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Synthesis and Photooxidation of the Trisubstituted Oxazole Fragment of the Marine Natural Product Salarin C

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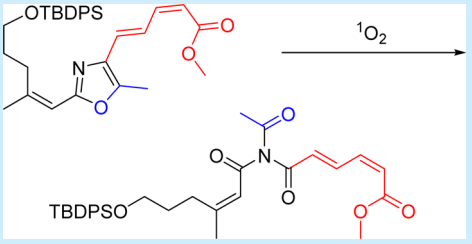
Supporting Information

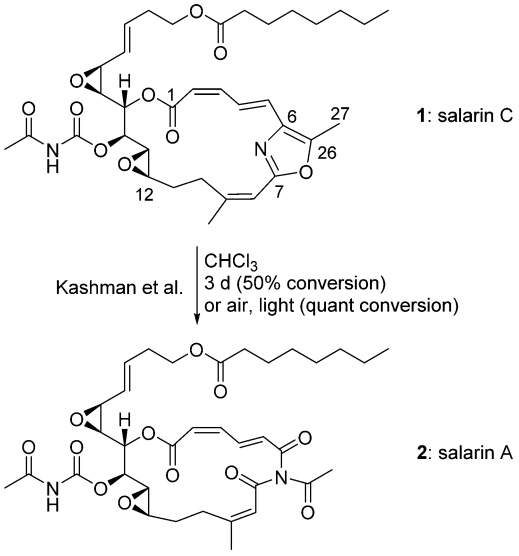
ABSTRACT: The eastern section of the macrocyclic marine natural product salarin C from the sponge *Fascaplysinopsis* sp. was synthesized employing a halogen dance reaction to assemble the trisubstituted oxazole moiety. The synthesis was inspired by Kashman's hypothesis on the biomimetic oxidation of salarin C to salarin A. Clean conversion to the triacylamine partial structure of salarin A occurred on treatment with photochemically generated singlet oxygen. Thus, a Wasserman-type oxidative rearrangement is chemically possible in this case.



The salarins constitute a remarkable group of macrolactone natural products that were isolated from the Madagascar marine sponge *Fascaplysinopsis* sp. by Kashman and co-workers.[1]

Salarin C (**1**, Scheme 1) was shown to exhibit potent activity against human leukemia cells (among them K562) in the low nanomolar range, inducing apoptosis.[1] All other salarins, including salarin A (**2**), were less active. Salarin C (**1**) contains a trisubstituted, bisalkenylated oxazole ring embedded in a macrocycle. Together with the bisepoxide section, that oxazole unit appears to be responsible for the biological activity of salarin C (**1**).

Scheme 1. Conversion of the Marine Natural Product Salarin C (1) to Salarin A (2) on Exposure to Light and Oxygen by Kashman et al.



Kashman et al. discovered that salarin C (**1**) is converted to the triacylamine salarin A (**2**) on exposure to air and oxygen, presumably via [4 + 2] cycloaddition of oxygen to the oxazole in a Wasserman-type rearrangement.[2] The instability of salarin C (**1**) does not appear to be shared by other macrocyclic polyketides that embed an oxazole ring, such as the leiodolides,[3] phorboxazole,[4] or rhizopodin.[5] In this paper, we report on the synthesis of the eastern fragment (C1−C11) of salarin C (**1**) and on its reactivity toward singlet oxygen. Surprisingly, there was not much known regarding the synthesis of trisubstituted 2,4-dialkenyl-5-methyloxazoles.[6] In fact, that partial structure seems to be restricted to the salarins.

Ideally, a 4-halo-5-methyl-2-sulfonyloxazole precursor would undergo sequential C−C-coupling reactions in the 4- and then in the 2-position. The required 2-sulfonyl substituent would be generated by oxidation of a sulfanyl moiety and replaced by treatment with an appropriate organolithium species.[7] The 4-alkenyl side chain could be introduced in Pd-catalyzed cross coupling reaction. Williams et al. have shown that 4-bromo-5-iodo-2-(phenylsulfanyl)oxazole can be accessed in a halogen dance reaction starting from easily accessible 5-bromo-2-(phenylsulfanyl)oxazole.[8] The sequence is believed to start by deprotonation at C4 followed by 1,2-migration of the halo substituent to the 4-position, placing the negative charge at C5.[9] In a similar manner, Stambuli et al. accessed disubstituted 2-aryl-4-alkenyloxazoles after a halogen dance reaction starting from 2-(*n*-butylsulfanyl)-5-iodooxazole.[10]

The halogen dance reaction proved to be more effective starting from 2-(*n*-butylsulfanyl)-5-bromo- and 5-iodooxazoles **3**[9] and **4**[9] than from 2-(phenylsulfanyl)-5-iodooxazole **5**[11] (90% compared to 40% yield, Scheme 2). Sonogashira coupling with propargyl alcohol only worked for the iodinated oxazoles **7** and **8** (83% and 47%, respectively). Hydrosilylation[12] of **9** and **10** afforded the (*Z*)-alkenylsilanes, which were desilylated to the

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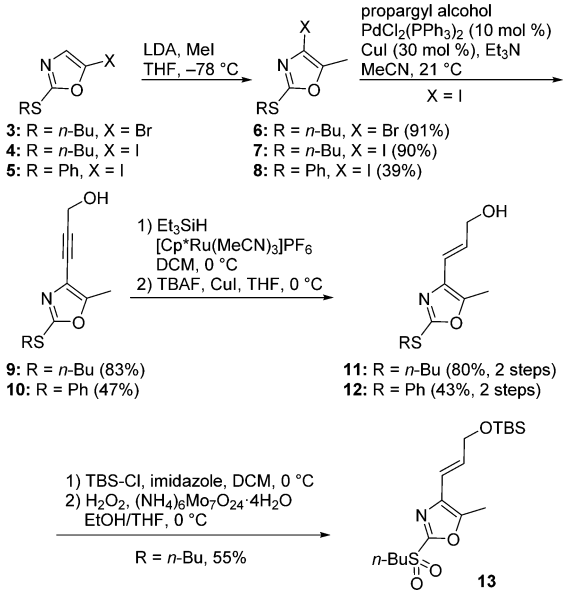
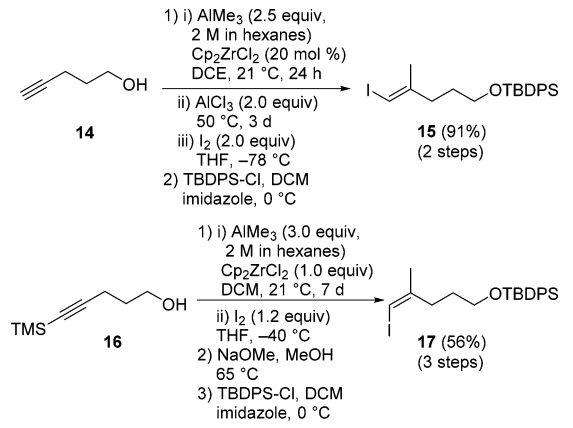
Scheme 2. Synthesis of 4-Alkenyl-5-methyl-2-butylsulfonyloxazole 13 by Halogen Dance Reaction



(*E*)-allylic alcohols **11** and **12**, respectively. Overall, the *n*-butylsulfanyl group allowed higher yields than the phenylsulfanyl group (60% vs 8% over four steps). *O*-Silylation of *n*-butylsulfanyloxazole **11**, followed by oxidation (H_2O_2, ammonium heptamolybdate), afforded 2-butanesulfonyloxazole **13** (55% over two steps).

We intended to synthesize the (*Z*)-iodoalkene coupling partner **17** from 4-pentyn-1-ol (**14**) via zirconium-catalyzed (20 mol %) carboalumination, followed by quenching with iodine (Scheme 3).[13] However, only the known (*E*)-isomer **15**[14] was

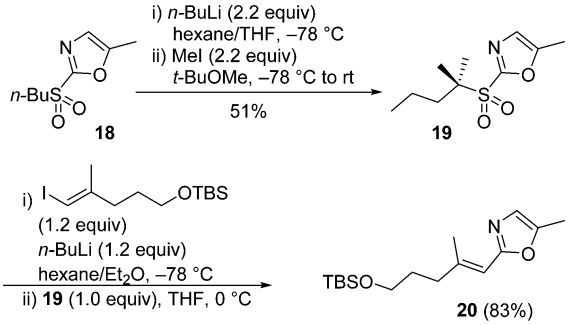
Scheme 3. Preparation of Iodoalkenes 15 and 17



formed. The pure (*Z*)-isomer was obtained when starting from the TMS-protected alkyne **16** using stoichiometric amounts of Cp_2ZrCl_2 at room temperature and omitting $AlCl_3$. Desilylation afforded (*Z*)-5-iodo-4-methylpent-4-en-1-ol (NaOMe, MeOH, 61%) followed by *O*-silylation to (*Z*)-iodoalkene **17**.[15]

It remained to be tested whether *n*-butanesulfonyloxazoles could undergo nucleophilic substitution with lithiated nucleophiles despite the presence of two α-protons adjacent to the sulfone moiety. A model coupling reaction of disubstituted 2-(*n*-butanesulfonyl)-5-methyloxazole (**18**, Scheme 4) and the lithioalkene derived from (*E*)-iodoalkene **15** failed. Probably,

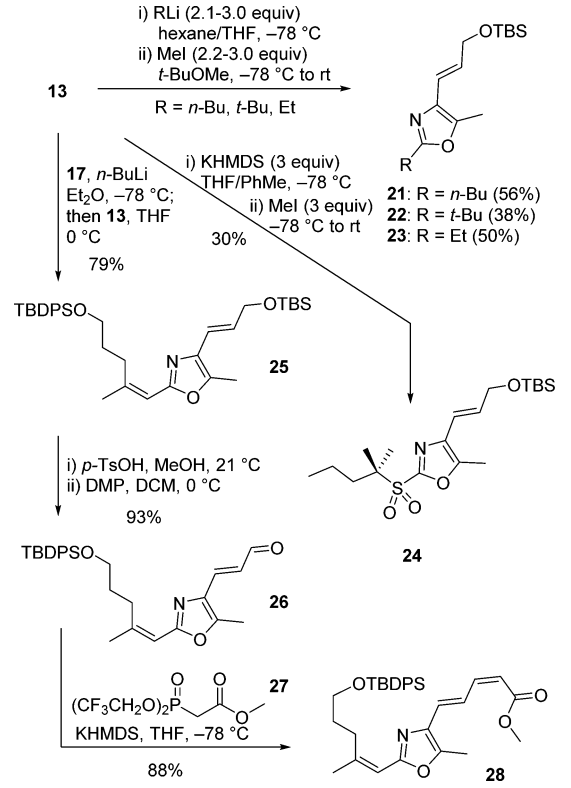
Scheme 4. α,α-Dimethylation of *n*-Butanesulfonyloxazole 18



the alkenyllithium species had α-deprotonated the *n*-butanesulfonyl group, preventing nucleophilic displacement via the tetrahedral intermediate. However, after α,α-dimethylation of **18** to **19** (*n*-BuLi, MeI, THF, –78 °C), nucleophilic 2-alkenylation of the oxazole unit became possible and afforded product **20** in 83% yield.

To our surprise, the *n*-butanesulfonyl side chain of trisubstituted oxazole **13** could not be α,α-dimethylated in the same manner as that of **18**. Instead, we observed substitution of the butanesulfonyl unit by an *n*-butyl group affording **21** (56%, Scheme 5). Formation of 2-*tert*-butyl- and 2-ethyloxazoles **22** and **23** with *t*-BuLi and EtLi, respectively, proved that the side chain stemmed form the alkyllithium reagent. α,α-Dimethylation was possible when KHMDS was used as base, followed by treatment with MeI. However, the low isolable yield of product **24** (30%) discouraged us from pursuing the dimethylation strategy further.

Scheme 5. Conversion of Trisubstituted *n*-Butanesulfonyloxazole 13 to the Model Partial Structure 28 of Salarin C (1)



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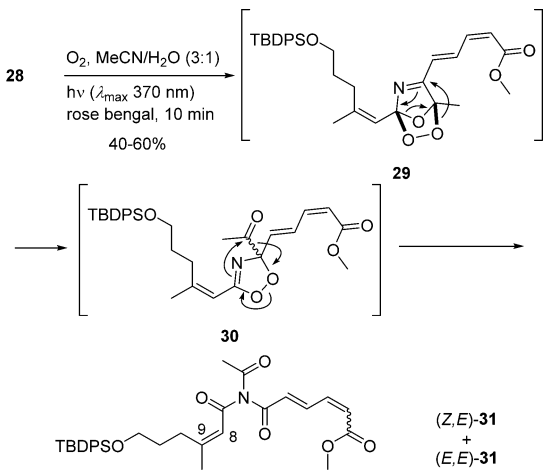
Instead, we chose to exploit the observed reactivity of *n*-butanesulfonyloxazole **13** toward *n*-BuLi for the coupling of **13** with the alkenyllithium species generated from (*Z*)-iodoalkene **17** (Scheme 5). The di(alkenyl)methyloxazole **25** was obtained in a stereospecific manner and in a good yield of 79%. As a final step toward target compound **28**, the 4-alkenyl side chain of the oxazole unit of **25** had to be transformed to the *α,β,γ,δ*-unsaturated ester moiety represented in salarin C (**1**). Chemoselective desilylation of **25** employing *p*-TsOH in MeOH only affected the TBS group while leaving the TBDPS group in place. Dess–Martin oxidation afforded *α,β*-unsaturated aldehyde **26**, which was submitted to a Still–Gennari olefination employing phosphonate **27**. The resulting (*E,Z*)-diene **28** could be stored in $CDCl_3$ for weeks without decomposition or isomerization.

The ^1H and ^{13}C NMR data (C_6D_6) of open-chain bisalkenyloxazole **28** and the corresponding substructure of macrocyclic salarin C (**1**) are very similar. As a small difference, 2-H shows a doublet of doublets with J = 11.7 and 0.6 Hz at δ_H 5.72 ppm for **28**, while salarin C (**1**) shows a doublet at δ_H 5.72 ppm with J = 12.1 Hz. While salarin C (**1**) exhibited singlets for the signals of 8-H and 22-H, bisalkenyloxazole **28** shows doublets with J = 1.4 Hz. A deviation among the oxazole ^{13}C NMR signals is observed for C6, which appears 6.0 ppm higher for **28**. In the $^1H,^{15}N$ HMBC spectrum of **28**, 5-H, 8-H, and 27-H_3 show correlations with the oxazole nitrogen (δ_N −130 ppm, referenced to nitromethane), similar as in the case of salarin C (**1**).

The stage was set for our experiment. The trisubstituted bisalkenyloxazole **28** was reacted with photochemically generated singlet oxygen (λ_{max} 370 nm, Rayonet reactor, rose bengal in MeCN/water, 10 min, Scheme 6). An approximately

Scheme 6. Reaction of Bisalkenyloxazole 28 with Singlet Oxygen



1:1 mixture of (*E/Z*)-isomeric products was isolated in 40–60% combined yield, both of which exhibited a mass (*m/z*) of 584.24405 (LTQ-Orbitrap), corresponding to a molecular formula of $C_{32}H_{39}NNaO_6Si$, counting for two oxygen atoms more than the starting material **28**. In the ^{13}C NMR spectrum, all oxazole signals had disappeared. Instead, we observed three new amide signals at *δ* 167.87/168.53, *δ* 167.87, *δ* 173.36/173.17 ppm. The ^{15}N NMR chemical shift had shifted upfield by 39 ppm (δ_N −169 ppm, referenced to nitromethane). Two diastereomeric triacylamines ((*Z,E*)-**31**, (*E,E*)-**31**) had been formed. The (*E*)-/(*Z*)-isomerism refers to the *α,β,γ,δ*-unsaturated methyl ester moieties of **31** ($\delta_{C=O}$ 165.55/166.18 and 51.74/52.00 ppm, $\delta_{3\text{-}H}$ 3.77/3.78 ppm) that were assigned on the basis of their $^3J_{HH}$ coupling constants of the *α,β*-double bond (J = 11.7 Hz for (*Z,E*)-**31**, J = 14.8 Hz for (*E,E*)-**31**). The (*Z*)-configuration of the *α,β*-unsaturated hexenoyl moiety was indicated by NOE correlations between the olefinic hydrogen and the methyl group. We observed the products (*Z,E*)-**31** and (*E,E*)-**31** as single rotamers, which were stable in C_6D_6 for weeks. In the ESIMS, loss of the acetyl group took place.

The ^1H, ^{13}C, and ^{15}N NMR data (C_6D_6) of triacylamine (*Z,E*)-**31** and of the corresponding partial structure of salarin A (**2**) showed full agreement, with one exception. The ^{13}C NMR signal of *β*-carbon C9 is shifted downfield by 10 ppm (δ_C 165.4 ppm) for (*Z,E*)-**31** in comparison to salarin A (**2**), whereas the neighboring *α*-C8 and 8-H deviate upfield by 3.3 ppm (δ_C 120 ppm) and 0.24 ppm (δ_H 5.74), respectively. Molecular modeling (MM2) indicates that the *α,β*-unsaturated (*Z*)-hexenoyl moiety of (*Z,E*)-**31** and (*E,E*)-**31** should obtain planar conformations. In contrast, the X-ray structure of salarin A (**2**) obtained by Kashman et al. shows a dihedral angle of 35.4° for the corresponding enone partial structure, which should lead to diminished conjugation and less pronounced downfield shift of the *β*-carbon atom. Rousseau et al. had published detailed NMR and IR data of *α,β*-unsaturated, *β*-substituted octenolides showing that deviation of an enone system from planarity leads to an upfield shift of the ^{13}C NMR signal of the *β*-carbon atom by more than 10 ppm.[16]

In summary, the result of our experiment is in agreement with Kashman's hypothesis on the conversion of salarin C (**1**) to salarin A (**2**).[1] The formation of (*Z,E*)-**31** and (*E,E*)-**31** is considered to start with a [4 + 2] cycloaddition providing cycloadduct **29**, followed by rearrangement to acetyloxadiazole derivative **30**, which undergoes a C–N transfer of the acetyl group accompanied by O–O bond cleavage (Scheme 6). Partial *E/Z*-isomerization occurred under the irradiation conditions. The formation of triacylamines by action of singlet oxygen on oxazoles has first been described by Wasserman.[2] The conversion of **28** to **31** appears to be the first example that starts from a bisalkenyloxazole. It should be mentioned that Evans et al. had obtained imides on treatment of mostly aryl-substituted oxazoles with CAN.[17] The reaction may even be interesting for a synthesis of salarin A (**2**). Bisalkenyloxazole **28** proved to be stable in $CDCl_3$ in the presence of air and light, although it contains the same *π*-system as the labile salarin C (**1**). This makes it likely that additional structural features of salarin C (**1**) contribute to its instability.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00845.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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