Tetrahedron Letters 50 (2009) 7310–7313

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An intramolecular [4+3]-cycloaddition approach to rameswaralide inspired by biosynthesis speculation

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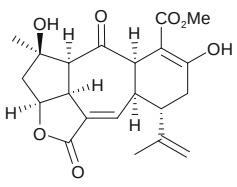
ARTICLE INFO

Article history:
Received 30 August 2009
Revised 28 September 2009
Accepted 9 October 2009
Available online 14 October 2009

ABSTRACT

A concise synthesis of the polycycle **27**, which incorporates the 5,5,7-tricyclic ring core of rameswaralide **1**, using a biogenetically inspired acid-catalysed [4+3]-cycloaddition approach starting from the furanobutenolide **26** is described, namely, **26**→**28**/**29**→**27**. Under thermal conditions, the same furanobutenolide **26** gives the alternative polycyclic compound **35**, resulting from a [4+2]-cycloaddition involving the furan as dienophile.

Rameswaralide **1** is a novel polycyclic diterpene isolated from the soft coral *Sinularia dissecta* collected off the coast of Mandapam near Rameswaram, India.[1] The metabolite co-occurs with mandapamate **2**[2] and its diastereoisomer **3**[3,4] in *S. dissecta*, which are structurally similar to plumarellide **4** and plumarellic acid ethyl ester **5** found in the gorgonian coral *Plumarella* sp.,[5] which inhabits the Kuril Island region of the Pacific Ocean. It seems probable that the five metabolites **1–5** are related biogenetically as products of oxidations followed by transannular ring-forming reactions from furanobutenolide-based cembranes, for example, rubifolide **6**, which are ubiquitous in corals and the marine environment. It also seems likely that enol ether structures, namely, **9** and **12**, derived from oxidation-hydrolysis reactions involving the alkenylfuran units in furanobutenolides, play a central role in these biosynthetic pathways.[6] Thus, we surmise that enzymatic epoxidation of the furylalkene bond in **6**, accompanied by other oxidation processes,



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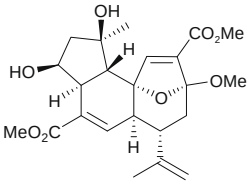

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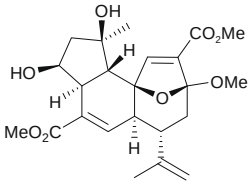

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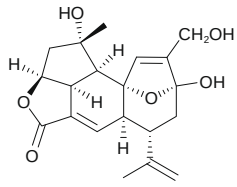

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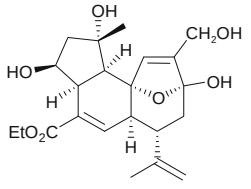

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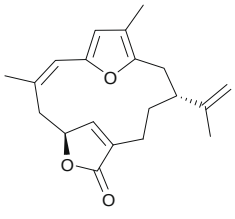

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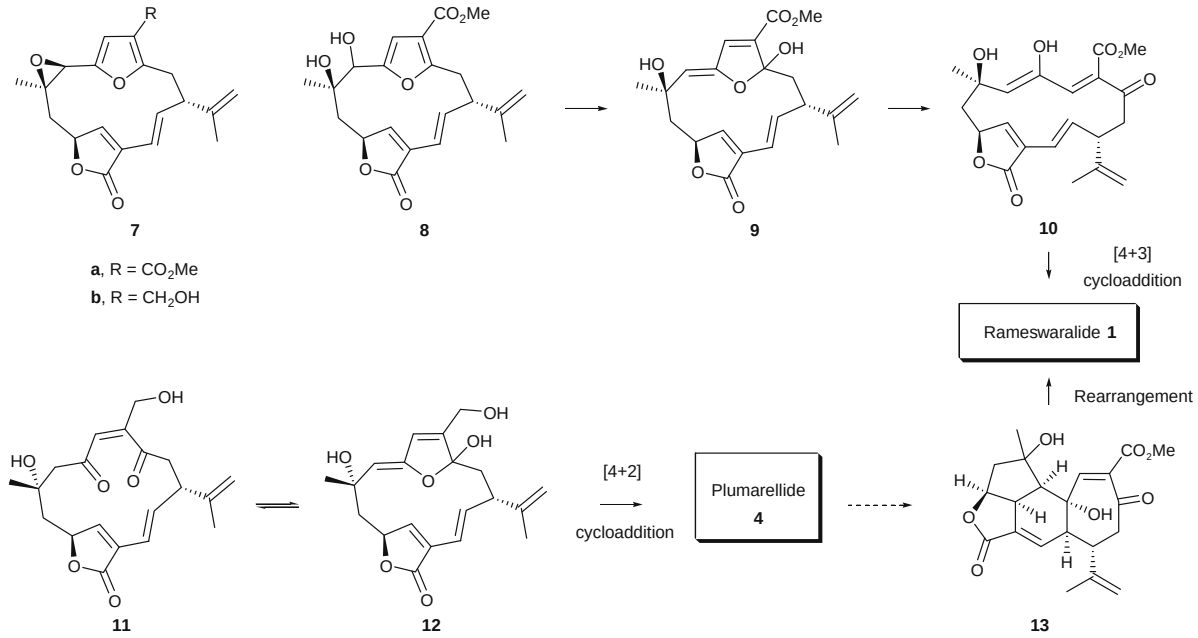
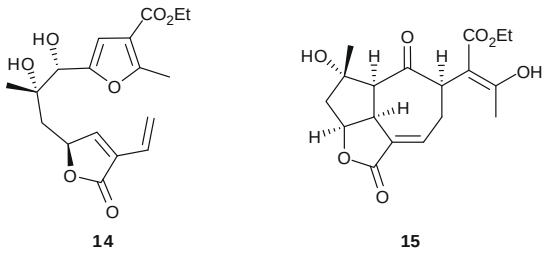
doi:10.1016/j.tetlet.2009.10.046



Scheme 1. Speculations on the origins of rameswaralide **1** and plumarellide **4** in nature via cyclic enol ether-hemiketal intermediates **9** and **12** and transannular cycloadditions.

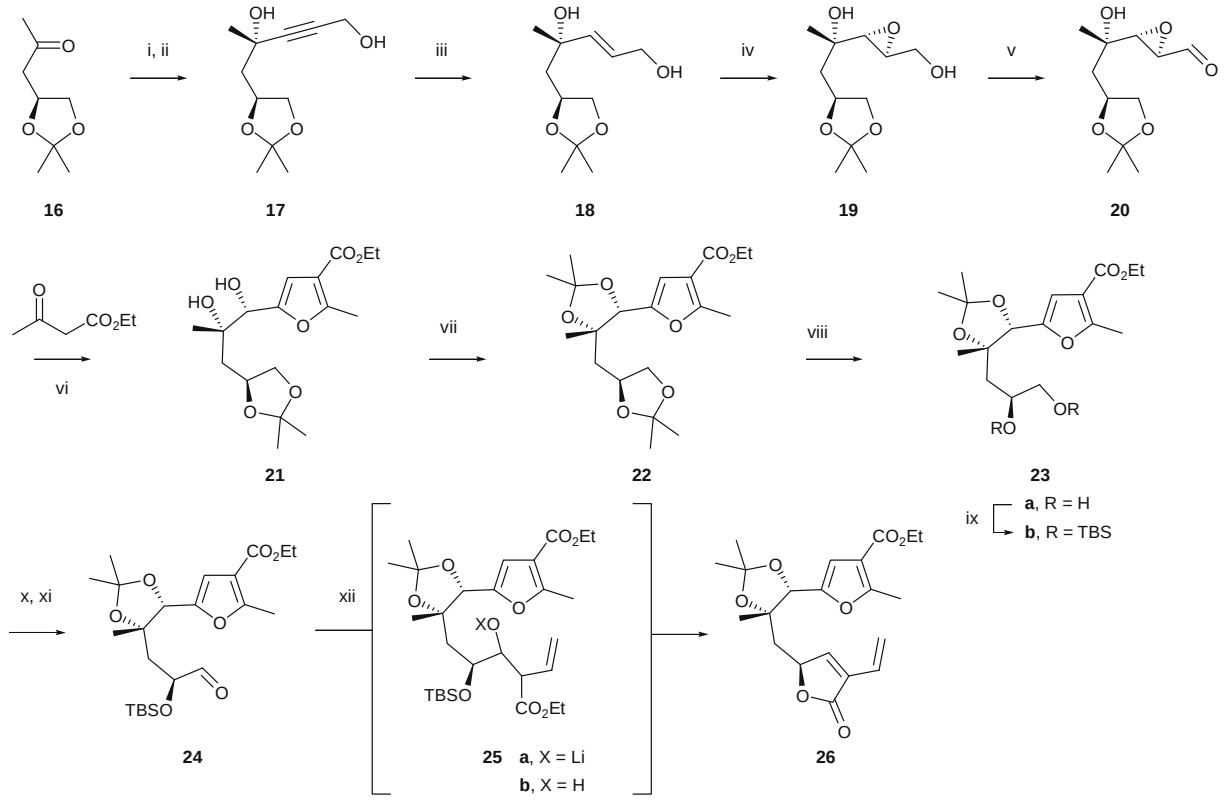
would produce the epoxide intermediate **7a** which by hydrolysis could then lead to the enol ether **9** either directly or via the vicinal diol isomer **8** (Scheme 1). Tautomerisation of **9** followed by isomerisation would next lead to the enedione intermediate **10** which by way of a transannular [4+3]-type cycloaddition would produce rameswaralide **1**. In an alternative sequence, perhaps to plumarellide **4**, oxidative cleavage of the furan ring in **6**, accompanied by other enzymatic oxidations and hydrolysis, could lead to the enedione **11**, a tautomer of the enol ether-cyclic hemiketal **12** (cf. **9**). A transannular [4+2]-cycloaddition would then lead to plumarellide **4**. Finally, it is also plausible that the ring systems in rameswaralide **1** and plumarellide **4** are related via the hydroxyketone tautomer **13**, cf. mandapamate **2** and carbon-to-carbon bond migration using an enzymatic vinylogous α-ketol rearrangement.[7]

Although the proposals summarised in Scheme 1 are speculative, they have inspired us to examine the feasibility of the key transannular cycloaddition steps **10**→**1** and **12**→**4** in the biosynthesis of rameswaralide and plumarellide involving unusual cyclic enol ether-hemiketal intermediates.[8] In this Letter, we describe a concise synthesis of the seco-furanobutenolide **14** related to the proposed precursor **8** to rameswaralide **1**, and studies of its acid-catalysed conversion into the core 5,5,7-tricyclic ring system **15** in the natural product.

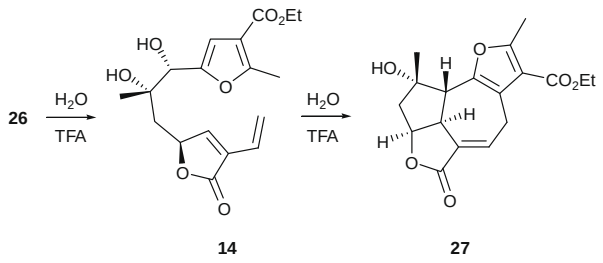


Thus, addition of the known ketone **16**, derived from (−)-malic acid,[9] to the carbanion produced from propargyl alcohol and 2 equiv of BuLi gave the corresponding tertiary alcohols as a 1:1 mixture of diastereoisomers in 70% yield (Scheme 2). Reduction of the separated diastereoisomer **17**, using $LiAlH_4$ in THF, next gave the *E*-allylic alcohol **18** (82%), which was then converted into the corresponding epoxide **19** using a Sharpless asymmetric epoxidation.[10] Oxidation of the epoxy-alcohol **19** using the Dess–Martin periodinane (DMP) led to the epoxy aldehyde **20** in 80% yield over two steps. When the epoxy aldehyde **20** was stirred with ethyl acetoacetate for two hours at 55 °C in the presence of a catalytic amount of piperidine, in a minimal amount of THF–HOAc, work-up and chromatography gave the substituted furanethane diol **21** as a single diastereoisomer in 40% overall yield.[11] The vicinal diol unit in **21** was next protected as the acetonide, and then the more sterically accessible terminal acetonide in the product **22** was deprotected leading to the new vicinal diol **23a**. Silylation of **23a** finally gave the bis-TBS ether **23b** in 90% yield over three steps. The primary TBS-ether group was next deprotected to the corresponding alcohol which was then oxidised, using DMP, leading to the TBS-protected α-hydroxyaldehyde **24** (70% yield over two steps). When the aldehyde **24** was added to the enolate anion obtained from ethyl crotonate using LiHMDS-HMPA at −78 °C, the anticipated aldol addition product **25b** was not observed. Instead, to our satisfaction, we isolated the required 2-vinylbut-2-enolide **26** in 55% overall yield, as a result of the lithium salt **25a** of the initially formed aldol adduct undergoing an anion relay-type cascade involving silyl group migration, lactonisation and E1cb elimination of the silyloxy group.

When a solution of the substituted furanobutenolide **26** in TFA, containing a few drops of water, was stirred at room temperature for 15 min, simple concentration in vacuo left the polycycle **27**, showing the 5,5,7-tricyclic ring system present in rameswaralide **1**, in essentially quantitative yield. The polycycle **27** was obtained as a colourless solid, mp 156–158 °C (needles from hexane/dichloromethane), $[\alpha]_D^{25}$ +70 (*c* 0.51 in $CHCl_3$), and its carbon connectivity was established by the detailed analysis of its 1D and 2D proton and carbon NMR spectra (COSY, HMQC and HMBC). Furthermore, measurements of the nuclear Overhauser enhancements following irradiations of the proton resonances around the cyclopentane ring in **27**, together with the observed *J* values, established the stereochemistry unambiguously (see Supplementary data).

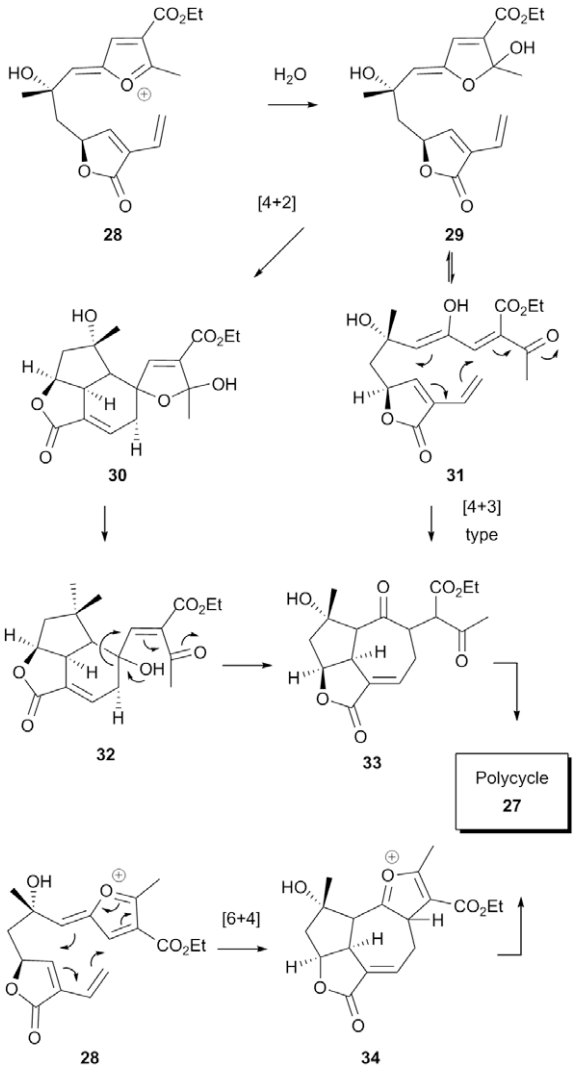


Scheme 2. Reagents and conditions: (i) HC≡CCH_2OH (3.5 equiv), ^{n}BuLi (7 equiv), THF, −40 °C to rt, 70%; (ii) chromatographic separation, 31% overall; (iii) $LiAlH_4$, THF, 0 °C to rt, 18 h, 82%; (iv) L-(+)-DET, $Ti(O^{i}Pr)_4$, ^{t}BuOOH, 4 Å MS, CH_2Cl_2, −20 °C to −5 °C, 4 h, 83%; (v) DMP (1.2 equiv), $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 h; (vi) ethyl acetoacetate (1.0 equiv), piperidine (cat), THF–HOAc, rt to 55 °C, 2 h, 40% from **19**; (vii) 2,2-dimethoxypropane, PPTS (cat.), reflux, 1 h, quant.; (viii) H_2O–HOAc (1:12), 50 °C, 3 h, quant.; (ix) TBSCl, imid., DMF, rt, 18 h, 90% from **21**; (x) HF·py, py-THF, 0 °C to rt, 5 h, 70%; (xi) DMP (1.5 equiv), $NaHCO_3$, CH_2Cl_2, rt, 95%; (xi) ethyl crotonate (1.0 equiv), LiHMDS (1.05 equiv), HMPA (1.45 equiv), −78 °C to −20 °C, 55%.

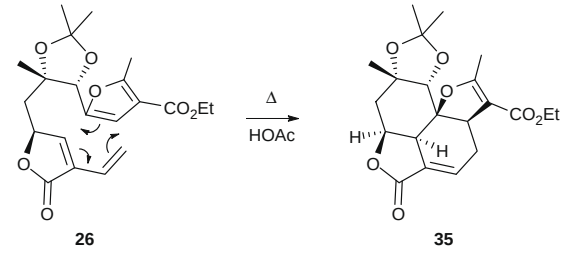


We rationalise the formation of **27** from **26**, following deprotection to the corresponding vicinal diol **14**, which then undergoes acid-catalysed hydrolysis via the oxonium ion intermediate **28** leading to the cyclic enol ether-hemiketal **29** (Scheme 3). Tautomerisation of **29** and isomerisation of the resulting *Z*-enedione could then produce the polyene precursor **31** for a tandem Michael [4+3]-type intramolecular cycloaddition leading to the ring-fused cycloheptenone **33**. The 1,4-dione functionality in **33** would then undergo furan ring formation leading to the observed product **27**. Alternatively, the intermediate **29** could undergo intramolecular [4+2]-cycloaddition producing the spirocyclic cyclohexene **30**, which then undergoes tautomerisation to **32** followed by ring 6→7 expansion leading to the 1,4-dione **33**. It is also conceivable that the furan ring in the precursor **14** remains intact during its conversion into **27**, and that the oxonium ion species **28** instead takes part in an intramolecular-concerted [6+4]-cycloaddition[12] leading to the new oxonium ion intermediate **34**. This process would represent a 6-electron homologue of the widely used [4+3]-cycloaddition of dienes and allyl cations.

The importance of the specific reaction conditions used to achieve the acid-catalysed conversion of **26** into **27** (i.e., wet TFA at room temperature) was underlined by some key observations made during the screening of various conditions. Thus, treatment of the furanobutenolide **26** with HCl in methanol at room temperature gave clean hydrolysis to the corresponding vicinal diol **14**. No polycyclic structures were observed under these conditions, even at elevated temperatures. However, the vicinal diol **14** underwent smooth conversion into the polycycle **27** in wet TFA at room temperature. The furanobutenolide **26** was inert to the action of acetic acid, containing a few drops of water, but it underwent very slow hydrolysis of the acetonide at elevated temperatures. Surprisingly, at reaction temperatures above 110 °C in wet acetic acid, furanobutenolide **26** underwent partial hydrolysis to **14**, together with the transformation into the tetracyclic product **35**, resulting from an intramolecular [4+2]-cycloaddition with the furan ring in **26** behaving as a dienophile; no evidence of the co-formation of the alternative polycycle **27** could be found under these conditions. Finally, when the furanobutenolide **26** was heated under reflux in glacial acetic acid (i.e., in the absence of water) for two hours, the polycycle **35** was the sole product (80%). Although instances of furans behaving as dienophiles in Diels–Alder reactions are relatively rare,[13] the conversion of **26** into **35** is no doubt favoured by the intramolecularity of the reaction.



Scheme 3. Rationalisation of the acid-catalysed formation of the polycycle **27** from the furanobutenolide **26**.



Although the exact sequence of events by which the furanobutenolide **14** is converted into the 5,5,7-tricyclic ring system **27** under acid catalysis is unclear, it does seem probable that the exo enol ether species **28**/**29** are important intermediates during the conversion. This conclusion not only supports the biosynthesis proposal for rameswaralide highlighted earlier (Scheme 1), but the construction of **27** from **14** provides a sound basis for our planned biogenetically inspired synthesis of rameswaralide and plumarellide featuring [4+3] and [4+2] cycloaddition reactions from enol ethers as key steps (see Scheme 1). Efforts to extend this study towards the synthesis of the cyclic enol ether-hemiketal precursors **9** and **12** for the natural products are now in progress.[14]

Acknowledgement

We thank the EPSRC for a Fellowship to support J.M.W.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.046.

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7. (a) The stereochemistries of rameswaralide **1** and plumarellide **4** were determined by analysis of coupling constants and NOE(SY) correlations in their 1H NMR spectra; see Refs. 1,5. They were shown to be epimeric at the *t* -hydroxy centre (C-8) in their cyclopentane rings. Similarly, plumarellic acid ethyl ester **5** is epimeric with the mandapamates **2** and **3**, at the same carbon centre.; (b) The suggestion of a relationship between the carbon skeletons in rameswaralide **1** and isomandapamate **3** was first made by Venkateswarlu and Faulkner; see Ref. 1.
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