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A Unified Synthetic Strategy to the Cryptocarya Family of Natural Products Exploiting Anion Relay Chemistry (ARC)

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Abstract

A unified synthetic strategy to the *Cryptocarya* family of natural products has been achieved employing four-component fragment unions in a “single flask” exploiting Anion Relay Chemistry (ARC). Functionalization of the ARC adducts permits rapid construction of five polyhydroxylated di- and tetrahydropyrone natural products of the *Cryptocarya* class (1–5), in a total of 7–9 steps from commercially available materials.

Recently, polyhydroxylated dihydropyrone natural products and derivatives have drawn significant attention from the biochemical and synthetic communities.¹ *Cryptocarya* diacetate **1**, *cryptocarya* triacetate **2**, *cryptocaryolone* **3** and the diacetate **4**, as well as *polyrhacitide* A **5**, all belong to this general class. The natural sources – the bark of South African *Cryptocarya latifolia* (**1–4**)² and the Chinese ant *Polyrhacis lamellidens* (**5**)³ – are used in folk medicine as analgesics. Structural analogs of **1** have also been associated with α -tubulin binding activity, based on the premise that the common α,β -unsaturated lactone moiety may operate as a Michael acceptor for a specific lysine α -tubulin residue (Lys³⁵²), in conjunction with stabilization of the adduct *via* hydrogen-bonding.^{1b}

Numerous strategically diverse syntheses have been reported leading to the construction of different subsets of these natural products.⁴ In particular, She *et al.* utilized Anion Relay Chemistry (ARC) in a concise route to **2–4**.^{4e} In this context, we recently developed an augmented ARC-based strategy to access members of the *Cryptocarya* class in a more efficient manner.

Anion Relay Chemistry (ARC) comprises a powerful tactic to assemble complex fragments in natural product total synthesis.⁵ The utility of ARC also resides in application to diversity-oriented syntheses (DOS); that is, the potential to introduce rapidly structural complexity from readily available fragments.⁶ In Type I ARC, two electrophiles are tethered to an anionic linchpin (**6**) *via* [1,4]-Brook rearrangement (Scheme 1a), whereas in Type II ARC, the use of a bifunctional linchpin (**8**) permits the relay of the negative charge of an initiating nucleophile to a distal carbon atom prior to electrophilic capture (Scheme 1b). The

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Supporting Information Available: Experimental details and spectral data for all new compounds.

latter version of ARC in particular holds the promise for iterative additions of diverse linchpins, by means of repeated charge relay in a way not dissimilar to “living polymerization.”⁷

Based on this paradigm, we envisioned that ARC could be extended *vis-à-vis* the work of She to construct the advanced carbon skeletons required for **1–5** *via* a four-component “single flask” union. Specifically, we reasoned that access to targets **1–5** (Scheme 2) could be achieved *via* acetylation or intramolecular oxa-Michael addition of polyol derivatives (**15**), which in turn would arise *via syn*-diastereoselective reduction of a suitable hydroxy-ketone (**16**). In all cases, formation of the dihydropyrone motif would arise from ring-closing metathesis of the corresponding polyketide precursor (**17**), the latter constructed utilizing appropriate ARC tactics.

Cryptocarya diacetate (**1**) comprised a useful first model to fuel the development of reaction conditions both for the key four-component ARC step (Scheme 3) and for the subsequent transformations. Towards this end, application of Type I ARC involving nucleophilic attack of (*S*)-methyl oxirane by 2-lithio-2-TBS-1,3-dithiane (Li-**22**), followed by a solvent-triggered Brook rearrangement to regenerate a carbon nucleophile at the 2-position of the dithiane (**24**), would permit capture of a second electrophile. The significant basicity of **24** however would preclude use of allyl-oxiranes as the terminating electrophile to access directly **27**, given the propensity of allylic epoxides for elimination. We turned instead to a more general synthetic approach, importantly involving minimal protecting-group manipulations, employing (*S*)-epichlorohydrin as the second electrophile.⁸ As previously reported, lithio-dithianes are known under our conditions to attack exclusively at the 3-position (in particular avoiding direct displacement of the chloride),⁹ with the resulting chlorohydrin anion (**25**) being stable at –40 °C. Formation of a new electrophilic terminal epoxide (**26**) can then be achieved simply by warming the reaction mixture to room temperature once consumption of **24** is complete (TLC). We also discovered that introduction of epichlorohydrin *prior* to triggering the Brook rearrangement, orchestrated by addition of hexamethyl phosphoramide (HMPA), results in a 1.6-fold increase in union efficiency; carbanion **24** thus reacts with the excess electrophile as soon as generated. Addition of vinylmagnesium bromide under copper-catalyzed conditions to epoxide **26** in the same flask completes construction of the advanced homoallylic alcohol skeleton **27**, obtained in 75% yield in a “single flask” from ethylene oxide. Pleasingly, the average yield for each of the three carbon-carbon bond forming steps nears 90% (Scheme 3).

Dithiane **27** was next subjected to mercury(II)-mediated hydrolysis,¹⁰ which proved to be superior to oxidative dithiane removal protocols.¹¹ Subsequent treatment with acryloyl chloride in the presence of Hünig’s base¹² furnishes acrylate **28** in 97% yield over 2 steps. Next, ring-closing metathesis (RCM), carried out under microwave irradiation,¹³ employing the Hoveyda-Grubbs 2nd generation catalyst, completed construction of the dihydropyrone moiety in 87% yield. For the RCM conversion, revealing the carbonyl moiety and maintaining TBS protection on the adjacent hydroxyl group in **28** proved to be beneficial. Following RCM, the silyl protecting group was removed in 84% yield employing trifluoroacetic acid (TFA) and thioanisole,¹⁴ thus setting the stage for a *syn*-diastereoselective reduction of the β -hydroxyketone in **29**.¹⁵ Use of diethyl methoxyborane and sodium borohydride proceeded smoothly, however, a boronate ester was initially isolated instead of the expected diol. Methanolysis released the desired diol (**30**) in 70% overall yield. Bis-acetylation then completed construction of cryptocarya diacetate **1**. The synthetic sequence proceeded in 7 steps and 25% overall yield (Scheme 4).

The syntheses of **2–5**, in turn, relied on Type II ARC, which permits introduction of the requisite additional carbinol motif in the polyol skeleton (Scheme 5). To this end, ARC

union of 2-methyl-1,3-dithiane **31** with bifunctional linchpin (*R*)-**20** and epichlorohydrin,¹⁶ followed by copper(I)-mediated addition of vinylmagnesium bromide, provided again in a “single flask” advanced homoallylic alcohol **32** in 52% yield. Application of the dithiane hydrolysis, acylation and ring-closing metathesis protocols developed for **1** permitted isolation of dihydropyrone **34** in 51% yield for the 3 steps from **32**. Deprotection and directed reduction with sodium borohydride next furnished *syn*-triol **36**, which without purification was either per-acetylated to yield cryptocarya triacetate **2** [65% over 2 steps, 17% overall, for 7 steps from (*R*)-**20**] or subjected to catalytic acid to trigger an intramolecular oxa-Michael cyclization to furnish cryptocaryolone **3** in 60% for the final 2 steps [16% overall also from (*R*)-**20**]. Cryptocaryolone diacetate (**4**) was then obtained in near quantitative yield upon treatment with acetic anhydride.^{4c}

To access polyrhacitide A (**5**), we exploited the previously developed ARC Type II protocol, now employing *n*-heptyldithiane **37**, prepared by condensation of 1,3-propanedithiol and *n*-octanal,¹⁷ as the initiating nucleophile (Scheme 6). The change in nature of the dithiane alkyl chain, however, had a detrimental impact on the ARC reaction efficiency (36%), probably due to the increased steric hindrance at the dithiane nucleophilic carbon. Notwithstanding this shortcoming, the reaction was carried out on gram-scale, thus readily furnishing material to complete the synthesis following a similar route designed for **2–4**. Specifically, dithiane removal, acylation of the homoallylic alcohol and RCM led to dihydropyrone **39** (59% over 3 steps). Removal of the TBS protecting group (95%), *syn*-diastereoselective reduction (83%) and oxa-Michael cyclization (98%) then completed construction of polyrhacitide A (**5**), in a total of 7 steps and 16% overall yield from (*S*)-**20** (Scheme 6).

In summary, Anion Relay Chemistry (ARC) has been exploited for the rapid construction of a small library of polyhydroxylated pyrone natural products, which could be accessed in 7–9 steps from commercially available materials. Initial studies, utilizing the Type I ARC tactic, led to the synthesis of (+)-cryptocarya diacetate **1**, which was extended to the Type II ARC protocol to furnish (+)-cryptocarya triacetate **2**, (–)-cryptocaryolone **3**, (–)-cryptocaryolone diacetate **4** and (+)-polyrhacitide A **5**. Application of ARC tactics for the construction of more complex congeners of this class of bioactive natural products continues in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. For a review of recent syntheses of dihydropyrone-containing natural products see Marco JA, Carda M, Murga J, Falomir E. Tetrahedron. 2007; 63:2929–2958. for biological background information including structure-activity relationship (SAR) studies see Carda M, Murga J, Díaz-Oltra S, García-Pla J, Paños J, Falomir E, Trigili C, Díaz JF, Barasoain I, Marco JA. Eur J Org Chem. 2013:1116–1123.
2. (a) Drewes SE, Sehlapelo BM, Horn MM, Scott-Shaw R, Sandor P. Phytochemistry. 1995; 38:1427–1430. (b) Zschocke S, van Staden J. J Ethnopharmacol. 2000; 71:473–478. [PubMed: 10940585]
3. Jiang ZH, Yang QX, Tanaka T, Kouno I. J Nat Prod. 2008; 71:724–727. [PubMed: 18298078]

4. (a) Jørgensen KB, Suenaga T, Nakata T. *Tetrahedron Lett.* 1999; 40:8855–8858. (b) Hunter TJ, O'Doherty GA. *Org Lett.* 2001; 3:2777–2780. [PubMed: 11506632] (c) Smith CM, O'Doherty GA. *Org Lett.* 2003; 5:1959–1962. [PubMed: 12762696] (d) Umarye JD, Lessmann T, García AB, Mamane V, Sommer S, Waldmann H. *Chem Eur J.* 2007; 13:3305–3319. [PubMed: 17310497] (e) Wang X, Wang W, Zheng H, Su Y, Jiang T, He Y, She X. *Org Lett.* 2009; 11:3136–3138. [PubMed: 19537772] (f) Mohapatra DK, Bhimireddy E, Sivarama Krishnarao P, Das PP, Yadav JS. *Org Lett.* 2011; 13:744–747. [PubMed: 21214256] (g) Albury AMM, Jennings MP. *J Org Chem.* 2012; 77:6929–6936. [PubMed: 22827503]
5. Smith AB III, Adams CM. *Acc Chem Res.* 2004; 37:365–377. [PubMed: 15196046]
6. Schreiber SL. *Science.* 2000; 287:1964–1969. [PubMed: 10720315] see: Smith AB III, Kim WS. *Proc Natl Acad Sci U S A.* 2011; 108:6787–6892. [PubMed: 21245309] Smith AB III, Han H, Kim WS. *Org Lett.* 2011; 13:3328–3331. [PubMed: 21644563]
7. Hirao A, Nakahama S. *Acta Polymer.* 1998; 49:133–144.
8. Inverting the order of electrophile addition resolved this problem in the (+)-rimocidin synthetic studies: Smith AB III, Foley M, Dong S, Orbin A. *J Org Chem.* 2009; 74:5987–6001. [PubMed: 19621880]
9. Smith AB III, Pitram SM, Boldi AM, Gaunt MJ, Sfougataki C, Moser WH. *J Am Chem Soc.* 2003; 125:14435–14445. and references within. [PubMed: 14624591]
10. Wang H, Shuhler BJ, Xian M. *J Org Chem.* 2007; 72:4280–4283. [PubMed: 17447817]
11. Examples in Chen MJ, Tsai YM. *Tetrahedron.* 2011; 67:1564–1574. Spangenberg T, Aubry S, Kishi Y. *Tetrahedron Lett.* 2010; 51:1782–1785. [PubMed: 20305830]
12. Trost BM, Yeh VSC. *Org Lett.* 2002; 4:3513–3516. [PubMed: 12323057]
13. Varray S, Gauzy C, Lamaty F, Lazaro R, Martinez J. *J Org Chem.* 2000; 65:6787–6790. [PubMed: 11052139]
14. Sunazuka T, Hirose T, Chikaraishi N, Harigaya Y, Hayashi M, Komiyama K, Sprengeler PA, Smith AB III, Mura S. *Tetrahedron.* 2005; 61:3789–3803.
15. Munakata R, Katakai H, Ueki T, Kurosaka J, Takao KI, Tadano K. *J Am Chem Soc.* 2003; 125:14722–14723. [PubMed: 14640644]
16. For the preparation of linchpin **20** (one step from commercially available **22**) and examples of Type II ARC see Smith AB III, Xian M. *J Am Chem Soc.* 2006; 128:66–67. [PubMed: 16390124]
17. Morokuma K, Takahashi K, Ishihara J, Hatakeyama S. *Chem Commun.* 2005:2265–2267.

a. Type I **b. Type II**

ASG = Anion-Stabilizing Group

Scheme 1.
 Type I and Type II Anion Relay Chemistry

This work:

Scheme 2.
Comparison of synthetic strategies

Scheme 3.
Type I ARC in the synthesis of **1**

Scheme 4.
 Synthesis of cryptocarya diacetate (**1**)

Scheme 5.
Synthesis of targets **2–4**

Scheme 6.
Synthesis of polyrhacitide A (**5**)