistry from Bucknell University and a PhD from The Rockefeller University. After a postdoctoral year at Rockefeller, he joined the Chemistry Department at the University of Pennsylvania; currently he is the Rhodes-Thompson Professor of Chemistry, the Associate Director of the Penn Center for Molecular Discovery, and the inaugural Editor-in-Chief of Organic Letters. From 1988 to 1996 he served as Chair of the Department. His research interests, recorded in over 500 articles, include organic synthesis, particularly the synthesis of architecturally complex bioactive natural products, bioorganic chemistry and materials science.

William M. Wuest received a BS degree in chemistry/business from the University of Notre Dame in 2003, and a PhD in chemistry from the University of Pennsylvania with Prof. Amos B. Smith, III in 2008. He is now working as a postdoctoral researcher with Prof. Christopher T. Walsh at Harvard Medical School. His current research is concerned with the combinatorial biosynthesis of architecturally diverse nonproteinogenic amino acids and peptide natural products.

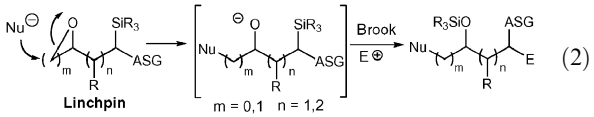
rearrangement wherein an anion is relayed from an alkoxide to the adjacent carbon atom *via* silyl group migration (*vide infra*).[5a,b] This review will focus on the evolution of through-space anion relay chemistry employing silyl groups as the transfer agent.

Further analysis reveals two fundamentally different types of through-space anion migration, differentiated by the final locus of the anion after relay. **Type I ARC** (eqn (1)) is defined as a multi-component coupling reaction that involves addition of an anion, derived from a bifunctional linchpin, to an electrophile capable of generating an anionic species that, with the aid of a transfer agent, relays the negative charge back to the originating nucleophilic locus on the linchpin.



(1)

Reaction with a second electrophile results in a tri-component adduct. **Type II ARC** (eqn (2)) also comprises a multi-component reaction that involves addition of an external nucleophile to a bifunctional electrophilic linchpin to generate an anionic species that, again with the aid of a transfer agent, relays the negative charge albeit to a new (*i.e.*, different) locus on the linchpin.

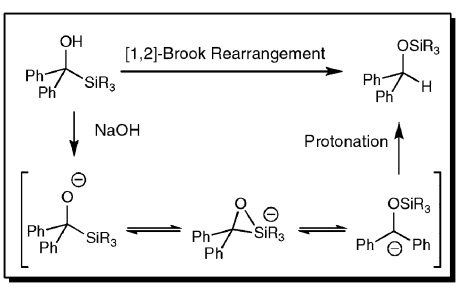


(2)

Reaction with a series of second electrophiles at the new distal site also results in tri-component adducts. Of paramount importance (*vide infra*), both the Type I and II ARC tactics hold the potential for multiple "iterations" by employing a series of bifunctional linchpins, a process not dissimilar to living polymerization.[6] Effective implementation of the ARC Type I and Type II tactics thus holds considerable promise for diversity-oriented synthesis (DOS; *vide infra*).

The Brook rearrangement

As generally defined, the Brook rearrangement (Scheme 1) involves the reversible migration of a silyl group from carbon to oxygen. Initial work by Brook and co-workers focused on the [1,2]-rearrangement, wherein a silyl group migrates intramolecularly *via* a hypervalent pentacoordinate ate species (*i.e.*, $sp^3 \rightarrow O$ migration). Elegant studies by the Hoffman group revealed that in some cases migration proceeds *via* retention of configuration at silicon and inversion of configuration at carbon.[5c–h] Later studies generalized the Brook rearrangement to encompass [1,*n*]-silyl group migration to oxygen, with crossover experiments carried out in our laboratory (*vide infra*) demonstrating that [1,4] and [1,5]-migrations proceed *via* complete intramolecular silyl group transfer.[7] Principal factors governing the equilibrium between the oxy- and carbanion include: (1) the strength of the oxygen–metal bond; (2) the anion stabilizing ability of the carbon substituents; and (3) the polarity of the solvent.

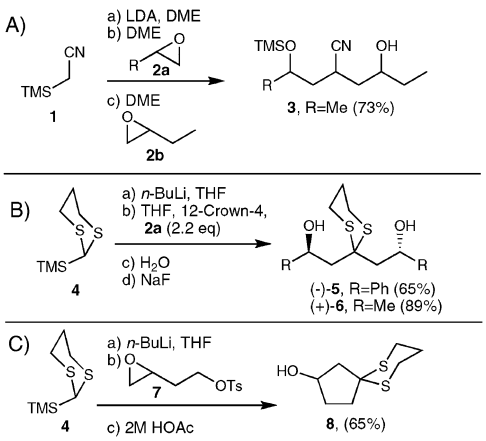


Scheme 1 First example of the [1,2]-Brook rearrangement.

Type I multi-component anion relay chemistry—early work

In 1979 Matsuda and co-workers reported the first example of a multi-component reaction involving through-space Type I anion relay chemistry.[8] Their intent was the development of an effective synthesis of trimethylsilyl acetonitrile (**1**). Importantly, they recognized that the lithio-derivative of **1** could serve as a viable linchpin. Implementation of **1** in a three-component union employing epoxides **2a** and **2b** successfully produced **3** in 73% yield (Scheme 2A). Critical to the observed sequential epoxide alkylations was the timing of the Brook rearrangement controlled through the reaction temperature. That is, raising the reaction temperature after introduction of the initial epoxide (**2a**) triggered the Brook rearrangement.

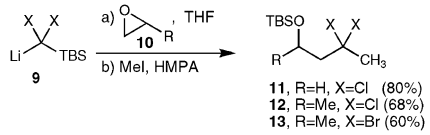
Related multi-component relay tactics, employing 2-trimethylsilyl-1,3-dithiane (**4**) as a progenitor of anionic linchpins, were disclosed independently in 1994 by the Tietze and Schaumann groups (Scheme 2B and 2C).[9a,b] In the first example, reactions of one equivalent of **4** with 2.2 equivalents of enantiopure epoxide (−)-**2a** (R = Ph or Me) efficiently furnished homocoupled 1,5-diols (−)-**5** and (+)-**6** in 65 and 89% yield, respectively. Timing of the Brook rearrangement however proved elusive. As a result only C_2 symmetric (*i.e.*, homocoupled) products were possible. This limitation restricts the utility of the Tietze reaction in multi-component sequences to symmetrical systems (*vide infra*). Schaumann elegantly implemented a dual-functionalized epoxide coupling partner (**7**) that, upon nucleophilic addition by linchpin **4**, promoted silicon migration and concomitant ring closure to provide cyclopentanol **8** in good yield.



Scheme 2 (A) First example of Type I ARC by Matsuda. (B) Initial work exploiting the TMS-dithiane linchpin by Tietze. (C) Cyclopentane formation exploiting the TMS-dithiane linchpin by Schaumann.

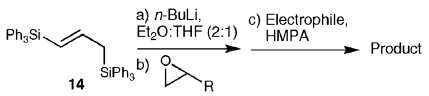
Brook rearrangement control exploiting solvent and additives

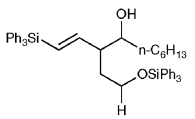
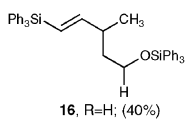
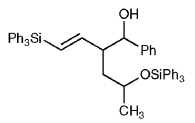
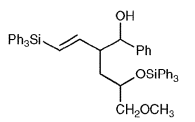
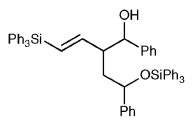
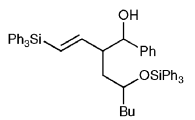
Building on the observations of both Matsuda and Tietze, Oshima and co-workers demonstrated that the timing of the Brook rearrangement could be controlled by the use of solvents and additives.[10] For example, reaction of **9** with various epoxides (*e.g.*, **10**), followed by addition of methyl iodide in HMPA cleanly furnished adducts **11–13** in good yield (Scheme 3). Here the use of the polar additive HMPA served to "trigger" the Brook rearrangement after the initial alkylation.



Scheme 3 First example of controlling the timing of the Brook rearrangement by Oshima.

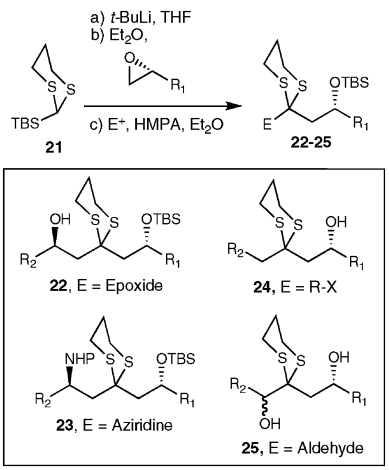
Table 1 Application of 1,3-bis(triphenylsilyl)-1-propene in ARC



Entry	Electrophile	Product (yield %)
1	n-$C_6H_{13}CHO$	 **15**, R=H; (39%)
2	CH_3I	 **16**, R=H; (40%)
3	PhCHO	 **17**, R=CH_3; (52%)
4	PhCHO	 **18**, R=CH_2OCH_3; (50%)
5	PhCHO	 **19**, R=Ph; (52%)
6	PhCHO	 **20**, R=Bu; (35%)

Later the Oshima group attempted to expand their method to an allyl linchpin, $Ph_3SiCH_2CH{=}CH_2$.[11] At issue however was the regioselective reactivity of the allyl anion after HMPA addition to trigger the Brook rearrangement. To address this issue, they devised 1,3-bis(triphenylsilyl)-1-propene (**14**; Table 1). Lithiation in this case results in a symmetrical anion. Reaction of a series of electrophiles with **14** proceeded exclusively in a regiodefined manner to provide a series of three-component adducts (**15–20**) in modest yield. Essential for success was the use of the mixed solvent Et_2O–THF (2 : 1) to control the precise timing of the Brook rearrangement. In THF alone, control of the rearrangement was not possible. A drawback of their method proved to be the modest efficiency, observed even when employing highly electrophilic species (*i.e.*, MeI, PhCHO). Presumably, steric encumbrance of the triphenylsilyl groups surrounding the Brook-derived internal allylic anion is responsible.

Recognizing the potential utility of the multi-component union process in complex molecule synthesis, we sought to expand the versatility of the original Tietze observation with 2-trialkylsilyl-1,3-dithianes (Scheme 4).[12] To this end, we disclosed in 1997 the multi-component linchpin union of silyl dithianes with two different epoxides, employing a solvent mediated Brook rearrangement (Type I ARC). From the strategic sense, location of the resultant silyl protecting group can be orchestrated by the order of electrophile addition. This method was subsequently extended to use a variety of reactive second electrophiles including aldehydes, alkyl and allylic halides, and aziridines to furnish adducts **22–25** (*vide infra*).



Scheme 4 Implementation of the 2-silyl-1,3-dithiane by Smith *et al.*

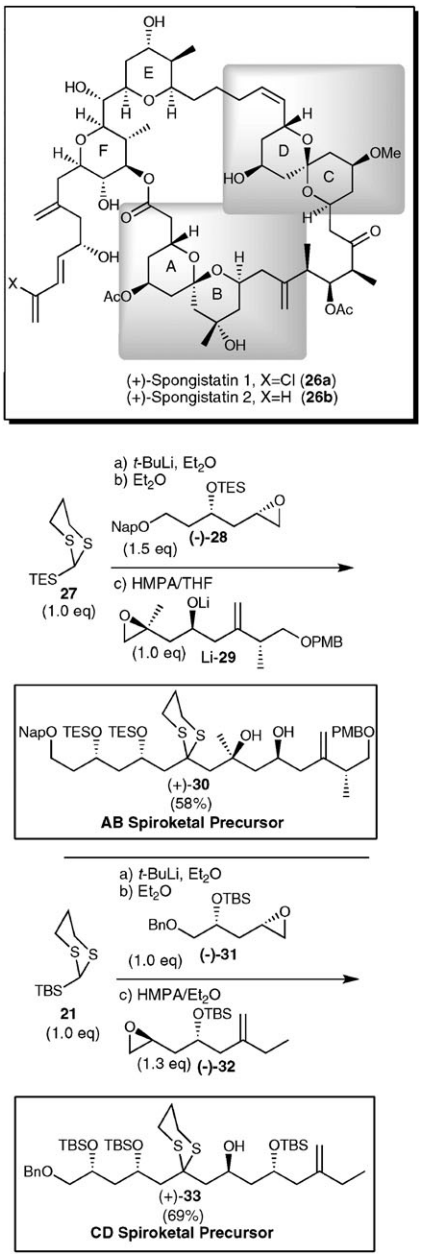
Type I ARC in natural product synthesis

Historically, the application of new methods in natural product total synthesis has been the standard by which the scope and benefit of new tactics are measured.[13] We envisioned that the early reports on anion relay chemistry, if harnessed effectively in a multi-component fashion, might permit rapid construction of structurally diverse scaffolds in a highly concise fashion, *en route* to complex natural and unnatural

products. Three prominent examples from our laboratory and one from the Hale group are presented to illustrate the utility of the Type I multi-component ARC tactic in complex molecule synthesis.

Spongistatins

The spongistatins (**26a/b**) comprise a family of extraordinarily potent, architecturally complex, tumor cell growth inhibitory natural products (Scheme 5).[14] The scarcity of these sponge metabolites, in conjunction with both their antitumor properties and intriguing architecture, led us[15] and others[16] to undertake their total synthesis. Recognizing the high level of symmetry in the carbon backbones of both the AB- and CD-spiroketals, we reasoned that the Type I multi-component tactic held considerable promise for their construction.[16]

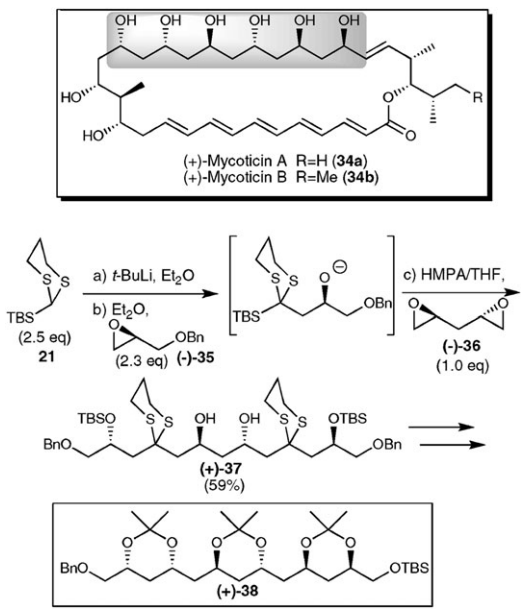


Scheme 5 Construction of the (+)-AB and (+)-CD spiroketal precursors through 2-silyl-1,3-dithiane linchpin in Type I ARC.

Two examples will illustrate. Treatment of **27** with *t*-BuLi followed by addition of epoxide (−)-**28** produced the intermediate alkoxide. Solvent mediated [1,4]-Brook rearrangement employing HMPA as a trigger, followed by addition of epoxide **29** furnished the linear AB-spiroketal precursor (+)-**30** in good yield. Similarly, performing the multi-component tactic with dithiane **21** employing respectively epoxides (−)-**31** and (−)-**32** provided the CD-spiroketal precursor (+)-**33** in a 69% yield. Notably, both multi-component reactions have been carried out on a 10 g scale, *en route* towards a now complete gram-scale synthesis of spongistatin 1 (**26a**).[15c]

Mycoticin

Having achieved success employing the Type I multi-component ARC tactic for the construction of the spongistatins, we embarked on an ARC project to elaborate the Schreiber advanced intermediate (+)-**38** employed in the total synthesis of mycoticin (Scheme 6).[17] Recognizing the *pseudo*-C_2 symmetry of the polyol backbone, we devised a five-component coupling tactic to yield the carbon skeleton of this key intermediate [*e.g.* (+)-**37**] in a single step![18]

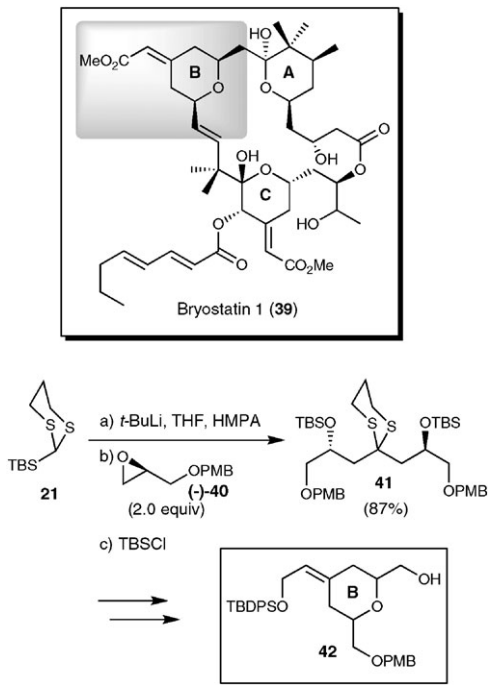


Scheme 6 Five-component coupling *via* Type I ARC toward the Schreiber intermediate of (+)-mycotocin.

Starting with 2.5 equivalents of lithiated **21**, addition of 2.3 equivalents of (−)-**35**, followed by a solvent mediated Brook rearrangement and addition of the second electrophile (−)-**36**, led to the five-component adduct (+)-**37** in a 59% yield (*cf.* 88% yield/C–C bond construction). The latter was then carried forward to the advanced Schreiber intermediate in seven steps. Pleasingly, the Type I multi-component ARC tactic provided access to (+)-**38** in eight steps, five fewer than the Schreiber *et al.* route.[17]

Bryostatin

In 2000, Hale and co-workers in their bryostatin paper sought to exploit the efficiency of the Type I multi-component ARC tactic in the synthesis of ring B (Scheme 7).[19] The bryostatins comprise a family of potent antitumor macrolides, which hold considerable promise in cancer therapy.[20] Not surprisingly, based on the unique structures and biological activity of these natural products, numerous synthetic investigations have been disclosed,[21] including total syntheses by Evans *et al.*,[21a] Yamamura *et al.*[21b] and Masamune *et al.*[21c] Recognizing the inherent symmetry of the bryostatin subunit, Hale developed a strategy exploiting the precedent established by Tietze to provide a C_2 symmetric multi-component adduct that would readily give access to the B-ring.

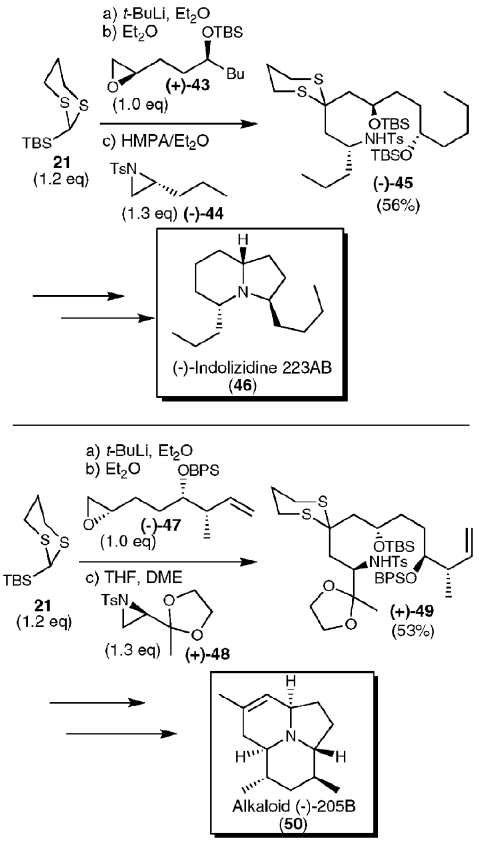


Scheme 7 Synthesis of the B-ring of bryostatin utilizing Type I ARC.

The Hale sequence entailed lithiation of TBS-dithiane, followed by treatment with two equivalents of PMB-glycidol ether (−)-**40** and subsequent alkoxide capture with TBSCl to furnish the four-component product **41** in 87% yield, which was then advanced to the bryostatin B-ring intermediate **42**.

Indolizidine alkaloids

We next turned to the indolizidines alkaloids, a class of neotropic frog toxins isolated by Daly *et al.*[22] Construction of the indolizidine backbone was envisioned to occur *via* a Type I multi-component ARC union of lithiated TBS-dithiane with two electrophiles, an epoxide and an aziridine (Scheme 8).[23] Reaction of dithiane **21** with epoxide (+)-**43**, followed by addition of the electrophilic aziridine (−)-**44** proceeded without incident to provide (−)-**45** in 56% yield. With (−)-**45** in hand, (−)-indolizidine 223AB was then constructed in four steps.



Scheme 8 Synthesis of the indolizidine natural products utilizing Type I ARC.

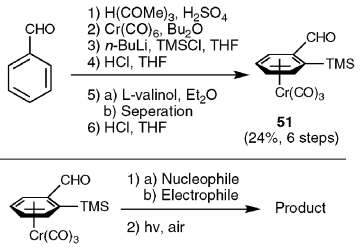
Encouraged by these results, we next took on the synthesis of the architecturally more challenging frog alkaloid (−)-205B, envisioning a similar strategy for construction of the tricyclic core (Scheme 8). After establishing viable syntheses of **21**, (−)-**47**, and (+)-**48**, the Type I ARC protocol furnished (+)-**49** in 53% yield, which in turn was converted to (−)-205B.

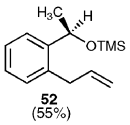
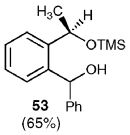
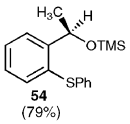
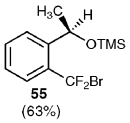
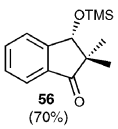
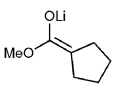
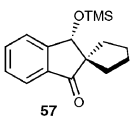
An inherent advantage of the multi-component ARC Type I tactic, as illustrated above, comprises the diversity of the tri-component scaffolds that can be elaborated readily *in a single operation* (*i.e.*, one purification), with precise stereochemical control from a range of enantiopure electrophiles including epoxides and aziridines as well as alkyl and allyl halides, aldehydes and ketones, many of which are commercially available. These products then stand as valuable intermediates for further elaboration to architecturally complex natural and unnatural products.

Multi-component reactions involving Type II anion relay chemistry

The first use of Type II anion relay chemistry in a multi-component reaction was reported by Moser and co-workers in 2000 employing the *o*-trimethylsilyl benzaldehyde chromium tricarbonyl complex **51** (Table 2).[24] Central to the success of the Moser reaction was the electron stabilizing effect of the tricarbonyl chromium complex on the aryl anion that results upon the [1,4]-Brook rearrangement (*i.e.*, O → sp^2 anion migration). Addition of alkyl lithiums and lithium enolates

Table 2 Application of the silyl-benzaldehyde chromium tricarbonyl complex in ARC



Entry	Nucleophile	Electrophile	Product (yield %)
1	MeLi		 **52** (55%)
2	MeLi	PhCHO	 **53** (65%)
3	MeLi	PhSSPh	 **54** (79%)
4	MeLi	BrF_2CCF_2Br	 **55** (63%)
5		—	 **56** (70%)
6		—	 **57** (72%)

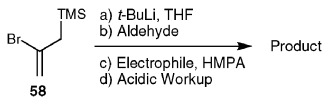
derived from esters to the aldehydic carbonyl in **51** served to initiate the process. Brook rearrangement, capture of the resulting aryl anion with a variety of carbon and heteroatom electrophiles, and facile removal of the chromium tricarbonyl moiety *via* air oxidation leads, in good to excellent yield (*i.e.*, 55–79%), to a series of diverse tri-component adducts. Particularly noteworthy is the effective internal capture of the Brook-derived aryl anion, employing an ester enolate to initiate the process.[25] This innovative sequence constitutes a formal [3 + 2] annulation.

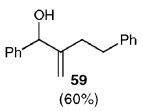
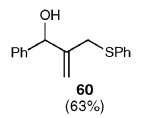
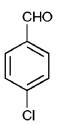
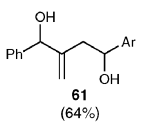
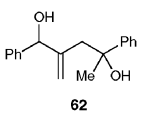
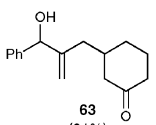
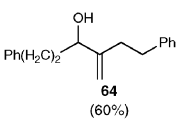
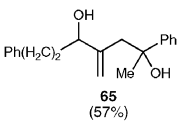
The Moser tactic unfortunately has not been widely adopted by the synthetic community, presumably due to two limitations. First, construction of the chromium tricarbonyl aldehyde complex, which serves as the linchpin, requires five steps and is not highly efficient.[26] The second comprises low atom efficiency, in conjunction with use of chromium, an environmental hazard.

2-Bromo-allyltrimethylsilane: an effective linchpin for the Type II multi-component tactic

In 2004, we reported what we now recognize as a Type II multi-component ARC reaction sequence, employing commercially available 2-bromo-trimethylallylsilane (**58**).[27] In this case, the reaction is initiated by halogen–metal exchange with *n*-butyl lithium (Table 3). Addition of a series of aldehydes as the first electrophile, followed by a solvent mediated Brook rearrangement (O → sp^3 anion migration) employing HMPA, and capture with diverse reactive second electrophiles, including alkyl, allyl and benzyl halides, as well as non-enolizable aldehydes, ketones, and heteroatom electrophiles (PhSSPh),

Table 3 Application of 2-bromo-allyltrimethylsilane in ARC



Entry	Aldehyde	Electrophile	Product (yield %)
1	PhCHO		 **59** (60%)
2	PhCHO	PhSSPh	 **60** (63%)
3	PhCHO		 **61** (64%)
4	PhCHO	PhCOMe	 **62** (63%)
5	PhCHO		 **63** (31%)
6	$Ph(CH_2)_2CHO$		 **64** (60%)
7	$Ph(CH_2)_2CHO$	PhCOMe	 **65** (57%)

furnished tricomponent adducts **59–65** in good yield. Interestingly, methyl iodide, when employed as the second electrophile, was more prone to react at oxygen than carbon to furnish the methyl ether.

Although at the time not completely cognizant of the full significance of this transformation, *vis-a-vis* through-space anion relay chemistry as defined in this review, a series of structurally diverse allylic alcohols were readily prepared. The principal drawback of this process however proved to be the basicity of the resultant allylic anion, generated upon Brook rearrangement. Thus, while aryl aldehydes served as effective second electrophiles, use of readily enolizable aldehydes, ketones, and α,β-unsaturated ketones (*i.e.*, Michael acceptors) proved less efficient, presumably due to deprotonation *via* the basic allyl anion.

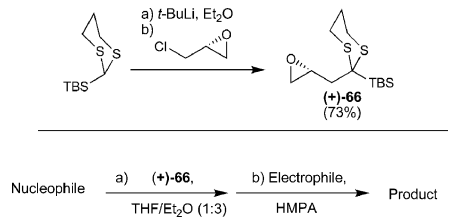
Rational design of bifunctional linchpins for the ARC Type II multi-component tactic: epoxy-methylene-TBS-dithiane

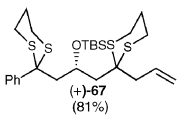
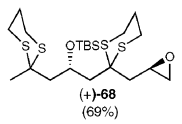
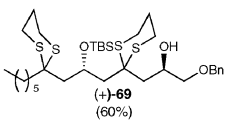
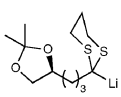
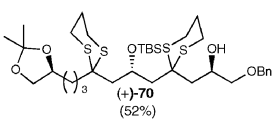
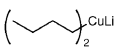
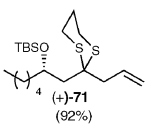
Convinced that the multi-component ARC Type II tactic, if generally applicable, would also hold great promise to enhance synthetic strategies directed toward complex natural and unnatural products, as well as diversity-oriented syntheses (DOS) leading to biologically relevant libraries, we initiated a research program in late 2004 to design a series of Type II ARC bifunctional linchpins.[3]

We began with the Moser precedent, in conjunction with our success with 2-bromo-allyltrimethylsilane, recognizing that a central design feature of any viable bifunctional linchpin would entail appropriate placement of the electrophilic center, the progenitor of the transfer agent, relative to the position of the anion stabilizing group (ASG), such that through-space anion migration would be both feasible and effective. We further reasoned that it should be possible to combine, in a single linchpin, the nucleophilicity of anions such as silyl dithianes with the reactivity of epoxides, as observed in our trialkylsilyl dithianes (Type II ARC), paying particular attention, of course, to the distance requirement for silyl transfer. With these considerations in mind, a linchpin composed of an epoxide and a trialkylsilyl dithiane separated by a methylene unit appeared to be a viable candidate [*cf.* (+)-**66**; Table 4]; pleasingly (+)-**66** could be readily prepared on the gram-scale (73% yield) *via* lithiation of TBS-dithiane, followed by reaction with enantiopure epichlorohydrin.

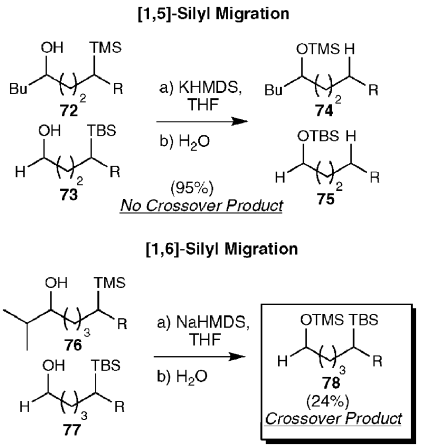
The ARC Type II multi-component process proceeded as anticipated. For example, reaction of (+)-**66** with a variety of alkyl and phenyl trialkylsilyl dithiane anions as initiating nucleophiles, followed by Brook rearrangement (O → sp^3 anion migration) and capture of the resultant anion with a series of primary epoxides, as well as reactive alkyl, allyl and benzyl halides, furnished tri-component adducts **67–71** in good to excellent yields.[3] Particularly interesting was use of epichlorohydrin as the second electrophile to furnish **68** (Table 4; Entry 2), possessing a new electrophilic epoxide site for potential further diversification with a variety of nucleophiles.

Table 4 Application of epoxy-silyl dithiane in ARC



Entry	Nucleophile	Electrophile	Product (yield %)
1			 (+)-**67** (81%)
2			 (+)-**68** (69%)
3			 (+)-**69** (60%)
4			 (+)-**70** (52%)
5			 (+)-**71** (92%)

Having achieved success with sp^3 → O silyl group migration with both the ARC Type I (*i.e.*, trialkylsilyl dithiane)[12] and ARC Type II (*i.e.*, epoxy-methylene-TBS-dithiane)[3] protocols, we next explored the feasibility of higher order Brook rearrangements, namely [1,5] and [1,6] sp^3 → O silyl group migrations, to expand both the scope of the ARC process and the diversity of substitution patterns of the multi-component adducts produced (Scheme 9). To this end, reaction of a series of 1,5-hydroxy trialkylsilyl dithianes (**72**, **73**, **76**, and **77**) with lithium bases (*cf.* *n*-BuLi, *t*-BuLi, or LHMDS; 1.1 eq.) at room temperature proceeded, albeit with slow migration of the silyl group, to furnish the corresponding silyl ethers. Yields were modest (*ca.* 30–40%). However, upon use of either NaHMDS or KHMDS at 0 °C dramatic increases in both the rate and yield occurred. Similarly, [1,6]-migrations occurred, but subsequent crossover experiments demonstrated that while the [1,5]-Brook rearrangement proceeds completely *via* intramolecular silyl group transfer, presumably involving a cyclic ate complex, significant (*ca.* 30%) intermolecular transfer occurs in the [1,6]-rearrangement manifold.[7]

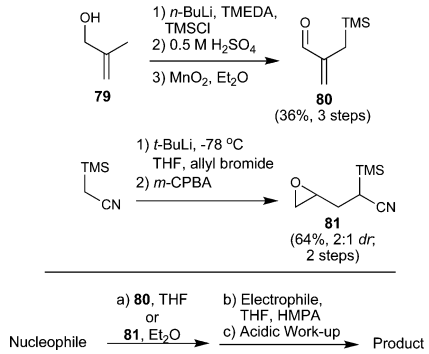


Scheme 9 Crossover experiments to demonstrate the maximum distance of the intramolecular Brook rearrangement.

α-TMS-methyl-acrolein and epoxy-methylene-acetonitrile

Continuing with the development of novel linchpins, we next introduced **80** and **81** (Table 5), and demonstrated their use in the Type II ARC multi-component process.[28] Importantly, both linchpins were readily available. Construction of **80** began with the commercially available allylic alcohol (**79**). Bis-silyation with *n*-BuLi, followed by selective hydrolysis of the silyl ether and allylic oxidation (MnO_2) furnished **80** in a 36% yield for the three steps. Linchpin **81** entailed union of the anion derived from TMS-acetonitrile with allyl bromide, followed by *m*-CPBA epoxidation to furnish **81** in good yield, albeit with modest diastereoselectivity (64%; 2 : 1 dr).[29] Both linchpins participated effectively in the Type II multi-component ARC process. Of particular significance

Table 5 Application of silyl-enal **80** and epoxy-nitrile **81** in ARC



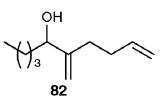
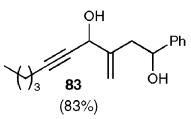
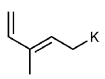
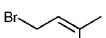
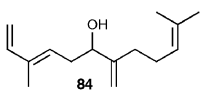
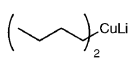
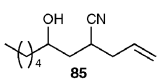
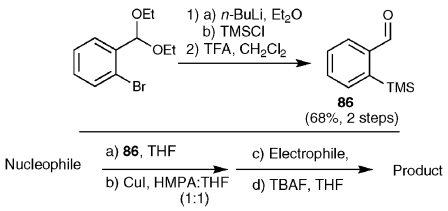
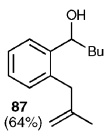
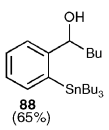
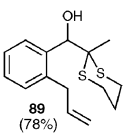
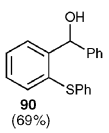
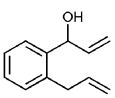
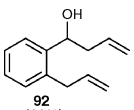
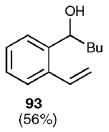
Entry	Nucleophile	Linchpin	Electrophile	Product (yield %)
1		**80**		 **82** (82%)
2		**80**	PhCHO	 **83** (83%)
3		**80**		 **84** (38%)
4		**81**		 **85** (58%)

Table 6 Application of *ortho*-TMS-benzaldehyde in ARC



Entry	Nucleophile	Electrophile	Product (yield %)
1			 **87** (64%)
2		Bu_3SnCl	 **88** (65%)
3			 **89** (78%)
4	PhLi	PhSSPh	 **90** (69%)
5			 **91** (68%)
6			 **92** (66%)
7[a]			 **93** (56%)

[a] Vinyl bromide, 3 mol% $Pd(PPh_3)_4$, THF.

was the use of cuprates and lithium alkyne anions to initiate the reaction sequence.

Ortho-TMS-benzaldehyde

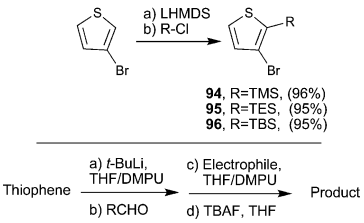
Inspired by the Moser aryl linchpin, albeit recognizing both the limitations on availability and the requirement for chromium intermediates, we sought to develop a more user-friendly linchpin (Table 6). Ultimately, we devised *o*-TMS-benzaldehyde (**86**), readily prepared from the commercially available diethyl acetal of 2-bromobenzaldehyde.[30] The two-step synthesis entailed halogen–metal exchange with *n*-butyl lithium, silylation with TMSCl, and in the same step hydrolysis of the acetal to furnish **86** in 68% yield.

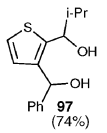
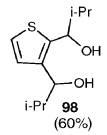
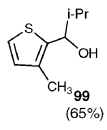
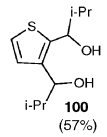
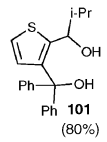
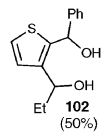
With linchpin **86** available on the gram-scale, we turned to the Type II multi-component ARC protocol. Recognizing that the lack of an anion stabilizing group (*cf*. the tricarbonyl chromium moiety in the Moser linchpin) might limit silyl group migration, we called upon the Takeda precedent that employed CuI in HMPA to promote the [1.4]-silyl group migration and stabilize the resultant anion after deprotonation of *o*-trimethylsilyl phenol.[31] With this scenario in mind, treatment of linchpin **86** in THF at −78 °C with a nucleophile (Table 6), followed in turn by cannula-addition of a solution of CuI (1.2 eq.) in a mixture of THF and HMPA (1 : 1), introduction of a series of electrophiles, including allyl halides, tri-*n*-butylstanyl chloride or diphenyl disulfide in THF, and work-up involving removal of the TMS group with TBAF, furnished multi-component adducts **87–93** in good to excellent yield. Of particular significance, a multi-component palladium-mediated cross coupling reaction sequence was achieved employing *n*-BuLi, linchpin **86** and vinyl bromide, in the presence of 3 mol% $Pd(PPh_3)_4$ (Table 6; Entry 7).[32] To our knowledge this comprises the first example of a Pd-mediated Type II multi-component ARC process. Studies to extend this intriguing observation are underway in our laboratory.

2-Trimethyl-3-bromothiophene

Concurrent with our development of the *o*-TMS-benzaldehyde linchpin, Xian and co-workers introduced an innovative series of thiophene linchpins (**94–96**; Table 7), readily prepared by silylation of 3-bromothiophine with LHMDS and the requisite trialkylchlorosilane, for the construction of diverse 2,3-disubstituted thiophenes of interest to the pharmaceutical industry.[33] Their protocol entailed halogen–metal exchange of **94–96** with *t*-BuLi, followed by addition of a series of alkyl and aryl aldehydes in THF, employing DMPU to trigger the [1,4]-Brook rearrangement. Subsequent addition of a range of second electrophiles, including alkyl aldehydes, ketones and methyl iodide, led in good yield to adducts **97–102**. In this case the anion stabilizing group, a prerequisite for the success of the ARC process, comprises the thiophene ring, well-known to stabilize an anion at the 2-position. Xian and co-workers note that related heteroaromatic linchpins also hold considerable promise for diversity-oriented synthesis of focused libraries of biomedical relevance.

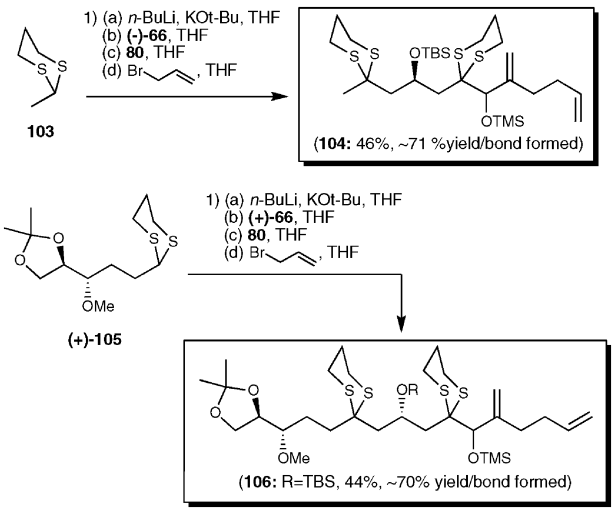
Table 7 Application of 2-bromo-3-silyl-thiophene in ARC



Entry	Thiophene	RCHO	Electrophile	Product (yield %)
1	**94**	i-PrCHO	PhCHO	 **97** (74%)
2	**94**	i-PrCHO	i-PrCHO	 **98** (60%)
3	**95**	i-PrCHO	MeI	 **99** (65%)
4	**95**	EtCHO	i-PrCHO	 **100** (57%)
5	**96**	i-PrCHO	$(Ph)_2CO$	 **101** (80%)
6	**96**	PhCHO	EtCHO	 **102** (50%)

Iterative use of bifunctional linchpins in the ARC Type II tactic

To demonstrate further the power of the ARC tactic, we next explored the iterative use of several linchpins (Scheme 10). Two examples are presented. The first entails use of linchpins (−)-**66** and **80**. Metalation of dithiane **103** with Schlosser base[34] followed by cannula introduction of linchpin **66** and then linchpin **80**, and termination of the ARC sequence with allyl bromide, provided **104** in 46% yield. In a similar fashion, deprotonation of (+)-**105**, followed by sequential treatment with (+)-**66** and **80** and termination with allyl bromide furnished four-component adduct **106** in 44% yield. Although the overall yields for these "one-flask" reaction sequences is only modest (*ca*. 46 and 44%, respectively), the four-component



Scheme 10 Type II ARC four-component couplings.

process results in creation of three new C–C bonds with an average yield per bond of *ca.* 70%, thus highlighting the ability of the ARC tactic to rapidly construct highly functionalized, advanced intermediates in a single operation.

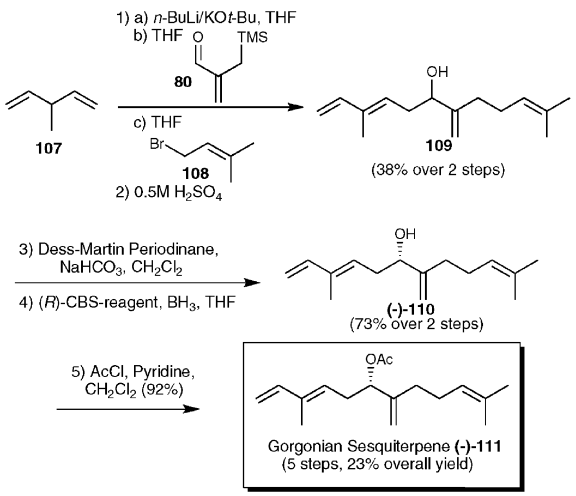
Type II anion relay chemistry in natural product and diversity-oriented synthesis

Given the efficiency of the ARC Type II multi-component process employing linchpins (−)-**66**, **80**, **81**, and **86** in conjunction with the iterative use of these linchpins, we are confident that this protocol will find extensive use in the diversity-oriented synthesis (DOS) of a wide variety of "natural product-like" chemical entities (*vide infra*).[32]

We have recently validated the power of the Type II multi-component ARC tactic both in complex molecule synthesis and in diversity oriented synthesis. Two synthetic and one DOS example from our laboratory will be presented.

A gorgonian sesquiterpene

To illustrate the Type II ARC tactic in complex molecule synthesis, we first took on a modest challenge, the construction of a gorgonian sesquiterpene (−)-**111** (Scheme 11), that possesses



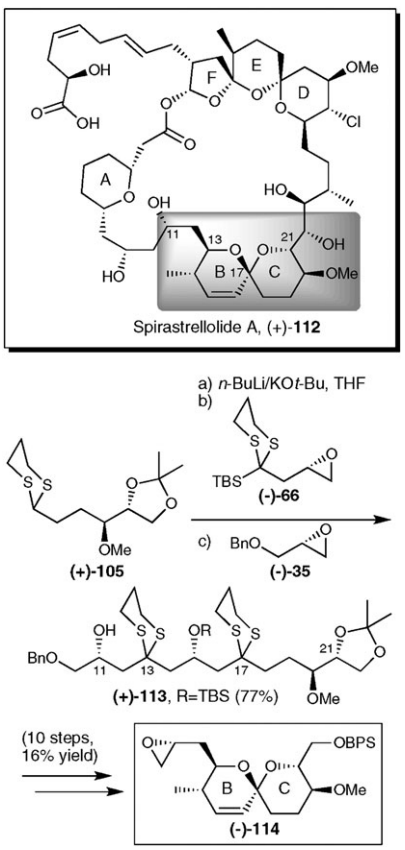
Scheme 11 Total synthesis of a gorgonian sesquiterpene.

moderate cytotoxicity against a variety of human cancer cell lines [IC50 values (mg/mL): 5.0 for A-549 (human lung carcinoma), 5.0 for HT-29 (human colon carcinoma), and 5.0 for MEL-28 (human melanoma)].[35] At the time the absolute configuration of (−)-**111** had not been defined. Particularly attractive was the possibility of assembling the complete carbon skeleton of the sesquiterpene in a single Type II multi-component ARC reaction.[38]

We began with commercially available 3-methyl-1,4-pentadiene (**107**). Metalation exploiting the Schlosser base,[36] followed by iterative addition of linchpin **80** and prenyl bromide (**108**) and in turn *in situ* hydrolysis of the resultant TMS-silyl ether with 0.5 M sulfuric acid provided the desired tri-component ARC adduct **109** in 38% overall yield. Although the yield was only modest, we had in fact achieved our goal of constructing the complete gorgonian backbone in a single reaction! Oxidation of the resultant racemic alcohol, followed by enantioselective reduction exploiting the Corey (*R*)-CBS reagent[37] and acylation furnished (−)-**111**, identical in all respects, including chiroptic properties. The absolute configuration of the intermediate alcohol arising from the Corey reduction, assigned initially on the basis of precedent, was confirmed by application of the modified Moser ester method. The overall synthesis, encompassing a longest linear sequence of five steps, with an overall yield of 23%, confirmed both the structural assignment and established the absolute configuration.

Spirastrellolide A

Having achieved success with the Type II multi-component ARC tactic with a modest synthetic target, we turned to an architecturally complex, highly potent (*cf.* IC50 of 1 nM) target, the



Scheme 12 Synthesis of the BC-spiroketal of spirastrellolide A.

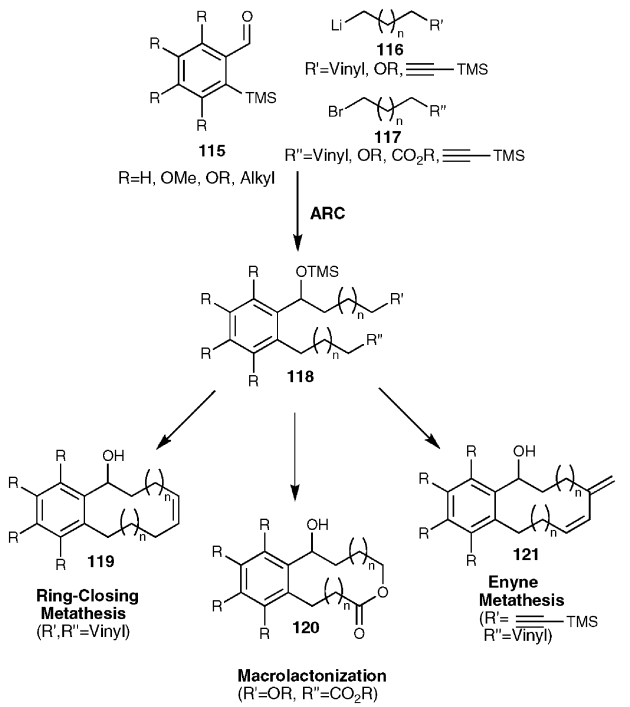
spirastrellolides A and B, potent, selective inhibitors of protein phosphatase PP2A (Scheme 12).[38] Not surprisingly, given the intricate structure and exquisite biological properties, the spirastrellolides have attracted considerable attention from the synthetic community.[39] We will focus here on the use of a Type II multi component ARC tactic to assemble the BC-spiroketal subunit.[40]

To this end, deprotonation of dithiane (+)-**105** with the Schlosser base, followed in turn by addition of linchpin (−)-**66** and benzyl glycidol ether (−)-**35** furnished the tri-component adduct **113** in 77% yield. Importantly, from the perspective of the now complete southern hemisphere of spirastrellolide A (**112**), similar yields were obtained when this reaction was carried out at the 5 gram-scale, thus demonstrating that the ARC Type II method is amenable to significant material advancement.[40]

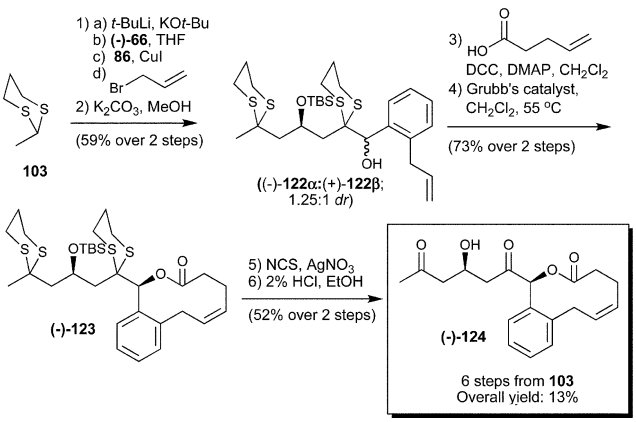
Diversity-oriented synthesis (DOS) exploiting Type II anion relay chemistry

The introduction of diversity-oriented synthesis (DOS) during the past decade has provided the biological and biomedical communities with access to libraries of structurally diverse compounds for high-throughput screening (HTS) campaigns to define both lead structures for the development of biologically useful probe molecules and candidates for drug development.[2] However, many of the libraries employed today, both in academia and the pharmaceutical industry, do not incorporate compounds with the rich, three dimensional shape characteristics of most natural products, in spite of the fact that greater than 70% of the currently marketed drugs have their origins in natural products.[41] It is here that we believe multi-component anion relay chemistry may hold the greatest potential, especially employing the iterative manifold. The ability to construct readily highly functionalized three dimensional carbon scaffolds in an efficient manner, exploiting the Type I and II ARC protocols, presents the chemist with great potential to enhance both the large high-throughput screening and smaller focused libraries. That is, by the rational design of the individual nucleophiles, linchpins and electrophiles (Scheme 13), hosting a wider variety of reactive functional groups, such as well positioned carboxylic acids, hydroxyl or amino groups, and/or olefins, capable of activation and further elaboration (*i.e.*, macrolactonization, macrolactamization, RCM, *etc.*) should permit access to a diverse supply of architecturally interesting "natural product-like" compounds.

One such program leading to a "proof of concept" reaction sequence to develop a focused library of natural product-like compounds, was recently completed in our laboratory employing the Type II multi-component ARC tactic (Scheme 14). The reaction sequence took advantage of the iterative use of two linchpins (−)-**66** and **86**. Deprotonation of methyl dithiane (**103**), followed by sequential addition of linchpins (−)-**66**, **86** and allyl bromide furnished the four-component products (−)-**122**α and (−)-**122**β in a combined yield of 59% for the two steps (1.25 : 1) after removal of the trimethylsilyl group with K_2CO_3 in methanol. Esterification of **122**α with 4-pentenoic acid, followed by ring closing metathesis (RCM), employing the recently introduced Grubbs catalyst[42] then provided the ten-membered lactone (−)-**123** in 73% for the



Scheme 13 Proposed implementation of Type II ARC in diversity-oriented synthesis.



Scheme 14 "Proof of concept" library of "natural product-like" compounds utilizing Type II ARC.

two steps. Final removal of the dithiane with NIS/$AgNO_3$ and the TBS group with 2% aq. HCl furnished **124**, a "natural product-like" macrolide available in six steps and 13% overall yield. The epimeric macrolide was also available in 12% overall yield *via* a similar end-game sequence. Currently we are reducing this "proof of concept" reactive sequence to practise to create a focused library of new "natural product-like" chemical entities (five points of diversity) for the NIH Roadmap Program.[43]

Conclusions

Significant advances have been made over the past decade with the Type I and II multi-component ARC tactics. Specifically, the ability to harness the Brook rearrangement has proven

critical to the new anion relay coupling reactions. A sampling of the current state of the ARC protocol has been highlighted in this review. However, even with these advances there remains a great need to design, interrogate and exploit new bifunctional linchpins for the developing of effective protocols for multi-component anion relay chemistry. In today's society, with great emphasis placed on environmentally responsible chemistry, the ability to unite multiple, structurally complex starting materials in a highly efficient, iterative and stereocontrolled manner employing only a single purification step holds great potential as we move closer to goal of "green" chemistry.

Acknowledgements

This work was funded by grants from the National Institute of Health (GM-029028, CA-019033 and GM-081253) and a fellowship from the University of Pennsylvania.

Notes and references

1 (*a*) D. E. Cane, C. T. Walsh and C. Khosla, *Science*, 1998, **282**, 63; (*b*) C. T. Walsh, *ChemBioChem*, 2002, **3**, 125.
2 (*a*) S. H. Bertz, *J. Am. Chem. Soc*., 1981, **103**, 3599; (*b*) S. H. Bertz and T. J. Sommer, *Chem. Commun*., 1997, 2409; (*c*) P. A. Wender, M. P. Croatt and B. Witulski, *Tetrahedron*, 2006, **62**, 7505 and references cited therein.
3 A. B. Smith, III and M. Xian, *J. Am. Chem. Soc*., 2006, **128**, 66.
4 For reviews on multi-component reactions, see: (*a*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed*., 2000, **39**, 3168; (*b*) L. F. Tietze, *Chem. Rev*., 1996, **96**, 115.
5 (*a*) A. G. Brook, *J. Am. Chem. Soc*., 1958, **80**, 1886; (*b*) W. H. Moser, *Tetrahedron*, 2001, **57**, 2065; (*c*) R. Hoffman and R. Bruckner, *Chem. Ber*., 1992, **125**, 1471; (*d*) F. Boche, A. Opel, M. Marsch, K. Harms, F. Haller and J. C. W. Lohrenz, *Chem. Ber*., 1992, **125**, 2265; (*e*) R. Hoffman and R. Buckner, *Chem. Ber*., 1992, **125**, 2731; (*f*) R. Hoffman, T. Ruckert and R. Bruckner, *Tetrahedron Lett*., 1993, **34**, 297; (*g*) J. Bousbaa, F. Ooms and A. Krief, *Tetrahedron Lett*., 1997, **38**, 7625; (*h*) Y. Wang and M. Dolg, *Tetrahedron*, 1999, **55**, 12751.
6 A. Hirao and S. Nakahama, *Acta Polym*., 1998, **48**, 208.
7 A. B. Smith, III, M. Xian, W.-S. Kim and D.-S. Kim, *J. Am. Chem. Soc*., 2006, **128**, 12368.
8 I. Matsuda, S. Murata and Y. Ishii, *J. Chem. Soc., Perkin Trans. 1*, 1979, 26.
9 (*a*) L. F. Tietze, H. Geissler, J. A. Gewert and U. Jakobi, *Synlett*, 1994, 511; (*b*) M.-R. Fischer, A. Kirschning, T. Michel and E. Schaumann, *Angew. Chem., Int. Ed. Engl*., 1994, **33**, 217.
10 H. Shinokubo, K. Miura, K. Oshima and K. Utimoto, *Tetrahedron*, 1996, **52**, 503.
11 K. Takaku, H. Shinokubo and K. Oshima, *Tetrahedron Lett*., 1998, **39**, 2575.
12 A. B. Smith, III and A. M. Boldi, *J. Am. Chem. Soc*., 1997, **119**, 69.
13 K. C. Nicolaou, D. Vourloumis, N. Winssinger and P. S. Baran, *Angew. Chem., Int. Ed*., 2002, **41**, 1668.
14 (*a*) G. R. Pettit, Z. A. Cichacz, F. Gao, C. L. Herald, M. R. Boyd, J. M. Schmidt and J. N. A. Hooper, *J. Org. Chem*., 1993, **58**, 1302; (*b*) G. R. Pettit, *Pure Appl. Chem*., 1994, **66**, 2271.
15 (*a*) A. B. Smith, III, V. A. Doughty, Q. Lin, L. Zhuang, M. D. McBriar, A. M. Boldi, W. H. Moser, N. Murase, K. Nakayama and M. Sobukawa, *Angew. Chem., Int. Ed*., 2001, **40**, 191; (*b*) A. B. Smith, III, Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, C. S. Brook, N. Murase and K. Nakayama, *Angew. Chem., Int. Ed*., 2001, **40**, 196; (*c*) A. B. Smith, III, T. Tomioka, C. A. Risatti, J. B. Sperry and C. Sfouggatakis, *Org. Lett*., 2008, **10**, 4359.
16 Total syntheses: (*a*) D. A. Evans, P. J. Coleman and L. C. Dias, *Angew. Chem., Int. Ed. Engl*., 1997, **36**, 2738; (*b*) D. A. Evans, B. W. Trotter, B. Côté and P. J. Coleman, *Angew. Chem., Int. Ed. Engl*., 1997, **36**, 2741; (*c*) D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, L. C. Dias and A. N. Tyler, *Angew. Chem., Int. Ed. Engl*., 1997, **36**, 2744; (*d*) D. A. Evans, B. W. Trotter, P. J. Coleman, B. Côté, L. C. Dias, H. A. Rajapakse and A. N. Tyler, *Tetrahedron*, 1999, **55**, 8671; (*e*) J. Guo, K. J. Duffy, K. L. Stevens, P. I. Dalko, R. M. Roth, M. M. Hayward and Y. Kishi, *Angew. Chem., Int. Ed*., 1998, **37**, 187; (*f*) M. M. Hayward, R. M. Roth, K. J. Duffy, P. I. Dalko, K. L. Stevens, J. Guo and Y. Kishi, *Angew. Chem., Int. Ed*., 1998, **37**, 192; (*g*) A. B. Smith, III, Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, C. S. Brook, N. Murase and K. Nakayama, *Angew. Chem., Int. Ed*., 2001, **40**, 196; (*h*) I. Paterson, D. Y.-K. Chen, M. J. Coster, J. L. Acena, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson and R. D. Norcross, *Angew. Chem., Int. Ed*., 2001, **40**, 4055; (*i*) M. T. Crimmins, J. D. Katz, D. G. Washburn, S. P. Allwein and L. F. McAtee, *J. Am. Chem. Soc*., 2002, **124**, 5661; (*j*) C. H. Heathcock and J. L. Hubbs, *J. Am. Chem. Soc*., 2003, **125**, 12836; (*k*) C. H. Heathcock, M. McLaughlin, J. Medina, J. L. Hubbs, G. A. Wallace, R. Scott, M. M. Claffey, C. J. Hayes and R. J. Ott, *J. Am. Chem. Soc*., 2003, **125**, 12844.
17 (*a*) S. L. Schreiber and M. T. Goulet, *Tetrahedron Lett*., 1987, **28**, 6001; (*b*) C. S. Poss, S. D. Rychnovsky and S. L. Schreiber, *J. Am. Chem. Soc*., 1993, **115**, 3360.
18 A. B. Smith, III and S. M. Pitram, *Org. Lett*., 1999, **1**, 2001.
19 K. J. Hale, M. C. Hummersone and G. S. Bhatia, *Org. Lett*., 2000, **2**, 2189.
20 Isolation: (*a*) G. R. Petit, C. L. Herald, J. Clardy, E. Arnold, D. L. Doubek and D. L. Herald, *J. Am. Chem. Soc*., 1982, **104**, 6848; Biological activity: (*b*) P. A. Philip, D. Rea, P. Thavasu, J. Carmichael, N. S. A. Sturat, H. Rockett, D. C. Talbot, T. Ganesan, G. R. Petit, F. Balkwill and A. L. Harris, *J. Natl. Cancer Inst*., 1993, **85**, 1812; (*c*) C. G. Jayson, D. Crowther, J. Prendiville, A. T. McGown, C. Scheid, P. Stern, R. Young, P. Benchley, S. Owens and G. R. Petit, *Br. J. Cancer*, 1995, **72**, 461.
21 Total synthesis of bryostatin 2: (*a*) D. A. Evans, P. H. Carter, E. M. Carreira, J. A. Prunet, A. B. Charette and M. Lautens, *Angew. Chem., Int. Ed*., 1998, **37**, 2354; Total synthesis of bryostatin 3: (*b*) K. Ohmori, Y. Ogawa, T. Obitsu, Y. Ishikawa, S. Nishiyama and S. Yamamura, *Angew. Chem., Int. Ed*., 2000, **39**, 2290; Total synthesis of bryostatin 7: (*c*) M. Kageyama, T. Tamura, M. H. Nantz, J. C. Roberts, P. Somfai, D. C. Whritenour and S. Masamune, *J. Am. Chem. Soc*., 1990, **112**, 7407; (*d*) S. Masamune, *Pure Appl. Chem*., 1988, **60**, 1587; (*e*) S. Manaviazar, M. Frigerio, G. S. Bhatia, M. G. Hummersone, A. E. Aliev and K. J. Hale, *Org. Lett*., 2006, **8**, 4477.
22 Isolation of (−)-indolizidine 223AB: (*a*) T. Tokuyama, N. Nishimori, I. K. Karle, M. W. Edwards and J. W. Daly, *Tetrahedron*, 1986, **42**, 3453; Isolation of (−)-205B: (*b*) T. Tokuyama, N. Nishimori, A. Shimada, M. W. Edwards and J. W. Daly, *Tetrahedron*, 1987, **43**, 643.
23 (*a*) A. B. Smith, III and D.-S. Kim, *Org. Lett*., 2004, **6**, 1493; (*b*) A. B. Smith, III and D.-S. Kim, *Org. Lett*., 2005, **7**, 3247; (*c*) A. B. Smith, III and D.-S. Kim, *J. Org. Chem*., 2006, **71**, 2547.
24 W. H. Moser, K. E. Endsley and J. T. Colyer, *Org. Lett*., 2000, **2**, 717.
25 W. H. Moser, J. Zhang, C. S. Lecher, T. L. Frazier and M. Pink, *Org. Lett*., 2002, **4**, 1981.
26 S. G. Davies and C. L. Goodfellow, *J. Chem. Soc., Perkin Trans. 1*, 1990, 393.
27 A. B. Smith, III and M. O. Duffey, *Synlett*, 2004, **8**, 1363.
28 A. B. Smith, III, D.-S. Kim and M. Xian, *Org. Lett*., 2007, **9**, 3307.
29 No attempt to date has been made to improve the epoxidation selectivity.
30 B.-H. Ye and Y. Naruta, *Tetrahedron*, 2003, **59**, 3593.
31 H. Taguchi, K. Takami, A. Tsubouchi and T. Takeda, *Tetrahedron Lett*., 2004, **45**, 429.
32 A. B. Smith, III, W.-S. Kim and W. M. Wuest, *Angew. Chem., Int. Ed*., 2008, **47**, 7082.
33 N. O. Devarie-Baez, B. J. Shuhler, H. Wang and M. Xian, *Org. Lett*., 2007, **9**, 4655.
34 M. Schlosser and S. Strunk, *Tetrahedron Lett*., 1984, **25**, 741.
35 A. Rueda, E. Zubia, M. J. Ortega and J. Salva, *J. Nat. Prod*., 2001, **64**, 401.
36 M. Schlosser, A. Zellner and F. Leroux, *Synthesis*, 2001, 1830.

37 E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551.
38 (*a*) D. E. Williams, M. Roberge, R. Van Soest and R. J. Andersen, *J. Am. Chem. Soc.*, 2003, **125**, 5296; (*b*) D. E. Williams, M. Lapawa, X. Feng, T. Tarling, M. Roberge and R. J. Andersen, *Org. Lett.*, 2004, **6**, 2607; (*c*) K. Warabi, D. E. Williams, B. O. Patrick, M. Roberge and R. J. Andersen, *J. Am. Chem. Soc.*, 2007, **129**, 508.
39 Total synthesis of spirastrellolide A methyl ester: (*a*) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas and C. Moessner, *Angew. Chem., Int. Ed.*, 2008, **47**, 3016; (*b*) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas and C. Moessner, *Angew. Chem., Int. Ed.*, 2008, **47**, 3021; Synthetic efforts toward spirastrellolide A: (*c*) J. Liu and R. P. Hsung, *Org. Lett.*, 2005, **7**, 2273; (*d*) Y. Pan and J. K. De Brabander, *Synlett*, 2006, 853; (*e*) C. Wang and C. J. Forsyth, *Org. Lett.*, 2006, **8**, 2997; (*f*) A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem.*, 2006, **118**, 5632 (*Angew. Chem., Int. Ed.*, 2006, **45**, 5506); (*g*) A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem.*, 2006, **118**, 5636 (*Angew. Chem., Int. Ed.*, 2006, **45**, 5510); (*h*) J. Liu, J. H. Yang, C. Ko and R. P. Hsung, *Tetrahedron Lett.*, 2006, **47**, 6121.
40 A. B. Smith, III and D.-S. Kim, *Org. Lett.*, 2007, **9**, 3311.
41 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2007, **70**, 461.
42 (*a*) R. H. Grubbs, *Tetrahedron*, 2004, **60**, 7117; Also see: (*b*) H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A. Washenfelder, D. A. Bussmann and R. H. Grubbs, *J. Am. Chem. Soc.*, 2000, **21**, 442.
43 D. M. Huryn and N. D. P. Cosford, *Annu. Rep. Med. Chem.*, 2007, **42**, 401; Also see http://nihroadmap.nih.gov/.