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Bifurcate, tandem ATRC reactions: towards 2-oxabicyclo[4.3.0]nonane core of eunicellins

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Dedicated to Professor S. V. Ley on the occasion of his 60th birthday

Abstract—Bifurcate, tandem ATRC reactions provide rapid access to 2-oxabicyclo[4.3.0]nonane ring system present in terpenes such as eunicellin.
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In 1968, Kenard and Djerassi reported[1] the structure of eunicellin, a novel diterpene, isolated from soft corals off the coast of Banyuls-sur-Mer. A diverse family of natural products are now known to possess the 2-oxabicyclo[4.3.0]nonane ring system, many of which (e.g., briarellin) exhibit interesting biological activity.[2] More recently, structurally related natural products, such as eleutherobin (Fig. 1) have also been isolated which, because of their ability to stabilize microtubules, have elicited interest from a number of synthetic groups.[3]

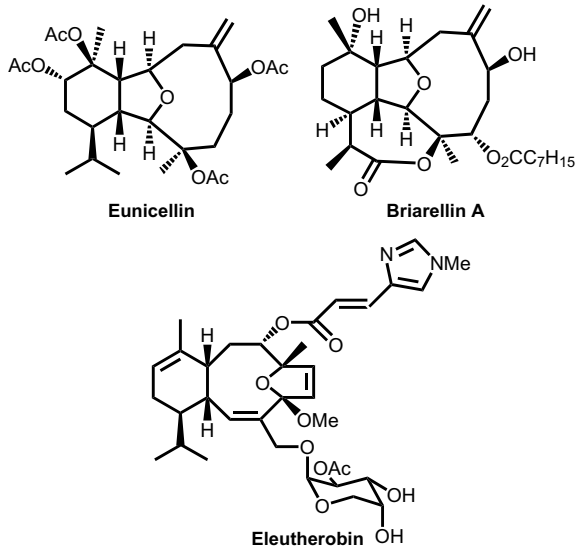

Figure 1.

As a continuation of our[4] studies into the use of atom transfer radical cyclization (ATRC) reactions in organic synthesis we wondered whether 2-oxabicyclo[4.3.0]nonane core of eunicellins,[5] as represented by **1**, could be prepared via a tandem, bifurcated radical cyclization reaction,[6] (Scheme 1). These cyclization reactions are very attractive from the synthetic standpoint as they can, in principle, transform structurally simple substrates into much more complex intermediates in a single synthetic operation. In this particular case, we envisaged that the key intermediates **3**, readily accessible from commercially available starting materials such as geraniol or citral, on exposure to a suitable transition metal catalyst, undergo sequential 5-*exo*-*trig* and then 6-*exo*-*trig* ATRC reactions ultimately generating the bicylic framework **2** (Scheme 1). However, since Nagashimas's original report[7] this method of lactone synthesis has enjoyed only sporadic interest[8] from the synthetic

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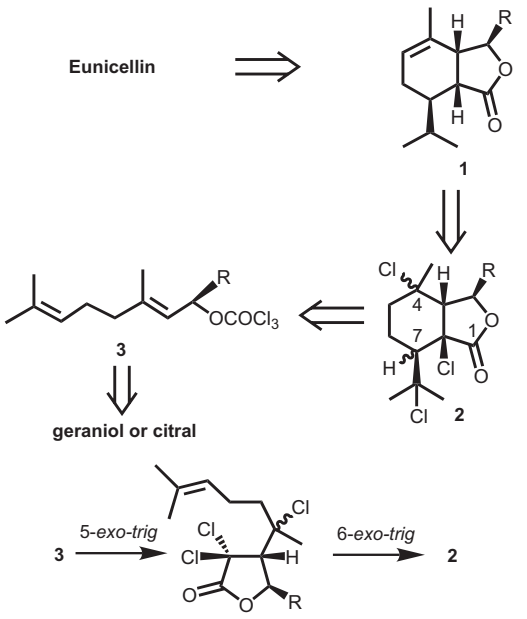


Scheme 1. Eunicellin—retrosynthetic analysis.

community and there were, to our knowledge, no examples of the tandem process which we wished to investigate.[9] This may in part be due to the fact that, in the case of the reactions leading to γ-lactones at least, stereoelectronic effects tend to disfavors product formation, leading in many cases to low-moderate isolated yields of product.[10] Indeed, a consideration of such effects led and Ueno and Stork[11] to suggest alternate, radical-based strategies, for the synthesis of tetrahydrofurans and γ-butyrolactones. In this study, therefore, we wished to question these basic mechanistic assumptions and hopefully arrive at a concise synthesis of the synthetic intermediates **2**.

Initially, we focused our attention on the cyclization of the chromatographically stable trichloroacetate **4**,[12] which itself was readily prepared in excellent yield from geraniol. In the crucial cyclization step, we found that addition of **4** to a preformed solution of a copper(I) catalyst[13] (CuCl, 5 mol %; dHbipy, 5 mol %) in degassed DCE at 20 °C followed by reaction at 90 °C for 3.5 h under an atmosphere of dinitrogen afforded the unstable trichlorolactones **5** and **6**.

Unfortunately, attempted purification of lactones **5** and **6** by column chromatography on silica gel promoted the clean elimination of HCl and led to the isolation of the stable isopropenyl lactones **7** and **8** in 75% overall yield (**7**:**8** = 2:1), Scheme 1. Purely fortuitously, and on one occasion only, the major product, **5**, of the initial cyclization reaction spontaneously crystallized during chromatography enabling a single crystal X-ray structure determination[14] to establish without equivocation its stereostructure which is depicted in Figure 2. This X-ray structure clearly revealed that cyclohexane ring of **5** adopts a chair conformation, with C4-Cl substituent axially disposed whereas the bulky, and presumably anchoring, isopropyl moiety at C7 is equatorially disposed to cyclohexane ring. Furthermore, the lactone ring is *cis*-fused, again with C7a-Cl substituent axially disposed with respect to cyclohexane ring. Extensive NOE measurements carried out on both of the isomeric products **7** and **8** suggests that this picture also pertains to their conformations in solution. The stereochemical outcome of this sequence is analogous to that previously reported by Itoh and Nagashima[9] for the related cyclization of geranylamine derivatives.

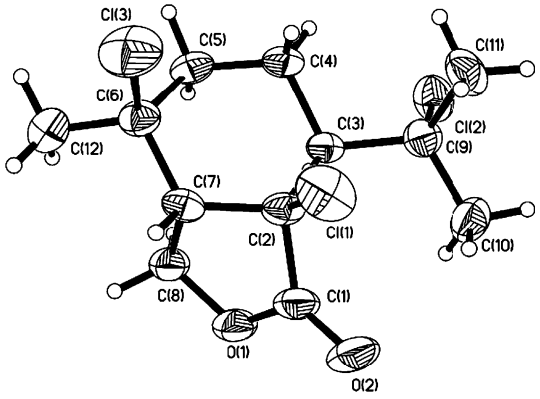
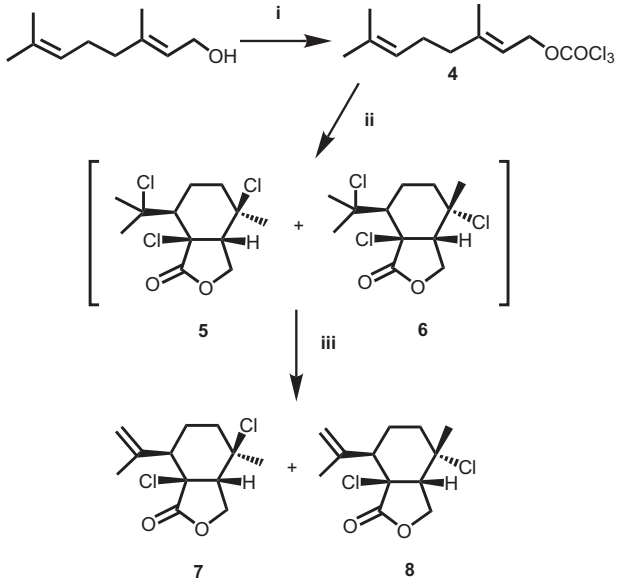


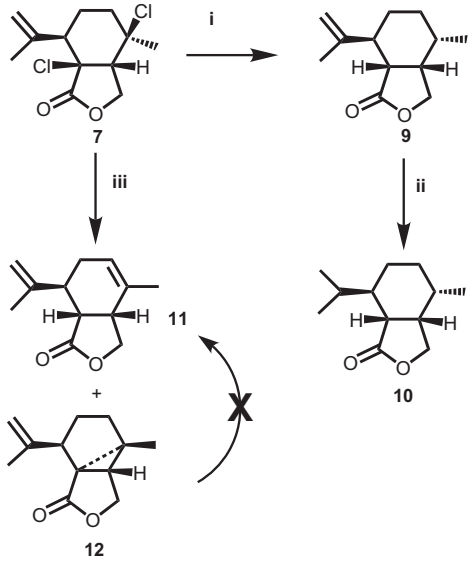
Figure 2. X-ray structure of **5**.

As a prelude to the synthesis of eunicellins, we have briefly investigated the functionalization of **7**. Intriguingly reduction of **7** using zinc metal was quite sensitive to the reaction conditions employed (Scheme 2).

Hence, exposure of **7** to zinc in acetic acid afforded lactone **9** as a single diastereoisomer, which, on catalytic hydrogenation at atmospheric pressure over palladium on charcoal generated the crystalline product **10** in



Scheme 2. Reagents and conditions: (i) $ClCOCCl_3$, 1.0 equiv; Et_3N, 1.0 equiv; Et_2O; 0–20 °C; 96%; (ii) (a) CuCl, 5 mol %; dHbipy, 5 mol %; DCE, 90 °C; 3.5 h; (iii) SiO_2; 75% yield over two steps; **7**:**8** = 2:1.



Scheme 3. Reagents and conditions: (i) Zn, 10 equiv; AcOH; 120 °C; 1 h; 79%; (ii) H_2, 1 atm; 10% Pd–C (50 wt %); EtOAc; 92%; (iii) Zn, 10 equiv; H_2O–AcOH (3:1); 120 °C; 1 h; 62%; **11**:**12** = 1:1.

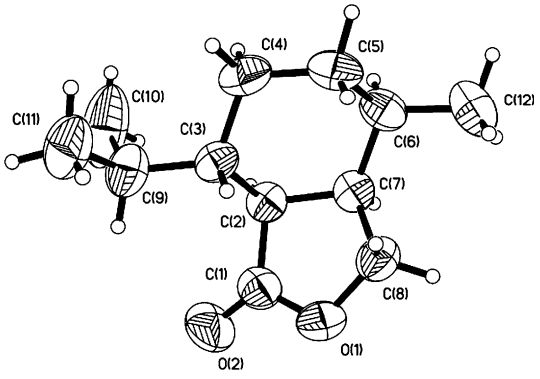
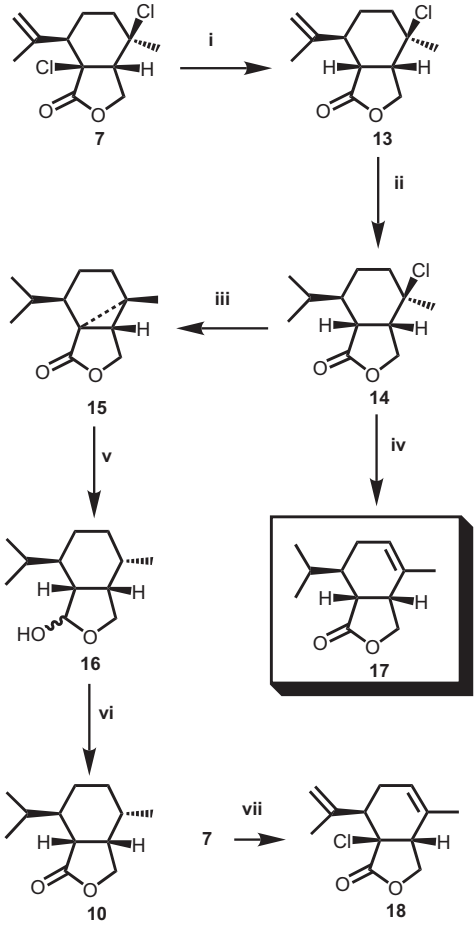


Figure 3. X-ray structure of **10**.



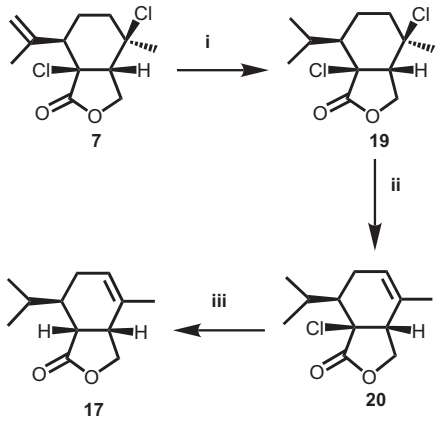
Scheme 4. Reagents and conditions: (i) Bu_3SnH, 1.1 equiv; AIBN, cat.; PhH; 80 °C; 2 h; 61%; (ii) H_2, 1 atm; 10% Pd–C (50 wt %); EtOAc; 88%; (iii) *t*-BuOK, 1.4 equiv; THF; 0 °C; 94%; (iv) LiCl, 1.5 equiv; Li_2CO_3, 2.5 equiv; DMF; 0.5 h; 140 °C; 96%; (v) Li, 2 equiv; NH_3 (l); −78 °C; 0.5 h; (vi) Jones reagent, acetone; 0 °C; 26% over two steps; (vii) LiCl, 1.5 equiv; Li_2CO_3, 2.5 equiv; DMF; 0.5 h; 140 °C; 98%.

92% isolated yield (Scheme 3) whose structure was proven by X-ray crystallography (Fig. 3).

Alternatively, exposure of **7** to zinc and aqueous acetic acid afforded the diene **11** (elimination–dehalogenation) in 31% yield together with cyclopropane **12** ('1,3-elimination'[15]), also in 31% isolated yield. Blank experiments established that diene **11** did not originate via the intermediacy of cyclopropane **12** (Scheme 3).

Selective dechlorination[16] of **7** could be cleanly achieved using tin chemistry (TBTH, 1.0 equiv; AIBN, 0.1 equiv; PhH; 80 °C; 1 h) affording the monochlorolactone **13** in 61% yield (Scheme 4). Catalytic hydrogenation of **13** proceeded without any detectable hydrogenolysis of C4–Cl bond and led to the isolation of lactone **14** in 88% yield. Chlorolactone **14** underwent highly selective elimination reactions whose outcome was dependent upon the base used. For example, exposure of **14** to KO-Bu^t (1.4 equiv) in THF at 0 °C afforded cyclopropane **15** in almost quantitative yield (overall '1,3-elimination'). The ease[17] in which cyclopropane **15** was generated, in this particular case, lends credence to our assertion that C4-chlorine substituent is axially disposed with respect to the cyclohexane ring, thereby enabling facile intramolecular SN_2 displacement once lactone enolate anion had been generated. Cyclopropane **15** proved to be extremely resilient to further reaction as exposure to electrophilic reagents (e.g., HBr or TFA) left the molecule essentially unchanged. However, Birch reduction[18] of **15** followed by Jones oxidation of the intermediate lactol **16** did furnish lactone **10** in modest overall yield (26%). By comparison, adopting the conditions[19] originally developed by Joly and Holysz effected a highly regioselective elimination reaction to $\Delta^{4,5}$-alkene **17** in 96% yield, whose spectral data was identical to that previously reported by Magnus.[20] Presumably, this elimination reaction proceeded via an 'E2-like' pathway[21] a process which could even be extended to dichlorolactone **7** which, under these reaction conditions, afforded the diene **18** in 98% yield (Scheme 4).

Catalytic hydrogenation of **7** proved to be highly selective affording dichlorolactone **19** which upon dehydrohalogenation, as above, generated $\Delta^{4,5}$-alkene **20** as a



Scheme 5. Reagents and conditions: (i) H_2, 1 atm; 10% Pd–C; (50 wt %); EtOAc; 91%; (ii) LiCl, 1.5 equiv; Li_2CO_3, 2.5 equiv; DMF; 0.5 h; 140 °C; 95%; (iii) Bu_3SnH, 1.1 equiv; AIBN, cat.; PhH; 80 °C; 1 h; 89%.

single regioisomer in 95% isolated yield. Dechlorination of **20** (TBTH; AIBN) provided an alternate route to lactone **17** in 77% overall yield from **7** (Scheme 5).

This particular sequence was amenable to scale-up, providing a facile route to **17** on a preparative scale. Noteworthy, is the fact that this particular reaction sequence the elimination reaction proceeded without additional loss of C7a-Cl substituent or isomerization to aromatized products,[9] (Scheme 5). Given that many of the eunicellins are oxygenated at C4/C5 we decided to investigate the functionalization of the $\Delta^{4,5}$-double bond in our model substrate **17**. Intriguingly, exposure of **17** to potassium osmate under the 'Upjohn' conditions[22] afforded the rearranged lactone **22** in 61% yield after chromatography. Presumably, the reagent approaches from the α-face[23] of the lactone **17** initially generating diol **21** which then suffers an intramolecular transacylation reaction[24] eventually leading to the rearranged lactone **22**. The structure assigned to **22** is again based on the result of a single crystal X-ray analysis (Fig. 4).

A minor component, believed to be the β-diol **23**, was also isolated from this reaction in 24% yield. Significantly, the ^{1}H NMR spectrum of **23** exhibits a resonance at δ 3.68 ppm (dd, $J = 10$, 4 Hz) which is in keeping with an equatorially disposed –OH group at C5. Epoxidation of **16** also proceeded in a diastereoselective manner, affording a major product, tentatively assigned as α-epoxide **24** in 74% yield together with trace amounts of a second product, presumably β-epoxide **25** (Scheme 6). Stereochemical assignments in the case of **24**, whilst tentative, are based upon the magnitude of the vicinal coupling constants[25] between the oxirane proton, C5-H, and the methylene protons at C6. Oxirane proton, H5, appears as a broad triplet at δ 3.19 ppm ($^3J_{H5-H6} = 2$ Hz) indicating that it is pseudoequatorially disposed with respect to the half-chair conformation of cyclohexane ring. Again isopropyl group at C7 is also equatorially disposed ($^3J_{H7-H7a} = 9$ Hz). It is tempting to suggest[5a,26] that the stereoselectivity observed in these oxidation reactions is a result of alkene **17** adopting a half-chair conformation in which isopropyl group is axially disposed and therefore shielding β-face of the molecule from attack. However, an analysis of the ^{1}H NMR spectrum of **17** leads us to conclude in this particular case, and in solution at least, that isopropyl group *prefers* to adopt a *pseudo*-equatorial disposition with respect to cyclohexene ring as judged by the magnitude[27] of the coupling constant between H7 and H7a ($^3J_{H7-H7a} = 12$ Hz).

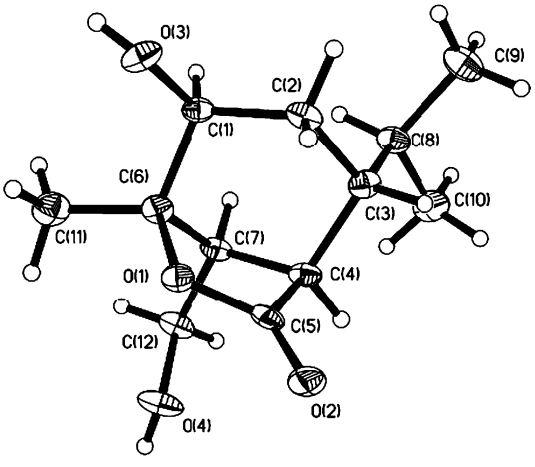
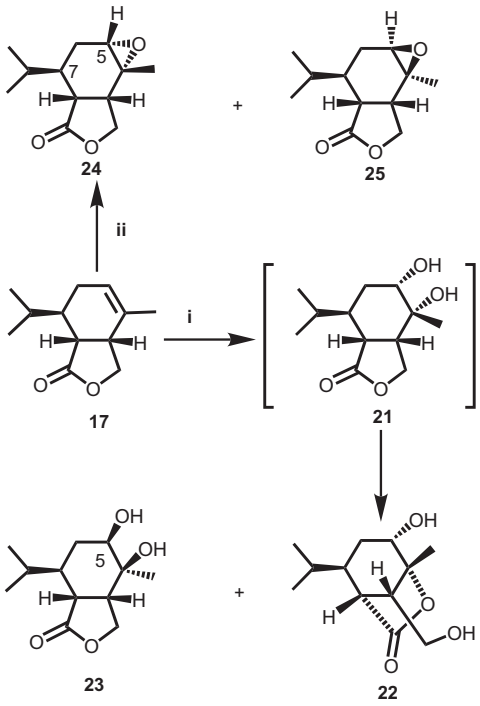


Figure 4. X-ray structure of **22**



Scheme 6. Reagents and conditions: (i) $K_2[OsO_2(OH)_4]$, cat.; NMO, 4 equiv; acetone–water (3:1); 20 °C; 20 h; 85%; **22**:**23** = 2.6:1; (ii) *m*CPBA, 1.2 equiv; CH_2Cl_2; 20 °C; 74%.

The stereoselectivity observed in the functionalization of **17** may, therefore, be controlled by subtle stereoelectronic effects,[28] prior co-ordination of the reagents with the polar lactone moiety[29] or be explained by Curtin–Hammett/Winstein–Holness kinetics,[30] (Fig. 5).

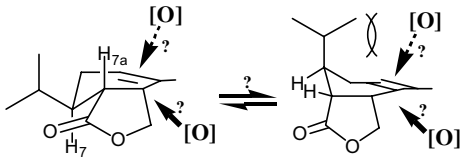


Figure 5.

In conclusion, we have demonstrated the synthetic potential of tandem ATRC reactions. Such sequences have the chemical equivalence of *endo*-selective cycloadditions. However, unlike the Diels–Alder reaction, they proceed without recourse[31] to the synthesis of diene/dienophile components. Synthetic applications of these radical reactions are now in progress.

Acknowledgements

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12. Selected spectroscopic data: **7** δ_H (300 MHz, $CDCl_3$) 1.6 (3H, s), 1.9 (3H, s), 1.6–2.4 (4H, m), 2.5 (1H, dd, $J = 3$, 11 Hz), 3.3 (1H, t, $J = 9$ Hz), 4.1 (1H, t, $J = 11$ Hz), 4.4 (1H, apparent t, $J = 9$ Hz), 4.8 (1H, s), 5.1 (1H, s); δ_C (75 MHz, $CDCl_3$) 172.2, 141.6, 117.15, 67.3, 66.1, 62.3, 56.0, 45.9, 37.9, 30.32, 22.9, 22.3; ν_{max} (Nujol) 1789 (s) cm^{-1}; *m/z* (EI) 263 (M, 35%); HRMS $C_{12}H_{19}Cl_3NO_2$ ($M+NH_4^+$) requires: 280.0792; found: 280.0870; **8** δ_H (300 MHz, $CDCl_3$) 1.9 (3H, s), 1.95 (3H, s), 1.8–2.2 (4H, m), 2.6 (1H, dd, $J = 3.5$, 11 Hz), 3.2 (1H, dd, $J = 8$, 10 Hz), 4.4 (1H, apparent t, $J = 10$ Hz), 4.6 (1H, dd, $J = 8$, 10 Hz), 4.8 (1H, s), 5.2 (1H, s); δ_C (75 MHz, $CDCl_3$) 171.9, 141.3, 117.0, 69.0, 67.5, 67.3, 55.6, 45.6, 38.4, 31.9, 24.7, 22.5. ν_{max} (evaporated film) 1794.8 (s) cm^{-1}; *m/z* (EI) 263 (100%); HRMS $C_{12}H_{19}Cl_3NO_2$ ($M+NH_4^+$) requires: 280.0793; found: 280.0870.
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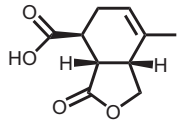

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