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Graphical Abstract

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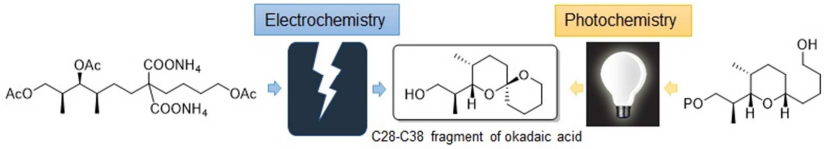

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ABSTRACT

Okadaic acid, a potent and selective inhibitor of Protein Phosphatases 1 and 2A (PP1 and PP2A), is widely used as a probe for various biochemical processes. We describe herein two innovative methods for the synthesis of the terminal C28-C38 fragment of the natural polyether. Suárez photochemical oxidative cyclization and electrochemical oxidation of malonates to their ketals equivalents have been successfully applied for the assembly of the key spiroketal core.

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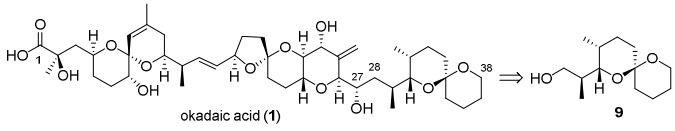
[1] Deceased

Figure 1: Structure of the marine toxin okadaic acid

1. Introduction

Okadaic acid (OA **1**, Figure 1), a complex natural polyether, is the leading member of the family of toxins that cause diarrheic shellfish poisoning.[1] It was originally isolated from the marine sponges *Halichondria okadai* and *Halichondria melanodocia*[2] and subsequently identified as being produced by the marine dinoflagellates *Prorocentrum lima* and *Dinophysis fortii*[3] which accumulated in the sponges through filter feeding.[3b] OA has been shown to be a potent and selective inhibitor of serine/threonine protein phosphatases 1 and 2A (IC_{50} of 3.4 and 0.07 nM respectively).[4] Thus, it is a valuable and widely used tool in biochemical studies involving these enzymes.[5]



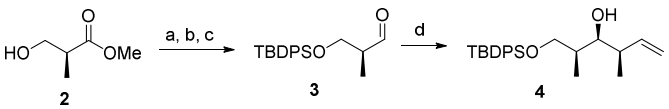
Its reactivity with the different protein phosphatases, together with a range of biological activities, including tumor-promoting activity[6] and ability to induce apoptosis,[7] attracted the attention of the synthetic community to this challenging target. To date, three independent total syntheses have been reported,[8] along with the synthesis of natural and non-natural analogues[9] and some fragment studies.[10] However, continuous improvement of the synthesis is still required to reach OA in an efficient, greener and shorter way.

Structure activity relationship (SAR) studies have shown that the terminal C28-C38 hydrophobic part of the polyether is particularly important for the phosphatase inhibition reactivity.[11] Previous syntheses of this fragment have relied largely on the formation of keto-diols and their acid catalyzed ketalization generating the spiroketal center.[8-10] While this approach allows the target spiroketal to be obtained in an efficient and even sometimes short manner, new methods that can improve atom economy and allow simple modification of the structure can facilitate the synthesis of new derivatives of OA, and more generally spiroketals.

Herein, two innovative approaches for the synthesis of the terminal C28-C38 fragment of OA starting from homoallylic alcohol **4**, scheme 1, are described which give access to spiroketal alcohol **9**, an intermediate used in previous syntheses of OA.[8,9] The first involves the construction of the spiroketal moiety through sequential tetrahydropyran formation using a modified Taddei-Ricci protocol[12] followed by a hydrogen atom transfer through the photochemical oxidative conditions described by Suárez.[13] The second route relies on an original method developed in the Markó group for the electrochemical oxidation of malonates into ketals.[14]

2. Results and Discussion

The starting point of both routes is the homoallylic alcohol **4**, obtained in four steps from commercial (*S*)-Roche ester **2** through a diastereoselective crotylstannation developed by Keck (Scheme 1).[10g, 15] This central building block possess all the chiral centers of the fragment with the exception of the thermodynamically controlled spiroketal center and can be obtained with both excellent dia- and enantioselectivity.



Scheme 1: **Reagents and conditions**: a) TBDPSCl, Et_3N, DMAP, DCM, RT, quant. b) DIBAL-H, DCM, -78 °C to RT, 88%. c) DMP, DCM, RT, 85%. d) Crotyltributylstananne, $BF_3{\cdot}OEt_2$, Et_2O, -100 to -78 °C, 83%, e.r.; d.r. > 98:2.

2.1 Photochemical route

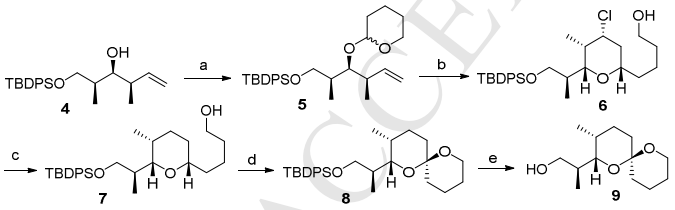
The first approach expands on a method described by the Markó group involving a key photochemical oxidative cyclization step using HgO/I_2.[10a] This method allowed direct synthesis of a spiroketal center starting from a model tetrahydropyran system. The excellent efficiency of this approach

notwithstanding, removal of the toxic reagents and harsh conditions would offer a significant improvement.

Suárez and co-workers have reported a photochemical method that allowed them to obtain a variety of spiroketals. Their approach makes use of (diacetoxyiodo)benzene (BAIB)/I_2 and involves the generation of an alkoxy radical followed by an intramolecular 1,6-hydrogen atom transfer (1,6-HAT).[13] This intramolecular HAT allows for the functionalization of diverse tetrahydropyrans and avoids the use of mercury reagents. Using this idea, a new method was envisaged involving the construction of the spiroketal moiety through sequential tetrahydropyran formation via a modified Taddei-Ricci[12] protocol followed by a hydrogen atom transfer through the photochemical oxidative conditions described by Suárez. This method allows for the formation of the spiroketal moiety of the C28-C38 fragment without using the classical keto-diol approach.

The synthesis of the target molecule started with the incorporation of the five carbons corresponding to the second ring of the spiroketal onto alcohol **4** through the formation of the THP-ketal **5** with excellent yield. This ketal **5** was then transformed to the tetrahydropyran **6** according to the modified Taddei-Ricci conditions formerly developed for the synthesis of a model fragment of okadaic acid.[10a] The reaction is described to occur by the addition of titanium tetrachloride allowing the opening of the ketal with formation of the corresponding oxonium. This intermediate is subsequently attacked by the terminal alkene with the help of a chloride ion, leading to tetrahydropyran **6** in very good yield and with excellent diastereoselectivity (Scheme 2).[16] Removal of the chlorine atom through TTMSS/AIBN mediated reduction led then to THP alcohol **7**, which is well suited for the photochemical cyclization.

Addition of BAIB and iodine to **7** under UV light gave spiroketal **8** as a single diastereomer with a good yield of 61%. As described by Suárez,[13c] this reaction should proceed through generation of the alkoxy radical which can undergo a 1,6-HAT to generate a radical on the THP ring. Its further oxidation to the oxonium permits the intramolecular attack of the alcohol to form the thermodynamic spiroketal. Final deprotection of the alcohol lead to the C28-C38 fragment **9** of OA in only five steps from **4**. Comparison of the spectroscopic data and optical rotation with the literature confirmed the relative and absolute configuration of **9**.[17]



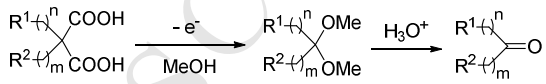
Scheme 2: **Reagents and conditions**: a) DHP, CSA cat., DCM, -20 °C, 95%. b) $TiCl_4$, DCM, -100 °C, 89%, *d.r.* = 95:5. c) TTMSS, AIBN, Tol, 110 °C, 65%. d) BAIB, I_2, hv, cyclohexane, 40 °C, 61%, *d.r.* >20:1. e) TBAF, THF, RT, 89%.

This very short assembly of the target molecule, requiring only five steps from the known alcohol **4**, represents the shortest access to date to the key intermediate **9**. It highlights also the great application of the Suárez photochemical oxidation conditions for the synthesis of complex spiroketals,[18] in particular because of the excellent atom economy and also because these conditions avoid the toxic reagents (HgO, CCl_4) used previously. Furthermore, it is the only example, except from the gold catalyzed spiroketalization of Forsyth,[10j] that does not use the keto-diol approach to reach the C28-C38 fragment of OA.

2.2 Electrochemical route

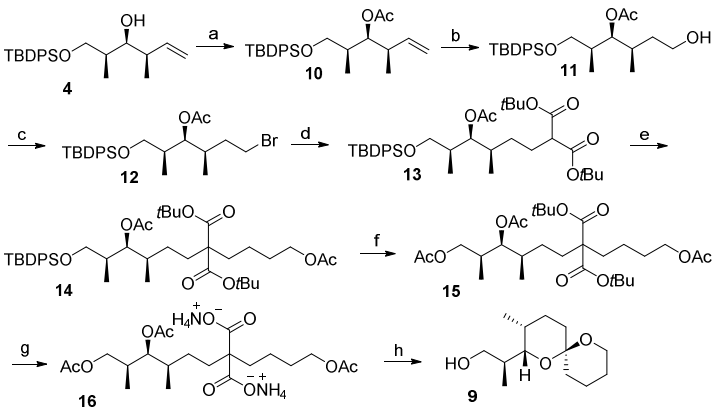
Over the last decades, organic electrochemistry has regained attention in the field of synthetic organic methods.[19] Classical chemical reducing or oxidizing agents are being replaced by electric current as an inexpensive and inherently safe reagent.

Recently, investigations in the Markó group on radical generation under electrolytic conditions[20] and on the Kolbe-type reaction of monocarboxylic acids[21] led to the development of a method to perform the electrolysis of malonic acids to their ketal equivalent under mild conditions.[14] This method allows for the umpolung-like facile assembly of unsymmetrical ketones or ketals with relatively good yields (Scheme 3). Furthermore, the presence of free alcohols on the R^1 or R^2 chains of malonic acid derivatives could permit the intramolecular capture of the carbocation intermediate and hence the formation of spiroketal equivalents such as the terminal fragment of okadaic acid. This approach can constitute therefore a second route to spiroketal **9**.



Scheme 3: Electrochemical oxidative decarboxylation of malonic acid derivatives

With this idea in mind, chiral alcohol **4** was converted into the corresponding bromide **12**, through initial protection of the alcohol as its acetate derivative **10**, followed by a two-step 9-BBN hydroboration/Appel bromination of the terminal alkene to give primary bromide **12** (Scheme 4). This alkylbromide, corresponding to the backbone of the substituted THP ring of the terminal fragment of OA **1**, was then connected to di-*tert*-butyl malonate to yield the malonate **13**. Finally, deprotonation of **13** with sodium hydride and alkylation with iodobutyl acetate furnished the adduct **14**, containing all the carbons of the full skeleton of the target molecule.



Scheme 4: **Reagents and conditions**: a) Ac_2O, DMAP cat., py, RT, 92%. b) i. 9-BBN, THF, 0 °C to RT; ii. NaH_2BO_4, H_2O, RT, >95%. c) CBr_4, PPh_3, DCM, 0 °C to RT, >95%. d) di-*tert*-butyl malonate, NaH, THF, 0 °C to RT then **12**, THF, 70 °C, 93%. e) NaH, THF, RT to 70 °C then 4-iodobutyl acetate, THF, 70 °C, 93%. f) TBAF, THF, 0 °C then Ac_2O, DMAP cat., RT, 93%. g) i. TFA, DCM, RT then ii. NH_3, MeOH, quant. h) i. Undivided cell,

Cgr/Cgr, 50 mA, MeOH, RT; ii. K_2CO_3, MeOH, RT; iii. HCl 1M, RT, 61%, d.r. > 20:1.

The next step of the reaction requires the *t*-Bu deprotection of the malonate group. This can be accomplished directly on **14** using freshly sublimed $AlCl_3$. However, as formation of HCl can lead to the removal of the TBDPS group, exchange of the silyl protecting group for the corresponding acetate **15** was performed to increase the reproducibility of this step. Malonic acid ammonium salt **16** was then obtained quantitatively using trifluoroacetic acid followed by treatment with ammonia.[22]

Finally, the electrochemical oxidation of malonic acid **16** to its dimethoxyketal derivative was conducted in an undivided cell using graphite electrodes and under a constant current of 50 mA.[23] The reaction was monitored by TLC and stopped when complete conversion was observed. *In situ* saponification of the three acetates using potassium carbonate in methanol followed by an acidification of the reaction medium gave the final spiroketal **9** with 61% yield.

From the same intermediate **4** used in the photochemical route, eight steps were needed to reach the same spiroketal adduct **9** with excellent yields over all the synthesis. Using this electrochemical umpolung approach, the assembly of a broad range of spiroketals could be envisaged, avoiding the use of a classical dithiane central building block. Hence, this could allow facile variation of each cycle of the spiroketal, independently, aiding in additional SAR studies of okadaic acid. Furthermore, the very mild, metal-free and eco-friendly electrochemical conditions of the final step make this approach an excellent candidate for further application and development in total synthesis.

3. Conclusion

In conclusion, we have developed two innovative and concise synthetic entries to the C28−C38 fragment of okadaic acid by exploiting green photochemical and electrochemical methodologies for the construction of the spiroketal unit. Our synthetic strategies allow for rapid assembly of complex spiroketals in high yield with longest linear sequences from commercially available material of nine and twelve steps for the photochemical and electrochemical approaches respectively.

4. Supplementary Material

Supplementary material (experimental procedures, ^1H and ^{13}C NMR data for the described compounds) associated with this article can be found, in the online version, at XXX.

Acknowledgments

This paper is dedicated to the memory of Professor István E. Markó. Financial support from the Fonds de la Recherche Scientifique (FRS-FNRS) via the Fonds pour la formation à la Recherche dans l'Industrie et dans l'Agriculture (FRIA fellowship for SD, JBN, DFD, and JFB), and the Université catholique de Louvain are gratefully acknowledged.

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16. A postulated transition state to explain the stereochemistry of the tetrahydropyran could be found in reference 10a.
17. Optical rotation values described for compound **9** are $^{25}[\alpha]_D$ +69 (*c* 1.55, $CHCl_3$)[8b], $^{20}[\alpha]_D$ +67 (*c* 0.75, $CHCl_3$)[10g] and $^{24}[\alpha]_D$ +92.2 (*c* 1.00, $CHCl_3$)[10k] as ours is $^{20}[\alpha]_D$ +74.2 (*c* 1.39, $CHCl_3$). Listing of the previous ^1H and ^{13}C NMR spectral data can be found in the supporting information.
18. For a review on the synthesis of natural products containing spiroketals *via* intramolecular hydrogen abstraction see : Sperry J, Liu YC, Brimble MA. *Org. Biomol. Chem.* 2010; 8:29.
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22. As mentioned in reference 14a, the malonic acid can be either isolated as so and electrolyzed in MeOH with 2 equivalents of NH_3 or isolated as the ammonium salt and electrolyzed as so in MeOH. The choice of one method to the other depends on the ease of the isolation of the acid. For **16**, the compound is more easily isolated as the ammonium salt.
23. Practical information on method and apparatus is presented in the supporting information.