

Progress towards the development of a new strategy for the highly stereoselective synthesis of alkene-containing macrocyclic ring systems by organocuprate oxidation

Avenços en el desenvolupament d'una nova estratègia per a la síntesi altament estereoselectiva de sistemes macrocíclics que contenen alquens per oxidació amb organocuprats

Warren R. J. D. Galloway and David R. Spring
University of Cambridge, Department of Chemistry

Abstract: Macrocyclic ring systems incorporating geometrically defined alkenes are the structural cores of a large number of biologically active molecules and thus represent targets of significant interest for chemical biology studies.

Catalytic ring-closing metathesis (RCM) is undoubtedly the most widely used method for the synthesis of such scaffolds and represents an exceptionally powerful general synthetic tool. However, there are some drawbacks associated with typical RCM methods in this context. From the perspective of bioactivity, perhaps the most significant of these is that control of the stereochemistry of the resulting olefin is problematic when typical reaction conditions are employed. In general, RCM reactions of unhindered alkenes using standard conditions to form medium/large rings tend to give mixtures of the (*E*)- and (*Z*)-configured cyclic olefins. As the stereochemical identity of the alkene can be critical to the biological activities of such molecules, such mixtures may be undesirable and it is often the case that the isomers are very difficult to separate. Thus the exploration of alternative, non-RCM-based strategies for the stereoselective synthesis of alkene-containing large-ring systems is warranted. Herein progress towards the development of a new strategy for the highly stereoselective synthesis of alkene containing macrocyclic ring systems, which is based around the use of organocuprate oxidation chemistry, is presented. As a proof-of-principle, the highly stereoselective synthesis of a 12-membered (*Z*)-configured cyclic olefin by intramolecular cyclisation, without recourse to high dilution conditions, is reported. This demonstrates the feasibility of the new strategy and provides a springboard for further studies.

Keywords: Macrocycles, organocuprates, alkenes, ring-closing, stereoselectivity.

Resum: En l'estructura d'un gran nombre de molècules biològicament actives i que, per tant, representen dianes de gran interès per a estudis químics i biològics es troben presents sistemes d'anells macrocíclics que incorporen alguns alquens definits geomètricament.

La metàtesi catalítica de tancament d'anell (MCTA) és, sens dubte, el mètode més emprat per a la síntesi d'aquestes estructures i representa una potent eina general de síntesi. No obstant això, en aquest context, hi ha alguns inconvenients associats als mètodes típics de MCTA. Des de la perspectiva de la bioactivitat, potser el més important d'aquests inconvenients és que el control de l'estereoquímica de l'olefina resultant és problemàtic quan s'empren les típiques condicions de reacció. En termes generals, les reaccions MCTA d'alquens estèricament impedits que fan ús de condicions estàndard per formar anells de mida mitjana o gran tendeixen a donar barreges de les olefines cícliques amb configuració (*E*) i (*Z*). Atès que la naturalesa estereoquímica de l'alquè pot ser crítica per a l'activitat biològica d'aquestes molècules, aquestes barreges poden ser indesitjables i sovint es dona el cas que els isòmers són difícils de separar. Com a conseqüència, el fet d'explorar estratègies alternatives no basades en MCTA per a la síntesi estereoselectiva de sistemes macrocíclics grans que contenen alquens és de gran interès. En aquest article es presenten els avenços que hem dut a terme en desenvolupar una nova estratègia, basada en l'ús d'organocuprats en reaccions d'oxidació per a la síntesi altament estereoselectiva d'anells macrocíclics que contenen alquens. Com a prova de viabilitat, es descriu la síntesi altament estereoselectiva d'una olefina cíclica de dotze baules d'estereoquímica (*Z*) mitjançant ciclació intramolecular i sense utilitzar condicions de dilució alta. Això demostra la viabilitat d'aquesta nova estratègia i obre la porta a la realització de nous estudis.

Paraules clau: Macrocicles, organocuprats, alquens, tancament d'anell, estereoselectivitat.

Introduction

Macrocyclic ring systems incorporating geometrically defined alkenes are the structural cores of a large number of biologically active molecules (figure 1) [1, 2]. The stereochemical identity of the alkene can be critical to the biological activities of such molecules [2].

In light of the biological importance of large-sized unsaturated ring systems, it is unsurprising that there has been considerable interest in the development of strategies for their synthesis. Catalytic ring-closing metathesis (RCM) is undoubtedly the most widely used method in this regard [1-4]. Indeed, synthetic routes to numerous molecules with cyclic olefin motifs (including a plethora of natural products) contain an RCM reaction as a key step [1]. However, there are some problems associated with the construction of large-ring alkenes by RCM. Macrocyclic formation by RCM generally requires high dilution conditions in order to minimise competing intermolecular reactions, which may be costly and result in the generation of large quantities of waste [5]. In addition, RCM-based macrocyclic formations are mainly entropically driven and large enthalpic barriers are very difficult to overcome [6, 7]. Therefore, the formation of highly strained products is problematic [8]. In addition, some RCM catalysts can be costly to purchase, somewhat laborious to prepare, or difficult to handle. From the perspective of bioactivity, perhaps the most significant drawback associated with generating large-ring alkenes by RCM is that control of the stereochemistry of the resulting olefin is problematic. Typically, RCM reactions to form medium/large rings from alkenes have tended to give mixtures of the (*E*)- and (*Z*)-configured cyclic olefins

if standard reaction systems are used and it is often difficult to predict a priori what the major stereoisomer will be [1, 2, 6, 9-14]. As the stereochemical identity of the alkene can be critical to the biological activities of such molecules, such mixtures may be undesirable and it is often the case that the isomers are very difficult to separate [2, 14]. Achieving high (*Z*)-selectivity in the formation of large rings by RCM involving two unhindered alkenes is known to be especially challenging; the kinetically generated (*Z*)-alkene can often readily undergo isomerisation to the (*E*)-isomer, thus eroding stereochemical purity [1, 2]. There has been considerable interest in the development of strategies that address the capriciousness of stereoselectivity of RCM reactions between alkenes. Recent years have witnessed major advances in this regard; several elegant approaches based around either altering substrate structure [13, 14] or catalyst structure [1, 2] in order to generate the desired alkene stereoselectively have been reported. These approaches are yet to find widespread application and there are specific drawbacks associated with each of them (e.g., the necessity for additional synthetic manipulations in the preparation of substrates or the modification of ring-closed products [2]) not to mention the aforementioned issues associated with RCM in general (e.g., catalyst cost and preparation difficulties and the general need for relatively high-dilution reaction conditions). Thus, the exploration of alternative, non-RCM-based strategies for the stereoselective synthesis of alkene-containing large-ring systems is clearly warranted, with potentially broad applications in target-oriented synthesis and also diversity-oriented synthesis [15], where controlled access to a diverse range of such compounds would provide much-needed further insight into the functional capabilities of this class of molecules and allow access to underexplored regions of chemical space. New approaches that allow for the highly stereoselective synthesis of (*Z*)-alkene containing large-ring systems would be especially valuable.

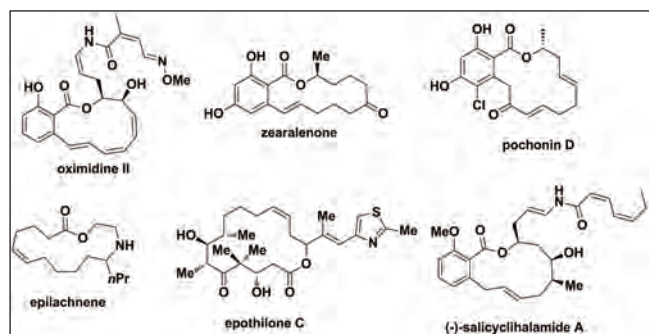


FIGURE 1. Some examples of biologically active compounds containing macrocyclic alkenes.

Synthesis of alkene-containing macrocyclic ring systems by organocuprate oxidation

Within our own group we have developed methods for carbon-carbon bond formation by the oxidative coupling of organocuprates readily generated from halide-substituted

substrates (figure 2) [16–22]. These coupling protocols utilize the following general sequence: halogen–metal exchange (iodine–magnesium, bromine–zinc, iodine–lithium or bromine–lithium); copper salt mediated transmetalation to form an intermediate organocuprate; and finally, organocuprate oxidation and carbon–carbon bond formation [18]. These chemistries have been successfully used to affect the intermolecular homocoupling of aryl, heteroaryl, benzylic and alkenyl halides. In addition, this methodology has also been used for the synthesis of sterically hindered functionalised biaryls, including highly-strained medium-ring-containing biaryls, by the intramolecular coupling of aryl organocuprates generated from aryl halides [18]. We thus envisaged that our organocuprate-based coupling methodologies could be applied to the synthesis of macrocyclic olefinic species (figure 3). It was anticipated that such scaffolds could be generated by the intramolecular coupling of aryl–vinyl cuprates **2** (accessed from substrates **3** containing both an aryl halide and vinyl halide) or vinyl–alkyl cuprates **4** (accessed from substrates **5** containing both a vinyl halide and an alkyl halide). Several features of this new proposed strategy towards cyclic olefin species are worthy of note. Unlike RCM, no expensive catalysts or additives would be required in the carbon–carbon bond-forming step. In our studies on intramolecular coupling to form biaryls it was found that high-

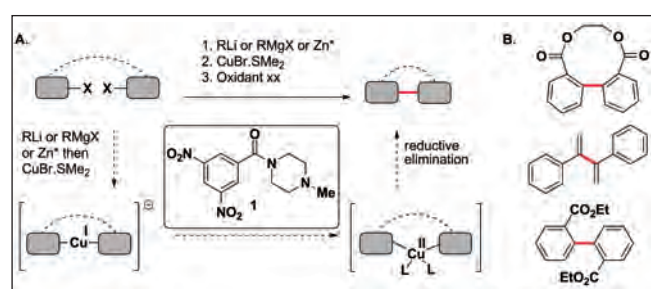


FIGURE 2. (A) An overview of previous work carried out within the group on intermolecular homocoupling and the synthesis of biaryl-containing medium-ring systems by organocuprate oxidation. Organolithium, organomagnesium or organozinc formation is followed by transmetalation to form the corresponding organocuprate. Oxidation then furnishes the ring-closed product. The oxidant **1** was developed within the group for use in these reactions [18]. Oxidant **1** and oxidant-derived by-products could be removed from the relatively non-polar organic reaction products by an aqueous wash during the work-up or by passage through silica gel. The precise mechanistic details of this process are yet to be fully delineated [18]. The initial organocuprate species is thought to contain a copper (I) atom, which is bonded linearly. Subsequent oxidation then generates a high-energy copper (II) intermediate which reductively eliminates to form the C–C bond and regenerate copper (0). The structures of the organometallic reagents and intermediates are simplified as they are most likely to be oligomeric in solution [18]. Zn* = Rieke zinc; (B) Some examples of compounds formed using our copper-based methods [16–11]. The C–C bonds formed by oxidative organocuprate coupling are highlighted in red.

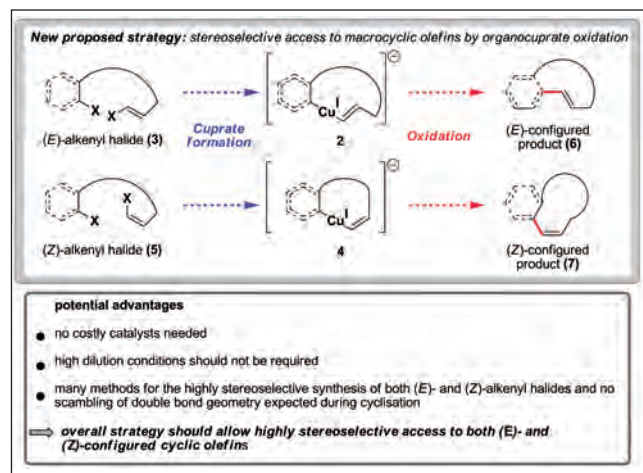


FIGURE 3. New proposed strategy for the synthesis of macrocyclic alkenes using our copper-based methods.

dilution conditions were not required; it was anticipated that this would also be the case for the formation of cyclic olefins using this approach [18]. Furthermore, on the basis of our previous studies it was anticipated that the double bond geometry of any cyclisation precursor would be retained in the cyclised product, i.e., no scrambling of double bond geometry would occur [16–22]. Conceivably therefore, both (E)- and (Z)-configured cyclic olefins, **6** and **7** respectively, could be generated with high levels of stereochemical purity from the corresponding geometrically defined halide precursors. Herein we describe our progress thus far towards the development of this new strategy for the stereoselective synthesis of alkene-containing macrocyclic ring systems, and present proof-of-concept work that demonstrates the feasibility of this approach [23].

As a proof-of-principle we decided to initially target the synthesis of (Z)-**8**, a 12-membered benzo-fused ring system containing a (Z)-alkene, by the cyclisation of compound (Z)-**9** (figure 4). Benzo-fused unsaturated macrocyclic ring motifs are found in numerous biologically interesting molecules;

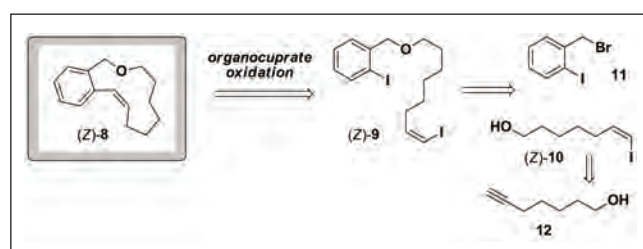


FIGURE 4. Initial retrosynthetic strategy towards the synthesis of (Z)-**8**.

12-membered lactone derivatives occur in a wide range of natural product classes, including the benzolactone enamides [24] and the resorcylic acid-type macrolides [25]. Despite the interesting biological properties associated with 12-membered benzo-fused unsaturated lactones, compounds containing the equivalent non-lactone ring systems (i.e., rings lacking the carbonyl functionality) are relatively scarce; examples with (*Z*)-configured olefins are particularly rare. Consequently, compounds containing this ring system are under-represented in current small molecules libraries. Methods to access compounds containing this structural core are therefore clearly of value in terms of accessing underexplored chemical space and probing the biological usefulness of a structural motif that has thus far largely escaped the attention of man, and perhaps even nature [26]. We envisaged that cyclisation substrate (*Z*)-9 could be generated by the coupling of (*Z*)-configured vinyl alcohol 10 with commercially available 2-bromobenzyl iodide (11). It was anticipated that 10 in turn could be synthesised from 7-octyn-1-ol (12).

7-octyn-1-ol (12) was readily prepared from 3-octyn-1-ol (13) by treatment with sodium hydride and ethylene-1,2-diamine (figure 5) [27]. This "contrathermodynamic" migration of the triple bond from the internal position to the terminus of the alkyl chain is believed to proceed through a sequence of 1,3-proton transfers between acetylenes and allenes affected by the sodium amide base that is generated in situ [27-30]. With the terminal alkyne 12 in hand, we were ready to attempt its conversion to the desired (*Z*)-iodo alkene (*Z*)-10. Takami and co-workers have reported a procedure for the trans-hydrometallation of alkynes by a combination of indium (III) trichloride and diisobutylaluminium hydride (DIBAL), which provides a one-pot method for the synthesis of (*Z*)-iodo

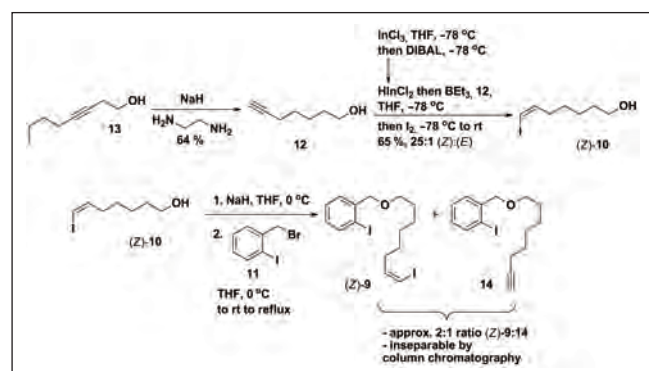


FIGURE 5. Attempted synthesis of (*Z*)-9. DIBAL = diisobutylaluminium hydride; rt = room temperature.

alkenes with very high stereoselectivity [31]. Reaction of 7-octyn-1-ol (12) under these conditions led to the generation of the desired compound (*Z*)-10. ¹H NMR analysis of the crude product material indicated that the reaction had proceeded with good stereoselectivity (approx. 25:1 (*Z*):(*E*)). Deprotonation of (*Z*)-10 with sodium hydride and treatment with 11 led to a mixture of the desired product (*Z*)-9, unreacted 11 and alkynyl derivative 14, which presumably results from base-mediated elimination of the vinyl moiety. Unfortunately, it proved impossible to isolate an analytically pure sample of (*Z*)-9 by column chromatography on silica from this mixture.

A second route to (*Z*)-9 was envisaged which involved coupling of alkynyl alcohol 12 with 2-iodobenzyl bromide (11), followed by conversion of the terminal alkyne into the desired (*Z*)-iodo alkene (figure 6).

Compound 14 was readily generated from 12 in good yield (figure 7). Unfortunately, the attempted conversion of alkyne 14 into the desired iodo alkene (*Z*)-9 by application of the indium (III) chloride-based conditions of Takami *et al.* again proved problematic; (*Z*)-9 was found to co-elute with residual starting material on silica gel, precluding its purification by column chromatography. Given these difficulties, it was decided to introduce the desired vinyl iodide functionality by an alternative means. Thus a third synthetic route to cyclisation substrate (*Z*)-9 was examined (figure 7). Silver-nitrate catalysed iodination of terminal alkyne 14 with *N*-iodosuccinimide produced iodoalkyne 15 in an excellent yield [32]. Dicyclohexyl borane reduction of 15 furnished the desired vinyl iodide (*Z*)-9 in a modest yield, but with an excellent geometrical selectivity (approx. 20:1 (*Z*):(*E*) by ¹H NMR analysis of the crude product material) [33].

With substrate (*Z*)-9 in hand we were ready to attempt the key organocuprate oxidative intramolecular carbon-carbon bond forming reaction. Treatment of (*Z*)-9 with tertiary butyl lithium (tBuLi), followed by transmetalation with copper (I)

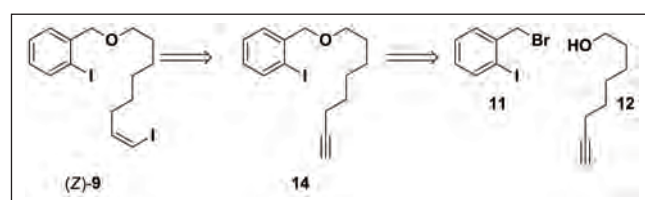


FIGURE 6. Revised retrosynthetic strategy towards the synthesis of (*Z*)-9.

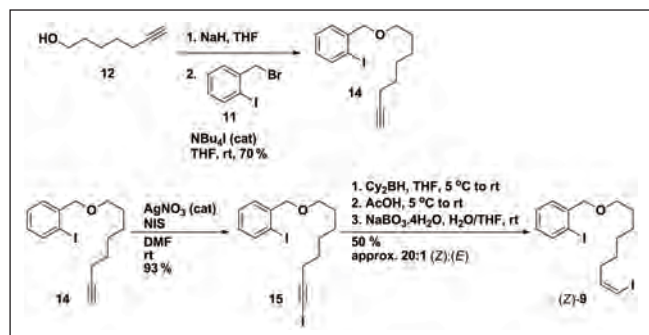


FIGURE 7. Successful synthesis and isolation of cyclisation substrate (Z)-9. cat = catalytic amount; rt = room temperature.

bromide dimethyl sulfide complex (CuBr.SMe₂) and subsequent intramolecular cuprate oxidation furnished the desired product (Z)-8 in a relatively low isolated yield after purification (figure 8).^{*} Crucially however, there was no evidence in the ¹H NMR of the crude product mixture for any (E) di-substituted alkene-containing products. Lithium-halogen exchange is known to proceed with retention of configuration at vinyl halides [34, 35]. It can therefore be inferred that the oxidative coupling step also proceeds with retention of configuration at the vinyl position. The only other identifiable component of the crude reaction mixture was de-iodinated starting material. This presumably resulted from a double halogen-lithium exchange followed by protonation (upon work-up or due to adventitious water present in the reaction

^{*}Experimental procedure for the synthesis of (Z)-8: A three-neck flask fitted with a nitrogen inlet was flame-dried for 2 min under high vacuum and then flushed with nitrogen. A solution of (Z)-9 (548.1 mg, 1.17 mmol, 1.0 equiv) in anhydrous THF (20 cm³) was added and cooled to -78 °C. ^tBuLi (1.7 M solution in pentane, 4.91 mmol, 2.90 cm³, 4.2 equiv) was added drop-wise. During addition the solution turned a bright yellow colour. The solution was stirred at -78 °C for 1 hr and the colour was observed to change to a dull-orange. An additional three-neck flask was flame-dried under vacuum for 2 min, charged with copper (I) bromide-dimethyl sulphide complex (0.361 g, 1.76 mmol, 1.5 equiv), evacuated, flushed with nitrogen and cooled to -50 °C. The organolithium solution was transferred by cannula onto the copper (I) bromide-dimethyl sulphide complex at -50 °C and stirred at this temperature for 2 hr, forming a dull-green suspension. A solution of oxidant 1 (0.86 g, 2.93 mmol, 2.5 equiv) in anhydrous THF (15 cm³) cooled to -50 °C was added by cannula to form a deep-red coloured solution which was stirred at -50 °C for 30 min, whereupon the cooling bath was removed and the solution stirred for a further 2 hours. The solution was filtered through a small pad of silica, eluting with 1:1 EtOAc: petroleum ether (30:40). The filtrate was concentrated *in vacuo*. The crude material was purified column chromatography (SiO₂; 9.9:0.1 petroleum ether (30:40): ethyl acetate) to yield (Z)-8 as a colourless oil (60 mg, 0.28 mmol, 25%). Spectroscopic data: ν_{max} (neat)/cm⁻¹ 2922 m, 2853 m (CH ether) 1644 w (C=C); δ_H (500 MHz; d₆ DMSO, 393.0 K) 7.33-7.22 (3H, m, aryl CH), 7.12 (1H, d, *J* 7.0 Hz, aryl CH), 6.60 (1H, d, *J* 11.5 Hz, CCHCHCH₂), 5.63 (1H, dt, *J* 11.5 Hz, 7.5 Hz, CCHCHCH₂), 4.42 (2H, s, CH₂OCH₂CH₂), 3.36-3.34 (2H, m, OCH₂CH₂), 2.18-2.14 (2H, m, CCHCHCH₂), 1.41-1.34 (4H, m, CH₂ groups), 1.26-1.21 (2H, m, CH₂ group), 1.15-1.09 (2H, m, CH₂ group); δ_C (125 MHz; CDCl₃) 138.5 (C), 136.5 (C), 133.3 (CH=CHCH₂), 130.6 (aryl CH), 130.4 (aryl CH), 129.0 (CH=CHCH₂), 127.7 (aryl CH), 126.3 (aryl CH), 71.8 (CH₂OCH₂CH₂), 67.3 (CH₂OCH₂CH₂), 28.2 (CH₂), 27.2 (CH₂), 26.6 (CH₂), 25.5 (CH₂), 23.8 (CH₂); HRMS (ESI+) *m/z* found [M+H]⁺ 217.1600, C₁₅H₂₁O⁺ required 217.1592.

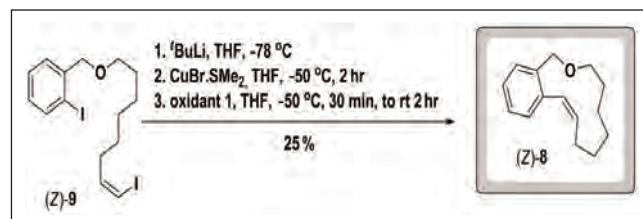


FIGURE 8. Synthesis of target macrocyclic olefin (Z)-8. rt = room temperature.

vessel). This proved difficult to separate from the desired product (Z)-8 by column chromatography on silica gel; it is conceivable that an alternative purification method may be more suitable in this regard and thus provide the desired compound in a higher isolated yield.

Interestingly, both the ¹H and ¹³C NMR spectra of (Z)-8 are temperature dependent. In both cases, there are broad peaks that resolve when the spectra are obtained under high-temperature conditions. This suggests that there are several similar energy conformations of the 12-membered ring that interconvert at a rate comparable to the NMR timescale in solution at room temperature. The conformational flexibility of this scaffold may have an important influence upon the biological properties of any compound containing it. Indeed, the interesting biological activities displayed by macrocyclic compounds has generally been attributed to their ability to represent a compromise between structural pre-organisation and conformational flexibility [36, 37].

This is the first reported synthesis of (Z)-8. However, it is illustrative to compare the substrate concentration used in the synthesis of this compound (0.06 M) with that reported in

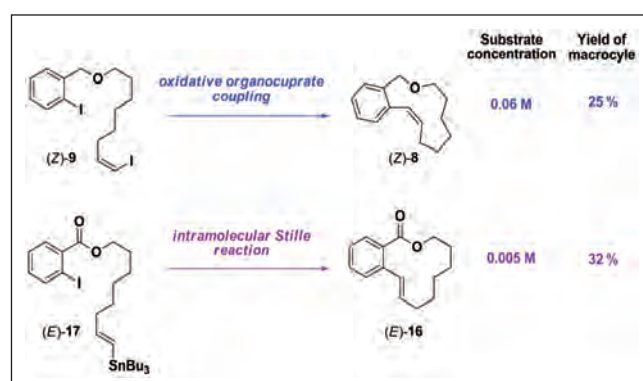


FIGURE 9. Comparison of the substrate concentrations used in the synthesis of 12-membered benzo-fused olefin-containing ring systems (Z)-8 (this work) and (E)-16 [25].

the literature for the synthesis of structurally related 12-membered benzo-fused lactone ring system **16** generated by palladium-mediated ring-closure of acyclic precursor **17** (figure 9) [25]. Although a direct quantitative comparison is not appropriate, the palladium-mediated cyclisation required significantly more dilute reaction conditions and furnished the cyclised product with a yield comparable to that obtained in this study.

Conclusion

In conclusion, we have proposed a novel strategy for the stereoselective synthesis of alkene-containing macrocyclic ring systems from geometrically defined alkenyl halide derivatives by intramolecular oxidative organocuprate coupling. These biologically interesting scaffolds are typically difficult to access in a stereoselective fashion using traditional methods, highlighting the value of novel protocols for their synthesis. This new strategy potentially offers a number of advantages over more standard cyclisation routes towards these ring systems. Expensive catalysts should not be needed and high dilution conditions should not be required. There are a variety of methods to prepare geometrically-defined alkenyl halides and no scrambling of double bond geometries is expected during cyclisation. Thus, the overall strategy should allow highly stereoselective access to both (*E*)- and (*Z*)-configured macrocyclic olefins in a completely predictable fashion. Proof-of-concept work demonstrated the feasibility of this approach; a 12-membered (*Z*)-configured cyclic olefin was accessed with a high level of geometrical purity without recourse to the use of high dilution conditions. Clearly, further optimisation of the key cyclisation step is required and the scope of the methodology needs to be examined fully. Nevertheless, the work described herein provides a validation of our new strategy for accessing macrocyclic olefins and represents an exciting platform for further studies, the results of which will be reported in due course.

References

- [1] WANG, C.; YU, M.; KYLE, A. F.; JAKUBEC, P.; DIXON, D. J.; SCHROCK, R. R.; HOVEYDA, A. H. *Chem. Eur. J.*, No. 19 (2013), p. 2726–2740.
- [2] YU, M.; WANG, C.; KYLE, A. F.; JAKUBEC, P.; DIXON, D. J.; SCHROCK, R. R.; HOVEYDA, A. H. *Nature*, No. 479 (2011), p. 88–93.
- [3] HOVEYDA, A. H.; ZHUGRALIN, A. R. *Nature*, No. 450 (2007), p. 243–251.
- [4] GRADILLAS, A.; PÉREZ-CASTELLS, J. *Angew. Chem., Int. Ed.*, No. 45 (2006), p. 6086–6101.
- [5] PENTZER, E. B.; GADZIKWA, T.; NGUYEN, S. T. *Org. Lett.*, No. 10 (2008), p. 5613–5615.
- [6] FURSTNER, A. *Angew. Chem., Int. Ed.*, 39 (2000), p. 3012–3043.
- [7] FURSTNER, A.; LANGEMANN, K. *Synthesis*, w/o No. (1997), p. 792–803.
- [8] FURSTNER, A.; GRELA, K. *Angew. Chem., Int. Ed.*, No. 39 (2000), p. 1234–1236.
- [9] CHEMLER, S. R.; DANISHEFSKY, S. J. *Org. Lett.*, No. 2 (2000), p. 2695–2698.
- [10] FURSTNER, A.; RADKOWSKI, K.; WIRTZ, C.; GODDARD, R.; LEHMANN, C. W.; MYNOTT, R. *J. Am. Chem. Soc.*, No. 124 (2002), p. 7061–7069.
- [11] FURSTNER, A.; MULLER, T. *Synlett*, w/o No. (1997), p. 1010–1012.
- [12] FURSTNER, A.; THIEL, O. R.; KINDLER, N.; BARTKOWSKA, B. *J. Org. Chem.*, No. 65 (2000), p. 7990–7995.
- [13] WANG, Y. K.; JIMÉNEZ, M.; HANSEN, A. S.; RAIBER, E. A.; SCHREIBER, S. L.; YOUNG, D. W. *J. Am. Chem. Soc.*, No. 133 (2011), p. 9196–9199.
- [14] WANG, Y.; JIMÉNEZ, M.; SHEEHAN, P.; ZHONG, C.; HUNG, A. W.; TAM, C. P.; YOUNG, D. W. *Org. Lett.*, No. 15 (2013), p. 1218–1221.
- [15] For recent reviews of diversity-oriented synthesis see: a) GALLOWAY, W. R. J. D.; SPRING, D. R. *Div. Orient. Synth.*, No. 1 (2013), p. 21–28; b) SCHREIBER, S. L. *Nature*, No. 457 (2009), p. 153; c) GALLOWAY, W. R. J. D.; ISIDRO-LLOBET, A.; SPRING, D. R. *Nature Commun.*, No. 1 (2010), p. 80.
- [16] SU, X. B.; FOX, D. J.; BLACKWELL, D. T.; TANAKA, K.; SPRING, D. R. *Chem. Commun.*, w/o No. (2006), p. 3883–3885.
- [17] SU, X. B.; SURRY, D. S.; SPANDL, R. J.; SPRING, D. R. *Org. Lett.*, No. 10 (2008), p. 2593–2596.
- [18] SU, X. B.; THOMAS, G. L.; GALLOWAY, W. R. J. D.; SURRY, D. S.; SPANDL, R. J.; SPRING, D. R. *Synthesis*, w/o No. (2009), p. 3880–3896.
- [19] SURRY, D. S.; FOX, D. J.; MACDONALD, S. J. F.; SPRING, D. R. *Chem. Commun.*, w/o No. (2005), p. 2589–2590.
- [20] SURRY, D. S.; SPRING, D. R. *Chem. Soc. Rev.*, No. 35 (2006), p. 218–225.
- [21] SURRY, D. S.; SU, X. B.; FOX, D. J.; FRANCKEVICIUS, V.; MACDONALD, S. J. F.; SPRING, D. R. *Angew. Chem., Int. Ed.*, No. 44 (2005), p. 1870–1873.
- [22] AVES, S. J.; PIKE, K. G.; SPRING, D. R. *Synlett*, w/o No. (2010), p. 2839–2842.
- [23] This work is taken from GALLOWAY, W. R. J. D. Ph.D. thesis. Cambridge: University of Cambridge, 2004.

- [24] MOLANDER, G. A.; DEHMEL, F. *J. Am. Chem. Soc.*, No. 126 (2004), p. 10313–10318.
- [25] KALIVRETENOS, A.; STILLE, J. K.; HEGEDUS, L. S. *J. Org. Chem.*, No. 56 (1991), p. 2883–2894.
- [26] GALLOWAY, W. R. J. D.; SPRING, D. R. *Exp. Opin. Drug Discov.*, No. 4 (2009), p. 467–472.
- [27] DENMARK, S. E.; YANG, S. M. *J. Am. Chem. Soc.*, No. 124 (2002), p. 2102–2103.
- [28] ABRAMS, S. R.; NUCCIARONE, D. D.; STECK, W. F. *Can. J. Chem.*, No. 61 (1983), p. 1073–1076.
- [29] ABRAMS, S. R.; SHAW, A. C. *J. Org. Chem.*, No. 52 (1987), p. 1835–1839.
- [30] BROWN, C. A.; YAMASHITA, A. *J. Am. Chem. Soc.*, No. 97 (1975), p. 891–892.
- [31] TAKAMI, K.; YORIMITSU, H.; OSHIMA, K. *Org. Lett.*, No. 4 (2002), p. 2993–2995.
- [32] HOFMEISTER, H.; ANNEN, K.; LAURENT, H.; WIECHERT, R. *Angew. Chem., Int. Ed.*, No. 23 (1984), p. 727–729.
- [33] BROWN, H. C.; BLUE, C. D.; NELSON, D. J.; BHAT, N. G. *J. Org. Chem.*, No. 54 (1989), p. 6064–6067.
- [34] JONES, K.; STOREY, J. M. D. *J. Chem. Soc., Perkin Trans. 1.*, w/o No. (2000), p. 769–774.
- [35] NEUMANN, H.; SEEBACH, D. *Tetrahedron. Lett.*, No. 17 (1976), p. 4839–4842.
- [36] O'CONNELL, K. M.; BECKMANN, H. S.; LARAIA, L.; HORSLEY, H. T.; BENDER, A.; VENKITARAMAN, A. R.; SPRING, D. R. *Org. Biomol. Chem.*, No. 10 (2012), p. 7545–7551.
- [37] WESSJOHANN, L. A.; RUIJTER, E.; GARCÍA-RIVERA, D.; BRANDT, W. *Mol. Divers.*, No. 9 (2005), p. 171–186.

Dr David Spring is currently a Reader at the University of Cambridge within the Chemistry Department and a Fellow of Trinity College. He gained his BA (Hons.) and MA in Chemistry from the University of Oxford, where he also achieved his D. Phil for work on the proposed biosynthesis of the manzamine alkaloids under the supervision of Sir Jack Baldwin. He then moved to Harvard University to work with Stuart Schreiber as a Wellcome Trust Postdoctoral Fellow and Fulbright Scholar, after which he joined the faculty at the University of Cambridge. Dr Spring's research programme is focused on diversity-oriented synthesis and the use of small molecules to probe biological processes.

Dr Warren Galloway is currently a postdoctoral research assistant for Dr David Spring and a Fellow of Pembroke College. He attended the University of Cambridge for his undergraduate chemistry degree and stayed at Cambridge for his PhD studies under the supervision of Dr David Spring, where he worked on the development of strategies for diversity-oriented synthesis. Dr Galloway's current research involves the design and synthesis of small-molecule modulators of biological processes.