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Graphical Abstract

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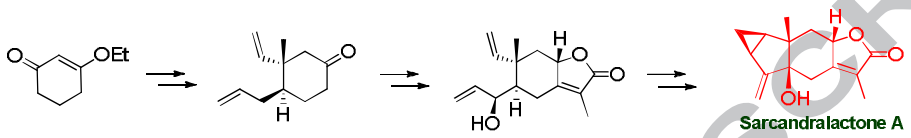

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A total synthesis of Sarcandralactone A: A general, concise, RCM enabled approach to lindenanolide sesquiterpenoids

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ABSTRACT

A total synthesis of lindenane-type sesquiterpenoid natural product sarcandralactone A and its close sibling 5-*epi*-shizukanolide has been accomplished through a concise strategy in which a one-pot γ-lactone annulation and a RCM reaction constitute pivotal steps.

First unraveled about half a century ago, lindenane sesquiterpenoid family has been steadily growing and has gathered considerable momentum (*vide infra*) in the recent past.[1] Numbering close to a hundred, lindenanes are predominantly found in the plants of *chloranthaceae* family[1b,d] although they have been sporadically encountered in other plant species including marine sources.[2] In structural terms, the lindenane **1** framework (1,3-cycloeudesmane) is a close sibling of the more abundant eudesmane **2** (Figure 1) skeleton in which C1 and C3 are conjoined to form a cyclopropane ring. A distinctive feature of lindenane sesquiterpenoids is that an oxidized C7-isopropyl group is embedded in its framework as an annulated furan or a α-butenolide moiety. Representative examples of resulting furanolindenanes **3 - 4** and lindenanolides **5 - 8** are displayed in Figure 2.

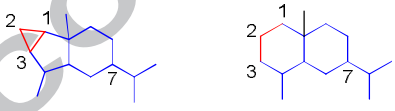

Figure 1. Lindenane and eudesmane skeleton.

In the preceding decade, an impressive number of complex, polycyclic, functionally embellished and stereochemically endowed, dimeric and oligomeric lindenanolides have surfaced in the literature. Some prototypical examples **9-12** are captured in Figure 3. In addition to their intricate molecular architecture, dimeric lindenanolides along with some of their oligomeric siblings exhibit remarkable range of bioactivity profile that includes immunomodulatory, anti-inflammatory, anti-cancer, anti HIV-1, antifungal and neuroprotective to name a few.[3,4]

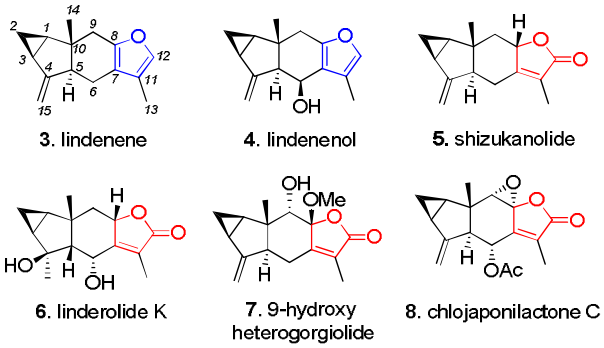

Figure 2. Representative examples of furanolindenane and lindenanolide.

Concurrently with their growing numbers, lindenanes, and in particular, lindenanolides are beginning to attract increasing attention from the practitioners of synthetic chemistry after a surprisingly long period of dormancy. Indeed, the first synthesis of a lindenanolide was only reported in 2007[5a] following which there has been a spate of activity[5] in the arena, largely stimulated through the challenge posed by the intricacy of the structures (Figures 2 & 3) and the prospect of enriching the chemical diversity space around their scaffold to explore the bioactivity potential. We were drawn in the fray as part of our interest in the synthesis of eudesmane based sesquiterpenoids wherein a RCM based strategy was effectively deployed to assemble the framework in a short, diversity oriented sequence.[6] From a conceptual perspective, a contextual RCM based strategy seemed very appropriate for the synthesis of lindenanes and lindenanolides but did not seem to have been previously applied

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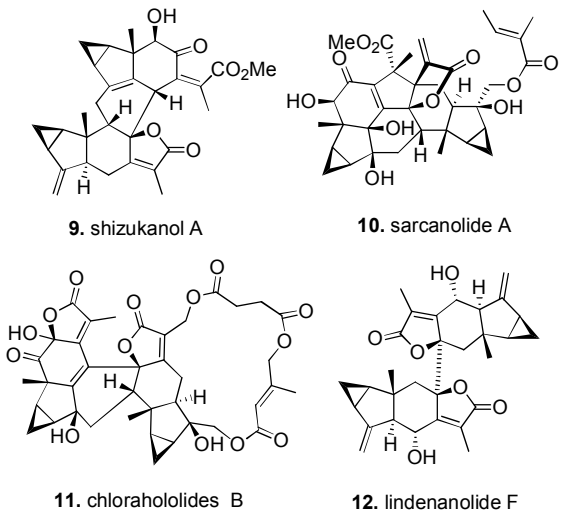


Figure 3. Representative examples of dimeric lindenanolides.

to this family of natural products.[5] It was therefore of interest to develop a concise, generally applicable route to lindenanolides wherein RCM was to serve as one of the pivotal steps. Realization of this objective through a total synthesis of a lindenanolide sesquiterpenoids sarcandralactone A **13** and 5-*epi*-shizukanolide **14** (Figure 4) is disclosed in this letter.

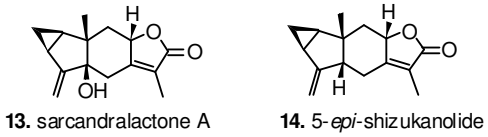
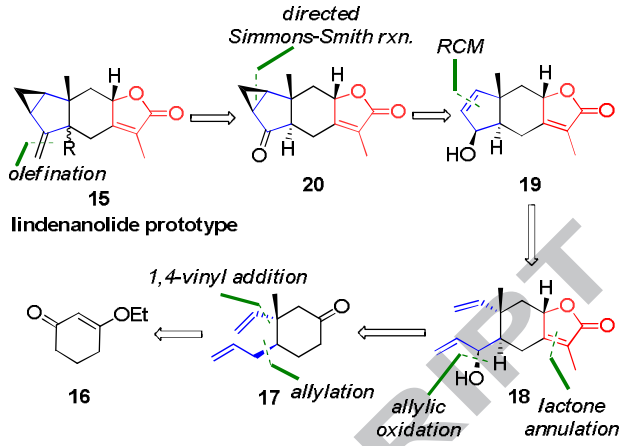


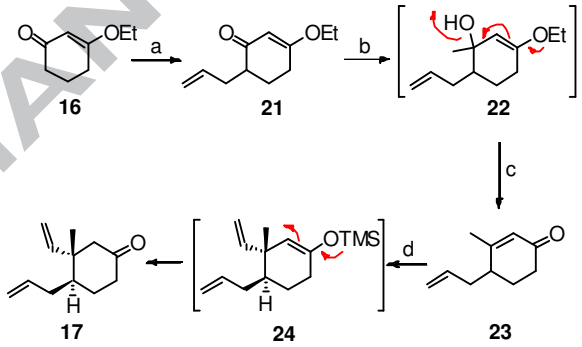
Figure 4. Lindenanolides: sarcandralactone A and 5-*epi*-shizukanolide

A retrosynthetic perspective from a prototypical lindenanolide **15** could be traced to a simple 1,3-cyclohexanedione enol ether precursor **16** and is depicted in Scheme 1. Evolution of the readily available **16** towards the synthetic target required setting-up of the quaternary carbon centre and installation of two terminal olefin bearing side arms with requisite stereodisposition following kinetically controlled allylation, sequential 1,2-addition, transposition and 1,4-vinyl addition (**16** →**17**). Further progress towards the objective required one step γ-lactone annulation in **17** in a regioselective manner and oxyfunctionalization of the allyl arm to deliver **18** which was now ready for the implementation of the RCM protocol to furnish **19**, Scheme 1. The intent in this plan was to implement a stereoselective Simmons-Smith cyclopropanation in **19** to ensure



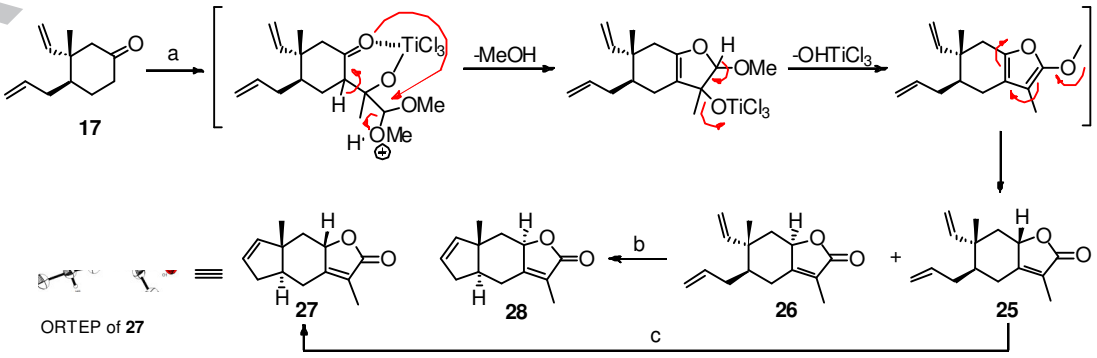
Scheme 1. Retrosynthetic analysis for lindenanolide prototype.

delivery of the three-membered ring on the β-face, *syn* to the methyl group at the quaternary centre, to furnish **20** bearing the basic tetracyclic framework of lindenanolides. The tetracycle **20** could then be subjected to either Wittig-type olefination and/or additional functional group manipulations to eventuate in the desired natural product target, Scheme 1.



Scheme 2. Reagents and conditions: (a) HMDS, *n*-BuLi, 0 °C, HMPA, allyl bromide, THF, -78 °C – rt, 4 h, 82%; (b) MeLi, -40 °C, THF, 1 h; (c) H_3O^+ 95%; (d) CuBr.Me_2S, vinylmagnesium bromide, THF, TMSCl, -78 °C, 1 h, 81%.

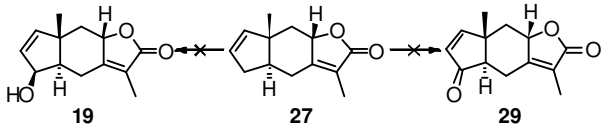
The retrosynthetic analysis presented in Scheme 1 unveiled the contours of a concise strategy to access lindenanolides from a readily available precursor **16** and set the stage for demonstrating its viability. In the event, **16** was subjected to allylation under conditions of kinetic control to regioselectively furnish **21**, Scheme 2. Addition of methyllithium to **21** led to enone **23** through the intermediate formation of tertiary alcohol **22** and concomitant acid mediated transposition as described earlier.[7]



Scheme 3. Reagents and conditions: (a) $TiCl_4$, Bu_3N, DCM, α,α-dimethoxyacetone, 17.5 h, 61%; (b) Grubbs' I (5 mol %), rt, 3 h, 89%; (c) Grubbs' I (5 mol %), rt, 2 h, 87%.

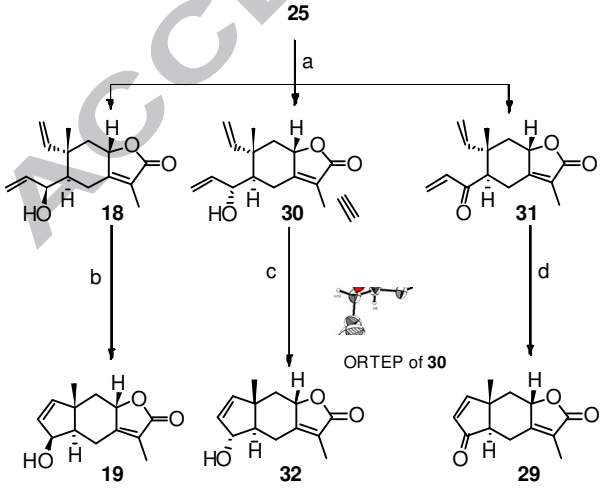
Conjugate addition of divinylcopper to **23** set-up the quaternary centre and delivered **17** via the intermediacy of the TMS-enolether **24** and with predictable stereochemistry dictated by the pre-existing allyl group, Scheme 2.[11] Doubly armed **17** was subjected to regioselective γ–lactone annulation following one pot Ti(IV) mediated cross aldol protocol of Tanabe *et* al.[8] using α,α-dimethoxyacetone and involving several intermediates (see, Scheme 3) to deliver bicylic diastereomeric lactones **25** and **26** in a ratio of 3.4:1.[11] Both the diastereomers **25** and **26** smoothly underwent the contemplated RCM to furnish diastereomeric tricycles **27** and **28**, respectively, Scheme 3.[11] The stereostructures of **27** and **28** were secured through single crystal X-ray structure determination of the major isomer **27** (Scheme 3).[10] All the three stereogenic centers in **27** had the requisite disposition for targeting lindenanolide natural products.

The intent now was to stereoselectively oxy-functionalize the allylic position of the cyclopentene ring in **27** to obtain **19**, for a directed Simmons – Smith cyclopropanation, either directly or through the intermediacy of the enone **29**, Scheme 4. Thus, **27** was exposed to several known allylic oxidation reagents like PDC-TBHP, CrO_3-3,5-dimethyl pyrazole, $Mn(OAc)_3$, SeO_2-TBHP etc. to obtain either **19** or **29** but to no avail. This unexpected resistance of **27** towards allylic oxidation forced us to revert to the pre-RCM stage to attempt oxy-functionalization of the allylic arm in diastereomer **25**, Scheme 5.



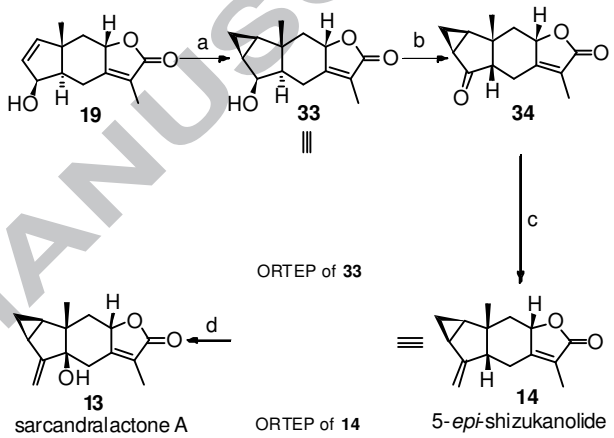
Scheme 4. Attempted oxy-functionalization of allylic position in **27**.

In this endeavor better luck awaited us and after some exploratory experiments, it was possible to devise conditions (SeO_2-excess TBHP) under which **25** delivered a mixture of readily separable oxy-functionalized products **18**, **30**, **31** in preoperatively useful yield and in a ratio of 1.6:1.6:1, Scheme 5.[11] Stereo-differentiation between the structures of **18** and **30** was arrived at through a single crystal X-ray structure determination on **30** (Scheme 5).[10] Quite pleasingly, all the three oxy-functionalized products **18, 30** & **31** underwent smooth RCM to furnish tricyclic products **19, 32** & **29** respectively, Scheme 5.[11] Tricyclic allylic alcohol **19** with desired stereochemistry attributes was now poised for elaboration to the natural products sarcandralactone A **13** and shizukanolide **5**.



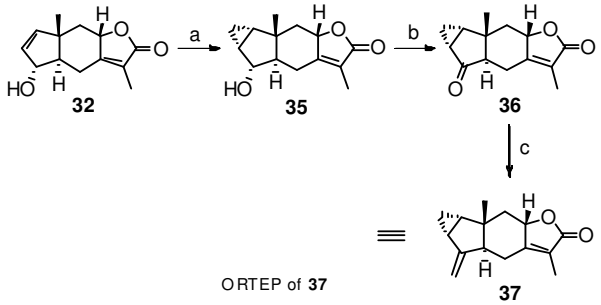
Scheme 5. Reagents and conditions: (a) SeO_2 / TBHP, CH_3CN/ DCM, 60 °C, 2 h, 1.6:1.6:1, 92% (BRSM); (b) Grubbs' I (5 mol %), CH_2Cl_2, rt, 2.5 h, 78%; (c) Grubbs' I (5 mol %), rt, 2.5 h, 83%; (d) Grubbs' I (5 mol %), rt, 6 h, 82%.

Towards this end, **19** was subjected to directed Simmons-Smith cyclopropanation with CH_2I_2 in the presence of diethylzinc to furnish **33** (X-ray structure displayed in Scheme 6) of desired stereochemistry.[10,11] DMP oxidation in **33** was unexpectedly eventful and furnished the tetracyclic ketone **34** in which a facile and aberrant epimerization at the C-5 centre had occurred to deliver a *cis*-hydrindane moiety as in **34.**[11] The observed epimerization of *trans*-hydrindane bearing framework to *cis*-hydrindane, as revealed by NOESY spectrum (see supplementary material), is not without precedence in such systems wherein the angular methyl groups and the cyclopropane ring are *cis*-disposed.[5f,h] Olefination of the carbonyl group in **34** following Julia-Kocienski protocol was smooth but delivered 5-*epi*-shizukanolide **14** as revealed by X-ray structure determination (Scheme 6)[10] and not the expected natural product shizukanolide **5**.[11] However, when **14** was subjected to allylic oxidation with SeO_2, our targeted natural product sarcandralactone A **13** was readily realized and its spectral characteristics (^1H & ^{13}C NMR) were exactly identical with those reported in the literature[5i, 9] for the natural compound, Scheme 6.



Scheme 6. Reagents and conditions: (a) CH_2I_2, Et_2Zn, ZnI_2, CH_2Cl_2, 0 - 10 °C, 18 h, 84%; (b) DMP, CH_2Cl_2, 0 °C- rt, 3 h, 86%; (c) 1-(tert-butyl)-5-(methylsulfonyl)-1*H*-tetrazole, NaHMDS, THF, -78 °C, 2.1 h, 72%; (d) SeO_2, dioxane, 80 °C, 20 min, 80%.

For the sake of completeness of this effort, we carried forward the epimeric allylic alcohol **32** towards the lindenanolide framework. Consequently, it was subjected to hydroxyl directed cyclopropanation with CH_2I_2 in the presence of diethylzinc to furnish tetracyclic product **35**, Scheme 7.[11] Further oxidation of **35** with DMP to **36** was in this case quite facile and uneventful. Interestingly, in the case of **36**, no epimerization of the *trans*-hydrindane moiety to the *cis*-isomer was observed during the DMP oxidation protocol (cf. **34**).[11] This observation clearly indicated that subtle interplay of stereoelectronic factors profoundly affect the relative *cis* vs *trans* thermodynamic stability of the embedded hydrindane systems.



Scheme 7. Reagents and conditions: (a) Et_2Zn, ZnI_2, CH_2I_2, CH_2Cl_2, 0-10 °C, 16 h, 81%; (b) DMP, CH_2Cl_2, 0 °C- rt, 2h, 84%; (c) 1-(tert-butyl)-5-(methylsulfonyl)-1*H*-tetrazole, NaHMDS, THF, -78 °C, 2.1 h, 75%.

Lastly, Julia-Kocienski olefination on the cyclopentanone carbonyl of **36** led to **37**, a diastereomer of natural product shizukanolide **5**.[11] A single crystal X-ray crystal structure determination of **37** is shown in Scheme 7 and secured its structure.[10]

In conclusion, we have outlined a concise approach of general applicability to lindenanolide sesquiterpenoids, from a readily accessible building block. The effort has culminated in the total synthesis of natural product sarcandralactone A and 5-*epi*-shizukanolide and paves the way for the adaptation of the approach for the syntheses of other members of this class.

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10. Single crystal X-ray data for **27** and **33** was collected on a Bruker AXS SMART APEX CCD diffractometer at 291 K using graphite monochromated MoK_α radiation (λ = 0.7107 Å). The data were reduced by *SAINTPLUS*; an empirical absorption correction was applied using the package *SADABS* and *XPREP* was used to determine the space group. The crystal structure was solved by direct methods using *SIR92* and refined by the full-matrix least-squares method on F^2 using *SHELXL97*. Crystal data for **27**: (CCDC 1046034), $C_{13}H_{16}O_2$, M = 204.26, monoclinic, *P2(1)/n*, *a* = 6.5954(15) Å, *b* = 16.390(4) Å, *c* = 10.327(2) Å, V = 1091.9(4) Å^3, Z = 4, ρ_{calcd} = 1.242 g/cm^3 , 6604 reflections measured, 2147 unique (R(int) = 0.0303), R1 = 0.0540 and wR2 = 0. 1873. Crystal data for **33**: (CCDC 1046037), $C_{14}H_{18}O_3$, M = 234.28, monoclinic, *P2(1)/n*, *a* = 11.204(6) Å, *b* = 10.011(5) Å, *c* = 11.797(6) Å, V = 1220.4(11) Å^3, Z = 4, ρ_{calcd} = 1.270 g/cm^3 , 11993 reflections measured, 2413 unique (R(int) = 0.0254), R1 = 0.0510 and wR2 = 0.1513.; Single crystal X-ray data for **30, 14, 37** was collected on Oxford CCD X-ray diffractometer (Yarnton, Oxford, UK) equipped with Cu-K_α radiation (k = 1.54 Å) source. The data were reduced by *SAINTPLUS*; an empirical absorption correction was applied using the package *SADABS* and *XPREP* was used to determine the space group. The crystal structure was solved by direct methods using *SIR92* and refined by the full-matrix least-squares method on F^2 using *SHELXL97*. Crystal data for **30**: (CCDC 1046036), $C_{15}H_{20}O_3$, M = 248.31, triclinic, *P-1*, *a* = 8.574(2) Å, *b* = 9.656(3) Å, *c* = 10.069(3) Å, V = 704.7(4) Å^3, Z = 2, ρ_{calcd} = 1.170 g/cm^3, 4946 reflections measured, 4104 unique (R(int) = 0.0459), R1 = 0.0874 and wR2 = 0.2526; Crystal data for **14**: (CCDC 1046040), $C_{15}H_{18}O_2$, M = 230.30, monoclinic, *P121/c1*, *a* = 15.0093(7) Å, *b* = 6.48902(19) Å, *c* = 13.0772(5) Å, V = 1209.67(8) Å^3, Z = 4, ρ_{calcd} = 1.253 g/cm^3, 4350 reflections measured, 2298 unique (R(int) = 0.0148), R1 = 0.0557 and wR2 = 0.1659; Crystal data for **37**: (CCDC 1046041), $C_{15}H_{18}O_2$, M = 230.30, monoclinic, *P2$_1$/c*, *a* = 8.3521(3) Å, *b* = 13.7763(5) Å, *c* = 10.9918(3) Å, V = 1262.23(7) Å^3, Z = 4, ρ_{calcd} = 1.212 g/cm^3 , 2435 reflections measured, 2369 unique (R(int) = 0.0213), R1 = 0.0621 and wR2 = 0.1987.
11. All compounds reported here are racemic and were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. Spectral data of selected compounds are given in the Supplementary material.