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Electrocyclic processes in aromatic biosynthesis: a biomimetic study of pseudorubrenoic acid A

Rodney W. Rickards* and Danielle Skropeta

Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia

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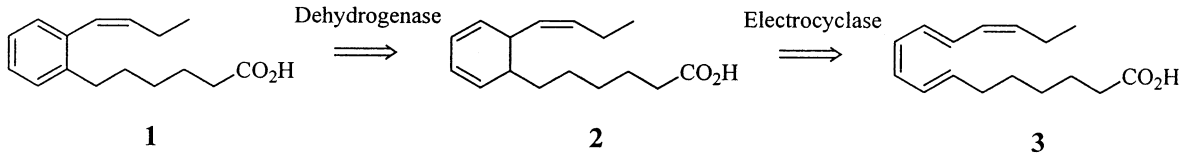
Abstract—The possible involvement of 6π electrocyclic ring closures, mediated by electrocyclase enzymes, of polyunsaturated acyclic polyketide intermediates in the biosynthesis of certain *o*-dialkyl-substituted benzenoid natural products is discussed. The feasibility of the process is illustrated by the electrocyclic ring closure of 7*E*,9*Z*,11*E*,13*Z*-1-*t*-butyldimethylsilyloxy-hexadeca-7,9,11,13-tetraene (**12a**) to the cyclohexadiene **13** followed by dehydrogenation to the analogue **14** of the *o*-dialkyl-substituted aromatic metabolite pseudorubrenoic acid A (**1**).

1. Introduction

Aromatic natural products usually contain diagnostic structural features that reflect their biosynthetic formation by one of several major well established biosynthetic routes.[1] A small group of *o*-dialkyl-substituted benzenoid microbial products, however, are exceptions. These include the pseudorubrenoic acids (e.g. pseudorubrenoic acid A, **1**), antimicrobial antibiotics produced by the soil bacterium *Pseudomonas fluorescens*,[2] the rubrenoic acids A–C from the marine bacterium *Alteromonas rubra*,[3] demetric acid from *Streptomyces umbrosus*,[4] serpentene from *Streptomyces* sp. Tü-3851,[5] and the amino-terminal acyl moieties of the PDGF-binding inhibitor RP-1776 from *Streptomyces* sp. KY11784,[6] the farnesyl-protein transferase inhibitors pepticinnamins A–F from *Streptomyces* sp. OH-4652[7] and the tachykinin antagonist WS9326A produced by *S. violaceusniger*.[8] Their even-numbered C_{12}, C_{14}, C_{16}, C_{18} and C_{20} carbon skeletons indicate that these structures are all acetate-derived. They are distinguished from most aromatic polyketides, however, by the absence of oxygen functionality on or adjacent to the aromatic ring, indicative of normal polyketide ring closure. Structural analysis suggests that these metabolites may be formed by a hitherto unrecognised biosynthetic route to aromatic systems involving 6π electrocyclisation of polyunsaturated acyclic precursors to dihydroaromatic intermediates, followed by dehydrogenation. The retrobiosynthetic analysis is illustrated (Scheme 1) for the formation of pseudorubrenoic acid A (**1**) from the hexadeca-7,9,11,13-tetraenoic acid (**3**) via the cyclohexadiene intermediate **2**. The acyclic precursors themselves could arise by well-known processes, either from fatty acids by enzymic desaturation, or from enzyme-bound oxygenated polyketide intermediates by reduction of carbonyl groups and subsequent elimination processes. In the present case, the acid **3** must necessarily have the 9*Z* olefinic configuration to permit electrocyclisation of the 7,9,11-triene component, and it is notable that this configuration is that found in the common Δ^9-unsaturated C_{16} fatty acid palmitoleic acid. The existence in Nature of *electrocyclase* enzymes capable of catalysing electrocyclic reactions would complement the two enzymes already reported to catalyse pericyclic reactions, *chorismate mutase*[9] and *Diels–Alderase*.[10]

Although Diels–Alder reactions have been proposed as key steps in the biosynthesis of a number of natural products,[11] electrocyclic reactions[12] have seldom been invoked in biosynthetic pathways, and never in aromatic biosynthesis. To our knowledge, the biosynthetic



Scheme 1. Retrobiosynthetic analysis of pseudorubrenoic acid A (**1**).

Keywords: biosynthesis; biomimetic synthesis; electrocyclase; electrocyclic reactions; pseudorubrenoic acid.
* Corresponding author. Tel.: +61-2-6125-3507; fax: +61-2-6125-8114; e-mail: rickards@rsc.anu.edu.au

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involvement of electrocyclic reactions has been suggested only in relation to vitamin D chemistry,[13] the polycyclic endiandric acids[14] and the eudesmane sesquiterpene (+)-occidentalol[15] from plants, the polypropionate-derived 9,10-deoxytridachione[16] produced by a marine mollusc, and a small number of pheromones isolated from a brown alga.[17]

Despite their lack of diagnostic oxygen functionality, however, biosynthesis of such *o*-dialkyl-substituted benzenoid metabolites from polyketide intermediates by aldol cyclisation processes cannot be entirely excluded. Three such processes can be distinguished, but each is accompanied by reactivity questions. In the case of pseudorubrenoic acid A (**1**), for example, the enzyme-bound trione intermediate A could undergo aldol cyclisation and aromatisation to afford the aromatic acid A (Scheme 2). Subsequent conversion to pseudorubrenoic acid A (**1**), however, would require the difficult reductive removal of the phenolic hydroxyl group. If this oxygen function is removed prior to cyclisation to give the minimally oxygenated enzyme-bound dione intermediate B, then the aldol cyclisation to the aromatic acid B becomes disfavoured both electronically and stereoelectronically. Partial reduction to the enzyme-bound hydroxy-dione intermediate C might avoid the disadvantages inherent in intermediates A and B, the aldol cyclisation product now yielding the same aromatic acid B by dehydration. The apparent ease of this sequence raises the question as to why so few aromatic metabolites corresponding to such a pathway are observed in Nature, compared to those formed from trione intermediates of the type A without subsequent removal of the phenolic hydroxyl group. It may be that methylene activation by two flanking ketonic groups, as in the trione A, is necessary for the enzymic aldol cyclisation. In all three cases, conversion of the residual aryl ketone of acid A or B to the styrene functionality of pseudorubrenoic acid A (**1**) by reduction and elimination would be enzymically straightforward.

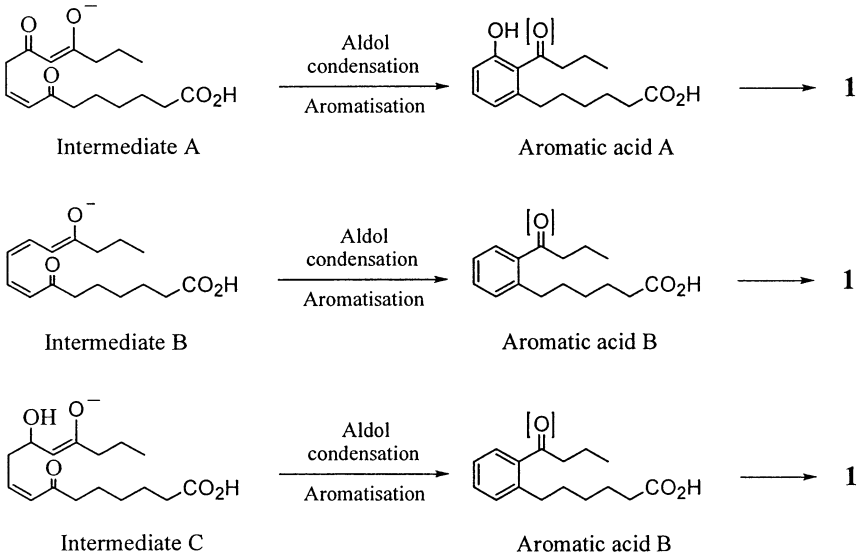
Ritzau and co-workers[5] suggested that serpentene might arise by Bergman cyclisation[18] of an enediyne precursor, and in principle such a process could also account for the related *o*-dialkyl-substituted aromatic structures cited above. Effective Bergman cyclisation, however, would require the enediynes to be constrained in medium ring systems,[19] and the present structures show no evidence of such precursors.

In order to illustrate the feasibility of electrocyclic processes in the biosynthesis of such aromatic natural products, and to provide access to possible biosynthetic intermediates, we describe here the synthesis of an analogue of the putative hexadeca-7,9,11,13-tetraenoic acid precursor (**3**) of pseudorubrenoic acid A (**1**) and its biomimetic conversion into the corresponding analogue of the natural acid itself.

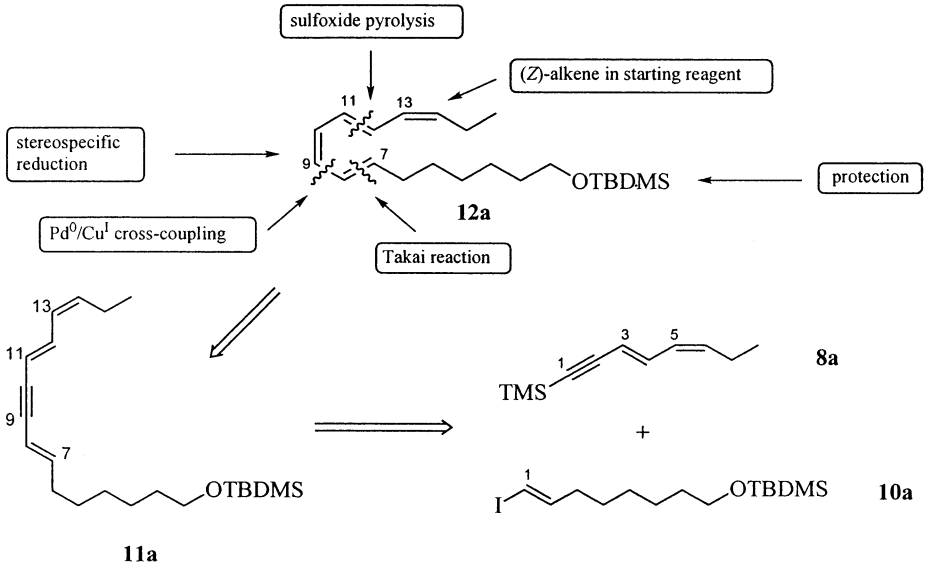
2. Results and discussion

2.1. Retrosynthetic analysis

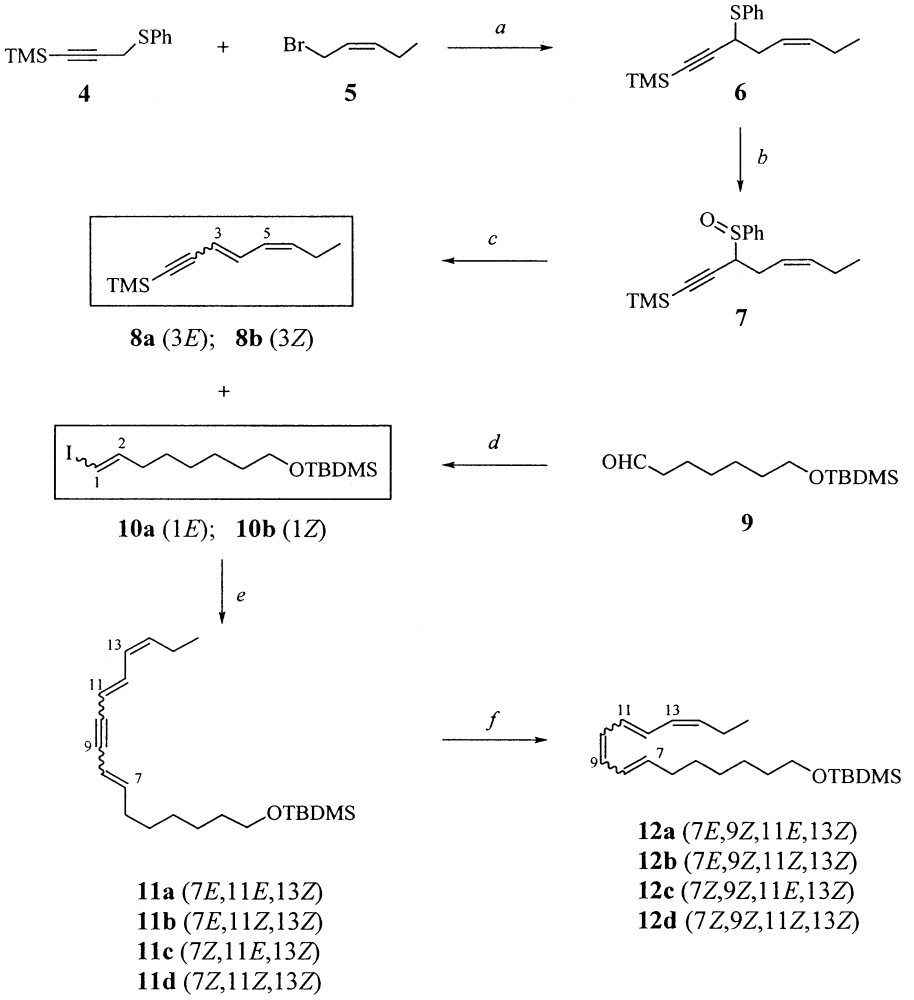
The natural electrocyclisation substrate in the case of pseudorubrenoic acid A (**1**) would probably be an enzyme-bound tetraenoic acid (e.g. **3**) or a related polyene. For increased stability and ease of handling we have focussed on the preparation and electrocyclisation of the silyl-protected tetraenol analogue **12a** rather than the carboxylic acid itself (Scheme 3). Apart from the necessary 9*Z*-configuration noted above, the tetraenoic acid **3** and hence its analogue **12a** require the 13*Z*-configuration to yield the ultimate *Z*-styrene. The 7- and 11-configurations cannot be defined in the proposed biosynthetic pathway since their stereochemistry is lost in the natural product **1**, but in conjunction with the electrocyclisation mechanism they will control the stereochemistry of the intermediate cyclohexadiene. We chose *E*-configurations for these latter olefins, to optimise orbital overlap in a thermal electrocyclisation designed to yield a *cis*-dihydrobenzene product. The retrosynthetic analysis employed (Scheme 3) for the required conjugated 7*E*,9*Z*,11*E*,13*Z*-tetraene **12a** comprises four key features: (1) the crucial *Z*-alkene at C-9 of the



Scheme 2. Hypothetical aldol-based biosynthetic routes to pseudorubrenoic acid (**1**).



Scheme 3. Retrosynthetic analysis of the tetraene **12a**.



Scheme 4. Synthesis of the tetraenes **12a–d**. *Reagents and conditions*: (a) 1.0 equiv. LDA, 0°C, 40 min, then add **5**, 2.0 equiv. HMPA, THF, 0°C, 1.5 h; 75%. (b) 1.2 equiv. *m*-CPBA, 1.6 equiv. $NaHCO_3$, CH_2Cl_2, −78°C, 5 h; 63%. (c) Piperidine, xylene, 50°C, 22 h; 55%. (d) 7 equiv. $CrCl_2$, 2 equiv. CHI_3, THF, room temperature, 18 h; 90%. (e) 0.06 equiv. $Pd[Ph_3]_4$, 0.06 equiv. CuI, 0.06 equiv. TEBACl, MeCN–50% aq. NaOH (1:1), 0–40°C, 18 h; 82%. (f) Zn(Cu/Ag), MeOH–H_20 (1:1), room temperature, 20 h; 84%.

tetraene is introduced in the last step of the synthesis by a selective, stereospecific reduction of the conjugated alkyne **11a**; (2) the C_{16}-trienyne skeleton is constructed by Pd-catalysed cross-coupling between the sp and sp^2 carbon centres of the components **8a** and **10a**; (3) the *E*-alkene at C-3 of the alkynyl coupling component **8a** is introduced via sulfoxide pyrolysis, the *Z*-alkene at C-5 being derived from the appropriate starting material; and (4) the *E*-alkene at C-1 of the alkenyl coupling component **10a** is generated by a Takai reaction.

This flexible strategy provides both an efficient route to the tetraene **12a** and also access to the other C-7 and C-11 alkene stereoisomers **12b–d** which are capable of undergoing electrocyclisation. Thus the sulfoxide pyrolysis used in the preparation of intermediate **8a** gives rise to a mixture of *E*- and *Z*-isomers of the newly formed double bond, and the *E*-alkene of intermediate **10a** can easily be replaced with a *Z*-alkene by employing a Wittig instead of a Takai reaction.

2.2. Synthesis

The synthesis of the silyloxytetraenes **12a–d** is presented in Scheme 4. Following the procedure of Nicolaou et al.,[20] lithium diisopropylamide-mediated alkylation of 1-trimethylsilyl-3-phenylthioprop-1-yne[20] (**4**) with *Z*-1-bromopent-2-ene[21] (**5**) gave the sulfide **6** (75% yield), which was subjected to mild oxidation with *m*-chloroperbenzoic acid and solid sodium hydrogen carbonate in dichloromethane to afford the sulfoxides **7** (63% yield) as a mixture of diastereomers (7:3[22]). No epoxidation of the double bond was observed.

Thermolysis of the diastereomeric mixture of sulfoxides **7** in the presence of piperidine[23] effected the *syn*-elimination of benzenesulfenic acid to furnish a mixture of the 3*E*- and 3*Z*-alkenes **8a**,**b** (3:2,[22] 55% yield), as desired. Thermolysis in the absence of an acid scavenger resulted in extensive *Z*- to *E*-isomerisation of the product.[23] The dienynes **8a** and **8b** were inseparable by flash chromatography, and were employed in the next synthetic step as the stereoisomeric mixture.

The C_{16}-skeleton of the 7*E*,11*E*,13*Z*-trienyne **11a** (and its stereoisomers **11b–d**) was assembled by a Pd-catalysed cross-coupling reaction similar to that described by Nicolaou et al.[24] The predominantly *E*-vinyl iodide **10a**,**b** (9:1[22]) required for the coupling was prepared (90% yield) by Takai methylenation[25] of 7-*t*-butyldimethylsilyloxyheptanal (**9**) with iodoform and chromous chloride, adopting the solvent modification (tetrahydrofuran–dioxane 1:6) suggested by Evans et al.[26] Use of the original reaction conditions described by Takai et al.[25] led to a lower yield (48%) of the iodide **10a** and poorer stereoselectivity (**10a**–**10b**=6:1[22]).

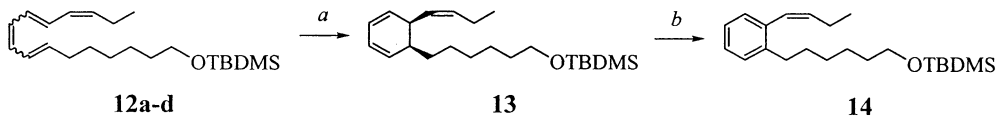
Attempts to couple the dienyne stereoisomers **8a**,**b** (3:2), after desilylation, with the vinyl iodide stereoisomers **10a**,**b** (9:1) under standard Sonogashira conditions[27] with catalytic amounts of tetrakis(triphenylphosphine)-palladium and cuprous iodide in benzene containing *n*-propylamine were unsuccessful. By combining elements of the procedure described by Roser et al.[28] for Si–C bond cleavage in silyl alkynes with that of Rossi et al.[29] for the Pd-catalysed coupling of aryl halides with free alkynes, however, and performing the cross-coupling under phase transfer conditions in acetonitrile–50% aqueous sodium hydroxide, the trienyne stereoisomers **11a–d** could be obtained in high yield (82%). The stereochemical composition of the resulting trienyne could not be quantitatively assessed since the stereoisomers **11a–d** were inseparable by HPLC. It was clear from ^{1}H spectroscopy, however, that the coupled product contained a dominant species, assigned as the 7*E*,11*E*,13*Z*-isomer **11a** in view of the composition of the starting materials. This conclusion was confirmed by cleavage of the silyl ether (in 86% yield) from a portion of the trienyne mixture **11a–d**. In contrast to the parent ethers, the resulting free trienynol stereoisomers were separable by HPLC, and the major product was clearly defined by ^{1}H NMR spectroscopy as the expected 7*E*,11*E*,13*Z*-isomer. Furthermore, the ^{1}H NMR spectrum of this major trienynol matched that of the dominant species seen in the parent trienyne ether mixture **11a–d**.

The selective, stereospecific partial reduction of an alkyne, centrally located in a conjugated system, to a *Z*-alkene is not trivial.[30] The partial reduction of the trienynes **11a–d** was achieved using the Cu/Ag-activated zinc metal described by Boland et al.[31] which works best for the partial reduction of alkynes in highly unsaturated substrates. In contrast to Lindlar's catalyst,[30] which gave a mixture of unreacted, dihydro and perhydro material, use of this activated zinc resulted in the selective reduction of the trienynes **11a–d** to the tetraenes **12a–d** in high yield (84%), with no over-reduced product detectable by analytical HPLC. A quantitative assessment of the stereoisomer ratio could not be made, as the tetraenes **12a–d** were again inseparable by HPLC. It was evident from ^{1}H and ^{13}C NMR spectroscopy, however, that the tetraene mixture contained primarily one species, presumably the 7*E*,9*Z*,11*E*,13*Z*-isomer **12a** in accord with the expected reduction of the dominant 7*E*,11*E*,13*Z*-trienyne **11a**.

The presence of minor tetraene stereoisomers **12b–d** contaminating the major isomer **12a** at this stage was not considered a problem. Tetraene **12a**, with the optimum triene arrangement for achieving orbital overlap, was expected to undergo 6π electrocyclisation at the lowest temperature, leaving the other stereoisomers unreacted and separable from the cyclohexadiene product **13**.

2.3. Biomimetic electrocyclisation

The tetraene mixture **12a–d** was heated in toluene at 150°C, conditions typical for 6π electrocyclisation of an *E*,*Z*,*E*-triene[12,32] (Scheme 5). HPLC purification of the complex reaction product gave an 11% yield of the cyclohexadiene **13**. A strong cross-peak in the NOESY spectrum between the methine protons 5-H and 6-H on the cyclohexadiene ring verified that the 5,6-substituents were *cis*-oriented. This stereochemistry accords with Woodward and Hoffmann's prediction for the thermal 6π electrocyclisation of an *E*,*Z*,*E*-triene,[33] and confirms that the observed product is derived from the major tetraene stereoisomer **12a**.



12a-d **13** **14**

Scheme 5. Electrocyclisation of the tetraene **12a**. *Reagents and conditions*: (a) sealed tube, toluene, 150°C, 18 h; 11%. (b) MnO_2, xylene, 120°C, 18 h; 100%.

The cyclohexadiene **13** was then dehydrogenated over manganese dioxide to afford the aromatic silyl ether **14** in quantitative yield (Scheme 5). Conversion of the silyl ether **14** into the natural product pseudorubrenoic acid A (**1**) would require only desilylation followed by oxidation of the resulting primary alcohol to a carboxylic acid, but was precluded by lack of material. This minor adjustment of oxygen functionality is immaterial to the consideration of the biosynthesis of the pseudorubrenoic acids.

3. Conclusion

The successful 6π electrocyclic ring closure of the 7*E*,9*Z*,11*E*,13*Z*-tetraene **12a** to the 5,6-*cis*-dialkylcyclohexadiene **13**, followed by dehydrogenation to the analogue **14** of pseudorubrenoic acid A (**1**), illustrates the feasibility of the proposal that the pseudorubrenoic acids and related *o*-dialkyl-substituted aromatic metabolites arise via biological 6π electrocyclisations of acyclic polyene precursors such as the enzyme-bound acid **3**. Given the submerged growth conditions of the *Pseudomonas*, *Alteromonas* and *Streptomyces* microoganisms known to produce such metabolites in culture, the biosynthetic electrocyclisations are unlikely to be photochemically promoted. In the present in vitro model, the cyclisation was effected thermally at a temperature well beyond that accessible in vivo. An enzyme, here termed an 'electrocyclase', would be needed to lower the activation energy of the process in vivo. In this connection, we note the dramatic acceleration of pericyclisation of a substrate analogue achieved by a purified Diels–Alderase, operating at ambient temperature in an aqueous medium,[10] compared to the thermal cyclisation of the same substrate in an organic solvent at 160°C.[34] The electrocyclase would constrain the triene moiety of the substrate into the less preferred *s-cis* conformation required for cyclisation, and could catalyse the cyclisation by electron transfer, a common process in biology. Whereas there are no reports to date of hole-catalysed 6π electrocyclisation, reversible one-electron electrochemical reduction to the radical anion has been reported to promote efficient 6π electrocyclisation.[35] The application of such electron transfer catalysis to the biomimetic synthesis of the pseudorubrenoic acids and related *o*-dialkyl-substituted aromatic metabolites is currently being explored in our laboratories.

4. Experimental

4.1. General

3-Phenylthio-1-trimethylsilylprop-1-yne[20,36] (**4**), (*Z*)-1-bromopent-2-ene[21] (**5**) and 7-*t*-butyldimethylsilyloxyheptanal[37] (**9**) were prepared as described in the literature. Unless specified otherwise, all reactions were performed under an inert atmosphere of argon with dry, freshly distilled solvents under anhydrous conditions. All reactions involving conjugated polyenes or polyenynes were protected from light. All reactions were monitored by TLC using Merck aluminium sheets coated with Merck Silica Gel 60 F254 and visualised using either UV light (254 or 366 nm) or a vanillin staining reagent.[38] The phrase 'work-up' refers to separation of an organic phase, washing with saturated aq. $NaHCO_3$, brine and then water, drying ($MgSO_4$), filtration and evaporation of the solvent under reduced pressure. Except for (7*E*,11*E*,13*Z*)-hexadeca-7,11,13-trien-9-yn-1-ol and the cyclohexadiene **13** (both purified by RP-HPLC), and the aromatic silyl ether **14** (obtained pure upon work-up), all compounds were purified by flash chromatography as described by Still et al.[39] using Merck Silica Gel 60 (particle size 40–63 m). Unless specified otherwise, the yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous material. NMR spectra were recorded for acid-free $CDCl_3$ solutions on a Varian Gemini-300 instrument at 300 MHz for ^{1}H and 75.43 MHz for ^{13}C. The solvent ^{1}H and ^{13}C signals, 7.27 ppm for residual $CHCl_3$ and 77.0 ppm for $CDCl_3$, were used as internal references. Signal assignments are based on direct spectrum analysis, selective proton decoupling, H,H-COSY and APT data. EIMS and HREIMS were recorded at 70 eV on VG AutoSpec or ZAB2-SEQ Mass Spectrometers. UV spectra were recorded on a Hewlett–Packard 8450A Spectrophotometer. Microanalyses were performed by the Australian National University Microanalytical Service on a Carlo Erba EA 1106 CHN-O analyser.

4.1.1. (*E*)- and (*Z*)-8-*t*-Butyldimethylsilyloxy-1-iodooct-1-enes (10a,b). 7-*t*-Butyldimethylsilyloxyheptanal (**9**) (125 mg, 511 μmol) and CHI_3 (394 mg, 1.00 mmol) in dioxane (9 mL) were added to flame-dried, anhydrous $CrCl_2$ (377 mg, 3.60 mmol) in THF (1.5 mL) and the resulting mixture stirred at room temperature. After 18 h, the reaction mixture was poured into water and extracted with Et_2O. The residue obtained upon work-up was chromatographed (5% CH_2Cl_2 in hexane) to afford the vinyl iodide stereoisomers **10a**,**b** (9:1[22]) as a colourless oil (170 mg, 90%) with ^{1}H NMR data identical to that reported by Makabe et al.[40]

4.1.2. (*Z*)-3-Phenylthio-1-trimethylsilyloct-5-en-1-yne (6). 3-Phenylthio-1-trimethylsilylprop-1-yne (**4**) (3.15 g, 14.3 mmol) in THF (10 mL) was added to a stirred solution of diisopropylamine (2.00 mL, 14.3 mmol) and *n*-BuLi (10.2 mL, 14.3 mmol, 1.4 M) in THF (20 mL) at 0°C. After 40 min, (*Z*)-1-bromopent-2-ene (**5**) (2.13 g, 14.3 mmol) and hexamethylphosphoramide (4.97 mL, 28.6 mmol) in THF (10 mL) were introduced and the stirring continued at 0°C. After 1.5 h, the resulting solution was warmed to room temperature, poured into water and extracted with Et_2O. The residue obtained upon work-up was chromatographed (100% pentane) to afford sulfide **6**

as a colourless oil (3.10 g, 75%) (Found: C, 70.8; H, 8.1. $C_{17}H_{24}SSi$ requires C, 70.8; H, 8.4%); δ_H 0.11 (s, 9H, $SiMe_3$), 0.97 (t, J=7.5 Hz, 3H, Me), 2.04 (quin, J=7.2 Hz, 2H, 7-H), 2.49 (t, J=6.9 Hz, 2H, 4-H), 3.80 (t, J=7.0 Hz, 1H, 3-H), 5.51 (m, 2H, 5-H and 6-H), 7.24–7.40 (m, 3H, *m*- and *p*-ArH), 7.50–7.62 (m, 2H, *o*-ArH); δ^C −0.10 (q, $SiMe_3$), 14.2 (q, C8), 20.8 (t, C7), 32.7 (t, C4), 39.6 (d, C3), 89.1 (s, C1), 105.1 (s, C2), 124.3 (d, ArC), 127.9 (d, ArC), 128.7 (d, ArC), 133.2 (s, ArC1), 133.6 (d, C5), 134.6 (d, C6) (the last two assignments may be reversed); *m*/*z* 288 (M^+, 22%), 273 ($[M-Me]^+$, 3), 219 ($[M-C_5H_9]^+$, 100), 205 (3), 191 (26), 151 (31), 129 (37), 109 (ArS^+, 30), 97 (Me_3SiCC^+, 20), 83 (26), 73 (Me_3Si^+, 81).

4.1.3. (*Z*)-3-Phenylsulfinyl-1-trimethylsilyloct-5-en-1-ynes (7). The sulfide **6** (229 mg, 794 μmol), *m*-chloroperbenzoic acid (166 mg, 962 μmol) and $NaHCO_3$ (108 mg, 1.28 mmol) in CH_2Cl_2 (4 mL) were stirred at −78°C. After 5 h, the reaction mixture was warmed to room temperature, filtered, the filtrate diluted with saturated aq. $NaHCO_3$, the organic phase separated and the aqueous phase extracted with Et_2O. The organic phases were combined, worked-up and chromatographed (9% EtOAc in hexane) to afford sulfoxide **7** as a mixture of diastereomers (154 mg, 63% yield; diastereomer A–diastereomer B 3:7[22]). Re-chromatography of the material using 7% EtOAc in hexane as eluent afforded first diastereomer A of sulfoxide **7** as a colourless oil (30.0 mg, 12%) (Found: MH^+, 305.1393. $C_{17}H_{25}OSSi$ requires 305.1395); δ_H 0.14 (s, 9H, $SiMe_3$), 0.95 (t, J=7.5 Hz, 3H, Me), 2.04 (quind, J=7.4, 1.5 Hz, 2H, 7-H), 2.13 (br ddd, J=14.0, 9.6, 7.4 Hz, 1H, 4-H_a), 2.80 (br ddd, J=14.0, 7.5, 5.3 Hz, 1H, 4-H_b), 3.55 (dd, J=9.6, 5.3 Hz, 1H, 3-H), 5.37 (br dt, J=10.8, 7.2 Hz, 1H, 5-H), 5.57 (br dt, J=10.8, 7.4 Hz, 1H, 6-H), 7.45–7.55 (m, 3H, *m*- and *p*-ArH), 7.65–7.72 (m, 2H, *o*-ArH); δ^C −0.3 ($SiMe_3$), 14.2 (q, Me), 20.7 (t, C7), 25.1 (t, C4), 57.6 (d, C3), 98.3 (s, C1), 103.2 (s, C2), 123.0, 125.4, 128.4, 131.3, 135.7 (unassigned doublets for C5, C6 and 4ArC, some signals overlapping), 143.0 (s, ArC1); *m*/*z* 305 ($[MH]^+$, 1%), 304 (M^+, 1), 289 ($[M-Me]^+$, 1), 288 ($[M-O]^+$, 1), 275 ($[M-Et]^+$, 1), 219 ($[M-O-C_5H_9]^+$, 5), 179 ($[M-ArSO]^+$, 26), 125 ($ArSO^+$, 32), 109 (ArS^+, 25), 97 (Me_3SiCC^+, 19), 77 (Ar^+, 30), 73 (Me_3Si^+, 100). This was followed by diastereomer B of sulfoxide **7**, also a colourless oil (53.5 mg, 22%) (Found: MH^+, 305.1371. $C_{17}H_{25}OSSi$ requires 305.1395); δ_H 0.10 (s, 9H, $SiMe_3$), 0.98 (t, J=7.5 Hz, 3H, Me), 2.13 (quind, J=7.5, 3.0 Hz, 2H, 7-H), 2.72 (br t, J=6.8 Hz, 2H, 4-H), 3.43 (dd, J=7.4, 5.3 Hz, 1H, 3-H), 5.50 (br dt, J=10.8, 7.0 Hz, 1H, 5-H), 5.55–5.70 (br dt, J=10.8, 6.7 Hz, 1H, 6-H), 7.45–7.57 (m, 3H, *m*- and *p*-ArH), 7.72–7.78 (m, 2H, *o*-ArH); δ^C −0.4 ($SiMe_3$), 14.2 (q, Me), 20.9 (t, C7), 27.0 (t, C4), 60.8 (d, C3), 94.6 (s, C1), 96.6 (s, C2), 122.4, 122.5, 125.6, 125.7, 128.5, 131.6, 135.9, (unassigned doublets for C5, C6 and 5ArC), 137.0 (s, ArC1); *m*/*z* 305 ($[MH]^+$, <1%), 304 (M^+, <1), 289 ($[M-Me]^+$, 1), 288 ($[M-O]^+$, 2), 275 ($[M-Et]^+$, 0.4), 219 ($[M-O-C_5H_9]^+$, 15), 179 ($[M-ArSO]^+$, 29), 163 (21), 126 ($ArSOH^+$, 13), 125 ($ArSO^+$, 9), 109 (ArS^+, 16), 97 (Me_3SiCC^+, 16), 77 (Ar^+, 11), 73 (Me_3Si^+, 100).

4.1.4. (3*E*,5*Z*)- and (3*Z*,5*Z*)-1-Trimethylsilylocta-3,5-dien-1-ynes (8a,b). The diastereomeric mixture of sulfoxides **7** (179 mg, 588 μmol), piperidine (58.2 μL, 588 μmol) and toluene (2 mL) were stirred at 50°C. After 22 h, the reaction mixture was cooled, poured into saturated aq. $NaHCO_3$, the organic phase separated and the aqueous phase extracted with Et_2O. The organic phases were combined, worked-up and chromatographed (100% hexane) to afford the dienyne stereoisomers **8a**,**b** (3:2[22]) as a colourless oil (57.4 mg, 55%) (Found: M^+, 178.1176. $C_{11}H_{18}Si$ requires 178.1178); δ_H 0.21 and 0.22 (each s, 18H, $SiMe_3$ of **8a/b**), 1.01 and 1.02 (each t, J=7.5 Hz, 6H, Me of **8a/b**), 2.19 (br quin, J=7.6 Hz, 4H, 7-H of **8a/b**), 5.47 (br d, J=10.8 Hz, 1H, 3-H of **8b**), 5.56 (dt, J=10.8, 7.8 Hz, 1H, 6-H of **8a**), 5.59 (d, J=15.4 Hz, 1H, 3-H of **8a**), 5.69 (br dt, J=10.7, 7.8 Hz, 1H, 6-H of **8b**), 5.99 (br t, J=11.1 Hz, 1H, 5-H of **8a**), 6.52 (br t, J=11.2 Hz, 1H, 5-H of **8b**), 6.72 (dt, J=11.2, 0.9 Hz, 1H, 4-H of **8b**), 6.95 (ddd, J=15.5, 11.5, 1.2 Hz, 1H, 4-H of **8a**); δ^C −0.1 and 0.0 (q, $SiMe_3$ of **8a/b**), 14.1 (q, Me of **8a/b**), 21.4 (t, C7 of **8a/b**), 96.8, 101.4, 102.2, 104.8 (s, C1/C2 of **8a/b**), 108.6, 110.5, 125.1, 127.1, 136.1, 137.5, 138.0, 138.1 (unassigned doublets for C3-6 of **8a/b**); *m*/*z* 178 (M^+, 55%), 163 ($[M-Me]^+$, 100), 145 (25), 135 (42), 89 (80), 83 (25), 75 (25), 73 (Me_3Si^+, 52).

4.1.5. (7*E*,11*E*,13*Z*)-, (7*E*,11*Z*,13*Z*)-, (7*Z*,11*E*,13*Z*)- and (7*Z*,11*Z*,13*Z*)-1-*t*-Butyldimethylsilyloxyhexadeca-7,11,13-trien-9-ynes (11a–d). Deaerated 50% aq. NaOH (1 mL) was added dropwise to the following reagents in deaerated acetonitrile (1 mL) at 0°C; the dienynes **8a**,**b** (3:2; 229 mg, 1.30 mmol), the vinyl iodides **10a**,**b** (9:1; 233 mg, 630 μmol), triethylbenzylammonium chloride (8.80 mg, 38.4 μmol), $Pd(PPh_3)_4$ (44.4 mg, 38.4 μmol) and CuI (7.30 mg, 38.4 μmol), and the resulting mixture stirred at 40°C. After 18 h, the organic material was extracted into CH_2Cl_2, worked-up and chromatographed (10% CH_2Cl_2 in hexane) to afford the trienyne stereoisomers **11a–d** as a yellow oil (180 mg, 82% yield) (Found: C, 76.3; H, 10.8. $C_{22}H_{38}OSi$ requires C, 76.2; H, 11.1%) (Found: M^+, 346.2697. $C_{22}H_{38}OSi$ requires 346.2692); δ_H 0.05 (s, 6H, $SiMe_2$), 0.90 (s, 9H, *t*-Bu), 1.02 (m, 3H, Me), 1.20–1.60 (m, 8H, 2-H to 5-H), 2.19–2.41 (m, 4H, 6-H and 15-H), 3.61 (t, J=7.5 Hz, 2H, 1-H), 5.41–6.92 (m, 6H, 7-H, 8-H and 11-H to 14-H); *m*/*z* 346 (M^+, 18%), 331 ($[M-Me]^+$, 1), 289 ($[M-t\text{-}Bu]^+$, 20), 215 ($[M-OTBDMS]^+$, 28), 157 (25), 145 (31), 143 (31), 131 (27), 129 (28), 119 (32), 117 (33), 115 (29), 105 (23), 91 (33), 88 (26), 77 (28), 75 ($HO{=}SiMe_2$, 100).

4.1.6. (7*E*,11*E*,13*Z*)-Hexadeca-7,11,13-trien-9-yn-1-ol. The trienyne silyl ethers **11a–d** (20.6 mg, 59.0 μmol) were stirred with TBAF (119 μL, 119 μmol, 1.0 M) in THF (1 mL) at 0°C for 5 min and then at room temperature for 80 min. The reaction was diluted with Et_2O, and after addition of saturated aq. $NaHCO_3$ worked-up in the usual manner. Flash chromatography (25% EtOAc in hexane) gave the trienynol stereoisomers (11.8 mg, 86% yield) as a bright yellow oil. Semi-preparative RP-HPLC (YMC column: 30 min methanol–water gradient (75/25–88/12), flow=4 mL/min, λ=295 nm) afforded the major stereoisomer (7*E*,11*E*,13*Z*)-hexadeca-7,11,13-trien-9-yn-1-ol as a yellow oil (Found: C, 82.9; H, 10.3. $C_{16}H_{24}O$ requires: C, 82.7; H, 10.4%) (Found: M^+, 232.1829. $C_{16}H_{24}O$ requires 232.1827); δ_H (assigned from homonuclear decoupling experiments) 1.00 (t, J=7.5 Hz, 3H, Me),

1.20–1.60 (m, 9H, 2-H to 5-H and OH), 2.13 (qd, $J_{6,5}\approx J_{6,7}$=7.5 Hz, $J_{6,8}$=1.5 Hz, 2H, 6-H), 2.21 (quind, $J_{15,14}\approx J_{15,16}$=7.5 Hz, $J_{15,13}$=1.5 Hz, 2H, 15-H), 3.63 (t, $J_{1,2}$=6.5 Hz, 2H, 1-H), 5.52 (dtt, $J_{14,13}$=10.8 Hz, $J_{14,15}$=7.7 Hz, $J_{14,12}\approx J_{14,11}$=1.0 Hz, 1H, 14-H), 5.62 (ddt, $J_{8,7}$=15.7 Hz, $J_{8,11}$=2.2 Hz, $J_{8,6}$=1.6 Hz, 1H, 8-H), 5.68 (brdd, $J_{11,12}$=15.4 Hz, $J_{11,8}$=2.3 Hz, 1H, 11-H), 6.01 (ttd, $J_{13,12}\approx J_{13,14}$=11.0 Hz, $J_{13,15}$=1.5 Hz, $J_{13,11}$=1.0 Hz, 1H, 13-H), 6.14 (dt, $J_{7,8}$=15.7 Hz, $J_{7,6}$=7.2 Hz, 1H, 7-H), 6.86 (ddd, $J_{12,11}$=15.5 Hz, $J_{12,13}$=11.5 Hz, $J_{12,14}$=1.5 Hz, 1H, 12-H); δ^C (assigned from HETCOR spectra) 14.7 (Me), 22.0 (C15), 26.1, 29.3, 29.4, and 33.2 (C2-5), 33.7 (C6), 63.6 (C1), 88.4 and 101.6 (C9 and C10), 110.4 (C8), 111.4 (C11), 127.9 (C13), 137.0 (C12), 137.2 (C14), 145.3 (C7); *m/z* 232 (M^+, 71%), 203 ($[M-Et]^+$, 10), 159 ($[M-C_4H_9O]^+$, 27), 145 (50), 143 (26), 131 (71), 130 (30), 129 (60), 128 (39), 118 (42), 117 (100), 116 (30), 115 (57), 105 (53), 103 (29), 91 (83), 79 (43), 77 (31).

4.1.7. (7*E*,9*Z*,11*E*,13*Z*)-, (7*E*,9*Z*,11*Z*,13*Z*)-, (7*Z*,9*Z*,11*E*,13*Z*)- and (7*Z*,9*Z*,11*Z*,13*Z*)-1-*t*-Butyldimethylsilyloxyhexadeca-7,9,11,13-tetraenes (12a–d). The trienynes **11a–d** (140 mg, 405 μmol) in MeOH (2 mL) were added to a stirred suspension of activated Zn[29] (freshly prepared from Zn (250 mg), $Cu[OAc]_2{\cdot}H_2O$ (25.0 mg) and $AgNO_3$ (25.0 mg)) in MeOH–water (1:1, 10 mL) at room temperature. After 20 h, the metal was removed by filtration through a short column of Celite and the filtrate concentrated and extracted with pentane. The residue obtained upon work-up was chromatographed (100% hexane) to afford the tetraene stereoisomers **12a–d** as a yellow oil (113 mg, 84%) (Found: C, 75.4; H, 11.2. $C_{22}H_{40}OSi$ requires C, 75.8; H, 11.6%) (Found: M^+, 348.2844. $C_{22}H_{40}OSi$ requires 348.2849); δ_H 0.06 (s, 6H, $SiMe_2$), 0.90 (s, 9H, *t*-Bu), 1.02 (t, *J*=7.5 Hz, 3H, Me), 1.25–1.55 (m, 8H, 2-H to 5-H), 2.13 (q, *J*=6.7 Hz, 2H, 6-H), 2.22 (quind, *J*=6.6, 1.5 Hz, 2H, 15-H), 3.60 (t, *J*=6.5 Hz, 2H, 1-H), 5.42–6.72 (m, 8H, 7-H to 14-H); *m/z* 349 ($[MH]^+$, 45%), 348 (M^+, 75), 333 ($[M-Me]^+$, 5), 291 ($[M-t\text{-}Bu]^+$, 35), 213 (35), 159 (22), 147 (25), 145 (44), 133 (36), 131 (32), 119 (40), 117 (39), 115 (22), 105 (45), 95 (34), 93 (25), 91 (58), 81 (28), 77 (40), 75 (HO=$SiMe_2$, 100).

4.1.8. *cis*-5-[(*Z*)-But-1′-enyl]-6-(6″-*t*-butyldimethylsilyloxyhexyl)cyclohexa-1,3-diene (13). The tetraene stereoisomers **12a–d** (80.7 mg, 231 μmol) in toluene (15 mL) were heated at 150°C in a sealed tube. After 18 h, the sealed tube was cooled to −78°C, opened, the toluene evaporated and the residue purified by semi-preparative RP-HPLC (YMC C_{18} column: 100% acetonitrile, flow 3 mL/min, UV detection 265 nm, R_t=32 min) to afford the cyclohexadiene **13** as a colourless oil (8.9 mg, 11% yield) (Found: M^+, 348.2849. $C_{22}H_{40}OSi$ requires 348.2849); δ_H 0.04 (s, 6H, $SiMe_2$), 0.89 (s, 9H, *t*-Bu), 0.96 (t, *J*=7.5 Hz, 3H, Me), 1.25–1.55 (m, 8H, 1″-H to 5″-H), 2.06 (quin, *J*=7.5 Hz, 2H, 3′-H), 2.46 (m, 1H, 6-H), 3.09 (m, 1H, 5-H), 3.59 (t, *J*=6.5 Hz, 2H, 6″-H), 5.37 (dt, *J*=11.0, 7.0 Hz, 1H, 2′-H), 5.45 (t, *J*=10.5 Hz, 1H, 1′-H), 5.58 (m, 1H, 1-H), 5.69 (m, 1H, 4-H), 5.86 (m, 2H, 2-H and 3-H); δ^C −4.2 (q, $SiMe_2$), 15.7 (q, Me), 18.4 (s, *t*-Bu), 22.0 (t, C3′), 27.1 (q, *t*-Bu), 26.9, 28.3, 30.7, 31.7, 33.9 (t, C1″ to C5″), 36.1 (d, C5), 38.3 (d, C6), 64.4 (t, C6″), 124.4, 125.0 (d, C2 and C3), 126.2 (d, C1′), 131.3 (d, C4), 132.1 (d, C1), 133.6 (d, C2′); *m/z* 348 (M^+, 31%), 333 ($[M-Me]^+$, 2), 291 ($[M-t\text{-}Bu]^+$, 79), 235 (21), 215 (21), 213 (17), 173 (34), 159 (44), 145 (96), 133 (76), 131 (46), 117 (59), 105 (50), 91 (97), 75 (HO=$SiMe_2$, 100). The cyclohexadiene **13** was not obtained when the tetraenes **12a–d** were heated under similar conditions at 130°C.

4.1.9. 1-([*Z*]-But-1′-enyl)-2-(6″-*t*-butyldimethylsilyloxyhexyl)benzene (14). The cyclohexadiene **13** (5.0 mg, 14.3 μmol) in xylene (0.75 mL) was added to a suspension of freshly prepared active MnO_2[41] (25.0 mg, 288 μmol) in xylene (0.75 mL) and the resulting mixture stirred at 120°C. (At temperatures >130°C, the xylene was oxidised to higher-boiling tolualdehyde, whereupon isolation of the desired product required flash chromatography.) After 18 h, the reaction mixture was filtered through a short pad of Celite and the solvent evaporated under high vacuum to afford essentially pure aromatic silyl ether **14** as a colourless oil (4.95 mg, 100%) (Found: M^+, 346.2694. $C_{22}H_{38}OSi$, M^+, requires 346.2692); δ_H 0.04 (s, 6H, $SiMe_2$), 0.89 (s, 9H, *t*-Bu), 1.00 (t, *J*=7.5 Hz, 3H, Me), 1.35 (m, 4H, $-[CH_2]_2-$), 1.53 (m, 4H, $-[CH_2]_2-$), 2.16 (quind, *J*=7.5, 1.6 Hz, 2H, 3′-H), 2.58 (t, *J*=7.5 Hz, 2H, 1″-H), 3.59 (t, *J*=6.5 Hz, 2H, 6″-H), 5.70 (dt, *J*=11.0, 7.0 Hz, 1H, 2′-H), 6.46 (dt, *J*=11.0, 1.7 Hz, 1H, 1′-H), 7.16 (m, 4H, ArH); δ^C −5.3 (q, $SiMe_2$), 14.3 (q, Me), 18.4 (s, *t*-Bu), 21.7 (t), 25.7 (t), 26.0 (q, *t*-Bu), 29.3 (t), 30.6 (t), 32.8 (t), 33.5 (t), 63.3 (t, C6″), 125.2, 126.8, 127.2, 128.8, 129.4, 134.6 (each d, C1′, C2′ and C3-6), 136.3, 141.0 (s, C1 and C2); *m/z* 346 (M^+, 3%), 331 ($[M-Me]^+$, 4), 289 ($[M-t\text{-}Bu]^+$, 100), 213 ($[M-OTBS]^+$, 28), 171 (26), 157 (40), 145 (63), 143 (78), 131 (38), 117 (59), 105 (50), 91 (97), 75 (HO=$SiMe_2$, 100).

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