RESEARCH ARTICLE doi.org/10.1002/adsc.202500080 ADVANCED SYNTHESIS & CATALYSIS

Synthesis of Oxadendralenes by Thermal Oxy-Cope Type Rearrangement of Bis(α-Hydroxyallenes)

Daniel San Martín,[a] Teresa Martínez del Campo,[a,*] and Pedro Almendros[b,*]

[a] Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040 Madrid, Spain
E-mail: tmcampo@quim.ucm.es
[b] Instituto de Química Orgánica General, IQOG, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain
E-mail: palmendros@iqog.csic.es

Manuscript received: January 21, 2025; Revised manuscript received: February 19, 2025;
Version of record online: March 12, 2025

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202500080

Abstract: We report the direct and selective synthesis of oxadendralenes starting from readily available bis(α-hydroxyallenes). The designed sequence involves a hitherto unknown oxy-Cope rearrangement of allenols by supplying a site for the migration of the 1,2-diene moiety. Moreover, the so-prepared oxadendralenes were converted into valuable polyfunctionalized scaffolds through effective late-stage diversification.

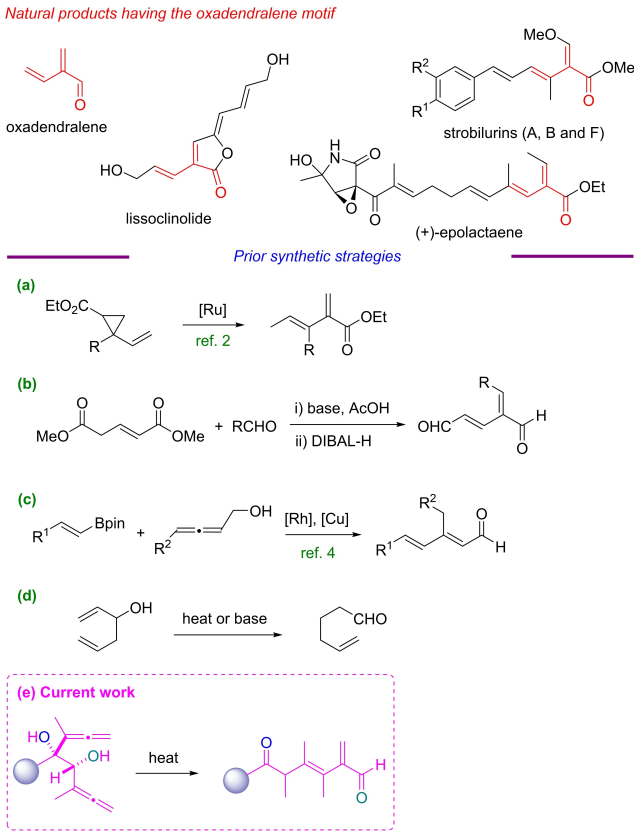
Keywords: Allenes; Carbonyls; Dienes; Rearrangement; Synthetic methods

Introduction

The oxadendralene unit, naturally occurring in the apocarotenoid peridinin, the antibiotic lissoclinolide, the fungicides strobilurins, and the neuritogenic (+)-epolactaene among others bioactive products (Scheme 1, top),[1] belongs to a relevant subclass of the important branched 1,3-diene family. Scarce established methods for the synthesis of oxadendralenes included ring-opening isomerization of vinyl cyclopropanes (VCPs) (Scheme 1a),[2] and Knoevenagel condensation of dimethyl glutaconate with aldehydes followed by reduction (Scheme 1b).[3] Despite the merits of the reported protocols, they require bases and metals, or harsh reaction conditions. Ma has recently described the rhodium-catalyzed reaction of alkenyl boronates with 2,3-allenols to yield linear dienals (Scheme 1 c),[4] while the rhodium- or palladium-catalyzed reactions of protected 2,3-allenols to form [3]dendralenes have been described by the groups of Glorius, Wu, and Lipshutz.[5] On the other hand, the venerable oxy-Cope rearrangement (Cope reaction of a 3-hydroxy substituted 1,5-diene giving rise to δ,ε-unsaturated carbonyls) (Scheme 1d) has never been reported in allenols.[6] Taking into account that allenes are more strained and consequently more reactive that alkenes and the unsaturation of the allene moiety is spread over three carbon atoms, distinct reactivity and regioselectivity may be encountered. Herein, we describe for the first time an oxy-Cope type-rearrangement in allenes, in which the thermal treatment of bis(α-hydroxyallenes) provides oxadendralenes (Scheme 1e).

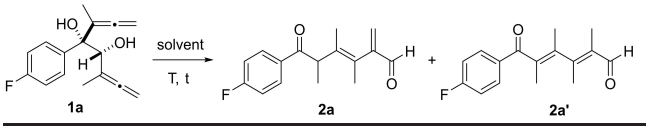
Results and Discussion

Rearrangement precursors, *syn*-bis(α-hydroxyallenes) **1** were prepared by regio- and diastereoselective indium-mediated Barbier-type allenylation reaction of arylglyoxals using our previously described method.[7] Bis(α-hydroxyallene) **1a** was chosen as model substrate for surveying the reaction parameters. The screening results of the oxy-Cope type-rearrangement are delineated in Table 1. It was soon evident that the use of basic promoters such as iodine-pretreated potassium hydride was detrimental, because significant decomposition was detected (entry 1). Following disappointing results through the anionic path, we decided to test the neutral variant. These control experiments demonstrated that heat in the absence of promoter led to a cleaner reaction. After screening several common solvents, toluene was selected as the solvent of choice. Using toluene as solvent in a sealed tube at 220 °C provided an inseparable mixture of 1,3-branched and 1,3-linear dienes **2a** and **2a'** (ratio **2a**/**2a'** = 1:4) (entry 3). We noted that lowering the temperature



Scheme 1. State of the art and current study.

Table 1. Synthesis of oxadendralene **2a** under modified reaction conditions.

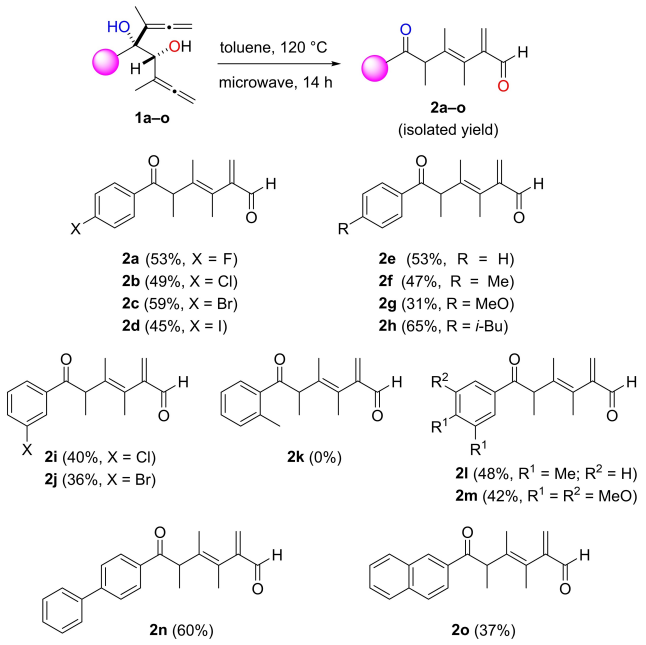


Entry	Conditions	Ratio **2a**/**2a'**	Yield (%)[b]
1	THF (0.1 M), KH, rt, 14 h	–	–
2	DMF (0.1 M), 220 °C, 6 h[a]	2/5	11
3	toluene (0.1 M), 220 °C, 6 h[a]	1/4	22
4	toluene (0.1 M), 220 °C, 14 h[a]	1/2	10
5	DCE (0.1 M), 120 °C, 14 h[a]	3/1	30
6	toluene (0.1 M), 120 °C, 14 h[a]	100/0	33
7	toluene (0.02 M), 120 °C, 14 h[a]	100/0	40
8	toluene (0.02 M), 120 °C, MW, 14 h	100/0	53

[a] The experiment was run in a sealed tube. MW = The experiment was run in a microwave reactor.
[b] Yield of pure, isolated product with correct analytical and spectral data.

deaccelerated the consumption of starting material **1a** and could result in a better selectivity. Noteworthy, a superior reaction outcome was noticed by moving from T = 220 °C to T = 120 °C and the oxadendralene **2a** was exclusively formed as single isomer in 33% yield (entry 6). To our delight, the yield of **2a** was improved to 53% when the reaction was carried out under microwave irradiation and the solvent concentration was 0.02 mol L^{-1} (entry 8).

Having in hand optimized reaction conditions, we surveyed the substrate scope for the rearrangement reaction (Scheme 2). We explored the impact of substitution on the aryl ring and found that both electron-withdrawing groups as well as electron-donating groups were tolerated. Indeed, bis(α-allenols) having halogen atoms, alkyl chains, methoxy group, and aryl nuclei were successful precursors, which points to little influence of the electronic nature of the substituent located at the aromatic ring. However, it was noticed a considerable steric dependence because lack of product formation was observed starting from *ortho*-substituted substrates (**2k**). Besides, a slightly diminished yield in dienals **2i** and **2j** *versus* **2b** and **2c** was encountered by comparison of precursors bearing *meta*-substitution (**1i** and **1j**) and *para*-substitution (**1b** and **1c**). Whereas *ortho*-substitution on the aryl ring was not tolerated and led to the degradation of the precursor **2k**, the use of both the aryl-disubstituted starting material **1l** and the aryl-trisubstituted starting material **1m** resulted in the generation of branched 1,3-dienes **2l** and **2m** in 48% and 42% yields, respectively. Interestingly, the presence of biphenyl and 2-naphthyl moieties was compatible with the above transformation, giving rise to the corresponding oxadendralenes **2n** and **2o** in fair yields as single isomers (Scheme 2). Bis(α-allenols) that hold substituents others than aromatic rings at their carbon-adjacent

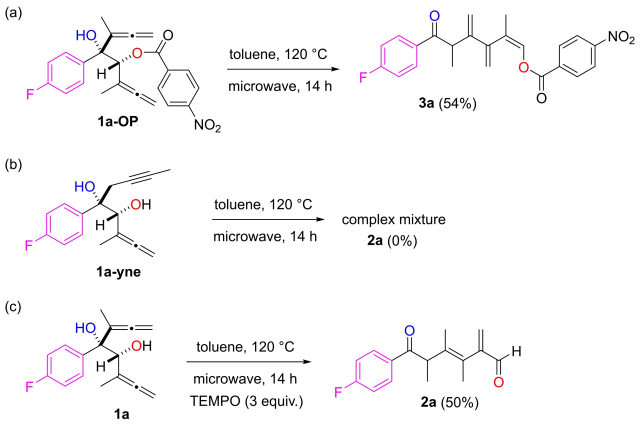


Scheme 2. Thermal synthesis of oxadendralenes **2a–o**.

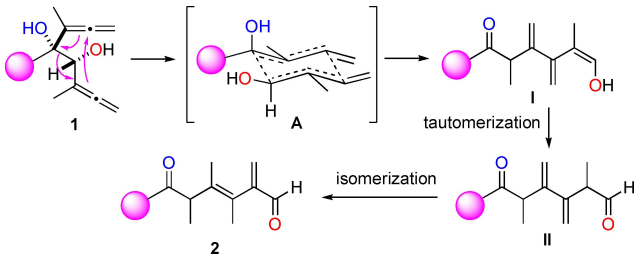
position, which would allow to obtain oxadendralenes bearing alkyl ketones, instead of aryl ones, are elusive precursors. Non-benzylic alcohols related to **1** are unknown compounds in the chemical literature. Only benzylic alcohols **1** were examined because *syn*-bis(α-hydroxyallenes) **1** can be prepared in a regiocontrolled and diastereoselective manner through the indium-mediated Barbier-type reaction of arylglyoxals with 1-bromobut-2-yne. The replacement of arylglyoxals by non-aromatic glyoxals in the Barbier-type allenylation reaction did not proceed in a controlled manner and this reaction was not synthetically useful.

Interestingly, the thermal treatment of the mono-protected hydroxy-bis(allene) **1 a-OP** allowed to isolate the electron-rich [3]dendralene **3 a** in a totally selective fashion (Scheme 3a). By contrast, the thermal treatment of the α,α'-dihydroxyallenyne **1 a-yne** resulted in a complex mixture (Scheme 3b). When the thermal reaction was carried out with diol **1 a** under otherwise identical standard conditions but with the presence of the radical scavenger TEMPO, the formation of oxadendralene **2 a** was attained in 50% yield (Scheme 3c), which should suggest a non-radical process.

A reasonable mechanistic proposal for the generation of oxadendralenes **2** from *syn*-bis(α-allenols) **1**, which should imply a concerted path, is depicted in Scheme 4. The implication of a pericyclic pathway



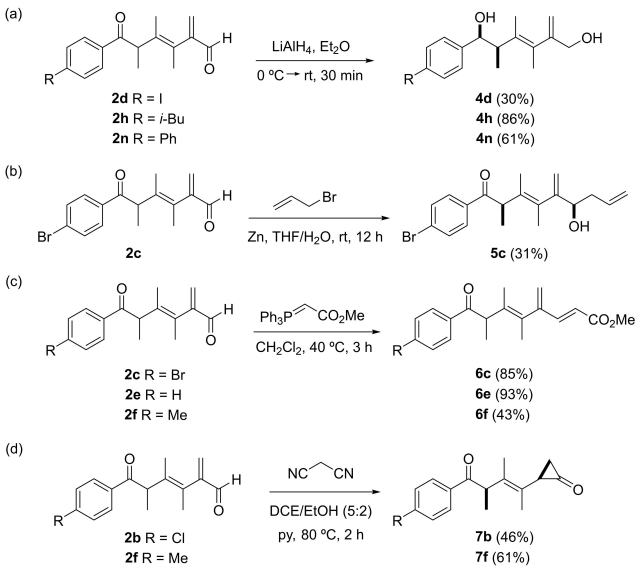
Scheme 3. Control experiments.



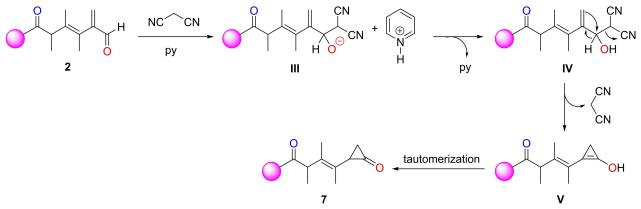
Scheme 4. Plausible pathway for the formation of oxadendralenes **2**.

should make clear the total stereoselectivity of the process. Unsaturated diols **1** should suffer a [3,3]-sigmatropic rearrangement via the chair-like six-membered cyclic transition states **A** in the way to hydroxytrienone intermediates **I**. It should be noted that triene **3 a** (Scheme 3a) must be considered as a trapping product of intermediate **I**. Keto-enol tautomerization of species **I** to form intermediates **II** and subsequent isomerization to a more stable dienal should form oxadendralenes **2** as final products. The driving force of the conversion of bis(α-hydroxyallenes) **1** into oxadendralenes **2** should be the formation of two carbonyl groups.

To illustrate the possibilities of the above obtained oxadendralenes, subsequent modifications were developed as depicted in Scheme 5. Selective carbonyl reduction of oxadendralenes **2 d,h,n** towards dienediols **4 d,h,n** was attained through the use of $LiAlH_4$ (Scheme 5a). The zinc-mediated chemoselective carbonyl-allylation of oxadendralene **2 c** was accomplished under Barbier conditions to yield the branched 1,3-diene-tethered homoallylic alcohol **5 c** (Scheme 5b). Additional diversification was exemplified when oxadendralenes **2 c,e,f** were subjected to the Wittig protocol by reaction with a stabilised ylide to form the electron-deficient [3]dendralenes **6 c,e,f** (Scheme 5c). Noteworthy, under classical Knoevenagel condensation conditions (malononitrile in presence of pyridine), the reaction suffered an interesting deviation because our oxadendralenes **2 b** and **2 f** are converted into cyclopropanones[8] **7 b** and **7 f** rather than in the expected α,β-unsaturated nitriles (Scheme 5). A plausible mechanism for the formation of cyclopropanones **7** is depicted in Scheme 6. Initial nucleophilic addition of the active hydrogen derivative to the carbaldehyde



Scheme 5. Synthetic utility of oxadendralenes **2**.



Scheme 6. Proposed pathway for the formation of cyclopropanones **7**.

moiety of oxadendralenes **2** to generate species **III**, should be followed by a protonation step with pyridin-1-ium, producing intermediate **IV**. Next, the dehydration step should be replaced by an intramolecular carbocyclization involving cyclopropenol **V** formation and concomitant malononitrile release. Final tautomerization should liberate the observed cyclopropanone products **7** within the reaction system. Examples in Scheme 5 show the potential of the enal moiety of oxadendralenes **2** as a synthetic lynchpin for the preparation of more complex chemical entities by simple modifications.

Conclusion

In conclusion, we described a thermal oxy-Cope type-rearrangement in allenes which allowed the efficient preparation of oxadendralenes in a selective manner. The sequence displayed elevated atom and step economy since it is not necessary to place any leaving group on the precursors. Besides, the unsaturated functionalities located at the oxadendralene molecules are prone for versatile synthetic manipulations to construct different chemical architectures in a controlled manner.

Experimental Section

Typical Procedure for the Preparation of Oxadendralenes 2; Synthesis of (*E*)-6-(4-Fluorophenyl)-3,4,5-Trimethyl-2-Methylene-6-Oxohex-3-Enal 2 a

A solution of the appropriate bis(α-hydroxyallene) **1 a** (42 mg, 0.16 mmol) in toluene (8 mL) was heated at 120 °C under microwave irradiation until disappearance of the starting material (TLC). Next, the solvent was evaporated under reduced pressure and the crude reaction was purified by column chromatography on neutral silica gel eluting with hexane/ethyl acetate (1:30) to give oxadendralene **2 a** (23 mg, 53%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 10.18 (s, 1H), 7.94 (dd, 2H, J = 8.9, 5.4 Hz), 7.12 (dd, 2H, J = 8.9, 8.3 Hz), 5.24 (d, 1H, J = 1.2 Hz), 5.01 (s, 1H), 4.25 (qd, 1H, J = 6.9, 1.1 Hz), 2.24 (q, 3H, J = 1.4 Hz), 1.63 (q, 3H, J = 1.4 Hz), 1.42 (d, 3H, J = 6.9 Hz); ^{13}C{1H} NMR (75 MHz, $CDCl_3$, 25 °C): δ 198.7, 192.0, 166.0 (d, 1 C, J = 255.5 Hz), 155.5, 149.1, 133.3, 133.1 (d, 1 C, J = 3.1 Hz), 131.1 (d, 2 C, J = 9.3 Hz), 116.1 (2 C), 115.9, 45.0, 17.4, 17.1, 13.1; IR ($CHCl_3$): ν 1696, 1670, 1092 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{17}FO_2Na$: 283.1105; found 283.1107.

Acknowledgements

This work was supported by MCIN/AEI/10.13039/501100011033/FEDER (Project PID2021-122183NB-C21) and UCM (PR3/23-30806). We are grateful to Eva Cerrón (UCM) for preliminary studies.

References

[1] a) B. S. Davidson, C. M. Ireland, *J. Nat. Prod.* **1990**, *53*, 1036–1038; b) H. Kakeya, I. Takahashi, G. Okada, K. Isono, H. Osada, *J. Antibiot.* **1995**, *48*, 733–735.
[2] M. Garbo, C. Mazet, *Org. Lett.* **2022**, *24*, 752–756.
[3] N. Hammer, L. A. Leth, J. Stiller, M. E. Jensen, K. A. Jorgensen, *Chem. Sci.* **2016**, *7*, 3649–3657.
[4] W. Wang, D. Huang, Y. Yu, H. Qian, S. Ma, *Angew. Chem. Int. Ed.* **2023**, *62*, e202307626.
[5] a) H. Wang, B. Beiring, D.-G. Yu, K. D. Collins, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 12430–12434; b) M. Mao, L. Zhang, Y.-Z. Chen, J. Zhu, L. Wu, *ACS Catal.* **2017**, *7*, 181–185; c) D. J. Lippincott, R. T. H. Linstadt, M. R. Maser, B. H. Lipshutz, *Angew. Chem. Int. Ed.* **2017**, *56*, 847–850.
[6] J. M. Alonso, P. Almendros, *Chem. Rev.* **2021**, *121*, 4193–4252.
[7] T. Martínez del Campo, D. San Martín, L. Gamarra, E. Cerrón, S. Cembellín, H. Yanai, P. Almendros, *J. Org. Chem.* **2024**, *89*, 14228–14232.
[8] The strained cyclopropane ring is abundant in bioactive molecules and behaves as valuable building block in organic synthesis. For selected reviews, see:a) L. A. Wessjohann, W. Brandt, T. Thiemann, *Chem. Rev.* **2003**, *103*, 1625–1648; b) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196; c) D. Y.-K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631–4642; d) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804–818; e) T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712–8756; f) C. Ebner, E. M. Carreira, *Chem. Rev.* **2017**, *117*, 11651–11679; g) M. R. Bauer, P. Di Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. I. Storer, B. C. Whitehurst, *RSC Med. Chem.* **2021**, *12*, 448–471.